

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

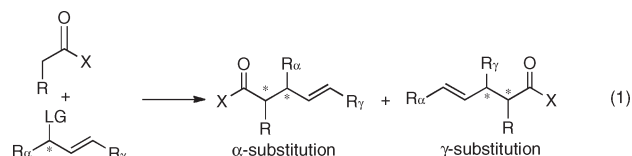
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Supporting Information

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.



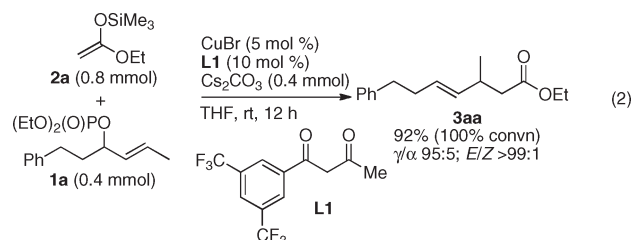
The issue of the allylic regiochemistry has been addressed in part by studies with transition metal catalysts.^{1,2} In fact, various transition metal complexes involving Pd,³ Rh,^{4–6} Ir,^{2j,7} Fe,⁸ Ru,⁹ etc. were used for regioselective enolate allylic alkylations with unsymmetrically substituted 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 Cs₂CO₃ (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).



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 CF₃ (**L2**) or NO₂ (**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

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

entry	ligand [R ¹ (O)CCH ₂ C(O)R ²]			yield (%) ^b	γ/α ^c
	L	R ¹	R ²		
1	L1	3,5-(CF ₃) ₂ -C ₆ H ₃	Me	92 (98)	95:5
2	L2	4-CF ₃ -C ₆ H ₄	Me	94 (98)	94:6
3	L3	4-NO ₂ -C ₆ H ₄	Me	92 (97)	94:6
4	L4	C ₆ H ₅	Me	89 (95)	89:11
5	L5	4-MeO-C ₆ H ₄	Me	85 (95)	84:16
6	L6	C ₆ H ₅	C ₆ H ₅	(85)	84:16
7	L7	4-CF ₃ -C ₆ H ₄	4-CF ₃ -C ₆ H ₄	(96)	94:6
8	L8	4-CF ₃ -C ₆ H ₄	4-MeO-C ₆ H 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 Cs₂CO₃ (0.2 mmol) in THF (1.0 mL) at rt for 12 h. ^b Isolated yield. The yield in parentheses was determined by ¹H NMR. Isomer ratio (*E/Z*) >99:1. ^c Determined by ¹H 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 Cs₂CO₃; changing the leaving group to carbonate or acetoxy groups inhibited the reaction;¹⁹ the use of a base such as K₂CO₃, KO^tBu, or Et₃N in place of Cs₂CO₃ 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

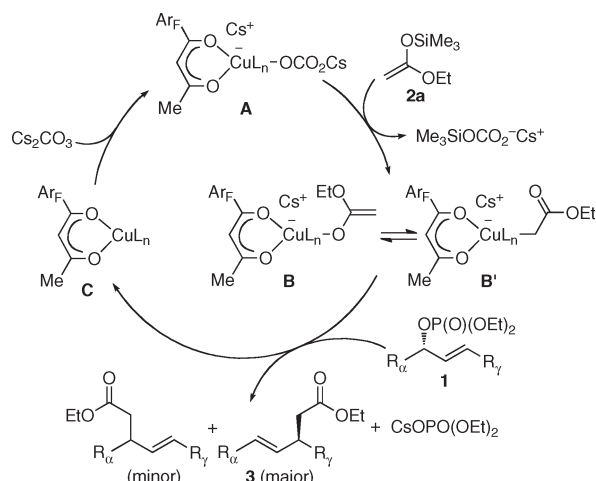
entry	phosphate 1	ketene silyl acetal 2	product	yield (%) ^{b,c}	γ/α ^d
1	(EtO) ₂ (O)PO-CH ₂ -CH ₂ -Ph (<i>Z</i>)- 1a	2a	Ph-CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₂ -CO ₂ Et 3aa	90	97:3
2	(EtO) ₂ (O)PO-CH ₂ -CH ₂ -TIPSO 1b	2a	TIPSO-CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₂ -CO ₂ Et 3b	94	98:2
3	(EtO) ₂ (O)PO-CH ₂ -CH ₂ -PivO 1c	2a	PivO-CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₂ -CO ₂ Et 3c	73	99:1
4	EtO-CO-CH ₂ -CH ₂ -OP(O)(OEt) ₂ 1d	2a	EtO-CO-CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₂ -CO ₂ Et 3d	89	98:2
5	Ph-CH ₂ -CH ₂ -CH ₂ -CH ₂ -OP(O)(OEt) ₂ 1e	2a	Ph-CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₂ -CO ₂ Et 3e	80	99:1
6	Br-Ph-CH ₂ -CH ₂ -CH ₂ -CH ₂ -OP(O)(OEt) ₂ 1f	2a	Br-Ph-CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₂ -CO ₂ Et 3f	90	96:4
7	Ph-CH ₂ -CH ₂ -CH ₂ -CH ₂ -OP(O)(OEt) ₂ 1g	2a	Ph-CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₂ -CO ₂ Et 3g	83	99:1
8	CH ₃ -CH ₂ -CH ₂ -CH ₂ -OP(O)(OEt) ₂ 1h	2a	CH ₃ -CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₂ -CO ₂ Et 3h	85	95:5
9	CH ₃ -CH ₂ -CH ₂ -CH ₂ -OP(O)(OEt) ₂ 1i	2a	CH ₃ -CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₂ -CO ₂ Et 3i	77	99:1
10	CH ₃ -CH ₂ -CH ₂ -CH ₂ -OP(O)(OEt) ₂ 1j	2a	CH ₃ -CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₂ -CO ₂ Et 3j	76	98:2
11 ^e	CH ₃ -CH ₂ -CH ₂ -CH ₂ -OP(O)(OEt) ₂ 1k	2a	CH ₃ -CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₂ -CO ₂ Et 3k	63	98:2
12 ^e	1a	2b (<i>E/Z</i> 4:1)	Ph-CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₂ -CO ₂ Me 3ab	70	95:5 ^f
13 ^e	1a	2c	Ph-CH ₂ -CH ₂ -CH ₂ -CH ₂ -CH ₂ -CO ₂ Me 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 Cs₂CO₃ (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 ¹H 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 Diastereomer ratio 75:25.

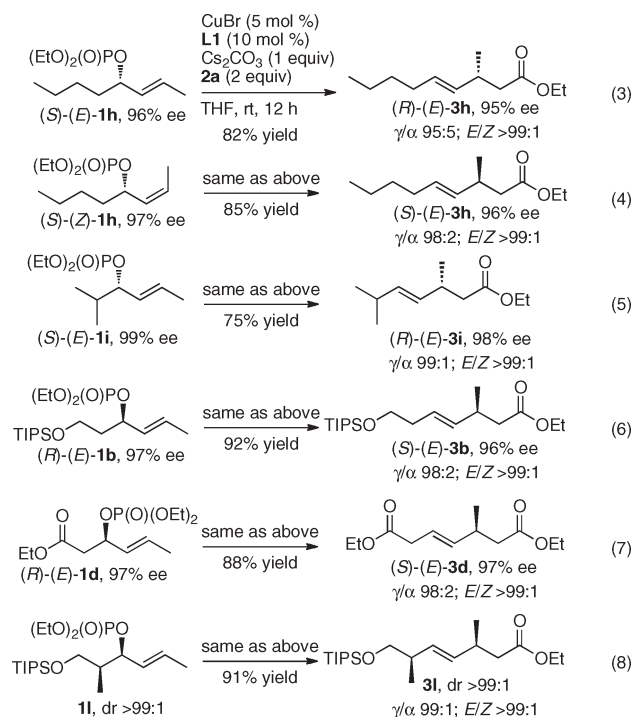
centers was not controlled (entry 12).²⁰ The γ-butyrolactone-derived cyclic ketene silyl acetal **2c** underwent the reaction with **1a** albeit with a low product yield and a moderate diastereoselectivity (dr 75:25) (entry 13).

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 Cs₂CO₃ 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

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 arylboronates 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 phosphates and alkylboronates, 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 Cs₂CO₃ 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 Cs₂CO₃ 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

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

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(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 allylic 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.

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