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Copper-Catalyzed γ-Selective Allyl−Alkyl Coupling between Allylic Phosphates and Alkylboranes

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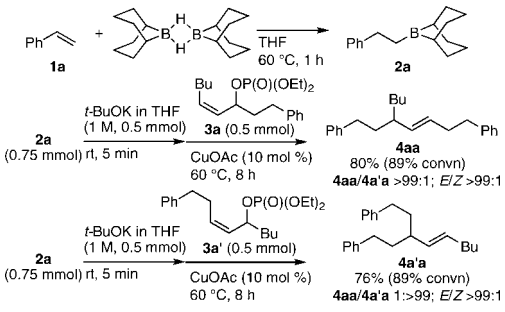
Organocopper species are useful reagents in organic synthesis because they exhibit characteristic reactivities toward various transformations.[1] They are generally prepared from basic organometallic reagents such as organolithium or Grignard reagents. In this regard, functional group-tolerable organoboron compounds would be an attractive alternative as a source of organocopper species. In fact, some synthetically useful catalytic reactions involving the formation of aryl- and allylcopper species from aryl- and allylboronic acid derivatives via boron-to-copper transmetalation have recently been developed.[2,3] The generation of organocopper reagents from alkylboron compounds is limited to a few cases, though,[4,5] and their application to organic synthesis is not well explored. Specifically, more than 30 years ago Suzuki et al. reported several copper-mediated alkyl group transfer reactions of lithium trialkylmethylborates that were prepared from trialkylboranes and methyllithium.[4] Recently, Knochel et al. reported the preparation of alkylcopper(I) reagents from more complex alkylboron compounds via the corresponding organozinc species, but the cumbersome procedure and its low atom efficiency hamper the wide application of this method.[5,6]

We report here a copper-catalyzed allylic substitution of (*Z*)-acyclic and cyclic allylic phosphates with alkylboron compounds (alkyl-9-BBN) that proceeds with excellent γ- and *E*-selectivities and preferential 1,3-*anti* stereochemistry.[7−11] The wide availability of alkylboranes via the established alkene hydroboration reaction is an attractive feature of this transformation. Furthermore, various functional groups are tolerated in both the allylic phosphate and the alkylborane. Catalytic mechanisms involving transmetalation between a trialkyl(alkoxo)borate and a copper(I) salt to form an alkylcopper(I) species are proposed.

Scheme 1. Hydroboration/Allyl−Alkyl Coupling Sequence



Specifically, a THF solution of alkylborane **2a** was prepared via hydroboration of styrene (**1a**) with 9-borabicyclo[3.3.1]nonane (9-BBN-H) dimer (**1a**/B 1.2:1) at 60 °C (Scheme 1). Subsequently, the THF solution of **2a** (0.75 mmol) was treated with *t*-BuOK (0.5 mmol, 1 M in THF) at rt for 5 min to yield an alkylborate, to which CuOAc (10 mol %) was added.[12] Allylic phosphate **3a** (0.5 mmol) was then added to the mixture, which was heated at 60 °C for 8 h to afford allyl−alkyl coupling product (*E*)-**4aa** in 80% isolated yield (based on **3a**; 89% convn of **3a**).[13] The NMR and GC analysis unambiguously confirmed complete γ- and *E*-selectivities. Conversely, the reaction of **3a′** afforded **4a′a**, an isomer of **4aa** with regard to the α/γ-regioselectivity, also with complete regio- (**4aa**/**4a′a** 1:>99) and *E*/*Z*- (>99:1) selectivities.

Several observations concerning the optimum reaction conditions are to be noted: while less expensive CuCl was as effective as CuOAc, providing **4aa** in 77% yield, the use of $Cu(OAc)_2$ resulted in lower reaction efficiency (66%); a ligand for the copper is not necessary; when *t*-BuOK was omitted, the allyl−alkyl coupling product was not obtained at all; and changing the leaving group to carbonate or acetoxy almost inhibited the transformation.

The reaction of allylic phosphate **3a** with the *E*-configuration proceeded with retention of γ-regioselectivity but significantly decreased *E*-selectivity (*E*/*Z* 62:38).[14] Thus, the applicability of this protocol seems to be limited to allylic substrates with *Z*-alkene geometry.

To determine the scope of the reaction, various alkenes and phosphates were subjected to the one-pot protocol involving the hydroboration of terminal alkenes (**1**) and the subsequent copper-catalyzed coupling reaction with allylic phosphates (**3**) (Table 1).[13] The reaction tolerates a variety of functional groups including silyl ether, ester, methoxy, acetal, and phthalimide moieties (entries 1−6).

The sterically more demanding alkylborane (**2d**), which was derived from a terminal alkene (**1d**) with a tertiary alkyl substituent, served as a coupling partner for **3a** to afford the corresponding product (**4ad**) in good yield (entry 4). The reaction of the β-branched alkylborane (**2g**), which was prepared from α-methylstyrene (**1g**), also proceeded smoothly to produce **4ag** in high yield (91%) as a mixture of diastereomers (1:1) (entry 7). Unfortunately, our attempt to use secondary alkylborane reagents prepared from internal alkenes resulted in no reaction.

The very high level of γ- and *E*-selectivities of the copper-catalyzed allyl−alkyl coupling were retained for various substitution patterns and steric demands of the (*Z*)-allylic phosphates (**3**). The butyl group at the γ-position of the allylic phosphate (**3a**) could be replaced with a methyl (entry 8) or isobutyl group (entry 9) to give the coupling product in good yield. The reaction of substrate **3e** bearing a bulky isobutyl group at the α-position, however, resulted in a low conversion and a poor yield (entry 10). Primary allylic phosphate **3f**, though, was converted to the corresponding coupling product **4f** with complete γ-selectivity (entry 11). Notably, even the γ,γ-disubstituted primary allylic phosphate **3g** reacted exclusively at the γ-position, constructing the all-carbon quaternary center albeit in lower yield (entry 12).

The coupling between α-chiral acyclic allylic phosphate (*S*)-(*Z*)-**3h** (95% ee) and alkylborane **2a** [60 °C, toluene/DMF (4:1)] afforded (*S*)-(*E*)-**4h** in 70% ee, indicating that the allylic substitution takes place preferentially with 1,3-*anti* stereochemistry (*anti*/*syn* 87:13) (Table 1, entry 13).[15] This stereochemical outcome is opposite to that of the palladium-catalyzed, γ-selective allyl−aryl coupling between allylic acetates and arylboronic acids (1,3-*syn*)[7] and is similar to that of the copper-catalyzed, γ-selective substitution of allylic carbonates with bis(pinacolato)diboron to form allylboron compounds (1,3-*anti*).[16]

The reaction was also applicable to cyclic allylic phosphates **3i**−**m** (Table 2).[13] Coupling of styrene (**1a**) with *cis*-4-cyclopenetene-1,3-diol derivative **3i** proceeded with excellent 1,3-*anti* stereoselectivity, giving

Table 1. Cu-Catalyzed Allyl−Alkyl Coupling of (*Z*)-Acyclic Allylic Phosphates[a]

entry	alkene	phosphate	product	yield (%)[b,c]
1	**1a**	**3b**	**4b**	57
2	**1b**	**3a**	**4ab**	90
3	**1c**	**3a**	**4ac**	78
4	**1d**	**3a**	**4ad**	79
5	**1e**	**3a'**	**4a'e**	85
6	**1f**	**3a'**	**4a'f**	73
7[d]	**1g**	**3a**	**4ag**	91
8	**1a**	**3c**	**4c**	77
9	**1a**	**3d**	**4d**	77
10	**1a**	**3e**	**4e**	21
11	**1a**	**3f**	**4f**	70
12	**1a**	**3g**	**4g**	35
13[e]	**1a**	(*S*)-(*Z*)-**3h**, 95% ee	(*S*)-(*E*)-**4h**, 70% ee	57

[a] The reaction was carried out with **3** (0.4 mmol), alkylborane **2** (0.6 mmol), CuOAc (10 mol %), and *t*-BuOK (0.4 mmol, 1 M in THF) in THF at 60 °C for 8 h. Alkylborane **2** was prepared in advance by hydroboration of **1** with 9-BBN dimer in THF at 60 °C for 1 h and used without purification. [b] Isolated yield based on **3**. [c] Isomeric ratios (γ/α > 99:1, *E*/*Z* > 99:1). Determined by ^{1}H NMR or GC of the crude product. [d] Diastereomeric ratio (1:1). [e] The reaction was carried out with (*S*)-(*Z*)-**3h** (0.1 mmol), alkylborane **2a** (0.15 mmol), CuOAc (10 mol %), and *t*-BuOK (0.1 mmol, solid) in toluene/DMF (4:1, 0.2 mL) at 60 °C for 8 h.

the *trans*-1,2-isomer in 84% yield (entry 1). Optically active cyclic substrate (1*R*,4*S*)-**3j** (>99% ee) with two stereogenic centers underwent highly stereoselective coupling to produce optically pure (1*S*,5*S*)-**4j** (*trans*/*cis* 97:3) (entry 2). The six-membered ring allylic phosphate **3k** served as a substrate (entry 3), as did the more challenging, highly substituted cyclohexane **3l**, which coupled with **2a** regardless of the considerable steric congestion at the γ-position (entry 4). The reaction of the seven-membered ring compound **3m** also proceeded efficiently to give **4m** in high yield (entry 5).

The synthetic utility of this protocol is demonstrated with the combination of a chemo- and stereoselective hydroboration of a chiral terminal alkene and the subsequent copper-catalyzed allyl−alkyl coupling reaction.[13] Specifically, the diastereoselective hydroboration of 20(21)-methylene steroid **1n** (0.286 mmol), which was prepared from pregrenone acetate, resulted in the formation of borylated steroid **2n** (dr 94:6).[17] The copper-catalyzed coupling of **2n** with (1*R*,4*S*)-**3j** (>99% ee) produced a

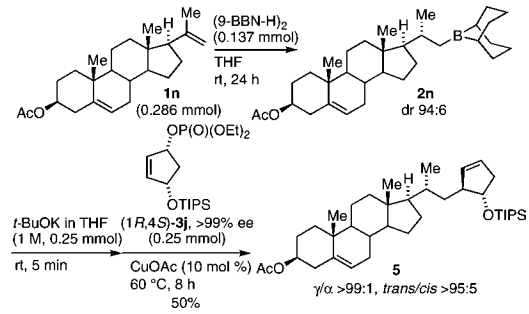
Table 2. Cu-Catalyzed Allyl−Alkyl Coupling of Cyclic Allylic Phosphates[a]

entry	alkene	phosphate	product	yield (%)[b]
1	**1a**	**3i**	**4i** *trans*/*cis* >95:5	84[c,d]
2[e]	**1d**	(1*R*,4*S*)-**3j** >99% ee	(1*S*,5*S*)-**4j**, *trans*/*cis* 97:3	68[c,d]
3	**1a**	**3k**	**4k**	74
4	**1a**	**3l**	**4l**	70[c]
5	**1a**	**3m**	**4m**	86

[a] The reaction was carried out with **3** (0.4 mmol), alkylborane **2** (0.6 mmol), CuOAc (10 mol %), and *t*-BuOK (0.4 mmol, 1 M in THF) in THF at 60 °C for 8 h. Alkylborane **2** was prepared in advance by hydroboration of **1** with 9-BBN dimer in THF at 60 °C for 1 h and used without purification. [b] Isolated yield based on **3**. [c] Isomeric ratio (γ/α > 99:1). Determined by ^{1}H NMR or GC of the crude product. [d] The *trans*/*cis* ratios were determined by ^{1}H NMR (entry 1, crude) or HPLC (entry 2, purified). [e] The reaction was carried out in 0.2 mmol scale.

steroid derivative (**5**) with an extended side chain and including two new well-defined stereogenic carbon centers (Scheme 2).[18]

Scheme 2

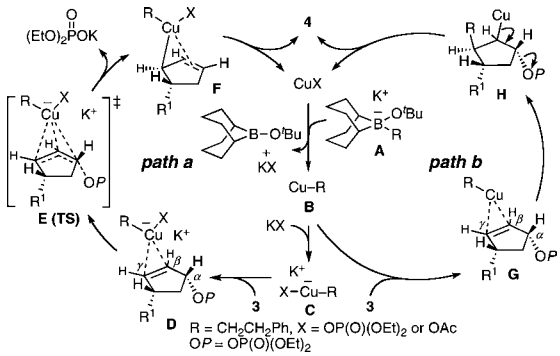


Once the scope and utility of the reaction was explored, we considered possible mechanisms that could explain the results of these studies. Two possible mechanisms for the copper-catalyzed reaction of cyclic allylic phosphates **3i** and (1*R*,4*S*)-**3j** can be postulated (Scheme 3). One involves formation of heterocuprate **C** followed by its nucleophilic attack at the γ-carbon (Scheme 3, path a), and the other involves the direct reaction of organocopper species **B** with the allylic phosphate (Scheme 3, path b).

Path a generally follows Nakamura's mechanism for the formal S_N2' substitution of heterocuprates (Me−Cu−X$^-$; X = CN, Cl, SMe, or NMe$_2$) with allyl acetate, which has been suggested by DFT calculations.[19] First, transmetalation between CuX [X = OP(O)(OEt)$_2$ or OAc] and the borate **A**[12] forms alkylcopper species **B**. The interaction between **B** and KX forms the nucleophilic heterocuprate **C** (R−Cu−X$^-$). Subsequently, **C** forms π-complex **D** with an allylic phosphate (**3**). Then, oxidative addition through the transition state **E(TS)** with *anti*-stereochemistry with respect to the phosphate group leads to (γ-σ-enyl)copper(III) species **F** (enyl[σ+π] complex). Finally, reductive elimination results in C−C bond formation at the γ-position and regenerates CuX.

Alternatively, path b is similar to the addition−elimination mechanisms that have been proposed for Cu−diboron systems[16] and Pd-catalyzed allyl−aryl coupling reactions.[7] Thus, the alkyl-

Scheme 3. Possible Mechanisms



copper species **B** forms π-complex **G** with **3**. The *syn*-addition of R−Cu across the C−C double bond of **3** occurs with *anti*-stereochemistry to form alkylcopper complex **H**. The regioselectivity in the addition reaction would be induced by stereoelectronic effects that stabilize the σ (C_β−Cu) orbital through interactions with the σ^* [C_α−OP(O)(OEt)$_2$] orbital. Finally, alkylcopper complex **H** undergoes *anti*-β-elimination to afford **4** and CuX.

At present, neither mechanism can be ruled out, but the latter addition−elimination mechanism (path b) may be more plausible for the following two reasons. First, the phosphate and acetate anion seem to be insufficiently basic to form a cuprate with the nucleophilicity required for the oxidative addition step.[20] Second, the γ-selectivity of the reported allylic substitutions of heterocuprates is not generally perfect.[10] Path b, therefore, would account for the complete γ-selectivity of the present allyl−alkyl coupling better than path a.

In summary, we have developed a copper-catalyzed γ-selective allyl−alkyl cross-coupling reaction between allylic phosphates and alkylboranes. 1,3-Chirality transfer in the allylic system occurs preferentially with *anti* stereochemistry; the selectivity is excellent for cyclic systems but only moderate (87% *anti*) for relevant acyclic systems.[21] The availability of alkylboranes through *in situ* alkene hydroboration and broad functional group compatibility in both the allylic and alkylboron substrates are attractive features from a synthetic viewpoint. Efforts to expand the utility of this reaction are ongoing in our laboratory.

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

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(8) For the Cu(I)-mediated, γ-selective substitution of cinnamyl chloride with $(Pr)_3BMeLi$ to form the corresponding 3-propylated terminal alkene, see ref 4d.

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(10) Although excellent γ-selectivity occurs in many cases, the γ-substitution product is in some cases contaminated with a small but significant amount of the corresponding α-isomer, while in other cases regioselectivity is almost lost. See ref 7b.

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(12) The clean conversion to a tetravalent borate (−1.4 ppm) was confirmed by ^{11}B NMR spectroscopy. See: (a) Köster, R.; Seidel, G.; Wagner, K.; Wrackmeyer, B. *Chem. Ber.* **1993**, *126*, 305–317. Subsequently, when CuOAc was mixed with the borate (1:1) at 60 °C for 1 h, the formation of 9-BBN-O^{t}Bu (55.1 ppm) was observed. See: (b) Brown, H. C.; Cha, J. S.; Nazer, B. *J. Org. Chem.* **1985**, *50*, 549–553. Meanwhile, the formation of styrene and ethylbenzene were observed by ^{1}H NMR spectroscopy (4 and 13% NMR yields, respectively). These compounds seem to be produced by β-hydride elimination and protonation of an alkylcopper species. See Supporting Information for the details of the NMR studies

(13) For Schemes 1 and 2, and Tables 1 and 2, unreacted allylic phosphate (**3**) was detected in the crude materials after removal of the catalyst.

(14) For the concept of allylic 1,3-strain in acyclic stereocontrol, see: Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841–1860.

(15) The solvent effect on the 1,3-chirality transfer was significant. When the Cu-catalyzed reaction was conducted in THF or THF/DMF (4:1), the enantiomeric purity of (*S*)-(*E*)-**4h** dropped to 46% ee (75% *anti*, 73% yield) and 60% ee (82% *anti*, 62% yield), respectively.

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(18) Increasing the amount of **2n** to 1.5 equiv improved the yield of **5** to 63%.

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(20) Note that the more basic and potentially anionic ligand ^{t}BuO is consumed in the formation of 9-BBN-O^{t}Bu. See note 12.

(21) According to the proposed mechanism and given the fact that no *Z*-**4h** was formed, the loss of enantionmeric purity on the coupling with the acyclic substrate (*S*)-(*Z*)-**3h** can be deduced to the pathway involving the *syn*-addition of organocopper **B** to the opposite diastereoface of (*S*)-(*Z*)-**3h** with the same ($A^{1,3}$-strain-minimized) conformation followed by *syn*-β-elimination; *Anti*-S_N2' reaction of the higher-energy conformer of (*S*)-(*Z*)-**3h** should yield (*R*)-(*Z*)-**4h**. See ref 14.

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