

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

Yuichiro Ashida

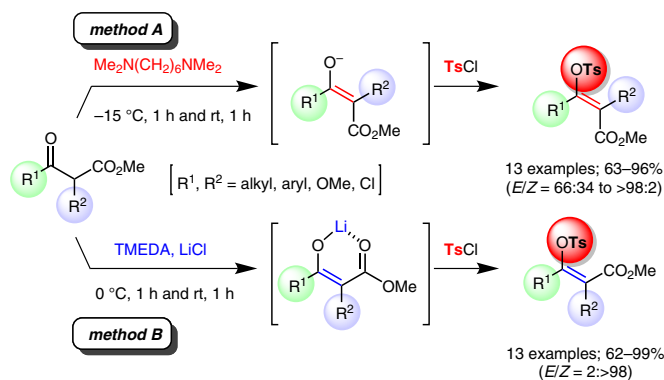
Yuka Sato

Atsushi Honda

Hidefumi Nakatsuji\*

Yoo Tanabe\*

Department of Chemistry, School of Science and Technology,  
Kwansei Gakuin University, 2-1 Gakuen, Sanda, Hyogo, 669-  
1337, Japan  
tanabe@kwansei.ac.jp



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**Abstract** A robust method for preparing (*E*)- and (*Z*)-stereodefined fully substituted enol tosylates is described.  $\alpha$ -Substituted  $\beta$ -keto esters undergo (*E*)-selective enol tosylations using  $\text{TsCl}-\text{Me}_2\text{N}(\text{CH}_2)_6\text{NMe}_2$  as the reagent (method A, 13 examples; 63–96%) and (*Z*)-selective enol tosylations using  $\text{TsCl}-\text{TMEDA}-\text{LiCl}$  as the reagent (method B, 13 examples; 62–99%). A plausible mechanism for the (*E*)- and (*Z*)-enol tosylation selectivity is proposed. A  $^1\text{H}$  NMR monitoring experiment revealed that  $\text{TsCl}$  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  $\beta$ -keto esters are well-recognized synthetic precursors of stereodefined olefins produced using stereoretentive cross-coupling methodology.<sup>1</sup> 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.

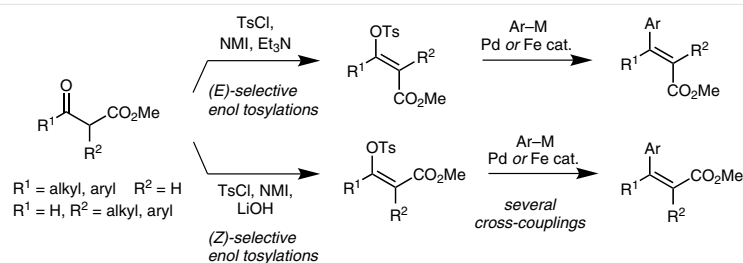
The Merck process group disclosed a characteristic protocol for (*E*)- and (*Z*)-stereocomplementary enol tosylations of specific  $\alpha$ - or  $\gamma$ -nitrogen-substituted  $\beta$ -keto esters using respective  $\text{Ts}_2\text{O}-\text{M}(\text{Li or Na})\text{HMDS}$  and  $\text{Ts}_2\text{O}-\text{amine}$  reagents.<sup>2</sup> 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 sulfonylations<sup>3</sup> and silylations<sup>4</sup> of various alcohols and carbonyl compounds, we previously presented a series of (*E*)- and (*Z*)-stereocomplementary enol tosylations of not only acyclic ' $\alpha$ -nonsubstituted'  $\beta$ -keto esters ( $\text{R}^1 = \text{alkyl or aryl}$ ,  $\text{R}^2 = \text{H}$ ), but also  $\alpha$ -formyl esters ( $\text{R}^1 = \text{H}$ ,  $\text{R}^2 = \text{alkyl or aryl}$ ), which were conducted by the  $\text{TsCl}-\text{N}$ -methylimidazole (NMI)–base system (Scheme 1).  $\text{TsCl}-\text{NMI}-\text{Et}_3\text{N}$  was used for the (*E*)-selective reactions, whereas  $\text{TsCl}-\text{NMI}-\text{LiOH}$  controlled the (*Z*)-selective reactions. Subsequent highly (*E*)- and (*Z*)-stereoretentive cross-couplings (Negishi,<sup>5a</sup> Sonogashira,<sup>5a</sup> SM,<sup>5b,d</sup> and Kochi–Fürstner<sup>5c</sup>) were successfully performed to produce the corresponding stereodefined  $\alpha,\beta$ -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 **1**,<sup>6a,b</sup> functionalized steroids,<sup>6c</sup> madangamine **A**,<sup>6d</sup> (*E*)- and (*Z*)-zimetidines,<sup>5d</sup> etc.

Very recently, the Merck process group reported a synthesis of chiral  $\beta$ -cyclopropyl- $\alpha$ -methyl-dihydrocinamates.<sup>7</sup> This notable pharmacophore was synthesized via (*E*)- and (*Z*)-stereocontrolled enol tosylations using a  $\beta$ -cyclopropyl- $\alpha$ -methyl- $\beta$ -keto ester; the (*E*)-isomer was prepared using  $\text{Ts}_2\text{O}-\text{NaHMDS}$  at  $-78\text{ }^\circ\text{C}$ , 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 ' $\alpha$ -substituted'  $\beta$ -keto esters as a relevant approach,<sup>8</sup> the  $(\text{PhO})_2\text{POCl}-\text{NMI}-\text{LiOt}-\text{Bu}$  reagent being used for preparing (*E*)-isomers, whereas the  $(\text{PhO})_2\text{POCl}-\text{NMI}-\text{KOt}-\text{Bu}-18-$



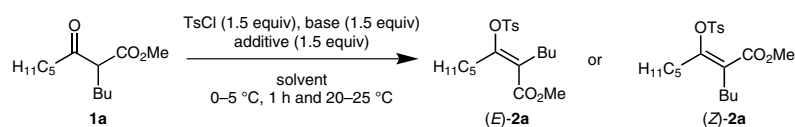
**Scheme 1** (*E*)- and (*Z*)-Stereocomplementary synthesis of (*E*)- and (*Z*)- $\alpha,\beta$ -unsaturated esters utilizing stereoselective enol tosylations and stereoretentive cross-couplings

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  $\alpha,\beta$ -unsaturated esters. This approach, however, has several conspicuous drawbacks compared with the reaction sequence via the enol tosylations; these include: (i) harsher reaction conditions (DMF, reflux) for the SM cross-coupling due to the poor reactivity of the  $(\text{PhO})_2\text{PO-}$  group, (ii) lower atom economy of the  $(\text{PhO})_2\text{PO-}$  group, (iii) a considerably more tedious separation procedure of (*E*)- and (*Z*)-enol phosphonates by column chromatography due to their similar  $R_f$  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 ' $\alpha$ -carbon-substituted'  $\beta$ -keto esters **1** ( $\text{R}^1, \text{R}^2 = \text{alkyl and/or aryl}$ ). We present herein a substrate-general and robust method for (*E*)- and (*Z*)-stereocomplementary enol tosylations of **1** using the  $\text{TsCl-Me}_2\text{N}(\text{CH}_2)_6\text{NMe}_2$  reagent for (*E*)-enol tosylates (*E*-**2**) and the  $\text{TsCl-TMEDA-LiCl}$  reagent for (*Z*)-enol tosylates (*Z*-**2**).<sup>9</sup>

Our initial attempt was intentionally guided using stereocongested methyl 2-butyl-3-oxooctanoate (**1a**)<sup>10</sup> as a much less reactive substrate probe (Table 1). As anticipated, the reported NMI-mediated method<sup>6</sup> resulted in almost no reaction (Table 1, entries 1 and 2). Notably, the use of inexpensive  $\text{Me}_2\text{N}(\text{CH}_2)_n\text{NMe}_2$  ( $n = 3$  or  $6$ )<sup>11</sup> alone afforded posi-

**Table 1** (*E*)- and (*Z*)-Stereocomplementary Enol Tosylation of **1a** Using  $\text{TsCl-N,N,N',N'}$ -Tetramethyldiamine Base with or without Additive



Entry	Base	Additive	Solvent	Yield (%) <sup>a</sup>	<i>E/Z</i> <sup>a</sup>
1	$\text{Et}_3\text{N}$	NMI	$\text{C}_6\text{H}_5\text{Cl}$	NR	–
2	KOt-Bu	NMI, 18-crown-6	THF	trace	–
3	TMEDA	–	MeCN	17	97/3
4	$\text{Me}_2\text{N}(\text{CH}_2)_3\text{NMe}_2$	–	MeCN	48	93/7
5	$\text{Me}_2\text{N}(\text{CH}_2)_6\text{NMe}_2$	–	MeCN	44	94/6
6	$\text{Me}_2\text{N}(\text{CH}_2)_6\text{NMe}_2$	–	MeCN	74, <sup>b</sup> 60 <sup>b,c</sup>	98/2
7	$\text{Me}_2\text{N}(\text{CH}_2)_6\text{NMe}_2$	–	EtOAc, DMF, THF, toluene	trace <sup>b</sup>	–
8	TMEDA	LiCl	MeCN	93 <sup>c</sup>	2/>98
9	TMEDA	LiCl	EtOAc	38	2/>98
10	TMEDA	LiCl	toluene	50	2/>98
11	$\text{Me}_2\text{N}(\text{CH}_2)_3\text{NMe}_2$	LiCl	MeCN	40	2/>98
12	$\text{Me}_2\text{N}(\text{CH}_2)_6\text{NMe}_2$	LiCl	MeCN	66	27/73
13	$\text{Et}_3\text{N}$	LiCl	MeCN	trace (33) <sup>d</sup>	–
14	LHMDS	–	toluene/MeCN (1:1)	11 (43) <sup>d</sup>	36/64

<sup>a</sup> Determined by  $^1\text{H}$  NMR of the crude products. NR = no reaction.

<sup>b</sup> Reaction conditions:  $-15^\circ\text{C}$ , 1 h and  $20-25^\circ\text{C}$ , 1 h.

<sup>c</sup> Yield of isolated product.

<sup>d</sup>  $\alpha$ -Chlorinated by-product of **1a**; see the experimental section.

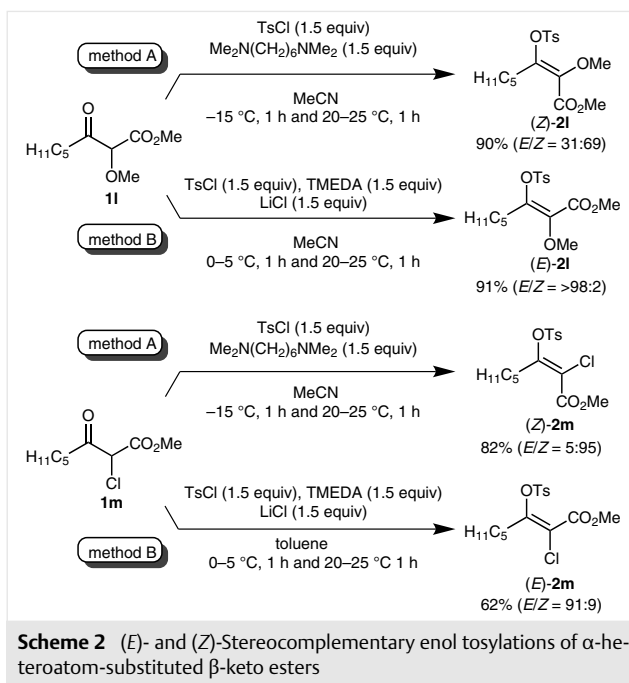
tive results for the (*E*)-selective reaction to give the desired enol tosylate (*E*)-**2a** (Table 1, entries 3–5). When using TMEDA, less reactive alcohols are prone to resist the tosylation reaction concomitant with the side production of TsNMe<sub>2</sub> via Hoffmann degradation of TMEDA with TsCl.<sup>3c</sup> This information led us to use Me<sub>2</sub>N(CH<sub>2</sub>)<sub>n</sub>NMe<sub>2</sub> (*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*)-**2a** 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 and 20–25 °C, 1 h) (Table 1, entry 8). The use of TMEDA produced satisfactory results eventually compared with Me<sub>2</sub>N(CH<sub>2</sub>)<sub>n</sub>NMe<sub>2</sub> (*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).<sup>12</sup>

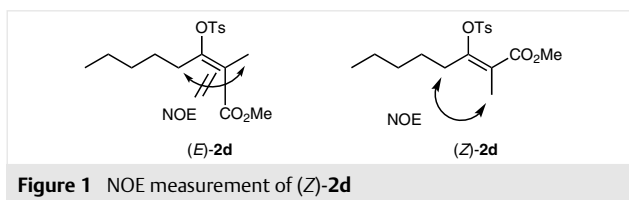
In the two cases using Et<sub>3</sub>N and LHMDS, considerable amounts of the  $\alpha$ -chlorinated by-product (methyl 2-butyl-2-chloro-3-oxooctanoate) of **1a** were detected (Table 1, entries 13 and 14).<sup>13</sup> The occurrence of this side reaction is ascribed to the fact that TsCl cannot be sufficiently activated (*vide infra*, Scheme 4). Accordingly, the present method is obviously more efficient than the NMI-mediated reactions.

With the successful outcome in hand, Table 2 lists the substrate generality using a variety of  $\alpha$ -substituted  $\beta$ -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 for method B). (iii) As a limitation, the (*E*)-selectivity using  $\alpha,\beta$ -diaryl substrates (*E*)-**1j** and (*E*)-**1k** was moderate (Table 2, entries 19 and 21). This tendency coincides with discussions in the precedent report<sup>5d</sup> 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  $\alpha$ -heteroatom (MeO and Cl) substituted  $\beta$ -keto esters **1l** 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.)

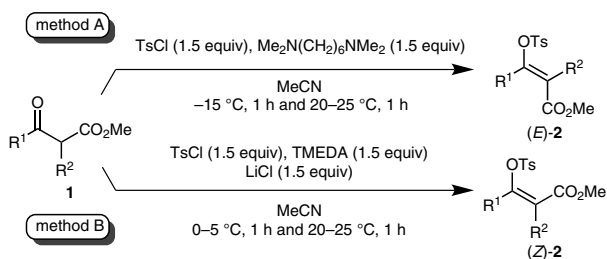


The (*E*)- and (*Z*)-stereochemistry was determined on the basis of the hitherto reported study.<sup>5</sup> In addition, NOE measurements exemplified by enol tosylates (*E*)-**2d** and (*Z*)-**2d**, determined unambiguous assignments (Figure 1).



A plausible mechanism for the successful emergence of (*E*)- and (*Z*)-enol tosylation selectivity is illustrated in Scheme 3.<sup>14</sup> The (*E*)-selective reaction with highly reactive intermediate **I** proceeds via a non-chelation pathway to give (*E*)-**2**; Me<sub>2</sub>N(CH<sub>2</sub>)<sub>6</sub>NMe<sub>2</sub> plays two different roles as a base reagent and as a partner of **I** through equilibrium. Me<sub>2</sub>N(CH<sub>2</sub>)<sub>6</sub>NMe<sub>2</sub> 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 <sup>1</sup>H NMR monitoring experiment (–40 °C in CD<sub>3</sub>CN) revealed that TsCl coupled with TMEDA formed a simple *N*-sulfonylammonium intermediate **IA** rather than a plausible *N,N'*-chelate-type intermediate **IB** (see a brief discussion in the Supporting Information). The apparent downfield chemical

**Table 2** (*E*)- and (*Z*)-Stereocomplementary Enol Tosylation of **1** Using TsCl–Me<sub>2</sub>N(CH<sub>2</sub>)<sub>6</sub>NMe<sub>2</sub> (Method A) and TsCl–TMEDA–LiCl (Method B)

Entry	R <sup>1</sup>	R <sup>2</sup>	Substrate	Method	Product	Yield (%)	<i>E/Z</i> <sup>a</sup>
1	Me	<i>n</i> -Bu	<b>1b</b>	A	( <i>E</i> )- <b>2b</b>	81	97/3
2	Me	<i>n</i> -Bu	<b>1b</b>	B	( <i>Z</i> )- <b>2b</b>	95	2/>98
3 <sup>b</sup>	Me	<i>i</i> -Pr	<b>1c</b>	A	( <i>E</i> )- <b>2c</b>	84	>98/2
4 <sup>c</sup>	Me	<i>i</i> -Pr	<b>1c</b>	B	( <i>Z</i> )- <b>2c</b>	85	2/>98
5	<i>n</i> -pentyl	Me	<b>1d</b>	A	( <i>E</i> )- <b>2d</b>	74	>98/2
6	<i>n</i> -pentyl	Me	<b>1d</b>	B	( <i>Z</i> )- <b>2d</b>	94	2/>98
7	Cl(CH <sub>2</sub> ) <sub>4</sub>	Me	<b>1e</b>	A	( <i>E</i> )- <b>2e</b>	77	>98/2
8	Cl(CH <sub>2</sub> ) <sub>4</sub>	Me	<b>1e</b>	B	( <i>Z</i> )- <b>2e</b>	85	2/>98
9			<b>1f</b>	A	( <i>E</i> )- <b>2f</b>	63	95/5
10			<b>1f</b>	B	( <i>Z</i> )- <b>2f</b>	91	2/>98
11	<i>n</i> -pentyl	<i>n</i> -Bu	<b>1a</b>	A	( <i>E</i> )- <b>2a</b>	74	>98/2
12	<i>n</i> -pentyl	<i>n</i> -Bu	<b>1a</b>	B	( <i>Z</i> )- <b>2a</b>	93	2/>98
13	Ph	Me	<b>1g</b>	A	( <i>E</i> )- <b>2g</b>	89	94/6
14	Ph	Me	<b>1g</b>	B	( <i>Z</i> )- <b>2g</b>	90	2/>98
15	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	Me	<b>1h</b>	A	( <i>E</i> )- <b>2h</b>	80	94/6
16	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	Me	<b>1h</b>	B	( <i>Z</i> )- <b>2h</b>	89	2/>98
17	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	Me	<b>1i</b>	A	( <i>E</i> )- <b>2i</b>	94	>98/2
18	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	Me	<b>1i</b>	B	( <i>Z</i> )- <b>2i</b>	96	2/>98
19	Ph	Ph	<b>1j</b>	A	( <i>E</i> )- <b>2j</b>	96 (49) <sup>d</sup>	74/26 (>98/2)
20	Ph	Ph	<b>1j</b>	B	( <i>Z</i> )- <b>2j</b>	93	2/>98
21	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	Ph	<b>1k</b>	A	( <i>E</i> )- <b>2k</b>	95 (26) <sup>d</sup>	66/34 (>98/2)
22	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	Ph	<b>1k</b>	B	( <i>Z</i> )- <b>2k</b>	99	2/>98

<sup>a</sup> Determined by <sup>1</sup>H NMR of the crude products.

<sup>b</sup> TsCl (3.0 equiv) and Me<sub>2</sub>N(CH<sub>2</sub>)<sub>6</sub>NMe<sub>2</sub> (3.0 equiv) were used.

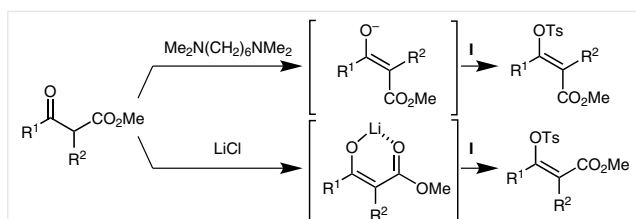
<sup>c</sup> TsCl (3.0 equiv), TMEDA (3.0 equiv), and LiCl (3.0 equiv) were used.

<sup>d</sup> Yield after recrystallization; see the experimental section for details.

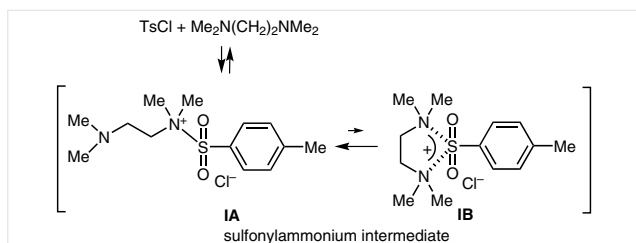
shifts of the tosyl moiety in **1A** are related to the higher reactivity of the present system. Based on the result, **1A** is likely to function as the key active species.<sup>15,16</sup>

In conclusion, we have developed a general and convenient protocol for (*E*)- and (*Z*)-stereocomplementary enol tosylations of  $\alpha$ -substituted  $\beta$ -keto esters using the TsCl–Me<sub>2</sub>N(CH<sub>2</sub>)<sub>6</sub>NMe<sub>2</sub> reagent (method A) and the TsCl–TMEDA–LiCl reagent (method B), respectively. A plausible

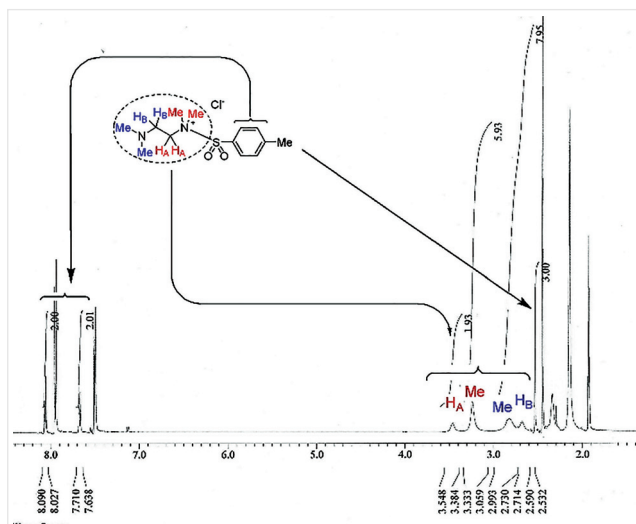
mechanism for the successful (*E*)- and (*Z*)-enol tosylation selectivity is proposed. A <sup>1</sup>H NMR monitoring experiment revealed that TsCl coupled with TMEDA formed a simple *N*-sulfonylammonium intermediate. Further investigation on various (*E*)- and (*Z*)-stereoretentive cross-couplings using the obtained fully substituted enol tosylates, a pair of latent and potential scaffolds, is now under progress in our laboratory.



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



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



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

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 60 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 spectrophotometer. NMR spectra were recorded on a JEOL DELTA 300 or JEOLRESONANCE ECX-500 spectrometer, operating at 300 MHz or 500 MHz for  $^1\text{H}$  NMR and 75 MHz or 125 MHz for  $^{13}\text{C}$  NMR. Chemical shifts ( $\delta$ ) (ppm) in  $\text{CDCl}_3$  are reported downfield from TMS

(0 ppm) for  $^1\text{H}$  NMR. For  $^{13}\text{C}$  NMR, chemical shifts are reported relative to  $\text{CDCl}_3$  (77.00 ppm) as an internal reference. Mass spectra were measured on a JEOL JMS-T100LC spectrometer.  $\beta$ -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 $\beta$ -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  $\beta$ -keto ester (1.00 mmol) and  $\text{Me}_2\text{N}(\text{CH}_2)_6\text{NMe}_2$  (258 mg, 1.50 mmol) in MeCN (1.0 mL) at  $-15\text{ }^\circ\text{C}$ , and the mixture was stirred at the same temperature for 1 h and at  $20\text{--}25\text{ }^\circ\text{C}$  for 1 h.  $\text{H}_2\text{O}$  (a large amount) was added to the mixture, which was extracted twice with EtOAc. The combined organic phase was washed with  $\text{H}_2\text{O}$ , sat. aq.  $\text{NaHCO}_3$  solution and brine, then dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated. The obtained crude product was purified by  $\text{SiO}_2$  column chromatography (hexane/EtOAc = 50:1 to 15:1) to give the desired product.

#### (*Z*)-Enol Tosylations of $\beta$ -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  $\beta$ -keto ester (1.00 mmol), TMEDA (258 mg, 1.50 mmol), and LiCl (64 mg, 1.50 mmol) in MeCN (1.0 mL) at  $0\text{--}5\text{ }^\circ\text{C}$ , and the mixture was stirred at the same temperature for 1 h and at  $20\text{--}25\text{ }^\circ\text{C}$  for 1 h.  $\text{H}_2\text{O}$  (a large amount) was added to the mixture, which was extracted twice with EtOAc. The combined organic phase was washed with  $\text{H}_2\text{O}$ , sat. aq.  $\text{NaHCO}_3$  solution and brine, then dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated. The obtained crude product was purified by  $\text{SiO}_2$  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 solution of methyl 2-butyl-3-oxooctanoate (**1a**) (3.42 g, 15.0 mmol) and  $\text{Me}_2\text{N}(\text{CH}_2)_6\text{NMe}_2$  (4.85 mL, 22.5 mmol) in MeCN (15.0 mL) at  $-15\text{ }^\circ\text{C}$ , and the mixture was stirred at the same temperature for 1 h and at  $20\text{--}25\text{ }^\circ\text{C}$  for 1 h.  $\text{H}_2\text{O}$  was added to the mixture, which was extracted twice with EtOAc. The combined organic phase was washed with  $\text{H}_2\text{O}$ , sat. aq.  $\text{NaHCO}_3$  solution and brine, then dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated. The obtained crude product was purified by  $\text{SiO}_2$  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-butyl-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  $0\text{--}5\text{ }^\circ\text{C}$ , and the mixture was stirred at the same temperature for 1 h and at  $20\text{--}25\text{ }^\circ\text{C}$  for 1 h.  $\text{H}_2\text{O}$  was added to the mixture, which was extracted twice with EtOAc. The combined organic phase was washed with  $\text{H}_2\text{O}$ , sat. aq.  $\text{NaHCO}_3$  solution and brine, then dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated. The obtained crude product was purified by  $\text{SiO}_2$  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.



IR (neat): 2956, 2931, 2872, 1720, 1644, 1598, 1435, 1374  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 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).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 13.6, 13.8, 21.5, 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.

HRMS (ESI):  $m/z$  [ $M + \text{Na}$ ] $^+$  calcd for  $\text{C}_{20}\text{H}_{30}\text{O}_5\text{SNa}$ : 405.1712; found: 405.1710.

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

Yield: 356 mg (93%); colorless oil.

IR (neat): 2959, 2872, 1728, 1655, 1599, 1458, 1375, 1310  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 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).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 13.7 (2 C), 21.5, 22.17, 22.22, 26.2, 29.0, 30.8, 30.9, 31.1, 51.7, 125.0, 127.9 (2 C), 129.6 (2 C), 134.0, 144.9, 151.2, 167.1.

#### 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  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 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).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 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.

HRMS (ESI):  $m/z$  [ $M + \text{Na}$ ] $^+$  calcd for  $\text{C}_{16}\text{H}_{22}\text{O}_5\text{SNa}$ : 349.1086; found: 349.1097.

#### 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  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 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).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 13.5, 17.7, 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-oxooctanoate (By-Product; Figure 3)

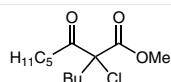


Figure 3 Structure of by-product

Colorless oil.

IR (neat): 2958, 2873, 1727, 1467, 1436, 1314, 1244, 1208  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 0.88 (t,  $J$  = 7.2 Hz, 3 H), 0.91 (t,  $J$  = 7.2 Hz, 3 H), 1.20–1.43 (m, 8 H), 1.62 (quin,  $J$  = 7.2 Hz, 2 H), 2.04–2.25 (m, 2 H), 2.58 (dt,  $J$  = 7.2 Hz,  $J_{\text{gem}}$  = 17.9 Hz, 1 H), 2.72 (dt,  $J$  = 7.2 Hz,  $J_{\text{gem}}$  = 17.5 Hz, 1 H), 3.81 (s, 3 H).

$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 13.7 (2 C), 22.3, 22.4, 23.5, 26.1, 30.9, 36.3, 37.9, 53.4, 75.9, 168.0, 200.8.

HRMS (ESI):  $m/z$  [ $M + \text{Na}$ ] $^+$  calcd for  $\text{C}_{13}\text{H}_{23}\text{ClO}_3\text{Na}$ : 285.1233; found: 285.1247.

#### Methyl (E)-2-Isopropyl-3-(tosyloxy)but-2-enoate [(E)-2c]

Yield: 131 mg (84%) (0.5 mmol scale); pale yellow oil.

IR (neat): 1968, 1725, 1667, 1598, 1435, 1372, 1276, 1193  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 0.94 (d,  $J$  = 6.9 Hz, 6 H), 2.04 (s, 3 H), 2.46 (s, 3 H), 2.85 (sept,  $J$  = 6.9 Hz, 1 H), 3.75 (s, 3 H), 7.33–7.39 (m, 2 H), 7.80–7.87 (m, 2 H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 18.9, 20.3 (2 C), 21.5, 27.2, 51.5, 127.8 (2 C), 129.8 (2 C), 131.4, 133.8, 145.3, 147.0, 167.9.

HRMS (ESI):  $m/z$  [ $M + \text{Na}$ ] $^+$  calcd for  $\text{C}_{15}\text{H}_{20}\text{O}_5\text{SNa}$ : 335.0929; found: 335.0928.

#### Methyl (Z)-2-Isopropyl-3-(tosyloxy)but-2-enoate [(Z)-2c]

Yield: 133 mg (85%) (0.5 mmol scale); pale yellow oil.

IR (neat): 2929, 2859, 1718, 1621, 1442, 1254, 1200, 1089  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.08 (d,  $J$  = 6.9 Hz, 6 H), 2.05 (s, 3 H), 2.45 (s, 3 H), 2.62 (sept,  $J$  = 6.9 Hz, 1 H), 3.55 (s, 3 H), 7.30–7.38 (m, 2 H), 7.76–7.82 (m, 2 H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 16.8, 20.7 (2 C), 21.6, 28.7, 51.4, 127.9 (2 C), 129.6 (2 C), 130.7, 133.8, 143.9, 145.0, 166.5.

#### Methyl (E)-2-Methyl-3-(tosyloxy)oct-2-enoate [(E)-2d]

Yield: 253 mg (74%); colorless oil.

IR (neat): 2954, 1720, 1650, 1598, 1435, 1373, 1276, 1191  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 0.83 (t,  $J$  = 7.2 Hz, 3 H), 1.10–1.26 (m, 4 H), 1.43 (quin,  $J$  = 7.2 Hz, 2 H), 1.73 (s, 3 H), 2.47 (s, 3 H), 2.68 (t,  $J$  = 7.2 Hz, 2 H), 3.74 (s, 3 H), 7.33–7.40 (m, 2 H), 7.81–7.88 (m, 2 H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 13.8 (2 C), 21.5, 22.1, 26.6, 31.1, 32.0, 51.8, 120.8, 127.7 (2 C), 129.8 (2 C), 134.1, 145.3, 158.6, 167.8.

HRMS (ESI):  $m/z$  [ $M + \text{Na}$ ] $^+$  calcd for  $\text{C}_{17}\text{H}_{24}\text{O}_5\text{SNa}$ : 363.1242; found: 363.1246.

#### Methyl (Z)-2-Methyl-3-(tosyloxy)oct-2-enoate [(Z)-2d]

Yield: 319 mg (94%); colorless oil.

IR (neat): 2954, 2863, 1715, 1598, 1434, 1372, 1306, 1180  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 0.84 (t,  $J$  = 7.2 Hz, 3 H), 1.11–1.32 (m, 4 H), 1.38–1.52 (m, 2 H), 1.89 (s, 3 H), 2.32 (t,  $J$  = 7.2 Hz, 2 H), 2.45 (s, 3 H), 3.60 (s, 3 H), 7.30–7.39 (m, 2 H), 7.76–7.87 (m, 2 H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 13.7, 14.8, 21.5, 22.1, 25.9, 31.0, 31.3, 51.7, 119.7, 127.9 (2 C), 129.6 (2 C), 134.1, 145.0, 151.9, 167.0.

**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<sup>-1</sup>.<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): 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).<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): 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.HRMS (ESI): *m/z* [M + Na]<sup>+</sup> calcd for C<sub>16</sub>H<sub>21</sub>O<sub>5</sub>ClSNa: 383.0696; found: 383.0678.**Methyl (Z)-7-Chloro-2-methyl-3-(tosyloxy)hept-2-enoate [(Z)-2e]**

Yield: 306 mg (85%); pale yellow oil.

IR (neat): 2952, 1720, 1598, 1435, 1371, 1307, 1108, 1086 cm<sup>-1</sup>.<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 1.58–1.83 (m, 4 H), 1.90 (s, 3 H), 2.38 (t, *J* = 6.9 Hz, 2 H), 2.45 (s, 3 H), 3.46 (t, *J* = 6.5 Hz, 2 H), 3.59 (s, 3 H), 7.32–7.38 (m, 2 H), 7.79–7.85 (m, 2 H).<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 14.6, 21.3, 23.3, 30.2, 31.3, 44.0, 51.5, 120.1, 127.6 (2 C), 129.5 (2 C), 133.5, 145.0, 150.5, 166.5.**Methyl (E)-2-(Non-8-en-1-yl)-3-(tosyloxy)trideca-2,12-dienoate [(E)-2f]**

Yield: 327 mg (63%); colorless oil.

IR (neat): 2927, 2854, 1720, 1640, 1598, 1376, 1192, 1178 cm<sup>-1</sup>.<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 1.08–1.49 (m, 22 H), 1.96–2.08 (m, 4 H), 2.17 (t, *J* = 7.6 Hz, 2 H), 2.46 (s, 3 H), 2.60 (t, *J* = 7.6 Hz, 2 H), 3.74 (s, 3 H), 4.89–5.05 (m, 4 H), 5.81 (ddt, *J* = 6.9, 10.3, 16.9 Hz, 2 H), 7.33–7.39 (m, 2 H), 7.81–7.87 (m, 2 H).<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 21.6, 27.1, 27.9, 28.1, 28.83, 28.85, 28.91, 28.98, 29.02 (2 C), 29.09, 29.2, 29.3, 32.2, 33.7 (2 C), 51.8, 114.1 (2 C), 125.8, 127.8 (2 C), 129.8 (2 C), 134.3, 139.1 (2 C), 145.2, 156.7, 168.1.HRMS (ESI): *m/z* [M + Na]<sup>+</sup> calcd for C<sub>30</sub>H<sub>46</sub>O<sub>5</sub>SNa: 541.2964; found: 541.2944.**Methyl (Z)-2-(Non-8-en-1-yl)-3-(tosyloxy)trideca-2,12-dienoate [(Z)-2f]**

Yield: 474 mg (91%); colorless oil.

IR (neat): 2926, 2855, 1726, 1640, 1599, 1376, 1194, 1180 cm<sup>-1</sup>.<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 1.15–1.52 (m, 22 H), 2.03 (q, *J* = 6.9 Hz, 4 H), 2.24 (t, *J* = 7.6 Hz, 2 H), 2.30 (t, *J* = 7.6 Hz, 2 H), 2.45 (s, 3 H), 3.59 (s, 3 H), 4.89–5.04 (m, 4 H), 5.80 (ddt, *J* = 6.9, 10.3, 16.9 Hz, 1 H), 5.81 (ddt, *J* = 6.9, 10.3, 16.9 Hz, 1 H), 7.31–7.37 (m, 2 H), 7.78–7.85 (m, 2 H).<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 21.5, 26.5, 28.6, 28.70, 28.75, 28.82, 28.91, 28.93, 28.98, 29.0 (2 C), 29.16, 29.18, 30.9, 33.6 (2 C), 51.6, 114.1 (2 C), 125.0, 127.9 (2 C), 129.5 (2 C), 134.0, 138.86, 138.89, 144.9, 151.1, 167.0.**Methyl (E)-2-Methyl-3-phenyl-3-(tosyloxy)prop-2-enoate [(E)-2g]**

Yield: 309 mg (89%); colorless crystals; mp 68–69 °C.

IR (neat): 1714, 1657, 1599, 1439, 1364, 1322, 1191, 1176 cm<sup>-1</sup>.<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 2.06 (s, 3 H), 2.36 (s, 3 H), 3.51 (s, 3 H), 7.07–7.27 (m, 7 H), 7.41–7.46 (m, 2 H).<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 14.8, 21.5, 51.8, 123.1, 127.6 (2 C), 127.8 (2 C), 128.7 (2 C), 129.2, 129.3 (2 C), 133.4, 133.8, 144.8, 151.6, 168.4.HRMS (ESI): *m/z* [M + Na]<sup>+</sup> calcd for C<sub>18</sub>H<sub>18</sub>O<sub>5</sub>SNa: 369.0773; found: 369.0758.**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<sup>-1</sup>.<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): 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).<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): 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<sup>-1</sup>.<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): 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).<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): 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.HRMS (ESI): *m/z* [M + Na]<sup>+</sup> calcd for C<sub>19</sub>H<sub>20</sub>O<sub>5</sub>SNa: 383.0929; found: 383.0926.**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<sup>-1</sup>.<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): 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).<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): 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), 129.3, 134.2, 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<sup>-1</sup>.<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): 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).<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): 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.HRMS (ESI): *m/z* [M + Na]<sup>+</sup> calcd for C<sub>18</sub>H<sub>17</sub>O<sub>5</sub>ClSNa: 403.0383; found: 403.0377.**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<sup>-1</sup>.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.92 (s, 3 H), 2.38 (s, 3 H), 3.80 (s, 3 H), 7.09–7.18 (m, 4 H), 7.13–7.15 (m, 2 H), 7.41–7.46 (m, 2 H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 15.8, 21.4, 52.1, 121.7, 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  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 2.35 (s, 3 H), 3.50 (s, 3 H), 6.94–7.03 (m, 2 H), 7.17–7.50 (m, 12 H).

$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 21.5, 52.3, 127.3, 127.7 (2 C), 128.0 (2 C), 128.1 (2 C), 128.2, 128.6 (2 C), 129.0 (2 C), 129.2 (2 C), 129.8, 132.2, 133.2, 133.4, 144.6, 149.1, 167.6.

HRMS (ESI): *m/z* [M + Na]<sup>+</sup> calcd for  $\text{C}_{23}\text{H}_{20}\text{O}_5\text{SNa}$ : 431.0929; found: 431.0907.

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

Yield: 381 mg (93%); colorless crystals; mp 111–112 °C.

IR (neat): 1726, 1448, 1431, 1369, 1253, 1209, 1174, 1053  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 2.38 (s, 3 H), 3.80 (s, 3 H), 6.96–7.06 (m, 4 H), 7.08–7.22 (m, 8 H), 7.47–7.53 (m, 2 H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 21.5, 52.5, 126.9, 127.0, 127.7 (2 C), 128.0 (2 C), 128.1, 128.3 (2 C), 129.3 (2 C), 129.7 (2 C), 129.9 (2 C), 131.9, 133.1, 134.0, 144.7, 148.5, 166.5.

#### Methyl (E)-3-(4-Methoxyphenyl)-2-phenyl-3-(tosyloxy)acrylate [(E)-2k]

Yield: 4.17 g (95%, *E/Z* = 66:34), 1.14 g (26%, *E/Z* = >98:2, after recrystallization from toluene) (10 mmol scale); colorless crystals; mp 116–118 °C.

IR (neat): 1720, 1633, 1605, 1506, 1435, 1375, 1206  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 2.35 (s, 3 H), 3.53 (s, 3 H), 3.82 (s, 3 H), 6.73–6.83 (m, 2 H), 6.94–7.07 (m, 2 H), 7.14–7.30 (m, 5 H), 7.34–7.44 (m, 4 H).

$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 21.5, 52.3, 55.2, 113.4 (2 C), 125.6, 126.1, 127.8 (2 C), 128.0 (3 C), 129.0 (2 C), 129.2 (2 C), 130.2 (2 C), 132.5, 133.4, 144.5, 149.3, 160.7, 167.8.

HRMS (ESI): *m/z* [M + Na]<sup>+</sup> calcd for  $\text{C}_{24}\text{H}_{22}\text{O}_6\text{SNa}$ : 461.1035; found: 461.1030.

#### Methyl (Z)-3-(4-Methoxyphenyl)-2-phenyl-3-(tosyloxy)acrylate [(Z)-2k]

Yield: 13.04 g (99%) (30 mmol scale); colorless crystals; mp 123–125 °C.

IR (neat): 1726, 1636, 1608, 1433, 1317, 1252, 1192  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 2.40 (s, 3 H), 3.72 (s, 3 H), 3.77 (s, 3 H), 6.47–7.56 (m, 2 H), 6.90–7.00 (m, 2 H), 7.06–7.24 (m, 7 H), 7.48–7.59 (m, 2 H).

$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 21.5, 52.3, 55.1, 113.2 (2 C), 124.1, 125.6, 127.9, 128.0 (2 C), 128.3 (2 C), 129.2 (2 C), 129.7 (2 C), 131.5 (2 C), 133.5, 134.2, 144.6, 148.8, 160.2, 166.6.

#### 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  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 0.85 (t, *J* = 7.2 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).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 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.

HRMS (ESI): *m/z* [M + Na]<sup>+</sup> calcd for  $\text{C}_{17}\text{H}_{24}\text{O}_6\text{SNa}$ : 379.1191; found: 379.1199.

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

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

IR (neat): 2934, 2862, 1725, 1598, 1436, 1376, 1294, 1208  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 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).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 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  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 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).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 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.

HRMS (ESI): *m/z* [M + Na]<sup>+</sup> calcd for  $\text{C}_{16}\text{H}_{21}\text{ClO}_5\text{SNa}$ : 383.0696; found: 383.0711.

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

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

IR (neat): 2955, 2862, 1734, 1622, 1597, 1435, 1382, 1256  $\text{cm}^{-1}$ .

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 0.85 (t, *J* = 6.9 Hz, 3 H), 1.16–1.30 (m, 4 H), 1.42–1.56 (m, 2 H), 2.47 (s, 3 H), 2.53 (t, *J* = 7.6 Hz, 2 H), 3.70 (s, 3 H), 7.33–7.41 (m, 2 H), 7.80–7.89 (m, 2 H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 13.7, 21.6, 22.1, 25.3, 30.9, 32.3, 52.9, 118.4, 128.2 (2 C), 129.8 (2 C), 133.3, 145.7, 155.1, 161.6.

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## Supporting Information

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



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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 TiCl<sub>4</sub> and Et<sub>3</sub>N at 0–5 °C for 1 h (93% yield); see the Supporting Information and ref. 8.
- (11) TMEDA: ca. \$80/500 g; Me<sub>2</sub>N(CH<sub>2</sub>)<sub>3</sub>NMe<sub>2</sub>: ca. \$110/500 g; Me<sub>2</sub>N(CH<sub>2</sub>)<sub>6</sub>NMe<sub>2</sub>: 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 Ts<sub>2</sub>O instead of TsCl.
- (14) This monitoring study resembles the case of TsCl–NMI (see refs. 5a and 5d) and (PhO)<sub>2</sub>POCl–NMI (see ref. 8) intermediates.
- (15) A related monitoring experiment using *p*-MeC<sub>6</sub>H<sub>4</sub>COCl with TMEDA was carried out in our hands; noticeable changes of <sup>1</sup>H NMR spectra were not observed under the identical conditions. The interactive action of TsCl, therefore, may be stronger than that of benzoyl chlorides.
- (16) Oriyama's group reported pioneering work on chiral-diamine-catalyzed desymmetric benzoylations of *meso*-diols with PhCOCl and speculation regarding the mechanism. Contrary to the present result, they proposed the corresponding *N,N'*-chelate-type intermediate; see (a) Sano, T.; Oriyama, T. *J. Synth. Org. Chem. Jpn.* **1999**, *57*, 598. (b) Oriyama, T.; Imai, K.; Sano, T.; Hosoya, T. *Tetrahedron Lett.* **1998**, *57*, 598. (c) Sano, T.; Miyata, H.; Oriyama, T. *Enantiomer* **2000**, *5*, 119. (d) Terakado, D.; Oriyama, T. *Org. Synth.* **2006**, *83*, 70.