


 Cite this: *RSC Adv.*, 2020, 10, 34421

 Received 10th July 2020
 Accepted 7th September 2020

DOI: 10.1039/d0ra06023b

rsc.li/rsc-advances

Lithium bromide: an inexpensive and efficient catalyst for imine hydroboration with pinacolborane at room temperature†

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An efficient protocol for the hydroboration of imines is reported. Lithium halide salts are effective catalysts to convert aldimines and ketimines to their corresponding amines. Here, we report excellent isolated yield of secondary amines (>95%) using 3 mol% lithium bromide in THF at room temperature. In addition, DFT calculations for a plausible reaction pathway are reported.

Introduction

The hydroboration reaction was first reported in 1956 by H. C. Brown and co-workers.¹ Thereafter, numerous alcohols and amines have been synthesized through hydroboration/borohydride reduction of carbonyls, imines and unsaturated hydrocarbons using boron hydride reagents such as NaBH₄ and LiBH₄.²

Amines are ubiquitous functional groups; they are found in many natural products and are used as building blocks for the production of agrochemicals, pharmaceuticals, polymers, and dyes.³ Therefore, the synthesis of amines and their derivatives has gained significant attention in chemistry and biology.

Catalytic hydroboration of imines is a simple and straightforward method for the preparation of amines, unlike conventional hydrogenation reactions and stoichiometric reductions, which are carried out at high pressure and temperature.⁴ Several catalytic systems for imine hydroboration have been reported, including the use of transition metals (*e.g.*, Ti, Co, Ni, Ru),⁵ rare-earth metal complexes (Er, Y, Dy, Gd),⁶ an actinide group metal (Th),⁷ main group metals (Li, Na, Mg, Al, *etc.*),⁸ non-metals (P, B),⁹ and frustrated Lewis pairs.¹⁰

Recently, the hydroboration of imines has also been realized under catalyst-free conditions. In 2019, Pandey *et al.* reported the catalyst-free, solvent-free hydroboration of imines using pinacolborane (HBpin).¹¹ However, although this method provided amines from aldimines in good to reasonable yields, the hydroboration of ketimines proceeded with lower yields, even under high temperatures and prolonged reaction times.

Speed *et al.* reported hydroboration of ketimines promoted by stoichiometric amounts of protic additives such as alcohols

or water. The method provided good yields for aliphatic imines, while aniline derived imines (electron deficient substituents) were highly ineffective. The dehydrocoupling of pinacolborane with additives is the major issue in this protocol.¹²

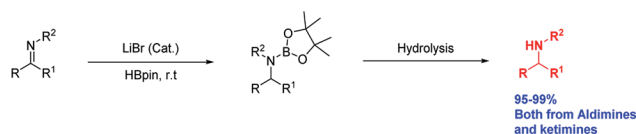
Thus, methods that achieve efficient hydroboration using sustainable protocols are necessitated.

Recently, our group reported that Li⁺ salts¹³ are superior and effective catalysts for the hydroboration of carbonyl compounds.¹⁴ Prompted by those results, we decided to extend the methodology to the hydroboration of other functional groups. Herein, we report an economical method for the hydroboration of imines with pinacolborane and LiBr under mild conditions to afford excellent yields of secondary amines from both aldimines and ketimines (Scheme 1).

Results and discussion

First, we investigated the hydroboration of *N*-benzylideneaniline with pinacolborane using various Li, Na, and K metal halide salts in THF at room temperature (Table 1). The Li⁺ salts—LiCl, LiBr, and LiI showed superior catalytic activity after 30 min reaction time (entries 2–4). Among these salts, LiBr was chosen as the catalyst for further optimization because of its easy availability and cost-effectiveness.

Moreover, further optimization of the reaction conditions was conducted by adjusting the catalyst loading, pinacolborane stoichiometry, type of solvent, and reaction time. The results are summarized in Table 2. When hydroboration was carried out in the absence of a catalyst, only 24% yield of the desired product

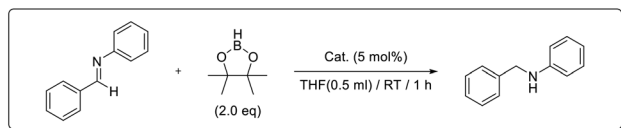


Scheme 1 Catalytic hydroboration of imines using LiBr as the catalyst.

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† Electronic supplementary information (ESI) available. See DOI: 10.1039/d0ra06023b



Table 1 Catalyst study for the hydroboration of *N*-benzylideneaniline

Entry	Cat	Time	Yield ^a (%) (imine/amine)
1	LiF	1 h	48/37 (15)
2	LiCl	30 min	0/99
3	LiBr	30 min	0/99
4	Lil	30 min	0/99
5	NaF	1 h	51/45 (4)
6	NaCl	1 h	52/39 (7)
7	NaBr	1 h	66/30 (4)
8	NaI	1 h	4/96
9	KF	1 h	47/38 (15)
10	KCl	1 h	55/28 (15)
11	KBr	1 h	77/18 (3)
12	KI	1 h	33/50 (16)

^a Yields were determined by GC. The values in parenthesis belong to those for aldehyde.

(*N*-benzylaniline) was afforded after 1 h (entry 1, Table 2). As expected, a dramatic improvement was observed in the presence of LiBr (3.0 mol%), affording quantitative conversion to the product (entry 6). Only moderate conversions were achieved with a reduced catalyst loading (entry 2), lower stoichiometries of pinacolborane (entries 3 and 4) and a shorter reaction time (entry 5). Next, the reaction was optimized in various solvent systems including *n*-hexane, toluene, diethyl ether, and dichloromethane (entries 7–10). Both diethyl ether and dichloromethane afforded yield comparable to THF, whereas the reaction performed poorly in *n*-hexane and toluene. We also

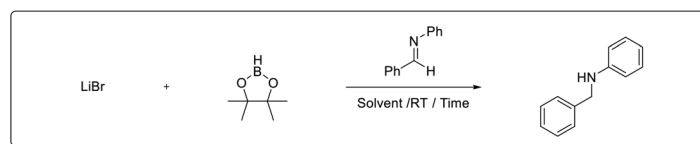
conducted hydroboration of imine in wet THF (trace amounts of water/^tBuOH with THF respectively under catalyst-free condition). A similar result (lower conversions) was observed from aniline derived imines as suggested by Speed *et al.* Consequently, the optimal reaction conditions for the hydroboration of *N*-benzylideneaniline was determined to be 3.0 mol% of LiBr, 1.5 equiv. of HBpin in THF with a reaction time of 1 h (entry 6).

Furthermore, the substrate scope was extended to aldimines **1b–o** (Table 3). We were pleased to observe that all aldimines tested underwent smooth hydroboration to afford the corresponding amines in excellent yield (**2b–k**). The reaction was equally efficient with aldimines bearing electron-withdrawing substituents (**1d**, and **1h–k**) and electron-donating substituents (**1b**, **1c**, and **1e–g**). Furthermore, polyaromatic imines **1l** and **1m** underwent hydroboration to afford the respective amines **2l** and **2m** in excellent yield. Although pyrenyl imine **1m** required a 3 h reaction time for complete conversion, it afforded amine **2m** in 97% isolated yield. In addition, the hydroboration of heteroaromatic imine **1n** and aliphatic imine **1o** proceeded smoothly, affording the respective amines **2n** and **2o** in excellent yield.

Next, the hydroboration of ketimines was investigated using *N*-(1-phenylethylidene)aniline (Table 4). We observed that 20% of the starting imine remained unreacted (entry 1, Table 4), and increasing the reaction time from 1 to 3 h showed only a marginal improvement in the conversion with 1.5 equiv. of HBpin (entry 2). Finally, with 2.0 equiv. of HBpin and 3 mol% LiBr, the ketimine underwent hydroboration smoothly to afford the desired product in 99% yield over 30 min reaction time (entry 4, Table 4).

Next, the substrate scope was extended to a range of ketimines (**3b–l**). Substrates bearing electron-withdrawing groups, *e.g.* 4-bromo (**3d** and **3g**) and 4-nitro (**3h**), and electron-donating substitutions, *e.g.* 4-methyl (**3b** and **3e**) and 4-methoxy (**3c** and **3f**), afforded their corresponding amines in excellent yield,

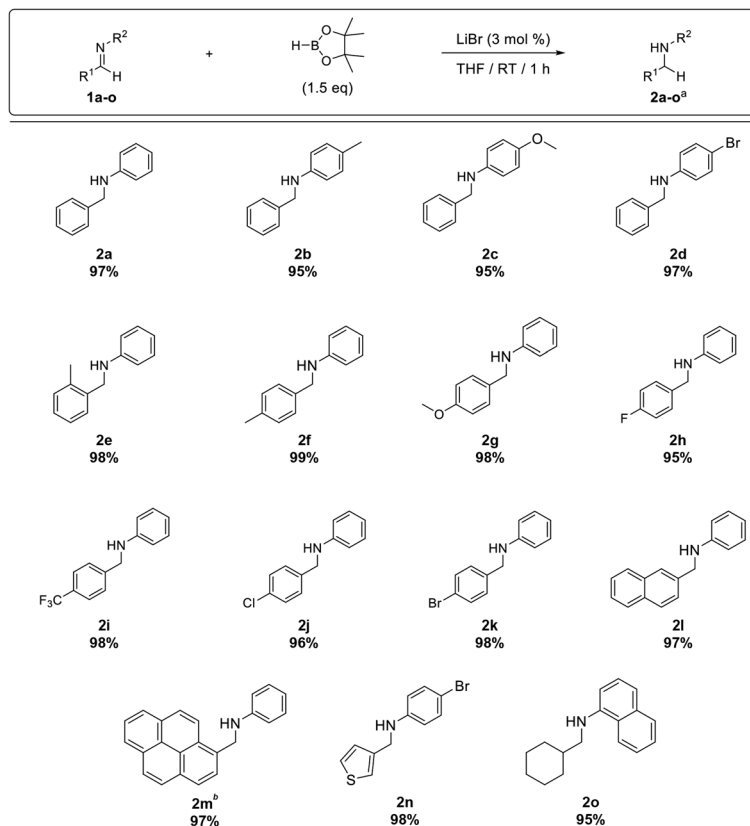
Table 2 Reaction conditions for the hydroboration of aldimine with pinacolborane and LiBr



Entry	LiBr (mol%)	Pinacolborane (equiv.)	Solvent (0.5 ml)	Time	Yield ^a (%) (S. M/product)
1	none	1.5	THF	1 h	71/24 (2)
2	1.0	1.5	THF	1 h	45/56 (2)
3	3.0	1.2	THF	1 h	16/76 (8)
4	3.0	1.2	THF	3 h	21/73 (4)
5	3.0	1.5	THF	30 min	13/82 (2)
6	3.0	1.5	THF	1 h	0/100
7	3.0	1.5	Hexane	1 h	86/7 (4)
8	3.0	1.5	Toluene	1 h	52/40 (4)
9	3.0	1.5	Ether	1 h	1/95
10	3.0	1.5	MC	1 h	6/87 (1)

^a Yields were determined by GC. The values in parenthesis belong to those for aldehyde.



Table 3 Substrate scope for the catalytic hydroboration of aldimines with pinacolborane and LiBr^a

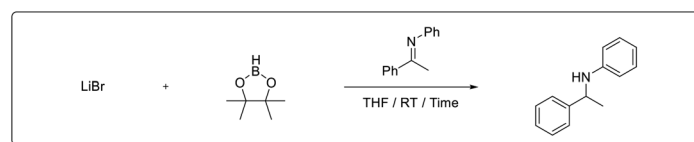
^a Isolated yields after column chromatography. ^b Reaction time: 3 h.

although the ketimines bearing a 4-methoxy substituent required 3.0 equiv. of HBpin for complete conversion. Similarly, 3.0 equiv. of HBpin was required to convert polyaromatic (**3i**) and sterically hindered imines (**3j-k**) to the desired amines (**4i-k**) in high yield. However, dihydronaphthalene imine **3l** underwent smooth hydroboration to afford the corresponding amine **4l** in 97% yield with 2.0 equiv. of pinacolborane (Table 5). The use of excess HBpin in the reaction is mainly due to the

decomposition of HBpin to B₂(pin)₃ during the reduction (¹¹B NMR of crude reaction, refer S62 in ESI[†]) which was observed comparatively more in ketamine hydroboration.

Finally, we investigated the chemoselectivity of our protocol. Accordingly, *N*-benzylideneaniline was treated with 3.0 equiv. of HBpin and 3 mol% LiBr in the presence of other reducible functional groups, such as esters and amides as well as nitrile, alkene, alkyne, alkyl halide, and epoxide moieties (Table 6). In

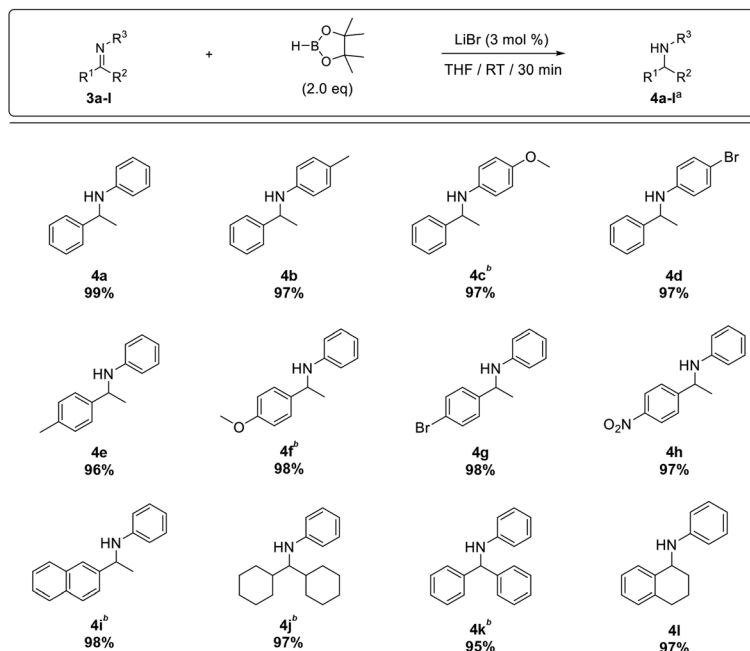
Table 4 Optimization of reaction conditions for ketamine hydroboration



Entry	LiBr (mol%)	Pinacolborane (equiv.)	Time	Yield ^a (%) (S. M/product)
1	3.0	1.5	1 h	20/79
2	3.0	1.5	3 h	14/83
3	3.0	2.0	10 min	18/82
4	3.0	3.0	30 min	0/99

^a Yields were determined by GC.



Table 5 Catalytic hydroboration of ketimines with LiBr^a

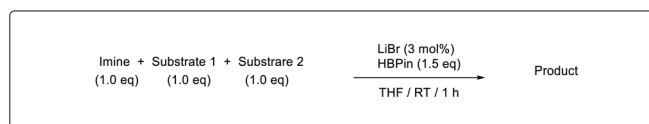
^a Isolated yields after silica column chromatography. ^b HBpin: 3.0 equiv.

all cases, our protocol exhibited high chemoselectivity toward imine hydroboration and excellent yield.

In addition, intramolecular hydroboration of imines was analyzed in the presence of an ester group. Both aldimine (5a)

and ketamine (5b) proceeded selective hydroboration with 3 mol% LiBr to afford desired amines 6a and 6b in 98% and 97% yield, respectively, by leaving the ester group unreacted (Scheme 3).

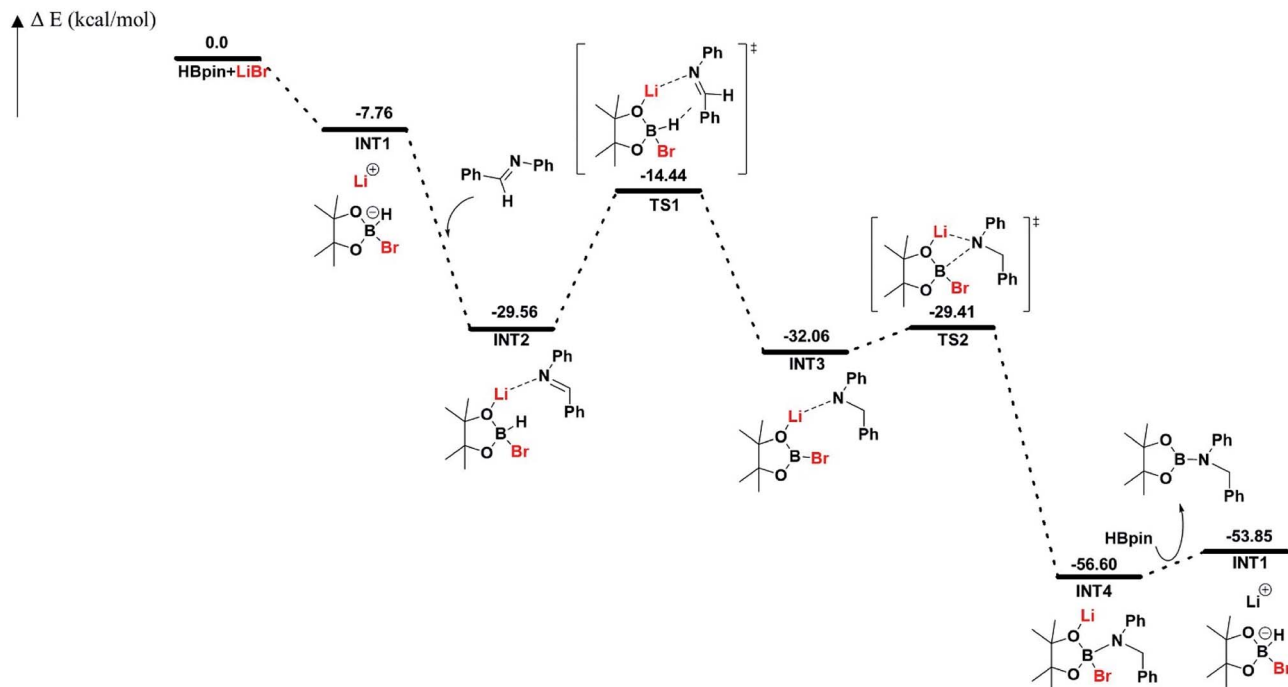
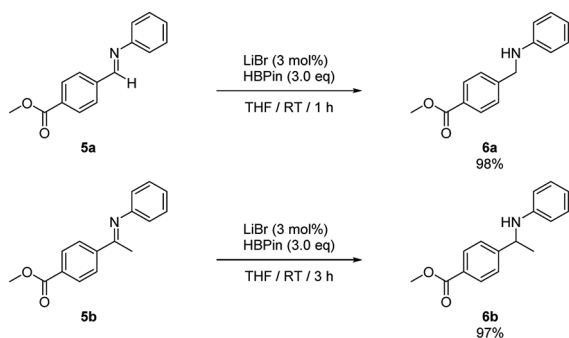
Table 6 Chemoselective catalytic hydroboration of imines over various functional groups



Entry	Imine	Substrate 1	Substrate 2	Yield ^a (%)		
				Imine (S. M/product)	Substrate 1 (S. M/product)	Substrate 2 (S. M/product)
1				0/98	97/0	98/0
2				0/99	96/0	95/0
3				0/99	99/0	99/0
4				0/99	99/0	97/0
5				5/92	99/0	95/0

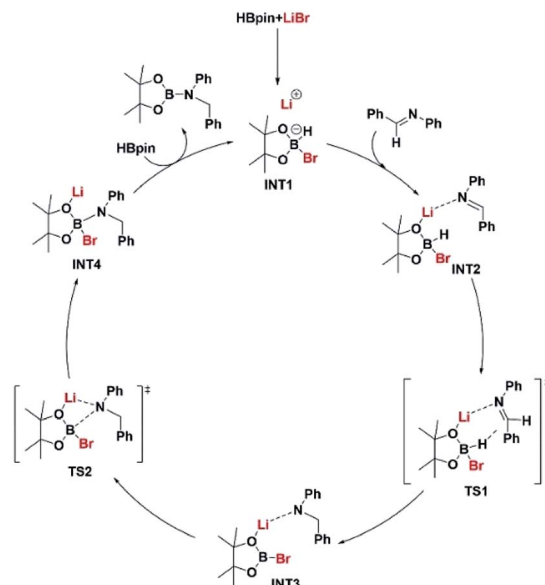
^a Yields were determined by GC.



Scheme 2 Free energy profile (in kcal mol⁻¹) for LiBr catalyzed hydroboration of aldimine (PhHCNPh).

Scheme 3 Chemoselective catalytic hydroboration from intramolecular compounds.

The reaction pathway for LiBr catalyzed hydroboration of aldimine (PhHCNPh) was explored using density functional theory (DFT) calculations at the M06-2X/6-31+G(d,p) level of theory. The electronic energy profile for the reaction pathway is illustrated in Scheme 2. The mechanism was predicted based on recent work done by Thomas¹⁵ *et al.*, Clark¹⁶ *et al.*, and Wuesthoff¹⁷ *et al.* Accordingly, HBpin undergoes reaction with LiBr catalyst initially to produce the hydridoborate intermediate **INT1**.^{15,16} The subsequent reaction of the **INT1** with aldimine generates the **INT2** which turns into the **INT3** through a hexagonal ring transition state **TS1**. **INT3** then undergoes a unimolecular transformation into the **INT4** through a four-membered ring transition state **TS2**. Upon the reaction of **INT4** with HBpin *via* ligand exchange, providing desired substrate dioxolan amine with regeneration of **INT1** for the next catalytic cycle (Scheme 4).



Scheme 4 A plausible mechanism based on the energy profiles shown in Scheme 2. Coordinates for the intermediate and transition state structures are provided in ESI.†

Conclusions

We demonstrated that LiBr, an inexpensive, mild, and stable reagent, efficiently catalyzes the hydroboration of imines at room temperature. Various imines (aldimines and ketimines) successfully underwent hydroboration with HBpin in the



presence of 3 mol% LiBr to afford the desired amines in excellent yield. Furthermore, we demonstrated the high chemoselectivity of our protocol. DFT calculations for a plausible reaction pathway are reported. The proposed method involving the use of a very mild and easy-to-handle catalyst (LiBr) is a potential, industrially viable protocol for the preparation of secondary amines through the hydroboration of imines.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This study was supported by the National Research Foundation of Korea Grant funded by the Korean Government (2017R1D1A1B03035412 for D. K. An and 2020R1I1A1A01073381 for J. H. Lee).

Notes and references

- H. C. Brown and B. S. Rao, A new technique for the conversion of olefins into organoboranes and related alcohols, *J. Am. Chem. Soc.*, 1956, **78**, 5694.
- (a) H. C. Brown, B. C. Subba Rao and I. Hydroboration, The reaction of olefins with sodium borohydride-aluminum chloride. a convenient route to organoboranes and the anti-Markownikoff hydration of olefins, *J. Am. Chem. Soc.*, 1959, **81**(24), 6423; (b) H. C. Brown and S. Krishnamurthy, Forty years of hydride reductions, *Tetrahedron*, 1979, **35**, 567; (c) H. C. Brown, Y. M. Choi and S. Narasimhan, Convenient procedure for the conversion of sodium borohydride into lithium borohydride in simple ether solvents, *Inorg. Chem.*, 1981, **20**, 4454; (d) N. Satyanarayana and M. Periyssamy, Hydroboration or hydrogenation of alkenes with $\text{CoCl}_2\text{-NaBH}_4$, *Tetrahedron Lett.*, 1984, **25**, 2501; (e) J. H. Billman and A. C. Diesing, Reduction of schiff bases with sodium borohydride, *J. Org. Chem.*, 1957, **22**, 1068.
- (a) T. C. Nugent and M. El-Shazly, Chiral amine synthesis—recent developments and trends for enamide reduction, reductive amination, and imine reduction, *Adv. Synth. Catal.*, 2010, **352**, 753; (b) C. Pubill-Ulldemolins, A. Bonet, C. Bo, H. Gulyás and E. Fernández, A new context for palladium mediated B-addition reaction: an open door to consecutive functionalization, *Org. Biomol. Chem.*, 2010, **8**, 2667; (c) C. C. Chong and R. Kinjo, Catalytic hydroboration of carbonyl derivatives, imines, and carbon dioxide, *ACS Catal.*, 2015, **5**, 3238.
- (a) K. Hayes, Industrial processes for manufacturing amines, *Appl. Catal.*, A, 2001, **221**, 187; (b) T. E. Muller, K. C. Hultzs, M. Yus, F. Foubelo and M. Tada, Hydroamination: direct addition of amines to alkenes and alkynes, *Chem. Rev.*, 2008, **108**, 3795; (c) S. Nishimura, *Handbook of heterogeneous catalytic hydrogenation for organic synthesis*, Wiley New York etc, 2001; (d) J. G. de Vries and C. J. Elsevier, *Handbook of homogeneous hydrogenation*, WeinheimWiley-VCH9783527311613, 2007.
- (a) C. C. Chong and R. Kinjo, Catalytic hydroboration of carbonyl derivatives, imines, and carbon dioxide, *ACS Catal.*, 2015, **5**, 3238; (b) A. Kaithal, B. Chatterjee and C. Gunanathan, Ruthenium-catalyzed selective hydroboration of nitriles and imines, *J. Org. Chem.*, 2016, **81**, 11153; (c) J. Wu, H. Zeng, J. Cheng, S. Zheng, J. A. Golen, D. R. Manke and G. Zhang, Cobalt(II) coordination polymer as a precatalyst for selective hydroboration of aldehydes, ketones, and imines, *J. Org. Chem.*, 2018, **83**, 9442.
- Z. Huang, S. Wang, X. Zhu, Q. Yuan, Y. Wei, S. Zhou and X. Mu, Well-Defined amidate-functionalized *N*-heterocyclic carbene-supported rare-earth metal complexes as catalysts for efficient hydroboration of unactivated imines and nitriles, *Inorg. Chem.*, 2018, **57**, 15069.
- S. Saha and M. S. Eisen, Catalytic recycling of a Th–H bond *via* single or double hydroboration of inactivated imines or nitriles, *ACS Catal.*, 2019, **9**, 5947.
- (a) K. Manna, P. Ji, F. X. Greene and W. Lin, Metal–organic framework nodes support single-site magnesium–alkyl catalysts for hydroboration and hydroamination reactions, *J. Am. Chem. Soc.*, 2016, **138**, 7488; (b) Y. Wu, C. Shan, J. Ying, J. Su, J. Zhu, L. L. Liu and Y. Zhao, Catalytic hydroboration of aldehydes, ketones, alkynes and alkenes initiated by NaOH, *Green Chem.*, 2017, **19**, 4169; (c) V. A. Pollard, M. Á. Fuentes, A. R. Kennedy, R. McLellan and R. E. Mulvey, Comparing neutral (monometallic) and anionic (bimetallic) aluminum complexes in hydroboration catalysis: influences of lithium cooperation and ligand set, *Angew. Chem., Int. Ed.*, 2018, **57**, 10651; (d) A. K. Jaladi, H. Kim, J. H. Lee, W. K. Shin, H. Hwang and D. K. An, Lithium diisobutyl-*tert*-butoxyaluminum hydride (LDBBA) catalyzed hydroboration of alkynes and imines with pinacolborane, *New J. Chem.*, 2019, **43**, 16524; (e) D. Yan, X. Wu, J. Xiao, Z. Zhu, X. Xu, X. Bao, Y. Yao, Q. Shen and M. Xue, *n*-Butyllithium catalyzed hydroboration of imines and alkynes, *Org. Chem. Front.*, 2019, **6**, 648.
- (a) Y. Lin, E. Hatzakis, S. M. McCarthy, K. D. Reichl, T. Lai, H. P. Yennawar and A. T. Radosevich, P–N Cooperative borane activation and catalytic hydroboration by a distorted phosphorous triamide platform, *J. Am. Chem. Soc.*, 2017, **139**, 6008; (b) C. Tien, M. R. Adams, M. J. Ferguson, E. R. Johnson and A. W. Speed, Hydroboration catalyzed by 1,2,4,3-triazaphospholenes, *Org. Lett.*, 2017, **19**, 5565; (c) T. Lundrigan, E. N. Welsh, T. Hynes, C. Tien, M. R. Adams, K. R. Roy, K. N. Robertson and A. W. Speed, Enantioselective imine reduction catalyzed by phosphonium ions, *J. Am. Chem. Soc.*, 2019, **141**, 14083.
- P. Eisenberger, A. M. Bailey and C. M. Cruden, Taking the F out of FLP: simple Lewis acid–base pairs for mild reductions with neutral boranes *via* borenium ion catalysis, *J. Am. Chem. Soc.*, 2012, **134**, 17384.



- 11 V. K. Pandey, S. N. R. Donthireddy and A. Rit, Catalyst-free and solvent-free facile hydroboration of imines, *Chem.-Asian J.*, 2019, **14**, 3255.
- 12 B. S. N. Huchenski and A. W. H. Speed, Protic additives or impurities promote imine reduction with pinacolborane, *Org. Biomol. Chem.*, 2019, **17**, 1999.
- 13 J. H. Kim, A. K. Jaladi, H. T. Kim and D. K. An, Lithium *tert*-butoxide-catalyzed hydroboration of carbonyl compounds, *Bull. Korean Chem. Soc.*, 2019, **40**, 971.
- 14 (a) M. M. Mojtahedi, E. Akbarzadeh, R. Sharifi and M. S. Abaee, Lithium bromide as a flexible, mild, and recyclable reagent for solvent-free Cannizzaro, Tishchenko, and Meerwein-Ponndorf-Verley reactions, *Org. Lett.*, 2007, **9**, 2791; (b) R. Patel, V. P. Srivastava and L. D. S. Yadav, The first example of saccharin-lithium bromide catalysis: direct synthesis of *N*-tosylimines from alcohols, *Adv. Synth. Catal.*, 2010, **352**, 1610; (c) C. N. Rao, C. Bentz and H. Reissig, Lithium bromide/water as additives in dearomatizing samarium-ketyl (hetero) arene cyclizations, *Chem.-Eur. J.*, 2015, **21**, 15951.
- 15 A. D. Bage, T. A. Hunt and S. P. Thomas, Hidden boron catalysis: nucleophile-promoted decomposition of HBpin, *Org. Lett.*, 2020, **22**(11), 4107.
- 16 I. P. Query, P. A. Squier, E. M. Larson, N. A. Isley and T. B. Clark, Alkoxide-catalyzed reduction of ketones with pinacolborane, *J. Org. Chem.*, 2011, **76**, 6453.
- 17 B. Rickborn and M. T. Wuesthoff, Kinetics, stereochemistry, and mechanism of the sodium borohydride reduction of alkyl-substituted cyclohexanones, *J. Am. Chem. Soc.*, 1970, **92**, 6894.

