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| Author(s)        | Yasuda, Yuto; Nagao, Kazunori; Shido, Yoshinori; Mori, Seiji; Ohmiya, Hirohisa; Sawamura, Masaya   |
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# Copper-Catalyzed $\gamma$ -Selective and Stereospecific Allylic Cross-Coupling with Secondary Alkylboranes

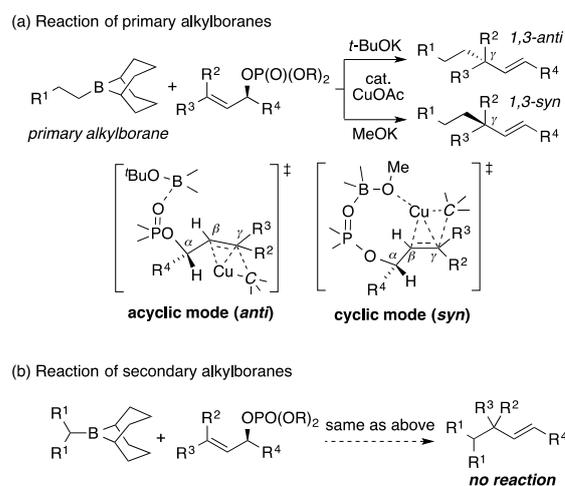
Yuto Yasuda,<sup>[a]</sup> Kazunori Nagao,<sup>[a]</sup> Yoshinori Shido,<sup>[a]</sup> Seiji Mori,<sup>[b]</sup> Hirohisa Ohmiya,<sup>\*[a]</sup> and Masaya Sawamura<sup>\*[a]</sup>

**Abstract:** The scope of the copper-catalyzed coupling reaction between organoboron compounds and allylic phosphates was expanded significantly by employing triphenylphosphine as a ligand for copper, allowing the use of *secondary* alkylboron compounds (alkyl-9-BBN). The reaction proceeded with complete  $\gamma$ -*E*-selectivity and preferential 1,3-*syn* stereoselectivity. Reaction of  $\gamma$ -silicon-substituted allylic phosphates afforded enantio-enriched  $\alpha$ -stereogenic allylsilanes.

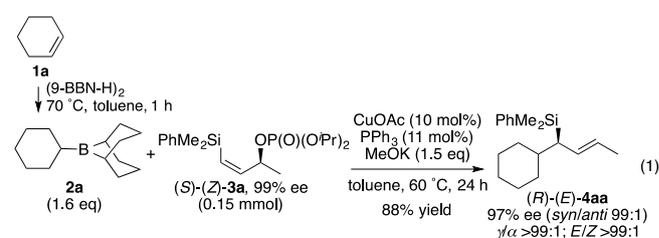
Copper-catalyzed allylic substitutions with organoboron compounds are of interest due to their broad substrate scope.<sup>[1,2]</sup> Previous reports have shown that  $sp^3$ -alkylboron compounds (alkyl-9-BBN) can be coupled with internal allylic systems with complete  $\gamma$ -selectivity using a catalytic amount of a copper(I) salt and a stoichiometric potassium alkoxide base.<sup>[3–5]</sup> Interestingly, the stereochemical cross-coupling between enantio-enriched chiral allylic phosphates and alkylboranes could be switched between the 1,3-*anti* and 1,3-*syn* forms relative to the leaving group by choosing the appropriate achiral alkoxide base with a specific steric demand: *t*-BuOK and MeOK showed 1,3-*anti* and 1,3-*syn* stereochemistry, respectively.<sup>[3c]</sup> Acyclic and cyclic bimodal participation of alkoxyborane species generated *in situ* in an organocopper addition–elimination sequence was proposed to account for the phenomenon of the *anti*-*syn* stereochemical reversal (Scheme 1a). However, only *primary* alkylboron compounds could be used as nucleophilic coupling partners. Neither the 1,3-*anti* and 1,3-*syn* form was effective in the reaction of *secondary* alkylboranes, probably due to increased steric demands of the transferring groups (Scheme 1b).

The present study describes the dramatic ligand effects of tertiary monophosphines, such as  $Ph_3P$ ,  $Cy_3P$ , and  $tBu_3P$ , which enabled copper-catalyzed allylic cross-coupling between secondary alkylboron compounds (alkyl-9-BBN) and (*Z*)-acyclic or cyclic allylic phosphates. These ligand effects were most pronounced when the ligands were used as additives for the 1,3-*syn*-selective protocol (CuOAc/MeOK/toluene) in a previous study.<sup>[6]</sup> This new copper catalysis using secondary alkylboranes

proceeded with complete  $\gamma$ -*E*-selectivity and preferential 1,3-*syn* stereoselectivity. These methods significantly broadened the scope of allylic C–C bond-forming cross-coupling reactions.



**Scheme 1.** Previous work (ref 3c).



In numerous studies for finding reaction conditions enabling the region- and stereoselective coupling between secondary alkylboron compounds and chiral secondary allylic electrophiles, we found critical effects of phosphine ligands for promoting this transformation. Specifically, the reaction between cyclohexylborane **2a**, which was prepared *via* hydroboration of cyclohexene (**1a**) and an enantio-enriched chiral  $\gamma$ -silylated allylic phosphate [(*S*)-(*Z*)-**3a** (99% ee)] containing a diisopropyl phosphate leaving group in the presence of CuOAc (10 mol%),  $PPh_3$  (11 mol%), and MeOK (1.5 eq) in toluene at 60 °C for 24 h afforded allylsilane (*R*)-(*E*)-**4aa** with 97% ee in 88% yield with complete  $\gamma$ - and *E*-selectivities (Eq 1 and Table 1, entry 3).<sup>[7]</sup> The absolute configuration of the coupling product indicated that the reaction occurred with 1,3-*syn* stereochemistry (*syn*:*anti* 99:1). The reported phosphine-free conditions, which gave 1,3-*syn* (CuOAc/MeOK/toluene) or 1,3-*anti* (CuOAc/*t*BuOK/THF) stereochemical outcomes in a previous study on the reaction of primary alkylboranes (Scheme 1a), did not produce any coupling

[a] Y. Yasuda, K. Nagao, Y. Shido, Prof. Dr. H. Ohmiya, Prof. Dr. M. Sawamura  
Department of Chemistry, Faculty of Science  
Hokkaido University  
Sapporo 060-0810, Japan  
E-mail: ohmiya@sci.hokudai.ac.jp;  
sawamura@sci.hokudai.ac.jp  
Homepage: <http://wwwchem.sci.hokudai.ac.jp/~orgmet/index.php>

[b] Prof. Dr. S. Mori  
Faculty of Science, Ibaraki University  
Mito 310-8512, Japan.

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product, leaving the substrates almost unreacted (Table 1, entries 1 and 2).<sup>[3c,8]</sup>

The effect of ligands on the reaction between **2a** and **3a** are shown in Table 1. Use of tri(4-methoxyphenyl)phosphine resulted in a significantly lower product yield and *syn*-stereoselectivity compared to PPh<sub>3</sub> (entry 4). No reaction occurred with the electron-deficient P[3,5-(CF<sub>3</sub>)C<sub>6</sub>H<sub>3</sub>]<sub>3</sub> phosphine was used (entry 5). Use of PMe<sub>3</sub> produced a very low yield with moderate *syn* selectivity (*syn:anti* 88:12) (entry 6). The PEt<sub>3</sub> and PBU<sub>3</sub> promoted coupling efficiently, but *syn*-selectivity was decreased slightly compared to the excellent selectivity obtained with PPh<sub>3</sub> (entries 7 and 8). Interestingly, the bulkier monodentate trialkylphosphines, such as PCy<sub>3</sub> and P<sup>t</sup>Bu<sub>3</sub>, were as effective as PPh<sub>3</sub> in terms of both product yield and *syn*-selectivity (entries 9 and 10). In contrast, bisphosphines such as DPPE and Xantphos, produced no reaction (entries 11 and 12). *N*-Heterocyclic carbene (NHC) monodentate ligands, such as IMes, SIMes, IPr, and SIPr, also did not promote the reaction (entries 13–16). Thus, PPh<sub>3</sub> was selected as the most useful additive for cost-effectiveness and handling ease (Eq. 1 and Table 1, entry 3).<sup>[9]</sup>

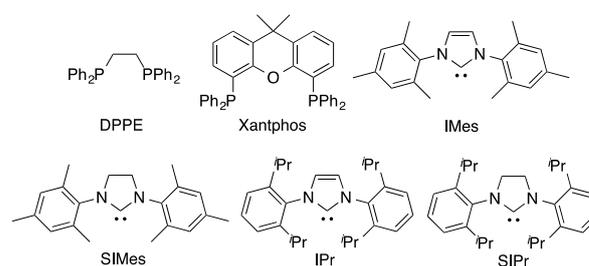
The effect of the stoichiometric base also is shown in Table 1. The use of EtOK instead of MeOK in the presence of PPh<sub>3</sub> resulted in a slight decrease in *syn*-stereoselectivity (entry 17). No reaction occurred with the sterically more demanding base <sup>t</sup>BuOK, which induced 1,3-*anti* stereochemistry under phosphine-free conditions in the reaction of primary alkylboranes (entry 18).<sup>[10]</sup>

**Table 1.** Effects of ligands and bases<sup>[a,b]</sup>

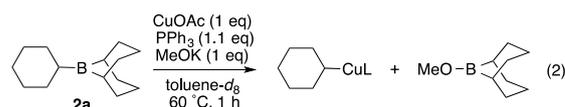
| entry | ligand   | base              | yield <sup>[c,d]</sup><br>(%) | <i>syn:anti</i> <sup>[e]</sup> |
|-------|--|-------------------|-------------------------------|--------------------------------|
| 1     | none   | MeOK              | 0                             | –                              |
| 2     | none   | <sup>t</sup> BuOK | 0                             | –                              |
| 3     | PPh <sub>3</sub> (eq 1)  | MeOK              | 88                            | 99.5:0.5                       |
| 4     | P(4-MeOC <sub>6</sub> H <sub>4</sub> ) <sub>3</sub>                  | MeOK              | 55                            | 96.5:3.5                       |
| 5     | P[3,5-(CF <sub>3</sub> )C <sub>6</sub> H <sub>3</sub> ] <sub>3</sub> | MeOK              | 0                             | –                              |
| 6     | PMe <sub>3</sub>   | MeOK              | 13                            | 88:12                          |
| 7     | PEt <sub>3</sub>   | MeOK              | 95                            | 98.5:1.5                       |
| 8     | PBU <sub>3</sub>   | MeOK              | 90                            | 92:8                           |
| 9     | PCy <sub>3</sub>   | MeOK              | 93                            | 99:1                           |
| 10    | P <sup>t</sup> Bu <sub>3</sub>                                       | MeOK              | 83                            | 99:1                           |
| 11    | DPPE   | MeOK              | 0                             | –                              |
| 12    | Xantphos   | MeOK              | 0                             | –                              |
| 13    | IMes   | MeOK              | 0                             | –                              |
| 14    | SIMes  | MeOK              | 0                             | –                              |
| 15    | IPr  | MeOK              | 0                             | –                              |
| 16    | SIPr   | MeOK              | 0                             | –                              |
| 17    | PPh <sub>3</sub>   | EtOK              | 99                            | 98:2                           |
| 18    | PPh <sub>3</sub>   | <sup>t</sup> BuOK | 0                             | –                              |

[a] Reaction was conducted using **3** (0.15 mmol), alkylborane **2** (0.24 mmol), CuOAc (10 mol%), ligand (11 mol%), and base (0.225 mmol) in toluene at 60 °C for 24 h. [b] Alkylborane **2** was prepared in advance by hydroboration of alkene **1** with 9-BBN dimer in toluene at 70 °C for 1 h and used without

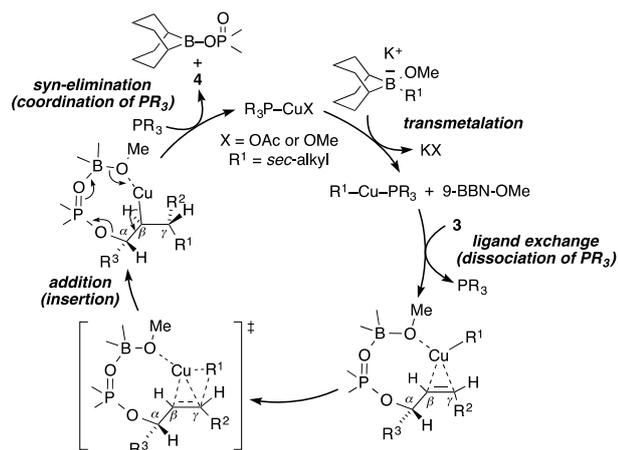
purification. [c] Isolated yield of product based on **3**. [d] Isomeric ratios (*γ/α* >99:1, *E/Z* >99:1). Determined by <sup>1</sup>H NMR or GC of the crude product. [e] Selectivity was determined by HPLC.



To gain understanding into the mechanism of Cu-catalyzed cross-coupling with secondary alkylboranes, the effect of PPh<sub>3</sub> on the stoichiometric reaction with CuOAc, MeOK and cyclohexylborane **2a** in toluene-*d*<sub>8</sub> at 60 °C for 1 h was investigated (Eq. 2). Reaction in the presence of PPh<sub>3</sub> caused the complete disappearance of the signal for **2a** ( $\delta$  86.4 ppm), confirmed by <sup>11</sup>B NMR spectroscopy, and a new signal for 9-BBN-OMe appeared at a higher magnetic field ( $\delta$  55.5 ppm). In contrast, reaction in the absence of PPh<sub>3</sub> did not result in formation of 9-BBN-OMe. Therefore, PPh<sub>3</sub> is essential for B/Cu transmetalation.



Molecular modelling studies suggested that tertiary monophosphines would not be able to coordinate to the copper center in the cyclic organocopper addition–elimination transition state due to steric effects (Scheme 1a).<sup>[11]</sup> Therefore, a catalytic cycle for the copper-catalyzed *γ-syn*-selective allylic cross-coupling with secondary alkylboranes should involve coordination and dissociation of the phosphine ligand as shown in Figure 1. According to these considerations, the reduction of yield and *syn* selectivity in the reaction with PMe<sub>3</sub> may suggest that the Cu–P interaction would be persistent in the addition–elimination step. This should be reasonable, considering the higher coordination ability of PMe<sub>3</sub> as a compact ligand. The marginal reduction of the *syn* selectivity in the reactions with PEt<sub>3</sub> and PBU<sub>3</sub> may be due to partial coordination of these ligands in the addition–elimination step. In this context, the common features of PPh<sub>3</sub>, PCy<sub>3</sub>, and P<sup>t</sup>Bu<sub>3</sub>, showing the high product yields and *syn* selectivities, may be due to their moderate coordination abilities toward Cu, allowing timely coordination/dissociation equilibria.



**Figure 1.** Proposed catalytic cycle for the copper-catalyzed  $\gamma$ -*syn*-selective allylic cross-coupling between secondary alkylboranes and secondary allylic phosphates.

The scope of copper-catalyzed regioselective and stereospecific cross-coupling reaction between secondary alkylboranes and enantio-enriched chiral  $\gamma$ -silylated allylic phosphates to afford enantio-enriched  $\alpha$ -stereogenic chiral allylsilanes is summarized in Table 2.<sup>[12–14]</sup> Cyclic secondary alkylboranes **2b,c** with five- and seven-membered carbocycles underwent reaction with excellent *syn*-stereoselectivities (entries 1 and 2). Acyclic isopropylborane **2d** also was tolerated with a high level of stereoselectivity retained (entries 3 and 7). The heterocyclic secondary alkylborane **2e** with a carbamate group underwent stereospecific reaction resulting in a moderate product yield (entry 4).

The Me group at the  $\alpha$ -position of **3a** could be replaced with *n*Pent (**3b**) or *i*Pr (**3c**) groups with excellent *syn*-selectivity retained (Table 2, entries 5–10). The allylic phosphate (S)-(*Z*)-**3d** with a BnMe<sub>2</sub>Si group at the  $\gamma$ -position reacted with cyclic secondary alkylboranes containing five-, six-, and seven-membered carbocycles with excellent *syn* selectivities (entries 11–13).

**Table 2.** Synthesis of chiral allylsilanes<sup>[a,b]</sup>

| entry | borane | phosphate                             | product | yield <sup>[c,d]</sup> (%) | syn:anti <sup>[e]</sup> |
|-------|--------|---------------------------------------|---------|----------------------------|-------------------------|
| 1     |        | (S)-( <i>Z</i> )- <b>3a</b><br>99% ee |         | 93                         | 97.5:2.5                |
| 2     |        | (S)-( <i>Z</i> )- <b>3a</b><br>99% ee |         | 80                         | 99:1                    |
| 3     |        | (S)-( <i>Z</i> )- <b>3a</b><br>99% ee |         | 94                         | 98.5:1.5                |

|                  |  |                                       |  |                   |           |
|------------------|--|---------------------------------------|--|-------------------|-----------|
| 4 <sup>[f]</sup> |  | (S)-( <i>Z</i> )- <b>3a</b><br>99% ee |  | 47 <sup>[f]</sup> | 98:2      |
| 5                |  | (S)-( <i>Z</i> )- <b>3b</b> , 99% ee  |  | 94                | >99.5:0.5 |
| 6                |  | (S)-( <i>Z</i> )- <b>3b</b><br>99% ee |  | 93                | >99.5:0.5 |
| 7                |  | (S)-( <i>Z</i> )- <b>3b</b><br>99% ee |  | 88                | >99.5:0.5 |
| 8                |  | (S)-( <i>Z</i> )- <b>3c</b> , 99% ee  |  | 93                | 99.5:0.5  |
| 9                |  | (S)-( <i>Z</i> )- <b>3c</b><br>99% ee |  | 96                | 99.5:0.5  |
| 10               |  | (S)-( <i>Z</i> )- <b>3c</b><br>99% ee |  | 38                | 99:1      |
| 11               |  | (S)-( <i>Z</i> )- <b>3d</b> , 99% ee  |  | 31                | 97:3      |
| 12               |  | (S)-( <i>Z</i> )- <b>3d</b><br>99% ee |  | 75                | 96.5:3.5  |
| 13               |  | (S)-( <i>Z</i> )- <b>3d</b><br>99% ee |  | 61                | 98.5:1.5  |

[a] Reaction was conducted with **3** (0.15 mmol), alkylborane **2** (0.24 mmol), CuOAc (10 mol%), PPh<sub>3</sub> (11 mol%), and MeOK (0.225 mmol) in toluene at 60 °C for 24 h. [b] Alkylborane **2** was prepared in advance by hydroboration of alkene **1** with 9-BBN dimer in toluene at 70 °C for 1 h and used without purification. [c] Isolated yield of the product based on **3**. [d] Isomeric ratios ( $\gamma/\alpha$  >99:1, E/Z >99:1). Determined by <sup>1</sup>H NMR or GC of the crude product. [e] Enantiomeric excess was determined by HPLC. [f] Diastereomeric ratio (1:1).

The usefulness of this protocol was not limited to allylsilane synthesis but also could be applied to reaction of non-silicon-substituted acyclic allylic phosphates (Table 3). For example, reaction between allylic phosphate (S)-(*Z*)-**5a** (97% ee) and cyclohexylborane **2a** occurred with 96% *syn* selectivity to produce the Me-branched product (R)-(*E*)-**6aa** (entry 1). Reaction of cyclic secondary alkylboranes with a five- or a seven-membered ring also occurred, but 1,3-*syn* stereoselectivity was only moderate (entries 2 and 3).

**Table 3.** Allyl-alkyl coupling with non-silicon-substituted allylic phosphates<sup>[a,b]</sup>

| entry | borane | product | yield <sup>[c,d]</sup> (%) | syn:anti <sup>[e]</sup> |
|-------|--------|---------|----------------------------|-------------------------|
| 1     |        |         | 96                         | 99:1                    |
| 2     |        |         | 75                         | 96:4                    |
| 3     |        |         | 61                         | 98.5:1.5                |

|   |           |  |    |           |
|---|-----------|--|----|-----------|
| 1 | <b>2a</b> |  | 88 | 96:4      |
|   |           | ( <i>R</i> )-(-)- <b>6aa</b><br>89% ee |    |           |
| 2 | <b>2b</b> |  | 98 | 84:16     |
|   |           | ( <i>R</i> )-(-)- <b>6ba</b><br>65% ee |    |           |
| 3 | <b>2c</b> |  | 78 | 74.5:25.5 |
|   |           | ( <i>R</i> )-(-)- <b>6ca</b><br>47% ee |    |           |

[a] The reaction was carried out with **5** (0.15 mmol), alkylborane **2** (0.24 mmol), CuOAc (10 mol %), PPh<sub>3</sub> (11 mol %), and MeOK (0.225 mmol) in toluene at 60 °C for 24 h. [b] Alkylborane **2** was prepared in advance by hydroboration of alkene **1** with 9-BBN dimer in toluene at 70 °C for 1 h and used without purification. [c] Yield of the isolated product based on **5**. [d] Isomeric ratios ( $\gamma/\alpha$  >99:1, E/Z >99:1). Determined by <sup>1</sup>H NMR or GC of the crude product. [e] The enantiomeric excess was determined by HPLC.

Cyclic allylic phosphates also could serve as substrates (Table 4). Coupling reactions between *trans*-2-cyclohexene-1,4-diol derivative **7a** and **2a** proceeded with excellent  $\gamma$ -selectivity and 1,3-*syn* selectivity relative to the leaving group, giving *trans*-1,2-isomer **8aa** (entry 1). Reactions with cyclopentyl or cycloheptylboranes also occurred with excellent 1,3-*syn* selectivity (entries 2 and 3). *Trans*-3-cyclohexene-1,2-diol derivative **7b** underwent coupling with excellent 1,3-*syn* selectivity (entry 4).

**Table 4.** Allyl-alkyl coupling with cyclic allylic phosphates<sup>[a,b]</sup>

| entry | borane    | phosphate | product | yield <sup>[c,d]</sup><br>(%) | syn:anti <sup>[e]</sup> |
|-------|-----------|-----------|---------|-------------------------------|-------------------------|
| 1     | <b>2a</b> |           |         | 85                            | >99:1                   |
| 2     | <b>2b</b> | <b>7a</b> |         | 90                            | >99:1                   |
| 3     | <b>2c</b> | <b>7a</b> |         | 73                            | >99:1                   |
| 4     | <b>2a</b> |           |         | 49                            | 93:7                    |

[a] Reaction was conducted with **7** (0.15 mmol), alkylborane **2** (0.24 mmol), CuOAc (10 mol%), PPh<sub>3</sub> (11 mol%), and MeOK (0.225 mmol) in toluene at 60 °C for 24 h. [b] Alkylborane **2** was prepared in advance by hydroboration of alkene **1** with 9-BBN dimer in toluene at 70 °C for 1 h and used without purification. [c] Isolated yield of the product based on **7**. [d] Isomeric ratios ( $\gamma/\alpha$  >99:1, E/Z >99:1). Determined by <sup>1</sup>H NMR or GC of the crude product. [e] The syn:anti selectivity was determined by <sup>1</sup>H NMR.

In summary, the scope of the copper-catalyzed coupling reaction between organoboron compounds and allylic phosphates was broadened significantly by employing triphenylphosphine as a ligand for copper, allowing the use of secondary alkylboron compounds (alkyl-9-BBN). The reaction proceeded with

complete  $\gamma$ -*E*-selectivity and preferential 1,3-*syn* stereoselectivity. This is the first catalytic allylic substitution reaction with secondary alkylboron derivatives.

## Experimental Section

Equation 1 shows a representative reaction. (9-BBN-H)<sub>2</sub> (30.2 mg, 0.12 mmol) was placed in a vial containing a magnetic stirring bar. The vial was sealed with a Teflon<sup>®</sup>-coated silicon rubber septum followed by evacuation of the vial, which was then filled with argon. Cyclohexene (**1a**) (0.027 mL, 0.27 mmol) and toluene (0.3 mL) were added to the vial, and the mixture stirred at 70 °C for 1 h to prepare a secondary alkylborane. Then, CuOAc (1.8 mg, 0.015 mmol), PPh<sub>3</sub> (4.0 mg, 0.0165 mmol), and MeOK (15.7 mg, 0.225 mmol) were placed in another vial, which was sealed with a Teflon<sup>®</sup>-coated silicon rubber septum, and then evacuated and filled with argon. Next, the alkylborane solution was transferred to the vial containing the Cu salt, followed by addition of (*S*)-(*Z*)-**3a** (55.6 mg, 0.15 mmol). After 24 h stirring at 60 °C, the mixture was filtered through a short plug of aluminum oxide, which was then washed with diethyl ether. After the solvent was removed under reduced pressure, flash chromatography on silica gel (hexane) gave (*R*)-(*E*)-**4aa** (35.6 mg, 0.132 mmol) in 88% yield.

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**Keywords:** Copper catalysis • Secondary alkylborane • Coupling • Allylic substitution • Stereoselectivity

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- [8] The use of Cu(acac)<sub>2</sub> or CuTC instead of CuOAc under phosphine-free conditions (Table 1, entry 1) resulted in no reaction.
- [9] The effect of ligands on the reaction of primary alkylborane also was examined (CuOAc/MeOK/toluene/60 °C). Reaction between 2-phenylethyl-9-BBN and (S)-(*Z*)-**3a** with PPh<sub>3</sub> or PCy<sub>3</sub> gave moderate 1,3-*syn* selectivity (*syn:anti* 79:21, 81% yield and *syn:anti* 89:11, 84% yield). In contrast, phosphine-free conditions resulted in greater 1,3-*syn* selectivity (*syn:anti* 97.5:2.5, 95% yield).
- [10] Several observations concerning the optimum reaction conditions should be noted. Reaction with cyclohexylboronic acid and its pinacolate ester instead of secondary alkyl-9-BBN reagents did not produce any coupling product, leaving unreacted substrates. Using diethyl phosphate instead of diisopropyl phosphate as a leaving group was useful, although it produced a slightly decreased stereoselectivity (*syn:anti* 98:2, 87%).
- [11] Details of the DFT calculations will be reported elsewhere.
- [12] For reviews on the synthesis of allylsilanes, see: a) C. E. Masse, J. S. Panek, *Chem. Rev.* **1995**, 95, 1293–1316; b) I. Fleming, A. Barbero, D. Walter, *Chem. Rev.* **1997**, 97, 2063–2192; c) L. Chabaund, P. James, Y. Landais, *Eur. J. Org. Chem.* **2004**, 3173–3199.
- [13] For the synthesis of enantio-enriched allylsilanes through Cu-catalyzed enantioselective allylic substitutions of prochiral  $\gamma$ -silylated primary allylic alcohol derivatives with organozinc or organoaluminum reagents, see: a) M. A. Kacprzynski, T. L. May, S. A. Kazane, A. H. Hoveyda, *Angew. Chem.* **2007**, 119, 4638–4642; *Angew. Chem. Int. Ed.* **2007**, 46, 4554–4558; b) F. Gao, K. P. McGrath, Y. Lee, A. H. Hoveyda, *J. Am. Chem. Soc.* **2010**, 132, 14315–14320. For the synthesis of allylsilanes via copper-catalyzed allylic substitutions with silylating reagents, see: c) D. J. Vyas, M. Oestreich, *Chem. Commun.* **2010**, 568–570; d) D. J. Vyas, M. Oestreich, *Angew. Chem.* **2010**, 122, 8692–8694; *Angew. Chem. Int. Ed.* **2010**, 49, 8513–8515.
- [14] For the synthesis of enantio-enriched allylsilanes through palladium-catalyzed allylic substitutions of enantio-enriched  $\gamma$ -silylated secondary allylic alcohol derivatives with organoboronic acids, see: D. Li, T. Tanaka, H. Ohmiya, M. Sawamura, *Org. Lett.* **2010**, 12, 3344–3347.

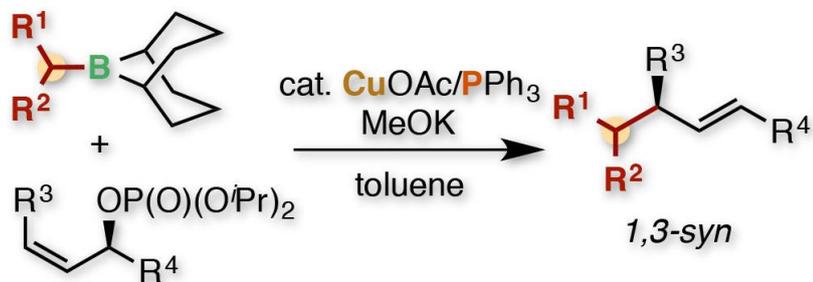
## COMMUNICATION

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Yuto Yasuda, Kazunori Nagao,  
Yoshinori Shido, Seiji Mori, Hirohisa  
Ohmiya,\* and Masaya Sawamura\*

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**Copper-Catalyzed  $\gamma$ -Selective and  
Stereospecific Allylic Cross-Coupling  
with Secondary Alkylboranes**

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