Development of Divergent and Parallel Synthetic Methods for (*E*)- and (*Z*)-Stereodefined Multi-Substituted Alkene Scaffolds

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Chapter 1.
General Introduction: Synthetic Methods for (E)- and (Z)-Stereodefined Alkenes

(*E*)- and (*Z*)-stereodefined alkenes are widely distributed in natural products, pharmaceuticals, and functional molecules. **Figure 1-1** displays representative examples of these alkenes: aromatic butenolides (gymnoascolide A−C),[1] protoilludane sesquiterpenes (tsugicoline A−D),[2] a promising antiulcer agent (nileprost),[3] antiulcer drug (plaunotol),[4] an orally active cyclooxygenase-2 inhibitor (vioxx®),[5] a selective serotonin reuptake inhibitor (SSRI) antidepressant [(*Z*)-zimelidine],[6] an antiestrogenic agent [(*Z*)-tamoxifen],[7] the chiral molecular switch,[8] and the chiral molecular motor.[9] Stereodefined alkenes also serve as useful scaffolds for a number of elaborated compounds through readily accessible transformations such as hydrogenation, epoxidation, and Michael addition to construct contiguous chiral and achiral centers.[10]

Due to the high demand, a number of stereocontrolled synthetic methods for (*E*)- and (*Z*)-multi-substituted stereodefined alkenes have been developed, and are generally categorized into six approaches (**Scheme 1-1**): 1) Wittig-type reactions, 2) carbometalations of alkynes using Cu, B, Sn, Mg, Pd, and so forth, followed by reactions with electrophiles, 3) cross-couplings with halogenovinyl templates, 4) elimination reactions of tertiary alcohols, 5) cross-metatheses between different alkenes, and 6) ynolate-mediated reactions derived from α,α-dibromoesters. However, the (*E*)- and (*Z*)-stereocomplementary method using the similar common starting materials with sufficient substrate-generality is quite limited to date.

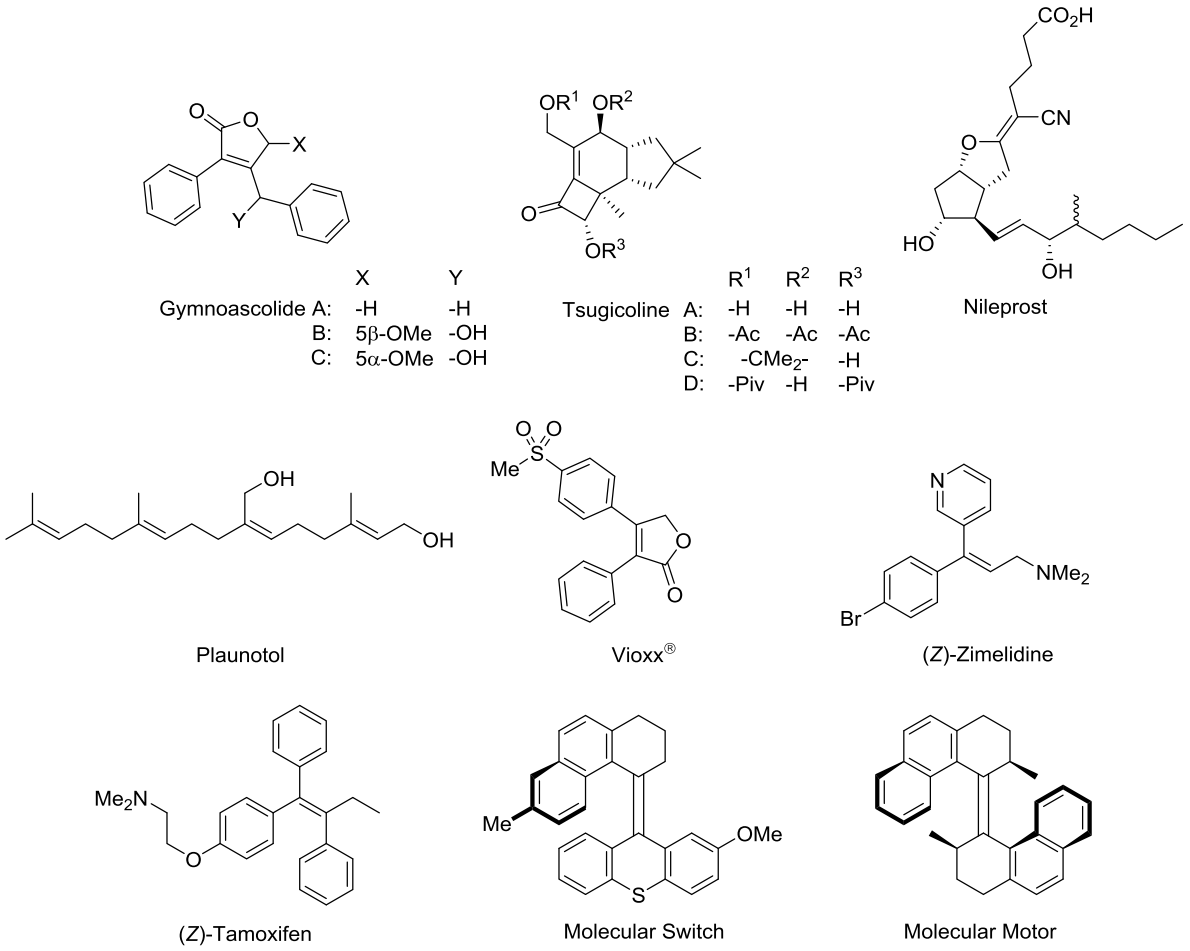
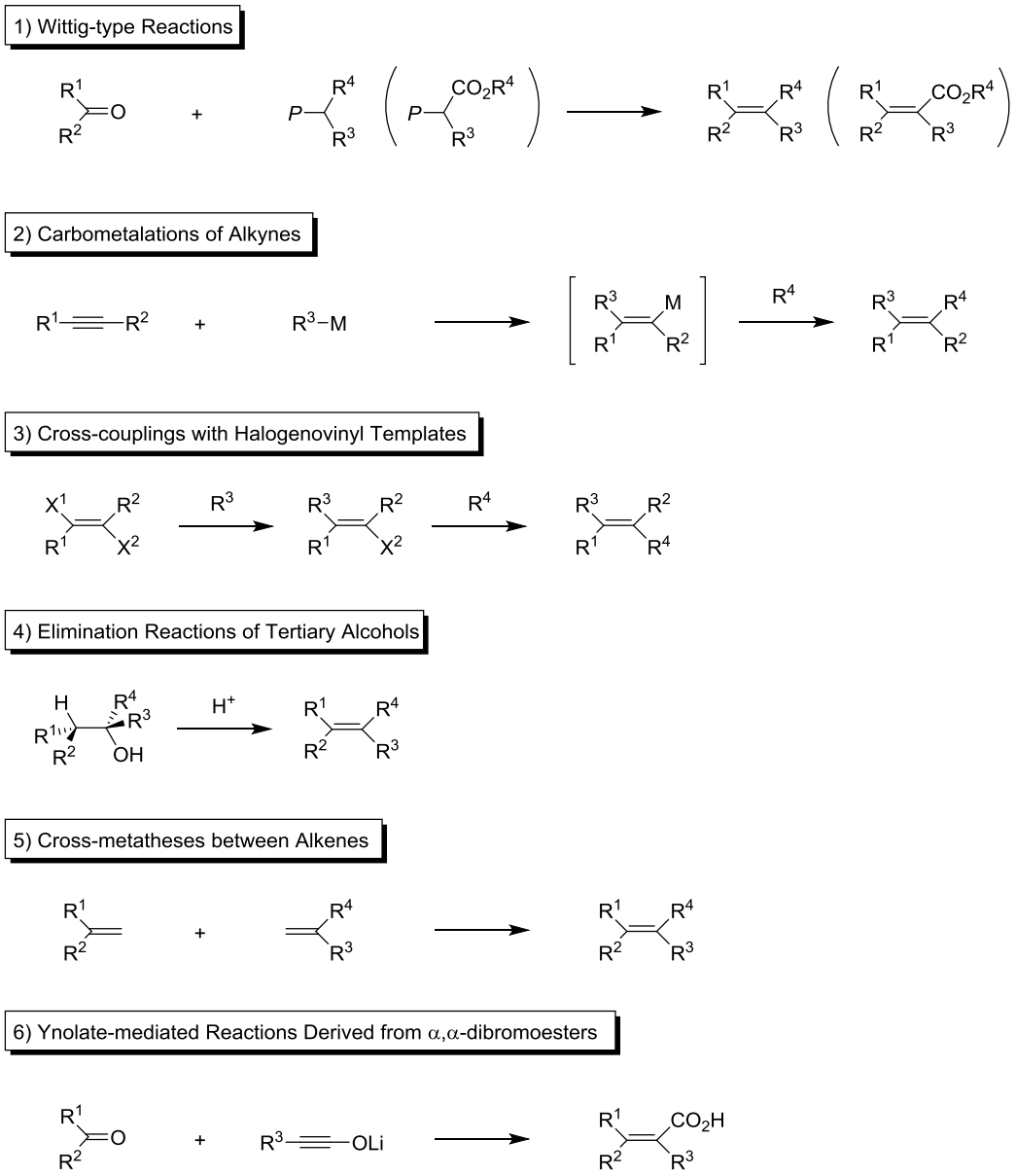


Figure 1-1. Examples of representative alkene containing pharmaceutical and functional molecules.

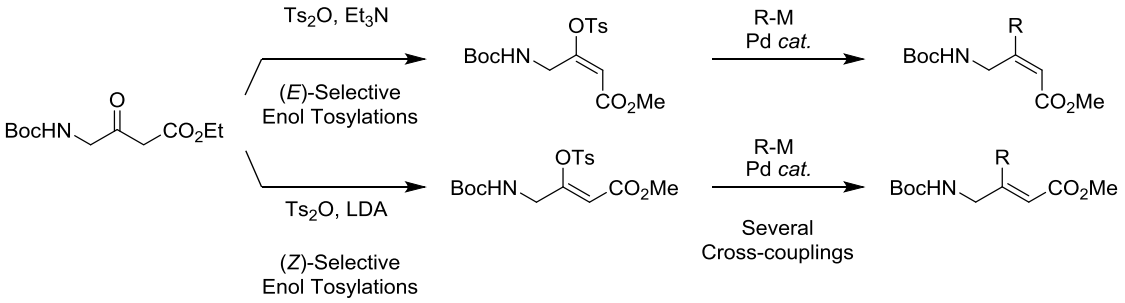


Scheme 1-1. Stereocontrolled synthetic methods for (*E*)- and (*Z*)-multi-substituted stereodefined alkenes.

Strategies based on cross-coupling reactions with stereodefined enol sulfonate[11] and phosphonate[12] partners derived from β-ketoesters, which emerged in recent decades, are considered as promising and reliable approaches compared with the above-mentioned methods, due to the following advantages: 1) various starting β-ketoester substrates are readily available,[13] and 2) parallel approach enhances the versatility of the method.

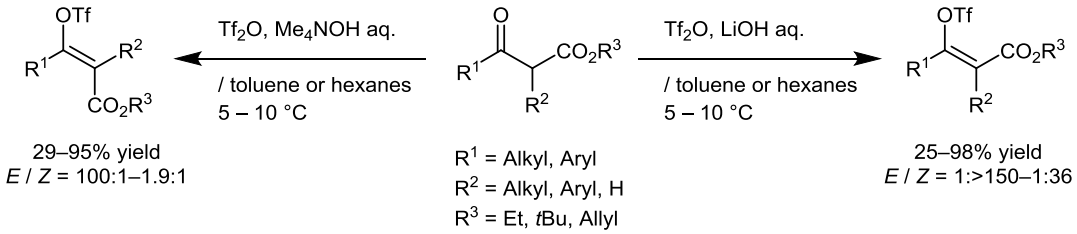
In 2005, the Merck process group disclosed a characteristic protocol for (*E*)- and (*Z*)-stereocomplementary enol tosylations of specific α- or γ-nitrogen-substituted β-ketoesters using respective Ts_2O−M(Li *or* Na)HMDS and Ts_2O−amine reagents (**Scheme 1-2**).[14] The obtained stereodefined enol tosylate scaffolds were successfully subjected to stereoretentive Suzuki-Miyaura (SM) cross-couplings for the synthesis of γ-aminobutanoic acid (GABA) precursors. In addition, they also reported a concise synthesis of chiral β-cyclopropyl-α-methyldihydrocinnamates.[15] This notable pharmacophore was synthesized via (*E*)- and

(*Z*)-stereocontrolled enol tosylations using a β-cyclopropyl-α-methyl-β-ketoester; the (*E*)-isomer was prepared using Ts_2O−NaHMDS at −78 °C, whereas the (*Z*)-isomer was prepared using the same reagent at room temperature. Throughout the study, they consistently use reactive but highly expensive Ts_2O instead of TsCl for enol tosylation of β-ketoeste to avoid α-chlorinated by-product.



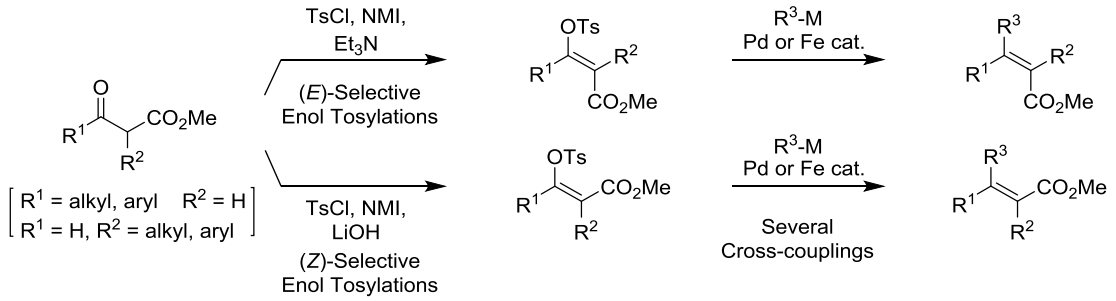
Scheme 1-2. (*E*)- and (*Z*)-stereocomplementary synthesis of γ-amino-substituted (*E*)- and (*Z*)-α,β-unsaturated esters utilizing stereoselective enol tosylations and stereoretentive cross-couplings reported by the Merck process group.

In 2008, Frantz's group has reported a practical preparative method for (*E*)- and (*Z*)-stereodefined enol triflates derived from β-ketoesters (**Scheme 1-3**).[16] Highly reactive these enol sulfonates have served as useful building blocks for the synthesis of natural products,[17] however, enol triflates methods have several drawbacks: (i) Tf_2O is ca. 15−30 times more expensive than TsCl, (ii) Tf_2O is highly toxic and hazardous with a low boiling point (81−83 °C) and reacts violently with water, and (iii) triflates are often unstable under cross-couplimg conditions due to their inherent reactivity.



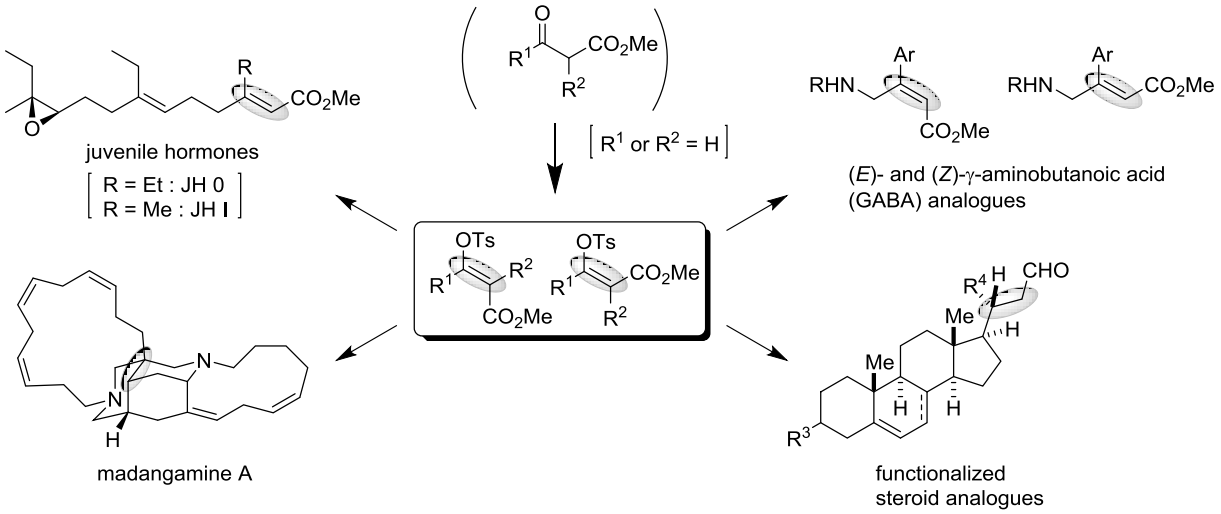
Scheme 1-3. (*E*)- and (*Z*)-Stereocomplementary preparation of enol triflates reported by Frantz's group.

As a part of our ongoing studies on mild but powerful sulfonylations[18] and silylations[19] of various alcohols and carbonyl compounds, in 2008 and 2009, our group has reported a series of (*E*)- and (*Z*)-stereocomplementary enol tosylations of not only acyclic "α-nonsubstituted" β-ketoesters (R^1 = alkyl or aryl, R^2 = H), but also α-formylesters (R^1 = H, R^2 = alkyl or aryl), which were conducted by a much more accessible TsCl−*N*-methylimidazole (NMI)−base system (**Scheme 1-4**). TsCl−NMI−Et_3N 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,[20a] Sonogashira,[20a] Suzuki-Miyaura,[20b] and Kochi−Fürstner[20c]) were successfully performed to produce the corresponding stereodefined α,β-unsaturated esters.



Scheme 1-4. (*E*)- and (*Z*)-stereocomplementary synthesis of 'not fully'-substituted (*E*)- and (*Z*)-α,β-unsaturated esters utilizing stereoselective enol tosylations and stereoretentive cross-couplings.

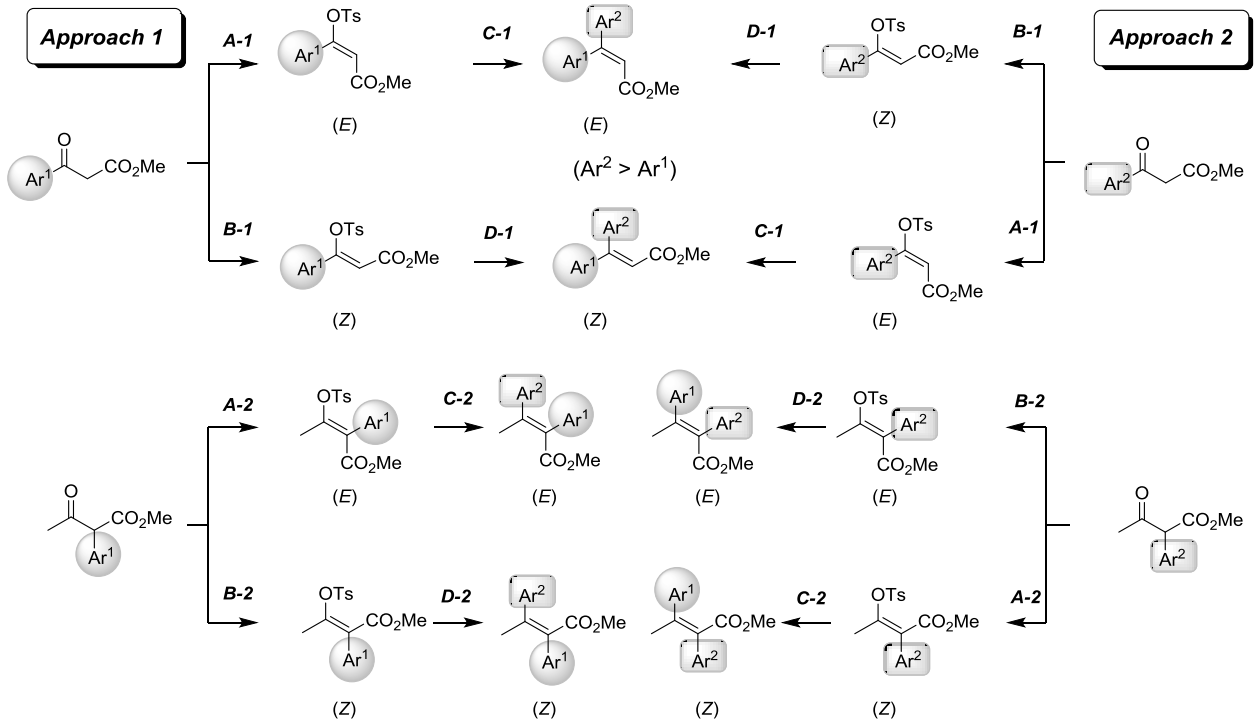
As depicted in **Scheme 1-5**, the current privileged robust and cost-effective protocols have been successfully adopted for the synthesis of elaborated natural and unnatural compounds, such as juvenile hormones 0 and I,[21a,b] madangamine A,[21c] and functionalized steroids,[21d] etc .



Scheme 1-5. Synthetic applications of "not fully"-substituted (*E*)- and (*Z*)-enol tosylates.

This background led the author to envisage a highly substrate-general synthesis of multi-substituted (*E*)- and (*Z*)-stereodefined alkene scaffolds, and especially with focusing on a parallel and stereocomplementary methodology.

In chapter 2, parallel and practical methods for the preparation of both (*E*)- and (*Z*)-β-aryl[1]-β-aryl[2]-α,β-unsaturated esters and (*E*)- and (*Z*)-α-aryl[1]-β-aryl[2]-α,β-unsaturated esters are described (**Scheme 1-6**). These methods involve accessible, robust, stereocomplementary *N*-methylimidazole (NMI)-mediated enol tosylations (14 examples, 70−99% yield), as well as stereoretentive Suzuki-Miyaura cross-couplings (36 examples, 64−99% yield). The highlighted feature of the present protocol is the use of parallel and stereocomplementary approaches to obtain (*E*)- and (*Z*)-products with high purity by utilizing sequential enol tosylations and cross-coupling reactions. An expeditious and parallel synthesis of (*E*)- and (*Z*)-zimelidine, which is a highly representative selective serotonin reuptake inhibitor (SSRI), was performed by utilizing the present methods.



Method A-1 & A-2 : (*E*)-Stereoselective Enol Tosylation **Method B-1 & B-2 : (*Z*)-Stereoselective Enol Tosylation**

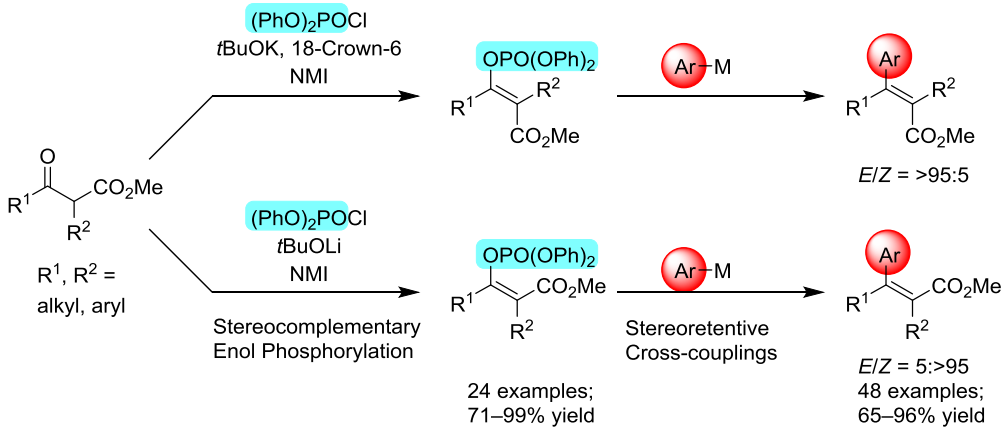
Method C-1 : Stereoretentive Suzuki-Miyaura Cross-coupling [$Pd(dppb)Cl_2$]

Method D-1 : Stereoretentive Suzuki-Miyaura Cross-coupling [$Pd(dppf)Cl_2$]

Method C-2 & D-2 : Stereoretentive Suzuki-Miyaura Cross-coupling [$Pd(OAc)_2$–SPhos]

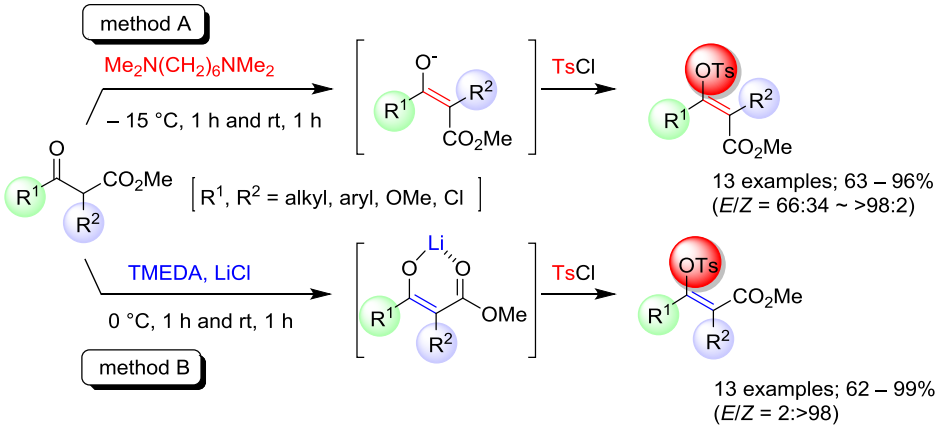
Scheme 1-6. Parallel and practical methods for the preparation of both (*E*)- and (*Z*)-β-aryl^1-β-aryl^2-α,β-unsaturated esters and (*E*)- and (*Z*)-α-aryl^1-β-aryl^2-α,β-unsaturated esters.

In chapter 3, a versatile, robust, and stereocomplementary synthesis of fully-substituted (*E*)- and (*Z*)-stereodefined α,β-unsaturated esters from accessible α-substituted β-ketoesters *via* (*E*)- and (*Z*)-enol phosphonates was achieved (**Scheme 1-7**). The present method involves two accessible reaction sequences: (i) (*E*)- and (*Z*)-stereocomplementary enol phosphorylations of a wide variety of β-ketoesters (24 examples; 71–99% yield, each >95:5 ds), and (ii) (*E*)- and (*Z*)-stereoretentive Suzuki–Miyaura cross-coupling (16 examples; 71–91% yield, >81:19 ds) and Negishi cross-coupling (32 examples; 65–96% yield, >95:5 ds) using (*E*)- and (*Z*)-enol phosphonates. ^{1}H NMR monitoring for a key reactive *N*-phosphorylammonium (imidazolium) intermediate **I** and an application in the synthesis of both (*E*)- and (*Z*)-tamoxifen precursors are described.



Scheme 1-7. Stereocomplementary synthesis of fully-substituted (*E*)- and (*Z*)-stereodefined α,β-unsaturated esters from accessible α-substituted β-ketoesters *via* (*E*)- and (*Z*)-enol phosphonates.

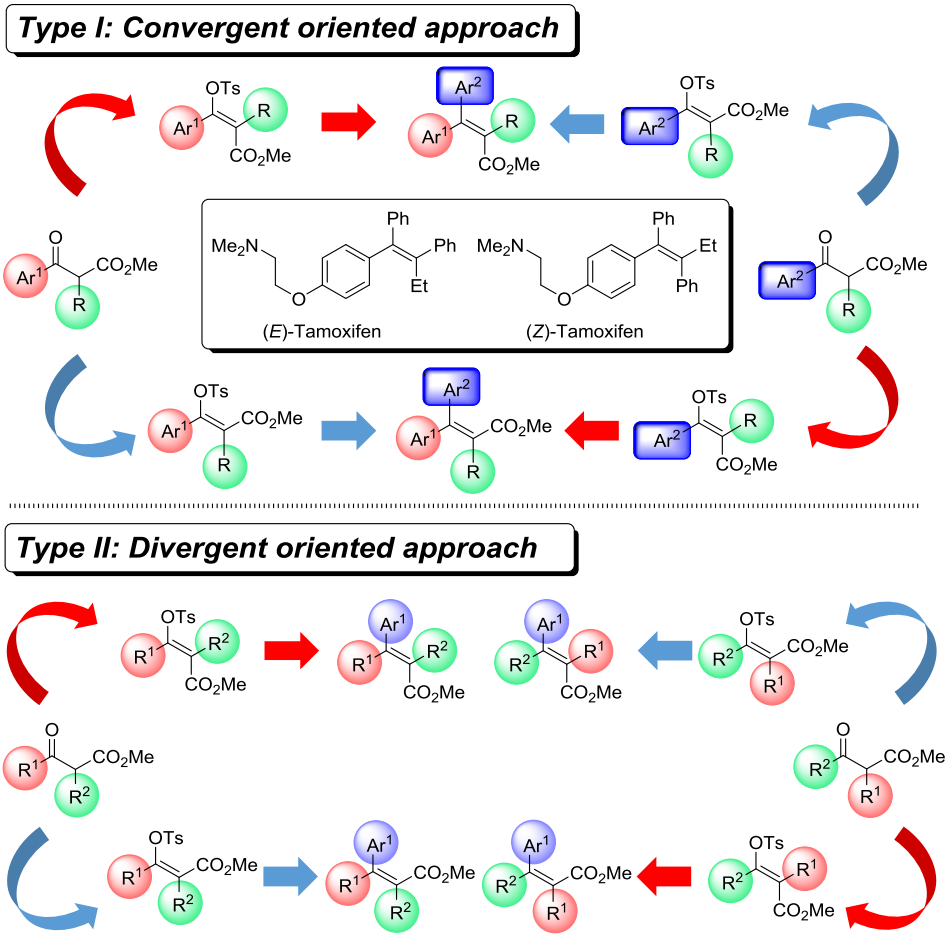
In chapter 4, a robust method for preparing (*E*)- and (*Z*)-stereodefined fully-substituted enol tosylates is described (**Scheme 1-8**). α-Substituted β-ketoesters undergo (*E*)-selective enol tosylations using TsCl–$Me_2N(CH_2)_6NMe_2$ as the reagent (method A, 13 examples; 63–96%) and (*Z*)-selective enol tosylations using TsCl–TMEDA–LiCl as the reagent (method B, 13 examples; 62–99%). A plausible mechanism for the (*E*)- and (*Z*)-enol tosylation selectivity is proposed. A ^{1}H NMR monitoring experiment revealed that TsCl coupled with TMEDA formed a simple *N*-sulfonylammonium intermediate.



Scheme 1-8. A robust method for preparing (*E*)- and (*Z*)-stereodefined fully-substituted enol tosylates.

In chapter 5, a highly substrate-general synthesis of all-carbon-substituted *E*- and *Z*-stereodefined olefins is performed (**Scheme 1-9**). The method comprises two sets of parallel and stereocomplementary preparations of (*E*)- and (*Z*)-α,β-unsaturated esters involving two robust and distinctive reactions: 1) stereocomplementary enol tosylations using readily available TsCl/diamine/(LiCl) base reagents, and 2) stereoretentive Negishi cross-coupling using the catalysts [Pd(dppe)Cl_2] (for *E*) and [Pd(dppb)Cl_2] (for *Z*). The present parallel approach is categorized as both type I (convergent approach: 16 examples, 56−87% yield) and type II (divergent approach: 18 examples, 70−95% yield). The following two developments are performed by Atsushi Honda, one of the author's colleagues: (i) The obtained (*E*)- and (*Z*)-α,β-unsaturated ester scaffolds

are successfully transformed into various *E*- and *Z*-stereodefined known and novel olefins (8x2 derivatization arrays). (ii) As a demonstration, application to the parallel synthesis of both (*E*)- and (*Z*)-tamoxifens, a representative motif of all-carbon-substituted olefins, is accomplished in a total of eight steps with overall yields of 58% (average 93%) and 57% (average 93%), respectively.

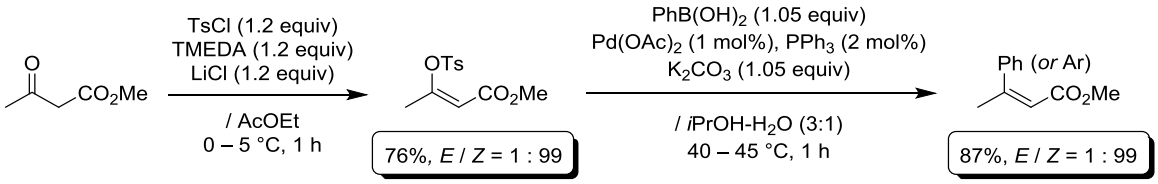


Scheme 1-9. Parallel and a highly substrate-general synthesis of all-carbon-substituted *E*- and *Z*-stereodefined olefins.

In the next two chapters 6 and 7, the author reports two subjects directed for the publication in *Organic Syntheses*. Unique features of this journal are as follows. 1) Each procedure and all characterization data are carefully checked for reproducibility in the laboratory of a member of the Board of Editors. 2) The procedure should be resulted in at least 5 g and no more than 50 g of the final product. 3) The purity of the final product should be at least 97%. The author has developed the procedure for two useful and less accessible building blocks in line with the criteria of *Organic Syntheses*.

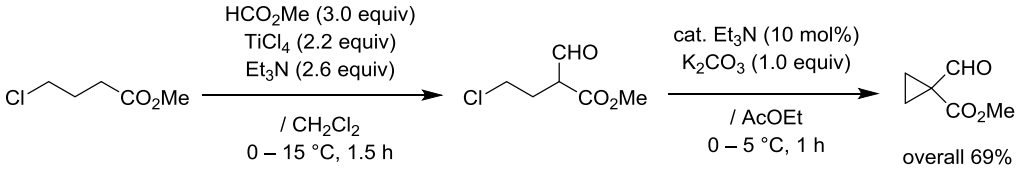
In chapter 6, a synthesis of methyl (*Z*)-3-phenyl-2-butenoate [methyl (*Z*)-β-methylcinnamate] directed for *Organic Syntheses* is presented (**Scheme 1-10**). Despite its simple structure, hitherto reported methods require multi-steps or expensive reagents, a low temperature, and a long reaction period. The enol tosylation of methyl acetoacetate utilizing TsCl−TMEDA−LiCl reagent in AcOEt solvent gives (*Z*)-3-(*p*-toluenesulfonyloxy)but-2-enoate, which is converted to methyl (*Z*)-3-phenyl-2-butenoate utilizing a

highly cost-effective $Pd(OAc)_2$ (1 mol%)/PPh_3 (2 mol%)-catalyzed Suzuki-Miyaura cross-coupling with nearly perfect (*Z*)-stereoretention. Throughout the procedure, tedious column chromatographic purification is not required. In addition, environmentally benign solvents, such as AcOEt, *i*PrOH, and H_2O, are employed for both of two reaction steps and the corresponding extraction (work-up) steps. In addition, the synthesis of the aryl analogues including stereocomplementary (*E*)-isomer are addressed.



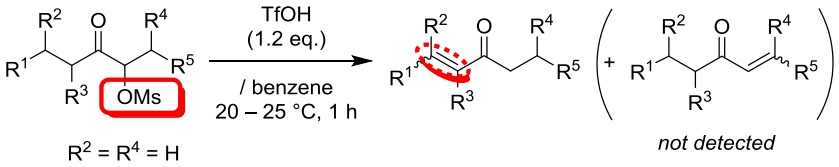
Scheme 1-10. A synthesis of methyl (*Z*)-3-phenyl-2-butenoate directed for *Organic Syntheses*.

In chapter 7, a synthesis of methyl 1-formylcyclopropanecarboxylate directerd for *Organic Syntheses* is disclosed (**Scheme 1-11**). Despite its utility to install cyclopropane segment into various pharmaceuticals, hitherto reported methods require multi-steps or expensive reagents, a low temperature, and a long reaction period. Starting methyl 4-chlorobutanoate, possessing base-sensitive γ-chloro moiety, can be successfully α-formylated utilizing distinctive $TiCl_4$/Et_3N-mediated (Ti-Claisen) condensation at 0−15 °C to give methyl 4-chloro-1-formylbutanoate. Without any purification of the α-formylester, successive cyclopropanation is performed in mild basic conditions [Et_3N (10 mol%)/K_2CO_3 (1 equiv) in AcOEt at 0−15 °C] to produce methyl 1-formylcyclopropanecarboxylate, which is easily purified by simple distillation (the boiling point was documented for the first time). Throughout the procedure, column chromatographic purification is not required.



Scheme 1-11. A synthesis of methyl 1-formylcyclopropanecarboxylate directed for *Organic Syntheses*.

In chapter 8, a highly regiocontrolled acid-induced Favorskii-type elimination reaction of acyloin mesylates proceeded smoothly to give more substituted α,β-unsaturated ketones (**Scheme 1-12**). Not only acyclic but also cyclic acyloin mesylates produced the corresponding higher substituted enones via double-bond-migration pathway. A mechanistic speculation and application to a synthesis of chiral muscone precursor are also described.



Scheme 1-12. Regiocontrolled acid-induced Favorskii-type elimination reaction using unsymmetrically-substituted acyloin mesylates.

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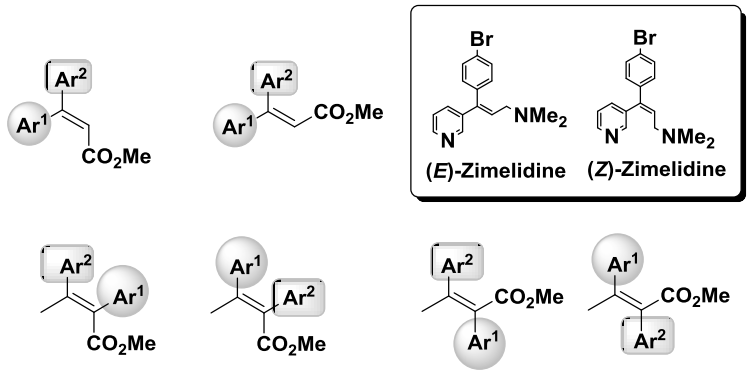
Chapter 2.
(E)-, (Z)-Parallel Preparative Methods for Stereodefined β,β-Diaryl- and α,β-Diaryl-α,β-unsaturated Esters: Application to Stereocomplementary Concise Synthesis of Zimelidine

Abstract

Parallel and practical methods for the preparation of both (*E*)- and (*Z*)-β-aryl[1]-β-aryl[2]-α,β-unsaturated esters **2-1** and (*E*)- and (*Z*)-α-aryl[1]-β-aryl[2]-α,β-unsaturated esters **2-2** are described. These methods involve accessible, robust, stereocomplementary *N*-methylimidazole (NMI)-mediated enol tosylations (14 examples, 70−99% yield), as well as stereoretentive Suzuki-Miyaura cross-couplings (36 examples, 64−99% yield). The highlighted feature of the present protocol is the use of parallel and stereocomplementary approaches to obtain highly (*E*)- and (*Z*)-pure products **2-1** and **2-2** by utilizing sequential enol tosylations and cross-coupling reactions. An expeditious and parallel synthesis of (*E*)- and (*Z*)-zimelidine (**2-3**), which is a highly representative selective serotonin reuptake inhibitor (SSRI), was performed by utilizing the present methods.



Introduction

The stereocontrolled preparation of ubiquitous (*E*)- and (*Z*)-α,β-unsaturated esters is pivotal in organic syntheses because these compounds serve as useful structural scaffolds for various stereodefined olefins and conjugate (Michael) addition acceptors. Both (*E*)- and (*Z*)-β-aryl[1]-β-aryl[2]-α,β-unsaturated esters **2-1** and (*E*)- and (*Z*)-α-aryl[1]-β-aryl[2]-α,β-unsaturated esters **2-2** are well-recognized synthetic building blocks among various α,β-unsaturated esters (**Figure 2-1**).

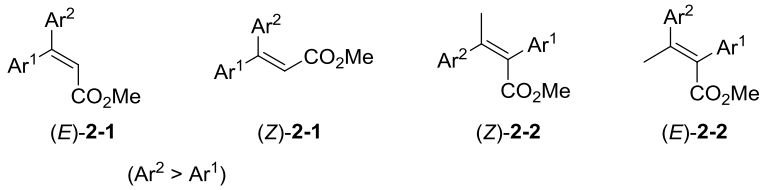
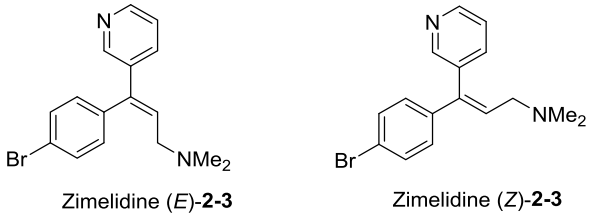


Figure 2-1. Examples of (*E*)- and (*Z*)-β-aryl[1]-β-aryl[2]-α,β-unsaturated esters **2-1** and (*E*)- and (*Z*)-α-aryl[1]-β-aryl[2]-α,β-unsaturated esters **2-2**.

Despite the reasonable demand for (*E*)- and (*Z*)-esters **2-1** and **2-2** for the synthesis of natural products, fine and supramolecules, and for process chemistry, stereoselective and general preparative methods have not yet been fully established due to the fundamental synthetic difficulty in differentiating between structurally similar diaryl (Ar^1 and Ar^2) moieties. A literature survey for the preparation of (*E*)- and (*Z*)-**2-1** reveals that 1) Mizoroki−Heck reactions,[1] 2) a recent notable oxidative Heck reaction sequence (Studer's group),[2] and 3) an excellent cooper-catalyzed conjugate addition of $ArB(OH)_2$ to alkynoates (Yamamoto's group),[3] are representative stereocontrolled methods. A stereoselective preparative method of (*E*)- and (*Z*)-**2-2** with sufficient substrate generality, however, is more limited. Sequential stereoretentive Suzuki-Miyaura cross-coupling with (*E*)-β-chloro-α-iodo-α,β-unsaturated esters should also be included as a successful example (Ogilvie's group).[4] Condensation of ynolates with acetophenone is a useful method (Shindo's group), but a sole example has been presented with moderate stereoselectivity.[5]

Consistent with our continued interest in finding a methodology for the stereocomplementary preparation of (*E*)- and (*Z*)-stereodefined α,β-unsaturated esters,[6] we disclose herein a parallel preparative method for (*E*)- and (*Z*)-**2-1** and (*E*)- and (*Z*)-**2-2**. The present reaction sequence utilizes accessible and robust *N*-methylimidazole (NMI)-mediated enol tosylations and Suzuki-Miyaura cross-couplings, as depicted in **Scheme 2-1**. The highlighted aspect of the present protocol is parallel and stereocomplementary Approaches 1 and 2 to obtain highly (*E*)- and (*Z*)- pure products **2-1** and **2-2** (or **2-2'**) by accessible and robust enol tosylations and cross-coupling reactions, which start from readily available β-ketoesters **2-4** (or **2-4'**) and **2-6** (or **2-6'**), respectively. The present dual-mode approach enhances the versatility of the project. To demonstrate the utility of the present method, we describe an expeditious and parallel synthesis of (*E*)- and (*Z*)-zimelidine (**2-3**),[7] which is a highly representative selective serotonin reuptake inhibitor (SSRI; **Figure 2-2**).

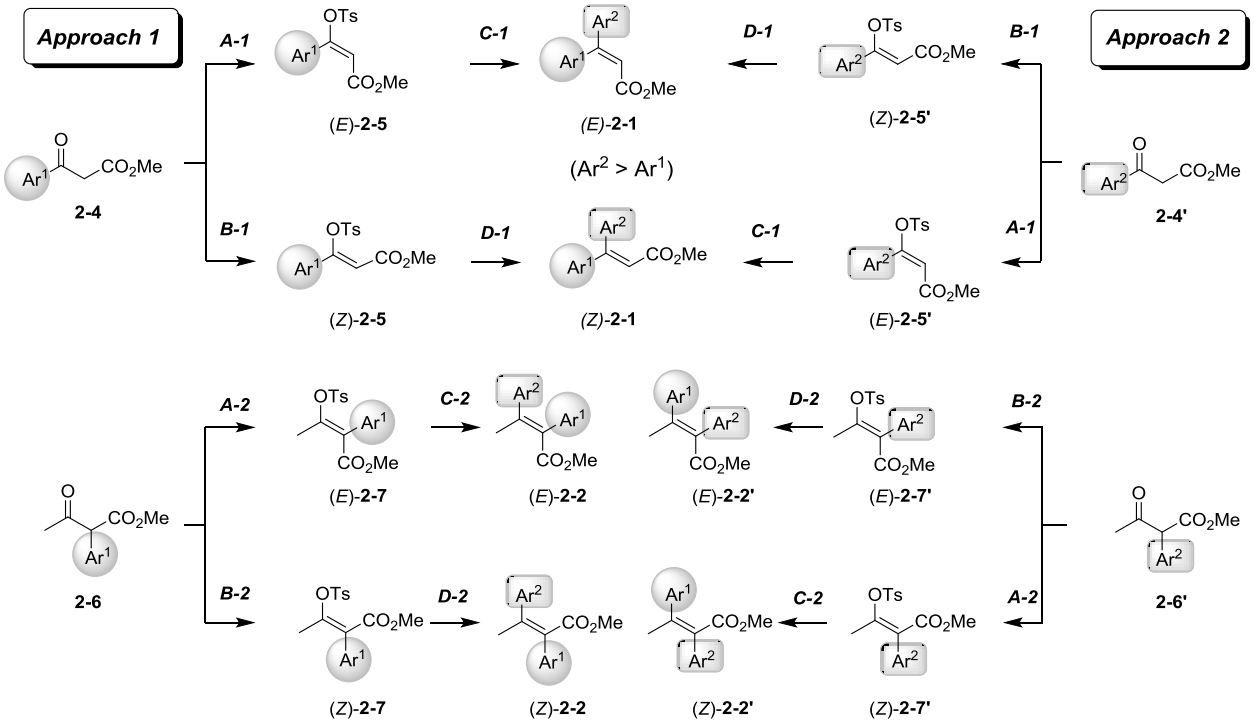


Zimelidine (*E*)-**2-3** Zimelidine (*Z*)-**2-3**

Figure 2-2. Structures of (*E*)- and (*Z*)-zimelidine (**3-3**) synthesized by means of the methodology described herein.

Results and Discussion

The initial (*E*)- and (*Z*)-stereocomplementary enol tosylations[8-10] of starting readily available β-ketoesters **2-4** were performed by utilizing a conventional procedure with TsCl/NMI/base, as listed in **Table 2-1**. The salient features are as follows: 1) (*E*)-enol tosylation proceeded in good to excellent yield, but poor stereoselectivity, despite screening a number of conditions (amine and solvent; Method A-1). 2) In clear contrast, the (*Z*)-enol tosylation exhibited nearly perfect stereoselectivity (Method B-1). 3) Fortunately, (*E*)- and (*Z*)-enol tosylates **2-5** were easily separated by column chromatography and/or recrystallization. This result markedly contrasted with that obtained when using relevant aliphatic α,β-unsaturated esters,[6] which was likely to be due to intrinsically more stable (*Z*)-β-aryl-α,β-unsaturated (cinnamic) ester moiety.[11] 4) It should be noted that all of these stereodefined (*E*)- and (*Z*)-enol tosylates **2-5** are novel compounds.



Method A-1 & A-2 : (*E*)-Stereoselective Enol Tosylation **Method B-1 & B-2 : (*Z*)-Stereoselective Enol Tosylation**

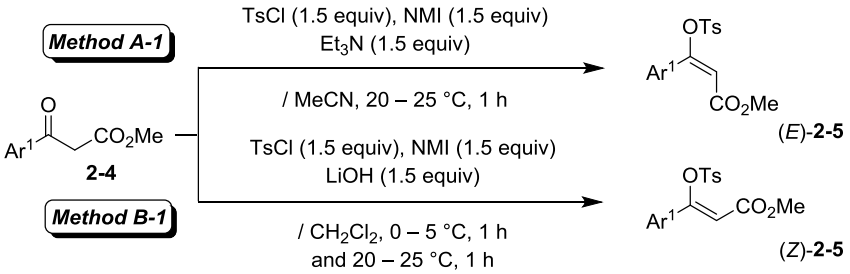
Method C-1 : Stereoretentive Suzuki-Miyaura Cross-coupling [Pd(dppb)Cl_2]

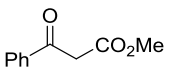
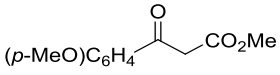
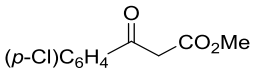
Method D-1 : Stereoretentive Suzuki-Miyaura Cross-coupling [Pd(dppf)Cl_2]

Method C-2 & D-2 : Stereoretentive Suzuki-Miyaura Cross-coupling [Pd$(OAc)_2$–SPhos]

Scheme 2-1. Parallel and stereocomplementary syntheses of both (*E*)- and (*Z*)-diaryl (Ar^1, Ar^2) α,β-unsaturated esters **2-4** and **2-6**. Ts = tosyl.

Table 2-1. (*E*)- and (*Z*)-Stereocomplementary enol tosylations using β-Ar^1-β-ketoesters **2.4**.

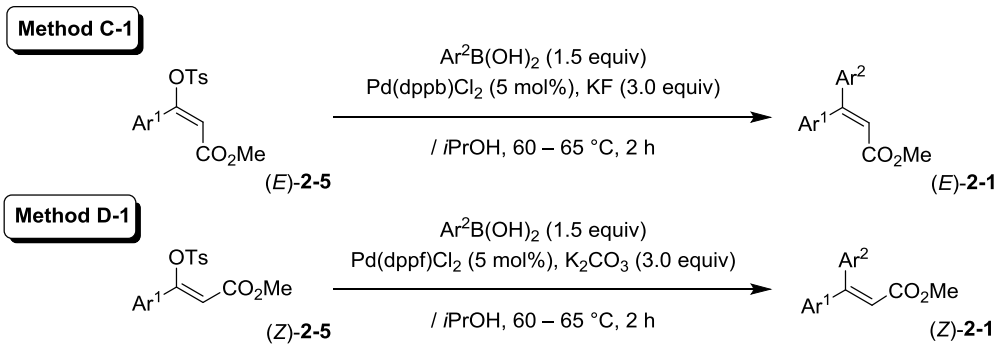


Entry	Ketoester **2-4**	Method	Product	Yield / %	*E*/*Z*[a]
1		A-1	(*E*)-**2-5a**	73	60:40
2		B-1	(*Z*)-**2-5a**	70	2:>98
3		A-1	(*E*)-**2-5b**	96	51:49
4		B-1	(*Z*)-**2-5b**	80[b]	2:>98
5		A-1	(*E*)-**2-5c**	98	59:41
6		B-1	(*Z*)-**2-5c**	85[c]	2:>98

a) Determined by ^{1}H NMR of the crude products. b) NaOH was used instead of LiOH. c) TsCl (2.0 equiv), LiOH (2.0 equiv), and NMI (2.0 equiv) were used.

Subsequent (*E*)- and (*Z*)-stereoretentive Suzuki-Miyaura cross-couplings[12] with (*E*)-**2-5** and (*Z*)-**2-5** were performed, as summarized in **Table 2-2**. The salient features are as follows: 1) Although reported catalysis with $Pd(OAc)_2$–PCy_3[6b] produced disappointing results (decomposition of (*E*)-**2-5**; a somewhat undesirable isomerization for (*Z*)-**2-5**), [Pd(dppb)Cl_2]/KF or /K_2CO_3 catalysis resulted from the reaction with (*E*)-**2-5**, whereas [Pd(dppf)Cl_2]/K_2CO_3 catalysis produced fruitful results for (*Z*)-**2-5** in good to excellent yield with consistent stereoretention. 2) In clear contrast to the case of relevant aliphatic type substrates,[6b] which

Table 2-2. The (E)- and (Z)-stereoretentive Suzuki–Miyaura cross-coupling of β-Ar1-enol tosylates 2-5.[a]



Entry	Ar^1	Substrate[b]	Ar^2	Method	Product	Yield / %	*E*/*Z*[c]
1	Ph	(*E*)-**2-5a**	(*p*-Me)C_6H_4	C-1	(*E*)-**2-1a**	92 (88)[d]	95:5 (95:5)
2		(*Z*)-**2-5a**		D-1	(*Z*)-**2-1a**	88	2:>98
3	Ph	(*E*)-**2-5a**	(*p*-MeO)C_6H_4	C-1	(*E*)-**2-1b**	83	95:5
4		(*Z*)-**2-5a**		D-1	(*Z*)-**2-1b**	64	2:98
5	Ph	(*E*)-**2-5a**	(*p*-Cl)C_6H_4	C-1	(*E*)-**2-1c**	55 (88)[d]	98:2
6		(*Z*)-**2-5a**		D-1	(*Z*)-**2-1c**	77	11:89
7	Ph	(*E*)-**2-5a**	(*p*-F)C_6H_4	C-1	(*E*)-**2-1d**	82	96:4
8		(*Z*)-**2-5a**		D-1	(*Z*)-**2-1d**	80	13:87
9	Ph	(*E*)-**2-5a**	(*p*-AcO)C_6H_4	C-1	(*E*)-**2-1e**	88	98:2
10		(*Z*)-**2-5a**		D-1	(*Z*)-**2-1e**	80	10:90
11	Ph	(*E*)-**2-5a**	(*o*-Me)C_6H_4	C-1	(*E*)-**2-1f**	93	96:4
12		(*Z*)-**2-5a**		D-1	(*Z*)-**2-1f**	80	10:90
13	Ph	(*E*)-**2-5a**	(*o*-Cl)C_6H_4	C-1	(*E*)-**2-1g**	93	96:4
14		(*Z*)-**2-5a**		D-1	(*Z*)-**2-1g**	80	10:90
15	(*p*-MeO)C_6H_4	(*E*)-**2-5b**	Ph	C-1	(*Z*)-**2-1b**	88[e]	14:86
16		(*Z*)-**2-5b**		D-1	(*E*)-**2-1b**	91	90:10
17	(*p*-Cl)C_6H_4	(*E*)-**2-5b**	Ph	C-1	(*Z*)-**2-1c**	87[f]	3:97
18		(*Z*)-**2-5b**		D-1	(*E*)-**2-1c**	95	95:5

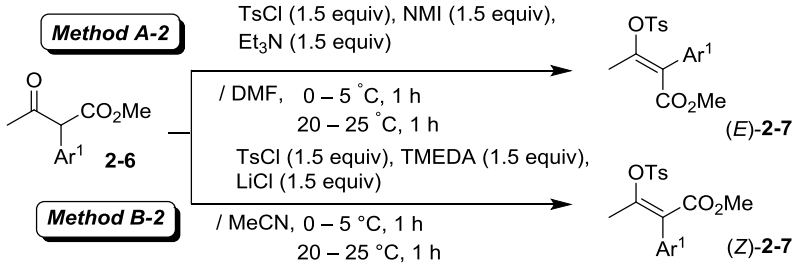
a) dppb=1,4-bis(diphenylphosphino)butane, dppf=1,1'-bis(diphenylphosphino)ferrocene. b) *E*- and *Z*-purities were up to >98% based on the ^{1}H NMR spectra. c) Determined by ^{1}H NMR spectroscopy of the crude products. d) K_2CO_3 was used instead of KF. e) 5.0 equivalents of $PhB(OH)_2$ were used. f) 3.0 equivalents of $PhB(OH)_2$ were used.

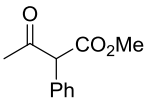
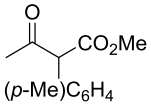
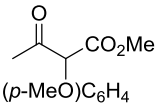
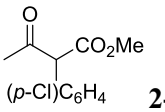
requires harsh conditions (reflux in DMF), the present reaction proceeded smoothly under considerably milder conditions (60 °C in *i*PrOH) to give the corresponding (*E*)- and (*Z*)-esters **2-1** (Methods C-1 and D-1). 3) The parallel preparation mode was performed to afford (*E*)-**2-1b**, (*Z*)-**2-1b**, (*E*)-**2-1c**, and (*Z*)-**2-1c** (Table 2-2, entries 3−6 and 15−18). 4) Various substituents on Ar^1 and/or Ar^2, such as *p*-Me, *p*-MeO, *p*-Cl, *p*-F, *p*-AcO *o*-Me, and *o*-Cl, were compatible (**Table 2-2**).

Our next study focused on a parallel approach for the preparation of (*E*)- and (*Z*)-α-aryl[1]-β-aryl[2]-α,β-unsaturated esters **2-2**. The reported method using a condensation reaction of ynolates with acetophenone produces a variety of tetrasubstituted α,β-unsaturated esters,[5] wherein a sole specific example, (*E*)-**2-2a** with *E*/*Z* = 86:14, is produced. To the best of our knowledge, there is no (*E*)- and (*Z*)-stereocomplementary method for the preparation of **2-2** with sufficient substrate-generality.

Table 2-3 lists successful (*E*)- and (*Z*)-stereocomplementary enol tosylations starting from β-ketoesters **2-6**. Notably, refinement of the reaction conditions led to highly satisfactory results (excellent yield and nearly perfect (*E*)- and (*Z*)-stereoselectivity); replacement of MeCN with DMF was effective for the preparation of (*E*)-**2-7** (Method A-2), and the combined use of TMEDA/LiCl displaced with NMI/LiOH was effective for (*Z*)-**2-7** (Method B-2). Similar to the case of **2-5**, all of these stereodefined (*E*)- and (*Z*)-enol tosylates **2-7** are novel compounds.

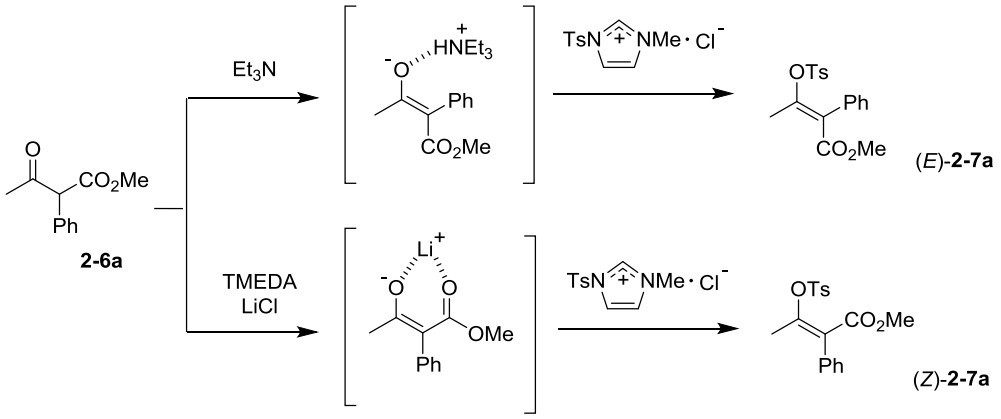
Table 2-3. The (*E*)- and (*Z*)-stereocomplementary enol tosylations of α-Ar^1-β-ketoesters **2-6**.[a]



Entry	Ketoesters **2-6**	Method	Product	Yield / %	*E*/*Z*[b]
1	 **2-6a**	A-2	(*E*)-**2-7a**	94	>98:2
2		B-2	(*Z*)-**2-7a**	93	2:>98
3	 **2-6b**	A-2	(*E*)-**2-7b**	98	>98:2
4		B-2	(*Z*)-**2-7b**	99	2:>98
5	 **2-6c**	A-2	(*E*)-**2-7c**	98	>98:2
6		B-2	(*Z*)-**2-7c**	99	2:>98
7	 **2-6d**	A-2	(*E*)-**2-7d**	92	>98:2
8		B-2	(*Z*)-**2-7d**	98	2:>98

a) TMEDA = *N*,*N*,*N*',*N*'-tetramethylethylenediamine. b) Determined by ^{1}H NMR spectroscopic analysis of the crude products.

A plausible mechanism for the successful emergence of (*E*)-, (*Z*)-enol tosylation stereoselectivity is depicted in **Scheme 2-2**, wherein substrate **2-6a** is exemplified. The addition of TsCl and NMI forms key a highly reactive sulfonyl ammonium salt, the existence of which is supported by ^{1}H NMR spectroscopic analysis.[6a] The (*E*)-stereoselective reaction proceeds through a non-chelation pathway to give (*E*)-**2-7a**; the quaternary ammonium cation aids (*E*)-enolate formation formation through dipole−dipole repulsive interactions between the oxy anion and ester function. In clear contrast, the (*Z*)-stereoselective reaction proceeds through a chelation mechanism to give (*Z*)-**2-7a**; Li cation facilitates (*Z*)-enolate formation.

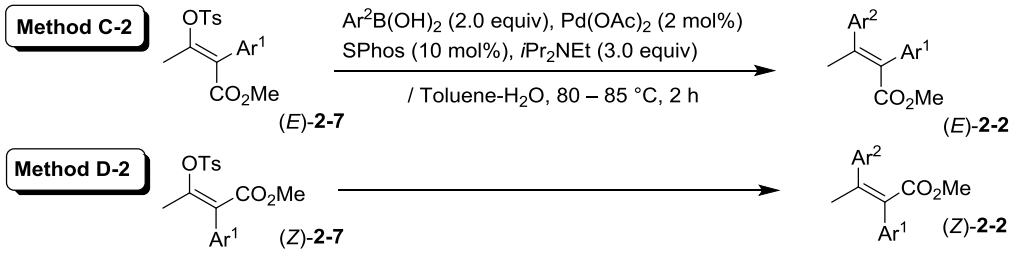


Scheme 2-2. Mechanistic investigation for (*E*)- and (*Z*)-stereoselective enol tosylation of **2-6a**.

Successful results of subsequent (*E*)- and (*Z*)-stereoretentive Suzuki-Miyaura cross-coupling reactions with enol tosylates (*E*)-**2-7** and (*Z*)-**2-7** are listed in **Table 2-4**. Unfortunately, the aforementioned catalytic reactions with [Pd(dppb)Cl_2]/KF and [Pd(dppf)]Cl_2/K_2CO_3 could not be applied for the respective preparation of (*E*)-**2-7** and (*Z*)-**2-7**; Under identical conditions, Methods C-1 and D-1 resulted in low conversion yield (ca. 20%). Several other catalytic reactions, such as those [Pd(PPh_3)$_4$], Pd(OAc)$_2$/PCy_3/base, and [Pd(PPh_3)$_2Cl_2$], gave similar disappointing results. After standard screening procedures, to our delight, the reaction with Pd(OAc)$_2$/2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos)/*i*Pr_2NEt catalysis proceeded smoothly to give the desired (*E*)-**2-2** and (*Z*)-**2-2**.

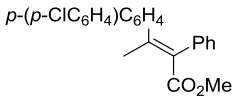
The salient features are as follows: 1) For both (*E*)-**2-7** and (*Z*)-**2-7** substrates, the use of Pd(OAc)$_2$/ SPhos/*i*Pr_2NEt catalyst system produced fruitful results. 2) Excellent yield was obtained in almost all cases examined (entries 1−6, 9−16). 3) Notably, almost perfect stereoretentivity was obtained in every case examined. 4) Two sets of the reactions with the (*p*-Cl)$C_6H_4B(OH)_2$ nucleophile (Ar^2) and substrates containing (*p*-Cl)C_6H_4 group (Ar^1) were concurrent with further cross-couplings (**Table 2-4**, entries 7, 8, 17, and 18). The structure of these byproducts was unambiguously determined based on ^{1}H NMR and ^{13}C NMR spectroscopy, IR spectroscopy, and HRMS measurements. This conspicuous problem was successfully resolved by using another catalyst (see below). 5) The addition of H_2O to the reaction system dramatically affected the results; In the absence of H_2O, the yield was decreased to ca. 20%. 6) Several substituents on Ar^1 and/or Ar^2, such as *p*-Me, *p*-MeO, and *p*-Cl, were compatible (**Table 2-4**, entries 3−8 and 13−18). 7) Heterocyclic furan-3-yl and 3-thiophen-3-yl boronic acids served as suitable nucleophiles (**Table 2-4**, entries

Table 2-4. The (*E*)- and (*Z*)-stereoretentive Suzuki-Miyaura cross-coupling of α-Ar^1-enol tosylates **2-7**.

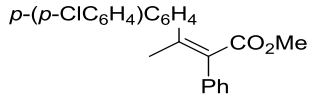


Entry	Ar^1	Substrate[a]	Ar^2	Method	Product	Yield/ %	*E*/*Z*[b]
1	Ph	(*E*)-**2-7a**	Ph	C-2	(*E*)-**2-2a**	94	>98:2
2		(*Z*)-**2-7a**		D-2	(*Z*)-**2-2a**	99	2:>98
3		(*E*)-**2-7a**	(*p*-Me)C_6H_4	C-2	(*E*)-**2-2b**	97	>98:2
4		(*Z*)-**2-7a**		D-2	(*Z*)-**2-2b**	99	2:>98
5		(*E*)-**2-7a**	(*p*-MeO)C_6H_4	C-2	(*E*)-**2-2c**	97	98:2
6		(*Z*)-**2-7a**		D-2	(*Z*)-**2-2c**	99	2:>98
7		(*E*)-**2-7a**	(*p*-Cl)C_6H_4	C-2	(*E*)-**2-2d**	48 (10)[c]	>98:2
8		(*Z*)-**2-7a**		D-2	(*Z*)-**2-2d**	41 (10)[d]	2:>98
9		(*E*)-**2-7a**		C-2	(*E*)-**2-2e**	92	>98:2
10		(*Z*)-**2-7a**		D-2	(*Z*)-**2-2e**	96	2:>98
11		(*E*)-**2-7a**		C-2	(*E*)-**2-2f**	94	>98:2
12		(*Z*)-**2-7a**		D-2	(*Z*)-**2-2f**	95	2:>98
13	(*p*-Me)C_6H_4	(*E*)-**2-7b**	Ph	C-2	(*E*)-**2-2g**	99	>98:2
14		(*Z*)-**2-7b**		D-2	(*Z*)-**2-2g**	97	2:>98
15	(*p*-MeO)C_6H_4	(*E*)-**2-7c**	Ph	C-2	(*E*)-**2-2h**	99	>98:2
16		(*Z*)-**2-7c**		D-2	(*Z*)-**2-2h**	99	2:>98
17	(*p*-Cl)C_6H_4	(*E*)-**2-7d**	Ph	C-2	(*E*)-**2-2i**	41 (50)[e]	>98:2
18		(*Z*)-**2-7d**		D-2	(*Z*)-**2-2i**	58 (39)[f]	2:>98

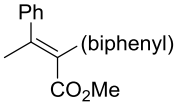
a) The *E*- and *Z*-purities were up to >98% based on the ^{1}H NMR spectra. b) Determined by ^{1}H NMR spectroscopy of the crude products.

c) 

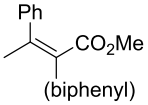
(*E*)-**2d-x**

d) 

(*Z*)-**2d-x**

e) 

(*E*)-**2i-x**

f) 

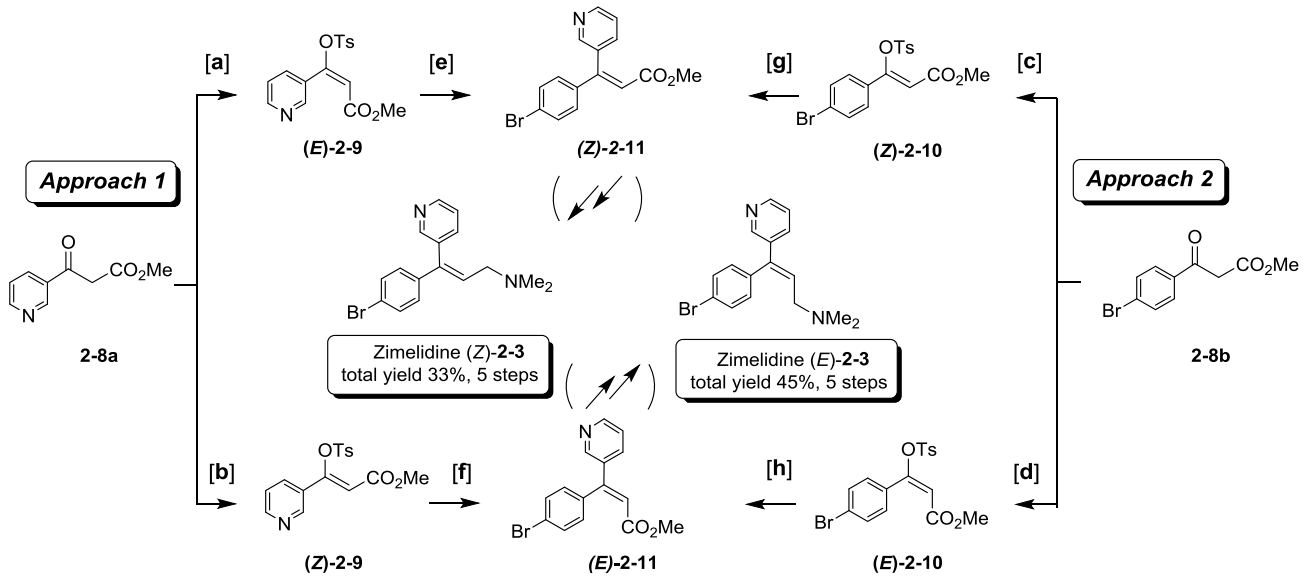
(*Z*)-**2i-x**

9−12).

With this successful outcome (Methods A-1, B-1, C-1, D-1) in our hands, we next envisaged an application for concise and parallel stereocontrolled synthesis of (*E*)- and (*Z*)-**2-3**. We referred fully to the pioneering works established by the groups of Bäckvall and Högberg.[13,14]

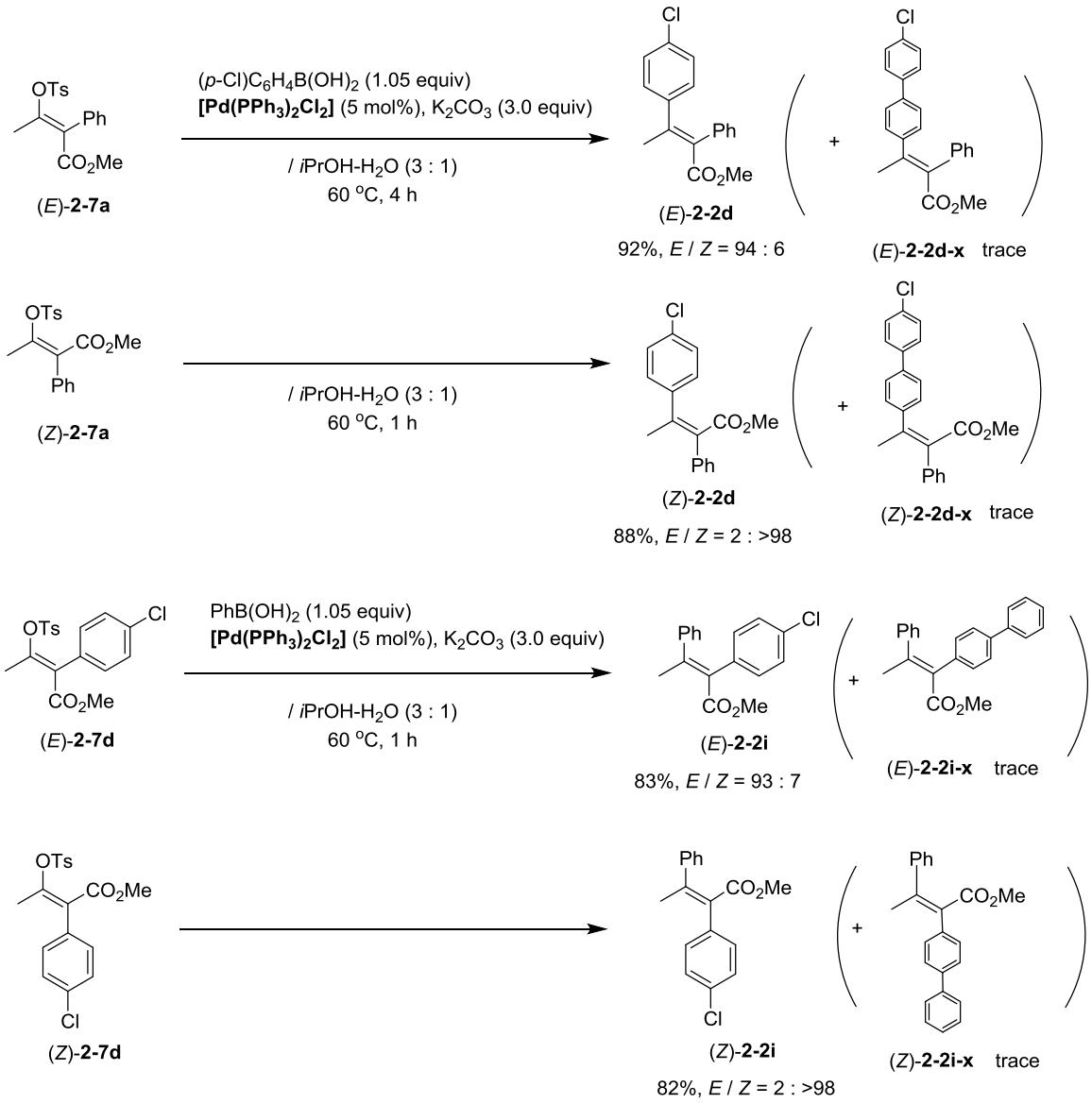
The reported nonstereoselective method[13] for the synthesis of **2-3** involves the following reaction sequence: 1) addition of allylmagnesium chloride with *p*-bromophenyl 3-pyridyl ketone, giving the tertiary allyl alcohol, 2) successive acid-promoted allyl rearrangement giving the allyl chloride; and 3) final dimethylamination. On the other hand, stereoselective synthesis[14] was performed proficiently by rigorous pH-controlled reductive amination procedure. Due to the difficulty of stereocontrol, and oxidation as a side reaction, reductive amination steps were required.

Our synthetic approach and the successful result are illustrated in **Scheme 2-3**. The salient features are as follows: 1) Steresoselective enol tosylations of β-ketoestes **2-8a** and **2-8b** successfully proceeded when using Methods A-1 and B-1, conditions [a]−[d]. 2) Contrary to our expectation, Suzuki-Miyaura cross-coupling with (3-Py)B(OH)$_2$ with (*E*)-**2-9** did not proceed (no reaction) under the identical conditions (Methods C-1 and D-1). Fortuitously, the use of small amounts of H_2O cosolvent resolved the problem for all four desired stereocomplementary reactions, conditions [e]−[h], in excellent yield (79−91%) with almost perfect stereoretention (*E*/*Z* = >97:3). 3) Despite the labile *p*-Br substituent, none of the four cross-couplings had serious side reactions, such as reduction or further couplings. 4) Compounds (*E*)- and (*Z*)-**2-3** were successfully obtained through the accessible reaction sequences, that is, DIBAL reduction, chlorination with $SOCl_2$/catalytic DMF, and final dimethylamination with aqueous solution of Me_2NH, conditions [i] and [j]. Despite the simple operation, undesirable isomerization between *E* and *Z* did not occur. 5) Overall yields were 33% for (*Z*)-**2-3** and 45% for (*E*)-**2-3** after each five parallel steps. Compared with extensive studies on the synthesis for (*E*)- and (*Z*)-**2-3**,[13,14] which involved MnO_2 oxidation of allylic alcohol followed by reductive amination or dimethylamination, the present method is of highly concise and orthogonal without tedious pH-dependent separation.



Scheme 2-3. Parallel and stereocomplementary syntheses of both (*E*)- and (*Z*)-**2-3**. Reagents and conditions: [a] TsCl (1.5 equiv)/NMI (1.5 equiv)/Et_3N (1.5 equiv)/*N*,*N*-dimethylacetamide (DMA), 20 – 25 °C, 1 h. 96%, *E* / *Z* = 75:25. Pure (*E*)-**2.9** was isolated in 66% (column chromatography). [b] TsCl (2.0 equiv)/NMI (2.0 equiv)/NaOH (1.5 equiv)/CH_2Cl_2, 20 – 25 °C, 2 h. 81%, *E*/*Z* = 8:92, 81%. Pure (*Z*)-**2-9** was isolated in 66% (washing with hexane). Notably, the reaction with LiOH is very sluggish (only 29% yield). [c] TsCl (1.5 equiv)/NMI (1.5 equiv)/LiOH (1.5 equiv)/CH_2Cl_2, 20 – 25 °C, 2 h. 72%, *E*/*Z* = 2:>98. [d] Similar conditions to [a], 92%, *E*/*Z* = 67:33. Pure (*Z*)-**2-10** was isolated in 62% (column chromatography). [e] (*p*-Br)$C_6H_4B(OH)_2$ (1.05 equiv), [$Pd(PPh_3)_2Cl_2$] (5 mol%), K_2CO_3 (3.0 equiv), *i*PrOH/H_2O (3:1), 60 – 65 °C, 1 h, 89%, *E*/*Z* = 2:>98. The use of [Pd(dppb)Cl_2] gave about 35% conversion. [f] (*p*-Br)$C_6H_4B(OH)_2$ (1.05 equiv), [$Pd(PPh_3)_2Cl_2$] (5 mol%), K_2CO_3 (3.0 equiv), *i*PrOH/H_2O (3:1), 60 – 65 °C, 1 h, 79%, *E*/*Z* = >98:2. [g] (3-Py)$B(OH)_2$ (1.05 equiv), [Pd(dppf)Cl_2] (5 mol%), K_2CO_3 (3.0 equiv), *i*PrOH/H_2O (3:1), 60 – 65 °C, 81%, *E*/*Z* = 2:>98. [h] Similar conditions to those given for [g], 81%, *E*/*Z* = 97:3. [i] i) diisobutylaluminum hydride (DIBAL; 4.0 equiv)/THF, −78 °C, 0.5 h. 82%; ii) $SOCl_2$ (1.5 equiv), DMF (5 mol%)/CH_2Cl_2, 20 − 25 °C, successive treatment with an aqueous solution of Me_2NH (10 equiv), 1 h, 91%, *E*/*Z* = 2:>98. [j] Similar conditions to those given for [i], overall 81%, *E*/*Z* = 98:2.

Encouraged by the successful synthesis of (*E*)- and (*Z*)-**2-3**, we reinvestigated two sets of cross-couplings by using a (*p*-Cl)$C_6H_4B(OH)_2$ nucleophile with (*E*)-**2-7a** and (*Z*)-**2-7a** and a $PhB(OH)_2$ nucleophile with acceptors (*E*)-**2-7d** and (*Z*)-**2-7d**, which contained the (*p*-Cl)C_6H_4 group (see unsatisfactory cases in **Table 2-4**, entries 7, 8, 17, and 18). Gratifyingly, as depicted in Scheme 2-4, the reaction catalyzed by [$Pd(PPh_3)_2Cl_2$]/K_2CO_3 in *i*PrOH/H_2O (3:1) at 60−65 °C proceeded very smoothly to give the desired products (*E*)-**2-2d**, (*Z*)-**2-2d**, (*E*)-**2-2i**, and (*Z*)-**2-2i** in good yield with excellent stereoretention; the amounts of respective undesirable further-coupled byproducts, (*E*)-**2-2d-x**, (*Z*)-**2-2d-x**, (*E*)-**2-2i-x**, and (*Z*)-**2-2i-x,** decreased to trace amounts. The present results contribute towards strengthening the substrate generality of Methods C-2 and D-2. This outcome may be attributed to the milder catalysis with [$Pd(PPh_3)Cl_2$] than that of powerful $Pd(OAc)_2$/SPhos/base catalysis[15] with regard to this specific case.



Scheme 2-4. Refinement for catalysis with the *p*-Cl-substituted nucleophile and substrate by using Methods C-2 and D-2.

Conclusion

An efficient, (*E*)- and (*Z*)-stereocomplementary, and parallel synthetic methods have been developed for the production of a variety of stereodefined β,β-diaryl- and α,β-diaryl-α,β-unsaturated esters. The present method involves a couple of readily accessible reaction sequences; (i) robust and (*E*)-, (*Z*)-stereocomplementary enol tosylations of β-ketoesters and (ii) successive stereoretentive Suzuki-Miyaura (SM) cross-couplings. Appropriate (subtle but laborious) tunings of the catalysts for SM cross-coupling improved the yield, stereoretentivity, and accessibility of the reaction conditions. In addition, 3-pyridyl and (*p*-bromo)phenyl group were compatible during the SM cross-coupling stage, which demonstrates the performance of the concise and parallel stereocontrolled syntheses of (*E*)- and (*Z*)-zimelidines. This method provides a new avenue for the synthesis of these stereodefined β,β-diaryl- and α,β-diaryl-α,β-unsaturated esters in the fields of natural product synthesis and process chemistry.

Experimental

General

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 were 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}H NMR and 75 MHz or 125 MHz for ^{13}C NMR. Chemical shifts (δ) (ppm) in $CDCl_3$ are reported downfield from TMS (0 ppm) for ^{1}H NMR. For ^{13}C NMR, chemical shifts are reported relative to $CDCl_3$ (77.00 ppm) as an internal reference. Mass spectra were measured on a JEOL JMS-T100LC spectrometer. *E*/*Z* ratios were determined by ^{1}H NMR of the crude products.

Starting β-ketoesters **2-4**, **2-8a**, and **2-8b** were prepared by the reported methods.[15,16] β,β-Diaryl-α,β-unsaturated esters (*E*)- and (*Z*)-**2-1a**,[1j] (*E*)-[1j] and (*Z*)-[2] **2-1b**, (*E*)- and (*Z*)-**2-1c**,[2] (*E*)- and (*Z*)-**2-1d**[2] are known compounds. α,β-Diaryl α,β-unsaturated esters (*E*)- and (*Z*)-**2-2a**,[17] as well as (*E*)- and (*Z*)-**2-2b**,[18] are known compounds. Starting β-ketoesters **2-6a**,[19] **2-6b**,[20] **2-6c**,[21] and **2-6d**[19a] were prepared according to reported methods.

Syntheses

Methyl 3-oxo-2-phenylbutanoate 2-6a:[19a] Methyl phenylacetate (15.0 g, 0.10 mol) and methyl acetate (22.2 g, 0.30 mol) in THF (50 mL) were successively added dropwise to a stirred suspension of *t*BuOK (8.42 g, 0.15 mol) in THF (50 mL) at −78 °C under an argon atmosphere, and the mixture was stirred at the same temperature for 2 h and at 40 – 45 °C for 11 h. 1M HCl aqueous solution (ca. 100 mL) 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 distillation to give the desired product (9.61 g, 51%) as a colorless oil. B.p. 108–110 °C/0.75 mmHg (ref. [19] 92–96 °C /0.6 mmHg); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.85 (s, 3H × 3.5/10; enol form), 2.18 (s, 3H × 6.5/10; keto form), 3.69 (s, 3H × 3.5/10; enol form), 3.76 (s, 3H × 6.5/10; keto form), 4.70 (s, 1H × 6.5/10; keto form), 7.12–7.43 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.6, 28.6, 51.6, 52.3, 65.4, 103.9, 126.9, 128.0, 128.1, 128.7, 129.2, 131.0, 132.5, 134.9, 168.8, 172.8, 173.9, 201.3 ppm; IR (neat): ν_{max} = 2953, 1749, 1718, 1645, 1610, 1438, 1344, 1264 cm^{-1}.

Methyl 3-oxo-2-(*p*-tolyl)butanoate 2-6b:[20] Following the procedure for the preparation of **2-6a**, the reaction of methyl *p*-tolylacetate (16.4 g, 0.10 mol) with methyl acetate (22.2 g, 0.30 mol) and *t*BuOK (8.42 g, 0.15 mol) gave the desired product (10.1 g, 49%) as a colorless oil.

B.p. 83–84 °C/0.53 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.85 (s, 3H x 4.0/10; enol form), 2.17 (s, 3H x 6.0/10; keto form), 2.35 (s, 3H × 6.0/10; keto form), 2.36 (s, 3H × 4.0/10; enol form), 3.69 (s, 3H × 4.0/10;

enol form), 3.75 (s, 3H × 6.0/10; keto form), 4.66 (s, 1H × 6.0/10; keto form), 7.02–7.25 ppm (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.6, 20.9, 20.9, 28.4, 51.5, 52.2, 64.9, 103.6, 128.7, 129.0, 129.4, 130.8, 131.9, 137.9, 168.9, 172.8, 173.8, 201.4 ppm; IR (neat): ν_{max} = 2953, 1717, 1644, 1514, 1439, 1340, 1264, 1228 cm^{-1}.

Methyl 2-(4-methoxyphenyl)-3-oxobutanoate 2-6c:[21] Following the procedure for the preparation of **2-6a**, the reaction of methyl *p*-methoxyphenylacetate (18.0 g, 0.10 mol) with methyl acetate (22.2 g, 0.30 mol) and *t*BuOK (8.42 g, 0.15 mol) gave the desired product (9.56 g, 43%) as a colorless oil.
B.p. 93–95 °C/0.56 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.85 (s, 3H × 3.0/10; enol form), 2.17 (s, 3H × 7.0/10; keto form), 3.69 (s, 3H × 3.0/10; enol form), 3.75 (s, 3H × 7.0/10; keto form), 3.81 (s, 3H × 7.0/10; keto form), 3.82 (s, 3H × 3.0/10; enol form), 4.65 (s, 1H × 7.0/10; keto form), 6.85–7.29 ppm (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.6, 28.5, 51.6, 52.3, 55.0, 55.1, 64.5, 103.3, 113.3, 113.4, 114.2, 124.5, 127.1, 130.3, 132.1, 158.5, 159.4, 169.2, 173.0, 174.0, 201.7 ppm; IR (neat): ν_{max} = 2954, 2839, 1714, 1609, 1512, 1441, 1355, 1247 cm^{-1}.

Methyl 2-(4-chlorophenyl)-3-oxobutanoate 2-6d: Following the procedure for the preparation of **2-6a**, the reaction of methyl *p*-chlorophenylacetate (18.5 g, 0.10 mol) with methyl acetate (22.2 g, 0.30 mol) and *t*BuOK (8.42 g, 0.15 mol) gave the desired product (8.84 g, 39%) as a colorless oil. B.p. 90–92 °C/0.49 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.85 (s, 3H × 8.0/10; enol form), 2.20 (s, 3H × 2.0/10; keto form), 3.69 (s, 3H × 8.0/10; enol form), 3.76 (s, 3H × 2.0/10; keto form), 4.69 (s, 1H × 2.0/10; keto form), 7.07–7.39 ppm (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.6, 28.6, 51.6, 52.4, 64.4, 102.8, 128.2, 128.8, 130.6, 130.9, 132.4, 133.4, 134.2, 168,4, 172.4, 174.1, 200.5 ppm; IR (neat): ν_{max} = 2953, 1718, 1645, 1611, 1492, 1340, 1266, 1224 cm^{-1}; HRMS (ESI): m/z calcd for $C_{11}H_{11}O_3Cl$ $[M+Na]^+$ 249.0294; found: 249.0303.

General procedure for (*E*)- and (*Z*)-stereocomplementary enol tosylations.
Method A-1: TsCl (2.86 g, 15 mmol) in MeCN (10 mL) was added to a stirred solution of β-ketoester **2-4** (10 mmol), NMI (1.23 g, 15 mmol), and Et_3N (1.52 g, 15 mmol) in MeCN (10 mL) at 20 − 25 °C under an Ar atmosphere, followed by being stirred for 1 h. Water was added to the stirred mixture, which was extracted with EtOAc. The organic phase was washed with 1M HCl aqueous solution, brine, dried (Na_2SO_4), and concentrated. The obtained crude product was purified by silica gel column chromatography (hexane/AcOEt = 20/1 – 5/1) or recrystallization to give the corresponding desired product (*E*)-**2-5**.

Method B-1: TsCl (2.86 g, 15 mmol) in CH_2Cl_2 (10 mL) was added to a stirred solution of a β-ketoester **2-4** (10 mmol), NMI (1.23 g, 15 mmol) and LiOH (359 mg, 15 mmol) in CH_2Cl_2 (10 mL) at 0 − 5 °C under an Ar atmosphere. The mixture was stirred at same temperature for 1 h and 20 − 25 °C for 1 h. A similar work up to that of Method A-1 gave the corresponding desired product (*Z*)-**2-5**.

Method A-2: TsCl (286 mg, 1.50 mmol) in DMF (1.0 mL) was added to a stirred solution of β-ketoester **2-6**

(1.00 mmol), NMI (124 mg, 1.50 mmol), and Et_3N (152 mg, 1.50 mmol) in DMF (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. A large amount of water was added to the mixture, which was extracted twice with AcOEt. The combined organic phase was washed with large amounts of water, a saturated aqueous solution of $NaHCO_3$, and brine; dried (Na_2SO_4); and concentrated. The obtained crude product was purified by column chromatography on silica gel (hexane/AcOEt=50/1 – 20/1) to give the corresponding desired product (*E*)-**2-7**.

Method B-2: TsCl (286 mg, 1.50 mmol) in MeCN (1.0 mL) was added to a stirred solution of β-ketoester **2-6** (1.00 mmol), TMEDA (258 mg, 1.50 mmol), and LiCl (64 mg, 1.5 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. A large amount of water was added to the mixture, which was extracted twice with AcOEt. The combined organic phase was washed with large amounts of water, a saturated aqueous solution of $NaHCO_3$, and brine; dried (Na_2SO_4); and concentrated. The obtained crude product was purified by column chromatography on silica gel (hexane/AcOEt= 50/1 – 20/1) to give the corresponding desired product (*Z*)-**2-7**.

Methyl (*E*)-3-phenyl-3-(tosyloxy)prop-2-enoate (*E*)-2-5a

Colorless crystals; mp 79−81 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.41 (s, 3H), 3.62 (s, 3H), 6.08 (s, 1H), 7.18−7.38 (m, 7H), 7.66 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.6, 51.6, 111.3, 127.7, 128.2, 129.2, 129.7, 130.4, 131.7, 132.9, 145.5, 159.6, 164.9; IR (neat): ν_{max} = 3058, 2952, 1730, 1645, 1597, 1435, 1377, 1193, 1038, 806 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{17}H_{16}O_5S$ $[M+Na]^+$ 355.0616; found: 355.0620.

Methyl (*Z*)-3-phenyl-3-(tosyloxy)prop-2-enoate (*Z*)-2-5a

Colorless crystals; mp 103−105 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.40 (s, 3H), 3.69 (s, 3H), 6.11 (s, 1H), 7.17−7.45 (m, 7H), 7.72 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.6, 51.6, 110.3, 126.9, 128.4, 129.4, 130.7, 133.0, 133.4, 145.2, 155.7, 163.8; IR (neat): ν_{max} = 1732, 1646, 1384, 1270, 1178, 763 cm^{-1}.

Methyl (*E*)-3-(4-methoxyphenyl)-3-(tosyloxy)prop-2-enoate (*E*)-2-5b

Pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.42 (s, 3H), 3.64 (s, 3H), 3.80 (s, 3H), 5.96 (s, 1H), 6.76 (d, *J* = 8.9 Hz, 2H), 7.24 (d, *J* = 7.9 Hz, 2H), 7.32 (d, *J* = 8.9 Hz, 2H), 7.67 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.6, 51.6, 55.3, 110.0, 113.1, 123.9, 128.3, 129.7, 131.1, 145.4, 159.7, 161.4, 165.2; IR (neat): ν_{max} = 2954, 2841, 1727, 1636, 1606, 1511, 1375, 1176, 1032, 779 cm^{-1}.

Methyl (*Z*)-3-(4-methoxyphenyl)-3-(tosyloxy)prop-2-enoate (*Z*)-2-5b

Pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.42 (s, 3H), 3.66 (s, 3H), 3.81 (s, 3H), 6.01 (s, 1H), 6.78 (d, *J* = 8.9 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.38 (d, *J* = 8.9 Hz, 2H), 7.75 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.5, 51.4, 55.3, 108.1, 113.8, 125.2, 128.4, 128.6, 129.4, 133.5, 145.1, 155.6, 161.7, 163.9; IR (neat): ν_{max} = 3019, 2952, 1730, 1645, 1605, 1511, 1257, 1176, 1037, 909, 731 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{18}H_{18}O_6S$ $[M+Na]^+$ 385.0722; found: 385.0717.

Methyl (*E*)-3-(4-chlorophenyl)-3-(tosyloxy)prop-2-enoate (*E*)-2-5c

Pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.43 (s, 3H), 3.64 (s, 3H), 6.07 (s, 1H), 7.17−7.31 (m, 6H), 7.65 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.6, 51.7, 111.9, 127.9, 128.2, 129.8, 130.1, 130.6, 132.7, 136.6, 145.8, 158.4, 164.7; IR (neat): ν_{max} = 3027, 2852, 1730, 1646, 1380, 1217, 1193, 1036, 755 cm^{-1}.

Methyl (*Z*)-3-(4-chlorophenyl)-3-(tosyloxy)prop-2-enoate (*Z*)-2-5c

Pale yellow crystals; mp 73−75 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.43 (s, 3H), 3.68 (s, 3H), 6.09 (s, 1H), 7.20−7.29 (m, 4H), 7.37 (d, *J* = 8.9 Hz, 2H), 7.74 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.5, 51.4, 55.3, 108.1, 113.8, 125.2, 128.4, 128.6, 129.4, 133.5, 145.1, 155.6, 161.7, 163.9; IR (neat): ν_{max} = 1732, 1646, 1435, 1268, 1178, 1038, 928, 765 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{17}H_{15}ClO_5S$ $[M+Na]^+$ 389.0226; found: 389.0238.

Methyl (*E*)-2-phenyl-3-(tosyloxy)but-2-enoate (*E*)-2-7a

Colorless crystals; mp 71−72 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.37 (s, 3H), 2.53 (s, 3H), 3.70 (s, 3H), 6.96−7.31 ppm (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.9, 21.4, 52.2, 125.9, 127.3, 127.5, 127.7, 129.3, 129.3, 132.7, 133.0, 144.7, 153.6, 167.2 ppm; IR (neat): ν_{max} = 2359, 1715, 1639, 1433, 1361, 1193, 1154, 1064 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{18}H_{18}O_5S$ $[M+Na]^+$ 369.0773; found: 369.0779.

Methyl (*Z*)-2-phenyl-3-(tosyloxy)but-2-enoate (*Z*)-2-7a

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.98 (s, 3H), 2.43 (s, 3H), 3.53 (s, 3H), 7.17−7.40 (m, 7H), 7.85−7.92 ppm (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.7, 21.4, 51.8, 126.2, 127.9, 128.1, 128.3, 128.9, 129.6, 133.2, 133.5, 145.2, 149.3, 165.4 ppm; IR (neat): ν_{max} = 1727, 1597, 1434, 1371, 1226, 1195, 1092, 1057 cm^{-1}.

Methyl (*E*)-2-(*p*-tolyl)-3-(tosyloxy)but-2-enoate (*E*)-2-7b

Colorless crystals; mp 79−80 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.30 (s, 3H), 2.36 (s, 3H), 2.50 (s, 3H), 3.68 (s, 3H), 6.84−6.91 (m, 2H), 6.91−6.98 (m, 2H), 7.01−7.08 (m, 2H), 7.26−7.32 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.0, 21.1, 21.5, 52.2, 125.9, 127.6, 128.4, 129.1, 129.2, 130.0, 133.0, 137.1, 144.6, 153.3, 167.4 ppm; IR (neat): ν_{max} = 2951, 1716, 1645, 1352, 1291, 1194, 1178, 1155 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{19}H_{20}O_5S$ $[M+Na]^+$ 383.0929; found: 383.0943.

Methyl (*Z*)-2-(*p*-tolyl)-3-(tosyloxy)but-2-enoate (*Z*)-2-7b

Colorless crystals; mp 95−96 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.00 (s, 3H), 2.35 (s, 3H), 2.46 (s, 3H), 3.55 (s, 3H), 7.08−7.14 (m, 2H), 7.14−7.20 (m, 2H), 7.34−7.40 (m, 2H), 7.86−7.92 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.8, 21.1, 21.5, 51.9, 126.2, 128.0, 128.9, 129.1, 129.7, 130.6, 133.5, 138.1, 145.2, 149.2, 165.8 ppm; IR (neat): ν_{max} = 1724, 1431, 1365, 1304, 1225, 1193, 1178, 1057 cm^{-1}.

Methyl (*E*)-2-(4-methoxyphenyl)-3-(tosyloxy)but-2-enoate (*E*)-2-7c

Pale yellow crystals; mp 90−91 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.38 (s, 3H), 2.49 (s, 3H), 3.71 (s, 3H), 3.79 (s, 3H), 6.64−6.70 (m, 2H), 6.88−6.95 (m, 2H), 7.04−7.10 (m, 2H), 7.30−7.36 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.1, 21.5, 52.2, 55.0, 113.1, 125.1, 125.6, 127.6, 129.2, 130.5, 132.9, 144.6, 152.9, 158.8, 167.6 ppm; IR (neat): ν_{max} = 2954, 1715, 1607, 1513, 1435, 1345, 1224, 1177 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{19}H_{20}O_6S$ $[M+Na]^+$ 399.0878; found: 399.0876.

Methyl (*Z*)-2-(4-methoxyphenyl)-3-(tosyloxy)but-2-enoate (*Z*)-2-7c

Pale yellow crystals; mp 67−68 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.99 (s, 3H), 2.44 (s, 3H), 3.55 (s, 3H), 3.78 (s, 3H), 6.84−6.92 (m, 2H), 7.10−7.19 (m, 2H), 7.33−7.41 (m, 2H), 7.84−7.91 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.7, 21.4, 51.8, 55.0, 113.8, 125.6, 125.9, 127.9, 129.6, 130.2, 133.4, 145.2, 148.8, 159.3, 165.9 ppm; IR (neat): ν_{max} = 1725, 1608, 1512, 1435, 1366, 1282, 1092, 1052 cm^{-1}.

Methyl (*E*)-2-(4-chlorophenyl)-3-(tosyloxy)but-2-enoate (*E*)-2-7d

Pale yellow crystals; mp 80−81 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.41 (s, 3H), 2.55 (s, 3H), 3.70 (s, 3H), 6.88−6.94 (m, 2H), 7.05−7.15 (m, 4H), 7.28−7.34 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.1, 21.3, 52.1, 124.5, 127.3, 127.7, 129.3, 130.7, 131.4, 132.9, 133.3, 145.0, 154.7, 166.6 ppm; IR (neat): ν_{max} = 1717, 1639, 1595, 1491, 1224, 1195, 1178, 1156 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{18}H_{17}O_5S$ $[M+Na]^+$ 403.0383; found: 403.0377.

Methyl (*Z*)-2-(4-chlorophenyl)-3-(tosyloxy)but-2-enoate (*Z*)-2-7d

Colorless crystals; mp 75−76 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.98 (s, 3H), 2.47 (s, 3H), 3.57 (s, 3H), 7.14−7.21 (m, 2H), 7.30−7.42 (m, 4H), 7.85−7.92 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.1, 21.7, 52.2, 125.2, 128.1, 128.8, 129.8, 130.6, 132.2, 133.5, 134.4, 145.4, 150.3, 165.3 ppm; IR (neat): ν_{max} = 1721, 1652, 1595, 1491, 1346, 1313, 1223, 1194 cm^{-1}.

General procedure of (*E*)-, (*Z*)-stereoretentive Suzuki-Miyaura cross couplings

Method C-1: A suspension of an enol tosylate (*E*)-**2-5** (0.50 mmol), $ArB(OH)_2$ (0.75 mmol), $[Pd(dppb)Cl_2]$ (15 mg, 0.025 mmol), and KF (87 mg, 1.5 mmol) in *i*PrOH (3.0 mL) was stirred at 60 − 65 °C under an Ar atmosphere 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, brine, dried (Na_2SO_4), and concentrated. The obtained crude product was purified by silica gel column chromatography (hexane/Et_2O = 100/1 – 20/1) to give the corresponding desired product (*E*)-**2-1**.

Method D-1: A suspension of an enol tosylate (*Z*)-**2-5** (0.50 mmol), $ArB(OH)_2$ (0.75 mmol), $[Pd(dppf)Cl_2]$ (18 mg, 0.025 mmol), and K_2CO_3 (207 mg, 1.5 mmol) in *i*PrOH (3.0 mL) was stirred at 60 − 65 °C under an Ar atmosphere 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, brine, dried (Na_2SO_4), and concentrated. The obtained crude product was purified by silica gel column chromatography (hexane/diethyl ether = 100/1 – 20/1) to give the corresponding desired product (*Z*)-**2-1**.

Method C-2: A suspension of enol tosylate (*E*)-**2-7** (0.50 mmol), $ArB(OH)_2$ (0.75 mmol), *i*Pr_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) was stirred at 80 − 85 °C under an argon atmosphere 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 column chromatography on silica gel (hexane/Et_2O = 200/1 – 100/1) to give the corresponding desired product (*E*)-**2-2**.

Method D-2: A suspension of enol tosylate (*Z*)-**2-7** (0.50 mmol), $ArB(OH)_2$ (0.75 mmol), *i*Pr_2NEt (194 mg, 1.5 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) was stirred at 80 – 85 °C under an argon atmosphere 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 column chromatography on silica gel (hexane/Et_2O = 200/1 – 100/1) to give the corresponding desired product (*Z*)-**2-2**.

Methyl (*E*)-3-(4-methylphenyl)-3-phenylprop-2-enoate (*E*)-2-1a[1j]

Pale yellow oil; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.35 (s, 3H), 3.60 (s, 3H), 6.35 (s, 1H), 7.12 (d, *J* = 7.9 Hz, 2H), 7.15−7.23 (m, 2H), 7.32–7.43 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.1, 51.1, 115.8, 127.7, 128.0, 128.2, 129.0, 137.9, 138.9, 139.6, 157.0, 166.4; IR (neat): ν_{max} = 3022, 2948, 1719, 1608, 1433, 1267, 1164, 910, 756 cm^{-1}.

Methyl (*Z*)-3-(4-methylphenyl)-3-phenylprop-2-enoate (*Z*)-2-1a[1j]

Colorless oil; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.39 (s, 3H), 3.63 (s, 3H), 6.32 (s, 1H), 7.10 (d, *J* = 7.9 Hz, 2H), 7.19 (d, *J* = 7.9 Hz, 2H), 7.27−7.42 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.3, 51.1, 116.4, 128.3, 128.3, 128.6, 129.1, 129.3, 135.7, 138.0, 141.1, 157.3, 166.4; IR (neat): ν_{max} = 3024, 2949, 1725, 1610, 1508, 1362, 1266, 1165, 722 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{17}H_{16}O_2$ $[M+Na]^+$ 275.1048; found: 275.1046.

Methyl (*E*)-3-(4-methoxylphenyl)-3-phenylprop-2-enoate (*E*)-2-1b[1j]

Brown colored oil; ^1H NMR (300 MHz, $CDCl_3$): δ = 3.59 (s, 3H), 3.81 (s, 3H), 6.31 (s, 1H), 6.84 (d, *J* = 8.9 Hz, 2H), 7.15−7.27 (m, 4H), 7.35−7.43 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 51.1, 55.3, 113.7, 114.6, 127.8, 128.0, 129.0, 129.7, 133.0, 139.0, 156.8, 160.8, 166.5; IR (neat): ν_{max} = 2950, 1717, 1607, 1509, 1248, 1166, 773 cm^{-1}.

Methyl (*Z*)-3-(4-methylphenyl)-3-phenylprop-2-enoate (*Z*)-2-1b[2]

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.64 (s, 3H), 3.84 (s, 3H), 6.27 (s, 1H), 6.91 (d, *J* = 8.6 Hz, 2H), 7.16 (d, *J* = 8.6 Hz, 2H), 7.23−7.42 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 51.2, 55.2, 113.2, 116.2, 128.3, 128.5, 129.3, 130.9, 130.9, 141.5, 157.0, 159.7, 166.6; IR (neat): ν_{max} = 3019, 2952, 1717, 1607, 1509, 1247, 1167, 908, 755 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{17}H_{16}O_3$ $[M+Na]^+$ 291.0997; found: 291.1019.

Methyl (*E*)-3-(4-chlorophenyl)-3-phenylprop-2-enoate (*E*)-2-1c[2]

Pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.61 (s, 3H), 6.34 (s, 1H), 7.14−7.32 (m, 6H), 7.35−7.45 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 51.2, 117.1, 127.9, 128.4, 128.6, 129.0, 129.5, 135.5, 138.3, 139.2, 155.6, 166.1; IR (neat): ν_{max} = 3019, 1716, 1617, 1488, 1434, 1215, 1168, 907, 732 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{16}H_{13}ClO_2$ $[M+Na]^+$ 295.0502; found: 295.0582.

Methyl (*Z*)-3-(4-chlorophenyl)-3-phenylprop-2-enoate (*Z*)-2-1c[2]

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.62 (s, 3H), 6.37 (s, 1H), 7.15 (d, *J* = 8.6 Hz, 2H), 7.22−7.40 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 51.2, 117.1, 128.1, 128.2, 128.4, 129.6, 130.5, 134.2, 137.1, 140.3, 155.8, 166.1; IR (neat): ν_{max} = 3021, 2950, 1718, 1617, 1488, 1272, 1167, 908, 756 cm^{-1}.

Methyl (*E*)-3-(4-fluorophenyl)-3-phenylprop-2-enoate (*E*)-2-1d[2]

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.61 (s, 3H), 6.31 (s, 1H), 7.00 (t, *J* = 8.9 Hz, 2H), 7.15−7.22 (m, 2H), 7.24−7.30 (m, 2H), 7.39 (t, *J* = 3.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 51.2, 115.2, 115.5, 116.6, 127.9, 128.3, 129.0, 130.1, 130.2, 138.6, 155.8, 166.2; IR (neat): ν_{max} = 3021, 2950, 1718, 1600, 1507, 1434, 1362, 1267, 1166, 909, 732 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{16}H_{13}FO_2$ $[M+Na]^+$ 279.0797; found: 279.0827.

Methyl (*Z*)-3-(4-fluorophenyl)-3-phenylprop-2-enoate (*Z*)-2-1d[2]

Pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.63 (s, 3H), 6.36 (s, 1H), 7.07 (t, *J* = 8.6 Hz, 2H), 7.20 (dd, *J* = 5.5, 8.3 Hz, 2H), 7.24−7.42 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 51.2, 114.7, 115.0, 117.0, 128.2, 128.4, 129.5, 131.0, 131.1, 140.7, 156.0, 166.2; IR (neat): ν_{max} = 3019, 1713, 1602, 1509, 1215, 1172, 908, 753 cm^{-1}.

Methyl (*E*)-3-(4-acetylphenyl)-3-phenylprop-2-enoate (*E*)-2-1e

Pale yellow crystals; mp 97–98 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.60 (s, 3H), 3.63 (s, 3H), 6.42 (s, 1H), 7.16−7.24 (m, 2H), 7.00 (t, *J* = 8.9 Hz, 2H), 7.34−7.46 (m, 5H), 7.39 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.6, 51.3, 118.6, 128.0, 128.2, 128.4, 129.0, 137.4, 138.0, 145.2, 155.4, 166.0, 197.3; IR (neat): ν_{max} = 3019, 1683, 1605, 1435, 1360, 1264, 1215, 906, 730 cm^{-1}.

Methyl (*Z*)-3-(4-acetylphenyl)-3-phenylprop-2-enoate (*Z*)-2-1e

Pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.63 (s, 3H), 3.62 (s, 3H), 6.44 (s, 1H), 7.22−7.42 (m, 7H), 8.00 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.5, 51.3, 117.3, 127.9, 128.0, 128.5, 129.2, 129.7,

136.5, 139.7, 143.9, 156.0, 166.0, 197.6; IR (neat): ν_{max} = 3020, 1682, 1604, 1434, 1360, 1267, 1215, 1169, 908, 754 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{18}H_{16}O_3$ $[M+Na]^+$ 303.0997; found: 303.1020.

Methyl (*E*)-3-(2-methylphenyl)-3-phenylprop-2-enoate (*E*)-2-1f

Colorless crystals; mp 94−98 °C; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.06 (s, 3H), 3.66 (s, 3H), 6.00 (s, 1H), 7.11−7.37 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.2, 51.2, 119.4, 125.6, 127.6, 128.4, 129.1, 129.5, 130.6, 135.9, 138.5, 141.9, 157.1, 166.6; IR (neat): ν_{max} = 3058, 1722, 1616, 1432, 1359, 1257, 1164, 1033, 909, 728 cm^{-1}.

Methyl (*Z*)-3-(2-methylphenyl)-3-phenylprop-2-enoate (*Z*)-2-1f

Colorless oil; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.07 (s, 3H), 3.58 (s, 3H), 6.53 (s, 1H), 7.02−7.11 (m, 1H), 7.17−7.40 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.5, 51.2, 116.9, 125.4, 127.4, 127.8, 128.3, 128.5, 129.5, 129.9, 135.3, 138.4, 139.2, 156.5, 166.0; IR (neat): ν_{max} = 3059, 2949, 1721, 1618, 1433, 1359, 1264, 1165, 1016, 908, 729 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{17}H_{16}O_2$ $[M+Na]^+$ 275.1048; found: 275.1071.

Methyl (*E*)-3-(2-chlorolphenyl)-3-phenylprop-2-enoate (*E*)-2-1g

Colorless oil; ^1H NMR (300 MHz, $CDCl_3$): δ = 3.66 (s, 3H), 6.10 (s, 1H), 7.19−7.40 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 51.3, 121.0, 126.6, 127.6, 128.5, 129.0, 129.5, 130.1, 130.9, 132.7, 137.8, 140.7, 154.0, 166.2; IR (neat): ν_{max} = 3060, 1724, 1621, 1433, 1360, 1245, 1166, 909, 728 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{16}H_{13}ClO_2$ $[M+Na]^+$ 295.0502; found: 295.0567.

Methyl (*Z*)-3-(2-chlorolphenyl)-3-phenylprop-2-enoate (*Z*)-2-1g

Pale yellow oil; ^1H NMR (300 MHz, $CDCl_3$): δ = 3.60 (s, 3H), 6.55 (s, 1H), 7.12−7.21 (m, 1H), 7.23−7.40 (m, 7H), 7.40−7.49 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 51.3, 118.1, 126.4, 127.3, 128.6, 129.1, 129.4, 129.6, 130.0, 132.5, 137.8, 138.5, 153.7, 165.6; IR (neat): ν_{max} = 3060, 2949, 1723, 1623, 1432, 1358, 1268, 1165, 1035, 909, 730 cm^{-1}.

Methyl (*E*)-2,3-diphenylbut-2-enoate (*E*)-2-2a[17]

Pale yellow oil; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.36 (s, 3H), 3.76 (s, 3H), 6.95−7.18 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.2, 51.9, 126.8, 127.0, 127.7, 127.8, 128.4, 129.8, 131.6, 137.1, 141.8, 144.6, 169.8; IR (neat): ν_{max} = 2950, 1719, 1599, 1491, 1433, 1375, 1304, 1250 cm^{-1}.

Methyl (*Z*)-2,3-diphenylbut-2-enoate (*Z*)-2-2a[17]

Pale yellow oil; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.05 (s, 3H), 3.43 (s, 3H), 7.29−7.44 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.2, 51.5, 126.8, 127.5, 128.1, 128.3, 129.1, 132.5, 137.1, 142.8, 143.9, 169.6; IR (neat): ν_{max} = 2941, 1719, 1491, 1433, 1375, 1304, 1252, 1210 cm^{-1}.

Methyl (*E*)-3-(4-methylphenyl)-2-phenylbut-2-enoate (*E*)-2-2b[18]

Pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.24 (s, 3H), 2.34 (s, 3H), 3.77 (s, 3H), 6.88−6.95 (m, 3H), 6.99−7.04 (m, 2H), 7.06−7.16 ppm (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.0, 23.2, 51.9, 126.7, 127.8, 128.4, 128.5, 129.9, 131.3, 136.7, 137.4, 138.8, 144.5, 169.9 ppm; IR (neat): ν_{max} = 2949, 2859, 1719, 1624, 1509, 1433, 1320, 1250 cm^{-1}.

Methyl (*Z*)-3-(4-methylphenyl)-2-phenylbut-2-enoate (*Z*)-2-2b[18]

Pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.03 (s, 3H), 2.36 (s, 3H), 3.46 (s, 3H), 7.05−7.28 (m, 5H), 7.29−7.43 ppm (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.2, 22.2, 51.6, 126.8, 127.4, 128.3, 128.3, 128.9, 129.2, 129.8, 137.3, 139.8, 143.9, 169.8 ppm; IR (neat): ν_{max} = 2950, 1721, 1626, 1512, 1433, 1375, 1304, 1250 cm^{-1}.

Methyl (*E*)-3-(4-methoxyphenyl)-2-phenylbut-2-enoate (*E*)-2-2c

Colorless crystals; mp 69−70 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.34 (s, 3H), 3.73 (s, 3H), 3.77 (s, 3H), 6.60−6.70 (m, 2H), 6.88−7.18 ppm (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.1, 51.9, 55.0, 113.2, 126.7, 127.8, 129.8, 129.9, 131.0, 133.9, 137.5, 144.1, 158.5, 170.1 ppm; IR (neat): ν_{max} = 2951, 1719, 1609, 1510, 1458, 1433, 1248, 1208 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{18}H_{18}O_3$ $[M+Na]^+$ 305.1154; found: 305.1157.

Methyl (*Z*)-3-(4-methoxyphenyl)-2-phenylbut-2-enoate (*Z*)-2-2c

Colorless crystals; mp 96−97 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.03 (s, 3H), 3.47 (s, 3H), 3.83 (s, 3H), 6.81−6.94 (m, 2H), 7.17−7.42 ppm (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.2, 51.7, 55.2, 113.6, 127.5, 128.2, 128.3, 129.2, 135.0, 137.4, 143.3, 159.1, 170.1 ppm; IR (neat): ν_{max} = 2945, 2869, 1728, 1607, 1574, 1499, 1435, 1296 cm^{-1}.

Methyl (*E*)-3-(4-chloro)-2-phenylbut-2-enoate (*E*)-2-2d

Colorless crystals; mp 68−69 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.33 (s, 3H), 3.78 (s, 3H), 6.91−7.03 (m, 4H), 7.07−7.17 ppm (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.9, 52.0, 127.0, 127.9, 128.1, 129.7, 129.8, 132.2, 132.8, 136.8, 140.2, 143.0, 169.5 ppm; IR (neat): ν_{max} = 2950, 1718, 1594, 1485, 1433, 1317, 1245, 1203 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{17}H_{15}O_2Cl$ $[M+Na]^+$ 309.0658; found: 309.0663.

Methyl (*Z*)-3-(4-chloro)-2-phenylbut-2-enoate (*Z*)-2-2d

Colorless crystals; mp 70−71 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.01 (s, 3H), 3.46 (s, 3H), 7.22−7.45 ppm (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.3, 51.8, 127.7, 128.3, 128.4, 128.4, 129.1, 133.0, 133.4, 136.8, 141.3, 142.8, 169.4 ppm; IR (neat): ν_{max} = 2950, 1717, 1634, 1483, 1432, 1296, 1258, 1208 cm^{-1}.

Methyl (*E*)-3-(3-furyl)-2-phenylbut-2-enoate (*E*)-2-2e

Pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.37 (s, 3H), 3.76 (s, 3H), 6.55−6.63 (m, 1H), 6.90−6.98 (m, 1H), 6.98−7.05 (m, 1H), 7.06−7.14 (m, 2H), 7.16−7.25 ppm (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.9, 51.8, 110.3, 126.0, 127.5, 128.4, 129.6, 130.4, 135.5, 138.1, 142.0, 142.4, 169.3 ppm; IR (neat): ν_{max} = 3138,

3023, 2950, 1710, 1597, 1433, 1321, 1205 cm^{-1}.

Methyl (*Z*)-3-(3-furyl)-2-phenylbut-2-enoate (*Z*)-2-2e

Pale yellow oil; ^1H NMR (300 MHz, $CDCl_3$): δ = 1.98 (s, 3H), 3.67 (s, 3H), 6.43−6.48 (m, 1H), 7.28−7.44 (m, 6H), 7.52−7.57 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.1, 52.0, 109.5, 126.0, 127.6, 128.3, 129.0, 130.8, 131.4, 136.6, 140.6, 142.9, 170.4 ppm; IR (neat): ν_{max} = 2997, 2949, 1716, 1634, 1493, 1434, 1379, 1207 cm^{-1}.

Methyl (*E*)-2-phenyl-3-(3-thienyl)but-2-enoate (*E*)-2-2f

Pale yellow oil; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.34 (s, 3H), 3.73 (s, 3H), 5.62−5.67 (m, 1H), 7.08−7.14 (m, 2H), 7.16−7.24 (m, 2H), 7.27−7.37 ppm (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.5, 51.8, 124.2, 124.4, 127.1, 128.0, 128.1, 129.5, 131.2, 137.6, 138.5, 141.7, 169.6 ppm; IR (neat): ν_{max} = 3139, 3026, 2952, 1710, 1608, 1504, 1433, 1205 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{15}H_{14}O_2S$ $[M+Na]^+$ 281.0612; found: 281.0603.

Methyl (*Z*)-2-phenyl-3-(3-thienyl)but-2-enoate (*Z*)-2-2f

Pale yellow oil; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.02 (s, 3H), 3.56 (s, 3H), 7.09−7.14 (m, 1H), 7.27−7.44 ppm (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.2, 51.8, 122.4, 125.3, 126.9, 127.6, 128.3, 129.0, 132.3, 136.1, 136.7, 142.4, 170.2 ppm; IR (neat): ν_{max} = 2993, 2946, 1715, 1623, 1492, 1433, 1299, 1211 cm^{-1}.

Methyl (*E*)-2-(4-methylphenyl)-3-phenylbut-2-enoate (*E*)-2-2g

Pale yellow oil; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.23 (s, 3H), 2.33 (s, 3H), 3.78 (s, 3H), 6.83−6.95 (m, 4H), 6.98−7.08 (m, 2H), 7.10−7.20 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.1, 23.2, 51.9, 126.9, 127.9, 128.4, 128.5, 129.1, 129.6, 134.1, 136.5, 142.0, 143.6, 170.1 ppm; IR (neat): ν_{max} = 3023, 1717, 1636, 1509, 1491, 1435, 1375, 1250 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{18}H_{18}O_2$ $[M+Na]^+$ 289.1204; found: 289.1210.

Methyl (*Z*)-2-(4-methylphenyl)-3-phenylbut-2-enoate (*Z*)-2-2g

Pale yellow oil; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.05 (s, 3H), 2.33 (s, 3H), 3.42 (s, 3H), 7.04−7.45 ppm (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.2, 22.3, 51.6, 126.9, 127.5, 128.2, 128.5, 129.1, 129.6, 134.2, 137.3, 143.0, 143.5, 169.9 ppm; IR (neat): ν_{max} = 2947, 1719, 1636, 1509, 1491, 1435, 1375, 1252 cm^{-1}.

Methyl (*E*)-2-(4-methoxyphenyl)-3-phenylbut-2-enoate (*E*)-2-2h

Pale yellow oil; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.33 (s, 3H), 3.71 (s, 3H), 3.79 (s, 3H), 6.58−6.68 (m, 2H), 6.85−6.95 (m, 2H), 7.09−7.22 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.1, 51.9, 55.0, 113.3, 126.9, 127.9, 128.5, 129.4, 131.0, 131.2, 142.0, 143.2, 158.3, 170.2 ppm; IR (neat): ν_{max} = 2951, 1719, 1609, 1576, 1509, 1458, 1375, 1248 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{18}H_{18}O_3$ $[M+Na]^+$ 305.1154; found: 305.1161.

Methyl (*Z*)-2-(4-methoxyphenyl)-3-phenylbut-2-enoate (*Z*)-2-2h

Pale yellow oil; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.06 (s, 3H), 3.42 (s, 3H), 3.84 (s, 3H), 6.87−6.97 (m, 2H),

7.21−7.40 ppm (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.2, 51.6, 55.2, 113.8, 126.9, 127.5, 128.2, 129.4, 130.4, 131.0, 132.2, 143.3, 159.0, 170.0 ppm; IR (neat): ν_{max} = 2951, 1719, 1655, 1601, 1541, 1509, 1437, 1250 cm^{-1}.

Methyl (*E*)-2-(4-chlorophenyl)-3-phenylbut-2-enoate (*E*)-2-2i

Pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.37 (s, 3H), 3.78 (s, 3H), 6.88−6.95 (m, 2H), 6.96−7.03 (m, 2H), 7.03−7.11 (m, 2H), 7.11−7.21 ppm (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.3, 52.0, 127.2, 128.0, 128.0, 128.3, 130.4, 131.3, 132.7, 135.7, 141.6, 146.0, 169.4 ppm; IR (neat): ν_{max} = 2949, 1707, 1619, 1591, 1489, 1434, 1251, 1206 cm^{-1}.

Methyl (*E*)-2-(biphenyl-4-yl)-3-phenylbut-2-enoate (*E*)-2i-x

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.38 (s, 3H), 3.82 (s, 3H), 7.03−7.09 (m, 4H), 7.12−7.17 (m, 3H), 7.29−7.42 (m, 4H), 7.49−7.54 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.3, 52.0, 126.4, 126.8, 127.1, 127.2, 127.9, 128.4, 128.6, 130.2, 131.3, 136.1, 139.3, 140.4, 141.8, 144.4, 169.9 ppm; IR (neat): ν_{max} = 3028, 2949, 1716, 1487, 1433, 1320, 1246, 1206 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{23}H_{20}O_2$ $[M+Na]^+$ 351.1361; found: 351.1375.

Methyl (*Z*)-2-(4-chlorophenyl)-3-phenylbut-2-enoate (*Z*)-2-2i

Colorless crystals; mp 115−116 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.04 (s, 3H), 3.42 (s, 3H), 7.24−7.44 ppm (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.4, 51.7, 126.8, 127.7, 128.2, 128.6, 130.6, 131.3, 133.5, 135.6, 142.6, 145.0, 169.2 ppm; IR (neat): ν_{max} = 2951, 1697, 1491, 1428, 1319, 1214, 1088, 1008 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{17}H_{15}O_2Cl$ $[M+Na]^+$ 309.0658; found: 309.0654.

Methyl (*Z*)-2-(biphenyl-4-yl)-3-phenylbut-2-enoate (*Z*)-2-2i-x

Colorless crystals; mp 107−108 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.11 (s, 3H), 3.45 (s, 3H), 7.27−7.51 (10 H, m), 7.58−7.70 ppm (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.4, 51.7, 126.9, 127.0, 127.4, 127.6, 128.2, 128.8, 129.7, 132.2, 136.1, 140.4, 140.6, 142.9, 144.1, 169.8 ppm; IR (neat): ν_{max} = 3028, 2955, 1726, 1600, 1488, 1434, 1259, 1217 cm^{-1}.

Methyl (*E*)-3-(3-pyridinyl)-3-(tosyloxy)prop-2-enoate (*E*)-2-9 (Scheme 2-3, [a])

TsCl (858 mg, 4.50 mmol) in DMA (3.0 mL) was added to a stirred solution of β-ketoester **2-8a** (538 mg, 3.00 mmol), NMI (369 mg, 4.50 mmol), and Et_3N (455 mg, 4.50 mmol) in DMA (3.0 mL) at 20 − 25 °C and the mixture was stirred at the same temperature for 1 h. Water was added to the mixture, which was extracted twice with Et_2O. The combined organic phase was washed three times with water, brine, dried (Na_2SO_4), and concentrated. The obtained crude product (96%, *E*/*Z* = 75:25) was purified by column chromatography on silica gel (hexane/*i*PrOH = 10/1) to give the desired product (*E*)**-2-9** (660 mg, 66%).

Red colored oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.43 (s, 3H), 3.65 (s, 3H), 6.18 (s, 1H), 7.22 (dd, *J* = 4.5 Hz, 7.9 Hz, 1H), 7.28 (d, *J* = 7.2 Hz, 2H), 7.64−7.73 (m, 3H), 8.50 (d, *J* = 1.7 Hz, 1H), 8.56 (dd, *J* = 1.4 Hz, 4.8

Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.7, 51.9, 113.1, 122.4, 128.2, 130.0, 132.5, 136.5, 146.0, 149.7, 150.9, 156.3, 164.5; IR (neat): ν_{max} = 3036, 2953, 1729, 1650, 1597, 1381, 1231, 1194, 1051, 820, 709 cm^{-1}.

Methyl (*Z*)-3-(3-pyridinyl)-3-(tosyloxy)prop-2-enoate (*Z*)-2-9 (Scheme 2-3, [b])

TsCl (191 mg, 1.00 mmol) in CH_2Cl_2 (0.50 mL) was added to a stirred solution of β-ketoester **2-8a** (90 mg, 0.50 mmol), NaOH (30 mg, 1.0 mmol), and NMI (82 mg, 0.75 mmol) in CH_2Cl_2 (0.50 mL) at 20 – 25 °C and the mixture was stirred at the same temperature for 1 h. Water was added to the mixture, which was extracted twice with AcOEt. The combined organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The obtained crude product was purified by column chromatography on silica gel (hexane/AcOEt = 2/1) to give the desired product (*Z*)-**2-9** (135 mg, 81%, *E*/*Z* = 8:92), which was washed with hexane to yield pure (*Z*)-**2-9** (110 mg, 66%).

Yellow crystals; mp 87−89 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.43 (s, 3H), 3.71 (s, 3H), 6.16 (s, 1H), 7.23 (dd, *J* = 4.8 Hz, 8.6 Hz, 1H), 7.27 (d, *J* = 8.3 Hz, 2H), 7.72−7.79 (m, 3H), 8.59 (dd, *J* = 1.7 Hz, 4.8 Hz, 1H), 8.68 (d, *J* = 2.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.6, 51.8, 111.9, 123.1, 128.4, 129.3, 129.7, 132.9, 134.2, 145.7, 147.6, 151.3, 152.8, 163.2; IR (neat): ν_{max} = 3087, 2953, 1728, 1643, 1380, 1316, 1269, 1181, 1162, 994, 933, 838, 672 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{16}H_{15}NO_5S$ $[M+Na]^+$ 356.0569; found: 356.0599.

Methyl (*Z*)-3-(4-bromophenyl)-3-(tosyloxy)prop-2-enoate (*Z*)-2-10 (Scheme 2-3, [c])

TsCl (143 mg, 0.750 mmol) in CH_2Cl_2 (0.50 mL) was added to a stirred solution of β-ketoester **2-8b** (129 mg, 0.50 mmol), LiOH (18 mg, 0.75 mmol), and NMI (62 mg, 0.75 mmol) in CH_2Cl_2 (0.50 mL) at 20 − 25 °C and the mixture was stirred at the same temperature for 2 h. Water was added to the mixture, which was extracted twice with AcOEt. The combined organic phase was washed with water, brine, dried (Na_2SO_4), and concentrated. The obtained crude product was purified by column chromatography on silica gel (hexane/AcOEt = 20/1) to give the desired product (*Z*)-**2-10** (149 mg, 72%).

Colorless crystals; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.43 (s, 3H), 3.68 (s, 3H), 6.10 (s, 1H), 7.26 (d, *J* = 8.9 Hz, 2H), 7.29 (d, *J* = 8.6 Hz, 2H), 7.41 (d, *J* = 8.6 Hz, 2H), 7.73 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.6, 51.7, 110.7, 125.4, 128.3, 128.5, 129.6, 131.7, 132.1, 133.2, 145.6, 154.6, 163.6; IR (neat): ν_{max} = 2948, 1733, 1649, 1587, 1484, 1433, 1378, 1188, 1152, 1036, 834, 765, 670 cm^{-1}.

Methyl (*E*)-3-(4-bromophenyl)-3-(tosyloxy)prop-2-enoate (*E*)-2-10 (Scheme 2-3, [d])

TsCl (14.3 g, 75.0 mmol) in DMA (50 mL) was added to a stirred solution of β-ketoester **2.8b** (12.9 g, 50.0 mmol), NMI (6.2 g, 75 mmol), and Et_3N (7.6 g, 75 mmol) in DMA (50 mL) at 20 − 25 °C for 0.5 h, and the mixture was stirred at the same temperature for 1 h. Water was added to the mixture, and organic layer was separated. Water phase was extracted twice with Et_2O. The combined organic phase was filtered through a glass filter followed by washing three times with H_2O, brine, dried (Na_2SO_4), and concentrated. The obtained crude product (92%, *E*/*Z* = 67:33) was purified by column chromatography on silica gel (hexane/AcOEt = 20/1) to give the desired product (*E*)-**2-10** (12.8 g, 62%).

Pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.44 (s, 3H), 3.64 (s, 3H), 6.08 (s, 1H), 7.19 (d, *J* = 8.6 Hz,

2H), 7.25 (d, J = 7.9 Hz, 2H), 7.38 (d, J = 8.3 Hz, 2H), 7.64 (d, J = 8.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.7, 51.8, 112.0, 125.1, 128.2, 129.8, 130.6, 130.8, 131.0, 132.7, 145.8, 158.5, 164.7; IR (neat): ν_{max} = 3069, 2952, 2846, 1727, 1644, 1589, 1487, 1379, 1220, 1177, 1033, 836, 754 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{17}H_{15}BrO_5S$ $[M+Na]^+$ 432.9721; found: 432.9720.

Methyl (*Z*)-3-(4-bromophenyl)-3-(3-pyridinyl)prop-2-enoate (*Z*)-2-11 (Scheme 2-3, [e])

A 3M K_2CO_3 aqueous solution (0.25 mL, 0.75 mmol) was added to a stirred suspension of enol tosylate (*E*)**-2-9** (83 mg, 0.25 mmol), (*p*-Br)$C_6H_4B(OH)_2$ (52 mg, 0.26 mmol), and $[Pd(PPh_3)_2Cl_2]$ (9 mg, 0.01 mmol) in *i*PrOH (0.75 mL) at 60 − 65 °C under an Ar atmosphere, and the mixture was stirred at the same temperature for 1 h. After cooling, water was added to the mixture, which was extracted three times with Et_2O. The combined organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The obtained crude product was purified by column chromatography on silica gel (hexane/AcOEt = 3/1) to give the desired product (*Z*)-**2-11** (70 mg, 89%, *E*/*Z* = 2:>98). The use of $[Pd(dppb)Cl_2]$ catalyst instead of $[Pd(PPh_3)_2Cl_2]$ resulted in 35% conversion yield.

Methyl (*E*)-3-(4-bromophenyl)-3-(3-pyridinyl)prop-2-enoate (*E*)-2-11 (Scheme 2-3, [f])

A 3M K_2CO_3 aqueous solution (0.25 mL, 0.75 mmol) was added to a stirred suspension of enol tosylate (*Z*)**-2-9** (83 mg, 0.25 mmol), (*p*-Br)$C_6H_4B(OH)_2$ (52 mg, 0.26 mmol), and $[Pd(PPh_3)_2Cl_2]$ (9 mg, 0.01 mmol) in *i*PrOH (0.75 mL) at 60 − 65 °C under an Ar atmosphere, and the mixture was stirred at the same temperature for 1 h. After cooling, water was added to the mixture, which was extracted three times with Et_2O. The combined organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The obtained crude product was purified by column chromatography on silica gel (hexane/AcOEt = 3/1) to give the desired product (*E*)**-2-11** (63 mg, 79%, *E*/*Z* = >98:2)

Methyl (*Z*)-3-(4-bromophenyl)-3-(3-pyridinyl)prop-2-enoate (*Z*)-2-11 (Scheme 2-3, [g])

A 3M K_2CO_3 aqueous solution (13.0 mL, 39.0 mmol) was added to a stirred suspension of enol tosylate (*Z*)**-2-10** (5.35 g, 13.0 mmol), (3-Py)$B(OH)_2$ (2.56 g, 21.0 mmol), and $[Pd(dppf)Cl_2]$ (476 mg, 0.65 mmol) in *i*PrOH (39.0 mL) at 60 − 65 °C under an Ar atmosphere, and the mixture was stirred at the same temperature for 3 h. After cooling, water was added to the mixture, which was extracted three times with Et_2O. The combined organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The obtained crude product was purified by column chromatography on silica gel (hexane/AcOEt = 3/1) to give the desired product (*Z*)**-2-11** (3.36 g, 81%, *E*/*Z* = 2:>98).

Red colored oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.63 (s, 3H), 6.44 (s, 1H), 7.15 (d, J = 8.6 Hz, 2H), 7.34 (dd, J = 4.8 Hz, 7.9 Hz, 1H), 7.45−7.57 (m, 3H), 8.45 (d, J = 2.4 Hz, 1H), 8.64 (dd, J = 1.6 Hz, 4.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 51.5, 118.6, 122.8, 124.4, 129.6, 131.8, 134.0, 136.5, 138.8, 149.5, 149.6, 152.2, 165.7; IR (neat): ν_{max} = 3435, 3029, 2949, 1849, 1907, 1720, 1618, 1583, 1272, 1166, 1073, 1009, 826, 752, 713 cm^{-1}.

Methyl (*E*)-3-(4-bromophenyl)-3-(3-pyridinyl)prop-2-enoate (*E*)-2-11 (Scheme 2-3, [h])

A 3M K_2CO_3 aqueous solution (0.50 mL, 1.5 mmol) was added to a stirred suspension of enol tosylate (*E*)-**2-10** (206 mg, 0.500 mmol), (3-Py)$B(OH)_2$ (92 mg, 0.75 mmol), and [Pd(dppf)Cl_2] (18 mg, 0.025 mmol) in *i*PrOH (1.5 mL) at 60 − 65 °C under an Ar atmosphere, and the mixture was stirred at the same temperature for 3 h. After cooling, water was added to the mixture, which was extracted three times with Et_2O. The combined organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The obtained crude product was purified by column chromatography on silica gel (hexane/AcOEt = 3/1) to give the desired product (*E*)-**2-11** (129 mg, 81%, *E*/*Z* = 97:3).

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.66 (s, 3H), 6.39 (s, 1H), 7.09 (d, *J* = 8.6 Hz, 2H), 7.27 (ddd, *J* = 0.7 Hz, 4.8 Hz, 7.9 Hz, 1H), 7.48−7.58 (m, 3H), 8.58 (d, *J* = 2.1 Hz, 1H), 8.60 (dd, *J* = 1.7 Hz, 4.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 51.5, 118.6, 123.0, 123.2, 130.7, 131.4, 135.5, 136.1, 136.5, 148.9, 150.5, 152.6, 165.6; IR (neat): ν_{max} = 3427, 3030, 2949, 2841, 1906, 1722, 1619, 1488, 1434, 1360, 1277, 1165, 1010, 824, 758, 708 cm^{-1}.

(*Z*)-3-(4-Bromophenyl)-3-(3-pyridinyl)prop-2-en-1-ol[14] (Scheme 2-3, [i]-i))

DIBAL (42.4 mL; 1.0 M in toluene) was added to a stirred solution of the ester (*Z*)-**2-11** (3.36 g, 10.6 mmol) in THF (21 mL) at −78 °C under an argon atmosphere, and the mixture was stirred at the same temperature for 0.5 h. MeOH (ca. 30 mL) and saturated Na/K tartrate aqueous solution (ca. 80 mL) were successively added to the mixture, followed by stirring for 1 h, which was extracted twice with AcOEt. The organic phase was dried (Na_2SO_4) and concentrated. The obtained pale yellow solid was washed (hexane/Et_2O = 5/1) to give the desired product (2.42 g, 79%).

Pale yellow crystals; mp 123−124 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.00 (br, 1H), 4.21 (d, *J* = 6.9 Hz, 2H), 6.34 (t, *J* = 6.9 Hz, 1H), 7.08 (d, *J* = 8.6 Hz, 2H), 7.32 (dd, *J* = 4.9, 7.9 Hz, 1H), 7.43 (d, *J* = 8.6 Hz, 2H), 7.48 (dt, *J* = 7.6, 2.1 Hz, 1H), 8.40 (d, *J* = 1.4 Hz, 1H), 8.58 (dd, *J* = 1.4, 4.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 59.8, 122.0, 123.4, 129.0, 130.7, 131.5, 134.5, 137.5, 138.7, 139.8, 148.6, 149.9; IR (neat): ν_{max} = 3241, 3038, 2922, 2844, 2669, 1488, 1414, 1028, 804, 718 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{14}H_{12}BrNO$ $[M+H]^+$ 290.0181; found: 290.0208.

(*E*)-3-(4-Bromophenyl)-3-(3-pyridinyl)prop-2-en-1-ol[14] (Scheme 2-3, [j]- i))

DIBAL (4.0 mL; 1.0 M in toluene) was added to a stirred solution of ester **2-11** (318 mg, 1.00 mmol) in THF (2.0 mL) at −78 °C under an argon atmosphere, and the mixture was stirred at the same temperature for 0.5 h. MeOH (ca. 3 mL) and saturated Na/K tartrate aqueous solution (ca. 8 mL) solution were successively added to the mixture, followed by stirring for 0.5 h, which was extracted twice with AcOEt. The organic phase was dried (Na_2SO_4) and concentrated. The obtained crude product was purified by column chromatography on silica gel (hexane/AcOEt = 1/1) to give the desired product (261 mg, 90%).

Colorless solid; mp 123–124 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.80 (br, 1H), 4.24 (d, *J* = 6.9 Hz, 2H), 6.30 (t, *J* = 6.9 Hz, 1H), 7.02 (d, *J* = 8.3 Hz, 2H), 7.24 (dd, *J* = 5.2, 7.9 Hz, 1H), 7.43−7.57 (m, 3H), 8.41–8.64 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 60.0, 122.2, 123.3, 130.7, 131.2, 131.7, 135.3, 136.7, 137.3, 139.3,

148.0, 148.2; IR (neat): ν_{max} = 3296, 2875, 1489, 1398, 1010, 822, 717 cm^{-1}.

(*Z*)-Zimelidine (*Z*)-2-3[14] (Scheme 2-3, [i]-ii))

$SOCl_2$ (0.10 mL, 1.4 mmol) and DMF (1 drop) were successively added to a stirred solution of the allyl alcohol (261 mg, 0.90 mmol) in CH_2Cl_2 (0.90 mL) at 20 − 25 °C, and the mixture was stirred at the same temperature for 10 min. Then, an aqueous solution of Me_2NH solution (0.95 mL; 9.5 M) was added to the mixture followed by stirring for 0.5 h. A saturated aqueous solution of $NaHCO_3$ was added to the mixture, which was extracted three times with AcOEt. The organic phase was washed with brine, dried (Na_2SO_4) and concentrated. The obtained crude product was purified by column chromatography on silica gel (AcOEt/Et_3N = 10/1) to give the desired product (*Z*)-**2-3** (260 mg, 91%).

Yellow oil; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.23 (s, 6H), 2.98 (d, *J* = 6.9 Hz, 2H), 6.29 (t, *J* = 6.9 Hz, 1H), 7.09 (d, *J* = 8.6 Hz, 2H), 7.33 (ddd, *J* = 1.0, 4.8, 7.6 Hz, 1H), 7.42 (d, *J* = 8.6 Hz, 2H), 7.46 (dt, *J* = 7.6, 2.1 Hz, 1H), 8.44 (dd, *J* = 0.7, 2.4 Hz, 1H), 8.60 (dd, *J* = 1.7, 4.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 45.3, 58.1, 121.7, 123.2, 128.8, 129.5, 131.4, 134.7, 137.1, 139.2, 140.2, 148.7, 150.5; IR (neat): ν_{max} = 3457, 3028, 2973, 2941, 2855, 2817, 2768, 1670, 1585, 1488, 1263, 1024, 817, 717 cm^{-1}.

(*E*)-Zimelidine (*E*)-2-3[14] (Scheme 2-3, [j]- ii))

$SOCl_2$ (0.06 mL, 0.75 mmol) and DMF (1 drop) were successively added to a stirred solution of the allyl alcohol (145 mg, 0.50 mmol) in CH_2Cl_2 (0.50 mL) at 20 − 25 °C, and the mixture was stirred at the same temperature for 10 min. Then, an aqueous solution of Me_2NH (0.53 mL; 9.5 M) was added to the mixture followed by stirring for 0.5 h. A saturated aqueous solution of $NaHCO_3$ was added to the mixture, which was extracted twice with AcOEt. The organic phase was washed with brine, dried (Na_2SO_4) and concentrated. The obtained crude product was purified by column chromatography on silica gel (AcOEt/Et_3N = 10/1) to give the desired product (*E*)-**2-3** (144 mg, 91%, *E*/*Z* = 92:8).

Yellow oil; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.24 (s, 6H), 3.00 (d, *J* = 6.5 Hz, 2H), 6.25 (t, *J* = 6.5 Hz, 1H), 7.04 (d, *J* = 8.6 Hz, 2H), 7.20 (dd, *J* = 4.8, 7.9 Hz, 1H), 7.46 (dt, *J* = 2.1, 7.9 Hz, 1H), 7.53 (d, *J* = 8.3 Hz, 2H), 8.49 (dd, *J* = 1.7, 4.8 Hz, 1H), 8.53 (d, *J* = 1.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 45.3, 58.0, 121.7, 122.9, 129.3, 131.3, 131.5, 134.3, 137.1, 137.3, 139.6, 148.3, 148.5; IR (neat): ν_{max} = 3394, 3027, 2971, 2940, 2854, 2817, 2768, 1669, 1567, 1487, 1412, 1262, 1174, 1011, 825, 732 cm^{-1}.

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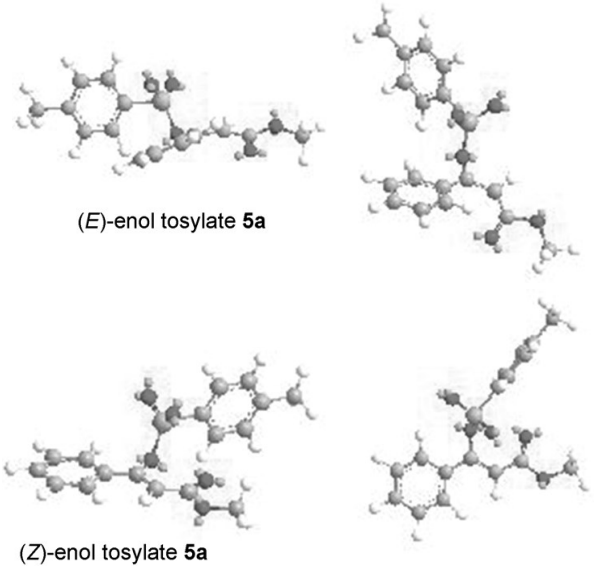
(*E*)-**2-5a** was more thermodynamically stable because it was about 16.1 kcal mol^{-1} smaller than that of (*Z*)-**2-5a**. 2) The conjugated system in (*Z*)-**2-5a** was normally in the plain, whereas that of (*E*)-**2-5a** was considerably twisted from the plain probably due to the stereocongestion between -Ph and -CO_2Me groups; see the figures bellow: (*E*)-Enol tosylate **2-5a**: non-1,4 van der Waals (VDW): −0.0528; 1,4 VDW: 20.5307; dipole/dipole: 25.0328; total energy: 226.9997 kcal mol^{-1}. (Z)-Enol tosylate **2-5a**: non-1,4 VDW: 0.8225; 1,4 VDW: 20.5523; dipole/dipole: 21.6711; total energy: 210.9178 kcal mol^{-1}.



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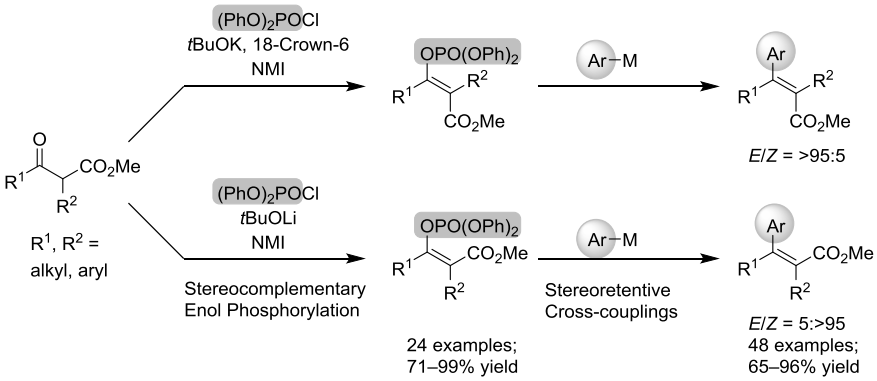
Chapter 3.
(E)- and (Z)-Stereodefined Enol Phosphonates Derived From β-Ketoesters: Stereocomplementary Synthesis of Fully-substituted α,β-Unsaturated Esters

Abstract

A versatile, robust, and stereocomplementary synthesis of fully-substituted (*E*)- and (*Z*)-stereodefined α,β-unsaturated esters **3-3** from accessible α-substituted β-ketoesters **3-1** *via* (*E*)- and (*Z*)-enol phosphonates was achieved. The present method involves two accessible reaction sequences: (i) (*E*)- and (*Z*)-stereocomplementary enol phosphorylations of a wide variety of β-ketoesters **3-1** (24 examples; 71–99% yield, each >95:5 ds), and (ii) (*E*)- and (*Z*)-stereoretentive Suzuki–Miyaura cross-coupling (16 examples; 71–91% yield, >81:19 ds) and Negishi cross-coupling (32 examples; 65–96% yield, >95:5 ds) using (*E*)- and (*Z*)-enol phosphonates **3-2**. ^{1}H-NMR monitoring for a key reactive *N*-phosphorylammonium (imidazolium) intermediate **I** and an application in the synthesis of both (*E*)- and (*Z*)-tamoxifen precursors **3-6** are described.

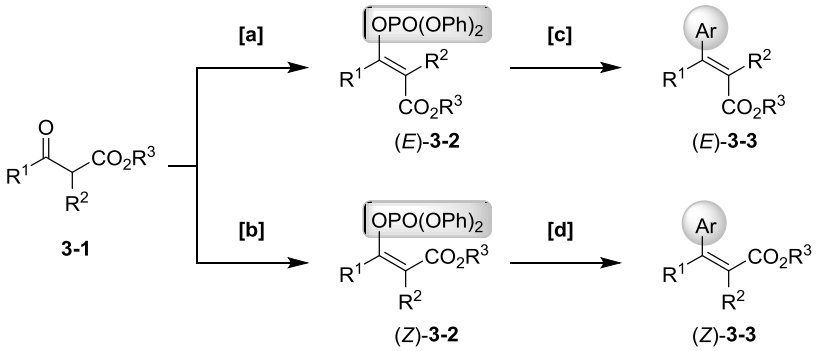


Introduction

(*E*)- and (*Z*)-α,β-unsaturated esters are widely distributed in natural products, pharmaceuticals, and supramolecules as key structural building blocks. They also serve as well-recognized useful structural scaffolds for various stereodefined olefins and conjugate (Michael) addition acceptors in organic synthesis. Stereocontrolled preparation of these (*E*)- and (*Z*)-esters is pivotal in organic synthesis and has been developed over the last few decades. Despite the demand for fully (tri)-substituted (*E*)- and (*Z*)-α,β-unsaturated esters, stereoselective synthetic methods are not yet fully established due to the inherent higher complexity in differentiating the substituents compared with mono- or di-substituted α,β-unsaturated esters.[1] Several excellent methods utilizing the carbometallation-mediated reaction using α-alkynyl esters,[2] Mizoroki–Heck reaction,[3] the ynolate-mediated reaction (Shindo's group),[4] cross-couplings using enol phosphonates (Skrydstrup's group),[5] Horner–Wadsworth–Emmons reaction,[6] and conjugate addition–elimination,[7] have been evaluated to date. However, the (*E*)- and (*Z*)-stereocomplementary method using the same common starting materials with sufficient substrate-generality is quite limited.

To investigate this critical topic, here it is presented a versatile synthesis of fully-substituted both (*E*)- and

(*Z*)-α,β-unsaturated esters **3-3** utilizing (*E*)- and (*Z*)-stereocomplementary enol phosphorylations of accessible α-substituted (R^2) β-ketoesters **3-1** and the subsequent (*E*)- and (*Z*)-stereoretentive Suzuki–Miyaura and Negishi cross-couplings (**Scheme 3-1**). A literature survey revealed no available general method for stereocomplementary enol phosphorylation of β-ketoesters **3-1**. Our longstanding interest in *N*-methylimidazole (NMI)-promoted acylations[8] and sulfonylations[9] led us to attempt this objective.



Scheme 3-1. Stereocomplementary synthesis of fully-substituted (*E*)- and (*Z*)-α,β-unsaturated esters **3-3**.

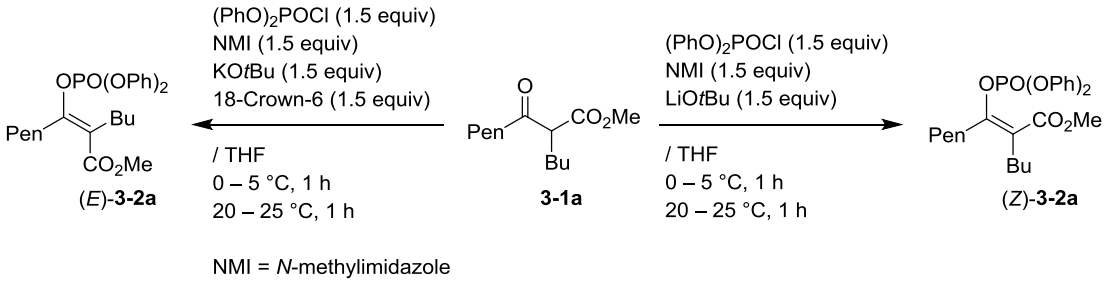
Results and Discussion

The initial stereoselective enol phosphorylation was intentionally guided using stereocongested methyl 2-butyl-3-oxooctanoate **3-1a**[10] as a much less reactive α-substituted β-ketoester probe (**Table 3-1**). Consequently, both (*E*)- and (*Z*)-selective phosphorylations of **3-1a** successfully proceeded in excellent yields with excellent stereoselectivity (>98:2) using $(PhO)_2POCl$–NMI–KO*t*Bu with 18-crown-6 (Method A) and $(PhO)_2POCl$–NMI–LiO*t*Bu (Method B) to give, respectively, (*E*)-**3-2a** and (*Z*)-**3-2a**, (entries 2, 4). Notably, the corresponding enol tosylation using the reported TsCl–NMI–base reagents[9] gave inferior results.[11] It is speculated that the present smooth enol phosphorylation can be attributed to the higher reactivity of $(PhO)_2POCl$ over TsCl.[12]

Table 3-2 lists the successful results of the present (*E*)- and (*Z*)-stereocomplementary enol phosphorylations of α-substituted β-ketoesters **3-1** using fine-tuned Methods A–D. A notable aspect is the high substrate-generality. The salient features are as follows. (i) All substrates **3-1a**–**3-1l** examined, produced good to excellent yields and excellent (*E*)- and (*Z*)-selectivities. (ii) Much less reactive (stereocongested) β-ketoesters **3-1a**, **3-1i**, and **3-1j**–**3-1l** could be applied successfully (entries 1, 2, 17–24). (iii) Not only α-aliphatic substrates but also α-aromatic substrates underwent the reaction smoothly using (*E*)-selective $(PhO)_2POCl$–NMI–DBU (Method C) and (*Z*)-selective $(PhO)_2POCl$–NMI–*i*Pr_2N–LiCl (Method D) (entries 19–24). (iv) Several functional groups such as ω-chloro, BnO, and a double bond were compatible (entries 11–16). (v) Because of the close R_f values of (*E*)- and (*Z*)-enol phosphonates **3-2** on thin layer chromatography excellent stereoselectivities of >95/5% are required for complete column chromatographic

purification with a high yield.[13]

Table 3-1. (*E*)- and (*Z*)-stereocomplementary enol phosphorylation of **3-1a** using $(PhO)_2POCl$–NMI–bases.

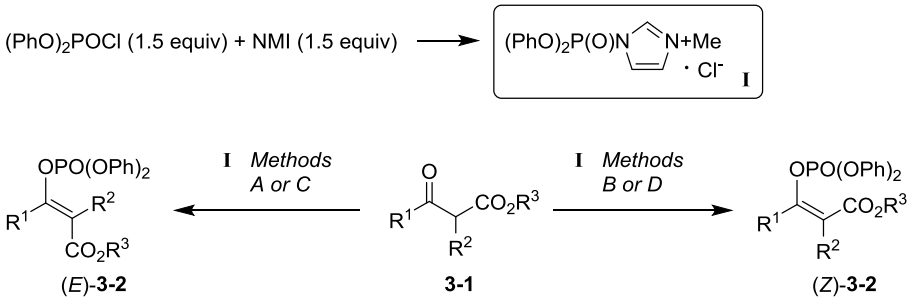


NMI = *N*-methylimidazole

Entry	Base	Additive	Method	Yield / %	E/Z^a
1	KO*t*Bu	–	–	44	2:>98
2	KO*t*Bu	18-Crown-6	A	84 (42[b])	98:2
3	LiHMDS	–	–	93	2:>98
4	LiO*t*Bu	–	B	97 (79[b])	2:>98

a) Determined by ^{1}H NMR of crude products. b) In the absence of NMI.

Table 3-2. (*E*)- and (*Z*)-Stereocomplementary enol phosphorylation of α-substituted β-ketoesters **3-1** using Methods A–D.



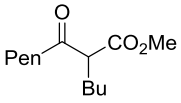
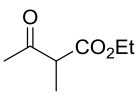
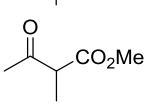
base (1.5 equiv)–additive (1.5 equiv) (Methods A–D)

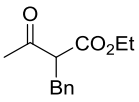
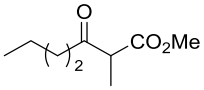
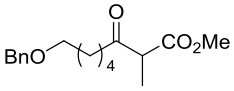
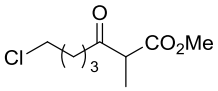
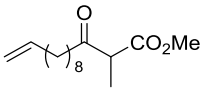
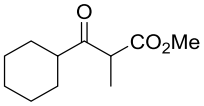
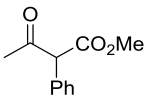
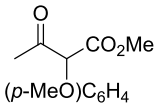
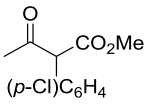
Method A KO*t*Bu–18-Crown-6 / THF; 0 – 5 °C, 1 h, 20 – 25 °C, 1 h

Method B LiO*t*Bu / THF; 0 – 5 °C, 1 h, 20 – 25 °C, 1 h

Method C DBU / DMF; 0 – 5 °C, 1 h

Method D iPr$_2$NEt–LiCl / THF; 0 – 5 °C, 1 h

Entry	Substrate		Method	Product	Yield / %	E/Z^b
1		**3-1a**	A	(*E*)-**3-2a**	84	98:2
2			B	(*Z*)-**3-2a**	97	2:>98
3		**3-1b**	A	(*E*)-**3-2b**	90	98:2
4			B	(*Z*)-**3-2b**	86	2:>98
5		**3-1c**	A	(*E*)-**3-2c**	71	>98:2
6			B	(*Z*)-**3-2c**	91	2:>98

7		**3-1d**	A	(*E*)-**3-2d**	83	>98:2
8			B	(*Z*)-**3-2d**	94	2:>98
9		**3-1e**	A	(*E*)-**3-2e**	87	95:5
10			B	(*Z*)-**3-2e**	90	2:>98
11		**3-1f**	A	(*E*)-**3-2f**	83	93:7
12			B	(*Z*)-**3-2f**	93	2:>98
13		**3-1g**	A	(*E*)-**3-2g**	75	>98:2
14			B	(*Z*)-**3-2g**	86	2:>98
15		**3-1h**	A	(*E*)-**3-2h**	83	97:3
16			B	(*Z*)-**3-2h**	98	2:>98
17		**3-1i**	A	(*E*)-**3-2i**	74	>98:2
18			B	(*Z*)-**3-2i**	86	2:>98
19		**3-1j**	C	(*E*)-**3-2j**	74	>98:2
20			D	(*Z*)-**3-2j**	86	2:>98
21		**3-1k**	C	(*E*)-**3-2k**	88	>98:2
22			D	(*Z*)-**3-2k**	97	2:>98
23		**3-1l**	C	(*E*)-**3-2l**	86	>98:2
24			D	(*Z*)-**3-2l**	88	2:>98

a) **3-1a** was prepared (ref. 10). **3-1b**–**3-1e**, **3-1g**, **3-1i**–**3-1l** were commercially available. **3-1f** and **3-1h** were prepared by the reported crossed Ti Claisen condensation (ref. 7b). b) Determined by ^{1}H NMR of the crude products.

As depicted in **Figure 3-1**, ^{1}H-NMR monitoring (−45 °C in CD_3CN) revealed that $(PhO)_2POCl$ coupled with NMI formed a highly reactive *N*-phosphorylammonium (imidazolium) intermediate **I**, which functioned as the key active species.[14]

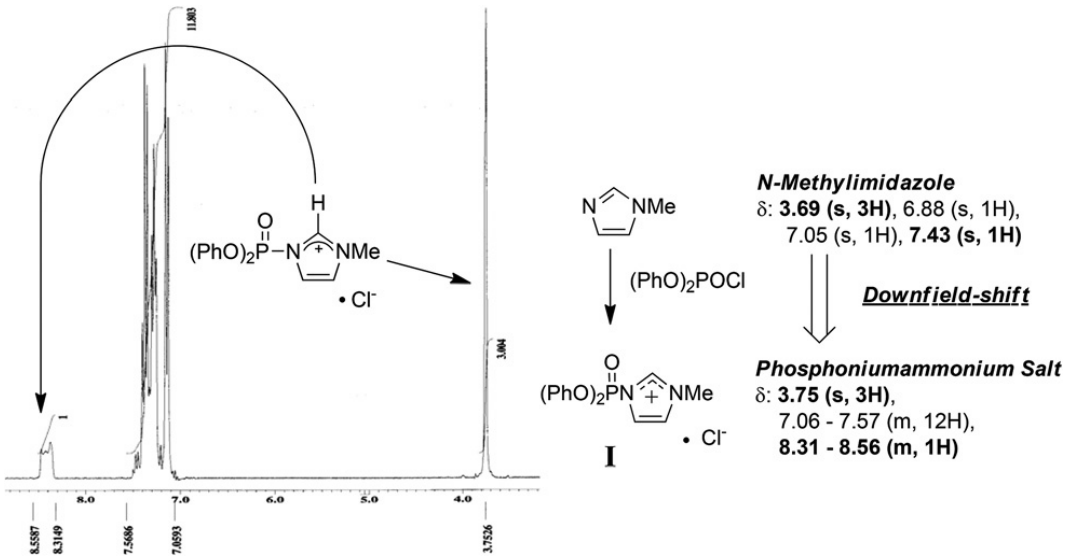
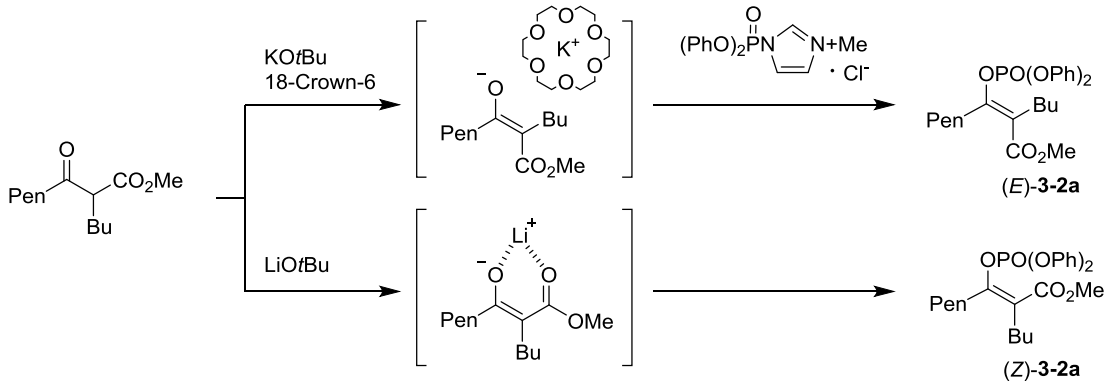


Figure 3-1. Formation of *N*-phosphorylammonium (imidazolium) intermediate **I** monitored by ^{1}H NMR measurement at −45 °C.

A plausible mechanism for the successful emergence of (*E*)- and (*Z*)-enol phosphorylation stereoselectivity is illustrated in **Scheme 3-2**, wherein substrate **3-1a** is exemplified. The (*E*)-stereoselective reaction with a highly reactive intermediate **I** proceeds *via* a non-chelation pathway to give (*E*)-**3-2a**; K-cation captured by 18-crown-6 aids (*E*)-enolate formation through dipole–dipole repulsive interactions between the oxy anion and ester function. In a clear contrast, the (*Z*)-stereoselective reaction proceeds *via* a chelation mechanism to give (*Z*)-**3-2a**; the Li-cation facilitates (*Z*)-enolate formation.

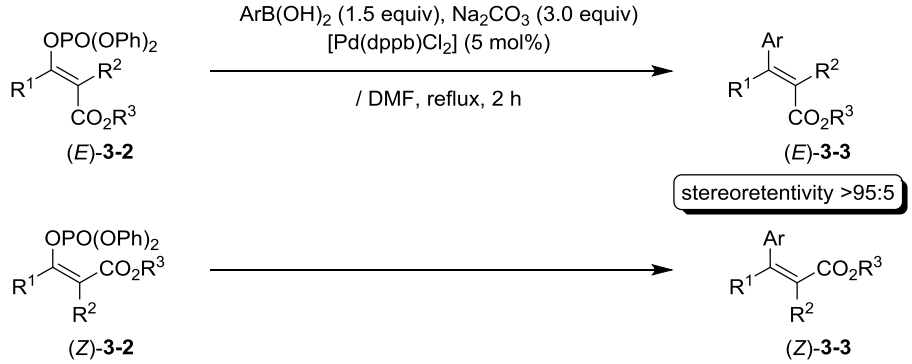


Scheme 3-2. Mechanistic investigation into the (E)- and (Z)-stereocomplementary enol phosphorylation of **3-1a**.

With the successful results in hand, stereoretentive Suzuki–Miyaura cross-coupling was investigated using (*E*)- and (*Z*)-stereodefined enol phosphonate partners **3-2a**–**3-2f** to obtain fully-substituted (*E*)- and (*Z*)-α,β-unsaturated esters **3-3a**–**3-3f**. **Table 3-3** lists the successful results, and the salient features are as follows. (i) Among the various catalysts screened, the Pd(dppb)Cl_2 catalyst produced a successful result.[15] (ii) Even the less reactive (stereocongested) substrate **3-2a** smoothly underwent the reaction (entries 1, 2). (iii) Three $ArB(OH)_2$ nucleophiles containing both electron-donating and electron-withdrawing substituents

(*p*-Me, *p*-OMe, *p*-Cl) were applicable (entries 5–10). (iv) High substrate-generality was obtained; good to excellent yields, and excellent (*E*)- and (*Z*)-stereoretention (>95:5) were achieved for most (*E*)- and (*Z*)-**3-2** examined. (v) Slight isomerization occurred in a few cases, however, likely due to the harsh DMF/reflux conditions (entries 1, 15). Since the substrates (*E*)-**3-2a** and (*E*)-**3-2f** are considerably less reactive due to the stereocongestion, slight isomerization is considered to occur. To address the obvious problems (high temperature and slight isomerization) resulting from Suzuki–Miyaura cross-coupling, Negishi cross-coupling was investigated using a variety of (*E*)- and (*Z*)-stereodefined enol phosphonate substrates **3-2a**, **3-2c**, **3-2f**–**3-2l**. **Table 3-4** (α-aliphatic substrates) and **Table 3-5** (α-aromatic substrates) list the positive results, and the salient features are as follows. (i) The substrate-generality was certainly enhanced in every case examined when using α-aliphatic as well as α-aromatic substrates with consistent and nearly perfect (*E*)- and (*Z*)-stereoretention to give the corresponding fully-substituted (*E*)- and (*Z*)-α,β-unsaturated esters **3-3a**, **3-3c-1**–**3-3c-8**, **3-3f**–**3-3l**. (ii) Milder conditions were applicable; MeCN/reflux for (*E*)-substrates **3-2** and THF/reflux for (*Z*)-substrates **3-2**. (iii) The loading quantity of the Pd(dppb)Cl_2 catalyst could be decreased from 5 mol% to 2 mol%. (iv) Various ArZnCl nucleophiles containing both electron-donating and electron-withdrawing substituents (*p*-Me, *p*-OMe, *o*-Me, *p*-Cl) and a bulky 1-naphthyl group, were employable (**Table 3-4**, entries 5–18). (v) Heterocyclic ZnCl nucleophiles (furan-2-yl and thiophen-2-yl) also underwent the reaction smoothly (**Table 3-4**, entries 15–18). (vi) Several functional groups, such as ω-BnO, ω-chloro, and a double bond were compatible (**Table 3-4**, entries 19–24). (vii) The reaction using α-aromatic substrates **3-2j**–3-2l proceeded smoothly under the identical conditions (**Table 3-5**).

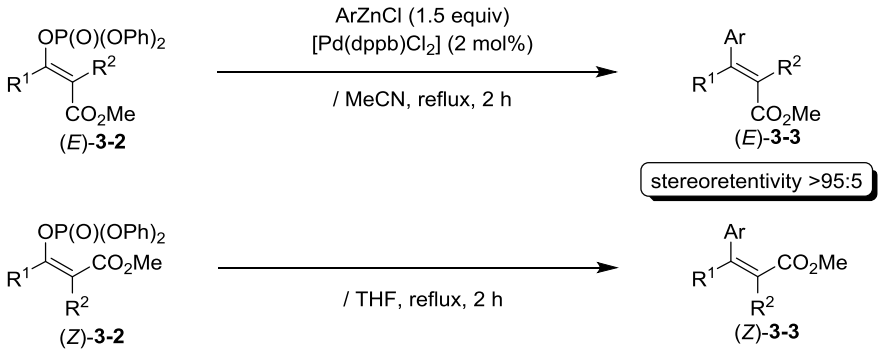
Table 3-3. Stereoretentive Suzuki–Miyaura cross-coupling of (*E*)- and (*Z*)-enol phosphonates **3-2**.



Entry	R^1	R^2	R^3	Substrate[a]	Ar	Product	Yield[b] / %
1	Pen	Bu	Me	(*E*)-**3-2a**	Ph	(*E*)-**3-3a**	83[c]
2				(*Z*)-**3-2a**		(*Z*)-**3-3a**	91
3	Me	Me	Et	(*E*)-**3-2b**	Ph	(*E*)-**3-3b-1**	81
4				(*Z*)-**3-2b**		(*Z*)-**3-3b-1**	81
5	Me	Me	Et	(*E*)-**3-2b**	(*p*-Me)C_6H_4	(*E*)-**3-3b-2**	83
6				(*Z*)-**3-2b**		(*Z*)-**3-3b-2**	83
7	Me	Me	Et	(*E*)-**3-2b**	(*p*-MeO)C_6H_4	(*E*)-**3-3b-3**	83
8				(*Z*)-**3-2b**		(*Z*)-**3-3b-3**	84
9	Me	Me	Et	(*E*)-**3-2b**	(*p*-Cl)C_6H_4	(*E*)-**3-3b-4**	71
10				(*Z*)-**3-2b**		(*Z*)-**3-3b-4**	82
11	Me	Bn	Et	(*E*)-**3-2d**	Ph	(*E*)-**3-3d**	88
12				(*Z*)-**3-2d**		(*Z*)-**3-3d**	83
13	Pen	Me	Me	(*E*)-**3-2e**	Ph	(*E*)-**3-3e**	81
14				(*Z*)-**3-2e**		(*Z*)-**3-3e**	80
15	$BnO(CH_2)_5$	Me	Me	(*E*)-**3-2f**	Ph	(*E*)-**3-3f**	90[d]
16				(*Z*)-**3-2f**		(*Z*)-**3-3f**	80

a) (*E*) or (*Z*): >98% purity based on ^{1}H NMR analysis. b) Isolated. Unless otherwise noted, *E*/*Z* = >95:5 for (*E*)-**3-3** and *E*/*Z* = 5:>95 for (*Z*)-**3-3**. c) *E*/*Z* = 83:17. d) *E*/*Z* = 81:19.

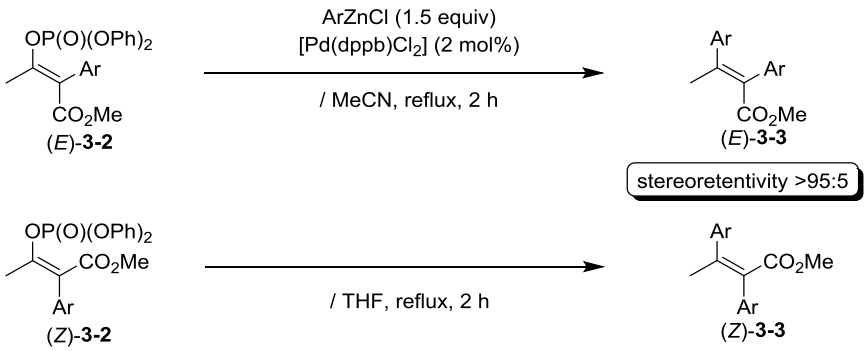
Table 3-4. Stereoretentive Negishi cross-coupling of aliphatic (*E*)- and (*Z*)-enol phosphonates **3-2**.



Entry	R^1	R^2	Substrate[a]	Ar	Product	Yield[b] / %
1	Pen	Bu	(*E*)-**3-2a**	Ph	(*E*)-**3-3a**	78
2			(*Z*)-**3-2a**		(*Z*)-**3-3a**	84
3	Me	Me	(*E*)-**3-2c**	Ph	(*E*)-**3-3c-1**	82
4			(*Z*)-**3-2c**		(*Z*)-**3-3c-1**	81
5	Me	Me	(*E*)-**3-2c**	(*p*-Me)C_6H_4	(*E*)-**3-3c-2**	91
6			(*Z*)-**3-2c**		(*Z*)-**3-3c-2**	81
7	Me	Me	(*E*)-**3-2c**	(*p*-MeO)C_6H_4	(*E*)-**3-3c-3**	79
8			(*Z*)-**3-2c**		(*Z*)-**3-3c-3**	85
9	Me	Me	(*E*)-**3-2c**	(*p*-Cl)C_6H_4	(*E*)-**3-3c-4**	83[c]
10			(*Z*)-**3-2c**		(*Z*)-**3-3c-4**	72[c]
11	Me	Me	(*E*)-**3-2c**	(*o*-Me)C_6H_4	(*E*)-**3-3c-5**	96
12			(*Z*)-**3-2c**		(*Z*)-**3-3c-5**	81
13	Me	Me	(*E*)-**3-2c**	1-Naph	(*E*)-**3-3c-6**	83
14			(*Z*)-**3-2c**		(*Z*)-**3-3c-6**	63
15	Me	Me	(*E*)-**3-2c**		(*E*)-**3-3c-7**	59
16			(*Z*)-**3-2c**		(*Z*)-**3-3c-7**	74
17	Me	Me	(*E*)-**3-2c**		(*E*)-**3-3c-8**	78
18			(*Z*)-**3-2c**		(*Z*)-**3-3c-8**	82
19	$BnO(CH_2)_5$	Me	(*E*)-**3-2f**	Ph	(*E*)-**3-3f**	71[d]
20			(*Z*)-**3-2f**		(*Z*)-**3-3f**	58[d]
21	$Cl(CH_2)_4$	Me	(*E*)-**3-2g**	Ph	(*E*)-**3-3g**	74[d]
22			(*Z*)-**3-2g**		(*Z*)-**3-3g**	76[d]
23	$CH_2{=}CH(CH_2)_8$	Me	(*E*)-**3-2h**	Ph	(*E*)-**3-3h**	88[d]
24			(*Z*)-**3-2h**		(*Z*)-**3-3h**	66[d]
25	Cyclohexyl	Me	(*E*)-**3-2i**	Ph	(*E*)-**3-3i**	81[d]
26			(*Z*)-**3-2i**		(*Z*)-**3-3i**	81[d]

(*E*) or (*Z*): >98% purity based on ^{1}H NMR analysis. b) Isolated. *E*/*Z* = >95:5 for (*E*)-**3-3** and *E*/*Z* = 5:>95 for (*Z*)-**3-3**. c) Reaction time: 1 h. d) 2 equiv. of PhZnCl were used.

Table 3-5. Stereoretentive Negishi cross-coupling of aromatic (*E*)- and (*Z*)-enol phosphonates **3-2**.

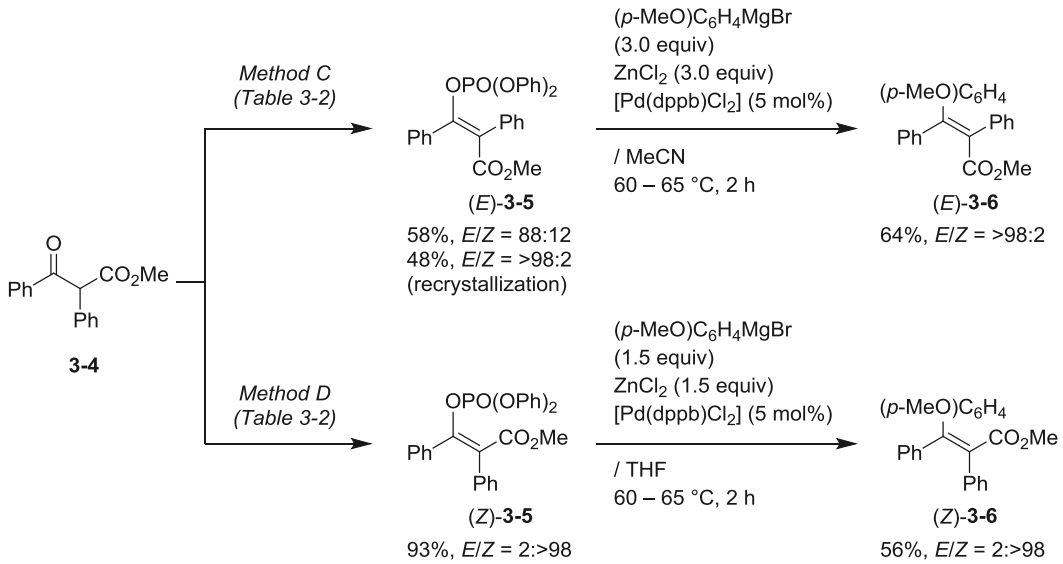


Entry	Ar	Substrate[a]	Product	Yield[b] / %
1	Ph	(*E*)-**3-2j**	(*E*)-**3-3j**	81
2		(*Z*)-**3-2j**	(*Z*)-**3-3j**	96
3	(*p*-MeO)C_6H_4	(*E*)-**3-2k**	(*E*)-**3-3k**	88[c,d]
4		(*Z*)-**3-2k**	(*Z*)-**3-3k**	92[c]
5	(*p*-Cl)C_6H_4	(*E*)-**3-2l**	(*E*)-**3-3l**	86[c,d]
6		(*Z*)-**3-2l**	(*Z*)-**3-3l**	88[c]

a) (*E*) or (*Z*): >98% purity based on ^{1}H NMR analysis. b) Isolated. *E*/*Z* = >95:5 for (*E*)-**3-3** and *E*/*Z* = 5:>95 for (*Z*)-**3-3**.
c) Reaction time: 1 h. d) 2.5 equiv. of ArZnCl was used.

The wide substrate-generality may be ascribed to the high reactivity and mildness of conditions of Negishi cross-coupling. Compared with the reported syntheses for several known compounds, **3-3b-1**, **3-3b-2**, **3-3b-3**, **3-3b-4**, **3-3c-1**, **3-3c-3**, **3-3d**, **3-3e**, **3-3j**, higher *E*/*Z*-selectivity was produced in almost all cases (details: Experimental).

Finally, to display the utility of the present method, a facile stereocomplementary synthesis of the precursor **3-6** for both (*E*)- and (*Z*)-tamoxifen,[16] an anti-tumor drug, is presented (**Scheme 3-3**). The same starting β-keto ester **3-4**[17] underwent stereocomplementary enol phosphorylations (**Table 3-2**, Methods C and D) smoothly to give (*E*)-**3-5** and (*Z*)-**3-5**, which were successfully converted to the desired (*E*)-**3-6** as well as (*Z*)-**3-6** by successive Negishi cross-coupling with certain stereoretention.[18]



Scheme 3-3. Stereocomplementary synthesis of fully-substituted (*E*)- and (*Z*)-tamoxifen precursor **3-6**.

Conclusion

A versatile synthesis of fully-substituted (*E*)- and (*Z*)-α,β-unsaturated esters utilizing (*E*)- and (*Z*)-stereocomplementary enol phosphorylations of β-ketoesters and the subsequent (*E*)- and (*Z*)-stereoretentive Suzuki–Miyaura and Negishi cross-couplings was achieved. Compared with the reported methods, the present method exhibits wider substrate-generality for the synthesis of synthetically inaccessible fully-substituted (*E*)- and (*Z*)-α,β-unsaturated esters. Further extension, especially for the parallel synthesis of fully-substituted olefins is disclosed in chapter 4 and 5.

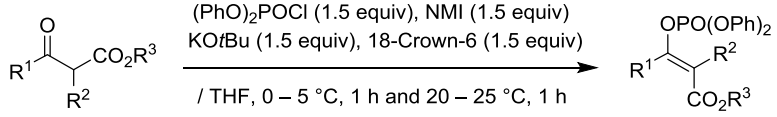
Experimental

Methyl 2-butyl-3-oxooctanoate 3-1a

$TiCl_4$ (114 g, 0.60 mol) and Et_3N (70.8 g, 0.70 mol) were successively added dropwise to a stirred solution of methyl hexanoate (65.1 g, 0.50 mol) in CH_2Cl_2 (500 mL) at 0 – 5 °C under an Ar atmosphere, and the mixture was stirred at the same temperature for 1 h. Water was added to the mixture, which was extracted twice with Et_2O. The combined organic phase was washed with sat. aq. $NaHCO_3$ solution, brine, dried (Na_2SO_4), and concentrated. The obtained crude product was purified by distillation to give the desired product (53.2 g, 93%).

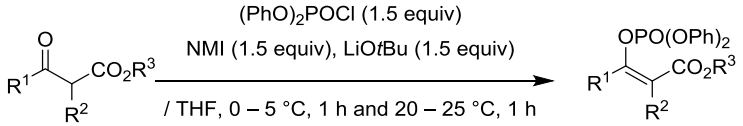
Colorless oil; bp 79−81 °C/0.49 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.2 Hz, 3H), 0.89 (t, *J* = 7.2 Hz, 3H), 1.16−1.39 (m, 8H), 1.58 (quin, *J* = 7.2 Hz, 2H), 1.78−1.90 (m, 2H), 2.45 (dt, *J* = 7.2 Hz, *Jgem* = 17.2 Hz, 1H), 2.54 (dt, *J* = 7.2 Hz, *Jgem* = 17.2 Hz, 1H), 3.43 (t, *J* = 7.2 Hz, 1H), 3.72 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.6, 13.7, 22.2, 22.3, 23.0, 27.8, 29.5, 31.0, 41.6, 52.0, 58.8, 170.2, 205.2.

General procedure for the (*E*)-stereoselective enol phosphorylation of β-ketoesters (*Method A*).



A β-ketoester (5.0 mmol − 1.0 mmol) in THF (5.0 mL − 1.0 mL), $(PhO)_2POCl$ (2.01 g − 0.40 g, 7.5 mmol – 1.5 mmol) in THF (5.0 mL − 1.0 mL), and *N*-methylimidazole (NMI: 0.62 g − 0.12 g, 7.5 mmol − 1.5 mmol) were successively added dropwise to a stirred suspension of KO*t*Bu (0.84 g − 0.17 g, 7.5 mmol − 1.5 mmol) and 18-Crown-6 (1.99 g − 0.40 g, 7.5 mmol − 1.5 mmol) in THF (5.0 mL − 1.0 mL) at 0 − 5 °C under an Ar atmosphere, and the mixture was stirred at the same temperature for 1 h and at 20 − 25 °C for 1 h. Water was added to the stirred mixture, which was extracted twice with EtOAc. The organic phase was washed with 1M HCl aqueous solution, brine, dried (Na_2SO_4), and concentrated. The obtained crude product was purified by SiO_2-column chromatography (hexane/AcOEt = 20/1 – 5/1) to give the desired product (*E*)-**3-2**.

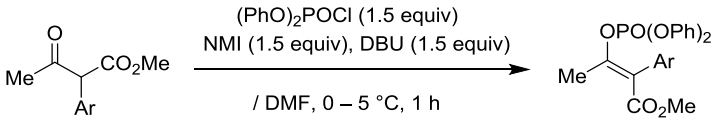
General procedure for the (*Z*)-stereoselective enol phosphorylation of β-ketoesters (*Method B*).



A β-ketoester (5.0 mmol − 1.0 mmol) in THF (5.0 mL − 1.0 mL), $(PhO)_2POCl$ (2.01 – 0.40 g, 7.5 mmol − 1.5 mmol) in THF (5.0 mL − 1.0 mL), and *N*-methylimidazole (NMI: 0.62 g − 0.12 g, 7.5 mmol – 1.5 mmol) were successively added dropwise to a stirred suspension of LiO*t*Bu (0.60 g – 0.12 g, 7.5 mmol − 1.5 mmol)

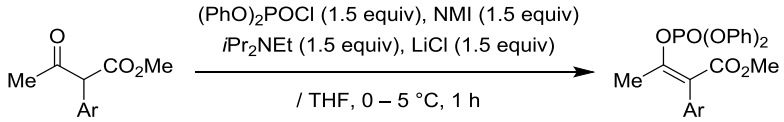
in THF (5.0 mL − 1.0 mL) at 0 − 5 °C under an Ar atmosphere, and the mixture was stirred at the same temperature for 1 h and at 20 − 25 °C for 1 h.. Water was added to the stirred mixture, which was extracted twice with EtOAc. The organic phase was washed with 1M HCl aqueous solution, brine, dried (Na_2SO_4), and concentrated. The obtained crude product was purified by SiO_2-column chromatography (hexane/AcOEt = 20/1 – 5/1) to give the desired product (*Z*)-**3-2**.

General procedure for the (*E*)-stereoselective enol phosphorylation of α-aryl-β-ketoesters with (*Method C*).



$(PhO)_2POCl$ (402 mg, 1.5 mmol) was added to a stirred solution of an α-aryl-β-ketoester (1.0 mmol), NMI (*N*-methylimidazole) (123 mg, 1.5 mmol), and DBU (228 mg, 1.5 mmol) in DMF (2.0 mL) at 0 − 5 °C under an Ar atmosphere, and the mixture was stirred at the same temperature for 1 h. Water was added to the reaction mixture, which was extracted twice with AcOEt. The organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. The obtained crude product was purified by SiO_2-column chromatography (hexane/AcOEt = 10/1 – 3/1) to give the desired product.

General procedure for the (*Z*)-stereoselective enol phosphorylation of α-aryl-β-ketoesters (*Method D*).



An α-aryl-β-ketoester (1.0 mmol), iPr_2NEt (194 mg, 1.5 mmol), NMI (*N*-methylimidazole) (123 mg, 1.5 mmol), and $(PhO)_2POCl$ (402 mg, 1.5 mmol) were successively added to a stirred suspension of LiCl (64 mg 1.5 mmol) in THF (1.0 mL) at 0 − 5 °C under an Ar atmosphere, and the mixture was stirred at the same temperature for 1 h. Water was added to the reaction mixture, which was extracted with twice AcOEt. The organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. The obtained crude product was purified by SiO_2-column chromatography (hexane/AcOEt = 10/1 – 3/1) to give the desired product.

Methyl (*E*)-2-butyl-3-((diphenoxyphosphoryl)oxy)oct-2-enoate (*E*)-3-2a

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.81 (t, *J* = 7.2 Hz, 3H), 0.83 (t, *J* = 7.2 Hz, 3H), 1.09−1.34 (m, 8H), 1.47–1.62 (m, 2H), 2.28 (t, *J* = 7.2 Hz, 2H), 2.76 (t, *J* = 7.2 Hz, 2H), 3.74 (s, 3H), 7.17–7.29 (m, 6H), 7.30–7.40 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7, 13.8, 22.2, 22.3, 27.0, 27.0, 30.6, 31.2, 32.5, 51.6, 119.9 [d, ^3J (^{13}C, ^{31}P) = 4.3 Hz], 121.6 [d, ^3J (^{13}C, ^{31}P) = 8.7 Hz], 125.5, 129.7, 150.3 [d, ^2J (^{13}C, ^{31}P) = 7.2 Hz], 157.9 [d, ^2J (^{13}C, ^{31}P) = 8.0 Hz], 168.2; ^{31}P NMR (202 MHz, $CDCl_3$): δ = −18.4; IR (neat): ν_{max} = 2957, 2872, 1721, 1647, 1593, 1489, 1302, 1275 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{25}H_{33}O_6P$ $[M+Na]^+$ 483.1912; found: 483.1912.

Methyl (*Z*)-2-butyl-3-((diphenoxyphosphoryl)oxy)oct-2-enoate (*Z*)-3-2a

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85 (t, *J* = 6.9 Hz, 3H), 0.90 (t, *J* = 6.9 Hz, 3H), 1.17−1.45 (m, 8H), 1.47−1.62 (m, 2H), 2.22−2.32 (m, 2H), 2.42 (t, *J* = 7.2 Hz, 2H), 3.56 (s, 3H), 7.13−7.39 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7, 22.2, 22.2, 26.4, 28.7, 31.0, 31.0, 31.2, 31.3, 51.5, 119.9 [d, ^{3}J (^{13}C, ^{31}P) = 5.1 Hz], 120.9 [d, ^{3}J (^{13}C, ^{31}P) = 7.2 Hz], 125.2, 129.6, 150.4 [d, ^{2}J (^{13}C, ^{31}P) = 7.2 Hz], 151.5 [d, ^{2}J (^{13}C, ^{31}P) = 8.7 Hz], 167.4; ^{31}P NMR (202 MHz, $CDCl_3$): δ = −18.4; IR (neat): ν_{max} = 2959, 2872, 1717, 1592, 1489, 1435, 1314, 1230 cm^{-1}.

Ethyl (*E*)-2-methyl-3-((diphenoxyphosphol)oxy)but-2-enoate (*E*)-3-2b

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.29 (t, *J* = 7.2 Hz, 3H), 1.76–1.82 (m, 3H), 2.44–2.49 (m, 3H), 4.19 (t, *J* = 7.2 Hz, 2H), 7.14–7.40 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.5, 13.8, 18.9, 60.3, 116.3 [d, ^{3}J (^{13}C, ^{31}P) = 9.4 Hz], 119.8 [d, ^{3}J (^{13}C, ^{31}P) = 5.1 Hz], 125.4, 129.6, 150.0 [d, ^{2}J (^{13}C, ^{31}P) = 7.2 Hz], 154.8 [d, ^{2}J (^{13}C, ^{31}P) = 8.0 Hz], 167.3; IR (neat): ν_{max} = 2982, 1717, 1655, 1592, 1489, 1456, 1379, 1281 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{19}H_{21}O_6P$ $[M+Na]^+$ 339.0973; found: 339.0973.

Ethyl (*Z*)-2-methyl-3-((diphenoxyphosphol)oxy)but-2-enoate (*Z*)-3-2b

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20 (t, *J* = 7.2 Hz, 3H), 1.89 (s, 3H), 2.13 (s, 3H), 4.09 (t, *J* = 7.2 Hz, 2H), 7.04–7.42 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 14.5, 17.9, 60.5, 115.4 [d, ^{3}J (^{13}C, ^{31}P) = 8.7 Hz], 119.9 [d, ^{3}J (^{13}C, ^{31}P) = 5.1 Hz], 125.2, 129.5, 147.9 [d, ^{2}J (^{13}C, ^{31}P) = 8.7 Hz], 150.2 [d, ^{2}J (^{13}C, ^{31}P) = 7.2 Hz], 166.6; IR (neat): ν_{max} = 2982, 1717, 1655, 1592, 1489, 1456, 1379, 1281 cm^{-1}.

Methyl (*E*)-2-methyl-3-((diphenoxyphosphoryl)oxy)but-2-enoate (*E*)-3-2c

Pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.80 (s, 3H), 2.48 (s, 3H), 3.74 (s, 3H), 7.19−7.28 (m, 6H), 7.33−7.38 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.7, 19.2, 51.7, 116.2 [d, ^{3}J (^{13}C, ^{31}P) = 9.6 Hz], 120.0 [d, ^{3}J (^{13}C, ^{31}P) = 4.8 Hz], 125.6, 129.8, 150.2 [d, ^{2}J (^{13}C, ^{31}P) = 8.4 Hz], 155.4 [d, ^{2}J (^{13}C, ^{31}P) = 8.4 Hz], 168.2; IR (neat): ν_{max} = 3066, 2952, 1718, 1655, 1590, 1488, 1284, 1186, 1099, 953, 762, 689 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{18}H_{19}O_6P$ $[M+Na]^+$ 385.0817; found: 385.0826.

Methyl (*Z*)-2-methyl-3-((diphenoxyphosphoryl)oxy)but-2-enoate (*Z*)-3-2c

Colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.89 (s, 3H), 2.13 (s, 3H), 3.56 (s, 3H), 7.16−7.27 (m, 6H), 7.30−7.39 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.7, 18.2, 51.6, 115.2, [d, ^{3}J (^{13}C, ^{31}P) = 8.4 Hz], 120.0 [d, ^{3}J (^{13}C, ^{31}P) = 6.0 Hz], 125.4, 129.7, 148.6 [d, ^{2}J (^{13}C, ^{31}P) = 8.4 Hz], 150.4, [d, ^{2}J (^{13}C, ^{31}P) = 8.4 Hz], 167.2; IR (neat): ν_{max} = 3071, 2952, 1720, 1590, 1488, 1298, 1188, 1136, 1020, 943, 773, 730 cm^{-1}.

Ethyl (*E*)-2-benzyl-3-((diphenoxyphosphol)oxy)but-2-enoate (*E*)-3-2d

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.16 (t, *J* = 7.2 Hz, 3H), 2.57 (s, 3H), 3.65 (s, 2H), 4.11 (t, *J* = 7.2 Hz, 2H), 7.05–7.40 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 19.1, 32.5, 60.7 , 119.7 [d, ^{3}J (^{13}C,

^{31}P) = 9.4 Hz], 121.4 [d, ^{3}J (^{13}C, ^{31}P) = 9.4 Hz], 125.6, 125.9, 128.1, 128.2, 129.8, 139.0, 150.1 [d, ^{2}J (^{13}C, ^{31}P) = 8.0 Hz], 155.4 [d, ^{2}J (^{13}C, ^{31}P) = 7.2 Hz], 167.1; IR (neat): ν_{max} = 2982, 1717, 1649, 1592, 1489, 1456, 1383, 1298 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{25}H_{25}O_6P$ [M+Na]$^+$ 475.1286; found: 475.1285.

Ethyl (*Z*)-2-benzyl-3-((diphenoxyphosphol)oxy)but-2-enoate (*Z*)-3-2d

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.09 (t, *J* = 7.2 Hz, 3H), 2.21 (*J* = 2.1 Hz, 3H), 3.68 (s, 2H), 4.02 (t, *J* = 7.2 Hz, 2H), 7.13–7.40 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 18.3, 34.7, 60.8, 119.5 [d, ^{3}J (^{13}C, ^{31}P) = 9.4 Hz], 120.0 [d, ^{3}J (^{13}C, ^{31}P) = 5.1 Hz], 125.5, 126.4, 128.1, 128.5, 129.7, 138.1, 149.7 [d, ^{2}J (^{13}C, ^{31}P) = 8.7 Hz], 150.4 [d, ^{2}J (^{13}C, ^{31}P) = 8.0 Hz], 166.3; IR (neat): ν_{max} = 2982, 1719, 1592, 1489, 1456, 1306, 1190, 1163 cm^{-1}.

Methyl (*E*)-2-methyl-3-((diphenoxyphosphol)oxy)oct-2-enoate (*E*)-3-2e

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85 (t, *J* = 7.6 Hz, 3H), 1.14–1.33 (m, 4H), 1.44–1.61 (m, 2H), 1.82 (d, *J* = 2.4 Hz, 3H), 2.81 (t, *J* = 7.6 Hz, 2H), 3.73 (s, 3H), 7.15–7.40 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.1, 13.9, 22.3, 27.0, 31.3, 32.5, 51.7, 116.6 [d, ^{3}J (^{13}C, ^{31}P) = 8.7 Hz], 120.0 [d, ^{3}J (^{13}C, ^{31}P) = 5.1 Hz], 125.6, 129.8, 150.3 [d, ^{2}J (^{13}C, ^{31}P) = 7.2 Hz], 159.4 [d, ^{2}J (^{13}C, ^{31}P) = 8.0 Hz], 168.1; IR (neat): ν_{max} = 2982, 1719, 1592, 1489, 1456, 1387, 1306, 1223, 1190 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{22}H_{27}O_6P$ [M+Na]$^+$ 441.1443; found: 441.1446.

Methyl (*Z*)-2-methyl-3-((diphenoxyphosphol)oxy)oct-2-enoate (*Z*)-3-2e

colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85 (t, *J* = 7.2 Hz, 3H), 1.18–1.34 (m, 4H), 1.54 (quin, *J* = 7.6 Hz, 2H), 1.91 (d, *J* = 3.1 Hz, 3H), 2.42 (t, *J* = 7.7 Hz, 2H), 3.57 (s, 3H), 7.06–7.42 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7, 14.5, 22.2, 26.0, 31.1, 31.8, 51.5, 115.3 [d, ^{3}J (^{13}C, ^{31}P) = 7.2 Hz], 119.9 [d, ^{3}J (^{13}C, ^{31}P) = 5.1 Hz], 125.2, 129.6, 150.4 [d, ^{2}J (^{13}C, ^{31}P) = 8.0 Hz], 152.4 [d, ^{2}J (^{13}C, ^{31}P) = 8.0 Hz], 167.3; IR (neat): ν_{max} = 2957, 2872, 1725, 1655, 1592, 1489, 1458, 1435 cm^{-1}.

Methyl (*E*)-2-methyl-3-((diphenoxyphosphoryl)oxy)-8-benzyloxyoct-2-enoate (*E*)-3-2f

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.37 (t, *J* = 7.2 Hz, 2H), 1.48−1.63 (m, 4H), 1.82 (d, *J* = 2.1 Hz, 3H), 2.83 (t, *J* = 7.2 Hz, 2H), 3.42 (t, *J* = 6.6 Hz, 2H), 3.72 (s, 3H), 4.47 (s, 2H), 7.13−7.39 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.0, 25.7, 27.0, 29.3, 32.4, 51.7, 70.1, 72.6, 116.7 [d, ^{3}J (^{13}C, ^{31}P) = 8.7 Hz], 119.9, 119.9, 125.5, 127.4, 128.2, 129.7, 138.5, 150.2 [d, ^{2}J (^{13}C, ^{31}P) = 7.2 Hz], 159.0 [d, ^{2}J (^{13}C, ^{31}P) = 8.7 Hz], 168.0; IR (neat): ν_{max} = 2936, 2863, 1719, 1655, 1590,1489, 1306, 1228 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{29}H_{33}O_7P$ [M+Na]$^+$ 547.1862; found: 547.1859.

Methyl (*Z*)-2-methyl-3-((diphenoxyphosphoryl)oxy)-8-benzyloxyoct-2-enoate (*Z*)-3-2f

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27−1.42 (m, 2H), 1.48−1.64 (m, 4H), 1.89 (d, *J* = 3.8 Hz, 3H), 2.43 (t, *J* = 7.2 Hz, 2H), 3.42 (t, *J* = 6.5 Hz, 2H), 3.57 (s, 3H), 4.47 (s, 2H), 7.06−7.40 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) □ 14.6, 25.6, 26.2, 29.3, 31.8, 51.6, 69.9, 72.7, 115.5 [d, ^{3}J (^{13}C, ^{31}P) = 7.2 Hz], 119.9,

120.0, 125.3, 127.5, 128.2, 129.6, 138.5, 150.4 [d, ^{2}J (^{13}C, ^{31}P) = 7.2 Hz], 152.2 [d, ^{2}J (^{13}C, ^{31}P) = 9.4 Hz], 167.2; IR (neat): ν_{max} = 2942, 2865, 1747, 1655, 1590, 1485, 1435, 1296 cm^{-1}.

Methyl (*E*)-2-methyl-3-((diphenoxyphosphoryl)oxy)-7-chlorohept-2-enoate (*E*)-3-2g

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.62−1.80 (m, 4H), 1.84 (d, *J* = 2.4 Hz, 3H), 2.86 (t, *J* = 7.2 Hz, 2H), 3.47 (t, *J* = 6.2 Hz, 2H), 3.74 (s, 3H), 7.11−7.45 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.1, 24.5, 31.6, 31.8, 44.5, 51.8, 117.3 [d, ^{3}J (^{13}C, ^{31}P) = 8.0 Hz], 120.0 [d, ^{3}J (^{13}C, ^{31}P) = 5.1 Hz], 125.6 [d, ^{3}J (^{13}C, ^{31}P) = 9.4 Hz], 129.8, 150.3 [d, ^{2}J (^{13}C, ^{31}P) = 8.0 Hz], 158.3 [d, ^{2}J (^{13}C, ^{31}P) = 8.0 Hz], 167.9; IR (neat): ν_{max} = 2953, 2872, 1721, 1649, 1492, 1489, 1458, 1298 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{21}H_{24}O_6ClP$ $[M+Na]^+$ 461.0896, found 461.0897.

Methyl (*Z*)-2-methyl-3-((diphenoxyphosphoryl)oxy)-7-chlorohept-2-enoate (*Z*)-3-2g

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.63−1.80 (m, 4H), 1.92 (d, *J* = 6.9 Hz, 3H), 2.46 (t, *J* = 6.9 Hz, 2H), 3.47 (t, *J* = 6.2 Hz, 2H), 3.58 (s, 3H), 7.12−7.39 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.7, 23.7, 31.1, 31.7, 44.3, 51.7, 116.2 [d, ^{3}J (^{13}C, ^{31}P) = 8.0 Hz], 120.0 [d, ^{3}J (^{13}C, ^{31}P) = 5.1 Hz], 125.4, 130.0, 150.5 [d, ^{2}J (^{13}C, ^{31}P) = 7.2 Hz], 151.3 [d, ^{2}J (^{13}C, ^{31}P) = 8.7 Hz], 167.2; IR (neat): ν_{max} = 2951, 2870, 1728, 1655, 1592, 1489, 1458, 1302 cm^{-1}.

Methyl (*E*)-2-methyl-3-((diphenoxyphosphoryl)oxy)-tridec-2,12-dienoate (*E*)-3-2h

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.10–1.61 (m, 12H), 1.82 (d, *J* = 2.1 Hz, 3H), 1.97–2.08 (m, 2H), 2.81 (t, *J* = 7.6 Hz, 2H), 3.73 (s, 3H), 4.89–5.03 (m, 2H), 5.80 (ddt, *J* = 6.9, 10.3, 17.2 Hz, 1H), 7.11–7.43 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.9, 27.1, 28.7, 28.9, 28.9, 29.0, 29.1, 32.4, 33.6, 51.6, 114.0, 116.4 [d, ^{3}J (^{13}C, ^{31}P) = 8.0 Hz], 119.9 [d, ^{3}J (^{13}C, ^{31}P) = 4.3 Hz], 125.4, 129.7, 138.9, 150.2 [d, ^{2}J (^{13}C, ^{31}P) = 7.2 Hz], 159.2 [d, ^{2}J (^{13}C, ^{31}P) = 8.0 Hz], 167.9; IR (neat): ν_{max} = 2953, 2870,1719, 1647, 1592, 1458, 1437, 1298 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{27}H_{35}O_6P$ $[M+Na]^+$ 509.2069; found: 509.2073.

Methyl (*Z*)-2-methyl-3-((diphenoxyphosphoryl)oxy)-tridec-2,12-dienoate (*Z*)-3-2h

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.16–1.65 (m, 12H), 1.91 (d, *J* = 3.1 Hz, 3H), 2.03 (q, *J* = 7.2 Hz, 2H), 2.43 (t, *J* = 7.6 Hz, 2H), 3.57 (s, 3H), 4.90–5.03 (m, 2H), 5.80 (ddt, *J* = 7.2, 10.3, 16.9 Hz, 1H), 7.09–7.44 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.5, 25.1, 26.2, 28.6, 28.8, 29.0, 29.0, 31.7, 33.5, 51.4, 114.0 [d, ^{3}J (^{13}C, ^{31}P) = 8.0 Hz], 115.3 [d, ^{3}J (^{13}C, ^{31}P) = 5.1 Hz], 125.2, 129.5, 138.8, 150.3 [d, ^{2}J (^{13}C, ^{31}P) = 7.2 Hz], 152.3 [d, ^{2}J (^{13}C, ^{31}P) = 8.7 Hz], 167.1; IR (neat): ν_{max} = 2932, 2855, 1721, 1655, 1593, 1489, 1436, 1316 cm^{-1}.

Methyl (*E*)-2-methyl-3-((diphenoxyphosphoryl)oxy)-3-cyclohexylpropenoate (*E*)-3-2i

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.01–1.86 (m, 10H), 1.93 (d, *J* = 2.1 Hz, 3H), 3.16–3.31 (m, 1H), 3.75 (s, 3H) 7.05–7.47 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 25.5, 25.9, 29.2, 41.4, 51.7, 116.3 [d, ^{3}J (^{13}C, ^{31}P) = 6.5 Hz], 119.8, 125.3, 129.6, 150.4 [d, ^{2}J (^{13}C, ^{31}P) = 7.2 Hz], 161.9 [d, ^{2}J (^{13}C, ^{31}P) =

10.8 Hz], 168.3; IR (neat): ν_{max} = 2932, 2857, 1719, 1647, 1592, 1489, 1456, 1314 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{23}H_{27}O_6P$ $[M+Na]^+$ 453.1443; found: 453.1445.

Methyl (*Z*)-2-methyl-3-((diphenoxyphosphoryl)oxy)-tridec-2,12-dienoate (*Z*)-3-2i

Colorless oil; ^1H NMR (300 MHz, $CDCl_3$): δ = 1.46–1.85 (m, 10H), 1.96 (d, *J* = 3.4 Hz, 3H), 2.50–2.62 (m, 1H), 3.62 (s, 3H), 7.11–7.37 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.6, 25.5, 26.0, 28.7, 41.2, 51.7, 114.7 [d, ^3J (^{13}C, ^{31}P) = 5.8 Hz], 120.0 [d, ^3J (^{13}C, ^{31}P) = 5.1 Hz], 125.2, 129.6, 150.7 [d, ^2J (^{13}C, ^{31}P) = 7.2 Hz], 152.3 [d, ^2J (^{13}C, ^{31}P) = 8.7 Hz], 167.8; IR (neat): ν_{max} = 2932, 2857, 1725, 1592, 1491, 1456, 1314, 1192 cm^{-1}.

Methyl (*E*)-2-phenyl-3-((diphenoxyphosphoryl)oxy)but-2-enoate (*E*)-3-2j

Colorless oil: ^1H NMR (500 MHz, $CDCl_3$): δ = 2.63 (d, *J* = 1.7 Hz, 3H), 3.69 (s, 3H) 6.89–6.93 (m, 4H), 7.13–7.30 (m, 11H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.2, 52.1, 119.9 [d, ^3J (^{13}C, ^{31}P) = 4.8 Hz], 121.7 [d, ^3J (^{13}C, ^{31}P) = 9.6 Hz], 125.4, 127.5, 128.0, 129.6, 129.7, 133.8, 150.0 [d, ^2J (^{13}C, ^{31}P) = 8.4 Hz], 155.6 [d, ^2J (^{13}C, ^{31}P) = 6.0 Hz], 167.5; IR (neat): ν_{max} = 3061, 2951, 1718, 1643, 1589, 1488, 1290, 1216 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{23}H_{21}O_6P$ $[M+Na]^+$ 477.0974; found: 477.0971.

Methyl (*Z*)-2-chloro-3-((diphenoxyphosphoryl)oxy)but-2-enoate (*Z*)-3-2j

Colorless oil: ^1H NMR (500 MHz, $CDCl_3$): δ = 2.07 (d, *J* = 1.7 Hz, 3H), 3.56 (s, 3H) 7.19–7.40 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.7, 52.0, 120.1 [d, ^3J (^{13}C, ^{31}P) = 4.8 Hz], 122.3 [d, ^3J (^{13}C, ^{31}P) = 9.6 Hz], 125.5, 128.1, 128.4, 129.4, 129.8, 134.0, 150.1 [d, ^2J (^{13}C, ^{31}P) = 8.4 Hz], 150.4 [d, ^2J (^{13}C, ^{31}P) = 8.4 Hz], 166.1; IR (neat): ν_{max} = 3061, 2951, 1724, 1646, 1590, 1488, 1382, 1300 cm^{-1}.

Methyl (*E*)-2-(4-methoxyphenyl)-3-((diphenoxyphosphoryl)oxy)but-2-enoate (*E*)-3-2k

Yellow oil: ^1H NMR (500 MHz, $CDCl_3$): δ = 2.59 (d, *J* =1.7 Hz, 3H), 3.69 (s, 3H), 3.78 (s, 3H), 6.75–6.79 (m, 2H), 6.95 (d, *J* = 7.5 Hz, 4H), 7.09–7.13 (m, 2H), 7.15 (t, *J* = 7.5 Hz, 2H), 7.25 (t, *J* = 7.5 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.3, 52.2, 55.1, 113.5, 119.9 [d, ^3J (^{13}C, ^{31}P) = 4.8 Hz], 121.5 [d, ^3J (^{13}C, ^{31}P) = 9.6 Hz], 125.4, 125.9, 129.7, 130.8, 150.1 [d, ^2J (^{13}C, ^{31}P) = 7.2 Hz], 155.0 [d, ^3J (^{13}C, ^{31}P) = 7.2 Hz],158.9; IR (neat): ν_{max} = 3068, 2952, 1718, 1590, 1489, 1295, 1181, 1069, 963, 774, 688 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{24}H_{23}O_7P$ $[M+Na]^+$ 477.1079; found: 477.1080.

Methyl (*Z*)-2-(4-methoxyphenyl)-3-((diphenoxyphosphoryl)oxy)but-2-enoate (*Z*)-3-2k

Pale yellow oil: ^1H NMR (500 MHz, $CDCl_3$): δ = 2.07 (d, *J* = 1.7 Hz, 3H), 3.55 (s, 3H), 3.81 (s, 3H), 6.87–6.91 (m, 2H), 7.17–7.24 (m, 4H), 7.29 (d, *J* = 8.6 Hz, 4H), 7.36 (t, *J* = 8.6 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.6, 51.9, 55.2, 113.9, 120.1 [d, ^3J (^{13}C, ^{31}P) = 4.8 Hz], 121.9 [d, ^3J (^{13}C, ^{31}P) = 8.4 Hz], 125.5, 126.1, 129.6, 129.8, 130.6, 149.6 [d, ^2J (^{13}C, ^{31}P) = 8.4 Hz], 150.4 [d, ^2J (^{13}C, ^{31}P) = 8.4 Hz], 159.3, 166.5; IR (neat): ν_{max} = 3002, 2952, 1725, 1591, 1489, 1292, 1227, 1185, 960, 774, 689 cm^{-1}.

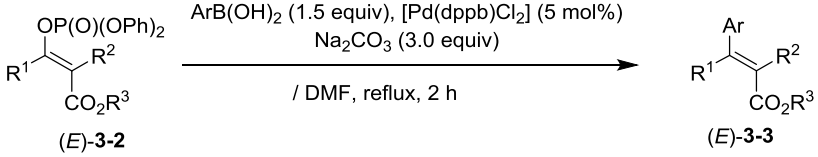
Methyl (*E*)-2-(4-chlorophenyl)-3-((diphenoxyphosphoryl)oxy)but-2-enoate (*E*)-3-2l

Yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.64 (d, *J* = 1.7 Hz, 3H), 3.68 (s, 3H), 6.95 (d, *J* = 7.5 Hz, 4H), 7.05–7.08 (m, 2H), 7.14–7.21 (m, 4H), 7.27 (t, *J* = 7.5 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.2, 52.2, 119.7 [d, ^{3}J (^{13}C, ^{31}P) = 4.8 Hz], 120.7 [d, ^{3}J (^{13}C, ^{31}P) = 10.8 Hz], 125.6, 128.2, 129.8, 131.0, 132.2, 133.4, 150.0 [d, ^{2}J (^{13}C, ^{31}P) = 8.4 Hz], 156.4 [d, ^{2}J (^{13}C, ^{31}P) = 7.2 Hz], 167.0; IR (neat): ν_{max} = 3067, 2953, 1719, 1591, 1490, 1289, 1183, 1071, 963, 774, 688 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{23}H_{20}ClO_6P$ $[M+Na]^+$ 481.0584; found: 481.0581.

Methyl (*Z*)-2-(4-chlorophenyl)-3-((diphenoxyphosphoryl)oxy)but-2-enoate (*Z*)-3-2l

Colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.05 (d, *J* = 1.7 Hz, 3H), 3.56 (s, 3H), 7.18–7.25 (m, 4H), 7.27–7.30 (m, 4H), 7.32–7.40 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.8, 52.0, 120.1 [d, ^{3}J (^{13}C, ^{31}P) = 4.80 Hz], 121.2 [d, ^{3}J (^{13}C, ^{31}P) = 8.4 Hz], 125.6, 128.7, 129.8, 130.9, 132.5, 134.2, 150.3 [d, ^{2}J (^{13}C, ^{31}P) = 8.4 Hz], 150.8 [d, ^{2}J (^{13}C, ^{31}P) = 8.4 Hz], 165.7; IR (neat): ν_{max} = 3069, 2952, 1725, 1591, 1489, 1299, 1224, 1185, 962, 773, 687 cm^{-1}.

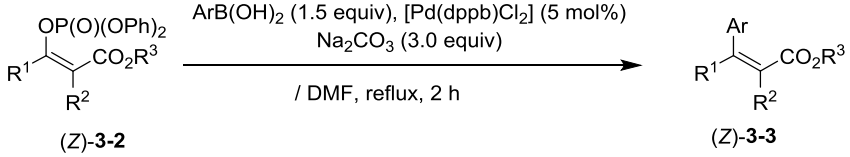
General procedure for the (*E*)-stereoretentive Suzuki−Miyaura cross-coupling using (*E*)-enol phosphonates 3-2.



(*E*)-**3-2** (*E*)-**3-3**

An (*E*)-enol phosphate **3-2** (0.50 mmol) was added to a stirred suspension of $ArB(OH)_2$ (0.75 mmol), Na_2CO_3 (159 mg, 1.50 mmol), $[Pd(dppb)Cl_2]$ (15 mg, 0.025 mmol) in DMF (0.5 mL) at 20 – 25 °C under an Ar atmosphere, and the mixture was stirred at 150 – 155 °C for 2 h. After cooling down, water was added to the stirred mixture, which was extracted twice with AcOEt. The organic phase was washed with brine, dried (Na_2SO_4), and concentrated to give the residue, which was purified by SiO_2-column chromatography (hexane/AcOEt = 50/1 – 20/1) to give the desired product (*E*)-**3-3**.

General procedure for the (*Z*)-stereoretentive Suzuki−Miyaura cross-coupling using (*Z*)-enol phosphonates 3-2.

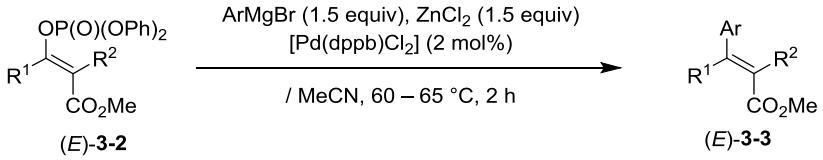


(*Z*)-**3-2** (*Z*)-**3-3**

An (*Z*)-enol phosphate **3-2** (0.50 mmol) was added to a stirred suspension of $ArB(OH)_2$ (0.75 mmol), Na_2CO_3 (159 mg, 1.50 mmol), $[Pd(dppb)Cl_2]$ (15 mg, 0.025 mmol) in DMF (0.5 mL) at 20 – 25 °C under an Ar atmosphere, and the mixture was stirred at 150 – 155 °C for 2 h. After cooling down, water was added to the stirred mixture, which was extracted twice with AcOEt. The organic phase was washed with brine, dried

(Na_2SO_4), and concentrated to give the residue, which was purified by SiO_2-column chromatography (hexane/AcOEt = 50/1 – 20/1) to give the desired product (*Z*)-**3-3**.

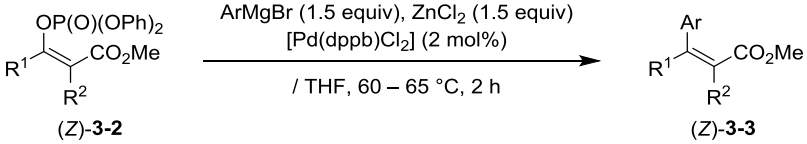
General procedure for the (*E*)-stereoretentive Negishi cross-coupling using (*E*)-enol phosphonates 3-2 with aromatic zinc reagents



(*E*)-**3-2** (*E*)-**3-3**

ArMgBr (0.68 mL; 1.10 M in THF) was added to a stirred suspension of $ZnCl_2$ (102 mg, 0.75 mmol) in MeCN (1.0 mL) at 0 − 5 °C under an Ar atmosphere, and the mixture was stirred at the same temperature for 0.5 h. An (*E*)-enol phosphonate **3-2** (0.50 mmol) in MeCN (0.50 mL) and [Pd(dppb)Cl_2] (6 mg, 0.01 mmol) in MeCN (0.50 mL) were successively added to the mixture, followed by stirring at 60 − 65 °C for 2 h. After cooling down, 1M HCl aqueous solution was added to the mixture, which was extracted twice with AcOEt. The combined organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. The obtained crude product was purified by SiO_2-column chromatography (hexane/AcOEt = 100/0 – 20/1) to give the desired product (*E*)-**3-3**.

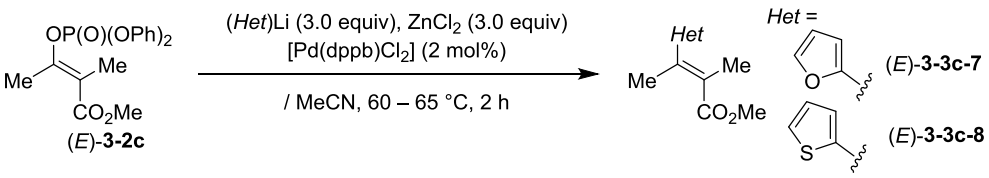
General procedure for the (*Z*)-stereoretentive Negishi cross-coupling using (*Z*)-enol phosphonates 3-2 with aromatic zinc reagents



(*Z*)-**3-2** (*Z*)-**3-3**

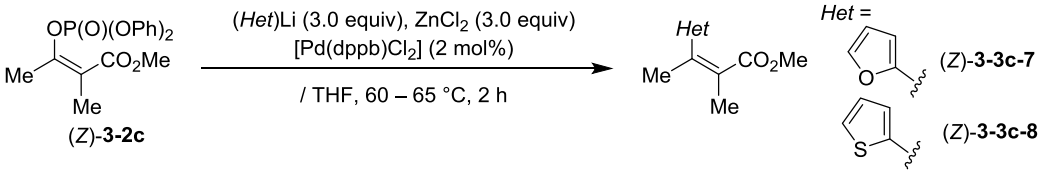
ArMgBr (0.68 mL; 1.10 M in THF) was added to a stirred suspension of $ZnCl_2$ (102 mg, 0.75 mmol) in THF (1.0 mL) at 0 − 5 °C under an Ar atmosphere, and the mixture was stirred at the same temperature for 0.5 h. An (*Z*)-enol phosphonate **3-2** (0.50 mmol) in THF (0.50 mL) and [Pd(dppb)Cl_2] (6 mg, 0.01 mmol) in THF (0.50 mL) were successively added to the mixture, followed by stirring at 60 − 65 °C for 2 h. After cooling down, 1M HCl aqueous solution was added to the mixture, which was extracted twice with AcOEt. The combined organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. The obtained crude product was purified by SiO_2-column chromatography (hexane/AcOEt = 100/0 – 20/1) to give the desired product (*Z*)-**3-3**.

General procedure for the (*E*)-stereoretentive Negishi cross-coupling using (*E*)-enol phosphonate 3-2c with heterocyclic zinc reagents



*n*BuLi (0.92 mL; 1.63 M in hexane) was added to a stirred solution of a *(Het)*H (1.50 mmol) in THF (1.5 mL) at 0 − 5 °C under an Ar atmosphere, and the mixture was stirred at the same temperature for 0.5 h. The solution was added to a stirred suspension of $ZnCl_2$ (204 mg, 1.50 mmol) in MeCN (1.0 mL) at 0 − 5 °C under an Ar atmosphere, and the mixture was stirred at the same temperature for 0.5 h. (*E*)-enol phosphonate **3-2c** (0.50 mmol) in MeCN (0.50 mL) and [Pd(dppb)Cl_2] (6 mg, 0.01 mmol) in MeCN (0.50 mL) were successively added to the mixture, followed by stirring at 60 − 65 °C for 2 h. After cooling down, 1M HCl aqueous solution was added to the mixture, which was extracted twice with AcOEt. The combined organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. The obtained crude product was purified by SiO_2-column chromatography (hexane/AcOEt = 100/1 – 50/1) to give the desired product (*E*)-**3-3c-7** or (*E*)-**3-3c-8**.

General procedure for the (*Z*)-stereoretentive Negishi cross-coupling using (*Z*)-enol phosphonate 3-2c with heterocyclic zinc reagents



*n*BuLi (0.92 mL; 1.63 M in hexane) was added to a stirred solution of *(Het)*H (1.50 mmol) in THF (1.5 mL) at 0 − 5 °C under an Ar atmosphere, and the mixture was stirred at the same temperature for 0.5 h. The solution was added to a stirred suspension of $ZnCl_2$ (204 mg, 1.5 mmol) in THF (1.0 mL) at 0 − 5 °C under an Ar atmosphere, and the mixture was stirred at the same temperature for 0.5 h. An (*Z*)-enol phosphonate **3-2c** (0.50 mmol) in THF (0.50 mL) and [Pd(dppb)Cl_2] (6 mg, 0.01 mmol) in THF (0.50 mL) were successively added to the mixture, followed by stirring at 60 − 65 °C for 2 h. After cooling down, 1M HCl aqueous solution was added to the mixture, which was extracted twice with AcOEt. The combined organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. The obtained crude product was purified by SiO_2-column chromatography (hexane/AcOEt = 100/1 – 50/1) to give the desired product (*Z*)-**3-3c-7** or (*Z*)-**3-3c-8**.

Methyl (*E*)-2-butyl-3-phenyloct-2-enoate (*E*)-3-3a

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.75 (t, *J* = 7.5 Hz, 3H), 0.82 (t, *J* = 7.5 Hz, 3H), 1.08–1.35 (m, 10H), 2.07 (t, *J* = 7.6 Hz, 2H), 2.46 (t, *J* = 7.6 Hz, 2H), 3.80 (s, 3H), 7.07–7.12 (m, 2H), 7.24−7.30 (m, 1H), 7.31–7.37 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 14.0. 22.3, 22.4, 27.6, 30.8, 31.2, 31.7, 36.4, 51.4, 126.8, 127.8, 128.1, 130.6, 141.4, 147.4, 170.8; IR (neat): ν_{max} = 2959, 1717, 1458, 1379, 1321, 1240, 1206, 1140 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{19}H_{28}O_2$ $[M+Na]^+$ 311.1987; found: 311.1987.

Methyl (*Z*)-2-butyl-3-phenyloct-2-enoate (*Z*)-3-3a

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.82 (t, *J* = 6.9 Hz, 3H), 0.96 (t, *J* = 7.5 Hz, 3H), 1.19–1.32 (m, 6H), 1.34–1.48 (m, 4H), 2.44 (t, *J* = 7.2 Hz, 4H), 3.33 (s, 3H), 7.09–7.14 (m, 2H), 7.20–7.32 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 22.4, 22.6, 27.5, 29.9, 31.1, 31.7, 34.0, 51.1, 126.9, 127.4, 127.9, 131.6, 142.7, 146.2, 171.3; IR (neat): ν_{max} = 2957, 2961, 1719, 1458, 1437, 1246, 1208, 1140 cm^{-1}.

Ethyl (*E*)-2-methyl-3-phenylbut-2-enoate (*E*)-3-3b-1[19]

Pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.35 (t, *J* = 7.2 Hz, 3H), 1.75 (d, *J* = 1.4 Hz, 3H), 2.25 (q, *J* = 1.4 Hz, 3H), 4.27 (q, *J* = 7.2 Hz, 2H), 7.11–7.18 (m, 2H), 7.22–7.49 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.3, 17.3, 23.1, 60.3, 124.8, 126.9, 127.2, 128.2, 143.4, 145.3, 169.9; IR (neat): ν_{max} = 2982, 1713, 1442, 1312, 1252, 1134, 1098, 1026 cm^{-1}.

Ethyl (*Z*)-2-methyl-3-phenylbut-2-enoate (*Z*)-3-3b-1

Pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.82 (t, *J* = 7.2 Hz, 3H), 2.02 (d, *J* = 1.0 Hz, 3H), 2.09 (d, *J* = 1.0 Hz, 3H), 3.84 (q, *J* = 7.2 Hz, 2H), 7.07–7.17 (m, 2H), 7.19–7.34 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.4, 16.3, 21.6, 60.1, 126.1, 126.8, 126.9, 127.9, 142.9, 142.2, 170.6; IR (neat): ν_{max} = 2982, 1709, 1443, 1372, 1310, 1244, 1140, 1096 cm^{-1}.

Ethyl (*E*)-2-methyl-3-(4-methylphenyl)but-2-enoate (*E*)-3-3b-2[20]

Pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.34 (dt, *J* = 0.7, 7.2 Hz, 3H), 1.75–1.79 (m, 3H), 2.22–2.26 (m, 3H), 2.36 (s, 3H), 4.26 (q, *J* = 7.2 Hz, 2H), 7.00–7.09 (m, 2H), 7.14–7.20 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2, 17.3, 21.0, 23.1, 60.2, 124.6, 127.1, 128.8, 136.6, 140.4, 145.3, 169.9; IR (neat): ν_{max} = 1713, 1630, 1512, 1449, 1316, 1250, 1130 cm^{-1}.

Ethyl (*Z*)-2-methyl-3-(4-methylphenyl)but-2-enoate (*Z*)-3-3b-2

Pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 7.2 Hz, 3H), 2.01 (d, *J* = 1.4 Hz, 3H), 2.07 (d, *J* = 1.4 Hz, 3H), 2.33 (s, 3H), 3.87 (q, *J* = 7.2 Hz, 2H), 6.98–7.14 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.4, 16.2, 21.0, 21.5, 59.9, 125.7, 126.7, 128.5, 136.4, 141.1, 142.6, 170.6; IR (neat): ν_{max} = 1713, 1512, 1445, 1372, 1306, 1250, 1142 cm^{-1}.

Ethyl (*E*)-2-methyl-3-(4-methoxylphenyl)but-2-enoate (*E*)-3-3b-3[21]

Pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.34 (t, *J* = 7.2 Hz, 3H), 1.78 (d, *J* = 1.0 Hz, 3H), 2.23 (d, *J* = 1.0 Hz, 3H), 3.82 (s, 3H), 4.26 (q, *J* = 7.2 Hz, 2H), 6.86–6.93 (m, 2H), 7.05–7.13 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2, 17.3, 23.1, 55.0, 60.2, 113.5, 124.5, 128.5, 135.5, 144.9, 158.5, 170.0; IR (neat): ν_{max} = 2934, 1711, 1609, 1510, 1458, 1510, 1458, 1248, 1134, 1034 cm^{-1}.

Ethyl (*Z*)-2-methyl-3-(4-methoxylphenyl)but-2-enoate (*Z*)-3-3b-3

Pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 7.2 Hz, 3H), 2.01 (d, *J* = 1.0 Hz, 3H), 2.07 (d, *J* = 7.2 Hz, 3H), 3.80 (s, 3H), 3.89 (q, *J* = 7.2 Hz, 2H), 6.78–6.86 (m, 2H), 7.04–7.12 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.5, 16.3, 21.4, 55.1, 59.9, 113.2, 125.6, 128.0, 136.3, 142.0, 158.5, 170.8; IR (neat): ν_{max} = 2934, 1707, 1609, 1510, 1460, 1314, 1248, 1142 cm^{-1}.

Ethyl (*E*)-2-methyl-3-(4-chlorophenyl)but-2-enoate (*E*)-3-3b-4[22]

Pale yellow crystals; mp 44−45 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.34 (t, *J* = 7.2 Hz, 3H), 1.72–1.77 (m, 3H), 2.20–2.24 (m, 3H), 4.26 (q, *J* = 7.2 Hz, 2H), 7.07–7.10 (m, 2H), 7.32–7.35 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2, 17.3, 22.9, 60.4, 125.5, 128.5, 128.7, 132.8, 141.7, 143.7, 169.6; IR (neat): ν_{max} = 2982, 1713, 1491, 1314, 1250, 1134, 1092, 1015 cm^{-1}.

Ethyl (*Z*)-2-methyl-3-(4-chlorophenyl) but-2-enoate (*Z*)-3-3b-4

Pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 7.2 Hz, 3H), 2.02 (d, *J* = 1.0 Hz, 3H), 2.06 (d, *J* = 1.0 Hz, 3H), 3.88 (q, *J* = 7.2 Hz, 2H), 7.00–7.11 (m, 2H), 7.21–7.31 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.5, 16.2, 21.5, 60.1, 126.6, 128.0, 128.2, 132.6, 141.6, 142.5, 170.0; IR (neat): ν_{max} = 2984, 1707, 1491, 1372, 1312, 1250, 1140, 1092 cm^{-1}.

Methyl (*E*)-2-methyl-3-phenylbut-2-enoate (*E*)-3-3c-1[4a]

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.75 (q, *J* = 1.4 Hz, 3H), 2.26 (q, *J* = 1.4 Hz, 3H), 3.80 (s, 3H), 7.12–7.15 (m, 2H), 7.27–7.38 (m, 3H); IR (neat): ν_{max} = 2949, 1716, 1433, 1253, 1133, 1099 cm^{-1}.

4) (a) *E*/*Z* = 80:20; Shindo, M.; Sato, Y.; Yoshikawa, T.; Koretsune, R.; Shishido, K. *J. Org. Chem.* **2004**, *69*, 3912.

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

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.05 (q, *J* = 0.6 Hz, 3H), 2.09 (q, *J* = 0.6 Hz, 3H), 3.39 (s, 3H), 7.12–7.14 (m, 2H), 7.23–7.32 (m, 3H); IR (neat): ν_{max} = 2947, 1714, 1433, 1316, 1243, 1139 cm^{-1}.

6) (d) 95% yield (*E*/*Z* = 14:86), Sano, S.; Takehisa, T.; Ogawa, S.; Yokoyama, K.; Nagao, Y. *Chem. Pharm. Bull*. **2002**, *50*, 1300.

Methyl (*E*)-2-methyl-3-(4-methylphenyl)but-2-enoate (*E*)-3-3c-2

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.74–1.78 (m, 3H), 2.22–2.27 (m, 3H), 2.35 (s, 3H), 3.79 (s, 3H), 7.04 (d, *J* = 8.3 Hz, 2H), 7.17 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.3, 21.0, 23.2, 51.3, 124.2, 127.0, 128.8, 136.6, 140.4, 146.1, 170.2; IR (neat): ν_{max} = 2949, 2866, 1716, 1629, 1511, 1433, 1317, 1252, 1132, 820 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{13}H_{16}O_2$ $[M+Na]^+$ 227.1048; found: 227.1046.

Methyl (*Z*)-2-methyl-3-(4-methylphenyl)but-2-enoate (*Z*)-3-3c-2

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.01 (s, 3H), 2.07 (s, 3H), 2.33 (s, 3H), 3.43 (s, 3H), 7.03 (d, *J* = 7.9 Hz, 2H), 7.10 (d, *J* = 7.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.3, 21.0, 21.5, 51.1, 125.3, 126.6, 128.6, 136.4, 140.9, 142.9, 170.9; IR (neat): ν_{max} = 2993, 2948, 1712, 1512, 1433, 1317, 1244, 1139, 819, 771 cm^{-1}.

Methyl (*E*)-2-methyl-3-(4-methoxylphenyl)but-2-enoate (*E*)-3-3c-3[6d]

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.78 (d, *J* = 1.4 Hz, 3H), 2.25 (d, *J* = 1.4 Hz, 3H), 3.79 (s, 3H), 3.82 (s, 3H), 6.87–6.91 (m, 2H), 7.06–7.10 (m, 2H); IR (neat): ν_{max} = 2950, 1714, 1608, 1510, 1248, 1132, 1032 cm^{-1}.

6) (d) 90% yield (*E*/*Z* = 41:59), Sano, S.; Takehisa, T.; Ogawa, S.; Yokoyama, K.; Nagao, Y. *Chem. Pharm. Bull.* **2002**, *50*, 1300.

Methyl (*Z*)-2-methyl-3-(4-methoxylphenyl)but-2-enoate (*Z*)-3-3c-3[6d]

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.01 (d, *J* = 0.9 Hz, 3H), 2.07 (d, *J* = 0.9 Hz, 3H), 3.44 (s, 3H), 3.80 (s, 3H), 6.81–6.85 (m, 2H), 7.05–7.10 (m, 2H); IR (neat): ν_{max} = 2948, 1711, 1608, 1509, 1288, 1247, 1179, 1138, 1032 cm^{-1}.

6) (d) 14% yield (*E*/*Z* = 4:96), Sano, S.; Takehisa, T.; Ogawa, S.; Yokoyama, K.; Nagao, *Chem. Pharm. Bull.* **2002**, *50*, 1300.

Methyl (*E*)-2-methyl-3-(4-chlorophenyl)but-2-enoate (*E*)-3-3c-4

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.75 (d, *J* = 1.4 Hz, 3H), 2.23 (d, *J* = 1.4 Hz, 3H), 3.80 (s, 3H), 7.04−7.11 (m, 2H), 7.30−7.37 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.3, 23.0, 51.4, 125.1, 128.5, 128.6, 132.8, 141.6, 144.6, 169.8; IR (neat): ν_{max} = 2950, 1716, 1631, 1490, 1433, 1316, 1250, 1133, 1092, 1014, 829 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{12}H_{13}ClO_2$ $[M+Na]^+$ 247.0502; found: 247.0499.

Methyl (*Z*)-2-methyl-3-(4-chlorophenyl)but-2-enoate (*Z*)-3-3c-4

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.02 (d, *J* = 1.0 Hz, 3H), 2.06 (d, *J* = 1.0 Hz, 3H), 3.44 (s, 3H), 7.02−7.10 (m, 2H), 7.24−7.31 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.3, 21.5, 51.2, 126.2, 128.1, 132.7, 142.0, 142.4, 170.4; IR (neat): ν_{max} = 2948, 1713, 1639, 1593, 1486, 1434, 1314, 1247, 1140, 1089, 1013, 828, 758 cm^{-1}.

Methyl (*E*)-2-methyl-3-(2-methylphenyl)but-2-enoate (*E*)-3-3c-5

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.60 (q, *J* = 1.7 Hz, 3H), 2.18 (s, 3H), 2.22 (q, *J* = 1.7 Hz, 3H), 3.80 (s, 3H), 6.91−6.99 (m, 1H), 7.14−7.21 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.7, 18.8, 22.5, 51.3, 124.6, 125.9, 126.4, 126.9, 130.0, 133.5, 143.0, 147.1, 169.6; IR (neat): ν_{max} = 3017, 2950, 2868, 1716, 1633, 1433, 1373, 1250, 1197, 1139, 1097, 764, 731 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{13}H_{16}O_2$ $[M+Na]^+$ 227.1048;

found: 227.1054.

Methyl (*Z*)-2-methyl-3-(2-methylphenyl)but-2-enoate (*Z*)-3-3c-5

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.02 (s, 3H), 2.03 (s, 3H), 2.19 (s, 3H), 3.37 (s, 3H), 6.85−6.97(m, 1H), 7.06−7.21 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.4, 19.1, 21.8, 51.0, 125.3, 125.4, 126.4, 126.6, 129.5, 133.9, 144.0, 145.2, 169.4; IR (neat): ν_{max} = 3015, 1949, 2863, 1711, 1641, 1434, 1315, 1238, 1141, 1087, 761, 726 cm^{-1}.

Methyl (*E*)-2-methyl-3-(1-naphthyl)but-2-enoate (*E*)-3-3c-6

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.55−1.61 (m, 3H), 2.33−2.38 (m, 3H), 3.85 (s, 3H), 7.19 (dd, *J* = 1.0, 7.2 Hz, 1H), 7.42−7.52 (m, 3H), 7.71−7.81 (m, 2H), 7.83−7.90 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.2, 23.4, 51.4, 123.7, 124.9, 125.5, 125.8, 126.2, 127.1, 128.4, 129.5, 133.6, 141.2, 145.6, 169.6; IR (neat): ν_{max} = 3058, 2995, 2949, 1715, 1631, 1506, 1433, 1265, 1193, 1143, 1094, 779 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{16}H_{16}O_2$ $[M+Na]^+$ 263.1048; found: 63.1050.

Methyl (*Z*)-2-methyl-3-(1-naphthyl)but-2-enoate (*Z*)-3-3c-6

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.16 (s, 3H), 2.18 (s, 3H), 3.16 (s, 3H), 7.12 (d, *J* = 7.2 Hz, 1H), 7.33−7.54 (m, 3H), 7.67−7.89 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.7, 22.6, 51.0, 123.4, 125.1, 125.2, 125.5, 125.8, 126.8, 127.1, 128.2, 130.4, 133.4, 142.4, 143.9, 169.3; IR (neat): ν_{max} = 3058, 2999, 2948, 1708, 1433, 1313, 1143, 1086, 778 cm^{-1}.

Methyl (*E*)-2-methyl-(2-furyl)but-2-enoate (*E*)-3-3c-7

Orange oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.15−2.19 (m, 3H), 2.22−2.26 (m, 3H), 3.79 (s, 3H), 6.43−6.49 (m, 2H), 7.47 (d, *J* = 1.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.8, 18.5, 51.6, 111.1, 111.7, 124.5, 131.7, 142.3, 154.1, 170.8; IR (neat): ν_{max} = 3424, 3149, 2952, 1767, 1713, 1610, 1434, 1251, 1134, 743 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{10}H_{12}O_3$ $[M+Na]^+$ 203.0684; found: 206.0685.

Methyl (*Z*)-2-methyl-(2-furyl)but-2-enoate (*Z*)-3-3c-7

Orange oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.01 (s, 6H), 3.73 (s, 3H), 6.28−6.41 (m, 2H), 7.33 (dd, *J* = 0.7, 1.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.3, 16.8, 51.7, 108.1, 111.0, 124.9, 125.9, 142.1, 153.6, 172.3; IR (neat): ν_{max} = 3433, 3122, 2950, 1768, 1720, 1434, 1312, 1251, 1127, 905, 732 cm^{-1}.

Methyl (*E*)-2-methyl-(2-thienyl)but-2-enoate (*E*)-3-3c-8

Pale red oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.04 (q, *J* = 1.4 Hz, 3H), 2.31 (q, *J* = 1.4 Hz, 3H), 3.80 (s, 3H), 6.93−7.10 (m, 2H), 7.33 (dd, *J* = 1.4, 5.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.0, 23.5, 51.6, 125.5, 126.1, 126.6, 126.7, 136.7, 144.1, 170.4; IR (neat): ν_{max} = 3104, 2996, 2950, 1715, 1609, 1433, 1279, 1242, 1121, 834, 701 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{10}H_{12}O_2S$ $[M+Na]^+$ 219.0456; found: 219.0454.

Methyl (*Z*)-2-methyl-(2-thienyl)but-2-enoate (*Z*)-3-3c-8

Pale red oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.02 (d, *J* = 1.0 Hz, 3H), 2.13 (d, *J* = 1.0 Hz, 3H), 3.57 (s, 3H), 6.84−6.97 (m, 1H), 7.23 (dd, *J* = 1.0, 4.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.9, 21.4, 51.6, 124.9, 125.0, 126.0, 127.2, 132.6, 144.6, 171.4; IR (neat): ν_{max} = 3106, 2994, 2947, 1714, 1631, 1432, 1298, 1238, 1134, 852, 697 cm^{-1}.

Ethyl (*E*)-2-benzyl-3-phenylbut-2-enoate (*E*)-3-3d[23]

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.73 (t, *J* = 7.2 Hz, 3H), 2.16 (s, 3H), 3.77 (t, *J* = 7.2 Hz, 2H), 3.84 (s, 2H), 7.06–7.39 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.3, 21.7, 36.1, 60.0, 126.0, 126.8, 127.0, 128.2, 128.3, 129.7, 139.0, 143.9, 144.4, 169.9 cm^{-1}; IR (neat): ν_{max} = 2982, 1705, 1495, 1455, 1375, 1314, 1242, 1134 cm^{-1}.

Ethyl (*Z*)-2-benzyl-3-phenylbut-2-enoate (*Z*)-3-3d

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.14 (t, *J* = 7.2 Hz, 3H), 2.31 (s, 3H), 3.55 (s, 2H), 4.12 (t, *J* = 7.2 Hz, 2H), 7.00–7.39 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 23.4, 36.8, 60.2, 125.8, 127.0, 127.2, 128.0, 128.1, 128.2, 128.4, 139.8, 142.8, 146.0, 169.0; IR (neat): ν_{max} = 2982, 1713, 1495, 1455, 1312, 1254, 1198, 1051 cm^{-1}.

Methyl 2-methyl-3-phenyloct-2-enoate (*E*)-3-3e[4a]

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.82 (t, *J* = 6.9 Hz, 3H), 1.11–1.39 (m, 6H), 1.71 (s, 3H), 2.58 (t, *J* = 6.9 Hz, 2H), 3.79 (s, 3H), 7.00–7.14 (m, 2H), 7.18–7.41 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 17.3, 22.3., 27.7, 31.7, 36.1, 51.3, 124.5, 126.9, 127.6, 128.1, 141.8, 150.0, 170.3; IR (neat): ν_{max} = 2955, 2860, 1720, 1435, 1250, 1190, 1136, 1109 cm^{-1}.

Methyl (*Z*)-2-benzyl-3-phenyloct-2-enoate (*Z*)-3-3e

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.84 (t, *J* = 7.2 Hz, 3H), 1.60–1.37 (m, 6H), 2.03 (s, 3H), 2.44 (t, *J* = 7.2 Hz, 2H), 3.36 (s, 3H), 7.05–7.16 (m, 2H), 7.18–7.34 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 15.8, 22.3, 26.9, 31.6, 34.8, 51.0, 125.7, 126.8, 127.2, 127.8, 142.8, 147.7, 171.0; IR (neat): ν_{max} = 2955, 2861, 1717, 1458, 1320, 1242, 1190, 1138 cm^{-1}.

Methyl (*E*)-8-benzyloxy-2-methyl-3-phenyloct-2-enoate (*E*)-3-3f

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23–1.39 (m, 4H), 1.47–1.60 (m, 2H), 1.70 (s, 3H), 2.55–2.65 (m, 2H), 3.96 (t, *J* = 6.5 Hz, 2H), 3.78 (s, 3H), 4.45 (s, 2H), 7.03–7.13 (m, 2H), 7.17–7.39 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.3, 26.0, 27.8, 29.4, 36.0, 51.3, 70.2, 72.7, 124.6, 126.9, 127.3, 127.4, 127.6, 128.1, 128.2, 138.6, 141.7, 149.8, 170.2; IR (neat): ν_{max} = 2938, 2859, 1717, 1433, 1364, 1254, 1132, 1111 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{23}H_{28}O_3$ $[M+Na]^+$ 375.1936; found: 375.1933.

Methyl (*Z*)-8-benzyloxy-2-methyl-3-phenyloct-2-enoate (*Z*)-3-3f

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.21–1.63 (m, 6H), 2.02 (s, 3H), 2.45 (t, *J* = 7.6 Hz, 2H), 3.36 (s, 3H), 3.40 (t, *J* = 6.5 Hz, 2H), 4.46 (s, 2H), 7.01–7.13 (m, 2H), 7.16–7.36 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.8, 25.9, 27.0, 29.4, 34.6, 51.0, 70.0, 72.7, 125.7, 126.7, 127.1, 127.3, 127.4, 127.7, 128.1, 138.4, 142.6, 147.3, 170.9; IR (neat): ν_{max} = 2940, 2861, 1717, 1433, 1318, 1242, 1138, 1102 cm^{-1}.

Methyl (*E*)-7-chloro-2-methyl-3-phenylhept-2-enoate (*E*)-3-3g

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.40–1.51 (m, 2H), 1.70–1.80 (m, 2H), 1.72 (s, 3H), 2.64 (t, *J* = 7.5 Hz, 2H), 3.47 (t, *J* = 6.9 Hz, 2H), 3.80 (s, 3H), 7.07–7.14 (m, 2H), 7.26–7.32 (m, 1H), 7.34–7.39 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.4, 25.2, 32.2, 35.1, 44.7, 51.5, 125.2, 127.1, 127.6, 128.3, 141.4, 149.2, 170.1; IR (neat): ν_{max} = 2950, 1714, 1624, 1599, 1491, 1433, 1255, 1122 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{15}H_{19}ClO_2$ $[M+Na]^+$ 289.0971; found: 289.0971.

Methyl (*Z*)-7-chloro-2-methyl-3-phenylhept-2-enoate (*Z*)-3-3g

Pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.40–1.51 (m, 2H), 1.70–1.79 (m, 2H), 2.04 (s, 3H), 2.49 (t, *J* = 8.2 Hz, 2H), 3.37 (s, 3H), 3.47 (t, *J* = 6.9 Hz, 2H), 7.08–7.13 (m, 2H), 7.22–7.33 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.9, 24.5, 32.1, 33.8, 44.5, 51.2, 126.4, 127.0, 127.2, 128.0, 142.3, 146.4, 170.8; IR (neat): ν_{max} = 2948, 1711, 1633, 1492, 1433, 1311, 1236, 1137 cm^{-1}.

Methyl (*E*)-2-methyl-3-phenyltrideca-2,12-dienoate (*E*)-3-3h

Colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.16−1.37 (m, 12H), 1.71 (s, 3H), 1.95−2.07 (m, 2H), 2.58 (t, *J* = 6.9 Hz, 2H), 3.79 (s, 3H), 4.89−5.03 (m, 2H), 5.79 (ddt, *J* = 17.2 Hz, 10.3 Hz, 6.9 Hz, 1H), 7.08−7.12 (m, 2H), 7.27−7.30 (m, 1H), 7.33−7.38 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.4, 28.0, 28.9, 29.0, 29.3, 29.3, 29.533.7, 36.2, 51.4, 114.0, 124.5, 126.9, 127.7, 128.2, 139.2, 141.8, 150.1, 170.4; IR (neat): ν_{max} = 3073, 2925, 2854, 1718, 1483, 1252, 1118, 994, 910, 772, 703 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{21}H_{30}O_2$ $[M+Na]^+$ 337.2143; found: 337.2173.

Methyl (*Z*)-2-methyl-3-phenyltrideca-2,12-dienoate (*Z*)-3-3h

Colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.19−1.38 (m, 12H), 1.96−2.04 (m, 5H), 2.44 (t, *J* = 6.9 Hz, 2H), 3.36 (s, 3H), 4.90−5.01 (m, 2H), 5.80 (ddt, *J* = 17.2 Hz, 10.3 Hz, 6.9 Hz, 1H), 7.08−7.12 (m, 2H), 7.21−7.25 (m, 1H), 7.27−7.31 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.9, 27.2, 28.8, 29.0, 29.3, 29.4, 33.7, 34.9, 51.1, 114.1, 125.7, 126.8, 127.2, 127.8, 139.1, 142.8, 147.8, 171.0; IR (neat): ν_{max} = 3078, 2925, 2854, 1714, 1639, 1434, 1317, 1238, 1137, 1084, 994, 910, 771, 700 cm^{-1}.

Methyl (*E*)-3-cyclohexyl-2-methyl-3-phenylacrylate (*E*)-3-3i

Colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.94 (tq, *J* = 3.4 Hz, 12.6 Hz, 1H), 1.01 (dq, *J* = 3.4 Hz, 12.6 Hz, 2H), 1.29 (tq, *J* = 3.4 Hz, 12.6 Hz, 2H), 1.53−1.59 (m, 4H), 1.63−1.74 (m, 4H), 2.93 (tt, *J* = 12.0 Hz, 2.9 Hz, 1H), 3.80 (s, 3H), 6.96−7.00 (m, 2H), 7.27−7.30 (m, 1H), 7.31−7.36 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.4, 25.8, 26.3, 31.6, 42.8, 51.4, 124.5, 126.6, 127.8, 128.2, 139.3, 153.1, 170.7; IR (neat): ν_{max} =

2925, 2853, 1718, 1447, 1251, 1125, 775, 707 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{17}H_{22}O_2$ $[M+Na]^+$ 281.1517; found: 281.1537.

Methyl (*Z*)-3-cyclohexyl-2-methyl-3-phenylacrylate (*Z*)-3-3i

Colorless oil: ^1H NMR (500 MHz, $CDCl_3$): δ = 1.00 (tq, *J* = 3.4 Hz, 13.2 Hz, 1H), 1.06 (dq, *J* = 3.4 Hz, 12.6 Hz, 2H), 1.30 (tq, *J* = 3.4 Hz, 13.2 Hz, 2H), 1.57−1.67 (m, 3H), 1.68−1.75 (m, 2H), 2.03 (s, 3H), 2.65 (tt, *J* = 3.4 Hz, 12.0 Hz, 1H), 3.29 (s, 3H), 6.98−7.01 (m, 2H), 7.21−7.29 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.0, 25.7, 26.4, 30.8, 41.5, 51.0, 125.5, 126.4, 127.2, 128.3, 140.4, 151.6, 170.8; IR (neat): ν_{max} = 2928, 2853, 1715, 1433, 1314, 1247, 1135, 1090, 771, 702 cm^{-1}.

Methyl (*E*)-2,3-diphenylbut-2-enoate (*E*)-3-3j[23]

Pale yellow oil; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.36 (s, 3H), 3.76 (s, 3H), 6.95−7.18 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.2, 51.9, 126.8, 127.0, 127.7, 127.8, 128.4, 129.8, 131.6, 137.1, 141.8, 144.6, 169.8; IR (neat): ν_{max} = 2950, 1719, 1599, 1491, 1433, 1375, 1304, 1250 cm^{-1}.

Methyl (*Z*)-2,3-diphenylbut-2-enoate (*Z*)-3-3j[23]

Pale yellow oil; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.05 (s, 3H), 3.43 (s, 3H), 7.29−7.44 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.2, 51.5, 126.8, 127.5, 128.1, 128.3, 129.1, 132.5, 137.1, 142.8, 143.9, 169.6; IR (neat): ν_{max} = 2941, 1719, 1491, 1433, 1375, 1304, 1252, 1210 cm^{-1}.

Methyl (*E*)-2-(4-methoxyphenyl)-3-phenylbut-2-enoate (*E*)-3-3k

Pale yellow oil; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.33 (s, 3H), 3.72 (s, 3H), 3.79 (s, 3H), 6.60−6.70 (m, 2H), 6.88−6.96 (m, 2H) , 7.10−7.20 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.0, 51.8, 54.8, 113.2, 126.8, 127.8, 128.3, 129.3, 130.8, 131.1, 141.9, 143.1, 158.2, 170.1; IR (neat): ν_{max} = 2951, 1719, 1609, 1576, 1509, 1458, 1375, 1248 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{18}H_{18}O_3$ $[M+Na]^+$ 305.1154; found: 305.1161.

Methyl (*Z*)-2-(4-methoxyphenyl)-3-phenylbut-2-enoate (*Z*)-3-3k

Pale yellow oil; ^1H NMR (500 MHz, $CDCl_3$): δ = 2.07 (s, 3H), 3.43 (s, 3H), 3.84 (s, 3H), 6.92−6.96 (m, 2H), 7.27−7.40 (m, 7H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.2, 51.6, 55.2, 113.8, 126.9, 127.5, 128.2, 129.4, 130.4, 132.2, 143.0, 143.3, 158.9, 170.1; IR (neat): ν_{max} = 2951, 1719, 1655, 1601, 1541, 1509, 1437, 1250 cm^{-1}.

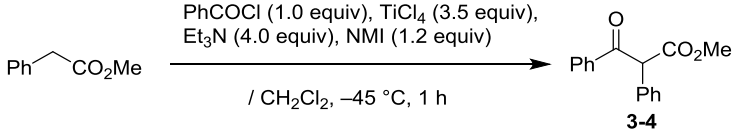
Methyl (*E*)-2-(4-chlorophenyl)-3-phenylbut-2-enoate (*E*)-3-3l

Pale yellow oil; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.37 (s, 3H), 3.78 (s, 3H), 6.88−6.95 (m, 2H), 6.97−7.03 (m, 2H), 7.03−7.11 (m, 2H), 7.11−7.12 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.3, 52.0, 127.2, 128.0, 128.0, 128.3, 130.4, 131.3, 132.7, 135.7, 141.6, 146.0, 169.4; IR (neat): ν_{max} = 2949, 1707, 1619, 1591, 1489, 1434, 1251, 1206 cm^{-1}.

Methyl (*Z*)-2-(4-chlorophenyl)-3-phenylbut-2-enoate (*Z*)-3-3l

Colorless crystals; mp 115–116 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.04 (s, 3H), 3.42 (s, 3H), 7.24−7.44 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.4, 51.7, 126.8, 127.7, 128.2, 128.6, 130.6, 131.3, 133.5, 135.6, 142.6, 145.0, 169.2; IR (neat): ν_{max} = 2951, 1697, 1491, 1428, 1319, 1214, 1088, 1008 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{17}H_{15}O_2Cl$ $[M+Na]^+$ 309.0658; found: 309.0654.

Methyl 2,3-diphenyl-3-oxopropanoate[24] utilizing crossed Ti-Claisen condensation

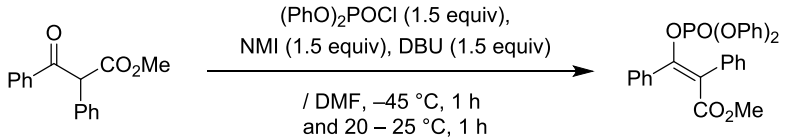


3-4

To a vigorously stirred solution of $PhCH_2CO_2Me$ (15.0 g, 0.10 mol) and PhCOCl (14.1 g, 0.10 mol) in CH_2Cl_2 (300 mL), NMI (9.85 g, 0.12 mol) was added dropwise at –45 °C under an Ar atmosphere. Then, using two dropping funnels, $TiCl_4$ (38.4 mL, 0.35 mol) (during ca. 20 min) and Et_3N (55.4 mL, 0.40 mol) (during ca. 1 h) were successively added, and the mixture was stirred at the same temperature for 1 h. Water was slowly added to the mixture, which was extracted twice with Et_2O. The combined organic phase was washed with water, brine, dried (Na_2SO_4), and concentrated to give the crude product (24.5 g), which was purified by recrystallization from *i*PrOH (22 mL) to give the desired product (18.7 g, 74%).

Colorless crystals; mp 73−74 °C (lit.[24a] 72−73 °C); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.76 (s, 3H), 5.63 (s, 1H), 7.29–7.45 (m, 7H), 7.51–7.58 (m, 1H), 7.90−8.01 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 52.7, 60.3, 128.1, 128.7, 128.8, 128.9, 129.5, 132.8, 133.5, 135.5, 169.3, 193.2.

(*E*)-Stereoselective enol phosphorylation of methyl 2,3-diphenyl-3-oxopropanoate (3-4) using *Method C*.



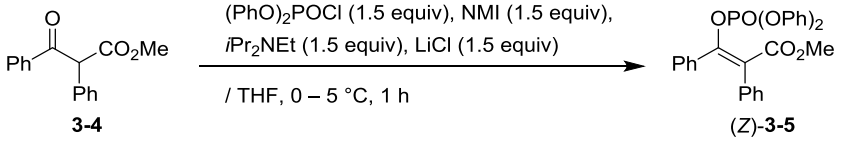
3-4 (*E*)-**3-5**

$(PhO)_2POCl$ (403 mg, 1.5 mmol) was added to a stirred solution of methyl 2,3-diphenyl-3-oxopropanoate (**3-4**) (254 mg, 1.0 mmol), NMI (123 mg, 1.5 mmol), and DBU (228 mg, 1.5 mmol) in DMF (2.0 mL) at −45 °C under an Ar atmosphere, and the mixture was stirred at the same temperature for 1 h and at the room temperature for 1 h. Water was added to the reaction mixture, which was extracted twice with AcOEt. The organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. The obtained crude product was purified by silica-gel column chromatography (hexane/AcOEt = 10/1 – 3/1) to give the crude solid (280 mg, 58%, *E*/*Z* = 88:12), which was purified by recrystallization from hexane/toluene = 8/1 (4.5 mL) to give the desired (*E*)-methyl 2,3-diphenyl-3-(diphenoxyphospholoxy)-2-propenoate [(*E*)-**3-5**] (204 mg, 42%, *E*/*Z* = >98:2).

Colorless crystals; mp 98−99 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.50 (s, 3H), 6.71–6.78 (m, 4H), 7.07–7.20 (m, 6H), 7.28–7.43 (m, 6H), 7.46–7.60 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 52.2, 119.8 [d, ^3J (^{13}C, ^{31}P) = 4.8 Hz], 124.2 [d, ^3J (^{13}C, ^{31}P) = 9.6 Hz], 125.2, 128.1, 128.1, 128.3, 129.0, 129.3, 129.5, 130.0, 132.9, 133.7,

150.1 [d, ^{2}J (^{13}C, ^{31}P) = 7.2 Hz], 150.8 [d, ^{2}J (^{13}C, ^{31}P) = 8.4 Hz], 167.7; IR (neat): ν_{max} = 3017, 2952, 1725, 1591, 1489, 1295, 1186, 1065 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{28}H_{23}O_6P$ $[M+Na]^+$ 509.1130; found: 509.1140.

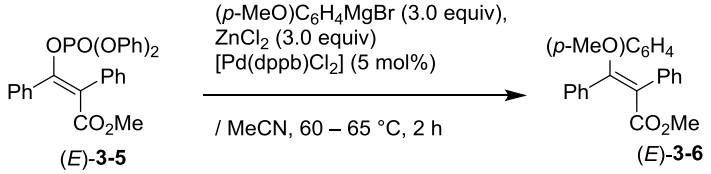
(*Z*)-Stereoselective enol phosphorylation of methyl 2,3-diphenyl-3-oxopropanoate (3-4) using *Method D*.



2,3-Diphenyl-3-oxopropanoate (**3-4**) (254 mg 1.0 mmol), *i*Pr$_2$NEt (194 mg, 1.5 mmol), NMI (123 mg, 1.5 mmol,), and (PhO)$_2$POCl (403 mg, 1.5 mmol) were successively added to a stirred suspension of LiCl (64 mg 1.5 mmol) in THF (2.0 mL) at 0 – 5 °C under an Ar atmosphere, and the mixture was stirred at the same temperature for 1 h. Water was added to the mixture, which was extracted with twice with AcOEt. The organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. The obtained crude product was purified by silica-gel column chromatography (hexane/AcOEt = 3/1) to give the desired (*Z*)-methyl 2,3-diphenyl-3-(diphenoxyphospholoxy)-2-propenoate [(*Z*)-**3-5**] (454 mg, 93%, *E*/*Z* = 2:>98).

Colorless crystals; mp 82−83 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.67 (s, 3H), 7.04–7.10 (m, 4H), 7.11–7.34 (m, 16H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 52.3, 120.0 [d, ^{3}J (^{13}C, ^{31}P) = 4.8 Hz], 120.1, 123.7 [d, ^{3}J (^{13}C, ^{31}P) = 9.6 Hz], 125.3, 127.9, 127.9, 128.3, 129.6, 129.6, 129.9 [d, ^{3}J (^{13}C, ^{31}P) = 3.6 Hz], 132.7, 133.6, 149.1 [d, ^{2}J (^{13}C, ^{31}P) = 8.4 Hz], 150.4 [d, ^{2}J (^{13}C, ^{31}P) = 7.2 Hz], 166.8. ; IR (neat): ν_{max} = 3015, 2952, 1726, 1489, 1297, 1207, 1186, 1011 cm^{-1}.

(*E*)-Stereoretentive Negishi cross-coupling using enol phosphonate (*E*)-3-5 with (*p*-MeO)C$_6$H$_4$ZnCl

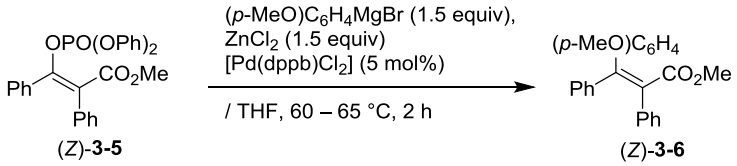


(*p*-MeO)C$_6$H$_4$MgBr (2.94 mL; 1.02 M in THF) was added to a stirred suspension of $ZnCl_2$ (409 mg, 3.0 mmol) in MeCN (1.0 mL) at 0 − 5 °C under an Ar atmosphere, and the mixture was stirred at the same temperature for 10 min. Enol phosphonate (*E*)-**3-5** (486 mg, 1.0 mmol) and [Pd(dppb)Cl$_2$] (30 mg, 0.05 mmol) in MeCN (1.0 mL) were successively added to the mixture, followed by being stirred at 60 − 65 °C for 2 h. After cooling down, 3M HCl aqueous solution was added to the mixture, which was extracted twice with AcOEt. The combined organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. The obtained crude product was purified by SiO_2-column chromatography (hexane/AcOEt = 4/1) to give the crude solid (565 mg, *E*/*Z* = >98:2), which was purified by recrystallization from hexane/toluene = 13/1 (7 mL) to give the desired methyl (*E*)-2,3-diphenyl-3-(*p*-methoxyphenyl)prop-2-enoate (*E*)-**3-6** (219 mg, 64%, *E*/*Z* = >98:2).

Colorless crystals; mp 113−115 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.53 (s, 3H), 3.74 (s, 3H), 6.61–6.68 (m,

2H), 6.87–6.94 (m, 2H), 7.08–7.14 (m, 2H), 7.15–7.23 (m, 3H), 7.24–7.29 (m, 2H), 7.29–7.39 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 51.9, 55.1, 113.2, 127.2, 128.1, 128.3, 129.1, 129.8, 132.3, 132.4, 132.7, 137.9, 142.7, 146.3, 159.1, 171.1; IR (neat): ν_{max} = 3020, 2949, 2837, 1715, 1605, 1508, 1247, 1217, 1176, 1149 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{23}H_{20}O_3$ $[M+Na]^+$ 367.1310; found: 367.1295.

(*Z*)-Stereoretentive Negishi cross-coupling using enol phosphonate (*Z*)-3-5 with (*p*-MeO)C_6H_4ZnCl



(*p*-MeO)C_6H_4MgBr (1.89 mL; 1.06 M in THF) was added to a stirred suspension of $ZnCl_2$ (273 mg, 2.0 mmol) in THF (1.0 mL) at 0 − 5 °C under an Ar atmosphere, and the mixture was stirred at the same temperature for 10 min. Enol phosphonate (*Z*)-**3-5** (486 mg, 1.0 mmol) and [Pd(dppb)Cl_2] (30 mg, 0.05 mmol) in THF (1.0 mL) were successively added to the mixture, followed by being stirred at 60 − 65 °C for 2 h. After cooling down, 3M HCl aqueous solution was added to the mixture, which was extracted twice with AcOEt. The combined organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. The obtained crude product was purified by SiO_2-column chromatography (hexane/AcOEt = 100/1 – 10/1) to give the crude solid (372 mg, *E*/*Z* = >98:2), which was purified by recrystallization from hexane/toluene = 7/1 (12 mL) to give the desired methyl (*Z*)-2,3-diphenyl-3-(*p*-methoxyphenyl)prop-2-enoate (*Z*)-**3-6** (192 mg, 56%, *E*/*Z* = 2:>98).

Colorless crystals; mp 130−131 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.59 (s, 3H), 3.82 (s, 3H), 6.83–6.88 (m, 2H), 6.97–7.03 (m, 2H), 7.04–7.23 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 52.0, 55.2, 113.6, 127.2, 127.6, 127.8, 128.2, 129.8, 130.4, 131.0, 132.4, 134.7, 137.7, 140.7, 146.0, 159.5, 171.2; IR (neat): ν_{max} = 3019, 2950, 2838, 1714, 1606, 1509, 1248, 1216, 1177, 1150 cm^{-1}.

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10. 50 g-scale preparation of **3-1a** was performed by the self Ti–Claisen condensation using methyl hexanoate with $TiCl_4$ and Et_3N at 0 – 5 °C for 1 h (93% yield). See the Experimental. cf. (a) Hamasaki, R.; Funakoshi, S.; Misaki, T.; Tanabe, Y. *Tetrahedron* **2000**, *56*, 7423. (b) Tanabe, Y.; Makita, A.; Funakoshi, S.; Hamasaki, R. Kawakusu, T. *Adv. Synth. Catal.* **2002**, *344*, 507.
11. For (*Z*)-**3-2a**; use of TsCl–NMI–Et_3N (or TMEDA) instead, resulted in only 15–25% yield with the side formation of an α-chlorinated by-product of **3-1a**. For (*E*)-**3-2a**; use of TsCl–NMI–LiOH (or TMEDA) instead gave only 20–30% yield.
12. $(PhO)_2POCl$ is commercially available on an industrial scale exemplified by the synthesis of 1-β-methylcarbapenem. (a) Berks, A. H. *Tetrahedron* **1996**, *52*, 331. (b) Williams, J. M.; Brands, K. M. J.; Skerlj, R. T.; Jobson, R. B.; Marchesini, G.; Conrad, K. M.; Pipik, B.; Savary, K. A.; Tsay, F.-R.; Houghton, P. G.; Sidler, D. R.; Dolling, U.-H.; DiMichele, L. M.; Novak, T. J. *J. Org. Chem.* **2005**, *70*, 7479.
13. For example, R_f values of (*E*)-**3-2j**: 0.48, (*Z*)-**3-2j**: 0.45 (Hexane/EtOAc = 1:1).
14. The result resembles the case of the TsCl–NMI intermediate.[9a]
15. (a) $[Pd(PPh_3)_4]$; (*E*): 10%, (*Z*): 13%. (b) $[Pd(PPh_3)_2Cl_2]$; (*E*): 24%, (*Z*): 11%. (c) $[Pd(dppe)Cl_2]$; (*E*): 25%, (*Z*): 0%. (d) $[Pd(dppf)Cl_2]$; (*E*): 8%, (*Z*): 0%. (e) $Pd(OAc)_2$–PCy_3; (*E*): 12%, (*Z*): 0%. For details, see the Experimental.
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17. 15 g-scale preparation was performed by the crossed Ti–Claisen condensation between methyl phenylacetate and benzoyl chloride using $TiCl_4$–Et_3N–NMI at −45 °C for 1 h (74% yield). Ref. 8b. See the Experimental.
18. Recent representative syntheses of (*Z*)-tamoxifen. (a) Matsumoto, K.; Shindo, M. *Adv. Synth. Catal.* **2012**, *354*, 642. (b) Cahiez, G.; Moyeux, A.; Poizat, M. *Chem. Commun.* **2014**, *50*, 8982. (c) Nagano, K.; Ohmiya, H.; Sawamura, M. *Org. Lett.* **2015**, *17*, 1304. Other previous syntheses cited therein.
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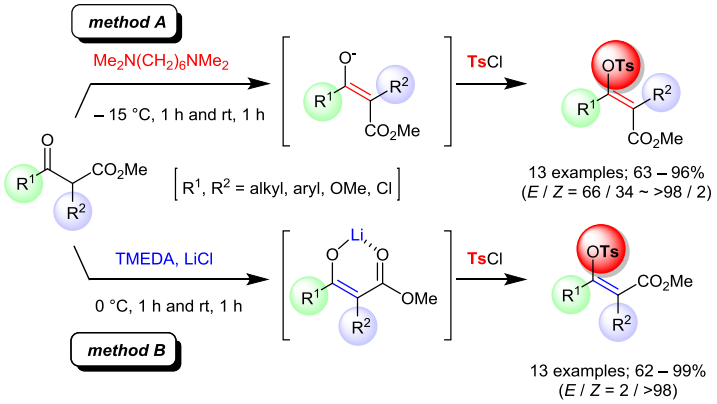
Chapter 4.
General and Robust Method for the Preparation of (E)- and (Z)-Stereodefined Fully-substituted Enol Tosylates: A Promising Cross-coupling Partner

Abstract

A robust method for preparing (*E*)- and (*Z*)-stereodefined fully-substituted enol tosylates is described. α-Substituted β-ketoesters undergo (*E*)-selective enol tosylations using TsCl–$Me_2N(CH_2)_6NMe_2$ 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 tosylation selectivity is proposed. A ^{1}H NMR monitoring experiment revealed that TsCl coupled with TMEDA formed a simple *N*-sulfonylammonium intermediate.



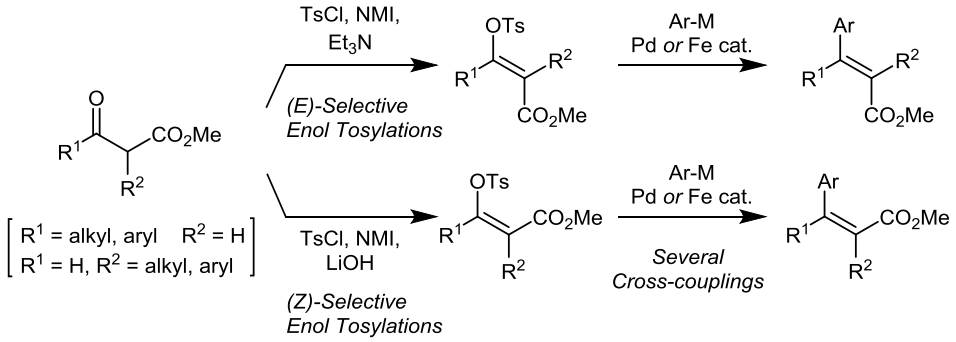
Introduction

Acyclic (*E*)- and (*Z*)-enol sulfonates (tosylates, triflates, etc.) and phosphonates derived from readily accessible β-ketoesters 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-ketoesters using respective Ts_2O–M(Li *or* Na)HMDS and Ts_2O–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.

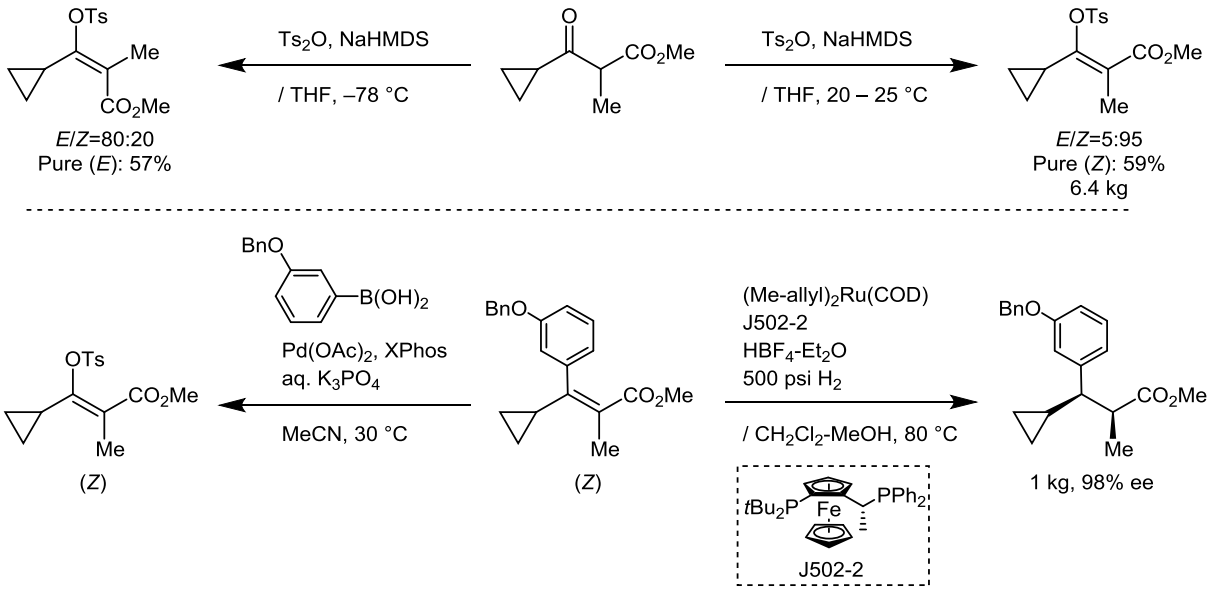
As part of our ongoing studies on mild but powerful sulfonylations[3] and silylations[4] of various alcohols and carbonyl compounds, we previously presented a series of (*E*)- and (*Z*)-stereocomplementary enol tosylations of not only acyclic 'α-nonsubstituted' β-ketoesters (R^1 = alkyl or aryl, R^2 = H), but also α-formylesters (R^1 = H, R^2 = alkyl or aryl), which were conducted by the TsCl–*N*-methylimidazole (NMI)–base system (**Scheme**

4-1). TsCl−NMI−Et_3N 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−Fürstner[5c]) 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,[6d] (*E*)- and (*Z*)-zimelidines,[5d] etc.



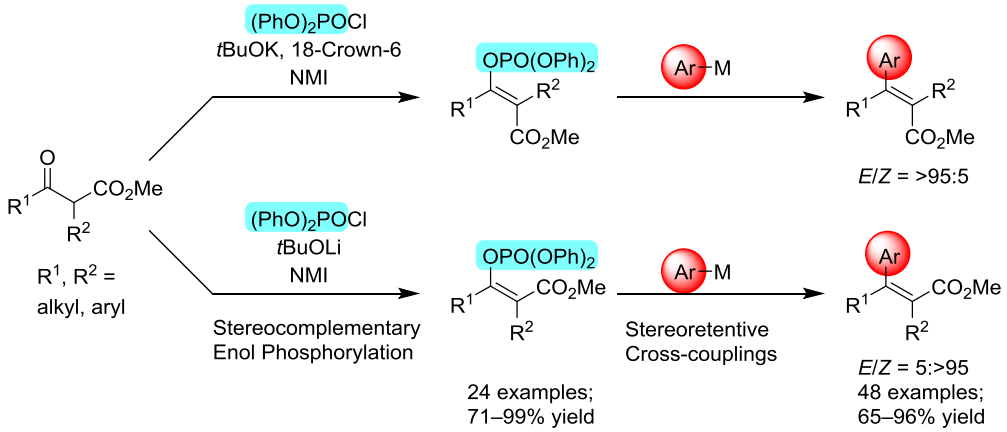
Scheme 4-1. (*E*)- and (*Z*)-Stereocomplementary synthesis of (*E*)- and (*Z*)-α,β-unsaturated esters utilizing stereoselective enol tosylations and stereoretentive cross-couplings.

Very recently, the Merck process group reported a synthesis of chiral β-cyclopropyl-α-methyldihydrocinnamates (**Scheme 4-2**).[7] This notable pharmacophore was synthesized via (*E*)- and (*Z*)-stereocontrolled enol tosylations using a β-cyclopropyl-α-methyl-β-ketoester; the (*E*)-isomer was prepared using Ts_2O−NaHMDS at −78 °C, whereas the (*Z*)-isomer was prepared using the same reagent at room temperature.



Scheme 4-2. A synthesis of chiral β-cyclopropyl-α-methyldihydrocinnamate reported by Merck process group.

On the other hand, as exhibited in Chapter 3, our group recently reported (*E*)- and (*Z*)-stereocomplementary enol phosphorylations of 'α-substituted' β-ketoesters as a relevant approach;[8] the $(PhO)_2POCl$−NMI−Li*O*t*Bu* reagent being used for preparing (*E*)-isomers, whereas the $(PhO)_2POCl$−NMI−K*O*t*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 (**Scheme 4-3**). 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 $(PhO)_2PO$- group, (ii) lower atom economy of the $(PhO)_2PO$- group, (iii) a considerably more tedious separation procedure between (*E*)- and (*Z*)-enol phosphonates by column chromatography due to their similar R_f values, and (iv) requires stoichiometric amounts of an expensive and highly toxic 18-crown-6 are required.



Scheme 4-3. (*E*)- and (*Z*)-Stereocomplementary synthesis of (*E*)- and (*Z*)-α,β-unsaturated esters utilizing stereoselective enol phosphorylations and stereoretentive cross-couplings.

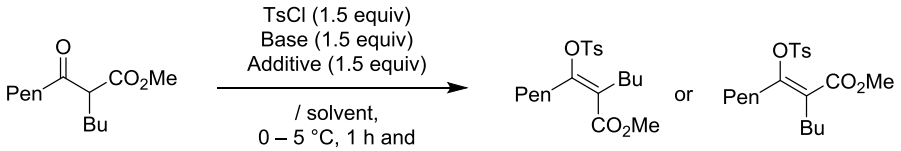
This background prompted us to search for a more efficient enol tosylation method using less reactive 'α-carbon-substituted' β-ketoesters **4-1** (R^1, R^2 = alkyl and/or aryl). We present herein a substrate-general and robust method for (*E*)- and (*Z*)-stereocomplementary enol tosylations of **4-1** using the TsCl−$Me_2N(CH_2)_6NMe_2$ reagent for (*E*)-enol tosylates (*E*)-**4-2** and the TsCl−TMEDA–LiCl reagent for (*Z*)-enol tosylates (*Z*)-**4-2**.[9]

Results and Discussion

The initial attempt was intentionally guided using stereocongested methyl 2-butyl-3-oxooctanoate **4-1a**[10] as a much less reactive substrate probe (**Table 4-1**). As anticipated, the reported NMI-mediated method[6] resulted in almost no reaction (**Table 4-1**, entries 1, 2). Notably, the use of inexpensive $Me_2N(CH_2)_nNMe_2$ (n=3 or 6)[11] alone afforded positive results for the (*E*)-selective reaction to give the desired enol tosylate (*E*)-**4-2a** (**Table 4-1**, 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.[3c] This information led us to use $Me_2N(CH_2)_nNMe_2$ (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 4-1**, entry 6). The best solvent was MeCN; EtOAc, DMF, THF, and toluene were apparently inferior (**Table 4-1**, entry 7). On the other hand, the (*Z*)-selective reaction proceeded smoothly to give (*Z*)-**4-2a** 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 4-1**, entry 8). The use of TMEDA produced satisfactory results eventually compared with $Me_2N(CH_2)_nNMe_2$ (n=3 or 6) (**Table 4-1**, entries 8−12). EtOAc and toluene gave moderate yields and the best solvent was MeCN (**Table 4-1**, entries 8−10).[12]

Table 4-1. (*E*)- and (*Z*)-Stereocomplementary enol tosylation of **4-1a** using TsCl−*N*,*N*,*N'*,*N'*-tetramethyldiamine base *with* or *without* additive.



4-1a (*E*)-**4-2a** (*Z*)-**4-2a**

Entry	Base	Additive	Solvent	Yield[a] / %	*E*/*Z*[a]
1	Et_3N	NMI	C_6H_5Cl	NR	−
2	KO*t*Bu	NMI, 18-Crown-6	THF	Trace	−
3	TMEDA	−	MeCN	17	97:3
4	$Me_2N(CH_2)_6NMe_2$	−	MeCN	48	93:7
5	$Me_2N(CH_2)_6NMe_2$	−	MeCN	44	94:6
6	$Me_2N(CH_2)_6NMe_2$	−	MeCN	74,[b] 60[b,c]	98:2
7	$Me_2N(CH_2)_6NMe_2$	−	EtOAc, DMF, THF, Toluene	Trace[b]	−
8	TMEDA	LiCl	MeCN	93[c]	2:>98
9	TMEDA	LiCl	EtOAc	38	2:>98
10	TMEDA	LiCl	Toluene	50	2:>98
11	$Me_2N(CH_2)_3NMe_2$	LiCl	MeCN	40	2:>98
12	$Me_2N(CH_2)_6NMe_2$	LiCl	MeCN	66	−
13	Et_3N	LiCl	MeCN	Trace (33)[d]	2:>98
14	LHMDS	−	Toluene-MeCN (1:1)	11 (43)[d]	36:64

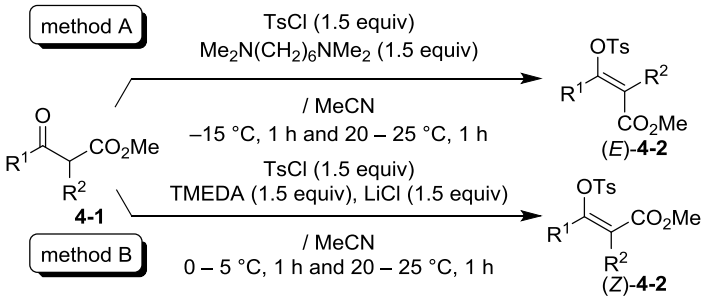
a) Determined by ^{1}H NMR of the crude products. b) Reaction conditions: −15 °C, 1 h and 20 − 25 °C, 1 h.
c) Isolated. d) α-Chlorinated by-product of **4-1a**; see the experimental section.

In the two cases using Et_3N and LHMDS, considerable amounts of α-chlorinated by-product (methyl 2-butyl-2-chloro-3-oxooctanoate) of **4-1a** were detected (**Table 4-1**, entries 13 and 14).[13] The occurrence of this side reaction is ascribed to that TsCl cannot be sufficiently activated (vide infra, **Scheme 4-6**).

Accordingly, the present method is obviously more efficient than the NMI-mediated reactions.

With the successful outcome in hands, **Table 4-2** lists the substrate generality using a variety of α-substituted β-ketoesters **4-1** [method A for (*E*)-isomers (*E*)-**4-2** and method B for (*Z*)-isomers (*Z*)-**4-2**]. 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 (>90:10 for method A and 2:>98 for method B). (iii) As a limitation, (*E*)-selectivity using α,β-diaryl substrates **4-1m** and **4-1n** was moderate (**Table 4-2**, entries 25 and 27). This tendency coincides with discussions in the precedent report[5d] which ascribes to the nature of intrinsically more stable (*Z*)-isomers. Fortunately, these crude products could be enriched to the pure (*E*)-products (*E*)-**4-2m** and (*E*)-**4-2n**, by recrystallization. It should be noted that all of these stereodefined (*E*)- and (*Z*)-enol tosylates **4-2** are novel compounds.

Table 4-2. (*E*)- and (*Z*)-Stereocomplementary enol tosylation of **4-1** using TsCl−$Me_2N(CH_2)_6NMe_2$ (Method A) and TsCl−TMEDA−LiCl (Method B)



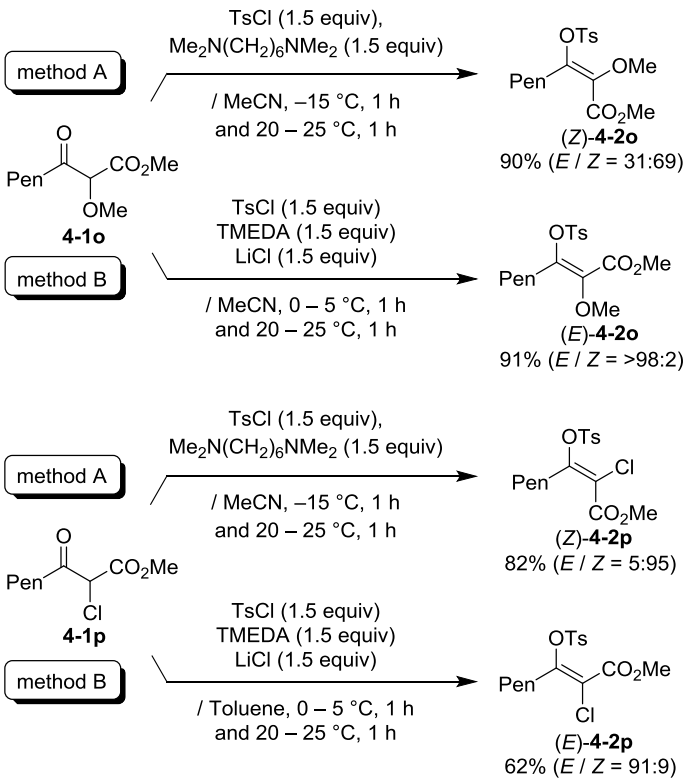
Entry	R^1	R^2	Substrate	Method	Product	Yield / %	E / Z [a]
1	Me	Me	**4-1b**	A	(*E*)-**4-2b**	84	>98:2
2	Me	Me	**4-1b**	B	(Z)-**4-2b**	72	2:>98
3	Me	*n*Bu	**4-1c**	A	(*E*)-**4-2c**	81	97:3
4	Me	*n*Bu	**4-1c**	B	(Z)-**4-2c**	95	2:>98
5	Me	*i*Pr	**4-1d**	A	(*E*)-**4-2d**	84[b]	>98:2
6	Me	*i*Pr	**4-1d**	B	(Z)-**4-2d**	85[c]	2:>98
7	*n*Bu	Me	**4-1e**	A	(*E*)-**4-2e**	74	>98:2
8	*n*Bu	Me	**4-1e**	B	(Z)-**4-2e**	62	2:>98
9	*n*Pen	Me	**4-1f**	A	(*E*)-**4-2f**	74	>98:2
10	*n*Pen	Me	**4-1f**	B	(Z)-**4-2f**	94	2:>98
11	$Cl(CH_2)_4$	Me	**4-1g**	A	(*E*)-**4-2g**	77	>98:2
12	$Cl(CH_2)_4$	Me	**4-1g**	B	(Z)-**4-2g**	85	2:>98
13	CH_2=$CH(CH_2)_8$	CH_2=$CH(CH_2)_7$	**4-1h**	A	(*E*)-**4-2h**	63	95:5
14	CH_2=$CH(CH_2)_8$	CH_2=$CH(CH_2)_7$	**4-1h**	B	(Z)-**4-2h**	91	2:>98
15	*n*Pen	*n*Bu	**4-1a**	A	(*E*)-**4-2a**	74	>98:2
16	*n*Pen	*n*Bu	**4-1a**	B	(Z)-**4-2a**	93	2:>98

17	Ph	Me	**4-1i**	A	(*E*)-**4-2i**	89	94:6
18	Ph	Me	**4-1i**	B	(Z)-**4-2i**	90	2:>98
19	(*p*-Me)C_6H_4	Me	**4-1j**	A	(*E*)-**4-2j**	80	94:6
20	(*p*-Me)C_6H_4	Me	**4-1j**	B	(Z)-**4-2j**	89	2:>98
21	(*p*-MeO)C_6H_4	Me	**4-1k**	A	(*E*)-**4-2k**	90	90:10
22	(*p*-MeO)C_6H_4	Me	**4-1k**	B	(Z)-**4-2k**	98	2:>98
23	(*p*-Cl)C_6H_4	Me	**4-1l**	A	(*E*)-**4-2l**	94	>98:2
24	(*p*-Cl)C_6H_4	Me	**4-1l**	B	(Z)-**4-2l**	96	2:>98
25	Ph	Ph	**4-1m**	A	(*E*)-**4-2m**	96 (49)[d]	74:26 (>98:2)
26	Ph	Ph	**4-1m**	B	(Z)-**4-2m**	93	2:>98
27	(*p*-MeO)C_6H_4	Ph	**4-1n**	A	(*E*)-**4-2n**	95 (26)[d]	66:34 (>98:2)
28	(*p*-MeO)C_6H_4	Ph	**4-1n**	B	(Z)-**4-2n**	99	2:>98

a) Determined by ^{1}H NMR of the crude products. b) TsCl (3.0 equiv) and $Me_2N(CH_2)_6NMe_2$ (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.

Next, an extension to α-heteroatom (MeO and Cl) substituted β-ketoesters **4-1o** and **4-1p** was examined (**Scheme 4-4**). Gratifyingly, the reaction proceeded smoothly to give the desired functionalized products (*E*)-, (*Z*)-**4-2o** and (*E*)-, (*Z*)-**4-2p**. (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.[5] In addition, NOE measurements exemplified by enol tosylates (*E*)-**4-2f** and (*Z*)-**4-2f**, determined unambiguous assignment (**Figure 4-1**).



Scheme 4-4. (*E*)- and (*Z*)-Stereocomplementary enol tosylation of α-heteroatom-substituted β-ketoesters **4-1o** and **4-1p**

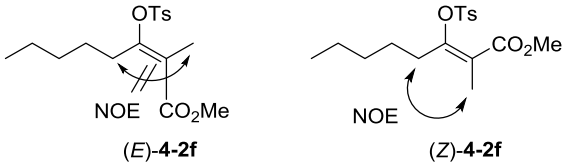
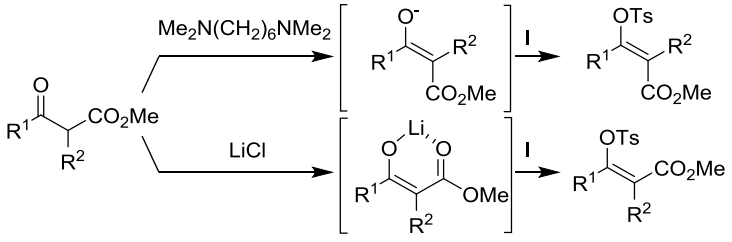
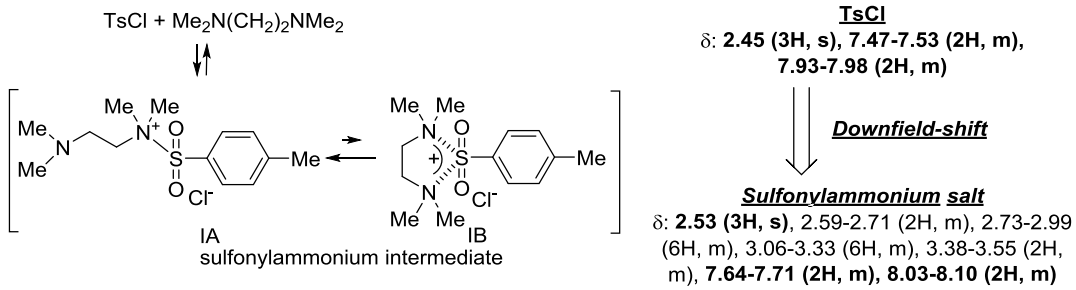


Figure 4-1. NOE measurement of (*Z*)-**4-2f**

A plausible mechanism for the successful emergence of (*E*)- and (*Z*)-enol tosylation selectivity is illustrated in **Scheme 4-5** and **Scheme 4-6**.[14] The (*E*)-selective reaction with highly reactive intermediate **I** proceeds via a non-chelation pathway to give (*E*)-**4-2**; $Me_2N(CH_2)_6NMe_2$ plays two different roles as a base reagent and a partner of **I** through equilibrium. $Me_2N(CH_2)_6NMe_2$ 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*)-**4-2**; the Li cation facilitates (*Z*)-enolate formation.



Scheme 4-5. A mechanistic investigation into the (*E*)- and (*Z*)-stereoselective enol tosylations



Scheme 4-6. Formation of sulfonylammonium intermediate **I** monitored by ^{1}H NMR measurements at −40 °C

As depicted in **Scheme 4-6** and **Figure 4-2**, a careful ^{1}H NMR monitoring experiment (−40 °C in CD_3CN) revealed that TsCl coupled with TMEDA formed a simple *N*-sulfonylammonium intermediate **IA** rather than a plausible *N,N'*-chelate-type intermediate **IB**. The apparent downfield chemical 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]

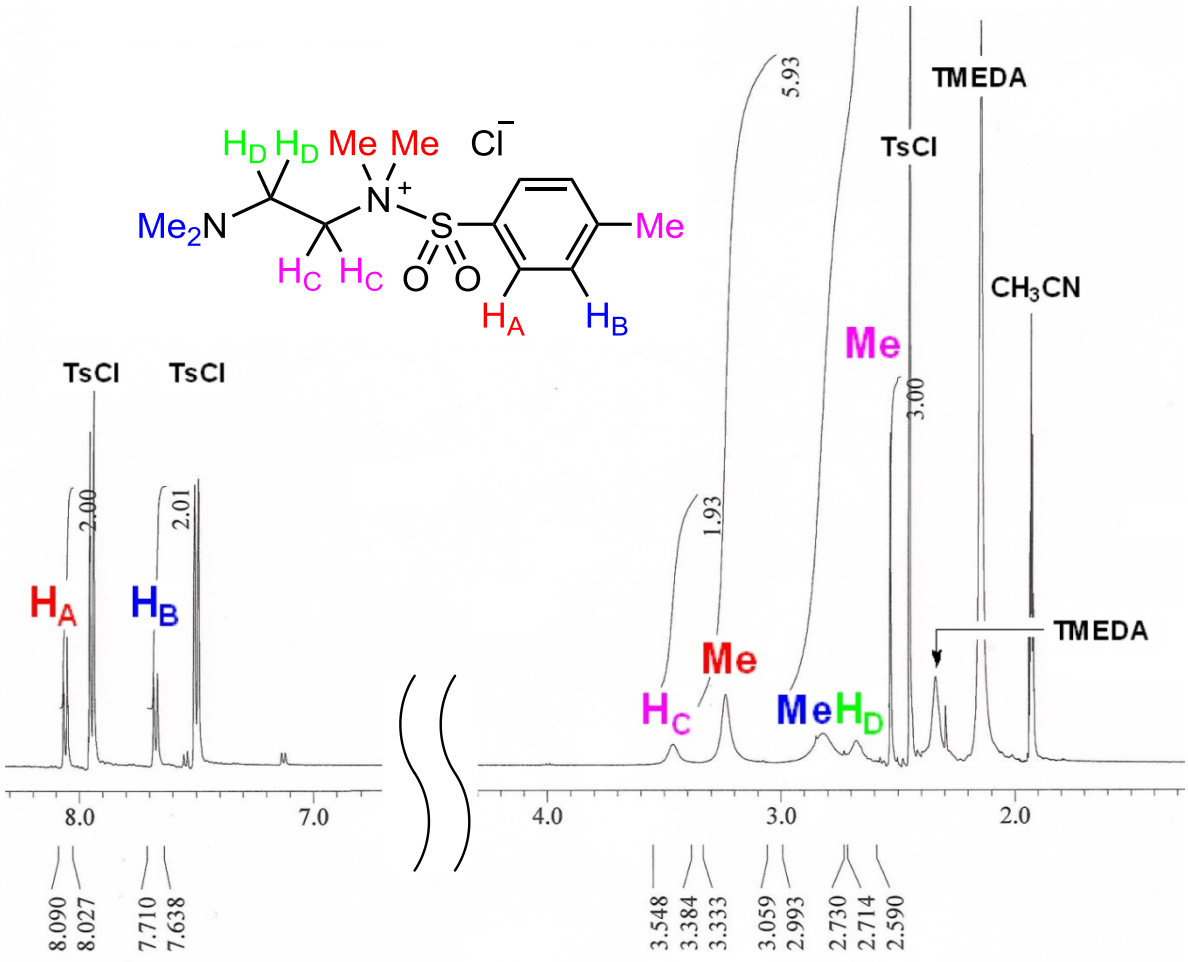
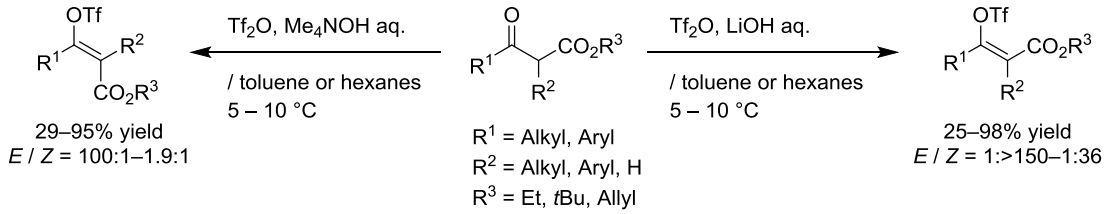


Figure 4-2. A ^{1}H NMR monitoring study using a 1:1 mixture of TsCl and TMEDA at −40 °C

Meanwhile, at the same time, Frantz's group reported a practical preparative method for (*E*)- and (*Z*)-stereodefined enol triflates derived from β-ketoesters (**Scheme 4-7**).[17] Highly reactive these enol sulfonates have served as useful building block for the synthesis of natural products,[18] however, enol triflates methods have several drawbacks: (i) Tf_2O is ca. 15−30 times more expensive than TsCl, (ii) Tf_2O is highly toxic and hazardous with a low boiling point (81−83 °C) and reacts violently with water, and (iii) Triflates are often unstable under cross-couplimg conditions due to its inherent reactivity.



Scheme 4-7. (*E*)- and (*Z*)-Stereocomplementary preparation of enol triflates reported by Frantz's group.

Conclusion

A general and convenient protocol has been developed for the production of (*E*)- and (*Z*)- enol tosylates of α-substituted β-ketoesters using readily available TsCl and *N,N,N',N'*-tetramethyldiamine for *E*-isomers or LiCl base for *Z*-isomers. The $Me_2N(CH_2)_6NMe_2$ reagent functions to produce (*E*)-selective reactions, whereas the TMEDA−LiCl reagent functions to produce (*Z*)-selective reactions. A plausible mechanism accounting for the successful (*E*)- and (*Z*)-selectivity is proposed; non-chelation pathway with dipole-dipole repulsion for *E* and Li-chelation pathway for *Z*. A ^{1}H NMR monitoring experiment revealed that TsCl coupled with TMEDA formed a simple *N*-sulfonylammonium intermediate, plausibly not *N,N'*-bidentate but *N*-monodentate intermediate. Chapter 5 disclosed notable application to various (*E*)- and (*Z*)-stereoretentive cross-couplings using the obtained fully substituted enol tosylates, a pair of latent and potential scaffolds.

Experimental

Preparation of β-ketoesters

Methyl 2-butyl-3-oxooctanoate[8,19b] 4-1a

$TiCl_4$ (114 g, 0.60 mol) and Et_3N (70.8 g, 0.70 mol) were successively added dropwise to a stirred solution of methyl hexanoate (65.1 g, 0.50 mol) in CH_2Cl_2 (500 mL) at 0 – 5 °C under an Ar atmosphere, and the mixture was stirred at the same temperature for 1 h. Water was added to the mixture, which was extracted twice with Et_2O. The combined organic phase was washed with sat. aq. $NaHCO_3$ solution, brine, dried (Na_2SO_4), and concentrated. The obtained crude product was purified by distillation to give the desired product (53.2 g, 93%).

Colorless oil; bp 79−81 °C/0.49 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.2 Hz, 3H), 0.89 (t, *J* = 7.2 Hz, 3H), 1.16−1.39 (m, 8H), 1.58 (quin, *J* = 7.2 Hz, 2H), 1.78−1.90 (m, 2H), 2.45 (dt, *J* = 7.2 Hz, *Jgem* = 17.2 Hz, 1H), 2.54 (dt, *J* = 7.2 Hz, *Jgem* = 17.2 Hz, 1H), 3.43 (t, *J* = 7.2 Hz, 1H), 3.72 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.6, 13.7, 22.2, 22.3, 23.0, 27.8, 29.5, 31.0, 41.6, 52.0, 58.8, 170.2, 205.2.

Methyl 2-acetylhexanoate[20] 4-1c

Methyl acetoacetate (3.49 g, 30 mmol) was added to a stirred suspension of NaH (50%, 1.72 g, 36 mmol) in DMF (15 mL) at 0 – 5 °C, and the mixture was stirred at 20 – 25 °C for 0.5 h with H_2 gas evolution. 1-Bromobutane (4.11 g, 30 mmol) was added at the same temperature and the mixture was stirred at 70 – 75 °C for 15 h. Water (large amount) was slowly added to the mixture, which was extracted with AcOEt. The combined organic phase was washed with water (large amount), brine, dried (Na_2SO_4), and concentrated. The obtained crude product was purified by SiO_2-column chromatography (hexane/AcOEt = 80/1 – 50/1) to give the desired product (2.16 g, 42%).

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.2 Hz, 3H × 8.5/10, keto form), 0.98 (t, *J* = 7.2 Hz, 3H × 1.5/10, enol form), 1.17−1.42 (m, 4H), 1.75−1.94 (m, 2H × 8.5/10, keto form), 2.01 (s, 3H × 1.5/10, enol form), 2.15 (t, *J* = 7.2 Hz, 2H × 1.5/10, enol form), 2.23 (s, 3H × 8.5/10, keto form), 3.42 (t, *J* = 7.2 Hz, 1H × 8.5/10, keto form), 3.74 (s, 3H × 8.5/10, keto form), 3.75 (s, 3H × 1.5/10, enol form); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.3, 13.5, 18.0, 22.0, 25.3, 27.5, 28.3, 29.1, 31.9, 50.9, 51.7, 59.1, 99.9, 169.9, 171.6, 173.3, 202.5.

Methyl 2-acetyl-3-methylbutanoate[21] 4-1d

Following the procedure for the preparation of **4-1c**, the reaction of methyl acetoacetate (4.65 g, 40 mmol) with 2-iodopropane (13.60 g, 40 mmol) using NaH (50%, 2.30 g, 48 mmol) gave the desired product (2.60 g, 41%).

colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (d, *J* = 6.5 Hz, 3H), 0.97 (d, *J* = 6.5 Hz, 3H), 2.22 (s, 3H), 2.42 (dsep, *J* = 6.5, 9.6 Hz, 1H), 3.20 (d, *J* = 9.6 Hz, 1H), 3.73 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.2, 28.5, 29.0, 51.9, 67.1, 169.4, 202.8.

Methyl 2-methyl-3-oxooctanoate[22] 4-1f

$TiCl_4$ (99.6 g, 0.53 mol) and Bu_3N (111 g, 0.60 mol) were successively added dropwise to a stirred solution of methyl propanoate (13.2 g, 0.15 mol), hexanoyl chloride (20.2 g, 0.15 mol), and 1,2-dimethylimidazole (17.3 g, 0.18 mol) in CH_2Cl_2 (450 mL) at –45 °C under an Ar atmosphere, and the mixture was stirred at the same temperature for 1 h. Water was added to the mixture, which was extracted twice with Et_2O. The combined organic phase was washed with saturated $NaHCO_3$ aqueous solution, brine, dried (Na_2SO_4), and concentrated. The obtained crude product was purified by distillation to give the desired product (15.5 g, 55%).

Colorless oil; bp 88−90 °C/0.30 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.9 Hz, 3H), 1.20−1.37 (m, 4H), 1.34 (d, *J* = 7.2 Hz, 3H), 1.53−1.65 (m, 2H), 2.48 (dt, *J* = 7.2 Hz, *Jgem* = 17.5 Hz, 1H), 2.57 (dt, *J* = 7.6 Hz, *Jgem* = 17.5 Hz, 1H), 3.54 (q, *J* = 6.9 Hz, 1H), 3.73 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.8, 13.8, 22.37, 23.2, 31.2, 41.3, 52.3, 52.7, 171.1, 205.9.

Methyl 7-chloro-2-methyl-3-oxoheptanoate[22b,23] 4-1g

Following the procedure for the preparation of **4-1f**, the reaction of methyl propanoate (4.41 g, 50 mmol) with 5-chloropentanoyl chloride (7.75 g, 50 mmol) using 1,2-dimethylimidazole (5.77 g, 60 mmol), $TiCl_4$ (33.20 g, 175 mmol), and Bu_3N (37.10 g, 200 mmol) gave the desired product (4.78 g, 47%).

Colorless oil; bp 79−80 °C/0.23 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.35 (d, *J* = 7.2 Hz, 3H), 1.75−1.79 (m, 4H), 2.46−2.71 (m, 2H), 3.50−3.57 (m, 3H), 3.74 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.7, 20.7, 31.6, 40.3, 44.5, 52.4, 52.5, 170.9, 205.2.

Methyl 2-(non-8-en-1-yl)-3-oxotridec-12-enoate 4-1h

Following the procedure for the preparation of **4-1a**, the reaction of methyl undec-10-enoate (198 mg, 1.0 mmol) using $TiCl_4$ (228 mg, 1.2 mmol) and Et_3N (142 mg, 1.4 mmol) gave the desired product (109 mg, 60%).

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.16−1.42 (m, 20H), 1.50−1.63 (m, 2H), 1.75−1.88 (m, 2H), 1.96−2.09 (m, 4H), 2.44 (dt, *J* = 7.2 Hz, *Jgem* = 17.2 Hz, 1H), 2.54 (dt, *J* = 7.2 Hz, *Jgem* = 17.2 Hz, 1H), 3.43 (t, *J* = 7.2 Hz, 1H), 3.72 (s, 3H), 4.88−5.03 (m, 4H), 5.73−5.88 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.4, 27.4, 28.2, 28.8, 28.8, 28.9, 29.0, 29.0, 29.1, 29.1, 29.2 (2C), 33.7 (2C), 41.8, 52.2, 59.0, 114.1 (2C), 139.1 (2C), 170.4, 205.4; IR (neat): ν_{max} = 3077, 2925, 2854, 1742, 1716, 1640, 1436, 1196 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{23}H_{40}O_3$ $[M+Na]^+$ 387.2875; found: 387.2883.

Methyl 2-methyl-3-oxo-3-phenylpropanoate[22b,24] 4-1i

Following the procedure for the preparation of **4-1f**, the reaction of methyl propanoate (2.64 g, 30 mmol) with benzoyl chloride (4.22 g, 30 mmol) using *N*-methylimidazole (2.96 g, 36 mmol), $TiCl_4$ (19.9 g, 105 mmol), and Bu_3N (22.2 g, 120 mmol) gave the desired product (4.31 g, 75%).

Colorless oil; bp 110−112 °C / 0.45 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.50 (d, *J* = 7.2 Hz, 3H), 3.69 (s, 3H), 4.41 (q, *J* = 7.2 Hz, 1H), 7.44−7.52 (m, 2H), 7.55−7.63 (m, 1H), 7.95−8.00 (m, 2H); ^{13}C NMR (75 MHz,

$CDCl_3$): δ = 13.8, 48.0, 52.5, 128.6, 128.7, 133.5, 135.7, 171.3, 195.8.

Methyl 2-methyl-3-oxo-3-(*p*-tolyl)propanoate[22b,25] 4-1j

Following the procedure for the preparation of **4-1f,** the reaction of methyl propanoate (1.76 g, 20 mmol) with 4-methylbenzoyl chloride (3.09 g, 20 mmol) using *N*-methylimidazole (1.97 g, 24 mmol), $TiCl_4$ (13.3 g, 70 mmol), and Bu_3N (14.8 g, 80 mmol) gave the desired product (2.97 g, 72%).

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.49 (d, *J* = 7.3 Hz, 3H), 2.42 (s, 3H), 3.69 (s, 3H), 4.40 (q, *J* = 7.3 Hz, 1H), 7.25−7.30 (m, 2H), 7.87−7.90 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 21.5, 47.8, 52.3, 128.7, 129.4, 133.1, 144.4, 171.3, 195.4.

Methyl 3-(4-chlorophenyl)-2-methyl-3-oxopropanoate[22b,26] 4-1l

Following the procedure for the preparation of **4-1f**, the reaction of methyl propanoate (1.76 g, 20 mmol) with 4-chlorobenzoyl chloride (3.50 g, 20 mmol) using *N*-methylimidazole (1.97 g, 24 mmol), $TiCl_4$ (13.3 g, 70 mmol), and Bu_3N 14.8 g, 80 mmol) gave the desired product (3.35 g, 74%).

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.50 (d, *J* = 7.3 Hz, 3H), 3.69 (s, 3H), 4.36 (q, *J* = 7.3 Hz, 1H), 7.43−7.48 (m, 2H), 7.89−7.95 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.6, 47.9, 52.4, 129.0, 130.0, 134.0, 140.0, 170.9, 194.5.

Methyl 3-oxo-2,3-diphenylpropanoate[27] 4-1m

To a vigorously stirred solution of $PhCH_2CO_2Me$ (4.51 g, 30.0 mmol) and PhCOCl (4.21 g, 30.0 mmol) in CH_2Cl_2 (90 mL), NMI (2.36 g, 36.0 mmol) was added dropwise at –45 °C under an Ar atmosphere. Then, using two dropping funnels, $TiCl_4$ (11.5 mL, 105 mmol) (during ca. 20 min) and Et_3N (16.6 mL, 120 mmol) (during ca. 1 h) were successively added, and the mixture was stirred at the same temperature for 1 h. Water was slowly added to the mixture, which was extracted twice with Et_2O. The combined organic phase was washed with water, brine, dried (Na_2SO_4), and concentrated to give the crude product (7.82 g). The obtained crude product was purified by SiO_2-column chromatography (hexane/AcOEt = 6/1 – 3/1) to give the desired product (6.66 g, 87%).

Colorless crystals; mp 73−74 °C (lit.[27] 72−73 °C); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.76 (s, 3H), 5.63 (s, 1H), 7.29−7.45 (m, 7H), 7.51−7.58 (m, 1H), 7.90−8.01 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 52.7, 60.3, 128.1, 128.7, 128.8, 128.9, 129.5, 132.8, 133.5, 135.5, 169.3, 193.2.

Methyl 3-(4-methoxyphenyl)-3-oxo-2-phenylpropanoate 4-1n

Following the procedure for the preparation of **4-1m**, the reaction of $PhCH_2CO_2Me$ (1.50 g, 10.0 mmol) with (*p*-MeO)C_6H_4COCl (1.71 g, 10.0 mmol) using *N*-methylimidazole (985 mg, 12.0 mmol), $TiCl_4$ (3.84 mL, 35 mmol), Et_3N (5.54 mL, 40.0 mmol) gave the desired product (2.48 g, 87%).

Colorless crystals; mp 92−94 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.76 (s, 3H), 3.84 (s, 3H), 5.59 (s, 1H), 6.83 (m, 2H), 7.27−7.51 (m, 5H), 7.87−8.01 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 52.6, 55.4, 60.1, 113.9, 128.0, 128.4, 128.7, 129.4, 131.3, 133.2, 163.8, 169.4, 191.7; IR (neat): ν_{max} = 1741, 1670, 1595, 1454,

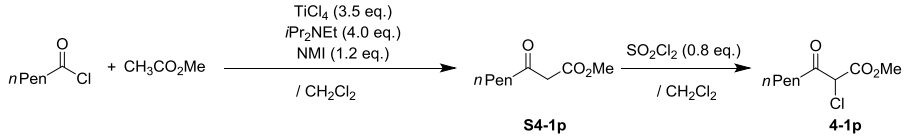
1325, 1215 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{17}H_{16}O_4$ $[M+Na]^+$ 307.0946; found: 307.0945.

Methyl 2-methoxy-3-oxooctanoate 4-1o

$TiCl_4$ (664 mg, 3.5 mmol) and Et_3N (405 mg, 4.0 mmol) were successively added dropwise to a stirred solution of methyl methoxyacetate (104 mg, 1.0 mmol), hexanoyl chloride (135 mg, 1.0 mmol), and 1,2-dimethylimidazole (115 mg, 1.2 mmol) in CH_2Cl_2 (3 mL) at –45 °C under an Ar atmosphere, and the mixture was stirred at the same temperature for 1 h. Water was added to the mixture, which was extracted twice with Et_2O. The combined organic phase was washed with saturated $NaHCO_3$ aqueous solution, brine, dried (Na_2SO_4), and concentrated. The obtained crude product was purified by SiO_2-column chromatography (hexane/AcOEt = 80/1 – 50/1) to give the desired product (162 mg, 80%).

Colorless oil; ^1H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.2 Hz, 3H), 1.20−1.41 (m, 4H), 1.58 (quin, *J* = 7.2 Hz, 2H), 2.60 (dt, *J* = 7.2 Hz, *Jgem* = 3.4 Hz, 1H), 2.61 (dt, *J* = 7.2 Hz, *Jgem* = 3.4 Hz, 1H), 3.47 (s, 3H), 3.81 (s, 3H), 4.30 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7, 22.2, 22.5, 31.0, 38.4, 52.5, 58.5, 86.6, 167.5, 203.9.; IR (neat): ν_{max} = 2955, 1750, 1726, 1438, 1402, 1272, 1203, 1119 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{10}H_{18}O_4$ $[M+Na]^+$ 225.1103; found: 225.1109.

Methyl 2-chloro-3-oxooctanoate 4-1p



$TiCl_4$ (99.7 g, 0.53 mol) and *i*Pr_2NEt (77.5 g, 0.60 mmol) were successively added dropwise to a stirred solution of methyl acetate (17.8 g, 0.24 mol), hexanoyl chloride (20.2 g, 0.15 mol), and 1,2-dimethylimidazole (17.3 g, 0.18 mol) in CH_2Cl_2 (450 mL) at –45 °C under an Ar atmosphere, and the mixture was stirred at the same temperature for 1 h. Water was added to the mixture, which was extracted twice with Et_2O. The combined organic phase was washed with saturated $NaHCO_3$ aqueous solution, brine, dried (Na_2SO_4), and concentrated. The obtained crude product was purified by distillation to give the corresponding β-ketoester **S4-1p** (18.9 g, 73%).

S4-1p; Colorless oil; bp 75−77 °C/0.41 mmHg; ^1H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.9 Hz, 3H), 1.20−1.39 (m, 4H), 1.60 (quin, *J* = 7.6 Hz, 2H), 2.19 (t, *J* = 7.6 Hz, 2H × 1.0/10, enol form), 2.53 (t, *J* = 7.6 Hz, 2H × 9.0/10, keto form), 3.45 (s, 2H × 9.0/10, keto form), 3.73 (s, 3H × 1.0/10, enol form), 3.74 (s, 3H × 9.0/10, keto form), 4.99 (s, 1H × 1.0/10, enol form), 12.02 (s, 1H × 1.0/10, enol form); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.5, 22.0, 22.8, 25.6, 30.8, 34.6, 42.6, 48.6, 50.6, 51.8, 88.3, 167.4, 172.7, 178.7, 202.5; IR (neat): ν_{max} = 2956, 2871, 1748, 1715, 1628, 1438, 1321, 1235 cm^{-1}.

SO_2Cl_2 (14.6 g, 104 mmol) was added to a stirred solution of the β-ketoester **S4-1p** (22.4 g, 130 mmol) in CH_2Cl_2 (260 mL) at –20 °C under an Ar atmosphere, and the mixture was stirred at 20 – 25 °C for 1 h. Water was added to the mixture, which was extracted twice with AcOEt. The combined organic phase was washed with saturated $NaHCO_3$ aqueous solution, brine, dried (Na_2SO_4), and concentrated. The obtained crude oil was purified by SiO_2-column chromatography (hexane/AcOEt = 80/1 – 50/1) to give the desired

product **4-1p** (21.0 g, 78%).

4-1p; Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84−0.95 (m, 3H), 1.23−1.40 (m, 4H), 1.57−1.70 (m, 2H), 2.51 (t, *J* = 7.6 Hz, 2H × 4.0/10, enol form), 2.70 (dt, *J* = 7.2 Hz, *Jgem* = 3.1 Hz, 2H × 6.0/10, keto form), 3.84 (s, 3H × 6.0/10, keto form), 3.85 (s, 3H × 4.0/10, enol form), 4.80 (s, 1H × 6.0/10, keto form), 12.32 (s, 1H × 4.0/10, enol form); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7, 22.2, 23.0, 25.3, 30.9, 31.2, 32.7, 38.8, 52.5, 53.5, 60.6, 96.1, 165.4, 169.7, 175.9, 198.7; IR (neat): ν_{max} = 2955, 2862, 1734, 1622, 1597, 1435, 1382, 1256 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_9H_{15}O_3Cl$ $[M+Na]^+$ 229.0607; found: 229.0611.

(*E*)-Enol Tosylation of β-Ketoesters (method A); General Procedure

TsCl (286 mg, 1.5 mmol) in MeCN (1.0 mL) was added to a stirred suspension of β-ketoester (1.0 mmol) and $Me_2N(CH_2)_6NMe_2$ (258 mg, 1.5 mmol) in MeCN (1.0 mL) at −15 °C and the mixture was stirred at the same temperature for 1 h and 20 − 25 °C for 1 h. Water (large amount) was added to the mixture, which was extracted twice with AcOEt. The combined organic phase was washed with water, saturated $NaHCO_3$ aqueous solution, brine, dried (Na_2SO_4), and concentrated. The obtained crude product was purified by SiO_2 column chromatography (hexane/AcOEt = 50/1 – 15/1) to give the desired product.

(*Z*)-Enol Tosylations of β-Ketoesters (method B); General Procedure

TsCl (286 mg, 1.5 mmol) in MeCN (1.0 mL) was added to a stirred suspension of β-ketoester (1.0 mmol), TMEDA (258 mg, 1.5 mmol), and LiCl (64 mg, 1.5 mmol) in MeCN (1.0 mL) at 0 – 5 °C and the mixture was stirred at the same temperature for 1 h and 20 – 25 °C for 1 h. Water (large amount) was added to the mixture, which was extracted twice with AcOEt. The combined organic phase was washed with water, saturated $NaHCO_3$ aqueous solution, brine, dried (Na_2SO_4), and concentrated. The obtained crude product was purified by SiO_2 column chromatography (hexane/AcOEt = 50/1 – 10/1) to give the desired product.

(*E*)-4-2a (method A); Typical Gram-Scale Procedure

TsCl (4.29 g, 23 mmol) in MeCN (15 mL) was added to a stirred solution of methyl 2-butyl-3-oxooctanoate (**4-1a**; 3.42 g, 15 mmol) and $Me_2N(CH_2)_6NMe_2$ (4.85 mL, 23 mmol) in MeCN (15 mL) at −15 °C, and the mixture was stirred at the same temperature for 1 h and 20 − 25 °C for 1 h. Water was added to the mixture, which was extracted twice with AcOEt. The combined organic phase was washed with water, saturated $NaHCO_3$ aqueous solution, brine, dried (Na_2SO_4), and concentrated. The obtained crude product was purified by SiO_2 column chromatography (hexane/AcOEt = 15/1) to give the desired product (*E*)-**4-2a** (3.46 g, 60%, *E*/*Z* = >98:2).

(*Z*)-4-2a (method B); Typical Gram-Scale Procedure

TsCl (4.29 g, 23 mmol) in MeCN (15 mL) was added to a stirred suspension of methyl 2-butyl-3-oxooctanoate (**4-1a**; 3.42 g, 15 mmol), TMEDA (3.35 mL, 23 mmol), and LiCl (954 mg, 23 mmol) in MeCN (15 mL) at 0 − 5 °C, and the mixture was stirred at the same temperature for 1 h and 20 − 25 °C for 1 h. Water was added to the mixture, which was extracted twice with AcOEt. The combined organic phase was washed with water,

saturated $NaHCO_3$ aqueous solution, brine, dried (Na_2SO_4), and concentrated. The obtained crude product was purified by SiO_2 column chromatography (hexane/AcOEt = 10/1) to give the desired product (*Z*)-**4-2a** (4.74 g, 82%, *E*/*Z* = 2:>98).

Methyl (*E*)-2-butyl-3-(tosyloxy)oct-2-enoate [(*E*)-4-2a][=(*E*)-5-4a]

Yield: 282 mg (74%); colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.81 (t, *J* = 7.2 Hz, 3H), 0.82 (t, *J* = 7.2 Hz, 3H), 1.10−1.27 (m, 8H), 1.43 (quin, *J* = 7.2 Hz, 2H), 2.18 (t, *J* = 7.2 Hz, 2H), 2.46 (s, 3H), 2.60 (t, *J* = 7.6 Hz, 2H), 3.74 (s, 3H), 7.31−7.40 (m, 2H), 7.80−7.88 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 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 (2C), 129.8 (2C), 134.2, 145.2, 156.6, 168.1; IR (neat): ν_{max} = 2956, 2931, 2872, 1720, 1644, 1598, 1435, 1374 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{20}H_{30}O_5S$ $[M+Na]^+$ 405.1712; found: 405.1710.

Methyl (*Z*)-2-butyl-3-(tosyloxy)oct-2-enoate [(*Z*)-4-2a][=(*Z*)-5-4a]

Yield: 356 mg (93%); colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.78−0.95 (m, 6H), 1.12−1.53 (m, 10H), 2.25 (t, *J* = 7.6 Hz, 2H), 2.31 (t, *J* = 7.6 Hz, 2H), 2.45 (s, 3H), 3.59 (s, 3H), 7.29−7.38 (m, 2H), 7.75−7.85 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7 (2C), 21.5, 22.17, 22.22, 26.2, 29.0, 30.8, 30.9, 31.1, 51.7, 125.0, 127.9 (2C), 129.6 (2C), 134.0, 144.9, 151.2, 167.1; IR (neat): ν_{max} = 2959, 2872, 1728, 1655, 1599, 1458, 1375, 1310 cm^{-1}.

Methyl (*E*)-2-methyl-3-(tosyloxy)but-2-enoate [(*E*)-4-2b][=(*E*)-5-4b]

Yield: 3.57 g (84%) (15 mmol scale); colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.69 (s, 3H), 2.30 (s, 3H), 2.27 (s, 3H), 3.74 (s, 3H), 7.37 (d, *J* = 8.6 Hz, 2H), 7.84 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.4, 19.8, 21.6, 51.8, 120.6, 127.8 (2C), 129.9 (2C), 133.8, 145.4, 154.9, 167.8; IR (neat): ν_{max} = 2953, 1719, 1655, 1597, 1369, 1281, 1171, 1080, 968, 899, 808, 723 cm^{-1}.

Methyl (*Z*)-2-methyl-3-(tosyloxy)but-2-enoate [(*Z*)-4-2b][=(*Z*)-5-4b]

Yield: 2.06 g (72%) (10 mmol scale); colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.87 (s, 3H), 2.02 (s, 3H), 2.46 (s, 3H), 3.58 (s, 3H), 7.35 (d, *J* = 8.6 Hz, 2H), 7.82 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.9, 18.2, 21.5, 51.7, 119. 6, 128.0 (2C), 129.6 (2C), 133.7, 145.1, 147.9, 166.7; IR (neat): ν_{max} = 2953, 1717, 1597, 1435, 1368, 1306, 1169, 1088, 970, 883, 806, 773, 739, 664 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{13}H_{16}O_5S$ $[M+Na]^+$ 307.0616; found: 307.0616.

Methyl (*E*)-2-butyl-3-(tosyloxy)but-2-enoate [(*E*)-4-2c][=(*E*)-5-4c]

Yield: 263 mg (81%); colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.81 (t, *J* = 6.9 Hz, 3H), 1.10−1.26 (m, 4H), 2.17 (t, *J* = 6.9 Hz, 2H), 2.27 (s, 3H), 2.46 (s, 3H), 3.74 (s, 3H), 7.33−7.42 (m, 2H), 7.80−7.88 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.6, 19.4, 21.6, 22.5, 27.4, 30.3, 51.8, 125.4, 127.8 (2C), 129.9 (2C), 134.1, 145.3, 153.4, 168.0; IR (neat): ν_{max} = 2956, 1719, 1650, 1598, 1435, 1372, 1279, 1088 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{16}H_{22}O_5S$ $[M+Na]^+$ 349.1086; found: 349.1097.

Methyl (*Z*)-2-butyl-3-(tosyloxy)but-2-enoate [(*Z*)-4-2c][=(*Z*)-5-4c]

Yield: 312 mg (96%); colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.2 Hz, 3H), 1.21−1.42 (m, 4H), 2.02 (s, 3H), 2.23 (t, *J* = 7.2 Hz, 2H), 2.44 (s, 3H), 3.57 (s, 3H), 7.30−7.39 (m, 2H), 7.75−7.84 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.5, 17.7, 21.4, 22.0, 28.9, 30.2, 51.5, 124.7, 127.8 (2C), 129.5 (2C), 133.5, 145.0, 147.3, 166.6; IR (neat): ν_{max} = 2956, 1724, 1598, 1370, 1306, 1196, 1164, 1090 cm^{-1}.

Methyl 2-butyl-2-chloro-3-oxooctanoate (by-product)

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.2 Hz, 3H), 0.91 (t, *J* = 7.2 Hz, 3H), 1.20−1.43 (m, 8H), 1.62 (quin, *J* = 7.2 Hz, 2H), 2.04−2.25 (m, 2H), 2.58 (dt, *J* = 7.2 Hz, *Jgem* = 17.9 Hz, 1H), 2.72 (dt, *J* = 7.2 Hz, *Jgem* = 17.5 Hz, 1H), 3.81 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.7 (2C), 22.3, 22.4, 23.5, 26.1, 30.9, 36.3, 37.9, 53.4, 75.9, 168.0, 200.8; IR (neat): ν_{max} = 2958, 2873, 1727, 1467, 1436, 1314, 1244, 1208 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{13}H_{23}ClO_3$ $[M+Na]^+$ 285.1233; found: 285.1247.

Methyl (*E*)-2-isopropyl-3-(tosyloxy)but-2-enoate [(*E*)-4-2d][=(*E*)-5-4d]

Yield: 131 mg (84%) (0.5 mmol scale); pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.94 (d, *J* = 6.9 Hz, 6H), 2.04 (s, 3H), 2.46 (s, 3H), 2.85 (sep, *J* = 6.9 Hz, 1H), 3.75 (s, 3H), 7.33−7.39 (m, 2H), 7.80−7.87 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.9, 20.3 (2C), 21.5, 27.2, 51.5, 127.8 (2C), 129.8 (2C), 131.4, 133.8, 145.3, 147.0, 167.9; IR (neat): ν_{max} = 1968, 1725, 1667, 1598, 1435, 1372, 1276, 1193 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{15}H_{20}O_5S$ $[M+Na]^+$ 335.0929; found: 335.0928.

Methyl (*Z*)-2-isopropyl-3-(tosyloxy)but-2-enoate [(*Z*)-4-2d][=(*Z*)-5-4d]

Yield: 133 mg (85%) (0.5 mmol scale); pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.08 (d, *J* = 6.9 Hz, 6H), 2.05 (s, 3H), 2.45 (s, 3H), 2.62 (sep, *J* = 6.9 Hz, 1H), 3.55 (s, 3H), 7.30−7.38 (m, 2H), 7.76−7.82 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.8, 20.7 (2C), 21.6, 28.7, 51.4, 127.9 (2C), 129.6 (2C), 130.7, 133.8, 143.9, 145.0, 166.5; IR (neat): ν_{max} = 2929, 2859, 1718, 1621, 1442, 1254, 1200, 1089 cm^{-1}.

Methyl (*E*)-2-methyl-3-(tosyloxy)hept-2-enoate [(*E*)-4-2e][=(*E*)-5-4c']

Yield: 1.21 g (74%) (5 mmol scale); pale yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.81 (t, *J* = 7.5 Hz, 3H), 1.22 (sext, *J* = 7.5 Hz, 2H), 1.43 (quin, *J* = 7.5 Hz, 2H), 1.72 (s, 3H), 2.47 (s, 3H), 2.70 (t, *J* = 7.5 Hz, 2H), 3.74 (s, 3H), 7.34–7.39 (m, 2H), 7.82–7.87 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.4, 13.7, 21.5, 21.9, 28.9, 31.7, 51.8, 120.8, 127.7 (2c), 129.8 (2C), 134.0, 145.3, 158.5, 167.8; IR (neat): ν_{max} = 1721, 1435, 1371, 1308, 1394, 1271, 1192, 1180, 1163 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{16}H_{22}O_5S$ $[M+Na]^+$ 349.1086; found: 349.1078.

Methyl (*Z*)-2-methyl-3-(tosyloxy)hept-2-enoate [(*Z*)-4-2e][=(*Z*)-5-4c']

Yield: 607 mg (62%) (3 mmol scale); pale yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.83 (t, *J* = 7.5 Hz, 3H), 1.25 (sext, *J* = 7.5 Hz, 2H), 1.44 (quin, *J* = 7.5 Hz, 2H), 1.90 (s, 3H), 2.33 (t, *J* = 7.5 Hz, 2H), 2.46 (s,

3H), 3.60 (s, 3H), 7.31–7.38 (m, 2H), 7.82–7.85 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.4, 14.7, 21.3, 21.8, 28.1, 30.9, 51.5, 119.6, 127.8 (2c), 129.5 (2C), 133.9, 144.9, 151.6, 166.8; IR (neat): ν_{max} = 1720, 1435, 1371, 1306, 1277, 1190, 1179, 1167, 1107 cm^{-1}.

Methyl (*E*)-2-methyl-3-(tosyloxy)oct-2-enoate [(*E*)-4-2f]

Yield: 253 mg (74%); colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.83 (t, *J* = 7.2 Hz, 3H), 1.10−1.26 (m, 4H), 1.43 (quin, *J* = 7.2 Hz, 2H), 1.73 (s, 3H), 2.47 (s, 3H), 2.68 (t, *J* = 7.2 Hz, 2H), 3.74 (s, 3H), 7.33−7.40 (m, 2H), 7.81−7.88 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8 (2C), 21.5, 22.1, 26.6, 31.1, 32.0, 51.8, 120.8, 127.7 (2C), 129.8 (2C), 134.1, 145.3, 158.6, 167.8; IR (neat): ν_{max} = 2954, 1720, 1650, 1598, 1435, 1373, 1276, 1191 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{17}H_{24}O_5S$ $[M+Na]^+$ 363.1242; found: 363.1246.

Methyl (*Z*)-2-methyl-3-(tosyloxy)oct-2-enoate [(*Z*)-4-2f]

Yield: 319 mg (94%); colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.84 (t, *J* = 7.2 Hz, 3H), 1.11−1.32 (m, 4H), 1.38−1.52 (m, 2H), 1.89 (s, 3H), 2.32 (t, *J* = 7.2 Hz, 2H), 2.45 (s, 3H), 3.60 (s, 3H), 7.30−7.39 (m, 2H), 7.76−7.87 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7, 14.8, 21.5, 22.1, 25.9, 31.0, 31.3, 51.7, 119.7, 127.9 (2C), 129.6 (2C), 134.1, 145.0, 151.9, 167.0; IR (neat): ν_{max} = 2954, 2863, 1715, 1598, 1434, 1372, 1306, 1180 cm^{-1}.

Methyl (*E*)-7-chloro-2-methyl-3-(tosyloxy)hept-2-enoate [(*E*)-4-2g][= (*E*)-5-4g]

Yield: 276 mg (77%); pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.57−1.72 (m, 4H), 1.73 (s, 3H), 2.47 (s, 3H), 2.75 (t, *J* = 6.5 Hz, 2H), 3.46 (t, *J* = 6.5 Hz, 2H), 3.75 (s, 3H), 7.34−7.41 (m, 2H), 7.81−7.88 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7, 21.4, 24.0, 31.1, 31.5, 44.2, 51.8, 121.3, 127.6 (2C), 129.8 (2C), 133.7, 145.4, 157.4, 167.5; IR (neat): ν_{max} = 2952, 1719, 1648, 1435, 1371, 1278, 1191, 1177 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{16}H_{21}O_5ClS$ $[M+Na]^+$ 383.0696; found: 383.0678.

Methyl (*Z*)-7-chloro-2-methyl-3-(tosyloxy)hept-2-enoate [(*Z*)-4-2g][= (*Z*)-5-4g]

Yield: 306 mg (85%); pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.58−1.83 (m, 4H), 1.90 (s, 3H), 2.38 (t, *J* = 6.9 Hz, 2H), 2.45 (s, 3H), 3.46 (t, *J* = 6.5 Hz, 2H), 3.59 (s, 3H), 7.32−7.38 (m, 2H), 7.79−7.85 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.6, 21.3, 23.3, 30.2, 31.3, 44.0, 51.5, 120.1, 127.6 (2C), 129.5 (2C), 133.5, 145.0, 150.5, 166.5; IR (neat): ν_{max} = 2952, 1720, 1598, 1435, 1371, 1307, 1108, 1086 cm^{-1}.

Methyl (*E*)-2-(non-8-en-1-yl)-3-(tosyloxy)trideca-2,12-dienoate [(*E*)-4-2h]

Yield: 327 mg (63%); colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.08−1.49 (m, 22H), 1.96−2.08 (m, 4H), 2.17 (t, *J* = 7.6 Hz, 2H), 2.46 (s, 3H), 2.60 (t, *J* = 7.6 Hz, 2H), 3.74 (s, 3H), 4.89−5.05 (m, 4H), 5.81 (ddt, *J* = 6.9, 10.3, 16.9 Hz, 2H), 7.33−7.39 (m, 2H), 7.81−7.87 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.6, 27.1, 27.9, 28.1, 28.83, 28.85, 28.91, 28.98, 29.02 (2C), 29.09, 29.2, 29.3, 32.2, 33.7 (2C), 51.8, 114.1 (2C), 125.8, 127.8 (2C), 129.8 (2C), 134.3, 139.1 (2C), 145.2, 156.7, 168.1 ; IR (neat): ν_{max} = 2927, 2854, 1720, 1640, 1598, 1376, 1192, 1178 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{30}H_{46}O_5S$ $[M+Na]^+$ 541.2964; found: 541.2944.

Methyl (*Z*)-2-(non-8-en-1-yl)-3-(tosyloxy)trideca-2,12-dienoate [(*Z*)-4-2h]

Yield: 474 mg (91%); colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.15−1.52 (m, 22H), 2.03 (q, *J* = 6.9 Hz, 4H), 2.24 (t, *J* = 7.6 Hz, 2H), 2.30 (t, *J* = 7.6 Hz, 2H), 2.45 (s, 3H), 3.59 (s, 3H), 4.89−5.04 (m, 4H), 5.80 (ddt, *J* = 6.9, 10.3, 16.9 Hz, 1H), 5.81 (ddt, *J* = 6.9, 10.3, 16.9 Hz, 1H), 7.31−7.37 (m, 2H), 7.78−7.85 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.5, 26.5, 28.6, 28.7, 28.7, 28.8, 28.91, 28.93, 28.98, 29.0 (2C), 29.16, 29.18, 30.9, 33.6 (2C), 51.6, 114.1 (2C), 125.0, 127.9 (2C), 129.5 (2C), 134.0, 138.86, 138.89, 144.9, 151.1, 167.0; IR (neat): ν_{max} = 2926, 2855, 1726, 1640, 1599, 1376, 1194, 1180 cm^{-1}.

Methyl (*E*)-2-methyl-3-phenyl-3-(tosyloxy)acrylate [(*E*)-4-2i][=(*E*)-5-2a]

Yield: 309 mg (89%); colorless crystals; mp 68–69 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.06 (s, 3H), 2.36 (s, 3H), 3.51 (s, 3H), 7.07−7.27 (m, 7H), 7.41−7.46 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.8, 21.5, 51.8, 123.1, 127.6 (2C), 127.8 (2C), 128.7 (2C), 129.2, 129.3 (2C), 133.4, 133.8, 144.8, 151.6, 168.4; IR (neat): ν_{max} = 1714, 1657, 1599, 1439, 1364, 1322, 1191, 1176 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{18}H_{18}O_5S$ $[M+Na]^+$ 369.0773; found: 369.0758.

Methyl (*Z*)-2-methyl-3-phenyl-3-(tosyloxy)acrylate [(*Z*)-4-2i][=(*Z*)-5-2a]

Yield: 312 mg (90%); colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.94 (s, 3H), 2.35 (s, 3H), 3.81 (s, 3H), 7.04−7.10 (m, 2H), 7.14−7.30 (m, 5H), 7.38−7.45 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.6, 21.1, 51.8, 120.9, 127.5 (2C), 127.6 (2C), 128.9 (2C), 129.0 (2C), 129.1, 131.8, 133.7, 144.3, 147.9, 166.9; IR (neat): ν_{max} = 2952, 1715, 1598, 1434, 1374, 1308, 1255, 1002 cm^{-1}.

Methyl (*E*)-2-methyl-3-(4-tolyl)-3-(tosyloxy)acrylate [(*E*)-4-2j][=(*E*)-5-2a']

Yield: 864 mg (80%) (3 mmol scale); colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.03 (s, 3H), 2.29 (s, 3H), 2.43 (m, 3H), 3.53 (s, 3H), 6.92−6.97 (m, 2H), 7.01−7.06 (m, 2H), 7.08−7.14 (m, 2H), 7.43−7.49 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.6, 21.1, 21.3, 51.6, 122.1, 127.7 (2C), 128.2 (2C), 128.5 (2C), 129.2 (2C), 130.3, 133.7, 139.2, 144.6, 151.7, 168.4; IR (neat): ν_{max} = 1717, 1651, 1597, 1435, 1371, 1240, 1190 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{19}H_{20}O_5S$ $[M+Na]^+$ 383.0929; found: 383.0926.

Methyl (*Z*)-2-methyl-3-(4-tolyl)-3-(tosyloxy)acrylate [(*Z*)-4-2j][=(*Z*)-5-2a']

Yield: 970 mg (89%) (3 mmol scale); colorless crystals; mp 94–96 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.92 (s, 3H), 2.30 (s, 3H), 2.36 (s, 3H), 3.78 (s, 3H), 6.95−7.01 (m, 2H), 7.04−7.13 (m, 4H), 7.39−7.46 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.9, 21.2, 21.4, 52.0, 120.6, 127.9 (2C), 128.5 (2C), 129.1 (2C), 129.2 (2C), 129.3, 134.2, 140.0, 144.3, 148.5, 167.3; IR (neat): ν_{max} = 1726, 1645, 1425, 1369, 1258, 1179, 1134 cm^{-1}.

Methyl (*E*)-3-(4-methoxyphenyl)-2-methyl-3-(tosyloxy)acrylate [(*E*)-4-2k][=(*E*)-5-2b']

Yield: 3.39 g (90%) (10 mmol scale); colorless crystals; mp 73–75 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.04

(s, 3H), 2.38 (s, 3H), 3.54 (s, 3H), 3.77 (s, 3H), 6.63–6.67 (m, 2H), 7.05–7.09 (m, 2H), 7.11–7.15 (m, 2H), 7.44–7.49 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.6, 21.3, 51.6, 55.0, 112.9 (2C), 121.6, 125.4, 127.7 (2C), 129.4 (2C), 130.1 (2C), 133.8, 144.6, 151.6, 160.2, 168.4; IR (neat): ν_{max} = 1717, 1607, 1508, 1369, 1250, 1190, 1175 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{19}H_{20}O_6S$ $[M+Na]^+$ 399.0878; found: 399.0864.

Methyl (*Z*)-3-(4-methoxyphenyl)-2-methyl-3-(tosyloxy)acrylate [(*Z*)-4-2k][=(*Z*)-5-2b']

Yield: 3.68 g (98%) (10 mmol scale); colorless crystals; mp 70–71 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.94 (s, 3H), 2.37 (s, 3H), 3.78 (s, 3H), 3.79 (s, 3H), 6.66–6.73 (m, 2H), 7.07–7.17 (m, 4H), 7.41–7.49 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.0, 21.5, 52.0, 55.3, 113.3 (2C), 120.1, 124.4, 127.9 (2C), 129.2 (2C), 130.9 (2C), 134.3, 144.4, 148.5, 160.4, 167.4; IR (neat): ν_{max} = 1724, 1645, 1607, 1508, 1456, 1371, 1256, 1244, 1184 cm^{-1}.

Methyl (*E*)-2-methyl-3-(4-chlorophenyl)-3-(tosyloxy) acrylate [(*E*)-4-2l][=(*E*)-5-2c']

Yield: 982 mg (94%) (3 mmol scale); colorless crystals; mp 71–73 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.06 (s, 3H), 2.40 (s, 3H), 3.54 (s, 3H), 7.04−7.12 (m, 4H), 7.13−7.17 (m, 2H), 7.42−7.48 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.7, 21.5, 52.0, 123.5, 127.8 (2C), 127.9 (2C), 129.4 (2C), 130.2 (2C), 131.8, 133.7, 135.3, 145.2, 150.5, 168.0; IR (neat): IR (neat): ν_{max} = 1722, 1651, 1593, 1487, 1371, 1244, 1190 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{18}H_{17}O_5ClS$ $[M+Na]^+$ 403.0383; found: 403.0377.

Methyl (*Z*)-2-methyl-3-(4-chlorophenyl)-3-(tosyloxy) acrylate [(*Z*)-4-2l][=(*Z*)-5-2c']

Yield: 1.01 g (96%) (3 mmol scale); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.92 (s, 3H), 2.38 (s, 3H), 3.80 (s, 3H), 7.09−7.18 (m, 4H), 7.13−7.15 (m, 2H), 7.41−7.46 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.8, 21.4, 52.1, 121.7, 127.8 (2C), 128.2 (2C), 129.2 (2C), 129.5, 130.6 (2C), 133.9, 135.5, 144.8, 146.9, 166.9; IR (neat): ν_{max} = 1732, 1595, 1489, 1435, 1314, 1248, 1161 cm^{-1}.

Methyl (*E*)-2,3-diphenyl-3-(tosyloxy)acrylate [(*E*)-4-2m]

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; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.35 (s, 3H), 3.50 (s, 3H), 6.94−7.03 (m, 2H), 7.17−7.50 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.5, 52.3, 127.3, 127.7 (2C), 128.0 (2C), 128.1 (2C), 128.2, 128.6 (2C), 129.0 (2C), 129.2 (2C), 129.8, 132.2, 133.2, 133.4, 144.6, 149.1, 167.6; IR (neat): ν_{max} = 1717, 1651, 1595, 1445, 1368, 1302, 1273, 1215, 1175 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{23}H_{20}O_5S$ $[M+Na]^+$ 431.0929; found: 431.0907.

Methyl (*Z*)-2,3-diphenyl-3-(tosyloxy)acrylate [(*Z*)-4-2m]

Yield: 381 mg (93%); colorless crystals; mp 111–112 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.38 (s, 3H), 3.80 (s, 3H), 6.96−7.06 (m, 4H), 7.08−7.22 (m, 8H), 7.47−7.53 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.5, 52.5, 126.9, 127.0, 127.7 (2C), 128.0 (2C), 128.1, 128.3 (2C), 129.3 (2C), 129.7 (2C), 129.9 (2C), 131.9, 133.1, 134.0, 144.7, 148.5, 166.5; IR (neat): ν_{max} = 1726, 1448, 1431, 1369, 1253, 1209, 1174, 1053 cm^{-1}.

Methyl (*E*)-3-(4-methoxyphenyl)-2-phenyl-3-(tosyloxy)acrylate [(*E*)-4-2n]

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; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.35 (s, 3H), 3.53 (s, 3H), 3.82 (s, 3H), 6.73−6.83 (m, 2H), 6.94−7.07 (m, 2H), 7.14−7.30 (m, 5H), 7.34−7.44 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.5, 52.3, 55.2, 113.4 (2C), 125.6, 126.1, 127.8 (2C), 128.0 (3C), 129.0 (2C), 129.2 (2C), 130.2 (2C), 132.5, 133.4, 144.5, 149.3, 160.7, 167.8; IR (neat): ν_{max} = 1720, 1633, 1605, 1506, 1435, 1375, 1206 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{24}H_{22}O_6S$ $[M+Na]^+$ 461.1035; found: 461.1030.

Methyl (*Z*)-3-(4-methoxyphenyl)-2-phenyl-3-(tosyloxy)acrylate [(*Z*)-4-2n]

Yield: 13.04 g (99%) (30 mmol scale); colorless crystals; mp 123–125 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.40 (s, 3H), 3.72 (s, 3H), 3.77 (s, 3H), 6.47−7.56 (m, 2H), 6.90−7.00 (m, 2H), 7.06−7.24 (m, 7H), 7.48−7.59 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.5, 52.3, 55.1, 113.2 (2C), 124.1, 125.6, 127.9, 128.0 (2C), 128.3 (2C),129.2 (2C), 129.7 (2C), 131.5 (2C), 133.5, 134.2, 144.6, 148.8, 160.2, 166.6; IR (neat): ν_{max} = 1726, 1636, 1608, 1433, 1317, 1252, 1192 cm^{-1}.

Methyl (*Z*)-2-methoxy-3-(tosyloxy)oct-2-enoate [(*Z*)-4-2o][= (*Z*)-3.3-4g]

Yield: 322 mg (90%); pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85 (t, *J* = 7.2 Hz, 3H), 1.14−1.34 (m, 4H), 1.50 (quin, *J* = 7.6 Hz, 2H), 2.45 (s, 3H), 2.71 (t, *J* = 7.6 Hz, 2H), 3.42 (s, 3H), 3.81 (s, 3H), 7.30−7.37 (m, 2H), 7.83−7.91 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7, 21.5, 22.1, 26.2, 30.6, 30.9, 52.0, 60.0, 127.8 (2C), 129.5 (2C), 134.4, 139.4, 144.9, 151.2, 163.9; IR (neat): ν_{max} = 2935, 1725, 1642, 1598, 1371, 1297, 1179, 1024 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{17}H_{24}O_6S$ $[M+Na]^+$ 379.1191; found: 379.1199.

Methyl (*E*)-2-methoxy-3-(tosyloxy)oct-2-enoate [(*E*)-4-2o][= (*E*)-3.3-4g]

Yield: 325 mg (91%); pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.84 (t, *J* = 7.6 Hz, 3H), 1.11−1.30 (m, 4H), 1.43 (quin, *J* = 7.6 Hz, 2H), 2.40 (t, *J* = 7.6 Hz, 2H), 2.46 (s, 3H), 3.60 (s, 3H), 3.68 (s, 3H), 7.30−7.40 (m, 2H), 7.77−7.87 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 21.6, 22.1, 25.7, 29.1, 31.0, 51.9, 60.2, 128.1 (2C), 129.6 (2C), 133.5, 141.1, 145.3, 150.0, 162.2; IR (neat): ν_{max} = 2934, 2862, 1725, 1598, 1436, 1376, 1294, 1208 cm^{-1}.

Methyl (*Z*)-2-chloro-3-(tosyloxy)oct-2-enoate [(*Z*)-4-2p]

Yield: 296 mg (82%); colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 6.9 Hz, 3H), 1.20−1.33 (m, 4H), 1.50−1.62 (m, 2H), 2.47 (s, 3H), 2.92 (t, *J* = 7.6 Hz, 2H), 3.82 (s, 3H), 7.34−7.40 (m, 2H), 7.86−7.93 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7, 21.5, 22.0, 26.5, 30.9, 32.5, 53.0, 116.2, 128.0 (2C), 129.8 (2C), 133.6, 145.7, 159.6, 162.7; IR (neat): ν_{max} = 2959, 2866, 1724, 1615, 1384, 1262, 1180, 1047 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{16}H_{21}ClO_5S$ $[M+Na]^+$ 383.0696; found: 383.0711.

Methyl (*E*)-2-chloro-3-(tosyloxy)oct-2-enoate [(*E*)-4-2p]

Yield: 261 mg (62%); colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85 (t, *J* = 6.9 Hz, 3H), 1.16−1.30 (m, 4H), 1.42−1.56 (m, 2H), 2.47 (s, 3H), 2.53 (t, *J* = 7.6 Hz, 2H), 3.70 (s, 3H), 7.33−7.41 (m, 2H), 7.80−7.89 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7, 21.6, 22.1, 25.3, 30.9, 32.3, 52.9, 118.4, 128.2 (2C), 129.8 (2C), 133.3, 145.7, 155.1, 161.6; IR (neat): ν_{max} = 2955, 2862, 1734, 1622, 1597, 1435, 1382, 1256 cm^{-1}.

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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. 50 g-scale preparation of **4-1a** was performed by the self Ti-Claisen condensation using methyl hexanoate with $TiCl_4$ and Et_3N at 0 – 5 °C for 1 h (93% yield); see Experimental and ref. 8.
11. TMEDA: ca. \$80/500 g: $Me_2N(CH_2)_3NMe_2$: ca. \$110/500 g: $Me_2N(CH_2)_6NMe_2$: 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_2O 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*-MeC_6H_4COCl 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.
16. Oriyama's group reported a 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. 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.
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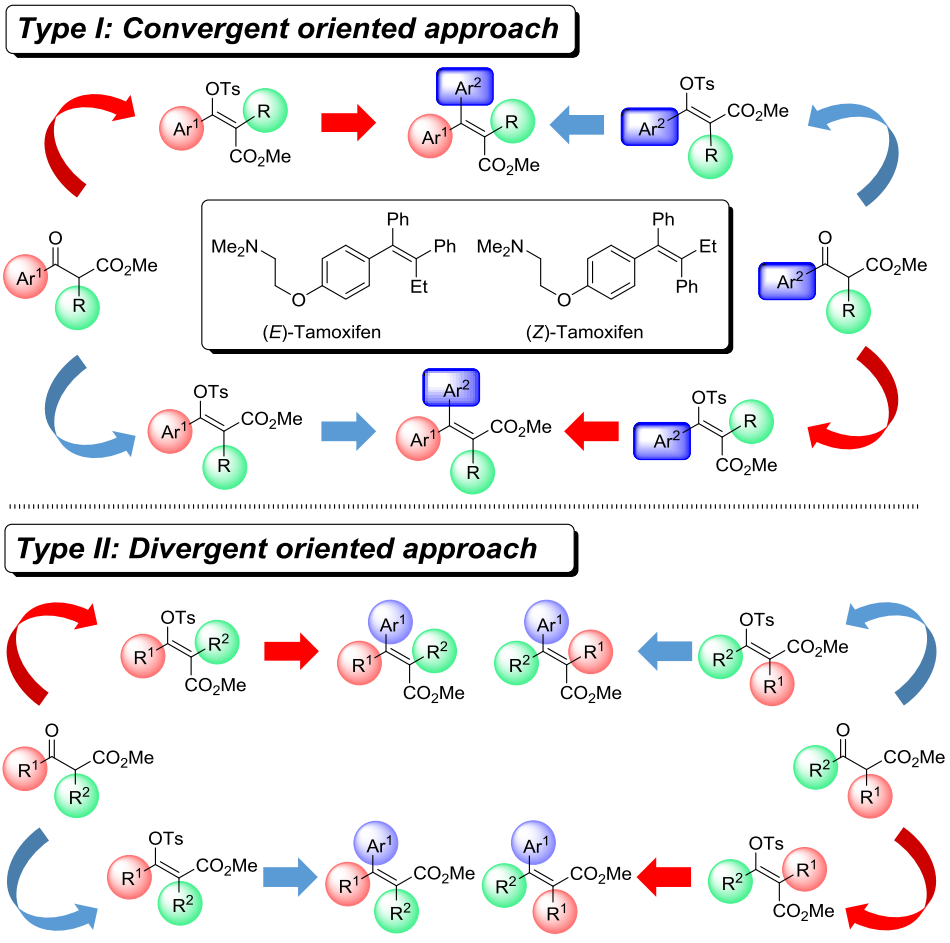
Chapter 5.
Divergent Synthetic Access to E- and Z-Stereodefined All-Carbon-Substituted Olefin Scaffolds: Application to Parallel Synthesis of (E)- and (Z)-Tamoxifens

Abstract

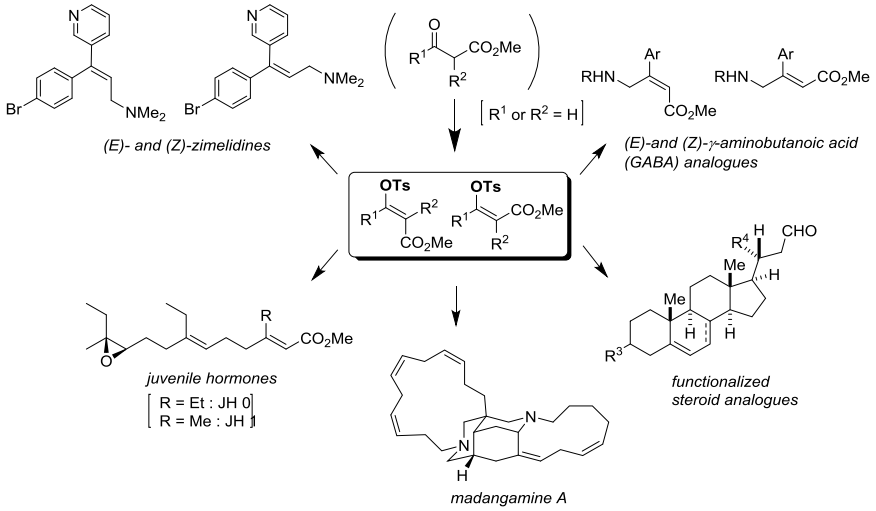
A highly substrate-general synthesis of all-carbon-substituted *E*- and *Z*-stereodefined olefins is performed. The method comprises two sets of parallel and stereocomplementary preparations of (*E*)- and (*Z*)-α,β-unsaturated esters involving two robust and distinctive reactions: 1) stereocomplementary enol tosylations using readily available TsCl/diamine/(LiCl) base reagents, and 2) stereoretentive Negishi cross-coupling using the catalysts [Pd(dppe)Cl_2] (for *E*) and [Pd(dppb)Cl_2] (for *Z*). The present parallel approach is categorized as both type I (convergent approach: 16 examples, 56–87% yield) and type II (divergent approach: 18 examples, 70–95% yield). The following two developments are performed by Atsushi Honda, one of our colleagues: (i) The obtained (*E*)- and (*Z*)-α,β-unsaturated ester scaffolds are successfully transformed into various *E*- and *Z*-stereodefined known and novel olefins (8x2 derivatization arrays). (ii) As a demonstration, application to the parallel synthesis of both (*E*)- and (*Z*)-tamoxifens, a representative motif of all-carbon-substituted olefins, is accomplished in a total of eight steps with an overall yield of 58% (average 93%) and 57% (average 93%), respectively.



Introduction

Regio- and stereo-controlled syntheses of *E*- and *Z*-stereodefined olefins are of pivotal importance in organic chemistry, because of their wide distribution in natural products, pharmaceuticals, and in supramolecules as key structural building blocks. Among the olefins, construction of acyclic stereodefined all-carbon-substituted olefins remains a challenge due to their structural complexity. Considerable efforts have been invested in this over the recent decades. The impressive progress in this area has been comprehensively reviewed.[1] The strategy for the synthesis of acyclic fully-substituted olefins is generally categorized into five approaches: 1) carbometalations of alkynes using Cu, B, Sn, Mg, Pd, and so forth, followed by reactions with electrophiles, 2) acid-induced carbonyl olefinations of unsymmetrically substituted ketones, 3) elimination reactions of tertiary alcohols, 4) cross-metatheses between olefins, and 5) ynolate-mediated reactions derived from α,α-dibromoesters.

Cross-coupling reactions with stereodefined enol sulfonate[2] and phosphonate[3] partners derived from β-ketoesters, which emerged in recent decades, are considered a promising and reliable approach compared with the above-mentioned methods, with the following advantages: 1) various starting β-ketoester substrates are readily available,[4] and 2) the *E*- and *Z*-stereocomplementary enol tosylation step is robust and costeffective.[5] *E*- and *Z*-stereoretention during the cross-coupling step is guaranteed, especially for Suzuki−Miyaura (SM) cross-coupling. Additionally, recent developments of cross-couplings using enol sulfonates facilitate and enhance this strategy. As depicted in **Scheme 5-1**, the current privileged protocols were adopted for the synthesis of "trisubstituted" (R^1 or R^2=H) elaborated natural products and pharmacophore-containing compounds, such as γ-aminobutanoic acid (GABA) analogues,[6] juvenile hormones 0 and I,[7] functionalized steroids,[8] madangamine A,[9] and (*E*)- and (*Z*)-zimelidines.[10]



Scheme 5-1. Synthetic applications of trisubstituted (*E*)- and (*Z*)-enol tosylates.

This background led us to envisage a highly substrate-general synthesis of fully all-carbon-substituted *E*- and *Z*-stereodefined olefins, and especially to focus on a parallel methodology. The author and co-workers present divergent access to a variety of acyclic stereodefined all-carbon-substituted olefins and the first

parallel synthesis of (*E*)- and (*Z*)-tamoxifens, representatives of these olefins (**Figure 5-1**).

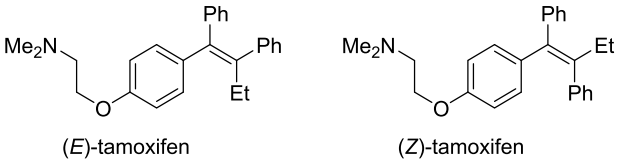
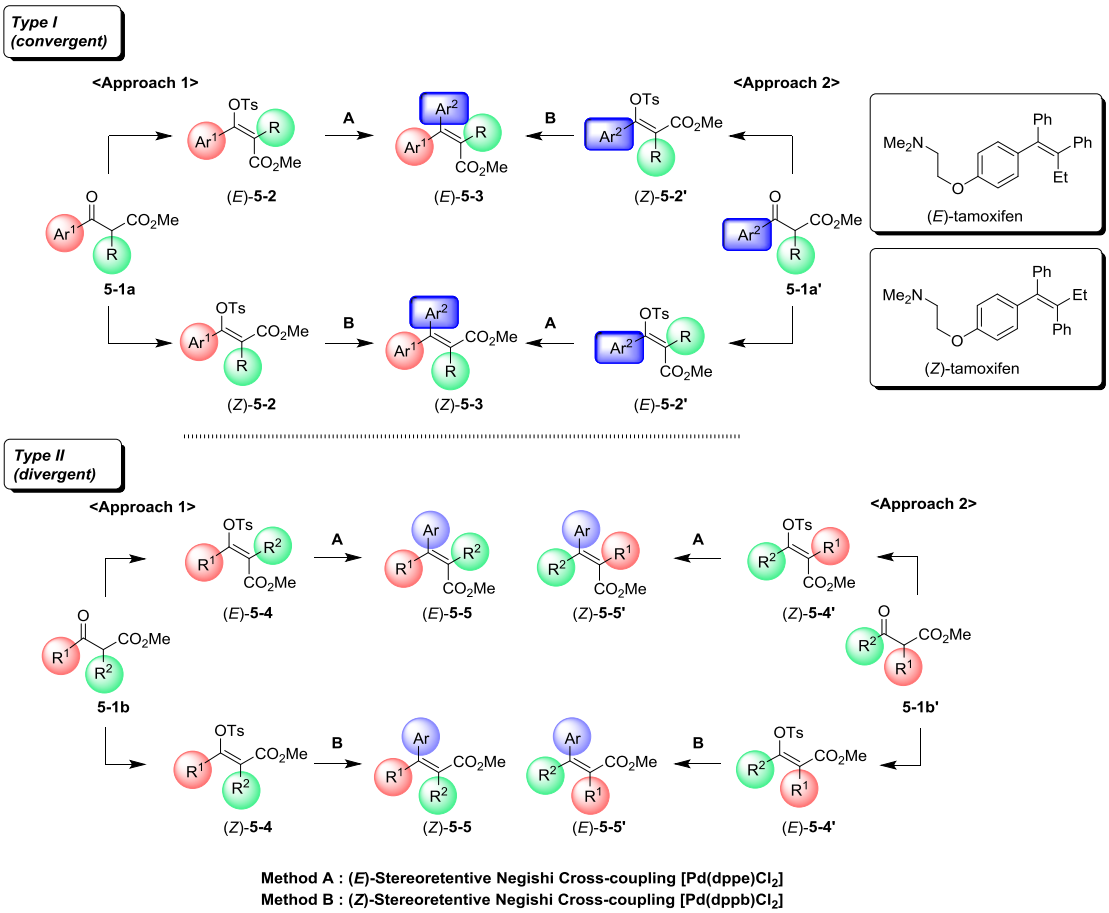


Figure 5-1. The structures of (*E*)- and (*Z*)-tamoxifens.

Results and Discussion

Stereocontrolled synthesis of ubiquitous (*E*)- and (*Z*)-α,β-unsaturated ester scaffolds occupies a central position in organic synthesis. Due to the intrinsic higher complexity in differentiating the substituents, synthesis of all-carbon-substituted *E*- and *Z*-stereodefined olefin precursors are not sufficiently established. Here we elaborate a plan for two distinctive parallel and stereoretentive syntheses for fully substituted (*E*)- and (*Z*)-α,β-unsaturated esters **5-3** and **5-5** starting from readily accessible β-ketoesters **5-1a** and **5-1b**, by utilizing type I and type II strategies via dual approaches 1 and 2 (**Scheme 5-2**).

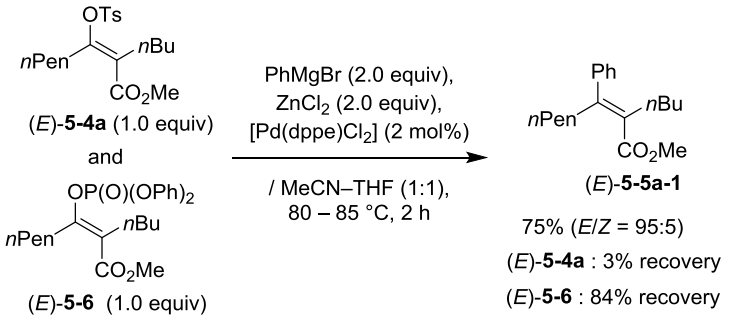


Scheme 5-2. Two types of parallel and stereoretentive syntheses of fully substituted (*E*)- and (*Z*)-α,β-unsaturated esters **5-3** and **5-5**.

In 2015, our group reported the synthesis of specific but substrate-general fully substituted α,β-diarylbut-2-enoic esters, utilizing a parallel approach.[10] Later in 2016, the Merck process group

independently disclosed asymmetric synthesis of α-methyl-β-cyclopropyldihydrocinnamates via the corresponding (*Z*)-enol tosylate of methyl 3-cyclopropyl-3-oxopropanoate (**Chapter 4, Scheme 4-2**).[11] Both methods utilize Suzuki−Miyaura (SM) cross-coupling for construction of the α,β-unsaturated esters. One key difference between the approaches of the two groups is the stereocomplementary enol tosylation reagents [our group: TsCl/*N*-methylimidazole or *N*,*N*,*N'*,*N'*-tetramethylenediamine (TMEDA)/LiCl; the Merck group: *para*-toluenesulfonic anhydride/lithium bis(trimethylsilyl)amide (LHMDS)].[12]

As part of our ongoing investigation,[13] it was recently observed that Negishi cross-coupling tends to exhibit higher reactivity with lower catalyst loadings for this type of synthetic approach (unpublished results). By contrast, enol phosphonates serve as effective SM and Negishi cross-coupling partners.[14] Against this background, as a preliminary evaluation, comparable Negishi cross-coupling experiments were examined using a 1:1 mixture of enol tosylate (*E*)-**5-4a** and enol phosphonate (*E*)-**5-6** (**Scheme 5-3**). The result indicated the superiority of (*E*)-**5-4a** as the cross-coupling partner. Thus, for this objective the author focused his attention on Negishi cross-coupling instead of SM cross-coupling using various enol tosylates **5-4**.

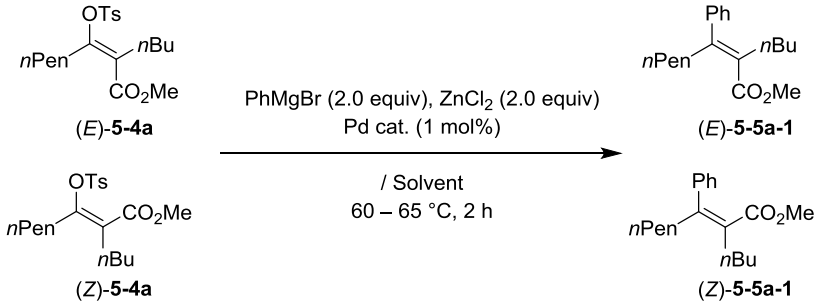


Scheme 5-3. Comparative experiment between enol tosylate (*E*)-**5-4a** and enol phosphonate (*E*)-**5-6**.

Starting enol tosylates **5-2** and **5-4** were conveniently prepared by using a recently improved robust and cost-effective method for *E*- and *Z*-stereocomplementary reactions of β-ketoesters [*E*: $Me_2N(CH_2)_6NMe_2$; *Z*: LiCl−TMEDA].[5]

The initial screening of several Pd catalysts for Negishi crosscoupling was guided by the reaction using intentionally less-reactive enol tosylates (*E*)-**5-4a** or (*Z*)-**5-4a** with PhMgBr/$ZnCl_2$ (in situ generation of PhZnCl; **Table 5-1**). Among them, [Pd(dppe)Cl_2] produced fruitful results in the *E*-stereoretentive reaction to give (*E*)-**5-5a-1** with high yield (82%) and selectivity (*E*/*Z*=96:4) in MeCN/THF (**Table 5-1**, entry 7). Notably, in contrast to the *E* isomer, reactions using (*Z*)-**5-4a** proceeded with nearly perfect *Z*-stereoretention in all cases examined to yield (*Z*)-**5-5a-1** and [Pd(dppb)Cl_2] afforded the best result (85 %, *E*/*Z*=2:98) in THF (**Table 5-1**, entry 5).

Table 5-1. Optimization of Negishi cross-coupling conditions.

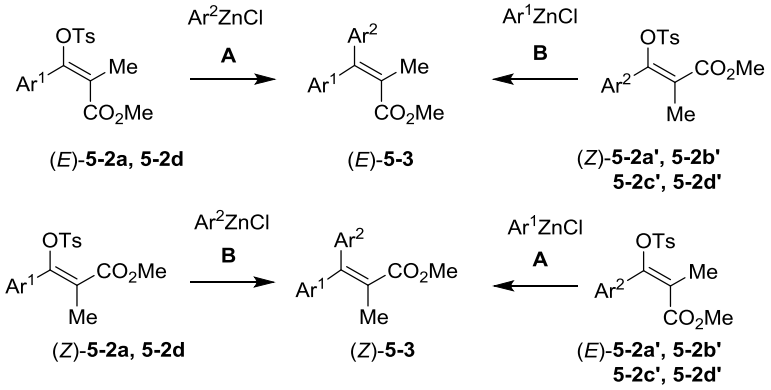


Entry	Catalyst	Solvent	Yield / % (E/Z)[a]	
			(E)-**5-5a-1**	(Z)-**5-5a-1**
1	$[Pd(PPh_3)_4]$	THF	4 (48:52)	74 (2:>98)
2	$[Pd(PPh_3)_2Cl_2]$	THF	8 (49:51)	38 (2:>98)
3	$[Pd(dppe)Cl_2]$	THF	24 (94:6)	39 (2:>98)
4	$[Pd(dppp)Cl_2]$	THF	42 (78:22)	43 (2:>98)
5	$[Pd(dppb)Cl_2]$	THF	47 (72:28)	**85 (2:>98)**
6	$[Pd(dppf)Cl_2]$	THF	28 (75:25)	12 (2:>98)
7	$[Pd(dppe)Cl_2]$	MeCN/THF (2:1)	**82**[b,c] **(96:4)**	–

a) Determined by ^{1}H NMR spectroscopy of the crude products.
b) $[Pd(dppe)Cl_2]$ (2 mol%). C) 80 – 85 °C.

Table 5-2 shows the successful results of the present parallel synthesis (type I) (convergent oriented approach) by using the Negishi cross-coupling method under optimized conditions A and B (**Table 5-1**). Ar^1ZnCl and Ar^2ZnCl reagents containing both electron-donating groups (*p*-Me, *p*-MeO) and an electron-withdrawing (*p*-Cl) group were applicable. Two pairs of Ar^1- and Ar^2-substituted enol tosylates, (E)-**5-2**, **5-2'** and (Z)-**5-2**, **5-2'**, were transformed into the corresponding products, (E)-**5-3**, **5-3'** and (Z)-**5-3**, **5-3'**, respectively, through dual convergent pathways. The salient features are as follows: 1) for the four sets examined, all reactions proceeded in good to excellent yield; 2) excellent *Z*-selectivity was produced in all eight cases; 3) *E*-selectivity was slightly decreased in a few cases (**Table 5-1**, entries 5, 9, and 13).

Table 5-2. Parallel and stereoretentive syntheses for fully substituted (*E*)- and (*Z*)-α,β-unsaturated esters **5-3** (type I, convergent). Method A: ArMgBr (2.0 equiv), $ZnCl_2$ (2.0 equiv), [Pd(dppe)Cl_2] (2 mol%), MeCN/THF (2:1), 60 °C, 2 h. Method B: [Pd(dppb)Cl_2] (1 mol%) and THF instead of those given for method A.



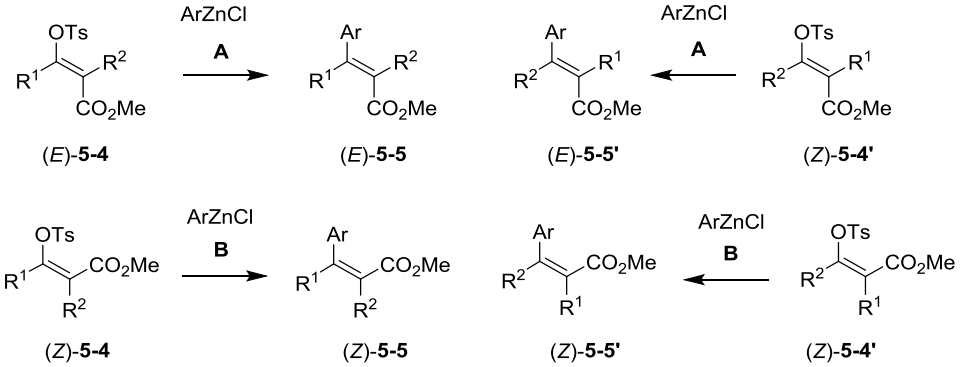
Entry	Ar^1	Ar^2	Substrate[a]	Method	Product	Yield / %	*E* / *Z* [b]
1	Ph	(*p*-Me)C_6H_4	(*E*)-**5-2a**	**A**	(*E*)-**5-3a**	75	84:16
2			(Z)-**5-2a**	**B**	(*Z*)-**5-3a**	84	2:>98
3			(*Z*)-**5-2a'**	**B**	(*E*)-**5-3a**	80	>98:2
4			(*E*)-**5-2a'**	**A**	(*Z*)-**5-3a**	83	2:>98
5	Ph	(*p*-MeO)C_6H_4	(*E*)-**5-2a**	**A**	(*E*)-**5-3b**	77	84:16
6			(Z)-**5-2a**	**B**	(*Z*)-**5-3b**	82	2:>98
7			(*Z*)-**5-2b'**	**B**	(*E*)-**5-3b**	80	>98:2
8			(*E*)-**5-2b'**	**A**	(*Z*)-**5-3b**	80	2:>98
9	Ph	(*p*-Cl)C_6H_4	(*E*)-**5-2a**	**A**	(*E*)-**5-3c**	54	83:17
10			(Z)-**5-2a**	**B**	(*Z*)-**5-3c**	85	2:>98
11			(*Z*)-**5-2c'**	**B**	(*E*)-**5-3c**	70	>98:2
12			(*E*)-**5-2c'**	**A**	(*Z*)-**5-3c**	70	2:>98
13	(*p*-MeO)C_6H_4	(*p*-Cl)C_6H_4	(*E*)-**5-2d**	**A**[c]	(*E*)-**5-3d**	85	68:32
14			(*Z*)-**5-2d**	**B**	(*Z*)-**5-3d**	80	2:>98
15			(*Z*)-**5-2d'**	**B**	(*E*)-**5-3d**	87	>98:2
16			(*E*)-**5-2d'**	**A**[c]	(*Z*)-**5-3d**	77	10:90

a) The purities of *E* and *Z* isomers were up to >98% based on the ^{1}H NMR spectra. b) Determined by ^{1}H NMR spectroscopy of the crude products. c) 3.0 equiv of ArZnCl was used in toluene at reflux.

Conversely, parallel synthesis (type II, divergent oriented approach) was investigated and the results are shown in **Table 5-3**. The salient features are as follows: 1) in all cases, good to excellent yield and almost perfect *E* and *Z* selectivities were achieved; 2) α,β-dimethyl enol tosylates (*E*)-**5-4b** and (*Z*)-**5-4b** were transformed into a total of six (*E*)- and (*Z*)-α,β-unsaturated ester analogues (*E*)-**5-5b** and (*Z*)-**5-5b** (**Table 5-3**, entries 1−6); 3) regioisomers (*E*)- and (*Z*)-**5-4c** and **5-4c'** afforded three sets of all four stereoisomers (*E*)- and (*Z*)-**5-5c-1**−**3** and **5-5c'-1**−**3** (**Table 5-3**, entries 7−10, 11−14, 15−18). To further strengthen the substrate

scope, seven syntheses using various (*E*)- and (*Z*)-α,β-unsaturated esters **5-5a** and **5-5d**−**g** are summarized in **Table 5-4**.

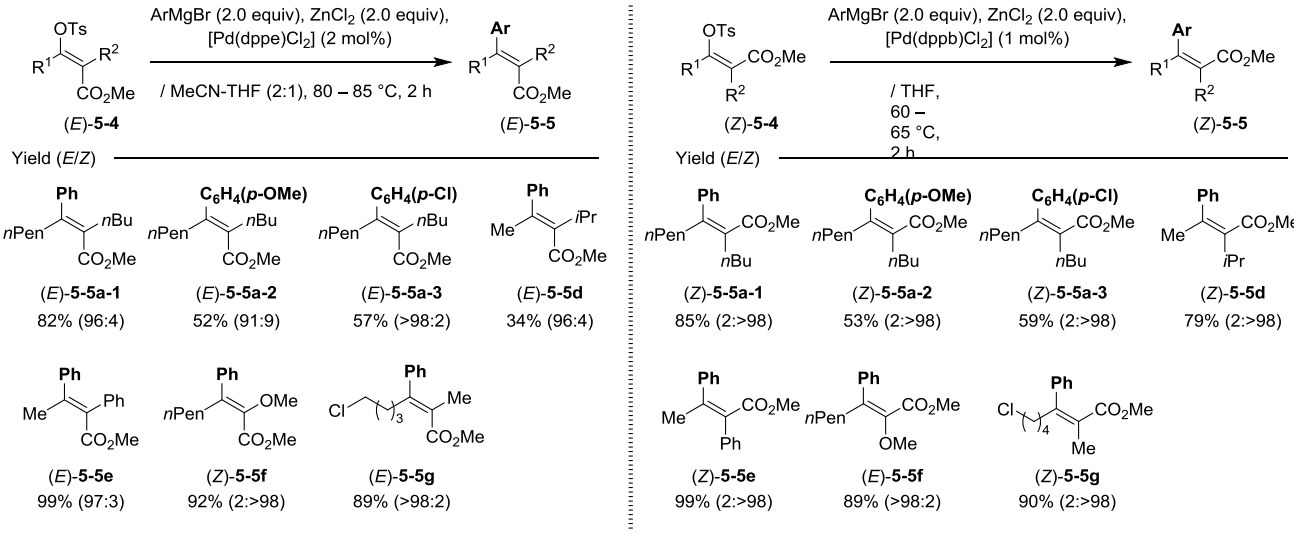
Table 5-3. Parallel and stereoretentive syntheses for fully substituted (*E*)- and (*Z*)-α,β-unsaturated esters **5-5** (type II, divergent). Method A: ArMgBr (2.0 equiv), $ZnCl_2$ (2.0 equiv), [Pd(dppe)Cl_2] (2 mol%), MeCN/THF (2:1), 60−65 °C, 2 h. Method B: [Pd(dppe)Cl_2] (1 mol%) and THF instead of those given for method A.



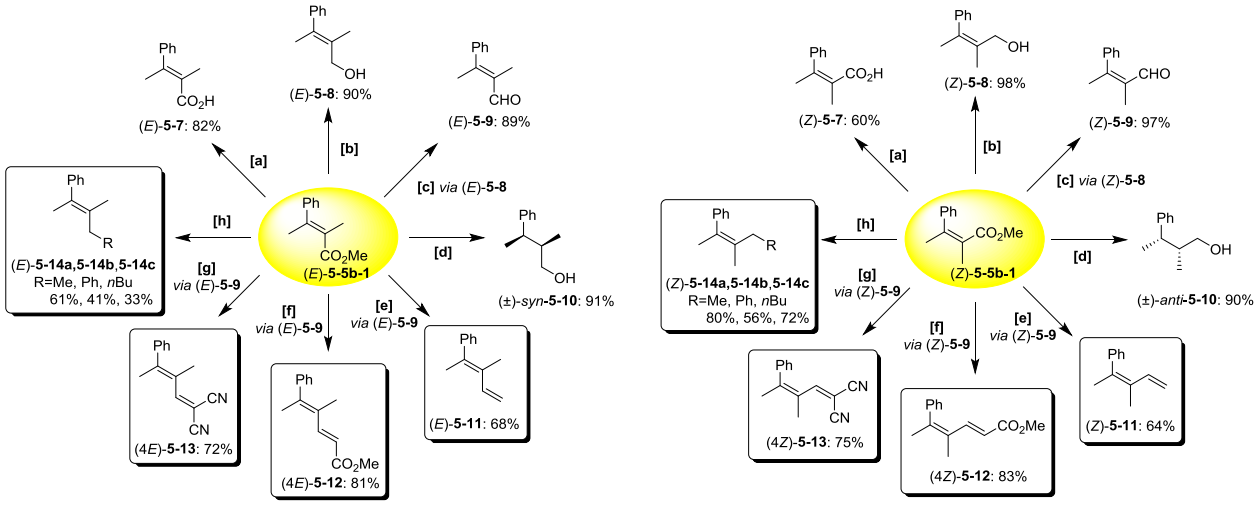
Entry	R^1	R^2	Substrate[a]	Ar	Method	Product	Yield / %	*E* / *Z* [b]
1	Me	Me	(*E*)-**5-4b**	Ph	**A**	(*E*)-**5-5b-1**	84	>98:2
2			(*Z*)-**5-4b**		**B**	(*Z*)-**5-5b-1**	83	2:>98
3	Me	Me	(*E*)-**5-4b**	(*p*-MeO)C_6H_4	**A**	(*E*)-**5-5b-2**	82	95:5
4			(*Z*)-**5-4b**		**B**	(*Z*)-**5-5b-2**	95	2:>98
5	Me	Me	(*E*)-**5-4b**	(*p*-Cl)C_6H_4	**A**	(*E*)-**5-5b-3**	93	98:2
6			(*Z*)-**5-4b**		**B**	(*Z*)-**5-5b-3**	80	2:>98
7	Me	*n*Bu	(*E*)-**5-4c**	Ph	**A**	(*E*)-**5-5c-1**	85	98:2
8			(*Z*)-**5-4c**		**B**	(*Z*)-**5-5c-1**	88	2:>98
9	Me	*n*Bu	(*E*)-**5-4c'**	Ph	**A**	(*E*)-**5-5c'-1**	72	>98:2
10			(*Z*)-**5-4c'**		**B**	(*Z*)-**5-5c'-1**	70	2:>98
11	Me	*n*Bu	(*E*)-**5-4c**	(*p*-MeO)C_6H_4	**A**	(*E*)-**5-5c-2**	89	91:9
12			(*Z*)-**5-4c**		**B**	(*Z*)-**5-5c-2**	91	2:>98
13	Me	*n*Bu	(*E*)-**5-4c'**	(*p*-MeO)C_6H_4	**A**	(*E*)-**5-5c'-2**	75	>98:2
14			(*Z*)-**5-4c'**		**B**	(*Z*)-**5-5c'-2**	82	2:>98
15	Me	*n*Bu	(*E*)-**5-4c**	(*p*-Cl)C_6H_4	**A**	(*E*)-**5-5c-3**	88	97:3
16			(*Z*)-**5-4c**		**B**	(*Z*)-**5-5c-3**	78	2:>98
17	Me	*n*Bu	(*E*)-**5-4c'**	(*p*-Cl)C_6H_4	**A**	(*E*)-**5-5c'-3**	78	>98:2
18			(*Z*)-**5-4c'**		**B**	(*Z*)-**5-5c'-3**	70	2:>98

a) The purities of *E* and *Z* isomers were up to >98% based on the ^{1}H NMR spectra. b) Determined by ^{1}H NMR spectroscopy of the crude products.

Table 5-4. Stereocomplementary syntheses for fully substituted (*E*)- and (*Z*)-α,β-unsaturated esters **5-5a** and **5-5d**−**g**.

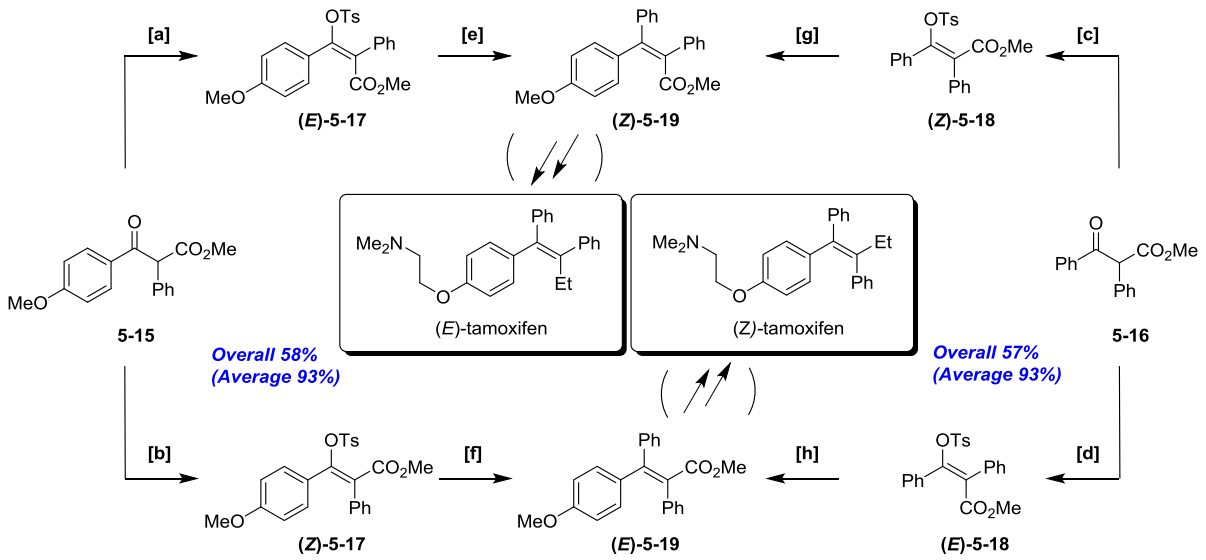


The next study was focused on stereoretentive and complementary derivatizations of (*E*)-**5-5b-1** and (*Z*)-**5-5b-1** to furnish various *E*- and *Z*-stereodefined fully substituted olefin scaffolds. A literature survey revealed few *E*- and *Z*-stereoretentive reactions of either α-alkyl- or aryl-substituted α,β-unsaturated esters.[1] **Scheme 5-4** shows the success of the derivatization array, which was performed by Atsushi Honda, one of the colleagues. Non-marked compounds **5-7**−**5-10** are known, whereas compounds **5-11**−**5-14** are novel. The reaction conditions can be summarized as follows: [a] acid hydrolysis gave acids (*E*)-**5-7** and (*Z*)-**5-7**;[15] [b] DIBAL reduction afforded allyl alcohols (*E*)-**5-8** and (*Z*)-**5-8**;[16] [c] MnO_2 allylic alcohol oxidation of (*E*)-**5-8** and (*Z*)-**5-8** yielded aldehydes (*E*)-**5-9** and (*Z*)-**5-9**, respectively;[16a] [d] dimethyl alcohols *syn*-**5-10** and isomeric *anti*-**5-10** were obtained by the reported catalytic hydrogenation (H_2−Pd/C), followed by lithium aluminum hydride (LAH) reduction.[16a] Conversion steps [b]−[d] were performed following the Serra group's reliable procedures; [e] Wittig methylene formation gave dienes (4*E*)-**5-11** and (4*Z*)-**5-11**; [f] Horner−Wadsworth−Emmons reaction using methyl phosphonoacetate yielded (2*E*,4*E*)-**5-12** and (2*E*,4*Z*)-**5-12**; [g] Knoevenagel condensation of (*E*)-**5-9** and (*Z*)-**5-9** under the Hayashi group's mild conditions[17] afforded (4*E*)-**5-13** and (4*Z*)-**5-13**; (h) notably, alkylations (Me and *n*Bu) and phenylation using acetates of (*E*)-**5-8** and (*Z*)-**5-8** proceeded smoothly to afford the corresponding all-carbon olefins (*E*)-**5-14a**−**c** and (*Z*)-**5-14a**−**c**; this finding was successfully applied for the parallel synthesis of (*E*)- and (*Z*)-tamoxifens (vide infra).



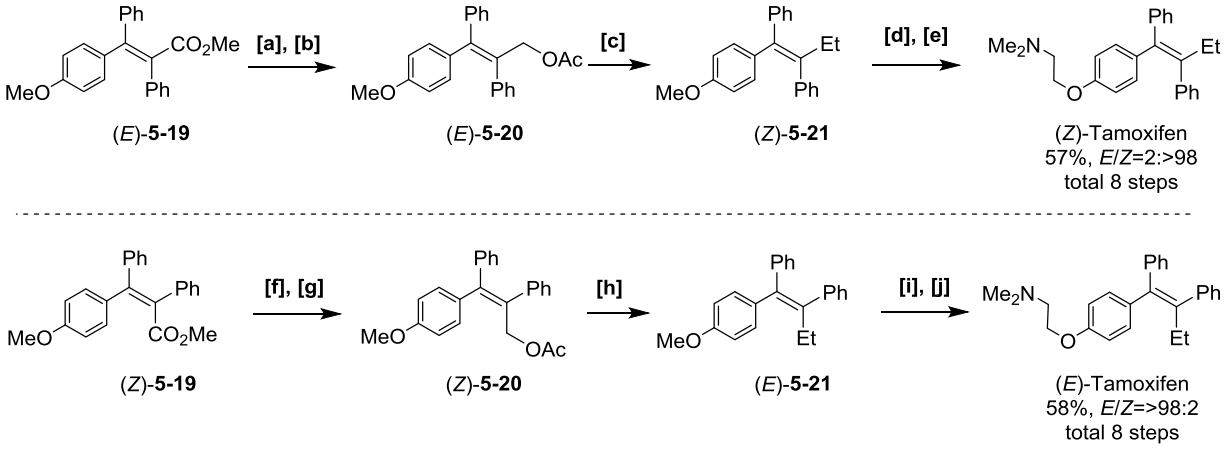
Scheme 5-4. Stereoretentive and complementary derivatization array of α,β-unsaturated esters (*E*)- and (*Z*)-**5-5b-1**. *Reagents and conditions*: [a] CF_3CO_2H–H_2O (2:1), 90 °C, 12 h; [b] DIBAL (3.0 equiv), CH_2Cl_2, RT, 1 h; [c] Using (*E*)- and (*Z*)-**5-8**, MnO_2 (40 equiv), CH_2Cl_2, RT, 1 h; [d] i) H_2/Pd–C, AcOEt, RT, 1 h; ii) LAH (1.0 equiv), Et_2O, 0 °C; [e] Using (*E*)- and (*Z*)-**5-9**, $MeP^+Ph_3{\bullet}I^-$ (4.0 equiv), *t*BuOK (4.0 equiv), CH_2Cl_2, RT, 1 h; [f] Using (*E*)- and (*Z*)-**5-9**, $(MeO)_2POCH_2CO_2Me$, DBU (1.2 equiv), LiCl (1.2 equiv), MeCN, RT, 1 h; [g] Using (*E*)- and (*Z*)-**5-9**, $H_2C(CN)_2$ (1.0 equiv), $Ti(OiPr)_4$ (0.5 equiv), *i*PrOH, RT, 24 h; [h] Using (*E*)- and (*Z*)-**5-8**, i) Ac_2O (1.2 equiv), Et_3N (1.2 equiv), DMAP (5 mol%), CH_2Cl_2, RT, 1 h; ii) RLi (6.0 equiv), CuI (3.5 equiv), THF, RT, 1 h.

Finally, with these successful outcomes in hand, the author introduces the first successful fully parallel synthesis of both (*E*)- and (*Z*)-tamoxifens,[18] a representative of all carbon (fully)-substituted olefins, utilizing the type I (convergent oriented approach: **Table 5-2** which was accomplished by Atsushi Honda, one of the colleagues). **Scheme 5-5** (preparation of precursors) and **Scheme 5-6** (synthesis in the final stage) illustrate this challenging task. The notable features in **Scheme 5-5** are as follows: 1) β-ketoester **5-15** was converted to enol tosylates (*E*)-**5-17** and (*Z*)-**5-17** following the reported (*E*)- and (*Z*)-stereocomplementary procedures[5] (conditions [a] and [b]); 2) in a similar approach, (*Z*)-**5-18** and (*E*)-**5-18** were prepared from β-ketoester **5-16** (conditions [c] and [d]); 3) Negishi cross-couplings using (*E*)-**5-17** and (*Z*)-**5-17** produced the corresponding α,β-unsaturated ester precursors (*Z*)-**5-19** and (*E*)-**5-19** in excellent yield (95% and 93%) with good to almost perfect stereoretention, respectively (conditions [e] and [f]); 4) in a similar approach, (*Z*)-**5-18** and (*E*)-**5-18** were transformed to (*Z*)-**5-19** and (*E*)-**5-19**, respectively in excellent yield (91% and 81%) with good to almost perfect stereoretention (conditions [g] and [h]).



Scheme 5-5. Parallel syntheses of both tamoxifen precursors (*E*)- and (*Z*)-**5-19**. *Reagents and conditions*: [a] TsCl (1.5 equiv), $Me_2N(CH_2)_6NMe_2$ (1.5 equiv), MeCN, −15° C, 1 h and 20−25 °C, 1 h, 95%, *E*/*Z*=66:34; pure (*E*)-**5-17** was isolated in 26% yield (recrystallized from toluene); [b] TsCl (1.5 equiv), TMEDA (1.5 equiv), LiCl (1.5 equiv), MeCN, 0−5 °C, 1 h and 20−25 °C, 1 h, 99%, *E*/*Z*=2:>98; [c] similar conditions to those given for [b], 97%, *E*/*Z*=2:98; [d] similar conditions to those given for [a], 92%, *E*/*Z*=74:26; pure (*E*)-**5-18** was isolated in 49% yield (recrystallized from AcOEt); [e] PhMgBr (3.0 equiv), $ZnCl_2$ (3.0 equiv), $[Pd(dppb)Cl_2]$ (2 mol%), MeCN/THF (2:3), 60−65 °C, 2 h, 95%, *E*/*Z*=16:84; [f] PhMgBr (2.0 equiv), $ZnCl_2$ (2.0 equiv), $Pd(OAc)_2$ (1 mol%), 1,4-bis(diphenylphosphino)butane (DPPB; 2 mol%), THF, 60−65 °C, 2 h, 93%, *E*/*Z*=98:2; [g] (*p*-MeO)C_6H_4MgBr (2.0 equiv), $ZnCl_2$ (2.0 equiv), $Pd(OAc)_2$ (1 mol%), DPPB (2 mol%), THF, 60−65 °C, 2 h, 99%, *E*/*Z*=2:98; [h] (*p*-MeO)C_6H_4MgBr (3.0 equiv), $ZnCl_2$ (3.0 equiv), $[Pd(dppb)Cl_2]$ (2 mol%), MeCN/THF (2:3), 60−65 °C, 2 h, 81%, *E*/*Z*=90:10.

The salient features in **Scheme 5-6** are that DIBAL reduction of precursors (*E*)-**5-19** and (*Z*)-**5-19**, followed by acetylation led to allylic acetates (*E*)-**5-20** and (*Z*)-**5-20**, respectively (conditions [a], [b], [f], and [g]). Utilizing the method for step [h] (**Scheme 5-4**), methylation of (*E*)-**5-20** and (*Z*)-**5-20** using MeLi/CuI proceeded smoothly to yield the corresponding fully substituted olefins (*E*)-**5-21** and (*Z*)-**5-21** (conditions [c] and [h]). A notable advantage of the present method is the reduced number of steps compared with reported transformations[16b, 18c, k, 19] (Dess−Martin oxidation, Wittig methylene formation, and catalytic hydrogenation).

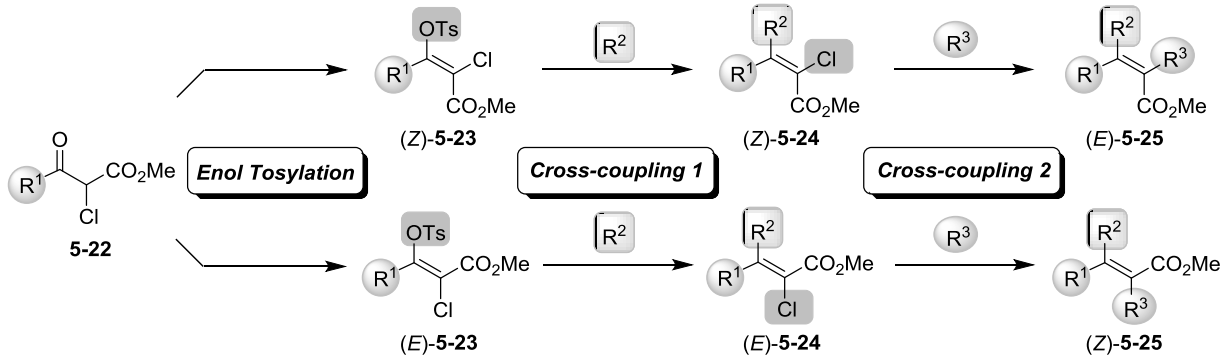


Scheme 5-6. Parallel syntheses of both (*E*)- and (*Z*)-tamoxifens. *Reagents and conditions*: [a] DIBAL (3.0 equiv), CH_2Cl_2, 0−5 °C, 98%, *E*/*Z*= >98:2; [b] Ac_2O (1.2 equiv), Et_3N (1.2 equiv), DMAP (5 mol%), CH_2Cl_2, 20−25 °C, 99%, *E*/*Z*= >98:2; [c] MeLi (4.0 equiv), CuI (2.5 equiv), THF, 0−5 °C, 1 h, 82%, *E*/*Z*=2:>98; [d] NaSEt (10 equiv), DMF, reflux, 1 h, 97%, *E*/*Z*=2:>98; [e]

$ClCH_2CH_2NMe_2$ · HCl (2.0 equiv), K_2CO_3 (4.0 equiv), toluene/EtOH (1:1), 80−85 °C, 3 h, 93%, *E*/*Z*=2:>98; [d] similar conditions to those given for [a] , 90% over two steps, *E*/*Z*=2:>98; [e] similar conditions to those given for [b], 80%, *E*/*Z*= >98:2; [f] similar conditions to those given for [c], 96% over two steps, *E*/*Z*= >98:2.

At the last stage of the synthesis, Miller and Al-Hassan's protocol for demethylation and subsequent *N*,*N*-dimethylethylene formation[20] furnished both (*E*)- and (*Z*)-tamoxifens in a total of 8 steps, with an overall 58% (average 93%) yield and an overall 57% (average 93%) yield, respectively. More than 50 syntheses of (*E*)- and/or (*Z*)-tamoxifens have appeared to date and these achievements are documented in an impressive review.[18a] To the best of our knowledge, this work is the first two sets (all four) of fully-parallel syntheses of both (*E*)- and (*Z*)-tamoxifens with excellent overall yields.

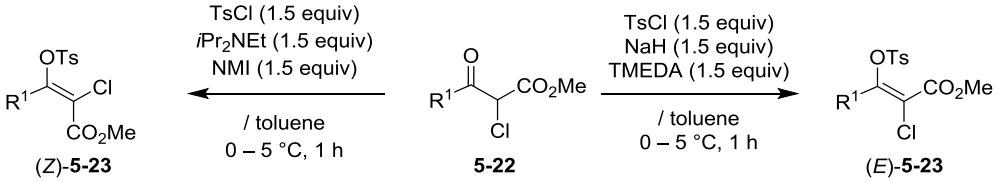
As a notable further extension, the author envisaged sequential cross-couplings using (*E*)- and (*Z*)-α-chlorinated enol tosylates **5-23**, which derived from readily available α-chloro-β-ketoesters **5-22** (**Scheme 5-7**).



Scheme 5-7. Sequential cross-couplings using (*E*)- and (*Z*)-α-chlorinated enol tosylates **5-23**.

After screening the stereocomplementary enol tosylation conditions, α-chlorinated enol tosylates (*E*)-**5-23** and (*Z*)-**5-23** were prepared from α-chloro-β-ketoesters **5-22** by using the TsCl−NMI−*i*Pr_2NEt reagent for *Z* and the TsCl−TMEDA−NaH reagent for *E* (**Table 5-5**).

Table 5-5. (*E*)- and (*Z*)-Stereocomplementary enol tosylation of α-chloro-β-ketoester **5-22**.

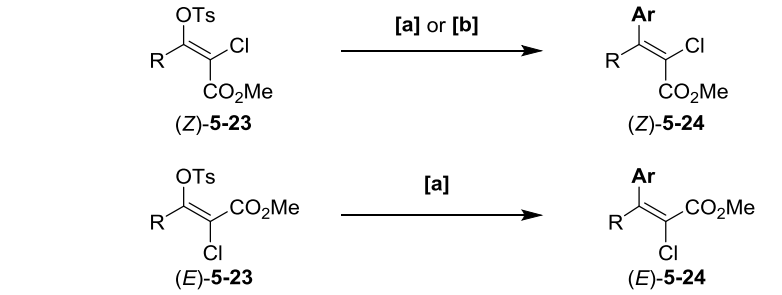


Entry	R^1	Substrate	Product	Yield / %	*E*/*Z*[a]
1	Me	**5-22a**	(*Z*)-**5-23a**	91	2:98
2		**5-22a**	(*E*)-**5-23a**	84	87:13
3	Ph	**5-22b**	(*Z*)-**5-23b**	83	2:98
4		**5-22b**	(*E*)-**5-23b**	89	94:6

a) Determined by ^{1}H NMR spectroscopy of the crude products.

TsO-group chemoselective cross-coupling of (*E*)- and (*Z*)-**5-23** underwent the most accessible Suzuki-Miyaura cross-coupling conditions [$Pd(OAc)_2$−PPh_3−K_2CO_3 in *i*PrOH−H_2O] to produce the desired (*E*)- and (*Z*)-α-chloroacrylates **5-24** in good to exellent yield with almost perfect stereoretention (**Table 5-6**). In the case of β-Ph-containing substrate (*Z*)-**5-23b,** however, considerable *Z*→*E* isomerization occurred under the identical conditions. This conspicuous isomerization could be successfully suppressed by using more refined conditions [$Pd(OAc)_2$−Ph-RuPhos−$NaHCO_3$ in toluene−H_2O].

Table 5-6. TsO-selective cross-coupling of α-chloro enol tosylates (*E*)- and (*Z*)-**5-23**.



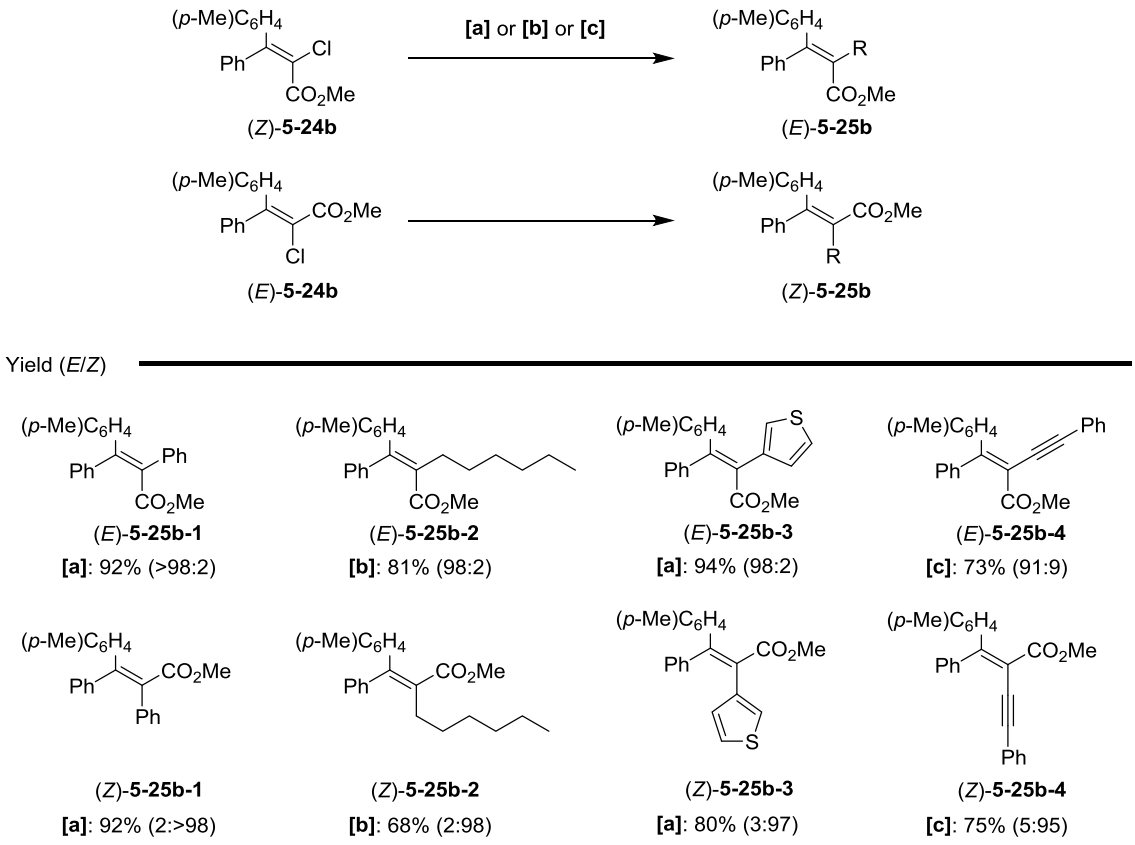
Yield (*E*/*Z*)

Ph, Me, Cl, CO_2Me (*Z*)-**5-24a**	Ph, Me, CO_2Me, Cl (*E*)-**5-24a**	(*p*-Me)C_6H_4, Ph, Cl, CO_2Me (*Z*)-**5-24b**	(*p*-Me)C_6H_4, Ph, CO_2Me, Cl (*E*)-**5-24b**
[a]: 86% (2:98) (60 – 65 °C)	**[a]**: 89% (>98:2) (60 – 65 °C)	**[a]**: 94% (19:81) (40 – 45 °C) **[b]**: 83% (7:93) (20 – 25 °C)	**[a]**: 89% (>98:2) (40 – 45 °C)

Reagents and conditions: [a] $ArB(OH)_2$ (1.2 equiv), $Pd(OAc)_2$ (5 mol%), PPh_3 (10 mol%), K_2CO_3 (1.2 equiv), *i*PrOH-H_2O (3:1), 1 h. [b] $ArB(OH)_2$ (1.2 equiv), $Pd(OAc)_2$ (1 mol%), Ph-RuPhos (2 mol%), $NaHCO_3$ (1.2 equiv), toluene-H_2O (3:1), 1 h.

Successful results of subsequent (*E*)- and (*Z*)-stereoretentive cross-couplings with α-chloroacrylates (*E*)-**5-24** and (*Z*)-**5-24** are summarized in **Table 5-7**. Suzuki-Miyaura cross-couplings with Ph-, (3-thienyl)-, and (*n*-hexyl)-boronic acids proceeded smoothly to give the desired products (*E*)- and (*Z*)-**5-25b-1−3** by using [$Pd(OAc)_2$−SPhos−K_2CO_3] catalysis. In addition, Sonogashira cross-couplings could be applied for the respective preparations of (*E*)-**5-25b-4** and (*Z*)-**5-25b-4** by using [$Pd(NCMe)_2Cl_2$−XPhos−Cs_2CO_3] catalysis, developed by Buchwald's group.[21] Notably, the synthesis of (*E*)- and (*Z*)-**5-25b-3**, **4** have been inaccessible because α-(3-thienyl) and α-alkynyl substituents could be hardly installed into these molecules by other reported methods.

Table 5-7. Suzuki-Miyaura and Sonogashira cross-coupling at α-chloro position with α-chloroacrylates (*E*)- and (*Z*)-**5-24**.



Reagents and conditions: [a] $ArB(OH)_2$ (1.2 equiv), $Pd(OAc)_2$ (1 mol%), SPhos (1 mol%), K_2CO_3 (1.2 equiv), toluene-H_2O (3:1), 80−85 °C, 1 h. [b] (*n*-hexyl)$B(OH)_2$ (1.8 equiv), $Pd(OAc)_2$ (3 mol%), SPhos (3 mol%), K_2CO_3 (1.8 equiv), toluene-H_2O (3:1), 80−85 °C, 1 h. [c] Phenylacetylene (1.3 equiv)), $[Pd(NCMe)_2Cl_2]$ (1 mol%), XPhos (3 mol%), Cs_2CO_3 (2.6 equiv), MeCN, reflux, 2 h.

Conclusion

Two sets (all four) of parallel and stereocomplementary synthetic pathway to access preparations of all-carbon-substituted (*E*)- and (*Z*)-α,β-unsaturated esters scaffolds were developed. This robust and distinctive method involves stereocomplementary enol tosylations using readily available TsCl/diamine reagents and highly stereoretentive Negishi cross-coupling reactions with fine-tuned catalysis. The parallel approach is categorized into a pair of type I and type II pathways. Among a number of (*E*)- and (*Z*)-α,β-unsaturated esters, a set of methyl (*E*)- and (*Z*)-α,β-dimethylcinnamates was transformed into various *E*- and *Z*-stereoretentive novel and known olefins with a total of 16 (8×2) derivatization arrays. As an attractive demonstration, the first parallel synthesis of both (*E*)- and (*Z*)-tamoxifens, a representative compound of all-carbon-substituted olefins, was accomplished in a total of eight steps with both high overall yields and individual step average yields. As a notable further extension, the sequential cross-couplings of (*E*)- and (*Z*)-α-chlorinated enol tosylates successfully strengthened the substrate generality of the present methodology with installing α-(3-thienyl) and α-alkynyl substituents.

Experimental

Methyl (*E*)-2-butyl-3-phenyloct-2-enoate [(*E*)-5-5a-1][= (*E*)-3-3a][14]

PhMgBr (0.92 mL, 1.00 mL; 1.09 M in THF) was added to a stirred suspension of $ZnCl_2$ (136 mg, 1.00 mmol) in MeCN (0.50 mL) at 0 − 5 °C under an Ar atmosphere, and the mixture was stirred at the same temperature for 0.5 h. Enol tosylate (*E*)-**5-4a**[5] (191 mg, 0.50 mmol) in MeCN (0.5 mL) and [Pd(dppe)Cl_2] (5.8 mg, 0.01 mmol) were successively added to the mixture, followed by being stirred at 60 − 65 °C for 2 h. After cooling to room temperature, 1 M-HCl aq. solution was added to the mixture, which was extracted twice with AcOEt. The combined organic phase was washed with 1 M-HCl aq. solution, water, brine, dried (Na_2SO_4) and concentrated. The obtained crude product was purified by SiO_2-column chromatography (hexane/AcOEt = 100:1) to give the desired product [(*E*)-**5-5a-1**, 118 mg, 82%, *E*/*Z* = 96:4].

Physical and spectral data were in accordance with (*Z*)-**3-3a**.

Methyl (*Z*)-2-butyl-3-phenyloct-2-enoate [(*Z*)-5-5a-1][= (*Z*)-3-3a][14]

PhMgBr (0.92 mL, 1.00 mL; 1.09 M in THF) was added to a stirred suspension of $ZnCl_2$ (136 mg, 1.00 mmol) in THF (0.50 mL) at 0 − 5 °C under an Ar atmosphere, and the mixture was stirred at the same temperature for 0.5 h. Enol tosylate (*Z*)-**5-4a**[5] (191 mg, 0.50 mmol) in THF (0.5 mL) and [Pd(dppb)Cl_2] (3.0 mg, 0.005 mmol) were successively added to the mixture, followed by being stirred at 60 − 65 °C for 2 h. After cooling to room temperature, 1 M-HCl aq. solution was added to the mixture, which was extracted twice with AcOEt. The combined organic phase was washed with 1 M-HCl aq. solution, water, brine, dried (Na_2SO_4) and concentrated. The obtained crude product was purified by SiO_2-column chromatography (hexane/AcOEt = 100:1) to give the desired product [(*Z*)-**5-5a-1**, 122 mg, 85%, *E*/*Z* = 2:>98].

Physical and spectral data were in accordance with (*Z*)-**3-3a**.

Methyl (*E*)-2-methyl-3-phenyl-3-(*p*-tolyl)acrylate [(*E*)-5-3a]

[Method A] Following the procedure for the preparation of (*E*)-**5-5a-1**, the reaction of enol tosylate (*E*)-**5-2a**[5] (173 mg, 0.50 mmol) using (*p*-Me)C_6H_4MgBr (0.94 mL, 1.00 mmol; 1.06 M in THF), $ZnCl_2$ (136 mg, 1.00 mmol), and [Pd(dppe)Cl_2] (5.8 mg, 0.01 mmol) gave the desired product [(*E*)-**5-3a**, 100 mg, 75%, *E*/*Z* = 84:16].

[Method B] Following the procedure for the preparation of (*Z*)-**5-5a-1**, the reaction of tosylate (*Z*)-**5-2a'** (188 mg, 0.50 mmol) using PhMgBr (1.04 mL, 1.00 mmol; 0.96 M in THF), $ZnCl_2$ (136 mg, 1.00 mmol), and [Pd(dppb)Cl_2] (3.0 mg, 0.005 mmol) gave the desired product [(*E*)-**5-3a**, 107 mg, 80%, *E*/*Z* = >98:2].

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.04 (s, 3H), 2.35 (s, 3H), 3.47 (s, 3H), 7.02−7.07 (m, 2H), 7.09−7.16 (m, 4H), 7.20−7.90 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 18.5, 21.2, 51.4, 127.3 (2C), 127.8 (2C), 128.6 (2C), 128.7 (2C), 129.5 (2C), 137.4, 137.8, 142.6, 146.8, 171.7; IR (neat): ν_{max} = 3023, 2947, 1710, 1509, 1432, 1324, 1253, 1123 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{18}H_{18}O_2$ $[M+Na]^+$ 289.1204; found: 289.1186.

Methyl (*Z*)-2-methyl-3-phenyl-3-(*p*-tolyl)acrylate [(*Z*)-5-3a]

[Method A] Following the procedure for the preparation of (*Z*)-**5-5a-1**, the reaction of enol tosylate (*Z*)-**5-2a**[5] (173 mg, 0.50 mmol) using (*p*-Me)C_6H_4MgBr (0.94 mL, 1.00 mmol; 1.06 M in THF), $ZnCl_2$ (136 mg, 1.00 mmol), and [Pd(dppb)Cl_2] (3.0 mg, 0.005 mmol) gave the desired product [(*Z*)-**5-3a**, 112 mg, 84%, *E*/*Z* = 2:>98].

[Method B] Following the procedure for the preparation of (*E*)-**5-5a-1**, the reaction of enol tosylate (*E*)-**5-2a'**, 188 mg, 0.50 mmol) using PhMgBr (1.04 mL, 1.00 mmol; 0.96 M in THF), $ZnCl_2$ (136 mg, 1.00 mmol), and [Pd(dppe)Cl_2] (5.8 mg, 0.01 mmol) gave the desired product [(*Z*)-**5-3a**, 110 mg, 83%, *E*/*Z* = 2:>98].

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.02 (s, 3H), 2.32 (s, 3H), 3.52 (s, 3H), 6.96−7.02 (m, 2H), 7.04−7.89 (m, 2H), 7.14−7.86 (m, 2H), 7.32−7.37 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 18.5, 21.2, 51.5, 127.3, 127.5, 128.0 (2C), 128.5 (2C), 128.6 (2C), 129.5 (2C), 137.8, 139.4, 141.0, 146.7, 171.7; IR (neat): ν_{max} = 3024, 2946, 1710, 1510, 1432, 1325, 1254, 1125 cm^{-1}.

Methyl (*E*)-3-(4-methoxyphenyl)-2-methyl-3-phenylacrylate [(*E*)-5-3b]

[Method A] Following the procedure for the preparation of (*E*)-**5-5a-1**, the reaction of enol tosylate (*E*)-**5-2a** (173 mg, 0.50 mmol) using (*p*-MeO)C_6H_4MgBr (0.98 mL, 1.00 mmol; 1.02 M in THF), $ZnCl_2$ (136 mg, 1.00 mmol), and [Pd(dppe)Cl_2] (5.8 mg, 0.01 mmol) gave the desired product [(*E*)-**5-3b**, 109 mg, 77%, *E*/*Z* = 84:16].

[Method B] Following the procedure for the preparation of (*Z*)-**5-5a-1 (method B)**, the reaction of enol tosylate (*Z*)-**5-2b'** (181 mg, 0.50 mmol) using PhMgBr (1.04 mL, 1.00 mmol; 0.96 M in THF), $ZnCl_2$ (136 mg, 1.00 mmol), and [Pd(dppb)Cl_2] (3.0 mg, 0.005 mmol) gave the desired product [(*E*)-**5-3b**, 113 mg, 80%, *E*/*Z* = >98:2].

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.07 (s, 3H), 3.46 (s, 3H), 3.81 (s, 3H), 6.83−6.89 (m, 2H), 7.06−7.13 (m, 4H), 7.21−7.30 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.5, 51.4, 55.1, 113.3 (2C), 127.0, 127.3, 127.8 (2C), 128.6 (2C), 131.0 (2C), 133.0, 142.7, 146.6, 159.0, 171.7; IR (neat): ν_{max} = 1709, 1605, 1508, 1443, 1325, 1304, 1288, 1277, 1175 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{18}H_{18}O_3$ $[M+Na]^+$ 305.1154; found: 305.1152.

Methyl (*Z*)-3-(4-methoxyphenyl)-2-methyl-3-phenylacrylate [(*Z*)-5-3b]

[Method A] Following the procedure for the preparation of (*Z*)-**5-5a-1**, the reaction of enol tosylate (*Z*)-**5-2a** (173 mg, 0.50 mmol) using (*p*-MeO)C_6H_4MgBr (1.02 mL, 1.00 mmol; 0.98 M in THF), $ZnCl_2$ (136 mg, 1.00 mmol), and [Pd(dppb)Cl_2] (3.0 mg, 0.005 mmol) gave the desired product [(*Z*)-**5-3b**, 115 mg, 82%, *E*/*Z* = 2:>98].

[Method B] Following the procedure for the preparation of (*E*)-**5-5a-1**, the reaction of enol tosylate (*E*)-**5-2b'** (181 mg, 0.50 mmol) using PhMgBr (1.04 mL, 1.00 mmol; 0.96 M in THF), $ZnCl_2$ (136 mg, 1.00 mmol), and [Pd(dppe)Cl_2] (5.8 mg, 0.01 mmol) gave the desired product [(*Z*)-**5-3b**, 113 mg, 80%, *E*/*Z* = 2:>98].

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.01 (s, 3H), 3.53 (s, 3H), 3.79 (s, 3H), 6.77–6.81 (m, 2H), 7.01–7.05 (m, 2H), 7.14–7.17 (m, 2H), 7.26–7.35 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.5, 51.5, 55.1, 113.3 (2C), 126.9, 127.5, 128.0 (2C), 129.6 (2C), 129.9 (2C), 134.7, 141.0, 146.2, 159.0, 171.9; IR (neat): ν_{max} = 2947, 2837, 1709, 1607, 1508, 1244, 1123, 1032, 775, 762, 700 cm^{-1}.

Methyl (*E*)-3-(4-chlorophenyl)-2-methyl-3-phenylacrylate [(*E*)-5-3c]

[Method A] Following the procedure for the preparation of (*E*)-**5-5a-1**, the reaction of enol tosylate (*E*)-**5-2a** (173 mg, 0.50 mmol) using (*p*-Cl)C_6H_4MgBr (0.96 mL, 1.00 mmol; 1.04 M in THF), $ZnCl_2$ (136 mg, 1.00 mmol), and [Pd(dppe)Cl_2] (5.8 mg, 0.01 mmol) gave the desired product [(*E*)-**5-3c**, 78 mg, 54%, *E*/*Z* = 83:17].

[Method B] Following the procedure for the preparation of (*Z*)-**5-5a-1**, the reaction of enol tosylate (*Z*)-**5-2c'** (183 mg, 0.50 mmol) using PhMgBr (1.04 mL, 1.00 mmol; 0.96 M in THF), $ZnCl_2$ (136 mg, 1.00 mmol), and [Pd(dppb)Cl_2] (3.0 mg, 0.005 mmol) gave the desired product [(*E*)-**5-3c**, 100 mg, 70%, *E*/*Z* = >98:2].

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.03 (s, 3H), 2.48 (s, 3H), 7.05−7.13 (m, 4H), 7.23−7.38 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): 18.5, 51.6, 127.6 (2C), 128.0 (2C), 128.4 (2C), 128.5 (2C), 130.9 (2C), 133.6, 139.1, 141.9, 145.4, 171.3; IR (neat): ν_{max} = 1712, 1489, 1433, 1325, 1254, 1016 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{17}H_{15}ClO_2$ $[M+Na]^+$ 309.0658; found: 309.0665.

Methyl (*Z*)-3-(4-chlorophenyl)-2-methyl-3-phenylacrylate [(*Z*)-5-3c]

[Method A] Following the procedure for the preparation of (*Z*)-**5-5a-1**, the reaction of enol tosylate (*Z*)-**5-2a** (173 mg, 0.50 mmol) using (*p*-Cl)C_6H_4MgBr (0.96 mL, 1.00 mmol; 1.04 M in THF), $ZnCl_2$ (136 mg, 1.00 mmol), and [Pd(dppb)Cl_2] (3.0 mg, 0.005 mmol) gave the desired product [(*Z*)-**5-3c**, 122 mg, 85%, *E*/*Z* = 2:>98].

[Method B] Following the procedure for the preparation of (*E*)-**5-5a-1**, the reaction of enol tosylate (*E*)-**5-2c'** (183 mg, 0.50 mmol) using PhMgBr (1.04 mL, 1.00 mmol; 0.96 M in THF), $ZnCl_2$ (136 mg, 1.00 mmol), and [Pd(dppe)Cl_2] (5.8 mg, 0.01 mmol) gave the desired product [(*Z*)-**5-3c**, 100 mg, 70%, *E*/*Z* = 2:>98].

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.03 (s, 3H), 3.52 (s, 3H), 7.02−7.07 (m, 2H), 7.11−7.15 (m, 2H), 7.21−7.25 (m, 2H), 7.28−7.38 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 18.4, 51.6, 127.8 (2C), 128.2 (2C), 128.4 (2C), 129.4 (2C), 129.9 (2C), 133.3, 140.3, 140.8, 145.5, 171.2; IR (neat): ν_{max} = 1712, 1489, 1443, 1433, 1323, 1252, 1125 cm^{-1}.

Methyl (*E*)-3-(4-chlorophenyl)-3-(4-methoxyphenyl)-2-methylacrylate [(*E*)-5-3d]

[Method A] Following the procedure for the preparation of (*E*)-**5-5a-1** (the reaction of enol tosylate (*E*)-**5-2d** (= **5-2b'**) (183 mg, 0.50 mmol) using (*p*-Cl)C_6H_4MgBr (1.00 mL, 1.00 mmol; 1.00 M in THF), $ZnCl_2$ (136 mg, 1.00 mmol), and [Pd(dppe)Cl_2] (5.8 mg, 0.01 mmol) in toluene (3 mL) at reflux gave the desired product [(*E*)-**5-3d**, 136 mg, 85%, *E*/*Z* = 68:32].

[Method B] Following the procedure for the preparation of (*Z*)-**5-5a-1**, the reaction of enol tosylate (*Z*)-**5-2d** (= **5-2c'**) (181 mg, 0.50 mmol) using (*p*-Cl)C_6H_4MgBr (1.00 mL, 1.00 mmol; 1.00 M in THF), $ZnCl_2$ (136

mg, 1.00 mmol), and [Pd(dppb)Cl_2] (3.0 mg, 0.005 mmol) gave the desired product [(*E*)-**5-3d**, 122 mg, 77%, *E*/*Z* = 90:10].

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.01 (s, 3H), 3.23 (s, 3H), 3.74 (s, 3H), 6.76−6.82 (m, 2H), 6.98–7.03 (m, 2H), 7.07−7.12 (m, 2H), 7.29–7.34 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.5, 51.5, 55.0, 113.3 (2C), 127.4, 128.9 (2C), 129.9 (2C), 131.0 (2C), 133.5, 134.1, 139.4, 144.8, 159.1, 171.5; IR (neat): ν_{max} = 1713, 1607, 1508, 1487, 1456, 1323, 1306, 1288, 1175 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{18}H_{17}ClO_3$ $[M+Na]^+$ 339.0764; found: 339.0762.

Methyl (*Z*)-3-(4-chlorophenyl)-3-(4-methoxyphenyl)-2-methylacrylate [(*Z*)-5-3d]

[Method A] Following the procedure for the preparation of (*Z*)-**5-5a-1**, the reaction of enol tosylate (*Z*)-**5-2c** (= **5-2b'**) (183 mg, 0.50 mmol) using (*p*-MeO)C_6H_4MgBr (1.00 mL, 1.00 mmol; 1.00 M in THF), $ZnCl_2$ (136 mg, 1.00 mmol), and [Pd(dppe)Cl_2] (5.8 mg, 0.01 mmol) in toluene (3 mL) at reflux gave the desired product [(*Z*)-**5-3d**, 127 mg, 80%, *E*/*Z* = 2:>98].

[Method B] Following the procedure for the preparation of (*E*)-**5-5a-1**, the reaction of enol tosylate [(*E*)-**5-2d'** (= **5-2c'**), 181 mg, 0.50 mmol] using (*p*-Cl)C_6H_4MgBr (1.00 mL, 1.00 mmol; 1.00 M in THF), $ZnCl_2$ (136 mg, 1.00 mmol), and [Pd(dppb)Cl_2] (3.0 mg, 0.005 mmol) gave the desired product [(*Z*)-**5-3d'**, 138 mg, 87%, *E*/*Z* = 2:>98].

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.06 (s, 3H), 3.50 (s, 3H), 3.82 (s, 3H), 6.84−6.89 (m, 2H), 7.01–7.09 (m, 4H), 7.21−7.26 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.6, 51.5, 55.1, 113.5 (2C), 127.5, 128.0 (2C), 130.0 (2C), 131.0 (2C), 132.6, 133.3, 141.2, 145.5, 159.2, 171.3; IR (neat): ν_{max} = 1605, 1508, 1489, 1456, 1433, 1321, 1304, 1288 cm^{-1}.

Methyl (*E*)-2-methyl-3-phenylbut-2-enoate [(*E*)-5-5b-1][=(*E*)-3-3c-1][20]

[Method A] Following the procedure for the preparation of (*E*)-**5-5a-1**, the reaction of enol tosylate (*E*)-**5-4b** (142 mg, 0.50 mmol) using PhMgBr (0.98 mL, 1.00 mmol; 1.02 M in THF), $ZnCl_2$ (136 mg, 1.00 mmol), and [Pd(dppe)Cl_2] (5.8 mg, 0.01 mmol) gave the desired product [(*E*)-**5-5b-1**, 80 mg, 84%, *E*/*Z* = 98:2]; Ref. [19a]: *E*/*Z* = 14:86; Ref. [19b]: *E*/*Z* = 80:20.

Physical and spectral data were in accordance with (*E*)-**3-3c-1**.

Methyl (*Z*)-2-methyl-3-phenylbut-2-enoate [(*Z*)-5-5b-1][=(*Z*)-3-3c-1][20a]

[Method B] Following the procedure for the preparation of (*Z*)-**5-5a-1**, the reaction of enol tosylate (*Z*)-**5-4b** (142 mg, 0.50 mmol) using PhMgBr (0.98 mL, 1.00 mmol; 1.02 M in THF), $ZnCl_2$ (136 mg, 1.00 mmol), and [Pd(dppb)Cl_2] (3.0 mg, 0.005 mmol) gave the desired product [(*Z*)-**5-5b-1**, 79 mg, 83%, *E*/*Z* = 2:>98]; Ref. [19a]: 95% yield, *E*/*Z* = 14:86.

Physical and spectral data were in accordance with (*Z*)-**3-3c-1**.

Methyl (*E*)-3-(4-methoxyphenyl)-2-methylbut-2-enoate [(*E*)-5-5b-2][=(*E*)-3-3c-3][20a]

[Method A] Following the procedure for the preparation of (*E*)-**5-5a-1**, the reaction of enol tosylate (*E*)-**5-4b** (142 mg, 0.50 mmol) using (*p*-MeO)C_6H_4MgBr (0.98 mL, 1.00 mmol; 1.02 M in THF), $ZnCl_2$ (136

mg, 1.00 mmol), and [Pd(dppe)Cl_2] (5.8 mg, 0.01 mmol) gave the desired product [(*E*)-**5-5b-2**, 90 mg, 82%, *E*/*Z* = 95:5]; Ref. [19a]: 14% yield, *E*/*Z* = 4:96; 90% yield, *E*/*Z* = 41:59.
Physical and spectral data were in accordance with (*E*)-**3-3c-3**.

Methyl (*Z*)-3-(4-methoxyphenyl)-2-methylbut-2-enoate [(*Z*)-5-5b-2][=(*Z*)-3-3c-3][14]

[Method B] Following the procedure for the preparation of (*Z*)-**5-5a-1**, the reaction of enol tosylate (*Z*)-**5-4b** (142 mg, 0.50 mmol) using (*p*-MeO)C_6H_4MgBr (1.03 mL, 1.00 mmol; 0.97 M in THF), $ZnCl_2$ (136 mg, 1.00 mmol), and [Pd(dppb)Cl_2] (3.0 mg, 0.005 mmol) gave the desired product [(*Z*)-**5-5b-2**, 104 mg, 95%, *E*/*Z* = 2:>98].
Physical and spectral data were in accordance with (*Z*)-**3-3c-3**.

Methyl (*E*)-3-(4-chlorophenyl)-2-methylbut-2-enoate [(*E*)-5-5b-3][=(*E*)-3-3c-4][14]

[Method A] Following the procedure for the preparation of (*E*)-**5-5a-1**, the reaction of enol tosylate (*E*)-**5-4b** (142 mg, 0.50 mmol) using (*p*-Cl)C_6H_4MgBr (1.03 mL, 1.00 mmol; 0.97 M in THF), $ZnCl_2$ (136 mg, 1.00 mmol), and [Pd(dppe)Cl_2] (5.8 mg, 0.01 mmol) gave the desired product [(*E*)-**5-5b-3**, 104 mg, 93%, *E*/*Z* = 98:2].
Physical and spectral data were in accordance with (*E*)-**3-3c-4**.

Methyl (*Z*)-3-(4-chlorophenyl)-2-methylbut-2-enoate [(*Z*)-5-5b-3][=(*Z*)-3-3c-4][14]

[Method B] Following the procedure for the preparation of (*Z*)-**5-5a-1**, the reaction of enol tosylate (*Z*)-**5-4b** (142 mg, 0.50 mmol) using (*p*-Cl)C_6H_4MgBr (1.03 mL, 1.00 mmol; 0.97 M in THF), $ZnCl_2$ (136 mg, 1.00 mmol), and [Pd(dppb)Cl_2] (3.0 mg, 0.005 mmol) gave the desired product [(*Z*)-**5-5b-3**, 90 mg, 80%, *E*/*Z* = 2:>98].
Physical and spectral data were in accordance with (*Z*)-**3-3c-4**.

Methyl (*E*)-2-(1-phenylethylidene)hexanoate [(*E*)-5-5c-1]

[Method A] Following the procedure for the preparation of (*E*)-**5-5a-1**, the reaction of enol tosylate (*E*)-**5-4c** (163 mg, 0.50 mmol) using PhMgBr (0.92 mL, 1.00 mmol; 1.09 M in THF), $ZnCl_2$ (136 mg, 1.00 mmol), and [Pd(dppe)Cl_2] (5.8 mg, 0.01 mmol) gave the desired product [(*E*)-**5-5c-1**, 99 mg, 85%, *E*/*Z* = 98:2].
Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.76 (t, *J* = 7.5 Hz, 3H), 1.15 (sext, *J* = 7.5 Hz, 2H), 1.23–1.32 (m, 2H), 2.13 (t, *J* = 8.0 Hz, 2H), 2.16 (s, 3H), 3.81 (s, 3H), 7.11–7.15 (m, 2H), 7.25–7.29 (m, 1H), 7.32–7.37 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.7, 22.3, 23.3, 30.6, 31.2, 51.4, 126.9, 127.1 (2C), 128.2 (2C), 130.6, 143.0, 143.5, 170.5; IR (neat): ν_{max} = 2955, 2860, 1718, 1490, 1434, 1316, 1258, 1136 cm^{-1}.

Methyl (*Z*)-2-(1-phenylethylidene)hexanoate [(*Z*)-5-5c-1]

[Method B] Following the procedure for the preparation of (*Z*)-**5-5a-1**, the reaction of enol tosylate (*Z*)-**5-4c** (163 mg, 0.50 mmol) using PhMgBr (0.92 mL, 1.00 mmol; 1.09 M in THF), $ZnCl_2$ (136 mg, 1.00 mmol), and [Pd(dppb)Cl_2] (3.0 mg, 0.005 mmol) gave the desired product [(*Z*)-**5-5c-1**, 88 mg, 88%, *E*/*Z* = 2:>98].

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.94 (t, *J* = 7.5 Hz, 3H), 1.34–1.51 (m, 4H), 2.10 (s, 3H), 2.44 (t, *J* = 8.0 Hz, 2H), 3.37 (s, 3H), 7.12–7.16 (m, 2H), 7.21–7.25 (m, 1H), 7.27–7.32 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.9, 20.8, 22.5, 30.4, 30.7, 51.1, 126.8 (2C), 126.9, 127.9 (2C), 131.5, 141.7, 144.0, 171.1; IR (neat): ν_{max} = 2955, 2871, 1714, 1492, 1433, 1318, 1240, 1139 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{15}H_{20}O_2$ $[M+Na]^+$ 255.1361; found: 255.1360.

Methyl (*E*)-2-methyl-3-phenylhept-2-enoate [(*E*)-5-5c'-1]

[Method A] Following the procedure for the preparation of (*E*)-**5-5a-1**, the reaction of enol tosylate (*E*)-**5-4c'** (163 mg, 0.50 mmol) using PhMgBr (1.04 mL, 1.00 mmol; 0.96 M in THF), $ZnCl_2$ (136 mg, 1.00 mmol), and $[Pd(dppe)Cl_2]$ (5.8 mg, 0.01 mmol) gave the desired product [(*E*)-**5-5c'-1**, 83 mg, 72%, *E*/*Z* = >98:2].

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.82 (t, *J* = 6.9 Hz, 3H), 1.21–1.34 (m, 4H), 1.71 (s, 3H), 2.59 (t, *J* = 6.9 Hz, 2H), 3.79 (s, 3H), 7.08−7.13 (m, 2H), 7.27–7.30 (m, 1H), 7.33−7.38 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.8, 17.4, 22.6, 30.9, 35.9, 51.4, 124.5, 126.9, 127.7 (2C), 128.1 (2C), 141.8, 150.0, 170.4; IR (neat): ν_{max} = 1717, 1441, 1433, 1246, 1190, 1134, 1105 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{15}H_{20}O_2$ $[M+Na]^+$ 255.1361; found: 255.1362.

Methyl (*Z*)-2-methyl-3-phenylhept-2-enoate [(*Z*)-5-5c'-1]

[Method B] Following the procedure for the preparation of (*Z*)-**5-5a-1**, the reaction of enol tosylate (*Z*)-**5-4c'** (163 mg, 0.50 mmol) using PhMgBr (10.4 mL, 1.00 mmol; 0.96 M in THF), $ZnCl_2$ (136 mg, 1.00 mmol), and $[Pd(dppb)Cl_2]$ (3.0 mg, 0.005 mmol) gave the desired product [(*Z*)-**5-5c'-1**, 79 mg, 70%, *E*/*Z* = 2:>98].

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.85 (t, *J* = 6.9 Hz, 3H), 1.24–1.33 (m, 4H), 2.03 (s, 3H), 2.45 (*t*, J = 6.9 Hz, 2H), 3.36 (s, 3H), 7.08−7.11 (m, 2H), 7.22–7.31 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.8, 15.8, 22.5, 29.6, 34.6, 51.1, 125.7, 126.8, 127.2 (2C), 127.8 (2C), 142.8, 147.7, 171.0; IR (neat): ν_{max} = 1713, 1433, 1315, 1240, 1136, 1084 cm^{-1}.

Methyl (*E*)-2-[1-(4-methoxyphenyl)ethylidene]hexanoate [(*E*)-5-5c-2]

[Method A] Following the procedure for the preparation of (*E*)-**5-5a-1**, the reaction of enol tosylate (*E*)-**5-4c** (163 mg, 0.50 mmol) using (*p*-MeO)C_6H_4MgBr (0.98 mL, 1.00 mmol; 1.02 M in THF), $ZnCl_2$ (136 mg, 1.00 mmol), and $[Pd(dppe)Cl_2]$ (5.8 mg, 0.01 mmol) gave the desired product [(*E*)-**5-5c-2**, 117 mg, 89%, *E*/*Z* = 91:9].

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.78 (t, *J* = 7.5 Hz, 3H), 1.17 (sext, *J* = 7.5 Hz, 2H), 1.24–1.32 (m, 2H), 2.14 (s, 3H), 2.15 (t, *J* = 8.0 Hz, 2H), 3.80 (s, 3H), 3.82 (s, 3H), 6.86–6.90 (m, 2H), 7.04–7.09 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ =13.7, 22.3, 23.4, 30.7, 31.3, 51.3, 55.1, 113.6 (2C), 128.3 (2C), 130.5, 135.3, 143.1, 158.5, 170.7; IR (neat): ν_{max} = 2955, 2837, 1715, 1609, 1508, 1244, 1134, 1032, 831 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{16}H_{22}O_3$ $[M+Na]^+$ 285.1467; found: 285.1466.

Methyl (*Z*)-2-[1-(4-methoxyphenyl)ethylidene]hexanoate [(*Z*)-5-5c-2]

[Method B] Following the procedure for the preparation of (*Z*)-**5-5a-1**, the reaction of enol tosylate (*Z*)-**5-4c**

(163 mg, 0.50 mmol) using (*p*-MeO)C_6H_4MgBr (0.98 mL, 1.00 mmol; 1.02 M in THF), $ZnCl_2$ (136 mg, 1.00 mmol), and [Pd(dppb)Cl_2] (3.0 mg, 0.005 mmol) gave the desired product [(*Z*)-**5-5c-2**, 119 mg, 91%, *E*/*Z* = 2:>98].

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.93 (t, *J* = 7.5 Hz, 3H), 1.33–1.49 (m, 4H), 2.07 (s, 3H), 2.42 (t, *J* = 7.5 Hz, 2H), 3.41 (s, 3H), 3.80 (s, 3H), 6.81–6.85 (m, 2H), 7.06–7.11 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.9, 20.8, 22.6, 30.6, 30.8, 51.2, 55.1, 113.4 (2C), 128.1 (2C), 131.1, 136.3, 141.0, 158.6, 171.6; IR (neat): ν_{max} = 2955, 2837, 1711, 1607, 1510, 1244, 1138, 1026, 831 cm^{-1}.

Methyl (*E*)-3-(4-methoxyphenyl)-2-methylhept-2-enoate [(*E*)-5-5c'-2]

[Method A] Following the procedure for the preparation of (*E*)-**5-5a-1**, the reaction of enol tosylate (*E*)-**5-4c'** (163 mg, 0.50 mmol) using (*p*-MeO)C_6H_4MgBr (0.98 mL, 1.00 mmol; 1.02 M in THF), $ZnCl_2$ (136 mg, 1.00 mmol), and [Pd(dppe)Cl_2] (5.8 mg, 0.01 mmol) gave the desired product [(*E*)-**5-5c'-2**, 98 mg, 75%, *E*/*Z* = >98:2].

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.82 (t, *J* = 6.9 Hz, 3H), 1.20–1.33 (m, 4H), 1.73 (s, 3H), 2.57 (t, *J* = 6.9 Hz, 2H), 3.78 (s, 3H), 3.82 (s, 3H), 6.86−6.92 (m, 2H), 7.02–7.07 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.9, 17.5, 22.6, 30.4, 36.1, 51.4, 55.2, 113.5 (2C), 124.4, 129.0 (2C), 134.0, 149.7, 158.5, 170.6; IR (neat): ν_{max} = 1715, 1609, 1508, 1456, 1433, 1287, 1242, 1177, 1132 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{16}H_{22}O_3$ $[M+Na]^+$ 285.1467; found: 285.1458.

Methyl (*Z*)-3-(4-methoxyphenyl)-2-methylhept-2-enoate [(*Z*)-5-5c'-2]

[Method B] Following the procedure for the preparation of (*Z*)-**5-5a-1**, the reaction of enol tosylate (*Z*)-**5-4c'** (163 mg, 0.50 mmol) using (*p*-MeO)C_6H_4MgBr (0.98 mL, 1.00 mmol; 1.02 M in THF), $ZnCl_2$ (136 mg, 1.00 mmol), and [Pd(dppb)Cl_2] (3.0 mg, 0.005 mmol) gave the desired product [(*Z*)-**5-5c'-2**, 108 mg, 82%, *E*/*Z* = 2:>98].

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.85 (t, *J* = 6.9 Hz, 3H), 1.22–1.33 (m, 4H), 2.01 (s, 3H), 2.43 (*t*, J = 6.9 Hz, 2H), 3.41 (s, 3H), 3.80 (s, 3H), 6.80−6.85 (m, 2H), 7.02–7.07 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.8, 15.9, 22.5, 29.5, 34.5, 51.1, 55.0, 113.2 (2C), 125.3, 128.4 (2C), 134.9, 147.0, 158.5, 171.3; IR (neat): ν_{max} = 1711, 1607, 1508, 1456, 1433, 1317, 1288 cm^{-1}.

Methyl (*E*)-2-[1-(4-chlorophenyl)ethylidene]hexanoate [(*E*)-5-5c-3]

[Method A] Following the procedure for the preparation of (*E*)-**5-5a-1**, the reaction of enol tosylate (*E*)-**5-4c** (163 mg, 0.50 mmol) using (*p*-Cl)C_6H_4MgBr (0.96 mL, 1.00 mmol; 1.04 M in THF), $ZnCl_2$ (136 mg, 1.00 mmol), and [Pd(dppe)Cl_2] (5.8 mg, 0.01 mmol) gave the desired product [(*E*)-**5-5c-3**, 117 mg, 88%, *E*/*Z* = 97:3].

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.77 (t, *J* = 7.5 Hz, 3H), 1.16 (sext, *J* = 7.5 Hz, 2H), 1.23–1.30 (m, 2H), 2.11 (t, *J* = 8.0 Hz, 2H), 2.13 (s, 3H), 3.80 (s, 3H), 7.05–7.09 (m, 2H), 7.31–7.34 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.7, 22.3, 23.2, 30.7, 31.2, 51.5, 128.5 (2C), 128.6 (2C), 131.3, 132.8, 141.3, 142.0, 170.3; IR (neat): ν_{max} = 2955, 2860, 1717, 1489, 1433, 1258, 1246, 1206, 1136, 1092, 1015, 827 cm^{-1}; HRMS

(ESI): *m/z* calcd for $C_{115}H_{19}O_2Cl$ $[M+Na]^+$ 289.0971; found: 289.0966.

Methyl (*Z*)-2-[1-(4-chlorophenyl)ethylidene]hexanoate [(*Z*)-5-5c-3]

[Method B] Following the procedure for the preparation of (*Z*)-**5-5a-1**, the reaction of enol tosylate (*Z*)-**5-4c** (163 mg, 0.50 mmol) using (*p*-Cl)C_6H_4MgBr (0.96 mL, 1.00 mmol; 1.04 M in THF), $ZnCl_2$ (136 mg, 1.00 mmol), and [Pd(dppb)Cl_2] (3.0 mg, 0.005 mmol) gave the desired product [(*Z*)-**5-5c-3**, 104 mg, 78%, *E*/*Z* = 2:>98].

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.94 (t, *J* = 6.9 Hz, 3H), 1.33–1.49 (m, 4H), 2.06 (s, 3H), 2.43 (t, *J* = 6.9 Hz, 2H), 3.41 (s, 3H), 7.06–7.09 (m, 2H), 7.24–7.28 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.9, 20.8, 22.5, 30.4, 30.7, 51.2, 128.15 (2C), 128.23 (2C), 132.1, 132.7, 140.6, 142.4, 170.7; IR (neat): ν_{max} = 2955, 2872, 1713, 1485, 1433, 1315, 1242, 1138, 1090, 1013, 827 cm^{-1}.

Methyl (*E*)-3-(4-chlorophenyl)-2-methylhept-2-enoate [(*E*)-5-5c'-3]

[Method A] Following the procedure for the preparation of (*E*)-**5-5a-1**, the reaction of enol tosylate (*E*)-**5-4c'** (163 mg, 0.50 mmol) using (*p*-Cl)C_6H_4MgBr (0.96 mL, 1.00 mmol; 1.04 M in THF), $ZnCl_2$ (136 mg, 1.00 mmol), and [Pd(dppe)Cl_2] (5.8 mg, 0.01 mmol) in toluene (3 mL) at reflux gave the desired product [(*E*)-**5-5c'-3**, 104 mg, 78%, *E*/*Z* = >98:2].

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.82 (t, *J* = 6.9 Hz, 3H), 1.21–1.31 (m, 4H), 1.70 (s, 3H), 2.56 (t, *J* = 6.9 Hz, 2H), 3.79 (s, 3H), 7.02−7.07 (m, 2H), 7.31–7.36 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): 13.8, 17.4, 22.6, 30.2, 35.8, 51.5,125.2, 128.5 (2C), 129.2 (2C), 132.8, 140.1, 148.5, 170.2; IR (neat): ν_{max} = 1717, 1489, 1456, 1433, 1246, 1134, 1115 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{15}H_{19}ClO_2$ $[M + Na]^+$ 289.0971; found: 289.0966.

Methyl (*Z*)-3-(4-chlorophenyl)-2-methylhept-2-enoate [(*Z*)-5-5c'-3]

[Method B] Following the procedure for the preparation of (*Z*)-**5-5a-1**, the reaction of enol tosylate (*Z*)-**5-4c'** (163 mg, 0.50 mmol) using (*p*-Cl)C_6H_4MgBr (0.96 mL, 1.00 mmol; 1.04 M in THF), $ZnCl_2$ (136 mg, 1.00 mmol), and [Pd(dppb)Cl_2] (3.0 mg, 0.005 mmol) gave the desired product [(*Z*)-**5-5c'-3**, 93 mg, 70%, *E*/*Z* = 2:>98].

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.85 (t, *J* = 6.9 Hz, 3H), 1.22–1.32 (m, 4H), 2.02 (s, 3H), 2.41 (*t*, J = 6.9 Hz, 2H), 3.41 (s, 3H), 7.01−7.06 (m, 2H), 7.24–7.29 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.8, 15.9, 22.5, 29.4, 34.6, 51.3, 126.3, 128.1 (2C), 128.6 (2C), 132.7, 141.3, 146.6, 170.6; IR (neat): ν_{max} = 1715, 1489, 1433, 1315, 1238, 1136 cm^{-1}.

Methyl (*E*)-2-butyl-3-(4-methoxyphenyl)oct-2-enoate [(*E*)-5-5a-2]

[Method A] Following the procedure for the preparation of (*E*)-**5-5a-1**, the reaction of enol tosylate (*E*)-**5-4a** (191 mg, 0.50 mmol) using (*p*-MeO)C_6H_4MgBr (1.00 mL, 1.00 mmol; 1.00 M in THF), $ZnCl_2$ (136 mg, 1.00 mmol), and [Pd(dppe)Cl_2] (5.8 mg, 0.010 mmol) gave the desired product [(*E*)-**5-5a-2**, 82 mg, 52%, *E*/*Z* = 91:9].

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.77 (t, *J* = 6.9 Hz, 3H), 0.82 (t, *J* = 6.9 Hz, 3H), 1.11–1.34 (m, 10H), 2.10 (t, *J* = 8.0 Hz, 2H), 2.43 (t, *J* = 8.0 Hz, 2H), 3.79 (s, 3H), 3.82 (s, 3H), 6.86−6.90 (m, 2H), 7.00–7.05 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.8, 14.0, 22.37, 22.39, 27.7, 30.8, 31.3, 31.7, 36.6, 51.3, 55.2, 113.5 (2C), 128.9 (2C), 130.6, 133.7, 147.0, 158.4, 170.9; IR (neat): ν_{max} = 2954, 2927, 2859, 1717, 1608, 1509, 1463, 1245 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{20}H_{30}O_3$ $[M+Na]^+$ 341.2093; found: 341.2095.

Methyl (*Z*)-2-butyl-3-(4-methoxyphenyl)oct-2-enoate [(*Z*)-5-5a-2]

[Method B] Following the procedure for the preparation of (*Z*)-**5-5a-1**, the reaction of enol tosylate (*Z*)-**5-4a** (191 mg, 0.500 mmol) using (*p*-MeO)C_6H_4MgBr (1.00 mL, 1.00 mmol; 1.00 M in THF), $ZnCl_2$ (136 mg, 1.00 mmol), and [Pd(dppb)Cl_2] (3.0 mg, 0.0050 mmol) gave the desired product [(*Z*)-**5-5a-2**, 84 mg, 53%, *E*/*Z* = 2:>98].

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.83 (t, *J* = 6.9 Hz, 3H), 0.93 (t, *J* = 7.5 Hz, 3H), 1.20–1.29 (m, 6H), 1.33–1.46 (m, 4H), 2.38–2.45 (m, 4H), 3.38 (s, 3H), 3.80 (s, 3H), 6.80−6.84 (m, 2H), 7.03–7.07 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.9 (2C), 22.4, 22.5, 27.5, 30.0, 31.1, 31.6, 34.0, 51.1, 55.1, 113.3 (2C), 128.5 (2C), 131.3, 134.8, 145.5, 158.5, 171.6; IR (neat): ν_{max} = 2955, 2871, 1710, 1607, 1509, 1462, 1323, 1244 cm^{-1}.

Methyl (*E*)-2-butyl-3-(4-chlorophenyl)oct-2-enoate [(*E*)-5-5a-3]

[Method A] Following the procedure for the preparation of (*E*)-**5-5a-1**, the reaction of enol tosylate (*E*)-**5-4a** (191 mg, 0.50 mmol) using (*p*-Cl)C_6H_4MgBr (1.00 mL, 1.00 mmol; 1.00 M in THF), $ZnCl_2$ (136 mg, 1.00 mmol), and [Pd(dppe)Cl_2] (5.8 mg, 0.01 mmol) gave the desired product [(*E*)-**5-5a-3**, 92 mg, 57%, *E*/*Z* = >98:2].

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.77 (t, *J* = 7.5 Hz, 3H), 0.82 (t, *J* = 6.9 Hz, 3H), 1.11–1.31 (m, 10H), 2.06 (t, *J* = 8.0 Hz, 2H), 2.43 (t, *J* = 8.0 Hz, 2H), 3.79 (s, 3H), 7.02−7.06 (m, 2H), 7.30–7.34 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.8, 13.9, 23.3, 23.4, 27.6, 30.8, 31.1, 31.6, 36.3, 51.4, 128.4 (2C), 129.2 (2C), 131.3, 132.8, 139.8, 145.8, 170.5; IR (neat): ν_{max} = 2956, 2929, 2860, 1720, 1489, 1462, 1433, 1204 cm^{-1}.

Methyl (*Z*)-2-butyl-3-(4-chlorophenyl)oct-2-enoate [(*Z*)-5-5a-3]

[Method B] Following the procedure for the preparation of (*Z*)-**5-5a-1**, the reaction of enol tosylate (*Z*)-**5-4a** (191 mg, 0.50 mmol) using (*p*-Cl)C_6H_4MgBr (1.00 mL, 1.00 mmol; 1.00 M in THF), $ZnCl_2$ (136 mg, 1.00 mmol), and [Pd(dppb)Cl_2] (3.0 mg, 0.005 mmol) gave the desired product [(*Z*)-**5-5a-3**, 96 mg, 59%, *E*/*Z* = 2:>98].

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.83 (t, *J* = 6.9 Hz, 3H), 0.93 (t, *J* = 6.9 Hz, 3H), 1.19–1.29 (m, 6H), 1.34–1.46 (m, 4H), 2.37–2.45 (m, 4H), 3.38 (s, 3H), 7.02−7.07 (m, 2H), 7.23–7.28 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.9 (2C), 22.4, 22.5, 27.4, 29.9, 31.0, 31.6, 34.0, 51.2, 128.1 (2C), 128.8 (2C), 132.2, 132.7, 141.1, 145.0, 170.9; IR (neat): ν_{max} = 2956, 2860, 1715, 1488, 1466, 1432, 1242, 1139 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{19}H_{27}O_2Cl$ $[M+Na]^+$ 345.1597; found: 345.1611.

Methyl (*E*)-2-isopropyl-3-phenylbut-2-enoate [(*E*)-5-5d]

[Method A] Following the procedure for the preparation of (*E*)-**5-5a-1**, the reaction of enol tosylate (*E*)-**5-4d** (156 mg, 0.50 mmol) using PhMgBr (0.92 mL, 1.00 mmol; 1.09 M in THF), $ZnCl_2$ (136 mg, 1.00 mmol), and [Pd(dppe)Cl_2] (5.8 mg, 0.01 mmol) gave the desired product [(*E*)-**5-5d**, 37 mg, 34%, *E*/*Z* = 96:4].
Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.00 (d, *J* = 7.5 Hz, 6H), 1.99 (s, 3H), 2.54 (hept, *J* = 7.5 Hz, 1H), 3.82 (s, 3H), 7.14−7.17 (m, 2H), 7.25–7.30 (m, 1H), 7.33–7.38 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.4 (2C), 23.3, 29.8, 51.2, 126.9, 127.2 (2C), 128.3 (2C), 136.8, 137.3, 142.2, 170.5; IR (neat): ν_{max} = 2964, 1723, 1599, 1492, 1433, 1301, 1243, 1143 cm^{-1}.

Methyl (*Z*)-2-isopropyl-3-phenylbut-2-enoate [(*Z*)-5-5d]

[Method B] Following the procedure for the preparation of (*Z*)-**5-5a-1**, the reaction of enol tosylate (*Z*)-**5-4d** (156 mg, 0.50 mmol) using PhMgBr (0.92 mL, 1.00 mmol; 1.09 M in THF), $ZnCl_2$ (136 mg, 1.00 mmol), and [Pd(dppb)Cl_2] (3.0 mg, 0.005 mmol) gave the desired product [(*Z*)-**5-5d**, 86 mg, 79%, *E*/*Z* = 2:>98].
Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.17 (d, *J* = 7.5 Hz, 6H), 2.08 (s, 3H), 2.94 (hept, *J* = 7.5 Hz, 1H), 3.36 (s, 3H), 7.16−7.31 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.6, 20.8 (2C), 29.3, 50.8, 126.9, 127.0 (2C), 128.0 (2C), 136.7, 137.8, 143.7, 170.4; IR (neat): ν_{max} = 2968, 1717, 1431, 1385, 1304, 1239, 1138, 1014 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{14}H_{18}O_2$ $[M+H]^+$ 219.1385; found: 219.1384.

Methyl (*E*)-2,3-diphenylbut-2-enoate [(*E*)-5-5e][=(*E*)-3-3j][14]

[Method A] Following the procedure for the preparation of (*E*)-**5-5a-1**, the reaction of enol tosylate (*E*)-**5-4e** (180 mg, 0.50 mmol) using PhMgBr (0.92 mL, 1.00 mmol; 1.09 M in THF), $ZnCl_2$ (136 mg, 1.00 mmol), and [Pd(dppe)Cl_2] (5.8 mg, 0.01 mmol) gave the desired product [(*E*)-**5-5e**, 126 mg, >99%, *E*/*Z* = 97:3].
Physical and spectral data were in accordance with (*E*)-**3-3j**.

Methyl (*Z*)-2,3-diphenylbut-2-enoate [(*Z*)-5-5e][=(*Z*)-3-3j][14,22]

[Method A] Following the procedure for the preparation of (*Z*)-**5-5a-1**, the reaction of enol tosylate (*Z*)-**5-4e** (180 mg, 0.50 mmol) using PhMgBr (0.92 mL, 1.00 mmol; 1.09 M in THF), $ZnCl_2$ (136 mg, 1.00 mmol), and [Pd(dppb)Cl_2] (3.0 mg, 0.005 mmol) gave the desired product [(*Z*)-**5-5e**, 125 mg, 99%, *E*/*Z* = 2:>98].
Physical and spectral data were in accordance with (*Z*)-**3-3j**.

Methyl (*Z*)-2-methoxy-3-phenyloct-2-enoate [(*Z*)-5-5f]

[Method A] Following the procedure for the preparation of (*E*)-**5-5a-1**, the reaction of enol tosylate (*Z*)-**5-4f** (178 mg, 0.50 mmol) using PhMgBr (0.92 mL, 1.00 mmol; 1.09 M in THF), $ZnCl_2$ (136 mg, 1.00 mmol), and [Pd(dppe)Cl_2] (5.8 mg, 0.01 mmol) gave the desired product [(*Z*)-**5-5f**, 121 mg, 92%, *E*/*Z* = 2:>98].
Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.80−0.86 (m, 3H), 1.19–1.40 (m, 6H), 2.67–2.73 (m, 2H), 3.34 (s, 3H), 3.85 (s, 3H), 7.24−7.38 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.9, 22.3, 28.0, 31.6, 32.8, 51.6, 59.5, 127.3, 127.9 (2C), 128.0 (2C), 138.9, 140.6, 142.1, 165.3; IR (neat): ν_{max} = 2929, 2859, 1718, 1442,

1254, 1200, 1137, 1089 cm^{-1}.

Methyl (*E*)-2-methoxy-3-phenyloct-2-enoate [(*E*)-5-5f]

[Method B] Following the procedure for the preparation of (*Z*)-**5-5a-1**, the reaction of enol tosylate (*E*)-**5-4f** (178 mg, 0.50 mmol) using PhMgBr (0.92 mL, 1.00 mmol; 1.09 M in THF), $ZnCl_2$ (136 mg, 1.00 mmol), and [Pd(dppb)Cl_2] (3.0 mg, 5.0 μmol) gave the desired product [(*E*)-**5-5f**, 117 mg, 89%, *E*/*Z* = >98:2].

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.81−0.87 (m, 3H), 1.21–1.33 (m, 6H), 2.52 (t, *J* = 8.0 Hz, 2H), 3.49 (s, 3H), 3.65 (s, 3H), 7.09−7.14 (m, 2H), 7.24−7.34 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.9, 22.3, 17.0, 31.6, 32.5, 51.3, 59.0, 127.1, 127.6 (2C), 127.8 (2C), 138.6, 139.4, 142.9, 164.9; IR (neat): ν_{max} = 2928, 1720, 1631, 1434, 1318, 1259, 1205, 1144 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{16}H_{22}O_3$ $[M+Na]^+$ 285.1467; found: 285.1461.

Methyl (*E*)-7-chloro-2-methyl-3-phenylhept-2-enoate [(*E*)-5-5g][=(*E*)-3-3g][14]

[Method A] Following the procedure for the preparation of (*E*)-**5-5a-1**, the reaction of enol tosylate (*E*)-**5-4g** (180 mg, 0.50 mmol) using PhMgBr (0.92 mL, 1.00 mmol; 1.09 M in THF), $ZnCl_2$ (136 mg, 1.00 mmol), and [Pd(dppe)Cl_2] (5.8 mg, 0.01 mmol) gave the desired product [(*E*)-**5-5g**, 119 mg, 89%, *E*/*Z* = >98:2].

Physical and spectral data were in accordance with (*E*)-**3-3g**.

Methyl (*Z*)-7-chloro-2-methyl-3-phenylhept-2-enoate [(*Z*)-5-5g][=(*Z*)-3-3g][14]

[Method B] Following the procedure for the preparation of (*Z*)-**5-5a-1**, the reaction of enol tosylate (*Z*)-**5-4g** (180 mg, 0.50 mmol) using PhMgBr (0.92 mL, 1.00 mmol; 1.09 M in THF), $ZnCl_2$ (136 mg, 1.00 mmol), and [Pd(dppb)Cl_2] (3.0 mg, 0.005 mmol) gave the desired product [(*Z*)-**5-5g**, 120 mg, 90%, *E*/*Z* = 2:>98].

Physical and spectral data were in accordance with (*Z*)-**3-3g**.

Methyl (*Z*)-2-chloro-3-(tosyloxy)but-2-enoate [(*Z*)-5-23a]

TsCl (714 mg, 3.75 mmol) in toluene (2.5 mL) was added to a stirred suspension of 2-chloro-3-oxobutanoate **5-22a** (2.50 mmol), NMI (304 mg, 3.75 mmol), and *i*Pr_2NEt (484 mg, 3.75 mmol) in toluene (2.5 mL) at 0 − 5 °C and the mixture was stirred at the same temperature for 1 h. Water was added to the mixture, which was extracted twice with AcOEt. The combined organic phase was washed with water, brine, dried (Na_2SO_4), and concentrated. The obtained crude product was purified by SiO_2 column chromatography (hexane/AcOEt = 10:1) to give the desired product [(*Z*)-**5-23a**, 695 mg, 91%, *E*/*Z* = 2:98].

Colorless crystals; mp 35−36 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.47 (s, 3H), 2.53 (s, 3H), 3.82 (s, 3H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.89 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.0, 21.7, 53.1, 115.8, 128.2 (2C), 129.9 (2C), 133.4, 145.9, 156.0, 162.9; IR (neat): ν_{max} = 2955, 1725, 1626, 1437, 1373, 1271, 1205, 1169, 1062, 1041, 909, 803, 719 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{12}H_{13}O_5ClS$ $[M+Na]^+$ 327.0070; found: 327.0077.

Methyl (*E*)-2-chloro-3-(tosyloxy)but-2-enoate [(*E*)-5-23a]

2-Chloro-3-oxobutanoate **5-22a** (150 mg, 1.00 mmol) in toluene (1.0 mL) was added to a stirred suspension of NaH (60%; 60 mg, 1.50 mmol) and TMEDA (174 mg, 1.50 mmol) in toluene (1.0 mL) at 0 − 5 °C, followed by addition of TsCl (286 mg, 1.50 mmol). The reaction mixture was stirred at the same temperature for 1 h. Water was added to the mixture, which was extracted twice with AcOEt. The combined organic phase was washed with water, brine, dried (Na_2SO_4), and concentrated. The obtained crude product was purified by SiO_2 column chromatography (hexane/AcOEt = 10/1) to give the desired product [(*E*)-**5-23a**, 257 mg, 84%, *E*/*Z* = 87:13].

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.21 (s, 3H), 2.47 (s, 3H), 3.67 (s, 3H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.82−7.86 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.5, 21.6, 52.8, 118.5, 128.2 (2C), 129.8 (2C), 132.8, 145.8, 151.3, 161.2; IR (neat): ν_{max} = 2955, 1732, 1632, 1435, 1375, 1287, 1258, 1165, 1091, 943, 909, 814, 723 cm^{-1}.

Methyl (*Z*)-2-chloro-3-phenyl-3-(tosyloxy)acrylate [(*Z*)-5-23b]

TsCl (21.1 g, 111 mmol) in toluene (75 mL) was added to a stirred suspension of 2-chloro-3-phenyl-3-oxobutanoate **5-22b** (15.7 g, 73.8 mmol), NMI (9.11 g, 111 mmol), and *i*Pr$_2$NEt (14.3 g, 111 mmol) in toluene (75 mL) at 0 − 5 °C and the mixture was stirred at the same temperature for 1 h. Water was added to the mixture, which was extracted twice with AcOEt. The combined organic phase was washed with water, brine, dried (Na_2SO_4), and concentrated. The obtained crude solid was recrystallized (*i*PrOH 35 mL) to give the desired product [(*Z*)-**5-23b**, 22.4 g, 83%, *E*/*Z* = 2:98].

Colorless crystals; mp 82−83 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.40 (s, 3H), 3.61 (s, 3H), 7.17 (d, *J* = 8.6 Hz, 2H), 7.22−7.28 (m, 4H), 7.33−7.38 (m, 1H), 7.54 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.6, 53.0, 117.1, 128.0 (2C), 128.1 (2C), 129.1 (2C), 129.5 (2C), 130.5, 131.7, 133.6, 145.4, 153.2, 163.1; IR (neat): ν_{max} = 2953, 1734, 1598, 1384, 1280, 1192, 1178, 1044, 806 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{17}H_{15}O_5ClS$ $[M+Na]^+$ 389.0226; found: 389.0225.

Methyl (*E*)-2-chloro-3-phenyl-3-(tosyloxy)acrylate [(*E*)-5-23b]

2-Chloro-3-phenyl-3-oxobutanoate **5-22b** (106 mg, 0.50 mmol) in toluene (0.50 mL) was added to a stirred suspension of NaH (60%; 30 mg, 0.75 mmol) and TMEDA (87 mg, 0.75 mmol) in toluene (0.50 mL) at 0 − 5 °C, followed by addition of TsCl (143 mg, 0.75 mmol). The reaction mixture was stirred at the same temperature for 1 h. Water was added to the mixture, which was extracted twice with AcOEt. The combined organic phase was washed with water, brine, dried (Na_2SO_4), and concentrated. The obtained crude product was purified by SiO_2 column chromatography (hexane/AcOEt = 8/1) to give the desired product [(*E*)-**5-23b**, 160 mg, 89%, *E*/*Z* = 94:6].

Colorless crystals; mp 69−71 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.37 (s, 3H), 3.89 (s, 3H), 7.10 (d, *J* = 8.6 Hz, 2H), 7.20 (t, *J* = 8.0 Hz, 2H), 7.28−7.33 (m, 1H), 7.34−7.38 (m, 2H), 7.44 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.5, 53.2, 118.5, 127.8 (2C), 128.0 (2C), 129.36 (2C), 129.38 (2C), 130.3, 130.9, 133.3, 145.1, 150.2, 162.2; IR (neat): ν_{max} = 2954, 1735, 1597, 1384, 1252, 1192, 1178, 1016, 734 cm^{-1}.

Methyl (*Z*)-2-chloro-3-phenylbut-2-enoate [(*Z*)-5-24a]

A suspension of enol tosylate (*Z*)-**5-23a** (152 mg, 0.50 mmol), $PhB(OH)_2$ (73 mg, 0.60 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), PPh_3 (13 mg, 0.050 mmol), and K_2CO_3 (83 mg, 0.60 mmol) in *i*PrOH (1.5 mL)/water (0.50 mL) was stirred at 60 − 65 °C under an argon atmosphere for 1 h. After cooling to room temperature, 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 column chromatography on silica gel (hexane/AcOEt = 30:1) to give the desired product [(*Z*)-**5-24a**, 90 mg, 86%, *E*/*Z* = 2:98].

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.42 (s, 3H), 3.88 (s, 3H), 7.25 (d, *J* = 7.5 Hz, 2H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.40 (t, *J* = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.4, 52.7, 118.5, 126.9 (2C), 127.9, 128.3 (2C), 141.5, 148.5, 164.4; IR (neat): ν_{max} = 2953, 2843, 1721, 1595, 1491, 1435, 1374, 1254 cm^{-1}.

Methyl (*E*)-2-chloro-3-phenylbut-2-enoate [(*E*)-5-24a]

Following the procedure for the preparation of (*Z*)-**5-24a**, the reaction of enol tosylate (*E*)-**5-23a** (159 mg, 0.52 mmol) using $PhB(OH)_2$ (76 mg, 0.63 mmol), $Pd(OAc)_2$ (5.8 mg, 0.026 mmol), PPh_3 (14 mg, 0.052 mmol), and K_2CO_3 (87 mg, 0.63 mmol) gave the desired product [(*E*)-**5-24a**, 98 mg, 89%, *E*/*Z* = >98:2].

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.30 (s, 3H), 3.53 (s, 3H), 7.14−7.19 (m, 2H), 7.29−7.37 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.4, 52.4, 120.0, 126.7 (2C), 128.0, 128.2 (2C), 140.8, 146.1, 164.4; IR (neat): ν_{max} = 2951, 2845, 1721, 1595, 1491, 1435, 1374, 1254 cm^{-1}.

Methyl (*Z*)-2-chloro-3-phenyl-3-(*p*-tolyl)acryate [(*Z*)-5-24b]

Following the procedure for the preparation of (*Z*)-**5-24a**, the reaction of enol tosylate (*Z*)-**5-23b** (367 mg, 1.00 mmol) using (*p*-Me)$C_6H_4B(OH)_2$ (163 mg, 1.20 mmol), $Pd(OAc)_2$ (2.2 mg, 0.010 mmol), Ph-RuPhos (9.1 mg, 0.020 mmol), and K_2CO_3 (101 mg, 1.20 mmol) at 20 − 25 °C gave the desired product [(*Z*)-**5-24b**, 238 mg, 83%, *E*/*Z* = 7:93].

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.36 (s, 3H), 3.57 (s, 3H), 7.13−7.22 (m, 6H), 7.29−7.33 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.3, 52.6, 119.2, 128.2 (2C), 128.5, 128.7 (2C), 128.8 (2C), 129.6 (2C), 136.1, 138.8, 140.3, 148.0, 165.7; IR (neat): ν_{max} = 3065, 2953, 1732, 1597, 1381, 1246, 1177, 1011, 731 cm^{-1}.

Methyl (*E*)-2-chloro-3-phenyl-3-(*p*-tolyl)acryate [(*E*)-5-24b]

Following the procedure for the preparation of (*Z*)-**5-24a**, the reaction of enol tosylate (*E*)-**5-23b** (3.67 g, 10.0 mmol) using (*p*-Me)$C_6H_4B(OH)_2$ (1.63 g, 12.0 mmol), $Pd(OAc)_2$ (112 mg, 0.500 mmol), PPh_3 (262 mg, 1.00 mmol), and K_2CO_3 (1.66 g, 12.0 mmol) at 40 − 45 °C gave the desired product [(*E*)-**5-24b**, 2.54 g, 89%, *E*/*Z* = >98:2].

Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.36 (s, 3H), 3.57 (s, 3H), 7.13−7.22 (m, 6H), 7.29−7.33 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.3, 52.6, 119.2, 128.2 (2C), 128.5, 128.7 (2C), 128.8 (2C), 129.6

(2C), 136.1, 138.8, 140.3, 148.0, 165.7; IR (neat): ν_{max} = 3059, 2953, 1722, 1597, 1379, 1298, 1177, 1045, 804, 733 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{17}H_{15}O_2Cl$ $[M+Na]^+$ 309.0658; found: 309.0647.

Methyl (*E*)-2,3-diphenyl-3-(*p*-tolyl)acrylate [(*E*)-5-25b-1]

A suspension of enol tosylate (*Z*)-**5-24b** (143 mg, 0.50 mmol), $PhB(OH)_2$ (73 mg, 0.60 mmol), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), SPhos (2.0 mg, 0.005 mmol), and K_2CO_3 (83 mg, 0.60 mmol) in toluene (1.5 mL)/water (0.50 mL) was stirred at 80 − 85 °C under an argon atmosphere for 1 h. After cooling to room temperature, 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 solid was washed with hexane to give the desired product [(*E*)-**5-25b-1**, 151 mg, 92%, *E*/*Z* = >98:2].

Colorless solid; mp 128−129 °C; ^1H NMR (500 MHz, $CDCl_3$): δ = 2.26 (s, 3H), 3.53 (s, 3H), 6.87 (d, *J* = 8.0 Hz, 2H), 6.93 (d, *J* = 8.0 Hz, 2H), 7.09−7.13 (m, 2H), 7.16−7.21 (m, 3H), 7.24−7.28 (m, 2H), 7.30−7.34 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.2, 51.9, 127.3, 128.0, 128.1 (2C), 128.2 (2C), 128.5 (2C), 129.0 (2C), 129.8 (2C), 130.9 (2C), 132.9, 137.49, 137.55, 137.7, 142.6, 146.4, 171.0; IR (neat): ν_{max} = 3022, 2947, 1717, 1493, 1431, 1217, 1148, 1042, 816, 752, 696 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{23}H_{20}O_2$ $[M+Na]^+$ 351.1361; found: 351.1345.

Methyl (*Z*)-2,3-diphenyl-3-(*p*-tolyl)acrylate [(*Z*)-5-25b-1]

Following the procedure for the preparation of (*E*)-**5-25b-1**, the reaction of enol tosylate (*E*)-**5-24b** (143 mg, 0.50 mmol) using $PhB(OH)_2$ (73 mg, 0.60 mmol), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), SPhos (2.0 mg, 0.005 mmol), and K_2CO_3 (83 mg, 0.60 mmol) gave the desired product [(*Z*)-**5-25b-1**, 151 mg, 92%, *E*/*Z* = 2:>98].

Colorless solid; mp 146−147 °C; ^1H NMR (500 MHz, $CDCl_3$): δ = 2.36 (s, 3H), 3.58 (s, 3H), 6.97−7.01 (m, 2H), 7.06−7.20 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.3, 52.0, 127.3, 127.6, 127.8 (2C), 128.2 (2C), 128.91 (2C), 128.93 (2C), 129.8 (2C), 130.9 (2C), 132.9, 137.6, 138.0, 139.4, 140.7, 146.3, 171.1; IR (neat): ν_{max} = 3021, 2949, 1717, 1429, 1263, 1220, 1146, 1040, 822, 754, 694 cm^{-1}.

Methyl (*E*)-2-(phenyl(*p*-tolyl)methylene)octanoate [(*E*)-5-25b-2]

A suspension of enol tosylate (*Z*)-**5-24b** (72 mg, 0.25 mmol), (*n*hexyl)$B(OH)_2$ (58 mg, 0.45 mmol), $Pd(OAc)_2$ (1.7 mg, 0.0075 mmol), SPhos (3.1 mg, 0.0075 mmol), and K_2CO_3 (62 mg, 0.45 mmol) in toluene (0.75 mL)/water (0.25 mL) was stirred at 80 − 85 °C under an argon atmosphere for 3 h. After cooling to room temperature, 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 column chromatography on silica gel (hexane/AcOEt = 50:1) to give the desired product [(*E*)-**5-25b-2**, 68 mg, 81%, *E*/*Z* = 98:2].

Colorless oil; ^1H NMR (500 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 6.9 Hz, 3H), 1.19−1.32 (m, 6H), 1.43−1.52 (m, 2H), 2.33−2.39 (m, 2H), 2.35 (s, 3H), 3.45 (s, 3H), 7.02−7.06 (m, 2H), 7.09−7.16 (m, 4H), 7.19−7.27 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.0, 21.2, 22.5, 28.9, 29.1, 31.5, 32.3, 51.4, 127.3, 127.9 (2C), 128.5 (2C), 128.8 (2C), 129.1 (2C), 133.5, 137.3, 138.0, 142.6, 145.4, 171.7; IR (neat): ν_{max} = 2924, 2857, 1715,

1431, 1325, 1246, 1132, 818, 727, 700 cm^{-1}.

Methyl (*Z*)-2-(phenyl(*p*-tolyl)methylene)octanoate [(*Z*)-5-25b-2]

Following the procedure for the preparation of (*E*)-**5-25b-2**, the reaction of enol tosylate (*E*)-**5-24b** (72 mg, 0.25 mmol) using (*n*hexyl)$B(OH)_2$ (58 mg, 0.45 mmol), $Pd(OAc)_2$ (1.7 mg, 0.0075 mmol), SPhos (3.1 mg, 0.0075 mmol), and K_2CO_3 (62 mg, 0.45 mmol) gave the desired product [(*Z*)-**5-25b-2**, 57 mg, 68%, *E*/*Z* = 2:98].

Colorless oil; ^1H NMR (500 MHz, $CDCl_3$): δ = 0.85 (t, *J* = 6.9 Hz, 3H), 1.16−1.30 (m, 6H), 1.42−1.50 (m, 2H), 2.29−2.36 (m, 2H), 2.31 (s, 3H), 3.50 (s, 3H), 6.98−7.02 (m, 2H), 7.03−7.07 (m, 2H), 7.13−7.17 (m, 2H), 7.26−7.35 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.0, 21.2, 22.5, 28.9, 29.1, 31.4, 32.3, 51.4, 127.4, 128.1 (2C), 128.4 (2C), 128.6 (2C), 129.1 (2C), 133.2, 137.1, 139.3, 141.1, 145.3, 171.7; IR (neat): ν_{max} = 2924, 2857, 1718, 1431, 1325, 1244, 1132, 908, 818, 731, 700 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{23}H_{28}O_2$ $[M+Na]^+$ 359.1987; found: 359.1993.

Methyl (*E*)-3-phenyl-2-(thiophen-3-yl)-3-(*p*-tolyl)acrylate [(*E*)-5-25b-3]

Following the procedure for the preparation of (*E*)-**5-25b-2**, the reaction of enol tosylate (*Z*)-**5-24b** (72 mg, 0.25 mmol) using (3-thienyl)$B(OH)_2$ (38 mg, 0.30 mmol), $Pd(OAc)_2$ (0.6 mg, 0.0025 mmol), SPhos (1.0 mg, 0.0025 mmol), and K_2CO_3 (41 mg, 0.30 mmol) gave the desired product [(*E*)-**5-25b-3**, 79 mg, 94%, *E*/*Z* = 98:2].

Colorless solid; mp 110−112 °C; ^1H NMR (500 MHz, $CDCl_3$): δ = 2.31 (s, 3H), 3.54 (s, 3H), 6.66 (dd, *J* = 5.2, 1.2 Hz, 1H), 6.94−6.97 (m, 3H), 7.01 (d, *J* = 8.0 Hz, 2H), 7.09 (dd, *J* = 5.2, 2.9 Hz, 1H), 7.22−7.25 (m, 2H), 7.28−7.33 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.2, 51.9, 124.6, 125.1, 127.7, 128.0, 128.1 (2C), 128.5, 128.8 (2C), 128.9 (2C), 130.3 (2C), 137.4, 137.8, 137.9, 142.3, 145.7, 170.8; IR (neat): ν_{max} = 3022, 2947, 1717, 1431, 1219, 1142, 1040, 754, 719 cm^{-1}.

Methyl (*Z*)-3-phenyl-2-(thiophen-3-yl)-3-(*p*-tolyl)acrylate [(*Z*)-5-25b-3]

Following the procedure for the preparation of (*E*)-**5-25b-1**, the reaction of enol tosylate (*E*)-**5-24b** (72 mg, 0.25 mmol) using (3-thienyl)$B(OH)_2$ (38 mg, 0.30 mmol), $Pd(OAc)_2$ (0.6 mg, 0.0025 mmol), SPhos (1.0 mg, 0.0025 mmol), and K_2CO_3 (41 mg, 0.30 mmol) gave the desired product [(*Z*)-**5-25b-3**, 67 mg, 80%, *E*/*Z* = 3:97].

Colorless solid; mp 131−133 °C; ^1H NMR (500 MHz, $CDCl_3$): δ = 2.35 (s, 3H), 3.59 (s, 3H), 6.62 (d, *J* = 4.6 Hz, 1H), 6.93 (d, *J* = 2.9 Hz, 1H), 7.05−7.15 (m, 7H), 7.18−7.25 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.3, 52.0, 124.6, 125.1, 127.6, 127.8, 128.0 (2C), 128.5, 128.8 (2C), 128.9 (2C), 130.3 (2C), 137.4, 137.9, 139.1, 141.0, 145.5, 170.9; IR (neat): ν_{max} = 3022, 2947, 1717, 1431, 1258, 1219, 142, 1036, 743, 698 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{21}H_{18}O_2S$ $[M+Na]^+$ 357.0925; found: 359.0937.

Methyl (*E*)-4-phenyl-2-(phenyl(*p*-tolyl)methylene)but-3-ynoate [(*E*)-5-25b-4]

A suspension of enol tosylate (*Z*)-**5-24b** (72 mg, 0.25 mmol), phenylacetylene (33 mg, 0.33 mmol),

[$Pd(NCMe)_2Cl_2$] (1.0 mg, 0.0025 mmol), XPhos (3.6 mg, 0.0075 mmol), and Cs_2CO_3 (212 mg, 0.65 mmol) in MeCN (0.50 mL) was stirred at 90 − 95 °C under an argon atmosphere for 3 h. After cooling to room temperature, 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 column chromatography on silica gel (hexane/AcOEt = 30:1) to give the desired product [(*E*)-**5-25b-4**, 64 mg, 73%, *E*/*Z* = 91:9].

Orange solid; mp 150−152 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.39 (s, 3H), 3.61 (s, 3H), 7.15−7.21 (m, 4H), 7.27−7.36 (m, 8H), 7.41−7.44 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.4, 52.3, 87.4, 94.1, 113.4, 123.1, 128.0 (2C), 128.2 (2C), 128.3, 128.4 (2C), 128.6, 129.2 (2C), 130.5 (2C), 131.5 (2C), 137.0, 139.3, 140.9, 155.9, 167.4; IR (neat): ν_{max} = 3028, 2949, 1726, 1487, 1435, 1327, 1229, 1098, 756 cm^{-1}.

Methyl (*Z*)-4-phenyl-2-(phenyl(*p*-tolyl)methylene)but-3-ynoate [(*Z*)-5-25b-4]

Following the procedure for the preparation of (*E*)-**5-25b-4**, the reaction of enol tosylate (*E*)-**5-24b** (72 mg, 0.25 mmol) using phenylacetylene (33 mg, 0.33 mmol), [$Pd(NCMe)_2Cl_2$] (1.0 mg, 0.0025 mmol), XPhos (3.6 mg, 0.0075 mmol), and Cs_2CO_3 (212 mg, 0.65 mmol) gave the desired product [(*Z*)-**5-25b-4**, 66 mg, 75%, *E*/*Z* = 5:95].

Yellow solid; mp 136−137 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.36 (s, 3H), 3.66 (s, 3H), 7.08 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 7.24−7.30 (m, 5H), 7.34−7.38 (m, 3H) , 7.48−7.53 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.3, 52.3, 87.4, 94.0, 113.6, 123.0, 127.6 (2C), 128.2 (2C), 128.3, 128.8 (2C), 129.0, 129.1 (2C), 130.5 (2C), 131.4 (2C), 137.6, 138.7, 140.2, 156.1, 167.4; IR (neat): ν_{max} = 3022, 2953, 1730, 1487, 1435, 1327, 1225, 1163, 1099, 910, 750, 685 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{25}H_{20}O_2$ $[M+Na]^+$ 375.1361; found: 375.1351.

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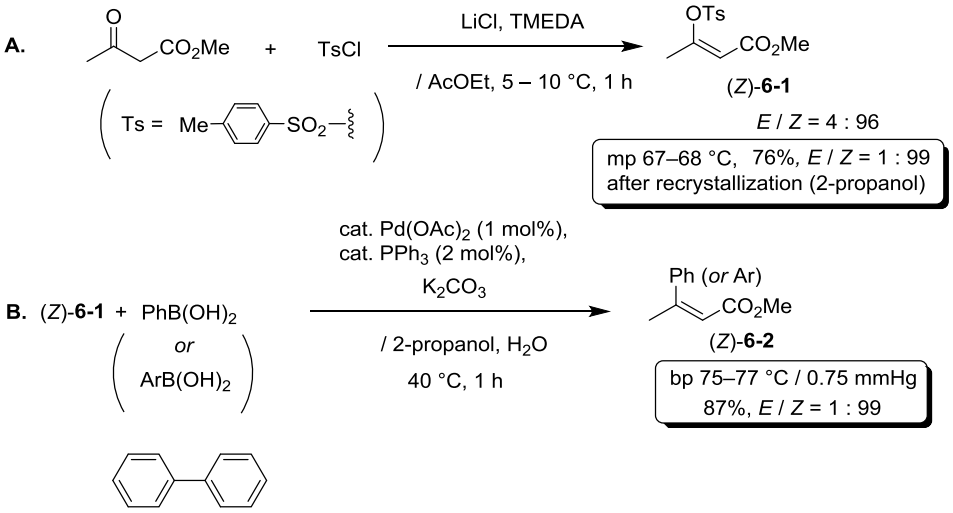
Chapter 6.
(Z)-Enol p-Tosylate Derived from Methyl Acetoacetate: A Useful Cross-coupling Partner for the Synthesis of Methyl (Z)-3-Phenyl (or Aryl)-2-butenoate

Abstract

A synthesis of methyl (*Z*)-3-phenyl-2-butenoate [methyl (*Z*)-β-methylcinnamate] (*Z*)-**6-2** directed for *Organic Syntheses* is presented. Despite its simple structure, hitherto reported methods require multi-steps or expensive reagents, low temperature, and long reaction period. The enol tosylation of methyl acetoacetate utilizing TsCl−TMEDA−LiCl reagent in AcOEt solvent gives (*Z*)-3-(*p*-toluenesulfonyloxy)but-2-enoate (*Z*)-**6-1**, which is converted to (*Z*)-**6-2** utilizing a highly cost-effective $Pd(OAc)_2$ (1 mol%)/PPh_3 (2 mol%)-catalyzed Suzuki-Miyaura cross-coupling with nearly perfect (*Z*)-stereoretention. Throughout the procedure, tedious column chromatographic purification is not required. In addition, environmentally benign solvents, such as AcOEt, *i*PrOH, and H_2O, are employed for both of two reaction steps and the corresponding extraction (work-up) steps. In addition, the synthesis of the aryl analogues including stereocomplementary (*E*)-isomer are addressed.



In this chapter, according to the policy of "Organic Syntheses" as shown in below, the author describes the procedure section in the first place.

"Since 1921, *Organic Syntheses* has provided the chemistry community with detailed, reliable, and carefully checked procedures for the synthesis of organic compounds. Some procedures describe practical methods for the preparation of specific compounds of interest, while other procedures illustrate important synthetic methods with general utility. Each procedure is written in considerably more detail as compared to typical experimental procedures in other journals, and each reaction with its characterization data has been repeated several times and carefully "checked" for reproducibility in the laboratory of a member of the Board of Editors."

"All organic chemists have experienced frustration at one time or another when attempting to repeat reactions based on experimental procedures found in journal articles. To ensure reproducibility, *Organic Syntheses* requires experimental procedures written with considerably more detail as compared to the typical procedures found in other journals and in the "Supporting Information" sections of papers. In addition, each *Organic Syntheses* procedure is carefully "checked" for reproducibility in the laboratory of a member of the Board of Editors."

"The appropriate scale for procedures will vary widely depending on the nature of the chemistry and the compounds synthesized in the procedure. However, some general guidelines are possible. For procedures in which the principal goal is to illustrate a synthetic method or strategy, it is expected, in general, that the procedure should result in at least 5 g and no more than 50 g of the final product. In cases where the point of the procedure is to provide an efficient method for the preparation of a useful reagent or synthetic building block, the appropriate scale also should be between 5 and 50 g of final product. Exceptions to these guidelines may be granted in special circumstances. For example, procedures describing the preparation of reagents employed as catalysts will often be acceptable on a scale of less than 5 g."

Procedure

A. *(Z)-3-(p-toluenesulfonyloxy)but-2-enoate [(Z)-**6-1**)].* A 500-mL, three-necked, round-bottomed flask attached to a $CaCl_2$ drying tube, capped with a glass stopper, and fitted with a thermometer, a Teflon-coated magnetic stir bar (**Note 1**) is charged with methyl 3-oxobutanoate (methyl acetoacetate) (17.4 g, 150 mmol) (**Note 2**) and AcOEt (150 mL). To a stirred mixture, LiCl (7.63 g, 180 mmol) (**Note 3**) is added in one portion. TMEDA (26.8 mL, 180 mmol) (**Note 4**) is added dropwise over 2 min to the suspension.

The vigorously stirred white-colored suspension is immersed in an ice-cooling bath, and *p*-toluenesulfonyl (tosyl) chloride (TsCl) (34.3 g, 180 mmol) (**Note 5**) is added portionwise (3 portions) over 10–15 min after temporarily removing the glass stopper while maintaining the inner temperature below 10 °C (**Note 6**) <**Figure 6-1**>. The suspension becomes a well-equalized white slurry <**Figure 6-2**> after ca. 10 min of the addition of TsCl.

Figure 6-1. Addition of TsCl.

Figure 6-2. The reaction mixture in step A.

The reaction mixture is stirred for 1 h at ~5 °C, and water (75 mL) is added to the resulting mixture for ca. 1

min to maintain the inner temperature below 15 °C. The suspension immediately develops two transparent phases <**Figure 6-3**>.

Figure 6-3. The reaction mixture after quench with H_2O.

The mixture is moved into a 500-mL separatory funnel [the flask is rinsed twice with AcOEt (10 x 2 mL)]. The organic phase is separated and the aqueous phase is re-extracted with AcOEt (50 mL). The combined organic phase is washed with aqueous 1M HCl (75 mL) and brine (75 mL), dried over Na_2SO_4 (75 g), filtered, and concentrated under reduced pressure using a rotary evaporator (15-20 mmHg), (bath temperature, ca. 40–45 °C) and a vacuum pump with gentle heating using a dryer to remove the AcOEt completely.

The obtained slightly orange-colored oil solidifies after a few min (**Note 7**) <**Figure 6-4**>. The crude solid (38.9 g) in a 100 mL round bottom flask was crushed into particles, which was transferred to a 100 mL Erlenmeyer flask using 2-propanol (40 mL) (**Note 8**). The solid was completely dissolved with heating by a dryer at 50−55 °C with shaking for ca. 5 min. The solution was then allowed to cool to room temperature (20−25 °C). Crystallization was initiated by adding a small amounts of seed crystals (crude solid), and the flask was kept at 0−5 °C for 15 h. Using a glass filter (G3, 70 mm diameter) the first crop is collected and washed twice with 2-propanol (40 x 2 mL) to yield 30.7 g (76%, ≥98% ds) of the desired product (*Z*)-**6-1** as colorless crystals (**Note 9**) <**Figure 6-5**>.

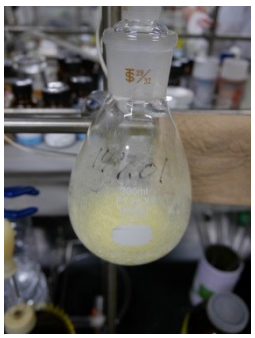


Figure 6-4. The crude solid obtained in step A.

Figure 6-5. Pure (*Z*)-**6-1** after recrystallization.

B. *Methyl (Z)-3-phenyl (or Aryl)-2-butenoate [(Z)-**6-2**]*. A 100-mL, three-necked, round-bottomed flask equipped with a pressure-equalizing Ar baloon, capped with a glass stopper, a thermometer, and a

Teflon-coated magnetic stirring bar (**Note 10**), is charged with 2-propanol (75 mL) and water (25 mL) (**Note 11**).

The stirred white-colored suspension is immersed in a temperature-controlled water bath and (*Z*)-enol tosylate [(*Z*)-**6-1**] (13.5 g, 50 mmol), $PhB(OH)_2$ (6.40 g, 52.5 mmol) (**Note 12**), and K_2CO_3 (7.26 g, 52.5 mmol) (**Note 13**) are successively added, each in one portion after temporarily removing the glass stopper. The reaction mixture is warmed to 30–35 °C (inner temperature) with vigorous stirring. PPh_3 (262 mg, 1.0 mmol) (**Note 14**) and $Pd(OAc)_2$ (112 mg, 0.5 mmol) (**Note 15**) are then successively added to the mixture, each in one portion while maintaining the inner temperature below 40 °C, followed by stirring for 1 h (**Note 16**).

Water (50 mL) is added to the reaction mixture, which is filtered through a glass filter (G3, 70 mm diameter) with 10 g of Celite® pad washing with AcOEt (100 mL). The filtrate is moved into a 300-mL separatory funnel [the flask is rinsed twice with AcOEt (10 x 2 mL)]. The organic phase is separated and the aqueous phase is re-extracted with AcOEt (50 mL). The combined organic phase is washed with aqueous 1M NaOH (50 mL) and brine (50 mL), dried over Na_2SO_4 (50 g), filtered, and concentrated under reduced pressure using a rotary evaporator (15−20 mmHg), (bath temperature, ca. 40–45 °C).

The obtained black colored oil (8.75 g) is moved into a 20-mL round-bottomed flask, into which a Teflon-coated magnetic stir bar is put. Distillation while immersed in a temperature-controlled oil bath under reduced pressure using a vacuum pump gives the desired product (*Z*)-**6-2** (7.64 g, 87% yield, ≥98% ds) as a colorless oil (Note 17) <**Figure 6-6**>.

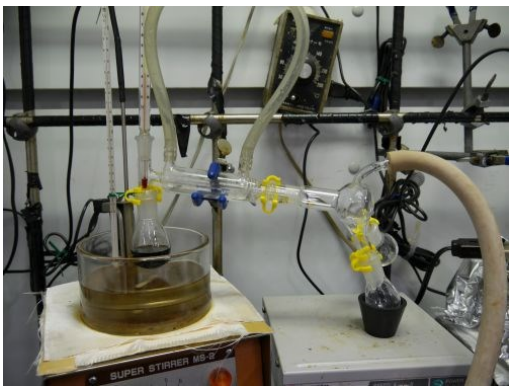


Figure 6-6. Distillation set-up in step B.

Notes

1. A magnetic stirring bar (for example, egg-shaped, 50 mm length x 20 mm diameter) is used, since the reaction mixture produces a large quantity of salts. The white slurry is smoothly stirred throughout the reaction.
2. Methyl 3-oxobutanoate (Methyl acetoacetate) (GC purity 99.0%) was purchased from Tokyo Chemical Industry Co., Ltd. and used as received.
3. Lithium chloride (LiCl) (99.0%) anhydrous was purchased from Wako Pure Chemical Industries, Ltd. and used as received.
4. *N*,*N*,*N*',*N*'-Tetramethylethylenediamine (TMEDA) (>98.0%) was purchased from Tokyo Chemical

Industry Co., Ltd. and used as received.

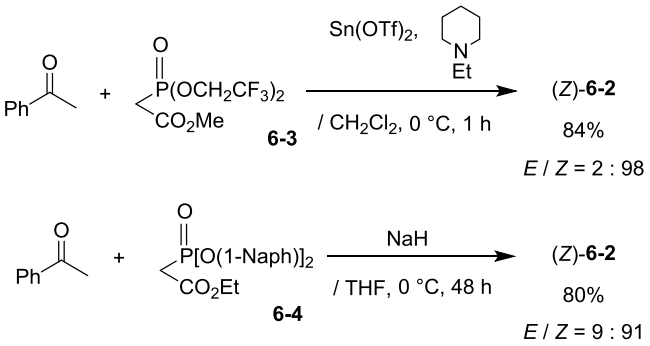
5. *p*-Toluenesulfonyl (tosyl) chloride (TsCl) (>99.0%) was purchased from Tokyo Chemical Industry Co., Ltd. and used as received; a fresh lot was used. Once the cap was opened, it should be surely put the cap after the use.
6. An exothermic reaction with production of salts.
7. Usually, the compound solidified immediately when it is left.
8. 2-Propanol (>99.7%, GLC) was purchased was purchased from Wako Pure Chemical Industries, Ltd. and used as received.
9. Stable solids can be stored in a brown colored bottle at room temperature over months. Physical and spectroscopic properties of (*Z*)-**6-1**: colorless crystals; mp 67.0–68.0 °C [lit. (Our group, *Org. Lett.* **2008**, *10*, 2131), 62.0–63.0 °C]; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.14 (s, 3H), 2.46 (s, 3H), 3.58 (s, 3H), 5.50 (s, 1H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.91 ppm (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.6, 51.2, 110.2, 128.2, 129.6, 133.2, 145.4, 156.4, 163.1 ppm. IR (KBr): ν_{max} = 3447, 2924, 1738, 1669, 1497, 1445, 1373, 1335 cm^{-1}. Anal. calcd for $C_{12}H_{14}O_5S$: C, 53.32; H, 5.22. Found; C, 53.30; H, 5.20. The second crop did not appear. Concentration of 2-propanol of the mother and the washing liquors by vacuum pump, gave yellow colored oil (8.59 g), [Molar ratio; (*Z*)-**6-1**, (*E*)-**6-1**, and unreacted TsCl = c.a. 1 : 0.4 : 0.6]. The first recrystallization efficiency seems to be sufficient and the total material balance is reasonable.
10. A magnetic stirring bar (for example, egg-shaped, 40 mm length x 20 mm diameter) is used, since the reaction mixture produces a large quantity of salts.
11. Distilled water was used.
12. Phenylboronic acid [$PhB(OH)_2$] was purchased from Wako Pure Chemical Industries, Ltd. and used as received.
13. Potassium carbonate (K_2CO_3) (>99.5%) was purchased from Wako Pure Chemical Industries, Ltd. and used as received.
14. Triphenylphosphine (PPh_3) (>95.0%) was purchased from Tokyo Chemical Industry Co., Ltd. and used as received.
15. Palladium acetate [$Pd(OAc)_2$] (>97.0%) was purchased from Wako Pure Chemical Industries, Ltd. and used as received.
16. A slight exothermic reaction with production of salts.
17. Physical and spectroscopic properties of (*Z*)-**6-2**: 75−77 °C/0.75 mmHg. colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.19 (d, *J* = 0.9 Hz, 3H), 3.55 (s, 3H), 7.18−7.23 (m, 2H), 7.29−7.38 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.1, 50.9, 117.0, 126.7, 127.7, 127.8, 140.5, 155.8, 166.1; ν_{max} = 2950, 1734, 1637, 1491, 1437, 1375, 1233, 1165 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{11}H_{12}O_2$ $[M+Na]^+$ 199.0735; found: 199.0735. The purity of (*Z*)-**6-2** is estimated at least >97%.

Discussion

Stereocontrolled preparation of ubiquitous (*E*)- and (*Z*)-α,β-unsaturated esters is pivotal in organic syntheses, because these important compounds serve as useful structural scaffolds for various (*E*)- and (*Z*)-stereodefined olefins, conjugate (Michael) addition acceptors, and catalytic asymmetric hydrogenation substrates. Methyl (*Z*)-3-aryl-2-butenoates [methyl (*Z*)-β-methylcinnamates] [aryl = Ph; (*Z*)-**6-2**] have a simple structure, but are promising synthetic building blocks for various stereodefined alkenes. Despite the high demand, (*Z*)-stereoselective synthetic methods are quite limited compared with those for (*E*)-isomers, due to the inherent (*E*)-stable nature of cinnamate esters. Here we present a practical, accessible, and robust synthesis of (*Z*)-**6-2** and its aryl analogues, including stereocomplementary (*E*)-isomers.

The relevant reported methods for the synthesis of (*Z*)-**6-2** are as follows. Utilization of Horner-Wadsworth-Emmons (HWE) reactions between acetophenone and elaborate HWE reagents is regarded as the most straightforward method. A literature survey revealed two methods producing high (*Z*)-stereoselectivity. One is a $Sn(OTf)_2$ (Tf = SO_2CF_3)/*N*-ethylpiperidine-mediated reaction using Still-Gennari's HWE reagent **6-3** with acetophenone to afford 84% yield, *E*/*Z* =2:98 ratio, which was developed by Sano and Nagao's group (**Scheme 6-1**).[1] Another noteworthy example developed by Kojima's group[3] is the reaction using $(1\text{-naphthoxy})_2P(O)CH_2CO_2Et$ HWE reagent **6-4** with acetophenone using NaH to afford 80% yield, *E*/*Z* = 9:91, although it requires conditions of 0 °C for 48 h.

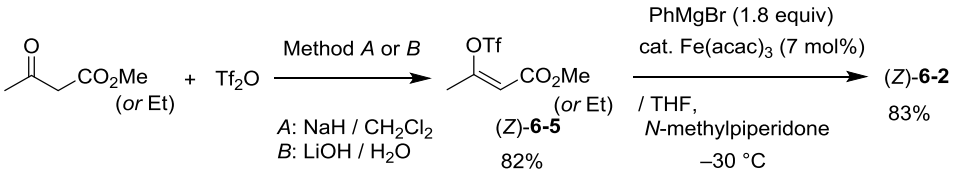
These one-step methods produce high yields with good to excellent *E*/*Z*-ratios, but a couple of the reagents [**6-3** and $Sn(OTf)_2$] are very expensive and reagent **6-4** is not commercially available. Other HWE-conducted methods result in moderate to low yield and/or *E*/*Z*-selectivity. On the whole, these approaches suffer from a lack of the atom-economy due to use of the specific phosphonate reagents. In addition, the yield and *E*/*Z*-selectivity using other aryl methyl ketone acceptors apparently depends on the nature of the employed ketones.



Scheme 6-1. Two representative methods utilizing the Horner-Wadsworth-Emmons (HWE) reaction.

Iron-catalyzed cross-coupling of Grignard reagents with an enol triflate of methyl or ethyl acetoacetate (*Z*)-**6-5** was developed by Fürstner's group (Scheme 6-2).[3-5] The preparation of (*Z*)-**6-5** utilizes triflic anhydride (Tf_2O) / NaH (Method A). This excellent method is the most relevant for our strategy. A major drawback is that Tf_2O is ca. 15−30 times more expensive than TsCl. In addition, Tf_2O is highly toxic and hazardous with a low boiling point (81−83 °C) and reacts violently with water. Enol triflate (*Z*)-**6-5** is an oil

compound but its stability for distillation is unclear and only flash column chromatography is required for its purification. A practical preparative method for (*Z*)-**6-5**, developed by Frantz's group (Method B) also requires flash column chromatographic purification.[6] This iron-catalyzed cross-coupling requires 1.8 equiv of PhMgBr at low temperature (–30 °C).



Scheme 6-2. Method utilizing iron-catalyzed cross-coupling of enol triflate (*Z*)-**6-5**.

Other syntheses of (*Z*)-**6-2** are listed in chronologic order. (i) Dianion of 1-(1,2,4-triazolo-1-yl)phenylpropargyl ethyl ether, treated with MeI gave (*Z*)-**6-2** in 87% yield with *E*/*Z* = 1:4 selectivity (Katritzky's group).[7] (ii) $MeReO_3$ (5 mol%)-catalyzed condensation between ethyl diazoacetate and acetophenone in the presence of an equimolar amount of PPh_3 gave (*Z*)-**6-2** in 65% yield with *E*/*Z* = 13:87 selectivity (Kühn's group).[8] (iii) TMSOTf (equimolar amount)-promoted carbocupration of PhMgBr/CuI•2LiCl with a relatively expensive ethyl 2-butynoate gave (*Z*)-**6-2** in 88% yield with *E*/*Z* = 1:5 selectivity (Jennings and Mueller).[9]

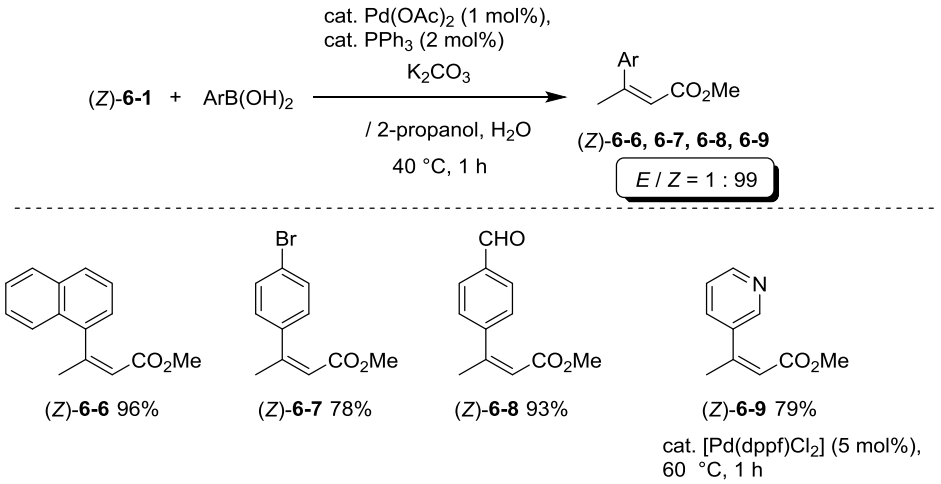
Compared with the above-mentioned methods, the present approach utilizing Suzuki-Miyaura (SM) cross-coupling with enol tosylate (*Z*)-**6-1** (≥98% ds) produced methyl (*Z*)-3-phenyl-2-butenoate (*Z*)-**6-2** and its aryl analogues in high yields with excellent (*Z*)-stereoretention (≥98% ds) in a consistent substrate-general manner and functional group compatibility (vide infra). (*Z*)-**6-1** is an easy-to-handle stable solid that can be stored neat without detectable decomposition at ambient temperature. The original preparative method[10] of (*Z*)-**6-1** utilizes LiOH/*N*-methylimidazole reagent in C_6H_5Cl or CH_2Cl_2 solvent, which was replaced with AcOEt solvent for LiCl/TMEDA. This improvement significantly increases the scalability with accessible reaction temperature (0–40 °C), short reaction periods (1 h), and easy operations for all of the procedures.

In general, although the enol triflates exhibit higher reactivity than the enol tosylates, (*Z*)-**6-1** is sufficient for the synthesis of (*Z*)-**6-2** and its aryl analogues as a robust, productive, and considerably inexpensive SM cross-coupling partner. The reaction proceeded smoothly under mild conditions with nearly perfect (*Z*)-stereoretention. The present combination of $Pd(OAc)_2$/PPh_3 is the most accessible and cost-effective catalysis among a myriad of SM cross-couplings. The loading quantity of $Pd(OAc)_2$ catalyst and PPh_3 ligand were decreased to 1 mol% and 2 mol%, respectively. A simple work-up and isolation procedure eliminating column chromatographic purification can be partially attributed to this feature. As an additional advantage, environmentally benign solvents, such as AcOEt, 2-propanol, and H_2O, could be employed for both of two reaction steps and the corresponding extraction (work-up) steps throughout the procedure.

On the other hand, stereocomplementary isomer (*E*)-**6-1**, an oil compound, is readily prepared from the same methyl acetoacetate with *E*/*Z* = 96:4 (crude product) using a different reagent, TsCl/Et_3N/*N*-methylimidazole.[10] Due to the different Rf values [(*E*)-**6-1**: 0.36, (*Z*)-**6-1**: 0.21 (hexane/AcOEt

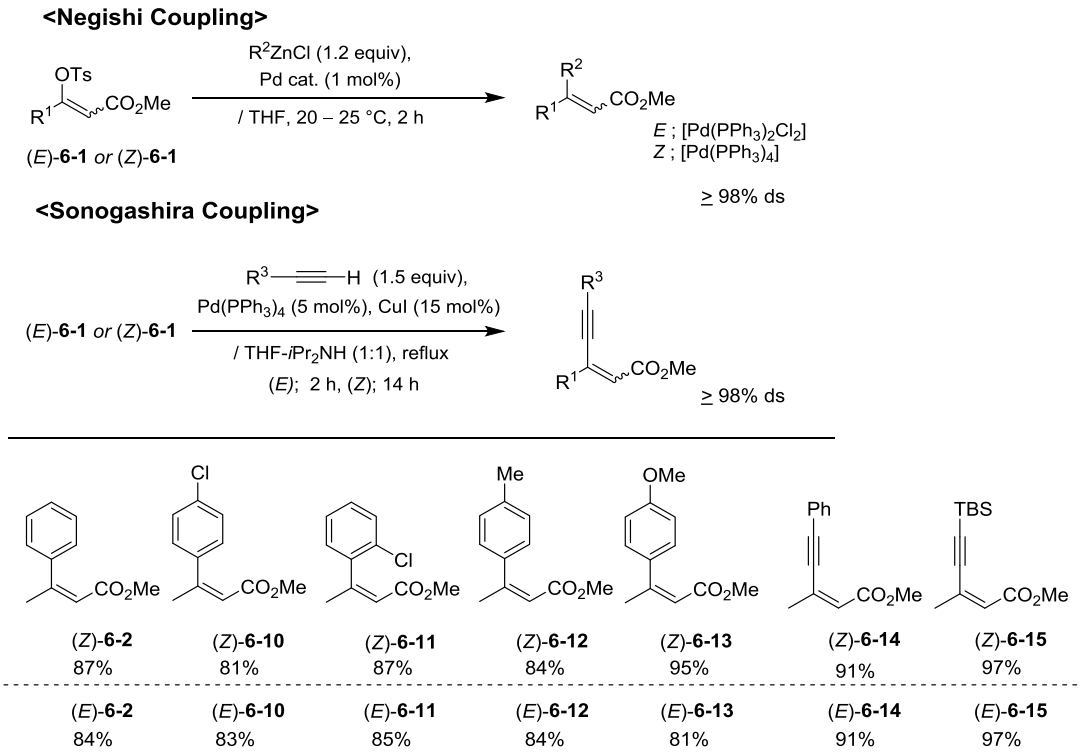
= 5:1)], column chromatographic purification of the crude product was easily performed to give (*E*)-**6-1** in 86% yield (≥98% ds). A variety of the relevant (*Z*)- and (*E*)-enol tosylates derived from other β-ketosters,[10] α-formyl esters,[11,12] β-aryl or α-aryl β-ketoesters,[13] and α-substituted β-ketoesters[14,15] can be almost readily prepared by similar approaches. We speculate that this stereocomplementary method proceeds through a Li-chelation pathway for (*Z*)-**6-1**, whereas non-chelation pathway for (*E*)-**6-1**.[10,13]

Under the identical conditions, three $ArB(OH)_2$ and (3-pyridyl)$B(OH)_2$ also underwent the present SM cross-coupling to afford the corresponding analogues (*Z*)-**6-6**, **6-7**, **6-8**, and **6-9** with similarly good to excellent yields and nearly perfect *Z*-stereoretention (**Scheme 6-3**). Naphthalene analog (*Z*)-**6-6** is a known compound, but its synthesis results in poor yield (58%) and *E*/*Z* selectivity (79:21).[16] The other analogues, (*Z*)-**6-7**, **6-8**, and **6-9**, are new compounds distinct from the known compounds (*E*)-**6-7**, **6-8**, and **6-9**, demonstrating the poor accessibility of (*Z*)-compounds to date. Noteworthy is the compatibility of labile functional groups such as Br- and -CHO groups, which are susceptible to other cross-couplings and organometal-mediated methods. The reaction of heterocyclic 3-pyridyl compound (*Z*)-**6-9** was conducted using [Pd(dppf)Cl_2] catalyst instead of $Pd(OAc)_2/PPh_3$.[13] SM cross-coupling exhibits superb and reliable stereoretention control in the related synthesis of amino acid derivatives using β-ketoester-derived enol tosylates.[17,18]



Scheme 6-3. Suzuki-Miyaura (SM) cross-coupling giving methyl (*Z*)-3-aryl-2-butenoates (*Z*)-**6-6**, **6-7**, **6-8**, and **6-9**.

As depicted in **Scheme 6-4**, (*Z*)-**6-1** as well as (*E*)-**6-1** can also serve as the Negishi and Sonogashira cross-couplings partners,[10] wherein a high and reliable level of *E*, *Z*-stereoretention (each ≥98% ds) is guaranteed.



Scheme 6-4. (*E*)- and (*Z*)-Stereocomplementary Negishi and Sonogashira cross-couplings using (*E*)-**6-1** and (*Z*)-**6-1** partners.

(*E*)-**6-2** type compounds are a representative probe for asymmetric hydrogenation to produce important chiral 3-arylbutanoates.[19-21] The relevant investigation using (*Z*)-**6-2** and its analogues is, however, hitherto not reported certainly due to the fatal lack of practical supply of these precursors.

Conclusion

A simple and useful but inaccessible compound, methyl (*Z*)-3-phenyl-2-butenoate, has been synthesized by user-friendly procedure in practical 10 g scale through 2 steps. The first (*Z*)-stereoselective enol tosylation of methyl acetoacetate was performed utilizing TsCl−TMEDA−LiCl reagent in AcOEt solvent to give (*Z*)-3-(*p*-tosyloxy)but-2-enoate. Recrystallization of the crude product gave pure crystals [mp 67−68 °C]. The obtained (*Z*)-enol tosylate was smoothly converted to (*Z*)-3-phenyl-2-butenoate utilizing Suzuki-Miyaura cross-coupling. A cost-effective catalysis [$Pd(OAc)_2$−PPh_3] showed sufficient reactivity and nearly perfect (*Z*)-stereoretentivity [bp 75−77 °C/0.75 mmHg, >97% purity (Q ^{1}H NMR)] in overall 56% yield. As substrate generality, this protocol was applicable to syntheses of the other aryl analogues. This strategy will contribute to produce the construction of a library for (*E*)-and (*Z*)-stereodefined α,β-unsaturated esters, which provides a new promising avenue for synthetic organic chemistry.

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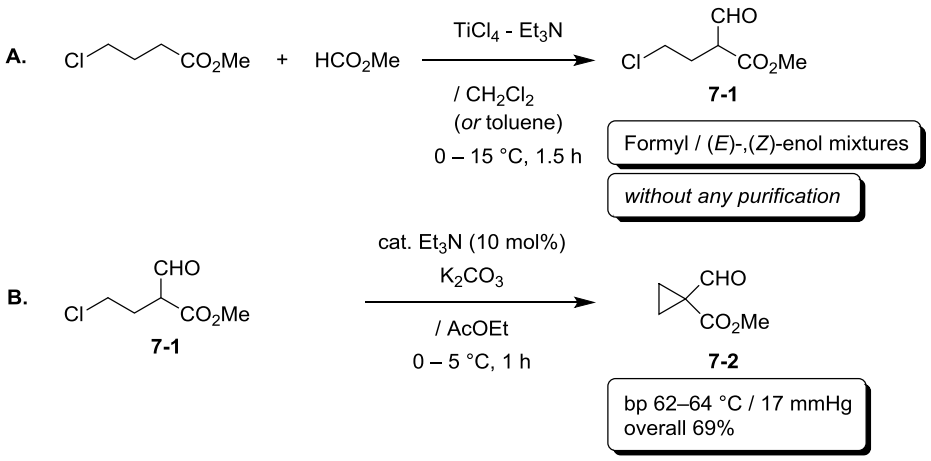
Chapter 7.
Synthesis of Methyl 1-Formylcyclopropanecarboxylate utilizing Ti-Claisen Condensation

Abstract

A synthesis of methyl 1-formylcyclopropanecarboxylate **7-2** directerd for *Organic Syntheses* is disclosed. Despite its utility to install cyclopropane segment into various pharmaceuticals, hitherto reported methods require multi-steps or expensive reagents, low temperature, and long reaction period. Starting methyl 4-chlorobutanoate, possessing base-sensitive γ-chloro moiety, can be successfully α-formylated utilizing distinctive $TiCl_4$/Et_3N-mediated (Ti-Claisen) condensation at 0−15 °C to give methyl 4-chloro-1-formylbutanoate **7-1**. Without any purification of **7-1**, successive cyclopropanation is performed in mild basic conditions [Et_3N (10 mol%)/K_2CO_3 (1 equiv) in AcOEt at 0−15 °C] to produce methyl 1-formylcyclopropanecarboxylate **7-2**, which is easily purified by simple distillation (the boiling point was documented for the first time). Throughout the procedure, column chromatographic purification is not required.



In this chapter, according to the policy of "Organic Syntheses" as shown in chapter 6, the author describes the procedure section in the first place.

Procedure

A. *Methyl 4-chloro-2-formylbutanoate (7-1).* An oven-dried 500-mL, threenecked (24/40), round-bottomed flask equipped with a Teflon-coated magnetic stirring bar (egg-shaped, 32 mm length x 15 mm diameter), an internal thermometer, a 50-mL pressure-equalizing addition funnel fitted with a nitrogen inlet (central neck), and a second 60-mL pressure-equalizing addition funnel is charged with methyl 4-chlorobutanoate (12 mL, 13.7 g, 100 mmol, 1 equiv) (**Notes 1** and **2**), HCO_2Me (18 mL, 18 g, 300 mmol, 3 equiv) (**Note 3**), and CH_2Cl_2 (100 mL) (**Notes 4** and **5**) (**Figure 7-1**). The stirred solution is immersed in an ice bath, cooling the internal temperature to 0 °C, and $TiCl_4$ (24 mL, 41.7 g, 220 mmol, 2.2 equiv) is added dropwise through a 60-mL dropping funnel (**Figure 7-1**, right side) (**Notes 6** and **7**) over a period of 20 min, while maintaining the internal temperature at 5–10 °C (**Note 8**).

Figure 7-1. Reaction Set-up for Step A.

Triethylamine (36 mL, 26.3 g, 260 mmol, 2.6 equiv) (**Note 9**) is then added dropwise to the vigorously stirred yellow reaction mixture over a period of 30 min using the 50-mL addition funnel in the center neck of the flask, while maintaining the internal temperature at 15 °C or lower (**Note 10**) (**Figure 7-2**). After complete addition, the dark orange reaction is stirred (500 rpm) at 0 °C for 1 h (**Note 11**), then quenched dropwise with water (100 mL) over a period of 10 min to maintain the internal temperature at 10 °C or lower (**Note 12**). The biphasic mixture is then transferred to a 500-mL round-bottomed flask and the initial reaction flask is rinsed with EtOAc (2 x 10 mL). The solution is concentrated using a rotary evaporator (22 °C, 46 mmHg). The mixture is then transferred to a 500-mL separatory funnel with EtOAc (50 mL), and the aqueous phase is separated and re-extracted with EtOAc (50 mL). The combined organic phase is washed with water (100 mL) and brine (50 mL), dried over Na_2SO_4 (20 g), filtered through a 150-mL medium porosity sintered glass funnel and concentrated using a rotary evaporator (45 °C, 25 mmHg) to furnish α-formyl ester **7-1** as a yellow liquid (16.39 g), which is used for the next step without any purification (**Notes 13** and **14**).

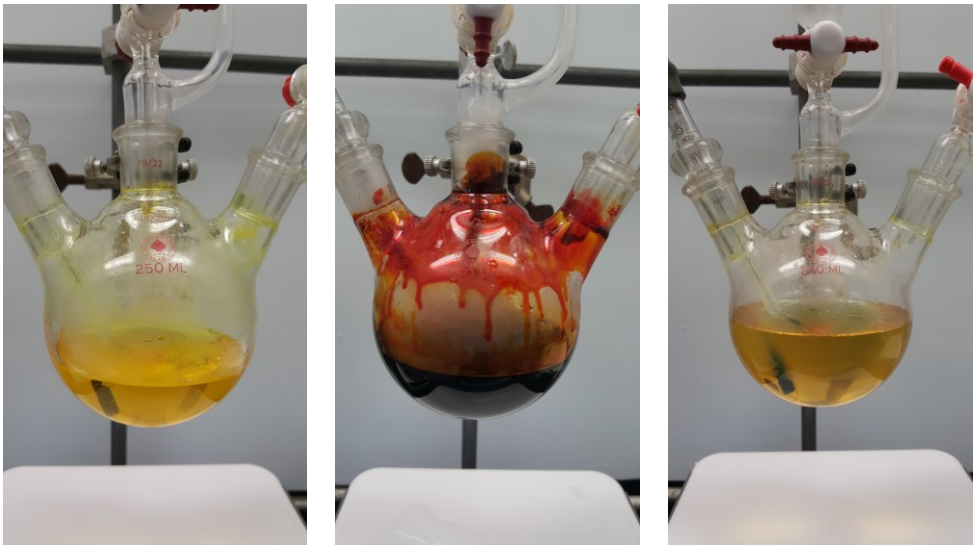


Figure 7-2. Color Transitions Observed in Step A.
after $TiCl_4$ addition after Et_3N addition after quench with H_2O

*B. Methyl 1-formylcyclopropanecarboxylate [7-2] (**Note 15**).* An oven-dried 250-mL, three-necked (24/40), round-bottomed flask equipped with a Teflon-coated magnetic stirring bar (egg-shaped, 26 mm length x 13 mm diameter), an internal thermometer, a glass stopper (central neck), and a Dryrite drying tube (Note 16) (**Figure 7-3**) is charged with crude α-formylester **7-1** (16.39 g) in AcOEt (100 mL). The light orange solution is stirred and immersed in an ice bath, cooling the internal temperature to 0 °C, and then potassium carbonate (K_2CO_3) (13.9 g, 100 mmol, 1 equiv) (**Note 17**) is added portionwise (split into five equal parts) over 10 min after temporarily removing the glass stopper (**Note 18**). Immediately after the addition is complete, triethylamine (1.4 mL, 1.00 g, 10.0 mmol, 0.1 equiv) is added in one portion.

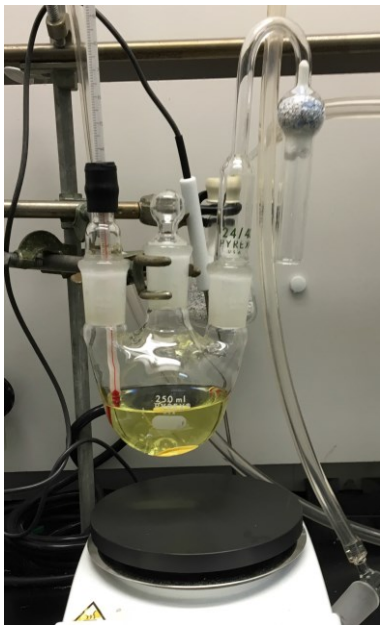


Figure 7-3. Reaction Set-up for Step B

After stirring (600 rpm) the suspension at 0 °C for 1 h, the reaction is quenched with water (100 mL) and transferred to a 500-mL separatory funnel. The initial reaction flask is rinsed with EtOAc (2 x 5 mL) and H_2O (2 x 5 mL), which are added to the separatory funnel. The organic phase is separated and the aqueous phase is re-extracted with EtOAc (20 mL). The combined organic phase is washed with water (20 mL) and brine (20 mL), dried over Na_2SO_4 (20 g), filtered through a 150-mL medium porosity sintered glass funnel, then concentrated under reduced pressure using a rotary evaporator (45 °C, 25 mmHg) to furnish an amber-colored liquid. The obtained crude product (ca. 12 g) is moved into a 25-mL roundbottomed flask with a Teflon-coated magnetic stir bar (**Note 19**) (**Figure 7-4**). Distillation while immersed in a temperature-controlled oil bath under reduced pressure (84–86 °C, 19–25 mmHg) provides the desired product **7-2** (8.68 g, 69% overall yield) as a colorless liquid (**Notes 20**, **21**, and **22**).

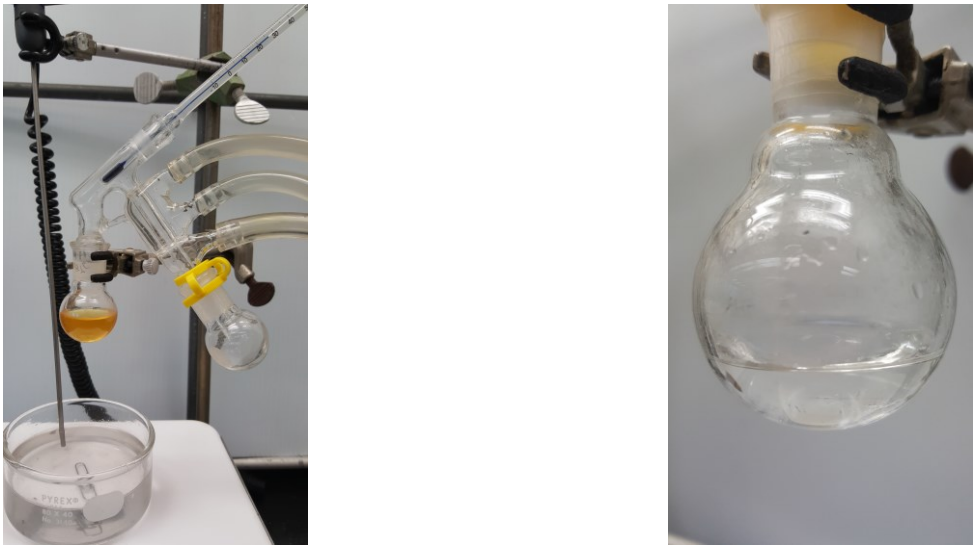


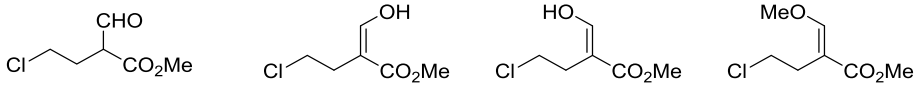
Figure 7-4. Distillation Set-up and Pure Final Product

Notes

1. The methyl 4-chlorobutanoate, methyl formate, and dichloromethane must be added by temporary removal of one of the addition funnels followed by purging of the system with nitrogen.
2. The checkers used methyl 4-chlorobutyrate (98+%) from Acros Organics. The submitters used methyl 4-chlorobutanoate (GC purity >98%) purchased from Tokyo Chemical Industry Co., Ltd. and used as received.
3. The checkers used methyl formate (97%, pure) from Acros Organics. The submitters used methyl formate (HCO_2Me) (GC purity >95%) purchased from Tokyo Chemical Industry Co., Ltd. and used as received.
4. The checkers used non-stabilized dichloromethane (20-L drum, ACS Reagent) from J. T. Baker, which was then passed through two packed columns of neutral alumina in a solvent purification system manufactured by SG Water U.S.A., LLC. The submitters used dichloromethane (CH_2Cl_2) (purity 99.5%) was purchased from Wako Pure Chemical Industries, Ltd. and used as received without any purification.

5. The submitters studied the use of CH_2Cl_2 and toluene as reaction solvents and noted the reaction to be homogeneous with the former, whereas the use toluene results in formation of yellow precipitate and a viscous reaction mixture. The checkers employed only CH_2Cl_2.
6. The checkers used titanium (IV) chloride (sure-sealed 200 g bottle, ReagentPlus, 99.9% trace metal basis) obtained from Sigma-Aldrich. The submitters used titanium tetrachloride ($TiCl_4$) (99.0%, 500 g bottle) purchased from Wako Pure Chemical Industries, Ltd. and used as received.
7. The checkers charged the 60 mL addition funnel with $TiCl_4$ (from a suresealed bottle) using a syringe. The submitters report delivering the $TiCl_4$ using a 10 mL pipet, wherein the operation should be rapidly and carefully conducted to take care of white smoke evolution.
8. The submitters note this step to be slightly exothermic when using addition rates of 24 mL of $TiCl_4$ over 5–10 min. However, the checkers observed a steady temperature at 5−10 °C when adding 24 mL $TiCl_4$ dropwise over 20 min. A feature not noted by the submitters is the formation of yellow crystals around the tip of the addition funnel. These crystals tend to fall off with time and slowly dissolve in the dichloromethane.
9. The checkers purchased triethylamine (≥99.5%) from Sigma-Aldrich and distilled it from CaH_2 immediately prior to use. The submitters used triethylamine (Et_3N) (purity 99%) purchased from Wako Pure Chemical Industries, Ltd. and used it as received.
10. The submitters note the reaction to be considerably exothermic. The checkers found that by adding the Et_3N dropwise over 30 min (approx. 1−1.2 mL per minute) it was possible to maintain an internal temperature at 10 °C or lower without affecting the formation of the expected dark orange reaction mixture.
11. The checkers note that the reaction progress can be monitored by ^{1}H NMR.
12. The submitters caution that this quench is exothermic. The checkers found that adding the water dropwise over 10 min was sufficient to maintain an internal temperature at 10 °C or lower, while the submitters' addition over 5 min was sufficient to maintain temperatures below 20 °C.
13. The checkers performed two half-scale and two full-scale reaction. The crude yields were 97% (7.94 g), 99% (8.14 g), 98% (16.13 g), and 99% (16.39 g) respectively. Analysis of the crude reaction mixture by ^{1}H NMR and ^{13}C NMR revealed that the mixture consists of three tautomers **7-1a**, (*Z*)-**7-1b**, (*E*)-**7-1b** and a very small amount of by-product tentatively assigned as (*E*)-**7-1x**, in an approximate ratio of 36:44:16:4.
14. Although not necessary for step B the submitters and checkers established in parallel studies that this reaction mixture could be purified via flash chromatography through SiO_2. In the checker's hands 5 g of the crude product was purified using 25 g of silica (Silicycle Silica, Flash P60, 40-63 μm, 230-400 mesh) loaded into a 30 mm diameter column. The column was slurry packed, the sample loaded with hexane and then eluted with a gradient of EtOAc/hexanes (5% increasing by approximately 2% every 10-12 fractions). Fractions were collected (6.7 mL) at a flow rate of 0.8 mL/sec. Overall, 72 fractions were collected and product was observed at fractions 10-32. These fractions were concentrated in vacuo to furnish 2.51 g of a colorless oil, which was determined by ^{1}H NMR to be (*Z*)-**7-1b** and trace **7-1a**. The submitters note the composition of the chromatographed material (5 g) to be a mixture of **7-1** (4.45 g, 85%) with cyclopropane

7-2 (ca. 6% based on ^{1}H NMR). The checkers did not observe cyclopropane **7-2** at this stage. Compound **7-1** has been found to slightly decompose on silica and distillation results in decomposition. Compound **7-1** gradually solidified at ambient temperature, and over a week undergoes slow tautomerization to enols (*Z*)-**7-1b** and (*E*)-**7-1b**. The checkers note the purified sample of (*Z*)-**7-1b** was observed to undergo slow crystallization**,** which upon collection and trituration (hexanes) of the resulting white solid revealed them to be (*E*)-**7-1b** by ^{1}H NMR.



7-1a (*Z*)-**7-1a** (*E*)-**7-1a** (*E*)-**7-1x**

Physical and spectroscopic properties of (*Z*)-**7-1b**: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.52 (td, *J* = 7.0, 0.7 Hz, 2H), 3.55 (t, *J* = 6.9 Hz, 2H), 3.80 (s, 3H), 7.11 (d, *J* = 12.8 Hz, 1H), 11.49 (d, *J* = 12.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl^3$) δ: 31.2, 44.05, 51.8, 101.1, 163.3, 172.1; IR (neat) 2957, 1721, 1672, 1612, 1446, 1397, 1350, 1328, 1281, 1222, 1189, 1166, 1124, 989, 956, 811, 740, 653, 574, 452 cm^{-1}; HRMS (+ESI) *m/z* $[M+H]^+$ calcd for $C_6H_9ClO_3$ 165.0313, found 165.0313; Anal. Calcd for $C_6H_9ClO_3$: C, 43.79; H, 5.51; Cl, 21.54. Found; C, 43.56; H, 5.48; Cl, 21.28.

Those of (*E*)-**7-1b**: colorless crystals; mp 72–80 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.77 (t, *J* = 7.0 Hz, 2H), 3.63 (t, *J* = 6.9 Hz, 2H), 3.73 (s, 3H), 6.17 (brs, 1H), 7.77 (d, *J* = 9.0 Hz, 1H); ^{13}C NMR (101 MHz, CDCl3) δ: 27.4, 43.6, 51.7, 107.3, 155.3, 168.8; IR (neat) 3208, 1667, 1634, 1444, 1397, 1331, 1308, 1283, 1203, 1169, 1105, 746, 731 cm^{-1}.

15. Step B should be carried out within a week due to the sensitivity of the starting material.
16. The half-scale reaction utilized an oven-dried 100-mL, three-necked, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar (egg-shaped, 20 mm length x 10 mm diameter), an internal thermometer, a glass stopper (central neck) and a $CaCl_2$ drying tube.
17. The checkers used potassium carbonate (anhydrous, 99%) from Alfa Aesar.
18. The submitters note this to be a slightly exothermic reaction. The checkers did not observe a rise in temperature when adding the potassium carbonate in five equal portions over 10 min. However, the quench with water after reaction completion is observed to be exothermic, but the temperature can be maintained at 5–10 °C if the water is added over 5 min. Reaction progress monitoring in step B is possible by TLC using $KMnO_4$ staining [10% AcOEt in hexanes; Rf = 0.23 (**7-1**) and 0.33 (**7-2**)] or by ^{1}H NMR comparison of aliquots.
19. Full-scale utilized a 25-mL round-bottomed flask equipped with a magnetic stirring bar (egg-shaped, 18 mm length x 10 mm diameter) with a short path distillation apparatus (110 mm height x 110 mm width). Half scale employed a 10-mL round-bottomed flask and a magnetic stirring bar (rod shaped, 10 mm length x 3 mm diameter). The receiving flask is cooled to 0 °C by immersion in an ice-water bath.
20. The submitters note: 1st fraction: 42–62 °C / 20 mmHg (bath temp. 82–87 °C), 0.24 g. 2nd fraction: 62–64 °C / 17 mmHg (bath temp. 87–111 °C), 8.82 g (overall yield, 69% in 2 steps). 3rd fraction: 64–52 (fade out) °C / 17 mmHg (bath temp. 111–123 °C), 0.17 g. The submitters also noted the bp to be 59–63 °C / 16 mmHg and the purity based on quantitative ^{1}H NMR analysis was 97−99%. The checkers

performed a fractional distillation collecting distillate boiling at 84–86 °C / 25 mmHg (bath temp. 104–124 °C). The checkers note: 1st fraction (135 mg, boiling temp. 84–86 °C / 25 mmHg, bath temp. 100–104 °C). 2nd fraction (8.68 g, boiling temp. 84–86 °C / 25 mmHg, bath temp. 104–124 °C). The collection of the 2nd fraction was not stopped until the internal temperature dropped.

21. The checkers performed two half-scale and two full-scale reactions. The yields after distillation were 73% (4.70 g), 68% (4.33 g), 77% (9.82 g), and 69% (8.68 g) respectively.

22. Physical and spectroscopic properties of **7-2**: colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.58–1.62 (m, 2H), 1.64–1.68 (m, 2H), 3.80 (s, 3H), 10.37 (s, 1H); ^{13}C NMR (101 MHz, CDCl3) δ: 22.5, 33.4, 52.3, 171.4, 198.6; IR (neat) 2958, 2868, 1700, 1440, 1319, 1285, 1196, 1147, 1085, 1047, 1002, 959, 888, 810, 781, 742, 698, 474 cm^{-1}; HRMS (+ESI) *m/z* [M + H]+ calcd for $C_6H_9O_3$ 129.0546, found 129.0543; quantitative ^{1}H NMR analysis was performed with ethylene carbonate (purchased from TCI, purity >99.0%) as the internal standard and obtained in 97.6% purity.

Discussion

Methyl or ethyl 1-formylcyclopropanecarboxylate (**7-2**) or (**7-2'**) is a unique bifunctional compound with both aldehyde and ester functionalities at the same C-1 position in a simple cyclopropane molecule. Cyclopropane **7-2** or **7-2'**, therefore, serves as a useful synthetic building block, especially for medicinal and process chemistry, and natural product synthesis. As illustrated in **Figure 7-5**, characteristic cyclopropane segments are installed in various pharmaceuticals utilizing **7-2** or **7-2'**. The key feature is the chemoselective condensation of the aldehyde group in preference to the ester group.

(i) A traditional barbituric acid analog **I** containing a 5-spirocyclopropane moiety for a dihydroorotate dehydrogenase inhibitor,[1] (ii) arylpyrazole compound **II** containing cyclopropanecarboxamide for a parasiticidal agent,[2] (iii) arylsulfonylpiperazine **III** containing cyclopropanecarboxamide for a 11β-hydroxysteroid dehydrogenase inhibitor,[3] (iv) 5,7,8,9-tetrahydropyrimido[4,5-b][1,4]diazepin-6-ones compound **IV** containing 3-spirocyclopropane moiety for a protein kinase inhibitor,[4] (v) oxo-substituted aza-heterocylic compound **V** containing cyclopropane-carboxylic acid for the treatment and/or prevention of cardiovascular conditions,[5] (vi) oxazolo[5,4-b]pyridine-5-yl compound **VI** containing cyclopropanecarboxylate for the treatment of cancer,[6] (vii) 2,6-disubstituted benzobisoxazole compound **VII** containing cyclopropanecarboxylic acid for lysophosphatidic acid receptor antagonists,[7] (viii) [1,2,4]triazolopyridine compound **VIII** containing cyclopropanecarboxylate for phosphodiestererase inhibitors,[8] and (ix) 3-pyridyl-substituted benzamide compound **IX** containing 1-(difluoromethyl)cyclopropane for purinergic $2X_7$ ($P2X_7$) receptor inhibitors.[9]

As described above, **7-2** or **7-2'** has a significant role in the structural scaffolds of a variety of pharmaceuticals possessing cyclopropanecarboxylic acid derivatives. Noteworthy is that application of this manipulation has increased as a screening technique to discover new pharmaceuticals, likely because cyclopropanes are requisite isosteres for the corresponding dimethyl compounds.

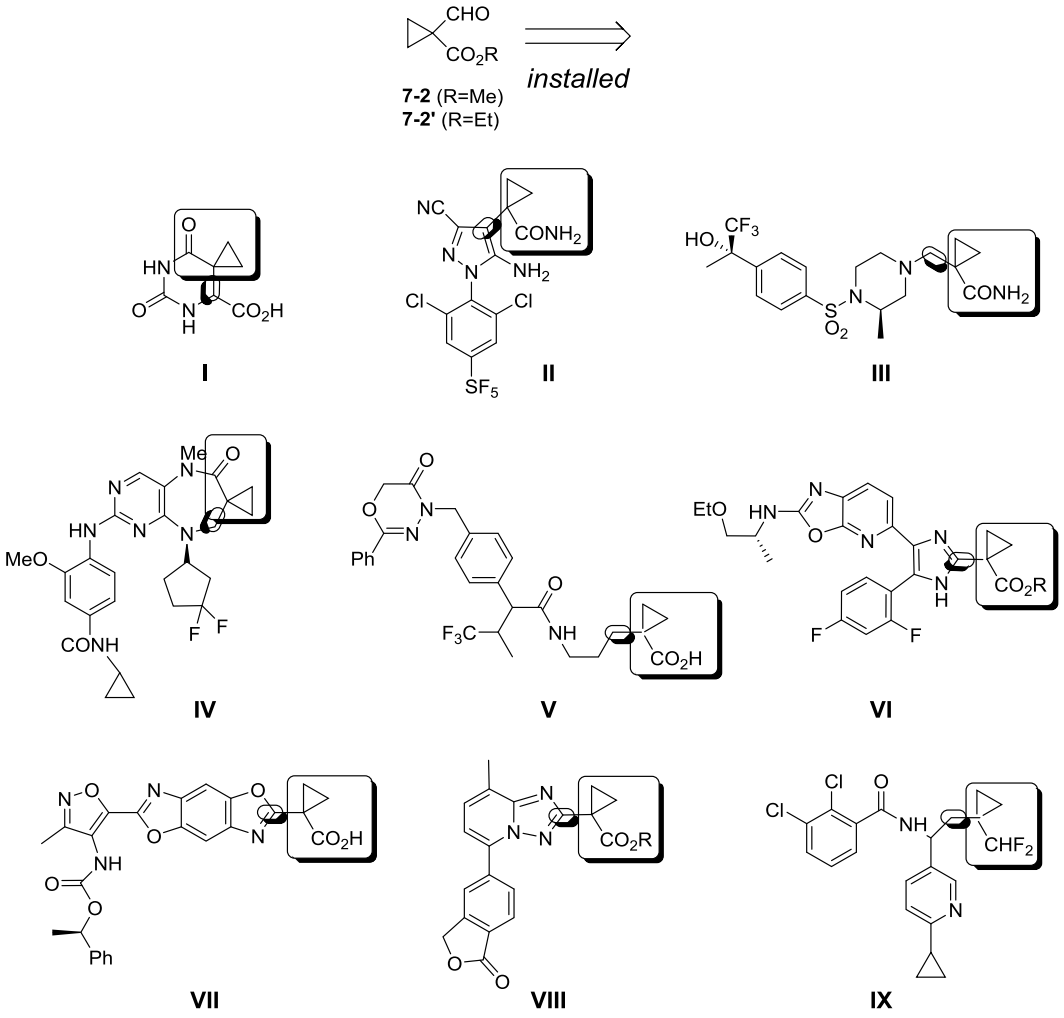
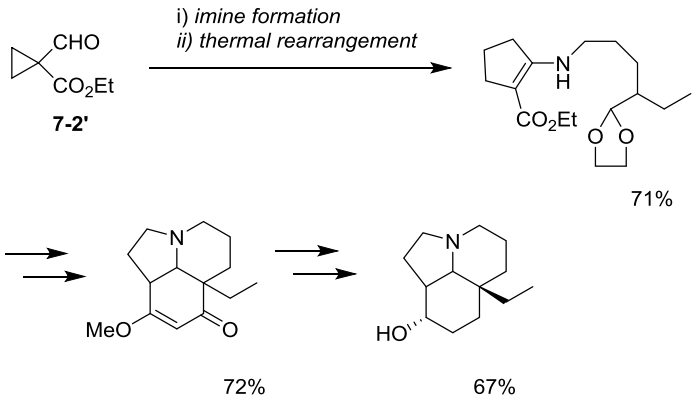


Figure 7-1. Pharmaceuticals incorporating cyclopropanecarboxylic acid or ester segments utilizing methyl or ethyl 1-formylcyclopropanecarboxylate (**2-2**) or (**2-2'**).

On the other hand, cyclopropane **7-2** contributed as the starting compound to a formal synthesis of aspidospermine, a distinctive aspidosperma alkaloid,[10,11] in that a notable acid-catalyzed thermal rearrangement of cyclopropyl imine intermediate to 2-pyrroline is the key starting step (**Scheme 7-1**).[12]



Scheme 7-1. Formal synthesis of aspidospermine alkaloid starting from ethyl 1-formylcyclopropanecarboxylate (**7-2'**).

On the whole, the reported synthetic methods for **7-2** or **7-2'** are categorized into four approaches.

(i) As illustrated in **Scheme 7-2**, Ayers' half reduction protocol of methyl and ethyl cyclopropanedicarboxylates (**7-3** and **7-3'**) is the most representative.[13] Commercially available **7-3** and **7-3'** (ca. twice as expensive as methyl 4-chlorobutanoate) were converted by the treatment with more than 2.0 equiv of Li(*t*BuO)$_3$AlH, not to desired aldehyde **7-2** and **7-2'** directly, but to alcohols **7-4** and **7-4'** in 88% and 79% yield, respectively.[3,5,8] Dess-Martin (DM) oxidation of **7-4** or **7-4'** using ca. 2 equiv of DM periodinane successfully afforded **7-2** (24%) or **7-2'** (76%). The DIBAL reduction method with **7-3** was also applied, but required harsh conditions such as –78 °C and 7 h.[4]

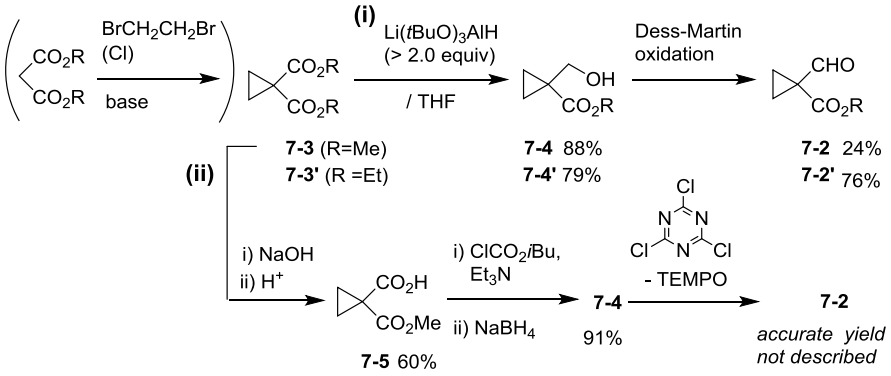
Although this approach is likely the most accessible, Li(*t*BuO)$_3$AlH is quite expensive (ca. $ 150 / 100 mL, 1.0 M) among commercially available hydride reagents and is not hydride atom-economical. DM periodinane is also expensive and problematic with regard to atom-economy.

(ii) As an alternative method to (i),[6] **7-3** was converted by a half-hydrolysis reaction to monocarboxylic acid **7-5**, which was transformed to **7-2** through mixed anhydride formation and successive $NaBH_4$ reduction to give common intermediate **7-4**. TEMPO oxidation of **7-4** with trichloroisocyanuric acid afforded the desired product **7-2**, although an accurate yield was not described. This approach, however, is not straightforward and requires tedious procedures.

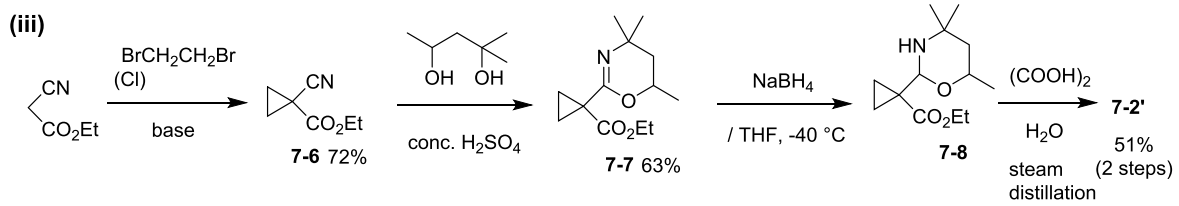
(iii) As depicted in **Scheme 7-3**, this approach utilizes the notable protocol of A. I. Meyer's group.[14,15] Ethyl cyanoacetate was converted to ethyl 1-cyanocyclopropanecarboxylate **7-6** (commercially available in 5-g scale, but extreamely expensive), which is transformed to masked aldehyde **7-8** through 1,3-dioxadine formation and successive $NaBH_4$ reduction. Finally, acid hydrolysis of **7-8** gave the desired compound **7-2'**. This method also requires four steps with high (80 °C) and low (–40 °C) temperature reactions, the use of large amounts of conc. H_2SO_4, and steam distillation purification.

(iv) **Scheme 7-4** depicts a method starting from γ-butyrolactone developed by Kuraray's group,[16] which is the most relevant for our strategy. γ-Butyrolactone was α-formylated using HCO_2Me/NaH and protected with an ethoxycarbonyl group to give **7-9**. Conventional ring opening with chlorination using $SOCl_2$ and $ZnCl_2$ in EtOH gave precursor **7-10**. Finally, cyclopropanation concomitant with deprotection was performed to afford **7-2'**. This approach required a protective and deprotective sequence and afforded a moderate total yield (26%).

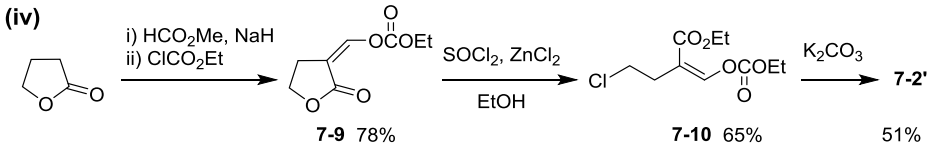
Due to the utility of **7-2** or **7-2'**, 5−100 g scale production methods have been disclosed in recent medicinal chemistry patents. The reported synthetic methods for **7-2** or **7-2'**, however, require column chromatographic purification despite the high volatility, or crude product is used in the next condensation step without purification. Our concise and straightforward method involves a simple distillation purification (the boiling point was documented for the first time) without the use of column chromatography, and is performed within short reaction and purification periods.



Scheme 7-2. Half-reduction method of cyclopropane precursor **3** or **3'** derived from dimethyl malonate.



Scheme 7-3. A. I. Meyers' transformation method starting from ethyl cyanoacetate.



Scheme 7-4. Kuraray group's method starting from γ-butyrolactone.

Among the various carbon homologation methods, α-formylation of simple esters with HCO_2Me is a well-recognized useful reaction. A literature survey (SciFinder®) revealed reports of ca. 100 examples utilizing base reagent (e.g. NaOR, NaH, LDA, and LiHMDS)-mediated methods and 5 examples using $TiCl_4$/amine-mediated methods. In general, a major conventional reaction using bases (e.g. NaOR, NaH) requires long reaction periods and results in moderate yield in almost all cases. LDA- and LiHMDS-promoted methods are superb with regard to yield but require rigorous procedures (reaction time schedule and accurate reagent equivalents) and low temperature (–78 ˚C).

α-Formylation of simple esters utilizing $TiCl_4$/amine-mediated (Ti-Claisen) condensation[17,18] for the synthesis of α-formylated esters **7-11** is depicted in **Table 7-1** (13 examples). Ti (*or* Zr)-self-Claisen condensations between two of the same esters,[19-21] Ti-crossed-Claisen condensations between esters or acids with acid chlorides,[22,23] and Ti-Dieckmann (intramolecular Claisen) condensations[24-26] have several advantages, including: (i) powerful C-C bond forming reactivity; (ii) highly available reagents with robust reactions; (iii) accessible temperature (0 °C to ambient); (iv) compatibility with base-labile functional groups such as γ-halogeno, γ-ketone carbonyl, etc., despite the high reactivity. On the other hand, a mild variant

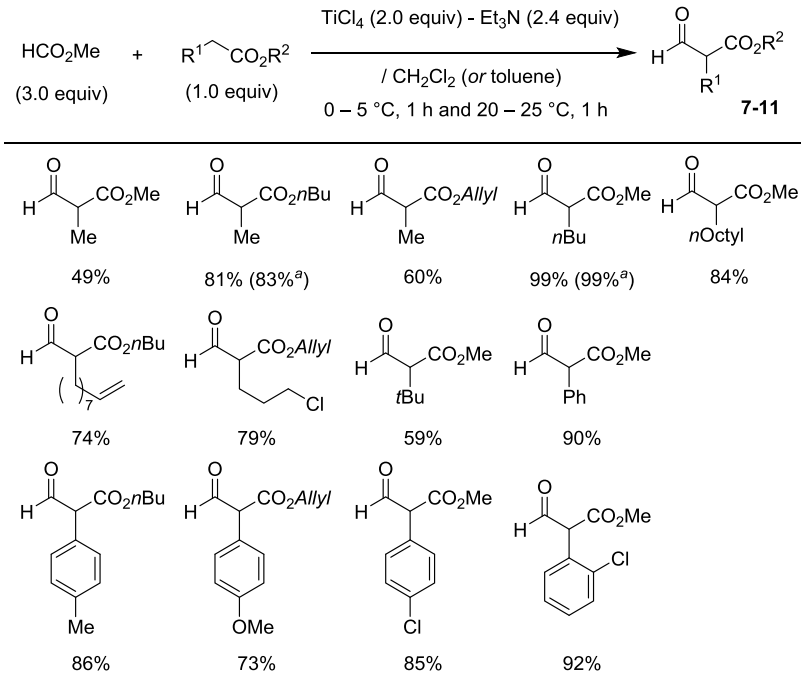
Ti-Claisen condensation method using ketene silyl acetals with acid chlorides also satisfies the four listed features [(i)-(iv)].[27]

The present α-formylation reaction of methyl 4-chlorobutanoate (**7-1**) is a distinctive example of the compatibility with a base-sensitive γ-chloro group. Synthesis of **7-2** is not possible using the base-mediated α-formylation method due to undesirable and predominant cyclopropane formation leading to methyl cyclopropanecarboxylate.

Conclusion

A unique and useful but inaccessible building block, methyl 1-formylcyclopropanecarboxylate, has been synthesized by utilizing straightforward and accessible strategy in practical 10 g scale through 2 steps. $TiCl_4$−Et_3N-mediated Ti-Claisen condencation (α-formylation) of methyl 4-chlorobutanoate with methyl formate proceeded smoothly to afford methyl 4-chloro-1-formylbutanoate in good yield. As a distinctive feature, 4-chloro group was compatible in apparent contrast to base reagent-mediated method. The obtained crude α-formylester smoothly underwent cyclopropanation under mild basic conditions [*cat.* Et_3N−K_2CO_3/AcOEt] to produce the desired methyl 1-formylcyclopropanecarboxylate [bp 84−86 °C/25 mmHg, 97.6% purity (Q ^{1}H NMR)] in overall 69% yield. The present synthetic strategy provides a new promising avenue, especially for pharmaceutical syntheses.

Table 7-1. α-Formylation of esters utilizing Ti-Claisen condensation.



a) Use of toluene solvent.

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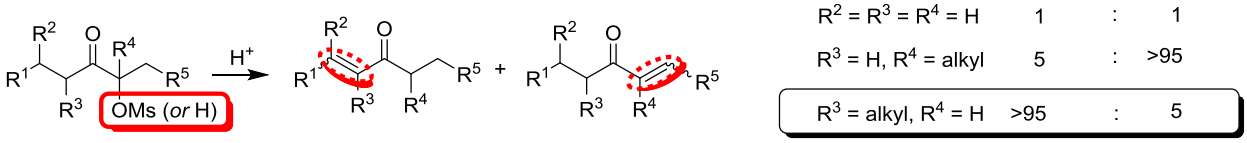
Chapter 8.
Acid-induced Favorskii-type Reaction: Regiocontrolled Elimination of Acyloin Mesylates Leading to α,β-Unsaturated Ketones

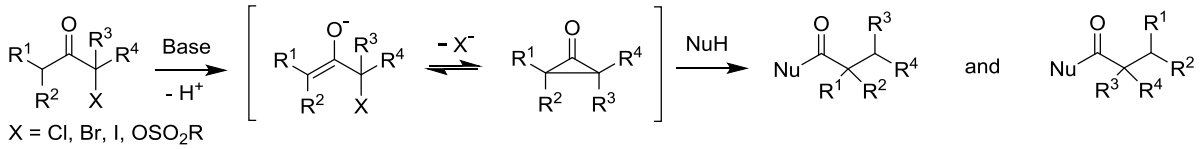
Abstract

A highly regiocontrolled acid-induced Favorskii-type elimination reaction of acyloin mesylates proceeded smoothly to give more substituted α,β-unsaturated ketones. Not only acyclic but also cyclic acyloin mesylates produced the corresponding higher substituted enones via double-bond-migration pathway. A mechanistic speculation and application to a synthesis of chiral muscone precursor are also described.



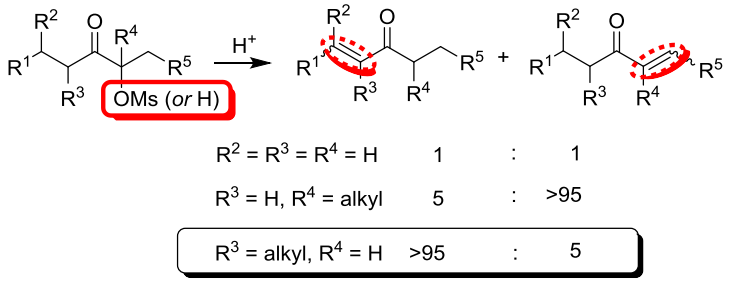
Introduction

The Favorskii rearrangement reaction (FR reaction) is a well-recognized, unique, and useful C-C bond transformation among organic name reactions.[1] The FR reaction has been successfully applied for natural product and fine chemical syntheses in the past few decades.[1c,e] The most general reaction mode involves a base-induced formation of cyclopropane intermediates derived from α-halogenated (or α-sulfonyloxy) ketones, followed by ring cleavage concomitant with one carbon extrusion (**Scheme 8-1**). A ^{13}C-labeld experiment supports this well-known mechanism. Other relevant homo- and quasi- variants of the FR reaction are also documented.[1c–e]



Scheme 8-1. Representative Favorskii rearrangement reaction.

These FR reactions are conducted under basic conditions, wherein the elimination of α-leaving groups, such as halogens and sulfonyloxy groups adjacent to ketone carbonyls, is a common and crucial process. Here it is presented that a unique cation-induced highly regioselective FR-type elimination reaction using methanesulfonates (mesylates) of α-hydroxyketones (acyloins) produces more substituted α,β-unsaturated ketones with distinctive double-bond migration as illustrated in **Scheme 8-2**. To the best of our knowledge, this is the first report of a cation-induced distinctive FR-type reaction.



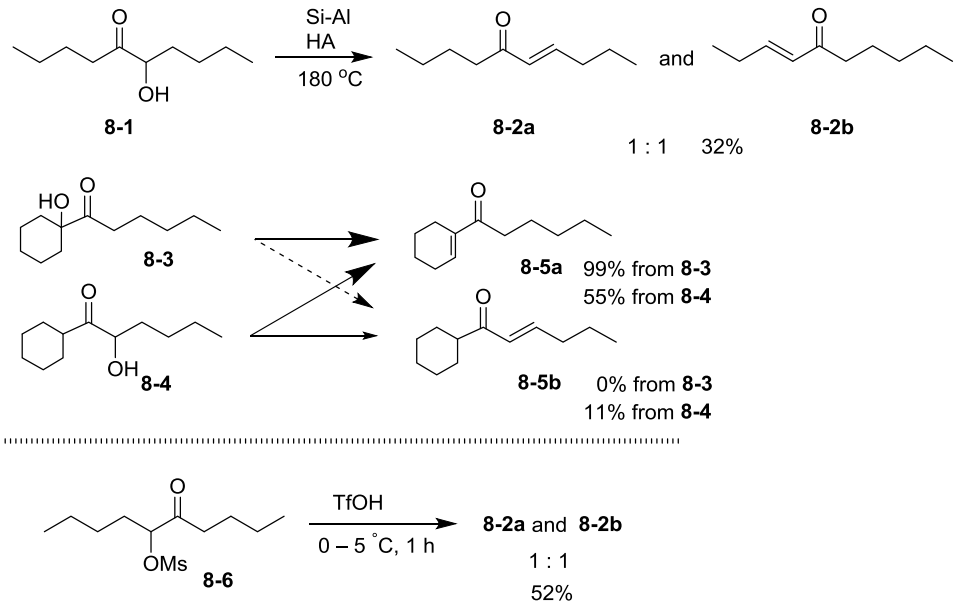
Scheme 8-2. Regiocontrolled acid-induced Favorskii-type elimination.

Results and Discussion

In clear contrast to the feasible dehydration of relevant β-hydroxyketones (aldols), isosteric acyloins strongly resist a similar type of cation-induced dehydration, because α-cation formation on the ketone carbonyls is extreamly thermodynamically unfavorable. Dehydration reactions of 15-membered acyloin are documented, both without the use of a catalyst[2a] and with the use of a Si-Al heteropolyacid catalyst.[2b] These methods, however, required harsh conditions (>200 °C). Taking the background into accounts, the initial examination was guided by the dehydration of valeroin (**8-1**) using this Si-Al heteropolyacid catalyst (**Scheme 8-3**). Actually, a reflux conditions in 1,2-dichlorobenzene (ca. 180 °C) led to the dehydration of **8-1**.

The reaction afforded not only uneventful dec-6-en-5-one **8-2a**, but also unexpected dec-3-en-5-one **8-2b** as 1:1 mixtures in 32% total yield. Noteworthy is that the crossover reactions using α-hydroxy cyclohexyl pentyl ketone regioisomers **8-3** and **8-4** afforded the corresponding *endo*-product **8-5a** exclusively in 99% yield as predicted, and in clear contrast *exo*-product **8-5b** in 66% total in a 5:1 ratio.

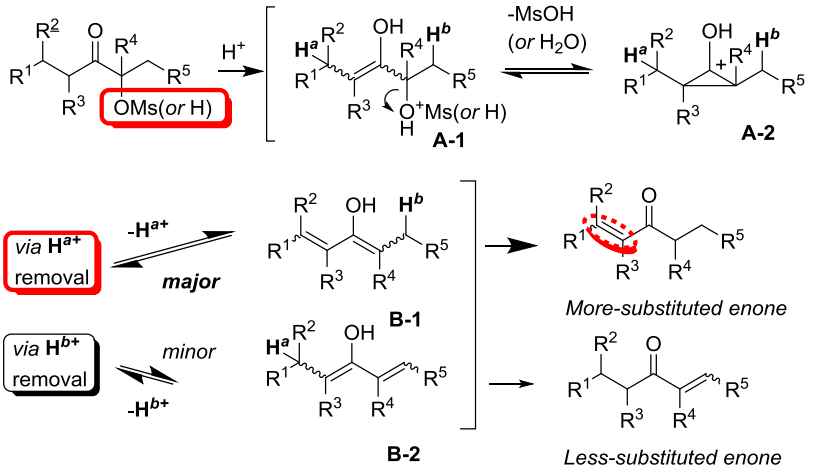
The latter abnormal dehydration mode led us to screen milder and higher yield conditions. A literature survey revealed three promising and accessible methods for the elimination using tosylates or mesylates of acyloins, mediated by UV-light (neutral),[3] LiBr–Li_2CO_3 (weak basic),[4] and CF_3SO_3H (acidic)[5] to give α,β-unsaturated ketones *via* the *usual* elimination pathway. Thus, the acid-induced method[5] was selected, that was developed by Yoda and Takabe group, using mesylate **8-6** derived from **8-1**. The reaction under treatment with CF_3SO_3H at 0 – 5 °C for 1 h afforded a 1:1 mixture of the products **8-2a** and **8-2b** in higher 52% total yield than that using valeroin **8-1**.



Scheme 8-3. Initial examination for acid-induced Favorskii-type elimination.

To obtain a working hypothesis for this outcome we investigated the reactions using three *unsymmetrically* substituted acyclic acyloin mesylates **8-7**–**8-9**. **Table 8-1** lists the successful results. The desired enones **8-5a**, **8-10**, and **8-11** were obtained in good to excellent yield. The intriguing feature of the present reaction is that nearly complete regioselectivity (double-bond migration) emerged to give more thermodynamically stable substituted enones.

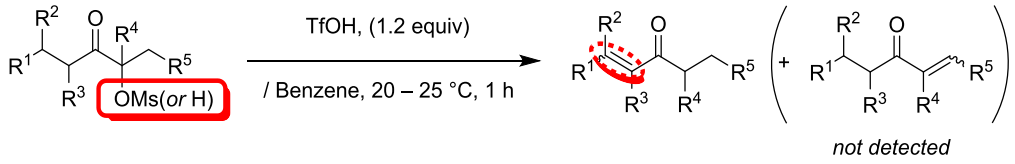
Scheme 8-4 depicts a plausible mechanism for the present FR-type elimination. Initial protonation of an acyloin mesylate or an acyloin with isomeric enol and/or cyclopropane formations proceeds to give cationic intermediate **A-1** and/or cyclopropane intermediate **A-2**, respectively. A successive crucial step for regioselective MsOH (or H_2O) elimination concomitant with H^a and H^b withdrawal leads to the corresponding intermediates, major E1'-like dienol **B-1** and minor E1-like dienol **B-2**. Final tautomerization affords more substituted α,β-unsaturated ketones almost exclusively.



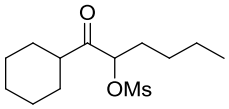
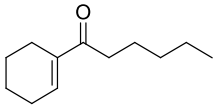
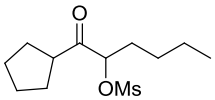
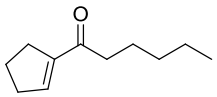
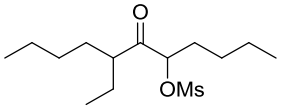
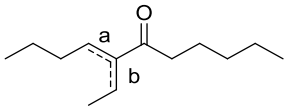
Scheme 8-4. Plausible mechanism for the regiocontrolled cation-induced Favorskii-type elimination.

Encouraged by the successful results obtained using acyclic acyloin mesylates **8-7**–**8-9** listed in **Table 8-1**, we further investigate the scope of the reaction using 6-, 7-, 8-, and 15-membered cyclic substrates **8-12**–**8-15** (**Table 8-2**). Noteworthy is that a complete regiocontrolled double-bond migration mode was observed in all cases examined, affording the desired trisubstituted α,β-unsaturated ketones **8-16**–**8-19** in good yield.

Table 8-1. Regiocontrolled cation-induced Favorskii-type reaction using acyclic acyloin mesylates **8-7–8-9**.

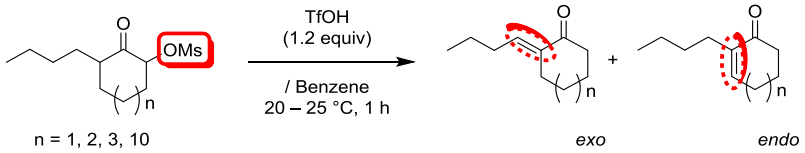


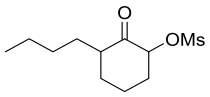
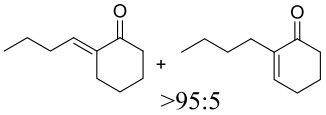
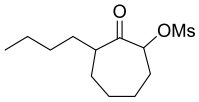
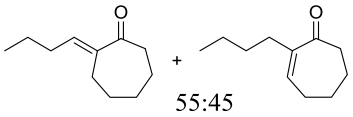
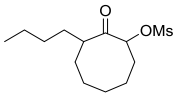
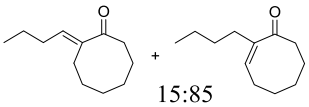
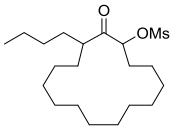
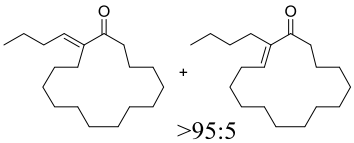
not detected

Entry	Substrate		Product		Yield / %[a]
1		**8-7**		**8-5a**	97
2		**8-8**		**8-10**	65
3		**8-9**		**8-11**	85[b]

a) Isolated. b) Regioisomeric mixture; **a**:**b** = ca. 1:1.5.

Table 8-2. Regiocontrolled acid-induced Favorskii-type elimination using cyclic acyloin mesylates **8-12**–**8-15**.

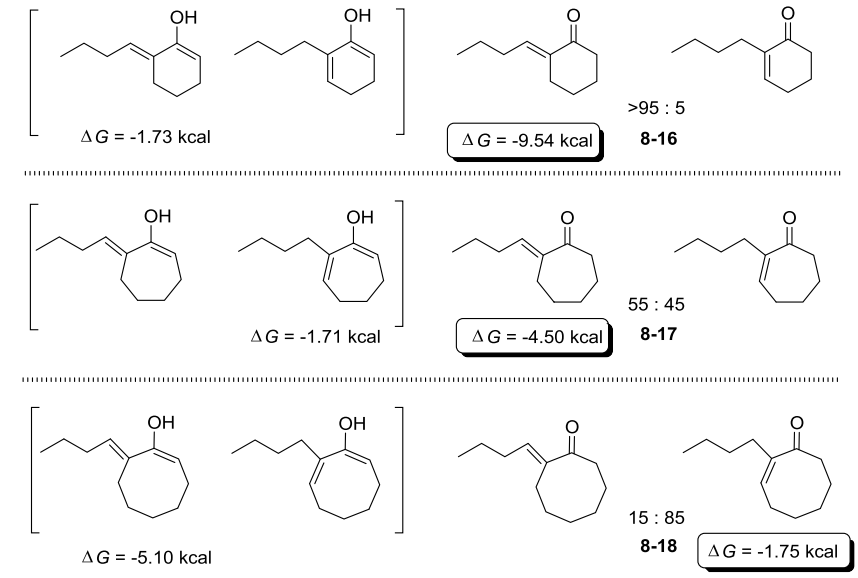


Entry	Substrate		Product			Yield / %[a]
			exo	*endo*		
1		**8-12**	 >95:5		**8-16**	60
2		**8-13**	 55:45		**8-17**	75[b]
3		**8-14**	 15:85		**8-18**	69[b]
4		**8-15**	 >95:5		**8-19**	76[b]

a) Isolated. b) 2.0 equiv of TfOH was used.

Another intriguing feature of the present reaction is its *exo*/*endo* selectivity. The 6- and 15-membered substrates **8-12** and **8-15** produced the corresponding *exo*-products **8-16** and **8-19** almost exclusively (≥95:5) (entries 1, 4), whereas a slight excess of *exo*-product **8-17** was obtained when using 7-membered substrate **8-13** (entry 2). In contrast, the reaction using 8-membered substrate **8-14** afforded *endo*-product **8-18** predominantly. To predict the *exo*/*endo* selectivity we performed a computer-assisted calculation[6] for three products, **8-16**, **8-17**, and **8-18**, as well as the corresponding key dienol intermediates (**B-1**). The results are summarized in **Table 8-3**. The energy difference, i.e., Δ*G*/kcal values, indicates that *exo*-**8-16**, *exo*-**8-17**, and *endo*-**8-18** products were more thermodynamically stable, compared with the corresponding isomeric *endo*-**8-16**, *endo*-**8-17**, and *exo*-**8-18** products. This tendency of the calculation results approximately reflects the experimental *exo*/*endo* selectivity. On the other hand, the order of the Δ*G*/kcal values of the comparable data of **B-1** did not match that of the experimental *exo*/*endo* selectivity. Together, these results suggest that the present reaction afforded thermodynamically stable α,β-unsaturated ketone products **8-16**–**8-18**.

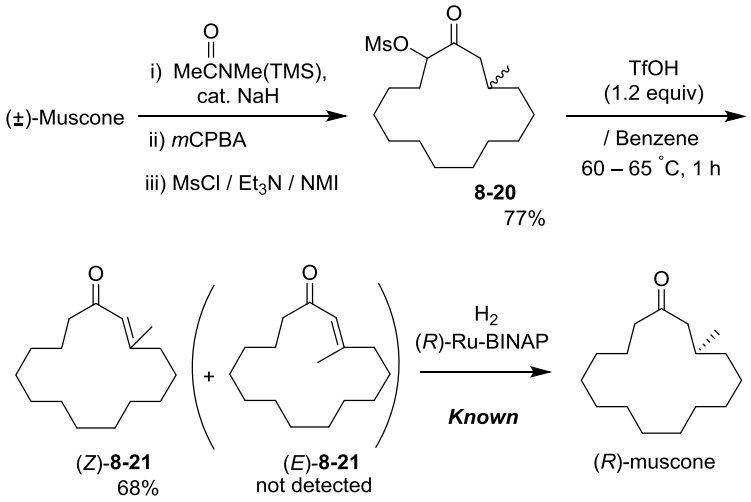
Table 8-3. MM2 force field calculation utilizing ChemBio3D®.



Finally, a useful synthetic application utilizing the present reaction was demonstrated in the preparation of (*R*)-muscone precursor (*Z*)-**8-21** (**Table 8-4**).[7] Practical synthesis of natural macrocyclic musks, especially (*R*)-muscone and (*Z*)-civetone, is a major topic in perfume chemistry.[8] Both 3-methylcyclopentadecenones (*E*)- and (*Z*)-**8-21** are valuable precursors for (*R*)-muscone, because the Takasago group reported that (*S*)- and (*R*)-Ru-BINAP-catalyzed asymmetric hydrogenation using enones (*E*)-**8-21** and **(***Z*)-**8-21**, respectively, leads to (*R*)-muscone with nearly perfect enantioselectivity (ca. 99%ee).[7]

Acyloin mesylate **8-20** was readily prepared from readily available (±)-3-methylcyclopentadecanone (racemic muscone) in three reaction sequences; mild enol trimethylsilylation using *N*-TMS-*N*-methylacetamide/cat. NaH,[9] *m*CPBA oxidation, and mesylation (MsCl/Et_3N/*N*-methylimidazole) in 77% overall yield. Gratifyingly, **8-20** was successfully converted to the desired enone (*Z*)-**8-21**. Raising the reaction temperature led to an increase in both region- and stereoselectivities, and yield. This strategy allows for the formal total synthesis of (*R*)-muscone from readily available "racemic" muscone.

Table 8-4. Synthesis of (*R*)-muscone precursor (*Z*)-**8-21**.



Entry	Temp. / °C	(*Z*)-**8-21** : (*E*)-**8-21**[a]	Yield[b] / %
1	20 – 25	69 : 31	28
2	40 – 45	95 : 5	55
3	60 – 65		68

a) Determined by ^{1}H NMR. b) Isolated.

Conclusion

A unique acid-induced (Favorskii-type) elimination reaction of acyloin mesylates has been developed, wherein both acyclic and cyclic α,β-unsaturated ketones were produced. The most characteristic feature of the present protocol lies in the regioselectivity of unsymmetrically substituted acyloin mesylates to give a variety of alkenes. Higher substituted (thermodynamically stable) α,β-unsaturated ketones were predominantly obtained via distinctive double-bond-migration pathway. As an application, the formal synthesis of (*R*)-muscone precursor starting from "racemic" muscone is demonstrated. The present mode of reaction provides a new concept and application for the regioselective synthesis of α,β-unsaturated ketone structural units.

Experimental

Favorskii-type dehydration reaction of valeroin 8-1 leading to unsymmetrical α,β-unsatureted ketones 8-2a and 8-2b

Dec-6-en-5-one 8-2a [10a] and dec-3-en-5-one 8-2b [10b]

Commercially available 6-hydroxy-5-decanone (valeroin; **8-1**) (172 mg, 1.00 mmol) and Si-Al HA^{TM} (69 mg) in 1,2-dichlorobenzene (6.0 mL) was refluxed (ca. 180 °C) for 1.5−2 h under an Ar atmosphere. Water was added to the mixture, which was extracted twice with Et_2O. The combined organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. The obtained crude product was purified by SiO_2-column chromatography (hexane) to give the 1:1 mixture of products (49 mg, 32%), dec-6-en-5-one (**8-2a**)[10a] and dec-3-en-5-one (**8-2b**).[10b]

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87−0.97 (m, 4.5H), 1.80 (t, *J* = 7.5 Hz, 1.5H), 1.26−1.66 (m, 6H), 2.15−2.29 (m, 2H), 2.50−2.56 (m, 2H), 6.06−6.13 (m, 1H), 6.77−6.92 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.2, 13.6, 13.8, 13.9, 21.3, 22.36, 22.41, 24.0, 25.5, 26.4, 31.5, 34.4, 39.8, 40.0, 129.4, 130.4, 146.9, 148.4, 200.9, 200.9; IR (neat): ν_{max} = 2935, 2858, 1690, 1661, 1628, 1451, 1373, 1331, 1310, 1294 cm^{-1}.

Preparation of acyloins (8-3) and (8-4)

Methyl 2-butyl-3-cyclohexyl-3-oxopropanoate[11]

According to a reported method for Ti-crossed Claisen condensation,[11] cyclohexanecarbonyl chloride (1.47 g, 10.0 mmol) was added to a solution of methyl haxanoate (1.30 g 10.0 mmol) and *N*-methylimidazole (985 mg, 12.0 mmol) in CH_2Cl_2 (30 mL) at –45 °C under an Ar atmosphere, followed by being stirred at the same temperature for 10 min. Then, $TiCl_4$ (3.84 mL, 35.0 mmol) and Bu_3N (9.51 mL, 40.0 mmol) were successively added to the mixture, which was stirred at the same temperature for 0.5 h. Water was added to the mixture, which was extracted twice with Et_2O. The combined organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. The obtained crude oil was purified by SiO_2-column chromatography (hexane/AcOEt = 20/1) to give methyl 2-butyl-3-cyclohexyl-3-oxopropanoate (2.24 g, 91%).

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.9 Hz, 3H), 1.15−1.46 (m, 9H), 1.62−1.87 (m, 7H), 2.42-2.58 (m, 1H), 3.60 (t, *J* = 7.2 Hz, 1H), 3.71 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 22.5, 25.5, 25.6, 25.7, 28.1, 28.2, 28.6, 29.8, 50.5, 52.2, 57.0, 170.4, 208.3; IR (neat): ν_{max} = 2932, 1748, 1713, 1451, 1246 cm^{-1}.

1-Cyclohexylhexan-1-one[12]

Methyl 2-butyl-3-cyclohexyl-3-oxopropanoate (2.24 g, 9.10 mmol) in 5M KOH aqueous solution (18 mL) and THF (18 mL) was refluxed for 4 h. 6M HCl aqueous solution (25 mL) was added to the mixture, followed by being refluxed for 6 h. Water was added to the mixture, which was extracted twice with Et_2O.

The combined organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. The obtained crude oil was purified by SiO_2-column chromatography (hexane/AcOEt = 50/1) to give the desired product (1.53 g, 92%).

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 6.9 Hz, 3H), 1.07−1.41 (m, 9H), 1.55 (quint, *J* = 7.2 Hz, 1H), 1.61−1.90 (m, 6H), 2.33 (tt, *J* = 3.5, 11.0 Hz, 1H), 2.42 (t, *J* = 7.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 22.5, 23.4, 25.7, 25.9, 28.5, 31.5, 40.6, 50.8, 214.4; IR (neat): ν_{max} = 2930, 2855, 1707 cm^{-1}.

1-(1-Hydroxycyclohexyl)hexan-1-one (8-3) and 1-cyclohexyl-2-hydroxyhexan-1-one (8-4)

According to a reported method,[9] *N*-Methl-*N*-trimethylsilylacetamide (MSA) (2.68 mL, 16.8 mmol) was added to a stirred suspension of 1-cyclohexylhexan-1-one (1.53 g, 8.40 mmol) and NaH (17 mg, 0.40 mmol) in DMF (27 mL) at 20 − 25 °C under an Ar atmosphere, followed by being stirred at 60 − 65 °C for 1 h. The reaction mixture was poured into ice water, which was extracted twice with hexane. The combined organic phase was washed with ice water, brine, dried (Na_2SO_4) and concentrated. The obtained crude product was purified by Florisil®-chromatography (hexane) to give the intermediary two enol silyl ethers (regioisomers; 1.39 g, 73%). *m*CPBA (70%, 1.65 g, 6.70 mmol) was added to a stirred suspension of the enol silyl esters (1.39 g, 6.10 mmol) and $NaHCO_3$ (666 mg, 7.90 mmol) in CH_2Cl_2 (60 mL) at 0 − 5 °C under an Ar atmosphere. The mixture was stirred at the same temperature for 0.5 h and at 20 − 25 °C for 10 h. Sat. $NaHCO_3$ aqueous solution was added to the mixture, which was extracted twice with Et_2O. The combined organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated to give the crude epoxide. Then, a mixture of the crude epoxide and PPTS (77 mg, 0.30 mmol) in THF (15 mL) and H_2O (3 mL) was stirred at 20 − 25 °C for 12 h. Sat. $NaHCO_3$ aqueous solution was added to the mixture, which was extracted twice with Et_2O. The combined organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. The obtained crude product was purified by SiO_2-column chromatography (hexane/AcOEt = 20/1) to give the desired products **8-3** (278 mg, 23%) and **8-4** (484 mg, 40%).

8-3; Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 6.9 Hz, 3H), 1.14−1.86 (m, 16H), 2.53 (t, *J* = 7.2 Hz, 2H), 3.61 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 21.1, 22.4, 23.4, 25.3, 31.4, 33.8, 35.6, 77.9, 214.9; IR (neat) 3476, 2936, 2861, 1701, 1449, 1379, 1181, 1043, 989 cm^{-1}.

8-4; Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92 (t, *J* = 6.9 Hz, 3H), 1.18-1.57 (m, 10H), 1.61-1.89 (m, 6H), 2.55 (tt, *J* = 3.7, 11.0 Hz, 1H), 3.49 (brs, 1H), 4.26−4.33 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 22.5, 25.1, 25.6, 25.8, 27.2, 27.4, 29.7, 33.3, 45.9, 74.9, 215.3; IR (neat): ν_{max} = 3482, 2932, 2859, 1701, 1400, 1143, 1051 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{12}H_{22}O_2$ $[M+Na]^+$ 221.1517; found: 221.1518.

Favorskii-type elimination reaction using valeroin mesylate (8-6) leading to unsymmetrical α,β-unsatureted ketones (8-2a) and (8-2b)

6-Oxodecan-5-yl methanesulfonate (8-6)

According to a reported method for mild mesylation method,[13] MsCl (344 mg, 3.00 mmol) was added to a stirred solution of 6-hydroxy-5-decanone (valeroin; **8-1**) (345 mg, 2.00 mmol), *N*-methylimidazole (246 mg,

3.00 mmol), and Et_3N (304 mg, 3.00 mmol) in toluene (10 mL) at 20 − 25 °C under an Ar atomosphere, and the mixture was stirred at the same temperature for 1 h. Water was added to the mixture, which was extracted twice with AcOEt. The organic phase was washed with water, brine, dried (Na_2SO_4), and concentrated. The crude oil was purified by SiO_2-column chromatography (hexane/AcOEt = 20/1) to give the desired product **8-6** (473 mg, 95%).

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89−0.95 (m, 6H), 1.29−1.47 (m, 6H), 1.53−1.64 (m, 2H), 1.74−1.91 (m, 2H), 2.51−2.56 (m, 2H), 3.12 (s, 3H), 4.96 (dd, *J* = 4.8, 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.7, 13.8, 22.1, 22.1, 25.1, 26.9, 31.1, 38.2, 38.8, 84.1, 206.4; IR (neat): ν_{max} = 2961, 2874, 1719, 1509, 1458, 1364, 1178, 955 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{11}H_{22}O_4S$ $[M+Na]^+$ 273.1136; found: 273.1128.

Favorskii-type elimination reaction

CF_3SO_3H (60 mg, 0.40 mmol) was added to a stirred solution of 6-oxodecan-5-yl methanesulfonate **8-6** (250 mg, 1.00 mmol) in hexane (0.50 mL) at 0 − 5 °C under an Ar atmosphere, and the mixture was stirred at the same temperature for 1 h. Sat. $NaHCO_3$ aqueous solution was added to the mixture, which was extracted twice with Et_2O. The combined organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. The obtained crude product was purified by SiO_2-column chromatography (hexane/AcOEt = 70/1) to give the desired 1 : 1 mixture products of **8-2a**[10a] and **8-2b**[10b] (80 mg, 52%).

Preparation of acyloin mesylates (8-7)-(8-9)

1-Cyclohexyl-1-oxohexan-2-yl methanesulfonate (8-7)

Following the procedure for the preparation of **8-6**, the mesylation reaction of **8-4** (198 mg, 1.00 mmol) with MsCl (229 mg, 2.00 mmol), *N*-methylimidazole (123 mg, 1.50 mmol), and Et_3N (152 mg, 1.50 mmol) gave the desired product **8-7** (246 mg, 89%).

Colorless crystals; mp 43−45 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92 (t, *J* = 7.3 Hz, 3H), 1.16−1.53 (m, 9H), 1.65−1.96 (m, 7H), 2.56 (tt, *J* = 11.0, 3.7 Hz, 1H), 3.12 (s, 3H), 5.12 (dd, *J* = 8.2, 3.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.7, 22.1, 25.1, 25.6, 25.7, 27.2, 27.5, 29.3, 30.8, 39.0, 46.7, 83.1, 208.8; IR (KBr): ν_{max} = 2928, 2859, 1723, 1360, 1339, 1175, 949 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{13}H_{24}O_4S$ $[M+Na]^+$ 299.1293; found: 299.1291.

Methyl 2-butyl-3-cyclopentyl-3-oxopropanoate (SSS8-8)

Following the procedure for the preparation of methyl 2-butyl-3-cyclohexyl-3-oxopropanoate, Ti-Claisen condensation reaction of cyclopentanecarbonyl chloride (2.64 g, 20.0 mmol) and methyl hexanoate (2.60 g, 20.0 mmol) gave the titled compound **SSS8-8** (4.16 g, 92%).

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.9 Hz, 3H), 1.18−1.39 (m, 4H), 1.51−1.90 (m, 10H), 3.03 (quin, *J* = 7.6 Hz, 1H), 3.55 (t, *J* = 7.3 Hz, 1H), 3.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.7, 22.4, 25.9, 28.0, 29.1, 29.5, 29.7, 50.7, 52.2, 58.3, 170.4, 207.9; IR (neat): ν_{max} = 2955, 2870, 1744, 1711,

1435, 1167, 1011 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{13}H_{22}O_3$ $[M+Na]^+$ 249.1467; found: 249.1469.

1-Cyclopentylhexan-1-one[12] (SS8-8)

Following the procedure for the preparation of 1-cyclohexylhexan-1-one, the reaction of **SSS8-8** (4.07 g, 18.0 mmol) gave the titled ketone **SS8-8** (1.85 g, 61%).

Colorless oil; ^1H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.9 Hz, 3H), 1.20−1.37 (m, 4H), 1.51−1.85 (m, 10H), 2.44 (t, *J* = 7.3 Hz, 2H), 2.86 (quint, *J* = 7.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 22.5, 23.5, 26.0, 28.9, 31.5, 41.7, 51.3, 213.5; IR (neat): ν_{max} = 2955, 2868, 1709, 1452, 1369, 1128, 756 cm^{-1}.

1-Cyclopentyl-2-hydroxyhexan-1-one (S8-8)

*n*BuLi (1.60 M in hexane, 6.75 mL, 11.0 mmol) was added to a stirred solution of *i*Pr_2NH (1.11 g, 11.0 mmol) in THF (10 mL) at 0 − 5 °C under an Ar atmosphere. To the mixture was added a solution of **SS8-8** (1.68 g, 10.0 mmol) in THF (10 mL) at –78 °C and the mixture was stirred at the same temperature for 1 h. TMSCl (1.96 g, 18.0 mmol) was added to the mixture, followed by being stirred at –78 °C and gradually warmed to 20 − 25 °C for 2 h. The mixture was slowly and reversely added to ice-water, which was extracted with hexane. The organic phase was washed with cooled water, brine, dried (Na_2SO_4) and concentrated to give the crude TMS enol ether (2.33 g). *m*CPBA (70%, 2.71 g, 11.0 mmol) was added to a stirred suspension of the TMS enol ether and $NaHCO_3$ (1.09 g, 13.0 mmol) in CH_2Cl_2 (30 mL) at 0 − 5 °C under an Ar atmosphere, followed by being stirred at 20 − 25 °C for 1 h. Sat. $NaHCO_3$ aqueous solution was added to the mixture, which was extracted twice with AcOEt. The combined organic phase was washed with brine, dried (Na_2SO_4) and concentrated to give the crude epoxide. Then, a mixture of the crude epoxide and 3M HCl aqueous solution in THF (10 mL) and MeOH (5 mL) was stirred at 20 − 25 °C for 1 h. Sat. $NaHCO_3$ aqueous solution was added to the mixture, which was extracted twice with AcOEt. The combined organic phase was washed with 1M NaOH aqueous solution, brine, dried (Na_2SO_4) and concentrated. The obtained crude product was purified by SiO_2-column chromatography (hexane/AcOEt = 25/1) to give the 1 : 1 mixture of titled compound **S8-8** (286 mg, 16%).

Colorless oil; ^1H NMR (400 MHz, $CDCl_3$): δ = 0.92 (t, *J* = 6.9 Hz, 3H), 1.24−1.98 (m, 14H), 3.01 (quint, *J* = 8.2 Hz, 1H), 3.48−3.54 (m, 1H), 4.24−4.31 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 22.5, 25.9, 26.1, 27.1, 28.7, 31.1, 33.2, 46.4, 75.9, 215.5; IR (neat): ν_{max} = 3478, 2955, 2870, 1703, 1452, 1356, 1076, 1047, 731 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{11}H_{20}O_2$ $[M+Na]^+$ 207.1361; found: 207.1365.

1-Cyclopentyl-1-oxohexan-2-yl methanesulfonate (8-8)

Following the procedure for the preparation of **8-6**, the mesylation reaction of 1-cyclopentyl-2-hydroxyhexan-1-one **S8-8** (400 mg, 2.20 mmol) with MsCl (504 mg, 4.40 mmol), *N*-methylimidazole (268 mg, 3.30 mmol), and Et_3N (330 mg, 3.30 mmol) gave the desired product **8-8** (520 mg, 91%).

Colorless oil; ^1H NMR (400 MHz, $CDCl_3$): δ = 0.90−0.95 (m, 3H), 1.23−2.04 (m, 14H), 3.06 (quint, *J* = 8.7 Hz, 1H), 3.13 (s, 3H), 5.09 (dd, *J* = 8.2, 4.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.7, 22.1, 26.0, 26.2,

27.1, 28.7, 30.5, 30.9, 39.0, 47.0, 83.9, 208.9; IR (neat): ν_{max} = 2961, 2872, 1728, 1360, 1177, 963, 917, 733 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{12}H_{22}O_4S$ $[M+Na]^+$ 285.1136; found: 285.1138.

7-Ethyl-5-hydroxyundecan-6-one (S8-9)

According to the a reported method for prepararion of a solution of SmI_2,[14] suspension of Sm powder (301 mg, 1.00 mmol, Aldrich, 99%, -40 mesh) in THF (9.0 mL) was sonicated for 15 min under an Ar atmosphere. A solution of I_2 (254 mg, 1.00 mmol) in THF (1.0 mL) was added to the stirred suspension at 20 − 25 °C, which was stirred at 60 − 65 °C for 16 h. After the resulting blue mixture was cooled to ambient temperature, a solution of 2-ethylhexanecarbonyl chloride (73 mg, 0.45 mmol) and pentanal (39 mg, 0.45 mmol) in THF (1.0 mL) was successively added dropwise and stirred at the same temparature for 3 h. 1M HCl aqueous solution was added to the mixture, which was extracted twice with AcOEt. The combined organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. The obtained crude product was purified by SiO_2-column chromatography (hexane/AcOEt = 20/1) to give titled compound **S8-9** (57 mg, 59%). Diastereomixtures; pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83−0.94 (m, 9H), 1.14−1.88 (m, 14H), 2.55−2.66 (m, 1H), 3.47−3.48 (m, 1H), 4.14−4.22 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.4, 12.1, 13.8, 13.9, 22.5, 22.8, 22.8, 23.5, 25.9, 27.4, 27.5, 29.2, 29.6, 29.8, 32.5, 32.9, 33.0, 48.3, 48.7, 76.4, 216.1, 216.2; IR (neat): ν_{max} = 3480, 2957, 2932, 2874, 2860, 1705, 1460, 1379, 1043 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{13}H_{26}O_2$ $[M+Na]^+$ 237.1830; found: 237.1833.

7-Ethyl-6-oxoundecan-5-yl methanesulfonate (7.9)

Following the procedure for the preparation of **8-6**, the mesylation reaction of 7-ethyl-5-hydroxyundecan-6-one **S8-9** (279 mg, 1.30 mmol) with MsCl (298 mg, 2.60 mmol), *N*-methylimidazole (160 mg, 1.95 mmol), and Et_3N (198 mg, 1.95 mmol) gave the 1 : 1 mixture of desired product **8-9** (316 mg, 83%).

Diastereomixtures; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83−0.96 (m, 9H), 1.13−1.54 (m, 10H), 1.59−1.79 (m, 3H), 1.86−1.96 (m, 1H), 2.57−2.66 (m, 1H), 3.14 (s, 3H x 1/2), 3.14 (s, 3H x 1/2), 5.08 (t, *J* = 3.7 Hz, 1H x 1/2), 5.10 (t, *J* = 3.7 Hz, 1H x 1/2); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.2, 11.9. 13.7, 13.8, 22.0, 22.6, 22.7, 23.1, 24.8, 27.1, 29.0, 29.3, 29.6, 30.3, 31.2, 39.1, 48.9, 49.0, 83.8, 83.8, 208.8, 208.8; IR (neat): ν_{max} = 2961, 2874, 1730, 1458, 1362, 1177, 961, 841, 735 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{14}H_{28}O_4S$ $[M+Na]^+$ 315.1606; found: 322.1609.

Favorskii-type elimination reaction using acyloin mesylate (8-7)-(8-9)

1-Cyclohexenylhexan-1-one[15] (8-5a)

Following the procedure for the case using **8-6**, the reaction of **8-7** (111 mg, 0.400 mmol) and CF_3SO_3H (72 mg, 0.48 mmol) at 20 − 25 °C gave the desired product **8-5a** (72 mg, 97%).

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.9 Hz, 3H), 1.22−1.38 (m, 4H), 1.55−1.68 (m, 6H), 2.19−2.28 (m, 4H), 2.61 (t, *J* = 7.3 Hz, 2H), 6.86−6.92 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9,

21.5, 21.9, 22.5, 23.1, 24.5, 26.0, 31.6, 36.9, 139.2, 139.4, 201.7; IR (neat): ν_{max} = 3431, 2932, 2861, 1667, 1638, 1458, 1190 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{12}H_{20}O$ $[M+Na]^+$ 203.1412; found: 203.1412.

1-Cyclopentenylhexan-1-one (8-10)

Following the procedure for the case using **8-6**, the reaction of **8-8** (104 mg, 0.400 mmol) and CF_3SO_3H (72 mg, 0.48 mmol) at 20 − 25 °C gave the desired product **8-10** (56 mg, 85%).

Colorless oil; ^1H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.3 Hz, 3H), 1.24−1.39 (m, 4H), 1.62 (*J* = 7.3 Hz, 2H,), 1.92 (quint, *J* = 7.8 Hz, 2H), 2.49−2.60 (m, 4H), 2.64 (t, *J* = 7.8 Hz, 2H), 6.70−6.73 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 22.4, 22.7, 24.4, 30.6, 31.5, 33.8, 38.9, 143.0, 145.6, 199.4; IR (neat): ν_{max} = 2957, 2860, 1665, 1615, 1466, 1379, 1298, 1256, 1173 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{11}H_{18}O$ $[M+Na]^+$ 189.1255; found: 189.1255.

5-Ethyl-5-undecen-6-one and **5-Ethyl-7-undecen-6-one (8-11)**

Following the procedure for the case using **8-6**, the reaction of **8-9** (117 mg, 0.400 mmol) and CF_3SO_3H (72 mg, 0.48 mmol) gave the 1 : 1 mixture of desired product **8-11** (57 mg, 72%).

Regioisomer mixtures; colorless oil; ^1H NMR (400 MHz, $CDCl_3$): δ = 0.88−1.00 (m, 12H x 1/2), 1.21−1.37 (m, 12H x 1/2), 1.46−1.65 (m, 6H x 1/2), 1.86 (d, *J* = 6.9 Hz, 3H x 1/2), 2.23 (q, *J* = 6.9 Hz, 2H x 1/2), 2.26−2.33 (m, 4H x 1/2), 2.61 (t, *J* = 7.3 Hz, 2H x 1/2), 2.62 (t, *J* = 7.3 Hz, 2H x 1/2), 6.55 (t, *J* = 6.9 Hz, 1H x 1/2), 6.69 (q, *J* = 6.9 Hz, 1H x 1/2); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 13.9, 14.5, 18.8, 22.2, 22.5, 22.8, 24.7, 24.7, 25.0, 30.6, 31.1, 31.5, 37.2, 37.3, 136.6, 141.7, 143.1, 143.4, 201.8, 201.9; IR (neat): ν_{max} = 3424, 3410, 2959, 2931, 2872, 1671, 1638, 1458 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{13}H_{24}O$ $[M+Na]^+$ 219.1725; found: 219.1728.

Preparation of acyloin mesylates (8-12)-(8-15)

2-Butyl-6-hydroxycyclohexanone (S8-12)

*n*BuLi (1.60 M in hexane, 5.35 mL, 8.56 mmol) was added to a stirred solution of *i*Pr_2NH (1.20 mL, 8.56 mmol) in THF (12 mL) at 0 − 5 °C under an Ar atmosphere. To the mixture was added a solution of 2-butylcyclohexanone[16] (1.20 g, 7.78 mmol) in THF (4.0 mL) at –78 °C and the mixture was stirred at the same temperature for 1 h. TMSCl (1.77 mL, 14.0 mmol) was added to the mixture, followed by being stirred at –78 °C and gradually warmed to 20 − 25 °C for 2 h. The mixture was slowly and reversely added to ice-water, which was extracted with hexane. The organic phase was washed with cooled water, brine, dried (Na_2SO_4) and concentrated to give the desired crude 1-trimethylsilyloxy-2-butylcyclohexene (1.76 g). *m*CPBA (70%, 2.11 g, 8.56 mmol) was added to a stirred suspension of the TMS enol ether and $NaHCO_3$ (849 mg, 10.1 mmol) in CH_2Cl_2 (24 mL) at 0 − 5 °C under an Ar atmosphere, followed by being stirred at 20 − 25 °C for 1 h. Sat. $NaHCO_3$ aqueous solution was added to the mixture, which was extracted twice with AcOEt. The combined organic phase was washed with brine, dried (Na_2SO_4) and concentrated to give crude epoxide. Then, a mixture of the crude epoxide and 3M HCl aqueous solution in THF (10 mL) and MeOH (5

mL) was stirred at 20 − 25 °C for 1 h. Sat. $NaHCO_3$ aqueous solution was added to the mixture, which was extracted twice with AcOEt. The combined organic phase was washed with 1M NaOH aqueous solution, brine, dried (Na_2SO_4) and concentrated. The obtained crude product was purified by SiO_2-column chromatography (hexane/AcOEt = 10/1) to give the 1 : 1 mixture of the desired product **S12** (893 mg, 67%).

3-Butyl-2-oxocyclohexyl methanesulfonate (8-12)

MsCl (172 mg, 1.50 mmol) in toluene (1.0 mL) was added to a stirred solution of **S8-12** (170 mg, 1.00 mmol), *N*-methylimidazole (123 mg, 1.50 mmol), and Et_3N (152 mg, 1.50 mmol) in toluene (1.0 mL) at 20 − 25 °C under an Ar atmosphere, followed by being stirred at the same temperature for 1 h. Water was added to the mixture, which was extracted twice with AcOEt. The combined organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. The obtained crude product was purified by SiO_2-column chromatography (hexane/AcOEt = 5/1) to give the 1 : 1 mixture of the desired products **8-12** (134 mg, 54%). Diasteromixture; colorless crystals; mp 50−53 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.84−0.95 (m, 3H), 1.17−1.49 (m, 6H), 1.65−2.37 (m, 6H), 2.44−2.56 (m, 1H x 1/2), 2.64−2.74 (m, 1H x 1/2), 3.15 (s, 3H x 1/2), 3.23 (s, 3H x 1/2), 5.03−5.14 (m, 1H); ^{13}C NMR (75 MHz; $CDCl_3$): δ = 13.8, 13.9, 19.5, 22.5, 22.8, 23.1, 28.0, 29.2, 29.8, 32.1, 33.5, 34.4, 35.0, 39.0, 39.5, 49.5, 49.8, 81.3, 82.9, 205.3, 207.3; IR (neat): ν_{max} = 2951, 2869, 1730, 1358, 1177, 974, 833, 752 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{11}H_{20}O_4S$ $[M+Na]^+$ 271.0980; found: 271.0969.

3-Butyl-2-oxocycloheptyl methanesulfonate (8-13)

Following the procedure for the preparation of **S8-12** and **8-12**, the reaction of 2-butylcycloheptanone[17] gave 2-butyl-7-hydroxycycloheptan-1-one, and the mesylation reaction of 2-butyl-7-hydroxycycloheptan-1-one (488 mg, 2.70 mmol) with MsCl (619 mg, 5.40 mmol), *N*-methylimidazole (326 mg, 4.05 mmol), and Et_3N (402 mg, 4.05 mmol) gave the desired product **8-13** (598 mg, 86%).

Colorless crystals; mp 84−85 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.83−0.95 (m, 3H), 1.13−2.07 (m, 13H), 2.08−2.21 (m, 1H), 2.41−2.54 (m, 1H), 3.11 (s, 3H), 5.21 (dd, *J* = 11.0, 3.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 22.4, 26.2, 26.6, 29.0, 29.4, 32.1, 32.8, 39.1, 50.7, 82.4, 209.1; IR (neat): ν_{max} = 2959, 1721, 1456, 1366, 1167, 968, 837, 740 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{12}H_{22}O_4S$ $[M+Na]^+$ 285.1136; found: 285.1133.

2-Butylcyclooctanone (SS8-14)

*n*BuLi (1.60 M in hexane, 20.6 mL, 33.0 mmol) was added to a stirred solution of *i*Pr_2NH (3.34 g, 33.0 mmol) in THF (40 mL) at 0 − 5 °C under an Ar atmosphere. To the mixture was added a solution of cyclooctanone (3.80 g, 30.0 mmol) in THF (15 mL) at –78 °C and the mixture was stirred at the same temperature for 1 h. HMPA (4.0 mL) and 1-iodobutane (1.77 mL, 14.0 mmol) were successively added to the mixture, followed by being stirred at –78 °C and gradually warmed to 20 − 25 °C for 2 h. The mixture

was slowly and reversely added to ice-water, which was extracted twice with AcOEt. The combined organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. The obtained crude product was purified by SiO_2-column chromatography (hexane : AcOEt = 40/1) to give the titled compound **SS8-14** (2.57 g, 47%,).

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.3 Hz, 3H), 1.10−1.51 (m, 9H), 1.55−1.70 (m, 4H), 1.75−1.85 (m, 2H), 1.91−2.05 (m, 1H), 2.28 (ddd, *J* = 13.3, 6.9, 3.2 Hz, 1H), 2.44 (ddd, *J* = 13.3, 11.5, 3.7 Hz, 1H), 2.50−2.60 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 22.7, 24.7, 25.4, 25.8, 27.3, 29.6, 32.3, 32.7, 41.9, 50.6, 220.3; IR (neat): ν_{max} = 2926, 2857, 1699, 1466, 1375, 1161, 754 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{12}H_{22}O$ $[M+Na]^+$ 205.1568; found: 205.1570.

2-Butyl-8-hydroxycyclooctanone (S8-14)

Following the procedure for the preparation of **S8-12**, the reaction of 2-butylcyclooctanone **SS8-14** (1.82 g, 10.0 mmol) gave 2-butyl-8-hydroxycyclooctan-1-one **S8-14** (1.11 g, 56%).

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.3 Hz, 3H), 1.03−1.80 (m, 14H), 1.82−1.95 (m, 1H), 2.10−2.19 (m, 1H), 2.44−2.54 (m, 1H), 3.11 (brs, 1H), 4.38 (dd, *J* = 8.2, 4.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 21.1, 22.5, 24.9, 26.8, 28.5, 29.3, 33.6, 37.1, 51.5, 72.3, 219.7; IR (neat): ν_{max} = 3449, 2928, 2859, 1697, 1466, 1030, 752 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{12}H_{22}O_2$ $[M+Na]^+$ 221.1517; found: 221.1524.

3-Butyl-2-oxocyclooctyl methanesulfonate (8-14)

Following the procedure for the preparation of **8-12**, the mesylation reaction of **S8-14** (1.00 g, 5.04 mmol) with MsCl (1.15 g, 10.1 mmol), *N*-methylimidazole (621 mg, 7.56 mmol), and Et_3N (764 mg, 7.56 mmol) gave the desired product **8-14** (1.31 g, 94%).

Colorless crystals; mp 39−41 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.9 Hz, 3H), 1.15−1.78 (m, 13H), 1.89−1.98 (m, 1H), 2.06−2.20 (m, 2H), 2.71−2.80 (m, 1H), 3.06 (s, 3H), 5.09 (dd, *J* = 7.8, 5.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 21.2, 22.5, 24.8, 26.1, 29.4, 30.8, 32.1, 33.9, 38.6, 48.9, 81.7, 212.7; IR (KBr): ν_{max} = 2959, 2860, 1720, 1707, 1468, 1346, 1174, 970, 845 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{13}H_{24}O_4S$ $[M+Na]^+$ 299.1293; found: 229.1295.

2-Butylcyclopentadecanone (SS8-15)

Following the procedure for preparation of **SS8-14**, the alkylation of cyclopentadecanone (4.49 g, 20.0 mmol) gave a mixture of the desired product **SS8-15** and a byproduct (5.96 g).

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 6.9 Hz, 3H), 1.10−1.44 (m, 26H), 1.48−1.77 (m, 4H), 2.36 (dt, *J* = 16.5, 6.9 Hz, 1H), 2.47 (dt, *J* = 16.5, 6.9 Hz, 1H), 2.43−2.54 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 22.3, 22.8, 26.0, 26.2, 26.3, 26.3, 26.4, 26.6, 27.0, 27.4, 27.5, 29.8, 31.9, 32.0, 41.6, 52.2, 215.7; IR (neat): ν_{max} = 2926, 2855, 1709, 1458, 1375, 1063, 733 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{19}H_{36}O$ $[M+Na]^+$ 303.2664; found: 303.2663.

2-Butyl-15-hydroxylcyclopentadecanone (S8-15)

Following the procedure for the preparation of **S8-12**, 2-butylcyclopentadecan-1-one (5.96 g) gave the desired product **S8-15** (2.89 g, 49%).

Diastereomixtures; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 7.3 Hz, 3H x 3/10), 0.88 (t, *J* = 7.3 Hz, 3H x 7/10), 1.09−1.97 (m, 30H), 2.64−2.80 (m, 1H), 3.48 (d, *J* = 5.0 Hz, 1H x 7/10), 3.53 (d, *J* = 5.5 Hz, 1H x 3/10), 4.16 (ddd, *J* = 11.0, 5.0, 2.3 Hz, 1H x 7/10), 4.26 (q, *J* = 5.5 Hz, 1H x 3/10); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 13.9, 22.3, 22.8, 22.9, 23.5, 24.8, 25.2, 25.4, 25.5, 25.6, 25.9, 25.9, 26.3, 26.3, 26.4, 26.5, 26.6, 26.6, 26.7, 27.1, 27.6, 29.4, 29.7, 30.1, 30.4, 31.2, 32.5, 32.7, 32.9, 45.0, 46.7, 74.7, 76.8, 216.6, 217.2; IR (neat): ν_{max} = 3480, 2926, 2857, 1703, 1458, 1373, 1238, 1045, 908, 731 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{19}H_{36}O_2$ $[M+Na]^+$ 319.2613; found: 319.2621.

3-Butyl-2-oxocyclopentadecyl methanesulfonate (8-15)

Following the procedure for the preparation of **8-12**, the mesylation reaction of **S8-15** (700 mg, 2.36 mmol) with MsCl (541 mg, 4.72 mmol), *N*-methylimidazole (291 mg, 3.54 mmol), and Et_3N (358 mg, 3.54 mmol) gave the 7 : 3 mixture of desired product 8-**15** (761 mg, 86%).

Diastereomixtures; colorless crystals; mp 42−45 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.84−0.93 (m, 3H), 1.11−1.52 (m, 26H), 1.59−1.84 (m, 3H), 1.90−2.08 (m, 1H), 2.55−2.65 (m, 1H x 3/10), 2.73−2.82 (m, 1H x 7/10), 3.14 (s, 3H), 5.05 (dd, *J* = 9.2, 3.7 Hz, 1H x 7/10), 5.21 (t, *J* = 5.0 Hz, 1H x 3/10); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 22.5, 22.6, 22.7, 23.0, 25.3, 25.4, 25.6, 25.7, 25.7, 26.1, 26.3, 26.5, 26.6, 27.6, 28.9, 29.1, 29.5, 29.7, 29.9, 30.6, 31.2, 31.9, 39.0, 39.2, 45.9, 47.7, 83.3, 83.4, 208.4, 209.9; IR (KBr): ν_{max} = 2957, 2849, 1713, 1460, 1358, 1172, 968, 858 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{20}H_{38}O_4S$ $[M+Na]^+$ 397.2388; found: 397.2380.

Favorskii-type elimination reaction using acyloin mesylate (8-12)-(8-15)

2-Butylidenecyclohexanone (8-16)[18]

Following the procedure for the case using **8-6**, the reaction of **8-12** (50 mg, 0.20 mmol) and CF_3SO_3H (36 mg, 0.24 mmol) at 20 − 25 °C gave the desired product **8-16** (18 mg, 60%).

Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.93 (t, *J* = 7.3 Hz, 3H), 1.48 (sext, *J* = 7.3 Hz, 2H), 1.70−1.79 (m, 2H), 1.81−1.89 (m, 2H), 2.08 (q, *J* = 7.3 Hz, 2H), 2.43 (t, *J* = 6.4 Hz, 2H), 2.49 (t, *J* = 6.4 Hz, 2H), 6.63 (tt, *J* = 7.3, 1.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 21.7, 23.3, 23.6, 26.6, 29.8, 40.1, 136.3, 139.5, 201.2; IR (neat): ν_{max} = 2926, 1688, 1619, 1456, 1321, 1246, 1175, 941 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{10}H_{16}O$ $[M+Na]^+$ 175.1099; found: 175.1097.

2-Butylidenecycloheptanone (*exo*-8-17) and 2-butylcyclohept-2-enone (*endo*-8-17)

Following the procedure for the case using **8-6**, the reaction of **8-13** (52 mg, 0.20 mmol) and CF_3SO_3H (61 mg, 0.40 mmol) at 20 − 25 °C gave the product (*exo*-**8-17**; 13 mg, 39% and *endo*-**8-17**; 12 mg, 36%).

exo-**8-17a**: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (t, *J* = 7.2 Hz, 3H), 1.47 (sext, *J* = 7.2 Hz, 2H),

2.12 (dt, *J* = 7.6, 7.2 Hz, 2H), 2.38−2.46 (m, 2H), 2.56−2.64 (m, 2H), 6.58 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 22.0, 25.2, 27.1, 29.8, 30.0, 31.4, 43.3, 139.1, 140.7, 204.8; IR (neat) 2928, 2856, 1686, 1619, 1458, 1321, 1177, 943 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{18}O$ ($M+Na^+$) 189.1255, found 189.1255. *endo*-**8-17b**: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.2 Hz, 3H), 1.21−1.41 (m, 2H), 1.65−1.83 (m, 2H), 2.18−2.27 (m, 2H), 2.32−2.41 (m, 2H), 2.52−2.60 (m, 2H), 6.46 (tt, *J* = 6.2, 1.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 21.5, 22.4, 25.0, 27.4, 31.3, 32.8, 42.6, 140.9, 144.0, 205.4; IR (neat): ν_{max} = 2934, 2863, 1671, 1458, 1379 cm^{-1}.

2-Butylidenecyclooctanone (*exo*-8-18) and **2-butylcyclooct-2-enone (*endo*-8-18)**

Following the procedure for the case using **8-6**, the reaction of **8-14** (55 mg, 0.20 mmol) and CF_3SO_3H (61 mg, 0.40 mmol) at 20 − 25 °C gave the desired product (*exo*-**8-18**; 3 mg, 8% and *endo*-**8-18**; 22 mg, 61%). *endo*-**8-18**: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.2 Hz, 3H), 1.24−1.38 (m, 4H), 1.53−1.64 (m, 4H), 1.82−1.90 (m, 2H), 2.15−2.23 (m, 2H), 2.27−2.35 (m, 2H), 2.50−2.56 (m, 2H), 5.91 (tt, *J* = 6.4, 0.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 22.3, 22.4, 22.9, 27.4, 29.1, 30.8, 35.3, 44.3, 132.8, 140.5, 211.3; IR (neat): ν_{max} = 2932, 1684, 1655, 1458, 1379, 1230, 1115 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{12}H_{20}O$ $[M+Na]^+$ 203.1412; found: 203.1418.

2-Butylidenecyclopentadecanone (*exo*-8-19)

Following the procedure for the case using **8-6**, the reaction of **8-15** (55 mg, 0.20 mmol) and CF_3SO_3H (61 mg, 0.40 mmol) at 20 − 25 °C gave the desired product (*exo*-**8-19**; 40 mg, 72% and *endo*-**8-19**; 2 mg, 4%). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.98 (t, *J* = 7.3 Hz, 3H), 1.12−1.41 (m, 20H), 1.50 (sext, *J* = 7.3 Hz, 2H), 1.61−1.70 (m, 2H), 2.23 (q, *J* = 7.3 Hz, 2H), 2.40 (t, *J* = 6.4 Hz, 2H), 2.67 (t, *J* = 6.4 Hz, 2H), 6.56 (t, *J* = 7.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 22.2, 24.9, 25.0, 26.0, 26.4, 26.4, 26.5, 26.7, 26.8, 27.2, 27.5, 27.6, 28.5, 30.9, 36.9, 142.1, 142.2, 203.0; IR (neat): ν_{max} = 2928, 2859, 1671, 1636, 1458, 1281, 1117 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{19}H_{34}O$ $[M+Na]^+$ 301.2507; found: 301.2503.

Synthesis of (*R*)-muscone precursor (*Z*)-8-21

4-Methyl-2-oxocyclopentadecyl methanesulfonate (8-20)

Following the procedure for the preparation of **8-4**, 3-methylcyclopentadecanone[19] (4.77 g, 20.0 mmol) gave 2-hydroxy-14-methylcyclopentadecanone (1.37 g, 27%). The mesylation reaction of 2-hydroxy-14-methylcyclopentadecanone (1.77 g, 7.00 mmol) with MsCl (1.60 g, 14.0 mmol), *N*-methylimidazole (858 mg, 10.5 mmol), and Et_3N (1.06 g, 10.5 mmol) gave the desired product **20** (1.79 g, 77%)

Diastereomixtures; colorless crystals; mp 64−67 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93−1.03 (m, 3H), 1.09−1.55 (m, 20H), 1.78−2.26 (m, 3.5H), 2.31 (dd, *J* = 16.9, 5.5 Hz, 1H x 1/2), 2.52 (dd, *J* = 17.2, 7.2 Hz, 1H x 1/2), 2.73 (dd, *J* = 17.2, 6.5 Hz, 1H x 1/2), 3.11 (s, 3H x 1/2), 3.14 (s, 3H x 1/2), 4.94 (t, *J* = 6.2 Hz, 1H x 1/2), 5.08 (t, *J* = 5.5 Hz, 1H x 1/2); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.5, 20.6, 22.4, 22.8, 24.7, 25.0, 25.7,

26.1, 26.3, 26.3, 26.7, 26.4, 26.5, 26.5, 26.6, 26.7, 26.8, 27.0, 27.7, 27.9, 30.7, 30.2, 35.5, 38.7, 39.2, 45.2, 46.1, 83.5, 83.7, 205.3, 207.2; IR (KBr): ν_{max} = 2853, 1721, 1456, 1370, 1284, 1165, 961, 841 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{17}H_{32}O_4S$ $[M+Na]^+$ 362.1919; found: 362.1921.

(*Z*)-3-Methylcyclopentadec-2-enone [(*Z*)-8-21][7f,j]

Following the procedure for case using **8-6**, the reaction of **8-20** (55 mg, 0.20 mmol) and CF_3SO_3H (36 mg, 0.24 mmol) at 60 − 65 °C gave the desired product **(*Z*)-8-21** (32 mg, 68%).

Pale yellow oil; ^1H (300 MHz, $CDCl_3$): δ = 1.14−1.41 (m, 16H), 1.50−1.72 (m, 4H), 2.14 (d, *J* = 1.4 Hz, 3H), 2.15−2.22 (m, 2H), 2.33−2.41 (m, 2H), 6.15 (d, *J* = 1.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.7, 25.2, 25.5, 25.6, 26.4, 26.6, 26.7, 26.8, 26.9, 27.1, 40.0, 44.5, 123.7, 159.0, 202.4; IR (neat): ν_{max} = 2928, 2857, 1684, 1613, 1458, 1389, 1364, 1225 cm^{-1}.

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