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# Fluorous 4-*N*,*N*-Dimethylaminopyridine (DMAP) Salts as Simple Recyclable Acylation Catalysts

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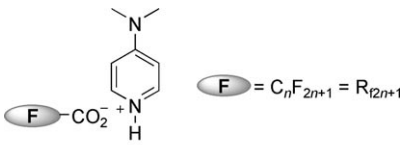
*Dedicated to Dr. Jean-Pierre Bégué on the occasion of his 70th birthday*

The recyclability of organic- and metal-based catalysts is of prime interest for the development of sustainable synthesis processes.[1,2] Since the pioneering work of the groups of Litvinenko and Steglich, who independently reported organocatalyzed acylation reactions with 4-*N*,*N*-dimethylaminopyridine (DMAP),[3] dialkylaminopyridines still remain in the limelight. Thus, remarkable developments are regularly reported, as exemplified by the emergence of more potent analogues, even chiral,[4,5] as catalysts for a diverse range of reactions.[6] Unfortunately, these powerful organocatalysts exhibit acute dermal toxicity,[7] whereas the corresponding salts only produce local irritation by skin contact.[8] To avoid dissemination of these harmful chemicals in the environment, recyclable 4-aminopyridines have been prepared through immobilization on organic or inorganic supports.[9–11] Although some remarkable systems emerged, those exhibiting significant activity coupled with complete recyclability are scarce. In 2007, Gun'ko, Connon, and co-workers reported a very elegant magnetic-nanoparticle-supported DMAP that can be used several times without loss in activity and that is simply recovered by using an external magnet.[11a,12] However, a limit in the molecular weight of the support is highly desirable to avoid the use of a quantity of immobilized catalyst larger than that of the substrate.

Alternatively, fluorous techniques also offer a very attractive way to selectively recover a compound tagged with perfluorinated chains from a complex reaction mixture.[13] Although this strategy originally involved fluorous solvents[14] or silica,[15] the current trend tends toward simple solubility modulation of fluorous catalysts in conventional media, for recovery through precipitation.[16,17] In the field of catalysis, the fluorous approach has been widely applied to metal catalysts by means of fluorinated ligands.[13,14] In contrast, reports on fluorous organocatalysis are still scarce,[18,19] and the field is only at an early stage of development. In this context, we recently reported the preparation of an efficient fluorous aminopyridine for esterification of hindered alcohols, which suffered from poor recyclability.[18d] We now report the use of an easily accessible fluorous salt of DMAP, **1**-$R_f$, as an active and recyclable acylation catalyst, under simple conditions.




**1**-$R_f$

Usually, the DMAP-catalyzed esterification reaction of an alcohol is performed in nonpolar solvents with an anhydride as the acyl donor, in the presence of a base in stoichiometric amounts (triethylamine or Hünig's base). According to the pathway depicted in Scheme 1 with acetic anhydride, DMAP is protonated by the acetic acid released at the end of the cycle, and the assistance of the auxiliary base is essential for regenerating the catalyst in neutral form.[6a,20]

Nevertheless, in a recent study, Ishihara and co-workers reported that this catalytic acylation reaction could occur without any external base, if the reaction was performed in a concentrated medium (neat), or in a highly apolar solvent, such as heptane.[21] Under these conditions, the regeneration of DMAP occurs in situ, allowing continuation of the catalytic cycle and affords ester products in excellent yields. At the end of the reaction, the catalyst is in the acetate salt form (AcOH·DMAP), which is soluble in organic media and, therefore, often difficult to separate from the product.

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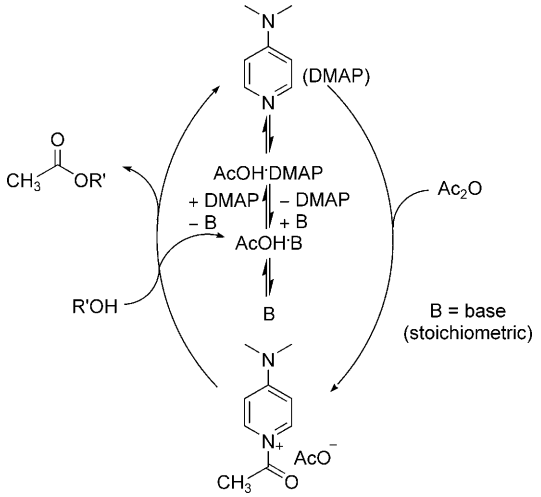



Scheme 1. DMAP-catalyzed esterification with acetic anhydride.

In relation to these observations, we reasoned that a compound $R_fCO_2H$·DMAP (**1**, $R_f$ = perfluoroalkyl) could provide the following advantages as a catalyst: 1) according to the particular solubility of perfluorinated molecules, compound **1** could be solubilized in an appropriate reaction medium to deliver active DMAP, and then promote acylation; 2) in spite of the release of acetic acid during the esterification step, the stronger acidity of $R_fCO_2H$ ($pK_a$(AcOH) = 4.7 versus $pK_a(C_7F_{15}CO_2H) \approx 0$)[22] should favor the regeneration of **1** after completion of the reaction, allowing its recovery with an appropriate work up; 3) since there is no modification of the backbone of DMAP, the reactivity of **1** should only depend on the presence of proton-free DMAP (even in tiny amounts) in the medium; 4) catalyst **1** can be readily prepared in a single step and since aminopyridinium salts are innocuous, the handling of **1** would be safe.[8]

Thus, two fluorous aminopyridinium salts $C_7F_{15}CO_2H$·DMAP **1**-$R_{f15}$ and $C_{11}F_{23}CO_2H$·DMAP **1**-$R_{f23}$ were prepared by simply mixing the amine with the acid (>98% yield each after crystallization). To assess the second point of our strategy (see above), $^1$H NMR spectroscopy experiments with DMAP, AcOH, $C_7F_{15}CO_2H$, and related pyridinium salts were performed: they confirmed that the competition between AcOH·DMAP and $C_7F_{15}CO_2H$·DMAP was in favor of the latter.[23] Subsequently, to assess the ability of **1**-$R_f$ to release free DMAP in a reaction medium for catalysis purposes, the acetylation of 1-phenylethanol with acetic anhydride (1.1 equiv) was performed in the presence of **1**-$R_{f15}$ or **1**-$R_{f23}$ as the catalyst (10 mol%) under the conditions reported by Ishihara and co-workers (base- and solvent-free at room temperature). The results are presented in Figure 1.

In the absence of catalyst, no reaction took place and the alcohol remained unchanged, even after 8 h. Delightfully, with fluorous salts **1**-$R_{f15}$ and **1**-$R_{f23}$ the reaction occurred to afford the corresponding ester. It emerged that **1**-$R_{f15}$ exhibited a significantly better activity than **1**-$R_{f23}$: 92 versus 58% conversion after 8 h. To prove that the promotion of the reaction was not the result of acid catalysis, 1-phenylethanol and acetic anhydride were treated with $C_7F_{15}CO_2H$ ($R_{f15}CO_2H$, 10 mol%): it appeared that $R_{f15}CO_2H$ catalyzed the reaction, but had only a low activity (42% for $R_{f15}CO_2H$ versus 92% for **1**-$R_{f15}$ after 8 h).[24] From these results, it can be assumed that the overall kinetics of the catalytic esterification largely depend on the equilibrium between **1**-$R_{f15}$ and free DMAP, the latter being the active catalytic species.[25]

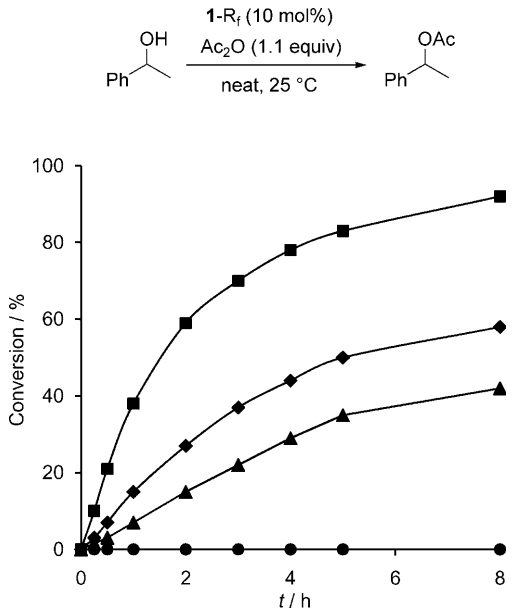



Figure 1. Influence of various catalysts (0.2 mmol) on the acetylation of 1-phenylethanol (2 mmol) with $Ac_2O$ (2.2 mmol) under solvent- and base-free conditions at 25°C (monitoring by $^1$H NMR spectroscopy): **1**-$R_{f15}$ (■), **1**-$R_{f23}$ (◆), $R_{f15}CO_2H$ alone (▲), without catalyst (●).

These experiments thus validate our model for **1**-$R_f$-type catalysts as esterification promoters and the recyclability of the best catalyst **1**-$R_{f15}$ was tested for the same reaction (Table 1). The reaction was conducted overnight for complete conversion to take place. Then the acetic acid was evaporated and catalyst **1**-$R_{f15}$ partially precipitated in the medium; complete precipitation occurred by adding a small amount of pentane or toluene. After filtration, the catalyst was separated from the ester product (95% yield), and recovered quantitatively (>99%; Table 1, entry 1). Catalyst **1**-

Table 1. Assessment of **1**-$R_{f15}$ as a recyclable catalyst in the acetylation of 1-phenylethanol under solvent- and base-free conditions[a]

| Run | Recovery of **1**-$R_{f15}$ [%] | Yield of ester [%] | Run | Recovery of **1**-$R_{f15}$ [%] | Yield of ester [%] |
|---|---|---|---|---|---|
| 1 | >99 | 95 | 6 | >99 | 95 |
| 2 | >99 | 96 | 7 | 98 | 96 |
| 3 | >99 | 95 | 8 | >99 | 94 |
| 4 | >99 | 97 | 9 | >99 | 97 |
| 5 | 98 | 94 | 10[b] | 99 | 96 |

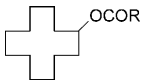
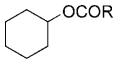
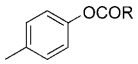
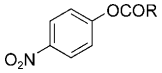
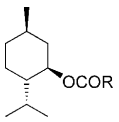
[a] Reaction conditions: 1-phenylethanol (2 mmol), $Ac_2O$ (2.2 mmol) and **1**-$R_{f15}$ (0.2 mmol; 107 mg), neat, 25°C, 17 h. [b] 103 mg of **1**-$R_{f15}$ recovered after the 10th run.

$R_{f15}$ was then engaged in further runs. Remarkably, the catalyst was able to undergo 10 iterative runs without any loss in activity and with excellent recovery (Table 1, entries 2–10).

The scope of this acylation reaction with **1**-$R_{f15}$ was then extended to several secondary and tertiary alcohols, with acetic and isobutyric anhydrides (Table 2). Benzylic alcohols (1-phenylethanol, 1-indanol) underwent facile esterification with both anhydrides within 17 h. After removal of the acid released and precipitation of the catalyst, the corresponding products were afforded with excellent purity and in excellent yields (89–97%; Table 2, entries 1–4). Aliphatic alcohols, dodecanol and cyclohexanol, also behaved very well and full conversions were obtained within 17 and 8 h, respectively, (85–98% yield; Table 2, entries 5–8). Even the tertiary alcohol 1-methylcyclopentanol was a suitable partner in this reaction, but reacted more sluggishly: warming the reaction mixture to 60 °C for 24 h was required to obtain a good conversion (68–70% yield; Table 2, entries 9 and 10). As substrates, aromatic alcohols 4-methylphenol and 4-nitrophenol also yielded the corresponding esters (>90% yield; Table 2, entries 11–14). Our last concern dealt with the possible negative impact of the strong acid $C_7F_{15}CO_2H$ on the stability of the reaction products. It is worth noting that starting from (−)-menthol as the substrate, the products were afforded in high yields, with acetic and isobutyric anhydrides, without any trace of epimerization products (Table 2, entries 15 and 16).

Table 2. **1**-$R_{f15}$-catalyzed esterification of alcohols with anhydrides under solvent- and base-free conditions[a]

| Entry | Product | R | *T* [°C] | *t* [h] | Yield [%] |
|---|---|---|---|---|---|
| 1 |  | Me | 25 | 17 | 97 |
| 2 | | *i*Pr | 25 | 17 | 89 |
| 3 |  | Me | 25 | 17 | 93 |
| 4 | | *i*Pr | 25 | 17 | 97 |
| 5 |  | Me | 25 | 17 | 98 |
| 6 | | *i*Pr | 25 | 17 | 91 |
| 7 |  | Me | 25 | 8 | 85 |
| 8 | | *i*Pr | 25 | 8 | 92 |
| 9 |  | Me | 60 | 24 | 70 |
| 10 | | *i*Pr | 60 | 24 | 68 |
| 11 |  | Me | 25 | 17 | 90 |
| 12 | | *i*Pr | 25 | 17 | 93 |
| 13 |  | Me | 25 | 17 | 98 |
| 14 | | *i*Pr | 25 | 17 | 93 |
| 15 |  | Me | 25 | 17 | 92 |
| 16 | | *i*Pr | 25 | 17 | 95 |

[a] Reaction conditions: alcohol (2 mmol), anhydride (2.2 mmol), and **1**-$R_{f15}$ (0.2 mmol), neat, 25 °C.

Finally, to prove the usefulness of the process, the **1**-$R_{f15}$-catalyzed acetylation of 1-phenylethanol was performed on a 10 g scale. After 17 h, the acetic acid was distilled, the catalyst was precipitated and fully recovered, and the ester was obtained in 98% yield.

In summary, we prepared a simple fluorous salt of DMAP as an effective and recyclable organocatalyst for esterification reactions, under solvent- and base-free conditions. The simplicity of the process (readily accessible catalyst, easy to handle and to recover) makes it an attractive alternative for cleaner and safer acylation reactions, which could be used with asymmetric dialkylaminopyridines, or in other transformations, such as the Baylis–Hillman reaction. Moreover, these results constitute an interesting approach for fluorous labeling with noncovalent bonds.

## Experimental Section

The alcohol (2 mmol) and the anhydride (2.2 mmol) were mixed in a 10 mL round-bottomed flask and **1**-$R_{f15}$ (0.2 mmol) was added. The flask was then capped and the reaction mixture was stirred at room temperature (except for 1-methylcyclopentanol: 60 °C). After 17 h (8 h for cyclohexanol), the acid effluent was evaporated in vacuo. The residue was then allowed to cool to room temperature and the catalyst was precipitated by adding pentane or toluene (2 mL). After filtration, catalyst **1**-$R_{f15}$ was recovered and evaporation of the solvent from the filtrate afforded the pure ester product.

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[23] In an NMR tube, AcOH (1 equiv) was added to a solution of DMAP in $CDCl_3$: a downfield shift of the proton in position 2 from $\delta = 6.47$ ppm to $\delta = 6.53$ ppm was observed, characteristic of AcOH·DMAP. A further equivalent of $C_7F_{15}CO_2H$ was then added, which provoked a further shift to $\delta = 6.72$ ppm, matching with the NMR spectroscopy data of pure $C_7F_{15}CO_2H$·DMAP **1**-$R_{f15}$ ($\delta =$ 6.71 ppm) (see the Supporting Information for details).

[24] With **1**-$R_{f15}$, total conversion of the alcohol to the ester occurred in less than 17 h, whereas the reaction was still incomplete after 30 h in the presence of $C_7F_{15}CO_2H$ as a catalyst.

[25] Note that $C_7F_{15}CO_2H$ and **1**-$R_{f15}$ slowly solubilize in the reaction medium, whereas **1**-$R_{f23}$ is only sparingly soluble. According to the report by Ishihara and co-workers (ref. [21]), it can be assumed that the low solubility of **1**-$R_{f23}$ disfavors the release of free DMAP, thus, explaining the moderate activity in the acetylation reaction (58% conversion after 8 h).

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