Communication

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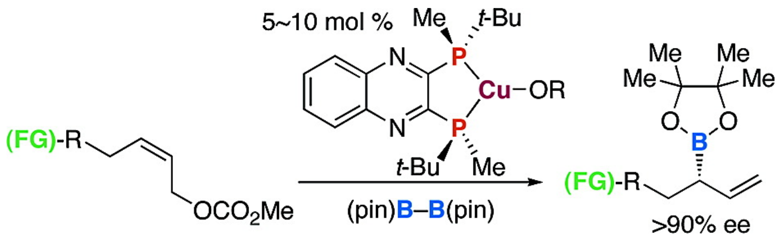

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Copper-Catalyzed Enantioselective Substitution of Allylic Carbonates with Diboron: An Efficient Route to Optically Active α-Chiral Allylboronates

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Among the highly stereoselective addition reactions of allylboronates to carbonyl compounds, those that involve optically active allylboronates that have a stereogenic carbon at the α-position of the boryl group are able to offer a nearly perfect chirality transfer to afford chiral building blocks.[1] Typically, the synthesis of such α-chiral allylboronates have focused on stoichiometric reactions that utilize a chiral auxiliary on the boron atom.[2] Recently reported syntheses include more attractive catalytic enantioselective reactions that involve an asymmetric hetero[4+2] reaction, 1,4-silaboration of 1,3-diene, diboration of allenes, and alkylation of 3-halo- or 3-acetoxy-2-propenylboronates.[3]

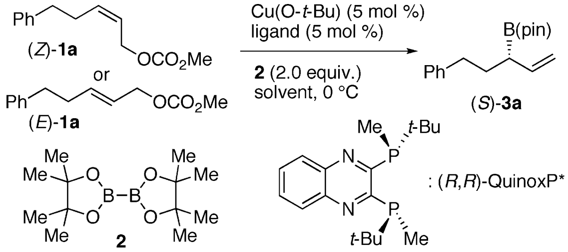
Alternatively, nucleophilic boryl reagents have recently emerged as a novel synthetic tool to afford boryl compounds.[4−7] We have previously reported a versatile Cu(I)-catalyzed synthesis of allylboronates, which involves the reaction of an achiral nucleophilic boryl−copper intermediate.[5a] Herein, we describe a novel method for the synthesis of α-chiral allylboronates featuring the Cu(I)-catalyzed enantioselective substitution of readily available allylic carbonates with a diboron. Using this method, various α-chiral allylboronates, including functionalized allylboronates, were successfully synthesized, with high enantiomeric purity. Although the asymmetric allylic alkylation using Cu(I) catalysts is an active area in organic synthesis,[8] our synthetic scheme, to the best of our knowledge, represents the first example of a Cu(I)-catalyzed asymmetric allylic substitution with a non-carbon nucleophile.

A series of Cu(I)−phosphine catalysts were prepared in situ by mixing Cu(O-*t*-Bu) with chiral ligands. Catalytic activity and enantioselectivity of the resulting Cu(I) complexes were determined using the yields and ee values of allylboronate **3a** (Table 1), which was obtained via reaction between allylic carbonate **1a** and bis(pinacolato)diboron (**2**) in the presence of 5 mol % catalyst. Good yields of **3a** with high enantiomeric excesses (94−96% ees) were obtained for the reactions of (*Z*)-**1a** with the (*R*,*R*)-QuinoxP* chiral ligand,[9] in various solvents such as THP, THF, toluene, and DMI (entries 1−4). In comparison, the reaction employing (*R*,*R*)-Me-DuPhos showed good activity, but lower ee (80% ee, entry 5). The use of (*R*,*R*)-*i*-Pr-DuPhos, which should have stronger steric effects than that of Me-DuPhos, did not improve the enantioselectivity (entry 6).

For these reactions that resulted in high selectivities (entries 1−6), bis(dialkylphosphino)arene exists as a common structure among the ligands. Moderate yield with a low ee value was obtained for the reaction with (*R*)-DIOP (entry 7), whereas poor yields and low selectivities were obtained for axially chiral ligands such as (*R*)-SEGPHOS (entry 8) and (*R*)-BINAP (entry 9).

The enantioselectivity and absolute configuration of the product are greatly influenced by the *E*/*Z* configuration of the substrate− in contrast to that of (*Z*)-**1a**, the reaction of (*E*)-**1a** in the presence of Cu(I)−QuinoxP* afforded (*R*)-**3a** with only 44% ee (entry 10).

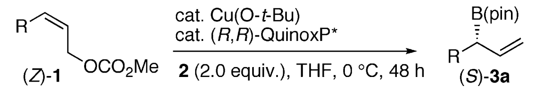
Table 1. Asymmetric Reaction of Allylic Carbonates (*Z*)-**1a** or (*E*)-**1a** with Diboron **2** in the Presence of Cu(I) Complex with Various Chiral Ligands[a]



entry	carbonate	ligand	solvent	time (h)	yield[b] (%)	ee[c] (%)
1	(*Z*)-**1a**	(*R*,*R*)-QuinoxP*	THP	20	77[d]	94
2	(*Z*)-**1a**	(*R*,*R*)-QuinoxP*	THF	20	85	95
3	(*Z*)-**1a**	(*R*,*R*)-QuinoxP*	toluene	20	78	96
4[e]	(*Z*)-**1a**	(*R*,*R*)-QuinoxP*	DMI	20	65	94
5	(Z)-**1a**	(*R*,*R*)-Me-DuPhos	THP	3	97	80
6	(Z)-**1a**	(*R*,*R*)-*i*-Pr-DuPhos	toluene	20	72	79 (*R*)
7	(Z)-**1a**	(*R*,*R*)-DIOP	THP	20	59	37
8	(Z)-**1a**	(*R*)-SEGPHOS	THP	21	19	20
9	(*Z*)-**1a**	(*R*)-BINAP	THP	20	16	31
10	(*E*)-**1a**	(*R*,*R*)-QuinoxP*	THP	20	94	44 (*R*)

[a] Conditions: Cu(O-*t*-Bu) (0.025 mmol), ligand (0.025 mmol), **1a** (0.5 mmol), **2** (1.0 mmol) at 0 °C in solvent (0.5 mL). [b] NMR yield. [c] The ee value of **3a** was determined by chiral GC analysis of the trifluoroacetate of the allylic alcohol derived from H_2O_2/NaOH oxidation of **3a**. [d] Isolated yield. [e] The reaction was carried out at room temperature.

Table 2. Asymmetric Reaction of Allylic Carbonates (*Z*)-**1** with Diboron **2** in the Presence of Cu(O-*t*-Bu)/(*R*,*R*)-QuinoxP* Catalyst[a]



entry	R	product	catalyst (mol %)	yield[b] (%)	ee (%)
1[c]	CH_3 (**1b**)	**3b**	5	68 (75)	95 (*S*)
2	$CH_3CH_2CH_2CH_2CH_2$ (**1c**)	**3c**	5	67	94 (*S*)
3	$(CH_3)_2CHCH_2$ (**1d**)	**3d**	10	62	91 (*S*)
4	$(CH_3)_2CH$ (**1e**)	**3e**	10	0	
5	(*t*-Bu)$Me_2SiOCH_2CH_2CH_2$ (**1f**)	**3f**	10	70 (80)	94 (*S*)
6	$PhCO_2CH_2CH_2CH_2$ (**1g**)	**3g**	5	67 (81)	94 (*S*)
7	$(CH_3)_2C{=}CHCH_2O(CH_2)_3$ (**1h**)	**3h**	10	64 (75)	90 (*S*)

[a] Conditions: Cu(O-*t*-Bu) (0.025 or 0.05 mmol), (*R*,*R*)-QuinoxP* (0.025 or 0.05 mmol), **1** (0.5 mmol), **2** (1.0 mmol) at 0 °C in THF (0.5 mL) unless otherwise noted. [b] Isolated yield. ^{1}H NMR yield is shown in parentheses. [c] Based on a 4.0 mmol scale (**1b**).

As shown in Table 2, various (*Z*)-allylic carbonates (**1b**−**h**) were subjected to the reaction with diboron using the Cu(I)−QuinoxP* catalyst. Optically active allylboronates that possess alkyl substituents (R = CH_3 (**3b**), $CH_3(CH_2)_4$ (**3c**)) were obtained in good yields with high enantioselectivities in the presence of 5 mol % of the catalyst (entries 1 and 2). The reaction of an allylic carbonate with a *β*-branched alkyl substituent (*i*-Bu, **1d**) required a higher catalyst loading (10 mol %) for a reasonable conversion (entry 3). No reaction proceeded with the allylic carbonate (**1e**) substituted with

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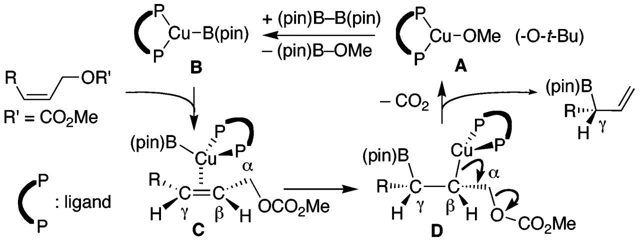
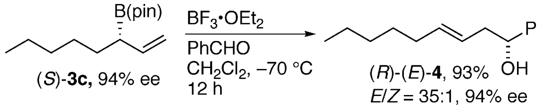
Scheme 1. Proposed Mechanism



a bulkier isopropyl group (entry 4).[10] Importantly, our asymmetric reaction was applicable over a wide range of functionalities: allylboronates that have silyloxy, benzoate, or prenyloxy groups were obtained with high enantioselectivities (entries 5−7).

To confirm the synthetic utility of the α-chiral allyboronates, a Lewis acid-mediated stereoselective reaction between **3c** and an aldehyde was carried out under similar conditions as reported by Hall.[3d,11] In our case, optically active (*R*)-(*E*)-homoallylic alcohol **4** (93%, *E*/*Z* = 35:1, 94% ee) was obtained from (*S*)-**3c** (94% ee) (eq 1).



(1)

A possible reaction mechanism for the copper-catalyzed reaction is illustrated in Scheme 1. First, boryl−copper intermediate **B** is formed through the reaction between alkoxycopper **A** and a diboron. After the formation of Cu−alkene π-complex **C**, addition of the B−Cu bond across the C−C double bond would afford β-borylalkylcopper intermediate **D** such that the Cu and B atoms are located at the β- and γ-positions, respectively. Stereoelectronic effects that stabilize the σ(Cu−C$_\beta$) bond through interactions with the σ^*(C$_\alpha$−O) bond would induce the regioselectivity. Finally, β-alkoxy elimination from alkylcopper intermediate **D** would produce the α-chiral allylboronate and a copper carbonate, which in turn, would regenerate alkoxycopper **A** through decarboxylation. This addition−elimination mechanism is supported by DFT calculations (see Supporting Information).[12,13]

The stereochemical outcome of the Cu(I)-catalyzed reactions of (*Z*)-**1** can be explained by comparing the transition states that occur during the addition of the Cu−B bond across the C−C double bond (Figure 1a). A rigid four-centered diastereomeric transition state is responsible for the high efficiency of the enantiofacial discrimination. The favored transition state **TS1** is free from steric repulsion between the substituents of (*Z*)-**1** and the *t*-Bu groups of the QuinoxP* ligand, thus delivering (*S*)-**3** as the major enantiomer. In contrast, the less-favored **TS2** is largely destabilized by steric congestion between the substituents of (*Z*)-**1** and one of the ligand *t*-Bu groups.

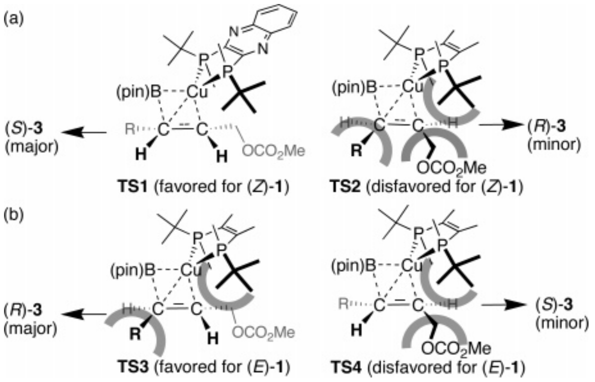


Figure 1. Transition-state models for the addition of the borylcopper (**B**) to (*Z*)- and (*E*)-**1**.

On the other hand, in the case of (*E*)-**1**, both the lower-energy **TS3** and the higher-energy **TS4** suffer from the steric repulsion between the ligand *t*-Bu group and one of the substituents of the substrate (Figure 1b). Accordingly, the energy difference between **TS3** and **TS4** is smaller than that between **TS1** and **TS2**.

In summary, we have successfully carried out various copper-catalyzed enantioselective allylic substitution reactions with a boryl nucleophile. These examples, which, to the best of our knowledge, are the first reported instances of such reactions, offer an efficient route to α-chiral allylboronates.

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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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