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 acyclic (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, R¹ = 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-Et₂N 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,j functionalized steroids,k madangamine Al,kd (E)- and (Z)-zimelidines,kd etc.

Very recently, the Merck process group reported a synthesis of chiral β-cyclopropyl-α-methylhydroxycinnamates.⁶ 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)₂POCl-NMI-LiOt-Bu reagent being used for preparing (E)-isomers, whereas the (PhO)₂POCl-NMI-KOt-Bu-18-
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An efficient enol tosylation method was developed using less reactive α-carbon-substituted β-keto esters 1 (R1, R2 = alkyl and/or aryl). This approach, however, has several drawbacks compared with the reaction sequence via the enol tosylations: (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 tosylations of 1 using the TsCl–Me2N(CH2)6NMe2 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)3NMe2 (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 ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et3N</td>
<td>NMI</td>
<td>CH2Cl</td>
<td>17</td>
<td>97/3</td>
</tr>
<tr>
<td>2</td>
<td>KOt-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)3NMe2</td>
<td>–</td>
<td>MeCN</td>
<td>48</td>
<td>93/7</td>
</tr>
<tr>
<td>5</td>
<td>Me2N(CH2)3NMe2</td>
<td>–</td>
<td>MeCN</td>
<td>44</td>
<td>94/6</td>
</tr>
<tr>
<td>6</td>
<td>Me2N(CH2)3NMe2</td>
<td>–</td>
<td>MeCN</td>
<td>74, 60%</td>
<td>98/2</td>
</tr>
<tr>
<td>7</td>
<td>Me2N(CH2)3NMe2</td>
<td>–</td>
<td>EtOAc, DMF, THF, toluene</td>
<td>trace</td>
<td>–</td>
</tr>
<tr>
<td>8</td>
<td>TMEDA</td>
<td>LiCl</td>
<td>MeCN</td>
<td>93%</td>
<td>2/&gt;98</td>
</tr>
<tr>
<td>9</td>
<td>TMEDA</td>
<td>LiCl</td>
<td>EtOAc</td>
<td>38</td>
<td>2/&gt;98</td>
</tr>
<tr>
<td>10</td>
<td>TMEDA</td>
<td>LiCl</td>
<td>toluene</td>
<td>50</td>
<td>2/&gt;98</td>
</tr>
<tr>
<td>11</td>
<td>Me2N(CH2)3NMe2</td>
<td>LiCl</td>
<td>MeCN</td>
<td>40</td>
<td>2/&gt;98</td>
</tr>
<tr>
<td>12</td>
<td>Me2N(CH2)3NMe2</td>
<td>LiCl</td>
<td>MeCN</td>
<td>66</td>
<td>27/73</td>
</tr>
<tr>
<td>13</td>
<td>Et3N</td>
<td>LiCl</td>
<td>MeCN</td>
<td>trace(33)%</td>
<td>–</td>
</tr>
<tr>
<td>14</td>
<td>LHMDS</td>
<td>–</td>
<td>toluene/MeCN(1:1)</td>
<td>11(43)%</td>
<td>36/64</td>
</tr>
</tbody>
</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 TsNMe2 via Hoffmann degradation of TMEDA with TsCl. This information led us to use Me2N(CH2)nNMe2 (n = 3 or 6) (Table 1, entries 8–12). EtOAc–TMEDA–LiCl under very accessible conditions (0–5 °C, 1 h) (vide infra) 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)-2a in good yield (93%) with excellent stereoselectivity (E/Z = 2;>98) using the available combined reagent, TsCl–TMEDA–LiCl under very accessible conditions (0–5 °C, 1 h and 20–25 °C, 1 h) (Table 1, entry 8). The use of TMEDA produced satisfactory results eventually compared with Me2N(CH2)nNMe2 (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 Et3N and LHMDS, considerable amounts of the α-chlorinated by-product (methyl 2-butyl-2-chloro-3-oxooctanoate) of 1a were detected (Table 1, entries 13 and 14). The occurrence of this side reaction is ascribed to the fact that TsCl cannot be sufficiently activated by the amine bases. The α-selective reaction with highly reactive alcohols (<94:6 for method A and 2:>98 for method B). (iii) As a limitation, the (E)-selectivity using α,β-diaryl substrates (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 11 and 1m was examined (Scheme 2). Gratifyingly, the reactions proceeded smoothly to give the desired functionalized products (E)-, (Z)-2l and (E)-, (Z)-2m. (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; Me2N(CH2)3NMe2 plays two different roles as a base reagent and as a partner of 1 through equilibrium. Me2N(CH2)3NMe2 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 1H NMR monitoring experiment (–40 °C in CD3CN) revealed that TsCl coupled with TMEDA formed a simple N-sulfonylamine intermediate IA rather than a plausible N,N′-chelate-type intermediate IB (see a brief discussion in the Supporting Information). The apparent downfield chemical
shifts of the tosyl moiety in \(1A\) are related to the higher reactivity of the present system. Based on the result, \(1A\) 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–Me\(_2\)N(CH\(_2\))\(_6\)NMe\(_2\) 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 2 \((E)\)- and \((Z)\)-Stereocomplementary Enol Tosylation of 1 Using TsCl–Me\(_2\)N(CH\(_2\))\(_6\)NMe\(_2\) (Method A) and TsCl–TMEDA–LiCl (Method B)

<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)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>n-Bu</td>
<td>1b</td>
<td>A</td>
<td>((E))-2b</td>
<td>81</td>
<td>97/3</td>
</tr>
<tr>
<td>2</td>
<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(^a)</td>
<td>Me</td>
<td>i-Pr</td>
<td>1c</td>
<td>A</td>
<td>((E))-2c</td>
<td>84</td>
<td>&gt;98/2</td>
</tr>
<tr>
<td>4(^a)</td>
<td>Me</td>
<td>i-Pr</td>
<td>1c</td>
<td>B</td>
<td>((Z))-2c</td>
<td>85</td>
<td>2/&gt;98</td>
</tr>
<tr>
<td>5</td>
<td>n-pentyl</td>
<td>Me</td>
<td>1d</td>
<td>A</td>
<td>((E))-2d</td>
<td>74</td>
<td>&gt;98/2</td>
</tr>
<tr>
<td>6</td>
<td>n-pentyl</td>
<td>Me</td>
<td>1d</td>
<td>B</td>
<td>((Z))-2d</td>
<td>94</td>
<td>2/&gt;98</td>
</tr>
<tr>
<td>7</td>
<td>Cl(CH(_2))(_4)</td>
<td>Me</td>
<td>1e</td>
<td>A</td>
<td>((E))-2e</td>
<td>77</td>
<td>&gt;98/2</td>
</tr>
<tr>
<td>8</td>
<td>Cl(CH(_2))(_4)</td>
<td>Me</td>
<td>1e</td>
<td>B</td>
<td>((Z))-2e</td>
<td>85</td>
<td>2/&gt;98</td>
</tr>
<tr>
<td>9</td>
<td>(\begin{array}{c} R_1 \ | \end{array})</td>
<td>(\begin{array}{c} R_2 \ | \end{array})</td>
<td>1f</td>
<td>A</td>
<td>((E))-2f</td>
<td>63</td>
<td>95/5</td>
</tr>
<tr>
<td>10</td>
<td>(\begin{array}{c} R_1 \ | \end{array})</td>
<td>(\begin{array}{c} R_2 \ | \end{array})</td>
<td>1f</td>
<td>B</td>
<td>((Z))-2f</td>
<td>91</td>
<td>2/&gt;98</td>
</tr>
<tr>
<td>11</td>
<td>n-pentyl</td>
<td>n-Bu</td>
<td>1a</td>
<td>A</td>
<td>((E))-2a</td>
<td>74</td>
<td>&gt;98/2</td>
</tr>
<tr>
<td>12</td>
<td>n-pentyl</td>
<td>n-Bu</td>
<td>1a</td>
<td>B</td>
<td>((Z))-2a</td>
<td>93</td>
<td>2/&gt;98</td>
</tr>
<tr>
<td>13</td>
<td>Ph</td>
<td>Me</td>
<td>1g</td>
<td>A</td>
<td>((E))-2g</td>
<td>89</td>
<td>94/6</td>
</tr>
<tr>
<td>14</td>
<td>Ph</td>
<td>Me</td>
<td>1g</td>
<td>B</td>
<td>((Z))-2g</td>
<td>90</td>
<td>2/&gt;98</td>
</tr>
<tr>
<td>15</td>
<td>p-MeC(_6)(_6)H(_4)</td>
<td>Me</td>
<td>1h</td>
<td>A</td>
<td>((E))-2h</td>
<td>80</td>
<td>94/6</td>
</tr>
<tr>
<td>16</td>
<td>p-MeC(_6)(_6)H(_4)</td>
<td>Me</td>
<td>1h</td>
<td>B</td>
<td>((Z))-2h</td>
<td>89</td>
<td>2/&gt;98</td>
</tr>
<tr>
<td>17</td>
<td>p-CIC(_6)(_6)H(_4)</td>
<td>Me</td>
<td>1i</td>
<td>A</td>
<td>((E))-2i</td>
<td>94</td>
<td>&gt;98/2</td>
</tr>
<tr>
<td>18</td>
<td>p-CIC(_6)(_6)H(_4)</td>
<td>Me</td>
<td>1i</td>
<td>B</td>
<td>((Z))-2i</td>
<td>96</td>
<td>2/&gt;98</td>
</tr>
<tr>
<td>19</td>
<td>Ph</td>
<td>Ph</td>
<td>1j</td>
<td>A</td>
<td>((E))-2j</td>
<td>96 (49)(^d)</td>
<td>74/26 (98/2)</td>
</tr>
<tr>
<td>20</td>
<td>Ph</td>
<td>Ph</td>
<td>1j</td>
<td>B</td>
<td>((Z))-2j</td>
<td>93</td>
<td>2/&gt;98</td>
</tr>
<tr>
<td>21</td>
<td>p-MeOC(_6)(_6)H(_4)</td>
<td>Ph</td>
<td>1k</td>
<td>A</td>
<td>((E))-2k</td>
<td>95 (26)(^d)</td>
<td>66/34 (98/2)</td>
</tr>
<tr>
<td>22</td>
<td>p-MeOC(_6)(_6)H(_4)</td>
<td>Ph</td>
<td>1k</td>
<td>B</td>
<td>((Z))-2k</td>
<td>99</td>
<td>2/&gt;98</td>
</tr>
</tbody>
</table>

\(^a\) Determined by \(^1\)H NMR of the crude products.
\(^b\) TsCl (3.0 equiv) and Me\(_2\)N(CH\(_2\))\(_6\)NMe\(_2\) (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.
**Synthesis**

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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 62F254 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 spectrophotometer. NMR spectra were recorded on a JEOL JMS-T100LC spectrometer.

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**Scheme 3** A mechanistic investigation into the (E)- and (Z)-stereoselective enol tosylation

**Scheme 4** Formation of sulfonylammonium intermediate I monitored by $^1$H NMR measurements at $-40 ^\circ$C

**Figure 2** $^1$H NMR monitoring study using a 1:1 mixture of TsCl and TMEDA at $-40 ^\circ$C

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Yield: 282 mg (74%); colorless oil.
Methyl (Z)-2-Butyl-3-(tosyloxy)oct-2-enoate [(Z)-2a]

Yield: 263 mg (93%); colorless oil.

IR (neat): 2956, 2932, 2872, 1720, 1444, 1358, 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, 18.5, 21.2, 21.4, 22.7, 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 (E)-2-Butyl-3-(tosyloxy)but-2-enoate [(E)-2b]

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

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

1H NMR (300 MHz, CDCl₃): δ = 0.81 (t, J = 6.9 Hz, 3 H), 1.10–1.26 (m, 4 H), 2.17 (t, J = 6.9 Hz, 2 H), 2.27 (s, 3 H), 2.46 (s, 3 H), 3.74 (s, 3 H), 7.33–7.42 (m, 2 H), 7.80–7.88 (m, 2 H).

13C NMR (75 MHz, CDCl₃): δ = 13.6, 19.4, 21.6, 22.5, 27.4, 30.3, 51.8, 125.4, 127.8 (2 C), 129.9 (2 C), 134.1, 145.3, 153.4, 168.0.


Methyl (Z)-2-Butyl-3-(tosyloxy)but-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), 3.57 (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, 18.5, 21.4, 22.0, 28.9, 30.2, 51.5, 124.7, 127.8 (2 C), 129.5 (2 C), 133.5, 145.0, 147.3, 166.6.

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

Figure 3 Structure of by-product
Yield: 327 mg (63%); pale yellow oil.

**IR (neat):** 2952, 1719, 1648, 1435, 1371, 1278, 1191, 1177 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 1.57–1.72 (m, 4 H, 1.73 (s, 3 H, 2.47 (s, 3 H)), 2.75 (t, J = 6.5 H z, 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, 157.4, 167.5.


**Methyl (Z)-2-Chloro-7-methyl-3-(tosyloxy)hept-2-enoate [(Z)-2e]**

Yield: 276 mg (77%); colorless oil.

IR (neat): 2952, 1719, 1648, 1435, 1371, 1278, 1191, 1177 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 1.57–1.72 (m, 4 H, 1.73 (s, 3 H, 2.47 (s, 3 H)), 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, 157.4, 167.5.

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Methyl (Z)-2-Methoxy-3-(tosyloxy)oct-2-enoate ([Z]-2l)

Yield: 322 mg (90%); pale yellow oil.

IR (neat): 2935, 1725, 1642, 1598, 1371, 1297, 1179, 1024 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 0.85 (t, J = 7.6 Hz, 3 H), 1.14–1.34 (m, 4 H), 1.50 (quin, J = 7.6 Hz, 2 H), 2.45 (s, 3 H), 2.71 (t, J = 7.6 Hz, 2 H), 3.42 (s, 3 H), 3.81 (s, 3 H), 7.30–7.37 (m, 2 H), 7.83–7.91 (m, 2 H).

13C NMR (75 MHz, CDCl₃): δ = 13.7, 21.5, 22.1, 26.2, 30.6, 30.9, 52.0, 60.0, 127.8 (2 C), 129.5 (2 C), 134.4, 139.4, 144.9, 151.2, 163.9.


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

Yield: 261 mg (62%); colorless oil.

IR (neat): 2955, 2862, 1734, 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), 2.52 (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.


Methyl (Z)-2-Methoxy-3-(tosyloxy)oct-2-enoate ([Z]-2l)

Yield: 325 mg (91%); pale yellow oil.

IR (neat): 2934, 2862, 1725, 1598, 1436, 1376, 1294, 1208 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 0.84 (t, J = 7.6 Hz, 3 H), 1.11–1.30 (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), 2.52 (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

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1562482.
References


(3) For selected examples, see: (a) Flynn, A. B.; Ogilvie, W. W.

(4) For selected examples, see: (a) Tanabe, Y.; Murakami, M.;

(5) For selected examples, see: (a) Tanabe, Y.; Okumura, H.; Maeda, A.; Murakami, M.


(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 Et2N at 0–5 °C for 1 h (93% yield); see the Supporting Information 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, EtOAc and toluene were available for reactive not fully, trisubstituted substrates.

(13) This issue is addressed in ref. 2a. To solve the problem, presumably, 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. 6a and 6b).

(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.