Chinese Chemical Letters 34 (2023) 108048

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

Transition-metal-free coupling reactions involving *gem*–diborylalkanes

Yongli Li, Dalong Shen, Hao Zhang, Zhenxing Liu*

College of Chemistry, Zhengzhou University, Zhengzhou 450002, China

ARTICLE INFO

Article history:
Received 25 September 2022
Revised 22 November 2022
Accepted 6 December 2022
Available online 8 December 2022

Keywords:
Transition-metal-free
Coupling reactions
gem–Diborylalkane
Sustainable chemistry
Radical

ABSTRACT

Due to the increasing demand for the sustainability of modern organic chemistry, the development of green and powerful methods for C-C and C-B bond formation is highly desired. Among them, the transition-metal-free coupling reactions of *gem*–diborylalkanes emerge as one valuable tool for organic chemists in the last decade. The review covers selected representative examples. A comparison of these reactions with transition-metal-catalyzed reactions is provided. The recent example of α-boryl radical formation from *gem*–diborylalkanes is also briefly discussed.

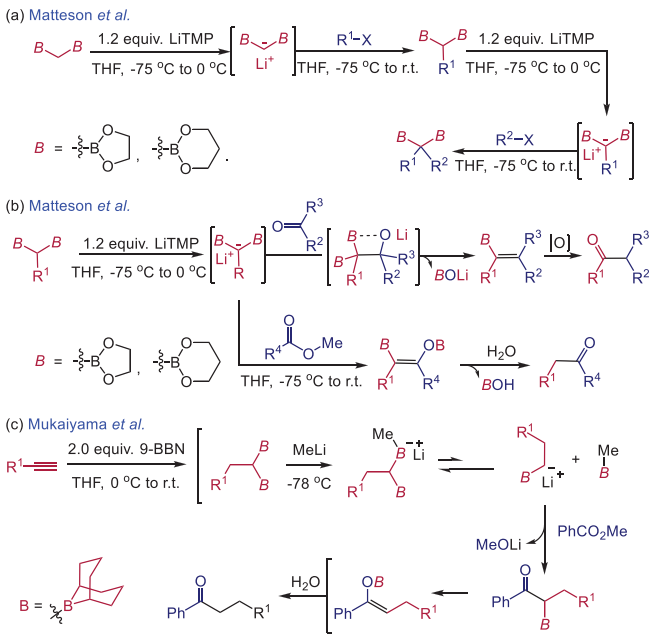
1. Introduction

Coupling reactions are now one of the most widely-used ways to construct molecule skeletons in organic synthesis, material science, and the pharmaceutical industry. Transition metal catalysis, notably those with noble metals (Pd, Ir, Rh, *etc.*), has been the mainstream in the development of such reactions, for example, the palladium-catalyzed carbon-carbon bond formation reactions [1–3]. Although successful, there are several issues with transition metal catalysis. One of them is the dwindling storage of noble metals on earth, which increases the price of many transition metal catalysts. The other issue is the metal residual contamination in the preparation of chemicals, which causes additional costs to remove them, especially in the pharmaceutical industry [4]. Furthermore, such transition metal catalysis is limited to a certain range of reactions, overreliance on which may ossify the chemical synthesis. Due to these issues, researchers are thrilled to discover novel synthetic methodologies, thus enabling a more sustainable chemical manufacturing process and wider chemical space to be found. In the last decades, transition-metal-free coupling reactions have emerged as an alternative and green way to make carbon-carbon and carbon-heteroatom bonds. These include not only the surrogates for classical transition-metal catalyzed coupling reactions but also brand-new reactions [5–7].

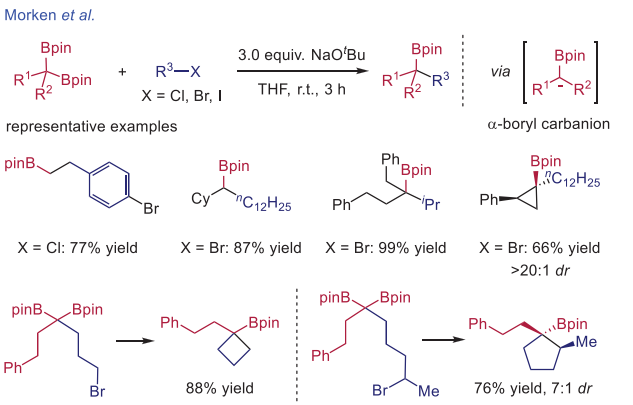
gem–Diborylalkanes, namely the 1,1-diboryl-substituted alkanes, have recently gained popularity in many aspects due to their versatile properties. These compounds have multi-sites to be functionalized. The α-C-Hs, if applicable, are acidic and can be easily deprotonated to afford the α,α-diboryl carbanions. On the other hand, the boryl group can be deborylated in the presence of a proper nucleophile to get the α-boryl carbanions. Both carbanions are stabilized by the α-boryl group and have found utilities in certain reactions [8–11]. In the early 1970s, Matteson and co-workers found that the reaction of ethylene glycol methanediboronate or bis(trimethylenedioxyboryl)methane with lithium 2,2,6,6-tetramethylpiperidide (LiTMP) yielded the carbanion at −75 °C, which could be alkylated with alkyl halides. The obtained *gem*–diborylalkanes could be further deprotonated and alkylated, offering a general way to prepare various *gem*–diborylalkane derivatives (Scheme 1a) [12]. When the α,α-diboryl carbanions were treated with ketone or aldehyde, alkenyl boronates were formed through the B-O elimination process. They could also react with the ester to make α-boryl enol borate (Scheme 1b) [13,14]. These obtained organoboron compounds were sensitive to moisture or oxygen and usually *in situ* transformed into ketone or aldehyde by oxidation or hydrolysis. One disadvantage of this method is the poor availability of the starting unsubstituted *gem*–diborylalkane, which needs several-step synthesis from triboryl or tetraboryl methane. In 1981, Mukaiyama and co-workers disclosed a novel aldol reaction involving α-boryl carbanion and ester (Scheme 1c) [15]. The α-boryl carbanion was derived from the deborylation of *gem*–diborylalkanes, which could be easily obtained by double hydroboration of terminal alkynes with 9-borabicyclo[3,3,1]nonane (9-BBN). The *gem*–diborylalkanes, however, were not stable and isolable.

* Corresponding author.
E-mail address: liuzhenxing@zzu.edu.cn (Z. Liu).

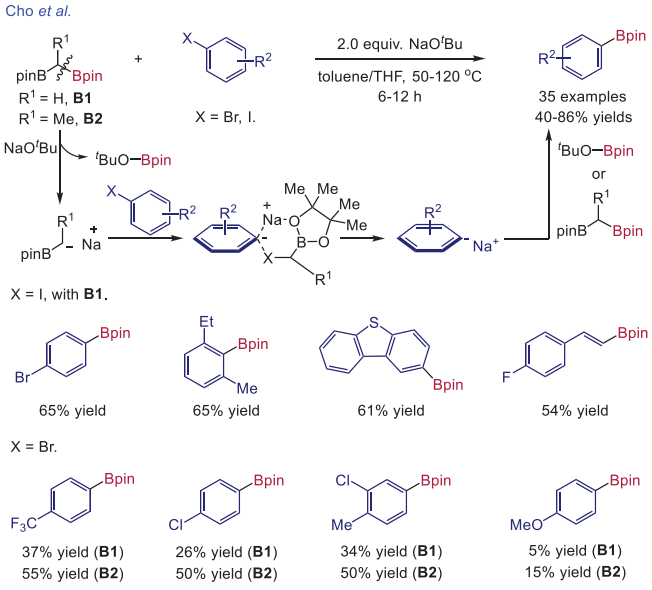
https://doi.org/10.1016/j.cclet.2022.108048
1001-8417/



Scheme 1. Earlier work on the transition-metal-free coupling reactions of *gem*–diborylalkanes.



Scheme 2. Transition-metal-free coupling deborylation-alkylation reactions of *gem*–diborylalkanes.



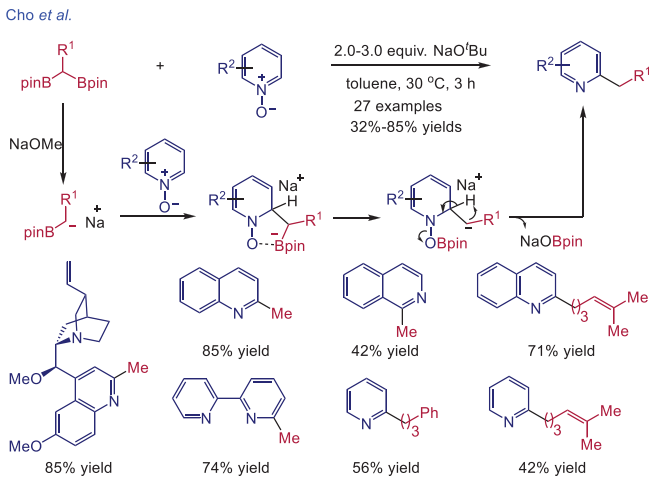
Scheme 3. Borylation of aromatic bromide/iodides using *gem*–diborylalkanes as borylation reagent.

This review discusses some recently developed coupling reactions of *gem*–diborylalkanes and their applications in organic synthesis. The contents discussed here are not a comprehensive collection of reactions but only selected examples. The selection criteria mainly include two aspects: (1) The reaction should be relatively general and has a reasonable substrate scope; (2) The reaction is better to be the fundamental transformations, for example, C-C/C=C bond formation and C-B bond formation. This review aims to draw the attention of more researchers to this field and stimulate the discovery of more promising applications based on this type of compound. Researchers in academia, fine chemical companies, and the pharmaceutical industry would all find this topic useful. Readers who are interested in the nucleophilic ring-opening reactions, 1,2-boryl shift process, and transition metal catalyzed reactions of *gem*–diborylalkanes are referred to some excellent reviews [16–19].

2. C-C and C-B bond formation

In 2014, the Morken group at Boston College reported a convenient deborylation-alkylation method to make alkyl Bpin from 1,1-bis[(pinacolato)boryl]alkanes (Scheme 2) [20]. Formally, this reaction could be viewed as a Suzuki-type coupling reaction for C(sp^3)-C(sp^3) bond formation. The reaction applies to primary, secondary, and tertiary alky Bpin compounds. Geminal bis(boryl)cyclopropanes could be functionalized in good yield and excellent diastereoselectivity. An intramolecular version of the reaction gave access to a range of cyclic alkyl Bpin with different ring sizes, which were otherwise difficult to prepare using other methods. The reaction possibly occurred *via* the α-boryl carbanion intermediate, like the aldol reaction mentioned in the introduction. Yet, two features of the reaction make it stand out. First, the starting 1,1-bis[(pinacolato)boryl]alkanes are readily available and bench-stable. Most of them are fine solids and can be easily made in grams in one batch. The unsubstituted $CH_2(Bpin)_2$ can be now purchased from many chemical manufacturers. Also, the reaction conditions are extremely simple and mild, under which the reaction can be completed by employing the widely used sodium *tert*–butanol (NaO^tBu) as the base. These merits make this method a practical way to make various functionalized alkyl Bpin and open the door for many more elegant transition-metal-free coupling reactions using 1,1-bis[(pinacolato)boryl]alkanes as the starting materials.

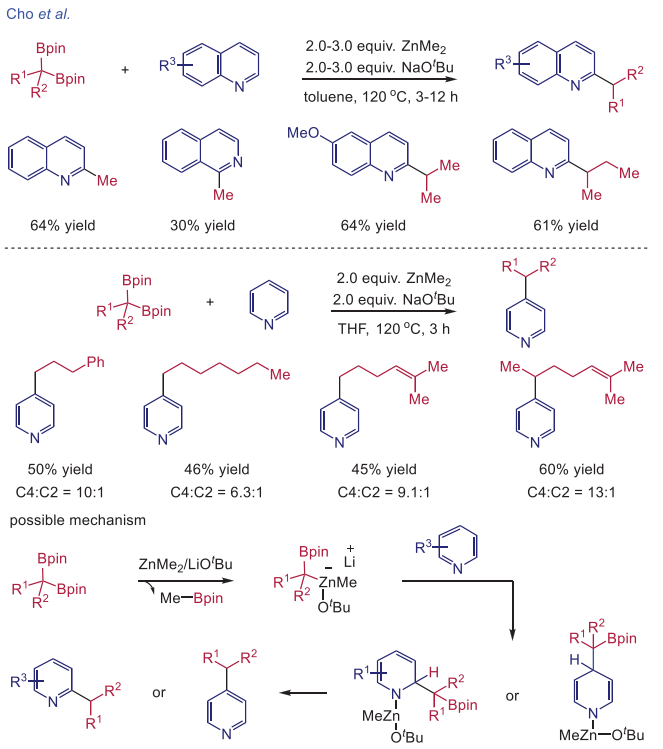
In the deborylation-alkylation process, the pinB-O^{t}Bu was formed as a by-product. Later in 2017, the deborylation process was cleverly used in the C-B bond formation reaction (Scheme 3) [21]. Unsubstituted *gem*–diborylalkane (**B1**) and methyl-substituted one (**B2**) were employed as the borylation reagent with NaO^tBu as a base. For aromatic iodides, commercially available **B1** worked well to afford the aromatic Bpin. For less reactive aromatic bromides, **B2** was generally better than **B1**, probably due to electronic factors. Mechanistic studies suggest the possible formation of Lewis acid/base adduct between organohalides and α-boryl carbanion. The obtained nucleophile then reacts with pinB-O^{t}Bu or *gem*–diborylalkane (**B1** or **B2**), affording the final products. Compared with the classical transition-metal-catalyzed borylation reaction (Pd-catalyzed Miyaura borylation, *etc.*), this is a rare example of a transition-metal-free borylation method, featuring good chemoselectivity (reactivity: I > Br > Cl) and functional group tolerance.



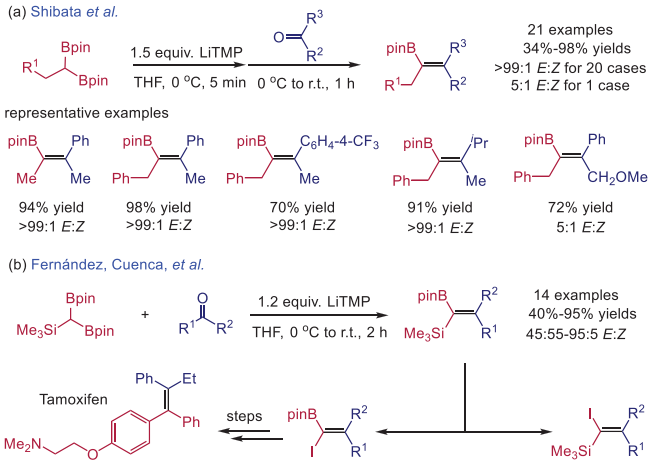
Scheme 4. C2-alkylation of pyridine *N*-oxides using *gem*–diborylalkanes as alkylating reagents.

The α-boryl carbanions obtained could also attack pyridine *N*-oxides, followed by boron migration from carbon to oxygen, intramolecular C2-H deprotonation, and aromatization (Scheme 4) [22]. The products obtained were C2-alkylated pyridine derivatives, which often require metal catalysts or suffer from regioselectivities with the established methods. $CH_2(Bpin)_2$ here behaved as a methyl source, which was less developed in the alkylation of pyridine derivatives, such as quinolines and isoquinolines. Other 1,1-diborylalkanes also worked well under the current conditions. All reactions had excellent C2 selectivity, thus enabling its application in the late-stage functionalization of complex molecules, for example, 9-*O*-methylquinine *N*-oxide.

In 2020, the same group found that the alkylation could work directly towards pyridine/quinoline when dimethyl zinc ($ZnMe_2$) was added as an additive and lithium *tert*–butanol (LiO^tBu) was the base (Scheme 5) [23]. The reaction had excellent C2 selectivity for substituted pyridine and quinoline derivatives. C4 selectivity was observed for unsubstituted pyridine (C4:C2 = 6.3:1–13:1). The reaction is proposed to start with the formation of α-boryl carbanion by the combination of $ZnMe_2$ and LiO^tBu. Nucleophilic addition then occurs between α-boryl carbanion and *N*-heterocycle at C2 or C4 position with zinc as Lewis acid activator. Oxidative aromatization finally delivers the alkylated products. These two reactions constitute the transition-metal-free analogues of the challenging C-H functionalization of pyridines.



Scheme 5. C2/C4-alkylation of pyridine *N*-oxides using *gem*–diborylalkanes as the alkylating reagent.



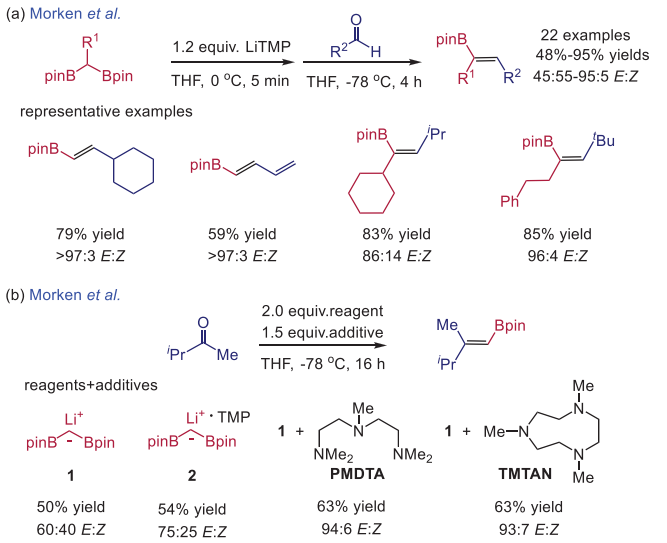
Scheme 6. Stereoselective synthesis of tetrasubstituted alkenes.

3. C=C bond formation

In the early work by Matteson and co-workers, they have shown that reaction between 1,1-diborylalkanes and aldehyde/ketone would form the alkenyl boronates compounds. The problem is the instability of the corresponding alkenyl boronates. With the development of coupling reactions, alkenyl boronates become more and more useful. They can be used as valuable building blocks in many important transformations. So, the discovery of practical and stereoselective methods to make them is highly desirable.

In 2010, Shibata, Endo and co-workers used the 1,1-bis[(pinacolato)boryl]alkanes as coupling partners for efficient tetrasubstituted alkenyl Bpin formation (Scheme 6a) [24,25]. The products were isolable through silica gel column chromatography. As of note was the *E* stereoselectivity for most substrates. The coordinating group could change stereoselectivity (>99:1 *vs.* 5:1 for OMe-containing substrate). In 2016, Fernández, Cuenca, and co-workers reported the application of $CH(Bin)_2(SiMe_3)$ as a coupling partner for the synthesis of 1-$SiMe_3$–1-Bpin-tetrasubstituted alkenes (Scheme 6b) [26]. The *E*:*Z* ratios ranged from 45:55 to 99:1. It is important to mention that even though configuration-defined tetrasubstituted alkenes and their analogues are of interest or have already been drug molecules (for example, tamoxifen) in the pharmaceutical industry, stereoselective methods for tetrasubstituted alkene synthesis are very rare. The two methods developed have been applied to the stereoselective synthesis of tamoxifen and its derivatives. Besides, the $SiMe_3$ and Bpin groups can be easily transformed into other functional groups, like halogens.

In 2015, the Morken group has developed the practical method for various di-, and trisubstituted alkenyl Bpin from 1,1-diborylalkanes and aldehydes (Scheme 7a) [27]. For 1,2-



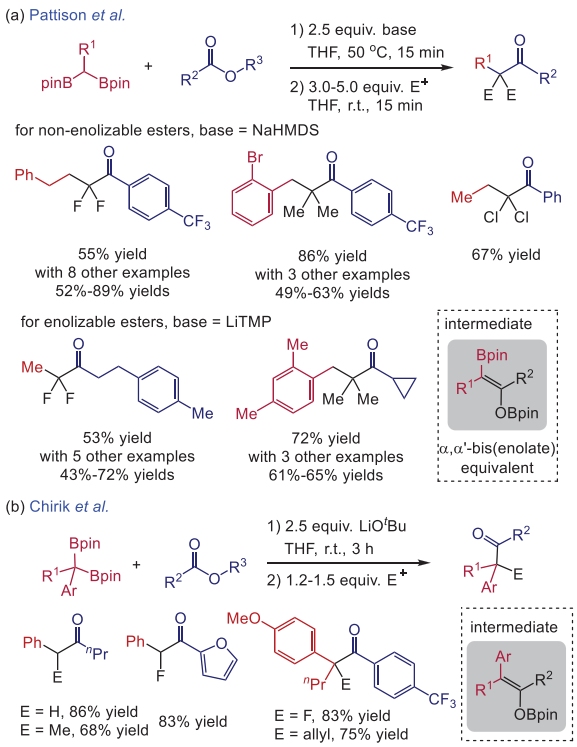
Scheme 7. Stereoselective synthesis of di-, and trisubstituted alkenes through boron-Wittig reaction.

disubstituted alkenyl Bpin, most of them had exclusively *E* selectivity. While the stereoselectivity of trisubstituted alkenyl Bpin was moderate to excellent. Later in 2019, the same group reported the reactions between deprotonated $CH_2(Bpin)_2$ with ketones (Scheme 7b) [28]. For the reaction with 3-methyl butan-2-one, the isolated $LiCH(Bpin)_2$ gave the product in 50% yield with 60:40 *E*:*Z*. The reaction with *in situ* formed $LiCH(Bpin)_2$ from $CH_2(Bpin)_2$ with LiTMP afforded the product with slightly higher yield and stereoselectivity (54% yield *vs*. 50% yield, 75:25 *E*:*Z* *vs*. 60:40 *E*:*Z*). This result was attributed to the existence of TMP in the *in situ* formed reagent. Based on this, the authors have explored several amine additives and found that triamine ligands, such as **PMDTA** and **TMTAN**, could greatly improve the stereoselectivity. The reason for the improved stereoselectivity might be that **PMTDA** and **TMTAN** help to convert the dimeric Li enolate into a monomer and thus facilitating the rapid B-O elimination to get the *E* isomer. Compared with other traditional methods for preparing these types of alkenes, it is clearly seen that the transition-metal coupling reactions involving *gem*–diborylalkanes enjoy good substrate scope and excellent stereoselectivity, especially those multi-substituted alkenes. Considering the versatile transformations of Bpin moiety, these reactions are expected to be used in many applications soon.

4. Coupling with carboxylic acid derivatives

Carboxylic acid derivatives are widespread compounds both in nature and in labs. Several decades after Matteson's report on the reaction between α,α-diboryl carbanion and ester, Pattison and co-workers further pushed this chemistry to a new level (Scheme 8a) [29]. The readily available 1,1-bis[(pinacolato)boryl]alkanes were used as substrates and the obtained intermediates could be viewed as bis(enolate) equivalents. In Matteson's report, these intermediates were only subject to hydrolysis. Here, three different electrophiles (NFSI, MeI, and trichloroisocyanuric acid) were used and various functionalized ketones were obtained. For non-enolizable esters, NaHMDS was enough to achieve a successful reaction. For enolizable esters, pre-addition of LiTMP and 1,1-diborylalkanes, followed by the addition of ester, was needed to ensure the efficiency of the reaction. This is probably due to the more efficient and complete deprotonation of the 1,1-diborylalkane with LiTMP than with NaHMDS.

Different from the basic yet less nucleophilic NaHMDS and LiTMP, metal *tert*–butanol salts are both basic and nucleophilic. Be-

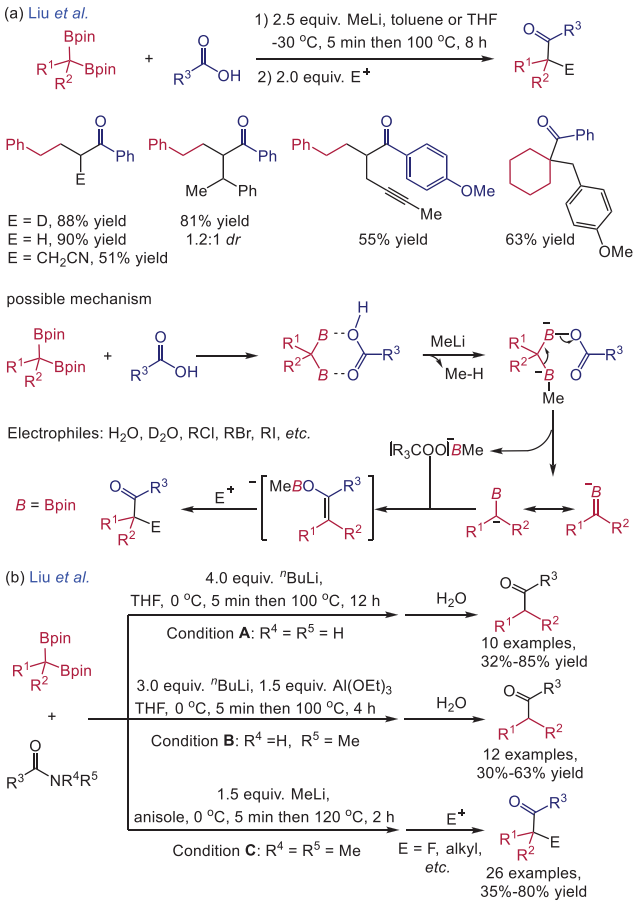


Scheme 8. Synthesis of functionalized ketones from *gem*-diborylalkanes and esters.

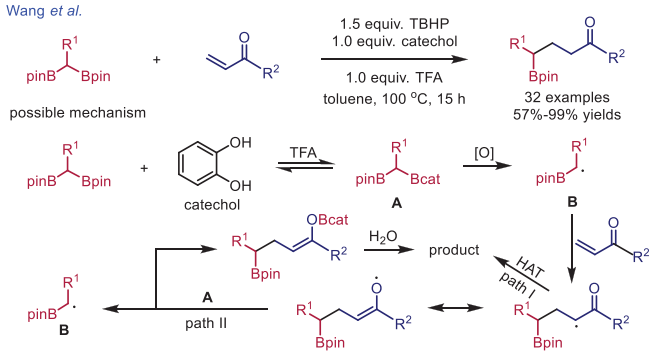
sides, metal *tert*–butanol salts easily attack the boryl species and form the ate complexes. In the latter case, deborylation instead of deprotonation would occur, as has been shown in Prof. Morken's reports on deborylation-alkylation. In 2020, Chirik and co-workers reported the ketone synthesis from benzyldiboronates and esters (Scheme 8b) [30]. LiO^tBu was used as the deborylation base and thus only mono(enolate) was formed. Different electrophiles including water, MeI, NFSI, and allyl bromide, were successfully employed in the reaction.

Compared with ester, direct coupling with a carboxylic acid is very attractive. In 2018, Liu and co-workers discovered that the coupling between 1,1-diborylalkanes and carboxylic acid could be achieved by adding methyl lithium (MeLi) as the base (Scheme 9a) [31,32]. The reaction had a wide substrate scope, including mono and di-substituted 1,1-diborylalkanes, aryl and alkyl carboxylic acids, and a range of electrophiles. Mechanistic studies indicate the formation of a complex between the two substrates. The addition of MeLi deprotonates the complex, generating α-boryl carbanion and ate complex from carboxylic anion and MeBpin. Nucleophilic addition then occurs, affording the final products. Later in 2020, the same group extended this reaction to amide substrates (Scheme 9b) [33]. Due to the diverse structures and high stability of amides, these substrates are more challenging. After a lot of attempts, Liu and co-workers developed three sets of conditions (condition **A** for primary amides, condition **B** for secondary amides, and condition **C** for tertiary amides) for successfully converting the 1,1-diborylalkanes and amides into functionalized ketones.

Functionalized ketones are frequently seen in bioactive molecules and are also versatile building blocks for many other compounds. Traditional methods to access them include enolate chemistry, Pd-catalyzed α functionalization, and organo-catalyzed methods. Compared with these methods, the most impressive characteristic of the reactions involving *gem*–diborylalkanes is the wide substrate scope, including the usually inapplicable acids/amides. With this merit and others, the methods are certainly to be used in future organic synthesis.



Scheme 9. Synthesis of functionalized ketones from *gem*–diborylalkanes and acids/amides.



Scheme 10. Access to α-boryl radical intermediates from *gem*–diborylalkanes.

5. Radical-type addition reaction

The above-mentioned reaction generally involves carbanion intermediates. Different bases were used to regulate the reactivity patterns. In 2021, Wang and co-workers reported an elegant approach to accessing α-boryl radical intermediates using *gem*–diborylalkanes as substrates under acidic conditions (Scheme 10) [34]. The acid (TFA) works as a mediator for transforming one Bpin to Bcat, which is oxidized to α-Bpin radical **B**. **B** then attacks the α,β-unsaturated ketones, affording the α-ketone radical. At this stage, two pathways may be possible. The path I is the direct hydrogen atom transfer (HAT) process, which furnishes the product. The other pathway (path II in Scheme 10) begins with the radical isomerization to oxygen radical, which reacts with *in situ* generated diboryl compound **A** to give radical **B** and boron enolate. Hydrolysis of boron enolate also affords the final product.

6. Conclusions

Thanks to the stability and easy accessibility of 1,1-bis[(pinacolato)boryl]alkanes, the last decade witnessed quick development in the transition-metal-free coupling reactions of these compounds. Both Bpin groups are vital to the properties of *gem*–diborylalkanes, including the stability of these compounds and the carbanion intermediates. The oxophilicity of boron enables the wide-applicable utilities of these compounds. For reactions involving α,α-bis[(pinacolato)boryl]alkane carbanions, alkenyl Bpin or α,α-bis(enolate) equivalents are formed. For reactions involving α-Bpin carbanions, either C-C or C-B bonds are formed. The coupling reactions with carboxylic acid derivatives provide a unique way to make various functionalized ketones. While α-boryl radical intermediate offers another direction in the development of novel reactions using this valuable *gem*–di(Bpin)alkanes. The future endeavor should be the discovery of enantioselective transition-metal-free coupling reactions, especially those involving α-Bpin carbanion intermediates. In this aspect, organocatalysis can make a good contribution. Besides, the application of these reactions to the synthesis of natural products or bioactive molecules is expected soon.

Declaration of competing interest

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, there is no professional or other personal interest of any nature of kind in any product, service and/or company that could be construed as influencing the position presented in, or the review of, the manuscript entitled.

Acknowledgment

We are grateful for the financial support from the National Natural Science Foundation of China (No. 22101261).

References

[1] K.C. N.icolaou, P.G. B.ulger, D. Sarlah, Angew. Chem. Int. Ed. 44 (2005) 4442–4489.
[2] J. Magano, J.R. D.unetz, Chem. Rev. 111 (2011) 2177–2250.
[3] C.C.C. Johansson Seechurn, M.O. K.itching, T.J. C.olacot, V. Snieckus, Angew. Chem. Int. Ed. 51 (2012) 5062–5085.
[4] C.E. G.arrett, K. Prasad, Adv. Synth. Catal. 346 (2004) 889–900.
[5] C.L. Sun, Z.J. Shi, Chem. Rev. 114 (2014) 9219–9280.
[6] W. Jo, J.H. L.ee, S.H. C.ho, Chem. Commun. 57 (2021) 4346–4353.
[7] Y. Hu, W. Sun, C. Liu, Synlett 30 (2019) 1105–1110.
[8] C. Wu, J. Wang, Tetrahedron Lett. 59 (2018) 2128–2140.
[9] R. Nallagonda, K. Padala, A. Masarwa, Org. Biomol. Chem. 16 (2018) 1050–1064.
[10] Miralles N, R.J. M.aza, E. Fernández, Adv. Synth. Catal. 360 (2018) 1306–1327.
[11] S. Li, J. Li, T. Xia, W. Zhao, Chin. J. Chem. 37 (2019) 462–468.
[12] D.S. M.atteson, R.J. M.ood, P.K. J.esthi, J. Am. Chem. Soc. 97 (1975) 5608–5609.
[13] D.S. M.atteson, R.J. M.oody, J. Am. Chem. Soc. 99 (1977) 3196–3197.
[14] D.S. M.atteson, R.J. M.oody, Organometallics 1 (1982) 20–28.
[15] T. Mukaiyama, M. Murakami, T. Oriyama, M. Yamaguchi, Chem. Lett. 10 (1981) 1193–1196.
[16] (a) C. Zhang, W. Hu, J.P. M.orken, ACS Catal. 11 (2021) 10660–10680.
[17] S. Paul, K.K. D.as, D. Aich, S. Manna, S. Panda, Org. Chem. Front. 9 (2022) 838–852.
[18] E. Fernández, R. Gava, Org. Biomol. Chem. 17 (2019) 6317–6325.
[19] F. Zhang, S. Liao, L. Zhou, et al., Chin. J. Chem. 40 (2022) 582–588.
[20] K. Hong, X. Liu, J.P. M.orken, J. Am. Chem. Soc. 136 (2014) 10581–10584.
[21] Y. Lee, S.-y Baek, J. Park, et al., J. Am. Chem. Soc. 139 (2017) 976–984.
[22] W. Jo, J. Kim, S. Choi, S.H. C.ho, Angew. Chem. Int. Ed. 55 (2016) 9690–9694.
[23] W. Jo, S. Baek, C. Hwang, et al., J. Am. Chem. Soc. 142 (2020) 13235–13245.
[24] K. Endo, M. Hirokami, T. Shibata, J. Org. Chem. 75 (2010) 3469–3472.
[25] K. Endo, A. Sakamoto, T. Ohkubo, T. Shibata, Chem. Lett. 40 (2011) 1440–1442.
[26] E.L. C.ascia, A.B. C.uenca, E. Fernández, Chem. Eur. J. 22 (2016) 18737–18741.
[27] J.R. C.oombs, L. Zhang, J.P. M.orken, Org. Lett. 17 (2015) 1708–1711.

[28] S. Namirembe, C. Gao, R.P. W.exler, J.P. M.orken, Org. Lett. 21 (2019) 4392–4394.
[29] C.E. I.acono, T.C. S.tephens, T.S. R.ajan, G. Pattison, J. Am. Chem. Soc. 140 (2018) 2036–2040.
[30] B. Lee, P.J. C.hirik, J. Am. Chem. Soc. 142 (2020) 2429–2437.
[31] W. Sun, L. Wang, C. Xia, C. Liu, Angew. Chem. Int. Ed. 57 (2018) 5501–5505.
[32] L.H. Zou, M. Fan, L. Wang, C. Liu, Chin. Chem. Lett. 31 (2020) 1911–1913.
[33] W. Sun, L. Wang, Y. Hu, et al., Nat. Commun. 11 (2020) 3113–3123.
[34] C. Wu, Z. Bao, B. Dou, J. Wang, Chem. Eur. J. 27 (2021) 2294–2298.