Asymmetric Catalysis

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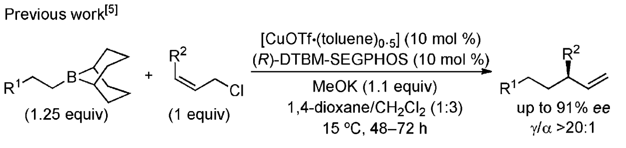
Construction of Quaternary Stereogenic Carbon Centers through Copper-Catalyzed Enantioselective Allylic Cross-Coupling with Alkylboranes**

Kentaro Hojoh, Yoshinori Shido, Hirohisa Ohmiya, and Masaya Sawamura**

Abstract: *A combination of an in situ generated chiral Cu^I/DTBM-MeO-BIPHEP catalyst system and EtOK enabled the enantioselective S_N2'-type allylic cross-coupling between alkylborane reagents and γ,γ-disubstituted primary allyl chlorides with enantiocontrol at a useful level. The reaction generates a stereogenic quaternary carbon center having three sp^3-alkyl groups and a vinyl group. This protocol allowed the use of terminal alkenes as nucleophile precursors, thus representing a formal reductive allylic cross-coupling of terminal alkenes. A reaction pathway involving addition/elimination of a neutral alkylcopper(I) species with the allyl chloride substrate is proposed.*

Catalytic enantioselective construction of all-carbon quaternary stereogenic centers in acyclic systems is one of the biggest challenges in organic synthesis.[1] One of the obstacles is low reactivity because of the steric repulsion that occurs in the carbon–carbon bond-formation step. It is also difficult to discriminate the enantiotopic faces because of steric congestion and the diminished steric difference between the non-hydrogen substituents. To this end, transition metal catalyzed enantioselective allylic substitutions with organometallic nucleophiles such as organolithium, Grignard, diorganozinc, or triorganoaluminum reagents have proven to be effective strategies.[2] Organoboron compounds have also been used for enantioselective construction of all-carbon quaternary stereogenic centers through allylic substitution, thus making this strategy more tolerant to various functional groups.[3] However, applied organoboron reagents are limited to aryl-, alkenyl-, allenyl-, and allylboron compounds. The methodology has not yet been generalized to allow the reaction of non-allylic alkylboron nucleophiles.[4]

Earlier, we reported the enantioselective S_N2'-type reaction between alkylboron compounds (alkyl-9-BBN) and substituted allyl chlorides under the catalysis of a Cu^I/DTBM-SEGPHOS system [Eq. (1); Tf = trifluoromethanesulfonyl].[5] However, the protocol was limited to the construction of tertiary carbon stereogenic centers using γ-monosubstituted primary allylic substrates. Herein we report that a combination of an in situ generated Cu^I/DTBM-MeO-BIPHEP chiral catalyst system and EtOK enabled the enantioselective S_N2'-type allylic cross-coupling between alkylborane (alkyl-9-BBN) reagents and γ,γ-disubstituted primary allyl chlorides with enantiocontrol at a useful level.[6–8] The reaction generates a quaternary carbon stereogenic center bearing three sp^3-alkyl groups and a vinyl group. The overall protocol employs terminal alkenes as nucleophile precursors, thus representing a formal reductive allylic cross-coupling of terminal alkenes.



(1)

Our earlier investigation on the copper-catalyzed enantioselective reaction between alkylboranes and γ-monosubstituted primary allyl chlorides indicated that introducing 3,5-di-*tert*-butyl-4-methoxyphenyl (DTBM) substituents on the phosphorus atoms of chiral bis(phosphine)s was important for promotion of the reaction.[5] We assumed that the introduction of the DTBM substituents would induce the deaggregation of the alkylcopper(I) species to form a catalytically active monomeric copper complex.[9] On the basis of this consideration, we examined copper complexes prepared from [$CuOTf\cdot(toluene)_{0.5}$] (10 mol%) and various DTBM-substituted chiral bisphosphine ligands for catalytic activity, γ-regioselectivity, and enantioselectivity in the reaction of the γ,γ-disubstituted allyl chloride (*E*)-**3a** with alkylborane **2a** in the presence of EtOK in 1,4-dioxane/CH_2Cl_2 (1:3) at 25 °C for 20 hours (**3a**/**2a**/EtOK 1:1.25:1.1) (Table 1, entries 1–4).[5,10,11] As in the previous study with γ-monosubstituted allyl chlorides, **2a** was prepared in advance through hydroboration of 3,4-dimethoxy-1-allylbenzene (**1a**) with $(9\text{-BBN-H})_2$ (**3a**/**1a**/B 1:1.3:1.25) at 60 °C for 1 hour and was used without purification. The conversion of **1a** into **2a** with a full consumption of 9-BBN-H was confirmed by ^1H and ^{11}B NMR spectroscopy. The amount of EtOK was adjusted so that **2a** was in a slight excess (**2a**/EtOK 1.1:1) to ensure full consumption of EtOK for the formation of CuOEt and a borate (**2a′**) species.[12] Accordingly, yields of the allylation product **4aa** were calculated based on **3a**. Specifically, the catalyst prepared from the DTBM-substituted TunePHOS-type chiral bis(phosphine) **L1** did not promote the reaction at all (entry 1).[13] (*R*)-DTBM-BINAP (**L2**) induced only low

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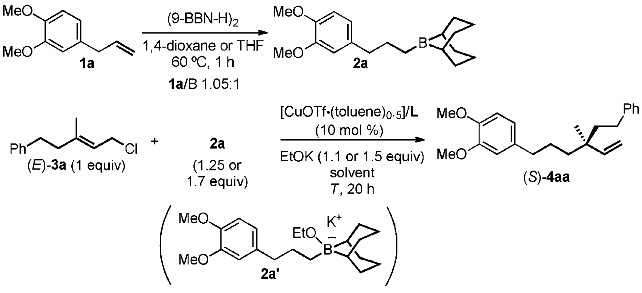
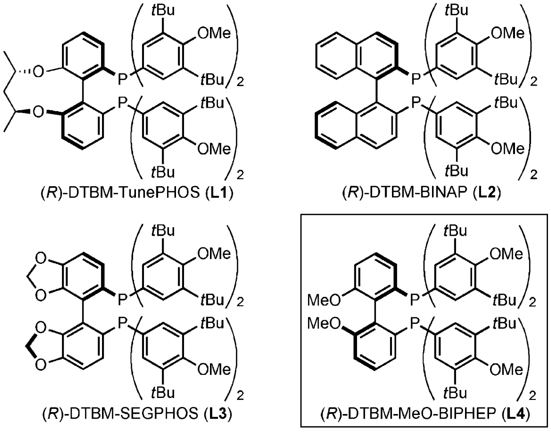
Table 1: Copper-catalyzed enantioselective cross-coupling between **2a** and (*E*)-**3a** under various reaction conditions.[a]



Entry	L	Solvent	*T* [°C]	Yield [%][b]	γ/α[c]	*ee* [%][d]
1	**L1**	1,4-1,4-dioxane/CH_2Cl_2	25	0	–	–
2	**L2**	1,4-dioxane/CH_2Cl_2	25	38	3.5:1	21
3	**L3**	1,4-dioxane/CH_2Cl_2	25	15	6:1	47
4	**L4**	1,4-dioxane/CH_2Cl_2	25	26	>20:1	83
5	**L4**	THF/CH_2Cl_2	25	56	>20:1	81
6[e]	**L4**	THF/CH_2Cl_2	15	65	>20:1	81

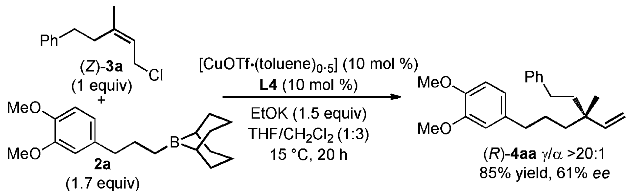
[a] Reaction conditions for hydroboration: **1a** (0.26 mmol), (9-BBN-H)$_2$ (0.125 mmol; **1a**/B 1.05:1); 60 °C, 1 h. **2a** (0.25 mmol) was used without purification. Reaction conditions for enantioselective coupling reaction: (*E*)-**3a** (0.2 mmol), **2a** (0.25 mmol), EtOK (0.22 mmol), [CuOTf·(toluene)$_{0.5}$] (10 mol %), **L** (10 mol %), solvent (0.8 mL), 20 h. [b] Yield of the isolated product. [c] Determined by ^{1}H NMR analysis of the crude reaction mixture. [d] The enantiomeric excess was determined by HPLC analysis. [e] Reaction at 0.3 mmol scale. **2a** (0.52 mmol) and EtOK (0.45 mmol) were used. THF = tetrahydrofuran.


(*R*)-DTBM-TunePHOS (**L1**)
(*R*)-DTBM-BINAP (**L2**)
(*R*)-DTBM-SEGPHOS (**L3**)
(*R*)-DTBM-MeO-BIPHEP (**L4**)

catalytic activity, γ-selectivity, and enantioselectivity (entry 2). (*R*)-DTBM-SEGPHOS (**L3**), which exhibited high performance in the previously reported reaction with γ-monosubstituted primary allyl chlorides [Eq. (1)], imparted moderate γ-selectivity (γ/α 6:1) and enantioselectivity (47 % *ee*), but the product yield was lower than that obtained with **L2** (entry 3). To our delight, the use of (*R*)-DTBM-MeO-BIPHEP (**L4**) led to a significant improvement in the regioselectivity and enantioselectivity (entry 4).[14] The alkylation occurred at the disubstituted γ-carbon atom of **3a** (γ/α > 20:1), thus constructing the all-carbon quaternary stereogenic center with 83 % *ee* in favor of the formation of (*S*)-**4aa** (Si face attack), albeit still with a low product yield. These results suggest that the catalytic activity, γ-selectivity, and enantioselectivity of this reaction are very sensitive to the dihedral angle of the axially chiral biaryl scaffolds in the Cu^I/bis(phosphine) complexes.

The product yield with the Cu/**L4** system could be increased to 56 % by changing the solvent to THF/CH_2Cl_2 (1:3) with the enantioselectivity almost unchanged (81 % *ee*; Table 1, entry 5). The yield was further improved to 65 % by conducting the reaction at 15 °C with an increased amount of the **2a**/EtOK reagent (**3a**/**2a**/EtOK 1:1.7:1.5; entry 6).

The reaction of the *Z*-configured allyl chloride (*Z*)-**3a** under the conditions optimal for the reaction of (*E*)-**3a** (Table 1, entry 6) provided (*R*)-**4aa**, the antipode of the product derived from (*E*)-**3a**, with 61 % *ee* in 85 % yield [Eq. (2)].[10,11] This enantioselectivity is lower than that for the reaction of (*E*)-**3** (see below for discussion on enantioselection models).



(2)

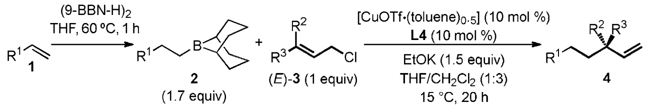
Various terminal alkenes were subjected to 9-BBN-hydroboration and were used for coupling with (*E*)-**3a** using [CuOTf·(toluene)$_{0.5}$] (10 mol %), **L4** (10 mol %), and EtOK in THF/CH_2Cl_2 (1:3) at 15 °C for 20 hours (Table 2, entries 1–7).[10,11] The copper-catalyzed coupling reactions proceeded with excellent γ-selectivity and good to high enantioselectivities. Various terminal alkenes having different functional groups such as acetal, ester, chloro, silyl ether, and benzyl ether moieties in the aliphatic chain were compatible with this protocol (entries 1–6).

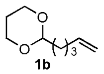
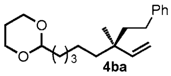
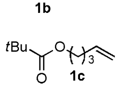
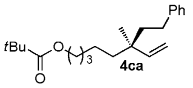
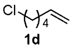
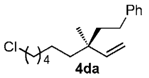
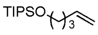
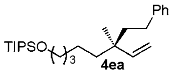
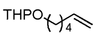
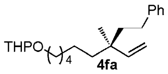
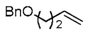
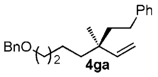
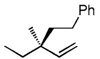
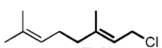
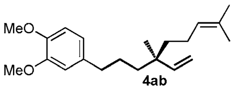
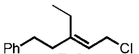
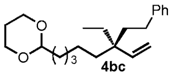
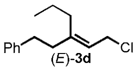
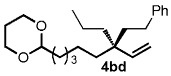
Ethylene also served as a suitable substrate (entry 7).[10,11] This reaction delivered an ethyl group to the fully substituted γ-carbon atom of (*E*)-**3a** with enantioselectivity at a useful level.

The scope with respect to the γ,γ-disubstituted allyl chlorides (**3**) is also shown in Table 2 (entries 8–10).[10,11] An additional trisubstituted alkene moiety in the allylic substrate (*E*)-**3b** was tolerated for the formation of the diene **4ab** (entry 8). The copper catalyst system enabled the enantioselective coupling of allyl chlorides having two alkyl substituents of almost equal steric demand at the γ-position (entries 9 and 10). For example, the allyl chloride (*E*)-**3c** having ethyl and phenylethyl groups at the γ-position, reacted with a high enantioselectivity (entry 9). Replacing the ethyl group at the γ-position of (*E*)-**3c** with a propyl group caused only a slight reduction in the enantioselectivity (entry 10).

A possible catalytic cycle for the γ-selective allylic coupling is illustrated in Figure 1.[5,6a–c] As proposed for the copper-catalyzed enantioselective reaction between alkylboranes and γ-monosubstituted primary allyl chlorides, the active organocopper species is likely in the form of a neutral organocopper(I) species (**C**) rather than a mono-organoheterocuprate, as EtOK is consumed for the formation of **2'** and the copper center bearing the alkyl ligand and **L4** is

Table 2: Scope of enantioselective allylic cross-coupling with alkylboranes.[a]



Entry	Alkene	Chloride	Product	Yield [%][b,c]	*ee* [%][d]
1	 **1b**	(*E*)-**3a**	 **4ba**	79	90
2	 **1c**	(*E*)-**3a**	 **4ca**	66	81
3[e]	 **1d**	(*E*)-**3a**	 **4da**	80	86
4	 **1e**	(*E*)-**3a**	 **4ea**	85	83
5[f]	 **1f**	(*E*)-**3a**	 **4fa**	70	86
6	 **1g**	(*E*)-**3a**	 **4ga**	68	81
7	 **1h**	(*E*)-**3a**	 **4ha**	63	71
8	**1a**	 (*E*)-**3b**	 **4ab**	54	73
9[e]	**1b**	 (*E*)-**3c**	 **4bc**	75	81
10[e]	**1b**	 (*E*)-**3d**	 **4bd**	67	71

[a] Reaction conditions for hydroboration: **1** (0.35 mmol), (9-BBN-H)$_2$ (0.17 mmol; **1**/B 1.05:1); 60 °C, 1 h. **2** (0.34 mmol) was used without purification. Reaction conditions for enantioselective coupling reaction: (*E*)-**3** (0.2 mmol), **2** (0.34 mmol), EtOK (0.3 mmol), [CuOTf·(toluene)$_{0.5}$] (10 mol%), **L4** (10 mol%), THF/CH$_2$Cl$_2$ (1:3, 0.8 mL); 15 °C, 20 h. [b] Yield of the isolated product. [c] Constitutional isomer ratio $\gamma/\alpha > 20:1$ (determined by ^{1}H NMR analysis of the crude reaction mixture). [d] The enantiomeric excess was determined by HPLC analysis. [e] Constitutional isomer ratio $\gamma/\alpha > 10:1$. [f] Diastereomeric ratio (1:1). THP = tetrahydropyran, TIPS = triisopropylsilyl.

coordinatively saturated upon alkene coordination.[12] Therefore, the reaction should proceed through an addition/β-elimination sequence with the neutral organocopper(I) species **B**. The enantioselection would occur at the transition state of the R^1–Cu addition across the C–C double bond of (*E*)-**3** [**C**→**D-TS**→(**E**→) **A** + **4** + 9-BBN-OEt]. During this addition/elimination step, 9-BBN-OEt may act as a Lewis acid to assist the elimination of the chloride leaving group.[5,6c]

The formation of the α-coupling product in the reaction with (*R*)-DTBM-BINAP (**L2**) or (*R*)-DTBM-SEGPHOS (**L3**) might be due to the formation of alkyl(ethoxo)cuprate species upon dissociation of one or two P atoms of the chiral ligands. Such cuprate species would undergo oxidative addition with **3** to form an isomeric mixture of ([σ+π]-allyl)copper(III) species with a C–Cu σ bond at either the α- or γ-carbon atom. Reductive elimination of these allylcopper(III) intermediates may form a mixture of the α- and γ-coupling product as a minor product.[15,16]

We propose the enantioselection models depicted in Figure 2 based on the fact that the reactions of *E* and *Z* isomers of **3a** gave the each of the antipodes of **4**, respectively, with the former showing higher enantioselectivity [Table 1, entry 6 versus Eq. (2)]. In the π-complex **C** (see Figure 1), the allyl chloride substrate (**3**) bound to the tetrahedral copper center is in proximity to the two P substituents Ar^1 and Ar^3, which are axial and equatorial substituents, respectively, of the bis(phosphine)/Cu chelate ring. The axial substituent Ar^1 points toward the substrate more than the equatorial Ar^3. R_l and R_s indicate the larger and smaller γ-substituents, respectively, of **3**. **C1**, which leads to the major enantiomer of **4** in the reaction of (*E*)-**3**, has steric repulsion only between R_s and Ar^3, while the corresponding π complex (**C2**), leading to the minor enantiomer, has larger steric repulsions between the ClCH$_2$ group and Ar^1 and between Ar^3 and R_l. A similar discussion should be applicable for the transition-state **D-TS**.

In the case of the reaction of (*Z*)-**3**, the π-complex **C3** (Figure 2), which leads to the major enantiomer and the antipode of the product from **C1**, has a steric repulsion between Ar^3 and R_l, and it should be larger than the steric repulsion that occurs in **C1** (R_l versus R_s). In contrast, the steric repulsion between Ar^3 and R_s in **C4** should be smaller than that between Ar^3 and R_l in **C2**. These considerations also match the observed trend that the enantioselectivity gradually decreased with the increase of the size of the R_s substituent of (*E*)-**3** (Table 2, entries 1, 9, and 10). This trend can be explained by the increasing steric repulsion between Ar^3 and R_s in **C1**.

In summary, we have developed an S$_N$2′-type enantioselective allylic cross-coupling between alkyl-9-BBN reagents and γ,γ-disubstituted primary allyl chlorides under the catalysis of a Cu^I/DTBM-MeO-

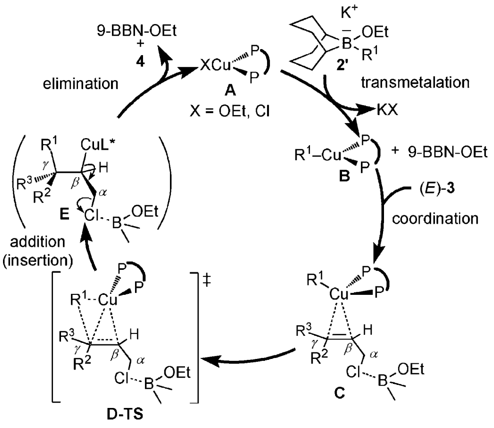
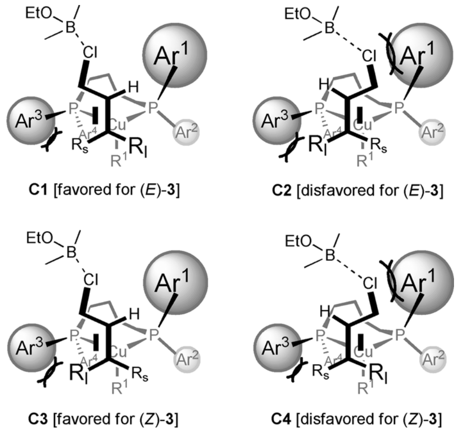


Figure 1. A possible catalytic cycle.



C1 [favored for (*E*)-**3**] **C2** [disfavored for (*E*)-**3**]

C3 [favored for (*Z*)-**3**] **C4** [disfavored for (*Z*)-**3**]

Figure 2. Proposed models for enantiodiscrimination. R_l and R_s are the larger and smaller γ-substituents, respectively, of **3**. Ar^1–Ar^4 are the P-substituents of **L4**. The biaryl scaffold of **L4** is simplified with a polygonal line.

BIPHEP system to deliver enantioenriched chiral products containing quaternary carbon stereogenic centers bearing three sp^3-alkyl groups and a vinyl group. This protocol allowed the use of terminal alkenes as nucleophile precursors, thus representing a formal reductive allylic cross-coupling of terminal alkenes. Efforts to expand the utility of this reaction and mechanistic works are ongoing in our laboratory.

Experimental Section

Typical procedure for copper-catalyzed enantioselective allylic cross-coupling with alkylboranes (Table 1, entry 6). 3,4-Dimethoxy-1-allylbenzene (**1a**; 93.4 μL, 0.54 mmol) and $(9\text{-BBN-H})_2$ (64.2 mg, 0.26 mmol) were placed in a vial containing a magnetic stirring bar. The vial was sealed with a Teflon®-coated silicon rubber septum and the vial was evacuated and filled with argon. THF (0.3 mL) was added to the vial, and then the mixture was stirred at 60 °C for 1 h to prepare an alkylborane. Meanwhile, $[\text{CuOTf}\cdot(\text{toluene})_{0.5}]$ (7.8 mg, 0.03 mmol), (*R*)-DTBM-MeO-BIPHEP (**L4**) (35.5 mg, 0.03 mmol), and EtOK (39.9 mg, 0.45 mmol) were placed in another vial. This vial was sealed with a Teflon®-coated silicon rubber septum and then evacuated and filled with argon. After CH_2Cl_2 (0.9 mL) was added to the vial, the mixture was stirred at 25 °C for 1 h. Next, the alkylborane solution was transferred to the vial containing the Cu^I/**L4** complex. Next, (*E*)-**3a** (58.5 mg, 0.3 mmol) was added. After 20 h of stirring at 15 °C, diethyl ether was added to the mixture. The mixture was filtered through a short plug of silica gel, and was then washed with diethyl ether. After the solvent was removed under reduced pressure, flash chromatography on silica gel (0–3 % EtOAc/hexane) provided **4aa** (66.0 mg, 0.20 mmol) at 81 % *ee* in 65 % yield.

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Keywords: allylic compunds · asymmetric catalysis · boron · copper · synthetic methods

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[8] Fu and co-workers reported the nickel-catalyzed enantioselective cross-couplings between alkyl-9-BBN and secondary alkyl halides. The methodology has not been expanded yet to the enantioselective construction of all-carbon quaternary stereogenic centers. See: a) B. Saito, G. C. Fu, *J. Am. Chem. Soc.* **2008**, *130*, 6694 – 6695; b) N. A. Owston, G. C. Fu, *J. Am. Chem. Soc.* **2010**, *132*, 11908 – 11909; c) Z. Lu, A. Wilsily, G. C. Fu, *J. Am. Chem. Soc.* **2011**, *133*, 8154 – 8157; d) S. L. Zultanski, G. C. Fu, *J. Am. Chem. Soc.* **2011**, *133*, 15362 – 15364; e) A. Wilsily, F. Tramutola, N. A. Owston, G. C. Fu, *J. Am. Chem. Soc.* **2012**, *134*, 5794 – 5797.

[9] For discussion on the effect of the DTBM groups in the enantioselective copper-catalyzed hydrosilylation of aryl ketones, see: B. H. Lipshutz, K. Noson, W. Chrisman, A. Lower, *J. Am. Chem. Soc.* **2003**, *125*, 8779 – 8789.

[10] For Tables 1 and 2, and Eq. (2), small amounts of dechlorinated compounds which stemmed solely from the allyl chloride (**3**) were detected in the crude reaction mixture after removal of the catalyst.

[11] The absolute configuration of **4ha** was determined by transforming it to a known compound. See the Supporting Information for details. Absolute configurations of **4aa** and the other

products listed in Table 2 were assigned by consideration of the stereochemical pathway.

[12] Rapid and quantitative formation of a tetravalent borate (**2′**) was confirmed by ^{11}B NMR spectroscopy. Treatment of **2a** with EtOK in THF/CH_2Cl_2 (1:3) at 25 °C for 10 min caused a complete disappearance of the signal for **2a** ($\delta = 69.6$ ppm, RT), and a new signal appeared at the higher magnetic field ($\delta = -3.1$ ppm), which was assigned to **2a'**.[6a] Subsequent mixing of the borate with one equiv of CuOTf·$(\text{toluene})_{0.5}$/(*R*)-DTBM-MeO-BIPHEP (**L4**) at 25 °C for 15 min formed 9-BBN-OEt ($\delta = 55.6$ ppm, RT). See the Supporting Information for details of the NMR studies.

[13] X. Sun, L. Zhou, W. Li, X. Zhang, *J. Org. Chem.* **2008**, *73*, 1143–1146.

[14] EtOK was optimal among the bases screened. The use of MeOK instead of EtOK under the reaction conditions used for entry 4 of Table 1, decreased the product yield (14 % yield) with the regioselectivity and enantioselectivity unchanged ($\gamma/\alpha > 20{:}1$, 83 % *ee*). The use of *t*BuOK resulted in no reaction.

[15] a) N. Yoshikai, S.-L. Zhang, E. Nakamura, *J. Am. Chem. Soc.* **2008**, *130*, 12862–12863; b) M. Yamanaka, S. Kato, E. Nakamura, *J. Am. Chem. Soc.* **2004**, *126*, 6287–6293; For a review, see: c) N. Yoshikai, E. Nakamura, *Chem. Rev.* **2012**, *112*, 2339–2372.

[16] Liu and co-workers proposed an S_N2-type substitution of arylcuparate species with primary alkyl (pseudo)halides in the copper-catalyzed cross-coupling reaction with arylboronate reagents. See: C.-T. Yang, Z.-Q. Zhang, Y.-C. Liu, L. Liu, *Angew. Chem.* **2011**, *123*, 3990–3993; *Angew. Chem. Int. Ed.* **2011**, *50*, 3904–3907.