A General and Robust Method for the Preparation of (E)- and (Z)-Stereodefined Fully Substituted Enol Tosylates: Promising Cross-Coupling Partners

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Abstract A robust method for preparing (E)- and (Z)-stereodefined fully substituted enol tosylates is described. α-Substituted β-keto esters undergo (E)-selective enol tosylations using TsCl–Me2N(CH2)6NMe2 as the reagent (method A, 13 examples; 63–96%) and (Z)-selective enol tosylations using TsCl–TMEDA–LiCl as the reagent (method B, 13 examples; 62–99%). A plausible mechanism for the (E)- and (Z)-enol tosylate selectivity is proposed. A 1H NMR monitoring experiment revealed that TsCl coupled with TMEDA formed a simple N-sulfonylammonium intermediate.

Key words stereocomplementary, stereodefined olefin, enol tosylate, tosyl chloride, TMEDA, diamine, NMR monitoring

Acyclic (E)- and (Z)-enol sulfonates (tosylates, triflates, etc.) and phosphonates derived from readily accessible β-keto esters are well-recognized synthetic precursors of stereodefined olefins produced using stereoretentive cross-coupling methodology.1 A number of biologically active compounds and functionally useful materials comprise these acyclic stereodefined olefins. Among several enol sulfonates, (E)- and (Z)-enol tosylates are particularly advantageous due to their stability, cost-effectiveness, and sufficient reactivity from the standpoints of fine and natural product synthesis and process chemistry. Representative examples of the synthetic utility of (E)- and (Z)-stereodefined enol sulfonates are addressed as follows.

The Merck process group disclosed a characteristic protocol for (E)- and (Z)-stereocomplementary enol tosylations of specific α- or γ-nitrogen-substituted β-keto esters using respective Ts2O–M(Li or Na)HMDS and Ts2O–amine reagents.2 The obtained stereodefined enol tosylate scaffolds were successfully subjected to stereoretentive Suzuki–Miyaura (SM) cross-couplings for the synthesis of various pharmaceutical precursors.

As part of our ongoing studies on mild but powerful sulfonylations3 and silylations4 of various alcohols and carbonyl compounds, we previously presented a series of (E)- and (Z)-stereocomplementary enol tosylations of not only acyclic ‘α-nonsubstituted’ β-keto esters (R1 = alkyl or aryl, R2 = H), but also α-formyl esters (R1 = H, R2 = alkyl or aryl), which were conducted by the TsCl–N-methylimidazole (NMI)–base system (Scheme 1). TsCl–NMI–Et3N was used for the (E)-selective reactions, whereas TsCl–NMI–LiOH controlled the (Z)-selective reactions. Subsequent highly (E)- and (Z)-stereoretentive cross-couplings (Negishi,5a Sonogashira,5a SM,5b,d and Kochi–Fürstner5c) were successfully performed to produce the corresponding stereodefined α,β-unsaturated esters. The current privileged robust and cost-effective protocols have been adopted for the synthesis of elaborated natural and unnatural compounds, such as juvenile hormones 0 and I,6a,b functionalized steroids,6c madangamine A,6,d (E)- and (Z)-zimelidines,5d etc.

Very recently, the Merck process group reported a synthesis of chiral β-cyclopropyl-α-methylhydrocin namates.7 This notable pharmacophore was synthesized via (E)- and (Z)-stereocomplementary enol tosylations using a β-cyclopropyl-α-methyl-β-keto ester; the (E)-isomer was prepared using Ts2O–NaHMDS at –78 °C, whereas the (Z)-isomer was prepared using the same reagent at room temperature.

On the other hand, our group recently reported (E)- and (Z)-stereocomplementary enol phosphorylations of ‘α-substituted’ β-keto esters as a relevant approach:8 the (PhO)3POCl–NMI–LiOt–Bu reagent being used for preparing (E)-isomers, whereas the (PhO)3POCl–NMI–KOt–Bu–18-
crown-6 reagent was employed for the (Z)-isomers. The application of this protocol to (E)- and (Z)-stereoretentive SM and Negishi cross-couplings produced the corresponding stereodefined all-carbon (fully) substituted α,β-unsaturated esters. This approach, however, has several conspicuous drawbacks compared with the reaction sequence via the enol tosylation; these include: (i) harsher reaction conditions (DMF, reflux) for the SM cross-coupling due to the poor reactivity of the (PhO)2PO- group, (ii) lower atom economy of the (PhO)2PO- group, (iii) a considerably more tedious separation procedure of (E)- and (Z)-enol phosphonates by column chromatography due to their similar Rf values, and (iv) stoichiometric amounts of expensive and highly toxic 18-crown-6 are required.

This background prompted us to search for a more efficient enol tosylation method using less reactive ‘α-carbon-substituted’ β-keto esters 1 (R1, R2 = alkyl and/or aryl). We present herein a substrate-general and robust method for (E)- and (Z)-stereocomplementary enol tosylation of 1 using the TsCl–Me2N(CH2)nNMe2 reagent for (E)-enol tosylates (E)-2 and the TsCl–TMEDA–LiCl reagent for (Z)-enol tosylates (Z)-2.

Our initial attempt was intentionally guided using stereocongested methyl 2-butyl-3-oxooctanoate (1a) as a much less reactive substrate probe (Table 1). As anticipated, the reported NMI-mediated method resulted in almost no reaction (Table 1, entries 1 and 2). Notably, the use of inexpensive Me2N(CH2)nNMe2 (n = 3 or 6) alone afforded posi-

### Table 1 (E)- and (Z)-Stereocomplementary Enol Tosylation of 1a Using TsCl–N,N,N′,N′-Tetramethyldiamine Base with or without Additive

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Additive</th>
<th>Solvent</th>
<th>Yield (%)</th>
<th>E/Z</th>
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<td>Et3N</td>
<td>NMI</td>
<td>C6H5Cl</td>
<td>NR</td>
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<tr>
<td>2</td>
<td>DODt-Bu</td>
<td>NMI, 18-crown-6</td>
<td>THF</td>
<td>trace</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>TMEDA</td>
<td>-</td>
<td>MeCN</td>
<td>17</td>
<td>97/3</td>
</tr>
<tr>
<td>4</td>
<td>Me2N(CH2)nNMe2</td>
<td>-</td>
<td>MeCN</td>
<td>48</td>
<td>93/7</td>
</tr>
<tr>
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<td>Me2N(CH2)nNMe2</td>
<td>-</td>
<td>MeCN</td>
<td>44</td>
<td>94/6</td>
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<td>6</td>
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<td>MeCN</td>
<td>74,6 60c</td>
<td>98/2</td>
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<tr>
<td>7</td>
<td>Me2N(CH2)nNMe2</td>
<td>-</td>
<td>EtOAc, DMF, THF, toluene</td>
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<td>-</td>
</tr>
<tr>
<td>8</td>
<td>TMEDA</td>
<td>LiCl</td>
<td>MeCN</td>
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<td>50</td>
<td>2/98</td>
</tr>
<tr>
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<td>MeCN</td>
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<td>2/98</td>
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<td>MeCN</td>
<td>66</td>
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<tr>
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<td>MeCN</td>
<td>trace (33)d</td>
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<td>LiCl</td>
<td>toluene/MeCN (1:1)</td>
<td>11 (43)d</td>
<td>36/64</td>
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</table>

* Determined by 1H NMR of the crude products. NR = no reaction.
* Reaction conditions: –15°C, 1 h and 20–25°C, 1 h.
* Yield of isolated product.
* α-Chlorinated by-product of 1a; see the experimental section.
tive results for the (E)-selective reaction to give the desired enol tosylate (E)-2a (Table 1, entries 3–5). When using TMEDA, less reactive alcohols are prone to resist the tosylation reaction concomitant with the side production of TsNMe$_2$ via Hoffmann degradation of TMEDA with TsCl. This information led us to use Me$_2$N(CH$_2$)$_n$NMe$_2$ (n = 3 or 6).

Optimization of the temperature and time (−15 °C, 1 h and 20–25 °C, 1 h) allowed for improvement in both the yield (74%) and the stereoselectivity (E/Z = >98:2) (Table 1, entry 6). The best solvent was MeCN; EtOAc, DMF, THF, and toluene were apparently inferior (Table 1, entry 7). On the other hand, the (Z)-selective reaction proceeded smoothly to give (Z)-2b in good yield (93%) with excellent selectivity (E/Z = 2:98) using the available combined reagent, TsCl–TMEDA–LiCl under very accessible conditions (0–5 °C, 1 h). The use of TMEDA produced satisfactory results eventually compared with Me$_2$N(CH$_2$)$_n$NMe$_2$ (n = 3 or 6) (Table 1, entries 8–12). EtOAc and toluene gave moderate yields and the best solvent was MeCN (Table 1, entries 8–10).

In the two cases using Et$_3$N and LHMDS, considerable amounts of the α-chlorinated by-product (methyl 2-butyl-2-chloro-3-oxoacetanoate) of 1a were detected (Table 1, entries 13 and 14). The occurrence of this side reaction is ascribed to the nature of intrinsically more stable (Z)-isomers. Fortunately, these crude products could be enriched to the pure (E)- and (Z)-2d, determined unambiguous assignments (Figure 1).

With the successful outcome in hand, Table 2 lists the substrate generality using a variety of α-substituted β-keto esters 1 [method A for (E)-isomers (E)-2 and method B for (Z)-isomers (Z)-2]. The salient features are as follows. (i) All reactions were completed under the identical optimized conditions in good to excellent yield. (ii) With regard to stereoselectivity, almost all cases produced positive and excellent results (>94:6 for method A and 2:98:9 for method B). (iii) As a limitation, the (E)-selectivity using α,β-dialky substated (E)-1j and (E)-1k was moderate (Table 2, entries 19 and 21). This tendency coincides with discussions in the precedent report which ascribes to the nature of intrinsically more stable (Z)-isomers. Fortunately, these crude products could be enriched to the pure (E)-products, (E)-2j and (E)-2k, by recrystallization. It should be noted that all of these stereodefined (E)- and (Z)-enol tosylates 2 are novel compounds.

Next, an extension to α-heteroatom (MeO and Cl) substituted β-keto esters 1l and 1m was examined (Scheme 2). Gratifyingly, the reactions proceeded smoothly to give the desired functionalized products (E)-1l and (E)-1m. (Note: due to the sequence rule, reverse configurations are indicated.)

The (E)- and (Z)-stereochemistry was determined on the basis of the hitherto reported study. In addition, NOE measurements exemplified by enol tosylates (E)-2d and (Z)-2d, determined unambiguous assignments (Figure 1).

A plausible mechanism for the successful emergence of (E)- and (Z)-enol tosylation selectivity is illustrated in Scheme 3. The (E)-selective reaction with highly reactive intermediate I proceeds via a non-chelation pathway to give (E)-2; Me$_2$N(CH$_2$)$_n$NMe$_2$ plays two different roles as a base reagent and as a partner of I through equilibrium. Me$_2$N(CH$_2$)$_n$NMe$_2$ aids (E)-enolate formation through dipole–dipole repulsive interactions between the oxy anion and ester function. In clear contrast, the (Z)-selective reaction proceeds via a chelation mechanism to give (Z)-2; the Li cation facilitates (Z)-enolate formation.

As depicted in Scheme 4 and Figure 2, a careful $^1$H NMR monitoring experiment (−40 °C in CD$_3$CN) revealed that TsCl coupled with TMEDA formed a simple N-sulfonlammonium intermediate 1A rather than a plausible $N,N'$-chelate-type intermediate IB (see a brief discussion in the Supporting Information).
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Shifts of the tosyl moiety in IA are related to the higher reactivity of the present system. Based on the result, IA is likely to function as the key active species.15,16

In conclusion, we have developed a general and convenient protocol for (E)- and (Z)-stereocomplementary enol tosylation of \( \alpha \)-substituted \( \beta \)-keto esters using the TsCl–Me₂N(CH₂)₆NMe₂ reagent (method A) and the TsCl–TMEDA–LiCl reagent (method B), respectively. A plausible mechanism for the successful (E)- and (Z)-enol tosylation selectivity is proposed. A \(^1\)H NMR monitoring experiment revealed that TsCl coupled with TMEDA formed a simple \( N \)-sulfonylammonium intermediate. Further investigation on various (E)- and (Z)-stereoretentive cross-couplings using the obtained fully substituted enol tosylates, a pair of latent and potential scaffolds, is now under progress in our laboratory.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R(^1)</th>
<th>R(^2)</th>
<th>Substrate</th>
<th>Method</th>
<th>Product</th>
<th>Yield (%)</th>
<th>( E/Z )(^{2a} )</th>
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<tr>
<td>1</td>
<td>Me</td>
<td>n-Bu</td>
<td>1b</td>
<td>A</td>
<td>(E)-2b</td>
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<td>97/3</td>
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<tr>
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<td>Me</td>
<td>n-Bu</td>
<td>1b</td>
<td>B</td>
<td>(Z)-2b</td>
<td>95</td>
<td>2/&gt;98</td>
</tr>
<tr>
<td>3(^b)</td>
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<td>1c</td>
<td>A</td>
<td>(E)-2c</td>
<td>84</td>
<td>&gt;98/2</td>
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<tr>
<td>4(^c)</td>
<td>Me</td>
<td>i-Pr</td>
<td>1c</td>
<td>B</td>
<td>(Z)-2c</td>
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<td>2/&gt;98</td>
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<tr>
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<td>B</td>
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<td>85</td>
<td>2/&gt;98</td>
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<td>63</td>
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<td>91</td>
<td>2/&gt;98</td>
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<td>n-Bu</td>
<td>1a</td>
<td>A</td>
<td>(E)-2a</td>
<td>74</td>
<td>&gt;98/2</td>
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<td>B</td>
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<td>(Z)-2h</td>
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<td>Ph</td>
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<td>96 (49)(^{d} )</td>
<td>74/26 (&gt;98/2)</td>
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<td>Ph</td>
<td>Ph</td>
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<td>B</td>
<td>(Z)-2j</td>
<td>93</td>
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</tr>
<tr>
<td>21</td>
<td>p-MeOC₆H₄</td>
<td>Ph</td>
<td>1k</td>
<td>A</td>
<td>(E)-2k</td>
<td>95 (26)(^{d} )</td>
<td>66/34 (&gt;98/2)</td>
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<tr>
<td>22</td>
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<td>Ph</td>
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<td>B</td>
<td>(Z)-2k</td>
<td>99</td>
<td>2/&gt;98</td>
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\(^a\) Determined by \(^1\)H NMR of the crude products.
\(^b\) TsCl (3.0 equiv) and Me₂N(CH₂)₆NMe₂ (3.0 equiv) were used.
\(^c\) TsCl (3.0 equiv), TMEDA (3.0 equiv), and LiCl (3.0 equiv) were used.
\(^d\) Yield after recrystallization; see the experimental section for details.
All reactions were carried out in oven-dried glassware under an argon atmosphere. Flash column chromatography was performed with silica gel (Merck 60, 230–400 mesh ASTM). TLC analysis was performed on 0.25 mm silica gel Merck 6 F254 plates. Melting points were determined on a hot stage microscope apparatus (AS ONE, ATM-01) and are uncorrected. IR spectra were recorded on a JASCO FT/IR-5300 spectrometer. NMR spectra were recorded on a JEOL DELTA 300 or JEOLRESONANCE ECX-500 spectrometer, operating at 300 MHz or 500 MHz for 1H NMR and 75 MHz or 125 MHz for 13C NMR. Chemical shifts (δ) (ppm) in CDCl₃ are reported downfield from TMS (0 ppm) for 1H NMR. For 13C NMR, chemical shifts are reported relative to CDCl₃ (77.00 ppm) as an internal reference. Mass spectra were measured on a JEOL JMS-T100LC spectrometer. β-Keto esters 1a, 1b, 1c, 1d, 1e, 1g, 1h, 1i, and 1j are known compounds, whilst 1f, 1k, and 1m are new compounds and were prepared by Ti-Claisen condensation or alkylation in a single step and on gram scale. Detailed procedures and physical and spectroscopic data are described in the Supporting Information.

(E)-Enol Tosylation of β-Keto Esters (Method A); General Procedure

TsCl (286 mg, 1.50 mmol) in MeCN (1.0 mL) was added to a stirred suspension of a β-keto ester (1.00 mmol) and Me₂N(CH₂)₆NMe₂ (258 mg, 1.50 mmol) in MeCN (1.0 mL) at −15 °C, and the mixture was stirred at the same temperature for 1 h and at 20–25 °C for 1 h. H₂O (a large amount) was added to the mixture, which was extracted twice with EtOAc. The combined organic phase was washed with H₂O, sat. aq NaHCO₃ solution and brine, then dried (Na₂SO₄), and concentrated. The obtained crude product was purified by SiO₂ column chromatography (hexane/EtOAc = 50:1 to 10:1) to give the desired product.

(Z)-Enol Tosylations of β-Keto Esters (Method B); General Procedure

TsCl (286 mg, 1.50 mmol) in MeCN (1.0 mL) was added to a stirred suspension of a β-keto ester (1.00 mmol), TMEDA (258 mg, 1.50 mmol), and LiCl (64 mg, 1.50 mmol) in MeCN (1.0 mL) at 0–5 °C, and the mixture was stirred at the same temperature for 1 h and at 20–25 °C for 1 h. H₂O (a large amount) was added to the mixture, which was extracted twice with EtOAc. The combined organic phase was washed with H₂O, sat. aq NaHCO₃ solution and brine, then dried (Na₂SO₄), and concentrated. The obtained crude product was purified by SiO₂ column chromatography (hexane/EtOAc = 50:1 to 10:1) to give the desired product.

(E)-2a (Method A); Typical Gram-Scale Procedure

TsCl (4.29 g, 22.5 mmol) in MeCN (15 mL) was added to a stirred suspension of methyl 2-buty-3-oxooctanoate (1a) (3.42 g, 15.0 mmol) and Me₂N(CH₂)₆NMe₂ (4.85 mL, 22.5 mmol) in MeCN (15 mL) at −15 °C, and the mixture was stirred at the same temperature for 1 h and at 20–25 °C for 1 h. H₂O (a large amount) was added to the mixture, which was extracted twice with EtOAc. The combined organic phase was washed with H₂O, sat. aq NaHCO₃ solution and brine, then dried (Na₂SO₄), and concentrated. The obtained crude product was purified by SiO₂ column chromatography (hexane/EtOAc = 15:1) to give the desired product (E)-2a (3.46 g, 60%, E/Z = 98/2).

(Z)-2a (Method B); Typical Gram-Scale Procedure

TsCl (4.29 g, 22.5 mmol) in MeCN (15 mL) was added to a stirred suspension of methyl 2-buty-3-oxooctanoate (1a) (3.42 g, 15.0 mmol), TMEDA (3.35 mL, 22.5 mmol), and LiCl (954 mg, 22.5 mmol) in MeCN (15 mL) at 0–5 °C, and the mixture was stirred at the same temperature for 1 h and at 20–25 °C for 1 h. H₂O was added to the mixture, which was extracted twice with EtOAc. The combined organic phase was washed with H₂O, sat. aq NaHCO₃ solution and brine, then dried (Na₂SO₄), and concentrated. The obtained crude product was purified by SiO₂ column chromatography (hexane/EtOAc = 10:1) to give the desired product (Z)-2a (4.74 g, 82%, E/Z = 2/98).

Methyl (E)-2-Butyl-3-(tosyloxy)oct-2-enoate [(E)-2a]

Yield: 282 mg (74%); colorless oil.
Yield: 312 mg (95%); colorless oil.

IR (neat): 2956, 1720, 1435, 1374 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 0.81 (t, J = 7.2 Hz, 3 H), 0.82 (t, J = 7.2 Hz, 3 H), 1.10–1.27 (m, 8 H), 1.43 (quin, J = 7.2 Hz, 2 H), 2.18 (t, J = 7.2 Hz, 2 H), 2.46 (s, 3 H), 2.60 (t, J = 7.6 Hz, 2 H), 3.74 (s, 3 H), 7.31–7.40 (m, 2 H), 7.80–7.88 (m, 2 H).

13C NMR (75 MHz, CDCl₃): δ = 13.6, 13.8, 21.9, 22.1, 22.4, 26.7, 27.6, 30.2, 31.0, 32.0, 51.8, 125.8, 127.7 (2 C), 129.8 (2 C), 134.2, 145.2, 156.6, 168.1.


Methyl (Z)-2-Butyl-3-(tosyloxy)oct-2-enoate [(Z)-2a]

Yield: 263 mg (81%); colorless oil.

IR (neat): 2956, 1719, 1650, 1598, 1435, 1372, 1279, 1088 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 0.78–0.95 (m, 6 H), 1.12–1.53 (m, 10 H), 2.25 (t, J = 7.6 Hz, 2 H), 2.31 (t, J = 7.6 Hz, 2 H), 2.45 (s, 3 H), 3.59 (s, 3 H), 7.29–7.38 (m, 2 H), 7.75–7.85 (m, 2 H).

13C NMR (75 MHz, CDCl₃): δ = 13.7 (2 C), 21.5, 22.1, 22.2, 22.6, 29.0, 30.8, 31.1, 51.7, 125.0, 127.9 (2 C), 129.6 (2 C), 134.0, 144.9, 151.2, 167.1.


Methyl (Z)-2-Butyl-3-(tosyloxy)oct-2-enoate [(Z)-2b]

Yield: 312 mg (95%); colorless oil.

IR (neat): 2956, 1724, 1598, 1370, 1306, 1196, 1164, 1090 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 0.88 (t, J = 7.2 Hz, 3 H), 1.21–1.42 (m, 4 H), 2.02 (s, 3 H), 2.23 (t, J = 7.2 Hz, 2 H), 2.44 (s, 3 H), 3.74 (s, 3 H), 7.30–7.39 (m, 2 H), 7.75–7.84 (m, 2 H).

13C NMR (75 MHz, CDCl₃): δ = 13.5, 13.7, 21.4, 22.0, 28.9, 30.2, 51.5, 124.7, 127.8 (2 C), 129.5 (2 C), 133.5, 147.3, 166.6.

Methyl 2-Butyl-2-chloro-3-oxooctanoate (By-Product; Figure 3)

Figure 3 Structure of by-product
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Synthesis

Methyl (E)-7-Chloro-2-methyl-3-(tosyloxy)hept-2-enoate [(E)-2e]:
Yield: 276 mg (77%); pale yellow oil.
IR (neat): 2952, 1719, 1648, 1435, 1371, 1278, 1191, 1177 cm⁻¹.
¹H NMR (300 MHz, CDCl₃): 2.75 (t, J = 6.5 Hz, 2 H), 3.46 (t, J = 6.5 Hz, 2 H), 3.75 (s, 3 H), 7.34−7.41 (m, 2 H), 7.81−7.88 (m, 2 H).
¹³C NMR (75 MHz, CDCl₃): δ = 13.7, 21.4, 24.0, 31.1, 31.5, 44.2, 51.8, 121.3, 127.6 (2 C), 129.8 (2 C), 133.7, 145.4, 154.7, 167.5.

Methyl (Z)-2-Methyl-3-phenyl-3-(tosyloxy)prop-2-enoate [(Z)-2g]:
Yield: 312 mg (90%); colorless oil.
IR (neat): 2952, 1715, 1598, 1434, 1374, 1308, 1255, 1002 cm⁻¹.
¹H NMR (300 MHz, CDCl₃): δ = 1.94 (s, 3 H), 2.35 (s, 3 H), 3.81 (s, 3 H), 7.04−7.10 (m, 2 H), 7.14−7.30 (m, 5 H), 7.38−7.45 (m, 2 H).
¹³C NMR (75 MHz, CDCl₃): δ = 15.6, 21.1, 51.8, 120.9, 127.5 (2 C), 127.6 (2 C), 128.9 (2 C), 129.0 (2 C), 129.1, 131.8, 133.7, 144.3, 147.9, 166.9.

Methyl (E)-2-Methyl-3-(4-tolyl)-3-(tosyloxy)prop-2-enoate [(E)-2h]:
Yield: 864 mg (80%) (3 mmol scale); colorless oil.
IR (neat): 1717, 1651, 1597, 1435, 1371, 1240, 1190 cm⁻¹.
¹H NMR (500 MHz, CDCl₃): δ = 2.03 (s, 3 H), 2.29 (s, 3 H), 2.43 (m, 3 H), 3.53 (s, 3 H), 6.92–6.97 (m, 2 H), 7.01–7.06 (m, 2 H), 7.08–7.14 (m, 2 H), 7.43−7.49 (m, 2 H).
¹³C NMR (125 MHz, CDCl₃): δ = 14.6, 21.1, 21.3, 51.6, 122.1, 127.7 (2 C), 128.2 (2 C), 128.5 (2 C), 129.2 (2 C), 130.3, 133.7, 139.2, 144.6, 151.7, 168.4.

Methyl (Z)-2-Methyl-3-(4-tolyl)-3-(tosyloxy)prop-2-enoate [(Z)-2h]:
Yield: 970 mg (89%) (3 mmol scale); colorless crystals; mp 94–96 °C.
IR (neat): 1726, 1645, 1425, 1369, 1258, 1179, 1134 cm⁻¹.
¹H NMR (500 MHz, CDCl₃): δ = 1.92 (s, 3 H), 2.30 (s, 3 H), 2.36 (s, 3 H), 3.78 (s, 3 H), 6.95–7.01 (m, 2 H), 7.04−7.13 (m, 4 H), 7.39−7.46 (m, 2 H).
¹³C NMR (125 MHz, CDCl₃): δ = 15.9, 21.2, 21.4, 52.0, 120.6, 127.9 (2 C), 128.5 (2 C), 129.1 (2 C), 129.2 (2 C), 132.3, 134.0, 140.0, 144.3, 148.5, 167.3.

Methyl (E)-2-Methyl-3-(4-chlorophenyl)-3-(tosyloxy)prop-2-enoate [(E)-2i]:
Yield: 982 mg (94%) (3 mmol scale); colorless crystals; mp 71–73 °C.
IR (neat): 1722, 1651, 1593, 1487, 1371, 1244, 1190 cm⁻¹.
¹H NMR (500 MHz, CDCl₃): δ = 2.06 (s, 3 H), 2.40 (s, 3 H), 3.54 (s, 3 H), 7.04−7.12 (m, 4 H), 7.13−7.17 (m, 2 H), 7.42−7.48 (m, 2 H).
¹³C NMR (125 MHz, CDCl₃): δ = 14.7, 21.5, 52.0, 123.5, 127.8 (2 C), 127.9 (2 C), 129.4 (2 C), 130.2 (2 C), 131.8, 133.7, 135.3, 145.2, 150.5, 168.0.

Methyl (Z)-2-Methyl-3-(4-chlorophenyl)-3-(tosyloxy)prop-2-enoate [(Z)-2i]:
Yield: 1.01 g (96%) (3 mmol scale); colorless oil.
IR (neat): 1732, 1595, 1489, 1435, 1314, 1248, 1161 cm⁻¹.
Yield: 13.04 g (99%) (30 mmol scale); colorless crystals; mp 123–126.1, 127.8 (2 C), 128.2 (2 C), 129.2 (2 C), 129.5, 130.6 (2 C), 133.9, 135.5, 144.8, 146.9, 166.9.

Methyl (E)-2,3-Diphenyl-3-(tosyloxy)prop-2-enoate [(E)-2j]

Yield: 3.91 g (96%, E/Z = 74:26), 2.02 g (49%, E/Z = >98:2 after recrystallization from EtOAc) (10 mmol scale); colorless crystals; mp 149–152 °C.

IR (neat): 1717, 1651, 1595, 1445, 1368, 1302, 1273, 1215, 1175 cm⁻¹.

1H NMR (500 MHz, CDCl₃) : δ = 2.35 (s, 3 H), 3.50 (s, 3 H), 6.94–7.03 (m, 2 H), 7.17–7.50 (m, 12 H).

13C NMR (125 MHz, CDCl₃) : δ = 21.5, 52.3, 127.3, 127.7 (2 C), 128.0 (2 C), 128.1 (1 C), 128.2, 128.6 (2 C), 129.0 (2 C), 129.8 (2 C), 132.2, 133.2, 133.4, 144.6, 149.1, 167.6.


1H NMR (300 MHz, CDCl₃) : δ = 0.85 (t, J = 6.9 Hz, 3 H), 1.16–1.30 (m, 4 H), 1.43 (quin, J = 7.6 Hz, 2 H), 2.40 (t, J = 7.6 Hz, 2 H), 2.46 (s, 3 H), 3.60 (s, 3 H), 3.68 (s, 3 H), 7.30–7.40 (m, 2 H), 7.77–7.87 (m, 2 H).

13C NMR (75 MHz, CDCl₃) : δ = 13.8, 21.6, 22.1, 25.7, 29.1, 31.0, 51.9, 60.2, 128.1 (2 C), 129.6 (2 C), 133.5, 141.1, 145.3, 150.0, 162.2.

Methyl (Z)-2-Chloro-3-(tosyloxy)oct-2-enoate [(Z)-2m]

Yield: 296 mg (82%); colorless oil.

IR (neat): 2959, 2866, 1724, 1615, 1384, 1262, 1180, 1047 cm⁻¹.

1H NMR (300 MHz, CDCl₃) : δ = 0.86 (t, J = 6.9 Hz, 3 H), 1.20–1.33 (m, 4 H), 1.50–1.62 (m, 2 H), 2.47 (s, 3 H), 2.92 (t, J = 7.6 Hz, 2 H), 3.82 (s, 3 H), 7.34–7.40 (m, 2 H), 7.86–7.93 (m, 2 H).

13C NMR (75 MHz, CDCl₃) : δ = 13.7, 21.5, 22.0, 26.5, 30.9, 32.5, 53.0, 116.2, 128.0 (2 C), 129.8 (2 C), 133.6, 145.7, 159.6, 162.7.


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Supporting Information

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(9) The use of LiCl instead of LiOH was also applied by Shinada’s
     group; see refs. 6a and 6b.

(10) The 50 gram-scale preparation of 1a was performed by the self-
     Ti-Claisen condensation using methyl hexanoate with TiCl4 and
     Et3N at 0–5 °C for 1 h (93% yield); see the Supporting Informa-
     tion and ref. 8.

(11) TMEDA: ca. $80/500 g; Me2N(CH2)3NMe2: ca. $110/500 g;
     Me2N(CH2)6NMe2: ca. $90/500 g. Reagent base.

(12) After finishing this work, Et3N and toluene were available for
     reactive not fully, trisubstituted substrates.

(13) This issue is addressed in ref. 2a. To solve the problem, presum-
     ably, the Merck group consistently uses reactive but highly
     expensive Ts2O instead of TsCl.

(14) This monitoring study resembles the case of TsCl–NMI (see refs.
     5a and 5d) and (PhO)2POCl–NMI (see ref. 8) intermediates.

(15) A related monitoring experiment using p-MeC6H4COCl with
     TMEDA was carried out in our hands; noticeable changes of 1H
     NMR spectra were not observed under the identical conditions.
     The interactive action of TsCl, therefore, may be stronger than
     that of benzoyl chlorides.

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