



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

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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 Tf₂NH, but the less acidic sulfonic acids TfOH and TsOH work equally well.

We recently developed the transfer hydrogenation¹ of imines² as well as alkenes³ 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 electrophilicity³ [R = H (1b) for imine reduction² and R = Me (1a) for alkene reduction³]. Both Wheland complexes act as strong Brønsted acids, and protonation of the σ - or π -basic substrate III (II \rightarrow V and III \rightarrow 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 \rightarrow VI).

The intermediacy of the highly Brønsted acidic Wheland complex⁴ 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 favorable⁵ than that from $[HB(C_6F_5)_3]^-$ [I \rightarrow II vs $[HB(C_6F_5)_3]^- \rightarrow B(C_6F_5)_3]^3$. Conversely, the cyclohexa-1,4-diene could become the





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.

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Organic Letters

We disclose here the Brønsted acid-catalyzed transfer hydrogenation⁶ 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 an 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 $(3 \rightarrow 4, \text{ Table } 1)$. With cyclohexa-1,4-diene 1a as reductant,

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

Ph I	H Ph R ¹ Me R ² H 1a-c (1.3 c	H R ¹ R ² H R ² H H H H H H H H H H H H H H H H H H H	d acid %) I (0.2 M) Ph °C	HN ^{, Ph} ↓ Me ⁺ H I	$ \begin{array}{c} H \\ R^1 \\ R^2 \\ R^2 \\ T \\ T$		
entry	surrogate	Brønsted acid	mol %	time (h)	$\operatorname{conv}^{a}(\%)$		
1	1a	C ₆ F ₅ CO ₂ H	10	12	_		
2	1a	$Ph_2P(O)OH$	10	12	_		
3	1a	TsOH	10	12	_		
4	1a	TfOH	10	12	30		
5	1a	Tf ₂ NH	10	12	50		
6	1b	Tf ₂ NH	10	12	18		
7	1c	Tf ₂ NH	10	12	_		
8	2	Tf ₂ NH	10	12	quant		
9	1a	Tf ₂ NH	10	48	82		
10	1a	Tf ₂ NH	15	48	98 (86) ^b		
11	1a	Tf ₂ NH	20	48	quant		
Determined by GLC analysis with reference to starting material							

^bIsolated yield after flash chromatography on silica gel in parentheses.

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 Tf₂NH 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 Tf₂NH-catalyzed ketimine transfer hydrogenation was generally slower than and not as clean as the B(C₆F₅)₃ catalysis where **1b** was sufficiently hydridic.²

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 $(10 \rightarrow 15, \text{ entry 4})$. The removable PMP group was tolerated but resulted in substantially diminished reactivity $(3' \rightarrow 4', \text{ entry 5})$. 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 temperature¹¹ (11 \rightarrow 16, entry 6). What is interesting here is that the protectinggroup tolerance is orthogonal to that of the B(C₆F₅)₃-catalyzed

Table 2. Tf ₂ NH-Catalyzed	Transfer	Hydrogenation	of Aryl-
Protected Imines			

N R ¹ 3' (PG ar 7–11 (P	, PG Me R ² = PMP) nd G = Ph)	H H H Me H Me 1a (1.3 equiv)	Tf ₂ NH (15 mol toluene (0 125 °(48 h	H <u>%)</u> 2 M) R C 4' (P 12–16	$HN^{PG} Me$ $H^{1} + R^{2}$ G = PMP) and G = Ph)	H Me 5a
entry	imine	\mathbb{R}^1	R ²	amine	$\operatorname{conv}^{a}(\%)$	yield ^b (%)
1	7	$4-CF_3C_6H_4$	Me	12	quant	77
2	8	4-BrC ₆ H ₄	Me	13	quant	84
3	9	4-MeOC ₆ H ₄	Me	14	35 ^c	—
4	10	Ph	<i>i</i> Bu	15	89	81
5	3′	Ph	Me	4′	66	62
6 ^{<i>d</i>,<i>e</i>,<i>f</i>}	11	Ph	Н	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 Tf₂NH. ^{*e*}12 h reaction time. ^{*f*}92% conversion at room temperature after 12 h reaction time.

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

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



R ¹	0 H + H ₂ N	R ²	Tf ₂ Nł 2 (10 mol 1a (1.3 e toluene (0 125 ° 12 h	H %) 0.2 M) C R ¹		R^2
entry	benzaldehyde	\mathbb{R}^1	aniline	\mathbb{R}^2	amine	yield ^a (%)
1	17	Н	20	Н	16	86
2	18	F	20	Н	23	84
3	19	NO_2	20	Н	24	92
4	17	Н	21	Cl	25	88
5	17	Н	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 temperature¹¹ with TsOH, TfOH, and Tf₂NH as catalysts (**27** \rightarrow **28**, Table 4, entries 3–7); C₆F₅CO₂H and Ph₂P(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).

Table 4. Optimization of the Brønsted Acid-CatalyzedTransfer Hydrogenation of Alkenes

Ph Ph 27	$H H$ $R^{1} + R^{2} X R$ H	Brønsted acid (mol %) CH ₂ Cl ₂ (0.2 M) rt 12 h	H Ph H H + 28	$ \begin{array}{c} H \\ R^{1} \\ R^{2} \\ 5a-c \text{ and } 6 \end{array} $
entry	surrogate	Brønsted acid	mol %	$\operatorname{conv}^{a}(\%)$
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 ₂ NH	10	quant
8	2	Tf ₂ NH	10	—
9	1a	Tf ₂ NH	5.0	quant (99) ^b

^aDetermined by GLC analysis with reference to starting material. ^bIsolated yield after flash chromatography on silica gel in parentheses.

Several 1,1-disubstituted alkenes were successfully subjected to the optimized procedure ($29-36 \rightarrow 37-44$, Table 5). As

Table 5. Tf₂NH-Catalyzed Transfer Hydrogenation of 1,1-Disubstituted Alkenes

$R^{1} R^{2} + M^{e} $					
entry	alkene	R^1	\mathbb{R}^2	alkane	yield ^a (%)
1	29	$4-FC_6H_4$	$4-FC_6H_4$	37	96
2	30	Ph	4-BrC ₆ H ₄	38	99
3	31	Ph	4-MeOC ₆ H ₄	39	71
4	32	Ph	Me	40	41 ^b
5	33	Ph	iPr	41	99 ^b
6	34	Ph	Су	42	99
7	35	Me	nHept	43	57 ^b
8	36	Су	Су	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. $9 \rightarrow 14$, 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 ($31 \rightarrow 39$, entry 3). Sterically less hindered alkenes with a methyl group were susceptible to thermoneutral dimerization³ ($32 \rightarrow 40$ and $35 \rightarrow 43$, entries 4 and 7); we had made the same observation in the B(C₆F₅)₃-catalyzed transfer hydrogenation.³ Generally, the results of the Brønsted acid catalysis compared well with those of the B(C₆F₅)₃ catalysis.³ A trisubstituted alkene was also hydrogenated in high yield ($45 \rightarrow 46$, 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 acidcatalyzed transfer hydrogenation. The reduction of imines, including examples of reductive amination, require a high Scheme 2. Transfer Hydrogenation of 1-Phenylcyclohex-1ene



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 structurally⁹ 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.or-glett.6b01016.

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

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Notes

The authors declare no competing financial interest.

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