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Regioselective Transfer Hydrodeuteration of Alkenes with a Hydrogen Deuteride Surrogate Using $B(C_6F_5)_3$ Catalysis

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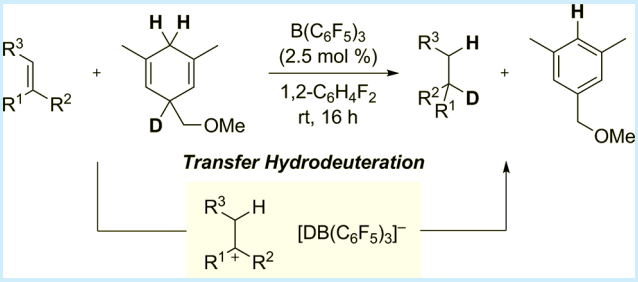
Supporting Information

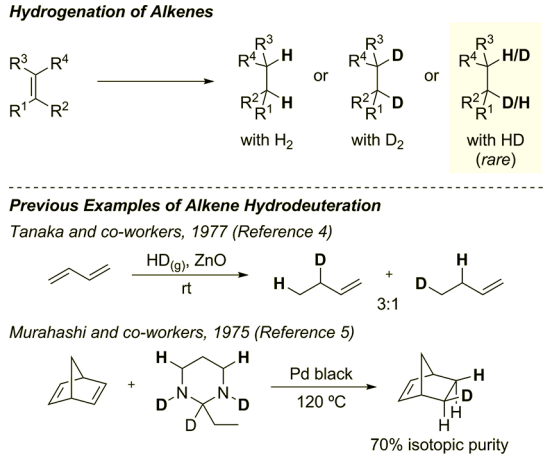
ABSTRACT: A regioselective hydrodeuteration of alkenes using monodeuterated cyclohexa-1,4-dienes as surrogates for hydrogen deuteride (HD) gas is reported. The metal-free process proceeds under $B(C_6F_5)_3$ catalysis presumably by deuteride abstraction to form borodeuteride $[DB(C_6F_5)_3]^-$ and highly Brønsted-acidic Wheland intermediates. Low catalyst loadings (2.5 mol %) are used, and the reaction proceeds at room temperature.



The hydrogenation of alkenes is an important transformation within synthetic chemistry.[1] Advances in catalyst design have produced an array of conditions capable of chemo-, regio-, and stereoselective hydrogenation that also exhibit impressive functional-group tolerance and have led to its widespread application within industry and academia.[1,2] Conventionally, dihydrogen gas (H_2) is used, but many examples of the use of deuterium gas (D_2) have also been reported.[3] By contrast, the use of the isotopically mixed congener hydrogen deuteride (HD) is exceptionally rare (Scheme 1, top).[4−6]

In part, this scarcity is due to the difficulty in discriminating between the two isotopes and selectively producing one of the two possible product regioisomers. Using a ZnO catalyst, Tanaka and co-workers achieved the hydrodeuteration of buta-1,3-diene with a modest 3:1 selectivity in favor of the internally deuterated product (Scheme 1, bottom).[4] In a mechanistic study, Murahashi and co-workers observed the transfer hydrodeuteration of norbornadiene from a deuterated 1,3-diazinane using palladium catalysis in 70% isotopic purity.[5] To the best of our knowledge, no further reports of hydrodeuteration with HD have been disclosed to date.

Scheme 1. Hydrodeuteration of Alkenes



Instead, alkene hydrodeuteration is often achieved by hydrometalation followed by deuterolysis (or deuterometalation and hydrogenolysis).[7] Using hydroboration, Brown and Murray demonstrated that, by employing BH_3/D^+ or BD_3/H^+, it was possible to prepare both regioisomers of hydrodeuterated norbornene in high isotopic purity (95 and 82%, respectively).[8] However, poor regioselectivity for the hydroboration of styrenes[9] and the two-step nature of the process somewhat limit its utility. Gronowitz and co-workers also reported the regioselective hydrozirconation/deuterolysis of styrenes, but this was accompanied by a number of side reactions.[10]

As part of our research program into the design of easy-to-handle surrogates of industrially relevant gases,[11] we recently exploited cyclohexa-1,4-diene **1** as an H_2 equivalent (Scheme 2, top).[12,13] By using the strong Lewis acid $B(C_6F_5)_3$,[14,15] the transfer hydrogenation of alkenes could be effected at room temperature, producing only mesitylene as a byproduct. Computations suggested a stepwise mechanism involving distinct borohydride and Brønsted-acidic Wheland intermediates.[12b] Recognizing this formal desymmetrization of H_2, we postulated that incorporating D and H at the formally hydridic and protic positions of the surrogate (as in **2**, Scheme 2, bottom) might enable the fully regioselective hydrodeuteration of alkenes for the first time.

The attempted synthesis of surrogate **2** began from 3,5-dimethylbenzoic acid (**3**) (Scheme 3, top). Birch reduction to **4** and deuteration of the corresponding enolate[16] followed by acid reduction furnished alcohol **5** in 84% yield over 3 steps. The

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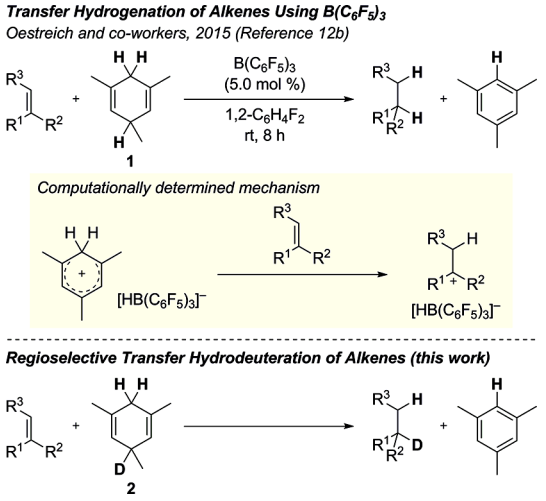
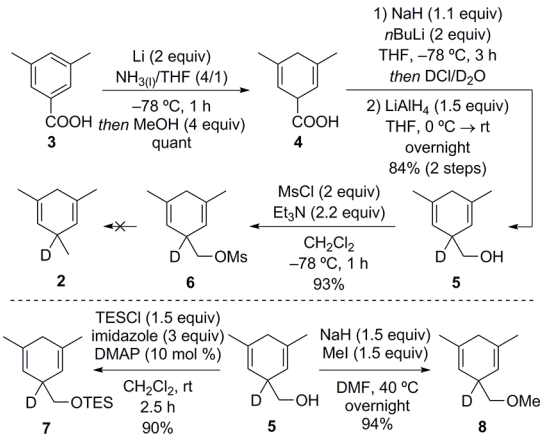
Scheme 2. Cyclohexa-1,4-dienes as H_2 or HD Surrogates



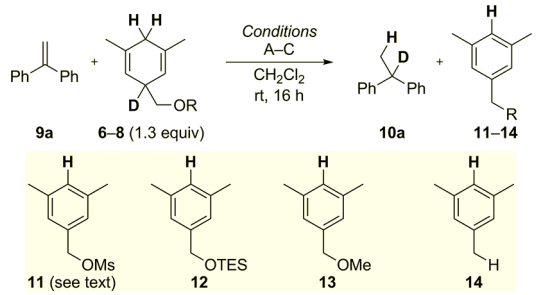
Scheme 3. Attempted Synthesis of Surrogate 2 and Synthesis of Surrogates 6−8



alcohol moiety could be activated as a leaving group by mesylation, but subsequent reaction with a range of hydride sources failed to deliver surrogate **2**.[17] Conversion of alcohol **5** to the corresponding iodide was not practical due to product instability (not shown); however, we wondered whether simple alcohol protection might provide a suitable alternative. We therefore prepared both the Et_3Si- and methyl-protected surrogates **7** and **8** in addition to mesylate **6** (Scheme 3, bottom).

We initially subjected surrogates **6**−**8** to our previously used conditions with alkene **9a** using both $B(C_6F_5)_3$ and Brønsted acid catalysis.[18] Cognizant of our $B(C_6F_5)_3$-catalyzed defunctionalization of primary tosylates with Et_3SiH,[19] we also attempted the reaction in the presence of Et_3SiH in the hope that the aromatized surrogates **11**−**13** would be converted to mesitylene (**14**) in situ. Although mesylate **6** either decomposed or was unreactive (not shown), both silyl- and methyl-protected surrogates **7** and **8** reacted as desired. Full conversion of alkene **9a** to hydrodeuterated product **10a** was observed with $B(C_6F_5)_3$ (Table 1, entries 1 and 4), and the Brønsted acid Tf_2NH also provided acceptable conversions (entries 2 and 5). However, neither surrogate performed in the presence of Et_3SiH (entries 3 and 6). Because of its better mass economy, we proceeded with surrogate **8** under $B(C_6F_5)_3$ catalysis.

Table 1. Surrogate Screen for Transfer Hydrodeuteration[a]

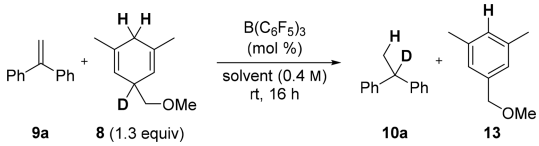


entry	surrogate	conditions[b]	conv[c] (%)
1	**7** (R = TES)	A: $B(C_6F_5)_3$	>99
2	**7** (R = TES)	B: Tf_2NH	66
3	**7** (R = TES)	C: $B(C_6F_5)_3$ + Et_3SiH	<1
4	**8** (R = Me)	A: $B(C_6F_5)_3$	>99
5	**8** (R = Me)	B: Tf_2NH	75
6	**8** (R = Me)	C: $B(C_6F_5)_3$ + Et_3SiH	decomp

[a]All reactions performed on 0.1 mmol scale. [b]A: $B(C_6F_5)_3$ (10 mol %), CH_2Cl_2 (0.4 M), rt, 16 h. B: Tf_2NH (10 mol %), CH_2Cl_2 (0.25 M), rt, 16 h. C: $B(C_6F_5)_3$ (10 mol %), Et_3SiH (1.3 equiv), CH_2Cl_2 (0.4 M), rt, 16 h. [c]Determined by ^1H NMR analysis with reference to unreacted alkene **9a**.

A brief optimization revealed that a lower catalyst loading (2.5 mol %) was sufficient for near full conversion of alkene **9a**, although further reductions were detrimental to the reaction (Table 2, entries 1−3). Reaction efficiency at the lowest catalyst

Table 2. Optimization of the Transfer Hydrodeuteration[a]



entry	solvent	$B(C_6F_5)_3$ (mol %)	yield[b] (%)
1	CH_2Cl_2	10	>99
2	CH_2Cl_2	2.5	99
3	CH_2Cl_2	1.0	72
4	C_6H_6	1.0	35
5	PhMe	1.0	79
6	1,2-$C_6H_4F_2$	1.0	94
7	1,2-$C_6H_4F_2$	2.5	96 (90)[c]
8[d]	1,2-$C_6H_4F_2$	2.5	86
9	1,2-$C_6H_4F_2$	none	<1
10[e]	1,2-$C_6H_4F_2$	5.0	85[c]

[a]All reactions performed on 0.1 mmol scale. [b]Determined by ^1H NMR analysis with reference to CH_2Br_2 as internal standard. [c]Isolated yield after flash column chromatography on silica gel. [d]Using 1.1 equiv of **8**. [e]On 1 mmol scale.

loadings could be restored by switching to 1,2-$C_6H_4F_2$ (entries 4−7), and high conversions were also achievable with only a small excess (1.1 equiv) of surrogate **8** (entry 8). No reaction was observed in the absence of $B(C_6F_5)_3$ (entry 9). The reaction could also be performed on 1 mmol scale with an isolated yield of 85% (entry 10).

With the optimized conditions in hand, we explored the scope of the hydrodeuteration (Scheme 4). In all cases, >19:1 deuterium incorporation was estimated by ^1H NMR analysis, and the synthesis of a single regioisomer was verified by the

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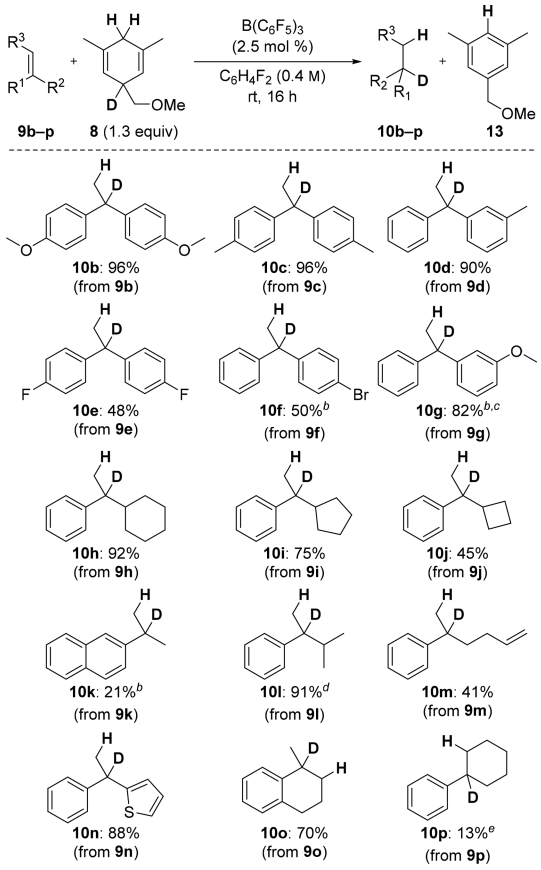
Scheme 4. Scope of Hydrodeuteration[a]



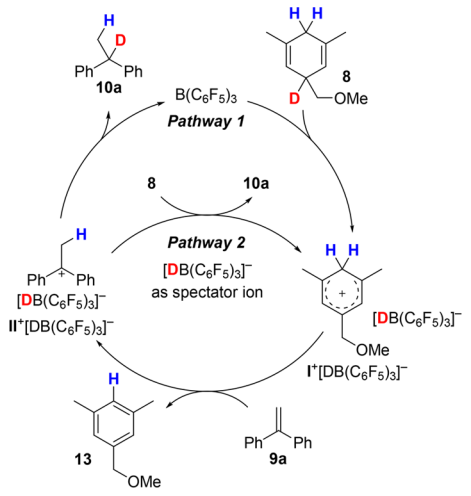
[a]All reactions performed on 0.2 mmol scale. [b]Using 5.0 mol % $B(C_6F_5)_3$. [c]Contains 6% unreacted starting material. [d]Yield determined by ^1H NMR analysis with reference to CH_2Br_2 as internal standard. Isolated yield of 39% due to product volatility. [e]Also recovered 52% of unreacted starting material.

presence of a single resonance signal in the ^2H NMR spectra. Electron-rich substituents afforded excellent reactivity with **10b**–**10d** all isolated in >90% yield. Electron-poor examples leading to **10e** and **10f** were less reactive. A higher catalyst loading was required to increase conversion to **10g** and enable easier purification (70% conversion with 2.5 mol % $B(C_6F_5)_3$). This result contrasts with that for **10d** bearing a Me group in the same position (90% yield), demonstrating the electron-withdrawing nature of the *meta*-OMe group.[20] Substrates bearing Lewis-basic, electron-withdrawing substituents such as nitro and amide groups did not react (see the Supporting Information).

Cyclic alkanes **10h**–**10j** were all tolerated, although the efficiency of the reaction decreased with smaller ring sizes. We propose that the decreasing ring size led to a greater propensity for cationic ring expansion; this was evident in the increasing decomposition present in the ^1H NMR spectra of the crude reaction mixtures.[21] Alkenes with acyclic aliphatic substitution were effective substrates, forming **10k** and **10l**, and selectivity for styrenes over alkenes lacking arene substitution was observed in the formation of **10m**. In this case, no product corresponding to the hydrodeuteration of the α-olefin was detected. Thiophene-containing **10n** was also formed in high yield, as was trisubstituted alkene **10o**. Other Lewis-basic heteroaromatic groups such as pyridine (no reaction) and furan (decomposition) were not tolerated (see the Supporting Information). Tetrasubstituted alkenes (no reaction) and purely aliphatic alkenes (side reactions predominated to give complex mixtures) were also unsuitable substrates.

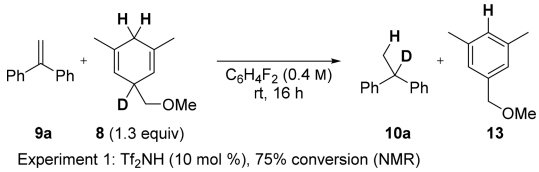
It is likely that the mechanism is analogous to that computationally determined for the $B(C_6F_5)_3$-catalyzed transfer hydrogenation of alkenes.[12b] Beginning with $B(C_6F_5)_3$, deuteride abstraction from **8** forms ion pair $\mathbf{I}^+[DB(C_6F_5)_3]^-$, and subsequent protonation of alkene **9a** by Wheland complex $\mathbf{I}^+$ leads to $\mathbf{II}^+[DB(C_6F_5)_3]^-$. Deuteride transfer then provides **10a** and returns the $B(C_6F_5)_3$ catalyst (pathway 1, Scheme 5).

Scheme 5. Catalytic Cycle



Recent calculations by Banerjee and Vanka suggest that the borohydride anion $[HB(C_6F_5)_3]^-$ may in fact be a spectator ion in related alkene hydrosilylation and imine hydrogenation chemistry, leading to the conclusion that $B(C_6F_5)_3$ takes on the role of an initiator rather than a bona fide catalyst.[22] Indeed, we have shown that the reaction may be performed in the absence of $B(C_6F_5)_3$ (and therefore $[DB(C_6F_5)_3]^-$) using Brønsted acid catalysis (experiment 1, Scheme 6). Under these conditions, the

Scheme 6. Control Experiments



Experiment 1: Tf_2NH (10 mol %), 75% conversion (NMR)
Experiment 2: $B(C_6F_5)_3$ (1 equiv), >99% conversion (NMR)
Experiment 3: $B(C_6F_5)_3$ (2.5 mol %), open flask, 90% conversion (NMR)

formal deuteride presumably originates from surrogate **8** directly (cf. pathway 2).[18] In the present case, however, it appears that $[DB(C_6F_5)_3]^-$ *can* act as a nucleophile, performing the reaction with equimolar quantities of $B(C_6F_5)_3$, and surrogate **8** led to full conversion of **9a** to **10a** (experiment 2, Scheme 6). However, we cannot exclude the possibility that $[DB(C_6F_5)_3]^-$ and surrogate **8** act simultaneously as nucleophiles under catalytic conditions (pathways 1 and 2, respectively).

In any case, the regioselectivity of deuterium incorporation under both $B(C_6F_5)_3$ and Brønsted acid catalysis is consistent with the proposed mechanism. In accordance with a stepwise mechanism, performing the reaction in an open flask led to minimal reduction in overall conversion, suggesting the formation and reactivation of gaseous HD was not a major pathway (experiment 3, Scheme 6).[23] Indeed, during ^1H NMR

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monitoring of both the model reaction and the $B(C_6F_5)_3$-catalyzed decomposition of surrogate **8**, no HD gas evolution was observed (see the Supporting Information).

In conclusion, we have reported the metal-free hydrodeuteration of alkenes using a cyclohexa-1,4-diene-based surrogate of HD gas. The stepwise mechanism provides a solution to the long-standing problem of achieving high levels of regioselectivity in hydrodeuteration chemistry. This represents a useful addition to the collection of methods for the isotopic labeling of organic compounds.[24]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02718.

General procedures, experimental details, and characterization/spectral data for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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