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O-Nucleophilic Amino Alcohol Acyl-Transfer Catalysts: the Effect of Acidity of the Hydroxyl Group on the Activity of the Catalyst

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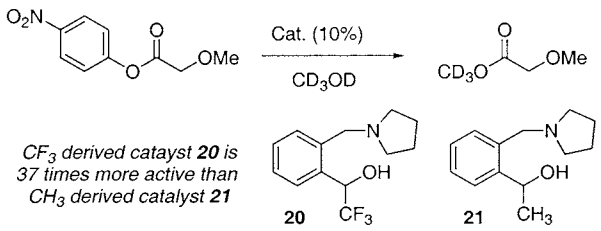
ABSTRACT



Amino alcohol-derived acyl-transfer catalysts are shown to operate by an *O*-nucleophilic mechanism, and catalysts bearing electron-withdrawing groups in proximity to the hydroxyl group are found to be more active. This is attributed to an increase in the acidity of the hydroxyl group of the catalyst.

The serine proteases are a class of enzymes which function by a mechanism in which the hydroxyl group of a serine residue at the active site attacks the carbonyl of an amide, thereby cleaving the amide and forming an acyl-enzyme intermediate.[1] This intermediate then undergoes hydrolysis to complete the catalytic cycle and provide the hydrolyzed amide. Both of these steps are catalyzed by basic residues at the active site, and since the elucidation of this mechanism, numerous workers have synthesized molecules bearing hydroxyl groups in proximity to basic residues in an attempt to mimic this mechanism of action.[2] In this paper, we explore the effect of acidity of the hydroxyl group on the activity of these catalysts.

We recently described a series of pyridine-derived acyl-transfer catalysts which are effective for the selective methanolysis of α-hydroxy esters over ordinary esters (**1**, Scheme 1).[3] These catalysts are bifunctional and contain a ketone or an aldehyde at the 2-position of a 4-aminopyridine. They operate by a mechanism in which the hydroxyl group of the hydroxy ester substrate (**2**) attacks the carbonyl of the catalyst, thereby forming a covalent complex (hemiacetal or hemiketal **3**). The hydroxyl group of the hemiacetal/hemiketal then attacks the carbonyl of the substrate and produces dioxolanone **4** in a step that is catalyzed by the neighboring pyridine. The dioxolanone then undergoes methanolysis in a step that is also catalyzed by the pyridine to produce the methyl ester of the product bound to the catalyst as the hemiacetal/hemiketal (**5**). Breakdown of the

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(1) Hedstrom, L. *Chem. Rev.* **2002**, *102*, 4501.

(2) For leading references of serine protease mimics and related compounds, see: (a) Hine, J.; Khan, M. N. *J. Am. Chem. Soc.* **1977**, *99*, 3847. (b) Madder, A.; De Clercq, P. J.; Declercq, J.-P. *J. Org. Chem.* **1998**, *63*, 2548. (c) Skorey, K. I.; Somayaji, V.; Brown, R. S. *J. Am. Chem. Soc.* **1989**, *111*, 1445. (d) Cram, D. J.; Katz, H. E. *J. Am. Chem. Soc.* **1983**, *105*, 135. (e) Ghosh, M.; Conroy, J. L.; Seto, C. T. *Angew. Chem., Int. Ed.* **1999**, *38*, 514. (f) Menger, F. M.; Whitesell, L. G. *J. Am. Chem. Soc.* **1985**, *107*, 707−708. (g) Breslow, R.; Dong, S. D. *Chem. Rev.* **1998**, *98*, 1997−2011. (h) Diederich, F.; Schürmann, G.; Chao, I. *J. Org. Chem.* **1988**, *53*, 2744−2757.

(3) (a) Sammakia, T.; Hurley, T. B. *J. Am. Chem. Soc.* **1996**, *118*, 8967. (b) Sammakia, T.; Hurley, T. B. *Org. Chem.* **1999**, *64*, 4652.

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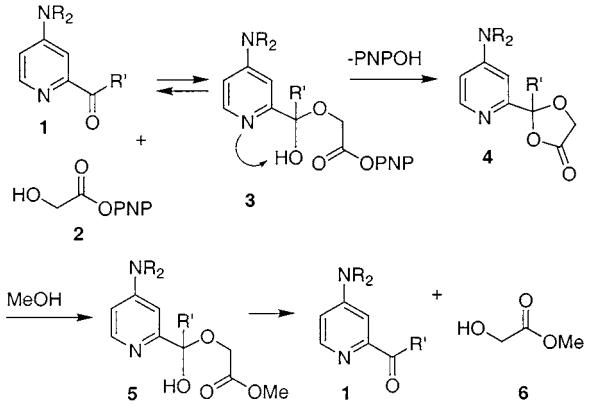
Scheme 1



hemiacetal/hemiketal provides the product (**6**) and regenerates the catalyst (**1**), ready to repeat the catalytic cycle. Substrates that lack a hydroxyl group cannot form the requisite hemiacetal/hemiketal and cannot undergo methanolysis by this mechanism, hence leading to the selectivity of these catalysts.

During the course of these studies, we found that ketone-derived catalysts are far more selective than aldehyde-derived catalysts (Figure 1). For example, aldehyde-derived catalyst

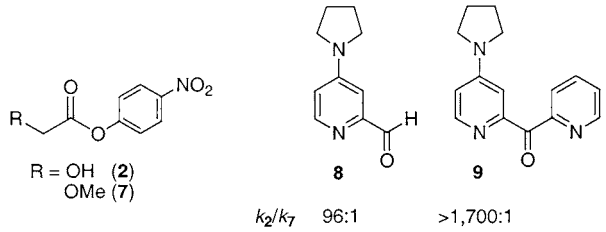
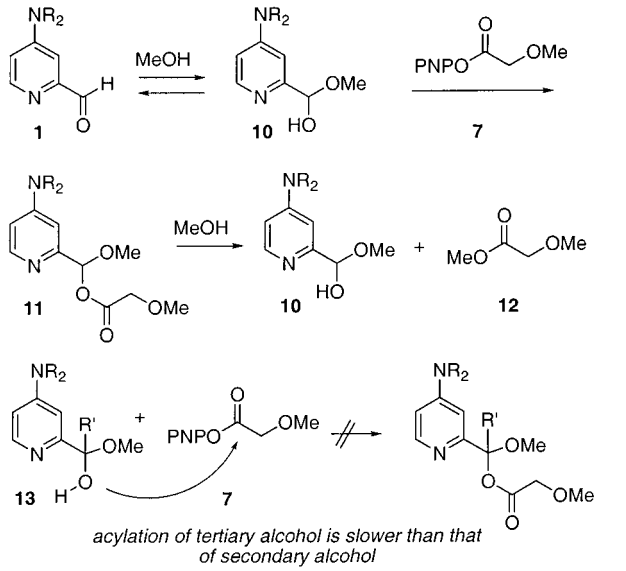


Figure 1. Aldehyde- and ketone-derived catalysts.

8 displays a rate difference of 96:1 in the methanolysis of **2** vs **7**, whereas ketone-derived catalyst **9** displays a rate difference of over 1700:1 for the same reaction. After extensive mechanistic studies, we found that this is due to an undirected background reaction reminiscent of the mechanism of action of the serine proteases (Scheme 2).[4] This undirected reaction proceeds by way of hemiacetal intermediate **10**, which is produced by the addition of methanol to the aldehyde of catalyst **8**. The hydroxyl group of this hemiacetal can attack the carbonyl of an active ester to produce the acyl catalyst intermediate **11** in a step that is catalyzed by the proximal basic pyridine. This intermediate can then undergo methanolysis, again with catalysis by the proximal pyridine, to provide the product (**12**) and regenerate the catalyst. In the case of the ketone-derived catalysts, addition of methanol produces a hemiketal (**13**), the nucleo-

(4) Sammakia, T.; Hurley, T. B. *J. Org. Chem.* **2000**, *65*, 974.

Scheme 2



philicity of which is greatly diminished due to the hindrance of the tertiary hydroxyl group that is produced. Thus, the background reaction does not occur within the limits of our detection, and these catalysts are very selective.

Hemiacetals are ~4−5 *pK* units more acidic than ordinary alcohols,[5] and we felt that this increase in acidity may facilitate both steps of the catalytic cycle. In the first step (nucleophilic attack of the alcohol on the ester), the more acidic hydroxyl group will be deprotonated to a greater extent by the pyridine, thereby leading to greater charge on the oxygen and producing a more nucleophilic species. In the second step (methanolysis of the acylated catalyst), the more acidic alcohol is a better leaving group. We have, therefore, designed a series of catalysts to test this idea wherein the acidity of the alcohol is varied by the presence of an electron-withdrawing group. In our design, we sought to keep the general features of compound **10** but to introduce the ability to modify the acidity of the alcohol. As such, we prepared catalysts bearing a 4-aminopyridine nucleus substituted with a hydroxyalkyl group at the 2-position and a methyl group at the 6-position (Figure 2). The 4-amino substituent

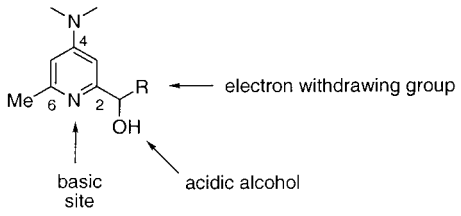


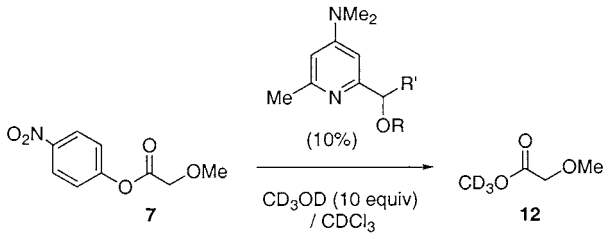
Figure 2. Design elements of new catalysts.

increases the basicity of the pyridine nitrogen, while the 6-methyl group renders it non-nucleophilic. The substituent R on the hydroxyalkyl group allows us to vary the electronics

and acidity of the hydroxyl group and study this effect on the rate of the reaction.

We prepared four catalysts with this structure in which the R substituent is trifluoromethyl (**14**), methyl (**15**), pentafluorophenyl (**17**), or phenyl (**18**, Table 1).[6,7] These

Table 1. Relative Rates of Reaction Using Pyridine-Derived Catalysts



entry	R	R′	$k_{(rel)}$	entry	R	R′	$k_{(rel)}$
1	H	CF_3 (**14**)	94	4	H	C_6F_5 (**17**)	130
2	H	CH_3 (**15**)	32	5	H	C_6H_5 (**18**)	60
3	CH_3	CF_3 (**16**)	1				

compounds were studied in the methanolysis of **7**. Reactions were conducted at a concentration of 0.1 M in $CDCl_3$ at a catalyst loading of 10%, with 10 equiv of deuteriomethanol, and were monitored by ^1H NMR. We find that reactions with catalysts bearing electron-withdrawing groups are faster (compare entry 1 vs entry 2, and entry 4 vs entry 5), which is consistent with our hypothesis. As a control experiment, we also studied compound **16** in which the hydroxyl group is blocked as a methyl ether and found this compound catalyzes the reaction 94 times slower than catalyst **14**, providing good evidence for an *O*-nucleophilic mechanism.

Because the reactions were monitored by NMR, we were able to identify several species in solution and measure their concentrations. Data from a reaction are plotted in Figure 3, and this plot provides further evidence for an *O*-nucleophilic mechanism.[8] At the onset of the reaction, the substrate and catalyst display a burst of reactivity and are rapidly consumed at the same rate that a new catalyst species, the acylated catalyst (**19**), appears. However, there is an induction period before the appearance of product (**12**) is observed, and this induction period correlates with the time required for the acylated catalyst to be formed. After this initial burst, there is a slower, steady-state reaction that is observed in which the product is formed at the same rate that the starting

(5) (a) Bell, R. P. In *Advances in Physical Organic Chemistry*; Gold, V., Ed.; Academic: New York, 1966; Vol 4, pp 12−16. (b) For data on the acidity of pyridine carboxaldehyde hydrates, see: Owen, T. C. *J. Heterocycl. Chem.* **1990**, *27*, 987.

(6) See the Supporting Information for the synthesis of these compounds.

(7) Trifluoromethyl-substituted alcohols are known to be more acidic than alkyl-substituted alcohols. For example, the pK_a of trifluoroethanol is 12.4, whereas as the pK_a of ethanol is 15.9. We therefore estimate the pK_a of the trifluoromethyl-substituted catalyst **14** to be about 3.5 units lower than the corresponding methyl-substituted catalyst **15**. See: Ballinger, P.; Long, F. A. *J. Am. Chem. Soc.* **1960**, *82*, 795−798

(8) This reaction was conducted at a catalyst loading of 20% in order to better observe the catalytic species by NMR.

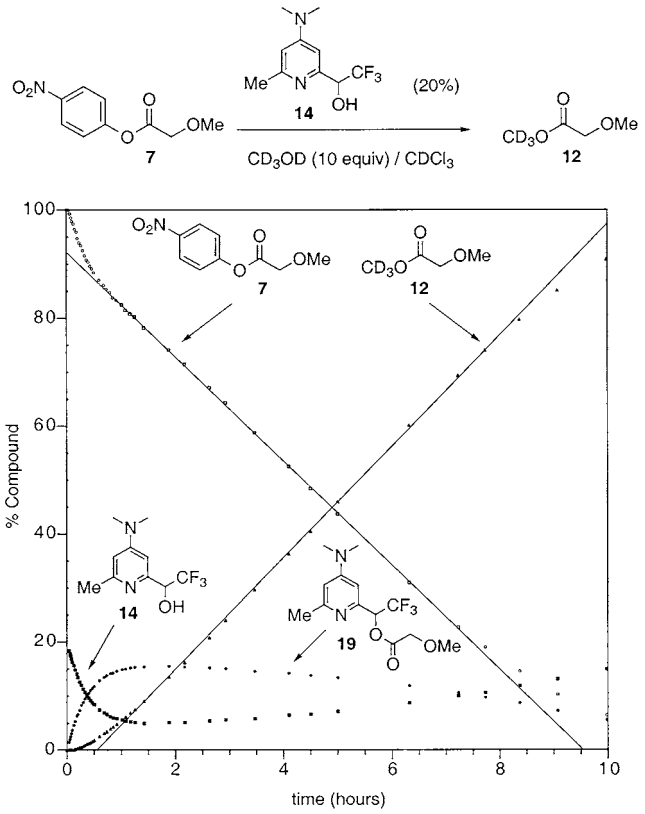
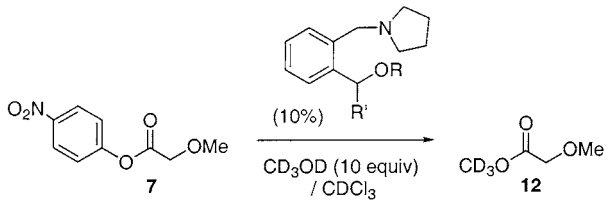


Figure 3. Kinetics of typical reaction using 20% of catalyst **14**.

material is consumed. As the reaction progresses, the concentration of the acylated catalyst decreases as does the rate of formation of product, deviating from steady state at high conversion. These data are consistent with a kinetic scheme in which the acylation of the catalyst is faster than the de-acylation until late in the reaction when most of the starting material has been consumed.

We have also studied catalyst designs in which the basic residue is further removed from the hydroxyl group (Table 2).[6] The methanolysis of **7** with these catalysts was studied under the same conditions as before, and in this case, there is a greater difference in the activity of the trifluoromethyl

Table 2. Relative Rates of Reaction Using Benzene-Derived Catalysts



entry	R	R′	$k_{(rel)}$	entry	R	R′	$k_{(rel)}$
1	H	CF_3 (**20**)	930	3	Me	CF_3 (**22**)	1
2	H	CH_3 (**21**)	25	4	H	H (**23**)	37

vs methyl bearing catalysts (**20** vs **21**, 37:1 rate difference). The more dramatic increase in rate for the CF_3-bearing catalyst can be attributed to the fact that the basic residue is well insulated from the CF_3 group. In the pyridine-derived catalysts, the substitution of an alkyl or aryl group for an electron-withdrawing perfluoroalkyl or perfluoroaryl group likely has two opposing effects: while it renders the hydroxyl group more acidic, we suspect that it also renders the pyridine less basic due to its proximity to the pyridine. In catalyst **20**, there is no decrease in the basicity of the pyrrolidine upon substitution of the methyl for a trifluoromethyl because it is far removed from the trifluoromethyl group.

Interestingly, the activating effect of a trifluoromethyl group is great enough to render reactions with catalyst **20** 930 times faster than those with blocked catalyst **22** bearing a methyl ether in place of the hydroxyl group and 25 times faster than **23**, which bears a primary alcohol and is less hindered. Reactions with catalyst **20** are also 3.9 times faster than those with catalyst **14** (Table 1).

In conclusion, we have described two classes of *O*-nucleophilic acyl transfer catalysts and have shown that alcohols in close proximity to electron-withdrawing groups provide more active catalysts. We attribute this effect to an acidification of the hydroxyl group, leading to more facile deprotonation by the neighboring base, and to the better leaving group ability of the more acidic alcohol. In catalysts where the hydroxyl group and basic residue are insulated from each other, there is a greater benefit to having an electron-withdrawing group near the hydroxyl group. Catalysts in which the hydroxyl group is blocked as a methyl ether are significantly less active, providing good evidence that the reaction proceeds by an *O*-nucleophilic mechanism. Furthermore, the kinetic plots show zero-order behavior in substrate, with the acyl-catalyst intermediate being the predominant form of the catalyst, suggesting that attack of methanol on the acylated catalyst is turnover limiting and that the rate enhancement in the systems bearing electron-withdrawing groups is due to the enhanced leaving-group ability of the alcohol. Further studies to prepare more active catalysts and to study asymmetric synthesis with these catalysts are in progress.

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Supporting Information Available: Experimental procedures for kinetic measurements and for the synthesis of all catalysts and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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