Reductive Ti-crossed Claisen Condensation between Methyl α-Bromocarboxylates and Acid Chlorides Utilizing a $TiCl_4$–PPh_3–*N*-Methylimidazole Reagent

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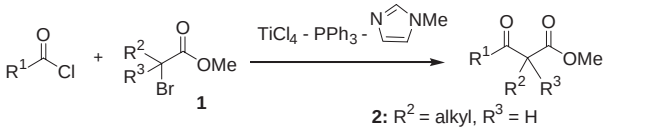
Reductive Ti-crossed Claisen condensation between methyl α-bromocarboxylates and acid chlorides utilizing a $TiCl_4$–PPh_3–*N*-methylimidazole reagent proceeded smoothly to give the α-monosubstituted and thermodynamically unfavorable α,α-disubstituted β-keto methyl esters in good to excellent yields (33 examples; 73–96% yield).

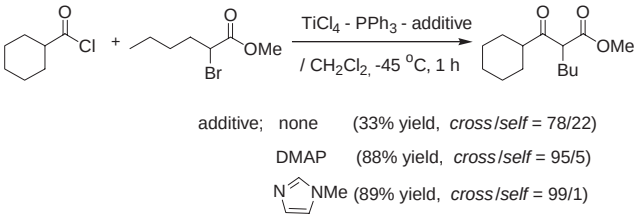
The Claisen condensation is recognized as a fundamental and useful C–C bond-forming reaction for obtaining β-keto esters in organic syntheses.[1] This reaction is categorized into two types; (i) traditional base-mediated condensations using MOR (M = Na and K), LDA, MHMDS (M = Li, Na, and K), and MH (M = Na and K),[1] and (ii) the Ti-Claisen condensation.[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 an α-hydrogen, generally affords all four products. To solve this problem, we recently reported a Ti-crossed Claisen condensation[3] and a NaOH-catalyzed crossed Claisen condensation.[4]

Hashimoto and co-workers reported an original reductive Ti-crossed Claisen condensation and related reactions using α-bromothioesters promoted by a Lewis acid–PPh_3 reagent.[5] This reductive Ti-crossed Claisen condensation,[5a] however, uses less accessible and less atom-economical 2,4,6-triisopropylphenyl α-bromothioesters and the yield of four examples was moderate (50–78%). As part of our ongoing project to develop practical Claisen condensations,[2–4] we present here an efficient reductive Ti-crossed Claisen condensation between a 1:1 mixture of methyl α-bromocarboxylates **1** and acid chlorides using a $TiCl_4$–PPh_3–*N*-methylimidazole reagent. The present method provides not only accessible α-monosubstituted β-keto esters **2**, but also thermodynamically unfavorable α,α-disubstituted β-keto esters **3** (Scheme 1).

The initial attempt was guided by the reaction between methyl 2-bromohexanoate and cyclohexanecarbonyl chloride using a $TiCl_4$–PPh_3 reagent (Scheme 2). The desired β-keto ester, however, was obtained in low yield (33%) with ca. 10% of undesirable self-condensation product, methyl 2-butyl-3-oxooctanoate (mainly, decomposed cyclohexanecarboxylic acid).[6] To solve the problem, DMAP or *N*-methylimidazole



Scheme 1.

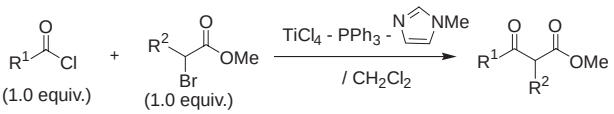


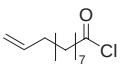
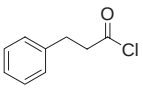
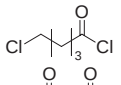
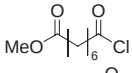
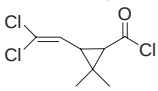
Scheme 2.

was employed as a co-catalyst, because acid chlorides are activated by these amines.[3,7,8] As expected, the yield was markedly increased (88 and 89%). *N*-methylimidazole was chosen as the key co-catalyst based on its higher *cross*/*self* selectivity (99/1) and cost-effectiveness.

Table 1 lists the successful results of the present reductive Ti-crossed Claisen condensations between bromoesters **1a**–**1c** and acid chlorides to obtain various α-monoalkyl-β-ketoesters

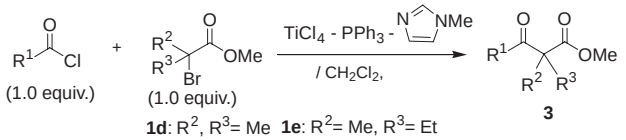
Table 1. Crossed Claisen condensation between methyl α-bromo-α-monosubstituted esters **1a**–**1c** and acid chlorides



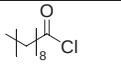
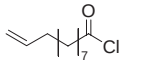
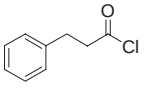
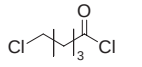
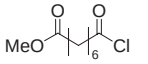
Entry	Acid chloride	α-Bromo-ester	Yield /%[a]	*Cross*/*Self*[b]
1		**1a**	95	98/2
2		**1b**	96	99/1
3		**1c**	86	99/1
4		**1b**	93	99/1
5		**1c**	86	99/1
6		**1a**	81	99/1
7		**1b**	76	99/1
8		**1b**	94	99/1
9		**1c**	82	99/1
10		**1a**	90	99/1
11		**1b**	77	99/1
12		**1c**	83	99/1
13		**1a**	85	99/1
14		**1b**	93	99/1
15		**1a**	84	97/3
16		**1b**	91	99/1
17		**1a**	74	97/3
18		**1b**	74	98/2

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

Table 2. Crossed Claisen condensation between methyl α-bromo-α,α-disubstituted esters **1d**–**1f** and acid chlorides



1d: R^2, R^3= Me **1e**: R^2= Me, R^3= Et
1f: R^2= Et, R^3= Ph

Entry	Acid chloride	α-Bromoester	Yield/%[a]
1		**1d**	83
2		**1e**	84
3		**1f**	94
4		**1d**	77
5		**1e**	82
6		**1f**	90
7		**1d**	81
8		**1e**	73
9		**1f**	85
10		**1d**	79
11		**1e**	79
12		**1f**	81
13		**1d**	83
14		**1e**	84
15		**1f**	87

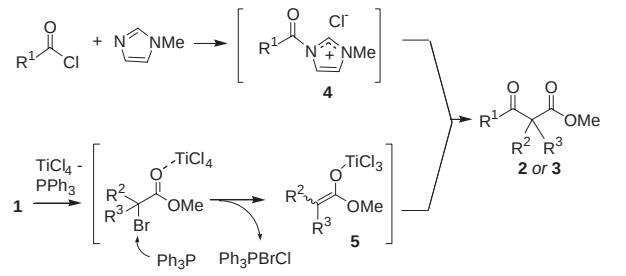
[a]Isolated.

2 (18 examples; 74–96%, *cross*:*self* = 97:3–99:1).[9] Note that the present reaction had consistently high *cross*-selectivity. This result is consistent with the those of a Ti-crossed Claisen condensation.[3] A terminal double bond, Cl atom, and methyl ester, cyclopropane functionalities were tolerated during the present reaction.

Next, we turned our attention to the reaction using methyl α-bromo-α,α-disubstituted carboxylates **1d**–**1f**. Because the desired β-keto ester product **3** lacks the ability to form stable β-keto ester metal enolates, the retro-Claisen condensation generally predominates.[1] Nonetheless, the desired reaction proceeded smoothly. Table 2 lists the successful results of the present protocol for obtaining various α,α-dialkyl-β-ketoesters **3** (15 examples; 73–94%).[9]

A plausible reaction mechanism is as follows. Acid chrorides couple with *N*-methylimidazole to form reactive acylammonium intermediate **4**. As Hashimoto's group proposed,[5] titanium enolate **5** is generated from α-bromoesters **1** by the action of $TiCl_4$–Ph_3P. Finally, Ti-Claisen condensation between **4** and **5** proceeds to give β-ketoesters **2** or **3** (Scheme 3).

In conclusion, we developed a reductive Ti-crossed Claisen condensation between a 1:1 mixture of acid chlorides and methyl α-bromocarboxylates. The present method will provide a new protocol for the synthesis of a variety of α-mono or α,α-disubstituted β-keto esters.



Scheme 3.

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Dedicated to Prof. Teruaki Mukaiyama on the occasion of his 80th birthday.

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6 At present, the reason for obtaining of self-condensation product is not so clear.

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9 General procedure: PPh_3 (210 mg, 0.8 mmol) in CH_2Cl_2 (1.0 mL) and $TiCl_4$ (323 mg, 1.7 mmol) were successively added to a stirred solution of an acid chloride (0.5 mmol), *N*-methylimidazole (49 mg, 0.6 mmol), and an α-bromoester (0.5 mmol) in CH_2Cl_2 (2.0 mL) at -45––-50 °C under an Ar atmosphere, followed by being stirred at same temperature for 1–2 h. The mixture was quenched with water (5.0 mL), which was extracted twice with ether. The combined organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. The obtained crude product was purified by SiO_2-column chromatography (Hexane/Et_2O = 3:1–80:1) to give the desired product.

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