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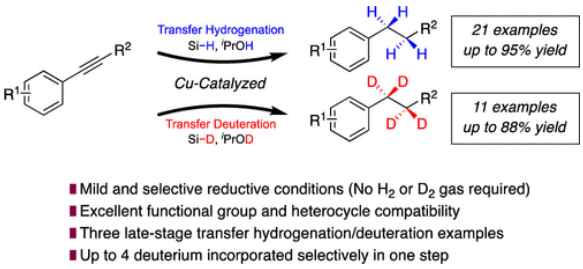
Abstract



A copper-catalyzed reduction of alkynes to alkanes and deuterated alkanes is described under transfer hydrogenation and transfer deuteration conditions. Commercially available alcohols and silanes are used interchangeably with their deuterated analogues as the hydrogen or deuterium sources. Transfer deuteration of terminal and internal aryl alkynes occurs with high levels of deuterium incorporation. Alkyne-containing complex natural product analogues undergo transfer hydrogenation and transfer deuteration selectively, in high yield. Mechanistic experiments support the reaction occurring through a *cis*-alkene intermediate and demonstrate the possibility for a regioselective alkyne transfer hydrodeuteration reaction.

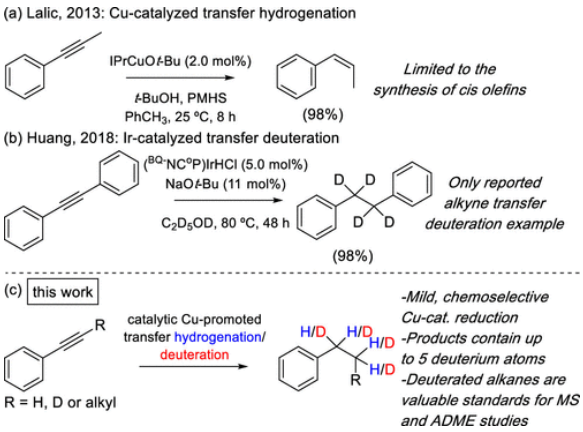
The reduction of an alkyne to an alkane is a fundamental reaction in organic chemistry commonly accomplished using a heterogeneous catalyst and hydrogen gas.(1) Transfer hydrogenation represents an alternative approach to reduce an alkyne, obviating the use of flammable hydrogen gas.(2) This not only avoids potential hazards involved with handling H_2, but also offers the opportunity for improving reaction selectivity.(1b) Transition-metal-catalyzed transfer hydrogenation has been extensively studied for the reduction of polarized π-functionality,(2,3) but remains less frequently explored for the reduction of alkynes to alkanes.(4) Furthermore, adaptation of transfer hydrogenation protocols to perform the selective installation of four deuterium atoms can pose significant challenges.

Recently, there has been a resurgence of interest in new method development focused on the installation of deuterium into small molecules.(5) Deuterated organic molecules are extensively used in chemical research. Small molecules with at least three or four deuterium atoms can serve as valuable standards for high-resolution mass spectrometry in analytical and bioanalytical chemistry.(5a,6) From an organometallic and synthetic organic chemistry context, deuterium-labeled compounds are used to elucidate reaction mechanisms and perform kinetic isotope effect measurements.(7) In drug discovery, deuterium labeling of metabolically labile sites in drug molecules is performed to alter the drug's absorption, distribution, metabolism, and excretion (ADME) properties.(8) The success of this approach came to fruition in 2017, when deutetrabenazine became the first FDA-approved deuterated drug.(9)

We are particularly interested in developing new alkyne reduction methods that can be easily manipulated to catalyze the selective installation of at least four deuterium atoms into small molecules under relatively mild conditions. Strategies for the synthesis of highly deuterated small molecules are often limited by low reaction selectivity or lengthy synthetic sequences. Recently, two techniques have been developed to selectively reduce a 1,1-disubstituted aryl alkene functionality to a deuterated alkane, under transfer hydrodeuteration conditions.(10) Because of the relatively mild conditions a transfer hydrogenation approach offers in the reduction of π-bonds, we began to explore a catalytic

transfer hydrogenation and transfer deuteration for the reduction and reductive deuteration of alkynes.

It is well-established that Cu–H is capable of reducing an alkyne to an alkene.(11) Lalic and co-workers elegantly demonstrated a *cis*-selective transformation that occurs in high yield (Scheme 1a).(11b) Importantly, most Cu–H catalysts are not sufficiently reactive to fully reduce an alkyne to an alkane. To the best of our knowledge, there are no copper-catalyzed transfer deuteration reactions for the reductive deuteration of an alkyne to a deuterated alkane. Recently, a precious metal-catalyzed transfer deuteration was demonstrated for the reduction of an alkyne to an alkane.(4a) Although several transfer hydrogenation examples were reported, the Ir-catalyzed transfer deuteration scope was limited to only diphenylacetylene (see Scheme 1b).



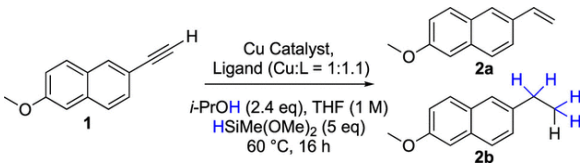
Scheme 1. Transfer Hydrogenation and Transfer Deuteration of Alkynes

Based on previous alkene and alkyne hydroamination work, we hypothesized that a highly reactive Cu–H species would promote the reduction of an alkyne to an alkane (Scheme 1c).(12) We considered dimethoxy(methyl)silane (DMMS) and ethanol or isopropanol to be logical choices as hydrogen donors for the desired transfer hydrogenation reactions. We also hypothesized that these reagents could be readily manipulated for use in the corresponding transfer deuteration reaction. Reaction development commenced by screening commercial copper sources and commercial phosphine-based ligands known to promote Cu–H formation when combined in situ with Si–H.(11a)

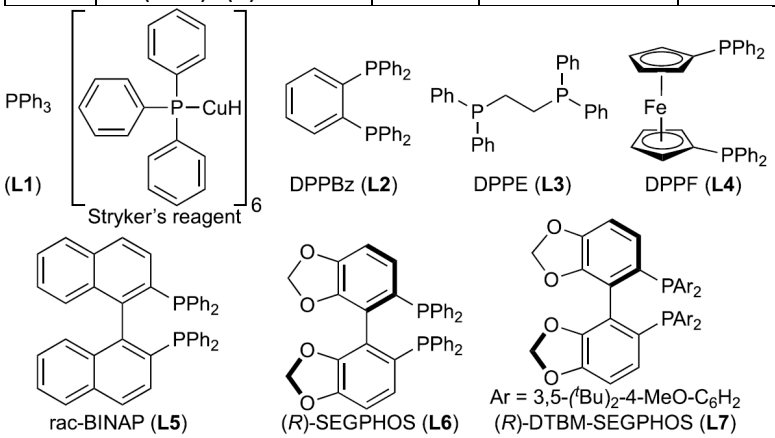
Commercially available 2-ethynyl-6-methoxynaphthalene **1** was used as the aryl acetylene for reaction optimization. We found that triphenylphosphine and achiral bidentate phosphine ligands were ineffective to provide the desired transfer hydrogenation alkane product (see Table 1, entries 1–5). We were hesitant to use chiral bidentate phosphine ligands to perform an achiral process, but given the precedent for these ligand types to support highly reactive Cu–H species, we opted to screen BINAP and SEGPHOS type ligands (Table 1, entries 6–8). We found that commercially available (*R*)-DTBM-SEGPHOS was the most effective ligand for the Cu–H-catalyzed reduction (Table 1, entry 8). Reducing the catalyst loading to 1 mol % led to a slight reduction in yield (Table 1, entry 9). The use of 2 mol % of catalyst was optimal and led to a high product yield (91% isolated yield; see Table 1, entry 10). It is noteworthy that (*R*)-DTBM-SEGPHOS and (*S*)-DTBM-SEGPHOS can be used interchangeably in this reaction, and no alkane product is formed in the absence of $Cu(OAc)_2$ or phosphine ligand (Table 1, entries 11 and 12). Gratifyingly, other silane reagents such as poly(methylhydrosiloxane) (PMHS) and

diethoxy(methyl)silane (DEMS) were successfully employed in the transfer hydrogenation reaction (Table 1, entries 13 and 14). We chose to use DMMS, because it is easily removed by evaporation from crude reaction mixtures and can be readily converted to the Si–D for transfer deuteration (vide infra).

Table 1. Reaction Optimizationa



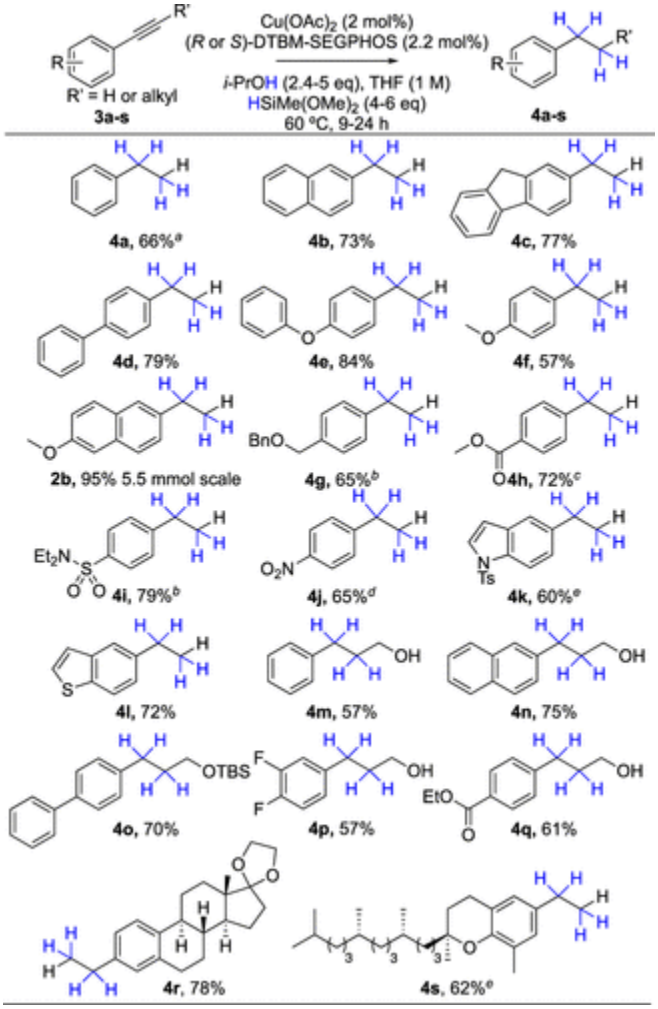
Entry	Cu Catalyst (mol%)[b]	Ligand	Yield of 2a (%)	Yield of 2b (%)	RSM 1 (%)
1	$Cu(OAc)_2$ (5)	L1	11	trace[c]	48
2	Stryker's Reagent (5)	N/A	53	trace[c]	6
3	$Cu(OAc)_2$ (5)	L2	5	trace[c]	85
4	$Cu(OAc)_2$ (5)	L3	8	trace[c]	78
5	$Cu(OAc)_2$ (5)	L4	11	trace[c]	72
6	$Cu(OAc)_2$ (5)	L5	12	trace[c]	49
7	$Cu(OAc)_2$ (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



[a]Reactions were conducted using 0.2 mmol of substrate. [b]$Cu(OAc)_2$ was used in the reactions as a 0.2 M solution in THF. [c]Yield was determined by ^1H NMR analysis of the crude reaction mixture, using 1,3,5-trimethylbenzene as an internal standard. [d]Yield determined after purification by flash column chromatography. [e]Poly(methylhydrosiloxane) (5 equiv) was used instead of dimethoxy(methyl)silane. [f]Diethoxy(methyl)silane (5 equiv) was used instead of dimethoxy(methyl)silane.

We evaluated the substrate scope for this transformation using commercially available $Cu(OAc)_2$, DTBM-SEGPHOS, DMMS, and ethanol or isopropanol (see Scheme 2). Examples using ethanol for transfer hydrogenation are scarce, and we were pleased that this inexpensive feedstock is a viable proton source.(4a,11k,13) During our evaluation of the reaction scope, we noticed that increasing the

equivalents of alcohol (up to 5 equiv) resulted in full conversion of less-reactive substrates. Hydrocarbons such as ethylbenzene, 2-ethylnaphthalene, 2-ethyl-9H-fluorene, and 4-ethyl-1,1′-biphenyl were prepared from the reduction of their respective alkynes in good yield (**4a**–**4d**, 66%–79% yield). Substituting aryl acetylenes with electron-donating phenoxy and methoxy groups was beneficial for conversion and led to enhanced yields (**4e**–**4f**, 57%–84% yield). We attempted a gram-scale reduction on the optimization substrate, 2-ethynyl-6-methoxynaphthalene, and isolated **2b** in 95% yield. A chemoselective alkyne reduction occurred in the presence of a benzyl ether under the mild transfer hydrogenation conditions, using ethanol instead of 2-propanol (**4g**, 65% yield). Importantly, no benzyl deprotection product was observed as previously reported under heterogeneous metal-catalyzed hydrogenation with H_2.(14) We also found that a methyl ester para to the alkyne was beneficial for conversion to product (**4h**, 72% yield). No ester reduction product was seen in the crude ^{1}H NMR or after purification.



Scheme 2. Transfer Hydrogenation Substrate Scope

[a]Yield determined by ^{1}H NMR analysis using 1,3,5-trimethylbenzene as an internal standard.

[b]2.4–2.6 equiv of EtOH used.

[c]Reaction performed at 40 °C.

[d]Reaction performed at 23 °C.

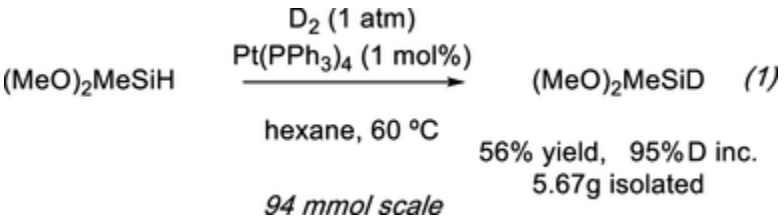
[e]5 mol % $Cu(OAc)_2$ and 5.5 mol % DTBM-SEGPHOS were used.

Because of their prevalence in bioactive molecules, nitrogen-containing compounds and heterocycles were examined under the transfer hydrogenation protocol.(15) An electron-withdrawing *para*-benzenesulfonamide was beneficial for reactivity (**4i**, 79%). Even nitro-groups, which are known to be reduced under heterogeneous reaction conditions, remained intact under the homogeneous transfer hydrogenation conditions (**4j**, 65% yield).(4c,16) Heterocycle-containing aryl acetylenes, such as a tosyl-protected indole and a benzothiophene, were efficiently reduced as well (**4k**–**4l**, 60%–72% yield).

Internal alkynes proved to be more-challenging substrates, because of the increased steric bulk surrounding the alkyne. Nonetheless, we found that 3-phenyl-2-propyn-1-ol reduced to 3-phenyl-1-propanol in moderate yield (**4m**, 57% yield), along with naphthyl and biaryl alkynes (**4n**-**4o**, 70%–75% yield). Further elucidation of the internal alkyne substrate scope revealed that alkynes substituted with electron-deficient aryl rings could also be reduced in good yield (**4p**–**4q**, 57%–61% yield).

We explored the capacity for the Cu–H catalyst to reduce alkyne-containing complex natural product analogues to their corresponding alkanes. Estrone analogue **4r** was isolated in 78% yield after reacting the corresponding alkyne starting material under the standard transfer hydrogenation conditions. Importantly, the alkyne was completely reduced, resulting in full conversion to alkane. A similar result was obtained when δ-tocopherol analogue **4s** was isolated in 62% yield from the corresponding alkyne analogue.

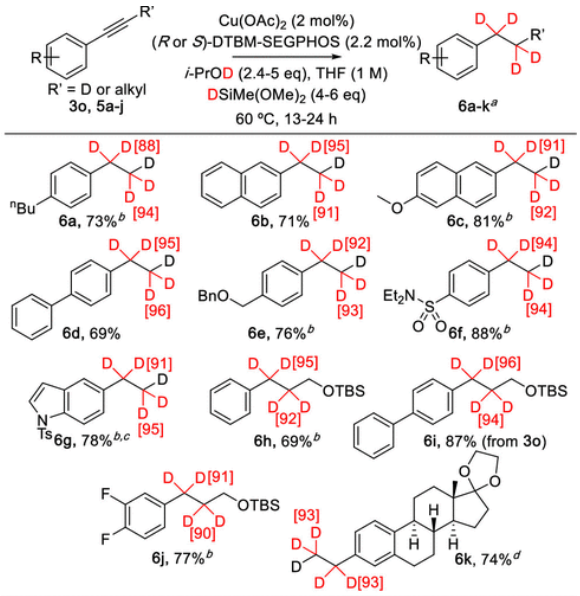
To achieve our goal of selectively installing four deuterium atoms across an alkyne, we hypothesized that using ethanol–OD or 2-propanol–OD and Si–D would permit deuterium installation in a mild manner. Inspired by previously reported work,(17) we were able to develop a scalable and reliable protocol to make the Si–D on a 94 mmol scale (eq 1):



For deuterated small molecules to be used as internal standards for quantitative bioanalytical liquid chromatography/mass spectrometry assays, it is typical that at least three to four deuterium atoms are contained in the molecule to allow for sufficient separation of peaks in the mass spectrum.(6b,18) For terminal alkynes, we proceeded to exchange the acetylenic hydrogen atom for a deuterium atom prior to transfer deuteration.(19) This permitted the synthesis of substrates with five deuterium atoms.

Our investigation into the transfer deuteration of aryl alkynes began with a *para*-substituted aryl acetylene (**6a**, 73% yield) (Scheme 3). It is noteworthy that efficient transfer deuteration occurs with electron-withdrawing and electron-donating *para*-substitution. Polyaromatic compounds such as 2-ethynylnaphthalene and 2-ethynyl-6-methoxynaphthalene, along with a biphenyl-substituted alkyne were reductively deuterated in high yields (**6b**–**6d**, 69%–81% yield). A benzyl group was found to be stable under the transfer deuteration conditions (**6e**, 76% yield), as no alcohol product was detected in the crude reaction mixture. Nitrogen-containing substrates, such as an aryl sulfonamide or indole-

substituted alkyne, afforded the corresponding d_5-alkane in good yields (**6f**–**6g**, 78%–88% yield). Internal aryl alkynes were also reductively deuterated in high yields, resulting in the synthesis of small molecules containing four deuterium atoms (**6h**–**6j**, 69%–87% yield). Importantly, the copper-catalyzed transfer deuteration was effective for deuterating an alkyne-containing natural product. Deuterated estrone analogue **6k** was isolated in 74% yield from the corresponding alkyne starting material. This represents a mild procedure to make a highly deuterated natural product that is suitable as an analytical standard for mass spectrometry.



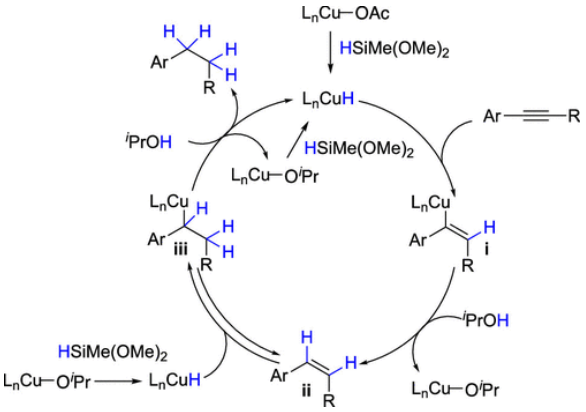
Scheme 3. Transfer Deuteration Substrate Scope

[a]Deuterium incorporation measured by ^{1}H NMR and/or ^{2}H NMR.

[b]2-propanol-d_8 used and found to be equally effective as *i*-PrOD.

[c]5 mol % $Cu(OAc)_2$ and 5.5 mol % DTBM SEGPHOS used. [d]Reaction run for 38 h.

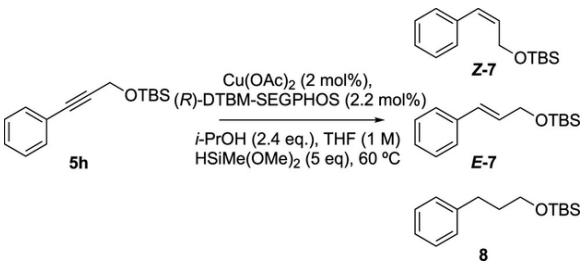
Mechanistically, under transfer hydrogenation conditions, we hypothesized that the formation of a Cu–H bond in the presence of dimethoxy(methyl)silane, followed by insertion of Cu–H bonds across an alkyne, would lead to alkenyl Cu species **i** (see Scheme 4). Protodecupration of **i** with isopropanol would extrude alkene **ii**. Regeneration of the Cu–H and addition across alkene **ii** to form alkyl Cu **iii**, followed by protodecupration of **iii**, would provide the desired alkane. Simply replacing the Si–H with Si–D and the alcohol with alcohol–OD permits the reaction to operate under transfer deuteration conditions.



Scheme 4. Postulated Reaction Mechanism

To test our hypothesis of the intermediacy of *cis*-alkene **ii** (Scheme 4), we evaluated the reduction of **5h** over several time periods. Consistent with the postulated mechanism, alkene ***Z*-7** appeared in the reaction mixture after 15 min (see Table 2, entry 1). The appearance of ***E*-7** after 30 min (Table 2, entry 2) suggested that Cu–H insertion into alkene **ii** to form alkyl copper intermediate **iii** is reversible. After 180 min, the reaction was almost finished (Table 2, entry 5), and it reached completion after 9 h (**8**, 79% yield; Table 2, entry 6). We also subjected ***E*-7** to the standard transfer hydrogenation conditions and isolated alkane **8** in 83% yield after 23 h.(20) Importantly, trace amounts of ***Z*-7** was observed in the crude ^{1}H NMR after 1 h. These data further support that ***E*-7** is a viable and reactive alkene for the second transfer hydrogenation step in the proposed mechanism and Cu–H insertion into alkene **ii** to form alkyl copper intermediate **iii** is reversible (Scheme 4).

Table 2. Reaction Analysis

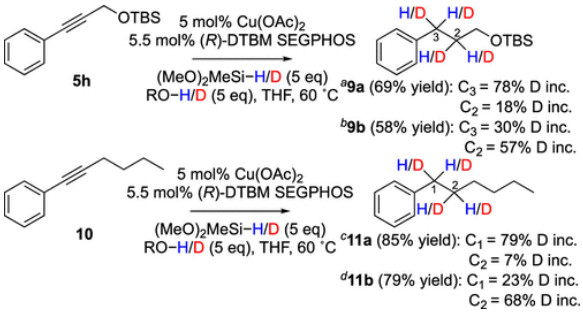


entry	reaction time	*Z*-7a (%)	*E*-7a (%)	8a (%)
1	15 min	74	0	6
2	30 min	48	2	25
3	45 min	40	5	36
4	90 min	17	7	54
5	180 min	7	5	61
6	9 h	0	0	79

[a]Yields of each product were determined by ^{1}H NMR of the combined products after purification.

To further probe the mechanism of the transfer hydrogenation, we performed the reaction under transfer hydrodeuteration conditions. We exchanged the alcohol reagent for ethanol–OD and made no changes to the silane. The reaction was only moderately regioselective (78% D inc. at C_3, 18% D inc. at

C_2), and isotopically labeled alkane **9a** was isolated in 69% yield (see Scheme 5). Switching to ethanol and $(MeO)_2MeSi$–D led to a flip in regioselectivity (**9b**, 58% yield, 30% D inc. at C_3, 57% D inc. at C_2).



Scheme 5. 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 °C. All yields are isolated and %D inc. was determined using ^1H NMR and/or ^2H NMR. [a]5 equiv $(MeO)_2MeSi$-H, 5 equiv EtOD, 24 h. [b]5 equiv $(MeO)_2MeSi$-D, 5 equiv EtOH, 24 h. **9b** was isolated as a mixture with alkene (23% yield) present due to incomplete conversion. See the Supporting Information for details. [c]5 equiv $(MeO)_2MeSi$-H, 5 equiv 2-propanol-d_8, 21 h. [d]5 equiv $(MeO)_2MeSi$-D, 5 equiv *i*-PrOH, 21 h.

To avoid any potential regioselectivity bias that could occur from proximal heteroatom functionality, similar transfer hydrodeuteration experiments were also performed with alkyne **10**. The reaction was slightly more regioselective, leading to selectively deuterated alkane **11a** (85% yield, 79% D inc. at C_1, 7% D inc. at C_2) and alkane **11b** (79% yield, 23% D inc. at C_1, 68% D inc. at C_2). Mild to good regioselectivity was observed in all four transfer hydrodeuteration experiments, and this supports a regioselective Cu–H/Cu–D addition across the alkyne and/or alkene. Ongoing investigations in our laboratory are focused on enhancing the regioselectivity of this transfer hydrodeuteration reaction.

In summary, we have developed a Cu–H-catalyzed transfer hydrogenation and transfer deuteration to reduce aryl alkynes to their corresponding alkanes and deuterated alkanes. The relatively mild transfer hydrogenation/deuteration permits the selective reduction of aryl alkynes that contain functionality commonly reduced under heterogeneous metal-catalyzed reductions. The reaction is scalable and due to the modularity of the reaction, a transfer deuteration is possible by simply changing the Si–H and alcohol to Si–D and alcohol–OD. This permitted facile access to aryl alkanes containing up to 5 deuterium atoms. The copper-catalyzed transfer hydrogenation and transfer deuteration protocols were successfully applied to aryl alkyne containing complex natural product analogs. As a result, we anticipate this method could be useful to synthesize highly deuterated analogs of drug molecules for ADME studies.

Supporting Information

The Supporting Information is available free of charge at https://0-pubs-acs-org.libus.csd.mu.edu/doi/10.1021/acs.orglett.0c03632.

- General information; procedures for transfer hydrogenation, transfer deuteration, and synthesis of starting materials; ^1H NMR, ^2H NMR (for selected compounds), ^{19}F NMR, and ^{13}C NMR spectra; and HRMS and IR data of all newly characterized products (PDF)

Terms & Conditions

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Notes

The authors declare no competing financial interest.

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