Communication

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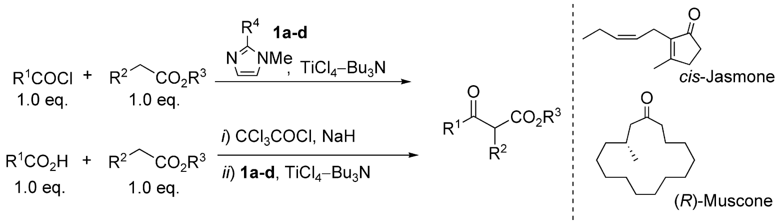

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Ti-*Crossed*-Claisen Condensation between Carboxylic Esters and Acid Chlorides or Acids: A Highly Selective and General Method for the Preparation of Various *β*-Keto Esters

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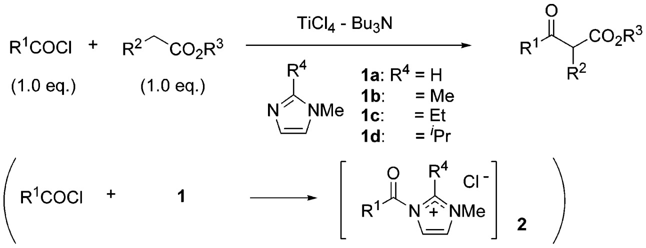
The Claisen condensation is recognized as a fundamental and useful C−C bond-forming reaction in organic syntheses.[1] In general, strong basic reagents (NaOR, LDA, MHMDS, MH, etc.) are used to conduct this reaction. The Ti- (*or* Zr-) *self*-Claisen condensation[2] possesses powerful reactivity compared with that of the conventional method using strong bases; this method afforded efficient and practical syntheses for *Z*-civetone,[3] 1*β*-methyl-carbapenem,[4] and an omuralide analogue.[5] A related Ti-direct aldol reaction, originally pioneered by Evans' group,[6] also exhibits powerful reactivity for the crossed addition between different ketones[7] and is utilized for the efficient syntheses of an anti-Methicillin-resistant *Staphylococcus aureus* carbapenem,[8] (*R*)-muscone,[7] and (*R*)-mintlactone.[9]

The major problem of the Claisen condensation lies in the difficulty in directing the reaction; that is, a general crossed condensation between different esters or between esters and acid chlorides, all of which possess α-protons, has not been documented. We disclose here the first general Ti-*crossed*-Claisen condensation between a 1:1 mixture of esters and acid chlorides to provide a variety of *β*-keto esters (Scheme 1). These functionalized *β*-keto esters served as a fundamental and useful precursor for organic syntheses, especially for chiral synthons utilizing asymmetric transformations such as hydrogenations,[10] metal hydride reductions,[11] enzymatic reductions,[12] and asymmetric alkylations at the α-position.[13]

Scheme 1

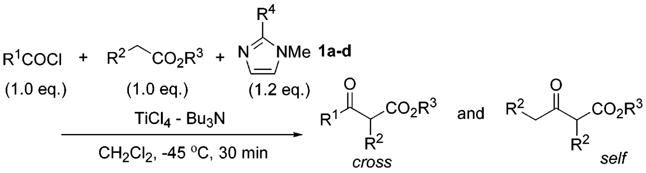


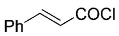
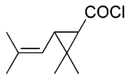
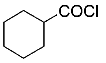
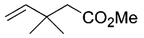
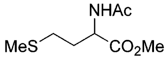
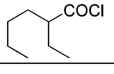
The Ti-*self*-Claisen condensation of simple esters proceeds very rapidly, even at −45 °C, within 0.5 h. Taking this information into account, to realize the Ti-*crossed*-Claisen condensation, we chose acid chlorides as the reactive acceptor electrophile.

As depicted in Table 1, the result of an initial attempted reaction of methyl hexanoate with propanoyl chloride at −45 °C for 0.5 h, however, was disappointing (entry 1). The major product was decomposed propanoic acid (ca. 80%) with undesirable *self*-condensed *β*-keto ester (ca. 30%), and the desired *cross*-condensed *β*-keto esters were obtained in low yield (15%).

To solve the problem, *N*-methylimidazoles **1** were employed as the key cocatalyst, because acid chlorides condense with *N*-methylimidazole to form an activated electrophilic acylammonium intermediate **2**.[14] Screening of some available *N*-methylimidazoles **1** revealed promising result with the 2-Et analogue **1c** (80%, cross/self = 98/2; entry 4). Thus, the reactions of several esters with linear (not branched) acid chlorides proceeded smoothly to give the desired *cross*-products in good yields with excellent selectivities (entries 6, 7, and 9).

Table 1. Ti-*Crossed*-Claisen Condensation between a 1:1 Mixture of Esters and Acid Chlorides



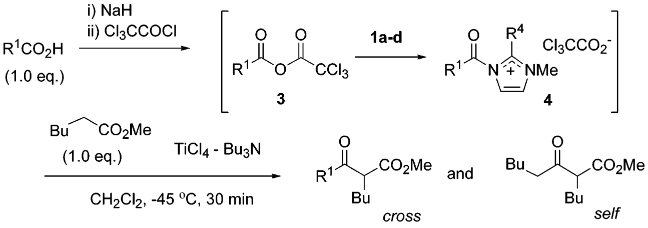
entry	R^1COCl	R^2⌒CO_2R^3	imidazole	yield (%)[a]	*cross* / *self*[b]
1	CH_3CH_2COCl	$CH_3(CH_2)_4CO_2Me$	non	15	35 / 65
2			**1a**	35	63 / 37
3			**1b**	67	92 / 8
4			**1c**	80	98 / 2
5			**1d**	52	83 / 17
6	 $(CH_2)_8COCl$	$CH_3(CH_2)_4CO_2Me$	**1c**	75	>99 / 1
7		$AcHNCH_2CO_2Me$	**1c**	79	>99 / 1
8		$(CH_3)_2CHCH_2CO_2Me$	**1a**	71	>99 / 1
9	$BnOCH_2COCl$	$AcHNCH_2CO_2Me$	**1c**	51	>99 / 1
10	$(CH_3)_2CHCH_2COCl$	$CH_3CH_2CO_2Me$	**1a**	56	91 / 9
11			**1b**	73	96 / 4
12			**1c**	66	93 / 7
13	$(CH_3)_3CCH_2COCl$	$CH_3(CH_2)_4CO_2Me$	**1a**	92	>99 / 1
14			**1b**	80	96 / 4
15			**1c**	63	89 / 11
16		$CH_3CO(CH_2)_2CO_2Et$	**1a**	47 (66)[c]	>99 / 1
17		$Ph(CH_2)_2CO_2Me$	**1a**	75	97 / 3
18		$AcOEt$[d]	**1a**	94[c]	–
19		$CH_3(CH_2)_4CO_2Me$	**1a**	95	>99 / 1
20			**1a**	69	>99 / 1
21		$PhCH_2CO_2Me$	**1a**	70	>99 / 1
22		$BnOCH_2CO_2Me$	**1a**	77	>99 / 1
23		$TsO(CH_2)_5CO_2Et$	**1a**	88	>99 / 1
24		$AcHNCH_2CO_2Me$	**1a**	81	>99 / 1
25			**1a**	48	>99 / 1
26		$AcOEt$[d]	**1a**	90[c,e]	–
27		$CH_3(CH_2)_4CO_2Me$	**1a**	78	>99 / 1

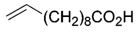
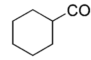
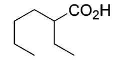
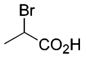
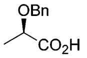
[a] Isolated. [b] Determined by ^1H NMR of crude products. [c] $^iPr_2NEt$ was used instead of Bu_3N. [d] 1.6 equiv of toluene solvent. [e] 0−5 °C.

For *β*-branched acid chlorides, 2-Me analogue cocatalyst **1b** matched the reaction with regard to yield and selectivity (cross/self → >91/9; entries 10−12). 2-H analogue **1a** was most favorable for *β*,*β*-disubstituted or α-branched acid chlorides (entries 13−27).[15]

10.1021/ja043833o CCC: $30.25

Table 2. Ti-*Crossed*-Claisen Condensation between a 1:1 Mixture of Methyl Hexanoate and Carboxylic Acids



entry	R^1CO_2H	*N*-methylimidazole	yield (%)[a]	*cross* / *self*[b]
1	$CH_3CH_2CO_2H$	**1c**	70	91 / 9
2		**1c**	78	>99 / 1
3		**1a**	92	>99 / 1
4		**1a**	76	95 / 5
5		**1a**	75	96 / 4
6		**1a**	82[c]	>99 / 1

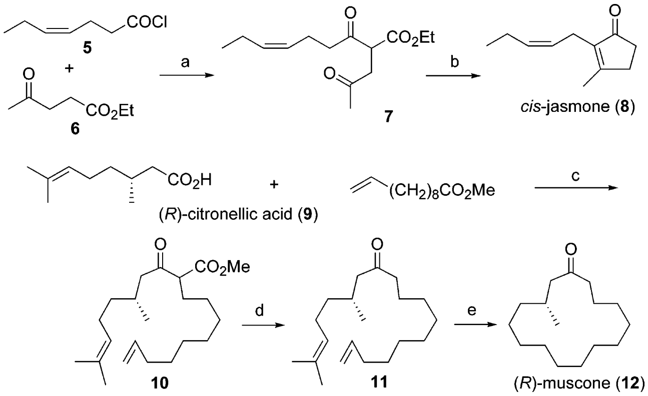
[a] Isolated. [b] Determined by ^{1}H NMR of the crude product. [c] Using the 2-benzloxy propanoic acid (97% ee), we obtained the desired β-keto ester (93% ee; see ESI).

Various functionalities in both esters and acid chlorides were tolerated during the Ti-*crossed*-Claisen condensation.

As a notable extension, we investigated the Ti-*crossed*-Claisen condensation using *carboxylic acids*. We designed a novel protocol utilizing mixed anhydrides **3** generated in situ between sodium carboxylates and $Cl_3CC(=O)Cl$. (Table 2) (for screening of the acyl chloride co-reagents, see Supporting Information). Thus, the plausible reactive intermediate **4** successfully reacted with methyl hexanoate to give the desired *cross*-condensed β-keto esters with good to excellent yield and selectivity.

Finally, to demonstrate the utility of the present Ti-*crossed*-Claisen condensation, we performed the efficient short-step syntheses of two natural, representative, and useful perfumes, *cis*-jasmone (**8**)[16] and (*R*)-muscone (**12**)[17] (Scheme 2). Synthesis of these compounds is a standard model for novel reactions due to their utility and interesting structures.

Scheme 2. Application to the Syntheses of Natural Perfumes, *cis*-Jasmone and (*R*)-Muscone[a]



[a] Conditions: (a) **1c**, $TiCl_4$−$^iPr_2NEt$, CH_2Cl_2 (61%). (b) 5 M aq KOH, EtOH, then 1 M aq HCl (76%). (c) **1b**, $TiCl_4$−Bu_3N, CH_2Cl_2 (76%). (d) 5 M aq NaOH, MeOH, then 6 M aq HCl (95%). (e) Grubbs catalyst second generation, $ClCH_2CH_2Cl$, then Pd−C, H_2, AcOEt (74%).

The Ti-*crossed*-Claisen condensation of ethyl levulinate (**6**) with readily available acid chloride **5** proceeded smoothly to give β-keto ester **7**. The high chemoselectivity should be noted: the reaction site of **6** was not the α-position of the ketone but that of the ester (see also Table 1, entry 16), and the ketone function did not require the protection.[18] A one-pot hydrolysis−decarboxylation and an aldol condensation afforded *cis*-jasmone (**8**) in 46% overall yield.

The Ti-*crossed*-Claisen condensation between both commercially available methyl 10-undecenate and (*R*)-citroneric acid afforded β-keto ester **10**, which was converted to ketone **11** by hydrolysis−decarboxylation. Second-generation ring-closing metathesis of **11**,[17] followed by catalytic hydrogenation, afforded (*R*)-muscone (**12**) in 53% overall yield. These two syntheses are regarded as simplest compared with hitherto reported methods.

In conclusion, we developed the Ti-*crossed*-Claisen condensation between a 1:1 mixture of esters and acid chlorides or carboxylic acids. The present method is a new avenue for the synthesis of a variety of β-keto esters, which will be useful achiral and chiral synthons. As a notable application, we utilized this method for the efficient short syntheses of *cis*-jasmone and (*R*)-muscone.

Supporting Information Available: Experimental details, analytical data, and characterization for reactions in Tables 1 and 2 (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Louie, J.; Bielawski, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 11312.
(18) The use of Bu_3N caused an undesirable condensation between methyl ketone of **6** with **5** in ∼10−20%. See also Table 1, entry 16. Bu_3N conducts a powerful crossed aldol additions (ref 7).

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