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On Indium(III) Chloride-Catalyzed Aldol Reactions of Silyl Enol Ethers with Aldehydes in Water

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Abstract: *Contrary to previous reports, it was found that hydrolysis of silyl enol ethers is superior to the desired condensation in $InCl_3$-catalyzed aldol reactions of silyl enol ethers with aldehydes in water. The reactions were found to proceed in certain amounts in the presence of a catalytic amount of a Lewis acid under neat (solvent-free) conditions, while substrate limitation was observed in these reactions. Use of $InCl_3$ as a Lewis acid in aldol reactions in micellar systems is also reported.*

In 1991 we reported the first water-stable Lewis acids, lanthanide triflates, which are excellent catalysts in aldol reactions of silyl enol ethers with aldehydes in aqueous media (water-THF).[1] After this report, we searched for metal salts other than lanthanides which are water-stable, and have found that some copper(II) and other metal salts are also water-stable and can work as Lewis acid catalysts in aqueous solution (water-THF, water-ethanol-toluene, etc.).[2] On the other hand, in 1996 a Singapore group reported that indium(III) chloride ($InCl_3$) was an efficient catalyst in the same aldol reactions of silyl enol ethers with aldehydes and that the reactions proceeded smoothly in pure water (without using organic solvents).[3] Their results were not consistent with the results which we had already obtained. We repeated the reactions and found that our results were reproducible. While several private communications were exchanged with the Singapore group and some discussion with other research groups in this field was performed, the Singapore group reported a revised paper,[4] which partially supported our results, but unfortunately, the conclusions were different from ours. We think this problem includes some significant points in organic synthesis in water, which is of great current interest as a unique reaction in a specific media as well as an environmentally friendly chemical process. In this paper, we would like to report our results and conclusions about this problem.

Our conclusion is that hydrolysis of silyl enol ethers is superior to the desired condensation in the $InCl_3$-catalyzed aldol reactions of silyl enol ethers with aldehydes in water. We tested several reaction procedures and

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conditions in a model reaction of benzaldehyde with 1-phenyl-1-trimethylsiloxyethene (**1**) using 0.2 eq. of $InCl_3$. The reaction was carried out by mixing benzaldehyde, **1**, and $InCl_3$ in water under various conditions, and in almost all cases the yields of the desired adduct were less than 20%.[5-7] The only exception was when water was added after combining all other substances, benzaldehyde, **1**, and $InCl_3$, whereupon the desired aldol adduct was obtained in a 57% yield. We thought at this stage that the reaction of the last case proceeded under neat (solvent-free) conditions (mixing benzaldehyde, **1**, and $InCl_3$ without solvents).[8] Our assumption was confirmed by combining the three compounds, benzaldehyde, **1**, and $InCl_3$ without solvents and monitoring the mixture by TLC. It was found from the TLC that certain amounts of the product formed. After 10 min, a large amount of water was added to quench the reaction. After a usual work up, the aldol adduct was obtained in a 61% yield.

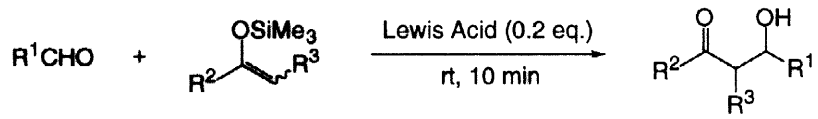
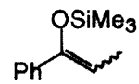
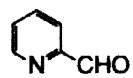


Table 1. Aldol Reactions under Neat (Solvent-Free) Conditions

Aldehyde	Silyl Enol Ether	Lewis Acid	Yield/%
PhCHO	 **1**	$Sc(OTf)_3$	37
		$Yb(OTf)_3$	46 (63)[a]
		$InCl_3$	61
		$Cu(OTf)_2$	57
		$AlCl_3$	49
		$TiCl_4$	47
		$SnCl_4$	27
		$BF_3{\cdot}OEt_2$	44
PhCHO	 **2**	$Sc(OTf)_3$	79
		$Yb(OTf)_3$	13
		$InCl_3$	51
		$Cu(OTf)_2$	19
	**1**	$Sc(OTf)_3$	26
		$InCl_3$	7
C_4H_9CHO	**1**	$Sc(OTf)_3$	15
		$InCl_3$	35
	**2**	$Sc(OTf)_3$	23 (25)[b]
		$Yb(OTf)_3$	4 (17)[b]
		$InCl_3$	5 (27)[b]
		$Cu(OTf)_2$	3 (21)[b]
		$AlCl_3$	trace (25)[b]
		$TiCl_4$	32 (25)[b,c]
		$BF_3{\cdot}OEt_2$	33 (37)[b]

[a]0.1 eq. of $Yb(OTf)_3$ was used. [b]Reaction time, 15 h. [c]Decomposition of the product was observed under the neat conditions.

Actually, the reaction of benzaldehyde with **1** proceeds in certain amounts under neat (solvent-free) conditions using other Lewis acids (Table 1). While a 57% yield of the aldol adduct was obtained when 0.2 eq. of $Cu(OTf)_2$ was used, the yield was improved to 63% when 0.1 eq. of $Yb(OTf)_3$ was used.[9] In the reaction of benzaldehyde with 1-phenyl-1-trimethylsiloxypropene (**2**), $Sc(OTf)_3$ (0.2 eq.) gave better results to afford the corresponding adduct in a 79% yield. In the presence of $InCl_3$, a 51% yield was obtained. On the other hand, it was also found that there was substrate limitation in the neat (solvent-free) aldol reactions. While the yields in the reactions of **2** with benzaldehyde were not very high, much lower yields were observed in the reactions of **2** with 3-phenylpropionaldehyde (a representative aliphatic aldehyde). For example, only a 27% yield of the adduct was obtained after 15 h at rt when 0.2 eq. of $InCl_3$ was used. Similarly, lower yields were observed in the reactions of 2-pyridinecarboxaldehyde and valeraldehyde (see Table 1).

Finally, use of $InCl_3$ in micellar systems was investigated. We have quite recently found that $Sc(OTf)_3$-catalyzed aldol reactions of silyl enol ethers with aldehydes proceeded smoothly in water without using any organic solvents in the presence of a small amount of a surfactant.[10] It was revealed from mechanistic studies that micelles were formed and that excellent hydrophobic reaction fields were constructed under these conditions. We tested the use of $InCl_3$ as a Lewis acid catalyst in these micellar systems. The reactions were carried out in the presence of 0.2 eq. of the Lewis acid and 0.2 eq. of sodium dodecylsulfate (SDS, 35 mM) at rt in water. Benzaldehyde and 3-phenylpropionaldehyde reacted with **2** under these conditions to afford the corresponding aldol adducts in 75% and 54% yields, respectively,[11] although the yields were not yet optimized. As water-stable Lewis acids, some scandium, yttrium, lanthanides, and copper salts are known, and it has been demonstrated that $InCl_3$ can also be used as a Lewis acid catalyst in the micellar systems (in the presence of a small amount of a surfactant in water) and that the catalytic ability of $InCl_3$ in the systems is similar to that of $Cu(OTf)_2$ (Table 2).

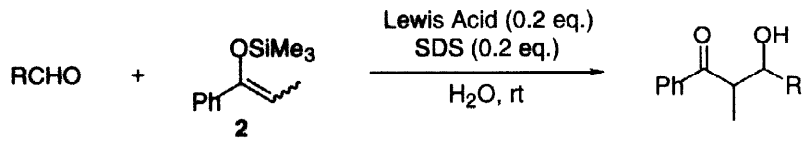


Table 2. Aldol Reactions in Micellar Systems

Aldehyde	Lewis Acid	Reactin Time/h	Yield/%
PhCHO	$Sc(OTf)_3$	4	88[a]
	$Yb(OTf)_3$	15	17
	$InCl_3$	8	75
	$Cu(OTf)_2$	15	69
Ph⌒CHO	$Sc(OTf)_3$	4	86[a]
	$Yb(OTf)_3$	15	21
	$InCl_3$	8	54
	$Cu(OTf)_2$	15	54

[a]Ref. 9. 0.1 eq. of the Lewis acid was used.

In summary, it was revealed that $InCl_3$-catalyzed aldol reactions of silyl enol ethers with aldehydes proceeded sluggishly in water. On the other hand, Lewis acid-catalyzed neat (solvent-free) reactions proceeded smoothly in some cases, but substrate limitation was observed. Finally, it was found that $InCl_3$-catalyzed aldol reactions proceeded smoothly in water using a small amount of a surfactant (in micellar systems).

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References and Notes

(1) Kobayashi, S. *Chem. Lett.* **1991**, 2187-2190; Kobayashi, S. *Synlett* **1994**, 689-701.

(2) Kobayashi, S.; Hachiya, I. *Tetrahedron Lett.* **1992**, *33*, 1625-1628; Kobayashi, S.; Hachiya, I.; Takahori, T. *Synthesis* **1993**, 371-373; Kobayashi, S.; Hachiya, I.; Ishitani, H.; Araki, M. *Synlett* **1993**, 472-474; Kobayashi, S.; Hachiya, I. *J. Org. Chem.* **1994**, *59*, 3590-3596; Kobayashi, S.; Hachiya, I.; Yamanoi, Y. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 2342-2344; Kobayashi, S.; Nagayama, S.; Busujima, T. *Chem. Lett.* **1997**, 959-960. Cf. Otto, S.; Engberts, J. B. F. N. *Tetrahedron Lett.* **1995**, *36*, 2645-2648; Otto, S.; Bertoncin, F.; Engberts, J. B. F. N., *J. Am. Chem. Soc.* **1996**, *118*, 7702-7707.

(3) Loh, T. P.; Pei, J.; Cao, G. Q. *J. Chem. Soc., Chem. Commun.* **1996**, 1819.

(4) Loh, T. P.; Pei, J.; Koh, K. S. V.; Cao, G. Q.; Li, X. R. *Tetrahedron Lett.* **1997**, *38*, 3465-3468; 3993-3994 (Corrigendum).

(5) Including the original procedure reported in Ref. 3 and the improved procedure (Ref. 4). We also checked the effects of $InCl_3$ purchased from some companies, and found that the same results were obtained in all cases. In addition, no significant effect was observed after purification of $InCl_3$ according to the procedure reported in Ref. 4.

(6) In the report from the Singapore group, the yield from the same reaction was 88%.[3]

(7) Water-promoted aldol reactions of silyl enol ethers with aldehydes were reported. Lubineau, A. *J. Org. Chem.* **1986**, *51*, 2142; Lubineau, A.; Meyer, E. *Tetrahedron* **1988**, *44*, 6065.

(8) In Corrigendum, the Singapore group also reported that the reaction proceeded under neat (solvent-free) conditions.

(9) As for the amounts of Lewis acids used, improvement of yields by reducing the amounts was not observed in other cases (Cf. Table 1).

(10) Kobayashi, S.; Wakabayashi, T.; Nagayama, S.; Oyamada, H. *Tetrahedron Lett.* **1997**, *38*, 4559-4562.

(11) Less than 20% yields were observed without a surfactant in water.