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Stereoselective Tandem Bis-Electrophile Couplings of Diborylmethane

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Abstract

A copper-catalyzed three-component linchpin coupling method for the stereoselective union of readily available epoxides and allyl electrophiles is disclosed. Transformations employ [B(pin)]₂-methane as a conjunctive reagent, resulting in the formation of two C–C bonds at a single carbon center bearing a C(sp³) organoboron functional group. Products are obtained in 42–99% yield, and up to >20:1 dr. The utility of the approach is highlighted by stereospecific transformations entailing allylation, tandem cross coupling, and application to the synthesis 1,3-polyol motifs.

Chemical processes that stereoselectively construct multiple C–C bonds through single operations provide efficient strategies for the synthesis of important, complex bioactive molecules.¹ In particular, substrate-controlled diastereoselective tandem processes have enjoyed significant attention as enabling strategies for rapid acyclic stereocontrol.² Consequently, a number of tandem reactions that construct two C–C bonds in a single operation through a linchpin single-carbon center have been developed. Such examples include the dithiane anion relay chemistry developed by Smith in which a dithiane unit (e.g., **A**) serves as a double carbanion equivalent (Scheme 1a).³ In such transformations the dithiane carbon does not turn into a new C(sp³) stereocenter. This is in contrast to silyl glyoxylates (e.g., **C**) utilized by Johnson and co-workers in multicomponent electrophile/nucleophile couplings (Scheme 1a).⁴ Such reagents represent dual cation/anion synthons, wherein the acyl carbon becomes an C(sp³) stereocenter.

1,1-Diborylalkanes (e.g., **D**) also represent potential versatile conjunctive reagents for stereoselective tandem linchpin couplings due to their versatile nature (Scheme 1c). Not only can both boron units be functionalized by deborylative processes,⁵ but due to the stabilizing effect of the two boron groups, the α -C–H bonds are rendered relatively acidic ($pK_a \sim 31$).^{6a,b} In the presence of lithium amide bases, [B(pin)]₂.C(H)Li (pin = pinacolato) can be generated, which reacts with electrophiles.⁶

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Supporting Information

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Experimental procedures and spectral and analytical data for all products (PDF)

Notes

The authors declare no competing financial interest.

Herein, we report a stereoselective one-pot three-component Cu-catalyzed coupling strategy that employs [B(pin)]₂methane as a conjunctive reagent, which enables the couplings of epoxides and allyl electrophiles. The general reaction design that affords 1,3-hydroxy-organoborons is illustrated in Scheme 1d. Ring-opening of readily available chiral epoxides with [B(pin)]₂-C(H)Li (**1**) results in the formation of diastereomeric cyclic boronates **E** and **F**. Through substrate-controlled cyclic boronate formation or interconversion, subsequent stereospecific deborylative transmetalation generates organocopper **G**, which can engage with an electrophile.⁷ Examples of stereocontrolled C–C bond forming reactions that proceed via the intermediacy of a chelated boron-stabilized carbanion include the coupling of zincated-hydrazones with alkenylboronates,⁸ and substrate-controlled deborylative alkylations of tris-boronates.^{5b} The overall transformation in Scheme 1d generates two C–C bonds and a new tertiary stereogenic center containing a versatile C(sp³)-B(pin) moiety.

We initiated our studies with the coupling of (*R*)-styrene oxide (**2**) and allyl halide (Table 1). A key objective of the first phase centered on the ability to efficiently form two C–C bonds to [B(pin)]₂methane in a single operation. When (*R*)-styrene oxide (**2**) is treated with [B(pin)]₂-C(H)Li **1** (1.5 equiv) in tetrahydrofuran (0 to 22 °C, 15 min), and the resulting mixture subjected to 15 mol % CuCl and allyl chloride at 22 °C, 52% conversion to 1,3-hydroxyboronate **3** is observed in 24 h (with a diastereomeric ratio, dr, of 3:1 anti/syn) (Table 1, entry 1).^{9,10} Reactions run at 45 and 60 °C proceeded with similar efficiency but in 2:1 dr (entries 2–3). Lower dr and diminished reactivity is furnished with phosphonate- and acetate-derived allyl electrophiles (entries 4–5). With allyl bromide the tandem reaction afforded **3** in 77% conversion and 8:1 dr (entry 6). Varying the copper salt resulted in either diminished conversion and/or selectivity (entries 7–9). Lastly, reactions in the presence of phosphine ligands proceed with similar efficiency but lower dr (entries 10–11).

A wide array of terminal and internal epoxides participate in the three-component coupling reaction. To facilitate isolation of the C(sp³) organoborons, the 1,3-hydroxyborons were protected as the TBS ethers. As illustrated in Scheme 2, aryl-substituted 1,3-hydroxyboronates (**4–8**) are generated in 45–70% yield and in high dr (8:1 to >20:1 dr anti/syn). Reactions with terminal epoxides bearing sterically less demanding alkyl substituents furnished **9–12** efficiently (61–80% yield) albeit in up to 3:1 dr. With cyclohexene oxide, tandem C–C bond formation results in the stereoselective synthesis of **13** in 74% isolated yield bearing three stereogenic centers in >20:1 dr. Notably, trans-epoxides failed to undergo efficient ring-opening by **2**; for example, *trans*- β -methylstyrene oxide results in <20% conversion to a complex mixture of regioisomers and diastereomers. Geminal disubstituted epoxides react with varying efficiency, as the reaction to form **14** proceeds in 58% yield and 5:1 dr, whereas β -pinene oxide derived **15** is furnished in 60% yield but 2:1 dr. Lastly, sterically congested limonene oxide provides **16** in 42% isolated yield as a single stereoisomer.

Increasing substitution on the 1,1-diboron was found to be tolerated in the epoxide-opening step; however, the corresponding cyclic borate failed to undergo transmetalation to Cu and allylic substitution. For example, reaction of **17** with 1-dodecene oxide efficiently generates ketone aldol product **18** in 80% yield after oxidation (eq 1).

Followup studies illustrated in Scheme 3, demonstrate that a variety of substituted allyl electrophiles as well as dienyl bromides perform efficiently under standard conditions (15

(1)

mol % CuCl, 1.0 equiv **2**, 1.5 equiv **1**), establishing two new C–C bonds and a stereocenter in good diastereoselectivity. Several features of these studies are notable: (1) Substituents at the 2-carbon of the allyl unit result in formation of the anti-product (e.g., **20**, **22**, and **24**) in high selectivity 7:1 to >20:1 dr. (2) 3-Substituted allyl bromides afford the desired alkyl-B(pin) products with good regiocontrol but with diminution in dr (e.g., **19**, **21**, and **23**). (3) Vinyl halides (**24**) but not esters (**25**) are tolerated under the reaction conditions. (4) Reaction with (*E*)-5-bromopenta-1,3-diene affords S_N2 substitution product **27** (45% yield, 7:1 dr). (5) Notably, reaction with racemic 3-bromocyclohex-1-ene furnishes **26** with good diastereocontrol for the *anti*-1,3-hydroxy-B(pin); however, the additional stereocenter is formed in 1:1 dr. The data above suggest that higher diastereoselectivity is associated with bromide electrophiles that can react via an S_N2' pathway.

Consistent with the proposed pathway in Scheme 1c, we set out to identify the cyclic boronates **E** and **F**, and provide support for a model to explain the reaction diastereoselectivity. As shown in Scheme 4a(i), monitoring the ring-opening of **2** (1 equiv) with **1** (1.5 equiv) by ¹H NMR in *d*₈-THF at 22 °C results in 73% conversion to diastereomers **I** and **II** in 56:44 dr. Each stereoisomer could be assigned through the absence of (e.g., **I**) or presence of (e.g., **II**) an NOE diaxial interaction between the carbinol methine (**H_a** and **H_b**) and the [(pin)B]₂C–H methane. ¹H NMR of the mixture of **I** and **II** at 60 °C, or after heating at 60 °C for 14 h, does not result in any changes in the diastereoisomer ratio. Treatment of the solution of **I** and **II** with 15 mol % CuCl and allyl bromide (Scheme 4a(ii)) results in consumption of both diastereoisomers at similar rates, and after 1 h ~20% **I** still remains. Further time points (Scheme 4b) demonstrate the dr of **28** (8:1) is independent of the time. This data indicates that although the cyclic boronates are formed in low dr, they both react at similar rates, and thus the high anti-selectivity must arise from the kinetic selectivity of Cu-alkyl species **III** and **IV** generated via transmetalation. However, it is not known whether **III** and **IV** are formed in high dr or if **III** and **IV** interconvert rapidly (Curtin–Hammett) prior to C–C bond formation.

The 1,3-hydroxy-homoallylboronates accessible through the linchpin three-component coupling method are amenable to a wide range of useful functionalizations (Scheme 5a). For example, TBS protected homoallyl boronates **4** can be efficiently converted to the corresponding 1,3-amino alcohol **31** in 85% yield,¹¹ a key intermediate in the stereoselective synthesis of (+)-allo-sedamine.¹² Homoallyl-B(pin) **29** in the presence of 2.5 mol % [Pd(μ-Br)(P*t*-Bu₃)₂]₂ and benzaldehyde results in situ isomerization and diastereoselective allyl addition to furnish homoallylic alcohol **30** in 69% yield.¹³ In addition, the three-component

coupling protocol can also be extended to include sequential stereoretentive cross coupling of the crude 1,3-hydroxy-B(pin) products (Scheme 5b).¹⁴ For example, treatment of crude **3** with 5 mol % Pd(dba)₂, 5 mol % RuPhos, and an aryl bromide in KOH_(aq) at 70 °C for 12 h delivers **32** and **33** in 40% and 54% isolated yield, respectively, and >10:1 dr. Furthermore, the utility of the diborylmethane linchpin coupling protocol is highlighted in the concise approach to 1,3-polyol motifs through an iterative sequence (Scheme 5c).¹⁵ Beginning with styrene oxide **2** (5 mmol scale) under standard conditions with 2-methylallyl bromide, *anti*-1,3-diol **28** (1.03 g) is isolated in 99% yield and 7:1 dr.¹⁶ Subsequent hydroxyl-directed epoxidation (5 mol % V(O)(acac)₂, *t*-BuOOH) of the terminal alkene,¹⁷ and ketal formation furnishes **34** in 55% yield and 25:3.5:1 dr (2 steps). Subjecting **34** to standard coupling conditions in Scheme 2 with allyl bromide delivers diol **35** in 75% yield and 4.5:1 dr (equivalent to a ketone allylation). The sequential four-step sequence enables the rapid stereoselective assembly of four C–C bonds and three stereocenters (41% overall from **2**).

To conclude, we have introduced a stereoselective linchpin coupling method that utilizes [B(pin)]₂-methane as a C₁ conjunctive reagent for the linking of epoxide and allyl electrophiles. Reactions proceed efficiently, delivering products with good levels of diastereoselectivity that are amenable to accessing a range of useful organic molecules. Further stereoselective reactions of cyclic borates are in progress.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Scheme 1.

C₁ Conjunctive Synthons that Form Two C–C Bonds at a Single Carbon Center per Chemical Step (2C)

Scheme 2. Three-Component Couplings with Various Epoxides^{a,b}

^aReactions performed under N₂ atm. ^bYield represents isolated yield of purified material and is an average of two experiments. ^cEpoxide opening: 22 °C for 24 h. ^dIsolated yield of diol after H₂O₂/NaOH oxidation. ^eEpoxide opening: 45 °C for 24 h.

Scheme 3. Tandem Coupling Electrophile Scope^{a,b}

^{a,b}See Scheme 2. ^c3:1 S_N2:S_N2'.

Scheme 4. Mechanistic Studies^a^aSee SI for details.

Scheme 5. Utility of 1,3-Hydroxy Homoallyl Boronates^a

^aSee SI for details. ^b¹H NMR yield (4:1 *E*-alkene isomers).

Table 1

Cu-Catalyzed Three-Component Coupling Optimization

entry	X	Cu salt	ligand	Temp (°C)	Conv (%) ^b	dr ^b
1	Cl	CuCl	–	22	52	3:1
2	Cl	CuCl	–	45	52	2:1
3	Cl	CuCl	–	60	58	2:1
4	OP(OEt) ₃	CuCl	–	60	45	1:1
5	OAc	CuCl	–	60	<2	–
6	Br	CuCl	–	60	77	8:1
7	Br	CuOAc	–	60	57	10:1
8	Br	CuBr·dms	–	60	55	8:1
9	Br	CuI	–	60	62	9:1
10	Br	CuCl	<i>rac</i> -binap	60	42	5:1
11	Br	CuCl	PPh ₃	60	65	2:1

^aReactions performed under N₂ atm.^bConversion to **3**; values determined by analysis of 400 or 600 MHz ¹H NMR spectra of unpurified mixtures with DMF as internal standard.