

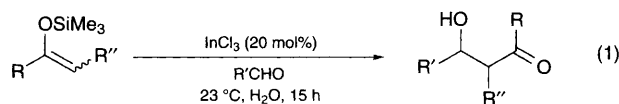
Indium trichloride catalysed Mukaiyama aldol reaction in water

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In the presence of a catalytic amount of indium(III) chloride (InCl_3) (20 mol%), aldehydes react smoothly with ketone trimethylsilyl enol ethers in water to afford the corresponding aldol adducts in good yields.

The Mukaiyama aldol reaction has become one of the most important C–C bond formation reactions for acyclic stereo-control.¹ Conventional methodology requires the reaction to be carried out under strict anhydrous and non-protic conditions.^{2–3} Recently, Kobayashi has shown that lanthanide triflates are excellent catalysts which promote the Mukaiyama aldol reaction in aqueous media.^{4–5} However, efforts to carry out the experiment in water afforded the products in only low yield. Here we demonstrate for the first time that the use of indium trichloride (InCl_3)⁶ is an efficient catalyst in Mukaiyama type reactions involving silyl enol ethers and aldehydes in water and affords the corresponding products in good yields at room temperature [eqn. (1)].



The reactions of several aldehydes with silyl enol ether **1** were conducted at ambient temperature in water in the presence of indium trichloride.† The results are summarized in Table 1.

Generally, the reactions were clean and the corresponding aldol products were obtained in high yields. In every case, the reactions proceeded smoothly under extremely mild conditions (almost neutral) to give the corresponding β -hydroxy carbonyl

compounds in high yields. The aqueous phase with the InCl_3 can be reused without a decrease in yields (Table 1, entry 1). Only a catalytic amount of InCl_3 (20 mol%)‡ was required to complete the reaction. The reaction proceeded smoothly either in THF or water. Of special interest was the fact that water soluble aldehydes such as glyoxylic acid and commercial formaldehyde solution could be used directly for these reactions.

In order to ascertain that the reaction was not catalysed by the presence of any adventitious HCl, we carried out a series of aldol experiments of benzaldehyde with silyl enol ether **1** with various molarities of HCl. It is interesting to note that when the reaction was carried out in 0.1 and 0.2 mol dm^{-3} solutions of HCl, no aldol product was observed even after stirring for 1 d. At a higher molarity (0.3 mol dm^{-3} and above), the silyl enol ether immediately hydrolysed to give the original ketone and no aldol adduct was obtained. In effect, the catalysis of this aqueous Mukaiyama type reaction may be totally attributed to the presence of InCl_3 .

Having ascertained the efficiency of indium trichloride as a good catalyst in the aldol reactions involving an open-chain silyl enol ether, this methodology was extended to a cyclic silyl enol ether. Thus, when trimethylsilyloxycyclohexene **2** was also treated with various aldehydes in the presence of InCl_3 in water, the corresponding β -ketoalcohols were again obtained in excellent yields as shown in Table 2.

A significant finding was the preferred formation of the *anti*-aldol stereoisomer in all cases except for 2-pyridine carboxaldehyde (Table 2, entry 4). It is worth noting that the preference of the *anti*-isomer is in accordance with the classical Mukaiyama aldol reaction.²


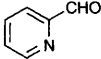
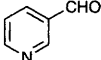
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Table 1 Indium trichloride-promoted Mukaiyama aldol reaction in water^a

Entry	Aldehyde	Silyl enol ether	Conditions	Yield (%) ^b
1	PhCHO		InCl_3 (20 mol%), H_2O (15 h)	88 (82) ^c
2	PhCHO	1	InCl_3 (20 mol%), THF (15 h)	85
3	HCHO	1	InCl_3 (20 mol%), H_2O (15 h)	91
4	$\text{HO}_2\text{CCHO}-\text{H}_2\text{O}$	1	InCl_3 (20 mol%), H_2O (15 h)	91
5		1	InCl_3 (20 mol%), H_2O (15 h)	96
6		1	InCl_3 (20 mol%), H_2O (15 h)	96

^a All reactions were carried out on a 0.5–1 mmol scale. ^b Isolated yield. ^c Yield (in parenthesis) obtained from reused InCl_3 .

Table 2 Indium trichloride-promoted Mukaiyama aldol reaction in water^a

Entry	Aldehyde	Silyl enol ether	Conditions	<i>anti</i> : <i>syn</i> ^b	Yield ^c (%)
1	HCHO		InCl ₃ (20 mol%), H ₂ O (15 h)	—	97
2	PhCHO	2	InCl ₃ (20 mol%), H ₂ O (15 h)	63 : 37	88
3	HO ₂ CCHO-H ₂ O	2	InCl ₃ (20 mol%), H ₂ O (15 h)	81 : 19	87
4		2	InCl ₃ (20 mol%), H ₂ O (15 h)	38 : 62	96
5		2	InCl ₃ (20 mol%), H ₂ O (15 h)	56 : 44	96

^a All reactions were carried out on a 0.5–1 mmol scale. ^b The isomer ratio was determined by ¹H NMR. ^c Isolated yield.

Footnotes

† A typical reaction procedure is as follows: To a solution of benzaldehyde (0.5 mmol, 53.1 mg, 1 equiv.) in the presence of indium trichloride (22.1 mg, 0.1 mmol, 20 mol%) in water (5 ml) was added acetophenone silyl enol ether (192.3 mg, 1 mmol, 2 equiv.). The resulting mixture was stirred at room temp. for 15 h. The product was extracted with ethyl acetate and purified in the usual manner. The corresponding aldol product was obtained in 88% yield (99.5 mg).

‡ We have found that using a smaller amount of InCl₃ (less than 20 mol%) resulted in incomplete reaction even after 20 h of stirring.

References

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- 5 S. Kobayashi and I. Hachiya, *J. Org. Chem.* 1994, **59**, 3590; S. Kobayashi, *Chem. Lett.*, 1991, 2187. Lanthanide triflates were used as catalyst in the Mukaiyama aldol reaction in aqueous media (THF-H₂O = 4 : 1).
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