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Enantio- and Diastereoselective Synthesis of Hydroxy Bis(boronates) via Cu-Catalyzed Tandem Borylation/1,2-Addition

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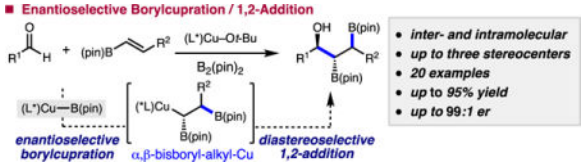
Abstract

Catalytic enantioselective synthesis of 1-hydroxy-2,3-bisboronate esters through multicomponent borylation/1,2-addition is reported. Catalyst and substrates are readily available, form both a C–B and C–C bond, and generate up to three contiguous stereocenters. The reaction is tolerant of aryl, vinyl, and alkyl aldehydes and ketones in up to 95% yield, >20:1 dr, and 99:1 er. Intramolecular additions to aldehydes and ketones result in stereodivergent processes. The hydroxy bis(boronate) ester products are amenable to site-selective chemical elaboration.

Graphical abstract



Keywords

Cu-catalyzed; tandem borylation

Enantioselective methods for the preparation of alcohols and sp^2-organoborons are important in the chemical synthesis of chiral bioactive molecules. Consequently, stereoselective reactions that render the syntheses of these important functional groups more efficient are highly desirable.[1] Addition of chiral non-racemic alkyl-metal reagents to carbonyls provides a direct approach for the enantioselective generation of chiral alcohols bearing a vicinal stereogenic center.[2] However, chiral organometallic sp^2-carbon nucleophiles (e.g., Grignards and organolithiums)[3] are generally preformed, air and moisture

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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.

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sensitive reagents that carry limited functionality, and are generated under cryogenic conditions to minimize enantiomerization.[4,5] Catalytic enantioselective in situ generation of chiral C(sp^3)-metal reagents from achiral starting materials provides an effective solution to generating such classes of non-racemic alkyl nucleophiles.[6,7] One class of versatile chiral nucleophiles are enantioenriched α-borylalkyl-Cu reagents; such intermediates undergo stereoselective C–C bond formations while simultaneously incorporating an organoboron moiety that can be further elaborated into a number of useful functional groups.[8]

Our group and others have recently developed catalytic methods for generating chiral α-borylalkyl organometallics via transmetallation of bench-stable 1,1-diborylalkanes.[9] Morken[10a-b] and Hall[11c] independently reported the enantioselective Pd-catalyzed cross coupling of substituted 1,1-diborylalkanes, while recent advances in catalytic enantioselective allylic substitution and diastereoselective additions to imines have focused on achiral diborylmethane.[11,12] We reported the enantio- and diastereoselective Cu-catalyzed addition of 1,1-diborylalkanes to aldehydes and α- Cu-catalyzed transmetalation of a 1,1-diborylalkane to generate an α-borylalkyl-Cu intermediate, which diastereoselectively adds to aldehydes or α-ketoesters (Scheme 1A). The transformation generates both a new C(sp^3)–C(sp^3) bond, and up to two stereogenic centers, including an enantioenriched alkylboron group.

Herein, we outline an alternative strategy for the generation of chiral non-racemic α-borylalkyl–Cu nucleophiles (**B**) (Scheme 1B) through an enantioselective borylcupration of vinyl boronate esters (e.g., **1**) by a (L)Cu–B(pin) species (**A**).[13] The resulting nucleophile can then undergo 1,2-addition to an aldehyde to generate 1-hydroxy bis(boronate) esters **D**.[14] This multicomponent process sequentially forms a C–C and a C–B bond in addition to installing two alkyl organoboron groups that may be further functionalized.

To determine the feasibility of the proposed multicomponent process, we obtained an initial result that established the ability of racemic phosphine-copper complexes to promote the sequential C–B/C–C bond forming sequence. As depicted in Equation 1, treatment of vinyl-B(pin), benzaldehyde, and $B_2(pin)_2$ with 5 mol % $[Cu(MeCN)_4]PF_6$, 6 mol % *rac*-binap, and 5 mol % KO*t*-Bu results in the multicomponent coupling to produce *rac*-**2a** in >98% conversion, and 9:1 dr favoring the *anti* diastereoisomer. Notably, it was discovered that the minor *syn* diastereoisomer of the product undergoes boron-Wittig type elimination during silica gel chromatography,[15] and after purification of the crude reaction mixture *rac*-**2a** is isolated in 77% yield as a single diastereomer. This is advantageous as the careful separation of diastereoisomers is not required for less selective substrates.

Having established the in situ preparation and diastereoselective reaction of α-borylalkyl-Cu reagents with vinyl-B(pin), we sought to render the process enantioselective. Table 1 summarizes our optimization studies with chiral phosphines in the Cu-catalyzed multicomponent reaction. Under identical reaction conditions to those in Equation 1, **L1** afford **2a** in 87% conv, 6.7:1 dr, and 77:23 er. Changing the solvent to toluene led to an increase in conversion (>98% conv) and enantioselectivity (82:18 er), with comparable diastereoselectivity. With chiral bidentate phosphines **L2** or **L3**, **2a** is formed in increased enantioselectivity (up to 95:5 er), albeit in low diastereoselectivity (entries 3–4). In order to

improve the diastereoselectivity of the reaction while maintaining high enantioselectivity, other mono- and bidentate chiral phosphines were screened (**L4**–**L7**), however, **2a** is formed in <12% conversion in all cases (Entries 5–8, Table 1). Biphenyl phosphine **L8** proved to be the most effective ligand for the Cu-catalyzed reaction, affording **2a** in >98% conv, 3.2:1 dr, and 95:5 er. These conditions, however, proved variable for other aldehyde substrates, and provided inconsistent conversion and enantioselectivities. We hypothesized that efficiently generating the phosphine-copper(alkoxide) complex in situ could be in part responsible, as such we employed CuO*t*-Bu as the copper source. Application of 10 mol % CuO*t*-Bu, in addition to benzene as solvent, delivers **2a** in >98% conv, 3.5:1 dr, and 95.5:4.5 er (Entry 11, Table 1).

With optimized conditions in hand, we set out to explore the scope of the Cu-catalyzed multicomponent borylation/1,2-addition reaction of **1** to various aryl and alkenyl aldehydes (Table 2).[16] Of note, the crude dr of the reactions varies from 1:1–>20:1, however, in general the products are isolated as the anti diastereoisomer after purification on silica gel due syn isomer elimination. In the presence of 10 mol % CuO*t*-Bu, 11 mol % **L8**, and 110 mol % $B_2(pin)_2$, **1** and benzaldehyde reacted to produce 1-hydroxy-2,3-bisboronate **2a** in 74% yield, and 96:4 er (Entry 1). A variety of substituted aryl aldehydes containing halogens, methoxy, or alkyl groups undergo efficient 1,2-addition to afford **2b**–**g** in 68–83% yield (5.7:1–>20:1 dr, 94:6–96:4 er) (entries 2–7). The catalytic protocol is tolerant of heteroaromatic aldehydes; for example, N-Boc indole **2h** and furan **2i** are generated in good yield and high enantioselectivity (entries 8–9). Bis-halogenated electron-deficient aryl aldehyde, **2j** is formed in 71% yield, and 95:5 er. 3-Pyridinecarboxaldehyde reacts sluggishly under the catalytic protocol, generating **2k** in 18% ^{1}H NMR yield (Entry 11). Alkenyl aldehydes effectively participate in the Cu-catalyzed multicomponent process delivering **2l** in 78% yield, and 93:7 er (entries 12). Alkyl aldehydes, which were previously found to be incompatible in the diastereoselective Cu-catalyzed 1,2-additions with 1,1-diborylalkanes, except in the case of *n*-BuLi as an irreversible activator,[17] were also found to function as effective substrates (Entries 13–15). For example, secondary alcohols **2m**–**2o** are furnished with moderate efficiency in 48–70% yield (crude 1:1–5.7:1 dr; 75:25–92:8 er).

We next sought to extend the methodology to substituted 1-alkenyl-B(pin) substrates, which possess the ability to generate three contiguous stereogenic centers. Initially, our investigations focused on intramolecular variants of the enantioselective reaction between **1** and several aldehydes. As illustrated in Scheme 2, treatment of *E*-**3a** with 10 mol % chiral Cu catalyst in toluene at 4 °C resulted in the desired cyclized product **4** in 49% yield, >20:1 dr, and 98.5:1.5 er. Although the multi-component process proceeds with very high selectivity, competitive 1,2-addition of Cu–B(pin) to the aldehyde is problematic, and could not be minimized.[18] To minimize this unfavorable pathway, we switched to more sterically encumbered ketones as substrates. Treatment of methyl ketone *E*-**3b** to the catalytic protocol but with **L1** as ligand and *t*-BuOH (100 mol %) in dioxane at 22 °C, affords tertiary alcohol **5** in 95% yield, >20:1 dr, and 94:6 er. In addition, three other intramolecular ketone substrates were evaluated, which afford aryl (**6**), alkyl (**7**), and N-heterocyclic (**8**) containing tertiary alcohols. Several features of these intramolecular studies are notable: (1) Congested tertiary alcohol hydroxydiboronates can be formed in good yields, and excellent diastereo-

(>20:1) and enantioselectivites (up to 97:3 er);[19] (2) The catalytic method is amenable to the enantioselective synthesis of alkyl and N-heterocyclic structures; (3) *tert*-Butanol serves to turn over the catalyst.

The divergence in the relative stereochemistry (anti-, syn- vs anti-, anti-) of the hydroxyl and B(pin) groups in **4** and **5** can be explained by the Cu–alkyl additions occurring via two different modes (Scheme 3): (1) The more reactive and sterically unhindered aldehyde is able to directly engage with the Cu–alkyl through a *stereoretentive* pathway (**I**) resulting in anti-,syn-**4**. (2) Conversely, the more sterically congested methyl ketone reacts with the α-boryl-Cu-alkyl through a *stereoinvertive* back-side addition (**II**) to afford anti-,anti-**5**. A similar invertive Cu–alkyl 1,2-addition mechanism was recently proposed in the enantioselective 1,2-addition of benzylic copper nucleophiles to imines.[7g]

The 1-hydroxy-2,3-bisboronate products synthesized via the Cu-catalyzed method may be further functionalized into synthetically useful molecules (Scheme 4). For example, oxidation to the corresponding 1,2,3-triols; treatment of **2p** with aqueous NaOH and 30% H_2O_2 to generate triol **9** in 93% yield is illustrative (Scheme 4a). Site-selective cross couplings of TBS-protected diboronate **10** (isolated in 62% yield from **2a**)[20] with isocrotyl bromide **11** catalyzed by 1 mol % Pd-RuPhos,[15c] results in efficient formation of homoallyl boronate **12** in 59% yield (Scheme 4b). The secondary boronate in **12** can also be further functionalized into amines (e.g., **14**)[21] and aryl groups (e.g., **13**), however, the congested nature of the B(pin) unit results in 30–52% yield.[22] Silyl ether protected cyclic hydroxy-diboronates, also undergo efficient stereospecific functionalization, however, both secondary alkyl-B(pin) units were found to react with equal efficiency. The bishomologation to form **16** in 78% yield in Scheme 4c is illustrative.

In conclusion, we have developed an efficient, enantioselective multicomponent borylation/1,2-addition reaction that generates in situ α,β-bisboryl-copper-alkyl nucleophiles, which add diastereoselectively inter- and intramolecular to aldehydes and ketones. Notably, intramolecular additions to ketones proceed via a stereoinvertive pathway. The hydroxy(bis)boronates formed by this method are amenable to stereospecific and site-selective functionalizations including oxidation, cross-coupling, and homologation. Mechanistic studies, as well as development of other enantioselective multicomponent reactions are in progress.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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16. In a number of cases in Table 2, L8 could not be separated from the product; an issue unique to L8. Residual ligand does not interfere with subsequent transformations (see Supplementary Information).
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19. The corresponding intermolecular variant with substituted 1-alkenyl-B(pin) results in <2% conv. under the current catalytic conditions.
20. Protection of the alcohol is required to prevent boron-Wittig alkene formation, which occurs under the reactions conditions with the secondary alcohol.
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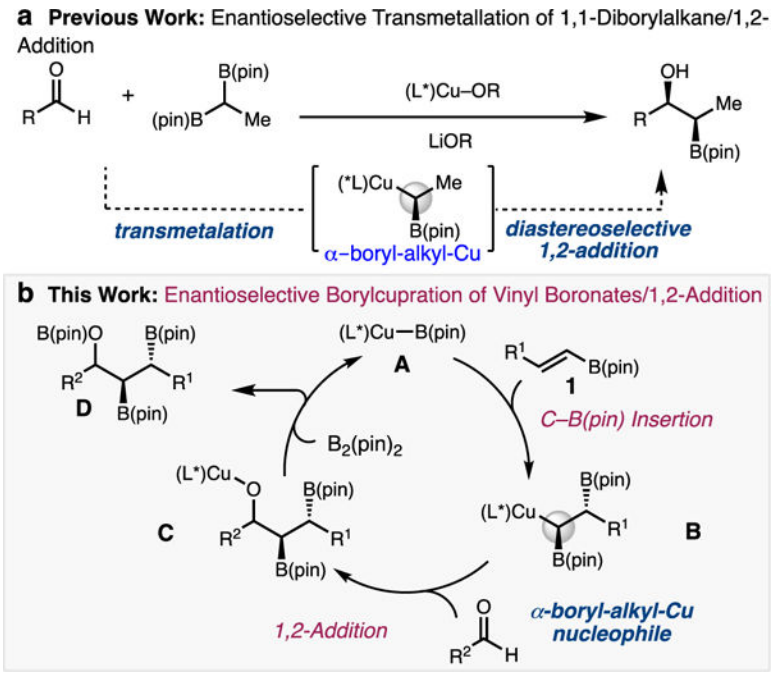
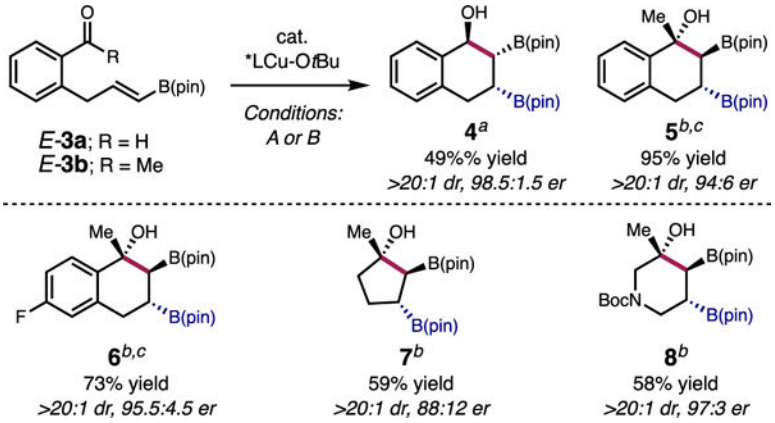
22. See Supporting Information for details.



Scheme 1.

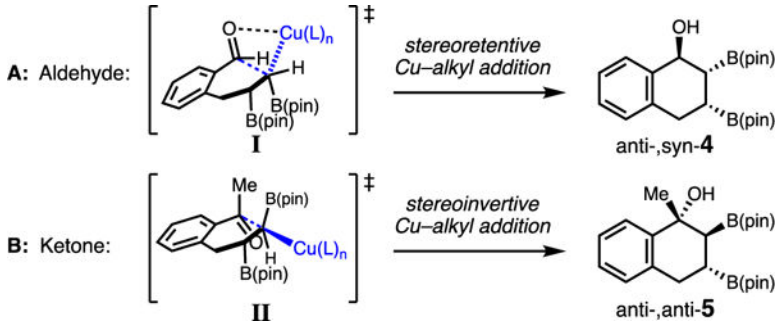
Development of Multicomponent Strategy for the Synthesis of Hydroxy Bis(boronates).



Scheme 2.

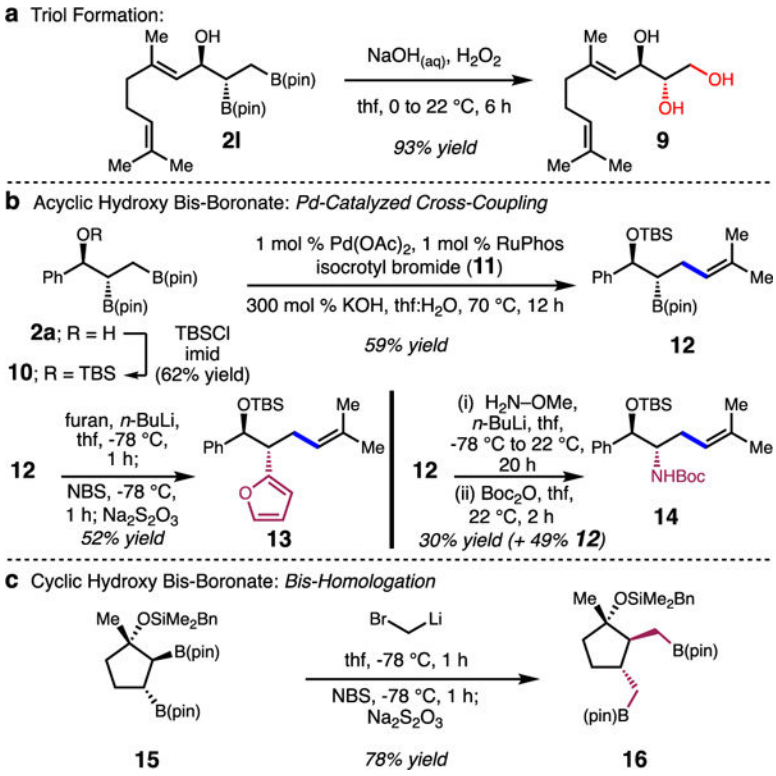
Diastereo- and Enantioselective Intramolecular Cyclizations to Form Three Stereogenic Centers.

[a]Conditions A: 10 mol % CuOt-Bu, 12 mol % L8, 110 mol % $B_2(pin)_2$, toluene, 4 °C, 48 h. [b]Conditions B: 10 mol % CuOt-Bu, 12 mol % L1, 110 mol % $B_2(pin)_2$, 100 mol % t-BuOH, dioxane, 22 °C, 18 h. [c]Isolated yield of the corresponding triol.



Scheme 3.

Proposed Transition States for Aldehydes and Ketones Involving Stereoretentive and Stereoinvertive Additions.

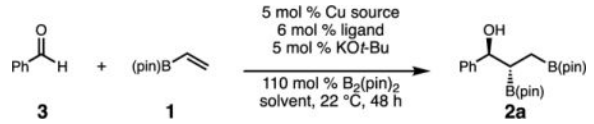


Scheme 4.

Functionalizations of 1-Hydroxy-2,3-Bisboronate Esters.

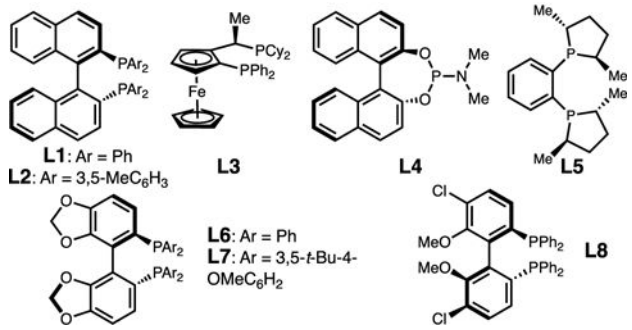
Table 1

Evaluation of Chiral Copper Complexes[a]



entry	ligand	Cu source	solvent	NMR yield (%)[b]	dr[b]	er[c,d]
1	**L1**	$Cu(MeCN)_4PF_6$	thf	87	6.7:1	77:23
2	**L1**	$Cu(MeCN)_4PF_6$	toluene	>98	4.6:1	82:18
3	**L2**	$Cu(MeCN)_4PF_6$	toluene	98	1.7:1	92:8
4	**L3**	$Cu(MeCN)_4PF_6$	toluene	88	1:1	95:5
5	**L4**	$Cu(MeCN)_4PF_6$	toluene	<2	–	–
6	**L5**	$Cu(MeCN)_4PF_6$	toluene	<2	–	–
7	**L6**	$Cu(MeCN)_4PF_6$	toluene	12	11.5:1	–
8	**L7**	$Cu(MeCN)_4PF_6$	toluene	<2	–	–
9	**L8**	$Cu(MeCN)_4PF_6$	toluene	>98	3.2:1	95:5
10	**L8**	CuO*t*-Bu	toluene	87	3:1	95:5
11[e]	**L8**	CuO*t*-Bu	C_6H_6	>98	3.5:1	95.5:4.5

Ligands:



[a] Reactions performed under N_2 atmosphere.

[b] Determined by analysis of 400 or 600 MHz ^{1}H NMR spectra of crude reactions with hexamethyldisiloxane as internal standard.

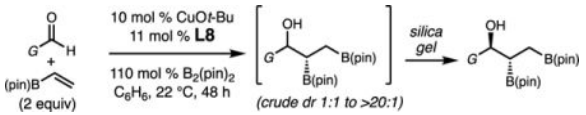
[c] Determined by HPLC analysis; see the Supporting Information for details.

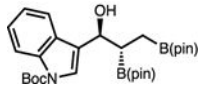
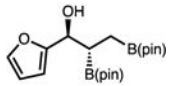
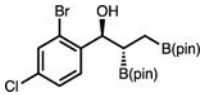
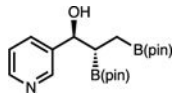
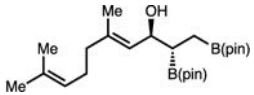
[d] The er of the syn diastereoisomer is not reported due to its propensity to undergo elimination.

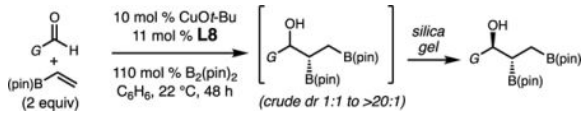
[e] [0.167 M] in benzene with 2 equivalents of **1**.

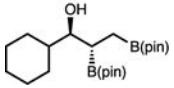
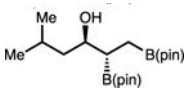
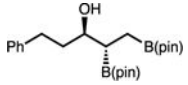
Table 2

Enantioselective Cu-Catalyzed Multicomponent Borylation/1,2-Addition of Vinyl-B(pin) to Aryl, Alkenyl and Alkyl Aldehydes[a]



entry		product	isolated yield (%)[d]	isolated dr (*anti syn*)[b]	er[c]
1	**2a**	G = Ph	74	>20:1	96:4
2	**2b**	G=*p*-FC_6H_4	70	>20:1	96:4
3	**2c**	G = *p*-BrC_6H_4	68	5.7:1	95:5
4	**2d**	G = *p*-$OMeC_6H_4$	70	>20:1	94:6
5[e]	**2e**	G =*m*-MeC_6H_4	75(77)	>20:1 (4:1)	95:5
6	**2f**	G = *o*-MeC_6H_4	81	>20:1	96:4
7	**2g**	G = *o*-BrC_6H_5	83	>20:1	96:4
8	**2h**		63	3:1	94:6
9[e]	**2i**		52 (57)	>20:1 (3.5:1)	97:3
10	**2j**		71	>20:1	95:5
11	**2k**		18[f]	–	–
12	**2l**		78 (36)	>20:1 (>20:1 dr)	93:7



entry		product	isolated yield (%)[d]	isolated dr (*anti syn*)[b]	er[c]
13	**2m**		63	>20:1	92:8
14	**2n**		48	>20:1	75:25
15[e]	**2o**		70[f] (52)	3:1 (3:1)	90:10

[a–c] See Table 1.

[d] Isolated yield of the anti diastereoisomer unless otherwise stated.

[e] Values in parentheses correspond to the TBS protected hydroxydiboronate, resulting from protection of the crude reaction mixture (see Supporting Information for details).

[f] NMR yield.