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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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Simple Access to Elusive α-Boryl Carbanions and Their Alkylation: An Umpolung Construction for Organic Synthesis

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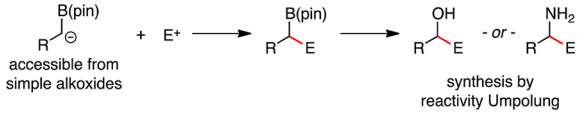
Supporting Information

ABSTRACT: The reaction of 1,1-bis(pinacolboronate) esters with alkyl halides can be effected by metal alkoxides and provides a strategy for the construction of organoboronate compounds. The reaction is found to occur by alkoxide-induced deborylation and generation of a boron-stabilized carbanion.

Alkylboronic esters are an important class of compounds that can be converted to a variety of useful building blocks by both catalytic and noncatalytic processes.[1] Whereas strategies for constructing these compounds by olefin hydroboration[2] or by addition of organometallics to borate ester derivatives[3] (i.e., pinBOMe) are well developed, recently emerging methods involving borylation of organic electrophiles[4] promise to provide expanded access to these motifs. In this report, we describe an alternate disconnection that provides simple and high yielding access to primary, secondary, and tertiary alkylboronic esters through the generation and electrophilic trap of α-boryl anions (Scheme 1).[5] In so far as alkyl pinacol boronates are subject to

Scheme 1. Utility of α-Boryl Carbanions

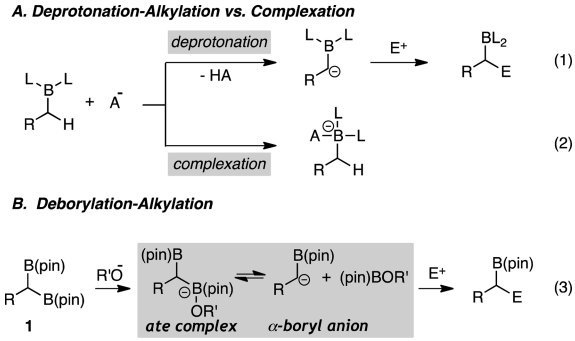


efficient oxidation[6] and amination,[7] these methods constitute a reactivity Umpolung[8] for alcohol and amine synthesis, and they offer convenient access to important reagents for other boron-based transformations.

The valence deficiency of three-coordinate boron can be used to stabilize anions at adjacent carbon centers.[5] Thus, significant attention has been paid to the synthesis and reactions of these species. While the pK_a of alkylboranes is low enough that they may be deprotonated with common amide bases (eq 1, Scheme 2),[9] the inherent electrophilicity of the boron center often results in competing complexation between the Brønsted base and the Lewis acidic boron center (eq 2). To avoid this outcome, large ligand frameworks (i.e., L = mesityl, Scheme 2) are often employed and these may complicate substrate synthesis and also limit transformations of the product.[10] Indeed, generation of α-monoboryl anions bearing commonly used boron substituents (i.e., pinacol boronates) by deprotonation pathways is generally ineffective.[11,12]

Recent studies in our laboratory have focused on the Pd-catalyzed enantioselective cross-couplings of geminal bis-

Scheme 2. Generation of α-Boryl Carbanions by Deborylation versus Deprotonation



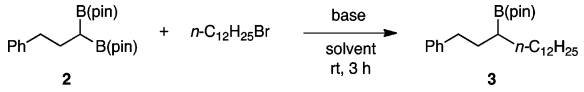
(boronates) such as **1** (Scheme 2).[13,14] Mechanistic studies showed that transmetalation involving **1**, in the presence of KOH, occurs with stereoinversion at carbon.[15] This outcome is consistent with a mechanism involving a reaction of an "ate" complex with an electrophilic Pd center. This reactivity pattern appeared consonant with that of an α-boryl anion, and it was of interest to determine if Pd might be replaced with other electrophiles, thereby enabling alkylations such as that in eq 3. This reactivity paradigm would be in line with studies by Aggarwal on the stereospecific (invertive) reaction between electrophiles and secondary boron ate complexes.[16,17] While related deborylative alkylations have been accomplished with geminal bis(dialkyl)boranes,[18] only two examples involving bis(pinacol)boronates have been described and they were both limited to benzylic substrates and employed strong base promoters under cryogenic conditions.[19] In this report, we describe an alkoxide-promoted deborylative alkylation of geminal boronates that applies to aliphatic primary, secondary, and tertiary derivatives and that can enable highly hindered C−C couplings between geminal boronates and alkyl halide electrophiles. We also provide the first direct experimental evidence that these reactions proceed through the intermediacy of highly reactive α-boryl carbanions. Given that geminal bis(boronates) are easily accessed on a large scale, such a reactivity pattern constitutes a practical strategy for the construction of common alkyl pinacol boronic esters.

To begin examining the deborylative alkylation reaction, preliminary experiments were conducted with geminal bis(boronate) **2** and bromododecane in the presence of anionic oxygen bases (Table 1). In analogy with our prior studies on

Received: May 30, 2014
Published: July 14, 2014

   dx.doi.org/10.1021/ja505455z | J. Am. Chem. Soc. 2014, 136, 10581−10584

Table 1. Effect of Base and Solvent on the Deborylative Alkylation of Geminal Bis(boronate) 2[a]



entry	base	solvent	conversion (%)[b]	yield (%)[c]
1	KOH	THF	<5	–[d]
2	LiO*t*-Bu	THF	<5	–[d]
3	NaO*i*-Pr	THF	<5	–[d]
4	NaO*t*-Bu	THF	100	91
5	KOMe	THF	30	–[d]
6	KO*t*-Bu	THF	100	68
7	NaO*t*-Bu	dioxane	75	70
8	NaO*t*-Bu	toluene	<5	–[d]
9	KO*t*-Bu	toluene	80	76

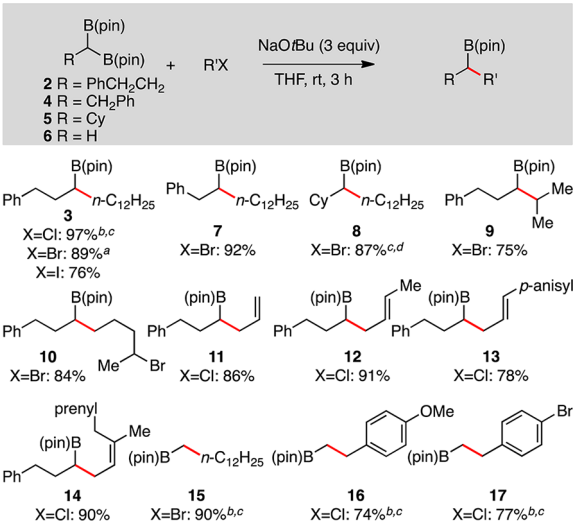
[a]Conditions: Bromododecane (0.10 mmol, 0.2 M), **2** (0.13 mmol), and base (0.30 mmol). [b]Refers to consumption of bromododecane and was determined by ^{1}H NMR versus an internal standard. [c]Isolated yield of purified material. [d]Partial protodeboronation of **2**.

cross-coupling, potassium hydroxide was examined as a promoter. In this experiment, little alkylation product **3** was detected with protodeboronation of the starting material **2** as the only reaction product. This outcome is consistent with eq 3, but with H^+ as the electrophile. To favor the alkylation pathway, subsequent reactions were conducted under anhydrous reaction conditions and with alkoxide bases. As depicted in Table 1, reactions with *tertiary* sodium and potassium alkoxides were highly effective and delivered the deborylative alkylation product **3** in good to excellent yield after 3 h of reaction at rt. From the data in Table 1, it can be concluded that important features of effective reactions are that the promoters are strong nucleophiles (*tert*-butoxides > methoxides) and that dissociation of the metal alkoxide ion pair enhances reactivity (K^+ > Na^+ in toluene; THF > toluene for sodium alkoxides). For a full analysis of reaction conditions and promoters, see the Supporting Information (SI).

The scope of the alkoxide-promoted deborylative alkylation was investigated with a panel of substrates. As shown in Table 2, with 3 equiv of NaO*t*Bu in THF, monosubstituted geminal boronates react with primary halides to furnish the secondary organoboronates in good yield. In addition to bromododecane examined in Table 1, it was found that chloro- and iododododecane also react efficiently to give **3** although iododododecane gives a slightly lower yield due to elimination of the iodide. While geminal bis(boronate) **5** required an elevated temperature and extended reaction time for an efficient reaction, it was still processed cleanly to the derived alkylation product **8**. Of note, secondary alkyl bromide electrophiles are also suitable substrates (compound **9**) and, importantly, a reactivity difference between primary and secondary alkyl halides enables selective alkylation of a primary bromide in the presence of the secondary one (compound **10**). Allylic chlorides also reacted cleanly in an S_N2 fashion (compounds **11**–**14**). Lastly, it is notable that deborylative alkylation with diborylmethane **6** is an efficient strategy for single-carbon homologation/borylation of alkyl halides (compounds **15**–**17**). With this substrate class, it is important to note that the unhindered diborylmethane **6** is vulnerable to deprotonation with NaO*t*Bu; however, KO*t*-Bu in toluene allows effective transformation.

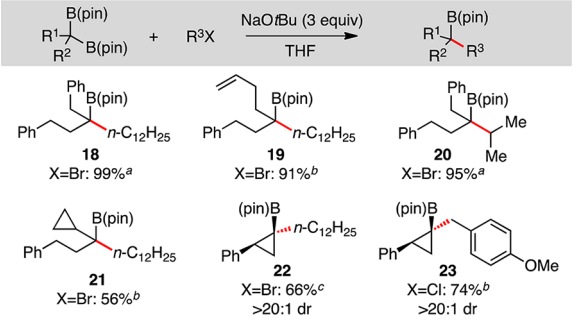
The alkoxide-promoted deborylative alkylation also extends to internal geminal bis(boronates) and allows construction of tertiary organoboronates (Table 3). While some alkylations

Table 2. Substrate Scope for Alkoxide-Promoted Deborylative Alkylation of Geminal Bis(boronates)



[a]This experiment was conducted on 1 g scale. [b]2.0 equiv of diboron, 5.0 equiv of KO*t*-Bu, toluene. [c]This experiment was conducted for 14 h. [d]This experiment was conducted at 40 °C.

Table 3. Deborylative Alkylation of Internal Geminal Bis(boronates)



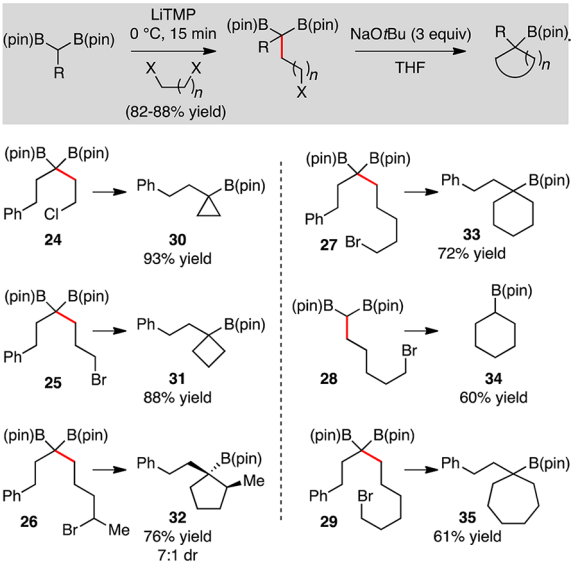
[a]This experiment was conducted at rt for 3 h. [b]This experiment was conducted at 50 °C for 14 h. [c]This experiment was conducted at 60 °C for 14 h.

required slightly elevated reaction temperatures, it is remarkable that construction of highly hindered reaction product **20** could proceed effectively at rt. Also of note, geminal bis(boryl)cyclopropanes, readily available from borylation of the corresponding 1,1-dibromocyclopropane,[20] could be alkylated with good yield and with outstanding levels of stereocontrol (compounds **22** and **23**).

Many of the substrates in Tables 2 and 3 were prepared by deprotonation and alkylation of readily available $RCH(Bpin)_2$ precursors. When 1,n-dihalides are employed in this alkylation reaction, the product is predisposed for intramolecular ring-forming deborylative alkylation. As depicted in Table 4, this strategy provides an efficient route to cyclic organoboronates that are not readily available by other methods. In the event, LiTMP-mediated deprotonation of the geminal bis(boronate) occurs rapidly at 0 °C (15 min), and subsequent alkylation generally proceeds to completion within 30 min. This alkylation reaction reliably delivered cyclization precursors **24**–**29** in good yield. Subsequent treatment with sodium *tert*-butoxide in THF provided carbocyclic derivatives **30**–**35** in good yield. Of note, the stereocenter in the tether of **26** lends a useful level of

dx.doi.org/10.1021/ja505455z | J. Am. Chem. Soc. 2014, 136, 10581–10584

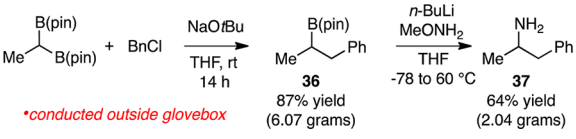
Table 4. Intramolecular Deborylative Alkylation for the Construction of Carbocyclic Organoboronates



stereocontrol in the deborylative cyclization, furnishing **32** as a 7:1 mixture of diastereomers.

To probe the utility of the deborylative alkylation for larger scale synthesis of important target structures, the construction of pharmaceutically relevant phenethylamines was examined. As depicted in Scheme 3, deborylative alkylation of 1,1-bis(boryl)-

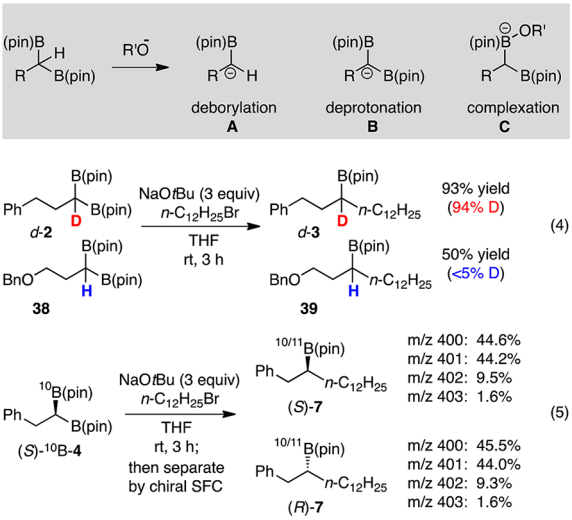
Scheme 3. Deborylative Alkylation for the Construction of Phenethylamine Building Blocks



ethane with benzyl chloride was conducted under nitrogen, but without the aid of a drybox during weighing and transfer manipulations. The construction of **36** occurred in 87% yield, and of note, this reaction sequence was conducted on a scale that delivered >6 g of **36**. Amination of the pinacol boronate with lithiated methoxyamine[7a] proceeded with reasonable efficiency furnishing phenethylamine derivative **37** on a synthetically useful scale.

Regarding the reaction mechanism, generation of an α-boryl carbanion (**A**, Scheme 4), followed by alkylation, is one plausible pathway. For some substrates, it is also tenable that deprotonation of the bis(boronate) generates anion **B**, which then undergoes alkylation and protodeboronation. Lastly, it was considered that complexation between the alkoxide and the bis(boronate) might provide an "ate" complex (**C**) that participates directly in alkylation. To distinguish these pathways, the experiments in eqs 4 and 5 were conducted. When an equimolar mixture of **38** and deuterium-labeled **2** were subjected to the reaction conditions (eq 4), deuterium-labeled **3** was isolated in 93% yield with only a slight loss of deuterium content. This result suggests that alkylation of **B** is not likely the predominant pathway. To establish whether **A** or **C** is the reactive species involved in direct alkylation, deborylative alkylation of ^{10}B-labeled nonracemic **4** was examined (eq 5). After separation of the product enantiomers, mass spectrometry

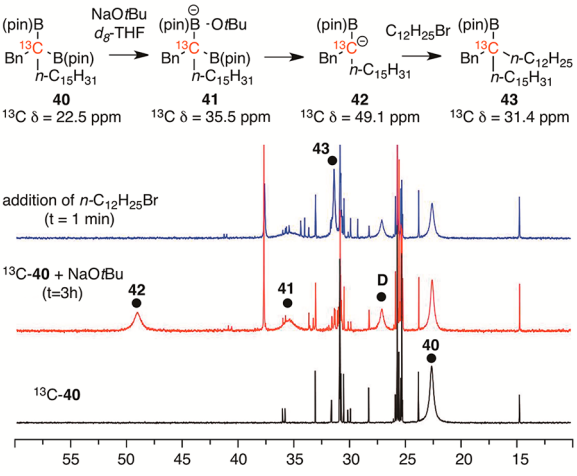
Scheme 4. Mechanistic Analysis of Deborylative Alkylation of Geminal Bis(boronates)



revealed an identical isotopic distribution for each, suggesting a nonstereospecific reaction mechanism.[21] Had **C** been involved in the direct stereoinvertive alkylation, then (*S*)-^{10}B-**4** would have given (*R*)-7 enriched in ^{10}B and (*S*)-7 enriched in ^{11}B. Thus, the observed experimental outcome is most consistent with the participation of an α-boryl carbanion (**A**) as opposed to nucleophilic "ate" complex **C**.

While multiple boron-containing species present in the reaction rendered ^{11}B NMR analysis uninformative, spectroscopic support for the intermediacy of an α-boryl carbanion was gained through ^{13}C NMR analysis (Scheme 5). Upon subjection

Scheme 5. ^{13}C-NMR Analysis of Deborylative Alkylation



of ^{13}C-labeled **40** (^{13}C δ = 22.5 ppm) to NaO*t*Bu in THF, three new resonances (**D**, **41**, and **42**, Scheme 5) appear over the course of 3 h. The resonance at 27.1 ppm (**D**, Scheme 5) corresponds to the product of protodeboronation of **40**; the resonance at 35.5 ppm appears at the beginning of the reaction and is attributed to ate complex **41** (Scheme 5); and the resonance at 49.1 ppm grows in more slowly than **41** and, on the basis of its reactivity, is assigned to α-boryl carbanion **42**. Upon addition of bromododecane to the reaction mixture, the resonance at 49.1 ppm is immediately replaced with a resonance at 31.4 ppm, the latter of which corresponds to deborylative

dx.doi.org/10.1021/ja505455z | J. Am. Chem. Soc. 2014, 136, 10581−10584

alkylation product **43**. Two features are of note in this experiment: first, the chemical shift of putative intermediate **42** is far more downfield than is typical for an alkali-metal-derived carbanion (^{13}C δ = −15.3 ppm for CH_3Li[22]), presumably a consequence of delocalization of the electron density of the anion with the empty *p* orbital of the adjacent boron (C═B bonding). This bonding mode has been noted previously in the Mes_2BCH_2 anion.[10] A second notable feature is the remarkable reaction rate between **42** and the alkyl halide, clearly suggesting that, for this reagent pair, the deborylation is the rate-limiting step of the overall reaction.[23]

In summary, α-boryl carbanions are versatile reagents for organic synthesis and they are easily generated under mild reaction conditions from readily accessible starting materials. Their configurational instability may render them verastile prochiral nucleophiles in asymmetric catalysis, and these features are being probed. Studies to further characterize the properties of α-(pinacolato)boronate anions are also in progress.

■ ASSOCIATED CONTENT

Supporting Information

Procedures, characterization, and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The NIH (GM-59471) is acknowledged for financial support; AllyChem is acknowledged for a donation of $B_2(pin)_2$.

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