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Kinetic resolution of racemic alcohols catalyzed by minimal artificial acylases derived from L-histidine

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Abstract—The artificial acylases, *tert*-butyldiphenylsilyl ether and tris(trimethylsilyl)silyl ether of *N*(π)-methyl-*N*(α)-(2,4,6-triisopropylbenzenesulfonyl)-L-histidinol, are simple and small molecules, which contain only one chiral carbon center that originates from natural L-histidine. Asymmetric acylation of racemic secondary alcohols with isobutyric anhydride induced by these artificial acylases gave optically active isobutyrates and optically active alcohols with an $S(k_{\text{fast-reacting enantiomer}}/k_{\text{slow-reacting enantiomer}})$ value of up to 132. One hydrogen bonding interaction between a sulfonamidyl group of the catalysts and a substrate should be essential for inducing the high level of kinetic resolution through catalytic asymmetric acylation. Furthermore, a reusable polystyrene-bound artificial acylase was developed to examine its practicality.

1. Introduction

The kinetic resolution of racemic secondary alcohols through catalytic asymmetric acylation is a convenient and powerful method for obtaining optically active alcohols, which are useful as chiral building blocks for the synthesis of pharmaceutical and natural compounds.[1] Enzymatic kinetic resolution has been established as one of the most effective methods.[2] Several impressive examples of the non-enzymatic kinetic resolution of racemic alcohols with achiral anhydrides have been reported using nucleophilic chiral analogues of trialkylphosphine,[3] 4-(dimethylamino)pyridine (DMAP),[4] 1-alkylimidazole (1-alkyl-IMD),[5] and bicyclic amidines and bicyclic isothioureas.[6] In particular, Miller's biomimetic approach[5] 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. Very recently, we reported the rational design of an L-histidine-derived minimal artificial acylases **1c** and **3** (Fig. 1).[7] The artificial acylase **1c** is a simple and small molecule (molecular weight=660) that contains only one chiral carbon center that originates from natural L-histidine. Furthermore, reusable polystyrene-bound catalyst **3** has been developed to evaluate the practicality of **1c**. In this paper, we describe the details of the rational design of L-histidine-derived sulfonamide catalysts for asymmetric acylation of racemic alcohols. In addition, we report that a more bulky tris(trimethylsilyl)silyl [$(Me_3Si)_3Si$] ether (**2a**) of *N*(π)-methyl-*N*-(2,4,6-triisopropylbenzenesulfonyl)-L-histidinol is superior than **1c** for the asymmetric induction.

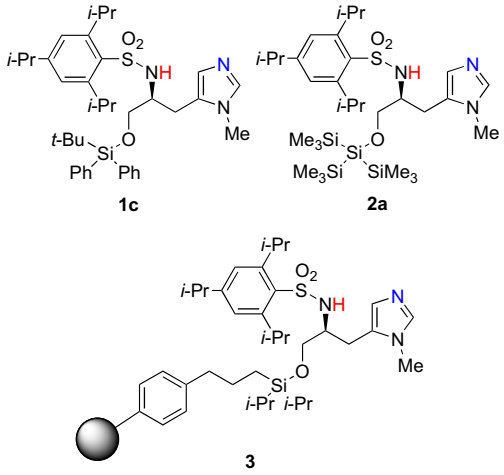

Figure 1. Homo- and heterogeneous artificial acylases **1c**, **2a**, and **3**.

2. Results and discussion

Initially, the catalytic activity of dimethylimidazole (Me_2-IMD) in the acetylation of L-menthol with acetic anhydride was investigated (Table 1). 1,5-Me_2-IMD was nucleophilically the most active catalyst among 1,2-, 1,4-, and 1,5-Me_2-IMD and 1-Me-IMD, although it was less active

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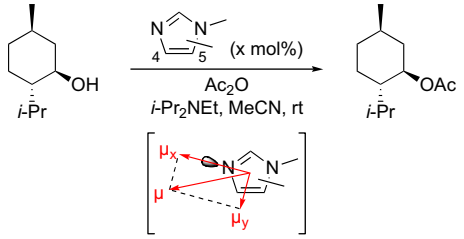
Table 1. Comparison of the catalytic activities of bases for the acetylation of L-menthol with acetic anhydride[a]



Catalyst	X	Time (h)	Yield (%)	$[\mu]$[b] (D)	$[\mu_x]$[b] (D)
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

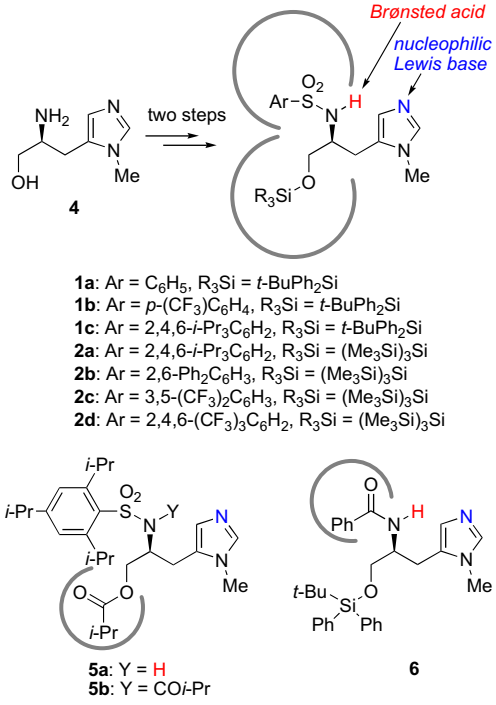
[a] Unless otherwise noted, L-menthol (1 mmol), Ac_2O (1.5 mmol), i-Pr_2EtN (1.5 mmol), and MeCN (2 mL) were used.
[b] $\mu=\mu_x+\mu_y$, dipole moment of catalyst. $[\mu]$ was calculated at the B3LYP/6-311++G(d,p) level.

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-position. Thus, Miller's L-histidine-derived peptide was determined to be 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.[5] Thus, sulfonamides **1**, **2**, **5**, and carboxamide **6** were prepared from $N(\pi)$-methyl-L-histidinol (**4**)[8] in two steps (Scheme 1).

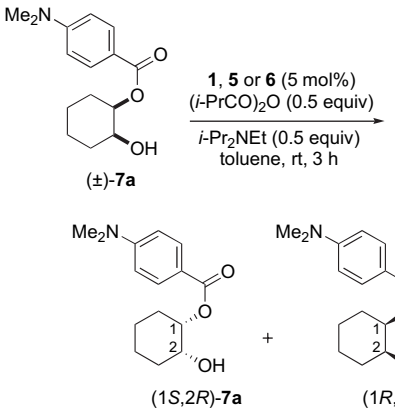
Compounds **1**, **5**, and **6** were evaluated as catalysts for the kinetic resolution of (±)-*cis*-1-[*p*-(dimethylamino)benzoyloxy]-2-cyclohexanol (**7a**) with $(i\text{-PrCO})_2O$.[4c] Reactions were allowed to proceed for 3 h at room temperature in toluene using 5 mol % of catalyst based on **7a**. As shown in Table 2, all of the L-histidine-derived catalysts examined resulted in the preferential acylation of (1*R*,2*S*)-**7a**. When sulfonamide **1c** bearing two sterically bulky groups, 2,4,6-triisopropylbenzenesulfonyl group and *tert*-butyldiphenylsilyl group, was used, (1*R*,2*S*)-**8a** was obtained in 47% conversion with 83% ee (S=24) (entry 6). The use of sulfonamide **1a** gave (1*R*,2*S*)-**7a** much more selectively and rapidly than carboxamide **6** (entry 1 vs entry 2). In addition, higher asymmetric induction was observed with the use of a more acidic sulfonamide catalyst such as **1b** (entry 2 vs entry 3). In contrast, aprotic catalyst **5b** was less active and showed almost no selectivity (S=1) (entry 4 vs entry 5). These results suggest that hydrogen bonding between sulfonamide **1** and (1*R*,2*S*)-**7a** may be a key interaction for attaining a high level of kinetic resolution.

If hydrogen bonding between **1d** and **7a** is truly a key interaction, *cis*-cyclohexan-1,2-diol monoprotected by a more electron-donating group should give better results than **7a**. As shown in Table 3, carbamates **7b** and **7c** were more effective than **7a** (entries 5–8). In particular, the S value for the kinetic resolution of (±)-**7** was dramatically increased to



Scheme 1. Preparation of artificial acylases **1**, **2**, **5**, and **6** derived from **4**.

Table 2. Kinetic resolution of (±)-**7a**[a]



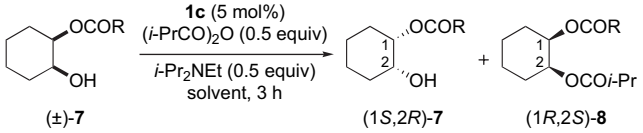
Entry	Catalyst	Conv.[b] (%)	ee of **7a**[c] (%)	ee of **8a**[c] (%)	S[d]
1	**6**	36	3	5	1
2	**1a**	51	60	57	7
3	**1b**	42	52	71	10
4	**5a**	48	70	77	16
5	**5b**	30	3	7	1
6	**1c**	47	74	83	24

[a] Unless otherwise noted, (±)-**7a** (1 equiv), $(i\text{-PrCO})_2O$ (0.5 equiv), i-Pr_2EtN (0.5 equiv), catalyst (5 mol %), and toluene (2 mL) were used.
[b] Conversion (%)=100×(ee of **6**)/(ee of **7**+ee of **8**).
[c] HPLC analysis.
[d] Selectivity factor=$S(k_{\text{fast-reacting enantiomer}}/k_{\text{slow-reacting enantiomer}})$, see Ref. 9.

87 by using **7c** in place of **7a** (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 **1c**-induced kinetic resolution of (±)-secondary alcohols, the acylation of several

Table 3. Screening of protecting groups (R) in (±)-**7** and solvent effect on the kinetic resolution of (±)-**7** induced by **1c**[a]



(±)-**7** (1*S*,2*R*)-**7** (1*R*,2*S*)-**8**

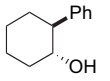
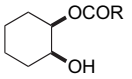
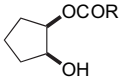
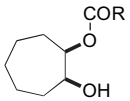
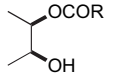
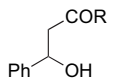
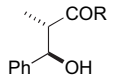
Entry	Alcohol	R	Solvent	Temp (°C)	Conv.[b] (%)	ee of **7**[c] (%)	ee of **8**[c] (%)	*S*[d]
1	**7a**	*p*-(Me_2N)C_6H_4	CH_3CN	rt	30	25	57	5
2	**7a**	*p*-(Me_2N)C_6H_4	THF	rt	39	38	59	6
3	**7a**	*p*-(Me_2N)C_6H_4	CH_2Cl_2	rt	43	66	50	8
4	**7a**	*p*-(Me_2N)C_6H_4	Toluene	rt	47	74	83	24
5	**7a**	*p*-(Me_2N)C_6H_4	CCl_4	rt	49	81	83	27
6	**7b**	Me_2N	CCl_4	rt	53	96	83	42
7[e]	**7b**	Me_2N	CCl_4	0	54	99	83	64
8[e]	**7c**	$(CH_2CH_2)_2N$	CCl_4	0	52	97	90	87

[a] See footnote a in Table 2.
[b] Conversion (%)=100×(ee of **6**)/(ee of **7**+ee of **8**).
[c] HPLC analysis.
[d] Selectivity factor=$S(k_{\text{fast-reacting enantiomer}}/k_{\text{slow-reacting enantiomer}})$, see Ref. 9.
[e] The reaction was carried out at 0 °C for 3 h.

structurally diverse alcohols with $(i\text{-PrCO})_2O$ was examined (Table 4). Although the acylation of *trans*-2-phenyl-1-cyclohexanol (**9**), which does not have any proton accepting groups except for 1-hydroxy group, was not selective, the acylations of not only cyclic 1,2-diol derivatives **7c**, **10**, and **11** but also acyclic **12** gave *S* values greater than 68. In particular, the *S* value was up to 132 when the reaction was conducted at −20 °C in *cis*-1,2-dihydroxycyclopentane derivative **10**. β-Hydroxycarboxylic acid derivatives **13** and **14** and amino alcohol derivatives **15**–**18** were also suitable substrates.

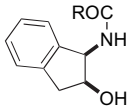
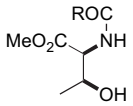
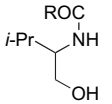
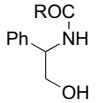
Furthermore, catalyst **1c** was improved by altering its *t*-$BuPh_2Si$ group. Compounds **2a**–**d** were evaluated with regard to the kinetic resolution of (±)-**14** (Table 5). The tris(trimethylsilyl)silyl [$(Me_3Si)_3Si$] group was a more bulky hydroxyl protecting group than a *t*-$BuPh_2Si$ group, and when **2a** bearing $(Me_3Si)_3Si$ group was used instead of **1c**, (−)-**14** was obtained in 52% conversion with 92% ee (*S*=45) (entry 1 vs entry 2). However, more bulky catalyst **2b** was not induced (−)-**14** (*S*=21) (entry 3). More acidic sulfonamide catalysts **2c** and **2d** also showed moderate selectivity (*S*=8) (entries 4 and 5). Therefore, the balance between the acidity of a sulfonamide and the basicity of an imidazole seems to be important for attaining high enantioselectivity for the kinetic resolution of racemic alcohols.

Table 4. Kinetic resolution of racemic alcohols **7c**, **9**–**18** [R=$(CH_2CH_2)_2N$] induced by **1c**[a]

Entry	Alcohol	Conv.[b] (%)	ee of recov. alcohol[c] (%)	ee of acyl. product[c] (%)	*S*[d]
1[e]	**9** 	43	10	13	1
2[e]	**7c** 	52	97 (1*S*,2*R*)	90 (1*R*,2*S*)	87
3[e]	**10** 	49	90	94	93
4[f]	**10**	41	67	97	132
5[e]	**11** 	50	93	92	83
6[e]	**12** 	47	82	93	68
7[e]	**13** 	44	64 (*S*)	82 (*R*)	19
8[e]	**14** 	49	80	82	25

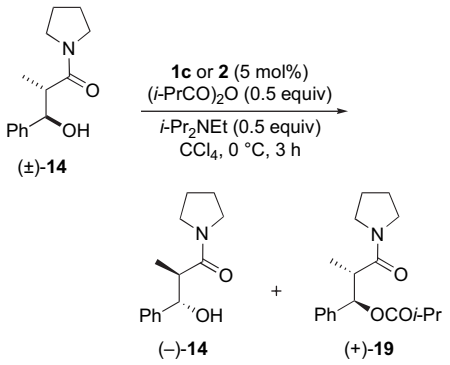
(*continued*)

Table 4. (*continued*)

Entry	Alcohol	Conv.[b] (%)	ee of recov. alcohol[c] (%)	ee of acyl. product[c] (%)	*S*[d]
9[g]	**15** 	42	67 (1*S*,2*R*)	93 (1*R*,2*S*)	51
10[h]	**16** 	39	51 (2*R*,3*R*)	80 (2*S*,3*S*)	15
11[e]	**17** 	50	88 (*S*)	86 (*R*)	39
12[i]	**18** 	53	83	74	17

[a] See footnote a in Table 2.
[b] Conversion (%)=100×(ee of recovered alcohol)/(ee of recovered alcohol+ee of acylated product).
[c] HPLC analysis.
[d] Selectivity factor=$S(k_{\text{fast-reacting enantiomer}}/k_{\text{slow-reacting enantiomer}})$, see Ref. 9.
[e] 0 °C, 3 h; CCl_4.
[f] −20 °C, 3 h; CCl_4.
[g] 0 °C, 3 h; $CHCl_3$–CCl_4 (2:3).
[h] 0 °C, 4 h; $CHCl_3$–CCl_4 (1:5).
[i] 0 °C, 3 h; $CHCl_3$–CCl_4 (2:5).

Table 5. Kinetic resolution of (±)-**14** induced by **1c** or **2**[a]



Entry	Catalyst	Conv.[b] (%)	ee of **14**[c] (%)	ee of **19**[c] (%)	S[d]
1	**1c**	49	80	82	25
2	**2a**	52	92	86	45
3	**2b**	47	72	82	21
4	**2c**	36	39	69	8
5	**2d**	44	53	66	8

[a] See footnote a in Table 2.
[b] Conversion (%)=100×(ee of **14**)/(ee of **14**+ee of **19**).
[c] HPLC analysis.
[d] Selectivity factor=$S(k_{\text{fast-reacting enantiomer}}/k_{\text{slow-reacting enantiomer}})$, see Ref. 9.

According to an X-ray structural analysis, a N–H bond and IMD ring in **1c** are parallel to each other on the same side, probably due to steric limitations imposed by the two bulky substituents (Fig. 2). A transition-state assembly formed from **1c**, (1*R*,2*S*)-**7c**, and (*i*-PrCO)$_2$O was proposed based on this X-ray structure (Fig. 2). The conformation of the acyl group in the acylammonium salt generated from **1c** 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. This electrostatic interaction was expected by the results of calculation at the B3LYP/6-311++G(d,p) level for 3-acetyl-1,5-dimethylimidazolium cation (Fig. 3).[10,11] The calculations show that the attractive interaction between an acyl oxygen and an imidazoyl proton in conformer **II** is stronger than that in conformer **I**. Hydrogen bonding between the sulfonylamino proton of acylammonium salt and the carbamoyl oxygen of **7c** preferentially promotes the acylation of (1*R*,2*S*)-**7c** by a proximity effect. On the other hand, similar hydrogen bonding with (1*S*,2*R*)-**7c** inhibits its acylation.

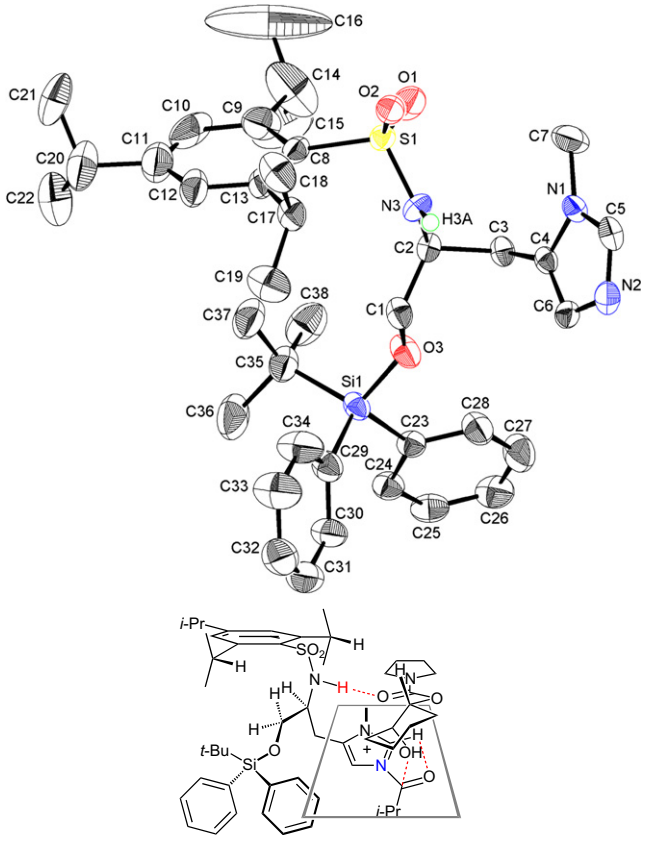


Figure 2. ORTEP plot of **1c** and a proposed transition-state assembly. The crystal structure of **1c** is drawn with 50% probability, and hydrogen atoms except for the SO_2NH moiety are omitted for clarity.

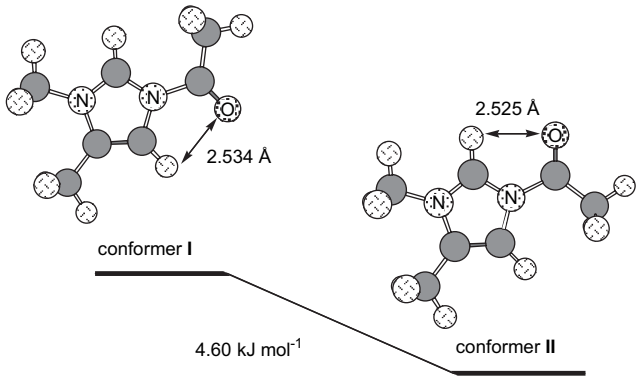
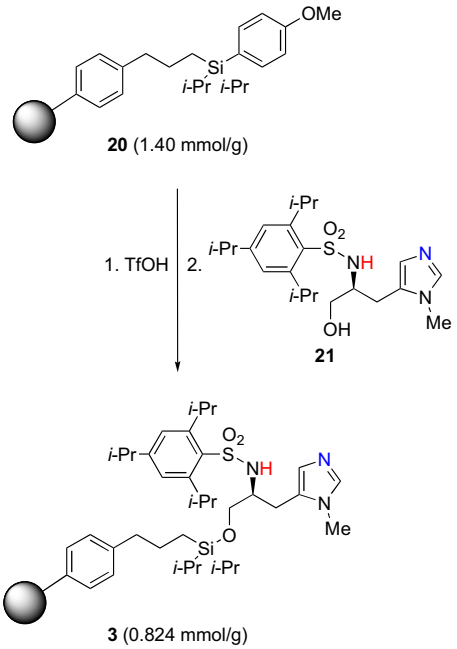


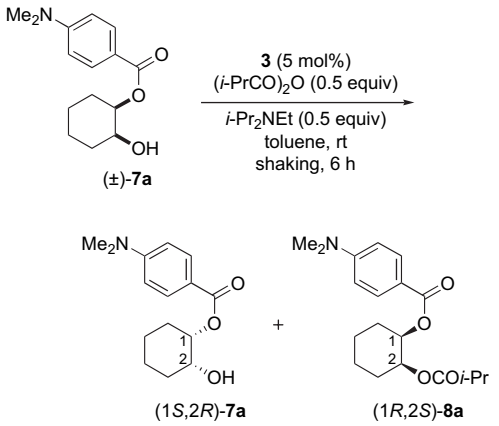
Figure 3. The conformers **I** and **II** of 3-acetyl-1,5-dimethylimidazolium cation.

Polymer-bound catalyst **3** was easily prepared from commercially available resin **20**[12] and *N*(π)-methyl-*N*-(2,4,6-triisopropylbenzenesulfonyl)-L-histidinol **21** (Scheme 2).[4h]



Scheme 2. Preparation of polystyrene resin-bound catalyst **3**.

Table 6. Recycling of catalyst **3** in the kinetic resolution of (±)-**7a**[a]



Run	Conv.[b] (%)	ee of **7a**[c] (%)	ee of **8a**[c] (%)	S[d]
1	44	82	64	20
2	43	84	62	21
3	44	84	65	23
4	42	86	62	25
5	42	86	62	26

[a] See footnote a in Table 2.
[b] Conversion (%)=100×(ee of **7**)/(ee of **7**+ee of **8**).
[c] HPLC analysis.
[d] Selectivity factor=$S(k_{\text{fast-reacting enantiomer}}/k_{\text{slow-reacting enantiomer}})$, see Ref. 9.

Compound **3** (5 mol %) was reused more than five times for the acylation of (±)-**7a** (1 equiv) with (i-PrCO)$_2$O (0.5 equiv) under shaking at room temperature in toluene for 6 h in the presence of i-Pr$_2$EtN (0.5 equiv) without any loss of activity or selectivity (Table 6).

3. Conclusion

In summary, we have designed minimal artificial acylases **1c** and **2a** derived from L-histidine by introducing a sulfonylamino group in place of a polypeptide chain based on the notion that sulfonamide hydrogen bonding is much stronger than the corresponding carboxamide interaction. In addition, we developed a reusable organocatalyst **3**, which should greatly contribute to green and sustainable chemistry.

4. Experimental

4.1. General

Infrared (IR) spectra were recorded on a Jasco FT/IR 460 plus spectrometer. ^{1}H NMR spectra were measured on a Varian Gemini-2000 spectrometer (300 MHz) at ambient temperature. Data were recorded as follows: chemical shift in parts per million from internal tetramethylsilane on the δ scale, multiplicity (s=singlet; d=doublet; t=triplet; m=multiplet), coupling constant (Hz), integration, and assignment. ^{13}C NMR spectra were measured on Varian Gemini-2000 (75 MHz) spectrometer. Chemical shifts were recorded in parts per million from the solvent resonance employed as the internal standard (deuterochloroform at 77.00 ppm). High performance liquid chromatography (HPLC) analysis was conducted using Shimadzu LC-10 AD coupled diode array-detector SPD-MA-10A-VP and chiral column of Daicel CHIRALCEL OD-H (4.6 mm× 25 cm), AD-H (4.6 mm×25 cm), or Daicel CHIRALPAK AS-H (4.6 mm×25 cm). Optical rotations were measured on a RUDOLPH AUTOPOL IV digital polarimeter. GC analysis was performed with Shimadzu 17A instruments using TCI CHIRALDEX γ-TA (0.25 mm I.D.×20 m× 0.125 μm). Melting points were determined using a Yanaco MP-J3. All experiments were carried out under an atmosphere of dry nitrogen. For thin-layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF_{254} 0.25 mm or silica gel NH_2 F_{254S} 0.25 mm) were used. The products were purified by column chromatography on silica gel (E. Merck Art. 9385 or Fuji Silysia Chemical Ltd., Cromatorex® NH-DM1020). Microanalyses were performed at the Graduate School of Agriculture, Nagoya University. High resolution mass spectral analysis (HRMS) was performed at Chemical Instrument Center, Nagoya University. In experiments that required dry solvent, ether, *N*,*N*-dimethylformamide (DMF), and tetrahydrofuran (THF) were purchased from Aldrich or Wako as the 'anhydrous' and stored over 4A molecular sieves. Benzene, hexane, toluene, and dichloromethane were freshly distilled from calcium hydride. Other simple chemicals were of analytical-grade and obtained commercially.

4.2. General procedure for the preparation of *N*(π)-methyl-*N*(α)-arenesulfonyl-L-histidinol

To a solution of **4**[8] (4.0 mmol) in pyridine (20 mL) was added the corresponding arenesulfonyl chloride (5.5 mmol) at 0 °C. After the mixture was stirred for 5 h at room temperature, the solvent was removed under reduced pressure. The crude product was dissolved in EtOAc and washed with water and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on Cromatorex® NH-DM1020 (eluent: EtOAc) to give *N*(π)-methyl-*N*(α)-(arenesulfonyl)-L-histidinol in good yield. The corresponding physical and spectroscopic data for compounds follow.

4.2.1. (+)-*N*(π)-Methyl-*N*(α)-benzenesulfonyl-L-histidinol. TLC (silica gel NH_2 F_{254S}, EtOAc–MeOH=11:1) R_f=0.25; purification by column chromatography on Cromatorex® NH-DM1020 (EtOAc–MeOH=10:1); $[\alpha]_D^{20}$ 6.0 (c 1.06, $CHCl_3$); IR (KBr) 3600–3250, 2924, 1636, 1510, 1447, 1324, 1158, 1093, 690, 592 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.75 (dd, J=6.0, 15.3 Hz, 1H), 2.88 (dd, J=7.5, 15.3 Hz, 1H), 3.32–3.38 (m, 1H), 3.39 (s, 3H), 3.49 (d, J=4.2 Hz, 2H), 4.48–4.95 (br, 1H), 6.61 (s, 1H), 7.26 (s, 1H), 7.42 (t, J=7.4 Hz, 2H), 7.51 (t, J=7.4 Hz, 1H), 7.77 (d, J=7.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.9, 31.4, 54.3, 62.3, 126.7 (2C), 127.4, 127.9, 129.0 (2C), 132.4, 137.8, 140.5. Anal. Calcd for $C_{13}H_{17}N_3O_3S$: C, 52.86; H, 5.80. Found: C, 52.81; H, 5.82.

4.2.2. *N*(π)-Methyl-*N*(α)-(4-trifluoromethylbenzenesulfonyl)-L-histidinol. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.84 (dd, J=6.0, 15.3 Hz, 1H), 2.92 (dd, J=7.1, 15.5 Hz, 1H), 3.41 (m, 1H), 3.49 (s, 3H), 3.54 (d, J=4.2 Hz, 2H), 6.02 (br, 1H), 6.60 (s, 1H), 7.28 (s, 1H), 7.67 (d, J=8.1 Hz, 2H), 7.93 (d, J=8.4 Hz, 2H). Anal. Calcd for $C_{14}H_{16}F_3N_3O_3S$: C, 46.28; H, 4.44. Found: C, 46.33; H, 4.41.

4.2.3. (+)-*N*(π)-Methyl-*N*(α)-(2,4,6-triisopropylbenzenesulfonyl)-L-histidinol (21). White solid (838 mg, 2.0 mmol, 50% yield); $[\alpha]_D^{20}$ 20.4 (*c* 1.0, $CHCl_3$); IR (KBr) 3486, 3114, 3053, 2958, 2928, 2869, 1601, 1461, 1316, 1294, 1146, 1113, 1059, 1041, 664, 561 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.248 (d, *J*=6.9 Hz, 12H), 1.255 (d, *J*=6.9 Hz, 6H), 2.75–3.02 (m, 3H), 3.42–3.52 (m, 3H), 3.53 (s, 3H), 4.13 (septet, *J*=6.9 Hz, 2H), 5.72 (d, *J*=6.6 Hz, 1H), 6.58 (s, 1H), 7.16 (s, 2H), 7.27 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.6, 24.9, 25.0, 26.2, 29.8, 31.5, 34.1, 53.7, 61.4, 123.8, 127.5, 128.1, 133.3, 137.7, 150.1, 152.8; MS (FAB+) $[M+H]^+$ *m*/*z* 422. Anal. Calcd for $C_{22}H_{35}N_3O_3S$: C, 62.67; H, 8.37. Found: C, 62.61; H, 8.39.

4.3. General procedure for the preparation of (*S*)-1-*tert*-butyldiphenylsilyloxy-3-(3′-methyl-3′*H*-imidazol-4′-yl)-2-(arenesulfonylamino)propane (1)

To a solution of *N*(π)-methyl-*N*(α)-arenesulfonyl-L-histidinol (0.95 mmol) in DMF (5 mL) were added *tert*-butylchlorodiphenylsilane (304 μL, 1.17 mmol) and imidazole (163 mg, 2.4 mmol) at 0 °C. After the mixture was stirred for 6 h at room temperature, the solvent was removed under reduced pressure to give the crude product. The residue was purified by flash column chromatography on NH silica gel (eluent: hexane–EtOAc=1:1) to give **1** in good yield. The corresponding physical and spectroscopic data for **1** follow.

4.3.1. (+)-(*S*)-1-*tert*-Butyldiphenylsilyloxy-3-(3′-methyl-3′*H*-imidazol-4′-yl)-2-(benzenesulfonylamino)propane (1a). TLC (silica gel NH_2 F_{254S}, hexane–EtOAc=1:2) R_f=0.15; purification by column chromatography on Cromatorex® NH-DM1020 (hexane–EtOAc=1:2–1:4); $[\alpha]_D^{20}$ 2.34 (*c* 0.51, $CHCl_3$); IR (KBr) 3069, 2930, 2857, 1509, 1428, 1324, 1158, 1113, 1070, 823, 706, 588 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.04 (s, 9H), 2.84 (dd, *J*=5.4, 15.0 Hz, 1H), 2.96 (dd, *J*=7.8, 15.0 Hz, 1H), 3.28–3.37 (m, 1H), 3.41 (s, 3H), 3.44 (dd, *J*=4.8, 10.5 Hz, 1H), 3.59 (dd, *J*=3.9, 10.5 Hz, 1H), 5.42 (br, 1H), 6.54 (s, 1H), 7.25 (s, 1H), 7.34–7.58 (m, 13H), 7.66 (d, *J*=8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.2, 26.4, 26.9 (3C), 31.3, 53.8, 63.7, 126.7 (2C), 127.0, 127.9 (4C), 128.0, 129.0 (2C), 130.0 (2C), 132.5 (2C), 135.4 (4C), 138.0 (2C), 140.1. Anal. Calcd for $C_{29}H_{35}N_3O_3SSi$: C, 65.26; H, 6.61. Found: C, 65.18; H, 6.66.

4.3.2. (*S*)-(+)-1-*tert*-Butyldiphenylsilyloxy-3-(3′-methyl-3′*H*-imidazol-4′-yl)-2-(4″-trifluoromethylbenzenesulfonylamino)propane (1b). TLC (silica gel NH_2 F_{254S}, hexane–EtOAc=1:2) R_f=0.26; purification by column chromatography on silica gel Cromatorex® NH-DM1020 (hexane–EtOAc=1:2–1:4) and recrystallization ($CHCl_3$–hexane); $[\alpha]_D^{20}$ 1.72 (*c* 0.93, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.02 (s, 9H), 2.88 (dd, *J*=6.0, 15.3 Hz, 1H), 2.98 (dd, *J*=6.6, 15.3 Hz, 1H), 3.32–3.42 (m, 1H), 3.44 (s, 3H), 3.47 (dd, *J*=6.0, 10.3 Hz, 1H), 3.57 (dd, *J*=4.2, 10.3 Hz, 1H), 5.55 (br, 1H), 6.57 (s, 1H), 7.21 (s, 1H), 7.33–7.39 (m, 4H), 7.41–7.48 (m, 2H), 7.50–7.56 (m, 4H), 7.57 (d, *J*=8.2 Hz, 2H), 7.73 (d, *J*=8.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.2, 26.2, 26.8 (3C), 31.3, 54.1, 63.9, 123.1 (q, *J*=273 Hz), 126.1 (q, *J*=3.7 Hz, 2C), 126.9, 127.1 (2C), 127.9 (4C), 128.1, 130.1 (2C), 132.46, 132.53, 133.9 (q, *J*=33.0 Hz), 135.4 (4C), 134.0, 144.1. Anal. Calcd for $C_{30}H_{34}F_3N_3O_3SSi$: C, 59.88; H, 5.69. Found: C, 59.83; H, 5.73.

4.3.3. (*S*)-(+)-1-*tert*-Butyldiphenylsilyloxy-3-(3′-methyl-3′*H*-imidazol-4′-yl)-2-(2″,4″,6″-triisopropylbenzenesulfonylamino)propane (1c). White solid (615 mg, 0.93 mmol, 98% yield); $[\alpha]_D^{20}$ 4.8 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.20 (d, *J*=6.9 Hz, 6H), 1.23 (d, *J*=6.9 Hz, 6H), 1.25 (d, *J*=6.9 Hz, 6H), 2.80–3.02 (m, 3H), 3.43 (s, 3H), 3.61 (br s, 3H), 4.10 (septet, *J*=6.9 Hz, 2H), 4.95–5.15 (br, 1H), 6.48 (s, 1H), 7.08 (s, 2H), 7.26–7.44 (m, 8H), 7.52–7.68 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.3, 23.6, 24.9, 26.2, 27.0, 29.8, 31.3, 34.2, 53.3, 63.6, 123.8, 127.3, 127.9, 128.0, 130.0, 130.1, 132.5, 132.6, 133.4, 135.47, 135.50, 138.0, 150.1, 152.9; IR (KBr) 4325, 3072, 3053, 2959, 2928, 2859, 2739, 1601, 1511, 1463, 1427, 1322, 1152, 1113, 1072, 741, 703, 661, 560, 506 cm^{-1}; MS (FAB+) $[M+H]^+$ *m*/*z* 660. Anal. Calcd for $C_{38}H_{53}N_3O_3SSi$: C, 69.15; H, 8.09. Found: C, 69.19; H, 8.03.

4.4. Preparation of (*S*)-1-tris(trimethylsilyl)silyloxy-3-(1-methyl-1*H*-imidazol-5-yl)propan-2-amine

To a solution of **4**[8] (2.0 mmol) and Et_3N (976 μL, 7.0 mmol) in DMF (8 mL) was added chlorotris(trimethylsilyl)silane (1.98 mg, 7.0 mmol) at 0 °C. The mixture was then stirred for 24 h at room temperature, diluted with $CHCl_3$, washed with water, and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4 and evaporated. The residue was purified by flash column chromatography on NH silica gel (eluent: EtOAc–MeOH=50:1) to give 559 mg (69% yield) of product as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 0.19 (s, 27H), 2.46 (dd, *J*=8.3, 14.9 Hz, 1H), 2.74 (dd, *J*=5.0, 14.9 Hz, 1H), 2.94–3.04 (m, 1H), 3.38 (dd, *J*=1.5, 5.4 Hz, 2H), 3.56 (s, 3H), 6.84 (s, 1H), 7.39 (s, 1H).

4.5. General procedure for the preparation of arenesulfonyl chlorides

To a solution of 2,6-diphenyliodobenzene[14] (1.42 g, 4 mmol) or 1,3,5-tris(trifluoromethyl)benzene (0.746 mL, 4 mmol) in Et_2O was added dropwise BuLi (2.56 mL, 1.56 M in hexane, 4 mmol) at 0 °C. The mixture turned yellow and a white solid precipitated. After the mixture was stirred for 8 h at room temperature, the freshly distilled sulfuryl chloride (0.643 mL, 8 mmol) was added slowly at −78 °C. The mixture was stirred overnight at room temperature, cooled to 0 °C, poured onto 1 M HCl, and extracted with Et_2O. The organic layer was washed with water and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was recrystallized from $CHCl_3$–hexane to give the corresponding arenesulfonyl chloride in good or modest yield. The corresponding physical and spectroscopic data for arenesulfonyl chloride follow.

4.5.1. 2,6-Diphenylbenzenesulfonyl chloride.[13] Brown solid (924 mg, 2.8 mmol, 70% yield); ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.52 (m, 12H) 7.63 (dd, *J*=7.5, 8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 128.0, 128.2, 129.0, 133.0, 133.3, 140.0, 141.7, 143.7; IR (KBr) 3443, 3049, 1574, 1446, 1385, 1191, 811, 765, 748, 701 cm^{-1}.

4.5.2. 2,4,6-Tris(trifluoromethyl)benzenesulfonyl chloride.[13,15] White solid (453 mg, 1.2 mmol, 30% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 121.6 (q, J=277 Hz), 130.2, 133.6 (q, J=35 Hz), 137.1 (q, J=36 Hz), 145.4; IR (KBr) 3435, 3113, 1405, 1198, 1273, 1198, 1140, 1088, 924, 863, 712, 687 cm^{-1}.

4.6. General procedure for the preparation of (*S*)-1-tris(trimethylsilyl)silyloxy-3-(3′-methyl-3′*H*-imidazol-4′-yl)-2-(arenesulfonylamino)propane (2)

To a solution of (*S*)-1-tris(trimethylsilyl)silyloxy-3-(1-methyl-1*H*-imidazol-5-yl)propan-2-amine (300 mg, 0.45 mmol) and pyridine (44.5 μL, 0.55 mmol) in CH_2Cl_2 (5 mL) was added the corresponding arenesulfonyl chloride (0.55 mmol) at 0 °C. After the mixture was stirred for 24 h at room temperature, the solvent was removed under reduced pressure to give the crude product. The residue was purified by flash column chromatography on NH silica gel (eluent: hexane–EtOAc=1:1) to give **2** in good yield. The corresponding physical and spectroscopic data for **2** follow.

4.6.1. (*S*)-(−)-1-Tris(trimethylsilyl)silyloxy-3-(3′-methyl-3′*H*-imidazol-4′-yl)-2-(2″,4″,6″-triisopropylbenzenesulfonylamino)propane (2a). White solid (597 mg, 0.89 mmol, 89% yield); $[\alpha]_D^{22}$ −11.9 (*c* 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.14 (s, 27H), 1.18–1.34 (m, 18H), 2.72 (dd, J=4.1, 15.2 Hz, 1H), (dd, J=7.4, 22.0 Hz, 1H), 2.90 (septet, J=6.8 Hz, 1H), 3.37 (d, J=4.5 Hz, 2H), 3.50 (s, 3H), 3.50–3.63 (m, 1H), 4.14 (septet, J=6.7 Hz, 2H), 4.82 (d, 9.0 Hz, 1H), 6.74 (s, 1H), 7.16 (s, 2H), 7.35 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.4 (9C), 23.7 (2C), 25.0 (2C), 25.1 (2C), 25.6, 29.8 (2C), 31.5, 34.3, 53.4, 67.4, 123.9 (2C), 127.3, 128.3, 133.5, 138.2, 150.1 (2C), 153.0; IR (KBr) 3435, 2957, 2894, 1602, 1464, 1269, 1246, 1155, 1071, 961, 838, 744, 688, 661 cm^{-1}; HRMS(FAB) calcd for $C_{31}H_{52}N_3O_3SSi_4$ [(M+H)$^+$] 668.3589. Found: 668.3571.

4.6.2. (*S*)-(−)-1-Tris(trimethylsilyl)silyloxy-3-(3′-methyl-3′*H*-imidazol-4′-yl)-2-(2″,6″-diphenylbenzenesulfonylamino)propane (2b). White solid (226 mg, 0.33 mmol, 41% yield); $[\alpha]_D^{22}$ −3.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.09 (s, 27H), 2.23 (dd, J=5.3, 15.0 Hz, 1H), 2.50 (dd, J=7.8, 15.0 Hz, 1H), 3.00 (dd, J=6.0, 9.6 Hz, 1H), 3.06 (dd, J=4.1, 9.6 Hz, 1H), 3.32 (s, 3H), 3.10–3.42 (m, 1H), 3.60 (d, J=8.4 Hz, 1H), 6.47 (s, 1H), 7.27 (d, J=6.6 Hz, 2H), 7.34 (d, J=7.8 Hz, 2H), 7.38–7.56 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.4, 25.2, 31.3, 54.4, 67.7, 127.1, 128.2, 129.5, 130.7, 132.1, 138.0, 140.4, 141.4, 142.2; IR (KBr) 3388, 3058, 2950, 1572, 1503, 1443, 1410, 1336, 1245, 1157, 1062, 838, 761, 701 cm^{-1}; HRMS(FAB) calcd for $C_{34}H_{52}N_3O_3SSi_4$ [(M+H)$^+$] 694.2807. Found: 694.2808.

4.6.3. (*S*)-(−)-1-Tris(trimethylsilyl)silyloxy-3-(3′-methyl-3′*H*-imidazol-4′-yl)-2-[3″,5″-bis(trifluoromethyl)benzenesulfonylamino]propane (2c). White solid (77 mg, 0.11 mmol, 69% yield); $[\alpha]_D^{21}$ −11.9 (*c* 0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.13 (s, 27H), 2.80 (dd, J=5.7, 15.3 Hz, 1H), 2.90 (dd, J=7.2, 15.3 Hz, 1H), 3.33 (dd, J=5.6, 9.8 Hz, 1H), 3.42 (dd, J=3.3, 9.8 Hz, 1H), 3.42–3.51 (m, 1H), 3.55 (s, 3H), 5.30–6.04 (br, 1H), 6.65 (s, 1H), 7.28 (s, 1H), 8.05 (s, 1H), 8.24 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 0.3 (9C), 26.3, 31.5, 55.0, 67.6, 122.5 (q, J=273 Hz), 126.4, 127.0, 127.0, 128.4, 133.2 (q, J=34 Hz), 138.3, 144.0; IR (KBr) 3423, 3112, 2957, 2897, 1626, 1422, 1353, 1281, 1165, 1144, 1077, 840 cm^{-1}; HRMS(FAB) calcd for $C_{24}H_{42}F_6N_3O_3SSi_4$ [(M+H)$^+$] 678.1928. Found: 678.1937.

4.6.4. (*S*)-1-Tris(trimethylsilyl)silyloxy-3-(3′-methyl-3′*H*-imidazol-4′-yl)-2-(2″,4″,6″-tris(trifluoromethyl)benzenesulfonylamino)propane (2d). White solid (140 mg, 0.19 mmol, 42% yield); $[\alpha]_D^{22}$ −10.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.15 (s, 27H), 3.84 (dd, J=6.0, 15.0 Hz, 1H), 2.91 (dd, J=8.6, 15.0 Hz, 1H), 3.41 (dd, J=3.9, 9.6 Hz, 1H), 3.54 (dd, J=2.7, 9.6 Hz, 1H), 3.57 (s, 3H), 3.87–3.99 (m, 1H), 5.32–5.49 (br, 1H), 6.67 (s, 1H), 7.30 (s, 1H), 8.28 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.2 (9C), 27.1, 31.3, 55.4, 67.6, 121.9 (q, J=274 Hz), 122.2 (q, J=275 Hz, 2C), 127.1, 128.5, 129.5, 132.0 (q, J=33 Hz, 2C), 134.1 (q, J=35 Hz), 138.2, 145.7; IR (KBr) 3600–3300, 2953, 2896, 1626, 1509, 1423, 1367, 1274, 1179, 1083, 917, 838 cm^{-1}; HRMS(FAB) calcd for $C_{25}H_{41}F_9N_3O_3SSi_4$ [(M+H)$^+$] 746.1802. Found: 746.1814.

4.7. Preparation of (*S*)-3-(3′-methyl-3′*H*-imidazol-4′-yl)-2-(2″,4″,6″-triisopropylbenzenesulfonylamino)propyl isobutyrate (5a) and (*S*)-2-[*N*-isobutyryl(2′,4′,6′-triisopropylbenzenesulfonyl)amino]-3-(3″-methyl-3″*H*-imidazol-4″-yl)-propyl isobutyrate (5b)

To a solution of *N*(π)-methyl-*N*(α)-2″,4″,6″-triisopropylbenzenesulfonyl-L-histidinol (1 mmol) in $CHCl_3$ (10 mL) were added isobutyryl chloride (105 μL, 1 mmol) and Et_3N (101 μL, 1 mmol) at 0 °C. After the mixture was stirred for 6 h at room temperature, the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on NH silica gel (eluents: EtOAc–MeOH) to give **5a** (143 mg, 0.29 mmol) and **5b** (185 mg, 0.33 mmol) in respective yield of 29% and 33% as white solids. The corresponding physical and spectroscopic data for **5** follow.

4.7.1. (*S*)-(+)-5a. TLC (silica gel NH_2 F_{254S}, hexane–EtOAc=1:2) R_f=0.22; $[\alpha]_D^{20}$ 15.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (s, 1H), 7.15 (s, 1H), 6.70 (d, J=8.1 Hz, 1H), 6.45 (s, 1H), 4.17 (m, 2H), 4.05 (dd, J=4.7, 11.3 Hz, 1H), 3.95 (dd, J=6.5, 11.3 Hz, 1H), 5.79 (m, 1H), 3.65 (s, 3H), 3.01 (dd, J=8.0, 15.5 Hz, 1H), 2.90 (m, 2H), 2.15 (m, 1H), 1.24 (m, 18H), 1.04 (d, J=7.2 Hz, 3H), 0.99 (d, J=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.76, 18.83, 23.6, 24.8, 25.0, 27.2, 29.7, 31.7, 33.5, 34.1, 51.5, 64.2, 123.8, 126.6, 128.0, 134.0, 137.9, 149.8, 152.6, 176.7; IR (KBr) 3436, 2961, 2929, 2871, 1735, 1601, 1466, 1321, 1194, 1151, 1113, 663, 570 cm^{-1}; MS (FAB+) [M+H]$^+$ *m*/*z* 492. Anal. Calcd for $C_{26}H_{41}N_3O_4S$: C, 63.51; H, 8.40. Found: C, 63.55; H, 8.34.

4.7.2. (*S*)-(−)-5b. TLC (silica gel NH_2 F_{254S}, hexane–EtOAc=1:2) R_f=0.37; $[\alpha]_D^{20}$ −3.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (s, 1H), 7.23 (s, 2H), 6.59 (s, 1H), 4.32 (m, 3H), 3.95 (m, 2H), 3.48 (s, 3H), 3.44 (m, 2H), 2.92 (m, 1H), 2.71 (dd, J=3.6, 15.6 Hz, 1H), 2.38 (m,

1H), 1.26 (m, 18H), 1.12 (d, J=6.6 Hz, 3H), 1.06 (d, J=1.5 Hz, 3H), 1.04 (dd, J=1.5, 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.6, 18.8, 19.1, 19.6, 23.5, 24.6, 24.7, 25.9, 29.4, 31.2, 33.7, 34.2, 35.7, 57.7, 64.1, 124.4, 127.7, 128.1, 131.6, 137.9, 151.1, 154.9, 176.3, 179.3; IR (KBr) 3439, 2964, 2934, 2873, 1742, 1689, 1601, 1466, 1386, 1367, 1336, 1204, 1145, 952, 664, 588, 564 cm^{-1}; MS (FAB+) $[M+H]^+$ m/z 562. Anal. Calcd for $C_{30}H_{47}N_3O_5S$: C, 64.14; H, 8.43. Found: C, 64.23; H, 8.51.

4.8. Preparation of (−)-*N*(π)-methyl-*N*(α)-benzoyl-L-histidinol

To a solution of **4** (621 mg, 4 mmol) in pyridine (20 mL) was added benzoyl chloride (0.638 mL, 5.5 mmol) at 0 °C. After the mixture was stirred for 5 h at room temperature, the solvent was removed under reduced pressure. The crude product was dissolved in EtOAc and washed with water and brine. The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on NH silica gel (eluent: EtOAc) to give *N*(π)-methyl-*N*(α)-benzoyl-L-histidinol in good yield. TLC (silica gel NH_2 F_{254S}, EtOAc–MeOH=10:1) R_f=0.21; $[\alpha]_D^{20}$ −28.2 (c 1.0, $CHCl_3$); IR (neat) 3500–3300 (br), 2923, 2852, 1638, 1542 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.99 (s, 1H), 3.01 (d, J=3.0 Hz, 1H), 3.72 (s, 3H), 3.77 (d, J=1.5 Hz, 1H), 3.78 (d, J=1.2 Hz, 1H), 4.23 (m, 1H), 6.77 (d, J=7.8 Hz, 1H), 6.83 (s, 1H), 7.43 (m, 3H), 7.52 (m, 1H), 7.74 (m, 1H); ^{13}C NMR ($CDCl_3$) 25.0, 31.6, 50.8, 61.5, 126.9, 127.5, 128.5 (2C), 128.7, 131.6, 134.1, 137.8, 167.7. Anal. Calcd for $C_{14}H_{17}N_3O_2$: C, 64.85; H, 6.61. Found: C, 64.90; H, 6.59.

4.9. Preparation of (*S*)-(+)-1-*tert*-butyldiphenylsilyloxy-3-(3′-methyl-3′*H*-imidazol-4′-yl)-2-benzoylamino-propane (6)

(*S*)-(+)-**6** was synthesized from *N*(π)-methyl-*N*(α)-benzoyl-L-histidinol and *tert*-butylchlorodiphenylsilane according to the procedure shown in Section 4.3. TLC (silica gel NH_2 F_{254S}, hexane–EtOAc=1:2) R_f=0.17; purification by column chromatography on silica gel Cromatorex® NH-DM1020 (hexane–EtOAc=1:2–1:4); $[\alpha]_D^{20}$ 15.5 (c 0.62, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (s, 9H), 2.93 (dd, J=5.0, 15.0 Hz, 1H), 3.05 (dd, J=9.0, 15.0 Hz, 1H), 3.70 (s, 3H), 3.77 (dd, J=3.6, 10.4 Hz, 1H), 3.86 (dd, J=2.7, 10.4 Hz, 1H), 4.20 (m, 1H), 6.64 (br, 1H), 6.66 (s, 1H), 7.42 (m, 10H), 7.64 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.3, 25.5, 26.9 (3C), 31.4, 50.0, 63.2, 126.7 (2C), 127.87, 127.94 (4C), 128.1, 128.6 (2C), 130.0, 130.1, 131.6, 132.6, 132.9, 134.1, 135.46 (2C), 135.53 (2C), 138.1, 166.9. Anal. Calcd for $C_{30}H_{35}N_3O_2Si$: C, 72.40; H, 7.09. Found: C, 72.48; H, 7.06.

4.10. General procedure for the preparation of 1-(*N*-pyrrolidine-1′-carbonyloxy)-2-alcohols (7c, 10–12) derived from *meso*-1,2-diols

Treatment of *meso*-1,2-diols (20 mmol) with bis(trichloromethyl)carbonate (triphosgene) (20 mmol) in dichloromethane (100 mL) in the presence of pyridine (10 mL) at room temperature gave the corresponding cyclic carbonates in quantitative yield.[16] Subsequent aminolysis of cyclic carbonates (20 mmol) with pyrrolidine (10 mL) in THF (40 mL) under reflux conditions gave 1-(*N*-pyrrolidine-1′-carbonyloxy)-2-alcohols (**7c**, **10**–**12**) in quantitative yield. For spectral and analytical data of **7c**, **10**–**12**, see Sections 4.11.5, 4.11.7, 4.11.9, and 4.11.11, respectively.

4.11. General procedure for the kinetic resolution of racemic alcohols with isobutyric anhydride induced by nucleophilic catalysts

To a solution of racemic alcohol (0.25 mmol) and catalyst (0.0125 mmol) in toluene (2.5 mL) were added *i*-Pr_2NEt (21.8 μL, 0.125 mmol) and isobutyric anhydride (20.7 μL, 0.125 mL). After being stirred for 3 h at room temperature or 0 °C (for each reaction temperature, see Tables 2–6), the reaction mixture was treated with 0.1 M HCl aqueous solution and extracted with EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated under reduced pressure. The ee values of the recovered alcohol and the acylated product were determined by HPLC analysis of the crude products. The conversion (c) was estimated by the following equation, c (%)=[ee (recovered alcohol)]/[ee (recovered alcohol)+ee (acylated product)].[9] The S value was estimated by the following equation, $S=\ln[(1-c)(1-ee_{alcohol})]/\ln[(1-c)(1+ee_{alcohol})]$.[9] The corresponding physical and spectroscopic data for the recovered alcohols and the acylated products follow.

4.11.1. (1*S*,2*R*)-*cis*-1-[*p*-(Dimethylamino)benzoyloxy]-2-cyclohexanol (7a) (entry 5, Table 3).[4c] TLC (hexane–EtOAc=2:1) R_f=0.11; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34–1.52 (m, 2H), 1.60–1.78 (m, 4H), 1.84 (q, J=8.6 Hz, 1H), 1.99 (q, J=9.8 Hz, 1H), 2.17 (d, J=4.2 Hz, 1H), 3.05 (s, 6H), 3.91–3.98 (m, 1H), 5.15–5.19 (m, 1H), 6.52 (d, J=9.1 Hz, 2H), 7.93 (d, J=9.1 Hz, 2H); HPLC (Daicel Chiralpak OD-H, hexane–2-propanol=20:1, flow rate=1.0 mL/min) t_R=26.9 ((1*R*,2*S*), minor) and 55.5 ((1*S*,2*R*), major) min. The absolute stereochemistry of **7a** was determined by comparison of its HPLC-analytical data with the ones reported in the literatre.[4c]

4.11.2. (1*R*,2*S*)-(−)-*cis*-1-[*p*-(Dimethylamino)benzoyloxy]-2-cyclohexyl isobutyrate (8a) (entry 5, Table 3).[4c] TLC (hexane–EtOAc=2:1) R_f=0.60; $[\alpha]_D^{20}$ −48.0 (c 1.0, $CHCl_3$) for **8a** of 83% ee; HPLC (Daicel Chiralcel OD-H, hexane–2-propanol=20:1, flow rate=1.0 mL/min) t_R=9.4 ((1*S*,2*R*), minor) and 12.1 ((1*R*,2*S*), major) min; IR (film) 3019, 2943, 1725, 1697, 1608, 1526, 1368, 1281, 1216, 1184, 1109, 760, 668 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (q, J=3.6 Hz, 6H), 1.42–15.6 (m, 2H), 1.63–1.81 (m, 4H), 1.87–2.02 (m, 2H), 2.54 (septet, J=6.9 Hz, 1H), 3.04 (s, 6H), 5.07–5.13 (m, 1H), 5.19–5.26 (m, 1H), 6.64 (d, J=6.9 Hz, 2H), 7.90 (d, J=8.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.9, 19.0, 27.79 (2C), 27.83, 27.9, 34.2, 40.0 (2C), 70.7, 71.0, 110.6 (2C), 117.2, 131.2 (2C), 153.2, 160.0, 176.3. The absolute stereochemistry of **8a** was determined by comparison of its $[\alpha]_D$- and HPLC-analytical data with the ones reported in the literature.[4c]

4.11.3. (1*S*,2*R*)-*cis*-1-Dimethylcarbamoyloxy-2-cyclohexanol (7b) (entry 6, Table 3). TLC (hexane–EtOAc=2:1) R_f=0.11; GC (CHIRALDEX γ-TA (20 m), inj. temp

140 °C, col. temp 110 °C, N_2 (80 Pa)) t_R=29.4 ((1*R*,2*S*)-**7b**, minor), 31.6 ((1*S*,2*R*)-**7b**, major) min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25–1.50 (m, 2H), 1.50–1.64 (m, 2H), 1.64–1.80 (m, 3H), 1.80–1.90 (m, 1H), 2.66 (s, 1H), 2.94 (s, 3H), 2.95 (s, 3H), 3.83 (br, 1H), 4.89–4.95 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4, 22.0, 28.1, 29.9, 35.9, 36.4, 70.2, 74.6, 156.8. Anal. Calcd for $C_9H_{17}NO_3$: C, 57.73; H, 9.15. Found: C, 57.78; H, 9.22. The absolute stereochemistry of **7b** was determined by analogy with that of **7a**.

4.11.4. (1*R*,2*S*)-*cis*-1-Dimethylcarbamoyloxy-2-cyclohexyl isobutyrate (8b) (entry 6, Table 3). HPLC (Daicel Chiralpak AD-H, hexane–2-propanol=40:1, flow rate=0.25 mL/min) t_R=57.8 ((1*R*,2*S*)-**8b**, major), 61.0 ((1*S*,2*R*)-**8b**, minor) min. Anal. Calcd for $C_{13}H_{23}NO_4$: C, 60.68; H, 9.01. Found: C, 60.59; H, 9.14. The absolute stereochemistry of **8b** was determined by analogy with that of **8a**.

4.11.5. (1*S*,2*R*)-(−)-*cis*-*N*-(2-Hydroxycyclohexanoxycarbonyl)pyrrolidine (7c) (entry 2, Table 4). TLC (hexane–EtOAc=2:1) R_f=0.17; $[\alpha]_D^{20}$ −2.7 (*c* 1.0, $CHCl_3$) for 97% ee; HPLC (Daicel Chiralpak AS-H, hexane–2-propanol=20:1, flow rate=1.0 mL/min) t_R=24.7 ((1*R*,2*S*)-**7c**, minor), 30.1 ((1*S*,2*R*)-**7c**, major) min; IR (film) 3500–3350 (br), 2938, 2871, 1680, 1429, 1360, 1181, 1129, 1109, 984, 768 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24–2.15 (m, 12H), 2.78 (s, 1H), 3.40 (t, *J*=6.6 Hz, 4H), 3.83 (br, 1H), 4.92 (dt, *J*=2.4, 6.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.3, 22.0, 24.9, 25.6, 28.2, 29.8, 45.8, 46.1, 70.1, 74.1, 155.1. Anal. Calcd for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.98. Found: C, 61.91; H, 9.01. The absolute stereochemistry of **7c** was determined by analogy with that of **7a**.

4.11.6. (1*R*,2*S*)-(−)-*cis*-*N*-(2-Isobutyryloxycyclohexanoxycarbonyl)pyrrolidine (8c) (entry 2, Table 4). TLC (hexane–EtOAc=2:1) R_f=0.27; $[\alpha]_D^{20}$ −24.4 (*c* 1.0, $CHCl_3$) for 90% ee; HPLC (Daicel Chiralpak AS-H, hexane–2-propanol=20:1, flow rate=0.5 mL/min) t_R=13.5 ((1*S*,2*R*)-**8c**, minor), 14.5 ((1*R*,2*S*)-**8c**, major) min; IR ($CHCl_3$) 2876, 2943, 2875, 1728, 1694, 1425, 1372, 1196, 1128, 1105, 756 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16 (d, *J*=3.3 Hz, 3H), 1.19 (d, *J*=3.3 Hz, 3H), 1.36–1.52 (m, 2H), 1.52–1.75 (m, 4H), 1.75–1.94 (m, 6H), 2.56 (septet, *J*=6.9 Hz, 1H), 3.31 (t, *J*=6.3 Hz, 2H), 3.38 (t, *J*=6.0 Hz, 2H), 4.86–4.93 (m, 1H), 5.04–5.10 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.9, 19.0, 21.2, 22.2, 24.9, 25.6, 27.8, 28.1, 34.2, 45.6, 46.0, 70.8, 71.7, 154.3, 176.1. Anal. Calcd for $C_{15}H_{25}NO_4$: C, 63.58; H, 8.89. Found: C, 63.46; H, 8.97. The absolute stereochemistry of **8c** was determined by analogy with that of **8a**.

4.11.7. (−)-*cis*-1-(*N*-Pyrrolidine-1′-carbonyloxy)-2-cyclopentanol (10) (entry 3, Table 4).[4c] TLC (hexane–EtOAc=2:1) R_f=0.09; $[\alpha]_D^{20}$ −7.9 (*c* 1.0, $CHCl_3$) for 90% ee; HPLC (Daicel Chiralpak AD-H, hexane–2-propanol=20:1, flow rate=1.0 mL/min) t_R=16.8 (major) and 24.8 (minor) min; IR (KBr) 3450–3350, 2980, 2951, 2874, 1661, 1443, 1360, 1173, 1115, 1037, 860, 769, 606, 504 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.49–1.61 (m, 1H), 1.61–1.77 (m, 1H), 1.77–2.02 (m, 8H), 2.54 (d, *J*=3.3 Hz, 1H), 3.34–3.43 (m, 4H), 4.13–4.21 (m, 1H), 4.93 (dt, *J*=4.7, 6.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.4, 24.9, 25.7, 28.5, 30.5, 45.8, 46.2, 73.7, 77.4, 155.1.

4.11.8. (−)-*cis*-1-(*N*-Pyrrolidine-1′-carbonyloxy)-2-cyclopentyl isobutyrate (entry 3, Table 4).[4c] TLC (hexane–EtOAc=2:1) R_f=0.28; $[\alpha]_D^{20}$ −32.4 (*c* 1.0, $CHCl_3$) for 94% ee; HPLC (Daicel Chiralpak AS-H, hexane–2-propanol=20:1, flow rate=1.0 mL/min) t_R=8.6 (major) and 10.2 (minor) min; IR (KBr) 2973, 2876, 1736, 1708, 1419, 1345, 1198, 1155, 1128, 1109, 767 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (d, *J*=1.8 Hz, 3H), 1.17 (d, *J*=1.8 Hz, 3H), 1.56–1.72 (m, 1H), 1.72–1.80 (m, 1H), 1.80–1.92 (m, 6H), 1.92–2.06 (m, 2H), 2.53 (septet, *J*=6.9 Hz, 1H), 3.31 (t, *J*=6.3 Hz, 2H), 3.37 (t, *J*=6.3 Hz, 2H), 5.08 (dt, *J*=4.2, 6.0 Hz, 1H), 5.15 (dt, *J*=4.2, 5.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.8, 18.9, 19.2, 24.9, 25.7, 28.3, 28.4, 34.1, 45.7, 46.1, 74.3, 74.8, 154.4, 176.2.

4.11.9. (−)-*cis*-1-(*N*-Pyrrolidine-1′-carbonyloxy)-2-cycloheptanol (11) (entry 5, Table 4).[4c] TLC (hexane–EtOAc=2:1) R_f=0.09; $[\alpha]_D^{20}$ −8.8 (*c* 1.0, $CHCl_3$) for 93% ee; HPLC (two linear Daicel Chiralcel OD-H columns, hexane–2-propanol=20:1, flow rate=1.0 mL/min) t_R=37.0 (major) and 39.6 (minor) min; IR (film) 3500–3400 (br), 2933, 2871, 1678, 1429, 1180, 1129, 1106, 769 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40–1.62 (m, 4H), 1.62–1.84 (m, 6H), 1.84–2.00 (m, 4H), 3.09 (s, 1H), 3.40 (t, *J*=6.6 Hz, 4H), 3.88–3.96 (m, 1H), 4.97 (dt, *J*=2.4, 7.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.5, 22.8, 24.9, 25.7, 26.9, 28.9, 31.4, 73.5, 78.5, 155.4.

4.11.10. (−)-*cis*-1-(*N*-Pyrrolidine-1′-carbonyloxy)-2-cycloheptyl isobutyrate (entry 5, Table 4).[4c] TLC (hexane–EtOAc=2:1) R_f=0.36; $[\alpha]_D^{20}$ −17.9 (*c* 1.0, $CHCl_3$) for 92% ee; HPLC (two linear Daicel Chiralcel OD-H columns, hexane–2-propanol=20:1, flow rate=1.0 mL/min) t_R=15.4 (minor) and 16.3 (major) min; IR (film) 2936, 2872, 1733, 1703, 1419, 1195, 1157, 1100, 768 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17 (d, *J*=7.0 Hz, 3H), 1.18 (d, *J*=7.0 Hz, 3H), 1.47–1.81 (m, 8H), 1.81–2.01 (m, 6H), 2.58 (septet, *J*=7.0 Hz, 1H), 3.26–3.43 (m, 4H), 4.94–5.01 (m, 1H), 5.10–5.16 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.9, 19.0, 22.5, 22.7, 24.9, 25.7, 26.6, 28.8, 29.1, 34.2, 45.6, 46.0, 74.5, 75.2, 154.4, 176.2.

4.11.11. (2*RS*,3*SR*)-(−)-2-(*N*-Pyrrolidine-1′-carbonyloxy)-3-butanol (12) (entry 6, Table 4).[17] TLC (hexane–EtOAc=2:1) R_f=0.10; $[\alpha]_D^{20}$ −2.3 (*c* 1.0, $CHCl_3$) for 82% ee; HPLC (Daicel Chiralpak AD-H, hexane–2-propanol=20:1, flow rate=1.0 mL/min) t_R=15.9 (major) and 20.8 (minor) min; IR (film) 3500–3350 (br), 2977, 2877, 1679, 1426, 1130, 1106, 769 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16 (d, *J*=6.3 Hz, 3H), 1.22 (d, *J*=6.6 Hz, 3H), 1.82–1.95 (m, 4H), 2.81 (s, 1H), 3.33–3.43 (m, 4H), 3.83–3.93 (m, 1H), 4.84 (dq, *J*=2.7, 12.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.3, 17.2, 24.9, 25.6, 45.8, 46.2, 70.0, 75.1, 155.2.

4.11.12. (2*RS*,3*SR*)-(−)-2-(*N*-Pyrrolidine-1′-carbonyloxy)-3-butyl isobutyrate (entry 6, Table 4).[17] TLC (hexane–EtOAc=2:1) R_f=0.33; $[\alpha]_D^{20}$ −25.2 (*c* 1.0, $CHCl_3$) for 93% ee; HPLC (Daicel Chiralpak AD-H, hexane–2-propanol=20:1, flow rate=1.0 mL/min) t_R=7.1 (major) and 8.4 (minor) min; IR (film) 2978, 2877, 1734, 1705, 1416, 1196, 1160, 1103, 768 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16 (d, *J*=7.2 Hz, 3H), 1.17 (d, *J*=6.8 Hz, 3H), 1.21 (d, *J*=6.3 Hz, 3H), 1.24 (d, *J*=6.8 Hz, 3H), 1.82–1.92 (m,

4H), 2.54 (septet, J=7.0 Hz, 1H), 3.30 (t, J=6.3 Hz, 2H), 3.38 (t, J=6.3 Hz, 2H), 4.88 (dq, J=4.1, 6.5 Hz, 1H), 3.38 (t, J=6.3 Hz, 2H), 4.88 (dq, J=4.1, 6.5 Hz, 1H), 5.03 (dq, J=4.1, 6.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.3, 15.5, 18.8, 19.0, 24.9, 25.6, 34.1, 45.6, 46.0, 71.3, 72.0, 154.3, 176.3.

4.11.13. (*S*)-(−)-*N*-(3-Hydroxy-3-phenylpropionyl)pyrrolidine (13) (entry 7, Table 4). TLC (hexane–EtOAc=2:1) R_f=0.22; $[\alpha]_D^{20}$ −51.5 (c 1.0, $CHCl_3$) for 64% ee; HPLC (Daicel Chiralpak AD-H, hexane–2-propanol=20:1, flow rate=1.0 mL/min) t_R=30.2 (minor) and 32.1 (major) min; IR (KBr) 3300–3200 (OH), 1609 (C=O), 1474, 1065, 707 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.80–2.00 (m, 4H), 2.58 (dd, J=8.7, 16.2 Hz, 1H), 2.65 (dd, J=3.6, 16.2 Hz, 1H), 3.31 (t, J=6.6 Hz, 2H), 3.48 (t, J=6.3 Hz, 2H), 4.97 (d, J=3.0 Hz, 1H), 5.16 (dt, J=3.3, 8.7 Hz, 1H), 7.24–7.45 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.3, 25.8, 43.0, 45.5, 46.5, 70.3, 125.6 (2C), 127.4, 128.4 (2C), 143.1, 170.7. Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81. Found: C, 71.19; H, 7.99. The absolute stereochemistry of **13** was determined by comparison with authentic (*S*)-**13** derived from ethyl (*S*)-3-phenylpropionate, which was commercially available.

4.11.14. (*R*)-(+)-*N*-(3-Isobutyryloxy-3-phenylpropionyl)pyrrolidine. TLC (hexane–EtOAc=1:2) R_f=0.35; $[\alpha]_D^{20}$ 29.5 (c 1.0, $CHCl_3$); HPLC (Daicel Chiralpak AD-H, hexane–2-propanol=20:1, flow rate=1.0 mL/min) t_R=36.5 (major) and 45.0 (minor) min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (t, J=7.1 Hz, 6H), 1.76–1.95 (m, 4H), 2.56 (septet, J=7.1 Hz, 1H), 2.65 (dd, J=5.4, 15.0 Hz, 1H), 2.94 (dd, J=8.3, 15.0 Hz, 1H), 3.22–3.31 (m, 1H), 3.40–3.51 (m, 3H), 6.21 (dd, J=5.4, 8.3 Hz, 1H), 7.24–7.41 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.8 (2C), 24.3, 26.0, 33.9, 42.0, 45.6, 46.7, 72.6, 126.2 (2C), 127.9, 128.5 (2C), 140.5, 167.6, 175.6. Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01. Found: C, 70.67; H, 7.93. The absolute stereochemistry of this compound was determined by comparison with authentic sample derived from ethyl (*S*)-3-phenylpropionate, which was commercially available.

4.11.15. (2*SR*,3*RS*)-(−)-*N*-(3-Hydroxy-2-methyl-3-phenylpropionyl)pyrrolidine (14) (entry 1, Table 5). TLC (hexane–EtOAc=1:2) R_f=0.35; $[\alpha]_D^{20}$ −80.1 (c 1.0, $CHCl_3$) for 80% ee; HPLC (Daicel Chiralpak AD-H, hexane–2-propanol=20:1, flow rate=1.0 mL/min) t_R=26.6 (major) and 28.4 (minor) min; IR (KBr) 3400–3300 (OH), 2976, 2872, 1613, 1469, 1447, 1047, 756, 702 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (d, J=7.2 Hz, 3H), 1.65–1.87 (m, 4H), 2.86 (dq, J=7.2, 2.1 Hz, 1H), 2.96–3.05 (m, 1H), 3.23–3.32 (m, 1H), 3.34–3.41 (m, 2H), 4.64 (d, J=7.2 Hz, 1H), 4.77 (dd, J=5.1, 6.9 Hz, 1H), 7.21–7.37 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.3, 24.1, 25.8, 44.8, 45.4, 46.5, 76.6, 125.9 (2C), 127.4, 128.2 (2C), 143.3, 174.1. Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21. Found: C, 72.21; H, 8.13.

4.11.16. (+)-*N*-(3-Isobutyryloxy-2-methyl-3-phenylpropionyl)pyrrolidine (19) (entry 1, Table 5). TLC (hexane–EtOAc=1:1) R_f=0.19; $[\alpha]_D^{20}$ 55.8 (c 1.0, $CHCl_3$) for 82% ee; HPLC (Daicel Chiralpak AD-H, hexane–2-propanol=20:1, flow rate=1.0 mL/min) t_R=27.4 (minor) and 49.7 (major) min; IR (KBr) 2973, 2875, 1731, 1628, 1459, 1438, 1200, 1162, 703 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (d, J=7.2 Hz, 3H), 1.07 (d, J=7.2 Hz, 3H), 1.09 (d, J=7.2 Hz, 3H), 1.82–1.94 (m, 2H), 1.94–2.05 (m, 2H), 2.45 (septet, J=6.9 Hz, 1H), 3.60 (dq, J=3.9, 6.9 Hz, 1H), 3.45–3.56 (m, 3H), 3.68–3.78 (m, 1H), 5.77 (d, J=10.2 Hz, 1H), 7.26–7.39 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 18.5, 18.8, 24.4, 26.1, 33.9, 43.6, 45.8, 46.7, 78.4, 127.3 (2C), 128.1, 128.4 (2C), 138.9, 172.1, 174.9. Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31. Found: C, 71.18; H, 8.43.

4.11.17. (−)-*cis*-*N*-(2′-Hydroxyindan-1′-yl)pyrrolidine-1-carboxamide (15) (entry 9, Table 5).[4e,g] TLC (EtOAc) R_f=0.40; $[\alpha]_D^{20}$ −36.6 (c 1.0, $CHCl_3$) for 67% ee; HPLC (Daicel Chiralpak AD-H, hexane–2-propanol=9:1, flow rate=1.0 mL/min) t_R=11.9 (major), 15.0 (minor) min; IR (KBr) 3405, 3205, 1618, 1523, 1474, 1404, 1180, 1060, 744 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.90–1.97 (m, 4H), 1.93 (s, 1H), 2.96 (dd, J=3.6, 16.5 Hz, 1H), 3.17 (dd, J=5.6, 16.5 Hz, 1H), 3.34–3.44 (m, 4H), 4.61–4.68 (m, 1H), 4.71 (d, J=7.5 Hz, 1H), 5.29 (dd, J=5.3, 7.4 Hz, 1H), 7.19–7.36 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.5 (2C), 39.1, 45.7 (2C), 58.8, 73.9, 124.7, 125.3, 127.1, 128.3, 140.4, 141.3, 157.2.

4.11.18. (+)-*cis*-*N*-(2′-Isobutyryloxyindan-1′-yl)pyrrolidine-1-carboxamide (entry 9, Table 5).[4e,g] TLC (hexane–EtOAc=1:2) R_f=0.34; $[\alpha]_D^{20}$ 70.0 (c 1.0, $CHCl_3$) for 93% ee; HPLC (Daicel Chiralpak AD-H, hexane–2-propanol=9:1, flow rate=1.0 mL/min) t_R=16.7 (major), 24.6 (minor) min; IR (KBr) 3550–3300 (br), 1729, 1642, 1622, 1524, 1403, 1189, 1151, 1037 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (d, J=6.0 Hz, 3H), 1.05 (d, J=6.0 Hz, 3H), 1.82–1.90 (m, 4H), 2.40 (septet, J=7.0 Hz, 1H), 2.89 (d, J=17.4 Hz, 1H), 3.16 (dd, J=5.1, 17.4 Hz, 1H), 3.23–3.38 (m, 4H), 4.62 (d, J=9.3 Hz, 1H), 5.48 (dt, J=0.9, 5.6 Hz, 1H), 5.58 (dd, J=5.6, 9.2 Hz, 1H), 7.13–7.21 (m, 3H), 7.25–7.30 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.7, 19.1, 23.5 (2C), 34.0, 37.7, 45.6 (2C), 56.7, 76.0, 123.9, 124.9, 127.1, 127.9, 139.4, 141.9, 156.2, 176.2.

4.11.19. (2*R*,3*R*)-(−)-2-(*N*-Pyrrolidine-1′-carboxamino)-3-hydroxybutyric acid methyl ester (16) (entry 10, Table 4). TLC (hexane–EtOAc=1:5) R_f=0.17; $[\alpha]_D^{20}$ −32.0 (c 1.0, $CHCl_3$) for 51% ee; HPLC (Daicel Chiralpak AS-H, hexane–2-propanol=5:1, flow rate=0.5 mL/min) t_R=23.5 (major), 27.7 (minor) min; IR (KBr) 3400–3300 (br), 2987, 2956, 2879, 1751, 1616, 1526, 1433, 1191, 1163 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.11 (d, J=6.3 Hz, 3H), 1.91–1.96 (m, 4H), 3.36–3.42 (m, 4H), 3.79 (s, 3H), 4.17–4.27 (m, 1H), 4.40 (d, J=5.4 Hz, 1H), 4.68 (dd, J=3.3, 6.0 Hz, 1H), 5.25 (d, J=5.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.0, 25.5 (2C), 45.7 (2C), 52.6, 59.1, 69.1, 157.0, 171.6. Anal. Calcd for $C_{10}H_{18}N_2O_4$: C, 52.16; H, 7.88. Found: C, 52.11; H, 7.90. The absolute stereochemistry of **16** was determined by comparison with authentic (*S*)-**16** derived from (2*S*,3*S*)-L-allothreonine, which was commercially available.

4.11.20. (2*S*,3*S*)-(+)-2-(*N*-Pyrrolidine-1-carboxamino)-3-isobutyryloxybutyric acid methyl ester (entry 10, Table 4). TLC (hexane–EtOAc=1:2) R_f=0.34; $[\alpha]_D^{20}$ 1.1 (c 1.0, $CHCl_3$) for 80% ee; HPLC (Daicel Chiralpak AS-H,

hexane–2-propanol=5:1, flow rate=0.5 mL/min) t_R=12.6 (major), 15.6 (minor) min; IR (KBr) 3354, 3290, 2979, 2944, 2875, 1739, 1639, 1535, 1416, 1197, 1161 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.14 (d, J=4.8 Hz, 3H), 1.32 (d, J=4.8 Hz, 3H), 1.36 (d, J=6.6 Hz, 3H), 1.89–1.94 (m, 4H), 2.53 (septet, J=7.0 Hz, 1H), 3.33–3.39 (m, 4H), 3.77 (s, 3H), 4.69 (dd, J=3.6, 8.1 Hz, 1H), 5.13 (dq, J=3.3, 12.9 Hz, 1H), 5.21 (d, J=8.1 Hz, 1H), 4.69 (dd, J=3.6, 8.1 Hz, 1H), 5.13 (dq, J=3.3, 12.9 Hz, 1H), 5.21 (d, J=8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.2, 18.7, 18.9, 25.5 (2C), 34.0, 45.5 (2C), 52.3, 57.3, 71.4, 155.7, 171.0, 176.9. Anal. Calcd for $C_{14}H_{24}N_2O_5$: C, 55.98; H, 8.05. Found: C, 55.91; H, 8.08. The absolute stereochemistry of this compound was determined by comparison with authentic sample derived from (2*S*,3*S*)-L-allothreonine, which was commercially available.

4.11.21. (*S*)-(−)-3-Methyl-2-(*N*-pyrrolidine-1-carboxamino)-1-butanol (17) (entry 11, Table 4). TLC (EtOAc) R_f=0.14; $[\alpha]_D^{20}$ −37.2 (*c* 1.0, $CHCl_3$) for 88% ee; HPLC (Daicel Chiralpak AS-H, hexane–2-propanol=5:1, flow rate=0.5 mL/min) t_R=11.1 (major), 14.5 (minor) min; IR (KBr) 3364, 3292, 2969, 2869, 1608, 1525, 1408, 1335, 1086 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.95 (d, J=5.1 Hz, 3H), 0.97 (d, J=5.1 Hz, 3H), 1.84–1.99 (m, 5H), 3.31–3.39 (m, 4H), 3.55–3.68 (m, 2H), 3.68–3.78 (m, 1H), 3.98 (t, J=4.8 Hz, 1H), 4.39 (d, J=6.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.8, 19.6, 25.5 (2C), 29.4, 45.6 (2C), 58.2, 65.4, 157.9. Anal. Calcd for $C_{10}H_{20}N_2O_2$: C, 59.97; H, 10.07. Found: C, 59.89; H, 10.12. The absolute stereochemistry of **17** was determined by comparison with authentic (*S*)-**16** derived from (*S*)-L-valine, which was commercially available.

4.11.22. (*R*)-(+)-Isobutyryloxy-3-methyl-2-(*N*-pyrrolidine-1-carboxamino)butane (entry 11, Table 4). TLC (hexane–EtOAc=1:5) R_f=0.33; $[\alpha]_D^{20}$ 30.6 (*c* 1.0, $CHCl_3$) for 86% ee; HPLC (Daicel Chiralpak AS-H, hexane–2-propanol=5:1, flow rate=0.5 mL/min) t_R=9.0 (minor), 13.0 (major) min; IR (KBr) 3313, 2969, 2872, 1731, 1625, 1533, 1469, 1405, 1195, 1161, 1081 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.96 (d, J=6.6 Hz, 6H), 1.14 (d, J=2.1 Hz, 3H), 1.17 (d, J=2.1 Hz, 3H), 1.84 (septet, J=6.7 Hz, 1H), 1.87–1.94 (m, 4H), 2.56 (septet, J=7.0 Hz, 1H), 3.32 (t, J=6.6 Hz, 4H), 3.90–4.06 (m, 2H), 4.23–4.35 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.6, 18.9, 19.2, 25.5 (2C), 29.9, 34.0, 45.4 (2C), 54.3, 64.7, 156.4, 177.5. Anal. Calcd for $C_{14}H_{26}N_2O_3$: C, 62.19; H, 9.69. Found: C, 62.22; H, 9.75. The absolute stereochemistry of this compound was determined by comparison with authentic sample derived from (*S*)-L-valine, which was commercially available.

4.11.23. (−)-*N*-(2-Hydroxy-1-phenylethyl)pyrrolidine-1-carboxamide (18) (entry 12, Table 4). $[\alpha]_D^{20}$ −3.9 (*c* 2.4, $CHCl_3$) for 83% ee; HPLC (Daicel Chiralpak AS-H, hexane–2-propanol=5:1, flow rate=1.0 mL/min) t_R=7.4 (major), 11.4 (minor) min; IR (KBr) 3350, 2971, 2875, 2360, 1616, 1545, 1522, 1412, 1346, 1075, 755, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.86–1.98 (m, 4H), 3.24–3.44 (m, 4H), 3.84 (d, J=5.4 Hz, 2H), 4.08 (br, 1H), 4.88 (d, J=6.0 Hz, 1H), 4.96 (q, J=5.5 Hz, 2H), 7.23–7.41 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.5 (2C), 45.7 (2C), 57.3, 67.2, 126.6, 127.7, 128.8, 140.1, 157.3.

4.11.24. (−)-2-Phenyl-2-(pyrrolidine-1-carboxamino)-ethyl isobutyrate (entry 12, Table 4). $[\alpha]_D^{20}$ −1.9 (*c* 3.7, $CHCl_3$) for 74% ee; HPLC (Daicel Chiralpak AS-H, hexane–2-propanol=5:1, flow rate=1.0 mL/min) t_R=7.4 (minor), 11.8 (major) min; IR (KBr) 3441, 3325, 2974, 2874, 1731, 1627, 1544, 1411, 1191, 1153, 703, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.11 (d, J=6.91 Hz, 6H) 1.85–1.96 (m, 4H), 2.54 (septet, J=7.0 Hz, 1H), 3.26–3.42 (m, 4H), 4.22 (dd, J=4.8, 11.4 Hz, 1H), 4.51 (dd, J=7.5, 11.4 Hz, 1H), 4.97 (br, 1H), 5.22 (dt, J=4.8, 7.5 Hz, 1H), 7.23–7.36 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.9 (2C), 25.5 (2C), 33.9, 45.4 (2C), 53.8, 66.4, 126.6 (2C), 127.5, 128.5 (2C), 139.6, 155.8, 177.7.

4.12. Procedure for the preparation of polystyrene-bound catalyst 3

(4-Methoxyphenyl)diisopropylsilylpropyl polystyrene (**20**, 1.40 mmol of Si/g, 50–100 mesh; the polymer matrix is copolystyrene–1% divinylbenzene)[12] that had been dried under vacuum for 12 h was weighted (212 mg, 0.297 mmol) into a flask and swollen in CH_2Cl_2 (2.1 mL, 10 mL of solvent per gram of resin) under a N_2 atmosphere for 30 min. The solvent was then drained under positive N_2 pressure and a 4% trifluoromethanesulfonic acid–CH_2Cl_2 solution (6 equiv of TfOH relative to Si) was added by syringe. The resin turned bright red/orange upon acid treatment and then gently agitated for 30 min while still under the N_2 atmosphere. Once activation was complete, the resin was washed twice with CH_2Cl_2 to remove excess acid. Treatment of silyl triflate functionalized resin with 2,6-lutidine (280 μL, 2.40 mmol, 8 equiv relative to Si) for 15 min followed by the addition of an azeotropically dried solution of **21** (253 mg, 0.600 mmol) in CH_2Cl_2 (1.2 mL) resulted in a colorless resin. The beads were then gently agitated for an additional 10 h under a N_2 atmosphere. The beads were drained, exposed to room temperature, and subjected to the following wash protocol: CH_2Cl_2 (2×3 mL× 45 min), THF (2×3 mL×30 min), THF–*i*-Pr_2EtN (3:1, 2×3 mL×30 min), THF–IPA (3:1, 2×3 mL×30 min), THF–H_2O (3:1, 2×3 mL×30 min), and THF–IPA (3:1, 2×3 mL×30 min), DMF (2×3 mL×30 min), THF (2× 3 mL×30 min). The resin was air-dried for 3 h and then placed under high vacuum for 24 h to remove trace solvent and H_2O to give **3**. The mass of **3** was 278 mg (0.229 mmol, 0.824 mmol of imidazole moiety per gram), indicating an apparent loading efficiency of 77% based on weight gain.

4.13. Procedure for the kinetic resolution of (±)-7a induced by reusable catalyst 3

To a suspension of (±)-**7a** (53.3 mg, 0.25 mmol) and **3** (15.2 mg, 0.0125 mmol, 0.824 mmol/g) in CCl_4 (2.5 mL) were added *i*-Pr_2NEt (21.8 μL, 0.125 mmol) and isobutyric anhydride (20.7 μL, 0.125 mmol). After being shaken at 0 °C for 7 h, **3** was recovered by filtration and washed with toluene (2×3 mL). Thus, **3** was reused more than five times without any loss of activity or selectivity. The combined filtrate was concentrated under reduced pressure and the residue was analyzed without purification. The ee values for the recovered alcohol **7a** and the acylated product **8a** were determined by HPLC analysis: (1*S*,2*R*)-**7a** (major

enantiomer), 82–86% ee and (1*R*,2*S*)-**8a** (major enantiomer), 62–65% ee. The conversion from **7a** to **8a** was determined to be 42–44% by the following equation, conversion (%)=[ee (recovered alcohol)]/[ee (recovered alcohol)+ee (acylated product)].[9]

4.14. Computational methods

Theoretical calculations were performed using the Gaussian 98 program.[10] Gradient-corrected density functional theory (DFT) with Becke's three-parameter exchange with the Lee, Yang, and Parr correlation functional (B3LYP)[11] were carried out using the 6-311++G(d,p) basis set. After satisfactory optimization, the vibrational spectrum of each species was calculated.

4.15. X-ray diffraction analysis of 1c

X-ray crystallographic analysis was performed with a Bruker SMART APEX diffractometer (graphite monochromator, Mo Kα radiation, λ=0.71073 Å) and the structure was solved by direct methods and expanded using Fourier techniques (Sir97 and SHELXL[18]).

Recrystallization of **1c** was carried out in the solution of chloroform–hexane at room temperature. Mp 178 °C. Crystallographic data have been deposited with Cambridge Crystallographic Data Centre: Deposition number CCDC 253176. Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk) (Table 7).

Table 7. Crystallographic data and structure refinement for **1c**

Compound	**1c**
Empirical formula	$C_{38}H_{53}N_3O_3SSi$
Formula weight	659.98
T	173(2) K
λ	0.71073 Å
Crystal system	Orthorhombic
Space group	$P212121$
A	10.1626(9) Å
B	21.9774(19) Å
C	34.178(3) Å
α	90.00°
β	90.00°
γ	90.00°
V	7633.6(11) Å^3
Z	8
D_{calcd}	1.149 g/cm^3
Absorption coefficient	0.154 mm^{-1}
$F(000)$	2848
Crystal size	0.30×0.20×0.20 mm^3
Theta range for data collection	1.51–29.18°
Reflections collected	58,323
Independent reflections	20,367
R_{int}	0.0378
Refinement based on F^2	
No. of data	20,367
No. of parameters	849
No. of restraints	0
GOF	1.079
$R(F)$ for $I>2\sigma(I)$	0.0627
$wR_2(F^2)$ for all data	0.1716
$\Delta\rho_{min}$	−0.340 e Å^{-3}
$\Delta\rho_{max}$	0.918 e Å^{-3}

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