Biomimetic trifunctional organocatalyst showing a great acceleration for the transesterification between vinyl ester and alcohol†

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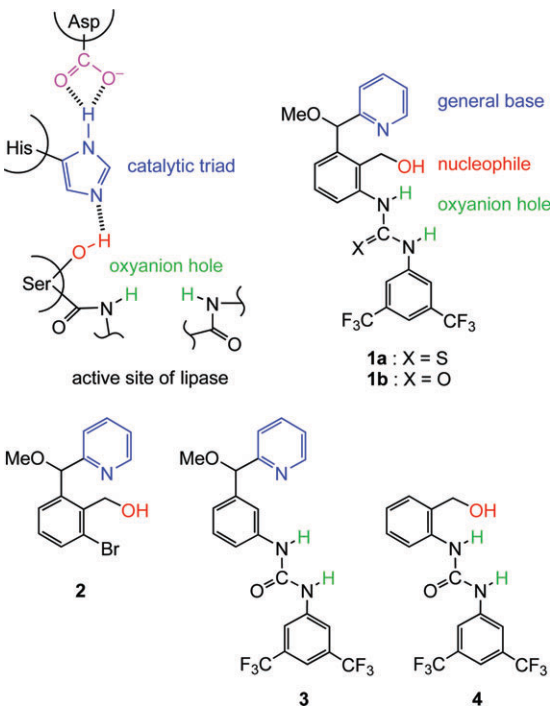
Trifunctional organocatalysts 1a and 1b mimicking the active site of serine hydrolases showed high catalytic activity with up to a 3 700 000-fold acceleration for the acyl-transfer reactions from vinyl trifluoroacetate to alcohol.

The creation of an organic compound with an enormous catalytic power like an enzyme is an important and exciting subject. Using useful synthetic methods and accumulated mechanistic knowledge, chemists have tried to create artificial enzymes with high catalytic activity.[1,2] A rapidly growing area related to this subject is asymmetric organocatalysis,[3–10] which is aimed at synthetic application. Although some of the organocatalysts developed so far can work in very small amounts,[10] 5–20 mol% of catalyst is used in many cases.[3a] On the other hand, the catalytic activity and turnover number of an enzyme are extremely high; for example, the apparent second-order rate constant for an enzymatic reaction, ranging from 10^7 to 10^8 M^{-1} s^{-1}, is close to that for the diffusion-controlled encounter frequency of an enzyme and a substrate in water, 10^9 M^{-1} s^{-1}.[11] Although various artificial enzymes and organocatalysts have been developed, they are still inferior to natural enzymes in catalytic activity and turnover.[1f] Therefore, it is worth constructing a highly active catalyst by mimicking the active site of an enzyme, during which we can learn various factors and clues to the dramatic improvement of catalytic activity. Here we report highly active biomimetic organocatalysts capable of catalyzing the acyl-transfer reactions from vinyl trifluoroacetate to alcohol in an organic solvent.

Serine hydrolases, such as lipases, esterases, and serine proteases, are widely used as biocatalysts in organic synthesis.[12,13] Because the reaction mechanisms together with their crystal structures are well elucidated,[13] and because they can catalyze even transesterifications in organic solvents to find valuable synthetic utility,[12] we decided to design and synthesize an organocatalyst mimicking the active site of serine hydrolases, particularly lipases. The candidates, searched by performing MO calculations on the tetrahedral intermediates, are shown in Scheme 1. Trifunctional compounds **1** bear a hydroxy group expected to act as a nucleophile, a pyridine moiety as a base, and a (thio)urea group as an oxyanion hole to stabilize the carbonyl oxyanion in the transition state. The 3,5-bis(trifluoromethyl)phenyl group was used to enhance the hydrogen-bond donor ability of the (thio)urea group.[4d,8a,8c] The carboxylate anion of the catalytic triad was omitted in this study. Compounds **2–4** lack one of the three functional groups, enabling us to investigate the role of each catalytic group. We involved no binding sites for attracting a substrate because we aimed at creation of a catalyst capable of accelerating the reaction by stabilizing the transition state, independent of substrate binding. Synthetic procedures for **1–4** are given in ESI.†

To evaluate the catalytic power of **1–4**, we first examined vinyl acetate as an acyl donor because it is used frequently in lipase-catalyzed transesterifications.[12,13] However, vinyl acetate was not consumed at all even in the presence of 1 equiv. of **1a** in CD_3OD as measured by ^1H NMR. We therefore examined a more reactive acyl donor, vinyl trifluoroacetate. When vinyl trifluoroacetate (100 mM) was added to a solution of **1a** (1 equiv.) and MeOH (500 mM) in $CDCl_3$, to our delight, the reaction was too fast to monitor by means of ^{19}F NMR.



Scheme 1

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† Electronic supplementary information (ESI) available: Synthetic procedures, copies of ^1H, ^{13}C, and ^{19}F NMR spectra, evidence for the generation of **1b-Ac**, and the derivation of eqn (1) followed by the determination of the rate constants. See DOI: 10.1039/b718763g

We therefore used a catalytic amount of **1a** (1 mol%) under otherwise the same reaction conditions, which allowed us to monitor the progress of the reaction (Fig. 1). The signal for methyl trifluoroacetate increased with a decrease in that for vinyl trifluoroacetate (Fig. 1a). The time course of the reaction is plotted in Fig. 1b. Fig. 1b clearly shows that the addition of only 1 mol% of **1a** accelerated the transesterification, which reached almost 100% conversion in 1 h. We also examined the corresponding urea derivative **1b**. Surprisingly, **1b** showed a greater acceleration, completing the reaction within 30 min. With a catalyst loading of 0.1 mol% of **1a** and **1b**, the reactions were almost complete within 16 h and 4 h, respectively (data not shown). We also found that **1a** and **1b** (1 mol%) can accelerate the acylation of *i*-PrOH (Fig. 1b). On the other hand, the control compounds **2**–**4**, lacking either the hydroxy, pyridine, or (thio)urea moiety, showed little or no acceleration under the same reaction conditions (data not shown in Fig. 1b). These results demonstrate that the three functional groups work cooperatively to decrease the activation energy.

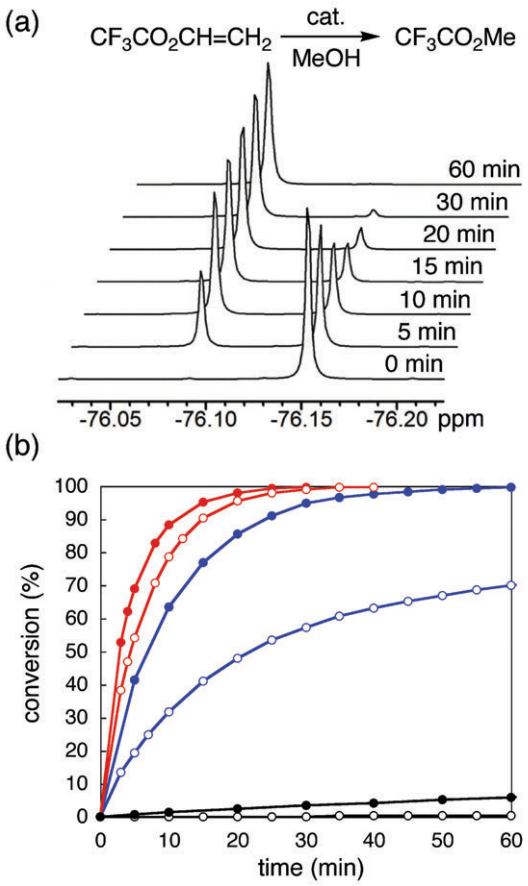
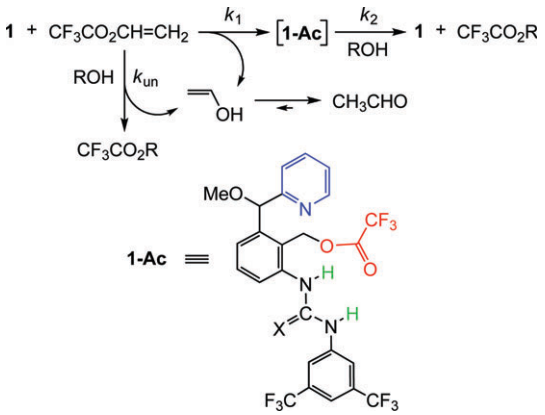


Fig. 1 (a) Change of 565 MHz ^{19}F NMR spectra of a mixture of **1a** (1 mM), vinyl trifluoroacetate (100 mM) and MeOH (500 mM) in $CDCl_3$ at 22 °C. (b) Time courses of the acyl-transfer reactions from vinyl trifluoroacetate to MeOH (filled circles) and *i*-PrOH (open circles). The reactions catalyzed by **1a** and **1b** (1 mol%) are shown in blue and red, respectively, and the background reactions are shown in black. The data for **2**, **3**, and **4**, all of which were very close to the background reactions, are omitted for clarity.



Scheme 2

We assumed the catalytic cycle shown in Scheme 2 for the following reasons: (i) the fact that the hydroxy group in **1** is essential to the catalysis strongly supports covalent catalysis *via* the acyl-catalyst intermediate, **1-Ac**, which was detected by ^{19}F NMR; (ii) the use of vinyl ester makes the reaction irreversible;[12,13] (iii) the acyl-transfer reactions catalyzed by **1**, which has no binding sites to form a catalyst–substrate complex prior to the reaction, are likely to proceed *via* collisional encounters; indeed, the binding constants were too small to determine when NMR titrations were done to estimate the binding affinity of **1** for vinyl acetate instead of vinyl trifluoroacetate. We applied the steady-state approximation to the acyl-catalyst intermediate, **1-Ac**, to derive eqn (1). The rate constants were determined under pseudo-first-order conditions and are listed in Table 1. The derivation of eqn (1) and the procedure for the determination of the rate constants are given in ESI.†

$$v = \frac{k_1 k_2[\mathbf{1}][\mathrm{A}][\mathrm{S}]}{k_1[\mathrm{A}] + k_2[\mathrm{S}]} + k_{\mathrm{un}}[\mathrm{A}][\mathrm{S}] \quad (1)$$

$$(\mathrm{A}: \mathrm{CF_3CO_2CH{=}CH_2};\ \mathrm{S}: \mathrm{ROH})$$

The great enhancements of the rate constants were confirmed (Table 1). In the acyl-transfer reactions to MeOH, the k_1 values for the acylations of **1a** and **1b** were 32 000- and 190 000-fold greater, respectively, than the k_{un} value for the uncatalyzed, background reaction, while the k_2 values for the subsequent deacylations of intermediates, **1a-Ac** and **1b-Ac**, were 3800- and 8300-fold greater, respectively, than the k_{un} value. In the acyl-transfer reactions to *i*-PrOH, the k_1 values for the acylations of **1a** and **1b** were 650 000- and 3 700 000-

Table 1 Second-order rate constants for the **1**-catalyzed transesterifications between vinyl trifluoroacetate and alcohol in $CDCl_3$ at 22 °C[a]

1	ROH	$k_1/\mathrm{M^{-1}\ s^{-1}}$	$k_2/\mathrm{M^{-1}\ s^{-1}}$	k_1/k_{un}	k_2/k_{un}
1a	MeOH	2.4	0.29	32 000	3800
1b	MeOH	14.4	0.63	190 000	8300
1a	*i*-PrOH	2.6	0.12	650 000	30 000
1b	*i*-PrOH	14.9	0.61	3 700 000	150 000

[a] For the detailed procedure, see ESI.† The k_{un} values for the acylations of MeOH and *i*-PrOH were 7.6×10^{-5} and 4.0×10^{-6} $\mathrm{M^{-1}\ s^{-1}}$, respectively.

fold greater, respectively, than the k_{un} value, while the k_2 values for the deacylations of **1a-Ac** and **1b-Ac** were 30 000- and 150 000-fold greater, respectively, than the k_{un} value. These values are very high despite the lack of a substrate-binding site in **1**. The acceleration was greater for *i*-PrOH than for MeOH, which is due to the lower background level of the former.

The results in Fig. 1b and Table 1 have three important implications. First, the nucleophilicity of the hydroxy group of a catalyst can be enhanced dramatically when a base, pyridine in this case, is disposed in close proximity. Indeed, catalyst **3**, lacking the hydroxy group, cannot activate MeOH or *i*-PrOH well enough to attack the acylating agent. These results are consistent with the fact that serine hydrolases employed the side chain of the serine residue, but not H_2O, as a nucleophile in the course of evolution.[11] Second, the rate constant for the acylation step (k_1) is greater than that for the deacylation of the acyl-catalyst intermediate (k_2), and the latter reaction is the rate-determining step. The same trend has been observed for natural and artificial enzymes;[1b,2f,9a,11] for example, when *p*-nitrophenyl acetate was hydrolyzed, the acyl-enzyme/catalyst intermediate was accumulated after a burst reaction had taken place, giving off 1 equiv. of *p*-nitrophenolate anion.[1b,2f] Third, Table 1 clearly indicates that urea catalyst **1b** shows higher activity in each step than thiourea catalyst **1a**, which suggests that the urea group is a better mimic of the oxyanion hole of serine hydrolases.

In summary, trifunctional organocatalysts **1** reminiscent of the active site of serine hydrolases were designed and synthesized. Up to a 3 700 000-fold acceleration with high catalytic turnover was achieved by **1b** at room temperature. Comparisons between **1** and **2–4** demonstrate that the three functional groups in **1** work cooperatively to stabilize the transition state and accelerate the reaction. This is, to the best of our knowledge, the first example of a biomimetic organocatalyst bearing a nucleophilic OH group, a base, and an oxyanion hole, which can catalyze the transesterification between vinyl ester and alcohol.[14] Further work is in progress to optimize the structure of the catalyst and apply the catalyst to asymmetric synthesis.

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