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Chemoselective Benzylation of Aldehydes Using Lewis Base Activated Boronate Nucleophiles

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Abstract

A benzylation of aldehydes using primary and secondary benzylboronic acid pinacol esters is reported. Activation of the boronic ester with *s*-butyllithium rendered it nucleophilic toward aldehydes. The activated nucleophile chemoselectively transfers the benzyl group over the *s*-butyl group, providing excellent yields of the benzylated products. ^{11}B NMR experiments were performed to study the mechanism of this transformation.

Graphical Abstract

INTRODUCTION

Organoboron reagents are useful intermediates in organic synthesis.¹ The boronic acid pinacol ester functional group has been exploited in natural product synthesis through the Suzuki-Miyaura cross-coupling reaction.^{1a} Benzylboronic esters are a subclass of organoboron reagents that are less developed in their synthetic applications than the widely used arylboronic acids.² Traditionally, benzylboronic esters are synthesized from the corresponding alkyl halide either through Grignard formation,³ or the use of a transition metal catalyst.^{4–6} More recently, these compounds have been prepared through C-H activation using transition metal catalysts^{7–10} or other methods.^{11–14}

While our interests were in developing a reaction between the primary benzylboronic acid pinacol ester and aldehydes, the use of secondary and tertiary benzylic boronic esters has received much attention in the development of stereospecific transformations employing enantioenriched benzylic boronic esters.¹⁵ Stereospecific synthesis and subsequent

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Supporting Information

The Supporting Information including experimental procedures and ^1H , ^{13}C , and ^{11}B spectra is available free of charge on the ACS Publications website.

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oxidations of tertiary boronic esters have provided tertiary alcohols¹⁶ and amines.^{17,18} Numerous other stereospecific reactions have provided arylation,¹⁹ protodeboronation,²⁰ halogenation,²¹ and various carbon homologations of secondary and tertiary benzylic boronic esters.^{15a} There are examples of Rh-catalyzed addition of secondary benzylboronic esters to aldehydes²² and imines;²³ however, electrophiles required electron-withdrawing groups to obtained good yields.

In contrast, there are only a few reported examples of primary benzylboronic esters as reactants (Scheme 1). Previous reports have demonstrated the oxidation of benzylboronic acid pinacol ester (BnBpin) to the corresponding alcohol, iodide, and amine compounds.^{8,17} Additionally, BnBpin has been employed in Pd-catalyzed cross-coupling reactions as well as Cu-catalyzed Chan-Lam type couplings with anilines and phenols.^{8,24} BnBpin is not moisture sensitive and commercially available, making it attractive reagent for further development. We sought to develop a reaction using BnBpin as a nucleophile with aldehydes.

Primary benzylboronic esters are more challenging substrates than substituted benzylboronic esters. Mayr and Aggarwal have combined BnBpin and phenyllithium to form a boronate nucleophile and measured its nucleophilicity in reactions with dibenzylic carbocations.²⁵ These studies found the boronate species generated from BnBpin to be less nucleophilic than boronates from secondary benzylboronic esters. We anticipated that using an alkylolithium to generate the boronate nucleophile would increase the nucleophilicity of the benzyl moiety, opening a new class of reactivity.

We began our investigations with examining the nucleophilic addition of BnBpin to benzaldehyde (Table 1). Activating BnBpin with *n*-BuLi and no additives provided a 38% yield of the desired product along with benzyl alcohol and trace amounts of benzoic acid (entry 1). Formation of benzyl alcohol can be formed by β -hydride transfer from the butyl group when attached to the boronate,²⁶ a Cannizzaro side reaction catalyzed by Li ions²⁷ or air oxidation of BnBpin.²⁸ The inclusion of polar aprotic additives was then pursued to favor nucleophilic benzyl addition over formation of benzyl alcohol.²⁹ The addition of NMP was effective, providing the desired product in 82% yield (entry 2). Use of DMPU and TMEDA as additives also showed an improvement in the yield (entries 3–4). *s*-BuLi was found to be equally effective as *n*-BuLi with NMP as an additive (entry 5). A control experiment revealed NMP was not necessary when using *s*-BuLi (entry 6). *s*-BuLi has previously been used to activate alkylboronic esters for Pd-catalyzed cross-coupling.³⁰ Examination of other organometal activating agents including PhLi found *s*-BuLi to be the most effective (entries 7–9).

It is significant that no butyl addition to the aldehyde was observed, indicating a chemoselective transfer of the benzyl group is possible with alkylolithium activation of BnBpin. This result was consistent across all organometallic Lewis base reagents examined, with the benzyl group always being selectively transferred with no evidence of the other group being transferred during the optimization. Control experiments confirmed there was no reaction observed between BnBpin and benzaldehyde in a variety of solvents with heating. Activation of BnBpin with metal alkoxides also provided none of the desired

reactivity, suggesting that irreversible coordination of a Lewis base was necessary to obtain the desired reactivity.

With optimal conditions in hand, the substrate scope with respect to the aldehyde was examined. Excellent yields were obtained with aromatic aldehydes (Table 2). Both electron-donating and electron-withdrawing substituents performed well under these reaction conditions, with all of these reactions going to completion in 3 h. This benzylation proved to be very tolerant of electronic changes on the aldehyde.^{22a} Given the lack of difference in reaction efficiency with electronically differentiated *para* substituents, a competition experiment was performed that found *p*-trifluoromethylbenzaldehyde reacted faster than *p*-methoxybenzaldehyde as would be expected.³¹ Reactions with heterocyclic aldehydes also gave respectable yields under these reaction conditions (**10** and **11**). A reaction with cyclohexylcarboxaldehyde resulted in a 68% yield of **12**, providing an example of an aliphatic aldehyde substrate.

¹¹B NMR was used to support the proposed intermediates in the mechanism (Scheme 2). BnBpin has a ¹¹B NMR resonance at 33 ppm. Addition of one equivalent of *s*-BuLi resulted in the appearance of a resonance at 8 ppm, consistent with the chemical shift of LiArBnBpin intermediates previously observed by Aggarwal.³² At the conclusion of the reaction, a new resonance was observed at 34.5 ppm, which matches the reported data for *s*-BuBpin.³³

A secondary benzylic boronic acid pinacol ester was also examined as a nucleophile (Scheme 3). With benzaldehyde as the electrophile, the secondary alcohol was isolated in a 79% yield. The efficiency of this reaction compares favorably to a previously reported Rh-catalyzed addition of secondary benzylic trifluoroborate salts to aldehydes that required an electron-withdrawing substituent on the aldehyde to obtain yields above 50%.^{22a} A 1:1 mixture of diastereomers was isolated. This result was not surprising since this addition is presumed to go through an open transition state.

In summary, a method for the benzylation of aldehydes using Lewis base activated boronate nucleophiles was described. Activation of the BnBPin by an alkylolithium reagent was necessary to render the benzyl group nucleophilic. An important discovery was the chemoselective transfer of the benzyl group over butyl substituents of the activated boronate nucleophile under the reaction conditions, allowing for formation of the benzylation products in excellent yields, especially with aryl aldehydes. The presence of electron-donating or electron-withdrawing substituents on the aldehyde did not affect the efficiency of the reaction. In our laboratory we plan to pursue the benzylation of other electrophiles using this methodology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

- (1). (a)Suzuki A Cross-Coupling Reactions Of Organoboranes: An Easy Way To Construct C–C Bonds. *Angew. Chem. Int. Ed* 2011, 50, 6722–6737;(b)Jana R; Pathak TP; Sigman MS Advances in Transition Metal (Pd,Ni,Fe)-Catalyzed Cross-Coupling Reactions Using Alkyl-Organometallics as Reaction Partners. *Chem. Rev* 2011, 111, 1417–1492; [PubMed: 21319862] (c)Partyka DV Transmetalation of Unsaturated Carbon Nucleophiles from Boron-Containing Species to the Mid to Late d-Block Metals of Relevance to Catalytic C–X Coupling Reactions (X = C, F, N, O, Pb, S, Se, Te). *Chem. Rev* 2011, 111, 1529–1595; [PubMed: 21391563] (d)Qiao JX; Lam PYS Copper-Promoted Carbon-Heteroatom Bond Cross-Coupling with Boronic Acids and Derivatives. *Synthesis* 2011, 829–856;(e)Wu X; Anbarasan P; Neumann H; Beller M From noble metal to Nobel Prize: palladium-catalyzed coupling reactions as key methods in organic synthesis. *Angew. Chem. Int. Ed* 2010, 49, 9047–9050;(f)Crudden CM; Glasspoole BW; Lata CJ Expanding the scope of transformations of organoboron species: carbon-carbon bond formation with retention of configuration. *Chem. Commun* 2009, 6704–6716;(g)Doucet H Suzuki–Miyaura Cross-Coupling Reactions of Alkylboronic Acid Derivatives or Alkyltrifluoroborates with Aryl, Alkenyl or Alkyl Halides and Triflates. *Eur. J. Org. Chem* 2008, 2013–2030;(h)Miyaura N Metal-Catalyzed Reactions of Organoboronic Acids and Esters. *Bull. Chem. Soc. Jpn* 2008, 81, 1535–1553;(i)Xu L; Zhang S; Li P Boron-selective reactions as powerful tools for modular synthesis of diverse complex molecules. *Chem. Soc. Rev* 2015, 44, 8848–8858. [PubMed: 26393673]
- (2). Sandford C; Aggarwal VK Stereospecific functionalizations and transformations of secondary and tertiary boronic esters. *Chem. Commun* 2017, 53, 5471–5494.
- (3). (a)Pintaric C; Olivero S; Gimbert Y; Chavant PY; Duñach E An Opportunity for Mg-Catalyzed Grignard-Type Reactions: Direct Coupling of Benzylic Halides with Pinacolborane with 10 mol % of Magnesium. *J. Am. Chem. Soc* 2010, 132, 11825–11827. [PubMed: 20687557] (b)Clary JW; Rettenmaier TJ; Snelling R; Bryks W; Banwell J; Wipke WT; Singaram B Hydride as a leaving group in the reaction of pinacolborane with halides under ambient Grignard and Barbier conditions. One-pot synthesis of alkyl, aryl, heteroaryl, vinyl, and allyl pinacolboronic esters. *J. Org. Chem* 2011, 76, 9602–9610. [PubMed: 22040316]
- (4). Attack TC; Lecker RM; Cook SP Iron-catalyzed borylation of alkyl electrophiles. *J. Am. Chem. Soc* 2014, 136, 9521–9523. [PubMed: 24955892]
- (5). (a)Ito H; Kubota K Copper(I)-Catalyzed Boryl Substitution of Unactivated Alkyl Halides. *Org. Lett* 2012, 14, 890–893. [PubMed: 22260229] (b)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* 2012, 51, 528–532.
- (6). Murata M; Oyama T; Watanabe S; Masuda Y Synthesis of Benzylboronates via Palladium-Catalyzed Borylation of Benzyl Halides with Pinacolborane. *Synth. Commun* 2002, 32, 2513–2517.
- (7). Palmer WN; Obligation JV; Pappas I; Chirik PJ Cobalt-Catalyzed Benzylic Borylation: Enabling Polyborylation and Functionalization of Remote, Unactivated C(sp³)–H Bonds. *J. Am. Chem. Soc* 2016, 138, 766–769. [PubMed: 26714178]
- (8). Larson MA; Wilson CV; Hartwig JF Iridium-Catalyzed Borylation of Primary Benzylic C–H Bonds without a Directing Group: Scope, Mechanism, and Origins of Selectivity. *J. Am. Chem. Soc* 2015, 137, 8633–8643. [PubMed: 26076367]
- (9). 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.
- (10). Ishiyama T; Ishida K; Takagi J; Miyaura N Palladium-Catalyzed Benzylic C–H Borylation of Alkylbenzenes with Bis(pinacolato)diboron or Pinacolborane. *Chem. Lett* 2001, 30, 1082–1083.
- (11). (a)Zhang H; Hagihara S; Itami K Making Dimethylamino a Transformable Directing Group by Nickel-Catalyzed C–N Borylation. *Chem. Eur. J* 2015, 21, 16796–16800. [PubMed: 26435307]

- (b)Hu J; Sun H; Cai W; Pu X; Zhang Y; Shi Z Nickel-Catalyzed Borylation of Aryl- and Benzyltrimethylammonium Salts via C–N Bond Cleavage. *J. Org. Chem* 2016, 81, 14–24. [PubMed: 26628255]
- (12). (a)Cao Z-C; Luo F-X; Shi W-J; Shi Z-J Direct borylation of benzyl alcohol and its analogues in the absence of bases. *Org. Chem. Front* 2015, 2, 1505–1510.(b)Mao L; Szabó KJ; Marder TB Synthesis of Benzyl-, Allyl-, and Allenyl-boronates via Copper-Catalyzed Borylation of Alcohols. *Org. Lett* 2017, 19, 1204–1207. [PubMed: 28207271]
- (13). Li H; Wang L; Zhang Y; Wang J Transition-Metal-Free Synthesis of Pinacol Alkylboronates from Tosylhydrazones. *Angew. Chem. Int. Ed* 2012, 51, 2943–2946.
- (14). for one-carbon homologation of arylBpin see: Wu C; Wu G; Zhang Y; Wang J One-carbon homologation of arylboronic acids: a convenient approach to the synthesis of pinacol benzylboronates. *Org. Chem. Front* 2016, 3, 817–822.
- (15). (a)Leonori D; Aggarwal VK Lithiation–Borylation Methodology and Its Application in Synthesis. *Acc. Chem. Res* 2014, 47, 3174–3183. [PubMed: 25262745] (b)Leonori D; Aggarwal VK Stereospecific Couplings of Secondary and Tertiary Boronic Esters. *Angew. Chem. Int. Ed* 2014, 54, 1082–1096.(c)Scott HK; Aggarwal VK Highly Enantioselective Synthesis of Tertiary Boronic Esters and their Stereospecific Conversion to other Functional Groups and Quaternary Stereocentres. *Chem. Eur. J* 2011, 17, 13124–13132. [PubMed: 22052475]
- (16). Stymiest JL; Bagutski V; French RM; Aggarwal VK Enantiodivergent conversion of chiral secondary alcohols into tertiary alcohols. *Nature* 2008, 456, 778–782. [PubMed: 19079057]
- (17). Mlynarski SN; Karns AS; Morken JP Direct Stereospecific Amination of Alkyl and Aryl Pinacol Boronates. *J. Am. Chem. Soc* 2012, 134, 16449–16451. [PubMed: 23002712]
- (18). Bagutski V; Elford TG; Aggarwal VK Synthesis of Highly Enantioenriched C-Tertiary Amines From Boronic Esters: Application to the Synthesis of Igmesine. *Angew. Chem. Int. Ed* 2011, 50, 1080–1083.
- (19). Bonet A; Odachowski M; Leonori D; Essafi S; Aggarwal VK Enantiospecific sp(2)–sp(3) Coupling of Secondary and Tertiary Boronic Esters. *Nat. Chem* 2014, 6, 584–589. [PubMed: 24950327]
- (20). Nave S; Sonawane RP; Elford TG; Aggarwal VK Protodeboration of Tertiary Boronic Esters: Asymmetric Synthesis of Tertiary Alkyl Stereogenic Centers. *J. Am. Chem. Soc* 2010, 132, 17096–17098. [PubMed: 21080646]
- (21). (a)Larouche-Gauthier R; Elford TG; Aggarwal VK Ate Complexes of Secondary Boronic Esters as Chiral Organometallic-Type Nucleophiles for Asymmetric Synthesis. *J. Am. Chem. Soc* 2011, 133, 16794–16797. [PubMed: 21939203] (b)Sandford C; Rasappan R; Aggarwal VK Synthesis of Enantioenriched Alkylfluorides by the Fluorination of Boronate Complexes. *J. Am. Chem. Soc* 2015, 137, 10100–10103. [PubMed: 26244235]
- (22). (a)Ros A; Aggarwal VK Complete Stereoretention in the Rhodium-Catalyzed 1,2-Addition of Chiral Secondary and Tertiary Alkyl Potassium Trifluoroborate Salts to Aldehydes. *Angew. Chem. Int. Ed* 2009, 48, 6289–6292.(b)Zhang C; Yun J Rh-catalyzed Addition of β -Carbonyl Pinacol Alkylboronates to Aldehydes: Asymmetric Synthesis of γ -Butyrolactones. *Org. Lett* 2013, 15, 3416–3419. [PubMed: 23773146]
- (23). Lee S; Lee WM; Yun J Rhodium-Catalyzed Addition of Alkyltrifluoroborate Salts to Imines. *Adv. Synth. Catal* 2015, 357, 2219–2222.
- (24). Sueki S; Kuninobu Y Copper-Catalyzed N- and O-Alkylation of Amines and Phenols using Alkylborane Reagents. *Org. Lett* 2013, 15, 1544–1547. [PubMed: 23521042]
- (25). Feeney K; Berionni G; Mayr H; Aggarwal VK Structure and Reactivity of Boron-Ate Complexes Derived from Primary and Secondary Boronic Esters. *Org. Lett* 2015, 17, 2614–2617. [PubMed: 25973673]
- (26). Hatano M; Suzuki S; Ishihara K Highly Efficient Alkylation to Ketones and Aldimines with Grignard Reagents Catalyzed by Zinc(II) Chloride. *J. Am. Chem. Soc* 2006, 128, 9998–9999. [PubMed: 16881613]
- (27). Mojtahedi MM; Akbarzadeh E; Sharifi R; Abaee MS Lithium Bromide as a Flexible, Mild, and Recyclable Reagent for Solvent-Free Cannizzaro, Tischenko, and Meerwein–Ponndorf–Verley Reactions. *Org. Lett* 2007, 9, 2791–2793. [PubMed: 17580879]

- (28). Jiang M; Yang H; Fu H Visible-Light Photoredox Borylation of Aryl Halides and Subsequent Aerobic Oxidative Hydroxylation. *Org. Lett* 2016, 18, 5248–5251. [PubMed: 27690142]
- (29). Mukhopadhyay T; Seebach D Substitution of HMPT by the cyclic urea DMPU as a cosolvent for highly reactive nucleophiles and bases. *Helv. Chim. Acta* 1982, 65, 385–391.
- (30). Zou G; Falck JR Suzuki–Miyaura Cross-Coupling of Lithium n-Alkylborates. *Tetrahedron Lett* 2001, 42, 5817–5819.
- (31). See Supporting Information for details.
- (32). Llaveria J; Leonori D; Aggarwal VK Stereospecific Coupling of Boronic Esters with N-Heteroaromatic Compounds. *J. Am. Chem. Soc* 2015, 137, 10958–10961. [PubMed: 26292943]
- (33). Bose SK; Brand S; Omereghe HO; Haehnel M; Maier J; Bringmann G; Marder TB Highly Efficient Synthesis of Alkylboronate Esters via Cu(II)-Catalyzed Borylation of Unactivated Alkyl Bromides and Chlorides in Air. *ACS Catal* 2016, 6, 8332–8335.

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Scheme 1.
Reactions with BnBpin

Scheme 2.
¹¹B NMR of Reaction

Scheme 3.
Secondary Benzyl Boronate Nucleophile

Table 1.

Optimization of Reaction Conditions

entry	change from standard conditions	yield % ^a
1	<i>n</i> -BuLi	38
2	<i>n</i> -BuLi with NMP	82
3	<i>n</i> -BuLi with DMPU	71
4	<i>n</i> -BuLi with TMEDA	74
5	<i>s</i> -BuLi with NMP	82
6	<i>s</i> -BuLi with no additives	100 (98) ^b
7	MeLi	54
8	PhLi	6
9	MeMgBr	20

^a yields determined by NMR using an internal standard

^b Isolated

Table 2.

Aldehyde Substrate Scope