Transfer Hydrogenation

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$B(C_6F_5)_3$-Catalyzed Transfer Hydrogenation of Imines and Related Heteroarenes Using Cyclohexa-1,4-dienes as a Dihydrogen Source**

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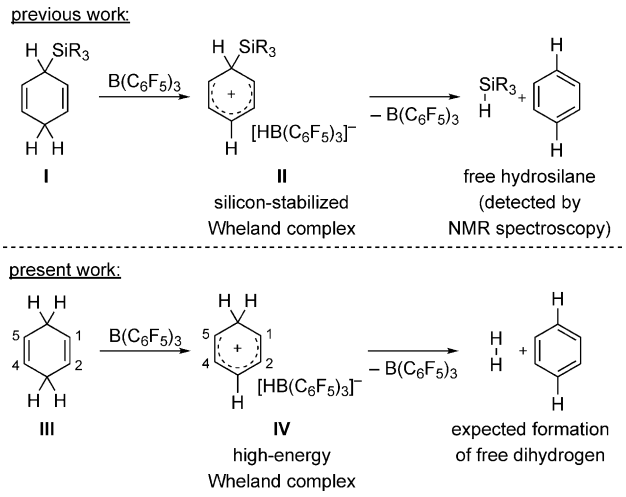
Abstract: *The strong boron Lewis acid tris(pentafluorophenyl)borane, $B(C_6F_5)_3$, is shown to abstract a hydride from suitably donor-substituted cyclohexa-1,4-dienes, eventually releasing dihydrogen. This process is coupled with the FLP-type (FLP = frustrated Lewis pair) hydrogenation of imines and nitrogen-containing heteroarenes that are catalyzed by the same Lewis acid. The net reaction is a $B(C_6F_5)_3$-catalyzed, i.e., transition-metal-free, transfer hydrogenation using easy-to-access cyclohexa-1,4-dienes as reducing agents. Competing reaction pathways with or without the involvement of free dihydrogen are discussed.*

The potent Lewis acid $B(C_6F_5)_3$ mediates the heterolytic splitting of Si–H and H–H bonds in the presence of both weak and strong Lewis bases, provided that Lewis pair formation is either reversible[1] or frustrated.[2] The hydride is transferred to the boron atom to yield $[HB(C_6F_5)_3]^-$, and the silicon cation or the proton are absorbed by the Lewis base. The borohydride generated by that unique bond activation engages in various reduction processes where the silicon cation or proton lower the energy of the lowest unoccupied molecular orbital of the acceptor. In this way, several transition-metal-free hydrosilylations[1,3–6] and hydrogenations[7–12] catalyzed by $B(C_6F_5)_3$ became possible.

We recently discovered that $B(C_6F_5)_3$ is also capable of hydride abstraction from cyclohexa-1,4-dienes **I** that bear a silicon group in the 3-position (Scheme 1, top).[13] The $C(sp^3)$–H bond in **I** develops hydridic character through hyperconjugation with the $C(sp^3)$–Si bond that later stabilizes the resulting Wheland intermediate **II**. With $[HB(C_6F_5)_3]^-$ as the counteranion, **II** collapses to liberate the free hydrosilane along with benzene at room temperature. The net reaction is catalytic in $B(C_6F_5)_3$ and was then coupled with $B(C_6F_5)_3$-catalyzed alkene hydrosilylation, thereby enabling the previously unprecedented ionic transfer hydrosilylation.[13] These findings led us to consider the related but more demanding $B(C_6F_5)_3$-catalyzed release of dihydrogen from cyclohexa-1,4-dienes **III** (Scheme 1, bottom). The challenge resides in the unfavorable formation of the high-energy intermediate **IV**. We disclose here the successful implementation of this unusual hydride abstraction[14] in the transfer hydrogenation of imines.[15] While a $B(C_6F_5)_3$-catalyzed transfer hydrogenation of imines using amines as the dihydrogen source is known (Meerwein–Ponndorf–Verley-type reduction),[16,17] an unsaturated hydrocarbon is used in the present approach.[18]



Scheme 1. $B(C_6F_5)_3$-catalyzed release of hydrosilanes (verified) and dihydrogen (planned) from cyclohexa-1,4-dienes.

We began our investigation by screening easily accessible cyclohexa-1,4-dienes **1** in the reduction of an aldimine (Scheme 2). The *tert*-butyl group at the imine nitrogen atom was shown before to be compatible with $B(C_6F_5)_3$-catalyzed hydrogenation.[9] We anticipated that elevated reaction temperatures would be necessary to facilitate hydride abstraction but cyclohexa-1,4-diene itself was reluctant to react even at 125 °C (**1a**, Scheme 2). We reasoned that +I and +M substituents in the appropriate positions of **1** (1,5 rather than 2,4, favoring the hydrogen atoms at the C3- over the C6-methylene group) could render the formation of the corresponding Wheland complexes possible at high temperature. We were then delighted to find that full conversion was seen with 1,5-dimethylcyclohexa-1,4-diene, forming *m*-xylene as the sole byproduct (**1b**, Scheme 2). The methyl groups are also capable of hyperconjugation, thereby lending further stabilization to the phenonium ion intermediate. Surprisingly, 1,5-dimethoxycyclohexa-1,4-diene was slightly less effective (**1c**, Scheme 2), and we attribute this to formation of a Lewis pair between $B(C_6F_5)_3$ and the ether oxygen atoms.[14] The poor reactivity of γ-terpinene with its unprofitable 1,4-substitution pattern emphasizes the requirement of elec-

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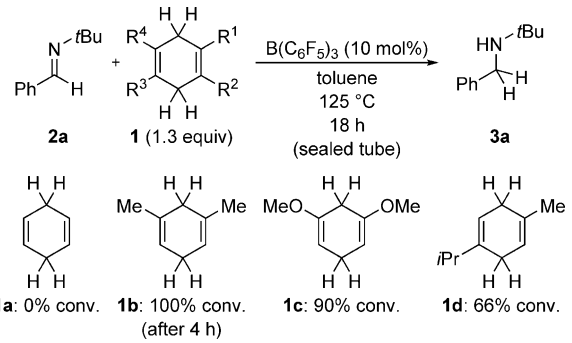


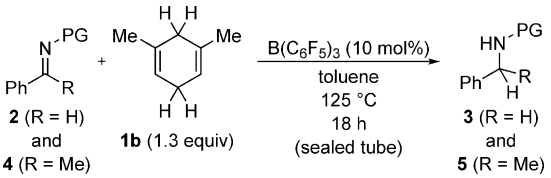
Scheme 2. Screening of various cyclohexa-1,4-dienes.

tron-donating groups in the 1,5-positions of **1** (**1d**, Scheme 2). This trend is in accordance with the dramatic effect of a silicon group in the bisallylic position, allowing for hydride abstraction at room temperature.[13] The reaction temperature of 125 °C is in the range of those reported for the $B(C_6F_5)_3$-catalyzed imine hydrogenations under moderate dihydrogen pressure.[9] Reactions were routinely maintained at that temperature for 18 h but monitoring the progress by ^{1}H NMR spectroscopy indicated full conversion after 4 h (**1b**, Scheme 2). Again, similar results were obtained with dihydrogen as the reductant.[9] Lowering the catalyst loading to 5.0 mol% was detrimental to conversion, resulting in markedly prolonged reaction times.

After the identification of **1b** as the reducing agent, we screened typical protecting groups (Table 1) at the aldimine nitrogen atom (entries 1–7) and tested a series of ketimine protecting groups (entries 8–12). Of the oxygen donor-free groups, only *tert*-butyl and benzhydryl imparted optimal steric shielding of the nitrogen lone pair (Table 1, entries 1 and 3). A benzyl group was too small (Table 1, entry 2), in agreement with observations made by Stephan and co-workers with FLPs.[19] Decreased Lewis basicity accounts for the lack of reactivity seen with the phenyl-substituted aldimine (Table 1, entry 4). As described earlier for the imine reduction with dihydrogen,[9b] the tosyl group was compatible with $B(C_6F_5)_3$ but other oxygen-containing groups were not (Table 1, entries 5–7). The results were different with the more Lewis basic ketimines, and the *N*-phenyl-substituted ketimine was fully converted into the corresponding amine in 12 h (Table 1, entry 9). This prompted us to also test the removable *para*-methoxyphenyl (PMP) group, and that worked equally well (Table 1, entry 12). As expected, protection with the less hindered benzyl group and coordinating groups was unsuccessful (Table 1, entries 8, 10, and 11). The *N*-tosylated ketimine was much less reactive than the related aldimine (entry 10 vs. entry 5).

The survey of the substrate scope held a surprise (Table 2). A handful of aldimines protected by the useful tosyl group reacted smoothly, even with *ortho* substitution (entry 4) or a peri position (entry 5). Phenyl-substituted ketimines were generally sufficiently reactive but increased electron density at the imine (or iminium ion) carbon atom thwarted the borohydride reduction. A 4-anisyl group was not tolerated (entry 10), and the cyclohexanone-derived imine was also completely unreactive (entry 14).

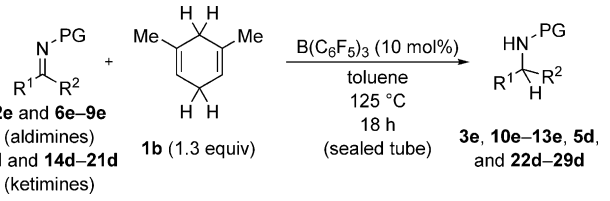
Table 1: Variation of the protecting group at the imine nitrogen atom.



Entry	Imine	R	PG	Amine	Conv. [%][a]	Yield [%][b]
1[c]	**2a**	H	*t*Bu	**3a**	100	quant.
2	**2b**	H	CH_2Ph	**3b**	0	–
3	**2c**	H	$CHPh_2$	**3c**	100	95
4	**2d**	H	Ph	**3d**	0	–
5	**2e**	H	$S(O)_2Tol$	**3e**	82	73
6	**2f**	H	$P(O)Ph_2$	**3f**	0	–
7	**2g**	H	C(O)O*t*Bu	**3g**	0	–
8	**4b**	Me	CH_2Ph	**5b**	0	–
9[d]	**4d**	Me	Ph	**5d**	100	94
10	**4e**	Me	$S(O)_2Tol$	**5e**	20	–
11	**4f**	Me	$P(O)Ph_2$	**5f**	0	–
12	**4g**	Me	PMP	**5g**	100	99

[a] Determined by GLC analysis with reference to starting material. [b] Isolated after flash chromatography on silica gel. [c] 4 h reaction time. [d] 12 h reaction time. PG = protecting group.

Table 2: Substrate scope for tosyl-protected aldimines and phenyl-substituted ketimines.



Entry	Imine	R^1	R^2	PG	Amine	Yield [%][a]
1	**2e**	Ph	H	$S(O)_2Tol$	**3e**	73
2	**6e**	4-MeC_6H_4	H	$S(O)_2Tol$	**10e**	85
3	**7e**	4-ClC_6H_4	H	$S(O)_2Tol$	**11e**	71
4	**8e**	2-BrC_6H_4	H	$S(O)_2Tol$	**12e**	71
5	**9e**	1-naphthyl	H	$S(O)_2Tol$	**13e**	83
6	**4d**	Ph	Me	Ph	**5d**	94
7	**14d**	4-$CF_3C_6H_4$	Me	Ph	**22d**	98
8	**15d**	4-BrC_6H_4	Me	Ph	**23d**	96
9	**16d**	3,5-$Me_2C_6H_3$	Me	Ph	**24d**	93
10	**17d**	4-$MeOC_6H_4$	Me	Ph	**25d**	no reaction
11	**18d**	Ph	Et	Ph	**26d**	99
12	**19d**	Ph	*i*Bu	Ph	**27d**	91
13	**20d**	Ph	Ph	Ph	**28d**	75[b]
14	**21d**	-$(CH_2)_5$-		Ph	**29d**	no reaction

[a] Isolated after flash chromatography on silica gel. [b] 84% conversion.

We also subjected a few nitrogen-containing heteroarenes, known to undergo partial hydrogenation with $B(C_6F_5)_3$,[11] to the transfer-hydrogenation protocol (Figure 1). Their Lewis acid/Lewis base pairing with $B(C_6F_5)_3$ had been analyzed by NMR spectroscopy at room temperature previously showing 50% adduct formation for acridine (**30**) and 2-methylquinoline (**32**) and traces for 2-phenylquinoline (**31**).[11a] Gratifyingly, transfer hydrogenation of **30**–**32** afforded **33**–**35** in high

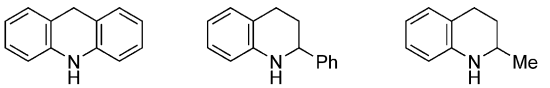
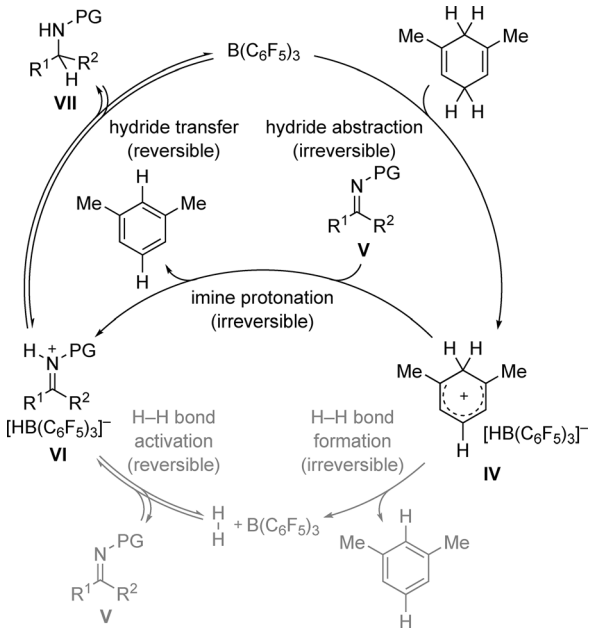


Figure 1. Transfer hydrogenation of acridine (**30**→**33** using 1.3 equiv of **1b**) and 2-substituted quinolines (**31** or **32**→**34** or **35** using 2.6 equiv of **1b**).

yields. Quinolines **31** and **32** required double the amount of 1,5-dimethylcyclohexa-1,4-diene (**1b**, 2.6 equiv) as the reduction did not stop at the dihydroquinoline. Close to equimolar ratios of the tetrahydroquinoline and the starting material were obtained with 1.3 equiv of **1b**, indicating that the second reduction is faster than the first.

We had initially assumed that the overall process consists of the proposed $B(C_6F_5)_3$-mediated release of dihydrogen from cyclohexa-1,4-dienes and the known FLP-type imine reduction[9,20] (Scheme 3, catalytic cycle with gray pathway).



Scheme 3. Simplified catalytic cycle with alternative pathways for iminium ion formation.

The fate of Wheland complex **IV** is, however, not obvious. It is a potent Brønsted acid[21] that could protonate imine **V** to directly arrive at the ion pair **VI** rather than react with the hydridic $[HB(C_6F_5)_3]^-$ counteranion (Scheme 3, catalytic cycle with black pathway). The instability of the Wheland intermediate **IV** in the absence of Lewis basic **V** was verified by ^{1}H NMR spectroscopy. Treatment of 1,5-dimethylcyclohexa-1,4-diene with $B(C_6F_5)_3$ at 125 °C yielded *m*-xylene and dihydrogen quantitatively in less than 4 h with no **IV**, i.e., protonated *m*-xylene,[21] detectable (slow reaction at room temperature with equimolar amounts of $B(C_6F_5)_3$ and **1b**).

To distinguish between these alternatives in the presence of Lewis basic **V**, we followed the transfer hydrogenation by ^{1}H NMR spectroscopy, again using a 1.3-fold excess of the cyclohexa-1,4-diene. Interestingly, the outcome is different for representative aldimines and less reactive ketimines. With aldimines (e.g., **2a**), full conversion is reached within 4 h with no detection of intermediates, and traces of dihydrogen are only seen in the ^{1}H NMR spectrum at $\delta = 4.55$ ppm after full consumption of the aldimine. Conversely, dihydrogen is present at an early stage yet not immediately in the reduction of ketimines (e.g., **4d**). Highly acidic **IV** rapidly protonates **V**, and the resultant ion pair **VI** will transform into amine **VII** at a low rate. That final step of the catalytic cycle hence competes with dihydrogen release from ion pair **VI**. The backward reaction, that is FLP-type dihydrogen activation, is relatively slow, and that is a logical explanation for the initial accumulation of dihydrogen. More importantly, product formation is very slow at the beginning but increases significantly once the amine **VII** starts to form. The induction period and the rate acceleration are consistent with the reported phenomenon of autocatalysis[9,20] where the more basic amine **VII** replaces imine **V** in the reversible FLP-type dihydrogen-activation step[22] as well as in the deprotonation of **IV**. These experimental observations clearly corroborate the notion that deprotonation of **IV** by the nitrogen atoms of imine **V** or (once formed) amine **VII** outcompetes dihydrogen release from **IV**. Instead, liberation of dihydrogen from ion pair **VI** occurs through an FLP-type equilibrium if **VI** is sufficiently stable. The net reaction is the result of a complex interplay of several reaction channels and protonation equilibria that is further complicated by the reversibility of the hydride-transfer step (**VI**→**VII**→**VI**).[16,23]

To recap, we described here the transfer hydrogenation of imine-type functional groups catalyzed by $B(C_6F_5)_3$.[24] The new method distinguishes itself from the work of Stephan and co-workers[16] in that cyclohexa-1,4-dienes instead of amines serve as reducing agents. The mechanism may or may not involve free dihydrogen depending on the basicity of the imine nitrogen atom and the electrophilicity of the carbon atom of the iminium ion intermediate. Initiation of the transfer hydrogenation process by hydride abstraction from cyclohexa-1,4-dienes to generate the actual reductant sets this Lewis acid catalysis apart from the highly efficient organocatalytic methods employing 1,4-dihydropyridines.[25]

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[1] W. E. Piers, A. J. V. Marwitz, L. G. Mercier, *Inorg. Chem.* **2011**, *50*, 12252 – 12262 and references cited therein.
[2] D. W. Stephan, G. Erker, *Angew. Chem. Int. Ed.* **2010**, *49*, 46 – 76; *Angew. Chem.* **2010**, *122*, 50 – 81 and references cited therein.
[3] For C=O hydrosilylation catalyzed by $B(C_6F_5)_3$, see: a) D. J. Parks, W. E. Piers, *J. Am. Chem. Soc.* **1996**, *118*, 9440 – 9441; b) D. J. Parks, J. M. Blackwell, W. E. Piers, *J. Org. Chem.* **2000**, *65*, 3090 – 3098; c) S. Rendler, M. Oestreich, *Angew. Chem. Int. Ed.* **2008**, *47*, 5997 – 6000; *Angew. Chem.* **2008**, *120*, 6086 – 6089.

[4] For C=N hydrosilylation catalyzed by $B(C_6F_5)_3$, see: a) J. M. Blackwell, E. R. Sonmor, T. Scoccitti, W. E. Piers, *Org. Lett.* **2000**, *2*, 3921 – 3923; b) D. T. Hog, M. Oestreich, *Eur. J. Org. Chem.* **2009**, 5047 – 5056; c) J. Hermeke, M. Mewald, M. Oestreich, *J. Am. Chem. Soc.* **2013**, *135*, 17537 – 17546.

[5] For alkene hydrosilylation catalyzed by $B(C_6F_5)_3$, see: M. Rubin, T. Schwier, V. Gevorgyan, *J. Org. Chem.* **2002**, *67*, 1936 – 1940.

[6] For partial reduction of nitrogen-containing heterocycles catalyzed by $B(C_6F_5)_3$, see: a) M. Tan, Y. Zhang, *Tetrahedron Lett.* **2009**, *50*, 4912 – 4915; b) S. J. Geier, P. A. Chase, D. W. Stephan, *Chem. Commun.* **2010**, *46*, 4884 – 4886; c) L. D. Curless, E. R. Clark, J. J. Dunsford, M. J. Ingleson, *Chem. Commun.* **2014**, *50*, 5270 – 5272.

[7] For reviews of mainly FLP- but also $B(C_6F_5)_3$-catalyzed hydrogenation, see: a) L. J. Hounjet, D. W. Stephan, *Org. Process Res. Dev.* **2014**, *18*, 385 – 391; b) J. Paradies, *Angew. Chem. Int. Ed.* **2014**, *53*, 3552 – 3557; *Angew. Chem.* **2014**, *126*, 3624 – 3629; c) J. Paradies, *Synlett* **2013**, 777 – 780; d) D. W. Stephan, *Org. Biomol. Chem.* **2012**, *10*, 5740 – 5746.

[8] C=O hydrogenation catalyzed by $B(C_6F_5)_3$ is an unsolved problem. J. Nyhlén, T. Privalov, *Dalton Trans.* **2009**, 5780 – 5786.

[9] For C=N hydrogenation catalyzed by $B(C_6F_5)_3$, see: a) P. A. Chase, T. Jurca, D. W. Stephan, *Chem. Commun.* **2008**, 1701 – 1703; b) D. Chen, J. Klankermayer, *Chem. Commun.* **2008**, 2130 – 2131; c) C. Jiang, O. Blacque, H. Berke, *Chem. Commun.* **2009**, 5518 – 5520; d) Z. Heiden, D. W. Stephan, *Chem. Commun.* **2011**, *47*, 5729 – 5731.

[10] For hydrogenation of oxime ethers catalyzed by $B(C_6F_5)_3$, see: J. Mohr, M. Oestreich, *Angew. Chem. Int. Ed.* **2014**, *53*, 13278 – 13281; *Angew. Chem.* **2014**, *126*, 13494 – 13497.

[11] For partial hydrogenation of nitrogen-containing heterocycles catalyzed by $B(C_6F_5)_3$, see: a) Reference [6b]; b) D. W. Stephan, S. Greenberg, T. W. Graham, P. Chase, J. J. Hastie, S. J. Geier, J. M. Farrell, C. C. Brown, Z. M. Heiden, G. C. Welch, M. Ullrich, *Inorg. Chem.* **2011**, *50*, 12338 – 12348; c) G. Erős, K. Nagy, H. Mehdi, I. Pápai, P. Nagy, P. Király, G. Tárkányi, T. Soós, *Chem. Eur. J.* **2012**, *18*, 574 – 585; d) T. Mahdi, J. N. del Castillo, D. W. Stephan, *Organometallics* **2013**, *32*, 1971 – 1978.

[12] For the hydrogenation of anilines mediated by $B(C_6F_5)_3$, see: T. Mahdi, Z. M. Heiden, S. Grimme, D. W. Stephan, *J. Am. Chem. Soc.* **2012**, *134*, 4088 – 4091.

[13] a) A. Simonneau, M. Oestreich, *Angew. Chem. Int. Ed.* **2013**, *52*, 11905 – 11907; *Angew. Chem.* **2013**, *125*, 12121 – 12124; b) A. Simonneau, J. Friebel, M. Oestreich, *Eur. J. Org. Chem.* **2014**, 2077 – 2083.

[14] Stephan, Crudden, and co-workers accomplished the $B(C_6F_5)_3$-mediated hydride abstraction from Hantzsch esters: J. D. Webb, V. S. Laberge, S. J. Geier, D. W. Stephan, C. M. Crudden, *Chem. Eur. J.* **2010**, *16*, 4895 – 4902.

[15] We chose imines as substrates[9] because hydrogenations of carbonyl compounds[8] and alkenes catalyzed by $B(C_6F_5)_3$ alone have not been accomplished yet.

[16] J. M. Farrell, Z. M. Heiden, D. W. Stephan, *Organometallics* **2011**, *30*, 4497 – 4500.

[17] Stephan and co-workers recently reported the transfer hydrogenation of alkenes using dihydrogen generated from dehydrogenative Si–N and Si–O couplings. Both the alkene reduction and the dehydrogenative coupling are catalyzed by Stephan's Lewis acidic phosphonium ion $[(C_6F_5)_3PF]^+$ with $[B(C_6F_5)_4]^-$ as the counteranion. M. Pérez, C. B. Caputo, R. Dobrovetsky, D. W. Stephan, *Proc. Natl. Acad. Sci. USA* **2014**, *111*, 10917 – 10921.

[18] Gandon and co-workers reported a gallium(III)-assisted transfer hydrogenation of alkenes with cyclohexa-1,4-diene as the dihydrogen surrogate. The mechanism and the role of the main-group metal remains to be clarified though: B. Michelet, C. Bour, V. Gandon, *Chem. Eur. J.* **2014**, *20*, 14488 – 14492.

[19] P. A. Chase, G. C. Welch, T. Jurca, D. W. Stephan, *Angew. Chem. Int. Ed.* **2007**, *46*, 8050 – 8053; *Angew. Chem.* **2007**, *119*, 8196 – 8199.

[20] T. A. Rokob, A. Hamza, A. Stirling, I. Pápai, *J. Am. Chem. Soc.* **2009**, *131*, 2029 – 2036.

[21] For pK_a values of protonated arenes, see: R. More O'Ferrall in *Advances in Physical Organic Chemistry*, *Vol. 44* (Ed.: J. P. Richard), Academic Press, Oxford, **2010**, pp. 19 – 122.

[22] V. Sumerin, F. Schulz, M. Nieger, M. Leskelä, T. Repo, *Angew. Chem. Int. Ed.* **2008**, *47*, 6001 – 6003; *Angew. Chem.* **2008**, *120*, 6090 – 6092.

[23] N. Millot, C. C. Santini, B. Fenet, J. M. Basset, *Eur. J. Inorg. Chem.* **2002**, 3328 – 3335.

[24] For transfer hydrogenation with ammonia–borane or amine–boranes, see: a) N. E. Stubbs, A. P. M. Robertson, E. M. Leitao, I. Manners, *J. Organomet. Chem.* **2013**, *730*, 84 – 89 (review); b) X. Yang, L. Zhao, T. Fox, Z.-X. Wang, H. Berke, *Angew. Chem. Int. Ed.* **2010**, *49*, 2058 – 2062; *Angew. Chem.* **2010**, *122*, 2102 – 2106 (imine reduction).

[25] For a recent review of transfer hydrogenation with Hantzsch esters and related hydride donors, see: C. Zheng, S.-L. You, *Chem. Soc. Rev.* **2012**, *41*, 2498 – 2518.

