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Radical Deoxygenation of Xanthates and Related Functional Groups with New Minimalist N-Heterocyclic Carbene Boranes

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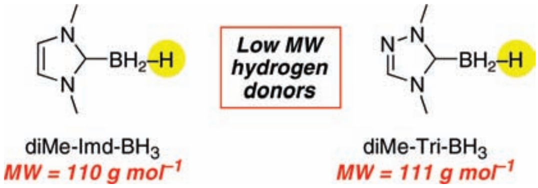
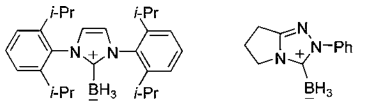
ABSTRACT



Minimalist N-heterocyclic carbene boranes 1,3-dimethylimidazol-2-ylideneborane and 2,4-dimethyl-1,2,4-triazol-3-ylideneborane are readily available and have low molecular weights. They exhibit superior performance to first-generation NHC−boranes, providing improved yields in reductions of xanthates and related functional groups.

Radical reactions are commonly used as key steps in modern organic synthesis,[1] and this has spurred research to provide attractive alternatives to traditional radical reducing agents such as tributyltin hydride.[2,3] We have recently learned that N-heterocyclic carbene−borane complexes **1** and **2** (hereafter called NHC−boranes, Figure 1) can reduce xanthates and related functional groups,[4] and we have accumulated strong evidence that these reductions occur through a radical mechanism involving N-heterocyclic carbene boryl radicals $(NHC-BH_2^{\bullet})$.[5−7]


imidazol-2-ylidene borane, **1**
MW = 402 g mol−1

1,2,4-triazol-3-ylidene borane, **2**
MW = 199 g mol−1

Figure 1. Structures of first-in-class N-heterocyclic carbene boranes used in xanthate reductions. (Formal charges are shown here but not in subsequent diagrams.)

These NHC−boranes are attractive for radical, ionic,[8] and organometallic[9] reactions because they are stable and easy

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(1) (a) Fossey, J.; Lefort, D.; Sorba, J. *Free Radicals in Organic Chemistry*; Wiley: New York, 1995. (b) Giese, B.; Kopping, B.; Göbel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. *Org. React.* **1996**, *48*, 301–856. (c) *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001. (d) Albert, M.; Fensterbank, L.; Lacte, E.; Malacria, M. *Top. Curr. Chem.* **2006**, *264*, 1–62.

(2) Review of tin and related hydrides: Chatgilialoglu, C.; Newcomb, M. *Adv. Organomet. Chem.* **1999**, *44*, 67–112.

(3) Alternatives to tin hydrides: (a) Baguley, P. A.; Walton, J. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3072–3082. (b) Studer, A.; Amrein, S. *Synthesis* **2002**, 835–849. (c) Gilbert, B. C.; Parsons, A. F. *J. Chem. Soc., Perkin Trans. 2* **2002**, 367–387. (d) Darmency, V.; Renaud, P. *Top. Curr. Chem.* **2006**, *263*, 71–106.

(4) Ueng, S.-H.; Makhlouf Brahmi, M.; Derat, E.; Fensterbank, L.; Lacôte, E.; Malacria, M.; Curran, D. P. *J. Am. Chem. Soc.* **2008**, *130*, 10082–10083.

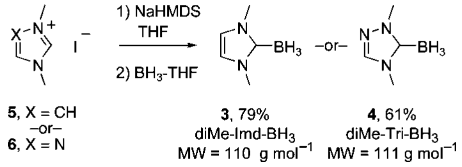
10.1021/ol101015m

to handle and are built only from common second-row elements. Although **1** and **2** are readily made, their carbene precursors (an imidazolium or triazolium salt) are rather expensive. The reagents are not ideally efficient in xanthate reductions (often 2 equiv are used to maximize yield), and the more well-studied reagent **1** has a relatively high molecular weight of 402 g mol^{-1}. Compare this to tributyltin hydride at 291 g mol^{-1} or tris(trimethylsilyl)silane at 249 g mol^{-1}.

Herein we report that "minimalist" NHC−boranes **3** (110 g mol^{-1}) and **4** (111 g mol^{-1}) prepared from simple, readily available imidazolium or triazolium salts are superior to first-in-class reagents **1** and **2** in reductions of xanthates and related functional groups.

1,3-Dimethylimidazol-2-ylideneborane (**3**) (hereafter called diMe-Imd-BH_3) was readily prepared by deprotonation of 1,3-dimethylimidazolium iodide (**5**) with NaHMDS followed by addition of borane in THF (Scheme 1).[5c] Isolation by flash chromatography was convenient on 1 g scale, and **3** was obtained in 79% yield as a white solid, mp 134−137 °C. A similar reaction of 2,4-dimethyl-1,2,4-triazolium iodide (**6**) provided 2,4-dimethyl-1,2,4-triazol-3-ylideneborane (**4**) (hereafter called diMe-Tri-BH_3) in 61% yield after flash chromatography, mp 57−58 °C. Both compounds were fully characterized by the usual means (including ^{11}B NMR spectroscopy)[10] and were stable to prolonged storage under standard ambient conditions.

Scheme 1. Synthesis of 1,3-Dimethylimidazol-2-ylideneborane (**3**, diMe-Imd-BH_3) and 2,4-Dimethyltriazol-3-ylideneborane (**4**, diMe-Tri-BH_3)



Imidazol-2-ylideneborane (**1**) is the most well understood NHC−borane reagent to date, so we chose this as a benchmark. In kinetic experiments described in the previous paper,[11] the rate constant for hydrogen abstraction from **3** by a primary alkyl radical was found to be $k_H = 8 \times 10^4$ M^{-1} s^{-1} (See Figure 2). The measured rate constant for **4** was comparable to **3**. Contrast this to **1**, which is about 4 times less reactive.[5a]

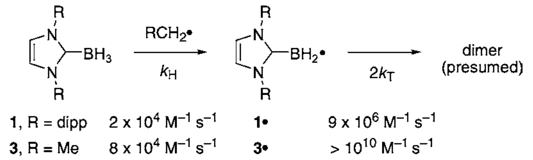


Figure 2. Comparison of rate constants for generation and termination of NHC−boryl radicals **1•** and **3•**. (The rate constants k_H and $2k_T$ were measured in different experiments.)

Like **1•**, the NHC−boryl radical **3•** generated by hydrogen abstraction from **3** by *t*-BuO• was detected by EPR spectroscopy.[5c] Boryl radical **3•** reacted with itself (presumably by dimerization) at rates approaching the diffusion controlled limit ($2k_T > 10^{10}$ M^{-1} s^{-1}). In contrast, boryl radical **1•** was persistent ($2k_T = 9 \times 10^6$ M^{-1} s^{-1}). Both of these results can be understood by steric effects; the radical **3•** is easier to generate and reacts more rapidly than **1•**.

Based on these kinetic results, we undertook a series of preparative experiments to evaluate the potential of **3** and **4** as radical reducing agents in more detail. The results of an initial set of comparison experiments of diMe-Imd-BH_3 (**3**) with current standard **1** in the reduction of xanthate, phenylthionocarbonate, and imidazolyl derivatives of several secondary alcohols are summarized in Table 1.

In a typical pair of experiments under thermal conditions (A), a benzene solution of xanthate **7a**, NHC−borane **1** or **3** (1 equiv), and AIBN (1 equiv) was heated at reflux for 2 h. The solvent was evaporated, and the crude product was purified by flash chromatography to provide the isolated yield of **10**. In the reaction with **3**, the xanthate was consumed, and the reduced product **10** was isolated in 77% yield (entry 1). In contrast, the reaction with **1** provided only 15% yield of **10** along with 73% of recovered xanthate **7a** (entry 2). Similar results were obtained in reductions of xanthates **8a** (78% of **11** compared 8%; entries 3 and 4) and **9a** (88% of **12** compared to 42%; entries 9 and 10). In the reduction of **8a** with **1**, the major component was again recovered starting material (64%). The yields with **1** are significantly lower than previously reported because the reaction conditions are

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(5) (a) Ueng, S.-H.; Solovyev, A.; Yuan, X.; Geib, S. J.; Fensterbank, L.; Lacôte, E.; Malacria, M.; Newcomb, M.; Walton, J. C.; Curran, D. P. *J. Am. Chem. Soc.* **2009**, *131*, 11256–11262. (b) Matsumoto, T.; Gabbaï, F. P. *Organometallics* **2009**, *28*, 4252–4253. (c) Walton, J. C.; Makhlouf Brahmi, M.; Fensterbank, L.; Lacôte, E.; Malacria, M.; Chu, Q.; Ueng, S.-H.; Solovyev, A.; Curran, D. P. *J. Am. Chem. Soc.* **2010**, *132*, 2350–2358. (d) 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.

(6) For pioneering work on amine and phosphine boryl radicals, see: (a) Dang, H.-S.; Roberts, B. P. *Tetrahedron Lett.* **1992**, *33*, 6169–6172. (b) Dang, H.-S.; Diart, V.; Roberts, B. P.; Tocher, D. A. *J. Chem. Soc., Perkin Trans. 2* **1994**, 1039–1045. (c) Roberts, B. P.; Steel, A. J. *J. Chem. Soc., Perkin Trans. 2* **1994**, 2411–2422. (d) Barton, D. H. R.; Jacob, M. *Tetrahedron Lett.* **1998**, *39*, 1331–1334. (e) Lucarini, M.; Pedulli, G. F.; Valgimigli, L. *J. Org. Chem.* **1996**, *61*, 1161–1164. (f) Baban, J. A.; Roberts, B. P. *J. Chem. Soc., Perkin Trans. 2* **1988**, 1195–1200. (g) Sheeller, B.; Ingold, K. U. *J. Chem. Soc., Perkin Trans. 2* **2001**, 480–486. (h) Lalevée, J.; Tehfe, M. A.; Allonas, X.; Fouassier, J. P. *Macromolecules* **2008**, *41*, 9057–9062.

(7) These transformations are members of a larger class called Barton−McCombie reactions: Crich, D.; Quintero, L. *Chem. Rev.* **1989**, *89*, 1413–1432.

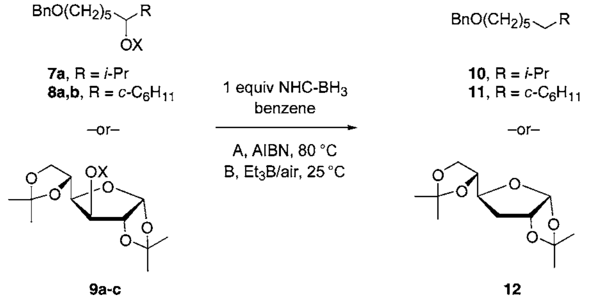
(8) (a) Chu, Q.; Makhlouf Brahmi, M.; Solovyev, A.; Ueng, S.-H.; Curran, D. P.; Malacria, M.; Fensterbank, L.; Lacôte, E. *Chem.−Eur. J.* **2009**, *15*, 12937–12940. (b) Lindsay, D. M.; McArthur, D. *Chem. Commun.* **2010**, *46*, 2474–2476.

(9) Monot, J.; Makhlouf Brahmi, M. M.; Ueng, S.-H.; Robert, C.; Murr, M. D.-E.; Curran, D. P.; Malacria, M.; Fensterbank, L.; Lacôte, E. *Org. Lett.* **2009**, *11*, 4914–4917.

(10) The preparation and characterization of **3** are described in the Supporting Information of ref 5c, while the corresponding information for **4** is in the Supporting Information of this paper.

(11) Solovyev, A.; Ueng, S.-H.; Monot, J.; Malacria, M.; Fensterbank, L.; Lacôte, E.; Curran, D. P. *Org. Lett.* **2010**, *12*, DOI: 10.1021/ol101014q.

Table 1. Preliminary Reductions of Xanthate and Related Derivatives with diMe-Imd-BH$_3$ (**3**) and dipp-Imd-BH$_3$ (**1**) (Control)



entry	substrate	X	NHC−BH$_3$	conditions[a]	product; yield[b] (%)	SM[b] (%)
1	**7a**	C(=S)SMe	**3**	A	**10**; 77	n.d.
2	**7a**	C(=S)SMe	**1**	A	**10**; 15	73
3	**8a**	C(=S)SMe	**3**	A	**11**; 78	n.d.
4	**8a**	C(=S)SMe	**1**	A	**11**; 8	64
5	**8b**	C(=S)OPh	**3**	A	**11**; 74	12
6	**8b**	C(=S)OPh	**1**	A	**11**; n.d.	90
7	**8b**	C(=S)OPh	**3**	B	**11**; 81	14
8	**8b**	C(=S)OPh	**1**	B	**11**; n.d.	90
9	**9a**	C(=S)SMe	**3**	A	**12**; 88	n.d.
10	**9a**	C(=S)SMe	**1**	A	**12**; 42	n.d.
11	**9b**	C(=S)OPh	**3**	B	**12**; 83	n.d.
12	**9b**	C(=S)OPh	**1**	B	**12**; 25	n.d.
13	**9c**	C(=S)Imd	**3**	A[c]	**12**; 67	n.d.
14	**9c**	C(=S)Imd	**1**	A[c]	**12**; 42	n.d.

[a] A = 1 equiv of AIBN, 80 °C, 2 h; B = 1 equiv of Et$_3$B, rt, 2 h, ambient air. [b] Isolated yield after flash chromatography, n.d. = not determined. [c] AIBN initiation in toluene at 110 °C.

different; optimal yields with **1** require an excess of reagent and a longer reaction time.[4]

Likewise, the reduction of the thionocarbonate **8b** under fixed-time (2 h) thermal conditions with **3** provided **11** in 74% yield (12% recovered **8b**; entry 5), while reduction with **1** provided substantially recovered **8b** (90%, entry 6). Reduction of imidazolyl derivative **9c** under thermal conditions in refluxing toluene with **3** and **1** provided **12** in 67% and 42% yields, respectively (entries 13 and 14).

DiMe-Imd-BH$_3$ reagent **3** was also superior to **1** in room-temperature experiments (conditions B) with triethylborane (1 equiv) and air (admitted through a narrow needle open to the atmosphere). Again, the time was fixed at 2 h. Reduction of thionocarbonate **8b** with **3** provided **11** in 81% yield alongside 14% recovered starting material (entry 7), while **1** provided only recovered starting material (90%; entry 8). Likewise, **9b** was reduced to **12** in 83% yield with **3** but only 25% yield with **1** (entries 11 and 12). Taken together, the data of the kinetic and preparative experiments show that **3** is a better radical reducing agent than **1**.

According to the chain mechanism for reduction of xanthates,[7] the boron-containing product from the reductions with **3** should be dithiocarbonate diMe-Imd-BH$_2$SC(=O)SMe (**13**).[5a] Attempts to isolate this compound by flash chromatography were not successful, perhaps due to its instability on silica gel.

To learn about the nature of the boron products formed, a reaction between **7a** and **3** was conducted in an NMR tube at room temperature with Et$_3$B/air initiation (conditions B). The progress of the reaction was followed by ^{11}B NMR spectroscopy, and Figure 3 shows a portion of the spectrum at the first time point (10 min). The quartet resonance of the starting borane at −36.4 ppm is already substantially diminished, and a new triplet appears at −25.9 ppm. Both the multiplicity and the chemical shift of the peak are consistent with the proposed structure diMe-Imd-BH$_2$SC(=O)SMe (**13**).[5a] After 60 min, the quartet of **3** disappeared, leaving the triplet of **13** as the only significant resonance in the spectrum (see the Supporting Information). We conclude that **13** is indeed the primary boron-containing product of these reactions.

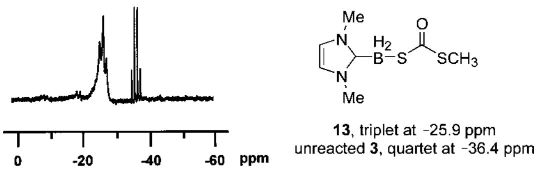


Figure 3. Structure of **13** and a part of the 96.3 MHz ^{11}B NMR spectrum showing the evidence for its formation in the reaction of **7a** and **3** after 10 min at room temperature.

Next, we undertook a set of preparative deoxygenations with **3** to explore the scope, and the results of these reactions are shown in Table 2. As before, only 1 equiv of **3** was used with either thermal (AIBN, conditions A) or room-temperature (Et$_3$B/air, conditions B) initiation. The reactions were substantially complete after 2 h, and the products were isolated by flash chromatography as usual. Reduction of **14** provided **19** in comparable yields (79% and 81%) under thermal and rt conditions (entries 1 and 2).

Reductions of cyclopropylcarbinyl xanthate **15** provided ring-opened products **20** and **21** (entries 3 and 4). The major product under both thermal and rt conditions was reduced **20** (52% and 63%), while the minor product **21** (17% and 22%) resulted from a competing xanthate group transfer reaction. In contrast, reduction of xanthate precursor **16** of a hexenyl radical under both conditions (entries 5 and 6) gave primarily ring closed, reduced product **22** (73% and 64%). There were also minor amounts of the directly reduced product (4% and 10%; this product is not shown and was not separated from **22**) and the cyclized xanthate transfer product **23** (5% in both reactions).[12] The results of these competitions—complete opening of a cyclopropylcarbinyl radical, almost complete closing of a hexenyl radical, minor xanthate transfer products from primary radicals—are all qualitatively consistent with the intermediate value of the rate constant for hydrogen transfer from **3**.

Two *syn*-thionocarbonates **17** and **18** were also deoxygenated with **3**. Reduction of monothionocarbonate **17** provided **24** in 68% yield under thermal conditions (entry

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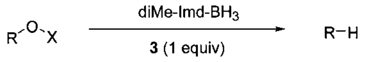
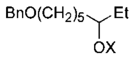
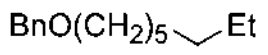
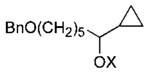
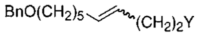
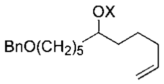
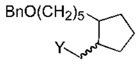
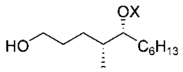
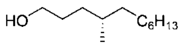
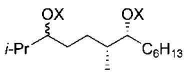
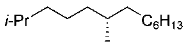
(12) Quiclet-Sire, B.; Zard, S. Z. *Top. Curr. Chem.* **2006**, *264*, 201–236.

Table 2. Preparative Deoxygenations of Xanthates and Thionocarbonates with **3** under Thermal (A) and Room-Temperature (B) Conditions



entry	substrate	conditions[a]	product, yield
			
1	**14**, X = C(=S)SMe	A	**19**, 79%
2	**14**, X = C(=S)SMe	B	**19**, 81%
			 **20**, Y = H **21**, Y = SC(=O)SMe
3	**15**, X = C(=S)SMe	A	**20**, 52% ; **21**, 17%
4	**15**, X = C(=S)SMe	B	**20**, 63% ; **21**, 22%
			 **22**, Y = H **23**, Y = SC(=O)SMe
5	**16**, X = C(=S)SMe	A	**22**, 73%[b,c]; **23**, 5%
6	**16**, X = C(=S)SMe	B	**22**, 64%[d,e]; **23**, 5%
7	 **17**, X = C(=S)OPh	A	 **24**, 68%
8	 **18**, X = C(=S)OPh	A[f]	 **25**, 40% (49%)[g]

[a] A = 1 equiv of AIBN, 80 °C, 2 h. B = 1 equiv of Et_3B, rt, 2 h. [b] Diastereomeric ratio 2.2:1. [c] Cyclization/reduction ratio 16.7:1. [d] Diastereomeric ratio 2.7:1. [e] Cyclization/reduction ratio 5.7:1. [f] 2.6 equiv of AIBN and **3** were used. [g] Yield determined by GC analysis with dodecane as internal standard.

7), while reduction of bis-thionocarbonate **18** provided **25** in 40% isolated and 49% GC yield (entry 8).

We briefly surveyed the ability of **3** to reduce several primary xanthates and related derivatives. Such reductions are much less common than with secondary derivatives. The results of this series of experiments are shown in Table S1 of the Supporting Information. Though the yields are moderate (typically 30−50%), they are comparable to other examples of reductions of primary derivatives.[13]

Having a good understanding of the capabilities of reagent **3**, we closed this preliminary study with a short series of experiments comparing it to diMe-Tri-BH_3 (**4**). Reductions were done with 1 equiv of each reagent for 2 h under thermal and room temperature conditions, as usual. The results for reductions of thionocarbonates **8b** and **9b** and xanthate **9a** are summarized in Table 3 (see Table 1 for structures). The yields of all three pairs of reactions were comparable and were uniformly high (81−89%). Thus, it seems that **3** and **4** are roughly equivalent as radical reducing agents toward xanthates and thionocarbonates. (The results also show the reproducibility in reductions with **3**; entries 1, 3, and 5 in Table 3 are repeat experiments of entries 5, 9, and 11 in Table 1 and give comparable yields.)

Table 3. Comparison of Yields of **3** and **4** in Reductions of **8b** and **9a**,**b** (Precursor and Product Structures Are Shown in Table 1)

entry	substrate	NHC−BH_3	conditions[a]	product; yield (%)
1	**8b**	**3**	A	**11**; 89
2	**8b**	**4**	A	**11**; 87
3	**9a**	**3**	B	**12**; 88
4	**9a**	**4**	B	**12**; 86
5	**9b**	**3**	A	**12**; 81
6	**9b**	**4**	A	**12**; 80

[a] A = 1 equiv of AIBN, 80 °C, 2 h; B = 1 equiv of Et_3B, rt, 2 h.

We attempted to dissolve both **3** and **4** in water and found that 2,4-dimethyl-1,2,4-triazol-3-ylideneborane **4** exhibits considerable solubility. It is also stable in water, and an NMR spectrum recorded in D_2O is shown in the Supporting Information. This suggests that **4** might be a useful reagent either for conducting radical reactions in water or for procedures involving aqueous workup.[14]

In summary, "minimalist" NHC−boranes 1,3-dimethylimidazol-2-ylideneborane (**3**) and 2,4-dimethyl-1,2,4-triazol-3-ylideneborane (**4**) are attractive new reagents for reduction of xanthates and related functional groups. They are readily available and have low molecular weights, and they provide good yields in both thermal and room temperature reductions. Unlike the first-generation reagent **1**, the reactions with **3** and **4** are rapid, and excesses of the reagents are not needed. These results clearly show that changing the N-substituents on N-heterocyclic carbene boranes is a valuable tool to alter reactivity in radical and presumably other reactions.

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Supporting Information Available: Procedures, characterization of new compounds, and data on reduction of primary xanthates. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Spiegel, D. A.; Wiberg, K. B.; Schacherer, L. N.; Medeiros, M. R.; Wood, J. L. *J. Am. Chem. Soc.* **2005**, *127*, 12513–12515.

(14) A preliminary experiment with **4** and the xanthate of 2-propanol was conducted, and the crude product was washed with water and then assayed by ^{11}B NMR spectroscopy. While the resonance for **4** was gone, there was a large new triplet at −29.3 ppm, presumably diMe-Tri-$BH_2SC(O)SMe$. Apparently, the byproduct is less soluble in water than the starting borane. Successful separations by aqueous washing with other substrates will be reported in due course.