Organic & Biomolecular Chemistry

PAPER

View Article Online
View Journal

Cite this: DOI: 10.1039/c8ob02330a

Protic additives or impurities promote imine reduction with pinacolborane†

Blake S. N. Huchenski and Alexander W. H. Speed *

Received 20th September 2018,
Accepted 6th November 2018

DOI: 10.1039/c8ob02330a

rsc.li/obc

We report here that addition of stoichiometric amounts of alcohols or water to mixtures of imines and pinacolborane promote reduction reactions. The reactions of several imines were examined, revealing that alkyl imines were reduced, while aniline derived imines were not effectively reduced. The use of binol as an additive resulted in modest enantioinduction, however other chiral additives that were screened gave negligible enantioinduction. While the reactions described herein are not competitive in conversion with established imine reduction technologies, this work reveals that the presence of protic impurities must be considered as a promoter of side reactions in catalyzed imine hydroborations. Amines also promote imine reduction in certain cases, raising the possibility of a slow autocatalytic reaction. The ability of water or other protic impurities to promote the reduction of imines with pinacolborane represents an important identification of a potential source of background reaction in catalyzed reductions of imines.

Introduction

The use of pinacolborane as a reductant for carbonyl and imine compounds has undergone extensive growth in recent years.[1] A variety of protocols and catalysts have been disclosed for carbonyl reduction with pinacolborane. Frequently, Lewis-base activation of the borane is an integral part of the reduction mechanism.[2] Alkoxides, and recently butyllithium have been used as Lewis-bases in the reduction of carbonyls.[3] Under neat conditions, it has been shown that the hydride transfer can proceed from pinacolborane to aldehydes or benzophenone imine in an uncatalyzed manner.[4]

Imine reduction by neutral boranes such as pinacolborane has undergone many relatively recent developments (Fig. 1).

In contrast to Lewis-base mediated ketone and aldehyde hydroborations with pinacolborane, Lewis or Brønsted acid mechanisms appear to be more prevalent in imine hydroboration. Seminal reports on imine hydroboration with catecholborane showed that coinage metal complexes could catalyse imine hydroboration.[5] Catecholborane slowly reacts with imines in the absence of catalysis, however Brønsted acid catalysed imine reductions with catecholborane employing chiral phosphoric acids did allow significant enantioinduction, demonstrating the merit of exploring catalysed processes even when a background reaction exists.[6] Despite the initial use of coinage metal complexes in imine hydroboration with catecholborane, main-group element-based catalytic systems have grown to occupy a pre-eminent position in imine hydroboration reactions with pinacolborane, which is considered to be less reactive than catecholborane.[7] In 2012, Crudden and coworkers reported borenium catalysed imine hydroboration

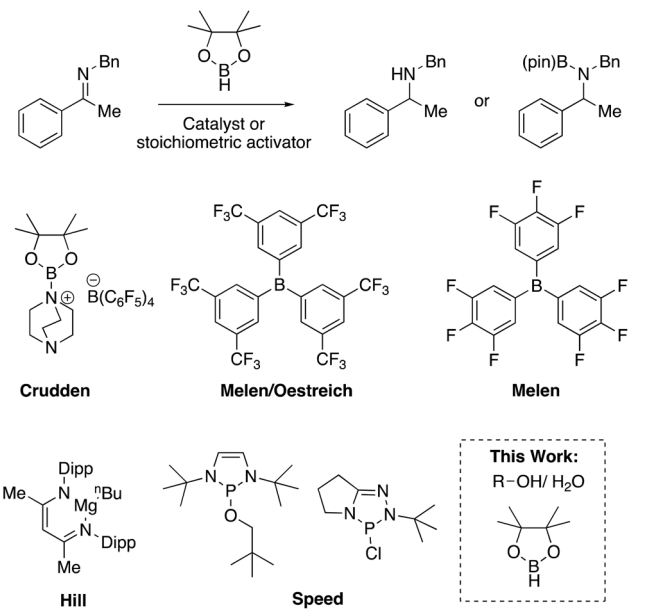


Fig. 1 Selected existing systems for imine reduction with pinacolborane.

Department of Chemistry, Dalhousie University, 6274 Coburg Road, Halifax, Nova Scotia, Canada, B3H 4R2. E-mail: aspeed@dal.ca

†Electronic supplementary information (ESI) available. See DOI: 10.1039/c8ob02330a

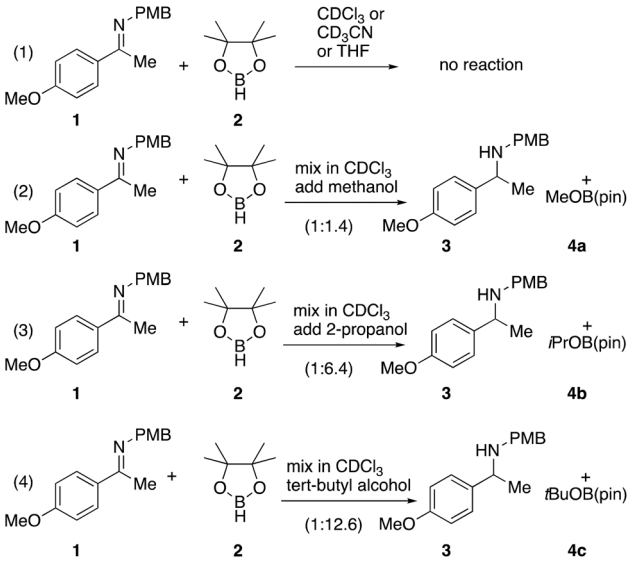
with pinacolborane, which did not undergo a non-catalyzed background reaction with imines.[8] The proposed mechanism for this reaction involves hydride delivery from a borane–imine complex to an imine activated by complexation to a borenium cation. After this report, a number of protocols for imine hydroboration with pinacolborane have been reported, involving several different mechanistic proposals.[9] Neutral boron-based Lewis acids have been shown to catalyse imine hydroboration, with a proposed mechanism involving imine activation by the Lewis acid, rather than a borenium-catalyzed reaction.[10] Magnesium centres have also proven competent at imine hydroboration, *via* the intermediacy of magnesium hydrides which are regenerated through pinacolborane.[11] Most recently, the use of diazaphospholene-based phosphorus hydride complexes for imine hydroboration has recently been reported by our group and others.[12] Diazaphospholene hydrides effect reduction through delivery of a phosphorus hydride to an imine, and represent one of the least Lewis-acidic catalyst systems for imine reduction. Finally, several transition metal based catalysts, including ruthenium, rhenium, and cobalt-based catalysts have been employed in imine hydroboration.[13] These reductions are typically proposed to occur through the intermediacy of metal-hydride bonds.

During the course explorations of catalysed imine hydroboration reactions, we explored the use of methanol to rapidly quench reactions. We observed that with the use of methanol as a quenching agent, even control reactions without added catalyst showed high conversions to the amine product. Since previous reports of imine hydroboration had not reported background reactions between pinacolborane and imines, this result suggested that methanol was promoting the observed reduction reaction. In addition, we conducted experiments verifying no background reaction between pinacolborane and the imines under question in the absence of methanol, suggesting that other contaminants in our solvents or substrates were not promoting this observed background reaction.

Results and discussion

It has been reported that reduction of carbonyl functionality with pinacolborane occurs in some cases in the absence of solvent, while addition of solvent supresses the reduction reaction.[4] Verifying the absence of a background reaction for imine reduction at room temperature under neat conditions, mixing imine **1** with pinacolborane (**2**) for 3 hours, followed by dissolution in chloroform-*d* showed no reduction reaction. Upon addition of 10 equiv. of methanol as a 2 M solution in chloroform-*d* to a mixture of **1** and **2** we observed conversion to the amine by NMR spectroscopy (eqn (1), Scheme 1).

Spectra were obtained within 10 minutes of mixing, with the time limitation being transport of the sample to the spectrometer, and subsequent pre-acquisition steps of sample insertion, locking, and shimming. No additional conversion was observed after further reaction time. Supporting this lack of further reactivity, unreacted boron hydride was not observed



Scheme 1 Investigation of primary, secondary, and tertiary alcohols as reduction promoters.

in the ^{11}B NMR spectra during acquisition of the initial spectra in these experiments. Conversion was measured by measuring ratios of starting material to product as determined by integration of the ^{1}H NMR spectra of the reaction mixtures. The ratios are shown under the corresponding equation arrows in Scheme 1. The reduction reactions were relatively clean, generally only showing starting material and product as the only nitrogen containing compounds, supporting the use of this measurement method. Use of ferrocene as an internal standard in some cases to calculate NMR yield gave good agreement with the ratios of starting material to product determined by NMR spectroscopy. Switching to isopropyl alcohol or *tert*-butyl alcohol resulted in higher conversions (eqn (3) and (4), Scheme 1). Use of isopropyl alcohol allowed determination of the fate of the B(pin) moiety. The boron was transferred to the isopropyl alcohol with concomitant loss of the proton, as revealed by comparison of spectral data of the reaction mixture with an authentic sample of iPrOB(pin) in chloroform-*d*.

Despite the use of excess pinacolborane relative to imine, some imine starting material remained, despite complete consumption of the pinacolborane, indicating that dehydrocoupling of the alcohol and pinacolborane is a competitive process. Non-catalyzed dehydrocoupling of HB(pin) and alcohols, amines, and thiols with concomitant loss of hydrogen gas has been reported by Bertrand and co-workers.[14]

In these dehydrocoupling reactions, simple mixing of the pinacolborane, with the protic substrates in the presence or absence of solvent results in loss of hydrogen, and formation of a boron–heteroatom bond. In our reactions, gas bubbles, presumed to be hydrogen, were observed during the mixing process. In conjunction with the formation of iPrOB(pin), these results show a dehydrocoupling process is also active under our reported reaction conditions. We attribute the

higher conversions for imine reduction with the bulkier alcohols isopropyl alcohol and *tert*-butyl alcohol to a slower rate of dehydrocoupling relative to imine reduction.

Given the ability of alcohols to promote reduction of imines by pinacolborane, we decided to explore the ability of water to promote this reaction. While pinacolborane rapidly reacts with water and is therefore intrinsically dry, water would be expected to be the most common protic contaminant in solvents or imines that have not been adequately dried. If water can promote imine reduction in a fashion analogous to alcohols, this would represent an important source of non-catalyzed reactivity of the reactions of imines with pinacolborane. This could lead to unexpected outcomes, or erosion of stereoselectivity in reactions conducted with chiral catalysts. We prepared a 0.25 M solution of water in either THF or acetonitrile. These water-miscible and hygroscopic solvents are commonly used in imine reduction chemistry.[11] While addition of 1.25 equivalents of water in either acetonitrile (eqn (1), Scheme 2) or tetrahydrofuran (eqn (2), Scheme 2) to neat mixtures of pinacolborane and imine **1** resulted in rapid gas release indicating significant reaction of pinacolborane with water, concentration of the resulting mixture and analysis by NMR spectroscopy in chloroform-*d* showed approximately 80% conversion to the amine, indicating water is also an effective promoter of this reduction reaction. The gas release was observed only for the first couple of seconds of mixing, implying that reaction of pinacolborane with water is rapid. For the observed levels of reduction of the imine to have occurred, the imine reduction must also be rapid. These results indicate the importance of ensuring the dryness of solvent and substrate in the exploration of catalytic hydroboration reactions, especially asymmetric ones, since a rapid and uncatalyzed water-mediated background reaction would erode catalyst-mediated selectivity.

We explored several other reducible substrates, including electron rich and poor aniline derived imines **5** and **6**, chalcone **7**, ketone **8**, pyridine **9**, and cyclic imine **10**, which is a precursor to the pharmaceutical candidate SIB-1508Y (Fig. 2).[15] In the case of aniline derived imines **5**, and **6**, only trace conversion to the product amines was observed, in contrast to the relatively high conversion observed with **1**. Chalcone **7**, ketone **8**, pyridine **9**, and imine **10** did not undergo reduction reactions, with dehydrocoupling of the pinacolborane being the only observed reaction.

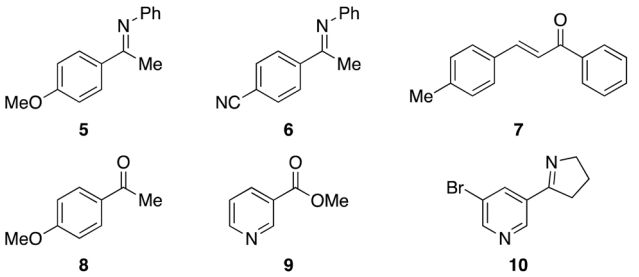
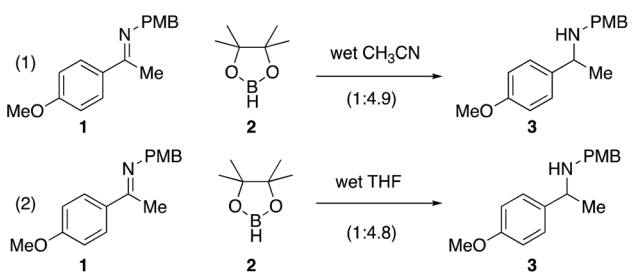


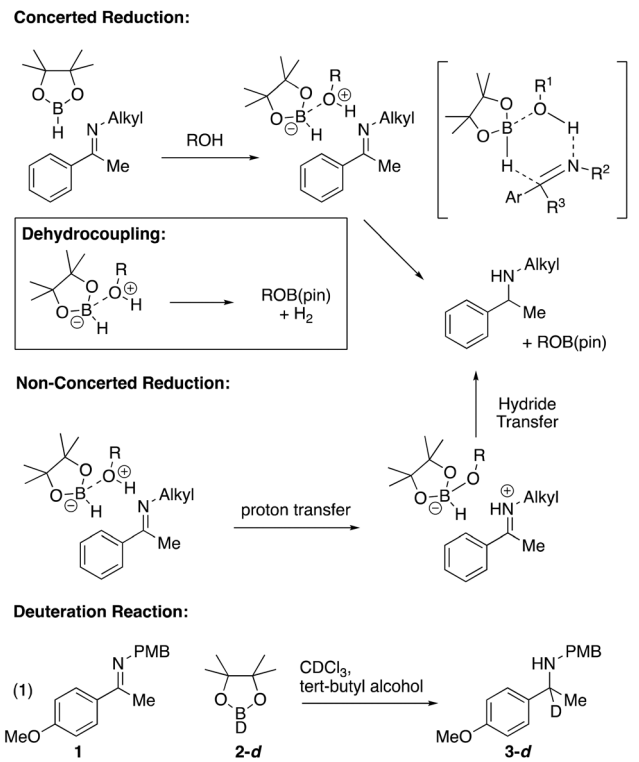
Fig. 2 Substrates that were not efficiently reduced with pinacolborane/alcohol mixtures.

Aniline derived imines have lower Lewis-basicity than alkyl imines. The above results suggest that a relatively basic alkyl imine is important for high conversion, and that addition of alcohol or water is necessary for reduction to take place. A mechanism involving a six membered transition state is proposed for the reduction reaction (Scheme 3).

Association of the HB(pin) and alcohol would be expected to increase both the acidity of the alcohol, and hydricity of the boron hydride.[13] In the absence of an imine, dehydrocoupling and release of hydrogen would occur. In the presence of a reducible imine, the hydride and hydrogen could be delivered to the imine *via* the cyclic six-membered transition state. The current data do not rule out an open transition state or non concerted proton/hydride transfer for this reaction and this scenario is also shown in Scheme 3. The use of deuterated



Scheme 2 Water as a reduction promoter.

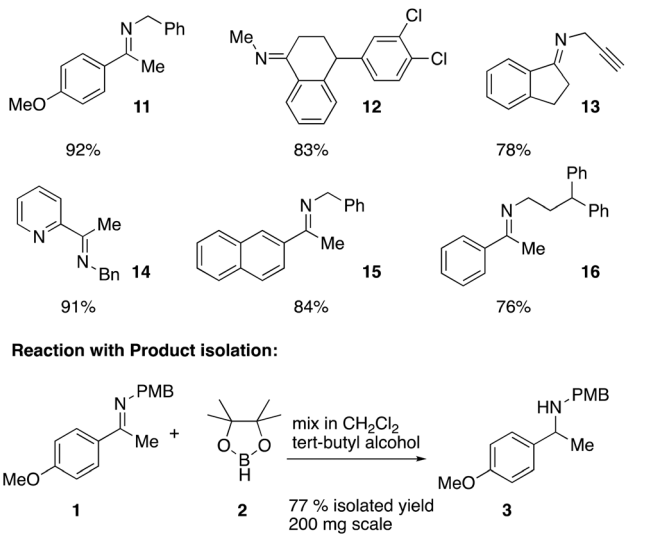


Scheme 3 Proposed mechanism for imine reduction.

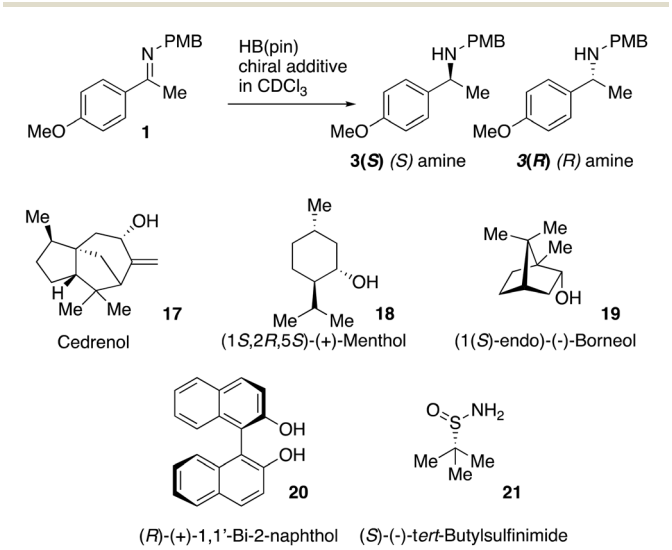
pinacolborane as a reductant resulted in delivery of the deuterium to the imine carbon, which is consistent with the mechanistic proposals presented in Scheme 3.[16] The results of the small substrate screen shown in Fig. 2 suggest that having a relatively basic substrate is important. We postulate that the reduced basicity of the aniline derived imines reduces the extent of intermolecular interaction with the HB(pin)/alcohol complex, either by hydrogen bonding, or a full deprotonation, increasing the relative proportion of dehydrocoupling within the complex. The other unreactive substrates shown in Fig. 2 can be considered in this context: carbonyl-based substrates **7** and **8** are also less basic than alkyl imines, corroborating the need for a relatively basic substrate. The failure of pyridine **9** to undergo reduction may be a consequence of the added energetic penalty of pyridine dearomatization making the rate of reduction uncompetitive with dehydrocoupling. The failure of imine **10** to undergo reduction was slightly more unexpected, since it is an alkyl imine. In this case, the basicity of the pyridine may interfere with imine reduction by changing the site of protonation on the molecule.

We subsequently explored a small scope of alkyl imines. The imines shown in Scheme 4 were reduced with varying conversions. The yields reported under substrates **11–16** were obtained by integration of NMR spectra with addition of 0.050 mmol of ferrocene as an internal standard. These numbers were in good agreement with observed ratios of starting material to product, showing that the reactions were relatively clean. Substitution of the 4-methoxybenzyl (PMB) group for a benzyl group (**11**) did not perturb the reaction. The precursor to the antidepressant sertraline (**12**) was reduced, however an essentially 1 : 1 mixture of diastereomers was obtained.[17] An alkyne in the precursor to rasagiline (**13**) did not interfere with the reaction. A pyridyl imine (**14**) was reduced, in contrast to imine **10**. In this substrate, the imine in the 2 position of the pyridyl ring may attenuate the pyridine basicity by withdrawing electrons through conjugation, reducing its interference in proton transfer, as compared with imine **10**. It is also possible that even if the pyridine is protonated, the close proximity of the imine nitrogen would allow rapid proton transfer, and subsequent imine reduction. Imines **15** and **16** were reduced uneventfully. Imine **16** is the precursor to fendiline, which is a pharmaceutical molecule. A reduction of imine **1** on 200 mg scale was also conducted using *tert*-butyl alcohol. The product was isolated and purified, affording amine **3** in 77% isolated yield. These reaction conditions are convenient, however imine reductions employing alternative reagents such as sodium borohydride or catecholborane can reach higher conversions, which means this reported method does not have added preparative value.

Since alcohols promote the observed reduction, we decided to investigate if the use of chiral non-racemic alcohols could result in chirality transfer. Solutions of the alcohols in chloroform-*d* were added to mixtures of **1** and pinacolborane (**2**). The use of the alcohols cedrenol (**17**), (1*S*,2*R*,5*S*)-(+)-menthol (**18**), 1 (*S*)-and *endo*-(−)-borneol (**19**) did provide varying levels of conversion, however the amines obtained were essentially racemic. Use of (*R*)-(+)-1,1′-bi-2-naphthol resulted in modest induction (63 : 37 *R* to *S*). The sense of induction was determined by HPLC on a chiral stationary phase, and by comparing the order of elution a previous report of analysis of amine **3** of known configuration under the same HPLC conditions.[11] Finally, we investigated the use of Ellman's (*S*)-(−)-*tert*butylsulfinimide (**21**), to examine if this protic functionality could also promote hydroboration. Meng and Du have reported catalytic reductions of imines employing an adduct of Piers' borane and Ellman's sulfinimide.[18] While addition of **21** to a mixture of imine **1** and pinacolborane (2) did promote reduction, but in our case, no asymmetric reduction was observed (Scheme 5).



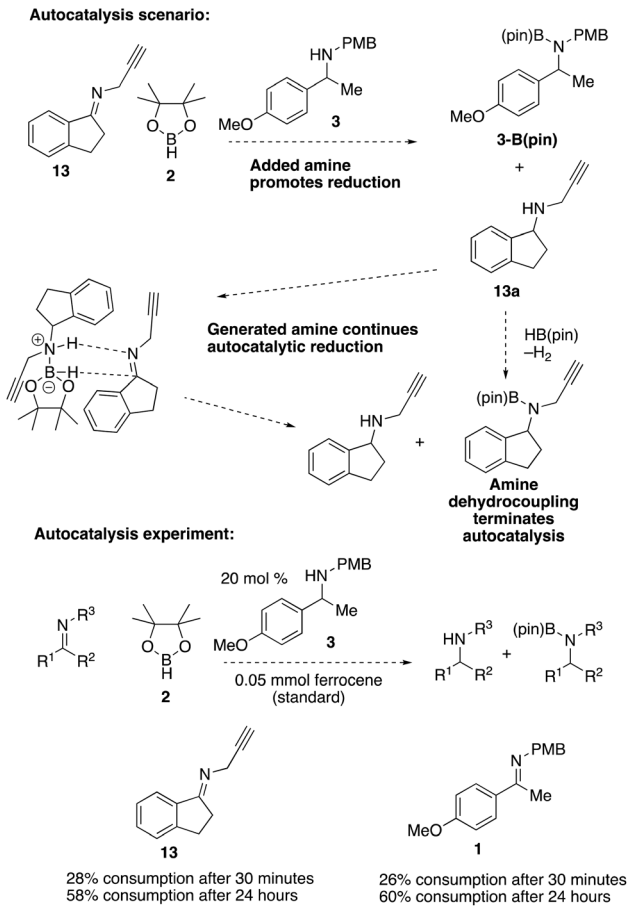
Scheme 4 Imines reduced with *tert*-butyl alcohol/pinacolborane (NMR yields from integration with internal standard).



Scheme 5 Investigation of chiral additives.

The observation that nitrogen containing compound **21** promoted reduction raised the possibility that other nitrogen-containing compounds may promote the reaction. Of special interest as promoters are alkyl amines, since these are the products of the reduction reaction of imines, raising the possibility that imine reduction by pinacolborane could occur *via* an autocatalytic reaction. Since imines are typically made from the condensation of an amine and carbonyl compound, excess amine is a likely impurity in imines, representing another potentially confounding factor in amine reduction.

To test for autocatalysis, two substrates were examined. Imines **1** and **13** were separately mixed with pinacolborane in chloroform-*d*, in the presence of ferrocene as an internal standard (Scheme 6). Amine **3** was added to each sample. NMR spectra were obtained for each reaction after approximately 30 minutes, then again after 24 hours. In both cases, approximately 30% consumption of starting imine was observed in the 30-minute NMR spectra. Neither reaction went to completion in the 24-hour timeframe but there was an increase in conversion to approximately 60% consumption of starting material for each reaction in the 24-hour measurement. The spectra were complicated compared to those obtained from the use of stoichiometric protic additives because of the presence of a mixture of borylated and non-borylated amines, so rather than measuring product formation, decrease of peak area corresponding to imine starting material were used to ascertain starting material consumption. The observation of continued conversion over several hours, in contrast to results with the water and alcohol mediated reactions suggests that autocatalysis is occurring, however the reaction is slow relative to the reduction observed in the presence of alcohols or water. Dehydrocoupling of amine with pinacolborane and loss of hydrogen would terminate the autocatalytic process by removing free amine without producing more amine to continue the catalytic cycle. The structure (steric environment) of the imine and amine is probably a factor in the extent of autocatalysis, and some substrates may prove to be more susceptible to autocatalysis than others. Because of the lack of high conversion for the substrates tested, and slow progression, amine autocatalysis is probably not a significant factor in ketimine reductions with pinacolborane, but ensuring imine substrates are free of amines would ensure absence of this possible background reaction in future catalytic investigations.



Scheme 6 Investigation of amine autocatalysis.

Conclusion

We have demonstrated that a combination of pinacolborane and alcohol or water results in the reduction of alkyl imines. Imines that are electron deficient are not reduced under these conditions. The use of chiral alcohols in chloroform-*d* did not result in chirality transfer except for binol, which afforded modest selectivity. This transformation is operationally simple and rapid, however the preparative value is limited by incomplete conversion of imine to amine because of competitive dehydrocoupling of the pinacolborane with the protic additive. The most important consideration arising from this work is that the promotion of imine reduction with pinacolborane by protic contaminants represents an important potential background reaction that must be considered in future studies of catalysed reductions of imines, since this reactivity could erode intended selectivity of catalytic systems.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Mr. Toren Hynes is thanked for preparation of substrate **10**. Mr. Casper Macaulay is thanked for preparation of DB(pin). Dr. Alex McLellan and NeuroQuest are thanked for the donation of a rotary evaporator, scale and vacuum pump. The Killam Foundation and the Nova Scotia Graduate Scholarship funded B. S. N. H.'s PhD studies. NSERC of Canada is thanked for a Discovery Grant.

Notes and references

1 C. C. Chong and R. Kinjo, *ACS Catal.*, 2015, **5**, 3238.
2 F. Schömberg, Y. Zi and I. Vilotijevic, *Chem. Commun.*, 2018, **54**, 3266.
3 (*a*) I. P. Query, P. A. Squier, E. M. Larson, N. A. Isley and T. B. Clark, *J. Org. Chem.*, 2011, **76**, 6452; (*b*) Z. Zhu, X. Wu, X. Xu, Z. Wu, M. Xue, Y. Yao, Q. Shen and X. Bao, *J. Org. Chem.*, 2018, **83**, 10677.
4 H. Stachowiak, J. Kaźmierczak, K. Kuciński and G. Hreczycho, *Green Chem.*, 2018, **20**, 1738.
5 R. T. Baker, J. C. Calabrese and S. A. Westcott, *J. Organomet. Chem.*, 1995, **498**, 109.
6 (*a*) D. Enders, A. Rembiak and M. Seppelt, *Tetrahedron Lett.*, 2013, **54**, 470; (*b*) D. Enders, A. Rembiak and B. A. Stöckel, *Adv. Synth. Catal.*, 2013, **355**, 1937.
7 C. E. Tucker, J. Davidson and P. Knochel, *J. Org. Chem.*, 1992, **57**, 3482.
8 P. Eisenberger, A. M. Bailey and C. M. Crudden, *J. Am. Chem. Soc.*, 2012, **134**, 17384.
9 (*a*) M. K. Bisai, S. Pahar, T. Das, K. Vanka and S. S. Sen, *Dalton Trans.*, 2017, **46**, 2420; (*b*) V. A. Pollard, M. Á. Fuentes, A. R. Kennedy, R. McLellan and R. R. Mulvey, *Angew. Chem., Int. Ed.*, 2018, **57**, 10651.
10 (*a*) Q. Yin, Y. Soltani, R. L. Melen and M. Oestreich, *Organometallics*, 2017, **36**, 2381; (*b*) J. R. Lawson, L. C. Wilkins and R. L. Melen, *Chem. – Eur. J.*, 2017, **23**, 10997.
11 (*a*) M. Arrowsmith, M. S. Hill and G. Kociok-Köhn, *Chem. – Eur. J.*, 2013, **19**, 2776; (*b*) K. Manna, P. Ji, F. X. Greene and W. Lin, *J. Am. Chem. Soc.*, 2016, **138**, 7488.
12 (*a*) M. R. Adams, C. H. Tien, B. S. N. Huchenski, M. J. Ferguson and A. W. H. Speed, *Angew. Chem., Int. Ed.*, 2017, **56**, 6268; (*b*) M. R. Adams, C. H. Tien, R. McDonald and A. W. H. Speed, *Angew. Chem., Int. Ed.*, 2017, **56**, 16660; (*c*) Y.-C. Lin, E. Hatzakis, S. M. McCarthy, K. D. Reichl, T.-Y. Lai, H. P. Yennawar and A. T. Radosevich, *J. Am. Chem. Soc.*, 2017, **139**, 6008; (*d*) C. H. Tien, M. R. Adams, M. J. Ferguson, E. R. Johnson and A. W. H. Speed, *Org. Lett.*, 2017, **19**, 5565.
13 (*a*) L. Koren-Selfridge, H. N. Londino, J. K. Vellucci, B. J. Simmons, C. P. Casey and T. B. Clark, *Organometallics*, 2009, **28**, 2085; (*b*) A. Kaithal, B. Chatterjee and C. Gunanathan, *J. Org. Chem.*, 2016, **81**, 11153; (*c*) R. Arévalo, C. M. Vogels, G. A. MacNeil, L. Riera, J. Pérez and S. A. Westcott, *Dalton Trans.*, 2017, **46**, 7750; (*d*) J. Wu, H. Zeng, J. Cheng, S. Zheng, J. A. Golen, D. R. Manke and G. Zhang, *J. Org. Chem.*, 2018, **83**, 9442.
14 E. A. Romero, J. L. Peltier, R. Jazzar and G. Bertrand, *Chem. Commun.*, 2016, **52**, 10563.
15 L. S. Bleicher, N. D. P. Cosford, A. Herbaut, J. S. McCallum and I. A. McDonald, *J. Org. Chem.*, 1998, **63**, 1109.
16 C. S. Wei, C. A. Jiménez-Hoyos, M. F. Videa, J. F. Hartwig and M. B. Hall, *J. Am. Chem. Soc.*, 2010, **132**, 3078.
17 K. Vukics, T. Fodor, J. Fischer, I. Fellegvári and S. Lévai, *Org. Process Res. Dev.*, 2002, **6**, 82.
18 S. Li, G. Li, W. Meng and H. Du, *J. Am. Chem. Soc.*, 2016, **138**, 12956.

