Scandium(III) or lanthanide(III) triflates as recyclable catalysts for the direct acetylation of alcohols with acetic acid

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Scandium(III) or lanthanide(III) triflates are found to efficiently catalyse the direct acetylation of primary, secondary or tertiary alcohols with acetic acid; the catalyst can be recovered quantitatively and re-used with no loss of activity.

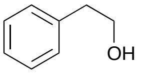
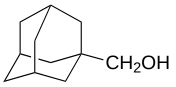
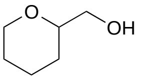
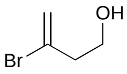
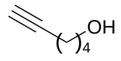
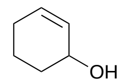
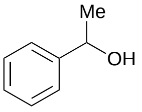
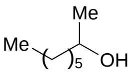
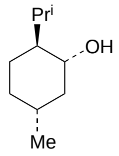
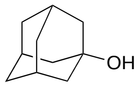
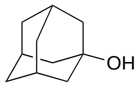
Esterification of carboxylic acids and the acylation of alcohols are fundamental processes in organic chemistry.[1,2] The direct acylation of alcohols with carboxylic acids, the Fischer esterification, can be brought about with mineral acids or sulfonic acids where the only by-product is water, *i.e.* formally an atom economic process.[3] However, the reaction is reversible and typically large excesses of either the alcohol or acid are required. Alternatively, Fischer esterifications can be driven to completion by azeotropic removal of water. However the use of strong mineral acids leads to highly acidic waste streams posing an environmental problem for industrial processes.

In order to circumvent the problem of equilibria, typically acylation of alcohols is performed with activated acyl groupings such as (mixed) acid anhydrides or acid chlorides with a stoichiometric quantity of amine base in the presence of basic catalysts such as 4-dimethylaminopyridine or 4-pyrrolidinopyridine.[2,4] These acylations work extremely well, but from an atom economic standpoint are found wanting when compared to the Fischer esterification. Acylation of alcohols can also be brought about by the action of Lewis acidic reagents in conjunction with carboxylic acids, but the Lewis acid is destroyed in the work-up procedure.[5] Similarly, Lewis acids are known to activate acid anhydrides for the acylation of alcohols,[6] but the conversion is inherently wasteful since half of every acid anhydride molecule is lost as a carboxylic acid. Furthermore, from an industrial point of view, and tonne for tonne, anhydrides are significantly more expensive than the corresponding carboxylic acid.

Lanthanides have found increasing use as mild and selective reagents in organic synthesis.[7] In particular, scandium(iii) or lanthanide(iii) trifluoromethanesulfonates (triflates)[8] have been used to good effect as Lewis acids in Diels–Alder,[9] allylation,[10] Friedel–Crafts[11] and Mukaiyama aldol[12,13] reactions. Many of these publications stress the ability of the catalyst to function effectively in protic media.[13,14] Indeed, for the Mukaiyama reaction the optimum solvent system was found to be aqueous THF, the catalyst recycled *via* aqueous work up and used repeatedly with little detriment to rate or yield.[13] Recently the catalytic use of scandium(iii) triflate has been described for the acylation of alcohols with acid anhydrides, or with carboxylic acids in the presence of 1.5 equiv. of *p*-nitrobenzoic anhydride.[15,16] In a similar vein, the methanolysis of methoxyacetates with ytterbium(iii) triflate has also been reported.[17] The compatibility of lanthanide(iii) triflate salts with water and other protic solvents and yet their apparent ability to function as strong Lewis acids is somewhat paradoxical. We sought to harness this water tolerant Lewis acidity and have instigated a program in the area of clean technology using lanthanide(iii) triflates for atom economic transformations.† In the course of our investigations we found that these lanthanide salts were active acylation catalysts. Herein we report the direct acylation of primary, secondary and tertiary alcohols using acetic acid in the presence of a catalytic quantity of scandium(iii) or lanthanide(iii) triflates. The use of acetic acid rather than acetic anhydride or acetyl chloride is both economically and environmentally advantageous. Furthermore, the catalysts are readily recyclable *via* a simple aqueous work-up.

Table 1 Direct acetylation of alcohols with acetic acid catalysed by scandium(iii) triflate

$$\mathrm{ROH + AcOH \xrightarrow{cat.\ Sc(OTf)_3} ROAc + H_2O}$$

Entry	Alcohol[a]	$Sc(OTf)_3$ (mol%)	*t*/h	*T*/°C	Conv. (%)[b]	Yield (%)
1		5	24	room temp.	> 99	99
		—	48	room temp.	10	—
		5	0.5	reflux	> 99	98
		—	0.5	reflux	37	—
2		5	24	room temp.	> 99	92
		—	48	room temp.	11	—
3		5	24	room temp.	> 99	96
		—	48	room temp.	trace	—
4		5	24	room temp.	> 99	88
		—	48	room temp.	36	—
5		5	24	room temp.	> 99	95
		—	48	room temp.	10	—
6		5	1	room temp.	> 99	97
		—	24	room temp.	trace	—
7		5	2	65	> 99	98
			18	65	17	—
8		5	6	65	> 99	98
		—	18	65	23	—
9		5	24	65	> 99	95
		—	18	65	16	—
10		5	0.5	reflux	71	—
		—	0.5	reflux	trace	—
		5	3	reflux	71	—
		—	0.5	reflux	trace	—
11		5	0.5	reflux	88	—
		—	0.5	reflux	trace	—
		5	18	reflux	88	81[c]
		—	18	reflux	23	—

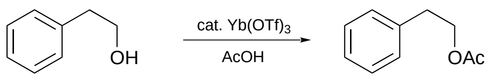
[a] 1 mmol of alcohol in 2 ml HOAc, except entry 10 (1 mmol in 5 ml HOAc) and entry 11 (1 mmol in 25 ml HOAc). [b] GC–MS determination. [c] After flash chromatography on silica gel.

The experimental procedure for these acetylations is remarkably simple, requiring neither dry glassware nor inert atmospheres: a catalytic quantity of lanthanide(iii) salt (5–10 mol%) was added to a stirred solution of the alcohol (1 mmol) in acetic acid (2 ml). In the case of primary alcohols the reactions can be run at room temperature: quantitative acetylation occurs over 24 h and a range of functional groups can be tolerated (Table 1, entries 1–5). In the control experiments with no lanthanide(iii) salts only small quantities of the alcohols were converted to their acetates over the same reaction time. Alternatively, the reaction can be carried out at higher temperature and acetylation is essentially complete in the time taken to bring the reaction mixture to reflux. For simple secondary alcohols somewhat elevated temperatures are required for acceptable reaction times, and again quantitative acetylation occurred (Table 1, entries 6–9). It is of interest to note that no elimination adducts were observed. Cyclohex-2-enol, an allylic alcohol, was acetylated remarkably quickly, the reaction being complete within 1 h at room temperature, while in the corresponding control experiment only traces of the acetate were detected after 24 h (Table 1, entry 5). Acetylation of adamantan-1-ol, an extremely bulky tertiary alcohol, was somewhat less successful (Table 1, entries 10 and 11). However a remarkable rate acceleration was observed and the equilibrium position was obtained in less than 0.5 h in refluxing acetic acid in the presence of a catalytic quantity of scandium(iii) triflate.

Partition work-up with CH_2Cl_2 and water leads to the isolation of the acetylated alcohols which are essentially single components by standard analytical techniques (^1H and ^{13}C NMR) and require no further purification (primary and secondary alcohols). The aqueous phase containing both the catalyst and acetic acid can be evaporated under reduced pressure to furnish the lanthanide(iii) salt as a white solid which can be recycled and used repeatedly without loss of activity (Table 2).‡

Of the metal triflates examined in this study, scandium(iii) triflate was found to be the most effective. The lanthanide(iii) triflates were less active but ytterbium(iii) triflate was appreciably more effective than lanthanum, praeseodymium or europium triflates (Table 3).

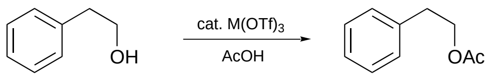
Table 2 Recycling ytterbium(iii) triflate for the acetylation of phenethyl alcohol with acetic acid



Run[a]	Isolated yield (%)	Recovery $Yb(OTf)_3$ (%)
1	95	98
2	99	> 99
3	97	> 99
4	98	> 99

[a] Phenethyl alcohol (3 mmol) in refluxing acetic acid (5 ml) for 0.5 h with ytterbium(iii) triflate (10 mol% for run 1).

Table 3 The effect of various lanthanide(iii) triflates for the acetylation of phenethyl alcohol with acetic acid[a]



	Conversion (%)[c]	
$M(OTf)_3$[b]	After 3 h	After 21 h
Sc	79	100
La	22	63
Pr	28	77
Eu	23	70
Yb	41	92

[a] All reactions run with alcohol (1 mmol) in acetic acid (2 ml) at room temp. [b] 10 mol%. [c] GC–MS determination.

In conclusion, we have demonstrated the use of scandium(iii) or lanthanide(iii) triflates for the acetylation of alcohols using acetic acid only as the acetyl source and where the catalyst is readily recovered and re-used. This underscores the use of lanthanide salts as environmentally acceptable catalysts for atom economic transformations.

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Footnotes

† Scandium(iii) and lanthanide(iii) triflates are commercially available from the Aldrich chemical company as their hydrated forms.

‡ The FT-IR spectrum of the recovered material was identical to that of the commercially available salt.

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