Radical Reduction

DOI: 10.1002/anie.200805362

Linking Borane with N-Heterocyclic Carbenes: Effective Hydrogen-Atom Donors for Radical Reactions**

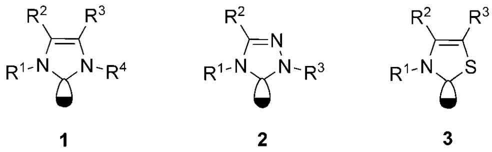
John C. Walton*

boron · C−H activation · N-heterocyclic carbenes · radicals · reduction

The search for simple, nontoxic, nonexplosive compounds to mediate free-radical syntheses has led to a great deal of interesting and original chemistry. Numerous compounds suitable for radical generation, including silicon hydrides, germanium hydrides, xanthates, phosphites, and cyclohexadiene derivatives, have been described,[1] but all have a limited range of applicability. Much radical chemistry has been based on organoboranes. For example, trialkyl boranes have found application in radical alkylation reactions,[2] and the system Et_3B/O_2, introduced by Nozaki et al.,[3] has been widely used to initiate radical reactions. *B*-Alkyl catecholboranes (2-alkyl-1,3,2-benzodioxaboroles), developed by Renaud and co-workers, are particularly flexible reagents for the alkylation of enones, the allylation of alkenes, alkynylation, methanimination, cyanation, and related reactions.[4]

A new direction has been given to this line of research by a recent article from the research groups of Fensterbank, Lacôte, Malacria, and Curran (hereafter referred to as FLMC), who described a marriage of organoboron chemistry with that of N-heterocyclic carbenes (NHCs).[5] The offspring of this union are NHC–borane complexes, which show great promise as a new class of hydrogen-atom donors for radical reactions. The bond-dissociation energy (BDE) of borane (BH_3) is much too high at 445.5 kJ mol^{-1} for this compound to function as an H-atom donor. It is known, however, that this property can be modulated by ligating borane with Lewis bases. Amine–borane and phosphine–borane complexes were studied extensively in the 1980s and 1990s by Roberts and co-workers.[6] They found that electrophilic radicals selectively removed a hydrogen atom from the boron atom of RNH_2–BH_2R complexes to initially generate amine–boryl radicals, which rapidly rearranged to aminyl–borane radicals. The amine–boryl radicals were nucleophilic in character and were selective H-atom abstractors. They were therefore suitable for use in polarity-reversal catalysis.[6,7] The studies of Roberts and co-workers indicated that the B−H BDE was reduced by complexation with an amine (or phosphine), a result supported by later DFT computations,[8] which gave values in the range 393–435 kJ mol^{-1}. Phosphine–boranes[9] and amine–boranes[10] have both been used successfully as reducing agents in homolytic preparative procedures. Furthermore, stereoselective H-atom donation by chiral amine–boranes was also observed,[6,11] but only exploited to a limited extent in organic synthesis.

The great structural versatility of NHCs provides divers opportunities to tune their physicochemical properties. A large variety of scaffolds, including imidazolium, triazolium, and thiazolium derivatives (**1**, **2**, and **3**, respectively, Scheme 1) can be constructed readily and have found numerous uses in organocatalysis and organometallic catalysis.[12] The heteroatom donor groups remove the degeneracy of the carbene orbitals and thus enhance the nucleophilicity of the carbon atom. These singlet carbenes possess low-energy highest-occupied molecular orbitals (HOMOs) and high-energy lowest-unoccupied molecular orbitals (LUMOs). They are stronger electron-pair donors than amines, because the electronegativity of the carbene carbon atom is lower than that of a nitrogen atom. Since the amino groups are π-donating and σ-withdrawing, 2,3-dihydro-1*H*-imidazol-2-ylidenes benefit from a “push–pull” effect.[12] NHCs act as σ-type ligands for many metals and have been called “phosphine mimics”.



Scheme 1. Archetypal 6π N-heterocyclic carbenes.

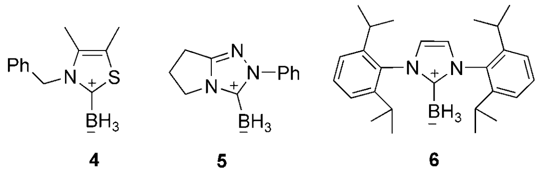
The key idea behind the research of FLMC was that complexes of NHCs and borane would have weakened B−H bonds and be better H-atom donors than amine–boranes or phosphine–boranes. In an elegant example of theory complementing experiment, FLMC first carried out DFT computations on the NHC–borane complexes **4**–**6** (Scheme 2). The B−H BDEs of these complexes were predicted to be approximately 125 kJ mol^{-1} lower than that of BH_3.

Thus, the computed B−H BDEs were only marginally greater than the BDEs of the analogous bonds in the good donors Bu_3Sn−H and $(Me_3Si_3)_3Si$−H. Next, complexes **5** and **6**

---

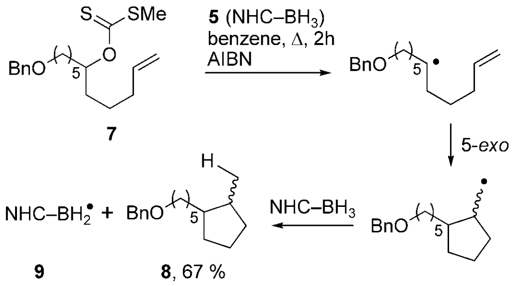
[*] Prof. Dr. Dr. J. C. Walton
School of Chemistry, University of St. Andrews
St. Andrews, Fife, KY16 9ST (UK)
Fax: (+44) 1334-463-808
E-mail: jcw@st-and.ac.uk

[**] I thank EaStChem for financial support.



Scheme 2. N-heterocyclic carbene–borane complexes.

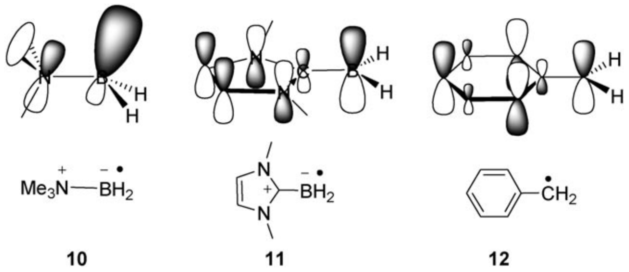
were tested as radical reducing reagents in experiments with a series of secondary and benzylic xanthates. With AIBN as the initiator, reduced products were isolated in yields ranging from 57 to 70%. In a second set of experiments, Et_3B/O_2 was used as the initiator at room temperature; generally higher yields were observed (71–84%). The hypothesis that these reactions were mediated by radicals was supported by the fact that the hexenyl xanthate **7** yielded the cyclopentyl derivative **8** through a 5-*exo* ring closure favored by radicals (Scheme 3). A xanthate precursor to a cyclopropyl carbinyl radical afforded the ring-opened product. These results demonstrated that NHC–boranes are competent H-atom donors to C-centered radicals. Of course, their applicability in other types of radical reduction has yet to be tested, and the rate constant for hydrogen-atom transfer has still to be determined. Many achiral as well as chiral NHCs are available, so opportunities to modify the chemical environment of the B–H bond, its strength and accessibility, will be plentiful. Chiral NHCs ligated to metals have proved useful in controlling the stereochemical outcome of reactions in numerous catalytic applications. There is clear opportunity for the development of practical stereoselective radical reduction protocols around NHC–borane reagents.



Scheme 3. Reduction of a secondary hexenyl xanthate with the NHC–borane **5**. AIBN = azobisisobutyronitrile, Bn = benzyl.

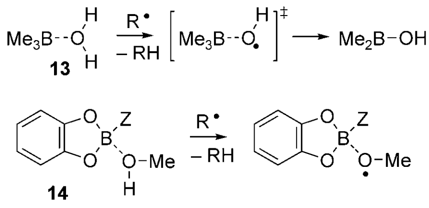
The NHC–boryl radical **9** and related radicals generated by H-atom transfer from the corresponding NHC–BH_3 complexes are particularly intriguing. EPR spectroscopic observations of amine–boryl radicals, such as $Me_3N{\cdots}BH_2^{\bullet}$, showed them to be σ-type radicals pyramidal at boron and nucleophilic in character.[7,13] They rapidly and selectively abstracted H atoms from C atoms adjacent to electron-withdrawing substituents.[6] It is probable, however, that amine–boryl or phosphine–boryl radicals are not good models for most NHC–boryl radicals. In NHC–boryl radicals, the unpaired electron is initially created at the BH_2 group adjacent to a quasiaromatic imidazolium ring. Delocalization of the unpaired electron into the NHC π system is the probable consequence.

Rough sketches based on DFT computations (B3LYP with a 6-31G(d) basis set) of the singly occupied molecular orbitals (SOMOs) of $Me_3N{\cdots}BH_2^{\bullet}$ (**10**), the NHC–boryl radical **11**, and the benzyl radical **12** are displayed in Scheme 4. The NHC–boryl radical is predicted to be quite unlike the bent σ amine–boryl radical, but quite like the π-delocalized benzyl radical. The calculated structure of **11** is essentially planar. Its π system is strikingly similar to that of the benzyl radical and extends to all skeletal atoms. Similar delocalized electronic structures are expected for imidazolium, triazolium, and thiazolium NHC–boryl species. Consequently, NHC–boryl radicals should be stabilized significantly by resonance, that is, thermodynamically. The formation of such resonance-stabilized radicals is thought to be a major factor in lowering the transition-state energy of H-atom-transfer reactions of NHC–boranes. Like benzyl radicals, NHC–boryl radicals are not expected to abstract H atoms easily (except from species with even lower X–H BDEs than NHC–boranes, for example, RSH). This characteristic would not lead to long lifetimes (i.e. persistence) in the case of sterically uncrowded NHC–boryl radicals, because dimerization is a reaction channel that is always open to them. Furthermore, resonance-stabilized radicals, such as the benzyl radical, are known to attack sulfur-containing functional groups and add to multiple bonds. By analogy, NHC–boryl radicals probably react with the xanthate moiety to propagate the chain reaction.



Scheme 4. Sketches of the frontier semioccupied orbitals of model amine–boryl and NHC–boryl radicals and the benzyl radical.

A further arresting feature associated with organoborane complexes is that, whereas the B–H BDE of BH_3 is lowered by ligated HNCs and by ligated Lewis bases, boron appears to "return the compliment" by lowering the O–H BDE of ligated H_2O and MeOH in complexes such as **13** and **14** (Scheme 5). Remarkably, reagents **13** and **14** were found to be good H-atom donors to radicals derived from xanthates and alkyl catecholboranes.[14] The crucial feature of these complexes is that Lewis acid–base interactions between the boranes and hydroxylic compounds substantially reduce their O–H BDEs. For the case of water complexed with Me_3B, the O–H BDE was computed to be decreased by 125 kJ mol^{-1} from the BDE of the O–H bond in uncomplexed water. Clearly, further theoretical study needs to be devoted to the importance of Lewis acid–base interactions in comparison



Scheme 5. Reductions with borane-ligated water and methanol ligated to a boronic ester. Z = alkyl or OMe.

with the resonance stabilization of product species for both borane–NHC and borane–OHR complexes.

The sheer size of the decrease in the B–H BDE brought about by complexation with NHCs is remarkable and chemically very significant. One immediate result is the development by FLMC of a new and promising suite of reagents for mediating radical reductions. The growing popularity of NHCs owes much to their scope for structural modulation. Much profitable transfer of know-how from NHC chemistry to synthetic radical chemistry can be expected. In the longer term, this discovery suggests that sizeable reductions in the strengths of other bonds may also result from Lewis acid–base interactions. NHC complexes with other types of boranes (BX_3) as well as other hydrides (YH_n) are known. Important developments along these divergent pathways can be anticipated.

---

[1] P. A. Baguley, J. C. Walton, *Angew. Chem.* **1998**, *110*, 3272–3283; *Angew. Chem. Int. Ed.* **1998**, *37*, 3072–3082; A. Studer, S. Amrein, *Synthesis* **2002**, 835–849; J. C. Walton, A. Studer, *Acc. Chem. Res.* **2005**, *38*, 794–802; B. Quiclet-Sire, S. Z. Zard, *Top. Curr. Chem.* **2006**, *264*, 201–236.

[2] A. G. Davies, B. P. Roberts, *J. Chem. Soc. B* **1967**, 17–22; A. G. Davies, B. P. Roberts, *J. Chem. Soc. B* **1969**, 311–317; G. W. Kabalka, H. C. Brown, A. Suzuki, S. Honma, A. Arase, M. Itoh, *J. Am. Chem. Soc.* **1970**, *92*, 710–712.

[3] K. Nozaki, K. Oshima, K. Utimoto, *J. Am. Chem. Soc.* **1987**, *109*, 2547–2549.

[4] A. P. Schaffner, V. Darmency, P. Renaud, *Angew. Chem.* **2006**, *118*, 5979–5981; *Angew. Chem. Int. Ed.* **2006**, *45*, 5847–5849; P. Schaffner, F. Montermini, D. Pozzi, V. Darmency, E. M. Scanlan, P. Renaud, *Adv. Synth. Catal.* **2008**, *350*, 1163; for a review, see: P. Renaud, A. Beauseigneur, A. Brecht-Forster, B. Becattini, V. Darmency, S. Khandasarmy, F. Montermini, C. Ollivier, P. Panchaud, D. Pozzi, E. M. Scanlan, A. P. Schaffner, V. Weber, *Pure Appl. Chem.* **2007**, *79*, 223–233.

[5] S.-H. Ueng, M. M. Brahmi, É. Derat, L. Fensterbank, E. Lacôte, M. Malacria, D. P. Curran, *J. Am. Chem. Soc.* **2008**, *130*, 10082–10083.

[6] B. P. Roberts, *Chem. Soc. Rev.* **1999**, *28*, 25–35.

[7] V. Paul, B. P. Roberts, C. A. S. Robinson, *J. Chem. Res. Synop.* **1988**, 264–265.

[8] P. R. Rablen, *J. Am. Chem. Soc.* **1997**, *119*, 8350–8360.

[9] J. A. Baban, B. P. Roberts, *J. Chem. Soc. Perkin Trans. 2* **1988**, 1195–1200; D. H. R. Barton, M. Jacob, *Tetrahedron Lett.* **1998**, *39*, 1331–1334.

[10] J. A. Baban, B. P. Roberts, *J. Chem. Soc. Perkin Trans. 2* **1984**, 1717–1722; I. G. Green, R. L. Hudson, B. P. Roberts, *J. Chem. Soc. Perkin Trans. 2* **1987**, 1173–1179.

[11] P. L. H. Mok, B. P. Roberts, *Tetrahedron Lett.* **1992**, *33*, 7249–7252; H.-S. Dang, V. Diart, B. P. Roberts, D. A. Tocher, *J. Chem. Soc. Perkin Trans. 2* **1994**, 1039–1045; M. B. Haque, B. P. Roberts, *Tetrahedron Lett.* **1996**, *37*, 9123–9126; M. B. Haque, B. P. Roberts, D. A. Tocher, *J. Chem. Soc. Perkin Trans. 1* **1998**, 2881–2889; Y. Cai, B. P. Roberts, D. A. Tocher, *J. Chem. Soc. Perkin Trans. 1* **2002**, 1376–1386.

[12] For reviews on HNCs, see: W. A. Herrmann, C. Köcher, *Angew. Chem.* **1997**, *109*, 2256–2282; *Angew. Chem. Int. Ed. Eng.* **1997**, *36*, 2162–2187; W. A. Herrmann, *Angew. Chem.* **2002**, *114*, 1342–1363; *Angew. Chem. Int. Ed.* **2002**, *41*, 1290–1309; D. Enders, O. Niemeier, A. Henseler, *Chem. Rev.* **2007**, *107*, 5606–5665.

[13] N. Kirwan, B. P. Roberts, *J. Chem. Soc. Perkin Trans. 2* **1989**, 539–550.

[14] D. A. Spiegel, K. B. Wiberg, L. N. Schacherer, M. R. Medeiros, J. L. Wood, *J. Am. Chem. Soc.* **2005**, *127*, 12513–12515; D. Pozzi, E. M. Scanlan, P. Renaud, *J. Am. Chem. Soc.* **2005**, *127*, 14204–14205; M. R. Medeiros, L. N. Schacherer, D. A. Spiegel, J. L. Wood, *Org. Lett.* **2007**, *9*, 4427–4429; J. Jin, M. Newcomb, *J. Org. Chem.* **2007**, *72*, 5098–5103.