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Highly Regioselective Copper-Catalyzed Transfer of Hydrodeuteration of Unactivated Terminal Alkenes

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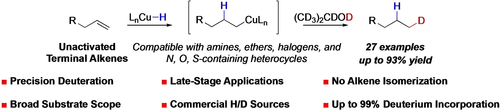
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# Graphical Abstract

**Precision deuteration of unactivated alkenes**: A copper-catalyzed alkene transfer hydrodeuteration for the synthesis of precisely deuterated small molecules is described. It is the most regio- and chemoselective transfer hydrodeuteration of unactivated terminal alkenes reported to date. The transformation was performed across a broad scope of substrates and even demonstrated on two natural product derivatives.

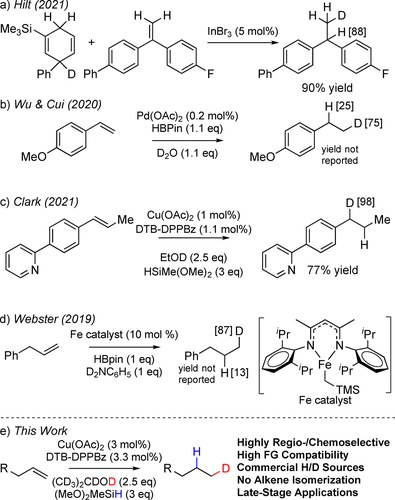
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# Abstract

Catalytic transfer hydrodeuteration of unactivated alkenes is challenging because of the requirement that chemically similar hydrogen and deuterium undergo selective insertion across a π-bond. We now report a highly regioselective catalytic transfer hydrodeuteration of unactivated terminal alkenes across a variety of heteroatom- or heterocycle-containing substrates. The base-metal-catalyzed reaction is also demonstrated on two complex natural products. Reaction studies indicate modular conditions that can also be extended to perform either an alkene transfer hydrogenation or transfer deuteration.

Selectively deuterated small molecules are extensively used in chemical research and in pharmaceuticals. In chemical research, they can serve as probes for mechanistic studies or for the determination of a kinetic isotope effect.1-4 They are useful tools for determining the stereochemical outcome of reactions,5-8 and selectively labeled molecules have even been used in total synthesis to control reaction selectivity in key transformations.9-11 In pharmaceuticals, deuterium is selectively incorporated at sites prone to metabolic oxidation as a strategy to alter the pharmacokinetics of a small molecule drug.12-17 This has the potential to improve the safety profile of therapeutics without altering the potency and efficacy of the parent drug.18, 19 These applications have driven demand for the development of precision deuteration reactions, in which deuterium is precisely installed at the target site within a small organic molecule.12, 15, 20

Catalytic transfer hydrodeuteration is an emerging area in organic synthesis for the selective deuteration of alkenes (Scheme **1**).20 A unique attribute of transfer hydrodeuteration is that hydrogen (H) can be distinguished from deuterium (D) for regioselective installation across a π-bond. Catalytic transfer hydrodeuteration reactions also obviate the use of H2, HD or D2 gas but can still be reactive with less-activated alkene types, especially those found to be unreactive under other reductive deuteration protocols.21, 22 Despite these benefits, selectivity and reactivity issues persist. Catalytic transfer hydrodeuteration reactions that are regioselective are typically limited to activated 1,1-disubstituted and trisubstituted alkenes (Scheme **1**a),23-25 or activated alkenes in conjugation with a carbonyl (e. g., α,β-unsaturated ketone substrates).20, 26 Alternatively, a Pd-catalyzed transfer hydrodeuteration has been reported for terminal styrenes but is only moderately regioselective and not demonstrated on internal aryl alkenes or unactivated terminal alkene substrate types (Scheme **1**b).27

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**Scheme 1** Catalytic alkene hydrodeuteration (THD) overview.

We recently reported a mild and general Cu-catalyzed transfer hydrodeuteration reaction that regioselectively incorporates one H and one D across both terminal and internal aryl alkene substrates to make [D1]alkanes selectively deuterated at the benzylic position (Scheme **1**c).28 Encouragingly, this report included one example of an unactivated terminal alkene undergoing regioselective transfer hydrodeuteration, however it required that we change the deuterium source to [D8]isopropanol and increase the catalyst loading to 3 mol%. While this single example was successful, we were intrigued that reactions of unactivated terminal alkenes generally did not reach full conversion and trace alkene isomerization by-product was forming under the standard conditions for promoting alkenyl arene transfer hydrodeuteration (Table **1**, entry 1). This was problematic for two reasons. Firstly, unreacted starting material is oftentimes inseparable from the desired product using standard flash chromatography purification techniques. Secondly, an alkene isomerization by-product is not only inseparable from the desired product but could undergo transfer hydrodeuteration, and thus form inseparable and complex isotopomer product mixtures.

**Table 1.**Reaction optimization.[a]



|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | ***T* [°C]** | **D source** | **1 [%][b]** | **2 a [%][b]** | **2 b [%][b]** |
| 1 | 40 | EtOD | 23 | 60 | 3 |
| 2 | 60 | EtOD | – | 85 | 7 |
| 3 | 23 | EtOD | 55 | 22 | 5 |
| 4[c] | 40 | EtOD | 32 | 34 | 3 |
| 5[d] | 40 | EtOD | 42 | 39 | – |
| 6[e] | 40 | EtOD | 80 | – | – |
| 7 | 40 | [D8]IPA | 6 | 70 | – |
| 8[f] | 40 | [D8]IPA | – | 90 | – |
| 9[f] | 40 | *t*BuOD | – | 55 | – |
| 10[f] | 40 | MeOD | 85 | 3 | – |
| 11[f,g] | 40 | [D8]IPA | 7 | 80 | – |

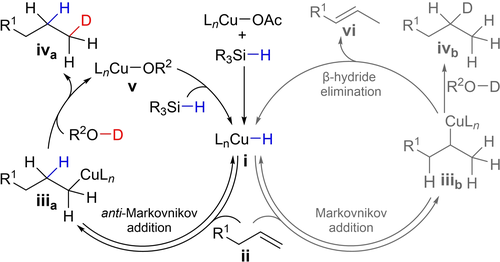
[a] All reactions preformed on a 0.2 mmol scale. [b] Yields were determined after purification by flash chromatography. [c] Reaction performed at 2 M concentration. [d] Reaction performed with PhCH3 instead of THF. [e] Reaction performed with CH2Cl2 instead of THF. [f] Reaction performed with 3 mol % Cu(OAc)2 and 3.3 mol % DTB-DPPBz. [g] Reaction performed with polymethylhydrosiloxane instead of dimethoxymethylsilane.

To the best of our knowledge, there exists only two other reports in which metal-catalyzed unactivated terminal alkene transfer hydrodeuteration is performed.29, 30 Although very few examples of unactivated terminal alkene substrates are reported (Scheme **1**d), these fundamental works by Webster and co-workers underscore the reactivity and selectivity challenges hindering the development of a general protocol for selectively installing H and D across an unactivated alkene type. Although protocols that employ H2, HD or D2 gas are sometimes reactive with unactivated alkenes, they are insufficient at discriminating between H and D for regioselective hydrodeuteration.31, 32 Under catalytic transfer hydrodeuteration conditions, a different challenge arises where catalysts that react with unactivated terminal alkenes can also promote competing alkene isomerization pathways which can lead to mixtures of inseparable isotopomers.29, 30, 33

Given the mild and general protocol we established for the transfer hydrodeuteration of alkenyl arene substrates, we were interested in exploring alternate reactions conditions to extend reactivity to unactivated terminal alkenes while retaining the high reaction selectivities found in our initial report.28 The regioselectivity of the Cu−H addition across a terminal unactivated alkene is likely influenced by the steric environment of the substrate, where Cu adds to the least sterically hindered alkene position. This has been elegantly demonstrated in several Cu−H catalyzed terminal alkene hydrofunctionalization reactions.34-37 Therefore, to unlock a highly selective and general terminal unactivated alkene transfer hydrodeuteration, we sought to uncover reaction conditions that quell alkene isomerization pathways and promote full conversion of the alkene to the desired deuterated product. We now report a Cu-catalyzed transfer hydrodeuteration that is both highly reactive for unactivated terminal alkenes and highly regioselective for the precise installation of H and D across the alkene (Scheme **1**e).

Returning to the conditions previously reported by our research group for Cu-catalyzed aryl alkene transfer hydrodeuteration, we recognized the necessity to optimize the reaction for complete conversion of alkene **1** to precisely deuterated alkane **2 a** without promoting the formation of by-product **2 b** (Table **1**).28 Unactivated terminal alkene **1** was chosen as the optimization substrate because the terminal alkene is distal from functionality. Compared to our previously reported conditions (entry 1), efforts to increase the yield of desired product **2 a** were successful by increasing the reaction temperature to 60 °C, however this also led to a slightly higher yield of alkene isomerization by-product **2 b** (entry 2). Performing the reaction at room temperature resulted in lower conversion to product **2 a** and alkene isomerization by-product was still formed (entry 3). Doubling the reaction concentration also led to a low yield of **2 a** and trace **2 b** (entry 4). Changing the reaction solvent to PhCH3 led to a suboptimal yield of **2 a** while changing to CH2Cl2 completely inhibited the reaction (entries 5 and 6). In both cases, no alkene isomerization was detected.

The role of the alcohol and/or silane in Cu-catalyzed alkene and alkyne hydrofunctionalization processes has been previously studied.28, 38-43 Given that changing temperature, concentration and solvent did not lead to an optimal reaction, we decided to explore other alcohol-OD sources. The alcohol-OD reagent is important in the reaction because it is involved in the deuterodecupration of intermediates **iiia** and **iiib** (Scheme **2**). The resulting copper alkoxide species **v** is also directly formed from the alcohol-OD reagent. We examined using [D8]isopropanol instead of ethanol-OD and isolated the desired product **2 a** in a higher yield relative to entry 1 (Table **1**, entry 7). Furthermore, we were surprised that no isomerization product **2 b** was seen in the crude 1H NMR or after purification.

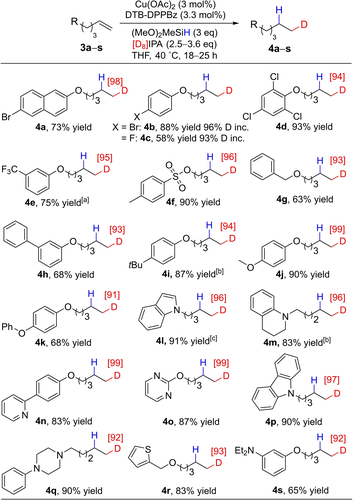
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**Scheme 2** Mechanistic hypothesis.

In a previous study by our group, we performed a Cu-catalyzed alkyne transfer hydrogenation reaction using isopropanol as one of the H-sources.41 This study revealed that hydrometalation of the alkene likely occurs in a reversible manner, similar to what is depicted for both the desired *anti-*Markovnikov and undesired Markovnikov Cu−H addition steps (Scheme **2**). In the present study, we hypothesize that a Markovnikov addition of Cu−H **i** across alkene **ii** can lead to formation of the alkene isomerization by-product **vi** by β-hydride elimination occurring in intermediate **iiib**. When EtOD is used as the alcohol-OD reagent, no Markovnikov transfer hydrodeuteration product **ivb** is observed. It appears that intermediate **iiib** undergoes β-hydride elimination instead of deuterodecupration. With [D8]isopropanol, neither **ivb** nor **vi** is observed. Taken together, reversibility of the undesired Markovnikov addition step could account for no isomerization product or Markovnikov transfer hydrodeuteration product being detected in entry 7.

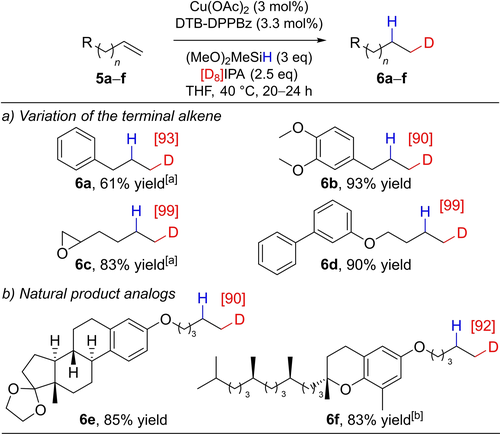
We discovered that full conversion of alkene **1** can be achieved by increasing the catalyst loading to 3 mol% (entry 8, 90 % yield of **2 a**, >20 : 1 regioisomeric ratio). Consistent with entry 7, no alkene isomerization by-product was detected when using [D8]isopropanol. We also observed that no alkene isomerization by-product was detected using the sterically hindered *t*BuOD reagent (entry 9). However, only a moderate 55 % yield of the desired product was isolated. Switching to the less sterically encumbered CH3OD led to minimal conversion of alkene **1** to product **2 a** (entry 10). Lastly, changing the silane reagent to polymethylhydrosiloxane (PMHS) led to a slight decrease in yield because full conversion of alkene **1** to product **2 a** was not achieved (entry 11).

The substrate scope of unactivated alkenes was investigated on organic molecules containing a pent-1-ene substituent (Scheme **3**). The reaction was highly chemoselective for alkene transfer hydrodeuteration in the presence of Br-, Cl-, F-, or CF3-substituted arenes (**4 a**–**4 e**, 58–93 % yield). Importantly, no reductive deuterodehalogenation side products were observed in these reactions. The reaction was also chemoselective for alkene hydrodeuteration in the presence of a tosyl or benzyl protected alcohol (**4 f**–**4 g**, 63–90 % yield). Phenol derivatives where the arene is substituted with either a phenyl, *tert-*butyl, methoxy or phenoxy group efficiently undergo transfer hydrodeuteration at the pendant unactivated terminal alkene (**4 h**–**4 k**, 68–90 % yield). The hydrodeuteration protocol was also examined in substrates containing heterocycles commonly found in small molecule drugs and drug candidates.44-46 This included substrates with N-containing heterocycles such as indole, tetrahydroquinoline, pyridine, pyrimidine, carbazole and piperazine (**4 l**–**4 q**, 83–91 %). Even a terminal alkene substrate containing a remote thiophene heterocycle underwent regioselective transfer hydrodeuteration in good yield (**4 r**, 83 % yield). Lastly, an aniline containing substrate performed well in the reaction (**4 s**, 65 % yield).

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**Scheme 3** Unactivated terminal alkene substrate scope. [a] 4 equiv. of silane used. [b] 4–4.4 mol% Cu(OAc)2, 4.4–4.8 mol% DTB-DPPBz, 4–4.6 equiv. DMMS used. [c] 6 mol% Cu(OAc)2, 6.6 mol% DTB-DPPBz, 4.8 equiv. DMMS used.

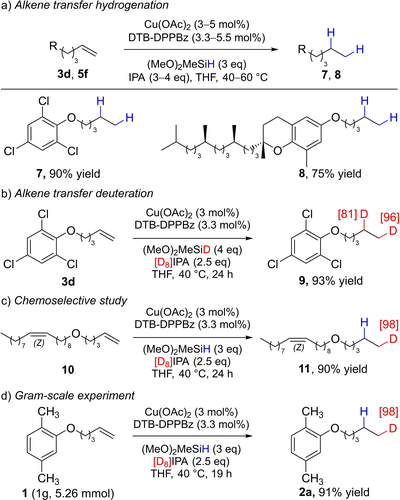
The reaction was also evaluated in substrates not containing a pent-1-ene chain (Scheme **4**). Allyl benzene, a substrate type known to undergo a thermodynamically driven metal hydride catalyzed alkene isomerization,30, 47 underwent hydrodeuteration with high precision at the terminal alkene (**6 a**, 61 % yield by 1H NMR). In a similar fashion, methyl eugenol was precisely deuterated at the terminal position when subjected to the Cu-catalyzed transfer hydrodeuteration protocol (**6 b**, 93 % yield). Importantly, no deuterium was detected at any other position when **6 b** was isolated and evaluated by 1H, 2H and 13C NMR. Evaluation of an epoxide-containing substrate revealed hydrodeuteration of the terminal alkene as the major product (**6 c**, 83 % yield by 1H NMR). No epoxide opening products were observed in this case. We also found that a butene appended to 3-phenylphenol also undergoes regioselective hydrodeuteration in high yield (**6 d**, 90 % yield).

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**Scheme 4** Scope of substrates containing various alkene chain lengths and natural product analogs. [a] Yield determined by 1H NMR analysis using 1,3,5-trimethylbenzene as internal standard. [b] Reaction performed at 60 °C.

Catalytic alkene transfer hydrodeuteration has been scarcely reported in complex natural product settings,28 and to the best of our knowledge, there are no reports of unactivated alkenes undergoing alkene transfer hydrodeuteration in complex small molecule settings.20 Estrone and δ-tocopherol natural product derivatives, each containing a pendant terminal alkene, were evaluated under the Cu-catalyzed transfer hydrodeuteration conditions. In both cases, high yields and regioselectivities were observed after isolation of the deuterated products (**6 e**–**6 f**, 83–85 % yield).

Due to the modularity of the Cu-catalyzed transfer hydrodeuteration protocol, the corresponding transfer hydrogenation and transfer deuteration protocols can be readily carried out. Returning to substrate **3 d** and δ-tocopherol natural product derivative **5 f**, transfer hydrogenation occurs in good yield for both substrates by simply replacing [D8]isopropanol with isopropanol (Scheme **5**a, **7**–**8**, 75–90 % yield). Changing to the readily accessible Si−D derivative of dimethoxymethylsilane and [D8]isopropanol, the corresponding alkene transfer deuteration can also be performed. In the case of substrate **3 d**, this led to a 93 % yield of the di-deuterated product **9** (Scheme **5**b). The reaction was also performed on an oleic acid derivative to evaluate the reaction chemoselectivity when two alkenes are present in a molecule. Importantly, this natural product derivative contains both a *cis-*internal alkene and a terminal alkene. Under the optimal reaction conditions, only hydrodeuteration of the terminal alkene was observed and product **11** was obtained in excellent yield (Scheme **5**c, 90 % yield). Lastly, a gram-scale experiment was performed with the optimization substrate **1**. This resulted in a 91 % isolated yield of the desired deuterated alkane.

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**Scheme 5** Reaction modularity and chemoselectivity studies.

In conclusion, a highly regioselective Cu-catalyzed transfer hydrodeuteration of unactivated alkenes is reported. This transformation fills a major void in catalytic transfer hydrodeuteration of alkenes because targeted deuteration can be performed on unactivated terminal alkene substrates in order to deuterate small molecules precisely at the terminal carbon. We found that more sterically encumbered alcohol-OD reagents obviate alkene isomerization by-products and lead to exclusive formation of the desired precisely deuterated alkane product with excellent levels of regioselectivity. A diverse array of functionality is compatible with the reported transformation. In addition to several heterocycle-containing alkene substrates undergoing selective hydrodeuteration, two complex natural product analogs proved successful in the reaction. The modularity of the reaction permits both the corresponding alkene transfer hydrogenation and deuteration reactions to be readily carried out. We envision that these protocols will find important applications in the development of precisely deuterated pharmaceuticals and isotopically pure deuterated small-molecule reaction probes. Ongoing studies in our research group are focused on examining the role that sterically encumbered alcohol reagents play in obviating alkene isomerization pathways.

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# Conflict of interest

The authors declare no conflict of interest.

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