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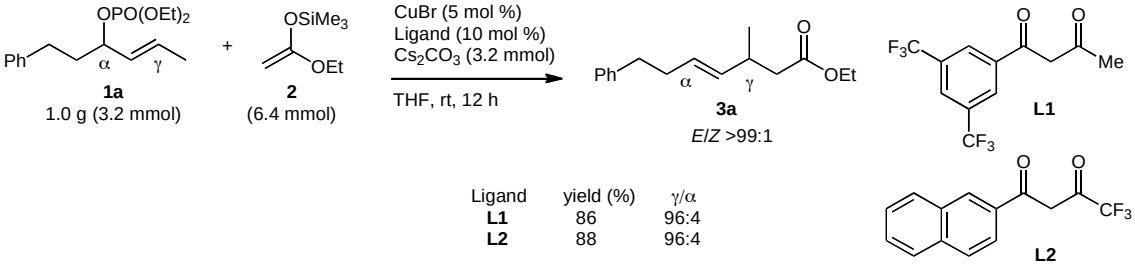
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Abstract: Copper-catalyzed allylic alkylation of ketene silyl acetals proceeded with excellent γ-*E*-selectivity. Efficient α-to-γ chirality transfer with *anti*-selectivity occurred in the reaction of enantioenriched secondary allylic phosphates, affording enantioenriched β-branched γ,δ-unsaturated esters. The reaction was readily scalable and highly reliable in terms of product yield and stereoselectivities.

Key words: *γ,δ*-unsaturated esters, copper, allylic alkylation, ketene silyl acetal, regioselectivity



Scheme 1 Copper-catalyzed γ-*E*-selective allylic alkylation of allylic phosphates with an acetate-derived ketene silyl acetal

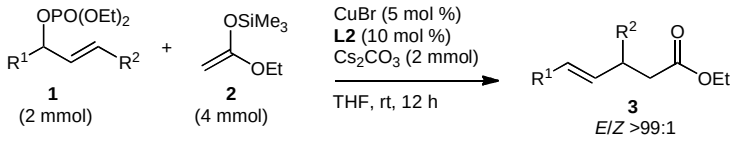
Transition-metal catalyzed allylic alkylations of enolates are useful carbon–carbon bond formation methods in organic synthesis due to the versatility of the carbonyl and alkene functionalities for stereoselective derivatization.[1–3] However, the control of regioselectivity on the reaction with unsymmetrically substituted secondary allylic substrates is still difficult.[4–9] Most studies 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]

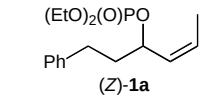
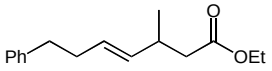
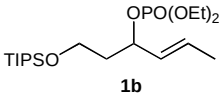
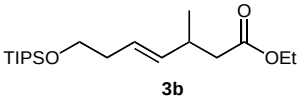
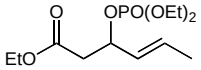
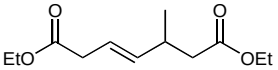
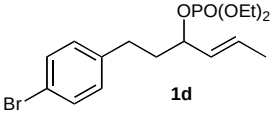
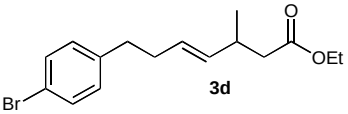
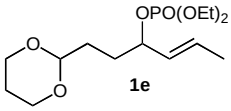
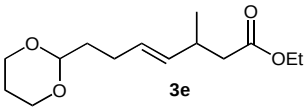
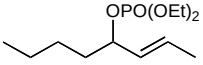
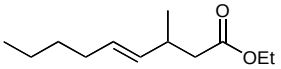
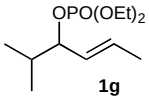
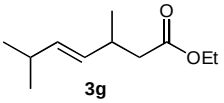
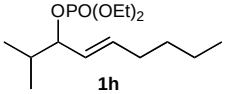
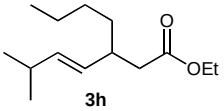
Earlier, we reported a copper-catalyzed allylic alkylation of allylic phosphates with acetate-derived ketene silyl acetals that proceeds with excellent *γ*- and *E*-selectivities.[10–12] The reactions of enantioenriched allylic phosphates having an *α*-stereogenic center occurred with excellent *α*-to-*γ* chirality transfer with *anti*-stereochemistry, and gave the corresponding enantioenriched *β*-branched *γ,δ*-unsaturated esters with an allylic stereogenic center at the *β*-position of the ester carbonyl group. 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.[13] Mild reaction conditions and the resulting broad functional group compatibility would be benefits of using the present copper-catalyzed method.[14,15] Herein, we report that the copper-catalyzed enolate allylic alkylation is readily scalable. Thus, the protocol allows a practical synthetic access to functionalized, enantioenriched, *β*-branched *γ,δ*-unsaturated esters.

The allylic phosphate substrates are readily accessible in large scale from corresponding allylic alcohols without elaborate purification.[16] (*E*)-Allylic phosphate **1a** (3.2 mmol) and ketene silyl acetal **2** (6.4 mmol) were subjected to the standard conditions; CuBr (5 mol %), electron-deficient benzoylacetone **L1**[17] (10 mol %) as a ligand and Cs_2CO_3 (3.2 mmol) in THF for 12 h at rt. The gram-scale reaction proceeded smoothly to afford the corresponding γ,δ-unsaturated ester with the excellent regio- (*γ*/*α* 96:4) and *E*/*Z*- (>99:1) selectivities (Scheme 1). Moreover, 1-(2-naphthoyl)-3,3,3-trifluoroacetone (**L2**) can be used instead of **L1** without any influence to the product yield and, regio- and stereoselectivities. It is noteworthy that **L2** is commercially available with a reasonable price, which should be more appealing as a practical synthetic procedure.

Various substrates were subjected in the 2 mmol-scale reaction (> 500 mg), and the reactions proceeded in good to excellent yields, and with high level of *γ*/*α*- (96:4–99:1) and *E*/*Z*-selectivities (>99:1).

Table 1 Copper-catalyzed allylic alkylation with ketene silyl acetal **2** of allylic phosphates **1**



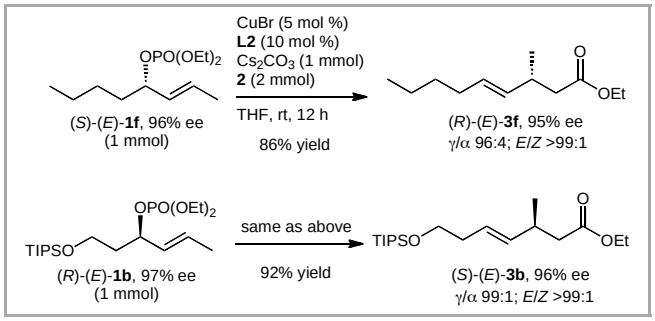
entry	allylic phosphate (**1**)	product (**3**)	yield (%)[a, b]	γ/α[c]
1	 (*Z*)-**1a**	 **3a**	89	98:2
2	 **1b**	 **3b**	91	99:1
3	 **1c**	 **3c**	90	98:2
4	 **1d**	 **3d**	86	96:4
5	 **1e**	 **3e**	78	99:1
6	 **1f**	 **3f**	85	96:4
7	 **1g**	 **3g**	80	99:1
8	 **1h**	 **3h**	78	98:2

[a] Isolated yield.
[b] Isomeric ratio *E*/*Z* >99:1.
[c] Determined by ^{1}H NMR and/or GC analysis.

The reaction was not significantly influenced by the alkene geometry of the allylic substrate. The reaction of the allylic phosphate (*Z*)-**1a** with the *Z*-configuration proceeded with somewhat higher regioselectivity with the excellent *E* stereoselectivity retained (90% yield; γ/α 98:2; *E*/*Z* >99:1) (entry 1). Functional groups such as silyl ether, ester, arylbromide, and acetal were compatible in the allylic substrates (entries 2–5).

Steric demand was tolerated in the allylic substrate. The 2-phenylethyl group at the α-position of **1a** could be replaced by a Bu group (**1f**) without a significant change in the product yield and regioselectivity (entry 6). When a much bulkier isopropyl group was on the α-position (**1g**), the product yield slightly decreased while the regioselectivity was much higher (entry 7). The γ-Me substituent of **1g** could be replaced with a Bu group with virtually no deviation in the product yield and selectivity (entry 8). 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 reaction of enantioenriched allylic phosphates was also scalable, and proceeded with excellent α-to-γ chirality transfer with 1,3-*anti* stereochemistry to afford enantioenriched, β-branched γ,δ-unsaturated esters (Scheme 2). The reaction of (*S*)-(*E*)-**1f** (96% ee), which has α-Bu and γ-Me substituents, with **2** gave (*R*)-(*E*)-**3f** (95% ee) with virtually no reduction of enantiomeric purity. The allylic phosphate [(*R*)-(*E*)-**1b**] with a siloxy group in the α-substituent also reacted with **2** to afford (*S*)-(*E*)-**3b** in 92% yield with excellent 1,3-chirality transfer.



Scheme 2 Synthesis of enantioenriched β-branched γ,δ-unsaturated esters

In summary, we have demonstrated that a copper-catalyzed γ-selective and stereospecific allylic alkylation of a ketene silyl acetal was readily scalable and highly reliable in terms of product yield and stereoselectivities.

All reactions were carried out under nitrogen or argon atmosphere. Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. CuBr was purchased from Wako Pure Chemicals. Cs_2CO_3 was purchased from Junsei Chemical Co. The ligand **L2** was purchased from Tokyo Kasei Kogyo Co., Ltd. THF was purchased from Kanto Chemical Co., stored under argon. NMR spectra were recorded on a Varian Gemini 2000 spectrometer, operating at 300 MHz for ^{1}H NMR and 75.4 MHz for ^{13}C NMR. High-resolution mass spectra were recorded on a Thermo Scientific Exactive or JEOL JMS-T100LP mass spectrometer at the Instrumental Analysis Division, Equipment Management Center, Creative Research Institution, Hokkaido University. Elemental analysis was performed at the Instrumental Analysis Division, Equipment Management Center, Creative Research Institution, Hokkaido University. HPLC analyses were conducted on a HITACHI ELITE LaChrom system with a HITACHI L-2455 diode array detector. TLC analyses were performed on commercial glass plates bearing 0.25-mm layer of Merck Silica gel 60F_{254}. Silica gel (Kanto Chemical Co., Silica gel 60 N, spherical, neutral) and aluminum oxide (Nacalai Tesuque, Alumina Activated 200) were used for column chromatography.

(*E*)-Ethyl 3-Methyl-7-phenyl-4-heptenoate (3a): Typical Procedure for Copper-Catalyzed Allylic Alkylation of Ketene Silyl Acetal

CuBr (23.0 mg, 0.16 mmol), **L2** (85.2 mg, 0.32 mmol) and Cs_2CO_3 (1.04 g, 3.20 mmol) were placed in a round bottom falsk which was sealed with a rubber plug. The flask was evacuated and refilled with argon (3 times). THF (16 mL) was introduced, and the mixture was stirred at room temperature for 5 min. Then, (1-ethoxyvinyloxy)trimethylsilane (**2**) (1.03 g, 6.40 mmol) was added. The mixture was stirred for 5 min, and then allylic phosphate **1a** (1.00 g, 3.2 mmol) was added. After 12 h stirring at room temperature, the mixture was filtered through a short plug of aluminum oxide, washed with Et_2O and the solvent was removed under reduced pressure. Flash silica gel chromatography (5% EtOAc/hexane) of the crude product provided **3a** as a colorless liquid (694 mg, 2.81 mmol) in 88% yield.

R_f = 0.40 (5% EtOAc/hexane).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.01 (d, J = 6.9 Hz, 3H), 1.24 (t, J = 7.2 Hz, 3H), 2.17–2.32 (m, 4H), 2.58–2.68 (m, 3H), 4.12 (q, J = 7.2 Hz, 1H), 5.36 (dd, J = 15.3, 6.9 Hz, 1H), 5.48 (dt, J = 15.3, 6.3 Hz, 1H), 7.15–7.20 (m, 3H), 7.25–7.30 (m, 2H).

^{13}C NMR (75.4 MHz, $CDCl_3$) δ 14.14, 20.19, 33.52, 34.22, 35.89, 41.82, 60.07, 125.78, 128.29, 128.51, 128.54, 134.88, 142.04, 172.79.

HRMS–EI (*m/z*): $[M]^+$ calcd for $C_{16}H_{22}O_2$, 246.16198; found, 246.16198.

(*S*)-(*E*)-Ethyl 3-Methyl-7-triisopropylsilyloxy-4-heptenoate (3b): Typical Procedure for the Copper-Catalyzed Allylic Alkylation of Enantioenriched Allylic Phosphate

CuBr (7.20 mg, 0.05 mmol), **L2** (26.6 mg, 0.10 mmol) and Cs_2CO_3 (325.8 mg, 1.0 mmol) were placed in a round bottom falsk which was sealed with a rubber plug. The flask was evacuated and then refilled with argon (3 times). THF (5 mL) was introduced and the mixture was stirred at room temperature for 5 min. After (1-ethoxyvinyloxy)trimethylsilane (**2**, 320 mg, 2.0 mmol) was added to the mixture, the resulting mixture was stirred for 5 min. Then, allylic phosphate (*R*)-(*E*)-**1b** (408.6 mg, 1.0 mmol) was added. After 12 h stirring at room temperature, the mixture was filtered through a short plug of alumina and washed with Et_2O. The solvent was removed under reduced pressure. Flash silica gel chromatography (5% EtOAc/hexane) of the crude product provided (*S*)-(*E*)-**3b** (316 mg, 0.92 mmol) in 92% yield. The ee value was determined by chiral HPLC analysis of the *p*-nitrobenzoate derivative obtained by the desilylation followed by benzoylation from **3b**. HPLC analysis [CHIRALCEL® OD-3 column, 4.6 mm×250 mm, hexane/2-propanol = 99:1, Daicel Chemical Industries, 0.5 mL/min, 40 °C, 254 nm UV detector, retention time = 41.1 min for *S* isomer and 42.5 min for *R* isomer] revealed that the enantiomeric excess of **3b** was 96%.

R_f = 0.45 (5% EtOAc/hexane). 96% ee, $[\alpha]_D^{21}$ +13.65 (*c* 1.03, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.01–1.10 (m, 24H), 1.24 (t, J = 7.2 Hz, 3H), 2.18–2.34 (m, 4H), 2.59–2.68 (m, 1H), 3.67 (t, J = 6.9 Hz, 3H), 4.12 (q, J = 7.2 Hz, 1H), 5.37–5.52 (m, 2H).

^{13}C NMR (75.4 MHz, $CDCl_3$) δ 11.85, 14.15, 17.89, 36.27, 41.81, 60.07, 63.37, 125.85, 136.11, 172.83.

Anal. Calcd for $C_{19}H_{38}O_3Si$: C, 66.61; H, 11.18%. Found: C, 66.31; H, 11.19%.

Acknowledgment

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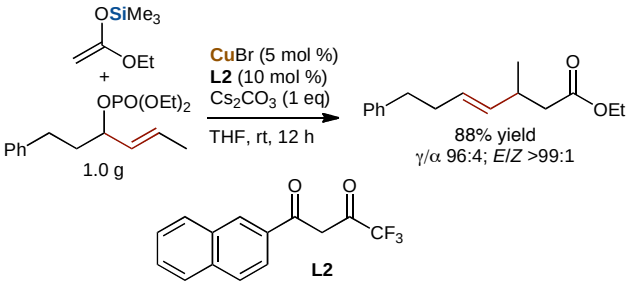
(14) For the Rh-catalyzed reductive Claisen rearrangement and discussions about the functional group compatibility of the Ireland–Claisen rearrangement, see: Miller, S. P.; Morken, J. P. *Org. Lett*. **2002**, *4*, 2743.

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(16) See supporting information of ref 6 for the procedures.

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