



Copper-catalyzed enantioselective allylic cross-coupling with alkylboranes



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ABSTRACT

We have presented full details of our work on alkylboranes, which we have introduced as new reagents for copper-catalyzed S_N2' -type enantioselective allylic substitutions. The copper catalysis delivered enantioenriched chiral products containing tertiary or quaternary carbon stereogenic centers branched with functionalized sp^3 -alkyl groups. The wide availability of alkylboranes via the established alkene hydroboration reaction is an attractive feature of these transformations. Various functional groups are tolerated in the substrates. A reaction pathway involving addition–elimination of a neutral alkylcopper(I) species with the allyl chloride substrate is proposed.

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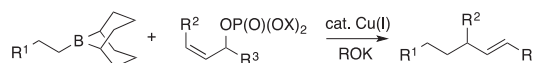
1. Introduction

Enantioselective allylic substitutions of organometallic reagents under the influence of chiral transition metal catalysts are efficient and versatile methods for asymmetric carbon–carbon bond formation.¹ In recent decades, reactions using organoboron compounds as organometallic reagents for allylic substitutions have achieved remarkable advances, given their broad substrate scopes and functional group compatibilities.^{2–6} Unfortunately, however, usable organoboron reagents have generally been limited to aryl-, alkenyl-, allyl-, and allenylboron compounds, and the reactions of alkylboron derivatives have been rare and underdeveloped until very recently.^{7a} In 2012, we reported the first catalytic enantioselective allylic substitution reaction with alkylboron compounds under catalysis of a chiral Cu(I) complex system. Later, the system was extended to catalytic enantioselective construction of all-carbon quaternary stereogenic centers.^{7b} Herein, we present full details of our studies on the use of alkylboranes for copper-catalyzed S_N2' -type enantioselective allylic substitutions.^{8,9}

2. Results/discussion

2.1. Construction of tertiary carbon stereogenic centers using γ -monosubstituted primary allylic substrates

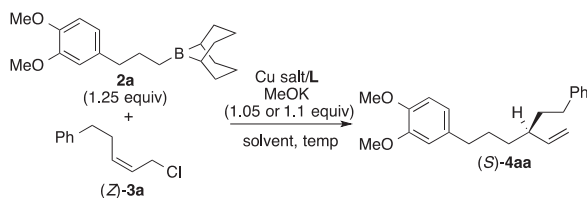
2.1.1. Optimization. Previously, we reported that the allyl–alkyl coupling between enantioenriched chiral secondary (*Z*)-allylic phosphates and alkyl-9-BBN reagents proceeded with excellent γ -selectivity and stereospecificity under the influence of a catalytic amount of a copper(I) salt and a stoichiometric potassium alkoxide base (Scheme 1).^{8a–c} On the basis of this knowledge, we initiated a program to develop an unprecedented catalytic enantioselective allylic alkylation with alkylboranes. Initial screening of ligands was conducted for the reaction of alkylborane **2a** (0.25 mmol), which was prepared from dimethoxyallylbenzene (**1a**), and γ -monosubstituted primary allyl chloride (*Z*)-**3a** (0.2 mmol) in the presence of CuCl (5 mol %) and MeOK in 1,4-dioxane at 35 °C (Table 1).¹⁰ The ring-unsaturated C_2 -symmetric *N*-heterocyclic carbene ligand



Scheme 1. Copper-catalyzed cross-coupling between alkylboranes and secondary (*Z*)-allylic phosphates.

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Table 1
Copper-catalyzed enantioselective allylic substitutions between alkylborane **2a** and (*Z*)-**3a** under various conditions^a



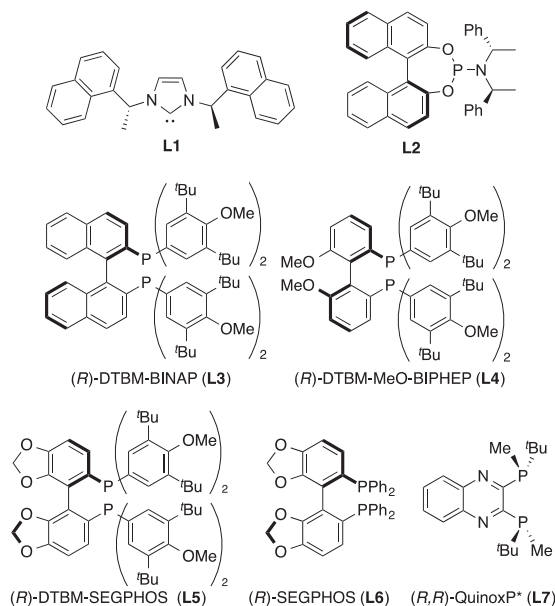
Entry	Cu/L (mol %)	Cu salt	L	Solvent	Temp (°C)	Yield ^{b,c} (%)	ee ^d (%)
1	5	CuCl	L1	Dioxane	35	3	0
2	5	CuCl	L2	Dioxane	35	0	—
3	5	CuCl	L3	Dioxane	35	5	37
4	5	CuCl	L4	Dioxane	35	25	47
5	5	CuCl	L5	Dioxane	35	48	61
6	5	CuCl	L6	Dioxane	35	0	—
7	5	CuCl	L7	Dioxane	35	99	7
8	5	CuCl	L5	THF	35	11	40
9	5	CuCl	L5	Toluene	35	7	41
10	5	CuCl	L5	DCM	35	Trace	—
11	10	CuCl	L5	Dioxane	10	23	74
12	10	CuCl	L5	Dioxane/DCM	10	81	77
13	10	CuOTf·(toluene) _{0.5}	L5	Dioxane/DCM	10	83	77
14	10	CuOTf·(toluene) _{0.5}	L5	Dioxane/DCM	5	55	80

^a The reaction was carried out with (*Z*)-**3a** (0.2 mmol), **2a** (0.25 mmol), Cu salt, ligand (**L**), and MeOK (0.21 mmol, entries 1–10; 0.22 mmol, entries 11–14) in solvent (0.8 mL) for 12 h (entries 1–10) or 48 h (entries 11–14). Alkylborane **2** was prepared in advance by hydroboration of **1** with the 9-BBN dimer at 60 °C (1 h) and used without purification.

^b The yield was determined by ¹H NMR.

^c Constitutional isomer ratio $\gamma/\alpha > 20:1$ (determined by ¹H NMR analysis of the crude product).

^d The enantiomeric excess was determined by HPLC analysis.



(**L1**)¹¹ having 1-(1-naphthyl)ethyl groups at both nitrogen atoms gave racemic **4aa** (entry 1). The chiral phosphoramidite ligand (**L2**) did not form an active catalyst (entry 2). Further screening of various chiral ligands revealed that introducing 3,5-di-*tert*-butyl-4-methoxyphenyl (DTBM) substituents on the phosphorus atoms of chiral bisphosphines was essential not only for enantiocontrol, but also for catalytic activity with bisphosphine-based chiral copper catalysts. (*R*)-DTBM-BINAP (**L3**) induced low catalytic activity and enantioselectivity (entry 3). The use of DTBM-MeO-BIPHEP (**L4**) gave better product yield and enantioselectivity (entry 4). The use of (*R*)-DTBM-SEGPHOS¹² (**L5**) led to an improvement in the product yield and enantioselectivity (entry 5), giving the branched γ -substitution product (*S*)-**4aa** ($\gamma/\alpha > 20:1$). In contrast, non-DTBM-

substituted chiral bisphosphines, (*R*)-SEGPHOS (**L6**) or (*R,R*)-Quinox P* (**L7**),¹³ resulted in complete inhibition of the reaction or loss of enantiocontrol, respectively (entries 6 and 7). The introduction of the DTBM substituents may have induced the deaggregation of alkylcopper(I) species to form a catalytically active monomeric copper complex.¹⁴

Next, the effect of solvent was examined in the reaction between **2a** and (*Z*)-**3a** with the CuCl–**L5** catalyst system (Table 1, entries 8–12). The use of THF or toluene as a solvent instead of 1,4-dioxane resulted in poor yields (11% and 7%) and lower enantioselectivities (40% and 41% ees) (entries 8 and 9). Dichloromethane (DCM) as solvent inhibited the reaction almost completely (entry 10). The enantioselection was improved to 74%

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