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Exploring New Techniques For Precision Deuteration of Alkenes and Alkynes

by

Zoua Pa Vang, B.A.

A Dissertation submitted to the Faculty of the Graduate School,
Marquette University,
in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy

Milwaukee, Wisconsin

May 2023

ABSTRACT

Exploring New Techniques For Precision Deuteration of Alkenes and Alkynes

Zoua Pa Vang, B.A.

Marquette University, 2023

Deuterium labeled compounds are often utilized in chemical research as internal standards in mass spectrometry, to study reaction mechanisms and in the pharmaceutical industry to slow the rate of metabolism. With the increase interest for deuterium labeled molecules, there is a renewed interest in selective methods for the installation of deuterium atoms into small organic molecules. However, current methods to incorporate deuterium atoms into organic molecules can lead to isotopic mixtures such as isotopologues and isotopomers. These isotopic species are indistinguishable due to their similar physical properties, leading to inseparable products by common purification techniques. Furthermore, common spectroscopic techniques to specifically characterize and measure the precise location of the deuterium atom and sample composition of isotopic species are deficient.

Catalytic transfer hydrodeuteration and deuteration reactions are emerging powerful techniques for site-selective and chemo-selective reactions to install deuterium atoms into small molecules. This method offers advantageous opportunities to improve selectivity and access precisely deuterated molecules as it offers tunable reaction conditions and tolerates a broad substrate scope. Additionally, this method uses inexpensive, readily available, easy to handle deuterium donors precluding the need of highly flammable deuterium gas. Herein, methods to precisely install deuterium atom(s) in a single step across alkene and alkyne functionalities under copper-catalyzed transfer deuteration and hydrodeuteration conditions are described. In this dissertation, reactivity, regioselectivity, and enantioselectivity is investigated.

Molecular rotational resonance (MRR) spectroscopy is also employed for characterization of possible isotopic species present in the reaction mixture from Cu-catalyzed transfer hydrodeuteration reactions. Through MRR spectroscopy, confirmation of regioselectivity was acquired and any possible isotopologues and isotopomers were quantified. Lastly, by using chiral tagging in MRR spectroscopy, we report the first general spectroscopic technique for enantiomeric excess and absolute configuration determination of chiral by virtue of deuterium substitution compounds synthesized by a novel metal-catalyzed enantioselective transfer hydrodeuteration method.

DEDICATION

This Dissertation is dedicated to my parents

Paul Thoua Vang

and

Ong Her

who are my heroes,
who came to America with nothing but the clothes on their backs to live the American
Dream.

You both are the definition of resilience and love.
Your dreams are my dreams.

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Zoua Pa Vang, B.A.

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Mom and dad, you both are my reason. Kuv paub tias neb ob leeg tau tos hnuv no tau ntev. Ua tsuag rau neb txoj kev hlub thiab kev txhawb nqa. Kuv yuav tsis nyob ntawm no yog tsis muaj neb ob leeg. Kuv thov txim uas kuv tau nyob deb ntawm neb tau ntev. Kuv vam tias neb ob leeg yuav nrog kuv zoo siab haib tais kuv tau kuv daim Ph.D. Thank you for raising me with so much love. I hope to one day give you both all the things you both deserve. Kuv hlub neb ob leeg. To my siblings: Tou, Samantha, Sheng, and Adam, you are all the definition of great achievers. You all inspire me to be diligent and dedicated to my work. I am thankful we get to share this lifetime together as siblings. To my friends, thank you for all the support and encouragement.

Lastly, I could not have undertaken this journey without my best friend and partner, Daniel Yang. I cannot thank you enough for your endless support and patience. Every time I felt defeated to every milestone I achieved; you were there to witness it all. You celebrated me at my highest and still loved me even at my lowest. You are my rock. Thank you.

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Introduction

Deuterium incorporation into small molecules is an emerging field in new reaction discovery. In 1932, Harold Urey discovered the deuterium atom now known as a naturally occurring, stable, non-radioactive isotope of hydrogen differing only by a single neutron.¹ Since then, deuterium has been used extensively in chemical research and medicine. Small molecules with three to four deuterium atoms can serve as valuable standards in high-resolution mass-spectroscopy in analytical and bioanalytical chemistry.²⁻⁴ Deuterated small molecules are used to elucidate reaction mechanisms and perform kinetic isotope effect measurements.^{5,6} Furthermore, deuteration is utilized in drug discovery to modify medicinal compounds.⁷⁻¹⁰

Deuterated compounds are similar to their parent compounds due to their comparable shapes and sizes, making them essentially indistinguishable. Even so, deuterium can be used to alter and improve pharmacokinetic properties, toxicity, and metabolic stability of drug candidates.¹¹ By incorporating deuterium at metabolically labile sites, properties of the molecules such as the absorption, distribution, metabolism, and excretion (ADME) can be altered.⁷ However, it is also important to have high deuterium incorporation at the metabolically active site as low deuterium incorporation can result in shorter half-life values.¹² The success of altering properties in drug candidates was demonstrated when Deutetrabenazine became the first U.S Food and Drug Administration (FDA) approved deuterated drug in 2017 (Figure 1).¹³ With the hydrogen atoms exchanged to deuterium, Deutetrabenazine can resist metabolic degradation and remain active longer

in the body than the parent compound, leading to less frequent dosing while maintaining its potency.

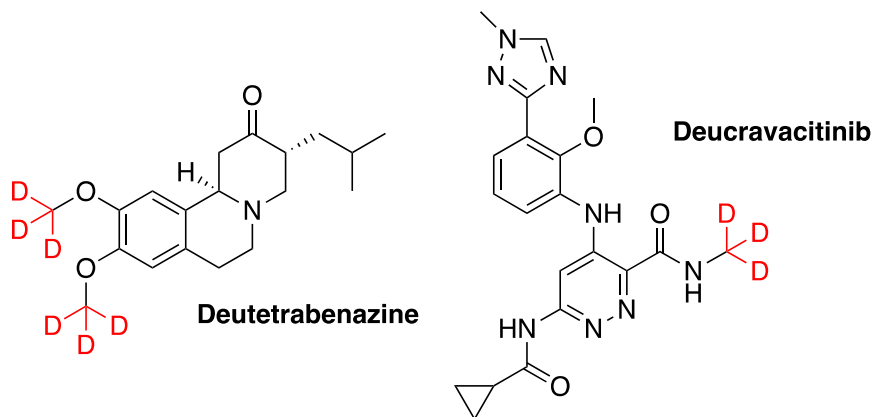


Figure 1. Deuterated drug candidates approved by the U.S Food and Drug Administration

Recently, in 2021, Deucravacitinib was approved by the U.S Food and Drug Administration for the treatment of adults with moderate to severe plaque psoriasis.¹⁴ With the success of Deutetrabenazine and Deucravacitinib, there is a rising interest in the development of deuterated compounds. For example, deuterated drug candidates pending phase 3 clinical trials include Donafenib, di-deuterated linoleic acid ethyl ester (RT001), a vitamin A analog (ALK-001), and an enzalutamide analog (HC-1119) (Figure 2).¹⁵

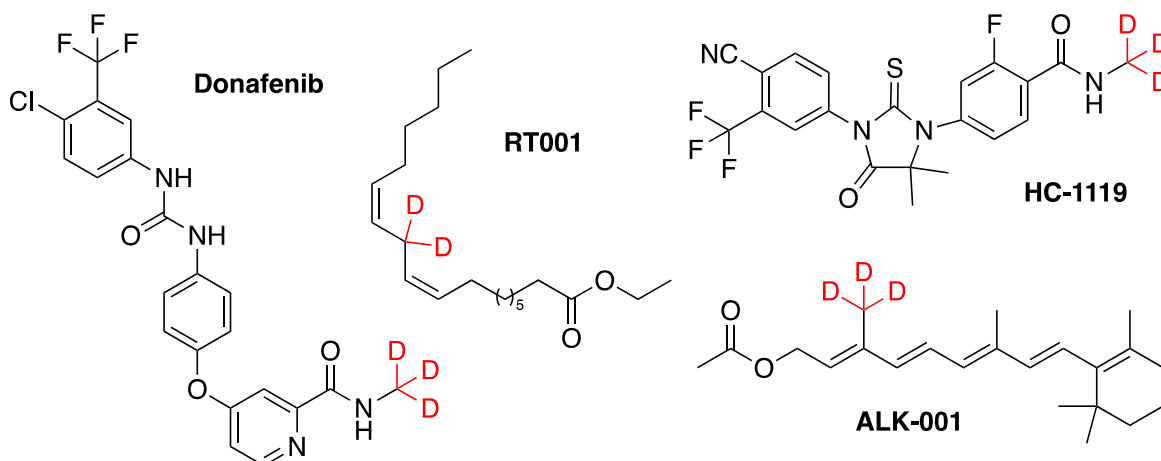


Figure 2. Deuterated drug candidates in phase 3 clinical trials

Strategic incorporation of deuterium atoms into medicinal compounds to alter its properties can be appreciated due to the deuterium kinetic isotope effect.^{7,8} A deuterium kinetic isotope effect is when a change in the reaction rate of a chemical reaction occurs due to a replacement of the hydrogen atom by its isotope, deuterium. C—D bonds are shorter and more stable to oxidative processes due to their higher mass. A molecule with a C—D bond will have a lower vibrational frequency compared to its lighter counterpart, thus, a lower ground state energy. To reach the transition state for bond cleavage, a greater energy is needed, leading to a slower reaction rate.

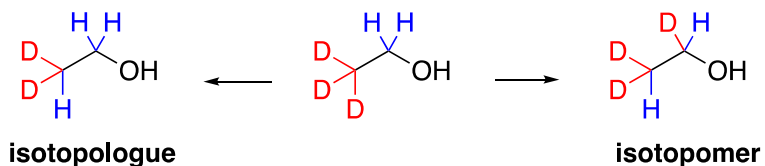


Figure 3. Isotopologues versus Isotopomers

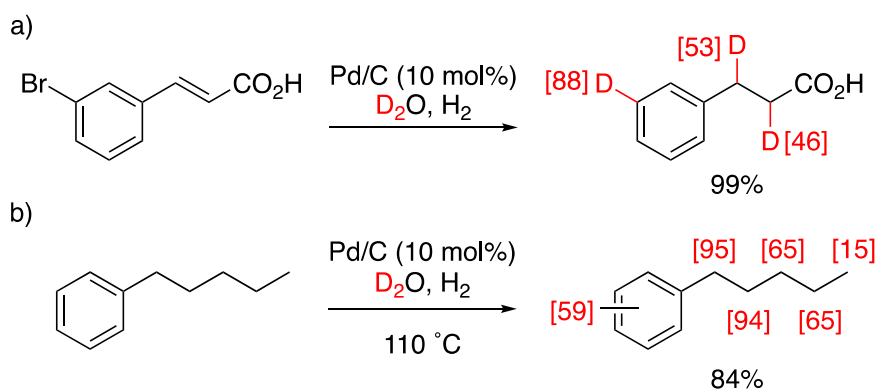
While the interest in deuterium incorporation into small molecules has increased and is being utilized more often for its application, isotopic mixtures such as isotopologues and isotopomers are possible products in deuteration reactions (Figure 3). Isotopologues

and isotopomers are indistinguishable due to their similarities in structure. Due to similar physical properties of deuterium relative to hydrogen, isotopic mixtures are inseparable using common purification techniques. Furthermore, common spectroscopic techniques to specifically characterize and measure the precise location of deuterium atoms and sample composition of isotopic species are deficient. The presence of these isotopic species may lead to misleading or compromised data in ADME studies, kinetic studies, or drug development if unknown quantities of underdeuterated or misdeuterated species exist in a mixture with the desired deuterated target molecule.¹² Therefore, it is important to develop highly selective deuteration reaction methods to access targeted high value deuterated molecules.

Nuclear magnetic resonance (NMR) spectroscopy is a common characterization tool to determine deuterium incorporation in deuterated compounds. However, NMR cannot differentiate between the possible isotopic species that can be present and it cannot determine the isotopomer ratio. Molecular rotational resonance (MRR) spectroscopy is an analytical technique that uses quantized rotational kinetic energies of a molecule in the gas-phase to provide quantitative characterization data.¹⁶ MRR has the ability to observe different isotopic species without spectral overlap due to its high spectral resolution. Thus, it can be used as a characterization technique to determine and measure total deuterium content, site-specific deuterium content, residual hydrogen impurities in deuterated products, and accurately characterize isotopologues and isotopomers.

One of the most fundamental transformations in organic synthesis is hydrogenation. There are a few strategies to employ hydrogenation: direct hydrogenation and transfer hydrogenation. However, due to the prevalence of deuterated organic compounds, catalytic

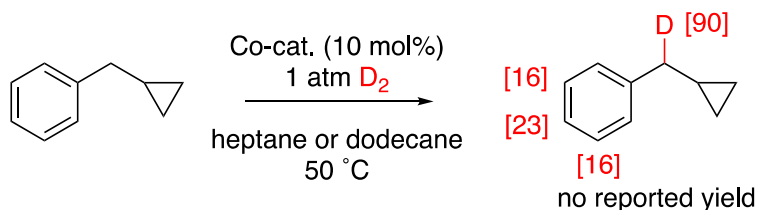
deuteration, metal-catalyzed hydrogen isotope exchange (HIE), and transfer deuteration/hydrodeuteration are explored. Catalytic deuteration typically uses a metal catalyst and requires the use of flammable deuterium gas, which is flagged as a potential hazard.¹⁷ Additionally, this method can be difficult in controlling chemo-selectivity. In Scheme 1a, Sajiki *et al.* were able to reduce the alkene functionality to install deuterium but deuterodehalogenation of the bromine was also observed.¹⁸



Scheme 1. Deuteration using Pd/C-Catalyzed H/D exchange by the Sajiki group, 2004 & 2007.

Besides catalytic deuteration, hydrogen isotope exchange is another method for selective deuterium incorporation (Scheme 2).^{2,19} While HIE provides a powerful strategy to incorporate deuterium atoms into small molecules, a major drawback is controlling site-selectivity and the quantity of deuterium atoms. This method permits possible over-deuteration due to multiple C—H bonds within a molecule. Possible under deuteration of the desired site can also be observed. In Scheme 1b, the Sajiki group performed an H/D exchange on an alkyl benzene substrate resulting in an unselective deuterium incorporation of the final product.²⁰ In Scheme 2, the Chirik group used a homogeneous metal-catalyzed

HIE method to exchange the hydrogen at the benzylic position with a deuterium atom but also observed deuterium incorporation on the arene as well as arene reduction.²¹



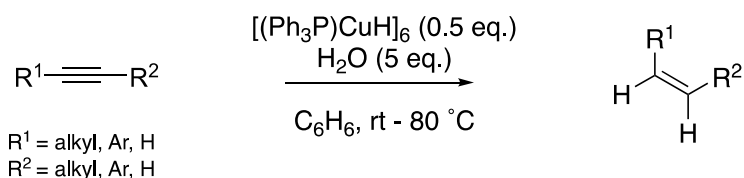
Scheme 2. Metal-catalyzed HIE using a Co-catalyzed method by the Chirik group, 2017.

Transfer hydrogenation is defined as the addition of hydrogen to a molecule from a non-hydrogen gas source.¹⁷ This method represents an alternative approach to hydrogenation and HIE as transfer hydrogenation uses readily available, inexpensive, and easy to handle hydrogen donors. This closely mirrors catalytic transfer deuteration and hydrodeuteration reactions as the hydrogen donors switch to deuterium surrogates to obtain the deuterated product allowing for tunable reaction conditions. This approach permits advantageous opportunities to improve selectivity and access highly deuterated molecules.

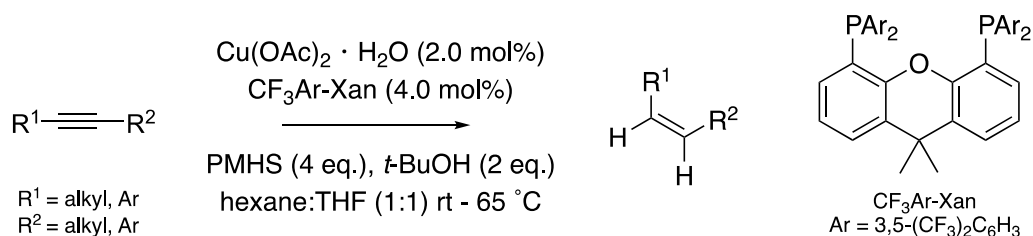
Catalytic transfer hydrogenation, deuteration, and hydrodeuteration reactions mainly use abundant and inexpensive transition metals and can be applied to a variety of reducible functional groups such as: carbonyls, alkenes, alkynes, nitriles, nitro groups, and imines. However, due to the commonality of unsaturated C—C bonds in organic molecules, we are specifically interested in alkene and alkyne functionalities for the selective installation of deuterium.

The catalytic transfer hydrogenation, deuteration, and hydrodeuteration described in this dissertation uses copper hydride (Cu—H) chemistry. Cu—H chemistry is known to undergo semi-reductions of alkynes to alkenes. Early work of the semi-reduction of alkynes

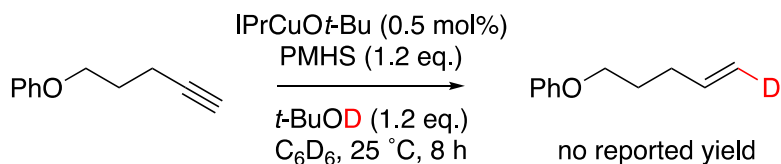
to alkenes was in 1990 from the Stryker group.²² Stryker's group developed a method using a hexameric copper hydride complex to generate *cis*-alkene products from disubstituted alkynes (Scheme 3). In 2012, the Tsuji group developed a catalytic Cu—H method for the formation of *cis*-alkene products by using a bidentate phosphine Xantphos derivative or *N*-heterocyclic carbene (NHC) ligand in the presence of silane and *tert*-butanol (Scheme 4).²³ Similarly, in 2013, the Lalic group exploited a copper-catalyzed reaction using silane, and *tert*-butanol to reduce alkynes to yield the *cis*-alkene product.²⁴ In a deuterium labelling experiment, deuterium was installed regioselectively at the terminal position of the alkene in a single isomer (Scheme 5). Both the Tsuji and Lalic methods were able to expand the substrate scope from internal alkynes to terminal alkynes.



Scheme 3. Semi-reduction of alkynes to alkenes using Stryker's reagent, 1990.

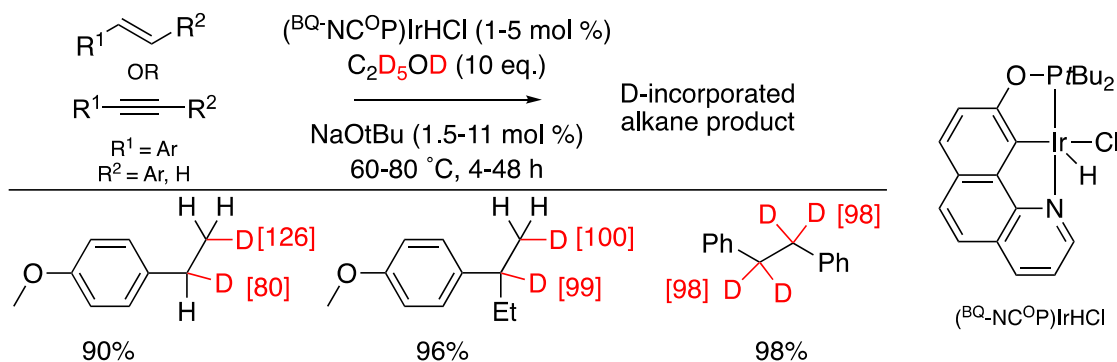


Scheme 4. Catalytic semi-reduction under copper-catalyzed conditions by the Tsuji group, 2012.



Scheme 5. Deuterium labeling under catalytic semi-reduction copper-catalyzed conditions by the Lalic group, 2013.

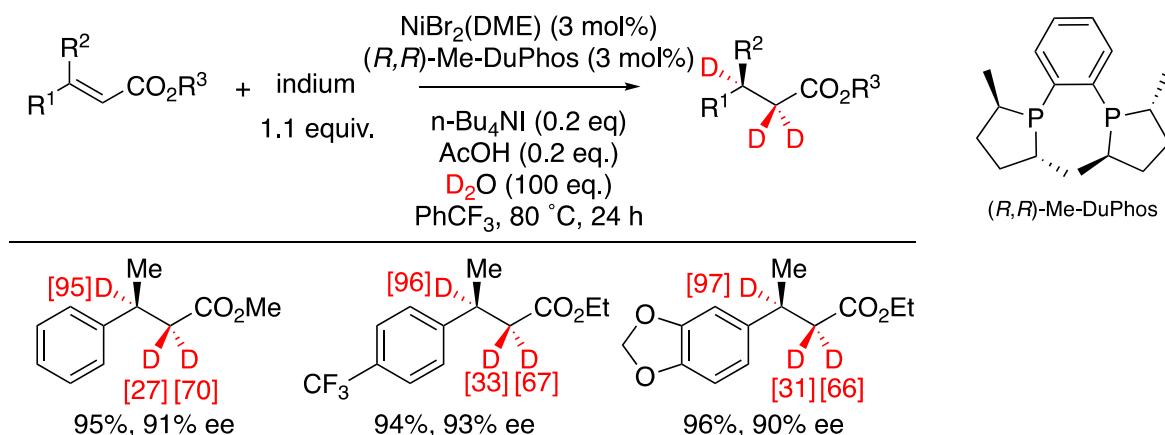
Aside from copper hydride chemistry, there are other transition metal complexes that can undergo transfer hydrogenation, deuteration, and hydrodeuteration transformations. In 2018, the Huang group developed a general approach to transfer deuteration using an *N*-confused porphyrin (NCP) pincer iridium complex and C_2D_5OD as a deuterium source (Scheme 6).²⁵ Dideuterated alkanes were accessible starting with alkene-containing substrates. The authors were also able to form the d_4 -alkane from diphenylacetylene in a high yield. Transfer hydrogenated products could be obtained using hydrogenated reagents. Chiral products can also be obtained using a chiral ligand with 1,1-diarylethene substrates.²⁶



Scheme 6. Transfer deuteration of aryl alkenes/alkyne using an iridium catalyst by the Huang group, 2018.

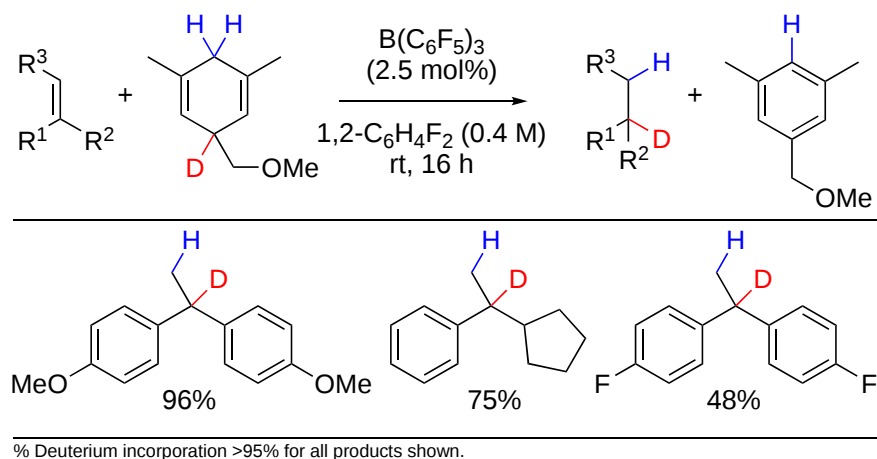
The Zhou group has reported transfer deuteration and hydrodeuteration reactions.^{27,28} Recently, in 2020, the Zhou group installed deuterium atoms into both the α - and β - positions of unsaturated esters utilizing a nickel/DuPhos catalyst. Indium powder was used as an electron donor and a catalytic amount of acetic acid in D_2O was used as the

deuterium source (Scheme 7).²⁹ Both electron-poor and electron-rich substrates afforded high yields with excellent enantioselectivity.



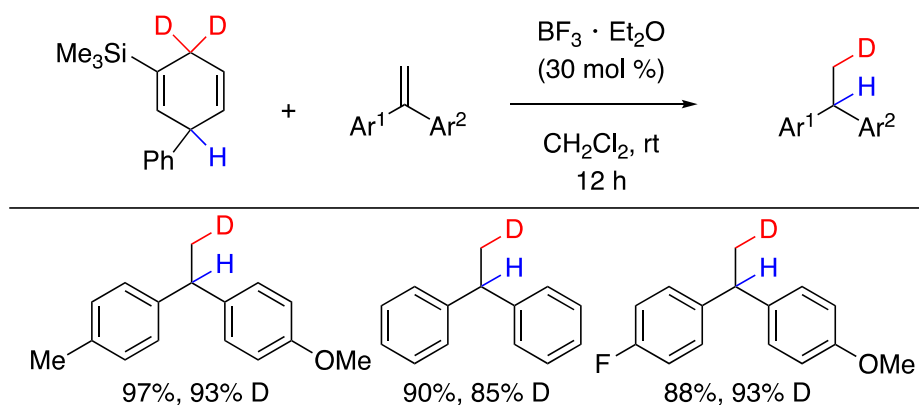
Scheme 7. Transfer deuteration by the Zhou group using a nickel catalyst, 2020.

Catalytic transfer hydrodeuteration reactions are challenging to perform as it requires the regioselective addition of a hydrogen atom and deuterium atom across the functionality. However, in 2018, the Oestreich group reported a highly regioselective catalytic transfer hydrodeuteration of aryl alkenes using $\text{B}(\text{C}_6\text{F}_5)_3$ and monodeuterated 1,4-cyclohexadienes as a hydrogen deuteride surrogate (Scheme 8).³⁰ The substrate scope contained highly reactive electron-rich 1,1-diaryl alkenes in good to excellent yields, but electron-poor alkenes were not as effective. In general, at least one substituent must be an aryl group for the reaction to proceed. Monosubstituted alkenes were shown not to be effective substrates for the transformation.

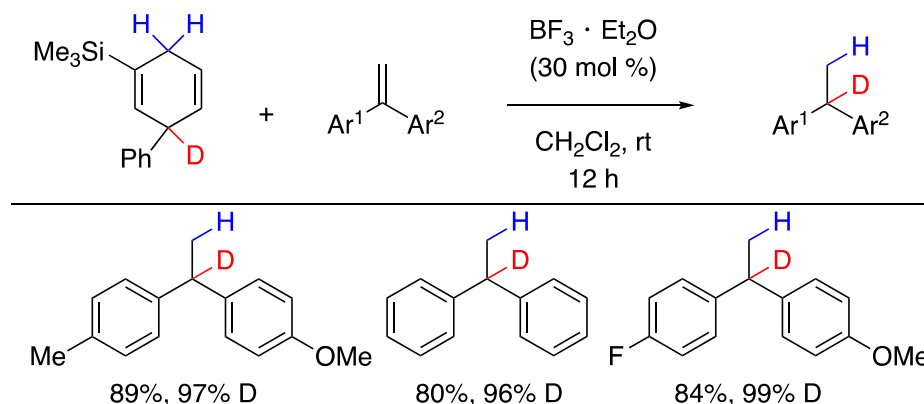


Scheme 8. Transfer hydrodeuteration of 1,1-diaryllkenes using a boron catalyst by the Oestreich group, 2018.

Inspired by the Oestreich group, Hilt and coworkers developed a switchable transfer hydrodeuteration of 1,1-diaryllkenes using a similar protocol and mechanism.^{31,32} Due to their modular synthesis of the hydrogen and deuterium surrogate, regioselective deuterohydrogenation (Scheme 9) or hydrodeuteration (Scheme 10) of electron-rich 1,1-diaryllkenes was achievable in good to excellent yield and deuterium incorporation.

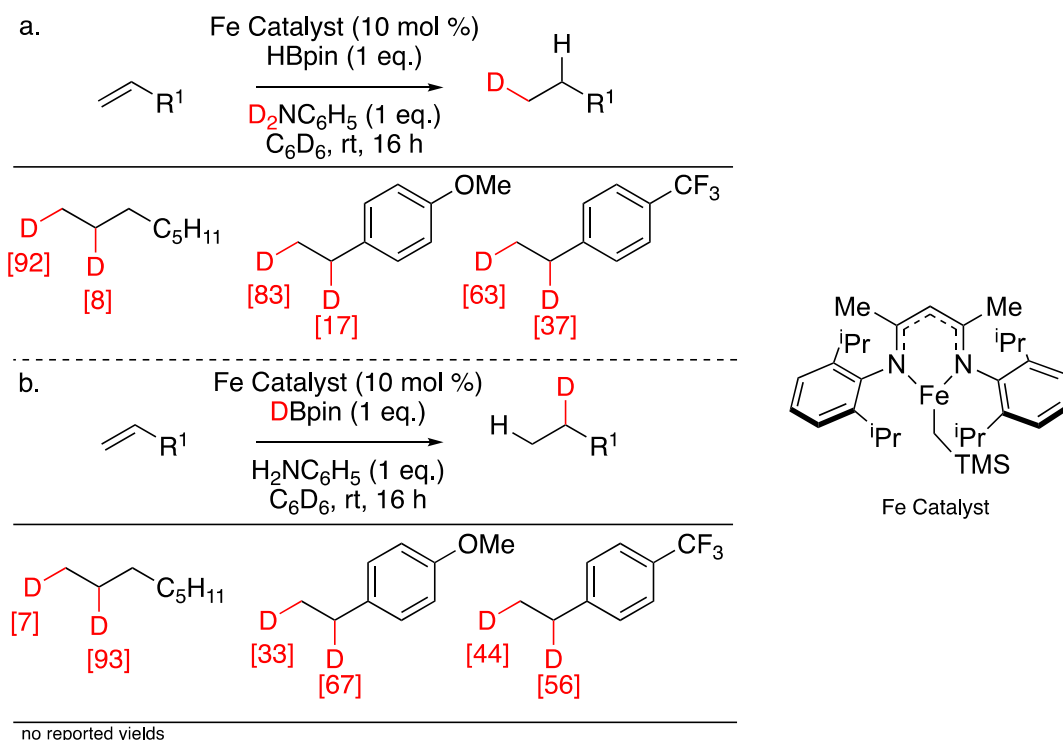


Scheme 9. Transfer deuterohydrogenation of 1,1-diaryllkenes using a boron catalyst by the Hilt group, 2020.



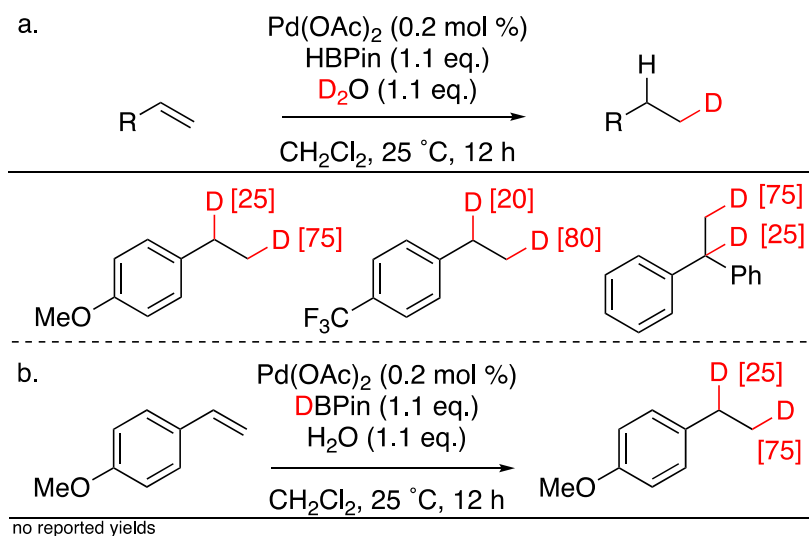
Scheme 10. Transfer hydrodeuteration of 1,1-diaryllalkenes using a boron catalyst by the Hilt group, 2020.

In 2019, the Webster group developed a method using an iron catalyst to promote selective alkene transfer hydrodeuteration.³³ Notably, the reagents in the reaction conditions dictate the reaction selectivity (Scheme 11a and 11b). When $\text{D}_2\text{NC}_6\text{H}_5$ was employed, electron-poor substrates underwent transfer hydrodeuteration but with moderate levels of regioselectivity. However, when DBpin was used, transfer hydrodeuteration was almost unselective with electron-poor alkene substrates. Higher regioselectivity was obtained with electron-rich and neutral alkene substrates under both reaction conditions. Additionally, the Webster group continued to expand the substrate scope to by developing a general protocol for selectively installing deuterium atom across unactivated alkenes.³⁴ However, sometimes products arising from alkene isomerization were observed.³⁵



Scheme 11. Transfer hydrodeuteration of aryl alkenes using a Fe-catalyst by the Webster group, 2019.

Recently, the Wu group reported a method utilizing $Pd(OAc)_2$ for the transfer hydrodeuteration of aryl alkenes.³⁶ HBpin was used as the hydrogen source and D_2O as the deuterium source (Scheme 12a). Under these reaction conditions, electron-poor substituents on the aryl ring led to higher levels of deuterium incorporation at the terminal site leading to selective formation of the anti-Markovnikov product. When D_2O was replaced with H_2O and HBpin with DBpin, the selectivity did not change (Scheme 12b).



Scheme 12. Transfer hydrodeuteration of aryl alkenes using a palladium catalyst by the Wu group, 2020.

Deuterium installation into small organic molecules is the smallest change possible to make on a molecule and is advantageous in many applications, such as when applied in metabolic soft spots of small drug molecules. Though the synthesis of deuterated molecules seems trivial and straightforward, it is challenging as there are many factors to consider: regioselectivity, chemo-selectivity, high deuterium incorporation, and substrate scope versatility. These remain challenging to achieve in the field of deuterated molecules. Additionally, previous literature of copper hydride chemistry reduction of alkynes only demonstrated reactivity to the alkyne product with no detection of the alkyl product. Lastly, a longstanding challenge is the incorporation of deuterium at the desired position without the formation of isotopomer and isotopologues. Furthermore, there is a lack of characterization present to quantitatively analyze possible isotopic species in the reaction mixture. Therefore, this dissertation focuses on new techniques to develop a highly reactive and regioselective catalytic transfer deuteration and hydrodeuteration with an expanded substrate scope to form only the deuterated alkyl product from alkyne and alkene

functionalities. After obtaining reactivity and regioselectivity, enantioselectivity is investigated where it's possible to synthesize molecules that are chiral due to deuterium substitution.

In chapter 1, a general method for copper-catalyzed transfer hydrogenation and deuteration of aryl alkynes was developed. Chapter 2 expanded on the regioselective installation of 2 deuterium atoms at the benzylic position by the employment of one deuterium and one hydrogen source. In chapter 3 and chapter 4, transfer hydrodeuteration methods for the installation of one deuterium atom at the benzylic position were explored. Chapter 3 featured molecular rotational resonance (MRR) spectroscopy to confirm regioselectivity and quantitatively characterized the deuterated product, whereas chapter 4 expanded on the substrate scope to cyclic compounds. In chapter 5, a chiral by virtue of deuterium substitution compound was synthesized in one step using the copper-catalyzed transfer hydrodeuteration method leading to a high enantiomeric excess with confirmed absolute configuration measured by MRR spectroscopy. Chapter 6 aimed to improved diminished EE in *N*-heterocycles using an IsoMRR instrument to undergo high throughput screening of several reactions conditions to achieve the highest enantiomeric excess. Chapter 7 explored the challenge of installing a deuterium atom across unactivated terminal alkenes.

CHAPTER 1

Copper-Catalyzed Formal Transfer Hydrogenation/Deuteration of Aryl Alkynes³⁷

Introduction

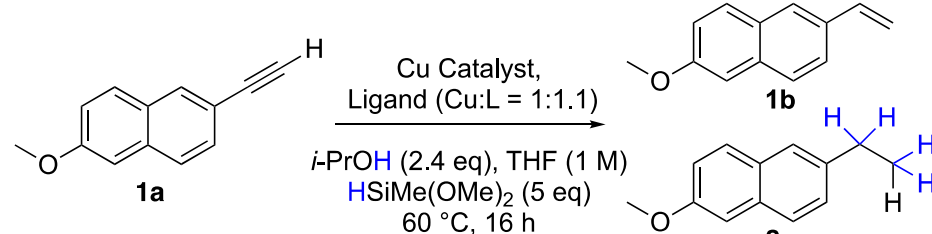
A fundamental reaction in organic chemistry is the reduction of an alkyne to an alkane. This reaction is commonly accomplished by using a heterogeneous catalyst and hydrogen gas. However, to avoid the use of flammable hydrogen gas, transfer hydrogenation is an alternative approach to reduce π -bond functionalities. Therefore, we were interested in developing new tunable alkyne reduction methods that are under mild conditions. Cu—H chemistry is a well-established field capable of reducing alkynes to alkenes.^{22-24, 38-42} However, there has yet to be a copper-catalyzed method on the reduction of alkynes to hydrogenated or deuterated alkanes. Therefore, we hypothesized that a highly reactive Cu—H species in the presence of a silane and alcohol source would promote the reduction of an alkyne to an alkane. Furthermore, these reagents could readily be manipulated for use in the corresponding transfer deuteration reaction. We first screened for transfer hydrogenation reaction conditions for the transformation of aryl alkynes to aryl alkanes and later obtained transfer deuteration products through optimized reaction conditions by changing the hydrogen donors to deuterated alcohols.

Results and Discussion

For the reaction optimization substrate, commercially available 2-ethynyl-6-methoxynaphthalene **1a** was used as the aryl acetylene. Commercial copper sources and phosphine-based ligands known to promote Cu—H formation when combined in situ with a silane source were screened. We found that triphenylphosphine and achiral bidentate

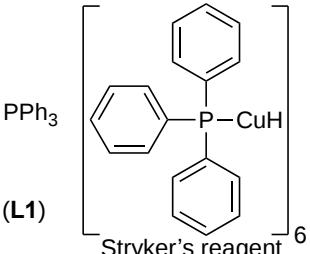
phosphine ligands were ineffective to form the desired transfer hydrogenated alkane product (Table 1, entries 1-8). Due to no desired product formation from achiral ligands, we opted to screen BINAP and SEGPHOS type ligands. Even though these are chiral bidentate phosphine ligands, precedent literature report that these types of ligands support highly reactive Cu—H species.⁴²⁻⁴⁴ We found that (*R*)-DTBM-SEGPHOS was the most effective ligand for a copper-catalyzed transfer hydrogenation transformation. However, (*S*)-DTBM-SEGPHOS and (*R*)-DTBM-SEGPHOS can be used interchangeably in this reaction. When we reduced the catalyst loading to 1 mol %, it led to a slight reduction in yield (Table 1, entry 9), but when catalyst loading increased to 2 mol % a high product yield was obtained and deemed optimal (Table 1, entry 10). In the absence of Cu(OAc)₂ or a phosphine ligand no alkane product was formed (Table 1, entries 11-12). Lastly, other silane reagents such as poly(methylhydrosiloxane) (PMHS)⁴⁵ and diethoxy(methyl)silane (DEMS) were effective for the transfer hydrogenation reaction (Table 1, entries 13-14). We chose to use dimethoxy(methyl)silane (DMMS) as it can be readily converted to Si-D for transfer deuteration and for an easier purification.

Table 1. Reaction optimization of transfer hydrogenation of aryl alkynes^a

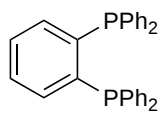


Entry	Cu Catalyst (mol%) ^b	Ligand	Yield of 1b (%)	Yield of 2 (%)	RSM 1a (%)
1	Cu(OAc) ₂ (5)	L1	11	trace ^c	48
2	Stryker's Reagent	N/A	53	trace ^c	6
3	Cu(OAc) ₂ (5)	L2	5	trace ^c	82
4	Cu(OAc) ₂ (5)	L3	8	trace ^c	75
5	Cu(OAc) ₂ (5)	L4	11	trace ^c	72
6	Cu(OAc) ₂ (5)	L5	12	trace ^c	49
7	Cu(OAc) ₂ (5)	L6	30	4 ^d	45

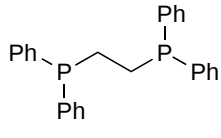
8	Cu(OAc) ₂ (5)	L7	0	98 ^d	0
9	Cu(OAc) ₂ (1)	L7	3.5	87 ^d	0
10	Cu(OAc) ₂ (2)	L7	0	91 ^d	0
11	N/A	N/A	4	0 ^c	86
12	Cu(OAc) ₂ (2)	N/A	3	0 ^c	80
13 ^e	Cu(OAc) ₂ (2)	L7	0	95 ^d	0
14 ^f	Cu(OAc) ₂ (2)	L7	0	93 ^d	0



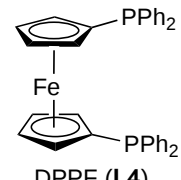
(L1)
Stryker's reagent



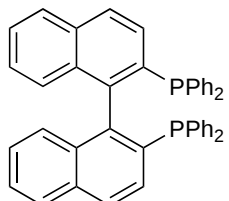
DPPBz (L2)



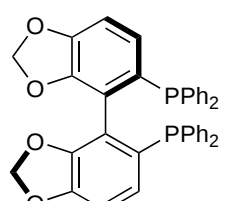
DPPE (L3)



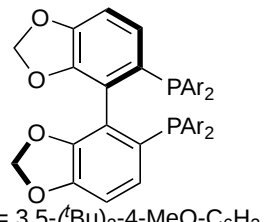
DPPF (L4)



rac-BINAP (L5)



(R)-SEGPHOS (L6)



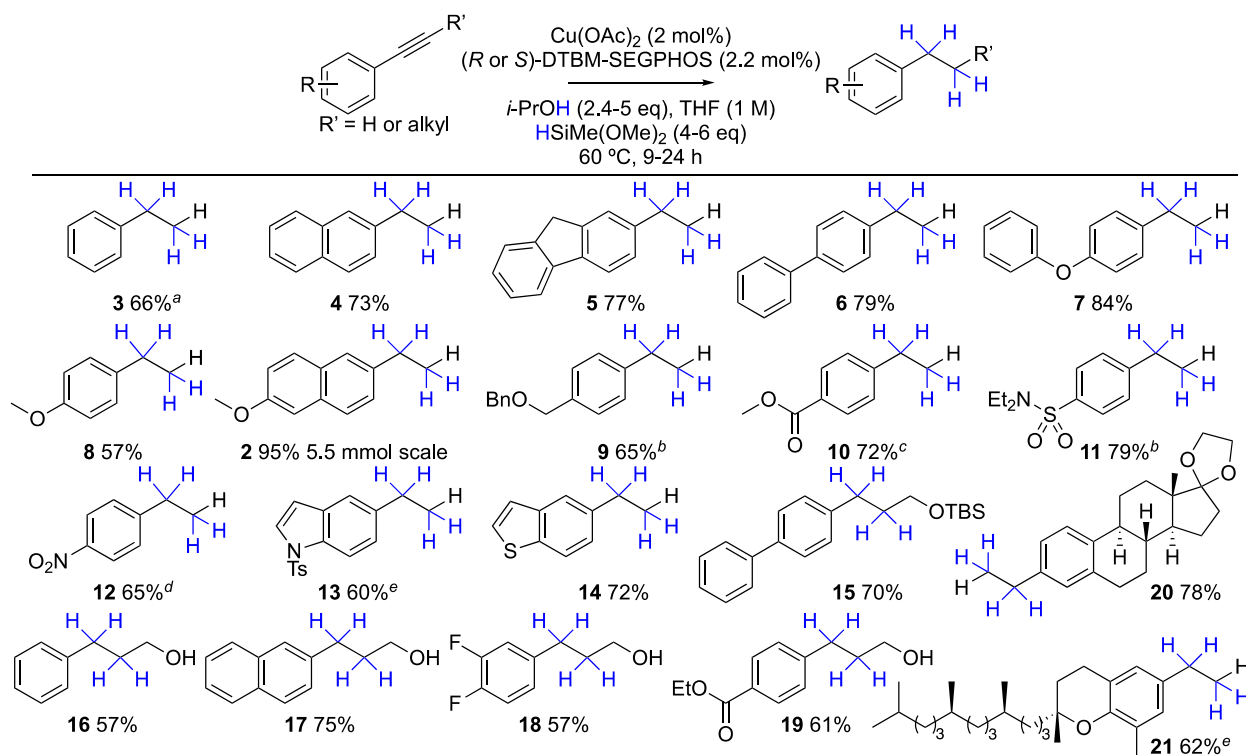
(R)-DTBM-SEGPHOS (L7)

Ar = 3,5-(^tBu)₂-4-MeO-C₆H₂

^aReactions were conducted using 0.2 mmol of substrate. ^bCu(OAc)₂ was used in the reactions as a 0.2 M solution in THF. ^cYield was determined by ¹H NMR analysis of the crude reaction mixture, using 1,3,5-trimethylbenzene as an internal standard. ^dYield determined after purification by flash column chromatography. ^ePoly(methylhydrosiloxane) (5 eq) was used instead of dimethoxy(methyl)silane. ^fDiethoxy(methyl)silane (5 eq) was used instead of dimethoxy(methyl)silane.

With the discovered optimized transfer hydrogenation reaction conditions, we evaluated the substrate scope. We have 21 examples with a variety of substrates such as hydrocarbons (**3-6**, 66%-79% yield), electron-donating phenoxy and methoxy groups (**7-9**, 57%-95% yield), and reducible functionality methyl ester underwent chemoselective transfer hydrogenation (**10**, 72% yield). During our investigation, we noticed that increasing equivalents of alcohol up to 5 equivalents resulted in full conversion of less-reactive substrates. Nitrogen-containing compounds were also examined under transfer hydrogenation protocol. An electron-withdrawing *para*-benzenesulfonamide and nitro group underwent transfer hydrogenation efficiently (**11-12**, 65%-79% yield). Heterocycle-containing aryl acetylenes, such as a tosyl-protected indole and a benzothiophene were reduced to the alkane product in good yields (**13-14**, 60%-72% yields). Internal alkynes

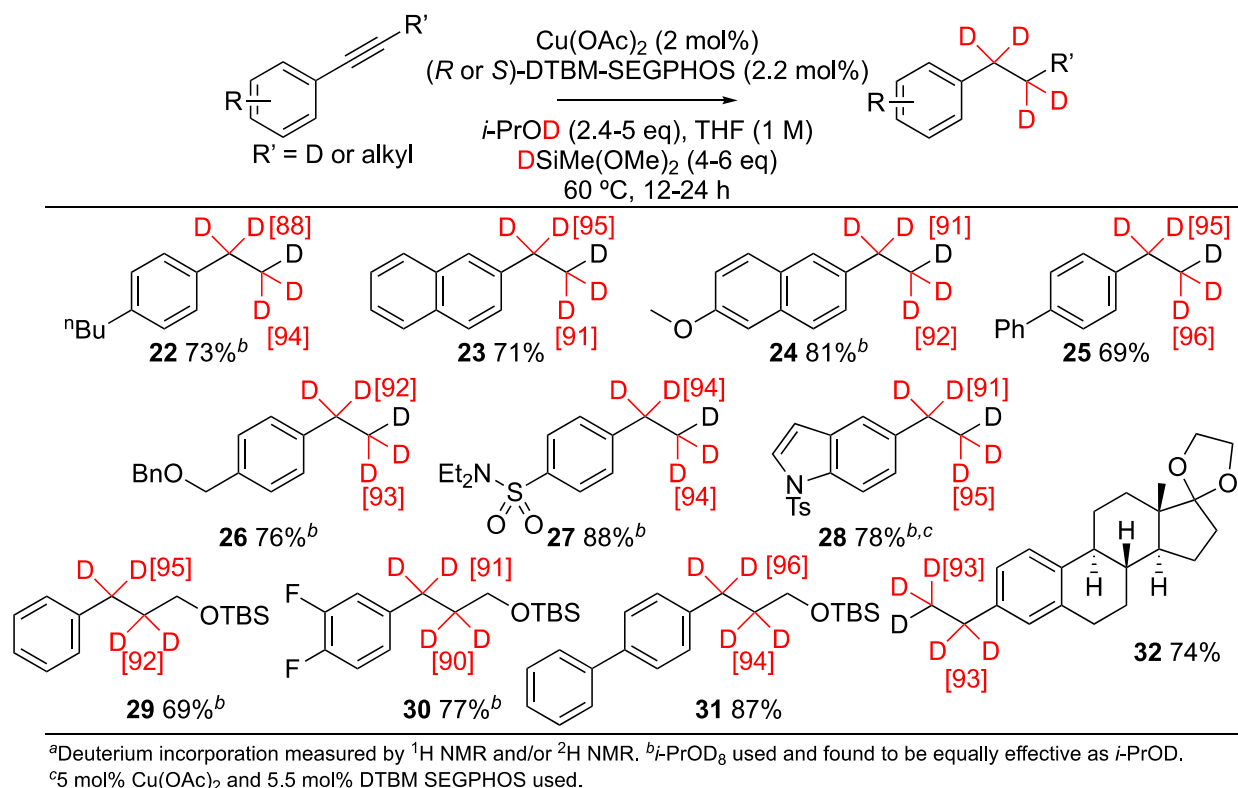
were also examined along with alkyne-containing complex natural product analogues. Under the transfer hydrogenation substrate scope, challenging substrates such as electron-neutral internal alkynes (**15-17**, 57-75% yield) and electron-withdrawing internal alkynes **18** and **19** (57-61% yield) were reduced efficiently. There were no indications of an ester reduction in product **19**. These were isolated with only moderate to good yields due to a possible silane protection of the alcohol in the reaction mixture. We were also able to reduce alkyne-containing complex natural product analogues to their corresponding alkane product. Hydrogenated estrone analogue **20** and δ -tocopherol analogue **21** were isolated in good yields with no starting material present (62%-78% yield).



^aYield determined by ^1H NMR analysis using 1,3,5-trimethylbenzene as an internal standard. ^b2.4-2.6 eq of EtOH used. ^cReaction performed at 40 °C. ^dReaction performed at 23 °C. ^e5 mol% Cu(OAc)_2 and 5.5 mol% DTBM-SEGPHOS used.

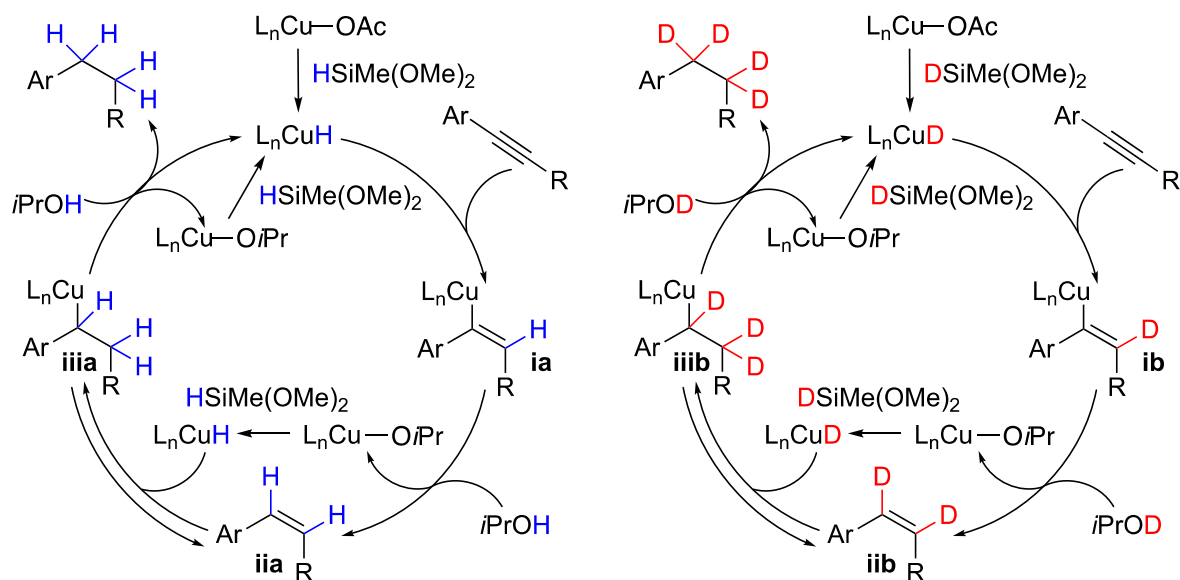
Scheme 1. Cu-catalyzed alkyne transfer hydrogenation substrate scope

By switching the hydrogen alcohol source to alcohol—OD and Si—H to Si—D,⁴⁶ we were able to install up to 4 deuterium atoms into one molecule. Deuterated small molecules can be used as an internal standard for quantitative bioanalytical liquid chromatography/mass spectrometry. However, these deuterated small molecules must contain at least three to four deuterium atoms to allow for sufficient separation of peak in the mass spectrum.³ In the terminal alkyne substrate scope, we exchanged the acetylenic hydrogen atom for a deuterium atom before subjecting the substrate to transfer deuteration. We were able to subject *para*-substituted aryl acetylene and polyaromatic compounds 2-ethynylnaphthalene and 2-ethynyl-6-methoxynaphthalene to transfer deuteration conditions with good yields (**22-24**, 71%-81% yield). It is noteworthy that electron-withdrawing and electron-donating *para*-substituted substrates allow for efficient transfer deuteration transformations. A biphenyl-substituted alkyne was reduced to the deuterated product in high yield (**25**, 69% yield). A benzyl group was found to be stable under transfer deuteration conditions as no alcohol product was detected in the crude reaction mixture (**26**, 76% yield). Nitrogen-containing substrates such as aryl sulfonamide and indole-substituted alkyne afforded the deuterated product (**27-28**, 78%-88%yield). Internal alkynes were able to be reduce to the alkane product yielding 4 deuterium atoms (**29-31**, 69%-87% yield). Internal alkynes containing alcohol groups had to be protected to refrain from any possible deuterium and hydrogen exchange leading to lower deuterium incorporation. However, the deuterated alkane can be deprotected after being subjected to transfer deuteration conditions. Lastly, a deuterated estrone analogue underwent transfer deuteration efficiently and was isolated in a good yield (**32**, 74%yield).



Scheme 2. Cu-catalyzed alkyne transfer deuteration substrate scope

We proposed that under transfer hydrogenation conditions, the Cu—H bond will form in the presence of dimethoxy(methyl)silane followed by insertion of the Cu—H bond across the alkyne. This would lead to alkenyl Cu species **ia**. Protodecupration of **ia** with isopropanol will generate alkene **ii****a**. Regeneration of the Cu—H and addition across alkene **ii****a** will form alkyl Cu species **iii****a** followed by protodecupration of **iii****a** to provide the desired alkane. By replacing Si—H with Si—D and alcohol with alcohol—OD the reaction can operate under transfer deuteration conditions (Scheme 3).



Scheme 3. Proposed mechanism under transfer hydrogenation/deuteration reaction conditions

In the proposed mechanism, we hypothesized the intermediacy of alkene **ia/b** to be *cis*. To test our hypothesis, we evaluated the reduction of **33** over several time periods (Table 2). From this, we observed the appearance of alkene **Z-33a** in the reaction mixture after 15 minutes, which is consistent with the postulated mechanism. After 30 minutes, the appearance of alkene **E-33b** was observed, and this suggested that Cu—H insertion in alkene **ia/b** to form alkyl copper intermediate **iiia/b** is reversible. The reaction reached completion after 9 hours.

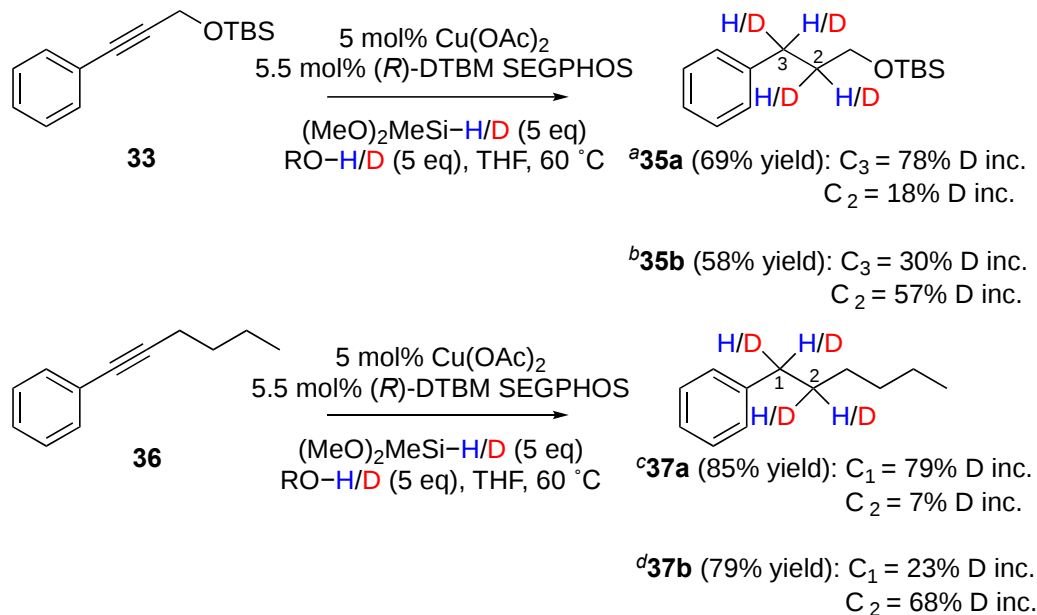
Table 2. Reaction analysis

Entry	Reaction Time (min)	Z-33a^a (%)	E-33b^a (%)	34^a (%)
1	15	74	0	6
2	30	48	2	25
3	45	40	5	36
4	90	17	7	54
5	180	7	5	61
6	9h	0	0	79

^aYields of each product were determined by ¹H NMR of the combined products after purification.

We also were interested about the regioselectivity if transfer hydrodeuteration reaction conditions were applied to aryl alkynes (Scheme 4). Therefore, we subjected alkyne **33** and to transfer hydrodeuteration reaction condition using ethanol—OD and regular silane. The reaction was only moderately regioselective with deuterated alkane **35a**, 78% D incorporation at C₃ and 18% D incorporation at C₂. When the alcohol was switched to ethanol and *d*-dimethoxy(methyl)silane to flip the regioselectivity, there was a less selective reaction of 30% D incorporation at C₃ and 57% D incorporation at C₂ (**35b**). The lower deuterium incorporation could be attributed to the heteroatom binding and directing the Cu—H insertion leading to a lower regioselective reaction. However, similar transfer hydrodeuteration experiments were performed with hydrocarbon alkyne **36**. The regioselectivity was slightly higher with deuterated alkane **37a** with 79% D incorporation at C₁ and 7% D incorporation at C₂, whereas deuterated alkane **37b** had 23% D incorporation at C₁ and 68% D incorporation at C₂. Though the regioselectivity was slightly

higher, we believe that the first Cu—H insertion into the alkyne substrate is unselective and the highly selective step would be from the alkene intermediate to the alkyl copper species reported by previous work.^{42,45,47,48} We explore this in chapter 2 and 3. However, these initial results are promising for a transfer hydrodeuteration of aryl alkynes.



All reactions performed with Cu(OAc)₂ (5 mol%), (R)-DTBM-SEGPBOS (5.5 mol%), THF (0.2 M, based on alkyne substrate), 60 °C. All yields are isolated and %D inc. was determined using ¹H NMR and/or ²H NMR. ^a5 eq (MeO)₂MeSi-H, 5 eq EtOD, 24 h. ^b5 eq (MeO)₂MeSi-D, 5 eq EtOH, 24 h. Alkane **9b** was isolated as a mixture with alkene (23% yield) present due to incomplete conversion. See SI for details. ^c5 eq (MeO)₂MeSi-H, 5 eq *i*-PrOD₈, 21 h. ^d5 eq (MeO)₂MeSi-D, 5 eq *i*-PrOD, 21 h.

Scheme 4. Regioselective transfer hydrodeuteration preliminary results

Conclusion

In summary, we developed a mild and selective reductive transfer hydrogenation and transfer deuteration method using commercially available alcohol and silane sources. These sources can be used interchangeably by their deuterated analogs to reduce aryl alkynes to their corresponding alkanes and deuterated alkanes. This method has excellent functional group and heterocycle compatibility and can incorporate up to 4 deuterium

atoms selectively in one step. As a result, we anticipate that this method could be useful to synthesize highly deuterated analogs of drug molecules for ADME studies.

CHAPTER 2

Precision Deuteration Using Cu-Catalyzed Transfer Hydrodeuteration to Access Small Molecules Deuterated at the Benzylic Position⁴⁹

Introduction

A renewed interest in selectively deuterated small molecules has sparked with the recent FDA approval and success of deuterated drug candidates Deutetrabenzaine and Deucravacitinib.^{13,14} These deuterated bioisosteres are designed to increase the half-life of drugs or divert a specific metabolic pathway.¹³ We are specifically interested in the benzylic position as these benzylic C(sp³)—H bonds in small drug molecules frequently undergo metabolic oxidation. For example, small molecule drugs like Salmeterol,⁵⁰ Metoprolol,⁵¹ and Pioglitazone⁵² are all metabolized at the benzylic position (Figure 1). Methods to access selectively deuterated small molecules are becoming increasingly important as the presence of isotopomers and isotopologues lead to challenges in separation, quantification, and characterization and compromised pharmacokinetics. Therefore, highly selective reactions for the synthesis of small molecules containing deuterium at the benzylic position are significant. Inspired by our previous results of the moderately selective transfer hydrodeuteration of aryl alkynes,³⁷ we turned our focus to develop an efficient copper-catalyzed method to selectively install deuterium at the benzylic site.

Reactivity and selectivity are challenges to access small bis-deuterated molecules at the benzylic site. In copper-catalyzed alkyne transfer hydrodeuteration chemistry, the reaction must be sufficiently reactive enough to reduce an alkyne to alkane. Furthermore, to obtain compounds with a high precision of two deuterium atoms at the benzylic position, a high regiocontrol is required for both alkyne and alkene hydrocupration steps. In our

previous results, we were able to overcome reactivity, but controlling regioselectivity remained unsolved. This project investigates the features influencing regioselectivity for internal aryl alkyne hydrocupration.

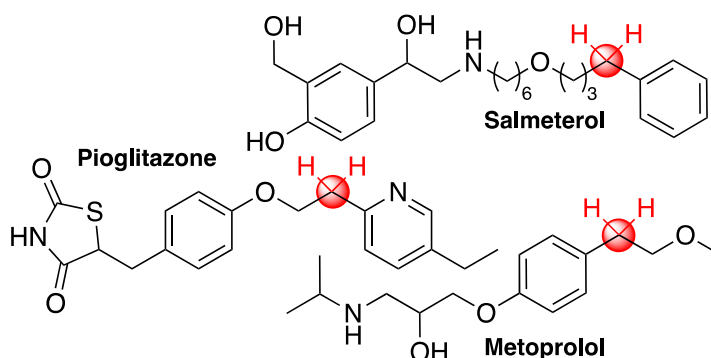
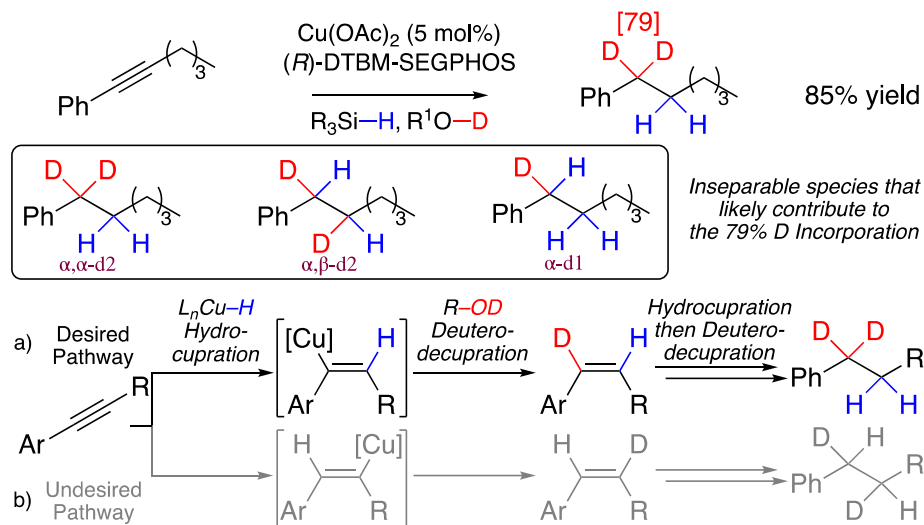


Figure 1. Drug candidates containing benzylic metabolites

Results and Discussion

In the previous alkyne transfer hydrodeuteration reaction where we observed moderate selectivity (Scheme 1), we hypothesized that there are three isotopic species that contribute to the 79% benzylic deuterium incorporation. One isotopic species is the desired α,α - d_2 -isotopomer, where the alkene and alkyne hydrocupration step is highly controlled (Scheme 1a). The second possible isotopic species is the α,β - d_2 -isotopomer, where the alkyne hydrocupration step is unselective (Scheme 1b). Many previously reported Cu—H catalyzed alkyne hydrofunctionalization reactions reveals that aryl or alkyl-substituted terminal alkynes proceed with anti-Markovnikov hydrocupration, resulting to Cu inserting at the least sterically hindered terminal position.⁵³⁻⁵⁶ However, with the increased steric hinderance of an internal alkyne it will lead the Cu inserting α to the arene, this follows the observed product with the modestly. The third possible species is the α - d_1 -isotopologue, where the alkene hydrocupration step is selective for the benzylic position likely due to the

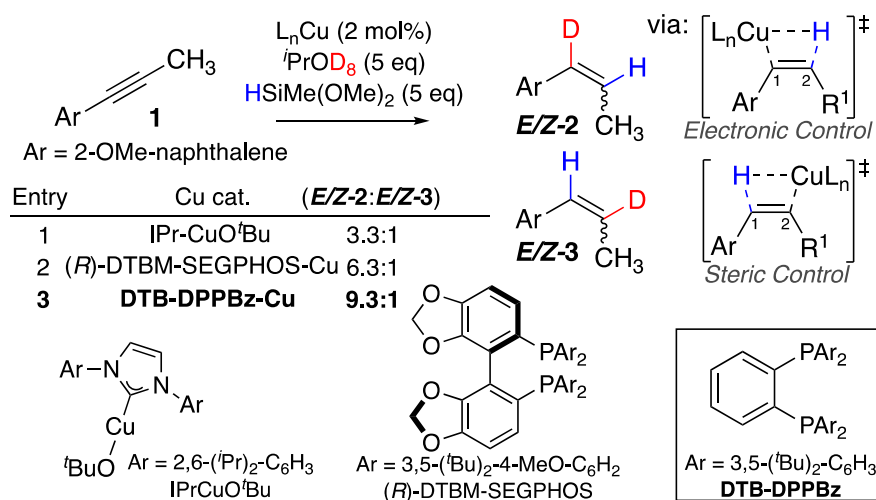
thermodynamic favorability of the benzylic copper intermediate. We realized that to improve the regioselectivity of alkyne hydrocupration step, a minimum 9:1 r.r. for internal aryl alkyne hydrocupration must be achieved. Therefore, we conducted regioselectivity studies on different ligands to observe regioselectivity ratio.



Scheme 1. Previous result and proposed reaction pathways for alkyne transfer hydrodeuteration

In our regioselectivity studies, we studied the alkyne hydrocupration step at early time points using substrate **1** because we understood that the alkene hydrocupration step was highly selective. By stopping the reaction early, we observed the semi-reduction of substrate **1** which was the α and β -deuterated styrene products *E/Z*-**2** and *E/Z*-**3**. The first ligand we explored was an NHC type ligand due to its prevalence in alkyne hydrofunctionalization reactions.^{23,24} Therefore, the IPr-Cu catalyst was found to be moderately regioselective for alkyne hydrometallation (Scheme 2, entry 1) with a r.r of 3.3:1. This result was consistent with previously reported internal alkyne hydrofunctionalization using NHC-Cu catalysts. We investigated the DTBM-SEGPHOS

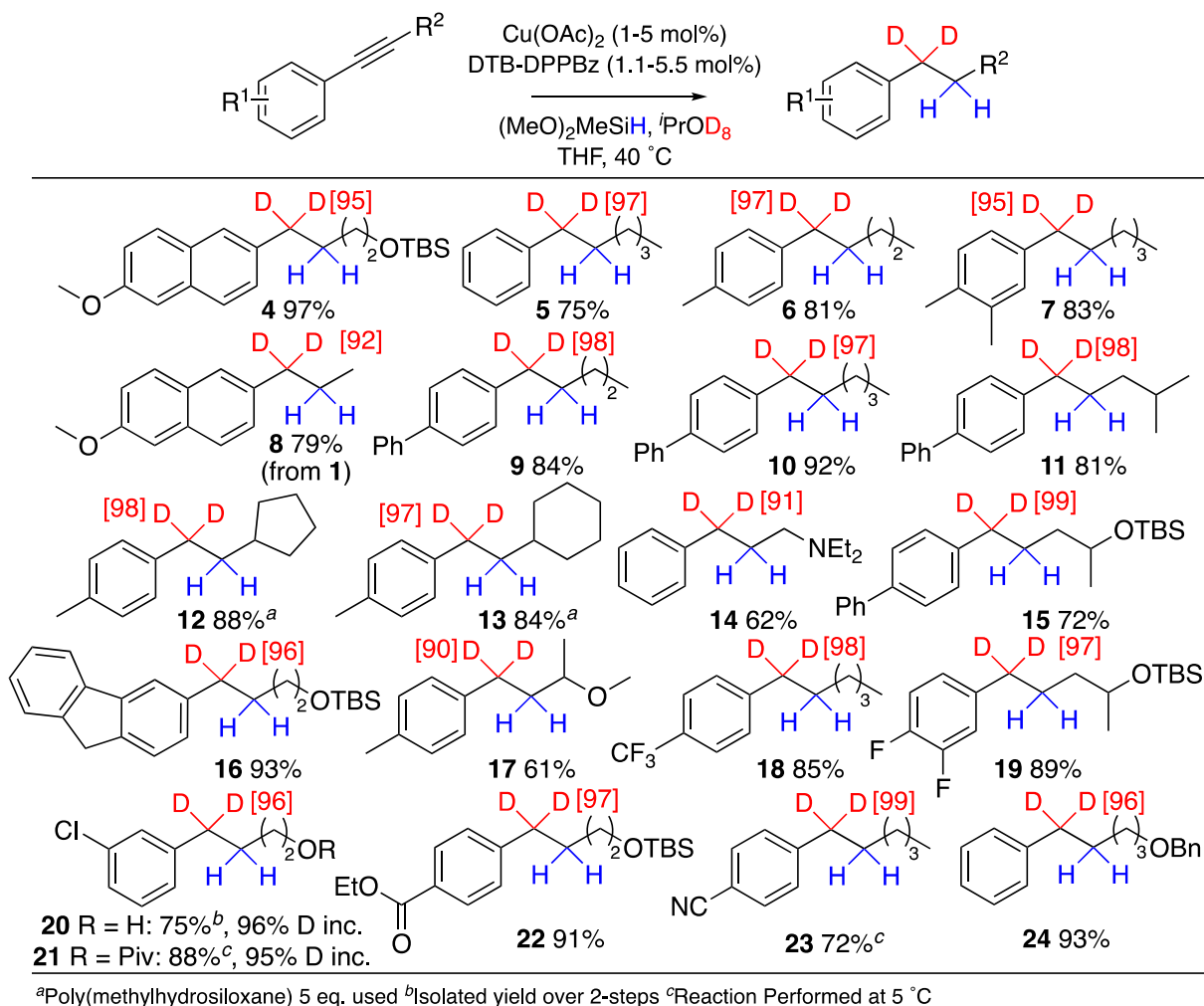
ligand as this was previously evaluated for alkyne transfer hydrodeuteration and in Buchwald and coworkers alkyne hydroamination reactions.⁵⁷⁻⁶⁰ The result was near doubling the NHC-Cu catalyst with a 6.3:1 r.r in the hydrocupration regioselectivity (Scheme 2, entry 2). Switching the ligand to DTB-DPPBz led to a significant increase in alkyne hydrocupration regioselectivity (Scheme 2, entry 3, 9.3:1 r.r). Interestingly, the presence of 3,5-di-*tert*-butyl groups substituted on the aryl groups of the ligand enhances reactivity in the case for copper catalysts.⁶¹



Scheme 2. Ligand studies of transfer hydrodeuteration of aryl alkynes

After we identified the ligand that induced the highest regioselectivity, we conducted optimization studies to obtain the fully reduced di-deuterated alkane product. We were able to use 2-methoxy-6-(1-propyn-1-yl)naphthalene as our optimization substrate to obtain **4** in high yield and deuterium incorporation (optimization studies can be found in the Supporting Information). The reaction scope was further investigated containing a variety of functional groups (Scheme 3). Under optimal reaction conditions the desired α,α -*d*2-isotopomer from phenyl hexyne and arene substituted substrates with

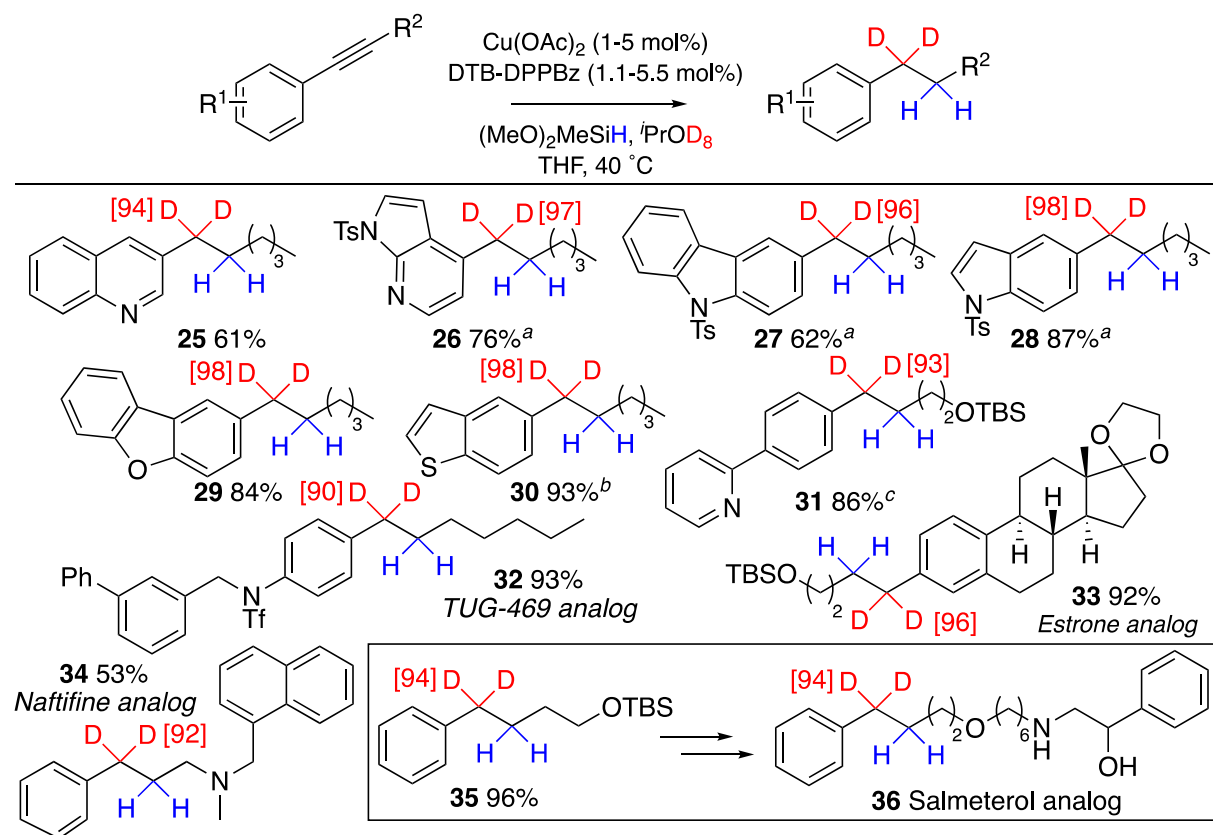
one or two methyl groups (Scheme 2, **5-7**, 75%-83% yield) were obtained with high deuterium incorporation. When the alkane chain length varied from a propyne, pentyne, or hexyne chain excellent yields were obtained (**8-10**, 79%-92% yield). It is noteworthy that when steric hinderance increased on the alkyne coupling partner from iso-butyl, cyclopentyl and cyclohexyl, the reactivity was not affected (**11-13**, 81%-84% yield). Lewis-basic nitrogen functionality is compatible with copper-catalyzed transfer hydrodeuteration conditions while alcohol-containing substrates required a protecting group to avoid competitive protodecupration (**14-17**, 61%-93% yield). Halogenated substrates along with aryl alkyne substrates containing reducible functionality such as ethyl ester, cyano, and benzyl ether underwent chemoselective alkyne transfer hydrodeuteration efficiently (**18-24**, 72%-93% yield).



Scheme 3. Aryl alkyne transfer hydrodeuteration substrate scope

Heterocycle-containing aryl alkyne substrates were also evaluated for selective copper-catalyzed alkyne transfer hydrodeuteration due to their prevalence in small molecule drugs (Scheme 4). Quinoline, tosyl-protected aza-indole, tosyl-protected carbazole, and tosyl-protected indole aryl alkynes underwent highly selective transfer hydrodeuteration (**25-28**, 61%-87% yield). Dibenzofuran and a thiophene substituted substrate were also able to undergo alkyne transfer hydrodeuteration (**29-30**, 84%-93% yield). For more challenging substrates, such as substrate **30**, we observed that increasing the equivalence of silane can help the reaction go into completion as it may promote the reformation of

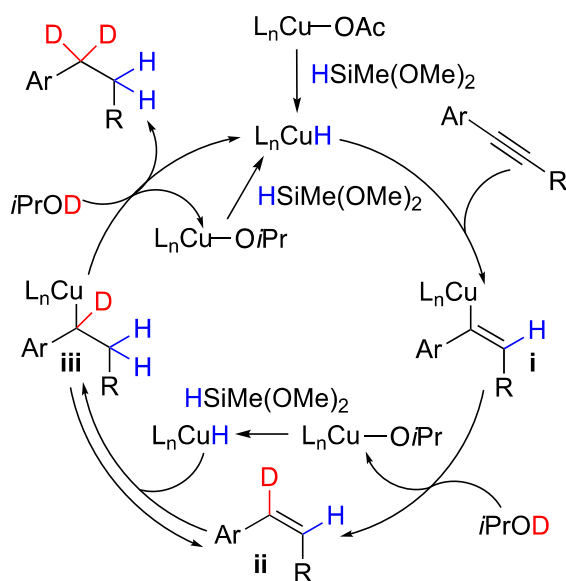
Cu—H more efficiently. Lastly, the substituted phenyl alkyne with a pyridine resulted in a high yield of the deuterated product (**31**, 86% yield).



^aReaction performed at 60 °C ^b6 eq. of $(\text{MeO})_2\text{MeSiH}$ was used. ^c6.8 mol% $\text{Cu}(\text{OAc})_2$ and 7.4 mol% DTB-DPPBz used

Scheme 4. Heterocycle and complex small molecule scope

Four complex bioactive molecules were synthesized with the alkyne substituted functionality and underwent late-stage transfer hydrodeuteration where the benzylic position was exclusively deuterated (**32-34**, 53%-93% yield). Lastly, **35** was isolated in 96% yield with high deuterium incorporation at the benzylic position. This deuterated building block was then used to synthesize a Salmeterol analog **36**, where the benzylic position is prone for metabolic oxidation.⁵⁰



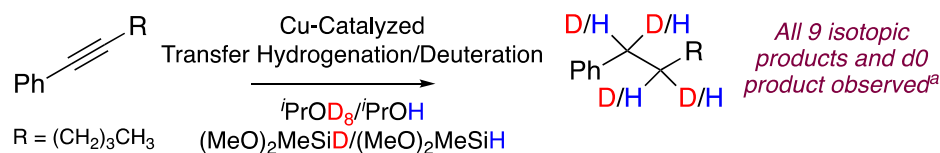
Scheme 5. Proposed mechanism for transfer hydrodeuteration of aryl alkynes

The proposed catalytic cycle closely follows the transfer hydrogenation/deuteration mechanism (Scheme 5). $\text{Cu}(\text{OAc})_2$, in the presence of dimethoxy(methyl)silane, will undergo a σ -bond metathesis and generate the $\text{Cu}-\text{H}$ species. The $\text{Cu}-\text{H}$ bond will insert across the alkyne and lead to alkenyl Cu intermediate **i**. Deuterodecupration of **i** with isopropanol- d_8 will lead to alkene **ii**. Regeneration of the $\text{Cu}-\text{H}$ and addition across alkene **ii** will form alkyl Cu **iii** followed by deuterodecupration to yield the final product.

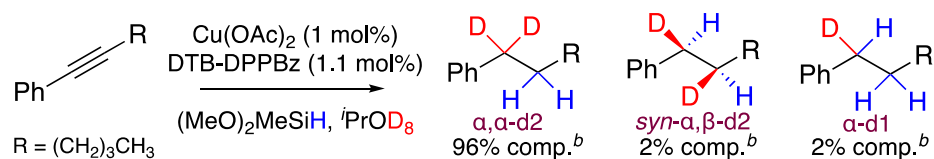
MRR spectroscopy is an emerging technology for the characterization and quantification of isotopically labeled compounds. It offers a practical solution to observe and quantify different isotopic species compared to NMR spectroscopy. If a product mixture containing isotopologues and isotopomers share deuterium substitution at the same atom, several species will contribute to the same $^1\text{H}/^2\text{H}$ resonance.⁶²⁻⁶³ MRR analysis was performed on the isolated deuterated alkane product of the phenyl hexyne substrate. The analysis was performed in two steps (Scheme 5). First, a non-selectively deuterated sample (Scheme 5a) was analyzed to observe all 10 possible species associated with the hydrogen

and/or deuterium insertion at any of the α - or β -benzylic C—H positions. This was obtained using the broadband chirped-pulse Fourier transform microwave spectrometer. The reaction mixture from the selective deuteration process (Scheme 5b) was analyzed by using the IsoMRR instrument that employs cavity-enhanced Fourier transform microwave spectroscopy. The IsoMRR allows the advantage of reducing measurement time and sample consumption. After analysis, it was observed that the two separate samples had nearly identical composition. Only two isotopic impurities were detected above the measurement threshold of 0.5%. It is important to note that the homochiral and heterochiral diastereomers for the α,β -d2 species have different rotational spectra and thus are easily distinguished in the analysis. The observation of the heterochiral diastereomer is consistent with the reaction mechanism that favors *syn* addition of the [Cu—H] in both the alkyne and alkene addition steps. Lastly, the analysis confirmed the regioselectivity of the α,α -d2-isotopomer as the desired product.

a) Alkyne Reduction to Access All Possible Isotopic Species



b) Regioselective Transfer Hydrodeuteration Reaction Measured by MRR

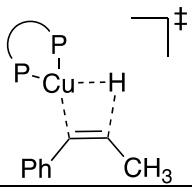
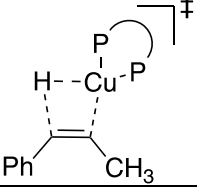


^aSee SI for all isotopic products ^bDenotes the average percent composition of isolated product from two runs

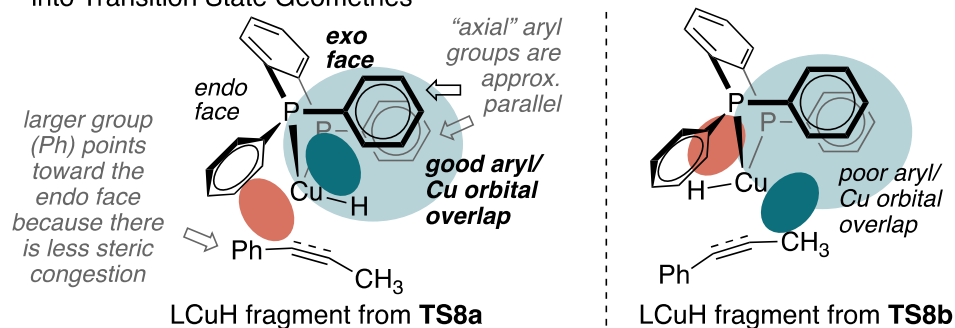
Scheme 5. Analysis by Molecular Rotational Resonance

We were driven to investigate the factors influencing regiocontrol as our initial studies observed moderate selectivity. Therefore, density functional theory (DFT) calculations were performed to understand the enhanced alkyne hydrocupration regioselectivity observed with the DTB-DPPBz ligand in comparison to the DTBM-SEGPBOS ligand. During the alkyne hydrocupration step of the (DTB-DPPBz)CuH to 1-phenylpropyne, the Cu favors the insertion α to the arene by 5.0 kcal/mol (Figure 2a). In contrast, the Cu from (DTBM-SEGPBOS)CuH shows a slight preference for the position β to the arene, indicating that (DTBM-SEGPBOS)CuH is unselective. Concluding that the DTB-DPPBz ligand promotes higher selectivity for α -deuteration than DTBM-SEGPBOS. These predictions from DFT calculations are qualitatively consistent with the experiments observed.

a) Transition Structure Energies Relative to Separated Reactants (kcal mol⁻¹)

ligand		
DTB-DPPBz	+20.3 (TS9a)	+25.3 (TS9b)
DTBM-SEGPBOS	+23.0 (TS10a)	+22.2 (TS10b)

b) Frontier Molecular Orbital Analysis of (DTB-DPPBz)CuH When Distorted into Transition State Geometries^a



^aStructures simplified for clarity (^tBu groups not shown, one *P*-aryl not shown)
Image represents lowest-energy unoccupied MO with significant density on Cu

Figure 2. a) selectivity comparison of DTB-DPPBz ligand and DTBM-SEGPHOS ligand
b) DFT Analysis of Alkyne Hydrocupration with (DTB-DPPBz)CuH

The increase in selectivity from DTB-DPPBz is related to orbital mixing between the ligand and the Cu during the favored transition state (Figure 2b, **TS8a**). In both **TS8a** and **TS8b**, the 5-membered cupracycle of DTB-DPPBzCu-H adopts an “envelope” conformation and the phenyl group of the substrate points towards the *endo* face of the cupracycle due to less steric hindrance (Figure 2b). In this geometry, the two *P*-aryl groups are pseudo-axial with respect to the 5-membered cupracycle. When the hydride is on the *exo* face on the cupracycle in **TS8a**, the π^* orbitals of the aryl groups can mix with the metal-centered *p*-type orbital to form the LUMO (Figure 2). The mixing between orbitals lowers the energy of the LUMO of (DTB-DPPBz)Cu-H and facilitates electron donation from the alkyne to copper. However, when the hydride is on the *endo* face of the cupracycle as in **TS8b**, there is poor orbital overlap between ligand and metal orbitals and the LUMO energy is higher than the ground-state. The conformational preference of the 5-membered cupracycle is critical to the difference between **TS8a** and **TS8b**. For (DTBM-SEGPHOS)Cu-H, the Cu is part of a 7-membered ring and therefore does not result in the same orbital mixing effect. However, the LUMO energy of (DTBM-SEGPHOS)CuH is slightly higher by distortion into the **TS9a** geometry, but is not significantly affected in **TS9b** (see SI for more DFT analysis). This could be the reason why (DTBM-SEGPHOS)CuH shows a slight preference for β -deuteration.

Conclusion

In conclusion, we reported the first highly regioselective transfer hydrodeuteration reaction of aryl alkynes across a broad substrate scope along with complex bioactive

molecules. MRR was used to analyze possible isotopic impurities in the product mixture and confirm the regioselectivity of the α,α - d_2 -isotopomer. DFT calculations were performed and revealed that the high regioselectivity in the alkyne hydrocupration step is attributed to enhanced electronic interactions between the substrate and (DTB-DPPBz)CuH complex. We anticipate that this reaction will be useful in the development of precisely deuterated small molecules for pharmaceutical applications.

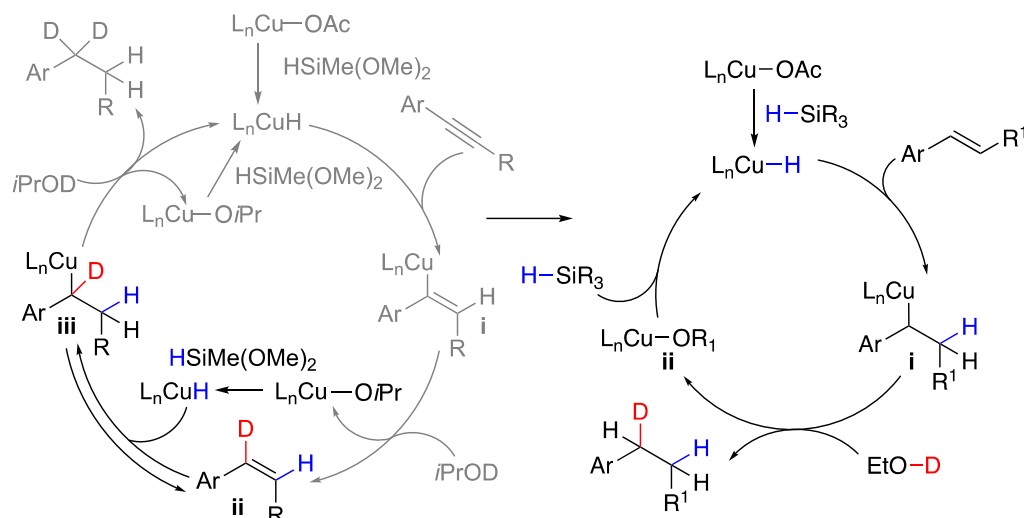
CHAPTER 3

Copper-Catalyzed Transfer Hydrodeuteration of Aryl Alkenes with Quantitative Isotopomer Purity Analysis by Molecular Rotational Resonance Spectroscopy⁶³

Introduction

In chapter 1, we explored transfer hydrodeuteration reactions on aryl alkynes where selectivity was only moderately observed. We hypothesized that in the reaction mechanism the hydrocupration to the alkenyl intermediate step was unselective. Therefore, to confirm that the first step from the alkyne substrate to the alkenyl intermediate was unselective, we subjected an alkene substrate to transfer hydrodeuteration reaction conditions. Results inferred that the alkene substrate yielding to the final deuterated alkane product was highly selective.

Previous works on transfer hydrodeuteration of aryl alkenes had a limited substrate scope or moderate regioselectivity.^{29-34,36} We envisioned that with our transfer hydrodeuteration reaction conditions, the reaction will occur with excellent regioselectivity because of the thermodynamic favorability of the benzylic copper intermediate. We also reasoned that the hydrogen donor and the deuterium donor would operate at distinct points during the reaction and therefore allow for precise insertion of each atom at the desired location within the aryl alkene.



Scheme 1. Proposed catalytic cycle from transfer hydrodeuteration of alkynes to alkenes

Inspired by the transfer hydrodeuteration experimental results in chapter 1 and 2, we observed that the selective step in the catalytic cycle was the alkene hydrocupration. Therefore, we propose a mechanism starting with the Cu—H species (Scheme 1). The Cu—H species will selectively insert across the aryl alkene to afford alkyl intermediate **i** and deuterocupration will yield the final mono-deuterated product. Byproduct **ii** will eventually regenerate Cu—H in the presence of the silane reagent.

In this work we are also interested in quantitatively analyzing our deuterated products and confirming regioselectivity. Our reason of interest lies in the possibility of our reaction mixture containing three isotopic species and these contribute to two NMR resonances,⁶² thus, NMR spectroscopy will not be able to differentiate the signals. We used molecular rotational resonance spectroscopy as it has the capabilities to analyze isotopic reaction products.

Results and Discussion

Table 1. Reaction development of transfer hydrodeuteration of alkenes

trans-1

2

Entry	Cu(OAc) ₂	Ligand	D-Source	<i>trans</i> -1 (%)	2 (%)
1	2 mol%	L1	EtOD	69 ^b	-
2	2 mol%	L2	EtOD	70 ^b	-
3	2 mol%	L3	EtOD	89 ^b	-
4	2 mol%	L4	EtOD	47 ^b	-
5	2 mol%	L5	EtOD	-	85 ^c
6	2 mol%	L5	MeOD	8 ^c	69 ^c
7	2 mol%	L5	D ₂ O	59 ^c	21 ^c
8	1 mol%	L5	IPA- <i>d</i> ₈	-	85 ^c
9	1 mol%	L5	EtOD	-	90 ^c

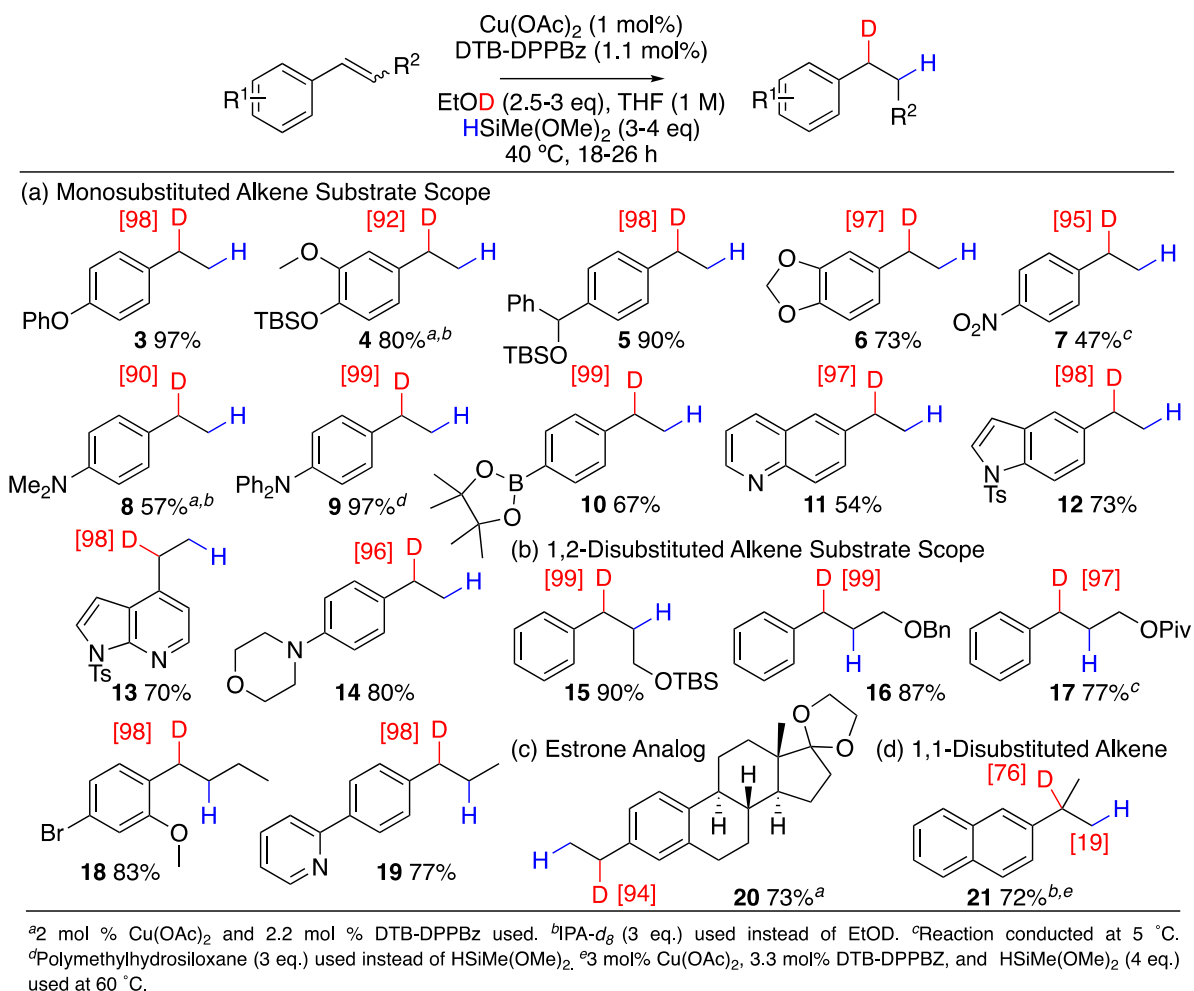
^aReactions conducted using 0.2 mmol of substrate and Cu(OAc)₂ was used as a 0.2 M solution in THF.

^bYield was determined by ¹H NMR analysis of the crude reaction mixture, using mesitylene as an internal standard. ^cDenotes isolated product yield.

We used TBS-protected cinnamyl alcohol *trans*-1 as the aryl alkene for reaction optimization. We found that bidentate ligands such as DPPE, DPPF, rac-BINAP, DPPBz were not efficient at supporting the desired transformation (Table 1, entries 1-4). Switching to a more sterically crowded DTB-DPPBz ligand dramatically affected reactivity and deuterated aryl alkane **2** was isolated in 85% yield (entry 5). Varying the deuterium source revealed that methanol—OD led to a decrease in yield (entry 6) while D₂O only led to partial conversion to product **2** (entry 7). 2-propanol-*d*₈ was similarly efficient as ethanol—OD with lower catalyst loading (entry 8). Ultimately, when we returned to reaction conditions from entry 5 and decreased the catalyst loading to 1 mol %, it was found to be optimal (entry 9). It should be noted that product **2** was evaluated by ¹H and ²H NMR to confirm one deuterium atom incorporated exclusively at the benzylic position (>20:1).

The substrate scope of the reaction was evaluated after the optimal reaction conditions were obtained. Monosubstituted alkenyl arenes were first investigated. Electron-rich substrates containing oxygen functionality were found to perform well in the

reaction with excellent yields (Scheme 2, **3-6**, 73-97% yield). Alternatively, electron-withdrawing nitro group substituted on the arene also provided a modest yield under transfer hydrodeuteration conditions at 5 °C (**7**, 47% yield). Nitrogen substitution on the alkenyl arene substrate underwent transfer hydrodeuteration efficiently (**8-9**, 57-97% yield). Importantly, we demonstrated that PMHS can be used instead of DMMS in the synthesis of **9**. (4-vinylphenyl) boronic acid pinacol ester can also undergo Cu-catalyzed transfer hydrodeuteration in moderate yield (**10**, 67% yield). Since nitrogen- and oxygen-containing heterocycles are prevalent in bioactive molecules,^{64, 65} we were pleased to find that quinoline, indole, and azaindole substituted alkenes performed well in the transfer hydrodeuteration reaction (**11-13**, 54-73% yield). Additionally, an alkenyl arene substituted with a morpholine ring was efficiently converted to the deuterated aryl alkane product (**14**, 80% yield).

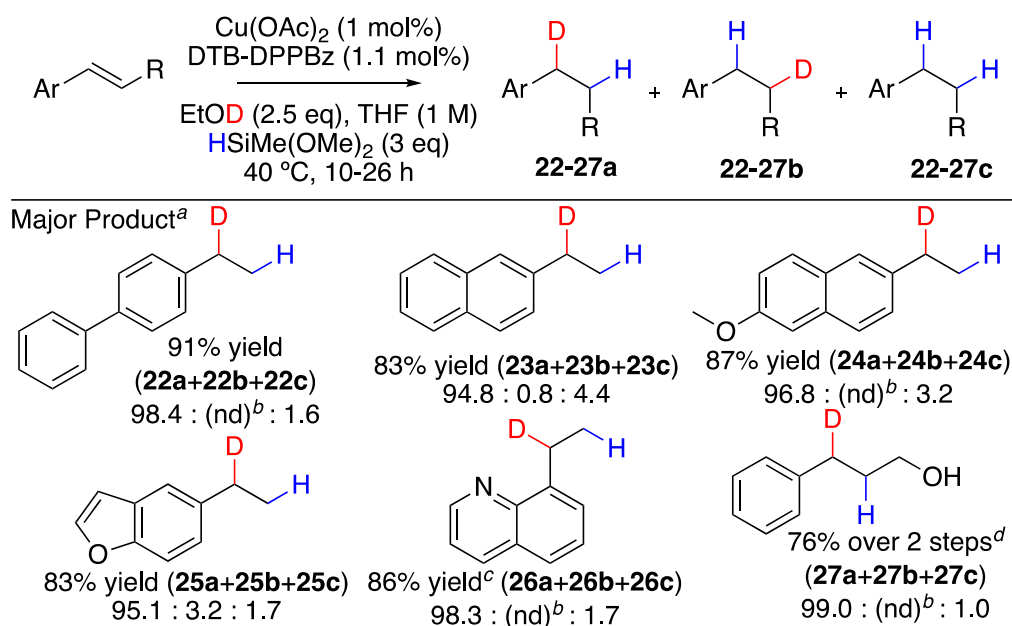


Scheme 2. Transfer hydrodeuteration of aryl alkenes substrate scope

Internal alkene substrates were also subjected to transfer hydrodeuteration reaction conditions. Cinnamyl alcohol derivatives were evaluated when the alcohol was protected with a tert-butyldimethylsilyl (TBS), benzyl (Bn), and pivaloyl (Piv) group. All three derivatives were deuterated in high yield (**15-17**, 77-90% yield). No reduction of the carbonyl of the pivaloyl group was detected and no benzyl deprotection of the product was observed. A bromine substituted alkenyl arene and pyridine substituted alkenyl arene was also isolated in high yield (**18-19**, 77-83% yield). Notably, no dehalogenation product was observed in the synthesis of **18**.

Our transfer hydrodeuteration reactions conditions were also explored on a complex small molecule vinyl-substituted estrone analog, in which the estrone analog was deuterated in good yield (**20**, 73% yield). Lastly, we evaluated a 1,1-disubstituted aryl alkene for reaction selectivity. The synthesis of **21** was only modestly selective with deuterium incorporation favoring the benzylic position (4:1 benzylic:methyl selectivity). The steric environment of the 1,1-disubstituted alkene may inhibit the copper catalyst from approaching the benzylic site contributing to the modest selectivity.

The alkenyl arene transfer hydrodeuteration scope was further extended to be analyzed by molecular rotational resonance spectroscopy (Scheme 3). In our transfer hydrodeuteration reaction, it is possible to form isotopic impurities such the misdeuterated impurity **b**, and the underdeuterated impurity **c**, defined as no deuterium incorporation. The misdeuterated **b** species could be obtained by the deuterium inserting into the homobenzylic position and the hydrogen at the benzylic site of the alkenyl substrate. We attribute no deuterium incorporation to hydrogen impurities in the alcohol—OD reagent or trace H₂O in the alkenyl arene substrate and silane. We were able to readily convert polyaromatic substrates such as 4-vinylbiphenyl, 2-vinylnaphthalene, and 2-methoxy-6-vinylnaphthalene to their corresponding deuterated products (**22-24**, 83-91% yield). Heterocycle-containing aryl alkenes **25-26** and internal alkene **27** were also evaluated under transfer hydrodeuteration conditions (76-86% yield). In all six examples, the major product, **a**, was obtained in high yield with high regioselectivity analyzed by the IsoMRR and broadband MRR instruments.



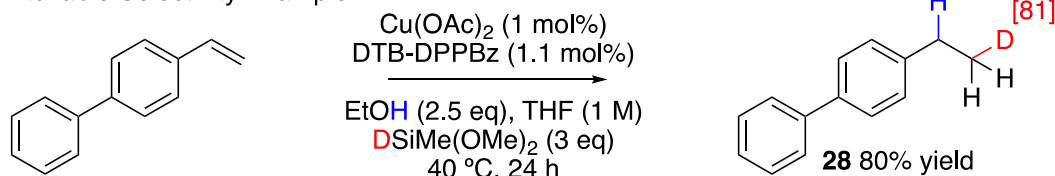
^aThe major products were **22-27a**, the product distribution was determined by MRR and the ratio represents the ratio of all products in the product mixture after purification. ^bCompound not detected (nd) by ²H NMR or MRR. See SI for detection limits. ^c2 mol % Cu(OAc)₂ and 2.2 mol % DTB-DPPBz were used. ^dTransfer deuteration product was purified then subjected to TBS deprotection.

Scheme 3. Substrate scope analyzed by molecular rotational resonance (MRR)

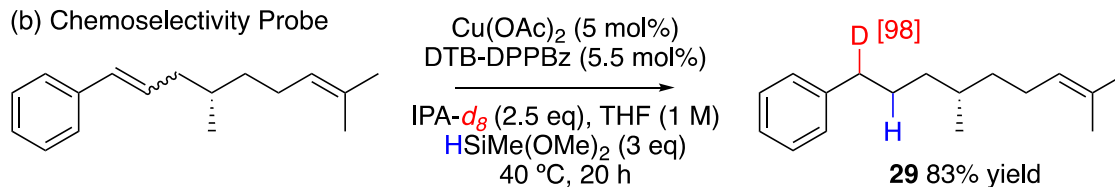
We further explored other capabilities of the copper-catalyzed alkene transfer hydrodeuteration reaction. To demonstrate the versatility of the reaction, we hypothesized flipping the regioselectivity of the reaction would be possible by replacing Si—H and ethanol—OD with Si—D and ethanol. This was examined with 4-vinylbiphenyl (Scheme 4a) and resulted in an 80% yield with 81% deuterium incorporation (**28**). Interestingly, an increase of the “underdeuterated” side product was observed in this reaction likely due to the reduced deuterium content in the Si—D reagent or water impurity in the reagent. We also performed transfer hydrodeuteration on a substrate containing both a 1,2 disubstituted styrenyl alkene and 1,1,2-trisubstituted alkene to probe chemoselectivity (Scheme 4b). We observed high selectivity for the deuterium incorporation at the benzylic position and no reduction of the 1,1,2-trisubstituted alkene. Additionally, we evaluated the potential for an unactivated alkene to undergo regioselective transfer hydrodeuteration and observed

product **30**, with no reduction of the sterically hindered tri-substituted alkene. Lastly, we probed whether the selectivity of the Cu—H insertion into the alkene occurred with *syn* or *anti* addition using 1,2,2-trisubstituted alkene (Scheme 4c). We were able to isolate product **31** in 77% yield. We observed the *anti*-product **31** due to a *syn*-addition of the Cu—H across the alkene. This was analyzed by comparison of the coupling constants of the hydrogen at the benzylic position and the hydrogen at the homo-benzylic on ^1H NMR. Product **31** also further indicates that trisubstituted alkenes are viable substrates for regioselective transfer hydrodeuteration reactions.

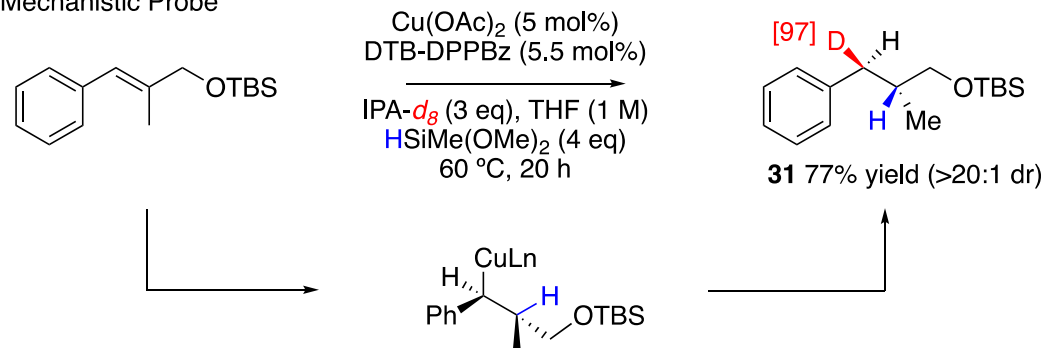
(a) Switchable Selectivity Example



(b) Chemoselectivity Probe



(c) Mechanistic Probe



Scheme 4. Reaction analysis studies

We further analyzed the isotopic compositions of the reaction products presented in Scheme 21 by MRR. In MRR, a rotational spectrum is produced through electric-dipole transitions between the quantized rotational kinetic energy levels of the molecules⁶⁶ In the rigid rotor approximation, the energy levels can be calculated from the three-rotational constants (A, B, C) derived from the moment-of-inertia for rotation about the three principal rotational axes (IA, IB, IC), where the moment-of-inertia is calculated from the nuclear masses and the shortest distance of each nucleus to the rotation axis.

$$A = \left(\hbar^2 / 2 \right) I_A^{-1} \quad (1)$$

$$I_A = \sum_i m_i r_{Ai}^2 \quad (2)$$

The intensities of the rotational transitions are possible due to the electric dipole moment and polarity of the molecule. The molecule must be polar to have a rotational spectrum.

One of the most important features of rotational spectroscopy in regard to deuterated molecules is that each isotopic variant has its own unique spectral signature. Thus, MRR spectroscopy can accurately characterize isotopologue and isotopomer mixtures, whereas mass spectroscopy can only analyze the isotopologue composition. Nuclear magnetic resonance (NMR) spectroscopy also has a limitation and cannot analyze sample composition when isotopologues and isotopomers present in the mixture share deuterium substitution at the same atom. MRR can measure total deuterium content and sample composition, confirm the position of substitution, detect residual hydrogen impurities, and determine enantioselectivity of chiral by virtue of deuterium substituted compounds. Since MRR uses quantum chemistry to predict equilibrium geometry in high accuracy, reference samples are not required to identify isotopic species.^{67, 68}

Rotational spectrum for species in Scheme 3 were on measured on the broadband instrument using a chirped-pulse Fourier transform microwave (CP-FTMW) spectrometer operating in the 2-8 GHz frequency range.⁶⁹⁻⁷¹ This permits enough of the rotational spectrum to obtain a highly characteristic spectral pattern for each isotopic variant present in the mixture. The sensitivity that comes from the broadband instrument to allow isotopologue and isotopomer analysis is the dispersion of the sample in neon (0.1% mixture) into the spectrometer vacuum chamber and then cooling of the gas with a rotational temperature of 1 K. This induces the measurement sensitivity through reduction of the partition function and the reduced Doppler broadening of the pulsed jet expansion will produce a high-resolution spectrum. This feature is crucial in isotopologue/isotopomer analysis because it is not possible to separate the different species by chromatography.⁷²

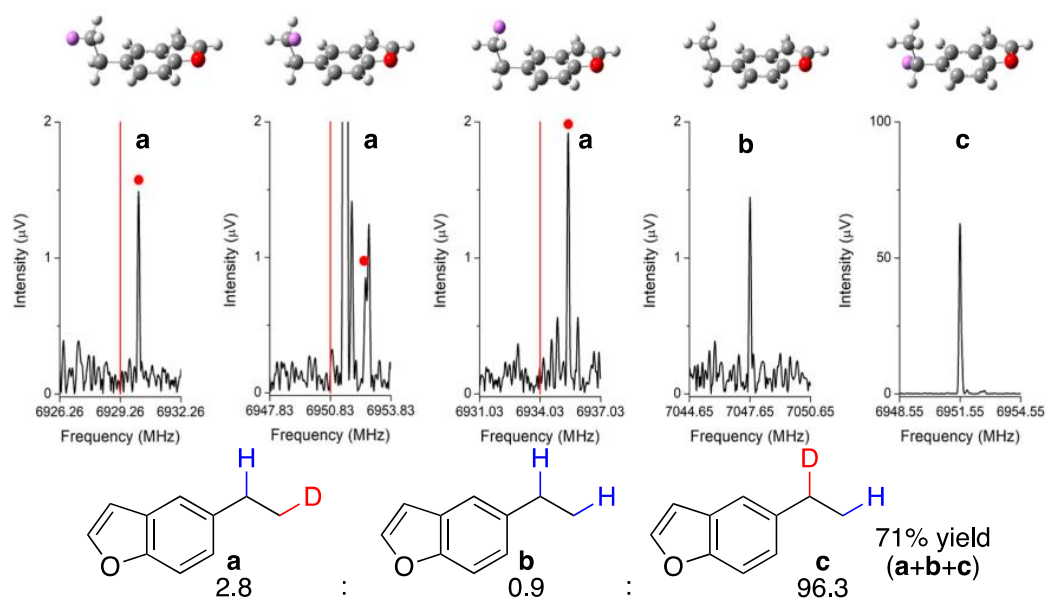


Figure 1. Detection of misdeuterated isotopomer of 5-ethylbenzofuran- d_1

Since the misdeuterated product **25b** (Scheme 3) was observed, we expected three equal intensity rotational spectra from the conformational isomer of this isotopomer

(Figure 1). The first three rotational spectra displayed in Figure 1 are 6 MHz frequency bandwidth window of the predicted transition frequencies obtained using quantum chemistry equilibrium geometry (calculated using the B3LYP density functional theory with Grimme's D3 dispersion correction including Becke-Johnson damping and the 6-311++G(d,p) basis set model chemistry in Gaussian16).⁷³ There are three different conformers of the d_1 -methyl isotopomer, hence the different spectra (denoted as the purple atom is the deuteration position in the structure above the spectral region). The red dot is assigned to the transition matched to each isotopomer whereas the red line is the predicted transition from quantum chemistry. The fourth panel is centered on the observed transition of the underdeuterated isotopologue. Lastly, the fifth panel presents the rotational transition for the major desired product of 5-ethylbenzofuran- d_1 . Note the change in the intensity of the axis scale, the other isotopomers and isotopologue are nearly undetectable. Figure 2 shows the strongest rotational transitions of 2-ethylnaphthalene- d_1 . We do not observe any of the misdeuterated isotopomer as displayed on the first three panels where no transitions in the prediction window are assigned. The fourth panel identifies the underdeuterated isotopologue and the fifth panel is the transition of the desired major product of 2-ethylnaphthalene- d_1 .

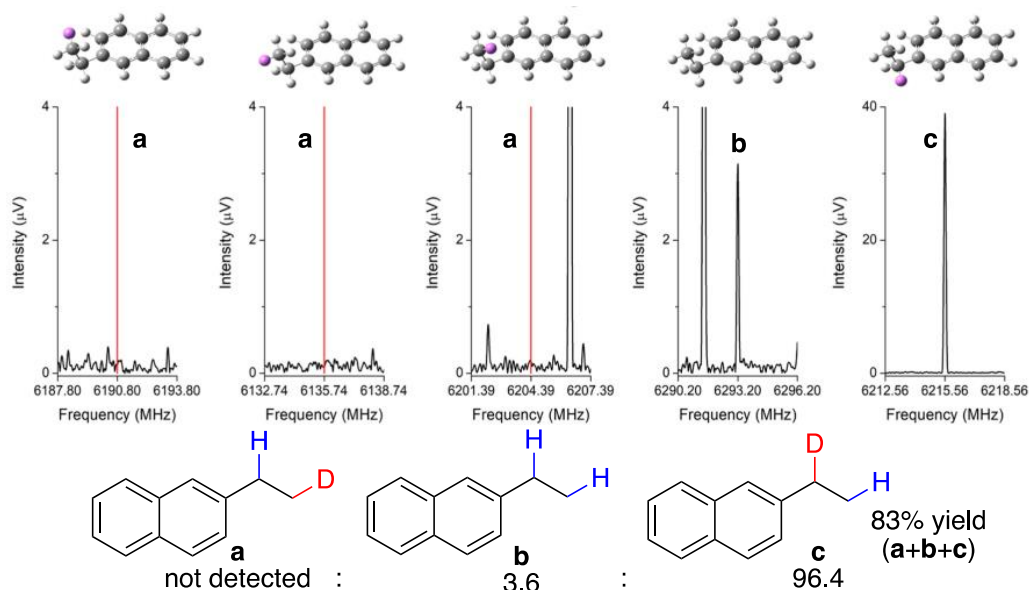


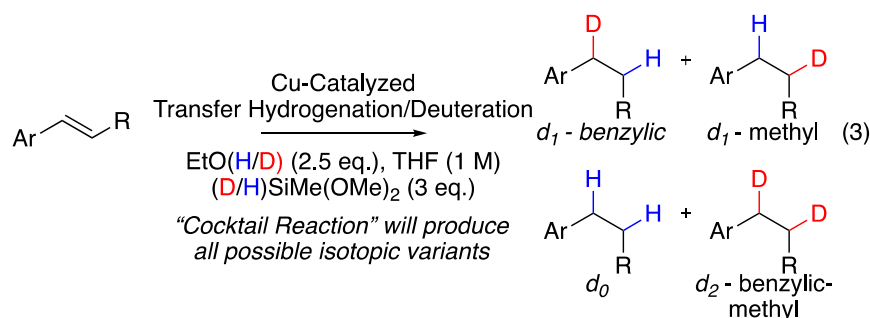
Figure 2. Nondetection of misdeuterated isotomer of 2-ethylnaphthalene- d_1

After the initial analyses of the six reaction products in Scheme 3, a modified MRR analysis approach was developed to address some weaknesses in the application of MRR to the development of synthetic methodologies for selective deuteration chemistry. One of the first limitations to the CP-FTMW analysis is the possible overlook of a spectral signature of an isotopic impurity. This is possible if the quantum chemistry predictions of the rotational spectrum identify the spectrum near the detection limit. Next, one sample consumption could be up to 60-100 mg to reach a detection limit of about 1% on the expected isotopic impurity. Lastly, shorter measurement time would be more ideal to facilitate screening of new reaction conditions to optimize the method selectivity.

The new measurement approach uses a commercial MRR instrument called the IsoMRR from BrightSpec, Inc., which combines the broadband MRR spectroscopy to obtain spectral signatures of all possible isotopic species with high-throughput sample analysis. The BrightSpec IsoMRR instrument uses a tunable cavity-enhanced FTMW design introduced by Balle and Flygare.⁷⁴ Additionally, the IsoMRR spectrometer has

approximately one order-of-magnitude greater sensitivity than the broadband spectrometer for equal sample consumption. However, the cavity resonator limits the measurement bandwidth to about 1 MHz. Efficient use of the IsoMRR instrument would rely on the availability of the transition frequencies of each isotopic species to be studied and these are supplied from the broadband analysis.

The process of using the new IsoMRR method is to have a “cocktail” sample analyzed by broadband MRR. The “cocktail” sample is prepared by performing the reaction with a 1:1 mixture of H and D reagents so all possible reaction products is produced (Eq 3). Once the sample is analyzed, the spectral signatures are used to set up a high-speed measurement script using the cavity enhanced FTMW spectrometer. This measurement methodology was tested on the isolated products from the copper-catalyzed “cocktail” reactions performed with 4-vinylbiphenyl, 2-vinylnaphthalene, and 5-vinylbenzofuran.



Illustrated in Figure 3 is the analyzed copper-catalyzed “cocktail” reaction from 2-vinylnaphthalene. Panels A and B present a spectrum of the commercial sample ethyl-naphthalene- d_0 , which is also the dominant species in the cocktail reaction mixture. Panel A shows a small frequency range of the full 2-8 GHz measured spectrum, where shown in

blue is the predicted rotational spectrum from equilibrium geometry and dipole moments obtained from quantum chemistry, shown as a close match to the observed pattern. Panel B shows an expanded frequency region for the two transitions in ethyl-naphthalene- d_0 . Where the spectrum labeled blue is from quantum chemistry and the red spectrum simulation uses the experimental fit rotational constants. Panel C shows the comparison between the predicted transition of the 6_{16} — 5_{15} rotational transitions of the six conformers of the d_2 -benzylic-methyl isotopomer to the measured spectrum. The predicted spectral signatures of the deuterated species can be predicted to high accuracy using scaled quantum chemistry of ethyl-naphthalene- d_0 . The agreement is on the order of 0.01%. Lastly, panel D depicts the $J=6 - J=5$ spectral region of the reaction product mixture and the residual spectrum (blue) after all isotopic species are cut from the spectrum. Consistent with the proposed reaction products, only d_0 , d_1 -benzylic, d_1 -methyl, and d_2 -benzylic-methyl were identified.

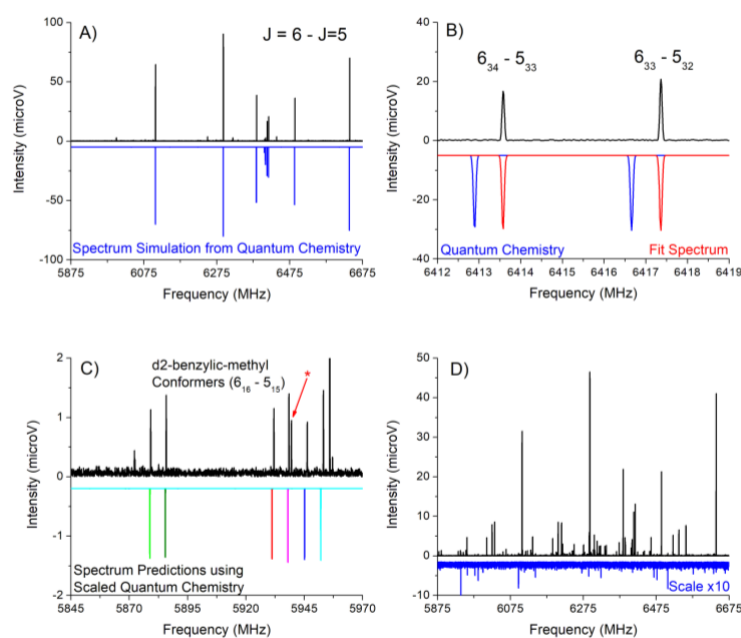


Figure 3. Predicted and experimental analysis of 2-ethylnaphthalene product mixture from cocktail reaction. Panel B) The assignment listed above each transition uses the usual notation in rotational spectroscopy that labels the energy levels J_{KaKc} .⁶⁶

In Table 2, 8 transitions in the 2-ethylnaphthalene spectrum were used to perform a quantitative analysis of the reaction product mixture measured by the broadband instrument. To average fluctuations from the frequency-dependent electric fields of the chirped excitation pulse, the total intensity of a set of rotational transitions was used. The analysis includes the spectral intensity from all conformers of a given isotopomer.

Table 2. Isotopic Composition of the 2-Ethylnaphthalene Mixture Giving the Total Intensity for 8 Transitions of Each Conformer for the Four Chemically Distinct Isotopic Variants Observed in the Spectrum

d_0		d_1 -benzylic		d_1 -methyl		d_2 -benzylic-methyl	
	280 μ V	D19 ^a	57.0 μ V	D22	38.0 μ V	D19 D22	8.17 μ V
		D20	55.4 μ V	D23	36.3 μ V	D19 D23	8.72 μ V
				D24	41.9 μ V	D19 D24	7.82 μ V
						D20 D22	9.25 μ V
						D20 D23	9.38 μ V
						D20 D24	10.6 μ V
Total	280 μ V		112.4 μ V		116.2 μ V		53.9 μ V
%	49.8		20.0		20.7		9.6
d_1-methyl conformers: Mean: 38.7 μ V σ = 2.84 μ V							
d_2-benzylic-methyl conformers: Mean: 8.99 μ V σ = 0.98 μ V							

^aThe isotope labels, like D19, refer to the atom labeling from the quantum chemistry geometry optimization.

The accuracy of the sample composition analysis by broadband MRR spectroscopy was validated by comparison to the integration of specific resonances in the ¹H and ²H NMR spectra of the reaction mixture. However, it is important to note that one the limitation of NMR spectroscopy is the composition of the reaction mixture cannot be analyzed. The resonances used in NMR analysis are assigned to the benzylic and methyl

protons. Since the reaction mixture contain three isotopic species (*d*₁-benzylic, *d*₁-methyl, and *d*₂-benzylic-methyl) that contribute to the two resonances, this makes it impossible to analyze the sample composition by NMR spectroscopy. Since all isotopic variants have unique spectral signatures, MRR can perform the analysis. Presented in Table 3 is the quantitative comparison between MRR and NMR resonance integrations for the four reaction mixtures that were analyzed in this work. The mean absolute percent difference between the results is 1% for the ¹H integration.

Table 3. Comparison Between Calculated NMR Integration Using MRR Sample Composition and Measured NMR Integration

NMR Resonance	Ethylbenzofuran		Ethyl-naphthalene		Ethylbiphenyl		Ethylbiphenyl (D-enhanced)	
	MRR ^a	NMR	MRR	NMR	MRR	NMR	MRR	NMR
Methyl ¹ H	2.72(1)	2.69	2.70(2)	2.71	2.69(2)	2.73	2.46(2)	2.46
Benzylic ¹ H	1.45(2)	1.43	1.70(2)	1.71	1.66(2)	1.69	1.31(2)	1.29
Methyl ² H	0.28(1)	0.31	0.30(2)	0.29	0.31(2)	0.27	0.54(2)	0.52
Benzylic ² H	0.55(2)	0.57	0.30(2)	0.28	0.34(2)	0.30	0.69(2)	0.71
Mean Absolute Percent Difference (¹H Only): 1.0%								
Mean Absolute Percent Difference (All): 4.0%								

^aThe MRR integrations give the 1σ uncertainty derived from the composition uncertainty.

Table 4 comprises of the composition analysis from the two MRR instruments and show that both are in good agreement with a variation of about 5%. Importantly, IsoMRR measurements are repeatable in back-to-back analysis runs. This measurement precision shows that the technique would be able to reliably detect changes in the sample composition for high-throughput screening of the reaction conditions. Furthermore, 2-ethyl-naphthalene, 5-ethylbenzofuran, and ethyl-biphenyl used about 2.5-5 mg of sample with approximately 10-20 minutes of measurement time. This is a major improvement over sample analysis by broadband MRR.

Table 4. Comparison of Sample Composition Analysis by Broadband and Cavity-Enhanced MRR Spectroscopy

Ethylbenzofuran	Run 1	Run 2	Run 3	IsoMRR ^a	CP-FTMW ^b	Difference
d ₀	29.4%	30.3%	30.0%	29.9(0.45)	34(2.4)	4.1%
d ₁ -benzylic	33.7%	31.9%	31.8%	32.6(1.1)	38(2.1)	5.4%
d ₁ -methyl	13.4%	14.3%	15.1%	14.3(0.85)	11.4(0.8)	2.9%
d ₂ -methyl-benzylic	23.5%	23.5%	23.1%	23.4(0.23)	16.8(0.9)	6.6%
Ethyl naphthalene	Run 1	Run 2	Run 3	IsoMRR ^a	CP-FTMW ^b	Difference
d ₀	55.2%	54.3%	54.2%	54.6(0.55)	50(2.7)	4.6%
d ₁ -benzylic	14.9%	15.1%	14.8%	14.9(0.15)	20(1.6)	5.1%
d ₁ -methyl	21.0%	21.5%	21.4%	21.3(0.26)	21(1.4)	0.3%
d ₂ -methyl-benzylic	9.0%	9.2%	9.6%	9.3(0.31)	9.6(0.6)	0.3%
Ethylbiphenyl	Run 1	Run 2		IsoMRR ^a	CP-FTMW ^b	Difference
d ₀	49.7%	51.7%		50.7(1.4)	46(2.7)	4.9%
d ₁ -benzylic	18.7%	18.0%		18.4(0.49)	23(1.7)	4.7%
d ₁ -methyl	20.8%	20.3%		20.6(0.35)	21(1.4)	0.4%
d ₂ -methyl-benzylic	10.8%	9.9%		10.4(0.64)	10.6(0.7)	0.2%

^aThe IsoMRR results are the mean value of the replicate measurements with a 1 σ sample standard deviation reported in parenthesis. ^bThe measurement uncertainty reported for the CP-FTMW broadband measurements is a 1 σ standard deviation determined by assuming that there is a 10% relative uncertainty in the intensity measurement ($(\sigma_I/I) = 0.1$) for each rotationally distinct species in the sample mixture.

Final results from using the IsoMRR instrument to analyze the reaction products from the optimized reaction conditions of Scheme 3 contains the detection of d₁-methyl isotopomer in 2-ethylnaphthalene that was not observable in the broadband analysis: 94.8% d₁-benzylic **23a**, 4.4% d₀ **23c**, 0.8% d₁-methyl **23b**, <0.6% d₂-benzylic-methyl (nd). For 5-ethylbenzofuran, the IsoMRR analysis agrees with the broadband analysis within the performance comparison limits of Table 4: 95.1% d₁-benzylic **25a**, 1.7% d₀ **25c**, 3.2% d₁-methyl **25b**, <0.7% d₂-benzylic-methyl (nd). For 4-ethylbiphenyl, only the underdeuterated isotopic impurity was detected: 98.4% d₁-benzylic **22a**, 1.6 % d₀ **22c**, <0.7% d₁-methyl **22b**, <1.3% d₂-benzylic-methyl (nd). Additionally, three separate preparations of 4-

ethylbiphenyl using the optimized chemistry were analyzed and the only two species detected were the desired d_1 -benzylic and the underdeuterated d_0 isotopologue. The amount of d_0 **22c** impurity in the three samples was 1.6%, 2.3%, and 1.8%. From these results, MRR analysis demonstrates a new analytical chemistry capability for the analysis of isotopologues/isotopomer sample mixtures. Furthermore, MRR spectroscopy can be performed in a high-throughput implementation to support the optimization of new synthetic chemistry methodologies.

Conclusion

In summary, we reported a highly regioselective alkene transfer hydrodeuteration using mild reaction conditions across a broad range of aryl alkene substrates, including those containing heterocycles and reduceable functionality. The Cu-catalyzed reaction is able incorporate both a hydrogen and a deuterium across an alkene with high levels of precision. Molecular rotational resonance was used to analyze selectivity and sample composition of the possible isotopic species of six reaction product mixtures. The misdeuterated isotopic impurity was only detected in two product mixtures, indicating a highly regioselective reaction. An efficient measurement methodology for MRR analysis was also described for high-throughput screening with less time and sample consumption. The advantages of MRR spectroscopy for characterization of isotopic products are: 1) Isotopomers have distinct MRR spectra that can be predicted to high accuracy making it possible to identify isotopomers with high confidence. 2) Instruments for MRR provide high spectral resolution so that isotopologue and isotopomer mixtures can be quantitatively analyzed without signal overlap. 3) High-throughput analysis of possible screen a wide variety of reaction conditions.

CHAPTER 4

Highly Selective Catalytic Transfer Hydrodeuteration of Cyclic Alkenes⁷⁵

Introduction

Transfer hydrodeuteration reactions have demonstrated highly selective deuterium incorporation across various alkene substrates as presented in previous work.^{28-36,63} The catalytic cycle can differentiate between the hydrogen and deuterium donors allowing the incorporation of each atom at distinct points within the catalytic cycle. This was demonstrated in our previous work on Cu-catalyzed transfer hydrodeuteration of aryl alkenes.⁶³ We were able to incorporate one deuterium atom and one hydrogen across the double bond with high regioselectivity. Despite the broad alkenyl arene substrates demonstrated, cyclic alkenes were not explored. Previous work involving a HIE method used a Rh catalyst to incorporate one deuterium atom at multiple benzylic positions. This led to a limited cyclic substrate scope and moderate deuterium incorporation.⁷⁶ Considering the prevalence of cyclic ring structures in pharmaceuticals,⁶⁴ we were interested in expanding our Cu-catalyzed transfer hydrodeuteration reaction to include cyclic alkenes and heterocycles where the double bond is contained in a ring. This would allow precision deuteration of cyclic hydrocarbon frameworks and heterocycles to expand access to selectively deuterated chromans and quinolinones.

Results and Discussion

A key challenge in our initial investigation of cyclic alkene substrate types under Cu-catalyzed transfer hydrodeuteration reaction conditions was reaching complete conversion to the desired selectively deuterated product. Full conversion to the preferred

product is important as the recovered starting material is difficult to separate from the product. Therefore, we investigated the optimal reaction conditions using 1,2-dihydronaphthalene **1** as a substrate. We were pleased to observe that the reaction went to full conversion to the deuterated product using 2 mol% catalyst loading, 2.2 mol% DTB-DPPBz ligand, ethanol-OD (2.6 eq), dimethoxymethylsilane (DMMS, 4 eq), and THF at 40 °C (Table 1, entry 1). Lowering the catalyst/ligand loading and silane loading, the reaction still proceeded yielded similar results to entry 1 (entry 2). Switching the deuterium donor to isopropanol-*d*8 resulted in full conversion to the desired product **2** (entry 3-4). However, investigating D₂O, methanol-OD and *tert*-butanol-OD as the deuterium sources was not effective as the reaction did not go to full completion (entry 5-7). Product **2** can also be obtained by changing the silane source to polymethylhydrosiloxane (PMHS) in a high yield (entry 8) as well as running the reaction at room temperature (entry 9). While entries 1-4, 8, and 9 resulted in complete conversion to the desired product, reaction conditions in entry 1 were generally used for evaluation for the substrate scope, because more challenging substrates such as those with heteroatom functionality or heterocycle did not always reach completion under milder conditions.

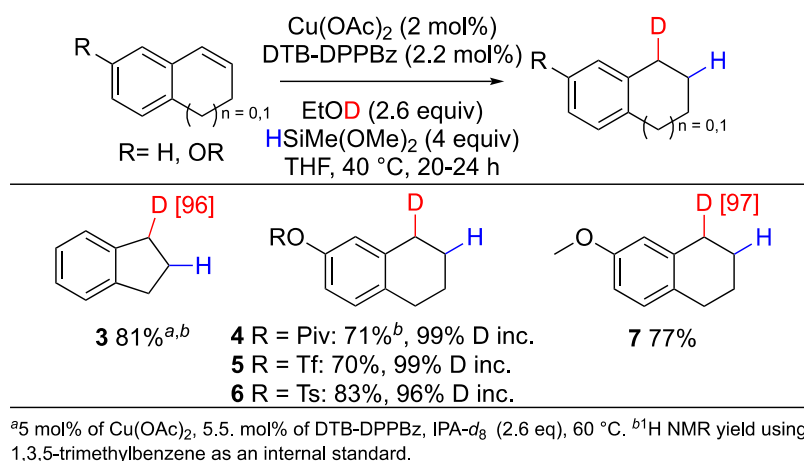
Table 1. Optimization table

Entry	D-Source	Silane	Yield ^a (%)	RSM (%)
1	EtOD	DMMS	77 ^b	-
2	EtOD	DMMS	80 ^c	-
3	EtOD	DMMS	91	-
4	IPA- <i>d</i> 8	DMMS	77	-
5	D ₂ O	DMMS	17	83
6	MeOD	DMMS	47	33
7	<i>t</i> BuOD	DMMS	65	10

8	EtOD	PMHS	90	-
9	EtOD	DMMS	85 ^d	-

All deuterium incorporations greater than 95%. With optimal conditions (Entry 1), deuterium incorporation is 98% ^a¹H NMR yield using 1,3,5-trimethylbenzene as an internal standard ^bisolated yield ^c1 mol % catalyst loading ^dreaction performed at rt.

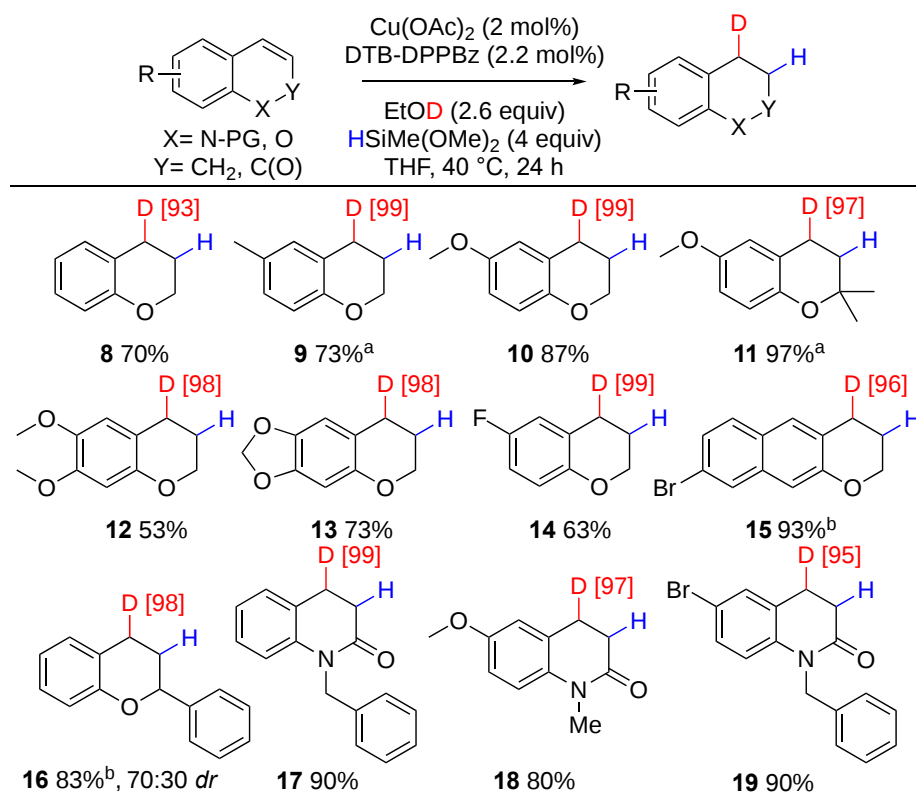
In the substrate scope, we first explored an unsaturated bicyclo[4.3.0] component that underwent transfer hydrodeuteration successfully. This was demonstrated on 1*H*-indene reducing to the desired deuterated product (Scheme 1, **3**, 85% by ¹H NMR yield). In this example, the initial reaction did not go to full completion using Table 1, entry 1 conditions. Therefore, we found that with 5 mol% catalyst/5.5% ligand loading, isopropanol-*d*8 (2.6 eq.), and at 60 °C the desired deuterated product **3** could be obtained. We continued to expand the substrate scope with our optimized conditions to more complex substrates beginning with hydrodeuteration of dihydronaphthyl derivatives. Reduction of the 1,2-dihydronaphthylene derivatives will form the bicyclic products, a common structural feature of several important natural product classes, such as steroids and diterpenes. Dihydronaphthyl derivatives protected with electron-withdrawing protecting groups such as pivalate (Piv), triflate (Tf), and toluenesulfonyl (Ts) functionalities were tolerated under transfer hydrodeuteration reaction conditions (**4-6**, 70%-83% yield). Additionally, an electron-rich dihydronaphthyl derivative was reduced to the deuterated product **7** in 77% yield, indicating that electronics do not have a negative impact on cyclic alkenes undergoing transfer hydrodeuteration.



Scheme 1. Transfer hydrodeuteration of 1*H*-indene and dihydronaphthyl derivatives

We were also interested in subjecting other common cyclic alkene motifs to transfer hydrodeuteration reaction conditions, including those containing heteroatoms (Scheme 2). An important class of heterocyclic compounds are 2*H*-chromenes, which exhibits a variety of biological activities.⁷⁷ Subjecting these scaffolds to transfer hydrodeuteration conditions would deliver the *dI*-chromane derivative. These chromane scaffolds have structural features of small molecule drugs and vitamins, such as vitamin E and nebivolol. Under transfer hydrodeuteration conditions, we were able to isolate deuterated products **8**, **9**, **10** in high yields (**8-10**, 70%-87%). A deuterated chromane containing a structural analogue of tocopherol was isolated in high yield (**11**, 97% yield). Substrates containing highly electron-rich arenes were also accessible in good to high yields (**12-13**, 53%-73% yield). 2*H*-chromene with electron-withdrawing functionality did not have a detrimental impact on reactivity (**14**, 63% yield). A fused tricyclic chromane-*dI* was isolated in a high yield although a higher catalyst loading was utilized (**15**, 93% yield). A substrate containing a sterically constrained environment proximal to the olefin did not affect the reactivity and a high deuterium incorporation was obtained with a diastereomeric ratio of 70:30 (**16**, 83%).

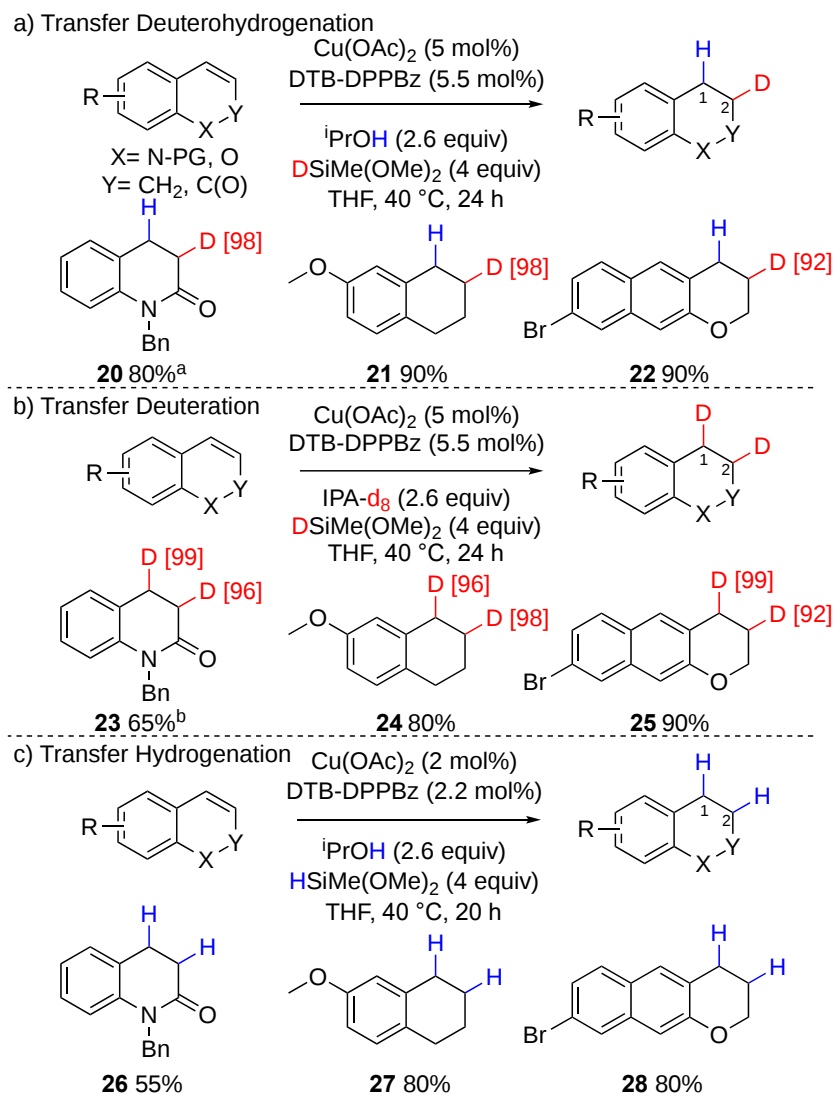
Quinolinone substrates were also of interest for our transfer hydrodeuteration protocol as they are prevalent in pharmaceuticals and natural products with anticancer, antiviral, and antihypertensive properties.^{78,79} We were pleased to observe that the carbonyl of the aryl unsubstituted α,β -unsaturated amide **17** did not reduce and the reaction was chemoselective for only the olefin. We were able to isolate deuterated product in a 90% yield (Scheme 2). Introducing different electron densities to the bicyclic structure such as a methoxy group **18** and a bromine group **19**, did not impact the reactivity negatively and the deuterated product was isolated in good yields (80%-90% yields).



^aIPA- d_8 (2.6 equiv) used instead of EtOD. ^b5 mol% $\text{Cu}(\text{OAc})_2$, 5.5 mol% DTB-DPPBz, and IPA- d_8 (2.6 equiv) used.

Scheme 2. Transfer hydrodeuteration of chromenes and quinolinones

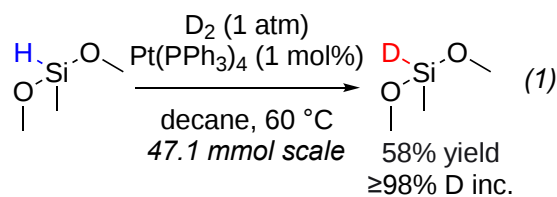
We previously discussed that in our Cu-catalyzed transfer hydrodeuteration reaction, regioselectivity can be controlled by modifying the transfer reagents. This important feature of our reaction design allows the possibility of accessing multiple products such as the mono-deuterated product at the benzylic or homobenzylic site. The di-deuterated product can also be obtained where the deuterium atom is at both the benzylic and homobenzylic sites or the hydrogenated product can be synthesized. We first investigated a regioselective incorporation of deuterium at the homobenzylic position by switching to a deuterated silane ($\text{DSiMe}(\text{OMe})_2$) and isopropanol (Scheme 3a). This reaction was performed across three distinct cyclic alkene substrate types including a quinolinone, dihydronaphthalene and *2H*-chromene leading to the selectively deuterated product **20-22** with high deuterium incorporation at the homobenzylic position (80%-90% yield). Transfer deuteration reactions were also explored to obtain the di-deuterated products. Di-deuterated products **23-25** with one deuterium atom at the benzylic (C1) and homobenzylic (C2) position was obtained by using deuterated silane and isopropanol-*d*8 (Scheme 3b, 65%-90% yield). Lastly, transfer hydrogenation reactions were performed changing to the transfer reagents to normal isotopic species and resulted in **26-28** being isolated in moderate to good yield (Scheme 3c, 55%-80% yield).



^aUsed EtOH (2.6 equiv) instead of $i\text{PrOH}$, 2 mol% Cu(OAc)_2 , and 2 mol% DTB-DPPBz.

^bUsed EtOD (2.6 equiv) instead of IPA-d_8 , 2 mol% Cu(OAc)_2 , and 2 mol% DTB-DPPBz.

Scheme 3. Examples of transfer deuterohydrodenation, deuteration and hydrogenation



In previous reports of switchable selectivity pertaining alkyne and alkene transfer hydrodeuteration reactions, we were only able to ready modest levels of deuterium

incorporation at the target site.^{37,63} We hypothesized this was due to the synthesis of DSiMe(OMe)_2 where hexane is used as a solvent and purification included a distillation after the reaction reached completion. After distillation, the deuterated silane was isolated in hexane. However, hydrogen impurities in hexanes or exposure of the DSiMe(OMe)_2 to air or water will likely impact the deuterium incorporation levels in transfer hydrodeuterations/deuteration reactions even with precaution. Therefore, we modified the procedure using decane as a solvent for the synthesis of DSiMe(OMe)_2 , allowing for DSiMe(OMe)_2 to be isolated neat after distillation (Eq 1). Eventually, higher levels of deuterium incorporation at the homobenzylic site (>90% in all cases) could be achieved with this modified protocol.

Conclusion

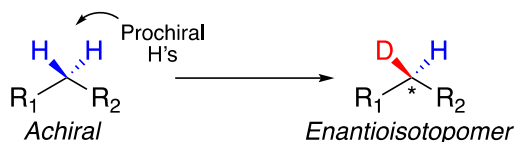
In summary, we expanded the substrate scope of our previous work by demonstrating a highly selective transfer hydrodeuteration to cyclic olefins, including those that are a part of motifs commonly found in biologically active molecules. Scaffolds such as dihydronaphthalene, chromene, and quinolinone were shown to undergo selective transfer hydrodeuteration. We were also able to install one deuterium atom at the homobenzylic position by switching the deuterium and hydrogen transfer reagents. Furthermore, chemoselective transfer hydrogenation and deuteration reactions of cyclic alkenes were performed. We anticipate this methodology will facilitate future studies that utilize selectively deuterated small molecules.

CHAPTER 5

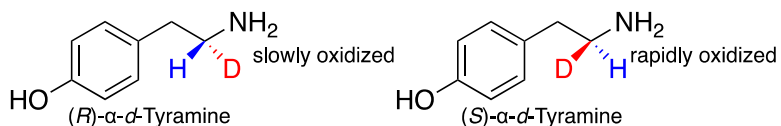
Enantioselective Synthesis of Enantioisotopomers with Quantitative Chiral Analysis by Chiral Tag Rotational Spectroscopy⁸⁰

Introduction

Chiral by virtue of deuterium compounds are chiral due to hydrogen/deuterium isotopic substitution also known as enantioisotopomers (Scheme 1). This fundamentally small difference in isotopically chiral molecules pushes the limits of both synthesis and spectroscopic analysis. These chiral molecules have inspired impacting discoveries in asymmetric synthesis,^{81,82} elucidation of enzymatic mechanisms,^{83,84} polymer chemistry,^{85,86} and spectroscopy.⁸⁷⁻⁹² Furthermore, in medicinal chemistry, chiral recognition, and stereochemistry of an atom in a bioactive molecule is important because enzymes display a high degree of optical specificity between enantioisotopomers (Scheme 2). Other than introducing deuterium atom to increase drug half-lives, deuterium substitution can be used to stabilize enantiomers of a drug into the desired orientation.¹³



Scheme 1. Chiral by Virtue of Deuterium Substitution



Scheme 2. Enzyme differentiation of chiral isotopologues

Despite the huge impact that enantioisotopomers have in chemical research, there are no general and highly selective protocols for their synthesis. Practical methods to

access, prepare, and characterize enantioisotopomers has been a challenge highlighted over the decades in the pursuit of synthesizing (*S*)-ethylbenzene-*d*1 in high enantiopurity. In 1978, the Mosher group provided a lengthy 7-step synthesis to obtain (*S*)-ethylbenzene-*d*1 in an overall 34% yield with assumed high enantiopurity (See SI for synthesis).⁹³ In 2019, the Christoffers group offered a 2-step route to make (*S*)-ethylbenzene-*d*1 and then developed another 2-step derivatization of (*S*)-ethylbenzene-*d*1 to generate diastereomers for enantiomeric excess (EE) determination (See SI for synthesis).⁹⁴ These synthetic routes usually require an enantioenriched starting material, are low yielding, and lack sufficient characterization.

The scarcity of analytical techniques for establishing absolute configuration at the stereogenic center and measuring enantiomeric excess has been a challenge for the preparation and characterization of enantioisotopomers. Analytical techniques such as direct liquid chromatography have been demonstrated on a small number of analytes containing a highly deuterated phenyl substituent.^{95,96} However, these separations are time consuming, and the absolute configuration can only be established through comparisons between retention times of structurally similar analytes requiring additional synthetic work. Nuclear magnetic resonance (NMR) spectroscopy has been used to measure enantiomeric excess of enantioisotopomers using chiral derivatization. Chiral derivatization approaches require molecule specific development of the derivatizing agent and eventually poses a challenge for high confidence absolute configuration determination.⁹⁴ With many challenges to synthesize and characterize chiral by virtue of deuterium substitution compounds, we report the first one-step and highly enantioselective Cu-catalyzed synthesis of enantioisotopomers along with the first general spectroscopic technique for assignment

of the absolute configuration and quantitative determination of the enantiomeric excess using molecular rotational resonance spectroscopy.

Results and Discussion

There are four unique strengths of rotational spectroscopy for the isotope analysis:

1) Each chemically distinct isotopic variant has a unique spectral signature. 2) Complex isotopic mixtures can be analyzed without chromatographic separation because of the exceptionally high spectral resolution of MRR allowing it to be possible to measure the spectrum without overlap. This is important because separation of isotopic mixtures is generally impossible. 3) All isotopic species have the same equilibrium geometry, and this geometry is used to calculate the transition frequencies for all isotopic variants. 4) The equilibrium geometry can be calculated to high accuracy by quantum chemistry, permitting high confidence identification of isotopic species without the need for reference compounds.

The focus of this work is the analysis of enantioisotopomers, which have identical rotational spectra at any practical spectral resolution. However, MRR analysis occurs in the gas phase and uses noncovalent derivatization of the enantioisotopomer with a small chiral molecule of known configuration to produce distinguishable diastereomers. This small chiral molecule is called a chiral tag and is added to the neon carrier gas used in the molecular beam experiments. The chiral tag attaches to the deuterated sample (analyte) during the cluster formation in the pulsed jet expansion. Analysis of the spectra of these chiral tag complexes permits determination of both the absolute configuration and enantiomeric excess of the analyte.

This chiral tag analysis method is validated using samples of ethylbenzene-*d*1 prepared by two literature methods. The first sample from Mosher and coworkers uses a synthetic route designed to ensure high enantiopurity and known absolute configuration of the prepared (*S*)-ethylbenzene-*d*1 sample. The second sample is a method prepared by Christoffers and coworkers where they described a molecule-specific chiral derivatization method for NMR analysis to find EE=92.

The absolute configuration requires assigning a theoretical equilibrium geometry of the chiral tag complex to each observed rotational spectrum. Under the Born-Oppenheimer approximation, all isotopic variants of the chiral tag complex have the same equilibrium geometry. As a result, using the normal isotopic species of the analyte, the non-deuterated sample, the validation of the geometry can be performed.

To determine the absolute configuration for ethylbenzene-*d*1, 1,1,1-trifluoroisopropanol (TFIP) was used as the chiral tag, with the initial analysis using the normal species of ethylbenzene. TFIP was chosen because of its high volatility. This is important as a gas mixture of the tag is needed in the neon carrier gas. TFIP also has a large dipole moment which will allow the signal strength to increase in the rotational spectrum of the tag complex. The equilibrium geometries for the chiral tag complex are obtained from quantum chemistry to estimate the rotational constants. The purpose of the theoretical rotational spectra of the complexes is to aid the analysis of the experimental spectrum. In general, several isomers of the tag complex are formed in the pulsed jet expansion and can be identified. The lowest energy structure for ethylbenzene/TFIP complex is shown in Figure 1.

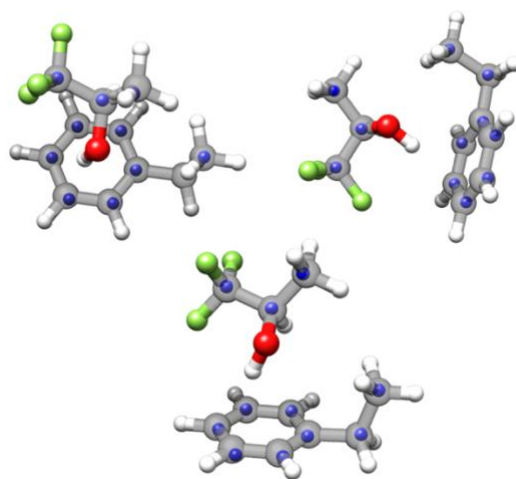


Figure 1. Three different views of the lowest energy chiral tag complexes formed between ethylbenzene and 1,1,1-trifluoroisopropanol. The full structure us the equilibrium geometry obtained from quantum chemistry. The blue spheres are experimental carbon atom positions that are superimposed on the quantum chemistry structure.

The absolute configuration of ethylbenzene-*d*1 is established in two steps illustrated in Figure 2A, using a sample prepared by Mosher and coworkers. The first measurement uses a racemic sample of the TFIP tag molecule to ensure that both the homochiral and the heterochiral complexes are formed regardless of the enantiopurity of the analyte. The homochiral and heterochiral designations use the Cahn-Ingold-Prelog labeling of the chiral centers, where they are either (*R*) or (*S*) defined by ranking the priority of the groups attached to the chiral center, in ethylbenzene-*d*1 and TFIP. The ability to generate both diastereomers improves the confidence in assigning a spectrum to either the homochiral or heterochiral complex. A comparison of the theoretical rotational spectra of the homochiral and heterochiral complexes experiment is shown in Figure 2A. The spectrum prediction uses the equilibrium geometry from quantum chemistry to obtain the rotational constants of each diastereomer. The theoretical predications are a close match to the experimental spectra, which will help assign the spectra for the homochiral and heterochiral tag

complexes. The position of the deuterium atom can be determined using Kraitchman's method from the assigned spectra.⁹⁷ Carbon to hydrogen bonds and carbon to deuterium bonds can be expected to give different average bond lengths but are too small to affect analysis conclusions.⁹⁸ This structural information is reported in Table 1 to support the identification of the homochiral and heterochiral tag complexes. The results for the analysis of the second highest intensity spectrum of the ethylbenzene/TFIP complex are also reported in Figure 2A and in Table 1(Isomer 2).

Table 1. Spectroscopic results used to establish the absolute configuration of the enantioisotopomers

		Normal Species Chiral Tag Complex ^a				Coordinate ^b	<i>d1</i> -Heterochiral		<i>d1</i> -Homochiral	
		Rotational Constant	Theory	Exp	Error (%)		Theory	Exp	Theory	Exp
Ethylbenzene	Isomer 1	A / MHz	836.2805	842.60004(2)	+0.75	a / Å	3.849	3.731	4.034	4.082
		B / MHz	389.1585	377.19543(1)	-3.17	b / Å	1.558	1.596	1.598	1.673
		C / MHz	320.6218	312.716200(9)	-2.53	c / Å	1.214	1.430	0.529	0.316
	Isomer 2	A / MHz	788.1058	786.34600(3)	-0.22	a / Å	1.144	1.254	0.736	0.495
		B / MHz	388.0129	384.433110(9)	-0.93	b / Å	2.072	2.030	2.336	2.443
		C / MHz	324.3261	321.904190(9)	-0.75	c / Å	1.482	1.524	0.203	[0] ^c
2-Ethynaphthalene	Isomer 1	A / MHz	418.0842	414.112380(64)	-0.96	a / Å	0.056	[0] ^c	0.818	1.079
		B / MHz	352.6475	351.472620(47)	-0.33	b / Å	3.590	3.624	4.440	4.408
		C / MHz	247.8086	247.272360(48)	-0.22	c / Å	1.742	1.743	0.410	0.415
	Isomer 2	A / MHz	428.5449	422.465040(63)	-1.44	a / Å	3.973	3.700	2.813	2.765
		B / MHz	334.0264	335.780650(59)	+0.52	b / Å	2.567	2.790	2.555	2.681
		C / MHz	242.0888	241.910620(49)	-0.07	c / Å	0.491	0.431	1.808	1.785
3-Phenyl-1-propanol	Isomer 1	A / MHz	757.6193	749.80158(18)	-1.04	a / Å	1.048	1.192	0.386	0.587
		B / MHz	598.8914	588.92377(10)	-1.69	b / Å	2.395	2.349	1.408	1.352
		C / MHz	414.6116	407.15502(10)	-1.83	c / Å	1.843	1.850	1.744	1.697
	Isomer 2	A / MHz	799.1322	802.90592(21)	+0.47	a / Å	0.262	[0] ^c	1.901	2.334
		B / MHz	481.4207	468.04195(15)	-2.86	b / Å	1.546	1.533	2.156	2.020
		C / MHz	333.0144	326.033770(90)	-2.14	c / Å	1.644	1.634	1.663	1.644

a) The initial agreement of a calculated equilibrium geometry to an observed spectrum made by comparing the experimental and theoretical rotational constants of the complex formed between the tag and the normal species of the analyte. Isomers 1 and 2 are the highest intensity spectra. (b) The coordinated give the position of the hydrogen in the normal species chiral tag complex that undergoes deuterium substitution using the principal axis system for molecular rotation. (c) Denotes a small coordinate where the position determination is dominated by the inertial defect from zero-point motion from Kraitchman analysis.

The second measurement uses a high enantiopurity tag such as (*S*)-TFIP (EE=99.4). The Mosher synthesis was designed to produce (*S*)-ethylbenzene-*d*1 in high enantiopurity, so it is expected that the homochiral spectra will be observed at higher signal levels. As seen in Figure 3A, this result is found for both isomers of the chiral tag complex. The enantiomeric excess for ethylbenzene-*d*1 is obtained from the ratio of the transition intensities for homochiral and heterochiral complexes. This method has been presented in previous work.^{63,99} The measurement uses transition intensities from the spectrum acquired using the racemic tag sample to correct for the instrument response. The normalized transition intensities in the homochiral spectrum are defined as:

$$N_{Homochiral} = \frac{I_{enantiopure\ tag}}{I_{racemic\ tag}} \quad (1)$$

with a similar definition for the normalized heterochiral transition intensities. From any pair of homochiral and heterochiral transitions, the signal, *R*, is defined as:

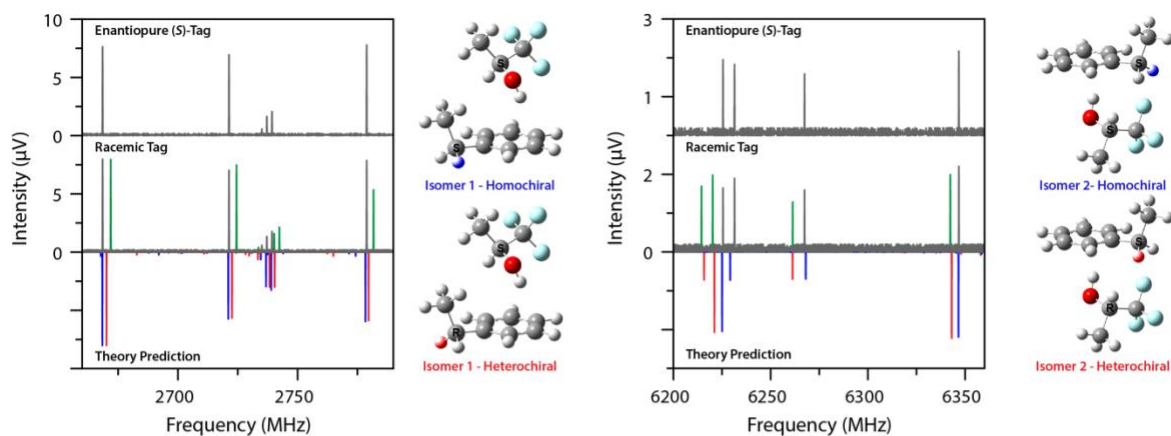
$$R = \frac{N_{Homochiral}}{N_{Heterochiral}} \quad (2)$$

This ratio is used to determine the enantiomeric excess through the expression:

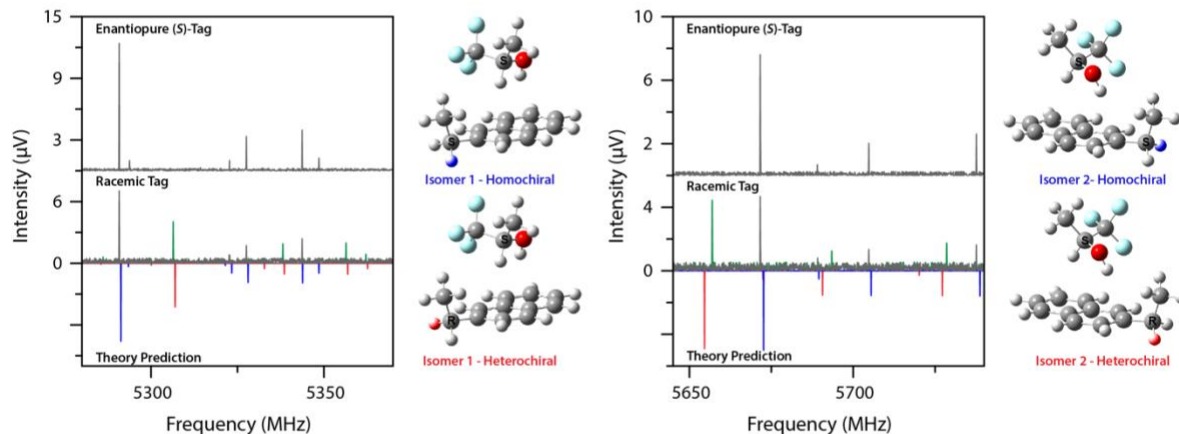
$$\frac{R - 1}{R + 1} = (ee_{tag})(ee_{analyte}) \quad (3)$$

where *ee* is the fractional enantiomeric excess for either tag or analyte (the usual present enantiomeric excess, EE, is related to the fractional *ee* through: EE = *ee* x 100). The tag EE is known from separate calibration measurements. For EE determinations using broadband rotational spectra, the average value of the EE is determined from all possible pairs of strong transitions in the homochiral and heterochiral spectra. The standard deviation of *R* is used to estimate the measurement uncertainty via the standard error.

A) Ethylbenzene-d1 / TFIP - Mosher Synthesis



B) 2-Ethynaphthalene-d1 / TFIP - CuH Synthesis



C) 3-Phenyl-1-propanol-d1 / PO - CuH Synthesis

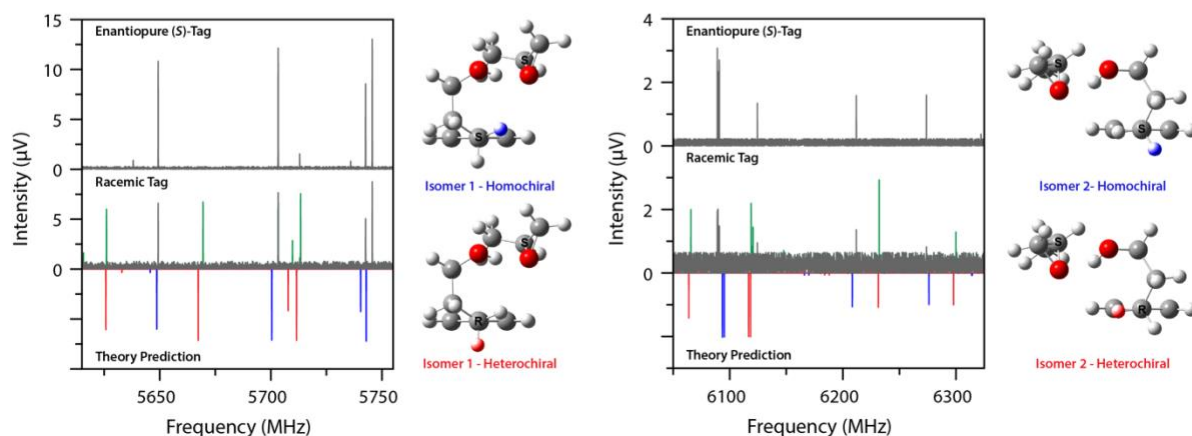


Figure 2. Illustrates how high-confidence assignment of the absolute configuration of the enantioisotopomers is made using MRR spectroscopy. (A) shows the results for the sample prepared by the Moser synthetic route. The left side of the panel in (A) shows the spectrum prediction from using the theoretical structure. The right side presents the spectrum predictions using the structure assigned to the second highest intensity experimental

spectrum (Isomer 2). The second half of the spectrum with the inversed transitions compares the theoretical spectra to the measurement using racemic TFIP (blue = homochiral, red = heterochiral). These figures only show a small portion of the overall rotational spectrum which is recorded over 2-8 GHz. Transitions associated with TFIP and ethylbenzene-*d1* has been cut from experimental spectra for clarity. The experimental spectra are assigned based on the patterns predicted using quantum chemistry structures (black = homochiral, green = heterochiral). (B) shows the spectrum analysis for sample 2-ethylnaphthalene-*d1* from CuH chemistry. (C) shows the spectrum analysis for sample 3-phenyl-propanol-*d1* from CuH chemistry. In both (B) and (C), the homochiral tag complex is dominant in the enantiopure tag measurement showing that the samples have the (*S*)-configuration with high enantiopurity.

The EE determination method is validated by using a sample prepared following the synthetic route of Christoffers and coworkers. In the synthetic route developed by the Christoffers group, EE was determined by a chiral derivatization NMR method. The chiral tag rotational spectroscopy measurement using this sample is shown in Figure 3A. In the same figure, a small spectral region of the enantiopure (*S*)-TFIP tag measurement is shown and is compared to the result for the Mosher synthesis as well as the Cu-catalyzed transfer hydrodeuteration synthesis. A key difference in the compared measurements is the significant intensity in the heterochiral spectrum for the Christoffers sample, indicating a higher level of (*R*)-ethylbenzene-*d1*. If the intensity of the heterochiral spectrum is significant, this implies a lower EE value. It was determined that the chiral tag rotational spectroscopy result is EE=85.7(3) after creating a histogram using 64 of the highest intensity transitions of the homochiral and heterochiral spectra shown in Figure 3B. The reproducibility of the method was tested by performing three separate measurements over different days with results: 85.7(3), 85.4(3), 85.5(2). The value in the parentheses is the 1 σ standard error in the units of the last decimal place.

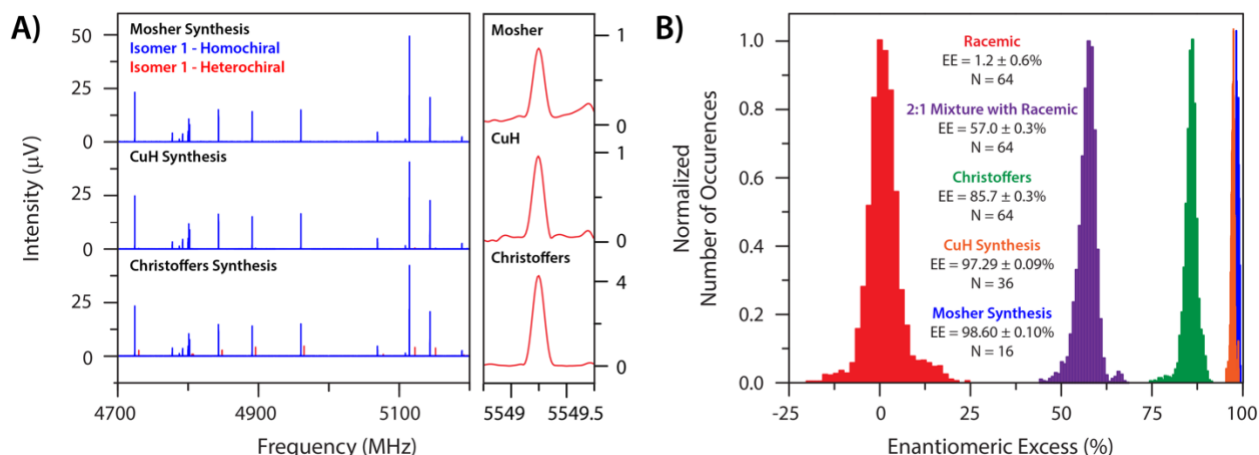


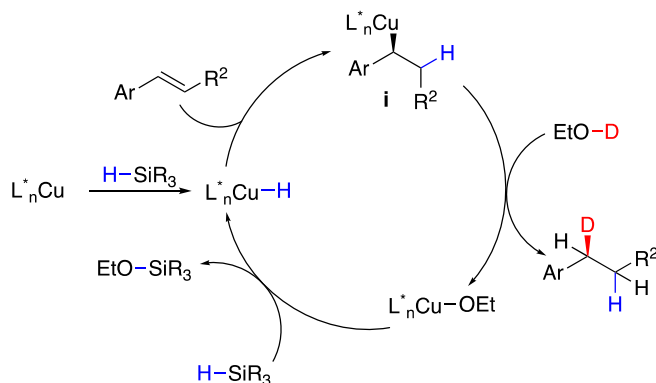
Figure 3. Enantiomeric excess determination for the three ethylbenzene-*d*1 samples used in this study. (A) shows the spectroscopic measurement using enantiopure (*S*)-TFIP tag for the three samples, in a small frequency range of the full spectrum. Transitions relating to the heterochiral complex (*R*)-ethylbenzene-*d*1. An expanded scale view of the spectrum is centered on the strongest transition showing the heterochiral signals in the Mosher, CuH, and Christoffers samples. (B) shows the histogram distribution of the pairwise EE values. EE determination uses the statistics from all pairwise using individual transitions from the homochiral and heterochiral spectra. Fewer transitions are used in the Mosher and CuH analyses due to their higher enantiopurity compared to the Christoffers samples.

Since there are no existing reference methodologies, it is difficult to validate the accuracy of the chiral tag method for applications to enantioisotopomers. Therefore, we made a test of the accuracy of Eq. (3) over the full EE scale. A racemic sample of ethylbenzene-*d*1 was prepared using racemic starting materials in the Christoffers synthesis. The EE determination for this sample was an EE=1.2(6) (Figure 3B). A sample formed from a 2:1 mixture of the enantioenriched and racemic Christoffers samples were also analyzed. The racemic preparation of the EE using the chiral tag rotational spectroscopy result for the enantioenriched sample is EE=55. The chiral tag spectroscopy determination for sample was in good agreement: EE=57.0(3) (Figure 3B). The Mosher sample has an EE=98.6(1) and validates that this designed synthesis gives (*S*)-ethylbenzene-*d*1 in high enantiopurity (Figure 3B). The (*S*)-ethylbenzene-*d*1 sample

prepared by the CuH reported in this work also has a high enantiopurity, EE=97.3(1) (Figure 3B).

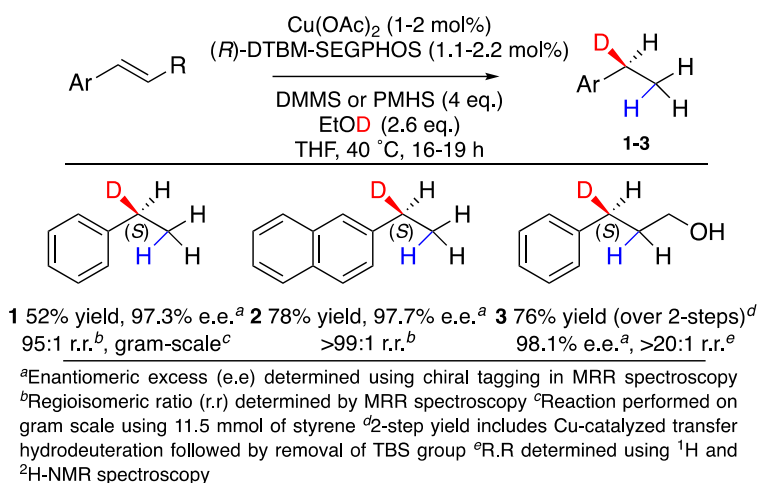
Our Cu-catalyzed transfer hydrodeuteration method is highly regioselective as reflected in our previous work. We believe that the observed regioselectivity is attributed to the high degree of catalyst control in the reaction. As the Cu species inserts across the alkenyl substrate, hydrogen and deuterium transfer reagents will operate at distinct points in the mechanism. Since regioselectivity for this reaction is already achieved, we propose that synthesizing enantioisotopomers could also be achieved by employing an appropriate chiral ligand in the reaction. Therefore, we adopted reaction conditions similar to those reported by us in prior work^{63,49} and motivated by highly enantioselective processes for [Cu—H] catalyzed alkene hydrofunctionalizations.^{38,42,47} This led us to select (*R*)-DTBM-SEGPBOS as the chiral ligand.

We hypothesized that using a chiral ligand, (*R*)-DTBM-SEGPBOS, under copper-catalyzed protocols would synthesize chiral-by-virtue of deuterium products in one step. In the proposed mechanism, Cu—H species is formed by transmetalation between the copper catalyst and the silane reagent. The regioselective insertion of the Cu—H into the alkene will lead to the alkyl copper intermediate **i**. Deuterodecupration of the alkyl copper species with ethanol—OD will yield the final product and in the presence of silane, the Cu—H is regenerated. The enantioselective step is hypothesized to be the insertion step of the Cu—H while the following step occurs with retention of configuration.³⁸



Scheme 1. Proposed mechanism for enantioselective transfer hydrodeuteration of aryl alkenes

For the enantioselective synthesis of ethylbenzene-*d1*, the reaction was performed on a gram-scale leading to a 52% yield of the desired product **1** after purification (Scheme 1). The absolute configuration and enantiomeric excess were determined using the chiral methodology as described above. The final deuterated product was revealed to be (*S*)-ethylbenzene-*d1* with an enantiomeric excess of 97.3. Possible isotopomer impurities and regioisomers from deuteration were found to be minimal as analyzed using the methods described in previous work.⁶³



Scheme 2. Cu-catalyzed enantioselective alkene transfer hydrodeuteration reaction scope

We extended this method to other aryl alkene substrates such as vinyl naphthalene and an internal alkene cinnamyl alcohol. We were able to isolate the deuterated product **2** in 78% yield. Product **2** was determined to have an EE = 97.7 and the *S* configuration at the established stereogenic center after chiral tagging analysis. The chiral tag measurement determining the absolute configuration is shown in Figure 2B, which also presents the high enantiopurity of the sample through the much lower transition intensity of the heterochiral complex (i.e. (*R*)-ethylnaphthalene-*d*1/(*S*)-TFIP) in the measurement using high enantiopurity (*S*)-TFIP tag. *Tert*-butyldimethylsilane protected cinnamyl alcohol underwent transfer hydrodeuteration with an isolated yield of 76% (over 2-steps) after deprotection. Alcohols do not inhibit the reactivity but a protecting group for the alcohol is required to avoid a competitive protodecupration pathway.³⁷ Analysis of the deuterated product **3** by MRR revealed the reaction to be highly enantioselective, EE = 98.1 and an *S* configuration at the stereogenic center (Figure 2C). In this example, propylene oxide was used as the tag molecule to take advantage of the strong hydrogen bond donor-acceptor interaction as shown in the structures of the tag complexes of Figure 2C. Figure 2C also demonstrates the high enantiopurity of the product by observing the low transition intensity for the heterochiral tag complex spectrum when (*S*)-propylene oxide is used as the tag.

Interestingly, when we utilized the (*R*)-DTBM-SEGPHOS ligand, we obtained the (*S*) stereogenic center. We hypothesize this is the case due to the steric bulk between the pseudoequatorial aryl groups on the ligand and the phenyl group on the substrate. Therefore, if the substrate approaches *re* face, there is less steric hinderance between the aryl groups on the substrate and on the ligand and the insertion of the Cu—H from the *re* face would result in the opposite enantiomer, (*S*).¹⁰⁰

Conclusion

In summary, a new synthetic methodology for the preparation of molecules chiral by virtue of deuterium substitution compounds is reported representing the first metal-catalyzed reaction for the enantioselective synthesis of enantioisotopomers. The synthetic methodology is a one-step Cu-catalyzed transfer hydrodeuteration reaction to prepare highly enantioenriched molecules precisely deuterated at the benzylic position from readily available alkene substrates. A full analysis of the isotopic composition of deuteration reaction products is possible using molecular rotational resonance spectroscopy. This work demonstrated the use of chiral tag rotational spectroscopy for the analysis of enantioisotopomers. Both the assignment of absolute configuration and the measurement of the enantiomeric excess are determined without the need for any reference samples of the analyte. We anticipate the synthetic and spectroscopic advances discussed will enable future developments in precision deuteration reactions and will serve to expedite the use of enantioisotopomers as novel tools or molecule entities in high impacting chemistry research.

CHAPTER 6

Rapid Enantiomeric Excess Measurements of Enantioisotopomers by Molecular Rotational Resonance Spectroscopy¹⁰¹

Introduction

In our initial studies of highly enantioselective deuteration reactions, we discovered several reactions that resulted in diminished EE of the enantioisotopomer product. We noticed that substrates containing *N*-heterocycles were producing a drop in EE of the final product. Given the ubiquity of pyridine and quinoline heterocycles in drug molecules,⁶⁴⁻⁶⁵ we explored further reaction optimization studies with substrates containing these heterocycles to try and improve the diminished EE. However, a high-throughput technique for the rapid measurement of EE for enantioisotopomers is required to support reaction optimization. A high-throughput technique consuming minimal amount of sample, short analysis time, and provides reproducible and reliable data is ideal. High-throughput techniques are necessary for EE determination as they provide the ability to screen catalysts for asymmetric reactions and to develop chiral building blocks in drug discovery.^{102,103} MRR spectroscopy is an emerging spectroscopic technique for analytical chemistry as it offers high chemical specificity allowing the presence of regioisomers or diastereomers to be solved directly from the crude reaction mixture.¹⁰⁴ MRR spectroscopy has recently been extended to chiral analysis using chiral tag rotational spectroscopy. This measurement methodology is extended in the present analysis of enantioisotopomers. Motivated by the lack of existing techniques for rapid measurement of EE for enantioisotopomers, this work focuses on developing the first high-throughput chiral tag technique for EE determination of enantioisotopomers. We also present a method by which the EE of a new

enantioisotopomeric compound can be determined without the need for any spectroscopic analysis.

Results and Discussion

Principles and advantages of MRR spectroscopy have been described in previous chapters (Ch. 4 and Ch. 5). Principles of chiral tag rotational spectroscopy will be briefly described. MRR spectrometers operate in either broadband^{105,106} or narrowband modes^{74,107,108}. Broadband spectrometers use chirped-pulse excitation to achieve large excitation bandwidths recording a large portion of the MRR spectrum for spectroscopic analysis, however, this method is time consuming due to assignment of spectra to specific geometries based on agreement of experimental and theoretical rotational constants. Additionally, broadband rotational spectroscopy requires about 2 hours and consumes about 100 mg of sample. These conditions are rather unfavorable for reaction condition screening studies or applications requiring rapid EE monitoring. Narrowband instruments perform measurements in a cavity resonator – pioneered by Balle and Flygare.⁷⁴ The resonator restricts the measurement to a single transition of the full spectrum, but the use of a high-quality factor (Q) cavity significantly enhances the detection sensitivity, reducing measurement time and sample consumption. This design is compatible to chemical monitoring applications^{107,109} and is employed in this work for high-throughput EE measurements. Both instrument designs offer remarkably high spectral resolution with the advantage that there is negligible overlap in spectral patterns of different species, even for complex mixtures, thus; the method does not require chromatography to separate the mixture prior to analysis.

Chiral molecules exist in two forms called enantiomers, which are identical but can behave differently when placed in a chiral environment. Since MRR spectroscopy performs measurements on isolated, freely rotating molecules, the rotational spectra of the enantiomers would be identical. Chiral derivatization, an approach also used for NMR spectroscopy, can also be used for MRR spectroscopy for chiral analysis.¹¹⁰⁻¹¹² In chiral derivatization, a single enantiomer of a new chiral molecule, called a chiral tag, is attached to the analyte to provide a local chiral environment that can differentiate the analyte enantiomers. Introducing a new chiral center will create distinguishable molecules known as diastereomers. The new chiral molecule will create tag-analyte diastereomers and can be designated as homochiral when the two chiral centers both have (*S*) or (*R*) chirality, and heterochiral when the labels differ. Chiral derivatization in chiral tag MRR spectroscopy uses non-covalent interactions such as hydrogen bonds to attach the derivatizing agent.^{99, 113-117} Clusters of the tag and analyte are automatically generated when the tag is added to the neon gas carrier, which is used to introduce the sample into the vacuum. This derivatization method requires no additional chemical preparation step, and the non-covalent interactions will not cause racemization in the analyte that would compromise the measurement accuracy.

The chiral tag methodology involves two measurements, which is discussed in the previous chapter. First, a spectrum of the complexes formed between the analyte and a racemic sample of the tag is obtained. This is used to calibrate the instrument response as well as spectroscopic factors that determine the measured signal intensities. Second, a high enantiopurity tag sample is used to obtain a second spectrum enabling the enantiomer composition of the analyte based on the relative signal intensities. The derivation of the

formula used to determine the enantiomeric excess has one fundamental assumption: the number densities of the homochiral and heterochiral complexes are linearly proportional to the number of the tag and analyte in the pulsed jet expansion.¹¹³ Under this assumption, the intensities for rotational transitions in the spectra of the homochiral and heterochiral tag and analyte complexes can be written:

$$I_{Homo} = C_{Homo}([(+)\text{-Analyte}][(+)\text{-Tag}] + [(-)\text{-Analyte}]((-)\text{-Tag})) \quad (1)$$

$$I_{Hetero} = C_{Hetero}([(-)\text{-Analyte}][(+)\text{-Tag}] + [(+)\text{-Analyte}]((-)\text{-Tag})) \quad (2)$$

The constants, C_{Homo} and C_{Hetero} include the instrument response functions, spectroscopic factors that determine the transition intensity, and the populations of the homochiral and heterochiral complexed in the pulsed jet expansion. The EE determination uses the normalized transition intensities using the intensities in the spectra acquired using the racemic and enantiopure tag. Equations can be found in the previous chapter.

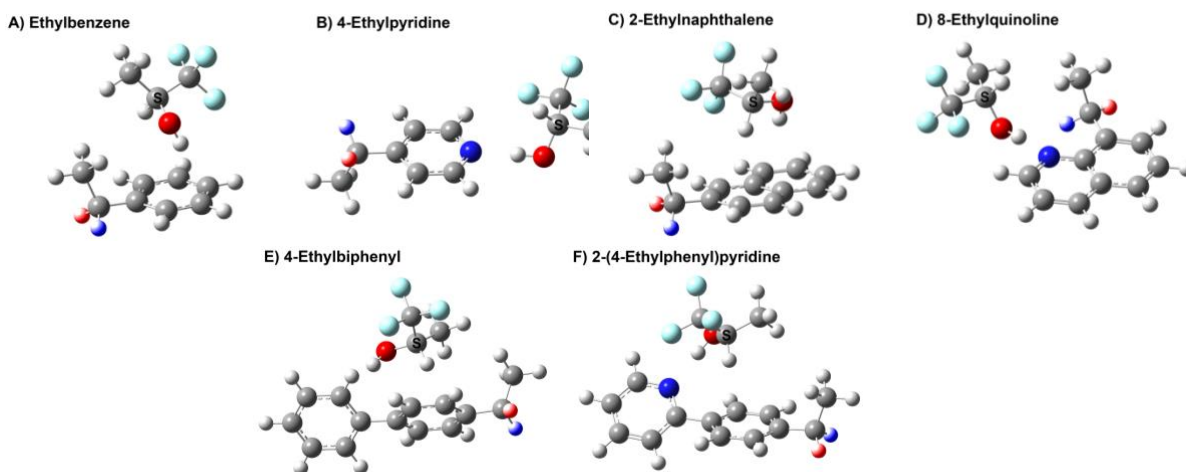


Figure 1. Structures between (*S*)-1,1,1-trifluoro-propan-2-ol and the six reaction products from the copper-catalyzed transfer hydrodeuteration reaction are presented. In each case, the lowest energy isomer of the chiral tag complex is shown. This is obtained from quantum chemistry. MRR spectra corresponding to these geometries are observed in the broadband MRR measurements. The prochiral positions shown in blue produce the (*S*)-enantiomer of the analyte, while the red positions give the (*R*)-enantiomer.

The chiral tag method is illustrated in Figures 1 and 2 for a set of deuterated compounds produced using the enantioselective Cu-catalyzed transfer hydrodeuteration reaction chemistry. There are three sets of analytes that are structurally similar, with one analyte in each set containing a nitrogen atom. Figure 1 presents the quantum chemistry structures of the chiral tag complexes formed between the deuterated reaction product and the enantiopure tag, (*S*)-1,1,1-trifluoropropan-2-ol (TFIP) that give rise to the highest intensity spectra in a broadband MRR measurement. The transfer hydrodeuteration reaction chemistry installs a single deuterium atom at the benzylic carbon creating either the (*S*)-enantiomer (blue position) or the (*R*)-enantiomer (red position) of the analyte. When the analyte complex with (*S*)-TFIP is formed, the mass change associated with deuteration will make changes to the moments-of-inertia. With spectroscopic analysis, it's possible to associate a specific enantiomer of the reaction product with each observed rotational spectrum. However, spectroscopic analysis supported by quantum chemistry is required to assign the absolute configuration.¹¹⁶

The enantiomeric excess of the deuterated product is determined from the transition intensities in the rotational spectra of the homochiral and heterochiral tag complexes. This determination can be made using a single transition from the full spectral signature of each complex. The six compounds shown in Figure 1 are also shown in Figure 2 for enantiomeric excess determination. For each reaction product, the intensity of a single transition from the broadband MRR spectrum of the homochiral and the heterochiral complex is shown. The spectrum shown in black uses the racemic TFIP tag sample to calibrate the instrument response. The response factors (C_{Homo} and C_{Hetero}) are nearly identical because the homochiral and heterochiral complexes are isotopomers of each

other. The red spectrum shows the transition intensities when the measurement is performed with the high enantiopure (*S*)-TFIP (EE = 0.993). Since the tag is highly enantiopure, the ratio of the transitions in the (*S*)-TFIP tag measurement is a good approximation to the enantiomer ratio of the analyte. The EE value is determined from the average using several transition pairs from the homochiral and heterochiral MRR spectra described in the previous chapter. These results illustrate the generality of the chiral tag MRR method. A single tag molecule can be used to analyze a wide range of molecules and attach at any position to generate distinguishable spectra. This is because deuterium substitution at the two possible positions (benzylic and homobenzylic) will produce different mass distributions.

The results from broadband MRR spectrum measurements reveal that the high EE achieved for hydrocarbon reaction products is not maintained when a nitrogen atom is present. The spectra for the structurally similar 4-ethylbiphenyl-*dl* and 2-(4-ethylphenyl)pyridine-*dl* show a second measurement in blue where the reaction was performed at 3 °C instead of at room temperature. In both cases, the EE increased at lower temperature reaction conditions. This observation motivated a study of reaction conditions, changing both temperature and solvent to optimize the EE of 8-ethylquinoline-*dl* with the highest EE under room temperature reaction conditions.

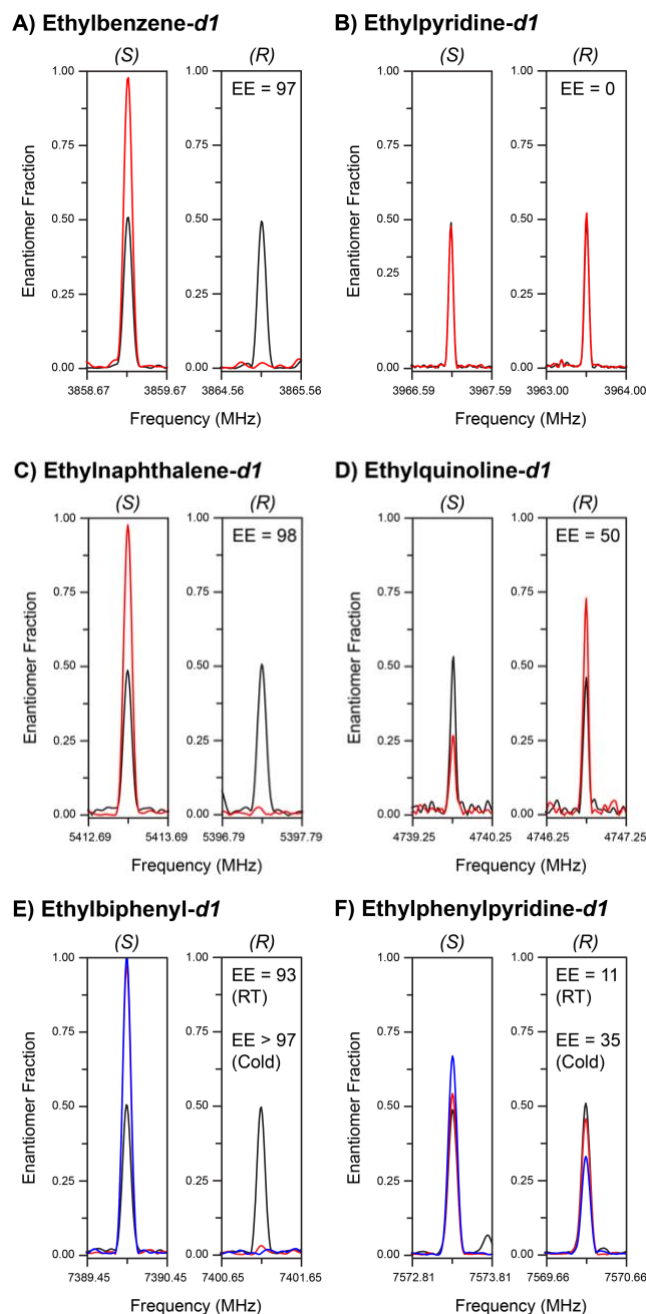


Figure 2. The EE measurements of the deuterated reaction products are illustrated. In each case, a single transition from the homochiral and heterochiral chiral tag complex MRR spectra is shown. Black = racemic tag sample, Red = high enantiopure (*S*)-TFIP. For the illustrated transitions, the racemic tag gives signal intensities that are approximately equal for the diastereomeric complexes. The red spectrum transition intensities reflect the enantiomer composition. For the hydrocarbon compounds, the reaction product has a high enantiomeric excess of the (*S*)-enantiomer. Whereas a lower EE is observed for nitrogen containing reaction products. For (E) and (F), a second sample was prepared and performed under cold room conditions and increased the EE (blue).

Since chiral tag MRR spectroscopy can be used in an efficient manner that avoids the need for any spectroscopic analysis, this technique allows for efficient sample analysis where a set of samples under different reaction conditions can be analyzed in a timely manner to obtain EE. Thus, chiral tag MRR spectroscopy is used to analyze 8-ethylquinoline-*d*1 where a set of samples are prepared under different reaction conditions to measure the optimal EE. As mentioned previously, the first step of the measurement requires identifying transitions in the MRR spectra of the homochiral and heterochiral complexes. This can be used for the determination of EE. This identification can be made using the variation in transition intensity in a broadband MRR measurement between the racemic and enantiopure tag measurements. A potential complication is the formation of several isomers of the chiral tag complexes in the pulse jet expansion. For example, in the 8-ethylquinoline/TFIP system, there are two isomers that dominate the isomer population (Figure 3). This is a spectroscopy-free analysis approach where it has the potential to select transitions from different isomers, whereas in the full spectroscopic analysis, transitions for the homochiral and heterochiral complexes of the parent structure are chosen for the EE analysis.

The EE analysis (based on Eq. (1) & (2)) will still be valid even if there are multiple isomers as long as the isomer populations are stable from measurement-to-measurement. This is assessed in Figure 4, where the histogram of EE determinations from pairs of homochiral and heterochiral transitions of the two isomers of the 8-ethylquinoline/TFIP complexes are compared. Within the measurement, the EE determination does not depend on the isomer chosen for either the homochiral or heterochiral transition.

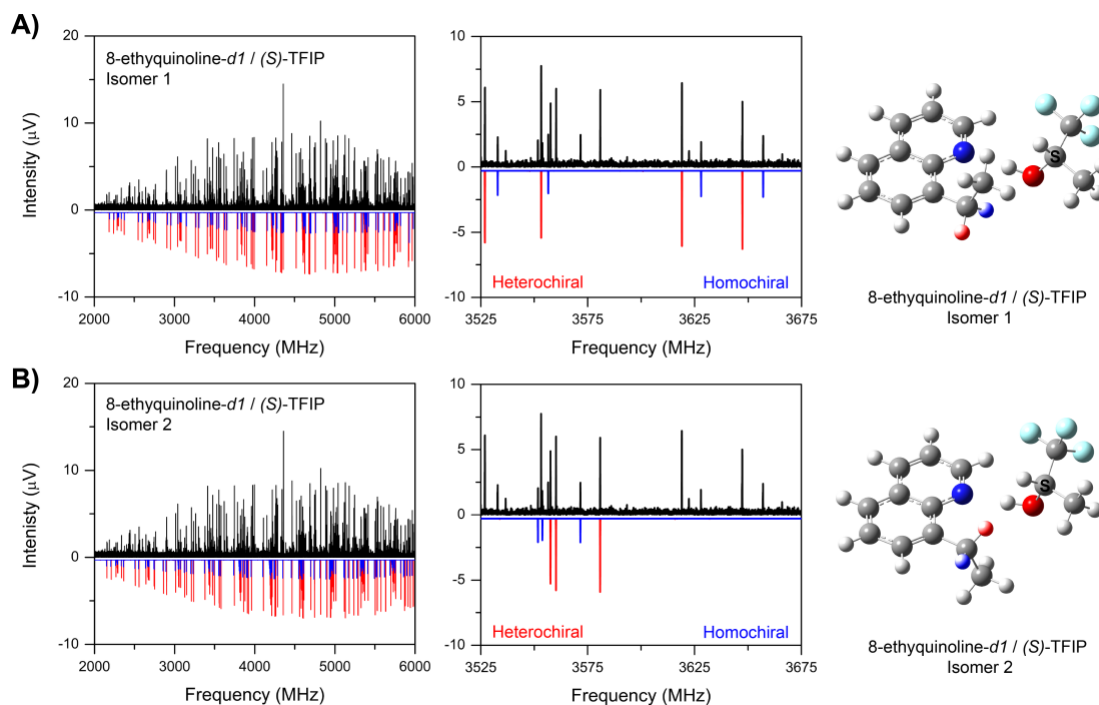


Figure 3. The broadband MRR spectrum of 8-ethylquinoline-*d*1 with (*S*)-TFIP is displayed. Left panel: shows the transition that require the presence of both the tag and analyte. Black: experimental, average of 65,000 acquisitions (a 40-minute measurement consuming approximately 20 mg of sample). Inverse transitions: calculated spectra for the homochiral (blue) and heterochiral (red) tag complexes shown in the right panel using the fit rotational constants. Middle panel: small frequency range of the spectrum is presented. The observation of a higher intensity spectrum for the heterochiral tag complex indicates that the (*R*)-enantiomer is in excess. (B) shows the experimental spectrum, but with the calculated spectra corresponding to the second highest energy isomer of the chiral tag complex identified using quantum chemistry. This second isomer accounts for the additional strong transitions as they can be seen by comparing middle panels (A) and (B).

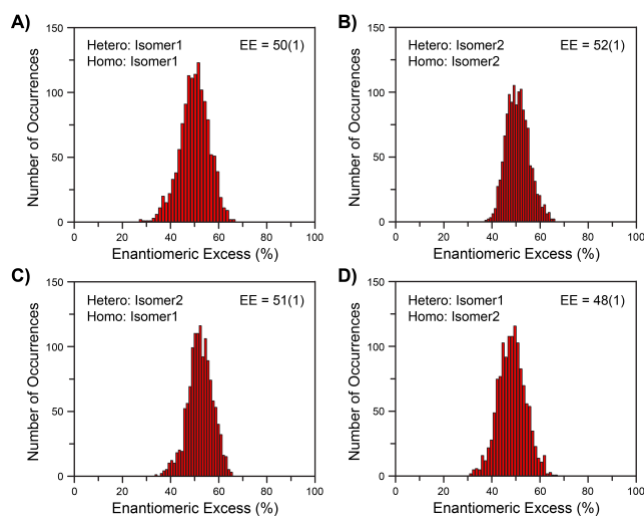


Figure 4. Enantiomeric excess determinations using 36 highest intensity MRR transitions in each isomer spectrum. The EE is obtained from the mean value set of transition pairs. The error estimate reported for the determinations is obtained from the standard error of the distribution. Panels (A) through (D) give similar EE values, indicating that the isomer ratios are stable in the MRR spectrometer.

The results implied in Figure 4 is that the normalized transition intensity is the same for all transitions in the rotational spectra of isomers of the homochiral and heterochiral complexes. This result is validated in Figure 5 where shows a histogram of measurements containing normalized transition intensities for the 100 most intense spectroscopic transitions of the chiral tag complexes. Only transitions related to the interaction of the tag and analyte are analyzed. Cutting out the transitions of the TFIP and 8-ethylquinoline-*dl* does not simultaneously remove a significant number of transitions associated with the tag complexes due to the high spectral resolution of MRR spectroscopy. Pairs of homochiral and heterochiral transitions are selected to determine the EE using Ch. 5 Eq (3), results are shown in Figure 5, without the need for any spectroscopic analysis. However, without spectral analysis, these transitions cannot be designated as homochiral or heterochiral, thus, the absolute configuration of the dominant enantiomer cannot be determined. Therefore, once a homochiral-heterochiral transition pair is selected based on the normalized transition intensity in the broadband spectrum, EE determinations can be performed using the narrowband MRR spectrometer to reduce measurement time and sample consumption. Figure 6 shows an example measurement, where the measurement requires measuring the intensities of two transitions corresponding to the different analyte enantiomers (at frequencies 6336.21 MHz and 6341.35 MHz).

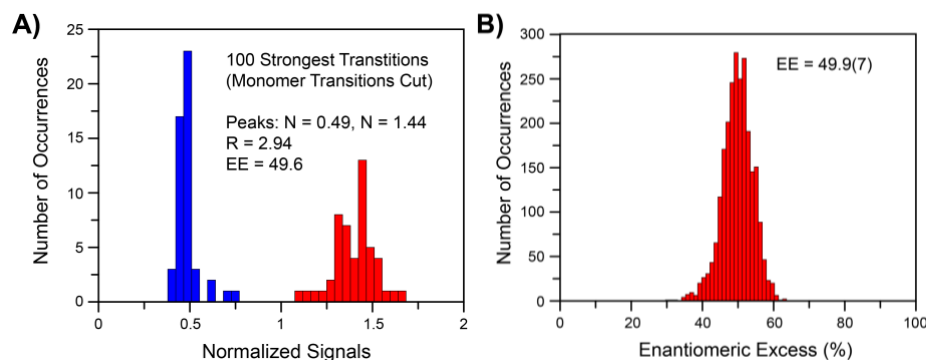
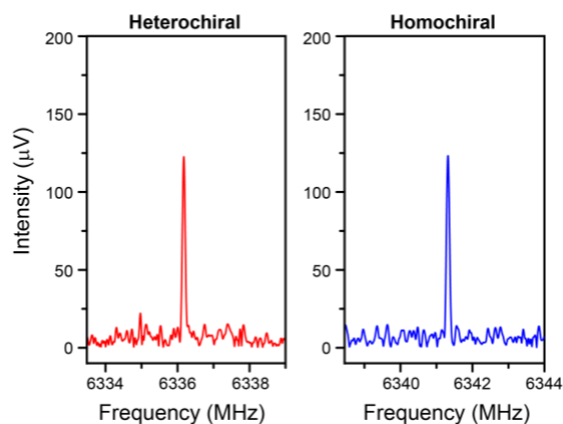


Figure 5. (A) the distribution of normalized transition intensities for the broadband MRR spectrum of Figure 3 is shown for the 100 highest intensity transitions of the chiral tag complex. (B) Using clear separation of the normalized intensities observed in (A), an EE determination is made from all transition pairs between the two sets. In this case, it is not possible to determine which enantiomer is in excess since no spectroscopic analysis is performed.

A) 8-ethylquinoline-d1 / RS-TFIP



B) 8-ethylquinoline-d1 / S-TFIP

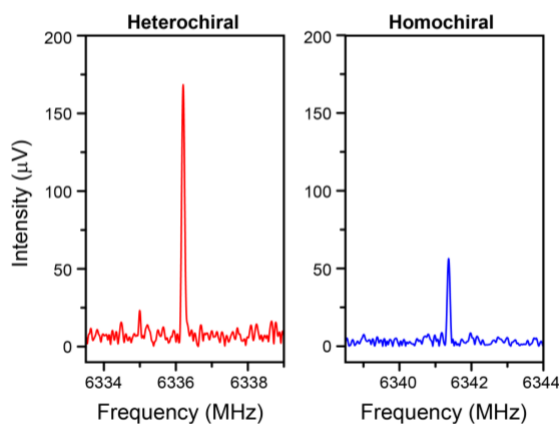
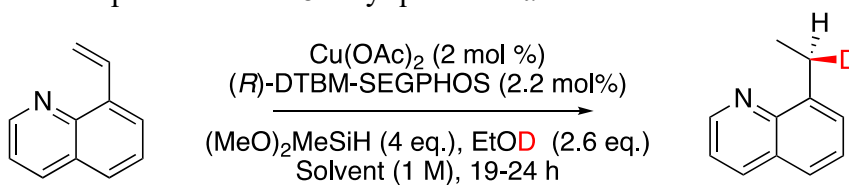


Figure 6. The narrowband (IsoMRR cavity-enhanced) spectrometer measurements are shown for one sample of 8-ethylquinoline-*d*1 (Table 1, Entry 1). (A) transitions intensities for racemic tag sample are used to calibrate the instrument response. (B) shows transitions

for the heterochiral and homochiral tag complexes using enantiopure tag ($EE = 0.993$). Heterochiral measurement time = 40 seconds, homochiral measurement time is 160 seconds.

The calibration process measures the transition using a racemic TFIP tag sample which are used to calculate the normalized transition intensities using Eq. (1) from Ch. 5 and then is used to calculate EE in Eq (5) from Ch. 5. The calibration step makes it possible to determine the number of averages required to measure the two transitions to sufficient sensitivity to make the EE determination. After this process is complete, the automated EE analysis proceeds using the enantiopure TFIP tag sample. In the 8-ethylquinoline-*dl* measurements, three separate EE determinations are performed for each sample for measurement precision. In all cases, the precision is about ± 1.5 in percent EE, which is comparable to chiral gas chromatography mass spectroscopy measurements. The signal intensity of a MRR transition of the 8-ethylquinoline-*dl* monomer is checked at the beginning and end of the measurement to verify that the sample is not depleted during chiral analysis. The measurement sequence for 8-ethylquinoline-*dl* was performed using 3 mg of sample and a cycle time including system purging to prepare subsequent analysis was 10 minutes. This is a significant reduction compared to the broadband MRR measurement methodology used for enantioisotopomer analysis.

Table 1. Reaction optimization of 8-ethylquinoline-*dl*



Entry	Solvent	Temperature	Yield ^a (%)	ee ^b (%)
1	THF	40 °C	82	47.8(1.5)
2	THF	rt	89	53.8(1.4)
3	THF	3 °C	77	48.0(1.5)

4	THF	-20 °C	87	49.5(1.5)
5 ^c	THF	-45 °C	41	48.2(1.5)
6	THF	-45 °C	45	49.6(1.5)
7	1,4-dioxane	3 °C	86	40.2(1.7)

Reactions were conducted on a 0.6 mmol scale. ^aYields are of the isolated product. ^bMeasurement uncertainties are the standard deviation from three replicate measurements. ^cProduct contained trace recovered starting material

The varying reaction conditions and EE determination for 8-ethylquinoline-*d*1 samples are reported in Table 1. The high-throughput EE determination on the 40 °C sample in THF solvent revealed to be EE = 47.8(1.5), is in good agreement with the broadband MRR spectroscopy EE determination, EE = 50(1). These two measurements used different samples that were prepared in different times. In the case of varying reaction conditions, changing temperature and solvent, the EE did not increase significantly. Therefore, other paths to improve enantiopurity still need to be explored. We hypothesize that the EE of 8-ethylquinoline-*d*1 is modest possibly because the nitrogen heteroatom can bind to the metal catalyst and decrease the EE.

Conclusion

In summary, we reported a rapid determination of EE for enantioisotopomers that are chiral by virtue of deuterium substitution by performing chiral tagging experiments on an isoMRR spectrometer. This is the first spectroscopic technique for high-throughput EE determination of enantioisotopomers where 1-3mg of sample are consumed for each measurement and 10-15 minutes for analysis. Additionally, we present that it is possible to perform the enantiomeric excess determination without assigning molecular spectra, giving the option to perform high-throughput reaction optimization without performing time-intensive spectroscopic analysis. This spectroscopic technique was developed to be useful

in supporting enantioselective reaction optimization involving the synthesis of both isotopically or non-isotopically labeled compounds.

CHAPTER 7

Highly Regioselective Copper-Catalyzed Transfer Hydrodeuteration of Unactivated Terminal Alkenes¹¹⁸

Introduction

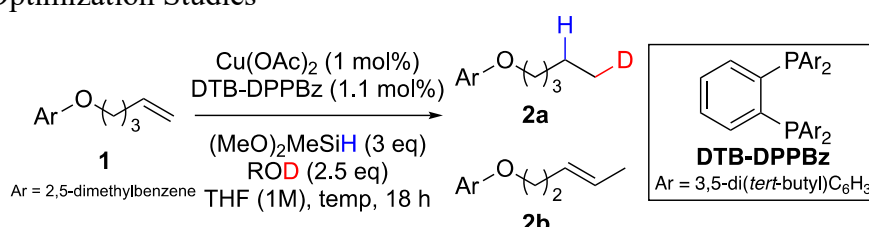
In our earlier work, we reported a mild and general Cu-catalyzed transfer hydrodeuteration reaction that regioselectively incorporated one hydrogen and one deuterium atom across both terminal and internal aryl alkene substrates.⁶³ This method afforded *dl*-alkanes selectively deuterated at the benzylic position. In the same work, we reported one example of an unactivated terminal alkene undergoing regioselective transfer hydrodeuteration. While we successfully isolated the deuterated product, it required that we change the deuterium source to isopropanol-*d*8 and increase the catalyst loading to 3 mol%. We were intrigued that reactions of unactivated terminal alkenes did not reach full conversion under standard conditions as there were trace alkene isomerization by-products forming. This posed two challenges. First, unreacted starting material is inseparable from the desired product using flash column chromatography purification techniques and second, an alkene isomerization product is not only inseparable but forms complex isotopomer product mixtures.

Metal-catalyzed unactivated terminal alkene transfer hydrodeuteration is not commonly reported and often presents very few examples. Webster and co-workers highlight the reactivity and selectivity challenges that hinder the development of a general protocol for selectively installing hydrogen and deuterium atoms across unactivated alkene substrates.³³⁻³⁵ While protocols using hydrogen deuterium gas or deuterium gas are sometimes reactive with unactivated alkenes, they are unable to discriminate between hydrogen and deuterium for regioselective hydrodeuteration.^{119,120} Under catalytic transfer

hydrodeuteration conditions, regioselectivity is not a challenge, but instead can promote competing alkene isomerization pathways which can possibly undergo transfer hydrodeuteration and lead to mixtures of inseparable isotopomers.³¹ This work focuses on developing a Cu-catalyzed transfer hydrodeuteration method of unactivated alkenes with high regioselectivity while avoiding alkene isomerization pathways.

Results and Discussion

Table 1. Optimization Studies

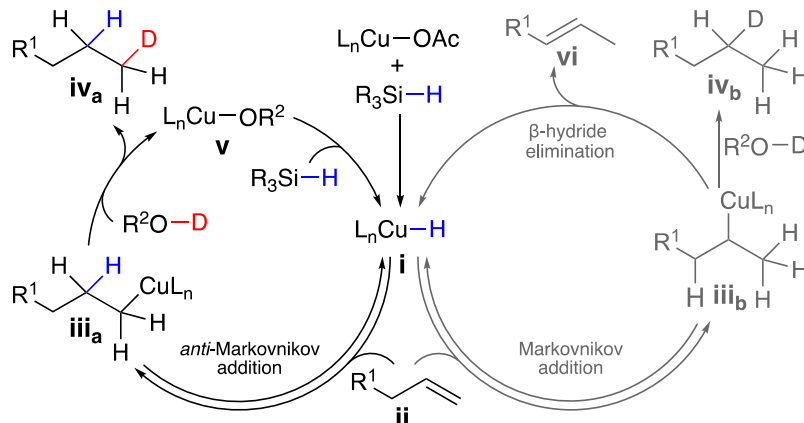


Entry	Temp. (°C)	D-Source	1 ^a (%)	2a ^a (%)	2b ^a (%)
1	40	EtOD	23	60	3
2	60	EtOD	-	85	7
3	23	EtOD	55	22	5
4 ^b	40	EtOD	32	34	2
5 ^c	40	EtOD	42	39	-
6 ^d	40	EtOD	80	-	-
7	40	IPA- <i>d</i> 8	6	70	-
8 ^e	40	IPA- <i>d</i> 8	-	90	-
9 ^e	40	<i>t</i> BuOD	-	55	-
10 ^e	40	MeOD	85	3	-
11 ^{e,f}	40	IPA- <i>d</i> 8	7	80	-

All reaction performed on a 0.2 mmol scale. ^aYields were determined after purification by flash column chromatography ^bReaction performed at 2 M concentration ^cReaction performed with PhCH₃ instead of THF ^dReaction performed with CH₂Cl₂ instead of THF ^eReaction performed with 3 mol% Cu(OAc)₂ and 3.3 mol% DTB-DPPBz ^fReaction performed with polymethylhydrosiloxane

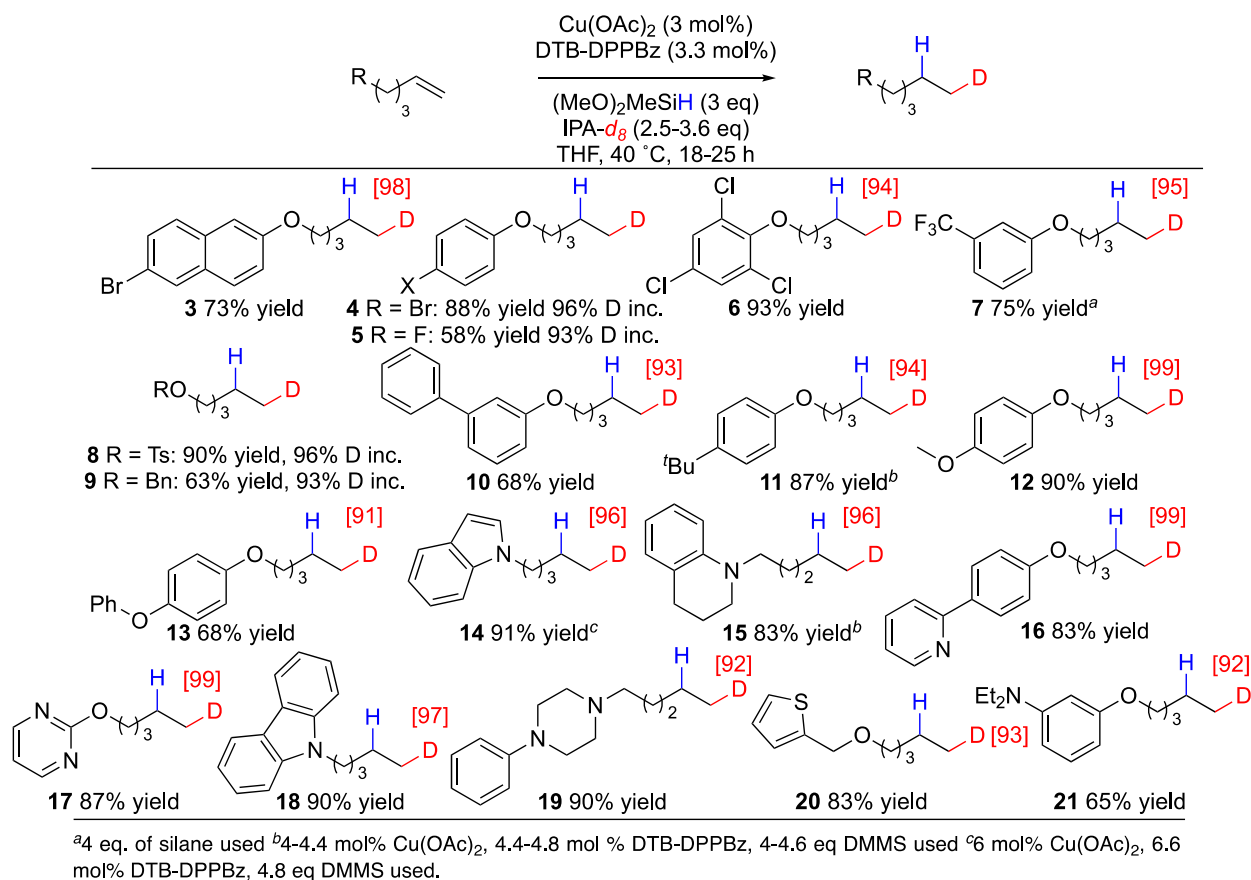
Though we reported a mild and general protocol for transfer hydrodeuteration of alkenyl arene substrates,⁶³ we were interested in exploring alternate reaction conditions to extend reactivity to unactivated terminal alkenes. We hypothesize that the regioselectivity of the Cu—H insertion across the unactivated terminal alkene will be anti-Markovnikov,

likely influenced by the steric environment of the substrate. This has been demonstrated in several Cu—H catalyzed terminal alkene hydrofunctionalization reactions.^{42,99,121,122} Therefore, for reaction optimization, we returned to conditions previously reported for Cu-catalyzed aryl alkene transfer hydrodeuteration,⁶³ and observed an incomplete reaction with trace isomerization (Table 1, entry 1). To try and increase the yield of the desired product, the temperature was increased to 60 °C. This led to an increase in yield but higher alkene isomerization by-product (entry 2). Performing the reaction at room temperature resulted in lower conversion to product with formation of the alkene isomerization by-product (entry 3). Doubling the reaction concentration to 2M led to a decrease in yield and trace isomerization by-product (entry 4). Changing the solvent to toluene led to sub-optimal yield whereas dichloromethane completely inhibited the reaction (entry 5 and 6). Given that changing temperature, concentration, and solvent did not lead to an optimal reaction, we decided to explore alcohol-OD reagents. The role of the alcohol reagent is important in the reaction as it is involved in the deuterodecupration of intermediates **iii_a** and **iii_b** (Scheme 1). The byproduct copper alkoxide species **v** is also formed from the alcohol-OD reagent. We first evaluated isopropanol-*d*8 instead of ethanol-OD and observed full conversion to the desired product with no isomerization product (entry 7). Increasing the catalyst loading to 3 mol% led to full conversion of alkene **1** with no isomerization product (entry 8). Changing from isopropanol-OD to the sterically hindered *tert*-butanol-OD also led to full conversion but a lower yield relative to entry 7 (entry 9). Switching to the less sterically hindered methanol-OD led to minimal conversion of alkene **1** to the desired product (entry 10). Lastly, the reaction did not undergo full conversion to the desired product when the silane reagent was changed to polymethylhydrosiloxane (PMHS) (entry 11).



Scheme 1. Mechanistic hypothesis

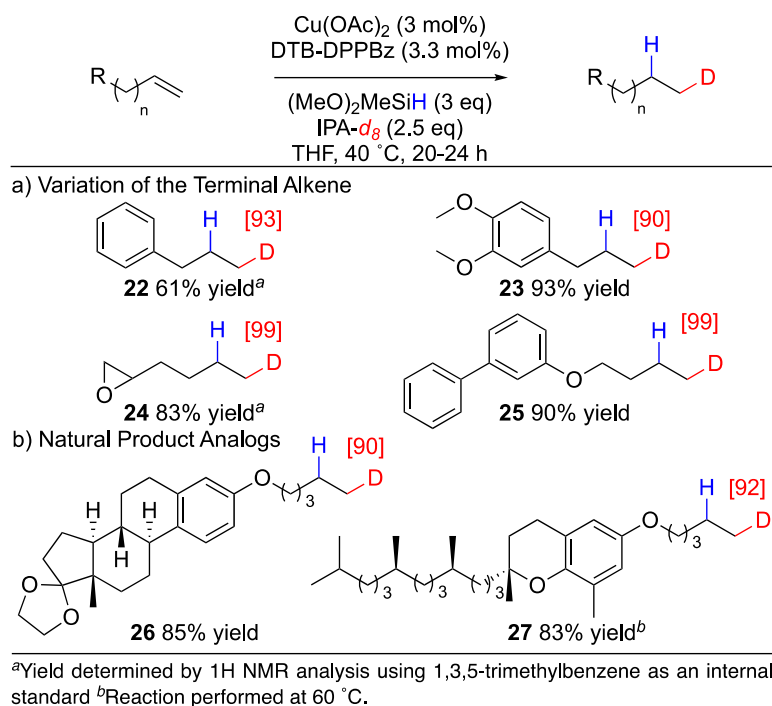
Our mechanistic hypothesis (Scheme 1) for the alkene isomerization by-product is derived from a previous study on Cu-catalyzed alkyne transfer hydrogenation.³⁷ This study revealed that hydrometallation of the alkene is likely to occur in a reversible manner from either **IIIa** or **IIIb** (Scheme 1). Therefore, to obtain the desired product, we hypothesize that a Markovnikov addition of the $Cu-H$ **I** across alkene **II** will form alkylcopper intermediate **IIIa** followed by deuterodecupration will yield the final product. However, due to the reversibility of the alkene, the alkene isomerized product is possibly formed by the β -hydride elimination of intermediate **IIIb** after the $Cu-H$ inserts into alkene **II** by a Markovnikov addition. It is noteworthy that intermediate **IVb** is never observed, thus, intermediate **IIIb** does not undergo deuterodecupration.



Scheme 2. Unactivated terminal alkene substrate scope

The substrate scope was investigated on organic molecules containing a pent-1-ene substituent (Scheme 2). Halogenated substituted arenes containing Br-, Cl-, F-, or CF₃- underwent chemoselective transfer hydrodeuteration as no reductive deuterodehalogenation side products were observed (**3-7**, 73%-93% yield). The reaction also tolerated tosyl (Ts) and benzyl (Bn) protected alcohols (**8-9**, 63%-90% yield). Phenol derivatives where the arene is substituted with either a phenyl, *tert*-butyl, methoxy or phenoxy group underwent transfer hydrodeuteration efficiently at the unactivated terminal alkene (**10-13**, 68%-90% yield). Heterocycles were also examined as they are commonly found in small molecule drugs and drug candidates.^{64,65} Nitrogen-containing heterocycles including indole, tetrahydroquinoline, pyridine, pyrimidine, carbazole, and piperazine

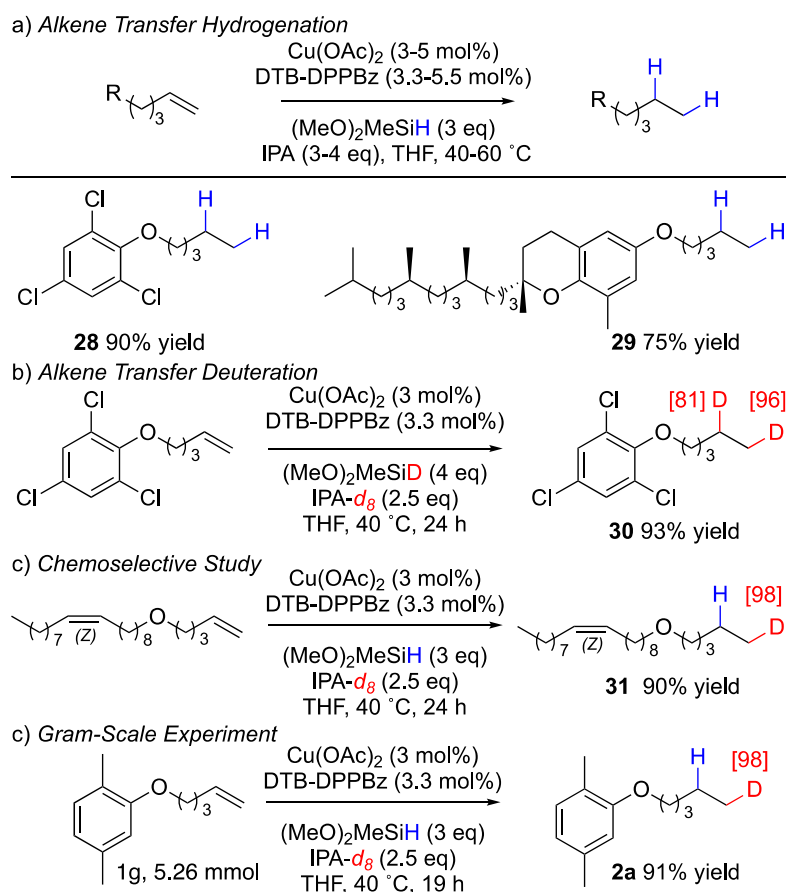
were all converted to the deuterated product in great yields (**14-19**, 83%-91% yield). Additionally, a terminal alkene containing a remote thiophene heterocycle underwent regioselective transfer hydrodeuteration in good yield (**20**, 83% yield). Lastly, an aniline containing substrate performed well under transfer hydrodeuteration reaction conditions (**21**, 65% yield).



Scheme 3. Unactivated terminal alkene substrate varying chain lengths and natural product analogs

The substrate scope was extended to varying the chain lengths of the terminal alkene (Scheme 3). Substrates such as allyl benzene and methyl eugenol were precisely deuterated at the terminal position when subjected to transfer hydrodeuteration conditions (**22-23**, 61%-93% yield). It is noteworthy as this substrate type are known to undergo thermodynamically driven metal hydride catalyzed alkene isomerization.^{33-35,123} However, we did not observe any alkene isomerized product or deuterium atoms at any other position.

An epoxide-containing substrate revealed deuteration occurred only at the terminal carbon after transfer hydrodeuteration (**24**, 83% yield). No epoxide ring-opening products were observed. Lastly, a butene chain appended to 3-phenylphenol also underwent regioselective hydrodeuteration in high yield (**25**, 90% yield). Complex natural product analogs were also investigated revealing that an estrone analog and δ -tocopherol derivative containing a pendant terminal alkene underwent Cu-catalyzed transfer hydrodeuteration in good yields (**26-27**, 83%-85% yield).



Scheme 4. Reaction modularity and chemoselectivity studies

Due to the modularity of the Cu-catalyzed transfer hydrodeuteration protocol, the corresponding transfer hydrogenation and transfer deuteration reactions were readily

carried out (Scheme 4). We were able to perform transfer hydrogenation on 1,3,5-trichloro-2-(4-penten-1-yloxy)benzene and δ -tocopherol natural product derivative (**28-29**, 75%-90% yield). We were also able to undergo transfer deuteration by changing Si—H to Si—D and using isopropanol-*d*8. The di-deuterated product was isolated in excellent yields (**30**, 93% yield). Importantly, the oleic acid derivative was chemoselective for the terminal alkene under transfer deuteration conditions (**31**, 90% yield). Lastly, a gram-scale experiment was performed with the optimization substrate and resulted in an excellent yield of 91% of the desired deuterated alkane product **2a**.

Conclusion

In conclusion, this method performed Cu-catalyzed transfer hydrodeuteration on unactivated terminal alkenes substrates to selectively install one deuterium atom at the terminal carbon. We found that more sterically encumbered deuterated alcohol reagents prevent alkene isomerization by-products and lead to the formation of the desired product with high regioselectivity. However, studies to examine the role of the alcohol reagent inhibiting alkene isomerization is ongoing. The substrate scope included a variety of functional group compatibility and complex natural product analogs. The modularity of the reaction allows both the corresponding alkene transfer hydrogenation and transfer deuteration reactions to be readily carried out. We envision that these protocols will be useful in the applications in the development of precisely deuterated pharmaceuticals and isotopically pure deuterated small-molecule reaction probes.

Conclusion

In conclusion, we developed several methods to selectively install deuterium across aryl alkyne and aryl alkene functionalities. We first focused on obtaining full reactivity from alkyne to alkane products. This was achieved first by developing a general transfer hydrogenation method using (*R*)-DTBM-SEGPHOS as the ligand with terminal and internal alkyne substrates. Using deuterated donors such as deuterated silane and a deuterated alcohol source, we were able to install 4 deuterium atoms across terminal and internal alkynes in a single step. Due to the modularity of the reaction conditions, we realized that a regioselective process could be achieved by using one hydrogen transfer reagent and one deuterium transfer reagent. Using a deuterated alcohol source along with an achiral bisphosphine DTB-DPPBz ligand, two deuterium atoms were selectively installed at the benzylic position. A method for the regioselective transfer hydrodeuteration of aryl alkenes with the ability to install one deuterium atom at the benzylic site was also developed. It was necessary to utilize molecular rotational resonance spectroscopy to confirm regioselectivities and sample composition of different isotopic species due to inadequate common spectroscopic techniques. From MRR, we concluded that we could achieve a regioselectivity ratio of >140:1. This method was further expanded to cyclic compounds. Furthermore, we accomplished an enantioselective transfer hydrodeuteration process synthesizing chiral by virtue of deuterium substitution compounds. EE was analyzed using a chiral tagging method by MRR spectroscopy. It was determined that the Cu-catalyzed transfer hydrodeuteration method produces high EE. Absolute configuration was also confirmed using MRR spectroscopy. For *N*-heterocyclic compounds, enantiomeric excess diminished compared to hydrocarbon substrates. We developed a

high-throughput technique using an IsoMRR instrument to rapidly analyze EE when optimizing reaction conditions. Unfortunately, even after reaction optimization, EE did not significantly increase. Future work to understand the reaction design is underway. Lastly, we expanded the substrate scope to unactivated terminal alkenes, installing one deuterium atom at the terminal position. No alkene isomerization or deuterium scrambling was observed. Future work will focus on the expansion of the scope to 1,1-disubstituted alkenes to make chiral centers by deuterium substitution using a transfer hydrodeuteration method. Overall, we achieved full reactivity to the deuterated alkyl product from alkyne and alkene starting materials, obtained highly selective deuterated products, and developed an enantioselective transfer hydrodeuteration method.

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EXPERIMENTAL (Supplementary Information)

CHAPTER 1 SUPPLEMENTARY INFORMATION Copper-Catalyzed Formal Transfer Hydrogenation/Deuteration of Aryl Alkynes

General Information

The following chemicals were purchased from commercial vendors and were used as received: Cu(OAc)₂ (99.999% from Alfa Aesar); (*R*)-(-)-4,4'-bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-3,3'-bi(1,2-methylenedioxybenzene) ((*R*)-DTBM-SEGPHOS) and (*S*)-(+)-4,4'-bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-3,3'-bi(1,2-methylenedioxybenzene) ((*S*)-DTBM-SEGPHOS) (TCI), dimethoxy(methyl)silane (TCI); 2-propanol-OD (Millipore Sigma); 2-propanol-*d*₈ (Acros Organic); ethanol (Oakwood Chemical); *tert*-butyldimethylsilyl chloride (TBSCl); D₂O (Oakwood Chemical).

Anhydrous tetrahydrofuran (THF) was purified by an MBRAUN solvent purification system (MB-SPS). Prior to use, triethylamine (Et₃N) was distilled over CaH₂ and stored over 3 Å molecular sieves. Chloroform-*d* (CDCl₃) was stored over 3 Å molecular sieves. Thin-layer chromatography (TLC) was conducted with Silicycle silica gel 60 Å F254 pre-coated plates (0.25 mm) and visualized with UV, Iodine and KMnO₄ stains. Flash chromatography was performed using Silia Flash® P60, 40-60 mm (230-400 mesh), purchased from Silicycle. For reactions that required heating (optimization, transfer hydrogenation and deuteration reactions), a PolyBlock for 2 dram vials was used on top of a Heidolph heating/stir plate.

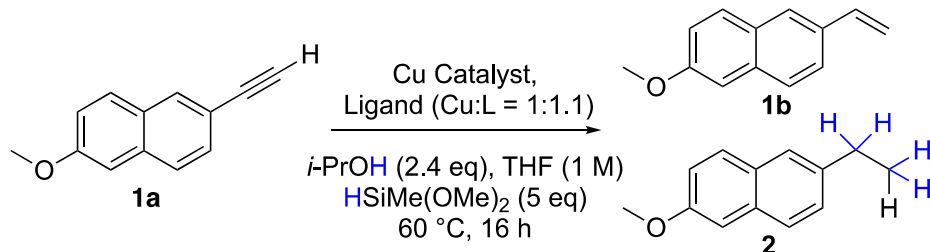
¹H NMR spectra were recorded on a Varian 300 or 400 MHz spectrometer and are reported in ppm using solvent as an internal standard (CDCl₃ at 7.26 ppm). Data reported as: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sxt = sextet, hep = heptet, sep = septet, oct = octet, m = multiplet, br = broad; coupling constant(s) in Hz; integration. ¹³C NMR spectra were recorded on a Varian 76 MHz or 101 MHz spectrometer and are reported in ppm using solvent as an internal standard (CDCl₃ at 77.16 ppm). ¹⁹F NMR spectra were recorded on a Varian 376 MHz spectrometer. ²H NMR spectra were recorded on a Varian 61 MHz spectrometer. Labeled solvent impurities were calculated out when reporting isolated yields.

High-resolution mass spectra were obtained for all new compounds not previously reported using the resources of the Chemistry Instrument Center (CIC), University at Buffalo, SUNY, Buffalo, NY. Specifically, high resolution accurate mass analysis was conducted using the following instruments: 12T Bruker SolarixR 12 Hybrid FTMS, provided through funding from the National Institutes of Health, NIH S10 RR029517; a Thermo Q-Exactive Focus Orbitrap Liquid Chromatograph Tandem Mass Spectrometer and a Thermo Q-Exactive Orbitrap Gas Chromatograph Tandem Mass Spectrometer, provided through funding from the National Science Foundation, MRI-1919594.

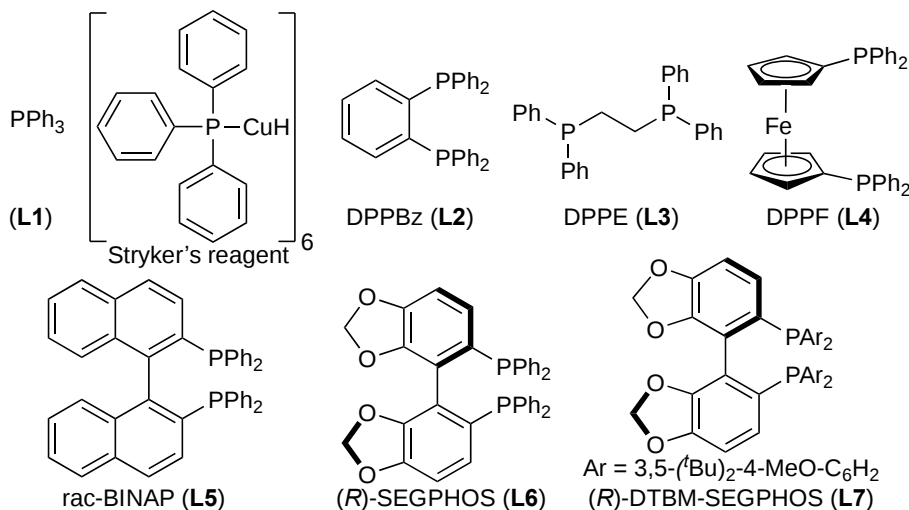
Optimization Studies

General procedure A for optimization studies in Table S1. In a N₂ filled glovebox, ligand, Cu catalyst (Cu:L = 1:1.1), and THF were added to an oven-dried 2-dram vial followed by dropwise addition of dimethoxy(methyl)silane (123 μL, 1 mmol, 5 eq.). A color change from green/blue to orange was observed while stirring for 15 minutes. In a separate oven-dried 1-dram vial was added 2-ethynyl-6-methoxynaphthalene (36.4 mg, 0.2 mmol, 1 eq.), THF (0.1 mL), and 2-propanol (37 μL, 0.48 mmol, 2.4 eq.). The solution in the 1-dram vial was added dropwise over 20 seconds to the 2-dram vial. The total volume of THF was calculated based on having a final reaction concentration of 1M based on the alkyne substrate. The 2-dram vial was capped with a red pressure relief cap, taken out of the glovebox, and stirred for 16 h at 60 °C at which point the reaction was filtered through a 1" silica plug with 20 mL of Et₂O or CH₂Cl₂ followed by an additional 80 mL of the appropriate solvent to elute the crude product into a 200 mL round bottom flask. The solvent was removed by rotary evaporation, and the product was analyzed by ¹H NMR using 1,3,5-trimethylbenzene as an internal standard. Yields for all entries were obtained by isolating the product after flash column chromatography if greater than 5% NMR yield was observed for **2b** in the crude ¹H NMR.

Table S1. Reaction Optimization



Entry	Cu Catalyst (mol%) ^b	Ligand	Yield of 1b (%)	Yield of 2 (%)	RSM 1a (%)
1	Cu(OAc) ₂ (5)	L1	11	trace ^c	48
2	Stryker's Reagent	N/A	53	trace ^c	6
3	Cu(OAc) ₂ (5)	L2	5	trace ^c	82
4	Cu(OAc) ₂ (5)	L3	8	trace ^c	75
5	Cu(OAc) ₂ (5)	L4	11	trace ^c	72
6	Cu(OAc) ₂ (5)	L5	12	trace ^c	49
7	Cu(OAc) ₂ (5)	L6	30	4 ^d	45
8	Cu(OAc) ₂ (5)	L7	0	98 ^d	0
9	Cu(OAc) ₂ (1)	L7	3.5	87 ^d	0
10	Cu(OAc) ₂ (2)	L7	0	91 ^d	0
11	N/A	N/A	4	0 ^c	86
12	Cu(OAc) ₂ (2)	N/A	3	0 ^c	80
13 ^e	Cu(OAc) ₂ (2)	L7	0	95 ^d	0
14 ^f	Cu(OAc) ₂ (2)	L7	0	93 ^d	0



^aReactions were conducted using 0.2 mmol of substrate. ^bCu(OAc)₂ was used in the reactions as a 0.2 M solution in THF. ^cYield was determined by ¹H NMR analysis of the crude reaction mixture, using 1,3,5-trimethylbenzene as an internal standard. ^dYield determined after purification by flash column chromatography. ^ePoly(methylhydrosiloxane) (5 eq) was used instead of dimethoxy(methyl)silane. ^fDiethoxy(methyl)silane (5 eq) was used instead of dimethoxy(methyl)silane.

Entry 1. According to the general procedure A for optimization studies, a stirring solution of triphenylphosphine **L1** (5.8 mg, 0.022 mmol, 0.11 eq.), Cu(OAc)₂ (50 μL of a 0.2 M solution in THF, 0.01 mmol, 0.05 eq.), and dimethoxy(methyl)silane (123 μL, 1.0 mmol, 5 eq.) in THF (0.05 mL) was prepared, and to this was added a solution of 2-ethynyl-6-methoxynaphthalene (36.4 mg, 0.2 mmol, 1 eq.) and 2-

propanol (37 μ L, 0.48 mmol, 2.4 eq.) in THF (0.1 mL) dropwise. The reaction stirred for 16 h at 60°C, after which it was filtered through a silica plug with Et₂O (20 mL) and eluted with Et₂O (80 mL). The solvent was removed by rotary evaporation, and the crude product was analyzed by ¹H NMR with 1,3,5-trimethylbenzene as an internal standard, (11% **1b**, trace **2**, 48% RSM **1**).

Entry 2. According to the general procedure A for optimization studies, a stirring solution of (triphenylphosphine)copper hydride hexamer (Stryker's Reagent) (3.3 mg, 0.0017 mmol, 0.00083 eq.), and dimethoxy(methyl)silane (123 μ L, 1.0 mmol, 5 eq.) in THF (0.1 mL) was prepared, and to this was added a solution of 2-ethynyl-6-methoxynaphthalene (36.4 mg, 0.2 mmol, 1 eq.) and 2-propanol (37 μ L, 0.48 mmol, 2.4 eq.) in THF (0.1 mL) dropwise. The reaction stirred for 16 h at 60°C, after which it was filtered through a silica plug with Et₂O (20 mL) and eluted with Et₂O (80 mL). The solvent was removed by rotary evaporation, and the crude product was analyzed by ¹H NMR with 1,3,5-trimethylbenzene as an internal standard (53% **1b**, 2.5% **2**, 6% RSM **1**).

Entry 3. According to the general procedure A for optimization studies, a stirring solution of 1,2-bis(diphenylphosphino)benzene **L2** (4.9 mg, 0.011 mmol, 0.055 eq.), Cu(OAc)₂ (50 μ L of a 0.2 M solution in THF, 0.01 mmol, 0.05 eq.), and dimethoxy(methyl)silane (123 μ L, 1.0 mmol, 5 eq.) in THF (0.05 mL) was prepared, and to this was added a solution of 2-ethynyl-6-methoxynaphthalene (36.4 mg, 0.2 mmol, 1 eq.) and 2-propanol (37 μ L, 0.48 mmol, 2.4 eq.) in THF (0.1 mL) dropwise. The reaction stirred for 16 h at 60°C, after which it was filtered through a silica plug with Et₂O (20 mL) and eluted with Et₂O (80 mL). The solvent was removed by rotary evaporation, and the crude product was analyzed by ¹H NMR with 1,3,5-trimethylbenzene as an internal standard (5% **1b**, trace **2**, 82% RSM **1**).

Entry 4. According to the general procedure A for optimization studies, a stirring solution of 1,2-bis(diphenylphosphino)ethane **L3** (4.4 mg, 0.011 mmol, 0.055 eq.), Cu(OAc)₂ (50 μ L of a 0.2 M solution in THF, 0.01 mmol, 0.05 eq.), and dimethoxy(methyl)silane (123 μ L, 1.0 mmol, 5 eq.) in THF (0.05 mL) was prepared, and to this was added a solution of 2-ethynyl-6-methoxynaphthalene (36.4 mg, 0.2 mmol, 1 eq.) and 2-propanol (37 μ L, 0.48 mmol, 2.4 eq.) in THF (0.1 mL) dropwise. The reaction stirred for 16 h at 60°C, after which it was filtered through a silica plug with Et₂O (20 mL) and eluted with Et₂O (80 mL). The solvent was removed by rotary evaporation, and the crude product was analyzed by ¹H NMR with 1,3,5-trimethylbenzene as an internal standard (8% **1b**, trace **2**, 75% RSM **1**).

Entry 5. According to the general procedure A for optimization studies, a stirring solution of 1,1'-bis(diphenylphosphino)-ferrocene **L4** (6.1 mg, 0.011 mmol, 0.055 eq.), Cu(OAc)₂ (50 μ L of a 0.2 M solution in THF, 0.01 mmol, 0.05 eq.), and dimethoxy(methyl)silane (123 μ L, 1.0 mmol, 5 eq.) in THF (0.05 mL) was prepared, and to this was added a solution of 2-ethynyl-6-methoxynaphthalene (36.4 mg, 0.2 mmol, 1 eq.) and 2-propanol (37 μ L, 0.48 mmol, 2.4 eq.) in THF (0.1 mL) dropwise. The reaction stirred for 16 h at 60°C, after which it was filtered through a silica plug with Et₂O (20 mL) and eluted with Et₂O (80 mL). The solvent was removed by rotary evaporation, and the crude product was analyzed by ¹H NMR with 1,3,5-trimethylbenzene as an internal standard (11% **1b**, trace **2**, 72% RSM **1**).

Entry 6. According to the general procedure A for optimization studies, a stirring solution of ($\pm$)-2,2'-bis(diphenylphosphino)-1,1'-binaphthalene **L5** (6.8 mg, 0.011 mmol, 0.055 eq.), Cu(OAc)₂ (50 μ L of a 0.2 M solution in THF, 0.01 mmol, 0.05 eq.), and dimethoxy(methyl)silane (123 μ L, 1.0 mmol, 5 eq.) in THF (0.05 mL) was prepared, and to this was added a solution of 2-ethynyl-6-methoxynaphthalene (36.4 mg, 0.2 mmol, 1 eq.) and 2-propanol (37 μ L, 0.48 mmol, 2.4 eq.) in THF (0.1 mL) dropwise. The reaction stirred for 16 h at 60°C, after which it was filtered through a silica plug with Et₂O (20 mL) and eluted with Et₂O (80 mL). The solvent was removed by rotary evaporation, and the crude product was analyzed by ¹H NMR with 1,3,5-trimethylbenzene as an internal standard (12% **1b**, trace **2**, 49% RSM **1**).

Entry 7. According to the general procedure A for optimization studies, a stirring solution of (*R*)-(+)-5,5'-bis(diphenylphosphino)-4,4'-bi-1,3-benzodioxole **L6** (6.7 mg, 0.011 mmol, 0.055 eq.), Cu(OAc)₂ (50 μ L of a 0.2 M solution in THF, 0.01 mmol, 0.05 eq.), and dimethoxy(methyl)silane (123 μ L, 1.0 mmol, 5 eq.) in THF (0.05 mL) was prepared, and to this was added a solution of 2-ethynyl-6-methoxynaphthalene (36.4 mg, 0.2 mmol, 1 eq.) and 2-propanol (37 μ L, 0.48 mmol, 2.4 eq.) in THF (0.1 mL) dropwise. The reaction stirred

for 16 h at 60°C, after which it was filtered through a silica plug with Et₂O (20 mL) and eluted with Et₂O (80 mL). The solvent was removed by rotary evaporation, and the crude product was analyzed by ¹H NMR with 1,3,5-trimethylbenzene as an internal standard. The crude product was dry loaded onto silica gel, and was purified by flash column chromatography using gradient elution (50 mL of hexane, 100 mL of 2% ethyl acetate in hexane, and 50 mL of 5% ethyl acetate in hexane) to yield a white solid (28.8 mg, 30% **1b**, 4% **2**, 45% RSM **1**).

Entry 8. According to the general procedure A for optimization studies, a stirring solution of (*R*)-(-)-5,5'-bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4'-bi-1,3-benzodioxole **L7** (13.0 mg, 0.011 mmol, 0.055 eq.), Cu(OAc)₂ (50 μL of a 0.2 M solution in THF, 0.01 mmol, 0.05 eq.), and dimethoxy(methyl)silane (123 μL, 1.0 mmol, 5 eq.) in THF (0.05 mL) was prepared, and to this was added a solution of 2-ethynyl-6-methoxynaphthalene (36.4 mg, 0.2 mmol, 1 eq.) and 2-propanol (37 μL, 0.48 mmol, 2.4 eq.) in THF (0.1 mL) dropwise. The reaction stirred for 16 h at 60°C, after which it was filtered through a silica plug with Et₂O (20 mL) and eluted with Et₂O (80 mL). The solvent was removed by rotary evaporation, and the crude product was analyzed by ¹H NMR with 1,3,5-trimethylbenzene as an internal standard. The crude product was dry loaded onto silica gel, and was purified by column chromatography using gradient elution (50 mL of hexanes, 100 mL of 2% ethyl acetate in hexane, and 50 mL of 5% ethyl acetate in hexane) to yield a white solid (36.4 mg, 0.195 mmol, 98% yield).

Entry 9. According to the general procedure A for optimization studies, a stirring solution of (*R*)-(-)-5,5'-bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4'-bi-1,3-benzodioxole **L7** (2.6 mg, 0.0022 mmol, 0.011 eq.), Cu(OAc)₂ (10 μL of a 0.2 M solution in THF, 0.002 mmol, 0.01 eq.), and dimethoxy(methyl)silane (123 μL, 1.0 mmol, 5 eq.) in THF (0.09 mL) was prepared, and to this was added a solution of 2-ethynyl-6-methoxynaphthalene (36.4 mg, 0.2 mmol, 1 eq.) and 2-propanol (37 μL, 0.48 mmol, 2.4 eq.) in THF (0.1 mL) dropwise. The reaction stirred for 16 h at 60°C, after which it was filtered through a silica plug with Et₂O (20 mL) and eluted with Et₂O (80 mL). The solvent was removed by rotary evaporation, and the crude product was analyzed by ¹H NMR with 1,3,5-trimethylbenzene as an internal standard. The crude product was dry loaded onto silica gel, and was purified by column chromatography using gradient elution (50 mL of hexane, 100 mL of 2% ethyl acetate in hexane, and 50 mL of 5% ethyl acetate in hexane) to yield a white solid (33.8 mg, 3.5% **1b**, 87% **2**).

Entry 10. According to the general procedure A for optimization studies, a stirring solution of (*R*)-(-)-5,5'-bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4'-bi-1,3-benzodioxole **L7** (5.2 mg, 0.0044 mmol, 0.022 eq.), Cu(OAc)₂ (20 μL of a 0.2 M solution in THF, 0.004 mmol, 0.02 eq.), and dimethoxy(methyl)silane (123 μL, 1.0 mmol, 5 eq.) in THF (0.08 mL) was prepared, and to this was added a solution of 2-ethynyl-6-methoxynaphthalene (36.4 mg, 0.2 mmol, 1 eq.) and 2-propanol (37 μL, 0.48 mmol, 2.4 eq.) in THF (0.1 mL) dropwise. The reaction stirred for 16 h at 60°C, after which it was filtered through a silica plug with Et₂O (20 mL) and eluted with Et₂O (80 mL). The solvent was removed by rotary evaporation, and the crude product was analyzed by ¹H NMR with 1,3,5-trimethylbenzene as an internal standard. The crude product was dry loaded onto silica gel, and was purified by column chromatography using gradient elution (50 mL of hexane, 100 mL of 2% ethyl acetate in hexane, and 50 mL of 5% ethyl acetate in hexane) to yield a white solid (33.8 mg, 0.182 mmol, 91% yield).

Entry 11. According to the general procedure A for optimization studies, a stirring solution of dimethoxy(methyl)silane (123 μL, 1.0 mmol, 5 eq.) in THF (0.1 mL) was prepared, and to this was added a solution of 2-ethynyl-6-methoxynaphthalene (36.4 mg, 0.2 mmol, 1 eq.) and 2-propanol (37 μL, 0.48 mmol, 2.4 eq.) in THF (0.1 mL) dropwise. The reaction stirred for 16 h at 60°C, after which it was filtered through a silica plug with Et₂O (20 mL) and eluted with Et₂O (80 mL). The solvent was removed by rotary evaporation, and the crude product was analyzed by ¹H NMR with 1,3,5-trimethylbenzene as an internal standard (4% **1b**, 86% RSM **1**).

Entry 12. According to the general procedure A for optimization studies, a stirring solution of Cu(OAc)₂ (20 μL of a 0.2 M solution in THF, 0.004 mmol, 0.02 eq.) and dimethoxy(methyl)silane (123 μL, 1.0 mmol, 5 eq.) in THF (0.08 mL) was prepared, and to this was added a solution of 2-ethynyl-6-methoxynaphthalene (36.4 mg, 0.2 mmol, 1 eq.) and 2-propanol (37 μL, 0.48 mmol, 2.4 eq.) in THF (0.1 mL) dropwise. The

reaction stirred for 16 h at 60°C, after which it was filtered through a silica plug with Et₂O (20 mL) and eluted with Et₂O (80 mL). The solvent was removed by rotary evaporation, and the crude product was analyzed by ¹H NMR with 1,3,5-trimethylbenzene as an internal standard (3% **1b**, 80% RSM **1**).

Entry 13. According to the general procedure A for optimization studies, a stirring solution of (*S*)-(-)-5,5'-bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4'-bi-1,3-benzodioxole **L7** (5.2 mg, 0.0044 mmol, 0.022 eq.), Cu(OAc)₂ (20 μL of a 0.2 M solution in THF, 0.004 mmol, 0.02 eq.), and poly(methylhydrosiloxane) (67 μL, 1.0 mmol, 5 eq.) in THF (0.08 mL) was prepared, and to this was added a solution of 2-ethynyl-6-methoxynaphthalene (36.4 mg, 0.2 mmol, 1 eq.) and 2-propanol (37 μL, 0.48 mmol, 2.4 eq.) in THF (0.1 mL) dropwise. The reaction stirred for 16 h at 60°C, after which it was filtered through a silica plug with Et₂O (20 mL) and eluted with Et₂O (80 mL). The solvent was removed by rotary evaporation, and the crude product was analyzed by ¹H NMR with 1,3,5-trimethylbenzene as an internal standard. The crude product was dry loaded onto silica gel, and was purified by column chromatography using gradient elution (50 mL of hexane, 100 mL of 2% ethyl acetate in hexane, and 50 mL of 5% ethyl acetate in hexane) to yield a white solid (35.4 mg, 0.19 mmol, 95% yield).

Entry 14. According to the general procedure A for optimization studies, a stirring solution of (*S*)-(-)-5,5'-bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4'-bi-1,3-benzodioxole **L7** (5.2 mg, 0.0044 mmol, 0.022 eq.), Cu(OAc)₂ (20 μL of a 0.2 M solution in THF, 0.004 mmol, 0.02 eq.), and diethoxy(methyl)silane (160 μL, 1.0 mmol, 5 eq.) in THF (0.08 mL) was prepared, and to this was added a solution of 2-ethynyl-6-methoxynaphthalene (36.4 mg, 0.2 mmol, 1 eq.) and 2-propanol (37 μL, 0.48 mmol, 2.4 eq.) in THF (0.1 mL) dropwise. The reaction stirred for 16 h at 60°C, after which it was filtered through a silica plug with Et₂O (20 mL) and eluted with Et₂O (80 mL). The solvent was removed by rotary evaporation, and the crude product was analyzed by ¹H NMR with 1,3,5-trimethylbenzene as an internal standard. The crude product was dry loaded onto silica gel, and was purified by column chromatography using gradient elution (50 mL of hexane, 100 mL of 2% ethyl acetate in hexane, and 50 mL of 5% ethyl acetate in hexane) to yield a white solid (34.7 mg, 0.186 mmol, 93% yield).

Transfer Hydrogenation Reaction Scope

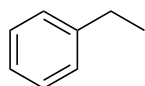
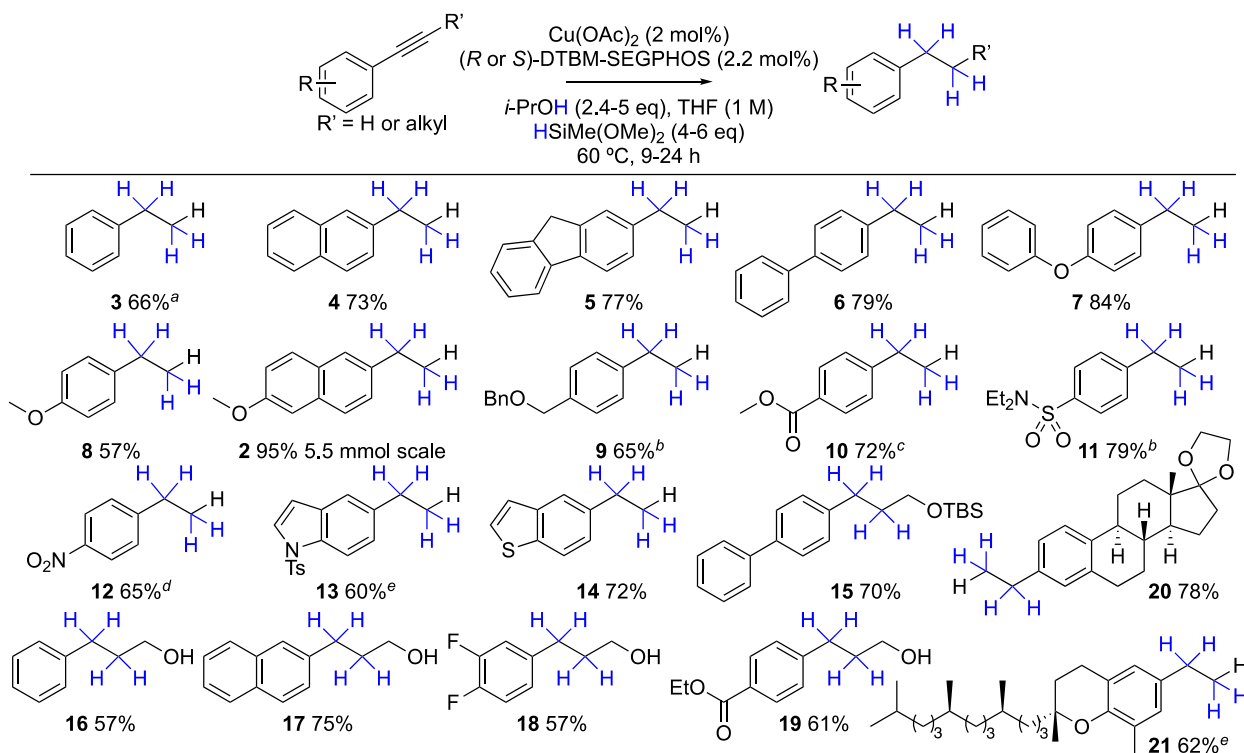
General procedure for transfer hydrogenation (B)

In a N₂ filled glovebox, (*R* or *S*)-DTBM-SEPHOS (10.4 mg, 0.0088 mmol, 0.022 eq.), Cu(OAc)₂ (40 μL of a 0.2 M solution in THF, 0.008 mmol, 0.02 eq.), and THF (0.16 mL) were added to an oven-dried 2-dram vial followed by dropwise addition of dimethoxy(methyl)silane (247 μL, 2 mmol, 5 eq.). A color change from green/blue to orange was observed while stirring for 15 minutes. In a separate oven-dried 1-dram vial was added the alkyne substrate (0.4 mmol, 1 eq.), THF (0.2 mL), and either ethanol or 2-propanol (2.4-5 eq. based on substrate). The solution in the 1-dram vial was added dropwise over 20 seconds to the 2-dram vial. The total volume of THF was calculated based on having a final reaction concentration of 1M based on the alkyne substrate. The 2-dram vial was capped with a red pressure relief cap, taken out of the glovebox, and stirred for 9-24 h at the appropriate temperature at which point the reaction was filtered through a 1" silica plug with 20 mL of Et₂O followed by 80 mL of Et₂O to elute the remaining product into a 200 mL round bottom flask. After removing the Et₂O by rotary evaporation, the crude product was isolated by flash column chromatography.

General purification for alcohol containing substrates after transfer hydrogenation reaction (C)

The crude product was dissolved in THF (1.6 mL) and tetrabutylammonium fluoride (0.8 mL of 1.0 M in THF solution, 2 eq.) was added. The reaction was stirred at room temperature for 1-2 hours until complete by TLC analysis. Upon completion, reaction mixture was diluted with Et₂O (10 mL) and quenched with saturated aqueous NH₄Cl (5 mL). The aqueous layer was extracted with Et₂O (3 x 10 mL) and the combined organic layers were washed with water (10 mL) and brine (10 mL), then dried over anhydrous Na₂SO₄. The mixture was filtered, and the solvent was removed by rotary evaporation. The crude product was purified by flash column chromatography to give the desired product.

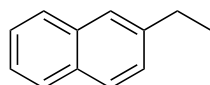
Scheme S1. Transfer Hydrogenation Substrate Scope



Ethyl Benzene [3]. According to the general transfer hydrogenation procedure B, (*S*)-DTBM-SEGPPOS (10.4 mg, 0.0088 mmol, 0.022 eq.), Cu(OAc)₂ (40 μL of a 0.2 M solution in THF, 0.008 mmol, 0.02 eq.), THF (0.16 mL), then dimethoxy(methyl)silane (247 μL, 2 mmol, 5 eq.) were combined in a 2-dram vial followed by addition of a solution of ethynylbenzene (40.9 mg, 0.4 mmol, 1 eq.), THF (0.2 mL), and 2-propanol (74 μL, 0.96 mmol, 2.4 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 10 h at 60 °C. After silica plug filtration using diethyl ether (100 mL) as the eluent, the solvent was concentrated, and 18.5 μL of 1,3,5-trimethylbenzene was used as an internal standard to determine the ¹H NMR crude yield (66% crude yield by ¹H NMR).

¹H NMR: (400 MHz, CDCl₃)

δ 7.29 (t, *J* = 7.6 Hz, 2H), 7.25 – 7.16 (m, 3H), 2.66 (q, *J* = 7.6 Hz, 2H), 1.27 (t, *J* = 7.6 Hz, 3H).



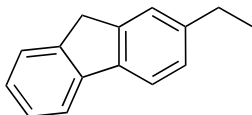
2-Ethylnaphthalene [4]. According to the general transfer hydrogenation procedure B, (*S*)-DTBM-SEGPPOS (10.4 mg, 0.0088 mmol, 0.022 eq.), Cu(OAc)₂ (40 μL of a 0.2 M solution in THF, 0.008 mmol, 0.02 eq.), THF (0.16 mL), then dimethoxy(methyl)silane (247 μL, 2 mmol, 5 eq.) were combined in a 2-dram vial followed by addition of a solution of 2-ethynyl-naphthalene (60.9 mg, 0.4 mmol, 1 eq.), THF (0.2 mL), and 2-propanol (74 μL, 0.96 mmol, 2.4 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 14 h at 60 °C. After silica plug filtration using diethyl ether (100 mL) as the eluent, the solvent was concentrated, and the crude brown oil was dry loaded onto a silica gel column. Flash chromatography using 350 mL of hexanes as eluent gave the pure product as a clear, colorless oil (45.8 mg, 0.29 mmol, 73% yield). The spectra for the title compound matched previously reported spectra.¹

¹H NMR: (400 MHz, CDCl₃)

δ 7.86 – 7.76 (m, 3H), 7.65 (s, 1H), 7.51 – 7.39 (m, 2H), 7.38 (d, J = 8.4 Hz, 1H), 2.84 (q, J = 7.6 Hz, 2H), 1.36 (t, J = 7.6 Hz, 3H).

^{13}C NMR: (101 MHz, CDCl_3)

δ 141.9, 133.9, 132.1, 127.9, 127.7, 127.6, 127.2, 126.0, 125.7, 125.1, 29.20, 15.7.



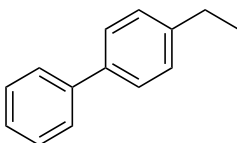
2-Ethyl-9H-fluorene [5]. According to the general transfer hydrogenation procedure B, (*S*)-DTBM-SEGPPOS (10.4 mg, 0.0088 mmol, 0.022 eq.), $\text{Cu}(\text{OAc})_2$ (40 μL of a 0.2 M solution in THF, 0.008 mmol, 0.02 eq.), THF (0.16 mL), then dimethoxy(methyl)silane (247 μL , 2 mmol, 5 eq.) were combined in a 2-dram vial followed by addition of a solution of 2-ethynyl-9H-Fluorene (76.1 mg, 0.4 mmol, 1 eq.), THF (0.2 mL), and 2-propanol (74 μL , 0.96 mmol, 2.4 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 9 h at 60 $^\circ\text{C}$. After silica plug filtration using diethyl ether (100 mL) as the eluent, the solvent was concentrated. The crude brown oil was dry loaded onto a silica gel column. Flash chromatography using 100 mL of hexanes as eluent gave the pure product as a yellow solid (60.0 mg, 0.309 mmol, 77% yield). The spectra for the title compound matched previously reported spectra.²

^1H NMR: (400 MHz, CDCl_3)

δ 7.77 (d, J = 7.6, 1H), 7.71 (d, J = 7.8 Hz, 1H), 7.56 – 7.52 (m, 1H), 7.42 – 7.34 (m, 2H), 7.31 – 7.26 (m, 1H), 7.25 – 7.21 (m, 1H), 3.89 (s, 2H), 2.75 (q, J = 7.6 Hz, 2H), 1.31 (t, J = 7.6 Hz, 3H).

^{13}C NMR: (101 MHz, CDCl_3)

δ 143.7, 143.3, 143.3, 141.9, 139.5, 126.8, 126.6, 126.3, 125.1, 124.7, 119.8, 119.7, 37.0, 29.2, 16.1.



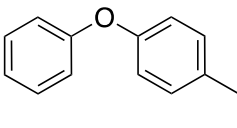
4-Ethyl-1,1'-biphenyl [6]. According to the general transfer hydrogenation procedure B, (*S*)-DTBM-SEGPPOS (10.4 mg, 0.0088 mmol, 0.022 eq.), $\text{Cu}(\text{OAc})_2$ (40 μL of a 0.2 M solution in THF, 0.008 mmol, 0.02 eq.), THF (0.16 mL), then dimethoxy(methyl)silane (247 μL , 2 mmol, 5 eq.) were combined in a 2-dram vial followed by addition of a solution of 4-ethynyl-1,1'-Biphenyl (71.3 mg, 0.4 mmol, 1 eq.), THF (0.2 mL), and 2-propanol (74 μL , 0.96 mmol, 2.4 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 9 h at 60 $^\circ\text{C}$. After silica plug filtration using diethyl ether (100 mL) as the eluent, the solvent was concentrated, and the crude brown oil was dry loaded onto a silica gel column. Flash chromatography using 100 mL of hexanes as eluent gave the pure product as a clear, yellow oil (57.5 mg, 0.316 mmol, 79% yield). The spectra for the title compound matched previously reported spectra.¹

^1H NMR: (400 MHz, CDCl_3)

δ 7.63 – 7.60 (m, 2H), 7.58 – 7.53 (m, 2H), 7.48 – 7.43 (m, 2H), 7.38 – 7.33 (m, 1H), 7.31 (d, J = 8.1 Hz, 2H), 2.73 (q, J = 7.6 Hz, 2H), 1.32 (t, J = 7.6 Hz, 3H).

^{13}C NMR: (101 MHz, CDCl_3)

δ 143.5, 141.4, 138.8, 128.8, 128.4, 127.2, 127.2, 127.1, 28.7, 15.7.



1-Ethyl-4-phenoxybenzene [7]. According to the general transfer hydrogenation procedure B, (*S*)-DTBM-SEGPPOS (10.4 mg, 0.0088 mmol, 0.022 eq.), $\text{Cu}(\text{OAc})_2$ (40 μL of a 0.2 M solution in THF, 0.008 mmol,

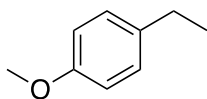
0.02 eq.), THF (0.16 mL), then dimethoxy(methyl)silane (247 μ L, 2 mmol, 5 eq.) were combined in a 2-dram vial followed by addition of a solution of 1-ethynyl-4-phenoxy-benzene (77.7 mg, 0.4 mmol, 1 eq.), THF (0.2 mL), and 2-propanol (74 μ L, 0.96 mmol, 2.4 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 9 h at 60 $^{\circ}$ C. After silica plug filtration using diethyl ether (100 mL) as the eluent, the solvent was concentrated, and the crude brown oil was dry loaded onto a silica gel column. Flash chromatography using 100 mL of hexanes as eluent gave the pure product as a clear, yellow oil (66.5 mg, 0.335 mmol, 84% yield). The spectra for the title compound matched previously reported spectra.³

¹H NMR: (400 MHz, CDCl₃)

δ 7.37 – 7.30 (m, 2H), 7.18 (d, J = 8.5 Hz, 2H), 7.12 – 7.06 (m, 1H), 7.04 – 6.99 (m, 2H), 6.98 – 6.94 (m, 2H), 2.66 (q, J = 7.6 Hz, 2H), 1.26 (t, J = 7.6 Hz, 3H).

¹³C NMR: (101 MHz, CDCl₃)

δ 157.9, 155.0, 139.4, 129.8, 129.2, 123.0, 119.2, 118.6, 28.3, 15.9.



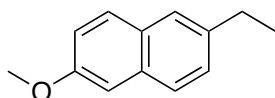
1-Ethyl-4-methoxybenzene [8]. According to the general transfer hydrogenation procedure B, (*S*)-DTBM-SEGPPOS (10.4 mg, 0.0088 mmol, 0.022 eq.), Cu(OAc)₂ (40 μ L of a 0.2 M solution in THF, 0.008 mmol, 0.02 eq.), THF (0.16 mL), then dimethoxy(methyl)silane (247 μ L, 2.0 mmol, 5 eq.) were combined in a 2-dram vial followed by addition of a solution of 1-ethynyl-4-methoxybenzene (52.9 mg, 0.4 mmol, 1 eq.), THF (0.2 mL), and 2-propanol (153 μ L, 2.0 mmol, 5 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 12 h at 60 $^{\circ}$ C. After silica plug filtration using diethyl ether (100 mL) as the eluent, the solvent was concentrated, and the crude colorless liquid was dry loaded onto a silica gel column. Flash chromatography using 100 mL of hexanes as eluent gave the pure product as a clear and colorless liquid (30.9 mg, 0.227 mmol, 57% yield). The spectra for the title compound matched previously reported spectra.⁴

¹H NMR: (300 MHz, CDCl₃)

δ 7.12 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 8.5 Hz, 2H), 3.79 (s, 3H), 2.60 (q, J = 7.6 Hz, 2H), 1.22 (t, J = 7.5 Hz, 3H).

¹³C NMR: (75 MHz, CDCl₃)

δ 157.7, 136.5, 128.9, 113.9, 55.4, 28.1, 16.0.



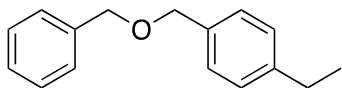
2-Ethyl-6-methoxynaphthalene [2]. According to the general transfer hydrogenation procedure B, (*S*)-DTBM-SEGPPOS (142.4 mg, 0.12 mmol, 0.022 eq.), Cu(OAc)₂ (0.549 mL of a 0.2 M solution in THF, 0.11 mmol, 0.02 eq.), THF (2.5 mL), then dimethoxy(methyl)silane (3.39 mL, 27.45 mmol, 5 eq.) were combined in a 20-dram vial followed by addition of a solution of 2-ethynyl-6-methoxynaphthalene (1.0 g, 5.49 mmol, 1 eq.), THF (2.5 mL), and 2-propanol (1.01 mL, 13.18 mmol, 2.4 eq.). The 20-dram vial was capped with a red pressure relief cap, and the reaction stirred for 15 h at 60 $^{\circ}$ C. After silica plug filtration using diethyl ether (200 mL) as the eluent, the solvent was concentrated under vacuum. Purification by flash chromatography using gradient elution (100 mL of hexanes, 200 mL of 5% of ethyl acetate in hexanes, 500 mL of 8% ethyl acetate in hexanes) gave the pure product as a cream colored solid (0.97 g, 5.21 mmol, 95% yield). The spectra for the title compound matched previously reported spectra.¹

¹H NMR: (400 MHz, CDCl₃)

δ 7.70 – 7.64 (m, 2H), 7.57 – 7.54 (m, 1H), 7.32 (dd, J = 8.4, 1.8 Hz, 1H), 7.15 – 7.09 (m, 2H), 3.91 (s, 3H), 2.78 (q, J = 7.6 Hz, 2H), 1.31 (t, J = 7.6, 3H).

¹³C NMR: (101 MHz, CDCl₃)

δ 157.2, 139.6, 133.0, 129.3, 129.0, 127.7, 126.8, 125.6, 118.7, 105.8, 55.4, 29.0, 15.8.



1-((Benzyloxy)methyl)-4-ethylbenzene [9]. According to the general transfer hydrogenation procedure B, (S)-DTBM-SEPHOS (10.4 mg, 0.0088 mmol, 0.022 eq.), Cu(OAc)₂ (40 μL of a 0.2 M solution in THF, 0.008 mmol, 0.02 eq.), THF (0.16 mL), then dimethoxy(methyl)silane (296 μL, 2.4 mmol, 6 eq.) were combined in a 2-dram vial followed by addition of a solution of 1-ethynyl-4-[(phenylmethoxy)methyl]-benzene (88.9 mg, 0.4 mmol, 1 eq.), THF (0.2 mL), and ethanol (61 μL, 1.04 mmol, 2.6 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 18 h at 60 °C. After silica plug filtration using diethyl ether (100 mL) as the eluent, the solvent was concentrated, and the crude brown oil was dry loaded onto a silica gel column. Flash chromatography using gradient elution (75 mL of hexanes, 100 mL of 1% ethyl acetate in hexanes, 100 mL of 2% ethyl acetate in hexanes, 200 mL of 5% ethyl acetate in hexanes) gave the pure product as a clear, yellow oil (58.5 mg, 0.26 mmol, 65% yield).

¹H NMR: (400 MHz, CDCl₃)

δ 7.43 – 7.35 (m, 4H), 7.34 – 7.28 (m, 3H), 7.22 (d, *J* = 7.9 Hz, 2H), 4.57 (d, *J* = 7.6 Hz, 4H), 2.68 (q, *J* = 7.6 Hz, 2H), 1.26 (t, *J* = 7.6 Hz, 3H).

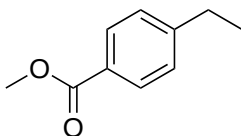
¹³C NMR: (101 MHz, CDCl₃)

δ 143.9, 138.6, 135.6, 128.5, 128.1, 128.0, 127.9, 127.7, 72.2, 72.1, 28.8, 15.8.

ATR-IR (cm⁻¹):

3029, 2964, 2929, 2856, 1718, 1090, 1072.

HRMS: (ESI⁺) *m/z*: [M+Na]⁺ Calcd for C₁₆H₁₈NaO 249.1250; Found 249.1257.



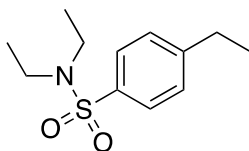
Methyl 4-ethylbenzoate [10]. According to the general transfer hydrogenation procedure B, (S)-DTBM-SEPHOS (10.4 mg, 0.0088 mmol, 0.022 eq.), Cu(OAc)₂ (40 μL of a 0.2 M solution in THF, 0.008 mmol, 0.02 eq.), THF (0.16 mL), then dimethoxy(methyl)silane (247 μL, 2 mmol, 5 eq.) were combined in a 2-dram vial followed by addition of a solution of methyl 4-ethynylbenzoate (64.1 mg, 0.4 mmol, 1 eq.), THF (0.2 mL), and 2-propanol (74 μL, 0.96 mmol, 2.4 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 22 h at 40 °C. After silica plug filtration using diethyl ether (100 mL) as the eluent, the solvent was concentrated under vacuum. Purification by flash chromatography using gradient elution (100 mL of hexanes, 200 mL of 10% of DCM in hexanes, 200 mL of 20% DCM in hexanes, 200 mL of 30% DCM in hexanes) gave the pure product as a clear colorless liquid (47.0 mg, 0.286 mmol, 72% yield). The spectra for the title compound matched previously reported spectra.⁵

¹H NMR: (400 MHz, CDCl₃)

δ 7.95 (d, *J* = 8.2 Hz, 2H), 7.25 (d, *J* = 8.1 Hz, 2H), 3.89 (s, 3H), 2.70 (q, *J* = 7.6 Hz, 2H), 1.25 (t, *J* = 7.6 Hz, 3H).

¹³C NMR: (101 MHz, CDCl₃)

δ 167.3, 149.9, 129.8, 128.0, 127.8, 52.1, 29.1, 15.3.



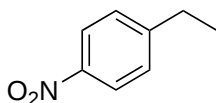
***N,N,4-Triethylbenzenesulfonamide* [11].** According to the general transfer hydrogenation procedure B, (S)-DTBM-SEGPPOS (10.4 mg, 0.0088 mmol, 0.022 eq.), Cu(OAc)₂ (40 μ L of a 0.2 M solution in THF, 0.008 mmol, 0.02 eq.), THF (0.16 mL), then dimethoxy(methyl)silane (247 μ L, 2 mmol, 5 eq.) were combined in a 2-dram vial followed by addition of a solution of *N,N*-diethyl-4-ethynyl-benzenesulfonamide (95 mg, 0.4 mmol, 1 eq.), THF (0.2 mL), and ethanol (56 μ L, 0.96 mmol, 2.4 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 20 h at 60 °C. After silica plug filtration using diethyl ether (100 mL) as the eluent, the solvent was concentrated, and the crude brown oil was dry loaded onto a silica gel column. Flash chromatography using gradient elution (100 mL of hexanes, 100 mL of 5% ethyl acetate in hexanes, 100 mL of 6% ethyl acetate in hexanes, 200 mL of 8% ethyl acetate in hexanes, 200 mL of 10% ethyl acetate in hexanes, 200 mL of 12% ethyl acetate in hexanes) gave the pure product as a clear, yellow oil (76.4 mg, 0.317 mmol, 79% yield). The spectra for the title compound matched previously reported spectra.⁶

¹H NMR: (400 MHz, CDCl₃)

δ 7.70 (d, J = 8.3 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2H), 3.21 (q, J = 7.2 Hz, 4H), 2.69 (q, J = 7.6 Hz, 2H), 1.24 (t, J = 7.6 Hz, 3H), 1.11 (t, J = 7.2 Hz, 6H).

¹³C NMR: (101 MHz, CDCl₃)

δ 149.2, 137.7, 128.5, 127.2, 42.2, 28.8, 15.2, 14.3.



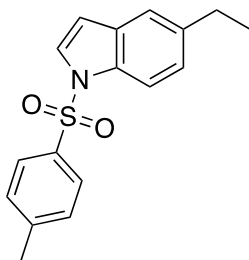
4-Ethylnitrobenzene [12]. According to the general transfer hydrogenation procedure B, (S)-DTBM-SEGPPOS (10.4 mg, 0.0088 mmol, 0.022 eq.), Cu(OAc)₂ (40 μ L of a 0.2 M solution in THF, 0.008 mmol, 0.02 eq.), THF (0.16 mL), then dimethoxy(methyl)silane (247 μ L, 2 mmol, 5 eq.) were combined in a 2-dram vial followed by addition of a solution of methyl-4-ethynylnitrobenzene (58.9 mg, 0.4 mmol, 1 eq.), THF (0.2 mL), and 2-propanol (74 μ L, 0.96 mmol, 2.4 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 24 h at room temperature. After silica plug filtration using diethyl ether (100 mL) as the eluent, the solvent was concentrated, under vacuum. Purification by flash chromatography using gradient elution (100 mL of hexanes, 200 mL of 5% ethyl acetate in hexanes 200 mL of 10% of ethyl acetate in hexanes, 200 mL of 20% ethyl acetate in hexanes) gave the pure product as a clear brown liquid (39.4 mg, 0.26 mmol, 65% yield). The spectra for the title compound matched previously reported spectra.⁷

¹H NMR: (400 MHz, CDCl₃)

δ 8.13 (d, J = 8.7 Hz, 2H), 7.33 (d, J = 8.5 Hz, 2H), 2.75 (q, J = 7.6 Hz, 2H), 1.27 (t, J = 7.6 Hz, 3H).

¹³C NMR: (101 MHz, CDCl₃)

δ 152.2, 146.3, 128.7, 123.7, 29.0, 15.2.



5-Ethyl-1-tosyl-1H-indole [13]. According to the general transfer hydrogenation procedure B, (S)-DTBM-SEPHOS (13.0 mg, 0.011 mmol, 0.055 eq.), Cu(OAc)₂ (50 μ L of a 0.2 M solution in THF, 0.01 mmol, 0.05 eq.), THF (0.05 mL), then dimethoxy(methyl)silane (123 μ L, 1.0 mmol, 5 eq.) were combined in a 2-dram vial followed by addition of a solution of 5-ethynyl-1-tosyl-1H-indole (59.1 mg, 0.2 mmol, 1 eq.), THF (0.1 mL), and 2-propanol (77 μ L, 1.0 mmol, 5 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 24 h at 60 °C. After silica plug filtration using diethyl ether (100 mL) as the eluent, the solvent was concentrated, and the crude brown liquid was dry loaded onto a silica gel column. Flash chromatography using gradient elution (100 mL of 10% ethyl acetate in hexanes, 100 mL of 20% ethyl acetate in hexanes followed by 200 mL of 30% ethyl acetate in hexanes) gave the pure product as a clear and colorless oil (36.1 mg, 0.12 mmol, 60% yield).

¹H NMR: (400 MHz, CDCl₃)

δ 7.90 (d, J = 8.5 Hz, 1H), 7.76 (d, J = 8.3 Hz, 2H), 7.53 (d, J = 3.6 Hz, 1H), 7.33 (s, 1H), 7.20 (d, J = 8.2 Hz, 2H), 7.16 (d, J = 8.5 Hz, 1H), 6.59 (d, J = 3.6 Hz, 1H), 2.70 (q, J = 7.6 Hz, 2H), 2.33 (s, 3H), 1.25 (t, J = 7.6 Hz, 3H).

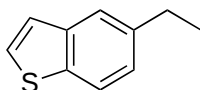
¹³C NMR: (101 MHz, CDCl₃)

δ 144.9, 139.5, 135.5, 133.3, 131.1, 130.0, 126.9, 126.5, 125.1, 120.1, 113.4, 109.1, 28.8, 21.7, 16.1.

ATR-IR (cm⁻¹):

2962, 2926, 2873, 1596, 1367, 1130.

HRMS: (ESI⁺) m/z : [M+Na]⁺ Calcd for C₁₇H₁₇NNaO₂S 322.0872; Found 322.0882.



5-Ethylbenzo[*b*]thiophene [14]. According to the general transfer hydrogenation procedure B, (S)-DTBM-SEPHOS (10.4 mg, 0.0088 mmol, 0.022 eq.), Cu(OAc)₂ (40 μ L of a 0.2 M solution in THF, 0.008 mmol, 0.02 eq.), THF (0.16 mL), then dimethoxy(methyl)silane (247 μ L, 2 mmol, 5 eq.) were combined in a 2-dram vial followed by addition of a solution of 5-ethynylbenzo[*b*]thiophene (63 mg, 0.4 mmol, 1 eq.), THF (0.2 mL), and 2-propanol (74 μ L, 0.96 mmol, 2.4 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 13 h at 60 °C. After silica plug filtration using diethyl ether (100 mL) as the eluent, the solvent was concentrated under vacuum. Purification by flash chromatography using gradient elution (100 mL of hexanes, 200 mL of 5% ethyl acetate in hexanes) gave the pure product as a clear red oil (46.9 mg, 0.289 mmol, 72% yield).

¹H NMR: (400 MHz, CDCl₃)

δ 7.82 (d, J = 8.1 Hz, 1H), 7.69 – 7.66 (m, 1H), 7.43 (d, J = 5.4 Hz, 1H), 7.31 (dd, J = 5.4, 0.8 Hz, 1H), 7.24 (dd, J = 8.2, 1.7 Hz, 1H), 2.80 (q, J = 7.6 Hz, 2H), 1.33 (t, J = 7.6 Hz, 3H).

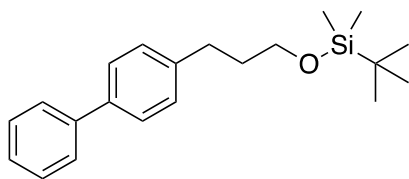
¹³C NMR: (101 MHz, CDCl₃)

δ 140.6, 140.1, 137.3, 126.5, 125.1, 123.8, 122.4, 122.3, 29.0, 16.2.

ATR-IR (cm⁻¹):

2962, 2928, 2868, 1738, 808, 691.

HRMS: (EI⁺) m/z : [M]⁺ Calcd for C₁₀H₁₀S 162.0503; Found 162.0496.



(3-([1,1'-Biphenyl]-4-yl)propoxy)(*tert*-butyl)dimethylsilane [15]. According to the general transfer hydrogenation procedure B, (S)-DTBM-SEGPPOS (8.0 mg, 0.0068 mmol, 0.022 eq.), Cu(OAc)₂ (31 μ L of a 0.2 M solution in THF, 0.0628 mmol, 0.02 eq.), THF (0.12 mL), then dimethoxy(methyl)silane (191 μ L, 1.55 mmol, 5 eq.) were combined in a 2-dram vial followed by addition of a solution of ((3-([1,1'-biphenyl]-4-yl)prop-2-yn-1-yl)oxy)(*tert*-butyl)dimethylsilane (100 mg, 0.31 mmol, 1 eq.), THF (0.15 mL), and 2-propanol (119 μ L, 1.55 mmol, 5 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 10 h at 60 °C. After silica plug filtration using diethyl ether (100 mL) as the eluent, the solvent was concentrated. Flash chromatography using gradient elution (100 mL of hexanes, 100 mL of 2% ethyl acetate in hexanes, 100 mL of 5% ethyl acetate in hexanes) gave the pure product as a white crystalline solid (71 mg, 0.217 mmol, 70% yield).

¹H NMR: (400 MHz, CDCl₃)

δ 7.59 (d, J = 7.2 Hz, 2H), 7.52 (d, J = 8.2 Hz, 2H), 7.44 (t, J = 7.6 Hz, 2H), 7.36 – 7.30 (m, 1H), 7.30 – 7.26 (m, 2H), 3.68 (t, J = 6.3 Hz, 2H), 2.76 – 2.70 (m, 2H), 1.95 – 1.83 (m, 2H), 0.93 (s, 9H), 0.08 (s, 6H).

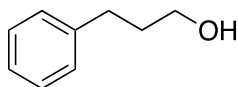
¹³C NMR: (75 MHz, CDCl₃)

δ 141.6, 141.3, 138.8, 129.0, 128.8, 127.2, 127.1, 127.1, 62.5, 34.6, 31.9, 26.1, 18.5, -5.1.

FT-IR (thin film, cm⁻¹):

2930, 2925, 2854, 1250, 1098, 1077.

HRMS: (ESI⁺) m/z : [M+Na]⁺ Calcd for C₂₁H₃₀NaOSi 349.1958; Found 349.1968.



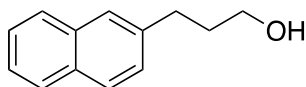
3-Phenyl-1-propanol [16]. According to the general transfer hydrogenation procedure B, (S)-DTBM-SEGPPOS (10.4 mg, 0.0088 mmol, 0.022 eq.), Cu(OAc)₂ (40 μ L of a 0.2 M solution in THF, 0.008 mmol, 0.02 eq.), THF (0.16 mL), then dimethoxy(methyl)silane (247 μ L, 2.0 mmol, 5 eq.) were combined in a 2-dram vial followed by addition of a solution of 3-phenyl-2-propyn-1-ol (52.9 mg, 0.4 mmol, 1 eq.), THF (0.2 mL), and 2-propanol (74 μ L, 0.96 mmol, 2.4 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 18 h at 60 °C. After silica plug filtration using diethyl ether (100 mL) as the eluent, the solvent was concentrated. The clear crude oil was treated with tetrabutylammonium fluoride following the general procedure C. Flash chromatography using gradient elution (100 mL of hexanes, 100 mL of 5% ethyl acetate in hexanes, 100 mL of 10% ethyl acetate in hexanes, 200 mL of 15% ethyl acetate in hexanes) gave the pure product as a clear and colorless oil (31 mg, 0.227 mmol, 57% yield). The spectra for the title compound matched previously reported spectra.⁸

¹H NMR (400 MHz, CDCl₃)

δ 7.33 – 7.27 (m, 2H), 7.24 – 7.17 (m, 3H), 3.68 (t, J = 6.5 Hz, 2H), 2.72 (t, J = 7.64 Hz, 2H), 1.95 – 1.86 (m, 2H), 1.64 (s, 1H).

¹³C NMR (101 MHz, CDCl₃)

δ 141.9, 128.5, 128.5, 126.0, 62.4, 34.3, 32.2.



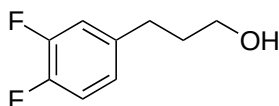
2-Naphthalenepropanol [17]. According to the general transfer hydrogenation procedure B, (S)-DTBM-SEGPPOS (10.4 mg, 0.0088 mmol, 0.022 eq.), Cu(OAc)₂ (40 μ L of a 0.2 M solution in THF, 0.008 mmol, 0.02 eq.), THF (0.16 mL), then dimethoxy(methyl)silane (247 μ L, 2.0 mmol, 5 eq.) were combined in a 2-dram vial followed by addition of a solution of 3-(2-Naphthalenyl)-2-propyn-1-ol (72.8 mg, 0.4 mmol, 1 eq.), THF (0.2 mL), and 2-propanol (74 μ L, 0.96 mmol, 2.4 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 18 h at 60 °C. After silica plug filtration using diethyl ether (100 mL) as the eluent, the solvent was concentrated. The clear crude oil was treated with tetrabutylammonium fluoride following the general procedure C. Flash chromatography using gradient elution (100 mL of hexanes, 100 mL of 5% ethyl acetate in hexanes, 200 mL of 10% ethyl acetate in hexanes, 200 mL of 15% ethyl acetate in hexanes) gave the pure product as a white solid (56 mg, 0.30 mmol, 75% yield). The spectra for the title compound matched previously reported spectra.⁹

¹H NMR (400 MHz, CDCl₃)

δ 7.85 – 7.74 (m, 3H), 7.65 (s, 1H), 7.50 – 7.40 (m, 2H), 7.36 (d, J = 8.4 Hz, 1H), 3.72 (t, J = 6.4 Hz, 2H), 2.89 (t, J = 7.6 Hz, 2H), 2.03 – 1.93 (m, 2H), 1.76 (s, 1H).

¹³C NMR (75 MHz, CDCl₃)

δ 139.4, 133.7, 132.1, 128.1, 127.7, 127.5, 127.4, 126.5, 126.0, 125.3, 62.3, 34.1, 32.3.



3,4-Difluorobenzenepropanol [18]. According to the general transfer hydrogenation procedure B, (S)-DTBM-SEGPPOS (10.4 mg, 0.0088 mmol, 0.022 eq.), Cu(OAc)₂ (40 μ L of a 0.2 M solution in THF, 0.008 mmol, 0.02 eq.), THF (0.16 mL), then dimethoxy(methyl)silane (247 μ L, 2.0 mmol, 5 eq.) were combined in a 2-dram vial followed by addition of a solution of 3,4-difluorobenzenepropynol (67.3 mg, 0.4 mmol, 1 eq.), THF (0.2 mL), and 2-propanol (74 μ L, 0.96 mmol, 2.4 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 19 h at 60 °C. After silica plug filtration using diethyl ether (100 mL) as the eluent, the solvent was concentrated. The clear crude oil was treated with tetrabutylammonium fluoride following the general procedure C. Flash chromatography using gradient elution (100 mL of hexanes, 100 mL of 5% ethyl acetate in hexanes, 100 mL of 10% ethyl acetate in hexanes, 200 mL of 15% ethyl acetate in hexanes) gave the pure product as a clear oil (39.0 mg, 0.227 mmol, 57% yield).

¹H NMR (400 MHz, CDCl₃)

δ 7.10 – 6.95 (m, 2H), 6.92 – 6.86 (m, 1H), 3.66 (q, J = 5.9 Hz, 2H), 2.67 (t, J = 7.4, 2H), 1.90 – 1.81 (m, 2H), 1.31 (s, 1H).

¹³C NMR (101 MHz, CDCl₃)

δ 150.8 (dd, J = 144.6, 12.6 Hz), 148.3 (dd, J = 142.6, 12.7 Hz), 138.9 (dd, J = 5.5, 3.9 Hz), 124.3 (dd, J = 6.0, 3.5 Hz), 117.2 (d, J = 16.6 Hz), 117.1 (d, J = 16.8 Hz), 61.9, 34.1, 31.3.

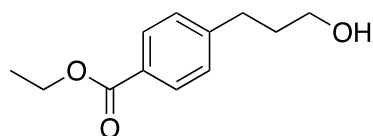
¹⁹F NMR (376 MHz, CDCl₃)

δ -138.53, -142.39.

ATR-IR (cm⁻¹):

3319, 2934, 2868, 1717, 1510, 1209, 1116, 1048.

HRMS: (ESI⁺) m/z : [M+H]⁺ Calcd for C₉H₁₁OF₂ 173.0778; Found 173.0780.



Ethyl-4-(-3-hydroxypropyl)benzoate [19]. According to the general transfer hydrogenation procedure B, (S)-DTBM-SEGPBOS (10.4 mg, 0.0088 mmol, 0.022 eq.), Cu(OAc)₂ (40 μ L of a 0.2 M solution in THF, 0.008 mmol, 0.02 eq.), THF (0.16 mL), then dimethoxy(methyl)silane (247 μ L, 2.0 mmol, 5 eq.) were combined in a 2-dram vial followed by addition of a solution of ethyl-4-(-3-hydroxypropynyl)benzoate (81.8 mg, 0.4 mmol, 1 eq.), THF (0.2 mL), and 2-propanol (73.9 μ L, 0.96 mmol, 2.4 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 18 h at 60 °C. After silica plug filtration using diethyl ether (100 mL) as the eluent, the solvent was concentrated. The clear crude oil was treated with tetrabutylammonium fluoride following the general procedure C. Flash chromatography using gradient elution (100 mL of hexanes, 100 mL of 5% ethyl acetate in hexanes, 100 mL of 10% ethyl acetate in hexanes, 200 mL of 15% ethyl acetate in hexanes) gave the pure product as a clear yellow oil (51 mg, 0.244 mmol, 61% yield).

¹H NMR (400 MHz, CDCl₃)

δ 7.95 (d, J = 8 Hz, 2H), 7.25 (d, J = 7.7 Hz, 2H), 4.35 (q, J = 7 Hz, 2H), 3.66 (t, J = 6.3 Hz, 2H), 2.76 (t, J = 8, 2H), 1.90 (p, 2H), 1.65 (s, 1H), 1.37 (t, J = 7.1 Hz, 3H).

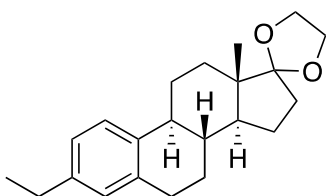
¹³C NMR (101 MHz, CDCl₃)

δ 166.8, 147.5, 129.8, 128.5, 128.2, 62.0, 60.9, 33.9, 32.2, 14.4.

ATR-IR (cm⁻¹):

3412, 2986, 2933, 2873, 1713, 1610, 1272, 1102, 1041, 1020.

HRMS: (ESI⁺) m/z : [M+Na]⁺ Calcd for C₁₂H₁₆NaO₃ 231.0992; Found 231.0999.



(8R,9S,13S,14S)-3-Ethyl-13-methyl-6,7,8,9,11,12,13,14,15,16-

decahydrospiro[cyclopenta[a]phenanthrene-17,2'-[1,3]dioxolane] [20]. According to the general procedure B, (S)-DTBM-SEGPBOS (5.7 mg, 0.00486 mmol, 0.022 eq.), Cu(OAc)₂ (22 μ L of a 0.2 M solution in THF, 0.0044 mmol, 0.02 eq.), THF (0.1 mL), then dimethoxy(methyl)silane (136 μ L, 1.1 mmol, 5 eq.) were combined in a 2-dram vial followed by addition of a solution of (8R,9S,13S,14S)-3-(ethynyl)-13-methyl-6,7,8,9,11,12,13,14,15,16 decahydrospiro[cyclopenta[a]phenanthrene-17,2'-[1,3]dioxolane] (71.3 mg, 0.22 mmol, 1 eq.), THF (0.1 mL), and 2-propanol (85 μ L, 1.1 mmol, 5 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 19 h at 60 °C. After silica plug filtration using dichloromethane as the eluent (100 mL), the solvent was concentrated, and the crude brown oil was dry loaded onto a silica gel column. Flash chromatography using gradient elution (100 mL of hexanes, 100 mL of 3% ethyl acetate in hexanes, 100 mL of 5% ethyl acetate in hexanes, 100 mL of 8% ethyl acetate in hexanes, 200 mL of 9% ethyl acetate in hexanes, 100 mL of 10% ethyl acetate in hexanes) gave the pure product as a clear, yellow oil (56.2 mg, 0.172 mmol, 78% yield).

¹H NMR (400 MHz, CDCl₃)

δ 7.25 (d, J = 7.9 Hz, 1H), 7.00 (d, J = 8.0 Hz, 1H), 6.95 (s, 1H), 4.02 – 3.86 (m, 4H), 2.94 – 2.80 (m, 2H), 2.60 (q, J = 7.6 Hz, 2H), 2.41 – 2.23 (m, 2H), 2.11 – 2.00 (m, 1H), 1.96 – 1.73 (m, 4H), 1.71 – 1.60 (m, 1H), 1.59 – 1.30 (m, 5H), 1.24 (t, J = 7.6 Hz, 3H), 0.90 (s, 3H).

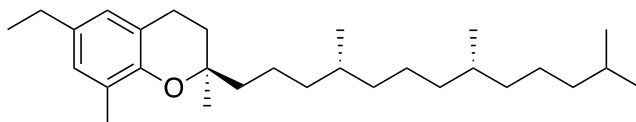
¹³C NMR (101 MHz, CDCl₃)

δ 141.6, 137.8, 136.7, 128.6, 125.5, 125.3, 119.6, 65.4, 64.7, 49.6, 46.3, 44.1, 39.1, 34.4, 30.9, 29.7, 28.4, 27.2, 26.1, 22.5, 15.8, 14.5.

ATR-IR (cm⁻¹):

2965, 2933, 2872, 1735, 1693, 1610, 1103, 1040.

HRMS: (ESI⁺) m/z: [M+H]⁺ Calcd for C₂₂H₃₁O₂ 327.2319; Found 327.2329.



(R)-6-Ethyl-2,8-dimethyl-2-((4R,8R)-4,8,12-trimethyltridecyl)chromane [21]. According to the general procedure B, (S)-DTBM-SEPHOS (13 mg, 0.011 mmol, 0.055 eq.), Cu(OAc)₂ (50 μ L of a 0.2 M solution in THF, 0.01 mmol, 0.05 eq.), THF (0.05 mL), then dimethoxy(methyl)silane (99 μ L, 0.8 mmol, 4 eq.) were combined in a 2-dram vial followed by addition of a solution of (R)-6-ethynyl-2,8-dimethyl-2-((4R,8R)-4,8,12-trimethyltridecyl)chromane (82.1 mg, 0.2 mmol, 1 eq.), THF (0.1 mL), and 2-propanol (77 μ L, 1.0 mmol, 5 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 16 h at 60 °C. After silica plug filtration using diethyl ether (100 mL) as the eluent, the solvent was concentrated, and the crude colorless liquid was dry loaded onto a silica gel column. Flash chromatography using gradient elution (100 mL of hexanes followed by 200 mL of 2% ethyl acetate in hexanes) gave the pure product as a clear and colorless liquid (51.2 mg, 0.124 mmol, 62% yield).

¹H NMR: (400 MHz, CDCl₃)

δ 6.80 (s, 1H), 6.73 (s, 1H), 2.80 – 2.66 (m, 2H), 2.53 (q, *J* = 7.6 Hz, 2H), 2.15 (s, 3H), 1.87 – 1.68 (m, 2H), 1.62 – 1.47 (m, 3H), 1.46 – 1.01 (m, 24H), 0.92 – 0.81 (m, 12H).

¹³C NMR: (101 MHz, CDCl₃)

δ 150.2, 134.5, 128.0, 126.1, 126.0, 120.3, 75.9, 40.4, 39.5, 37.6, 37.6, 37.4, 33.0, 32.9, 31.5, 28.1, 28.1, 25.0, 24.6, 24.5, 22.9, 22.8, 22.5, 21.2, 19.9, 19.8, 16.2, 16.1.

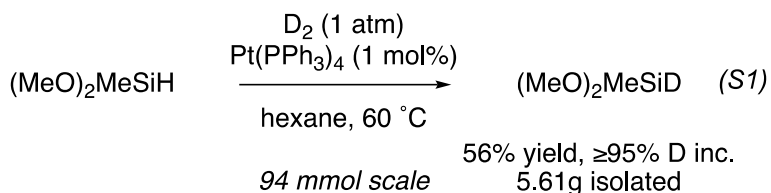
ATR-IR (cm⁻¹):

2957, 2924, 2854, 1733, 1598, 1220, 1151.

HRMS: (ESI⁺) m/z: [M+H]⁺ Calcd for C₂₉H₅₁O 415.3934; Found 415.3946.

Transfer Deuteration Reaction Scope

Procedure for the synthesis of dimethoxy(methyl)silane-*d*



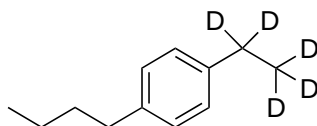
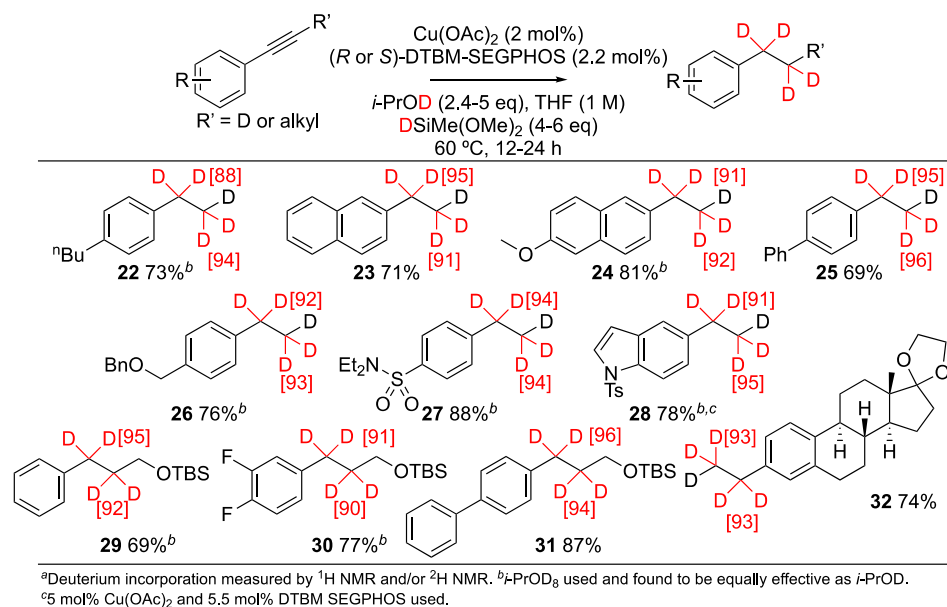
The procedure was adapted from a previously reported method.¹⁰ To an oven-dried 500 mL Schlenk flask equipped with a Teflon stir bar in a N₂ filled glovebox was added the Pt(PPh₃)₄ (1.17 g, 0.941 mmol, 0.01 eq.), dimethoxy(methyl)silane (11.6 mL, 94.1 mmol, 1 eq.), and 5.0 mL of degassed anhydrous hexanes. The Schlenk flask was sealed with a rubber septa and removed from the glovebox, connected to a manifold line, and cooled to -78 °C. A single freeze-pump-thaw cycle was performed, and the Schlenk flask was backfilled with D₂ gas from a D₂ purged balloon at room temperature. The flask was sealed with parafilm and heated to 60 °C. After 2 hours, the reaction was cooled to room temperature and then a single freeze-pump-thaw was performed again, backfilling with D₂ gas. The process was repeated 6 times or until the ¹H NMR showed $\geq 95\%$ D incorporation. It is important to maintain a N₂ (g) inert atmosphere while obtaining a minimal quantity of sample for ¹H NMR analysis.

The solution was purified through a distillation apparatus; the set up consisted of a flame-dried 25 mL round-bottom receiving flask and a cannula. The 25 mL round-bottom receiving flask was flame-dried, and then filled with N₂. Once the receiving flask reached room temperature, the cannula was inserted, maintaining positive pressure, and tightly sealed with parafilm to prevent condensation from entering. Upon confirmation of positive N₂ flow, the open end of the cannula was inserted into the Schlenk reaction flask. The 25 mL round-bottom receiving flask was cooled to -78 °C and closed to the manifold line, and then the Schlenk flask was heated to 80 °C. The heat initiated the distillation of the dimethoxy(methyl)silane-*d* and the hexane through the cannula which were trapped in the cold 25 mL round-bottom receiving flask. Vacuum was also applied to the 25 mL round-bottom receiving flask to promote this process. Once all of the silane and hexane were trapped in the 25 mL round-bottom receiving flask, the flask was removed from the heat and the manifold was closed to vacuum line while the 25 mL round-bottom receiving flask warmed to room temperature. Under positive nitrogen flow, the cannula was removed from the 25 mL round-bottom receiving flask, while keeping it inserted in the Schlenk reaction flask. The 25 mL round-bottom receiving flask was tightly sealed with parafilm, and stored in the -4 °C freezer. The final product was in a solution of hexane, and the molarity was calculated by ¹H NMR using 1,3,5-trimethylbenzene as an internal standard, and used for the transfer deuteration reactions (5.61 g in a 5.29 M hexane solution, 52.9 mmol, 56% yield). *Note: it is important to monitor that the end of the cannula does not get clogged by frozen solvent/silane. If this occurs, remove the Schlenk reaction flask from heat and close manifold to vacuum line. Warm the 25 mL round-bottom receiving flask until the solids on the tip of the cannula melt, and then distillation can be resumed.

General procedure for transfer deuteration. (D)

In a N₂ filled glovebox, (*R* or *S*)-DTBM-SEPHOS (10.4 mg, 0.0088 mmol, 0.022 eq.), Cu(OAc)₂ (40 μL of a 0.2 M solution in THF, 0.008 mmol, 0.02 eq.), and THF (0.16 mL) were added to an oven-dried 2-dram vial followed by dropwise addition of dimethoxy(methyl)silane-*d* in hexanes (2 mmol, 5 eq.). A color change from green/blue to orange was observed while stirring for 15 minutes. In a separate 1-dram vial was added the alkyne substrate (0.4 mmol, 1 eq.), THF (0.2 mL), and either 2-propanol-OD or 2-propanol-*d*₈ (2.4-5 eq. based on substrate). The solution in the 1-dram vial was added dropwise over 20 seconds to the 2-dram vial. The total volume of THF was calculated based on having a final reaction concentration of 1M based on the alkyne substrate. The 2-dram vial was capped with a red pressure relief cap, taken out of the glovebox, and stirred for 9-24 h at 60 °C at which point the reaction was filtered through a 1" silica plug with 20 mL of Et₂O followed by 80 mL of Et₂O to elute the remaining product into a 200 mL round bottom flask. After removing the Et₂O by rotary evaporation, the crude product was isolated by flash chromatography. Method for calculating deuterium incorporation at each labeled carbon of each substrate: In the ¹H NMR spectra, if both benzylic and homobenzylic peaks were clearly visible and no overlap with other peaks was observed, then the deuterium incorporation was calculated from the integration of the protonated peak. If overlap of other peaks or overlap with an impurity such as water or grease was observed in the homobenzylic region of the ¹H NMR spectra, a ²H NMR spectra was obtained. The ratio of the two peaks that appear in the ²H NMR spectra was correlated to the calculated deuterium incorporation at the benzylic peak in the ¹H NMR spectra. *2-propanol-*d*₈ was used due to a 2-propanol-OD backorder from the supplier during COVID-19.

Scheme S2. Transfer Deuteration Substrate Scope



1-Butyl-4-(ethynyl-*d*₅)benzene [22]. According to the general procedure D, (*S*)-DTBM-SEGPHOS (5.2 mg, 0.0044 mmol, 0.022 eq.), Cu(OAc)₂ (20 μL of a 0.2 M solution in THF, 0.004 mmol, 0.02 eq.), THF (0.08 mL), then dimethoxy(methyl)silane-*d*₈ (0.17 mL of a 5.9 M solution in hexanes, 1.0 mmol, 5 eq.) were combined in a 2-dram vial followed by addition of a solution of 1-butyl-4-(ethynyl-*d*)benzene (31.8 mg, 0.2 mmol, 1 eq.), THF (0.1 mL), and 2-propanol-*d*₈ (77 μL, 1.0 mmol, 5 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 17 h at 60 °C. After silica plug filtration using diethyl ether (100 mL) as the eluent, the solvent was concentrated, and the crude yellow liquid was dry loaded onto a silica gel column. Flash chromatography using 200 mL of hexanes as eluent gave the pure product as a colorless oil (24.4 mg, 0.146 mmol, 73% yield).

¹H NMR: (400 MHz, CDCl₃)

δ 7.12 (s, 4H), 2.62 – 2.57 (m, 2.24H due to overlap of two benzylic sites), 1.65 – 1.55 (m, 2H), 1.43 – 1.31 (m, 2H), 1.19 (br s, integration not determined due to overlap with grease), 0.94 (t, *J* = 7.3 Hz, 3H).

²H NMR: (61 MHz, CHCl₃)

δ 2.58 (br s, 1.76D), 1.19 (br s, 2.82D).

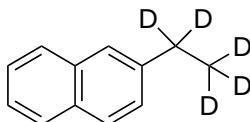
¹³C NMR: (101 MHz, CDCl₃)

δ 141.4, 140.2, 128.5, 127.8, 35.4, 34.0, 28.3 – 27.2 (m), 22.6, 15.5 – 14.6 (m), 14.1.

ATR-IR (cm⁻¹):

2956, 2927, 2857, 2222, 2079, 1514.

HRMS: (EI⁺) *m/z*: [M]⁺ Calcd for C₁₂H₁₃D₅ 168.1722; Found 167.1716.



2-(Ethyl-*d*₅)naphthalene [23]. According to the general procedure D, (*S*)-DTBM-SEGPPOS (10.4 mg, 0.0088 mmol, 0.022 eq.), Cu(OAc)₂ (40 μ L of a 0.2 M solution in THF, 0.008 mmol, 0.02 eq.), THF (0.16 mL), then dimethoxy(methyl)silane-*d* (0.38 mL of 5.3 M solution in hexanes, 2 mmol, 5 eq.) were combined in a 2-dram vial followed by addition of a solution of 2-(ethynyl-*d*)naphthalene (61.2 mg, 0.4 mmol, 1 eq.), THF (0.2 mL), and 2-propanol-OD (74 μ L, 0.96 mmol, 2.4 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 21 h at 60 °C. After silica plug filtration using diethyl ether (100 mL) as the eluent, the solvent was concentrated, and the crude brown oil was dry loaded onto a silica gel column. Flash chromatography using 350 mL of hexanes as eluent gave the pure product as a clear, yellow oil (46.0 mg, 0.285 mmol, 71% yield).

¹H NMR: (400 MHz, CDCl₃)

δ 7.85 – 7.75 (m, 3H), 7.64 (s, 1H), 7.51 – 7.40 (m, 2H), 7.37 (d, *J* = 8.4, 1H), 2.80 (br s, 0.11H), 1.30 (br s, integration not determined due to overlap with grease).

²H NMR: (61 MHz, CHCl₃)

δ 2.80 (br s, 1.89D), 1.31 (br s, 2.72D).

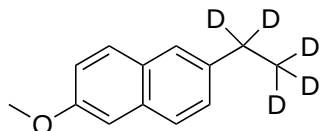
¹³C NMR: (101 MHz, CDCl₃)

δ 141.9, 133.9, 132.1, 127.9, 127.7, 127.6, 127.2, 126.0, 125.7, 125.1, 29.0 – 27.7 (m), 15.5 – 13.9 (m).

FT-IR (thin film, cm⁻¹):

2961, 2922, 2851, 2221, 1508, 1462.

HRMS: (EI⁺) *m/z*: [M]⁺ Calcd for C₁₂H₇D₅ 161.1253; Found 161.1247.



2-(Ethyl-*d*₅)-6-methoxynaphthalene [24]. According to the general procedure D, (*R*)-DTBM-SEGPPOS (5.2 mg, 0.0044 mmol, 0.022 eq.), Cu(OAc)₂ (20 μ L of a 0.2 M solution in THF, 0.004 mmol, 0.02 eq.), THF (0.08 mL), then dimethoxy(methyl)silane-*d* (0.17 mL of a 5.9 M solution in hexanes, 1.0 mmol, 5 eq.) were combined in a 2-dram vial followed by addition of a solution of 2-(ethynyl-*d*)-6-methoxynaphthalene (36.6 mg, 0.2 mmol, 1 eq.), THF (0.10 mL), and 2-propanol-*d*₈ (77 μ L, 1.0 mmol, 5 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 17 h at 60 °C. After silica plug filtration using diethyl ether (100 mL) as the eluent, the solvent was concentrated and the crude colorless solid was dry loaded onto a silica gel column. Flash chromatography using elution (50 mL of hexanes, 200 mL of 2% ethyl acetate in hexanes) gave the pure product as a white solid (31.0 mg, 0.162 mmol, 81% yield).

¹H NMR: (400 MHz, CDCl₃)

δ 7.72 – 7.67 (m, 2H), 7.58 (d, *J* = 0.9 Hz, 1H), 7.34 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.17 – 7.12 (m, 2H), 3.93 (s, 3H), 2.77 (br s, 0.18H), 1.29 (br s, integration not determined due to overlap with grease).

²H NMR: (61 MHz, CHCl₃)

δ 2.77 (br s, 1.82D), 1.30 (br s, 2.77D).

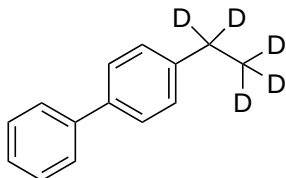
¹³C NMR: (101 MHz, CDCl₃)

δ 157.2, 139.5, 133.0, 129.3, 129.0, 127.7, 126.8, 125.6, 118.7, 105.7, 55.4, 28.6 – 27.7 (m), 15.2 – 14.5 (m).

ATR-IR (cm⁻¹):

2961, 2938, 2838, 2218, 2062, 1161.

HRMS: (ESI⁺) *m/z*: [M+H]⁺ Calcd for C₁₃H₁₀D₅O 192.1436; Found 192.1426.



4-(Ethyl-*d*₅)-1,1'-biphenyl [25]. According to the general procedure D, (*S*)-DTBM-SEGPPOS (10.4 mg, 0.0088 mmol, 0.022 eq.), Cu(OAc)₂ (40 μ L of a 0.2 M solution in THF, 0.008 mmol, 0.02 eq.), THF (0.16 mL), then dimethoxy(methyl)silane-*d* (0.51 mL of 3.9 M solution in hexanes, 2 mmol, 5 eq.) were combined in a 2-dram vial followed by addition of a solution of 4-ethynyl-*d*-1,1'-biphenyl (71.6 mg, 0.4 mmol, 1 eq.), THF (0.2 mL), and 2-propanol-OD (74 μ L, 0.96 mmol, 2.4 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 13 h at 60 °C. After silica plug filtration using diethyl ether (100 mL) as the eluent, the solvent was concentrated, and the crude brown oil was dry loaded onto a silica gel column. Flash chromatography using 350 mL of hexanes as eluent gave the pure product as a clear, yellow oil (51.6 mg, 0.276 mmol, 69% yield).

¹H NMR (400 MHz, CDCl₃)

δ 7.68 – 7.59 (m, 2H), 7.59 – 7.52 (m, 2H), 7.50 – 7.42 (m, 2H), 7.40 – 7.33 (m, 1H), 7.33 – 7.29 (m, 2H), 2.70 (br s, 0.10H), 1.27 (br s, integration not determined due to overlap with grease).

²H NMR: (61 MHz, CHCl₃)

δ 2.70 (br s, 1.90D), 1.28 (br s, 2.87D).

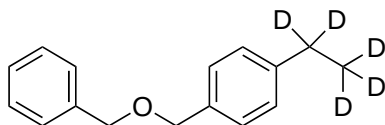
¹³C NMR (75 MHz, CDCl₃)

δ 143.5, 141.3, 138.7, 128.8, 128.4, 127.2, 127.2, 127.1, 28.6 – 27.0 (m), 15.7 – 14.1 (m).

ATR-IR (cm⁻¹):

3054, 3028, 2936, 2221, 2067.

HRMS: (EI⁺) *m/z*: [M+H]⁺ Calcd for C₁₄H₉D₅ 187.1409; Found 187.1404.



1-((Benzyloxy)methyl)-4-(ethyl-*d*₅)benzene [26]. According to the general procedure D, (*S*)-DTBM-SEGPPOS (5.2 mg, 0.0044 mmol, 0.022 eq.), Cu(OAc)₂ (20 μ L of a 0.2 M solution in THF, 0.004 mmol, 0.02 eq.), THF (0.08 mL), then dimethoxy(methyl)silane-*d* (0.20 mL of a 5.9 M solution in hexanes, 1.2 mmol, 6 eq.) were combined in a 2-dram vial followed by addition of a solution of 1-((benzyloxy)methyl)-4-(ethynyl-*d*)benzene (45 mg, 0.2 mmol, 1 eq.), THF (0.1 mL), and 2-propanol-*d*₈ (77 μ L, 1.0 mmol, 5 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 18 h at 60 °C. After silica plug filtration using diethyl ether (100 mL) as the eluent, the solvent was concentrated, and the crude brown oil was dry loaded onto a silica gel column. Flash chromatography using gradient elution (50 mL of hexanes, 100 mL of 3% ethyl acetate in hexanes, 200 mL of 5% ethyl acetate in hexanes) gave the pure product as a colorless oil (35.0 mg, 0.151 mmol, 76% yield).

¹H NMR: (400 MHz, CDCl₃)

δ 7.42 – 7.35 (m, 4H), 7.34 – 7.29 (m, 3H), 7.22 (d, *J* = 8.1 Hz, 2H), 4.58 (s, 2H), 4.56 (s, 2H), 2.64 (br s, 0.17H), 1.21 (br s, integration not determined due to overlap with grease).

²H NMR: (61 MHz, CHCl₃)

δ 2.64 (br s, 1.83D), 1.22 (br s, 2.78D).

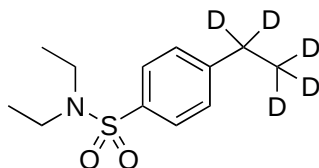
¹³C NMR: (101 MHz, CDCl₃)

δ 143.8, 138.5, 135.6, 128.5, 128.1, 128.0, 127.9, 127.7, 72.1, 72.1, 28.4 – 27.3 (m), 15.5 – 14.3 (m).

ATR-IR (cm⁻¹):

3029, 2853, 2222, 2081, 1615, 1090, 1071.

HRMS: (ESI⁺/FTICR) m/z: [M+Na]⁺ Calcd for C₁₆H₁₃D₅NaO 254.1564; Found 254.1570.



***N,N*-Diethyl-4-(ethyl-*d*₅)benzenesulfonamide [27].** According to the general procedure D, (*S*)-DTBM-SEGPPOS (10.4 mg, 0.0088 mmol, 0.022 eq.), Cu(OAc)₂ (40 μL of a 0.2 M solution in THF, 0.008 mmol, 0.02 eq.), THF (0.16 mL), then dimethoxy(methyl)silane-*d* (0.38 mL of 5.3 M solution in hexanes, 2 mmol, 5 eq.) were combined in a 2-dram vial followed by addition of a solution of *N,N*-diethyl-4-(ethynyl-*d*)benzenesulfonamide (95 mg, 0.4 mmol, 1 eq.), THF (0.2 mL), and 2-propanol-*d*₈ (153 μL, 2.0 mmol, 5 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 24 h at 60 °C. After silica plug filtration using diethyl ether (100 mL) as the eluent, the solvent was concentrated, and the crude brown oil was dry loaded onto a silica gel column. Flash chromatography using gradient elution (100 mL of hexanes, 100 mL 4% ethyl acetate in hexane, 300 mL of 8% ethyl acetate in hexanes) gave the pure product as a clear, yellow oil (86.1 mg, 0.35 mmol, 88% yield).

¹H NMR (400 MHz, CDCl₃)

δ 7.68 (d, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 8.2 Hz, 2H), 3.19 (q, *J* = 7.2 Hz, 4H), 2.63 (br s, 0.12H), 1.16 (br s, integration not determined due to overlap with grease), 1.09 (t, *J* = 7.2 Hz, 6H).

²H NMR: (61 MHz, CHCl₃)

δ 2.63 (br s, 1.88D), 1.17 (br s, 2.83D).

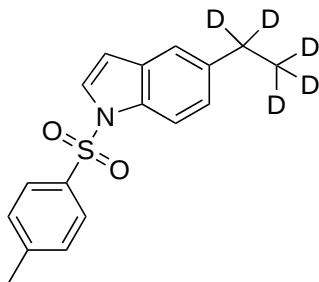
¹³C NMR (101 MHz, CDCl₃)

δ 149.0, 137.6, 128.4, 127.1, 42.1, 32.3 – 31.6 (m), 28.5 – 27.4 (m), 14.2.

ATR-IR (cm⁻¹):

2976, 2936, 2870, 2225, 2079, 1332, 1150.

HRMS: (ESI⁺/FTICR) m/z: [M+Na]⁺ Calcd for C₁₂H₁₄D₅NNaO₂S 269.1343; Found 269.1351.



5-(Ethyl-*d*₅)-1-tosyl-1H-indole [28]. According to the general procedure D, (*S*)-DTBM-SEGPPOS (13.0 mg, 0.011 mmol, 0.055 eq.), Cu(OAc)₂ (50 μL of a 0.2 M solution in THF, 0.01 mmol, 0.05 eq.), THF (0.05 mL), then dimethoxy(methyl)silane-*d* (0.17 mL of a 5.9 M solution in hexanes, 1.0 mmol, 5 eq.) were combined in a 2-dram vial followed by addition of a solution of 5-(ethynyl-*d*)-1-tosyl-1H-indole (59.3 mg, 0.2 mmol, 1 eq.), THF (0.1 mL), and 2-propanol-*d*₈ (77 μL, 1.0 mmol, 5 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 24 h at 60 °C. After silica plug filtration using diethyl ether (100 mL) as the eluent, the solvent was concentrated, and the crude brown liquid was dry loaded

onto a silica gel column. Flash chromatography using gradient elution (100 mL of hexanes, 100 mL of 5% ethyl acetate in hexanes, 200 mL of 10% ethyl acetate in hexanes) gave the pure product as a colorless oil (47.7 mg, 0.156 mmol, 78% yield).

¹H NMR: (400 MHz, CDCl₃)

δ 7.90 (d, *J* = 8.5 Hz, 1H), 7.76 (d, *J* = 8.3 Hz, 2H), 7.53 (d, *J* = 3.6 Hz, 1H), 7.33 (d, *J* = 1.4 Hz, 1H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.16 (dd, *J* = 8.5, 1.4 Hz, 1H), 6.60 (d, *J* = 3.6 Hz, 1H), 2.66 (br s, 0.18H), 2.32 (s, 3H), 1.20 (br s, integration not determined due to overlap with grease).

²H NMR: (61 MHz, CHCl₃)

δ 2.66 (br s, 1.82D), 1.21 (br s, 2.84D).

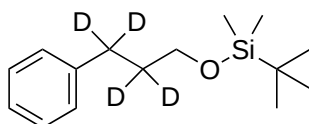
¹³C NMR: (101 MHz, CDCl₃)

δ 144.9, 139.4, 135.4, 133.3, 131.1, 129.9, 126.9, 126.5, 125.1, 120.1, 113.4, 109.1, 28.5 – 27.4 (m), 21.7, 15.9 – 14.6 (m).

ATR-IR (cm⁻¹):

3038, 2922, 2221, 2081, 1367, 1130.

HRMS: (ESI⁺/FTICR) *m/z*: [M+Na]⁺ Calcd for C₁₇H₁₂D₅NNaO₂S 327.1186; Found 327.1195.



tert-Butyldimethyl(3-phenylpropoxy-2,2,3,3-*d*₄)silane [29]. According to the general procedure D, (*R*)-DTBM-SEGPPOS (7.8 mg, 0.0066 mmol, 0.022 eq.), Cu(OAc)₂ (30 μL of a 0.2 M solution in THF, 0.006 mmol, 0.02 eq.), THF (0.12 mL), then dimethoxy(methyl)silane-*d* (0.28 mL, 1.5 mmol, 5.3 M solution in hexanes, 5 eq.) were combined in a 2-dram vial followed by addition of a solution of ((3-(phenyl)prop-2-yn-1-yl)oxy)(*tert*-butyl)dimethylsilane (73.8 mg, 0.3 mmol, 1 eq.), THF (0.15 mL), and 2-propanol-*d*₈ (115 μL, 1.5 mmol, 5.0 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 19 h at 60 °C. After silica plug filtration using diethyl ether (100 mL) as the eluent, the solvent was concentrated, and the crude brown oil was dry loaded onto a silica gel column. Flash chromatography using gradient elution (100 mL of hexanes) gave the pure product as a clear and colorless oil (53.0 mg, 0.208 mmol, 69% yield).

¹H NMR (300 MHz, CDCl₃)

δ 7.38 – 7.26 (m, 2H), 7.22 – 7.19 (m, 3H), 3.65 (s, 2H), 2.67 (br s, 0.11H), 1.83 (br s, 0.16H), 0.94 (s, 9H), 0.08 (s, 6H).

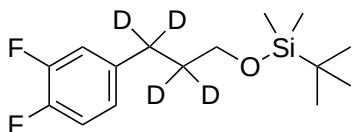
¹³C NMR (75 MHz, CDCl₃)

δ 142.3, 128.6, 128.4, 125.8, 62.4, 34.5 – 33.1 (m), 32.2 – 30.7 (m), 26.1, 18.5, -5.1.

ATR-IR (cm⁻¹):

2928, 2894, 2856, 2211, 2116, 1085.

HRMS: (ESI⁺) *m/z*: [M+H]⁺ Calcd for C₁₅H₂₃D₄OSi 255.2082; Found 255.2072.



tert-Butyl(3-(3,4-difluorophenyl)propoxy-2,2,3,3-*d*₄)dimethylsilane [30]. According to the general procedure D, (*S*)-DTBM-SEGPPOS (5.2 mg, 0.0044 mmol, 0.022 eq.), Cu(OAc)₂ (20 μL of a 0.2 M solution in THF, 0.004 mmol, 0.02 eq.), THF (0.08 mL), then dimethoxy(methyl)silane-*d* (0.14 mL of a 5.9 M solution in hexanes, 0.8 mmol, 4 eq.) were combined in a 2-dram vial followed by addition of a solution of 1-

((benzyloxy)methyl)-4-(ethynyl-*d*)benzene (56.5 mg, 0.2 mmol, 1 eq.), THF (0.1 mL), and 2-propanol-*d*₈ (77 μ L, 1.0 mmol, 5 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 24 h at 60 °C. After silica plug filtration using diethyl ether (100 mL) as the eluent, the solvent was concentrated, and the crude colorless oil was dry loaded onto a silica gel column. Flash chromatography using gradient elution (100 mL of hexanes followed by 200 mL of 1% ethyl acetate in hexanes) gave the pure product as a clear and colorless oil (44.6 mg, 0.154 mmol, 77% yield).

¹H NMR: (400 MHz, CDCl₃)

δ 7.08 – 6.95 (m, 2H), 6.90 – 6.85 (m, 1H), 3.60 (s, 2H), 2.61 (br s, 0.19H), 1.76 (br s, 0.20H), 0.91 (s, 9H), 0.05 (s, 6H).

¹³C NMR: (75 MHz, CDCl₃)

δ 150.3 (dd, *J* = 247.1, 12.6 Hz), 148.8 (dd, *J* = 245.1, 12.6 Hz), 139.3 (dd, *J* = 4.3 Hz), 124.3 (dd, *J* = 5.7, 3.5 Hz), 117.3 (d, *J* = 16.6 Hz), 117.0 (d, *J* = 16.9 Hz), 61.9, 34.2 – 32.8 (m), 31.3 – 30.1 (m), 26.1, 18.5, -5.2.

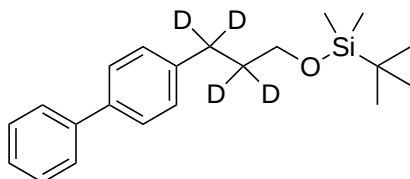
¹⁹F NMR: (376 MHz, CDCl₃)

δ -138.80, -142.71.

ATR-IR (cm⁻¹):

2955, 2929, 2857, 2211, 2119, 1607, 1518, 1254, 1087.

HRMS: (ESI⁺) *m/z*: [M+H]⁺ Calcd for C₁₅H₂₁D₄F₂OSi 291.1894; Found 291.1881.



(3-([1,1'-Biphenyl]-4-yl)propoxy-2,2,3,3-*d*₄)(*tert*-butyl)dimethylsilane [31]. According to the general procedure D, (*S*)-DTBM-SEGPHOS (8 mg, 0.0068 mmol, 0.022 eq.), Cu(OAc)₂ (31 μ L of a 0.2 M solution in THF, 0.0062 mmol, 0.02 eq.), THF (0.13 mL), then dimethoxy(methyl)silane-*d* (0.29 mL, 1.55 mmol, 5.3M solution in hexanes, 5 eq.) were combined in a 2-dram vial followed by addition of a solution of ((3-([1,1'-biphenyl]-4-yl)prop-2-yn-1-yl)oxy)(*tert*-butyl)dimethylsilane (100 mg, 0.31 mmol, 1 eq.), THF (0.15 mL), and 2-propanol-OD (119 μ L, 1.55 mmol, 5 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 24 h at 60 °C. After silica plug filtration using diethyl ether (100 mL) as the eluent, the solvent was concentrated. Flash chromatography using gradient elution (100 mL of hexanes, 100 mL of 2% ethyl acetate in hexanes, 100 mL of 5% ethyl acetate in hexanes) gave the pure product as a white crystalline solid (89 mg, 0.27 mmol, 87% yield).

¹H NMR: (400 MHz, CDCl₃)

δ 7.64 – 7.59 (m, 2H), 7.55 (d, *J* = 8.2 Hz, 2H), 7.46 (t, *J* = 8.4 Hz, 2H), 7.38 – 7.32 (m, 1H), 7.32 – 7.27 (m, 2H), 3.69 (s, 2H), 2.73 (br s, 0.08 H), 1.88 (t, *J* = 6.6 Hz, 0.13 H), 0.96 (d, *J* = 2.6 Hz, 9H), 0.11 (d, *J* = 1.3 Hz, 6H).

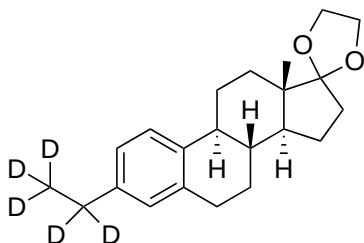
¹³C NMR: (101 MHz, CDCl₃)

δ 141.5, 141.3, 138.8, 129.0, 128.8, 127.2, 127.1, 127.1, 62.4, 34.3 – 33.2 (m), 31.5 – 30.7 (m), 26.1, 18.5, -5.1.

ATR-IR (cm⁻¹):

2953, 2926, 2854, 2203, 2115, 1251, 1110, 1065.

HRMS: (ESI⁺/FTICR) *m/z*: [M + Na]⁺ Calcd for C₂₁H₂₆D₄NaOSi 353.2209; Found 353.2219.



(8*R*,9*S*,13*S*,14*S*)-3-(Ethyl-*d*₅)-13-methyl-6,7,8,9,11,12,13,14,15,16-

decahydrospiro[cyclopenta[*a*]phenanthrene-17,2'-[1,3]dioxolane] [32]. According to the general procedure D, (*R*)-DTBM-SEPHOS (5.2 mg, 0.0044 mmol, 0.022 eq.), Cu(OAc)₂ (20 μL of a 0.2 M solution in THF, 0.004 mmol, 0.02 eq.), THF (0.08 mL), then dimethoxy(methyl)silane-*d* (0.19 mL of 5.3 M solution in hexanes, 1 mmol, 5 eq.) were combined in a 2-dram vial followed by addition of a solution of (8*R*,9*S*,13*S*,14*S*)-3-(ethynyl-*d*)-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydrospiro[cyclopenta[*a*]phenanthrene-17,2'-[1,3]dioxolane] (64.6 mg, 0.2 mmol, 1 eq.), THF (0.1 mL), and 2-propanol-OD (77 μL, 1.0 mmol, 5 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 38 h at 60 °C. After silica plug filtration using diethyl ether (100 mL) as the eluent, the solvent was concentrated, and the crude brown oil was dry loaded onto a silica gel column. Flash chromatography using gradient elution (100 mL of hexanes, 100 mL of 3% ethyl acetate in hexane, 100 mL of 5% ethyl acetate in hexanes, 100 mL of 8% ethyl acetate in hexanes, 200 mL of 9% ethyl acetate in hexanes, 100 mL of 10% ethyl acetate in hexanes) gave the pure product as a clear, yellow oil (48.7 mg, 0.147 mmol, 74% yield).

¹H NMR (400 MHz, CDCl₃)

δ 7.25 (d, *J* = 8.0 1H), 7.01 (d, *J* = 8.0, 1H), 6.95 (s, 1H), 4.08 – 3.83 (m, 4H), 2.92 – 2.83 (m, 2H), 2.58 (br s, 0.15H), 2.41 – 2.24 (m, 2H), 2.11 – 2.00 (m, 1H), 1.96 – 1.74 (m, 4H), 1.71 – 1.61 (m, 1H), 1.60 – 1.30 (m, 5H), 1.20 (br s, 0.20H), 0.90 (s, 3H).

²H NMR: (61 MHz, CHCl₃)

δ 2.58 (br s, 1.85D), 1.21 (br s, 2.80D).

¹³C NMR (101 MHz, CDCl₃)

δ 141.5, 137.8, 136.7, 128.6, 125.5, 125.3, 119.6, 65.4, 64.7, 49.6, 46.3, 44.1, 39.1, 34.4, 30.9, 29.7, 28.1 – 27.4 (m), 27.2, 26.1, 22.5, 15.5 – 14.2 (m), 14.5.

ATR-IR (cm⁻¹):

2966, 2936, 2872, 2221, 2075, 1700, 1610, 1103, 1042.

HRMS: (ESI⁺) *m/z*: [M + Na]⁺ Calcd for C₂₂H₂₅D₅NaO₂ 354.2452; Found 354.2462.

Synthesis of Alkyne Substrates

General TBS protection of internal alkynes (E)

To a flame-dried round bottom flask was added the alcohol substrate (2.5 mmol, 1 eq.), dry DCM (7.5 mL) followed by imidazole (340 mg, 5.0 mmol, 2 eq.) and *tert*-butyldimethylsilyl chloride (414 mg, 2.75 mmol, 1.1 eq.). The reaction was stirred at room temperature overnight. Upon completion, the reaction mixture was quenched with water (20 mL) and extracted with diethyl ether (2 x 15 mL). The combined organic layers were washed with brine (15 mL) and dried over anhydrous Na₂SO₄. The mixture was filtered, and the solvent was removed by rotary evaporation. The crude product was purified by flash column chromatography to give the desired TBS protected alcohol.

General Sonogashira Coupling for the synthesis of internal alkynes¹¹ (F)

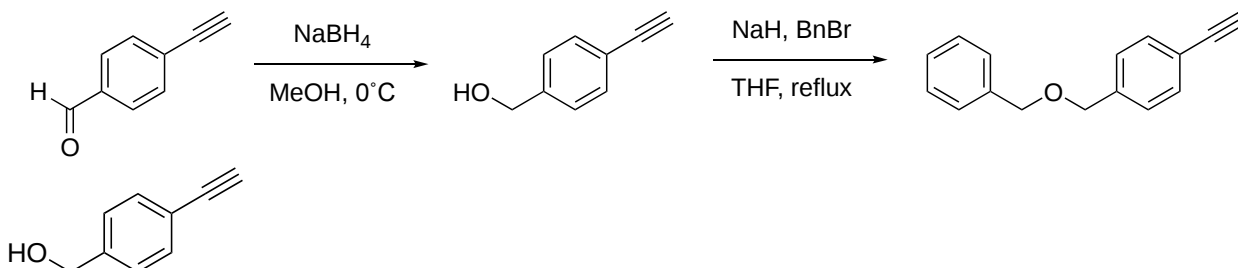
To a flame-dried round bottom flask under N₂ was added triethylamine (15 mL), which was degassed for 10 minutes. The aryl halide (3.0 mmol, 1 eq.), Pd(PPh₃)₂Cl₂ (42 mg, 0.06 mmol, 0.02 eq.) and CuI (23 mg, 0.12

mmol, 0.04 eq.) were then sequentially added at room temperature. The mixture was stirred for 10 minutes followed by the addition of propargyl alcohol (3.3 mmol, 1.1 eq.). After 16 h of stirring at room temperature, the reaction was quenched with water (10 mL) and extracted with ethyl acetate (3 x 15 mL). The organic layers were washed with water (4 x 10 mL) and then dried over anhydrous Na₂SO₄. The mixture was filtered, and the solvent was removed by rotary evaporation. The crude product was purified by flash column chromatography to give the desired aryl substituted propargyl alcohol.

General Aryl Finkelstein procedure¹² (G)

In a N₂ filled glovebox, a 25 mL dry Schlenk tube was charged with CuI (46.1 mg, 0.242 mmol, 0.05 eq.), aryl bromide compound (4.83 mmol, 1 eq.), and NaI (1.45g, 9.66 mmol, 2 eq.), followed by addition of trans-*N,N'*-dimethyl-1,2-cyclohexane diamine (0.076 mL, 0.483 mmol, 0.1 eq.) and anhydrous dioxane (4.83 mL). The Schlenk tube was equipped with a cold finger condenser, sealed and removed from the glovebox. The reaction was stirred at reflux in an oil bath under N₂ for 24 hours. Upon completion, the reaction was cooled to room temperature and was quenched with ammonia aqueous solution (prepared by diluting 0.5 mL of 0.5 M NH₃/dioxane solution in 40 mL of water). The aqueous layer was then extracted with CH₂Cl₂ (3 x 15 mL). The combined organic layers were washed with water (1 x 20 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under vacuum. The crude product was purified by column chromatography to give the desired aryl iodide.

Scheme S3: Synthesis of 1-((benzyloxy)methyl)-4-ethynylbenzene

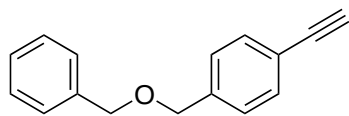


4-Ethynylbenzyl alcohol

To a flame dried 500 mL round bottom flask equipped with a Teflon stir bar was added 4-ethynylbenzaldehyde (3.94 g, 30.3 mmol, 1 eq.), NaBH₄ (2.29 g, 60.6 mmol, 2 eq.), and anhydrous methanol (235 mL). Reaction was stirred in ice bath until completion, monitored by TLC. Upon completion, the reaction was quenched with saturated NaHCO₃ aqueous solution and extracted with CH₂Cl₂ (4 x 100 mL). The combined organic layers were washed with water, dried over Na₂SO₄, and concentrated under vacuum. Excess solvent was removed by vacuum, and pure product was afforded as a yellow solid (3.38 g, 25.6 mmol, 85% yield). The spectra for the title compound matched previously reported spectra.¹³

¹H NMR (400 MHz, CDCl₃)

δ 7.49 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 4.70 (s, 2H), 3.07 (s, 1H), 1.75 (s, 1H).



1-((Benzyloxy)methyl)-4-ethynylbenzene [7-SM]

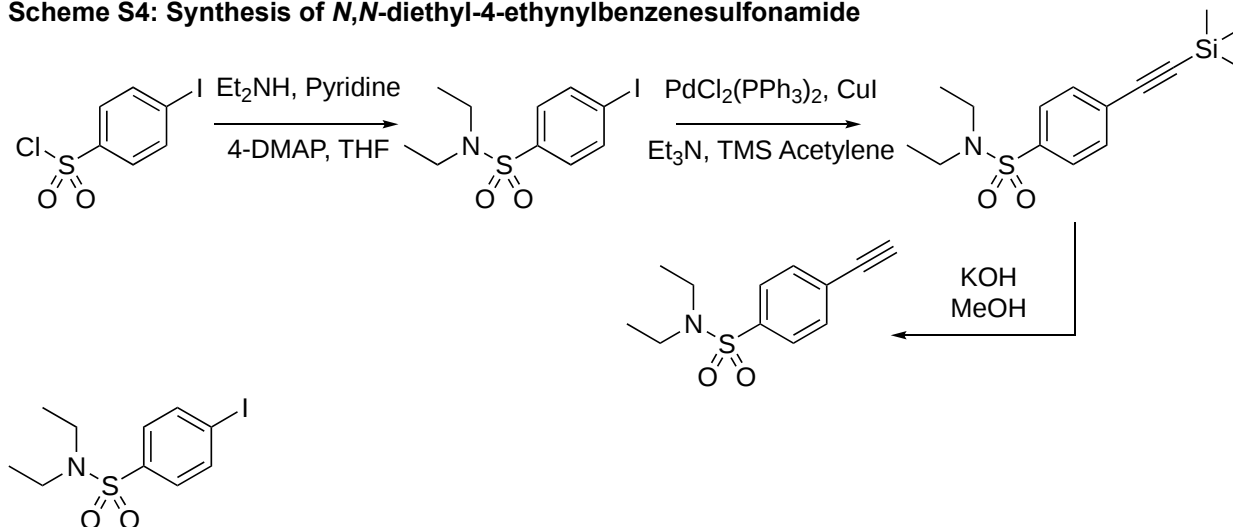
The benzyl protection was performed using a procedure adapted from the literature¹⁴, a flame dried 300 mL round bottom flask was equipped with a Teflon stir bar and to this was added 4-ethynylbenzyl alcohol (1.0 g, 7.57 mmol, 1 eq.), THF (7.8 mL), and NaH (60% dispersion in mineral oil) (0.303 g, 7.57 mmol, 1 eq.). Reaction was heated to reflux in an oil bath for 30 minutes, then cooled to room temperature. Benzyl bromide (0.89 mL, 7.5 mmol, 0.99 eq.) was added, and reaction was heated to reflux for 48 hours. Reaction was monitored by TLC and when reaction reached completion, reaction was cooled to room temperature followed by addition of water (10 mL). Solvent was removed by rotary evaporation, and 3M KOH was added into the round bottom flask until pH = 12 was reached. The crude reaction mixture was transferred to a separatory funnel with DCM and extracted with DCM (3 x 10 mL). The combined organic layers were washed with

brine (2 x 10 mL), dried over anhydrous Na_2SO_4 , and concentrated under vacuum. Crude product was dry loaded onto a column, and the pure product was purified by flash column chromatography with elution gradient (100 mL of hexanes, 200 mL of 10% ethyl acetate in hexanes, 400 mL of 25% ethyl acetate in hexanes), the title compound was afforded as a colorless oil (1.15 g, 5.17 mmol, 68% yield). The spectra for the title compound matched previously reported spectra.¹⁵

¹H NMR (400 MHz, CDCl_3)

δ 7.49 (d, J = 8.1 Hz, 2H), 7.39 – 7.28 (m, 7H), 4.56 (s, 2H), 4.55 (s, 2H), 3.07 (s, 1H).

Scheme S4: Synthesis of *N,N*-diethyl-4-ethynylbenzenesulfonamide

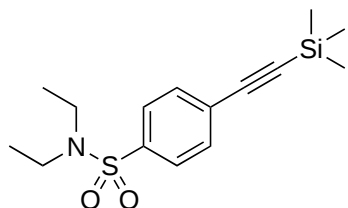


***N,N*-Diethyl-4-iodobenzenesulfonamide**

To a flame-dried round bottom flask was added pyridine (11 mL) and 4-iodo-benzenesulfonylchloride (2.0 g, 6.6 mmol, 1 eq.), followed by addition of diethyl amine (0.75 mL, 7.27 mmol, 1.1 eq.) in THF (4 mL). The reaction flask was cooled over an ice bath and was added 4-DMAP (4-dimethylaminopyridine) (6.5 mg, 0.053 mmol, 0.008 eq.). The reaction was then warmed to room temperature and stirred for 48 hours. Reaction was monitored by TLC and upon completion, the mixture was poured into water (30 mL). The resulting precipitate was collected by vacuum filtration and rinsed with water (2 x 10 mL). The solid was dissolved in ethyl acetate (15 mL) and washed with 5% HCl (3 x 10 mL), water (2 x 10 mL), and brine (10 mL). The ethyl acetate solution was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude product was dry loaded onto a column, and the pure product was eluted out through flash column chromatography (200 mL of hexanes, 300 mL of 5% ethyl acetate in hexanes, 300 mL of 10% ethyl acetate in hexanes, 300 mL of 15% ethyl acetate in hexanes, and 300 mL of 20% ethyl acetate in hexanes) to afford the pure product (1.40 g, 4.14 mmol, 63% yield). The spectra for the title compound matched previously reported spectra.¹⁶

¹H NMR (300 MHz, CDCl_3)

δ 7.74 (d, J = 8.6 Hz, 2H), 7.41 (d, J = 8.6 Hz, 2H), 3.10 (q, J = 7.2 Hz, 4H), 0.99 (t, J = 7.2 Hz, 6H).



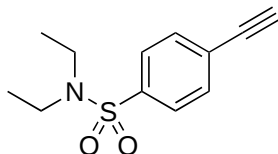
***N,N*-Diethyl-4-trimethylsilylethynylbenzenesulfonamide**

Under N_2 atmosphere, to a stirred solution of *N,N*-diethyl-4-iodo-benzenesulfonamide (1.40 g, 4.14 mmol, 1 eq.) in degassed triethylamine (7 mL) was added $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (58 mg, 0.083 mmol, 0.02 eq.) and CuI (39 mg, 0.21 mmol, 0.05 eq.) at room temperature. The mixture was then stirred for 10 minutes followed by the addition of trimethylsilyl acetylene (0.86 mL, 6.21 mmol, 1.5 eq.). Reaction was stirred at 60 °C in an oil

bath overnight, and upon completion, was quenched with water (10 mL) and extracted with diethyl ether (3 x 15 mL). The combined organic layers were washed with 1 M HCl (100 mL) and water (4 x 10 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under vacuum. The crude product was purified by flash column chromatography (100 mL of hexanes, 200 mL of 5% ethyl acetate in hexanes, 300 mL of 10% ethyl acetate in hexanes, 200 mL of 20% ethyl acetate in hexanes) to afford the pure orange solid product. Quantitative yield was assumed, and product was taken immediately to the TMS-deprotection step.

¹H NMR (300 MHz, CDCl₃)

δ 7.72 (d, *J* = 8.5 Hz, 2H), 7.54 (d, *J* = 8.5 Hz, 2H), 3.21 (q, *J* = 7.2 Hz, 4H), 1.09 (t, *J* = 7.2 Hz, 6H), 0.24 (s, 9H).



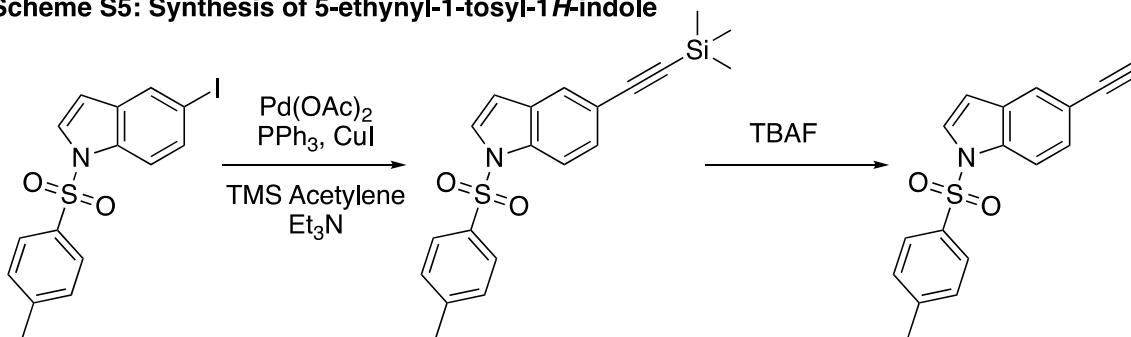
***N,N*-Diethyl-4-ethynylbenzenesulfonamide [11-SM].**

The mixture of the TMS-protected sulfonamide (1.28 g, 4.14 mmol, 1 eq.), KOH (4.55 mL of 1 M aqueous solution, 4.55 mmol, 1.1 eq.), and MeOH (26 mL) were stirred at room temperature for 14 hours. The reaction progress was monitored by TLC. Upon completion, the reaction mixture was diluted with water (10 mL) and extracted with Et₂O (3 x 15 mL). The combined organic layers were washed with 1 M HCl (20 mL), water (20 mL) and brine (20 mL), dried over anhydrous Na₂SO₄, and filtered. The solvent was then removed by rotary evaporation. The crude product was dry loaded onto a column, and purified by flash column chromatography (100 mL of hexanes, 200 mL of 5% ethyl acetate in hexanes, 800 mL of 10% ethyl acetate in hexanes, 200 mL of 20% ethyl acetate in hexanes) to afford the pure orange solid product (703 mg, 2.96 mmol, 72% yield). The spectra for the title compound matched previously reported spectra.¹⁷

¹H NMR: (400 MHz, CDCl₃)

δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.57 (d, *J* = 8.2 Hz, 2H), 3.27 – 3.17 (m, 5H), 1.10 (t, *J* = 7.2 Hz, 6H).

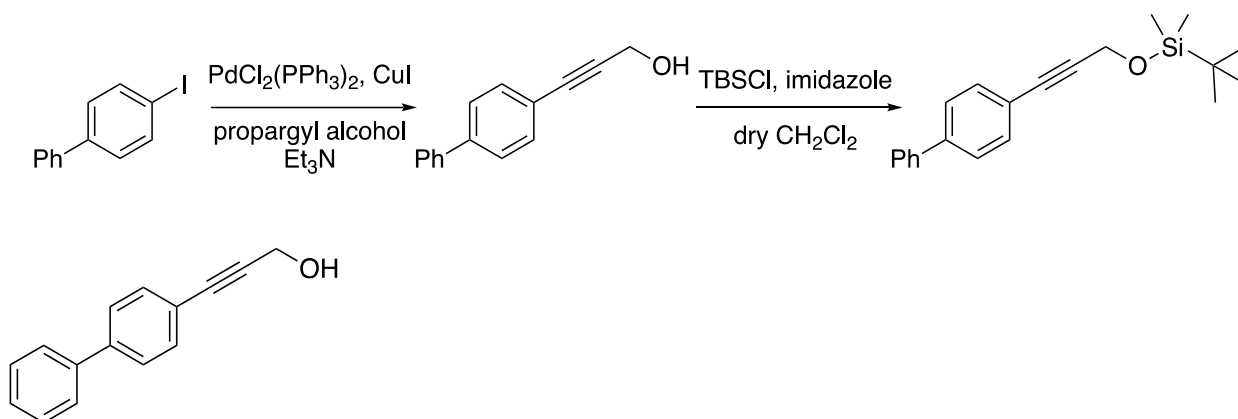
Scheme S5: Synthesis of 5-ethynyl-1-tosyl-1*H*-indole



5-Ethynyl-1-tosyl-1*H*-indole [13-SM]. Following a previously reported method, from 5-iodo-1-tosyl-1*H*-indole (0.863 g, 2.17 mmol), the title compound was obtained as a yellow solid (0.492 g, 1.67 mmol, 77% yield). The spectra for the title compound matched previously reported spectra.¹⁸

¹H NMR: (300 MHz, CDCl₃)

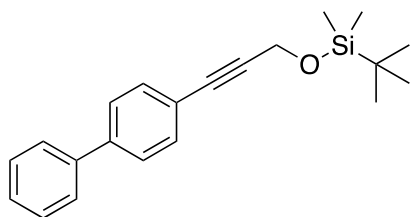
δ 7.96 (d, *J* = 8.6 Hz, 1H), 7.75 (d, *J* = 8.3 Hz, 2H), 7.67 (d, *J* = 1.4 Hz, 1H), 7.59 (d, *J* = 3.7 Hz, 1H), 7.44 (dd, *J* = 8.6, 1.4 Hz, 1H), 7.19 (d, *J* = 8.3 Hz, 2H), 6.61 (d, *J* = 3.7, 1H), 3.05 (s, 1H), 2.29 (s, 3H).

Scheme S6: Synthesis of ((3-([1,1'-biphenyl]-4-yl)prop-2-yn-1-yl)oxy)(*tert*-butyl)dimethylsilane


((3-([1,1'-Biphenyl]-4-yl)prop-2-yn-1-yl)). Synthesized according to the general procedure F from 4-iodo-1,1'-biphenyl (1.00 g, 3.57 mmol), the title compound was obtained as a light yellow solid (633 mg, 3.04 mmol, 85%). The spectra for the title compound matched previously reported spectra.¹⁹

¹H NMR (300 MHz, CDCl_3)

δ 7.63 – 7.48 (m, 6H), 7.45 (t, 2H), 7.40 – 7.32 (m, 1H), 4.53 (d, $J = 6.2$, 2H), 1.66 (t, $J = 6.1$ Hz, 1H).



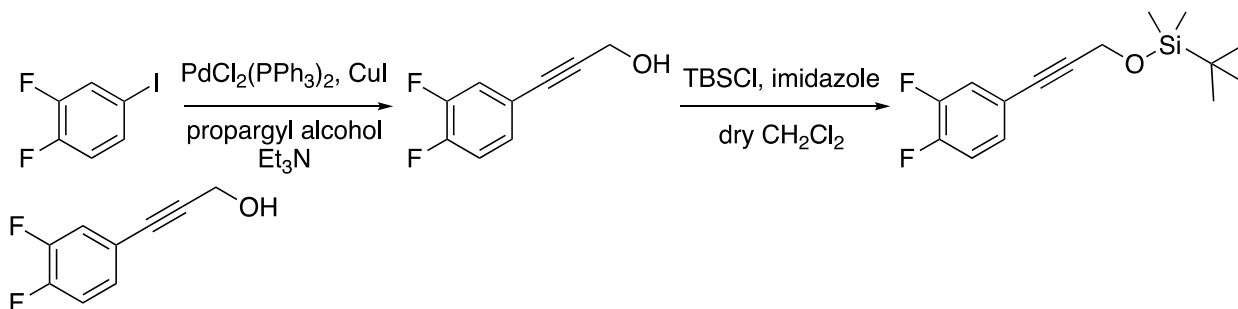
((3-([1,1'-Biphenyl]-4-yl)prop-2-yn-1-yl)oxy)(*tert*-butyl)dimethylsilane [15/31-SM]. Following the general procedure E, the alcohol substrate (500 mg, 2.4 mmol, 1 eq.) in dry DCM (7.5 mL) followed by imidazole (327 mg, 4.8 mmol, 2 eq.) and *tert*-butyldimethylsilyl chloride (398 mg, 2.64 mmol, 1.1 eq.). Purified with flash column chromatography using gradient elution (100 mL of hexanes, 100 mL of 3% ethyl acetate in hexanes, 300 mL of 5% of ethyl acetate in hexanes), the title compound was obtained as a light yellow solid (633 mg, 1.96 mmol, 82% yield). The spectra for the title compound matched previously reported spectra.²⁰

¹H NMR (400 MHz, CDCl_3)

δ 7.61 – 7.56 (m, 2H), 7.54 (d, $J = 8.4$ Hz, 2H), 7.50 (d, $J = 8.0$ Hz, 2H), 7.44 (t, $J = 7.7$ Hz, 2H), 7.36 (t, $J = 7.4$ Hz, 1H), 4.57 (s, 2H), 0.95 (s, 9H), 0.19 (s, 6H).

¹³C NMR (75 MHz, CDCl_3)

δ 141.1, 140.4, 132.1, 128.9, 127.7, 127.1, 127.0, 122.0, 88.7, 84.8, 52.4, 26.0, 18.5, -4.9.

Scheme S7: Synthesis of *tert*-butyl((3-(3,4-difluorophenyl)prop-2-yn-1-yl)oxy)dimethylsilane


3-(3,4-Difluorophenyl)-2-propyn-1-ol [18-SM]. Following the general procedure F, Pd(PPh₃)₂Cl₂ (117 mg, 0.167 mmol, 0.02 eq.) and CuI (63 mg, 0.33 mmol, 0.04 eq.) were sequentially added to a solution of 1,2-difluoro-4-iodobenzene (2.0 g, 8.34 mmol, 1 eq.) in degassed triethylamine (42 mL) under nitrogen at room temperature. To the reaction mixture was added propargyl alcohol (0.53 mL, 9.17 mmol, 1.1 eq.). The reaction mixture was stirred for 22 hr. Crude product was purified with flash chromatography using gradient elution (100 mL of hexanes, 100 mL of 5% ethyl acetate in hexanes, 100 mL of 10% of ethyl acetate in hexanes, 400 mL of 15% of ethyl acetate in hexanes), **3u** was obtained as a clear dark yellow oil (0.959 g, 5.70 mmol, 68.4% yield).

¹H NMR (400 MHz, CDCl₃)

δ 7.25 – 7.18 (m, 1H), 7.17 – 7.12 (m, 1H), 7.11 – 7.03 (m, 1H), 4.47 (s, 2H), 2.34 (br s, 1H).

¹³C NMR (75 MHz, CDCl₃)

δ 152.1 (dd, *J* = 58.5, 12.8 Hz), 148.7 (dd, *J* = 55.8, 12.7 Hz), 128.5 (dd, *J* = 6.5, 3.6 Hz), 119.5 (dd, *J* = 7.6, 4.2 Hz), 121.1 – 116.9 (m), 87.9, 83.7, 51.5.

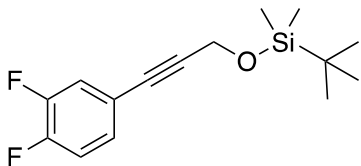
¹⁹F NMR (376 MHz, CDCl₃)

δ -135.60, -137.11.

ATR-IR (cm⁻¹):

3321, 2927, 2866, 2232, 1734, 1512, 1216, 1167.

HRMS: (EI⁺) *m/z*: [M]⁺ Calcd for C₉H₆OF₂ 168.0400; Found 168.0380.



tert-Butyl(3-(3,4-difluorophenyl)prop-2-yn-1-yl)oxydimethylsilane [30-SM]. According to the general procedure E, from alcohol **3u** (0.330g, 1.96 mmol) the title compound was obtained as a clear and colorless oil (0.47 g, 1.66 mmol, 85% yield).

¹H NMR: (300 MHz, CDCl₃)

δ 7.26 – 7.03 (m, 3H), 4.51 (s, 2H), 0.94 (s, 9H), 0.16 (s, 6H).

¹³C NMR: (101 MHz, CDCl₃)

δ 150.7 (dd, *J* = 251.3, 12.5 Hz), 150.1 (dd, *J* = 249.1, 13.1 Hz), 128.3 (dd, *J* = 5.8, 3.9 Hz), 120.7 (d, *J* = 18.4 Hz), 120.0 (dd, *J* = 7.4, 4.3 Hz), 117.5 (d, *J* = 17.8 Hz), 88.7, 82.8, 52.2, 26.0, 18.5, -5.0.

¹⁹F NMR: (376 MHz, CDCl₃)

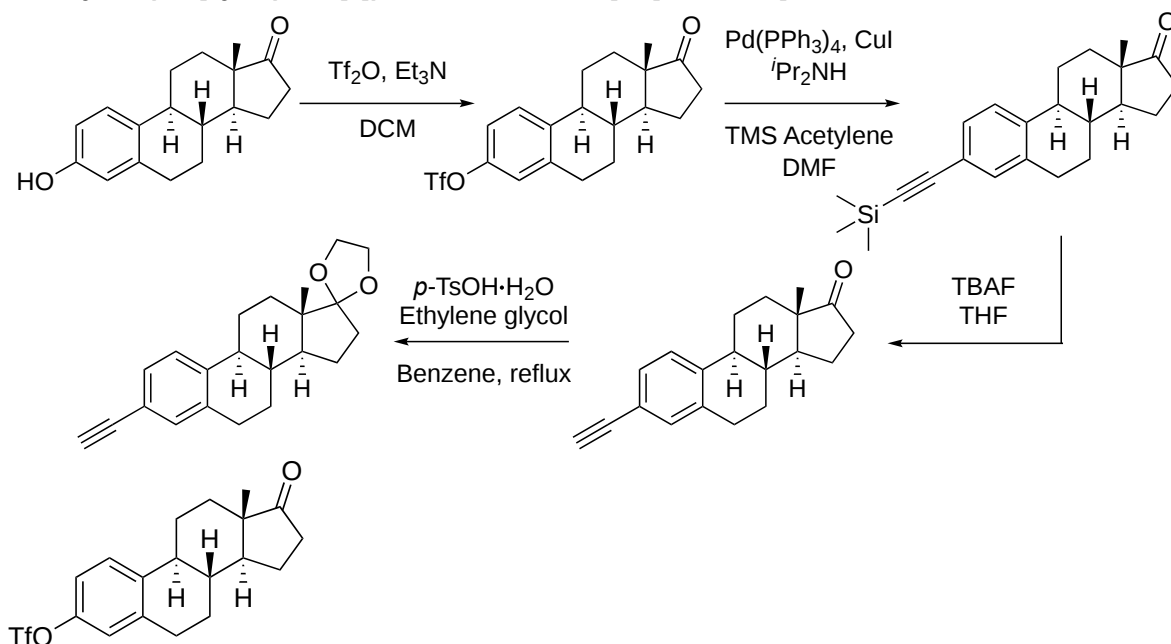
δ -136.07, -137.28.

ATR-IR (cm⁻¹):

2954, 2856, 2215, 1513, 1251, 1217, 1080.

HRMS: (ESI⁺) *m/z*: [M+Na]⁺ Calcd for C₁₅H₂₀F₂NaOSi 305.1144; Found 305.1147.

Scheme S8: Synthesis of (8*R*,9*S*,13*S*,14*S*)-3-ethynyl-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydrospiro[cyclopenta[*a*]phenanthrene-17,2'-[1,3]dioxolane]

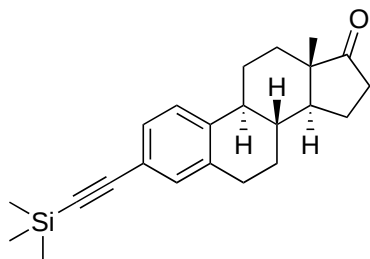


(8*R*,9*S*,13*S*,14*S*)-13-Methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-

cyclopenta[*a*]phenanthren-3-yl trifluoromethanesulfonate. In a 100 mL flame dried round bottom flask equipped with a Teflon stir bar was added estrone (1 g, 3.7 mmol, 1 eq.), Et₃N (1.03 mL, 7.4 mmol, 2 eq.), and DCM (18 mL), and was stirred in an ice bath for 15 minutes. Triflic anhydride (0.685 mL, 4.07 mmol, 4 eq.) was added dropwise, and a brown color persisted in the reaction flask. The reaction was stirred at room temperature for 8 hours and progress was monitored by TLC. Upon completion the reaction was quenched with saturated aqueous NaHCO₃ (10 mL). The aqueous layer was extracted with DCM (3 x 20 mL), the combined organic layers were washed with brine (20 mL), dried over Na₂SO₄ and concentrated under vacuum. The crude product was dry loaded onto a column, and purified by flash column chromatography (100 mL of hexanes, 100 mL of 5% ethyl acetate in hexanes, 100 mL of 7% ethyl acetate in hexanes, 100 mL of 10% ethyl acetate in hexanes, 300 mL of 12% ethyl acetate in hexanes, 300 mL of 15% ethyl acetate in hexanes, and 300 mL of 17% ethyl acetate in hexanes) to afford the pure, white solid product (1.36 g, 3.38 mmol, 91% yield). The spectra for the title compound matched previously reported spectra.²¹

¹H NMR (400 MHz, CDCl₃)

δ 7.34 (d, 1H), 7.07 – 6.97 (m, 2H), 2.99 – 2.88 (m, 2H), 2.52 (dd, *J* = 18.8, 8.7 Hz, 1H), 2.46 – 2.36 (m, 1H), 2.35 – 2.27 (m, 1H), 2.23 – 1.94 (m, 4H), 1.72 – 1.40 (m, 6H), 0.92 (s, 3H).



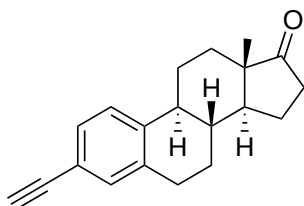
(8*R*,9*S*,13*S*,14*S*)-13-Methyl-3-((trimethylsilyl)ethynyl)-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-

cyclopenta[*a*]phenanthren-17-one. In a 100 mL oven dried Schlenk tube equipped with a Teflon stir bar was added (8*R*,9*S*,13*S*,14*S*)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl trifluoromethanesulfonate (1 g, 2.49 mmol, 1 eq.), DMF (30 mL), Pd(PPh₃)₄ (287 mg, 0.249 mmol, 0.1 eq.), CuI (47 mg, 0.249 mmol, 0.1 eq.), and *i*Pr₂NH (1.05 mL, 7.46 mmol, 3 eq.). The reaction mixture was degassed with N₂ for 20 minutes, followed by addition of trimethylsilyl acetylene

(0.414 mL, 2.99 mmol, 1.2 eq.). Using a cold finger condenser, the reaction was heated to reflux in an oil bath for 24 hours. The reaction progress was monitored by TLC. Upon completion, reaction was diluted with Et₂O, washed with brine (3 x 10 mL), dried over Na₂SO₄, and concentrated under vacuum. The crude product was dry loaded onto a column, and purified by flash column chromatography (200 mL of hexanes, 100 mL of 2% ethyl acetate in hexanes, 300 mL 4% ethyl acetate in hexanes, 600 mL of 6% ethyl acetate in hexanes, 500 mL of 7% ethyl acetate in hexanes, and 600 mL of 8% ethyl acetate in hexanes) to afford the pure white solid product (474 mg, 1.35 mmol, 54% yield). The spectra for the title compound matched previously reported spectra.²²

¹H NMR (400 MHz, CDCl₃)

δ 7.25 – 7.18 (m, 3H), 2.92 – 2.83 (m, 2H), 2.51 (dd, *J* = 18.8, 8.7 Hz, 1H), 2.45 – 2.35 (m, 1H), 2.34 – 2.24 (m, 1H), 2.21 – 1.91 (m, 4H), 1.70 – 1.36 (m, 6H), 0.91 (s, 3H), 0.24 (s, 9H).

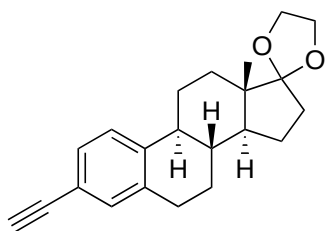


(8*R*,9*S*,13*S*,14*S*)-3-Ethynyl-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta[*a*]phenanthren-17-one.

In a round bottom flask, (8*R*,9*S*,13*S*,14*S*)-13-methyl-3-((trimethylsilyl)ethynyl)-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta[*a*]phenanthren-17-one (514 mg, 1.47 mmol, 1 eq.), TBAF (1.62 mL of 1 M TBAF in THF, 1.1 eq.) and THF (6.6 mL) were combined and stirred for 5 hours, reaction progress was monitored by TLC. Upon completion, the reaction was quenched with distilled water (20 mL), extracted with DCM (3 x 10 mL), dried over Na₂SO₄, and concentrated under vacuum. The crude product was dry loaded onto a column, and purified by flash column chromatography (100 mL of hexanes, 100 mL of 2% ethyl acetate in hexanes, 100 mL 4% ethyl acetate in hexanes, 300 mL of 6% ethyl acetate in hexanes, and 600 mL of 8% ethyl acetate in hexanes) to afford the white solid product (310 mg, 1.11 mmol, 76% yield). The spectra for the title compound matched previously reported spectra.²²

¹H NMR (400 MHz, CDCl₃)

δ 7.30 – 7.19 (m, 3H), 3.02 (s, 1H), 2.94 – 2.85 (m, 2H), 2.51 (dd, *J* = 18.8, 8.7 Hz, 1H), 2.45 – 2.37 (m, 1H), 2.36 – 2.25 (m, 1H), 2.21 – 1.92 (m, 4H), 1.69 – 1.38 (m, 6H), 0.91 (s, 3H).



(8*R*,9*S*,13*S*,14*S*)-3-Ethynyl-13-methyl-6,7,8,9,11,12,13,14,15,16-

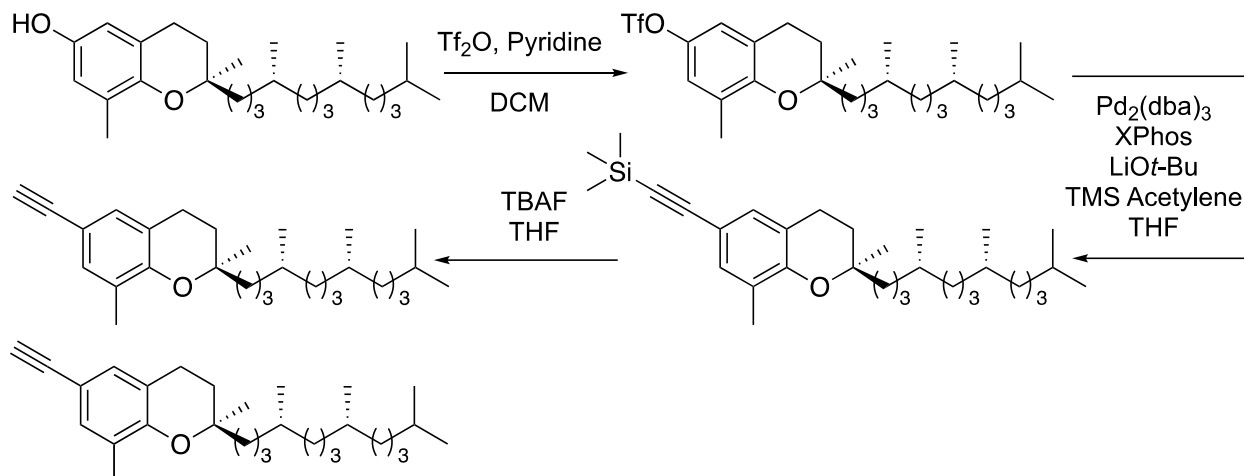
decahydrospiro[cyclopenta[*a*]phenanthrene-17,2'-[1,3]dioxolane] [20-SM] To a 100 mL round bottom flask equipped with a Teflon stir bar was added (8*R*,9*S*,13*S*,14*S*)-3-ethynyl-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta[*a*]phenanthren-17-one (307 mg, 1.1 mmol, 1 eq.), *p*-TsOH·H₂O (19 mg, 0.10 mmol, 0.091 eq.), ethylene glycol (1.23 mL, 22 mmol, 20 eq.), and benzene (8 mL). The reaction flask was fitted with a condenser equipped with a Dean Stark trap for the removal of water, and heated to reflux in an oil bath. Progress was monitored by TLC, and upon completion, reaction was poured into 10 mL of water, and extracted with DCM (3 x 10 mL). The combined organic layers were washed with water (10 mL), brine (10 mL), and dried over Na₂SO₄. Solvent was removed by rotary evaporation, and the crude product was dry loaded onto a column, and purified by flash column chromatography (80 mL of hexanes, 100 mL of 3% ethyl acetate in hexanes, 100 mL of 5% ethyl acetate in hexanes, 100 mL of 6% ethyl acetate in hexanes, 100 mL of 8% ethyl acetate in hexanes, and 500 mL of 9% ethyl acetate in hexanes) to

afford the white solid product (148 mg, 0.459 mmol, 42% yield). The spectra for the title compound matched previously reported spectra.¹⁸

¹H NMR: (400 MHz, CDCl₃)

δ 7.28 – 7.21 (m, 3H), 4.01 – 3.84 (m, 4H), 3.00 (s, 1H), 2.87 – 2.80 (m, 2H), 2.37 – 2.22 (m, 2H), 2.08 – 1.98 (m, 1H), 1.96 – 1.71 (m, 4H), 1.69 – 1.59 (m, 1H), 1.59 – 1.28 (m, 5H), 0.88 (s, 3H).

Scheme S9: Synthesis of (*R*)-6-Ethynyl-2,8-dimethyl-2-((4*R*,8*R*)-4,8,12-trimethyltridecyl)chromane

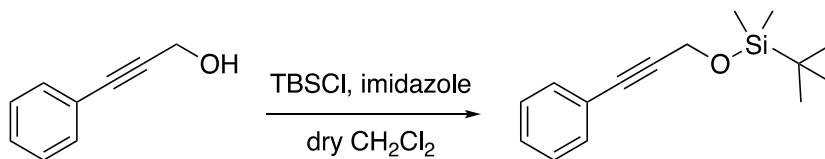


(*R*)-6-Ethynyl-2,8-dimethyl-2-((4*R*,8*R*)-4,8,12-trimethyltridecyl)chromane [21-SM]. Following a previously reported method, from (*R*)-2,8-dimethyl-2-((4*R*,8*R*)-4,8,12-trimethyltridecyl)chroman-6-yl trifluoromethanesulfonate (1.07 g, 2.00 mmol), the title compound was obtained as a pale yellow oil (0.41 g, 1.00 mmol, 50% yield). The spectra for the title compound matched previously reported spectra.¹⁸

¹H NMR: (300 MHz, CDCl₃)

δ 7.17 – 7.06 (m, 2H), 2.94 (s, 1H), 2.79 – 2.67 (m, 2H), 2.16 (s, 3H), 1.90 – 1.70 (m, 2H), 1.67 – 1.04 (m, 24H), 0.97 – 0.81 (m, 12H).

Scheme S10: Synthesis of ((3-(phenyl)prop-2-yn-1-yl)oxy)(*tert*-butyl)dimethylsilane



((3-(Phenyl)prop-2-yn-1-yl)oxy)(*tert*-butyl)dimethylsilane [29-SM]. The compound was synthesized according to the general procedure E. 3-phenylprop-2-yn-1-ol (2.0 g, 15.1 mmol, 1 eq.) and dry DCM (45 mL) were added to a flame dried 200 mL round bottom flask equipped with a Teflon stir bar, followed by imidazole (1.87 g, 30.2 mmol, 2 eq.) and *tert*-butyldimethylsilyl chloride (2.50 g, 16.6 mmol, 1.1 eq.). The reaction was allowed to stir at room temperature overnight. The mixture was then transferred to a separatory funnel and extracted with diethyl ether (2 x 30 mL). The combined organic layers were washed with brine (15 mL) and dried over anhydrous Na₂SO₄. The mixture was filtered, and the solvent was removed by rotary evaporation. The crude oil was purified by flash chromatography (250 mL of hexanes, 200 mL of 2% ethyl acetate in hexanes) to afford a clear oil (3.6 g, 14.6 mmol, 97%). The spectra for the title compound matched previously reported spectra.²³

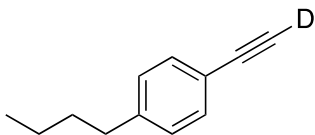
¹H NMR (300 MHz, CDCl₃)

δ 7.50 – 7.36 (m, 2H), 7.35 – 7.27 (m, 3H), 4.55 (s, 2H), 0.95 (s, 9H), 0.18 (s, 6H).

Synthesis of D-alkyne Substrates

General Procedure for Preparation of D-alkynes (H)

Following a previously reported procedure for the terminal deuteration of alkynes²⁴, a flame dried round bottom flask equipped with a Teflon stir bar was purged with N₂ and to this was added, aryl alkyne (1 eq.), anhydrous K₂CO₃ (1.5 eq.), and anhydrous CH₃CN sequentially. After stirring for 30 minutes, D₂O (50 eq.) was added to the round bottom flask and the reaction was stirred at room temperature for 12 – 48 hours. Reaction progress was followed by ¹H NMR. Upon completion, the mixture was extracted with dichloromethane or diethyl ether. The combined organic extracts were dried over anhydrous Na₂SO₄, filtered, and concentrated under vacuum. The products were used in the next step without further purification.



1-Butyl-4-(ethynyl-d)benzene [22-SM]. Following the general procedure H, in a N₂ filled glovebox, 1-butyl-4-ethynylbenzene (0.63 g, 4.0 mmol, 1 eq.), anhydrous K₂CO₃ (0.83 g, 6.0 mmol, 1.5 eq.) and anhydrous CH₃CN (12.0 mL) were stirred for 30 min. D₂O (3.61 mL, 200 mmol, 50 eq.) was added to the reaction, and the mixture was stirred for 36 h at room temperature under nitrogen atmosphere. Upon completion, the reaction was extracted with diethyl ether (3 x 10 mL). The combined extracts were dried over anhydrous Na₂SO₄, filtered, and concentrated under vacuum to afford the title compound as a light yellow liquid (0.52 g, 3.27 mmol, 82% yield).

¹H NMR: (400 MHz, CDCl₃)

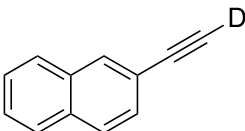
δ 7.44 (d, *J* = 8.1 Hz, 2H), 7.15 (d, *J* = 8.1 Hz, 2H), 3.05 (br s, 0.07H), 2.63 (t, *J* = 7.5 Hz, 2H), 1.67 – 1.55 (m, 2H), 1.44 – 1.30 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H).

¹³C NMR: (101 MHz, CDCl₃)

δ 144.0, 132.1, 128.5, 119.3, 83.5 (t, *J* = 7.6 Hz, 1C), 76.8 – 75.9 (multiplet overlapping with CDCl₃ signal, 1C), 35.7, 33.5, 22.4, 14.1.

ATR-IR (cm⁻¹): 3296, 3081, 3028, 2957, 2929, 2871, 2859, 2584, 1910, 1508, 1466, 821.

HRMS: (EI⁺) *m/z*: [M]⁺ Calcd for C₁₂H₁₃D 159.1200; Found 159.1153.



2-(Ethynyl-d)naphthalene [23-SM]. Following the general procedure H, in a N₂ filled glovebox, 2-ethynyl-naphthalene (200 mg, 1.31 mmol, 1 eq.), K₂CO₃ (272 mg, 1.97 mmol, 1.5 eq.), and CH₃CN (2.0 mL) were added to a flame dried 200 mL round bottom flask equipped with a Teflon stir bar. After stirring for 30 minutes, deuterium oxide (1.18 mL, 66.5 mmol, 50 eq.) was added to round bottom flask. After stirring at room temperature for 12 h, the reaction was quenched with distilled water (10 mL), and extracted with dichloromethane (3 x 10 mL). The organic layers were combined, dried over anhydrous Na₂SO₄ and concentrated to afford the white solid (200 mg, 1.31 mmol, >99% yield).

¹H NMR: (400 MHz, CDCl₃)

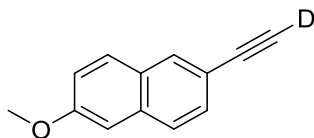
δ 8.04 (s, 1H), 7.87 – 7.76 (m, 3H), 7.57 – 7.47 (m, 3H), 3.15 (br s, 0.09H).

¹³C NMR: (75 MHz, CDCl₃)

δ 133.2, 132.9, 132.4, 128.7, 128.2, 127.9 (+ 1 overlapping signal), 127.0, 126.7, 119.5, 83.7 (t, *J* = 7.3 Hz, 1C), 77.9 – 77.3 (multiplet overlapping with CDCl₃ signal, 1C).

ATR-IR (cm⁻¹): 3276, 3049, 2922, 2572, 1971, 1593.

HRMS: (EI⁺) m/z : [M]⁺ Calcd for C₁₂H₇D 153.0700; Found 153.0680.



2-(Ethynyl-*d*)-6-methoxynaphthalene [24-SM]. Following the general procedure H, in a N₂ filled glovebox, 2-ethynyl-6-methoxynaphthalene, (0.18 g, 0.99 mmol, 1 eq.) anhydrous K₂CO₃ (0.205 g, 1.49 mmol, 1.5 eq.) and anhydrous CH₃CN (3.0 mL) were stirred for 30 min. D₂O (0.90 mL, 50 mmol, 50 eq.) was added to the reaction. The reaction mixture was stirred for 36 h at room temperature under nitrogen atmosphere. Upon completion, the reaction was extracted with diethyl ether (3 x 5 mL). The combined extracts were dried over anhydrous Na₂SO₄, filtered, and concentrated under vacuum to afford the title compound as a light yellow solid (0.18 g, 0.98 mmol, 99% yield).

¹H NMR: (400 MHz, CDCl₃)

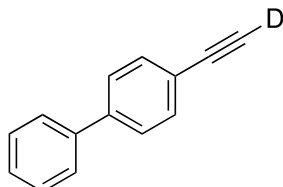
δ 7.96 (s, 1H), 7.69 (t, J = 8.8 Hz, 2H), 7.50 (dd, J = 8.2, 1.0 Hz, 1H), 7.17 (dd, J = 8.9, 2.3 Hz, 1H), 7.10 (d, J = 2.2 Hz, 1H), 3.92 (s, 3H), 3.13 (br s, 0.06H).

¹³C NMR: (75 MHz, CDCl₃)

δ 158.6, 134.5, 132.2, 129.5, 129.3, 128.4, 127.0, 119.6, 117.0, 105.9, 83.9 (t, J = 7.2 Hz, 1C), 77.0 – 76.2 (multiplet overlapping with CDCl₃ signal, 1C), 55.5.

ATR-IR (cm⁻¹): 3257, 3059, 3002, 2967, 2938, 2903, 2841, 2564, 1225, 1028.

HRMS: (EI⁺) m/z : [M]⁺ Calcd for C₁₃H₉DO 183.0800; Found 183.0788.



4-(Ethynyl-*d*)-1,1'-biphenyl [25-SM]. Following the general procedure H, in a N₂ filled glovebox, 4-ethynyl-1,1'-biphenyl (200 mg, 1.12 mmol, 1 eq.), K₂CO₃ (0.698 g, 5.05 mmol, 4.5 eq.), and CH₃CN (1.5 mL) were combined. After stirring for 30 minutes, D₂O (75 μL, 4.14 mmol, 3.7 eq.) was added to round bottom flask and the reaction was stirred at room temperature for 12 h. The reaction was quenched with distilled water, and extracted with dichloromethane (3 x 10 mL). The organic layers were combined and dried over anhydrous Na₂SO₄ then concentrated. The reaction was repeated three times to allow for full deuterium incorporation. The title compound was afforded as an orange solid product (200 mg, 1.12 mmol, >99% yield).

¹H NMR (300 MHz, CDCl₃)

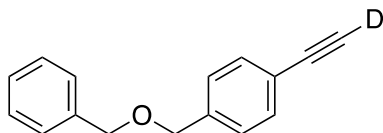
δ 7.65 – 7.52 (m, 6H), 7.50 – 7.41 (m, 2H), 7.41 – 7.32 (m, 1H), 3.14 (br s, 0.09H).

¹³C NMR (75 MHz, CDCl₃)

δ 141.7, 140.4, 132.7, 129.0, 127.9, 127.2, 127.1, 121.1, 83.2 (t, J = 6.9 Hz, 1C), 78.3 – 77.3 (multiplet overlapping with CDCl₃ signal, 1C).

ATR-IR (cm⁻¹): 3272, 3056, 3028, 2922, 2851, 2572.

HRMS: (EI⁺) m/z : [M]⁺ Calcd for C₁₄H₉D 179.0800; Found 179.0837.



1-((Benzyloxy)methyl)-4-(ethynyl-*d*)benzene [26-SM]. Following the general procedure H, in a N₂ filled glovebox, 1-((benzyloxy)methyl)-4-ethynylbenzene (1.11 g, 4.99 mmol, 1 eq.), anhydrous K₂CO₃ (1.04 g, 7.49 mmol, 1.5 eq.) in anhydrous CH₃CN (15.0 mL) were stirred for 30 min. D₂O (4.51 mL, 250 mmol, 50 eq.) was added to the reaction. The reaction mixture was stirred for 36 h at room temperature under nitrogen atmosphere. Upon completion, the reaction was extracted with diethyl ether (3 x 15 mL). The combined extracts were dried over anhydrous Na₂SO₄, filtered, and concentrated under vacuum to afford the title compound as a white solid (1.05 g, 4.70 mmol, 94% yield).

¹H NMR: (300 MHz, CDCl₃)

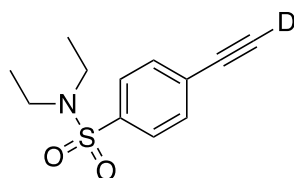
δ 7.55 (d, *J* = 8.4 Hz, 2H), 7.48 – 7.33 (m, 7H), 4.61 (s, 2H), 4.60 (s, 2H), 3.13 (s, 0.00H).

¹³C NMR: (75 MHz, CDCl₃)

δ 139.2, 138.1, 132.2, 128.5, 127.8, 127.8, 127.6, 121.3, 83.2 (t, *J* = 7.1 Hz, 1C), 77.4 – 76.6 (multiplet overlapping with CDCl₃ signal), 72.3, 71.6.

ATR-IR (cm⁻¹): 3287, 3087, 3063, 3031, 2925, 2856, 2580, 1702, 1087, 1070

HRMS: (ESI⁺) *m/z*: [M+Na]⁺ Calcd for C₁₆H₁₃DNaO 246.1000; Found 246.1002.



***N,N*-Diethyl-4-(ethynyl-*d*)benzenesulfonamide [27-SM].** Following the general procedure H, in a N₂ filled glovebox, *N,N*-diethyl-4-(ethynyl)-benzenesulfonamide (500 mg, 2.11 mmol, 1 eq.), K₂CO₃ (0.437 g, 3.16 mmol, 1.5 eq.), and CH₃CN (3.24 mL) were added to a 200 mL flame dried round bottom flask equipped with a Teflon stirbar. After stirring for 30 minutes, D₂O (1.91 mL, 106 mmol, 50 eq.) was added to the reaction and stirred at room temperature for 12 h. The reaction was quenched with distilled water (10 mL), and extracted with dichloromethane (3 x 10 mL). The organic layers were combined and dried over anhydrous Na₂SO₄, then concentrated to afford the product as a yellow solid (470 mg, 1.97 mmol, 93% yield).

¹H NMR: (400 MHz, CDCl₃)

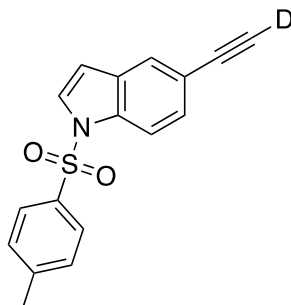
δ 7.75 (d, *J* = 8.5 Hz, 2H), 7.58 (d, *J* = 8.5 Hz, 2H), 3.22 (q, *J* = 7.1 Hz, 4.1H), 1.11 (t, *J* = 7.2 Hz, 6H).

¹³C NMR: (101 MHz, CDCl₃)

δ 140.5, 132.7, 127.0, 126.4, 81.8 (t, *J* = 7.1 Hz, 1C), 80.6 (t, *J* = 19.7 Hz, 1C), 42.1, 14.2.

ATR-IR (cm⁻¹): 3253, 2977, 2923, 2565, 1963, 1331, 1154.

HRMS: (ESI⁺) *m/z*: [M+Na]⁺ Calcd for C₁₂H₁₄DNNaO₂S 261.0778; Found 261.0781.



5-(Ethynyl-*d*)-1-tosyl-1H-indole [28-SM]. Following the general procedure H, in a N₂ filled glovebox, 5-(ethynyl)-1-tosyl-1H-indole (0.40 g, 1.35 mmol, 1 eq.), anhydrous K₂CO₃ (0.280 g, 2.03 mmol, 1.5 eq.) in anhydrous CH₃CN (4.0 mL) were stirred for 30 min. D₂O (1.22 mL, 67.5 mmol, 50 eq.) was added to the reaction. The reaction mixture was stirred for 36 h at room temperature under nitrogen atmosphere. Upon completion, the reaction was extracted with ethyl acetate (3 x 10 mL). The combined extracts were dried over anhydrous Na₂SO₄, filtered, and concentrated under vacuum to afford the title compound as a white solid (0.38 g, 1.28 mmol, 95% yield).

¹H NMR: (400 MHz, CDCl₃)

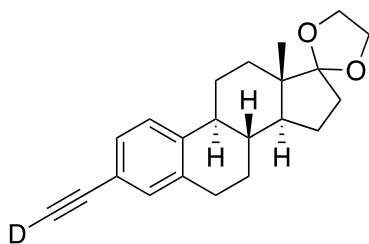
δ 7.97 (d, *J* = 8.6 Hz, 1H), 7.75 (d, *J* = 8.3 Hz, 2H), 7.67 (d, *J* = 1.6 Hz, 1H), 7.59 (d, *J* = 3.7 Hz, 1H), 7.45 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.18 (d, *J* = 8.3 Hz, 2H), 6.61 (d, *J* = 3.7 Hz, 1H), 3.07 (br s, 0.05H), 2.27 (s, 3H).

¹³C NMR: (75 MHz, CDCl₃)

δ 145.3, 134.9, 134.5, 130.6, 130.0, 128.4, 127.4, 126.8, 125.5, 117.1, 113.5, 108.8, 83.4 (t, *J* = 5.5 Hz, 1C), 76.4 (t, *J* = 38.4 Hz, 1C), 21.5.

ATR-IR (cm⁻¹): 3117, 2920, 2573, 1370, 1116.

HRMS: (ESI⁺) *m/z*: [M+Na]⁺ Calcd for C₁₇H₁₂DNNaO₂S 319.0622; Found 319.0626.



(8*R*,9*S*,13*S*,14*S*)-3-(Ethynyl-*d*)-13-methyl-6,7,8,9,11,12,13,14,15,16-

decahydrospiro[cyclopenta[*a*]phenanthrene-17,2'-[1,3]dioxolane] [32-SM]. Following the general procedure H, in a N₂ filled glovebox, (8*R*,9*S*,13*S*,14*S*)-3-(ethynyl)-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydrospiro[cyclopenta[*a*]phenanthrene-17,2'-[1,3]dioxolane (213 mg, 0.661 mmol, 1 eq.), K₂CO₃ (0.137 g, 0.991 mmol, 1.5 eq.), and CH₃CN (2 mL) were added to a flame dried 300 mL round bottom flask equipped with a Teflon stir bar. After stirring for 30 minutes, D₂O (0.597 mL, 33.1 mmol, 50 eq.) was added to round bottom flask. After stirring at room temperature for 24 h, reaction was quenched with distilled water, and extracted with dichloromethane (3 x 10 mL). The organic layers were combined and dried over Na₂SO₄, then concentrated to afford a white solid (215 mg, 0.665 mmol, >99% yield).

¹H NMR: (400 MHz, CDCl₃)

δ 7.25 – 7.22 (m, 2H), 7.22 – 7.19 (m, 1H), 3.99 – 3.81 (m, 4H), 2.99 (br s, 0.07H), 2.88 – 2.79 (m, 2H), 2.36 – 2.21 (m, 2H), 2.07 – 1.97 (m, 1H), 1.95 – 1.70 (m, 4H), 1.69 – 1.59 (m, 1H), 1.59 – 1.24 (m, 5H), 0.87 (s, 3H).

¹³C NMR: (101 MHz, CDCl₃)

δ 141.6, 137.0, 132.6, 129.3, 125.5, 119.4, 119.2, 83.6 (br s), 76.6 – 75.3 (multiplet overlapping with CDCl₃ signal, 1C), 65.3, 64.7, 49.5, 46.2, 44.2, 38.7, 34.3, 30.7, 29.3, 26.8, 25.9, 22.4, 14.4.

ATR-IR (cm⁻¹):

2978, 2939, 2875, 2587, 2249, 1735, 1620, 1590, 1179, 1044.

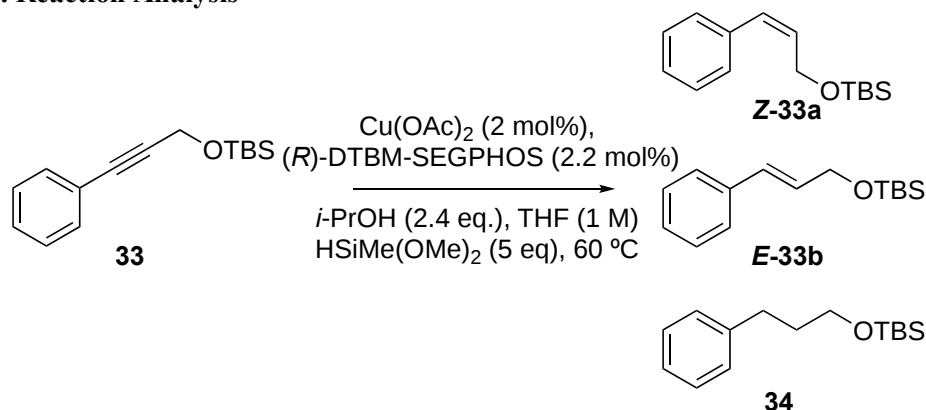
HRMS: (ESI⁺) *m/z*: [M + H]⁺ Calcd for C₂₂H₂₆DO₂ 324.2068; Found 324.2075.

Mechanistic Studies

General Procedure for Time Reaction Analysis

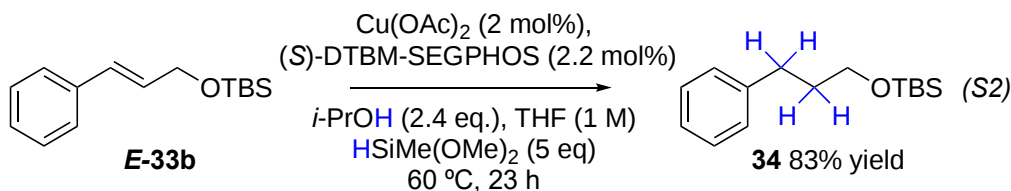
In a N₂ filled glovebox, (*R*)-DTBM-SEGP₂PHOS (5.2 mg, 0.0044 mmol, 0.022 eq.), Cu(OAc)₂ (20 μL of a 0.2 M solution in THF, 0.004 mmol, 0.02 eq.), and THF (0.08 mL) were added to an oven-dried 2-dram vial followed by dropwise addition of dimethoxy(methyl)silane (123 μL, 1 mmol, 5 eq.). A color change from green/blue to orange was observed while stirring for 15 minutes. In a separate oven-dried 1-dram vial was added the ((3-(phenyl)prop-2-yn-1-yl)oxy)(*tert*-butyl)dimethylsilane (49 mg, 0.2 mmol, 1 eq.), THF (0.1 mL), and 2-propanol (37 μL, 0.48 mmol, 2.4 eq.). The solution in the 1-dram vial was added dropwise over 20 seconds to the 2-dram vial. The total volume of THF was calculated based on having a final reaction concentration of 1M based on the alkyne substrate. The 2-dram vial was capped with a red pressure relief cap, taken out of the glovebox, and stirred at 60 °C for the designated time. The reaction mixture was then filtered through a 1" silica plug with 20 mL of Et₂O followed by 80 mL of Et₂O to elute the remaining product into a 200 mL round bottom flask. After removing the Et₂O by rotary evaporation, the crude product was isolated by flash column chromatography using gradient elution (100 mL of hexanes followed by 200 mL of 5% ethyl acetate in hexanes) to give *tert*-butyldimethyl(3-phenylpropoxy)silane as a clear, colorless oil. The spectra for the title compound matched previously reported spectra.²⁵

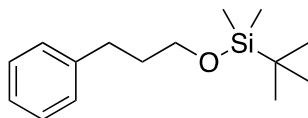
Table S2. Reaction Analysis



Entry	Reaction Time (min)	Z-33a ^a (%)	E-33b ^a (%)	34 ^a (%)
1	15	74	0	6
2	30	48	2	25
3	45	40	5	36
4	90	17	7	54
5	180	7	5	61
6	9h	0	0	79

^aYields of each product were determined by ¹H NMR of the combined products after purification.





***tert*-Butyldimethyl(3-phenylpropoxy)silane (34)**

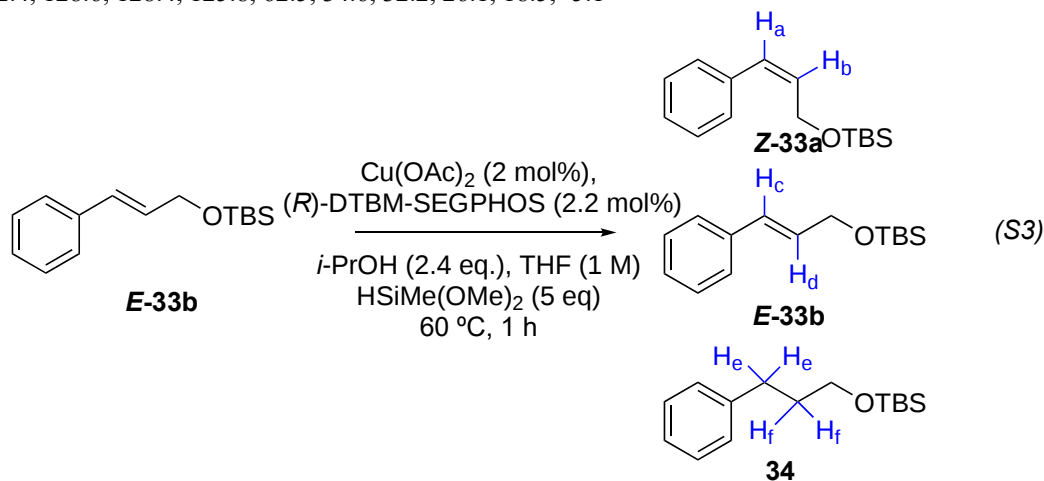
In a N₂ filled glovebox, (*S*)-DTBM-SEGPPOS (7.8 mg, 0.0066mmol, 0.022 eq.), Cu(OAc)₂ (30 μL of a 0.2 M solution in THF, 0.006 mmol, 0.02 eq.), and THF (0.12 mL) were added to an oven-dried 2-dram vial followed by dropwise addition of dimethoxy(methyl)silane (185 μL, 1.5 mmol, 5 eq.). A color change from green/blue to orange was observed while stirring for 15 minutes. In a separate oven-dried 1-dram vial was added the *E*-33b (74.5 mg, 0.3 mmol, 1 eq.), THF (0.15 mL), and 2-propanol (55 μL, 0.72 mmol, 2.4 eq.). The solution in the 1-dram vial was added dropwise over 20 seconds to the 2-dram vial. The total volume of THF was calculated based on having a final reaction concentration of 1M based on the alkyne substrate. The 2-dram vial was capped with a red pressure relief cap, taken out of the glovebox, and stirred at 60 °C for 23 h. The reaction mixture was then filtered through a 1" silica plug with 20 mL of Et₂O followed by 80 mL of Et₂O to elute the remaining product into a 200 mL round bottom flask. After removing the Et₂O by rotary evaporation, the crude product was isolated by flash column chromatography using gradient elution (100 mL of hexanes followed by 100 mL of 2% ethyl acetate in hexanes) to give *tert*-butyldimethyl(3-phenylpropoxy)silane as a clear, colorless oil (62 mg, 0.248 mmol, 83% yield). The spectra for the title compound matched previously reported spectra.²⁵

¹H NMR (400 MHz, CDCl₃)

δ 7.33 – 7.25 (m, 2H), 7.23 – 7.16 (m, 3H), 3.65 (t, *J* = 6.3 Hz, 2H), 2.69 (t, *J* = 7.9 Hz, 2H), 1.90 – 1.80 (m, 2H), 0.93 (s, 9H), 0.07 (s, 6H).

¹³C NMR (101 MHz, CDCl₃)

δ 142.4, 128.6, 128.4, 125.8, 62.5, 34.6, 32.2, 26.1, 18.5, -5.1



***tert*-Butyldimethyl(3-phenylpropoxy)silane (34)**

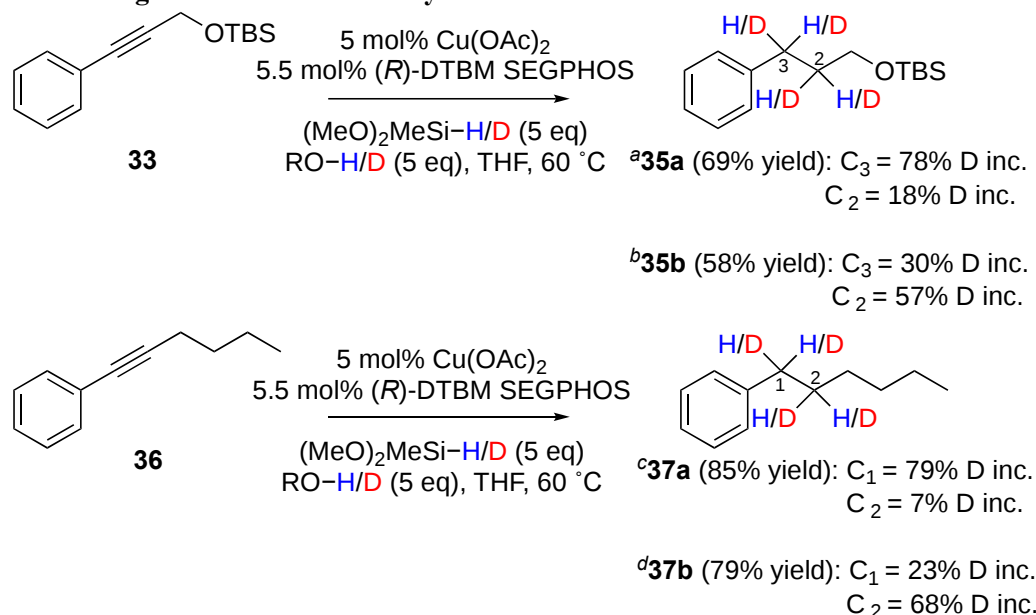
In a N₂ filled glovebox, (*S*)-DTBM-SEGPPOS (7.8 mg, 0.0066mmol, 0.022 eq.), Cu(OAc)₂ (30 μL of a 0.2 M solution in THF, 0.006 mmol, 0.02 eq.), and THF (0.12 mL) were added to an oven-dried 2-dram vial followed by dropwise addition of dimethoxy(methyl)silane (185 μL, 1.5 mmol, 5 eq.). A color change from green/blue to orange was observed while stirring for 15 minutes. In a separate oven-dried 1-dram vial was added the *E*-33b (74.5 mg, 0.3 mmol, 1 eq.), THF (0.15 mL), and 2-propanol (55 μL, 0.72 mmol, 2.4 eq.). The solution in the 1-dram vial was added dropwise over 20 seconds to the 2-dram vial. The total volume of THF was calculated based on having a final reaction concentration of 1M based on the alkyne substrate. The 2-dram vial was capped with a red pressure relief cap, taken out of the glovebox, and stirred at 60 °C for 1 h. The reaction mixture was then filtered through a 1" silica plug with 20 mL of Et₂O followed by 80 mL of Et₂O to elute the remaining product into a 200 mL round bottom flask. After removing the Et₂O by rotary evaporation, the crude product was isolated by flash column chromatography using gradient elution (100 mL of hexanes followed by 100 mL of 2% ethyl acetate in hexanes) to give *tert*-butyldimethyl(3-

phenylpropoxy)silane as a clear, colorless oil (61 mg combination of all products, 42% alkane **34**, 39% *E*-**33b**, trace *Z*-**33a**).

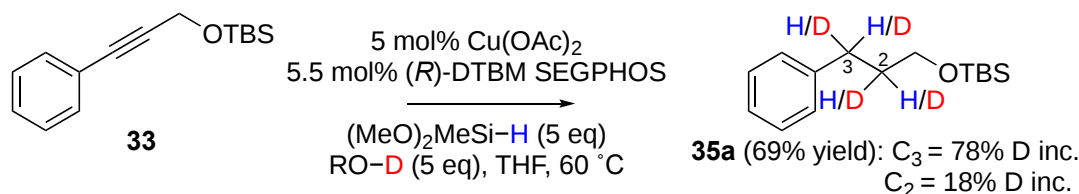
Transfer Hydrodeuteration Experiments:

Method for calculating deuterium incorporation at each carbon: In the ^1H NMR spectra, if both benzylic and homobenzylic peaks were clearly visible and no overlap with other peaks was observed, then the deuterium incorporation was calculated from the integration of the protonated peak. If overlap of other peaks or overlap with an impurity such as water or grease was observed in the homobenzylic region of the ^1H NMR spectra, a ^2H NMR spectra was obtained. The ratio of the two peaks that appear in the ^2H NMR spectra was correlated to the calculated deuterium incorporation at the benzylic peak in the ^1H NMR spectra.

Scheme S4: Regioselective Transfer Hydrodeuteration



All reactions performed with Cu(OAc)_2 (5 mol%), (R)-DTBM-SEGPHOS (5.5 mol%), THF (0.2 M, based on alkyne substrate), 60 $^\circ\text{C}$. All yields are isolated and %D inc. was determined using ^1H NMR and/or ^2H NMR. ^a5 eq $(\text{MeO})_2\text{MeSi-H}$, 5 eq EtOD, 24 h. ^b5 eq $(\text{MeO})_2\text{MeSi-D}$, 5 eq EtOH, 24 h. Alkane **9b** was isolated as a mixture with alkene (23% yield) present due to incomplete conversion. See SI for details. ^c5 eq $(\text{MeO})_2\text{MeSi-H}$, 5 eq *i*-PrOD, 21 h. ^d5 eq $(\text{MeO})_2\text{MeSi-D}$, 5 eq *i*-PrOD, 21 h.



Tert-butyldimethyl(3-phenylpropoxy)silane-*d*₂ [**35a**].

In a N_2 filled glovebox, (R)-DTBM-SEGPHOS (13 mg, 0.011 mmol, 0.055 eq.), Cu(OAc)_2 (50 μL of a 0.2 M solution in THF, 0.01 mmol, 0.05 eq.), and THF (0.05 mL) were added to an oven-dried 2-dram vial followed by dropwise addition of dimethoxy(methyl)silane (123 μL , 1 mmol, 5 eq.). A color change from green/blue to orange was observed while stirring for 15 minutes. In a separate oven-dried 1-dram vial was added the ((3-(phenylprop-2-yn-1-yl)oxy)(*tert*-butyl)dimethylsilane (49 mg, 0.2 mmol, 1 eq.), THF (0.10 mL), and ethanol-OD (58 μL , 1 mmol, 5 eq.). The solution in the 1-dram vial was added dropwise over 20 seconds to the 2-dram vial. The 2-dram vial was capped with a red pressure relief cap, taken out of the glovebox, and stirred at 60 $^\circ\text{C}$ for 24 h. The reaction mixture was then filtered through a 1" silica plug with

20 mL of Et₂O followed by 80 mL of Et₂O to elute the remaining product into a 200 mL round bottom flask. After removing the Et₂O by rotary evaporation, the crude product was isolated by flash column chromatography using gradient elution (100 mL of hexanes followed by 100 mL of 2% ethyl acetate in hexanes) to give *tert*-butyldimethyl(3-phenylpropoxy)silane-*d*₂ as a clear, colorless oil (34.9 mg, 0.138 mmol, 69% yield).

¹H NMR (400 MHz, CDCl₃):

δ 7.31 – 7.26 (m, 2H), 7.21 – 7.17 (m, 3H), 3.66 – 3.63 (m, 2H), 2.69 – 2.65 (m, 0.44H), 1.87–1.82 (m, 1.65H), 0.92 (s, 9H), 0.06 (s, 6H).

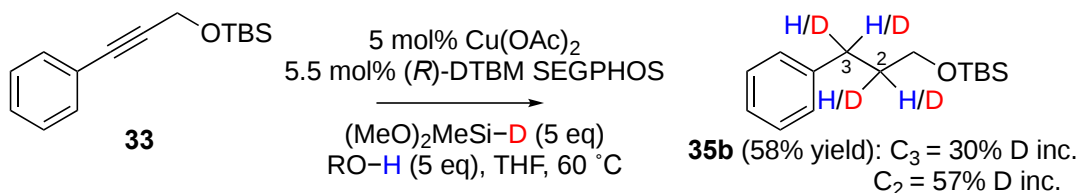
¹³C NMR (101 MHz, CDCl₃):

δ 142.3, 128.6, 128.4, 125.8, 62.5, 34.5–34.0 (m), 32.3 – 31.2 (m), 26.1, 18.5, -5.1.

ATR-IR (cm⁻¹):

3084, 3062, 3026, 2953, 2928, 2894, 2856, 2132, 1091.

HRMS: (ESI⁺) *m/z*: [M+Na]⁺ Calcd for C₁₅H₂₄D₂NaOSi 275.1771; Found 275.1773.



***Tert*-butyldimethyl(3-phenylpropoxy)silane-*d*₂ [35b].**

In a N₂ filled glovebox, (R)-DTBM-SEGPPOS (13 mg, 0.011 mmol, 0.055 eq.), Cu(OAc)₂ (50 μL of a 0.2 M solution in THF, 0.01 mmol, 0.05 eq.), and THF (0.05 mL) were added to an oven-dried 2-dram vial followed by dropwise addition of dimethoxy(methyl)silane-*d* (0.14 mL, 1 mmol, 7.1 M solution in hexanes, 5 eq.). A color change from green/blue to orange was observed while stirring for 15 minutes. In a separate oven-dried 1-dram vial was added the ((3-phenylprop-2-yn-1-yl)oxy)(*tert*-butyl)dimethylsilane (49 mg, 0.2 mmol, 1 eq.), THF (0.1 mL), and ethanol (58 μL, 1 mmol, 5 eq.). The solution in the 1-dram vial was added dropwise over 20 seconds to the 2-dram vial. The 2-dram vial was capped with a red pressure relief cap, taken out of the glovebox, and stirred at 60 °C for 24 h. The reaction mixture was then filtered through a 1" silica plug with 20 mL of Et₂O followed by 80 mL of Et₂O to elute the remaining product into a 200 mL round bottom flask. After removing the Et₂O by rotary evaporation, the crude product was isolated by flash column chromatography using gradient elution (100 mL of hexanes followed by 100 mL of 2% ethyl acetate in hexanes) to give *tert*-butyldimethyl(3-phenylpropoxy)silane-*d*₂ as a clear, colorless oil (40.5 mg, 58% alkane, 23% alkene).

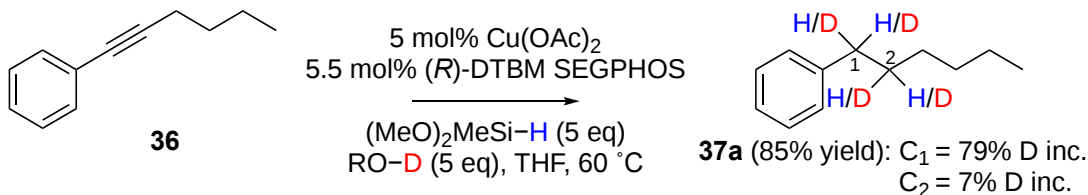
¹H NMR (300 MHz, CDCl₃):

δ 7.42 – 7.14 (m, 7.2H, overlap with alkene aromatic protons), 6.61 (d, *J* = 14.1 Hz, 0.12H), 6.50 (s, 0.14H), 6.35 – 6.23 (m, 0.11H), 5.89 – 5.78 (m, 0.10H), 4.50 – 4.41 (m, 0.4H), 4.40 – 4.33 (m, 0.38H), 3.73 – 3.55 (m, 2H), 2.75 – 2.55 (m, 1.4H), 1.92 – 1.74 (m, 0.87H), 0.96 (s, 1.79H), 0.92 (s, 10.5H), 0.13 (s, 1.24H), 0.06 (s, 6.76H).

ATR-IR (cm⁻¹):

3085, 3062, 3027, 2954, 2928, 2895, 2856, 2153, 1087.

HRMS: (EI⁺) *m/z*: [M-H]⁺ Calcd for C₁₅H₂₄D₂OSi 251.1830; Found 251.1795.



Hexylbenzene-*d*₂ [37a].

In a N₂ filled glovebox, (*R*)-DTBM-SEGPPOS (13 mg, 0.011 mmol, 0.055 eq.), Cu(OAc)₂ (50 μL of a 0.2 M solution in THF, 0.01 mmol, 0.05 eq.), and THF (0.05 mL) were added to an oven-dried 2-dram vial followed by dropwise addition of dimethoxy(methyl)silane (123 μL, 1 mmol, 5 eq.). A color change from green/blue to orange was observed while stirring for 15 minutes. In a separate oven-dried 1-dram vial was added the 1-hexyn-1-yl-benzene (31.7 mg, 0.2 mmol, 1 eq.), THF (0.1 mL), and 2-propanol-*d*₈ (77 μL, 1 mmol, 5 eq.). The solution in the 1-dram vial was added dropwise over 20 seconds to the 2-dram vial. The 2-dram vial was capped with a red pressure relief cap, taken out of the glovebox, and stirred at 60 °C for 21 h. The reaction mixture was then filtered through a 1" silica plug with 20 mL of Et₂O followed by 80 mL of Et₂O to elute the remaining product into a 200 mL round bottom flask. After removing the Et₂O by rotary evaporation, the crude product was isolated by flash column chromatography using gradient elution (200 mL of hexanes) to give hexylbenzene-*d*₂ as a clear, colorless oil (28 mg, 0.17 mmol, 85% yield).

¹H NMR (400 MHz, CDCl₃)

δ 7.32 – 7.24 (m, 2H), 7.22 – 7.13 (m, 3H), 2.64 – 2.55 (m, 0.42H), 1.66 – 1.54 (m, 1.94H, overlaps with H₂O), 1.40 – 1.21 (m, 6H, overlaps with grease), 0.89 (t, *J* = 6.7 Hz, 3H).

²H NMR: (61 MHz, CHCl₃)

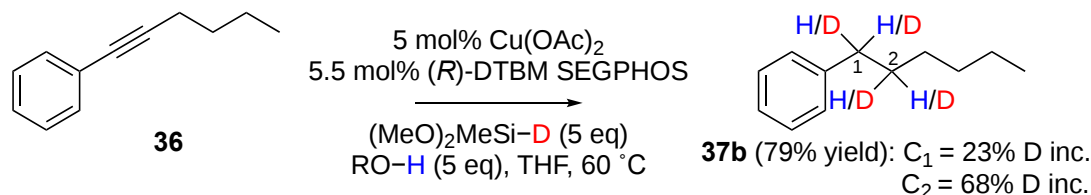
δ 2.59 (br s, 1.58D), 1.62 (br s, 0.13D).

¹³C NMR (101 MHz, CDCl₃)

δ 143.1, 128.5, 128.4, 125.7, 36.4 – 35.3 (m), 31.9, 31.8 – 30.9 (m), 29.2, 22.8, 14.2.

ATR-IR (cm⁻¹): 3084, 3061, 3025, 2956, 2923, 2855, 2191, 1074.

HRMS: (EI⁺) *m/z*: [M]⁺ Calcd for C₁₂H₁₆D₂ 164.1500; Found 164.1528.



Hexylbenzene-*d*₂ [37b].

In a N₂ filled glovebox, (*R*)-DTBM-SEGPPOS (26 mg, 0.022 mmol, 0.055 eq.), Cu(OAc)₂ (100 μL of a 0.2 M solution in THF, 0.02 mmol, 0.05 eq.), and THF (0.15 mL) were added to an oven-dried 2-dram vial followed by dropwise addition of dimethoxy(methyl)silane-*d* (288 μL, 2 mmol, 7.1 M solution in hexanes, 5 eq). A color change from green/blue to orange was observed while stirring for 15 minutes. In a separate oven-dried 1-dram vial was added the 1-hexyn-1-yl-benzene (63 mg, 0.4 mmol, 1 eq.), THF (0.15 mL), and 2-propanol (153 μL, 2 mmol, 5 eq.). The solution in the 1-dram vial was added dropwise over 20 seconds to the 2-dram vial. The 2-dram vial was capped with a red pressure relief cap, taken out of the glovebox, and stirred at 60 °C for 21 h. The reaction mixture was then filtered through a 1" silica plug with 20 mL of Et₂O followed by 80 mL of Et₂O to elute the remaining product into a 200 mL round bottom flask. After removing the Et₂O by rotary evaporation, the crude product was isolated by flash column chromatography using gradient elution (200 mL of hexanes) to give hexylbenzene-*d*₂ as a clear, colorless oil (52.0 mg, 0.317 mmol, 79% yield).

¹H NMR (400 MHz, CDCl₃)

δ 7.33 – 7.27 (m, 2H), 7.24 – 7.17 (m, 3H), 2.66 – 2.58 (m, 1.54H), 1.69 – 1.56 (m, 0.76H, overlaps with H₂O), 1.42 – 1.24 (m, 6H, overlaps with grease), 0.92 (t, *J* = 6.8 Hz, 3H).

²H NMR: (61 MHz, CHCl₃)

δ 2.61 (br s, 0.46D), 1.60 (br s, 1.34D).

¹³C NMR (101 MHz, CDCl₃)

δ 143.1, 128.5, 128.4, 125.7, 36.2-35.3 (m), 31.9, 31.7 – 30.9 (m), 29.1, 22.8, 14.3.

ATR-IR (cm⁻¹): 3085, 3063, 3026, 2956, 2921, 2871, 2855, 2361, 2150, 1077.

HRMS: (EI⁺) *m/z*: [M]⁺ Calcd for C₁₂H₁₆D₂ 164.1500; Found 164.1528.

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CHAPTER 2 SUPPLEMENTARY INFORMATION

Precision Deuteration Using Cu-Catalyzed Transfer Hydrodeuteration to Access Small Molecules Deuterated at the Benzylic Position Supplementary Information

General Information

The following chemicals were purchased from commercial vendors and were used as received: Cu(OAc)₂ (99.999% from Alfa Aesar); 1,2-Bis[bis[3,5-di(*t*-butyl)phenyl]phosphino]benzene (DTB-DPPBz) (Wako Pure Chemical Industries), dimethoxy(methyl)silane (TCI); 2-propanol-OD (Millipore Sigma); 2-propanol-*d*₈ (Acros Organic); 2-propanol (Alfa Aesar); *tert*-butyldimethylsilyl chloride (TBSCl); D₂O (Oakwood Chemical). Anhydrous tetrahydrofuran (THF) was purified by an MBRAUN solvent purification system (MB-SPS). Prior to use, triethylamine (Et₃N) was distilled over CaH₂ and stored over 3Å molecular sieves. Chloroform-*d* (CDCl₃) was stored over 3Å molecular sieves.

Thin-layer chromatography (TLC) was conducted with Silicycle silica gel 60Å F254 pre-coated plates (0.25 mm) and visualized with UV, Iodine and KMnO₄ stains. Flash chromatography was performed using Silia Flash® P60, 40-60 µm (230-400 mesh), purchased from Silicycle. For reactions that required heating (optimization, transfer hydrodeuteration reactions), a PolyBlock for 2 dram vials was used on top of a Heidolph heating/stir plate. ¹H NMR spectra were recorded on a Varian 300 or 400 MHz spectrometer and are reported in ppm using solvent as an internal standard (CDCl₃ at 7.26 ppm). Data reported as: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sxt = sextet, hep = heptet, m = multiplet, br = broad; coupling constant(s) in Hz; integration. ¹³C NMR spectra were recorded on a Varian 76 MHz or 101 MHz spectrometer and are reported in ppm using solvent as an internal standard (CDCl₃ at 77.16 ppm). ¹⁹F NMR spectra were recorded on a Varian 376 MHz spectrometer. ²H NMR spectra were recorded on a Varian 61 MHz spectrometer. Labeled solvent impurities were calculated out when reporting isolated yields. See published manuscript for Computational references.⁴⁹

Synthesis and Characterization of Organic Molecules

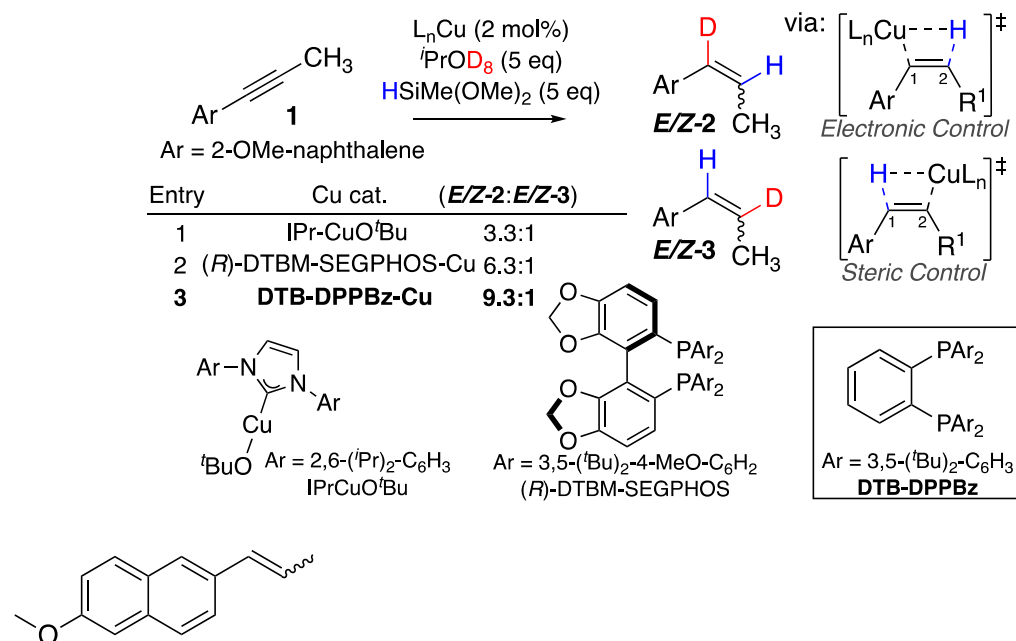
Regioselectivity Studies

General Procedure A for Regioselectivity Studies in Scheme S1:

In a N₂ filled glovebox, Cu. cat (0.00400 mmol, 0.0200 eq.) and THF (0.0800 mL) were added to an oven-dried 2-dram vial followed by dropwise addition of dimethoxy(methyl)silane (123 µL, 1.00 mmol, 5.00 eq.). A color change from green/blue to yellow was observed while stirring for 15 minutes. In a separate oven-dried 1-dram vial was added 6-methoxy-2-(1-propynyl)naphthalene **1** (39.3 mg, 0.200 mmol, 1.00 eq.), THF (0.100 mL), and 2-propanol-*d*₈ (76.6 µL, 1.00 mmol, 5.00 eq.). The solution in the 1-dram vial was added dropwise over 20 seconds to the 2-dram vial. The total volume of THF was calculated based on having a

final reaction concentration of 1M based on the alkyne substrate. The 2-dram vial was capped with a red pressure relief cap, taken out of the glovebox, and stirred for the respective time at 40 °C, at which point the reaction was filtered through a 1" silica plug with 50 mL of Et₂O followed by 50 mL of Et₂O to elute the remaining product into a 200 mL round bottom flask. After removing the solvent by rotary evaporation, the crude product was dry loaded onto silica gel and purified by flash column chromatography (100 mL of 100% hexanes and 200 mL 3% ethyl acetate in hexanes) and the ratio of product *E/Z*-2 to product *E/Z*-3 was determined by ¹H NMR analysis of the alkene region of the isolated product mixture. For clarity, only the signals in the alkene region is reported for each entry. These were assigned by direct comparison to a synthesized standard of the *E/Z* compound.

Scheme S2. Ligand studies of transfer hydrodeuteration of aryl alkynes



(*E/Z*)-2-methoxy-6-(prop-1-en-1-yl)naphthalene

Synthesized from a previously reported procedure¹, ethyltriphenylphosphoniumbromide (2.39 g, 6.44 mmol, 1.20 eq), NaH (60% dispersion in mineral oil, 0.969 g, 24.2 mmol, 4.51 eq), 6-methoxy-2-naphthalenecarboxaldehyde (1.00 g, 5.37 mmol, 1.00 eq), and THF (27.0 mL, 0.200 M) were combined to form the desired product as a cream colored solid (0.906 g, 4.57 mmol, 85% yield). This product was used as a reference standard for ¹H NMR analysis of the isolated product mixtures from entries 1-3 in Scheme S1.

¹H NMR (400 MHz, CDCl₃): δ 7.76 – 7.62 (m, 2.91H), 7.60 (s, 0.21H), 7.54 (dd, *J* = 8.5, 1.8 Hz, 0.20H), 7.43 (dd, *J* = 8.5, 1.8 Hz, 0.78H), 7.19 – 7.06 (m, 2.17H), 6.62 – 6.55 (m, 0.44H), 6.55 – 6.48 (m, 0.36H), 6.38 – 6.24 (m, 0.20H), 5.90 – 5.78 (m, 0.83H), 3.93 (s, 2.52H), 3.92 (s, 0.56H), 1.99 (dd, *J* = 7.2, 1.9 Hz, 2.27H), 1.94 (dd, *J* = 6.7, 1.7 Hz, 0.62H).

Entry 1. IPr-CuO^tBu was pre-formed by addition of IPrCuCl (100 mg, 0.205 mmol, 1.00 eq), NaO^tBu (19.7 mg, 0.205 mmol, 1.00 eq), and THF (1.03 mL, 0.200 M solution) to an oven-dried 20 mL vial. This was stirred at room temperature for 20 minutes. Then, according to the general procedure A, IPrCuO^tBu (20.0 μL of a 0.200 M solution in THF, 0.00400 mmol, 0.0200 eq), THF (0.080 mL), and dimethoxy(methyl)silane (123 μL, 1.00 mmol, 5.00 eq.) were combined in a 2-dram vial followed by addition of a solution of 6-methoxy-2-(1-propynyl)naphthalene (39.3 mg, 0.200 mmol, 1.00 eq.), THF (0.100 mL), and 2-propanol-*d*₈ (76.6 μL, 1.00 mmol, 5.00 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 5 h at 40 °C. Upon completion and crude ¹H NMR analysis, the crude product was dry loaded onto

silica gel and isolated by flash column chromatography (100 mL of 100% hexanes and 200 mL of 3% ethyl acetate in hexanes) to give a white solid containing a mixture of products (*E/Z*-2 : *E/Z*-3, 3.3:1).

¹H NMR (400 MHz, CDCl₃): δ 6.61-6.47 (m, 1H), 6.39-6.22 (m, 0.24H), 5.83 (q, *J* = 7.2 Hz, 3.05H)

Entry 2. According to the general procedure A, (*R*)-DTBM-SEPHOS (5.20 mg, 0.00440 mmol, 0.0220 eq), Cu(OAc)₂ (20.0 μL of a 0.200 M solution in THF, 0.00400 mmol, 0.0200 eq), THF (0.0800 mL), and dimethoxy(methyl)silane (123 μL, 1.00 mmol, 5.00 eq.) were combined in a 2-dram vial followed by addition of a solution of 6-methoxy-2-(1-propynyl)naphthalene (39.3 mg, 0.200 mmol, 1.00 eq.), THF (0.100 mL), and 2-propanol-*d*8 (76.6 μL, 1.00 mmol, 5.00 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 6 h at 40 °C. Upon completion and crude ¹H NMR analysis, the crude product was dry loaded onto silica gel and isolated by flash column chromatography (100 mL of 100% hexanes and 200 mL of 3% ethyl acetate in hexanes) to give a white solid containing a mixture of products (*E/Z*-2 : *E/Z*-3, 6.3:1).

¹H NMR (400 MHz, CDCl₃): δ 6.59-6.51 (m, 1H), 6.36-6.28 (m, 0.35H), 5.84 (q, *J* = 7.3 Hz, 5.9H).

Entry 3. According to the general procedure A, DTB-DPPBz (4.00 mg, 0.00440 mmol, 0.0220 eq), Cu(OAc)₂ (20.0 μL of a 0.200 M solution in THF, 0.00400 mmol, 0.0200 eq), THF (0.0800 mL), and dimethoxy(methyl)silane (123 μL, 1.00 mmol, 5.00 eq.) were combined in a 2-dram vial followed by addition of a solution of 6-methoxy-2-(1-propynyl)naphthalene (39.3 mg, 0.200 mmol, 1.00 eq.), THF (0.100 mL), and 2-propanol-*d*8 (76.6 μL, 1.00 mmol, 5.00 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 27 minutes at 40 °C. Upon completion and crude ¹H NMR analysis, the crude product was dry loaded onto silica gel and isolated by flash column chromatography (100 mL of 100% hexanes and 200 mL of 3% ethyl acetate in hexanes) to give a white solid containing a mixture of products (*E/Z*-2 : *E/Z*-3, 9.3:1).

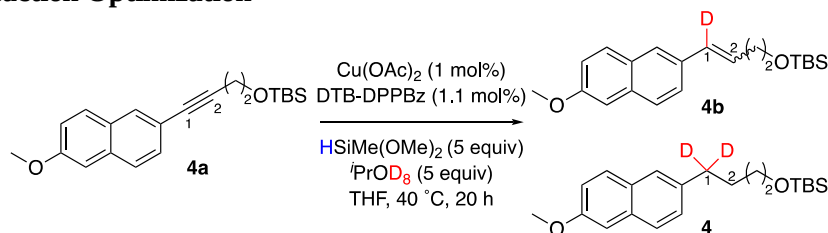
¹H NMR (400 MHz, CDCl₃): δ 6.59-6.54 (m, 1H), 6.38-6.25 (m, 0.28H), 5.85 (q, *J* = 7.3 Hz, 9H).

Optimization Studies

General Procedure B for Optimization Studies in Table S1:

In a N₂ filled glovebox, ligand, Cu catalyst (Cu:L = 1:1.1), and THF were added to an oven-dried 2-dram vial followed by dropwise addition of R₃Si-H (1.00 mmol, 5.00 eq.). A color change from green/blue to orange was observed while stirring for 15 minutes. In a separate oven-dried 1-dram vial was added *tert*-butyl((4-(6-methoxynaphthalen-2-yl)but-3-yn-1-yl)oxy)dimethylsilane **4a** (68.1 mg, 0.200 mmol, 1.00 eq.), THF (0.100 mL), and the alcohol-OD (1.00 mmol, 5.00 eq.). The solution in the 1-dram vial was added dropwise over 20 seconds to the 2-dram vial. The total volume of THF was calculated based on having a final reaction concentration of 1M based on the alkyne substrate. The 2-dram vial was capped with a red pressure relief cap, taken out of the glovebox, and stirred for 20 h at the respective temperature at which point the reaction was filtered through a 1" silica gel plug with 50 mL of Et₂O followed by an additional 50 mL of Et₂O to elute the crude product into a 200 mL round bottom flask. The solvent was removed by rotary evaporation, and the product was analyzed by ¹H NMR using 1,3,5-trimethylbenzene as an internal standard. If greater than 5% ¹H NMR yield was observed for **5a** in the crude ¹H NMR, yields were obtained by isolating the product by flash column chromatography.

Table S1. Reaction Optimization



Entry	Deviations	4a (%)	4b (%)	4 (%)	D inc. ^b
1	none	0	0	97 ^c	95
2	rt	0	0	95 ^c	95
3 ^g	5 °C	0	3.5 ^c	84 ^c	97
4 ^g	PMHS ^e	0	0	75 ^c	94
5 ^g	DEMS ^f	0	0	89 ^c	94
6 ^g	EtOD	0 ^c	41 ^c	39 ^c	93
7 ^g	MeOD	10 ^c	53 ^c	12 ^c	
8 ^g	^t BuOD	20 ^c	47 ^c	14 ^c	
9 ^g	D ₂ O	75 ^d	15 ^d	0 ^d	
10 ^g	Stryker's Reagent	99 ^d	0	0	
11 ^g	No ligand	84 ^d	0	0	

^aReactions were conducted using 0.2 mmol of substrate. Cu(OAc)₂ was used in the reactions as a 0.2 M solution in THF. ^bDeuterium incorporation at C₁ of alkane **6** products. ^cYield was determined after purification by flash column chromatography. ^dYield was determined by ¹H NMR analysis of the crude reaction mixture using 1,3,5-trimethylbenzene as an internal standard. ^e*Poly*(methylhydrosiloxane). ^fDiethoxymethylsilane. ^g2 mol% Cu(OAc)₂ and 2.2 mol% DTB-DPPBz were used.

Entry 1. According to the general procedure B, DTB-DPPBz (2.00 mg, 0.00220 mmol, 0.0110 eq), Cu(OAc)₂ (10.0 µL of a 0.200 M solution in THF, 0.00200 mmol, 0.0100 eq), THF (0.0900 mL), and dimethoxy(methyl)silane (123 µL, 1.00 mmol, 5.00 eq.) were combined in a 2-dram vial followed by addition of a solution of *tert*-butyl((4-(6-methoxynaphthalen-2-yl)but-3-yn-1-yl)oxy)dimethylsilane **4a** (68.1 mg, 0.200 mmol, 1.00 eq.), THF (0.100 mL), and 2-propanol-*d*₈ (76.6 µL, 1.00 mmol, 5.00 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 20 h at 40 °C. Upon completion and crude ¹H NMR analysis, the crude product was dry loaded onto silica gel and isolated by flash column chromatography (100 mL of 100% hexanes, 200 mL of 2% ethyl acetate in hexanes) to give the pure product as an orange solid (**4**, 67.4 mg, 0.194 mmol, 97% yield).

Entry 2. According to the general procedure B, DTB-DPPBz (2.00 mg, 0.00220 mmol, 0.0110 eq), Cu(OAc)₂ (10.0 µL of a 0.200 M solution in THF, 0.00200 mmol, 0.0100 eq), THF (0.0900 mL), and dimethoxy(methyl)silane (123 µL, 1.00 mmol, 5.00 eq.) were combined in a 2-dram vial followed by addition of a solution of *tert*-butyl((4-(6-methoxynaphthalen-2-yl)but-3-yn-1-yl)oxy)dimethylsilane **4a** (68.1 mg, 0.200 mmol, 1.00 eq.), THF (0.100 mL), and 2-propanol-*d*₈ (76.6 µL, 1.00 mmol, 5.00 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 20 h at room temperature. Upon completion and crude ¹H NMR analysis, the crude product was dry loaded onto silica gel and isolated by flash column chromatography (100 mL of 100% hexanes, 200 mL of 2% ethyl acetate in hexanes) to give the pure product as an orange solid (**4**, 65.7 mg, 0.190 mmol, 95% yield).

Entry 3. According to the general procedure B, DTB-DPPBz (4.00 mg, 0.00440 mmol, 0.0220 eq), Cu(OAc)₂ (20.0 µL of a 0.200 M solution in THF, 0.00400 mmol, 0.0200 eq), THF (0.0800 mL), and dimethoxy(methyl)silane (123 µL, 1.00 mmol, 5.00 eq.) were combined in a 2-dram vial followed by addition of a solution of *tert*-butyl((4-(6-methoxynaphthalen-2-yl)but-3-yn-1-yl)oxy)dimethylsilane **4a** (68.1 mg, 0.200 mmol, 1.00 eq.), THF (0.100 mL), and 2-propanol-*d*₈ (76.6 µL, 1.00 mmol, 5.00 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 20 h at 5 °C. Upon completion and crude ¹H NMR analysis, the crude product was dry loaded onto silica gel and isolated by flash column chromatography (100 mL of 100% hexanes, 200 mL of 2% ethyl acetate in hexanes) to give the pure product as an orange solid (**5** and **6** isolated as an inseparable mixture, 60.7 mg (**4b**, 3.5% yield; **5a**, 84% yield).

Entry 4. According to the general procedure B, DTB-DPPBz (4.00 mg, 0.00440 mmol, 0.0220 eq), Cu(OAc)₂ (20.0 µL of a 0.200 M solution in THF, 0.00400 mmol, 0.0200 eq), THF (0.0800 mL), and poly(methylhydrosiloxane) (66.7 µL, 1.00 mmol, 5.00 eq.) were combined in a 2-dram vial followed by addition of a solution of *tert*-butyl((4-(6-methoxynaphthalen-2-yl)but-3-yn-1-yl)oxy)dimethylsilane **4a** (68.1 mg, 0.200 mmol, 1.00 eq.), THF (0.100 mL), and 2-propanol-*d*₈ (76.6 µL, 1.00 mmol, 5.00 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 20 h at 40 °C. Upon completion and crude ¹H NMR analysis, the crude product was dry loaded onto silica gel and isolated by flash column chromatography (100 mL of 100% hexanes, 200 mL of 2% ethyl acetate in hexanes) to give the pure product as an orange solid (**4**, 51.6 mg, 0.149 mmol, 75% yield).

Entry 5. According to the general procedure B, DTB-DPPBz (4.00 mg, 0.00440 mmol, 0.0220 eq), Cu(OAc)₂ (20.0 µL of a 0.200 M solution in THF, 0.00400 mmol, 0.0200 eq), THF (0.0800 mL), and diethoxy(methyl)silane (160 µL, 1.00 mmol, 5.00 eq.) were combined in a 2-dram vial followed by addition of a solution of *tert*-butyl((4-(6-methoxynaphthalen-2-yl)but-3-yn-1-yl)oxy)dimethylsilane **4a** (68.1 mg, 0.200 mmol, 1.00 eq.), THF (0.100 mL), and 2-propanol-*d*₈ (76.6 µL, 1.00 mmol, 5.00 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 20 h at 40 °C. Upon completion and crude ¹H NMR analysis, the crude product was dry loaded onto silica gel and isolated by flash column chromatography (100 mL of 100% hexanes, 200 mL of 2% ethyl acetate in hexanes) to give the pure product as an orange solid (**4**, 61.7 mg, 0.178 mmol, 89% yield).

Entry 6. According to the general procedure B, DTB-DPPBz (4.00 mg, 0.00440 mmol, 0.0220 eq), Cu(OAc)₂ (20.0 µL of a 0.200 M solution in THF, 0.00400 mmol, 0.0200 eq), THF (0.0800 mL), and dimethoxy(methyl)silane (123 µL, 1.00 mmol, 5.00 eq.) were combined in a 2-dram vial followed by addition of a solution of *tert*-butyl((4-(6-methoxynaphthalen-2-yl)but-3-yn-1-yl)oxy)dimethylsilane **4a** (68.1 mg, 0.200 mmol, 1.00 eq.), THF (0.100 mL), and ethanol-OD (58.4 µL, 1.00 mmol, 5.00 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 20 h at 40 °C. Upon completion and crude ¹H NMR analysis, the crude product was dry loaded onto silica gel and isolated by flash column chromatography (100 mL of 100% hexanes, 200 mL of 2% ethyl acetate in hexanes) to give the pure product as an orange solid (**4b** and **4** isolated as an inseparable mixture, 55.4 mg (**4b**, 41% yield; **4**, 39% yield)).

Entry 7. According to the general procedure B, DTB-DPPBz (4.00 mg, 0.00440 mmol, 0.0220 eq), Cu(OAc)₂ (20.0 µL of a 0.200 M solution in THF, 0.00400 mmol, 0.0200 eq), THF (0.0800 mL), and dimethoxy(methyl)silane (123 µL, 1.00 mmol, 5.00 eq.) were combined in a 2-dram vial followed by addition of a solution of *tert*-butyl((4-(6-methoxynaphthalen-2-yl)but-3-yn-1-yl)oxy)dimethylsilane **4** (68.1 mg, 0.200 mmol, 1.00 eq.), THF (0.100 mL), and methanol-OD (40.7 µL, 1.00 mmol, 5.00 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 20 h at 40 °C. Upon completion and crude ¹H NMR analysis, the crude product was dry loaded onto silica gel and isolated by flash column chromatography (100 mL of 100% hexanes, 200 mL of 2% ethyl acetate in hexanes) to give the pure product as an orange solid (**4a**, **8**, and **5a** isolated as an inseparable mixture, 51.2 mg (**4a**, 10%; **4b**, 53% yield; **4**, 12% yield)).

Entry 8. According to the general procedure B, DTB-DPPBz (4.00 mg, 0.00440 mmol, 0.0220 eq), Cu(OAc)₂ (20.0 µL of a 0.200 M solution in THF, 0.00400 mmol, 0.0200 eq), THF (0.0800 mL), and dimethoxy(methyl)silane (123 µL, 1.00 mmol, 5.00 eq.) were combined in a 2-dram vial followed by addition of a solution of *tert*-butyl((4-(6-methoxynaphthalen-2-yl)but-3-yn-1-yl)oxy)dimethylsilane **4a** (68.1 mg, 0.200 mmol, 1.00 eq.), THF (0.100 mL), and *tert*-butanol-OD (95.6 µL, 1.00 mmol, 5.00 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 20 h at 40 °C. Upon completion and crude ¹H NMR analysis, the crude product was dry loaded onto silica gel and isolated by flash column chromatography (100 mL of 100% hexanes, 200 mL of 2% ethyl acetate in hexanes) to give the pure product as an orange solid (**4a**, **4b**, and **4** isolated as an inseparable mixture, 55.5 mg (**4a**, 20%; **4b**, 47% yield; **4**, 14% yield)).

Entry 9. According to the general procedure B, DTB-DPPBz (4.00 mg, 0.00440 mmol, 0.0220 eq), Cu(OAc)₂ (20.0 µL of a 0.200 M solution in THF, 0.00400 mmol, 0.0200 eq), THF (0.0800 mL), and dimethoxy(methyl)silane (123 µL, 1.00 mmol, 5.00 eq.) were combined in a 2-dram vial followed by addition of a solution of *tert*-butyl((4-(6-methoxynaphthalen-2-yl)but-3-yn-1-yl)oxy)dimethylsilane **4a** (68.1 mg,

0.200 mmol, 1.00 eq.), THF (0.100 mL), and D₂O (18.0 μ L, 1.00 mmol, 5.00 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 20 h at 40 °C. Upon completion, the crude ¹H NMR was analyzed using 1,3,5-trimethylbenzene as an internal standard. (**4a**, 75% yield by ¹H NMR; **4b**, 15% yield by ¹H NMR).

Entry 10. According to the general procedure B, (triphenylphosphine)copper hydride hexamer (Stryker's reagent) (1.31 mg, 0.00066 mmol, 0.00330 eq), THF (0.100 mL), and dimethoxy(methyl)silane (123 μ L, 1.00 mmol, 5.00 eq.) were combined in a 2-dram vial followed by addition of a solution of *tert*-butyl((4-(6-methoxynaphthalen-2-yl)but-3-yn-1-yl)oxy)dimethylsilane **4a** (68.1 mg, 0.200 mmol, 1.00 eq.), THF (0.100 mL), and 2-propanol-*d*₈ (76.6 μ L, 1.00 mmol, 5.00 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 20 h at 40 °C. Upon completion, the crude ¹H NMR was analyzed using 1,3,5-trimethylbenzene as an internal standard. (**4a**, 99% yield by ¹H NMR).

Entry 11. According to the general procedure B, Cu(OAc)₂ (20.0 μ L of a 0.200 M solution in THF, 0.00400 mmol, 0.0200 eq), THF (0.0800 mL), and dimethoxy(methyl)silane (123 μ L, 1.00 mmol, 5.00 eq.) were combined in a 2-dram vial followed by addition of a solution of *tert*-butyl((4-(6-methoxynaphthalen-2-yl)but-3-yn-1-yl)oxy)dimethylsilane **4a** (68.1 mg, 0.200 mmol, 1.00 eq.), THF (0.100 mL), and 2-propanol-*d*₈ (76.6 μ L, 1.00 mmol, 5.00 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 20 h at 40 °C. Upon completion, the crude ¹H NMR was analyzed using 1,3,5-trimethylbenzene as an internal standard. (**4a**, 84% yield by ¹H NMR).

Transfer Hydrodeuteration Reaction Substrate Scope

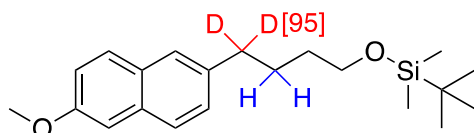
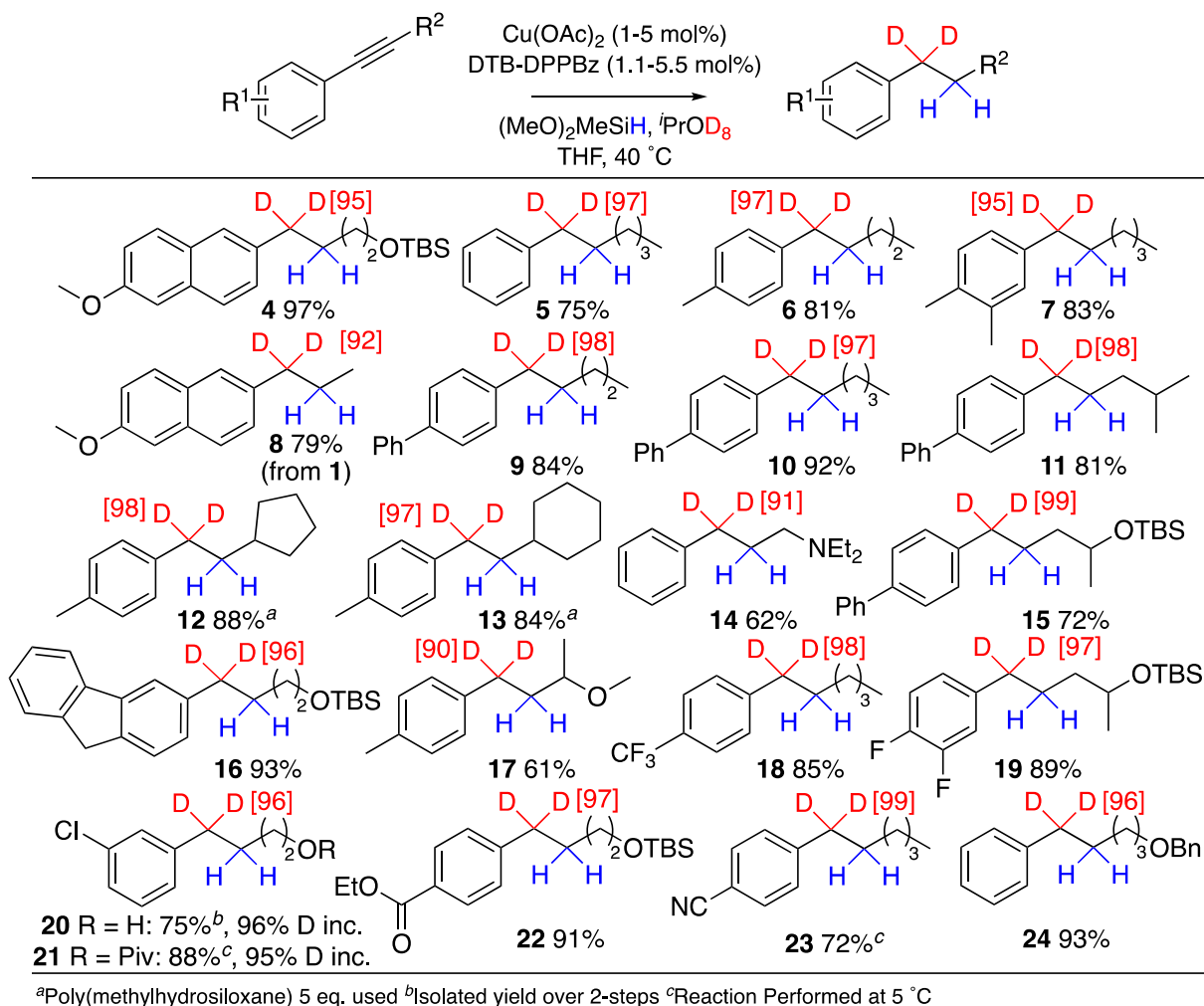
General Procedure C for Transfer Hydrodeuteration Reactions in Scheme S3 and Scheme S4:

In a N₂ filled glovebox, DTB-DPPBz (0.0110 eq.), Cu(OAc)₂ (0.200 M solution in THF, 0.0100 eq.), and THF were added to an oven-dried 2-dram vial followed by dropwise addition of dimethoxy(methyl)silane (185 μ L, 1.50 mmol, 5.00 eq.) or poly(methylhydrosiloxane) (100 μ L, 1.50 mmol, 5.00 eq based on Si-H). A color change from green/blue to yellow was observed while stirring for 15 minutes. In a separate oven-dried 1-dram vial was added the alkyne substrate (0.300 mmol, 1.00 eq.), THF (0.150 mL), and 2-propanol-*d*₈ (115 μ L, 1.50 mmol, 5.00 eq.). The solution in the 1-dram vial was added dropwise over 20 seconds to the 2-dram vial. The total volume of THF was calculated based on having a final reaction concentration of 1M based on the alkyne substrate. The 2-dram vial was capped with a red pressure relief cap, taken out of the glovebox, and stirred for the respective time at the appropriate temperature, at which point the reaction was filtered through a 1" silica plug with 50 mL of Et₂O or CH₂Cl₂ followed by 50 mL of Et₂O or CH₂Cl₂ to elute the remaining product into a 200 mL round bottom flask. After removing the solvent by rotary evaporation, the crude product was isolated by flash column chromatography.

Method for calculating deuterium incorporation at each labeled carbon of each substrate:

The ratio of the two peaks that appear in the ²H NMR spectra was correlated to the calculated deuterium incorporation at the benzylic peak in the ¹H NMR spectra.

Scheme S3. Aryl Alkyne transfer hydrodeuteration substrate scope



D₂-Tert-butyl-(4-(6-methoxy-2-naphthalene)-3-butan-1-oxy)-dimethylsilane [4, Entry 1 in Table S1].

According to the general procedure C, DTB-DPPBz (2.00 mg, 0.00220 mmol, 0.0110 eq.), Cu(OAc)₂ (10.0 μL of a 0.200 M solution in THF, 0.00200 mmol, 0.0100 eq.), THF (0.0900 mL) and dimethoxy(methyl)silane (123 μL, 1.00 mmol, 5.00 eq.) were combined in a 2-dram vial followed by addition of a solution of *tert*-butyl-(4-(6-methoxy-2-naphthalenyl)-3-butyne-1-oxy)-dimethylsilane (68.1 mg, 0.200 mmol, 1.00 eq.), THF (0.100 mL), and 2-propanol-d₈ (76.6 μL, 1.00 mmol, 5.00 eq). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 20 h at 40 °C. Upon completion and crude ¹H NMR analysis, the crude product mixture was dry loaded onto a silica gel column. Purification using silica gel flash column chromatography (100 mL of 100% hexanes, 200 mL of 2% ethyl acetate in hexanes) gives the pure product as a colorless oil (67.4 mg, 0.194 mmol, 97% yield).

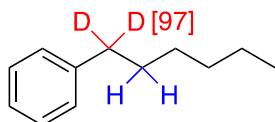
¹H NMR (400 MHz, CDCl₃): δ 7.70-7.65 (m, 2H), 7.55 (s, 1H), 7.31 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.16 – 7.09 (m, 2H), 3.92 (s, 3H), 3.66 (t, *J* = 6.4 Hz, 2H), 2.80 – 2.71 (m, 0.10H), 1.79 – 1.70 (m, 1.90H), 1.60 (p, *J* = 6.7 Hz, 2H), 0.92 (s, 9H), 0.07 (s, 6H).

²H NMR (61 MHz, CDCl₃): δ 2.75 (s, 1.90D), 1.74 (s, 0.02D).

¹³C NMR (75 MHz, CDCl₃): δ 157.20, 137.87, 133.05, 129.23, 129.02, 127.99, 126.78, 126.34, 118.71, 105.75, 63.20, 55.39, 35.02 (p, *J* = 19.5 Hz), 32.53, 27.61, 26.15, 18.51, -5.12.

IR: 3007, 2926, 2852, 2179, 1603, 1502, 1183.

HRMS: (ESI⁺) *m/z*: [M+Na]⁺ Calcd for C₂₁H₃₀D₂NaO₂Si 369.2197; Found 369.2189.



D₂-Hexyl-benzene [5]. According to the general procedure C, DTB-DPPBz (3.00 mg, 0.00330 mmol, 0.0110 eq.), Cu(OAc)₂ (15.0 μL of a 0.200 M solution in THF, 0.00300 mmol, 0.0100 eq.), THF (0.135 mL) and dimethoxy(methyl)silane (185 μL, 1.50 mmol, 5.00 eq.) were combined in a 2-dram vial followed by addition of a solution of 1-hexyn-1-yl-benzene (47.5 mg, 0.300 mmol, 1.00 eq.), THF (0.150 mL), and 2-propanol-d₈ (115 μL, 1.50 mmol, 5.00 eq). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 23 h at 40 °C. Upon completion, the crude product mixture was dry loaded onto a silica gel column. Purification using silica gel flash column chromatography (250 mL of 100% hexanes) gives the pure product as a clear colorless oil (37.0 mg, 0.225 mmol, 75% yield).

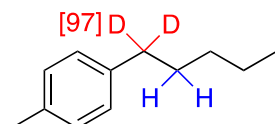
¹H NMR (400 MHz, CDCl₃): δ 7.33 – 7.24 (m, 2H), 7.23 – 7.14 (m, 3H), 2.64 – 2.56 (m, 0.07H), 1.67 – 1.57 (m, 1.95H), 1.42 – 1.29 (m, 6H), 0.95 – 0.86 (m, 3H).

²H NMR (61 MHz, CDCl₃): δ 2.61 (s, 1.93D), 1.63 (s, 0.02D).

¹³C NMR (75 MHz, CDCl₃): δ 143.05, 128.54, 128.36, 125.69, 35.40 (p, *J* = 19.2 Hz), 31.90, 31.49, 29.12, 22.77, 14.25.

IR: 3025, 2956, 2923, 2855, 2199, 1606, 1510, 696.

HRMS: (EI⁺) *m/z*: [M]⁺ Calcd for C₁₂H₁₆D₂ 164.1534; Found 164.1527.



1-Methyl-4-(pentyl-1,1-d₂)benzene [6]. According to the general procedure C, DTB-DPPBz (3.00 mg, 0.00330 mmol, 0.0110 eq.), Cu(OAc)₂ (15.0 μL of a 0.200 M solution in THF, 0.00300 mmol, 0.0100 eq.), THF (0.135 mL) and dimethoxy(methyl)silane (185 μL, 1.50 mmol, 5 eq.) were combined in a 2-dram vial followed by addition of a solution of 1-methyl-4-(pent-1-yn-yl)benzene (47.5 mg, 0.300 mmol, 1.00 eq.), THF (0.150 mL), and 2-propanol-d₈ (115 μL, 1.50 mmol, 5.00 eq). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 22 h at 40 °C. Upon completion, the crude product mixture was dry loaded onto a silica gel column. Purification using silica gel flash column chromatography (100 mL of 100% hexanes) gives the pure product as a clear colorless oil (39.7 mg, 0.242 mmol, 81% yield).

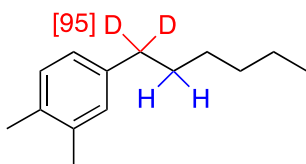
¹H NMR (400 MHz, CDCl₃): δ 7.13 - 7.06 (m, 4H), 2.58 – 2.52 (m, 0.07H), 2.33 (s, 3H), 1.65 – 1.56 (m, 1.92H), 1.42 – 1.25 (m, 4H), 0.90 (t, *J* = 7.1 Hz, 3H).

²H NMR (61 MHz, CDCl₃): δ 2.56 (s, 1.93D), 1.61 (s, 0.04D).

¹³C NMR (75 MHz, CDCl₃): δ 139.95, 135.07, 129.05, 128.41, 34.90 (p, *J* = 19.3 Hz), 31.63, 31.34, 22.73, 21.14, 14.19.

IR: 3019, 2956, 2922, 2858, 2190, 1515, 1466, 1116.

HRMS: (EI^+) m/z : $[\text{M}]^+$ Calcd for $\text{C}_{12}\text{H}_{16}\text{D}_2$ 164.1534; Found 164.1527.



D₂-4-hexyl-1,2-dimethyl-benzene [7]. According to the general procedure C, DTB-DPPBz (15.0 mg, 0.0165 mmol, 0.0550 eq.), $\text{Cu}(\text{OAc})_2$ (75.0 μL of a 0.200 M solution in THF, 0.0150 mmol, 0.0500 eq.), THF (0.0750 mL) and dimethoxy(methyl)silane (185 μL , 1.50 mmol, 5.00 eq.) were combined in a 2-dram vial followed by addition of a solution of 4-(1-hexyn-1-yl)-1,2-dimethyl-benzene (55.9 mg, 0.300 mmol, 1.00 eq.), THF (0.150 mL), and 2-propanol- d_8 (115 μL , 1.50 mmol, 5.00 eq). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 23 h at 40 °C. Upon completion, the crude product mixture was dry loaded onto a silica gel column. Purification using silica gel flash column chromatography (300 mL of 100% hexanes) gives the pure product as a colorless oil (48.0 mg, 0.250 mmol, 83% yield).

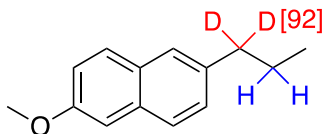
¹H NMR (400 MHz, CDCl_3): δ 7.07 (d, J = 7.6 Hz, 1H), 6.98 (s, 1H), 6.94 (dd, J = 7.6, 1.9 Hz, 1H), 2.57 – 2.51 (m, 0.10H), 2.27 (s, 3H), 2.25 (s, 3H), 1.65 – 1.55 (m, 1.96H), 1.41 – 1.29 (m, 6H), 0.96 – 0.86 (t, J = 6.6 Hz, 3H).

²H NMR (61 MHz, CDCl_3): δ 2.47 (s, 1.90D), 1.53 (s, 0.06D).

¹³C NMR (75 MHz, CDCl_3): δ 140.51, 136.40, 133.72, 129.92, 129.62, 125.85, 35.32 - 34.47 (m), 31.93, 31.70, 29.21, 22.78, 19.91, 19.45, 14.27.

IR: 3030, 2956, 2922, 2856, 2198, 1620, 1504, 1453, 806.

HRMS: (EI^+) m/z : $[\text{M}]^+$ Calcd for $\text{C}_{14}\text{H}_{20}\text{D}_2$ 192.1847; Found 192.1842.



D₂-2-methoxy-6-propyl-naphthalene [8]. According to the general procedure C, DTB-DPPBz (4.00 mg, 0.00440 mmol, 0.0220 eq.), $\text{Cu}(\text{OAc})_2$ (20.0 μL of a 0.200 M solution in THF, 0.00400 mmol, 0.0200 eq.), THF (0.0800 mL) and dimethoxy(methyl)silane (123 μL , 1.00 mmol, 5.00 eq.) were combined in a 2-dram vial followed by addition of a solution of 2-methoxy-6-(1-propyn-1-yl)-naphthalene **1** (39.3 mg, 0.200 mmol, 1.00 eq.), THF (0.100 mL), and 2-propanol- d_8 (77.0 μL , 1.00 mmol, 5.00 eq). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 21 h at 40 °C. Upon completion, the crude product mixture was dry loaded onto a silica gel column. Purification using silica gel flash column chromatography (100 mL of 100% hexanes and 200 mL 3% ethyl acetate in hexanes) gives the pure product as a clear orange solid (32.0 mg, 0.158 mmol, 79% yield).

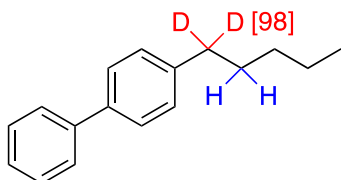
¹H NMR (400 MHz, CDCl_3): δ 7.69 (d, J = 4.2 Hz, 1H), 7.67 (d, J = 3.4 Hz, 1H), 7.55 (s, 1H), 7.31 (d, J = 8.3, 1H), 7.19 – 7.08 (m, 2H), 3.92 (s, 3H), 2.75 – 2.66 (m, 0.16H), 1.72 (q, J = 7.3 Hz, 1.81H), 0.98 (t, J = 7.4 Hz, 3H).

²H NMR (61 MHz, CDCl_3): δ 2.71 (s, 1.84D), 1.72 (s, 0.09D).

¹³C NMR (75 MHz, CDCl_3): δ 157.18, 137.94, 133.03, 129.22, 129.02, 128.08, 126.71, 126.39, 118.70, 105.76, 55.41, 37.36 (p, J = 20.2), 24.53, 13.95.

IR: 2961, 2925, 2874, 2190, 1602, 1462, 1029.

HRMS: (EI^+) m/z : $[\text{M}]^+$ Calcd for $\text{C}_{14}\text{H}_{14}\text{D}_2\text{O}$ 202.1327; Found 202.1320.



D₂-4-pentyl-1,1'-biphenyl [9]. According to the general procedure C, DTB-DPPBz (3.00 mg, 0.00330 mmol, 0.0110 eq.), Cu(OAc)₂ (15.0 μ L of a 0.200 M solution in THF, 0.00300 mmol, 0.0100 eq.), THF (0.135 mL) and dimethoxy(methyl)silane (185 μ L, 1.50 mmol, 5.00 eq.) were combined in a 2-dram vial followed by addition of a solution of 4-(1-pentyn-1-yl)-1,1'-biphenyl (66.1 mg, 0.300 mmol, 1.00 eq.), THF (0.150 mL), and 2-propanol-d₈ (115 μ L, 1.50 mmol, 5.00 eq). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 18 h at 40 °C. Upon completion, the crude product mixture was dry loaded onto a silica gel column. Purification using silica gel flash column chromatography (300 mL of 100% hexanes) gives the pure product as a colorless oil (57.0 mg, 0.252 mmol, 84% yield).

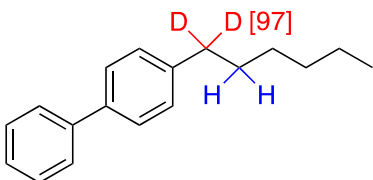
¹H NMR (400 MHz, CDCl₃): δ 7.62 (d, J = 7.2, 2H), 7.55 (d, J = 7.9 Hz, 2H), 7.46 (t, J = 7.6 Hz, 2H), 7.35 (t, J = 7.4 Hz, 1H), 7.29 (d, J = 8.4 Hz, 2H), 2.70 – 2.61 (m, 0.05H), 1.75 – 1.60 (m, 1.95H), 1.46 – 1.34 (m, 4H), 0.95 (t, J = 6.5 Hz, 3H).

²H NMR (61 MHz, CDCl₃): δ 2.66 (s, 1.95H), 1.68 (s, 0.03H).

¹³C NMR (75 MHz, CDCl₃): δ 142.18, 141.34, 138.68, 128.95, 128.83, 127.14, 127.13, 127.09, 34.99 (p, J = 19.6 Hz), 31.66, 31.19, 22.73, 14.20.

IR: 3027, 2955, 2922, 2200, 1601, 1520, 1486, 757.

HRMS: (EI⁺) m/z : [M]⁺ Calcd for C₁₇H₁₈D₂ 226.1691; Found 226.1684.



4-(hexyl-1,1-d₂)-1,1'-biphenyl [10]. According to the general procedure C, DTB-DPPBz (3.00 mg, 0.00330 mmol, 0.0110 eq.), Cu(OAc)₂ (15.0 μ L of a 0.200 M solution in THF, 0.00300 mmol, 0.0100 eq.), THF (0.135 mL) and dimethoxy(methyl)silane (185 μ L, 1.50 mmol, 5.00 eq.) were combined in a 2-dram vial followed by addition of a solution of 4-(1-hexyn-1-yl)-1,1'-biphenyl (70.3 mg, 0.300 mmol, 1.00 eq.), THF (0.150 mL), and 2-propanol-d₈ (115 μ L, 1.50 mmol, 5.00 eq). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 20 h at 40 °C. Upon completion, the crude product mixture was dry loaded onto a silica gel column. Purification using silica gel flash column chromatography (200 mL of 100% hexanes) gives the pure product as a clear crystalline solid (66.4 mg, 0.276 mmol, 92% yield).

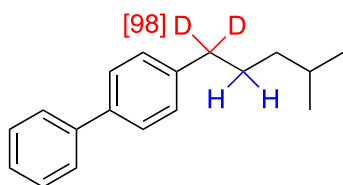
¹H NMR (400 MHz, CDCl₃): δ 7.60 (d, J = 8.0 Hz, 2H), 7.53 (d, J = 7.8 Hz, 2H), 7.44 (t, J = 7.6 Hz, 2H), 7.34 (t, J = 7.2 Hz, 1H), 7.27 (d, J = 7.4 Hz, 2H), 2.68 – 2.61 (m, 0.06H), 1.65 (t, J = 7.1 Hz, 1.93H), 1.44 – 1.29 (m, 6H), 0.91 (t, J = 6.3 Hz, 3H).

²H NMR (61 MHz, CDCl₃): δ 2.63 (s, 1.94D).

¹³C NMR (75 MHz, CDCl₃): δ 142.16, 141.33, 138.67, 128.94, 128.83, 127.12 (2 overlapping carbon signals), 127.07, 35.02 (p, J = 19.1 Hz), 31.92, 31.48, 29.17, 22.79, 14.28.

IR: 2955, 2917, 2855, 2169, 1599, 1521, 1485, 1118.

HRMS: (EI⁺) *m/z*: [M]⁺ Calcd for C₁₈H₂₀D₂ 240.1847; Found 240.1841.



D₂-4-(4-methylpentyl)-1,1'-biphenyl [11]. According to the general procedure C, DTB-DPPBz (13.0 mg, 0.0141 mmol, 0.0550 eq.), Cu(OAc)₂ (64.0 μL of a 0.200 M solution in THF, 0.0128 mmol, 0.0500 eq.), THF (0.0920 mL) and dimethoxy(methyl)silane (158 μL, 1.28 mmol, 5.00 eq.) were combined in a 2-dram vial followed by addition of a solution of 4-(4-methyl-1-pentyn-1-yl)-1,1'-biphenyl (60.0 mg, 0.256 mmol, 1.00 eq.), THF (0.100 mL), and 2-propanol-d₈ (98.0 μL, 1.28 mmol, 5.00 eq). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 22 h at 40 °C. Upon completion, the crude product mixture was dry loaded onto a silica gel column. Purification using silica gel flash column chromatography (300 mL of 100% hexanes) gives the pure product as a clear colorless oil (50.0 mg, 0.208 mmol, 81% yield).

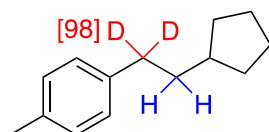
¹H NMR (400 MHz, CDCl₃): δ 7.61 (d, *J* = 8.0 Hz, 2H), 7.54 (d, *J* = 7.9 Hz, 2H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.34 (t, *J* = 7.2 Hz, 1H), 7.28 (d, *J* = 7.8 Hz, 2H), 2.68 – 2.58 (m, 0.05H), 1.71 – 1.55 (m, 2.94H), 1.28 (q, *J* = 7.4 Hz, 2H), 0.91 (d, *J* = 6.7 Hz, 6H).

²H NMR (61 MHz, CDCl₃): δ 2.64 (s, 1.95D), 1.67 (s, 0.03D).

¹³C NMR (75 MHz, CDCl₃): δ 142.19, 141.32, 138.68, 128.94, 128.84, 127.14, 127.13, 127.09, 38.79, 35.27 (p, *J* = 19.2), 29.38, 28.08, 22.76.

IR: 3027, 2953, 2925, 2199, 1601, 1520, 1485, 756.

HRMS: (EI⁺) *m/z*: [M]⁺ Calcd for C₁₈H₂₀D₂ 240.1847; Found 240.1840.



1-(2-cyclopentylethyl)-1,1-d₂-4-methylbenzene [12]. According to the general procedure C, DTB-DPPBz (3.00 mg, 0.00330 mmol, 0.0110 eq.), Cu(OAc)₂ (15.0 μL of a 0.200 M solution in THF, 0.00300 mmol, 0.0100 eq.), THF (0.135 mL) and poly(methylhydrosiloxane) (100 μL, 1.50 mmol, 5.00 eq based on Si-H) were combined in a 2-dram vial followed by addition of a solution of 1-(cyclopentylethynyl)-4-methylbenzene (55.3 mg, 0.300 mmol, 1.00 eq.), THF (0.150 mL), and 2-propanol-d₈ (115 μL, 1.50 mmol, 5.00 eq). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 20 h at 40 °C. Upon completion, the crude product mixture was dry loaded onto a silica gel column. Purification using silica gel flash column chromatography (200 mL of 100% hexanes) gives the pure product as a clear colorless oil (50.4 mg, 0.265 mmol, 88% yield).

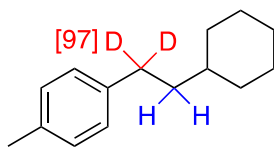
¹H NMR (400 MHz, CDCl₃): δ 7.09 (s, 4H), 2.60 – 2.53 (m, 0.04H), 2.33 (s, 3H), 1.84 – 1.73 (m, 3H), 1.66 – 1.43 (m, 6H), 1.20 – 1.07 (m, 2H).

²H NMR (61 MHz, CDCl₃): δ 2.57 (s, 1.96D), 1.62 (s, 0.03D)

¹³C NMR (75 MHz, CDCl₃): δ 140.05, 135.02, 129.06, 128.36, 39.74, 38.28, 34.08 (p, *J* = 19.2 Hz), 32.81, 25.39, 21.13.

IR: 3010, 2958, 2921, 2225, 1510, 1066, 814.

HRMS: (EI⁺) *m/z*: [M]⁺ Calcd for C₁₄H₁₈D₂ 190.1691; Found 190.1684.



1-(2-cyclohexylethyl-1,1- d_2)-4-methylbenzene [13]. According to the general procedure C, DTB-DPPBz (3.00 mg, 0.00330 mmol, 0.0110 eq.), $\text{Cu}(\text{OAc})_2$ (15.0 μL of a 0.200 M solution in THF, 0.00300 mmol, 0.0100 eq.), THF (0.135 mL) and poly(methylhydrosiloxane) (100 μL , 1.50 mmol, 5.00 eq based on Si-H) were combined in a 2-dram vial followed by addition of a solution of 1-(2-cyclohexylethynyl)-4-methylbenzene (59.5 mg, 0.300 mmol, 1.00 eq.), THF (0.150 mL), and 2-propanol- d_8 (115 μL , 1.50 mmol, 5.00 eq). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 20 h at 40 $^\circ\text{C}$. Upon completion, the crude product mixture was dry loaded onto a silica gel column. Purification using silica gel flash column chromatography (150 mL of 100% hexanes) gives the pure product as a clear colorless oil (51.6 mg, 0.253 mmol, 84% yield).

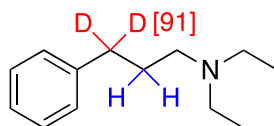
^1H NMR (400 MHz, CDCl_3): δ 7.09 (s, 4H), 2.61 – 2.53 (m, 0.06H), 2.33 (s, 3H), 1.83 – 1.61 (m, 5H), 1.48 (d, J = 6.7 Hz, 1.98H), 1.31 – 1.16 (m, 4H), 0.94 (q, J = 11.8 Hz, 2H).

^2H NMR (61 MHz, CDCl_3): δ 2.56 (s, 1.94D).

^{13}C NMR (75 MHz, CDCl_3): δ 140.23, 135.00, 129.07, 128.35, 39.57, 37.40, 33.48, 32.19 (p, J = 19.6 Hz), 26.87, 26.50, 21.13.

IR: 3018, 2919, 2849, 2196, 1515, 1447, 1116, 787.

HRMS: (EI^+) m/z : $[\text{M}]^+$ Calcd for $\text{C}_{15}\text{H}_{20}\text{D}_2$ 204.1847; Found 204.1841.



D_2 - N,N -diethyl-benzenepropanamine [14]. According to the general procedure C, DTB-DPPBz (6.00 mg, 0.00660 mmol, 0.0220 eq.), $\text{Cu}(\text{OAc})_2$ (30.0 μL of a 0.200 M solution in THF, 0.00600 mmol, 0.0200 eq.), THF (0.120 mL) and dimethoxy(methyl)silane (185 μL , 1.50 mmol, 5.00 eq.) were combined in a 2-dram vial followed by addition of a solution of N,N -diethyl-3-phenyl-2-propyn-1-amine (56.2 mg, 0.300 mmol, 1.00 eq.), THF (0.150 mL), and 2-propanol- d_8 (115 μL , 1.50 mmol, 5.00 eq). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 20 h at 40 $^\circ\text{C}$. Upon completion, the crude product mixture was dry loaded onto a neutral Brockmann Grade II alumina column. Purification using neutral Brockmann Grade II alumina flash column chromatography (100 mL of 100% hexanes, 100 mL of 2% ethyl acetate in hexanes, and 200 mL 3% ethyl acetate in hexanes) gives the pure product as a clear colorless oil (36.0 mg, 0.186 mmol, 62% yield).

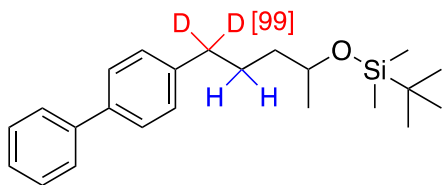
^1H NMR (400 MHz, CDCl_3): δ 7.32 – 7.23 (m, 2H), 7.23 – 7.13 (m, 3H), 2.64-2.57 (m, 0.18H), 2.57 – 2.42 (m, 6H), 1.77 (t, J = 7.7 Hz, 1.89H), 1.01 (t, J = 7.2 Hz, 6H).

^2H NMR (61 MHz, CDCl_3): δ 2.59 (s, 1.82D), 1.77 (s, 0.11D).

^{13}C NMR (101 MHz, CDCl_3): δ 142.51, 128.48, 128.40, 125.80, 52.55, 46.99, 34.28 – 32.54 (m), 28.72, 11.84.

IR: 3025, 2967, 2931, 2797, 2204, 1605, 1496, 1201, 697.

HRMS: (EI^+) m/z : $[\text{M}]^+$ Calcd for $\text{C}_{13}\text{H}_{19}\text{D}_2\text{N}$ 193.1800; Found 193.1793.



((5-([1,1'-biphenyl]-4-yl)(5,5-²H₂)pentan-2-yl)oxy)(*tert*-butyl)dimethylsilane [15]. According to the general procedure C, DTB-DPPBz (6.00 mg, 0.00660 mmol, 0.0220 eq.), Cu(OAc)₂ (30.0 μ L of a 0.200 M solution in THF, 0.00600 mmol, 0.0200 eq.), THF (0.120 mL) and dimethoxy(methyl)silane (185 μ L, 1.50 mmol, 5.00 eq.) were combined in a 2-dram vial followed by addition of a solution of ((5-([1,1'-biphenyl]-4-yl)pent-4-yn-2-yl)oxy)(*tert*-butyl)dimethylsilane (105 mg, 0.300 mmol, 1.00 eq.), THF (0.150 mL), and 2-propanol-d₈ (115 μ L, 1.50 mmol, 5.00 eq). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 21 h at 40 °C. Upon completion, the crude product mixture was dry loaded onto a silica gel column. Purification using silica gel flash column chromatography (100 mL of 100% hexanes and 150 mL of 1% ethyl acetate in hexanes) gives the pure product as a colorless oil (76.5 mg, 0.215 mmol, 72% yield).

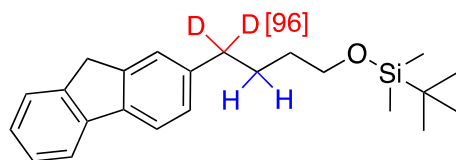
¹H NMR (400 MHz, CDCl₃): δ 7.68 – 7.61 (m, 2H), 7.57 (d, J = 8.4 Hz, 2H), 7.48 (t, J = 7.6 Hz, 2H), 7.37 (t, J = 7.3 Hz, 1H), 7.31 (d, J = 8.4 Hz, 2H), 3.89 (sext, J = 6.1 Hz, 1H), 2.72 – 2.64 (m, 0.03H), 1.86 – 1.64 (m, 2H), 1.63 – 1.45 (m, 2H) 1.20 (d, J = 6.1 Hz, 3H), 0.96 (s, 9H), 0.12 (s, 6H).

²H NMR (61 MHz, CDCl₃): δ 2.69 (s, 1.97D).

¹³C NMR (75 MHz, CDCl₃): δ 141.83, 141.29, 138.71, 128.91, 128.81, 127.12, 127.10, 127.06, 68.58, 39.35, 34.95 (p, J = 19.0 Hz), 27.37, 26.06, 23.97, 18.28, -4.23, -4.54.

IR: 3027, 2955, 2856, 2192, 1487, 1253, 1142, 1036, 1003, 831, 756.

HRMS: (ESI⁺) m/z : [M+Na]⁺ Calcd for C₂₃H₃₂D₂NaOSi 379.2404; Found 379.2397.



(4-(9H-fluoren-3-yl)butoxy-4,4-d₂)(*tert*-butyl)dimethylsilane [16]. According to the general procedure C, DTB-DPPBz (6.00 mg, 0.00660 mmol, 0.0220 eq.), Cu(OAc)₂ (30.0 μ L of a 0.200 M solution in THF, 0.00600 mmol, 0.0200 eq.), THF (0.120 mL), and dimethoxy(methyl)silane (185 μ L, 1.50 mmol, 5.00 eq.) were combined in a 2-dram vial followed by addition of a solution of ((4-(9H-fluoren-3-yl)but-3-yn-1-yl)oxy)(*tert*-butyl)dimethylsilane (105 mg, 0.300 mmol, 1.00 eq.), THF (0.150 mL), and 2-propanol-d₈ (115 μ L, 1.50 mmol, 5.00 eq). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 24 h at 40 °C. Upon completion, the crude product mixture was dry loaded onto a silica gel column. Purification using silica gel flash column chromatography (100 mL of 100% hexanes, and 100 mL of 2.5% ethyl acetate in hexanes) gives the pure product as a yellow solid (99.0 mg, 0.279 mmol, 93% yield).

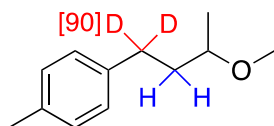
¹H NMR (400 MHz, CDCl₃): δ 7.78 (d, J = 7.7 Hz, 1H), 7.72 (d, J = 7.7 Hz, 1H), 7.55 (d, J = 7.3 Hz, 1H), 7.45 – 7.35 (m, 2H), 7.34 – 7.26 (m, 1H), 7.22 (d, J = 7.6 Hz, 1H), 3.89 (s, 2H), 3.69 (t, J = 6.1, 5.4 Hz, 2H), 2.75 – 2.68 (m, 0.09H), 1.78 – 1.70 (m, 2H), 1.68 – 1.58 (m, 2H), 0.95 (s, 9H), 0.15 – 0.05 (m, 6H).

²H NMR (61 MHz, CDCl₃): 2.86 (s, 1.91D), 1.35 (s, 0.05D).

¹³C NMR (75 MHz, CDCl₃): δ 143.56, 143.24, 141.91, 141.50, 139.52, 127.14, 126.76, 126.33, 125.19, 125.07, 119.73, 119.68, 63.20, 36.92, 35.24 (p, J = 19.2 Hz), 32.54, 27.92, 26.13, 18.51, -5.11.

IR: 3025, 2926, 2855, 2197, 1640, 1464, 1087, 832.

HRMS: (EI⁺) m/z: [M]⁺ Calcd for C₂₃H₃₀D₂Osi 354.2348; Found 354.2340.



D₂- 1-(3-methoxybutyl)-4-methylbenzene [17]. According to the general procedure C, DTB-DPPBz (9.00 mg, 0.00990 mmol, 0.0330 eq.), Cu(OAc)₂ (45.0 μL of a 0.200 M solution in THF, 0.00300 mmol, 0.0300 eq.), THF (0.105 mL) and dimethoxy(methyl)silane (222 μL, 1.80 mmol, 6.00 eq.) were combined in a 2-dram vial followed by addition of a solution of 1-(3-methoxybut-1-yn-1-yl)-4-methylbenzene (52.3 mg, 0.300 mmol, 1 eq.), THF (0.150 mL), and 2-propanol-d₈ (115 μL, 1.50 mmol, 5.00 eq). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 23 h at 40 °C. Upon completion, the crude product mixture was dry loaded onto a silica gel column. Purification using silica gel flash column chromatography (150 mL of 0.5% ethyl acetate in hexanes and 100 mL of 1% ethyl acetate in hexanes) gives the pure product as a colorless oil (33.0 mg, 0.183 mmol, 61% yield).

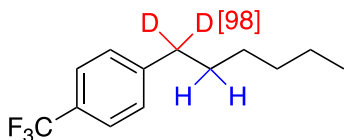
¹H NMR (400 MHz, CDCl₃): δ 7.14 – 7.09 (m, 4H), 3.38 – 3.28 (m, 4H), 2.70 – 2.59 (m, 0.20H), 2.34 (s, 3H), 1.84 (dd, *J* = 13.6, 7.1 Hz, 1H), 1.69 (dd, *J* = 13.3, 4.2 Hz, 1H), 1.19 (d, *J* = 6.1 Hz, 3H).

²H NMR (61 MHz, CDCl₃): δ 2.78 – 2.41 (m, 1.80D), 1.81 (s, 0.06D), 1.65 (s, 0.08D).

¹³C NMR (101 MHz, CDCl₃): δ 139.31, 135.21, 129.13, 128.41, 76.04, 56.05, 38.27, 30.65 (p, *J*=19.2 Hz), 21.11, 19.10.

IR: 3018, 2970, 2926, 2818, 2117, 1515, 1148, 1089

HRMS: (ESI⁺) m/z: [M+Na]⁺ Calcd for C₁₂H₁₆D₂NaO 203.1383; Found 203.1375.



1-(hexyl-1,1-d₂)-4-(trifluoromethyl)benzene [18]. According to the general procedure C, DTB-DPPBz (3.00 mg, 0.00330 mmol, 0.0110 eq.), Cu(OAc)₂ (15.0 μL of a 0.200 M solution in THF, 0.00300 mmol, 0.0100 eq.), THF (0.135 mL) and dimethoxy(methyl)silane (185 μL, 1.50 mmol, 5.00 eq.) were combined in a 2-dram vial followed by addition of a solution of 1-(1-hexyn-1-yl)-4-(trifluoromethyl)benzene (68.0 mg, 0.300 mmol, 1.00 eq.), THF (0.150 mL), and 2-propanol-d₈ (115 μL, 1.50 mmol, 5.00 eq). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 23 h at 40 °C. Upon completion, the crude product mixture was dry loaded onto a silica gel column. Purification using silica gel flash column chromatography (150 mL of 100% hexanes) gives the pure product as a clear colorless oil (59.4 mg, 0.256 mmol, 85% yield).

¹H NMR (400 MHz, CDCl₃): δ 7.53 (d, *J* = 7.8 Hz, 2H), 7.28 (d, *J* = 8.1 Hz, 2H), 2.68 – 2.60 (m, 0.04H), 1.67 – 1.57 (m, 2H), 1.41 – 1.24 (m, 6H), 0.90 (t, *J* = 6.6 Hz, 3H).

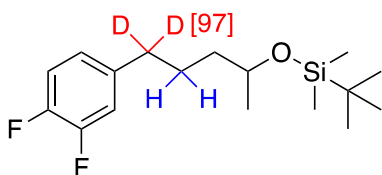
²H NMR (61 MHz, CDCl₃): δ 2.65 (s, 1.96D).

¹³C NMR (101 MHz, CDCl₃): δ 147.14, 128.82, 128.13 (q, *J* = 32.2 Hz), 125.29 (q, *J* = 3.8 Hz), 124.42 (q, *J* = 272.2 Hz), 35.23 (p, *J* = 19.2 Hz), 31.84, 31.20, 29.01, 22.75, 14.21.

¹⁹F NMR (376 MHz, Chloroform-*d*) δ -62.28 (s, 3F).

IR: 3020, 2958, 2927, 2859, 2197, 1621, 1581, 1467, 1323, 1066.

HRMS: (EI⁺) *m/z*: [M]⁺ Calcd for C₁₃H₁₅D₂F₃ 232.1408; Found 232.1403.



tert-butyl((5-(3,4-difluorophenyl)pentan-2-yl-5,5-d₂)oxy)dimethylsilane [19]. According to the general procedure C, DTB-DPPBz (3.00 mg, 0.00330 mmol, 0.0110 eq.), Cu(OAc)₂ (15.0 μL of a 0.200 M solution in THF, 0.00300 mmol, 0.0100 eq.), THF (0.135 mL) and dimethoxy(methyl)silane (185 μL, 1.50 mmol, 5.00 eq.) were combined in a 2-dram vial followed by addition of a solution of *tert*-butyl((5-(3,4-difluorophenyl)pent-4-yn-2-yl)oxy)dimethylsilane (93.1 mg, 0.300 mmol, 1.00 eq.), THF (0.150 mL), and 2-propanol-d₈ (115 μL, 1.50 mmol, 5.00 eq). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 20 h at 40 °C. Upon completion, the crude product mixture was dry loaded onto a silica gel column. Purification using silica gel flash column chromatography (100 mL of 100% hexanes, 100 mL of 3% ethyl acetate in hexanes) gives the pure product as a yellow oil (84.7 mg, 0.268 mmol, 89% yield).

¹H NMR (400 MHz, CDCl₃): δ 7.04 (q, *J* = 8.4 Hz, 1H), 6.99 – 6.91 (m, 1H), 6.89 – 6.82 (m, 1H), 3.79 (sxt, *J* = 5.6 Hz, 1H), 2.58 – 2.50 (m, 0.06H), 1.73 – 1.62 (m, 1H), 1.61 – 1.49 (m, 1H), 1.50 – 1.31 (m, 2H), 1.11 (d, *J* = 6.1 Hz, 3H), 0.88 (s, 9H), 0.03 (s, 6H).

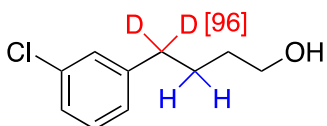
²H NMR (61 MHz, CDCl₃): δ 2.54 (s, 1.94D).

¹³C NMR (75 MHz, CDCl₃): δ 151.27 (dd, *J* = 247.3, 12.6 Hz), 148.77 (dd, *J* = 245.5, 12.7 Hz), 139.79 – 139.52 (m), 124.20 (dd, *J* = 6.0, 3.4 Hz), 117.03 (dd, *J* = 16.7, 11.2 Hz) (over-lap of two carbon signals), 68.45, 39.07, 35.33 – 33.67 (m), 27.19, 26.02, 23.94, 18.26, -4.24, -4.59.

¹⁹F NMR (376 MHz, Chloroform-*d*) δ -138.71 – -138.91 (m, 1F), -142.67 – -142.84 (m, 1F).

IR: 2955, 2929, 2857, 2237, 1604, 1516, 1255, 1099.

HRMS: (EI⁺) *m/z*: [M-H] Calcd for C₁₇H₂₅D₂F₂OSi 315.1940 Found 315.1920.



4-(3-chlorophenyl)butan-4,4-d₂-1-ol [20]. According to the general procedure C, DTB-DPPBz (3.00 mg, 0.00330 mmol, 0.011eq.), Cu(OAc)₂ (15.0 μL of a 0.200 M solution in THF, 0.00300 mmol, 0.0100 eq.), THF (0.135 mL) and dimethoxy(methyl)silane (185 μL, 1.50 mmol, 5.00 eq.) were combined in a 2-dram vial followed by addition of a solution of *tert*-butyl((4-(3-chlorophenyl)but-3-yn-1-yl)oxy)dimethylsilane (88.5 mg, 0.300 mmol, 1 eq.), THF (0.150 mL), and 2-propanol-d₈ (115 μL, 1.50 mmol, 5.00 eq). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 19 h at 40 °C. Upon completion, the crude product mixture was dry loaded onto a silica gel column. Purification using silica gel flash column chromatography (50 mL of 100% hexanes, 100 mL of 3% ethyl acetate in hexanes) gives *tert*-butyl(4-(3-chlorophenyl)butoxy-4,4-d₂)dimethylsilane as a clear colorless oil (86.3 mg, 0.287 mmol, 96% yield). The product was dissolved in THF (1.60 mL) and tetrabutylammonium fluoride (0.600 mL of 1.00 M in THF solution, 0.600 mmol, 2.00 eq.) was added. The reaction was stirred at room temperature for 1-2 hours until complete by TLC analysis. Upon completion, reaction mixture was diluted with Et₂O (10 mL) and quenched with saturated aqueous NH₄Cl (5 mL). The aqueous layer was extracted with Et₂O (3 x 10 mL) and the combined organic layers were washed with water (10 mL) and brine (10 mL), then dried over anhydrous Na₂SO₄. The mixture was filtered, and the solvent was removed by rotary evaporation. Purification using silica gel flash chromatography (100 mL of hexanes, 100 mL of 10% ethyl acetate in hexanes, 150 mL of 15% ethyl acetate in hexanes) gives the pure product as a clear oil (42.0 mg, 0.225 mmol, 75% yield).

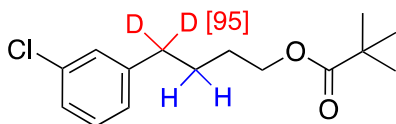
¹H NMR (400 MHz, CDCl₃): δ 7.23 – 7.13 (m, 3H), 7.05 (d, *J* = 7.2 Hz, 1H), 3.65 (t, *J* = 6.4 Hz, 2H), 2.63 – 2.55 (m, 0.08H), 1.73 – 1.63 (m, 2H), 1.63 – 1.54 (m, 3H, hydrogen on alcohol is present under peak).

²H NMR (61 MHz, CDCl₃): δ 2.59 (s, 1.92D), 1.67 (s, 0.03D).

¹³C NMR (75 MHz, CDCl₃): δ 144.41, 134.14, 129.65, 128.62, 126.72, 126.05, 62.73, 34.67 (p, *J* = 19.5 Hz), 32.20, 27.26.

IR: 3333, 3061, 2932, 2862, 2203, 1598, 1569, 1473, 1055.

HRMS: (EI⁺) *m/z*: [M]⁺ Calcd for C₁₀H₁₁D₂ClO 186.0780; Found 186.0773.



4-(3-chlorophenyl)butyl-4,4-d₂ pivalate [21]. According to the general procedure C, DTB-DPPBz (3.00 mg, 0.00330 mmol, 0.0110 eq.), Cu(OAc)₂ (15.0 μL of a 0.200 M solution in THF, 0.00300 mmol, 0.0100 eq.), THF (0.135 mL), and dimethoxy(methyl)silane (185 μL, 1.50 mmol, 5.00 eq.) were combined in a 2-dram vial followed by addition of a solution of 4-(3-chlorophenyl)but-3-yn-1-yl pivalate (79.4 mg, 0.300 mmol, 1.00 eq.), THF (0.150 mL), and 2-propanol-d₈ (115 μL, 1.50 mmol, 5.00 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 21 h at 5 °C. Upon completion, the crude product mixture was dry loaded onto a silica gel column. Purification using silica gel flash column chromatography (100 mL of 100% hexanes, 100 mL of 2.5% ethyl acetate in hexanes, and 100 mL of 5% ethyl acetate in hexanes) gives the pure product as a yellow oil (71.1 mg, 0.263 mmol, 88% yield).

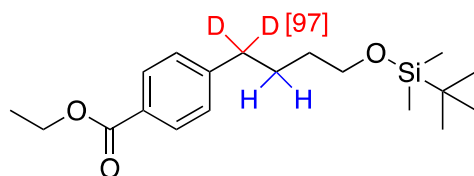
¹H NMR (400 MHz, CDCl₃): δ 7.24 – 7.12 (m, 3H), 7.08 – 7.00 (m, 1H), 4.07 (t, *J* = 6.0 Hz, 2H), 2.62 – 2.56 (m, 0.10H), 1.75 – 1.60 (m, 4H), 1.19 (s, 9H).

²H NMR (61 MHz, CDCl₃): δ 2.60 (s, 1.89D), 1.66 (s, 0.09D).

¹³C NMR (75 MHz, CDCl₃): δ 178.70, 144.18, 134.24, 129.72, 128.61, 126.69, 126.17, 64.11, 38.87, 35.08 – 33.93 (m), 28.22, 27.44, 27.34.

IR: 3050, 2958, 2870, 2201, 1725, 1598, 1570, 1479, 1283, 1151.

HRMS: (EI⁺) *m/z*: [M]⁺ Calcd for C₁₅H₁₉D₂O₂Cl 270.1356; Found 270.1350.



Ethyl 4-(4-((tert-butyldimethylsilyl)oxy)butyl-1,1-d₂)benzoate [22]. According to the general procedure C, DTB-DPPBz (3.00 mg, 0.00330 mmol, 0.0110 eq.), Cu(OAc)₂ (15.0 μL of a 0.200 M solution in THF, 0.00300 mmol, 0.0100 eq.), THF (0.135 mL) and dimethoxy(methyl)silane (185 μL, 1.50 mmol, 5.00 eq.) were combined in a 2-dram vial followed by addition of a solution of ethyl 4-(4-((tert-butyldimethylsilyl)oxy)but-1-yn-1-yl)benzoate (99.8 mg, 0.300 mmol, 1.00 eq.), THF (0.150 mL), and 2-propanol-d₈ (115 μL, 1.50 mmol, 5.00 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 21 h at 40 °C. Upon completion, the crude product mixture was dry loaded onto a silica gel column. Purification using silica gel flash column chromatography (100 mL of 100% hexanes, 100 mL of 3% ethyl acetate in hexanes) gives the pure product as a clear colorless oil (92.2 mg, 0.274 mmol, 91% yield).

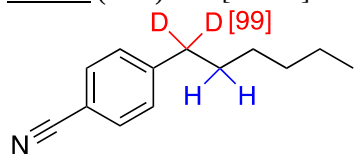
¹H NMR (400 MHz, CDCl₃): δ 7.95 (d, *J* = 8.2 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 4.36 (q, *J* = 7.1 Hz, 2H), 3.62 (t, *J* = 6.3 Hz, 2H), 2.71 – 2.62 (m, 0.07H), 1.73 – 1.63 (m, 2H), 1.59 – 1.50 (m, 2H), 1.38 (t, *J* = 7.1 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H).

²H NMR (61 MHz, CDCl₃): δ 2.66 (s, 1.93D).

¹³C NMR (75 MHz, CDCl₃): δ 166.84, 148.15, 129.74, 128.51, 128.19, 63.00, 60.86, 35.11 (p, *J* = 18.5 Hz), 32.40, 27.37, 26.09, 18.48, 14.49, -5.16.

IR: 3030, 2953, 2929, 2857, 2114, 1717, 1612, 1572, 1272, 1177, 1098.

HRMS: (ESI⁺) *m/z*: [M+Na]⁺ Calcd for C₁₉H₃₀D₂NaO₃Si 361.2146; Found 361.2138.



4-(hexyl-1,1-*d*₂)benzonitrile [23]. According to the general procedure C, DTB-DPPBz (2.00 mg, 0.00220 mmol, 0.0110 eq.), Cu(OAc)₂ (10.0 μL of a 0.200 M solution in THF, 0.00200 mmol, 0.0100 eq.), THF (0.0900 mL) and dimethoxy(methyl)silane (123 μL, 1.00 mmol, 5.00 eq.) were combined in a 2-dram vial followed by addition of a solution of 4-(hex-1-yn-1-yl)benzonitrile (36.7 mg, 0.200 mmol, 1 eq.), THF (0.100 mL), and 2-propanol-*d*₈ (77.0 μL, 1.00 mmol, 5.00 eq). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 24 h at 5 °C. Upon completion, the crude product mixture was dry loaded onto a silica gel column. Purification using silica gel flash column chromatography (100 mL of 100% hexanes, 100 mL of 1% ethyl acetate in hexanes, 100 mL of 2% ethyl acetate in hexanes, 100 mL of 4% ethyl acetate in hexanes) gives the pure product as a yellow oil (27.4 mg, 0.145 mmol, 72% yield).

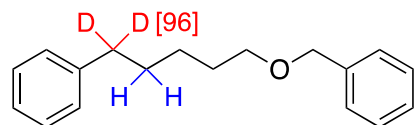
¹H NMR (400 MHz, CDCl₃): δ 7.56 (d, *J* = 7.9 Hz, 2H), 7.26 (d, *J* = 7.4 Hz, 2H), 2.67 – 2.60 (m, 0.03H), 1.59 (t, *J* = 6.9 Hz, 2H), 1.37 – 1.22 (m, 6H), 0.92 – 0.83 (m, 3H).

²H NMR (61 MHz, CDCl₃): δ 2.63 (s, 1.97D).

¹³C NMR (101 MHz, CDCl₃): δ 148.66, 132.19, 129.28, 119.33, 109.54, 36.04 - 34.98 (m), 31.71, 30.91, 28.89, 22.65, 14.16.

IR: 2956, 2925, 2856, 2227, 2080, 1610, 1504, 808.

HRMS: (EI⁺) *m/z*: [M]⁺ Calcd for C₁₃H₁₅D₂N 189.1487; Found 189.1480.



(5-(benzyloxy)pentyl-1,1-*d*₂)benzene [34]. According to the general procedure C, DTB-DPPBz (6.00 mg, 0.00660 mmol, 0.0220 eq.), Cu(OAc)₂ (30.0 μL of a 0.200 M solution in THF, 0.0600 mmol, 0.0200 eq.), THF (0.120 mL) and dimethoxy(methyl)silane (185 μL, 1.50 mmol, 5.00 eq.) were combined in a 2-dram vial followed by addition of a solution of (5-(benzyloxy)pent-1-yn-1-yl)benzene (75.0 mg, 0.300 mmol, 1 eq.), THF (0.150 mL), and 2-propanol-*d*₈ (115 μL, 1.50 mmol, 5.00 eq). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 24 h at 40 °C. Upon completion, the crude product mixture was dry loaded onto a silica gel column. Purification using silica gel flash column chromatography (50 mL of 100% hexanes, 100 mL of 2% ethyl acetate in hexanes, 100 mL of 5% ethyl acetate in hexanes) gives the pure product as a yellow oil (71.4 mg, 0.278 mmol, 93% yield).

¹H NMR (400 MHz, CDCl₃): δ 7.42 – 7.34 (m, 4H), 7.31 (t, *J* = 7.3 Hz, 3H), 7.25 – 7.17 (m, 3H), 4.53 (s, 2H), 3.50 (t, *J* = 6.6 Hz, 2H), 2.68 – 2.58 (m, 0.09H), 1.75 – 1.57 (m, 4H), 1.51 – 1.40 (m, 2H).

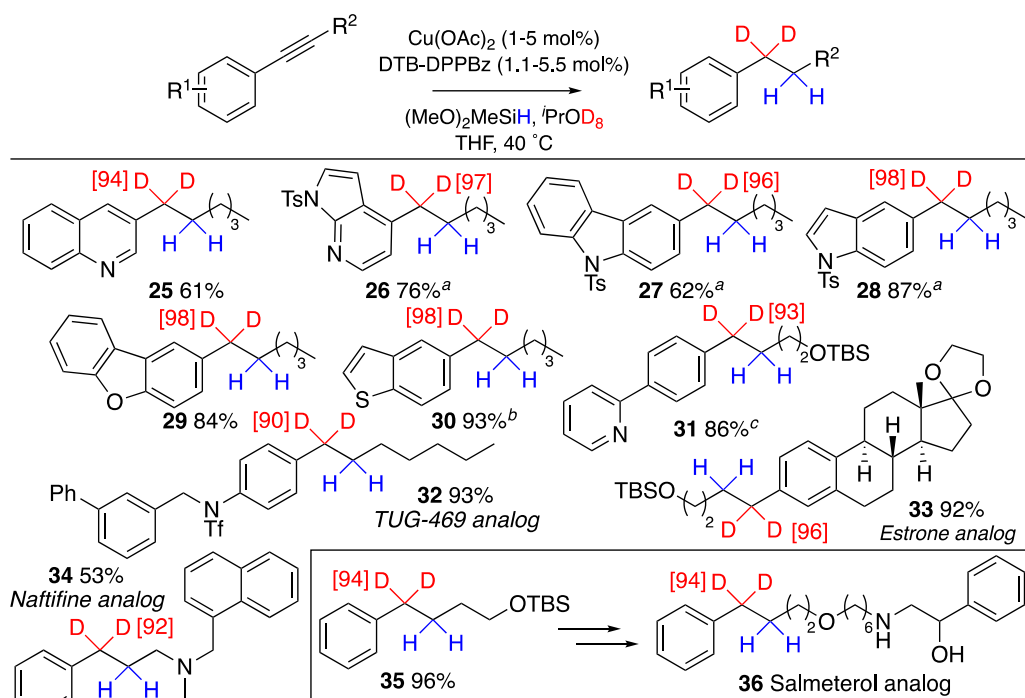
²H NMR (61 MHz, CDCl₃): δ 2.63 (s, 1.91D).

¹³C NMR (75 MHz, CDCl₃): δ 142.72, 138.79, 128.51, 128.46, 128.36, 127.74, 127.60, 125.74, 72.99, 70.45, 35.28 (p, *J* = 19.4 Hz), 31.31, 29.76, 25.95.

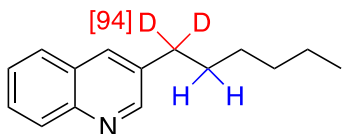
IR: 3025, 2929, 2855, 2188, 1604, 1495, 1098, 731.

HRMS: (ESI⁺) *m/z*: [M+Na]⁺ Calcd for C₁₈H₂₀D₂NaO 279.1696; Found 279.1688.

Scheme S3. Heterocycle and Complex Small Molecule Scope



^aReaction performed at 60 °C ^b6 eq. of (MeO)₂MeSiH was used. ^c6.8 mol% Cu(OAc)₂ and 7.4 mol% DTB-DPPBz used



D₂-3-hexyl-quinoline [25]. According to the general procedure C, DTB-DPPBz (9.80 mg, 0.0110 mmol, 0.0550 eq.), Cu(OAc)₂ (50.0 μL of a 0.200 M solution in THF, 0.0100 mmol, 0.0500 eq.), THF (0.0500 mL) and dimethoxy(methyl)silane (123 μL, 1.00 mmol, 5.00 eq.) were combined in a 2-dram vial followed by addition of a solution of 3-(1-hexyn-1-yl)-quinoline (41.9 mg, 0.200 mmol, 1.00 eq.), THF (0.100 mL), and 2-propanol-d₈ (77.0 μL, 1.00 mmol, 5.00 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 22 h at 40 °C. Upon completion, the crude product mixture was dry loaded onto a neutral alumina brock column. Purification using neutral alumina brock flash column chromatography (100 mL of 100% hexanes and 200 mL of 1% ethyl acetate in hexanes) gives the pure product as a colorless oil (26.0 mg, 0.121 mmol, 61% yield).

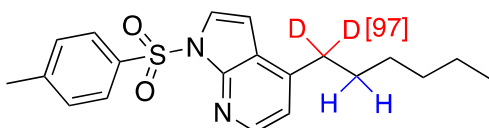
¹H NMR (400 MHz, CDCl₃): δ 8.78 (d, *J* = 2.3 Hz, 1H), 8.07 (d, *J* = 8.4 Hz, 1H), 7.90 (d, *J* = 2.2 Hz, 1H), 7.76 (d, *J* = 8.1 Hz, 1H), 7.65 (t, *J* = 7.3 Hz, 1H), 7.51 (t, *J* = 7.5 Hz, 1H), 2.82 – 2.71 (m, 0.13H), 1.75 – 1.64 (m, 1.96H), 1.46 – 1.20 (m, 6H), 0.96 – 0.81 (m, 3H).

²H NMR (61 MHz, CDCl₃): δ 2.77 (s, 1.87D), 1.70 (s, 0.02D).

¹³C NMR (75 MHz, CDCl₃): δ 152.31, 146.94, 135.46, 134.19, 129.32, 128.58, 128.34, 127.43, 126.61, 33.31 – 31.93 (m), 31.79, 31.09, 28.95, 22.72, 14.21.

IR: 3025, 2923, 2856, 2091, 1569, 1492, 785.

HRMS: (EI⁺) *m/z*: [M]⁺ Calcd for C₁₅H₁₇D₂N 215.1643; Found 215.1638.



D₂-4-(hexane)-1-tosyl-1H-pyrrolo[2,3-*b*] [26]. According to the general procedure C, DTB-DPPBz (9.80 mg, 0.0110 mmol, 0.0550 eq.), Cu(OAc)₂ (50.0 μL of a 0.200 M solution in THF, 0.0100 mmol, 0.0500 eq.), THF (0.0500 mL) and dimethoxy(methyl)silane (123 μL, 1.00 mmol, 5.00 eq.) were combined in a 2-dram vial followed by addition of a solution of 1-tosyl-4-hexyn-yl-1H-pyrrolo[2,3-*b*]pyridine (71.0 mg, 0.200 mmol, 1.00 eq.), THF (0.100 mL), and 2-propanol-*d*₈ (77.0 μL, 1.00 mmol, 5.00 eq). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 25 h at 60 °C. Upon completion, the crude product mixture was dry loaded onto a neutral alumina brock column. Purification using neutral alumina brock flash column chromatography (100 mL of 100% hexanes, 100 mL 3% ethyl acetate in hexanes, 200 mL 5% ethyl acetate in hexanes) gives the pure product as a colorless oil (54.0 mg, 0.151 mmol, 76% yield).

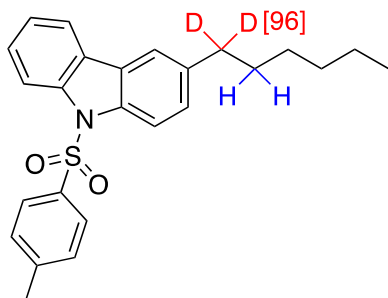
¹H NMR (400 MHz, CDCl₃): δ 8.30 (d, *J* = 4.9 Hz, 1H), 8.06 (d, *J* = 8.0 Hz, 2H), 7.67 (d, *J* = 4.0 Hz, 1H), 7.32 – 7.19 (m, 2H), 6.96 (d, *J* = 4.9 Hz, 1H), 6.60 (d, *J* = 4.0 Hz, 1H), 2.80 – 2.70 (m, 0.06H), 2.34 (s, 3H), 1.69 – 1.54 (m, 2H), 1.37 – 1.20 (m, 6H), 0.91 – 0.78 (m, 3H).

²H NMR (61 MHz, CDCl₃): δ 2.75 (s, 1.94D).

¹³C NMR (75 MHz, CDCl₃): 147.16, 145.76, 145.13, 144.96, 135.64, 129.70, 128.12, 125.63, 122.58, 118.67, 103.79, 32.47 – 30.73 (m), 31.67, 29.79, 29.12, 22.61, 21.71, 14.13.

IR: 3100, 2923, 2856, 2110, 1594, 1517, 1367, 1176.

HRMS: (EI⁺) *m/z*: [M]⁺ Calcd for C₂₀H₂₂D₂N₂O₂S 358.1684; Found 358.1679.



3-(1,1-D)hexyl-9-((4-methylphenyl)sulfonyl)-9H-carbazole [27]. According to the general procedure C, DTB-DPPBz (15.0 mg, 0.0170 mmol, 0.0550 eq.), Cu(OAc)₂ (75.0 μL of a 0.200 M solution in THF, 0.0150 mmol, 0.0500 eq.), THF (0.0750 mL) and dimethoxy(methyl)silane (222 μL, 1.80 mmol, 6.00 eq.) were combined in a 2-dram vial followed by addition of a solution of 3-(hex-1-yn-1-yl)-9-((4-methylphenyl)sulfonyl)-9H-carbazole (121 mg, 0.30 mmol, 1.00 eq.), THF (0.150 mL), and 2-propanol-*d*₈ (115 μL, 1.50 mmol, 5.00 eq). The 2-dram vial was capped with a red pressure relief cap, and the reaction

stirred for 20 h at 60 °C. Upon completion, the crude product mixture was dry loaded onto a silica gel column. Purification using silica gel flash column chromatography (50 mL of 100% hexanes, 100 mL 2% ethyl acetate in hexanes, and 100 mL of 4% ethyl acetate in hexanes) gives the pure product as a colorless oil (75.9 mg, 0.186 mmol, 62% yield).

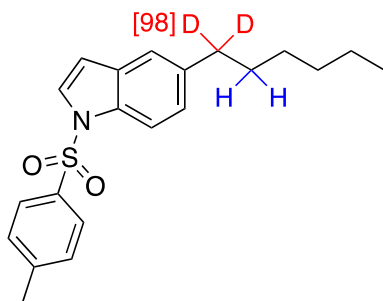
¹H NMR (400 MHz, CDCl₃): δ 8.32 (d, *J* = 8.2 Hz, 1H), 8.23 (d, *J* = 8.6 Hz, 1H), 7.88 (d, *J* = 7.7 Hz, 1H), 7.73 – 7.66 (m, 3H), 7.47 (t, *J* = 7.8 Hz, 1H), 7.40 – 7.28 (m, 2H), 7.07 (d, *J* = 8.6 Hz, 2H), 2.75–2.69 (m, 0.08H), 2.24 (s, 3H), 1.66 (t, *J* = 7.3 Hz, 2H), 1.44 – 1.25 (m, 6H), 0.94 – 0.86 (m, 3H).

²H NMR (61 MHz, CDCl₃): δ 2.72 (s, 1.92D).

¹³C NMR (75 MHz, CDCl₃): δ 144.82, 138.85, 138.74, 136.76, 135.13, 129.71, 128.13, 127.27, 126.64, 126.60, 126.57, 123.88, 120.00, 119.48, 115.28, 114.98, 35.18 (p, *J* = 19.4 Hz), 31.86, 31.76, 29.07, 22.73, 21.58, 14.23.

IR: 2921, 2848, 2119, 1597, 1443, 1187, 1172, 1089, 974.

HRMS: (ESI⁺) *m/z*: [M+Na]⁺ Calcd for C₂₅H₂₅D₂NNaO₂S 430.1788; Found 430.1780.



5-(1,1-²H₂)hexyl-1-((4-methylphenyl)sulfonyl)-1H-indole [28]. According to the general procedure C, DTB-DPPBz (15.0 mg, 0.0170 mmol, 0.0550 eq.), Cu(OAc)₂ (75.0 μL of a 0.200 M solution in THF, 0.0150 mmol, 0.0500 eq.), THF (0.0750 mL) and dimethoxy(methyl)silane (222 μL, 1.80 mmol, 6.00 eq.) were combined in a 2-dram vial followed by addition of a solution of 5-(hex-1-yn-1-yl)-1-((4-methylphenyl)sulfonyl)-1H-indole (105 mg, 0.300 mmol, 1.00 eq.), THF (0.150 mL), and 2-propanol-d₈ (115 μL, 1.50 mmol, 5.00 eq). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 21 h at 60 °C. Upon completion, the crude product mixture was dry loaded onto a silica gel column. Purification using silica gel flash column chromatography (50 mL of 100% hexanes, 100 mL 2% ethyl acetate in hexanes, and 100 mL of 4% ethyl acetate in hexanes) gives the pure product as a colorless oil (93.7 mg, 0.262 mmol, 87% yield).

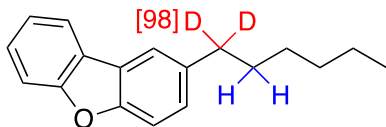
¹H NMR (400 MHz, CDCl₃): δ 7.89 (d, *J* = 8.5 Hz, 1H), 7.76 (d, *J* = 8.4 Hz, 2H), 7.52 (d, *J* = 3.6 Hz, 1H), 7.31 (d, *J* = 1.0 Hz, 1H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.14 (dd, *J* = 8.5, 1.4 Hz, 1H), 6.59 (d, *J* = 3.6 Hz, 1H), 2.67 – 2.59 (m, 0.05H), 2.33 (s, 3H), 1.68 – 1.51 (m, 2H), 1.39 – 1.23 (m, 6H), 0.93 – 0.84 (m, 3H).

²H NMR (61 MHz, CDCl₃): δ 2.64 (s, 1.95D), 1.61 (s, 0.02D).

¹³C NMR (101 MHz, CDCl₃): δ 144.87, 138.12, 135.52, 133.33, 131.04, 129.91, 126.90, 126.43, 125.51, 120.68, 113.30, 109.04, 35.17 (p, *J* = 19.3 Hz), 31.84, 31.80, 29.05, 22.71, 21.62, 14.20.

IR: 3029, 2923, 2854, 2116, 1597, 1369, 1174, 1128, 1091, 995, 752, 670.

HRMS: (EI⁺) *m/z*: [M]⁺ Calcd for C₂₁H₂₃D₂NO₂S 357.1732; Found 357.1723.



2-(1,1-²H₂)hexyldibenzo[*b,d*]furan [29]. According to the general procedure C, DTB-DPPBz (6.00 mg, 0.00660 mmol, 0.0220 eq.), Cu(OAc)₂ (30.0 μ L of a 0.200 M solution in THF, 0.00600 mmol, 0.0200 eq.), THF (0.120 mL) and dimethoxy(methyl)silane (185 μ L, 1.50 mmol, 5.00 eq.) were combined in a 2-dram vial followed by addition of a solution of 2-(hex-1-yn-1-yl)dibenzo[*b,d*]furan (74.5 mg, 0.300 mmol, 1.00 eq.), THF (0.150 mL), and 2-propanol-*d*₈ (115 μ L, 1.50 mmol, 5.00 eq). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 22 h at 40 °C. Upon completion, the crude product mixture was dry loaded onto a silica gel column. Purification using silica gel flash column chromatography (100 mL of 1% ethyl acetate in hexanes and 100 mL of 2% ethyl acetate in hexanes) gives the pure product as a colorless oil (63.8 mg, 0.251 mmol, 84% yield).

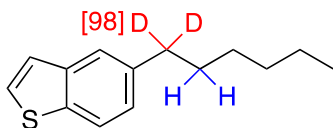
¹H NMR (400 MHz, CDCl₃): δ 7.96 (d, *J* = 7.7 Hz, 1H), 7.78 (d, *J* = 1.7 Hz, 1H), 7.59 (d, *J* = 8.2 Hz, 1H), 7.54 – 7.42 (m, 2H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.30 (dd, *J* = 8.4, 1.8 Hz, 1H), 2.81-2.74 (m, 0.05H), 1.72 (t, *J* = 6.9 Hz, 2H), 1.47-1.31 (m, 6H), 0.98 – 0.89 (m, 3H).

²H NMR (61 MHz, CDCl₃): δ 2.77 (s, 1.95D), 1.72 (s, 0.02D).

¹³C NMR (75 MHz, CDCl₃): δ 156.59, 154.78, 137.51, 127.78, 126.99, 124.46, 124.24, 122.61, 120.65, 120.10, 111.73, 111.27, 35.29 (p, *J* = 19.0 Hz), 32.09, 31.92, 29.07, 22.78, 14.26.

IR: 3050, 2955, 2924, 2855, 2200, 1479, 1449, 1195.

HRMS: (EI⁺) *m/z*: [M]⁺ Calcd for C₁₈H₁₈D₂O 254.1640; Found 254.1635.



5-(hexyl-1,1-*d*₂)benzo[*b*]thiophene [30]. According to the general procedure C, DTB-DPPBz (3.00 mg, 0.00330 mmol, 0.0110 eq.), Cu(OAc)₂ (15.0 μ L of a 0.200 M solution in THF, 0.00300 mmol, 0.0100 eq.), THF (0.135 mL) and dimethoxy(methyl)silane (222 μ L, 1.80 mmol, 6.00 eq.) were combined in a 2-dram vial followed by addition of a solution of 5-(hex-1-yn-1-yl)benzo[*b*]thiophene (64.3 mg, 0.300 mmol, 1.00 eq.), THF (0.150 mL), and 2-propanol-*d*₈ (115 μ L, 1.50 mmol, 5.00 eq). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 23 h at 40 °C. Upon completion, the crude product mixture was dry loaded onto a silica gel column. Purification using silica gel flash column chromatography (150 mL of 100% hexanes) gives the pure product as a clear colorless oil (61.5 mg, 0.279 mmol, 93% yield).

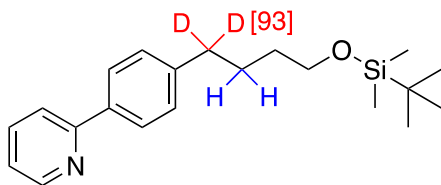
¹H NMR (400 MHz, CDCl₃): δ 7.79 (d, *J* = 8.2 Hz, 1H), 7.64 (s, 1H), 7.42 (d, *J* = 5.4 Hz, 1H), 7.29 (d, *J* = 5.4 Hz, 1H), 7.20 (d, *J* = 8.2 Hz, 1H), 2.77 – 2.68 (m, 0.05H), 1.75 – 1.61 (m, 2H), 1.43 – 1.25 (m, 6H), 1.02 – 0.84 (m, 3H).

²H NMR (61 MHz, CDCl₃): δ 2.71 (s, 1.95D).

¹³C NMR (101 MHz, CDCl₃): δ 140.03, 139.11, 137.24, 126.41, 125.54, 123.74, 123.06, 122.22, 35.29 (p, *J* = 19.2 Hz), 31.92, 31.81, 29.08, 22.77, 14.26.

IR: 3100, 2954, 2922, 2854, 2192, 1605, 1550, 1435, 1088.

HRMS: (EI⁺) *m/z*: [M]⁺ Calcd for C₁₄H₁₆D₂S 220.1255; Found 220.1249.



2-(4-(4-((*tert*-butyldimethylsilyl)oxy)butyl-1,1-*d*₂)phenyl)pyridine [31]. According to the general procedure C, DTB-DPPBz (15.0 mg, 0.0165 mmol, 0.0740 eq.), Cu(OAc)₂ (75.0 μ L of a 0.200 M solution in THF, 0.0150 mmol, 0.0680 eq.), THF (0.750 mL), and dimethoxy(methyl)silane (222 μ L, 1.80 mmol, 8.10 eq.) were combined in a 2-dram vial followed by addition of a solution of 2-(4-(4-((*tert*-butyldimethylsilyl)oxy)but-1-yn-1-yl)phenyl)pyridine (75.0 mg, 0.222 mmol, 1.00 eq.), THF (0.150 mL), and 2-propanol-*d*₈ (0.115 mL, 1.50 mmol, 6.80 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 21 h at 40 °C. Upon completion, the crude product mixture was dry loaded onto a neutral alumina Brock column. Purification using neutral alumina Brock flash column chromatography (150 mL of 100% hexanes, and 100 mL of 2.5% ethyl acetate in hexanes) gives the pure product as a yellow solid (65.3 mg, 0.190 mmol, 86% yield).

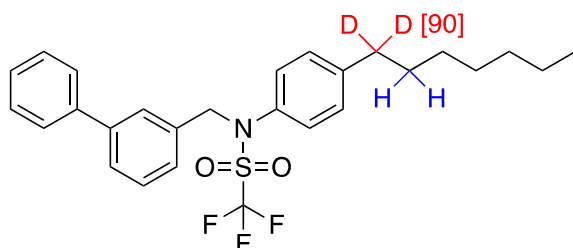
¹H NMR (400 MHz, CDCl₃): δ 8.68 (d, *J* = 4.9 Hz, 1H), 7.90 (d, *J* = 8.2 Hz, 2H), 7.79 – 7.68 (m, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.23–7.18 (m, 1H), 3.64 (t, *J* = 6.4 Hz, 2H), 2.69–2.63 (m, 0.14H), 1.74 – 1.65 (m, 2H), 1.63 – 1.53 (m, 2H), 0.89 (s, 9H), 0.05 (s, 6H).

²H NMR (61 MHz, CDCl₃): δ 2.66 (s, 1.86D), 1.70 (s, 0.04D)

¹³C NMR (75 MHz, CDCl₃): δ 157.59, 149.66, 143.78, 136.95, 136.85, 128.97, 126.95, 121.93, 120.44, 63.12, 35.55 – 34.17 (m), 32.47, 27.55, 26.11, 18.50, -5.14.

IR: 3020, 2927, 2212, 1600, 1588, 1465, 1253, 1093, 832.

HRMS: (ESI⁺) *m/z*: [M+H]⁺ Calcd for C₂₁H₃₀D₂NOSi 344.2380; Found 344.2369.



N-([1,1'-biphenyl]-3-ylmethyl)-1,1,1-trifluoro-N-(4-(heptyl-1,1-*d*₂)phenyl)methanesulfonamide [32].

According to general procedure C, DTB-DPPBz (9.85 mg, 0.0110 mmol, 0.0567 eq.), Cu(OAc)₂ (50.0 μ L of a 0.200 M solution in THF, 0.0100 mmol, 0.0515 eq.), THF (0.0500 mL) and dimethoxy(methyl)silane (123 μ L, 1.00 mmol, 5.15 eq.) were combined in a 1-dram vial. In a separate 2-dram vial equipped with a Teflon stir bar was added N-([1,1'-biphenyl]-3-ylmethyl)-1,1,1-trifluoro-N-(4-(hept-1-yn-1-yl)phenyl)methanesulfonamide (94.3 mg, 0.194 mmol, 1.00 eq), 3 Å molecular sieve powder (20.0 mg), THF (0.600 mL), and 2-propanol-*d*₈ (77.0 μ L, 1.01 mmol, 5.21 eq.). The catalyst solution in the 1-dram vial was transferred by 1,4-dioxane (174 μ L) to the 2-dram vial. The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 48 h at 40 °C. Upon completion, the crude product mixture was wet loaded onto a silica gel column. Purification using silica gel flash column chromatography (100 mL of 10% ethyl acetate in hexane) gave the desired product. The desired product was then purified by flash C18-reverse phase column chromatography (stationary: C₁₈ 60 silica, elution: 150 mL of 100% methanol) to give the pure compound as a colorless oil (89.0 mg, 0.181 mmol, 93%).

¹H NMR (400 MHz, CDCl₃): δ 7.63 – 7.33 (m, 8H), 7.30 – 7.08 (m, 5H), 5.01 (s, 2H), 2.64 – 2.57 (m, 0.20H), 1.69 – 1.56 (m, 2H), 1.44 – 1.26 (m, 8H), 1.04 – 0.86 (m, 3H).

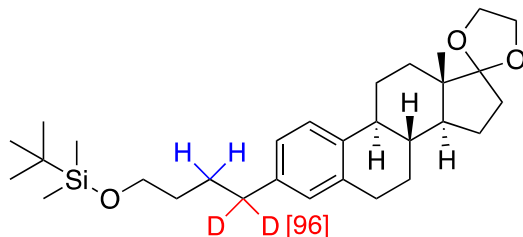
²H NMR (61 MHz, CDCl₃): δ 2.61 (s, 1.80D).

¹³C NMR (75 MHz, CDCl₃): δ 144.45, 144.42, 141.60, 140.59, 135.04, 134.12, 129.47, 129.31, 129.19, 128.92, 127.98, 127.65, 127.33, 127.17, 120.70 (q, *J* = 323 Hz), 57.55, 35.75 – 34.80 (m), 31.88, 31.12, 29.33, 29.23, 22.77, 14.21.

¹⁹F NMR (376 MHz, Chloroform-*d*) δ -73.59 (s, 3F).

IR: 3061, 3033, 2956, 2927, 2856, 2196, 1394, 1194

HRMS: (ESI⁺) *m/z*: [M+Na]⁺ Calcd for C₂₇H₂₈D₂F₃NO₂SiNa 514.1972; Found 514.1963.



tert-butyldimethyl(4-((8R,9S,13S,14S)-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydrospiro[cyclopenta[a]phenanthrene-17,2'-[1,3]dioxolan]-3-yl)butoxy-4,4-*d*₂)silane[33].

According to the general procedure C, DTB-DPPBz (9.85 mg, 0.0110 mmol, 0.0550 eq.), Cu(OAc)₂ (50.0 μL of a 0.200 M solution in THF, 0.0100 mmol, 0.0500 eq.), THF (0.0500 mL) and dimethoxy(methyl)silane (148 μL, 1.20 mmol, 6.00 eq.) were combined in a 2-dram vial followed by addition of a solution of *tert*-butyldimethyl((4-((8R,9S,13S,14S)-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydrospiro[cyclopenta[a]phenanthrene-17,2'-[1,3]dioxolan]-3-yl)but-3-yn-1-yl)oxy)silane (96.2 mg, 0.200 mmol, 1.00 eq.), THF (0.100 mL), and 2-propanol-*d*₈ (77.0 μL, 1.00 mmol, 5.00 eq). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 72 h at 40 °C. Upon completion, the crude product mixture was dry loaded onto a silica gel column. Purification using silica gel flash column chromatography (50 mL of 100% hexanes, 100 mL of 2% ethyl acetate in hexanes, 100 mL of 3% ethyl acetate in hexanes) gives the pure product as a yellow oil (89.2 mg, 0.183 mmol, 92% yield).

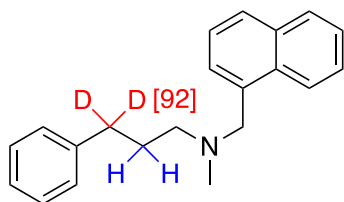
¹H NMR (400 MHz, CDCl₃): δ 7.22 (d, *J* = 8.0 Hz, 1H), 6.97 (d, *J* = 8.8 Hz, 1H), 6.91 (s, 1H), 4.02 – 3.85 (m, 4H), 3.63 (t, *J* = 6.2 Hz, 2H), 2.90 – 2.80 (m, 2H), 2.59 – 2.51 (m, 0.08H), 2.41 – 2.21 (m, 2H), 2.11 – 1.97 (m, 1H), 1.96 – 1.71 (m, 4H), 1.71 – 1.20 (m, 10H), 0.90 (s, 9H), 0.89 (s, 3H), 0.06 (s, 6H).

²H NMR (61 MHz, CDCl₃): δ 2.54 (s, 1.92D).

¹³C NMR (75 MHz, CDCl₃): δ 139.88, 137.82, 136.65, 129.12, 125.80, 125.38, 119.59, 77.16, 65.39, 64.72, 63.20, 49.61, 46.30, 44.10, 39.07, 35.16 – 33.96 (m), 34.37, 32.66, 30.91, 29.69, 27.63, 27.17, 26.13, 22.50, 18.51, 14.46, -5.12.

IR: 2927, 2857, 2241, 1650, 1500, 1100, 1045, 833

HRMS: (ESI⁺) *m/z*: [M+Na]⁺ Calcd for C₃₀H₄₆D₂NaO₃Si 509.3398; Found 509.3395.



N-methyl-N-(naphthalen-1-ylmethyl)-3-phenylpropan-1-amine-3,3-*d*₂ [34]. According to general procedure C, DTB-DPPBz (9.85 mg, 0.0110 mmol, 0.0550 eq.), Cu(OAc)₂ (50.0 μL of a 0.200 M solution

in THF, 0.0100 mmol, 0.0500 eq.), THF (0.0500 mL) and dimethoxy(methyl)silane (123 μ L, 1.00 mmol, 5.00 eq) were combined in a 2-dram vial followed by the addition of a solution of *N*-methyl-*N*-(naphthalen-1-ylmethyl)-3-phenylprop-2-yn-1-amine (57.1 mg, 0.200 mmol, 1.00 eq), THF (0.720 mL), and 2-propanol-*d*₈ (77.0 μ L, 1.00 mmol, 5.00 eq.). The total volume of THF was calculated based on having a final reaction concentration of 0.24 M based on the alkyne substrate. The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 20 h at 40 °C. Upon completion, the crude product mixture was filtered through a short silica gel plug and eluted with 25 mL DCM. The solvent was removed by rotary evaporation to afford the crude product. The crude product was dry loaded onto a silica gel column. Two purifications using silica gel flash column chromatography (first purification: 100 mL of 10% ethyl acetate in hexane with 1% triethyl amine; second purification: 100 mL 5% ethyl acetate in hexane, 100 mL 10% acetone in hexane, 100 mL 15% acetone in hexane), gave the desired compound as a pale-yellow oil (31.0 mg, 0.106 mmol, 53%).

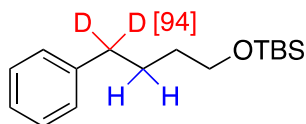
¹H NMR (400 MHz, CDCl₃): δ 8.32 (d, *J* = 7.8 Hz, 1H), 7.85 (d, *J* = 8.2 Hz, 1H), 7.78 (d, *J* = 7.8 Hz, 1H), 7.56 – 7.44 (m, 2H), 7.44 – 7.37 (m, 2H), 7.26 – 7.22 (m, 2H), 7.17 (d, *J* = 7.1 Hz, 1H), 7.13 (d, *J* = 7.4 Hz, 2H), 3.89 (s, 2H), 2.63 – 2.58 (m, 0.16H), 2.51 (t, *J* = 6.9 Hz, 2H), 2.22 (s, 3H), 1.88 (t, *J* = 6.5 Hz, 1.84H).

²H NMR (61 MHz, CDCl₃): δ 2.61 (s, 1.84D), 1.90 (s, 0.08D).

¹³C NMR (101 MHz, CDCl₃): δ 142.49, 135.17, 133.98, 132.66, 128.54, 128.50, 128.37, 127.94, 127.50, 125.86, 125.76, 125.68, 125.24, 124.87, 61.04, 57.49, 42.38, 33.58 – 32.38 (m), 29.13.

IR: 3057, 3023, 2936, 2838, 2789, 2199, 1146

HRMS: (EI⁺) *m/z*: [M]⁺ Calcd for C₂₁H₂₁D₂N 291.1956; Found 291.1950.



***Tert*-butyldimethyl(4-phenylbutoxy-4,4-*d*₂)silane [35].** According to the general procedure C, DTB-DPPBz (98.5 mg, 0.110 mmol, 0.0550 eq.), Cu(OAc)₂ (500 μ L of a 0.200 M solution in THF, 0.100 mmol, 0.0500 eq.), THF (4.10 mL) and dimethoxy(methyl)silane (1.23 mL, 10.0 mmol, 5.00 eq.) were combined in a 100 mL oven-dried round bottom flask equipped with a Teflon stir bar, followed by addition of a solution of *tert*-butyldimethyl((4-phenylbut-3-yn-1-yl)oxy)silane (521 mg, 2.00 mmol, 1.00 eq.), THF (4.10 mL), and 2-propanol-*d*₈ (0.766 mL, 10.0 mmol, 5.00 eq). The total volume of THF was calculated based on having a final reaction concentration of 0.23 M based on the alkyne substrate. The 100 mL round bottom flask was capped with a Teflon septa, and the reaction stirred for 24 h at 40 °C under a N₂ filled balloon. Upon completion, the crude product mixture was dry loaded onto a silica gel column. Purification using silica gel flash column chromatography (200 mL of 100% hexanes, 600 mL of 3% ethyl acetate in hexanes) gave the desired product as a clear, colorless oil (511 mg, 1.92 mmol, 96% yield).

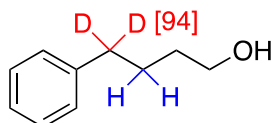
¹H NMR (400 MHz, CDCl₃): δ 7.34 – 7.28 (m, 2H), 7.24 – 7.18 (m, 3H), 3.67 (t, *J* = 6.3 Hz, 2H), 2.68 – 2.61 (m, 0.13H), 1.74 – 1.67 (m, 1.87H), 1.65 – 1.55 (m, 2H), 0.94 (s, 9H), 0.09 (s, 6H).

²H NMR (61 MHz, CDCl₃): δ 2.65 (s, 1.87D), 1.71 (s, 0.06D).

¹³C NMR (75 MHz, CDCl₃): δ 142.69, 128.53, 128.38, 125.77, 63.15, 35.19 (p, *J* = 19.1 Hz), 32.53, 27.65, 26.13, 18.50, -5.13.

IR: 3020, 2985, 2950, 2925, 2890, 2110, 1100

HRMS: (EI⁺) *m/z*: [M-C₄H₉]⁺ Calcd for C₁₂H₁₇D₂O₂Si 209.1331; Found 209.1323. The major ion peak represents the parent molecule after loss of the *t*-Bu cation.



4-Phenylbutan-4,4- d_2 -1-ol. *Tert*-butyldimethyl(4-phenylbutoxy-4,4- d_2)silane (451 mg, 1.69 mmol, 1.00 eq.) was dissolved in THF (17 mL) and tetrabutylammonium fluoride (3.38 mL of a 1.00 M in THF solution, 3.38 mmol, 2.00 eq.) was added to the reaction mixture. The reaction was stirred at room temperature overnight. Upon completion, the reaction mixture was quenched with saturated aqueous NH_4Cl (20 mL) and evaporated to remove the THF. The aqueous layer was extracted with ethyl acetate (3 x 20 mL) and the combined organic layers were washed with brine (10 mL) then dried over anhydrous Na_2SO_4 . The mixture was filtered, and the solvent was removed by rotary evaporation. Purification using silica gel flash column chromatography (100 mL of hexanes, 100 mL of 10% ethyl acetate in hexanes, 500 mL of 15% ethyl acetate in hexanes) gave the pure product as a clear oil (217 mg, 1.43 mmol, 85% yield).

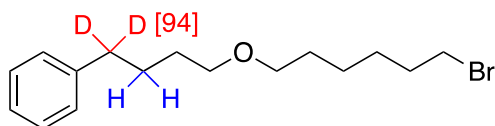
^1H NMR (400 MHz, CDCl_3): δ 7.34 – 7.27 (m, 2H), 7.24 – 7.17 (m, 3H), 3.64 (t, J = 6.4 Hz, 2H), 2.69 – 2.59 (m, 0.13H), 2.31 – 2.07 (m, 1H), 1.73 – 1.66 (m, 1.87H), 1.65 – 1.58 (m, 2H).

^2H NMR (61 MHz, CDCl_3): δ 2.64 (s, 1.87D), 1.71 (s, 0.06D).

^{13}C NMR (75 MHz, CDCl_3): δ 142.35, 128.47, 128.36, 125.81, 62.73, 35.10 (p, J = 19.3 Hz), 32.28, 27.47.

IR: 3327, 3060, 3024, 2931, 2862, 2197, 1604, 1495

HRMS: (EI^+) m/z : [M] $^+$ Calcd for $\text{C}_{10}\text{H}_{12}\text{D}_2\text{O}$ 152.1170; Found 152.1164.



(4-((6-Bromohexyl)oxy)butyl-1,1- d_2)benzene. According to a previously reported procedure¹, to an oven dried 50 mL Schlenk tube equipped with a Teflon stir bar was added 4-Phenylbutan-4,4- d_2 -1-ol [7k] (148 mg, 0.972 mmol, 1.00 eq.) dissolved in THF (10 mL). This was cooled to 0 °C for 10 minutes followed by addition of NaH (60% dispersion in mineral oil, 78.0 mg, 1.94 mmol, 2.00 eq.). This was stirred at 0 °C for 10 minutes followed by dropwise addition of 1,6-dibromohexane (237 mg, 0.972 mmol, 1.00 eq.). The reaction was equipped with a cold finger condenser and heated in a silicon oil bath to 75 °C overnight. Upon completion, the reaction was quenched with DI water (10 mL) and extracted with ethyl acetate (3 X 20 mL). The combined organic layers were washed with brine (1 X 20 mL), and dried over anhydrous Na_2SO_4 . The mixture was filtered, dry loaded on to silica gel, and purified twice by flash column chromatography (first purification: 200 mL 100% hexane, 200 mL 0.5% ethyl acetate in hexane, 200 mL 1.5% ethyl acetate in hexane, 400 mL 3% ethyl acetate in hexane, 200 mL 20% ethyl acetate in hexane; second purification: 100 mL 100% hexanes, 100 mL 0.5% diethyl ether in hexanes, 300 mL 1% diethyl ether in hexanes) to give the desired product as a clear oil (53.0 mg, 0.168 mmol, 17% yield).

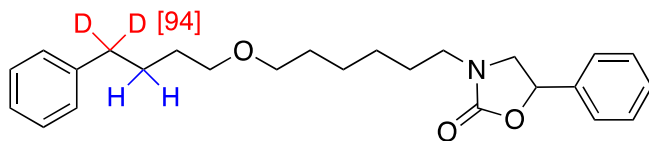
^1H NMR (400 MHz, CDCl_3): δ 7.31 – 7.25 (m, 2H), 7.21 – 7.16 (m, 3H), 3.47 – 3.35 (m, 6H), 2.66 – 2.58 (m, 0.13H), 1.87 (p, J = 6.9 Hz, 2H), 1.73 – 1.53 (m, 6H), 1.51 – 1.33 (m, 4H).

^2H NMR (61 MHz, CDCl_3): δ 2.63 (s, 1.87D).

^{13}C NMR (75 MHz, CDCl_3): δ 142.54, 128.52, 128.37, 125.79, 70.86, 70.83, 35.11 (p, J = 19.6 Hz), 33.99, 32.86, 29.69, 29.47, 28.12, 28.04, 25.55.

IR: 3073, 2990, 2887, 2811, 2224, 1020, 673

HRMS: (ESI^+) m/z : [$\text{M}+\text{H}$] $^+$ Calcd for $\text{C}_{16}\text{H}_{24}\text{D}_2\text{OBr}$ 315.1294; Found 315.1284.



5-Phenyl-3-(6-(4-phenylbutoxy-4,4- d_2)hexyl)oxazolidin-2-one. According to a previously reported procedure², to an oven dried 25 mL round bottom flask equipped with a Teflon stir bar was added a solution of NaH (60% dispersion in mineral oil, 5.15 mg, 0.129 mmol, 1.11 eq) in DMF (0.300 mL). Under N₂, the mixture was cooled to 0 °C for 10 minutes and then a solution of **5-phenyloxazolidin-2-one** (18.9 mg, 0.116 mmol, 1.00 eq) in DMF (0.600 mL) was added dropwise and stirred at 0 °C for 10 minutes. A solution of (4-((6-Bromohexyl)oxy)butyl-1,1- d_2)benzene (56.4 mg, 0.179 mmol, 1.54 eq) in DMF (0.300 mL) was then added dropwise and the reaction stirred at 0 °C for 1 h and then at room temperature for 3 h. Upon reaction completion, the mixture was re-cooled to 0 °C and quenched with 2 M HCl (4 mL) dropwise. The organic phase was extracted with ethyl acetate (1 X 20 mL) and then the organic phase was washed with brine (1 X 20 mL) and dried over anhydrous Na₂SO₄. The mixture was filtered, dry loaded onto silica gel, and purified by flash column chromatography (100 mL of 100% hexane, 100 mL of 10% ethyl acetate in hexanes, 100 mL of 20% ethyl acetate in hexanes, 100 mL 30% ethyl acetate in hexanes, 100 mL 50% ethyl acetate in hexanes) to give the desired product as a clear oil (43.0 mg, 0.108 mmol, 93% yield).

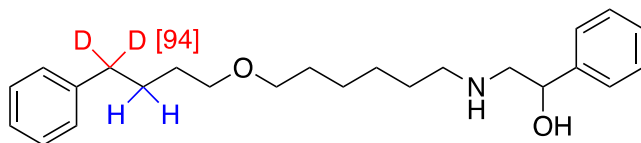
¹H NMR (400 MHz, CDCl₃): δ 7.44 – 7.32 (m, 5H), 7.30 – 7.24 (m, 2H), 7.21 – 7.13 (m, 3H), 5.47 (t, J = 8.1 Hz, 1H), 3.89 (t, J = 8.7 Hz, 1H), 3.44 – 3.35 (m, 5H), 3.35 – 3.21 (m, 2H), 2.66 – 2.57 (m, 0.13H), 1.73 – 1.48 (m, 8H), 1.43 – 1.28 (m, 4H).

²H NMR (61 MHz, CDCl₃): δ 2.61 (s, 1.87D), 1.66 (s, 0.04D)

¹³C NMR (75 MHz, CDCl₃): δ 157.98, 142.52, 138.99, 128.98, 128.84, 128.49, 128.33, 125.75, 125.57, 74.37, 70.82, 70.79, 52.23, 44.22, 35.08 (p, J = 20.1 Hz), 29.71, 29.44, 28.02, 27.41, 26.56, 25.95.

IR: 3061, 3014, 2934, 2860, 2196, 1744, 1216, 1111

HRMS: (ESI⁺) m/z : [M+H]⁺ Calcd for C₂₅H₃₂D₂NO₃ 398.2666; Found 398.2661.



1-Phenyl-2-((6-(4-phenylbutoxy-4,4- d_2)hexyl)amino)ethan-1-ol [36]. According to a previously reported procedure², to an oven dried 50 mL Schlenk tube equipped with a Teflon stir bar was added 5-Phenyl-3-(6-(4-phenylbutoxy-4,4- d_2)hexyl)oxazolidin-2-one (36.3 mg, 0.0913 mmol, 1.00 eq) and THF (0.850 mL). This was stirred under N₂ for 10 minutes followed by addition of KOSiMe₃ (21.7 mg, 0.169 mmol, 1.85 eq.). The reaction was equipped with a cold finger condenser and heated to 75 °C for 6 h and the reaction progress was monitored by TLC. Upon reaction completion, the reaction was cooled to room temperature and quenched with DI water (5 mL). The organic phase was extracted with ethyl acetate (3 X 10 mL) and then the combined organic layers were washed with brine (1 X 10 mL) and then dried over Na₂SO₄. This was filtered and then concentrated by rotary evaporation to give the desired product as a yellow solid (18.6 mg, 0.0500 mmol, 55% yield).

¹H NMR (400 MHz, CDCl₃): δ 7.41 – 7.31 (m, 4H), 7.30 – 7.24 (m, 3H, peak overlaps with residual CHCl₃ peak), 7.20 – 7.14 (m, 3H), 4.81 (d, J = 6.1 Hz, 1H), 3.93 (s, 2H), 3.39 (dt, J = 13.4, 6.5 Hz, 4H), 3.00 – 2.58 (m, 4.13H), 1.71 – 1.52 (m, 8H), 1.36 – 1.30 (m, 4H).

²H NMR (61 MHz, CDCl₃): δ 2.61 (s, 1.87D).

¹³C NMR (75 MHz, CDCl₃): δ 142.58, 142.46, 128.54 (2 carbons overlapping), 128.39, 127.68, 125.93, 125.81, 71.27, 70.94, 70.87, 56.91, 49.30, 35.14 (p, *J* = 19.9 Hz), 29.86, 29.81, 29.51, 28.07, 27.14, 26.19.

IR: 3297, 3083, 3060, 3025, 2927, 2853, 2796, 2191, 1557, 1119

HRMS: (ESI⁺) *m/z*: [M+H]⁺ Calcd for C₂₄H₃₄D₂NO₂ 372.2873; Found 372.2862.

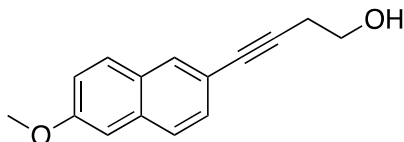
Synthesis of Alkyne Starting Materials

General Sonogashira Coupling Procedure for the Synthesis of Internal Alkynes³ (D)

To a flame-dried round bottom flask or Schlenk tube under N₂ was added triethylamine (15.0 mL, 0.200 M), which was degassed for 15 minutes. The aryl halide (3.00 mmol, 1.00 eq.), Pd(PPh₃)₂Cl₂ (42.0 mg, 0.06 mmol, 0.02 eq.) and CuI (23.0 mg, 0.120 mmol, 0.0400 eq.) were then sequentially added at room temperature. The mixture was stirred for 10 minutes followed by the addition of the alkyne reagent (3.30 mmol, 1.10 eq.). After 16 h of stirring at either room temperature or reflux, the reaction was cooled to room temperature, quenched with water (10 mL) and extracted with ethyl acetate (3 x 15 mL). The organic layers were washed with brine (3 x 10 mL) and then dried over anhydrous Na₂SO₄. The mixture was filtered, and the solvent was removed by rotary evaporation. The crude product was purified by flash column chromatography to give the desired aryl substituted alkyne.

General TBS protection of alcohol containing substrates³ (E)

To a flame-dried round bottom flask under a N₂ atmosphere with a Teflon stirbar, was added the alcohol substrate (1.86 mmol, 1.00 eq.), dry dichloromethane (5.00 mL) followed by imidazole (253 mg, 3.72 mmol, 2.00 eq.) and *tert*-butyldimethylsilyl chloride (307 mg, 2.04 mmol, 1.10 eq.). The reaction was stirred at room temperature overnight. Upon completion, the reaction mixture was quenched with water (20 mL) and extracted with diethyl ether (2 x 15 mL). The combined organic layers were washed with brine (15 mL) and dried over anhydrous Na₂SO₄. The mixture was filtered, and the solvent was removed by rotary evaporation. The crude product was purified by flash column chromatography to give the desired TBS protected alcohol.



4-(6-Methoxy-2-naphthalenyl)-3-butyn-1-ol. Following general procedure D, triethylamine (38.0 mL), 2-iodo-6-methoxynaphthalene (2.14 g, 7.55 mmol, 1.00 eq.), Pd(PPh₃)₂Cl₂ (106 mg, 0.151 mmol, 0.0200 eq.) and CuI (72.0 mg, 0.378 mmol, 0.0500 eq.) were added to a flame dried round bottom flask, and was stirred for 15 minutes under N₂ at room temperature. 3-Butyn-1-ol (0.629 mL, 8.31 mmol, 1.10 eq.) was then added in one portion, the reaction was equipped with a cold finger condenser, and the reaction was heated to 60°C and stirred under N₂ overnight. Post-reaction work up, the crude product was purified by flash column chromatography (500 mL 10% ethyl acetate in hexanes and 1500 mL 20% ethyl acetate in hexanes) to give the pure product as a white solid (1.34 g, 5.92 mmol, 78% yield).

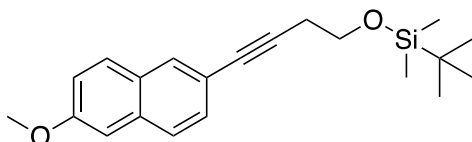
¹H NMR (400 MHz, CDCl₃):

δ 7.86 (s, 1H), 7.66 (t, *J* = 8.5 Hz, 2H), 7.46 – 7.41 (m, 1H), 7.14 (dd, *J* = 8.9, 2.4 Hz, 1H), 7.11 – 7.07 (m, 1H), 3.91 (s, 3H), 3.85 (t, *J* = 8.5 Hz, 2H), 2.74 (t, *J* = 6.2 Hz, 2H) 1.95 (br s, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 158.15, 133.91, 131.20, 129.18, 129.17, 128.43, 126.74, 119.34, 118.19, 105.72, 85.85, 82.94, 61.24, 55.33, 23.94.

IR: 3244, 3066, 3002, 2958, 2936, 2882, 2831, 1593, 1238, 1030.

HRMS: (ESI⁺) *m/z*: [M+H]⁺ Calcd for C₁₅H₁₅O₂ 227.1074 Found 227.1069.



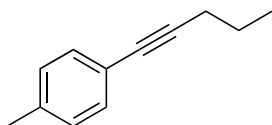
Tert-butyl-(4-(6-methoxy-2-naphthalenyl)-3-butyn-1-oxy)-dimethylsilane [4-SM]. Following a previously reported procedure³, 4-(6-methoxy-2-naphthalenyl)-3-butyn-1-ol (1.34 g, 5.92 mmol, 1.00 eq.), dry DCM (18.0 mL), imidazole (804 mg, 11.8 mmol, 2.00 eq.), and *tert*-butyldimethylsilyl chloride (981 mg, 6.51 mmol, 1.10 eq.) were combined in a flame-dried round bottom flask. Post-reaction work up, the crude product was purified by flash column chromatography (500 mL 1.5% ethyl acetate in hexanes, 500 mL 3% ethyl acetate in hexanes) to give the pure product as a white solid (1.92 g, 5.64 mmol, 95% yield).

¹H NMR (400 MHz, CDCl₃): δ 7.84 (s, 1H), 7.66 (t, *J* = 9.5 Hz, 2H), 7.46 – 7.39 (m, 1H), 7.17 – 7.11 (m, 1H), 7.11 – 7.07 (m, 1H) 3.91 (s, 3H), 3.86 (t, *J* = 7.1 Hz, 2H), 2.68 (t, *J* = 7.1 Hz, 2H), 0.94 (s, 9H), 0.13 (s, 6H).

¹³C NMR (101 MHz, CDCl₃): δ 158.18, 133.91, 131.14, 129.37, 129.30, 128.62, 126.79, 119.37, 118.83, 105.85, 86.83, 82.11, 62.20, 55.45, 26.07, 24.07, 18.53, -5.07.

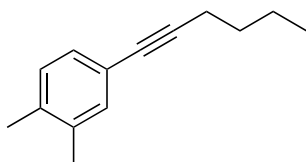
IR: 3025, 2954, 2933, 2914, 2861, 1603, 1203, 1248, 1099.

HRMS: (ESI⁺) *m/z*: [M+Na]⁺ Calcd for C₂₁H₂₈NaO₂Si 363.1759 Found 363.1751.



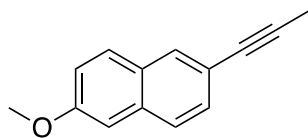
1-Methyl-4-(pent-1-yn-yl)benzene [6-SM]. Following general procedure D, triethylamine (12.0 mL), 4-iodotoluene (500 mg, 2.29 mmol, 1.00 eq), Pd(PPh₃)₂Cl₂ (32.1 mg, 0.0458 mmol, 0.0200 eq.), CuI (17.4 mg, 0.0916 mmol, 0.0400 eq.) were added to a 100 mL flame dried round bottom flask, and was stirred for 15 minutes under N₂ at room temperature. 1-pentyne (0.248 mL, 2.52 mmol, 1.10 eq.) was then added in one portion, the reaction was stirred at room temperature under N₂ overnight. Post-reaction work up, the crude product was purified by flash column chromatography (500 mL of 100% hexanes) to give the pure product as a clear colorless oil (289 mg, 1.83 mmol, 80% yield). The NMR data was consistent with previously reported spectra.⁴

¹H NMR (400 MHz, CDCl₃): δ 7.29 (d, *J* = 7.7 Hz, 2H), 7.08 (d, *J* = 7.7 Hz, 2H), 2.38 (t, *J* = 7.0 Hz, 2H), 2.33 (s, 3H), 1.63 (sxt, *J* = 7.3 Hz, 2H), 1.04 (t, *J* = 7.4 Hz, 3H).



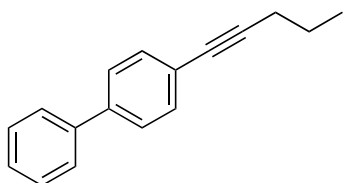
4-(1-hexyn-1-yl)-1,2-dimethyl-benzene [7-SM]. Following general procedure D, triethylamine (25.0 mL), 4-iodo-1,2-dimethyl-benzene (0.614 mL, 4.31 mmol, 1.00 eq), Pd(PPh₃)₂Cl₂ (60.5 mg, 0.0862 mmol, 0.0200 eq.), CuI (32.8 mg, 0.172 mmol, 0.0400 eq.) were added to a 100 mL flame dried round bottom flask, and was stirred for 15 minutes under N₂ at room temperature. 1-Hexyne (0.544 mL, 4.74 mmol, 1.10 eq.) was then added in one portion, the reaction was equipped with a cold finger condenser, and the reaction was heated to 100°C and stirred under N₂ overnight. Post-reaction work up, the crude product was purified by flash column chromatography (500 mL of 100% hexanes) to give the pure product as a red oil (484 mg, 2.60 mmol, 60% yield). The NMR data was consistent with previously reported spectra.⁵

¹H NMR (400 MHz, CDCl₃): δ 7.19 (s, 1H), 7.13 (d, *J* = 7.8 Hz, 1H), 7.04 (d, *J* = 7.7 Hz, 1H), 2.40 (t, *J* = 7.0 Hz, 2H), 2.24 (s, 3H), 2.22 (s, 3H), 1.65 – 1.54 (m, 2H), 1.54 – 1.44 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H).



2-methoxy-6-(1-propyn-1-yl)-naphthalene [1]. Adapted from a previously reported procedure⁶, triethylamine (5.00 mL), 2-iodo-6-methoxy-naphthalene (500 mg, 1.76 mmol, 1.00 eq), Pd(PPh₃)₂Cl₂ (24.7 mg, 0.0352 mmol, 0.0200 eq.), CuI (13.4 mg, 0.0704 mmol, 0.0400 eq.) were added to a 100 mL flame dried round bottom flask, and was stirred for 15 minutes under N₂ at 50°C. 1-Propyne in THF (1.94 mL of a 1M solution, 1.94 mmol, 1.10 eq.) was then added in one portion and the reaction stirred under N₂ overnight. Post-reaction work up, the crude product was purified by flash column chromatography (100 mL of 100% hexanes, 400 mL of 2% ethyl acetate in hexanes) to give the pure product as a light yellow solid (221 mg, 1.13 mmol, 64% yield). The NMR data was consistent with previously reported spectra.⁷

¹H NMR (400 MHz, CDCl₃): δ 7.82 (s, 1H), 7.65 (t, *J* = 9.5 Hz, 2H), 7.41 (d, *J* = 8.6 Hz, 1H), 7.17 – 7.06 (m, 2H), 3.92 (s, 3H), 2.09 (s, 3H).



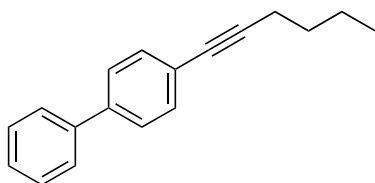
4-(1-pentyn-1-yl)-1,1'-biphenyl [9-SM]. Following general procedure D, triethylamine (18.0 mL), 4-iodo-1,1'-biphenyl (1.00 g, 3.57 mmol, 1.00 eq), Pd(PPh₃)₂Cl₂ (50.1 mg, 0.0714 mmol, 0.0200 eq.), CuI (27.2 mg, 0.143 mmol, 0.0400 eq.) were added to a 100 mL flame dried round bottom flask, and was stirred for 15 minutes under N₂ at room temperature. 1-pentyne (0.387 mL, 3.93 mmol, 1.10 eq.) was then added in one portion, the reaction was equipped with a cold finger condenser, and the reaction was heated to 100°C and stirred under N₂ overnight. Post-reaction work up, the crude product was purified by flash column chromatography (500 mL of 100% hexanes) to give the pure product as a yellow oil (649 mg, 2.95 mmol, 83% yield).

¹H NMR (400 MHz, CDCl₃): δ 7.60 (d, *J* = 7.2 Hz, 2H), 7.56 – 7.51 (m, 2H), 7.51 – 7.42 (m, 4H), 7.36 (t, *J* = 7.4 Hz, 1H), 2.43 (t, *J* = 7.1 Hz, 2H), 1.67 (sxt, *J* = 7.2 Hz, 2H), 1.08 (t, *J* = 7.4 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃): δ 140.60, 140.29, 132.07, 128.91, 127.55, 127.07, 126.98, 123.18, 91.10, 80.72, 22.37, 21.60, 13.70.

IR: 3045, 2957, 2867, 1690, 1580, 1482, 1005, 839.

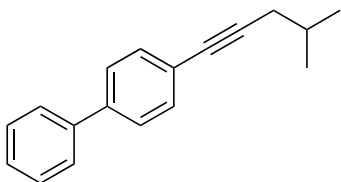
HRMS: (EI⁺) *m/z*: [M]⁺ Calcd for C₁₇H₁₆ 220.1252; Found 220.1247.



4-(1-hexyn-1-yl)-1,2-dimethyl-benzene [10-SM]. Following general procedure D, triethylamine (18.0 mL), 4-iodo-1,1'-biphenyl (1.00 g, 3.57 mmol, 1.00 eq), Pd(PPh₃)₂Cl₂ (50.1 mg, 0.0714 mmol, 0.0200 eq.), CuI (27.2 mg, 0.143 mmol, 0.0400 eq.) were added to a 100 mL flame dried round bottom flask, and was stirred for 15 minutes under N₂ at room temperature. 1-hexyne (0.451 mL, 3.93 mmol, 1.10 eq.) was then added in one portion, the reaction was stirred at room temperature under N₂ overnight. Post-reaction work up, the crude product was purified by flash column chromatography (500 mL of 100% hexanes) to give the pure

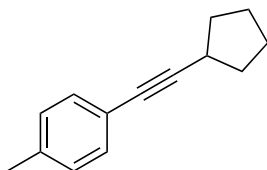
product as a yellow-orange oil (737 mg, 3.15 mmol, 88% yield). The NMR data was consistent with previously reported spectra.⁸

¹H NMR (300 MHz, CDCl₃): δ 7.59 (d, *J* = 7.1 Hz, 2H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.50 – 7.41 (m, 4H), 7.35 (t, *J* = 7.4 Hz, 1H), 2.45 (t, *J* = 7.0 Hz, 2H), 1.67 – 1.57 (m, 2H), 1.56 – 1.45 (m, 2H), 0.97 (t, *J* = 7.2 Hz, 3H).



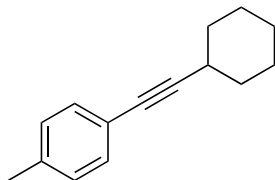
4-(4-methyl-1-pentyn-1-yl)-1,1'-biphenyl [11-SM]. Following general procedure D, triethylamine (10.0 mL), 4-iodo-1,1'-biphenyl (500 mg, 1.79 mmol, 1.00 eq), Pd(PPh₃)₂Cl₂ (25.1 mg, 0.0358 mmol, 0.0200 eq.), CuI (13.6 mg, 0.0716 mmol, 0.0400 eq.) were added to a 100 mL flame dried round bottom flask, and was stirred for 15 minutes under N₂ at room temperature. 4-methyl-1-pentyne (0.232 mL, 1.97 mmol, 1.10 eq.) was then added in one portion and the reaction stirred under N₂ overnight. Post-reaction work up, the crude product was purified by flash column chromatography (500 mL of 100% hexanes) to give the pure product as an orange oil (223 mg, 0.952 mmol, 53% yield). The NMR data was consistent with previously reported spectra.⁸

¹H NMR (400 MHz, CDCl₃): δ 7.59 (d, *J* = 7.4 Hz, 2H), 7.53 (d, *J* = 8.2 Hz, 2H), 7.50 – 7.40 (m, 4H), 7.35 (t, *J* = 7.6 Hz, 1H), 2.33 (d, *J* = 6.7 Hz, 2H), 1.93 (hep, *J* = 6.8 Hz, 1H), 1.06 (d, *J* = 6.7 Hz, 6H).



1-(cyclopentylethynyl)-4-methylbenzene [12-SM]. Following general procedure D, triethylamine (10.0 mL), 4-iodotoluene (1.22 g, 5.58 mmol, 1.05 eq), Pd(PPh₃)₂Cl₂ (37.3 mg, 0.0531 mmol, 0.0100 eq.), CuI (50.7 mg, 0.266 mmol, 0.0500 eq.) were added to a 100 mL flame dried round bottom flask, and was stirred for 15 minutes under N₂ at room temperature. Cyclopentylacetylene (0.616 mL, 5.31 mmol, 1.00 eq.) was then added in one portion, the reaction was refluxed at 60 °C N₂ overnight. Post-reaction work up, the crude product was purified by flash column chromatography (400 mL of 100% hexanes) to give the pure product as a clear colorless oil (867 mg, 4.70 mmol, 89% yield). The NMR data was consistent with previously reported spectra.⁹

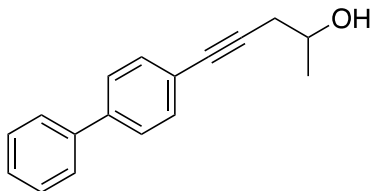
¹H NMR (400 MHz, CDCl₃): δ 7.28 (d, *J* = 8.3 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 2H), 2.81 (p, *J* = 7.5 Hz, 1H), 2.33 (s, 3H), 2.05 – 1.93 (m, 2H), 1.84 – 1.55 (m, 6H).



1-(cyclohexylethynyl)-4-methylbenzene [13-SM]. Following general procedure D, triethylamine (15.0 mL, 0.500 M), 4-iodotoluene (1.69 g, 7.77 mmol, 1.05 eq), Pd(PPh₃)₂Cl₂ (52.0 mg, 0.0740 mmol, 0.0100 eq.), CuI (70.5 mg, 0.370 mmol, 0.0500 eq.) were added to a 100 mL flame dried round bottom flask, and was stirred for 15 minutes under N₂ at room temperature. Cyclohexylacetylene (0.968 mL, 7.40 mmol, 1.00 eq.) was then added in one portion, the reaction was refluxed at 60 °C N₂ overnight. Post-reaction work up, the crude product was purified by flash column chromatography (400 mL of 100% hexanes) to give the pure

product as a clear colorless oil (1.41 g, 7.11 mmol, 96% yield). The NMR data was consistent with previously reported spectra.⁹

¹H NMR (400 MHz, CDCl₃): δ 7.30 (d, J = 8.0 Hz, 2H), 7.08 (d, J = 7.8 Hz, 2H), 2.62 – 2.53 (m, 1H), 2.33 (s, 3H), 1.93 – 1.84 (m, 2H), 1.81 – 1.70 (m, 2H), 1.60 – 1.47 (m, 3H), 1.42 – 1.28 (m, 3H).



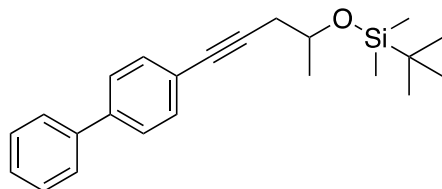
5-([1,1'-biphenyl]-4-yl)pent-4-yn-2-ol. Following general procedure D, triethylamine (9.00 mL), 4-iodo-1,1'-biphenyl (500 mg, 1.79 mmol, 1.00 eq.), Pd(PPh₃)₂Cl₂ (25.1 mg, 0.0358 mmol, 0.0200 eq.), CuI (17.0 mg, 0.0895 mmol, 0.0500 eq.) were added to a 25 mL flame dried Schlenk tube, and was stirred for 15 minutes under N₂. 4-pentyn-2-ol (0.186 mL, 1.97 mmol, 1.10 eq.) was then added in one portion, and the reaction stirred under N₂ at room temperature overnight. Post-reaction work up, the crude product was purified by flash column chromatography (500 mL of 10% ethyl acetate in hexanes, 250 mL of 20% ethyl acetate in hexanes) to give the pure product as a white solid (347 mg, 1.47 mmol, 82% yield).

¹H NMR (400 MHz, CDCl₃): δ 7.61 – 7.42 (m, 8H), 7.36 (t, J = 7.5 Hz, 1H), 4.07 (sxt, J = 6.2 Hz, 1H), 2.70 – 2.53 (m, 2H), 1.88 (br s, 1H), 1.35 (d, J = 6.3 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃): δ 140.84, 140.51, 132.21, 128.98, 127.72, 127.14, 127.10, 122.39, 86.92, 83.08, 66.72, 30.26, 22.58.

IR: 3306, 3029, 2978, 2932, 2212, 1447, 1093, 1073.

HRMS: (EI⁺) m/z : [M]⁺ Calcd for C₁₇H₁₆O 236.1201; Found 236.1195.



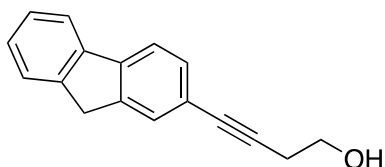
((5-([1,1'-biphenyl]-4-yl)pent-4-yn-2-yl)oxy)(tert-butyl)dimethylsilane [15-SM]. Following general procedure E, 5-([1,1'-biphenyl]-4-yl)pent-4-yn-2-ol (283 mg, 1.20 mmol, 1.00 eq.), dry DCM (6.00 mL), imidazole (163 mg, 2.40 mmol, 2.00 eq.), and *tert*-butyldimethylsilyl chloride (199 mg, 1.32 mmol, 1.10 eq.) were combined in a flame-dried round bottom flask. Post-reaction work up, the crude product was purified by flash column chromatography (100 mL 100% hexanes, 150 mL 1% ethyl acetate in hexanes) to give the pure product as a colorless solid (354 mg, 1.01 mmol, 84% yield).

¹H NMR (400 MHz, CDCl₃): δ 7.64 – 7.43 (m, 8H), 7.37 (t, J = 7.3 Hz, 1H), 4.11 (sxt, J = 6.1 Hz, 1H), 2.68 – 2.49 (m, 2H), 1.35 (d, J = 6.0 Hz, 3H), 0.97 (s, 9H), 0.17 (s, 3H), 0.15 (s, 3H).

¹³C NMR (75 MHz, CDCl₃): δ 140.60, 140.45, 132.08, 128.94, 127.61, 127.10, 127.01, 122.99, 88.63, 81.85, 68.03, 30.61, 25.99, 23.75, 18.29, -4.49, -4.51.

IR: 2927, 2855, 1470, 1387, 1248, 1187, 1096, 840, 771.

HRMS: (ESI⁺) m/z : [M+Na]⁺ Calcd for C₂₃H₃₀NaOSi 373.1966; Found 373.1958.



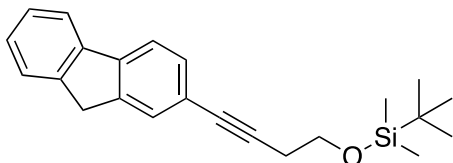
4-(9H-fluoren-2-yl)but-3-yn-1-ol. Following general procedure D, to a flame-dried round bottom flask under N₂ was added triethylamine (8.50 mL). The aryl iodide (0.500 g, 1.71 mmol, 1.00 eq.), Pd(PPh₃)₂Cl₂ (24.0 mg, 0.0342 mmol, 0.0200 eq.) and CuI (13.0 mg, 0.0684 mmol, 0.0400 eq.) were then sequentially added at room temperature. The mixture was stirred for 10 minutes followed by the addition of 3-butyn-1-ol (0.142 mL, 1.88 mmol, 1.10 eq.) and the reaction stirred under N₂ at room temperature overnight. Post-reaction work up, the crude product was purified by flash column chromatography (200 mL of hexanes, 200 mL of 5% ethyl acetate in hexanes, 200 mL of 10% ethyl acetate in hexanes, 500 mL of 15% ethyl acetate in hexanes) to give the pure product as an off-white solid (288 mg, 1.23 mmol, 72% yield).

¹H NMR (400 MHz, CDCl₃): δ 7.77 (d, *J* = 7.5 Hz, 1H), 7.71 (d, *J* = 7.8 Hz, 1H), 7.60 (s, 1H), 7.54 (d, *J* = 7.4 Hz, 1H), 7.44 (d, *J* = 7.9 Hz, 1H), 7.38 (t, *J* = 7.4 Hz, 1H), 7.31 (t, *J* = 7.1 Hz, 1H), 3.88 (s, 2H), 3.84 (t, *J* = 6.2 Hz, 2H), 2.73 (dd, *J* = 6.8, 5.4 Hz, 2H).

¹³C NMR (101 MHz, CDCl₃): δ 143.61, 143.27, 141.69, 141.22, 130.63, 128.39, 127.20, 127.02, 125.21, 121.45, 120.26, 119.84, 86.30, 83.30, 61.37, 36.84, 24.08.

IR: 3292, 3095, 2931, 2220, 1635, 1419, 1035, 835.

HRMS: (ESI⁺) *m/z*: [M+Na]⁺ Calcd for C₁₇H₁₄NaO 257.0945; Found 257.0936.



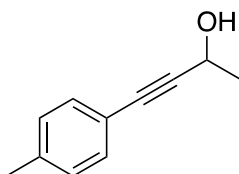
((4-(9H-fluoren-3-yl)but-3-yn-1-yl)oxy)(tert-butyl)dimethylsilane [16-SM]. Following general procedure E, to a flame-dried round bottom flask was added 4-(9H-fluoren-2-yl)but-3-yn-1-ol (288 mg, 1.23 mmol, 1.00 eq.), dry DCM (2.46 mL) followed by imidazole (167 mg, 2.46 mmol, 2.00 eq.) and *tert*-butyldimethylsilyl chloride (204 mg, 1.35 mmol, 1.10 eq.). The reaction was stirred at room temperature overnight. Post-reaction work up, the crude product was purified by flash column chromatography (200 mL of hexanes, 400 mL of 2.5% ethyl acetate in hexanes) to give the pure product as an off-white solid (418 mg, 1.20 mmol, 98% yield).

¹H NMR (400 MHz, CDCl₃): δ 7.76 (d, *J* = 7.5 Hz, 1H), 7.70 (d, *J* = 7.9 Hz, 1H), 7.58 (s, 1H), 7.54 (d, *J* = 7.4 Hz, 1H), 7.43 (d, *J* = 8.1 Hz, 1H), 7.38 (t, *J* = 7.3 Hz, 1H), 7.31 (t, *J* = 8.1, 7.4 Hz, 1H), 3.92 – 3.83 (m, 4H), 2.67 (t, *J* = 7.1 Hz, 2H), 0.94 (s, 9H), 0.13 (s, 6H).

¹³C NMR (101 MHz, CDCl₃): δ 143.59, 143.21, 141.41, 141.31, 130.54, 128.28, 127.08, 126.98, 125.17, 121.96, 120.19, 119.78, 87.17, 82.32, 62.19, 36.84, 26.07, 24.07, 18.53, -5.07.

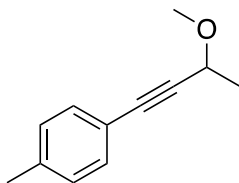
IR: 3050, 2953, 2205, 1590, 1420, 1250, 1093, 832, 731.

HRMS: (ESI⁺) *m/z*: [M+Na]⁺ Calcd for C₂₃H₂₈NaOSi 371.1809; Found 371.1804.



4-(4-methylphenyl)but-3-yn-2-ol. Following general procedure D, triethylamine (23.0 mL), 4-methyl-1-iodobenzene (1.00 g, 4.59 mmol, 1.00 eq.), Pd(PPh₃)₂Cl₂ (64.4 mg, 0.0918 mmol, 0.0200 eq.), CuI (44.7 mg, 0.230 mmol, 0.0500 eq.) were added to a 100 mL flame dried round bottom flask, and was stirred for 15 minutes under N₂. 3-Butyn-2-ol (0.396 mL, 5.05 mmol, 1.10 eq.) was then added in one portion and the reaction stirred at room temperature under N₂ overnight. Post-reaction work up, the crude product was purified by flash column chromatography (500 mL of 5% ethyl acetate in hexanes, 800 mL of 20% ethyl acetate in hexanes) to give the pure product as a pale yellow solid (609 mg, 3.80 mmol, 83% yield). The spectra were consistent with the previously reported data.¹⁰

¹H NMR (400 MHz, CDCl₃): δ 7.34 (d, *J* = 8.1 Hz, 2H), 7.08 (d, *J* = 8.2 Hz, 2H), 4.78 (q, *J* = 6.6 Hz, 1H), 3.35 (br s, 1H), 2.33 (s, 3H), 1.57 (d, *J* = 6.7 Hz, 3H)



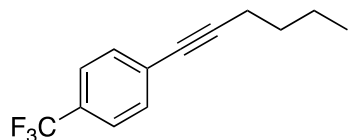
1-(3-methoxybut-1-yn-1-yl)-4-methylbenzene [17-SM]. To a flame dried 25 mL round bottom flask equipped with a magnetic stir bar was added 4-(4-methylphenyl)but-3-yn-2-ol (230 mg, 1.44 mmol, 1.00 eq.) and THF (5.00 mL). The solution was cooled to 0°C, and to this, NaH (60% dispersion in mineral oil, 69.2 mg, 1.73 mmol, 1.20 eq.) was added and stirred for 10 minutes before methyl iodide (0.269 mL, 4.32 mmol, 3.00 eq.) was added dropwise. Reaction progress was monitored by TLC. After 4 hours, reaction was quenched with water (5 mL) and diluted with 10 mL dichloromethane. The aqueous layer was extracted with dichloromethane (2 x 10 mL), and the combined organic fractions were washed with water (3 x 10 mL) and brine (1 x 10 mL), dried over Na₂SO₄, and the crude oil was purified by flash column chromatography (50 mL 100% hexanes, 100 mL 1% ethyl acetate in hexanes, 100 mL 1.5% ethyl acetate in hexanes) to give the pure product as a clear oil (217 mg, 1.25 mmol, 87% yield).

¹H NMR (300 MHz, CDCl₃): δ 7.34 (d, *J* = 8.1 Hz, 2H), 7.11 (d, *J* = 7.8 Hz, 2H), 4.30 (q, *J* = 6.6 Hz, 1H), 3.47 (s, 3H), 2.35 (s, 3H), 1.52 (d, *J* = 6.6 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃): δ 138.53, 131.74, 129.14, 119.77, 88.19, 85.35, 67.48, 56.47, 22.21, 21.59.

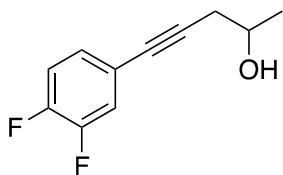
IR: 3029, 2986, 2934, 2819, 1509, 1114, 1098.

HRMS: (ESI⁺) *m/z*: [M+Na]⁺ Calcd for C₁₂H₁₄NaO 197.0945 Found 197.0937.



1-(1-Hexyn-1-yl)-4-(trifluoromethyl)benzene [18-SM]. Following general procedure D, triethylamine (9.00 mL), 4-iodobenzotrifluoride (500 mg, 1.84 mmol, 1.00 eq), Pd(PPh₃)₂Cl₂ (25.8 mg, 0.0368 mmol, 0.0200 eq.), CuI (14.2 mg, 0.0748 mmol, 0.0400 eq.) were added to a 100 mL flame dried round bottom flask, and was stirred for 15 minutes under N₂ at room temperature. 1-Hexyne (0.232 mL, 2.02 mmol, 1.10 eq.) was then added in one portion, the reaction was stirred at room temperature under N₂ overnight. Post-reaction work up, the crude product was purified by flash column chromatography (500 mL of 100% hexanes) to give the pure product as a clear colorless oil (228 mg, 1.01 mmol, 55% yield). The NMR data was consistent with previously reported spectra.¹¹

¹H NMR (300 MHz, CDCl₃): δ 7.56 – 7.42 (m, 4H), 2.43 (t, *J* = 6.9 Hz, 2H), 1.66 – 1.39 (m, 4H), 0.96 (t, *J* = 7.2 Hz, 3H).



5-(3,4-difluorophenyl)pent-4-yn-2-ol. Following general procedure D, triethylamine (10.0 mL), 1,2-difluoro-4-iodobenzene (500 mg, 2.08 mmol, 1.00 eq), Pd(PPh₃)₂Cl₂ (29.2 mg, 0.0416 mmol, 0.0200 eq.), CuI (19.8 mg, 0.104 mmol, 0.0500 eq.) were added to a 100 mL flame dried round bottom flask, and was stirred for 15 minutes under N₂ at room temperature. 4-Pentyn-2-ol (0.216 mL, 2.29 mmol, 1.10 eq.) was then added in one portion, the reaction was stirred at room temperature under N₂ overnight. Post-reaction work up, the crude product was purified by flash column chromatography (400 mL of 10% ethyl acetate in hexanes, 300 mL of 20% ethyl acetate in hexanes) to give the pure product as a brown oil (320 mg, 1.63 mmol, 78% yield).

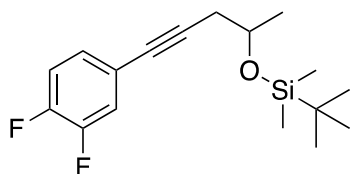
¹H NMR (400 MHz, CDCl₃): δ 7.21 (ddd, *J* = 10.9, 7.6, 2.0 Hz, 1H), 7.16 – 7.11 (m, 1H), 7.10 – 7.03 (m, 1H), 4.05 (h, *J* = 6.3, 5.2 Hz, 1H), 2.65 – 2.47 (m, 2H), 2.03 (s, 1H), 1.32 (d, *J* = 6.2 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃): δ 150.44 (dd, *J* = 250.6, 12.3 Hz), 150.02 (dd, *J* = 249.0, 12.7 Hz), 128.35 (dd, *J* = 6.3, 3.6 Hz), 120.71 (d, *J* = 18.3 Hz), 120.36 (dd, *J* = 7.8 Hz), 117.47 (dd, *J* = 17.6, 1.2 Hz), 87.06 (d, *J* = 1.7 Hz), 81.60 – 80.99 (m), 66.60, 29.96, 22.62.

¹⁹F NMR (376 MHz, CDCl₃): δ -136.41 – -137.01 (m, 1F), -137.45 (ddd, *J* = 21.4, 10.8, 7.9 Hz, 1F).

IR: 3464, 3076, 2980, 2930, 1719, 1610, 1084, 771.

HRMS: (EI⁺) *m/z*: [M]⁺ Calcd for C₁₁H₁₀OF₂ 196.0700; Found 196.0693.



tert-butyl((5-(3,4-difluorophenyl)pent-4-yn-2-yl)oxy)dimethylsilane [19-SM]. Following general procedure E, 5-(3,4-difluorophenyl)pent-4-yn-2-ol (0.295 g, 1.50 mmol, 1.00 eq.), dry DCM (5.00 mL), imidazole (204 mg, 3.00 mmol, 2.00 eq.), and *tert*-butyldimethylsilyl chloride (249 mg, 1.65 mmol, 1.10 eq.) were combined in a flame-dried round bottom flask. Post-reaction work up, the crude product was purified by flash column chromatography (200 mL of 2% ethyl acetate in hexanes) to give the pure product as a light yellow oil (364 mg, 1.17 mmol, 78% yield).

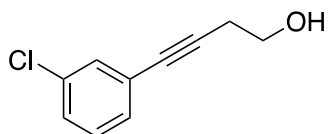
¹H NMR (400 MHz, CDCl₃): δ 7.18 (ddd, *J* = 11.0, 7.6, 1.8 Hz, 1H), 7.14 – 7.01 (m, 2H), 4.03 (h, *J* = 6.2 Hz, 1H), 2.59 – 2.40 (m, 2H), 1.27 (d, *J* = 6.1 Hz, 3H), 0.90 (d, *J* = 1.1 Hz, 9H), 0.09 (s, 6H).

¹³C NMR (101 MHz, CDCl₃): δ 150.27 (dd, *J* = 245.6, 8.0 Hz), 149.87 (dd, *J* = 246.8, 11.5 Hz), 128.17 (dd, *J* = 6.2, 3.5 Hz), 120.89 (dd, *J* = 7.8, 4.2 Hz), 120.68 – 120.43 (m), 117.51 – 117.26 (m), 88.65 (d, *J* = 1.7 Hz), 80.25 – 79.84 (m), 67.79, 30.39, 25.95, 23.73, 18.27, -4.49, -4.59.

¹⁹F NMR (376 MHz, CDCl₃): δ -137.08 – -137.30 (m, 1F), -137.66 (ddd, *J* = 21.5, 10.8, 7.7 Hz, 1F).

IR: 2963, 2930, 2858, 2888, 1597, 1514, 1258, 1170, 1098.

HRMS: (ESI⁺) *m/z*: [M+Na]⁺ Calcd for C₁₇H₂₄F₂NaOSi 333.1464; Found 333.1457.



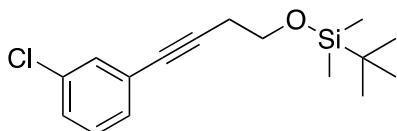
4-(3-chlorophenyl)but-3-yn-1-ol. Following general procedure D, triethylamine (10.5 mL), 3-Chloriodobenzene (501 mg, 2.10 mmol, 1.00 eq), Pd(PPh₃)₂Cl₂ (29.5 mg, 0.0420 mmol, 0.0200 eq.), CuI (16.0 mg, 0.0840 mmol, 0.0400 eq.) were added to a 100 mL flame dried round bottom flask, and was stirred for 15 minutes under N₂ at room temperature. 3-Butyn-1-ol (0.175 mL, 2.31 mmol, 1.10 eq.) was then added in one portion, the reaction was stirred at room temperature under N₂ overnight. Post-reaction work up, the crude product was purified by flash column chromatography (100 mL of 100% hexanes, 100 mL of 10% ethyl acetate in hexanes, 1000 mL of 15% ethyl acetate in hexanes) to give the pure product as a brown oil (365 mg, 2.02 mmol, 96% yield).

¹H NMR (400 MHz, CDCl₃): δ 7.40 (s, 1H), 7.32 – 7.18 (m, 3H), 3.82 (t, *J* = 6.3 Hz, 2H), 2.69 (t, *J* = 6.3 Hz, 2H), 1.97 – 1.80 (m, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 134.18, 131.72, 129.92, 129.60, 128.37, 125.18, 87.98, 81.23, 61.18, 23.89.

IR: 3348, 3061, 2949, 2884, 1721, 1592, 1038.

HRMS: (EI⁺) *m/z*: [M]⁺ Calcd for C₁₀H₉OCl 180.0342; Found 180.0335.



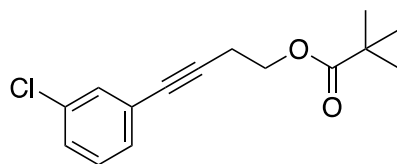
tert-butyl((4-(3-chlorophenyl)but-3-yn-1-yl)oxy)dimethylsilane [20-SM]. Following general procedure E, 4-(3-chlorophenyl)but-3-yn-1-ol (365 mg, 2.02 mmol, 1.00 eq.), dry dichloromethane (6.00 mL), imidazole (270 mg, 3.96 mmol, 2.00 eq.) and *tert*-butyldimethylsilyl chloride (329 mg, 2.18 mmol, 1.10 eq.) were added to a 100 mL flame dried round bottom flask. The crude product was purified by flash column chromatography (100 mL of 100% HPLC hexanes, 600 mL of 2% ethyl acetate in HPLC hexanes) to yield the title compound as a clear colorless oil (516 mg, 1.75 mmol, 87% yield).

¹H NMR (400 MHz, CDCl₃): δ 7.38 (s, 1H), 7.29 – 7.17 (m, 3H), 3.81 (t, *J* = 7.0 Hz, 2H), 2.62 (t, *J* = 7.1 Hz, 2H), 0.92 (s, 9H), 0.10 (s, 6H).

¹³C NMR (101 MHz, CDCl₃): δ 134.12, 131.63, 129.83, 129.53, 128.08, 125.66, 88.85, 80.43, 61.90, 26.03, 23.94, 18.49, -5.11.

IR: 3075, 2928, 2856, 1593, 1560, 1472, 1251, 1094.

HRMS: (ESI⁺) *m/z*: [M+Na]⁺ Calcd for C₁₆H₂₃ClNaOSi 317.1107; Found 317.1099.



4-(3-chlorophenyl)but-3-yn-1-yl pivalate [21-SM]. To an oven-dried round bottom flask, under N₂, equipped with a stir bar, was added 4-(3-chlorophenyl)but-3-yn-1-ol (757 mg, 4.19 mmol, 1.00 eq) and DCM (8.38 mL). The solution was cooled to 0 °C and Et₃N (0.818 mL, 5.87 mmol, 1.40 eq) was added, followed by 4-dimethylaminopyridine (51.2 mg, 0.419 mmol, 0.100 eq). Then, pivaloyl chloride (0.671 mL, 5.45 mmol, 1.30 eq) was added dropwise. The reaction was allowed to stir for 18 h at room temperature. Upon completion, the reaction was quenched with NaHCO₃ (10 mL). Then extracted with DCM (20 mL). The

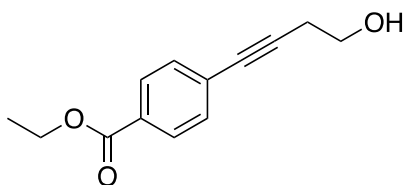
organic layer was then washed with 0.1 M HCl (10 mL) and brine (10 mL). The organic layer was then dried over Na₂SO₄. Solvent was removed by rotary evaporation, and the crude product was dry loaded onto a column, and purified by flash column chromatography (200 mL of hexanes, 200 mL of 2.5% ethyl acetate in hexanes, 200 mL of 3% ethyl acetate in hexanes, 200 mL of 5% ethyl acetate in hexanes, 200 mL of 7.5% ethyl acetate in hexanes, and 200 mL of 10% ethyl acetate in hexanes). The title compound was afforded as a yellow oil (674 mg, 2.55 mmol, 61% yield).

¹H NMR (400 MHz, CDCl₃): δ 7.40 – 7.35 (m, 1H), 7.32 – 7.18 (m, 3H), 4.24 (t, *J* = 6.7 Hz, 2H), 2.74 (t, *J* = 6.7 Hz, 2H), 1.22 (s, 9H).

¹³C NMR (101 MHz, CDCl₃): 190.45, 134.19, 131.64, 129.88, 129.60, 128.33, 125.29, 87.21, 80.72, 62.06, 38.93, 27.31, 20.05.

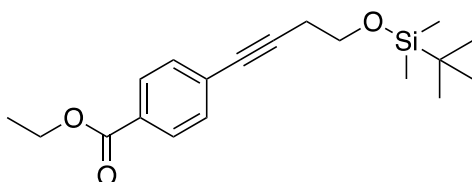
IR: 3080, 2971, 1727, 1593, 1561, 1476, 1281, 1143.

HRMS: (ESI⁺) *m/z*: [M+Na]⁺ Calcd for C₁₅H₁₇ClNaO₂ 287.0817; Found 287.0809.



Ethyl 4-(4-hydroxybut-1-yn-1-yl)benzoate. Following general procedure D, triethylamine (18.0 mL), ethyl 4-iodobenzoate (1.00 g, 3.62 mmol, 1.00 eq), Pd(PPh₃)₂Cl₂ (50.8 mg, 0.0724 mmol, 0.0200 eq.), CuI (27.6 mg, 0.145 mmol, 0.0400 eq.) were added to a 100 mL flame dried round bottom flask, and was stirred for 15 minutes under N₂ at room temperature. 3-Butyn-1-ol (0.301 mL, 3.98 mmol, 1.10 eq.) was then added in one portion, the reaction was stirred at room temperature under N₂ overnight. Post-reaction work up, the crude product was purified by flash column chromatography (100 mL of 100% hexanes, 100 mL of 10% ethyl acetate in hexanes, 100 mL of 20% ethyl acetate in hexanes, 100 mL of 25% ethyl acetate in hexanes, 350 mL of 30% ethyl acetate in hexanes) to give the pure product as a brown oil (707 mg, 3.24 mmol, 90% yield). The NMR data was consistent with previously reported spectra.¹²

¹H NMR (400 MHz, CDCl₃): δ 7.94 (d, *J* = 8.2 Hz, 2H), 7.43 (d, *J* = 8.0 Hz, 2H), 4.34 (q, *J* = 7.1 Hz, 2H), 3.81 (t, *J* = 6.3 Hz, 2H), 2.69 (t, *J* = 6.4 Hz, 2H), 1.37 (t, *J* = 7.2 Hz, 3H). Hydrogen on alcohol not detected.



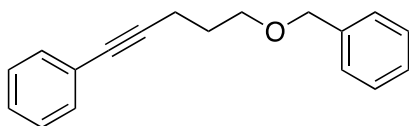
Ethyl 4-(4-((tert-butyldimethylsilyl)oxy)but-1-yn-1-yl)benzoate [22-SM]. According to the general procedure E, ethyl 4-(4-hydroxybut-1-yn-1-yl)benzoate (406 mg, 1.86 mmol, 1.00 eq.), dry dichloromethane (6.20 mL), imidazole (253 mg, 3.72 mmol, 2.00 eq.) and *tert*-butyldimethylsilyl chloride (309 mg, 2.05 mmol, 1.10 eq.) were combined. The crude product was purified by flash column chromatography (100 mL of 100% HPLC hexanes, 350 mL of 3% ethyl acetate in HPLC hexanes) to yield the title compound as a clear colorless oil (615 mg, 1.85 mmol, 99% yield).

¹H NMR (400 MHz, CDCl₃): δ 7.96 (d, *J* = 8.3 Hz, 2H), 7.44 (d, *J* = 8.1 Hz, 2H), 4.37 (q, *J* = 7.2 Hz, 2H), 3.83 (t, *J* = 7.0 Hz, 2H), 2.65 (t, *J* = 7.0 Hz, 2H), 1.39 (t, *J* = 7.2 Hz, 3H), 0.91 (s, 9H), 0.10 (s, 6H).

¹³C NMR (101 MHz, CDCl₃): δ 166.30, 131.59, 129.51, 128.59 (2 overlapping carbon signals), 90.79, 81.22, 61.87, 61.19, 26.03, 24.07, 18.50, 14.46, -5.11.

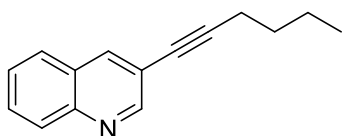
IR: 2928, 2856, 1717, 1606, 1472, 1269, 1094.

HRMS: (ESI⁺) *m/z*: [M+Na]⁺ Calcd for C₁₉H₂₈NaO₃Si 355.1708; Found 355.1700.



(5-(benzyloxy)pent-1-yn-1-yl)benzene [24-SM]. Following a previously reported procedure¹³, 5-phenyl-4-pentyn-1-ol (800 mg, 4.99 mmol, 1.00 eq), sodium hydride (200 mg, 4.99 mmol, 1.00 eq), benzyl bromide (0.593 mL, 4.99 mmol, 1.00 eq), THF (5.14 mL) were combined to form the desired product as a yellow oil (746 mg, 2.98 mmol, 60% yield). The NMR data was consistent with previously reported spectra.¹⁴

¹H NMR (400 MHz, CDCl₃): δ 7.42 – 7.32 (m, 6H), 7.32 – 7.25 (m, 4H), 4.55 (s, 2H), 3.64 (t, *J* = 6.2 Hz, 2H), 2.55 (t, *J* = 7.0 Hz, 2H), 1.92 (p, *J* = 6.6 Hz, 2H).



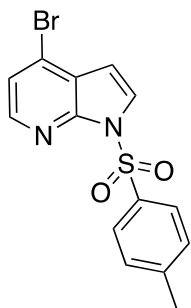
3-(1-hexyn-1-yl)-quinoline [25-SM]. Following general procedure D, triethylamine (24.0 mL), 3-bromo-quinoline (999 mg, 4.80 mmol, 1.00 eq), Pd(PPh₃)₂Cl₂ (67.4 mg, 0.096 mmol, 0.0200 eq.), CuI (36.6 mg, 0.192 mmol, 0.0400 eq.) were added to a 100 mL flame dried round bottom flask, and was stirred for 15 minutes under N₂ at room temperature. 1-Hexyne (0.606 mL, 5.28 mmol, 1.10 eq.) was then added in one portion, the reaction was equipped with a cold finger condenser, and the reaction was heated to 100°C and stirred under N₂ overnight. Post-reaction work up, the crude product was purified by flash column chromatography (500 mL of 100% hexanes, 300 mL of 6% ethyl acetate in hexanes, 500 mL of 8% ethyl acetate in hexanes, 300 mL of 10% ethyl acetate in hexanes) to give the pure product as a red oil (934 mg, 4.46 mmol, 93% yield).

¹H NMR (400 MHz, CDCl₃): δ 8.87 (d, *J* = 2.1 Hz, 1H), 8.15 (d, *J* = 2.1 Hz, 1H), 8.06 (d, *J* = 8.5 Hz, 1H), 7.74 (d, *J* = 8.2 Hz, 1H), 7.71 – 7.64 (m, 1H), 7.57 – 7.49 (m, 1H), 2.48 (t, *J* = 7.1 Hz, 2H), 1.70 – 1.58 (m, 2H), 1.58 – 1.45 (m, 2H), 0.97 (t, *J* = 7.3 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃): δ 152.43, 146.46, 137.78, 129.49, 129.26, 127.33, 127.27, 126.98, 118.20, 94.00, 77.92, 30.63, 22.02, 19.19, 13.61.

IR: 3075, 2956, 2931, 1596, 1566, 1344, 749.

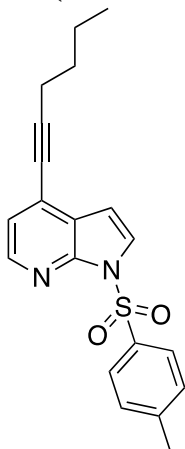
HRMS: (ESI⁺) *m/z*: [M+Na]⁺ Calcd for C₁₅H₁₅NNa 232.1104; Found 232.1097.



4-Bromo-1-tosyl-1H-pyrrolo[2,3-b]pyridine. Following a previously reported procedure¹⁵, 3-bromo-1H-pyrrolo[2,3-b]pyridine (1.00 g, 5.10 mmol, 1.00 eq), THF (36.0 mL), NaH (60% dispersion in mineral oil, 245 mg, 6.12 mmol, 1.20 eq.), and *p*-toluenesulfonyl chloride (1.26 g, 6.63 mmol, 1.30 eq) were reacted and purified by column chromatography (100 mL 100% hexanes, 200 mL 5% ethyl acetate in hexanes, 800 mL

10% ethyl acetate in hexanes) to afford the title compound as a white solid (1.50 g, 4.27 mmol, 84% yield). The spectra matched previously reported data.¹⁵

¹H NMR (400 MHz, CDCl₃): δ 8.24 (d, *J* = 5.2 Hz, 1H), 8.10 (d, *J* = 8.4 Hz, 2H), 7.81 (d, *J* = 4.0 Hz, 1H), 7.32 (d, *J* = 5.2 Hz, 1H), 7.29 – 7.19 (m, 2H), 6.61 (d, *J* = 4.0 Hz, 1H), 2.31 (s, 3H).



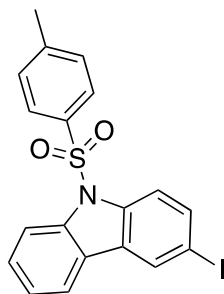
1-Tosyl-4-hexyn-1H-pyrrolo[2,3-b]pyridine [26-SM]. Following general procedure D, triethylamine (7.00 mL), 4-Bromo-1-tosyl-1H-pyrrolo[2,3-b]pyridine (500 mg, 1.42 mmol, 1.00 eq), Pd(PPh₃)₂Cl₂ (20.0 mg, 0.0284 mmol, 0.0200 eq.), CuI (10.8 mg, 0.0568 mmol, 0.0400 eq.) were added to a 100 mL flame dried round bottom flask, and was stirred for 15 minutes under N₂ at room temperature. 1-Hexyne (0.179 mL, 1.56 mmol, 1.100 eq.) was then added in one portion, the reaction was equipped with a cold finger condenser, and the reaction stirred at 100°C under N₂ overnight. Post-reaction work up, the crude product was purified by flash column chromatography (100 mL of 100% hexanes, 100 mL of 2% ethyl acetate in hexanes, 300 mL of 5% ethyl acetate in hexanes, and 300 mL of 10% ethyl acetate in hexanes) to give the pure product as an dark oil (395 mg, 1.12 mmol, 79% yield).

¹H NMR (400 MHz, CDCl₃): δ 8.32 (d, *J* = 5.1 Hz, 1H), 8.03 (d, *J* = 8.3 Hz, 2H), 7.71 (d, *J* = 4.0 Hz, 1H), 7.29 – 7.19 (m, 2H), 7.12 (d, *J* = 5.1 Hz, 1H), 6.69 (d, *J* = 4.0 Hz, 1H), 2.48 (t, *J* = 7.0 Hz, 2H), 2.36 (s, 3H), 1.67 – 1.56 (m, 2H), 1.56 – 1.42 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃): δ 147.24, 145.29, 144.68, 135.39, 129.71, 128.04, 126.46, 125.60, 124.15, 121.06, 104.92, 99.05, 76.59, 30.57, 22.06, 21.69, 19.41, 13.67.

IR: 3098, 2931, 2871, 1583, 1513, 1261, 1145.

HRMS: (ESI⁺) *m/z*: [M+Na]⁺ Calcd for C₂₀H₂₀N₂NaO₂S 375.1145; Found 375.1138.



3-iodo-9-((4-methylphenyl)sulfonyl)-9H-carbazole. To a flame dried 100 mL round bottom flask equipped with a magnetic stir bar was added 3-iodo-9H-carbazole (2.00 g, 6.82 mmol, 1.00 eq.) and THF (50.0 mL). The solution was cooled to 0°C, and to this, NaH (60% dispersion in mineral oil, 355 mg, 8.87 mmol, 1.30 eq.) was added and stirred for 10 minutes before *p*-toluenesulfonyl chloride (1.94 g, 10.2 mmol, 1.50 eq.) was added and left to stir overnight. Reaction was quenched with water (50 mL) and diluted with 50 mL

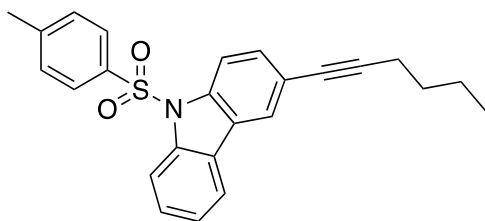
ethyl acetate. The organic layer was washed with water (3 x 30 mL) and brine (1 x 20 mL), dried over Na₂SO₄, and the crude solid was purified by flash column chromatography (500 mL 5% ethyl acetate in hexanes, 1000 mL 10% ethyl acetate in hexanes), to give the product as a white solid (2.60 g, 5.81 mmol, 85% yield).

¹H NMR (400 MHz, CDCl₃): δ 8.31 (d, *J* = 8.5 Hz, 1H), 8.21 (d, *J* = 1.8 Hz, 1H), 8.10 (d, *J* = 8.8 Hz, 1H), 7.84 (d, *J* = 7.7 Hz, 1H), 7.75 (dd, *J* = 8.8, 1.8 Hz, 1H), 7.67 (d, *J* = 8.5 Hz, 2H), 7.55 – 7.48 (m, 1H), 7.40 – 7.34 (m, 1H), 7.11 (d, *J* = 8.0 Hz, 2H), 2.27 (s, 3H).

¹³C NMR (101 MHz, CDCl₃): δ 145.31, 138.54, 137.91, 135.94, 134.80, 129.91, 129.12, 128.81, 128.24, 126.60, 125.08, 124.32, 120.28, 117.13, 115.29, 87.89, 21.67.

IR: 3059, 2922, 2788, 1594, 1434, 1364, 1202, 1166, 1156, 1011, 1088, 984

HRMS: (ESI⁺) *m/z*: [M+Na]⁺ Calcd for C₁₉H₁₄INNaO₂S 469.9690; Found 469.9686.



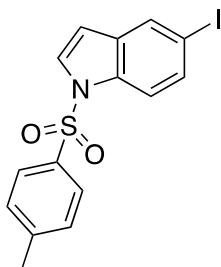
3-(hex-1-yn-1-yl)-9-((4-methylphenyl)sulfonyl)-9H-carbazole [27-SM]. Following general procedure D, triethylamine (5.50 mL), 3-iodo-9-((4-methylphenyl)sulfonyl)-9H-carbazole (500 mg, 1.12 mmol, 1.00 eq.), Pd(PPh₃)₂Cl₂ (15.7 mg, 0.0224 mmol, 0.0200 eq.), CuI (10.7 mg, 0.0560 mmol, 0.0500 eq.) were added to a 25 mL flame dried Schlenk tube, and was stirred for 15 minutes under N₂. 1-Hexyne (0.141 mL, 1.23 mmol, 1.10 eq.) was then added in one portion, and the reaction stirred at room temperature under N₂ overnight. The crude product was purified by flash column chromatography (1000 mL of 10% ethyl acetate in hexanes, followed by trituration with *n*-pentane to afford the product as a tan solid (0.370 g, 0.922 mmol, 82% yield).

¹H NMR (400 MHz, CDCl₃): δ 8.31 (d, *J* = 8.3 Hz, 1H), 8.25 (d, *J* = 8.7 Hz, 1H), 7.93 (s, 1H), 7.86 (d, *J* = 7.7 Hz, 1H), 7.67 (d, *J* = 8.3 Hz, 2H), 7.55 – 7.46 (m, 2H), 7.35 (t, *J* = 7.5 Hz, 1H), 7.08 (d, *J* = 8.3 Hz, 2H), 2.45 (t, *J* = 7.0 Hz, 2H), 2.25 (s, 3H), 1.67 – 1.57 (m, 2H), 1.56 – 1.45 (m, 2H), 0.97 (t, *J* = 7.3 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃): δ 145.13, 138.84, 137.57, 134.88, 130.94, 129.81, 127.80, 126.58 (2 overlapping carbon signals), 126.03, 124.19, 123.23, 120.21, 119.87, 115.33, 115.17, 90.39, 80.39, 31.00, 22.19, 21.63, 19.26, 13.81.

IR: 2923, 2854, 1597, 1443, 1307, 1187, 1173, 1132, 1019, 969

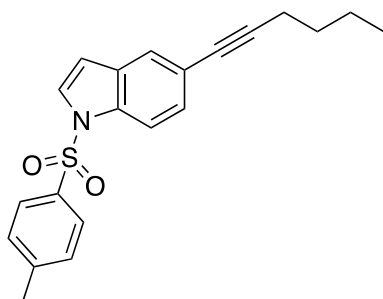
HRMS: (ESI⁺) *m/z*: [M+Na]⁺ Calcd for C₂₅H₂₃NNaO₂S 424.1349 Found 424.1342.



5-(iodo)-1-((4-methylphenyl)sulfonyl)-1H-indole. To a flame dried 100 mL round bottom flask equipped with a magnetic stir bar was added 5-iodo-1H-indole (2.00 g, 8.23 mmol, 1.00 eq.) and THF (60.0 mL). The solution was cooled to 0°C, and to this, NaH (60% dispersion in mineral oil, 428 mg, 10.7 mmol, 1.30 eq.)

was added and stirred for 10 minutes before *p*-toluenesulfonyl chloride (2.34 g, 12.3 mmol, 1.50 eq.) was added and left to stir overnight. Reaction was quenched with water (50 mL) and diluted with 50 mL ethyl acetate. The organic layer was washed with water (3 x 40 mL) and brine (1 x 30 mL), dried over Na₂SO₄, and the crude solid was purified by flash column chromatography (500 mL 5% ethyl acetate in hexanes, 500 mL 10% ethyl acetate in hexanes, 500 mL 20% ethyl acetate in hexanes), to give the product as a brown solid (2.10 g, 5.29 mmol, 64% yield). The spectra were consistent with previously reported data.¹⁶

¹H NMR (400 MHz, CDCl₃): δ 7.88 – 7.86 (m, 1H), 7.78 – 7.70 (m, 3H), 7.57 (dd, *J* = 8.8, 1.8 Hz, 1H), 7.54 – 7.50 (m, 1H), 7.25 – 7.20 (m, 2H), 6.59 – 6.56 (m, 1H), 2.35 (s, 3H).



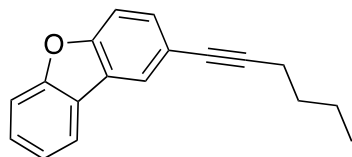
5-(hex-1-yn-1-yl)-1-((4-methylphenyl)sulfonyl)-1H-indole [28-SM]. Following general procedure D, triethylamine (7.00 mL), 5-(iodo)-1-((4-methylphenyl)sulfonyl)-1H-indole (500 mg, 1.26 mmol, 1.00 eq.), Pd(PPh₃)₂Cl₂ (17.7 mg, 0.0252 mmol, 0.0200 eq.), CuI (12.0 mg, 0.0630 mmol, 0.0500 eq.) were added to a 25 mL flame dried Schlenk tube, and was stirred for 15 minutes under N₂. 1-Hexyne (0.160 mL, 1.39 mmol, 1.10 eq.) was then added in one portion and the reaction stirred at room temperature under N₂ overnight. The crude product was purified by flash column chromatography (50 mL 100% hexanes, 100 mL 4% ethyl acetate in hexanes, 100 mL 8% ethyl acetate in hexanes, 100 mL 10% ethyl acetate in hexanes) to give the pure product as an orange oil (427 mg, 1.21 mmol, 96% yield).

¹H NMR (400 MHz, CDCl₃): δ 7.89 (d, *J* = 8.6 Hz, 1H), 7.73 (d, *J* = 8.3 Hz, 2H), 7.58 – 7.51 (m, 2H), 7.33 (d, *J* = 8.7 Hz, 1H), 7.20 (d, *J* = 8.1 Hz, 2H), 6.59 (d, *J* = 3.6 Hz, 1H), 2.40 (t, *J* = 7.0 Hz, 2H), 2.33 (s, 3H), 1.63 – 1.53 (m, 2H), 1.47 (h, *J* = 7.0 Hz, 2H), 0.94 (t, *J* = 7.3 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃): δ 145.19, 135.21, 134.02, 130.84, 130.01, 128.22, 127.17, 126.88, 124.68, 119.28, 113.54, 109.02, 89.64, 80.59, 31.00, 22.13, 21.68, 19.21, 13.78.

IR: 3143, 2955, 2930, 2860, 1596, 1455, 1370, 1286, 1234, 1173, 1158, 1124, 993, 811, 666.

HRMS (ESI⁺) *m/z*: [M+Na]⁺ Calcd for C₂₁H₂₁NNaO₂S 374.1193; Found 374.1185.



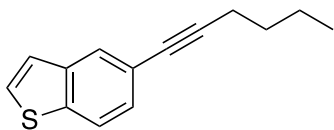
2-(hex-1-yn-1-yl)dibenzo[b,d]furan [29-SM]. Following general procedure D, triethylamine (8.00 mL), 2-iododibenzo[b,d]furan (500 mg, 1.70 mmol, 1.00 eq.), Pd(PPh₃)₂Cl₂ (23.9 mg, 0.0340 mmol, 0.0200 eq.), CuI (16.2 mg, 0.0850 mmol, 0.0500 eq.) were added to a 25 mL flame dried Schlenk tube, and was stirred for 15 minutes under N₂. 1-Hexyne (0.215 mL, 1.87 mmol, 1.10 eq.) was then added in one portion, and the reaction stirred at room temperature under N₂ overnight. The crude product was purified by flash column chromatography (250 mL of 1% ethyl acetate in hexanes, 250 mL of 2% ethyl acetate in hexanes) to give the pure product as a yellow oil (300 mg, 1.21 mmol, 71% yield).

¹H NMR (400 MHz, CDCl₃): δ 8.00 (s, 1H), 7.92 (d, *J* = 7.7 Hz, 1H), 7.56 (d, *J* = 8.3 Hz, 1H), 7.53 – 7.42 (m, 3H), 7.35 (t, *J* = 7.5 Hz, 1H), 2.46 (t, *J* = 7.0 Hz, 2H), 1.70 – 1.58 (m, 2H), 1.58 – 1.45 (m, 2H), 0.98 (t, *J* = 7.3 Hz, 3H).

¹³C NMR (75 MHz, CDCl₃): 156.67, 155.50, 130.90, 127.58, 124.43, 124.02, 123.88, 123.05, 120.88, 118.76, 111.88, 111.71, 89.48, 80.58, 31.07, 22.22, 19.27, 13.84.

IR: 2957, 2929, 2871, 2858, 1590, 1448, 1474, 1192, 1178, 1116, 815.

HRMS: (EI⁺) m/z: [M]⁺ Calcd for C₁₈H₁₆O 248.1201; Found 248.1196.



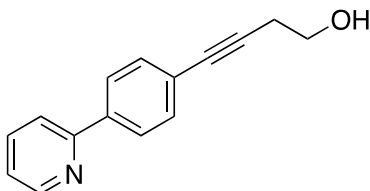
5-(hex-1-yn-1-yl)benzo[b]thiophene [30-SM]. Following general procedure D, triethylamine (10.0 mL), 5-iodo-1-benzothiophene (530 mg, 2.04 mmol, 1.00 eq), Pd(PPh₃)₂Cl₂ (28.6 mg, 0.0408 mmol, 0.0200 eq.), CuI (15.5 mg, 0.0816 mmol, 0.0400 eq.) were added to a 100 mL flame dried round bottom flask, and was stirred for 15 minutes under N₂ at room temperature. 1-Hexyne (0.257 mL, 2.24 mmol, 1.10 eq.) was then added in one portion, the reaction was stirred at room temperature under N₂ overnight. Post-reaction work up, the crude product was purified by flash column chromatography (850 mL of 100% hexanes) to give the pure product as a brown oil (345 mg, 1.61 mmol, 79% yield).

¹H NMR (400 MHz, CDCl₃): δ 7.89 – 7.87 (m, 1H), 7.78 (d, *J* = 8.1 Hz, 1H), 7.44 (d, *J* = 5.5 Hz, 1H), 7.37 (d, *J* = 8.3 Hz, 1H), 7.28 (d, *J* = 5.5 Hz, 1H), 2.45 (t, *J* = 7.0 Hz, 2H), 1.67 – 1.58 (m, 2H), 1.58 – 1.46 (m, 2H), 0.98 (t, *J* = 7.3 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃): δ 139.65, 138.97, 127.60, 127.19, 126.83, 123.73, 122.36, 120.13, 89.99, 80.79, 31.02, 22.18, 19.29, 13.82.

IR: 3075, 2955, 2929, 2859, 1597, 1539, 1436.

HRMS: (EI⁺) m/z: [M]⁺ Calcd for C₁₄H₁₄S 214.0816; Found 214.0808.



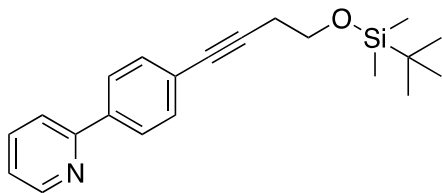
4-(4-(pyridin-2-yl)phenyl)but-3-yn-1-ol. Following general procedure D, triethylamine (22.0 mL), 2-(4-iodophenyl)pyridine (1.20 g, 4.27 mmol, 1.00 eq.), Pd(PPh₃)₂Cl₂ (59.9 mg, 0.0854 mmol, 0.0200 eq.) and CuI (32.6 mg, 0.171 mmol, 0.0400 eq.) were added to a 100 mL flame dried round bottom flask at room temperature and this was stirred for 15 minutes. 3-Butyn-1-ol (0.356 mL, 4.70 mmol, 1.10 eq.) was then added in one portion and the reaction was stirred at room temperature overnight. Post-reaction work up, the crude product was purified by flash column chromatography (200 mL of hexanes, 200 mL of 5% ethyl acetate in hexanes, 200 mL of 10% ethyl acetate in hexanes, 200 mL of 15% ethyl acetate in hexanes, 200 mL of 17% ethyl acetate in hexanes, 200 mL of 30% ethyl acetate in hexanes, 200 mL of 40% ethyl acetate in hexanes, 500 mL of 50% ethyl acetate in hexanes) to give the pure product as a red oil (318 mg, 1.42 mmol, 33% yield).

¹H NMR (300 MHz, CDCl₃): δ 8.67 (d, *J* = 5.2 Hz, 1H), 7.92 (d, *J* = 8.4 Hz, 2H), 7.78 – 7.61 (m, 2H), 7.50 (d, *J* = 8.3 Hz, 2H), 7.25 – 7.14 (m, 1H), 3.81 (t, *J* = 5.8 Hz, 2H), 2.69 (t, *J* = 6.4 Hz, 2H), 2.56 (br s, 1H).

¹³C NMR (75 MHz, CDCl₃): δ 156.71, 149.81, 138.77, 136.97, 131.56, 126.82, 124.12, 122.44, 120.70, 88.00, 82.34, 61.21, 24.03.

IR: 3262, 3081, 3039, 2952, 2932, 2901, 2853, 1590, 1470, 1289, 1052, 784.

HRMS: (ESI⁺) *m/z*: [M+Na]⁺ Calcd for C₁₅H₁₃NNaO 246.0897; Found 246.0888.



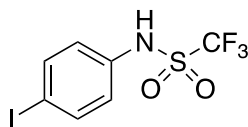
2-(4-(4-((*tert*-butyldimethylsilyl)oxy)but-1-yn-1-yl)phenyl)pyridine [31-SM]. Following general procedure E, to a flame-dried round bottom flask was added 4-(4-(pyridin-2-yl)phenyl)but-3-yn-1-ol (318 mg, 1.42 mmol, 1.00 eq.), dry DCM (2.85 mL) followed by imidazole (193 mg, 2.84 mmol, 2.00 eq.) and *tert*-butyldimethylsilyl chloride (235 mg, 1.56 mmol, 1.10 eq.). The reaction was stirred at room temperature overnight and post-reaction work up, the crude product was purified by flash column chromatography (200 mL of hexanes, 500 mL of 5% ethyl acetate in hexanes) to give the pure product as a yellow oil (218 mg, 0.646 mmol, 45% yield).

¹H NMR (600 MHz, CDCl₃): δ 8.66 (d, *J* = 4.8 Hz, 1H), 7.92 (d, *J* = 8.5 Hz, 2H), 7.72 – 7.62 (m, 2H), 7.49 (d, *J* = 8.5 Hz, 2H), 7.19 – 7.14 (m, 1H), 3.83 (t, *J* = 7.0 Hz, 2H), 2.65 (t, *J* = 7.0 Hz, 2H), 0.92 (s, 9H), 0.10 (s, 6H).

¹³C NMR (75 MHz, CDCl₃): δ 156.64, 149.73, 138.49, 136.78, 132.01, 126.69, 124.48, 121.52, 120.46, 88.70, 81.55, 61.96, 25.97, 23.99, 18.41, -5.17.

IR: 2955, 2925, 2859, 1586, 1467, 1247, 1092, 775.

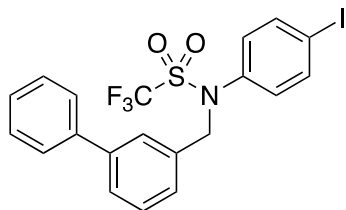
HRMS: (ESI⁺) *m/z*: [M+Na]⁺ Calcd for C₂₁H₂₇NNaOSi 360.1762; Found 360.1753.



1,1,1-trifluoro-*N*-(4-iodophenyl)methanesulfonamide

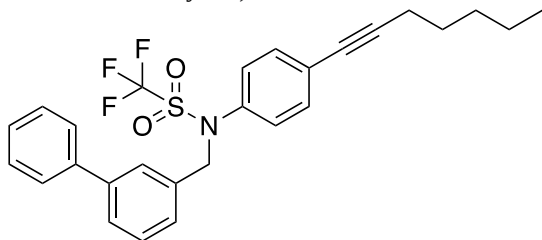
In a 100 mL flame dried round bottom flask equipped with a Teflon stir bar was added 4-iodoaniline (1.10 g, 5.02 mmol, 1.00 eq), Et₃N (1.05 mL, 7.53 mmol, 1.50 eq), and DCM (10.0 mL). The reaction mixture was cooled to 0 °C and stirred for 5 minutes. Trifluoromethanesulfonic anhydride (0.99 mL, 6.02 mmol, 1.20 eq) was then added dropwise to the reaction mixture. The reaction mixture was stirred at room temperature under nitrogen overnight. Upon reaction completion, monitored by TLC, the reaction was quenched with brine (15 mL), extracted with DCM (3 x 30 mL), and the combined organic layers were dried over anhydrous Na₂SO₄. The mixture was filtered and the solvent was removed by rotary evaporation. The crude product was wet loaded onto a silica gel column and purified by silica gel flash column chromatography (1000 mL of 50% DCM in hexane) to give the desired compound as a white crystal (697 mg, 1.99 mmol, 40% yield). Spectra matches previously reported data.¹⁷

¹H NMR (400 MHz, CDCl₃): δ 7.87 (d, *J* = 8.8 Hz, 2H), 7.12 (d, *J* = 8.5 Hz, 2H).



***N*-([1,1'-biphenyl]-3-ylmethyl)-1,1,1-trifluoro-*N*-(4-iodophenyl)methanesulfonamide.**

In an oven-dried 20 mL vial equipped with a Teflon stir bar and a pressure relief cap was added 1,1,1-trifluoro-*N*-(4-iodophenyl)methanesulfonamide (527 mg, 1.50 mmol, 1.00 eq), 3-(bromomethyl)-1,1'-biphenyl (445 mg, 1.80 mmol, 1.20 eq), K₂CO₃ (249 mg, 1.80 mmol, 1.20 eq), and DMF (2.70 mL). The reaction was heated to 65 °C in an oil bath under nitrogen overnight. Upon reaction completion, the reaction mixture was cooled to room temperature and diluted with DI water (15 mL), extracted with ethyl acetate (3 x 30 mL), and the combined organic layers were washed with DI water (30 mL) and brine (50 mL) and then dried over anhydrous Na₂SO₄. The mixture was filtered, and the solvent was removed by rotary evaporation. The crude product was afforded as a pink oil and taken forward without further characterization (681 mg, 1.32 mmol, 88% yield).



***N*-([1,1'-biphenyl]-3-ylmethyl)-1,1,1-trifluoro-*N*-(4-(hept-1-yn-1-yl)phenyl)methanesulfonamide [32-SM].** Following general procedure D, triethylamine (6.50 mL), *N*-([1,1'-biphenyl]-3-ylmethyl)-1,1,1-trifluoro-*N*-(4-iodophenyl)methanesulfonamide (673 mg, 1.30 mmol, 1.00 eq), Pd(PPh₃)₂Cl₂ (18.2 mg, 0.0260 mmol, 0.0200 eq), and CuI (9.90 mg, 0.0520 mmol, 0.0400 eq) were added to an oven dried 20 mL vial equipped with a teflon stir bar and a pressure relief cap at room temperature, and this was stirred and heated to 40 °C for 15 minutes. 1-Heptyne (163 μ L, 1.24 mmol, 0.954 eq) was then added dropwise and the reaction mixture was stirred at 40 °C overnight. Upon reaction completion, monitored by TLC, the crude product was purified by silica gel flash column chromatography (250 mL of 5% ethyl acetate in hexane and 250 mL of 10% ethyl acetate in hexane). The collected product was then purified again by flash C18-reverse phase column chromatography (stationary: C₁₈ silica, elution: 150 mL of 100% methanol) to give the desired compound as a colorless oil (484 mg, 0.997 mmol, 77% yield).

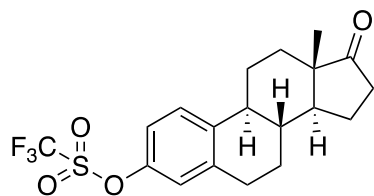
¹H NMR (400 MHz, CDCl₃): δ 7.52 – 7.44 (m, 3H), 7.44 – 7.35 (m, 3H), 7.36 – 7.28 (m, 4H), 7.16 – 7.08 (m, 3H), 4.93 (s, 2H), 2.36 (t, *J* = 7.1 Hz, 2H), 1.58 (p, *J* = 7.0 Hz, 2H), 1.46 – 1.27 (m, 4H), 0.91 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (101 MHz, CDCl₃): δ 141.73, 140.43, 135.49, 134.69, 132.61, 129.28, 129.22, 128.93, 127.86, 127.73, 127.67, 127.41, 127.14, 125.50, 120.60 (q, *J* = 324.0 Hz), 92.89, 79.46, 57.28, 31.16, 28.36, 22.29, 19.41, 14.05.

¹⁹F NMR (376 MHz, Chloroform-*d*) δ -73.55.

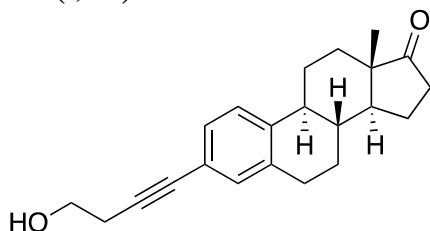
IR: 3061, 3036, 2957, 2933, 2860, 1394, 1195, 1145

HRMS: (ESI⁺) *m/z*: [M+H]⁺ Calcd for C₂₇H₂₇F₃NO₂S 486.1716; Found 486.1708.



(8R,9S,13S,14S)-13-Methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[*a*]phenanthren-3-yl trifluoromethanesulfonate. Synthesized according to a previously reported procedure³ to afford the pure white solid product (1.30 g, 3.23 mmol, 88% yield). The spectra for the title compound matched the previously reported spectra.³

¹H NMR (400 MHz, CDCl₃): δ 7.34 (d, *J* = 8.7 Hz, 1H), 7.08 – 6.96 (m, 2H), 3.00 – 2.89 (m, 2H), 2.52 (dd, *J* = 27.7, 8.6 Hz, 1H), 2.46 – 2.37 (m, 1H), 2.37 – 2.23 (m, 1H), 2.23 – 1.94 (m, 4H), 1.71 – 1.40 (m, 6H), 0.92 (s, 3H).



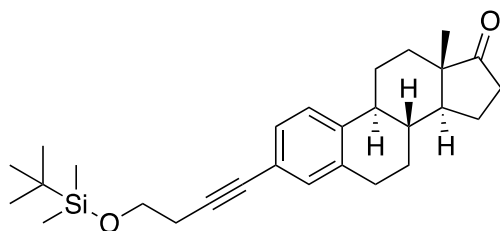
(8R,9S,13S,14S)-3-(4-hydroxybut-1-yn-1-yl)-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17H-cyclopenta[a]phenanthren-17-one. In a 100 mL oven dried round bottom flask equipped with a Teflon stir bar was added (8R,9S,13S,14S)-13-Methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yl trifluoromethanesulfonate (1.40 g, 3.47 mmol, 1.00 eq.), DMF (42.0 mL), Pd(PPh₃)₄ (401 mg, 0.347 mmol, 0.100 eq.), CuI (66.1 mg, 0.347 mmol, 0.100 eq.), and ⁱPr₂NH (1.47 mL, 10.4 mmol, 3.00 eq.). The reaction mixture was degassed with N₂ for 20 minutes, followed by addition of 3-butyn-1-ol (0.315 mL, 4.16 mmol, 1.20 eq.). Using a condenser, the reaction was heated to reflux in an oil bath for 19 hours. The reaction progress was monitored by TLC. Upon completion, reaction was diluted with Et₂O, washed with brine (3 x 10 mL), dried over Na₂SO₄, and concentrated under vacuum. The crude product was dry loaded onto a column, and purified by flash column chromatography (200 mL of hexanes, 200 mL of 5% ethyl acetate in hexanes, 200 mL 10% ethyl acetate in hexanes, 200 mL of 12% ethyl acetate in hexanes, 200 mL of 15% ethyl acetate in hexanes, 200 mL of 17% ethyl acetate in hexanes, 200 mL of 25% ethyl acetate in hexanes, and 600 mL of 50% ethyl acetate in hexanes) to afford as a yellow solid (742 mg, 2.30 mmol, 66% yield).

¹H NMR (300 MHz, CDCl₃): δ 7.28 (s, 1H), 7.25 – 7.17 (m, 2H), 3.83 (q, *J* = 6.3 Hz, 2H), 2.94 – 2.85 (m, 2H), 2.71 (t, *J* = 6.2 Hz, 2H), 2.53 (dd, *J* = 18.3, 8.4 Hz, 1H), 2.48 – 2.38 (m, 1H), 2.38 – 2.26 (m, 1H), 2.24 – 1.93 (m, 4H), 1.84 (t, *J* = 6.4 Hz, 1H), 1.73 – 1.37 (m, 6H), 0.93 (s, 3H).

¹³C NMR (101 MHz, CDCl₃): δ 220.98, 140.02, 136.66, 132.29, 129.09, 125.46, 120.73, 85.66, 82.66, 61.34, 50.61, 48.09, 44.54, 38.10, 35.98, 31.67, 29.21, 26.47, 25.71, 24.01, 21.71, 13.97.

IR: 2952, 2927, 2856, 1737, 1595, 1469, 1248, 1098, 774.

HRMS: (ESI⁺) *m/z*: [M+Na]⁺ Calcd for C₂₂H₂₆NaO₂ 345.1833; Found 345.1824.



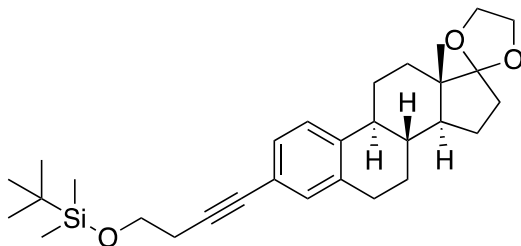
(8R,9S,13S,14S)-3-(4-((tert-butyldimethylsilyl)oxy)but-1-yn-1-yl)-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17H-cyclopenta[a]phenanthren-17-one. To a flame-dried round bottom flask was added (8R,9S,13S,14S)-3-(4-hydroxybut-1-yn-1-yl)-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17H-cyclopenta[a]phenanthren-17-one (742 mg, 2.30 mmol, 1.00 eq.), dry DCM (4.60 mL) followed by imidazole (313 mg, 4.60 mmol, 2.00 eq.) and *tert*-butyldimethylsilyl chloride (381 mg, 2.53 mmol, 1.10 eq.). The reaction was stirred at room temperature overnight. Upon completion, the reaction mixture was quenched with water (20 mL) and extracted with diethyl ether (2 x 15 mL). The combined organic layers were washed with brine (15 mL) and dried over anhydrous Na₂SO₄. The mixture was filtered, and the solvent was removed by rotary evaporation. Crude product was dry loaded onto a column, and the pure product was purified by flash column chromatography (200 mL of hexanes, 200 mL of 2% ethyl acetate in hexanes, and 400 mL of 4% ethyl acetate in hexanes), the title compound was afforded as a white solid (596 mg, 1.36 mmol, 59% yield).

¹H NMR (400 MHz, CDCl₃): δ 7.23 – 7.12 (m, 3H), 3.80 (t, *J* = 7.1 Hz, 2H), 2.90 – 2.82 (m, 2H), 2.61 (t, *J* = 7.1 Hz, 2H), 2.51 (dd, *J* = 18.8, 8.7 Hz, 1H), 2.44 – 2.34 (m, 1H), 2.33 – 2.23 (m, 1H), 2.21 – 1.92 (m, 4H), 1.69 – 1.34 (m, 6H), 0.93 – 0.89 (m, 12H), 0.10 (s, 6H).

¹³C NMR (75 MHz, CDCl₃): δ 220.91, 139.67, 136.54, 132.19, 129.03, 125.38, 121.24, 86.53, 81.63, 62.18, 50.64, 48.09, 44.55, 38.13, 35.98, 31.70, 29.23, 26.51, 26.06, 25.72, 24.00, 21.72, 18.51, 13.97, -5.08.

IR: 2952, 2361, 1737, 1595, 1469, 1248, 1098, 774.

HRMS: (ESI⁺) *m/z*: [M+Na]⁺ Calcd for C₂₈H₄₀NaO₂Si 459.2698; Found 459.2696.



tert-butyltrimethylsilyl((4-((8*R*,9*S*,13*S*,14*S*)-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydrospiro[cyclopenta[*a*]phenanthren-17,2'-[1,3]dioxolan]-3-yl)but-3-yn-1-yl)oxy)silane [33-SM].

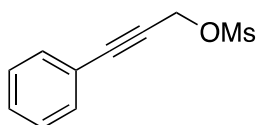
To a 100 mL round bottom flask equipped with a Teflon stir bar was added (8*R*,9*S*,13*S*,14*S*)-3-(4-((*tert*-butyltrimethylsilyl)oxy)but-1-yn-1-yl)-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta[*a*]phenanthren-17-one (596 mg, 1.36 mmol, 1.00 eq.), *p*-TsOH·H₂O (23.6 mg, 0.124 mmol, 0.0910 eq.), ethylene glycol (1.52 mL, 27.2 mmol, 20.0 eq.), and benzene (9.00 mL). The reaction flask was fitted with a condenser equipped with a Dean Stark trap for the removal of water, and heated to reflux in an oil bath. Progress was monitored by TLC, and upon completion, reaction was poured into 10 mL of water, and extracted with DCM (3 x 10 mL). The combined organic layers were washed with water (10 mL), brine (10 mL), and dried over Na₂SO₄. Solvent was removed by rotary evaporation, and the crude product was dry loaded onto a column, and purified by flash column chromatography (200 mL of hexanes, 200 mL of 1% ethyl acetate in hexanes, 200 mL of 2% ethyl acetate in hexanes, and 500 mL of 3% ethyl acetate in hexanes) to give the pure product as a white solid (451 mg, 0.938 mmol, 69% yield).

¹H NMR (400 MHz, CDCl₃): δ 7.23 – 7.10 (m, 3H), 4.00 – 3.86 (m, 4H), 3.80 (t, *J* = 7.1 Hz, 2H), 2.85 – 2.75 (m, 2H), 2.61 (t, *J* = 7.1 Hz, 2H), 2.36 – 2.19 (m, 2H), 2.08 – 1.97 (m, 1H), 1.94 – 1.71 (m, 4H), 1.68 – 1.23 (m, 6H), 0.91 (s, 9H), 0.88 (s, 3H), 0.09 (s, 6H).

¹³C NMR (75 MHz, CDCl₃): δ 140.43, 136.84, 132.16, 128.84, 125.39, 120.92, 119.53, 86.26, 81.78, 65.41, 64.74, 62.22, 49.60, 46.25, 44.23, 38.82, 34.36, 30.84, 29.37, 26.96, 26.07, 25.95, 24.01, 22.50, 18.52, 14.46, -5.08.

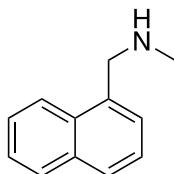
IR: 2980, 2883, 1600, 1469, 1383, 1087, 836.

HRMS: (ESI⁺) *m/z*: [M+Na]⁺ Calcd for C₃₀H₄₄NaO₃Si 503.2960; Found 503.2960.



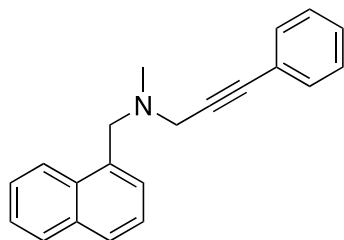
3-Phenylprop-2-yn-1-yl methanesulfonate. Following a previously reported procedure¹⁸, in an oven-dried 50 mL round bottom flask equipped with a Teflon stir bar was added 3-phenylprop-2-yn-1-ol (502 mg, 3.80 mmol, 1.00 eq), Et₃N (0.800 mL, 5.70 mmol, 1.50 eq), and THF (15.0 mL). The reaction mixture was cooled to 0 °C and stirred for 10 min. Methanesulfonyl chloride (0.353 mL, 4.56 mmol, 1.20 eq) was then added

dropwise to the reaction mixture. The reaction mixture was stirred at room temperature under nitrogen for 30 mins. Upon reaction completion, monitored by TLC, the reaction mixture was quenched with brine (20 mL), extracted with ethyl acetate (3 x 30 mL), and the combined organic layers were washed with 2 M HCl (50 mL), DI water (50 mL), saturated NaHCO₃ solution (50 mL), and brine (50 mL). The organic layers were dried over Na₂SO₄. The mixture was filtered, and the solvent was removed by rotary evaporation. The crude product was taken forward without further purification.



***N*-methyl-1-(naphthalen-1-yl)methanamine.** According to a previously reported procedure¹⁹, in an oven-dried 50 mL round bottom flask equipped with a Teflon stir bar was added 1-naphthaldehyde (2.34 g, 15.0 mmol, 1.00 eq) and MeOH (30 mL). The methylamine solution (7.5 mL of a 2 M in THF solution, 15.0 mmol, 1.00 eq) was then added dropwise over 3 h via a syringe. After the addition of methylamine was complete, NaBH₄ (284 mg, 7.50 mmol, 0.500 eq) was added to reaction mixture and the reaction mixture was heated to 40°C overnight. Upon reaction completion, the solvent was removed by rotary evaporation to afford the crude product which was purified by flash column chromatography (1000 mL of 25% MeOH in DCM) to give the desired compound as a yellow oil (1.64 g, 9.58 mmol, 64%). Spectra matched previously reported data.²⁰

¹H NMR (400 MHz, CDCl₃): δ 8.13 (d, *J* = 8.3 Hz, 1H), 7.87 (d, *J* = 8.1 Hz, 1H), 7.78 (d, *J* = 7.8 Hz, 1H), 7.57 – 7.40 (m, 4H), 4.21 (s, 2H), 2.56 (s, 3H), 1.55 (s, 1H).



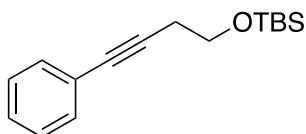
***N*-methyl-*N*-(naphthalen-1-ylmethyl)-3-phenylprop-2-yn-1-amine [34-SM].** In an oven-dried 20 mL vial equipped with a Teflon stir bar and a pressure relief cap was added Cs₂CO₃ (4.07 g, 12.5 mmol, 5.00 eq), *N*-methyl-1-(naphthalen-1-yl)methanamine (428 mg, 2.50 mmol, 1.00 eq) in acetonitrile (3.80 mL), and 3-phenylprop-2-yn-1-yl methanesulfonate (553 mg, 2.63 mmol, 1.05 eq) in acetonitrile (3.80 mL). The reaction mixture was stirred at 70°C overnight and upon reaction completion, monitored by TLC, the reaction mixture was diluted with DI water (15 mL), extracted with ethyl acetate (3 x 15 mL), and the combined organic layers were washed with brine (50 mL) and dried over anhydrous Na₂SO₄. The mixture was filtered and the solvent was removed by rotary evaporation. The crude product was dry loaded onto a silica gel column and the product was purified by silica gel flash column chromatography (200 mL of 5% ethyl acetate in hexane, 200 mL of 10% ethyl acetate in hexane, 200 mL of 15% ethyl acetate in hexane) to give the desired compound as an orange oil (444 mg, 1.55 mmol, 62%).

¹H NMR (300 MHz, CDCl₃): δ 8.37 (d, *J* = 8.1 Hz, 1H), 7.86 (dd, *J* = 17.6, 7.8 Hz, 2H), 7.62 – 7.31 (m, 9H), 4.10 (s, 2H), 3.59 (s, 2H), 2.50 (s, 3H).

¹³C NMR (101 MHz, CDCl₃): δ 134.41, 134.01, 132.73, 131.87, 128.55, 128.45, 128.32, 128.17, 127.86, 126.14, 125.76, 125.27, 124.78, 123.48, 86.05, 84.68, 58.36, 46.00, 42.34.

IR: 3044, 2939, 2835, 2791, 1597, 1122.

HRMS: (ESI⁺) *m/z*: [M+H]⁺ Calcd for C₂₁H₂₀N 286.1597; Found 286.1585.



Tert-butyldimethyl((4-phenylbut-3-yn-1-yl)oxy)silane [35-SM]. According to the general procedure E, 4-phenylbut-3-yn-1-ol (1.27 g, 8.68 mmol, 1.00 eq.), dry dichloromethane (18.0 mL), imidazole (1.18 g, 17.36 mmol, 2.00 eq.) and *tert*-butyldimethylsilyl chloride (1.44 g, 9.55 mmol, 1.10 eq.) were combined. The crude product was purified by flash column chromatography (200 mL of 100% hexanes, 800 mL of 3% ethyl acetate in hexanes) to yield the desired compound as a clear colorless oil (1.68 g, 6.45 mmol, 74% yield).

¹H NMR (400 MHz, CDCl₃):

δ 7.45 – 7.39 (m, 2H), 7.32 – 7.27 (m, 3H), 3.85 (t, *J* = 7.1 Hz, 2H), 2.65 (t, *J* = 7.1 Hz, 2H), 0.95 (s, 9H), 0.13 (s, 6H).

¹³C NMR (101 MHz, CDCl₃): δ 131.70, 128.31, 127.77, 123.91, 87.30, 81.69, 62.09, 26.04, 23.97, 18.49, -5.11.

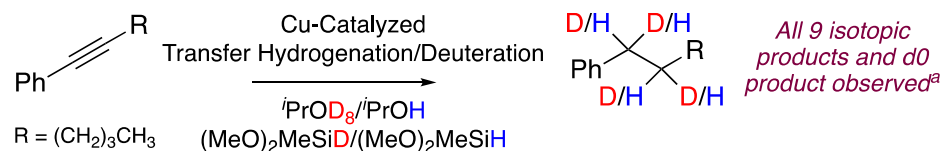
IR: 3081, 2954, 2928, 2856, 1100

HRMS: (ESI⁺) *m/z*: [M+H]⁺ Calcd for C₁₆H₂₅OSi 261.1676; Found 261.1669.

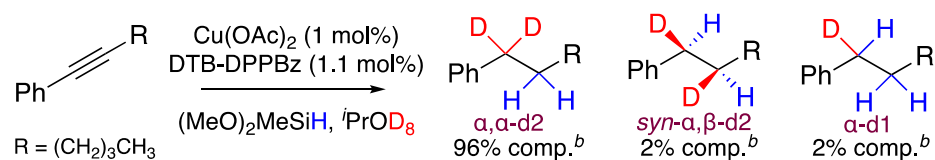
Analysis by Molecular Rotational Resonance

Scheme S5. Analysis by Molecular Rotational Resonance

a) Alkyne Reduction to Access All Possible Isotopic Species



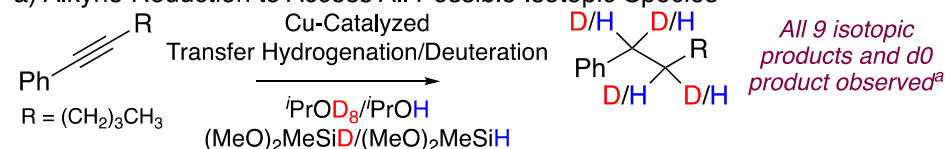
b) Regioselective Transfer Hydrodeuteration Reaction Measured by MRR



^aSee SI for all isotopic products ^bDenotes the average percent composition of isolated product from two runs

Scheme S5a)

a) Alkyne Reduction to Access All Possible Isotopic Species



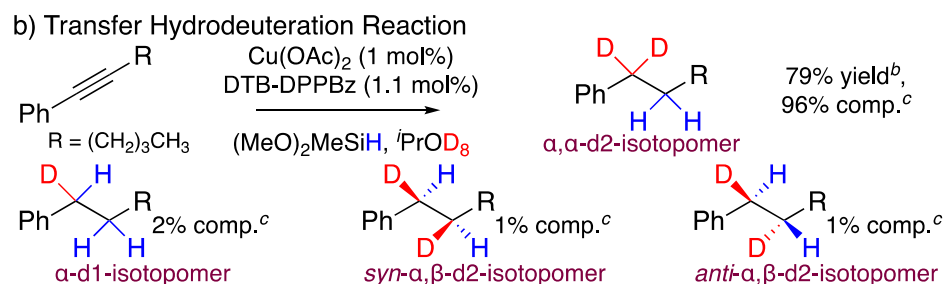
In a N₂ filled glovebox, DTB-DPPBz (62.2 mg, 0.0695 mmol, 0.0220 eq.), Cu(OAc)₂ (316 μL of a 0.200 M solution in THF, 0.0632 mmol, 0.0200 eq.), and THF (1.42 mL) were added to a flame-dried 100 mL round

bottom flask followed by dropwise addition of dimethoxy(methyl)silane (974 μL , 7.90 mmol, 2.50 eq.) and dimethoxy(methyl)silane-*d* (1.47 mL of a 5.36 M solution in hexanes, 7.90 mmol, 2.50 eq.). A color change from green/blue to brown was observed while stirring for 15 minutes. In a separate oven-dried 2-dram vial was added 1-phenyl-1-hexyne (500 mg, 3.16 mmol, 1.00 eq.), THF (1.42 mL), 2-propanol (605 μL , 7.90 mmol, 2.50 eq), and 2-propanol-*d*₈ (605 μL , 7.90 mmol, 2.50 eq). The solution in the 2-dram vial was added dropwise over 20 seconds to the 100 mL round bottom flask. The total volume of THF was calculated based on having a final reaction concentration of 1M based on the alkene substrate. The 100 mL round bottom flask was capped with a septum, taken out of the glovebox, and a balloon filled with N₂ was inserted through the septum as the reaction stirred for 24 h at 40°C. Upon completion, the crude product mixture was dry loaded onto a silica gel column and purified by flash column chromatography using 100% hexanes to give the product as a clear oil (437 mg, 2.66 mmol, 84% yield). Since the product contains a mixture of d₀, d₁ and d₂ isotopologues and isotopomers, isolated yields were calculated based on an average deuterium incorporation of two deuterium.

¹H NMR (400 MHz, CDCl₃): 7.32 – 7.27 (m, 2H), 7.24 – 7.17 (m, 3H), 2.66 – 2.57 (m, 0.92H), 1.68 – 1.54 (m, 1.24H), 1.41 – 1.27 (m, 6H), 0.95 – 0.87 (m, 3H).

²H NMR (61 MHz, CDCl₃): δ 2.63 (s, 1.08D), 1.65 (s, 0.85D).

Scheme S5b)

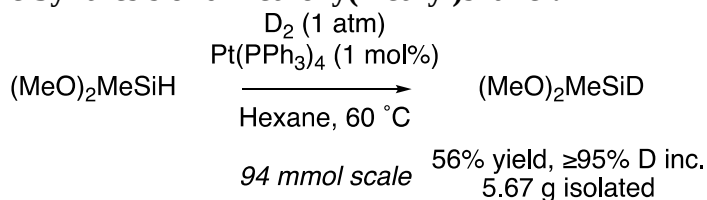


D₂-Hexyl-benzene [5b-MRR]. According to the general procedure C, DTB-DPPBz (4.00 mg, 0.00440 mmol, 0.0110 eq.), Cu(OAc)₂ (20.0 μL of a 0.200 M solution in THF, 0.00400 mmol, 0.0100 eq.), THF (0.180 mL) and dimethoxy(methyl)silane (247 μL , 2.00 mmol, 5.00 eq.) were combined in a 2-dram vial followed by addition of a solution of 1-hexyn-1-yl-benzene **4b** (63.3 mg, 0.400 mmol, 1.00 eq.), THF (0.200 mL), and 2-propanol-*d*₈ (153 μL , 2.00 mmol, 5.00 eq). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 23 h at 40 °C. Upon completion, the crude product mixture was dry loaded onto a silica gel column. Purification using silica gel flash column chromatography (250 mL of 100% hexanes) gives the pure product as a clear colorless oil (52.0 mg, 0.317 mmol, 79% yield).

¹H NMR (400 MHz, CDCl₃): δ 7.34 – 7.27 (m, 2H), 7.25 – 7.16 (m, 3H), 2.66 – 2.57 (m, 0.04H), 1.69 – 1.57 (m, 2H), 1.41 – 1.26 (m, 6H), 0.98 – 0.85 (m, 3H).

²H NMR (61 MHz, CDCl₃): δ 2.62 (s, 1.96D), 1.65 (s, 0.02D).

Procedure for the Synthesis of dimethoxy(methyl)silane-*d*



The procedure was adapted from a previously reported method.²¹ To an oven-dried 500 mL Schlenk flask equipped with a Teflon stir bar in a N₂ filled glovebox was added the Pt(PPh₃)₄ (1.17 g, 0.941 mmol, 0.0100 eq.), dimethoxy(methyl)silane (11.6 mL, 94.1 mmol, 1.00 eq.), and 5.00 mL of degassed anhydrous hexanes. The Schlenk flask was sealed with a rubber septa and removed from the glovebox, connected to a manifold line, and cooled to -78 °C. A single freeze-pump-thaw cycle was performed, and the Schlenk flask was backfilled with D₂ gas from a D₂ purged balloon at room temperature. The flask was sealed with parafilm and heated to 60 °C. After 2 hours, the reaction was cooled to room temperature and then a single freeze-pump-thaw was performed again, backfilling with D₂ gas. The process was repeated 6 times or until the ¹H NMR showed ≥95% D incorporation. It is important to maintain a N₂ (g) inert atmosphere while obtaining a minimal quantity of sample for ¹H NMR analysis. The solution was purified through a distillation apparatus; the set up consisted of a flame-dried 25 mL round-bottom receiving flask and a cannula. The 25 mL round-bottom receiving flask was flame-dried, and then filled with N₂. Once the receiving flask reached room temperature, the cannula was inserted, maintaining positive pressure, and tightly sealed with parafilm to prevent condensation from entering. Upon confirmation of positive N₂ flow, the open end of the cannula was inserted into the Schlenk reaction flask. The 25 mL round-bottom receiving flask was cooled to -78 °C and closed to the manifold line, and then the Schlenk flask was heated to 80 °C. The heat initiated the distillation of the dimethoxy(methyl)silane-d and the hexane through the cannula which were trapped in the cold 25 mL round-bottom receiving flask. Vacuum was also applied to the 25 mL round-bottom receiving flask to promote this process. Once all of the silane and hexane were trapped in the 25 mL round-bottom receiving flask, the flask was removed from the heat and the manifold was closed to vacuum line while the 25 mL round-bottom receiving flask warmed to room temperature. Under positive nitrogen flow, the cannula was removed from the 25 mL round-bottom receiving flask, while keeping it inserted in the Schlenk reaction flask. The 25 mL round-bottom receiving flask was tightly sealed with Parafilm, and stored in the -4 °C freezer. The final product was in a solution of hexane, and the molarity was calculated by ¹H NMR using 1,3,5-trimethylbenzene as an internal standard, and used for the transfer deuteration reactions (5.67 g in a 5.29 M hexane solution, 52.9 mmol, 56% yield).

*Note: it is important to monitor that the end of the cannula does not get clogged by frozen solvent/silane. If this occurs, remove the Schlenk reaction flask from heat and close manifold to vacuum line. Warm the 25 mL round-bottom receiving flask until the solids on the tip of the cannula melt, and then distillation can be resumed.

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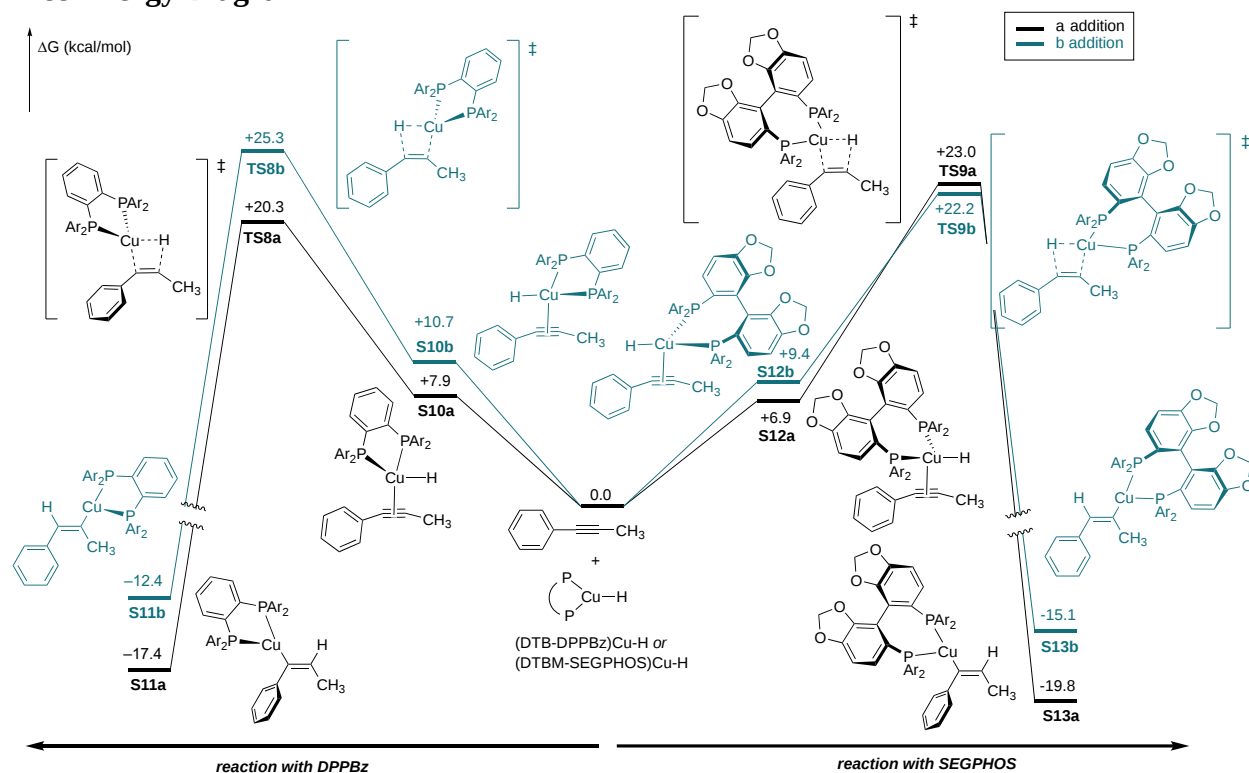
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Computational Details

General Methods

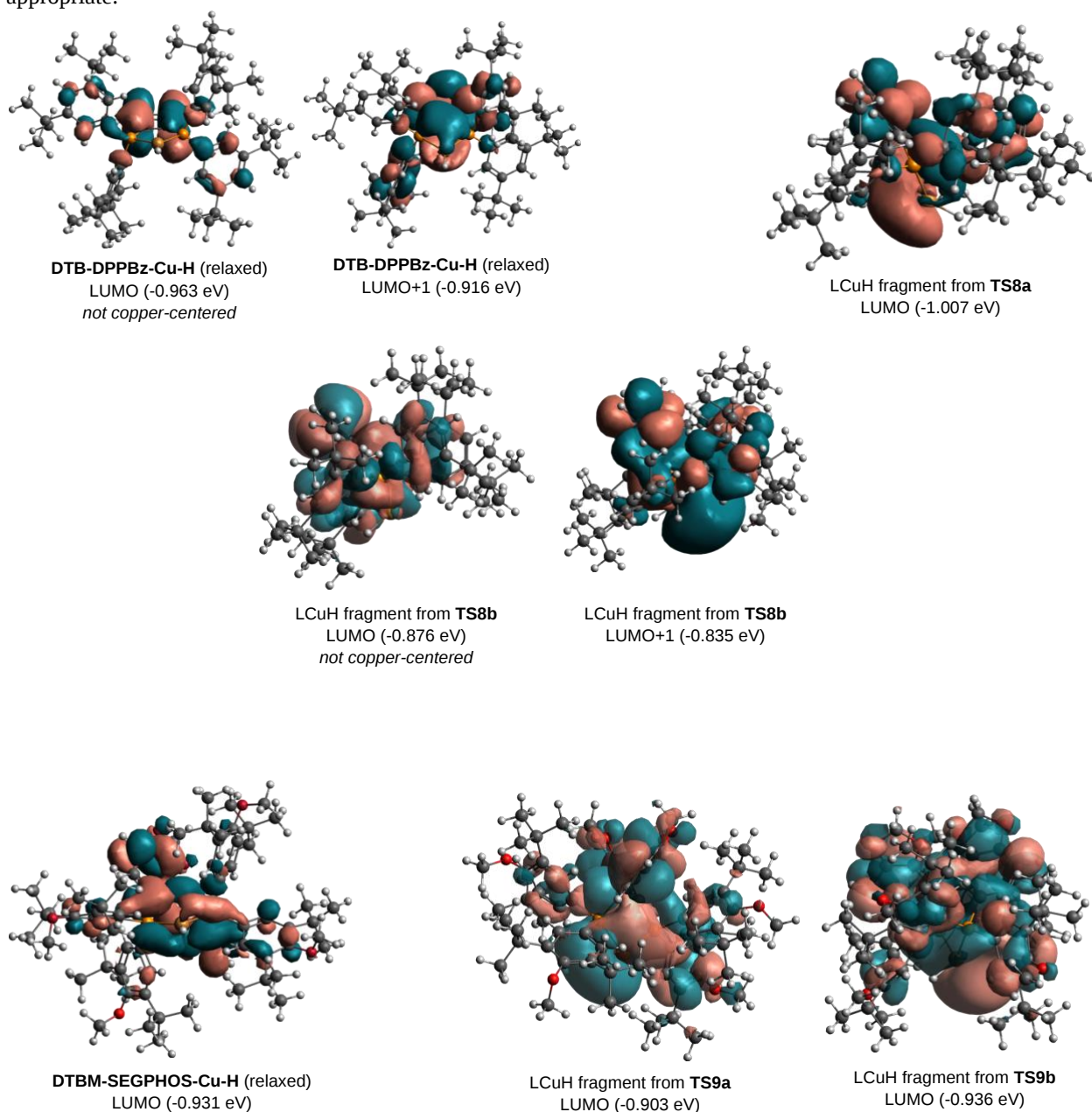
Calculations were performed with Gaussian 16.ⁱ An ultrafine integration grid and the keyword 5d were used for all calculations. Geometry optimizations of stationary points were carried out with B3LYP,¹ SDDⁱⁱ for Cu, and 6-31G(d) for all other atoms ("BS1"). Frequency analyses were carried out at the same level to evaluate the zero-point vibrational energy and thermal corrections at 298.15 K. The nature of the stationary points was determined in each case according to the appropriate number of negative eigenvalues of the Hessian matrix. Forward and reverse intrinsic reaction coordinate (IRC) calculations were carried out on the optimized transition structures to ensure that the TSs indeed connect the appropriate reactants and products.ⁱⁱⁱ Multiple conformations were considered for all structures, and the lowest energy conformations are reported. The final reported energies were obtained from single point energy calculations on the optimized geometries using M06,^{iv} the SMD continuum solvation model^v (THF), and a larger basis set for the light atoms (6-311+G(d,p) for all atoms other than Cu, SDD for Cu, "BS2"). Gibbs free energy values are reported after applying Cramer and Truhlar's anharmonic correction to frequencies that are less than 100 cm⁻¹.^{vi} 3D images of molecular orbitals were generated with Avogadro.^{vii}

Free Energy Diagram



MO Details

Molecular orbitals were calculated at the B3LYP/BS1 level of theory using the keyword pop=full. For distorted LCuH complexes, the substrate (alkyne) portion of the optimized transition structures was deleted and a single-point energy calculation was performed on the remaining LCuH fragment at the B3LYP/BS1 level of theory. The energies of the lowest unoccupied Cu-centered MOs of the (DTB-DPPBz)CuH and (DTBM-SEGPBz)CuH fragments are reported in the manuscript. In two cases, this orbital corresponds to the LUMO+1 rather than the LUMO (for the relaxed (DTB-DPPBz)CuH and for the (DTB-DPPBz)CuH distorted fragment obtained from **TS8b** for addition of Cu to the β -carbon). In these two cases, the LUMO is ligand-centered rather than Cu-centered. The energies and images of the LUMOs for all relaxed and distorted LCuH fragments are depicted below, together with the energies and images of the LUMO+1 orbitals when appropriate.



Energies, Entropies, and Lowest Frequencies of Minimum Energy Structures

Structure	E _{elec} (Hartree)	E _{elec} + ZPE (Hartree)	H (Hartree)	S (cal mol ⁻¹ K ⁻¹)	G ^b (Hartree)	G _{corrected} ^c (Hartree)	Lowest freq. (cm ⁻¹)	# of imag freq.
phenylpropyne	-347.530380	-347.392113	-347.382786	93.6	-347.427281	-347.425113	11.2	0
(DTB-DPPBz)CuH	-3295.082488	-3293.724182	-3293.647893	411.4	-3293.843358	-3293.813867	4.8	0
(DTBM- SEGPBOS)CuH	-4360.917730	-4359.313223	-4359.218840	479.7	-4359.446775	-4359.418645	6.1	0
S10a	-3642.627578	-3641.128865	-3641.043393	451.7	-3641.258017	-3641.226394	3.8	0
S10b	-3642.623037	-3641.124311	-3641.038831	453.0	-3641.254071	-3641.221889	3.7	0
TS8a	-3642.607237	-3641.109790	-3641.024850	447.4	-3641.237422	-3641.206652	-640.8	1
TS8b	-3642.598530	-3641.101320	-3641.016213	450.6	-3641.230325	-3641.198637	-733.8	1
S11a	-3642.673115	-3641.169555	-3641.084465	452.0	-3641.299206	-3641.266720	6.6	0
S11b	-3642.665661	-3641.161805	-3641.076811	455.2	-3641.293095	-3641.258710	5.5	0
S12a	-4708.463134	-4706.718872	-4706.614695	523.5	-4706.863441	-4706.832829	10.4	0
S12b	-4708.459708	-4706.715242	-4706.611473	520.6	-4706.858803	-4706.828716	6.8	0
TS9a	-4708.437646	-4706.693811	-4706.590658	516.2	-4706.835905	-4706.807044	-649.2	1
TS9b	-4708.437217	-4706.694530	-4706.590658	521.4	-4706.838407	-4706.808332	-681.0	1
S13a	-4708.511903	-4706.762131	-4706.658782	520.8	-4706.906246	-4706.875284	6.8	0
S13b	-4708.504041	-4706.754727	-4706.651466	521.4	-4706.899222	-4706.867821	5.4	0

^aEnergy values calculated at the SMD(THF)-M06/BS2//B3LYP/BS1 level of theory. 1 Hartree = 627.51 kcal mol⁻¹. Thermal corrections at 298.15 K. ^bSolvent-corrected free energy given by $G = E_{\text{elec}} + G_{\text{corr}}$, where G_{corr} is the thermal correction to Gibbs free energy. ^cSolvent-corrected free energy given by $G = E_{\text{elec}} + G_{\text{corr}}^*$, where G_{corr}^* is the thermal correction to Gibbs free energy obtained after applying Cramer and Truhlar's anharmonic correction.^{vi} See published manuscript for Computational references.⁴⁹

CHAPTER 3 SUPPLEMENTARY INFORMATION

Copper-Catalyzed Transfer Hydrodeuteration of Aryl Alkenes with Quantitative Isotopomer Purity Analysis by Molecular Rotational Resonance Spectroscopy

General Information

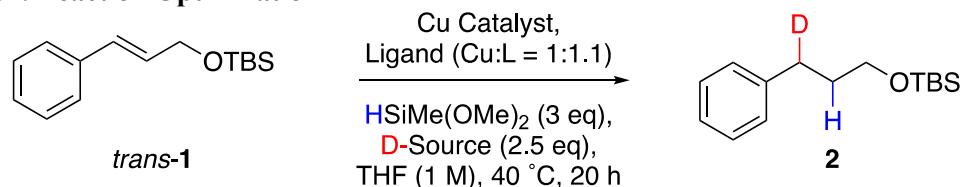
The following chemicals were purchased from commercial vendors and were used as received: Cu(OAc)₂ (99.999% from Alfa Aesar); 1,2-Bis[bis[3,5-di(*t*-butyl)phenyl]phosphino]benzene (DTB-DPPBz) (Wako Pure Chemical Industries), dimethoxy(methyl)silane (TCI); ethanol-OD (Millipore Sigma); 2-propanol-*d*₈ (Millipore Sigma); poly(methylhydrosiloxane) average M_n 1700-3200 (Millipore Sigma); *tert*-butyldimethylsilyl chloride (TBSCl) (Oakwood Chemical); methyltriphenylphosphonium bromide (Oakwood Chemical); Sodium hydride (in oil dispersion) 60% dispersion in mineral oil (Oakwood Chemical); sodium bis(trimethylsilyl)amide 2M in THF (Oakwood Chemical) potassium trifluoro(vinyl)borate (Oakwood Chemical); cesium carbonate (Ambeed Inc.); *n*-butyl lithium (Millipore Sigma).

Anhydrous tetrahydrofuran (THF) was purified by an MBRAUN solvent purification system (MB-SPS). Chloroform-*d* (CDCl₃) was stored over 3Å molecular sieves. Thin-layer chromatography (TLC) was conducted with Silicycle silica gel 60Å F254 pre-coated plates (0.25 mm) and visualized with UV and a KMnO₄ stain. Flash chromatography was performed using SiliaFlash® P60, 40-60 mm (230-400 mesh), purchased from Silicycle. For reactions that required heating (optimization, transfer hydrodeuteration), a PolyBlock for 2-dram vials was used on top of a Heidolph heating/stir plate. ¹H NMR spectra were recorded on a Varian 300 or 400 MHz spectrometer and are reported in ppm using deuterated solvent as an internal standard (CDCl₃ at 7.26 ppm). Data reported as: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sxt = sextet, m = multiplet, br = broad; coupling constant(s) in Hz; integration. ¹³C NMR spectra were recorded on a Varian 76 MHz or 101 MHz spectrometer and are reported in ppm using deuterated solvent as an internal standard (CDCl₃ at 77.16 ppm). ²H NMR spectra were recorded on a Varian 61 MHz spectrometer. ¹¹B NMR spectra were recorded on a Varian 128 MHz spectrometer. See published manuscript for MRR data and supplementary information.⁶³

High-resolution mass spectra were obtained for all new compounds not previously reported using the resources of the Chemistry Instrument Center (CIC), University at Buffalo, SUNY, Buffalo, NY. Specifically, high resolution accurate mass analysis was conducted using the following instruments: 12T Bruker SolarixXR 12 Hybrid FTMS with Imaging MALDI and Nano-LC, provided through funding from the National Institutes of Health, NIH S10 RR029517; a Thermo Q-Exactive Focus Orbitrap Liquid Chromatograph Tandem Mass Spectrometer and a Thermo Q-Exactive Orbitrap Gas Chromatograph Tandem Mass Spectrometer, provided through funding from the National Science Foundation, MRI-1919594.

Optimization Studies

Table S1. Reaction Optimization



Entry	Cu(OAc) ₂	Ligand	D-Source	<i>trans</i> - 1 (%)	2 (%)
1	2 mol%	L1	EtOD	69 ^b	-
2	2 mol%	L2	EtOD	70 ^b	-
3	2 mol%	L3	EtOD	89 ^b	-
4	2 mol%	L4	EtOD	47 ^b	-
5	2 mol%	L5	EtOD	-	85 ^c
6	2 mol%	L5	MeOD	8 ^c	69 ^c
7	2 mol%	L5	D ₂ O	59 ^c	21 ^c
8	1 mol%	L5	IPA- <i>d</i> 8	-	85 ^c
9	1 mol%	L5	EtOD	-	90 ^c

^aReactions conducted using 0.2 mmol of substrate and Cu(OAc)₂ was used as a 0.2 M solution in THF.

^bYield was determined by ¹H NMR analysis of the crude reaction mixture, using mesitylene as an internal standard. ^cDenotes isolated product yield.

General procedure (A) for optimization studies:

In a N₂ filled glovebox, ligand, Cu catalyst (Cu:L = 1:1.1), and THF were added to an oven-dried 2-dram vial followed by dropwise addition of R₃Si-H (0.60 mmol, 3 eq.). A color change from green/blue to yellow was observed while stirring for 15 minutes. In a separate oven-dried 1-dram vial was added (*E*)-1-*tert*-butyldimethylsilyloxy-3-phenyl-2-propene (50 mg, 0.20 mmol, 1 eq.), THF (0.100 mL), and D-Source (0.50 mmol, 2.5 eq.). The solution in the 1-dram vial was added dropwise over 20 seconds to the 2-dram vial. The total volume of THF was calculated based on having a final reaction concentration of 1M based on the alkene substrate. The 2-dram vial was capped with a red pressure relief cap, taken out of the glovebox, and stirred for 20 h at 40 °C at which point the reaction was filtered through a 1" silica plug with 100 mL of diethyl ether into a 200 mL round bottom flask. The solvent was removed by rotary evaporation, and the product was analyzed by ¹H NMR using 1,3,5-trimethylbenzene as an internal standard. Yields for all entries were obtained by isolating the product after flash column chromatography if greater than 5% NMR yield was observed for **2** in the crude ¹H NMR.

Entry 1. According to general procedure A for the optimization studies, a stirring solution of 1,2-Bis(diphenylphosphino)ethane **L1** (1.8 mg, 0.0044 mmol, 0.022 eq), Cu(OAc)₂ (20 μL of a 0.2 M solution in THF, 0.004 mmol, 0.02 eq.), and dimethoxy(methyl)silane (74 μL, 0.60 mmol, 3eq.) in THF (0.08 mL) was prepared, and to this was added dropwise a solution of (*E*)-1-*tert*-butyldimethylsilyloxy-3-phenyl-2-propene (50 mg, 0.20 mmol, 1 eq.) and ethanol-OD (29 μL, 0.50 mmol, 2.5 eq.) in THF (100 μL). The reaction stirred for 20 h at 40 °C, after which it was filtered through a silica plug with diethyl ether (20 mL) and eluted with an additional (80 mL) of diethyl ether. The solvent was removed by rotary evaporation, and the crude product was analyzed by ¹H NMR with 1,3,5-trimethylbenzene as an internal standard (**1**, 69% yield by ¹H NMR).

Entry 2. According to general procedure A for optimization studies, a stirring solution of 1,1'-Bis(diphenylphosphino)ferrocene **L2** (2.4 mg, 0.0044 mmol, 0.022 eq.), Cu(OAc)₂ (20 μ L of a 0.2 M solution in THF, 0.004 mmol, 0.02 eq.), and dimethoxy(methyl)silane (74 μ L, 0.60 mmol, 3 eq.) in THF (0.080 mL) was prepared, and to this was added dropwise a solution of (*E*)-1-*tert*-butyldimethylsilyloxy-3-phenyl-2-propene (50 mg, 0.20 mmol, 1 eq.) and ethanol-OD (29 μ L, 0.50 mmol, 2.5 eq.) in THF (0.10 mL). The reaction stirred for 20 h at 40 °C, after which it was filtered through a silica plug with diethyl ether (20 mL) and eluted with an additional (80 mL) of diethyl ether. The solvent was removed by rotary evaporation, and the crude product was analyzed by ¹H NMR with 1,3,5-trimethylbenzene as an internal standard, (**1**, 70% yield by ¹H NMR).

Entry 3. According to general procedure A for the optimization studies, a stirring solution of (±)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene **L3** (2.9 mg, 0.0044 mmol, 0.022 eq), Cu(OAc)₂ (20 μ L of a 0.2 M solution in THF, 0.004 mmol, 0.02 eq.), and dimethoxy(methyl)silane (74 μ L, 0.6 mmol, 3eq.) in THF (0.08 mL) was prepared, and to this was added dropwise a solution of (*E*)-1-*tert*-butyldimethylsilyloxy-3-phenyl-2-propene (50 mg, 0.2 mmol, 1 eq.) and ethanol-OD (29 μ L, 0.5 mmol, 2.5 eq.) in THF (0.10 mL). The reaction stirred for 20 h at 40 °C, after which it was filtered through a silica plug with diethyl ether (20 mL) and eluted with an additional (80 mL) of diethyl ether. The solvent was removed by rotary evaporation, and the crude product was analyzed by ¹H NMR with 1,3,5-trimethylbenzene as an internal standard (**1**, 89% yield by ¹H NMR).

Entry 4. According to general procedure A for the optimization studies, a stirring solution of 1,2-Bis(diphenylphosphino)benzene **L4** (2.0 mg, 0.0044 mmol, 0.022 eq), Cu(OAc)₂ (20 μ L of a 0.2 M solution in THF, 0.004 mmol, 0.02 eq.), and dimethoxy(methyl)silane (74 μ L, 0.6 mmol, 3eq.) in THF (0.08 mL) was prepared, and to this was added dropwise a solution of (*E*)-1-*tert*-butyldimethylsilyloxy-3-phenyl-2-propene (50 mg, 0.2 mmol, 1 eq.) and ethanol-OD (29 μ L, 0.5 mmol, 2.5 eq.) in THF (0.10 mL). The reaction stirred for 20 h at 40 °C, after which it was filtered through a silica plug with diethyl ether (20 mL) and eluted with an additional (80 mL) of diethyl ether. The solvent was removed by rotary evaporation, and the crude product was analyzed by ¹H NMR with 1,3,5-trimethylbenzene as an internal standard (**1**, 47% yield by ¹H NMR).

Entry 5. According to general procedure A for optimization studies, a stirring solution of 1,2-Bis[bis(3,5-di(*t*-butyl)phenyl)phosphino]benzene **L5** (3.9 mg, 0.0044 mmol, 0.022 eq.), Cu(OAc)₂ (20 μ L of a 0.2 M solution in THF, 0.004 mmol, 0.02 eq.), and dimethoxy(methyl)silane (74 μ L, 0.60 mmol, 3 eq.) in THF (0.08 mL) was prepared, and to this was added dropwise a solution of (*E*)-1-*tert*-butyldimethylsilyloxy-3-phenyl-2-propene (50 mg, 0.20 mmol, 1 eq.) and ethanol-OD (29 μ L, 0.50 mmol, 2.5 eq.) in THF (0.100 mL). The reaction stirred for 20 h at 40 °C, after which it was filtered through a silica plug with diethyl ether (20 mL) and eluted with an additional (80 mL) of diethyl ether. The solvent was removed by rotary evaporation, and the crude product was analyzed by ¹H NMR with 1,3,5-trimethylbenzene as an internal standard. The crude product was dry loaded onto silica gel, and purified by flash column chromatography using gradient elution (100 mL of 100% hexanes, 100 mL of 2% ethyl acetate in hexanes) to yield a clear colorless oil (**2**, 43 mg, 0.17 mmol, 85% yield).

Entry 6. According to general procedure A for optimization studies, a stirring solution of 1,2-Bis[bis(3,5-di(*t*-butyl)phenyl)phosphino]benzene **L5** (3.9 mg, 0.0044 mmol, 0.022 eq.), Cu(OAc)₂ (20 μ L of a 0.2 M solution in THF, 0.004 mmol, 0.02 eq.), and dimethoxy(methyl)silane (74 μ L, 0.60 mmol, 3 eq.) in THF (0.08 mL) was prepared, and to this was added dropwise a solution of (*E*)-1-*tert*-butyldimethylsilyloxy-3-phenyl-2-propene (50 mg, 0.20 mmol, 1 eq.) and methanol-OD (20 μ L, 0.50 mmol, 2.5 eq.) in THF (0.10 mL). The reaction stirred for 20 h at 40 °C, after which it was filtered through a silica plug with diethyl ether (20 mL) and eluted with an additional (80 mL) of diethyl ether. The solvent was removed by rotary evaporation, and the crude product was analyzed by ¹H NMR with 1,3,5-trimethylbenzene as an internal standard. The crude product was dry loaded onto silica gel, and was purified by flash column chromatography using gradient elution (100 mL of 100% hexanes, 100 mL of 2% ethyl acetate in hexanes) to yield a clear colorless oil (**1** and **2** isolated as an inseparable mixture, 39 mg (**1**, 8% yield; **2**, 69% yield).

Entry 7. According to general procedure A for optimization studies, a stirring solution of 1,2-Bis[bis[3,5-di(*t*-butyl)phenyl]phosphino]benzene **L5** (3.9 mg, 0.0044 mmol, 0.022 eq.), Cu(OAc)₂ (20 μ L of a 0.2 M solution in THF, 0.004 mmol, 0.02 eq.), and dimethoxy(methyl)silane (74 μ L, 0.60 mmol, 3 eq.) in THF (0.08 mL) was prepared, and to this was added dropwise a solution of (*E*)-1-*tert*-butyldimethylsilyloxy-3-phenyl-2-propene (50 mg, 0.20 mmol, 1 eq.) and D₂O (9 μ L, 0.50 mmol, 2.5 eq.) in THF (0.10 mL). The reaction stirred for 20 h at 40 °C, after which it was filtered through a silica plug with diethyl ether (20 mL) and eluted with an additional (80 mL) of diethyl ether. The solvent was removed by rotary evaporation, and the crude product was analyzed by ¹H NMR with 1,3,5-trimethylbenzene as an internal standard. The crude product was dry loaded onto silica gel, and was purified by flash column chromatography using gradient elution (100 mL of 100% hexanes, 100 mL of 2% ethyl acetate in hexanes) to yield a clear colorless oil (1 and 2 isolated as an inseparable mixture, 40 mg (**1**, 59% yield; **2**, 21% yield).

Entry 8. According to general procedure A for optimization studies, a stirring solution of 1,2-Bis[bis[3,5-di(*t*-butyl)phenyl]phosphino]benzene **L5** (3.9 mg, 0.0044 mmol, 0.011 eq.), Cu(OAc)₂ (20 μ L of a 0.2 M solution in THF, 0.004 mmol, 0.01 eq.), and dimethoxy(methyl)silane (74 μ L, 0.60 mmol, 3 eq.) in THF (0.08 mL) was prepared, and to this was added dropwise a solution of (*E*)-1-*tert*-butyldimethylsilyloxy-3-phenyl-2-propene (50 mg, 0.20 mmol, 1 eq.) and 2-propanol-*d*₈ (38 μ L, 0.50 mmol, 2.5 eq.) in THF (0.10 mL). The reaction stirred for 20 h at 40 °C, after which it was filtered through a silica plug with diethyl ether (20 mL) and eluted with an additional (80 mL) of diethyl ether. The solvent was removed by rotary evaporation, and the crude product was analyzed by ¹H NMR with 1,3,5-trimethylbenzene as an internal standard. The crude product was dry loaded onto silica gel, and was purified by flash column chromatography using gradient elution (100 mL of 100% hexanes, 100 mL of 2% ethyl acetate in hexanes) to yield a clear colorless oil (**2**, 42 mg, 0.17 mmol, 85% yield).

Entry 9. According to general procedure A for optimization studies, a stirring solution of 1,2-Bis[bis[3,5-di(*t*-butyl)phenyl]phosphino]benzene **L5** (2.0 mg, 0.0022 mmol, 0.011 eq.), Cu(OAc)₂ (10 μ L of a 0.2 M solution in THF, 0.002 mmol, 0.01 eq.), and dimethoxy(methyl)silane (74 μ L, 0.60 mmol, 3 eq.) in THF (0.09 mL) was prepared, and to this was added dropwise a solution of (*E*)-1-*tert*-butyldimethylsilyloxy-3-phenyl-2-propene (50 mg, 0.20 mmol, 1 eq.) and ethanol-OD (29 μ L, 0.50 mmol, 2.5 eq.) in THF (0.10 mL). The reaction stirred for 20 h at 40 °C, after which it was filtered through a silica plug with diethyl ether (20 mL) and eluted with an additional (80 mL) of diethyl ether. The solvent was removed by rotary evaporation, and the crude product was analyzed by ¹H NMR with 1,3,5-trimethylbenzene as an internal standard. The crude product was dry loaded onto silica gel, and purified by flash column chromatography using gradient elution (100 mL of 100% hexanes, 100 mL of 2% ethyl acetate in hexanes) to yield a clear colorless oil (**2**, 46 mg, 0.18 mmol, 90% yield).

Table S2. Reaction Optimization^a

Entry	Cu(OAc) ₂	Ligand	D-Source	1 (%)	2 (%)
1	Stryker's Reagent	-	EtOD	>99 ^b	-
2	2 mol%	L5	EtOD	21 ^d	41 ^d
3	-	L5	EtOD	97 ^b	-
4	2 mol%	L5	EtOD	82 ^b	-
5	2 mol%	L5	-	84 ^b	-
6	2 mol%	L5	EtOD	82 ^b	-
7	1 mol%	L5	EtOD	-	75 ^d

^aReactions conducted using 0.2 mmol of substrate. Cu(OAc)₂ was used as a 0.2 M solution in THF.

^bYield was determined by ¹H NMR analysis of the crude reaction mixture, using mesitylene as an internal standard. ^cPoly(methylhydrosiloxane) was used instead of dimethoxy(methyl)silane. ^eNo silane source was used. ^dDenotes isolated product yield. ^fReaction stirred at 23 °C.

Entry 1. According to general procedure A for the optimization studies, a stirring solution of (triphenylphosphine)copper hydride hexamer (Stryker's reagent) (7.8 mg, 0.004 mmol, 0.02 eq.), and

dimethoxy(methyl)silane (74 μL , 0.60 mmol, 3 eq.) in THF (0.10 mL) was prepared, and to this was added dropwise a solution of (*E*)-1-*tert*-butyldimethylsilyloxy-3-phenyl-2-propene (50 mg, 0.20 mmol, 1 eq.) and ethanol-OD (29 μL , 0.50 mmol, 2.5 eq.) in THF (0.10 mL). The reaction stirred for 20 h at 40 $^{\circ}\text{C}$, after which it was filtered through a silica plug with diethyl ether (20 mL) and eluted with an additional (80 mL) of diethyl ether. The solvent was removed by rotary evaporation, and the crude product was analyzed by ^1H NMR with 1,3,5-trimethylbenzene as an internal standard (**1**, >99% yield by ^1H NMR).

Entry 2. According to general procedure A for optimization studies, a stirring solution of 1,2-Bis[bis(3,5-di(*t*-butyl)phenyl)phosphino]benzene **L5** (3.9 mg, 0.0044 mmol, 0.022 eq.), $\text{Cu}(\text{OAc})_2$ (20 μL of a 0.2 M solution in THF, 0.004 mmol, 0.02 eq.), and poly(methylhydrosiloxane) (40 μL , 0.60 mmol, 3 eq. based on Si-H)⁶⁷ in THF (0.08 mL) was prepared, and to this was added dropwise a solution of (*E*)-1-*tert*-butyldimethylsilyloxy-3-phenyl-2-propene (50 mg, 0.20 mmol, 1 eq.) and ethanol-OD (29 μL , 0.50 mmol, 2.5 eq.) in THF (0.10 mL). The reaction stirred for 20 h at 40 $^{\circ}\text{C}$, after which it was filtered through a silica plug with diethyl ether (20 mL) and eluted with an additional (80 mL) of diethyl ether. The solvent was removed by rotary evaporation, and the crude product was analyzed by ^1H NMR with 1,3,5-trimethylbenzene as an internal standard. The crude product was dry loaded onto silica gel, and was purified by flash column chromatography using gradient elution (100 mL of 100% hexanes, 100 mL of 2% ethyl acetate in hexanes) to yield a clear colorless oil (**1** and **2** isolated as an inseparable mixture, 31 mg (**1**, 21% yield; **2**, 41% yield).

Entry 3. According to general procedure A for optimization studies, a stirring solution of 1,2-Bis[bis(3,5-di(*t*-butyl)phenyl)phosphino]benzene **L5** (3.9 mg, 0.0044 mmol, 0.022 eq.) and dimethoxy(methyl)silane (74 μL , 0.60 mmol, 3 eq.) in THF (0.10 mL) was prepared, and to this was added dropwise a solution of (*E*)-1-*tert*-butyldimethylsilyloxy-3-phenyl-2-propene (50 mg, 0.20 mmol, 1 eq.) and ethanol-OD (29 μL , 0.50 mmol, 2.5 eq.) in THF (0.10 mL). The reaction stirred for 20 h at 40 $^{\circ}\text{C}$, after which it was filtered through a silica plug with diethyl ether (20 mL) and eluted with an additional (80 mL) of diethyl ether. The solvent was removed by rotary evaporation, and the crude product was analyzed by ^1H NMR with 1,3,5-trimethylbenzene as an internal standard, (**24**, 97% yield by ^1H NMR).

Entry 4. According to general procedure A for the optimization studies, a stirring solution of $\text{Cu}(\text{OAc})_2$ (20 μL of a 0.2 M solution in THF, 0.004 mmol, 0.02 eq.), and dimethoxy(methyl)silane (74 μL , 0.60 mmol, 3 eq.) in THF (0.08 mL) was prepared, and to this was added dropwise a solution of (*E*)-1-*tert*-butyldimethylsilyloxy-3-phenyl-2-propene (50 mg, 0.20 mmol, 1 eq.) and ethanol-OD (29 μL , 0.50 mmol, 2.5 eq.) in THF (0.10 mL). The reaction stirred for 20 h at 40 $^{\circ}\text{C}$, after which it was filtered through a silica plug with diethyl ether (20 mL) and eluted with an additional (80 mL) of diethyl ether. The solvent was removed by rotary evaporation, and the crude product was analyzed by ^1H NMR with 1,3,5-trimethylbenzene as an internal standard (**1**, 82% yield by ^1H NMR).

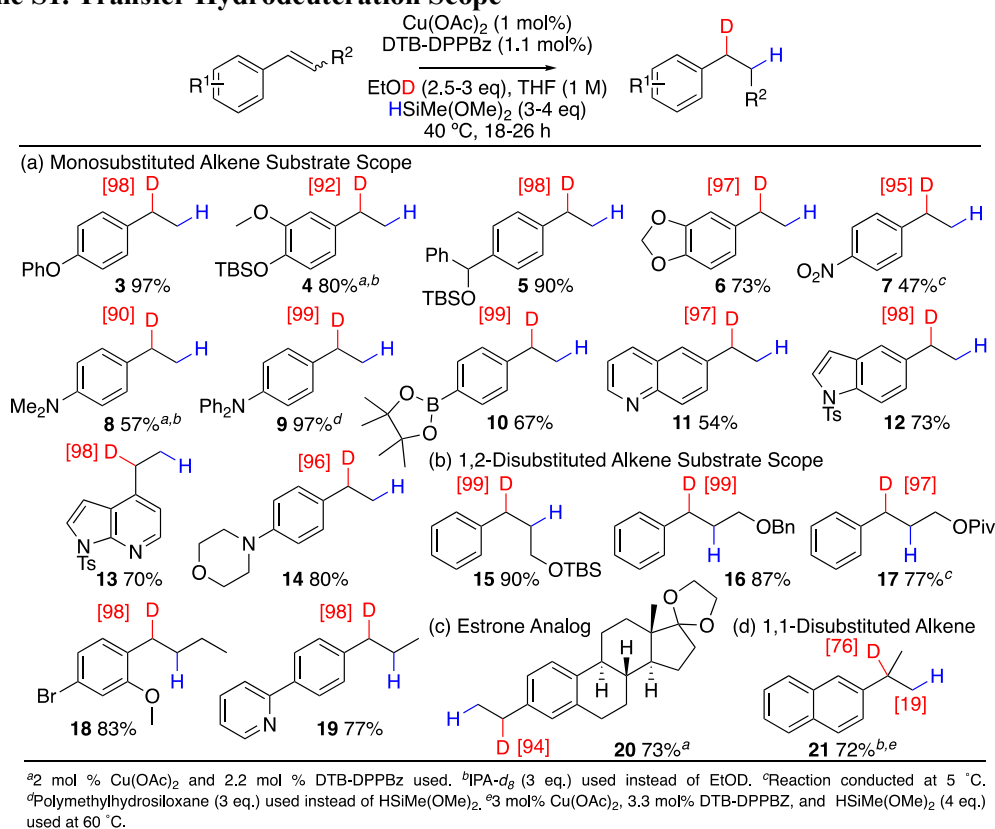
Entry 5. According to general procedure A for optimization studies, a stirring solution of 1,2-Bis[bis(3,5-di(*t*-butyl)phenyl)phosphino]benzene **L5** (3.9 mg, 0.0044 mmol, 0.022 eq.), $\text{Cu}(\text{OAc})_2$ (20 μL of a 0.2 M solution in THF, 0.004 mmol, 0.02 eq.), and dimethoxy(methyl)silane (74 μL , 0.60 mmol, 3 eq.) in THF (0.08 mL) was prepared, and to this was added dropwise a solution of (*E*)-1-*tert*-butyldimethylsilyloxy-3-phenyl-2-propene (50 mg, 0.20 mmol, 1 eq.) in THF (0.10 mL). The reaction stirred for 20 h at 40 $^{\circ}\text{C}$, after which it was filtered through a silica plug with diethyl ether (20 mL) and eluted with an additional (80 mL) of diethyl ether. The solvent was removed by rotary evaporation, and the crude product was analyzed by ^1H NMR with 1,3,5-trimethylbenzene as an internal standard (**1**, 84% yield by ^1H NMR).

Entry 6. According to general procedure A for the optimization studies, a stirring solution of 1,2-Bis[bis(3,5-di(*t*-butyl)phenyl)phosphino]benzene **L5** (3.9 mg, 0.0044 mmol, 0.022 eq) and $\text{Cu}(\text{OAc})_2$ (20 μL of a 0.2 M solution in THF, 0.004 mmol, 0.02 eq) in THF (0.08 mL) was prepared, and to this was added dropwise a solution of (*E*)-1-*tert*-butyldimethylsilyloxy-3-phenyl-2-propene (50 mg, 0.20 mmol, 1 eq.) and ethanol-OD (29 μL , 0.50 mmol, 2.5 eq.) in THF (0.10 mL). The reaction stirred for 20 hr at 40 $^{\circ}\text{C}$, after which it was filtered through a silica plug with diethyl ether (20 mL) and eluted with an additional (80 mL) of diethyl ether. The solvent was removed by rotary evaporation, and the crude product was analyzed by ^1H NMR with 1,3,5-trimethylbenzene as an internal standard (**1**, 82% yield by ^1H NMR).

Entry 7. According to general procedure A for optimization studies, a stirring solution of 1,2-Bis[bis(3,5-di(*t*-butyl)phenyl)phosphino]benzene **L5** (2.0 mg, 0.0022 mmol, 0.011 eq.), Cu(OAc)₂ (10 μ L of a 0.2 M solution in THF, 0.002 mmol, 0.01 eq.), and dimethoxy(methyl)silane (74 μ L, 0.60 mmol, 3 eq.) in THF (0.09 mL) was prepared, and to this was added dropwise a solution of (*E*)-1-*tert*-butyldimethylsilyloxy-3-phenyl-2-propene (50 mg, 0.20 mmol, 1 eq.) and ethanol-OD (29 μ L, 0.50 mmol, 2.5 eq.) in THF (0.10 mL). The reaction stirred for 20 h at 23 °C, after which it was filtered through a silica plug with diethyl ether (20 mL) and eluted with an additional (80 mL) of diethyl ether. The solvent was removed by rotary evaporation, and the crude product was analyzed by ¹H NMR with 1,3,5-trimethylbenzene as an internal standard. The crude product was dry loaded onto silica gel, and purified by flash column chromatography using gradient elution (100 mL of 100% hexanes, 100 mL of 2% ethyl acetate in hexanes) to yield a clear colorless oil (**2**, 37 mg, 0.15 mmol, 75% yield).

Transfer Hydrodeuteration Substrate Scope

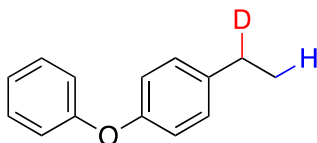
Scheme S1. Transfer Hydrodeuteration Scope



General procedure for Transfer Hydrodeuteration (B)

In a N₂ filled glovebox, DTB-DPPBz (3.0 mg, 0.0033 mmol, 0.011 eq.), Cu(OAc)₂ (15 μ L of a 0.2 M solution in THF, 0.003 mmol, 0.01 eq.), and THF (0.135 mL) were added to an oven-dried 2-dram vial followed by dropwise addition of dimethoxy(methyl)silane (111 μ L, 0.90 mmol, 3 eq.) or poly(methylhydrosiloxane) (60 μ L, 0.90 mmol, 3 eq based on Si-H)⁶⁷. A color change from green/blue to yellow was observed while stirring for 15 minutes. In a separate oven-dried 1-dram vial was added the alkene substrate (0.30 mmol, 1 eq.), THF (0.150 mL), and ethanol-OD/2-propanol-*d*₈ (2.5 eq based on substrate). The solution in the 1-dram vial was added dropwise over 20 seconds to the 2-dram vial. The total volume of THF was calculated based on having a final reaction concentration of 1M based on the alkene substrate. The 2-dram vial was capped with a red pressure relief cap, taken out of the glovebox, and stirred for 9-24 h at the appropriate temperature at which point the reaction was filtered through a 1" silica plug with 20 mL of diethyl ether followed by 80 mL of

diethyl ether to elute the remaining product into a 200 mL round bottom flask. After removing the diethyl ether by rotary evaporation, the crude product was isolated by flash column chromatography.



1-(ethyl-1-*d*)-4-phenoxybenzene [3]. According to the general procedure B, DTB-DPPBz (3.0 mg, 0.0033 mmol, 0.011 eq.), Cu(OAc)₂ (15 μ L of a 0.2 M solution in THF, 0.003 mmol, 0.01 eq.), and THF (0.135 mL) then dimethoxy(methyl)silane (111 μ L, 0.90 mmol, 3 eq.) were combined in a 2-dram vial followed by addition of a solution of 1-Ethenyl-4-phenoxybenzene (59 mg, 0.30 mmol, 1 eq.), THF (0.150 mL), and ethanol-OD (44 μ L, 0.75 mmol, 2.5 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 18 h at 40 $^{\circ}$ C. Upon completion, the crude product mixture was dry loaded onto a silica gel column. Flash column chromatography (300 mL of 100% hexanes) to give the pure product as a clear colorless oil (57 mg, 0.29 mmol, 97% yield).

¹H NMR: (400 MHz, CDCl₃)

δ 7.34 (t, J = 8.0 Hz, 2H), 7.18 (d, J = 8.4 Hz, 2H), 7.09 (t, J = 7.3 Hz, 1H), 7.02 (d, J = 8.2 Hz, 2H), 6.96 (d, J = 8.4 Hz, 2H), 2.70 – 2.59 (m, 1.02 H), 1.26 (d, J = 7.5 Hz, 3H).

²H NMR: (61 MHz, CHCl₃):

δ 2.64 (s, 0.98D), 1.26 (s, 0.01D).

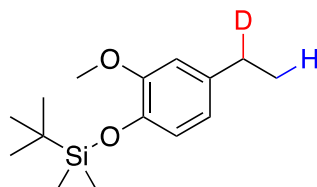
¹³C NMR: (101 MHz, CDCl₃)

δ 157.89, 155.02, 139.40, 129.78, 129.16, 122.95, 119.21, 118.56, 27.95 (t, J = 19.5 Hz), 15.81.

ATR-IR (cm⁻¹):

3030, 2962, 2927, 2873, 2136, 1230, 1165.

HRMS: (EI⁺) m/z : [M]⁺ Calcd for C₁₄H₁₃DO 199.1107; Found 199.1100.



tert-butyl(4-(ethyl-1-*d*)-2-methoxyphenoxy)dimethylsilane [4]. According to the general procedure B, DTB-DPPBz (6.0 mg, 0.0066 mmol, 0.022 eq.), Cu(OAc)₂ (30 μ L of a 0.2 M solution in THF, 0.006 mmol, 0.02 eq.), THF (0.120 mL), then dimethoxy(methyl)silane (148 μ L, 1.20 mmol, 4 eq.) were combined in a 2-dram vial followed by addition of a solution of *tert*-butyl(2-methoxy-4-vinylphenoxy)dimethylsilane (79 mg, 0.30 mmol, 1 eq.), THF (0.150 mL), 2-propanol-*d*₈ (69 μ L, 0.90 mmol, 3 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 25 h at 40 $^{\circ}$ C. After silica plug filtration using diethyl ether (100 mL) as the eluent, the solvent was concentrated, and the crude oil was dry loaded onto a silica gel column. Flash column chromatography using gradient elution (100 mL of 100% HPLC hexanes, 200 mL of 1% ethyl acetate in HPLC hexanes) gave the pure product as a light-yellow oil (65 mg, 0.24 mmol, 80%).

¹H NMR: (400 MHz, CDCl₃)

δ 6.78 (d, J = 7.9 Hz, 1H), 6.70 (s, 1H), 6.65 (d, J = 7.9, 1H), 3.81 (s, 3H), 2.64 – 2.52 (m, 1.08 H), 1.22 (d, J = 7.6 Hz, 3H), 1.01 (s, 9H), 0.17 (s, 6H).

²H NMR: (61 MHz, CHCl₃)

δ 2.58 (s, 0.92D), 1.22 (s, 0.08D).

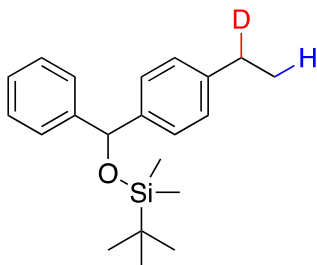
¹³C NMR: (101 MHz, CDCl₃)

δ 150.77, 142.97, 137.85, 120.74, 119.88, 112.12, 55.59, 28.30 (t, *J* = 19.6 Hz), 25.90, 18.58, 15.78, -4.50.

ATR-IR (cm⁻¹):

3035, 2957, 2929, 2895, 2856, 2142, 1231, 1162, 1126.

HRMS: FT-ICR-MS (+) ion tune *m/z*: [M]⁺ Calcd for C₁₅H₂₅DO₂SiNa 290.1665; Found 290.1656.



tert-butyl((4-(ethyl-1-*d*)phenyl) (phenyl)methoxy)dimethylsilane [5]. According to the general procedure B, DTB-DPPBz (3 mg, 0.0033 mmol, 0.01 eq.), Cu(OAc)₂ (15 μL of a 0.2 M solution in THF, 0.003 mmol, 0.01 eq.), THF (0.135 mL), then dimethoxy(methyl)silane (111 μL, 0.90 mmol, 3 eq.) were combined in a 2-dram vial followed by addition of a solution of *tert*-butyldimethyl(phenyl(4-vinylphenyl)methoxy)silane (97 mg, 0.30 mmol, 1 eq.), THF (0.150 mL), ethanol-OD (44 μL, 0.75 mmol, 2.5 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 18 h at 40 °C. After silica plug filtration using diethyl ether (100 mL) as the eluent, the solvent was concentrated, and the crude oil was dry loaded onto a silica gel column. Flash chromatography using gradient elution (100 mL of 100% HPLC hexanes, 100 mL of 1% ethyl acetate in HPLC hexanes, 100 mL of 2% ethyl acetate in HPLC hexanes, 100 mL of 4% ethyl acetate in HPLC hexanes) gave the pure product as a light-yellow oil (90 mg, 0.27 mmol, 90% yield).

¹H NMR (400 MHz, CDCl₃)

δ 7.45 (d, *J* = 7.5 Hz, 2H), 7.40 – 7.33 (m, 4H), 7.29 (d, *J* = 7.3, 1H), 7.20 (d, *J* = 8.1 Hz, 2H), 5.83 (s, 1H), 2.73 – 2.63 (m, 1.02 H), 1.29 (d, *J* = 7.5 Hz, 3H), 1.02 (s, 9H), 0.07 (d, *J* = 3.6 Hz, 6H).

²H NMR (61 MHz, CHCl₃)

δ 2.67 (s, 0.98D), 1.28 (s, 0.02D).

¹³C NMR (101 MHz, CDCl₃)

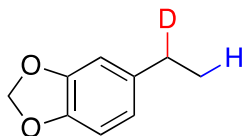
δ 145.60, 142.88, 142.69, 128.27, 127.76, 126.98, 126.42, 126.37, 76.66, 28.27 (t, *J* = 19.4 Hz), 26.03, 18.46, 15.55, -4.66.

ATR-IR (cm⁻¹):

2956, 2928, 2884, 2856, 2141, 1250, 1084, 1064.

HRMS: (EI⁺) *m/z*: [M-C₄H₉]⁺ Calcd for C₁₇H₂₀DOSi 270.1424; Found 270.1418.

The major ion peak represents the parent molecule after loss of the *t*-Bu cation.



5-(ethyl-1-*d*)-benzo-1,3-dioxole [6]. According to the general procedure B, DTB-DPPBz (3.0 mg, 0.0033 mmol, 0.011 eq.), Cu(OAc)₂ (15 μL of a 0.2 M solution in THF, 0.003 mmol, 0.01eq.), THF (0.135 mL), then dimethoxy(methyl)silane (111 μL, 0.90 mmol, 3 eq.) were combined in a 2-dram vial followed by addition of a solution of 5-vinyl-benzo-1,3-dioxole (44 mg, 0.30 mmol, 1 eq.), THF (0.150 mL), ethanol-OD (44 μL, 0.75 mmol, 2.5 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 18 h at 40 °C. Upon completion, the crude product mixture was dry loaded onto a silica gel column.

Flash column chromatography (200 mL of 100% HPLC hexanes) gave the pure product as a clear colorless oil (33 mg, 0.22 mmol, 73% yield).

^1H NMR: (400 MHz, CDCl_3)

δ 6.77 – 6.69 (m, 2H), 6.66 (d, J = 7.9 Hz, 1H), 5.92 (s, 2H), 2.62 – 2.51 (m, 1.03H), 1.21 (d, J = 7.6 Hz, 3H).

^2H NMR: (61 MHz, CHCl_3)

δ 2.56 (s, 0.97D), 1.21 (s, 0.02D).

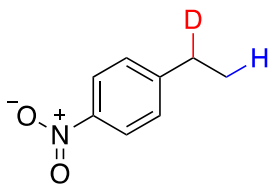
^{13}C NMR: (75 MHz, CDCl_3)

δ 147.64, 145.53, 138.32, 120.53, 108.55, 108.22, 100.82, 28.44 (t, J = 19.2 Hz), 16.03.

ATR-IR (cm^{-1}):

2963, 2876, 2142, 1233, 1036.

HRMS: (EI^+) m/z : $[\text{M}]^+$ Calcd for $\text{C}_9\text{H}_9\text{DO}_2$ 151.0700; Found 151.0737.



1-(ethyl-1-*d*)-4-nitrobenzene [7]. According to the general procedure B, DTB-DPPBz (3.0 mg, 0.0033 mmol, 0.011 eq.), $\text{Cu}(\text{OAc})_2$ (15 μL of a 0.2 M solution in THF, 0.003 mmol, 0.01 eq.), THF (0.135 mL), then dimethoxy(methyl)silane (111 μL , 0.90 mmol, 3 eq.) were combined in a 2-dram vial followed by addition of a solution of 1-ethenyl-4-nitrobenzene (45 mg, 0.30 mmol, 1 eq.), THF (0.150 mL), ethanol-OD (44 μL , 0.75 mmol, 2.5 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 19 h at 5 $^\circ\text{C}$. Upon completion, the crude product mixture was dry loaded onto a silica gel column. Flash chromatography using gradient elution (100 mL of 100% HPLC hexanes, 100 mL of 1% ethyl acetate in HPLC Hexanes, 100 mL of 2% ethyl acetate in HPLC hexanes) gave the pure product as a clear yellow oil (22 mg, 0.14 mmol, 47% yield).

^1H NMR (400 MHz, CDCl_3)

δ 8.14 (d, J = 8.6 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 2.79 – 2.69 (m, 1.05H), 1.27 (d, J = 7.7 Hz, 3H).

^2H NMR (61 MHz, CHCl_3)

δ 2.74 (s, 0.95D).

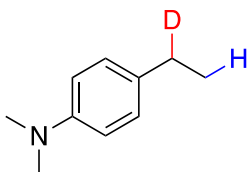
^{13}C NMR (101 MHz, CDCl_3)

δ 152.13, 146.36, 128.78, 123.78, 28.66 (t, J = 19.7 Hz), 15.13.

ATR-IR (cm^{-1}):

3078, 2969, 2933, 2876, 1516.

HRMS: (EI^+) m/z : $[\text{M}]^+$ Calcd for $\text{C}_8\text{H}_8\text{DNO}_2$ 152.0696; Found 152.0698.



4-(ethyl-1-*d*)-*N,N*-dimethylaniline [8]. According to the general procedure B, DTB-DPPBz (6.0 mg, 0.0066 mmol, 0.022 eq.), $\text{Cu}(\text{OAc})_2$ (30 μL of a 0.2 M solution in THF, 0.006 mmol, 0.02 eq.), THF (0.12 mL), then

dimethoxy(methyl)silane (148 μ L, 1.20 mmol, 4 eq.) were combined in a 2-dram vial followed by addition of a solution of *N,N*-dimethyl-4-vinylaniline (44 mg, 0.30 mmol, 1 eq.), THF (0.15 mL), 2-propanol-*d*₈ (69 μ L, 0.90 mmol, 3 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 22 h at 40 °C. After silica plug filtration using diethyl ether (100 mL) as the eluent, the solvent was concentrated, and the crude oil was dry loaded onto a neutral alumina Brock column. Flash column chromatography (300 mL of 100% HPLC hexanes) gave the pure product as a clear colorless oil (26 mg, 0.17 mmol, 57% yield).

¹H NMR: (400 MHz, CDCl₃)

δ 7.11 (d, *J* = 8.1 Hz, 2H), 6.74 (d, *J* = 8.3 Hz, 2H), 2.93 (s, 6H), 2.63 – 2.51 (m, 1.1H), 1.22 (d, 3H).

²H NMR: (61 MHz, CHCl₃)

δ 2.57 (s, 0.90D), 1.22 (s, 0.08D).

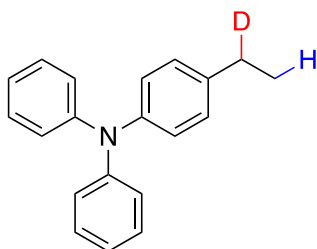
¹³C NMR: (101 MHz, CDCl₃)

δ 149.11, 132.76, 128.53, 113.27, 41.15, 27.58 (t, *J* = 19.0 Hz), 16.00.

ATR-IR (cm⁻¹):

2959, 2926, 2871, 2796, 2130, 1343.

HRMS: (EI⁺) *m/z*: [M]⁺ Calcd for C₁₀H₁₄DN 150.1267; Found 150.1261.



4-(ethyl-1-*d*)-*N,N*-diphenylaniline [9]. According to the general procedure B, DTB-DPPBz (3.0 mg, 0.0033 mmol, 0.011 eq.), Cu(OAc)₂ (15 μ L of a 0.2 M solution in THF, 0.003 mmol, 0.01 eq.), THF (0.135 mL), then poly(methylhydrosiloxane) (60 μ L, 0.90 mmol, 3 eq. based on Si-H) were combined in a 2-dram vial followed by addition of a solution of *N,N*-diphenyl-4-vinylaniline (81 mg, 0.30 mmol, 1 eq.), THF (0.150 mL), ethanol-OD (44 μ L, 0.75 mmol, 2.5 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 18 h at 40 °C. Upon completion, the crude product mixture was dry loaded onto a silica gel column. Flash column chromatography (200 mL of 100% HPLC hexanes) gave the pure product as a clear colorless oil (79 mg, 0.29 mmol, 97% yield).

¹H NMR: (400 MHz, CDCl₃)

δ 7.27 (t, *J* = 7.6 Hz, 4H), 7.17 – 7.11 (m, 6H), 7.09 (d, *J* = 8.3 Hz, 2H), 7.02 (t, *J* = 7.3 Hz, 2H), 2.72 – 2.59 (m, 1.01H), 1.29 (d, *J* = 7.6 Hz, 3H).

²H NMR: (61 MHz, CHCl₃)

δ 2.67 (s, 0.99D), 1.31 (s, 0.01D).

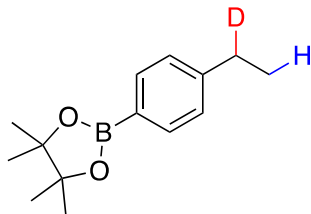
¹³C NMR: (101 MHz, CDCl₃)

δ 148.16, 145.52, 139.13, 129.23, 128.77, 124.94, 123.79, 122.35, 28.01 (t, *J* = 19.3 Hz), 15.63.

ATR-IR (cm⁻¹):

3059, 3022, 2960, 2927, 2870, 2135, 1269.

HRMS: (ESI⁺) *m/z*: [M]⁺ Calcd for C₂₀H₁₈ND 274.1600; Found 274.1575.



2-[4-(ethyl-1-*d*)-phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane [10]. According to the general procedure B, DTB-DPPBz (3.0 mg, 0.0033 mmol, 0.011 eq.), Cu(OAc)₂ (15 μ L of a 0.2 M solution in THF, 0.003 mmol, 0.01 eq.), THF (0.135 mL), then dimethoxy(methyl)silane (111 μ L, 0.90 mmol, 3.0 eq) were combined in a 2-dram vial followed by addition of a solution of 2-(4-Ethenylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (69 mg, 0.30 mmol, 1 eq.), THF (0.150 mL), ethanol-OD (44 μ L, 0.75 mmol, 2.5 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 18 h at 40 °C. Upon completion, the crude product mixture was dry loaded onto a silica gel column. Flash column chromatography using gradient elution (100 mL of 100% HPLC hexanes, 100 mL of 1% ethyl acetate in HPLC hexanes, 100 mL of 2% ethyl acetate in HPLC hexanes) gave the pure product as a clear colorless oil (46 mg, 0.20 mmol, 67% yield).

¹H NMR: (400 MHz, CDCl₃)

δ 7.75 (d, J = 7.8 Hz, 2H), 7.22 (d, J = 7.7 Hz, 2H), 2.71 – 2.61 (m, 1.01H), 1.35 (s, 12H), 1.24 (d, J = 7.6, 1.1 Hz, 3H).

²H NMR: (61 MHz, CHCl₃)

δ 2.67 (0.99 D)

¹³C NMR: (101 MHz, CDCl₃)

δ 147.83, 135.04, 127.48, 83.74, 28.90 (t, J = 19.5 Hz), 24.99, 15.53.

*A resonance of a carbon directly attached to boron was not observed due to quadrupolar relaxation.⁶⁸

¹¹B NMR: (128 MHz, CDCl₃)

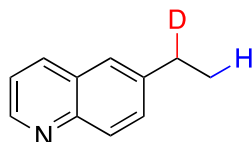
δ 31.39

*Boron impurity present from boron silicate NMR tube²

ATR-IR (cm⁻¹):

2972, 2929, 2868, 1944, 1140.

HRMS: (EI⁺) m/z : [M]⁺ Calcd for C₁₄H₂₀DBO₂ 233.1697; Found 233.1691.



6-(ethyl-1-*d*)-naphthalene [11]. According to the general procedure B, DTB-DPPBz (6.0 mg, 0.0066 mmol, 0.022 eq.), Cu(OAc)₂ (30 μ L of a 0.2 M solution in THF, 0.0060 mmol, 0.02 eq.), THF (0.120 mL), then dimethoxy(methyl)silane (111 μ L, 0.90 mmol, 3 eq) were combined in a 2-dram vial followed by addition of a solution of 6-Vinylnaphthalene (47 mg, 0.30 mmol, 1.0 eq.), THF (0.150 mL), ethanol-OD (44 μ L, 0.75 mmol, 2.5 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 18 h at 40 °C. Upon completion, the crude product mixture was dry loaded onto a silica gel column. Flash column chromatography using gradient elution (100 mL of 100% HPLC hexanes, 100 mL of 5% ethyl acetate in HPLC hexanes, 100 mL of 7% ethyl acetate in HPLC hexanes) gave the pure product as a clear colorless oil (25 mg, 0.16 mmol, 54% yield).

¹H NMR: (300 MHz, CDCl₃)

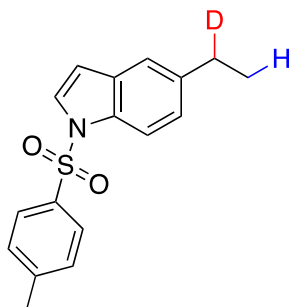
δ 8.87 (br s, 1H), 8.12 – 7.98 (m, 2H), 7.62 – 7.56 (m, 2H), 7.41 – 7.31 (m, 1H), 2.89 – 2.75 (m, 1.03H), 1.36 – 1.29 (m, 3H).

^2H NMR: (61 MHz, CHCl_3)
 δ 2.85 (s, 0.97D).

^{13}C NMR: (101 MHz, CDCl_3)
 δ 149.67, 147.29, 142.72, 135.66, 130.83, 129.42, 125.43, 121.24, 28.64 (t, J = 19.7 Hz), 15.44.

ATR-IR (cm^{-1}):
 3012, 2964, 2932, 2906, 2873, 2169, 1363.

HRMS: (ESI) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{11}\text{H}_{10}\text{ND}$ 159.1034; Found 159.1025.



5-(ethyl-1-*d*)-*N*-tosylindole [12]. According to the general procedure B, DTB-DPPBz (3.0 mg, 0.0033 mmol, 0.011 eq.), $\text{Cu}(\text{OAc})_2$ (15 μL of a 0.2 M solution in THF, 0.003 mmol, 0.01 eq.), and THF (0.135 mL), then dimethoxy(methyl)silane (111 μL , 0.90 mmol, 3 eq) were combined in a 2-dram vial followed by addition of a solution of 5-vinyl-*N*-tosylindole (89 mg, 0.3 mmol, 1 eq.), THF (0.150 mL), and ethanol-OD (44 μL , 0.75 mmol, 2.5 eq). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 23 h at 40 $^\circ\text{C}$. After silica plug filtration using diethyl ether (100 mL) as the eluent, the solvent was concentrated, and the crude oil was dry loaded onto a silica gel column. Flash column chromatography using gradient elution (100 mL 100% hexanes, 100 mL 3% ethyl acetate in hexanes, and 100 mL 6% ethyl acetate in hexanes) to give the pure product as a purple oil (66 mg, 0.22 mmol, 73% yield).

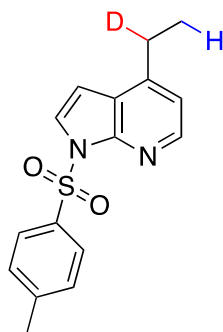
^1H NMR: (400 MHz, CDCl_3)
 δ 7.91 (d, J = 8.5 Hz, 1H), 7.77 (d, J = 8.2 Hz, 2H), 7.53 (d, J = 3.7 Hz, 1H), 7.34 (d, J = 1.8 Hz, 1H), 7.23 – 7.14 (m, 3H), 6.60 (d, J = 3.6 Hz, 1H), 2.75 – 2.63 (m, 1.02H), 2.32 (s, 3H), 1.24 (d, J = 7.6 Hz, 3H).

^2H NMR: (61 MHz, CHCl_3)
 δ 2.70 (s, 0.98D).

^{13}C NMR: (101 MHz, CDCl_3)
 δ 144.89, 139.47, 135.47, 133.31, 131.10, 129.93, 126.89, 126.48, 125.07, 120.10, 113.39, 109.06, 28.47 (t, J = 19.5 Hz), 21.63, 16.02.

ATR-IR (cm^{-1}):
 3142, 3113, 2963, 2929, 2873, 2360, 1590, 1366, 1170

HRMS: (EI^+) m/z : $[\text{M}]^+$ Calcd for $\text{C}_{17}\text{H}_{16}\text{DNO}_2\text{S}$ 300.1000; Found 300.1035.



4-(ethyl-1-*d*)-1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine [13]. According to the general procedure B, DTB-DPPBz (3.0 mg, 0.0033 mmol, 0.011 eq.), Cu(OAc)₂ (15 μ L of a 0.2 M solution in THF, 0.003 mmol, 0.01 eq.), and THF (0.135 mL), then dimethoxy(methyl)silane (111 μ L, 0.90 mmol, 3 eq) were combined in a 2-dram vial followed by addition of a solution of 1-tosyl-4-vinyl-1*H*-pyrrolo[2,3-*b*]pyridine (90 mg, 0.30 mmol, 1 eq.), THF (0.150 mL), and ethanol-OD (44 μ L, 0.75 mmol, 2.5 eq). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 23 h at 40 °C. After silica plug filtration using diethyl ether (100 mL) as the eluent, the solvent was concentrated, and the crude oil was dry loaded onto a silica gel column. Flash column chromatography using gradient elution (50 mL 100% hexanes, 100 mL 10% ethyl acetate in hexanes, and 100 mL 15% ethyl acetate in hexanes) to give the pure product as a yellow solid (63 mg, 0.21 mmol, 70% yield).

¹H NMR: (400 MHz, CDCl₃)

δ 8.33 (d, *J* = 5.0 Hz, 1H), 8.06 (d, *J* = 8.5 Hz, 2H), 7.68 (d, *J* = 4.1 Hz, 1H), 7.24 (d, *J* = 8.4 Hz, 2H), 6.99 (d, *J* = 5.1 Hz, 1H), 6.61 (d, *J* = 4.1 Hz, 1H), 2.86 – 2.74 (m, 1.02H), 2.34 (s, 3H), 1.26 (d, *J* = 7.5 Hz, 3H).

²H NMR: (61 MHz, CHCl₃)

δ 2.82 (s, 0.98D).

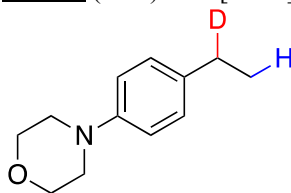
¹³C NMR: (75 MHz, CDCl₃)

δ 147.28, 146.73, 145.25, 145.10, 135.63, 129.68, 128.08, 125.60, 122.21, 117.88, 103.66, 25.44 (t, *J* = 19.6 Hz), 21.70, 13.97.

ATR-IR (cm⁻¹):

3151, 3117, 2964, 2929, 2879, 2323, 1592, 1367, 1145.

HRMS: (ESI⁺) *m/z*: [M+H]⁺ Calcd for C₁₆H₁₆DN₂O₂S 302.1080; Found 302.1065.



4-[4-(ethyl-1-*d*)-phenyl]-morpholine [14]. According to the general procedure B, DTB-DPPBz (3.0 mg, 0.0033 mmol, 0.011 eq.), Cu(OAc)₂ (15 μ L of a 0.2 M solution in THF, 0.003 mmol, 0.01 eq.), THF (0.135 mL), then dimethoxy(methyl)silane (111 μ L, 0.90 mmol, 3 eq.) were combined in a 2-dram vial followed by addition of a solution of 4-(4-ethenylphenyl)-morpholine (57 mg, 0.30 mmol, 1 eq.), THF (0.150 mL), ethanol-OD (44 μ L, 0.75 mmol, 2.5 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 19 h at 40 °C. Upon completion, the crude product mixture was dry loaded onto a silica gel column. Flash chromatography using gradient elution (100 mL 100% HPLC hexanes, 100 mL of 1% ethyl acetate in HPLC hexanes, 100 mL of 2% ethyl acetate in HPLC hexanes, 200 mL of 3% ethyl acetate in HPLC hexanes, 100 mL of 5% ethyl acetate in HPLC hexanes) gave the pure product as a red solid (47 mg, 0.24 mmol, 80% yield).

¹H NMR (300 MHz, CDCl₃)

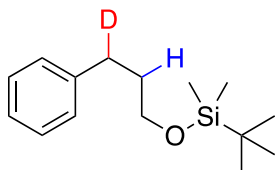
δ 7.13 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.5 Hz, 2H), 3.87 (t, J = 4.6 Hz, 4H), 3.13 (t, J = 4.6 Hz, 4H), 2.64 – 2.52 (m, 1.04H), 1.22 (d, J = 7.6 Hz, 3H).

$^2\text{H NMR}$ (61 MHz, CHCl_3)
 δ 2.60 (s, 0.96D), 1.24 (s, 0.04).

$^{13}\text{C NMR}$ (75 MHz, CDCl_3)
 δ 149.46, 136.11, 128.63, 116.10, 67.12, 49.95, 27.68 (t, J = 19.4 Hz), 15.80.

ATR-IR (cm^{-1}):
 2959, 2924, 2863, 2833, 2141, 1226, 1118.

HRMS: (ESI^+) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{12}\text{H}_{17}\text{NOD}$ 193.1453; Found 193.1445.



(Z)-1-tert-butyldimethylsilyloxy-3-phenyl-(propane-3-d) [15]: According to the general procedure B, DTB-DPPBz (3.0 mg, 0.0033 mmol, 0.011 eq.), $\text{Cu}(\text{OAc})_2$ (15 μL of a 0.2 M solution in THF, 0.003 mmol, 0.01 eq.), THF (0.135 mL), then dimethoxy(methyl)silane (111 mL, 0.90 mmol, 3 eq.) were combined in a 2-dram vial followed by addition of a solution of (Z)-1-tert-butyldimethylsilyloxy-3-phenyl-2-propene (75 mg, 0.30 mmol, 1 eq.), THF (0.150 mL), ethanol-OD (44 μL , 0.75 mmol, 2.5 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 23 h at 40 $^\circ\text{C}$. Upon completion, the crude product mixture was dry loaded onto a silica gel column. Flash chromatography using gradient elution (100 mL of 100% HPLC hexanes, 100 mL of 1% ethyl acetate in HPLC hexanes, 100 mL of 2% ethyl acetate in HPLC hexanes) gave the pure product as a clear colorless oil (67 mg, 0.27 mmol, 90% yield).

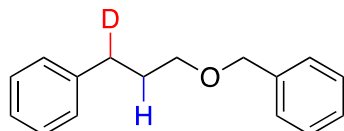
$^1\text{H NMR}$ (400 MHz, CDCl_3)
 δ 7.31 (t, J = 7.4 Hz, 2H), 7.25 – 7.17 (m, 3H), 3.67 (t, J = 6.3 Hz, 2H), 2.74 – 2.65 (m, 1.01H), 1.87 (q, J = 6.8 Hz, 2H), 0.95 (s, 9H), 0.09 (s, 6H).

$^2\text{H NMR}$ (61 MHz, CHCl_3)
 δ 2.69 (s, 0.99D)

$^{13}\text{C NMR}$ (101 MHz, CDCl_3)
 δ 142.36, 128.61, 128.41, 125.81, 62.48, 34.55, 31.89 (t, J = 19.4 Hz), 26.11, 18.48, -5.13.

ATR-IR (cm^{-1}):
 3026, 2953, 2928, 2893, 2856, 2172, 1252, 1099.

HRMS: (EI^+) m/z : $[\text{M}-\text{C}_4\text{H}_9]^+$ Calcd for $\text{C}_{11}\text{H}_{16}\text{DOSi}$ 194.1111; Found 194.1105.
 The major ion peak represents the parent molecule after loss of the *t*-Bu cation.



(3-(benzyloxy)propyl-1-d)benzene [16]. According to the general procedure B, DTB-DPPBz (3.0 mg, 0.0033 mmol, 0.011 eq.), $\text{Cu}(\text{OAc})_2$ (15 μL of a 0.2 M solution in THF, 0.003 mmol, 0.01 eq.), THF (0.135 mL), then dimethoxy(methyl)silane (111 μL , 0.90 mmol, 3 eq.) were combined in a 2-dram vial followed by addition of a solution of (*E*)-(3-(benzyloxy)prop-1-en-1-yl)benzene (67 mg, 0.30 mmol, 1 eq.), THF (0.150 mL), ethanol-OD (44 μL , 0.75 mmol, 2.5 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 18 h at 40 $^\circ\text{C}$. Upon completion, the crude product mixture was dry loaded onto

a silica gel column. Flash chromatography using gradient elution (100 mL of 100% HPLC hexanes, 100 mL of 1% ethyl acetate in HPLC hexanes) gave the pure product as a clear colorless oil (59 mg, 0.26 mmol, 87% yield).

¹H NMR: (400 MHz, CDCl₃)

δ 7.40 (m, *J* = 4.3 Hz, 4H), 7.37-7.29 (m, 3H), 7.26-7.21 (m, 3H), 4.56 (s, 2H), 3.54 (t, *J* = 6.3 Hz, 2H), 2.80-2.72 (m, 1.01H), 1.99 (q, *J* = 6.7 Hz, 2H)

²H NMR: (61 MHz, CHCl₃)

δ 2.76 (s, 0.99D).

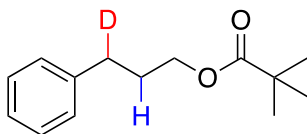
¹³C NMR: (101 MHz, CDCl₃)

δ 142.06, 138.70, 128.59, 128.49, 128.43, 127.78, 127.65, 125.87, 73.03, 69.58, 32.14 (t, *J* = 19.6 Hz), 31.42.

ATR-IR (cm⁻¹):

3084, 3026, 2933, 2853, 2140, 1603, 1096.

HRMS: (EI⁺) *m/z*: [M]⁺ Calcd for C₁₆H₁₇DO 227.1420; Found 227.1412.



3-phenylpropyl-3-*d* pivalate [17]: According to the general procedure B, DTB-DPPBz (3.0 mg, 0.0033 mmol, 0.011 eq.), Cu(OAc)₂ (15 μL of a 0.2 M solution in THF, 0.003 mmol, 0.01 eq.), THF (0.135 mL), then dimethoxy(methyl)silane (111 μL, 0.90 mmol, 3 eq.) were combined in a 2-dram vial followed by addition of a solution of cinnamyl pivalate (65 mg, 0.30 mmol, 1 eq.), THF (0.150 mL), ethanol-OD (44 μL, 0.75 mmol, 2.5 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 22 h at 5 °C. Upon completion, the crude product mixture was dry loaded onto a silica gel column. Flash chromatography using gradient elution (100 mL of 100% HPLC hexanes, 100 mL of 1% ethyl acetate in HPLC hexanes, 100 mL of 2% ethyl acetate in HPLC hexanes, 100 mL of 3% ethyl acetate in HPLC hexanes) gave the pure product as a clear colorless oil (50 mg, 0.23 mmol, 77% yield).

¹H NMR (400 MHz, CDCl₃)

δ 7.30 (t, *J* = 7.4 Hz, 2H), 7.21 (t, *J* = 7.6 Hz, 3H), 4.09 (t, *J* = 6.4 Hz, 2H), 2.74 – 2.65 (m, 1.03H), 1.97 (q, *J* = 6.8 Hz, 2H), 1.24 (s, 9H).

²H NMR (61 MHz, CHCl₃)

δ 2.71 (s, 0.97D).

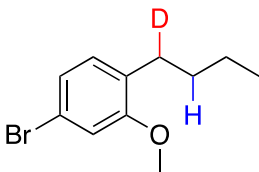
¹³C NMR (101 MHz, CDCl₃)

δ 178.67, 141.34, 128.56, 128.53, 126.11, 63.64, 38.89, 31.92 (t, *J* = 19.3 Hz), 30.35, 27.35.

FT-IR (thin film, cm⁻¹):

3085, 3062, 3026, 2972, 2934, 2872, 2159, 1728, 1157.

HRMS: FT-ICR-MS low mass (+) ion tune *m/z*: [M+H]⁺ Calcd for C₁₄H₂₀DO₂ 222.1606; Found 222.1600.



4-bromo-1-butyl-*d*-2-methoxy-benzene [18]. According to the general procedure B, DTB-DPPBz (3.0 mg, 0.0033 mmol, 0.011 eq.), Cu(OAc)₂ (15 μL of a 0.2 M solution in THF, 0.003 mmol, 0.01 eq.), THF (0.135

mL), then dimethoxy(methyl)silane (111 μ L, 0.90 mmol, 3 eq) were combined in a 2-dram vial followed by addition of a solution of (*E/Z*)-4-bromo-1-(but-1-en-1-yl)-2-methoxybenzene (72 mg, 0.30 mmol, 1 eq.), THF (0.150 mL), ethanol-OD (44 μ L, 0.75 mmol, 2.5 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 17 h at 40 °C. Upon completion, the crude product mixture was dry loaded onto a silica gel column. Flash column chromatography (200 mL of 100% HPLC hexanes) gave the pure product as a clear colorless oil (61 mg, 0.25 mmol, 83% yield).

¹H NMR: (400 MHz, CDCl₃)

δ 7.29 – 7.27 (m, 1H), 7.26 – 7.24 (m, 1H), 6.72 (d, J = 8.4 Hz, 1H), 3.81 (s, 3H), 2.60 – 2.52 (m, 1.02H), 1.59 – 1.50 (m, 2H), 1.37 (sxt, J = 7.3 Hz, 2H), 0.94 (t, J = 7.3 Hz, 3H).

²H NMR: (61 MHz, CHCl₃)

δ 2.57 (s, 0.98 D)

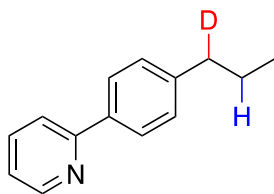
¹³C NMR: (101 MHz, CDCl₃)

δ 156.56, 133.66, 132.34, 129.27, 112.52, 111.82, 55.48, 31.71, 29.43 (t, J = 19.6 Hz), 22.53, 13.98.

ATR-IR (cm⁻¹):

3001, 2955, 2929, 2871, 2860, 2835, 2158, 1240, 1032.

HRMS: (EI⁺) m/z : [M]⁺ Calcd for C₁₁H₁₄DOBr 243.0369; Found 243.0363.



2-(4-(propyl-1-*d*)phenyl)pyridine [19]. According to the general procedure B, DTB-DPPBz (3.0 mg, 0.0033 mmol, 0.011 eq.), Cu(OAc)₂ (15 μ L of a 0.2 M solution in THF, 0.003 mmol, 0.01 eq.), and THF (0.135 mL) then dimethoxy(methyl)silane (111 μ L, 0.90 mmol, 3 eq.) were combined in a 2-dram vial followed by addition of a solution of (*E/Z*)-2-(4-(prop-1-en-1-yl)phenyl)pyridine (59 mg, 0.30 mmol, 1 eq.), THF (0.150 mL), and ethanol-OD (44 μ L, 0.75 mmol, 2.5 eq). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 22 h at 40 °C. After silica plug filtration using diethyl ether (100 mL) as the eluent, the solvent was concentrated, and the crude oil was dry loaded onto a silica gel column. Flash column chromatography using gradient elution (100 mL of 100% HPLC hexanes, 300 mL 3% ethyl acetate in HPLC hexanes, and 100 mL 5% ethyl acetate in HPLC hexanes) to give the pure product as a yellow oil (45 mg, 0.23 mmol, 77% yield).

¹H NMR: (400 MHz, CDCl₃)

δ 8.68 (d, J = 4.1 Hz, 1H), 7.92 (d, J = 8.0 Hz, 2H), 7.77 – 7.68 (m, 2H), 7.29 (d, J = 7.8 Hz, 2H), 7.24 – 7.16 (m, 1H), 2.68 – 2.58 (m, 1.02H), 1.68 (p, J = 7.4 Hz, 2H), 0.97 (t, J = 7.4 Hz, 3H).

²H NMR: (61 MHz, CHCl₃)

δ 2.63 (s, 0.98D).

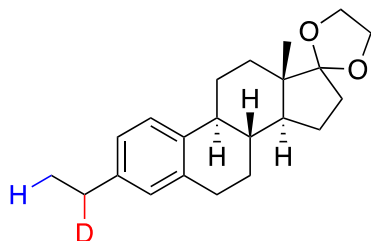
¹³C NMR: (75 MHz, CDCl₃)

δ 157.65, 149.72, 143.82, 137.00, 136.75, 129.01, 126.88, 121.88, 120.38, 37.90 (s, peak represents dihydrogen at the benzylic carbon), 37.52 (t, J = 19.3 Hz), 24.51, 13.90.

ATR-IR (cm⁻¹):

3050, 3008, 2958, 2928, 2870, 2359, 1296.

HRMS: (ESI⁺) m/z : [M+H]⁺ Calcd for C₁₄H₁₅DN 199.1380; Found 199.1338.



(8*R*,9*S*,13*S*,14*S*)-3-(ethyl-1-*d*)-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydrospiro[cyclopenta[*a*]phenanthrene-17,2'-[1,3]dioxolane] [20]. Following the general procedure B, in a N₂ filled glovebox, DTB-DPPBz (6.0 mg, 0.0066 mmol, 0.022 eq.), Cu(OAc)₂ (30 μL of a 0.2 M solution in THF, 0.006 mmol, 0.02 eq.), and THF (0.120 mL) then dimethoxy(methyl)silane (111 μL, 0.90 mmol, 3 eq.) were combined in a 2-dram vial followed by addition of a solution of 8*R*,9*S*,13*S*,14*S*)-13-methyl-3-vinyl-6,7,8,9,11,12,13,14,15,16-decahydrospiro[cyclopenta[*a*]phenanthrene-17,2'-[1,3]dioxolane] (97 mg, 0.30 mmol, 1 eq.), THF (0.150 mL), and ethanol-OD (44 μL, 0.75 mmol, 2.5 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 26 h at 40 °C. After silica plug filtration using diethyl ether (100 mL) as the eluent, the solvent was concentrated, and the crude oil was dry loaded onto a silica gel column. Flash column chromatography using gradient elution (100 mL 100% HPLC hexanes, 100 mL 5% ethyl acetate in HPLC hexanes, and 100 mL 9% ethyl acetate in HPLC hexanes) to give the pure product as a viscous yellow oil (72 mg, 0.22 mmol, 73% yield).

¹H NMR: (400 MHz, CDCl₃)

δ 7.25 (d, *J* = 8.5 Hz, 1H), 7.02 (d, *J* = 8.0 Hz, 1H), 6.95 (s, 1H), 4.04 – 3.86 (m, 4H), 2.97 – 2.81 (m, 2H), 2.65 – 2.54 (m, 1.06H), 2.41 – 2.24 (m, 2H), 2.11 – 2.01 (m, 1H), 1.98 – 1.74 (m, 4H), 1.73 – 1.61 (m, 1H), 1.61 – 1.33 (m, 5H), 1.24 (d, *J* = 7.6 Hz, 3H), 0.90 (s, 3H).

²H NMR: (61 MHz, CHCl₃)

δ 2.60 (s, 0.94D), 1.25 (s, 0.02D).

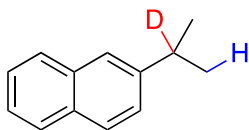
¹³C NMR: (101 MHz, CDCl₃)

δ 141.51, 137.77, 136.72, 128.59, 125.46, 125.28, 119.56, 65.38, 64.71, 49.58, 46.28, 44.09, 39.06, 34.35, 30.89, 29.70, 28.08 (t, *J* = 19.6 Hz), 27.16, 26.09, 22.49, 15.69, 14.45.

ATR-IR (cm⁻¹):

2933, 2872, 1739, 1614, 1104, 1044.

HRMS: (EI⁺) *m/z*: [M]⁺ Calcd for C₂₂H₂₉DO₂ 327.2309; Found 327.2303.



2-(1-methyl-1-*d*-ethyl)naphthlene [21]: According to the general procedure B, DTB-DPPBz (8.9 mg, 0.0099 mmol, 0.033 eq.), Cu(OAc)₂ (45 μL of a 0.2 M solution in THF, 0.009 mmol, 0.03 eq.), THF (0.105 mL), then dimethoxy(methyl)silane (148 μL, 1.20 mmol, 4 eq.) were combined in a 2-dram vial followed by addition of a solution of 2-(1-methylethenyl)-naphthlene (50 mg, 0.30 mmol, 1 eq.), THF (0.150 mL), 2-propanol-*d*₈ (69 μL, 0.9 mmol, 3 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 24 h at 60°C. Upon completion, the crude product mixture was dry loaded onto a silica gel column. Flash chromatography (150 mL of 100% HPLC hexanes) gave the pure product as a clear colorless oil (37 mg, 0.22 mmol, 73% yield).

¹H NMR (400 MHz, CDCl₃)

δ 7.91 – 7.81 (m, 3H), 7.70 (s, 1H), 7.54 – 7.42 (m, 3H), 3.13 (m, *J* = 7.1 Hz, 0.24H), 1.39 (s, 5.81H).

^2H NMR (61 MHz, CHCl_3)
 δ 3.03 (s, 0.76D), 1.33 (s, 0.19D).

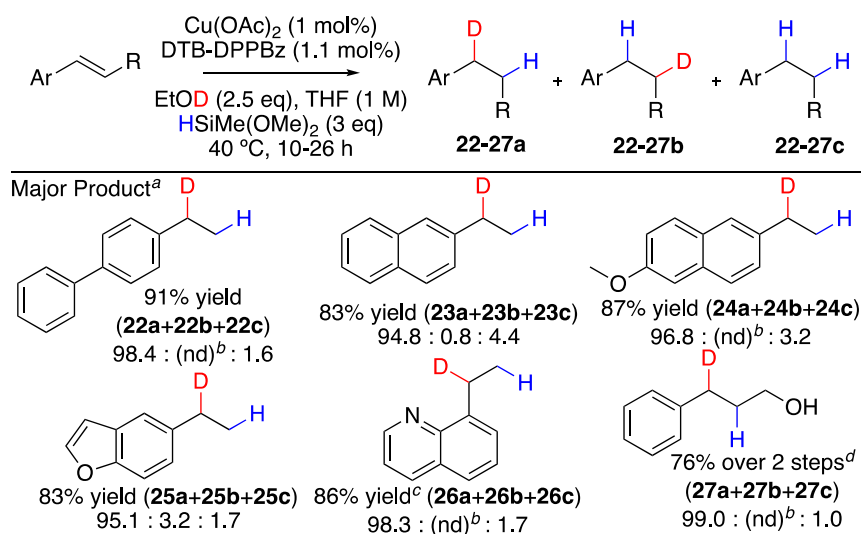
^{13}C NMR (101 MHz, CDCl_3)
 δ 146.42, 133.80, 132.23, 127.97, 127.70, 125.94, 125.86, 125.19, 124.22, 34.29, 33.94 (t, $J = 19.5$ Hz), 24.06, 23.97, 23.77 (t, $J = 19.2$ Hz).

FT-IR (thin film, cm^{-1}):
 3053, 3017, 2959, 2926, 2867, 2145, 1914, 1633, 1600.

HRMS: (EI^+) m/z : $[\text{M}]^+$ Calcd for $\text{C}_{13}\text{H}_{13}\text{D}_1$ 171.1200; Found 171.1151.

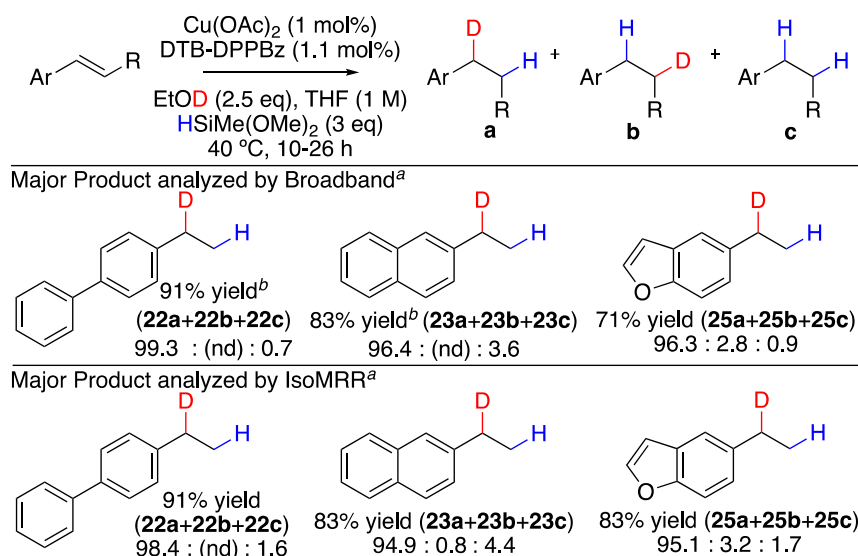
Transfer Hydrodeuteration Substrate Scope Analyzed by MRR

Scheme S2. Transfer Hydrodeuteration Substrate Scope Analyzed by MRR

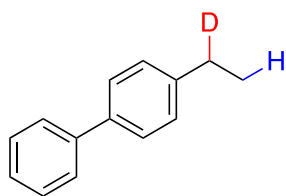


^aThe major products were **22-27a**, the product distribution was determined by MRR and the ratio represents the ratio of all products in the product mixture after purification. ^bCompound not detected (nd) by ^2H NMR or MRR. See SI for detection limits. ^c2 mol % $\text{Cu}(\text{OAc})_2$ and 2.2 mol % DTB-DPPBz were used. ^dTransfer deuteration product was purified then subjected to TBS deprotection.

Table S2.1 Substrate Scope Analyzed by MRR – Broadband/IsoMRR instrument



^aThe major products were **a,b,c** and the ratio represents the ratio of all products in the product mixture after purification. ^bPolymethylhydrosiloxane (3 eq.) used instead of dimethoxy(methyl)silane (3 eq.).



4-(ethyl-1-*d*)-biphenyl [22a]. According to the general procedure B but on a 2.17x scale, DTB-DPPBz (6.4 mg, 0.00715 mmol, 0.011 eq.), Cu(OAc)₂ (33 μ L of a 0.2 M solution in THF, 0.0065 mmol, 0.01 eq.), THF (0.297 mL), then poly(methylhydrosiloxane) (130 μ L, 1.95 mmol, 3 eq. based on Si-H)¹ were combined in a 2-dram vial followed by addition of a solution of 4-Vinylbiphenyl (117 mg, 0.65 mmol, 1 eq.), THF (0.320 mL), ethanol-OD (95 μ L, 1.63 mmol, 2.5 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 26 h at 40 $^\circ$ C. Upon completion, the crude product mixture was dry loaded onto a silica gel column. Flash column chromatography (200 mL of 100% HPLC hexanes) gave the pure product as a white crystalline solid (109 mg, 0.59 mmol, 91% isolated yield of isotopic product mixture). *Product was analyzed by the Broadband instrument.

¹H NMR: (300 MHz, CDCl₃)

δ 7.60 (d, J = 7.4 Hz, 2H), 7.54 (d, J = 7.9 Hz, 2H), 7.42 (t, J = 7.4 Hz, 2H), 7.36 – 7.30 (m, 1H), 7.27 (d, J = 7.9 Hz, 2H), 2.79 – 2.56 (m, 1H), 1.28 (d, J = 7.5 Hz, 3H).

²H NMR: (61 MHz, CHCl₃)

δ 2.68 (s, 1D).

¹³C NMR: (75 MHz, CDCl₃)

δ 143.40, 141.29, 138.72, 128.82, 128.47, 127.18, 127.10, 127.07, 28.29 (t, J = 19.5 Hz), 15.64.

ATR-IR (cm⁻¹):

3054, 3028, 2962, 2930, 2873, 2135.

HRMS: (EI⁺) m/z : [M]⁺ Calcd for C₁₄H₁₃D 183.1200; Found 183.1152.

MRR Spectroscopy: See MRR SI in publication⁶³ for characterization details.

4-(ethyl-1-*d*)-biphenyl [22a]. According to the general procedure B but on a 2.17x scale, DTB-DPPBz (6.4 mg, 0.00715 mmol, 0.011 eq.), Cu(OAc)₂ (33 μ L of a 0.2 M solution in THF, 0.0065 mmol, 0.01 eq.), THF (0.297 mL), then dimethoxy(methyl)silane (241 μ L, 1.95 mmol, 3 eq.) were combined in a 2-dram vial followed by addition of a solution of 4-Vinylbiphenyl (117 mg, 0.65 mmol, 1 eq.), THF (0.320 mL), ethanol-OD (95 μ L, 1.63 mmol, 2.5 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 19 h at 40 °C. Upon completion, the crude product mixture was dry loaded onto a silica gel column. Flash column chromatography (200 mL of 100% HPLC hexanes) gave the pure product as a white crystalline solid (108 mg, 0.59 mmol, 91% isolated yield of isotopic product mixture). *Product was analyzed by the IsoMRR instrument.

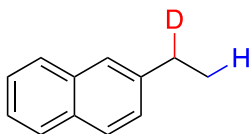
¹H NMR: (300 MHz, CDCl₃)

δ 7.59 (d, J = 7.2 Hz, 2H), 7.53 (d, J = 8.3 Hz, 2H), 7.43 (t, J = 7.4 Hz, 2H), 7.37 – 7.32 (m, 1H), 7.29 (d, J = 8.3 Hz, 2H), 2.76 – 2.62 (m, 1H), 1.27 (d, J = 7.7 Hz, 3H).

²H NMR: (61 MHz, CHCl₃)

δ 2.70 (s, 1D).

MRR Spectroscopy: See MRR SI in publication⁶³ for characterization details.



2-(ethyl-1-*d*)-naphthalene [23a]. According to the general procedure B but on a 2.17x scale, DTB-DPPBz (6.4 mg, 0.00715 mmol, 0.011 eq.), Cu(OAc)₂ (33 μ L of a 0.2 M solution in THF, 0.0065 mmol, 0.01 eq.), THF (0.297 mL), then poly(methylhydrosiloxane) (173 μ L, 2.60 mmol, 4 eq. based on Si-H)¹ were combined in a 2-dram vial followed by addition of a solution of 2-Vinylnaphthalene (100 mg, 0.65 mmol, 1 eq.), THF (0.320 mL), ethanol-OD (95 μ L, 1.63 mmol, 2.5 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 9.5 h at 40 °C. Upon completion, the crude product mixture was dry loaded onto a silica gel column. Flash column chromatography (200 mL of 100% HPLC hexanes) gave the pure product as a clear colorless oil (85 mg, 0.54 mmol, 83% isolated yield of isotopic product mixture). *Product was analyzed by the Broadband instrument.

¹H NMR: (400 MHz, CDCl₃)

δ 7.88 – 7.76 (m, 3H), 7.65 (s, 1H), 7.50 – 7.40 (m, 2H), 7.37 (d, J = 8.5 Hz, 1H), 2.88 – 2.77 (m, 1.01H), 1.34 (d, J = 7.6 Hz, 3H).

²H NMR: (61 MHz, CHCl₃)

δ 2.82 (s, 0.99D).

¹³C NMR: (101 MHz, CDCl₃)

δ 141.88, 133.82, 132.06, 127.93, 127.73, 127.55, 127.22, 125.96, 125.68, 125.14, 28.84 (t, J = 19.3 Hz), 15.61.

ATR-IR (cm⁻¹):

3049, 2962, 2930, 2872, 2166, 1506, 1454.

HRMS: (EI⁺) m/z : [M]⁺ Calcd for C₁₂H₁₁D 157.1000; Found 157.0995.

MRR Spectroscopy: See MRR SI in publication⁶³ for characterization details.

2-(ethyl-1-*d*)-naphthalene [23a]. According to the general procedure B but on a 2.17x scale, DTB-DPPBz (6.4 mg, 0.00715 mmol, 0.011 eq.), Cu(OAc)₂ (33 μ L of a 0.2 M solution in THF, 0.0065 mmol, 0.01 eq.), THF (0.297 mL), then dimethoxy(methyl)silane (241 μ L, 1.95 mmol, 3 eq.) were combined in a 2-dram vial followed by addition of a solution of 2-Vinylnaphthalene (100 mg, 0.65 mmol, 1 eq.), THF (0.320 mL),

ethanol-OD (95 μ L, 1.63 mmol, 2.5 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 20 h at 40 °C. Upon completion, the crude product mixture was dry loaded onto a silica gel column. Flash column chromatography (200 mL of 100% HPLC hexanes) gave the pure product as a clear colorless oil (85 mg, 0.54 mmol, 83% isolated yield of isotopic product mixture). *Product was analyzed by the IsoMRR instrument.

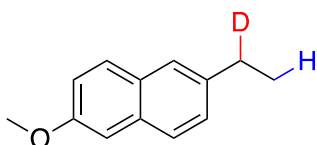
^1H NMR: (300 MHz, CDCl_3)

δ 7.87 – 7.75 (m, 3H), 7.65 (s, 1H), 7.51 – 7.40 (m, 2H), 7.37 (d, J = 8.4 Hz, 1H), 2.90 – 2.75 (m, 1H), 1.35 (d, J = 7.6 Hz, 3H).

^2H NMR: (61 MHz, CHCl_3)

δ 2.83, (s, 0.94D).

MRR Spectroscopy: See MRR SI in publication⁶³ for characterization details.



2-(ethyl-1-*d*)-6-methoxynaphthalene [24a]. According to the general procedure B, DTB-DPPBz (3.0 mg, 0.0033 mmol, 0.011 eq.), $\text{Cu}(\text{OAc})_2$ (15 μ L of a 0.2 M solution in THF, 0.003 mmol, 0.01 eq.), THF (0.135 mL), then dimethoxy(methyl)silane (111 μ L, 0.90 mmol, 3 eq) were combined in a 2-dram vial followed by addition of a solution of 2-Ethenyl-6-methoxynaphthalene (55 mg, 0.30 mmol, 1 eq.), THF (0.150 mL), ethanol-OD (44 μ L, 0.75 mmol, 2.5 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 17 h at 40°C. Upon completion, the crude product mixture was dry loaded onto a silica gel column. Flash column chromatography using gradient elution (100 mL of 100% HPLC hexanes, 100 mL of 1% ethyl acetate in HPLC hexanes) gave the pure product as a white solid (48 mg, 0.26 mmol, 87% isolated yield of isotopic product mixture).

^1H NMR: (300 MHz, CDCl_3)

δ 7.70 (dd, J = 8.0, 2.2 Hz, 2H), 7.58 (s, 1H), 7.34 (dd, J = 8.4, 1.8 Hz, 1H), 7.18 – 7.10 (m, 2H), 3.93 (s, 3H), 2.85 – 2.72 (m, 1.04H), 1.33 (d, J = 7.9 Hz, 3H).

^2H NMR: (61 MHz, CHCl_3)

δ 2.78 (s, 0.96 D)

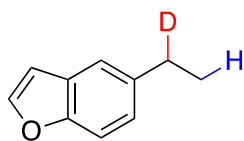
^{13}C NMR: (75 MHz, CDCl_3) δ 157.21, 139.55, 133.02, 129.30, 129.03, 127.68, 126.82, 125.56, 118.72, 105.79, 55.41, 28.62 (t, J = 19.2 Hz), 15.69.

ATR-IR (cm^{-1}):

2980, 2958, 2926, 2908, 2889, 2868, 2280, 1160.

HRMS: (EI^+) m/z : $[\text{M}]^+$ Calcd for $\text{C}_{13}\text{H}_{13}\text{DO}$ 187.1107; Found 187.1101.

MRR Spectroscopy: See MRR SI in publication⁶³ for characterization details.



5-(ethyl-1-*d*)-benzofuran [25a]. According to the general procedure B but on a 2.33x scale, DTB-DPPBz (7.0 mg, 0.0077 mmol, 0.011 eq.), $\text{Cu}(\text{OAc})_2$ (35 μ L of a 0.2 M solution in THF, 0.007 mmol, 0.01 eq.), THF (0.315 mL), then dimethoxy(methyl)silane (259 μ L, 2.10 mmol, 3 eq.) were combined in a 2-dram vial followed by addition of a solution of 5-Vinylbenzofuran (101 mg, 0.70 mmol, 1 eq.), THF (0.350 mL),

ethanol-OD (102 μ L, 1.75 mmol, 2.5 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 25.5 h at 40°C. Upon completion, the crude product mixture was dry loaded onto a silica gel column. Flash column chromatography (150 mL of 100% HPLC hexanes) gave the pure product as a clear colorless oil (73 mg, 0.50 mmol, 71% isolated yield of isotopic product mixture). * Product was analyzed by the Broadband instrument.

^1H NMR: (400 MHz, CDCl_3)

δ 7.63 – 7.59 (m, 1H), 7.48 – 7.41 (m, 2H), 7.16 (d, J = 8.6 Hz, 1H), 6.75 – 6.72 (m, 1H), 2.80 – 2.68 (m, 1.05H), 1.30 (d, J = 7.6, 3H).

^2H NMR: (61 MHz, CHCl_3)

δ 2.75 (s, 0.95D), 1.30 (s, 0.03D)

^{13}C NMR: (75 MHz, CDCl_3)

δ 153.62, 145.16, 138.89, 127.61, 124.61, 119.89, 111.11, 106.53, 28.61 (t, J = 19.5 Hz), 16.40.

ATR-IR (cm^{-1}):

3022, 2959, 2923, 2853, 2170, 1258.

HRMS: (EI^+) m/z : $[\text{M}]^+$ Calcd for $\text{C}_{10}\text{H}_9\text{DO}$ 147.0800; Found 147.0789.

MRR Spectroscopy: See MRR SI in publication⁶³ for characterization details.

5-(ethyl-1-*d*)-benzofuran [25a]. According to the general procedure B but on a 2.17x scale, DTB-DPPBz (6.4 mg, 0.00715 mmol, 0.011 eq.), $\text{Cu}(\text{OAc})_2$ (33 μ L of a 0.2 M solution in THF, 0.0065 mmol, 0.01 eq.), THF (0.297 mL), then dimethoxy(methyl)silane (241 μ L, 1.95 mmol, 3 eq.) were combined in a 2-dram vial followed by addition of a solution of 5-Vinylbenzofuran (93.7 mg, 0.65 mmol, 1 eq.), THF (0.320 mL), ethanol-OD (95 μ L, 1.63 mmol, 2.5 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 25 h at 40 °C. Upon completion, the crude product mixture was dry loaded onto a silica gel column. Flash column chromatography (200 mL of 100% HPLC hexanes) gave the pure product as a clear colorless oil (80 mg, 0.54 mmol, 83% isolated yield of isotopic product mixture). *Product was analyzed by the IsoMRR instrument.

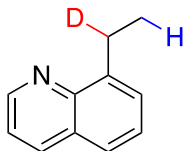
^1H NMR: (400 MHz, CDCl_3)

δ 7.62 – 7.58 (m, 1H), 7.46 – 7.40 (m, 2H), 7.15 (d, J = 8.0 Hz, 1H), 6.75 – 6.70 (m, 1H), 2.79 – 2.68 (m, 1H), 1.29 (d, J = 7.5 Hz, 3H).

^2H NMR: (61 MHz, CHCl_3)

δ 2.75 (s, 0.96D), 1.29 (s, 0.02D).

MRR Spectroscopy: See MRR SI in publication⁶³ for characterization details.



8-(ethyl-1-*d*)-quinoline [26a]. According to the general procedure B but on a 2.17x scale, DTB-DPPBz (12.8 mg, 0.0143 mmol, 0.022 eq.), $\text{Cu}(\text{OAc})_2$ (65 μ L of a 0.2 M solution in THF, 0.013 mmol, 0.02 eq.), THF (0.260 mL), then dimethoxy(methyl)silane (241 μ L, 1.95 mmol, 3 eq.) were combined in a 2-dram vial followed by addition of a solution of 8-Vinylquinoline (101 mg, 0.65 mmol, 1 eq.), THF (0.325 mL), ethanol-OD (95 μ L, 1.63 mmol, 2.5 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 25 h at 40 °C. Upon completion, the crude product mixture was dry loaded onto a neutral alumina Brock column. Flash column chromatography using gradient elution (300 mL of 100% HPLC hexanes, 100

mL of 2% ethyl acetate in HPLC hexanes) gave the pure product as a yellow oil (89 mg, 0.56 mmol, 86% isolated yield of isotopic product mixture).

¹H NMR: (400 MHz, CDCl₃)

δ 8.95 (d, *J* = 4.0 Hz, 1H), 8.17–8.10 (m, 1H), 7.66 (d, *J* = 8.1 Hz, 1H), 7.58 (d, *J* = 7.0 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 1H), 7.42 – 7.36 (m, 1H), 3.36 – 3.25 (m, 1.02H), 1.39 (d, *J* = 7.5 Hz, 3H).

²H NMR: (61 MHz, CHCl₃)

δ 3.33 (s, 0.98D).

¹³C NMR: (101 MHz, CDCl₃)

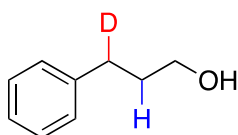
δ 149.37, 146.87, 143.01, 136.50, 128.50, 128.05, 126.55, 125.94, 120.92, 24.40 (t, *J* = 19.4 Hz), 15.10.

ATR-IR (cm⁻¹):

3039, 3002, 2962, 2930, 2870, 2185, 1364.

HRMS: (ESI⁺) *m/z*: [M+H]⁺ Calcd for C₁₁H₁₁DN 159.1080; Found 159.1026.

MRR Spectroscopy: See MRR SI in publication⁶³ for characterization details.



3-phenyl-(propan-3-*d*)-1-ol [27a]. According to the general procedure B but on a 4.07x scale, DTB-DPPBz (12.0 mg, 0.0134 mmol, 0.011 eq.), Cu(OAc)₂ (61 μL of a 0.2 M solution in THF, 0.0122 mmol, 0.01 eq.), THF (0.549 mL), then dimethoxy(methyl)silane (451 μL, 3.66 mmol, 3 eq.) were combined in a 2-dram vial followed by addition of a solution of 1-*tert*-butyldimethylsilyloxy-3-phenyl-2-propene (303 mg, 1.22 mmol, 1 eq.), THF (0.610 mL), ethanol-OD (178 μL, 3.05 mmol, 2.5 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 23 h at 40 °C. After silica plug filtration using diethyl ether (200 mL) as the eluent, the solvent was concentrated, and the crude oil was treated with tetrabutylammonium fluoride (2.44 mL, 2 eq.) and THF (5 mL) for 23 h. Upon completion, reaction mixture was quenched with saturated aqueous NH₄Cl (5 mL) and water (10mL). The aqueous layer was extracted with diethyl ether (3 x 10 mL) and the combined organic layers were washed with water (10 mL) and brine (10 mL), then dried over anhydrous Na₂SO₄. The mixture was filtered, and the solvent was removed by rotary evaporation. Flash column chromatography using gradient elution (100 mL of 100% HPLC hexanes, 100mL of 5% ethyl acetate in HPLC hexanes, 100mL of 10% ethyl acetate in HPLC hexanes, 300mL of 15% ethyl acetate in HPLC hexanes) gave the pure product as a clear colorless oil (127mg, 0.93 mmol, 76% isolated yield over 2 steps of isotopic product mixture).

¹H NMR: (400 MHz, CDCl₃)

δ 7.33 – 7.27 (m, 2H), 7.24 – 7.17 (m, 3H), 3.68 (td, *J* = 6.5, 1.1 Hz, 2H), 2.75 – 2.65 (m, 1H), 1.90 (q, *J* = 6.7 Hz, 2H), 1.56 (br s, 1H).

²H NMR: (61 MHz, CHCl₃)

δ 2.70 (s, 1D).

¹³C NMR: (75 MHz, CDCl₃)

δ 141.90, 128.55, 128.52, 125.99, 62.37, 34.26, 31.84 (t, *J* = 19.5 Hz).

ATR-IR (cm⁻¹):

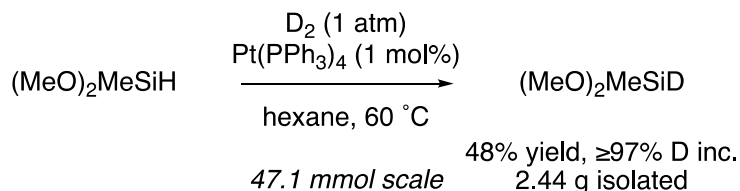
3325, 3060, 3025, 2934, 2873, 2153, 1054.

HRMS: (EI⁺) *m/z*: [M]⁺ Calcd for C₉H₁₁DO 137.1000; Found 137.0945.

MRR Spectroscopy: See MRR SI in publication⁶³ for characterization details.

Synthesis of dimethoxy(methyl)silane-*d*

Procedure for the synthesis of dimethoxy(methyl)silane-*d*



The procedure was adapted from a previously reported method.²⁷ To an oven-dried 500 mL Schlenk flask equipped with a Teflon stir bar in a N₂ filled glovebox was added the Pt(PPh₃)₄ (586 mg, 0.471 mmol, 0.01 eq.), dimethoxy(methyl)silane (5.81 mL, 47.1 mmol, 1 eq.), and 2.5 mL of degassed anhydrous hexanes. The Schlenk flask was sealed with a rubber-septa and removed from the glovebox, connected to a manifold line, and cooled to -78 °C. A single freeze-pump-thaw cycle was performed, and the Schlenk flask was backfilled with D₂ gas from a D₂ purged balloon at room temperature. The flask was sealed with parafilm and heated to 60°C. After 2 hours, the reaction was cooled to room temperature and then a single freeze-pump-thaw was performed again, backfilling with D₂ gas. This process was repeated 6 times or until the ¹H NMR showed ≥95% D incorporation. It is important to maintain a N₂ (g) inert atmosphere while obtaining a minimal quantity of sample for ¹H NMR analysis.

After reaction completion, the solution was purified through a distillation apparatus. The set up consist of a flame-dried 25 mL round-bottom receiving flask sealed with a rubber-septum and a cannula inserted along with a line for a positive N₂ flow. While the receiving flask cools to room temperature, a positive N₂ flow is maintained through the receiving flask and cannula. Upon cooling, the open end of the cannula was inserted into the Schlenk reaction flask. The rubber-septum on the receiving flask was tightly sealed with Parafilm. The 25 mL round-bottom receiving flask was cooled to -78 °C and the N₂ flow from the manifold was closed and then the Schlenk flask was heated to 80°C. The heat initiated the distillation of the dimethoxy(methyl)silane-*d* and the hexane through the cannula, which were trapped as a mixture in the cold 25 mL round-bottom receiving flask. Vacuum was also applied to the 25 mL round-bottom receiving flask to promote this process. Once all of the silane and hexane were trapped in the 25 mL round-bottom receiving flask, the Schlenk flask was removed from the heat and the manifold was closed to the vacuum line and the entire apparatus was put under a positive N₂ atmosphere while the 25 mL round-bottom receiving flask warmed to room temperature. Under positive nitrogen flow, the cannula was removed from the 25 mL round-bottom receiving flask, while keeping it inserted in the Schlenk reaction flask. The 25 mL round-bottom receiving flask was tightly sealed with parafilm, and stored in a -4 °C freezer. The final product was in a solution of hexane, and the molarity was calculated by ¹H NMR using 1,3,5-trimethylbenzene as an internal standard, and used for the transfer hydrodeuteration reaction as needed (2.44 g in a 5.29 M hexane solution, 22.7 mmol, 48% yield).

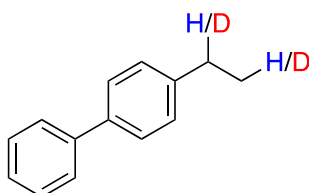
*Note: During the distillation process, it is important to monitor that the end of the cannula does not get clogged by frozen solvent/silane. If this occurs, remove the Schlenk reaction flask from heat and close the manifold to vacuum line. Warm the 25 mL round-bottom receiving flask until the solids on the tip of the cannula melt, and then distillation can be resumed.

Preparation of Isotopic Mixtures (Cocktail Reactions)

General procedure for the synthesis of isotopic mixtures (C)

In a N₂ filled glovebox, (*R*)-DTBM-SEGPHOS (57.1 mg, 0.0484 mmol, 0.022eq.), Cu(OAc)₂ (220 μL of a 0.2 M solution in THF, 0.0440 mmol, 0.02 eq.), and THF (0.780 mL) were added to a flame-dried 100 mL round bottom flask followed by dropwise addition of dimethoxy(methyl)silane (407 μL, 3.30 mmol, 1.5 eq.) and dimethoxy(methyl)silane-*d* (624 μL of a 5.29 M solution in hexanes, 3.30 mmol, 1.5 eq.). A color change from green/blue to brown was observed while stirring for 15 minutes. In a separate oven-dried 2-dram vial

was added the alkene substrate (2.2 mmol, 1 eq.), THF (1.20 mL), ethanol (161 μ L, 2.75 mmol, 1.25 eq), and ethanol-OD (161 μ L, 2.75 mmol, 1.25 eq). The solution in the 2-dram vial was added dropwise over 20 seconds to the 100 mL round bottom flask. The total volume of THF was calculated based on having a final reaction concentration of 1M based on the alkene substrate. The 100 mL round bottom flask was capped with a septum, taken out of the glovebox, and a balloon filled with N₂ was inserted through the septum as the reaction stirred for 19-43 h at the appropriate temperature. Upon completion, the crude product mixture was dry loaded onto a silica gel column and purified by flash column chromatography. Since the product contains a mixture of d₀, d₁ and d₂ isotopologues and isotopomers, isolated yields were calculated based on an average deuterium incorporation of one deuterium.



4-ethylbiphenyl isotopic mixture. According to the general procedure C, (*R*)-DTBM-SEGPPOS (57.6 mg, 0.0488 mmol, 0.022 eq.), Cu(OAc)₂ (222 μ L of a 0.2 M solution in THF, 0.0444 mmol, 0.02 eq.), and THF (0.778 mL) then dimethoxy(methyl)silane (411 μ L, 3.33 mmol, 1.5 eq.) and dimethoxy(methyl)silane-*d* (629 μ L of a 5.29 M solution in hexanes, 3.33 mmol, 1.5 eq.) were combined in a 100 mL round bottom flask followed by addition of a solution of 4-Vinylbiphenyl (400 mg, 2.22 mmol, 1 eq.), THF (1.22 mL), ethanol (162 μ L, 2.78 mmol, 1.25 eq.), and ethanol-OD (162 μ L, 2.78 mmol, 1.25 eq). The 100 mL round bottom flask was capped with a septum, and the reaction stirred for 23 h at 40 °C. Upon completion, the crude product mixture was dry loaded onto a silica gel column. Flash column chromatography (500 mL of 100% HPLC hexanes) to give the pure product as a white crystalline solid (369 mg, 2.01 mmol, 91% isolated yield of the isotopic product mixture).

¹H NMR: (400 MHz, CDCl₃)

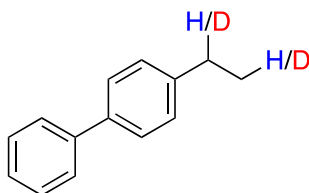
δ 7.59 (d, *J* = 8.1 Hz, 2H), 7.52 (d, *J* = 8.1 Hz, 2H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.36 – 7.31 (m, 1H), 7.28 (d, *J* = 7.9 Hz, 2H), 2.75 – 2.64 (m, 1.69H), 1.32 – 1.23 (m, 2.73H).

²H NMR: (61 MHz, CHCl₃)

δ 2.71 (s, 0.31D), 1.30 (s, 0.27D).

¹³C NMR: (75 MHz, CDCl₃)

δ 143.53, 141.34, 138.75, 128.84, 128.43, 127.22, 127.16, 127.10, 28.76 – 28.51 (m), 15.83 – 15.58 (m).



4-ethylbiphenyl isotopic mixture. The reaction was performed according to the general procedure C but with an increased ratio of the deuterium sources relative to hydrogen sources. Accordingly, (*R*)-DTBM-SEGPPOS (16.9 mg, 0.0143 mmol, 0.022 eq.), Cu(OAc)₂ (65 μ L of a 0.2 M solution in THF, 0.0013 mmol, 0.02 eq.), and THF (0.260 mL) then dimethoxy(methyl)silane (60 μ L, 0.49 mmol, 0.75 eq.) and dimethoxy(methyl)silane-*d* (276 μ L of a 5.29 M solution in hexanes, 1.46 mmol, 2.25 eq.) were combined in a 2-dram vial followed by addition of a solution of 4-Vinylbiphenyl (117 mg, 0.65 mmol, 1 eq.), THF (0.325 mL), ethanol (24 μ L, 0.41 mmol, 0.63 eq.), and ethanol-OD (71 μ L, 1.22 mmol, 1.88 eq). The 2-dram vial was capped with a red pressure relief cap and the reaction stirred for 19 h at 40 °C. Upon completion, the crude product mixture was dry loaded onto a silica gel column. Flash column chromatography (200 mL of 100% HPLC hexanes) to give the pure product as a white crystalline solid (114 mg, 0.62 mmol, 95% isolated yield of the isotopic product mixture).

¹H NMR: (400 MHz, CDCl₃)

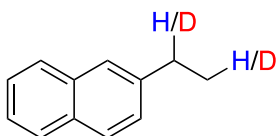
δ 7.59 (d, *J* = 8.2 Hz, 2H), 7.53 (d, *J* = 8.0 Hz, 2H), 7.44 (t, *J* = 7.8 Hz, 2H), 7.37 – 7.32 (m, 1H), 7.30 (d, *J* = 8.0 Hz, 2H), 2.76 – 2.64 (m, 1.29H), 1.31 – 1.26 (m, 2.46H).

²H NMR: (61 MHz, CHCl₃)

δ 2.68 (s, 0.71D), 1.27 (s, 0.52D).

¹³C NMR: (75 MHz, CDCl₃)

δ 143.51, 141.34, 138.75, 128.84, 128.43, 127.22, 127.15, 127.10, 28.78 – 27.91 (m), 15.86 – 15.03 (m).



2-ethylnaphthalene isotopic mixture. According to the general procedure C, (*R*)-DTBM-SEGPPOS (67.2 mg, 0.0570 mmol, 0.022 eq.), Cu(OAc)₂ (259 μL of a 0.2 M solution in THF, 0.0518 mmol, 0.02 eq.), and THF (1.03 mL) then dimethoxy(methyl)silane (480 μL, 3.89 mmol, 1.5 eq.) and dimethoxy(methyl)silane-*d* (735 μL of a 5.29 M solution in hexanes, 3.89 mmol, 1.5 eq.) were combined in a 100 mL round bottom flask followed by addition of a solution of 2-Vinylnaphthalene (400 mg, 2.59 mmol, 1 eq.), THF (1.30 mL), ethanol (189 μL, 3.24 mmol, 1.25 eq.), and ethanol-OD (189 μL, 3.24 mmol, 1.25 eq.). The 100 mL round bottom flask was capped with a septum, and the reaction stirred for 23 h at 40 °C. Upon completion, the crude product mixture was dry loaded onto a silica gel column. Flash column chromatography (300 mL of 100% HPLC hexanes) to give the pure product as a clear colorless oil (358 mg, 2.28 mmol, 88% isolated yield of the isotopic product mixture).

¹H NMR: (400 MHz, CDCl₃)

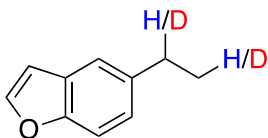
δ 7.89 – 7.75 (m, 3H), 7.66 (s, 1H), 7.53 – 7.42 (m, 2H), 7.39 (d, *J* = 8.5 Hz, 1H), 2.92 – 2.78 (m, 1.71H), 1.42 – 1.30 (m, 2.71H).

²H NMR: (61 MHz, CHCl₃)

δ 2.83 (s, 0.29D), 1.35 (s, 0.29D).

¹³C NMR: (101 MHz, CDCl₃)

δ 141.89, 133.82, 132.05, 127.93, 127.73, 127.55, 127.22, 125.96, 125.67, 125.14, 29.31 – 28.52 (m), 15.74 – 15.07 (m).



5-ethylbenzofuran isotopic mixture. According to the general procedure C, (*R*)-DTBM-SEGPPOS (71.8 mg, 0.0609 mmol, 0.022 eq.), Cu(OAc)₂ (277 μL of a 0.2 M solution in THF, 0.0554 mmol, 0.02 eq.), and THF (1.11 mL) then dimethoxy(methyl)silane (683 μL, 5.54 mmol, 2 eq.) and dimethoxy(methyl)silane-*d* (1.05 mL of a 5.29 M solution in hexanes, 5.54 mmol, 2 eq.) were combined in a 100 mL round bottom flask followed by addition of a solution of 5-Vinylbenzofuran (400 mg, 2.77 mmol, 1 eq.), THF (1.38 mL), ethanol (202 μL, 3.46 mmol, 1.25 eq.), and ethanol-OD (202 μL, 3.46 mmol, 1.25 eq.). The 100 mL round bottom flask was capped with a septum, and the reaction stirred for 43 h at 23 °C. Upon completion, the crude product mixture was dry loaded onto a silica gel column. Flash column chromatography (500 mL of 100% HPLC hexanes) to give the pure product as a clear colorless oil (267 mg, 1.81 mmol, 65% isolated yield of the isotopic product mixture).

¹H NMR: (400 MHz, CDCl₃)

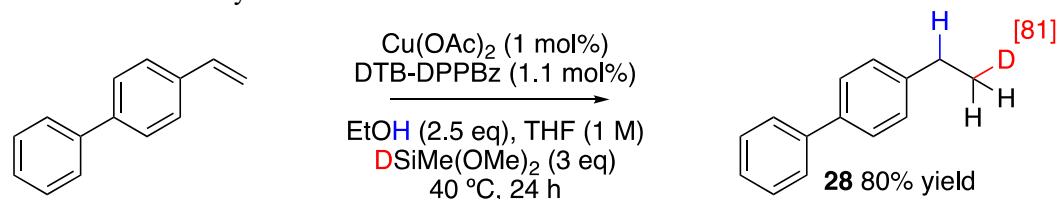
δ 7.62 – 7.59 (m, 1H), 7.45 – 7.39 (m, 2H), 7.15 (d, *J* = 8.5 Hz, 1H), 6.75 – 6.71 (m, 1H), 2.80 – 2.69 (m, 1.43H), 1.32 – 1.24 (m, 2.69H).

^2H NMR: (61 MHz, CHCl_3)
 δ 2.75 (s, 0.57D), 1.30 (s, 0.31D).

^{13}C NMR: (75 MHz, CDCl_3)
 δ 153.62, 145.16, 138.92, 127.61, 124.62, 119.89, 111.11, 106.53, 29.03 – 28.21 (m), 16.61 – 15.89 (m).

Reaction Studies

(a) Switchable Selectivity



4-(ethyl-2-*d*)-biphenyl [28]. According to the general procedure B, DTB-DPPBz (2.0 mg, 0.0022 mmol, 0.011 eq.), Cu(OAc)_2 (10 μL of a 0.2 M solution in THF, 0.002 mmol, 0.01 eq.), THF (0.09 mL), then dimethoxy(methyl)silane-*d* (113 μL of a 5.29 M solution in hexanes, 0.60 mmol, 3 eq.) were combined in a 2-dram vial followed by addition of a solution of 4-Vinylbiphenyl (36 mg, 0.20 mmol, 1 eq.), THF (0.10 mL), ethanol (29 μL , 0.50 mmol, 2.5 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 24 h at 40°C . After silica plug filtration using diethyl ether (100 mL) as the eluent, the solvent was concentrated, and the crude oil was dry loaded onto a silica gel column. Flash column chromatography (150 mL of 100% HPLC hexanes) gave the pure product as a white crystalline solid (30 mg, 0.16 mmol, 80% yield).

^1H NMR: (400 MHz, CDCl_3)
 δ 7.62 (d, $J = 7.6$ Hz, 2H), 7.55 (d, $J = 7.8$ Hz, 2H), 7.46 (t, $J = 7.6$ Hz, 2H), 7.36 (t, $J = 7.2$ Hz, 1H), 7.31 (d, $J = 7.8$ Hz, 2H), 2.72 (t, $J = 7.6$ Hz, 2H), 1.34 – 1.25 (m, 2.19H).

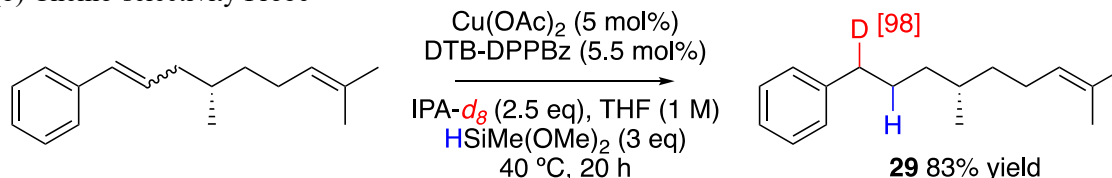
^2H NMR: (61 MHz, CHCl_3)
 δ 1.29 (s, 0.81 D)

^{13}C NMR: (101 MHz, CDCl_3)
 δ 143.52, 141.32, 138.73, 128.84, 128.42, 127.21, 127.15, 127.10, 28.57, 15.45 (t, $J = 19.5$ Hz).

ATR-IR (cm^{-1}):
 3054, 3029, 2930, 2850, 2176.

HRMS: (EI^+) m/z : $[\text{M}]^+$ Calcd for $\text{C}_{14}\text{H}_{13}\text{D}$ 183.1158; Found 183.1151.

(b) Chemo-selectivity Probe



(*S*)-(4,8-dimethylnon-7-en-1-yl-1-*d*)benzene [29]. According to the general procedure B, DTB-DPPBz (14.8 mg, 0.0165 mmol, 0.055 eq.), Cu(OAc)_2 (75 μL of a 0.2 M solution in THF, 0.015 mmol, 0.05 eq.), THF (0.075 mL), then dimethoxy(methyl)silane (111 μL , 0.90 mmol, 3 eq) were combined in a 2-dram vial followed by addition of a solution of (*E/Z*)-(*S*)-(4,8-dimethylnona-1,7-dien-1-yl)benzene (68 mg, 0.30 mmol, 1 eq.), THF (0.150 mL), 2-propanol-*d*₈ (57 μL , 0.75 mmol, 2.5 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 20 h at $40\text{ }^\circ\text{C}$. Upon completion, the crude product mixture was dry loaded onto a silica gel column. Flash column chromatography (100 mL of 100% HPLC hexanes) gave the pure product as a clear colorless oil (57 mg, 0.25 mmol, 83% yield).

¹H NMR: (400 MHz, CDCl₃)

δ 7.34 – 7.28 (m, 2H), 7.24 – 7.18 (m, 3H), 5.14 (t, *J* = 7.1 Hz, 1H), 2.66 – 2.55 (m, 1H), 2.10 – 1.91 (m, 2H), 1.73 (s, 3H), 1.64 (s, 3H), 1.70 – 1.57 (m, 2H), 1.54 – 1.43 (m, 1H), 1.43 – 1.32 (m, 2H), 1.27 – 1.14 (m, 2H), 0.91 (d, *J* = 6.6 Hz, 3H).

²H NMR (61 MHz, CDCl₃)

δ 2.60 (s, 0.99D).

¹³C NMR: (101 MHz, CDCl₃)

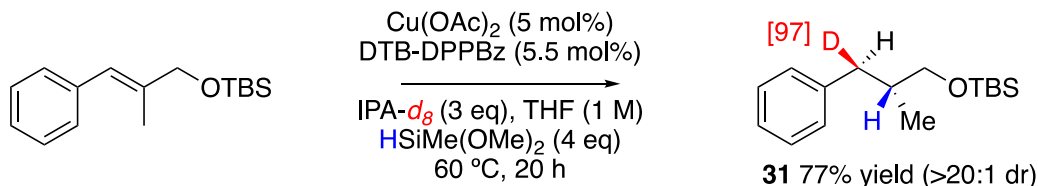
δ 143.04, 131.15, 128.52, 128.37, 125.71, 125.15, 37.20, 36.77, 36.09 (t, *J* = 19.6 Hz), 32.45, 29.09, 25.87, 25.70, 19.70, 17.77.

ATR-IR (cm⁻¹):

3084, 2962, 2923, 2855, 2151, 1800, 1604, 740.

HRMS: (EI⁺) *m/z*: [M]⁺ Calcd for C₁₇H₂₅D, 231.2100; Found 231.2091.

(c) Mechanistic Probe



***tert*-butyldimethyl(2-methyl-3-phenylpropoxy-3-*d*)silane [*anti*-31]:** According to the general procedure B, DTB-DPPBz (14.8 mg, 0.0165 mmol, 0.055 eq.), Cu(OAc)₂ (75 μL of a 0.2 M solution in THF, 0.015 mmol, 0.05 eq.), THF (0.075 mL), then dimethoxy(methyl)silane (148 μL, 1.20 mmol, 4 eq.) were combined in a 2-dram vial followed by addition of a solution of (*E*)-*tert*-butyldimethyl((2-methyl-3-phenylallyl)oxy)silane (79 mg, 0.30 mmol, 1 eq.), THF (0.150 mL), 2-propanol-*d*₈ (69 μL, 0.9 mmol, 3 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 24 h at 60°C. Upon completion, the crude product mixture was dry loaded onto a silica gel column. Flash chromatography using gradient elution (200 mL of 100% HPLC hexanes, 100 mL 1% ethyl acetate in HPLC hexanes) gave the pure product as a clear colorless oil (62 mg, 0.23 mmol, 77% yield).^{4,5}

¹H NMR (400 MHz, CDCl₃)

δ 7.29 (t, *J* = 7.4 Hz, 2H), 7.24 – 7.15 (m, 3H), 3.46 (d, *J* = 5.9 Hz, 2H), 2.87 – 2.78 (m, 0.03H), 2.32 (d, *J* = 8.4 Hz, 1H), 1.90 (hept, *J* = 6.1 Hz, 1H), 0.94 (s, 9H), 0.88 (d, *J* = 6.7 Hz, 2H), 0.07 (s, 6H).

*We attribute the signal at 2.87-2.78ppm that integrates to 0.03 to the *d*₀ impurity, which is consistent with the measurements in scheme 2.

²H NMR (61 MHz, CHCl₃)

δ 2.83 (s, 0.97H).

¹³C NMR (101 MHz, CDCl₃)

δ 141.29, 129.36, 128.24, 125.79, 67.62, 39.35 (t, *J* = 19.5 Hz), 38.00, 26.11, 18.49, 16.56, -5.20 (d, *J* = 3.1 Hz).

ATR-IR (cm⁻¹):

3026, 2954, 2928, 2157, 1802, 1605, 1087.

HRMS: (EI⁺) *m/z*: [M]⁺ Calcd for C₁₂H₁₈DOSi 208.1300; Found 208.1260.

The major ion peak represents the parent molecule after loss of the *t*-Bu cation.

Synthesis of Alkene Starting Materials

General Wittig procedure (D)

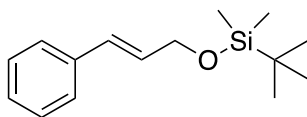
Adapted from a previously reported procedure⁶, to a flame-dried round bottom flask under N₂ atmosphere containing a Teflon stirbar was added dry THF (15 mL, 0.25M) and alkyltriphenylphosphonium bromide (4.03 mmol, 1.1 eq.). The round bottom flask was cooled to 0 °C and sodium hydride or sodium bis(trimethylsilyl)amide 2M in THF (4.03 mmol, 1.1 eq) was added slowly. The mixture stirred for 15 minutes at 0 °C. The aldehyde substrate (3.67 mmol, 1 eq.) was added in portions and the reaction stirred at room temperature for 18 hr. Upon completion, the reaction was placed in an ice bath, and quenched with water (20 mL) and extracted with ether (3 x 15 mL). The combined organic layers were washed with brine (20 mL) and then dried over anhydrous Na₂SO₄. The mixture was filtered, and the solvent was removed by rotary evaporation. The crude product was purified by flash column chromatography to give the desired vinyl arene product.

General TBS protection of alcohol containing substrates (E)

To a flame-dried round bottom flask under a N₂ atmosphere with a Teflon stirbar, was added the alcohol substrate (1.86 mmol, 1 eq.), dry dichloromethane (5 mL) followed by imidazole (253 mg, 3.72 mmol, 2 eq.) and *tert*-butyldimethylsilyl chloride (307 mg, 2.04 mmol, 1.1 eq.). The reaction was stirred at room temperature overnight. Upon completion, the reaction mixture was quenched with water (20 mL) and extracted with diethyl ether (2 x 15 mL). The combined organic layers were washed with brine (15 mL) and dried over anhydrous Na₂SO₄. The mixture was filtered, and the solvent was removed by rotary evaporation. The crude product was purified by flash column chromatography to give the desired TBS protected alcohol.

General Suzuki-Miyaura Coupling procedure (F)

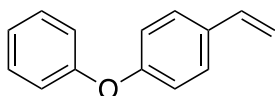
Adapted from a previously reported procedure⁷, to a flame-dried round bottom flask was added a Teflon stir bar, THF/H₂O (7 mL, 9:1) and the solution was degassed for 15 minutes using N₂. In an oven-dried 25 mL pressure vessel under N₂ was added potassium trifluoro(vinyl)borate (477 mg, 3.56 mmol, 1 eq.), cesium carbonate (1.74g, 5.34 mmol, 1.5 eq.), PdCl₂(PPh₃)₂ (50 mg, 0.071 mmol, 0.02 eq.), and the halogen substrate (3.56 mmol, 1 eq.). The THF/H₂O solution was added to the 25 mL pressure vessel and kept under a nitrogen atmosphere while the reaction was stirred in an oil bath at 85 °C for 16-18 hr. Upon completion, the reaction mixture was cooled to room temperature, quenched with H₂O, and extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried over anhydrous Na₂SO₄. The mixture was filtered, and the solvent was removed by rotary evaporation. The crude product was purified by flash column chromatography to give the desired vinyl arene product.



(E)-1-*tert*-Butyldimethylsilyloxy-3-phenyl-2-propene [1] was prepared according to the general procedure E, using the **3-Phenyl-2-propen-1-ol** (2.00 g, 14.91 mmol, 1 eq.), dry dichloromethane (100 mL) followed by imidazole (2.03 g, 29.81 mmol, 2 eq.) and *tert*-butyldimethylsilyl chloride (2.47 g 16.40 mmol, 1.1 eq.). The crude product was purified by flash column chromatography using gradient elution (300 mL of 100% hexanes, 600 mL of 1% ethyl acetate in hexanes) to yield a clear colorless oil (2.64 mg, 10.64 mmol, 71%). The NMR data was consistent with previously reported spectra.⁸

¹H NMR: (400 MHz, CDCl₃)

δ 7.39 (d, *J* = 7.7 Hz, 2H), 7.32 (t, *J* = 7.4 Hz, 2H), 7.23 (t, *J* = 7.4 Hz, 1H), 6.60 (dd, *J* = 15.8, 1.8 Hz, 1H), 6.29 (dt, *J* = 15.7, 4.9 Hz, 1H), 4.36 (dd, *J* = 5.0, 1.4 Hz, 2H), 0.95 (s, 9H), 0.12 (s, 6H)



1-ethenyl-4-phenoxybenzene [3-SM] was prepared according to general procedure D, using dry THF (5 mL), methyltriphenylphosphonium bromide (1.01 g, 2.83mmol, 1.12 eq.), sodium bis(trimethylsilyl)amide 2M in THF (1.41 mL, 2.82 mmol, 1.12 eq.) and 4-Phenoxybenzaldehyde (500 mg, 2.52 mmol, 1 eq.). The

crude product was purified by flash column chromatography (400 mL of 100% hexanes) to obtain the product as a clear colorless oil (483 mg, 2.46 mmol, 98% yield).

¹H NMR: (300 MHz, CDCl₃)

δ 7.53 – 7.37 (m, 4H), 7.20 (t, *J* = 7.1 Hz, 1H), 7.15–7.04 (m, 4H), 6.79 (dd, *J* = 17.6 Hz, 1H), 5.77 (d, *J* = 17.5 Hz, 1H), 5.29 (d, *J* = 10.9 Hz, 1H).

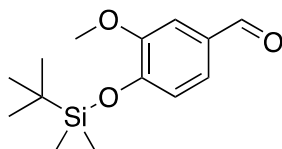
¹³C NMR: (75 MHz, CDCl₃)

δ 157.20, 157.05, 136.10, 132.89, 129.85, 127.68, 123.42, 119.00, 118.93, 112.93.

ATR-IR (cm⁻¹):

3064, 3040, 3008, 2981, 1230, 1165.

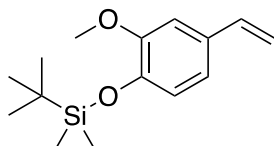
HRMS: (EI⁺) *m/z*: [M]⁺ Calcd for C₁₄H₁₂O 196.0888; Found 196.0881.



4-[(1,1-Dimethylethyl)dimethylsilyloxy]-3-methoxybenzaldehyde was prepared according to general procedure E, using 4-Hydroxy-3-methoxybenzaldehyde (300 mg, 1.97 mmol, 1 eq.), dry dichloromethane (6 mL), imidazole (268 mg, 3.94 mmol, 2 eq.) and *tert*-butyldimethylsilyl chloride (327 mg, 2.17 mmol, 1.1 eq.). The crude product was purified by flash column chromatography using gradient elution (100 mL of 100% HPLC hexanes, 100 mL of 5% ethyl acetate in HPLC hexanes, 200 mL of 10% ethyl acetate in HPLC hexanes) to yield the pure benzaldehyde product as a clear colorless oil (379 mg, 1.42 mmol, 72% yield). The NMR data was consistent with previously reported spectra.⁹

¹H NMR: (400 MHz, CDCl₃)

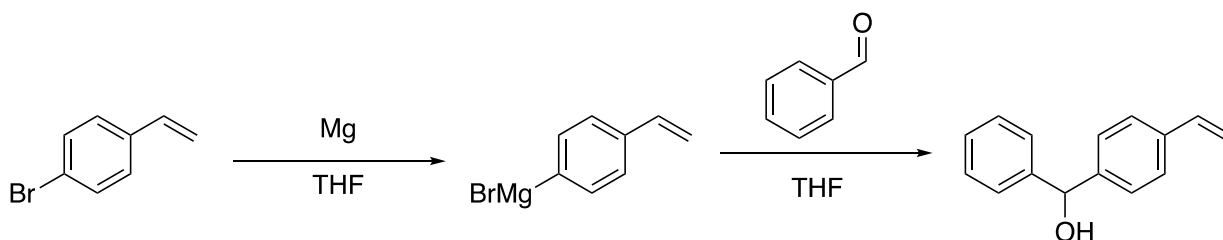
δ 9.84 (s, 1H), 7.42 – 7.34 (m, 2H), 6.99 – 6.93 (m, 1H), 3.87 (s, 3H), 1.00 (s, 9H), 0.19 (s, 6H).



***tert*-butyl(2-methoxy-4-vinylphenoxy)dimethylsilane [4-SM]** was prepared according to general procedure D, using dry THF (7 mL), methyltriphenylphosphonium bromide (568 g, 1.59 mmol, 1.12 eq.), sodium bis(trimethylsilyl)amide 2M in THF (0.80 mL, 1.59 mmol, 1.12 eq.) and 4-[(1,1-Dimethylethyl)dimethylsilyloxy]-3-methoxybenzaldehyde (379 mg, 1.42 mmol, 1 eq.). The crude product was purified by flash column chromatography using gradient elution (100 mL of hexanes, 100 mL of 1% ethyl acetate in hexanes, 400 mL of 2% of ethyl acetate in hexanes), the title compound was obtained as a light yellow oil (301 mg, 1.14 mmol, 80% yield). The NMR data was consistent with previously reported spectra.¹⁰

¹H NMR: (300 MHz, CDCl₃)

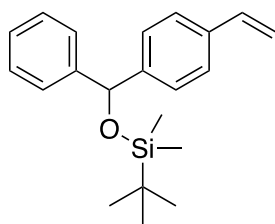
δ 6.96–6.75 (m, 3H), 6.64 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.61 (dd, *J* = 17.6, 1.0 Hz, 1H), 5.14 (dd, *J* = 10.9, 1.0 Hz, 1H), 3.83 (s, 3H), 1.00 (s, 9H), 0.16 (s, 6H).



phenyl(4-vinylphenyl)methanol was prepared the addition of Magnesium turnings (837 mg, 34.4 mmol, 1.5 eq) to a 200 mL round-bottom flask and flame-dried. Upon cooling under N₂, dry THF (25 mL) and a chip of iodine were added along with a drop 1,2-diiodoethane and 100 mg of 4-bromostyrene. Upon initiation, 4-bromostyrene (4.08 g, 22.8 mmol (total amount), 1 eq.) was added dropwise in a solution of THF (25 mL). The reaction refluxed for 3 h. In a separate flame-dried round bottom flask under N₂ was added dry THF (25 mL) and benzaldehyde (1.74 mL, 17.1 mmol, 0.75 eq). The aryl-Grignard solution was added dropwise to the reaction-flask containing the benzaldehyde solution and stirred overnight at room temperature. Upon completion, the reaction was placed in an ice bath and the reaction was quenched with ammonium chloride (20 mL) and extracted with diethyl ether (2 x 20 mL). The combine organic layers were washed with brine (20 mL) and then dried over anhydrous Na₂SO₄. The mixture was filtered, and the solvent was removed by rotary evaporation. The crude product was purified by flash column chromatography using gradient elution (100 mL of 100% hexanes, 100 mL of 2.5% ethyl acetate in hexanes, 100 mL of 5% ethyl acetate in hexanes, 100 mL of 7.5% ethyl acetate in hexanes, 100 mL of 10% ethyl acetate in hexanes) to give phenyl(4-vinylphenyl)methanol as a white solid (2.64 g, 12.6 mmol, 55% yield).¹¹

¹H NMR (400 MHz, CDCl₃)

δ 7.39 – 7.28 (m, 8H), 7.28 – 7.21 (m, 1H), 6.68 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.78 (s, 1H), 5.71 (d, *J* = 17.6 Hz, 1H), 5.22 (d, *J* = 10.9 Hz, 1H), 2.31 (br s, 1H).



tert-butyl dimethyl(phenyl(4-vinylphenyl)methoxy)silane [5-SM] was prepared according to the general procedure E, using phenyl(4-vinylphenyl)methanol (500 mg, 2.38 mmol, 1 eq.), dry dichloromethane (5 mL), imidazole (324 mg, 4.76 mmol, 2 eq.) and *tert*-butyl dimethylsilyl chloride (395 mg, 2.62 mmol, 1.1 eq.). The crude product was purified by flash column chromatography using gradient elution (100mL of 100% HPLC hexanes, 100 mL of 1% ethyl acetate in HPLC hexanes, 100 mL of 2% ethyl acetate in HPLC hexanes, 100 mL of 4% ethyl acetate in HPLC hexanes) to yield the title compound as a clear colorless oil (680 mg, 2.10 mmol, 88% yield).

¹H NMR (400 MHz, CDCl₃)

δ 7.37 – 7.25 (m, 8H), 7.23 – 7.17 (m, 1H), 6.68 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.74 (s, 1H), 5.70 (d, *J* = 17.7 Hz, 1H), 5.20 (d, *J* = 10.9 Hz, 1H), 0.92 (s, 9H), -0.02 (s, 6H).

¹³C NMR (101 MHz, CDCl₃)

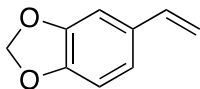
δ 145.25, 145.07, 136.75, 136.41, 128.33, 127.11, 126.58, 126.37, 126.23, 113.58, 76.57, 26.00, 18.45, -4.66.

ATR-IR (cm⁻¹):

3086, 3027, 2954, 2928, 2884, 28856, 1251, 1085, 1065.

HRMS: (EI⁺) *m/z*: [M-C₄H₉]⁺ Calcd for C₁₁H₁₆DOSi 267.1205; Found 267.1198.

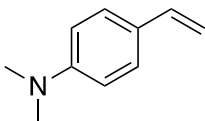
The major ion peak represents the parent molecule after loss of the *t*-Bu cation.



5-Vinylbenzo-1,3-dioxole [6-SM] was prepared according to general procedure D, using dry THF (67 mL), methyltriphenylphosphonium bromide (5.72 g, 16.00 mmol, 1.2 eq.), sodium hydride (2.40 g calculated based off of 60% dispersion in mineral oil, 60.0 mmol, 4.51 eq.) and 1,3-Benzodioxole-5-carbaldehyde (2.00 g, 13.3 mmol, 1 eq.). The crude product was purified by flash column chromatography (1000 mL of 100% hexanes) the title compound was obtained as a clear colorless oil (400 mg, 2.70 mmol, 20% yield). The NMR data was consistent with previously reported spectra.¹²

¹H NMR: (400 MHz, CDCl₃)

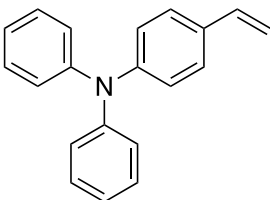
δ 6.97 (s, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 6.76 (d, *J* = 8.1 Hz, 1H), 6.63 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.96 (s, 2H), 5.58 (d, *J* = 17.5 Hz, 1H), 5.13 (d, *J* = 10.8 Hz, 1H).



N,N-dimethyl-4-vinylaniline [8-SM] was prepared according to general procedure D, using dry THF (67 mL), methyltriphenylphosphonium bromide (5.74 g, 16.1 mmol, 1.2 eq.), sodium hydride (2.42 g calculated based off of 60% dispersion in mineral oil, 60.4 mmol, 4.51 eq.) and 4-dimethylamino-benzaldehyde (2.00 g, 13.4 mmol, 1 eq.). The crude product was purified by flash column chromatography (1000 mL of 100% hexanes), the title compound was obtained as a red oil (580 mg, 3.94 mmol, 29% yield). The NMR data was consistent with previously reported spectra.¹³

¹H NMR: (400 MHz, CDCl₃)

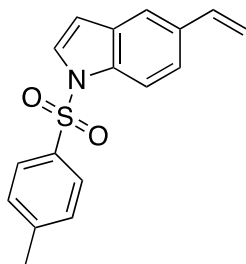
δ 7.32 (d, *J* = 8.8 Hz, 2H), 6.69 (d, *J* = 8.8 Hz, 2H), 6.63 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.55 (d, *J* = 17.5 Hz, 1H), 5.03 (d, *J* = 10.9 Hz, 1H), 2.97 (s, 6H).



N,N-diphenyl-4-vinylaniline [9-SM] was prepared according to general procedure D, using dry THF (15 mL), methyltriphenylphosphonium bromide (2.88 g, 8.05 mmol, 2.2 eq.), sodium hydride (322 mg calculated based off of 60% dispersion in mineral oil, 8.05 mmol, 2.2 eq.) and 4-(N,N-Diphenylamino)benzaldehyde (1.00 g, 3.66 mmol, 1 eq.). The crude product was purified by flash column chromatography using gradient elution (100 mL of hexanes, 100 mL of 3% ethyl acetate in hexanes, 300 mL of 5% of ethyl acetate in hexanes), the title compound was obtained as a beige solid (774 mg, 2.85 mmol, 78% yield). The NMR data was consistent with previously reported spectra.¹⁴

¹H NMR: (400 MHz, CDCl₃)

δ 7.33 – 7.24 (m, 6H), 7.12 (d, *J* = 7.6 Hz, 4H), 7.08 (m, 4H), 6.69 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.66 (d, *J* = 17.6 Hz, 1H), 5.18 (d, *J* = 10.9 Hz, 1H).



5-Vinyl-N-tosylindole [12-SM] was prepared following general procedure F, using THF/H₂O (9:1) (7 mL) solution, potassium trifluoro(vinyl)borate (477 mg, 3.56 mmol, 1 eq.), cesium carbonate (1.740g, 5.34 mmol, 1.5 eq.), the 5-bromo-1-tosylindole (1.25 g, 3.56 mmol, 1 eq.), and PdCl₂(PPh₃)₂ (50 mg, 0.071 mmol, 0.02 eq.). The crude product was purified by flash column chromatography using gradient elution (100 mL 100% hexanes, 200 mL 5% ethyl acetate in hexanes, and 200 mL 10% ethyl acetate in hexanes) to provide the title compound as a yellow solid (518 mg, 1.74 mmol, 49% yield).

¹H NMR: (400 MHz, CDCl₃)

δ 7.93 (d, *J* = 8.6 Hz, 1H), 7.75 (d, *J* = 8.2 Hz, 2H), 7.55 – 7.49 (m, 2H), 7.40 (d, *J* = 8.6 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 2H), 6.76 (dd, *J* = 17.6, 10.9 Hz, 1H), 6.63 (d, *J* = 3.6 Hz, 1H), 5.73 (d, *J* = 17.5 Hz, 1H), 5.21 (d, *J* = 10.9 Hz, 1H), 2.33 (s, 3H).

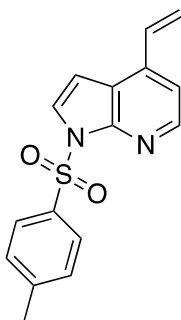
¹³C NMR: (101 MHz, CDCl₃)

δ 145.11, 136.86, 135.33, 134.60, 133.26, 131.22, 130.01, 127.00, 126.91, 122.92, 119.38, 113.68, 113.32, 109.35, 21.69.

ATR-IR (cm⁻¹):

3141, 3118, 2980, 2920, 2851, 1594, 1367, 1169.

HRMS: (EI⁺) *m/z*: [M]⁺ Calcd for C₁₇H₁₅NO₂S 297.0823; Found 297.0816.



1-tosyl-4-vinyl-1H-pyrrolo[2,3-*b*]pyridine [13-SM] was prepared following general procedure F, using THF/H₂O (9:1) (5 mL) solution, potassium trifluoro(vinyl)borate (336 mg, 2.51 mmol, 1 eq.), cesium carbonate (1.23 g, 3.77 mmol, 1.5 eq.), 4-bromo-1-tosyl-1H-pyrrolo[2,3-*b*]pyridine (882 mg, 2.51 mmol, 1 eq.), and PdCl₂(PPh₃)₂ (35 mg, 0.050 mmol, 0.02 eq.). The crude product was purified by flash column chromatography using gradient elution (100 mL 100% hexanes, 200 mL 2% ethyl acetate in hexanes, 200 mL 4% ethyl acetate in hexanes, 200 mL 6% ethyl acetate in hexanes, and 200 mL 8% ethyl acetate in hexanes) to provide the title product as a yellow solid (406 mg, 1.36 mmol, 54% yield).

¹H NMR: (400 MHz, CDCl₃)

δ 8.38 (d, *J* = 5.1 Hz, 1H), 8.06 (d, *J* = 8.3 Hz, 2H), 7.74 (d, *J* = 4.1 Hz, 1H), 7.26 (d, *J* = 8.1 Hz, 2H), 7.22 (d, *J* = 5.1 Hz, 1H), 6.93 (dd, *J* = 17.7, 11.0 Hz, 1H), 6.75 (d, *J* = 4.1 Hz, 1H), 6.02 (d, *J* = 17.6, 0.9 Hz, 1H), 5.59 (dd, *J* = 11.1, 0.8 Hz, 1H), 2.36 (s, 3H).

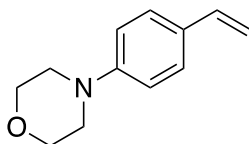
¹³C NMR: (101 MHz, CDCl₃)

δ 147.99, 145.23, 145.00, 138.58, 135.39, 132.33, 129.67, 128.05, 126.44, 120.70, 120.23, 114.96, 103.74, 21.66.

ATR-IR (cm⁻¹):

3152, 3115, 2975, 2924, 1590, 1364, 1149

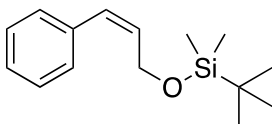
HRMS: (ESI⁺) m/z: [M+H]⁺ Calcd for C₁₆H₁₅N₂O₂S 299.0880; Found 299.0848.



4-(4-ethenylphenyl)-morpholine [14-SM] was prepared according to general procedure D, using dry THF (27 mL), methyltriphenylphosphonium bromide (2.24 g, 6.28 mmol, 1.2 eq.), sodium hydride (943 mg calculated based off of 60% dispersion in mineral oil, 23.5 mmol, 4.5 eq.) and 4-Morpholin-4-yl-benzaldehyde (1.00 g, 5.23 mmol, 1 eq.). The crude product was purified by flash column chromatography using gradient elution (100 mL of 100% hexanes, 100 mL of 2% ethyl acetate in hexanes, 100 mL of 5% ethyl acetate in hexanes), the title compound was obtained as an orange solid (748 mg, 3.95 mmol, 76% yield). The NMR data was consistent with previously reported spectra.¹⁵

¹H NMR: (400 MHz, CDCl₃)

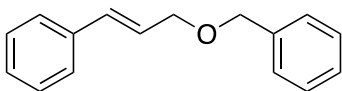
δ 7.34 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 6.65 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.61 (dd, *J* = 17.6, 1.3 Hz, 1H), 5.11 (dd, *J* = 10.9, 1.2 Hz, 1H), 3.86 (t, *J* = 4.7 Hz, 4H), 3.17 (t, *J* = 4.7, 4.0 Hz, 4H).



(Z)-1-tert-Butyldimethylsilyloxy-3-phenyl-2-propene [15-SM] was prepared according to the general procedure E, using **3-Phenyl-2-propen-1-ol** (250 mg, 1.86 mmol, 1 eq.), dry dichloromethane (5 mL) followed by imidazole (254 mg, 3.73 mmol, 2 eq.) and *tert*-butyldimethylsilyl chloride (307 mg 2.04 mmol, 1.1 eq.). The crude product was purified by flash column chromatography using gradient elution (100 mL of 100% hexanes, 400 mL of 2% ethyl acetate in hexanes) to yield a clear colorless oil (266 mg, 1.07 mmol, 58%). The NMR data was consistent with previously reported spectra.¹⁶

¹H NMR: (400 MHz, CDCl₃)

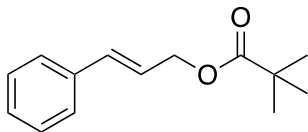
δ 7.35 (t, *J* = 7.6 Hz, 2H), 7.26 (t, *J* = 7.1 Hz, 1H), 7.20 (d, *J* = 7.8 Hz, 2H), 6.50 (d, *J* = 11.8 Hz, 1H), 5.83 (dt, *J* = 11.9, 5.9 Hz, 1H), 4.46 (d, *J* = 6.1 Hz, 2H), 0.90 (s, 9H), 0.06 (s, 6H).



(E)-(3-(benzyloxy)prop-1-en-1-yl)benzene [16-SM]. In a flame-dried round bottom flask under N₂ was added 3 Å molecular sieves, **3-Phenyl-2-propen-1-ol** (500 mg, 3.73 mmol, 1 eq.), THF (4 mL), and sodium hydride (148 mg, 3.73 mmol, 1 eq.). The reaction was refluxed at 70°C for 30 minutes. The reaction was allowed to cool to room temperature, and benzyl bromide (439 μL, 3.69 mmol, 1 eq.) was added. The reaction was heated to 85 °C and stirred for 16 h. Upon completion, deionized water (10 mL) was added, and the reaction was cooled to room temperature. The solvent was removed by rotary evaporation and 3M potassium hydroxide was added to the reaction mixture until the pH reached 12. The organic layers were then extracted using dichloromethane (3 x 15 mL) and washed with brine (15 mL). The combined organic layers were then dried over anhydrous Na₂SO₄. The crude product was purified by flash chromatography using gradient elution (200 mL of 100% hexanes, 200 mL of 1% ethyl acetate in hexanes, 200 mL of 2.5% ethyl acetate in hexanes) to yield the pure product as a yellow oil (629 mg, 2.81 mmol, 75% yield). The NMR data was consistent with previously reported spectra.¹⁷

¹H NMR (400 MHz, CDCl₃):

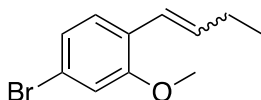
δ 7.43-7.28 (m, 9H), 7.28-7.21 (m, 1H), 6.64 (d, *J* = 15.9 Hz, 1H), 6.34 (dt, *J* = 15.9, 6.0 Hz, 1H), 4.58 (s, 2H), 4.21 (d, *J* = 6.1 Hz, 2H).



cinnamyl pivalate [17-SM]. Following a previously reported procedure¹⁸, using dry DCM (15 mL), **3-Phenyl-2-propen-1-ol** (1.00 g, 7.45 mmol, 1 eq.), Et₃N (1.45 mL, 10.4 mmol, 1.4 eq.), DMAP (91 mg, 0.75 mmol, 0.1 eq.), and trimethylacetyl chloride (1.16 mL, 9.69 mmol, 1.3 eq.). The crude product was purified by flash column chromatography using gradient elution (100 mL of 100% hexanes, 200 mL of 1% ethyl acetate in hexanes, 200 mL of 2% ethyl acetate in hexanes, 200 mL of 3% ethyl acetate in hexanes) gave the pure product as a clear colorless oil (1.39 g, 6.36 mmol, 85% yield). The NMR data was consistent with previously reported spectra.¹⁸

¹H NMR (300 MHz, CDCl₃)

δ 7.38 (d, *J* = 7.7 Hz, 2H), 7.31 (t, *J* = 7.3 Hz, 2H), 7.24 (t, *J* = 7.0 Hz, 1H), 6.63 (d, *J* = 16.0 Hz, 1H), 6.27 (dt, *J* = 15.8, 6.2 Hz, 1H), 4.70 (d, *J* = 6.2 Hz, 2H), 1.22 (s, 9H).



(*E/Z*)-4-bromo-1-(but-1-en-1-yl)-2-methoxybenzene [18-SM] was prepared according to general procedure D, using dry THF (9 mL), propyltriphenylphosphonium bromide (1.99 g, 5.12 mmol, 1.1 eq.), sodium hydride (205 mg calculated based off of 60% dispersion in mineral oil, 5.12 mmol, 1.1 eq.) and 4-Bromo-2-methoxybenzaldehyde (1.00 g, 4.65 mmol, 1.00 eq.). The crude product was purified by flash chromatography using gradient elution (200 mL of 100% hexanes, 200 mL of 1% ethyl acetate in hexanes, 200 mL of 2% ethyl acetate in hexanes) to yield the pure product as a yellow oil which is a mixture of *E/Z* isomers (1.08 g, 4.50 mmol, 97% yield).

¹H NMR: (400 MHz, CDCl₃) mixture of *E/Z* isomers

δ 7.55 - 7.50 (m, 0.11H) 7.35 - 7.23 (m, 1.77H), 6.76 - 6.68 (m, 0.93H), 6.62 (dd, *J* = 16.0, 2.0 Hz, 0.11H), 6.40 (dt, *J* = 11.6, 1.9 Hz, 0.77H), 6.25 (dt, *J* = 15.9, 6.5 Hz, 0.11H), 5.74 (dt, *J* = 11.5, 7.3 Hz, 0.80H), 3.81 (m, 3H), 2.26 (m, 1.94H), 1.10 (t, *J* = 7.4 Hz, 0.34H), 1.04 (t, *J* = 7.4 Hz, 2.62H).

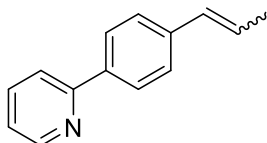
¹³C NMR: (101 MHz, CDCl₃) mixture of *E/Z* isomers

δ 156.22, 155.39, 135.92, 134.88, 132.57, 130.56, 130.25, 129.26, 129.07, 128.67, 122.48, 122.30, 113.23, 112.52, 112.37, 112.11, 55.79, 26.57, 22.12, 14.45, 13.76.

ATR-IR (cm⁻¹):

3007, 2961, 2933, 2873, 2834, 1242, 1029.

HRMS: (EI⁺) *m/z*: [M]⁺ Calcd for C₁₁H₁₃OBr 240.0150; Found 240.0144.



(*E/Z*)-2-(4-(prop-1-en-1-yl)phenyl)pyridine [19-SM] was prepared according to general procedure D, using dry THF (30 mL), ethyltriphenylphosphonium bromide (4.56 g, 12.3 mmol, 1.5 eq.), *n*-butyl lithium (10.4 mL calculated based off 1.18 M solution, 12.3 mmol, 1.5 eq.) and 4-Pyridin-2-yl-benzaldehyde (1.5 g,

8.19 mmol, 1 eq.) The crude product was purified by flash chromatography using gradient elution (100 mL of 100% hexanes, 200 mL of 5% ethyl acetate in hexanes, 200 mL of 7.5% ethyl acetate in hexanes, and 200 mL of 10% ethyl acetate in hexanes) to yield the pure product as a yellow solid which is a mixture of *E/Z* isomers (74 mg, 3.8 mmol, 46% yield).

¹H NMR: (400 MHz, CDCl₃) mixture of *E/Z* isomers

δ 8.72-8.66 (m, 0.96H), 8.06 – 7.96 (m, 0.46H), 7.96 – 7.92 (m, 1.54H), 7.77 – 7.69 (m, 2.15H), 7.48 – 7.39 (m, 2.11H), 7.24 – 7.17 (m, 1.08H), 6.51 – 6.40 (m, 1H), 6.33 (dq, *J* = 15.8, 6.5 Hz, 0.8H), 5.85 (dq, *J* = 11.6, 7.2 Hz, 0.2H), 1.95 (dd, *J* = 7.2, 1.8 Hz, 0.62H), 1.91 (dd, *J* = 6.5, 1.5 Hz, 2.4H).

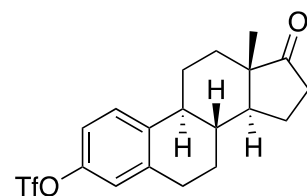
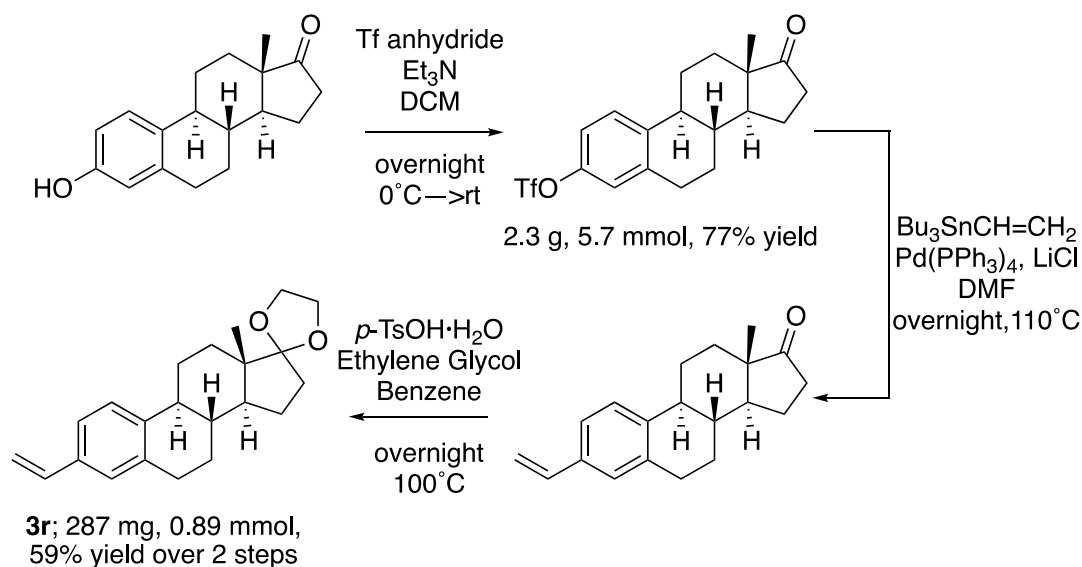
¹³C NMR: (101 MHz, CDCl₃) mixture of *E/Z* isomers

δ 157.26, 157.23, 149.79, 149.75, 138.69, 138.44, 137.75, 137.46, 136.84, 136.81, 130.70, 129.54, 129.36, 127.68, 127.09, 126.72, 126.70, 126.30, 122.10, 122.02, 120.49, 120.37, 18.75, 14.94.

ATR-IR (cm⁻¹):

3050, 3004, 2929, 2909, 2851, 1265.

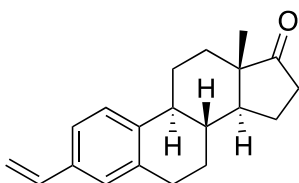
HRMS: (ESI⁺) *m/z*: [M+H]⁺ Calcd for C₁₄H₁₄N 196.108; Found 196.1120.



3-(Trifluoromethanesulfonyl)estrone was synthesized following a previously reported procedure¹⁹, using estrone (2.0 g, 7.4 mmol, 1 eq.), Et₃N (2.05 mL, 14.8 mmol, 2 eq.), dichloromethane (37 mL, 0.2 M solution), and triflic anhydride (1.37 mL, 8.14 mmol, 1.1 eq.). The crude product was purified by flash column chromatography using gradient elution (100 mL of 100% hexanes, 100 mL of 5% ethyl acetate in hexanes, 100 mL of 10% ethyl acetate in hexanes, and 300 mL of 5% ethyl acetate in hexanes) to yield a white solid (2.3 g, 5.7 mmol, 77% yield). The NMR data were consistent with previously reported spectra.¹⁹

¹H NMR: (300 MHz, CDCl₃)

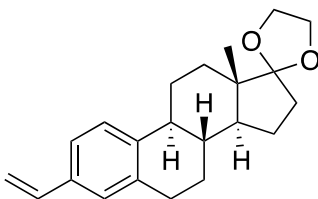
δ 7.34 (d, J = 8.6 Hz, 1H), 7.04 (dd, J = 8.6, 2.9 Hz, 1H), 6.99 (d, J = 2.8 Hz, 1H), 3.02 – 2.87 (m, 2H), 2.52 (dd, J = 18.3, 8.5 Hz, 1H), 2.45 – 2.36 (m, 1H), 2.36 – 2.23 (m, 1H), 2.23 – 1.92 (m, 4H), 1.78 – 1.37 (m, 6H), 0.92 (s, 3H).



3-Vinyl-estrone was synthesized following a previously reported procedure,²⁰ using 3-(Trifluoromethanesulfonyl)estrone (600 mg, 1.49 mmol, 1 eq.), vinyltributylstannane (436 μ L, 1.49 mmol, 1 eq.), Pd(PPh₃)₄ (35 mg, 0.03 mmol, 0.02 eq), LiCl (316 mg, 7.45 mmol, 5 eq.), and DMF (23 mL, 0.067M solution). The crude product was purified by flash column chromatography using gradient elution (500 mL of 100% hexanes, 200 mL of 5% ethyl acetate in hexanes, and 300 mL of 8% ethyl acetate in hexanes) to yield 313 mg of a white solid containing an alkyl tin byproduct impurity. The NMR data was consistent with previously reported spectra.²⁰ The impurity was carried through to the next reaction step and removed after isolation of **3q**.

¹H NMR: (400 MHz, CDCl₃)

δ 7.27 (d, J = 8.1 Hz, 1H), 7.23 (d, J = 8.3 Hz, 1H), 7.16 (s, 1H), 6.68 (dd, J = 17.6, 10.9 Hz, 1H), 5.72 (d, J = 17.6 Hz, 1H), 5.21 (d, J = 10.8 Hz, 1H), 2.97 – 2.89 (m, 2H), 2.52 (dd, J = 18.8, 9.0 Hz, 1H), 2.47 – 2.39 (m, 1H), 2.35 – 2.25 (m, 1H), 2.22 – 1.94 (m, 4H), 1.80 – 1.22 (m, 9H, includes an alkyl impurity likely from an inseparable tin byproduct), 0.93 (s, 3H).



(8R,9S,13S,14S)-13-methyl-3-vinyl-6,7,8,9,11,12,13,14,15,16-decahydrospiro[cyclopenta[a]phenanthrene-17,2'-[1,3]dioxolane] [20-SM]. To a flame-dried 25 mL round bottom flask equipped with a Teflon stir bar, was added *p*-TsOH • H₂O (19 mg, 0.102 mmol, 0.091 eq.), 3-vinyl-estrone (313 mg, 1.12 mmol, 1 eq.), ethylene glycol (1.3 mL, 22.4 mmol, 20 eq.), and benzene (8 mL, 0.144 M solution). A Dean Stark trap fitted with a condenser was connected to the 25 mL round bottom flask was heated to 100 °C and stirred open to air until deemed complete by TLC analysis. Upon reaction completion, the reaction was poured into 20 mL of water and extracted with dichloromethane (3 x 10 mL). The combined organic layers were washed with brine (3 x 10 mL) and dried over anhydrous Na₂SO₄. The reaction was dry loaded onto silica gel and purified by flash column chromatography using gradient elution (800 mL of 100% hexanes, 200 mL of 5% ethyl acetate in hexanes, 300 mL of 8% ethyl acetate in hexanes) to provide the title product as a yellow oil (287 mg, 0.885 mmol, 59% yield over 2 steps).

¹H NMR: (400 MHz, CDCl₃)

δ 7.26 (d, 1H), 7.20 (d, J = 8.1, 1.9 Hz, 1H), 7.13 (s, 1H), 6.67 (dd, J = 17.6, 10.9 Hz, 1H), 5.70 (d, J = 17.6 Hz, 1H), 5.18 (d, J = 10.8 Hz, 1H), 4.01 – 3.85 (m, 4H), 2.91 – 2.83 (m, 2H), 2.41 – 2.23 (m, 2H), 2.09 – 1.98 (m, 1H), 1.95 – 1.72 (m, 4H), 1.71 – 1.60 (m, 1H), 1.60 – 1.28 (m, 5H), 0.89 (s, 3H).

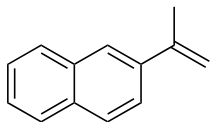
¹³C NMR: (101 MHz, CDCl₃)

δ 140.39, 136.99, 136.80, 135.07, 126.97, 125.69, 123.55, 119.54, 113.09, 65.41, 64.73, 49.58, 46.26, 44.26, 38.96, 34.36, 30.86, 29.66, 27.07, 26.07, 22.50, 14.46.

ATR-IR (cm⁻¹):

3083, 2971, 2936, 2870, 1740, 1630, 1103, 1044.

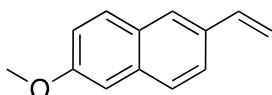
HRMS: (EI^+) m/z : $[\text{M}]^+$ Calcd for $\text{C}_{22}\text{H}_{28}\text{O}_2$ 324.2089; Found 324.2082.



1-ethenyl-4-phenoxybenzene [21-SM] was prepared according to general procedure D, using dry THF (6.0 mL), methyltriphenylphosphonium bromide (1.15 g, 3.23 mmol, 1.1 eq.), sodium bis(trimethylsilyl)amide 2M in THF (1.62 mL, 3.23 mmol, 1.1 eq.) and 2-acetonaphthone (500 mg, 2.94 mmol, 1 eq.). The crude product was purified by flash column chromatography (400 mL of 100% hexanes) to obtain the product as a clear colorless oil (450 mg, 2.67 mmol, 91% yield). The NMR data was consistent with previously reported spectra.²¹

^1H NMR: (400 MHz, CDCl_3)

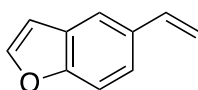
δ 7.89 – 7.78 (m, 4H), 7.69 (dd, J = 8.6, 1.9 Hz, 1H), 7.51 – 7.43 (m, 2H), 5.55 (s, 1H), 5.21 (s, 1H), 2.28 (s, 3H).



2-ethenyl-6-methoxynaphthalene [24-SM] was prepared according to general procedure D, using dry THF (27 mL) and methyltriphenylphosphonium bromide (2.30 g, 6.45 mmol, 1.2 eq.) and sodium hydride (970 mg calculated based off of 60% dispersion in mineral oil, 24.2 mmol, 4.5 eq.) and 6-Methoxy-2-naphthaldehyde (1.00 g, 5.37 mmol, 1 eq.). The crude product was purified by flash chromatography (300 mL of 100% hexanes) and gave the pure product as a clear colorless oil (935 mg, 5.08 mmol, 95% yield). The NMR data was consistent with previously reported spectra.²²

^1H NMR: (400 MHz, CDCl_3)

δ 7.74 – 7.67 (m, 3H), 7.63 – 7.58 (m, 1H), 7.16 – 7.10 (m, 2H), 6.85 (dd, J = 17.6, 10.9 Hz, 1H), 5.82 (d, J = 17.8 Hz, 1H), 5.28 (d, J = 11.1 Hz, 1H), 3.92 (s, 3H).



5-vinylbenzofuran [25-SM]. To a flame-dried round bottom flask under N_2 , containing a Teflon stir bar, was added dimethyl sulfoxide (20 mL). The round bottom flask was heated to 60 °C and sodium hydride (683 mg calculated based off of 60% dispersion in mineral oil, 17.1 mmol, 5 eq.) was slowly added. The mixture stirred for 15 minutes. The reaction flask was cooled to room temperature and methyltriphenylphosphonium bromide (6.11 g, 17.1 mmol, 5 eq.) was added. After addition, the reaction mixture was stirred for 10 minutes at room temperature, at which point benzofuran-5-carbaldehyde (500 mg, 3.42 mmol, 1 eq.) was added and the reaction stirred at room temperature for 18 h. Upon completion, the reaction was placed in an ice bath and quenched with water (20 mL) and extracted with ether (3 x 15 mL). The combined organic layers were washed with brine (20 mL) and then dried over anhydrous Na_2SO_4 . The mixture was filtered, and the solvent was removed by rotary evaporation. The crude product was purified by flash column chromatography (300 mL of 100% HPLC hexanes) to give a clear colorless oil (334 mg, 2.32 mmol, 68% yield).

^1H NMR: (400 MHz, CDCl_3)

δ 7.65 – 7.58 (m, 2H), 7.46 (d, J = 8.7 Hz, 1H), 7.41 (dd, J = 8.6, 1.8 Hz 1H), 6.83 (dd, J = 17.6, 10.9 Hz, 1H), 6.78 – 6.72 (m, 1H), 5.74 (dd, J = 17.6, 0.9 Hz 1H), 5.23 (dd, J = 10.9, 1.0 Hz 1H).

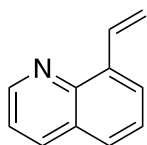
^{13}C NMR: (101 MHz, CDCl_3)

δ 154.90, 145.57, 137.11, 132.87, 127.82, 122.75, 119.15, 112.77, 111.46, 106.80.

ATR-IR (cm^{-1}):

3086, 3005, 2924, 2853, 1262.

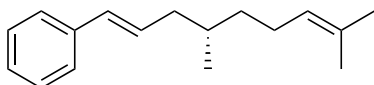
HRMS: (EI⁺) *m/z*: [M]⁺ Calcd for C₁₀H₈O, 144.0600; Found 144.0569.



8-Vinylquinoline [26-SM] was prepared according to general procedure D, using dry THF (6.40 mL), methyltriphenylphosphonium bromide (1.27 g, 3.56 mmol, 1.12 eq.), sodium bis(trimethylsilyl)amide 2M in THF (1.59 mL, 3.56 mmol, 1.12 eq.) and 8-Quinolincarboxaldehyde (500 mg, 3.18 mmol, 1 eq.). The crude product was purified by flash column chromatography using gradient elution (200 mL of 100% hexanes, 100 mL of 2% ethyl acetate in hexanes, 300 mL of 5% ethyl acetate in hexanes), the title compound was obtained as a yellow oil (427 mg, 2.75 mmol, 87% yield). The NMR data was consistent with previously reported spectra.²³

¹H NMR: (400 MHz, CDCl₃)

δ 8.95 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.14 (dd, *J* = 8.2, 1.7 Hz, 1H), 8.00 (dd, *J* = 17.8, 11.1 Hz, 1H), 7.92 (dd, *J* = 7.2, 1.5 Hz, 1H), 7.75 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.53 (t, *J* = 7.7 Hz, 1H), 7.41 (dd, *J* = 8.4, 4.1 Hz, 1H), 5.96 (dd, *J* = 17.8, 1.5 Hz, 1H), 5.52 (dd, *J* = 11.1, 1.5 Hz, 1H).



(*E/Z*)-(S)-(4,8-dimethylnona-1,7-dien-1-yl)benzene was prepared according to general procedure D, using dry THF (6.50 mL), benzyltriphenylphosphonium bromide (1.57 g, 3.63 mmol, 1.12 eq.), sodium bis(trimethylsilyl)amide 2M in THF (1.82 mL, 3.63 mmol, 1.12 eq.) and (-)-Citronellal (0.583 mL, 3.24 mmol, 1 eq.). The crude product was purified by flash column chromatography (400 mL of 100% hexanes) to yield the pure product as a clear colorless oil as a mixture of *E/Z* isomers (512.6 mg, 2.24 mmol, 69% yield).

¹H NMR: (400 MHz, CDCl₃) mixture of *E/Z* isomers

δ 7.38 – 7.32 (m, 2H), 7.30 (dd, *J* = 8.5, 6.7 Hz, 2H), 7.24 – 7.17 (m, 1H), 6.45 (d, *J* = 11.6 Hz, 0H), 6.37 (d, *J* = 15.7 Hz, 1H), 6.22 (dt, *J* = 15.7, 7.2 Hz, 1H), 5.69 (dt, *J* = 11.7, 7.2 Hz, 0H), 5.17 – 5.04 (m, 1H), 2.41 – 2.29 (m, 0.36H), 2.28 – 2.14 (m, 1H), 2.12 – 1.91 (m, 2.87zH), 1.69 (d, *J* = 4.5 Hz, 3H), 1.60 (d, *J* = 13.3 Hz, 3H), 1.65 – 1.55 (m, 1H), 1.47 – 1.34 (m, 1H), 1.27 – 1.12 (m, 1H), 0.96 – 0.90 (m, 3H).

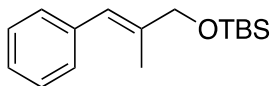
¹³C NMR: (101 MHz, CDCl₃) mixture of *E/Z* isomers

δ 138.08, 138.02, 132.01, 131.29, 131.09, 131.07, 129.78, 129.58, 128.94, 128.59, 128.20, 126.90, 126.51, 126.08, 124.97, 124.94, 40.66, 36.94, 36.88, 35.84, 33.54, 33.08, 25.87, 25.85, 25.79, 25.74, 19.72, 19.68, 17.79, 17.77.

ATR-IR (cm⁻¹):

3081, 2962, 2911, 2870, 1800, 1599, 738.

HRMS: (EI⁺) *m/z*: [M]⁺ Calcd for C₁₇H₂₄, 228.1900; Found 228.1870.



(1*E*)-3-(1-tert-butyldimethylsilyloxy)-2-methyl-1-propen-1-yl-benzene was prepared according to the general procedure E, using the (**2*E*)-2-Methyl-3-phenyl-2-propen-1-ol**) (500 mg, 3.37 mmol, 1 eq.), dry dichloromethane (8.5 mL) followed by imidazole (459 mg, 6.74 mmol, 2 eq.) and *tert*-butyldimethylsilyl chloride (559 mg 3.71 mmol, 1.1 eq.). The crude product was purified by flash column chromatography using

gradient elution (100 mL of 100% hexanes, 400 mL of 2% ethyl acetate in hexanes) to yield a clear colorless oil (683 mg, 2.60 mmol, 77%). The NMR data was consistent with previously reported spectra.²⁴

¹H NMR: (400 MHz, CDCl₃)

δ 7.37 – 7.29 (m, 2H), 7.31 – 7.24 (m, 2H), 7.25 – 7.16 (m, 1H), 6.54 (s, 1H), 4.19 (s, 2H), 1.84 (s, 3H), 0.96 (s, 9H), 0.12 (s, 6H).

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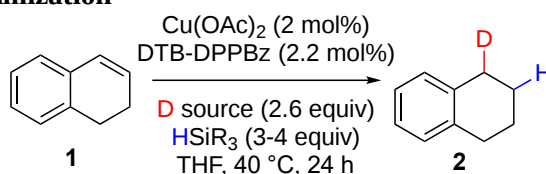
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CHAPTER 4 SUPPLEMENTARY INFORMATION

Highly Selective Catalytic Transfer Hydrodeuteration of Cyclic Alkenes

Optimization Studies

Table S1. Reaction Optimization

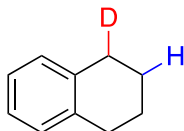


Entry	D-Source	Silane	Yield ^a (%)	RSM (%)
1	EtOD	DMMS	77 ^b	-
2	EtOD	DMMS	80 ^c	-
3	EtOD	DMMS	91	-
4	IPA- <i>d</i> 8	DMMS	77	-
5	D ₂ O	DMMS	17	83
6	MeOD	DMMS	47	33
7	<i>t</i> BuOD	DMMS	65	10
8	EtOD	PMHS	90	-
9	EtOD	DMMS	85 ^d	-

All deuterium incorporations greater than 95%. With optimal conditions (Entry 1), deuterium incorporation is 98% ^a¹H NMR yield using 1,3,5-trimethylbenzene as an internal standard ^bisolated yield ^c1 mol % catalyst loading ^dreaction performed at rt.

General Procedure for Optimization Studies

In a N₂ filled glovebox, DTB-DPPBz, Cu(OAc)₂ (0.2 M solution in THF) (Cu:L = 1:1.1), and THF (0.120 mL) were added to an oven-dried 2-dram vial with an oven-dried stir bar followed by dropwise addition of R₃Si-H (3-4 eq.). A color change from a green/blue to orange was observed while stirring for 10 mins. In a separate oven-dried 1-dram vial was added the alkene (0.3 mmol, 1 eq.), THF (150 μ L), and D-source (2.6 eq.) The overall THF quantity was calculated as 1 M based on the alkene substrate. The solution in the 1-dram vial was added dropwise to the 2-dram vial. The 2-dram vial was capped with a pressure relief cap, removed from the glovebox, and left to stir for 24 h at the given temperature. After this time, the reaction was filtered through a 1" silica plug with 100 mL of diethyl ether into a 200 mL round bottom flask. The solvent was removed by rotary evaporation, and the crude product was analyzed by ¹H NMR using 1,3,5-trimethylbenzene as an internal standard. Deuterium incorporation was calculated by integration of the benzylic proton(s) of the desired product in the ¹H NMR, and regioselectivity was confirmed using ²H NMR.



1,2,3,4-tetrahydronaphthalene-1-*d* [2] (Entry 1). According to the general procedure for optimization studies, DTB-DPPBz (5.9 mg, 0.0066 mmol, 0.022eq.), Cu(OAc)₂ (30 μL of a 0.2 M solution in THF, 0.006 mmol, 0.02 eq.), and THF (0.120 mL) then dimethoxy(methyl)silane (148 μL, 1.20 mmol, 4 eq.) were combined in a 2-dram vial followed by addition of a solution of 1,2-dihydronaphthalene (39 mg, 0.30 mmol, 1 eq.), THF (0.150 mL), and ethanol-OD (46 μL, 0.78 mmol, 2.6 eq). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 24 h at 40 °C. Upon completion, the crude product mixture was dry loaded and isolated by flash column chromatography (100 mL of 100% hexanes) to give the pure product **2** as a clear colorless oil (30 mg, 0.23 mmol, 77% yield).

¹H NMR: (400 MHz, CDCl₃)

δ 7.15 – 7.08 (m, 4H), 2.86 – 2.77 (m, 3.02H), 1.87 – 1.81 (m, 4H).

²H NMR: (61 MHz, CHCl₃)

δ 2.82 (s, 0.98D).

¹³C NMR: (101 MHz, CDCl₃)

δ 137.29, 137.21 (signal overlap, 2C), 129.25, 125.54, 125.53, 29.52, 29.15 (t, *J* = 19.4 Hz), 23.34, 23.26.

HRMS: (EI⁺) *m/z*: [M]⁺ Calcd. for C₁₀H₁₁D 133.1002; Found 133.0996.

Entry 2. According to the general procedure for optimization studies, DTB-DPPBz (3 mg, 0.0033 mmol, 0.011 eq.), Cu(OAc)₂ (15 μL of a 0.2 M solution in THF, 0.003 mmol, 0.01 eq.), and THF (0.135 mL) then dimethoxy(methyl)silane (111 μL, 0.9 mmol, 3 eq.) were combined in a 2-dram vial followed by addition of a solution of 1,2-dihydronaphthalene (39 mg, 0.30 mmol, 1 eq.), THF (0.150 mL), and ethanol-OD (46 μL, 0.78 mmol, 2.6 eq). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 24 h at 40 °C. After this time, the reaction was filtered through a 1” silica plug with 100 mL of diethyl ether into a 200 mL round bottom flask. The solvent was removed by rotary evaporation, and the crude product was added 1,3,5-trimethylbenzene (13.8 μL) as an internal standard for ¹H NMR, which showed the desired product **2** in 80% yield.

Entry 3. According to the general procedure for optimization studies, DTB-DPPBz (5.9 mg, 0.0066 mmol, 0.022eq.), Cu(OAc)₂ (30 μL of a 0.2 M solution in THF, 0.006 mmol, 0.02 eq.), and THF (0.120 mL) then dimethoxy(methyl)silane (111 μL, 0.9 mmol, 3 eq.) were combined in a 2-dram vial followed by addition of a solution of 1,2-dihydronaphthalene (39 mg, 0.30 mmol, 1 eq.), THF (0.150 mL), and ethanol-OD (46 μL, 0.78 mmol, 2.6 eq). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 24 h at 40 °C. After this time, the reaction was filtered through a 1” silica plug with 100 mL of diethyl ether into a 200 mL round bottom flask. The solvent was removed by rotary evaporation, and the crude product was added 1,3,5-trimethylbenzene (13.8 μL) as an internal standard for ¹H NMR, which showed the desired product **2** in 91% yield.

Entry 4. According to the general procedure for optimization studies, DTB-DPPBz (5.9 mg, 0.0066 mmol, 0.022eq.), Cu(OAc)₂ (30 μL of a 0.2 M solution in THF, 0.006 mmol, 0.02 eq.), and THF (0.120 mL) then dimethoxy(methyl)silane (111 μL, 0.9 mmol, 3 eq.) were combined in a 2-dram vial followed by addition of a solution of 1,2-dihydronaphthalene (39 mg, 0.30 mmol, 1 eq.), THF (0.150 mL), and isopropanol-*d*₈ (60 μL, 0.78 mmol, 2.6 eq). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 24 h at 40 °C. After this time, the reaction was filtered through a 1” silica plug with 100 mL of diethyl ether into a 200 mL round bottom flask. The solvent was removed by rotary evaporation, and the crude product was added 1,3,5-trimethylbenzene (13.8 μL) as an internal standard for ¹H NMR, which showed the desired product **2** in 77% yield.

Entry 5. According to the general procedure for optimization studies, DTB-DPPBz (5.9 mg, 0.0066 mmol, 0.022eq.), Cu(OAc)₂ (30 μ L of a 0.2 M solution in THF, 0.006 mmol, 0.02 eq.), and THF (0.120 mL) then dimethoxy(methyl)silane (111 μ L, 0.9 mmol, 3 eq.) were combined in a 2-dram vial followed by addition of a solution of 1,2-dihydronaphthalene (39 mg, 0.30 mmol, 1 eq.), THF (0.150 mL), and D₂O (15 μ L, 0.78 mmol, 2.6 eq). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 24 h at 40 °C. After this time, the reaction was filtered through a 1" silica plug with 100 mL of diethyl ether into a 200 mL round bottom flask. The solvent was removed by rotary evaporation, and the crude product was added 1,3,5-trimethylbenzene (13.8 μ L) as an internal standard for ¹H NMR, which showed the desired product **2** in 17% yield with 83% alkene remaining.

Entry 6. According to the general procedure for optimization studies, DTB-DPPBz (5.9 mg, 0.0066 mmol, 0.022eq.), Cu(OAc)₂ (30 μ L of a 0.2 M solution in THF, 0.006 mmol, 0.02 eq.), and THF (0.120 mL) then dimethoxy(methyl)silane (111 μ L, 0.9 mmol, 3 eq.) were combined in a 2-dram vial followed by addition of a solution of 1,2-dihydronaphthalene (39 mg, 0.30 mmol, 1 eq.), THF (0.150 mL), and methanol-OD (32 μ L, 0.78 mmol, 2.6 eq). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 24 h at 40 °C. After this time, the reaction was filtered through a 1" silica plug with 100 mL of diethyl ether into a 200 mL round bottom flask. The solvent was removed by rotary evaporation, and the crude product was added 1,3,5-trimethylbenzene (13.8 μ L) as an internal standard for ¹H NMR, which showed the desired product **2** in 47% yield with 33% alkene remaining.

Entry 7. According to the general procedure for optimization studies, DTB-DPPBz (5.9 mg, 0.0066 mmol, 0.022eq.), Cu(OAc)₂ (30 μ L of a 0.2 M solution in THF, 0.006 mmol, 0.02 eq.), and THF (0.120 mL) then dimethoxy(methyl)silane (148 μ L, 1.2 mmol, 4 eq.) were combined in a 2-dram vial followed by addition of a solution of 1,2-dihydronaphthalene (39 mg, 0.30 mmol, 1 eq.), THF (0.150 mL), and *tert*-butanol-OD (74.6 μ L, 0.78 mmol, 2.6 eq). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 24 h at 40 °C. After this time, the reaction was filtered through a 1" silica plug with 100 mL of diethyl ether into a 200 mL round bottom flask. The solvent was removed by rotary evaporation, and the crude product was added 1,3,5-trimethylbenzene (13.8 μ L) as an internal standard for ¹H NMR, which showed the desired product **2** in 65% yield with 10% alkene remaining.

Entry 8. According to the general procedure for optimization studies, DTB-DPPBz (5.9 mg, 0.0066 mmol, 0.022eq.), Cu(OAc)₂ (30 μ L of a 0.2 M solution in THF, 0.006 mmol, 0.02 eq.), and THF (0.120 mL) then polymethylhydrosiloxane (40 μ L, 0.60 mmol, 3 eq. based on Si-H)¹ were combined in a 2-dram vial followed by addition of a solution of 1,2-dihydronaphthalene (39 mg, 0.30 mmol, 1 eq.), THF (0.150 mL), and ethanol-OD (46 μ L, 0.78 mmol, 2.6 eq). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 24 h at 40 °C. After this time, the reaction was filtered through a 1" silica plug with 100 mL of diethyl ether into a 200 mL round bottom flask. The solvent was removed by rotary evaporation, and the crude product was added 1,3,5-trimethylbenzene (13.8 μ L) as an internal standard for ¹H NMR, which showed the desired product **2** in 90% yield.

Entry 9. According to the general procedure for optimization studies, DTB-DPPBz (5.9 mg, 0.0066 mmol, 0.022eq.), Cu(OAc)₂ (30 μ L of a 0.2 M solution in THF, 0.006 mmol, 0.02 eq.), and THF (0.120 mL) then dimethoxy(methyl)silane (111 μ L, 0.9 mmol, 3 eq.) were combined in a 2-dram vial followed by addition of a solution of 1,2-dihydronaphthalene (39 mg, 0.30 mmol, 1 eq.), THF (0.150 mL), and ethanol-OD (46 μ L, 0.78 mmol, 2.6 eq). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 24 h at room temperature. After this time, the reaction was filtered through a 1" silica plug with 100 mL of diethyl ether into a 200 mL round bottom flask. The solvent was removed by rotary evaporation, and the crude product was added 1,3,5-trimethylbenzene (13.8 μ L) as an internal standard for ¹H NMR, which showed the desired product **2** in 85% yield.

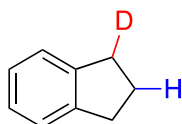
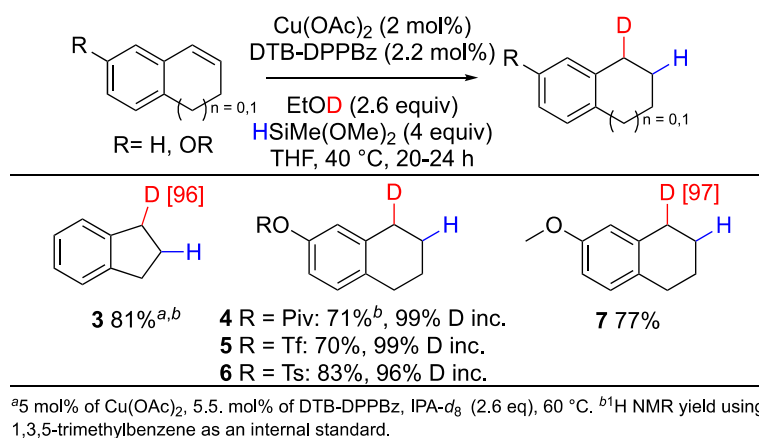
General procedure for Transfer Hydrodeuteration (A)

In a N₂ filled glovebox, DTB-DPPBz (5.9 mg, 0.0066 mmol, 0.022eq.), Cu(OAc)₂ (30 μ L of a 0.2 M solution in THF, 0.006 mmol, 0.02 eq.), and THF (0.120 mL) were added to an oven-dried 2-dram vial followed by dropwise addition of dimethoxy(methyl)silane (148 μ L, 1.20 mmol, 4 eq.). A color change from green/blue to yellow was observed while stirring for 15 minutes. In a separate oven-dried 1-dram vial was added the alkene substrate (0.30 mmol, 1 eq.), THF (0.150 mL), and ethanol-OD/2-propanol-*d*₈ (2.6 eq based on

substrate). The solution in the 1-dram vial was added dropwise over 20 seconds to the 2-dram vial. The total volume of THF was calculated based on having a final reaction concentration of 1M based on the alkene substrate. The 2-dram vial was capped with a red pressure relief cap, taken out of the glovebox, and stirred for 20-24 h at the appropriate temperature. Upon completion, diethyl ether (10 mL x 2) was added to the reaction vial and transferred to a 200 mL round bottom flask and was purified by flash column chromatography, at which point the reaction was filtered through a 1" silica plug with 20 mL of diethyl ether followed by 80 mL of diethyl ether to elute the remaining product into a 200 mL round bottom flask. After removing the diethyl ether by rotary evaporation, the crude product was isolated by flash column chromatography. Deuterium incorporation was calculated by integration of the benzylic proton(s) of the desired product and regioselectivity was confirmed using ^2H NMR.

Transfer Hydrodeuteration Reaction Scope

Scheme S1. 1*H*-indene and dihydronaphthyl derivatives

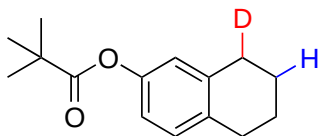


2,3-dihydro-1*H*-indene-1-*d* [3]. According to the general procedure A, DTB-DPPBz (14.8 mg, 0.0165 mmol, 0.055eq.), $\text{Cu}(\text{OAc})_2$ (75 μL of a 0.2 M solution in THF, 0.015 mmol, 0.05 eq.), and THF (0.75mL) then dimethoxy(methyl)silane (148 μL , 1.20 mmol, 4 eq.) were combined in a 2-dram vial followed by addition of a solution of Indene (35 mg, 0.30 mmol, 1 eq.), THF (0.150 mL), isopropanol-*d*₈ (60 μL , 0.78 mmol, 2.6 eq). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 22 h at 40 °C. Upon completion, diethyl ether (24 mL) was added to the crude mixture and filtered through a 1-inch

silica plug. Then the mixture was concentrated and 1,3,5- trimethylbenzene (0.33 eq.) was used as an internal standard to determine ^1H NMR crude yield (81% crude yield by ^1H NMR). The NMR data matched previously reported spectra.²

^1H NMR: (300 MHz, CDCl_3)

δ 7.25 – 7.20 (m, 2H), 7.16 – 7.09 (m, 2H), 2.95 – 2.85 (m, 3.04H), 2.11—2.01 (m, 2H).



5,6,7,8-tetrahydronaphthalen-2-yl-8-d pivalate [4]. According to the general procedure A, DTB-DPPBz (5.9 mg, 0.0066 mmol, 0.022eq.), $\text{Cu}(\text{OAc})_2$ (30 μL of a 0.2 M solution in THF, 0.006 mmol, 0.02 eq.), and THF (0.120 mL) then dimethoxy(methyl)silane (148 μL , 1.20 mmol, 4 eq.) were combined in a 2-dram vial followed by addition of a solution of 5,6-dihydronaphthalen-2-yl pivalate (69 mg, 0.30 mmol, 1 eq.), THF (0.150 mL), and ethanol-OD (46 μL , 0.78 mmol, 2.6 eq). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 20 h at 40 $^\circ\text{C}$. Upon completion, diethyl ether (24 mL) was added to the crude mixture and filtered through a 1-inch silica plug. The mixture was concentrated and 1,3,5-trimethylbenzene (0.33 eq.) was used as an internal standard to determine ^1H NMR crude yield (71% crude yield by ^1H NMR). Attempting to purify the product using column chromatography led to significant deprotection of the pivalate group, but enough material was obtained for full characterization of the purified product.

^1H NMR: (400 MHz, CDCl_3)

δ 7.05 (d, J = 7.9 Hz, 1H), 6.78-6.74 (m, 2H), 2.78-2.70 (m, 3.01H), 1.82-1.74 (m, 4H), 1.35 (s, 9H).

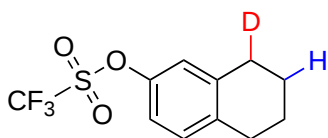
^2H NMR: (61 MHz, CHCl_3)

δ 2.74 (s, 0.99D).

^{13}C NMR: (101 MHz, CDCl_3)

δ 177.53, 148.78, 138.40, 134.56, 129.98, 121.63, 118.63, 39.13, 29.17 (t, J = 19.3 Hz), 29.00, 27.30, 23.24, 22.94.

HRMS: (EI^+) m/z : $[\text{M}]^+$ Calcd. for $\text{C}_{15}\text{H}_{19}\text{DO}_2$: 233.1526; Found 233.1519.



5,6,7,8-tetrahydronaphthalen-2-yl-8-d trifluoromethanesulfonate [5]. According to the general procedure A, DTB-DPPBz (5.9 mg, 0.0066 mmol, 0.022eq.), $\text{Cu}(\text{OAc})_2$ (30 μL of a 0.2 M solution in THF, 0.006 mmol, 0.02 eq.), and THF (0.120 mL) then dimethoxy(methyl)silane (148 μL , 1.20 mmol, 4 eq.) were combined in a 2-dram vial followed by addition of a solution of 5,6-dihydronaphthalen-2-yl trifluoromethanesulfonate (83 mg, 0.30 mmol, 1 eq.), THF (0.150 mL), and ethanol-OD (46 μL , 0.78 mmol, 2.6 eq). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 20 h at 40 $^\circ\text{C}$. Upon completion, the crude product mixture was purified using gradient flash column chromatography (200 mL of 100% hexanes, 200 mL of 1% ethyl acetate in hexanes, 200 mL of 2% ethyl acetate in hexanes, 300 mL 5% ethyl acetate in hexanes) to give the pure product as a clear colorless oil (58 mg, 0.21 mmol, 70% yield).

^1H NMR: (600 MHz, CDCl_3)

δ 7.12 (d, J = Hz, 1H), 6.98 (d, J = Hz, 2H), 2.77 (s, 3.01H), 1.80 (s, 4H).

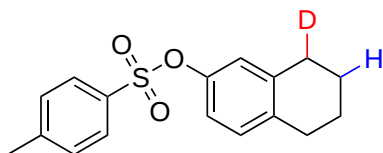
^2H NMR: (61 MHz, CHCl_3)

δ 2.79 (s, 0.99D).

¹⁹F NMR: (376 MHz, CDCl₃)
 δ -73.00 (s, 3F).

¹³C NMR: (101 MHz, CDCl₃)
 δ 147.28, 139.06, 137.66, 130.77 (d, J = 28.2 Hz), 121.49 (d, J = 25.9 Hz), 120.49 (q, J = 320.3 Hz), 118.26 (d, J = 30.5 Hz), 29.01 (both benzylic signals overlap, 1 triplet, 1 singlet), 22.86, 22.57.

HRMS: (EI⁺) m/z : [M]⁺ Calcd. for C₁₁H₁₀DF₃O₃S 281.0444; Found 281.0435.



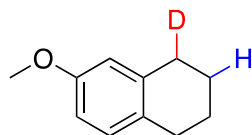
5,6,7,8-tetrahydronaphthalen-2-yl-8-d 4-methylbenzenesulfonate [6]. According to the general procedure A, DTB-DPPBz (5.9 mg, 0.0066 mmol, 0.022eq.), Cu(OAc)₂ (30 μ L of a 0.2 M solution in THF, 0.006 mmol, 0.02 eq.), and THF (0.120 mL) then dimethoxy(methyl)silane (148 μ L, 1.20 mmol, 4 eq.) were combined in a 2-dram vial followed by addition of a solution of 5,6-dihydronaphthalen-2-yl 4-methylbenzenesulfonate (90 mg, 0.30 mmol, 1 eq.), THF (0.150 mL), and ethanol-OD (46 μ L, 0.78 mmol, 2.6 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 24 h at 40 °C. Upon completion, the crude product mixture was purified using flash column chromatography (5% ethyl acetate in hexanes) to give the pure product as a white solid (76 mg, 0.25 mmol, 83% yield).

¹H NMR: (300 MHz, CDCl₃)
 δ 7.73 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 6.92 (d, J = 8.4 Hz, 1H), 6.73 (s, 1H), 6.61 (d, J = 8.4 Hz, 1H), 2.73-2.61 (m, 3.04H), 2.45 (s, 3H), 1.75 (s, 4H)

²H NMR: (61 MHz, CHCl₃)
 δ 2.70 (s, 0.96D)

¹³C NMR: (101 MHz, CDCl₃)
 δ 147.33, 145.22, 138.81, 136.24, 132.89, 130.08, 129.78, 128.63, 122.66, 119.24, 29.09 (t, J = 19.3 Hz), 28.98, 23.00, 22.70, 21.84.

HRMS: (EI⁺) m/z : [M]⁺ Calcd. for C₁₇H₁₇DO₃S 303.1039; Found 303.1032.



6-methoxy-1,2,3,4-tetrahydronaphthalene-4-d [7]. According to the general procedure A, DTB-DPPBz (5.9 mg, 0.0066 mmol, 0.022eq.), Cu(OAc)₂ (30 μ L of a 0.2 M solution in THF, 0.006 mmol, 0.02 eq.), and THF (0.120 mL) then dimethoxy(methyl)silane (148 μ L, 1.20 mmol, 4 eq.) were combined in a 2-dram vial followed by addition of a solution of 1,2-Dihydro-6-methoxynaphthalene (48 mg, 0.30 mmol, 1 eq.), THF (0.150 mL), and ethanol-OD (46 μ L, 0.78 mmol, 2.6 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 20 h at 40 °C. Upon completion, the crude product mixture was purified using flash column chromatography (300 mL of 100% hexanes) to give the pure product as a clear colorless oil (37mg, 0.23 mmol, 77% yield).

¹H NMR: (600 MHz, CDCl₃)
 δ 6.99 (d, J = 8.4 Hz, 1H), 6.69 (d, J = 8.4 Hz, 1H), 6.64 – 6.62 (m, 1H), 3.79 (s, 3H), 2.77 – 2.68 (m, 3.03H), 1.83 – 1.76 (m, 4H).

²H NMR: (61 MHz, CHCl₃)

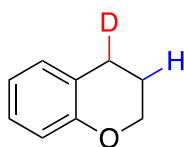
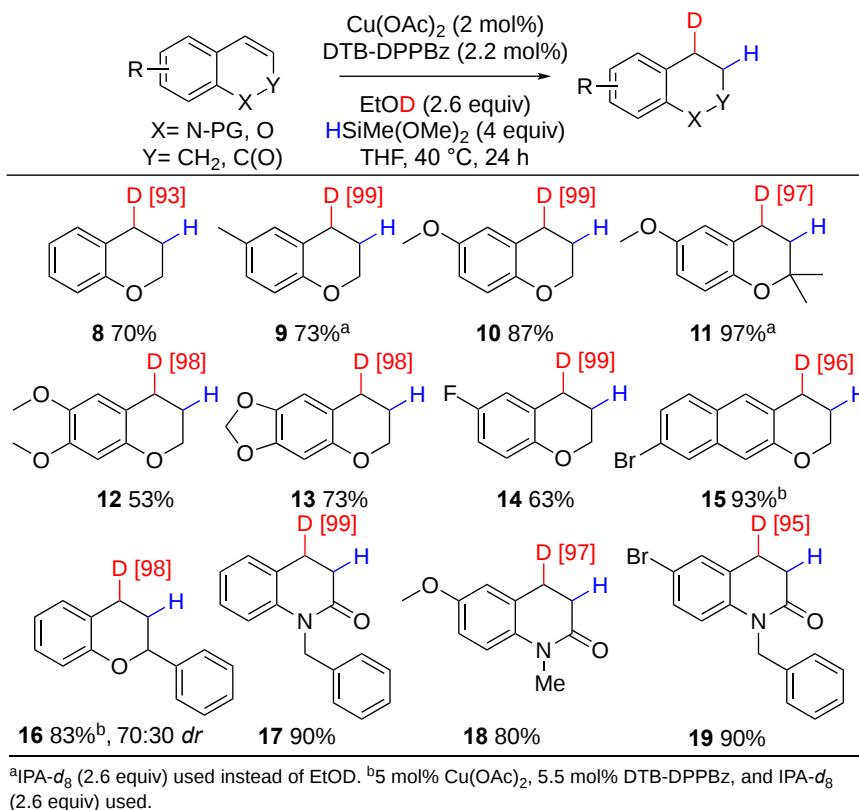
δ 2.78 (s, 0.97D).

¹³C NMR: (101 MHz, CDCl₃)

δ 157.51, 138.25, 130.06, 129.43, 113.83, 111.91, 55.38, 34.82, 28.71, 25.43, 23.57, 23.22.

HRMS: (ESI⁺) *m/z*: [M+H]⁺ Calcd. for C₁₁H₁₄DO 164.1187; Found 164.1183.

Scheme S2. Substrate scope of Chromenes and quinolinone derivatives

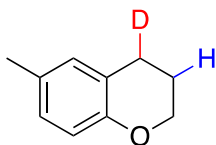


Chromane-4-*d* [8]. According to the general procedure A, DTB-DPPBz (5.9 mg, 0.0066 mmol, 0.022eq.), Cu(OAc)₂ (30 μ L of a 0.2 M solution in THF, 0.006 mmol, 0.02 eq.), and THF (0.120 mL) then dimethoxy(methyl)silane (148 μ L, 1.20 mmol, 4 eq.) were combined in a 2-dram vial followed by addition of a solution of 2H-chromene (40 mg, 0.30 mmol, 1 eq.), THF (0.150 mL), and ethanol-OD (46 μ L, 0.78 mmol, 2.6 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 24 h at 40 °C. Upon completion, the crude product mixture was purified using gradient flash column chromatography (200 mL of 100% hexanes, 300 mL of 2% ethyl acetate in hexanes) to give the pure product as a clear colorless oil (28 mg, 0.21 mmol, 70% yield). The NMR matched previously reported spectra.³

Note: Product is volatile and can evaporate when removing solvent, the ethyl acetate remaining in the ¹H NMR is a result of avoiding product loss.

¹H NMR: (600 MHz, CDCl₃)

δ 7.09 (t, *J* = 7.7 Hz, 1H), 7.04 (d, *J* = 6.5 Hz, 1H), 6.84 (t, *J* = 7.4 Hz, 1H), 6.80 (d, *J* = 8.2 Hz, 1H), 4.19 (t, *J* = 5.1 Hz, 2H), 2.80 – 2.74 (m, 1.07H), 2.01 (q, *J* = 5.9 Hz, 2H).



6-methylchromane-4-*d* [9]. According to the general procedure A, DTB-DPPBz (5.9 mg, 0.0066 mmol, 0.022eq.), Cu(OAc)₂ (30 μ L of a 0.2 M solution in THF, 0.006 mmol, 0.02 eq.), and THF (0.120 mL) then dimethoxy(methyl)silane (148 μ L, 1.20 mmol, 4 eq.) were combined in a 2-dram vial followed by addition of a solution of 6-Methyl-2*H*-chromene (44 mg, 0.30 mmol, 1 eq.), THF (0.150 mL), and isopropanol-*d*8 (60 μ L, 0.78 mmol, 2.6 eq). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 20 h at 40 °C. Upon completion, the crude product mixture was dry loaded and isolated by using gradient elution flash column chromatography (300 mL of 100% hexanes, 100 mL of 2% ethyl acetate in hexanes) to give the pure product as a light yellow oil (33 mg, 0.22 mmol, 73% yield).

¹H NMR: (400 MHz, CDCl₃)

δ 6.91 (d, J = 8.4 Hz, 1H), 6.88 (s, 1H), 6.72 (d, J = 8.2 Hz, 1H), 4.18 (t, J = 5.0 Hz, 2H), 2.78 – 2.72 (m, 1.01H), 2.28 (s, 3H), 2.01 (q, J = 5.8 Hz, 2H).

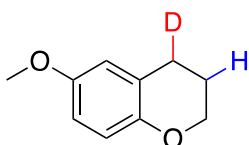
²H NMR: (61 MHz, CHCl₃)

δ 2.76 (s, 0.99D).

¹³C NMR: (101 MHz, CDCl₃)

δ 152.77, 130.27, 129.32, 127.89, 121.90, 116.49, 66.46, 24.58 (t, J = 20.1 Hz), 22.49, 20.57.

HRMS: (EI⁺) m/z : [M]⁺ Calc. for C₁₀H₁₁DO 149.0951; Found 149.0944.



6-methoxychromane-4-*d* [10]. According to the general procedure A, DTB-DPPBz (5.9 mg, 0.0066 mmol, 0.022eq.), Cu(OAc)₂ (30 μ L of a 0.2 M solution in THF, 0.006 mmol, 0.02 eq.), and THF (0.120 mL) then dimethoxy(methyl)silane (148 μ L, 1.20 mmol, 4 eq.) were combined in a 2-dram vial followed by addition of a solution of 6-methoxy-2*H*-chromene (49 mg, 0.30 mmol, 1 eq.), THF (0.150 mL), and ethanol-OD (46 μ L, 0.78 mmol, 2.6 eq). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 20 h at 40 °C. Upon completion, the crude product mixture was purified using flash column chromatography (300 mL of 100% hexanes) to give the pure product as a clear colorless oil (43 mg, 0.26 mmol, 87% yield).

¹H NMR: (400 MHz, CDCl₃)

δ 6.75 – 6.71 (m, 1H), 6.67 (dd, J = 8.9, 3.0 Hz, 1H), 6.59 (d, J = 2.9 Hz, 1H), 4.14 (t, J = 5.0 Hz, 2H), 3.75 (s, 3H), 2.79 – 2.72 (m, 1.01H), 1.98 (q, J = 6.0 Hz, 2H).

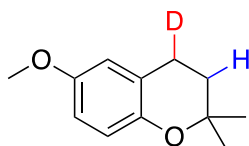
²H NMR: (61 MHz, CHCl₃)

δ 2.77 (s, 0.99D).

¹³C NMR: (101 MHz, CDCl₃)

δ 153.29, 149.10, 122.79, 117.31, 114.44, 113.36, 66.42, 55.81, 24.91 (t, J = 20.1 Hz), 22.46.

HRMS: (ESI⁺) m/z : [M+H]⁺ Calcd. for C₁₀H₁₂DO₂ 166.0980; Found 166.0971.



6-methoxy-2,2-dimethylchromane-4-*d* [11]. According to the general procedure A, DTB-DPPBz (5.9 mg, 0.0066 mmol, 0.022eq.), Cu(OAc)₂ (30 μ L of a 0.2 M solution in THF, 0.006 mmol, 0.02 eq.), and THF (0.120 mL) then dimethoxy(methyl)silane (148 μ L, 1.20 mmol, 4 eq.) were combined in a 2-dram vial followed by addition of a solution of 6-Methoxy-2,2-dimethyl-2*H*-chromene (57 mg, 0.30 mmol, 1 eq.), THF (0.150 mL), and isopropanol-*d*8 (60 μ L, 0.78 mmol, 2.6 eq). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 20 h at 40 °C. Upon completion, the crude product mixture was dry loaded and isolated by using gradient elution flash column chromatography (100 mL of 100% hexanes, 100 mL of 3% ethyl acetate in hexanes) to give the pure product as a yellow oil (57 mg, 0.29 mmol, 97% yield).

¹H NMR: (400 MHz, CDCl₃)

δ 6.75 – 6.67 (m, 2H), 6.64 – 6.61 (m, 1H), 3.76 (s, 3H), 2.78 – 2.71 (m, 1.03H), 1.79 (d, *J* = 6.8 Hz, 2H), 1.33 (s, 6H).

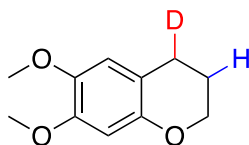
²H NMR: (61 MHz, CHCl₃)

δ 2.74 (s, 0.97D).

¹³C NMR: (101 MHz, CDCl₃)

δ 152.93, 148.03, 121.46, 117.78, 113.98, 113.45, 73.84, 55.75, 32.77, 26.83, 26.81, 22.54 (t, *J* = 19.7 Hz).

HRMS: (EI⁺) *m/z*: [M]⁺ Calc. for C₁₂H₁₅DO₂ 193.1213; Found 193.1206.



6,7-dimethoxychromane-4-*d* [12]. According to the general procedure A, DTB-DPPBz (5.9 mg, 0.0066 mmol, 0.022eq.), Cu(OAc)₂ (30 μ L of a 0.2 M solution in THF, 0.006 mmol, 0.02 eq.), and THF (0.120 mL) then dimethoxy(methyl)silane (148 μ L, 1.20 mmol, 4 eq.) were combined in a 2-dram vial followed by addition of a solution of 6,7-Dimethoxy-2*H*-chromene (58 mg, 0.30 mmol, 1 eq.), THF (0.150 mL), and ethanol-OD (46 μ L, 0.78 mmol, 2.6 eq). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 20 h at 40 °C. Upon completion, the crude product mixture was dry loaded and isolated by using gradient elution flash column chromatography (100 mL of 100% hexanes, 100 mL of 4% ethyl acetate in hexanes, 100 mL of 8% ethyl acetate) to give the pure product as a clear colorless oil (32mg, 0.16 mmol, 53% yield).

¹H NMR: (400 MHz, CDCl₃)

δ 6.52 (s, 1H), 6.37 (s, 1H), 4.12 (t, *J* = 5.1 Hz, 2H), 3.81 (s, 6H), 2.72 – 2.61 (m, 1.02H), 1.96 (q, *J* = 5.8 Hz, 2H).

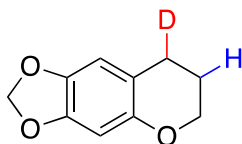
²H NMR: (61 MHz, CHCl₃)

δ 2.68 (s, 0.98D).

¹³C NMR: (101 MHz, CDCl₃)

δ 148.81, 148.30, 143.01, 112.65, 112.62, 100.93, 66.40, 56.53, 55.94, 24.06 (t, *J* = 20.0 Hz), 22.60.

HRMS: (EI⁺) *m/z*: [M]⁺ Calc. for C₁₁H₁₃DO₃ 195.1006; Found 195.0998.



7,8-dihydro-6H-[1,3]dioxolo[4,5-g]chromene-8-d [13]. According to the general procedure A, DTB-DPPBz (5.9 mg, 0.0066 mmol, 0.022eq.), Cu(OAc)₂ (30 μ L of a 0.2 M solution in THF, 0.006 mmol, 0.02 eq.), and THF (0.120 mL) then dimethoxy(methyl)silane (148 μ L, 1.20 mmol, 4 eq.) were combined in a 2-dram vial followed by addition of a solution of 6,7-methylenedioxy-2H-1-benzopyrane (53 mg, 0.30 mmol, 1 eq.), THF (0.150 mL), and ethanol-OD (46 μ L, 0.78 mmol, 2.6 eq). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 21 h at 40 °C. Upon completion, the crude product mixture was dry loaded and isolated by using gradient elution flash column chromatography (100 mL of 100% hexanes, 100 mL of 2% ethyl acetate in hexanes) to give the pure product as a white crystalline solid (40 mg, 0.22 mmol, 73% yield).

¹H NMR: (300 MHz, CDCl₃)

δ 6.48 (s, 1H), 6.35 (s, 1H), 5.85 (s, 2H), 4.10 (t, J = 5.8 Hz, 2H), 2.71 – 2.62 (m, 1.02H), 1.95 (q, J = 5.9 Hz, 2H).

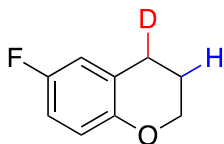
²H NMR: (61 MHz, CHCl₃)

δ 2.66, (s, 0.98D).

¹³C NMR: (101 MHz, CDCl₃)

δ 149.55, 146.40, 141.31, 113.57, 108.57, 100.82, 98.66, 66.47, 24.61 (t, J = 19.9 Hz), 22.44.

HRMS: (EI⁺) m/z : [M]⁺ Calc. for C₁₀H₉DO₃ 179.0693; Found 179.0686.



6-fluorochromane-4-d [14]. According to the general procedure A, DTB-DPPBz (5.9 mg, 0.0066 mmol, 0.02 eq.), Cu(OAc)₂ (30 μ L of a 0.2 M solution in THF, 0.006 mmol, 0.02 eq.), and THF (0.120 mL) then dimethoxy(methyl)silane (148 μ L, 1.2 mmol, 4 eq.) were combined in a 2-dram vial followed by addition of a solution of 6-fluoro-2H-chromene (45 mg, 0.3 mmol, 1 eq.), THF (0.150 mL), and ethanol-OD (46 μ L, 0.76 mmol, 2.6 eq). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 20 h at 40 °C. Upon completion, the crude product mixture was dry loaded and isolated by using gradient elution flash column chromatography (100 mL of 100% hexanes, 200 mL of 1% ethyl acetate in hexanes, 200 mL of 2% ethyl acetate in hexanes) to give the pure product as a yellow oil (29 mg, 0.19 mmol, 63% yield).

¹H NMR: (400 MHz, CDCl₃)

δ 6.81 – 6.69 (m, 3H), 4.15 (t, J = 5.3 Hz, 2H), 2.79 – 2.70 (m, 1.01H), 1.98 (q, J = 5.5 Hz, 2H).

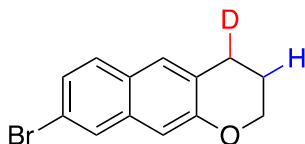
²H NMR: (61 MHz, CHCl₃)

δ 2.77 (s 0.99D).

¹³C NMR: (101 MHz, CDCl₃)

δ 157.94, 155.57, 151.05, 117.63 (d, J = 8.0 Hz), 115.79 (d, J = 22.9 Hz), 114.10 (d, J = 23.1 Hz), 66.51, 24.78 (t, J = 20.6 Hz), 22.10.

HRMS: (EI⁺) m/z : [M]⁺ Calc. for C₉H₈DFO 153.0700; Found 153.0693.



8-bromo-3,4-dihydro-2H-benzo[g]chromene-4-d [15]. According to the general procedure A, DTB-DPPBz (14.8 mg, 0.0165 mmol, 0.055 eq.), Cu(OAc)₂ (75 μ L of a 0.2 M solution in THF, 0.0150 mmol, 0.05 eq.), and THF (0.075 mL) then dimethoxy(methyl)silane (148 μ L, 1.20 mmol, 4 eq.) were combined in a 2-dram vial followed by addition of a solution of 8-bromo-2H-benzo[g]chromene (75 mg, 0.30 mmol, 1.0 eq.), THF (0.150 mL), and isopropanol-*d*8 (60 μ L, 0.78 mmol, 2.6 eq). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 19 h at 40 °C. Upon completion, the crude product mixture was dry loaded and isolated by using gradient elution flash column chromatography (100 mL of 100% hexanes, 200 mL of 5% dichloromethane in hexanes) to give the pure product as off-white crystals (73 mg, 0.28 mmol, 93% yield).

¹H NMR: (400 MHz, CDCl₃)

δ 7.96 – 7.93 (m, 1H), 7.60 (d, *J* = 8.6 Hz, 1H), 7.56 (d, *J* = 8.9 Hz, 1H), 7.41 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.05 (d, *J* = 8.9 Hz, 1H), 4.28 – 4.22 (m, 2H), 3.00 – 2.91 (m, 1.04H), 2.19 – 2.11 (m, 2H).

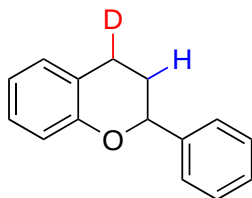
²H NMR: (61 MHz, CHCl₃)

δ 2.95 (s, 0.96D).

¹³C NMR: (101 MHz, CDCl₃)

δ 153.42, 134.72, 130.07, 127.58, 127.36, 126.49, 124.42, 120.94, 119.63, 113.20, 66.24, 22.01, 20.94 (t, *J* = 19.8 Hz).

HRMS: (EI⁺) *m/z*: [M]⁺ Calc. for C₁₃H₁₀DBrO 263.0056; Found 263.0049.



2-phenylchromane-4-d [16]. According to the general procedure A, DTB-DPPBz (17.7 mg, 0.0198 mmol, 0.055 eq.), Cu(OAc)₂ (90 μ L of a 0.2 M solution in THF, 0.0180 mmol, 0.05 eq.), and THF (0.090 mL) then dimethoxy(methyl)silane (178 μ L, 1.44 mmol, 4 eq.) were combined in a 2-dram vial followed by addition of a solution of 2-Phenyl-2H-chromene (75 mg, 0.36 mmol, 1 eq.), THF (0.180 mL), and isopropanol-*d*8 (72 μ L, 0.94 mmol, 2.6 eq). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 20 h at 40 °C. Upon completion, the crude product mixture was dry loaded and isolated by using gradient elution flash column chromatography (100 mL of 100% hexanes, 200 mL of 1% ethyl acetate in hexanes) to give the pure product as a yellow oil (63 mg, 0.30 mmol, 83% yield). The product was isolated as a diastereomeric mixture with a d.r. of 70:30.

¹H NMR: (400 MHz, CDCl₃)

δ 7.54 – 7.44 (m, 4H), 7.43 – 7.37 (m, 1H), 7.24 – 7.15 (m, 2H), 7.04 – 6.93 (m, 2H), 5.14 (dd, *J* = 10.1, 2.4 Hz, 1H), 3.10 – 3.00 (m, 0.72H), 2.88 – 2.82 (m, 0.30H), 2.33 – 2.23 (m, 1H), 2.21 – 2.10 (m, 1H).

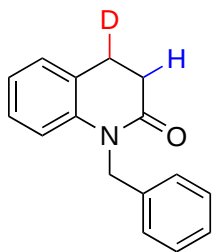
²H NMR: (61 MHz, CHCl₃)

δ 3.05 (s, 0.28D), 2.86 (s, 0.70D).

¹³C NMR: (101 MHz, CDCl₃)

δ 155.23, 141.84, 129.61, 128.61, 127.92, 127.44, 126.09, 121.86, 120.41, 117.02, 77.81, 29.95, 24.85 (t, *J* = 20.3 Hz).

HRMS: (ESI⁺) *m/z*: [M+H]⁺ Calc. for C₁₅H₁₄DO 212.1187; Found 212.1186.



1-benzyl-3,4-dihydroquinolin-2(1H)-one-4-d [17]. According to the general procedure A, DTB-DPPBz (5.9 mg, 0.0066 mmol, 0.022eq.), Cu(OAc)₂ (30 μ L of a 0.2 M solution in THF, 0.006 mmol, 0.02 eq.), and THF (0.120 mL) then dimethoxy(methyl)silane (148 μ L, 1.20 mmol, 4 eq.) were combined in a 2-dram vial followed by addition of a solution of 1-benzylquinolin-2(1H)-one (57 mg, 0.30 mmol, 1 eq.), THF (0.150 mL), and ethanol-OD (60 μ L, 0.78 mmol, 2.6 eq). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 20 h at 40 °C. Upon completion, the crude product mixture was dry loaded and isolated by using gradient elution flash column chromatography (100 mL of 100% hexanes, 200 mL of 10% ethyl acetate in hexanes, 200 mL of 20% ethyl acetate in hexanes, 200 mL of 30% ethyl acetate in hexanes) to give the pure product as a light yellow solid (64 mg, 0.27 mmol, 90% yield).

¹H NMR: (400 MHz, CDCl₃)

δ 7.31 (t, J = 7.2 Hz, 2H), 7.23 (t, J = 7.6 Hz, 3H), 7.17 (d, J = 7.3 Hz, 1H), 7.11 (t, J = 7.9 Hz, 1H), 6.97 (t, J = 7.4 Hz, 1H), 6.87 (d, J = 8.1 Hz, 1H), 5.19 (s, 2H), 2.98 (d, J = 7.6 Hz, 2H), 2.83 – 2.73 (m, 1.01H).

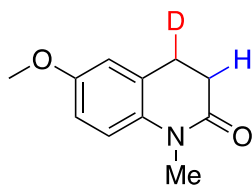
²H NMR: (61 MHz, CHCl₃)

δ 2.80 (s, 0.99D).

¹³C NMR: (101 MHz, CDCl₃)

δ 170.61, 139.94, 137.06, 128.79, 127.91, 127.49, 127.11, 126.42 (2 overlapping signals), 122.99, 115.66, 46.22, 31.64 (t, J = 20.3 Hz), 25.54.

HRMS: (ESI⁺) m/z : [M+H]⁺ Calc. for C₁₆H₁₅DNO 239.1296; Found 239.1290.



6-methoxy-1-methyl-3,4-dihydroquinolin-2(1H)-one-4-d [18]. According to the general procedure X, DTB-DPPBz (5.9 mg, 0.0066 mmol, 0.022eq.), Cu(OAc)₂ (30 μ L of a 0.2 M solution in THF, 0.006 mmol, 0.02 eq.), and THF (0.120 mL) then dimethoxy(methyl)silane (148 μ L, 1.20 mmol, 4 eq.) were combined in a 2-dram vial followed by addition of a solution of 6-methoxy-1-methylquinolin-2(1H)-one (57 mg, 0.30 mmol, 1 eq.), THF (0.150 mL), and ethanol-OD (46 μ L, 0.78 mmol, 2.6 eq). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 20 h at 40 °C. Upon completion, the crude product mixture was dry loaded and isolated by using gradient elution flash column chromatography (100 mL of 100% hexanes, 200 mL of 10% ethyl acetate in hexanes, 200 mL of 20% ethyl acetate in hexanes) to give the pure product as a yellow oil (46 mg, 0.24 mmol, 80% yield).

¹H NMR: (600 MHz, CDCl₃)

δ 6.90 – 6.86 (m, 1H), 6.79 – 6.74 (m, 1H), 6.73 (s, 1H), 3.78 (s, 3H), 3.32 (s, 3H), 2.858 – 2.82 (m, 2H), 2.64 – 2.56 (m, 1.03H).

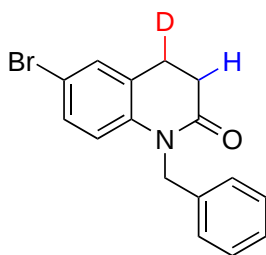
²H NMR: (61 MHz, CHCl₃)

δ 2.62 (s, 0.97D).

¹³C NMR: (101 MHz, CDCl₃)

δ 170.21, 155.39, 134.37, 127.82, 115.66, 114.02, 111.91, 55.68, 31.48 (t, J = 20.1 Hz), 29.76, 25.70.

HRMS: (ESI⁺) m/z : [M+H]⁺ Calc. for C₁₁H₁₃DNO₂ 193.1089; Found 193.1093.



1-benzyl-6-bromo-3,4-dihydroquinolin-2(1H)-one-4-d [19]. According to the general procedure X, DTB-DPPBz (5.9 mg, 0.0066 mmol, 0.022eq.), Cu(OAc)₂ (30 μ L of a 0.2 M solution in THF, 0.006 mmol, 0.02 eq.), and THF (0.120 mL) then dimethoxy(methyl)silane (148 μ L, 1.20 mmol, 4 eq.) were combined in a 2-dram vial followed by addition of a solution of 1-benzyl-6-bromoquinolin-2(1H)-one (94 mg, 0.30 mmol, 1 eq.), THF (0.150 mL), and ethanol-OD (46 μ L, 0.78 mmol, 2.6 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 20 h at 40 °C. Upon completion, the crude product mixture was dry loaded and isolated by using gradient elution flash column chromatography (100 mL of 100% hexanes, 100 mL of 10% ethyl acetate in hexanes, 300 mL of 20% ethyl acetate in hexanes) to give the pure product as a yellow solid (86 mg, 0.27 mmol, 90% yield).

¹H NMR: (600 MHz, CDCl₃)

δ 7.32 – 7.28 (m, 3H), 7.25 – 7.16 (m, 4H), 6.73 (d, J = 8.8 Hz, 1H), 5.16 (s, 2H), 2.95 (d, J = 7.9 Hz, 2H), 2.78 – 2.73 (m, 1.05H).

²H NMR: (61 MHz, CHCl₃)

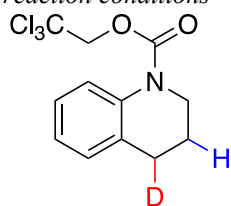
δ 2.74 (s, 0.95D).

¹³C NMR: (101 MHz, CDCl₃)

δ 170.17, 139.03, 136.57, 130.74, 130.31, 128.91, 128.55, 127.33, 126.42, 117.29, 115.72, 46.14, 31.29 (t, J = 20.1 Hz), 25.31.

HRMS: (ESI⁺) m/z : [M+H]⁺ Calc. for C₁₆H₁₄DBrNO 317.0402; Found 317.0407.

Example of a dihydroquinoline transfer hydrodeuteration that did not perform well under the optimal reaction conditions



2,2,2-trichloroethyl 3,4-dihydroquinoline-1(2H)-carboxylate-4-d [S29] According to general procedure A, DTB-DPPBz (15 mg, 0.017 mmol, 0.055 eq.), Cu(OAc)₂ (75 μ L of a 0.2 M solution in THF, 0.015 mmol, 0.05 eq.), and THF (80 μ L) followed by dimethoxy(methyl)silane (150 μ L, 1.2 mmol, 4 eq.) were added to an oven-dried 2-dram vial with an oven-dried stir bar. In a separate oven-dried 1-dram vial was added 2,2,2-trichloroethyl quinoline-1(2H)-carboxylate (105 mg, 0.3 mmol, 1 eq.), THF (150 μ L), and 2-propanol-*d*₈ (60 μ L, 0.78 mmol, 2.6 eq.). The solution in the 1-dram vial was added dropwise to the 2-dram vial. The 2-dram vial was capped with a pressure relief cap, removed from the glovebox, and left to stir for 24 h at 40 °C. Upon completion, the reaction mixture was subjected to column chromatography to yield pure 2,2,2-trichloroethyl 3,4-dihydroquinoline-1(2H)-carboxylate-4-d as a brown oil (51.4 mg, 48%) with 49% deuterium incorporation.

¹H NMR: (600 MHz, CDCl₃)

δ 8.07-7.99 (m, 3H), 4.88 (s, 2H), 3.93 (t, J = 5.9 Hz, 2H), 2.93-2.84 (m, 1.51H), 2.08-1.99 (m, 2H).

Synthesis of Starting Materials

General Procedures

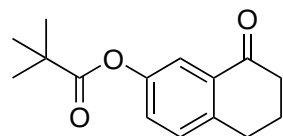
Williamson Ether Synthesis (B):

To a stirred suspension of the phenol (1.0 eq.) and cesium carbonate (1.2 eq.) in *N,N*-dimethylformamide (1.0 M) was added propargyl bromide (80% solution in toluene, 1.3 eq.) after 20 minutes. The reaction mixture was stirred for 4 h at room temperature under N_2 . Upon completion, the reaction mixture was diluted with diethyl ether and extracted with diethyl ether (3 x 20 mL). The combined organic layers were washed with deionized water (7 x 20 mL), brine (20 mL), dried over Na_2SO_4 , and concentrated. The crude product was purified by gradient flash column chromatography.

Alkyne Cyclization (C): To a solution of the aryl propargyl ether (1.0 eq.) in dry dichloromethane (0.5 M) was added $Ph_3PAuNTf_2$ (0.01 eq.) at room temperature. After 24 h, the residue was concentrated and was purified by flash column chromatography.

Synthesis of $Ph_3PAuNTf_2$:

Modified based on a previously reported procedure (see reference 49 in manuscript). In a N_2 -filled glovebox, to a 20-dram vial was added Chloro(triphenylphosphine)gold(I) (250 mg, 0.505 mmol, 1.0 eq.) followed by dichloromethane (10 mL, 0.05M). While stirring, Silver bis(trifluoromethanesulfonyl)imide (196 mg, 0.505 mmol, 1.0 eq.) was added to the reaction mixture and a light purple salt immediately precipitated from solution. The reaction was stirred in the glovebox at room temperature for 30 minutes to ensure complete metathesis. After this time, the reaction mixture was filtered over a short pad of celite and rinsed with 5 mL of dichloromethane. The resulting solution was assumed in quantitative yield (0.505 mmol, 15 mL, 0.034 M in DCM) and used in our $Ph_3PAuNTf_2$ -catalyzed alkyne cyclizations.



8-oxo-5,6,7,8-tetrahydronaphthalen-2-yl pivalate. 3,4-Dihydro-7-hydroxy-1(2H)-naphthalenone (1.0 g, 6.17 mmol, 1 eq.) was dissolved in dichloromethane (12 mL, 0.5 M) and cooled to 0° C. Triethylamine (0.91 mL, 6.5 mmol, 1.05 eq.) was added dropwise, followed by dropwise addition of pivaloyl chloride (0.80 mL, 6.5 mmol, 1.05 eq.). The reaction was cooled to room temperature and allowed to stir for 16 hours. After 16 hours, the solvent was removed *in vacuo* and the mixture was taken up in 25 mL of ethyl acetate. The solution was washed with deionized water and the aqueous layer was extracted with ethyl acetate (3 x 25 mL). The organic layers were dried over sodium sulfate, filtered, and purified by flash column chromatography (25% ethyl acetate in hexanes) to yield a burgundy solid (1.14 g, 4.6 mmol, 74% yield).

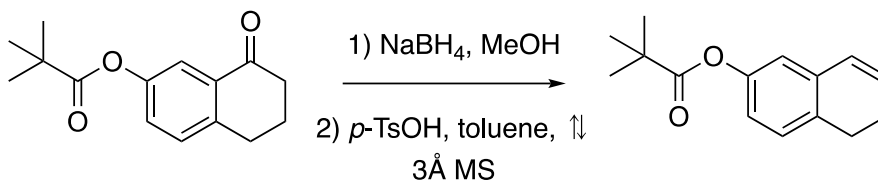
1H NMR: (400 MHz, $CDCl_3$)

δ 7.66 (s, 1H), 7.25 (d, J = 7.6 Hz, 1H), 7.15 (d, J = 8.4 Hz, 1H), 2.94 (t, J = 5.5 Hz, 2H), 2.63 (t, J = 6.6 Hz, 2H), 2.21-2.07 (m, 2H), 1.33 (s, 9H).

^{13}C NMR: (101 MHz, $CDCl_3$)

δ 197.63, 177.10, 149.81, 141.85, 133.67, 130.01, 127.00, 119.72, 39.12, 38.87, 29.19, 27.18, 23.25.

HRMS: (El^+) m/z : $[M]^+$ Calc. for $C_{15}H_{18}O_3$ 246.1256; Found 246.1250.



5,6-dihydronaphthalen-2-yl pivalate [4-SM]. In a 100 mL round bottom flask, 8-oxo-5,6,7,8-tetrahydronaphthalen-2-yl pivalate (700 mg, 2.84 mmol, 1 eq.) was dissolved in methanol (5 mL, 0.5M) and cooled to 0° C. Sodium borohydride (215 mg, 5.68 mmol, 2 eq.) was added portionwise to avoid vigorous bubbling. After gas evolution was complete, the reaction was warmed to room temperature and stirred for 3 hours until completion of the reaction was seen on TLC. The solvent was removed *in vacuo* and the mixture was diluted with deionized water (30 mL). The aqueous layer was extracted with dichloromethane (3x30 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo* to yield crude 8-hydroxy-5,6,7,8-tetrahydronaphthalen-2-yl pivalate. The crude alcohol (363 mg, 1.47 mmol, 1 eq.) was dissolved in toluene (15 mL, 0.1 M) and to this solution was added oven-dried 3 Å molecular sieves and a catalytic (~20 mg) amount of *p*-toluenesulfonic acid. The mixture was heated at reflux while stirring overnight for 16 hours. After the reaction was complete, it was filtered over cotton and concentrated to yield the pure clear oil (256 mg, 1.11 mmol, 39% over 2 steps).

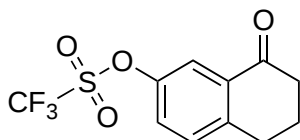
¹H NMR: (400 MHz, CDCl₃)

δ 7.09 (d, *J* = 8.1 Hz, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 6.74 (s, 1H), 6.42 (d, *J* = 9.6 Hz, 1H), 6.07 (dt, *J* = 9.1, 4.4 Hz, 1H), 2.78 (t, *J* = 8.3 Hz, 2H), 2.36-2.27 (m, 2H), 1.37 (s, 9H).

¹³C NMR: (101 MHz, CDCl₃)

δ 177.43, 149.73, 135.35, 132.79, 129.68, 128.27, 127.45, 119.48, 118.86, 39.15, 27.29, 27.02, 23.34.

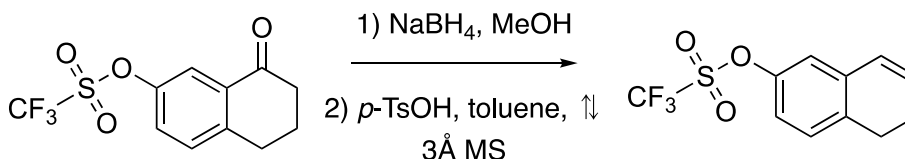
HRMS: (EI⁺) *m/z*: [M]⁺ Calc. for C₁₅H₁₈O₂: 230.1307; Found 230.1300.



5,6,7,8-Tetrahydro-8-oxo-2-naphthalenyl 1,1,1-trifluoromethanesulfonate. 3,4-Dihydro-7-hydroxy-1(2H)-naphthalenone (500 mg, 3.08 mmol, 1 eq.) was dissolved in dichloromethane (6 mL, 0.5 M) and cooled to 0° C. Triethylamine (0.47 mL, 3.38 mmol, 1.1 eq.) was added dropwise, followed by dropwise addition of trifluoromethanesulfonic anhydride (0.51 mL, 3.08 mmol, 1 eq.). After the release of gasses, the reaction was slowly cooled to room temperature and allowed to stir for 16 hours. After 16 hours, the solvent was removed *in vacuo* and the mixture was taken up in 25 mL of ethyl acetate. The solution was washed with sodium bicarbonate (2x25 mL) and brine (2x25 mL), and the organic layer was dried over sodium sulfate. The combined organic layers were concentrated and purified by flash column chromatography (15% ethyl acetate in hexanes) to yield a yellow oil (527 mg, 1.79 mmol, 58% yield). The NMR spectra matched with previously reported data.⁴

¹H NMR: (400 MHz, CDCl₃)

δ 7.90 (s, 1H), 7.37 (s, 2H), 3.00 (t, *J* = 6.2 Hz, 2H), 2.69 (t, *J* = 5.7 Hz, 2H), 2.17 (t, *J* = 5.8 Hz, 2H)



5,6-dihydronaphthalen-2-yl trifluoromethanesulfonate [5-SM]. In a 100 mL round bottom flask, 5,6,7,8-Tetrahydro-8-oxo-2-naphthalenyl 1,1,1-trifluoromethanesulfonate (300 mg, 1.02 mmol, 1 eq.) was dissolved

in methanol (5.1 mL, 0.2M) and cooled to 0° C. Sodium borohydride (77.1 mg, 2.04 mmol, 2 eq.) was added portionwise to avoid vigorous bubbling. After gas evolution was complete, the reaction was warmed to room temperature and stirred for 4 hours until completion of the reaction was seen on TLC. The solvent was removed *in vacuo* and the mixture was diluted with deionized water (30 mL). The aqueous layer was extracted with dichloromethane (3x30 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo* to yield 8-hydroxy-5,6,7,8-tetrahydronaphthalen-2-yl trifluoromethanesulfonate. This procedure was repeated to obtain more material for the next step. The crude 8-hydroxy-5,6,7,8-tetrahydronaphthalen-2-yl trifluoromethanesulfonate (350 mg, 1.18 mmol, 1 eq.) was dissolved in toluene (11.8 mL, 0.1 M) and to this mixture was added oven-dried 3Å molecular sieves and a catalytic (~20 mg) amount of *p*-toluenesulfonic acid. The mixture was heated at reflux while stirring overnight for 16 hours. After the reaction was complete, it was filtered over cotton and concentrated to yield the pure clear oil (245 mg, 0.88 mmol, 75%).

¹H NMR: (600 MHz, CDCl₃)

δ 7.14 (d, *J* = 8.2 Hz, 1H), 7.00 (d, *J* = 8.2 Hz, 1H), 6.92 (s, 1H), 6.43 (d, *J* = 9.7 Hz, 1H), 6.18 – 6.12 (m, 1H), 2.80 (t, *J* = 8.3 Hz, 2H), 2.38 – 2.29 (m, 2H).

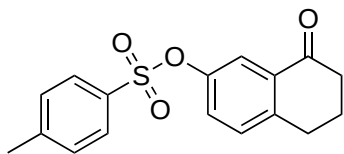
¹⁹F NMR: (376 MHz, CDCl₃)

δ -72.93 (s, 3F).

¹³C NMR: (101 MHz, CDCl₃)

δ 148.21, 136.20, 135.63, 131.09, 128.85, 126.53, 118.96, 120.49 (q, *J* = 320.0 Hz), 118.20, 26.77, 22.88.

HRMS: (ESI⁺) *m/z*: [M+H]⁺ Calc. for C₁₁H₁₀F₃O₃S 279.0304; Found 279.0304.



8-oxo-5,6,7,8-tetrahydronaphthalen-2-yl 4-methylbenzenesulfonate. 3,4-Dihydro-7-hydroxy-1(2H)-naphthalenone (1.00 g, 6.17 mmol, 1 eq.) was dissolved in dichloromethane (6 mL, 0.5 M) and cooled to 0° C. Triethylamine (0.89 mL, 6.42 mmol, 1.04 eq.) was added dropwise, followed by addition of 4-Toluenesulfonyl chloride (1.22 g, 6.42 mmol, 1.04 eq.). The reaction was cooled to room temperature and allowed to stir for 16 hours. After 16 hours, the solvent was removed *in vacuo* and the mixture was taken up in 25 mL of ethyl acetate. The solution was washed with deionized water and the aqueous layer was extracted with ethyl acetate (3 x 25 mL). The organic layers were washed with 1M HCl (25 mL) and brine (25 mL), dried over sodium sulfate, filtered, and purified by flash column chromatography (20% ethyl acetate in hexanes) to yield a white powder (1.82 g, 5.75 mmol, 93% yield).

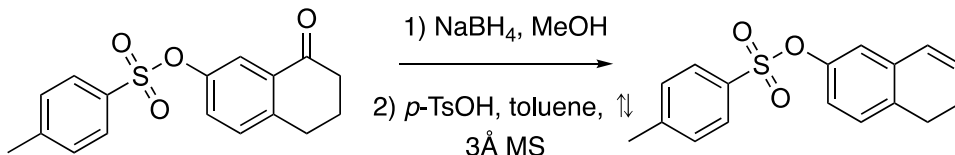
¹H NMR: (300 MHz, CDCl₃)

δ 7.69 (d, *J* = 8.3 Hz, 2H), 7.49 (s, 1H), 7.30 (d, *J* = 8.1 Hz, 2H), 7.19 (s, 2H), 2.91 (t, *J* = 6.2 Hz, 2H), 2.59 (t, *J* = 6.2 Hz, 2H), 2.42 (s, 3H), 2.09 (m, 2H)

¹³C NMR: (101 MHz, CDCl₃)

δ 196.94, 148.44, 145.71, 143.34, 133.84, 132.39, 130.52, 130.01, 128.64, 127.63, 120.45, 38.76, 29.22, 23.06, 21.86.

HRMS: (EI⁺) *m/z*: [M]⁺ Calc. for C₁₇H₁₆O₄S: 316.0769; Found 316.0764.



5,6-dihydronaphthalen-2-yl 4-methylbenzenesulfonate [6-SM]. In a 100 mL round bottom flask, 8-oxo-5,6,7,8-tetrahydronaphthalen-2-yl 4-methylbenzenesulfonate (1.00 g, 3.16 mmol, 1 eq.) was dissolved in methanol (6 mL, 0.5M) and cooled to 0° C. Sodium borohydride (239 mg, 6.32 mmol, 2 eq.) was added portionwise to avoid vigorous bubbling. After gas evolution was complete, the reaction was warmed to room temperature and stirred for 4 hours until completion of the reaction was seen on TLC. The solvent was removed *in vacuo* and the mixture was diluted with deionized water (30 mL). The aqueous layer was extracted with dichloromethane (3x30 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo* to yield 8-hydroxy-5,6,7,8-tetrahydronaphthalen-2-yl 4-methylbenzenesulfonate. The crude 8-hydroxy-5,6,7,8-tetrahydronaphthalen-2-yl 4-methylbenzenesulfonate (732 mg, 2.30 mmol, 1 eq.) was dissolved in toluene (23 mL, 0.1 M) and to this mixture was added oven-dried 3Å molecular sieves and a catalytic (~20 mg) amount of *p*-toluenesulfonic acid. The mixture was heated at reflux while stirring overnight for 16 hours. After the reaction was complete, it was filtered over cotton and concentrated to yield a pure clear oil (362 mg, 1.20 mmol, 38% over 2 steps).

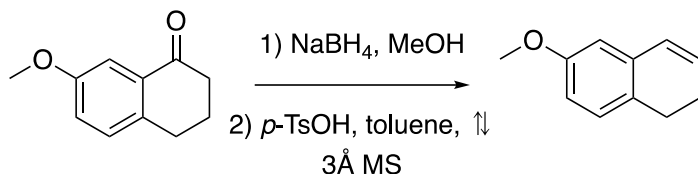
¹H NMR: (600 MHz, CDCl₃)

δ 7.69 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.1 Hz, 2H), 6.93 (d, *J* = 8.1 Hz, 1H), 6.71-6.58 (m, 2H), 6.30 (d, *J* = 9.6 Hz, 1H), 6.08-5.96 (m, 1H), 2.70 (t, *J* = 8.3 Hz, 2H), 2.41 (s, 3H), 2.31-2.18 (m, 2H).

¹³C NMR: (101 MHz, CDCl₃)

δ 148.20, 145.31, 135.31, 134.28, 132.54, 130.13, 129.77, 128.52, 128.34, 126.97, 120.12, 119.55, 26.82, 23.02, 21.74.

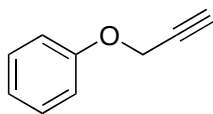
HRMS: (ESI⁺) *m/z*: [M+H]⁺ Calc. for C₁₇H₁₆O₃S 300.0820; Found 300.0816.



7-methoxy-1,2-dihydronaphthalene [7-SM]. In a 100 mL round bottom flask, 3,4-dihydro-7-methoxy-1(2*H*)-naphthalenone (500 mg, 2.83 mmol, 1 eq.) was dissolved in methanol and cooled to 0° C. Sodium borohydride (215 mg, 5.67 mmol, 2 eq.) was added portionwise to avoid vigorous bubbling. After gas evolution was complete, the reaction was warmed to room temperature and stirred for 4 hours until completion of the reaction was seen on TLC. The solvent was removed *in vacuo* and the mixture was diluted with deionized water (30 mL). The aqueous layer was extracted with dichloromethane (3x30 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. In a 100 mL round bottom flask, the crude product (350 mg, 1.18 mmol, 1 eq.) was dissolved in toluene (11.8 mL, 0.1 M) and to this mixture was added oven-dried 3Å molecular sieves and a catalytic (~20 mg) amount of *p*-toluenesulfonic acid. The mixture was heated at reflux while stirring overnight for 16 hours. After the reaction was complete, it was filtered over cotton and concentrated to yield the pure clear oil (221 mg, 1.38 mmol, 48% over 2 steps). NMR data matched previously reported spectra.⁵

¹H NMR: (400 MHz, CDCl₃):

δ 7.02 (d, *J* = 8.2 Hz, 1H), 6.68 (d, *J* = 8.1 Hz, 1H), 6.61 (s, 1H), 6.43 (d, *J* = 9.6 Hz, 1H), 6.09 – 6.02 (m, 1H), 3.80 (s, 3H), 2.74 (t, *J* = 8.2 Hz, 2H), 2.35 – 2.26 (m, 2H).

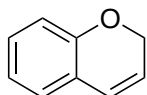


(2-Propyn-1-yloxy)benzene. Following general procedure B was added propargyl bromide (2.056 g, 13.82 mmol, 80% solution in toluene, 1.3 eq.) to a stirred suspension of phenol (1 g, 10.63 mmol, 1.0 eq) and cesium carbonate (4.15 g, 12.76 mmol, 1.2 eq.) in N,N-dimethylformamide (10 mL, 1 M). The reaction

mixture was stirred for 14 h at room temperature under N₂. The crude product was purified by gradient flash column chromatography (100 mL of 100% hexanes, 500 mL of 1% ethyl acetate in hexanes) to yield a clear oil (1.1 g, 8.3 mmol, 78% yield). The NMR spectra matched with previously reported data.⁶

¹H NMR: (600 MHz, CDCl₃):

δ 7.36 (t, *J* = 8.1 Hz, 2H), 7.07 – 7.02 (m, 3H), 4.74 – 4.71 (m, 2H), 2.57 – 2.54 (m, 1H).

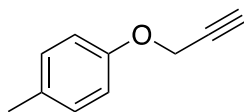


2H-chromene [8-SM]. Following general procedure C was added Ph₃PAuNTf₂ (11.2 mg, 0.0152 mmol, 0.01 eq.) to a solution of (prop-2-yn-1-yloxy)benzene (290 mg, 1.52 mmol, 1.0 eq.) in dry dichloromethane (3.04 mL, 0.50 M) at room temperature. After 6 h, the residue was concentrated and was purified by flash column chromatography (100 mL of 100% hexanes, 200 mL of 3% ethyl acetate in hexanes). The product mixed with recovered starting material was resubjected to the same reaction conditions and purified by flash column chromatography to yield a clear oil (114 mg, 0.60 mmol, 39% yield). The NMR spectra matched with previously reported data.⁶

Note: Product is prone to degradation and will decompose within hours. Trace ethyl acetate is present in the spectra to avoid loss of product under vacuum.

¹H NMR: (300 MHz, CDCl₃):

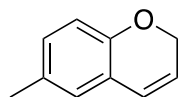
δ 7.10 (t, *J* = 7.6 Hz, 1H), 6.99 – 6.92 (m, 1H), 6.86 (t, *J* = 7.3 Hz, 1H), 6.78 (d, *J* = 8.1 Hz, 1H), 6.42 (d, *J* = 9.8 Hz, 1H), 5.82 – 5.72 (m, 1H), 4.83 (s, 2H).



1-Methyl-4-(2-propyn-1-yloxy)benzene. Following general procedure B was added propargyl bromide (17.9 g, 120 mmol, 80% solution in toluene, 1.3 eq.) to a stirred suspension of 4-methylphenol (10.0 g, 92.5 mmol, 1.0 eq.) and cesium carbonate (36.2 g, 111 mmol, 1.2 eq.) in N,N-dimethylformamide (185 mL, 0.5 M). The reaction mixture was stirred for 16 h at room temperature under N₂. The crude product was purified by gradient flash column chromatography to yield a light yellow oil (9.2 g, 63 mmol, 68% yield). The NMR spectra matched with previously reported data.⁶

¹H NMR: (400 MHz, CDCl₃)

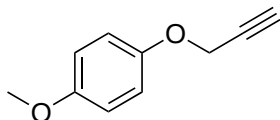
δ 7.12 (d, *J* = 8.2 Hz, 2H), 6.90 (d, *J* = 8.3 Hz, 2H), 4.70 – 4.66 (m, 2H), 2.54 – 2.50 (m, 1H), 2.31 (s, 3H).



6-Methyl-2H-chromene [9-SM]. Following general procedure C was added Ph₃PAuNTf₂ (36.97 mg, .05 mmol, 0.01 eq.) to a solution of 1-Methyl-4-(2-propyn-1-yloxy)benzene (730.95 mg, 5.0 mmol, 1 eq.) in dry dichloromethane (20 mL, 0.25 M) at room temperature. After 24 h, the residue was concentrated and was purified by flash column chromatography to yield a clear oil (519 mg, 3.55 mmol, 71% yield). The NMR spectra matched with previously reported data.⁶

¹H NMR: (400 MHz, CDCl₃)

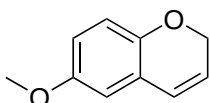
δ 6.95 (d, *J* = 8.2 Hz, 1H), 6.82 (s, 1H), 6.74 (d, *J* = 8.1 Hz, 1H), 6.43 (d, *J* = 9.8 Hz, 1H), 5.79 (dt, *J* = 9.8, 3.6 Hz, 1H), 4.85 – 4.80 (m, 2H), 2.30 (s, 3H).



1-methoxy-4-(prop-2-yn-1-yloxy)benzene. Following general procedure B was added propargyl bromide (3.11 g, 20.9 mmol, 80% solution in toluene, 1.3 eq.) to a stirred suspension of 4-methoxyphenol (2.00 g, 16.1 mmol, 1.0 eq) and cesium carbonate (6.29 g, 19.3 mmol, 1.2 eq.) in N,N-dimethylformamide (16.1 mL, 1 M). The reaction mixture was stirred for 16 h at room temperature under N₂. The crude product was purified by flash column chromatography (100% hexanes) to yield a pale yellow oil (2.22 g, 13.7 mmol, 85% yield). The NMR spectra matched with previously reported data.⁶

¹H NMR: (600 MHz, CDCl₃):

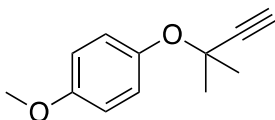
δ 6.93 (d, *J* = 9.1 Hz, 2H), 6.85 (d, *J* = 9.1 Hz, 2H), 4.64 (d, *J* = 2.5 Hz, 2H), 3.77 (s, 3H), 2.53 (t, *J* = 2.0 Hz, 1H).



6-methoxy-2H-chromene [10-SM]. Following general procedure C was added Ph₃PAuNTf₂ (1.49 mL, .046 mmol, 0.031 M solution in dichloromethane) was added to a stirred suspension of 1-methoxy-4-(2-propyn-1-yloxy)benzene (750 mg, 4.62 mmol, 1 eq.) in dichloromethane (7.8 mL, 0.5 M). The reaction mixture was stirred for 16 h at room temperature under N₂. After 16 h, the reaction was loaded onto silica and purified by flash column chromatography (100% hexanes) to yield a clear oil (495 mg, 3.05 mmol, 66% yield). The NMR spectra matched with previously reported data.⁶

¹H NMR: (600 MHz, CDCl₃):

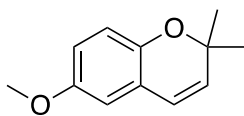
δ 6.72 (d, *J* = 7.9 Hz, 1H), 6.66 (d, *J* = 8.6 Hz, 1H), 6.55 (d, *J* = 2.7 Hz, 1H), 6.40 (d, *J* = 9.9 Hz, 1H), 5.84 – 5.79 (m, 1H), 4.77 – 4.74 (m, 2H), 3.75 (s, 3H).



1-Methoxy-4-(2-methylbut-3-yn-2-yloxy)benzene. To a 100 mL round bottom flask was added 3-chloro-3-methyl-but-1-yne (0.905 mL, 8.06 mmol, 2.0 eq.) to 4-methoxyphenol (500 mg, 4.03 mmol, 1.0 eq.) in dry N,N-dimethylformamide (20 mL, 0.20 M). Potassium iodide (5.01 g, 30.2 mmol, 7.5 eq) and potassium carbonate (3.07 g, 22.2 mmol, 5.5 eq.) were added sequentially under N₂ and the reaction mixture stirred at 60 °C overnight. Upon completion, the reaction mixture was gravity filtered and HCl (2M, 20 mL) was added to the filtrate and was extracted with diethyl ether (2 x 20 mL). The combined organic layer was washed with deionized water (7 x 20 mL), washed with brine (20 mL), and dried over anhydrous Na₂SO₄. The mixture was filtered, and the solvent was concentrated. The crude product was purified by flash column chromatography using gradient elution (200 mL of 100% hexanes, 400 mL of 2% ethyl acetate in hexanes) to yield a yellow oil (291 mg, 1.53 mmol, 38% yield). The NMR spectra matched with preciously reported data.⁶

¹H NMR: (300 MHz, CDCl₃)

δ 7.17 – 7.10 (m, 2H), 6.85 – 6.77 (m, 2H), 3.78 (s, 3H), 2.53 (s, 1H), 1.60 (s, 6H).

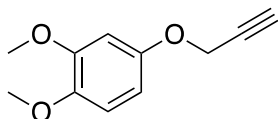


6-Methoxy-2,2-dimethyl-2H-chromene [11-SM]. Following general procedure C was added Ph₃PAuNTf₂ (11.2 mg, 0.0152 mmol, 0.01 eq.) to a solution of 1-Methoxy-4-(2-methylbut-3-yn-2-yloxy)benzene (290 mg, 1.52 mmol, 1.0 eq.) in dry dichloromethane (3.04 mL, 0.50 M) at room temperature. After 6 h, the residue

was concentrated and was purified by flash column chromatography (100 mL of 100% hexanes, 200 mL of 3% ethyl acetate in hexanes). The product mixed with recovered starting material was resubjected to the same reaction conditions and purified by flash column chromatography to yield a clear oil (114 mg, 0.60 mmol, 39% yield). The NMR spectra matched with preciously reported data.⁶

¹H NMR: (400 MHz, CDCl₃)

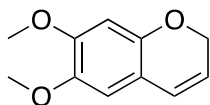
δ 6.75 – 6.64 (m, 2H), 6.55 (d, *J* = 2.6 Hz, 1H), 6.29 (d, *J* = 9.8 Hz, 1H), 5.64 (d, *J* = 9.8 Hz, 1H), 3.75 (s, 3H), 1.41 (s, 6H).



1,2-Dimethoxy-4-(2-propyn-1-yloxy)benzene. Following general procedure B was added propargyl bromide (0.625 g, 4.21 mmol, 80% solution in toluene, 1.3 eq.) to a stirred suspension of 3,4-dimethoxyphenol (500 mg, 3.24 mmol, 1.0 eq.) and cesium carbonate (1.27 g, 3.89 mmol, 1.2 eq.) in N,N-dimethylformamide (3.24 mL, 1 M). The reaction mixture was stirred for 4 h at room temperature under N₂. The crude product was purified by gradient flash column chromatography (100 mL of 100% hexanes, 100 mL of 2% ethyl acetate in hexanes, 100 mL of 4% ethyl acetate in hexanes, 100 mL of 6% ethyl acetate in hexanes, 500 mL of 8% ethyl acetate in hexanes) to yield a brown oil (552 mg, 2.87 mmol, 89% yield). The NMR spectra matched with previously reported data.⁷

¹H NMR: (300 MHz, CDCl₃)

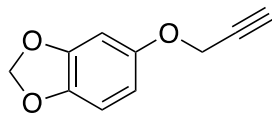
δ 6.78 (d, *J* = 8.7 Hz, 1H), 6.59 (d, *J* = 2.7 Hz, 1H), 6.48 (dd, *J* = 8.7, 2.9 Hz, 1H), 4.64 (d, *J* = 2.4 Hz, 2H), 3.84 (d, *J* = 4.7 Hz, 6H), 2.52 (t, *J* = 2.4 Hz, 1H).



6,7-Dimethoxy-2H-chromene [12-SM]. Following general procedure C was added Ph₃PAuNTf₂ (11.5 mg, 0.0156 mmol, 0.01 eq.) to a solution of 1,2-Dimethoxy-4-(2-propyn-1-yloxy)benzene (300 mg, 1.56 mmol, 1.0 eq.) in dry dichloromethane (3.12 mL, 0.50 M) at room temperature. After 24 h, the residue was concentrated and was purified by flash column chromatography (100 mL of 100% hexanes, 100 mL of 2% ethyl acetate in hexanes, 100 mL of 4% ethyl acetate in hexanes, 100 mL of 6% ethyl acetate in hexanes, 500 mL of 8% ethyl acetate in hexanes) to yield a brown oil (84 mg, 0.44 mmol, 28% yield). The NMR spectra matched with preciously reported data.⁷

¹H NMR: (400 MHz, CDCl₃)

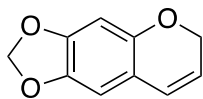
δ 6.52 (s, 1H), 6.41 (s, 1H), 6.34 (d, *J* = 9.8 Hz, 1H), 5.68 – 5.62 (m, 1H), 4.75 – 4.71 (m, 2H), 3.83 (d, *J* = 4.6 Hz, 6H).



5-(2-Propyn-1-yloxy)-1,3-benzodioxole. Following general procedure B was added propargyl bromide (0.700 g, 4.71 mmol, 80% solution in toluene, 1.3 eq.) to a stirred suspension of Sesamol (500 mg, 3.62 mmol, 1.0 eq) and cesium carbonate (1.41 g, 4.34 mmol, 1.2 eq.) in N,N-dimethylformamide (3.62 mL, 1 M). The reaction mixture was stirred for 14 h at room temperature under N₂. The crude product was purified by gradient flash column chromatography (100 mL of 100% hexanes, 500 mL of 2% ethyl acetate in hexanes) to yield a brown oil (554 mg, 3.14 mmol, 87% yield). The NMR spectra matched with previously reported data.⁸

¹H NMR: (400 MHz, CDCl₃)

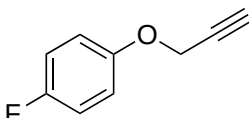
δ 6.72 (d, J = 8.5 Hz, 1H), 6.57 (d, J = 2.0 Hz, 1H), 6.42 (dd, J = 8.5, 2.0 Hz, 1H), 5.93 (s, 2H), 4.63 – 4.60 (m, 2H), 2.53 – 2.51 (m, 1H).



6,7-methylenedioxy-2H-1-benzopyrane [13-SM]. Following general procedure C was added $\text{Ph}_3\text{PAuNTf}_2$ (8.43 mg, 0.0114 mmol, 0.01 eq.) to a solution of 5-(2-Propyn-1-yloxy)-1,3-benzodioxole (200 mg, 1.14 mmol, 1.0 eq.) in dry dichloromethane (2.28 mL, 0.50 M) at room temperature. After 25 h, the residue was concentrated and was purified by flash column chromatography (100 mL of 100% hexanes, 500 mL of 2% ethyl acetate in hexanes) to yield yellow oil (108 mg, 0.61 mmol, 54% yield). The NMR spectra matched with preciously reported data.⁸

¹H NMR: (400 MHz, CDCl_3)

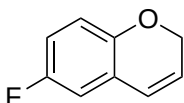
δ 6.47 (s, 1H), 6.39 (s, 1H), 6.32 (d, J = 9.7 Hz, 1H), 5.88 (s, 2H), 5.66 (dt, J = 9.7, 3.7 Hz, 1H), 4.72 – 4.68 (m, 2H).



1-Fluoro-4-(2-propyn-1-yloxy)benzene. Following general procedure B was added propargyl bromide (1.724 g, 11.6 mmol, 80% solution in toluene, 1.3 eq.) to a stirred suspension of 4-fluorophenol (1 g, 8.93 mmol, 1.0 eq) and cesium carbonate (3.489 g, 10.71 mmol, 1.2 eq.) in *N,N*-dimethylformamide (9 mL, 1 M). The reaction mixture was stirred for 14 h at room temperature under N_2 . The crude product was purified by gradient flash column chromatography (100 mL of 100% hexanes, 100 mL of 1% ethyl acetate in hexanes, 200 mL of 2% ethyl acetate in hexanes, 300 mL of 5% ethyl acetate in hexanes) to yield a pale oil (1.27 g, 8.45 mmol, 95% yield). The NMR spectra matched with previously reported data.⁶

¹H NMR: (300 MHz, CDCl_3)

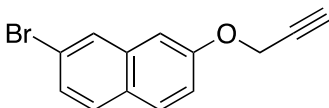
δ 7.05 – 6.89 (m, 4H), 4.66 (d, J = 2.2 Hz, 2H), 2.52 (t, J = 2.3 Hz, 1H).



6-fluoro-2H-chromene [14-SM]. Following general procedure C, $\text{Ph}_3\text{PAuNTf}_2$ (2.7 mL, .0839 mmol, 0.031 M solution in dichloromethane) was added to a stirred suspension of 1-Fluoro-4-(2-propyn-1-yloxy)benzene (1.26 g, 8.39 mmol, 1 eq.) in dichloromethane (16 mL, 0.5 M). The reaction mixture was stirred for 16 h at room temperature under N_2 . After 16 h, the reaction was loaded onto silica and purified by flash column chromatography (5% ethyl acetate in hexanes) to yield a clear oil (845 mg, 5.6 mmol, 67% yield). The NMR spectra matched with preciously reported data.⁶

¹H NMR: (400 MHz, CDCl_3):

δ 6.82 – 6.73 (m, 1H), 6.73 – 6.64 (m, 2H), 6.38 (d, J = 9.9 Hz, 1H), 5.87 – 5.79 (m, 1H), 4.78 (s, 2H).



2-bromo-7-(prop-2-yn-1-yloxy)naphthalene. Following general procedure B was added propargyl bromide (0.520 g, 3.50 mmol, 80% solution in toluene, 1.3 eq.) to a stirred suspension of 7-bromonaphthalen-2-ol (600 mg, 2.69 mmol, 1.0 eq.) and cesium carbonate (1.05 g, 3.23 mmol, 1.2 eq.) in *N,N*-dimethylformamide (2.69 mL, 1 M). The reaction mixture was stirred for 15 h at room temperature under N_2 . The crude product was purified by gradient flash column chromatography (100 mL of 100% hexanes, 200 mL of 5%

dichloromethane in hexanes, 400 mL of 10% dichloromethane in hexanes) to yield a white fluffy solid (622 mg, 2.38 mmol, 88% yield).

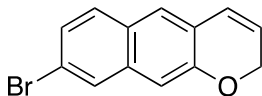
¹H NMR: (400 MHz, CDCl₃)

δ 7.93 – 7.91 (m, 1H), 7.72 (d, *J* = 8.9 Hz, 1H), 7.63 (d, *J* = 8.6 Hz, 1H), 7.43 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.19 (dd, *J* = 8.9, 2.6 Hz, 1H), 7.14 (d, *J* = 2.6 Hz, 1H), 4.80 (d, *J* = 2.4 Hz, 2H), 2.57 (t, *J* = 2.4 Hz, 1H).

¹³C NMR: (101 MHz, CDCl₃)

δ 156.27, 135.61, 129.66, 129.39, 129.03, 127.78, 127.45, 120.79, 119.28, 106.69, 78.32, 76.04, 55.97.

HRMS: (ESI⁺) *m/z*: [M+H]⁺ Calc. for C₁₃H₁₀BrO 260.9917; Found 260.9912.



8-bromo-2H-benzo[g]chromene [15-SM]. *N,N*-Dimethylamine was added to 2-bromo-7-(prop-2-yn-1-yloxy)naphthalene in a 25mL Schlenk flask and the reaction was refluxed for 27 h. Upon completion, the reaction flask was cooled to room temperature and was diluted with 2M HCl and diethyl ether (10 mL) and was extracted with diethyl ether (2 x 20 mL). The combined organic layers were washed with deionized water (10mL) and brine (10 mL), dried over Na₂SO₄ and concentrated. The crude product was purified by flash column chromatography (100 mL of 100% hexanes, 600 mL of 5% dichloromethane in hexanes) to yield an orange solid (428 mg, 1.64 mmol, 77% yield).

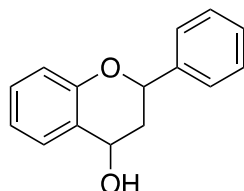
¹H NMR: (400 MHz, CDCl₃)

δ 8.09 – 8.04 (m, 1H), 7.60 (d, *J* = 8.8 Hz, 2H), 7.40 (dd, *J* = 8.7, 1.9 Hz, 1H), 7.06 (d, *J* = 9.0 Hz, 1H), 7.02 (d, *J* = 10.0 Hz, 1H), 5.92 (dt, *J* = 9.9, 3.9 Hz, 1H), 4.88 (dd, *J* = 3.9, 1.8 Hz, 2H).

¹³C NMR: (101 MHz, CDCl₃)

δ 153.10, 131.21, 130.19, 129.35, 127.82, 127.00, 123.97, 121.27, 120.81, 120.53, 118.19, 114.67, 65.42.

HRMS: (EI⁺) *m/z*: [M-H]⁺ Calc. for C₁₃H₈BrO 258.9753; Found 258.9752.

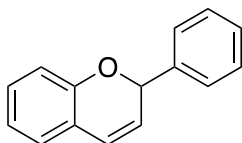


3,4-Dihydro-2-phenyl-2H-benzopyran-4-ol. To a 100 mL round bottom flask under N₂ was added degassed THF/MeOH (1:1, 12 mL, 0.37 M) to Flavanone (1.00 g, 4.46 mmol, 1.0 eq.). The flask was placed in an ice bath and sodium borohydride (253 mg, 6.69 mmol, 1.5 eq.) was added in portions. The reaction was allowed to warm up to room temperature and stirred for 10 h. Upon completion, the reaction flask was placed in an ice bath, and quenched with water (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine (20 mL), and then dried over anhydrous Na₂SO₄. The mixture was filtered, and the solvent was concentrated. The crude product was purified by flash column chromatography using gradient elution (100 mL of 100% hexanes, 100 mL of 5% ethyl acetate in hexanes, 300 mL of 10% ethyl acetate in hexanes, 400 mL of 15% ethyl acetate in hexanes, and 1000 mL of 20% ethyl acetate in hexanes) to yield a white solid (931 mg, 4.11 mmol, 92% yield). The NMR spectra matched with previously reported data.⁹

¹H NMR: (600 MHz, CDCl₃)

δ 7.53 (d, *J* = 7.7 Hz, 0.80H), 7.49 (d, *J* = 7.7 Hz, 0.23H), 7.47 – 7.44 (m, 1.59H), 7.41 (t, *J* = 7.5 Hz, 1.81H), 7.35 (t, *J* = 7.3 Hz, 1.02H), 7.28 (d, *J* = 7.4 Hz, 0.11H), 7.22 (t, *J* = 7.7 Hz, 0.81H), 7.02 – 6.96 (m, 1.01H), 6.91 (d, *J* = 8.2 Hz, 0.78H), 5.29 (d, *J* = 11.3 Hz, 0.13H), 5.19 (d, *J* = 11.6 Hz, 0.79H), 5.12 (q, *J* = 8.9 Hz,

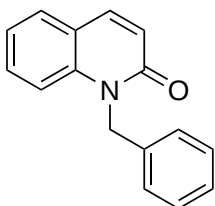
0.80H), 4.88 – 4.84 (m, 0.11H), 2.54 (dd, $J = 13.1, 6.2$ Hz, 0.83H), 2.31 – 2.27 (m, 0.12H), 2.20 – 2.12 (m, 0.93H), 1.99 – 1.96 (m, 0.10H), 1.75 (d, $J = 8.6$ Hz, 0.79H). Extra peaks are of the diastereomer.



2-Phenyl-2H-chromene [16-SM]. To a 100 mL round bottom flask was added dichloromethane (6.65 mL, 0.20 M) and triethylamine (0.556 mL, 3.99 mmol, 3.0 eq.) to 3,4-Dihydro-2-phenyl-2H-benzopyran-4-ol (300 mg, 1.33 mmol, 1.0 eq.). The reaction flask was placed in an ice bath and methanesulfonic anhydride (272 mg, 1.56 mmol, 1.17 eq.) was added. The reaction was allowed to warm up to room temperature and stirred under N_2 for 6 h. Upon completion, the solvent was removed by rotary evaporation and was purified by flash column chromatography using gradient elution (100 mL of 100% hexanes, 200 mL of 3% ethyl acetate in hexanes) to yield a colorless oil (75 mg, 0.36 mmol, 27% yield). The NMR spectra matched with previously reported data.¹⁰

¹H NMR: (400 MHz, $CDCl_3$)

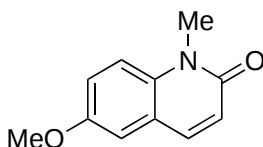
δ 7.53 – 7.48 (m, 2H), 7.46 – 7.34 (m, 3H), 7.16 (t, $J = 7.7$ Hz, 1H), 7.06 (d, $J = 7.5$ Hz, 1H), 6.92 (t, $J = 7.4$ Hz, 1H), 6.86 (d, $J = 8.0$ Hz, 1H), 6.58 (d, $J = 9.8$ Hz, 1H), 5.98 – 5.95 (m, 1H), 5.84 (dd, $J = 9.8, 3.3$ Hz, 1H).



1-benzylquinolin-2(1H)-one [17-SM]. To a 25 mL round bottom flask was added 2(1H)-Quinolinone (725 mg, 5.0 mmol, 1.0 eq) and N,N-dimethylformamide (5 mL, 1 M). After stirring until the solution was homogenous, NaH (240 mg, 6.0 mmol, 1.2 eq) was added in one portion. The solution was stirred until the complete dispersion of gas bubbles (about 20 minutes). Benzyl bromide (0.713 mL, 6.0 mmol, 1.2 eq.) was added dropwise. The reaction mixture was heated to 60° C and stirred under N_2 for 16 hours. Upon completion, the reaction was quenched with 5 mL deionized water, extracted with ethyl acetate (3x20 mL), washed three times with 10 mL portions of deionized water, and washed with one 10 mL portion of brine. After drying over sodium sulfate, the solution was filtered and purified by gradient flash column chromatography (300 mL of 25% ethyl acetate in hexanes, 250 mL 30% ethyl acetate in hexanes) to yield a light orange solid (593 mg, 2.5 mmol, 50% yield). The NMR spectra matched with previously reported data.¹¹

¹H NMR: (400 MHz, $CDCl_3$)

δ 7.63 – 7.51 (m, 1H), 7.44 – 7.33 (m, 1H), 7.30 – 6.95 (m, 8H), 6.75 – 6.66 (m, 1H), 5.52 – 5.35 (br s, 2H).

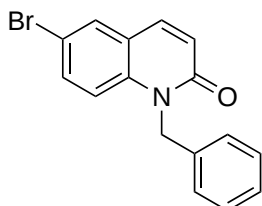


6-methoxy-1-methylquinolin-2(1H)-one [18-SM]. In a glovebox, to a 20 mL oven dried vial was added 2-hydroxyquinoline (500 mg, 3.1 mmol, 1 eq.) and N,N-dimethylformamide (5 mL, 0.6 M). While stirring, 60% NaH in a mineral oil dispersion (212 mg, 5.3 mmol, 1.7 eq.) was added in one portion and the reaction was stirred until the formation of gas bubbles ceased (about 20 minutes). Dimethyl sulfate (0.75 mL, 7.9 mmol, 2.5 eq.) was added dropwise while stirring and the reaction was capped, removed from the glovebox, and allowed to stir for 24 hours at 60°C. After 24 hours, the reaction was diluted with 100 mL of deionized

water and extracted 3x with 20 mL portions of ethyl acetate. The combined organic layers were washed 5x with 20 mL portions of brine, dried over Na₂SO₄, and concentrated in vacuo to yield the crude product. The crude product was purified using flash column chromatography (40% ethyl acetate in hexanes) to yield a white solid (133 mg, 0.7 mmol, 24% yield). The NMR spectra matched with previously reported data.¹²

¹H NMR: (600 MHz, CDCl₃)

δ 7.55 (d, *J* = 9.5 Hz, 1H), 7.24 (d, *J* = 9.1 Hz, 1H), 7.13 (dd, *J* = 9.2, 2.9 Hz, 1H), 6.96 – 6.93 (m, 1H), 6.66 (d, *J* = 9.4 Hz, 1H), 3.82 (s, 3H), 3.65 (s, 3H).



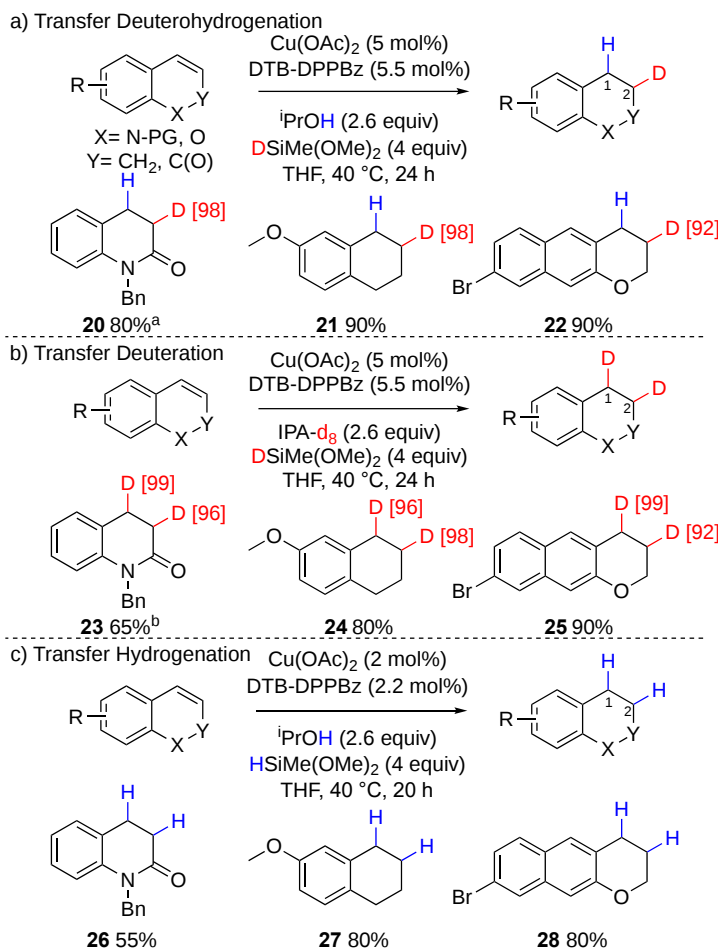
1-benzyl-6-bromoquinolin-2(1H)-one [19-SM]. To a 25 mL round bottom flask was added 6-Bromo-2(1H)-quinolinone (1 g, 4.46 mmol, 1.0 eq) and N,N-dimethylformamide (4.5 mL, 1 M). After stirring until the solution was homogenous, NaH (214 mg, 5.36 mmol, 1.2 eq) was added in one portion. The solution was stirred until the complete dispersion of gas bubbles (about 20 minutes). Benzyl bromide (0.713 mL, 6.0 mmol, 1.2 eq.) was added dropwise. The reaction mixture was heated to 60° C and stirred under N₂ for 16 hours. Upon completion, the reaction was quenched with 5 mL deionized water, extracted with ethyl acetate (3x20 mL), washed three times with 10 mL portions of deionized water, and washed with one 10 mL portion of brine. After drying over sodium sulfate, the solution was filtered and purified by gradient flash column chromatography (100 mL of hexanes, 100 mL of 5% ethyl acetate in hexanes, 100 mL of 10% ethyl acetate in hexanes, 300 mL of 20% ethyl acetate in hexanes to yield a yellow powder (483 mg, 1.54 mmol, 34% yield). The NMR spectra matched with previously reported data.¹¹

¹H NMR: (600 MHz, CDCl₃)

δ 7.69 (d, *J* = 2.3 Hz, 1H), 7.65 (d, *J* = 9.5 Hz, 1H), 7.48 (dd, *J* = 6.8, 2.2 Hz, 1H), 7.30 (t, *J* = 7.5 Hz, 2H), 7.27 – 7.20 (m, 1H), 7.18 (d, *J* = 7.2 Hz, 2H), 7.12 (d, *J* = 9.1 Hz, 1H), 6.83 (d, *J* = 9.5 Hz, 1H), 5.53 (s, 2H).

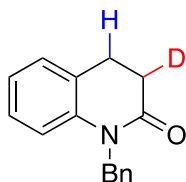
Switchable Selectivity Reaction Scope

Scheme 3. Transfer deuterohydrogenation, deuteration, and hydrogenation scope



^aUsed EtOH (2.6 equiv) instead of $i\text{PrOH}$, 2 mol% Cu(OAc)_2 , and 2 mol% DTB-DPPBz.

^bUsed EtOD (2.6 equiv) instead of IPA-d_8 , 2 mol% Cu(OAc)_2 , and 2 mol% DTB-DPPBz.



1-benzyl-3,4-dihydroquinolin-2(1H)-one-3-d [20] According to general procedure A, DTB-DPPBz (4 mg, 0.044 mmol, 0.022 eq.), Cu(OAc)_2 (20 μL of a 0.2 M solution in THF, 0.004 mmol, 0.02 eq.), and THF (50 μL) followed by dimethoxy(methyl)silane-*d* (100 μL , 0.8 mmol, 4 eq.) were added to an oven-dried 2-dram vial with an oven-dried stir bar. In a separate oven-dried 1-dram vial was added 1-benzylquinolin-2(1H)-one (47 mg, 0.2 mmol, 1 eq.), THF (100 μL), and EtOH (30 μL , 0.52 mmol, 2.6 eq.). The solution in the 1-dram vial was added dropwise to the 2-dram vial. The 2-dram vial was capped with a pressure relief cap, removed from the glovebox, and left to stir for 24 h at 40 °C. Upon completion, the product was isolated by flash column chromatography using gradient elution (100 mL of 100% hexanes, 200 mL of 1% dichloromethane in hexanes) to give the pure product as an off-white solid (37 mg, 0.16 mmol, 80% yield).

¹H NMR: (400 MHz, CDCl_3)

δ 7.31 (t, $J = 7.2$ Hz, 2H), 7.23 (t, $J = 7.0$ Hz, 3H), 7.17 (d, $J = 7.3$ Hz, 1H), 7.11 (t, $J = 7.8$ Hz, 1H), 6.97 (t, $J = 7.4$ Hz, 1H), 6.87 (d, $J = 8.1$ Hz, 1H), 5.19 (s, 2H), 2.97 (t, $J = 7.7$ Hz, 1.02H), 2.79 (d, $J = 7.5$ Hz, 2H).

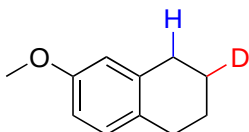
²H NMR: (61 MHz, CHCl_3)

δ 2.98 (s, 0.98D).

^{13}C NMR: (101 MHz, CDCl_3)

δ 170.55, 139.90, 137.00, 128.72, 127.82, 127.42, 127.04, 126.36, 126.30, 122.92, 115.59, 46.17, 31.80 25.24 (t, J = 19.9 Hz).

HRMS: (ESI^+) m/z : $[\text{M}+\text{H}]^+$ Calc. for $\text{C}_{16}\text{H}_{15}\text{DNO}$ 239.1296; Found 239.12854.



6-methoxy-1,2,3,4-tetrahydronaphthalene-3-*d* [21] According to general procedure A, DTB-DPPBz (9.8 mg, 0.011 mmol, 0.055 eq.), $\text{Cu}(\text{OAc})_2$ (50 μL of a 0.2 M solution in THF, 0.01 mmol, 0.05 eq.), and THF (50 μL) followed by dimethoxy(methyl)silane-*d* (100 μL , 0.8 mmol, 4 eq.) were added to an oven-dried 2-dram vial with an oven-dried stir bar. In a separate oven-dried 1-dram vial was added 6-methoxy-1,2-dihydronaphthalene (32 mg, 0.2 mmol, 1 eq.), THF (100 μL), and 2-propanol (40 μL , 0.52 mmol, 2.6 eq.). The solution in the 1-dram vial was added dropwise to the 2-dram vial. The 2-dram vial was capped with a pressure relief cap, removed from the glovebox, and left to stir for 24 h at 40 $^\circ\text{C}$. Upon completion, the product was isolated by flash column chromatography using gradient elution (100 mL of 100% hexanes, 200 mL of 1% dichloromethane in hexanes) to give the pure product as a clear oil (30 mg, 0.18 mmol, 90% yield).

^1H NMR: (400 MHz, CDCl_3)

δ 6.98 (d, J = 8.4 Hz, 1H), 6.67 (d, J = 8.4 Hz, 1H), 6.64-6.58 (m, 1H), 3.78 (s, 3H), 2.78-2.66 (m, 4H), 1.82-1.70 (m, 3.02H).

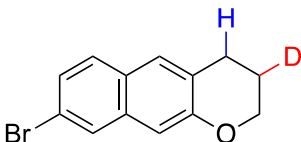
^2H NMR: (61 MHz, CHCl_3)

δ 1.96 (s, 0.98D)

^{13}C NMR: (101 MHz, CDCl_3)

δ 157.51, 138.30, 130.05, 129.41, 113.83, 111.90, 55.38, 29.76, 28.68, 23.48, 22.93 (t, J = 19.3 Hz)

HRMS: (ESI^+) m/z : $[\text{M}+\text{H}]^+$ Calc. for $\text{C}_{11}\text{H}_{14}\text{DO}$ 164.1187; Found 164.1176.



8-bromo-3,4-dihydro-2*H*-benzo[*g*]chromene-3-*d* [22] According to general procedure A, DTB-DPPBz (9.8 mg, 0.011 mmol, 0.055 eq.), $\text{Cu}(\text{OAc})_2$ (50 μL of a 0.2 M solution in THF, 0.01 mmol, 0.05 eq.), and THF (50 μL) followed by dimethoxy(methyl)silane-*d* (100 μL , 0.8 mmol, 4 eq.) were added to an oven-dried 2-dram vial with an oven-dried stir bar. In a separate oven-dried 1-dram vial was added 8-bromo-2*H*-benzo[*g*]chromene (52 mg, 0.2 mmol, 1 eq.), THF (100 μL), and 2-propanol (40 μL , 0.52 mmol, 2.6 eq.). The solution in the 1-dram vial was added dropwise to the 2-dram vial. The 2-dram vial was capped with a pressure relief cap, removed from the glovebox, and left to stir for 24 h at 40 $^\circ\text{C}$. Upon completion, the product was isolated by flash column chromatography using gradient elution (100 mL of 100% hexanes, 200 mL of 1% dichloromethane in hexanes) to give the pure product as a white solid (47 mg, 0.18 mmol, 90% yield).

^1H NMR: (400 MHz, CDCl_3)

δ 7.94 (s, 1H), 7.63-7.52 (m, 2H), 7.41 (dd, J = 8.6, 2.0 Hz, 1H), 7.04 (d, J = 8.9 Hz, 1H), 4.25 (d, J = 5.3 Hz, 2H), 2.98 (d, J = 6.6 Hz, 2H), 2.20-2.08 (m, 1.08H).

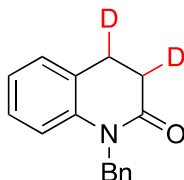
^2H NMR: (61 MHz, CHCl_3)

δ 2.14 (s, 0.92D).

^{13}C NMR: (101 MHz, CDCl_3):

δ 153.43, 134.74, 130.11, 127.60, 127.39, 126.54, 124.45, 120.97, 119.66, 113.29, 66.24, 21.79 (t, J = 19.8 Hz), 21.22

HRMS: (EI⁺) m/z : [M]⁺ Calc. for C₁₃H₁₀DBrO 263.0056; Found 263.0048.



1-benzyl-3,4-dihydroquinolin-2(1H)-one-3,4-*d*₂ [23] According to general procedure A, DTB-DPPBz (4 mg, 0.0044 mmol, 0.022 eq.), Cu(OAc)₂ (20 μ L of a 0.2 M solution in THF, 0.004 mmol, 0.02 eq.), and THF (50 μ L) followed by dimethoxy(methyl)silane-*d* (100 μ L, 0.8 mmol, 4 eq.) were added to an oven-dried 2-dram vial with an oven-dried stir bar. In a separate oven-dried 1-dram vial was added 1-benzylquinolin-2(1H)-one (47 mg, 0.2 mmol, 1 eq.), THF (100 μ L), and EtOD (30 μ L, 0.52 mmol, 2.6 eq.). The solution in the 1-dram vial was added dropwise to the 2-dram vial. The 2-dram vial was capped with a pressure relief cap, removed from the glovebox, and left to stir for 24 h at 40 °C. Upon completion, the product was isolated by flash column chromatography using gradient elution (100 mL of 100% hexanes, 200 mL of 1% dichloromethane in hexanes) to give the pure product as an off-white solid (31 mg, 0.13 mmol, 65% yield).

¹H NMR: (300 MHz, CDCl₃)

δ 7.36-7.04 (m, 7H), 6.96 (t, J = 7.4 Hz, 1H), 6.86 (d, J = 8.1 Hz, 1H), 5.18 (s, 2H), 3.00-2.90 (m, 1.04H), 2.82-2.71 (m, 1.01H).

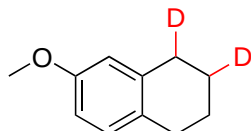
²H NMR: (61 MHz, CHCl₃)

δ 2.95 (s, 0.96D), 2.77 (s, 0.99D).

¹³C NMR: (101 MHz, CDCl₃)

δ 170.67, 140.00, 137.10, 128.83, 127.94, 127.53, 127.14, 126.46, 126.40, 123.03, 115.70, 46.27, 31.59 (t, J = 20.2 Hz), 25.25 (t, J = 20.4 Hz)

HRMS: (ESI⁺) m/z : [M+H]⁺ Calc. for C₁₆H₁₄D₂NO 240.1359; Found 240.1368.



6-methoxy-1,2,3,4-tetrahydronaphthalene-3,4-*d*₂ [24] According to general procedure A, DTB-DPPBz (9.8 mg, 0.011 mmol, 0.055 eq.), Cu(OAc)₂ (50 μ L of a 0.2 M solution in THF, 0.01 mmol, 0.05 eq.), and THF (50 μ L) followed by dimethoxy(methyl)silane-*d* (100 μ L, 0.8 mmol, 4 eq.) were added to an oven-dried 2-dram vial with an oven-dried stir bar. In a separate oven-dried 1-dram vial was added 6-methoxy-1,2-dihydronaphthalene (32 mg, 0.2 mmol, 1 eq.), THF (100 μ L), and 2-propanol-*d*₈ (40 μ L, 0.52 mmol, 2.6 eq.). The solution in the 1-dram vial was added dropwise to the 2-dram vial. The 2-dram vial was capped with a pressure relief cap, removed from the glovebox, and left to stir for 24 h at 40 °C. Upon completion, the product was isolated by flash column chromatography using gradient elution (100 mL of 100% hexanes, 200 mL of 1% dichloromethane in hexanes) to give the pure product as a clear oil (27 mg, 0.16 mmol, 80% yield).

¹H NMR: (400 MHz, CDCl₃)

δ 6.98 (d, J = 8.4 Hz, 1H), 6.67 (d, J = 8.4 Hz, 1H), 6.63-6.58 (m, 1H), 3.78 (s, 3H), 2.77-2.63 (m, 3.04H), 1.82-1.70 (m, 3.02H).

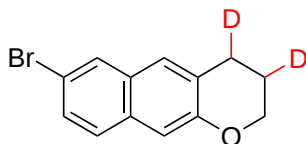
²H NMR: (61 MHz, CHCl₃)

δ 2.75 (s, 0.96D), 1.77 (s, 0.98D)

¹³C NMR: (101 MHz, CDCl₃)

δ 157.49, 138.23, 130.04, 129.41, 113.81, 111.89, 55.35, 29.37 (t, *J* = 19.4 Hz), 28.66, 23.45, 22.82 (t, *J* = 19.8, 19.3 Hz)

HRMS: (ESI⁺) *m/z*: [M+H]⁺ Calc. for C₁₁H₁₃D₂O 165.1250; Found 165.1246.



8-bromo-3,4-dihydro-2H-benzo[g]chromene-3,4-*d*₂ [25] According to general procedure A, DTB-DPPBz (9.8 mg, 0.011 mmol, 0.055 eq.), Cu(OAc)₂ (50 μL of a 0.2 M solution in THF, 0.01 mmol, 0.05 eq.), and THF (50 μL) followed by dimethoxy(methyl)silane-*d* (100 μL, 0.8 mmol, 4 eq.) were added to an oven-dried 2-dram vial with an oven-dried stir bar. In a separate oven-dried 1-dram vial was added 8-bromo-2H-benzo[g]chromene (52 mg, 0.2 mmol, 1 eq.), THF (100 μL), and 2-propanol-*d*₈ (40 μL, 0.52 mmol, 2.6 eq.). The solution in the 1-dram vial was added dropwise to the 2-dram vial. The 2-dram vial was capped with a pressure relief cap, removed from the glovebox, and left to stir for 24 h at 40 °C. Upon completion, the product was isolated by flash column chromatography using gradient elution (100 mL of 100% hexanes, 200 mL of 1% dichloromethane in hexanes) to give the pure product as a white solid (49 mg, 0.18 mmol, 90% yield).

¹H NMR: (400 MHz, CDCl₃)

δ 7.94 (s, 1H), 7.64-7.52 (m, 2H), 7.41 (d, *J* = 8.6 Hz, 1H), 7.04 (d, *J* = 8.9 Hz, 1H), 4.25 (d, *J* = 5.6 Hz, 2H), 3.00-2.93 (m, 1.01H), 2.19-2.09 (m, 1.08H).

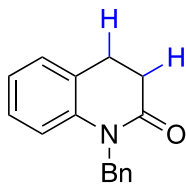
²H NMR: (61 MHz, CHCl₃)

δ 2.96 (s, 0.99D), 2.14 (s, 0.92D)

¹³C NMR: (101 MHz, CDCl₃)

δ 153.47, 134.77, 130.12, 127.62, 127.41, 126.55, 124.48, 120.98, 119.67, 113.25, 66.23, 29.85, 21.70 (t, *J* = 19.7 Hz), 20.89 (t, *J* = 19.7 Hz)

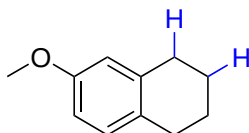
HRMS: (ESI⁺) *m/z*: [M+H]⁺ Calc. for C₁₃H₁₀D₂BrO 265.0199; Found 265.0193.



1-benzyl-3,4-dihydroquinolin-2(1H)-one [26] According to general procedure A, DTB-DPPBz (3.9 mg, 0.0044 mmol, 0.022 eq.), Cu(OAc)₂ (20 μL of a 0.2 M solution in THF, 0.004 mmol, 0.02 eq.), and THF (80 μL) followed by dimethoxy(methyl)silane (100 μL, 0.8 mmol, 4 eq.) were added to an oven-dried 2-dram vial with an oven-dried stir bar. In a separate oven-dried 1-dram vial was added 1-benzylquinolin-2(1H)-one (47 mg, 0.2 mmol, 1 eq.), THF (100 μL), and 2-propanol (40 μL, 0.52 mmol, 2.6 eq.). The solution in the 1-dram vial was added dropwise to the 2-dram vial. The 2-dram vial was capped with a pressure relief cap, removed from the glovebox, and left to stir for 24 h at 40 °C. Upon completion, the product was isolated by flash column chromatography using gradient elution (100 mL of 100% hexanes, 200 mL of 1% dichloromethane in hexanes) to give the pure product as an off-white solid (27 mg, 0.11 mmol, 55% yield). The NMR data matched previously reported spectra.¹³

¹H NMR: (400 MHz, CDCl₃)

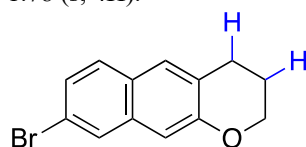
δ 7.36-7.14 (m, 6H), 7.11 (t, *J* = 7.8 Hz, 1H), 6.97 (t, *J* = 7.4 Hz, 1H), 6.88 (d, *J* = 8.2 Hz, 1H), 5.19 (s, 2H), 2.99 (t, *J* = 7.4 Hz, 2H), 2.80 (t, *J* = 7.4 Hz, 2H).



6-methoxy-1,2,3,4-tetrahydronaphthalene [27] According to general procedure A, DTB-DPPBz (3.9 mg, 0.0044 mmol, 0.022 eq.), Cu(OAc)₂ (20 μ L of a 0.2 M solution in THF, 0.004 mmol, 0.02 eq.), and THF (80 μ L) followed by dimethoxy(methyl)silane (100 μ L, 0.8 mmol, 4 eq.) were added to an oven-dried 2-dram vial with an oven-dried stir bar. In a separate oven-dried 1-dram vial was added 6-methoxy-1,2-dihydronaphthalene (32 mg, 0.2 mmol, 1 eq.), THF (100 μ L), and 2-propanol (40 μ L, 0.52 mmol, 2.6 eq.). The solution in the 1-dram vial was added dropwise to the 2-dram vial. The 2-dram vial was capped with a pressure relief cap, removed from the glovebox, and left to stir for 24 h at 40 °C. Upon completion, the product was isolated by flash column chromatography using gradient elution (100 mL of 100% hexanes, 200 mL of 1% dichloromethane in hexanes) to give the pure product as a clear oil (26 mg, 0.16 mmol, 80% yield). The NMR data matches previously reported spectra.¹⁴

¹H NMR: (400 MHz, CDCl₃)

δ 6.98 (d, J = 7.1 Hz, 1H), 6.68 (d, J = 8.3 Hz, 1H), 6.62 (s, 1H), 3.78 (m, 3H), 2.74 (d, J = 17.8 Hz, 4H), 1.78 (s, 4H).



8-bromo-3,4-dihydro-2H-benzo[g]chromene [28] According to general procedure A, DTB-DPPBz (3.9 mg, 0.0044 mmol, 0.022 eq.), Cu(OAc)₂ (20 μ L of a 0.2 M solution in THF, 0.004 mmol, 0.02 eq.), and THF (80 μ L) followed by dimethoxy(methyl)silane (100 μ L, 0.8 mmol, 4 eq.) were added to an oven-dried 2-dram vial with an oven-dried stir bar. In a separate oven-dried 1-dram vial was added 8-bromo-2H-benzo[g]chromene (52 mg, 0.2 mmol, 1 eq.), THF (100 μ L), and 2-propanol (40 μ L, 0.52 mmol, 2.6 eq.). The solution in the 1-dram vial was added dropwise to the 2-dram vial. The 2-dram vial was capped with a pressure relief cap, removed from the glovebox, and left to stir for 24 h at 40 °C. Upon completion, the product was isolated by flash column chromatography using gradient elution (100 mL of 100% hexanes, 200 mL of 1% dichloromethane in hexanes) to give the pure product as a white solid (41 mg, 0.16 mmol, 80% yield).

¹H NMR: (400 MHz, CDCl₃)

δ 7.94 (s, 1H), 7.64-7.51 (m, 2H), 7.41 (d, J = 8.6 Hz, 1H), 7.41 (d, J = 8.6 Hz, 1H), 4.30-4.20 (m, 2H), 2.97 (t, J = 6.6 Hz, 2H), 2.21-2.09 (m, 2H).

¹³C NMR: (101 MHz, CDCl₃)

δ 153.41, 134.71, 130.08, 127.58, 127.37, 126.51, 124.43, 120.95, 119.64, 113.26, 66.27, 22.12, 21.29.

HRMS: (EI⁺) m/z : [M]⁺ Calc. for C₁₃H₁₁BrO 261.9993; Found 261.9986.

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CHAPTER 5 SUPPLEMENTARY INFORMATION

Enantioselective Synthesis of Enantioisotopomers with Quantitative Chiral Analysis by Chiral Tag Rotational Spectroscopy

General Information

The following chemicals were purchased from commercial vendors and were used as received: (*R*)-(-)-Methyl Mandelate (Oakwood Chemicals); Lithium Aluminum Hydride (LiAlH₄) (Acros Organics); Lithium Aluminum Deuteride (LiAlD₄) (Boc Sciences); 1,2-Dimethoxyethane (Oakwood Chemicals); 2,2-dimethoxypropane (Oakwood Chemicals); 1,1,1-trimethoxyethane (Oakwood Chemicals); Trimethylsilyl Chloride (Alfa Aesar); (*S*)-1-Phenylethanol (Ambeed Inc.); 1-Formalpyrrolidine (Oakwood Chemicals); *p*-toluenesulfonyl chloride (Oakwood Chemicals); Cu(OAc)₂ (99.999% from Alfa Aesar); Dimethoxy(methyl)silane (TCI); Ethanol-OD (Millipore Sigma); Poly(methylhydrosiloxane) average M_n 1700-3200 (Millipore Sigma); (*S*)-Propylene Oxide (TCI America); (*S*)-1,1,1-Trifluoroisopropanol (Synquest).

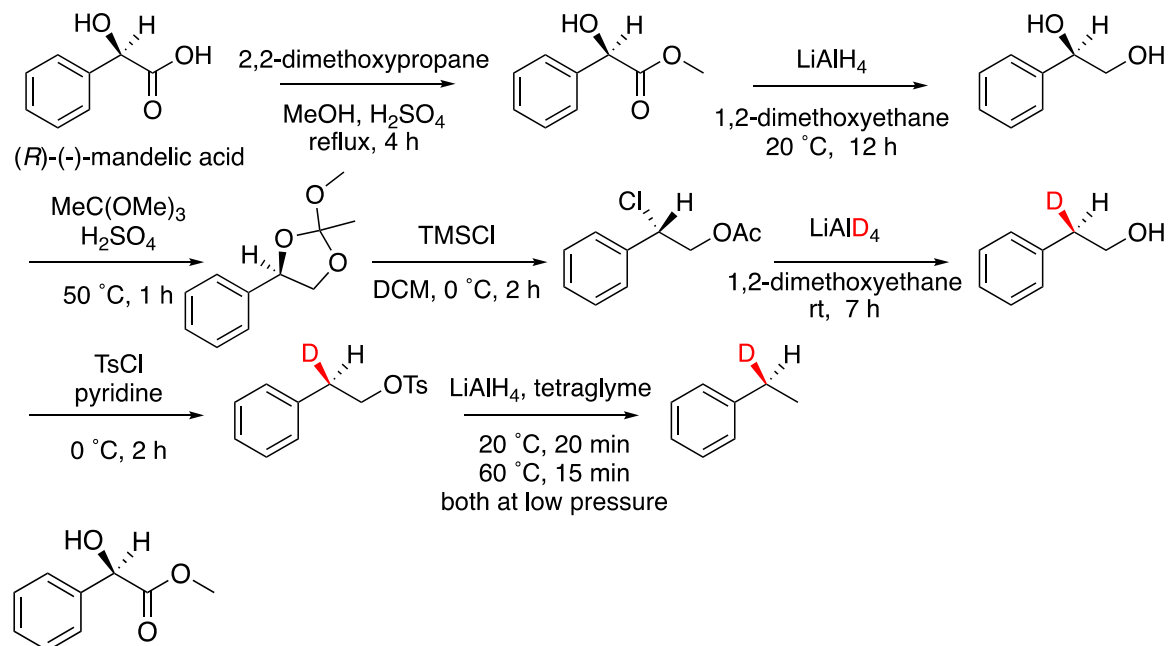
Anhydrous tetrahydrofuran (THF) and diethyl ether (Et₂O) were purified by an MBRAUN solvent purification system (MB-SPS). 1,2-Dimethoxyethane (DME) and Chloroform-*d* (CDCl₃) were stored over 3 Å molecular sieves. Thin-layer chromatography (TLC) was conducted with Silicycle silica gel 60 Å F254 pre-coated plates (0.25 mm) and visualized with UV and a KMnO₄ stain. Flash chromatography was performed using SiliaFlash® P60, 40-60 mm (230-400 mesh), purchased from Silicycle. For reactions that required heating (transfer hydrodeuteration), a PolyBlock for 2-dram vials was used on top of a Heidolph heating/stir plate. ¹H NMR spectra were recorded on a Varian 300, 400 MHz or 600 MHz spectrometer and are reported in ppm using deuterated solvent as an internal standard (CDCl₃ at 7.26 ppm). Data reported as: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, br = broad; coupling constant(s) in Hz; integration. ¹³C NMR spectra were recorded on a Varian 76 MHz or 101 MHz spectrometer and are

reported in ppm using deuterated solvent as an internal standard (CDCl_3 at 77.16 ppm). ^2H NMR spectra were recorded on a Varian 61 MHz spectrometer. See published manuscript for MRR data and supplementary information.⁷⁹

High-resolution mass spectra were obtained for all new compounds not previously reported using the resources of the Chemistry Instrument Center (CIC), University at Buffalo, SUNY, Buffalo, NY. Specifically, high resolution accurate mass analysis was conducted using the following instruments: 12T Bruker SolarixXR 12 Hybrid FTMS with Imaging MALDI and Nano-LC, provided through funding from the National Institutes of Health, NIH S10 RR029517; a Thermo Q-Exactive Focus Orbitrap Liquid Chromatograph Tandem Mass Spectrometer and a Thermo Q-Exactive Orbitrap Gas Chromatograph Tandem Mass Spectrometer, provided through funding from the National Science Foundation, MRI-1919594.

Mosher's Synthesis

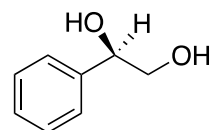
All procedures were performed in a manner mostly consistent with the prior report by Mosher.¹ The major changes to the prior reported procedures are the scales in which each reaction is performed. Detailed procedures are outlined below, and all spectral data is consistent with previously reported spectra.



(R)-(-)-Methyl Mandelate. To a 300 mL round bottom flask was added (R)-mandelic acid (30.0 g, 0.197 mol, 1.0 eq.), MeOH (10.4 mL, 0.256 mol, 1.3 eq.), and 2,2-dimethoxypropane (24.2 mL, 0.197 mol, 1.0 eq.), followed by concentrated H_2SO_4 (1.5 mL). The reaction mixture was refluxed for 4 h and then concentrated under reduced pressure. The resulting dark brown oil was recrystallized (hexanes 750 mL) to give (R)-(-)-methyl mandelate as a white solid (20 g, 0.120 mol, 61% yield). The NMR data was consistent with previously reported spectra.¹

^1H NMR: (400 MHz, CDCl_3)

δ 7.44 – 7.31 (m, 5H), 5.18 (s, 1H), 3.77 (s, 3H), 3.04 (br s, 1H).

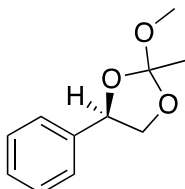


(R)-(-)-Phenylethylene Glycol. To a flame-dried 500 mL Schlenk tube under a N_2 atmosphere was added a solution of LiAlH_4 (1.90 g, 0.050 mol 1.1 eq.) in DME (15 mL) followed by a slow addition of (R)-(-)-methyl

mandelate (7.48 g, 0.045 mol, 1.0 eq.) in DME (100 mL). The mixture was stirred for 12 h at 23 °C then hydrolyzed with saturated aqueous NH_4Cl (10 mL) followed by HCl (20 mL, 2 M). The DME layer was set aside and the aqueous layer was extracted with Et_2O (3 x 20 mL). HCl (2 M) was added to the aqueous layer until the salts were completely dissolved and the aqueous layer was extracted with ether Et_2O (3 x 20 mL). The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. The resulting crude mixture was recrystallized in benzene/hexane (30 mL, 3:1) to give (*R*)-(-)-phenylethylene glycol as a white solid (5.5 g, 0.040 mol, 89% yield). The NMR data was consistent with previously reported spectra.¹

¹H NMR: (400 MHz, CDCl_3)

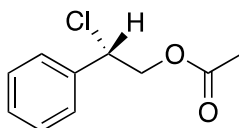
δ 7.38 – 7.34 (m, 4H), 7.34 – 7.28 (m, 1H), 4.85 – 4.79 (m, 1H), 3.79 – 3.72 (m, 1H), 3.70 – 3.62 (m, 1H), 2.76 – 2.71 (m, 1H), 2.34 – 2.26 (m, 1H).



(2*R*, 4*R*)-2-Methoxy-2-methyl-4-phenyl-1,3-dioxolane. A mixture of (*R*)-(-)-phenylethylene glycol (2.0 g, 0.014 mol, 1.0 eq.), 1,1,1-trimethoxyethane (4.58 mL, 0.036 mol, 2.6 eq.) and concentrated H_2SO_4 (30 μL) was stirred in a 50 mL round bottom flask at 23 °C for 10 min followed by heating at 50 °C for 1 h under reduced pressure. The residual red oil was dry loaded onto a silica gel column and purified by flash column chromatography (200 mL of 10% EtOAc in hexanes) to give diastereomers (2*R*, 4*R*)-2-methoxy-2-methyl-4-phenyl-1,3-dioxolane as a red oil (1.02 g, 0.0053 mol, 38% yield). The NMR data was consistent with previously reported spectra.¹

¹H NMR: (400 MHz, CDCl_3)

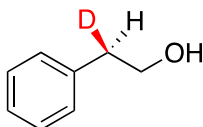
δ 7.46 – 7.27 (m, 5H), 5.25 (dd, J = 7.9, 7.2 Hz, 0.57H), 5.13 (dd, J = 9.6, 6.5 Hz, 0.35H), 4.46 (dd, J = 8.0, 6.9 Hz, 0.60H), 4.33 (dd, J = 8.0, 6.5 Hz, 0.38H), 3.86 (dd, J = 9.6, 8.0 Hz, 0.38H), 3.79 (dd, J = 8.5, 7.8 Hz, 0.60H), 3.42 (s, 1.07H), 3.38 (s, J = 0.6 Hz, 1.72H), 1.71 (s, 1.81H), 1.66 (s, 1.11H).



(*S*)-(-)-2-Chloro-2-Phenethyl Acetate. To a flame-dried 25 mL Schlenk tube under a N_2 atmosphere was added a solution of (2*R*, 4*R*)-2-methoxy-2-methyl-4-phenyl-1,3-dioxolane (800 mg, 4.12 mmol, 1.0 eq.) in CH_2Cl_2 (2 mL) at 0 °C followed by trimethylsilyl chloride (1.57 mL, 12.4 mmol, 3.0 eq.). After stirring for 2 h at 0 °C the mixture was concentrated under reduced pressure. The residual beige colored oil was dry loaded onto a silica gel column and purified by flash column chromatography (200 mL of 10% EtOAc in hexanes) to give (*S*)-(-)-2-chloro-2-phenethyl acetate as a light brown oil (650 mg, 3.27 mmol, 79% yield). The NMR data was consistent with previously reported spectra.¹

¹H NMR: (400 MHz, CDCl_3)

δ 7.44 – 7.34 (m, 5H), 5.07 (dd, J = 7.9, 7.2 Hz, 1H), 4.52 – 4.39 (m, 2H), 2.07 (s, 3H).

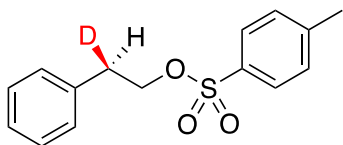


(*R*)-(+)-2-Phenylethanol-2-*d*₁. A suspension of LiAlD_4 (158 mg, 3.76 mmol, 1.15 eq.) in DME (7 mL) was stirred under N_2 at 23 °C for 30 min in a flame-dried 25 mL Schlenk tube followed by a slow addition of (*S*)-(-)-2-chloro-2-phenethyl acetate (650 mg, 3.27 mmol, 1.0 eq.) in DME (2.5 mL). After stirring for 7 h at 23 °C, the mixture was hydrolyzed with saturated aqueous NH_4Cl (5 mL) and then HCl (5 mL, 2 M). The DME layer was set aside and the aqueous layer was extracted with Et_2O (3 x 10 mL). HCl (2 M) was added to the

aqueous layer until the salts were completely dissolved and the aqueous layer was extracted with Et₂O (3 x 10 mL). The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The resulting yellow oil was dry loaded onto a silica gel column and purified by gradient flash column chromatography (100 mL of 10% EtOAc in hexanes, 200 mL of 20% EtOAc in hexanes) to give (*R*)-(+)-2-phenylethanol-2-*d*₁ as a light-yellow oil (384 mg, 3.12 mmol, 95% yield). The NMR data was consistent with previously reported spectra.¹

¹H NMR: (400 MHz, CDCl₃)

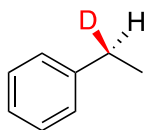
δ 7.39 – 7.29 (m, 2H), 7.29 – 7.20 (m, 3H), 3.91 – 3.79 (m, 2H), 2.92 – 2.81 (m, 1H), 1.51 (br s, 1H).



(*R*)-(+)-2-Phenylethyl-2-*d*₁-tosylate. To a flame-dried 25 mL Schlenk tube under a N₂ atmosphere was added (*R*)-(+)-2-phenylethanol-2-*d*₁ (384 mg, 3.12 mmol, 1.0 eq.) and pyridine (3.8 mL) and cooled on an ice bath followed by slow addition of *p*-toluenesulfonyl chloride (713 mg, 3.74 mmol, 1.2 eq.). After stirring at 23 °C for 1 h, the reaction vessel was placed in the refrigerator overnight. The reaction mixture was poured onto ice water and extracted with Et₂O (4 x 15 mL). The combined organic layers were washed with aqueous 10 % H₂SO₄ (15 mL) solution followed by saturated aqueous NaHCO₃ (15 mL) and then dried over Na₂SO₄. The combined organic layers were concentrated under reduced pressure, dry loaded onto a silica gel column and purified by gradient flash column chromatography (100 mL hexanes, 100 mL of 5 % Et₂O in hexanes, 100 mL of 10 % Et₂O in hexanes, 100 mL of 15% Et₂O in hexanes) to yield (*R*)-(+)-2-phenylethyl-2-*d*₁-tosylate as a light-yellow solid (444 mg, 1.60 mmol, 51% yield).

¹H NMR: (400 MHz, CDCl₃)

δ 7.69 (d, *J* = 8.1 Hz, 2H), 7.31 – 7.19 (m, 5H), 7.12 (d, 2H), 4.20 (d, *J* = 7.1 Hz, 2H), 2.99 – 2.89 (m, 1H), 2.43 (s, 3H).



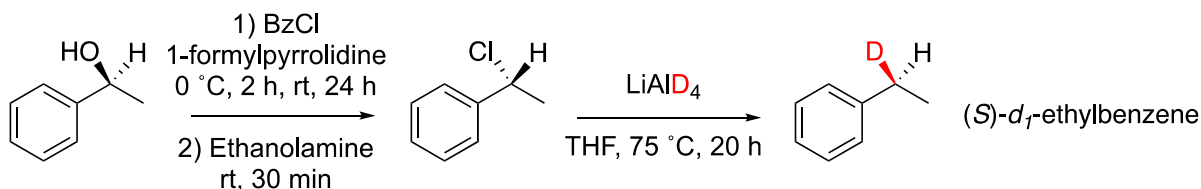
(*S*)-(+)-1-Phenylethane-1-*d*₁. To a flame-dried 10 mL round bottom flask under a N₂ atmosphere was added LiAlH₄ (97.2 mg, 2.56 mmol, 1.6 eq.) and tetraglyme (3 mL). The flask was evacuated with stirring to remove any volatile impurities. Upon refilling the flask with N₂, (*R*)-(+)-2-phenylethanol-2-*d*₁ (444 mg, 1.60 mmol, 1.0 eq.) was added and the flask was re-evacuated. The flask was fitted with a distillation head and heated at 60 °C under vacuum to give (*S*)-(+)-1-Phenylethane-1-*d*₁ in a cold trap (34 mg, 0.32 mmol, 20% yield). The NMR data was consistent with previously reported spectra.¹

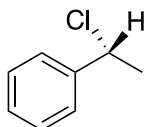
¹H NMR: (400 MHz, CDCl₃)

δ 7.30 (t, *J* = 7.5 Hz, 2H), 7.25 – 7.16 (m, 3H), 2.71 – 2.60 (m, 1.03H), 1.29 – 1.22 (m, 3H).

Christoffers's Synthesis

All procedures were performed in a manner mostly consistent with the prior report by Christoffers.² The major changes to the prior reported procedures are the scales in which each reaction is performed. Detailed procedures are outlined below, and all spectral data is consistent with previously reported spectra.

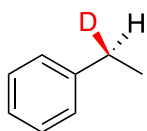




(R)-(1-Chloroethyl)benzene. To a flame-dried 100 mL Schlenk tube under a N₂ atmosphere was added (*S*)-1-phenylethanol (2.44 g, 20.0 mmol, 1.0 eq.) and 1-formylpyrrolidine (0.381 mL, 4.00 mmol, 0.20 eq.). The mixture was cooled to 0 °C and benzoyl chloride (3.49 mL, 30.0 mmol, 1.5 eq.) was added slowly over 5 min and the reaction was stirred at 0 °C for 2 h, then at 23 °C for 24 h. After 24 h, Ethanolamine (2.44 mL, 40.0 mmol, 2.0 eq.) was added, and the mixture was stirred at 23 °C for 30 min. The reaction was diluted with Et₂O (60 mL) and cooled on an ice bath. Saturated aqueous NaHCO₃ (20 mL) and water (10 mL) were added, and the mixture was stirred for 5 min at 0 °C. The layers were separated, and the organic layer was washed with saturated aqueous NaHCO₃ (20 mL) and dried over Na₂SO₄. The mixture was filtered, and the solvent was removed by rotary evaporation. The resulting crude oil was dry loaded onto a silica gel column and purified by flash column chromatography (300 mL of 0.5% Et₂O in *n*-pentane) to give (*R*)-(1-Chloroethyl)benzene as a clear colorless oil (1.55 g, 11.0 mmol, 55% yield). The NMR data was consistent with previously reported spectra.²

¹H NMR: (400 MHz, CDCl₃)

δ 7.46 – 7.41 (m, 2H), 7.37 (t, *J* = 6.4 Hz, 2H), 7.33 – 7.28 (m, 1H), 5.10 (q, *J* = 6.8 Hz, 1H), 1.86 (d, *J* = 6.8 Hz, 3H).



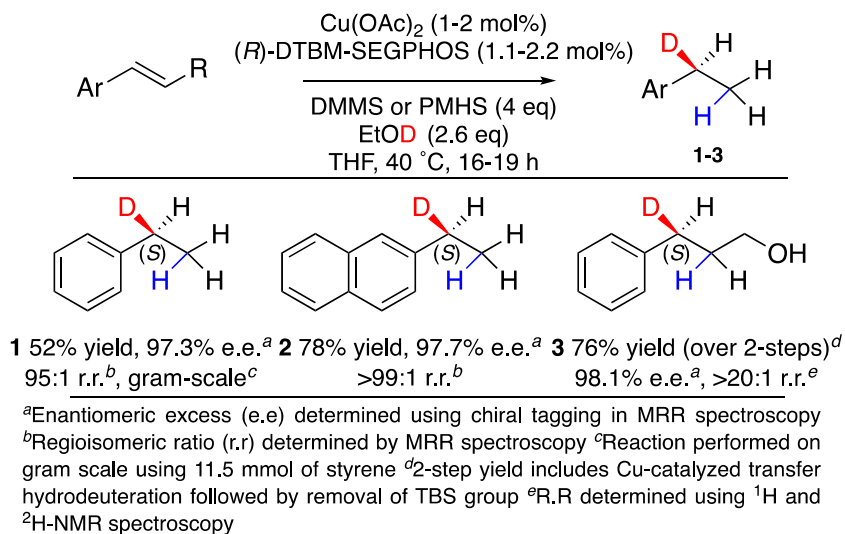
(S)-(+)-1-Phenylethane-1-*d*₁. To a flame-dried 250 mL round bottom flask under a N₂ atmosphere was added (*R*)-(1-chloroethyl)benzene (1.55 g, 11.0 mmol, 1.0 eq.) and THF (82 mL). The reaction was cooled on an ice bath and LiAlD₄ (924 mg, 22.0 mmol, 2.0 eq.) was added to the mixture and the reaction vessel was fitted with a condenser and stirred at 75 °C for 20 h. The heat was removed, and the reaction was cooled on an ice bath and diluted with ice-cold water (10 mL). The aqueous layer was extracted with *n*-pentane (3 x 10 mL) and the combined organic layers were washed in the following sequence using phosphoric acid (85%, 30 mL), water (30 mL), saturated aqueous NaHCO₃ (30 mL), water (30 mL), and brine (30 mL). The combined organic layers were dried over MgSO₄, filtered, and the solvent was removed by evaporation (50 °C, 1 atm) to yield (*S*)-(+)-1-phenylethane-1-*d*₁ as a clear colorless oil (750 mg, 7.00 mmol, 64% yield). The NMR data was consistent with previously reported spectra.²

¹H NMR: (400 MHz, CDCl₃)

δ 7.30 (t, *J* = 7.6 Hz, 2H), 7.25 – 7.16 (m, 3H), 2.72 – 2.58 (m, 1.01H), 1.27 – 1.22 (m, 3H).

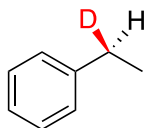
Cu-catalyzed Transfer Hydrodeuteration Method

Scheme S2. Enantioselective alkene transfer hydrodeuteration substrate scope



General Procedure (A)

In a N₂ filled glovebox, (*R*)-(-)-DTBM-SEGPPOS (12.9 mg, 0.011 mmol, 0.022eq.), Cu(OAc)₂ (50 μL of a 0.2 M solution in THF, 0.010 mmol, 0.02 eq.), and THF (0.200 mL) were added to an oven-dried 2-dram vial followed by dropwise addition of dimethoxy(methyl)silane (246 μL, 2.00 mmol, 4 eq.) or poly(methylhydrosiloxane) (2.00 mmol, 4 eq based on Si-H).³ A color change from green/blue to orange was observed while stirring for 15 minutes at room temperature. In a separate oven-dried 1-dram vial was added the alkene substrate (0.50 mmol, 1 eq.), THF (0.250 mL), and ethanol-OD (76 μL, 1.30 mmol, 2.6 eq.). The solution in the 1-dram vial was added dropwise over 20 seconds to the 2-dram vial. The total volume of THF was calculated based on having a final reaction concentration of 1M based on the alkene substrate. The 2-dram vial was capped with a red pressure relief cap, taken out of the glovebox, and stirred for 16-20 h at 40 °C in either an oil bath or a PolyBlock for 2-dram vials. Upon completion, diethyl ether (10 mL x 2) was added to the reaction vial and transferred to a 200 mL round bottom flask to dry load and was purified by flash column chromatography.



(S)-(+)-1-Phenylethane-1-d [1]. According to general procedure A, (*R*)-(-)-DTBM-SEGPPOS (150 mg, 0.127 mmol, 0.011 eq.), Cu(OAc)₂ (600 μL of a 0.2 M solution in THD, 0.12 mmol, 0.01 eq.), and THF (5.45 mL) were added to an oven-dried 20-dram vial followed by dropwise addition of poly(methylhydrosiloxane) (3.07 mL, 46.0 mmol, 4.0 eq. based on Si-H).³ In a separate oven-dried 100 mL round bottom flask was added vinylbenzene (1.32 mL, 11.5 mmol, 1.0 eq.), THF (5.45 mL), and ethanol-OD (1.75 mL, 29.9 mmol, 2.6 eq.). The reaction stirred for 16 h at 40 °C in an oil bath. Upon completion, the reaction was filtered through a 2'' silica plug with 50 mL of pentane by an additional 250 mL into a 500 mL round bottom flask. The crude product was dry loaded by rotary evaporation on an ice bath for 30-45 minutes and purified by flash column chromatography (300 mL of 100% pentane) to yield a clear colorless oil (642 mg, 6.00 mmol, 52% yield).

¹H NMR: (400 MHz, CDCl₃)

δ 7.30 (t, *J* = 7.5 Hz, 2H), 7.24 – 7.16 (m, 3H), 2.70 – 2.60 (m, 1.01 H), 1.26 – 1.23 (m, 3H).

²H NMR: (61 MHz, CHCl₃)

δ 2.65 (s, 0.99D).

^{13}C NMR: (101 MHz, CDCl_3)

δ 144.37, 128.45, 128.00, 125.72, 28.68 (t, $J = 19.2$ Hz), 15.71.

ATR-IR (cm^{-1}):

2963, 2926, 2170, 1603, 1495, 1449.

HRMS: (EI^+) m/z : $[\text{M}]^+$ Calcd for $\text{C}_8\text{H}_9\text{D}$, 107.0800; Found 107.0839.

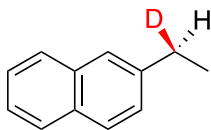
Optical Rotation: Performed neat (no solvent)

$[\alpha]_{365}^{20} = +1.213$

$[\alpha]_{436}^{20} = +0.687$

$[\alpha]_{546}^{20} = +0.371$

$[\alpha]_{589}^{20} = +0.309$



(S)-(+)-2-(ethyl-1-d)-naphthalene [2]. According to the general procedure A, (*R*)-(-)-DTBM-SEGPHOS (12.9 mg, 0.011 mmol, 0.022 eq.), $\text{Cu}(\text{OAc})_2$ (50 μL of a 0.2 M solution in THF, 0.010 mmol, 0.02 eq.), and THF (0.200 mL) then dimethoxy(methyl)silane (246 μL , 2.00 mmol, 4 eq.) were combined in a 2-dram vial followed by addition of a solution of 2-vinylnaphthalene (77.0 mg, 0.50 mmol, 1 eq.), THF (0.250 mL), and ethanol-OD (76 μL , 1.30 mmol, 2.6 eq). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 19 h at 40 $^\circ\text{C}$. Upon completion, the crude product mixture was dry loaded and isolated by flash column chromatography (120 mL of 100% hexanes) to give the pure product as a clear colorless oil (61 mg, 0.39 mmol, 78% yield). The procedure was repeated on a 10 mmol scale to obtain optical rotation.

^1H NMR: (600 MHz, CDCl_3)

δ 7.94 – 7.86 (m, 3H), 7.74 (s, 1H), 7.59 – 7.49 (m, 2H), 7.46 (d, $J = 8.4$ Hz, 1H), 2.95 – 2.86 (m, 1H), 1.44 (d, $J = 7.7$ Hz, 3H).

^2H NMR: (61 MHz, CHCl_3)

δ 2.91 (s, 0.99D).

^{13}C NMR: (101 MHz, CDCl_3)

δ 141.83, 133.85, 132.08, 127.94, 127.73, 127.55, 127.19, 125.95, 125.68, 125.13, 28.83 (t, $J = 19.3$ Hz), 15.60.

ATR-IR (cm^{-1}):

3049, 2962, 2930, 2167, 1507, 1453.

HRMS: (EI^+) m/z : $[\text{M}]^+$ Calcd for $\text{C}_{12}\text{H}_{11}\text{D}$, 157.1002; Found 157.0996.

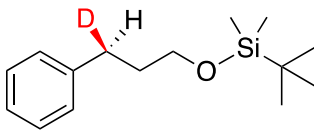
Optical Rotation: Performed neat (no solvent)

$[\alpha]_{365}^{20} = +1.669$

$[\alpha]_{436}^{20} = +0.734$

$[\alpha]_{546}^{20} = +0.347$

$[\alpha]_{589}^{20} = +0.280$



(+)-1-*tert*-butyldimethylsilyloxy-3-phenyl-(propane-3-*d*). According to the general procedure A, (*R*)-(-)-DTBM-SEGPHOS (51.9 mg, 0.044 mmol, 0.022 eq.), Cu(OAc)₂ (200 μ L of a 0.2 M solution in THF, 0.040 mmol, 0.02 eq.), and THF (0.800 mL) then dimethoxy(methyl)silane (992 μ L, 8.04 mmol, 4 eq.) were combined in an oven-dried 100 mL round bottom flask followed by addition of a solution of (*E*)-1-*tert*-Butyldimethylsilyloxy-3-phenyl-2-propene (500 mg, 2.01 mmol, 1 eq.), THF (1.00 mL), and ethanol-OD (305 μ L, 5.23 mmol, 2.6 eq.). The 2-dram vial was capped with a red pressure relief cap, and the reaction stirred for 19 h at 40 °C. Upon completion, the crude product mixture was dry loaded and isolated by flash column chromatography (700 mL of 100% hexanes) to give the pure product as a clear colorless oil (455 mg, 1.81 mmol, 90% yield). The procedure was repeated on a 23 mmol scale to obtain optical rotation.

¹H NMR: (600 MHz, CDCl₃)

δ 7.32 (t, *J* = 7.0 Hz, 2H), 7.25 – 7.19 (m, 3H), 3.71 – 3.65 (m, 2H), 2.73 – 2.67 (m, 1.01H), 1.91 – 1.83 (m, 2H), 0.96 (s, 9H), 0.10 (s, 6H).

²H NMR: (61 MHz, CHCl₃)

δ 2.70 (s, 0.99D).

¹³C NMR: (101 MHz, CDCl₃)

δ 142.37, 128.62, 128.41, 125.81, 62.48, 34.55, 31.90 (t, *J* = 19.4 Hz), 26.12, 18.48, -5.12.

ATR-IR (cm⁻¹):

3027, 2954, 2156, 1605, 1252, 1100.

HRMS: (EI⁺) *m/z*: [M-C₄H₉]⁺ Calcd for C₁₁H₁₆DOSi, 194.1111; Found 194.1106.

The major ion peak represents the parent molecule after loss of the *t*-Bu cation.

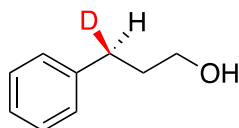
Optical Rotation: Performed neat (no solvent)

[α]₃₆₅²⁰ = no data

[α]₄₃₆²⁰ = +0.188

[α]₅₄₆²⁰ = +0.079

[α]₅₈₉²⁰ = +0.070



(*S*)-(+)-3-phenyl-(propan-3-*d*)-1-ol [3]. To a 100 mL round bottom was added tetrabutylammonium fluoride in 1M THF (3.66 mL, 3.66 mmol, 2 eq.) to (+)-1-*tert*-butyldimethylsilyloxy-3-phenyl-(propane-3-*d*) (455 mg, 1.81 mmol, 1 eq.) in THF (9.15 mL). The reaction stirred at room temperature for 2 h. Upon completion, the reaction was quenched with saturated aqueous ammonium chloride (10 mL) and extracted with ether (3 x 20 mL). The combined organic layers were washed with brine (20 mL) and dried over anhydrous Na₂SO₄. The crude product was purified by flash column chromatography using gradient elution (100 mL of 100% hexanes, 200 mL of 5% ethyl acetate in hexanes, 200 mL of 10% ethyl acetate in hexanes, 500 mL of 15% ethyl acetate in hexanes) to yield a colorless oil (211 mg, 1.54 mmol, 84% yield).

¹H NMR: (400 MHz, CDCl₃)

δ 7.30 (t, *J* = 7.6 Hz, 2H), 7.24 – 7.17 (m, 3H), 3.68 (t, *J* = 6.4 Hz, 2H), 2.74 – 2.65 (m, 1.01H), 1.90 (q, *J* = 7.1 Hz, 2H), 1.43 (br s, 1H).

²H NMR: (61 MHz, CHCl₃)

δ 2.70 (s, 0.99D).

¹³C NMR: (101 MHz, CDCl₃)

δ 141.91, 128.54, 128.52, 125.98, 62.35, 34.26, 31.93 (t, *J* = 19.4 Hz).

ATR-IR (cm⁻¹):

3316, 3025, 2934, 2872, 2142, 1604, 1450, 1029.

HRMS: (EI⁺) *m/z*: [M]⁺ Calcd for C₉H₁₁DO, 137.0951; Found 137.0946.

References

1. Mosher, H. S. & Elsenbaumer, R.L. Enantiomerically Pure (*R*)-(+)-2-Phenylethanol-2-*d* and -1,1,2-*d*₃, and (*S*)-(+)-1-Phenylethane-1-*d*, -1,2-*d*₂, -1,2,2-*d*₃, and -1,2,2,2-*d*₄. *J. Org. Chem.* **1979**, *44*, 600-604.
2. Küppers, J.; Rabus, R.; Wilkes, H.; Christoffers, J. Optically Active 1-Deuterio-1-phenylethane – Preparation and Proof of Enantiopurity. *Eur. J. Org. Chem.* **2019**, 2629-2634
3. Nishikawa, D.; Hirano, K.; Miura, M., Asymmetric Synthesis of α-Aminoboronic Acid Derivatives by Copper-Catalyzed Enantioselective Hydroamination. *J. Am. Chem. Soc.* **2015**, *137*, 15620-15623.

CHAPTER 6 SUPPLEMENTARY INFORMATION

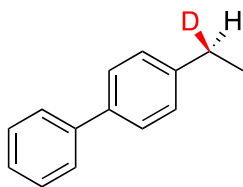
Rapid Enantiomeric Excess Measurements of Enantioisotopomers by Molecular Rotational Resonance Spectroscopy

General Information.

The following chemicals were purchased from commercial vendors and were used as received: Cu(OAc)₂ (99.999% from Alfa Aesar); Dimethoxy(methyl)silane (TCI); Ethanol-OD (Millipore Sigma); (*R*)-(-)-DTBM-SEGPPOS (TCI). Anhydrous tetrahydrofuran (THF) was purified by an MBRAUN solvent purification system (MB-SPS). Chloroform-*d* (CDCl₃) were stored over 3 Å molecular sieves. Thin-layer chromatography (TLC) was conducted with Silicycle silica gel 60 Å F254 pre-coated plates (0.25 mm) and visualized with UV and a KMnO₄ stain. Flash chromatography was performed using SiliaFlash® P60, 40-60 mm (230-400 mesh), purchased from Silicycle. For reactions that required heating (transfer hydrodeuteration), a PolyBlock for 2-dram vials was used on top of a Heidolph heating/stir plate. ¹H NMR spectra were recorded on a Varian 300, 400 MHz or 600 MHz spectrometer and are reported in ppm using deuterated solvent as an internal standard (CDCl₃ at 7.26 ppm). Data reported as: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, br = broad; coupling constant(s) in Hz; integration. ¹³C NMR spectra were recorded on a Varian 76 MHz or 101 MHz spectrometer and are reported in ppm using deuterated solvent as an internal standard (CDCl₃ at 77.16 ppm). ²H NMR spectra were recorded on a Varian 61 MHz spectrometer. Data for (*S*)-ethylbenzene-*d*1 and (*S*)-ethylnaphthalene-*d*1 in Figure 2 was previously published.⁷⁹ See published manuscript for MRR data and supplementary information.¹⁰⁰

General Procedure.

In a N₂ filled glovebox, (*R*)-(-)-DTBM-SEGPPOS (12.9 mg, 0.011 mmol, 0.022eq.), Cu(OAc)₂ (50 μL of a 0.2 M solution in THF, 0.010 mmol, 0.02 eq.), and THF (0.200 mL) were added to an oven-dried 2-dram vial followed by dropwise addition of dimethoxy(methyl)silane (246 μL, 2.00 mmol, 4.0 eq.). A color change from green/blue to orange was observed while stirring for 15 minutes at room temperature. In a separate oven-dried 1-dram vial was added the alkene substrate (0.50 mmol, 1.0 eq.), THF (0.250 mL), and ethanol-OD (76 μL, 1.30 mmol, 2.6 eq.). The solution in the 1-dram vial was added dropwise over 20 seconds to the 2-dram vial. The total volume of THF was calculated based on having a final reaction concentration of 1M based on the alkene substrate. The 2-dram vial was capped with a red pressure relief cap, taken out of the glovebox, and stirred for 16-20 h at the desired temperature in a PolyBlock for 2-dram vials. Upon completion, diethyl ether (10 mL x 3) was added to the reaction vial and transferred to a 200 mL round bottom flask to dry load and was purified by flash column chromatography. Deuterium incorporation for all reaction products was >97% at the desired benzylic position.



(S)-4-(ethyl-1-d)-1,1'-biphenyl. Reactions were performed according to the general procedure, with reaction one occurring at room temperature and reaction two occurring at 5 °C. Flash column chromatography using 100% hexanes to yield the pure product as a white crystalline solid. The room temperature reaction gave the final product in 95% yield with 93% ee and the 3 °C reaction gave the final product in 93% yield with 97% ee.

¹H NMR (400 MHz, CDCl₃):

δ 7.70 (d, *J* = 8.1 Hz, 2H), 7.63 (d, *J* = 8.2 Hz, 2H), 7.52 (t, *J* = 7.9 Hz, 2H), 7.46 – 7.40 (m, 1H), 7.38 (d, *J* = 8.1 Hz, 2H), 2.83 – 2.74 (m, 1.01H), 1.38 (d, *J* = 7.7 Hz, 3H).

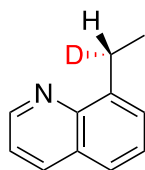
²H NMR (61 MHz, CHCl₃):

δ 2.79, (s, 0.99D).

¹³C NMR (101 MHz, CDCl₃):

δ 143.45, 141.30, 138.73, 128.83, 128.41, 127.20, 127.13, 127.08, 28.30 (t, *J* = 19.3 Hz), 15.66.

HRMS (EI⁺) *m/z*: [M]⁺ Calculated for C₁₄H₁₃D 183.1158; Found 183.1150.



(R)-8-(ethyl-1-d)-quinoline. Reactions were performed according to the general procedure. See Table 1 for specific changes to the reaction conditions for each entry. Flash column chromatography using gradient elution with 98% hexanes, 2% ethyl acetate was performed to yield the pure product as a yellow oil.

¹H NMR (400 MHz, CDCl₃):

δ 8.96 – 8.93 (m, 1H), 8.15 – 8.11 (m, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 7.2 Hz, 1H), 7.51 – 7.45 (m, 1H), 7.41 – 7.36 (m, 1H), 3.35 – 3.25 (m, 1.02H), 1.39 (d, *J* = 7.7 Hz, 3H).

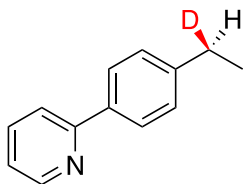
²H NMR (61 MHz, CHCl₃):

δ 3.33 (s, 0.98D).

¹³C NMR (75 MHz, CDCl₃):

δ 149.31, 146.83, 142.95, 136.43, 128.45, 128.00, 126.50, 125.89, 120.86, 24.37 (t, *J* = 19.5 Hz), 15.06.

HRMS (EI⁺) *m/z*: [M]⁺ Calculated for C₁₁H₁₀DN 158.0954; Found 158.0945.



(S)-(4-(ethyl-1-d)-phenyl)pyridine. Reactions were performed according to the general procedure, with reaction one occurring at room temperature and reaction two occurring at 5 °C. Flash column chromatography using gradient elution with 95% hexanes, 5% ethyl acetate was performed to yield the pure product as a clear colorless oil. The room temperature reaction gave the final product in 67% yield with 11% ee and the 3 °C reaction gave the final product in 89% yield with 35% ee.

¹H NMR (400 MHz, CDCl₃):

δ 8.69 (dd, *J* = 4.7, 1.8 Hz, 1H), 7.97 – 7.91 (m, 2H), 7.75 – 7.67 (m, 2H), 7.35 – 7.29 (m, 2H), 7.23 – 7.15 (m, 1H), 2.74 – 2.65 (m, 1.01H), 1.29 (d, *J* = 7.6 Hz, 3H).

²H NMR (61 MHz, CHCl₃):

δ 2.71 (s, 0.99D).

¹³C NMR (75 MHz, CDCl₃):

δ 157.55, 149.66, 145.32, 136.93, 136.73, 128.36, 126.93, 121.86, 120.35, 28.38 (t, *J* = 19.3 Hz), 15.54.

HRMS (EI⁺) *m/z*: [M]⁺ Calculated for C₁₃H₁₂DN 184.1111; Found 184.1104.

CHAPTER 7 SUPPLEMENTARY INFORMATION

Highly Regioselective Copper-Catalyzed Transfer Hydrodeuteration of Unactivated Terminal Alkenes

General Information

The following chemicals were purchased from commercial vendors and were used as received: Cu(OAc)₂ (99.999% from Alfa Aesar); 1,2-Bis[bis[3,5-di(*t*-butyl)phenyl]phosphino]benzene (Wako Pure Chemical Industries) (note this ligand was synthesized according to previously reported procedure¹ part way through the project due to back order from Wako Pure Chemical Industries), dimethoxy(methyl)silane (TCI); ethanol-OD (Millipore Sigma); 2-propanol-*d*₈ (Fischer Scientific), 2-propanol (Alfa Aesar); 5-bromo-1-pentene (Ambeed), 4-penten-1-ol (Ambeed); potassium carbonate (Ambeed); acetonitrile (Millipore Sigma); dimethylformamide (Oakwood Chemicals); methylene chloride (CH₂Cl₂) (Fischer Scientific); sodium Hydride 60% in oil dispersion (Oakwood Chemicals); triethylamine (Oakwood Chemicals).

Anhydrous Tetrahydrofuran (THF) was purified by an MBRAUN solvent purification system (MB-SPS). Chloroform-*d* (CDCl₃) was stored over 3Å molecular sieves. Triethylamine was dried by distillation at 89°C and stored under 3Å molecular sieves. Thin-layer chromatography (TLC) was conducted with Silicycle silica gel 60Å F254 pre-coated plates (0.25 mm) and visualized with UV and KMnO₄ stains. Flash chromatography was performed using Silia Flash® P60, 40-60 mm (230-400 mesh), purchased from Silicycle. For reactions that required heating (optimization, transfer hydrodeuteration, transfer hydrogenation and deuteration reactions), a PolyBlock for 2-dram vials was used on top of a Heidolph heating/stir plate. ¹H NMR spectra were recorded on a Varian 300 or 400 MHz spectrometer and are reported in ppm using solvent as an internal standard (CHCl₃ at 7.26 ppm). Data reported as: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, hep = heptet, m = multiplet, br = broad; coupling constant(s) in Hz; integration. ¹³C NMR spectra were recorded on a Varian 76 MHz or 101 MHz spectrometer and are reported in ppm using solvent as an internal standard (CDCl₃ at 77.16 ppm). ¹⁹F NMR spectra were recorded on a Varian 376 MHz spectrometer. ²H NMR spectra were recorded on a Varian 61 MHz spectrometer using CHCl₃. Labeled solvent impurities were calculated out when reporting isolated yields.

High-resolution mass spectra were obtained for all new compounds not previously reported using the resources of the Chemistry Instrument Center (CIC), University at Buffalo, SUNY, Buffalo, NY and Montana State University, Bozeman, MT. Specifically, high resolution accurate mass analysis was conducted using the following instruments: 12T Bruker SolarixR 12 Hybrid FTMS, provided through funding from the National Institutes of Health, NIH S10 RR029517; a Thermo Q-Exactive Focus Orbitrap Liquid Chromatograph Tandem Mass Spectrometer and a Thermo Q-Exactive Orbitrap Gas Chromatograph Tandem Mass Spectrometer, provided through funding from the National Science Foundation, MRI-1919594. Funding for the Proteomics, Metabolomics and Mass Spectrometry Facility used in this publication was made possible in part by the M.J. Murdock Charitable Trust, the National Institute of General Medical Sciences of the National Institutes of Health under Award Numbers P20GM103474 and S10OD28650, and the MSU Office of Research, Economic Development and Graduate Education. The content is solely the

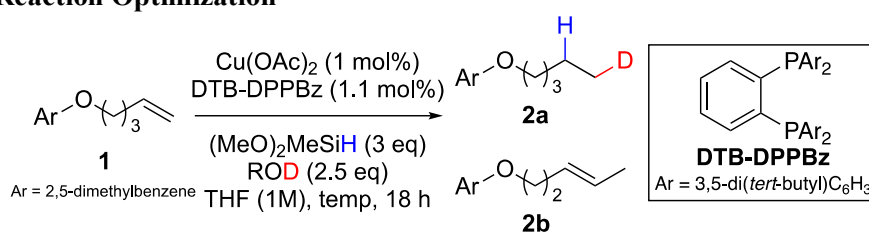
responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Method for calculating deuterium incorporation at the terminal position of each substrate:

In the ^1H NMR spectra, the terminal peak is typically visible with no overlap of other peaks. The deuterium incorporation was calculated based on a known integration of a protonated peak as the difference of the terminal integration is taken. If there was an overlap with an impurity or other peaks, a quantitative ^{13}C NMR spectrum was obtained, and a protonated peak (singlet) was integrated against the deuterated peak (triplet). A ^{13}C NMR spectrum of the hydrogenated product was also obtained to compare the position of the terminal peak. The integration of the ^2H NMR spectra was correlated to the calculated deuterium incorporation at the terminal position in the ^1H NMR spectra.

Optimization Studies

Table S1. Reaction Optimization



Entry	Temp. ($^{\circ}\text{C}$)	D-Source	1 ^a (%)	2a ^a (%)	2b ^a (%)
1	40	EtOD	23	60	3
2	60	EtOD	-	85	7
3	23	EtOD	55	22	5
4 ^b	40	EtOD	32	34	2
5 ^c	40	EtOD	42	39	-
6 ^d	40	EtOD	80	-	-
7	40	IPA- <i>d</i> 8	6	70	-
8 ^e	40	IPA- <i>d</i> 8	-	90	-
9 ^e	40	<i>t</i> BuOD	-	55	-
10 ^e	40	MeOD	85	3	-
11 ^{e,f}	40	IPA- <i>d</i> 8	7	80	-

All reaction performed on a 0.2 mmol scale. ^aYields were determined after purification by flash column chromatography ^bReaction performed at 2 M concentration ^cReaction performed with PhCH_3 instead of THF ^dReaction performed with CH_2Cl_2 instead of THF ^eReaction performed with 3 mol% $\text{Cu}(\text{OAc})_2$ and 3.3 mol% DTB-DPPBz ^fReaction performed with polymethylhydrosiloxane

In a N_2 filled glovebox, ligand, $\text{Cu}(\text{OAc})_2$ ($\text{Cu}:\text{L} = 1:1$), and THF (80 μL) were added to an oven-dried 2-dram vial with an oven-dried stir bar followed by dropwise addition of $\text{R}_3\text{Si-H}$ (3 eq.). A color change from a green/blue to yellow was observed while stirring for 10 mins. In a separate oven-dried 1-dram vial was added the alkene (0.2 mmol, 1 eq.), THF (100 μL), and D-source (2.5 eq.). The overall THF quantity was calculated as 1 M based on the alkene substrate. The solution in the 1-dram vial was added dropwise to the 2-dram vial. The 2-dram vial was capped with a pressure relief cap, removed from the glovebox, and left to stir for 18 h at 40 $^{\circ}\text{C}$. After this time, the reaction was filtered through a 1" silica plug with 100 mL of CH_2Cl_2 into a 200 mL round bottom flask. The solvent was removed by rotary evaporation, and the crude product was analyzed by ^1H NMR using 1,3,5-trimethylbenzene as an internal standard.

Entry 1. According to general procedure A for the optimization studies, in a N₂ filled glovebox, 1,2-Bis[bis[3,5-di(*t*-butyl)phenyl]phosphino]benzene (**DTB-DPPBz**) (2.0 mg, 0.0022 mmol, 0.011 eq.), Cu(OAc)₂ (10 µL of a 0.2 M solution in THF, 0.002 mmol, 0.01 eq.), and THF (90 µL) followed by dimethoxy(methyl)silane (74 µL, 0.60 mmol, 3 eq.) were added to an oven-dried 2-dram vial with an oven-dried stir bar. In a second oven-dried 1-dram vial, a solution of 1,4-dimethyl-2-(4-penten-1-yloxy)benzene (38 mg, 0.20 mmol, 1 eq.) and ethanol-OD (29 µL, 0.50 mmol, 2.5 eq.) in THF (100 µL) was made and added dropwise to the first vial. The reaction stirred for 18 h at 40 °C, after which it was purified by flash column chromatography (250 mL of hexanes) to yield the product mixture as a clear oil (**1**, 8.5 mg, 0.045 mmol, 23% yield; **2a**, 24 mg, 0.12 mmol, 60% yield; **2b**, 1.3 mg, 0.0068 mmol, 3% yield).

Entry 2. According to general procedure A for the optimization studies, in a N₂ filled glovebox, 1,2-Bis[bis[3,5-di(*t*-butyl)phenyl]phosphino]benzene (**DTB-DPPBz**) (2.0 mg, 0.0022 mmol, 0.011 eq.), Cu(OAc)₂ (10 µL of a 0.2 M solution in THF, 0.002 mmol, 0.01 eq.), and THF (90 µL) followed by dimethoxy(methyl)silane (74 µL, 0.60 mmol, 3 eq.) were added to an oven-dried 2-dram vial with an oven-dried stir bar. In a second oven-dried 1-dram vial, a solution of 1,4-dimethyl-2-(4-penten-1-yloxy)benzene (38 mg, 0.20 mmol, 1 eq.) and ethanol-OD (29 µL, 0.50 mmol, 2.5 eq.) in THF (100 µL) was made and added dropwise to the first vial. The reaction stirred for 18 h at 60 °C, after which it was purified by flash column chromatography (250 mL of hexanes) to yield the product mixture as a clear oil (**2a**, 32 mg, 0.17 mmol, 85% yield; **2b**, 2.5 mg, 0.013 mmol, 7% yield).

Entry 3. According to general procedure A for the optimization studies, in a N₂ filled glovebox, 1,2-Bis[bis[3,5-di(*t*-butyl)phenyl]phosphino]benzene (**DTB-DPPBz**) (2.0 mg, 0.0022 mmol, 0.011 eq.), Cu(OAc)₂ (10 µL of a 0.2 M solution in THF, 0.002 mmol, 0.01 eq.), and THF (90 µL) followed by dimethoxy(methyl)silane (74 µL, 0.60 mmol, 3 eq.) were added to an oven-dried 2-dram vial with an oven-dried stir bar. In a second oven-dried 1-dram vial, a solution of 1,4-dimethyl-2-(4-penten-1-yloxy)benzene (38 mg, 0.20 mmol, 1 eq.) and ethanol-OD (29 µL, 0.50 mmol, 2.5 eq.) in THF (100 µL) was made and added dropwise to the first vial. The reaction stirred for 18 h at 23 °C, after which it was purified by flash column chromatography (250 mL of hexanes) to yield the product mixture as a clear oil (**1**, 20 mg, 0.11 mmol, 55% yield; **2a**, 8.6 mg, 0.044 mmol, 22% yield; **2b**, 1.8 mg, 0.0095 mmol, 5% yield).

Entry 4. According to general procedure A for the optimization studies, in a N₂ filled glovebox, 1,2-Bis[bis[3,5-di(*t*-butyl)phenyl]phosphino]benzene (**DTB-DPPBz**) (2.0 mg, 0.0022 mmol, 0.011 eq.), Cu(OAc)₂ (10 µL of a 0.2 M solution in THF, 0.002 mmol, 0.01 eq.), and THF (90 µL) followed by dimethoxy(methyl)silane (74 µL, 0.60 mmol, 3 eq.) were added to an oven-dried 2-dram vial with an oven-dried stir bar. In a second oven-dried 1-dram vial, a solution of 1,4-dimethyl-2-(4-penten-1-yloxy)benzene (38 mg, 0.20 mmol, 1 eq.) and ethanol-OD (29 µL, 0.50 mmol, 2.5 eq.) was made and added dropwise to the first vial. The reaction stirred for 18 h at 40 °C, after which it was purified by flash column chromatography (250 mL of hexanes) to yield the product mixture as a clear oil (**1**, 12 mg, 0.063 mmol, 32% yield; **2a**, 13 mg, 0.067 mmol, 34% yield; **2b**, 1.0 mg, 0.0053 mmol, 3% yield).

Entry 5. According to general procedure A for the optimization studies, in a N₂ filled glovebox, a solution of 0.04 M Cu(OAc)₂ with 1,2-Bis[bis[3,5-di(*t*-butyl)phenyl]phosphino]benzene (**DTB-DPPBz**) in PhCH₃ (50 µL, 0.0022 mmol, 0.011 eq.) was added to an oven-dried 2-dram vial with an oven-dried stir bar. An additional 50 µL of PhCH₃ was added to the 2-dram vial followed by dimethoxy(methyl)silane (74 µL, 0.60 mmol, 3 eq.). In a second oven-dried 1-dram vial, a solution of 1,4-dimethyl-2-(4-penten-1-yloxy)benzene (38 mg, 0.20 mmol, 1 eq.) and ethanol-OD (29 µL, 0.50 mmol, 2.5 eq.) in PhCH₃ (100 µL) was made and added dropwise to the first vial. The reaction stirred for 18 h at 40 °C, after which it was purified by flash column chromatography (250 mL of hexanes) to yield the product mixture as a clear oil (**1**, 16 mg, 0.084 mmol, 42% yield; **2a**, 15 mg, 0.078 mmol, 39% yield).

Entry 6. According to general procedure A for the optimization studies, in a N₂ filled glovebox, a solution of 0.04 M Cu(OAc)₂ with 1,2-Bis[bis[3,5-di(*t*-butyl)phenyl]phosphino]benzene (**DTB-DPPBz**) in CH₂Cl₂ (50 µL, 0.0022 mmol, 0.011 eq.) was added to an oven-dried 2-dram vial with an oven-dried stir bar. An additional 50 µL of CH₂Cl₂ was added to the 2-dram vial followed by dimethoxy(methyl)silane (74 µL, 0.60 mmol, 3 eq.). In a second oven-dried 1-dram vial, a solution of 1,4-dimethyl-2-(4-penten-1-yloxy)benzene (38 mg, 0.20 mmol, 1 eq.) and ethanol-OD (29 µL, 0.50 mmol, 2.5 eq.) in CH₂Cl₂ (100 µL) was made and

added dropwise to the first vial. The reaction stirred for 18 h at 40 °C, after which it was purified by flash column chromatography (250 mL of hexanes) to yield the pure product as clear oil (**1**, 31 mg, 0.16 mmol, 80% yield).

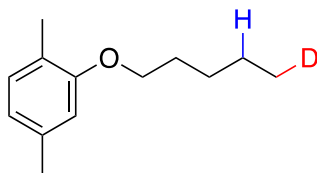
Entry 7. According to general procedure A for the optimization studies, in a N₂ filled glovebox, 1,2-Bis[bis[3,5-di(*t*-butyl)phenyl]phosphino]benzene (**DTB-DPPBz**) (2.0 mg, 0.0022 mmol, 0.011 eq.), Cu(OAc)₂ (10 µL of a 0.2 M solution in THF, 0.002 mmol, 0.01 eq.), and THF (90 µL) followed by dimethoxy(methyl)silane (74 µL, 0.60 mmol, 3 eq.) were added to an oven-dried 2-dram vial with an oven-dried stir bar. In a second oven-dried 1-dram vial, a solution of 1,4-dimethyl-2-(4-penten-1-yloxy)benzene (38 mg, 0.20 mmol, 1 eq.) and IPA-*d*₈ (38 µL, 0.50 mmol, 2.5 eq.) in THF (100 µL) was made and added dropwise to the first vial. The reaction stirred for 18 h at 40 °C, after which it was purified by flash column chromatography (250 mL of hexanes) to yield the product mixture as a clear oil (**1**, 2.3 mg, 0.012 mmol, 6% yield; **2a**, 27 mg, 0.14 mmol, 70% yield).

Entry 8. According to general procedure A for the optimization studies, in a N₂ filled glovebox, 1,2-Bis[bis[3,5-di(*t*-butyl)phenyl]phosphino]benzene (**DTB-DPPBz**) (5.9 mg, 0.0066 mmol, 0.033 eq.), Cu(OAc)₂ (30 µL of a 0.2 M solution in THF, 0.006 mmol, 0.03 eq.), and THF (70 µL) followed by dimethoxy(methyl)silane (74 µL, 0.60 mmol, 3 eq.) were added to an oven-dried 2-dram vial with an oven-dried stir bar. In a second oven-dried 1-dram vial, a solution of 1,4-dimethyl-2-(4-penten-1-yloxy)benzene (38 mg, 0.20 mmol, 1 eq.) and IPA-*d*₈ (38 µL, 0.50 mmol, 2.5 eq.) in THF (100 µL) was made and added dropwise to the first vial. The reaction stirred for 18 h at 40 °C, after which it was purified by flash column chromatography (250 mL of hexanes) to yield the pure product as clear oil (**2a**, 34 mg, 0.18 mmol, 90% yield).

Entry 9. According to general procedure A for the optimization studies, in a N₂ filled glovebox, 1,2-Bis[bis[3,5-di(*t*-butyl)phenyl]phosphino]benzene (**DTB-DPPBz**) (5.9 mg, 0.0066 mmol, 0.033 eq.), Cu(OAc)₂ (30 µL of a 0.2 M solution in THF, 0.006 mmol, 0.03 eq.), and THF (70 µL) followed by dimethoxy(methyl)silane (74 µL, 0.60 mmol, 3 eq.) were added to an oven-dried 2-dram vial with an oven-dried stir bar. In a second oven-dried 1-dram vial, a solution of 1,4-dimethyl-2-(4-penten-1-yloxy)benzene (38 mg, 0.20 mmol, 1 eq.) and *tert*-butanol-OD (48 µL, 0.50 mmol, 2.5 eq.) in THF (100 µL) was made and added dropwise to the first vial. The reaction stirred for 18 h at 40 °C, after which it was purified by flash column chromatography (250 mL of hexanes) to yield the pure product as clear oil (**2a**, 21 mg, 0.11 mmol, 55% yield).

Entry 10. According to general procedure A for the optimization studies, in a N₂ filled glovebox, 1,2-Bis[bis[3,5-di(*t*-butyl)phenyl]phosphino]benzene (**DTB-DPPBz**) (5.9 mg, 0.0066 mmol, 0.033 eq.), Cu(OAc)₂ (30 µL of a 0.2 M solution in THF, 0.006 mmol, 0.03 eq.), and THF (70 µL) followed by dimethoxy(methyl)silane (74 µL, 0.60 mmol, 3 eq.) were added to an oven-dried 2-dram vial with an oven-dried stir bar. In a second oven-dried 1-dram vial, a solution of 1,4-dimethyl-2-(4-penten-1-yloxy)benzene (38 mg, 0.20 mmol, 1 eq.) and MeOD (20 µL, 0.50 mmol, 2.5 eq.) in THF (100 µL) was made and added dropwise to the first vial. The reaction stirred for 18 h at 40 °C, after which it was purified by flash column chromatography (250 mL of hexanes) to yield the product mixture as a clear oil (**1**, 32 mg, 0.17 mmol, 85% yield; **2a**, 1.1 mg, 0.0057 mmol, 3% yield).

Entry 11. According to general procedure A for the optimization studies, in a N₂ filled glovebox, 1,2-Bis[bis[3,5-di(*t*-butyl)phenyl]phosphino]benzene (**DTB-DPPBz**) (5.9 mg, 0.0066 mmol, 0.033 eq.), Cu(OAc)₂ (30 µL of a 0.2 M solution in THF, 0.006 mmol, 0.03 eq.), and THF (70 µL) followed by polymethylhydrosiloxane (40 µL, 0.60 mmol, 3 eq. based on Si-H)² were added to an oven-dried 2-dram vial with an oven-dried stir bar. In a second oven-dried 1-dram vial, a solution of 1,4-dimethyl-2-(4-penten-1-yloxy)benzene (38 mg, 0.20 mmol, 1 eq.) and IPA-*d*₈ (38 µL, 0.50 mmol, 2.5 eq.) in THF (100 µL) was made and added dropwise to the first vial. The reaction stirred for 18 h at 40 °C, after which it was purified by flash column chromatography (250 mL of hexanes) to yield the product mixture as a clear oil (**1**, 2.6 mg, 0.014 mmol, 7% yield; **2a**, 30 mg, 0.16 mmol, 80% yield).



1,4-dimethyl-2-((pentyl-5-*d*)oxy)-benzene [2a] According to general procedure B, in a N₂ filled glovebox, DTB-DPPBz (46.6 mg, 0.052 mmol, 0.033 eq.), Cu(OAc)₂ (235 μ L of a 0.2 M solution in THF, 0.047 mmol, 0.03 eq.), and THF (500 μ L) followed by dimethoxy(methyl)silane (0.58 mL, 4.74 mmol, 3 eq.) were added to an oven-dried 2-dram vial with an oven-dried stir bar. In a separate oven-dried 1-dram vial was added 1,4-dimethyl-2-(4-penten-1-yloxy)benzene (300 mg, 1.58 mmol, 1 eq.), THF (845 μ L), and 2-propanol-*d*₈ (302 μ L, 3.95 mmol, 2.5 eq.). The solution in the 1-dram vial was added dropwise to the 2-dram vial. The 2-dram vial was capped with a pressure relief cap, removed from the glovebox, and left to stir for 23 h at 40 °C. Upon completion, the product was isolated by flash column chromatography using gradient elution (100 mL of 100% distilled hexanes, 300 mL of 1% ethyl acetate in distilled hexanes) to give the pure product as a clear and colorless oil (261 mg, 1.35 mmol, 85% yield).

¹H NMR: (300 MHz, CDCl₃)

δ 7.04 (d, J = 7.4 Hz, 1H), 6.69 (d, J = 7.7 Hz, 1H), 6.67 (s, 1H), 3.97 (t, J = 6.4 Hz, 2H), 2.34 (s, 3H), 2.22 (s, 3H), 1.83 (p, J = 6.7 Hz, 2H), 1.54 – 1.33 (m, 4H), 1.01 – 0.91 (m, 2.01H).

²H NMR: (61 MHz, CHCl₃)

δ 0.95 (s, 0.99D).

¹³C NMR: (75 MHz, CDCl₃)

δ 157.26, 136.56, 130.38, 123.76, 120.65, 112.08, 67.96, 29.26, 28.46, 22.53, 21.56, 15.95, 13.92 (t, J = 19.1 Hz).

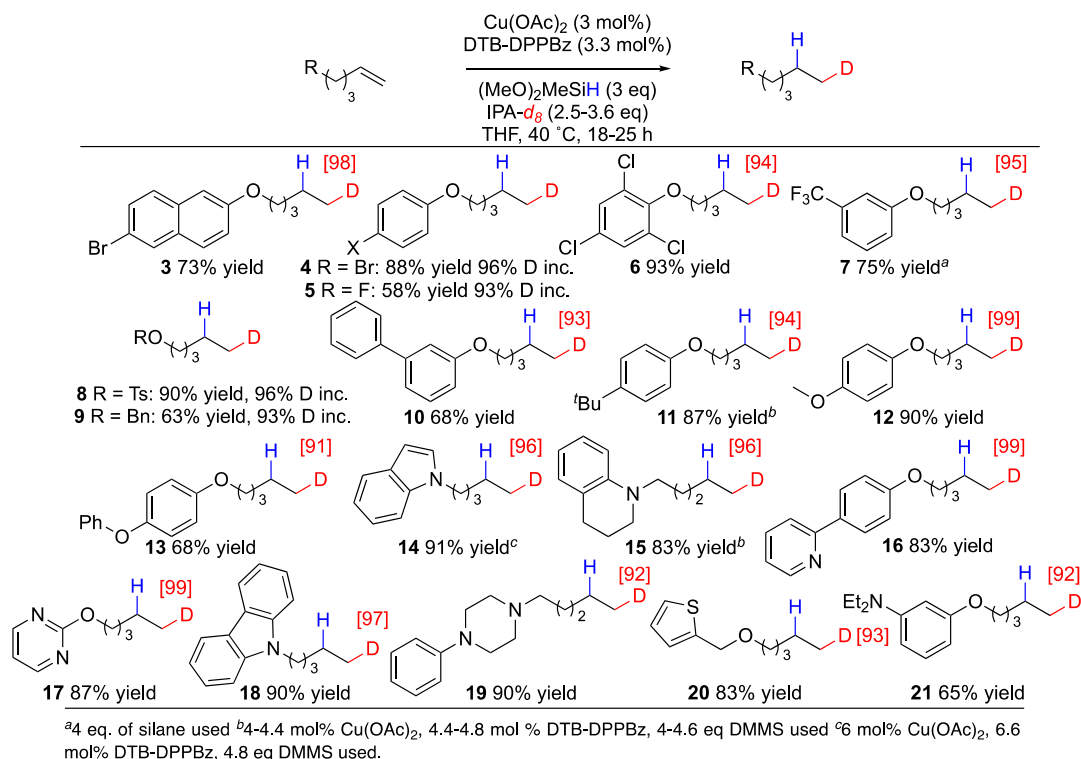
ATR-IR (cm⁻¹):

2928, 2860, 2173, 1508, 1434, 1263, 1129.

HRMS: (ESI⁺) m/z : [M+H]⁺ Calcd for C₁₃H₁₉DO 194.1655; Found 194.1651.

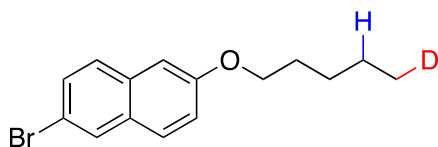
Transfer Hydrodeuteration Reaction Scope

Scheme S4. Unactivated Terminal Alkenes Substrate Scope



General Procedure for Transfer Hydrodeuteration (B)

In a N₂ filled glovebox, DTB-DPPBz (0.033 eq.), Cu(OAc)₂ (0.03 eq) and THF followed by dimethoxy(methyl)silane (3 eq.) were added to an oven-dried 2-dram vial with an oven-dried stir bar (*note a color change from a green/blue to yellow was observed while stirring for 10 mins). In a separate oven-dried 1-dram vial was added the alkene (1 eq.), THF, and 2-propanol-*d*₈ (2.5-3.6 eq.). The solution in the 1-dram vial was added dropwise to the 2-dram vial. The total volume of THF was calculated as 1 M based on the alkene substrate. The 2-dram vial was capped with a pressure relief cap, removed from the glovebox, and left to stir for 18-25 h at 40 °C. Upon reaction completion, all contents of the reaction were dry loaded onto a silica gel column and purified by column chromatography.



2-Bromo-6-((pentyl-5-*d*)oxy)naphthalene [3] According to general procedure B, in a N₂ filled glovebox, DTB-DPPBz (11.6 mg, 0.013 mmol, 0.033 eq.), Cu(OAc)₂ (60 μL of a 0.2 M solution in THF, 0.012 mmol, 0.03 eq.), and THF (140 μL) followed by dimethoxy(methyl)silane (148 μL, 1.20 mmol, 3 eq.) were added to an oven-dried 2-dram vial with an oven-dried stir bar. In a separate oven-dried 1-dram vial was added 2-bromo-6-(4-penten-1-yloxy)naphthalene (116 mg, 0.40 mmol, 1 eq.), THF (200 μL), and 2-propanol-*d*₈ (77 μL, 1.0 mmol, 2.5 eq.). The solution in the 1-dram vial was added dropwise to the 2-dram vial. The 2-dram vial was capped with a pressure relief cap, removed from the glovebox, and left to stir for 24 h at 40 °C. Upon completion, the product was isolated by flash column chromatography using gradient elution (100 mL of 100% hexanes, 100 mL of 1% ethyl acetate in hexanes, 100 mL of 2% ethyl acetate in hexanes) to give the pure product as a beige solid (84 mg, 0.29 mmol, 73% yield).

¹H NMR: (400 MHz, CDCl₃)

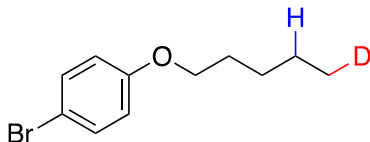
δ 7.90 (s, 1H), 7.64 (d, *J* = 9.0 Hz, 1H), 7.58 (d, *J* = 8.8 Hz, 1H), 7.52 – 7.45 (m, 1H), 7.20 – 7.12 (m, 1H), 7.08 (s, 1H), 4.05 (t, *J* = 6.6 Hz, 2H), 1.85 (p, *J* = 6.7 Hz, 2H), 1.53 – 1.36 (m, 4H), 1.00 – 0.89 (m, 2.02H).

²H NMR: (61 MHz, CHCl₃)
 δ 0.94 (s, 0.98D).

¹³C NMR: (101 MHz, CDCl₃)
 δ 157.51, 133.21, 130.01, 129.73, 129.62, 128.52, 128.45, 120.19, 116.97, 106.54, 68.17, 29.03, 28.35, 22.53, 13.89 (t, J = 19.2 Hz).

ATR-IR (cm⁻¹):
 2929, 2858, 2182, 1585, 1261, 1014.

HRMS: (ESI⁺) m/z : [M+H]⁺ Calcd for C₁₅H₁₇DOBr 294.0604; Found 294.0595.



1-Bromo-4-((pentyl-5-d)oxy)benzene [4] According to general procedure B, in a N₂ filled glovebox, DTB-DPPBz (11.6 mg, 0.013 mmol, 0.033 eq.), Cu(OAc)₂ (60 μ L of a 0.2 M solution in THF, 0.012 mmol, 0.03 eq.), and THF (140 μ L) followed by dimethoxy(methyl)silane (148 μ L, 1.20 mmol, 3 eq.) were added to an oven-dried 2-dram vial with an oven-dried stir bar. In a separate oven-dried 1-dram vial was added 1-bromo-4-(pent-4-en-1-yloxy)benzene (96 mg, 0.40 mmol, 1 eq.), THF (200 μ L), and 2-propanol-*d*₈ (77 μ L, 1.0 mmol, 2.5 eq.). The solution in the 1-dram vial was added dropwise to the 2-dram vial. The 2-dram vial was capped with a pressure relief cap, removed from the glovebox, and left to stir for 24 h at 40 °C. Upon completion, the product was isolated by flash column chromatography using gradient elution (100 mL of 100% hexanes, 100 mL of 1% ethyl acetate in hexanes, 100 mL of 2% ethyl acetate in hexanes) to give the pure product as a light-yellow oil (86 mg, 0.35 mmol, 88% yield).

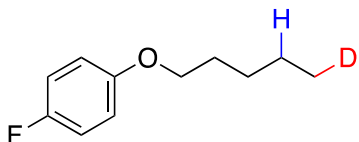
¹H NMR: (400 MHz, CDCl₃)
 δ 7.40 – 7.31 (m, 2H), 6.81 – 6.72 (m, 2H), 3.91 (t, J = 6.6 Hz, 2H), 1.77 (p, J = 6.6 Hz, 2H), 1.51 – 1.31 (m, 4H), 0.98 – 0.87 (m, 2.04H).

²H NMR: (61 MHz, CHCl₃)
 δ 0.91 (s, 0.96D).

¹³C NMR: (101 MHz, CDCl₃)
 δ 158.35, 132.30, 116.39, 112.65, 68.34, 29.00, 28.25, 22.50, 13.87 (t, J = 19.0 Hz).

ATR-IR (cm⁻¹):
 2930, 2860, 2170, 1488, 1240, 1001.

HRMS: (EI⁺) m/z : [M]⁺ Calcd for C₁₁H₁₄DOBr 243.0369; Found 243.0364.



1-Fluoro-4-(5-d-pentan-1-yloxy)benzene [5] According to general procedure B, in a N₂ filled glovebox, DTB-DPPBz (11.6 mg, 0.013 mmol, 0.033 eq.), Cu(OAc)₂ (60 μ L of a 0.2 M solution in THF, 0.012 mmol, 0.03 eq.), and THF (140 μ L) followed by dimethoxy(methyl)silane (148 μ L, 1.20 mmol, 3 eq.) were added to an oven-dried 2-dram vial with an oven-dried stir bar. In a separate oven-dried 1-dram vial was added 1-fluoro-4-(pent-4-en-1-yloxy)benzene (72 mg, 0.40 mmol, 1 eq.), THF (200 μ L), and 2-propanol-*d*₈ (77 μ L, 1.0 mmol, 2.5 eq.). The solution in the 1-dram vial was added dropwise to the 2-dram vial. The 2-dram vial was capped with a pressure relief cap, removed from the glovebox, and left to stir for 18 h at 40 °C. Upon completion, the product was isolated by flash column chromatography using gradient elution (150 mL of

100% hexanes, 100 mL of 1% ethyl acetate in hexanes, 100 mL of 5% ethyl acetate in hexanes) to give the pure product as a clear and colorless oil (43 mg, 0.23 mmol, 58% yield).

¹H NMR: (400 MHz, CDCl₃)

δ 7.02 – 6.91 (m, 2H), 6.88 – 6.78 (m, 2H), 3.91 (t, *J* = 6.6 Hz, 2H), 1.77 (p, *J* = 6.6 Hz, 2H), 1.49 – 1.34 (m, 4H), 0.98 – 0.87 (m, 2.07H).

²H NMR: (61 MHz, CHCl₃)

δ 0.92 (s, 0.93D).

¹³C NMR: (101 MHz, CDCl₃)

δ 157.22 (d, *J* = 237.7 Hz), 155.38 (d, *J* = 2.1 Hz), 115.74 (d, *J* = 41.1 Hz), 115.46 (d, *J* = 26.1 Hz), 68.75, 29.13, 28.30, 22.52, 13.87 (t, *J* = 19.4 Hz).

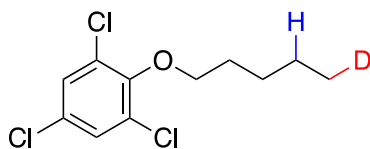
¹⁹F NMR: (61 MHz, CDCl₃)

δ -124.49 – -124.58 (m, 1F).

ATR-IR (cm⁻¹):

2931, 2864, 2166, 1504, 1247, 1207.

HRMS: (EI⁺) *m/z*: [M]⁺ Calcd for C₁₁H₁₄ODF 183.1170; Found 183.1164.



1,3,5-trichloro-2-((pentyl-5-*d*)oxy)benzene [6] According to general procedure B, in a N₂ filled glovebox, DTB-DPPBz (11.6 mg, 0.013 mmol, 0.033 eq.), Cu(OAc)₂ (60 μL of a 0.2 M solution in THF, 0.012 mmol, 0.03 eq.), and THF (140 μL) followed by dimethoxy(methyl)silane (148 μL, 1.20 mmol, 3 eq.) were added to an oven-dried 2-dram vial with an oven-dried stir bar. In a separate oven-dried 1-dram vial was added 1,3,5-trichloro-2-(pent-4-en-1-yloxy)benzene (106 mg, 0.40 mmol, 1 eq.), THF (200 μL), and 2-propanol-*d*₈ (77 μL, 1.0 mmol, 2.5 eq.). The solution in the 1-dram vial was added dropwise to the 2-dram vial. The 2-dram vial was capped with a pressure relief cap, removed from the glovebox, and left to stir for 24 h at 40 °C. Upon completion, the product was isolated by flash column chromatography using gradient elution (200 mL of 100% hexanes, 100 mL of 1% ethyl acetate in hexanes) to give the pure product as a colorless oil (99 mg, 0.37 mmol, 93% yield).

¹H NMR: (400 MHz, CDCl₃)

δ 7.29 (s, 2H), 3.98 (t, *J* = 6.7 Hz, 2H), 1.90 – 1.80 (m, 2H), 1.54 – 1.45 (m, 2H), 1.44 – 1.34 (m, 2H), 0.97 – 0.88 (m, 2.06H).

²H NMR: (61 MHz, CHCl₃)

δ 0.92 (s, 0.94D).

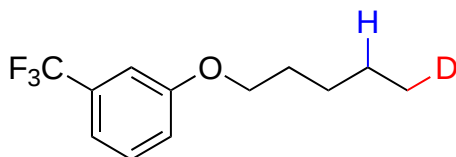
¹³C NMR: (101 MHz, CDCl₃)

δ 150.88, 130.27, 129.31, 128.84, 74.11, 29.84, 28.03, 22.52, 13.87 (t, *J* = 19.2 Hz).

ATR-IR (cm⁻¹):

2930, 2860, 2174, 1448, 1255, 1138.

HRMS: (EI⁺) *m/z*: [M]⁺ Calcd for C₁₁H₁₂DOCl₃ 267.0095; Found 267.0087.



1-((pentyl-5-*d*)oxy)-3-(trifluoromethyl)benzene [7] According to general procedure B, in a N₂ filled glovebox, DTB-DPPBz (11.6 mg, 0.013 mmol, 0.033 eq.), Cu(OAc)₂ (60 μL of a 0.2 M solution in THF, 0.012 mmol, 0.03 eq.), and THF (140 μL) followed by dimethoxy(methyl)silane (197 μL, 1.60 mmol, 4 eq.) were added to an oven-dried 2-dram vial with an oven-dried stir bar. In a separate oven-dried 1-dram vial was added 1-(4-penten-1-yloxy)-3-(trifluoromethyl)-benzene (92 mg, 0.40 mmol, 1 eq.), THF (200 μL), and 2-propanol-*d*₈ (107 μL, 1.40 mmol, 3.5 eq.). The solution in the 1-dram vial was added dropwise to the 2-dram vial. The 2-dram vial was capped with a pressure relief cap, removed from the glovebox, and left to stir for 18 h at 40 °C. Upon completion, the product was isolated by flash column chromatography using gradient elution (150 mL of 100% hexanes, 100 mL of 1% ethyl acetate in hexanes) to give the pure product as a clear and colorless oil (71 mg, 0.30 mmol, 75% yield).

¹H NMR: (400 MHz, CDCl₃)

δ 7.37 (t, *J* = 8.0 Hz, 1H), 7.19 (d, *J* = 7.6 Hz, 1H), 7.12 (s, 1H), 7.06 (d, *J* = 8.3 Hz, 1H), 3.98 (t, *J* = 6.5 Hz, 2H), 1.81 (p, *J* = 6.7 Hz, 2H), 1.52 – 1.31 (m, 4H), 0.97 – 0.88 (m, 2.05H).

²H NMR: (61 MHz, CHCl₃)

δ 0.93 (s, 0.95D).

¹³C NMR: (101 MHz, CDCl₃)

δ 159.41, 131.90 (d, *J* = 32.2 Hz), 130.02, 124.18 (d, *J* = 272.3 Hz), 118.12 (d, *J* = 1.4 Hz), 117.25 (q, *J* = 3.8 Hz), 111.33 (q, *J* = 3.9 Hz), 68.41, 28.98, 28.27, 22.50, 13.85 (t, *J* = 19.1 Hz).

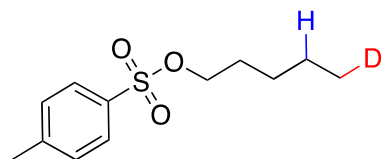
¹⁹F NMR: (61 MHz, CDCl₃)

δ -62.73 (s, 3F).

ATR-IR (cm⁻¹):

2934, 2863, 2172, 1449, 1327, 1121.

HRMS: (EI⁺) *m/z*: [M]⁺ Calcd for C₁₂H₁₄DOF₃ 233.1138; Found 233.1132.



Pentyl-5-*d* 4-methylbenzenesulfonate [8] According to general procedure B, in a N₂ filled glovebox, DTB-DPPBz (11.6 mg, 0.013 mmol, 0.033 eq.), Cu(OAc)₂ (60 μL of a 0.2 M solution in THF, 0.012 mmol, 0.03 eq.), and THF (140 μL) followed by dimethoxy(methyl)silane (148 μL, 1.20 mmol, 3 eq.) were added to an oven-dried 2-dram vial with an oven-dried stir bar. In a separate oven-dried 1-dram vial was added 4-penten-1-yl 4-methylbenzenesulfonate (96 mg, 0.40 mmol, 1 eq.), THF (200 μL), and 2-propanol-*d*₈ (77 μL, 1.0 mmol, 2.5 eq.). The solution in the 1-dram vial was added dropwise to the 2-dram vial. The 2-dram vial was capped with a pressure relief cap, removed from the glovebox, and left to stir for 22 h at 40 °C. Upon completion, the product was isolated by flash column chromatography using gradient elution (100 mL of 100% hexanes, 100 mL of 1% ethyl acetate in hexanes) to give the pure product as a clear yellow oil (87 mg, 0.36 mmol, 90% yield).

¹H NMR: (400 MHz, CDCl₃)

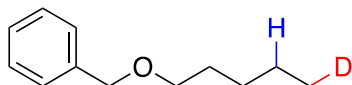
δ 7.78 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 4.01 (t, *J* = 6.5 Hz, 2H), 2.44 (s, 3H), 1.63 (p, *J* = 6.7 Hz, 2H), 1.32 – 1.16 (m, 4H), 0.88 – 0.78 (m, 2.04H).

^2H NMR: (61 MHz, CHCl_3)
 δ 0.82 (s, 0.96D).

^{13}C NMR: (101 MHz, CDCl_3)
 δ 144.73, 133.30, 129.88, 127.93, 70.79, 28.58, 27.48, 22.00, 21.69, 13.58 (t, J = 19.3 Hz).

ATR-IR (cm^{-1}):
 2936, 2864, 2174, 1356, 1188, 1173, 1097.

HRMS: (ESI^+) m/z : $[\text{M}+\text{Na}]^+$ Calcd for $\text{C}_{12}\text{H}_{17}\text{DO}_3\text{NaS}$ 266.0937; Found 266.0931.



(((Pentyl-5- d)oxy)methyl)benzene [9] According to general procedure B, in a N_2 filled glovebox, DTB-DPPBz (11.6 mg, 0.013 mmol, 0.033 eq.), $\text{Cu}(\text{OAc})_2$ (60 μL of a 0.2 M solution in THF, 0.012 mmol, 0.03 eq.), and THF (140 μL) followed by dimethoxy(methyl)silane (148 μL , 1.20 mmol, 3 eq.) were added to an oven-dried 2-dram vial with an oven-dried stir bar. In a separate oven-dried 1-dram vial was added the ((4-Penten-1-yloxy)methyl)benzene (71 mg, 0.40 mmol, 1 eq.), THF (200 μL), and 2-propanol- d_8 (77 μL , 1.0 mmol, 2.5 eq.). The solution in the 1-dram vial was added dropwise to the 2-dram vial. The 2-dram vial was capped with a pressure relief cap, removed from the glovebox, and left to stir for 25 h at 40 $^\circ\text{C}$. Upon completion, the product was isolated by flash column chromatography using gradient elution (100 mL of 100% hexanes, 100 mL of 1% ethyl acetate in hexanes) to give the pure product as a clear yellow oil (45 mg, 0.25 mmol, 63% yield).

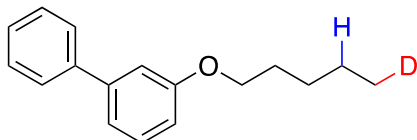
^1H NMR: (400 MHz, CDCl_3)
 δ 7.40 – 7.34 (m, 4H), 7.34 – 7.27 (m, 1H), 4.53 (s, 2H), 3.49 (t, J = 6.7 Hz, 2H), 1.65 (p, J = 6.8 Hz, 2H), 1.44 – 1.31 (m, 4H), 0.96 – 0.88 (m, 2.07H).

^2H NMR: (61 MHz, CHCl_3)
 δ 0.91 (s, 0.93D).

^{13}C NMR: (101 MHz, CDCl_3)
 δ 138.83, 128.44, 127.72, 127.56, 72.97, 70.63, 29.60, 28.47, 22.59, 13.87 (t, J = 19.1 Hz).

ATR-IR (cm^{-1}):
 2929, 2855, 2173, 1453, 1097, 1008.

HRMS: (EI^+) m/z : $[\text{M}]^+$ Calcd for $\text{C}_{12}\text{H}_{17}\text{DO}$ 179.1420; Found 179.1414.



3-((pentyl-5- d)oxy)-1,1'-biphenyl [10] According to general procedure B, in a N_2 filled glovebox, DTB-DPPBz (11.6 mg, 0.013 mmol, 0.033 eq.), $\text{Cu}(\text{OAc})_2$ (60 μL of a 0.2 M solution in THF, 0.012 mmol, 0.03 eq.), and THF (140 μL) followed by dimethoxy(methyl)silane (148 μL , 1.20 mmol, 3 eq.) were added to an oven-dried 2-dram vial with an oven-dried stir bar. In a separate oven-dried 1-dram vial was added 3-(4-penten-1-yloxy)-1,1'-biphenyl (95 mg, 0.40 mmol, 1 eq.), THF (200 μL), and 2-propanol- d_8 (77 μL , 1.0 mmol, 2.5 eq.). The solution in the 1-dram vial was added dropwise to the 2-dram vial. The 2-dram vial was capped with a pressure relief cap, removed from the glovebox, and left to stir for 24 h at 40 $^\circ\text{C}$. Upon completion, the product was isolated by flash column chromatography using gradient elution (100 mL of 100% hexanes, 100 mL of 1% ethyl acetate in hexanes, 100 mL of 2% ethyl acetate in hexanes) to give the pure product as a yellow oil (65 mg, 0.27 mmol, 68% yield).

¹H NMR: (400 MHz, CDCl₃)

δ 7.60 (d, *J* = 7.6 Hz, 2H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.35 (t, *J* = 7.7 Hz, 2H), 7.18 (d, *J* = 7.7 Hz, 1H), 7.14 (s, 1H), 6.94 – 6.86 (m, 1H), 4.03 (t, *J* = 6.6 Hz, 2H), 1.89 – 1.77 (m, 2H), 1.52 – 1.37 (m, 4H), 0.98 – 0.90 (m, 2.07H).

²H NMR: (61 MHz, CHCl₃)

δ 0.94 (s, 0.93D).

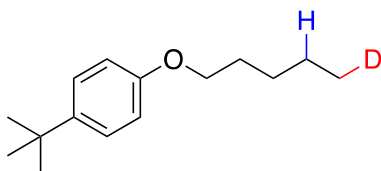
¹³C NMR: (101 MHz, CDCl₃)

δ 159.62, 142.81, 141.28, 129.83, 128.83, 127.48, 127.32, 119.58, 113.62, 113.34, 68.14, 29.17, 28.35, 22.54, 13.90 (t, *J* = 19.2 Hz).

ATR-IR (cm⁻¹):

2928, 2859, 2172, 1295, 1203, 1502, 1017.

HRMS: (ESI⁺) *m/z*: [M+H]⁺ Calcd for C₁₇H₁₉DO 242.1655; Found 242.1650.



1-(*tert*-butyl)-4-((pentyl-5-*d*)oxy)benzene [11] According to general procedure B, in a N₂ filled glovebox, DTB-DPPBz (53.7 mg, 0.060 mmol, 0.048 eq.), Cu(OAc)₂ (10 mg, 0.055 mmol, 0.044 eq.), and THF (630 μL) followed by dimethoxy(methyl)silane (722 μL, 5.85 mmol, 4.6 eq.) were added to an oven-dried 100-mL round bottom flask with an oven-dried stir bar. In a separate oven-dried 1-dram vial was added 1-(*tert*-butyl)-4-(4-penten-1-yloxy)benzene (275 mg, 1.26 mmol, 1 eq.), THF (630 μL), and 2-propanol-*d*₈ (347 μL, 4.53 mmol, 3.6 eq.). The solution in the 1-dram vial was added dropwise to the 100-mL round bottom flask. The round bottom was sealed with a rubber septum, removed from the glovebox, and left to stir for 24 h at 40 °C under N₂ gas. Upon completion, the product was isolated by flash column chromatography using gradient elution (300 mL of 100% hexanes, 100 mL of 1 % ethyl acetate in hexanes) to give the pure product as a colorless oil (238 mg, 1.09 mmol, 87% yield).

¹H NMR: (400 MHz, CDCl₃)

δ 7.32 (dd, *J* = 8.9, 1.4 Hz, 2H), 6.86 (dd, *J* = 8.7, 1.8 Hz, 2H), 3.96 (t, *J* = 6.6 Hz, 2H), 1.86 – 1.74 (m, 2H), 1.50 – 1.35 (m, 4H), 1.32 (s, 9H), 0.99 – 0.89 (m, 2.06H).

²H NMR: (61 MHz, CHCl₃)

δ 0.93 (s, 0.94D).

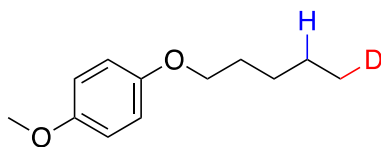
¹³C NMR: (101 MHz, CDCl₃)

δ 156.99, 143.19, 126.30, 114.01, 68.02, 34.17, 31.67, 29.20, 28.35, 22.54, 13.89 (t, *J* = 18.9 Hz).

ATR-IR (cm⁻¹):

2951, 2864, 2172, 1513, 1475, 1244, 1024.

HRMS: (EI⁺) *m/z*: [M]⁺ Calcd for C₁₅H₂₃DO 221.1890; Found 221.1883.



1-methoxy-4-((pentyl-5-*d*)oxy)benzene [12] According to general procedure B, in a N₂ filled glovebox, DTB-DPPBz (11.6 mg, 0.013 mmol, 0.033 eq.), Cu(OAc)₂ (60 μ L of a 0.2 M solution in THF, 0.012 mmol, 0.03 eq.), and THF (140 μ L) followed by dimethoxy(methyl)silane (148 μ L, 1.20 mmol, 3 eq.) were added to an oven-dried 2-dram vial with an oven-dried stir bar. In a separate oven-dried 1-dram vial was added 1-methoxy-4-(4-penten-1-yloxy)-benzene (77 mg, 0.40 mmol, 1 eq.), THF (200 μ L), and 2-propanol-*d*₈ (77 μ L, 1.0 mmol, 2.5 eq.). The solution in the 1-dram vial was added dropwise to the 2-dram vial. The 2-dram vial was capped with a pressure relief cap, removed from the glovebox, and left to stir for 23 h at 40 °C. Upon completion, the product was isolated by flash column chromatography using gradient elution (100 mL of 100% hexanes, 200 mL of 1% ethyl acetate in hexanes) to give the pure product as a clear yellow oil (70 mg, 0.36 mmol, 90% yield).

¹H NMR: (400 MHz, CDCl₃)

δ 6.84 (s, 4H), 3.91 (t, J = 6.6 Hz, 2H), 3.77 (s, 3H), 1.77 (p, J = 6.7 Hz, 2H), 1.48 – 1.33 (m, 4H), 0.95 – 0.87 (m, 2.01H).

²H NMR: (61 MHz, CHCl₃)

δ 0.92 (s, 0.99D).

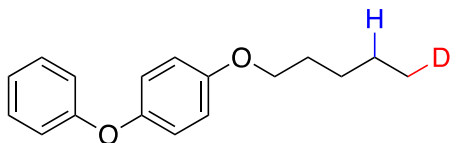
¹³C NMR: (101 MHz, CDCl₃)

δ 153.76, 153.42, 115.52, 114.71, 68.75, 55.84, 29.23, 28.33, 22.54, 13.87 (t, J = 19.2 Hz).

ATR-IR (cm⁻¹):

2934, 2866, 2180, 1510, 1229, 1035.

HRMS: (EI⁺) m/z : [M]⁺ Calcd for C₁₂H₁₇DO₂ 195.1370; Found 195.1363.



1-((pentyl-5-*d*)oxy)-4-phenoxybenzene [13] According to general procedure B, in a N₂ filled glovebox, DTB-DPPBz (11.6 mg, 0.013 mmol, 0.033 eq.), Cu(OAc)₂ (60 μ L of a 0.2 M solution in THF, 0.012 mmol, 0.03 eq.), and THF (140 μ L) followed by dimethoxy(methyl)silane (148 μ L, 1.20 mmol, 3 eq.) were added to an oven-dried 2-dram vial with an oven-dried stir bar. In a separate oven-dried 1-dram vial was added 1-(4-penten-1-yloxy)-4-phenoxybenzene (102 mg, 0.40 mmol, 1 eq.), THF (200 μ L), and 2-propanol-*d*₈ (77 μ L, 1.0 mmol, 2.5 eq.). The solution in the 1-dram vial was added dropwise to the 2-dram vial. The 2-dram vial was capped with a pressure relief cap, removed from the glovebox, and left to stir for 22 h at 40 °C. Upon completion, the product was isolated by flash column chromatography (300 mL of 100% hexanes) to give the pure product as a yellow solid (69 mg, 0.27 mmol, 68% yield).

¹H NMR: (400 MHz, CDCl₃)

δ 7.30 (t, J = 8.0 Hz, 2H), 7.04 (t, J = 7.5 Hz, 1H), 6.96 (t, J = 9.6 Hz, 4H), 6.88 (d, J = 8.8 Hz, 2H), 3.94 (t, J = 6.6 Hz, 2H), 1.79 (p, J = 6.8 Hz, 2H), 1.52 – 1.33 (m, 4H), 0.97 – 0.89 (m, 2.09H).

²H NMR: (61 MHz, CHCl₃)

δ 0.93 (s, 0.91D).

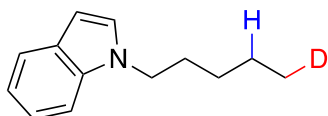
¹³C NMR: (101 MHz, CDCl₃)

δ 158.70, 155.61, 150.01, 129.71, 122.47, 120.95, 117.65, 115.57, 68.57, 29.17, 28.32, 22.53, 13.88 (t, J = 19.1 Hz).

ATR-IR (cm⁻¹):

2930, 2861, 2173, 1488, 1215, 1023.

HRMS: (EI⁺) m/z : [M]⁺ Calcd for C₁₇H₁₉DO₂ 257.1526; Found 257.1520.



1-(pentyl-5-*d*)-1*H*-indole [14] According to general procedure B, in a N₂ filled glovebox, DTB-DPPBz (79.7 mg, 0.089 mmol, 0.066 eq.), Cu(OAc)₂ (405 μ L of a 0.2 M solution in THF, 0.081 mmol, 0.06 eq.), and THF (420 μ L) followed by dimethoxy(methyl)silane (800 μ L, 6.48 mmol, 4.8 eq.) were added to an oven-dried 2-dram vial with an oven-dried stir bar. In a separate oven-dried 1-dram vial was added 1-(4-penten-1-yl)-1*H*-indole (250 mg, 1.35 mmol, 1 eq.), THF (525 μ L), and 2-propanol-*d*₈ (372 μ L, 4.86 mmol, 3.6 eq.). The solution in the 1-dram vial was added dropwise to the 2-dram vial. 2-dram vial was capped with a pressure relief cap, removed from the glovebox, and left to stir for 24 h at 40 °C. Upon completion, the product was isolated by flash column chromatography (300 mL of distilled hexanes) to give the pure product as a clear and colorless oil (231 mg, 1.23 mmol, 91% yield).

¹H NMR: (400 MHz, CDCl₃)

δ 7.66 (d, J = 7.6 Hz, 1H), 7.37 (d, J = 8.1 Hz, 1H), 7.29 – 7.17 (m, 1H), 7.17 – 7.06 (m, 2H), 6.51 (d, J = 3.1 Hz, 1H), 4.13 (t, J = 7.2 Hz, 2H), 1.86 (p, J = 7.2 Hz, 2H), 1.45 – 1.23 (m, 4H), 0.96 – 0.83 (m, 2.04H).

²H NMR: (61 MHz, CHCl₃)

δ 0.89 (s, 0.96D).

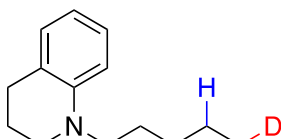
¹³C NMR: (101 MHz, CDCl₃)

δ 136.08, 128.69, 127.92, 121.40, 121.05, 119.26, 109.51, 100.93, 46.53, 30.10, 29.26, 22.39, 13.80 (t, J = 19.3 Hz).

ATR-IR (cm⁻¹):

2928, 2858, 2173, 1463, 1314, 1085.

HRMS: (ESI⁺) m/z : [M+H]⁺ Calcd for C₁₃H₁₇DN 189.1502; Found 189.1497.



1-(pentyl-5-*d*)-1,2,3,4-tetrahydroquinoline [15]. According to general procedure B, in a N₂ filled glovebox, DTB-DPPBz (11.6 mg, 0.013 mmol, 0.044 eq.), Cu(OAc)₂ (60 μ L of a 0.2 M solution in THF, 0.012 mmol, 0.04 eq.), and THF (90 μ L) followed by dimethoxy(methyl)silane (148 μ L, 1.20 mmol, 4 eq.) were added to an oven-dried 2-dram vial with an oven-dried stir bar. In a separate oven-dried 1-dram vial was added 1-(pent-4-en-1-yl)-1,2,3,4-tetrahydroquinoline (60 mg, 0.30 mmol, 1 eq.), THF (150 μ L), and 2-propanol-*d*₈ (69 μ L, 0.90 mmol, 3 eq.). The solution in the 1-dram vial was added dropwise to the 2-dram vial. The 2-dram vial was capped with a pressure relief cap, removed from the glovebox, and left to stir for 24 h at 40 °C. Upon completion, the product was isolated by flash column chromatography using gradient elution (100 mL of 100% hexanes, 100 mL of 2% ethyl acetate in hexanes) to give the pure product as a red oil (51 mg, 0.25 mmol, 83% yield).

¹H NMR: (400 MHz, CDCl₃)

δ 7.09 (t, J = 7.8 Hz, 1H), 6.98 (d, J = 7.3 Hz, 1H), 6.64 – 6.55 (m, 2H), 3.32 (t, J = 5.7 Hz, 2H), 3.28 (t, J = 7.7 Hz, 2H), 2.80 (t, J = 6.4 Hz, 2H), 1.99 (p, J = 6.1 Hz, 2H), 1.64 (p, J = 7.5 Hz, 2H), 1.46 – 1.29 (m, 4H), 1.04 – 0.89 (m, 2.04H).

²H NMR: (61 MHz, CHCl₃)

δ 0.96 (s, 0.96D)

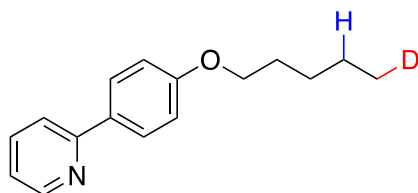
¹³C NMR: (101 MHz, CDCl₃)

δ 145.47, 129.21, 127.15, 122.22, 115.27, 110.54, 51.61, 49.54, 29.56, 28.34, 26.02, 22.68, 22.38, 13.94 (t, $J = 19.2$ Hz).

ATR-IR (cm^{-1}):

2927, 2858, 2173, 1601, 1502, 1456, 1201.

HRMS: (ESI^+) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{14}\text{H}_{21}\text{DN}$ 205.1815; Found 205.1830.



2-(4-((Pentyl-5- d)oxy)-phenyl)pyridine [16] According to general procedure B, in a N_2 filled glovebox, DTB-DPPBz (11.6 mg, 0.013 mmol, 0.033 eq.), $\text{Cu}(\text{OAc})_2$ (60 μL of a 0.2 M solution in THF, 0.012 mmol, 0.03 eq.), and THF (140 μL) followed by dimethoxy(methyl)silane (148 μL , 1.20 mmol, 3 eq.) were added to an oven-dried 2-dram vial with an oven-dried stir bar. In a separate oven-dried 1-dram vial was added 2-(4-(4-penten-1-yloxy)phenyl)pyridine (96 mg, 0.40 mmol, 1 eq.), THF (200 μL), and 2-propanol- d_8 (77 μL , 1.0 mmol, 2.5 eq.). The solution in the 1-dram vial was added dropwise to the 2-dram vial. The 2-dram vial was capped with a pressure relief cap, removed from the glovebox, and left to stir for 24 h at 40 $^\circ\text{C}$. Upon completion, the product was isolated by flash column chromatography using gradient elution (100 mL of 100% hexanes, 100 mL of 2% ethyl acetate in hexanes, 200 mL of 5% ethyl acetate in hexanes) to give the pure product as a clear and colorless oil (81 mg, 0.33 mmol, 83% yield).

^1H NMR: (400 MHz, CDCl_3)

δ 8.69 – 8.60 (m, 1H), 7.94 (d, $J = 8.8$ Hz, 2H), 7.80 – 7.60 (m, 2H), 7.21 – 7.10 (m, 1H), 6.99 (d, $J = 8.8$ Hz, 2H), 4.01 (t, $J = 6.6$ Hz, 2H), 1.89 – 1.74 (m, 2H), 1.54 – 1.31 (m, 4H), 1.00 – 0.86 (m, 2.01H).

^2H NMR: (61 MHz, CHCl_3)

δ 0.92 (s, 0.99D).

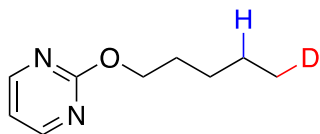
^{13}C NMR: (101 MHz, CDCl_3)

δ 160.16, 157.28, 149.64, 136.73, 131.88, 128.21, 121.44, 119.85, 114.76, 68.17, 29.08, 28.29, 22.51, 13.86 (t, $J = 19.0$ Hz)

ATR-IR (cm^{-1}):

2938, 2956, 2174, 1463, 1253, 1016.

HRMS: (ESI^+) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{16}\text{H}_{19}\text{DNO}$ 243.1607; Found 243.1646.



2-((Pentyl-5- d)oxy)pyrimidine [17]. According to general procedure B, in a N_2 filled glovebox, DTB-DPPBz (8.9 mg, 0.0099 mmol, 0.033 eq.), $\text{Cu}(\text{OAc})_2$ (45 μL of a 0.2 M solution in THF, 0.009 mmol, 0.03 eq.), and THF (105 μL) followed by dimethoxy(methyl)silane (111 μL , 0.90 mmol, 3 eq.) were added to an oven-dried 2-dram vial with an oven-dried stir bar. In a separate oven-dried 1-dram vial was added 2-(4-penten-1-yloxy)pyrimidine (49 mg, 0.30 mmol, 1 eq.), THF (150 μL), and 2-propanol- d_8 (57 μL , 0.75 mmol, 2.5 eq.). The solution in the 1-dram vial was added dropwise to the 2-dram vial. The 2-dram vial was capped with a pressure relief cap, removed from the glovebox, and left to stir for 22h at 40 $^\circ\text{C}$. Upon completion, the product was isolated by flash column chromatography using gradient elution (100 mL of 100% hexanes, 100 mL of 7% ethyl acetate in hexanes, 100 mL of 14% ethyl acetate in hexanes) to give the pure product as a yellow oil (44 mg, 0.26 mmol, 87% yield).

¹H NMR: (400 MHz, CDCl₃)

δ 8.51 (br s, 2H), 6.90 (s, 1H), 4.30 (t, *J* = 6.6 Hz, 2H), 1.77 (p, *J* = 6.8 Hz, 2H), 1.48 – 1.23 (m, 4H), 0.90 – 0.81 (m, 2.01H).

²H NMR: (61 MHz, CHCl₃)

δ 0.85 (s, 0.99D).

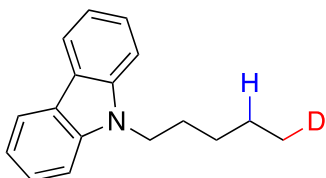
¹³C NMR: (75 MHz, CDCl₃)

δ 165.40, 159.10, 115.15, 67.70, 28.53, 28.06, 22.34, 13.71 (t, *J* = 19.1 Hz).

ATR-IR (cm⁻¹):

2930, 2860, 2182, 1561, 1422, 1320, 1045, 1017.

HRMS: (ESI⁺) *m/z*: [M+H]⁺ Calcd for C₉H₁₄DN₂O 168.1247; Found 168.1221.



9-(Pentyl-5-*d*)-9H-carbazole [18] According to general procedure B, in a N₂ filled glovebox, DTB-DPPBz (11.6 mg, 0.013 mmol, 0.033 eq.), Cu(OAc)₂ (60 μL of a 0.2 M solution in THF, 0.012 mmol, 0.03 eq.), and THF (140 μL) followed by dimethoxy(methyl)silane (148 μL, 1.20 mmol, 3 eq.) were added to an oven-dried 2-dram vial with an oven-dried stir bar. In a separate oven-dried 1-dram vial was added 9-(4-penten-1-yl)-9H-carbazole (94 mg, 0.40 mmol, 1 eq.), THF (200 μL), and 2-propanol-*d*₈ (77 μL, 1.0 mmol, 2.5 eq.). The solution in the 1-dram vial was added dropwise to the 2-dram vial. The 2-dram vial was capped with a pressure relief cap, removed from the glovebox, and left to stir for 23 h at 40 °C. Upon completion, the product was isolated by flash column chromatography using gradient elution (100 mL of 100% hexanes, 100 mL of 1% ethyl acetate in hexanes) to give the pure product as a yellow oil (85 mg, 0.36 mmol, 90% yield).

¹H NMR: (400 MHz, CDCl₃)

δ 8.17 (d, *J* = 7.9 Hz, 2H), 7.57 – 7.48 (m, 2H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.33 – 7.26 (m, 2H), 4.33 (t, *J* = 7.3 Hz, 2H), 1.98 – 1.86 (m, 2H), 1.49 – 1.37 (m, 4H), 0.98 – 0.88 (m, 2.03H).

²H NMR: (61 MHz, CHCl₃)

δ 0.92 (s, 0.97D).

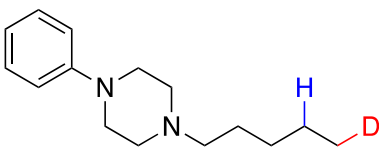
¹³C NMR: (75 MHz, CDCl₃)

δ 140.54, 125.68, 122.92, 120.46, 118.80, 108.7, 43.15, 29.52, 28.81, 22.54, 13.80 (t, *J* = 19.1 Hz).

ATR-IR (cm⁻¹):

3052, 2925, 2855, 2175, 1924, 1883, 1850, 1768, 1324.

HRMS: (ESI⁺) *m/z*: [M+H]⁺ Calcd for C₁₇H₁₉DN 239.1658; Found 239.1653.



1-(Pentyl-5-*d*)-4-phenylpiperazine [19] According to general procedure B, in a N₂ filled glovebox, DTB-DPPBz (11.6 mg, 0.013 mmol, 0.033 eq.), Cu(OAc)₂ (60 μL of a 0.2 M solution in THF, 0.012 mmol, 0.03 eq.), and THF (140 μL) followed by dimethoxy(methyl)silane (148 μL, 1.20 mmol, 3 eq.) were added to an oven-dried 2-dram vial with an oven-dried stir bar. In a separate oven-dried 1-dram vial was added 1-(4-

penten-1-yl)-4-phenylpiperazine (92 mg, 0.40 mmol, 1 eq.), THF (200 μ L), and 2-propanol- d_8 (77 μ L, 1.0 mmol, 2.5 eq.). The solution in the 1-dram vial was added dropwise to the 2-dram vial. The 2-dram vial was capped with a pressure relief cap, removed from the glovebox, and left to stir for 24 h at 40 °C. Upon completion, the product was isolated by flash column chromatography using gradient elution (100 mL of 100% CH_2Cl_2 , 200 mL 2% MeOH in CH_2Cl_2) to give the pure product as an orange oil (84 mg, 0.36 mmol, 90% yield).

$^1\text{H NMR}$: (400 MHz, CDCl_3)

δ 7.26 (t, J = 7.9 Hz, 2H), 6.93 (d, J = 8.1 Hz, 2H), 6.85 (t, J = 7.5 Hz, 1H), 3.26 – 3.17 (m, 4H), 2.66 – 2.58 (m, 4H), 2.40 (t, J = 7.9 Hz, 2H), 1.59 – 1.49 (m, 2H), 1.38 – 1.27 (m, 4H), 0.92 – 0.86 (m, 2.08H).

$^2\text{H NMR}$: (61 MHz, CHCl_3)

δ 0.89 (s, 0.92D)

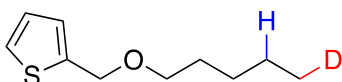
$^{13}\text{C NMR}$: (101 MHz, CDCl_3)

δ 151.43, 129.20, 119.77, 116.15, 53.39, 49.18, 31.51, 29.88, 26.63, 22.66, 13.88 (t, J = 19.1 Hz).

ATR-IR (cm^{-1}):

2928, 2814, 2177, 1600, 1502, 1232.

HRMS: (ESI^+) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{15}\text{H}_{24}\text{N}_2$ 234.2080; Found 234.2063.



2-(((Pentyl-5- d)oxy)methyl)thiophene [20] According to general procedure B, in a N_2 filled glovebox, DTB-DPPBz (11.6 mg, 0.013 mmol, 0.033 eq.), $\text{Cu}(\text{OAc})_2$ (60 μ L of a 0.2 M solution in THF, 0.012 mmol, 0.03 eq.), and THF (140 μ L) followed by dimethoxy(methyl)silane (148 μ L, 1.20 mmol, 3 eq.) were added to an oven-dried 2-dram vial with an oven-dried stir bar. In a separate oven-dried 1-dram vial was added 2-(((4-penten-1-yloxy)methyl)thiophene (73 mg, 0.40 mmol, 1 eq.), THF (200 μ L), and 2-propanol- d_8 (77 μ L, 1.0 mmol, 2.5 eq.). The solution in the 1-dram vial was added dropwise to the 2-dram vial. The 2-dram vial was capped with a pressure relief cap, removed from the glovebox, and left to stir for 24 h at 40 °C. Upon completion, the product was isolated by flash column chromatography using gradient elution (200 mL of 2% ethyl acetate in hexanes, 200 mL of 5% ethyl acetate in hexanes) to give the pure product as a light-yellow oil (62 mg, 0.33 mmol, 83% yield).

$^1\text{H NMR}$: (400 MHz, CDCl_3)

δ 7.28 (d, J = 5.0 Hz, 1H), 7.02 – 6.95 (m, 2H), 4.67 (s, 2H), 3.48 (t, J = 6.7 Hz, 2H), 1.61 (p, J = 6.8 Hz, 2H), 1.38 – 1.29 (m, 4H), 0.93 – 0.85 (m, 2.07H).

$^2\text{H NMR}$: (61 MHz, CHCl_3)

δ 0.89 (s, 0.93D).

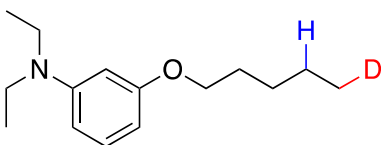
$^{13}\text{C NMR}$: (101 MHz, CDCl_3)

δ 141.62, 126.66, 126.20, 125.69, 70.29, 67.40, 29.47, 28.37, 22.54, 13.85 (t, J = 18.9 Hz).

ATR-IR (cm^{-1}):

2930, 2853, 2169, 1168, 1088.

HRMS: (EI^+) m/z : $[\text{M}]^+$ Calcd for $\text{C}_{10}\text{H}_{15}\text{DOS}$ 185.0985; Found 185.0978.



***N,N*-diethyl-3-((pentyl-5-*d*)oxy)aniline [21]** According to general procedure B, in a N₂ filled glovebox, DTB-DPPBz (11.6 mg, 0.013 mmol, 0.033 eq.), Cu(OAc)₂ (60 μL of a 0.2 M solution in THF, 0.012 mmol, 0.03 eq.), and THF (140 μL) followed by dimethoxy(methyl)silane (148 μL, 1.20 mmol, 3 eq.) were added to an oven-dried 2-dram vial with an oven-dried stir bar. In a separate oven-dried 1-dram vial was added *N,N*-diethyl-3-(4-penten-1-yloxy)aniline (93 mg, 0.40 mmol, 1 eq.), THF (200 μL), and 2-propanol-*d*₈ (77 μL, 1.0 mmol, 2.5 eq.). The solution in the 1-dram vial was added dropwise to the 2-dram vial. The 2-dram vial was capped with a pressure relief cap, removed from the glovebox, and left to stir for 24 h at 40 °C. Upon completion, the product was isolated by flash column chromatography using gradient elution (100 mL of 100% hexanes, 100 mL of 1% ethyl acetate in hexanes, 100 mL of 2% ethyl acetate in hexanes) to give the pure product as a dark green oil (61 mg, 0.26 mmol, 65% yield).

¹H NMR: (400 MHz, CDCl₃)

δ 7.11 (t, *J* = 8.1 Hz, 1H), 6.30 (d, *J* = 8.1 Hz, 1H), 6.25 – 6.18 (m, 2H), 3.95 (t, *J* = 6.6 Hz, 2H), 3.34 (q, *J* = 6.9 Hz, 4H), 1.84 – 1.74 (m, 2H), 1.50 – 1.32 (m, 4H), 1.16 (t, *J* = 7.0 Hz, 6H), 0.95 – 0.87 (m, 2.08H).

²H NMR: (61 MHz, CHCl₃)

δ 0.92. (s, 0.92D).

¹³C NMR: (101 MHz, CDCl₃)

δ 160.56, 149.18, 129.91, 105.02, 100.76, 99.02, 67.79, 44.49, 29.24, 28.33, 22.52, 13.85 (t, *J* = 19.0 Hz), 12.71.

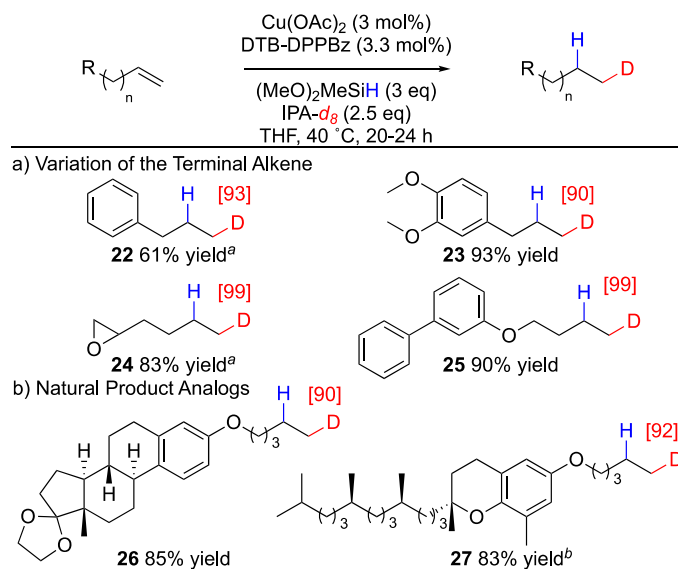
ATR-IR (cm⁻¹):

2928, 2868, 2171, 1284, 1214, 1142, 1053.

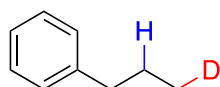
HRMS: (ESI⁺) *m/z*: [M+H]⁺ Calcd for C₁₅H₂₅DNO 237.2077; Found 237.2099.

Varving Chain Lengths and Natural Product Analogs

Scheme S3. Unactivated terminal alkene substrate varying chain lengths and natural product analogs



^aYield determined by ¹H NMR analysis using 1,3,5-trimethylbenzene as an internal standard ^bReaction performed at 60 °C.



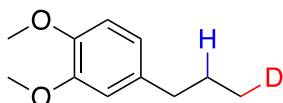
(Propyl-3-*d*)-benzene [22]. According to general procedure B, in a N₂ filled glovebox, DTB-DPPBz (8.9 mg, 0.0099 mmol, 0.033 eq.), Cu(OAc)₂ (45 μ L of a 0.2 M solution in THF, 0.009 mmol, 0.03 eq.), and THF (105 μ L) followed by dimethoxy(methyl)silane (111 μ L, 0.90 mmol, 3 eq.) were added to an oven-dried 2-dram vial with an oven-dried stir bar. In a separate oven-dried 1-dram vial was added allyl benzene (35 mg, 0.30 mmol, 1 eq.), THF (150 μ L), and 2-propanol-*d*₈ (57 μ L, 0.75 mmol, 2.5 eq.). The solution in the 1-dram vial was added dropwise to the 2-dram vial. The 2-dram vial was capped with a pressure relief cap, removed from the glovebox, and left to stir for 23 h at 40 °C. Upon completion, ether (24 mL) was added to the crude mixture and filtered through a 1-inch silica plug. Then the mixture was concentrated and 1,3,5-trimethylbenzene (0.33 eq.) was used as an internal standard to determine ¹H NMR crude yield (61% crude yield by ¹H NMR).

¹H NMR: (400 MHz, CDCl₃) of the crude product

δ 7.20 – 7.15 (m, 2H), 7.07 (d, *J* = 7.1 Hz, 3H), 2.50 (t, *J* = 7.5 Hz, 2H), 1.56 (p, *J* = 7.5 Hz, 2H), 0.88 – 0.82 (m, 2.07H).

²H NMR: (61 MHz, CHCl₃) of the crude product

δ 0.85 (s, 0.93D).



1,2-dimethoxy-4-(propyl-5-*d*)benzene [23]. According to general procedure B, in a N₂ filled glovebox, DTB-DPPBz (8.9 mg, 0.0099 mmol, 0.033 eq.), Cu(OAc)₂ (45 μ L of a 0.2 M solution in THF, 0.009 mmol, 0.03 eq.), and THF (105 μ L) followed by dimethoxy(methyl)silane (111 μ L, 0.90 mmol, 3 eq.) were added to an oven-dried 2-dram vial with an oven-dried stir bar. In a separate oven-dried 1-dram vial was added 3-(3,4-dimethoxyphenyl)-1-propene (53 mg, 0.30 mmol, 1 eq.), THF (150 μ L), and 2-propanol-*d*₈ (57 μ L, 0.75 mmol, 2.5 eq.). The solution in the 1-dram vial was added dropwise to the 2-dram vial. The 2-dram vial was capped with a pressure relief cap, removed from the glovebox, and left to stir for 23 h at 40 °C. Upon completion, the product was isolated by flash column chromatography using gradient elution (100 mL of 100% hexanes, 100 mL of 2% ethyl acetate in hexanes, 100 mL of 4% ethyl acetate in hexanes) to give the pure product as a clear yellow oil (50 mg, 0.28 mmol, 93% yield).

¹H NMR: (400 MHz, CDCl₃)

δ 6.80 – 6.76 (m, 1H), 6.73 – 6.70 (m, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 2.53 (t, *J* = 7.5 Hz, 2H), 1.66 – 1.56 (m, 2H), 0.95 – 0.88 (m, 2.10H).

²H NMR: (61 MHz, CHCl₃)

δ 0.92 (s, 0.90D).

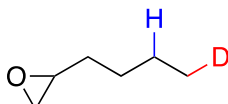
¹³C NMR: (101 MHz, CDCl₃)

δ 148.71, 147.01, 135.41, 120.22, 111.76, 111.08, 55.92, 55.79, 37.69, 24.76, 13.59 (t, *J* = 19.0 Hz).

ATR-IR (cm⁻¹):

2952, 2932, 2176, 1513, 1232, 1154, 1028.

HRMS: (ESI⁺) *m/z*: [M+H]⁺ Calcd for C₁₁H₁₆DO₂ 182.1291; Found 182.1287.



2-(butyl-4-*d*)oxirane [24]. According to general procedure B, in a N₂ filled glovebox, DTB-DPPBz (11.6 mg, 0.013 mmol, 0.033 eq.), Cu(OAc)₂ (60 μ L of a 0.2 M solution in THF, 0.012 mmol, 0.03 eq.), and THF (140 μ L) followed by dimethoxy(methyl)silane (148 μ L, 1.20 mmol, 3 eq.) were added to an oven-dried 2-dram vial with an oven-dried stir bar. In a separate oven-dried 1-dram vial was added 2-butyloxirane (39 mg,

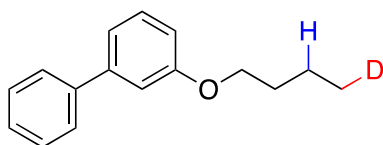
0.40 mmol, 1 eq.), THF (200 μ L), and 2-propanol- d_8 (77 μ L, 1.0 mmol, 2.5 eq.). The solution in the 1-dram vial was added dropwise to the 2-dram vial. The 2-dram vial was capped with a pressure relief cap, removed from the glovebox, and left to stir for 23 h at 40 °C. Upon completion, the reaction mixture was filtered with ether (3 mL) through a pasteur pipette loaded with 1 cm of cotton and 3.5 cm of silica gel. Afterwards, 1,3,5-trimethylbenzene (0.33 eq.) was added as internal standard to determine the crude ^1H NMR yield (83% crude yield by ^1H NMR).

^1H NMR: (400 MHz, CDCl_3) of the crude product

δ 2.91 – 2.80 (m, 1H), 2.72 – 2.65 (m, 1H), 2.43 – 2.37 (m, 1H), 1.53 – 1.23 (m, 6H), 0.90 – 0.80 (m, 2.01H).

^2H NMR: (61 MHz, CHCl_3) of the crude product

δ 0.84 (s, 0.99D)



3-((butyl-4- d)oxy)-1,1'-biphenyl [25]. According to general procedure B, in a N_2 filled glovebox, DTB-DPPBz (8.9 mg, 0.0099 mmol, 0.033 eq.), $\text{Cu}(\text{OAc})_2$ (45 μ L of a 0.2 M solution in THF, 0.009 mmol, 0.03 eq.), and THF (105 μ L) followed by dimethoxy(methyl)silane (111 μ L, 0.90 mmol, 3 eq.) were added to an oven-dried 2-dram vial with an oven-dried stir bar. In a separate oven-dried 1-dram vial was added 3-(3-buten-1-yloxy)-1,1'-biphenyl (67 mg, 0.30 mmol, 1 eq.), THF (150 μ L), and 2-propanol- d_8 (57 μ L, 0.75 mmol, 2.5 eq.). The solution in the 1-dram vial was added dropwise to the 2-dram vial. The 2-dram vial was capped with a pressure relief cap, removed from the glovebox, and left to stir for 20 h at 40 °C. Upon completion, the product was isolated by flash column chromatography using gradient elution (100 mL of 100% hexanes, 100 mL of 2% ethyl acetate in hexanes) to give the pure product as a yellow oil (62 mg, 0.27 mmol, 90% yield).

^1H NMR: (300 MHz, CDCl_3)

δ 7.66 (d, $J = 7.3$ Hz, 2H), 7.48 (t, $J = 7.4$ Hz, 2H), 7.39 (t, $J = 7.4$ Hz, 2H), 7.25 – 7.18 (m, 2H), 6.95 (d, $J = 8.3$ Hz, 1H), 4.07 (t, $J = 6.4$ Hz, 2H), 1.92 – 1.78 (m, 2H), 1.65 – 1.49 (m, 2H), 1.09 – 0.97 (m, 2.01H).

^2H NMR: (61 MHz, CHCl_3)

δ 1.03 (s, 0.99D).

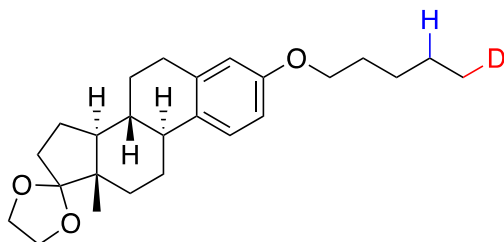
^{13}C NMR: (75 MHz, CDCl_3)

δ 159.63, 142.81, 141.28, 129.82, 128.82, 127.47, 127.30, 119.57, 113.62, 113.34, 67.82, 31.48, 19.33, 13.72 (t, $J = 19.2$ Hz).

ATR-IR (cm^{-1}):

2935, 2868, 2175, 1295, 1202, 1052, 1036.

HRMS: (ESI^+) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{16}\text{H}_{18}\text{DO}$ 228.1498; Found 228.1494.



(8R,9S,13S,14S)-13-methyl-3-((pentyl-5- d)oxy)-6,7,8,9,11,12,13,14,15,16-

decahydrospiro[cyclopenta[a]phenanthrene-17,2'-[1,3]dioxolane] [26] According to general procedure B, in a N_2 filled glovebox, DTB-DPPBz (11.6 mg, 0.013 mmol, 0.033 eq.), $\text{Cu}(\text{OAc})_2$ (60 μ L of a 0.2 M

solution in THF, 0.012 mmol, 0.03 eq.), and THF (140 μ L) followed by dimethoxy(methyl)silane (148 μ L, 1.20 mmol, 3 eq.) were added to an oven-dried 2-dram vial with an oven-dried stir bar. In a separate oven-dried 1-dram vial was added the (8*R*,9*S*,13*S*,14*S*)-13-methyl-3-(4-penten-1-yloxy)-6,7,8,9,11,12,13,14,15,16-decahydrospiro[cyclopenta[*a*]phenanthrene-17,2'-[1,3]dioxolane (153 mg, 0.40 mmol, 1 eq.), THF (200 μ L), and 2-propanol-*d*₈ (77 μ L, 1.0 mmol, 2.5 eq.). The solution in the 1-dram vial was added dropwise to the 2-dram vial. The 2-dram vial was capped with a pressure relief cap, removed from the glovebox, and left to stir for 24 h at 40 °C. Upon completion, the product was isolated by flash column chromatography using gradient elution (100 mL of 100% hexanes, 100 mL of 2% ethyl acetate in hexanes, 100 mL of 5% ethyl acetate in hexanes) to give the pure product as a pale yellow/green viscous oil (130 mg, 0.34 mmol, 85% yield).

¹H NMR: (300 MHz, CDCl₃)

δ 7.20 (d, *J* = 8.4 Hz, 1H), 6.71 (dd, *J* = 8.6, 2.7 Hz, 1H), 6.63 (d, *J* = 2.7 Hz, 1H), 4.02 – 3.86 (m, 6H), 2.94 – 2.77 (m, 2H), 2.38 – 2.18 (m, 2H), 2.10 – 1.99 (m, 1H), 1.95 – 1.73 (m, 6H), 1.72 – 1.60 (m, 1H), 1.59 – 1.51 (m, 1H), 1.50 – 1.29 (m, 8H), 0.96 – 0.86 (m, 5.10H).

²H NMR: (61 MHz, CHCl₃)

δ 0.92 (s, 0.90D).

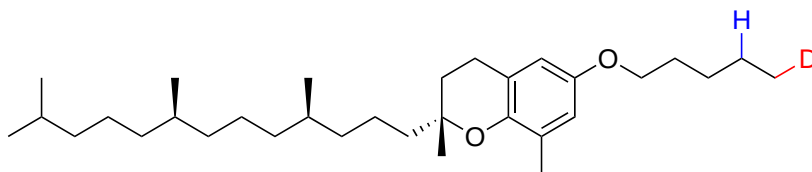
¹³C NMR: (75 MHz, CDCl₃)

δ 157.10, 138.05, 132.61, 126.38, 119.56, 114.55, 112.11, 67.99, 65.37, 64.70, 49.48, 46.29, 43.75, 39.20, 34.36, 31.44, 30.86, 29.18, 28.32, 27.14, 26.27, 22.50, 22.49, 14.46, 13.87 (t, *J* = 19.1 Hz).

ATR-IR (cm⁻¹):

2933, 2867, 2174, 1606, 1497, 1309, 1103, 1045.

HRMS: (ESI⁺) *m/z*: [M+H]⁺ Calcd for C₂₅H₃₆DO₃ 386.2805; Found 386.2802.



(*R*)-2,8-dimethyl-6-((pentyl-5-*d*)oxy)-2-((4*R*,8*R*)-4,8,12-trimethyltridecyl)chromane [27] According to general procedure B, in a N₂ filled glovebox, DTB-DPPBz (8.9 mg, 0.0099 mmol, 0.033 eq.), Cu(OAc)₂ (45 μ L of a 0.2 M solution in THF, 0.009 mmol, 0.03 eq.), and THF (105 μ L) followed by dimethoxy(methyl)silane (111 μ L, 0.90 mmol, 3 eq.) were added to an oven-dried 2-dram vial with an oven-dried stir bar. In a separate oven-dried 1-dram vial was added (*R*)-2,8-dimethyl-6-(4-penten-1-yloxy)-2-((4*R*,8*R*)-4,8,12-trimethyltridecyl)chromane (141 mg, 0.30 mmol, 1 eq.), THF (150 μ L), and 2-propanol-*d*₈ (57 μ L, 0.75 mmol, 2.5 eq.). The solution in the 1-dram vial was added dropwise to the 2-dram vial. The 2-dram vial was capped with a pressure relief cap, removed from the glovebox, and left to stir for 24 h at 60 °C. Upon completion, the product was isolated by flash column chromatography using gradient elution (100 mL of 100% hexanes, 200 mL of 0.5%) to give the pure product as a clear oil (118 mg, 0.25 mmol, 83% yield).

To determine deuterium incorporation, a quantitative ¹³C NMR was performed. The quantitative ¹³C NMR is included along with a zoomed in spectrum of the region containing the triplet corresponding to the terminal carbon with the incorporated deuterium. It was verified by examining the transfer hydrogenation product (**8**) that the terminal CH₃ overlaps with the most downfield peak of the CH₂D triplet. Therefore, each peak of the triplet was separately integrated, and it was determined that the deuterium incorporation was at least 92%.

¹H NMR: (400 MHz, CDCl₃) extra proton observed due to signal overlapping with H grease

δ 6.56 (d, *J* = 3.0 Hz, 1H), 6.44 (d, *J* = 3.0 Hz, 1H), 3.86 (t, *J* = 6.6 Hz, 2H), 2.71 (t, *J* = 7.1 Hz, 2H), 2.14 (s, 3H), 1.82 – 1.70 (m, 4H), 1.60 – 1.47 (m, 4H), 1.46 – 1.34 (m, 8H), 1.31 – 1.21 (m, 10H), 1.18 – 1.02 (m, 7H), 0.93 – 0.82 (m, 14H).

^2H NMR: (61 MHz, CHCl_3)
 δ 0.91 (s)

^{13}C NMR: (101 MHz, CDCl_3)
 δ 151.78, 146.12, 127.19, 120.97, 115.53, 111.89, 75.59, 68.48, 40.09, 39.53, 37.60, 37.44, 32.95, 32.83, 31.56, 29.88, 29.37, 28.41, 28.13, 24.97, 24.60, 24.28, 22.88, 22.84, 22.79, 22.57, 21.13, 19.90, 19.81, 16.36, 13.91 ($t = 19.3$ Hz).

ATR-IR (cm^{-1}):
 2925, 2859, 2175, 1468, 1250, 1154, 1056.

HRMS: (ESI^+) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{32}\text{H}_{56}\text{DO}_2$ 474.4418; Found 474.4415.

Synthesis of Dimethoxy(methyl)silane-*d*

The procedure was adopted from a previously reported procedure.²

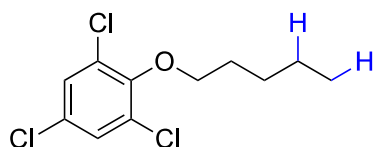
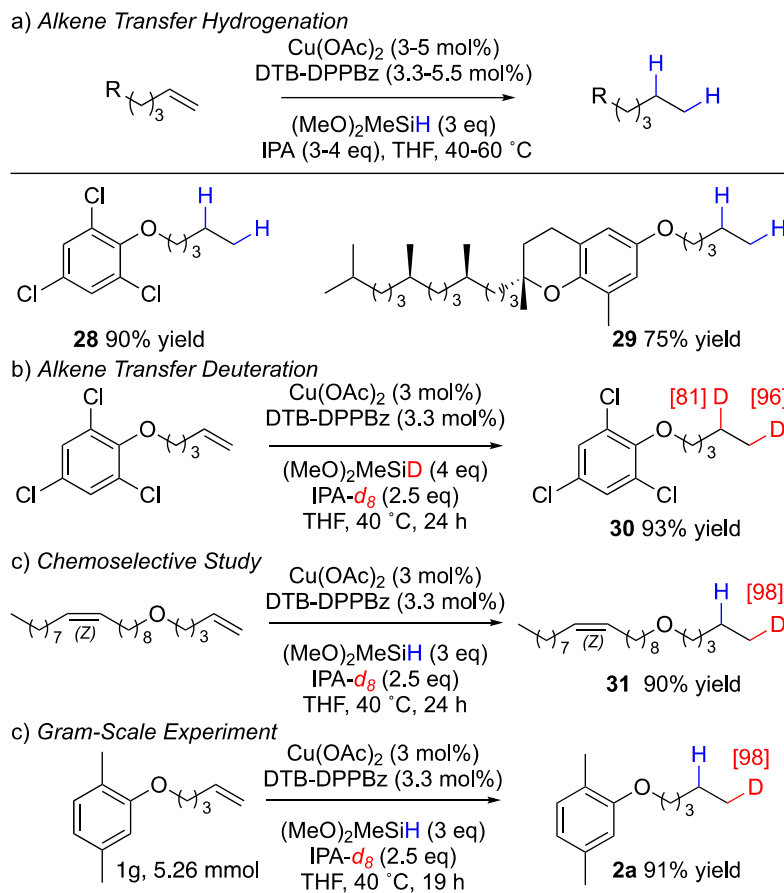
To an oven-dried 500 mL Schlenk flask equipped with a Teflon stir bar in a N_2 filled glovebox was added the $\text{Pt}(\text{PPh}_3)_4$ (585.8 mg, 0.471 mmol, 0.01 eq.), dimethoxy(methyl)silane (5.81 mL, 47.1 mmol, 1 eq.), and 2.5 mL of degassed anhydrous hexanes. The Schlenk flask was sealed with a rubber septum, removed from the glovebox, connected to a manifold line, and cooled to -78°C . A single freeze-pump-thaw cycle was performed, and the Schlenk flask was backfilled with D_2 gas from a D_2 purged balloon at room temperature. The flask was sealed with parafilm and heated to 60°C . After 2 hours, the reaction was cooled to room temperature and then a single freeze-pump-thaw was performed again, backfilling with D_2 gas. The process was repeated 6 times or until the ^1H NMR showed $\geq 95\%$ Deuterium incorporation. It is important to maintain a N_2 (g) inert atmosphere while obtaining a minimal quantity of sample for ^1H NMR analysis.

The solution was purified through a distillation apparatus; the set up consisted of a flame-dried 25 mL round-bottom receiving flask and a cannula. The 25 mL round-bottom receiving flask was flame-dried, and then filled with N_2 . Once the receiving flask reached room temperature, the cannula was inserted, maintaining positive pressure, and tightly sealed with parafilm to prevent condensation from entering. Upon confirmation of positive N_2 flow, the open end of the cannula was inserted into the Schlenk reaction flask. The 25 mL round-bottom receiving flask was cooled to -78°C and closed to the manifold line and then the Schlenk flask was heated to 80°C . The heat initiated the distillation of the dimethoxy(methyl)silane-*d* and the hexane through the cannula which were trapped in the cold 25 mL round-bottom receiving flask. Vacuum was also applied to the 25 mL round-bottom receiving flask to promote this process. Once all the silane and hexane were trapped in the 25 mL round-bottom receiving flask, the flask was removed from the heat and the manifold was closed to vacuum line while the 25 mL round-bottom receiving flask warmed to room temperature. Under positive nitrogen flow, the cannula was removed from the 25 mL round-bottom receiving flask, while keeping it inserted in the Schlenk reaction flask. The 25 mL round-bottom receiving flask was tightly sealed with Parafilm and stored in the -4°C freezer. The final product was in a solution of hexane, and the molarity was calculated by ^1H NMR using 1,3,5-trimethylbenzene as an internal standard, and used for the transfer deuteration reaction (2.66 g in a 6.05 M hexane solution, 24.8 mmol, 53% yield).

*Note: it is important to monitor that the end of the cannula does not get clogged by frozen solvent/silane. If this occurs, remove the Schlenk reaction flask from heat and close manifold to vacuum line. Warm the 25 mL round-bottom receiving flask until the solids on the tip of the cannula melt, and then distillation can be resumed.

Key Reaction Studies

Scheme S4. Reaction modularity and chemoselectivity studies



1,3,5-Trichloro-2-(pentyloxy)-benzene [28] According to general procedure B, in a N_2 filled glovebox, DTB-DPPBz (14.8 mg, 0.0165 mmol, 0.055 eq.), Cu(OAc)_2 (75 μL of a 0.2 M solution in THF, 0.015 mmol, 0.05 eq.), and THF (125 μL) followed by dimethoxy(methyl)silane (185 μL , 1.50 mmol, 5 eq.) were added to an oven-dried 2-dram vial with an oven-dried stir bar. In a separate oven-dried 1-dram vial was added 2,4,6-trichloro-4-(5-pentan-1-yloxy)-benzene (80 mg, 0.30 mmol, 1 eq.), THF (100 μL), and 2-propanol (92 μL , 1.2 mmol, 4 eq.). The solution in the 1-dram vial was added dropwise to the 2-dram vial. The 2-dram vial was capped with a pressure relief cap, removed from the glovebox, and left to stir for 24 h at 40 °C. Upon completion, the product was isolated by flash column chromatography using gradient elution (200 mL of 100% hexanes, 100 mL of 1% ethyl acetate in hexanes) to give the pure product as a colorless oil (72 mg, 0.27 mmol, 90% yield).

$^1\text{H NMR}$: (400 MHz, CDCl_3)

δ 7.29 (s, 2H), 3.98 (t, $J = 6.7$ Hz, 2H), 1.89 – 1.78 (m, 2H), 1.54 – 1.33 (m, 4H), 0.94 (t, $J = 7.2$ Hz, 3H).

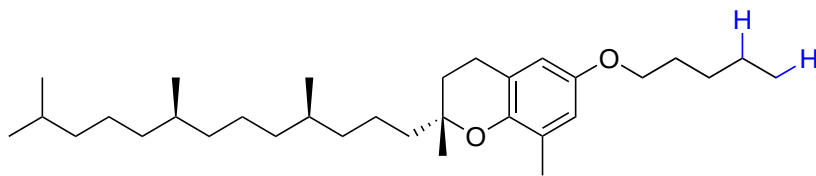
$^{13}\text{C NMR}$: (101 MHz, CDCl_3)

δ 150.91, 130.28, 129.31, 128.84, 74.11, 29.84, 28.07, 22.61, 14.16.

ATR-IR (cm^{-1}):

3081.97, 2955.97, 1551.16, 1448.49, 1255.61, 1044.22

HRMS: (EI^+) m/z : $[\text{M}]^+$ Calcd for $\text{C}_{11}\text{H}_{13}\text{OCl}_3$ 266.0032; Found 266.0037.



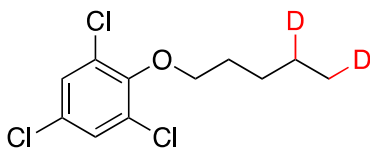
(*R*)-2,8-dimethyl-6-((pentyl)oxy)-2-((4*R*,8*R*)-4,8,12-trimethyltridecyl)chromane [29] According to general procedure B, in a N₂ filled glovebox, DTB-DPPBz (5.9 mg, 0.0066 mmol, 0.033 eq.), Cu(OAc)₂ (30 μ L of a 0.2 M solution in THF, 0.006 mmol, 0.03 eq.), and THF (70 μ L) followed by dimethoxy(methyl)silane (74 μ L, 0.60 mmol, 3 eq.) were added to an oven-dried 2-dram vial with an oven-dried stir bar. In a separate oven-dried 1-dram vial was added (*R*)-2,8-dimethyl-6-(4-penten-1-yloxy)-2-((4*R*,8*R*)-4,8,12-trimethyltridecyl)chromane (94 mg, 0.20 mmol, 1 eq.), THF (100 μ L), and 2-propanol (38 μ L, 0.50 mmol, 2.5 eq.). The solution in the 1-dram vial was added dropwise to the 2-dram vial. The 2-dram vial was capped with a pressure relief cap, removed from the glovebox, and left to stir for 24 h at 60 °C. Upon completion, the product was isolated by flash column chromatography using gradient elution (100 mL of 100% hexanes, 200 mL of 0.5% ethyl acetate in hexanes) to give the pure product as a clear oil (69 mg, 0.15 mmol, 75% yield).

¹H NMR: (400 MHz, CDCl₃) extra proton observed due to signal overlapping with H grease
 δ 6.56 (d, *J* = 3.0 Hz, 1H), 6.44 (d, *J* = 3.0 Hz, 1H), 3.86 (t, *J* = 6.6 Hz, 2H), 2.71 (t, *J* = 6.6 Hz, 2H), 2.14 (s, 3H), 1.84 – 1.68 (m, 4H), 1.61 – 1.49 (m, 4H), 1.45 – 1.32 (m, 8H), 1.30 – 1.19 (m, 11H), 1.17 – 1.00 (m, 7H), 0.96 – 0.81 (m, 15H).

¹³C NMR: (101 MHz, CDCl₃)
 δ 151.77, 146.14, 127.22, 121.03, 115.53, 111.92, 75.64, 68.54, 40.11, 39.52, 37.60, 37.57, 37.43, 32.95, 32.84, 31.55, 29.35, 28.43, 28.13, 24.96, 24.60, 24.29, 22.88, 22.84, 22.78, 22.65, 21.13, 19.90, 19.81, 16.36, 14.20.

ATR-IR (cm⁻¹):
 2925, 2867, 1606, 1468, 1216, 1057.

HRMS: (ESI⁺) *m/z*: [M+H]⁺ Calcd for C₃₂H₅₇DO₂ 473.4258; Found 473.4353.



2,4,6-Trichloro-4-(5-(4,5-*d*₂)-pentan-1-yloxy)-benzene [30] According to general procedure B, in a N₂ filled glovebox, DTB-DPPBz (8.9 mg, 0.0099 mmol, 0.033 eq.), Cu(OAc)₂ (45 μ L of a 0.2 M solution in THF, 0.009 mmol, 0.03 eq.), and THF (105 μ L) followed by dimethoxy(methyl)silane-*d* (198 μ L of a 6.05 M solution in hexane, 1.20 mmol, 4 eq.) were added to an oven-dried 2-dram vial with an oven-dried stir bar. In a separate oven-dried 1-dram vial was added 2,4,6-trichloro-4-(5-pentan-1-yloxy)-benzene (80 mg, 0.30 mmol, 1 eq.), THF (150 μ L), and 2-propanol-*d*₈ (57 μ L, 0.75 mmol, 2.5 eq.). The solution in the 1-dram vial was added dropwise to the 2-dram vial. The 2-dram vial was capped with a pressure relief cap, removed from the glovebox, and left to stir for 24 h at 40 °C. Upon completion, the product was isolated by flash column chromatography using gradient elution (200 mL of 100% hexanes, 100 mL of 1% ethyl acetate in hexanes) to give the pure product as a colorless oil (75 mg, 0.28 mmol, 93% yield).

¹H NMR: (400 MHz, CDCl₃)
 δ 7.29 (s, 2H), 3.98 (t, *J* = 6.6 Hz, 2H), 1.89 – 1.78 (m, 2H), 1.48 (q, *J* = 7.6 Hz, 2H), 1.43 – 1.32 (m, 1.19H), 0.96 – 0.88 (m, 2.04H).

²H NMR: (61 MHz, CHCl₃)

δ 1.36 (s, 0.81D), 0.91 (s, 0.96D).

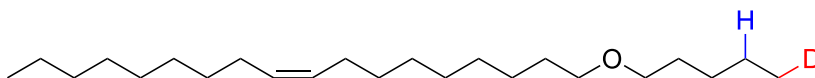
¹³C NMR: (101 MHz, CDCl₃)

δ 150.89, 130.27, 129.31, 128.83, 74.11, 29.82, 27.93, 22.13 (t, J = 19.2 Hz), 13.75 (t, J = 19.1 Hz).

ATR-IR (cm⁻¹):

2928, 2857, 2169, 1448, 1256, 1138.

HRMS: (EI⁺) m/z : [M]⁺ Calcd for C₁₁H₁₁D₂OCl₃ 268.0158; Found 268.0149.



(Z)-(5-*d*-pentan-1-yloxy)-9-octadecene [31] According to general procedure B, in a N₂ filled glovebox, DTB-DPPBz (5.9 mg, 0.0066 mmol, 0.033 eq.), Cu(OAc)₂ (30 μ L of a 0.2 M solution in THF, 0.006 mmol, 0.03 eq.), and THF (70 μ L) followed by dimethoxy(methyl)silane (74 μ L, 0.60 mmol, 3 eq.) were added to an oven-dried 2-dram vial with an oven-dried stir bar. In a separate oven-dried 1-dram vial was added (Z)-(5-*d*-pentan-1-yloxy)-9-octadecene (67 mg, 0.20 mmol, 1 eq.), THF (100 μ L), and 2-propanol-*d*₈ (38 μ L, 0.50 mmol, 2.5 eq.). The solution in the 1-dram vial was added dropwise to the 2-dram vial. The 2-dram vial was capped with a pressure relief cap, removed from the glovebox, and left to stir for 24 h at 40 °C. Upon completion, the product was isolated by flash column chromatography using gradient elution (100mL of 100% hexanes, 100mL of 1% ethyl acetate in hexanes, 100mL of 2% ethyl acetate in hexanes) to give the pure product as a colorless oil (61 mg, 0.18 mmol, 90% yield).

¹H NMR: (400 MHz, CDCl₃)

δ 5.40 – 5.29 (m, 2H), 3.39 (t, J = 6.8 Hz, 4H), 2.09 – 1.96 (m, 4H), 1.61 – 1.52 (m, 4H), 1.39 – 1.23 (m, 26H), 0.92 – 0.84 (m, 5.02H).

²H NMR: (61 MHz, CHCl₃)

δ 0.88. (s, 0.98D).

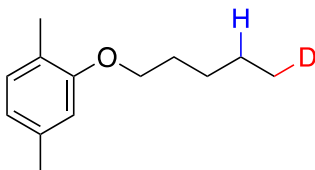
¹³C NMR: (101 MHz, CDCl₃)

δ 130.04, 129.97, 71.10, 71.10, 32.06, 29.92, 29.90, 29.68, 29.68, 29.65, 29.65, 29.63, 29.47, 29.47, 29.40, 28.49, 27.34, 27.33, 26.34, 22.83, 22.62, 14.26, 13.90 (t = 19.1 Hz).

ATR-IR (cm⁻¹):

2924, 2856, 2173, 1465, 1117.

HRMS: (ESI⁺) m/z : [M+H]⁺ Calcd for C₂₃H₄₆DO 340.3689; Found 340.3686.



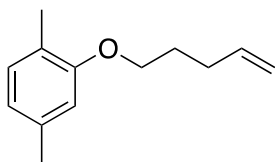
1,4-dimethyl-2-((pentyl-5-*d*)oxy)-benzene [2a] According to general procedure B, in a N₂ filled glovebox, DTB-DPPBz (156 mg, 0.174 mmol, 0.033 eq.), Cu(OAc)₂ (29 mg, 0.158 mmol, 0.03 eq.), and THF (3 mL) followed by dimethoxy(methyl)silane (1.95 mL, 15.78 mmol, 3 eq.) were added to an oven-dried 50 mL round bottom flask with an oven-dried stir bar. In a separate oven-dried 2-dram vial was added 1,4-dimethyl-2-(4-penten-1-yloxy)benzene (1.00 g, 5.26 mmol, 1 eq.), THF (2.26 mL), and 2-propanol-*d*₈ (1.01 mL, 13.15 mmol, 2.5 eq.). The solution in the 2-dram vial was added dropwise to the round bottom flask. The reaction was left for 10 minutes in the glovebox stirring. Once the reaction settled from bubbling, it was capped tightly with a rubber septum and sealed with parafilm, removed from the glovebox, and left to stir for 19 h at 40 °C under N₂. Upon completion, the product was isolated by flash column chromatography (400 mL of 100%

HPLC hexanes using 5 inches of silica gel) to give the pure product as a clear and colorless oil (925 mg, 4.79 mmol, 91% yield). The spectra were consistent with our previously obtained spectra for 2a in table 1.

Synthesis of Alkene Substrates

General Procedure for William Ether Synthesis (C)

Adapted from a previously reported procedure³, in a 25 mL oven-dried Schlenk flask equipped with an oven-dried Teflon stir bar, was added the phenol substrate (2 mmol, 1 eq.), K₂CO₃ (5 mmol, 2.5 eq.), and acetonitrile (0.25 M). To the stirring mixture, 5-bromopentene (2 eq.) was added and the reaction was allowed to reflux (90 °C) under N₂. Upon completion, the reaction was concentrated *in vacuo* followed by addition of H₂O to quench the reaction and extracted with CH₂Cl₂. The combined organic layers were washed with H₂O and brine and then dried over Na₂SO₄. The mixture was gravity filtered and concentrated *in vacuo* to afford the pure product.



1,4-dimethyl-2-(4-penten-1-yloxy)-benzene [1] was prepared according to procedure C, in a 25 mL oven-dried Schlenk flask equipped with an oven-dried Teflon stir bar, was added 2,5-dimethylphenol (1.5 g, 12.3 mmol, 1 eq.), K₂CO₃ (4.26 g, 30.8 mmol, 2.5 eq.), and acetonitrile (49 mL, 0.25 M). To this stirring mixture, 5-bromopentene (2.9 mL, 24.6 mmol, 2 eq) was added and the reaction was allowed to reflux (90 °C) under N₂. Upon completion, the reaction was concentrated *in vacuo* followed by addition of H₂O (40 mL) to quench the reaction and extracted with CH₂Cl₂ (3 x 45 mL). The combined organic layers were washed with H₂O (40 mL) and brine (40 mL) and then dried over Na₂SO₄. This was gravity filtered and concentrated *in vacuo* to afford the pure product as a clear and colorless oil (1.78 g, 9.35 mmol, 76% yield).

¹H NMR: (400 MHz, CDCl₃)

δ 7.01 (d, *J* = 7.4 Hz, 1H), 6.67 (d, *J* = 7.6 Hz, 1H), 6.64 (s, 1H), 5.88 (ddt, *J* = 16.9, 10.1, 6.6 Hz, 1H), 5.07 (dd, *J* = 17.1, 1.2 Hz, 1H), 5.01 (dd, *J* = 10.2, 1.0 Hz, 1H), 3.96 (t, *J* = 6.3 Hz, 2H), 2.32 (s, 3H), 2.31 – 2.22 (q, *J* = 7.3 Hz, 2H), 2.19 (s, 3H), 1.96 – 1.85 (m, 2H).

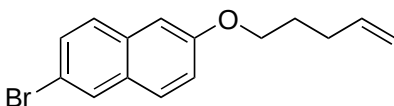
¹³C NMR: (101 MHz, CDCl₃)

δ 157.14, 138.19, 136.60, 130.42, 123.77, 120.77, 115.18, 112.10, 67.12, 30.42, 28.78, 21.56, 15.95.

ATR-IR (cm⁻¹):

3077, 2942, 2868, 1614, 1508, 1413, 1262, 1129, 1041.

HRMS: (ESI⁺) *m/z*: [M+H]⁺ Calcd for C₁₃H₁₉O 191.1436; Found 191.1427.



2-Bromo-6-(4-penten-1-yloxy)-naphthalene [3-SM] was prepared according to procedure C, in a 25 mL oven-dried Schlenk flask equipped with an oven-dried Teflon stir bar, was added 6-bromo-2-naphthalenol (0.669 g, 3.00 mmol, 1 eq.), K₂CO₃ (1.04 g, 7.50 mmol, 2.5 eq.), and acetonitrile (12 mL, 0.25 M). To this stirring mixture, 5-bromopentene (0.711 mL, 6.00 mmol, 2 eq) was added and the reaction was allowed to reflux (90 °C) under N₂. Upon completion, the reaction was concentrated *in vacuo* followed by addition of H₂O (10 mL) to quench the reaction and extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were washed with H₂O (10 mL) and brine (10 mL) and then dried over Na₂SO₄. This was gravity filtered and concentrated *in vacuo* to afford the pure product as an off white solid (0.830 g, 2.85 mmol, 95% yield).

¹H NMR: (400 MHz, CDCl₃)

δ 7.91 (s, 1H), 7.64 (d, J = 9.0 Hz, 1H), 7.58 (d, J = 8.7 Hz, 1H), 7.49 (dd, J = 8.7, 2.1 Hz, 1H), 7.17 (dd, J = 9.1, 2.4 Hz, 1H), 7.08 (s, 1H), 5.89 (ddt, J = 16.9, 10.2, 6.7 Hz, 1H), 5.10 (d, J = 17.2 Hz, 1H), 5.04 (d, J = 10.2 Hz, 1H), 4.07 (t, J = 6.5 Hz, 2H), 2.29 (q, J = 7.2 Hz, 2H), 2.01 – 1.90 (m, 2H).

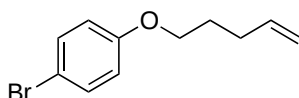
^{13}C NMR: (101 MHz, CDCl_3)

δ 157.43, 137.87, 133.19, 130.06, 129.75, 129.67, 128.56, 128.47, 120.16, 117.05, 115.46, 106.61, 67.34, 30.28, 28.46.

ATR-IR (cm^{-1}):

3073.77, 2945.36, 1642.08, 1623.71, 1498.73, 1261.00.

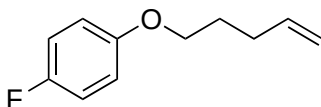
HRMS: (EI^+) m/z : $[\text{M}]^+$ Calcd for $\text{C}_{15}\text{H}_{15}\text{OBr}$ 290.0306; Found 290.0300.



1-bromo-4-(4-penten-1-yloxy)-benzene [4-SM] was prepared according to procedure C, in a 25 mL oven-dried Schlenk flask equipped with an oven-dried Teflon stir bar, was added 4-bromophenol (0.520 g, 3.00 mmol, 1 eq.), K_2CO_3 (1.04 g, 7.50 mmol, 2.5 eq.), and acetonitrile (12 mL, 0.25 M). To this stirring mixture, 5-bromopentene (0.711 mL, 6.00 mmol, 2 eq.) was added and the reaction was allowed to reflux (90 °C) under N_2 . Upon completion, the reaction was concentrated *in vacuo* followed by addition of H_2O (10 mL) to quench the reaction and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with H_2O (10 mL) and brine (10 mL) and then dried over Na_2SO_4 . This was gravity filtered and concentrated *in vacuo* to afford the pure product as a light-yellow oil (0.469 g, 1.95 mmol, 65% yield). The spectra for the title compound matched previously reported spectra.⁴

^1H NMR: (400 MHz, CDCl_3)

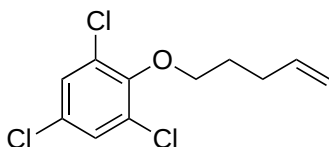
δ 7.36 (d, J = 8.8 Hz, 2H), 6.78 (d, J = 8.8 Hz, 2H), 5.85 (ddt, J = 17.0, 10.2, 6.7 Hz, 1H), 5.07 (d, J = 17.1 Hz, 1H), 5.01 (d, J = 10.2 Hz, 1H), 3.93 (t, J = 6.4 Hz, 2H), 2.24 (q, J = 7.0 Hz, 2H), 1.88 (p, J = 6.9 Hz, 2H).



1-fluoro-4-(4-penten-1-yloxy)-benzene [5-SM] was prepared according to procedure C, in a 25 mL oven-dried Schlenk flask equipped with an oven-dried Teflon stir bar, was added 4-fluorophenol (0.224 g, 2.00 mmol, 1 eq.), K_2CO_3 (0.691 g, 5.00 mmol, 2.5 eq.), and acetonitrile (8.0 mL, 0.25 M). To this stirring mixture, 5-bromopentene (0.474 mL, 4.00 mmol, 2 eq.) was added and the reaction was allowed to reflux (90 °C) under N_2 . Upon completion, the reaction was concentrated *in vacuo* followed by addition of H_2O (10 mL) to quench the reaction and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with H_2O (10 mL) and brine (10 mL) and then dried over Na_2SO_4 . This was gravity filtered and concentrated *in vacuo* to afford the pure product as a yellow oil (0.293 g, 1.63 mmol, 82% yield). The spectra for the title compound matched previously reported spectra.⁵

^1H NMR: (400 MHz, CDCl_3)

δ 7.02 – 6.91 (m, 2H), 6.88 – 6.78 (m, 2H), 5.85 (ddt, J = 16.9, 10.0, 6.6 Hz, 1H), 5.07 (dd, J = 17.1, 1.8 Hz, 1H), 5.01 (dd, J = 10.7, 1.5 Hz, 1H), 3.93 (t, J = 6.4 Hz, 2H), 2.29 – 2.18 (m, 2H), 1.93 – 1.82 (m, 2H).



2,4,6-Trichloro-4-(4-penten-1-yloxy)-benzene [6-SM] was prepared according to procedure C, in a 25 mL oven-dried Schlenk flask equipped with an oven-dried Teflon stir bar, was added 2,4,6-trichlorophenol (0.395

g, 2.00 mmol, 1 eq.), K_2CO_3 (0.691 g, 5.00 mmol, 2.5 eq.), and acetonitrile (8.0 mL, 0.25 M). To this stirring mixture, 5-bromopentene (0.474 mL, 4.00 mmol, 2 eq.) was added and the reaction was allowed to reflux (90 °C) under N_2 . Upon completion, the reaction was concentrated *in vacuo* followed by addition of H_2O (10 mL) to quench the reaction and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with H_2O (10 mL) and brine (10 mL) and then dried over Na_2SO_4 . This was gravity filtered and concentrated *in vacuo* to afford the pure product as a colorless oil (0.271 g, 1.02 mmol, 51% yield).

$^1\text{H NMR}$: (400 MHz, CDCl_3)

δ 7.30 (s, 2H), 5.87 (ddt, $J = 16.9, 10.2, 6.6$ Hz, 1H), 5.09 (dd, $J = 17.1, 1.5$ Hz, 1H), 5.01 (dd, $J = 10.3, 1.3$ Hz, 1H), 4.00 (t, $J = 6.4$ Hz, 2H), 2.35 – 2.36 (m, 2H), 1.94 (p, $J = 6.6$ Hz, 2H).

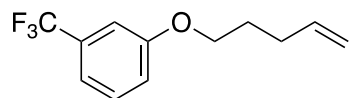
$^{13}\text{C NMR}$: (101 MHz, CDCl_3)

δ 150.78, 137.91, 130.23, 129.40, 128.84, 115.32, 73.31, 30.10, 29.36.

ATR-IR (cm^{-1}):

3079.23, 2945.36, 1642.08, 1448.12, 1255.28, 1039.49

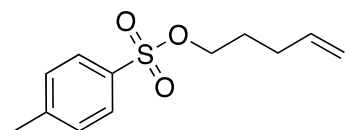
HRMS: (EI^+) m/z : $[\text{M}]^+$ Calcd for $\text{C}_{11}\text{H}_{11}\text{OCl}_3$ 263.9875; Found 263.9871.



1-(4-penten-1-yloxy)-3-(trifluoromethyl)-benzene [7-SM] was prepared according to procedure C, in a 25 mL oven-dried Schlenk flask equipped with an oven-dried Teflon stir bar, was added 3-(trifluoromethyl)-phenol (0.324 g, 2.00 mmol, 1 eq.), K_2CO_3 (0.691 g, 5.00 mmol, 2.5 eq.), and acetonitrile (8.0 mL, 0.25 M). To this stirring mixture, 5-bromopentene (0.474 mL, 4.00 mmol, 2 eq.) was added and the reaction was allowed to reflux (90 °C) under N_2 . Upon completion, the reaction was concentrated *in vacuo* followed by addition of H_2O (10 mL) to quench the reaction and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with H_2O (10 mL) and brine (10 mL) and then dried over Na_2SO_4 . This was gravity filtered and concentrated *in vacuo* to afford the pure product as a clear and colorless oil (0.388 g, 1.69 mmol, 85% yield). The spectra for the title compound matched previously reported spectra.⁶

$^1\text{H NMR}$: (400 MHz, CDCl_3)

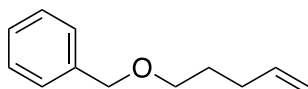
δ 7.42 – 7.33 (m, 1H), 7.19 (d, $J = 7.6$ Hz, 1H), 7.12 (s, 1H), 7.09 – 7.02 (m, 1H), 5.86 (ddt, $J = 16.9, 10.2, 6.6$ Hz, 1H), 5.07 (d, $J = 17.1$ Hz, 1H), 5.02 (d, $J = 10.2$ Hz, 1H), 4.00 (t, $J = 6.4$ Hz, 2H), 2.31 – 2.20 (q, m, 2H), 1.91 (p, $J = 6.6$ Hz, 2H).



1-(4-methylbenzenesulfonate)-4-penten-1-ol [8-SM] Adapted from a previously reported procedure⁷, in an oven-dried 25 mL Schlenk flask with an oven dried Teflon stir bar, was added dry CH_2Cl_2 (5.0 mL, 0.40 M), and 4-penten-1-ol (0.206 mL, 2.00 mmol, 1 eq.) at 0 °C and stirred. Dry Et_3N (0.334 mL, 2.40 mmol, 1.2 eq.) and 4-toluenesulfonyl chloride (0.381 g, 2.00 mmol, 1 eq.) were added sequentially and the reaction stirred to room temperature overnight. Upon completion, sat. NaHCO_3 (15 mL) was added, and the reaction mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine (10 mL) and dried over Na_2SO_4 . The crude reaction mixture was purified by flash column chromatography using gradient elution (100 mL of 100% hexanes, 100 mL of 25% CH_2Cl_2 in hexanes, 150 mL of 50% CH_2Cl_2 in hexanes) to afford the pure product as a clear and colorless oil (0.319 g, 1.33 mmol, 67% yield). The spectra for the title compound matched previously reported spectra.⁸

$^1\text{H NMR}$: (400 MHz, CDCl_3)

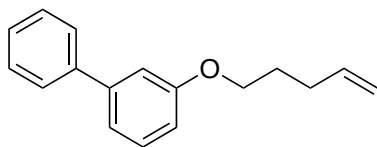
δ 7.78 (d, $J = 8.1$ Hz, 2H), 7.34 (d, $J = 8.1$ Hz, 2H), 5.75 – 5.62 (m, 1H), 5.00 – 4.90 (m, 2H), 4.03 (t, $J = 6.4$ Hz, 2H), 2.45 (s, 3H), 2.13 – 2.02 (m, 2H), 1.74 (p, $J = 6.6$ Hz, 2H).



[(4-penten-1-yloxy)methyl]benzene [9-SM] Adapted from a previously reported procedure⁹, in an oven-dried 25 mL Schlenk flask under N₂ with an oven dried Teflon stir bar, was added 4-penten-1-ol (0.300 mL, 2.90 mmol, 1 eq.) and THF (2.9 mL, 1.0 M). The solution was cooled to 0 °C and NaH (128 mg, 60% w/w dispersion in mineral oil, 3.19 mmol, 1.1 eq.) was added. The reaction stirred for 20 mins and Benzyl Bromide (0.38 mL, 3.19 mmol, 1.1 eq.) was added. After 5 h, the reaction was quenched with H₂O (10 mL) and extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were washed with brine (10 mL) and dried over Na₂SO₄. The crude reaction mixture was isolated by flash column chromatography using gradient elution (150 mL of 100% hexanes, 200 mL of 1% ethyl acetate in hexanes) to afford the pure product as a clear and colorless oil (0.408 g, 2.31 mmol, 80% yield). The spectra for the title compound matched previously reported spectra.⁹

¹H NMR: (400 MHz, CDCl₃)

δ 7.37 – 7.32 (m, 4H), 7.32 – 7.27 (m, 1H), 5.83 (ddt, *J* = 16.9, 10.3, 6.7 Hz, 1H), 5.08 – 4.99 (m, 1H), 4.99 – 4.94 (m, 1H), 4.51 (s, 2H), 3.49 (t, *J* = 6.5 Hz, 2H), 2.21 – 2.10 (m, 2H), 1.73 (p, *J* = 6.6 Hz, 2H).



3-(4-penten-1-yloxy)-1,1'-biphenyl [10-SM] was prepared according to procedure C, in a 25 mL oven-dried Schlenk flask equipped with an oven-dried Teflon stir bar, was added 3-phenylphenol (0.511 g, 3.00 mmol, 1 eq.), K₂CO₃ (1.04 g, 7.50 mmol, 2.5 eq.), and acetonitrile (12 mL, 0.25 M). To this stirring mixture, 5-bromopentene (0.71 mL, 6.00 mmol, 2 eq.) was added and the reaction was allowed to reflux (90 °C) under N₂. Upon completion, the reaction was concentrated *in vacuo* followed by addition of H₂O (10 mL) to quench the reaction and extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were washed with H₂O (10 mL) and brine (10 mL) and then dried over Na₂SO₄. This was gravity filtered and concentrated *in vacuo* to afford the pure product as a yellow oil (0.589 g, 2.5 mmol, 83% yield).

¹H NMR: (400 MHz, CDCl₃)

δ 7.65 – 7.58 (m, 2H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.37 (t, *J* = 8.0 Hz, 2H), 7.20 (d, *J* = 7.6 Hz, 1H), 7.17 – 7.15 (m, 1H), 6.95 – 6.88 (m, 1H), 5.90 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.11 (dd, *J* = 17.1, 1.8 Hz, 1H), 5.04 (dd, *J* = 10.2, 1.7 Hz, 1H), 4.06 (t, *J* = 6.4 Hz, 2H), 2.33 – 2.24 (m, 2H), 1.99 – 1.90 (m, 2H).

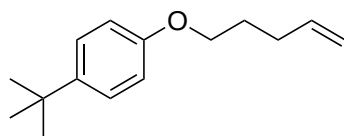
¹³C NMR: (101 MHz, CDCl₃)

δ 159.49, 142.72, 141.15, 137.86, 129.78, 128.77, 127.42, 127.21, 119.57, 115.28, 113.55, 113.24, 67.14, 30.20, 28.53.

ATR-IR (cm⁻¹):

3063, 2940, 2871, 1596, 1470, 1202, 1053, 938.

HRMS: (ESI⁺) *m/z*: [M+H]⁺ Calcd for C₁₇H₁₉O 239.1436; Found 239.1430.

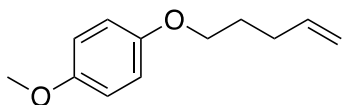


4-(tert-butyl)-1-(pent-4-en-1-yloxy)benzene [11-SM] was prepared according to procedure C, in a 25 mL oven-dried Schlenk flask equipped with an oven-dried Teflon stir bar, was added 4-tertbutylphenol (1.00 g, 6.66 mmol, 1 eq.), K₂CO₃ (2.31 g, 16.7 mmol, 2.5 eq.), and acetonitrile (13 mL, 0.5 M). To this stirring mixture, 5-bromopentene (1.6 mL, 13.3 mmol, 2 eq) was added and the reaction was allowed to reflux (90

°C) under N₂. Upon completion, the reaction was concentrated *in vacuo* followed by addition of H₂O (10 mL) to quench the reaction and extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were washed with H₂O (10 mL) and brine (10 mL) and then dried over Na₂SO₄. This was gravity filtered and concentrated *in vacuo* to afford the pure product as a clear and colorless oil (1.29 g, 5.91 mmol, 89% yield). The spectra for the title compound matched previously reported spectra.¹⁰

¹H NMR: (400 MHz, CDCl₃)

δ 7.32 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 5.88 (ddt, *J* = 16.9, 10.1, 6.5 Hz, 1H), 5.08 (dd, *J* = 17.1, 1.8 Hz, 1H), 5.02 (dd, *J* = 10.2, 2.0 Hz, 1H), 3.97 (t, *J* = 6.4 Hz, 2H), 2.26 (q, *J* = 7.0 Hz, 2H), 1.97 – 1.82 (m, 2H), 1.32 (s, 9H).



1-methoxy-4-(4-penten-1-yloxy)-benzene [12-SM] was prepared according to procedure C, in a 25 mL oven-dried Schlenk flask equipped with an oven-dried Teflon stir bar, was added 4-methoxyphenol (0.248 g, 2.00 mmol, 1 eq), K₂CO₃ (0.691 g, 5.00 mmol, 2.5 eq.), and acetonitrile (8.0 mL, 0.25 M). To this stirring mixture, 5-bromopentene (0.47 mL, 4.00 mmol, 2 eq.) was added and the reaction was allowed to reflux (90 °C) under N₂. Upon completion, the reaction was concentrated *in vacuo* followed by addition of H₂O (10 mL) to quench the reaction and extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were washed with H₂O (10 mL) and brine (10 mL) and then dried over Na₂SO₄. This was gravity filtered and concentrated *in vacuo* to afford the pure product as a white solid (0.354 g, 1.84 mmol, 92% yield). The spectra for the title compound matched previously reported spectra.¹⁰

¹H NMR: (400 MHz, CDCl₃)

δ 6.84 (s, 4H), 5.86 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.06 (dd, *J* = 17.1, 1.8 Hz, 1H), 5.00 (dd, *J* = 10.4, 1.8 Hz, 1H), 3.92 (t, *J* = 6.5 Hz, 2H), 3.77 (s, 3H), 2.29 – 2.18 (m, 2H), 1.86 (p, *J* = 6.6 Hz, 2H).

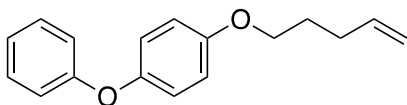
¹³C NMR: (101 MHz, CDCl₃)

δ 153.86, 153.35, 138.06, 115.60, 115.25, 114.75, 67.99, 55.88, 30.26, 28.68.

ATR-IR (cm⁻¹):

3075, 2940, 2870, 1505, 1226, 1037.

HRMS: (ESI⁺) *m/z*: [M+H]⁺ Calcd for C₁₂H₁₇O₂ 193.1228; Found 193.1224.



4-phenoxy-1-(4-penten-1-yloxy)-benzene [13-SM] was prepared according to procedure C, in a 25 mL oven-dried Schlenk flask equipped with an oven-dried Teflon stir bar, was added 4-phenoxyphenol (0.125 g, 0.671 mmol, 1 eq.), K₂CO₃ (0.232 g, 1.68 mmol, 2.5 eq.), and acetonitrile (2.7 mL, 0.25 M). To this stirring mixture, 5-bromopentene (0.16 mL, 1.34 mmol, 2 eq.) was added and the reaction was allowed to reflux (90 °C) under N₂. Upon completion, the reaction was concentrated *in vacuo* followed by addition of H₂O (10 mL) to quench the reaction and extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were washed with H₂O (10 mL) and brine (10 mL) and then dried over Na₂SO₄. This was gravity filtered and concentrated *in vacuo* to afford the pure product as a white solid (0.154 g, 0.61 mmol, 91% yield).

¹H NMR: (400 MHz, CDCl₃)

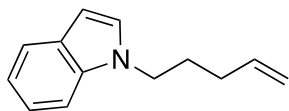
δ 7.35 – 7.23 (m, 2H), 7.08 – 7.00 (m, 1H), 7.00 – 6.91 (m, 4H), 6.91 – 6.84 (m, 2H), 5.87 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.14 – 4.96 (m, 2H), 3.96 (t, *J* = 6.4 Hz, 2H), 2.32 – 2.19 (m, 2H), 1.97 – 1.81 (m, 2H).

¹³C NMR: (101 MHz, CDCl₃)

δ 158.67, 155.51, 150.13, 137.97, 129.74, 122.52, 120.95, 117.70, 115.64, 115.35, 67.79, 30.27, 28.62.

ATR-IR (cm⁻¹):

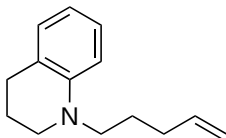
3079, 2936, 2874, 1590, 1470, 1214, 1022.

HRMS: (ESI⁺) *m/z*: [M+H]⁺ Calcd for C₁₇H₁₉O₂ 255.1385; Found 255.1373.

1-(4-penten-1-yl)-1H-indole [14-SM] Adapted from a previously reported procedure¹², in an oven dried 100 mL round bottom with an oven dried stir bar under N₂, equip the flask with 1H-indole (0.500 g, 4.3 mmol, 1 eq.), potassium hydroxide (0.241 g, 4.3 mmol, 1 eq.), and dimethylformamide (20 mL, 0.22 M). To this stirring solution, 5-bromopentene (1.0 mL, 8.6 mmol, 2 eq.) was added and the reaction heated to 60 °C overnight. Upon completion, the reaction was quenched with H₂O (40 mL) and extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layer was washed with H₂O (15 mL), brine (15 mL) and dried over Na₂SO₄. The crude reaction was isolated by flash column chromatography using gradient elution (300 mL of 100% hexanes, 100 mL of 1% ethyl acetate in hexanes) to give the pure product as a clear and colorless oil (0.601 g, 3.24 mmol, 75% yield). The spectra for the title compound matched previously reported spectra.¹³

¹H NMR: (400 MHz, CDCl₃)

δ 7.65 (d, *J* = 7.9 Hz, 1H), 7.36 (d, *J* = 8.2 Hz, 1H), 7.23 (t, *J* = 7.7 Hz, 1H), 7.16 – 7.08 (m, 2H), 6.51 (d, *J* = 3.0 Hz, 1H), 5.82 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 1H), 5.10 – 5.00 (m, 2H), 4.15 (t, *J* = 7.0 Hz, 2H), 2.09 (q, *J* = 7.1 Hz, 2H), 1.96 (p, *J* = 7.1 Hz, 2H).



1-(pent-4-en-1-yl)-1,2,3,4-tetrahydroquinoline [15-SM]. was prepared according to procedure C, in a 25 mL oven-dried Schlenk flask equipped with an oven-dried Teflon stir bar, was added 1,2,3,4-tetrahydroquinoline (0.300 g, 2.25 mmol, 1 eq.), K₂CO₃ (0.778 g, 5.63 mmol, 2.5 eq.), and acetonitrile (4.5 mL, 0.50 M). To this stirring mixture, 5-bromopentene (0.533 mL, 4.50 mmol, 2 eq.) was added and the reaction was allowed to reflux (90 °C) under N₂. Upon completion, H₂O (10 mL) was added to quench the reaction and extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layer was washed with H₂O (15 mL), brine (20 mL) and then dried over Na₂SO₄. The crude product was purified by flash column chromatography using gradient elution (100 mL of 100% hexanes, 250 mL of 2% ethyl acetate in hexanes) to give the pure product as a light brown oil (0.314 g, 1.56 mmol, 69% yield).

¹H NMR: (400 MHz, CDCl₃)

δ 7.06 (t, *J* = 7.4 Hz, 1H), 6.96 (d, *J* = 7.0 Hz, 1H), 6.62 – 6.54 (m, 2H), 5.95 – 5.80 (m, 1H), 5.12 – 4.98 (m, 2H), 3.34 – 3.23 (m, 4H), 2.83 – 2.74 (m, 2H), 2.18 – 2.08 (m, 2H), 2.03 – 1.91 (m, 2H), 1.78 – 1.67 (m, 2H).

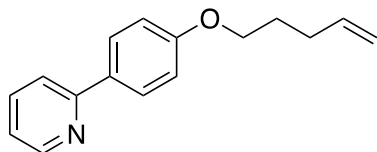
¹³C NMR: (101 MHz, CDCl₃)

δ 145.37, 138.35, 129.27, 127.17, 122.29, 115.38, 115.01, 110.55, 51.01, 49.60, 31.44, 28.30, 25.40, 22.34.

ATR-IR (cm⁻¹):

3066, 2930, 2840, 1601, 1503, 1456, 1345.

HRMS: (ESI⁺) *m/z*: [M+H]⁺ Calcd for C₁₄H₂₀N 202.1595; Found 202.1600.



2-[4-(4-penten-1-yloxy)-phenyl]-pyridine [16-SM] was prepared according to procedure C, in a 25 mL oven-dried Schlenk flask equipped with an oven-dried Teflon stir bar, was added 4-(2-pyridinyl)-phenol (0.342 g, 2 mmol, 1 eq.), K_2CO_3 (0.691 g, 5.00 mmol, 2.5 eq.), and acetonitrile (8.0 mL, 0.25 M). To this stirring mixture, 5-bromopentene (0.47 mL, 4.00 mmol, 2 eq.) was added and the reaction was allowed to reflux (90 °C) under N_2 . Upon completion, the reaction was concentrated *in vacuo* followed by addition of H_2O (10 mL) to quench the reaction and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with H_2O (10 mL) and brine (10 mL) and then dried over Na_2SO_4 . This was gravity filtered and concentrated *in vacuo* to afford the pure product as a light purple solid (0.415 g, 1.73 mmol, 87% yield).

1H NMR: (400 MHz, $CDCl_3$)

δ 8.68 – 8.62 (m, 1H), 7.94 (d, J = 8.5 Hz, 2H), 7.74 – 7.63 (m, 2H), 7.21 – 7.12 (m, 1H), 6.99 (d, J = 8.5 Hz, 2H), 5.87 (ddt, J = 17.1, 10.0, 6.6 Hz, 1H), 5.08 (d, J = 17.2 Hz, 1H), 5.01 (d, J = 10.2 Hz, 1H), 4.03 (t, J = 6.5 Hz, 2H), 2.31 – 2.21 (m, 2H), 1.91 (p, J = 6.8 Hz, 2H).

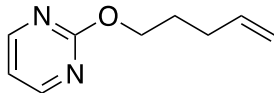
^{13}C NMR: (101 MHz, $CDCl_3$)

δ 160.07, 157.29, 149.67, 137.92, 136.77, 132.02, 128.25, 121.50, 119.91, 115.39, 114.80, 67.36, 30.24, 28.54.

ATR-IR (cm^{-1}):

3046, 2948, 2908, 1462, 1244, 1034.

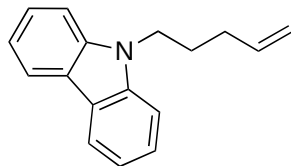
HRMS: (ESI⁺) m/z : $[M+H]^+$ Calcd for $C_{16}H_{18}NO$ 240.1388; Found 240.1398.



2-(4-penten-1-yloxy)pyrimidine [17-SM]. Adapted from a previously reported procedure¹¹, in a 100 mL oven-dried round bottom flask equipped with an oven-dried Teflon stir bar, was 2-pyrimidinecarbonitrile (1.00 g, 9.50 mmol, 1 eq.), Cs_2CO_3 (3.10 g, 9.50 mmol, 1 eq.), and 4-penten-1-ol (1.48 mL, 14.3 mmol, 1.5 eq.) in dry dimethylsulfoxide (20 mL, 0.48 M). The reaction stirred overnight at 80 °C under N_2 . Upon completion, the reaction was quenched with H_2O (12 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with H_2O (20 mL) and brine (20 mL) and then dried over Na_2SO_4 . The crude product was purified by flash column chromatography using gradient elution (100 mL of 100% hexanes, 100 mL of 5% ethyl acetate in hexanes, 100 mL of 10% ethyl acetate in hexanes, 500 mL of 20% ethyl acetate in hexanes) to give the pure product as a clear colorless oil (1.35 g, 8.2 mmol, 86% yield). The spectra for the title compound matched previously reported spectra.⁷

1H NMR: (400 MHz, $CDCl_3$)

δ 8.47 (d, J = 4.8 Hz, 2H), 6.88 (t, J = 4.8 Hz, 1H), 5.81 (ddt, J = 16.9, 10.2, 6.6 Hz, 1H), 5.03 (d, J = 17.1 Hz, 1H), 4.95 (d, J = 10.2 Hz, 1H), 4.32 (t, J = 6.6 Hz, 2H), 2.27 – 2.16 (m, 2H), 1.88 (p, J = 6.8 Hz, 2H).

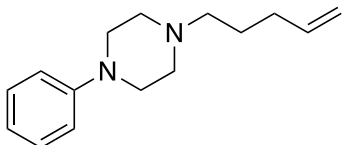


9-(4-penten-1-yl)-9H-carbazole [18-SM] Adapted from a previously reported procedure¹², in a 250 mL round bottom with a Teflon stir bar, was added dimethylformamide (30 mL, 0.10 M) and potassium hydroxide (0.168 g, 3.00 mmol, 1 eq.) under N_2 . 5-bromopentene (0.71 mL, 6.00 mmol, 2 eq.) and 9H-carbazole (0.520 g, 3.00 mmol, 1 eq.) were added sequentially and the reaction stirred at 50 °C overnight.

Upon completion, the reaction was quenched with H₂O (30 mL) and extracted with ether (3 x 20 mL). The combined organic layers were washed with brine (20 mL) and dried over Na₂SO₄. The crude mixture was purified by flash column chromatography using gradient elution (100 mL of 100% hexanes, 300 mL of 2% ethyl acetate in hexanes) to afford a pure white solid (0.448 g, 1.90 mmol, 63% yield). The spectra for the title compound matched previously reported spectra.¹²

¹H NMR: (400 MHz, CDCl₃)

δ 8.15 (d, *J* = 7.7 Hz, 2H), 7.54 – 7.47 (m, 2H), 7.47 – 7.41 (m, 2H), 7.32 – 7.23 (m, 2H), 5.88 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 1H), 5.16 – 5.04 (m, 2H), 4.35 (t, *J* = 7.2 Hz, 2H), 2.18 (q, *J* = 7.0 Hz, 2H), 2.02 (p, *J* = 7.3 Hz, 2H).



1-(4-penten-1-yl)-4-phenyl-piperazine [19-SM] was prepared according to procedure C, in a 25 mL oven-dried Schlenk flask equipped with an oven-dried Teflon stir bar, was added 1-Phenylpiperazine (0.325 g, 2 mmol, 1 eq.), K₂CO₃ (0.691 g, 5.00 mmol, 2.5 eq.), and acetonitrile (8.0 mL, 0.25 M). To this stirring mixture, 5-bromopentene (0.47 mL, 4.00 mmol, 2 eq.) was added and the reaction was allowed to reflux (90 °C) under N₂. Upon completion, the reaction was concentrated *in vacuo* followed by addition of H₂O (10 mL) to quench the reaction and extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were washed with H₂O (10 mL) and brine (10 mL) and then dried over Na₂SO₄. This was gravity filtered and concentrated *in vacuo* to afford the pure product (0.360 g, 1.56 mmol, 78% yield).

¹H NMR: (400 MHz, CDCl₃)

δ 7.33 – 7.21 (m, 2H), 6.97 – 6.90 (m, 2H), 6.90 – 6.80 (m, 1H), 5.84 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.11 – 4.92 (m, 2H), 3.26 – 3.17 (m, 4H), 2.66 – 2.56 (m, 4H), 2.46 – 2.35 (m, 2H), 2.18 – 2.04 (m, 2H), 1.72 – 1.58 (m, 2H).

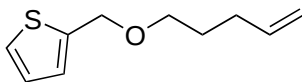
¹³C NMR: (101 MHz, CDCl₃)

δ 151.49, 138.57, 129.22, 119.75, 116.13, 114.84, 58.28, 53.44, 49.28, 31.83, 26.23.

ATR-IR (cm⁻¹):

3062, 2939, 2814, 1599, 1501, 1231, 1141.

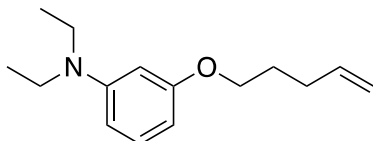
HRMS: (ESI⁺) *m/z*: [M+H]⁺ Calcd for C₁₅H₂₃N₂ 231.1861; Found 231.1898.



2-[(4-penten-1-yloxy)methyl]thiophene [20-SM] was prepared according to procedure C, in a 100 mL oven-dried Schlenk flask equipped with an oven-dried Teflon stir bar, was added 2-thiophene methanol (0.82 mL, 8.76 mmol, 1 eq.), K₂CO₃ (3.03 g, 21.9 mmol, 2.5 eq.), and acetonitrile (35 mL, 0.25 M). To this stirring mixture, 5-bromopentene (2.1 mL, 17.5 mmol, 2 eq) was added and the reaction was allowed to reflux (90 °C) under N₂. An additional 0.5 eq of NaH (60%) in oil dispersion (0.175 g, 4.38 mmol, 0.5 eq.) were added after 12 hours. After 24 hours, H₂O (15 mL) was added to quench the reaction and extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were washed with H₂O (25 mL), Brine (30 mL) and then dried over Na₂SO₄. This was gravity filtered and concentrated *in vacuo* to afford the pure product as a light-yellow oil (0.964 g, 5.29 mmol, 60% yield). The spectra for the title compound matched previously reported spectra.¹³

¹H NMR: (400 MHz, CDCl₃)

δ 7.31 – 7.27 (m, 1H), 7.03 – 6.94 (m, 2H), 5.89 – 5.74 (m, 1H), 5.14 – 4.89 (m, 2H), 4.67 (s, 2H), 3.50 (t, *J* = 6.5 Hz, 2H), 2.14 (q, *J* = 7.1 Hz, 2H), 1.71 (p, *J* = 6.9 Hz, 2H).



***N,N*-diethyl-3-(4-penten-1-yloxy)aniline [21-SM]** was prepared according to procedure C, in a 25 mL oven-dried Schlenk flask equipped with an oven-dried Teflon stir bar, was added 3-*N,N*-(Diethyl)aminophenol (0.5 g, 3.0 mmol, 1 eq.), K₂CO₃ (1.04 g, 7.5 mmol, 2.5 eq.), and acetonitrile (12 mL, 0.25 M). To this stirring mixture, 5-bromopentene (0.71 mL, 6.0 mmol, 2 eq.) was added and the reaction was allowed to reflux (90 °C) under N₂. Upon completion, the reaction was concentrated *in vacuo* followed by addition of H₂O (10 mL) to quench the reaction and extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were washed with H₂O (10 mL) and brine (10 mL) and then dried over Na₂SO₄. This was gravity filtered and concentrated *in vacuo* to afford the pure product as a colorless oil (0.285 g, 1.22 mmol, 41% yield).

¹H NMR: (400 MHz, CDCl₃)

δ 7.11 (t, *J* = 8.0 Hz, 1H), 6.31 (d, *J* = 8.1 Hz, 1H), 6.27 – 6.18 (m, 2H), 5.94 – 5.80 (m, 1H), 5.08 (d, *J* = 16.9 Hz, 1H), 5.01 (d, *J* = 10.1 Hz, 1H), 4.01 – 3.93 (m, 2H), 3.39 – 3.29 (m, 4H), 2.30 – 2.20 (m, 2H), 1.94 – 1.82 (m, 2H), 1.20 – 1.12 (m, 6H).

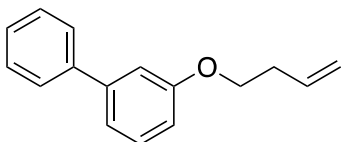
¹³C NMR: (101 MHz, CDCl₃)

δ 160.48, 149.21, 138.05, 129.91, 115.11, 105.04, 100.73, 98.99, 66.98, 44.44, 30.28, 28.66, 12.71.

ATR-IR (cm⁻¹):

3077, 2969, 2870, 1609, 1498, 1275, 1177, 1140.

HRMS: (ESI⁺) *m/z*: [M+H]⁺ Calcd for C₁₅H₂₄NO 234.1858; Found 234.1902.



3-(3-buten-1-yloxy)-1,1'-biphenyl [25-SM] was prepared according to procedure C, in a 25 mL oven-dried Schlenk flask equipped with an oven-dried Teflon stir bar, was added 3-phenylphenol (0.300 g, 1.76 mmol, 1 eq.), K₂CO₃ (0.608 g, 4.4 mmol, 2.5 eq.), and acetonitrile (3.5 mL, 0.50 M). To this stirring mixture, 4-bromobutene (0.36 mL, 3.52 mmol, 2 eq.) was added and the reaction was allowed to reflux (90 °C) under N₂. Upon completion, the reaction was concentrated *in vacuo* followed by addition of H₂O (10 mL) to quench the reaction and extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were washed with H₂O (10 mL) and brine (10 mL) and then dried over Na₂SO₄. This was gravity filtered and concentrated *in vacuo* to afford the pure product as a clear and colorless oil (0.111 g, 0.495 mmol, 28% yield).

¹H NMR: (300 MHz, CDCl₃)

δ 7.69 (d, *J* = 7.4 Hz, 2H), 7.52 (t, *J* = 7.5 Hz, 2H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.33 – 7.22 (m, 2H), 7.04 – 6.94 (m, 1H), 6.03 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.35 – 5.19 (m, 2H), 4.16 (t, *J* = 6.7 Hz, 2H), 2.67 (q, *J* = 6.7 Hz, 2H).

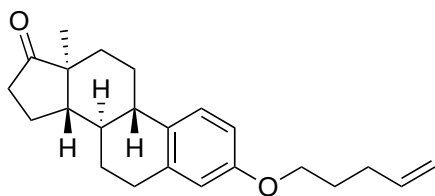
¹³C NMR: (75 MHz, CDCl₃)

δ 159.36, 142.79, 141.15, 134.56, 129.83, 128.81, 127.48, 127.26, 119.75, 117.15, 113.67, 113.34, 67.29, 33.79.

ATR-IR (cm⁻¹):

3074, 2973, 2870, 1597, 1470, 1202, 1037, 912.

HRMS: (ESI⁺) *m/z*: [M+H]⁺ Calcd for C₁₆H₁₇O 245.1279; Found 245.1273.

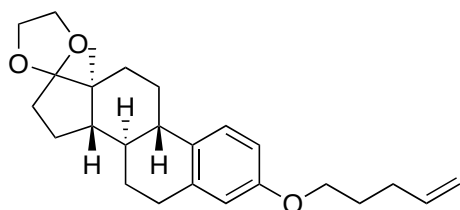


(8*R*,9*S*,13*S*,14*S*)-13-methyl-3-(pent-4-en-1-yloxy)-7,8,9,11,12,13,15,16-octahydro-6*H*-

cyclopenta[a]phenanthrene-17(14*H*)-one was prepared according to general procedure C, in an oven dried 25 mL Schlenk flask under N₂ with an oven dried Teflon stir bar, was added Estrone (0.541g, 2 mmol, 1 eq.), K₂CO₃ (0.691g, 5.00 mmol, 2.5 eq.), and acetonitrile (8.0 mL, 0.25 M). To this stirring mixture, 5-bromopentene (0.47 mL, 4.00 mmol, 2 eq.) was added and the reaction was allowed to reflux (90 °C) under N₂. Upon completion, the reaction was concentrated *in vacuo* followed by addition of H₂O (10 mL) to quench the reaction and extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layer was washed with H₂O (15 mL) and Brine (20 mL) and then dried over Na₂SO₄. This was gravity filtered and concentrated *in vacuo* to afford the pure product as a white solid (0.574g, 1.70 mmol, 85% yield). The spectra for the title compound matched previously reported spectra.¹⁴

¹H NMR: (400 MHz, CDCl₃)

δ 7.20 (d, *J* = 8.6 Hz, 1H), 6.72 (dd, *J* = 8.6, 2.8 Hz, 1H), 6.67 – 6.62 (m, 1H), 5.86 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.06 (dd, *J* = 17.1, 1.8 Hz, 1H), 5.00 (dd, *J* = 10.1, 1.7 Hz, 1H), 3.95 (t, *J* = 6.4 Hz, 2H), 2.94 – 2.83 (m, 2H), 2.51 (dd, *J* = 18.8, 8.6 Hz, 1H), 2.45 – 2.35 (m, 1H), 2.30 – 2.19 (m, 3H), 2.17 – 1.92 (m, 4H), 1.87 (p, *J* = 6.6 Hz, 2H), 1.65 – 1.41 (m, 6H), 0.91 (s, 3H).



(8*R*,9*S*,13*S*,14*S*)-13-methyl-3-(pent-4-en-1-yloxy)-6,7,8,9,11,12,13,14,15,16-

decahydrospiro[cyclopenta[a]phenanthrene-17,2'-[1,3]dioxolane [26-SM] Adapted from a previously reported procedure¹⁵, in an oven-dried 50 mL round bottom flask with an oven-dried Teflon stir bar, was added *p*-TsOH •H₂O (32 mg, 0.17 mmol, 0.1 eq.), (8*R*,9*S*,13*S*,14*S*)-13-methyl-3-(pent-4-en-1-yloxy)-7,8,9,11,12,13,15,16-octahydro-6*H*-cyclopenta[a]phenanthrene-17(14*H*)-one (0.574g, 1.7 mmol, 1 eq.), ethylene glycol (1.9 mL, 34 mmol, 20 eq.), and benzene (11 mL, 0.15 M). A dean Stark trap fitted with a condenser connected to the 50 mL round bottom flask was heated to 100 °C while stirred open to air overnight. Upon completion, H₂O (10 mL) was added, and the reaction mixture was extracted with ether (3 x 10 mL). The combined organic layers were washed with H₂O (15 mL) and brine (20 mL) and then dried over Na₂SO₄. The title compound was isolated by flash column chromatography using gradient elution (200 mL of 100% hexanes, 200 mL of 2% ethyl acetate in hexanes, 200 mL of 5% ethyl acetate in hexanes) to afford the product as a colorless viscous oil (0.586 g, 1.53 mmol, 90% yield).

¹H NMR: (400 MHz, CDCl₃)

δ 7.20 (d, *J* = 8.6 Hz, 1H), 6.70 (dd, *J* = 8.7, 2.7 Hz, 1H), 6.65 – 6.60 (m, 1H), 5.85 (ddt, *J* = 17.4, 10.1, 7.1 Hz, 1H), 5.09 – 5.02 (m, 1H), 5.02 – 4.97 (m, 1H), 4.03 – 3.85 (m, 6H), 2.89 – 2.78 (m, 2H), 2.37 – 2.28 (m, 1H), 2.28 – 2.18 (m, 3H), 2.09 – 1.98 (m, 1H), 1.94 – 1.81 (m, 4H), 1.81 – 1.71 (m, 2H), 1.68 – 1.59 (m, 1H), 1.58 – 1.27 (m, 5H), 0.88 (s, 3H).

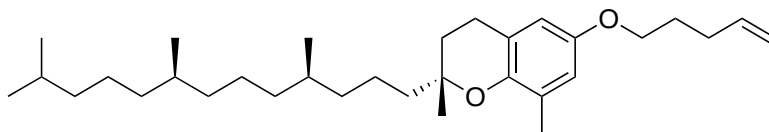
¹³C NMR: (101 MHz, CDCl₃)

δ 157.02, 138.12, 138.08, 132.74, 126.43, 119.59, 115.24, 114.59, 112.15, 67.19, 65.40, 64.73, 49.49, 46.30, 43.77, 39.20, 34.38, 30.87, 30.29, 29.95, 28.65, 27.14, 26.28, 22.50, 14.48.

ATR-IR (cm⁻¹):

3075, 2937, 2867, 1608, 1498, 1309, 1180, 1042.

HRMS: (ESI⁺) *m/z*: [M+H]⁺ Calcd for C₂₅H₃₅O₃ 383.2586; Found 383.2584.



(R)-2,8-dimethyl-6-(pent-4-en-1-yloxy)-2-((4R,8R)-4,8,12-trimethyltridecyl)chromane [27-SM] was prepared according to procedure C, in a 25 mL oven-dried Schlenk flask equipped with an oven-dried Teflon stir bar, was added (+)- δ -Tocopherol (0.942 g, 2.00 mmol, 1 eq.), K₂CO₃ (0.552g, 4.00 mmol, 2 eq.), and acetonitrile (8 mL, 0.25 M). To this stirring mixture, 5-bromopentene (0.47 mL, 4.00 mmol, 2 eq.) was added and the reaction was allowed to reflux (90 °C) under N₂. Upon completion, H₂O (10 mL) was added to quench the reaction and extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layer was washed with H₂O (15 mL) and brine (20 mL), dried over Na₂SO₄. This was gravity filtered and concentrated *in vacuo* to afford the pure product as a clear orange oil (0.494 g, 1.05 mmol, 53% yield).

¹H NMR: (400 MHz, CDCl₃)

δ 6.58 (d, *J* = 3.0 Hz, 1H), 6.45 (d, *J* = 2.9 Hz, 1H), 5.87 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.07 (dd, *J* = 17.1, 1.9 Hz, 1H), 5.00 (dd, *J* = 10.2, 1.6 Hz, 1H), 3.89 (t, *J* = 6.4 Hz, 2H), 2.76 – 2.68 (m, 2H), 2.28 – 2.18 (m, 2H), 2.15 (s, 3H), 1.90 – 1.82 (m, 2H), 1.81 – 1.69 (m, 2H), 1.61 – 1.50 (m, 3H), 1.47 – 1.35 (m, 4H), 1.35 – 1.19 (m, 12H), 1.16 – 1.03 (m, 3H), 0.92 – 0.83 (m, 14H).

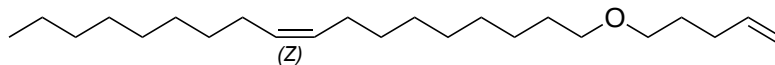
¹³C NMR: (101 MHz, CDCl₃)

δ 151.65, 146.18, 138.16, 127.22, 120.98, 115.54, 115.11, 111.93, 75.61, 67.70, 40.08, 39.51, 37.58, 37.55, 37.42, 32.93, 32.81, 31.51, 30.34, 28.80, 28.12, 24.95, 24.58, 24.27, 22.87, 22.81, 22.78, 21.11, 19.89, 19.80, 16.36.

ATR-IR (cm⁻¹):

2924, 2867, 1746, 1468, 1218, 1153, 1059, 908.

HRMS: (ESI⁺) *m/z*: [M+H]⁺ Calcd for C₃₂H₅₅O₂ 471.4202; Found 471.4197.



(Z)-(4-penten-1-yloxy)-9-octadecene [31-SM] was prepared according to procedure C, in a 25 mL oven-dried Schlenk flask equipped with an oven-dried Teflon stir bar, was added oleyl alcohol (0.400 g, 1.49 mmol, 1 eq.), NaH (0.148 g, calculated based off 60% dispersion in mineral oil, 3.73 mmol, 2.5 eq.), and acetonitrile (3 mL, 0.5 M). To this stirring mixture, 5-bromopentene (0.35 mL, 2.98 mmol, 2 eq) was added and the reaction was allowed to reflux (90 °C) under N₂. Upon completion, H₂O (10 mL) was added to quench the reaction and extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layer was washed with H₂O (15 mL), brine (20 mL) and then dried over Na₂SO₄. This was gravity filtered and concentrated *in vacuo* to afford the pure product as a clear and colorless oil (0.221 g, 0.657 mmol, 44% yield).

¹H NMR: (400 MHz, CDCl₃)

δ 5.82 (ddt, *J* = 16.9, 10.3, 6.7 Hz, 1H), 5.40 – 5.31 (m, 2H), 5.02 (dd, *J* = 17.1, 1.9 Hz, 1H), 4.95 (d, *J* = 10.1 Hz, 1H), 3.39 (q, *J* = 6.7 Hz, 4H), 2.11 (q, *J* = 7.3 Hz, 2H), 2.00 (q, *J* = 6.6 Hz, 2H), 1.72 – 1.60 (m, 2H), 1.60 – 1.50 (m, 2H), 1.37 – 1.21 (m, 24H), 0.90 – 0.86 (m, 3H).

¹³C NMR: (101 MHz, CDCl₃)

δ 138.50, 130.05, 129.97, 114.76, 71.12, 70.26, 32.06, 30.49, 29.91, 29.91, 29.90, 29.67, 29.65, 29.62, 29.47, 29.47, 29.40, 29.06, 27.35, 27.33, 26.34, 22.83, 14.26.

ATR-IR (cm⁻¹):

2922, 2853, 1465, 1116, 910.

HRMS: (ESI⁺) m/z: [M+H]⁺ Calcd for C₂₃H₄₅O 337.3470; Found 337.3466.

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