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The indium(III) chloride-catalysed hydrolysis and in situ Mukaiyama-type reaction of arylmethyl ketone derived silyl enol ethers under solvent-free conditions

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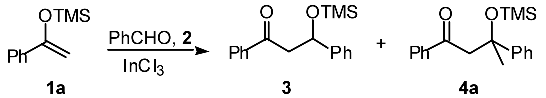
This paper is dedicated with respect and admiration to Professor Teruaki Mukaiyama

Abstract—Treatment of trimethylsilyl enol ethers of arylmethyl ketones with catalytic amounts of indium(III) chloride under solvent-free conditions leads to a remarkably efficient process of in situ hydrolysis and Mukaiyama-type addition to the resulting ketones.

As part of a program directed towards the development of new nucleophilic addition ring closure [NARC]-based synthetic protocols,[1] we had occasion to examine solvent-free[2] $InCl_3$-catalysed Mukaiyama aldol reactions.[3,4] In the case of the reaction of the trimethylsilyl enol ether of acetophenone (**1a**) with benzaldehyde, which was expected to generate **3**, the consistent formation of a by-product (**4a**, Scheme 1) was observed.

Adduct **4a** appeared to be the result of addition of enol ether **1a** to acetophenone rather than to benzaldehyde. As there were several interesting aspects to this discovery a more systematic investigation of the origin and limitations of the process was carried out the results of which are reported here.[5]

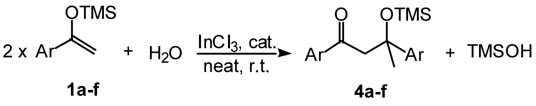
Mukaiyama-type additions of ketone silyl enol ethers to simple ketones have been reported using metallic iodide-activated bismuth(III) chloride,[6] titanium and zirconium triflates[7] and electrogenerated acid catalysis.[8]



Scheme 1. Mukaiyama coupling of silyl enol ethers to aldehydes under neat conditions.

In this work it was found that simply mixing a TMS enol ether, such as **1a**, with a catalytic amount of $InCl_3$ generated the corresponding adduct **4a**. Scheme 2 provides a balanced equation for this process.[9]

The amount of water present in these reactions appears to be critical to the success of the reaction. We found that the combination of the use of flame-dried apparatus and the passage of moist air across the catalyst surface for several minutes prior to addition of the silyl enol ether led to smooth conversion to the corresponding adduct **4** (Table 1, entries 1–6). Under these controlled conditions hydrolysis is apparently sufficiently slow to enable the aldol-like addition to occur. The remaining silyl enol ether essentially 'traps' the ketone as it is formed. In order to minimise hydrolysis of the product silyl ethers it was important to remove the $InCl_3$ prior to chromatography or other manipulations. Hence the crude product was suspended in ethyl acetate and immediately washed with aqueous potassium carbonate. However, in two cases some alcohol was still generated after chromatography (entries 5 and 6).



Scheme 2. Balanced equation for the reaction of arylsilyl enol ethers under $InCl_3$ catalysis.

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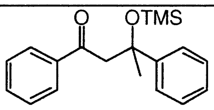
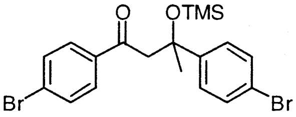
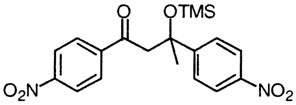
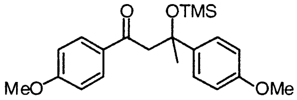
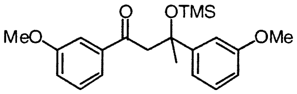
Table 1. $InCl_3$-promoted self-coupling aldol reactions

Entry	Enol ether	Product	$InCl_3$ [mol%]	Reaction time	Yield of **4**[a] [%]
1	**1a**	 **4a**	20	50 min	72
2	**1b**	 **4b**	10	1 h	75 (96[b])
3	**1b**		1	28 h	35[c]
4	**1c**	 **4c**	15	4 h	90
5	**1d**	 **4d**	10	1.2 h	76[d]
6	**1e**	 **4e**	20	1 h	95[e]

a. Isolated yield. b. Yield determined by GC. c. Yield determined by NMR spectroscopy. d. Including 35% of the corresponding alcohol e. Including 22% of the corresponding alcohol.

From Table 1 the process appears to be relatively insensitive to the presence of either electron-withdrawing or electron-donating substituents on the aromatic ring. In addition, catalyst concentrations as low as 1 mol% still gave modest conversion albeit after much longer reaction times (compare entries 2 and 3). Catalyst loadings ranging from 10 to 20 mol% appeared to provide the best conversion.

Remarkably, several of the relatively simple β-hydroxyketone derivatives described here, such as **4b**, **4d** and **4e**, have not been reported previously in the open literature. Some of the adducts were crystalline and the X-ray structure of one of these, **4b**, is shown in Figure 1.[10]

Attempts to apply this procedure to β-substituted enol ethers such as cyclohexanone and propiophenone TMS enol ethers were unsuccessful leading only to hydrolysis of the starting material.

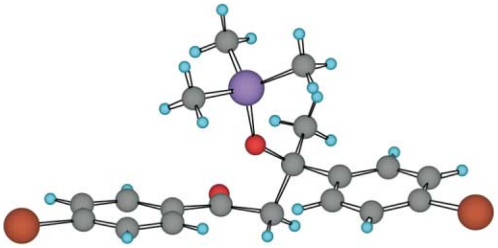
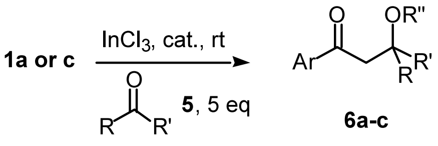


Figure 1. X-Ray crystal structure of adduct **4b**.



a, Ar = Ph, R = R' = CH_3, 60%
b, Ar = Ph, R = CH_3, R' = CH_2CH_3, 58%
c, Ar = p-NO_2Ph, R = R' = CH_3, 42%

Scheme 3. $InCl_3$-catalysed cross-coupling of silyl enol ethers with simple ketones under neat conditions.

It was also of interest to establish whether or not this process could be diverted to enable other ketones to react with silyl enol ethers such as **1a** or **1c**. Indeed employing an excess of acetone (**5a**) or 2-butanone (**5b**), gave the corresponding Mukaiyama-type adducts, **6**, in reasonable (although not optimised) yields (Scheme 3). Adducts **6a** and **6b** were obtained as mixtures of TMS ethers ($R''=TMS$) and free alcohols ($R''=H$) whereas for **6c** only the TMS ether was isolated. In these cases no prior passage of moist air was necessary as there was apparently sufficient water in each of the ketones. Only traces of the 'self-coupled' products, **4a** or **4c**, were observed.

In conclusion, we have discovered a new, operationally simple, mild, solvent-free catalytic process for converting trimethylsilyl enol ethers of arylmethyl ketones into the corresponding β-silyloxyketones of general structures **4** and **6**.

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References

1. Perlmutter, P. In *Topics in Current Chemistry*; Metz, P., Ed.; Springer: Heidelberg, 1997; Vol. 190, p. 87.
2. For a recent review on solvent free reactions, see: Tanaka, K.; Toda, F. *Chem. Rev.* **2000**, *100*, 1025.
3. Mukaiyama, T. *Org. React.* **1982**, *28*, 203.
4. Kobayashi, S.; Busujima, T.; Nagayama, S. *Tetrahedron Lett.* **1998**, *39*, 1579. See also: Loh, T.-P.; Huang, J.-M.; Goh, S.-H.; Vittal, J. J. *Org. Lett.* **2000**, *2*, 1291.
5. For a review of the applications of $InCl_3$ in synthesis, see: Babu, G.; Perumal, P. T. *Aldrichim. Acta* **2000**, *33*, 16.
6. Le Roux, C.; Gaspard-Iloughmane, H.; Dubac, J. *J. Org. Chem.* **1993**, *58*, 1835.
7. Hollis, T. K.; Robinson, N. P.; Bosnich, B. *Tetrahedron Lett.* **1992**, *33*, 6423.
8. Torii, S.; Inokuchi, T.; Takagishi, S.; Horike, H.; Kuroda, H.; Uneyama, K. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 2173.
9. For examples and discussion of $InCl_3$-catalysed Mukaiyama reactions in water, see: Loh, T.-P.; Pei, J.; Cao, G.-Q. *J. Chem. Soc.*, *Chem. Commun.* **1996**, 1819. See also: Loh, T.-P.; Pei, J.; Koh, K. S.-V.; Coao, G.-Q.; Li, X.-R. *Tetrahedron Lett.* **1997**, *38*, 3465 and Ref. 4.
10. Crystallographic data (excluding structure factors) for the structures in this paper, have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 195029. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).