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InI_3/Me_3SiI-catalyzed Direct Alkylation of Enol Acetates Using Alkyl Acetates or Alkyl Ethers

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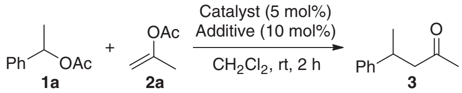
A combined Lewis acid of InI_3 and Me_3SiI was used to catalyze the direct coupling reactions of enol acetates with alkyl acetates or alkyl ethers without generating metal waste. The easily-handled alkylating reagents enlarged the application area of this coupling reaction.

The α-alkylation of carbonyl compounds is one of the most fundamental carbon–carbon bond-forming reactions in organic synthesis. In particular, the coupling reaction between alkyl electrophiles and metal enolates is a useful protocol,[1–4] but metal enolates often lead to problems with handling, poor chemoselectivity, and the generation of metal wastes. Therefore, we focused on the displacement of metal enolates to enol acetates, which are helpful metal-free enol derivatives in terms of availability, easy handling, and stability.[5] We recently developed the direct coupling between enol acetates and either alcohols or silyl ethers.[5e,5g] However, these couplings have some disadvantages, as alcohols often cause alcoholysis of substrates, and silyl ethers bring silyl compounds as a side product. Therefore, we wish to report the direct coupling of enol acetates with either alkyl acetates or alkyl ethers, which were activated by a combined Lewis acid of InI_3 and Me_3SiI.[6]

The effects of Lewis acid catalysts were evaluated in the reaction of secondary benzylic acetate **1a** with enol acetate **2a** (Table 1). The use of InI_3, which is based on our previous work, gave the desired α-alkylated ketone **3** in unsatisfying yield of 54% (Entry 1).[5e,5g] However, the addition of Me_3SiI increased the yield to a quantitative value (Entry 2). No catalytic attribute of Me_3SiI indicated a high plausibility for the cooperation of InI_3 with Me_3SiI (Entry 3).[7] Although the reaction between Me_3SiI and ester moieties had been expected,[8] the combination catalyst selectively promoted the desired coupling. Combinations using either $InCl_3$ or $InBr_3$ were inferior to that using InI_3 (Entries 4 and 5). Representative Lewis acids such as $Sc(OTf)_3$, $ZnCl_2$, $BF_3{\cdot}OEt_2$, and $AlCl_3$ provided unsatisfying results even in the presence of Me_3SiI (Entries 6–9).

Table 1. Screening of catalysts[a]



Entry	Catalyst	Additive	Yield/%[b]
1	InI_3	—	54
2	InI_3	Me_3SiI	quant.
3	—	Me_3SiI	0
4	$InCl_3$	Me_3SiI	72
5	$InBr_3$	Me_3SiI	87
6	$Sc(OTf)_3$	Me_3SiI	27
7	$ZnCl_2$	Me_3SiI	0
8	$BF_3{\cdot}OEt_2$	Me_3SiI	0
9	$AlCl_3$	Me_3SiI	0

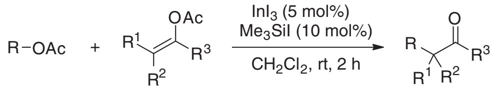
[a]Reaction conditions: alkyl acetate **1a** (1 mmol), enol acetate **2a** (2 mmol), Lewis acid (0.05 mmol), Me_3SiI (0.1 mmol), CH_2Cl_2 (2 mL), rt, 2 h. [b]Yields were determined by ^1H NMR analysis using an internal standard for crude products.

With the optimized conditions in hand, we investigated the scope and limitations of alkyl acetates **1** and enol acetates **2** (Table 2). Enol acetate **2b** derived from acetophenone gave the α-alkylated aromatic ketone **4** quantitatively (Entry 1). The reactions using aliphatic enol acetates **2c** and **2d** furnished the corresponding products effectively (Entries 2 and 3). Unsymmetrical ketone-derived **2e** was applicable without isomerization (Entry 4). Sterically hindered **2f** also provided the desired product **8** and led to the constitution of a quaternary carbon center at the α-position of the carbonyl group (Entry 5). Unexpectedly, in the reaction using aldehyde-derived enol acetate **2g**, geminal diacetate **9** was obtained instead of the α-alkylated aldehyde product (Entry 6). This result indicates that the α-alkylated aldehyde reacted with acetic anhydride which was generated as a side product.[9,10] Although primary benzylic acetate **1b** did not produce the desired α-alkylated ketone, allylic and propargylic acetates effectively gave the corresponding products **11** and **12**, respectively (Entries 7–9).

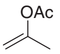
To our delight, we found that alkyl ethers instead of alkyl acetates were also applicable in the reaction conditions using the InI_3/Me_3SiI combined system, and the results are summarized in Table 3. Secondary benzylic and benzhydryl methyl ethers provided the corresponding α-alkylated ketones **3** and **14** in 89 and 98% yields, respectively (Entries 1 and 2). Gratifyingly, benzyl methyl ether (**13c**) furnished **10** in 41% yield despite the inertness of benzyl acetate (**1b**), as shown in Entry 7, Table 2 (Entry 3). Although the reason for this result cannot yet be explained, alkyl methyl ethers could be used in a supplemental fashion. The reactions using methyl ethers **13d** proceeded to give desired products effectively (Entry 4). Unfortunately, *tert*-butyl methyl ether and diisopropyl ether did not provide the corresponding α-alkylated ketones at all, but 1-methoxyadamantane (**13e**) furnished **15** quantitatively (Entry 5). Not only methyl ether but *n*-butyl ether **13f** produced the desired ketone quantitatively (Entry 6). These results, as shown in Table 3, are noteworthy because there have been few reports on the α-alkylation of carbonyl compounds by the direct use of alkyl ethers as an alkyl electrophile.[3] In addition, the generation of alkyl acetate as a side product is an advantage of this system in terms of preventing side reactions.

Figure 1 shows a plausible mechanism. First, InI_3 and Me_3SiI form a combined Lewis acid **16**, and the silicon center of

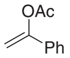
Table 2. Reactions of alkyl acetate **1** with various enol acetates **2**[a]



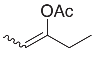
1 **2** **4-12**



2a

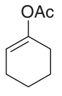


2b

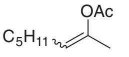


(*E*/*Z* = 69:31)

2c

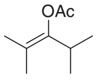


2d

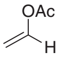


(*E*/*Z* = 67:33)

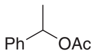
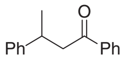
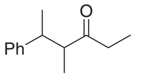
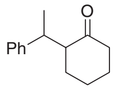
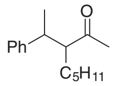
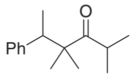
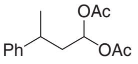
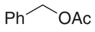
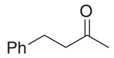
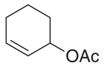
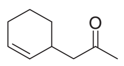
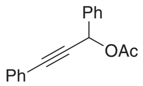
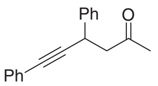
2e



2f



2g

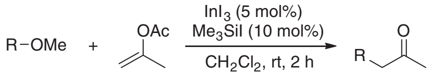
Entry	Alkyl acetate	1	2	Product		Yield / %[b]
1		**1a**	**2b**		**4**	quant. (58)
2		**1a**	**2c**		**5**	quant. (68)[c]
3		**1a**	**2d**		**6**	77 (59)[d]
4		**1a**	**2e**		**7**	98 (60)[e]
5[f]		**1a**	**2f**		**8**	51 (36)
6[g]		**1a**	**2g**		**9**	53 (45)
7[f]		**1b**	**2a**		**10**	0
8[h]		**1c**	**2a**		**11**	74 (45)
9[i]		**1d**	**2a**		**12**	67 (48)

[a]Reaction conditions: alkyl acetate **1** (1 mmol), enol acetate **2** (2 mmol), InI_3 (0.05 mmol), Me_3SiI (0.1 mmol), CH_2Cl_2 (2 mL), rt, 2 h. [b]Yields were determined by ^1H NMR analysis using an internal standard for crude products. Values in parentheses are isolated yields. [c]dr 64:36. [d]dr 59:41. [e]dr 55:45. [f]$ClCH_2CH_2Cl$ (2 mL), 83 °C, 2 h. [g]**2g** (5 mmol), $ClCH_2CH_2Cl$ (2 mL), 83 °C, 1 h. [h]0 °C, 2 h. [i]MeCN (2 mL), rt, 2 h.

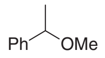
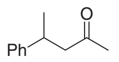
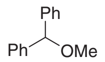
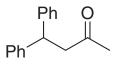
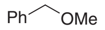
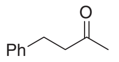
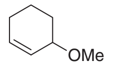
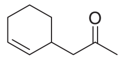
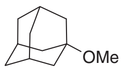
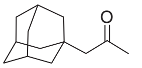
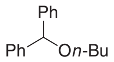
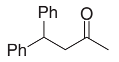
16 interacts with the leaving group (OR′) of **17**, as illustrated. Then, cationic species **18** is generated along with the elimination of Me_3SiOR' **19**. Enol acetate **2** reacts with **18** to produce α-alkylated carbonyl compound **20**. Finally, acyl cationic species **21** reacts with **19** to regenerate the combined Lewis acid InI_3/Me_3SiI with the formation of a metal-free side product **22**.[11]

In conclusion, the direct coupling between enol acetates and alkyl electrophiles, such as alkyl acetates and alkyl ethers, was catalyzed via the combination catalyst InI_3/Me_3SiI. This reaction system is environmentally benign, as it produces no metal waste.

Table 3. Reactions of various alkyl ethers **13** with enol acetate **2a**[a]



13 **2a**

Entry	Alkyl ether	13	Product		Yield /%[b]
1		**13a**		**3**	89 (68)
2		**13b**		**14**	98 (84)
3[c]		**13c**		**10**	41 (35)
4[d]		**13d**		**11**	58 (40)
5[c]		**13e**		**15**	quant. (74)
6		**13f**		**14**	quant. (90)

[a]Reaction conditions: alkyl ether **13** (1 mmol), enol acetate **2a** (2 mmol), InI_3 (0.05 mmol), Me_3SiI (0.1 mmol), CH_2Cl_2 (2 mL), rt, 2 h. [b]Yields were determined by ^1H NMR analysis using an internal standard for crude products. Values in the parenthesis are isolated yields. [c]$ClCH_2CH_2Cl$ (2 mL), 83 °C, 2 h. [d]0 °C, 2 h.

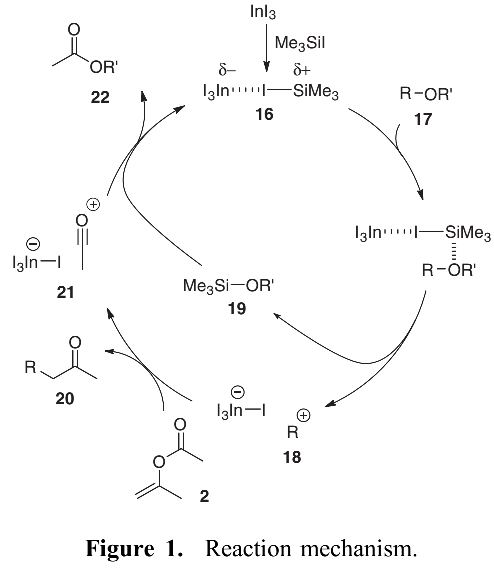


Figure 1. Reaction mechanism.

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7 Other combinations of indium halides and trimethylsilyl halides were investigated; see Supporting Information.[12]

8 For a review on synthetic applications of Me_3SiI, see: G. A. Olah, S. C. Narang, *Tetrahedron* **1982**, *38*, 2225.

9 P. G. M. Wuts, T. W. Greene, in *Greene's Protective Groups in Organic Synthesis*, 4th ed., WILEY, New York, **2007**, Chap. 4, pp. 446–447.

10 Selected papers, see: a) K. S. Kochhar, B. S. Bal, R. P. Deshpande, S. N. Rajadhyaksha, H. W. Pinnick, *J. Org. Chem.* **1983**, *48*, 1765. b) V. K. Aggarwal, S. Fonquerna, G. P. Vennall, *Synlett* **1998**, 849. c) L. Yin, Z.-H. Zhang, Y.-M. Wang, M.-L. Pang, *Synlett* **2004**, 1727.

11 Acetic anhydride and methyl acetate were observed in situ by ^{1}H and ^{13}C NMR.

12 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.