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Copper-Catalyzed Enantioselective Intramolecular Alkylboron Allylic Alkylation

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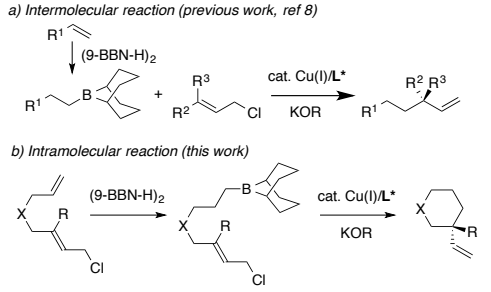
A reductive C–C-bond-forming cyclization of vinyl-terminated allyl chlorides *via* alkene hydroboration with 9-BBN-H followed by Cu-catalyzed asymmetric intramolecular allylic alkylation with a new chiral phosphoramidite ligand produced six-membered ring compounds with a tertiary or quaternary stereogenic center in the ring with high enantioselectivity.

Keywords: *Copper catalysis, Alkylboranes, Allylic Alkylation, Asymmetric Synthesis, Intramolecular Reaction*

Transition metal catalyzed enantioselective allylic substitution of organometallic reagents is one of the most powerful and versatile methods for asymmetric C−C bond formation.[1] Recently, allylic substitution reactions utilizing organoboron compounds have made a remarkable advance, allowing the expansion of substrate scopes with great functional group compatibilities.[2-6] Although the applicable organoboron reagents had been limited to aryl-, alkenyl-, allyl-, propargyl-, and allenylboron derivatives, more recently we introduced protocols for using alkyl-9-BBN reagents for stereoselective γ-selective allylic alkylation.[7-8]



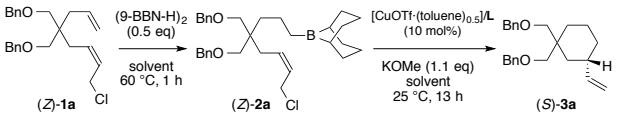
Scheme 1. Copper-Catalyzed Enantioselective Inter- and Intramolecular Allylic Substitution Reactions.

In the reported intermolecular copper-catalyzed enantioselective allylic alkylation reactions with alkyl-9-BBN reagents, we identified C_2-symmetric bisphosphine ligands with axially chiral biaryl backbone and bulky *P*-aryl substituents to be suitable for producing highly active and enantioselective copper catalysts (Scheme 1a).[8] The reactions afforded enantioenriched chiral terminal alkenes containing tertiary or quaternary carbon stereogenic centers branched with sp^3-alkyl groups at the allylic position. The wide availability of alkylboranes *via* alkene hydroboration and their great functional group compatibility are attractive features of these transformations. Based on this knowledge, we sought to develop a method for synthesizing cyclic compounds with a stereogenic carbon center in a ring through intramolecular enantioselective reductive allylic alkylation of bifunctional molecules with a terminal alkene and an allyl (psheudo)halide moiety with a possibility for coexistence of the trialkylborane and the electrophilic allyl moiety in mind.[10]

Herein, we report enantioselective reductive cyclization of allyl chlorides tethered to a terminal alkene that goes through 9-BBN hydroboration of the terminal alkene followed by copper-catalyzed enantioselective intramolecular allylic alkylation with a new chiral phosphoramidite ligand (Scheme 1b). The reaction afforded functionalized chiral six-membered ring compounds containing tertiary or quaternary carbon stereogenic centers substituted with a vinyl group with high enantioselectivities.

An initial screening of chiral ligand for the enantioselective copper-catalyzed cyclization was conducted with alkylborane (*Z*)-**2a**, which was prepared by hydroboration of (*Z*)-**1a**, in the presence of [CuOTf·(toluene)$_{0.5}$] (10 mol%) and KOMe in toluene at 25 °C (Table 1). (*R*)-DTBM-SEGPHOS (**L1**), which exhibited high performance in the intermolecular reaction, induced low enantioselectivity (74% yield, 43% ee) (entry 1).[8a] On the other hand, the screening has revealed that some phosphoramidite-type chiral monodentate phosphine ligand are more suitable than the bidentate phosphine ligands in terms of both catalytic activity and enantioselectivity.[11] The reaction proceeded most efficiently (82% yield, 85% ee) in the presence of a newly synthesized phosphoramidite ligand (**L2**), which consists of a (*S*)-H_8-binaphthol backbone and two *N*-(*R*)-1-(α-naphthyl)ethyl groups (entry 2). Changing the α-naphthyl groups of **L2** to sterically less hindered phenyl groups slightly reduced the product yield and enantioselectivity (78% yield, 80% ee) (entry 3).[12] While a ligand (**L4**) with an achiral biphenol backbone instead of the (*S*)-H_8-binaphthol backbone of **L2** retained some enentioselectivity (30% yield, 39% ee) (entry 4),[13] replacement of the *N*-(*R*)-1-(α-naphthyl)ethyl groups of **L2** with *N*-methyl groups (**L5**) resulted in complete loss of enantioselectivity (entry 5).[14] Thus, the chiral amine moiety is more important than the diol moiety for the enantiocontrol.

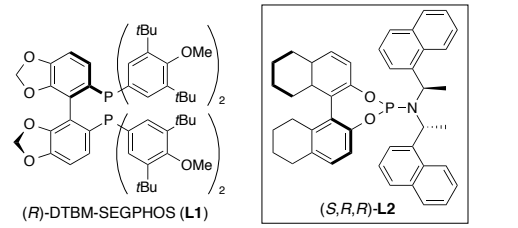
Table 1. Hydroboration of (*Z*)-**1a** and Subsequent Copper-Catalyzed Enantioselective Intramolecular Allylic Alkylation of (*Z*)-**2a** under Various Conditions.[a]

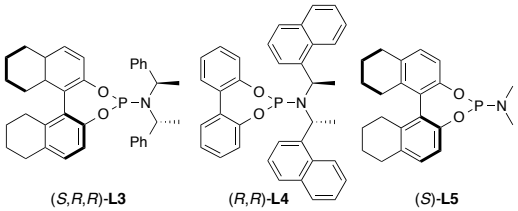


entry	ligand	solvent	yield (%)[b]	ee (%)[c]

1	**L1**	toluene	73	43
2	**L2**	toluene	82	85
3	**L3**	toluene	78	80
4	**L4**	toluene	30	39
5	**L5**	toluene	57	racemic
6	**L2**	mesitylene	85	90
7	**L2**	THF	5	–
8	**L2**	CPME	70	87
9	**L2**	mesitylene/MTBE	84	91

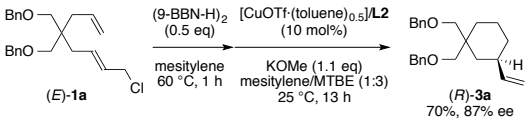
[a]Reaction conditions for hydroboration: (*Z*)-**1a** (0.1 mmol), (9-BBN-H)$_2$ (0.05 mmol; (*Z*)-**1a**/B 1:1); 60 ˚C, 1 h. (*Z*)-**2a** (0.1 mmol) was used without purification. Reaction conditions for enantioselective coupling reaction: (*Z*)-**2a** (0.1 mmol), KOMe (0.11 mmol), [CuOTf·(toluene)$_{0.5}$] (10 mol%), **L** (10 mol%), solvent (0.4 mL), 25 ˚C, 13 h. [b]Yield of the isolated product. [c]The enantiomeric excess was determined by HPLC analysis.





Using **L2** as the optimal chiral ligand, effects of solvents were examined (Table 1, entries 6−9). Mesitylene gave better product yield and enantioselectivity (85% yield and 90% ee) than toluene (entry 6). THF inhibited the reaction almost completely (entry 7). In contrast, cyclopentyl methyl ether (CPME) was suitable for the reaction (70% yield and 87% ee), suggesting that weaker coordination ability or lower polarity of solvent is favorable (entry 8). The highest enantioselectivity (91% ee) was observed with a mixed solvent system mesitylene/methyl *tert*-butyl ether (MTBE) (1:3) (entry 9).

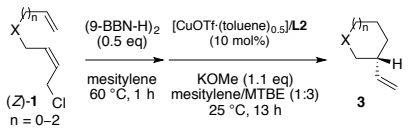
The reaction with (*E*)-**1a** under the optimal conditions (Table 1, entry 9) provided (*R*)-**3a**, the antipode of the product from (*Z*)-**1a**, with 87% ee in 70% yield (Scheme 2). Thus, *Z*-configuration is more favorable than *E*-configuration in the allyl chloride moiety, and the substitution pattern at the position β to the chlorine atom is more important than that at the γ-position for enantiodiscrimination by the catalyst.

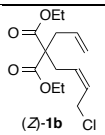
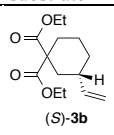
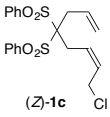
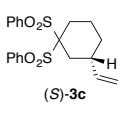
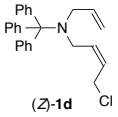
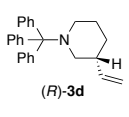
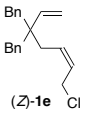
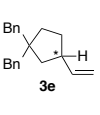


Scheme 2. Cu-catalyzed Enantioselective Intramolecular Allylic Substitution of (*E*)-**1a**.

Other substrates with different linkers between the vinyl group and allyl chloride moiety were subjected to the hydroboration-cyclization protocol under the same conditions. The results are summarized in Table 2.[15–17] This study demonstrates good functional group tolerance of the protocol. For example, the reaction of diethyl malonate-tethered substrate **1b** afforded the corresponding product **3b** in good enantioselectivity (85% ee), albeit in moderate yield (50% yield) (entry 1). The reaction of sulfone derivative **1c** gave **3c** with 89% ee (entry 2). The protocol is applicable for the synthesis of a chiral *N*-tritylpiperidine derivative (**3d**, 90% ee) through the reaction of the corresponding *N*-tethered substrate (**1d**) (entry 3). The five-membered ring formation with ~~a~~ 1,1-dibenzylmethylene tethered substrate **1e** gave the expected cyclic product (**3e**) in low yield and low enantioselectivity (34% yield, 33% ee) (entry 4). A restricted coordination geometry of the alkene may be unfavorable for enantioselection by the catalyst.[18]

Table 2. Scope of (*Z*)-allyl chrorides.[a]

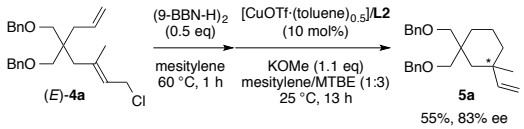


entry	isocyanide	allylic substrate	yield (%)[b]	ee (%)[c]
1	 (*Z*)-**1b**	 (*S*)-**3b**	50[d]	85
2	 (*Z*)-**1c**	 (*S*)-**3c**	40[d]	89
3	 (*Z*)-**1d**	 (*R*)-**3d**	60	90
4	 (*Z*)-**1e**	 **3e**	34	33

[a]Reaction conditions for hydroboration: (*Z*)-**1** (0.1 mmol), (9-BBN-H)$_2$ (0.05 mmol; (*Z*)-**1**/B 1:1); mesitylene, 60 ˚C, 1 h. (*Z*)-**2** (0.1 mmol) was used without purification. Reaction conditions for enantioselective coupling reaction: (*Z*)-**2** (0.1 mmol), KOMe (0.11 mmol), [CuOTf·(toluene)$_{0.5}$] (10 mol%), **L2** (10 mol%), mesitylene/MTBE (1:3, 0.4 mL), 25 ˚C, 13 h. [b]Yield of the isolated product. [c]The enantiomeric excess was determined by HPLC analysis. [d]The isolated products were contaminated with traces amount of unidentified materials.

Next, the applicability of the protocol toward the construction of a quaternary carbon stereogenic center was tested with γ,γ-disubstituted allyl chloride (*E*)-**4** as a model substrate.[8b,19] To our delight, the corresponding six-membered ring containing an all carbon quaternary

stereogenic center was obtained with an enantioselectivity as high as 83% ee (Scheme 3).[20]



Scheme 3. Construction of a Quaternary Carbon Stereogenic Center.

A possible reaction pathway for the intramolecular allylic alkylation catalyzed by the CuX-**L2** system (**A**, CuX-P, X = Cl or OMe) is proposed in Figure 1.[8] Similarly to the intermolecular reaction reported previously, this intramolecular reaction should be initiated by transmetalation between the copper(I) complex **A** and borate **B**, which is formed from **2** and KOMe, to produce a neutral alkylcopper(I) complex (**C**) coordinated with the monophosphine **L2** (P) and the alkene moiety of the allylic substrate.[21] The intramolecular η^2-coordination of the alkene in **C** should be more feasible than the coordination of alkene in the intermolecular allylic alkylation. This difference in alkene coordination may be a cause of the experimentally observed difference in preferred denticity for phosphine coordination. Next, the alkylcopper(I) intermediate **C** undergoes C–Cu addition across the bound C–C double bond, forming **E**. Then, Cu–Cl elimination affords **3** and regenerates **A** for the next catalytic cycle.

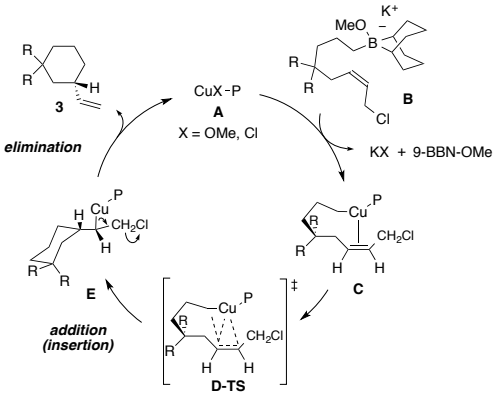


Figure 1. A possible reaction pathway for the copper-catalyzed intramolecular allylic alkylation of an alkyl-9-BBN derivative.

In summary, we developed the reductive cyclization reaction of allyl chlorides tethered to a terminal alkene *via* alkene hydroboration followed by in-situ enantioselective intramolecular allylic alkylation of organoboron intermediates catalyzed by a copper(I)-phosphoramidite system. The reaction afforded functionalized chiral cyclic compounds bearing enantioenriched tertiary or quaternary carbon stereogenic centers.

Supporting Information.
Experimental details and characterization data for all new compounds (PDF). This material is available free of charge via the Internet at http://dx.doi.org/

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15 The addition of 9-BBN-H occurs at the terminal alkene exclusively.

16 The intermolecular coupling product was not observed.

17 The absolute configuration of **3d** was determined by transforming it to a known compound. See the Supporting Information for details. Absolute configurations of **3a** and the other products listed in Table 2 were assigned by consideration of the stereochemical pathway.

18 An attempt to form a seven-membered ring failed. No cyclization product was observed in a crude mixture by ^{1}H NMR spectroscopy.

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20 The absolute configuration of **5a** was not determined.

21 Participation of a potassium alkyl(methoxo)cuprate as a major species is unlikely because the reaction with 0.1 equiv of KOMe occurred with only slightly reduced efficiency. See Supporting Information for details.