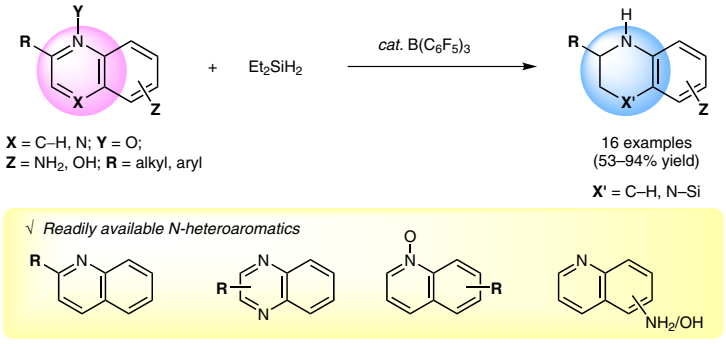
Synlett N. Gandhamsetty et al. Cluster

Boron-Catalyzed Hydrogenative Reduction of Substituted Quinolines to Tetrahydroquinolines with Hydrosilanes

Narasimhulu Gandhamsetty[a,b]
Sehoon Park*[a,b]
Sukbok Chang*[a,b]

[a] Center for Catalytic Hydrocarbon Functionalizations, Institute for Basic Science (IBS), Daejeon 305-701, South Korea
[b] Department of Chemistry, Korea Advanced Institute of Science & Technology (KAIST), Daejeon 305-701, South Korea
sehoonp@kaist.ac.kr
sbchang@kaist.ac.kr

Published as part of the Cluster *Silicon in Synthesis and Catalysis*



Received: 30.03.2017
Accepted after revision: 09.05.2017
Published online: 23.05.2017
DOI: 10.1055/s-0036-1588442; Art ID: st-2017-b0216-c

Abstract A metal-free procedure for the hydrogenative reduction of substituted N-heteroaromatics has been developed by using hydrosilanes as reducing agents. The optimized conditions were successfully applied to the reactions of quinolines, quinoxalines, and quinoline *N*-oxides. They were also effective for the reduction of quinolines bearing amino or hydroxy groups, where H_2 was evolved through dehydrogenative silylation of the amine or hydroxy moieties. Preliminary mechanistic studies revealed that the initial step in the catalytic cycle involves 1,4-addition of the hydrosilane to the quinoline to give a 1,4-dihydroquinoline; this is followed by (transfer) hydrogenation to deliver the tetrahydroquinoline as the final product.

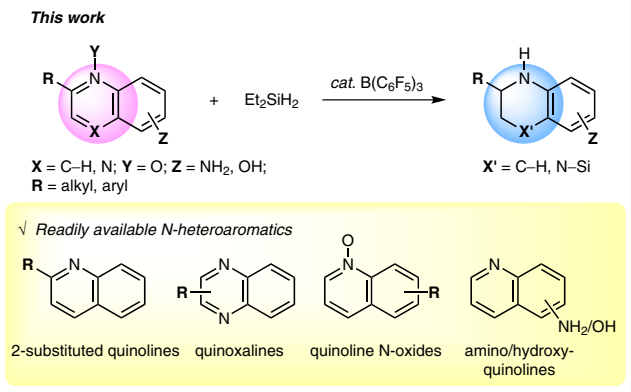
Key Words Lewis acids, boranes, quinolines, quinoxalines, hydrosilanes, hydrogenation

Dearomative catalytic reduction of N-heteroarenes is among the most straightforward strategies applicable to a variety of azacyclic compounds.[1] This transformation, however, is often ineffective due to the intrinsic features of the N-aromatic unit: significant resonance stabilization and strong basicity.[2] Among the obtainable dearomatized N-heterocycle products, tetrahydroquinolines, accessible through hydrogenation of quinolines, are of special interest in the pharmaceutical and agricultural fields, and also in the chemistry of dyes and ligands.[3] A handful of elegant catalytic procedures for the optionally enantioselective hydrogenation of quinoline derivatives are mainly based on precious metals such as rhodium or iridium and they frequently require harsh reaction conditions, high pressures, and/or reactive additives (e.g., I_2, HCO_2H, or H_2O).[4] As alternatives to transition-metal catalysts, a few organocatalytic systems have been documented for the reduction of quinolines with H_2.[5] For instance, Stephan and co-workers found that the Lewis acidic borane $B(C_6F_5)_3$ promotes (transfer) hydrogenation of quinolines to give tetrahydroquinolines with H_2 or *i*-Pr_2NH as the reductant.[6] Although a $B(C_6F_5)_3/H_2$ catalytic system offers an environmentally benign and atom-economic route to saturated N-heterocycles, the high catalyst loadings and/or limited substrate scope remain as problems to be solved.

In this regard, we envisioned that the use of a hydrosilane instead of H_2 as a reducing agent in the presence of $B(C_6F_5)_3$ catalyst might provide a sharper weapon for the reduction of quinoline derivatives. Although the $B(C_6F_5)_3$-catalyzed reduction of optionally substituted 1*H*-indoles with silanes to give a range of *N*-silylindolines has been previously reported,[7a,b] no example of a hydrogenative reduction of a six-membered N-heteroaromatic with the $B(C_6F_5)_3$/silane catalytic system had been communicated until very recently, when Wang and co-workers disclosed the $B(C_6F_5)_3$-catalyzed reduction of pyridines and other N-hetarenes with hydrosilanes and amines as reducing reagents.[7c] In a related study, our group recently developed a $B(C_6F_5)_3$-promoted silylative reduction of quinolines to give high yields of tetrahydroquinoline products bearing sp^3 C–Si bond(s) in the position β to the nitrogen atom.[8] This reaction was found to be subject to competitive side reaction(s), particularly with quinoline substrates possessing alkyl or aryl substituents in the C-2 position. Crabtree and co-workers reported a catalytic reduction of (iso)quinolines to tetrahydro(iso)quinolines with $PhSiH_3$ in the presence of a cationic Rh complex[9] or with $LiHBEt_3$[10] as a catalyst.

The key to success in the present development was in the choice of a suitable silane to avoid undesired side pathways, thereby improving both the scope of the reaction and the performance of the catalyst. Here, we report the borane-catalyzed reduction of the N-aromatic ring of substituted quinoline derivatives with hydrosilanes (Scheme 1). The present catalyst system is conveniently active, not only for the direct reduction of 2-substituted quinolines, quinox-

alines, or quinoline *N*-oxides, but also for the transfer hydrogenation of aminoquinolines and hydroxyquinolines with H_2 generated in situ upon dehydrogenative silylation of an amino or hydroxy group on the quinoline substrate.

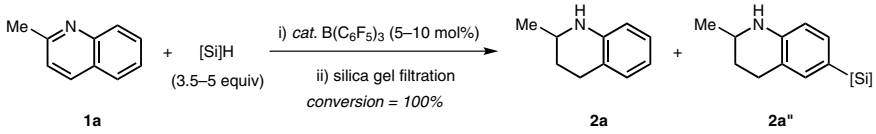


Scheme 1 $B(C_6F_5)_3$-catalyzed hydrogenative reduction of N-heteroarenes with hydrosilanes

At the outset of this study, the optimal reaction conditions were explored for the $B(C_6F_5)_3$-catalyzed reduction of 2-methylquinoline (**1a**) with various silanes (Table 1). The reaction of **1a** with Et_2SiH_2 in the presence of $B(C_6F_5)_3$ (5 mol%) proceeded smoothly at 65 °C during six hours to afford 2-methyl-1,2,3,4-tetrahydroquinoline (**2a**) in 79% isolated yield after silica-gel filtration (Table 1, entry 1). Increasing the catalyst loading to 10 mol% accelerated the conversion, but gave a lower yield of **2a** after 3 hours at 65 °C (entry 2). An investigation of the effects of various solvents revealed that the use of chlorobenzene or toluene as solvent provided **2a** in somewhat lower yields (58 and 68%, respectively; entries 3 and 4). Pleasingly, the reaction of **1a** with $PhMe_2SiH$ (3.5 or 5 equiv) took place efficiently to furnish the tetrahydroquinoline product **2a** in 75 and 66% yield, respectively (entries 5 and 6). A reaction with the bulkier silane Et_3SiH required a higher temperature to obtain a satisfactory yield of **2a** (entry 7). Less bulky silanes such as Ph_2SiH_2 and $PhSiH_3$ were reactive in the presence of catalytic $B(C_6F_5)_3$, albeit affording **2a** in moderate yields of 41 and 49%, respectively (entries 8 and 9).[11] In all catalytic runs shown in Table 1, except for entry 9, the corresponding C-6 silylated tetrahydroquinolines **2a″** were obtained as by-products in 12–26% yields.

With the optimal conditions in hand [5 mol% of $B(C_6F_5)_3$, 3.5–5 equiv of Et_2SiH_2], the scope of substrate reactivity was next investigated (Scheme 2). Upon catalytic reduction, the crude reaction mixture was initially treated with an ethereal solution of HCl, followed by a solution of $Na_2CO_3{\cdot}H_2O$ in MeOH to neutralize the crude solution, eventually giving rise to the corresponding NH form of reduction product. Whereas 2-methylquinoline (**1a**) underwent the desired hydrogenative reduction with Et_2SiH_2 to give **2a** in 76% yield at 65 °C, the reductions of 2-phenylquinoline (**1b**) or 2-tolylquinoline (**1c**) were sluggish, requiring prolonged reaction times of 24 hours to obtain satisfactory product yields of **2b** and **2c**, respectively. Similarly, a double hydrogenative reduction occurred in both N-aromatic units of 2,2′-biquinoline at 65 °C to produce the corresponding octahydro compound **2d** as a single diastereomer in 53% yield. Gratifyingly, the hydrogenative reduction of quinoxaline with Et_2SiH_2 proceeded smoothly at 25 °C to furnish 1,2,3,4-tetrahydroquinoxaline (**2e**) in high yield. Likewise, the reac-

Table 1 Screen of Reaction Conditions[a]



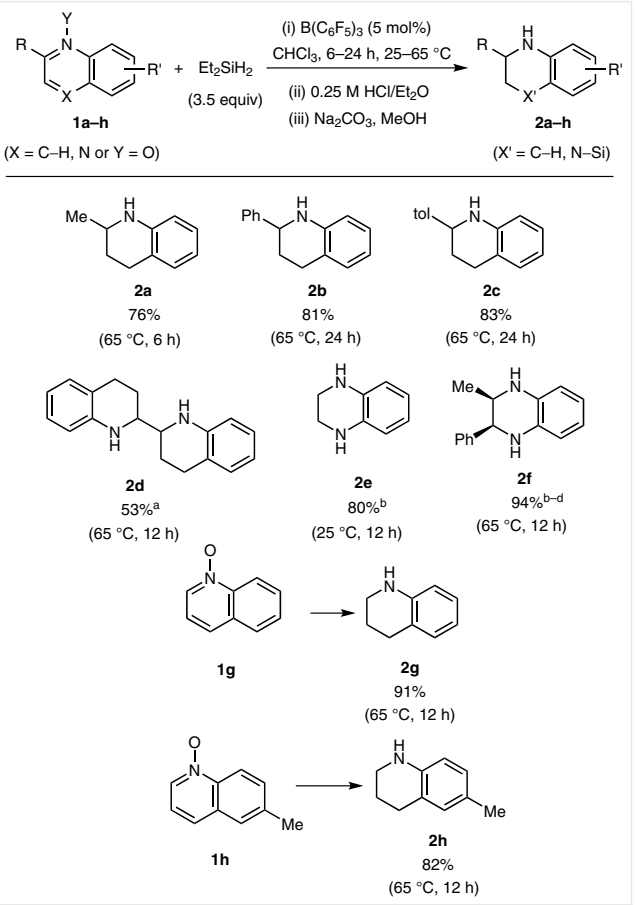
1a **2a** **2a"**

Entry	Silane (equiv)	Solvent	Temp (°C)	Time (h)	Yield[b] of **2a** (%)	Yield[b] of **2a′′** (%)
1	Et_2SiH_2 (3.5)	$CDCl_3$	65	6	79	16
2[c]	Et_2SiH_2 (3.5)	$CDCl_3$	65	3	60	14
3	Et_2SiH_2 (3.5)	C_6D_5Cl	65	12	58	18
4	Et_2SiH_2 (3.5)	toluene-d_8	65	12	68	26
5	$PhMe_2SiH$ (3.5)	$CDCl_3$	65	12	75	21
6	$PhMe_2SiH$ (5.0)	$CDCl_3$	65	6	66	21
7	Et_3SiH (3.5)	DCE-d_4	85	12	77	16
8	Ph_2SiH_2 (3.5)	$CDCl_3$	65	12	41	12
9	$PhSiH_3$ (3.5)	$CDCl_3$	25	2	49	<1

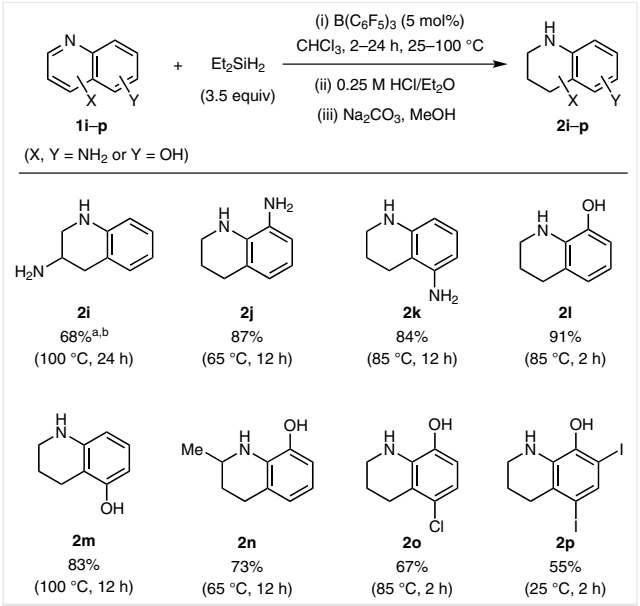
[a] Reaction conditions: $B(C_6F_5)_3$ (0.025–0.05 mmol), **1a** (0.5 mmol), silane (1.75–2.5 mmol), solvent (0.5 mL).
[b] The conversions and yields of **2a** and **2a′′** were determined by ^1H NMR, with 1,1,2,2-tetrachloroethane as internal standard, after silica-gel filtration.
[c] $B(C_6F_5)_3$ (10 mol%) was used.

tion of a 2,3-disubstituted quinoxaline worked well at 65 °C to give hydrogenated product **2f** as the *cis*-diastereomer in excellent yield. Interestingly, quinoline *N*-oxides **1g** and **1h** turned out to be highly effective substrates, being converted into the desired tetrahydroquinoline products **2g** and **2h** in high yields in the presence of catalytic $B(C_6F_5)_3$.

Next, we turned our attention to amino- or hydroxy-substituted quinolines as other substrate types with which transfer hydrogenation mediated by $B(C_6F_5)_3$ might take place upon dehydrogenative silylation of the amino or hydroxy groups (Scheme 3). Gratifyingly, quinolin-3-amine (**1i**) reacted with Et_2SiH_2 (5 equiv) in the presence of $B(C_6F_5)_3$ (10 mol%) to produce the desired hydrogenation product **2i** in 68% yield at 100 °C. Similarly, quinolin-5-amine (**1j**) and quinolin-8-amine (**1k**) were also cleanly converted into the corresponding tetrahydroquinolines **2j** and **2k** in high yields with borane catalysis. Subsequently, a



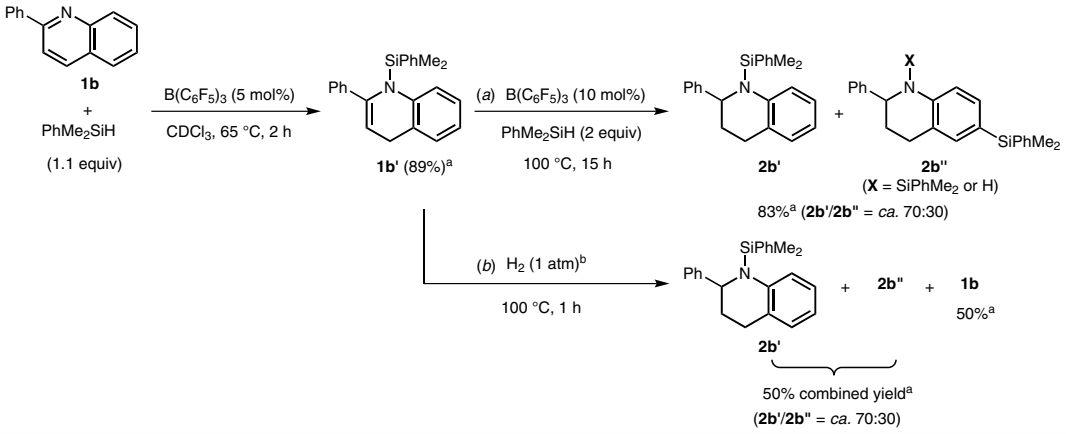
Scheme 2 Substrate scope of the $B(C_6F_5)_3$-catalyzed hydrogenative reduction of N-heteroaromatics. *Reagents and conditions*: $B(C_6F_5)_3$ (0.025 mmol), **1a–h** (0.5 mmol), Et_2SiH_2 (1.75 mmol), $CHCl_3$ (0.6 mL), 25–65 °C, 6–24 h, unless otherwise stated. [a] 7 equivalents of the silane were used. [b] Isolated by column chromatography (silica gel) without acidic or basic workup. [c] 5 equivalents of the silane were used. [d] Isolated as the *cis*-diastereomer.



Scheme 3 Substrate scope of the $B(C_6F_5)_3$-catalyzed transfer hydrogenation of amino- or hydroxy-substituted quinolines. *Reagents and conditions*: $B(C_6F_5)_3$ (0.025 mmol), **1i–p** (0.5 mmol), Et_2SiH_2 (1.75 mmol), $CHCl_3$ (0.6 mL), 25–100 °C, 2–24 h. The crude reaction mixture was initially treated with 0.25 N ethereal HCl, followed by sat. methanolic $Na_2CO_3{\cdot}H_2O$ to neutralize the reaction solution. Finally, the pure products from the neutralized solution were isolated by column chromatography (silica gel). [a] 5 equivalents of the silane were used. [b] 10 mol% of $B(C_6F_5)_3$ was used.

range of hydroxyquinolines were examined. The hydroxy group of quinoline substrates reacted vigorously with Et_2SiH_2; this was followed by hydrogenative reduction of the N-aromatic ring at 85–100 °C to give the corresponding tetrahydroquinoline products **2l–o** in 67–91% yield. Interestingly, the reaction of **1p**, an 8-hydroxyquinoline bearing two iodo groups, proceeded at 25 °C to afford the tetrahydro product **2p** in 55% yield; in this case, C(sp^2)–X bonds (X = O, I) were tolerated.

To gain insights into the reaction details, preliminary mechanistic studies were conducted. Initially, a less reactive substrate **1b** was subjected to the reaction conditions using 1.1 equivalent of $PhMe_2SiH$ (Scheme 4). As a result, the 1,4-dihydro product **1b′** was obtained as a single product in 89% yield after two hours at 65 °C,[8] but no 1,2-addition product was detected at all. Heating the solution at 100 °C with additional $B(C_6F_5)_3$ (10 mol%) together with $PhMe_2SiH$ (2 equiv) gave the desired product **2b′** as well as the C-6 silylated tetrahydroquinoline **2b″** in 83% combined yield (**2b′**/**2b″** ≈ 70:30) (Scheme 4, a). This result indicates that (i) the current reduction proceeds by an initial 1,4-addition pathway, (ii) dehydrogenative silylation at the C-6 position can occur competitively,[12] and (iii) most of the hydrogen required for the conversion of **1b′** into **2b′** is generated during the dehydrogenative silylation at the C-6 posi-



Scheme 4 Preliminary mechanistic studies. Catalytic formation of the 1,4-product **1b′**, followed by addition of $B(C_6F_5)_3$ and $PhMe_2SiH$ (a) or H_2 (1 atm) (b). [a] The yield was determined by ^1H NMR with 1,1,2,2-tetrachloroethane as the internal standard. [b] The crude solution of **1b′** was degassed by freeze–pump–thaw cycling before H_2 was introduced into the reactor.

tion.[13] Similarly, exposing a solution of intermediate **1b′** to an H_2 atmosphere (1 atm) at 100 °C in the presence of $B(C_6F_5)_3$ (5 mol%) gave a mixture of **2b′** and **2b″** in 50% combined yield (**2b′**/**2b″** ≈ 70:30), together with ~50% of the starting material **1b** (Scheme 4, b). These results strongly suggest that H_2 generated in situ is the reductant involved in the conversion of **1b′** into the tetrahydroquinoline products **2b′** and **2b″**, and that the conversion of **1b** into **1b′** is reversible, as evidenced by the formation of **1b** upon heating a solution containing **1b′** at 100 °C for one hour.

In summary, we have developed the borane-catalyzed reduction of substituted N-heteroaromatics with hydrosilanes, providing dearomatized azacyclic compounds. The use of a hydrosilane as the reductant offers a convenient procedure with a broad substrate scope that includes quinolines, quinoxalines, and quinoline *N*-oxides within the $B(C_6F_5)_3$ catalyst system. Moreover, amino- or hydroxy-substituted quinolines were also reduced to the corresponding tetrahydroquinolines in one pot with good to excellent yields. Preliminary mechanistic studies suggested a stepwise reduction sequence involving 1,4-hydrosilylation followed by reduction of the enamine intermediate with the H_2 generated in situ during the catalytic turnover.

Funding Information

This research was supported by the Institute for Basic Science (IBS-R010-D1) in Korea.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1588442.

References and Notes

(1) (a) Stout, D. M.; Meyers, A. I. *Chem. Rev.* **1982**, *82*, 223. (b) Forrest, T. P.; Dauphinee, D. A.; Deraniyagala, S. A. *Can. J. Chem.* **1985**, *63*, 412. (c) Keay, J. G. *Adv. Heterocycl. Chem.* **1986**, *39*, 1. (d) Keay, J. G. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, **1991**, 579. (e) Gribble, G. W. *Chem. Soc. Rev.* **1998**, *27*, 395. (f) Pitts, M. R.; Harrison, J. R.; Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 955. (g) Hollmann, F.; Arends, I. W. C. E.; Buehler, K. *ChemCatChem* **2010**, *2*, 762. (h) Bull, J. A.; Mousseau, J. J.; Pelletier, G.; Charette, A. B. *Chem. Rev.* **2012**, *112*, 2642. (i) Wan, J.-P.; Liu, Y. *RSC Adv.* **2012**, *2*, 9763. (j) Park, S.; Chang, S. *Angew. Chem. Int. Ed.* **2017**, in pressDOI: 10.1002/anie.201612140.

(2) (a) Krygowski, T. M.; Cryański, M. K. *Chem. Rev.* **2001**, *101*, 1385. (b) Balaban, A. T.; Oniciu, D. C.; Katritzky, A. R. *Chem. Rev.* **2004**, *104*, 2777. (c) Pape, A. R.; Kaliappan, K. P.; Kündig, E. P. *Chem. Rev.* **2000**, *100*, 2917.

(3) (a) Katritzky, A. R.; Rachwal, S.; Rachwal, B. *Tetrahedron* **1996**, *52*, 15031. (b) Sridharan, V.; Suryavanshi, P. A.; Menéndez, J. C. *Chem. Rev.* **2010**, *111*, 7157.

(4) (a) Wu, J.; Wang, C.; Tang, W.; Pettman, A.; Xiao, J. *Chem. Eur. J.* **2012**, *18*, 9525. (b) Tang, W.-J.; Tan, J.; Xu, L.-J.; Lam, K.-H.; Fan, Q.-H.; Chan, A. S. C. *Adv. Synth. Catal.* **2010**, *352*, 1055. (c) Wu, J.; Tang, W.; Pettman, A.; Xiao, J. *Adv. Synth. Catal.* **2013**, *355*, 35. (d) Ye, Z.-S.; Chen, M.-W.; Chen, Q.-A.; Shi, L.; Duan, Y.; Zhou, Y.-G. *Angew. Chem. Int. Ed.* **2012**, *51*, 10181. (e) Dobereiner, G. E.; Nova, A.; Schley, N. D.; Hazari, N.; Miller, S. J.; Eisenstein, O.; Crabtree, R. H. *J. Am. Chem. Soc.* **2011**, *133*, 7547. (f) Adam, R.; Cabrero-Antonino, J. R.; Spannenberg, A.; Junge, K.; Jackstell, R.; Beller, M. *Angew. Chem. Int. Ed.* **2017**, *56*, 3216. (g) Chen, F.; Surkus, A.-E.; He, L.; Pohl, M.-M. *Radnik J., Topf C., Junge K., Beller M.* **2015**, *137*, 11718.

(5) (a) Hounjet, L. J.; Stephan, D. W. *Org. Process Res. Dev.* **2014**, *18*, 385. (b) Stephan, D. W.; Greenberg, S.; Graham, T. W.; Chase, P.; Hastie, J. J.; Geier, S. J.; Farrell, J. M.; Brown, C. C.; Heiden, Z. M.; Welch, G. C.; Ulrich, M. *Inorg. Chem.* **2011**, *50*, 12338. (c) Paradies, J. *Synlett* **2013**, *24*, 777. (d) Erős, G.; Nagy, K.; Mehdi, H.; Pápai, I.; Nagy, P.; Király, P.; Tárkányi, G.; Soós, T. *Chem. Eur. J.* **2012**, *18*, 574. (e) Maier, A. F. G.; Tussing, S.; Schneider, T.; Flörke, U.; Qu, Z.-W.; Grimme, S.; Paradies, J.

Angew. Chem. Int. Ed. **2016**, *55*, 12219. (f) Eisenberger, P.; Bestvater, B. P.; Keske, E. C.; Crudden, C. M. *Angew. Chem. Int. Ed.* **2015**, *54*, 2467.

(6) (a) Geier, S. J.; Chase, P. A.; Stephan, D. W. *Chem. Commun. (Cambridge)* **2010**, *46*, 4884. (b) Farrell, J. M.; Heiden, Z. M.; Stephan, D. W. *Organometallics* **2011**, *30*, 4497.

(7) (a) Tan, M.; Zhang, Y. *Tetrahedron Lett.* **2009**, *50*, 4912. (b) Greb, L.; Tamke, S.; Paradies, J. *Chem. Commun. (Cambridge)* **2014**, *50*, 2318. (c) Liu, Z.-Y.; Wen, Z.-H.; Wang, X.-C. *Angew. Chem. Int. Ed.* **2017**, *56*, 5817.

(8) (a) Gandhamsetty, N.; Joung, S.; Park, S.-W.; Park, S.; Chang, S. *J. Am. Chem. Soc.* **2014**, *136*, 16780. (b) Gandhamsetty, N.; Park, S.; Chang, S. *J. Am. Chem. Soc.* **2015**, *137*, 15176.

(9) Voutchkova, A.; Gnanamgari, M. D.; Jakobsche, C. E.; Butler, C.; Miller, S. J.; Parr, J.; Crabtree, R. H. *J. Organomet. Chem.* **2008**, *693*, 1815.

(10) Manas, M. G.; Sharninghausen, L. S.; Balcells, D.; Crabtree, R. H. *New J. Chem.* **2014**, *38*, 1694.

(11) **2-Methyl-1,2,3,4-tetrahydroquinoline (2a);[14] Typical Procedure**

In a 1.5 mL reaction vial, $B(C_6F_5)_3$ (0.025 mmol, 5.0 mol%) was dissolved in $CHCl_3$ (0.60 mL), and Et_2SiH_2 (1.75 mmol, 3.5 equiv) was added. To this catalyst solution was subsequently added 2-methylquinoline (**1a**; 0.50 mmol, 1.0 equiv). The mixture was stirred at 65 °C for 6 h, allowed to cool to r.t., and concentrated under reduced pressure to give a crude product. This was treated sequentially with 0.25 N ethereal HCl solution (7 mL) and sat. methanolic $Na_2CO_3{\cdot}H_2O$ (1.0 mL) to neutralize the crude solution. Finally, the neutralized mixture was purified by column chromatography [silica gel, EtOAc–hexane (1:9)] to give a light-yellow liquid; yield: 56 mg (76%, 0.38 mmol). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.03– 6.91 (m, 2 H), 6.62 (t, *J* = 7.4 Hz, 1 H), 6.48 (d, *J* = 8.3 Hz, 1 H), 3.68 (s, 1 H), 3.46 – 3.34 (m, 1 H), 2.91–2.79 (m, 1 H), 2.79–2.67 (m, 1 H), 2.00–1.84 (m, 1 H), 1.67–1.51 (m, 1 H), 1.22 (d, *J* = 6.3 Hz, 3 H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 144.7, 129.2, 126.6, 121.1, 116.9, 113.9, 47.1, 30.1, 26.6, 22.6.

(12) Ma, Y.; Wang, B.; Zhang, L.; Hou, Z. *J. Am. Chem. Soc.* **2016**, *138*, 3663.

(13) Although we observed hydrogen evolution through dehydrogenative silylation at the C-6 position during the catalytic turnover, homocoupling of the hydrosilane[15] giving rise to a disilane and H_2 should also be considered as another minor pathway under borane catalysis.

(14) Guo, Q.-S.; Du, D.-M.; Xu, J. *Angew. Chem. Int. Ed.* **2008**, *47*, 759.

(15) Brown-Wensley, K. A. *Organometallics* **1987**, *6*, 1590.