JACS JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

pubs.acs.org/JACS

Catalytic Generation of Borenium Ions by Cooperative B−H Bond Activation: The Elusive Direct Electrophilic Borylation of Nitrogen Heterocycles with Pinacolborane

Timo Stahl,[†,§] Kristine Müther,[†,‡,§] Yasuhiro Ohki,[*,‡] Kazuyuki Tatsumi,[*,‡] and Martin Oestreich[*,†]

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

[‡]Department of Chemistry, Graduate School of Science and Research Center for Materials Science, Nagoya University, Furo-cho, Chikusa-ku, Nagoya 464-8602, Japan

Ⓢ *Supporting Information*

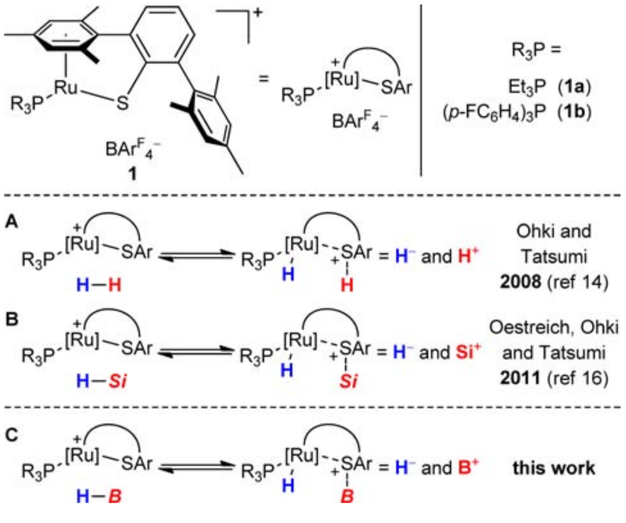
ABSTRACT: The B−H bond of typical boranes is heterolytically split by the polar Ru−S bond of a tethered ruthenium(II) thiolate complex, affording a ruthenium(II) hydride and borenium ions with a dative interaction with the sulfur atom. These stable adducts were spectroscopically characterized, and in one case, the B−H bond activation step was crystallographically verified, a snapshot of the σ-bond metathesis. The borenium ions derived from 9-borabicyclo[3.3.1]nonane dimer [$(9\text{-BBN})_2$], pinacolborane (pinBH), and catecholborane (catBH) allowed for electrophilic aromatic substitution of indoles. The unprecedented electrophilic borylation with the pinB cation was further elaborated for various nitrogen heterocycles.

The importance of (hetero)aryl boronic acid derivatives in laboratory- and industrial-scale synthesis is beyond doubt.[1] The preparation of these building blocks typically involves multistep processes involving halogenated intermediates and stoichiometric use of organometallic reagents.[2] An often more efficient methodology is the direct transformation of a $C(sp^2)$−H into a $C(sp^2)$−B bond by transition-metal (mainly iridium-based) catalysts.[3] The classic approach to $C(sp^2)$−H borylation is, however, electrophilic aromatic substitution (S_EAr), but harsh protocols employing BX_3 activated by AlX_3 (X = Cl, Br, and I)[4] or X_2BH (X = H or F, Cl, and Br)[5] as boron sources limit applications.[6] Milder reaction temperatures are possible for intramolecular S_EAr, usually directed by a benzylic amine and pyridine nitrogen atom.[7] Aside from these contributions, this area of boron chemistry had remained largely unexplored until the groups of Vedejs[8] and Ingleson[9] made substantial progress by using strong (charged) boron electrophiles[10] in intermolecular $C(sp^2)$−H borylation.[6,11,12]

Vedejs and co-workers introduced a 1,8-bis(dimethylamino)-naphthalene-derived boronium salt as a robust reagent for the borylation of indoles and pyrroles.[8] Inspired by the seminal experiments of Muetterties,[4a,c,d] Ingleson and co-workers activated several chloroboranes ($catBCl$,[9a] BCl_3,[9b] and 2-chloro-1,3,2-benzodithiaborole[9c]) by $AlCl_3$ in the presence of amine bases as proton scavengers. These stoichiometric methods are a major step forward but catalytic dehydrogenative methods, i.e., S_EAr directly utilizing boranes with release of H_2, are still a challenge. A report by Ingleson and co-workers demonstrated the feasibility of that strategy.[13] A catalytic amount of $[Et_3Si]^+[\textit{closo}\text{-}CB_{11}H_6Br_6]^-$ is capable of yielding a highly electrophilic, transient boron intermediate from catBBr that rapidly borylates selected arenes using catBH (but not pinBH, suffering ring-opening due to tertiary carbenium ion formation) as the stoichiometric boron source. We report here a catalytic process that generates sulfur-coordinated borenium ions from various boranes for the S_EAr of sufficiently nucleophilic nitrogen heterocycles. The net transformation is a direct electrophilic $C(sp^2)$−H borylation with representative boranes (including pinBH) concomitant with H_2 formation.

Our laboratories introduced the coordinatively unsaturated ruthenium(II) complexes **1a**[14] and **1b**[15] for cooperative bond activation (Scheme 1, top). The polar Ru−S bond in **1** was shown to split H−H[14] and Si−H[16] bonds into a ruthenium(II) hydride as well as a sulfur-stabilized proton and a silicenium ion, respectively (Scheme 1A/B). We reasoned that B−H

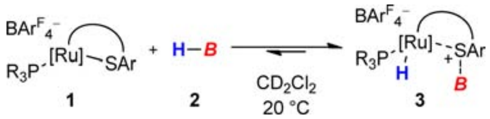
Scheme 1. Tethered Ruthenium(II) Thiolate Complex for H−H (A), Si−H (B), and B−H (C) Bond Activation [Ar^F = 3,5-Bis(trifluoromethyl)phenyl]



Received: June 13, 2013
Published: July 15, 2013

bonds might be activated the same way, thereby affording borenium ions[10,11] with a dative bond from the sulfur atom (Scheme 1C).

Table 1. ^{1}H NMR Shifts of the Borane Hydrides and Ruthenium(II) Hydride in the Borane Complexes[a]



entry	H–B	H–B ^{1}H NMR [ppm]	H–B + 1a ^{1}H NMR[b] [ppm]	H–B + 1b ^{1}H NMR[b] [ppm]
1	(9-BBN)$_2$ (**2a**)	1.5[c]	−11.9 (**3aa**)	−11.8 (**3ba**)
2	Cy$_2$BH (**2b**)	0.9[c]	−12.1 (**3ab**)	−11.4 (**3bb**)
3	pinBH (**2c**)	3.8[d]	−8.9 (**3ac**)	−8.1 (**3bc**)
4	catBH (**2d**)	4.8[d]	−9.7 (**3ad**)[e]	−8.6 (**3bd**)

[a] Experiments were performed in an NMR tube using **1** (1.0 equiv) and borane (2.0 equiv) in CD$_2$Cl$_2$ at 20 °C. [b] Resonance signal observed as doublet due to coupling to the ^{31}P nucleus. [c] Determined by ^{1}H,^{11}B HMQC measurements. [d] Resonance signal observed as quartet due to coupling to the ^{11}B nucleus (s = 3/2). [e] Broad singlet.

The B–H bond activation by **1** was investigated by ^{1}H NMR spectroscopy (Table 1). Determination of the hydride shifts of (9-BBN)$_2$ (**2a**) and Cy$_2$BH (**2b**) was difficult since these are superimposed by aliphatic resonance signals (column 3, entries 1 and 2). Conversely, oxygen-substituted boranes pinBH (**2c**) and catBH (**2d**) show an isolated quartet with a coupling constant of approximately 180 Hz, indicating a ^{1}J coupling to the ^{11}B nucleus (column 3, entries 3 and 4). When treating these boranes **2** with complexes **1a** or **1b**, a pronounced shift of the hydride resonance to higher field ($\Delta\delta \approx 13.0$ ppm) was detected for coordinatively saturated complexes **3** (columns 4 and 5). All four hydride shifts of **3** appear as doublets due to coupling to the ^{31}P nucleus. A coupling to the boron atom is no longer observed; the absence of that quartet is already an indication of the B–H bond weakening (if not cleavage) in complexes **3**. Rapid quadrupolar relaxation of the ^{11}B nuclei in **3** prevented their detection.

To gain deeper insight into the B–H/Ru–S interaction, we attempted to crystallize adducts **3**. Single crystals suitable for X-ray diffraction were obtained at room temperature from a solution of (9-BBN)$_2$ (**2a**) and complex **1a** (R = Et$_3$P) in benzene layered with *n*-hexane (Figure 1). The molecular structure of adduct **1a·2a** (or complex **3aa** depending on the magnitude of the bond order of the B–H bond) proves that the boron atom is connected to the sulfur atom (bond length = 1.94 Å) and that the hydride is bound to the ruthenium center (bond length = 1.80 Å). These bond lengths are in the range of those found in previously reported crystal structures containing a four-membered H–Ru–S–B ring.[17] The B–H bond length (1.55 Å) is, however, increased by about 30% relative to usual B–H bonds (0.98 Å[18]–1.19 Å[19]). This fascinating structural characterization of adduct **1a·2a** might be viewed as a snapshot of the σ-bond metathesis that eventually forms the ruthenium(II) hydride and the sulfur-coordinated borenium ion. Combined with the above ^{1}H NMR data of complex **3aa**, we were convinced that catalytic generation of borenium ions from boranes **2** by B–H bond activation with coordinatively unsaturated complexes **1** would be possible.

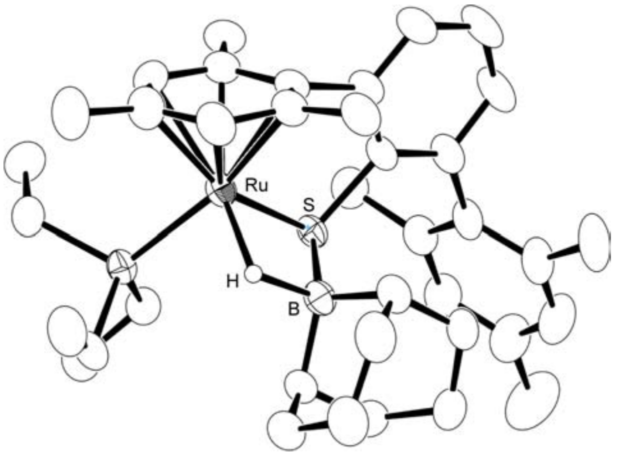
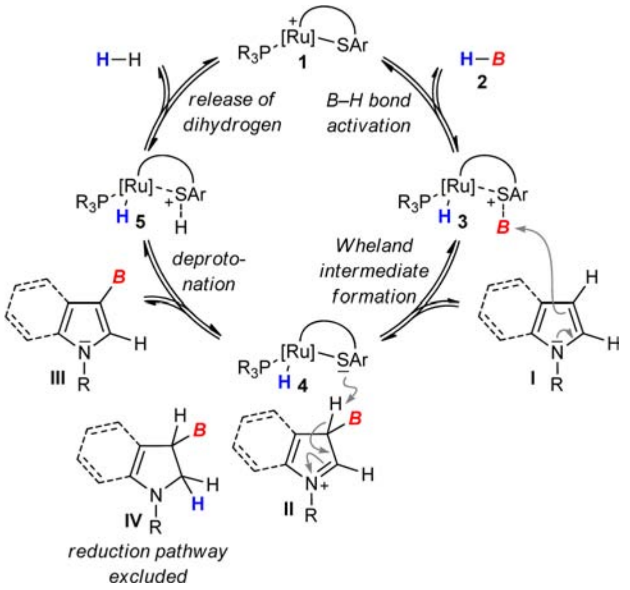


Figure 1. Crystal structure of **1a·2a** (or **3aa**): An ORTEP plot of the molecular structure (counteranion omitted for the sake of clarity). Selected experimental bond lengths (Å): B–H, 1.55(4); B–S, 1.940(5); Ru–H, 1.80(4); Ru–S, 2.3626(16).

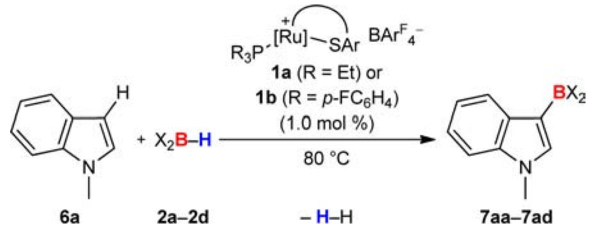
Scheme 2. Projected Catalytic Cycle of Electrophilic Borylation of Nitrogen Heterocycles (BAr$^F_4$$^-$ as Counteranion Omitted for Clarity)



The plan then was to react the catalytically generated borenium ion (**1** → **3**) with sufficiently nucleophilic nitrogen heterocycles (**I** → **II**), e.g., indole or pyrrole (Scheme 2). Deprotonation of the Wheland intermediate would yield the borylated heterocycle (**II** → **III**) and the short-lived H$_2$ adduct of catalyst **1** (**4** → **5**) that immediately releases H$_2$[14] (**5** → **1**). The neutral ruthenium(II) hydride **4** could also act as a hydride donor (**4** → **1**), reducing the iminium ion to the corresponding partially saturated heterocycle (**II** → **IV**) followed by oxidation (**IV** → **III**). We rule out this pathway as no deuterium incorporation was seen in the related electrophilic silylation.[16a]

The identification of an effective protocol for the electrophilic borylation commenced with a borane screening in the reaction of a simple indole catalyzed by catalyst **1a** (**6a** → **7aa–7ad**, Table 2, entries 1–4). Using an excess of the indole (8.0 equiv), we were delighted to see that, except for Cy$_2$BH (**2b**),

Table 2. Borane and Substrate-to-Reagent Ratio Screening in the Catalytic Electrophilic Borylation of Indole[a]

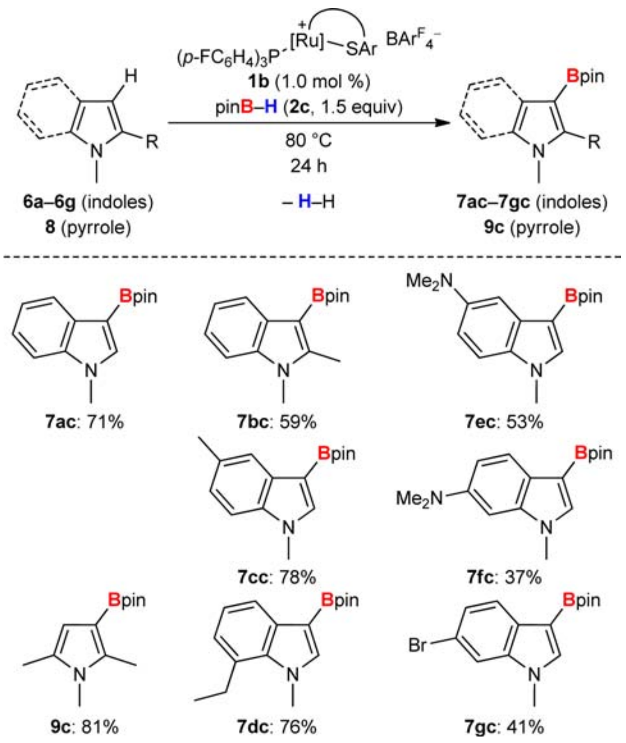


entry	**1**	borane (**2**)	ratio **6a**:**2**	solvent	*t* [h]	conv. [%][b]
1[c]	**1a**	(9-BBN)$_2$ (**2a**)	8:1	neat	12	>95 **7aa**
2[c]	**1a**	Cy$_2$BH (**2b**)	8:1	neat	12	—[d] **7ab**
3	**1a**	pinBH (**2c**)	8:1	neat	12	>95 **7ac**
4	**1a**	catBH (**2d**)	8:1	neat	12	>95 **7ad**
5	**1a**	pinBH (**2c**)	1:1.5	neat	24	4 **7ac**
6	**1a**	pinBH (**2c**)	1:1.5	toluene	24	1 **7ac**
7	**1a**	pinBH (**2c**)	1:1.5	*n*-hexane	24	2 **7ac**
8	**1b**	pinBH (**2c**)	1:1.5	neat	24	>95 **7ac**
9	**1b**	pinBH (**2c**)	1:1.5	toluene	24	10 **7ac**
10	**1b**	pinBH (**2c**)	1:1.5	*n*-hexane	24	25 **7ac**

[a] All reactions were performed according to the General Procedures 2 (for 8:1 indole-to-borane ratio) and 3 (for 1:1.5 indole-to-borane ratio). [b] Consumption of **2** monitored by ^{11}B NMR spectroscopy. Conversion based on minor component determined by ^{1}H NMR spectroscopy and/or GLC analysis using *n*-tetracosane as internal standard. [c] 100 °C. [d] Decomposition.

the catalyses yielded full conversion at elevated temperature without any solvent and added base (for more detailed data, see the Supporting Information). Even pinBH (**2c**) reacted cleanly (entry 3), and we decided to elaborate the unprecedented S$_E$Ar with this synthetically useful borane further. The situation changed dramatically when the substrate-to-reagent ratio was inverted from 8:1 to 1:1.5 still using catalyst **1a** (**6a** → **7ac**, entries 5−7). Hardly any conversion was obtained without added solvent (entry 5), and performing the catalysis in either *n*-hexane (entry 6) or toluene (entry 7) was also not productive. To increase the electrophilicity of the borenium ion, we replaced the electron-donating phosphine ligand Et$_3$P in **1a** by electron-withdrawing (p-FC$_6$H$_4$)$_3$P to afford catalyst **1b**. That trick had also served us well in the hydrodefluorination with silicenium ions catalyzed by these complexes.[15] With **1b** as catalyst, the electrophilic borylation with pinBH (**2c**) proceeded smoothly at 80 °C but added solvent was again detrimental to the reaction rate (**6a** → **7ac**, entries 8−10). A slight excess of the borane was still necessary to avoid too high viscosity. The C-3 regioselectivity (expected for an S$_E$Ar) was assigned by 2D NMR measurements, and the regioisomeric ratio of >99:1 was determined by GLC analysis prior to purification.

Scheme 3. Substrate Scope of the Catalytic Electrophilic Borylation with pinBH[a]



[a] All reactions were performed according to the General Procedure 3 (Supporting Information).

With the optimized protocol in hand, we investigated the scope of the catalytic electrophilic borylation (Scheme 3). The previous model reaction (**6a** → **7ac**, cf. Table 2, entry 8) afforded 71% isolated yield at full conversion. Alkylated indoles with different substitution patterns reacted in satisfying isolated yields (**6c** → **7cc** and **6d** → **7dc**), including indole methylated in the C-2 position (**6b** → **7bc**). In turn, a methyl group at C-3 did not steer the borylation toward the C-2 position (not shown); no reaction occurred. We had seen the same C-3 preference in the related electrophilic silylation.[16a] Functionalization with an NMe$_2$ group is also tolerated, and the C-3 borylation proceeded in decent yields (**6e** → **7ec** and **6f** → **7fc**). *N*,*N*-Dimethylaniline was not nucleophilic enough. Also, indole brominated at C-6 underwent the C−H borylation (**6g** → **7gc**). As an example of a pyrrole (parent *N*-methylpyrrole failed to react), 1,2,5-trimethylpyrrole is also selectively monoborylated in high yield (**8** → **9c**). The methyl group at the nitrogen atom emerged as crucial as silylated substrates were unreactive, e.g., *i*-Pr$_3$Si-protected indole.

To summarize, we disclosed here a new way for the catalytic generation of borenium ions that allows for the C-3-selective electrophilic C−H borylation of indoles (and one pyrrole). By this, it became possible to install the synthetically useful pinB group at nitrogen heterocycles in an S$_E$Ar reaction for the first time. No added base is required, and H$_2$ is released as the sole byproduct. A systematic NMR investigation into the B−H bond activation as well as an intriguing X-ray analysis of the borane adduct of the ruthenium(II) thiolate catalyst provided significant insight into the generation of the boron electrophile, likely to emerge from a σ-bond metathesis.

ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization data, as well as ^{1}H, ^{11}B, ^{13}C, ^{19}F, and ^{31}P NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

martin.oestreich@tu-berlin.de; ohki@chem.nagoya-u.ac.jp; i45100a@nucc.cc.nagoya-u.ac.jp

Author Contributions

§T.S. and K.M. contributed equally.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This research was supported by the Fonds der Chemischen Industrie (predoctoral fellowship to T.S., 2011−2013), the Studienstiftung des deutschen Volkes (predoctoral fellowship to K.M., 2009−2012), and (in part) the Deutsche Forschungsgemeinschaft (International Research Training Group Münster-Nagoya, GRK 1143). M.O. is indebted to the Einstein Foundation (Berlin) for an endowed professorship. We thank Dr. Sebastian Kemper (TU Berlin) for expert advice with the NMR measurements.

REFERENCES

(1) *Boronic Acids: Preparation and Applications in Organic Synthesis, Medicine and Materials*, 2nd ed.; Hall, D. G., Ed.; Wiley-VCH: Weinheim, 2011.

(2) Tyrrell, E.; Brookes, P. *Synthesis* **2003**, 469−483.

(3) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890−931.

(4) (a) Muetterties, E. L. *J. Am. Chem. Soc.* **1959**, *81*, 2597. (b) Bujwid, Z. J.; Gerrard, W.; Lappert, M. F. *Chem. Ind.* **1959**, 1091−1092. (c) Muetterties, E. L. *J. Am. Chem. Soc.* **1960**, *82*, 4163−4166. (d) Muetterties, E. L.; Tebbe, F. N. *Inorg. Chem.* **1986**, *7*, 2663−2664.

(5) (a) Hurd, D. T. *J. Am. Chem. Soc.* **1948**, *70*, 2053−2055. (b) Paetzold, P.; Hoffmann, J. *Chem. Ber.* **1980**, *113*, 3724−3733 and references cited therein.

(6) For a brief review, see: Ingleson, M. J. *Synlett* **2012**, 1411−1415.

(7) (a) Genaev, A. M.; Nagy, S. M.; Salnikov, G. E.; Shubin, V. G. *Chem. Commun.* **2000**, 1587−1588. (b) De Vries, T. S.; Prokofjevs, A.; Harvey, J. N.; Vedejs, E. *J. Am. Chem. Soc.* **2009**, *131*, 14679−14687. (c) Ishida, N.; Moriya, T.; Goya, T.; Murakami, M. *J. Org. Chem.* **2010**, *75*, 8709−8712. (d) Hatakeyama, T.; Hashimoto, S.; Seki, S.; Nakamura, M. *J. Am. Chem. Soc.* **2011**, *133*, 18614−18617.

(8) Prokofjevs, A.; Kampf, J. W.; Vedejs, E. *Angew. Chem., Int. Ed.* **2011**, *50*, 2098−2101.

(9) (a) Del Grosso, A.; Singleton, P. J.; Muryn, C. A.; Ingleson, M. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 2102−2106. (b) Del Grosso, A.; Helm, M. D.; Solomon, S. A.; Caras-Quintero, D.; Ingleson, M. J. *Chem. Commun.* **2011**, *47*, 12459−12461. (c) Solomon, S. A.; Del Grosso, A.; Clark, E. R.; Bagutski, V.; McDouall, J. J. W.; Ingleson, M. J. *Organometallics* **2012**, *31*, 1908−1916.

(10) For excellent reviews, see: (a) Piers, W. E.; Bourke, S. C.; Conroy, K. D. *Angew. Chem., Int. Ed.* **2005**, *44*, 5016−5036. (b) Kölle, P.; Nöth, H. *Chem. Rev.* **1985**, *85*, 399−418.

(11) For an authoritative review of the synthetic chemistry of cationic boron electrophiles, see: De Vries, T. S.; Prokofjevs, A.; Vedejs, E. *Chem. Rev.* **2012**, *112*, 4246−4282.

(12) For borenium ion catalysis, see: (a) Farrell, J. M.; Hatnean, J. A.; Stephan, D. W. *J. Am. Chem. Soc.* **2012**, *134*, 15728−15731. (b) Eisenberger, P.; Bailey, A. M.; Crudden, C. M. *J. Am. Chem. Soc.* **2012**, *134*, 17384−17387. (c) Clark, E. R.; Del Grosso, A.; Ingleson, M. J. *Chem.*−*Eur. J.* **2013**, *19*, 2462−2466 (all hydrogenation). (d) Chen, J.; Lalancette, R. A.; Jäkle, F. *Chem. Commun.* **2013**, *49*, 4893−4895 (hydrosilylation).

(13) Del Grosso, A.; Pritchard, R. G.; Muryn, C. A.; Ingleson, M. J. *Organometallics* **2010**, *29*, 241−249.

(14) Ohki, Y.; Takikawa, Y.; Sadohara, H.; Kesenheimer, C.; Engendahl, B.; Kapatina, E.; Tatsumi, K. *Chem. Asian J.* **2008**, *3*, 1625−1635.

(15) Stahl, T.; Klare, H. F. T.; Oestreich, M. *J. Am. Chem. Soc.* **2013**, *135*, 1248−1251.

(16) (a) Klare, H. F. T.; Oestreich, M.; Ito, J.-i.; Nishiyama, H.; Ohki, Y.; Tatsumi, K. *J. Am. Chem. Soc.* **2011**, *133*, 3312−3315. (b) Königs, C. D. F.; Klare, H. F. T.; Ohki, Y.; Tatsumi, K.; Oestreich, M. *Org. Lett.* **2012**, *14*, 2842−2845. (c) Königs, C. D. F.; Müller, M. F.; Aiguabella, N.; Klare, H. F. T.; Oestreich, M. *Chem. Commun.* **2013**, *49*, 1506−1508.

(17) (a) Bianchini, C.; Masi, D.; Meli, A.; Peruzzini, M.; Vizza, F.; Zanobini, F. *Organometallics* **1998**, *17*, 2495−2502. (b) Sellmann, D.; Hille, A.; Heinemann, F. W.; Moll, M.; Reiher, M.; Hess, B. A.; Bauer, W. *Chem.*−*Eur. J.* **2004**, *10*, 4214−4224.

(18) Fuller, A.-M.; Hughes, D. L.; Lancaster, S. J.; White, C. M. *Organometallics* **2010**, *29*, 2194−2197.

(19) (a) Jones, M. E.; Hedberg, K.; Schomaker, V. *J. Am. Chem. Soc.* **1953**, *75*, 4116. (b) Lorbach, A.; Bolte, M.; Lerner, H.-W.; Wagner, M. *Chem. Commun.* **2010**, *46*, 3592−3594.