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Highly Efficient and Versatile Acylation of Alcohols with $Bi(OTf)_3$ as Catalyst

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The acylation of alcohols is an important transformation in organic synthesis.[1] Despite a number of precedents, new efficient methods are still in strong demand. Acid anhydrides are the most commonly used reagents in the presence of an acid or base catalyst[2] and the utility of this protocol was boosted by the discovery of the dimethylaminopyridine (DMAP) catalyst.[2a] More recently, metal triflates, such as scandium triflate,[2d] trimethylsilyl triflate,[2e] and indium triflate,[2f] were found to be effective as well. These catalysts are very useful, but also suffer from some drawbacks. Scandium triflate is rather expensive and must be used under anhydrous conditions. Trimethylsilyl triflate is labile towards moisture, and its acidity is too strong for acid-sensitive alcohols as reagents.[2e] In the development of organotin acylation catalysts,[2g,h, 3] we have established that they are so mild that various selective acylation reactions are feasible but their acidity is not strong enough to perform acylation of sterically hindered alcohols. In this context, we were intrigued to employ bismuth triflate $Bi(OTf)_3$[4] since it had proved to be easy to handle due to its stability in the air and to be acidic enough to catalyze Friedel – Crafts,[5] Diels – Alder,[6] and ene reactions.[7]

As shown in Table 1, $Bi(OTf)_3$ can promote the acetylation of primary, secondary, and tertiary alcohols in acetic anhydride at 25 °C [Eq. (1)]. For the acetylation of 2-phenylethanol a catalyst loading as low as 0.01 mol % was sufficient to afford the acetate quantitatively within 10 min (entry 1).

Table 1. $Bi(OTf)_3$-catalyzed acetylation of alcohols [Eq. (1)].[a]

$$R{-}OH + Ac_2O \xrightarrow{Bi(OTf)_3} R{-}OAc \qquad (1)$$

Entry	Alcohol	Mol % of the catalyst	Time [h]	Yield [%][b]
1	2-phenylethanol	0.01	0.167	98
2	2-phenylethanol	0.005	2	99
3[c]	2-phenylethanol	0.5	4	92
4	1-phenylethanol	0.005	2	95
5	2-octanol	0.005	17	98
6[d]	2-octanol	0.005	3	98
7	1-adamantanol	0.01	6	98

[a] Reaction conditions: alcohol (1.0 mmol), acetic anhydride (10 equiv), 25 °C. [b] Determined by GC. [c] Acetic anhydride (1.5 equiv), CH_2Cl_2 (wet, 1.0 mL). [d] At 40 °C.

Even with 0.005 mol % of $Bi(OTf)_3$, this acetylation proceeded quantitatively, but took longer to complete (entry 2). It is possible to employ a solvent different from the anhydride as well. For example, 2-phenylethanol in CH_2Cl_2 was acetylated by 1.5 equivalents of Ac_2O, where CH_2Cl_2 was used without any purification (vide infra and entry 3). Secondary alcohols such as 1-phenylethanol and 2-octanol were also smoothly converted into the corresponding acetates in the presence of 0.005 mol % of $Bi(OTf)_3$ (entries 4 and 5). Although 2-octanol is less reactive than 1-phenylethanol, quantitative acetylation was possible by using longer reaction times or higher reaction temperatures (entries 5 and 6). Surprisingly, even for the acetylation of 1-adamantanol a catalyst loading of 0.01 mol % was enough (entry 7).

After these preliminary examinations, acetylation of functionalized alcohols was scrutinized at 25 °C (Table 2). Although acid-sensitive geraniol and furfuryl alcohol were acetylated in 81 % and 80 % yields, respectively (entries 1 and 3), further improvements of the yields were attained by adding a donor solvent, such as acetonitrile or THF (entries 2 and 4). Not only primary but also secondary and tertiary alcohols with functional groups or phenol units underwent smooth acetylation (entries 5 – 15). Alcohols having an ester or amine function did not react more slowly or show decomposition of the functional groups. More importantly, neither racemization nor epimerization was detected (entries 7 – 9).

Notably, tertiary alcohols can be acetylated at ambient temperatures (entries 10 – 14). For example, the $Bi(OTf)_3$-catalyzed acetylation of an α,α-dimethyl-substituted tertiary

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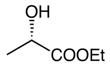
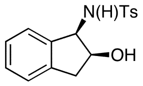
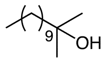
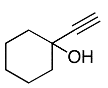
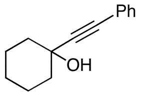
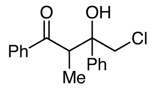
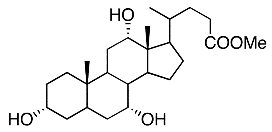
Table 2. Acetylation of functionalized alcohols [Eq. (1)].[a]

$$\mathrm{R{-}OH} + \mathrm{Ac_2O} \xrightarrow{\mathrm{Bi(OTf)_3}} \mathrm{R{-}OAc} \qquad (1)$$

Entry	Alcohol	mol% of the catalyst	Conditions		
			cosolvent/vol. [mL]	time [h]	yield [%][b]
1	geraniol	0.01	none	3.5	81
2	geraniol	1.0	MeCN/1	8.5	95
3	furfuryl alcohol	0.05	none	5.5	80
4	furfuryl alcohol	0.05	THF/0.5	4	93
5	borneol	0.5	THF/3	7	99
6	borneol	0.5	toluene/1[c]	3	95
7		0.5	THF/5	2	91
8		0.1	$\mathrm{CH_2Cl_2}$/5[c]	5	92
9		1.0	none	5	98[d]
10		0.5	THF/5	7	95
11		0.5	MeCN/2	4	94
12		0.5	THF/2	2	81
13		3.0	MeCN/3	1	96[d]
14	linalool	0.5	THF/3	12	80
15	2,4,6-trimethylphenol	0.5	$\mathrm{CH_2Cl_2}$/1[c]	2.5	92
16		5.0	THF/1	7	100[e]

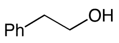
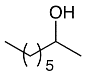
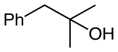
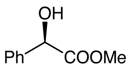
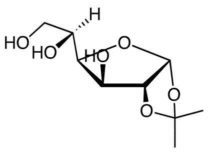
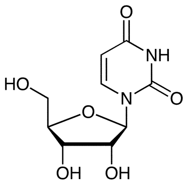
[a] Reaction conditions: alcohol (1.0 mmol), acetic anhydride (10 equiv), 25 °C. [b] Determined by GC. [c] Wet solvent was used. [d] Isolated product. [e] The triacetate was obtained as the sole product.

alcohol proceeded smoothly at 25 °C (entry 10), while the use of $\mathrm{Sc(OTf)_3}$ at room temperature for a similar substrate was reported to lead to the elimination product in 39% yield.[2d] Exposure of tertiary propargyl alcohols to $\mathrm{Bi(OTf)_3/Ac_2O}$ at 25 °C furnished the desired acetates in 94% and 81% yields (entries 11 and 12). On the other hand, acetylation of these substrates under $\mathrm{Sc(OTf)_3}$ or $\mathrm{Me_3SiOTf}$ catalysis should be run at lower temperatures (0 to −20 °C) for obtaining good yields.[2d,e] Furthermore, the present protocol allows the acetylation of a tertiary aldol with a β-chlorine substituent at 25 °C without significant elimination (entry 13). This aldol substrate is sensitive toward acids as well as bases, so the conventional $\mathrm{DMAP/Ac_2O}$ method is not applicable. Linalool underwent acetylation at 25 °C to provide linalyl acetate quantitatively without any concomitant formation of the migration product geranyl acetate (entry 14). On the other hand, acetylation of linalool under $\mathrm{Sc(OTf)_3}$ catalysis at −20 °C gave rise to a mixture of the desired acetate (68%) and geranyl acetate (8%), and $\mathrm{Me_3SiOTf}$ at −10 °C led to a mixture of the desired acetate and the starting alcohol.[2d,e] As a further example, a steroidal alcohol was triacetylated efficiently despite the sterically hindered 12α-hydroxy group (entry 16).[8] Of synthetic use is also the successful employment of wet cosolvents. In essence, the existence of a small amount of water in the solvents (possibly less than ca. 2%) has no influence on the reactions, yet the increase of the water content retards the reaction. Thus, $\mathrm{CH_2Cl_2}$ directly from the bottle that contains only a small amount of water always gave satisfactory results (entries 8 and 15). THF and $\mathrm{CH_3CN}$ can also be used without purification, but reproducible yields were not easily obtained, probably due to a varying amount of water contained.

The $\mathrm{Bi(OTf)_3}$–acid anhydride system was further extended to benzoylation and pivalation [Eq. (2), Table 3]. A primary and an aromatic alcohol could be benzoylated smoothly (entries 1 and 6), but benzoylation of both secondary and tertiary alcohols failed (entries 3 and 5). On the other hand, a series of primary to tertiary alcohols was smoothly transformed into pivalates when exposed to pivalic anhydride in the presence of $\mathrm{Bi(OTf)_3}$ in $\mathrm{CH_2Cl_2}$ (entries 2, 4 and 7–9).

Table 3. Benzoylation[a] and pivalation[b] of alcohols with the $\mathrm{Bi(OTf)_3}$–acid anhydride system [Eq (2)].

$$\mathrm{R^1{-}OH} + \mathrm{(R^2CO)_2O} \xrightarrow{\mathrm{Bi(OTf)_3\ (3.0\ mol\%)}} \mathrm{R^1{-}OCOR^2} \qquad (2)$$

Entry	Alcohol	Conditions anhydride/equiv	time [h]	yield [%][c]
1[d]		$\mathrm{(PhCO)_2O}$/1.5	24	90[e]
2		$\mathrm{(\mathit{t}BuCO)_2O}$/1.5	4	96
3[f]		$\mathrm{(PhCO)_2O}$ /.5	8	2[e]
4		$\mathrm{(\mathit{t}BuCO)_2O}$/3.0	4	99
5[f]		$\mathrm{(PhCO)_2O}$/5.0	48	0
6[d]	2-naphthol	$\mathrm{(PhCO)_2O}$/3.0	1	100[e]
7	borneol	$\mathrm{(\mathit{t}BuCO)_2O}$/1.5	4	97
8		$\mathrm{(\mathit{t}BuCO)_2O}$/1.5	4	97
9	1-adamantanol	$\mathrm{(\mathit{t}BuCO)_2O}$/1.5	4	93
10		$\mathrm{(\mathit{t}BuCO)_2O}$/4.5	7	91[g]
11		$\mathrm{(\mathit{t}BuCO)_2O}$/4.5	23	99[g]

[a] Benzoylation of the alcohol (1.0 mmol) was done in $\mathrm{CH_2Cl_2}$ (3 mL, wet) at 25 °C. [b] Pivalation of the alcohol (1.0 mmol) was done in $\mathrm{CH_2Cl_2}$ (3 mL, wet) at 25 °C. After the pivalation, methanol (10 mL) was added and the mixture was stirred at 50 °C for 7 h in order to destroy the remaining anhydride. [c] Isolated product. [d] Catalyst concentration: 1.0 mol%. [e] Determined by GC. [f] Catalyst concentration: 5.0 mol%. [g] Isolated tripivalate.

After pivalation, it is often difficult to separate the pivalate esters from the remaining pivalic anhydride by column chromatography because of their similar polarity. In our protocol, methanol was added after consumption of the alcohol in order to convert the remaining anhydride to methyl pivalate. $Bi(OTf)_3$ effected the methanolysis of the pivalic anhydride quantitatively at 50 °C where methanol as well as CH_2Cl_2 was used without purification. The product pivalate esters could be readily isolated from the crude product mixture by simple filtration through a thin pad of silica gel with hexane as the solvent. The pivalate esters thus obtained were of sufficient purity. Methanolysis of the excess anhydride in the presence of $Sc(OTf)_3$ or Me_3SiOTf[9] under the same reaction conditions was not complete. Apparently, $Bi(OTf)_3$ is superior to the other metal triflates.

The pivalation of a mandelic ester proceeded with complete retention of the configuration (entry 8). Furthermore, this pivalation method was applicable to a sugar having an acetal as protecting group, which can not survive in the Me_3SiOTf protocol (entry 10).[2e] The acylation of a nucleoside with $Bi(OTf)_3/(tBuCO)_2O$ led quantitatively to the triply pivalated nucleoside despite the existence of an amide function (entry 11). In all the trials for pivalation, CH_2Cl_2 could be used directly from the bottle without purification.

In conclusion, a powerful and versatile acylation method has been developed based on $Bi(OTf)_3$ and acid anhydride. This method has several advantages: the catalyst is cheap and easy to handle, a variety of primary, secondary, and tertiary alcohols can be transformed, and the operations are simple because neither dry reaction conditions nor lowering of the reaction temperature for tertiary alcohols is required. The reactivity of $Bi(OTf)_3$ can be modified, if necessary, by changing the coordinating character of the cosolvent.

Experimental Section

Representative procedure for pivalation (entry 8, Table 3): A CH_2Cl_2 solution (3 mL, unpurified and wet) of methyl (*R*)-mandelate (166.2 mg, 1.0 mmol) and $(tBuCO)_2O$ (299.4 mg, 1.5 mmol) was stirred at 25 °C in the presence of $Bi(OTf)_3$ (21.8 mg, 3.0 mol %, calculated as the tetrahydrate) for 4 h. MeOH (10 mL, unpurified and wet) was added and the mixture was stirred at 50 °C for 7 h. The mixture was passed through a pad of silica gel with hexane as the solvent and the filtrate was evaporated. Ethyl acetate (30 mL) was added to the crude product, and the organic layer was washed three times with aqueous $NaHCO_3$ and dried ($MgSO_4$). Evaporation furnished the pure pivalate ester (97 % yield, 242.8 mg).

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[4] Both $Sc(OTf)_3$ and Sc_2O_3, which is a starting material for the triflate, can be purchased from Aldrich. The price of Sc_2O_3 is $159.9 for 5 g (72.5 mmol). Bi_2O_3, the starting compound for $Bi(OTf)_3$, is also commercially available, and its price is cheaper: $187.1 for 250 g (1.07 mol). $Bi(OTf)_3$ is accessible alternatively by the reaction of Ph_3Bi ($57.3, 25 g, 56.8 mmol) and TfOH. In this study, $Bi(OTf)_3$ was prepared as a tetrahydrate according to this procedure. M. Labrouillere, C. Le Roux, H. Gaspard, A. Laporterie, J. Dubac, *Tetrahedron Lett.* **1999**, *40*, 285, and references therein.

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Remarkable *In*/*out* Inversions at Bridgehead Phosphorus Atoms[**]

Roger W. Alder[*] and David Read

Phosphanes are more pyramidal and invert much less readily than amines. The C-P-C angles for trialkylphosphanes are typically about 100° and they have inversion barriers around 150 $kJ\,mol^{-1}$,[1] hence temperatures of well over 100 °C are required for the racemization of chiral phosphanes. In medium-sized bicyclic ring systems[2] *in*/*out* isomerism[3] is possible, and bridgehead nitrogen atoms are known to adopt whichever arrangement is more stable.[4] Thus 1,4-diazabicyclo[2.2.2]octane is *out*,*out*, 1,6-diazabicyclo[4.4.4]tetradecane is *in*,*in*,[5] 1,5-diazabicyclo[3.3.3]undecane has nearly planar nitrogen atoms,[6] and 1,9-diazabicyclo[7.3.1]tridecane is *in*, *out*.[7] We expected that in related phosphorus compounds *in*,*out* and *in*,*in* isomers would become preferred to *out*,*out* isomers as the ring systems became larger, and also that unstable isomers might be isolated as a result of the high inversion barriers for phosphanes. We find however that these barriers are much lower than expected. We focus here on a

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