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# N-Heterocyclic Carbene Boranes are Good Hydride Donors

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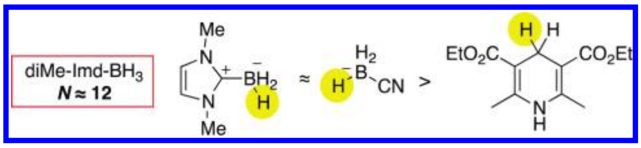
## ABSTRACT



**The nucleophilicity parameters (*N*) of 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene borane and 1,3-dimethylimidazol-2-ylidene borane are 9.55 and 11.88. This places N-heterocyclic carbene boranes (NHC-boranes) among the most nucleophilic classes of neutral hydride donors. Reductions of highly electron-poor C═N and C═C bonds provide hydrogenation products along with new, stable borylated products. The results suggest that NHC-boranes have considerable untapped potential as neutral organic reductants.**

Knowledge about the chemistry of N-heterocyclic carbene boranes (hereafter, NHC-boranes) has increased rapidly of late.[1] NHC-Trihydridoboranes (NHC-$BH_3$) are typically crystalline solids that are easy to make and handle.[2] Many are stable to air, strong bases,[3] mild acids[4] (including water and acetic acid), and chromatography. Boranes such as 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene borane[5] (dipp-Imd-$BH_3$, **1**) and 1,3-dimethylimidazol-2-ylidene borane[6] (diMe-Imd-$BH_3$, **2**) are useful reagents for radical[7,8] and organometallic reactions (Figure 1).[9]

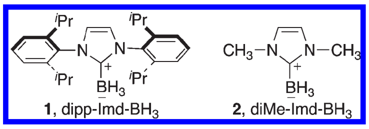


**Figure 1.** Structures of N-heterocyclic carbene boranes **1** and **2** with formal charges shown.

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(1) Curran, D. P.; Solovyev, A.; Makhlouf Brahmi, M.; Fensterbank, L.; Malacria, M.; Lacôte, E. *Angew. Chem., Int. Ed.* **2011**, *50*, 10294–10317.

(2) Makhouf Brahmi, M.; Monot, J.; Desage-El Murr, M.; Curran, D. P.; Fensterbank, L.; Lacôte, E.; Malacria, M. *J. Org. Chem.* **2010**, *75*, 6983–6985.

(3) Monot, J.; Solovyev, A.; Bonin-Dubarle, H.; Derat, É.; Curran, D. P.; Robert, M.; Fensterbank, L.; Malacria, M.; Lacôte, E. *Angew. Chem., Int. Ed.* **2010**, *49*, 9166–9169.

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(5) Wang, Y.; Quillian, B.; Wei, P.; Wannere, C. S.; Xie, Y.; King, R. B.; Schaefer, H. F.; Schleyer, P. v. R.; Robinson, G. H. *J. Am. Chem. Soc.* **2007**, *129*, 12412–12413.

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(7) (a) Ueng, S.-H.; Fensterbank, L.; Lacôte, E.; Malacria, M.; Curran, D. P. *Org. Biomol. Chem.* **2011**, *9*, 3415–3420. (b) Ueng, S.-H.; Fensterbank, L.; Lacôte, E.; Malacria, M.; Curran, D. P. *Org. Lett.* **2010**, *12*, 3002–3005. (c) Ueng, S.-H.; Makhlouf Brahmi, M.; Derat, É.; Fensterbank, L.; Lacôte, E.; Malacria, M.; Curran, D. P. *J. Am. Chem. Soc.* **2008**, *130*, 10082–10083.

(8) (a) Tehfe, M.-A.; Monot, J.; Makhlouf Brahmi, M.; Bonin-Dubarle, H.; Curran, D. P.; Malacria, M.; Fensterbank, L.; Lacôte, E.; Lalevée, J.; Fouassier, J.-P. *Polym. Chem.* **2011**, *2*, 625–631. (b) Tehfe, M.-A.; Makhlouf Brahmi, M.; Fouassier, J.-P.; Curran, D. P.; Malacria, M.; Fensterbank, L.; Lacôte, E.; Lalevée, J. *Macromolecules* **2010**, *43*, 2261–2267.

(9) Chu, Q.; Makhlouf Brahmi, M.; Solovyev, A.; Ueng, S.-H.; Curran, D.; Malacria, M.; Fensterbank, L.; Lacôte, E. *Chem.—Eur. J.* **2009**, *15*, 12937–12940.

10.1021/ol202836p

NHC-boranes have gained a reputation as weak ionic hydride donors[1] because of their stability under ambient conditions and because of their tolerance of ketones and other functional groups that are reduced by boron hydrides.

Much of this experience has been gained with dipp-Imd-$BH_3$ which reduces reactive primary halides and sulfonates ionically at temperatures well over 100 °C.[9] Only unhindered primary triflates are reduced near ambient temperature. The reductions of ketones by carbene-boranes can be promoted by Lewis acids.[10]

Here we report that the reputation of NHC-boranes as poor hydride donors may be undeserved. Measurements of "nucleophilicity parameters ($N$)"[11] place NHC-boranes **1** and especially **2** among the most reactive neutral hydride donors known.

*Measurement of N Values:* Benzhydrylium ions $Ar_2CH^+$ with variable *para*- and *meta*-substituents span a broad range of reactivity while the steric shielding of the reaction center is kept constant. Accordingly, they have been used as reference electrophiles for the construction of a comprehensive nucleophilicity scale based on eq 1. Electrophiles are characterized by $E$ (electrophilicity), and nucleophiles are characterized by the solvent-dependent parameters $s_N$ (sensitivity, previously termed $s$) and $N$ (nucleophilicity).[11]

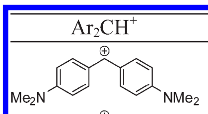
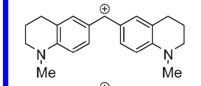
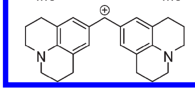
$$\log k_{20°C} = s_N(N + E) \qquad (1)$$

With the goals to incorporate N-heterocyclic carbene boranes into the nucleophilicity scale and to predict potential electrophilic reaction partners, we measured the rates of reactions of **1** and **2** with the substituted benzhydrylium ions **E1**–**E3** (Table 1) in $CH_2Cl_2$ at 20 °C.

Among the many NHC-boranes now available, dipp-Imd-$BH_3$ **1** was chosen because its ionic reactivity had already been demonstrated.[9] To complement **1**, we chose diMe-Imd-$BH_3$ **2** because it has a much lower molecular weight (110 compared to 402 g $mol^{-1}$) and because its $BH_3$ group is much less sterically shielded.

Reaction progress was followed photometrically by monitoring the absorbances of the benzhydrylium cations **E1**–**E3**. When **1** or **2** was added to solutions of the diarylcarbenium tetrafluoroborates in large excess ($[\mathbf{1}, \mathbf{2}] \gg [Ar_2CH^+]$), monoexponential decays of the absorbances were observed. This shows that there is a first-order dependence of the rates on the electrophile concentrations.

**Table 1.** Diarylcarbenium Ions Used as Electrophiles and Their Empirical Electrophilicity Parameters $E$ (from ref 11c)

| $Ar_2CH^+$ | | $E$ |
|---|---|---|
|  | **E1** | −7.02 |
|  | **E2** | −8.22 |
|  | **E3** | −9.45 |

A series of measurements with variable concentrations of **1** or **2** was performed for each electrophile–nucleophile combination, and Figure 2 shows the results from a typical run. The absorbance of **E3** at $\lambda$ = 643 nm decayed smoothly upon addition of **2**. A plot of the observed rate constants ($k_{obs}$) versus the concentration of the carbene-borane was linear, as illustrated in the insert of Figure 2. Consequently, the hydride transfer obeys the second-order rate law in eq 2, with the rate constant $k$ equaling the slope of the correlation line exemplified by Figure 2. The rate constants measured in this fashion are summarized in Table 2.

$$-d[Ar_2CH^+]/dt = k[Ar_2CH^+][Nu] \qquad (2)$$

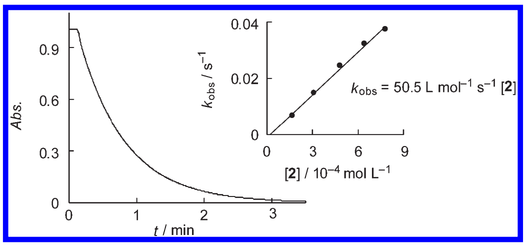


**Figure 2.** Absorbance decay at $\lambda$ = 643 nm for the reaction of **E3** ($c_0$ = 1.38 × $10^{-5}$ mol $L^{-1}$) with diMe-Imd-$BH_3$ **2** ($c$ = 4.84 × $10^{-4}$ mol $L^{-1}$), $k_{obs}$ = 2.45 × $10^{-2}$ $s^{-1}$, $CH_2Cl_2$, 20 °C. The insert is a plot of $k_{obs}$ versus [**2**], $k$ = 5.05 × $10^1$ L $mol^{-1}$ $s^{-1}$.

According to eq 1, the logarithms of $k$ should correlate linearly with the electrophilicity parameters $E$ of the benzhydrylium ions. This is confirmed by the plot in Figure 3. The derived reactivity parameters $N$ and $s_N$ are 9.55 and 0.81 for **1** and 11.88 and 0.71 for **2**.

Resonance interaction between the heterocyclic ring and the $N$-aryl rings of **1** is negligible because these rings are perpendicular.[4,5,12] So the aryl groups in **1** influence hydride transfer through the inductive effect. The smaller electron-donating effect and the larger size of the diisopropylphenyl rings compared to methyl groups explain why **1** is considerably less reactive than **2**.

**Table 2.** Second-Order Rate Constants for Hydride Transfers from the Carbene-Boranes **1** and **2** to Benzhydrylium Ions **E1**–**E3** ($CH_2Cl_2$, 20 °C), and the Derived Nucleophile-Specific Parameters $N$ and $s_N$

| donor | acceptor | $k$/L $mol^{-1}$ $s^{-1}$ | $N$ ($s_N$) |
|---|---|---|---|
| **1** | **E1** | 1.16 × $10^2$ | 9.55 (0.81) |
| | **E2** | 1.04 × $10^1$ | |
| | **E3** | 1.27 | |
| **2** | **E1** | 2.64 × $10^3$ | 11.88 (0.71) |
| | **E2** | 4.05 × $10^2$ | |
| | **E3** | 5.05 × $10^1$ | |

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(10) Lindsay, D. M.; McArthur, D. *Chem. Commun.* **2010**, *46*, 2474–2476.

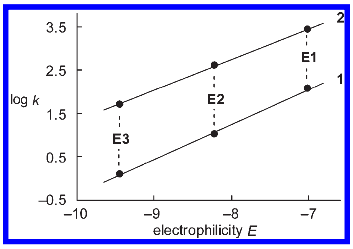


**Figure 3.** Plots of log $k$ versus the electrophilicity parameters $E$ of the benzhydrylium ions. Correlation equations: $\log k = 0.707 E + 8.40$ for **2**; $\log k = 0.807 E + 7.70$ for **1**.

Figure 4 shows a scale of $N$ parameters of representative neutral and anionic hydride donors.[13] With an $N$ parameter of about 12, carbene borane **2** is less nucleophilic than borohydride anion $BH_4^-$ in DMSO ($N \approx 15$) and roughly comparable to the cyanoborohydride anion ($BH_3CN^-$) in DMSO. Compared to neutral reference hydride donors, **2** is more reactive than trialkylamine-boranes, dihydropyridines, benzimidazolines, and even stannanes. Indeed, carbene borane **2** has one of the highest $N$ parameters of any neutral hydride donor measured to date.[14] Though less reactive than **2**, **1** is still a reactive hydride donor in the big picture for neutral reagents.

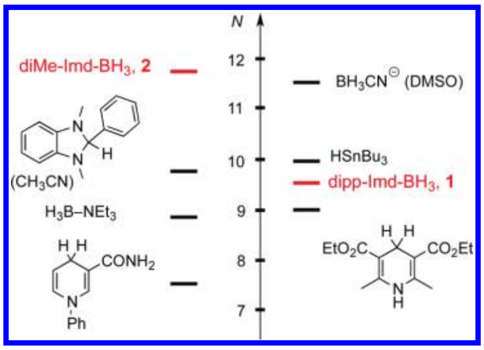


**Figure 4.** Nucleophilicity parameters $N$ of some hydride donors (in $CH_2Cl_2$ if not otherwise noted).

*Preparative Reductions:* Based on the high measured $N$ values, we undertook a preliminary survey of the potential to use the more readily available and more reactive reagent **2** in preparative reductions.

The second-order rate constant for a bimolecular process with both reactants at 1 M should be greater than $10^{-4}$ L mol$^{-1}$ s$^{-1}$ in order to achieve 50% conversion within 3 h. Substitution of this value into eq 1 leads to the rule of thumb that nucleophiles with $s_N \approx 0.8$ are likely to react with electrophiles at rt if eq 3 is fulfilled.

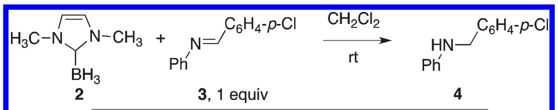
$$N + E \geq -5 \qquad (3)$$

Thus, **2** is not expected to react with typical alkyl- or aryl-substituted aldehydes ($E = -20$ to $-18$),[15] ketones, or imines in aprotic solvents. Yet, it should react with iminium ions and with C═N and even C═C double bonds substituted with strong electron-withdrawing groups.[13]

Reductions of iminium ions generated from imine **3** and acetic acid were conducted in dichloromethane (Scheme 1). In the control reaction of **2** and **3** without acid, no conversion occurred over 24 h (entry 1). Addition of 1.3 equiv of acetic acid resulted in the rapid disappearance of **2** over 1.5 h. *p*-Chlorobenzylaniline **4** was isolated in 84% yield by flash chromatography (entry 2). The amount of borane could be decreased to 0.5 equiv with little change in yield (entries 3, 4), though the reaction time increased. Even with 0.33 equiv of **2**, an 86% yield of **4** was obtained (entry 5). Apparently, reagent **2** can donate two and even three hydrides in iminium ion reductions.

For comparison, we reduced **3** with dipp-Imd-$BH_3$ **1** under the conditions of entry 2 (1 equiv **3**, 1.3 equiv **1**, 1.3 equiv HOAc). The reaction was slow at rt, so a preparative reaction was conducted at 80 °C for 2 days. This provided *p*-chlorobenzylaniline **4** in 77% yield.[16] Clearly, **2** is the better reagent for this reduction.

**Scheme 1.** Reductions of Preformed Imine **3** with **2**



| entry | equiv HOAc | equiv **2** | time | yield **4** |
|---|---|---|---|---|
| 1 | 0 | 1.3 | 24 h | – |
| 2 | 1.3 | 1.3 | 1.5 h | 84% |
| 3 | 1 | 0.7 | 16 h | 86% |
| 4 | 1 | 0.5 | 16 h | 94% |
| 5 | 1 | 0.33 | 3 d | 86% |

Since **2** does not react rapidly with carbonyl compounds, it should be possible to conduct one-pot reductive aminations starting from aldehydes and anilines. This was accomplished by mixing the components (RCHO, 1 equiv; aniline, 1.3 equiv; **2**, 0.5 or 1.3 equiv; HOAc, 1 equiv) in dichloromethane and then stirring for 1 h at rt. The yield of **4** by the one-pot method (91%, Table 3, entry 1) was comparable to the yield starting from the preformed imine **3**. Other pairs of partners also gave

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[11] (a) Mayr, H.; Ofial, A. R. *J. Phys. Org. Chem.* **2008**, *21*, 584–595. (b) Mayr, H.; Ofial, A. R. *Nachr. Chem.* **2008**, *56*, 871–877. (c) Mayr, H.; Bug, T.; Gotta, M. F.; Hering, N.; Irrgang, B.; Janker, B.; Kempf, B.; Loos, R.; Ofial, A. R.; Remennikov, G.; Schimmel, H. *J. Am. Chem. Soc.* **2001**, *123*, 9500–9512.

[12] Maji, B.; Breugst, M.; Mayr, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 6915–6919.

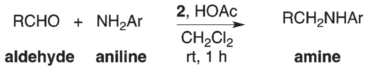
[13] The complete database is available at http://www.cup.uni-muenchen.de/oc/mayr/Dbintro/html.

[14] At $N = 14.6$, only 4-dimethylaminopyridine borane (DMAP-$BH_3$) has a higher parameter. However, this has only been determined against a single reference electrophile: Funke, M. A.; Mayr, H. *Chem.—Eur. J.* **1997**, *3*, 1214–1222.

[15] Appel, R.; Mayr, H. *J. Am. Chem. Soc.* **2011**, *133*, 8240–8251.

[16] Reaction with **1** gave **4** in 77% yield and dipp-Imd-$BH_2$OAc in 69% yield.

**Table 3.** One-Pot Reductive Aminations



$$\underset{\textbf{aldehyde}}{RCHO} + \underset{\textbf{aniline}}{NH_2Ar} \xrightarrow[CH_2Cl_2,\ rt,\ 1\ h]{\mathbf{2},\ HOAc} \underset{\textbf{amine}}{RCH_2NHAr}$$

| entry | R | Ar | equiv **2** | amine |
|---|---|---|---|---|
| 1 | $p$-$ClC_6H_4$ | $C_6H_5$ | 1.3 | 91% |
| 2 | $p$-$NO_2C_6H_4$ | $p$-$BrC_6H_4$ | 1.3 | 98% |
| 3 | $p$-$NO_2C_6H_4$ | $p$-$BrC_6H_4$ | 0.5 | 92% |
| 4 | $C_6H_5$ | $o$-$IC_6H_4$ | 1.3 | 73% |
| 5 | $C_6H_5$ | $o$-$IC_6H_4$ | 0.5 | 68% |
| 6 | ($E$)-$C_6H_5CH{=}CH$ | $p$-$BrC_6H_4$ | 1.3 | 76% |
| 7 | ($E$)-$C_6H_5CH{=}CH$ | $p$-$BrC_6H_4$ | 0.5 | 70% |
| 8 | $p$-$NO_2C_6H_4$ | $p$-$BrC_6H_4$ | 1.3 | 57% |

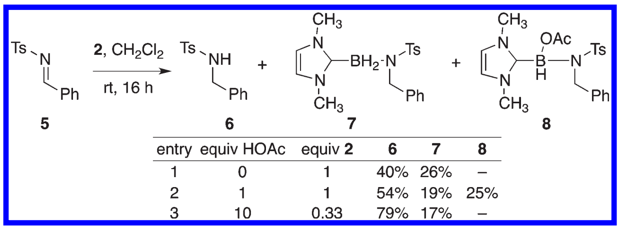
amines with only slight decreases in isolated yield when going from 1.3 to 0.5 equiv of **2**. An imine derived from cinnamaldehyde gave only the product of 1,2-reduction (entries 6 and 7).

Sodium cyanoborohydride ($NaBH_3CN$) is the classic reagent for such one-pot reductive aminations,[17] but cyanide is a liability because of its toxicity. $NaBH_3CN$ has been replaced by anionic reagents such as sodium triacetoxyborohydride ($NaBH(OAc)_3$)[18] and amine-boranes ($R_3N{-}BH_3$).[19] Using **2** is convenient because water workup and extractions can be omitted. Compared to amine-boranes, carbene-borane **2** appears to be both more stable[2] and more reactive (higher $N$ value). Both features are consistent with the high Lewis basicity of the carbenes.[12]

In line with its electrophilicity parameter $E$ of $-11.5$,[15] the tosyl imine **5** is also reduced at rt by **2**, with different products forming depending on the stoichiometry. Scheme 2 shows that reduction of **5** by **2** in dichloromethane without acetic acid followed by flash chromatography gave 40% of $N$-benzyltoluene sulfonamide **6** along with 26% of the reduced sulfonamide **7** containing the NHC-borane.

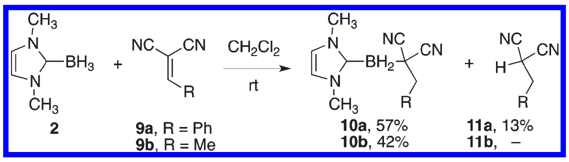
We added acetic acid in an effort to form more **6** at the expense of **7**. With 1 equiv of HOAc, the yield of **6** increased to 54% and that of **7** decreased to 19%, but a new stable product **8** was isolated in 25% yield (entry 2). Boron acetate **8** is apparently the product of an acid/base reaction of **7** with acetic acid. Increasing the amount of acetic acid gave more **6**, and again less than 1 equiv of borane could be used. Reduction of **5** with 10 equiv of HOAc and only 0.33 equiv of **2** provided **6** in 79% yield along with 17% of **7** (entry 3).

**Scheme 2.** Reduction of Tosyl Imine **5** with diMe-Imd-$BH_3$ **2**



| entry | equiv HOAc | equiv **2** | **6** | **7** | **8** |
|---|---|---|---|---|---|
| 1 | 0 | 1 | 40% | 26% | – |
| 2 | 1 | 1 | 54% | 19% | 25% |
| 3 | 10 | 0.33 | 79% | 17% | – |

**Scheme 3.** Reductions of Ylidene Malononitriles with **2**



NHC-borane **2** did not react rapidly at rt with arylidene or alkylidene malonic esters ($E = -24$ to $-18$), but it did react with the corresponding malononitriles. Stirring of **2** and **9a** ($E = -9.4$) for 15 min and then evaporation of the solvent and flash chromatography provided the stable reduced borylated malononitrile **10a** in 57% yield along with 13% of **11a** (Scheme 3).

Reduction of the corresponding ethylidene analog **9b** was much slower (18 h) and provided only the borylated product **10b** in 42% yield. Products **10a**,**b** are hydroboration products where the boron atom resides exclusively on the most substituted carbon atom.

Structures of the new types of carbene-boranes **7**, **8**, and **10a**,**b**, were secured by a combination of NMR spectroscopy and mass spectrometry (see Supporting Information).

In summary, measurements of $N$ parameters and results of preliminary reductions suggest that carbene-boranes have considerable unrecognized potential as neutral, organic hydride donors. 1,3-Dimethylimidazol-2-ylidene borane **2** looks especially promising because it has a high reactivity and a low molecular weight. It is stable, readily available, and easy to handle. Interesting borylated products with potential for onward transformations are isolated with some systems. Aqueous workups are not needed, and removal of the boron byproducts by flash chromatography is easy when nonborylated products are targeted.

**Acknowledgment.** We thank the National Science Foundation and the CNRS for support of this work, and we thank Mr. Andrey Solovyev, University of Pittsburgh, for help with assembling the Supporting Information.

**Supporting Information Available.** Includes complete experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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