JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

COMMUNICATION

pubs.acs.org/JACS

Copper-Catalyzed γ-Selective and Stereospecific Allylic Alkylation of Ketene Silyl Acetals

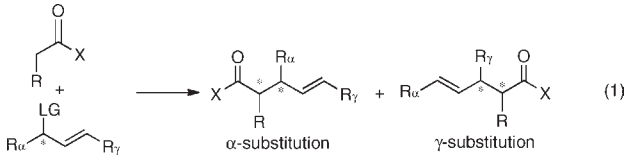
Dong Li, Hirohisa Ohmiya,* and Masaya Sawamura*

Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo 060-0810, Japan

Supporting Information

ABSTRACT: Copper-catalyzed allylic alkylation of ketene silyl acetals proceeded with excellent γ-*E*-selectivity. Efficient α-to-γ chirality transfer with *anti*-selectivity occurred in the reaction of enantioenriched secondary allylic phosphates, affording enantioenriched β-branched γ,δ-unsaturated esters. Excellent functional group compatibility was observed.

Allylic alkylations of metal enolates are fundamental carbon−carbon bond formation methods in organic synthesis due to the versatility of the carbonyl and alkene functionalities for stereoselective derivatization (eq 1). Nevertheless, the reaction of unsymmetrically substituted secondary allylic substrates with enolates occurs competitively at the α- and γ-positions.



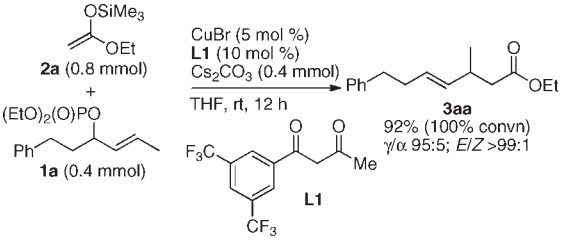
(1)

The issue of the allylic regiochemistry has been addressed in part by studies with transition metal catalysts.[1,2] In fact, various transition metal complexes involving Pd,[3] Rh,[4−6] Ir,[2j,7] Fe,[8] Ru,[9] etc. were used for regioselective enolate allylic alkylations with unsymmetrically substituted secondary allylic substrates. Most studies, however, focused on cases in which an allylic system is located at a terminal of a molecule or is highly asymmetrized by electronic and/or steric substituent effects. Among those, the Rh-catalyzed allylic alkylation of a copper enolate developed by Evans and co-workers would be most relevant to the present issue.[4] Nevertheless, the regioselective enolate alkylation with internal allylic systems is yet to be explored.[5]

Earlier, we reported that the reactions of unsymmetrically substituted internal allylic substrates with organopalladium or copper species that were formed catalytically through transmetalations between organoboron compounds and transition metal complexes proceeded with excellent γ-selectivity and stereo specificity.[10−12] We envisioned that the γ-selective allylic alkylation of an enolate might be possible, given that a metal *C*-enolate species could be generated by transmetalation using an enolate equivalent in place of an organoboron compound.[13,14]

Herein, we report a copper-catalyzed allylic substitution reaction of allylic phosphates with acetate-derived ketene silyl acetals that proceeds with excellent γ- and *E*-selectivities. The reactions of enantioenriched allylic phosphates having an α-stereogenic center occurred with excellent α-to-γ chirality transfer with *anti*-stereochemistry and gave the corresponding enantioenriched products with an allylic stereogenic center at the β-position of the ester carbonyl group. Notably, the use of a β-diketone as a ligand precursor for copper was essential for the efficacy of the catalytic system, and electron-deficient benzoylacetones (**L1**−**L3**) were favorable for higher γ-selectivity. In view of the applicability in organic synthesis, the protocol offers an alternative to Claisen rearrangement routes to γ,δ-unsaturated esters from allylic alcohols.[15] Mild reaction conditions and the resulting broad functional group compatibility would be benefits of using the present copper-catalyzed method.[16,17]

The reaction of (*E*)-allylic phosphate **1a** (0.4 mmol) with ketene silyl acetal **2a** (0.8 mmol) in the presence of CuBr (5 mol %), β-diketone **L1**[18] (10 mol %), and Cs_2CO_3 (0.4 mmol) in THF (2 mL) at room temperature for 12 h afforded the γ-alkylation product **3aa** in 92% isolated yield (98% NMR, 100% convn) with excellent regio- (γ/α 95:5) and *E*/*Z*- (>99:1) selectivities (eq 2 and Table 1, entry 1). The reaction of the allylic phosphate (*Z*)-**1a** with the *Z*-configuration proceeded with a significantly higher regioselectivity, with the excellent *E*-stereoselectivity retained (90% yield; γ/α 97:3; *E*/*Z* > 99:1) (see Table 2, entry 1).



(2)

Screening of β-diketones as a ligand precursor for the copper-catalyzed reaction of (*E*)-**1a** and **2a** revealed that the γ-selectivity is significantly influenced by the electronic nature of the β-diketones (Table 1). The benzoylacetone derivatives with an electron-withdrawing substituent such as CF_3 (**L2**) or NO_2 (**L3**) groups at the 4-position of the aromatic ring were comparable with **L1** in terms of the regioselectivity (entries 2 and 3). The unsubstituted benzoylacetone (**L4**) gave a significantly lower γ-selectivity (γ/α 89:11), and the selectivity was further decreased upon substitution with an electron-donating MeO group at the 4-position (84:16, entry 5). The ligand screening based on the dibenzoylmethane structure (**L6**−**L8**) did not lead to an improvement in the

Received: December 26, 2010
Published: March 28, 2011

dx.doi.org/10.1021/ja111645q | *J. Am. Chem. Soc.* 2011, 133, 5672–5675

Table 1. Ligand Effect in the Cu-Catalyzed Allylic Alkylation of Ketene Silyl Acetal 2a with Allylic Phosphate 1a[a]

	ligand [$R^1(O)CCH_2C(O)R^2$]				
entry	L	R^1	R^2	yield (%)[b]	γ/α[c]
1	**L1**	3,5-$(CF_3)_2$-C_6H_3	Me	92 (98)	95:5
2	**L2**	4-CF_3-C_6H_4	Me	94 (98)	94:6
3	**L3**	4-NO_2-C_6H_4	Me	92 (97)	94:6
4	**L4**	C_6H_5	Me	89 (95)	89:11
5	**L5**	4-MeO-C_6H_4	Me	85 (95)	84:16
6	**L6**	C_6H_5	C_6H_5	(85)	84:16
7	**L7**	4-CF_3-C_6H_4	4-CF_3-C_6H_4	(96)	94:6
8	**L8**	4-CF_3-C_6H_4	4-MeO-C_6H_4	(57)	89:11
9	**L9**	Me	Me	(84)	79:21
10	none			(60)	70:30

[a] The reaction was carried out with **1a** (0.2 mmol), **2a** (0.4 mmol), CuBr (5 mol %), **L** (10 mol %), and Cs_2CO_3 (0.2 mmol) in THF (1.0 mL) at rt for 12 h. [b] Isolated yield. The yield in parentheses was determined by ^{1}H NMR. Isomer ratio (*E*/*Z*) >99:1. [c] Determined by ^{1}H NMR or GC analysis of the crude product.

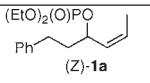
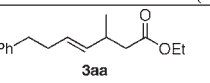
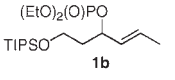
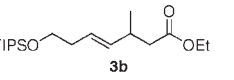
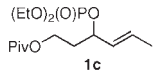
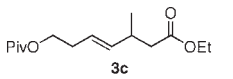
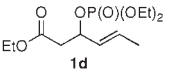
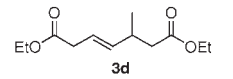
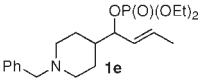
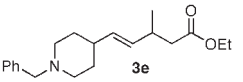
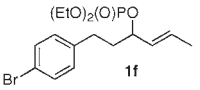
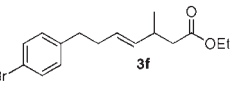
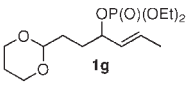
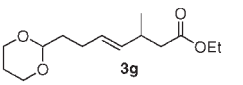
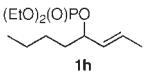
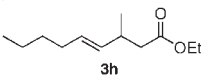
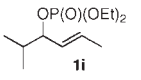
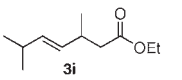
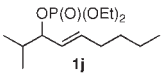
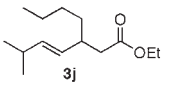
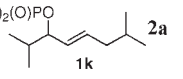
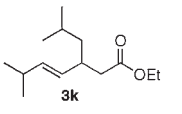
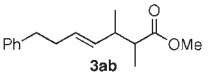
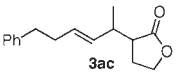
γ-selectivity (entries 6−8). The use of acetylacetone (**L9**) resulted in a moderate selectivity (entry 9). The reaction without a β-diketone did not reach a full conversion and showed even lower γ-selectivity (entry 10).

Several observations concerning the optimum reaction conditions (eq 2) are to be noted: no reaction occurred in the absence of CuBr; the use of CuCl, CuI, and CuOAc instead of CuBr resulted in decreased yields and regioselectivities (71% NMR, 91:9; 92% NMR, 93:7; 82% NMR, 93:7, respectively); no alkylation product was obtained without Cs_2CO_3; changing the leaving group to carbonate or acetoxy groups inhibited the reaction;[19] the use of a base such as K_2CO_3, KO^{t}Bu, or Et_3N in place of Cs_2CO_3 resulted in no reaction; and reducing the amount of **L1** to 5 mol % decreased the γ-selectivity (92:8, 84% NMR).

The copper-catalyzed reaction is applicable to a range of substrates, as shown in Table 2. Functional groups such as silyl ether, ester, tertiary amine, arylbromide, and acetal in **1** were compatible (entries 2−7). Particularly noteworthy is that the β,γ-unsaturated ester **3d** was obtained in a high yield (89%) without the alkene migration toward the conjugated ester to occur (entry 4, see also eq 7).

The high levels of γ/α- (95:5−99:1) and *E*/*Z*-selectivities (>99:1) of the copper-catalyzed coupling were retained with allylic phosphates (**1**) of various substitution patterns and steric demands. The 2-phenylethyl group at the α-position of **1a** could be replaced with a Bu group (**1h**) without a significant change in the product yield and regioselectivity (entry 8). Allylic phosphate **1i**, bearing a bulky isopropyl group at the α-position, was also efficiently coupled with **2a** (entry 9). The γ-Me substituent of **1i** could be replaced with a Bu group with virtually no deviation in the product yield and selectivity (entry 10). A sterically more demanding γ-substituent such as an isobutyl group was also tolerated (**3k**, 63%), with the excellent γ-regioselectivity (98:2) retained (entry 11). No reaction occurred under the identical conditions with a substrate bearing a cyclohexyl group at the γ-position, a cinnamyl-type substrate, and cyclic substrates such as 2-cyclopentenyl, 2-cyclohexenyl, and 2-cycloheptenyl phosphates (data not shown). The propionate-derived ketene silyl acetal **2b** (*E*/*Z* 4:1) served as a substrate for the reaction of **1a** to afford α,β-disubstituted ester **3ab** in a moderate yield, but unfortunately the relative stereochemistry of its consecutive chiral

Table 2. Cu-Catalyzed Allylic Alkylation of Ketene Silyl Acetals 2 with Allylic Phosphates 1[a]

entry	phosphate **1**	ketene silyl acetal **2**	product	yield (%)[b,c]	γ/α[d]
1	 (Z)-**1a**	**2a**	 **3aa**	90	97:3
2	 **1b**	**2a**	 **3b**	94	98:2
3	 **1c**	**2a**	 **3c**	73	99:1
4	 **1d**	**2a**	 **3d**	89	98:2
5	 **1e**	**2a**	 **3e**	80	99:1
6	 **1f**	**2a**	 **3f**	90	96:4
7	 **1g**	**2a**	 **3g**	83	99:1
8	 **1h**	**2a**	 **3h**	85	95:5
9	 **1i**	**2a**	 **3i**	77	99:1
10	 **1j**	**2a**	 **3j**	76	98:2
11[e]	 **1k**	**2a**	 **3k**	63	98:2
12[e]	**1a**	 **2b** (*E*/*Z* 4:1)	 **3ab**	70	95:5[f]
13[e]	**1a**	 **2c**	 **3ac**	37[g]	95:5[h,i]

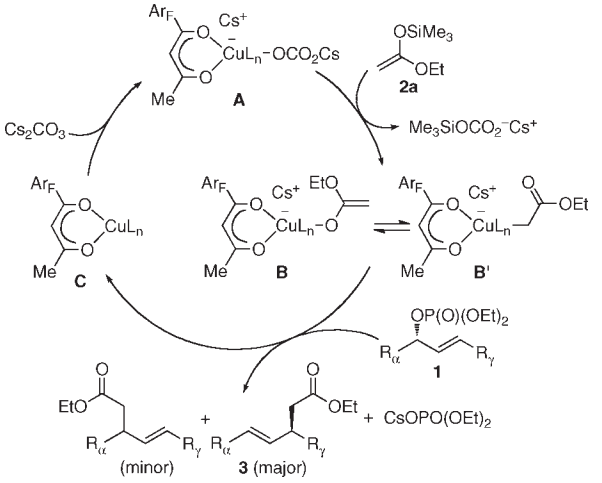
[a] The reaction was carried out with **1a** (0.4 mmol), **2a** (0.8 mmol), CuBr (5 mol %), **L1** (10 mol %), and Cs_2CO_3 (0.4 mmol) in THF (2.0 mL) at rt for 12 h. [b] Isolated yield. [c] Isomeric ratio (*E*/*Z*) > 99:1. [d] Determined by ^{1}H NMR or GC analysis of the purified product. [e] 1.2 mmol of **2** was used. [f] Diastereomer ratio 1:1. [g] The isolated product was contaminated with a small amount of an unidentified material. [h] Determined by GC analysis of the crude product. [i] Diastereoemer ratio 75:25.

centers was not controlled (entry 12).[20] The γ-butyrolactone-derived cyclic ketene silyl acetal **2c** underwent the reaction with **1a** albeit with a low product yield and a moderate diastereoselectivity (dr 75:25) (entry 13).

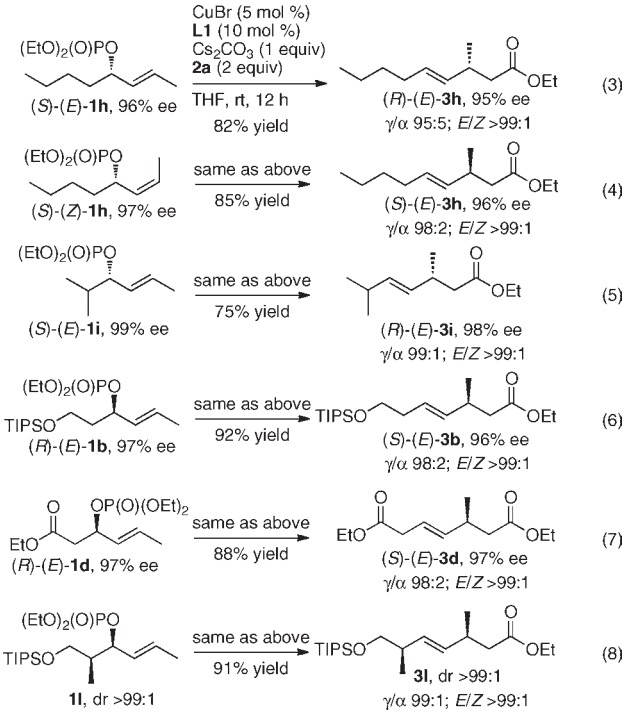
The γ-selective allylic alkylation of enantioenriched allylic phosphates proceeded with excellent α-to-γ chirality transfer with 1,3-*anti* stereochemistry to afford enantioenriched, β-branched γ,δ-unsaturated esters (eqs 3−8).[21] The reaction of (*S*)-(*E*)-**1h** (96% ee), which has α-Bu and γ-Me substituents, with **2a** in the presence of CuBr, **L1**, and Cs_2CO_3 gave (*R*)-(*E*)-**3h** (95% ee) with virtually no reduction of enantiomeric purity (eq 3).[22] When the alkene geometry of the allylic substrate (*S*)-(*E*)-**1h** was

dx.doi.org/10.1021/ja111645q | *J. Am. Chem. Soc.* 2011, 133, 5672–5675

Scheme 1. Proposed Reaction Pathway



changed to *Z* with the central chirality retained [(*S*)-(*Z*)-**1h** (97% ee)], the antipode of the γ,δ-unsaturated ester (*S*)-(*E*)-**3h** (96% ee) was obtained with an increased γ-selectivity (γ/α 95:5 to 98:2, eq 3 vs 4). The reaction of (*S*)-(*E*)-**1i** (99% ee), which has α-*i*-Pr and γ-Me substituents, with **2a** gave (*R*)-(*E*)-**3i** with 98% ee, suggesting that the efficiency of the chirality transfer is not significantly influenced by the steric demand of the α-substituent (eq 5). Functional groups such as silyl ether and ester were tolerated in the allylic phosphate (**1**), giving the corresponding coupling products (*S*)-(*E*)-**3b** and (*S*)-(*E*)-**3d** with excellent 1,3-chirality transfer (eqs 6 and 7). The reaction of allylic substrate **1l** with consecutive chiral centers proceeded with high diastereoselectivity (dr > 99:1) to afford **2l** in 91% yield (eq 8).



The present Cu-catalyzed allylic alkylation of ketene silyl acetals is similar to the Cu-catalyzed allyl–*aryl* coupling between allylic phosphates and *aryl*boronates in terms of the reaction conditions and of the incomplete selectivity pattern of the γ-selectivity.[11b] This implies that the reaction proceeds through oxidative addition of a cuprate species to an allylic phosphate to form allylcopper(III) intermediates rather than through addition–β-elimination of a neutral organocopper(I) species as proposed for the Cu-catalyzed allyl–alkyl coupling between allylic phoshates and alkylboranes, which proceeded with the complete and solid γ-selectivity.[11a] According to these considerations, we propose a possible reaction pathway for the Cu-catalyzed allylic alkylation of ketene silyl acetals as illustrated in Scheme 1. Initially, the reaction of CuBr, β-diketone ligand **L1**, and Cs_2CO_3 forms a copper(I) ate complex **A**. Transmetalation between **A** and the ketene silyl acetal **2a** forms a copper enolate, which may be in a tautomerism between *O*- and *C*-copper enolates (**B** or **B′**).[13] Formal *anti*-S_N2' substitution of **1** with the copper enolate **B**/**B′**, which proceeds through allylcopper(III) complexes,[23] then affords the γ-substitution product **3** and a neutral copper(I) complex **C**. The reaction of **C** with Cs_2CO_3 regenerates **A**.

In summary, we developed a copper-catalyzed γ-selective and stereospecific allylic alkylation of a ketene silyl acetal derived from ethyl acetate. The protocol involving the use of cuprous bromide, an electron-deficient β-diketone ligand, and cesium carbonate is applicable to the reaction of various unsymmetrically substituted internal allylic phosphates. The reaction of enantioenriched allylic substrates proceeded with excellent α-to-γ chirality transfer with *anti*-stereochemistry. As a result, the protocol allows a straightforward access to functionalized, enantioenriched, β-branched γ,δ-unsaturated esters.

■ ASSOCIATED CONTENT

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

■ AUTHOR INFORMATION

Corresponding Author
ohmiya@sci.hokudai.ac.jp; sawamura@sci.hokudai.ac.jp

■ ACKNOWLEDGMENT

This work was supported by Grants-in-Aid for Scientific Research (B) and for Young Scientists (B), JSPS. We thank MEXT for financial support in the form of a Global COE grant (Project No. B01: Catalysis as the Basis for Innovation in Materials Science).

■ REFERENCES

(1) Reviews on transition-metal-catalyzed allylic substitutions:(a) Tsuji, J. *Acc. Chem. Res.* **1969**, *2*, 144–152. (b) Trost, B. M. *Tetrahedron* **1977**, *33*, 2615–2649. (c) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395–422. (d) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921–2943. (e) Lu, Z.; Ma, S. *Angew. Chem. Int. Ed.* **2008**, *47*, 258–297.

(2) Selected examples of transition-metal-catalyzed enantioselective allylic alkylations with ketone enolates:(a) Trost, B. M.; Shroeder, G. M. *J. Am. Chem. Soc.* **1999**, *121*, 6759–6760. (b) Braun, M.; Laicher, F.; Meier, T. *Angew. Chem. Int. Ed.* **2000**, *39*, 3494–3498. (c) Burger, E. C.; Tunge, J. A. *Org. Lett.* **2004**, *6*, 4113–4115. (d) Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *126*, 15044–15045. (e) Yan, X.-X.; Liang, C.-G.; Zhang, Y.; Hong, W.; Cao, B.-X.; Dai, L.-X.; Hou, X.-L. *Angew. Chem. Int. Ed.* **2005**, *44*, 6544–6546. (f) Trost, B. M.; Xu, J. *J. Am. Chem.*

Soc. **2005**, *127*, 17180–17181. (g) Zheng, W.-H.; Zheng, B.-H.; Zhang, Y.; Hou, X.-L. *J. Am. Chem. Soc.* **2007**, *129*, 7718–7719. (h) Chen, J.-P.; Ding, C.-H.; Liu, W.; Hou, X.-L.; Dai, L.-X. *J. Am. Chem. Soc.* **2010**, *132*, 15493–15495. (i) Braun, M.; Meier, T. *Angew. Chem. Int. Ed.* **2006**, *45*, 6952–6955 and references therein. (j) Graening, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *127*, 17192–17193.

(3) The regioselectivity in Pd-catalyzed allylic substitutions that involve a (π-allyl)palladium intermediate is highly dependent on the substitution pattern of allylic substrates. See refs 1 and 2a−2i.

(4) Rh-catalyzed α-selective allylic alkylations of copper enolates derived from aryl ketones with chiral secondary allylic alcohol derivatives bearing a terminal alkene moiety:(a) Evans, P. A.; Leahy, D. K. *J. Am. Chem. Soc.* **2003**, *125*, 8974–8975. (b) Evans, P. A.; Lawler, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 8642–8643.

(5) Rh-catalyzed allylic substitution of allylic carbonates having allylic system in the internal position with enoxysilanes occurred competitively at the α- and γ-positions:Muraoka, T.; Matsuda, I.; Itoh, K. *Tetrahedron. Lett.* **2000**, *41*, 8807–8811.

(6) Rh-catalyzed α-selective allylic alkylations of malonates with secondary allylic substrates:(a) Evans, P. A.; Nelson, J. D. *Tetrahedron. Lett.* **1998**, *39*, 1725–1728. (b) Evans, P. A.; Nelson, J. D. *J. Am. Chem. Soc.* **1998**, *120*, 5581–5582. (c) Ashfeld, B. L.; Miller, K. A.; Martin, S. F. *Org. Lett.* **2004**, *6*, 1321–1324.

(7) Ir-catalyzed α-selective allylic alkylations of malonates with secondary allylic substrates:(a) Takeuchi, R.; Kashio, M. *J. Am. Chem. Soc.* **1998**, *120*, 8647–8655. (b) Bartels, B.; Helmchen, G. *Chem. Commun.* **1999**, 741–742.

(8) Fe-catalyzed α-selective allylic alkylations of soft carbon nucleophiles with secondary allylic substrates:(a) Yanagisawa, A.; Nomura, N.; Yamamoto, H. *Synlett* **1991**, 513–514. (b) Plietker, B. *Angew. Chem. Int. Ed.* **2006**, *45*, 1469–1473. (c) Holzwarth, M.; Dieskau, A.; Tabassam, M.; Plietker, B. *Angew. Chem. Int. Ed.* **2009**, *48*, 7251–7255.

(9) Ru-catalyzed α-selective allylic alkylations of malonates with secondary allylic substrates:(a) Trost, B. M.; Fraisse, P. L.; Ball, Z. T. *Angew. Chem. Int. Ed.* **2002**, *41*, 1059–1061. (b) Kawatsura, M.; Ata, F.; Hayase, S.; Itoh, T. *Chem. Commun.* **2007**, 4283–4285.

(10) Pd-catalyzed γ-selective and stereospecific allyl−aryl coupling between allylic esters and arylboronic acids:(a) Ohmiya, H.; Makida, Y.; Tanaka, T.; Sawamura, M. *J. Am. Chem. Soc.* **2008**, *130*, 17276–17277. (b) Ohmiya, H.; Makida, Y.; Li, D.; Tanabe, M.; Sawamura, M. *J. Am. Chem. Soc.* **2010**, *132*, 879–889. (c) Li, D.; Tanaka, T.; Ohmiya, H.; Sawamura, M. *Org. Lett.* **2010**, *12*, 2438–2440. (d) Makida, Y.; Ohmiya, H.; Sawamura, M. *Chem. Asian J.* **2011**, *6*, 410–414.

(11) Cu-catalyzed γ-selective and stereospecific allyl−alkyl and allyl−aryl couplings with organoboron compounds:(a) Ohmiya, H.; Yokobori, U.; Makida, Y.; Sawamura, M. *J. Am. Chem. Soc.* **2010**, *132*, 2895–2897. (b) Ohmiya, H.; Yokokawa, N.; Sawamura, M. *Org. Lett.* **2010**, *12*, 2438–2440. Cu-catalyzed conjugate additions of alkylboron compounds (alkyl-9-BBN) to imidazol-2-yl α,β-unsaturated ketones:(c) Ohmiya, H.; Yoshida, M.; Sawamura, M. *Org. Lett.* **2011**, *13*, 482–485. Cu-catalyzed carboxylations of alkylboron compounds (alkyl-9-BBN) with carbon dioxide:(d) Ohmiya, H.; Tanabe, M.; Sawamura, M. *Org. Lett.* **2011**, *13*, 1086–1088.

(12) Reviews on Cu-catalyzed allylic substitutions:(a) Hoveyda, A. H.; Hird, A. W.; Kacprzynski, M. A. *Chem. Commun.* **2004**, 1779–1785. (b) Yorimitsu, H.; Oshima, K. *Angew. Chem. Int. Ed.* **2005**, *44*, 4435–4439. (c) Falciola, C. A.; Alexakis, A. *Eur. J. Org. Chem.* **2008**, 3765–3780. (d) Alexakis, A.; Bäckvall, J. E.; Krause, N.; Pàmies, O.; Diéguez, M. *Chem. Rev.* **2008**, *108*, 2796–2823. (e) Harutyunyan, S. R.; den Hartog, T.; Geurts, K.; Minnaard, A. J.; Feringa, B. L. *Chem. Rev.* **2008**, *108*, 2824–2852.

(13) Transmetalation between Cu(I) complexes and ketene silyl acetals in the Cu(I)-catalyzed carbonyl 1,2-additions of ketene silyl acetals:(a) Oisaki, K.; Suto, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 5644–5645. (b) Oisaki, K.; Zhao, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 7164–7165. (c) Suto, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 500–501.

(14) Cu(II)-catalyzed enantioselective Michael additions of enolsilanes: (a) Evans, D. A.; Rovis, T.; Johnson, J. S. *Pure Appl. Chem.* **1999**, *71*, 1407–1415. (b) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325–335.

(15) Reviews on the Claisen rearrangement:(a) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423–1452. (b) Castro, A. M. M. *Chem. Rev.* **2004**, *104*, 2939–3002.

(16) Rh-catalyzed reductive Claisen rearrangement and discussions about the functional group compatibility of the Ireland−Claisen rearrangement:Miller, S. P.; Morken, J. P. *Org. Lett.* **2002**, *4*, 2743–2745.

(17) Discussions about the functional group compatibility of the Johnson−Claisen rearrangement:(a) Cosgrove, K. L.; McGeary, R. P. *Synlett* **2009**, 1749–1752. (b) Cosgrove, K. L.; McGeary, R. P. *Tetrahedron* **2010**, *66*, 3050–3057.

(18) Menéndez Pérez, B.; Hartung, J. *Tetrahedron. Lett.* **2009**, *50*, 960–962.

(19) Unsymmetrically substituted secondary allylic bromides and chlorides are not suitable as substrate because halogenation of the corresponding allylic alcohols is not regioselective. While almost no reaction occurred with a primary allylic bromide, a primary allylic chloride underwent the reaction in a poor product yield with a moderate α-selectivity.

(20) Reaction of **1a** with methyl isobutyrate-derived ketene silyl acetal resulted in low conversion (35%) and poor yield (13%). The use of propionate-derived bis-trimethylsilyl ketene acetal resulted in no reaction.

(21) The observed stereochemical outcome can be rationalized by the *anti*-attack of the copper enolate to the allyic phosphates in a conformation that avoids the $A^{1,3}$-strain. See also refs 11a,11b.

(22) The stereochemistry of the α-isomer has not been analyzed.

(23) (a) Yoshikai, N.; Zhang, S.-L.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 12862–12863. (b) Yamanaka, M.; Kato, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 6287–6293.