ChemComm

COMMUNICATION

View Article Online
View Journal

Cite this: DOI: 10.1039/c8cc08841a

Received 6th November 2018,
Accepted 21st December 2018

DOI: 10.1039/c8cc08841a

rsc.li/chemcomm

Facile reduction of carboxylic acids to primary alcohols under catalyst-free and solvent-free conditions†

Adimulam Harinath, ‡ Jayeeta Bhattacharjee ‡ and Tarun K. Panda *

We report the development of a facile protocol for the deoxygenative hydroboration of aliphatic and aryl carboxylic acids to afford corresponding primary alcohols under solvent-free and catalyst-free conditions. The reaction proceeds under ambient temperature exhibits good tolerance towards various functional groups and generates quantitative yields. The plausible mechanism involves the formation of Lewis acid–base adducts as well as the liberation of hydrogen gas.

The catalytic reduction of carboxylic acids into alkyl boronate esters is one of the most elementary and extensively employed transformations in synthetic organic chemistry.[1] Their availability, stability, and inexpensiveness make them attractive precursors for the synthesis of alcohols.[2] Numerous methods have been developed for the reduction of carboxylic acids to corresponding alcohols. Traditional methods involve highly reactive stoichiometric metal hydrides such as $LiAlH_4$ or $Zn(BH_4)_2$ or $NaBH_4$ or borane-reducing agents such as $BH_3{\cdot}SMe_2$ or 9-BBN solution (Fig. 1). However, these methods have their own drawbacks, such as the generation of inorganic waste, poor selectivity, air, and moisture sensitivity and the requirement of activators.[3] Although a wide range of expensive homogeneous and heterogeneous metal catalysts have been reported in the literature as being useful for the hydrogenation of carboxylic acids into alcohols, the methods used not only require harsh conditions such as high-pressure instruments and high temperature but also result in a selective reduction of aromatic rather than aliphatic carboxylic acids.[4]

On the other hand, transition metal-mediated hydrosilylation of carboxylic acids into alcohols has been extensively studied in the literature, albeit that this method shows limited substrate scope and substrate-dependent product selectivity, whether aldehyde or alcohol.[5] In contrast to hydrosilylation of carboxylic acids, catalytic hydroboration of carboxylic acids is not well explored in the literature. Very recently Gunanathan *et al.* reported a ruthenium-based catalyst for the deoxygenative hydroboration of carboxylic acids into alkyl boronates which upon further hydrolysis gives corresponding primary alcohols[6] (Fig. 1). Also, Leitner *et al.* reported the manganese pincer complex $[Mn(Ph_2PCH_2SiMe_2)_2{-}NH(CO)_2Br]$ that enables catalytic reductive functionalization for a broad range of substrates such as carboxylic acids, carbonates, and even CO_2 through hydroboration using pinacolborane as reducing agent.[7]

Thus, developing an alternative green protocol for chemoselective reduction of carboxylic acids to primary alcohols with wider functional group tolerance is still desirable. A solvent-free as well as a catalyst-free approach not only simplifies the reaction experimentally but also reduces the amount of waste which, in turn, reduces the environmental impact.[8,9] Nonetheless, catalyst-free or

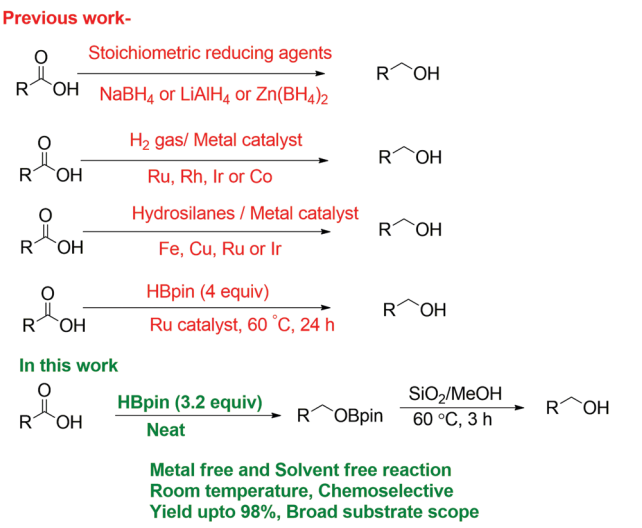


Fig. 1 Methods for reducing carboxylic acids to primary alcohols.

Department of Chemistry, Indian Institute of Technology Hyderabad, Kandi, Sangareddy 502285, Telangana, India. E-mail: tpanda@iith.ac.in; Fax: +91 40 2301 6032; Tel: +91 40 2301 6036

† Electronic supplementary information (ESI) available: Experimental details for the catalytic reactions, ^1H, $^{13}C\{^1H\}$ and $^{11}B\{^1H\}$ spectra of **1a–1z**, **2a–2m**, and **3a–3d**. See DOI: 10.1039/c8cc08841a

‡ Both the authors contributed equally to this work.

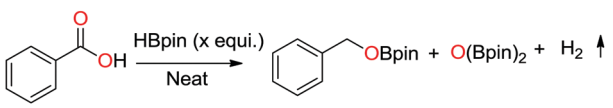
metal-free strategies to achieve the targeted molecule are not yet fully explored, apart from the pioneering research developed by Knochel *et al.* (hydroboration of alkenes),[10] Piers *et al.* (hydroboration of alkynes)[11,12] and Hreczycho *et al.* (hydroboration of aldehydes).[13] Hence, we became interested in developing a green protocol for the reduction of carboxylic acids to corresponding primary alcohols. Numerous research groups are working to develop metal-free and solvent-free organic reactions, and recently, a green protocol was developed by Bertrand *et al.* for the synthesis of amino boranes under catalyst-free conditions.[14] Hreczycho also reported the catalyst-free *O*-borylation of silanols and catalyst-free hydroboration of aldehydes under mild conditions.[15] Further, Xaio-Feng *et al.* reported the borylation of aryldiazonium salts under catalyst-free conditions.[16]

To examine the possibility of hydroboration of carboxylic acids under catalyst-free and solvent-free conditions, we carried out initial reactions using benzoic acid with various concentrations of HBpin under neat conditions. To our delight, we observed the smooth hydroboration of benzoic acid (1 mmol) to the corresponding boronate ester exclusively when HBpin (4 mmol, 3.5 mmol, and 3.2 mmol) was used. However, the reaction was slower in the presence of organic solvents such as THF, hexane, and toluene. The optimised results are tabulated in Table 1.

Armed with the knowledge of optimised conditions to explore the potential of this protocol, we then examined the reaction of a wide range of aromatic, aliphatic and heterocyclic carboxylic acids with electron-rich and electron-poor functional groups. All the carboxylic acids underwent smooth deoxygenative hydroboration and afforded the corresponding boronate esters quantitatively (up to 99% yield) with the liberation of hydrogen gas. Table 2 shows the summary of results.

Carboxylic acids with electron-donating groups such as 4-methyl and 4-methoxy benzoic acids proceeded to react smoothly with HBpin to furnish the corresponding boronate esters **1b** and **1c** with 99% conversion (Fig. FS4–9 in ESI†). There was no trace of over-reduced products, which is usually observed during iron-catalysed hydrosilylation of carboxylic acids.

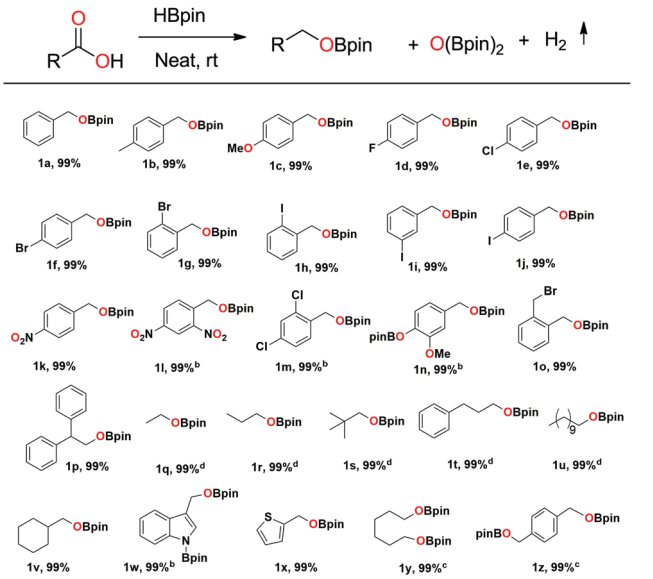
Table 1 Screening of catalytic reduction of carboxylic acids to primary alcohols using HBpin and benzoic acid



Entry	HBpin (*x* equiv.)	Solvent	Time (h)	Conversion (%)
1	4	Neat	6	70
2	4	Neat	8	99
3	3.5	Neat	8	99
4	3.2	Neat	8	99
5	3.2	THF	8	60
6	3.2	Tol	8	60
7	3.2	Hexane	8	40

Reaction conditions: benzoic acid (1 mmol) with pinacolborane at room temperature. The yield was calculated on the basis of characteristic product signal present in the reaction mixture using HMB (hexamethylbenzene) as the internal standard.

Table 2 Substrate scope for the hydroboration of carboxylic acids[a]

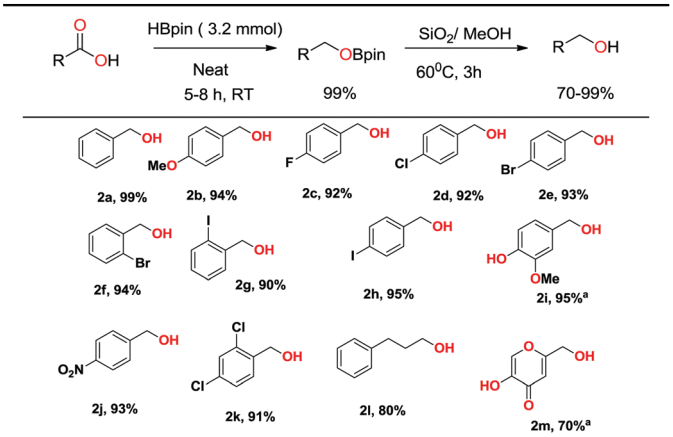


[a] Reaction conditions: carboxylic acids (0.25 mmol), HBpin (0.80 mmol), 5–8 hours. The yield calculated on the basis of ^{1}H NMR (400 MHz) integration of characteristic product signal present in the reaction mixture using HMB (hexamethyl benzene) as the internal standard. [b] HBpin (1.05 mmol). [c] HBpin (1.60 mmol). All reactions were performed at room temperature. [d] Reaction was conducted for five hours.

The reactions of 4-fluro, 4-chloro, 4-bromo and 4-iodo benzoic acids with HBpin produced a near-quantitative conversion to exclusive corresponding boronate esters **1d–1j**, confirming that electron-withdrawing groups had no impact on this reaction (Fig. FS10–31 in ESI†). Use of *o*- and *p*- substituted iodo benzoic acid also gave the corresponding products **1g**, **1h** and **1i** in quantitative yields (Fig. FS20–28 in ESI†). Benzoic acids with highly electron-deficient functional groups such as 4-nitro- and 2,4-nitrobenzoic acids were chemoselectively converted to corresponding boronate esters **1k–1m**, yielding up to 99% (Fig. FS32–40 in ESI†).

Next, we extended our substrate scope to aliphatic carboxylic acids, in order to explore the generality of the protocol. The initial reaction was carried out using acetic acid with HBpin in neat condition at room temperature. The reaction proceeded smoothly with the vigorous evolution of hydrogen gas and yielded the corresponding boronate ester **1q** quantitatively within five hours (Fig. FS50–52 in ESI†). Further, the reaction with propionic acid and phenyl propionic acid similarly yielded compounds **1r** and **1t** respectively in quantitative yield within eight hours (Fig. FS53–55 and FS59–61 in ESI†). Additionally, carboxylic acid with long-chain alkyl, undecanoic acid also efficiently converted to the corresponding boronate ester **1u** quantitatively (Fig. FS62–64 in ESI†). Carboxylic acids with heterocycles such as indole 3 acetic acid and thiophene carboxylic acid were also converted smoothly to give corresponding boronate esters **1w** and **1x** respectively in quantitative yields (Fig. FS68–73 in ESI†). Reaction with the bulkier aliphatic acid such as pivalic acid also proceeded smoothly in converting to its corresponding ester **1s** exclusively (Fig. FS56–58 in ESI†). Similarly, the reaction

Table 3 Hydrolysis of boronate ester to achieve corresponding primary alcohols

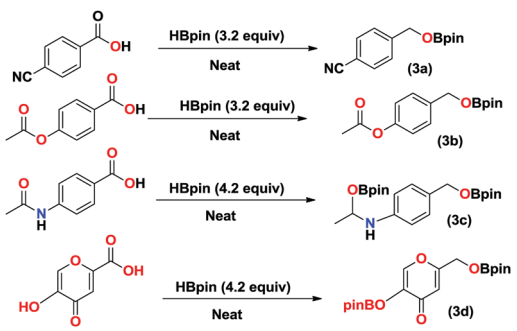


Reaction conditions: carboxylic acids (0.25 mmol) and HBpin (0.80 mmol) were stirred together for 5–8 hours in room temperature; isolated yields and products were purified by column chromatography. [a] HBpin (1.05 mmol) was used.

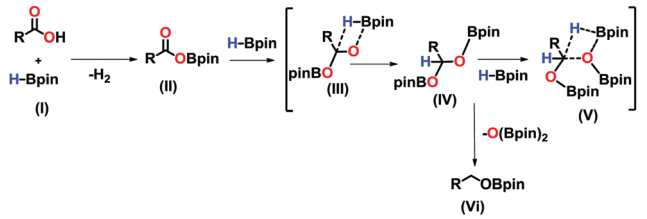
with dicarboxylic acids such as adipic acid and terephthalic acid also occurred efficiently to yield boronate esters **1y** and **1z**, indicating the versatile substrate scope of this protocol (Fig. FS74–79 in ESI†).

Further, we hydrolysed the selected boronate esters to their alcohols using known methodology[6] and in all cases, we obtained near-quantitative yields (**2a–2m**) (Fig. FS80–104, ESI†). The results are summarised in Table 3. Additionally, to examine the chemoselectivity of this methodology, we treated 4-cyano benzoic acid and 4-acetoxy benzoic acid with HBpin and observed the formation of exclusive deoxygneative hydroboration with acid functionality after 8 h. No trace of a corresponding product from hydroboration of the nitrile or ester moiety was found, indicating chemoselective hydroboration of the acid group (Fig. FS106–111 in ESI†). Additionally, in the reaction with 4-acetamido benzoic acid, both the acid and amido functionalities underwent hydroboration over dehydrocoupling of NH with HBpin in the substrate (Fig. FS112–114 in ESI†).[13] However, 5-hydroxy-4-oxo-4*H*-pyran-2-carboxylic acid underwent chemo-selective deoxygenative hydroboration, yielding only the corresponding boronate ester (Scheme 1, **3a–3d**, Fig. FS115–118 in ESI†).

In light of this outcome and previously reported literature reports[13,17] the most plausible mechanism for the deoxygenative



Scheme 1 Chemoselective hydroboration of carboxylic acids (**3a–3d**).



Scheme 2 Proposed mechanism for hydroboration of carboxylic acids.

hydroboration of carboxylic acid is depicted in Scheme 2. In the first step, cross-dehydrocupling of the COOH group occurs with HBpin, leading to the formation of intermediate species **II** with the elimination of H_2 gas. In the next step, the second molecule of HBpin reacts with species **II** to form a four-membered cyclic species **III**, which further rearranges itself to form **IV**. Species **IV** further reacts with the third molecule of HBpin through another four-membered cyclic intermediate to afford the desired boronate ester through the liberation of $[O(Bpin)_2]$ as a side product which was confirmed by ^1H, ^{11}B NMR spectra of all the boronate esters (**1a–1z**).

To summarise, we have developed a simple and facile protocol for the deoxygenative hydroboration of carboxylic acids to corresponding boronate esters under catalyst-free and solvent-free conditions, which upon hydrolysis furnishes primary alcohols. This reaction proceeds with quantitative chemo selective yields, exhibiting a broader substrate scope with both aliphatic and aromatic carboxylic acids, in short reaction times.

This work is supported by the JICA FRIENDSHIP Project under the Collaboration Kick-starter Programme (CKP). A. H. and J. B. thank CSIR and UGC India respectively for their PhD fellowships. We thank Prof. Kazushi Mashima and Prof. Hayato Tsurugi, Osaka University, Japan, for their generous support. We are also thankful to Dr S. R. Dey and Prof. Ch. Subrahmanyam, IIT Hyderabad for their help.

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 (*a*) N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457–2483; (*b*) A. J. Lennox and G. C. Lloyd-Jones, *Chem. Soc. Rev.*, 2014, **43**, 412–443; (*c*) H. C. Brown, G. W. Kramer, A. B. Levy and M. M. Midland, *Organic Syntheses via Boranes*, Wiley-Interscience, New York, 1975, vol. 1; (*d*) A. Pelter, K. Smith and H. C. Brown, *Borane Reagents*, Academic Press, London, 1988.
2 L. J. Gooßen, L. Rodriguez and K. Gooßen, *Angew. Chem., Int. Ed.*, 2008, **47**, 3100–3120.
3 (*a*) J. Seyden-Penne, *Reductions by the Alumino- and Borohydrides in Organic Synthesis*, Wiley, New York, 2nd edn, 1997; (*b*) P. N. Rylander, *Catalytic Hydrogenation in Organic Syntheses*, Academic Press, New York, 1979; (*c*) G. Kokotos and C. Noula, *J. Org. Chem.*, 1996, **61**, 6994–6996; (*d*) M. Bagheri and M. Karimkoshteh, *Iran. J. Chem. Chem. Eng.*, 2017, **36**, 37–43; (*e*) Y. Suseela and M. Periasamy, *Tetrahedron*, 1992, **48**, 371–376; (*f*) J. V. B. Kanth and M. Periasamy, *J. Org. Chem.*, 1991, **56**, 5964–5965; (*g*) S. Narasimhan, S. Madhavan and K. Ganeshwar Prasad, *J. Org. Chem.*, 1995, **60**, 5314–5315.
4 (*a*) T. Vom Stein, M. Meuresch, D. Limper, M. Schmitz, M. Holscher, J. Coetzee, D. J. Cole-Hamilton, J. Klankermayer and W. Leitner,

J. Am. Chem. Soc., 2014, **136**, 13217–13225; (*b*) J. Ullrich and B. Breit, *ACS Catal.*, 2018, **8**, 785–789; (*c*) T. P. Brewster, A. J. M. Miller, D. M. Heinekey and K. I. Goldberg, *J. Am. Chem. Soc.*, 2013, **135**, 16022–16025; (*d*) T. J. Korstanje, J. I. van der Vlugt, C. J. Elsevier and B. De Bruin, *Science*, 2015, **350**, 298–302; (*e*) X. Cui, Y. Li, C. Topf, K. Junge and M. Beller, *Angew. Chem., Int. Ed.*, 2015, **54**, 10596–10599; (*f*) J. E. Carnahan, T. A. Ford, W. F. Gresham, W. E. Grigsby and G. F. Hager, *J. Am. Chem. Soc.*, 1955, **77**, 3766–3768; (*g*) F. M. A. Geilen, B. Engendahl, M. Holscher, J. Klankermayer and W. Leitner, *J. Am. Chem. Soc.*, 2011, **133**, 14349–14358.

5 (*a*) L. C. Misal Castro, H. Li, J. B. Sortais and C. Darcel, *Chem. Commun.*, 2012, **48**, 10514–10516; (*b*) Y. J. Zhang, W. Dayoub, G. R. Chen and M. Lemaire, *Tetrahedron*, 2012, **68**, 7400–7407; (*c*) J. A. Fernandez-Salas, S. Manzini and S. P. Nolan, *Adv. Synth. Catal.*, 2014, **356**, 308–312; (*d*) Y. Corre, V. Rysak, X. Trivelli, F. Agbossou-Niedercorn and C. A. Michon, *Eur. J. Org. Chem.*, 2017, 4820–4826; (*e*) J. Zheng, S. Chevance, C. Darcel and J. B. Sortais, *Chem. Commun.*, 2013, **49**, 10010–10012.

6 S. Kishan, V. Krishna Kumar and C. Gunanathan, *ACS Catal.*, 2018, **8**, 4772–4776.

7 C. Erken, A. Kaithal, S. Sen, T. Weyhermüller, M. Hölscher, C. Werlé and W. Leitner, *Nat. Commun.*, 2018, **9**, 4521.

8 M. B. Gawande, V. D. Bonifacio, R. Luque, P. S. Branco and R. S. Varma, *ChemSusChem*, 2014, **7**, 24–44.

9 S. Anirban, S. Sougata, K. K. Shrishnu, H. Alakananda, V. Z. Grigory, N. C. Oleg, N. C. Valery and M. Adinath, *Green Chem.*, 2016, **18**, 4475–4525.

10 C. E. Tucker, J. Davidson and P. Knochel, *J. Org. Chem.*, 1992, **57**, 3482–3485.

11 D. J. Parks and W. E. Piers, *Tetrahedron*, 1998, **54**, 15469–15488.

12 D. J. Parks, W. E. Piers and G. P. A. Yap, *Organometallics*, 1998, **17**, 5492–5503.

13 H. Stachowiak, J. Kaźmierczak, K. Kuciński and G. Hreczycho, *Green Chem.*, 2018, **20**, 1738–1742.

14 E. A. Romero, J. L. Peltier, R. Jazzar and G. Bertrand, *Chem. Commun.*, 2016, **52**, 10563–10565.

15 K. Kuciński and G. Hreczycho, *ChemSusChem*, 2017, **10**, 4695–4698.

16 Q. Xinxin, L. Hao-peng, P. Jin-Bao and W. Xiao-Feng, *Tetrahedron Lett.*, 2017, **58**, 3851–3853.

17 J. V. Bhaskar Kanth and M. Periasamy, *J. Org. Chem.*, 1991, **56**, 5964–5965.

