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Communication

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Stereoselective Tandem Bis-Electrophile Couplings of Diborylmethane.

Stephanie A. Murray, Michael Z. Liang, and Simon J. Meek*

Department of Chemistry, The University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599-3290. *Supporting Information Placeholder*

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, substratecontrolled 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 silvl glyoxylates 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 $C(sp^3)$ 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 (pKa ~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

Scheme 1. C₁ Conjunctive Synthons that Form Two C–C Bonds at a Single Carbon Center Per Chemical Step (2C)



Herein, we report a stereoselective one-pot threecomponent Cu-catalyzed coupling strategy that employs [B(pin)]₂-methane as a conjunctive reagent, which enables the couplings of epoxide and allyl electrophiles. The general reaction design that affords 1,3-hydroxyorganoborons 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 substratecontrolled deborvlative 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 $C(sp^3)$ –B(pin) moiety.

Table 1. Cu-catalyzed Three-Component Coupling Optimization.

		,				
	Q	(pin)B	a. thf, 22 °	C, 15 min;	OH B(pin)
Ph 2 (1 ec	√ + (2 quiv)	(pin)B ⁻ Li 1 (1.5 equiv)	<i>b.</i> 15 mol % X	, 24 h	Ph 3	
entry	Х	Cu Salt	ligand	temp (°C)	conv (%) ^b	dr ^b
1	CI	CuCl	-	22	52	3:1
2	CI	CuCl	-	45	52	2:1
З	CI	CuCl	-	60	58	2:1
4	OP(OEt) ₃	CuCl	-	60	45	1:1
5	OAc	CuC	-	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	Cul	-	60	62	9:1
10	Br	CuCl	<i>rac</i> -binap	60	42	5:1
11	Br	CuCl	PPh_3	60	65	2:1

^{*a*}Reactions performed under N₂ atm. ^{*b*}Conversion to **3**; values determined by analysis of 400 or 600 MHz ¹H NMR spectra of unpurified mixtures with dmf as internal standard.

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)]₂-methane 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 °C 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 °C 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 diminshed 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 $C(sp^3)$ organoborons, the 1,3hydroxyborons were protected as the TBS ethers. As illustrated in Scheme 2, aryl-substituted 1,3hydroxyboronates (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

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



^{*a*}Reactions performed under N₂ atm. ^{*b*}Yield represents isolated yield of purified material and is an average of two experiments. ^{*c*}Epoxide opening: 22 °C for 24 h. ^{*d*}Isolated yield of diol after H₂O₂/NaOH oxidation. ^{*e*}Epoxide opening: 45 °C for 24 h.

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 (Equation 1).

$$Me \xrightarrow{(pin)B}_{+ (pin)B} Me \xrightarrow{(pin)B}_{Li} Me \xrightarrow{(pin)B}_{+ (pin)B} Me \xrightarrow{(pin)B}_{Li} MF, 60 \ ^{\circ}C, 24 h; \\ 15 \ ^{mol} \% CuCl, \\ allylbromide \\ THF, 60 \ ^{\circ}C, 24 h; \\ NaOH, H_2O_2 \\ Me \xrightarrow{(pin)B}_{B0\% yield} Me \xrightarrow{(1)}_{B0\% yield} Me$$

Follow up studies illustrated in Scheme 3, demonstrate that a variety of substituted allyl electrophiles as well as dienyl bromides perform efficiently under standard conditions (15 mol % CuCl, 1.0 equiv 2, 1.5 equiv 1), establishing two new C-C bonds and a sterocenter 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 $S_N 2$ 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(nin) however the additional

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 $S_N 2$ ' 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 1 H NMR in d⁸-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 % $[Pd(\mu-Br)(Pt-Bu_3)_2]_2$ and benzaldehyde results in situ isomerization and diastereoselective allyl addition to furnish homoallylic alcohol 30 in 69% vield.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 arylbromide 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 2methylallylbromide, 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 allylbromide delivers diol 35 in 75% yield and 4.5:1 dr (equivalent to a ketone allylation). The sequential fourstep sequence enables the rapid stereoselective assembly of four C–C bonds and three strereocenters (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.







^aSee SI for details. ^{b1}H NMR yield (4:1 *E*-alkene isomers).

ASSOCIATED CONTENT

Supporting Information. Experimental procedures and spectral and analytical data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

sjmeek@unc.edu

Notes

Authors declare no competing financial interests.

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(10) SFC analysis of **3** compared to **1**, indicates there is no loss of enantiopurity during the epoxide-opening/Cu-catalyzed allylation sequence.

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