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Powerful Ti-Crossed Claisen Condensation between Ketene Silyl Acetals or Thioacetals and Acid Chlorides or Acids

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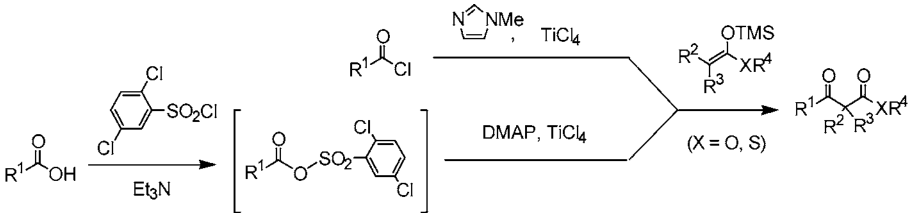
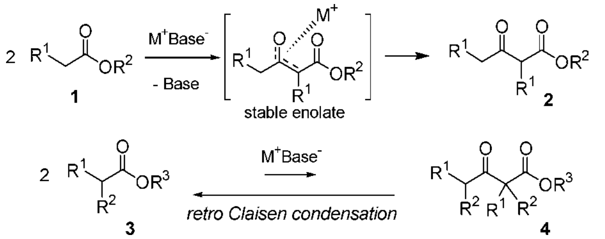
ABSTRACT



A powerful Ti-crossed Claisen condensation between ketene silyl acetals (KSAs) and acid chlorides was successfully performed to give α-monoalkylated esters and thermodynamically unfavorable (less accessible) α,α-dialkylated *β*-keto esters in good yield (46 examples; 41–98% yield). A closely related reaction between ketene silyl thioacetals (KSTAs) and acid chlorides also proceeded smoothly to give α-monoalkylated and α,α-dialkylated *β*-keto thioesters (21 examples; 61–97% yield). The present protocol was extended to the direct condensation of KSAs with carboxylic acids (14 examples; 71–97% yield).

The Claisen condensation is recognized as a fundamental and useful C−C bond-forming reaction for obtaining *β*-keto esters in organic syntheses.[1] This reaction is categorized into two types: (i) traditional base-mediated condensations using MOR (M = Na, K), LDA, MHMDS (M = Li, Na, K), and MH (M = Na, K)[2] and (ii) the Ti-Claisen condensation.[3] These methods, however, are limited to reactions of α-monoalkylated ester substrates **1** and cannot be applied to reactions of α,α-dialkylated esters **3** because the retro-Claisen condensation generally predominates; **4** lacks the ability to form stable *β*-keto ester metal enolates (Scheme 1).[1,4,5]

Scheme 1. Traditional Claisen Condensation Using α-Mono- and α,α-Disubstituted Esters



A recently reported NaOH-catalyzed crossed Claisen condensation of ketene silyl acetals (KSAs) with methyl esters[5] provides one solution to this issue.[6] Two drawbacks, however, remain: (i) 3 equiv of KSAs (vs esters) is generally required to complete the reaction and (ii) the carbonyl acceptor (methyl esters) should be simple and reactive. As

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[1] (a) For examples, see: Smith, M. B.; March, J. *Advanced Organic Chemistry*, 5th ed.; John Wiley: New York, 2001; p 569. (b) Vollhardt, K. P. C.; Schore, N. E. *Organic Chemistry*, 3rd ed.; Freeman: New York, 1999; p 1039. (c) Clayden, J.; Greeves, N.; Warren, S.; Wothers, P. *Organic Chemistry*; Oxford: New York, 2001; p 726. (d) Kürti, L.; Czakó, B. *Strategic Applications of Named Reactions in Organic Synthesis*; Elsevier: Burlington, 2005; p 86 and p 138.

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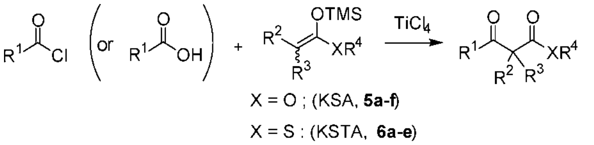
part of our ongoing project to develop practical Claisen condensations,[3−5] we present here an efficient powerful Ti-crossed Claisen condensation of KSAs **5a**−**f**, derived from both α-monoalkylated and α,α-dialkylated esters, with carboxylic acid chlorides or their parent acids (Scheme 2).

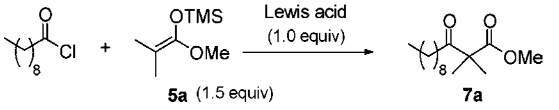
Scheme 2. Ti-Crossed Claisen Condensation Using Ketene Silyl Acetals (KSAs) and Ketene Silyl Thioacetals (KSTAs)



In addition, a closely related condensation between ketene silyl thioacetal acetals (KSTAs) **6a**−**e** and acid chlorides was performed. The present method, giving a variety of β-keto esters and thioesters, proved to be the most powerful among hitherto reported Claisen condensations.

The initial attempt was guided by the reaction between KSA **5a** (1.5 equiv) of methyl 2-methylpropionate and decanoyl chloride using several Lewis acid reagents (BF_3•Et_2O, $AlCl_3$, $ZnBr_2$, $SnCl_4$, $ZrCl_4$, $TiCl_4$) (Table 1). Although a BF_3•Et_2O-promoted Claisen-type condensation between KSAs and aryl-type acid chlorides was reported,[7] the corresponding reaction did not proceed (entry 1). Among five Lewis acids, $TiCl_4$ produced the best result (entry 6). Chlorobenzene, CH_2Cl_2, and toluene were used as solvents (entries 6−8).

Table 1. Screening of Lewis Acids

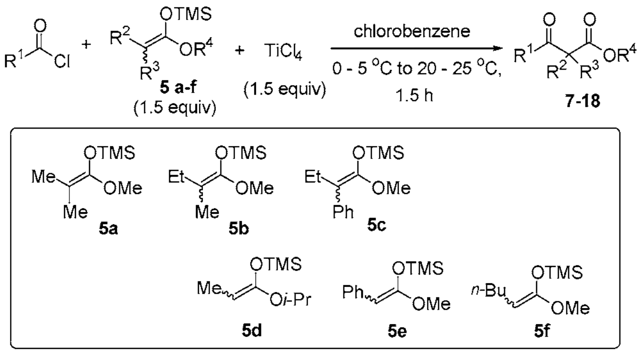


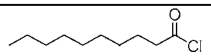
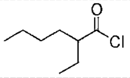
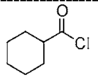
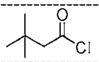
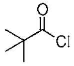
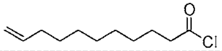
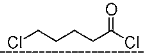
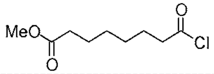
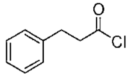
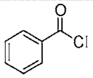
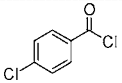
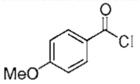
Entry	Lewis acid	Solvent	Yield/%[a]
1	BF_3•Et_2O	CH_2Cl_2	trace
2	$AlCl_3$	CH_2Cl_2	61
3	$ZnBr_2$	CH_2Cl_2	57
4	$SnCl_4$	CH_2Cl_2	23
5	$ZrCl_4$	CH_2Cl_2	66
6	$TiCl_4$	CH_2Cl_2	80
7	$TiCl_4$	toluene	72
8	$TiCl_4$	chlorobenzene	85

[a] Determined by ^{1}H NMR.

Table 2 lists the successful results of the present Ti-crossed Claisen condensation using a variety of KSAs **5a**−**f** and acid chlorides. The salient features are as follows: (i) The reaction, using both aliphatic and aromatic acid chlorides, proceeded smoothly to give the corresponding β-keto esters

Table 2. Claisen Condensation between KSAs **5** and Acid Chlorides



Entry	Acid chloride	KSA	Product	Yield / %[a]
1		**5a**	**7a**	92
2		**5b**	**7b**	95
3		**5c**	**7c**	61
4		**5d**	**7d**	45
5		**5e**	**7e**	44
6		**5f**	**7f**	41
7		**5a**	**8a**	88
8		**5b**	**8b**	92
9		**5a**	**9a**	91
10		**5b**	**9b**	91
11		**5a**	**10a**	83
12		**5b**	**10b**	85
13		**5a**	**11a**	72
14		**5b**	**11b**	75
15		**5a**	**12a**	86
16		**5b**	**12b**	88
17		**5a**	**13a**	88
18		**5b**	**13b**	81
19		**5a**	**14a**	71
20		**5b**	**14b**	74
21		**5a**	**15a**	85
22		**5b**	**15b**	88
23		**5a**	**16a**	85
24		**5b**	**16b**	98
25		**5a**	**17a**	89
26		**5b**	**17b**	92
27		**5a**	**18a**	95
28		**5b**	**18b**	96

[a] Isolated.

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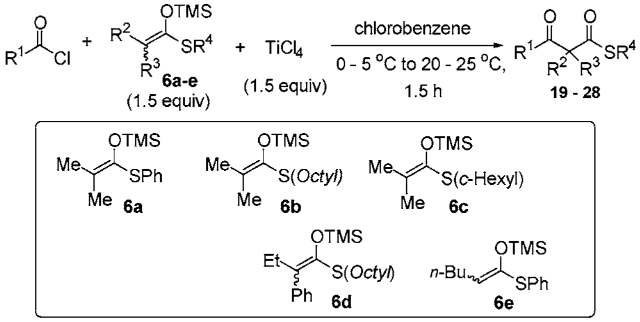
(2) (a) Fisher, N.; McElvain, S. M. *J. Am. Chem. Soc.* **1934**, *56*, 1766. (b) Yoshizawa, K.; Toyota, S.; Toda, F. *Tetrahedron Lett.* **2001**, *42*, 7983. (c) Cooke, M. P., Jr. *J. Org. Chem.* **1993**, *58*, 2910. (d) Loubinoux, B.; Sinnes, J.-L.; O'Sullivan, A. C. *J. Chem. Soc., Perkin Trans. 1* **1995**, 521. (e) Lombart, H.-G.; Lubell, W. D. *J. Org. Chem.* **1994**, *59*, 6147. (f) Austad, B. C.; Hart, A. C.; Burke, S. D. *Tetrahedron* **2002**, *58*, 2011. (g) Brown, C. A. *Synthesis* **1975**, 326. (h) McMurry, J. E.; Fleming, M. P.; Kees, K. L.; Krepski, L. R. *J. Org. Chem.* **1978**, *43*, 3255.

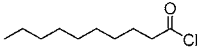
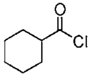
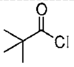
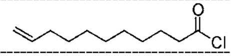
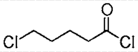
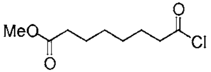
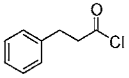
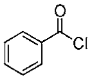
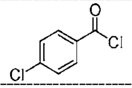
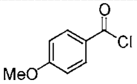
(3) (a) Tanabe, Y. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1917. (b) Crane, S. N.; Corey, E. J. *Org. Lett.* **2001**, *3*, 1395. (c) Tanabe, Y.; Makita, A.; Funakoshi, S.; Hamasaki, R.; Kawakusu, T. *Adv. Synth. Catal.* **2002**, *344*, 507. (d) Tanabe, Y.; Manta, N.; Nagase, R.; Misaki, T.; Nishii, Y.; Sunagawa, M.; Sasaki, A. *Adv. Synth. Catal.* **2003**, *345*, 967. (e) Hashimoto, Y.; Konishi, H.; Kikuchi, S. *Synlett* **2004**, 1264. (f) Misaki, T.; Nagase, R.; Matsumoto, K. Tanabe, Y. *J. Am. Chem. Soc.* **2005**, *127*, 2854. Other references cited therein.

in good to excellent yield (28 examples; 41−98%). (ii) KSA equivalents of **5a** were significantly reduced to 1.5, compared with the NaOH-catalyzed method, in which 3 equiv was used.[5] (iii) Terminal double bond, δ-chloro, and methyl ester functionalities were tolerated (entries 15−20) (note that methyl esters function as electrophiles in the NaOH-catalyzed method). (iv) Sterically congested KSA **5c** bearing ethyl and phenyl groups in α,α-positions resulted in a moderate yield (entry 3). (v) α-Monoalkylated KSAs **5d**−**f**, however, gave the products in low yield) (vide infra, Table 4).

The relevant reaction between KSTAs **6a**−**e** and acid chlorides was investigated. Table 3 lists the successful results. Similar to the case using KSAs, a variety of β-keto thioesters were obtained in good to excellent yield (21 examples; 61−97%). Note that good yield was obtained using sterically congested and α-monoalkylated KSTAs **6d** and **6e** (entries 4, 5, 7, 12, 15, and 19).

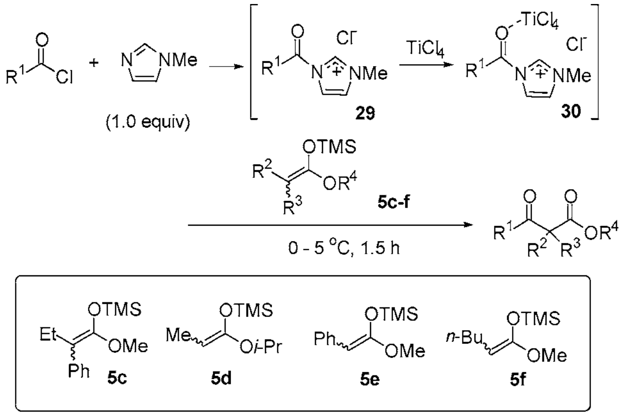
Table 3. Claisen Condensation between KSTAs **6a**−**e** and Acid Chlorides

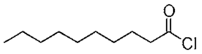
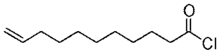
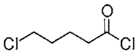
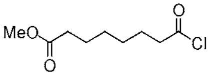
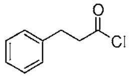
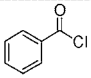
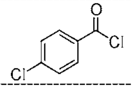
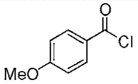


Entry	Acid chloride	KSTA	Product	Yield/ %[a]
1		**6a**	**19a**	97
2		**6b**	**19b**	97
3		**6c**	**19c**	92
4		**6d**	**19d**	86
5		**6e**	**19e**	64[b]
6		**6a**	**20a**	91
7		**6d**	**20d**	87
8		**6a**	**21a**	82
9		**6b**	**21b**	94
10		**6a**	**22a**	87
11		**6b**	**23b**	94
12		**6e**	**23e**	61[b]
13		**6a**	**24a**	85
14		**6b**	**25b**	95
15		**6e**	**25e**	65[b]
16		**6a**	**26a**	93
17		**6b**	**26b**	95
18		**6c**	**26c**	94
19		**6d**	**26d**	70
20		**6a**	**27a**	92
21		**6a**	**28a**	95

[a] Isolated. [b] 0−5 °C.

Table 4. Ti-Crossed Claisen Condensation between Less Reactive KSAs **5c**−**f** and Acid Chlorides



Entry	Acid chloride	KSA	Product	Yield / %[a]
1		**5c**	**7c**	95 (93)[b,c]
2		**5d**	**7d**	70
3		**5e**	**7e**	81[d]
4		**5f**	**7f**	86
5		**5c**	**12c**	90[c]
6		**5d**	**12d**	64
7		**5f**	**12f**	86
8		**5c**	**13c**	96[c]
9		**5d**	**13d**	69
10		**5e**	**13e**	92[d]
11		**5c**	**14c**	85[c]
12		**5d**	**14d**	80
13		**5e**	**14e**	78[d]
14		**5c**	**15c**	91[c]
15		**5f**	**15f**	88
16		**5c**	**16c**	81[c]
17		**5c**	**17c**	67[c]
18		**5c**	**18c**	65[c]

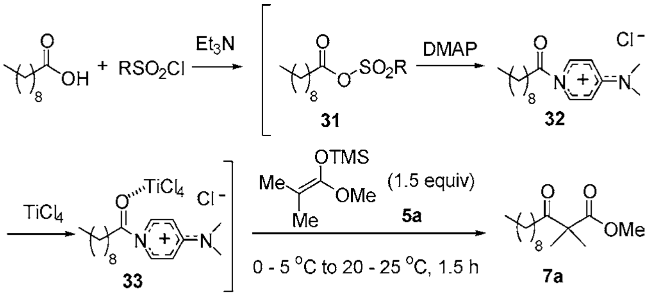
[a] Isolated. [b] Use of DMAP instead of *N*-methylimidazole. [c] 20−25 °C. [d] −40 to −45 °C.

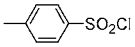
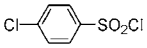
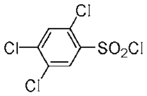
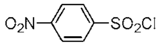
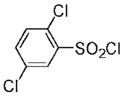
Next, to solve the lower yield problems referred to above in (iv) and (v) using KSAs **5c**−**f**, *N*-methylimidazole was employed as a key cocatalyst because acid chlorides condense with *N*-methylimidazole to form an activated acylammonium electrophilic intermediate **29**.[3f,8] As expected, the yield was markedly improved using a combined reagent, $TiCl_4$/*N*-methylimidazole, giving the desired β-keto esters (Table 4). We speculate that $TiCl_4$ coordinates with the carbonyl oxygen of **29** to afford a highly reactive, double-activated acylammonium intermediate **30**. Terminal double bond, Cl atom, and methyl ester functional groups were also tolerated during this reaction (entries 5−13). Greenwald and co-workers reported a relevant mechanism during an efficient esterification of tertiary alcohols utilizing a double-activated acylammonium intermediate, derived from a $Sc(OTf)_3$/DMAP reagent.[9]

The three methods presented here have a higher reactivity than the related NaOH-catalyzed method between KSAs and methyl ester. Indeed, the reactions using **5c**−**f** in the NaOH-catalyzed method did not proceed (low yield).

Finally, the present protocol was extended to Ti-crossed Claisen condensation using parent carboxylic acids as the electrophile. We expected the formation of double-activated acylammonium intermediate **33**, which was coordinated with $TiCl_4$ (Table 5). A plausible mechanism is as follows: Mixed anhydride **31** is initially formed in situ between decanoic acid and a sulfonyl chloride in the presence of Et_3N as an acid scavenger. Similar to the reaction shown in Table 4, **31** is transformed to reactive intermediate **33** through acylammonium **32** with DMAP.

Table 5. Screening of Sulfonyl Chlorides for the Reaction of Carboxylic Acids



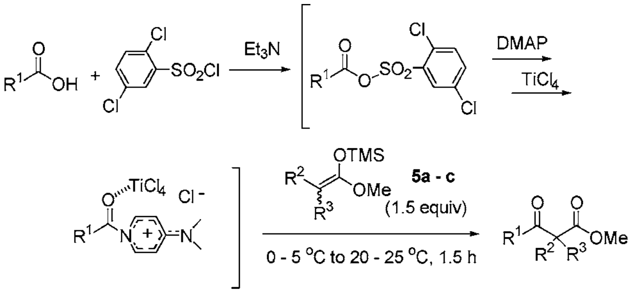
Entry	Sulfonyl chloride	Yield / %^{a,b}
1	Me_2NSO_2Cl	12
2	$OCNSO_2Cl$	20
3		65 (57)
4		41
5		76
6		trace
7		82 (73)

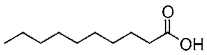
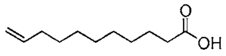
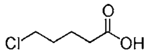
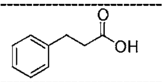
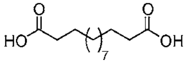
[a] Determined by ^1H NMR. [b] Parentheses indicate the cases using *N*-methylimidazole instead of DMAP.

Screening of sulfonyl chlorides revealed that 2,5-dichlorobenzenesulfonyl chloride gave the best result (entry 7). Note that DMAP (82%) produced somewhat better results than *N*-methylimidazole (73%) under conditions identical to those of entry 7.

On the basis of this result, Ti-crossed Claisen condensations between KSAs **5a**−**c** and several carboxylic acids were successfully performed to give the desired *β*-keto esters in good to excellent yield (Table 6) (14 examples; 71−97% yield).

Table 6. Ti-Crossed Claisen Condensation between KSAs and Carboxylic Acids



Entry	Acid	KSA	Product	Yield / %^{a}
1		**5a**	**7a**	81
2		**5b**	**7b**	87
3		**5c**	**7c**	97
4		**5a**	**12a**	73
5		**5b**	**12b**	80
6		**5c**	**12c**	90
7		**5a**	**13a**	73
8		**5b**	**13b**	77
9		**5c**	**13c**	88
10		**5a**	**15a**	80
11		**5b**	**15b**	90
12		**5c**	**15c**	91
13		**5a**	**34a**	69
14		**5b**	**34b**	71

[a] Isolated.

In conclusion, we developed a Ti-crossed Claisen condensation between a number of KSAs (or KSTAs) of α-monoalkylated esters and less accessible α,α-dialkylated esters and acid chlorides (or acids) (81 examples total). The present method exhibited high reactivity and generality, which will provide a new avenue for the Claisen condensation.

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Supporting Information Available: The 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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