Indium Triflate: An Efficient Catalyst For Acylation Reactions

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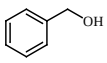
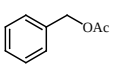
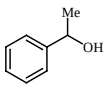
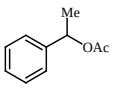
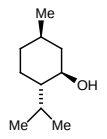
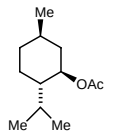
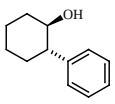
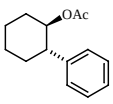
Abstract: Indium triflate is shown to be an extremely efficient catalyst for the acylation of alcohols and amines.

Key words: catalysis, indium, acetylation, alcohols, amines

The Lewis acid catalysed acylation of alcohols and amines with acid anhydrides is a mild, strategic alternative to basic and nucleophilic catalysts such as 4-(dimethylamino)pyridine (DMAP) or 4-pyrrolidinopyridine (PPY).[1] Although a number of catalysts have been reported to be useful, including tantalum chloride,[2] trimethylsilyl triflate[3] and most recently copper triflate,[4] most noteworthy is the reported high activity of scandium triflate in both inter- and intra-molecular esterification reactions.[5] As part of a research programme aimed at developing new indium based Lewis acid catalysts,[6] we have noted the rapid acylation of a diverse range of alcohols and amines using very low catalyst loadings of the considerably cheaper complex indium triflate.[7]

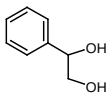
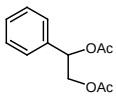
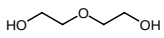
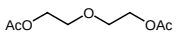
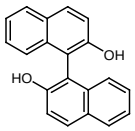
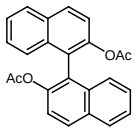
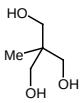
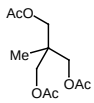
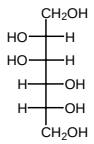
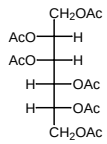
Table 1 The $In(OTf)_3$ catalysed acylation of alcohols

Entry	Alcohol	Time (hours)	Product	Yield (%)
1		0.25		97
2		0.5		98
3		0.5		95
4		0.25		97
5		0.25		97

The optimised acylation reactions were performed by adding acetic anhydride (1.5 equiv. per OH) to the substrate alcohol in acetonitrile at room temperature in the presence of just 0.1 mol % of indium triflate. The reactions were followed by TLC until all the starting material had been consumed and in each case the ^1H NMR of the crude reaction mixture revealed complete conversion to product. After a normal aqueous work-up the mixture was purified by flash chromatography to afford the product in high isolated yield (Table 1).[8]

The efficiency of the indium catalysed acylation reaction was reflected in the acetylation of polyhydroxy compounds under similar conditions. For example, both aliphatic and aromatic polyols were acetylated in very high isolated yield (Table 2).[9] Given the low catalyst loading, the exhaustive acetylation of D-mannitol at room temperature impressively demonstrates the practical utility of this method (Table 2, Entry 5).

Table 2 The $In(OTf)_3$ catalysed acylation of polyols

Entry	Polyol	Product	Yield (%)
1			93
2			92
3			93
4			96
5			94

The presented catalyst system was also effective for the acylation of amines. Aromatic and aliphatic amines were successfully acylated in the presence of 0.1 mol% of indium triflate (Table 3).[10]

Along with the use of acetic anhydride, we explored the utility of other acyl donors including ethyl acetate, acetic acid and 1-cyclohexenyl acetate in the acetylation of ben-

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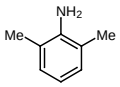
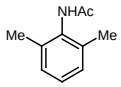
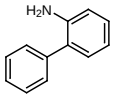
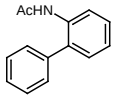
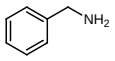
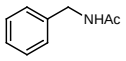
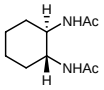
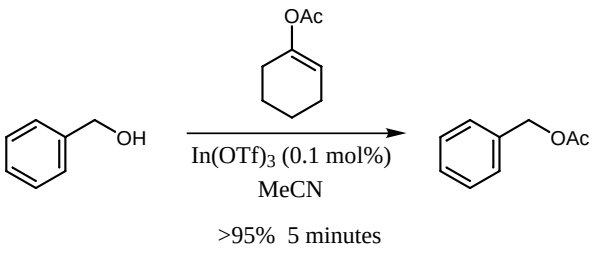
Table 3 The $In(OTf)_3$ catalysed acylation of amines

Entry	Amine	Product	Yield (%)
1			99
2			94
3			92
4			98
5			91

zyl alcohol. Of these, the only effective alternative proved to be 1-cyclohexenyl acetate which prompted an extremely rapid acetylation reaction (Scheme). This is no doubt due to the unstable enol liberated tautomerising instantaneously to the ketone and the reaction becoming completely irreversible.



Scheme

In summary, we have demonstrated that the inexpensive, commercially available complex indium triflate is a powerful catalyst for the acylation of alcohols. Although the optimum system employs enol esters as acyl donors, the relative cost of 1-cyclohexenyl acetate compared with acetic anhydride suggests that for practical purposes acetic anhydride is the donor of choice.

Acknowledgement

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References and Notes

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(6) For previous work on the use of indium complexes as Lewis acids see Ali, T.; Chauhan, K. K.; Frost C. G. *Tetrahedron Lett.* **1999**, 40, 5621 and references therein.
(7) Strem catalogue No. 17, 1997-99; Scandium triflate (min. 97%) £25.00/g; Indium triflate (99%) £8.00/g.
(8) All compounds have been adequately characterised. Acetoxymethylbenzene: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 2.07 (3H, s), 5.09 (2H, s), 7.32-7.35 (5H, m). 1-acetoxy-1-phenylethane: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.53 (3H, d, J=6.6 Hz), 2.06 (3H, s), 5.85 (1H, q, J= 6.6 Hz), 7.24-7.35 (5H, m). (1R)-(-)-menthylacetate: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 0.76 (3H, d, J= 7.0 Hz), 0.89 (3H, d, J= 7.0 Hz), 0.90 (3H, d, J= 6.6 Hz), 0.84-1.14 (3H, m), 1.30-1.60 (2H, m), 1.79-1.93 (2H, m), 1.93-2.04 (2H, m), 2.03 (3H, s), 4.67 (1H, dt, J= 4.4, 10.8 Hz). Trans-(±)-1-acetoxy-2-phenylcyclohexane: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.20-1.60 (4H, m), 1.70-1.90 (4H, m), 1.96 (3H, s), 2.6 (1H, dt, J= 3.8, 10.8 Hz), 4.90 (1H, m), 7.17-7.40 (5H, m). Acetoxybenzene: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 2.23 (3H, s), 7.04-7.36 (5H, m).
(9) All compounds have been adequately characterised. 1,2-diacetoxy-1-phenylethane: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 2.04 (3H, s), 2.11 (3H, s), 4.24-4.35 (2H, m), 6.00 (1H, q, J= 4.2 Hz) 7.26-7.37 (5H, m). bis-2-acetoxyethylether: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 2.09 (6H, d, J= 1.1 Hz), 3.69-3.73 (4H, m), 4.22-4.25 (4H, m). (±)-2,2'-diacetoxy-1,1'-binaphthyl: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.86 (6H, s), 7.16-7.49 (8H, m), 7.92-8.01 (4H, m). 1,1,1-tris-(acetoxymethyl)ethane: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.02 (3H, s), 2.07 (9H, s), 4.00 (6H, s). hexa-O-acetyl-D-mannitol: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 2.06 (6H, s), 2.08 (6H, s), 2.10 (6H, s), 4.10 (4H, m), 5.05 (2H, m), 5.44 (2H, m).
(10) All compounds have been adequately characterised. N-phenylacetamide: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 2.16 (3H, s), 7.07-7.48 (5H, m), 7.65 (1H, br s). N-(2,6-dimethylphenyl)acetamide: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.73 (1H, s), 2.15 (3H, s), 2.19 (6H, s), 7.03-7.17 (3H, m). N-(2-biphenyl)acetamide: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 2.02 (3H, s), 7.15-7.51 (9H, m), 8.24 (1H, d, J= 8.0 Hz). N-benzylacetamide: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 2.03 (3H, s), 4.43 (2H, d, J= 5.7 Hz), 6.17 (1H, br s), 7.27-7.34 (5H, m). trans-diacetamido-(1R, 2R)-(–)-1,2-cyclohexane: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.27 (4H, m), 1.75 (2H, m), 1.94 (6H, s), 2.03 (2H, m), 3.65 (2H, m), 6.15 (2H, br s).

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