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Copper-Catalyzed Tandem Hydrocupration and Diastereo- and Enantioselective Borylalkyl Addition to Aldehydes

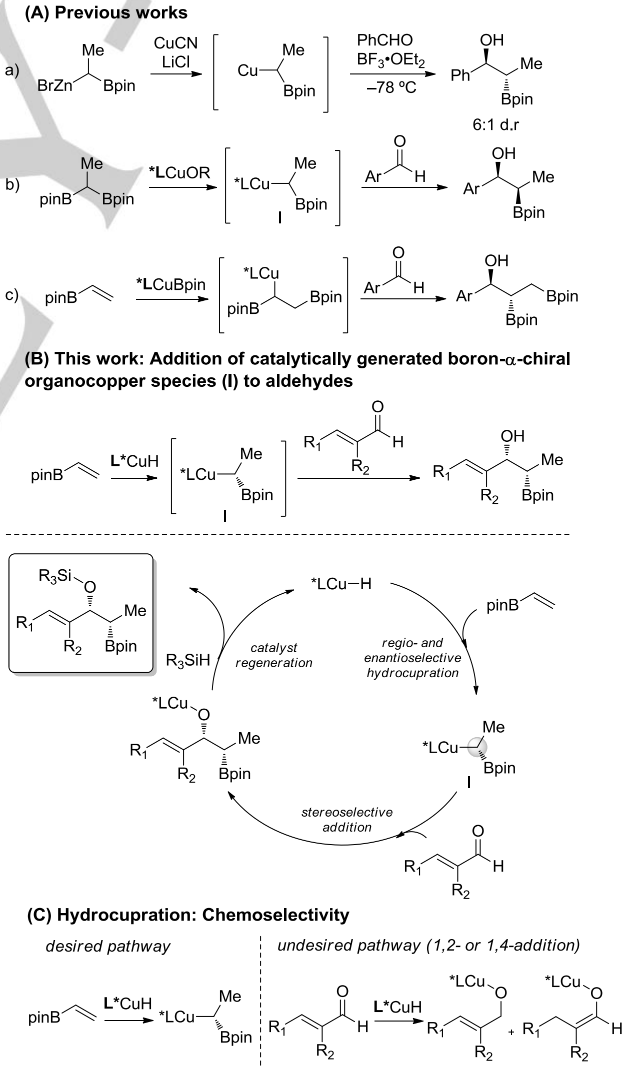
Won Jun Jang and Jaesook Yun*

Abstract: We report the copper-catalyzed stereoselective addition of in-situ generated chiral boron-α-alkyl intermediates to various aldehydes including α,β-unsaturated aldehydes under mild conditions. This tandem and multicomponent method facilitated the synthesis of enantiomerically enriched 1,2-hydroxyboronates bearing contiguous stereocenters in good yield with high diastereo-, and enantioselectivity up to a ratio of >98:2. In particular, α,β-unsaturated aldehydes were successfully used as electrophiles via 1,2-addition without significant reduction under Cu–H catalysis. The resulting 1,2-hydroxyboronates were utilized in various transformations.

Enantiomerically enriched organoboron compounds are important and versatile intermediates in chemical synthesis due to the wide applicability of the C–B bond and their stereospecific transformation.[1] Therefore, catalytic methods for the preparation of organoboron compounds with a carbon–boron stereogenic center have been developed and extensively investigated via introduction of a boron moiety to unsaturated C–C bonds with transition metal catalysts.[2] An alternative approach is to use boron-α-chiral reagents with various electrophiles or nucleophiles for C–C bond formation (Scheme 1). Traditionally, boron-α-chiral reagents such as asymmetric (α-haloalkyl)boronic esters were prepared by reaction of chiral boronic esters with stoichiometric (dichloromethyl)lithium and zinc chloride.[3] They reacted with a nucleophilic reagent such as Grignard and organolithium reagents[3] or were converted to organometallic species for further derivatization.[4] Since the stoichiometric use of chiral auxiliaries and strongly basic organometallic reagents limit their synthetic efficiency, catalytic strategies generating enantiomerically enriched boron-α-chiral derivatives from prochiral precursors are highly desired. Recently, generation of boron-α-chiral organometallic species have been reported by deborylation of 1,1-diborylalkanes despite their poor boron atom economy.[5] For example, Meek and co-workers reported copper-catalyzed enantioselective transmetalation of 1,1-diborylethane and its addition to aldehydes (Scheme 1b).[5c] The same group also reported borylative coupling of vinylboronate with aldehydes (Scheme 1c).[6] In contrast, hydrometalation of alkenylboronates[7] provides an efficient way to generate boron-α-chiral nucleophiles, and successful reactions with electrophiles could establish useful catalytic methodologies for the preparation of chiral organoboron compounds.

CuH–catalyzed reductive coupling of unsaturated compounds with electrophiles for asymmetric synthesis has been developed to produce useful structural organic frameworks.[8] However, alkenylboron compounds were rarely used, since alkenylboronates themselves can be used as organic nucleophiles generating by-products with copper catalysts.[9] Therefore, copper-catalyzed reactions of alkenylboronates were reported only with heteroatom-based electrophiles such as pinacolborane[7a] and hydroxylamine O-benzoate,[7c] not with unsaturated electrophiles. Only recently, the enantioselective Cu–H catalyzed reductive coupling of alkenylboron with allylic electrophiles has been developed by our group and by the Hoveyda group independently.[10]

On the other hand, carbonyl compounds such as aldehydes and ketones are useful electrophile candidates in asymmetric addition reactions as they produce enantiomerically pure alcohols.[11] In general, ketones are more challenging substrates



Scheme 1. Overview of Enantioselective Synthesis of 1,2-Hydroxyboronates using Cu–H Catalyst

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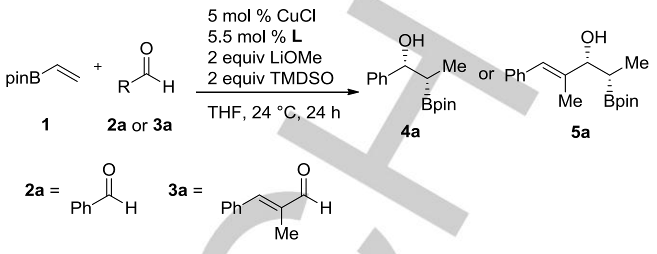
in nucleophilic addition reactions, However, in view of multicomponent and tandem reactions, aldehydes offer a greater chemoselectivity challenge due to their high reactivity, especially under Cu–H catalysis.[12] It is known that aldehyde compounds including α,β-unsaturated carbonyl compounds are highly reducible substrates by Cu–H catalysts, causing chemoselectivity issues. Consequently, the successful copper-catalyzed reductive couplings with carbonyls have been reported with active olefins such as alkenylazaarenes,[8f] enynes,[8g] and allenes[8j] in combination with ketones. To the best of our knowledge, the use of aldehydes as carbonyl electrophiles has not been reported in copper-catalyzed asymmetric reductive coupling.

Herein, we report a highly enantio- and diastereoselective, Cu–H catalyzed reaction of vinylboronate with aldehydes yielding 1,2-hydroxyboronates (Scheme 1B). This process generates two contiguous stereogenic centers bearing C–O and C–B bonds. A successful reaction: (1) generated α-chiral organocopper species via regio- and enantioselective hydrocupration (Scheme 1B), (2) resolved chemoselectivity issues between vinylboronate and competing aldehydes (Scheme 1C), and (3) led to subsequent diastereoselective addition of **I** to aldehydes (Scheme 1B).

Initially, we monitored the reactions of vinylboronate with benzaldehyde (**2a**) under various reaction conditions (Table 1). 1,1,3,3-Tetramethyldisiloxane (TMDSO) was an efficient source of stoichiometric hydride, and a catalytic combination of CuCl and racemic bisphosphine ligand **L1** afforded the desired product in good yield and high diasteromeric ratio (entry 1). The racemic results led to investigation of various chiral bisphosphine ligands. **L2** and **L3** ligands appropriate for the allylation[10a] of α-boryl organocopper species resulted in poor yield and low diasteromeric ratio (entry 2–3). The short-tethered ligands **L4** and **L5** increased the product yield and diasteromeric ratio, but displayed poor enantioselectivity (entry 4–5). Low reactivity and selectivity also resulted with **L6** (entry 6). With the josiphos ligand (**L7**), the desired product (**4a**) was obtained in good yield and high enantioselectivity, but with moderate diasteroselectivity (entry 7). The use of CF_3-Josiphos ligand (**L8**) significantly increased the diasteromeric ratio to 91:9, but with slightly reduced enantioselectivity (entry 8). Next, we carried out the reaction using a more challenging α,β-unsaturated aldehyde, α-methyl-cinnamaldehyde (**3a**) as the electrophile. It is known that enals are easily reduced by Cu–H catalyst to produce 1,2- or 1,4-reduction products.[12] Surprisingly, both reaction conditions using the **L7** and **L8** ligands resulted in the formation of the corresponding 1,2-addition product in high yield, and stereoselectivity without significant reduction of the aldehyde, proving **1** as a better Michael acceptor[13] than aldehyde **3**. When using **L7,** slightly higher enantioselectivity was obtained (entries 9 and 10). Therefore, we selected entry 8 for simple aldehydes and entry 9 for α,β-unsaturated aldehydes as the optimal conditions.[14]

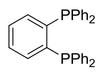
Under the optimized conditions, various aldehydes were explored in the reductive coupling with vinylborontate **1** (Table 2).[15] A variety of aldehydes were accommodated, yielding the corresponding chiral 1,2-hydroxyboronates in good yield with high diastereo- and enantioselectivities.

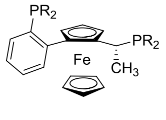
Table 1: Optimization of Reaction Conditions.[a]

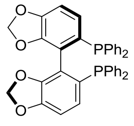


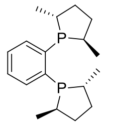
Entry	Aldehyde	Ligand	Yield [%][b]	d.r[c]	e.r[d]
1	**2a**	**L1**	90	96:4	-
2	**2a**	**L2**	0	-	-
3	**2a**	**L3**	28	65:35	68:32
4	**2a**	**L4**	63	95:5	55:45
5	**2a**	**L5**	94	97:3	55:45
6	**2a**	**L6**	44	60:40	53:47
7	**2a**	**L7**	71	72:28	99:1
8	**2a**	**L8**	70	91:9	95:5
9	**3a**	**L7**	74	>98:<2	98:2
10	**3a**	**L8**	76	>98:<2	95:5

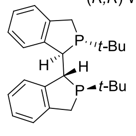
[a] General reaction conditions: **1** (0.5 mmol), **2a** or **3a** (1 mmol), CuCl (0.025 mmol), ligand (0.0275 mmol), LiOMe (1 mmol) and 1,1,3,3-tetramethyldisiloxane (1 mmol) in THF (1 mL); see the Supporting Information for details. [b] Isolated yield as a mixture of two diastereomers. [c] Diastereomeric ratio (d.r) was determined by ^1H NMR analysis of crude reaction mixture. [d] Enantiomeric ratio (e.r) was determined using HPLC.

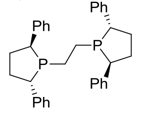

Dppbz (**L1**)

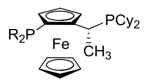

R = 3,5-$(CF_3)_2C_6H_3$, (*R,R*)-Walphos (**L2**)


(*R*)-Segphos (**L3**)


(*R,R*)-Me-Duphos (**L4**)

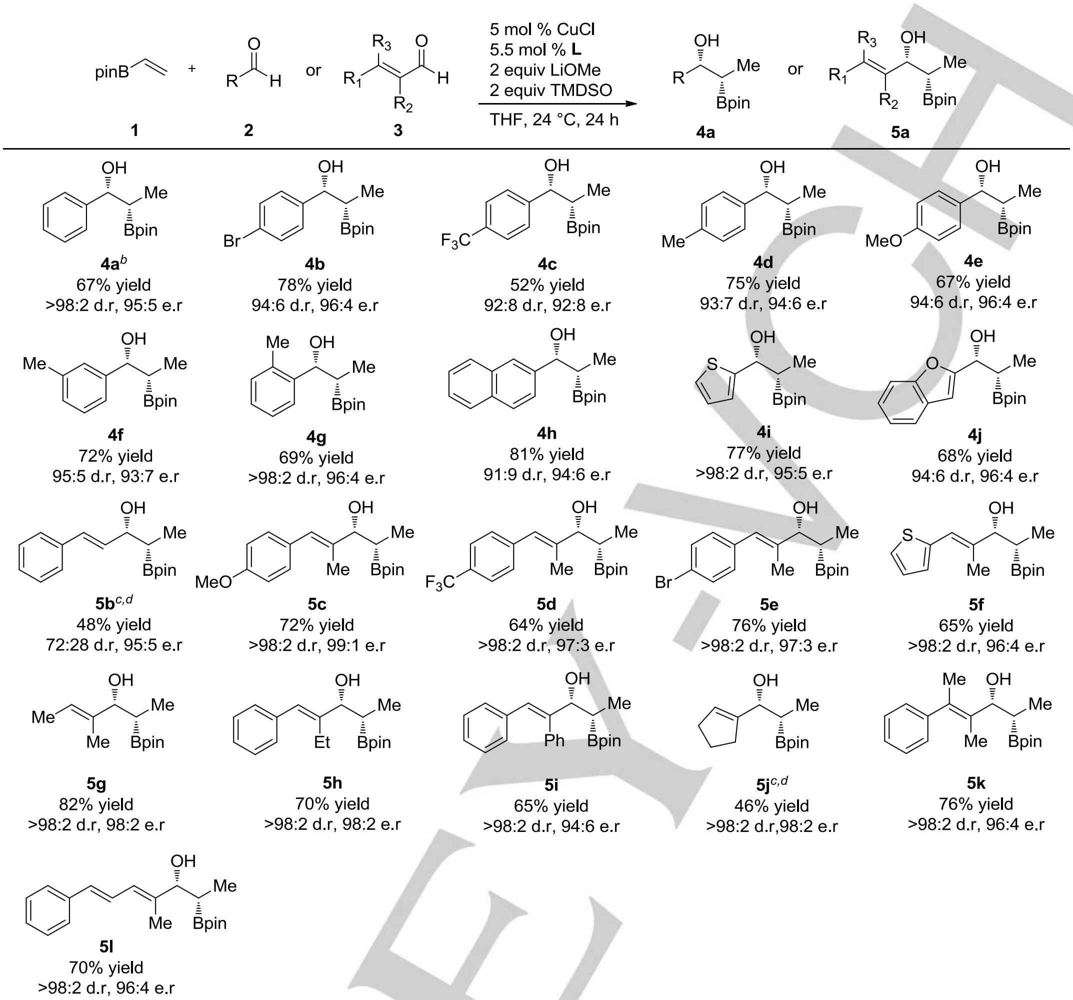

(1R,1'R,2S,2'S)-Duanphos (**L5**)


(*S,S*)-Ph-BPE (**L6**)


Josiphos, R = Ph (**L7**)
R = 3,5-$CF_3C_6H_4$ (**L8**)

The copper-catalyzed coupling reaction of **1** and **2a** could be conducted on a large scale; 1.5 mol% loading of catalyst was efficient enough to yield **4a**, which was isolated as a single diastereomer by silica gel column chromatography. Aryl aldehydes with halogen-, electron-withdrawing, electron-donating group, and a meta-substituent were appropriate substrates, affording the desired products (**4b–4f**). Sterically hindered, ortho-substituted aryl aldehyde also yielded **4g** with high enantioselectivity. A naphthyl group and heteroaryl groups were also incorporated (**4h–4j**).

Table 2: Copper-Catalyzed Diastereo- and Enantioselective Addition to Aldehydes.[a]



4a^{b} 67% yield >98:2 d.r, 95:5 e.r

4b 78% yield 94:6 d.r, 96:4 e.r

4c 52% yield 92:8 d.r, 92:8 e.r

4d 75% yield 93:7 d.r, 94:6 e.r

4e 67% yield 94:6 d.r, 96:4 e.r

4f 72% yield 95:5 d.r, 93:7 e.r

4g 69% yield >98:2 d.r, 96:4 e.r

4h 81% yield 91:9 d.r, 94:6 e.r

4i 77% yield >98:2 d.r, 95:5 e.r

4j 68% yield 94:6 d.r, 96:4 e.r

5b^{c,d} 48% yield 72:28 d.r, 95:5 e.r

5c 72% yield >98:2 d.r, 99:1 e.r

5d 64% yield >98:2 d.r, 97:3 e.r

5e 76% yield >98:2 d.r, 97:3 e.r

5f 65% yield >98:2 d.r, 96:4 e.r

5g 82% yield >98:2 d.r, 98:2 e.r

5h 70% yield >98:2 d.r, 98:2 e.r

5i 65% yield >98:2 d.r, 94:6 e.r

5j^{c,d} 46% yield >98:2 d.r,98:2 e.r

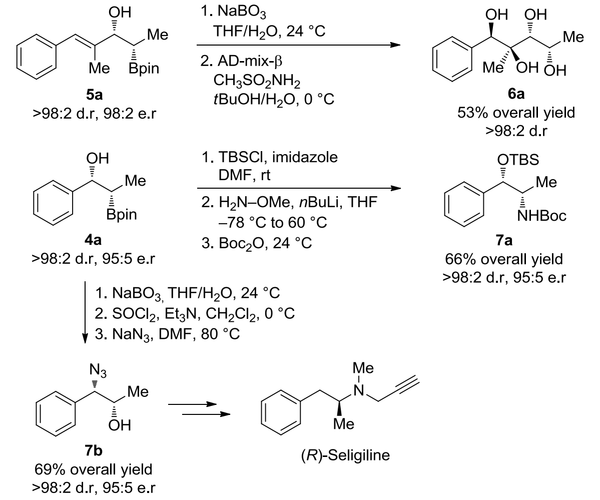
5k 76% yield >98:2 d.r, 96:4 e.r

5l 70% yield >98:2 d.r, 96:4 e.r

[a] Isolated yields containing a mixture of two diastereomers run on a 0.5 mmol scale. Ligand **L8** was used for simple aldehydes (**2**), and **L7** was used for α,β-unsaturated aldehydes (**3**). The diastereomeric ratio (d.r) was determined by ^{1}H NMR analysis of a crude reaction mixture. Enantiomeric ratio (e.r) was determined by HPLC analysis. [b] 1.5 mol % of copper catalyst on a 2 mmol scale. [c] **L8** was used instead of **L7**. [d] Yield of purified diol after oxidation of **5**

We next examined reductive coupling with α,β-unsaturated aldehydes using the josiphos ligand (**L7**) as the optimal ligand. A variety of unsaturated aldehydes containing aryl, heteroaryl, and alkyl substituents resulted in enantiomerically enriched homoallylic boronates containing an allylic alcohol in good yield via 1,2-addition. Aldehyde without an α-substituent resulted in moderate yield and diastereomeric ratio of product,[16] but with good enantioselectivity (**5b**). However, α,β-unsaturated aldehydes with both α,β-substituents resulted in high diastereo- and enantioselectivity. The reaction of α-methyl cinnamaldehyde derivatives yielded the corresponding homoallylic boronates (**5c**–**5e**) with high diasteromeric ratio (>98:2) and enantiomeric ratio (96:4–99:1). An electron-donating, electron-withdrawing, and halogen-substituted aryl group and heteroaromatic (**5f**) substituents at the β-position did not significantly affect the stereoselectivity of the reaction. Furthermore, the α,β-dialkyl-substituted substrate (**3g**), aldehydes with ethyl, and phenyl groups at the α-position (**3h**–**3i**), and cyclopentene-derived vinyl aldehyde (**3j**) also generated the corresponding products (**5g**–**5j**) with high levels of diastereo- and enantioselectivity. Moreover, the tetrasubstituted α,β-unsaturated aldehyde was reactive under the standard reaction conditions to give **5k** in good yield. Finally, 2-methyl-5-phenyl-2,4-pentadienal produced only 1,2-addition product (**5l**) in 70% yield and good diastereo- (>98:2) and enantioselectivity (96:4) without chemoselectivity issues.[17]

Transformations of the 1,2-hydroxyboronates obtained by our protocol were carried out to demonstrate their synthetic utility (Scheme 2). The C–B bond of **5a** was converted to C–O bond by oxidation, and the alkene moiety of the resulting diol compound was further oxidized to tetraol **6a** via the Sharpless asymmetric dihydroxylation.[18] 1,2-Hydroxyboronate **4a** was protected by the TBS group and aminated with lithiated methoxyamine[19] to yield amino alcohol **7a** without deterioration of the original diastereo- and enantiomeric ratio. In addition, the oxidation of **4a** and sequential treatment with $SOCl_2$ and sodium azide generated 1,2-azido alcohol **7b** in 69% overall yield, which is a known intermediate in the synthesis of (*R*)-Selegiline for Parkinson's disease treatment.[20]



Scheme 2. Transformation of 1,2-hydroxyboronates

In summary, we developed a copper-catalyzed chemo-, diastereo-, and enantioselective reductive coupling of vinylboronate with various aldehydes, providing direct catalytic synthesis of versatile 1,2-hydroxyboronates with high efficiencies. In the presence of a copper catalyst combined with josiphos-type ligands, the reaction facilitated installation of two contiguous stereogenic centers. In particular, the successful use of α,β-unsaturated aldehydes in this multicomponent and tandem protocol resulted in efficient synthesis of homoallylic boronates bearing multi-functional groups. The resulting chiral 1,2-hydroxyboronates were transformed to various compounds of value. Further studies are in progress.

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Keywords: copper • vinylboronate • aldehyde addition • asymmetric catalysis • enantioselective synthesis

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[14] For more screening results, see the Supporting Information (Table S1).

[15] With the currently developed catalytic conditions, the reaction of internal alkenylboronates resulted in low enantioselectivity and reaction with ketones did not afford the desired products, which need further improvement. See Scheme S1–S3 in the supporting information.

[16] 1,2-Reduction of cinnamaldehyde occurred to give the corresponding allylic alcohol as a side product, which reduced the yield of the coupled product **5b**. See Scheme S2 in the Supporting Information.

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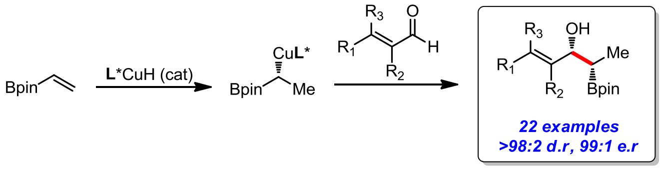

Stereoselective addition of in-situ generated chiral boron-α-alkyl intermediates via copper catalyst to various aldehydes under mild conditions is reported. This tandem and multicomponent system facilitated the synthesis of enantiomerically enriched 1,2-hydroxyboronates bearing contiguous stereocenters in good yield with high diastereo-, and enantioselectivity up to a ratio of >98:2.

*Won Jun Jang, Jaesook Yun**

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Copper-Catalyzed Tandem Hydrocupration and Diastereo- and Enantioselective Borylalkyl Addition to Aldehydes