Published in final edited form as:

J Am Chem Soc. 2020 February 05; 142(5): 2429–2437. doi:10.1021/jacs.9b11944.

Ketone Synthesis from Benzyldiboronates and Esters: Leveraging α -Boryl Carbanions for Carbon-Carbon Bond Formation

Boran Lee, Paul J. Chirik*

Department of Chemistry, Princeton University, Princeton, New Jersey 08544, United States

Abstract

An alkoxide-promoted method for the synthesis of ketones from readily available esters and benzyldiboronates is described. The synthetic method is compatible with a host of sterically differentiated alkyl groups, alkenes, acidic protons α to carbonyl groups, tertiary amides and aryl rings having common organic functional groups. With esters bearing α -stereocenters, high enantiomeric excess was maintained during ketone formation, establishing minimal competing racemization by deprotonation. Monitoring the reaction between benzyldiboronate and LiO^tBu in THF at 23 °C allowed for the identification of products arising from deborylation to form an α -boryl carbanion, deprotonation, and alkoxide addition to form an “-ate” complex. Addition of 4-trifluoromethylbenzoate to this mixture established the α -boryl carbanion as the intermediate responsible for C–C bond formation and ultimately ketone synthesis. Elucidation of the role of this intermediate leveraged additional bond-forming chemistry and enabled the one-pot synthesis of ketones with α -halogen atoms and quaternary centers with four-different carbon substituents.

Graphical Abstract

Introduction.

Methods for the construction of carbon–carbon bonds that rely on common functional groups and readily available reagents are attractive. Organoboronates have been classified as

*Corresponding Author: pchirik@princeton.edu.

Supporting Information

The Supporting Information is available free of charge via the internet at <http://pubs.acs.org>.

Experimental details; characterization data including NMR spectra of compounds (PDF)

The authors declare no competing financial interest.

synthetic lynchpins owing to their versatile and broad reactivity coupled with their straightforward preparation and relative ease of handling.¹ Geminal polyboronates, compounds bearing two or three borons on the same carbon atom, are emerging as a particularly interesting and distinct class of organoboron compounds due to their ability to promote unique C–C or C–heteroatom bond formations,² motivating additional studies to their applications in synthesis. Introduction of additional boron substituents on a carbon atom enhances the reactivity of the existing C–B bond through distinct activation modes.³ The empty p-orbital on boron stabilizes adjacent carbanions, facilitating deprotonation of the α -C–H bond under mild conditions, opening pathways to C–C bond formation (Scheme 1, Path I).⁴ Alternatively, the inherent electrophilicity of boron also promotes formation of borate complexes^{3a,4a} and subsequent deborylation provides access to synthetically versatile α -boryl carbanions (Scheme 1, Path II).⁵

Because of their potential value in synthesis, there has been increased emphasis on the development of reliable and straightforward methods for the preparation of *gem*-polyboronates including: the hydroboration of alkynes⁶ and borylalkenes,^{3b,7} diboration of carbonyls,⁸ carbamates,⁹ *N*-tosylhydrazones,¹⁰ and diazo compounds,^{5a,11} diborylation of dihalides,¹² and diborylation by transition-metal-catalyzed C(sp³)–H functionalization.¹³ For the C–H functionalization route, our group reported that α -diimine supported cobalt^{13d} and nickel^{13e} complexes promote the C(sp³)–H di- and triborylation of alkyl arenes. Borylation of the benzylic C(sp³)–H bond was predominant in most cases but chain running to remote positions along the alkyl chain was also observed broadening the scope of the method to functionalization of less activated positions.

Ketones are a particularly valuable class of compounds and methods for their preparation have been of interest to chemists for over a century. Classical methods rely on 1) addition of strong nucleophiles such as Grignard or alkyl lithium reagents to Weinreb amides¹⁴ and 2) reaction of lithiated dithianes with electrophiles.¹⁵ However, these approaches often require additional steps to prepare reagents and can be limited by scope of the reaction owing to the reliance on reactive organometallics.¹⁶ The discovery of methods that rely on milder conditions or reagents to expand the scope of the reaction continues to be an area of ongoing effort.¹⁷ Early examples with transition metals include hydroacylation of alkenes¹⁸ and carbonylative coupling between aryl halides and carbon nucleophiles.¹⁹ Most recently, photoredox²⁰ and electrochemical methods²¹ have been reported that exploit generation of radical intermediates under mild conditions.

The increased availability of polyboronates has accelerated interest in their synthetic application, including in the synthesis of ketones. Matteson pioneered the application of *gem*-diboronates to the synthesis of carbonyl compounds by generation of α,α -diboryl carbanions from treatment with a base such as LiTMP (lithium tetramethylpiperidide) and addition to alkyl halides and esters.^{4c} Pattison expanded this chemistry by trapping boron enolate intermediates with electrophiles, substituting the two C–B bonds with two new C–C or C–X (X = halogen) bonds (Scheme 2A, Path I).²² Mukaiyama has demonstrated that MeLi promotes the reaction between *gem*-diborylalkanes and esters by forming the reactive α -boryl carbanions through deborylation.²³ Subsequently, Liu and coworkers extended this activation mode to the transformation of carboxylic acids to ketones but harsh conditions (8

hours at 100 °C) were required (Scheme 2A, Path II).²⁴ *gem*-Diboronates have also been effective substrates for the synthesis of aldehydes through palladium cross coupling with aryl halides using DMF as the carbonyl source.²⁵

In our initial report of conjugate addition with benzyldiboronates,^{13e} an α,β -unsaturated ketone was identified as a minor product following the LiTMP-promoted addition of methyl tiglate (Scheme 2B). Identification of this product suggested that polyboron compounds may serve as versatile and straightforward pro-nucleophiles for the synthesis of ketones from readily available esters. The utility of the benzyldiboronates in a highly diastereoselective deborylative conjugate addition was demonstrated with the stereoselectivity likely derived from formation of a six-membered cyclic borate intermediate (Scheme 1B).^{13e} These initial results demonstrated that new C–C bond-forming chemistry was available from polyboronates and inspired additional studies to expand their role in organic synthesis. Here we describe realization of a versatile and general method for the synthesis of ketones from esters, tertiary amides, and carbonates using benzyldiboronates prepared from C(sp³)–H borylation. NMR spectroscopic studies support formation of an α -boryl carbanion, formed from the release of RO–BPin, as the reactive intermediate that is responsible for C–C bond formation with the carbonyl partner. With this mechanistic information in hand, three methods for the preparation of functionalized ketones were explored where the substitution pattern of the carbonyl product was controlled by changing the electrophile, starting material, and additional quenching reagent of an alkylation step.

Results and Discussion.

Reaction Scope.

Our study commenced with examination of the reactivity of benzyldiboronate **1** with methyl butyrate. In the presence of 1.5 equivalents of LiO^tBu (lithium *tert*-butoxide) in THF at 23 °C, ketone, **3a** was obtained in 86% yield. Compared to previous reports where an excess of alkyldiboronates were required,^{22,24} this procedure was effective with a single equivalent of **1**. These initial conditions were found to be optimal as changing the amount or identity of the base or reaction medium was deleterious for the overall yield (Table S1).

Attention was devoted to the scope of the ketone synthesis by alkoxide-promoted deborylative addition of benzyldiboronates to esters (Tables 1 and 2). The procedure proved tolerant to a range of sterically differentiated substituents on the ester as the high yield of **3a** was maintained with methyl, ethyl, and even *tert*-butyl butyrate. Esters with larger substituents on the α -carbon were also well tolerated with no measurable erosion of yield or discernable change in efficiency. (**3b–3d**). Methyl pivalate produced **3d** in slightly higher yield compared to smaller esters (**3a–3c**) despite the presence of a *tert*-butyl substituent, presumably due to the absence of α -protons on the carbonyl. In spite of the basicity of presumed intermediates, substrates bearing acidic protons were also well tolerated as esters containing an allylic proton (**3e**), a benzylic proton (**3f**), and α -protons adjacent to nitrogen (**3n** and **3o**) produced the corresponding ketone in high yield (80–90%).

To further explore the possibility of competing deprotonation, the compatibility of the reaction with enantioenriched esters was examined. Synthesis of **3g**, **3n** and **3o** was achieved

with little erosion in enantiomeric excess. This observation provides support for the intermediacy of boron enolates, which effectively mask the ketone products under the basic reaction conditions and render the α -protons less acidic, thereby minimizing racemization during the reaction.²⁶ Likewise, the silyl-protected alcohol, **3g** was compatible with the reaction conditions and deprotected to yield a free hydroxyl group (**3h**). Esters with electron-donating aryl rings (**3j**), electron-withdrawing groups (**3k** and **3m**), and boron (**3l**) substituents also generated the desired ketones in moderate to high yields (74–96%). With *N*-Boc-Pro-OMe and a dipeptide, C–C bond formation was observed selectively at the most electrophilic site, generating **3n** and **3o**, respectively. Finally, the transformation was also effective in the presence of heteroaromatic rings such as furan (**3p**) and pyridine (**3q**). In the case of **3q**, both ester groups were converted to ketones in a single step in high isolated yield (94%).

The scope of the benzyldiboronate partner on ketone synthesis was also evaluated (Table 2). Methyl butyrate and methyl 4-(trifluoromethyl)benzoate were selected as representative alkyl- and aryl-substituted esters, respectively. Independent of electron-donating (**3r**, **3t**, **3w**, **3x**, **3z**, and **3ac**) or electron-neutral (**3s** and **3y**) substituents at *para*- or *meta*-position, all diboryl reagents underwent coupling with esters to produce the desired ketones in high yields. Trimethylsilyl (**3u** and **3aa**) and pinacol boronate groups (**3v** and **3ab**) were also well tolerated. Also, excellent yield was obtained with 3-thienyl substituted substrate (**3ad**), showing the possibility that this transformation can be extended to heteroaryl-substituted *gem*-diboronates.

Carbonyl compounds less electrophilic than esters were also examined as substrates for ketones synthesis. As illustrated in Scheme 3, tertiary amides were effective coupling partners with benzyldiboronate **1** as ketone **3ae** was obtained in excellent yield. With diethyl carbonate, a mixture of two products, **3f** and **3af** was obtained when one equivalent of **1** was added with respect to carbonate.²⁷ Poor selectivity was observed when one equivalent of **1** was used but using two equivalents of the diboronate produced **3f** as a sole product. Conversions of carbamate (*N*-Boc-pyrrolidine) and urea (*N,N,N',N'*-tetramethylurea) were also attempted, but no reaction was observed.

Mechanistic Studies.

To detect potential intermediates and to gain insight into the preferred reaction pathway, the C–C bond-forming reaction was monitored by ¹H, ¹¹B, ¹H–¹³C HSQC and HMBC NMR spectroscopies. The interaction of alkyl-substituted *gem*-diboronates with bulky amide bases has been studied by Cho and coworkers and the corresponding lithiated products have been characterized by NMR spectroscopy and applied in a host of synthetic chemistries.²⁹ Related “-ate” complexes and deborylated compounds have also been generated from alkyl *gem*-diboronates and identified by NMR spectroscopy.^{3a,4a,5b} By contrast, few studies have been conducted on the interaction of benzyldiboronates with the bases used in this study.

Initial experiments were conducted in the absence of ester to explore the nature of the nucleophile generated from interaction of the benzyldiboronate with the base. Figure 1A illustrates three possible reactive species (**6–8**) and two boron-containing side products (**9**

and **10**) from the reaction of **1** and alkoxide base. Monitoring the reaction mixture after the addition of 1.5 equivalents of LiO^tBu to a THF-*d*₈ solution of **1** by both ¹H and ¹¹B NMR spectroscopies revealed formation of three boron-containing products (Figure 1B and 1C), one of which was transient, persisting on the order of one hour at 23 °C.³⁰ Independent syntheses and additional spectroscopic measurements were conducted to identify each of the components formed.

Generation of **8** as the sole product was first explored. Treatment of benzylmonoboronate **5** with LiTMP generated the same ¹H NMR resonances as the transient intermediate confirming the identity of this species as the α-boryl carbanion product, **8** arising from deborylation.³¹ Sharp resonances at 21 and 5 ppm in ¹¹B NMR spectrum support the formation of **9** and **10**, arising from deborylation and subsequent tert-butoxide association (Figure 1C).^{4a} The lithiated benzyldiboronate **6** was synthesized by addition of LiTMP to **1** (see Figure S28 and S30 for ¹H and ¹¹B NMR spectra of **6**) and was identified as the major (42%) component of the mixture.³² ¹H–¹³C HMBC correlations on the other major product, accounting for approximately 39% of the mixture, were consistent with the lithium “-ate” complex, **7** arising from addition of the alkoxide base (see Figure S19). A ¹H resonance at 7.08 ppm, which corresponds to the *ortho*-Ar–H of **7**, displays an HMBC correlation to a ¹³C resonance at 36 ppm from either -BPin or -O^tBu. This ¹³C resonance also has a HMBC correlation to a ¹H resonance at 1.11 ppm. The resonance at 8 ppm in ¹¹B NMR spectrum reveals another tetracoordinate boron complex is formed, assigned as **7**. In order to determine the fate of the transient species **8**, the experiment was repeated in the presence of *N,N*-dimethyl-*para*-toluidine as an internal standard. Monitoring by NMR spectroscopy demonstrated that **8** was converted into **6** (43%) and **7** (50%) over the course of 1 hour, and the ratio was constant over the course of 24 hours.

The α-boryl carbanion **8** proved stable over 24 hours following preparation by deprotonation of **5** with LiTMP (i.e. under alkoxide-free condition). To probe the interconversion between three intermediates **6**, **7**, and **8**, one equivalent of ^tBuO–BPin was added to the solution of **8**. Within 30 minutes, complete consumption of **8** and formation of **6** and **7** were observed in a 1:0.7 ratio (Figure S33–S35). To demonstrate the equilibrium between **6**–**8**, **1** was treated with LiTMP to generate α,α-diboryl carbanion **6**, followed by subsequent addition of one equivalent of *tert*-butanol. The ¹H and ¹¹B NMR spectra were then recorded over the course of one hour. Upon addition of ^tBuOH, conversion of **6** to a mixture of **7** and **8** was observed initially (5 min) with **8** disappearing over the course of 30 minutes, leaving 1:0.6 mixture of **6** and **7** along with small amount of unidentified impurities (Figure S36–S38). Based on these observations, **6**, **7**, and **8** interconvert and in the presence of alkoxides, the equilibrium shifted toward **6** and **7** with only trace amount of **8**.

Having identified each product from the interaction of **1** with LiO^tBu, two distinct mechanisms based on the observed reaction intermediates are proposed in Scheme 4. By a deprotonative pathway (top line), an α,α-diboryl ketone is generated, which is in equilibrium with *O*-bound boron enolate, **11**. In the bottom case, **12** arises from a deborylative pathway (from **7** or **8**). Alternatively, **12** can be obtained from the protodeboronation of **11** in the presence of alkoxide base or *tert*-butanol. As a vinyl C–H of

12 can be used as the NMR handle to probe which intermediate is formed during the C–C bond-forming reaction and to distinguish which path is operative, additional NMR experiments were performed in the presence of a representative ester to determine the relative reactivity of each intermediate towards C–C bond and ultimately ketone formation.

Under standard reaction conditions (e.g. treatment of **1** with 1.5 equivalents of LiO^tBu in the presence of methyl 4-(trifluoromethyl)benzoate, the ¹H NMR spectrum recorded after three hours established complete consumption of the esters with concomitant formation of new resonances (Figure 2, i). A diagnostic signal was observed at δ = 5.83 ppm assigned to a vinylic proton, supporting the formation of **12** through either a deborylative pathway or a deprotonative coupling followed by protodeboronation of **11**. When **8** was generated by addition of LiTMP to **5** and subsequently treated with the ester, an identical ¹H NMR spectrum was obtained as shown in Figure 2B, ii. However, the ¹H NMR spectrum obtained from deprotonation of **1** with LiTMP followed by addition of ester produced a different product, **11** (Figure 2, iii). The observation of broad peaks at 22 and 31 ppm in the ¹¹B NMR spectrum revealed a tricoordinate boron attached to C and that attached to O, supporting the presence of **11** (Figure S55). Treatment of 1 equivalent of LiO^tBu to this reaction mixture did not induce a significant change in ¹H NMR spectrum, eliminating the possibility that **11** is converted to **12** by alkoxide-promoted protodeboronation (Figure S56). To examine the possibility of deprotonative pathway followed by protodeboronation induced by *tert*-butanol generated from the initial deprotonation step, a crossover experiment was designed. Mixture of the isotopologue of **1** with aryl and benzylic C–D bonds and *p*-methoxybenzyl diboronate was subjected to the reaction conditions and the isotopic incorporation at the benzylic position of each ketone product was determined. Scrambling of the hydrogen isotopes was not observed ruling out protodeboronation of **11** induced by ^tBuOH (see Supporting Information for details).

To evaluate the reactivity of **7**, **1** was treated with LiO^tBu for one hour prior to the addition of the ester and the resulting reaction was monitored by ¹H NMR spectroscopy (Figure 2, iv). Because **8** was unstable and disappeared within 60 minutes at ambient temperature, only **6** and **7** existed at the time of ester addition. After 3 hours, **6**, **7** and the ester were consumed, and new peaks correspond to **11** (<27%), *tert*-butyl 4-(trifluoromethyl)benzoate (50%) and unidentified byproducts appeared. This observation indicates that **7** is unreactive toward deborylative addition to esters and decomposes to byproducts. Also, a series of experiments was conducted whereby LiO^tBu was added to **1** and the injection time of the ester was varied between 5, 15 and 60 minutes. The resulting reactions were monitored by ¹H NMR spectroscopy three hours later after the ester addition. At longer time interval between additions, where the unstable α -boryl carbanion **8** is converted to **6** and **7** and exist at low concentration, the intensity of the diagnostic vinylic proton resonance diminished (Figure S57). This is consistent with the hypothesis that **8** is responsible for C–C bond formation resulting in the boron enolate **12**.

A control experiment was performed where α -boryl carbanion **8** was alternatively prepared by deprotonation of benzylmonoboronate **5** and treated with an ester (Scheme 5). Although α -C–H bonds of alkylmonoboronates are typically not acidic enough to be deprotonated by

amide bases, stabilizing effect of the additional phenyl group enables deprotonation of **5**^{4c,33} and the subsequent addition of methyl butyrate affords **3a** in 74% yield. Attempts to extend the methodology to alkyl *gem*-diboronates were unsuccessful. Subsequent NMR studies established that addition of LiO^tBu to the solution of alkylidiboronate produced no detectable change, in contrast to the benzyldiboronate case (see Figure S69). These findings suggest that the presence of functional groups capable of stabilizing the carbanion arising from deborylation is crucial. To test the hypothesis, an alkyltriboronate (having an additional boryl group) and an allyldiboronate (having a C=C bond) were examined and the corresponding ketone products were formed, albeit in lower yields (54% and 41% yield, respectively, see Supporting Information for details).

Insights into the reaction mechanism and identification of a boron enolate inspired expansion of the method to leverage the utility of this intermediate in ketone synthesis. As summarized in Scheme 6, three different approaches were explored. The first involved coupling the C–C bond-forming event to an additional C–E bond-forming reaction enabled by quenching the boron enolate intermediate with a reagent other than a proton source (Scheme 6, Method A). As demonstrated previously,^{13e,22,24} alkyl electrophiles such as iodomethane (**13a**), propargyl bromide (**13b**), and Eschenmoser's salt (**13c**) were successfully employed to yield ketones **14a**, **14b**, and **14c**, respectively. Attempts to prepare the β -aminoketone, expected from a Mannich-type reaction product between boron enolate intermediate and **13c** was unsuccessful but intriguingly, the fully conjugated ketone, **14c** was obtained as the sole product following loss of dimethylamine. Incorporation of fluorine and bromine was achieved using NBS (*N*-bromosuccinimide, **13d**) and NFSI (*N*-fluorobenzenesulfonimide, **13e**) as the electrophile (**14d–14g**). In the case of the bromination reaction, introduction of the first halogen increases the acidity of the α -proton such that *tert*-butoxide or methoxide (liberated from the ester), promotes deprotonation and resulted in isolation of the doubly brominated ketone (**14f**). Increasing the amount of NBS in the reaction improved the yield of **14f**. Thiophene-substituted diboronate also afforded the corresponding α -fluoroketone in good yield (**14g**, 83%).

The boron enolate intermediate was utilized for the synthesis of quaternary centers with four different substituents. Given that the deborylative activation mode does not require terminal C–H bonds of the diboronate substrates, attempts were made to conduct these transformations with internal diboronates. These substrates were generated in situ by deprotonative alkylation of terminal benzyldiboronates and used directly in the subsequent coupling procedure with esters followed by trapping with the electrophile (Scheme 6, Method B). Fluorinated and allylated ketones **15a** and **15b** were obtained in 83 and 75% yield, respectively using this approach from a one-pot conversion from **1**. The tetramethylpiperidine byproduct formed from the LiTMP base had no discernable influence on the outcome of the reaction.

A third transformation involving deborylative addition of internal diboronates to an ester followed by trapping with an electrophile was also demonstrated (Scheme 6, Method C). The internal benzyldiboronate **16** was synthesized by selective Ni-catalyzed diborylation of benzylic C(sp³)–H bonds of pentylbenzene.^{13e} Despite the increased steric hindrance at α -carbon, **16** still proved to be a suitable reagent for deborylative addition to esters followed by

electrophile trapping, yielding **17a–17c** with good efficiency (62–73%). The results in Scheme 6 highlight the versatility of this transformation in that new bonds were selectively formed in a predictable manner without waste of any C–B bond and in the case of Method B, three different functional groups were introduced from two identical C–B bonds.

Concluding Remarks.

In summary, an efficient and operationally simple method for conversion of esters to ketones using benzyldiboronates has been developed. The method is tolerant of most common organic functional groups, including substrates with acidic α -protons adjacent to carbonyl groups, and has been extended to tertiary amides and carbonates. NMR spectroscopic studies support the formation of an α -boryl carbanion through an alkoxide-mediated deborylative pathway that in turn serves as a reactive intermediate for C–C bond formation and ultimately ketone synthesis. Based on these findings, three methods to synthesize ketones bearing tertiary and quaternary carbon centers were demonstrated.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

We thank the National Institutes of Health (R01 GM121441) for financial support. B. L. thanks Kwanjeong Educational Foundation. We thank Dr. Simon Krautwald, Dr. Matthew, Dr. Cayetana Zarate, and Dr. W. Neil Palmer for insightful discussions and helpful comments. We acknowledge Kenith Conover and Dr. István Pelczer for helpful discussions and assistance with NMR spectroscopy. The staff at Lotus Separations are gratefully acknowledged for measuring the enantiopurity of some products. We also thank Allychem for a generous gift of B₂Pin₂.

REFERENCES

- (1). (a)Brown HC; Singaram B The Development of a Simple General Procedure for Synthesis of Pure Enantiomers via Chiral Organoboranes. *Acc. Chem. Res* 1988, 21, 287–293.(b)Miyaura N; Suzuki A Palladium-Catalyzed Cross-Coupling Reactions of Organoboron Compounds. *Chem. Rev* 1995, 95, 2457–2483.(c)Neeve EC; Geier SJ; Mkhali IAI; Westcott SA; Marder TB Diboron(4) Compounds: From Structural Curiosity to Synthetic Workhorse. *Chem. Rev* 2016, 116, 9091–9161. [PubMed: 27434758] (d)Fyfe JWB; Watson AJB Recent Developments in Organoboron Chemistry: Old Dogs, New Tricks. *Chem* 2017, 3, 31–55.(e)Hartwig JF Borylation and Silylation of C–H Bonds: A Platform for Diverse C–H Bond Functionalizations. *Acc. Chem. Res* 2012, 45, 864–873. [PubMed: 22075137] (f)Hall DG Boronic Acids: Preparation, Applications in Organic Synthesis and Medicine, 2nd ed.; Wiley-VCH: Weinheim, 2011.
- (2). (a)Nallagonda R; Padala K; Masarwa A Gem-Diborylalkanes: Recent Advances in Their Preparation, Transformation and Application. *Org. Biomol. Chem* 2018, 16, 1050–1064. [PubMed: 29379940] (b)Abu Ali H; Dembitsky VM; Srebnik M Recent Developments in Bisdiborane Chemistry: B–C–B, B–C–C–B, B–C=C–B, and B–C≡C–B Compounds and Their Biological Applications. *Stud. Inorg. Chem* 2005, 22, 59–117.
- (3). (a)Endo K; Ohkubo T; Hirokami M; Shibata T Chemoselective and Regiospecific Suzuki Coupling on a Multisubstituted sp³-Carbon in 1,1-Diborylalkanes at Room Temperature. *J. Am. Chem. Soc* 2010, 132, 11033–11035. [PubMed: 20698667] (b)Lee JCH; McDonald R; Hall DG Enantioselective Preparation and Chemoselective Cross-Coupling of 1,1-Diboron Compounds. *Nat. Chem* 2011, 3, 894–899. [PubMed: 22024887]
- (4). (a)Joannou MV; Moyer BS; Goldfogel MJ; Meek SJ Silver(I)-Catalyzed Diastereoselective Synthesis of Anti-1,2-Hydroxyboronates. *Angew. Chem. Int. Ed* 2015, 54, 14141–14145.

- (b)Matteson DS; Moody RJ Carbanions from Deprotonation of *gem*-Diboronic Esters. *J. Am. Chem. Soc* 1977, 99, 3196–3197.(c)Matteson DS; Moody RJ Deprotonation of 1,1-Diboronic Esters and Reactions of the Carbanions with Alkyl Halides and Carbonyl Compounds. *Organometallics* 1982, 1, 20–28.
- (5). (a)Wommack AJ; Kingsbury JS On the Scope of the Pt-Catalyzed Srebnik Diborylation of Diazoalkanes. An Efficient Approach to Chiral Tertiary Boronic Esters and Alcohols via B-Stabilized Carbanions. *Tetrahedron Lett.* 2014, 55, 3163–3166.(b)Hong K; Liu X; Morken JP Simple Access to Elusive α -Boryl Carbanions and Their Alkylation: An Umpolung Construction for Organic Synthesis. *J. Am. Chem. Soc* 2014, 136, 10581–10584. [PubMed: 25019925]
- (6). (a)Soundararajan R; Matteson DS Hydroboration with Haloborane/Trialkylsilane Mixtures. *Organometallics* 1995, 14, 4157–4166.(b)Endo K; Hirokami M; Shibata T Synthesis of 1,1-Organodiboronates via Rh(I)Cl-Catalyzed Sequential Regioselective Hydroboration of 1-Alkynes. *Synlett* 2009, 2009, 1331–1335.(c)Zuo Z; Huang Z Synthesis of 1,1-Diboronate Esters by Cobalt-Catalyzed Sequential Hydroboration of Terminal Alkynes. *Org. Chem. Front* 2016, 3, 434–438.
- (7). (a)Feng X; Jeon H; Yun J Regio- and Enantioselective Copper(I)-Catalyzed Hydroboration of Borylalkenes: Asymmetric Synthesis of 1,1-Diborylalkanes. *Angew. Chem. Int. Ed* 2013, 52, 3989–3992.(b)Scheuermann ML; Johnson EJ; Chirik PJ Alkene Isomerization–Hydroboration Promoted by Phosphine-Ligated Cobalt Catalysts. *Org. Lett* 2015, 17, 2716–2719. [PubMed: 26010715]
- (8). Wang L; Zhang T; Sun W; He Z; Xia C; Lan Y; Liu C C–O Functionalization of α -Oxyboronates: A Deoxygenative *gem*-Diborylation and *gem*-Silylborylation of Aldehydes and Ketones. *J. Am. Chem. Soc* 2017, 139, 5257–5264. [PubMed: 28306251]
- (9). Zhao H; Tong M; Wang H; Xu S Transition-Metal-Free Synthesis of 1,1-Diboronate Esters with a Fully Substituted Benzylic Center via Diborylation of Lithiated Carbamates. *Org. Biomol. Chem* 2017, 15, 3418–3422. [PubMed: 28387416]
- (10). Li H; Shangguan X; Zhang Z; Huang S; Zhang Y; Wang J Formal Carbon Insertion of *N*-Tosylhydrazone into B–B and B–Si Bonds: *gem*-Diborylation and *gem*-Silylborylation of sp^3 Carbon. *Org. Lett* 2013, 16, 448–451. [PubMed: 24350698]
- (11). (a)Abu Ali H; Goldberg I; Kaufmann D; Burmeister C; Srebnik M Novel C1-Bridged Bisboronate Derivatives by Insertion of Diazoalkanes into Bis(Pinacolato)Diborane(4). *Organometallics* 2002, 21, 1870–1876.(b)Abu Ali H; Goldberg I; Srebnik M Addition Reactions of Bis(Pinacolato)Diborane(4) to Carbonyl Enones and Synthesis of (Pinacolato)₂BCH₂B and (Pinacolato)₂BCH₂CH₂B by Insertion and Coupling. *Organometallics* 2001, 20, 3962–3965.
- (12). (a)Atack TC; Cook SP Manganese-Catalyzed Borylation of Unactivated Alkyl Chlorides. *J. Am. Chem. Soc* 2016, 138, 6139–6142. [PubMed: 27158838] (b)Ito H; Kubota K Copper(I)-Catalyzed Boryl Substitution of Unactivated Alkyl Halides. *Org. Lett* 2012, 14, 890–893. [PubMed: 22260229] (c)Shimizu M; Schelper M; Nagao I; Shimono K; Kurahashi T; Hiyama T Synthesis and Applications of 1,1-Diborylated Cyclopropanes: Facile Route to 1,2-Diboryl-3-Methylenecyclopentenes. *Chem. Lett* 2006, 35, 1222–1223.(d)Yang C-T; Zhang Z-Q; Tajuddin H; Wu C-C; Liang J; Liu J-H; Fu Y; Czyzewska M; Steel PG; Marder TB; Liu L Alkylboronic Esters from Copper-Catalyzed Borylation of Primary and Secondary Alkyl Halides and Pseudohalides. *Angew. Chem. Int. Ed* 2011, 51, 528–532.
- (13). (a)Cho SH; Hartwig JF Iridium-Catalyzed Diborylation of Benzylic C–H Bonds Directed by a Hydrosilyl Group: Synthesis of 1,1-Benzylidiboronate Esters. *Chem. Sci* 2014, 5, 694–698. (b)Jayasundara CRK; Sabasovs D; Staples RJ; Oppenheimer J; Smith III MR; Maleczka RE Jr. Cobalt-Catalyzed C–H Borylation of Alkyl Arenes and Heteroarenes Including the First Selective Borylations of Secondary Benzylic C–H Bonds. *Organometallics* 2018, 37, 1567–1574.(c)Mita T; Ikeda Y; Michigami K; Sato Y Iridium-Catalyzed Triple C(sp^3)–H Borylations: Construction of Triborylated sp^3 -Carbon Centers. *Chem. Commun* 2013, 49, 5601–5603.(d)Palmer WN; Obligation JV; Pappas I; Chirik PJ Cobalt-Catalyzed Benzylic Borylation: Enabling Polyborylation and Functionalization of Remote, Unactivated C(sp^3)–H Bonds. *J. Am. Chem. Soc* 2016, 138, 766–769. [PubMed: 26714178] (e)Palmer WN; Zarate C; Chirik PJ Benzyltriboronates: Building Blocks for Diastereoselective Carbon–Carbon Bond Formation. *J. Am. Chem. Soc* 2017, 139, 2589–2592. [PubMed: 28156108] (f)Shimada S; Batsanov AS;

Howard JAK; Marder TB Formation of Aryl- and Benzylboronate Esters by Rhodium-Catalyzed C-H Bond Functionalization with Pinacolborane. *Angew. Chem. Int. Ed* 2001, 40, 2168–2171.

- (14). (a) Nahm S; Weinreb SM *N*-Methoxy-*N*-Methylamides as Effective Acylating Agents. *Tetrahedron Lett.* 1981, 22, 3815–3818. (b) Singh J; Satyamurthi N; Aidhen IS The Growing Synthetic Utility of Weinreb's Amide. *J. Prakt. Chem* 2000, 342, 340–347.
- (15). (a) Smith AB; Boldi AM Multicomponent Linchpin Couplings of Silyl Dithianes via Solvent-Controlled Brook Rearrangement. *J. Am. Chem. Soc* 1997, 119, 6925–6926. (b) Smith AB; Pitram SM; Boldi AM; Gaunt MJ; Sfougataki C; Moser, W. H. Multicomponent Linchpin Couplings. Reaction of Dithiane Anions with Terminal Epoxides, Epichlorohydrin, and Vinyl Epoxides: Efficient, Rapid, and Stereocontrolled Assembly of Advanced Fragments for Complex Molecule Synthesis. *J. Am. Chem. Soc* 2003, 125, 14435–14445. [PubMed: 14624591] (c) Tietze LF; Geissler H; Gewert JA; Jakobi U Tandem-Bisalkylation of 2-Trialkylsilyl-1,3-Dithiane: A New Sequential Transformation for the Synthesis of C2-Symmetrical Enantiopure 1,5-Diols and β , β' -Dihydroxyketones as Well as of Enantiopure 1,3,5-Triols. *Synlett* 1994, 1994, 511–512. (d) Yus M; Nájera C; Foubelo F The Role of 1,3-Dithianes in Natural Product Synthesis. *Tetrahedron* 2003, 59, 6147–6212.
- (16). (a) Erdik E; Ay M Electrophilic Amination of Carbanions. *Chem. Rev* 1989, 89, 1947–1980. (b) Seyferth D The Grignard Reagents. *Organometallics* 2009, 28, 1598–1605.
- (17). (a) Murphy JA; Commeureuc AGJ; Snaddon TN; McGuire TM; Khan TA; Hisler K; Dewis ML; Carling R Direct Conversion of *N*-Methoxy-*N*-Methylamides (Weinreb Amides) to Ketones via a Nonclassical Wittig Reaction. *Org. Lett* 2005, 7, 1427–1429. [PubMed: 15787523] (b) Simmons BJ; Weires NA; Dander JE; Garg NK Nickel-Catalyzed Alkylation of Amide Derivatives. *ACS Catal.* 2016, 6, 3176–3179.
- (18). Willis MC Transition Metal Catalyzed Alkene and Alkyne Hydroacylation. *Chem. Rev* 2010, 110, 725–748. [PubMed: 19873977]
- (19). Wu X-F; Neumann H; Beller M Palladium-Catalyzed Carbonylative Coupling Reactions between Ar-X and Carbon Nucleophiles. *Chem. Soc. Rev* 2011, 40, 4986–5009. [PubMed: 21792459]
- (20). (a) Amani J; Alam R; Badir S; Molander GA Synergistic Visible-Light Photoredox/Nickel-Catalyzed Synthesis of Aliphatic Ketones via N-C Cleavage of Imides. *Org. Lett* 2017, 19, 2426–2429. [PubMed: 28445061] (b) Capaldo L; Riccardi R; Ravelli D; Fagnoni M Acyl Radicals from Acylsilanes: Photoredox-Catalyzed Synthesis of Unsymmetrical Ketones. *ACS Catal.* 2017, 8, 304–309. (c) Chu L; Lipshultz JM; MacMillan DWC Merging Photoredox and Nickel Catalysis: The Direct Synthesis of Ketones by the Decarboxylative Arylation of α -Oxo Acids. *Angew. Chem. Int. Ed* 2015, 54, 7929–7933.
- (21). Ni S; Padial NM; Kingston C; Vantourout JC; Schmitt DC; Edwards JT; Kruszyk MM; Merchant RR; Mykhailiuk PK; Sanchez BB; Yang S; Perry MA; Gallego GM; Mousseau JJ; Collins MR; Cherney RJ; Lebed PS; Chen JS; Qin T; Baran PS A Radical Approach to Anionic Chemistry: Synthesis of Ketones, Alcohols, and Amines. *J. Am. Chem. Soc* 2019, 141, 6726–6739. [PubMed: 30943023]
- (22). Iacono CE; Stephens TC; Rajan TS; Pattison G A Coupling Approach for the Generation of α , α -Bis(Enolate) Equivalents: Regioselective Synthesis of *gem*-Difunctionalized Ketones. *J. Am. Chem. Soc* 2018, 140, 2036–2040. [PubMed: 29381360]
- (23). Mukaiyama T; Murakami M; Oriyama T; Yamaguchi M A New Aldol Reaction: A Method for the Generation of Vinyloxyboranes by the Acylation of Boron-Stabilized Carbanions. *Chem. Lett* 1981, 10, 1193–1196.
- (24). Sun W; Wang L; Xia C; Liu C Dual Functionalization of α -Monoboryl Carbanions through Deoxygenative Enolization with Carboxylic Acids. *Angew. Chem. Int. Ed* 2018, 57, 5501–5505.
- (25). (a) Zheng P; Zhai Y; Zhao X; XU T Difunctionalization of Ketones via *gem*-Bis(Boronates) to Synthesize Quaternary Carbon with High Selectivity. *Chem. Commun* 2018, 54, 13375–13378. (b) Zheng P; Zhai Y; Zhao X; XU T Palladium-Catalyzed Cross-Coupling of *gem*-Bis(Boronates) with Aryl Halides: An Alternative to Access Quaternary α -Aryl Aldehydes. *Org. Lett* 2019, 21, 393–396. [PubMed: 30592427]
- (26). A related example where the reaction of α , α -diborylcarbanion and a chiral aldehyde results in complete retention of stereochemistry: Stephens TC; Pattison G Transition-Metal-Free-

Homologative Cross-Coupling of Aldehydes and Ketones with Geminal Bis(boron) Compounds. *Org. Lett* 2017, 19, 3498–3501. [PubMed: 28605914]

- (27). Observation of **3f** is consistent with a second addition of the α -boryl carbanion **8** after the first addition to diethylcarbonate. This is consistent with formation of a reactive *C*-bound boron enolate **4a** as a reaction intermediate, species that are rare as compared to their *O*-bound tautomer, **4b**.²⁸ Byproduct **3af** was likely generated by nucleophilic attack of the *O*-bound boron enolate intermediate on diethylcarbonate. **3f** **8** **4b** **3af**

- (28). (a)He Z; Zajdlik A; Yudin AK α -Borylcarbonyl Compounds: From Transient Intermediates to Robust Building Blocks. *Dalton Trans.* 2014, 43, 11434–11451. [PubMed: 24941221] (b)Ng EWH; Low K-H; Chiu P Synthesis and Applications of Unquaternized *C*-Bound Boron Enolates. *J. Am. Chem. Soc* 2018, 140, 3537–3541. [PubMed: 29481069]
- (29). Lee Y; Park J; Cho SH Generation and Application of (Diborylmethyl)Zinc(II) Species: Access to Enantioenriched *gem*-Diborylalkanes by an Asymmetric Allylic Substitution. *Angew. Chem. Int. Ed* 2018, 57, 12930–12934.
- (30). The activation of **1** was also observed upon treatment of **1** equivalent of *n*BuLi. For details, see Supporting Information (Figure S58–S61).
- (31). This assignment was further corroborated by comparison to the NMR data obtained from the mixing of internal benzyldiboronate **16** and LiOtBu where the deborylated product was formed exclusively (Figure S41–S47).
- (32). The formation of *tert*-butanol, which is generated by the deprotonation event, was not observed presumably due to the interaction between *tert*-butanol and boron-containing molecules.
- (33). (a)Matteson DS; Majumdar D α -Trimethylsilyl Boronic Esters. Pinacol Lithio(Trimethylsilyl)Methaneboronate, Homologation of Boronic Esters with [Chloro(Trimethylsilyl)Methyl]Lithium, and Comparisons with Some Phosphorus and Sulfur Analogues. *Organometallics* 1983, 2, 230–236. (b)Matteson DS; Arne K Carbanions from Deprotonation of α -(Phenylthio)Alkaneboronic Esters. *J. Am. Chem. Soc* 1978, 100, 1325–1326. (c)Matteson DS; Arne KH Carbanions from α -Phenylthio Boronic Esters as Synthetic Intermediates. *Organometallics* 1982, 1, 280–288.

A. Activation of benzyldiboronate in the absence of ester **B. ^1H NMR** **C. ^{11}B NMR** **Figure 1.**

In situ monitoring of the treatment of benzyldiboronate **1** with LiO^tBu in $\text{THF-}d_8$ by ^1H and ^{11}B NMR spectroscopies.

Figure 2.

(A) Reactions between activated benzyldiboronates and an ester and (B) ¹H NMR spectrum of each reaction.

Scheme 1.
Activation of *gem*-Diboronates.

A. Coupling of activated *gem*-diboronates with esters followed by electrophile trapping

■ Path I. Deprotonative addition

■ Path II. Deborylative addition

B. Previous results with benzyldi/triboronates ^{ref 13e}

■ LiTMP-promoted addition

■ Alkoxide-promoted addition

C. Preparation of ketones with a tertiary/quaternary α -carbon from simple methyl/alkyl arenes

Scheme 2.

Conversion of 1,1-Diboronate Esters into Functionalized Ketones.

Scheme 3. Scope of Carbonyl Coupling Partners.

Isolated yields are reported. Conditions: **1** (1 equiv.), LiO^tBu (1.5 equiv.), carbonyl derivatives (1 equiv.), THF (0.05M with respect to **1**), 23 °C, 3 h. ^bOnly protodeboronated product **5** was observed in the NMR spectrum of the unpurified product.

Scheme 4.
Possible Mechanisms for C–C Bond Formation.

Scheme 5. Generation of α -Boryl Carbanion **8 and the Subsequent Coupling Reaction.**

Isolated yields are given. Conditions: **5** (1 equiv.), LiTMP (1 equiv.), THF (0.05 M with respect to **1**), 0 °C, 30 min, then methyl butyrate (1 equiv.), rt, 3 h. See Table 1 for the reaction from **1**.

Scheme 6. One-Pot Synthesis of Highly Substituted Ketones from Benzyldiboronates.

Isolated yields are given. See SI for experimental details. ^aLiOtBu (1 equiv.) ^b13a (1 equiv.) at 0 °C, then 23 °C, 10 h. ^c13b (2 equiv. 80 wt.% in toluene) at 23 °C then 45 °C, 2 h. ^d13c (1.2 equiv.), 23 °C, 18 h. ^e13e (1.5 equiv.), 23 °C, 1 h. ^f13d (1.2 equiv.), 23 °C, 1 h. ^g13d (2.5 equiv.), 23 °C, 1 h. ^h13e (1.2 equiv.), 23 °C, 1 h. ⁱ13f (1.5 equiv.) at 23 °C, then 45 °C, 10 h.

Table 1.

Examination of the scope of ester partners.

Isolated yields are given. Conditions: **1** (1 equiv.), ester (1 equiv.), LiO^tBu (1.5 equiv.), THF (0.05 M with respect to **1**), 23 °C, 3 h. ^aEthyl butyrate was used instead of methyl butyrate. ^b*tert*-Butyl butyrate was used instead of methyl butyrate. ^cEnantiopurity of the corresponding esters was >99% ee. Due to the non-polarity of **3g**, ee determination of **3g** was not successful. ^dConditions: **3g** (1 equiv.), TBAF (tetrabutylammonium

fluoride) solution (1 M in THF, 1 equiv.), 0 °C, 1 h. ^eConditions: **1** (2 equiv.), dimethyl 2,6-pyridinedicarboxylate (1 equiv.), LiO^tBu (2 equiv.), THF (0.05 M with respect to **1**), 23 °C, 3 h.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 2.

Scope of benzyldiboronates.

Isolated yields are given. Conditions: diboronate (1 equiv.), ester (1 equiv.), LiO^tBu (1.5 equiv.), THF (0.05 M with respect to diboronate), 23 °C, 3 h.