DOI: 10.1002/anie.200702798

Synthetic Methods

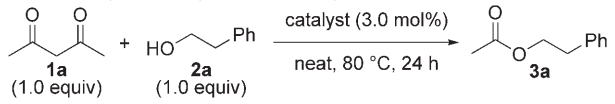
Indium-Catalyzed Retro-Claisen Condensation**

Atsushi Kawata, Kazumi Takata, Yoichiro Kuninobu, and Kazuhiko Takai**

Esters are indispensable compounds both in daily life and in academic and industrial laboratories. Thus, efficient methods for synthesizing esters are important.[1] To date, various methods have been employed for this purpose, including condensation of alcohols and carboxylic acids,[2,3] acid anhydrides,[4] or acyl halides;[5] transesterification;[6] ester-interchange reactions;[7] mercury-catalyzed reaction of carboxylic acids with acetylenes;[8] and enzyme-catalyzed methods.[9] Recently, chemical transformations via carbon–carbon bond cleavage have received much attention, because new skeletons can be constructed directly by using such reactions.[10] We report herein indium-catalyzed synthesis of esters via carbon–carbon bond cleavage, that is, retro-Claisen condensation.[11]

The reaction of 2,4-pentanedione (**1a**) with 2-phenylethanol (**2a**) in the presence of $[\{ReBr(CO)_3(thf)\}_2]$ as the catalyst at 80 °C for 24 h gave phenethyl acetate (**3a**) in 49% yield (Table 1, entry 1). In this reaction, starting materials **1a** and **2a** remained, and acetone was formed as a single side product. The reaction did not proceed in the absence of the catalyst (Table 1, entry 9). To improve the yield of the acetate, several Lewis acids were investigated (Table 1, entries 2–8). Scandium(III) triflate provided **3a** in 72% yield (Table 1, entry 2). This reactivity differs from that of ytterbium(III) triflate, despite the fact that scandium and ytterbium belong to the same group. Ytterbium(III) triflate provides a β-keto enol ether through nucleophilic attack of an alcohol on a 1,3-diketone followed by dehydration,[12] whereas lanthanum(III) triflate provided **3a** in 22% yield (Table 1, entry 3). The reaction proceeded smoothly with copper(II) triflate, and **3a** was obtained in 92% yield (Table 1, entry 4); however, copper(II) acetate did not catalyze the reaction (Table 1, entry 5). Silver(I) triflate gave **3a** in low yield (Table 1, entry 6). When indium(III) triflate was used as catalyst, **3a** was formed quantitatively (Table 1, entry 7).

Table 1: Catalytic activity of metal complexes.



Entry	Catalyst	Yield [%][a]	Entry	Catalyst	Yield [%][a]
1[b]	$[\{ReBr(CO)_3(thf)\}_2]$	49	6	AgOTf	4
2	$Sc(OTf)_3$	72	7	$In(OTf)_3$	98
3	$La(OTf)_3$	22	8	$InCl_3$	20
4	$Cu(OTf)_2$	92	9	none	0
5	$Cu(OAc)_2$	0			

[a] Determined by ^1H NMR spectroscopy. [b] 1.5 mol%.

The treatment of dissymmetric 1,3-diketone **1b** with 2-phenylethanol (**2a**) in the presence of 3 mol% of indium(III) triflate under solvent-free conditions at 80 °C for 24 h afforded phenethyl acetate (**3a**) with high selectivity, and benzoate **3b** was obtained as a side product (Table 2, entry 1). The 1,3-diketone bearing two phenyl groups provided the corresponding benzoate **3b** in 90% yield (Table 2, entry 2). Cyclohexane-1,3-dione (**1d**) afforded δ-keto ester **3c** by a ring-opening reaction in 95% yield, without any side products (Table 2, entry 3). A 1,3-diketone with a substituent on the active methylene moiety, namely, **1e**, gave the corresponding acetate **3a** in 95% yield (Table 2, entry 4). On using 2-acetylcyclopentanone (**1f**), the five-membered ring was opened, and ε-keto ester **3d** was produced in 86% yield (Table 2, entry 5).

Next we investigated several alcohols (Table 3). Alkyl alcohols **2a** and **2b** furnished acetates **3a** and **3e** in 95% and 94% yields, respectively (Table 3, entries 1 and 2).[13] Allyl alcohol afforded the corresponding allyl ester in 78% yield. However, it was difficult to isolate the allyl ester because of its low boiling point. Thus, 1,3-diketone **1a** was changed to 2-acetylcyclohexanone (**1g**). Treatment of **1g** with allyl alcohol **2c** provided allyl ester **3f** in 90% yield of isolated product (Table 3, entry 3). Alcohols containing functional groups such as carbon–carbon double and triple bonds, bromide, and ether groups remained unchanged during the reaction, and the corresponding acetates were formed in good to excellent yields (Table 3, entries 4–8).

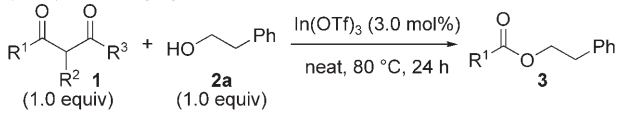
The proposed reaction mechanism (Scheme 1) is as follows: 1) coordination of a 1,3-dicarbonyl compound to a metal center (Lewis acid), 2) nucleophilic attack of an alcohol on a carbonyl group of 1,3-dicarbonyl compounds, 3) carbon–carbon bond cleavage in a retro-aldol-type reaction to give an ester, and 4) quenching of the resulting enolate by a proton to regenerate the metal catalyst. In this reaction, step 3 is important because it leads to the formation of esters and determines the activity of the reaction.

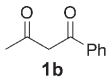
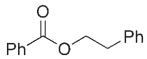
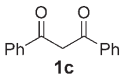
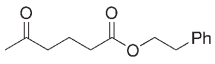
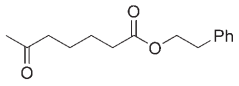
[*] A. Kawata, K. Takata, Dr. Y. Kuninobu, Prof. Dr. K. Takai
Division of Chemistry and Biochemistry
Graduate School of Natural Science and Technology
Okayama University
Tsushima, Okayama 700-8530 (Japan)
Fax: (+81) 86-251-8094
E-mail: kuninobu@cc.okayama-u.ac.jp
ktakai@cc.okayama-u.ac.jp

[**] Financial support by a Grant-in-Aid for Scientific Research on Priority Areas (No. 18037049, "Advanced Molecular Transformations of Carbon Resources") from the Ministry of Education, Culture, Sports, Science, and Technology of Japan, and for Young Scientists (B) (No. 18750088) from Japan Society for the Promotion of Science, and Okayama Foundation for Science and Technology is gratefully acknowledged.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

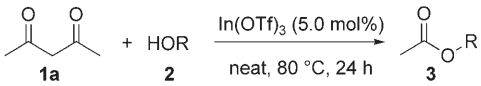
Table 2: Indium-catalyzed reaction of a 1,3-dicarbonyl compound **1** with 2-phenylethanol (**2a**).

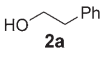
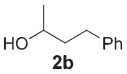
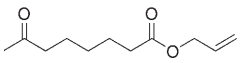
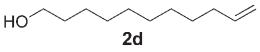
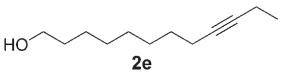
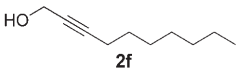
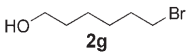
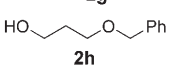


Entry	1,3-Dicarbonyl compound	Yield [%][a]	
1	 **1b**	**3a** 90 (93)	 **3b** 0 (2)
2[b]	 **1c**	**3b** 90 (92)	
3[c]	 **1d**	 **3c** 95 (98)	
4	 **1e**	**3a** 95 (98)	
5[d]	 **1f**	 **3d** 86 (88)	**3a** 4 (9)

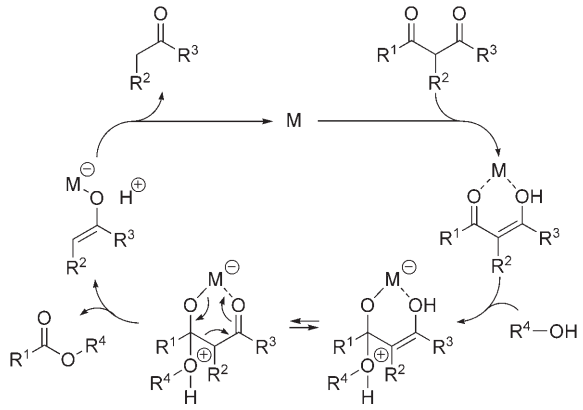
[a] Yield of isolated product. Yield determined by ^{1}H NMR spectroscopy is reported in parentheses. [b] **2a** (1.2 equiv), 115 °C. [c] **2a** (1.5 equiv), 115 °C. [d] **2a** (1.2 equiv).

Table 3: Indium-catalyzed reaction of 2,4-pentanedione (**1a**) with alcohol **2**.[a]



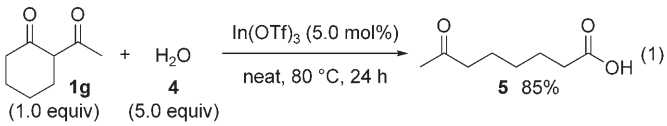
Entry	Alcohol	Yield [%][b]
1[c]	 **2a**	**3a** 95 (98)
2	 **2b**	**3e** 94 (96)
3[d]	 **2c**	 **3f** 90 (93)
4	 **2d**	**3g** 93 (>99)
5	 **2e**	**3h** 97 (>99)
6	 **2f**	**3i** 85 (86)
7	 **2g**	**3j** 91 (95)
8	 **2h**	**3i** 90 (91)

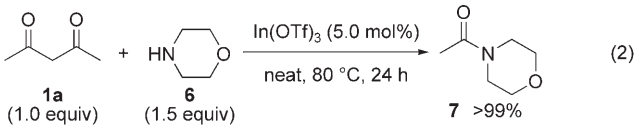
[a] **1a** (2.0 equiv), **2** (1.0 equiv). [b] Yield of isolated product. Yield determined by ^{1}H NMR is reported in parentheses. [c] $In(OTf)_3$ (3.0 mol%). [d] 2-Acetylcyclohexanone was used as 1,3-diketone.



Scheme 1. Proposed mechanism for the formation of esters.

On using water (**4**) or amine **6** instead of alcohols **2**, similar reactions proceeded, and the corresponding carboxylic acid **5** and amide **7** were obtained in 85 % and 99 % yields, respectively [Eqs. (1) and (2)].





In summary, we have developed the indium-catalyzed synthesis of esters by reactions of 1,3-dicarbonyl compounds with alcohols. These reactions proceed by nucleophilic attack of alcohols on a carbonyl group of 1,3-diketones and carbon–carbon bond cleavage in a retro-aldol-type reaction. From a different viewpoint, this can be regarded as a deacylation reaction. Water and an amine could also be used as nucleophiles, and resulted in the corresponding carboxylic acid and amide.

Experimental Section

Synthesis of ester **3a** (Table 3, entry 1): A mixture of 2,4-pentanedione (**1a**, 0.5 mmol), 2-phenylethanol (**2a**, 0.25 mmol), and $In(OTf)_3$ (4.2 mg, 0.0075 mmol) was stirred at 80 °C for 24 h. The product was isolated by column chromatography on silica gel to give **3a** as a colorless liquid.

Received: June 25, 2007
Published online: September 4, 2007

Keywords: C–C activation · esters · indium · retro reactions · synthetic methods

[1] *Esterification* (Ed.: J. Otera), Wiley-VCH, Weinheim, **2003**.

[2] a) G. Benz in *Comprehensive Organic Synthesis*, *Vol. 6* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, pp. 323 – 380; b) T. W. Greene, P. G. Wuts, *Protective Groups in Organic Synthesis*, 3rd ed., Wiley, New York, **1999**, pp. 369 – 453.

[3] a) S. W. Wright, D. L. Hageman, A. S. Wright, L. D. McClure, *Tetrahedron Lett.* **1997**, *38*, 7345 – 7348; b) K. Ishihara, S. Ohara, H. Yamamoto, *Science* **2000**, *290*, 1140 – 1142; c) J. Xiang, A. Orita, J. Otera, *Angew. Chem.* **2002**, *114*, 4291 – 4293; *Angew. Chem. Int. Ed.* **2002**, *41*, 4117 – 4119; d) K. Ramalinga, P. Vijayalakshmi, T. N. B. Kaimal, *Tetrahedron Lett.* **2002**, *43*, 879 – 882.

[4] a) K. Ishihara, M. Kubota, H. Kurihara, H. Yamamoto, *J. Org. Chem.* **1996**, *61*, 4560 – 4567; b) J.-H. Sun, C. A. Teleha, J.-S. Yan, J. D. Rodgers, D. A. Nugiel, *J. Org. Chem.* **1997**, *62*, 5627 – 5629; c) P. A. Procopiou, S. P. D. Baugh, S. S. Flack, G. G. A. Inglis, *J. Org. Chem.* **1998**, *63*, 2342 – 2347; d) K. Ishihara, A. Hasegawa, H. Yamamoto, *Angew. Chem.* **2001**, *113*, 4201 – 4203; *Angew. Chem. Int. Ed.* **2001**, *40*, 4077 – 4079; e) A. Orita, C. Tanahashi, A. Kakuda, J. Otera, *J. Org. Chem.* **2001**, *66*, 8926 – 8934; f) K. Mikami, Y. Mikami, H. Matsuzawa, Y. Matsumoto, J. Nishikido, F. Yamamoto, H. Nakajima, *Tetrahedron* **2002**, *58*, 4015 – 4021.

[5] a) C. McNicholas, T. J. Simpson, N. J. Willett, *Tetrahedron Lett.* **1996**, *37*, 8053 – 8056; b) T. Oriyama, Y. Hori, K. Imai, R. Sasaki, *Tetrahedron Lett.* **1996**, *37*, 8543 – 8546.

[6] a) J. Otera, N. Dan-oh, H. Nozaki, *J. Org. Chem.* **1991**, *56*, 5307 – 5311; b) T. Hanamoto, Y. Sugimoto, Y. Yokoyama, J. Inanaga, *J. Org. Chem.* **1996**, *61*, 4491 – 4492; c) D. Tashiro, Y. Kawasaki, S. Sakaguchi, Y. Ishii, *J. Org. Chem.* **1997**, *62*, 8141 – 8144; d) H. Hagiwara, K. Morohashi, H. Sakai, T. Suzuki, M. Ando, *Tetrahedron* **1998**, *54*, 5845 – 5852; e) J. Xiang, S. Toyoshima, A. Orita, J. Otera, *Angew. Chem.* **2001**, *113*, 3782 – 3784; *Angew. Chem. Int. Ed.* **2001**, *40*, 3670 – 3672; f) M.-H. Lin, T. V. RajanBabu, *Org. Lett.* **2002**, *4*, 1607 – 1610.

[7] a) T. Okano, Y. Hayashizaki, J. Kiji, *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1863 – 1865; b) M. G. Stanton, M. R. Gagne, *J. Am. Chem. Soc.* **1997**, *119*, 5075 – 5076; c) M. G. Stanton, C. B. Allen, R. M. Kissling, A. L. Lincoln, M. R. Gagne, *J. Am. Chem. Soc.* **1998**, *120*, 5981 – 5989.

[8] a) P. F. Hudrlik, A. M. Hudrlik, *J. Org. Chem.* **1973**, *38*, 4254 – 4258; b) T. Mitsudo, Y. Hori, Y. Yamakawa, Y. Watanabe, *Tetrahedron Lett.* **1986**, *27*, 2125 – 2126; c) Y. Kita, H. Maeda, K. Omori, T. Okuno, Y. Tamura, *J. Chem. Soc. Perkin Trans. 1* **1993**, 2999 – 3005.

[9] a) G. Kirchner, M. P. Scollar, A. M. Klibanov, *J. Am. Chem. Soc.* **1985**, *107*, 7072 – 7076; b) P. E. Sonnet, *J. Org. Chem.* **1987**, *52*, 3477 – 3479; c) R. Morrone, M. Piattelli, G. Nicolosi, *Eur. J. Org. Chem.* **2001**, 1441 – 1443.

[10] a) M. Murakami, Y. Ito, *Top. Organomet. Chem.* **1999**, *3*, 97 – 129 (Ed.: S. Murai); b) C.-H. Jun, *Chem. Soc. Rev.* **2004**, *33*, 610 – 618.

[11] There have been several reports on transformations by retro-Claisen condensation. For examples, see: a) W. C. Han, K. Takahashi, J. M. Cook, U. Weiss, J. V. Silverton, *J. Am. Chem. Soc.* **1982**, *104*, 318 – 321; b) Yu. G. Yatluk, S. V. Chernyak, A. L. Suvorov, E. A. Khrustaleva, V. I. Abramova, *Russ. J. Gen. Chem.* **2001**, *71*, 965 – 967; c) G. Grogan, J. Graf, A. Jones, S. Parsons, N. J. Turner, S. L. Flitsch, *Angew. Chem.* **2001**, *113*, 1145 – 1148; *Angew. Chem. Int. Ed.* **2001**, *40*, 1111 – 1114.

[12] M. Curini, F. Epifano, S. Genovese, *Tetrahedron Lett.* **2006**, *47*, 4697 – 4700.

[13] Tertiary and benzyl alcohols provided esters in low yields because another type of reaction proceeded. We will report these results elsewhere.

