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Stereoretentive Suzuki–Miyaura and Kumada–Tamao–Corriu Cross-Couplings for Preparing (*E*)- and (*Z*)-Stereodefined, Fully Substituted α,β-Unsaturated Esters: Application for a Pharmacophore Synthesis

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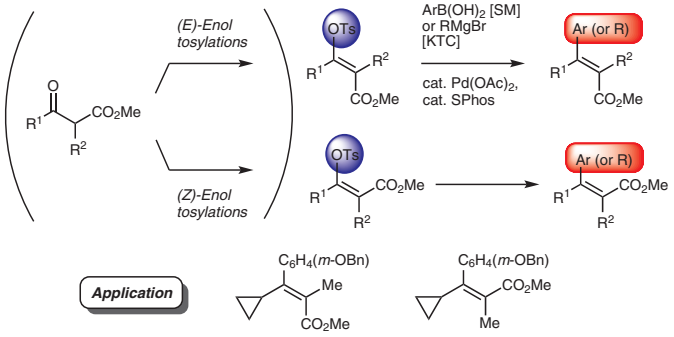
Dedicated to Professor Teruaki Mukaiyama on the celebration of his 90th birthday (Sotuju)



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Abstract Substrate-general stereocomplementary Suzuki–Miyaura (SM) cross-coupling and relevant Kumada–Tamao–Corriu (KTC) cross-coupling reactions for preparing (*E*)- and (*Z*)-stereodefined, fully substituted α,β-unsaturated esters are described. The SM cross-coupling reactions were performed under $Pd(OAc)_2$/SPhos/iPr_2NEt catalysis (24 examples, 66–99% yield). The KTC cross-coupling reactions were also performed under similar $Pd(OAc)_2$/SPhos conditions (11 examples, 50–98% yield). Application to a useful pharmacophore containing a cyclopropane structure was investigated, wherein distinctive (*E*)- and (*Z*)-stereochemical difference between XPhos and SPhos was observed. A plausible mechanism for the stereoretention and stereoinversion cross-coupling reactions is proposed.

Key words Suzuki–Miyaura cross-coupling, Kumada–Tamao–Corriu cross-coupling, fully substituted α,β-unsaturated esters, pharmacophore, stereoretention, XPhos, SPhos

Both (*E*)- and (*Z*)-stereodefined olefins are widely distributed as basic frameworks of natural products, pharmaceuticals, supramolecules, and so forth. The development of stereoselective preparative methods for these stereodefined olefins is, therefore, a valuable subject in synthetic chemistry. A comprehensive review and several books have addressed the distinctive progress in this area.[1] Especially, due to the structural complexity compared with di- or trisubstituted derivatives, the stereocontrolled syntheses of fully (all carbon) substituted olefins is attracting considerable attention as a challenging topic.[1a]

Among a variety of synthetic methods, stereocontrolled cross-coupling reactions using enol sulfonates derived from readily available β-keto esters are superb in view of their cost-effectiveness and sufficient reactivity, as well as their desirable stability.[2] Relevant methods using phosphonates[3] and carbamates[4] were recently disclosed. Fully substituted (*E*)- and (*Z*)-α,β-unsaturated esters, obtained by these methods, are distinctive scaffolds for the construction of inaccessible stereodefined olefins.

Consistent with our long-standing studies on (*E*)- and (*Z*)-stereocomplementary synthetic approaches, we have reported stereoretentive Suzuki–Miyaura (SM),[2e,5] Negishi,[6] Sonogashira,[2d] and iron-catalyzed cross-coupling[7] reactions starting from (*E*)- and (*Z*)-stereodefined enol tosylates. Applications to the (*E*)- and (*Z*)-parallel concise syntheses of zimelidine (use of the SM reaction)[5] and tamoxifen (use of the Negishi reaction),[6] representative probes for multisubstituted stereodefined olefins, were recently accomplished.

The SM cross-coupling reaction is the most privileged tool among various cross-coupling reactions. One representative SM cross-coupling reaction using (*Z*)-enol tosylates derived from methyl acetoacetate is the subject of a recent article in *Organic Syntheses*.[8] Our previous method using the SM cross-coupling reaction, however, did not deal with substrate-general, fully substituted α,β-unsaturated esters but rather with specific β,β-diaryl- and α,β-diaryl-α,β-unsaturated esters.[5] We report herein SM cross-coupling reactions and relevant Kumada–Tamao–Corriu (KTC) cross-coupling reactions to prepare more general α,α,β-fully substituted α,β-unsaturated esters (*E*)-**1** and (*Z*)-**1** (Figure 1). Both methods (SM and KTC) are conducted under similar catalytic systems (Scheme 1).

In addition, the present SM cross-coupling method can be successfully applied for a robust (*E*)- and (*Z*)-stereoretentive method as exemplified in a key pharmacophore **5**, which was recently developed by a Merck group (Scheme

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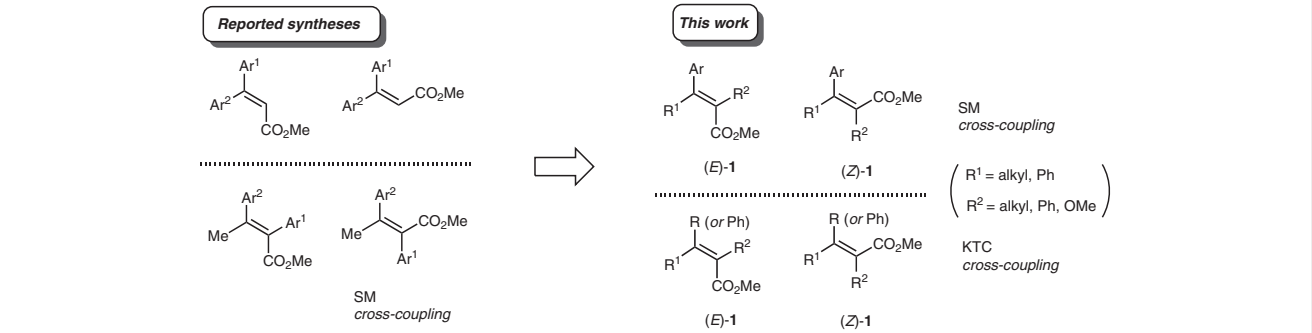
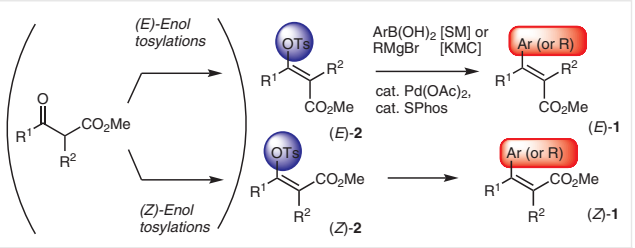
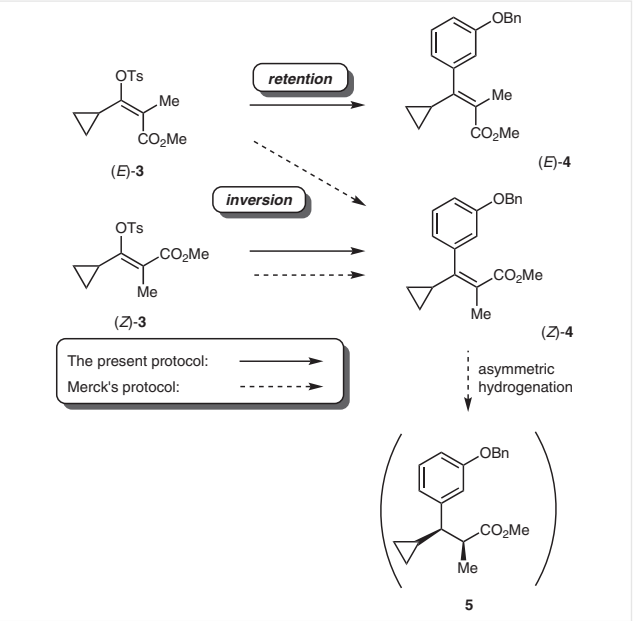


Figure 1 Our objective for the preparation of fully substituted α,β-unsaturated esters

2).[9] Notably, Merck's method resulted in (*E*)- to (*Z*)-inversion using enol tosylate (*E*)-**3**, whereas the present method proceeded with retention (i.e., in an (*E*)- and (*Z*)-stereocomplementary manner).



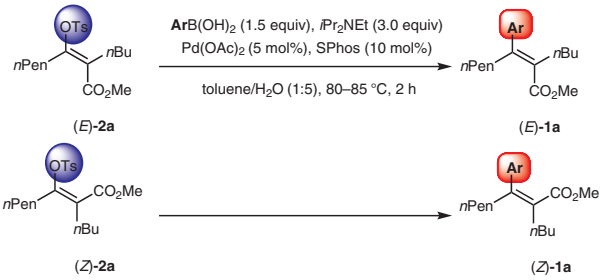
Scheme 1 (*E*)- and (*Z*)-stereocomplementary synthesis of fully substituted (*E*)- and (*Z*)-α,β-unsaturated esters



Scheme 2 (*E*)- and (*Z*)-stereoretentive synthesis of a pharmacophore

Our initial attempt to perform this SM cross-coupling reaction was intentionally guided using stereocongested enol tosylates (*E*)- and (*Z*)-**2a**[2f] derived from methyl 2-butyl-3-oxooctanoate[10] as a much less reactive substrate probe (Table 1). Catalysis system screening revealed that the combination of $Pd(OAc)_2$/SPhos/iPr_2NEt afforded the best (*E*/*Z*)-stereoretention.[11] In all cases examined, except that using *p*-$ClC_6H_4B(OH)_2$ reagent (entries 7, 8), the reaction proceeded smoothly to afford the desired products (*E*)- and (*Z*)-**1a-1**–**1a-6** in excellent yield with good to excellent

Table 1 Suzuki–Miyaura Cross-Coupling Reaction of (*E*)-**2a** and (*Z*)-**2a**



Entry	Substrate	Ar	Product	Yield (%)	*E*/*Z*[a]
1	(*E*)-**2a**	Ph	(*E*)-**1a-1**	97	92:8
2	(*Z*)-**2a**	Ph	(*Z*)-**1a-1**	99	2:>98
3	(*E*)-**2a**	*p*-MeC_6H_4	(*E*)-**1a-2**	96	91:9
4	(*Z*)-**2a**	*p*-MeC_6H_4	(*Z*)-**1a-2**	99	2:>98
5	(*E*)-**2a**	*p*-$MeOC_6H_4$	(*E*)-**1a-3**	99	89:11
6	(*Z*)-**2a**	*p*-$MeOC_6H_4$	(*Z*)-**1a-3**	95	2:>98
7	(*E*)-**2a**	*p*-ClC_6H_4	(*E*)-**1a-4**	66	92:8
8	(*Z*)-**2a**	*p*-ClC_6H_4	(*Z*)-**1a-4**	68 (11)[b]	2:>98
9	(*E*)-**2a**	3-furyl	(*E*)-**1a-5**	89	87:13
10	(*Z*)-**2a**	3-furyl	(*Z*)-**1a-5**	98	2:>98
11	(*E*)-**2a**	3-thienyl	(*E*)-**1a-6**	93	93:7
12	(*Z*)-**2a**	3-thienyl	(*Z*)-**1a-6**	91	2:>98

[a] Determined by ^1H NMR spectroscopy of the crude products.
[b] Methyl (*Z*)-2-butyl-3-(4′-chlorobiphenyl-4-yl)oct-2-enoate ((*Z*)-**1a-4′**) was obtained as a major byproduct.

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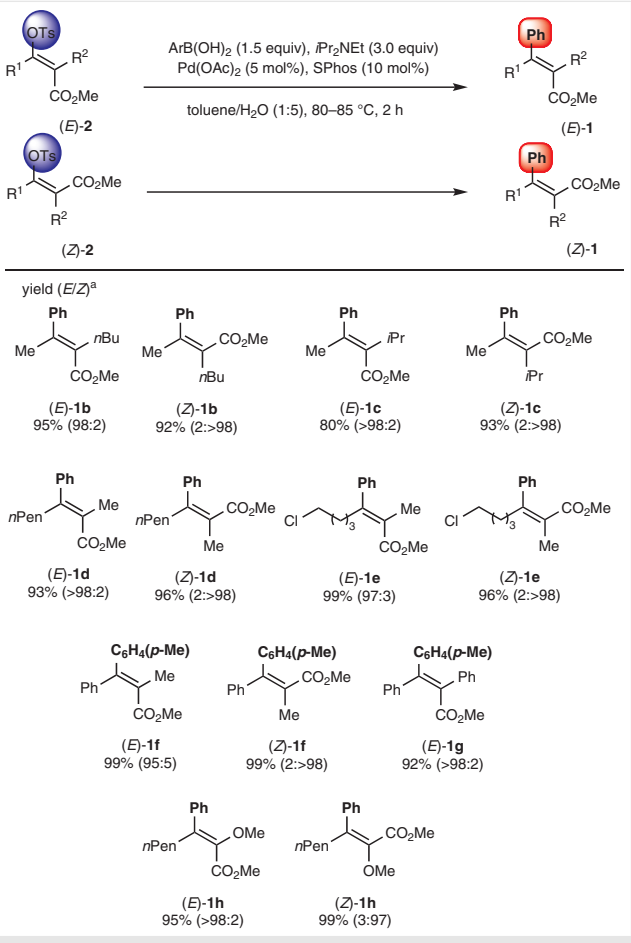
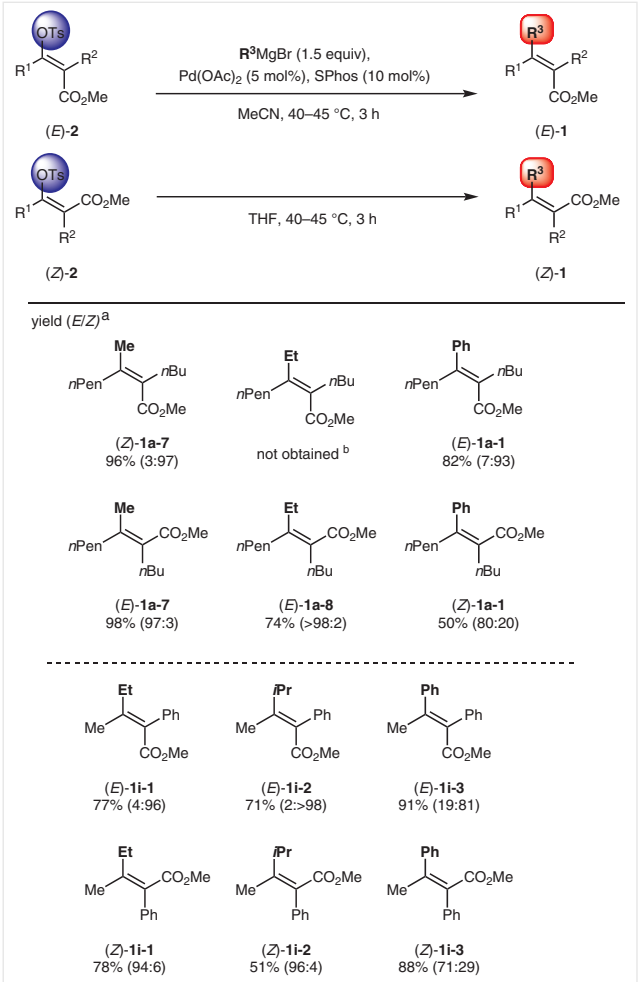
(*E*)- and (*Z*)-stereoretention. The heterocyclic 3-furyl- and 3-thienylboronic acid reactants also underwent the reaction successfully to afford the desired products (*E*)- and (*Z*)-**1a-5**, **1a-6** (entries 9–12). In general, relevant Negishi cross-coupling reactions cannot be applied for this type of heterocyclic reagent.

With the successful outcome in hand, the substrate-generality of the present SM cross-coupling reaction was examined (Scheme 3) using a variety of enol tosylates (*E*)- and (*Z*)-**2b**–**2h** under the identical conditions as in Table 1.[12] The salient features are as follows: (i) Three sets of aliphatic substrates underwent the reaction to give the corresponding products (*E*)- and (*Z*)-**1b**–**1d** in good to excellent yield with nearly complete (*E*)- and (*Z*)-stereoretention. (ii) A labile 7-chloro-substituted substrate was applicable, to give (*E*)- and (*Z*)-**1e**. (iii) Two sets of phenyl substrates also underwent the reaction successfully, affording the corresponding products (*E*)-**1f** and (*Z*)-**1f**, and (*E*)-**1g** in good to excellent yields with excellent (*E*)- and (*Z*)-stereoretention. (iv) An α-methoxy-substituted substrate was also applied in the reaction to yield the desired products (*E*)- and (*Z*)-**1h**.

Next, we turned our attention to KTC cross-coupling reactions of R^3MgBr (R^3 = alkyl, Ph) with enol tosylates (*E*)- and (*Z*)-**2a**, **2i** under conditions similar to those applied when using $Pd(OAc)_2$/SPhos catalysis (Scheme 4). The salient features are as follows: (i) In most cases good to excellent yield and selectivity were obtained. (ii) MeCN solvent matched the reaction using (*E*)-**2** substrates, whereas THF solvent matched that using (*Z*)-**2** substrates. (iii) R^3MgBr where R^3 = Me, Et, *i*Pr, and Ph were applicable as the reagent. (iv) A side reduction reaction of the TsO group occurred exclusively when the reaction of (*E*)-**2a** with EtMgBr was carried out, possibly due to a plausible β-hydride shift of the Et group. In contrast, the reaction using (*Z*)-**2a** gave satisfactory results. (v) The reaction using PhMgBr proceed-



Scheme 3 Substrate generality of the Suzuki–Miyaura cross-coupling reaction of (*E*)-**2** and (*Z*)-**2**. [a] Determined by ^1H NMR spectroscopy of the crude products.



Scheme 4 Kumada–Tamao–Corriu cross-coupling reaction of (*E*)-**2** and (*Z*)-**2**. [a] Determined by ^1H NMR spectroscopy of the crude products. [b] Instead, methyl (*Z*)-2-butyloct-2-enoate was obtained as the main product.

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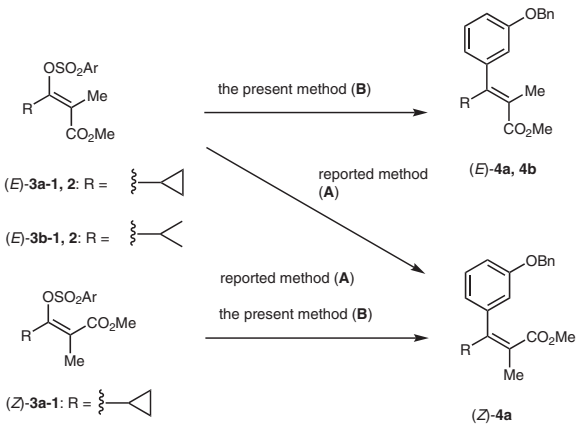
ed smoothly to give the desired product (*E*)- and (*Z*)-**1a-3** in excellent yield but slight (*E*)- to (*Z*)- and (*Z*)- to (*E*)-isomerization took place.

As a distinct application, we investigated the SM cross-coupling reaction for (*E*)- and (*Z*)-stereocomplementary synthesis of a key pharmacophore (*Z*)-**4a**[3] together with its stereoisomer (*E*)-**4a** (Table 2). Two sets of enol sulfonate analogues were used as the substrate: (*E*)-**3a-1** and (*E*)-**3b-1** (Ar = Ts), and (*E*)-**3a-2** and (*E*)-**3b-2** (Ar = *p*-$O_2NC_6H_4$). Merck group's reported conditions (Method A) utilized XPhos catalysis, whereas the present conditions utilized SPhos catalysis (Method B). The salient features are as follows: (i) Re-examination of Method A using (*E*)-**3a-1** and isopropyl analogue (*E*)-**3b-1** actually gave (*Z*)-**4a** and (*Z*)-**4b**, respectively, with apparent *stereoinversion* (*E* to *Z*) (entries 1, 2). (ii) Novel *p*-$O_2NC_6H_4$ analogues (*E*)-**3a-2** and (*E*)-**3b-2** similarly underwent the inversion reaction (entries 3, 4). (iii) To our delight, the present Method B was consistently *stereoretentive* to circumvent (*E*)- to (*Z*)-isomerization (entries 5–8). (iv) The reaction of (*Z*)-**3a-1** using both Methods A and B occurred in a highly (*Z*)-stereoretentive manner, as expected (entries 9, 10).

Table 2 Suzuki–Miyaura Cross-Coupling: Comparison of the Reported and Present Methods



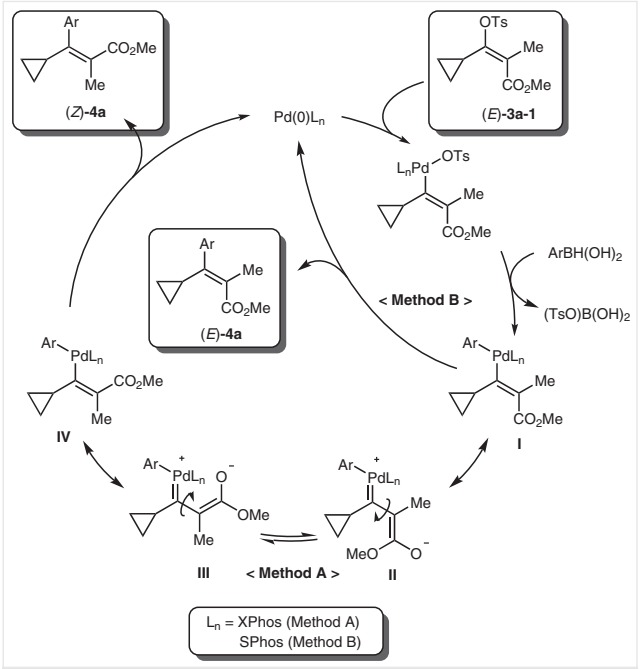
(A) *m*-(BnO)$C_6H_4B(OH)_2$ (1.5 equiv), *i*Pr_2NEt (3.0 equiv), $Pd(OAc)_2$ (5 mol%), XPhos (10 mol%), toluene–H_2O (1:5), 80–85 °C, 2 h

(B) *m*-(BnO)$C_6H_4B(OH)_2$ (1.5 equiv), *i*Pr_2NEt (3.0 equiv), $Pd(OAc)_2$ (5 mol%), SPhos (10 mol%), toluene–H_2O (1:5), 80–85 °C, 2 h

Entry	Method	Ar	Substrate	Major product	Yield (%)	*E*/*Z*[a]
1[b]	A	Ts	(*E*)-**3a-1**	(*Z*)-**4a**	59	5:**95**
2	A	Ts	(*E*)-**3b-1**	(*Z*)-**4b**	61	26:**74**
3	A	*p*-$O_2NC_6H_4$	(*E*)-**3a-2**	(*Z*)-**4a**	84	4:**96**
4	A	*p*-$O_2NC_6H_4$	(*E*)-**3b-2**	(*Z*)-**4b**	64	33:**67**
5	B	Ts	(*E*)-**3a-1**	(*E*)-**4a**	88	**86**:14
6	B	Ts	(*E*)-**3b-1**	(*E*)-**4b**	64	**95**:5
7	B	*p*-$O_2NC_6H_4$	(*E*)-**3a-2**	(*E*)-**4a**	44	**77**:23
8	B	*p*-$O_2NC_6H_4$	(*E*)-**3b-2**	(*E*)-**4b**	76	>**98**:2
9[c]	A	Ts	(*Z*)-**3a-1**	(*Z*)-**4a**	74[d]	0:**100**[e]
10	B	Ts	(*Z*)-**3a-1**	(*Z*)-**4a**	86	2:>**98**

[a] Determined by ^1H NMR spectroscopy of the crude products.
[b] Re-examination of the reported method.
[c] Reported data.
[d] Isolation data.
[e] The ratio of crude product was not reported.

The proposed mechanism for not only (*E*)-stereoretention, but also (*E*)- to (*Z*)-inversion processes, is depicted in Scheme 5; a catalytic cycle starting from (*E*)-**3a-1** yields product (*E*)-**4a** or (*Z*)-**4a**. $ArPdL_n$ (L_n = XPhos or SPhos) intermediate **I** is initially formed through the privileged pathway of the SM cross-coupling reaction. Stereoretentive product (*E*)-**4a** is in turn afforded with the regeneration of $Pd(0)L_n$ (Method B). When the zwitterion intermediate **II** is transformed to **III** with single-bond rotation by equilibrium, stereoinversion product (*Z*)-**4a** is obtained through $ArPdL_n$ intermediate **IV**. Although the concrete reason for the ligand effect is unclear at present, the present Method B using SPhos catalysis sufficiently retarded the (*E*)- to (*Z*)-stereoinversion compared with the reported Method A using XPhos catalysis.[13] This tendency coincides with the aforementioned initial catalysis screening.[11]



Scheme 5 Plausible reaction mechanism with retention and isomerization pathways

In conclusion, we have developed substrate-general stereoretentive SM cross-coupling and relevant KTC cross-coupling reactions for preparing (*E*)- and (*Z*)-stereodefined, fully substituted α,β-unsaturated esters. A synthetic applica-

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tion to a useful pharmacophore possessing a cyclopropane structure was performed, wherein we observed distinctive (*E*)- and (*Z*)-stereochemical difference between XPhos (stereoinversion) and SPhos (stereoretention) catalysis.

All reactions were carried out in oven-dried glassware under an argon atmosphere. Flash column chromatography was performed with Merck silica gel 60 (230–400 mesh ASTM). TLC analysis was performed on Merck 0.25 mm silica gel 60 F254 plates. Melting points were determined on a hot-stage microscope apparatus (AS ONE, ATM-01) and are uncorrected. NMR spectra were recorded on a JEOL DELTA 300 or JEOL RESONANCE ECX-500 spectrometer, operating at 300 MHz or 500 MHz for ^{1}H NMR and 75 MHz or 125 MHz for ^{13}C NMR acquisitions. Chemical shifts (δ, ppm) in $CDCl_3$ are reported downfield from TMS (0 ppm) for ^{1}H NMR data. For ^{13}C NMR data, chemical shifts are reported in the scale relative to $CDCl_3$ (77.00 ppm) as an internal reference. IR spectra were recorded on a JASCO FT/IR-5300 spectrophotometer. Mass spectra were measured on a JEOL JMS-T100LC spectrometer. Enol tosylates (*E*)-**2a**, (*Z*)-**2a**, (*E*)-**2b**, (*Z*)-**2b**, (*E*)-**2c**, (*Z*)-**2c**, (*E*)-**2d**, (*Z*)-**2d**, (*E*)-**2e**, (*Z*)-**2e**, (*E*)-**2f**, (*Z*)-**2f**, (*E*)-**2g**, (*E*)-**2h**, (*Z*)-**2h**, (*E*)-**2i**, and (*Z*)-**2i** are known compounds.[2f] (*E*)-**3a-1** and (*E*)-**3a-2** are also reported compounds.[9] The (*E*)- and (*Z*)-stereocomplementary enol tosylations of parent β-keto esters were carried out using the TsCl–$Me_2N(CH_2)_6NMe_2$ reagent for (*E*)-**2** and the TsCl–TMEDA–LiCl reagent for (*Z*)-**2**.[2f] (*E*)-**3a-2** and (*E*)-**3b-2** were prepared according to a Merck group's procedure.[9] All stereochemistries (*E*,*Z*) of the fully substituted (*E*)- and (*Z*)-α,β-unsaturated esters **1** and **4** were determined by comparison with reported compounds or by deduction from them.

Suzuki–Miyaura Cross-Couplings; General Procedure (Scheme 3)

An enol tosylate (0.50 mmol) was added to a stirred suspension of $ArB(OH)_2$ (0.75 mmol), iPr_2NEt (194 mg, 1.50 mmol), $Pd(OAc)_2$ (6 mg, 0.025 mmol), and SPhos (20 mg, 0.05 mmol) in toluene (0.7 mL)/water (3.3 mL) at 80–85 °C under an argon atmosphere, and the mixture was stirred for 2 h. After cooling, water was added to the mixture, which was extracted twice with AcOEt. The combined organic phase was washed with water and brine, dried (Na_2SO_4), and concentrated. The obtained crude product was purified by silica gel column chromatography (hexane/Et_2O, 200:1 to 100:1) to give the desired product.

Methyl (*E*)-2-Butyl-3-phenyloct-2-enoate ((*E*)-1a-1)[3]

Yield: 139 mg (97%, *E*/*Z* = 92:8); colorless oil.

Methyl (*Z*)-2-Butyl-3-phenyloct-2-enoate ((*Z*)-1a-1)[3]

Yield: 152 mg (99%, *E*/*Z* = 2:>98); colorless oil.

Methyl (*E*)-2-Butyl-3-(4-methylphenyl)oct-2-enoate ((*E*)-1a-2)

Yield: 146 mg (96%, *E*/*Z* = 91:9); oil.

IR (neat): 2956, 2927, 2860, 1718, 1509, 1457, 1203, 1136 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.76 (t, *J* = 7.2 Hz, 3 H), 0.82 (t, *J* = 7.2 Hz, 3 H), 1.09–1.36 (m, 10 H), 2.08 (t, *J* = 7.2 Hz, 2 H), 2.36 (s, 3 H), 2.44 (t, *J* = 7.2 Hz, 2 H), 3.79 (s, 3 H), 6.95–7.02 (m, 2 H), 7.11–7.19 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7, 13.9, 21.1, 22.3, 22.4, 27.7, 30.8, 31.2, 31.6, 36.5, 51.2, 127.6, 128.7, 130.5, 136.4, 138.4, 147.4, 170.7.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{30}O_2Na$: 325.2143; found: 325.2129.

Methyl (*Z*)-2-Butyl-3-(4-methylphenyl)oct-2-enoate ((*Z*)-1a-2)

Yield: 151 mg (99%, *E*/*Z* = 2:>98); colorless oil.

IR (neat): 2920, 1715, 1511, 1431, 1323, 1245, 1200, 1137 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.83 (t, *J* = 6.5 Hz, 3 H), 0.93 (t, *J* = 6.9 Hz, 3 H), 1.17–1.50 (m, 10 H), 2.32 (s, 3 H), 2.37–2.47 (m, 4 H), 3.37 (s, 3 H), 6.97–7.04 (m, 2 H), 7.05–7.12 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 21.1, 22.4, 22.6, 27.5, 30.0, 31.1, 31.7, 34.0, 51.1, 127.3, 128.6, 131.3, 136.4, 139.6, 146.1, 171.4.

Methyl (*E*)-2-Butyl-3-(4-methoxyphenyl)oct-2-enoate ((*E*)-1a-3)

Yield: 160 mg (99%, *E*/*Z* = 89:11); colorless oil.

IR (neat): 2954, 2927, 2859, 1717, 1608, 1509, 1463, 1245 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.76 (t, *J* = 7.2 Hz, 3 H), 0.82 (t, *J* = 7.2 Hz, 3 H), 1.08–1.34 (m, 10 H), 2.09 (t, *J* = 7.2 Hz, 2 H), 2.43 (t, *J* = 7.2 Hz, 2 H), 3.78 (s, 3 H), 3.82 (s, 3 H), 6.84–6.90 (m, 2 H), 6.99–7.05 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 14.0, 22.4, 27.7, 30.8, 31.3, 31.7, 36.6, 51.3, 55.2, 113.5, 128.9, 130.6, 133.7, 147.0, 158.4, 170.9.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{30}O_3Na$: 341.2093; found: 341.2095.

Methyl (*Z*)-2-Butyl-3-(4-methoxyphenyl)oct-2-enoate ((*Z*)-1a-3)

Yield: 151 mg (95%, *E*/*Z* = 2:>98); colorless oil.

IR (neat): 2955, 2871, 1710, 1607, 1509, 1462, 1323, 1244 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.83 (t, *J* = 6.9 Hz, 3 H), 0.93 (t, *J* = 6.9 Hz, 3 H), 1.17–1.48 (m, 10 H), 2.34–2.47 (m, 4 H), 3.38 (s, 3 H), 3.80 (s, 3 H), 6.77–6.85 (m, 2 H), 7.02–7.09 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 22.3, 22.5, 27.5, 30.0, 31.0, 31.5, 33.9, 51.0, 54.9, 113.2, 128.5, 131.2, 134.8, 145.4, 158.5, 171.5.

Methyl (*E*)-2-Butyl-3-(4-chlorophenyl)oct-2-enoate ((*E*)-1a-4)

Yield: 106 mg (66%, *E*/*Z* = 92:8); colorless oil.

IR (neat): 2956, 2929, 2860, 1720, 1489, 1462, 1433, 1204 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.76 (t, *J* = 7.2 Hz, 3 H), 0.82 (t, *J* = 7.2 Hz, 3 H), 1.07–1.36 (m, 10 H), 2.05 (t, *J* = 7.2 Hz, 2 H), 2.42 (t, *J* = 7.2 Hz, 2 H), 3.79 (s, 3 H), 7.00–7.07 (m, 2 H), 7.29–7.36 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7, 13.9, 22.3, 27.6, 30.8, 31.1, 31.6, 36.3, 51.4, 128.4, 129.2, 131.3, 132.8, 139.8, 145.8, 170.4.

Methyl (*Z*)-2-Butyl-3-(4-chlorophenyl)oct-2-enoate ((*Z*)-1a-4)

Yield: 110 mg (68%, *E*/*Z* = 2:>98); colorless oil.

IR (neat): 2956, 2860, 1715, 1488, 1466, 1432, 1242, 1139 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.83 (t, *J* = 6.9 Hz, 3 H), 0.93 (t, *J* = 6.9 Hz, 3 H), 1.18–1.49 (m, 10 H), 2.34–2.47 (m, 4 H), 3.38 (s, 3 H), 7.01–7.08 (m, 2 H), 7.22–7.29 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 22.4, 22.5, 27.4, 29.9, 31.0, 31.6, 34.0, 51.2, 128.1, 128.8, 132.2, 132.7, 141.1, 144.9, 170.8.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{27}O_2ClNa$: 345.1597; found: 345.1611.

Methyl (*Z*)-2-Butyl-3-(4′-chlorobiphenyl-4-yl)oct-2-enoate ((*Z*)-1a-4′)

19 mg (11%); colorless oil.

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IR (neat): 2955, 2927, 2859, 1714, 1485, 1457, 1432, 1241 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.84 (t, *J* = 7.2 Hz, 3 H), 0.94 (t, *J* = 7.2 Hz, 3 H), 1.16–1.51 (m, 10 H), 2.36–2.54 (m, 4 H), 3.36 (s, 3 H), 7.15–7.23 (m, 2 H), 7.36–7.43 (m, 2 H), 7.44–7.56 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 22.4, 22.6, 27.6, 30.0, 31.1, 31.7, 34.1, 51.2, 126.4, 128.0, 128.2, 128.9, 131.9, 133.3, 138.3, 139.2, 142.1, 145.7, 171.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{25}H_{31}O_2ClNa$: 421.1910; found: 421.1897.

Methyl (*E*)-2-Butyl-3-(3-furyl)oct-2-enoate ((*E*)-1a-5)

Yield: 124 mg (89%, *E*/*Z* = 87:13); pale yellow oil.

IR (neat): 2955, 2929, 2860, 1956, 1716, 1458, 1434, 1204 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.85 (t, *J* = 7.2 Hz, 6 H), 1.18–1.43 (m, 10 H), 2.30 (t, *J* = 7.2 Hz, 2 H), 2.37 (t, *J* = 7.2 Hz, 2 H), 3.78 (s, 3 H), 6.31–6.33 (m, 1 H), 7.31–7.33 (m, 1 H), 7.41–7.43 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 13.9, 22.3, 22.4, 28.2, 31.0, 31.0 (x2), 31.6, 35.8, 51.3, 110.9, 124.5, 131.6, 137.6, 139.7, 142.6, 170.6.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{26}O_3Na$: 301.1790; found: 301.1796.

Methyl (*Z*)-2-Butyl-3-(3-furyl)oct-2-enoate ((*Z*)-1a-5)

Yield: 136 mg (98%, *E*/*Z* = 2:>98); pale yellow oil.

IR (neat): 2926, 2860, 1718, 1637, 1503, 1461, 1433, 1330 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 6.9 Hz, 3 H), 0.92 (t, *J* = 6.9 Hz, 3 H), 1.18–1.48 (m, 10 H), 2.27–2.43 (m, 4 H), 3.58 (s, 3 H), 6.27–6.32 (m, 1 H), 7.30–7.39 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 13.8, 22.4, 22.5, 27.9, 30.0, 30.8, 31.6, 32.9, 51.3, 110.2, 125.6, 131.5, 134.1, 139.7, 142.5, 171.8.

Methyl (*E*)-2-Butyl-3-(3-thienyl)oct-2-enoate ((*E*)-1a-6)

Yield: 137 mg (93%, *E*/*Z* = 93:7); colorless oil.

IR (neat): 2955, 2927, 2859, 1717, 1457, 1433, 1200, 1132 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.80 (t, *J* = 7.2 Hz, 3 H), 0.83 (t, *J* = 7.2 Hz, 3 H), 1.13–1.37 (m, 10 H), 2.18 (t, *J* = 7.2 Hz, 2 H), 2.43 (t, *J* = 7.2 Hz, 2 H), 3.79 (s, 3 H), 6.89–6.94 (m, 1 H), 6.99–7.03 (m, 1 H), 7.28–7.33 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7, 13.9, 22.3, 28.0, 30.9, 31.3, 31.5, 36.2, 51.3, 121.8, 125.1, 127.7, 131.5, 141.3, 142.2, 170.5.

Methyl (*Z*)-2-Butyl-3-(3-thienyl)oct-2-enoate ((*Z*)-1a-6)

Yield: 134 mg (91%, *E*/*Z* = 2:>98); pale yellow oil.

IR (neat): 2924, 2856, 1713, 1457, 1431, 1312, 1235, 1201 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.84 (t, *J* = 6.9 Hz, 3 H), 0.92 (t, *J* = 6.9 Hz, 3 H), 1.18–1.48 (m, 10 H), 2.35–2.44 (m, 4 H), 3.45 (s, 3 H), 6.91–6.95 (m, 1 H), 7.01–7.05 (m, 1 H), 7.22–7.26 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 22.3, 22.5, 27.7, 29.9, 30.8, 31.5, 33.5, 51.2, 121.5, 124.7, 127.3, 132.0, 139.5, 142.4, 171.6.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{26}O_2SNa$: 317.1551; found: 317.1548.

Methyl (*E*)-2-(1-Phenylethylidene)hexanoate ((*E*)-1b)[6]

Yield: 134 mg (95%, *E*/*Z* = 98:2); colorless oil.

IR (neat): 2955, 2860, 1718, 1490, 1434, 1316, 1258, 1136 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.76 (t, *J* = 7.5 Hz, 3 H), 1.15 (sext, *J* = 7.5 Hz, 2 H), 1.23–1.32 (m, 2 H), 2.13 (t, *J* = 8.0 Hz, 2 H), 2.16 (s, 3 H), 3.81 (s, 3 H), 7.11–7.15 (m, 2 H), 7.25–7.29 (m, 1 H), 7.32–7.37 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.7, 22.3, 23.3, 30.6, 31.2, 51.4, 126.9, 127.1 (2 C), 128.2 (2 C), 130.6, 143.0, 143.5, 170.5.

Methyl (*Z*)-2-(1-Phenylethylidene)hexanoate ((*Z*)-1b)[6]

Yield: 134 mg (92%, *E*/*Z* = 2:>98); colorless oil.

IR (neat): 2955, 2871, 1714, 1492, 1433, 1318, 1240, 1139 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.94 (t, *J* = 7.5 Hz, 3 H), 1.34–1.51 (m, 4 H), 2.10 (s, 3 H), 2.44 (t, *J* = 8.0 Hz, 2 H), 3.37 (s, 3 H), 7.12–7.16 (m, 2 H), 7.21–7.25 (m, 1 H), 7.27–7.32 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.9, 20.8, 22.5, 30.4, 30.7, 51.1, 126.8 (2 C), 126.9, 127.9 (2 C), 131.5, 141.7, 144.0, 171.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{20}O_2Na$: 255.1361; found: 255.1360.

Methyl (*E*)-2-Isopropyl-3-phenylbut-2-enoate ((*E*)-1c)[6]

Yield: 87 mg (80%, *E*/*Z* = >98:2); colorless oil.

Methyl (*Z*)-2-Isopropyl-3-phenylbut-2-enoate ((*Z*)-1c)[6]

Yield: 102 mg (93%, *E*/*Z* = 2:>98); colorless oil.

Methyl (*E*)-2-Methyl-3-phenyloct-2-enoate ((*E*)-1d)[3]

Yield: 115 mg (93%, *E*/*Z* = >98:2); colorless oil.

Methyl (*Z*)-2-Methyl-3-phenyloct-2-enoate ((*Z*)-1d)[3]

Yield: 118 mg (96%, *E*/*Z* = 2:>98); colorless oil.

Methyl (*E*)-7-Chloro-2-methyl-3-phenylhept-2-enoate ((*E*)-1e)[3]

Yield: 143 mg (99%, *E*/*Z* = 97:3); colorless oil.

Methyl (*Z*)-7-Chloro-2-methyl-3-phenylhept-2-enoate ((*Z*)-1e)[3]

Yield: 128 mg (96%, *E*/*Z* = 2:>98); colorless oil.

Methyl (*E*)-2-Methyl-3-(4-methylphenyl)-3-phenylacrylate ((*E*)-1f)[6]

Yield: 132 mg (99%, *E*/*Z* = 95:5); pale yellow oil.

Methyl (*Z*)-2-Methyl-3-(4-methylphenyl)-3-phenylacrylate ((*Z*)-1f)[6]

Yield: 133 mg (99%, *E*/*Z* = 2:>98); pale yellow oil.

Methyl (*E*)-3-(4-Methylphenyl)-2,3-diphenylacrylate ((*E*)-1g)

Yield: 144 mg (92%, *E*/*Z* = >98:2); colorless crystals; mp 147–148 °C.

IR (neat): 2955, 1717, 1489, 1442, 1430, 1262, 1221, 1145 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.36 (s, 3 H), 3.58 (s, 3 H), 6.97–7.02 (m, 2 H), 7.07–7.19 (m, 12 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.2, 51.8, 127.2, 127.5, 127.7, 128.1, 128.8, 128.8, 129.7, 130.8, 132.8, 137.5, 137.9, 139.3, 140.6, 146.2, 170.9.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{20}O_2Na$: 351.1361; found: 351.1350.

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Methyl (*E*)-2-Methoxy-3-phenyloct-2-enoate ((*E*)-1h)[6]

Yield: 125 mg (95%, *E*/*Z* = >98:2); colorless oil.

Methyl (*Z*)-2-Methoxy-3-phenyloct-2-enoate ((*Z*)-1h)[6]

Yield: 132 mg (99%, *E*/*Z* = 3:97); colorless oil.

Kumada–Tamao–Corriu Cross-Couplings; General Procedure (Scheme 4)

R^3MgBr (0.76 mL; 0.99 M in THF) was added to a stirred solution of an (*E*)-enol tosylate (0.50 mmol), $Pd(OAc)_2$ (6 mg, 0.025 mmol), and SPhos (20 mg, 0.05 mmol) in MeCN (0.5 mL) at 40–45 °C under an argon atmosphere, and the mixture was stirred at that same temperature for 3 h. After cooling, 3 M aq HCl solution was added to the mixture, which was extracted twice with AcOEt. The combined organic phase was washed with water and brine, dried (Na_2SO_4), and concentrated. The obtained crude oil was purified by silica gel column chromatography (hexane/Et_2O, 200:1 to 100:1) to give the desired product.

R^3MgBr (0.76 mL; 0.99 M in THF) was added to a stirred solution of a (*Z*)-enol tosylate (0.50 mmol), $Pd(OAc)_2$ (6 mg, 0.025 mmol), and SPhos (20 mg, 0.05 mmol) in THF (0.5 mL) at 40–45 °C under an argon atmosphere, and the mixture was stirred at that same temperature for 3 h. After cooling, 3 M aq HCl solution was added to the mixture, which was extracted twice with AcOEt. The combined organic phase was washed with water and brine, dried (Na_2SO_4), and concentrated. The obtained crude oil was purified by silica gel column chromatography (hexane/Et_2O, 200:1 to 100:1) to give the desired product.

Methyl (*Z*)-2-Butyl-3-methyloct-2-enoate ((*Z*)-1a-7)

Yield: 109 mg (96%, *E*/*Z* = 3:97); colorless oil.

IR (neat): 2927, 2859, 1716, 1631, 1459, 1433, 1377, 1202 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.9 Hz, 3 H), 0.90 (t, *J* = 6.9 Hz, 3 H), 1.19–1.49 (m, 10 H), 1.77 (s, 3 H), 2.17–2.30 (m, 4 H), 3.71 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 14.0, 19.2, 22.5, 22.5, 28.1, 29.8, 31.1, 31.9, 36.4, 51.1, 128.2, 144.8, 170.5.

Methyl (*E*)-2-Butyl-3-methyloct-2-enoate ((*E*)-1a-7)

Yield: 111 mg (98%, *E*/*Z* = 97:3); colorless oil.

IR (neat): 2925, 1860, 1716, 1628, 1433, 1378, 1280, 1198 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 6.9 Hz, 6 H), 1.22–1.48 (m, 10 H), 1.90 (s, 3 H), 2.10 (t, *J* = 7.6 Hz, 2 H), 2.27 (t, *J* = 6.9 Hz, 2 H), 3.72 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 14.0, 20.8, 22.5, 22.6, 27.6, 29.3, 31.6, 31.9, 35.2, 51.1, 128.2, 144.9, 170.7.

Methyl (*Z*)-2-Butyloct-2-enoate

Yield: 34 mg (28%, *E*/*Z* = 3:93); colorless oil.

IR (neat): 2957, 2930, 2859, 1712, 1641, 1436, 1377, 1201 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.83–0.95 (m, 6 H), 1.21–1.46 (m, 10 H), 2.23 (t, *J* = 7.2 Hz, 2 H), 2.39 (t, *J* = 7.2 Hz, 2 H), 3.73 (s, 3 H), 5.84 (t, *J* = 7.2 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 14.0, 22.2, 22.5, 29.2, 29.5, 31.3, 31.5, 34.3, 51.1, 131.9, 141.8, 168.8.

Methyl (*E*)-3-Ethyl-2-butyloct-2-enoate ((*E*)-1a-8)

Yield: 89 mg (74%, *E*/*Z* = >98:2); colorless oil.

IR (neat): 2956, 2871, 1717, 1627, 1459, 1433, 1196, 1116 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.84–0.94 (m, 6 H), 1.03 (t, *J* = 7.6 Hz, 3 H), 1.21–1.46 (m, 10 H), 2.08 (t, *J* = 7.6 Hz, 2 H), 2.16–2.31 (m, 4 H), 3.72 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.4, 13.9, 13.9, 22.5, 22.5, 27.2, 28.1, 29.3, 31.5, 32.1, 51.0, 128.0, 149.7, 170.6.

Methyl (*E*)-3-Methyl-2-phenylpent-2-enoate ((*E*)-1i-1)

Yield: 79 mg (78%, *E*/*Z* = 94:6); colorless oil.

IR (neat): 2971, 2876, 1712, 1625, 1493, 1433, 1291, 1212 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 7.6 Hz, 3 H), 1.97 (q, *J* = 7.6 Hz, 2 H), 2.12 (s, 3 H), 3.66 (s, 3 H), 7.13–7.20 (m, 2 H), 7.24–7.37 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.4, 19.5, 29.3, 51.5, 126.9, 128.0, 129.3, 138.0, 150.6, 168.9.

Methyl (*Z*)-3-Methyl-2-phenylpent-2-enoate ((*Z*)-1i-1)

Yield: 79 mg (77%, *E*/*Z* = 4:96); colorless oil.

IR (neat): 2972, 2875, 1713, 1625, 1599, 1433, 1260, 1209 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.16 (t, *J* = 7.6 Hz, 3 H), 1.67 (s, 3 H), 2.46 (q, *J* = 7.6 Hz, 2 H), 3.66 (s, 3 H), 7.13–7.21 (m, 2 H), 7.23–7.39 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.9, 20.2, 29.2, 51.5, 126.9, 128.1, 129.4, 129.4, 138.1, 149.9, 168.8.

Methyl (*E*)-3,4-Dimethyl-2-phenylpent-2-enoate ((*E*)-1i-2)

Yield: 56 mg (51%, *E*/*Z* = 96:4); colorless oil.

IR (neat): 2962, 2871, 1713, 1620, 1433, 1292, 1225, 1206 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.94 (d, *J* = 6.9 Hz, 6 H), 1.99 (s, 3 H), 2.55 (sept, *J* = 6.9 Hz, 1 H), 3.65 (s, 3 H), 7.13–7.19 (m, 2 H), 7.27–7.37 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 20.2, 31.8, 51.5, 126.9, 128.1, 129.2, 138.0, 153.1, 169.2.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{18}O_2Na$: 241.1204; found: 241.1193.

Methyl (*Z*)-3,4-Dimethyl-2-phenylpent-2-enoate ((*Z*)-1i-2)

Yield: 78 mg (71%, *E*/*Z* = 2:>98); colorless oil.

IR (neat): 2961, 1715, 1599, 1433, 1291, 1229, 1205, 1089 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.11 (d, *J* = 6.5 Hz, 6 H), 1.56 (s, 3 H), 3.17 (sept, *J* = 6.9 Hz, 1 H), 3.68 (s, 3 H), 7.14–7.22 (m, 2 H), 7.23–7.38 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 20.8, 32.5, 51.6, 127.0, 128.1, 129.2, 129.3, 137.8, 150.4, 169.4.

Methyl (*E*)-2,3-Diphenylbut-2-enoate ((*E*)-1i-3)[3]

Yield: 111 mg (88%, *E*/*Z* = 71:29); colorless oil.

Methyl (*Z*)-2,3-Diphenylbut-2-enoate ((*Z*)-1i-3)[3]

Yield: 114 mg (91%, *E*/*Z* = 19:81); colorless oil.

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Methyl (*E*)-2,4-Dimethyl-3-(tosyloxy)pent-2-enoate ((*E*)-3b-1)

Yield: 31 mg (16%, *E*/*Z* = >98:2); colorless oil.

IR (neat): 1720, 1362, 1276, 1176, 1109, 1012 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.02 (d, *J* = 6.9 Hz, 6 H), 1.87 (s, 3 H), 2.47 (s, 3 H), 3.38–3.47 (m, 1 H), 3.76 (s, 3 H), 7.37 (d, *J* = 8.0 Hz, 2 H), 7.86 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.3, 19.5 (2 C), 21.7, 31.3, 52.0, 120.6, 127.7 (2 C), 129.7 (2 C), 134.6, 145.0, 161.6, 168.3.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{20}O_5SNa$: 335.0929; found: 335.0927.

Methyl (*E*)-3-Cyclopropyl-2-methyl-3-(((4-nitrophenyl)sulfonyl)oxy)acrylate ((*E*)-3a-2)

Yield: 51 mg (30%, *E*/*Z* = 91:9); colorless oil.

IR (neat): 1717, 1533, 1350, 1311, 1190, 1013 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.60–0.64 (m, 2 H), 0.70–0.75 (m, 2 H), 1.78 (s, 3 H), 7.05–7.18 (m, 1 H), 2.05–2.18 (m, 1 H), 3.79 (s, 3 H), 8.18 (d, *J* = 8.7 Hz, 2 H), 8.43 (d, *J* = 8.7 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 7.2 (2 C), 14.0, 14.9, 52.1, 124.4, 129.2, 142.7, 150.8, 156.8, 167.8.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{15}NO_7SNa$: 364.0467; found: 364.0448.

Methyl (*E*)-2,4-Dimethyl-3-(((4-nitrophenyl)sulfonyl)oxy)pent-2-enoate ((*E*)-3b-2)

Yield: 70 mg (41%, *E*/*Z* = >98:2); colorless oil.

IR (neat): 1717, 1533, 1350, 1277, 1184, 1109, 1007 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.02 (d, *J* = 6.8 Hz, 6 H), 1.88 (s, 3 H), 3.41–3.51 (m, 1 H), 3.78 (s, 3 H), 8.19 (d, *J* = 8.2 Hz, 2 H), 8.44 (d, *J* = 8.2 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.4, 19.5, 31.2, 52.2, 121.0, 124.4, 128.9, 142.9, 150.7, 161.4, 167.9.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{17}NO_7SNa$: 366.0623; found: 366.0623.

Methyl (*E*)-3-(3-(Benzyloxy)phenyl)-3-cyclopropyl-2-methylacrylate ((*E*)-4a)

Yield: 56 mg (88%, *E*/*Z* = 86:14); colorless oil.

IR (neat): 1709, 1574, 1431, 1319, 1255, 1194, 1107, 1047 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.26–0.30 (m, 2 H), 0.62–0.67 (m, 2 H), 1.59 (s, 3 H), 2.59–2.64 (m, 1 H), 3.81 (s, 3 H), 5.05 (s, 2 H), 6.54–6.56 (m, 2 H), 6.88–6.90 (m, 1 H), 7.24 (t, *J* = 8.0 Hz, 1 H), 7.30–7.43 (m, 5 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 5.5 (2 C), 14.6, 18.0, 51.3, 70.0, 113.6, 115.0, 121.2, 124.4, 127.5 (2 C), 128.0, 128.6 (2 C), 129.1, 136.8, 138.9, 151.6, 158.4, 170.5.

Methyl (*Z*)-3-(3-(Benzyloxy)phenyl)-3-cyclopropyl-2-methylacrylate ((*Z*)-4a)[9]

Yield: 75 mg (86%, *E*/*Z* = 2:>98); colorless oil.

IR (neat): 1717, 1575, 1431, 1321, 1249, 1192, 1028 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.29–0.31 (m, 2 H), 0.70–0.74 (dq, *J* = 8.0 Hz, 2 H), 1.80–1.85 (m, 1 H), 2.14 (s, 3 H), 3.34 (s, 3 H), 5.04 (s, 2 H), 6.57 (d, *J* = 8.0 Hz, 1 H), 6.60 (s, 1 H), 6.85 (d, *J* = 8.0 Hz, 1 H), 7.17 (t, *J* = 8.0 Hz, 1 H), 7.30–7.43 (m, 5 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 5.6 (2 C), 14.4, 15.5, 51.1, 69.8, 113.4, 114.9, 121.3, 126.0, 127.4 (2 C), 127.8, 128.4, 128.5 (2 C), 137.0, 140.3, 148.9, 157.9, 170.1.

Methyl (*E*)-3-(3-(Benzyloxy)phenyl)-2,4-dimethylpent-2-enoate ((*E*)-4b)

Yield: 41 mg (64%, *E*/*Z* = 95:5); colorless oil.

IR (neat): 1717, 1576, 1456, 1259, 1205, 1130, 1028 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.92 (d, *J* = 6.9 Hz, 6 H), 1.56 (s, 3 H), 3.24–3.30 (m, 1 H), 3.79 (s, 3 H), 5.06 (s, 2 H), 6.60–6.62 (m, 2 H), 6.90–6.92 (m, 1 H), 7.24 (t, *J* = 8.0 Hz, 1 H), 7.32–7.45 (m, 5 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.4, 21.4 (2 C), 31.9, 51.5, 70.0, 113.2, 115.3, 121.3, 124.5, 127.5 (2 C), 127.9, 128.5 (2 C), 128.9, 136.9, 139.7, 152.6, 158.3, 170.8.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{20}O_5SNa$: 347.1623; found: 347.1643.

Methyl (*Z*)-3-(3-(Benzyloxy)phenyl)-2,4-dimethylpent-2-enoate ((*Z*)-4b)

Yield: 92 mg (57%, *E*/*Z* = 33:67); colorless oil.

IR (neat): 1712, 1574, 1431, 1314, 1204, 1132, 1028 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.93 (d, *J* = 6.9 Hz, 6 H), 2.02 (s, 3 H), 2.99–3.07 (m, 1 H), 3.32 (s, 3 H), 5.05 (s, 2 H), 6.61–6.65 (m, 2 H), 6.86–6.88 (m, 1 H), 7.18 (t, *J* = 8.0 Hz, 1 H), 7.29–7.43 (m, 5 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.0, 20.7 (2 C), 30.5, 51.1, 69.8, 113.1, 115.2, 121.5, 125.4, 127.4 (2 C), 127.8, 128.2, 128.5 (2 C), 137.1, 141.0, 151.5, 157.8, 170.8.

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Supporting Information

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(10) A 50 g-scale preparation was performed by Ti-Claisen self-condensation using methyl hexanoate with $TiCl_4$ and Et_3N at 0–5 °C for 1 h (93% yield); see ref. 3.

(11) Tendency of (*E*/*Z*)-selectivities under the conditions [K_2CO_3/*i*PrOH–H_2O (7:1), 60 °C, 2 h] was as follows: $Pd(OAc)_2$/SPhos, 80:20; $Pd(OAc)_2$/DavePhos, 70:30; $Pd(dppe)Cl_2$, 62:38; $Pd(PPh_3)_4$, 60:40; $Pd(PPh_3)_2Cl_2$, 53:47; $Pd(OAc)_2$/XPhos, 47:53; $Pd(dppf)Cl_2$, 46:54; $Pd(dppb)Cl_2$, 39:61; $Pd(OAc)_2/PCy_3$, 24:76. The solvent effect on (*E*/*Z*)-selectivities using (*E*)-**2a** under the identical conditions was as follows: THF, 14:86; toluene, 18:82.

(12) Negishi cross-coupling reactions are generally more reactive with regard to catalyst loading than SM cross-coupling reactions (ref. 6). Against this outcome in the previous report, the present SM cross-coupling protocol using $Pd(OAc)_2$/SPhos/*i*Pr_2NEt catalysis displayed sufficient reactivity.

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