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On the role of triflic acid in the metal triflate-catalysed acylation of alcohols

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Abstract—The acylation of alcohols by anhydrides, catalysed by a wide range of metal triflates, is a powerful and mild method for the preparation of a variety of esters. Mechanistic insights demonstrate that triflic acid is generated under these reaction conditions and that, at least, two competing catalytic cycles are operating at the same time: a rapid one involving triflic acid and a slower one involving the metal triflate.

The acylation of an alcohol by an anhydride, to form the corresponding ester, is a key synthetic transformation that can be effected under numerous acidic or basic conditions.[1] Catalytic procedures based upon the use of metal triflates have recently received a lot of attention.[2] These readily available Lewis acids promote the esterification reaction efficiently and under mild conditions. During the course of the total synthesis of polycavernoside A,[3] a potent marine toxin, the transformation of the sensitive β-hydroxy sulfone **1** into the corresponding benzoate **2** was required (Scheme 1).

Initial attempts using base-promoted benzoylation failed to deliver the desired compound due to the rapid formation of the elimination product, trienyl sulfone **3**.[4] The sensitivity of **1** towards basic conditions prompted us to explore the $Sc(OTf)_3$-catalysed acylation of alcohols. Surprisingly, when 10 mol% of $Sc(OTf)_3$ were added to an acetonitrile solution of β-hydroxy sulfone **1** and benzoic anhydride, immediate deprotection of the TES substituent ensued, affording quantitatively diol **4**.[5] In stark contrast, $Sc(OTf)_3$-catalysed benzoylation of the simpler β-hydroxy sulfone **5** resulted in the smooth formation of **6** in 96% yield.

The unexpected desilylation of **1** in the presence of the scandium catalyst, coupled with the successful acylation of **5**, suggested that residual triflic acid might be the culprit responsible for the deprotection of the silyl ether. In order to neutralise these traces of triflic acid, 2,6-di-*tert*-butyl-4-methyl pyridine (DTBMP), a highly hindered organic base that does not interact with the metal catalyst, was added to the reaction mixture.[6] Much to our surprise, no benzoylation of **5** was observed, even after heating at 50 °C. This observation strongly suggests that triflic acid plays a prominent role in these metal-catalysed acylations. In order to shed some light on the nature of the catalytically active species, the benzoylation of the model alcohol **7**, using various metal triflates, in the absence (Table 1) and presence (Table 2) of DTBMP was investigated.

As can be seen from Table 1, the conversion of alcohol **7** into benzoate **9** proceeded in general with modest to good yields, depending upon the nature of the metal employed. Ytterbium triflate proved to be the best catalyst, affording complete conversion to the desired product after 25 h (Table 1, entry 1). In stark contrast, copper triflate barely catalysed the acylation reaction, providing **9** in only 3% yield after 25 h (Table 1, entry 5). Scandium, indium and bismuth triflate displayed intermediate behaviour, with scandium being the most reactive of the three complexes.

Addition of 15 mol% of DTBMP (3 equiv per metal triflate)[7] resulted in a dramatic effect, with the benzoylation reaction being almost completely suppressed. As can be seen from Table 2, ytterbium triflate still proved to be the most active catalyst, generating **9** in 11% yield

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Keywords: Triflic acid; Acylation; Metal triflate.

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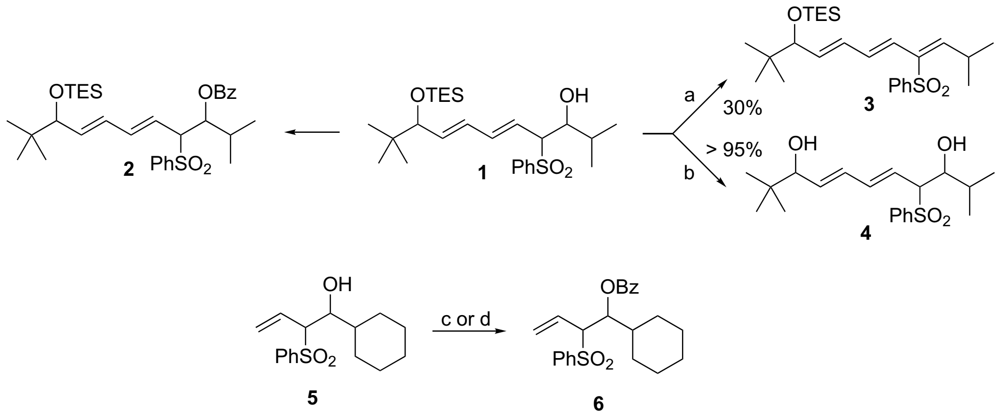
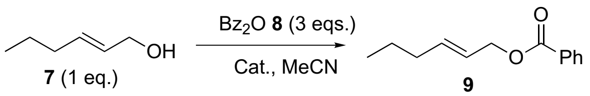


Scheme 1. Reagents and conditions: (a) BzCl, DMAP, Et_3N, DCM (**1**/**2**/**3** = 1:1:1); (b) $Sc(OTf)_3$ 10%, Bz_2O, CH_3CN, 5 min; (c) $Sc(OTf)_3$ (10%), Bz_2O (3 equiv), CH_3CN, 5 min, 20 °C—96% yield; (d) $Sc(OTf)_3$ (1 equiv), Bz_2O (3 equiv), DTBMP (1 equiv), CH_3CN, 24 h, 50 °C—traces.

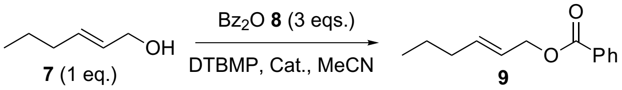
Table 1. Catalytic benzoylation without added base[a]



Entry	Cat. (5%)	Conversion (%)/h[a]			
		0.67	2.5	7	25 (h)
1	$Yb(OTf)_3$	4	19	51	99
2	$Bi(OTf)_3$	8	12	17	40
3	$In(OTf)_3$	5	15	24	34
4	$Sc(OTf)_3$	38	46	51	63
5	$Cu(OTf)_2$	0	0	Traces	3

[a] Measured by capillary GC after calibration of the response for each component.

Table 2. Catalytic benzoylation in the presence of DTBMP[a]

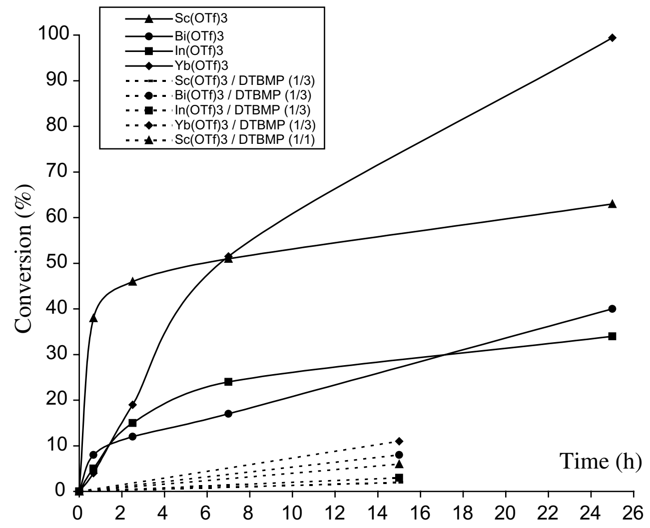


Entry	Cat. (5%)	DTBMP (%)	Conversion (%)/h[a]	
			0.67	15 (h)
1	$Yb(OTf)_3$	15	Traces	11
2	$Bi(OTf)_3$	15	Traces	8
3	$In(OTf)_3$	15	Traces	3
4	$Sc(OTf)_3$	15	Traces	2
5	$Sc(OTf)_3$	5	Traces	6

[a] Measured by capillary GC after calibration of the response for each component.

after 15 h (Table 2, entry 1). Scandium triflate, initially the second best in the absence of base, barely catalysed the reaction, affording **9** in a meagre 2% yield after 15 h. In this case, lowering the amount of DTBMP to 5 mol% led to a marginal improvement in the production of **9** (6% after 15 h). These results are collected in Graph 1.

In order to further verify our hypothesis that triflic acid might be an active catalytic species in these acylations, the benzoylation of **7** was repeated using variable amounts of TfOH under otherwise identical reaction conditions. Addition of 8 mol% of triflic acid to an acetonitrile solution of alcohol **7** and benzoic anhydride resulted in the formation of ester **9** (20% conversion) after a few minutes. The reaction then decelerates and only a 30% conversion of **7** is observed after 5 h. However, when a second portion (8 mol%) of TfOH was added, a rapid transformation of alcohol **7** into ester **9**



Graph 1.

ensued (82% conversion). After 20 h, complete disappearance of the starting material was observed.

Careful purification of the product afforded the desired ester **9**, albeit in only 68% yield, despite the complete conversion of alcohol **7**. This moderate yield results from the competitive dehydration of substrate **7** by triflic acid, affording volatile 1,3-hexadiene and water.[8]

These observations suggested that water, generated by this side reaction, might be responsible for the inhibition of the triflic acid catalytic activity, probably by buffering its acidity. Therefore, a 2:1 H_2O/TfOH solution in acetonitrile was prepared and added to a mixture of alcohol **7** and benzoic anhydride.[9] As expected, only a mediocre yield of **9** was obtained (21% after 30 min) and the reaction essentially stopped; no further increase in the conversion of **7** to **9** was observed after several more hours.

Taken all together, these results strongly support the intervention of triflic acid as an active catalytic species in these benzoylation reactions and demonstrate that water plays an important role in modulating its activity.[10] A plausible mechanistic rationale is depicted in Figure 1.

Upon addition of a metal triflate to a mixture of alcohol **14** and benzoic anhydride **8**, activation of the anhydride occurs, leading to the formation of the mixed triflic–benzoic species **12**.[11] Acylation of alcohol **14** by **12** then produces the desired ester **15** and releases triflic acid, which might react according to two different and competitive pathways. In the first catalytic cycle, triflic acid displaces the benzoate ligand from the mixed metal species **10**, regenerating the corresponding metal triflate, which initiates a new catalytic cycle (Cycle 1). Alternatively, triflic acid might react directly with benzoic anhydride to produce the mixed acylating derivative **12**.[12] Upon condensation with alcohol **14**, TfOH is regenerated, completing Cycle 2.

Besides triflic acid and the metal triflate, an important intermediate in this proposed catalytic cycle appears to be the acyl triflate **12**, which participates in both Cycles 1 and 2. In order to verify the involvement of **12** in this acylation reaction and, at the same time, provide further evidence for our postulated mechanism, we decided to prepare **12** independently[13] and employ it as the sole

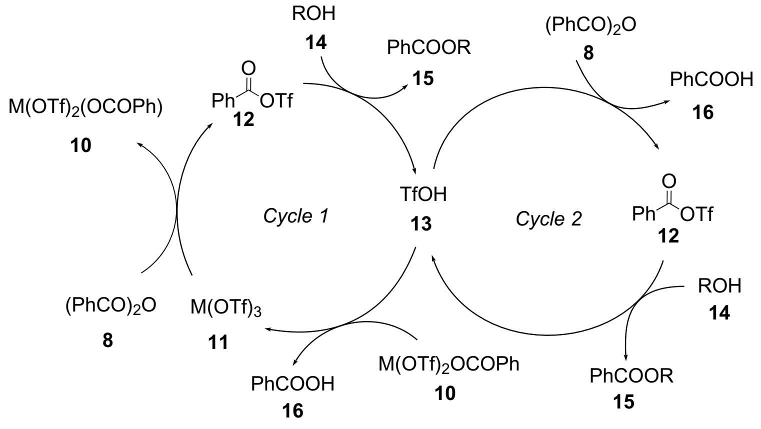
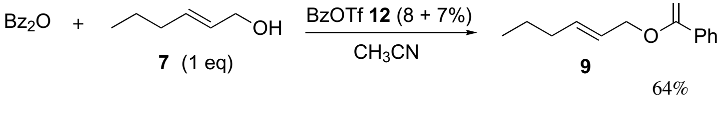
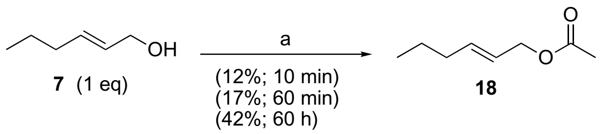


Figure 1.



Scheme 2.



Scheme 3. Reagents and conditions: (a) $Sc(OTf)_3$ (1 equiv), Ac_2O **17** (3 equiv), DTBMP (3 equiv), MeCN.

catalyst in the benzoylation of alcohol **7**. Under these conditions, both the yield and rate of acylation of **7** should be identical to those obtained using TfOH (Scheme 2).

Gratifyingly, and in perfect agreement with our postulated mechanism, the addition of **12** to alcohol **7** and Bz_2O resulted in the smooth formation of the benzoate **9** after 22 h, at room temperature (100% conversion, 64% yield).[14] These results unambiguously establish the intermediacy of benzoyl triflate **12** in Cycle 2 and provide yet another entry into this catalytic manifold.

This mechanism also rationalises the powerful inhibitory activity of DTBMP. Indeed, addition of DTBMP to the reaction mixture results in the removal of triflic acid—which holds a cardinal position at the junction between the two catalytic cycles—and the concomitant suppression of Cycle 2 and the second part of Cycle 1 (regeneration of the metal triflate catalyst). Only the initial two steps of Cycle 1 are still operative under these conditions.[15]

In order to verify that these mechanistic explanations were not limited to the benzoylation reaction—a relatively slow process—alcohol **7** was acetylated using acetic anhydride and $Sc(OTf)_3$ in the absence and presence of DTBMP (Table 3).

Due to the greater reactivity of Ac_2O, a blank experiment was initially performed. Reassuringly, less than 2% of acetate **18** was formed after 16 h. In the presence of 1 mol% of $Sc(OTf)_3$, complete conversion of **7** to **18** occurred in 5 min. Gratifyingly, addition of 3 mol% of DTBMP completely suppressed the acetylation and less than 5% of **18** was observed after 20 h. As predicted, the use of 3 mol% of TfOH resulted in the quantitative transformation of **7** to **18** after 5 min.

To shed some light on the relative rates between Cycle 2 and the first part of Cycle 1 (the key steps of this catalytic cycle), the stoichiometric acetylation of **7** was investigated (Scheme 3).

In the presence of 3 equiv of acetic anhydride, 1 equiv of $Sc(OTf)_3$ and 3 equiv of DTBMP, alcohol **7** underwent slow acetylation, affording acetate **18** in 12% conversion after 10 min, 17% after 60 min and 42% after 60 h. Since DTBMP completely inhibits both Cycle 2 and the second part of Cycle 1 (by removing triflic acid), the conversions obtained during this experiment reflect the ability of the metal triflate to catalyse the acylation of alcohols.[16]

From this experiment and the above-mentioned data, catalysis by triflic acid appears to be the dominant pathway in the absence of the hindered base and the metal triflates act as selective reservoirs of triflic acid, releasing it rapidly at the onset of the reaction. This is also evidenced by the shape of the conversion versus time curves (Graph 1) where a fast rate of reaction is initially observed (which mimics the activity of triflic acid alone), followed by a more sluggish reaction, eventually culminating in the complete conversion of **7** into **9**.

In summary, we have shown that the metal triflate promoted acylation of alcohols appears to be catalysed mainly by triflic acid, released at the onset of the reaction. Two catalytic cycles compete in this process. Cycle 2, which involves directly triflic acid, appears to predominate at the beginning of the reaction. Care must therefore be exercised when using acid sensitive substrates and when attempting to rationalise the particular selectivities often observed using metal triflates.

Acknowledgements

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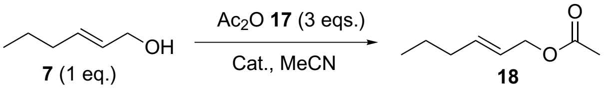
Table 3. Catalytic acetylation of alcohol **7**[a]



Entry	Cat. (5%)	DTBMP	Conversion (%)[a]	Time
1	—	—	<2	16 h
2	1% $Sc(OTf)_3$	—	>99	5 min
3	1% $Sc(OTf)_3$	3%	<5	20 h
4	3% TfOH	—	>99	5 min

[a] Measured by capillary GC after calibration of the response for each component.

with enlightening suggestions and samples of metal triflates. I.E.M. is grateful to Rhodia for the 2001 Rhodia Outstanding Award.

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4. See, for example: Keck, G. E.; Savin, K. A.; Weglarz, M. A. *J. Org. Chem.* **1995**, *60*, 3194–3204.
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7. Since up to three equivalents of triflic acid could theoretically be generated per metal triflate, we have decided to use a 1:3 ratio of metal complex/DTBMP. However, even one equivalent of the hindered base is sufficient to significantly reduce the rate of these acylation reactions (Table 2, entry 5).
8. Competitive elimination has also been observed in the metal triflate acylation of several allylic and tertiary alcohols (see Refs. 2a, g, i, j).
9. The 2:1 ratio of (H_2O/TfOH) was deduced from the ratio of acylated adduct versus elimination product.
10. Triflic acid has been used, and sometimes demonstrated to be the active species, in several catalytic processes: (a) Kotsuki, H.; Arimura, K.; Ohishi, T.; Maruzasa, R. *J. Org. Chem.* **1999**, *64*, 3770–3773; (b) Kotsuki, H.; Ohishi, T.; Inoue, M.; Kojima, T. *Synthesis* **1999**, 603–606; (c) Kotsuki, H.; Arimura, K.; Araki, T.; Shinohara, T. *Synlett* **1999**, 462–464; (d) Répichet, S.; Le Roux, C.; Dubac, J.; Desmurs, J.-R. *Eur. J. Org. Chem.* **1998**, 2743–2746; (e) Laurent-Robert, H.; Le Roux, C.; Dubac, J. *Synlett* **1998**, 1138–1140; (f) Tsuchimoto, T.; Tobita, K.; Hiyama, T.; Fukuzawa, S.-I. *J. Org. Chem.* **1997**, *62*, 6997–7005, see also Ref. 2g.
11. For reasons of clarity, only one benzoate is shown on the metal. However, it is quite possible that several species, formed by the exchange of one, two or three triflate ligands might be involved in these catalytic processes.
12. For a catalytic version of the Friedel–Crafts acylation using triflic acid and proceeding via the acyl triflate intermediate, see: Effenberger, F.; Epple, G. *Angew. Chem., Int. Ed.* **1972**, *11*, 300.
13. Brown, L.; Koreeda, M. *J. Org. Chem.* **1984**, *49*, 3875–3880.
14. As with TfOH, a second aliquot of **12** (7 mol%) had to be added after 18 h to reach full completion.
15. It is important to note that the triflate salt of DTBMP does not catalyse the acylation reaction.
16. The results of the stoichiometric acylation appear to suggest that one triflate ligand is released initially from the metal and that catalysts such as $MeCOOSc(OTf)_2$ are poorly active. Indeed, if only one triflate is exchanged, the maximum yield of acetate **18** should be 33%.