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(*E*)- and (*Z*)-Stereodefined enol phosphonates derived from β-ketoesters: Stereocomplementary synthesis of fully-substituted α,β-unsaturated esters

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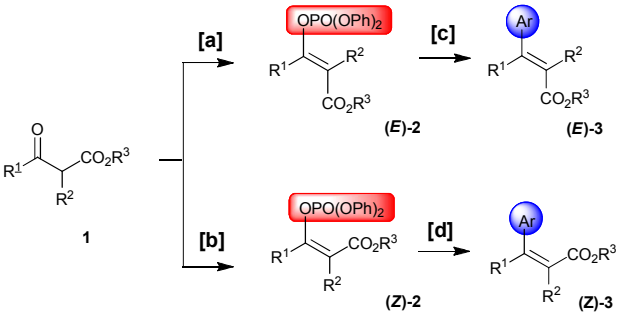
A versatile, robust, and stereocomplementary synthesis of full-substituted (*E*)- and (*Z*)-stereodefined α,β-unsaturated esters **3** from accessible α-substituted β-ketoesters **1** via (*E*)- and (*Z*)-enol phosphonates was achieved. The present method involves two accessible reaction sequences: (i) (*E*)- and (*Z*)-stereocomplementary enol phosphorylations of a wide variety of β-ketoesters **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 phosphates **2**. ^{1}H-NMR monitoring for a key reactive *N*-phosphorylammonium (imidazolium) intermediate **I** and an application to the synthesis of both (*E*)- and (*Z*)-tamoxifen precursors **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 phosphates (Skrydstrup's group),[5] Horner-Wadsworth-Emmons reaction,[6] and conjugate addition-elimination,[7] have been evaluated to date. However, (*E*)- and (*Z*)-stereocomplementary method using same common starting materials with sufficient substrate-generality is quite limited.

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



[a] : (*E*)-Stereoselective Enol Phosphorylation
[b] : (*Z*)-Stereoselective Enol Phosphorylation
[c] : (*E*)-Stereoretentive Suzuki-Miyaura *or* Negishi Cross-coupling
[d] : (*Z*)-Stereoretentive Suzuki-Miyaura *or* Negishi Cross-coupling

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

Results and discussion

The initial stereoselective enol phosphorylation was intentionally guided using stereocongested methyl 2-butyl-3-oxooctanoate **1a**[10] as a much less reactive α-substituted β-ketoester probe (Table 1). Consequently, both (*E*)- and (*Z*)-selective phosphorylations of **1a** successfully proceeded in excellent yield 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*)-**2a** and (*Z*)-**2a**, (entries 2, 4). Notably, the corresponding enol tosylation using reported TsCl–NMI–base reagents[7] gave inferior results.[11] We speculate that the present

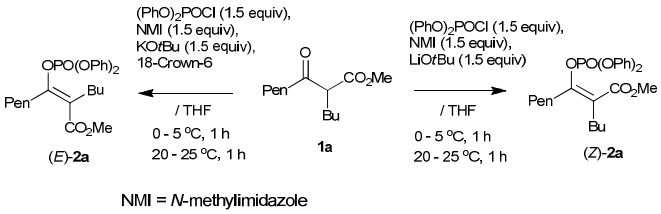
smooth enol phosphorylation can be attributed to the higher reactivity of $(PhO)_2POCl$ over TsCl.[12]

Table 2 lists the successful results of the present (*E*)- and (*Z*)-stereocomplementary enol phosphorylations of α-substituted β-ketoesters **1** using fine-tuned Methods A-D. A notable aspect is the high substrate-generality. The salient features are as follows. (i) All substrates **1a-1l** examined, produced good to excellent yield and excellent (*E*)- and (*Z*)-selectivities. (ii) Much less reactive (stereocongested) β-ketoesters **1a**, **1i**, and **1j-1l** could be applied successfully (entries 1, 2, 19-24). (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_2NEt–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 Rf values of (*E*)- and (*Z*)-enol phosphates **2** on thin layer chromatography excellent stereoselectivities of >95 / 5% are required for complete column chromatographic purification with high yield.[13]

As depicted in Figure 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]

A plausible mechanism for the successful emergence of (*E*)- and (*Z*)-enol phosphorylation stereoselectivity is illustrated in Scheme 2, wherein substrate **1a** is exemplified. The (*E*)-stereoselective reaction with highly reactive intermediate **I** proceeds via a non-chelation pathway to give (*E*)-**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 clear contrast, the (*Z*)-stereoselective reaction proceeds *via* a chelation mechanism to give (*Z*)-**2a**; the Li-cation facilitates (*Z*)-enolate formation.

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



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 in CD_3CN.

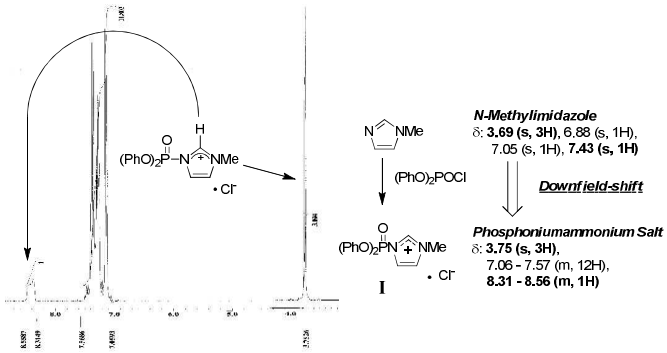
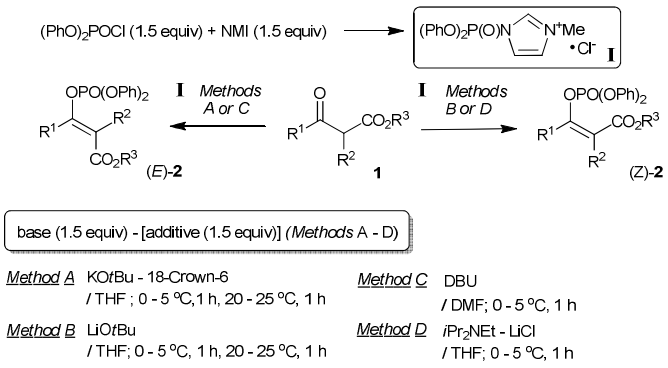
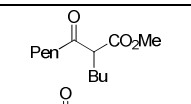
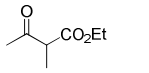
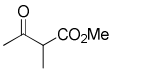
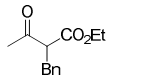
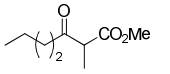
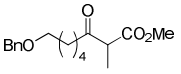
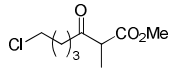
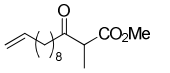
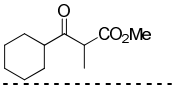
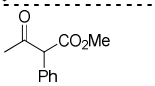
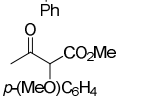
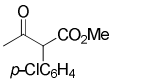


Figure 1. Formation of *N*-phosphorylammonium (imidazolium) intermediate **I** monitored by ^{1}H NMR measurement at −45 °C.

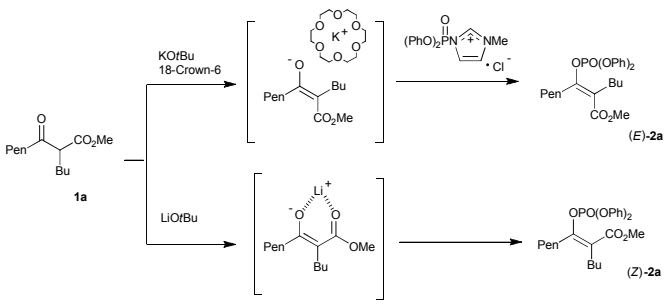
entry	substrate[a]	method	product	yield / %	*E* / *Z*[b]

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



1		**1a**	A	(*E*)-**2a**	84	98 / 2
2			B	(*Z*)-**2a**	97	2 / >98
3		**1b**	A	(*E*)-**2b**	90	98 / 2
4			B	(*Z*)-**2b**	86	2 / >98
5		**1c**	A	(*E*)-**2c**	71	>98 / 2
6			B	(*Z*)-**2c**	91	2 / >98
7		**1d**	A	(*E*)-**2d**	83	>98 / 2
8			B	(*Z*)-**2d**	94	5 / 95
9		**1e**	A	(*E*)-**2e**	87	95 / 5
10			B	(*Z*)-**2e**	90	2 / >98
11		**1f**	A	(*E*)-**2f**	83	93 / 7
12			B	(*Z*)-**2f**	93	2 / >98
13		**1g**	A	(*E*)-**2g**	75[c]	>98 / 2
14			B	(*Z*)-**2g**	86	2 / >98
15		**1h**	A	(*E*)-**2h**	83	97 / 3
16			B	(*Z*)-**2h**	98	2 / >98
17		**1i**	A	(*E*)-**2i**	74	>98 / 2
18			B	(*Z*)-**2i**	86	2 / >98
19		**1j**	C	(*E*)-**2j**	74	>98 / 2
20			D	(*Z*)-**2j**	86	2 / >98
21		**1k**	C	(*E*)-**2k**	88	>98 / 2
22			D	(*Z*)-**2k**	97	2 / >98
23		**1l**	C	(*E*)-**2l**	86	>98 / 2
24			D	(*Z*)-**2l**	88	2 / >98

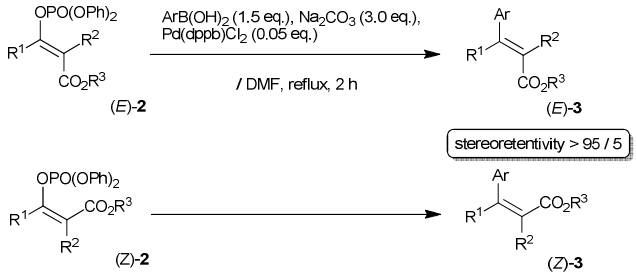
[a] **1a** was prepared (Ref. 10). **1b-1e**, **1g**, **1i-1l** were commercially available. **1f** and **1h** were prepared by the reported Ti-crossed condensation (Ref. 7b) [b] Determined by ^{1}H NMR of crude products. [c] TMEDA instead of *i*Pr_2NH.



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

With the successful results taken in hands, stereoretentive Suzuki-Miyaura cross-coupling was investigated using (*E*)- and (*Z*)-stereodefined enol phosphonate partners **2a-2f** to obtain fully-substituted (*E*)- and (*Z*)-α,β-unsaturated esters **3a-3f**. Table 3 lists the successful results, and the salient features are as follows. (i) Among various catalysts screened, the $Pd(dppb)Cl_2$ catalyst produced a successful result.[15] (ii) Even the less reactive (stereocongested) substrate **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 yield, and excellent (*E*)- and (*Z*)-stereoretention (>95:5) were achieved for most (*E*)- and (*Z*)-**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*)-**2a** and (*E*)-**2f** is considerably less reactive due to the stereocongestion, the slight isomerization is considered to occur.

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



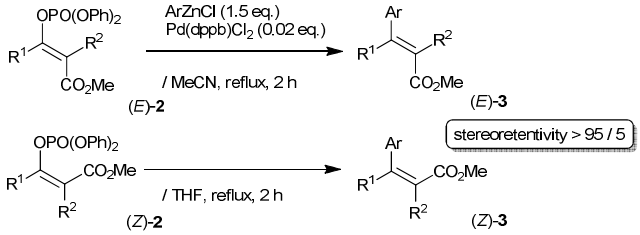
entry	R^1	R^2	R^3	substrate[a]	Ar	product	yield / %[b]
1	Pen	Bu	Me	(*E*)-**2a**	Ph	(*E*)-**3a**	83[c]
2				(*Z*)-**2a**		(*Z*)-**3a**	91
3	Me	Me	Et	(*E*)-**2b**	Ph	(*E*)-**3b-1**	81
4				(*Z*)-**2b**		(*Z*)-**3b-1**	81
5	Me	Me	Et	(*E*)-**2b**	(*p*-Me) C_6H_4	(*E*)-**3b-2**	83
6				(*Z*)-**2b**		(*Z*)-**3b-2**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

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

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 **2a**, **2c**, **2f-2l**. Table 4 (α-aliphatic substrates) and Table 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 **3a**, **3c-1**－**3c-8**, **3f**－**3l**. (ii) Milder conditions were applicable; MeCN/reflux for (*E*)-substrates **2** and THF/reflux for (*Z*)-substrates **2**. (iii) The loading quantity of the $Pd(dppb)Cl_2$ catalyst could be decreased from 0.05 equiv to 0.02 equiv. (iv) Various ArZnCl nucleophiles containing both electron-donating and electron-withdrawing substituents (*p*-Me, *p*-OMe, *o*-Me, *p*-Cl) and a bulky 1-naphtyl group, were employable (Table 4, entries 5-18). (v) Heterocyclic nucleophiles (furan-2-yl and thiophen-2-yl) also underwent the reaction smoothly (Table 4, entries 15-18). (vi) Several functional groups, such as ω-BnO, ω-chloro, and a double bond were compatible (Table 4, entries 19-24). (vii) The reaction using α-aromatic substrates **2j**－**2l** proceeded smoothly under the identical conditions (Table 5).

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, **3b-1**, **3b-2**, **3b-3**, **3b-4**, **3c-1**, **3c-3**, **3d**, **3e**, **3j**, higher *E*/*Z*-selectivity was produced in almost cases (details: ESI).

Table 4 Stereoretentive Negishi cross-coupling of R^1, R^2 aliphatic (*E*)- and (*Z*)-enol phosphates **2**.

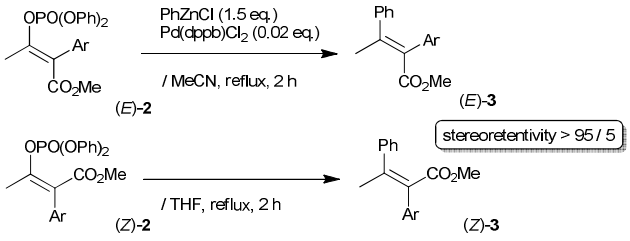


entry	R^1	R^2	Substrate[a]	Ar	product	Yield[b] / %
1	Pen	Bu	(*E*)-**2a**	Ph	(*E*)-**3a**	78
2			(*Z*)-**2a**		(*Z*)-**3a**	84
3	Me	Me	(*E*)-**2c**	Ph	(*E*)-**3c-1**	82
4			(*Z*)-**2c**		(*Z*)-**3c-1**	81

5	Me	Me	(*E*)-**2c**	(*p*-Me) C_6H_4	(*E*)-**3c-2**	91
6			(*Z*)-**2c**		(*Z*)-**3c-2**	81
7	Me	Me	(*E*)-**2c**	(*p*-MeO) C_6H_4	(*E*)-**3c-3**	79
8			(*Z*)-**2c**		(*Z*)-**3c-3**	85
9	Me	Me	(*E*)-**2c**	(*p*-Cl) C_6H_4	(*E*)-**3c-4**	83[c]
10			(*Z*)-**2c**		(*Z*)-**3c-4**	72[c]
11	Me	Me	(*E*)-**2c**	(*o*-Me) C_6H_4	(*E*)-**3c-5**	96
12			(*Z*)-**2c**		(*Z*)-**3c-5**	81
13	Me	Me	(*E*)-**2c**	1-Naph	(*E*)-**3c-6**	83
14			(*Z*)-**2c**		(*Z*)-**3c-6**	63
15	Me	Me	(*E*)-**2c**		(*E*)-**3c-7**	59
16			(*Z*)-**2c**		(*Z*)-**3c-7**	74
17	Me	Me	(*E*)-**2c**		(*E*)-**3c-8**	78
18			(*Z*)-**2c**		(*Z*)-**3c-8**	82
19	BnO $(CH_2)_5$	Me	(*E*)-**2f**	Ph	(*E*)-**3f**	71[d]
20			(*Z*)-**2f**		(*Z*)-**3f**	58[d]
21	$Cl(CH_2)_4$	Me	(*E*)-**2g**	Ph	(*E*)-**3g**	74[d]
22			(*Z*)-**2g**		(*Z*)-**3g**	76[d]
23	CH_2=CH $(CH_2)_8$	Me	(*E*)-**2h**	Ph	(*E*)-**3h**	88[d]
24			(*Z*)-**2h**		(*Z*)-**3h**	66[d]
25	Cyclo hexyl	Me	(*E*)-**2i**	Ph	(*E*)-**3i**	81[d]
			(*Z*)-**2i**		(*Z*)-**3i**	81[d]

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

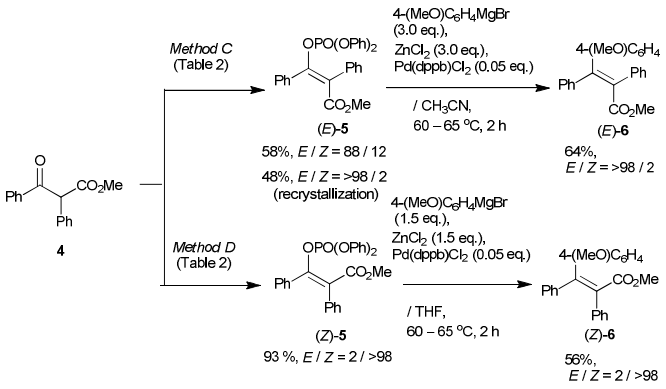
Table 5 Stereoretentive Negishi cross-coupling of R^2 aromatic (*E*)- and (*Z*)-enol phosphates **2**.



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

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

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



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

Conclusions

A versatile synthesis of fully-substituted both (*E*)- and (*Z*)-α,β-unsaturated esters utilizing (*E*)- and (*Z*)-stereocomplementary enol phosphorylations of β-ketoesters and 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 for fully-substituted olefins is now under investigation.

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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 ESI.
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