The synthesis of chiral *N*-heterocyclic carbene–borane and –diorganoborane complexes and their use in the asymmetric reduction of ketones†

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Chiral *N*-heterocyclic carbene–borane complexes have been synthesised, and have been shown to reduce ketones with Lewis acid promotion. Chiral *N*-heterocyclic carbene–borane and –diorganoborane complexes can reduce ketones with enantioselectivities up to 75% and 85% ee, respectively.

For more than 40 years, there has been intense interest in the study of *N*-heterocyclic carbenes (NHCs), initially focused on empirical research,[1,2] which led to the isolation of NHCs,[3] and their concomitant impact in catalysis for organic synthesis. The ligating ability of NHCs equals or surpasses that of phosphanes in a range of transition metal-catalysed reactions,[4] and the Lewis- and Brønsted basicity of NHCs has enabled their use as powerful organocatalysts.[5]

In contrast to the dramatic increase in the use of NHCs in transition metal and organocatalysis, the utility of NHC–main group complexes has received relatively little attention, with descriptions of the preparation of NHC–borane complexes[6] and their synthetic utility (Fig. 1: **1** and **2**, used in the radical reduction of xanthates,[7a–c] Suzuki–Miyaura cross-coupling reactions[7d] and the ionic reduction of halides[7e]) appearing only very recently.[8] Given the ubiquity and utility of organoboron reagents in organic synthesis, there is a conceptual attraction to activating an organoboron species to its NHC–*ate* complex, revealing a wealth of potential applications for NHC–boranes. To date, there have been no reports of chiral NHC–borane complexes, but herein we report the preparation of these species and describe their use in the reduction of ketones,[9] and show that asymmetric reductions are indeed possible.

In addition to forming the known IMes·BH_3, **3**·BH_3, borane was complexed with a range of chiral NHCs, comprising the imidazolyl NHCs **4**, **5** and **6**, based on the C_2-symmetric, bis(oxazoline)-derived "THIBO"[10] and "HIBDIO" NHCs,[11] (Fig. 2).

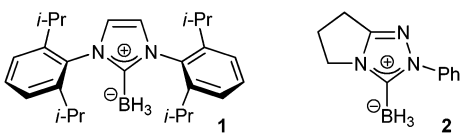


Fig. 1 *N*-Heterocyclic carbene–borane complexes.

The NHC–borane complexes **3–6**·BH_3 were readily prepared in good yield by deprotonation of imidazolium salts **3–6**·HX using either KHMDS or *n*-BuLi, followed by complexation with freshly-distilled BH_3·SMe_2 (Table 1).

With these novel, chiral NHC–borane complexes in hand, our attention turned to their use in the reduction of ketones. Although IMes-based **3**·BH_3 did not reduce acetophenone **7a**, either at room temperature or at reflux in CH_2Cl_2 (Table 2, entries 1 and 2), we were encouraged to observe that chiral complex **4**·BH_3 gave (*S*)-1-phenylethanol, (*S*)-**8a**, in 14% ee at room temperature, and 36% ee at 0 °C (Table 2, entries 3 and 4). Notwithstanding the challenge of optimizing yield and ee, this represented a proof-of-concept and the first example of asymmetric synthesis using a chiral NHC–borane complex.

We rationalized the reactivity difference between **3**·BH_3 and **4**·BH_3 as due to an electronic effect, with **4** being more electron-rich than **3**, hence generating a more nucleophilic hydride transfer agent,[12] though steric factors may also contribute to this difference in reactivity.

To improve the reactivity of this system, we next examined activation of the ketone, and after screening a small range of

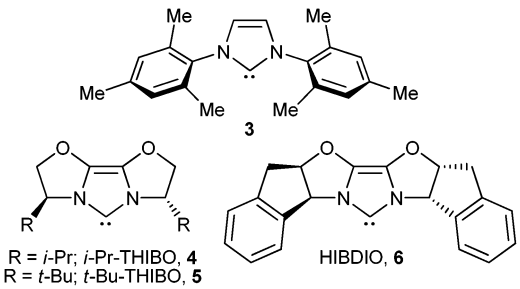
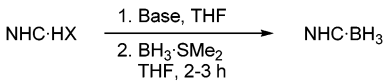


Fig. 2 *N*-Heterocyclic carbenes used in this work.

Table 1 Synthesis of NHC–borane complexes



Entry	NHC·HX	Base	NHC·BH_3	Yield (%)
1	**3**·HPF_6	KHMDS[a]	**3**·BH_3	88
2	**4**·HOTf	*n*-BuLi[b]	**4**·BH_3	96
3	**5**·HOTf	*n*-BuLi[b]	**5**·BH_3	95
4	**6**·HOTf	*n*-BuLi[b]	**6**·BH_3	46

Base and BH_3·SMe_2 added at[a] 0 °C, [b] −78 °C.

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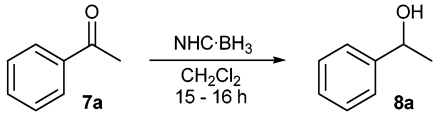
† Electronic supplementary information (ESI) available: Experimental procedures, spectral and analytical data for all new compounds and chiral GC or HPLC traces for asymmetric reactions. See DOI: 10.1039/c001466d

Table 2 Reduction of acetophenone with NHC–borane complexes



Entry	NHC·BH_3	Lewis acid	T/°C	Yield (%)	ee (%)
1	**3**·BH_3	—	rt	—	—
2	**3**·BH_3	—	40	—	—
3	**4**·BH_3	—	rt	44[a]	14 (*S*)
4	**4**·BH_3	—	0	10[a]	36 (*S*)
5	**4**·BH_3	$Sc(OTf)_3$[b]	−78	95	42 (*R*)
6	**5**·BH_3	$Sc(OTf)_3$[b]	−78	92	50 (*S*)
7	**6**·BH_3	$Sc(OTf)_3$[b]	−78	60	75 (*S*)

[a] % conversion, determined by GC. [b] 1 equiv. was used.

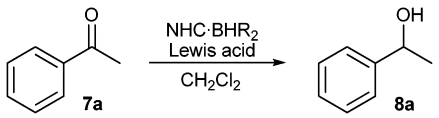
Lewis acids, $Sc(OTf)_3$ was found to both accelerate the reaction and increase the enantioselectivity (Table 2, entry 5); intriguingly, the sense of asymmetric induction was now *inverted*, compared to the reductions without Lewis acid.

Having identified $Sc(OTf)_3$ as an effective Lewis acid, we then examined the effect of structural variation of the NHC (Table 2, entries 6–9); again, the asymmetric induction observed was interesting. Thus, **5**·BH_3 (Table 2, entry 6) led to an encouraging increase in ee (to 50%), but with the absolute stereochemistry of the major product **8a** now (*S*), compared to the (*R*)-isomer which dominated in the reduction using *i*-Pr–THIBO complex **4**·BH_3. Such a switch in enantioselectivity within a homochiral ligand family is not unprecedented.[13,14] The highest enantioselectivity was observed using the amino-indanol derived **6**·BH_3 (Table 2, entry 7).

In order to expand on these very promising initial results, and especially given the apparent sensitivity of the reaction to steric influences (as shown by the variable absolute stereoinduction), we next sought to investigate the environment around boron by examining analogous chiral NHC–diorganoborane complexes.

Thus, the novel IMes·diorganoborane **3**·9-BBN (an air-stable, crystalline solid) was prepared and shown to reduce **7a** at room temperature without the need of a Lewis acid (Table 3, entry 1). The reduction using the analogous 9-BBN complex of NHC **4** (air-sensitive, generated and used *in situ*), in the presence of $Sc(OTf)_3$, proceeded in poor yield and with

Table 3 Asymmetric ketone reduction using NHC–dialkylborane complexes



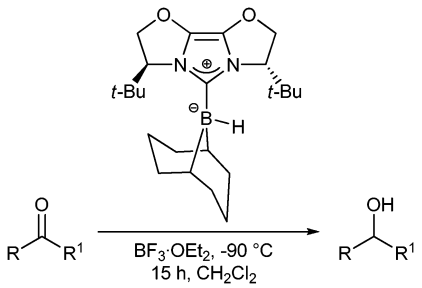
Entry	NHC·BHR_2	T/°C	t/h	Yield (%)	ee (%)
1	**3**·9-BBN[a]	rt	24	15[d]	—
2	**4**·9-BBN[b]	−78	15	40[d]	34 (*R*)
3	**4**·9-BBN[c]	−78	4	90[d]	56 (*R*)
4	**4**·9-BBN[c]	−90	15	82	60 (*R*)
5	**5**·9-BBN[c]	−90	15	80	84 (*S*)
6	**6**·9-BBN[c]	−90	15	45	10 (*S*)

[a] No Lewis acid additive. [b] 1 equiv. $Sc(OTf)_3$. [c] 1 equiv. $BF_3{\cdot}OEt_2$. [d] % conversion, determined by GC.

mediocre ee (Table 3, entry 2). We now considered that the increased steric bulk of the NHC–diorganoborane, combined with a relatively sterically demanding Lewis acid, was the root of this disappointing result.

Thus, we were pleased to observe that switching to a less sterically-demanding Lewis acid ($BF_3{\cdot}OEt_2$) led to an improvement in rate of reaction, yield and stereoselectivity and (*R*)-**8a** was obtained in 90% yield and 56% ee at −78 °C, and in 82% yield and 60% ee at −90 °C (Table 3, entries 3 and 4). Complex **5**·9-BBN proved most effective, delivering (*S*)-**8a** in 80% isolated yield and 84% ee (Table 3, entry 5), and, remarkably, an inversion in enantioselectivity (from *R* to *S*) was also observed in this NHC·9-BBN system, between *i*-Pr complex **4**·9-BBN and *tert*-Bu complex **5**·9-BBN.

Table 4 Asymmetric ketone reduction by **5**·9-BBN[a]



Entry	Ketone	Alcohol	Yield (%)	ee (%)
1	**7a**	**8a**	80	84
2	**7b**	**8b**	76	85
3	**7c**	**8c**	74	59
4	**7d**	**8d**	87	71
5	**7e**	**8e**	82	63
6	**7f**	**8f**	65	24
7	**7g**	**8g**	68	0
8	**7h**	**8h**	88	70
9	**7i**	**8i**	90	62

[a] 1 equiv. of **5**·9-BBN and 1 equiv. of $BF_3{\cdot}OEt_2$.

We next examined the scope of the reduction with respect to the ketone substrate. A variety of aryl alkyl- and dialkyl ketones were reduced, as summarized in Table 4. The ketones were reduced in good yields and with generally useful enantioinduction. In particular, phenethynyl methyl ketone **7h** was reduced to the corresponding alcohol **8h** in 70% ee (Table 4, entry 8), which compares favourably with reduction of the same substrate using Alpine-Borane and the CBS catalyst (78% ee[15] and 71% ee,[16] respectively). Pinacolone **7i** was reduced to **8i** in 62% ee (Table 4, entry 9), again comparing favourably with literature precedent.[17]

In summary, we have synthesised a range of chiral and achiral NHC–borane and –organoborane complexes, and shown, in the first example of asymmetric synthesis using structurally well-defined chiral NHC–main group complexes, their potential in the asymmetric reduction of ketones. Work in our laboratory is ongoing to identify more effective chiral NHCs to apply the methodology to other C=X[18] systems and to develop a catalytic, asymmetric variant of the reaction, and these studies will be described in due course.

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Notes and references

1 K. Öfele, *J. Organomet. Chem.*, 1968, **12**, P42–P43.

2 H.-W. Wanzlick and H.-J. Schönherr, *Angew. Chem., Int. Ed. Engl.*, 1968, **7**, 141–142.

3 For a review, see A. J. Arduengo, *Acc. Chem. Res.*, 1999, **32**, 913–921.

4 (*a*) N-*Heterocyclic Carbenes in Synthesis*, ed. S. P. Nolan, Wiley-VCH, Weinheim, 2006; (*b*) *Topics in Organometallic Chemistry*, ed. F. Glorius, Springer Berlin, Heidelberg, 2007, vol. 21.

5 For reviews, see: (*a*) N. Marion, S. Díez-González and S. P. Nolan, *Angew. Chem., Int. Ed.*, 2007, **46**, 2988–3000; (*b*) D. Enders, O. Niemeier and A. Henseler, *Chem. Rev.*, 2007, **107**, 5606–5655.

6 (*a*) N. Kuhn, G. Henkel, T. Kratz, J. Kreutzberg, J. Boese and A. H. Maulitz, *Chem. Ber.*, 1993, **126**, 2041–2045; (*b*) D. Enders, K. Breuer, J. Runsink and J. H. Teles, *Liebigs Ann.*, 1996, 2019–2028; (*c*) A. Wacker, H. Pritzkow and W. Siebert, *Eur. J. Inorg. Chem.*, 1998, 789–793; (*d*) A. J. Arduengo, F. Davidson, R. Krafczyk, W. J. Marshall and R. Schmutzler, *Monatsh. Chem.*, 2000, **131**, 251–265; (*e*) X. Zheng and G. E. Herberich, *Organometallics*, 2000, **19**, 3751–3753; (*f*) T. Ramnial, H. Jong, I. D. McKenzie, M. Jennings and J. A. C. Clyburne, *Chem. Commun.*, 2003, 1722–1723; (*g*) Y. Yamaguchi, T. Kashiwabara, K. Ogata, Y. Miura, Y. Nakamura, K. Kobayashi and T. Ito, *Chem. Commun.*, 2004, 2160–2161; (*h*) A. D. Phillips and P. P. Power, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.*, 2005, **61**, o291–o293; (*i*) R. Cariou, C. Fischmeister, L. Toupet and P. H. Dixneuf, *Organometallics*, 2006, **25**, 2126–2128; (*j*) D. Holschumacher, T. Bannenberg, C. G. Hrib, P. G. Jones and M. Tamm, *Angew. Chem., Int. Ed.*, 2008, **47**, 7428–7432; (*k*) P. A. Chase and D. W. Stephan, *Angew. Chem., Int. Ed.*, 2008, **47**, 7433–7437; (*l*) J. D. Masuda, W. W. Schoeller, B. B. Donnadieu and G. Bertrand, *J. Am. Chem. Soc.*, 2007, **129**, 14180–14181; (*m*) C. A. Dyker and G. Bertrand, *Science*, 2008, **321**, 1050–1051; (*n*) Y. Wang, Y. Xie, P. Wei, R. B. King, H. F. Schaefer III, P. v. R. Schleyer and G. H. Robinson, *Science*, 2008, **321**, 1069–1071; (*o*) Y. Wang, B. Quillian, P. Wei, Y. Xie, C. S. Wannere, R. B. King, H. F. Schaefer III, P. v. R. Schleyer and G. H. Robinson, *J. Am. Chem. Soc.*, 2008, **130**, 3298–3299.

7 (*a*) S. H. Ueng, M. M. Brahmi, É. Derat, L. Fensterbank, E. Lacôte, M. Malacria and D. P. Curran, *J. Am. Chem. Soc.*, 2008, **130**, 10082–10083; (*b*) see also J. C. Walton, *Angew. Chem., Int. Ed.*, 2009, **48**, 1726–1728; (*c*) S. H. Ueng, A. Solovyev, X. Yuan, S. J. Geib, L. Fensterbank, E. Lacôte, M. Malacria, M. Newcomb, J. C. Walton and D. P. Curran, *J. Am. Chem. Soc.*, 2009, **131**, 11256–11262; (*d*) J. Monot, M. M. Brahmi, S. H. Ueng, C. Robert, M. Desage-El Murr, D. P. Curran, M. Malacria, L. Fensterbank and E. Lacôte, *Org. Lett.*, 2009, **11**, 4914–4917; (*e*) Q. Chu, M. M. Brahmi, A. Solovyev, S. H. Ueng, D. P. Curran, M. Malacria, L. Fensterbank and E. Lacôte, *Chem.–Eur. J.*, 2009, **15**, 12937.

8 A recent report on the asymmetric conjugate borylation of α,β-unsaturated carbonyl systems notably invokes an NHC–boron intermediate: K. S. Lee, A. R. Zhugralin and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2009, **131**, 7253–7255.

9 There is a single report of the use of IMes·InH_3 in the reduction of acetophenone, although the extreme reactivity and difficulty of preparing and handling the indium hydride precursors may discourage their widespread use; C. D. Abernethy, M. L. Cole, A. J. Davies and C. Jones, *Tetrahedron Lett.*, 2000, **41**, 7567–7570.

10 THIBO is an acronym derived from the IUPAC name for the tricyclic core: tetrahydroimidazo[4,3-*b*:5,1-*b*′]bis[1,3]oxazol-4-ium. HIBDIO is an acronym derived from the IUPAC name for the heptacyclic core: 2,3,10,14,21,22-hexahydroimidazo[4,3-*b*:5,1-*b*′]-bis(3*aS*,8*aR*)-8,8*a*-dihydro-3*aH*-indeno[1,3]oxazol-11-ium.

11 (*a*) F. Glorius, G. Altenhoff, R. Goddard and C. W. Lehman, *Chem. Commun.*, 2002, 2704–2705; (*b*) G. Altenhoff, R. Goddard, C. W. Lehmann and F. Glorius, *J. Am. Chem. Soc.*, 2004, **126**, 15195–15201.

12 In contrast, studies carried out by Glorius suggest the THIBO/ "IBiox" ligand family is marginally *less* electron rich than standard ligands such as IMes, according to the calculated Tolman electronic parameter: G. Altenhoff, R. Goddard, C. W. Lehman and F. Glorius, *J. Am. Chem. Soc.*, 2004, **126**, 15195–15201.

13 M. Johannsen and K. A. Jørgensen, *J. Org. Chem.*, 1995, **60**, 5757–5762.

14 It should be noted that, although apparently dramatic, a switch from 42% ee (*S*) to 50% ee (*R*) at −78 °C corresponds to an energy difference of only 0.8 kcal mol^{-1}, whereas the switch reported by Jørgensen,[13] 83% ee to 85% ee at room temperature, corresponds to a much greater energy difference of 3 kcal mol^{-1}.

15 H. C. Brown and P. V. Ramachandran, *Acc. Chem. Res.*, 1992, **25**, 16–24.

16 K. A. Parker and M. W. Ledeboer, *J. Org. Chem.*, 1996, **61**, 3214–3217.

17 N. J. Gilmore, S. Jones and M. P. Muldowney, *Org. Lett.*, 2004, **6**, 2805–2808.

18 For a recent example of an organoborane-mediated reduction of imines, see D. Chen and J. Klankermayer, *Chem. Commun.*, 2008, 2130–2131.

