Catalytic Transfer Deuteration and Hydrodeuteration: Emerging Techniques to Selectively Transform Alkenes and Alkynes to Deuterated Alkanes

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Catalytic Transfer Deuteration and Hydrodeuteration: Emerging Techniques to Selectively Transform Alkenes and Alkynes to Deuterated Alkanes

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Abstract
Increasing demand for deuterium-labeled organic molecules has spurred a renewed interest in selective methods for deuterium installation. Catalytic transfer deuteration and transfer hydrodeuteration are emerging as powerful techniques for the selective incorporation of deuterium into small molecules. These reactions not only obviate the use of D₂ gas and pressurized reaction setups but provide new opportunities for selectively installing deuterium into small molecules.
Commercial or readily synthesized deuterium donors are typically employed as easy-to-handle reagents for transfer deuteration and hydrodeuteration reactions. In this minireview, recent advances in the catalytic transfer deuteration and hydrodeuteration of alkenes and alkynes for the selective synthesis of deuterated alkanes will be discussed.

1 Introduction

Since deuterium was first reported by Urey in 1932,1 deuterated small molecules have been extensively used in chemical research and medicine. In organic chemistry and organometallic chemistry, deuterated small molecules are commonly used to elucidate reaction mechanisms and perform kinetic isotope effect measurements.2 In biochemistry, deuterated compounds not only serve as probes to determine the stereochemical course of microbiological or enzymatic reactions but are utilized to elucidate biosynthetic pathways.3 From a physical and analytical chemistry perspective, deuterium-labeled compounds may serve as tools for spectroscopy or standards for high-resolution mass spectrometry.4

Deuterated small molecules are also employed to alter absorption, distribution, metabolism and excretion properties of small molecule drug candidates.3a, 4b, 5 With the arrival of the first FDA approved deuterated small molecule drug in 2017, installing deuterium into metabolic “soft spots” is becoming a key strategy to designing safer therapeutics.6 An additional advantage of designing deuterated small molecules for drug discovery is that deuterated drugs typically retain their original potency and selectivity relative to the parent drug. Despite the advantages of developing deuterated small molecule drugs, there remain significant drawbacks that must be solved in regard to new reaction development. For example, deuterated drug candidates synthesized as an isotopic mixture might lack deuterium at the metabolically active site under investigation. This could result in shorter half-life values for the drug candidate.7

Complications with unselective deuteration reactions are further amplified as isotopic mixtures cannot be separated with traditional purification techniques. Therefore, highly selective deuteration reactions remain a key strategy to accessing high-value deuterated molecules. Catalytic transfer deuteration and transfer hydrodeuteration reactions offer unique opportunities to accomplish selective deuterium installation. Recent advances demonstrate the potential these reactions have to overcome many of the formidable challenges faced when making high-purity deuterated small molecules. Additionally, recent advances in the field of spectroscopy are now being applied to characterize the products of transfer deuteration and transfer hydrodeuteration reactions. This minireview intends to highlight recent advances in catalytic transfer deuteration/hydrodeuteration.

2 Deuteration Background

Traditionally, deuterated organic molecules were accessed through multistep syntheses using readily available deuterated synthons. These routes commonly require significant time and resources to reach the target molecule. While outside of the scope of this review, one-step deuterium installation protocols such as reductive deuto-dehalogenation,8 hydrogen isotope exchange (HIE) reactions,9 and reductive deuteration of carbonyl functionality10 represent efficient strategies for deuterium incorporation. In fact, HIE reactions are now used to perform late-stage selective deuteration.11
 Unsaturated C–C bonds in organic molecules are very common, thus making alkene and alkyne functionalities ideal sites for selective deuterium incorporation. Catalytic deuteration and hydrodeuteration is typically carried out with D₂ or HD gas and a metal catalyst.¹² Potential drawbacks to these types of reactions include the use of flammable gas and difficulty controlling reaction chemoselectivity and/or regioselectivity. In this context, catalytic transfer deuteration and transfer hydrodeuteration represent a mild approach to selectively install deuterium into alkene and alkyne-containing small molecules. Catalytic transfer deuteration/hydrodeuteration closely mirrors catalytic transfer hydrogenation, a powerful approach to the mild and selective reduction of alkene and alkyne functionality.¹³

For the purpose of this minireview, we define transfer deuteration as the addition of D₂ to an organic molecule from a non-D₂ deuterium source or sources. Transfer hydrodeuteration is thus defined as the addition of HD to an organic molecule from a non-H₂, non-HD, and non-D₂ hydrogen/deuterium source or sources. Reactions in which D₂ or HD gas are generated in situ from a non-H₂, non-HD, and non-D₂ hydrogen/deuterium source or sources are often referred to as transfer deuteration/hydrodeuteration in the literature and are therefore covered in this review.

Both heterogeneous and homogeneous protocols have been reported in the catalytic transfer deuteration and transfer hydrodeuteration fields. Transition metals are typically used as catalysts for this transformation, however boron-catalyzed transfer deuteration and transfer hydrodeuteration have also been reported. These reactions often share common deuterium sources such as deuterium oxide, deuterated alcohols, Brønsted acids, silyl-deuterides, and boro-deuterides. The highest selectivities for catalytic transfer deuteration and transfer hydrodeuteration reactions have been reported using homogeneous processes. This minireview provides an examination of recent catalytic transfer deuteration/hydrodeuteration of alkenes and alkynes literature, with a focus on various catalytic systems, significant breakthroughs in the field, and opportunities and challenges to be encountered moving forward.

3 Recent Advances in Catalytic Transfer Deuteration (TD) and Transfer Hydrodeuteration (THD)

3.1 Homogeneous catalytic TD and THD

This section represents the most common approach to catalytic transfer deuteration and transfer hydrodeuteration reactions. In homogeneous transition metal catalyzed reactions, unique product selectivities are obtained depending on the metal catalyst employed. Several metals are highly selective for transfer deuteration, but Cu-catalyzed reactions are the most selective in transfer hydrodeuteration. When boron containing compounds are used as catalysts, typically a transfer hydrodeuteration reaction is carried out. These reactions are also highly selective.

3.1.1 Iridium-catalyzed reactions

Initial studies by the Himeda group demonstrate the viability of an Ir-catalyzed transfer deuteration.¹⁴ Using D₂O as both the reaction solvent and deuterium source, the authors report that iridium catalyst 4 is effective at promoting transfer deuteration in the presence of HCO₂H (Scheme 1, Eq. (1)). When DCO₂D was used instead of HCO₂H, and the solvent was changed to H₂O, lower deuterium incorporation was observed for the transfer deuteration of itaconic acid (Scheme 1, Eq. (2)).
This is consistent with formation of an Ir−H from exposure of Ir-cat 4 to HCO₂H. Rapid H/D exchange with D₂O results in the formation of an Ir−D species, which is responsible for adding an anionic deuteride to the alkene of itaconic acid. Subsequent deuteration with a D⁺ from D₂O yields the dideuterated final product.

Scheme 1 Ir-catalyzed transfer deuteration reactions.

Several years later, a more general approach to transfer deuteration was reported by Huang and coworkers.¹⁵ Using NCP pincer iridium complex (⁸⁰⁻NC⁰⁻P)IrHCl ⁸, transfer deuteration of unsaturated C−C bonds is possible using C₂D₅OD as a deuterium source. Starting with alkene-containing substrates, dideuterated alkanes are accessible in high yield (Scheme 2). The authors attribute the uneven D-distribution in product ⁵ to a reversible 2,1-insertion of alkene into the Ir−D bond. Switching to diphenylacetylene as a substrate leads to subsequent formation of the resulting d₄-alkane ⁷ in 98 % yield.

Scheme 2 Ir-cat. transfer deuteration of alkenes and an alkyne.

The authors propose a mechanism in which Ir(III) precatalyst ⁸I reacts with NaOttBu to generate Ir(I) species ⁸II (Scheme 3). Oxidative addition of C₂D₅OD converts the Ir(I) complex ⁸II to Ir(III) complex ⁸III. This can enter an off-cycle resting state when two molecules of C₂D₅OD are reversibly bound to the Ir catalyst. The active catalyst (Ir-complex ⁸III) undergoes δ-deuteride elimination to form Ir(III) dideuteride species ⁸IV, followed by the release of CD₃CDO. The CD₃CDO can react with C₂D₅OD to
form a hemiacetal that is dedeuterated to give per-deuterated ethyl acetate as a byproduct. Returning to the main catalytic cycle, coordination of the alkene to the dideuteride complex \(8\text{IV}\) affords Ir(III) complex \(8\text{V}\). The reversible deuteride migratory insertion into the alkene forms Ir(III) deuteride alkyl complex \(8\text{VI}\), which then undergoes reductive elimination to release the deuterated product.

**Scheme 3** Ir-catalyzed transfer deuteration proposed mechanism.

Sawamura and Iwai’s work complemented Huang’s method in terms of chemoselectivity.\(^{16}\) Utilizing an Ir/1,2-bis(dicyclohexylphosphino)ethane (DCyPE) catalyst, the authors devised a protocol for a chemoselective transfer hydrogenation of conjugated alkenes and internal alkynes with 1,4-dioxane as the hydrogen source. While the major focus of the work was transfer hydrogenation, the authors report one alkene transfer deuteration (10, 13 % yield, Scheme 4, Eq. (3)), and mechanistic studies revealed the potential of deuterated 1,4-dioxane as a surrogate for transfer deuteration reactions.

**Scheme 4** Alkene transfer deuteration.

The authors propose that coordination of the Ir(I) species to 1,4-dioxane-\(d_8\) (complex 11I) followed by oxidative-addition of a C(sp\(^3\))\(-D\) in 1,4-dioxane-\(d_8\) forms Ir(III) deuteride species 11II (Scheme 5). This can undergo 6-deuteride elimination, extruding Ir(III) species 11III. After alkene binding (complex 11IV), Ir–D is added across the alkene to form alkyl Ir species 11V, which undergoes reductive elimination to form the dideuterated product. The authors suggest the uneven deuterium distribution is due to the occurrence of a 6-hydride elimination of the benzylic alkyliridium intermediate.
Scheme 5 Proposed mechanism for the Ir-catalyzed transfer deuteration using 1,4-dioxane-$d_8$ as the deuterium surrogate.

In 2017, Diéguez and co-workers demonstrated a transfer deuteration of simple alkenes which was performed to evaluate mechanistic hypotheses in the corresponding transfer hydrogenation reactions.\textsuperscript{17} The deuteration was catalyzed by triazolylidene iridium(I) complex 16 and utilized 2-propanol-$d_8$ as the deuterium surrogate. For the two reported transfer deuterations, deuterium was incorporated at both the olefinic and allylic positions (13 and 15, Scheme 6, Eqs. (4) and (5)). This suggested that a fast olefin isomerization where double bond isomerization out-of-conjugation was operative during the reaction and explains the potential for uneven deuterium distribution.

Scheme 6 Ir-catalyzed transfer deuteration.

Recently, Parra-Hake and co-workers reported a transfer deuteration of $\alpha,\beta$-unsaturated carbonyl compounds using 2-propanol-$d_8$ as the deuterium source.\textsuperscript{18} Ir-catalyst 20, containing a pyrazole substituted ligand, was employed in the transfer deuteration reactions. This reaction was demonstrated on both internal and terminal alkenes (Scheme 7). The reaction occurred faster in the absence of an external base which led to the dideuterated product in high yield (17, 18). Importantly, the reaction is chemoselective and no carbonyl reduction was observed when the reaction was stopped after four hours. However, performing the reaction over 1 week led to reduction of both the alkene and carbonyl. Addition of an external base such as KOH led to the formation of the $d_3$-product 19, albeit with lower conversion.
3.1.2 Rhodium and ruthenium-catalyzed reactions

In 2006, the Inoue and Oi groups presented a rhodium-catalyzed hydrogenation of olefins with water as the hydrogen donor and zinc metal as the general reductant. After substituting H₂O for D₂O, an α,β-unsaturated ketone underwent transfer deuteration in near quantitative yield (21, Scheme 8). A sterically hindered cyclic alkene was much less reactive and afforded deuterated alkane 22 in 23% yield (1:1 syn:anti product ratio). Interestingly, when a simple olefin such as styrene was used, deuterium scrambling was observed to produce a mixture of d₁, d₂ and d₃-ethylbenzene products (24).

The authors propose a mechanism for alkene transfer deuteration in which oxidative addition of D₂O to 25I forms Rh complex 25II (Scheme 9). The olefin can coordinate to 25II, generating 25III. Metal complex 25III exists in equilibrium with rhodium adduct 25IV and the authors propose that the reversibility of this step explains the deuterium scrambling observed in the transfer deuteration of styrene. Lastly, deuteration of 25IV affords the deuterated product and rhodium complex 25V. Metal complex 25V undergoes reduction with zinc to regenerate the rhodium complex 25I.
The following year, Oltra and coworkers reported a single example of a Rh-catalyzed transfer deuteration.\textsuperscript{20} The deuterium transfer occurs from D\textsubscript{2}O and is facilitated by Ti\textsuperscript{III}. Ethyl cinnamate underwent transfer deuteration and the $\alpha,\beta$-dideuterated ester was isolated in 72\% yield (27, Scheme 10). No products were formed in the absence of Cp\textsubscript{2}TiCl, indicating that this reaction proceeds via the formation of Ti-D\textsubscript{2}O complex 28 which can act as a deuterium donor to the Rh-catalyst 29 (Scheme 10). Upon formation of the Rh dideuteride species 30, alkene transfer occurs.

In 2008, Grützmacher and co-workers also disclosed a single example of an alkene transfer deuteration.\textsuperscript{21} The authors use Rh-amido complex 33, and [D\textsubscript{5}]-ethanol as the deuterium source (Scheme 11, Eq. (6)). Notably, this early report employs an inexpensive deuterium source, which is often incompatible with metal-catalyzed transfer deuterations because of the potential for catalyst poisoning or undesirable side products. The authors demonstrated selective deuterium incorporation in the $\beta$-position of methylsuccinic acid dimethyl ester (31).

Recently, Dou and coworkers demonstrated the modularity of their rhodium-catalyzed transfer hydrogenation by performing an alkene transfer deuteration under similar conditions (Scheme...
 Whereas H$_2$O was used for the transfer hydrogenation, simply switching to D$_2$O allowed for efficient conversion of a 1,1-diphenylethene to the deuterated alkane ($35$, 93% yield).

![Scheme 12](image)

**Scheme 12** Rh-catalyzed alkene transfer deuteration and proposed mechanism.

The authors propose that after oxidative addition of diboron to Rh(I), intermediate $36I$ will react with D$_2$O and ultimately generate deuterium gas upon reductive elimination of $36II$. Insertion of D$_2$ into Rh(0) generates Rh(II) species $36III$, which adds across the alkene to form Rh(II) intermediate $36IV$. The authors attributed the deuterium scrambling in the alkane product to the reversibility of this step, thus explaining the uneven distribution of deuterium in the product. Lastly, reductive elimination provides the deuterated alkane product.

Despite the focus on Ru-catalyzed H/D exchange reactions, there has been a limited number of reports on the transfer deuteration of unsaturated carbon bonds catalyzed by ruthenium. One notable Ru-catalyzed transfer deuteration was reported in 2014 by Peese and co-workers. They developed a Ru-catalyzed tandem ring-closing metathesis/transfer hydrogenation of alkenes. This method highlights the practicality of transfer hydrogenation reagents, as they are directly added to a metathesis reaction to afford the hydrogenated product in a single reaction pot. They demonstrate that transfer deuteration is possible with deuterium sources such as NaBD$_4$ or CD$_3$OD. In the presence of one or a combination of these deuterium sources, a mixture of $d_0$, $d_1$ and $d_2$-alkane products were isolated (Table 1). The authors attribute the low deuterium content in the products to the presence of adventitious water in the reaction.

**Table 1.** Ru-cat. transfer deuteration experiments.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Hydride source</th>
<th>Proton source</th>
<th>%D$_0$/%D$_1$/%D$_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaBD$_4$</td>
<td>MeOH</td>
<td>54/36/10</td>
</tr>
<tr>
<td>2</td>
<td>NaBH$_4$</td>
<td>CD$_3$OD</td>
<td>44/43/13</td>
</tr>
<tr>
<td>3</td>
<td>NaBD$_4$</td>
<td>CD$_3$OD</td>
<td>19/43/38</td>
</tr>
</tbody>
</table>

The authors propose that the catalytic cycle is initiated by conversion of Grubbs Second Generation catalyst $39$ into Ru-deuteride $39I$ with NaBD$_4$ (Scheme 13). After alkene coordination, the Ru–D adds...
across the alkene to form alkyl ruthenium $\text{Ru}^{\text{III}}$. Deuteration by MeOD yields species alkyl ruthenium $\text{Ru}^{\text{IV}}$ and reductive elimination delivers the final product. Deuteride transfer from sodium borodeuteride regenerates the Ru(II)$D_2$ catalyst $39I$.

**Scheme 13** Proposed mechanism for Ru-cat. transfer deuteration.

### 3.1.3 Nickel and palladium-catalyzed reactions

The Zhou group reported a series of studies on asymmetric transfer hydrogenation of functionalized alkenes catalyzed by chiral nickel/bisphosphine complexes. By employing deuterated formic acid or D$_2$O as deuterium surrogates, transfer deuteration reactions were achieved with good to high deuterium incorporation. While Zhou and co-workers focused on making both $\beta$- and $\alpha$- amino acids as well as conjugated olefins in good to excellent enantioselectivity, they also report several transfer deuteration reactions as deuterium labelling studies in their series of publications (Scheme 14). High deuterium incorporation was obtained in the synthesis of $\beta$-amino acids (Scheme 14 a). When DCO$_2$D was replaced with HCO$_2$D, lower deuterium incorporation was observed (Scheme 14 b). Interestingly, this represents a rare example of a selective transfer hydrodeuteration reaction where H and D are distinguishable for incorporation. Returning to the optimal conditions, an (E)-cinnamate also undergoes transfer deuteration (Scheme 14 c).
These initial reports led to the Zhou group reporting an asymmetric umpolung deuteration of α,β-unsaturated esters.\(^{24c}\) Employing a nickel/DuPhos catalyst with indium powder as an electron donor and a catalytic amount of acetic acid in D\(_2\)O as the deuterium source, the authors were able to install deuterium in both the α- and β-positions of unsaturated esters (Scheme 15). Both electron-poor and electron-rich substrates afforded high yields with good to excellent ee. Heterocycles such as thiophene and pyridine were well-tolerated in the reaction. Notably, deuteration of an allylic alcohol substrate led to deuterium insertion at multiple sites of the isolated product (53).

The proposed mechanism involves a nickel deuteride complex generated from the reversible deuteration of the chiral Ni(0) complex by AcOD. The nickel deuteride complex inserts into the alkene, followed by deuteriolytic release of the product. Ultimately, indium reduces the Ni(II) complex to Ni(0) (Scheme 16).

A recently reported Ni-catalyzed alkene and alkyne transfer hydrogenation from Liu group disclosed several examples of an alkene and alkyne transfer deuteration reaction.\(^{25}\) Importantly, the reaction does not require an external ligand for the NiCl\(_2\) catalyst. By employing zinc as a reducing reagent and D\(_2\)O as a deuterium donor, the authors demonstrated that diphenylacetylene could undergo transfer
deuteration with high levels of deuterium incorporation (Scheme 17, Eq. (7)). Using 2-vinylnapthalene led to reduced levels of deuterium incorporation. The appearance of deuterium at benzylic and methyl positions indicates the possibility of a Ni–D addition to the alkene being a reversible step.

\[
\text{NiCl}_2 (10 \text{ mol\%) } \text{Zn flake (3 eq.)}
\]
\[
\text{dioxane/D}_2 \text{O = ca. 3/1 80 °C, 24 h (7)}
\]
\[
\text{Ph} \equiv \text{Ph} \text{ D} \equiv \text{Ph}
\]
\[
\text{NiCl}_2 (5 \text{ mol\%}) \text{Zn (2 eq.)}
\]
\[
\text{dioxane/D}_2 \text{O = ca. 3/1 80 °C, 10 h (6)}
\]

**Scheme 17** Ni-catalyzed transfer hydrogenation

Pd-catalyzed alkene and alkyne transfer deuteration is less commonly reported. A major contribution was made by Hayashi and coworkers in 2007, who reported a method for the installation of deuterium at the α- and β-positions of enones by combining a palladium catalyst with hexamethyldisilane and deuterium oxide. A variety of alkyl or aryl-substituted enones perform well in the reaction (Scheme 18). The authors propose that over-deuteration at the α-position is likely due to an acid-catalyzed H/D exchange via an enol intermediate. At the β-position, overdeuteration is likely the result of an H/D exchange occurring on the enone prior to reduction.

\[
\text{[PdCl(η^3-C_3H_5)]_2 62 (5 mol %)}
\]
\[
\text{Me}_3 \text{SiSiMe}_3 (1.5 eq.)}
\]
\[
\text{D}_2 \text{O (10.0 eq.)}
\]
\[
\text{R'} \equiv \text{R} \equiv \text{D}
\]
\[
\text{C}_9 \text{H}_8 \text{D}[125]
\]
\[
\text{[120] D}
\]
\[
\text{D} \equiv \text{Ph}
\]
\[
\text{60 85%}
\]

**Scheme 18** Pd-catalyzed transfer deuteration of enones.

The authors propose that under the given reaction conditions, a Pd–D catalytic species and Me₃Si–D are initially formed. The mechanism involves α-palladioketone and palladium enolate intermediates (Scheme 19). Accordingly, deuteriopalladation of the conjugate enone substrate will generate α-palladioketone 62II, which lies in equilibrium with palladium enolate 62III. Either complex can react with Me₃Si–D to regenerate the Pd–D catalytic species 62I and form silyl enolate 62IV, which undergoes deuteriolysis to afford the final product.
A more recent Pd-catalyzed example was reported by Fan and coworkers. They disclosed an asymmetric transfer deuteration of heterobicyclic alkene 63, using D2O as the deuterium source. Zinc powder was employed as terminal reductant in the reaction (Scheme 20, Eq. (9)). The authors noted that when using 1,4-dioxane-$d_8$ and H2O, no deuterium incorporation was observed, indicating that the deuterium is being transferred from D2O and not 1,4-dioxane-$d_8$.

The most notable Pd-catalyzed work was reported in 2020 by the Wu group. They developed a chemoselective transfer hydrodeuteration of alkenes catalyzed by Pd(OAc)$_2$. HBpin was used as the H source while D2O was employed as the deuterium source, however MeOD or AcOD could be used as an alternative deuterium source. This combination of reagents displayed higher selectivity for deuterium incorporation at the terminal site of the alkene, thus leading to selective formation of the anti-Markovnikov product. The reaction was demonstrated on several aryl alkenes, including those containing electron-rich aryl rings or electron-deficient aryl rings. The authors noted that reaction regioselectivity was better in substrates containing electron-deficient aryl rings (Scheme 21). Interestingly, the selectivity does not change when replacing D2O with H2O and replacing HBpin with DBpin. This might indicate that HD gas is being produced during the reaction.
A plausible mechanism (Scheme 22) for this transformation involves in situ formation of HD gas from the combination of D₂O/HBpin or H₂O/DBpin. Oxidative addition of HD to the Pd-catalyst 70I leads to formation of metal complex 70II. Alkene coordination to 70II, followed by insertion of Pd–H across the alkene, leads to alkyl-Pd intermediate 70III. Lastly, reductive elimination of Pd-intermediate 70III affords the hydrodeuterated product.

3.1.4 Iron and copper-catalyzed reactions

Alkene and alkyne transfer hydrodeuteration are challenging reactions to perform because they require the regioselective addition of an H atom and D atom across the functionality. Distinguishing between H and D is difficult and using transfer hydrodeuteration reaction conditions has provided an entry into efficiently distinguishing between chemically similar functionalities. A general alkene transfer hydrodeuteration was demonstrated by Wu and coworkers in 2020 (Scheme 21), but Webster and co-workers developed an iron catalyst capable of promoting selective alkene transfer hydrodeuteration a year earlier. This work has been expanded in recently published studies.

In the reaction developed by Webster and coworkers, the reagents dictate the reaction selectivity; for example, using D₂N₆H₅ and HBpin leads to the anti-Markovnikov addition of H and D (Scheme 23 a),
while using H₂NC₆H₅ and DBpin leads to the Markovnikov addition of H and D (Scheme 23b). Under the anti-Markovnikov conditions, selective monodeuteration at the terminal position of the alkene was achieved and deuterated alkanes such as 71 and 72 were regioselectively formed (Scheme 17a). Electron poor styrenes also underwent transfer hydrodeuteration, but with lower levels of regioselectivity. Similarly, the use of DBpin to deuterate the internal position of the alkene was more selective with electron-rich or neutral alkenes substrates while transfer hydrodeuteration was almost completely unselective with electron-poor alkene substrates (Scheme 23b).

A plausible mechanism for the transfer hydrodeuteration occurring with Markovnikov selectivity begins with the formation of Fe-deuteride active species 77III from Fe complex 77II. The deuteride is derived from the DBpin reagent in this step. Next a 1,2-insertion from the alkene substrate to the Fe-hydride complex 77III generates complex 77IV, which undergoes protonolysis in the presence of amine to generate the selectively deuterated alkyl product (Scheme 24).

![Scheme 23 Fe-cat. alkene transfer hydrodeuteration.](image1)

![Scheme 24 Fe-catalyzed alkene transfer hydrodeuteration proposed mechanism.](image2)
Another reaction that has been scarcely reported is a general alkyne transfer deuteration protocol. In 2020, the Clark group developed the first Cu-catalyzed transfer deuteration of aryl alkynes. The reaction employs dimethoxy(methyl)silane-$d_1$ and 2-propanol-OD (or ethanol-OD) as the deuterium sources and (R or S)-DTBM-SEGPHOS as a ligand for copper.

The authors successfully performed Cu-catalyzed transfer deuteration across a variety of terminal and internal aryl alkynes (Scheme 25). For terminal alkynes, an H/D exchange was performed on the substrate prior to use so that the [D$_5$]-alkane was isolated. In general, the aryl ring could be substituted with electron-rich or electron-poor functionality. Reduceable functionalities such as a benzyl ether or sulfonamide were stable under the mild reaction conditions. Lastly, an alkyne-containing complex natural product analog was deuterated in high yield.

Mechanistically, the authors hypothesized that formation of a Cu-D species 86I in the presence of DSiMe(OMe)$_2$ followed by insertion of Cu-D across the alkyne leads to alkenyl Cu species 86II (Scheme 26). Deuterodecupration of 86II with 2-propanol-OD extrudes the alkene intermediate. Regeneration of the Cu-D species and addition across the alkene forms alkyl Cu species 86III, followed by deuterodecupration of 86III to provide the desired deuterated alkane.
Building on their alkyne transfer deuteration reaction, the Clark group developed a Cu-catalyzed transfer hydrodeuteration of aryl alkenes (Scheme 27). A broad scope of aryl alkenes was investigated which included both terminal and internal alkenes. Alkenes substituted with electron-rich, electron-neutral or electron-poor aryl groups all performed well under the optimized conditions. Heterocycle containing aryl alkenes were also deuterated in high yield. Analysis of the isolated products by $^1$H, $^2$H and $^{13}$C NMR revealed that in most cases, only trace deuteration, if any, was observed at the methyl group. This indicated that the process occurred with high levels of regioselectivity.

Scheme 27 Cu-catalyzed alkene transfer hydrodeuteration.

To obtain a precise spectroscopic determination of the selectivity, molecular rotational resonance (MRR) spectroscopy was utilized to analyze substrates 87–89, confirming that product regioselectivity ratios of >140 : 1 are achievable under this mild protocol. MRR is capable of distinguishing between all isotopic species in an isotopic mixture. Additionally, it provides accurate identification of both the quantity and position of deuterium in each isotopic species.
3.1.5 Boron-catalyzed reactions

Prior to the report from Clark and coworkers, Oestreich and Walker reported a highly regioselective catalytic hydrodeuteration of aryl alkenes (Scheme 28). The reaction uses monodeuterated 1,4-cyclohexadienes as a surrogate for hydrogen deuteride (HD) gas and is catalyzed by B(C₆F₅)₃. Electron-rich 1,1-diaryl alkenes substrates were highly reactive compared to electron-poor alkenes. Substituting alkenes with both an aryl group and cycloalkane resulted in moderate to high yields of the transfer hydrodeuteration product, with a decrease in ring size giving a decrease in reactivity. In general, at least one substituent must be an aryl group for the reaction to proceed, and monosubstituted alkenes were not shown to be effective substrates. Significantly, this work represents the first example of a highly regioselective catalytic alken transfer hydrodeuteration.

![Scheme 28 Boron-catalyzed alkene transfer hydrodeuteration.](image)

The authors proposed that a desymmetrization of HD is responsible for the observed regioselectivity. D and H are incorporated at hydridic and protic positions of surrogate 96, resulting in deuteride abstraction by B(C₆F₅)₃. This generates an ion pair between DB(C₆F₅)₃⁻ and Wheland complex 96I (Scheme 29). Complex 96I protonates the alkene substrate to yield complex 105 and DB(C₆F₅)₃⁻. Subsequently, deuteride transfer occurs to provide the product.

![Scheme 29 Boron-catalyzed alkene transfer hydrodeuteration proposed mechanism.](image)
Inspired by the work from the Oestreich group, Hilt and coworkers developed a switchable transfer hydrodeuteration of 1,1-diaryl alkenes using a similar reaction protocol. The modular synthesis of the H and D surrogates permits a regioselective hydrodeuteration or deuterohydrogenation of a 1,1-diarylalkene. The position of the H and D in surrogates 106 and 114 depends on the site of deuteration in the diene starting material used in the Diels-Alder reaction to form each surrogate. The reaction generally employs electron-rich 1,1-diarylalkenes that undergo regioselective transfer hydrodeuteration in good to excellent yield (Scheme 30 and 31). The authors proposed that the reaction operates under a mechanism similar to the one proposed by the Oestreich group (Scheme 29).

![Scheme 30 Boron-catalyzed alkene transfer deuterohydrogenation.](image)

![Scheme 31 Boron-catalyzed alkene transfer hydrodeuteration.](image)

4 Heterogeneous Catalytic TD

4.1 Palladium-catalyzed reactions

Pd/C is among the most commonly reported heterogeneous catalyst for deuterium incorporation techniques. As reactive as they are, the Pd/C-catalyzed reactions often suffer from relatively low selectivity. Recent research has been directed to address this issue.

In 2014, Pihko and co-workers established a protocol for the chemoselective hydrosilylation of enals and enones with an activated Pd/C catalyst and a stoichiometric amount of Et₃SiH. While this reaction was performed across several substrates, transfer deuteration was only demonstrated once. Accordingly, a regioselective deuteration at the β-position of an enal was successfully performed, followed by addition of acid in a second step to yield the corresponding deuterated product (123, Scheme 32, Eq. (10)). Importantly, under the reductive conditions, the aldehyde was not reduced.
In 2015, Oba reported a transfer deuteration of alkenes and alkynes using deuterated hypophosphite as the deuterium source and Pd/C as the catalyst.\textsuperscript{8d} An internal alkyne such as phenylpropionic acid undergoes transfer deuteration in near quantitative yield under the optimal reaction conditions (Scheme 33, Eq. (11)). Alternatively, an alkene such as trans-stilbene also undergoes transfer deuteration in near quantitative yield (Scheme 33, Eq. (12)).

The Stokes group also utilized a Pd/C catalyst to perform a transfer deuteration of alkenes and alkynes.\textsuperscript{36} While transfer deuteration was not a focal point of the reported method, deuterium labelling studies demonstrate the viability of this protocol being used to perform a transfer deuteration. Importantly, the reaction utilizes D$_2$O as the deuterium source, and complete deuteration of diphenylacetylene 128 (Scheme 34, Eq. (13), 98 % D inc.) can be achieved under the optimal conditions. Alternatively, 1,1-diphenylethylene 34 also undergoes transfer deuteration (Scheme 34, Eq. (14)). In this example, the B$_2$(OD)$_4$ reagent is used in place of the B$_2$(cat)$_2$. Additionally, an uneven distribution of deuterium with a net incorporation of about one deuterium atom was found in the isolated product. This indicated a migration of hydrogen between the benzylic and homobenzylic carbons.

A major advance from the Stokes work was recently reported by Su and co-workers in 2019.\textsuperscript{37} They disclosed a photocatalytic system utilizing water spitting technology for selective deuteration of alkenes and alkynes. The catalytic system was promoted over a crystalline K cation intercalated polymeric carbon nitride (KPCN) semiconductor. Under visible light, the KPCN semiconductor anchored by a Pd co-catalyst is able to generate D$_2$ from D$_2$O and install deuterium into a broad scope of alkenes.
and alkynes. In all cases, good to excellent yields were obtained along with high levels of deuterium incorporation (Scheme 35). This included electron-rich and electron-deficient alkenes, α,β-unsaturated ketones, and terminal and internal alkynes. For α,β-unsaturated ketones, the transfer deuteration occurred chemoselectively at the alkene and no reduction of the carbonyl was reported.

<table>
<thead>
<tr>
<th>Scheme 35</th>
<th>Pd-cat. alkene transfer deuteration.</th>
</tr>
</thead>
<tbody>
<tr>
<td>alkene/alkyne</td>
<td>Pd/KPCN, LED (420 nm)</td>
</tr>
<tr>
<td>EA/D₂O, CD₂OD, AlCl₃</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>130</td>
<td>96%, 92% D</td>
</tr>
<tr>
<td>131</td>
<td>87%, 66% D</td>
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<tr>
<td>132</td>
<td>92%, 87% D</td>
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<tr>
<td>133</td>
<td>87%, 97% D</td>
</tr>
<tr>
<td>134</td>
<td>89%, &gt;96% D</td>
</tr>
<tr>
<td>135</td>
<td>90%, 95% D</td>
</tr>
</tbody>
</table>

5 Conclusion and Outlook
To keep up with current demand and meet future demand for selectively deuterated organic molecules, it is imperative to further develop catalytic transfer deuteration and hydrodeuteration reactions. Despite significant advances over the last 15 years, many opportunities for further reaction development exist. Expanding reaction scope and increasing reaction selectivity remain major challenges in this field, and transfer deuteration/hydrodeuteration reactions that proceed with exceptional functional group tolerance under mild reaction conditions remain underexplored. As milder and more selective approaches for deuterium installation into organic molecules are developed, light will continue to be shed on the potential of catalytic transfer deuteration and transfer hydrodeuteration to provide selectively deuterated organic molecules.

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Conflict of interest
The authors declare no conflict of interest.

References