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Advances in transition metal-free deborylative transformations of *gem*-diborylalkanes

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Carbanions serve as key intermediates in a variety of chemical transformations. Particularly, α -borylcarbanions have received considerable attention in recent years because of their peculiar properties, including the ability of boron atom resonance to stabilise the adjacent negatively charged carbon atom. This feature article summarises recent progress in the synthetic utilisation of α -borylcarbanions, including carbon–carbon bond formation with alkyl halides, alkenes, N-heteroarenes, and carbonyls. Carbon–boron bond formation in organohalides mediated by α -borylcarbanions is also summarised.

1. Introduction

Since the discovery of the Grignard reagent in 1900, carbanions have occupied a central position in organic synthesis together with carbocations and free radicals. Such electron-rich species have been used as key intermediates in a diverse range of chemical transformations such as substitution, addition, elimination, and rearrangement reactions, thereby revolutionising synthetic organic chemistry.

Consequently, various strategies have been devised to generate carbanions, including the cleavage of the relatively acidic C–H bond with an appropriate base, metal–halogen exchange in organohalides, transmetalation, and decarboxylation.¹ However, the carbanions formed by these classical routes require strictly controlled conditions (*e.g.* an inert gas atmosphere, the use of Schlenk techniques, and/or cryogenic conditions) when reacting with electrophiles due to their unstable nature.²

Owing to their unique properties such as stability and reactivity, α -borylcarbanions that bear an organoboron unit adjacent to an anionic carbon atom have recently received considerable attention from the synthetic chemistry community.³ The properties of α -borylcarbanions can be rationalised by their resonance stabilisation, which originates from the partial

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Woohyun Jo received his BS degree from Pohang University of Science and Technology (POSTECH) in 2016 and PhD degree at the same university under the guidance of Prof. Seung Hwan Cho in 2021. He is now working as a postdoctoral researcher at POSTECH in the same group and simultaneously pursuing mandatory military service. His current research is focusing on the development of transition-metal-free carbon–carbon bond forming reactions using *gem*-diborylalkanes as alkylating reagents.



Jun Hee Lee

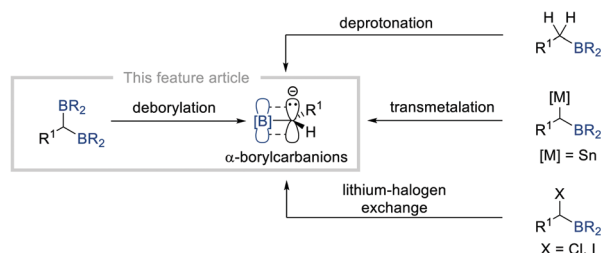
Jun Hee Lee received his BS (1995) degree in chemistry from Dongguk University and MS (1997) and PhD (2001) degrees in chemistry from Sogang University under the guidance of the late Prof. Jahyo Kang. After completing mandatory military service, he moved abroad to work with Professors Dean Toste (UC Berkeley) and Samuel J. Danishefsky (Columbia University) as a postdoctoral fellow between 2005 and 2010.

After several research careers in Korea, he joined Dongguk University Gyeongju Campus as an assistant professor in 2016. His current research interest focuses on highly chemoselective reactions for the synthesis of biologically active compounds.

 α -borylcarbanions

- stabilised by the boron group
- easy to prepare
- diverse transformations

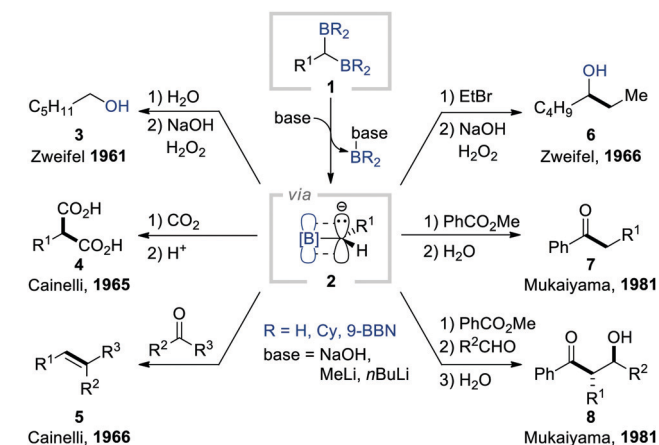
b) General procedures for generating α -borylcarbanions



Scheme 1 Approaches for the generation of α -borylcarbanions.

filling of the vacant p-orbital of sp^2 -hybridised boron with the electron pair from the adjacent negatively charged carbon, thus enabling various electrophiles to react under relatively mild conditions (Scheme 1a). Typically, α -borylcarbanions have been generated by the deprotonation of the α -C-H bond of alkylborons with a sterically hindered amide base [e.g. lithium diisopropylamide (LDA) and lithium 2,2,6,6-tetramethylpiperidide (LiTMP)],⁴ by the transmetalation of α -stannyl⁵ boronate esters, or by the lithium-halogen exchange of α -haloborons (Scheme 1b).^{5,6} While these procedures offer routes to generate α -borylcarbanions, they still suffer from several limitations, including harsh conditions, low functional group compatibility, and narrow substrate scope. In this context, the base-promoted deborylation of *gem*-diborylalkanes has emerged as a superb alternative to conventional methods for gaining access to α -borylcarbanions.⁷ The easy accessibility of *gem*-diborylalkanes from readily available starting materials renders this strategy an attractive approach to generate α -borylcarbanions.

This feature article focuses on recent advances in the usage of α -borylcarbanions, mainly those generated from *gem*-



Scheme 2 Early examples of the deborylative functionalisation of *gem*-diborylalkanes.

diborylalkanes in the presence of a base, for the selective forging of carbon–carbon bonds. We also cover carbon–boron bond formation in aryl halides with *gem*-diborylalkanes under transition metal-free conditions as α -borylcarbanions play a pivotal role in these reactions.

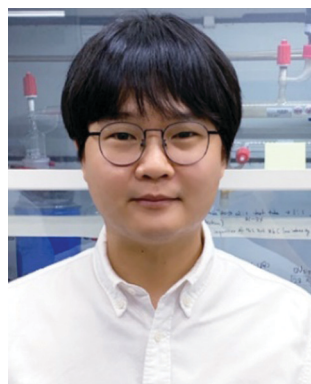
2. Carbon-carbon bond formation

2.1 Generation of α -borylcarbanions containing alkyl-substituted borane moieties and their applications

Brown and Zweifel first reported the generation of α -borylcarbanions from *gem*-diborylalkanes in 1961 (Scheme 2).⁸ They found that *gem*-diborylalkanes **1**, synthesised *via* the double hydroboration of terminal alkynes with diborane (B₂H₆), could be activated chemoselectively in the presence of NaOH as a base. The subsequent dissociation of the resulting boronate species gave α -borylcarbanions **2**, which were then trapped by H₂O as a proton source. The oxidation of the remaining borane by H₂O₂ afforded aliphatic alcohols **3**. Subsequently, Cainelli and Mukaiyama reported that one of the borane groups in *gem*-diborylalkanes could be selectively removed by employing alkyllithium as an activator to provide α -borylcarbanions **2**. These α -borylcarbanions could be captured by CO₂, carbonyls, alkyl halides, and esters to provide access to an assortment of useful building blocks such as *gem*-dicarboxylic acids (**4**),⁹ olefins (**5**),¹⁰ secondary carbinols (**6**),¹¹ alkyl(aryl)ketones (**7**),¹² and *trans*- α -alkyl- β -hydroxyketones (**8**).¹² However, all of these studies used *gem*-diborylalkanes possessing alkyl-substituted borane moieties, thereby limiting their synthetic applicability because of their narrow substrate scope and instability during column chromatography.

2.2 Alkylation of alkyl halides with α -(pinacolato)boryl alkyl anions

α -Borylcarbanion chemistry has experienced a renaissance since 2014 due to the development of many useful technologies for synthesising *gem*-diborylalkanes with a pinacolato group as a boron substituent, which are more stable than *gem*-diborylalkanes possessing alkyl-substituted borane moieties. Representative synthetic approaches include the hydroboration of alky-



Seung Hwan Cho

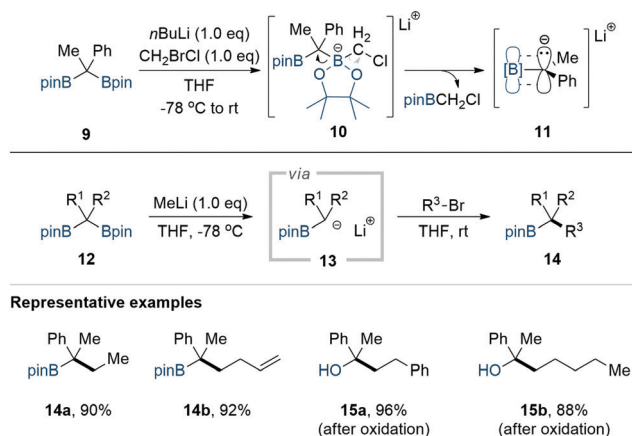
2018. His research interests are the design, synthesis and application of multi-organometallic compounds.

Seung Hwan Cho received his BS degree from Korea Advanced Institute of Science and Technology (KAIST) in 2006 and PhD degree at the same university under the guidance of Prof. Sukbok Chang in 2011. After postdoctoral experience with Prof. John F. Hartwig at University of California, Berkeley, he joined Pohang University of Science and Technology (POSTECH) as an assistant professor in 2014, and then promoted to associate professor in

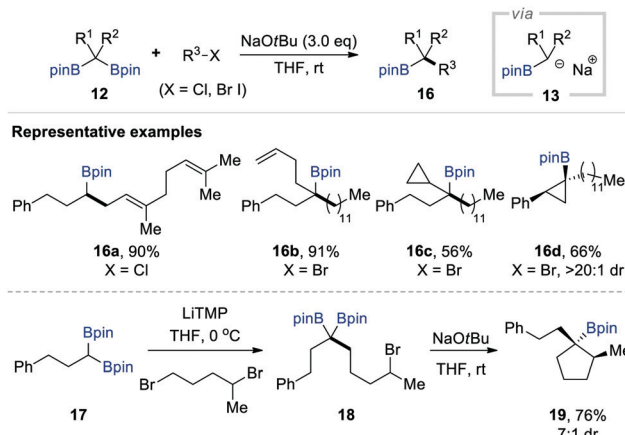
nes and alkenes with pinacolborane or bis(pinacolato)diboron, C–H borylation with bis(pinacolato)diboron, cross-coupling with bis(pinacolato)diboron, insertion of bis(pinacolato)diboron in diazo compounds, and the S_N2 reaction of alkyl halides with [bis(pinacolato)boryl]lithium.^{7a-c,13}

During an investigation into the utility of quaternary *gem*-bis[(pinacolato)boryl]alkanes **12**, prepared *via* the Pt-catalysed Srebnik diborylation of diazoalkanes, Kingsbury and Wammack serendipitously achieved the deborylative alkylation reaction of **12** in 2014.¹⁴ When they attempted the Matteson homologation^{15,16} of **9** ($R^1 = \text{Me}$, $R^2 = \text{Ph}$) using a cold mixture of bromochloromethane (1.0 equiv.) and *n*-butyllithium (1.0 equiv.) in THF, a tertiary carbinol having an *n*-butyl substituent instead of the anticipated homologated quaternary 1,2-diol was isolated in a decent yield of 86% after oxidative workup with alkaline H_2O_2 . They reasoned that the deborylation of the ate species **10** derived from the complexation of **9** with chloromethyl lithium delivered a boron-stabilised carbanion **11**. This scenario was confirmed by the further bimolecular alkylation of the same α -[(pinacolato)boryl]alkylanion, generated *in situ* from **9** ($R^1 = \text{Me}$, $R^2 = \text{Ph}$) by the action of a solution of MeLi, with several primary alkyl bromides such as ethyl bromide, *n*-butyl bromide, allyl bromide, and benzyl bromide (Scheme 3). The corresponding tertiary alkylboronate esters **14a** and **14b** or, when necessary, tertiary carbinols **15a** and **15b** were isolated after a basic peroxide workup.

After Kingsbury's work, Morken and co-workers independently reported an alkoxide-mediated deborylative alkylation of *gem*-bis[(pinacolato)boryl]alkanes that allowed the formation of carbon–carbon bonds between geminal boronates and alkyl halides, which could furnish a wide range of primary, secondary, and tertiary alkylboronate esters, including cyclopropyl derivatives **16c–d**, in good to excellent yield with high chemo- and diastereoselectivity (Scheme 4).¹⁷ Notably, five-membered carbocyclic organoboronate **19**, which is hardly accessible by other synthetic means, has been successfully prepared using an intramolecular version of this deborylative alkylation. Mechanistic studies have suggested α -[(pinacolato)boryl]alkylanion as



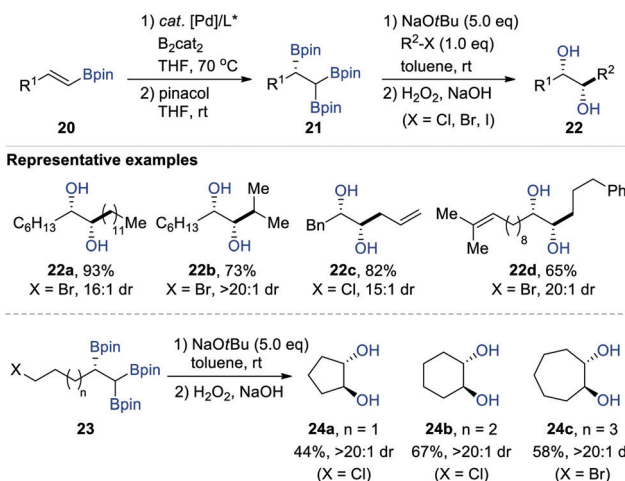
Scheme 3 Methyllithium-mediated deborylative alkylation of *gem*-bis[(pinacolato)boryl]alkanes.



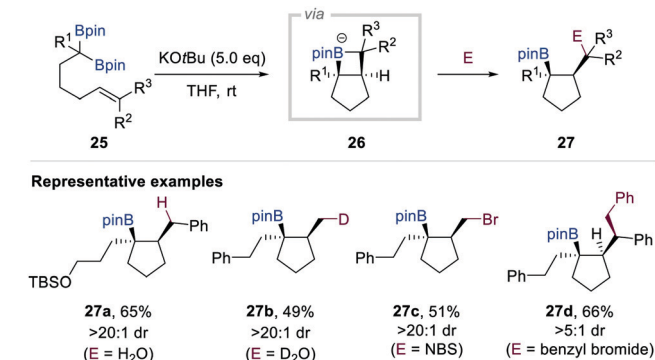
Scheme 4 NaOtBu-mediated deborylative alkylation of *gem*-bis[(pinacolato)boryl]alkanes.

an intermediate that can be generated *in situ* upon the treatment of **12** with NaOtBu *via* the selective mono-deborylation of an ate complex accompanied by the generation of *tert*-BuOBpin. Spectroscopic studies have also supported the intermediary presence of a boron alkylidene, which likely forms because of the significant sideways overlap between the Lewis-acidic trivalent boron atom and the negatively charged carbon centre.

Meanwhile, the Morken group also reported the NaOtBu-mediated diastereoselective deborylative alkylation of chiral enantioenriched 1,1,2-tris[(pinacolato)boryl]alkanes **21**, prepared *via* the Pt-catalysed enantioselective diboration of vinyl boronates **20**, with not only primary alkyl halides ($X = \text{Cl}$, Br , I), but also secondary electrophiles (Scheme 5).¹⁸ This transformation exclusively provided the *syn* diastereomers of 1,2-diols **22** in all cases upon oxidative workup with $\text{H}_2\text{O}_2/\text{NaOH}$. Moreover, an intramolecular version of this sequence enabled the synthesis of carbocyclic *anti*-1,2-diols **24a–c** containing five-, six-, and seven-membered rings with excellent diastereoselectivity ($>20:1$ dr).



Scheme 5 Diastereoselective alkylation of enantioenriched 1,1,2-tris[(pinacolato)boryl]alkanes.

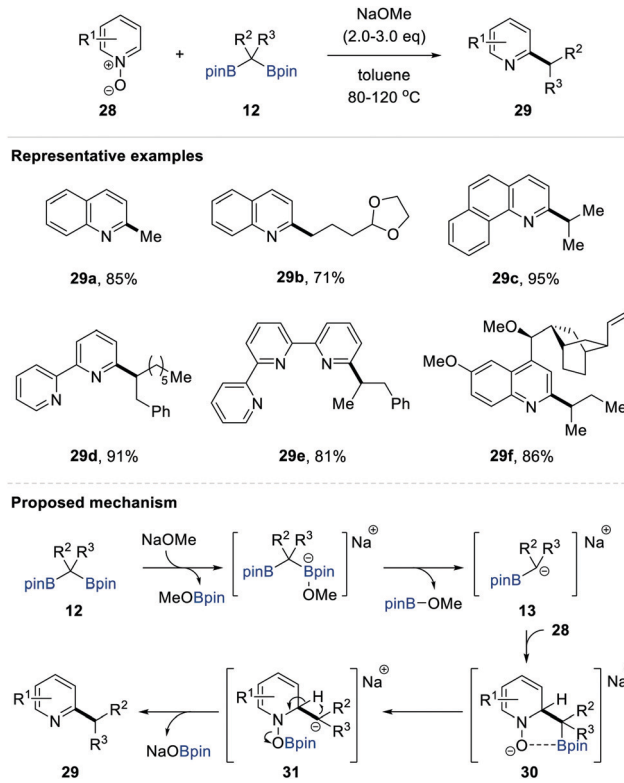


Scheme 6 Intramolecular net [2+2] cycloaddition and functionalisation.

In 2017, Morken *et al.* reported a new reactivity mode of boron alkylidenes, which are an alternative resonance hybrid of α -[(pinacolato)boryl]alkyl anions, based on intramolecular [2+2]-cycloaddition with alkene (Scheme 6).¹⁹ Whereas the S_N2 alkylation product was obtained when *gem*-bis[(pinacolato)boryl]alkane 25 bearing a tethered alkene was treated with additional alkyl halide in the presence of KOtBu, the unusual intramolecular deborylative [2+2] cycloadducts were formed when the reaction was conducted without the alkyl halide electrophile. Based on detailed mechanistic studies including isotope labelling experiments, radical clock experiments, and density functional theory (DFT) calculations, the authors proposed that an ate complex of 5-borata[3.2.0]bicycloheptane 26 is the key intermediate in this deborylative cyclisation. Moreover, they found that such intermediates could be trapped by various electrophiles including D₂O, *N*-bromosuccinimide (NBS), I₂, benzyl bromide, allyl bromide, and Eschenmoser salt to deliver a wide range of cyclopentane-containing products 27 (Scheme 6).

2.3 Alkylation of N-heteroarenes with α -[(pinacolato)boryl]alkyl anions

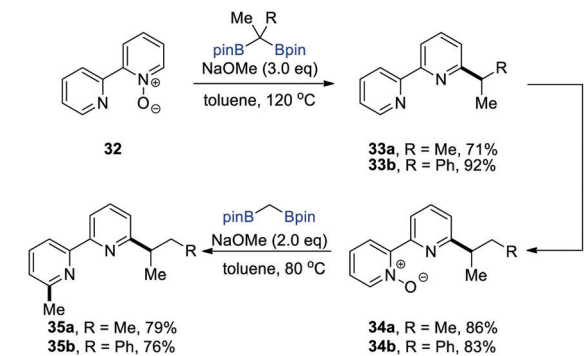
In 2016, Cho and co-workers reported the deoxygenative alkylation of N-heteroaromatic *N*-oxides 28 employing *gem*-bis[(pinacolato)boryl]alkanes 1 as versatile alkylating reagents; this reaction proceeds with perfect regioselectivity at the 2-positions of various N-heterocycles under transition metal-free conditions (Scheme 7).^{20a} The optimal reaction parameters (alkylation in toluene at 80 °C with NaOMe as the base) provided the deoxygenated C2-alkylated N-heteroarene 29. Given the importance of the site-selective methylation of N-heteroaromatic compounds (*i.e.* the so-called magic methyl effect) in drug discovery and medicinal chemistry,²¹ this alkylation enabled the incorporation of a wide range of primary alkyl groups, including methyl, ethyl, 3-phenylpropyl, 3-(*tert*-butyldimethylsilyloxy)propyl, and 5-methyl-4-hexenyl groups, into the cores of N-heterocycles with complete regiocontrol. The same group subsequently succeeded in the convenient secondary alkylation of N-heteroaromatic *N*-oxides using internal *gem*-bis[(pinacolato)boryl]alkanes 12.^{20b} Fixing all other conditions such as the base and solvent, an elevated temperature of 120 °C was necessary for these more challenging alkylation reactions. A wide range of internal alkylating

Scheme 7 C2-selective primary and secondary alkylation of N-heteroaromatic *N*-oxides with *gem*-bis[(pinacolato)boryl]alkanes.

reagents and N-heteroaromatic *N*-oxides were tolerated under the optimal conditions, offering an operationally convenient process to synthesise secondary alkylated N-heteroarenes without an additional deoxygenation step.²² Based on mechanistic studies including deuterium-labelling, cross-over, and NMR experiments, the authors proposed that the alkylation could proceed *via* the following three-step process (Scheme 7). First, the nucleophilic addition of *in situ*-generated α -[(pinacolato)boryl]alkyl anion 13 to the 2-position of *N*-oxide 28 occurred. The subsequent migration of the (pinacolato)boryl group of 30 to the anionic oxygen of the *N*-oxide gave carbanion 31 accompanied by the spontaneous release of NaOBpin *via* carbanion-induced intramolecular proton transfer, resulting in the formation of the C2-alkylated N-heteroaromatic compound 29.

To demonstrate the synthetic utility of this deoxygenative alkylation, the authors performed the sequential functionalisation of 2,2'-bipyridyl *N*-oxide (32) to prepare *N,N*-chelating ligands 35, which can be constructed in principle *via* sequential alkylations on each of the pyridine rings in 2,2'-bipyridyl (Scheme 8). The sequence commenced with the deoxygenative alkylation of 32 followed by the chemoselective oxidation of *m*-CPBA (*m*-chloroperbenzoic acid) at the less hindered pyridine moiety in the resulting bipyridines 33 to afford bipyridine mono-*N*-oxides 34. The second deoxygenative alkylation of 34 led to asymmetrically 3,3'-disubstituted 2,2'-bipyridines 35, which are valuable *N,N*-bidentate ligands in coordination chemistry.²³

The use of oxygenated N-heterocycle substrates is the main drawback of the NaOMe-mediated C2-selective primary

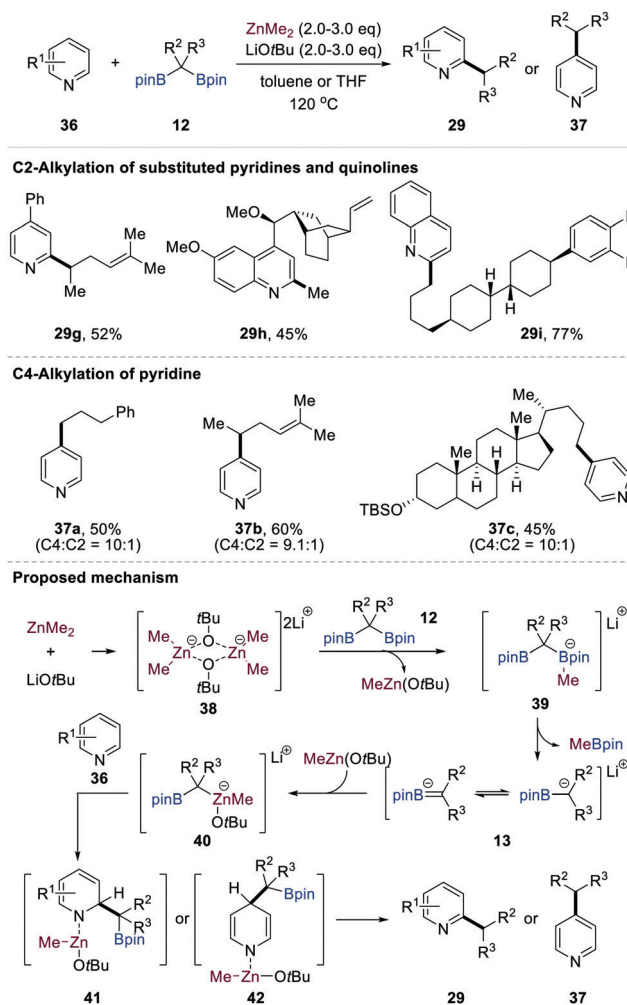


Scheme 8 Sequential alkylations of 2,2'-bipyridyl.

and secondary alkylation reactions developed by Cho and co-workers because minimising the number of redox steps is essential for streamlined organic synthesis from the viewpoint of modern redox economy.²⁴ In fact, the direct alkylation of pyridines and their derivatives, which are privileged scaffolds in natural products, pharmaceuticals, agrochemicals, and organic materials, is among the most promising strategies.²⁵ However, these methods, which are mostly based on transition metal-catalysed C–H activation, often have limited substrate scope and proceed under harsh conditions.²⁶ In particular, the incorporation of a methyl group into the N-heterocyclic core has proven challenging using these procedures. In principle, ideal methods for incorporating alkyl groups including methyl groups in pyridines and quinolines involve adding an appropriate carbon nucleophile at the electrophilic sites of N-heteroarenes followed by the rearomatisation of the resulting alkylated dihydro-N-heteroarenes.²⁷

Very recently, Baik and Cho reported the direct ZnMe_2 -mediated C2- or C4-selective primary and secondary alkylation of electron-deficient N-heteroarenes **36** (e.g. pyridines and quinolines) using *gem*-bis[(pinacolato)boryl]alkanes **12** as alkylating reagents (Scheme 9).²⁸ This single-step alkylation protocol features a remarkably broad substrate scope of N-heteroarenes **36** and *gem*-bis[(pinacolato)boryl]alkanes **12**, including derivatives bearing pharmaceutically relevant motifs, as exemplified by **29i** and **37c**, with complete regioselectivity. While substituted pyridines and quinolines exclusively provided C2-alkylated N-heterocycles, simple pyridine furnished C4-alkylated pyridine derivatives with high regioselectivity.

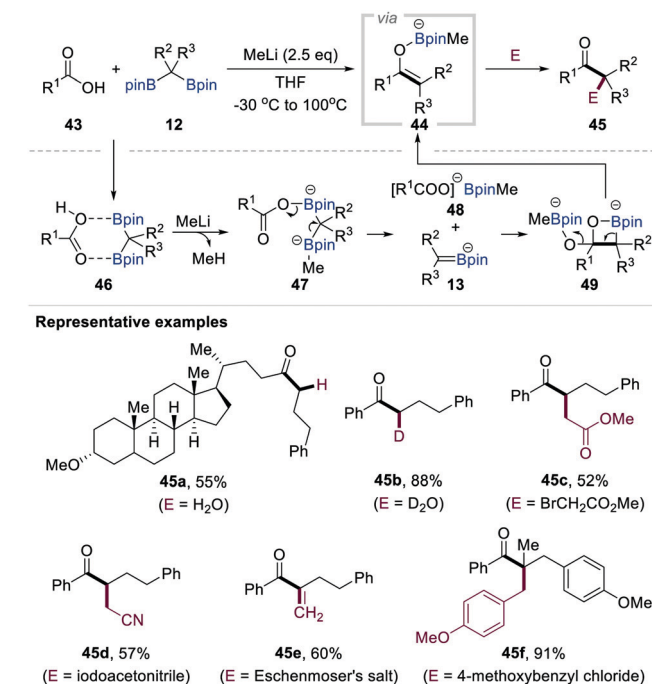
Based on a thorough investigation by various experimental methods combined with DFT calculations and NMR spectroscopic analysis, Baik and Cho proposed a plausible mechanism for the direct ZnMe_2 -mediated C2- or C4-selective alkylation of pyridine and quinoline derivatives (Scheme 9). The formation of dimeric intermediate **38**²⁹ facilitated a methyl transfer from ZnMe_2 to one of the boron atoms of *gem*-bis[(pinacolato)boryl]alkanes **12** to give MeZnOtBu and methyl boronate complexes **39**. The latter could generate transient anionic intermediates **13** with the liberation of MeBpin . The binding of **13** to MeZnOtBu species yielded stable zincates **40**. The MeZnOtBu fragment in **41** could bind to the nitrogen atom of N-heterocycles **36**, and this Lewis acid–base interaction increased the electrophilicity of **36**. The borylalkyl anion

Scheme 9 ZnMe_2 -Mediated direct alkylation of N-heteroarenes with *gem*-bis[(pinacolato)boryl]alkanes.

in **40** then attacked the C2-carbon as a nucleophile to afford dearomatised intermediates **41**. The DFT calculations showed that C2-alkylation is kinetically favoured over C4-alkylation. In sharp contrast, C4-alkylation is more feasible when pyridine is employed as the substrate, which agrees with the experimental outcomes. The aromatisation of intermediates **41** and **42** accompanied by the liberation of $\text{Zn}(0)$ and $t\text{BuOH}$ (or CH_4) followed by the protodeborylation of the resulting 2- or 4-(borylalkyl)-N-heterocycles provides C2-alkylated (**29**) or C4-alkylated (**37**) products.

2.4 Carbon–carbon bond-forming reaction of carbonyl derivatives with α -(pinacolato)borylalkylanions

In 2018, Liu and co-workers reported the first example of the dual functionalisation of both carbon–boron bonds of *gem*-bis[(pinacolato)boryl]alkanes **12** via deoxygenative enolisation with carboxylic acids followed by electrophilic trapping (Scheme 10).³⁰ The authors found that methyl lithium plays a pivotal role as an efficient activating reagent in this transformation. Careful monitoring of the reaction mixture by *in situ* infrared spectroscopy supported the initial interaction between the

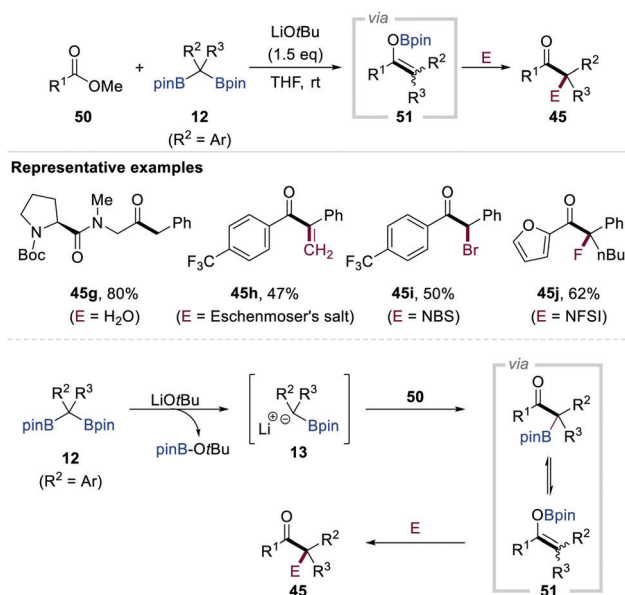


Scheme 10 Functionalisation of *gem*-bis[(pinacolato)boryl]alkanes with carboxylic acids.

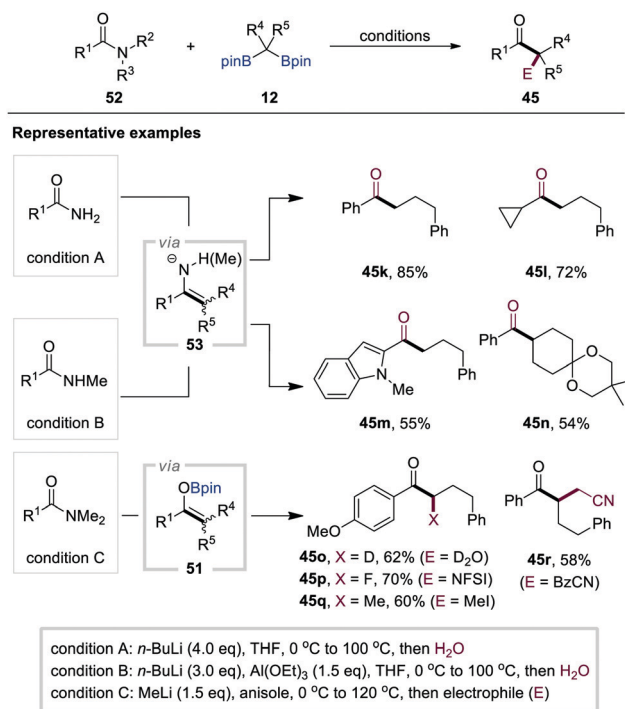
carboxylic acid **43** and *gem*-bis[(pinacolato)boryl]alkanes **12** to generate the chelating complex **46**. The acidic proton of **46** could then be removed by the addition of methyl lithium to afford dianion **47**, in which one of the boron centres is occupied by a methyl group, as a key intermediate. The fragmentation of **47** was promoted by heating the reaction mixture at 100 °C, affording α -(pinacolato)borylalkyl anion **13** along with carboxylate **48**. The combination of these reactive species generated boron enolate **44**, presumably *via* intermediate **49**. A diverse range of electrophiles could quench this reactive enolate, finally resulting in the formation of various α -mono-, di-, and trisubstituted ketones **45a–f** (Scheme 10).

Chirik *et al.* reported the chemoselective conversion of esters into ketones *via* the LiOtBu-promoted deborylative addition of *gem*-bis[(pinacolato)boryl]alkanes **12** ($R^2 = \text{Ar}$, $R^3 = \text{H}$) possessing aryl or heteroaryl substituents to the esters (Scheme 11).³¹ Extensive NMR spectroscopic studies supported the formation of α -(pinacolato)borylalkyl anions upon the release of *t*BuOBpin. These α -(pinacolato)borylalkyl anions then reacted with esters (**50**) to generate boron enolates **51** ($R^2 = \text{Ar}$, $R^3 = \text{H}$). Having identified boron enolates **51** ($R^2 = \text{Ar}$, $R^3 = \text{H}$) as the reactive intermediate, the authors also demonstrated three protocols to prepare ketones **45g–j** bearing tertiary and quaternary carbon centres by changing the electrophile, starting material, and additional quenching reagent of an alkylation step.

Based on their previous study on carboxylic acids (Scheme 10), in 2020, Liu and co-workers reported the chemodivergent transformation of primary, secondary, and tertiary amides **52** with *gem*-bis[(pinacolato)boryl]alkanes **12** as pronucleophiles (Scheme 12).³² For primary and secondary amides, the B–O elimination pathway was predominant in the generation of metallo-enamine intermediates **53** after the initial



Scheme 11 Functionalisation of *gem*-bis[(pinacolato)boryl]alkanes with esters.



Scheme 12 Functionalisation of *gem*-bis[(pinacolato)boryl]alkanes with esters.

addition of α -(pinacolato)borylalkyl anions to amides **52**. Furthermore, the authors found that *n*-butyllithium (4.0 equiv.) was the optimal base for primary amides, while a mixture of *n*-butyllithium (3.0 equiv.) and Al(OEt)₃ (1.5 equiv.) was necessary for the activation of secondary amides. In stark contrast, B–N elimination occurred predominantly for tertiary amides to generate boron enolate intermediates **51** using methyl lithium for the activation of *gem*-bis[(pinacolato)boryl]alkanes **12**. The

in situ trapping of either metallo-enamines or enolates with various electrophiles generated various functionalised ketones **45k-r**, enamides, α -alkylated cyclic amines, and β -ketoamides.

3. Carbon–boron bond formation

In contrast to the notable progress in the utilisation of *gem*-bis[(pinacolato)boryl]alkanes **12** for constructing carbon–carbon bonds *via* α -[(pinacolato)boryl]alkyl anion **13** species, the alternative use of *gem*-bis[(pinacolato)boryl]alkanes for the formation of carbon–boron bonds in aryl halides was only recently reported by Cho *et al.* in 2017 (Scheme 13).³³ When aryl and vinyl iodides **54** were treated with bis[(pinacolato)boryl]methane **12** ($R^2 = R^3 = H$) in the presence of NaOtBu as an activator in an equal mixture of toluene and THF at elevated temperature, the borylation of aryl and vinyl iodides occurred to afford aryl and vinylboronate esters **55** in good yields.

Experimental and theoretical investigations revealed that the formation of Lewis acid/base adducts between α -[(pinacolato)boryl]alkyl anions and organohalides facilitated the formation of six-membered coordinated intermediate **56** and released sodium aryl anion species **57**, which subsequently underwent carbon–boron bond formation reaction upon the adoption of [(pinacolato)boryl]iodoalkanes or *tert*-butoxyboronate ester as a boron source. Based on an understanding of the reaction

mechanism, the authors showed that aryl bromides also participated in the developed transition metal-free borylation reaction when *gem*-bis[(pinacolato)boryl]ethane ($R^2 = \text{Me}$, $R^3 = H$) was used as a borylating reagent in the presence of NaOtBu in THF at 120 °C.

4. Conclusion

This feature article focuses on the transition metal-free deborylative functionalisation of *gem*-diborylalkanes *via* α -borylcarbanions as the key intermediates. As exemplified by our independent works and the works of others, upon treatment with metal alkoxide or alkyl lithium, α -borylcarbanions generated from *gem*-diborylalkanes are sufficiently nucleophilic to react with various electrophiles, providing a diverse range of useful building blocks. Although α -borylcarbanions have been successfully applied to various carbon–carbon and carbon–boron bond-forming reactions, there are still multiple challenges. For example, a stoichiometric amount of alkoxide or alkyl lithium as an activator of *gem*-diborylalkanes makes the reaction less practical as these strong bases typically show low functional group compatibility. Consequently, the development of alternative methods for the activation of *gem*-diborylalkanes under milder conditions is highly desirable to encompass a wide range of substrates in given reactions. Radical-based approach might be an attractive alternative to the based-promoted activation of *gem*-diborylalkanes.^{34,35} Moreover, carbon–boron bond-forming reactions of aryl(vinyl) chlorides as electrophiles is another challenge to be overcome. Regardless of these issues, the last half-decade has seen significant advances in the deborylative functionalisation of *gem*-diborylalkanes *via* α -borylcarbanions as versatile intermediates and fascinating new developments in this area of research are continuously being developed. We hope that this feature article provides helpful guidance for future research in this promising, ever-growing research field.

Conflicts of interest

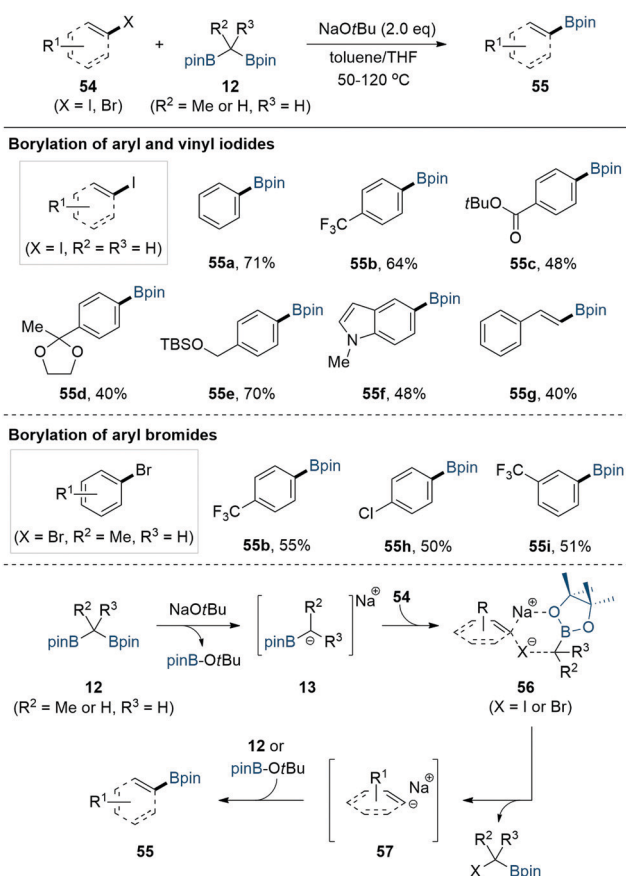
There are no conflicts to declare.

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Notes and references

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