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Complete List of Authors:	Bedi, Deepika; Texas Tech University, Chemistry & Biochemistry Brar, Aneelman; Texas Tech University, Chemistry & Biochemistry Findlater, Michael; Texas Tech University, Chemistry & Biochemistry

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Transition metal- and solvent-free double hydroboration of nitriles

Deepika Bedi, Aneelman Brar and Michael Findlater*

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A highly efficient, room temperature double hydroboration of nitriles under transition metal-free and solvent-free conditions is reported. Sodium triethylborohydride is used as a catalyst and yields up to 99% are disclosed. Mechanistic studies reveal the reaction proceeds in a stepwise manner with initial formation of a boryl-imine which undergoes a second hydroboration to afford diborylated amine product.

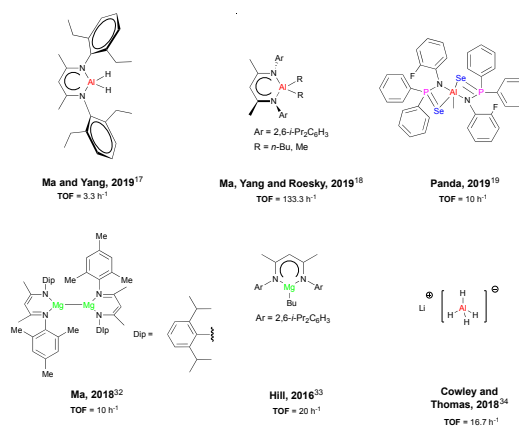
Introduction

Primary amines are ubiquitous in chemistry: as building blocks of proteins, drug molecules, agrochemicals and dyes.¹⁻⁴ Specifically, the utility of primary aromatic amines ranges from electro-conducting polymers in material chemistry⁵ to ligands for synthesis and catalysis.⁶ Owing to their widespread utility, numerous methods have been reported for their synthesis, the most conventional ones being reductive amination of aldehydes or ketones⁷⁻¹⁰ and *N*-alkylation of nitriles and ammonia.^{11, 12} However, generation of large quantities of organic waste, use of strong reductants and formation of mixtures of products limit their utility in organic synthesis.¹³ Still, another attractive method for synthesis of primary amines is reduction of nitriles and nitro compounds using molecular H₂¹⁴ which requires the use of precious metals and pressurized H₂ and offers poor selectivity. However, hydrofunctionalization is recently garnering attention due to milder reaction conditions and better selectivity of the products. Catalytic hydroboration is an attractive strategy for nitrile reduction because it employs mild reaction conditions and offers, typically, excellent functional group tolerance. Moreover, the borylated amine product which forms can act as an excellent synthetic surrogate, which can easily be transformed into a wide array of functional groups; for instance, *N*-substituted amides via direct C-N cross coupling.¹⁵ The C≡N bond in nitriles is extremely stable and has a high bond dissociation energy (212 kcal mol⁻¹).¹⁶ However, if the

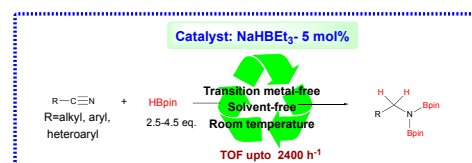
functionalization of this bond were possible, a range of valuable nitrogen-containing molecules could be accessed, making it an attractive substrate for hydroboration studies.

There has been significant progress reported in the development of hydroboration of nitriles using main group,¹⁷⁻¹⁹ *d*-^{15, 20-29} and *f*-block^{30, 31} elements during the past few years. Shown in **Figure 1** are current state-of-the-art *s*- and *p*-block complexes which have been shown to effect catalytic double borylation of nitriles. Notably, in this year alone there have been three reports of main group-based (aluminium) catalysts which have been disclosed. Ma and Yang reported an economical and environmentally friendly aluminium-hydride based catalyst for double borylation of nitriles.¹⁷

Figure 1: (a) Selected examples of catalysts for nitrile hydroboration and (b) representation of this work

(a) *s*- and *p*-block element complexes as catalysts

(b) This work



Department of Chemistry & Biochemistry, Texas Tech University, Lubbock, Texas 79423, USA. E-Mail: michael.findlater@ttu.edu

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In a subsequent paper Ma, Yang and Roesky reported the bis(*n*-butyl) aluminium complex $\text{LAl}(n\text{-Bu})_2$ ($\text{L} = (\text{ArNCMe})_2\text{CH}$, $\text{Ar} = 2,6\text{-}i\text{-Pr}_2\text{C}_6\text{H}_4$) which was capable of the chemoselective hydroboration of nitriles and carbodiimides under solvent-free conditions.¹⁸ Panda and co-workers also disclosed an aluminium alkyl complex $[\text{k}^2\text{-}\{2\text{-F-C}_6\text{H}_4\text{NP}(\text{Se})\text{Ph}_2\}_2\text{Al}(\text{Me})]$ that proved capable of catalysing the hydroboration of nitriles in the presence of either pinacolborane or catecholborane.¹⁹ Furthermore, there have been two reports of magnesium catalysed hydroboration. In 2018, Ma reported the synthesis and catalytic activity of a series of unsymmetrical β -diketiminato coordinated magnesium (I) complexes.³² In 2016, Hill group disclosed that β -diketiminato *n*-butylmagnesium complex could successfully hydroborate a variety of organic nitriles.³³ In 2018, Cowley and Thomas demonstrated the use of commercially available LiAlH_4 for hydroboration of alkenes. However only one example was shown for nitrile hydroboration.³⁴ Hence, an opportunity exists to develop main group catalysts that can effectively carry out the hydroboration of nitriles at room temperature with a wide substrate scope and broad functional group tolerance with operationally facile conditions.

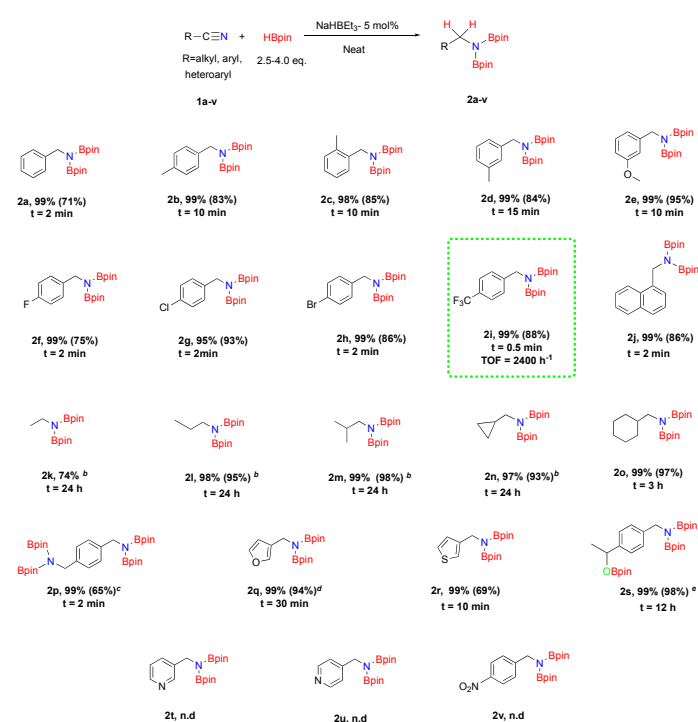
Our group has a long-standing interest in the areas of hydroboration and hydrosilylation.³⁵⁻³⁹ We have previously shown that commercially available base-metals salts can be employed for efficient hydrofunctionalization of a range of functional groups. For instance, carbonyls,^{40, 41} alkenes⁴¹ and *N*-heteroarenes⁴² were successfully hydroborated using $\text{Fe}(\text{acac})_3$, $\text{Co}(\text{acac})_3$ and $\text{Ni}(\text{acac})_2$ (acac: acetylacetonate) respectively. In pioneering work from the Kuciński group, lithium triethylborohydride was used as a catalyst to hydroborate a variety of ketones to effectively obtain boronate esters and subsequently secondary alcohols in excellent yields.⁴³ Given the exceptional activity of this borohydride we decided to probe the ability of a similar borohydride to effect the hydroboration of a more challenging substrate, namely, organic nitriles. Herein, we report the hydroboration of nitriles using commercially available and inexpensive sodium triethylborohydride (NaHBET_3), which can be used to afford bis(boryl) amines in excellent yield.

The reaction is carried out with 5 mol% catalytic loading at room temperature and most of the nitriles went to >99% conversion in less than 15 minutes. Additionally, we came across only one other example in the literature which is capable of catalysing this reaction at room temperature using pinacol borane.¹⁵ Moreover, by using NaHBET_3 as the catalyst, the use of inert atmosphere techniques (glovebox and Schlenk line) for laborious preparation of ligands and their metal complexes can be circumvented. Additionally, generation of stoichiometric amounts of metal waste are avoided; the only by-product generated was $(\text{pinB})_2\text{O}$, which was confirmed using GC-MS. The presence of $(\text{pinB})_2\text{O}$ may arise from the reaction of excess HBpin with residual moisture present in the nitrile substrates.

Results and discussions

Initial optimization of the reaction conditions was performed using benzonitrile (**1a**) as a model substrate. Thus, exposure of **1a** to NaHBET_3 (2 mol%) and HBpin (2.2 eq.) afforded diborylated amine (**2a**) in >99% conversion. The reaction was carried out under neat (solvent-free) conditions at 50 °C. It is worthwhile to mention here that GC-MS showed only benzylamine as the exclusive product with no trace of imine by-product. We repeated the reaction at room temperature and surprisingly, and to our delight, a similar yield was obtained in ca. 2 minutes. However, the nature (solid) of some nitrile substrates caused inefficient mixing of the reagents; the catalyst (NaHBET_3) and HBpin loadings were increased to 5 mol % and 2.5 eq., respectively. With these optimized conditions in hand, we explored a range of nitrile substrates to test the scope of this transformation; inclusion of electron releasing / withdrawing, halogen and heteroatom substituents and cyclic/ acyclic substrates all afforded diborylated amines in good to excellent yields (**Scheme 1**).

Scheme 1: Room temperature double borylation of organic nitriles with NaHBET_3 ^a



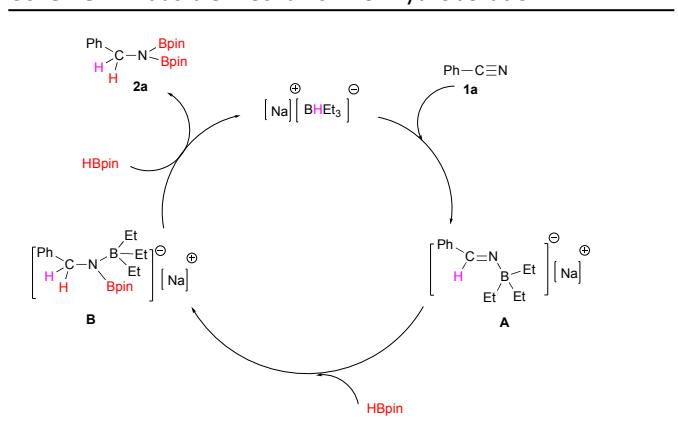
^aYields based on ¹H NMR using mesitylene as the internal standard ; ^b Reaction mixture heated at 80 °C; ^c 4 eq. of HBpin was used; ^d 3.5 eq. of HBpin was used; ^e 3.5 eq. of HBpin was used and reaction mixture heated at 80° C; n.d. = not detected
Yields in the parentheses are the isolated yields when the reaction was carried out on a 0.5 mmol scale

Nitriles with electron releasing groups (-Me and -OMe) afforded products (**2b-2e**) in 99% yield in ca. 10- 15 minutes. In the case of *o*-toluonitrile (**1c**) the sterically encumbering methyl group didn't adversely affect the formation of product, the reaction

proceeded smoothly without any deterioration of the yield (98%, 10 minutes). Additionally, substrates with electron-withdrawing functional groups (-F, -Cl, -Br and -CF₃) on the backbone were well tolerated and yields of about 95-99% were obtained (**2f-2i**). The rate of hydroboration in the case of 1-naphthothionitrile (**1j**) was also comparative to benzonitrile and 99% NMR yield was obtained in 2 minutes. Gratifyingly, acetonitrile also led to the formation of the desired product (**2k**), albeit in diminished yield and under more forcing conditions (74%, 24 h, 80 °C). Similarly, for other alkyl chain nitriles; the excellent yields of the products (**2l-2n**) were obtained only when the reaction mixture was heated at 80 °C. Cyclohexanecarbonitrile also afforded the diborylated product **2o** in 99% yield in 3 h when the reaction mixture was kept at room temperature. Electron deficient aryl nitrile **1p** led to borylation of both the cyano groups when 4 equivalents of HBpin were used.

We next turned our attention to heteroaromatic substrates. Interestingly, furan and thiophene-based substrates proved to be highly amenable to our reaction conditions, 3-furonitrile (**1q**) and 3-thiophenecarbonitrile (**1r**) afforded **2q** and **2r** respectively in 99% yield in a few minutes. The reaction of 3-acetylbenzonitrile led to the hydroboration of both ketone and nitrile functional groups (**2s**). Finally, for 3-pyridylcarbonitrile (**1t**), 4-nitrobenzonitrile (**1u**) and 4-nitrobenzonitrile (**1v**) no bis(boryl)amine product was formed even after prolonged reaction times. Formation of the products **2a-2s** (except **2l-2n**) was readily visualized. Upon addition of HBpin and NaHBET₃ to the substrate the reaction mixtures become homogenous before precipitation of a white solid (product) occurs or the entire reaction mixture solidifies, indicating the completion of the reaction (*Figure S1*). To further demonstrate the synthetic utility of our approach a gram-scale reaction was carried out of **1a**. An isolated yield of 2.21 g (63%) was obtained.

Scheme 2: Plausible mechanism for hydroboration



To help explore the reaction mechanism more fully, an equimolar amount of NaHBET₃ was added to **1a** in toluene-*d*₈ (**Scheme 2**). Analysis of the mixture using ¹¹B NMR spectroscopy reveals a sharp peak at -6.53 ppm which supports the formation of intermediate ion pair **A**. This is consistent with the previous report by Ramachandran, where *B*-iminotriethylborate is

characterized by a peak at -6 ppm in the ¹¹B NMR spectrum.⁴⁴ Upon addition of a further equivalent of HBpin, ¹H NMR spectroscopy shows a peak at 4.26 ppm in addition to a peak at 6.77 ppm indicating that some of the imine intermediate formed has been converted to the 1,1-bis(boryl) amine. Subsequently, addition of 0.5 eq. of HBpin, converts the entire imine to bis(boryl) amine product (*See Figure S44*). Based on these observations, we are led to propose the reaction mechanism shown in Scheme 2. Initially, the coordination of NaHBET₃ to benzonitrile (**1a**) affords iminoborate intermediate **A**. Subsequent addition of 1 eq. of HBpin to **A** generates the bis(boryl)amine intermediate **B**. Finally, on addition of another equivalent of HBpin, diborylated amine product **2a** is released with concomitant regeneration of NaHBET₃.

To put the synthetic utility of our system into context, a brief comparison to previously reported hydroboration catalysts is warranted. Two of the highest TOF values have been disclosed by Eisen using a thorium metallacycle (TOF = 500 h⁻¹)³⁰ and Baik and Trovitch employing a well-defined cobalt complex (TOF = 380 h⁻¹).¹⁵ Herein, we achieve a comparatively much higher TOF of up to 2400 h⁻¹ using a commercially available and relatively inexpensive sodium triethylborohydride (NaHBET₃) as catalyst. To the best of our knowledge, this is the maximum TOF value reported to date for nitrile hydroboration.

Conclusions

In conclusion, we have disclosed the ability of a commercially available reductant, NaHBET₃, to act as an efficient catalyst for room temperature, transition metal- and solvent-free hydroboration of organic nitriles. The key advantage of this process is that no metal waste is generated, and most substrates examined afford excellent conversions. Additionally, no other by-product is generated (intermediate imine) in addition to bis(boryl) amine. However, under optimized conditions substrates incorporating pyridine or nitro groups afforded no product even after prolonged reaction times. Additionally, competition studies revealed that carbonyl groups are reduced preferentially over the nitrile group.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

1. in *Ullmann's Encyclopedia of Industrial Chemistry*, DOI: 10.1002/14356007.o03_o07.pub2, pp. 1-14.
2. D. G. Hall, *Journal of the American Chemical Society*, 2005, **127**, 9655-9655.

3. B. Metz, G. F. A. Kersten, P. Hoogerhout, H. F. Brugghe, H. A. M. Timmermans, A. de Jong, H. Meiring, J. t. Hove, W. E. Hennink, D. J. A. Crommelin and W. Jiskoot, *Journal of Biological Chemistry*, 2004, **279**, 6235-6243.
4. S. E. Nissen, *New England Journal of Medicine*, 2006, **354**, 1445-1448.
5. G. D'Aprano, M. Leclerc, G. Zotti and G. Schiavon, *Chemistry of Materials*, 1995, **7**, 33-42.
6. F. Fache, E. Schulz, M. L. Tommasino and M. Lemaire, *Chemical Reviews*, 2000, **100**, 2159-2232.
7. E. Dorko, M. Szabo, B. Kotai, I. Papai, A. Domjan and T. Soos, *Angew Chem Int Ed Engl*, 2017, **56**, 9512-9516.
8. H. Kato, I. Shibata, Y. Yasaka, S. Tsunoi, M. Yasuda and A. Baba, *Chemical Communications*, 2006, DOI: 10.1039/B610614E, 4189-4191.
9. J. S. Sapsford, D. J. Scott, N. J. Allcock, M. J. Fuchter, C. J. Tighe and A. E. Ashley, *Advanced synthesis & catalysis*, 2018, **360**, 1066-1071.
10. D. Talwar, N. P. Salguero, C. M. Robertson and J. Xiao, *Chemistry—A European Journal*, 2014, **20**, 245-252.
11. I. Alshakova and G. Nikonov, *ChemCatChem*.
12. K. i. Fujita, S. Furukawa, N. Morishima, M. Shimizu and R. Yamaguchi, *ChemCatChem*, 2018, **10**, 1993-1997.
13. P. T. Anastas and J. C. Warner, *Green chemistry: theory and practice*, Oxford University Press, Oxford [England]; New York, 1998.
14. J. Seyden-Penne, *Reductions by the alumino- and borohydrides in organic synthesis*, John Wiley & Sons, 1997.
15. C. Ghosh, S. Kim, M. R. Mena, J.-H. Kim, R. Pal, C. L. Rock, T. L. Groy, M.-H. Baik and R. J. Trovitch, *Journal of the American Chemical Society*, 2019, **141**, 15327-15337.
16. E. Lippert, *Angewandte Chemie*, 1960, **72**, 602-602.
17. W. Liu, Y. Ding, D. Jin, Q. Shen, B. Yan, X. Ma and Z. Yang, *Green Chemistry*, 2019, **21**, 3812-3815.
18. Y. Ding, X. Ma, Y. Liu, W. Liu, Z. Yang and H. W. Roesky, *Organometallics*, 2019, **38**, 3092-3097.
19. A. Harinath, J. Bhattacharjee and T. K. Panda, *Advanced Synthesis & Catalysis*, 2019, **361**, 850-857.
20. I. Banerjee, S. Anga, K. Bano and T. K. Panda, *Journal of Organometallic Chemistry*, 2019, **902**, 120958.
21. M. Ito, M. Itazaki and H. Nakazawa, *Inorganic Chemistry*, 2017, **56**, 13709-13714.
22. H. Ben-Daat, C. L. Rock, M. Flores, T. L. Groy, A. C. Bowman and R. J. Trovitch, *Chemical Communications*, 2017, **53**, 7333-7336.
23. A. D. Ibrahim, S. W. Entsminger and A. R. Fout, *ACS Catalysis*, 2017, **7**, 3730-3734.
24. G. Nakamura, Y. Nakajima, K. Matsumoto, V. Srinivas and S. Shimada, *Catalysis Science & Technology*, 2017, **7**, 3196-3199.
25. S. Das, J. Bhattacharjee and T. K. Panda, *New Journal of Chemistry*, 2019, DOI: 10.1039/C9NJ04076E.
26. A. Y. Khalimon, P. M. Farha and G. I. Nikonov, *Dalton Transactions*, 2015, **44**, 18945-18956.
27. T. Kitano, T. Komuro and H. Tobita, *Organometallics*, 2019, **38**, 1417-1420.
28. A. Kaithal, B. Chatterjee and C. Gunanathan, *The Journal of Organic Chemistry*, 2016, **81**, 11153-11161.
29. J. B. Geri and N. K. Szymczak, *Journal of the American Chemical Society*, 2015, **137**, 12808-12814.
30. S. Saha and M. S. Eisen, *ACS Catalysis*, 2019, **9**, 5947-5956.
31. Z. Huang, S. Wang, X. Zhu, Q. Yuan, Y. Wei, S. Zhou and X. Mu, *Inorganic Chemistry*, 2018, **57**, 15069-15078.
32. J. Li, M. Luo, X. Sheng, H. Hua, W. Yao, S. A. Pullarkat, L. Xu and M. Ma, *Organic Chemistry Frontiers*, 2018, **5**, 3538-3547.
33. C. Weetman, M. D. Anker, M. Arrowsmith, M. S. Hill, G. Kociok-Köhn, D. J. Liptrot and M. F. Mahon, *Chemical Science*, 2016, **7**, 628-641.
34. A. Bismuto, M. J. Cowley and S. P. Thomas, *ACS Catalysis*, 2018, **8**, 2001-2005.
35. F. S. Wekesa, R. Arias-Ugarte, L. Kong, Z. Sumner, G. P. McGovern and M. Findlater, *Organometallics*, 2015, **34**, 5051-5056.
36. A. Saini, C. R. Smith, F. S. Wekesa, A. K. Helms and M. Findlater, *Organic & Biomolecular Chemistry*, 2018, **16**, 9368-9372.
37. S. R. Tamang and M. Findlater, *Dalton Transactions*, 2018, **47**, 8199-8203.
38. S. R. Tamang, A. F. Cozzolino and M. Findlater, *Organic & Biomolecular Chemistry*, 2019, **17**, 1834-1838.
39. S. R. Tamang and M. Findlater, *Molecules*, 2019, **24**, 3194.
40. S. R. Tamang and M. Findlater, *The Journal of Organic Chemistry*, 2017, **82**, 12857-12862.
41. S. R. Tamang, D. Bedi, S. Shafiei-Haghighi, C. R. Smith, C. Crawford and M. Findlater, *Organic Letters*, 2018, **20**, 6695-6700.
42. S. R. Tamang, A. Singh, D. K. Unruh and M. Findlater, *ACS Catalysis*, 2018, **8**, 6186-6191.
43. K. Kuciński and G. Hreczycho, *Green Chemistry*, 2019, **21**, 1912-1915.
44. P. V. Ramachandran and D. Biswas, *Organic Letters*, 2007, **9**, 3025-3027.