Dalton Transactions

ROYAL SOCIETY OF CHEMISTRY

COMMUNICATION

View Article Online
View Journal

Cite this: DOI: 10.1039/d0dt00232a

Received 22nd November 2019,
Accepted 22nd January 2020

DOI: 10.1039/d0dt00232a

rsc.li/dalton

Asymmetric ketone hydroboration catalyzed by alkali metal complexes derived from BINOL ligands†

Darren Willcox, [a,b] Jamie L. Carden,[a] Adam J. Ruddy,[a] Paul D. Newman *[a] and Rebecca L. Melen *[a]

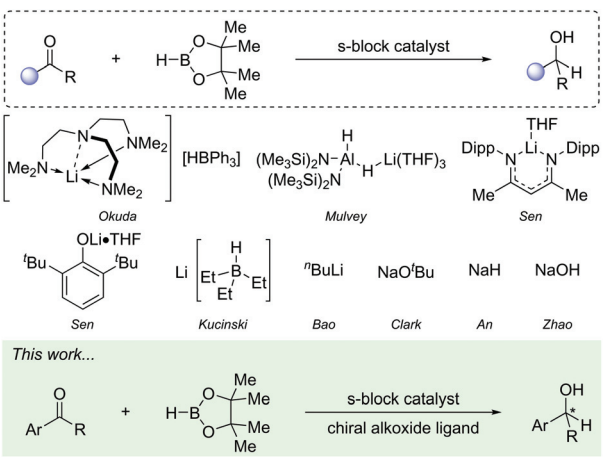
The ability of alkali metal complexes featuring functionalized BINOL-derived ligands to catalyze ketone hydroboration reactions was explored. The reduced products were formed in excellent yields and with variable enantioselectivities dependent upon the nature of the ligand and the alkali metal cation.

Catalytic carbonyl hydroboration to give, ultimately, primary or secondary alcohols has been realized utilizing a plethora of different catalysts derived from transition metal or f-block metal complexes.[1,2] Many of these catalysts are expensive and/or their preparation is synthetically challenging. This has prompted a number of groups to explore the application of main group compounds as alternative catalysts for this and other reductions.[3] While p-block elements have dominated this research,[4] the exploration of s-block catalysts is less prevalent with the alkaline Earth metals (mainly magnesium and calcium) taking centre stage.[5]

Encouraging results demonstrating the effective catalytic ability of group I metals in carbonyl hydroborations have been reported recently (Scheme 1). Pioneering work by the Okuda group revealed that a well-defined lithium hydridotriphenyl borate, bearing a chelating ligand (tris{2-(dimethylamino) ethyl}amine), was an extremely efficient catalyst for carbonyl reductions with low catalyst loadings (0.001 mol%).[6] The Mulvey group demonstrated that carbonyl reduction was achievable using a heterobimetallic lithium/aluminum complex capable of participating in cooperative catalysis leading to high yields of the desired alcohols.[7] Despite these elegant approaches, the applicability of these complexes is limited, mainly due to ligand specificity and catalyst pre-preparation. As a result, the utilization of simple, commercially available group I metal salts has been at the forefront of this research area.

Several groups have recently made major advancements demonstrating that simple sodium salts (NaO^{t}Bu, NaH and NaOH)[8–10] and lithium salts (^{n}BuLi and LiHBEt$_3$)[11–13] are highly active catalysts for carbonyl reductions. The simplicity of these alkali metal species suggests that they could serve as ideal pre-catalysts for the development of enantioselective s-block catalyzed ketone reductions in the presence of a chiral ligand. This *in situ* approach would bypass the need to synthesize complex species from lithium intermediates and could facilitate significant advancements in main group chemistry.

To this end, we sought to explore whether alkali metal catalysts in the presence of chiral alcohols, may be utilized for enantioselective ketone hydroboration. Asymmetric hydroborations are attractive as the products of such reactions furnish optically active organoboron compounds which are valuable building blocks for accessing a number of chiral structures.[14,15] The wide application of BINOL-derived frameworks in asymmetric catalysis led us to choose ligands



Scheme 1 Previously reported s-block ketone hydroboration catalysts; Dipp = 2,6-diisopropylphenyl.

[a]*Cardiff Catalysis Institute, School of Chemistry, Cardiff University, Main Building, Park Place, Cardiff, CF10 3AT Cymru/Wales, UK. E-mail: MelenR@cardiff.ac.uk, NewmanP1@cardiff.ac.uk*

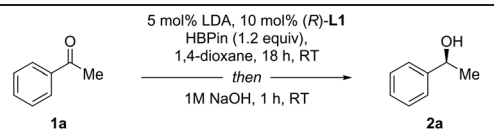
[b]*Department of Chemistry, University of Manchester, Oxford Rd, Manchester, M13 9PL, UK*

†Electronic supplementary information (ESI) available: Detailed experimental procedures, HPLC traces and compound data. See DOI: 10.1039/d0dt00232a

(R)-**L1**–**L7** for this study. Our initial investigations focussed on the reduction of acetophenone (**1a**).

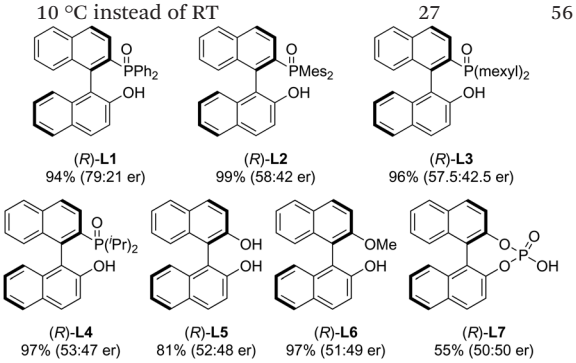
Under optimized reaction conditions, 1.2 equivalents of HBpin, 5 mol% of lithium diisopropylamide (LDA) and 10 mol% *(R)*-**L1** in 1,4-dioxane for 18 h (Table 1, entry 1) (see ESI† for optimization tables), the scalemic alcohol product (**2a**) was formed in 94% yield and 79 : 21 enantiomeric ratio. Ligand *(R)*-**L1** was chosen initially as it contains a single alcoholic proton, which would ideally lead to a single deprotonated species upon deprotonation by LDA. Furthermore, it was thought that the presence of the closely tethered phosphine oxide group may be required for stabilizing the alkali metal catalyst. Control experiments showed that, in the absence of alkali metal catalyst no reaction occurred (entries 2 and 3). However, in the presence of LDA but absence of ligand, no enantioselectivity was observed although the product was still observed in a high yield (85%, entry 4). A change in the stereoelectronic properties of the substituents on the phosphine oxide moiety of the ligand (*(R)*-**L1**–**L4**) proved to be critical for enantioselectivity (entry 5). Indeed, changing the phenyl group for the more sterically encumbered mesityl (*(R)*-**L2**) or mexyl (*(R)*-**L3**, 3,5-xylyl) groups led to the product with significantly decreased enantioselectivity (99% and 96% yield, and 58 : 42 and 57.5 : 42.5 er respectively). Changing the electronic properties of the phosphine oxide from phenyl to isopropyl groups (compare *(R)*-**L1** and *(R)*-**L4**), delivered the product in high yield but again with low levels of enantioselectivity (53 : 47 er). (*R*)-BINOL (*(R)*-**L5**) and the simple monomethylated BINOL (*(R)*-**L6**) were also tested with the products being observed in good yields but low enantioselectivity. In the case of *(R)*-**L5**, the low er could be due to the presence of two alcoholic protons potentially producing complex mixtures of active species upon deprotonation. Finally, (*R*)-1,1′-binaphthyl-2,2′-diyl-hydrogenphosphate (*(R)*-**L7**) was also screened as a ligand as chiral phosphoric acids have been demonstrated to be privileged ligands for certain asymmetric transformations.[16] Unfortunately, under our conditions *(R)*-**L7** produced racemic product. Decreasing the catalytic loading of *(R)*-**L1** from 10 mol% to 5 mol% was deleterious to the enantioselectivity (entry 6). The combination of LDA and (*S*)-**2a** was catalytically competent but gave 0% er of product proving that *(R)*-**L1** is critical for enantioselective induction.

Table 1 Selected optimization of reaction conditions



1a **2a**

Entry	Deviation from standard conditions[a]	Yield[b] (%)	er[c] (%)
1	None	94	79 : 21
2	No LDA	NR[d]	—
3	No LDA and no ligand	NR[d]	—
4	No ligand	85	50 : 50
5	**L2**–**L7** instead of **L1**	Listed below	
6	5 mol% **L1**	95	58 : 42
7	LiO^{t}Bu instead of LDA	99	70 : 30
8	LiH instead of LDA	70	68 : 32
9	THF instead of 1,4-dioxane	98	70 : 30
10	CH_2Cl_2 instead of 1,4-dioxane	98	56 : 44
11	Toluene instead of 1,4-dioxane	96	50 : 50
12	HBCat instead of HBPin	98	56 : 44
13	10 °C instead of RT	27	56 : 44



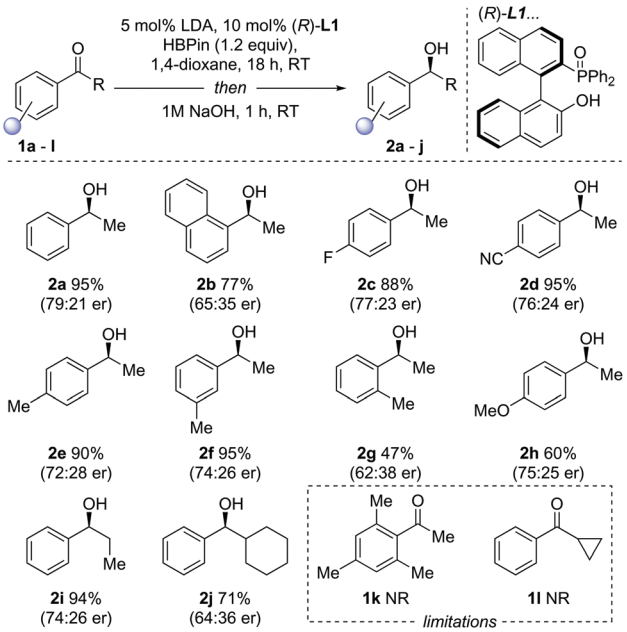
(*R*)-**L1** 94% (79:21 er) (*R*)-**L2** 99% (58:42 er) (*R*)-**L3** 96% (57.5:42.5 er)

(*R*)-**L4** 97% (53:47 er) (*R*)-**L5** 81% (52:48 er) (*R*)-**L6** 97% (51:49 er) (*R*)-**L7** 55% (50:50 er)

[a] All the reactions were run on a 0.25 mmol scale. [b] The yield was determined by ^{1}H NMR spectroscopy using 1,1,2,2-tetrachloroethane as the internal standard. [c] er determined by chiral HPLC analysis. Mexyl = 3,5-dimethylphenyl; mesityl = 2,4,6-trimethylphenyl. [d] Conversion analysed by ^{1}H NMR spectroscopy before workup. NR denotes no reaction.

The influence of the base was next evaluated. Replacing LDA for 5 mol% LiO^{t}Bu led to the desired product in an extremely high yield with a moderate 70 : 30 er (entry 7). Given the by-products from the pre-mixing of *(R)*-**L1** with either LDA or LiO^{t}Bu were diisopropylamine or *tert*-butanol respectively, it was possible these were forming catalytically competent racemic species *in situ*. With this in mind, we envisaged changing LDA for LiH would lead to higher enantioselectivity, as the by-product from pre-mixing would be H_2. Interestingly, an er of 68 : 32, very similar to LiO^{t}Bu but lower than LDA (entry 8), was observed suggesting that either the by-products are innocent and do not influence the catalyst or they are important for enantioselectivity (mainly for diisopropylamine). The reaction also proceeded in other ethereal solvents such as THF in good yields albeit with a slightly reduced er (entry 9). The use of other polar non-coordinating solvents, such as CH_2Cl_2 gave good yields but reduced er (56 : 44, entry 10). Changing from 1,4-dioxane to toluene, a non-polar and non-coordinating solvent led to only racemic products being observed (entry 11). This result can be attributed to the low solubility of the lithium phenolate salt in toluene (mixture remained heterogeneous). Replacing pinacol borane with catechol borane was also effective however due to the higher reactivity of catechol borane a decreased enantiomeric ratio was observed (entry 12). Finally, lowering the reaction temperature to 10 °C provided the desired product in low yield and enantioselectivity (entry 13). We attribute the lower er to insolubility of the lithium salt in this solvent at this temperature.

With suitable conditions in hand, we next explored a small substrate scope for this reaction (Scheme 2). A series of simple acetophenone (**1a**–**1l**) derivatives exhibiting different steric and electronic properties on the phenyl ring were evaluated. When electron neutral acetophenone derivatives were employed, the desired alcohols (**2a** and **2b**) could be obtained in good yields with moderate to good enantiomeric ratios (79 : 21 and 65 : 35, respectively). Introduction of electron withdrawing groups



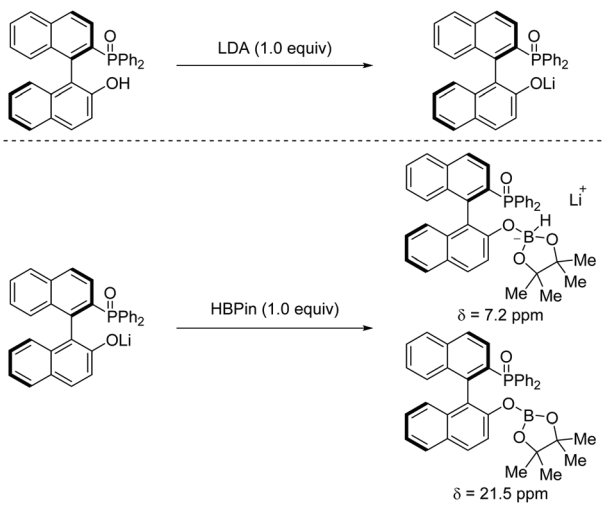
Scheme 2 Substrate scope. All the reactions were run on a 0.25 mmol scale. er determined by chiral HPLC analysis and given in parentheses. NR denotes no reaction.

such as fluorine or nitrile onto the phenyl ring were tolerated, resulting in good yields of the products (**2c** and **2d**) with moderate enantiomeric ratios (up to 77 : 23).

When the phenyl ring was substituted with mild inductive electron donating groups, such as methyl (**2e**–**2g**), good yields of the product could be observed for the *para* and *meta*-substituted acetophenones and similar enantiomeric ratios to acetophenone itself were observed. Moving the methyl group into the *ortho*-position (**2g**) led to an observed decrease in yield and enantiomeric ratio (47% and 62 : 38 respectively). The addition of a strong mesomeric electron-donating group, such as *p*-methoxy (**2h**), led to a decreased yield compared to the *para*-substituted methyl variant however similar enantiomeric ratios were observed (75 : 25 *vs.* 72 : 28). This lower yield can be attributed to a decreased electrophilicity of the carbonyl group. Altering the substitution on the alkyl side of the acetophenone was also achievable with both ethyl-(**2i**) and cyclohexyl-(**2j**) groups being tolerated in good to excellent yields. From this substrate scope, it is evident that steric factors play an important role in both the yield and enantioselectivity. Acetophenone derivatives bearing either *ortho* substituents (**2b** and **2g**) or bulky alkyl substituents (**2j**) all resulted in the formation of the desired products albeit with reduced yields and enantioselectivity. Whereas very sterically hindered substrates such as mesityl or cyclopropyl (**1k** and **1l**) resulted in recovery of the starting material. These observations suggest that there is a steric interaction between the active catalytic species, bearing the bulky binaphthyl backbone and the substrate, possibly favoring a faster uncatalyzed background reaction and resulting in diminished enantioselectivity.

In an effort to examine the nature of the species generated in solution, we first performed a stoichiometric reaction between **L1** and LDA in 1,4-dioxane (with benzene-d_6 lock) and probed it using multinuclear NMR spectroscopy (Scheme 3, top). As expected, deprotonation of the phenolic proton occurred rapidly and cleanly (within 5 min) and the loss of this proton was indicative by the disappearance of a resonance at δ = 9.28 ppm in the ^{1}H NMR spectrum.

The stoichiometric reaction between *(R)*-**L1**, LDA and pinacolborane in 1,4-dioxane was subsequently explored. There was no observable change in chemical shift in both the aromatic region and for the tetramethyl protons of the pinacol group in the ^{1}H NMR spectrum. However, two new singlets appeared at δ = 0.53 and 0.20 ppm. The ^{11}B NMR spectrum identified the presence of three boron containing species (δ = 28.4, 21.5, and 7.2 ppm). The doublet at δ = 28.4 ($^1J_{BH}$ = 173.0 Hz) is attributed to pinacolborane, indicating incomplete consumption of pinacolborane. The second resonance at δ = 21.5 ppm can be attributed to the formation of the borate species (Scheme 3, bottom). This species was also identifiable when *(R)*-**L1** and pinacolborane were reacted in a stoichiometric fashion. The final ^{11}B resonance at δ = 7.2 ppm can be attributed to the formation of the lithium trialkoxyborohydride species (Scheme 3, bottom). This ^{11}B NMR resonance is consistent with trialkyloxyborohydrides reported by Brown and Clark (δ = 0–7 ppm).[8,17] The resonance observed at δ = 7.2 ppm is significantly less intense than the corresponding resonance at δ = 21.5 ppm and it was noted that, at the concentration these stoichiometric reactions were performed (0.1 M), a large quantity of precipitate was observed and that the borohydride species was only sparingly soluble at this concentration. Evaluation of the ^{31}P NMR spectrum showed negligible changes in chemical shift upon both deprotonation and coordination with the pinacolborane. A repeat experiment using two equivalents of *(R)*-**L1** to mimic the most successful catalytic systems gave similar results to those detailed above except complete consumption of the pinacolborane and full conversion to the borate species at δ = 21.5 ppm was observed.



Scheme 3 NMR experiments to try and elucidate the nature of the catalytic species. All reactions were performed on a 0.1 mmol scale.

There was no observable lithium trialkoxyborate species in the NMR spectra under these conditions.

In conclusion, we have developed an enantioselective s-block catalyzed hydroboration of acetophenones. The chiral catalyst is comprised of a BINOL derived ligand and LDA. Using multinuclear NMR spectroscopy, we found that the phenolic proton in the ligand is cleanly deprotonated with LDA and subsequent addition of pinacol borane leads to the formation of a chiral trialkyloxyborohydride species. This catalyst provides access to scalemic secondary alcohols in good to excellent yields and is operationally simple. This methodology opens the door for other asymmetric s-block based catalysis.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We are grateful to the Leverhulme Trust for a research project grant (D. W., A. J. R., P. D. N. and R. L. M. RPG-2016-020). We also thank the EPSRC for funding: (J. L. C, EP/L016443/1; R. L. M, EP/R026912/1).

Notes and references

1 (*a*) N. Eedugurala, Z. Wang, U. Chaudhary, N. Nelson, K. Kandel, T. Kobayashi, I. I. Slowing, M. Pruski and A. D. Sadow, *ACS Catal.*, 2015, **5**, 7399–7414; (*b*) G. Zhang, H. Zeng, J. Wu, Z. Yin, S. Zheng and J. C. Fettinger, *Angew. Chem., Int. Ed.*, 2016, **55**, 14369–14372; (*c*) R. Arévalo, C. M. Vogels, G. A. MacNeil, L. Riera, J. Pérez and S. A. Westcott, *Dalton Trans.*, 2017, 7750–7757; (*d*) V. L. Weidner, C. J. Barger, M. Delferro, T. L. Lohr and T. J. Marks, *ACS Catal.*, 2017, **7**, 1244–1247; (*e*) A. Baishya, S. Baruah and K. Geetharani, *Dalton Trans.*, 2018, 9231–9236; (*f*) J. Wu, H. Zeng, J. Cheng, S. Zheng, J. A. Golen, D. R. Manke and G. Zhang, *J. Org. Chem.*, 2018, **83**, 9442–9448; (*g*) U. K. Das, C. S. Higman, B. Gabidullin, J. E. Hein and R. Tom Baker, *ACS Catal.*, 2018, **8**, 1076–1081; (*h*) G. Zhang, J. Cheng, K. Davis, M. G. Bonifacio and C. Zajaczkowski, *Green Chem.*, 2019, **21**, 1114–1121.

2 (*a*) S. Chen, D. Yan, M. Xue, Y. Hong, Y. Yao and Q. Shen, *Org. Lett.*, 2017, **19**, 3382–3385; (*b*) Z. Huang, S. Wang, X. Zhu, Q. Yuan, Y. Wei, S. Zhou and X. Mu, *Inorg. Chem.*, 2018, **57**, 15069–15078; (*c*) W. Wang, X. Shen, F. Zhao, H. Jiang, W. Yao, S. A. Pullarkat, L. Xu and M. Ma, *J. Org. Chem.*, 2018, **83**, 69–74; (*d*) H. Liu, K. Kulbitski, M. Tamm and M. S. Eisen, *Chem. – Eur. J.*, 2018, **24**, 5738–5742.

3 (*a*) S. Harder, *Chem. Rev.*, 2010, **110**, 3852–3876; (*b*) K. Revunova and G. I. Nikonov, *Dalton Trans.*, 2015, **44**, 840–866; (*c*) C. C. Chong and R. Kinjo, *ACS Catal.*, 2015, **5**, 3238–3259; (*d*) M. S. Hill, D. J. Liptrot and C. Weetman, *Chem. Soc. Rev.*, 2016, **45**, 972–988; (*e*) G. I. Nikonov, *ACS Catal.*, 2017, **7**, 7257–7266; (*f*) D. Mukherjee and J. Okuda, *Angew. Chem., Int. Ed.*, 2017, **57**, 1458–1473; (*g*) S. Dagorne and R. Wehmschulte, *ChemCatChem*, 2018, **10**, 2509–2520.

4 (*a*) M. Arrowsmith, T. J. Hadlington, M. S. Hill and G. Kociok-Köhn, *Chem. Commun.*, 2012, **48**, 4567–4569; (*b*) T. J. Hadlington, M. Hermann, G. Frenking and C. Jones, *J. Am. Chem. Soc.*, 2014, **136**, 3028–3031; (*c*) C. C. Chong, H. Hirao and R. Kinjo, *Angew. Chem., Int. Ed.*, 2014, **54**, 190–194; (*d*) Z. Yang, M. Zhong, X. Ma, S. De, C. Anusha, P. Parameswaran and H. W. Roesky, *Angew. Chem., Int. Ed.*, 2015, **54**, 10225–10229; (*e*) J. Schneider, C. P. Sindlinger, S. M. Freitag, H. Schubert and L. Wesemann, *Angew. Chem., Int. Ed.*, 2016, **56**, 333–337; (*f*) Y. Wu, C. Shan, Y. Sun, P. Chen, J. Ying, J. Zhu, L. (Leo) Liu and Y. Zhao, *Chem. Commun.*, 2016, **52**, 13799–13802; (*g*) V. K. Jakhar, M. K. Barman and S. Nembenna, *Org. Lett.*, 2016, **18**, 4710–4713; (*h*) M. K. Bisai, S. Pahar, T. Das, K. Vanka and S. S. Sen, *Dalton Trans.*, 2017, **46**, 2420–2424; (*i*) J. R. Lawson, L. C. Wilkins and R. L. Melen, *Chem. – Eur. J.*, 2017, **23**, 10997–11000.

5 (*a*) D. Mukherjee, A. Ellern and A. D. Sadow, *Chem. Sci.*, 2014, **5**, 959–964; (*b*) L. Fohlmeister and A. Stasch, *Chem. – Eur. J.*, 2016, **22**, 10235–10246; (*c*) D. Mukherjee, S. Shirase, T. P. Spaniol, K. Mashima and J. Okuda, *Chem. Commun.*, 2016, **52**, 13155–13158; (*d*) K. Manna, P. Ji, F. X. Greene and W. Lin, *J. Am. Chem. Soc.*, 2016, **138**, 7488–7491; (*e*) S. Yadav, S. Pahar and S. S. Sen, *Chem. Commun.*, 2017, **53**, 4562–4564.

6 (*a*) D. Mukherjee, H. Osseili, T. P. Spaniol and J. Okuda, *J. Am. Chem. Soc.*, 2016, **138**, 10790–10793; (*b*) H. Osseili, D. Mukherjee, K. Beckerle, T. P. Spaniol and J. Okuda, *Organometallics*, 2017, **36**, 3029–3034.

7 (*a*) R. McLellan, A. R. Kennedy, R. E. Mulvey, S. A. Orr and S. D. Robertson, *Chem. – Eur. J.*, 2017, **23**, 16853–16861; (*b*) V. A. Pollard, S. A. Orr, R. McLellan, A. R. Kennedy, E. Hevia and R. E. Mulvey, *Chem. Commun.*, 2018, **54**, 1233–1236.

8 I. P. Query, P. A. Squier, E. M. Larson, N. A. Isley and T. B. Clark, *J. Org. Chem.*, 2011, **76**, 6452–6456.

9 S. J. Yang, A. K. Jaladi, J. H. Kim, S. Gundeti and D. K. An, *Bull. Korean Chem. Soc.*, 2019, **40**, 34–38.

10 Y. Wu, C. Shan, J. Ying, J. Su, J. Zhu, L. L. Liu and Y. Zhao, *Green Chem.*, 2017, **19**, 4169–4175.

11 Z. Zhu, X. Wu, X. Xu, Z. Wu, M. Xue, Y. Yao, Q. Shen and X. Bao, *J. Org. Chem.*, 2018, **83**, 10677–10683.

12 K. Kucinski and G. Hreczycho, *Green Chem.*, 2019, **21**, 1912–1915.

13 M. K. Bisai, T. Das, K. Vanka and S. S. Sen, *Chem. Commun.*, 2018, **54**, 6843–6846.

14 P. Kaur, G. Khatik and S. Nayak, *A Review on Advances in Organoborane-Chemistry: Versatile Tool in Asymmetric Synthesis*, 2016, vol. 14.

15 D. G. Hall, in *Boronic Acids: Preparation and Applications in Organic Synthesis and Medicine*, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, FRG, 2006, pp. 1–99.

16 R. Maji, S. C. Mallojjala and S. E. Wheeler, *Chem. Soc. Rev.*, 2018, **47**, 1142–1158.

17 H. C. Brown, J. S. Cha and B. Nazer, *Inorg. Chem.*, 1984, **23**, 2929–2931.

