Stereocomplementary and Parallel Syntheses of Multi-Substituted \((E)\)-, \((Z)\)-Stereodefined \(\alpha,\beta\)-Unsaturated Esters: Application to Drug Syntheses

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This article is dedicated to the late professor Teruaki Mukaiyama who deceased in 2018 and the late professor Kenji Mori who deceased in 2019.
Abstract: Ubiquitous α,β-unsaturated esters are well recognized as key structural olefin scaffolds in organic chemistry. (E)- and (Z)-stereoselectivity is the most critical issue in their synthesis, however, (E)- and (Z)-stereocomplementary synthetic methods remain quite limited. The present account discloses general (E)-, (Z)-stereocomplementary syntheses of a variety of α,β-unsaturated esters from highly accessible (E)-, (Z)-stereodefined enol tosylates derived from β-ketoesters and α-formyl esters. Step 1 toward the stereocomplementary preparation of (E)-, (Z)-stereodefined enol tosylates is implemented by using inexpensive reagents under mild reaction conditions. Step 2 toward the highly stereoretentive synthesis of (E)- and (Z)-stereodefined α,β-unsaturated esters involves Suzuki-Miyaura, Negishi, Sonogashira, Iron-catalyzed, Mizoroki-Heck, and Buchwald-Hartwig cross-coupling reactions. Notably, this strategy was successfully applied for parallel drug syntheses of (E)- and (Z)-zimelidine, (E)- and (Z)-tamoxifen, and Merck’s cyclopropane pharmacophore. Representative successful utilizations by other groups are also introduced.

Keywords: Cross-coupling, Synthetic methods, (E)- and (Z)-α,β-unsaturated esters, Drug syntheses, (E)- and (Z)-stereocomplementary and parallel synthesis

1. Introduction

Regio- and stereo-controlled syntheses of ubiquitous (E)- and (Z)-stereodefined olefins are of particular importance in organic chemistry due to the wide distribution of these key structural components in natural products, pharmaceuticals, and functionalized molecules. Despite numerous available methods for synthesizing these olefins, the development of stereoselective syntheses of multi-carbon-substituted olefins has become a pivotal goal aimed at enhancing both (E)- and (Z)-stereoselectivity and facilitating separation of the stereoisomers. (1,2) (E)- and (Z)-α,β-Unsaturated esters serves as a well-recognized, useful, and accessible structural scaffolds for various (E)- and (Z)-stereodefined olefins. These esters contribute asymmetric hydrogenation precursors and conjugate (Michael) addition acceptors, etc.

Considerable effort has been devoted to the synthetic development of these stereodefined α,β-unsaturated esters the last few decades. Comprehensive reviews address the impressive progress in this area. (3,4) Scheme 1 depicts representative stereo-controlled methods: (i) (E)- or (Z)-stereoselective Horner-Wadsworth-Emmons reaction, (4) (ii) Mizoroki-Heck reactions (Buchwald’s group), (5) (iii) ynolate-mediated reactions derived from α,α-dibromoesters (Shindo’s group), (6) (iv) sequential stereoretentive Suzuki-Miyaura cross-coupling using (E)-β-chloro-α-iodo-α,β-unsaturated esters (Ogilvie’s group), (7) (v) Cu-catalyzed conjugate addition of ArB(OH)2 to alkynoates (Yamamoto’s group), (8) (vi) oxidative Heck reaction sequence (Studer’s group), (9) etc.

Despite the high demand, however, “(E)- and (Z)-stereocomplementary” synthetic methods for multi-substituted (E)- and (Z)-α,β-unsaturated esters are not yet established primarily due to the inherent high complexity in differentiating the substituents. Cross-coupling reactions with (E)- and (Z)-stereodefined enol sulfonate and phosphonate partners derived from β-ketoesters, which emerged in the last few decades, are considered a promising, accessible, and reliable approach compared with the above-mentioned methods and have the following advantages. (i) Various starting β-ketoester substrates are readily available, (ii) (E)- and (Z)-stereocomplementary enol tosylation step is robust and cost-effective, (10,11) and (iii) (E)- and (Z)-stereoretentivity during the

\[ \text{Scheme 1. Representative stereoselective synthetic approaches for (E)- and (Z)-α,β-unsaturated esters.} \]
cross-coupling step is guaranteed owing to recent developments in cross-coupling reactions.

This account describes our recent investigations on stereocomplementary and parallel syntheses of \((E)-\) and \((Z)-\) unsaturated esters derived from \(\beta\)-ketoester and \(\alpha\)-formylester substrates (Scheme 2), in which the strategy is categorized into convergent-oriented type-1 and divergent-oriented type-2 approaches. Distinctive application to parallel syntheses of two sets (all four) of pharmaceuticals, \((E)-\) and \((Z)-\) zimeridine and \((E)-\) and \((Z)-\) tamoxifen, are also demonstrated.

### 2. Origin and Motif

The \(p\)-toluenesulfonyl (Ts-) group is a well-established leaving group against various nucleophiles, and the reaction is recognized as textbook chemistry. Tosylation (\(p\)-toluenesulfonylation) of alcohols using TsCl in pyridine solvent is the most recognized as textbook chemistry. Tosylation \((p\)-toluenesulfonylation) of alcohols using TsCl in pyridine solvent is the most

Our 5 alternative methods for mild but powerful, cost-effective tosylation and the relevant mesylation (Ms-) (Methods A-E)[13] are depicted in Scheme 3. These methods are utilized for natural product and functionalized material syntheses such as (+)-vinblastine from Fukuyama and Tokuyama’s group,[14] fluorlescent amino acid precursor from Nau’s group,[15] and industrial production of a brockbuster herbicide, flumioxadine, by the Sumitomo Chemical group.[16] To date, there are over 100 exemplary applications indexed in the Web of Science.

Our group has been engaged in the research and development of self, crossed, and asymmetric Ti-Claisen condensations for the preparation of a wide variety of \(\beta\)-ketoesters and \(\alpha\)-formyl esters (Selected Abstract: Scheme 4).[17] The synthetic background of these longstanding interests of ours prompted us to envisage the present project.

### 3. \((E)-\) and \((Z)-\) Stereocomplementary Enol Tosylations of \(\beta\)-Ketoesters and \(\alpha\)-Formyl Esters

#### 3.1. “\(\alpha\)-Nonsubstituted” \(\beta\)-Ketoesters and \(\alpha\)-Formyl Esters

In 2005, the Merck process group disclosed \((E)-\) and \((Z)-\) stereocomplementary enol tosylation of specific \(\gamma\)-amino-\(\beta\)-keto butylates (GABA analogues) using a Ts\(_2\)O–Et\(_3\)N reagent for the \(E\) geometry and an expensive Ts\(_2\)O–LDA reagent for the \(Z\)-geometry.[11] TsCl is ca.1/10 less expensive than Ts\(_2\), but use of the TsCl–LDA reagent causes \(\alpha\)-chlorination at the methylene position as a critical side reaction.[12] Instead of using expensive reagents (Ts\(_2\)O and LDA) and a low temperature (\(-50^\circ\)C), our methods employ a much more accessible and robust procedure (reagent stability and benchtop handling) using a TsCl–N-methylimidazole (NMI)–Et\(_3\)N reagent for \(E\) (Method A: total 26 examples; 66–99\%); and a TsCl–NMI–LiOH or LiCl reagent for \(Z\) (Method B: total 26 examples; 60–99\%)[12] (Table 1; Selected and other examples).

The method covers various \(\alpha\)-nonsubstituted \(\beta\)-ketoesters and \(\alpha\)-formyl esters. A relevant \((E)-\) and \((Z)-\) stereocomplementary enol triflation was presented by Frantz’s group in the same year.[18]

Notably, NMI activator also functions well as an efficient activator for various condensation reactions, \(O\)-, \(N\)-, and \(S\)-acylations (esterification, amid e formation, thioesterification) (Scheme 5)[19] and distinctive \(C\)-acylation (crossed Ti-Claisen condensation).[17c,h]

The method in Scheme 5 has been utilized for ester and

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Yoo Tanabe received his B. S. degree at Tokyo (Professor Kenji Mori). He received his Ph.D. at Tokyo under the direction of Professor Teruaki Mukaiyama on the development of practical acylation reactions. After leaving Sumitomo Chemical Co., Ltd, Dr Tanabe moved to Kwansei Gakuin University in 1991 as Associate Professor and promoted to Full Professor (1997). In 1996–1997, he studied at University of Groningen with Professors Richard M. Kellogg and Ben L. Feringa. His research focuses on the exploitation of useful synthetic reactions directed for process chemistry: concise synthesis of useful fine chemicals and of total synthesis of biologically active natural products.
amide forming reactions in recent drug syntheses and functional molecule.

3.2. “α-Substituted” β-Ketoesters

The use of N,N,N’,N’-tetramethyldiamine bases instead of NMI, promotes (E)- and (Z)- stereocomplementary reactions for fully-substituted (α-substituted) enol tosylates. This accessible and substrate-general method involves (E)-selective enol tosylations using a TsCl–Me$_2$N(CH$_3$)$_2$NMe$_2$ reagent (Method A: total 13 examples; 63–96%) and (Z)-selective enol tosylations using a TsCl–TMEDA–LiCl reagent (Method B: total 13 examples; 62–89%) (Table 2; Selected and other examples).

3.3. “α-Chlorinated” β-Ketoesters

(Z)- and (E)-Stereocomplementary reactions of methyl α-chloro-β-oxoesters using novel reagents, TsCl–NaH–TMEDA–LiCl for Z (Method A: total 3 examples; 82–83%) and TsCl–Pr$_2$NEt–NMI for E (Method B: total 3 examples; 62–89%) afforded the corresponding α-chlorinated enol tosylates (Table 3). The obtained (E)- and (Z)-stereodefined tosylates were utilized for four types of sequential cross-couplings for (E)-, (Z)-stereocomplementary synthesis of fully-substituted α,β-unsaturated esters (see Section 8).
3.4. Mechanistic Explanation for the E- and Z-Selectivity Emergence

TsCl coupled with NMI and TMEDA are speculated to form key highly reactive sulfonylammonium salts I and IIA, respectively, which was supported by findings from a careful 1H-NMR monitoring experiment (−40°C in CD3CN)\(^{[20]}\) (Scheme 6, 1H-NMR charts are shown in the SI). A plausible mechanism for the successful emergence of (E)- and (Z)-stereoselectivity is as follows. The (E)-reaction proceeds via a non-chelation pathway, whereas the (Z)-reaction proceeds via a Li-chelation mechanism.\(^{[22]}\)

4. Stereoretentive Cross-Coupling Reactions of (E)- and (Z)-Stereodefined Enol Tosylates

These (E)- and (Z)-stereodefined enol tosylates function as various efficient stereoretentive cross-coupling partners. Despite the considerable demand for multi-substituted α,β-unsaturated (E)- and (Z)-stereodefined esters on the synthesis of natural products, pharmaceuticals, and supramolecular assemblies, there are no fully established stereocontrolled and substrate-general preparative methods due to the fundamental difficulties in differentiating between structurally similar substituents. The following methods provide reasonable solutions to this crucial demand.

4.1. (E)- and (Z)-Sterecomplementary Suzuki-Miyaura Cross-Coupling Reactions

The most accessible Suzuki-Miyaura cross-coupling method exhibits broad substrate-generality for the synthesis of not only tri-substituted but also stereocongested fully-substituted (E)- and (Z)-α,β-unsaturated esters with (E)- and (Z)-stereoretentive manner (E: total 40 examples; 41–99 % yield, > 86 : 14 selectivity and Z: total 39 examples; 41–99 % yield, > 89 : 11 selectivity)\(^{[20,22]}\) (Table 4; Selected and other examples). For less hindered enol tosylates Pd(OAc)\(_2\)/Ph\(_3\)P (or Cy\(_3\)P), Pd(dppb)Cl\(_2\), and Pd(dppf)Cl\(_2\) catalysts were
In particular, the present method provides a practical synthesis of less accessible (Z)-α,β-unsaturated esters, as exemplified in the Organic Syntheses procedure (Scheme 7), whereas the Pd(OAc)\(_2\)/SPhos catalyst was applied for stereocongested enol tosylates. Various aromatic and heterocyclic substituents (Ar) were incorporated and a few functional groups were tolerated.

### Table 1. (E)- and (Z)-stereocomplementary enol tosylations of "α-nonsubstituted" β-ketoesters and α-formyl esters.

| Method A | Method B |
|----------|----------|
| ![Diagram A](image1.png) | ![Diagram B](image2.png) |

| Method A | Method B |
|----------|----------|
| ![Diagram 3](image3.png) | ![Diagram 4](image4.png) |

a) Determined by \(^1\)H NMR of crude products.

### 4.2. (E)- and (Z)-Stereocomplementary Negishi Cross-Coupling Reactions

In a similar fashion, Negishi cross-coupling proceeded smoothly to provide multi-substituted (E)- and (Z)-α,β-unsaturated esters with (E)- and (Z)-stereoretentive manner and broad substrate-generality (E: total 34 examples; 34–99% yield, >68:32 selectivity and Z: total 34 examples; 53–99% selectivity).

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applied. In particular, the present method provides a practical synthesis of less accessible (Z)-α,β-unsaturated esters, as exemplified in the Organic Syntheses procedure (Scheme 7), whereas the Pd(OAc)\(_2\)/SPhos catalyst was applied for stereocongested enol tosylates. Various aromatic and heterocyclic substituents (Ar) were incorporated and a few functional groups were tolerated.
yield, > 95 : 5 selectivity\[12\textsuperscript{a},25\] (Table 5; Selected and other examples). The Pd(dppe)Cl\textsubscript{2} catalyst was employed for an E-stereoretentive reaction and, whereas the Pd(dpbb)Cl\textsubscript{2} catalyst was employed for a Z-stereoretentive reaction. Various aromatic substituents (Ar) were incorporated and some functional groups were tolerated. Throughout this project, we observed that Negishi cross-couplings tends to exhibit somewhat higher reactivity with lower catalyst loading than SM cross-couplings.

4.3. (E)- and (Z)-Stereoretentive Iron-Catalyzed and Kumada-Tamao-Corriu Cross-Coupling Reactions

Iron-catalyzed cross-coupling successfully produced a variety of the corresponding (E)- and (Z)-trisubstituted α,β-unsaturated esters (E: total 11 examples; 68–98% yield, > 95 : 5 selectivity and Z: total 13 examples; 58–98% yield, > 95 : 5 selectivity\[24\textsuperscript{b}\] (Table 6). The present method provides a practical synthesis of less accessible (Z)-α,β-unsaturated esters, as exemplified in Organic Syntheses procedure (Scheme 8).\[26\]

Extensions of Suzuki-Miyaura and Negishi couplings to aliphatic nucleophiles were not examined, but to overcome the limitation a Fe-catalyzed reaction method was addressing this problem.

The relevant Kumada-Tamao-Corriu cross-coupling reactions for preparing (E)- and (Z)-stereodefined fully-substituted α,β-unsaturated esters are developed using Pd(OAc)\textsubscript{2}/SPhos catalysis (11 examples; 50–96% yield) (Table 7).\[24\textsuperscript{b}\]

Table 2. (E)- and (Z)-stereocomplementary enol tosylation of “α-substituted” β-ketoesters.

< Selected examples >

| Method A | Method B |
|----------|----------|
| 74% (>98 / 2) | 95% (>98 / 2) |
| 84% (>98 / 2) | 94% (>98 / 2) |
| 77% (>98 / 2) | 95% (>98 / 2) |
| 90% (>98 / 2) | 96% (>98 / 2) |
| 93% (>98 / 2) | 93% (>98 / 2) |
| 95% (>98 / 2) | 95% (>98 / 2) |

| Method A | Method B |
|----------|----------|
| 98% (>98 / 2) | 98% (>98 / 2) |
| 98% (>98 / 2) | 98% (>98 / 2) |
| 92% (>98 / 2) | 92% (>98 / 2) |
| 81% (97 / 3) | 74% (>98 / 2) |
| 95% (>98 / 2) | 95% (>98 / 2) |
| 94% (>98 / 2) | 94% (>98 / 2) |

| Method A | Method B |
|----------|----------|
| 63% (95 / 5) | 63% (95 / 5) |
| 98% (94 / 6) | 98% (94 / 6) |
| 96% (74 / 26) | 96% (74 / 26) |
| 95% (>98 / 2) | 95% (>98 / 2) |
| 95% (>98 / 2) | 95% (>98 / 2) |

< other examples >

| Method A | Method B |
|----------|----------|
| 74% (>98 / 2) | 95% (>98 / 2) |
| 84% (>98 / 2) | 94% (>98 / 2) |
| 77% (>98 / 2) | 95% (>98 / 2) |
| 90% (>98 / 2) | 96% (>98 / 2) |
| 93% (>98 / 2) | 93% (>98 / 2) |
| 95% (>98 / 2) | 95% (>98 / 2) |

| Method A | Method B |
|----------|----------|
| 98% (>98 / 2) | 98% (>98 / 2) |
| 98% (>98 / 2) | 98% (>98 / 2) |
| 92% (>98 / 2) | 92% (>98 / 2) |
| 81% (97 / 3) | 74% (>98 / 2) |
| 95% (>98 / 2) | 95% (>98 / 2) |
| 94% (>98 / 2) | 94% (>98 / 2) |

| Method A | Method B |
|----------|----------|
| 63% (95 / 5) | 63% (95 / 5) |
| 98% (94 / 6) | 98% (94 / 6) |
| 96% (74 / 26) | 96% (74 / 26) |
| 95% (>98 / 2) | 95% (>98 / 2) |
| 95% (>98 / 2) | 95% (>98 / 2) |

< other examples >
4.4. (E)- and (Z)-Stereoretentive Sonogashira Cross-Coupling Reactions

Sonogashira cross-coupling also proceeds to afford the corresponding (E)- and (Z)-β-alkynyl-α,β-unsaturated esters (E: total 8 examples; 84–97% yield, >95:5 selectivity and Z: total 8 examples; 70–96% yield, >95:5 selectivity)\[12a\] (Table 8). The reaction using Z-tosylates required significantly longer reaction period, probably because steric reason.

5. (E)- and (Z)-Stereocomplementary Enol Phosphorylations of β-Ketoesters and Stereoretentive Cross-Coupling Reactions

In a relevant protocol, (E)- and (Z)-stereocomplementary enol phosphorylations and successive Suzuki-Miyaura and Negishi cross-couplings were performed (Scheme 9, Table 9).\[27\]

Although separation of (E)- and (Z)-enol phosphonates were primarily difficult, (E)- and (Z)-selectivity was nearly perfect (>95:5 ds). 1H-NMR monitoring for a key reactive N-phosphorylammunium (imidazolium) intermediate was carried out (See the SI).\[27\] Notably, on the whole, the cross-coupling reactivity slightly decreased compared with that using enol tosylates, despite of the wide substrate-generality.

6. Parallel and Stereocomplementary Synthesis: Application to (E)- and (Z)-Zimelidine

A highlighted feature of the present project is the use of “parallel and stereocomplementary approaches” to furnish highly (E)- and (Z)-pure olefinic products utilizing sequential enol tosylation and cross-coupling reactions. An expeditious and parallel synthesis of (E)- and (Z)-zimelidines, a highly representative selective serotonin reuptake inhibitor (SSRI), was performed (Scheme 10, Table 4).\[22\]

The salient features are as follows: (i) Parallel and stereocomplementary enol tosylation (see Section 3.1) ([a]–[d]), (ii) (E)- and (Z)-Stereocomplementary Suzuki-Miyaura cross-couplings using (3-Py)B(OH)\(_2\) (79–91%, E/Z = >97:3) ([e]–[h]), (iii) Toleration of a labile p-Br substituent on the benzene ring, (iv) Successful syntheses of both (E-) and (Z)-zimelidines through the short and accessible reaction sequences ([i], [j]), and (v) Excellent overall yields of 33% for (Z)-zimelidine and of 45% for (E)-zimelidine via each of the 5 parallel steps (Approaches I and II). Compared with the reported synthesis of (E)- and (Z)-zimelidines,\[28\] the present method is of highly concise and orthogonal, and eliminates tedious pH-dependent separation.
Table 4. (E)- and (Z)-stereocomplementary Suzuki-Miyaura cross-coupling reactions.

< Selected examples >

< other examples >

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a) Determined by $^1{H}$ NMR of crude products.
b) Conditions: ArB(OH) (1.5 eq.), Pd(OAc)$_2$ (5 mol%), $\text{P}$_{3}$\text{P}$ (10 mol%), Na$_2$CO$_3$ (3.0 eq.) in DMF, reflux, 2 h
c) Conditions: ArB(OH) (1.5 eq.), Pd($\text{P}$_{3}$\text{P}$)$_2$Cl$_2$ (5 mol%), KF (3.0 eq.) in $\text{PrOH}$, 60 – 66 °C, 2 h
d) Conditions: ArB(OH) (1.5 eq.), Pd($\text{P}$_{3}$\text{P}$)$_2$Cl$_2$ (5 mol%), K$_2$CO$_3$ (3.0 eq.) in $\text{PrOH}$, 60 – 66 °C, 2 h
e) Reaction was conducted at 120 – 125 °C.
f) K$_2$CO$_3$ was used instead of KF.
g) 8.0 equivalents of Ph$_2$B(OH)$_2$ were used.
h) 3.0 equivalents of Ph$_2$B(OH)$_2$ were used.
Table 5. \((E)\)- and \((Z)\)-stereocomplementary Negishi cross-coupling reactions.

**< Selected examples >**

| Yield \((E / Z)\) |
|------------------|
| \(\text{PhCO}_2\text{Et}\) | 87\%\(^\text{a}\) (95 / 5) |
| \(\text{PhCO}_2\text{Ph}\) | 75\%\(^\text{a}\) (95 / 5) |
| \(\text{nPrCO}_2\text{Ph}\) | 92\% (95 / 5) |
| \(\text{nBuCO}_2\text{Ph}\) | 99\% (95 / 5) |
| \(\text{MeCO}_2\text{Ph}\) | 89\% (95 / 5) |
| \(\text{MeCO}_2\text{Bu}\) | 88\% (95 / 5) |
| \(\text{MeCO}_2\text{Bu}\) | 86\% (95 / 5) |
| \(\text{MeCO}_2\text{Bu}\) | 89\% (95 / 5) |

**< other examples >**

| Yield \((E / Z)\) |
|------------------|
| \(\text{PhCO}_2\text{Et}\) | 83\% (95 / 95) |
| \(\text{PhCO}_2\text{Ph}\) | 88\% (95 / 95) |
| \(\text{nPrCO}_2\text{Ph}\) | 91\% (95 / 95) |
| \(\text{nBuCO}_2\text{Ph}\) | 78\% (95 / 95) |
| \(\text{MeCO}_2\text{Ph}\) | 89\% (95 / 95) |

\(^a\) Determined by \(^1\)H NMR of crude product.

\(^b\) Conditions: \(\text{ArMgBr (1.2 eq.), ZnCl}_2 (1.2 \text{ eq.)}, \text{Pd}(\text{PPh}_3)_4 \text{Cl}_2 (1 \text{ mol\%})\) in THF, 20 \(\rightarrow\) 25 °C, 2 h.

\(^c\) Conditions: \(\text{ArMgBr (1.2 eq.), ZnCl}_2 (1.2 \text{ eq.)}, \text{Pd}(\text{PPh}_3)_4 \text{Cl}_2 (1 \text{ mol\%})\) in THF, 20 \(\rightarrow\) 25 °C, 2 h.
Table 6. (E)-and (Z)-stereoretentive Iron-catalyzed cross-coupling reactions of enol tosylates derived from β-ketoesters and α-formylesters.

Scheme 8. (Z)-Enol tosylate derived from methyl phenyl(or aryl)acetate as Iron-catalyzed cross coupling partner.

Table 7. Kumada-Tamao-Corriu cross-coupling method.
7. Parallel and Stereocomplementary Synthesis of All-Carbon (Fully)-Substituted Olefins: Application to (E)- and (Z)-Tamoxifen

A divergent stereocomplementary synthesis of (E)- and (Z)-stereodefined all-carbon (fully)-substituted olefin scaffolds was performed. The method comprises 2 sets (all 4) of “parallel and stereocomplementary” syntheses of (E)- and (Z)-α,β-unsaturated esters involving 2 types of robust and distinctive reaction sequences (Scheme 11). The stereoretentive Negishi cross-coupling employed the Pd(dppe)Cl₂ catalyst for E (Method A) and the Pd(dppb)Cl₂ catalyst for Z (Method B).

The present parallel approach is categorized as both Type I (convergent oriented approach: 16 examples, 56–87 % yield) and Type II (divergent oriented approach: 18 examples, 70–95 % yield) (Table 5). A pair of obtained (E)- and (Z)-α,β-unsaturated ester scaffolds were successfully transformed into various (E)- and (Z)-stereodefined olefins (8 × 2 derivatization arrays; see the SI). As a notable application, the first parallel synthesis of both (E)- and (Z)-tamoxifens, a representative motif of all-carbon (fully)-substituted olefins, was demonstrated [total 8 steps, excellent overall 58 % yield (average 93 %) and 57 % (average 93 %), respectively] (Scheme 9).

Recent representative syntheses of “only (Z)”-tamoxifen are listed in the SI.

Table 8. (E)- and (Z)-stereoretentive Sonogashira cross-coupling reactions.

Scheme 9. Reaction sequence using (E)- and (Z)-stereodefined enol phosphonates.
Table 9. (E)- and (Z)-stereocomplementary enol phosphorylations of various β-ketoesters, and successive Suzuki-Miyaura and Negishi cross-couplings.

| Method | Reaction Conditions | Yield (E/Z<sup>a</sup>) | Product Structure |
|--------|---------------------|-------------------------|-------------------|
| A or C | THF; 0 °C, 1 h, 20-25 °C, 1 h | 84% (98/2) | ![Product Structure A or C](image)
| B or D | THF; 0 °C, 1 h, 20-25 °C, 1 h | 90% (98/2) | ![Product Structure B or D](image)
| E | DBU DMF; 0-5 °C, 1 h | 83% (98/2) | ![Product Structure E](image)
| F | PPh<sub>3</sub> - LiCl | 87% (99/3) | ![Product Structure F](image)

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

![Chemical Reaction Diagram](image)

Yield:<br>
- (E): 81%<sup>b</sup><br>
- (Z): 83%<sup>b</sup><br>
- (E): 83%<sup>c</sup><br>
- (Z): 81%<sup>c</sup><br>
- (E): 91%<sup>d</sup><br>
- (Z): 81%<sup>d</sup><br>

<sup>b</sup> Isolated. Unless otherwise noted, E/Z > 95/5.
<sup>c</sup> E/Z = 83/17.
<sup>d</sup> E/Z = 81/19.

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Scheme 10. Parallel and stereocomplementary synthesis of (E)- and (Z)-zimelidines.
8. Sequential Cross-Couplings Using (E)- and (Z)-Stereodefined α-Chloro-β-tosyloxy-α, β-unsaturated Esters

Readily available (E)- and (Z)-stereodefined α-chloro-β-tosyloxy-α, β-unsaturated esters (see Section 3.3) functioned as distinctive sequential cross-coupling partners for an (E)- and (Z)-stereocomplementary synthesis of fully-substituted α, β-unsaturated esters (Scheme 12). This strategy involves highly chemo- and stereoretentive Suzuki-Miyaura cross-couplings at the β-chloro position using an accessible [Pd(OAc)$_2$/XPhos] catalysis (total 4 examples: 89–94% yield), and subsequent highly stereoretentive Suzuki-Miyaura cross-couplings by a reactive [Pd(OAc)$_2$/SPhos–K$_2$CO$_3$] catalysis (total 24 examples; 63–94% yield, > 97:3 selectivity).

As a distinct extension, (Z)- and (E)-α-chloro-β-(p-tolyl) acrylate served as appropriate partners for (E)- and (Z)-stereoretentive Sonogashira, Mizoroki-Heck, and Buchwald-Hartwig cross-couplings (see Scheme 16).[21]

9. Stereoinversion vs Stereoretention Suzuki-Miyaura Cross-Couplings

We encountered a stereo-switch phenomenon during the Suzuki-Miyaura cross-coupling reaction (Scheme 13). Merck’s group reported a process chemistry of a key cyclopropane pharmacophore (Method A), in which the Suzuki-Miyaura cross-coupling proceeded in an unprecedented “stereoinverting” (E)→(Z) manner using Pd(OAc)$_2$/XPhos catalysis.[30] By clear contrast, our method using Pd(OAc)$_2$/SPhos catalysis proceeded in a “stereoretentive” (E)→(E) manner (Method B); that is, an (E)- and (Z)-stereocomplementary process resulted.

A plausible mechanism for the stereo-switch reaction pathways is proposed (Scheme 14). ArPdLnR (Ln=XPhos or SPhos) intermediate III derived from (E)-I is initially formed.
through the privileged pathway of Suzuki-Miyaura cross-coupling reaction. A stereoretentive product \((E)\)-II is in turn produced with the regeneration of Pd(0)Ln (Method B). When the zwitterion intermediate IV is transformed to V with the single-bond rotation by equilibrium, the stereoinversion product \((Z)\)-II is produced through ArPdLnR intermediate VI. Although the concrete reason for the ligand effect is currently unclear, our method B using SPhos catalysis sufficiently retarded the \((E)\) to \((Z)\) stereoinversion. \(^{30,31}\)

### 10. Utilization by Other Groups

The current privileged protocols were adopted for the synthesis of trisubstituted elaborated natural products and pharmacore compounds. Representative examples are as follows (Scheme 15).

That is \(\gamma\)-aminobutanoic acid (GABA) analogues (Merck’s group),\(^{11a}\) juvenile hormones 0 and I (Shinada’s group),\(^{32}\) deuterium-labelled geranylgeraniol (Shinada’s group),\(^{33}\) functionalized steroids (Mazet and Li),\(^{34}\) madangamine A (Chida’s group),\(^{35}\) asymmetric total synthesis of hispidanin A and

| Table 10. \((E)\)- and \((Z)\)-stereocomplementary first-step Suzuki-Miyaura cross-coupling using \(\alpha\)-chloro-\(\beta\)-tosloyloxy-\(\alpha,\beta\)-unsaturated esters. |
|---|---|
| \(\text{Ar} = \text{PhO}\), \(\text{L} = \text{PPh}_3\) | \(\text{R} = \text{Me}, \text{Cl}\) |
| \(\text{Me}_{2}C=\text{C}(\text{OMe})\text{CO}_{2}Me\) | \(\text{Ph}_{2}C=\text{C}(\text{OMe})\text{CO}_{2}Me\) |
| 80\% (trace)\(^f\) | 80\% (3.97) |
| \((E)\) | \((Z)\) |
| 98\% | 98.2 |

| Table 11. \((E)\)- and \((Z)\)-stereocomplementary second-step Suzuki-Miyaura cross-coupling using \(\alpha\)-chloro-\(\beta\)-tosloyloxy-\(\alpha,\beta\)-unsaturated esters. |
|---|---|
| \(\text{Ar} = \text{PhO}\), \(\text{L} = \text{PPh}_3\) | \(\text{R} = \text{Me}, \text{Cl}\) |
| \(\text{Me}_{2}C=\text{C}(\text{OMe})\text{CO}_{2}Me\) | \(\text{Ph}_{2}C=\text{C}(\text{OMe})\text{CO}_{2}Me\) |
| 80\% (trace)\(^f\) | 80\% (3.97) |
| \((E)\) | \((Z)\) |
| 98\% | 98.2 |

\(^a\) Determined by \(^1\)H NMR spectroscopy of the crude products.
\(^b\) The reaction using \(\text{Pd}(\text{OAc})_2\cdot\text{PPh}_3\cdot\text{K}_2\text{CO}_3\) catalysis in \(\text{PhOH}+\text{H}_2\text{O}\) solvent.
\(^c\) \(\text{Ar} = \text{B(OH)}_2\cdot\text{PPh}_3\cdot\text{K}_2\text{CO}_3\) \((2.0\text{ eq})\) with \(\text{Pd}(\text{OAc})_2\cdot\text{PPh}_3\cdot\text{K}_2\text{CO}_3\) \((10\text{ mol\%})\) \(\cdot\text{SPhos}\) \((10\text{ mol\%})\) \(\cdot\text{K}_2\text{CO}_3\) \((2.0\text{ eq})\) catalysis was used and the reaction period was 2 h.
\(^d\) \(n\)-Heptyl-\(\text{B(OH)}_2\) \((1.8\text{ eq})\), \(\text{SPhos}\) \((3\text{ mol\%})\), and \(\text{K}_2\text{CO}_3\) \((1.8\text{ eq})\) were used.
related diterpenoids (Liu and Qin’s group),[36,37] and γ-hydroxybutenolides (Schützenmeister’s group).[38]

11. Miscellaneous

Mizoroki-Heck reactions with methyl methacrylate mediated by [Pd₂(dba)₃-tBu₃P·HBF₄-Cy₂NMe] catalysis[39] produced the corresponding highly substituted (E) and (Z)-dienes in stereocomplementary manner (Scheme 16). Similarly, Buchwald-Hartwig cross-coupling reactions with BocNH₂ were performed by [Pd₂(dba)₃-Xantphos-Cs₂CO₃] catalysis,[40] to afford the corresponding products (Z) and (E) products, respectively in moderate yield with acceptable stereoretention.

(Z)-Steroselective carbon homologation (dehydration type Ti-Claisen condensation) of alkyl α-heteroatom (halo and sulfonyloxy)-substituted acetates (XCH₂CO₂R) with alkyl formates (HCO₂R) produced various alkyl β-alkoxy-α-halo or sulfonyloxy-substituted acrylates (24 examples; 51%–91% yield)[41] (Scheme 17). Subsequent stereoretentive Suzuki-Miyaura, Negishi, and Sonogashira cross-couplings using the obtained methyl β-methoxy-α-halo or sulfonyloxy-substituted acrylates proceeded smoothly to produce a variety of β-alkoxy-α-substituted acrylates in moderate to high yield (35 examples; 29%–99% yield).

As a successful application, a 3-step straightforward synthesis of strobilurin A was performed utilizing the present reaction sequence (dehydration type Ti-Claisen condensation and Suzuki-Miyaura cross-coupling), wherein the geometry of the three consecutive olefins (2E,3Z,5E) was completely maintained.

12. Closing Remarks

We achieved a variety of general (E)-, (Z)-stereocomplementary syntheses of α,β-unsaturated esters from highly accessible (E)-, (Z)-stereodefined enol tosylates derived from β-ketoesters and α-formyl esters. Preparations of (E)-, (Z)-stereodefined enol tosylates were implemented in these syntheses using inexpensive reagents under mild reaction conditions. Successive cross-coupling reactions have a wide ranges of applications, such as in Suzuki-Miyaura, Negishi, Sonogashira, Iron-catalyzed, Mizoroki-Heck, Buchwald-Hartwig reactions. Notably, this strategy was successfully applied for parallel drug
Scheme 15. Utilization of the present methods by other groups.

Scheme 16. Mizoroki-Heck and Buchwald-Hartwig cross-coupling reactions.

Scheme 17. Dehydration-type Ti-Claisen condensation (carbonhomologation) of α-heteroatom-substituted acetates and successive synthesis of (Z)-stereodefined alkyl β-alkoxy-α-halo or sulfonfolyx-substituted acrylates.
syntheses of (E)- and (Z)-zimeridine, (E)- and (Z)-tamoxifen, and Merck’s cyclopropane pharmacophore.

We believe that the present methodology opens a distinct avenue for the syntheses of multi-substituted (E)-, (Z)-stereo-defined α,β-unsaturated esters in the fields of natural product synthesis, pharmaceutical screening, functionalized molecule synthesis, and process chemistry.

Although enol tosylates has strong advantages (reasonable reactivity, economy, stability, accessibility, as a future perspective the use of more atom-economic substrates such as enol acetates (-OAc), methoxy acetates (-OME), and ideally intact much available β-ketoesters are challenging projects.

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