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General, Robust, and Stereocomplementary Preparation of α,β-Disubstituted α,β-Unsaturated Esters

Hidefumi Nakatsuji, Hiroshi Nishikado, Kanako Ueno, and Yoo Tanabe*

Department of Chemistry, School of Science and Technology, Kwansei Gakuin University, 2-1 Gakuen, Sanda, Hyogo 669-1337, Japan

tanabe@kwansei.ac.jp

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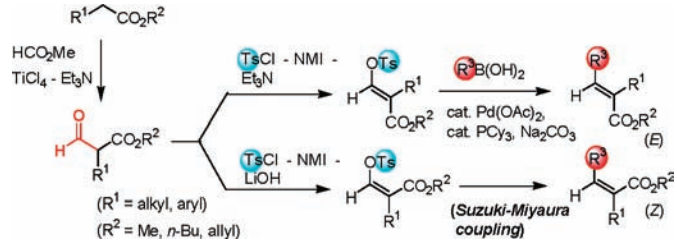
ABSTRACT



An (*E*)- and (*Z*)-stereocomplementary preparative method for α,β-disubstituted α,β-unsaturated esters is performed via three general and robust reaction sequences: (i) Ti−Claisen condensation (formylation) of esters to give α-formyl esters (12 examples, 60−99%), (ii) (*E*)- and (*Z*)-stereocomplementary enol *p*-toluenesulfonylation (tosylation) using TsCl−*N*-methylimidazole (NMI)−Et_3N and LiOH (24 examples, 82−99%), and (iii) stereoretentive Suzuki−Miyaura cross-coupling (18 examples, 64−96%).

Stereocontrolled preparation of (*E*)- and (*Z*)-olefins is a major topic in organic synthesis. Stereoretentive cross-couplings have been developed in natural products and pharmaceutical syntheses due to the wide range of possible substrates and catalysts, mild reaction conditions, and functional compatibility. Because (*E*)- and (*Z*)-α,β-unsaturated esters are useful structural scaffolds for various stereodefined olefins, their stereoselective preparation occupied a synthetically prominent position: Horner−Wadsworth−Emmons reaction,[1] dehydration of β-hydroxy esters,[2] Michael reaction,[3] or hydrometalation−alkylation[4] using α-alkynyl esters are representative preparative methods. Despite these well-established methods, a more efficient method with regard to stereo-, regio-, and chemoselectivities and substrate generality is in high demand. (*E*)- and (*Z*)-stereodefined enol sulfonates derived from β-carbonyl esters are promising stereoretentive cross-coupling partners. We previously reported a practical stereocomplementary preparation of simple β-ketoester enol *p*-toluenesulfonates (tosylates), followed by stereoretentive Negishi and Sonogashira cross-couplings to give β,β-disubstituted (*E*)- and (*Z*)-α,β-unsaturated esters.[5] This method, however, cannot be applied for the preparation of equally important (*E*)- and (*Z*)-stereodefined α,β-disubstituted

(1) (a) Smith, M. B.; March, J. *Advanced Organic Chemistry*, 6th ed.; Wiley: New York, 2007; p 1375. (b) Kürti L.; Czakó, B. *Strategic Applications of Named Reactions in Organic Synthesis*; Elsevier: Burlington, 2005; p 212.

(2) Representative examples for the stereoselective preparation: (a) Zimmerman, H. E.; Ahramjian, L. *J. Am. Chem. Soc.* **1959**, *81*, 2086. (b) Sai, H.; Ohmizu, H. *Tetrahedron Lett.* **1999**, *40*, 5019. (c) Feuillet, F. J. P.; Robinson, D. E. J.; Bull, S. D. *Chem. Commun.* **2003**, 2184. (d) Mani, N. S.; Mapes, C. M.; Wu, J.; Deng, X.; Jones, T. K. *J. Org. Chem.* **2006**, *71*, 5039.

(3) Reference,1a p 1501.

(4) Hayashi, T.; Inoue, K.; Taniguchi, N.; Ogasawara, M. *J. Am. Chem. Soc.* **2001**, *123*, 9918.

(5) (a) Nakatsuji, H.; Ueno, K.; Misaki, T.; Tanabe, Y. *Org. Lett.* **2008**, *10*, 2131. (b) Recent related stereocomplementary enol trifluoromethanesulfonylation: Babinski, D.; Soltani, O.; Frantz, D. E. *Org. Lett.* **2008**, *10*, 2901.

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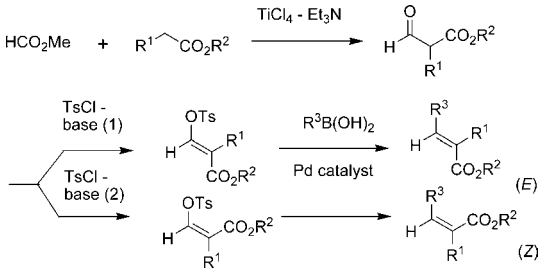
isosteres. This objective requires the following reaction sequences: (a) practical formylation of simple esters, (b) stereoselective enol *p*-toluenesulfonylation (tosylation), and (c) stereoretentive cross-coupling. We disclose here a $TiCl_4$-mediated α-formylation of a wide variety of esters, followed by (*E*)- and (*Z*)-stereocomplementary enoltosylation and stereoretentive Suzuki−Miyaura cross-coupling (Scheme 1).[3]

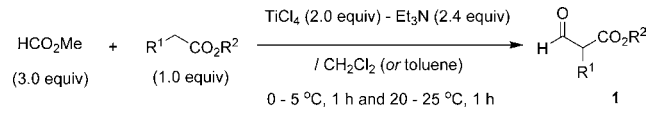
Scheme 1. Stereocomplementary Preparation of α,*β*-Disubstituted (*E*)- and (*Z*)-Stereodefined α,*β*-Unsaturated Esters

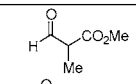
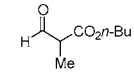
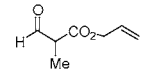
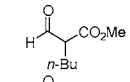
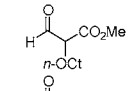
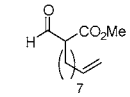
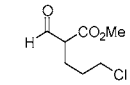
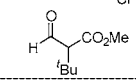
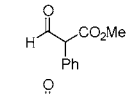
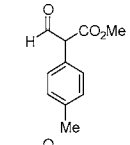
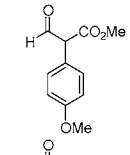
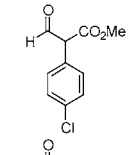
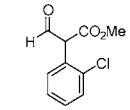


α-Formyl esters **1** are fundamental synthons for organic synthesis. α-Formylation of simple esters with HCO_2Me is a straightforward process, but classical methods using basic reagents such as NaOMe and NaH produce a highly unsatisfactory yield and low reaction velocity and require harsh and rigorous conditions.[6]

Application of the Ti−Claisen condensation[7] was promising and, to our delight, exhibited a high performance. Table 1 lists the successful results with the following salient features. (i) All examples produced good to excellent isolated yield, i.e., substrate generality, except for **1a-1** due to its unstable and volatile properties (entry 1). (ii) The use of butyl and allyl analogues in **1a-2** and **1a-3** solved this problem (entries 2 and 3). (iii) Various aliphatic esters underwent smooth reaction under mild and practical conditions (0−25 °C, total 2 h) (entries 2−8). (iv) As expected, Ti−Claisen condensation is also applicable to α-aryl methyl esters bearing a more acidic methylene group (entries 9−13). (v) Aliphatic α-formylesters **1a-1**, **-2**, **-3**, and **1b−f** were purified by simple distillation, whereas α-aryl products **1g−k** could be purified by either distillation or column chromatography due to higher stability.[8] (vi) Double bonds, *ω*-chloro, *p*-Me, *p*-MeO, and *o*- or *p*-Cl functional groups were tolerated

Table 1. $TiCl_4$-Promoted α-Formylation of Esters[a]



entry	R^1	R^2	product		bp °C / mmHg	yield / %
1	Me	Me		**1a-1**	40-50 / 23	49
2		*n*-Bu		**1a-2**	55-58 / 4	81 (83)[b]
3		Allyl		**1a-3**	63-66 / 23	60
4	*n*-Bu	Me		**1b**	67-76 / 11	99 (99)[b]
5	*n*-Oct			**1c**	60-65 / 0.2	84
6				**1d**	70-73 / 0.2	74
7				**1e**	65-73 / 2	79
8	*t*Bu			**1f**	52-58 / 20	59
9	Ph			**1g**	61-65 / 0.2	90
10	(*p*-Me)C_6H_4			**1h**	62-68 / 0.2	86
11	(*p*-MeO)C_6H_4			**1i**	68-80 / 0.2	73
12	(*p*-Cl)C_6H_4			**1j**	63-75 / 0.2	85
13	(*o*-Cl)C_6H_4			**1k**	61-64 / 0.2	92

[a] General procedure: $TiCl_4$ (8.78 mL, 80 mmol) and Et_3N (13.3 mL, 96 mmol) were successively added dropwise to a stirred solution of a methyl ester (40 mmol) and HCO_2Me (7.21 g, 120 mmol) in CH_2Cl_2 (80 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 mixture, which was extracted twice with AcOEt. The combined organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The obtained crude oil was purified by distillation or column chromatography to give the desired α-formyl ester. [b] Use of toluene solvent.

(6) Yields of the traditional basic method range from 0 to 40−50%. For examples, see: (a) Spengler, J. -P.; Schunack, W. *Arch. Pharm. (Weinheim)* **1984**, *317*, 425. (b) Davies, S. J.; Ayscough, A. P.; Beckett, R. P.; Bragg, R. A.; Clements, J. M.; Doel, S.; Grew, C.; Launchbury, S. B.; Perkins, G. M.; Pratt, L. M.; Smith, H. K.; Spavold, Z. M.; Thomas, S. W.; Todd, R. S.; Whittaker, M. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2709. Reexamination of NaH-promoted α-formylation using aliphatic simple esters such as $CH_3(CH_2)_4CO_2Me$ in our hands, however, was not reproducible under the identical conditions. This strongly basic and heterogeneous condition might be troublesome.

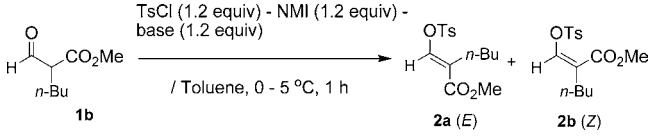
(7) (a) Tanabe, Y. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1917. (b) Yoshida, Y.; Hayashi, R.; Sumihara, H.; Tanabe, Y. *Tetrahedron Lett.* **1997**, *38*, 8727. These papers describe a sole example of α-formylation of $PhCH_2CH_2CO_2Me$ (∼50%) using $TiCl_4$−Bu_3N−catalytic TMSOTf reagent. Compared with these methods, the present method using more accessible $TiCl_4$−Et_3N remarkably improved the efficiency. (c) Misaki, T.; Nagase, R.; Matsumoto, K.; Tanabe, Y. *J. Am. Chem. Soc.* **2005**, *127*, 2854. (d) Iida, A.; Nakazawa, S.; Okabayashi, T.; Horii, A.; Misaki, T.; Tanabe, Y. *Org. Lett.* **2006**, *8*, 5215.

(entries 6, 7, and 10−13). Thus, the present Ti-mediated formylation has clear advantages over the traditional method.

Next, (*E*)- and (*Z*)-stereocomplementary enol tosylation was investigated. The Merck group disclosed an original stereocomplementary method for a sole specific γ-amino-β-keto ester using Ts_2O and Et_3N or LDA[9] and pointed out the advantages over the more frequently used enol triflates with regard to stability and benchtop handling procedures, etc. Despite the inferior reactivity of enol tosylates to that of enol triflates, tremendous rapid development of cross-coupling reactions will allow increasing applications for these enol tosylate partners.[10]

Our longstanding studies on mild, practical, and cost-effective condensation reactions reveal that *N*-methylimidazole (NMI) is a potential activator for *O*,*N*,*S*-acylations,[11] sulfonylation,[5] and *C*-acylation (i.e., crossed Ti−Claisen condensation).[7c,d] With this information in hand, we extended this protocol to stereocomplementary enol tosylations of α-formyl esters **1** utilizing TsCl−NMI−bases. The initial trial reaction was conducted using methyl 2-(formyl)hexanoate **1b** (Table 2). Among several available and inexpensive bases and conditions screened, respective (*E*)- and (*Z*)-selective reactions were performed using Et_3N and LiOH: the best conditions were entry 2 using Et_3N base for the (*E*)-form and entry 8 using LiOH base for the (*Z*)-form.

Table 2. (*E*)- and (*Z*)-Stereocomplementary Enol Tosylation of Methyl 2-(Formyl)hexanoate **1b** Using TsCl−NMI−Bases



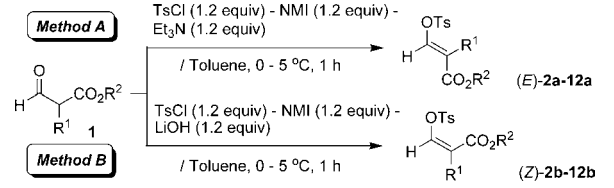
1b **2a** (*E*) **2b** (*Z*)

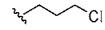
entry	base	yield[a]/%	*E*/*Z*[b]
1	Et_3N	82	98/2
2		**89**[c]	**97/3**
3		76[c]	97/3
4	Bu_3N	63	96/4
5	$^iPr_2NEt$	74	77/23
6	TMEDA	67	99/1
7	LiOH	81	2/98
8		**92**	**4/96**
9		46[c]	4/96
10	NaOH	65	7/93
11	KOH	62	34/66
14	LDA	49	47/53
15	LiHMDS	57	14/86

[a] Determined by ^{1}H NMR of the crude products using dibutyl oxalate as an internal standard. [b] Determined by ^{1}H NMR of the crude products using dibutyl oxalate as an internal standard. [c] In the absence of NMI.

Table 3 lists successful examples of the present (*E*)- and (*Z*)-stereocomplementary enol tosylation of various α-formylesters **1**. The salient features are as follows. (i) All reactions examined using **1a**−**k** produced good to excellent yield and (*E*)- and (*Z*)-selectivity under favorable conditions, especially for process chemistry (toluene, 0−5 °C, 1 h). (ii) These enol tosylates, **3a**,**b**−**12a**,**b**, were stable enough for recrystallization and/or column chromatographic purification with

Table 3. (*E*)- and (*Z*)-Stereocomplementary Enol Tosylation of α-Formyl Esters **1** Using TsCl−NMI−Bases[a]



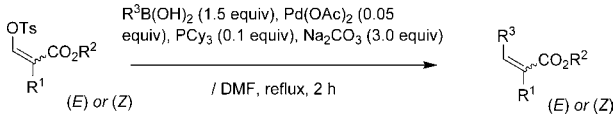
entry	sub-strate	R^1	R^2	method[b]	product	yield / %	*E* / *Z*[b]
1	**1a-1**	Me	Me	A	**3a-1**	92	99 / 1
2				B	**3b-1**	86	8 / 92
3	**1a-2**		Bu	A	**3a-2**	96	97 / 3
4				B	**3b-2**	99	4 / 96
5	**1b**	Bu	Me	A	**2a**	89	97 / 3
6				B	**2b**	92	4 / 96
7	**1c**	Octyl		A	**4a**	99	96 / 4
8				B	**4b**	98	4 / 96
9	**1d**			A	**5a**	90	98 / 2
10				B	**5b**	93	4 / 96
11	**1e**			A	**6a**	99	>99 / 1
12				B	**6b**	90	1/ 99
13	**1f**	^{t}Bu		A	**7a**	66	86 / 14
14				B	**7b**	92	1/ >99
15	**1g**	Ph		A	**8a**	89	93 / 7
16				B	**8b**	85	8/ 92
17	**1h**	(*p*-Me) C_6H_4		A	**9a**	83	97 / 3
18				B	**9b**	94	3 / 97
19	**1i**	(*p*-MeO) C_6H_4		A	**10a**	83	97 / 3
20				B	**10b**	94	5 / 95
21	**1j**	(*p*-Cl) C_6H_4		A	**11a**	82	>99 / 1
22				B	**11b**	85	15 / 85
23	**1k**	(*o*-Cl) C_6H_4		A	**12a**	92	>99 / 1
24				B	**12b**	85	20 / 80

[a] **General Procedure of Method A.** An α-formyl ester (1.00 mmol) in toluene (1 mL) and TsCl (228 mg, 1.20 mmol) in toluene (1 mL) were successively added dropwise to a stirred solution of *N*-methylimidazole (NMI) (99 mg, 1.20 mmol) and Et_3N (121 mg, 1.20 mmol) in toluene (1 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 AcOEt. The combined organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by SiO_2 column chromatography (hexane/AcOEt = 25:1−5:1) to give the desired (*E*)-enol tosylates. **Method B.** An α-formyl ester (1.00 mmol) in toluene (1 mL), TsCl (228 mg, 1.20 mmol) in toluene (1 mL), and NMI (99 mg, 1.20 mmol) were successively added dropwise to a stirred suspension of LiOH powder (commercially available, anhydrous; 29 mg, 1.20 mmol) in toluene (1 mL) at 0−5 °C under an Ar atmosphere, and the mixture was stirred at the same temperature for 1 h. A workup similar to that of method A gave the desired (*Z*)-enol tosylates. [b] Determined by ^{1}H NHR.

complete separation of the minor isomers. (iii) Sterically congested and α-aryl α-formyl esters could also be applied (entries 13−24).

Next, we focused our attention on the stereoretentive Suzuki−Miyaura coupling using the (*E*)- and (*Z*)-stereofixed enol tosylates. Table 4 lists the successful results, and the

Table 4. (*E*)- and (*Z*)-Stereoretentive Suzuki−Miyaura Coupling of Enol Tosylates[a]



entry	substrate[b]	R^1	R^2	R^3	product	yield / %
1	**3a-2** (*E*)	Me	Bu	Ph	**13a**	94
2	**3b-2** (*Z*)				**13b**	87 (*E*/*Z* = 6/94)
3	**2a** (*E*)	Bu	Me	Ph	**14a**	93
4	**2b** (*Z*)				**14b**	94
5	**2a** (*E*)	Bu	Me	(*p*-Me) C_6H_4	**15a**	96
6	**2b** (*Z*)				**15b**	92
7	**2a** (*E*)	Bu	Me	(*p*-MeO) C_6H_4	**16a**	84
8	**2b** (*Z*)				**16b**	97
9	**2a** (*E*)	Bu	Me	(*p*-Cl) C_6H_4	**17a**	68[c]
10	**2b** (*Z*)				**17b**	64[c]
11	**6a** (*E*)		Me	Ph	**18a**	85
12	**6b** (*E*)				**18b**	93
13	**8a** (*E*)	Ph	Me	Ph	**19a**	93
14	**8b** (*Z*)				**19b**	93
15	**10a** (*E*)	(*p*-MeO) C_6H_4			**20a**	96
16	**10b** (*Z*)				**20b**	84
17	**11a** (*E*)	(*p*-Cl) C_6H_4			**21a**	83
18	**11b** (*Z*)				**21b**	74 (*E*/*Z* = 4/96)

[a] An (*E*)- or (*Z*)-enol tosylate (0.50 mmol) was added to a stirred suspension of $PhB(OH)_2$ (91 mg, 0.75 mmol), Na_2CO_3 (159 mg, 1.50 mmol), $Pd(OAc)_2$ (6 mg, 0.025 mmol), and PCy_3 (14 mg, 0.05 mmol) in DMF (3.5 mL) at 20−25 °C under an Ar atmosphere, and the mixture was stirred at 150−155 °C for 2 h. After cooling, 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. [b] Use of (*E*) or (*Z*) ∼100% pure compounds. [c] Reaction temperature was kept at 120−125 °C to avoid the side dechlorination of the *p*-Cl group.

salient features are as follows. (i) Several condition screenings revealed that the $Pd(OAc)_2$−PCy−K_2CO_3 catalysis system[12] produced the best yield and stereoretention, which differed from those of the Merck group's protocol using $PdCl_2(PPh_3)_2$−K_2CO_3.[9] (ii) Almost all (*E*)- and (*Z*)-enol tosylates smoothly underwent the reaction in good to excellent yield with nearly complete stereoretention. (iii) Compared with β-monosubstituted β-ketoester enol tosylates,[5] the present reaction using α,β-disubstituted substrates required elevated temperature conditions (reflux in DMF), probably due to the steric effect of the α-substituents (R^1). This harsh condition might disrupt the *E*/*Z* stereochemistry slightly as in the case of **3b-2** and **11b** (entries 2 and 18).

In conclusion, we developed a general and robust preparation of (*E*)- and (*Z*)-stereodefined α,β-disubstituted α,β-unsaturated esters utilizing three reaction sequences, $TiCl_4$−Et_3N-mediated α-formylation of simple esters, (*E*)- and (*Z*)-stereocomplementary enol sulfonylation, and stereoretentive Suzuki−Miyaura cross-coupling. The present protocol provides a new avenue for practical, general, and stereocomplementary preparation of functionalized olefins.

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Supporting Information Available: Experimental procedure and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Although the simple distillation is possible, these aliphatic α-formyl esters are relatively unstable and have to be stored in a refrigerator (ca. −10 °C) to avoid decomposition. Within ca. 1 week, they should be transformed to the corresponding stable enol tosylates. Aromatic α-formyl esters are stable enough for refrigerator storage for some weeks. These α-formyl esters will be useful for the active methylene precursor.

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(12) Comparable reactions of **2a** (*E*) using other representative Pd catalysts were as follows. $Pd(PPh_3)_4$, trace; $Pd(dppf)_2Cl_2$·CH_2Cl_2, trace; $Pd(OAc)_2$-^{t}Bu_3·HBF_4, trace; $Pd(PPh_3)_2Cl_2$, 29%; $Pd(dppe)_2Cl_2$, 50%; $Pd(dppb)_2Cl_2$, 80%.