Organic Letters

Letter

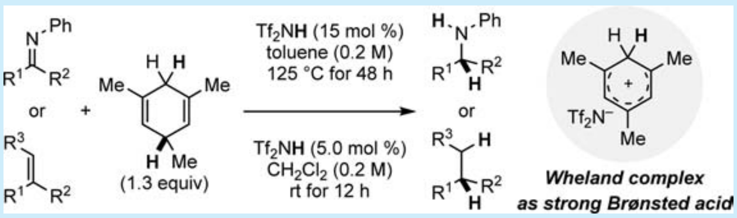
pubs.acs.org/OrgLett

Brønsted Acid-Catalyzed Transfer Hydrogenation of Imines and Alkenes Using Cyclohexa-1,4-dienes as Dihydrogen Surrogates

Indranil Chatterjee and Martin Oestreich*

Institut für Chemie, Technische Universität Berlin, Strasse des 17. Juni 115, 10623 Berlin, Germany

Supporting Information



ABSTRACT: Cyclohexa-1,4-dienes are introduced to Brønsted acid-catalyzed transfer hydrogenation as an alternative to the widely used Hantzsch dihydropyridines. While these hydrocarbon-based dihydrogen surrogates do offer little advantage over established protocols in imine reduction as well as reductive amination, their use enables the previously unprecedented transfer hydrogenation of structurally and electronically unbiased 1,1-di- and trisubstituted alkenes. The mild procedure requires 5.0 mol % of Tf_2NH, but the less acidic sulfonic acids TfOH and TsOH work equally well.

We recently developed the transfer hydrogenation[1] of imines[2] as well as alkenes[3] with $B(C_6F_5)_3$ as the Lewis acid catalyst and cyclohexa-1,4-dienes **1** as stoichiometric dihydrogen sources (Figure 1). The catalytic cycle of both

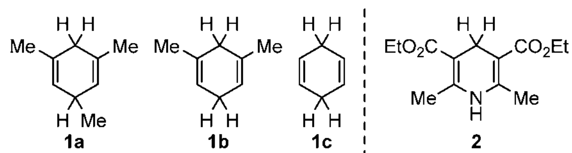
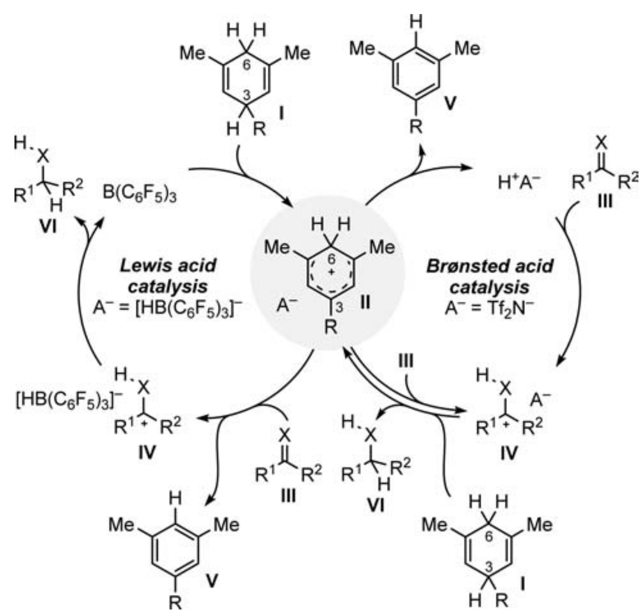


Figure 1. Dihydrogen surrogates for transfer hydrogenation.

reactions commences with $B(C_6F_5)_3$-mediated hydride abstraction from cyclohexa-1,4-diene **I** to form ion pair **II** with $A^- = [HB(C_6F_5)_3]^-$ in low concentration (Scheme 1, left cycle).[3] The methyl groups at C1 and C5 of **II** lend stabilization to the high-energy Wheland intermediate, and another methyl group at C3 is required to further lower its electrophilicity[3] [R = H (**1b**) for imine reduction[2] and R = Me (**1a**) for alkene reduction[3]]. Both Wheland complexes act as strong Brønsted acids, and protonation of the σ- or π-basic substrate **III** (**II** → **V** and **III** → **IV**) is followed by hydride transfer from $[HB(C_6F_5)_3]^-$ to cationic intermediate **IV** concomitant with regeneration of $B(C_6F_5)_3$ (**IV** → **VI**).

The intermediacy of the highly Brønsted acidic Wheland complex[4] as part of ion pair **II** led us to consider competing Brønsted acid catalysis where the cyclohexa-1,4-diene **I** would serve as the hydride source in the reduction of **IV** (Scheme 1, right cycle). Hydride transfer from **I** is, however, both kinetically and thermodynamically far less favorable[5] than that from $[HB(C_6F_5)_3]^-$ [**I** → **II** vs $[HB(C_6F_5)_3]^- \rightarrow B(C_6F_5)_3$].[3] Conversely, the cyclohexa-1,4-diene could become the

Scheme 1. Catalytic Cycles of the Lewis and Brønsted Acid-Catalyzed Transfer Hydrogenation



reductant in the absence of the borohydride ($A^- \neq [HB(C_6F_5)_3]^-$). This could be achieved by initiating the catalysis with Brønsted acids H^+A^-, and the Wheland intermediate with A^- as nonhydridic counteranion could even maintain catalytic turnover.

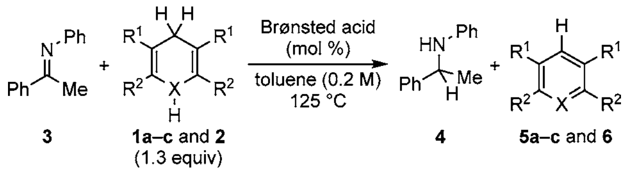
Received: April 8, 2016
Published: May 11, 2016

DOI: 10.1021/acs.orglett.6b01016
Org. Lett. 2016, 18, 2463−2466

We disclose here the Brønsted acid-catalyzed transfer hydrogenation[6] of the aforementioned substrates.[7] While common for imines,[8] the related reduction of alkenes is exceedingly rare.[9] Moreover, we introduce cyclohexa-1,4-dienes **1** as alternative to the well-established Hantzsch dihydropyridines, e.g., **2** (Figure 1).[10]

Imine Transfer Hydrogenation. We began with testing representative Brønsted acids in the reduction of acetophenone-derived **3** with a phenyl group at the nitrogen atom (**3** → **4**, Table 1). With cyclohexa-1,4-diene **1a** as reductant, carboxylic and phosphinic acids showed no conversion (entries 1 and 2). TsOH was also ineffective, but the stronger sulfonic acid TfOH afforded amine **4** in promising yield, which further improved with sulfonamide Tf_2NH as the catalyst (entries 3–5). Cyclohexa-1,4-dienes **1b** and **1c** with less or no methyl substitution were inferior to **1a** (entries 5–7). Not surprisingly,[8] Hantzsch dihydropyridine **2** furnished amine **4** in quantitative yield (entry 8). Optimization of the reaction by increasing the catalyst loading from 10 to 20 mol % and the reaction time from 12 to 48 h also led to full conversion and high isolated yield for cyclohexa-1,4-diene **1a** as the reducing agent (entries 9–11). The Tf_2NH-catalyzed ketimine transfer hydrogenation was generally slower than and not as clean as the $B(C_6F_5)_3$ catalysis where **1b** was sufficiently hydridic.[2]

Table 1. Optimization of the Brønsted Acid-Catalyzed Transfer Hydrogenation of Imines

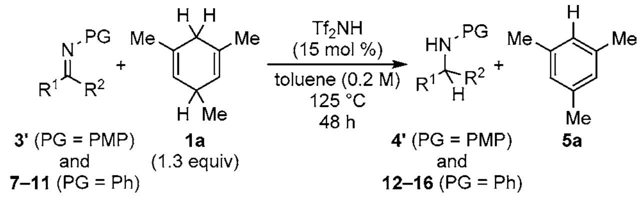


entry	surrogate	Brønsted acid	mol %	time (h)	conv[a] (%)
1	**1a**	$C_6F_5CO_2H$	10	12	—
2	**1a**	$Ph_2P(O)OH$	10	12	—
3	**1a**	TsOH	10	12	—
4	**1a**	TfOH	10	12	30
5	**1a**	Tf_2NH	10	12	50
6	**1b**	Tf_2NH	10	12	18
7	**1c**	Tf_2NH	10	12	—
8	**2**	Tf_2NH	10	12	quant
9	**1a**	Tf_2NH	10	48	82
10	**1a**	Tf_2NH	15	48	98 (86)[b]
11	**1a**	Tf_2NH	20	48	quant

[a]Determined by GLC analysis with reference to starting material. [b]Isolated yield after flash chromatography on silica gel in parentheses.

We applied the optimized protocol to a few electronically modified acetophenone-based ketimines and found low conversion for the methoxy derivative, indicating attenuated hydride affinity of the corresponding iminium ion intermediate (**7**–**9**, Table 2, entries 1–3). An isobutyl group at the imine carbon atom had a minor effect on conversion and yield (**10** → **15**, entry 4). The removable PMP group was tolerated but resulted in substantially diminished reactivity (**3′** → **4′**, entry 5). The aldimine derived from benzaldehyde was far more reactive than any of the ketimines, and full conversion was already obtained with a 10 mol % catalyst loading after 12 h; 92% conversion was even reached at room temperature[11] (**11** → **16**, entry 6). What is interesting here is that the protecting-group tolerance is orthogonal to that of the $B(C_6F_5)_3$-catalyzed transfer hydrogenation of aldimines.[2] The tosyl group was not stable toward strong Brønsted acids but is perfectly compatible with $B(C_6F_5)_3$. Conversely, unlike ketimines, *N*-phenyl-substituted aldimines did not participate in the $B(C_6F_5)_3$-catalyzed transfer hydrogenation.[2]

Table 2. Tf_2NH-Catalyzed Transfer Hydrogenation of Aryl-Protected Imines

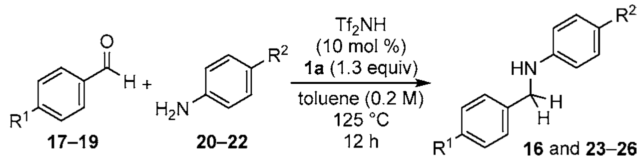


entry	imine	R^1	R^2	amine	conv[a] (%)	yield[b] (%)
1	**7**	$4\text{-}CF_3C_6H_4$	Me	**12**	quant	77
2	**8**	$4\text{-}BrC_6H_4$	Me	**13**	quant	84
3	**9**	$4\text{-}MeOC_6H_4$	Me	**14**	35[c]	—
4	**10**	Ph	*i*Bu	**15**	89	81
5	**3′**	Ph	Me	**4′**	66	62
6[d,e,f]	**11**	Ph	H	**16**	quant	87

[a]Determined by GLC analysis with reference to starting material. [b]Isolated yield after flash chromatography on silica gel. [c]Messy reaction. [d]10 mol % of Tf_2NH. [e]12 h reaction time. [f]92% conversion at room temperature after 12 h reaction time.

The facile aldimine reduction prompted us to briefly investigate the related Tf_2NH-catalyzed reductive amination (Table 3).[12] Combinations of (electron-deficient) benzaldehydes **17**–**19** and (electron-rich) anilines **20**–**22** furnished amines **16** and **23**–**26** in high isolated yields.

Table 3. Tf_2NH-Catalyzed Reductive Amination of Benzaldehydes with Anilines



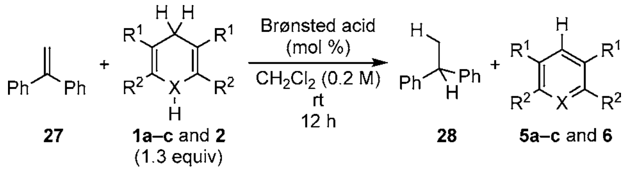
entry	benzaldehyde	R^1	aniline	R^2	amine	yield[a] (%)
1	**17**	H	**20**	H	**16**	86
2	**18**	F	**20**	H	**23**	84
3	**19**	NO_2	**20**	H	**24**	92
4	**17**	H	**21**	Cl	**25**	88
5	**17**	H	**22**	OMe	**26**	85

[a]Isolated yield after flash chromatography on silica gel.

Alkene Transfer Hydrogenation. We are aware of just one example of Brønsted acid-catalyzed transfer hydrogenation of alkenes.[9] Zhu, Lin, Sun, and co-workers accomplished the enantioselective reduction of 1,1-diaryl-substituted alkenes using **2** but an *ortho* hydroxy group at one of the aryl groups was required. We were therefore delighted to see that any of the cyclohexa-1,4-dienes **1a**–**1c** promoted the hydrogenation of 1,1-diphenylethylene at room temperature[11] with TsOH, TfOH, and Tf_2NH as catalysts (**27** → **28**, Table 4, entries 3–7); $C_6F_5CO_2H$ and $Ph_2P(O)OH$ were again ineffective (entries 1 and 2). Strikingly, Hantzsch dihydropyridine **2** did not show any conversion under the otherwise identical setup (entry 8). Lowering the catalyst loading from 10 to 5.0 mol % still afforded a quantitative isolated yield (entry 9).

DOI: 10.1021/acs.orglett.6b01016
Org. Lett. 2016, 18, 2463–2466

Table 4. Optimization of the Brønsted Acid-Catalyzed Transfer Hydrogenation of Alkenes

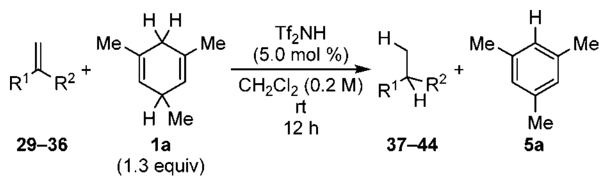


entry	surrogate	Brønsted acid	mol %	conv[a] (%)
1	**1a**	$C_6F_5CO_2H$	10	—
2	**1a**	$Ph_2P(O)OH$	10	—
3	**1a**	TsOH	10	93
4	**1a**	TfOH	10	92
5	**1a**	Tf_2NH	10	quant
6	**1b**	Tf_2NH	10	97
7	**1c**	Tf_2NH	10	quant
8	**2**	Tf_2NH	10	—
9	**1a**	Tf_2NH	5.0	quant (99)[b]

[a]Determined by GLC analysis with reference to starting material. [b]Isolated yield after flash chromatography on silica gel in parentheses.

Several 1,1-disubstituted alkenes were successfully subjected to the optimized procedure (**29**–**36** → **37**–**44**, Table 5). As

Table 5. Tf_2NH-Catalyzed Transfer Hydrogenation of 1,1-Disubstituted Alkenes



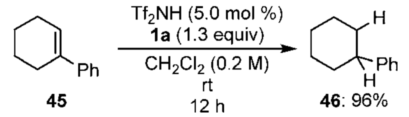
entry	alkene	R^1	R^2	alkane	yield[a] (%)
1	**29**	$4\text{-}FC_6H_4$	$4\text{-}FC_6H_4$	**37**	96
2	**30**	Ph	$4\text{-}BrC_6H_4$	**38**	99
3	**31**	Ph	$4\text{-}MeOC_6H_4$	**39**	71
4	**32**	Ph	Me	**40**	41[b]
5	**33**	Ph	*i*Pr	**41**	99[b]
6	**34**	Ph	Cy	**42**	99
7	**35**	Me	*n*Hept	**43**	57[b]
8	**36**	Cy	Cy	**44**	96[b]

[a]Isolated yield after flash chromatography on silica gel. [b]Determined by ^1H NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard added after the reaction.

before in the imine case (cf. **9** → **14**, Table 2, entry 3), an electron-donating methoxy group was detrimental to the hydride affinity of the carbenium ion intermediate; however, the isolated yield remained good (**31** → **39**, entry 3). Sterically less hindered alkenes with a methyl group were susceptible to thermoneutral dimerization[3] (**32** → **40** and **35** → **43**, entries 4 and 7); we had made the same observation in the $B(C_6F_5)_3$-catalyzed transfer hydrogenation.[3] Generally, the results of the Brønsted acid catalysis compared well with those of the $B(C_6F_5)_3$ catalysis.[3] A trisubstituted alkene was also hydrogenated in high yield (**45** → **46**, Scheme 2). However, α-olefins and 1,2-disubstituted alkenes did not work.

We demonstrated here that cyclohexa-1,4-dienes are viable alternatives to Hantzsch dihydropyridines in Brønsted acid-catalyzed transfer hydrogenation. The reduction of imines, including examples of reductive amination, require a high

Scheme 2. Transfer Hydrogenation of 1-Phenylcyclohex-1-ene



temperature and prolonged reaction time, offering little advantage over established protocols (aside from the separation of the pyridine waste). However, the use of cyclohexa-1,4-diene and methylated congeners thereof makes the ambient-temperature hydrogenation of structurally[9] and electronically unbiased alkenes possible. The Hantzsch dihydropyridine fails to react here whereas the hydrocarbon-based dihydrogen sources cleanly convert those alkenes into alkanes, even in the presence of the rather weak Brønsted acid TsOH.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01016.

General procedures, experimental details, characterization data, and ^1H, ^{13}C, and ^{19}F NMR spectra for all compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: martin.oestreich@tu-berlin.de.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was supported by the Cluster of Excellence *Unifying Concepts in Catalysis* of the Deutsche Forschungsgemeinschaft (EXC 314/2). M.O. is indebted to the Einstein Foundation (Berlin) for an endowed professorship.

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DOI: 10.1021/acs.orglett.6b01016
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(11) Hydride transfer from cyclohexa-1,4-dienes to ketiminium ions is likely to be kinetically disfavored and thermodynamically not particularly favored (for the computation of a model reaction, see the Supporting Information of ref 5), hence requiring a high reaction temperature. Less hindered and more electrophilic aldiminium ions are therefore expected to react at lower reaction temperatures. Likewise, carbenium ions do abstract hydride from cyclohexa-1,4-dienes at ambient temperature.

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DOI: 10.1021/acs.orglett.6b01016
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