Enhanced Selectivities for the Hydroxyl-Directed Methanolysis of Esters Using the 2-Acyl-4-aminopyridine Class of Acyl Transfer Catalysts: Ketones as Binding Sites

Tarek Sammakia* and T. Brian Hurley

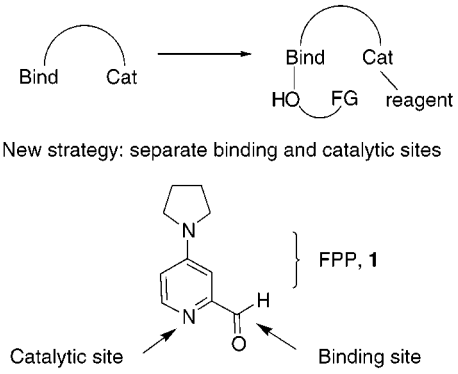
Department of Chemistry and Biochemistry, University of Colorado, Boulder, Colorado 80309-0215

Received July 27, 1999

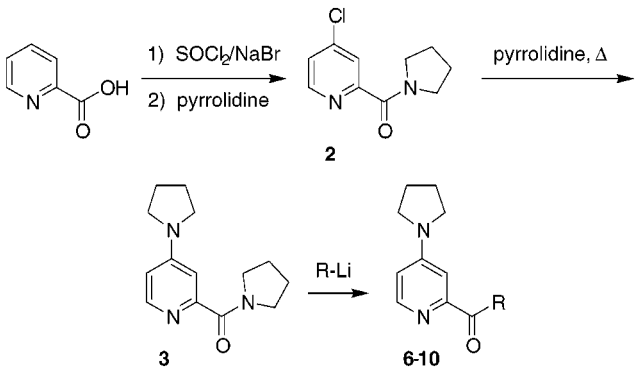
In this paper we describe the preparation of a series of 2-acyl-4-aminopyridines, and their use as catalysts for the hydroxyl-directed methanolysis of α-hydroxy esters in preference to α-methoxy esters. Hydroxyl-direction with these catalysts, which contain ketones at the 2-position of the pyridine, is achieved by reversible addition of the alcohol of the hydroxy ester to the ketone to provide the corresponding hemiketal. Their activity is compared to that of the previously described catalyst 2-formyl-4-pyrrolidinopyridine (FPP), which contains an aldehyde at the 2-position of the pyridine. The catalysts which contain ketones at the 2-position range in reactivity from 10 times slower to slightly faster than FPP, and certain of these are much more selective for the methanolysis of hydroxy esters than FPP. This increase in selectivity is ascribed to a decrease in the rate of the nondirected methanolysis reaction with the ketone-derived catalysts. The evidence suggests that the nondirected reaction does not proceed by an intermolecular general base mechanism, but rather via a nucleophilic catalysis mechanism in which the hydroxyl group of the hemiacetal formed upon addition of methanol to the aldehyde of FPP acts as the nucleophile. Since the hydroxyl group derived from a hemiketal is more hindered and less nucleophilic than that derived from a hemiacetal, the nondirected reaction is much slower for the catalysts containing ketones as binding sites.

We recently described a new strategy for the design of catalysts for hydroxyl-directed reactions[1] in which the catalysts contain spatially separate binding and catalytic sites (Scheme 1).[2] This strategy offers numerous advantages for selective catalysis, including the ability to convert catalysts which are not hydroxyl-directed into ones which are by the incorporation of a binding site. We have demonstrated the feasibility of this strategy by rendering the 4-aminopyridine class of acyl transfer catalysts hydroxyl-directed by incorporating a binding site at the 2-position of the pyridine. The binding site for our initial studies was an aldehyde, and the parent compound 2-formyl-4-pyrrolidinopyridine (FPP, **1**; Scheme 1) was found to display about 100:1 selectivity for the methanolysis of α-hydroxy esters over α-methoxy esters. In this paper we describe our work on the use of ketones as binding sites for this class of catalysts, report that certain ketone derivatives can provide greater than 1700:1 selectivities for the same process, and offer a mechanistic explanation for the origin of these enhanced selectivities.

Scheme 1



Scheme 2



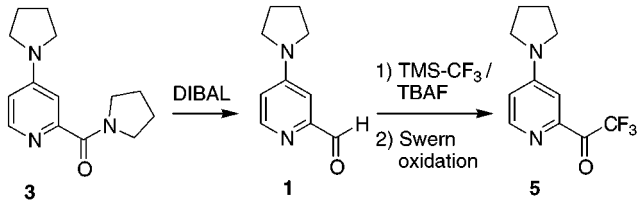
Results

Synthesis of the Ketone Catalysts. Amide **3** was found to be a versatile, readily accessible intermediate for the synthesis of the catalysts described in this study. The synthesis of **3** (Scheme 2) begins with the conversion of picolinic acid to 4-chloropicolinyl chloride according to the procedure of Sundberg,[3] followed by condensation of the crude acid chloride with pyrrolidine to provide the 4-chloro amide **2**. Nucleophilic aromatic substitution of the 4-chloro substituent of **2** in refluxing pyrrolidine then provides **3**. Both amide formation and nucleophilic aromatic substitution can be performed in one pot as a single step; however, we find that purification of **2** prior to

(1) For a review of substrate-directable reactions, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.
(2) (a) Sammakia, T.; Hurley, T. B. *J. Am. Chem. Soc.* **1996**, *118*, 8967. (b) Sammakia, T.; Hurley, T. B. *J. Org. Chem.* **1999**, *64*, 4652.
(3) Sundberg, R. J.; Songchun, J. *Org. Prep. Proced. Int.* **1997**, *29*, 117.

10.1021/jo991202k CCC: $19.00
Published on Web 01/26/2000

Scheme 3



substitution provides **3** in higher yield and purity. The synthesis of the ketone catalysts **6**−**10** consists of the addition of an alkyl- or aryllithium reagent to amide **3** in tetrahydrofuran at −78 °C.[4]

The trifluoromethyl ketone **5** was synthesized in a three-step procedure also starting from **3** (Scheme 3). DIBAL reduction of the amide to the aldehyde **1** (FPP)[5] was followed by addition of a trifluoromethyl group according to the procedure of Prakash and Olah[6] to provide the corresponding trifluoromethyl alcohol **4**. Swern oxidation[7] of this species provided the partially hydrated trifluoromethyl ketone, which was dehydrated by azeotropic removal of water with benzene to provide **5**.

Ester Methanolysis. We have studied the hydroxyl-directed methanolysis of esters using the ketone derivatives shown in Table 1, and compared these results with the same reaction using FPP (**1**). Using the *p*-nitrophenyl (PNP) esters of glycolic acid (**11**) and methoxyacetic acid (**12**), we measured the rates of methanolysis of these substrates using 5 mol % catalyst in $CDCl_3$ containing 10 equiv of methanol-d_4 (Table 1). We find that the ketones are competent catalysts for the methanolysis of **11**, though the methyl and phenyl ketones (compounds **6** and **7**) are 10 and 5 times slower than FPP, respectively. Catalysts **8**−**10** contain an additional basic site and are comparable in reactivity to FPP, with catalysts **9** and **10** being slightly faster. Catalyst **5**, which contains a trifluoromethyl ketone, is also more active than FPP, presumably because the electron-withdrawing trifluoromethyl group renders the dioxolanone intermediate (which is the resting state of the catalyst under the reaction conditions)[2b] more susceptible to methanolysis. Interestingly, the selectivity for methanolysis of PNP glycolate over PNP methoxyacetate was significantly greater with catalysts **5**−**8** than with FPP. As previously mentioned, FPP catalyzes the methanolysis of **11** about 100 times faster than **12**. However, with catalysts **6**−**8**, we saw no evidence of methanolysis of **12** even after 5 days, while with catalyst **5**, only 5% methanolysis of **12** was observed after 6 days. With catalyst **5**, 4.2 min is required for 5% conversion of **11** to the corresponding methyl ester, indicating that the selectivity for hydroxyl-directed methanolysis is 1700:1. This selectivity represents an approximate lower limit for catalysts **6**−**8** since we saw no evidence of methanolysis of **12** after 5 days. Catalysts **9** and **10** display selectivities comparable to that of the parent FPP.

(4) For compounds **8**−**10**, inverse addition of the amide to the organolithium was required to obtain high yields. Though an excess of the organilithium reagent was used in most cases, double addition to form the tertiary alcohol was not observed.

(5) Reduction of amide **3** provides a simpler and higher yielding alternative to the previously reported route to FPP.

(6) Prakash, G. K. S.; Krishnamurti, R.; Olah, G. A. *J. Am. Chem. Soc.* **1989**, *111*, 393.

(7) Mancuso, A. J.; Huang, S.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

Discussion

The hydroxyl-direction in these reactions requires the formation of a hemiacetal or hemiketal between the hydroxyl group of the substrate and the carbonyl of the catalyst.[2b] Since ketones are less prone to hemiketal formation than aldehydes are to hemiacetal formation,[8] we reasoned that they may make less effective binding sites, and expected the ketone-containing catalysts to be slower and less selective. The remarkably high selectivity observed with the ketone-containing catalysts requires a reappraisal of our rationale for the origin of the selectivity observed with this class of catalysts. We have extensively studied the mechanism of the hydroxyl-directed reaction with FPP and conclude that it proceeds by the path shown in Scheme 4.[2b] In this mechanism, the hydroxyl group of the α-hydroxy ester adds to the aldehyde of FPP to provide hemiacetal **13**. The nitrogen of the pyridine then acts as a general base, deprotonating the hydroxyl group of the hemiacetal while the oxygen acts as a nucleophile, attacking the bound ester to provide dioxolanone **14**. Methanolysis of the dioxolanone then occurs with general-base assistance from the pyridine, and is the turnover-limiting step of the catalytic cycle. The resting state of the catalyst is, therefore, dioxolanone **14**, and we have observed this species by NMR in reactions in progress.[9] Because the rate of the hydroxyl-directed reaction is comparable with the ketone and aldehyde catalysts, the increase in selectivity observed with the ketone catalysts must be due to a decrease in the rate of the nondirected reaction. We had assumed that this reaction proceeds via a simple intermolecular general-base catalysis pathway catalyzed by FPP, the corresponding methanol hemiacetal of FPP, or dioxolanone **14**. However, if this were the case, then the ketone-containing catalysts should provide rates of nondirected methanolysis similar to that of FPP. The difference in behavior of the ketone and aldehyde catalysts prompted us to consider an alternative mechanism for the nondirected reaction.

Our study of the mechanism of the non-hydroxyl-directed reaction began with the observation that in competition experiments between **11** and **12** using 6-methyl-FPP and 6-triethylsilyl-FPP (**15**),[10] there is a delay prior to the onset of the nondirected reaction. This is illustrated in Scheme 5 in which the 6-triethylsilyl derivative of FPP is used as a catalyst.[11] Interestingly, the delay roughly corresponds to the length of time that the hydroxyl-directed reaction (i.e., the methanolysis of **11**) is occurring. Since the resting state of the catalyst

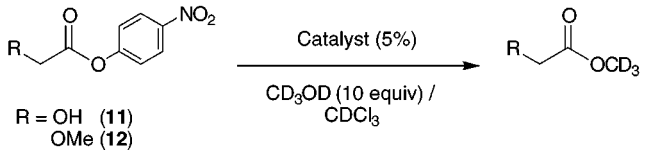
(8) For reviews on the hydration of aldehydes and ketones see: (a) Bell, R. P. In *Advances in Physical Organic Chemistry*; Gold, V., Ed.; Academic: New York, 1966; Vol. 4, pp 1−29. (b) Ogata, Y.; Kawasaki, A. In *The Chemistry of the Carbonyl Group*; Patai, S., Ed.; Interscience: London, 1970; Vol. 2, pp 1−61. For a recent study, see: (c) Wiberg, K. B.; Morgan, K. M.; Malltz, H. *J. Am. Chem. Soc.* **1994**, *116*, 11067. For a study of the hydration of pyridine carboxaldehydes, see: Pocker, Y.; Meany, J. E.; Nist, B. J. *J. Phys. Chem.* **1967**, *71*, 4509. Gianni, P.; Matteoli, E. *Gazz. Chim. Ital.* **1975**, *105*, 125.

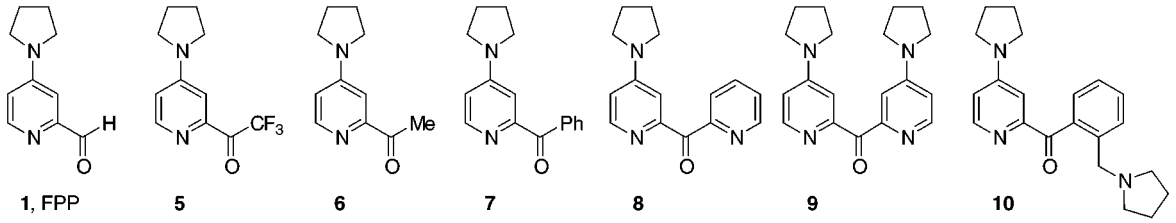
(9) See the Supporting Information in ref 2a for the characterization of compound **14**.

(10) The synthesis of 6-methyl-FPP has been previously reported. See ref 2b. 6-Triethylsilyl-FPP was synthesized from 2,6-diiodo-4-(pyrrolidin-1-yl)pyridine in two steps by sequential metal halogen exchange reactions trapping with chlorotriethylsilane and then DMF.

(11) The 6-triethylsilyl-FPP catalyst (**15**) was chosen to illustrate this point because it is the least selective of the FPP derivatives we have prepared, displaying the largest rate of the nondirected reaction. Due to the high rate of this reaction, a delay in the methanolysis of **12** would be most evident with this catalyst.

Table 1. Selectivities and Relative Rates for the Methanolysis of *p*-Nitrophenyl Esters of Glycolic Acid and Methoxyacetic Acid

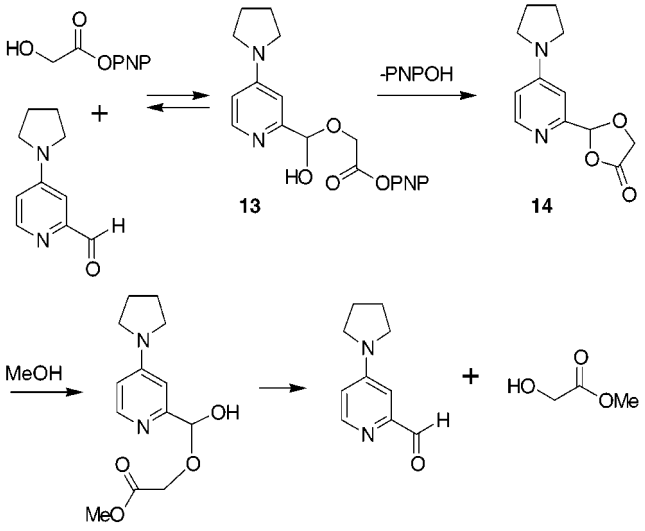




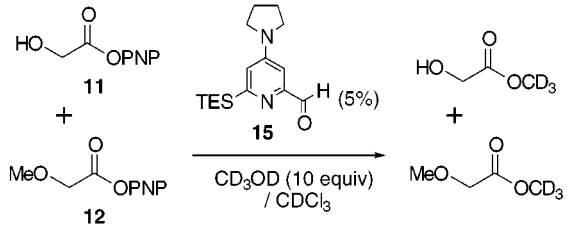
Catalyst	1	5	6	7	8	9	10
k_{rel} (HO-Gly-OPNP)	1	2.0	0.1	0.2	1	1.4	1.3
$\frac{k\ \text{HO-Gly-OPNP}}{k\ \text{MeO-Gly-OPNP}}$	96	1,700[a]	>1,700[b]	>1,700[b]	>1,700[b]	120	130

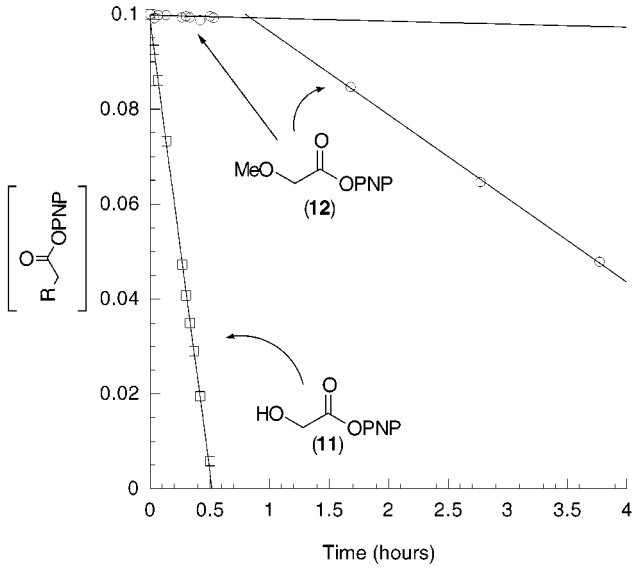
[a] 5% methanolysis of **12** was observed after 6 days. [b] No detectable methanolysis of **12** after 5 days.

Scheme 4



Scheme 5



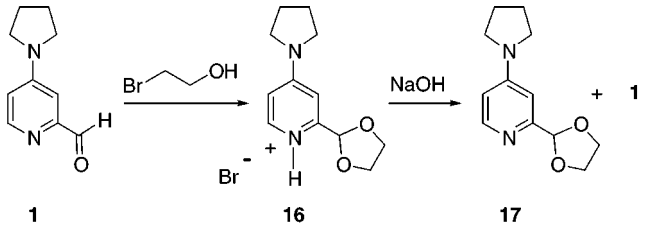


during the methanolysis of **11** is the dioxolanone, this suggests that this species is not an effective catalyst for the nondirected reaction.

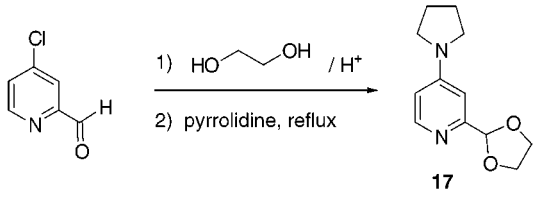
To test this hypothesis, we prepared the dioxolane acetal of FPP (**17**) as a model for dioxolanone **14**, and examined its ability to catalyze the methanolysis of **12** under our reaction conditions. We were unable to prepare **17** by standard acid-catalyzed acetal formation from FPP. However, when FPP was subjected to bromoethanol in DMF or neat, dioxolane hydrobromide **16** was isolated in 49% yield after purification (Scheme 6). The formation of **16** presumably occurs via a mechanism similar to that proposed for the formation of dioxolanone **14**. This reaction provides further evidence for the nucleophilicity of the FPP hemiacetal hydroxyl group and the general-base assistance by the pyridyl nitrogen for the formation of the dioxolanone intermediate.[12] Surprisingly, we were unable to convert **16** to **17** without extensive hydrolysis and ultimately prepared **17** from 2-formyl-4-chloropyri-

(12) No reaction is observed between benzaldehyde and bromoethanol.

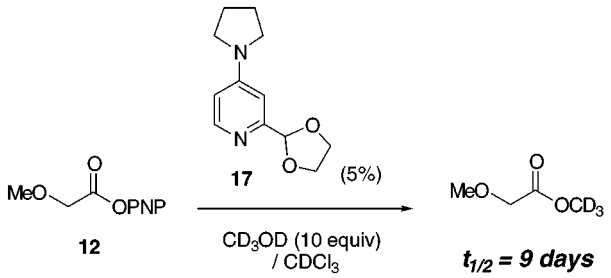
Scheme 6



Scheme 7



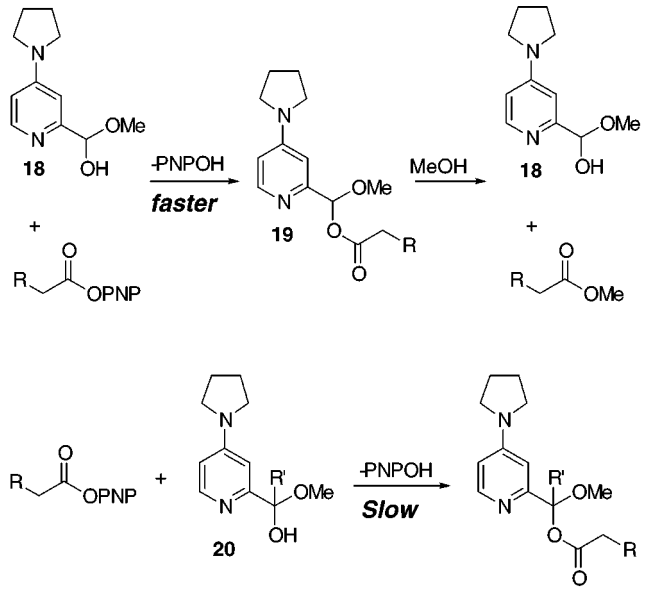
Scheme 8



dine by the method of Agrawal (Scheme 7).[13] In the event, the use of **17** as a catalyst for the methanolysis of **12** under our standard reaction conditions results in very slow methanolysis of the ester with a half-life of 9 days (Scheme 8).

If the nondirected reaction were operating by a general-base mechanism, there would be no obvious reason dioxolanone **14** or dioxolane **17** should not be effective catalysts for the methanolysis of **12**. The lack of reactivity of these species suggests that the nondirected reaction is operating by a mechanism other than intermolecular general-base catalysis, and offers an explanation for the enhanced selectivity observed with catalysts **5**−**8**. We suggest that the nondirected reaction is catalyzed by the hemiacetal formed upon addition of methanol to the aldehyde of FPP (**18**; Scheme 9). In fact, examination of the resting state of catalyst **15** by ^{1}H NMR during the methanolysis of **12** shows the catalyst exists as either the methanol hemiacetal or the acylated hemiacetal **19**.[14] The hemiacetal hydroxyl group is more acidic than those of ordinary alcohols[15] and can attack active esters with

Scheme 9



general-base assistance from the pyridyl nitrogen. The product of this step is ester **19**, and this compound can then undergo methanolysis with general-base assistance from the pyridyl nitrogen to provide the methyl ester and regenerate hemiacetal **18**.[16] Ketones are incapable of functioning by this mechanism for two reasons. First, the hemiketal formed upon addition of methanol to a ketone (**20**) is more hindered and less nucleophilic than the hemiacetal produced from the aldehyde-containing catalysts. Second, ketones are less prone to form hemiketals than aldehydes are to form hemiacetals.[17] Thus, there is a lower concentration of the hemiketal which is less reactive, leading to a decrease in the nondirected rate of reaction. Consistent with this mechanism is the fact that when the FPP-catalyzed methanolysis of **11** versus **12** is run in methanol-d_4 as the solvent, the selectivity for the methanolysis of **11** decreases from 96:1 (in $CDCl_3$) to 4:1. This is due to an increase in the concentration of the methanol hemiacetal of FPP and a corresponding increase in the rate of the nondirected reaction which is catalyzed by this species.

The mechanism for the nondirected reaction is similar to that first proposed by Werber and Shalitin for the reaction of tertiary β-amino alcohols with active esters in buffered aqueous solution.[18] In this system the tertiary amino group acts as an intramolecular general base to assist attack by the hydroxyl oxygen. When the ester contains an activated acyl moiety (such as that present

(13) Agrawal, K. C.; Booth, B. A.; DeNuzzo, S. M.; Sartorelli, A. C. *J. Med. Chem.* **1976**, *19*, 1209.

(14) We cannot readily distinguish between these species because the chemical shifts vary as the reaction progresses and *p*-nitrophenol is liberated. The data are most consistent with the resting state being the methanol hemiacetal **18**. Examination of the ^{1}H NMR spectrum of the competition reaction described in Scheme 5 at 100% conversion of **11** and 40% conversion of **12** revealed resonances for the catalyst at δ = 5.61 (s, 1H), 6.45 (d, J = 2.5 Hz, 1H), and 6.61 (d, J = 2.5 Hz, 1H). The remaining resonances are obscured by the reactants. The ^{1}H NMR spectrum of catalyst **15** (0.005 M) in CD_3OD (1.0 M) and PNPOH (0.1 M) in chloroform reveals resonances for the methanol hemiacetal at δ = 5.51 (s, 1H), 6.45 (br, 1H), and 6.55 (br, 1H). The ratio of the methanol hemiacetal to the aldehyde under these conditions is 2.7:1 in favor of the hemiacetal. If **19** were the resting state, we would expect to observe the acetal methine proton further downfield at about δ = 6.0.

(15) Carbonyl hydrates are about 4 pK_a units more acidic than the corresponding alcohol. See ref 8a, pp 12−16. For data on the acidity of pyridine carboxaldehyde hydrates, see: Owen, T. C. *J. Heterocycl. Chem.* **1990**, *27*, 987.

(16) Menger has described the use of aldehyde hydrates as catalysts for the hydrolysis of active esters. See: Menger, F. M.; Ladika, M. *J. Am. Chem. Soc.* **1987**, *109*, 3145. The use of the corresponding ketones results in a less active catalyst, consistent with our findings. See: Menger, F. M.; Persichetti, R. A. *J. Org. Chem.* **1987**, *52*, 3451.

(17) For example, under our reaction conditions the 6-triethylsilyl catalyst **15** exists as a 1:3 mixture of hemiacetal to aldehyde whereas catalysts **6**−**8** exist exclusively as the ketones as determined by ^{1}H NMR. The exception to this is the trifluoromethyl ketone **5**, which is found to exist as a 10:1 ratio of hemiketal/hydrate (due to adventitious moisture), with none of the free ketone being observed. In this case, the selectivity is due to the steric hindrance and resulting lack of nucleophilicity of the hemiketal adduct.

(18) Werber, M. M.; Shalitin, Y. *Bioorg. Chem.* **1973**, *2*, 202.

in a methoxyacetate ester), a subsequent deacylation step is also observed, which is believed to occur by intramolecular general-acid catalysis by the protonated amine. The overall reaction then consists of the hydrolysis of active esters using an amino alcohol to facilitate the reaction via an acylation−deacylation mechanism. Subsequently, there have been extensive investigations of the use of amino alcohols as models for protease enzymes.[19] In our system, it is interesting to note that both the directed and nondirected reactions proceed by mechanisms in which the hydroxyl group of a hemiacetal acts as a nucleophile. Further experiments to exploit this finding are in progress.

Acknowledgment. We thank the National Institutes of Health (Grant GM48498), Novartis Pharmaceuticals Corp., and Pfizer for financial support of this research. T.S. is a recipient of an American Cancer Society Junior Faculty Research Award and is an Alfred P. Sloan Research Fellow. T.B.H. is a recipient of an American Chemical Society Division of Organic Chemistry Fellowship sponsored by Eli Lilly and Co.

Supporting Information Available: Preparation and spectral characterization of compounds **2**, **3**, **5**−**10**, and **15**−**17**, and ^{1}H spectra for compounds **9**, **15**, and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO991202K

(19) (a) Hine, J.; Khan, N. M. *J. Am. Chem. Soc.* **1977**, *99*, 3847. (b) Khan, N. M. *J. Chem. Res. (S)* **1986**, 290. (c) Khan, N. M. *J. Org. Chem.* **1985**, *50*, 4851. (d) Brown, R. S. *J. Am. Chem. Soc.* **1989**, *111*, 1445. (e) Khan, N. M. *Indian J. Chem.* **1992**, *31B*, 427. (f) De Clercq, P. J.; Madder, A.; Declercq, J.-P. *J. Org. Chem.* **1998**, *63*, 2548.