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Rational Design of an L-Histidine-Derived Minimal Artificial Acylase for the Kinetic Resolution of Racemic Alcohols

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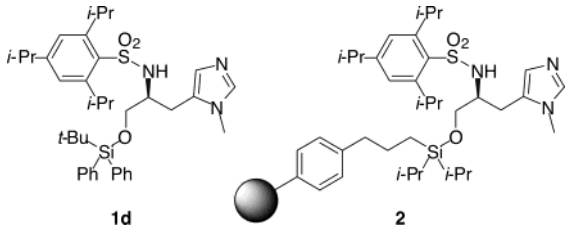
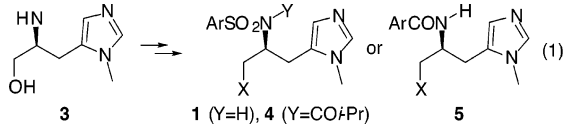
The kinetic resolution of racemic secondary alcohols has traditionally been achieved by using acylases.[1] Recently, several impressive examples of the nonenzymatic kinetic resolution of racemic alcohols with achiral anhydrides have been reported using nucleophilic chiral analogues of trialkylphosphine,[2] 4-(dimethylamino)pyridine (DMAP),[3] and 1-alkylimidazole (1-alkyl-IMD).[4] In particular, Miller's biomimetic approach[4] to the identification of artificial acylases based on β-turn peptide fragments with defined secondary structures that contain 1-alkyl-IMD residues prompted our present study. In this communication, we report the rational design of an L-histidine-derived minimal artificial acylase. The new artificial acylase **1d** is a simple and small molecule (molecular weight = 660) that contains only one chiral carbon center that originates from natural L-histidine. Reusable polystyrene-bound catalyst **2** was also developed to evaluate the practical usability of **1d** (Chart 1).

Chart 1. Homo- and Heterogeneous Artificial Acylases **1d** and **2**



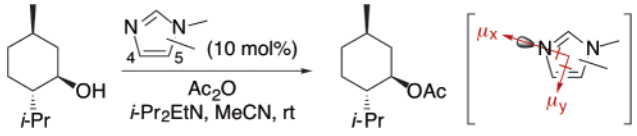
Initially, the catalytic activity of Me_2−IMD in the acetylation of menthol with acetic anhydride was investigated (Table 1). 1,5-Me_2−IMD was the most active among 1,2-, 1,4-, and 1,5-Me_2−IMD and 1-Me−IMD, although it was less active than DMAP. The catalytic activity increased in proportion to the intensity of the dipole moment (μ_x) on the *x*-axis parallel to a lone pair at the 3-positon. Thus, it was ascertained that Miller's L-histidine-derived peptide was suitable as an artificial acylase.

Our initial considerations for the design of new artificial acylases focused on two functional groups derived from L-histidine: (i) a 1,5-dialkyl-IMD component as a nucleophilic catalytic moiety and (ii) an amide component as a hydrogen-bonding domain.[4] Thus, sulfonamide **1** and carboxamide **5** were prepared from *N*(π)-Me-L-histidiol (**3**)[5] in two steps (eq 1).[6]



1, **4**, and **5** were evaluated as catalysts for the kinetic resolution of (±)-*cis*-1-[*p*-(dimethylamino)benzoyl]-2-hydroxyhexane (**6a**)

Table 1. Comparison of Catalytic Activities of Bases for the Acetylation of Menthol with Acetic Anhydride[a]



catalyst (mol %)	time (h)	yield (%)	$\lvert\mu\rvert$ (D)[b]	$\lvert\mu_x\rvert$ (D)[b]
DMAP, 5	0.5	100	4.84	4.83
1,5-Me_2−IMD, 5	0.5	47	4.46	4.26
1,5-Me_2−IMD, 5	3.0	100	4.46	4.26
1-Me−IMD, 10	3.0	73	4.27	3.93
1,4-Me_2−IMD, 10	3.0	29	3.87	3.61
1,2-Me_2−IMD, 10	3.0	23	4.11	3.58

[a] Unless otherwise noted, menthol (1 mmol), Ac_2O (1.5 mmol), *i*-Pr_2EtN (1.5 mmol), and MeCN (2 mL) were used. [b] $\mu = \mu_x + \mu_y$, dipole moment of catalyst. $\lvert\mu\rvert$ was calculated at the B3LYP/6-311++G(d,p) level.

with (*i*-PrCO)$_2$O (eq 2).[3c] Reactions were allowed to proceed for 3 h at room temperature in toluene under conditions using 5 mol % of catalyst relative to **6a**. As shown in Table 2, all of the L-histidine-

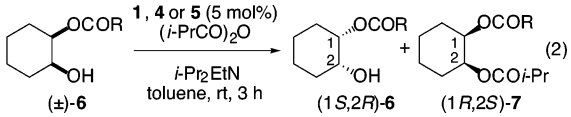


Table 2. Kinetic Resolution of (±)-**6a** [R = 4-(Me_2N)C_6H_4] (eq 2)[a]

catalyst (*S*)-**1**, **4**, or **5** (Ar, X)	**6a** → **7a** (%)[c]	ee (%)[b] **6a**	ee (%)[b] **7a**	*S*[c]
5 (C_6H_5, $OSiPh_2t$-Bu)	36	3	5	1
1a (C_6H_5, $OSiPh_2t$-Bu)	51	60	57	7
1b (*p*-(CF_3)C_6H_4, $OSiPh_2t$-Bu)	42	52	71	10
1c (2,4,6-*i*-$Pr_3C_6H_2$, OCO*i*-Pr)	48	70	77	16
4 (2,4,6-*i*-$Pr_3C_6H_2$, OCO*i*-Pr)	30	3	7	1
1d (2,4,6-*I*-$Pr_3C_6H_2$, $OSiPh_2t$-Bu)	47	74	83	24

[a] Unless otherwise noted, (±)-**6a** (1 equiv), (*i*-PrCO)$_2$O (0.5 equiv), *i*-Pr_2EtN (0.5 equiv), catalyst (5 mol %), and toluene (2 mL) were used. [b] HPLC analysis. [c] Calculated according to the method of ref 7.

derived catalysts examined resulted in the preferential acyltion of (1*R*,2*S*)-**6a**. When **1d** bearing two bulky groups, 2,4,6-*i*-$Pr_3C_6H_2$-SO_2 and *t*-$BuPh_2SiO$ groups, was used, (1*R*,2*S*)-**7a** was obtained in 83% ee at 47% conversion [*S* (k_{fast}/k_{slow}) = 24]. The use of sulfonamide **1a** gave (1*R*,2*S*)-**6a** much more selectively and rapidly than that of carboxamide **5**. In addition, higher asymmetric induction was observed with the use of a more acidic sulfonamide catalyst (**1a** versus **1b**). In contrast, aprotic catalyst **4** was less active and showed almost no selectivity (*S* = 1). These results suggest that hydrogen bonding between **1d** and **6a** may be a key interaction for attaining a high level of kinetic resolution.

If hydrogen bonding between **1d** and **6a** is truly a key interaction, then **6** bearing a more electron-donating group (R) should give better

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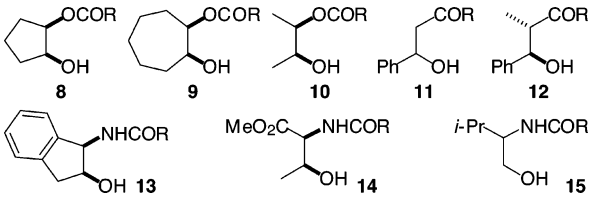
Table 3. Screening of R of (±)-**6** and Influence of Solvent on the Kinetic Resolution of (±)-**6** Induced by **1d** (eq 2)[a]

entry	racemic alcohol (±)-**6** [*R*-]	solvent	**6** → **7** (%)[c]	ee (%)[b] **6**	ee (%)[b] **7**	*S*[c]
1	**6a**[*p*-(Me_2N)C_6H_4−]	CH_3CN	30	25	57	5
2	**6a**[*p*-(Me_2N)C_6H_4−]	THF	39	38	59	6
3	**6a**[*p*-(Me_2N)C_6H_4−]	CH_2Cl_2	43	50	66	8
4	**6a**[*p*-(Me_2N)C_6H_4−]	toluene	47	74	83	24
5	**6a**[*p*-(Me_2N)C_6H_4−]	CCl_4	49	81	83	27
6	**6b**[Me_2N−]	CCl_4	53	96	83	42
7[d]	**6b**[Me_2N−]	CCl_4	54	99	83	64
8[d]	**6c**[(CH_2CH_2)$_2$N−]	CCl_4	52	97	90	87

[a] See footnote *a* in Table 2. [b] HPLC analysis. [c] See footnote *c* in Table 2. [d] The reaction was carried out at 0 °C for 3 h.

Table 4. Kinetic Resolution of Racemic Alcohols **8**−**15** [R = (CH_2CH_2)$_2$N−] Induced by **1d** (A = Alcohol; E = Isobutyrate of A)[a]



(±)-A	A → E (%)[b]	ee (%)[c] A, E	*S*[b]	(±)-A	A → E (%)[b]	ee (%)[c] A, E	*S*[b]
8[d]	49	90, 94	93	**12**[d]	49	80, 82	25
9[d]	50	93, 92	83	**13**[e]	42	67, 93	51
10[d]	47	82, 93	68	**14**[f]	39	51, 80	15
11[d]	44	64, 82	19	**15**[d]	50	88, 86	39

[a] See footnote *a* in Table 2. [b] See footnote *c* in Table 2. [c] HPLC or GC analysis. [d] 0 °C, 3 h; CCl_4. [e] 0 °C, 3 h; $CHCl_3$−CCl_4 (2:3). [f] 0 °C, 4 h; $CHCl_3$−CCl_4 (1:5).

results than **6a**. As shown in Table 3, carbamates **6b** and **6c** were more effective than **6a** (entries 5−8). In particular, the *S* value for the kinetic resolution of (±)-**6** was dramatically increased to 87 by using **6c** in place of **6a** (entry 8). In addition, CCl_4 and toluene were more suitable solvents, probably because less polar solvents did not inhibit hydrogen bonding interaction (entries 1−5).

To explore the generality and scope of the **1d**-induced kinetic resolution of secondary alcohols, the acylation of several structurally diverse alcohols with (i-PrCO)$_2$O was examined (Table 4). The acylations of not only cyclic 1,2-diol derivatives **8** and **9** but also acyclic **10** gave *S* values of more than 68. Hydroxycarboxylic acid derivatives **11** and **12** and amino alcohol derivatives **13**−**16** were also suitable substrates.

According to an X-ray structural analysis, a N−H bond and IMD ring in **1d** are parallel to each other on the same side, probably due to steric limitations imposed by the two bulky substituents (Figure 1). A transition-state assembly formed from **1d**, (1*R*,2*S*)-**6c**, and (i-PrCO)$_2$O was proposed on the basis of this X-ray structure (Figure 1). The conformation of the acyl group in the acylammonium salt generated from **1d** and (i-PrCO)$_2$O would be fixed by the attractive electrostatic interaction between its acyl oxygen and imidazoyl-2-proton or the dipole minimization effect.[8] Hydrogen bonding between the sulfonylamino proton of acylammonium salt and the carbamoyl oxygen of **6c** preferentially promotes the acylation of (1*R*,2*S*)-**6c** by a proximity effect. On the other hand, similar hydrogen bonding with (1*S*,2*R*)-**6c** inhibits its acylation.

Polymer-bound catalyst **2** was easily prepared from commercially available resin **16**[6] and **1** (Ar = 2,4,6-i-Pr$_3C_6H_2$, X = OH) (eq 3).[3h]

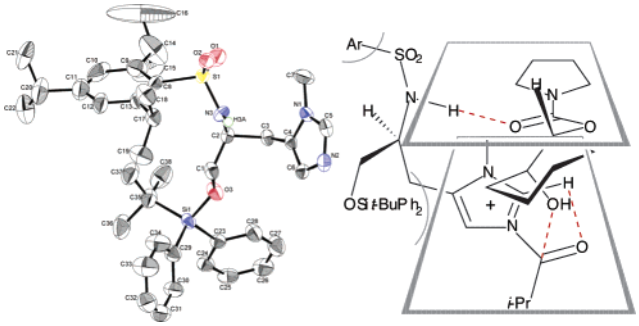
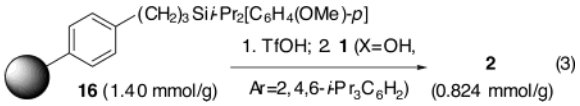


Figure 1. ORTEP plot of **1d** (left) and a proposed transition-state assembly (right). The figure is drawn with 50% probability, and hydrogen atoms except for the SO_2NH moiety are omitted for clarity (left).

2 (5 mol %) was reused more than 6 times for the acylation of (±)-**6c** (1 equiv) with (i-PrCO)$_2$O (0.5 equiv) under shaking at 0 °C for 7 h in the presence of i-Pr$_2$EtN (0.5 equiv) without any loss of activity or selectivity ((1*R*,2*S*)-**7c**: ∼48−49% yield, ∼87−90% ee; *S* value = 37).



In summary, we have designed a minimal artificial acylase **1d** derived from L-histidine by introducing a sulfonylamino group in place of a polypeptide chain on the basis of the notion that sulfonamide hydrogen bonding is much stronger than the corresponding carboxamide interaction. In addition, we developed a reusable organocatalyst **2**, which should greatly contribute to green and sustainable chemistry.

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Supporting Information Available: Experimental procedures, full characterization of new compounds, and crystallographic data for **1d** (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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