NaOH-catalyzed crossed Claisen condensation between ketene silyl acetals and methyl esters†

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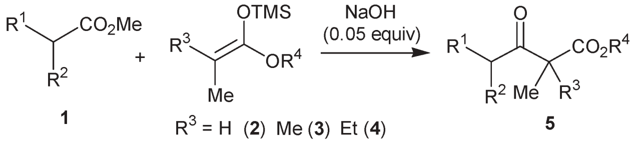
We have developed a practical crossed Claisen condensation between ketene silyl acetals and methyl esters using catalytic NaOH to obtain α-monoalkylated β-keto esters and inaccessible α,α-dialkylated β-keto esters.

The Claisen condensation is recognized as a fundamental and useful C–C bond forming reaction to obtain β-keto esters in organic syntheses.[1] There are several methods for reactions utilizing basic reagents such as NaOR, NaH, LDA, LiHMDS, *etc.*[1] and Lewis acid reagents such as $TiCl_2(OTf)_2$, $TiCl_4$ and $ZrCl_4$.[2] The major problem of the Claisen condensation lies in the difficulty in controlling the direction of the reaction: the reaction of a mixture of two different esters, each of which possesses α-hydrogens, generally affords all four products. Recently, as one solution to this problem, a Ti-crossed Claisen condensation was disclosed.[3]

The method utilizing ketene silyl acetals (KSAs), the activated substrate of esters, is regarded to be another promising candidate for resolution of this problem. The reported crossed Claisen condensation using KSAs,[4] however, lacks generality: (i) use of acid chlorides as the electrophile, (ii) limitation of the electrophile to aromatic and/or α,β-unsaturated acid chlorides that do not contain α-hydrogens. Recently, Mukaiyama and coworkers developed several base-catalyzed aldol-type reactions utilizing enol silyl ethers and KSAs with carbonyl acceptors.[5]

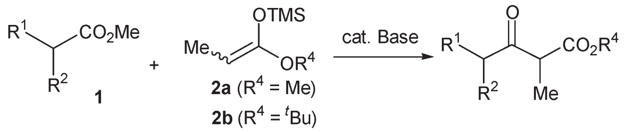
In connection with our studies on the development of practical Ti- (*or* Zr-) Claisen condensations[3] and related aldol addition,[6] originally exploited by the Evans group,[7] we report here the NaOH-catalyzed crossed Claisen condensation of KSAs **2**, **3**, and **4** derived from both α-monomethyl and α,α-dialkylated esters, with methyl esters **1** to afford a variety of α-monoalkylated and α,α-dialkylated β-keto esters **5**, respectively (Scheme 1).

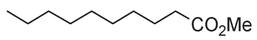
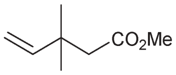
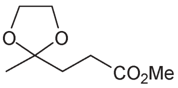
The initial trial was guided by the reaction of the KSA of methyl propanoate **2a** with methyl decanoate (Table 1, Entries 1–6). Among bases screened, NaOH (0.05 equiv) promoted the desired crossed condensation (Entry 6). The use of the KSA of ^{t}Bu propanoate **2b**[8] increased the yield (Entry 7), probably because the undesirable self condensation was sufficiently circumvented for ^{t}Bu propanoate, which was simultaneously produced during the reaction. The reaction of **2b** with some methyl esters **1** proceeded in moderate to good yields (Entries 7–10).



Scheme 1

Table 1 Crossed Claisen condensation between methyl esters **1** and KSAs **2** derived from using α-monoalkylated esters[a]



Entry	Ester	KSA	Base	Yield[b] (%)
1		**2a**	TBAF	trace
2			K_2CO_3	trace
3			LiOH	trace
4			CsOH	14
5			KOH	30
6			NaOH	48
7		**2b**	NaOH	64
8		**2b**	NaOH	58
9	$PhCO_2Me$	**2b**	NaOH	61
10		**2b**	NaOH	57

[a] In DMF at 15–20 °C for 1 h. Molar ratio; **1**:**2**:Base = 1.0:3.0:0.05.
[b] Isolated.

Next, we focused our attention on the reaction of KSAs **3** and **4** of α,α-dialkylated esters with methyl esters **1**. The retro-Claisen condensation of α,α-dialkylated β-ketoesters **8** usually predominates, because the reversible equilibrium barely shifts from **7** to the favorable production of **8**[1] (Scheme 2) due to the fact that **8** lacks the ability to force the formation of the stable β-ketoester enolate. $Ph_3C^-Na^+$[9]and $ZrCl_4$–$^iPr_2NEt$[2e] reagents are powerful enough to conduct this type of Claisen condensation between α,α-dialkylated esters. A few serious problems, however, remain: (i) limited to self condensation between same simple esters, (ii) phenyl esters must be used in the case of $ZrCl_4$–$^iPr_2NEt$, and (iii) low to moderate reaction yields.

To overcome these problems, we examined the use of KSAs **3** and **4** derived from α,α-dialkylated esters for the formation of inaccessible β-keto esters **9**. Table 2 lists the successful results under optimized conditions, and the salient features are as follows. (i)

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† Electronic supplementary information (ESI) available: experimental details. See http://www.rsc.org/suppdata/cc/b5/b504750a/
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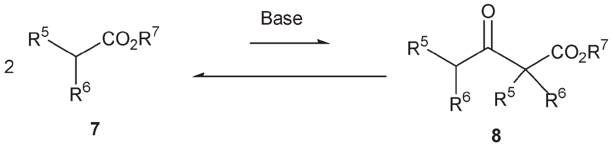


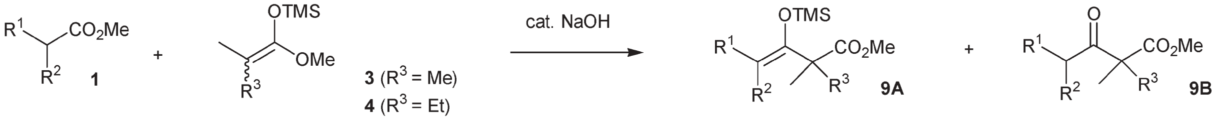
Scheme 2

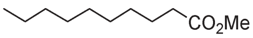
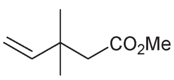
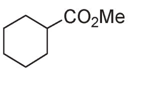
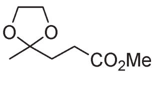
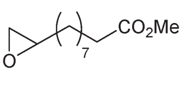
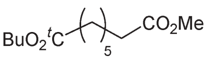
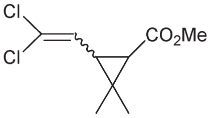
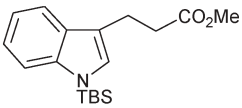
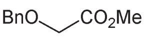
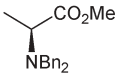
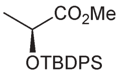
Surprisingly, the crossed-Claisen condensation using KSAs **3** and **4**, which looked like less reactive nucleophiles than KSAs **2**, proceeded smoothly and the yields were good to excellent in every case examined. (ii) As an apparent tendency, the reaction using linear esters **1** (R^2 = H) predominantly gave enol silyl enolates form **9A** of the parent β-keto esters, whereas that of branched esters (R^1 and $R^2 \neq$ H) exclusively afforded β-keto esters **9B**. (iii) Silyl enolates **9A** was easily converted to β-keto esters form **9B** on treatment with aqueous 1 M HCl. (iv) Several functionalities, such as an acetal, an epoxide, a *tert*-butyl ester, a cyclopropane, and an indole, and a benzyloxy, tolerated the reaction conditions (Entries 9–18). (v) Feature (ii) ensures that the use of optically active methyl lactate and alanine methyl ester analogs will not racemize during the reaction, because the sp^3 stereogenic center will be maintained. Indeed, two optically active substrates underwent the reaction without racemization (Entries 19 and 20).

A plausible reaction mechanism (catalytic cycle) is proposed in Scheme 3 as exemplified by the reaction between KSA **3** and α-monoalkylated linear methyl ester **10** (Scheme 3). First, the ester enolate **11** generated by HO^- condenses with **10** to give the β-ketoester **12** with the elimination of MeO^-. Next, MeO^- attacks **3** to give **11**, which in turn condenses with **12** to give ketone enolate **13**. **13** receives the TMS group from **3** to give the desired TMS enolate **14** by reforming **11**. Thus, more than 2 equiv of KSA were required to complete the reaction.

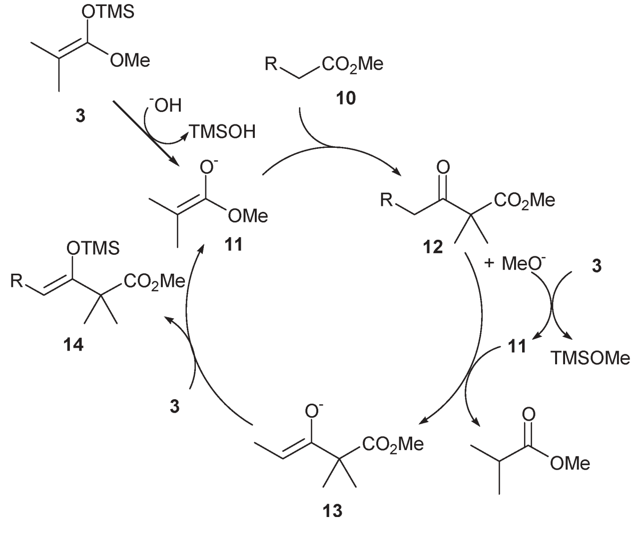
Finally, we planned the Mukaiyama aldol reaction (Method A) and Ti-direct aldol reaction (Method B) for further useful functionalization of both the obtained α,α-dialkylated β-keto esters **9A** and their TMS enolates **9B**, all of which are novel compounds. Table 3 lists these results. All six examples were successfully performed: α′-octyl substrate predominantly gave *syn* aldol-adducts (Entries 1–4), whereas α-benzyloxy substrate gave *anti* aldol-adducts (Entries 5 and 6). This stereoselectivity was significantly enhanced by the Ti-direct method B. We propose that

Table 2 NaOH-catalyzed crossed Claisen condensation between methyl esters **1** and KSAs **3**, **4** derived from α,α-dialkylated esters[a]



Entry	Ester	KSA	Yield[b] (%)	A:B
1		3	99	82:18
2		4	98	92:8
3		3	88	59:41
4		4	87	93:7
5	PhCO$_2$Me	3	85[c]	—
6		4	94[c]	—
7		3	83	0:100
8		4	82	0:100
9		3	88[d]	77:23
10		4	91[d]	86:14
11		3	83	42:58
12		4	92	27:73
13		3	85	51:49
14		4	90	54:46
15		3	89	0:100
16		4	88	0:100
17		3	67[e]	—
18		3	85	100:0
19[f]		3	85	0:100[g]
20[f]		3	89[g]	0:100[h]

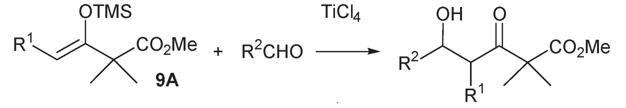
[a] In DMF at 15–20 °C for 1 h. Molar ratio; **1**:**3** (or **4**) :NaOH = 1.0:2.4:0.05. [b] Isolated. [c] KSA **3** or **4** is 1.2 equiv. [d] Reaction time is 3 h. [e] Because **9A** and **9B** were not separable, the mixture was treated with 1 M HCl to convert **9A** into **9B**. [f] Reaction temperature is 0 °C. [g] 97% ee by HPLC analysis. [h] 95% ee by HPLC analysis.



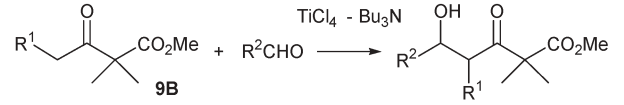
Scheme 3

Table 3 Ti-Aldol reactions of crossed Claisen adduct **9A** and **9B** with aldehydes

Method A (Mukaiyama Aldol Reaction)[a]



Method B (Ti - Direct Aldol Reaction)[b]



Entry	R^1	R^2	Method	Product	Yield[c] (%)	*syn:anti*[d]
1	Octyl[e]	Ph	A		73	93:7
2			B		78	93:7
3		Pentyl	A		80	72:28
4			B		83	>99:1
5	BnO[f]	Ph	A		67	25:75
6			B		80	2:98

[a] In CH_2Cl_2, −45 to −50 °C for 1 h. Molar ratio; **9A**:aldehydes:$TiCl_4$ = 1.0:1.2:1.2. [b] In CH_2Cl_2, 0–5 °C for 2 h. Molar ratio; **9B**:aldehydes:$TiCl_4$:Bu_3N = 1.0:1.2:1.2:1.4. [c] Isolated. [d] Determined by ^{1}H-NMR. [e] **9A** (*E*:*Z* = 1:>99) was used. [f] **9A** (*E*:*Z* = 5:95) was used.

the *syn* mechanism utilizes the conventional six-membered chair transition state, whereas the *anti* mechanism utilizes a benzoyloxy-coordination boat mechanism (See ESI†).

In conclusion, we developed a new mild, catalytic, practical and efficient method for preparing various β-ketoesters using α-mono or α,α-dialkylated KSAs and catalytic NaOH. Further functionalization utilizing two Ti-aldol reactions demonstrates a notable extension of the present method. Because the Claisen condensation of α,α-dialkylated esters is very difficult, the present method provide a new avenue for the preparation of inaccessible β-ketoesters.‡

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Notes and references

‡ Typical procedure: [(1-Methoxy-2-methyl-1-butenyl)oxy]trimethylsilane (452 mg, 2.40 mmol) was added to a stirred solution of methyl decanoate (186 mg, 1.0 mmol) and NaOH (crushed powder prepared under dry atmosphere; 2 mg, 0.05 mmol) in DMF (0.2 cm^3) at 15–20 °C under an Ar atmosphere, and the reaction mixture was stirred at that temperature for 1 h. Water was added to the reaction mixture, which was extracted with ether. 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:ether = 30:1 ∼ 100:1) to give methyl 2,2-dimethyl-3-(trimethylsiloxyl)dodec-3-enoate (**A**) (colorless oil, 270 mg, 82%) and methyl 2,2-dimethyl-3-oxododecanoate (**B**) (colorless oil, 44 mg, 17%). See ESI for NMR data.

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