Design of Small Catalysts with the Histidine Framework for Asymmetric Acylation

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Chapter 1

Introduction

1-1 Introduction

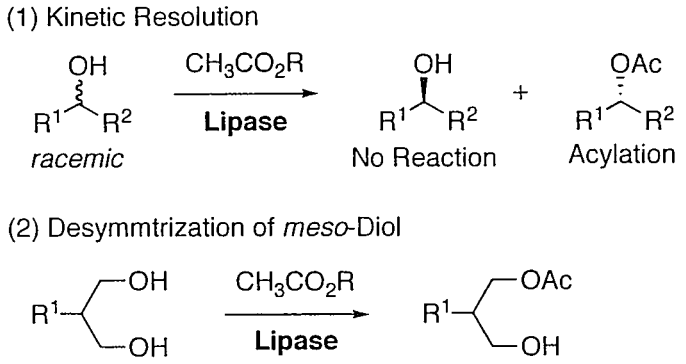
Living thing create the enzyme (biocatalyst) which consists of combinations of amino acids with molecular weights in the several tens of thousands which control various vital reactions. The enzyme lipase is widely used as a catalyst in kinetic resolution and desymmetrization by esterification and hydrolysis of racemic chemical compounds. However, the widespread practical application of enzymes is limited by several factors: 1) narrow substrate range, 2) complicated structure for the enzyme, and the mechanism of selectivity is not understood, 3) high cost of purified enzymes, 4) enzymes are available in just one enantiomeric form, 5) the need for stringent operating parameters, 6) batch to batch irreproducibility, and 7) enzymes consist of huge molecules, which makes it necessary to use large volumes as a catalyst.

When small compounds with molecular weight values in several hundreds are synthesized selectively, is it truly necessary to use enzymes with enormous and complicated 3-D structures? It may be possible to create small-molecule catalyst artificially by refining our chemical manipulations. If we could use the active site of the enzyme and make the minimum necessary chemical modification, could it be possible to develop a small-molecule artificial enzyme more efficiently? Therefore, we designed and synthesized small biomimetic catalysts with a histidine framework for asymmetric acylation.

We achieved high selectivity in the kinetic resolution of racemic alcohols with these catalysts. We also used them to achieve high selectivity in the kinetic resolution of racemic carboxylic acids.

1-2 Rational Design of an L-Histidine-derived Minimal Artificial Acylase for the Kinetic Resolution of Racemic Alcohols

Chiral alcohols and esters are an important class of compound that can be incorporated into various synthetic strategies. The kinetic resolution of these compounds has traditionally been achieved using enzymes, often with excellent results (Scheme 1).[1]



Scheme 1. Catalytic asymmetric acylation using enzymes

Nonenzymatic kinetic resolution of racemic alcohols via enantioselective acylation is a recent focus of attention in synthetic chemistry. Intensive efforts have been made to develop analogous processes using low-molecular-weight chiral nucleophilic catalysts. Several chiral nucleophilic phosphines,[2] diamines,[3] 4-dialkylpyridienes,[4-9] bicyclic amidines[10] and *N*-alkylimidazoles (1-alkyl-IMD)[11,12] that can deliver levels of enantioselectivity comparable to those of enzymes in the catalytic kinetic resolution of racemic alcohols via acylation have been developed[13](Figure 1).

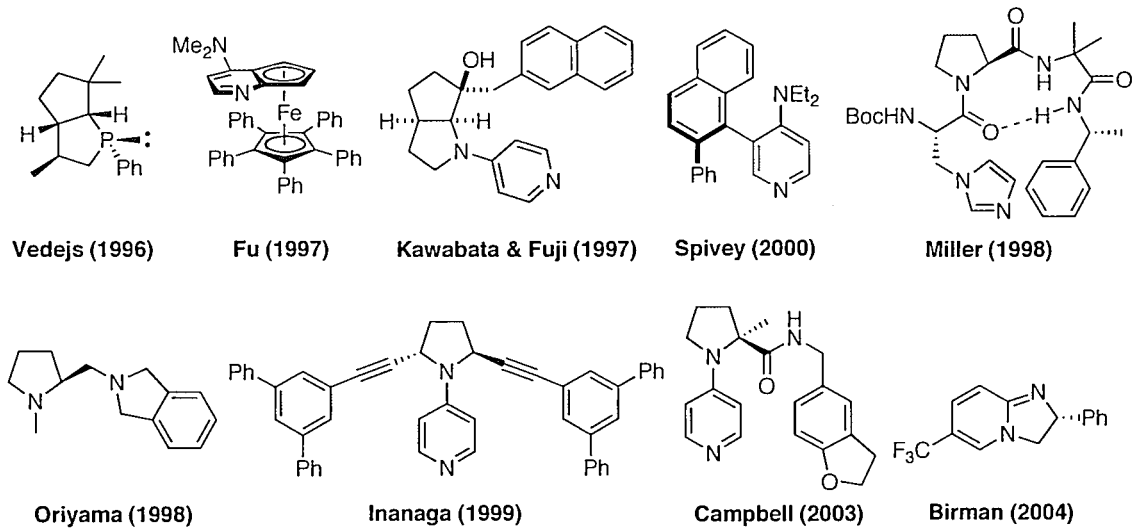
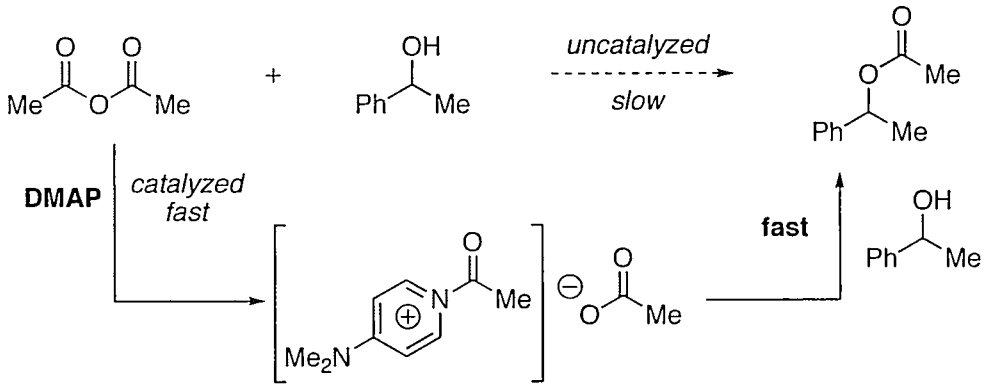


Figure 1. Chiral nucleophilic catalysts

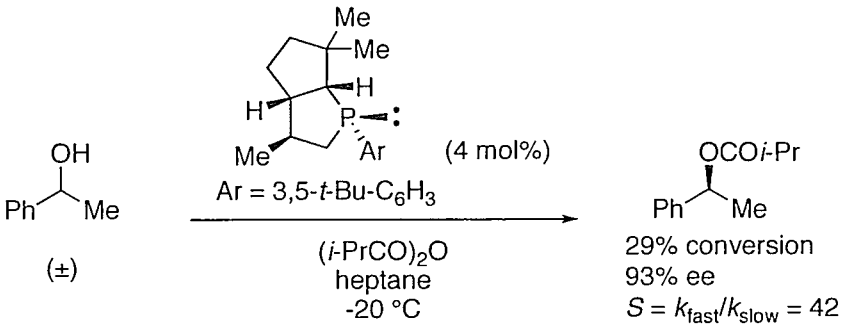
4-(*N*,*N*-Dimethylamino)pyridine (DMAP) and 1-alkyl-IMD are among the best known achiral acylation catalysts.[14,15] The mechanism by which DMAP accelerates this process illustrates how a nucleophile can catalyze chemical transformations (Scheme 2). Acylations typically occur several orders of magnitude more rapidly in the presence of DMAP than in its absence. Other nucleophilic catalysts, including phosphines, diamines,

bicyclic amidines and 1-alkyl-IMD, also catalyze the acylation of alcohols by the same mechanism.



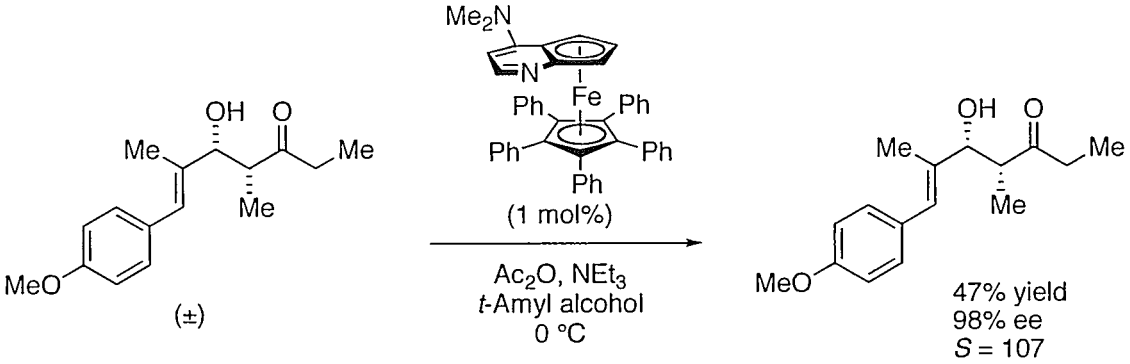
Scheme 2. Mechanism of the DMAP-catalyzed acylation of alcohols

In chiral phosphines, Vedejs developed a new class of chiral phosphines belonging to the *P*-aryl-2-phosphabicyclo[3.3.0]octane family.[2] These phosphines act as efficient catalysts for the kinetic resolution of aryl-alkyl carbinols (Scheme 3).



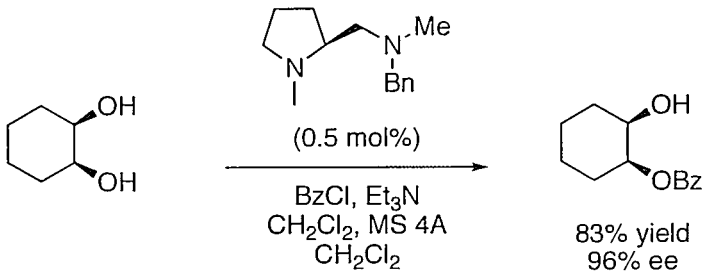
Scheme 3

In chiral DMAP derivatives, Fu and co-workers introduced "planar-chiral" DMAP derivatives as enantioselective catalysts.[4] DMAP itself is not chiral and possesses two mirror planes, the first in the plane of the pyridine ring and the second passing perpendicularly through the two nitrogens. They can effectively eliminate these two mirror planes, the first through π-complexation and the second by introducing a substituent at the 2-position of the pyridine ring. A variety of aryl-alkyl, alkenyl-alkyl and alkynyl-alkyl carbinols are good substrates for kinetic resolution (Scheme 4).



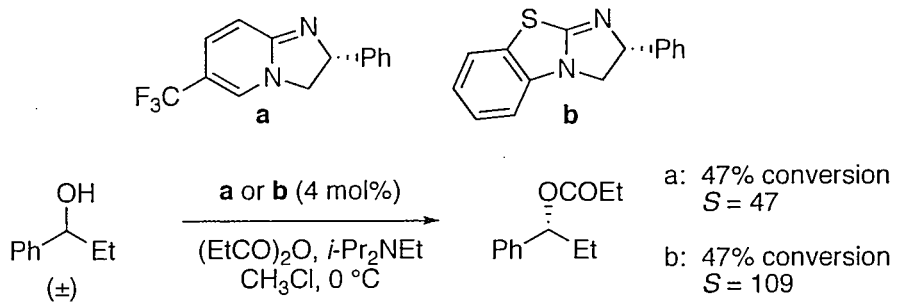
Scheme 4

With chiral diamines, Oriyama developed a highly enantioselective desymmetrization of meso-diols catalyzed by chiral diamine derived from proline.[3] This was found to be a highly efficient catalyst for the kinetic resolution of various racemic secondary alcohols (Scheme 5).



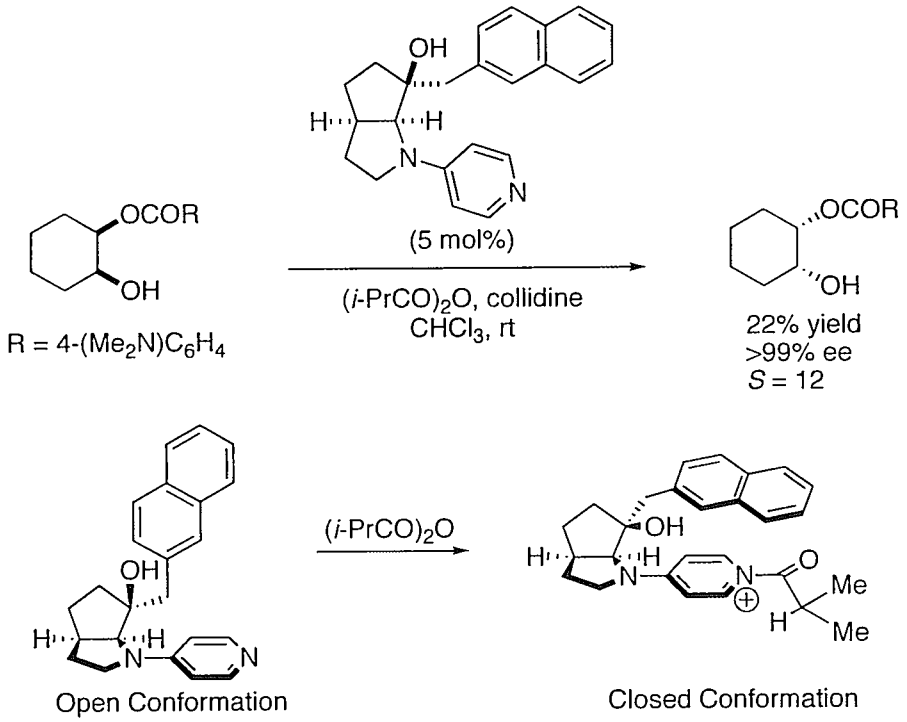
Scheme 5

In chiral bicyclic amidines, Birman developed easily obtainable chiral dihydroimidazo[1,2-*a*]pyridine (DHIP) derivatives[10] for the kinetic resolution of benzylic and allylic alcohols. In asymmetric acylation, bicyclic isothioureas[11] have shown improved catalytic activity and far superior enantioselectivity (Scheme 6).



Scheme 6

Two methods have been reported using a biomimetic approach. Fuji and Kawabata prepared an enantiomerically pure 4-pyrrolidinopyridiene derivative from an enantiopure natural alkaloid.[5] The authors referred to this conformational change as an "induced-fit" process, much like the conformational change that enzymes undergo upon binding with ligands. The aromatic ring of the substrate may be involved in another aromatic π-π interaction with the catalyst, to form a well-organized transition state that can account for the high stereoselectivity. This is consistent with the observation that electron-rich aromatic substrates afford higher selectivities, possibly through better π-π interaction with the electron-poor acylpyridinium ion (Scheme 7).

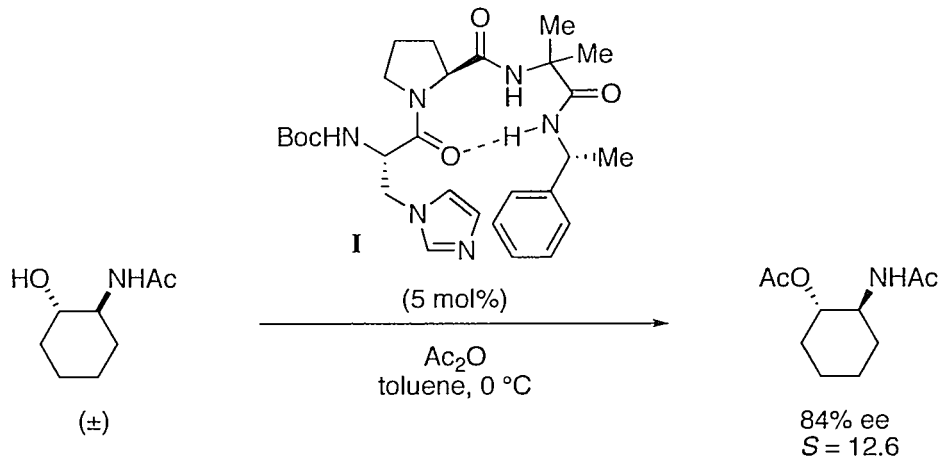


Scheme 7

Another biomimetic approach was reported by Miller and co-workers.[11] They developed protocols for the kinetic resolution of alcohols using nucleophilic peptides. The search for low-molecular-weight peptides that may act as enantioselective catalysts is based on the "biomimetic" principles of enzymatic catalysis. Peptide-substrate interactions are the hallmark of the fidelity that enzymes exhibit for their ligands.

Early work focused on peptides that had a propensity to form stable secondary structures in solution. First generation catalyst design drew heavily from the peptide-design literature. It was thought that by incorporating an amino acid residue that was an analogue

of the known nucleophilic catalyst *N*-methylimidazole (NMI) into a peptide scaffold, which was predicted to adopt a stable β-turn-type structure in solution, a viable enantioselective catalyst for asymmetric acyl transfer could be designed. The presence of an amide functionality increases the likelihood of a hydrogen bonding interaction with the peptide backbone. In this regard, racemic substrate was treated with Ac_2O in the presence of **I** (5 mol %) in toluene at 0 C to give the corresponding acetate in 84% ee (s = 12.6) (Scheme 8).



Scheme 8

In the development of enantioselective catalytic reactions, the rate-limiting step is very often the assay of the reaction products for selectivity. Often this involves some form of chiral HPLC or GC assay, which, depending on the time required for each assay, can be prohibitive if applied to the assay of hundreds or even thousands of catalysts that libraries may afford. Since reactivity is coupled to enantioselectivity in the above kinetic resolution reactions, it was possible to develop a simple fluorescence-based assay to identify new catalysts. During the kinetic resolution reaction, each turnover event results in the formation of acetic acid as a byproduct. Fluorophore was found to be highly fluorescent in the presence of acetic acid, and the fluorescence intensity was a function of the acetic acid concentration. Since reactivity is coupled to selectivity, it was possible to screen more catalysts within a given time, due to the ease of the simple visual assay (by eye or fluorescence micrograph) (Figure 2).

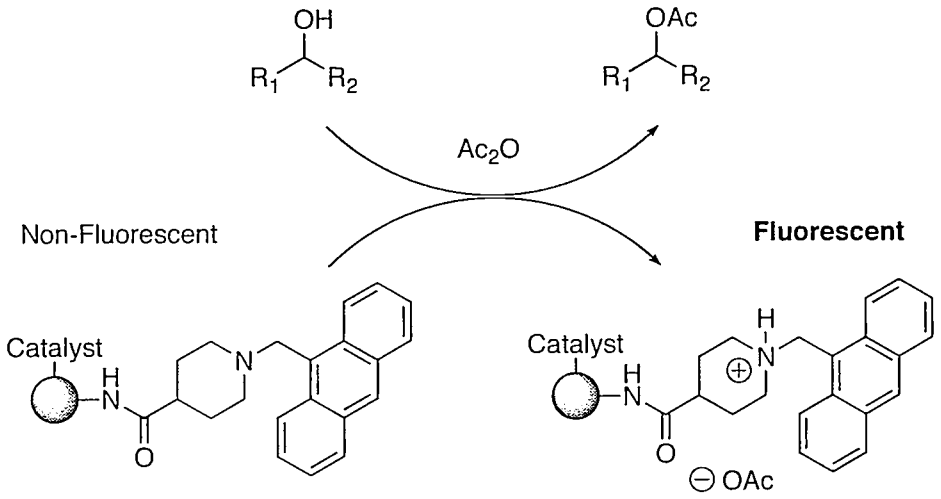
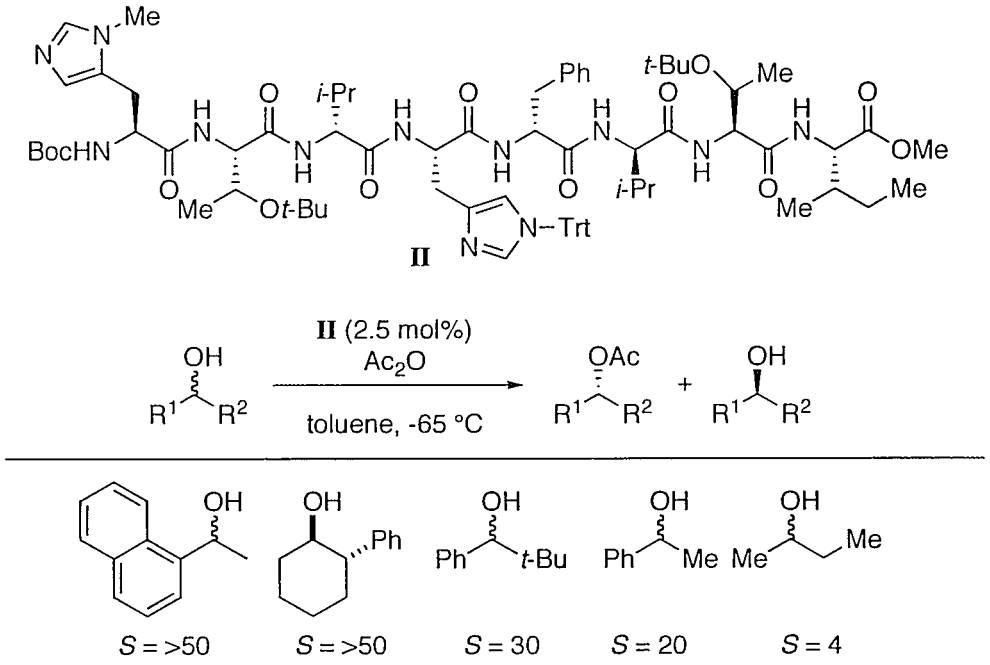


Figure 2

Using this technique, a fluorescence-labeled split-pool library (solid-support bound) of octapeptide catalysts was screened for activity in the kinetic resolution of *sec*-phenylethanol, an unfunctionalized alcohol which has not been resolved selectively with previously described peptides. This technique allowed for the development of a highly selective octapeptide **II**, which was an efficient catalyst for the kinetic resolution of several unfunctionalized secondary alcohols. This fluorescence-based assay was then extended to develop a screening method based on parallel enantiomer analysis. Peptide catalysts were evaluated in parallel for their reactivity with each enantiomer, and peptides that exhibited significant differences in reactivity for each enantiomer were selected for further study in kinetic resolution reactions (Scheme 9).



Scheme 9

Miller's biomimetic approach to the identification of artificial acylases based of β-turn peptide fragments with defined secondary structures that contain 1-alkyl-IMD residues prompted our present study. Nucleophilic enzymes originate from highly complex macromolecules, and the imidazole substituent at a histidine unit is an active site. It is advantageous to use histidine as a chiral backbone for catalytic asymmetric acylation: L-histidine has possessed an imidazole ring which is a nucleophilic catalytic moiety, contains a chiral carbon center, and is readily available as a natural amino acid. Therefore, we sought to design simple and small artificial acylases by adding the right substituent to the amino acid moiety. In addition, previously reported catalysts have required multistep syntheses[2,4,5,7-10] or preparative-scale chiral stationary phase (CSP) HPLC.[4] Such inaccessibility constitutes a significant disincentive to the widespread use of these catalysts and compromises their value as practical enzyme substitutes. Therefore, we also tried to design simpler methods for the synthesis of catalysts (Figure 3).

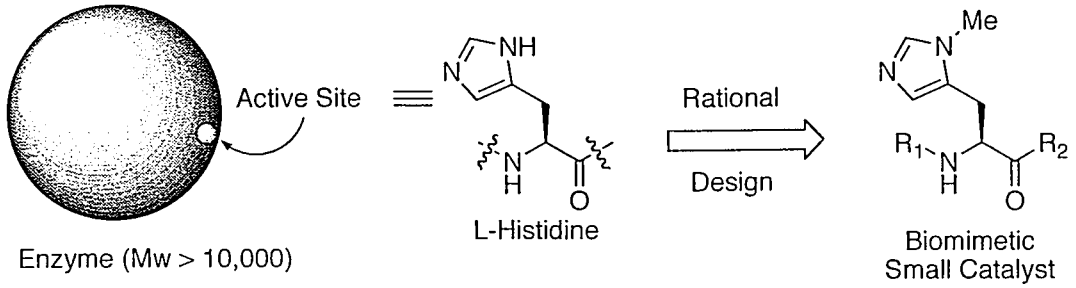


Figure 3

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. In a given catalytic acylation reaction, treatment of a catalyst with acid anhydride could generate acyl imidazolium ion, which is a potent acylating reagent. To increase the possibility of kinetically significant catalyst-substrate interaction in the transition state, which could lead to improved stereoselection, racemic alcohols that included a hydrogen-bonding donor were chosen as the substrate for kinetic resolution (Figure 4).

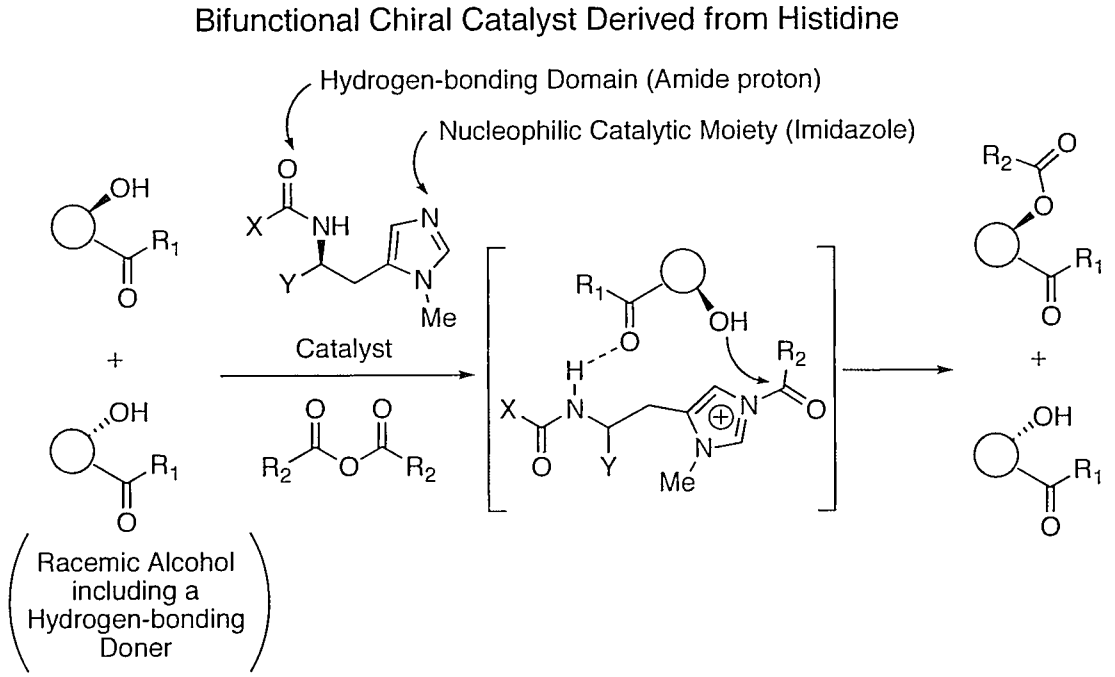
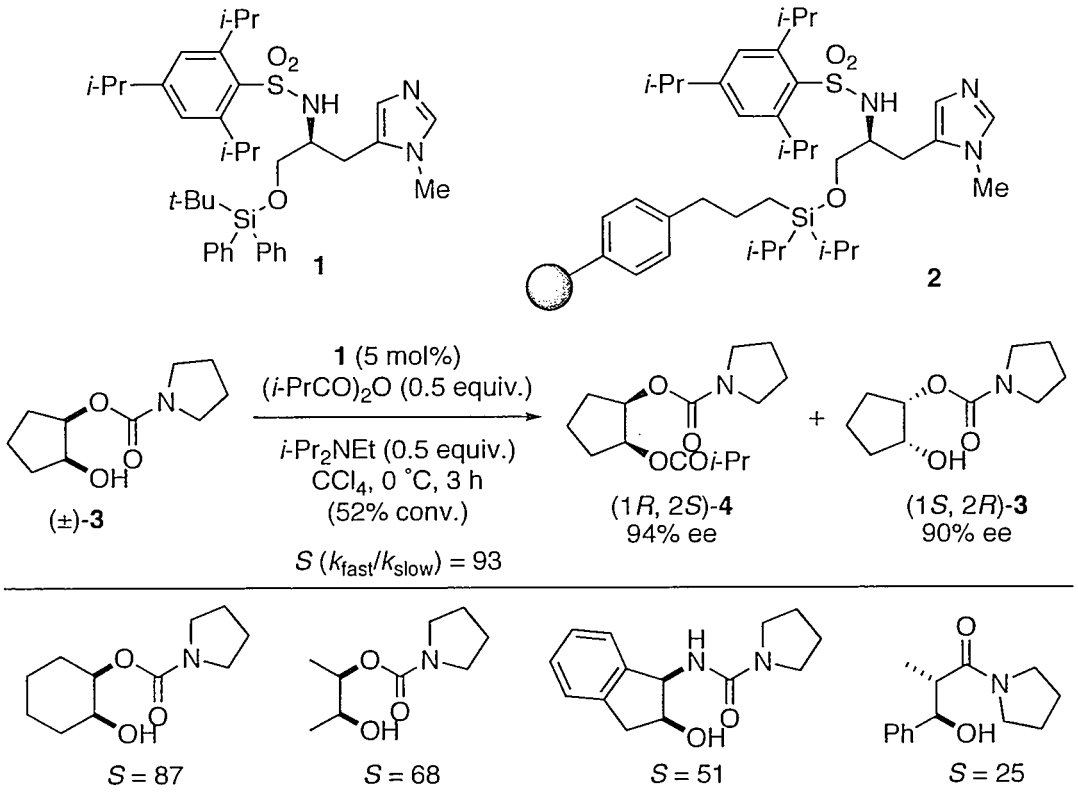


Figure 4

We succeeded in the rational design of a minimal artificial acylase derived from L-histidine by introducing a sulfonamidyl group in place of a long peptide chain based on the

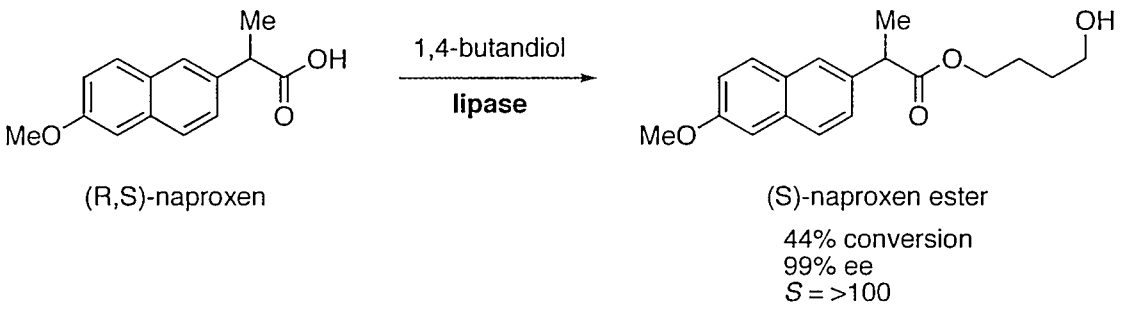
notion of hydrogen bonding between a carboxamidyl group and the substrate. Our new artificial acylase, *tert*-butyldiphenylsilyl ether of *N*-(2,4,6-triisopropylbenzenesulfonyl)-π(Me)-L-histidinol (molecular weight = 660),[12] contains a nucleophilic *N*-methylimidazole moiety and only one chiral carbon center that originates from natural L-histidine (Chapter 2). The kinetic resolution of racemic alcohols induced by our new artificial acylase showed an $S(k_{\text{fast-reacting enantiomer}}/k_{\text{slow-reacting enantiomer}})$ value of up to 132. A reusable polystyrene-bound artificial acylase was also developed to examine its practicality (Scheme 10).



Scheme 10

1-3 Kinetic Resolution of Racemic Carboxylic Acids Catalyzed by an L-Histidine-derived Minimal Artificial Acylase

The chiral carboxylic acids and esters, such as 2-arylpropionic acids are an important class of non-steroidal anti-inflammatory drug (NSAID), and hydroxy acids and amino acids are also ubiquitous structural motifs in numerous biologically interesting natural and unnatural compounds. A facile enzymatic esterification process for the direct synthesis of chiral carboxylic acids from racemic ones has been developed using lipases as the biocatalyst in organic solvent (Scheme 11).[16]



(R,S)-naproxen

(S)-naproxen ester

44% conversion
99% ee
S = >100

Scheme 11

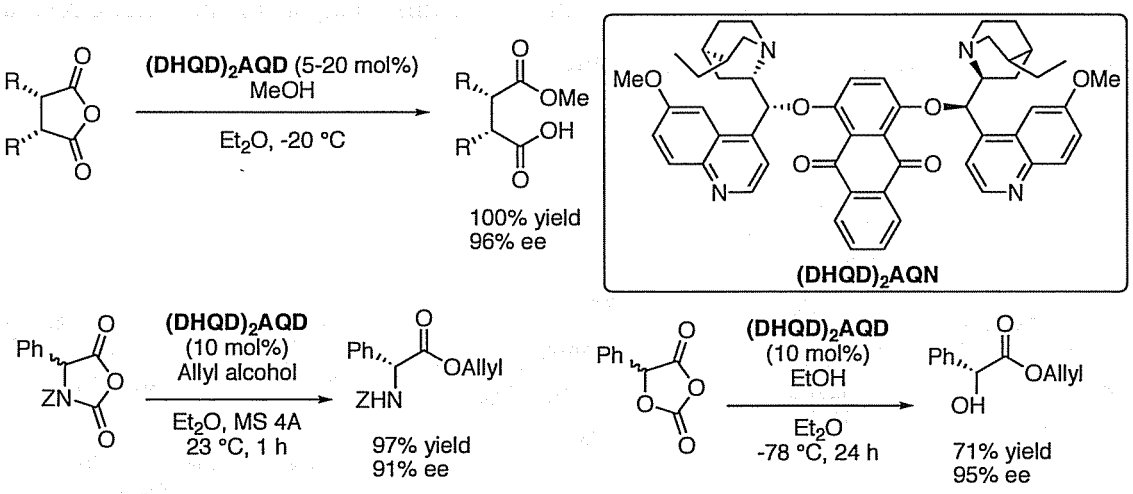
Several of the nonenzymatic asymmetric acylation catalysts developed to date achieve their highest enantioselectivity in the kinetic resolution of racemic alcohols. The development of synthetic catalysts to mimic lipase/esterases with the goal of further expanding the scope of asymmetric acyl transfer catalysis is of both conceptual and practical significance for asymmetric catalysis.[17] Although effective phosphines, diamines, 4-dialkylpyridienes, bicyclic amidines and *N*-alkyl-IMD have been described for the kinetic resolution of racemic alcohols, efforts to develop small molecule-catalyzed kinetic resolution of racemic carbonyl derivatives have met with limited success despite its great potential in asymmetric synthesis.[18] To the best of our knowledge, the direct catalytic kinetic resolution of racemic carboxylic acids has not been achieved previously using nonenzymatic catalysts.

Recently, some successful examples of nonenzymatic catalytic asymmetric acylation of carboxylic acid derivatives, cyclic anhydride,[19-24] urethane-protected α-amino acid *N*-carboxyanhydride (UNCA),[22] 1,3-dioxolane-2,4-diones[22] and *N*-acyl oxazolidinethiones,[25] have been reported using tertiary amines.

In 1985, the cinchona alkaloid-catalyzed alcoholysis of meso anhydrides was first reported by Oda.[19] The reaction shows moderate enantioselectivity when it is mediated by a catalytic amount (0.1 equiv) of natural cinchona alkaloid. Later, Aitken,[20] Bolm[21] and Deng[22] reported the improved highly enantioselective desymmetrization of meso anhydride using cinchona alkaloids. In particular, Deng developed a catalytic asymmetric procedure for the ring-opening anhydrides using a modified cinchona alkaloid [$(DHQD)_2AQN$].[22]

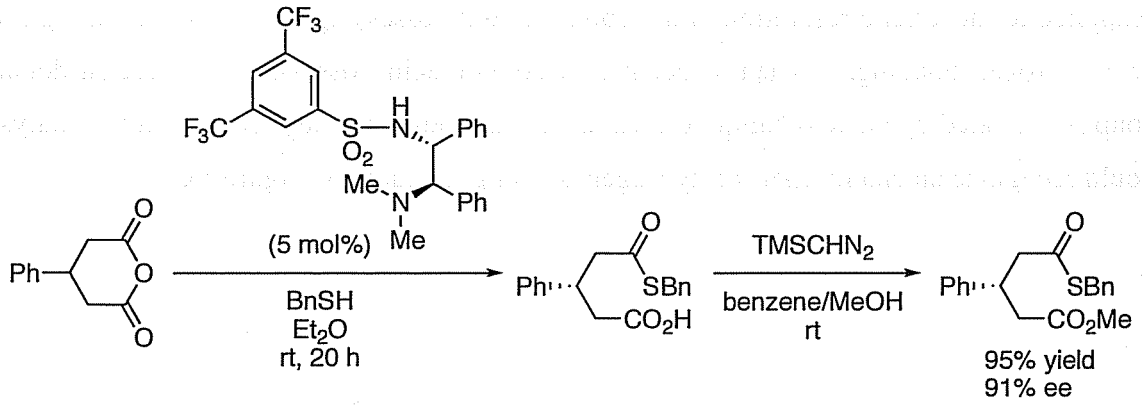
An asymmetric synthesis of α-amino acids through alkaloid-catalyzed dynamic kinetic resolution of urethan-protected α-amino acids *N*-carboxyanhydrides (UNCA)[22] was developed. Highly efficient dynamic kinetic resolution of α-aryl UNCAs at room temperature was realized via the dual-function catalysis of modified cinchona alkaloids. $(DHQD)_2AQN$ catalyzed both racemization and the ring-opening of α-aryl UNCAs.

Similarly, an asymmetric synthesis of α-hydroxy ester through alkaloid-catalyzed dynamic kinetic resolution of 1,3-dioxolane-2,4-diones[22] was recently discussed (Scheme 12).



Scheme 12

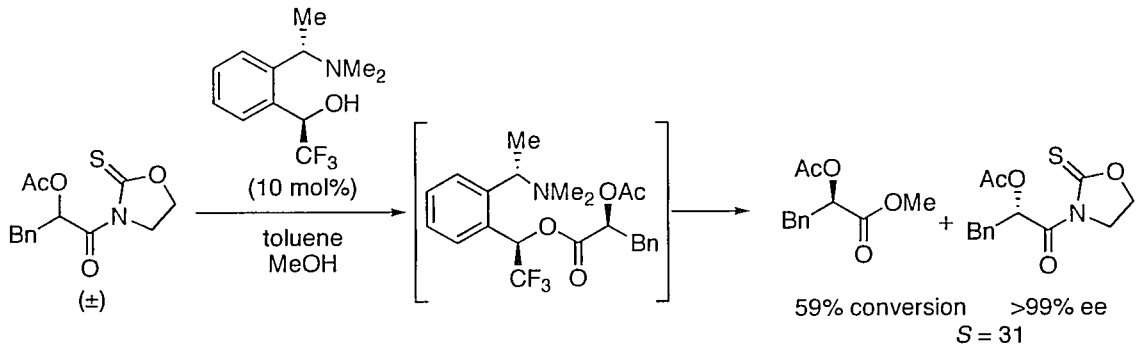
Recently, Nagao developed an enantioselective catalytic thiolysis of prochiral cyclic dicarboxylic anhydrides using a bifunctional chiral sulfonamide.[23] The nucleophilicity of the SH group can be enhanced by an amine base, and the electrophilicity of the carbonyl group may be activated by an acidic proton from the sulfonamide moiety. This is similar to the concept of our catalyst which uses a sulfonamide proton as a hydrogen bond interaction domain (Scheme 13).



Scheme 13

Sammakia recently described a method for the kinetic resolution of (α-acetoxy)oxazolidinethione imides using a chiral *O*-nucleophilic acyl transfer catalyst.[25a] This catalyst likely operates by an *O*-nucleophilic mechanism wherein the

selectivity-determining step involves attack of the substrate with general base catalysis from the proximal nitrogen of the catalyst to form an acyl-catalyst intermediate. Attack by methanol, again with base catalysis by the proximal nitrogen, provides the methyl ester and regenerates the catalyst. He also described the use of this catalyst for the kinetic resolution of protected α-amino acid derivatives (Scheme 14).[25b]



Scheme 14

In the above reports, the catalytic asymmetric reaction of carboxylic acid derivatives is achieved by alcoholysis using a tertiary amine base. There is no successful example of a nucleophilic catalyst for these reactions. Furthermore, to the best of our knowledge, the direct catalytic kinetic resolution of racemic carboxylic acids has not been achieved using nonenzymatic catalysts. We decided to attempt the kinetic resolution of carboxylic acid. Since it is important to use substrates that show hydrogen bonding interaction with our artificial acylase derived from L-histidine, we considered that this could be applied to the kinetic resolution of a carboxylic acid possessing an electron-donating group for a hydrogen bonding. When a racemic carboxylic acid possessing an electron-donating group is activated by an acid halide to form an acylammonium intermediate with a catalyst, it should recognize an enantiomer for hydrogen bonding interaction (Figure 5).

(±)-Carboxylic acid bearing an electron-donationg group for a hydrogen-bonding

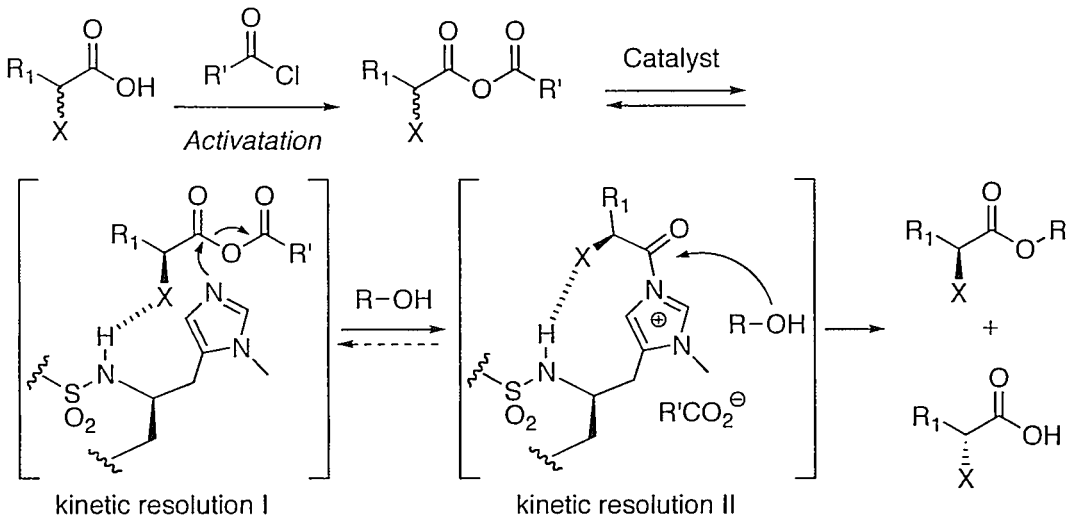


Figure 5.

By choosing *O*-protected hydroxy carboxylic acids as substrates for kinetic resolution, we achieved for the first time kinetic resolution of *O*-protected hydroxy carboxylic acids using a nucleophilic catalyst derived from L-histidine (Figure 15). We describe here for details (Chapter 3).

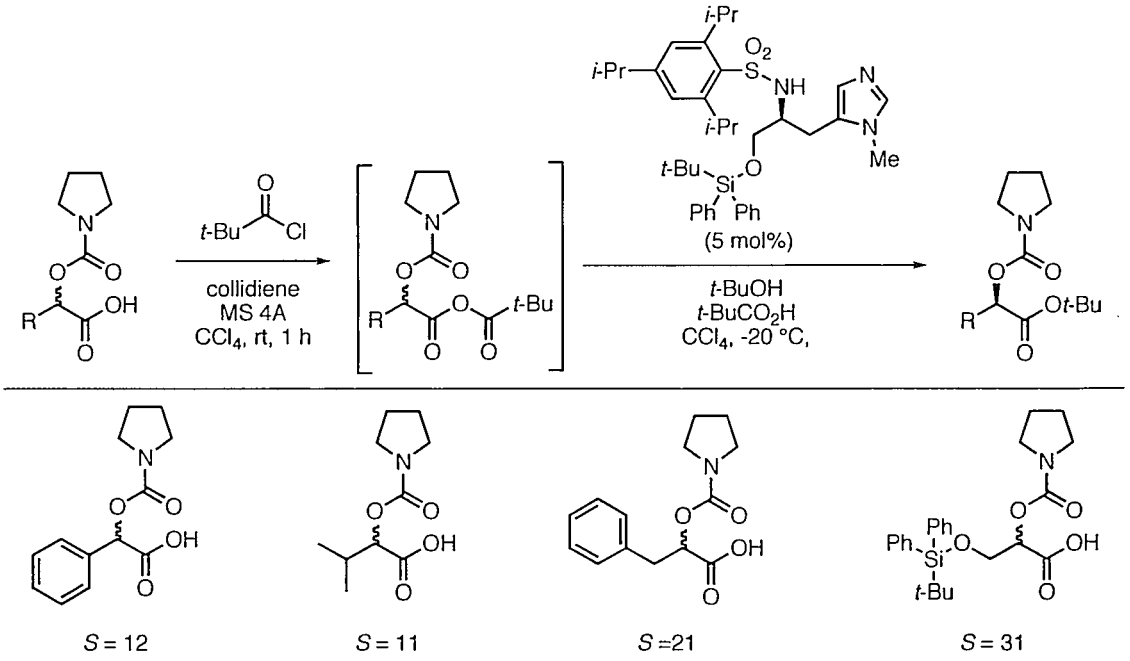


Figure 15

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Chapter 2

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

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. Asymmetic 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.

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 nonenzymatic 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** (Figure 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 to **1c** for the asymmetric induction.

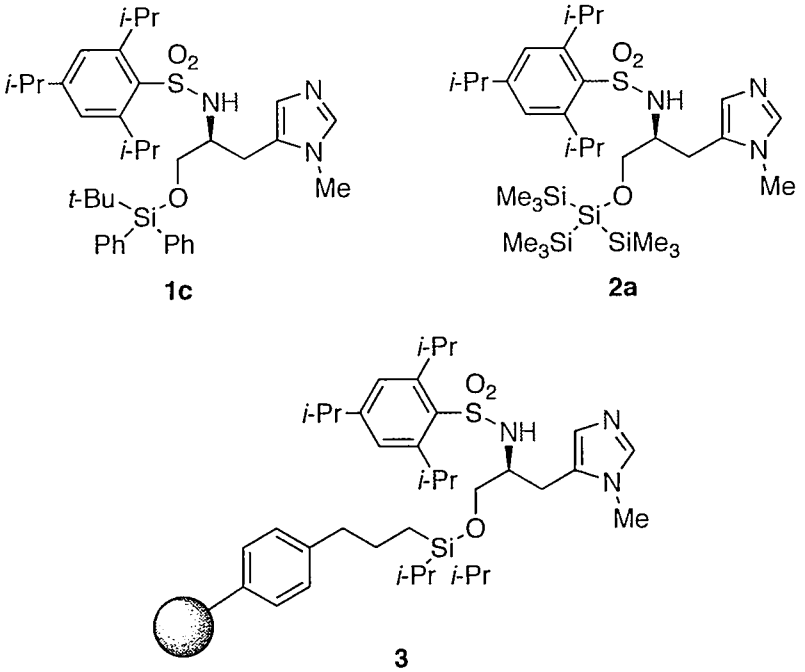
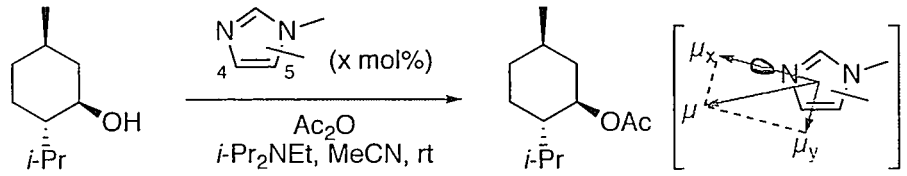


Figure 1. Homo- and heterogeneous artificial acylases **1c**, **2a** and **3**

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 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.

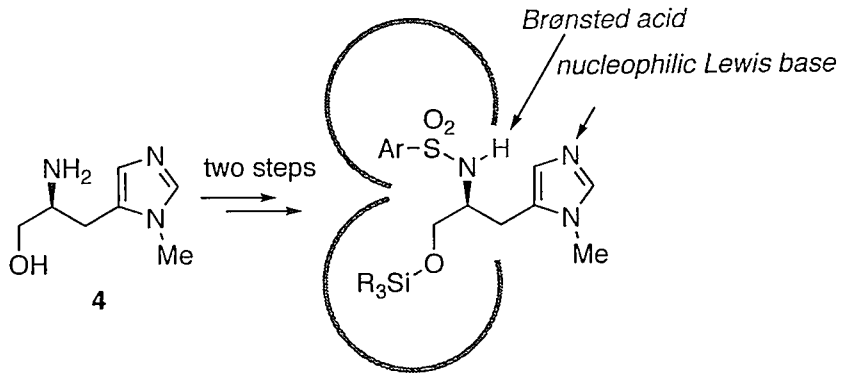
Table 1. Comparison of the catalytic activities of bases for the acetylation of *l*-menthol with acetic anhydride[a]



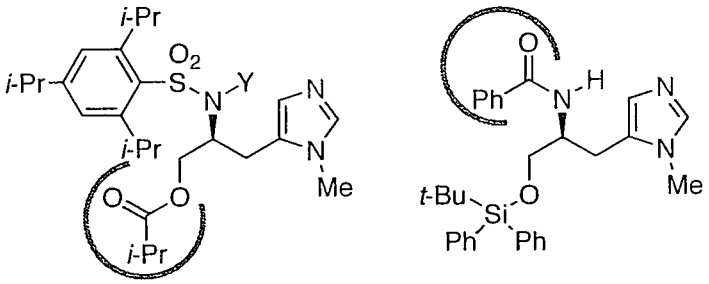
Catalyst	X	Time (h)	Yield (%)	$[\mu]$ (D)[b]	$[\mu_x]$ (D)[b]
DMAP	5	0.5	100	4.84	4.83
1,5-Me_2-IMD	5	0.5	47	4.46	4.26
1,5-Me_2-IMD	5	3.0	100	4.46	4.26
1-Me-IMD	10	3.0	73	4.27	3.93
1,4-Me_2-IMD	10	3.0	29	3.87	3.61
1,2-Me_2-IMD	10	3.0	23	4.11	3.58

[a] Unless otherwise noted, *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.

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**, and **5** and carboxamide **6** were prepared from *N*(π)-methyl-L-histidiol (**4**)[8] in two steps (Scheme 1).



1a: Ar = C_6H_5, R_3Si = *t*-$BuPh_2Si$
1b: Ar = *p*-$(CF_3)C_6H_4$, R_3Si = *t*-$BuPh_2Si$
1c: Ar = 2,4,6-*i*-$Pr_3C_6H_2$, R_3Si = *t*-$BuPh_2Si$
2a: Ar = 2,4,6-*i*-$Pr_3C_6H_2$, R_3Si = $(Me_3Si)_3Si$
2b: Ar = 2,6-$Ph_2C_6H_3$, R_3Si = $(Me_3Si)_3Si$
2c: Ar = 3,5-$(CF_3)_2C_6H_3$, R_3Si = $(Me_3Si)_3Si$
2d: Ar = 2,4,6-$(CF_3)_3C_6H_2$, R_3Si = $(Me_3Si)_3Si$



5a: Y = H
5b: Y = CO*i*-Pr

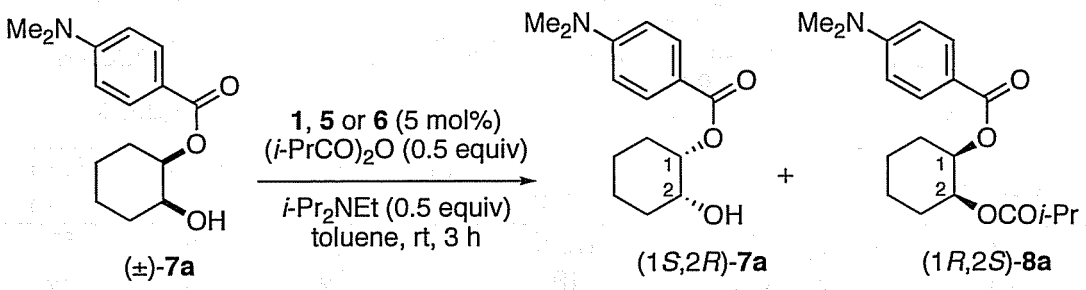
6

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

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 *t*-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 versus Entry 2). In addition, higher asymmetric induction was observed with the use of a more acidic sulfonamide catalyst such as **1b** (Entry 2 versus Entry 3). In contrast, aprotic catalyst **5b** was less active and showed almost no selectivity (S = 1) (Entry 4 versus 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.

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

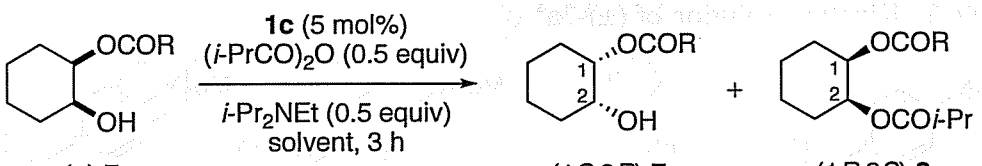


Entry	Catalyst	Conv. (%)[b]	Ee of **7a** (%)[c]	Ee of **8a** (%)[c]	S[d]
1	**6**	36	3	5	1
2	**1a**	51	60	57	7
3	**1b**	42	52	71	10
4	**5a**	48	70	77	16
5	**5b**	30	3	7	1
6	**1c**	47	74	83	24

[a] Unless otherwise noted, (±)-**7a** (1 equiv), (*i*-PrCO)$_2$O (0.5 equiv), *i*-Pr$_2$EtN (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.

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 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).

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



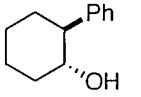
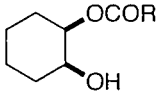
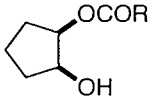
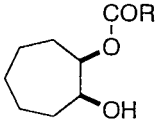
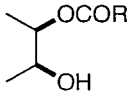
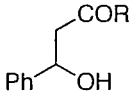
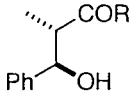
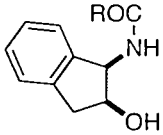
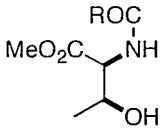
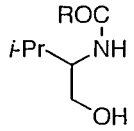
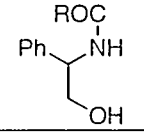
(±)-**7** (1*S*,2*R*)-**7** (1*R*,2*S*)-**8**

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.

To explore the generality and scope of the **1c**-induced kinetic resolution of (±)-secondary alcohols, the acylation of several structurally diverse alcohols with (i-PrCO)$_2$O 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.

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

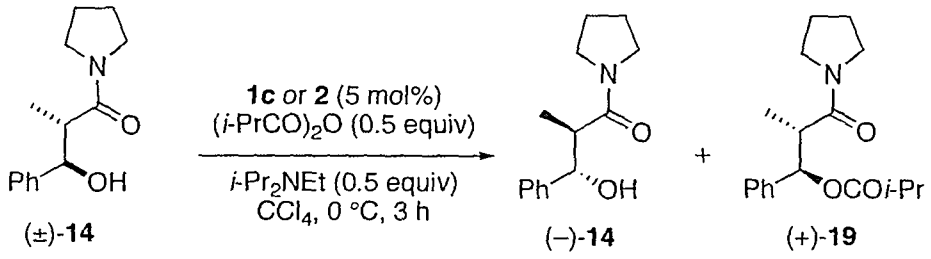
Entry		Alcohol	Conv. (%)[b]	Ee of recov. alcohol (%)[c]	Ee of acyl. product (%)[c]	S[d]
1[e]	**9**		43	10	13	1
2[e]	**7c**		52	97 (1*S*,2*R*)	90 (1*R*,2*S*)	87
3[e]	**10**		49	90	94	93
4[f]	**10**		41	67	97	132
5[e]	**11**		50	93	92	83
6[e]	**12**		47	82	93	68
7[e]	**13**		44	64(*S*)	82(*R*)	19
8[e]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

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 versus Entry 2). However, more

bulky catalyst **2b** was not induced (–)-**14** ($S = 21$) as well as we had expected (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 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 (Figure 2). A transition-state assembly formed from **1c**, (1*R*,2*S*)-**7c**, and $(i\text{-PrCO})_2O$ was proposed based on this X-ray structure (Figure 2). The conformation of the acyl group in the acylammonium salt generated from **1c** and $(i\text{-PrCO})_2O$ 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 (Figure 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.

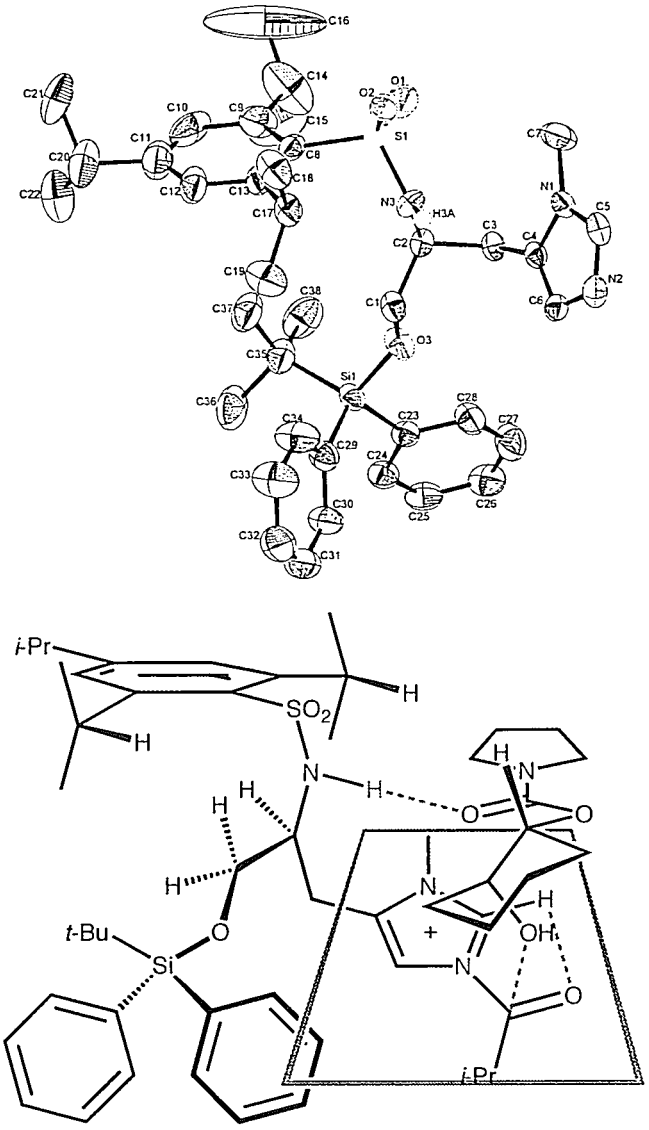


Figure 2. ORTEP plot of **1c** and a proposed transition-state assembly. The crystal structure of **1c** is drawn with 50% probability, and hydrogen atoms except for the SO_2NH moiety are omitted for clarity.

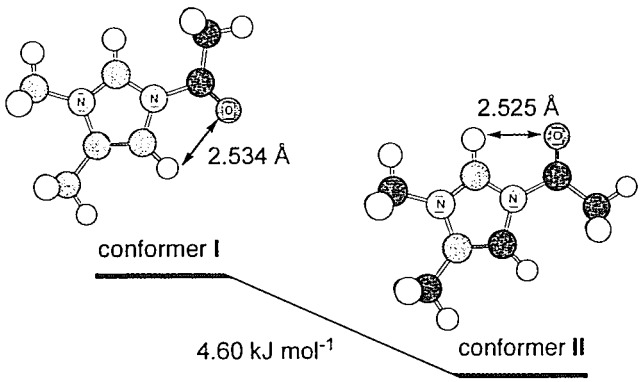
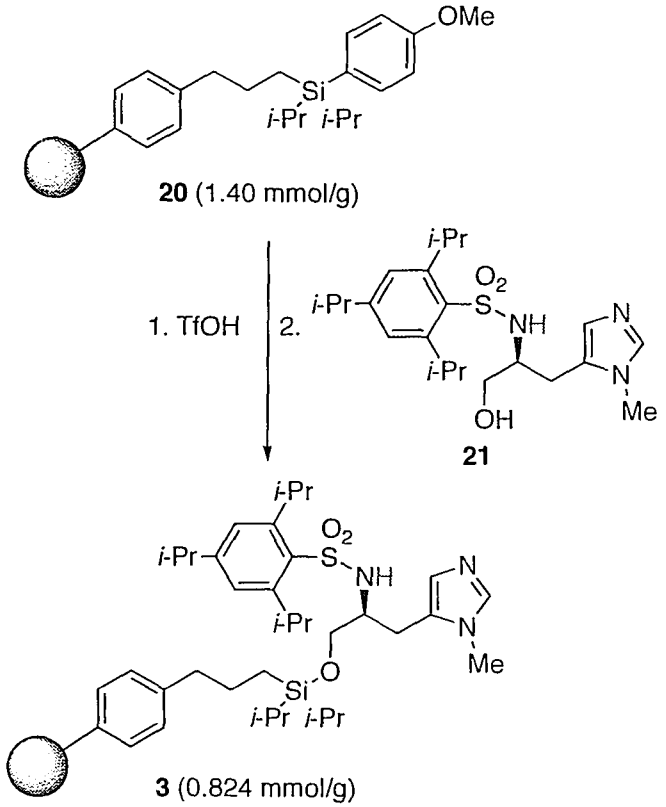


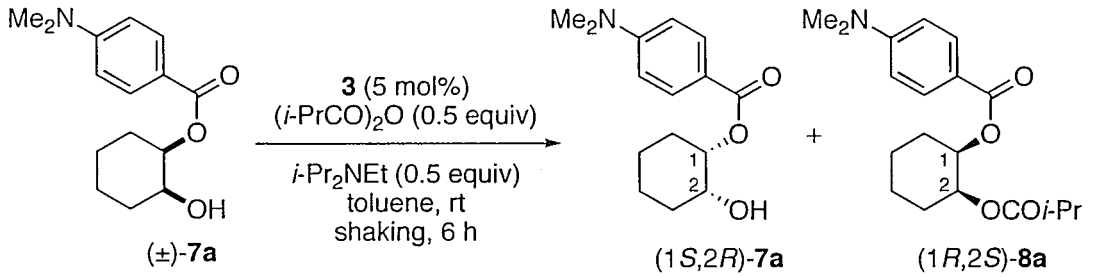
Figure 3. The conformers **I** and **II** of 3-acetyl-1,5-dimethylimidazolium cation.

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] Compound **3** (5 mol %) was reused more than 5 times for the acylation of (±)-**7a** (1 equiv) with $(i\text{-PrCO})_2O$ (0.5 equiv) under shaking at room temperature in toluene for 6 h in the presence of $i\text{-Pr}_2\text{EtN}$ (0.5 equiv) without any loss of activity or selectivity (Table 6).



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.

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.

Experimental Section

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 ppm 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 ppm 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 × 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. x 20 m x 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 tetrahydorofuran (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 analytical-grade and obtained commercially.

General procedure for the preparation of *N*(π)-methyl-*N*(α)-arenesulfonyl-L-hisitidinol. 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, filtrated, 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-hisitidinol in good yield. The corresponding physical and spectroscopic data for compounds follow.

(+)-*N*(π)-Methyl-*N*(α)-benzenesulfonyl-L-hisitidinol. 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}; ^1H 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.

***N*(π)-Methyl-*N*(α)-(4-trifluoromethylbenzenesulfonyl)-L-hisitidinol.** ^1H 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.

(+)-*N*(π)-Methyl-*N*(α)-(2,4,6-triisopropylbenzenesulfonyl)-L-hisitidinol (21). White solid (838 mg, 2.0 mmol, 50% yield); $[\alpha]_D^{20}$ = 20.4 (*c* = 1.0 in $CHCl_3$); 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; N. Found: C, 62.61; H, 8.39.

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)

was 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.

(+)-(*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.

(*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.

(*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 (brs 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.

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 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).

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.

2,6-Diphenylbenzenesulfonyl chloride.[13] Brown solid (924 mg, 2.8 mmol, 70% yield); ^{1}H 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}.

2,4,6-Tris(trifluoromethyl)benzenesulfonyl choride.[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}.

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 t he corresponding arenesulfonyl chloride (0.55 mmol) at 0 °C. After the mixture was stirred f or 24 h at room temperature, the solvent was removed under reduced pressure to give the crud e product. The residue was purified by flash column chromatography on NH silica gel (eluen t: hexane–EtOAc = 1:1) to give **2** in good yield. The corresponding physical and spectroscopi c data for **2** follow.

(*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); TLC (silica gel NH_2 F_{254S}, hexane:EtOAc:MeOH = 1:1:0.07) R_f = 0.40; $[\alpha]_D^{22}$ = –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.

(*S*)-(–)-1-Tris(trimethylsilyl)silyloxy-3-(3'-methyl-3'*H*-imidazol-4'-yl)-2-(2'',6''-diphenyl-

benzenesulfonylamino)propane (2b). White solid (226 mg, 0.33 mmol, 41% yield); TLC (silica gel NH_2 F_{254S}, hexane:EtOAc:MeOH = 1:1:0.07) R_f = 0.38; $[\alpha]_D^{22}$ = –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.

(*S*)-(–)-1-Tris(trimethylsilyl)silyloxy-3-(3'-methyl-3'*H*-imidazol-4'-yl)-2-[3'',5''-bis-(trifluorometyl)benzenesulfonylamino]propane (2c). White solid (77 mg, 0.11 mmol, 69% yield); TLC (silica gel NH_2 F_{254S}, hexane:EtOAc:MeOH = 1:1:0.07) R_f = 0.30; $[\alpha]_D^{21}$ = –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.

(*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); TLC (silica gel NH_2 F_{254S}, hexane:EtOAc:MeOH = 1:1:0.07) R_f = 0.30; $[\alpha]_D^{22}$ = –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.

Preparation of (*S*)-3-(3'-methyl-3'*H*-imidazol-4'-yl)-2-(2'',4'',6''-triisopropylbenzene-

sufonylamino)propyl isobutyrate (5a) and (*S*)-2-[*N*-isobutyryl(2',4',6'-triisopropylbenze-nesulfonyl)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) was 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.

(*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 in $CHCl_3$); ^{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: 63.55; H, 8.34.

(*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 in $CHCl_3$); ^{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.

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 reside 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 in $CHCl_3$); IR (neat) 3500–3300 (br), 2923, 2852, 1638, 1542 cm^{-1}; ^1H 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.

Preparation of (*S*)-(+)-1-*tert*-butyldiphenylsilyloxy-3-(3'-methyl-3'*H*-imidazol-4'-yl)-2-benzoylaminopropane (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, $CHCl_3$); ^1H 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, 10 H), 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.

General procedure for the preparation of 1-(*N*-pyrrolidine-1'-carbonyloxy)-2-alco-hols (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 Section 4.10.5, 4.10.7, 4.10.9, and 4.10.11, respectively.

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.

(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]

(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 literatre.[4c]

(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**.

(1*R*,2*S*)-*cis*-1-Dimethylcarbamoyloxy-2-cyclohexyl isobutyrate (8b) (Entry 6, Table 3). HPLC (Daicel Chiralpack 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**.

(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 Chiralpack 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**.

(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 Chiralpack 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**.

(–)-*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.

(–)-*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.

(–)-*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.

(–)-*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}; ^1H 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.

(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}; ^1H 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.

(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}; ^1H 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, 65. 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.

(*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 in $CHCl_3$) 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}; ^1H 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.

(*R*)-(+)-*N*-(3-Isobutyryloxy-3-phenylpropionyl)pyrrolidine. TLC (hexane–EtOAc = 1:2) R_f = 0.35; $[\alpha]_D^{20}$ = 29.5 (c = 1.0 in $CHCl_3$); 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, $CDCl_3$) δ1.15 (t, J = 7.1 Hz, 6 H), 1.76–1.95 (m, 4H), 2.56 (septet, J = 7.1 Hz, 1 H), 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.

(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 in $CHCl_3$) 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.

(+)-*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 in $CHCl_3$) 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.

(–)-*cis*-*N*-(2'-Hydroxyindan-1'-yl)pyrrolidine-1-carboxamide (15) (Entry 9, Table 5).[4e,4g] TLC (EtOAc) R_f = 0.40; $[\alpha]_D^{20}$ = –36.6 (c = 1.0, $CHCl_3$) for 67% ee; HPLC (Daicel Chiralpack 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.

(+)-*cis*-*N*-(2'-Isobutyryloxyindan-1'-yl)pyrrolidine-1-carboxamide (Entry 9, Table 5).[4e,4g] TLC (hexane–EtOAc = 1:2) R_f = 0.34; $[\alpha]_D^{20}$ = 70.0 (c = 1.0, $CHCl_3$) for 93% ee; HPLC (Daicel Chiralpack 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.

(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 Chiralpack 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.

(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 Chiralpack 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}; ^{1}H 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.

(*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 Chiralpack 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}; ^{1}H 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.

(*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 Chiralpack 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. Cald 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.

(–)-*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 Chiralpack 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.

(–)-2-Phenyl-2-(pyrrolidine-1-carboxamido)ethyl isobutyrate (Entry 12, Table 4). $[\alpha]_D^{20}$ = –1.9 (*c* = 3.7, $CHCl_3$) for 74% ee; HPLC (Daicel Chiralpack 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.

Procedure for the preparation of polystyrene-bound catalyst 3. (4-Methoxyphenyl)diisopropylsilylpropyl polystyrene (**20**, 1.40 mmol of Si per gram, 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 atomosphere 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 Å~ 3 mL Å~ 30 min), THF/IPA (3:1, 2 Å~ 3 mL Å~ 30 min), THF/H_2O (3:1, 2 Å~ 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.

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 (3 mL × 2). Thus, **3** was reused more than 5 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]

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.

X-Ray diffraction analysis of 1c

X-ray crystallographic analysis was performed with a Bruker SMART APEX diffractometer (graphite monochromator, MoKα 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: 114–116 °C. Crystallographic data have been deposited with Cambridge Crystallographic Data Centre: Deposition number CCDC 293029. 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. 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 x 0.20 x 0.20 mm^3
theta range for data collection	1.51 to 29.18°
reflections collected	58323
Independent reflections	20367
R_{int}	0.0378
refinement based on	F^2
no. of data	20367
no. of parameters	849
no. of restraints	0
GOF	1.079
R(F) for $I > 2\sigma(I)$	0.0627
wR2(F^2) for all data	0.1716
$\Delta\rho_{min}$	–0.340 $eÅ^{-3}$
$\Delta\rho_{max}$	0.918 $eÅ^{-3}$

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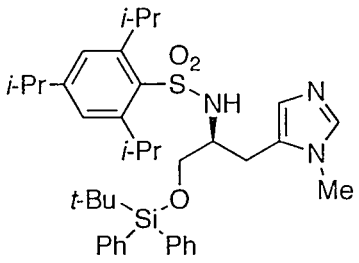
Chapter 3

Kinetic Resolution of Racemic Carboxylic Acids Catalyzed by an L-Histidine-derived Minimal Artificial Acylase

Abstract: The kinetic resolution of racemic carboxylic acids proceeds enantioselectively when catalyzed by a chiral nucleophilic acylase derived from L-histidine. This catalyst could recognize the substrate by hydrogen bonding interaction. The kinetic resolution of *O*-protected hydroxy carboxylic acids induced by a catalyst showed an $S(k_{\text{fast-reacting enantiomer}}/k_{\text{slow-reacting enantiomer}})$ value of up to 31.

Chiral carboxylic acids and esters, such as 2-arylpropionic acids are an important class of non-steroidal anti-inflammatory drugs, hydroxy acids and amino acids are also ubiquitous structural motifs in numerous biologically interesting natural and artificial compounds. A facile enzymatic esterification process for the direct synthesis of chiral carboxylic acids from racemic ones has been developed using lipases as a biocatalyst in organic solvent.[1] Chiral nucleophilic catalysts,[2] which have been developed over the past decade, have been shown to be highly efficient catalysts for the kinetic resolution of racemic alcohols with achiral anhydrides. The development of synthetic catalysts to mimic lipase/esterases with the goal of further expanding the scope of asymmetric acyl transfer catalysis is of both conceptual and practical significance for asymmetric catalysis.[3] In contrast, there are limited examples of the small molecule-catalyzed kinetic resolution of racemic carbonyl derivatives despite its great potential in asymmetric synthesis.[4] Recently, some successful examples of the nonenzymatic catalytic asymmetric acylation of activated carboxylic acid derivatives such as, cyclic anhydride,[5,6] urethane-protected α-amino acid *N*-carboxyanhydride,[5f] 1,3-dioxolane-2,4-diones[5f] and *N*-acyl oxazolidinethiones[7], have been reported using tertiary amines. These have been achieved by alcoholysis of activated carboxylic acid derivatives with tertiary amines as general bases. However, these procedures require the synthesis of activated carboxylic acid derivatives from the carboxylic acid, which requires at least two steps for the kinetic resolution of chiral carboxylic acids. Furthermore, to the best of our knowledge, the direct catalytic kinetic resolution of racemic carboxylic acids has not been achieved previously using nonenzymatic nucleophilic catalysts. In this communication, we report the first successful application of this process.

We recently described the rational design of an L-histidine-derived minimal artificial acylase **1**[8] by introducing a sulfonamidyl group in place of a long peptide chain based on the notion that hydrogen bonding between a sulfonamidyl group and a substrate is much stronger than the corresponding interaction between a carboxamidyl group and a substrate. This catalyst **1** contains a nucleophilic *N*-methylimidazole moiety and only one chiral carbon center that originates from natural L-histidine. Therefore, we sought to attempt the kinetic resolution of carboxylic acid possessing an electron-donating group for a hydrogen bonding. Since we considered that is was feasible to recognize one enantiomer of racemic carboxylic acids, provided that an acylammonium intermediate, which formed between a catalyst with the carboxylic acid activated by an acid halide, could interact between a catalyst and a substrate by a hydrogen bonding, we chose *O*-protected hydroxy carboxylic acids **2** as a substrate for the kinetic resolution (Scheme 1).



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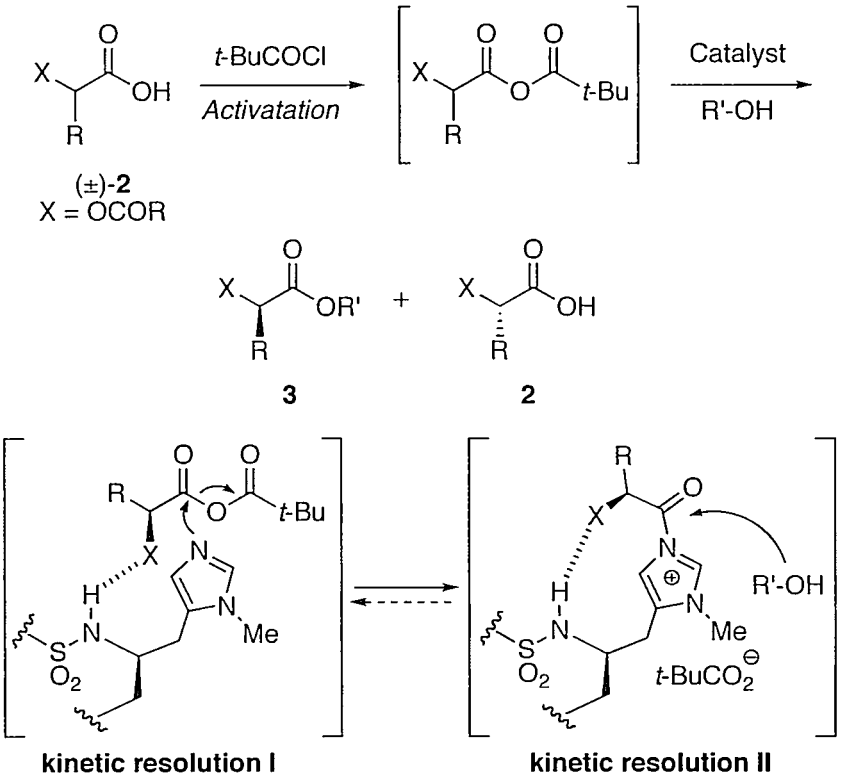
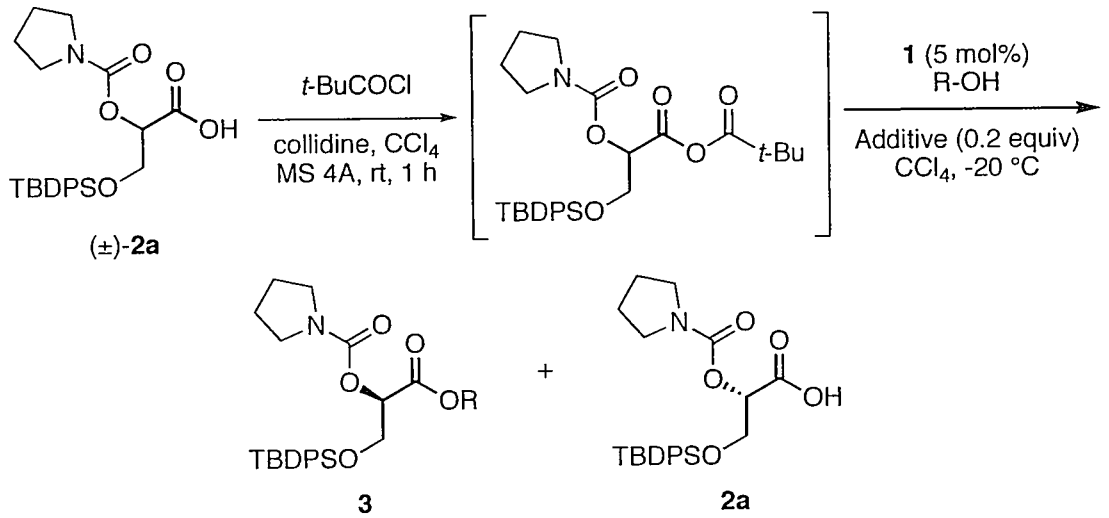
Scheme 1. Kinetic resolution of racemic carboxylic acids



First, the substrate **2a**, which was derived from (±)-glyceric acid, was investigated for kinetic resolution in the presence of **1**. Reactions were carried out as follows: **2a** was activated by *t*-BuCOCl for 1 h at room temperature, and 0.5~0.7 equiv of alcohol and 5 mol% of **1** relative to **2a** were then added at -20 °C. As shown in Table 1, we were disappointed by the poor selectivity with BnOH (Entry 1) and the low reactivity with *i*-PrOH (Entry 2). The reaction proceeded smoothly with *t*-$BuCO_2H$ as an additive. *t*-$BuCO_2H$ would probably serve as a Brønsted acid to activate mix anhydride. However, the selectivity was still moderate (Entry 3). Surprisingly, *t*-BuOH gave high enantioselectivity (S = $k_{\text{fast-reacting enantiomer}}/k_{\text{slow-reacting enantiomer}}$ = 31) (Entry 5). This dramatic improvement in selectivity upon switching from a secondary alcohol to a tertiary alcohol suggested that equilibrium between

mix anhydride and the acylammonium intermediate may be important for attaining a high level of kinetic resolution.[9] Thus, the first nucleophilic attack of the catalyst gave low selectivity (Scheme 1. kinetic resolution I). However, in equilibrium, in which one diastereomer of the acylammonium intermediate is stabilized by hydrogen bonding interaction, the second nucleophilic attack of the alcohol achieved high selectivity (Scheme 1. kinetic resolution II). Therefore, higher asymmetric induction was observed with the dropwise addition of *i*-PrOH (Entry 3 versus Entry 4).

Table 1. Kinetic resolution of **2a** induced by **1**[a]

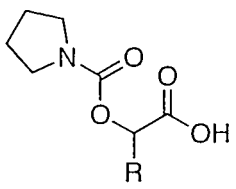


Entry	R-OH (equiv)	Additive	Time (h)	Yield of **3a** (%)	Ee of **3a** (%)[b]	S[c]
1	BnOH (0.5)	—	6	31	6	1
2	*i*-PrOH (0.7)	—		trace		
3	*i*-PrOH (0.7)	*t*-$BuCO_2H$	19	69	28	3
4[d]	*i*-PrOH (0.5)	*t*-$BuCO_2H$	25	50	69	11
5	*t*-BuOH (0.6)	*t*-$BuCO_2H$	52	39	89	31

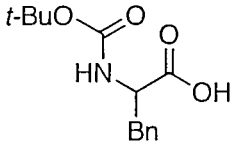
[a] (±)-**2a** (1 equiv), *t*-BuCOCl (1.2 equiv), collidine (2 equiv), **1** (0.5 equiv), R-OH, additive (0.2 equiv) and CCl_4 (1.5 ml) were used. [b] HPLC analysis. [c] Selectivity factor = $S(k_{\text{fast-reacting enantiomer}}/k_{\text{slow-reacting enantiomer}})$, see Ref. 10 [d] a solution of *i*-PrOH in CCl_4 (1 ml) was added dropwise for 24 h.

To explore the generality and scope of the **1**-induced kinetic resolution of racemic carboxylic acids, the acylation of several structurally diverse carboxylic acids was examined (Table 2). The acylation of *O*-protected hydroxy acids **2a-d** gave high selectivity (S = 11~31). *N*-Protected amino acid **4** and amide-acid **5** were also suitable substrates.

Table 2. Kinetic resolution of racemic carboxylic acids **2**, **4**, **5** induced by **1**[a]



2a: R = TBDPSOCH$_2$
2b: R = Ph
2c: R = Bn
2d: R = *i*-Pr



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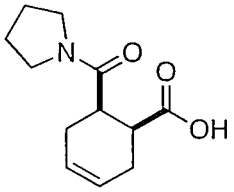

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Entry	Substrate	R-OH (equiv)	Time (h)	Yield of Ester (%)	Ee of Ester (%)[b]	S[c]
1	**2a**	*t*-BuOH	52	39	89	31
2	**2b**	*t*-BuOH	48	34	79	12
3	**2c**	*t*-BuOH	48	34	86	21
4	**2d**	*t*-BuOH	48	10	79	11
5	**4**	*t*-BuOH	48	32	68	7
6[d]	**5**	*i*-PrOH	25	42	76	13

[a] substrate (1 equiv), *t*-BuCOCl (1.2 equiv), collidine (2 equiv), 1 (0.5 equiv), R-OH, *t*-BuCO$_2$H (0.2 equiv) and CCl_4 (1.5 ml) were used. [b] HPLC analysis. [c] Selectivity factor = $S(k_{\text{fast-reacting enantiomer}}/k_{\text{slow-reacting enantiomer}})$, see Ref. 10 [d] a solution of *i*-PrOH in CCl_4 (1 ml) was added dropwise for 24 h.

A transition-state assembly formed from **1** and *O*-protected hydroxy acid was proposed (Figure 1). The conformation of the acyl group in the acylammonium salt generated from **1** and mix anhydride 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 and the carbamoyl oxygen of acylammonium salt preferentially stabilizes itself and promotes acylation of *t*-BuOH. On the other hand, another diastereomer of acylammonium salt is not stabilized for steric effect.

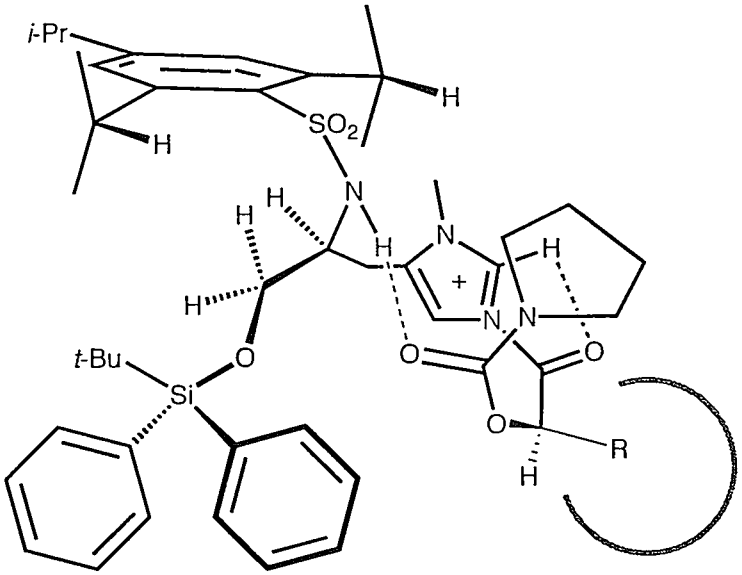


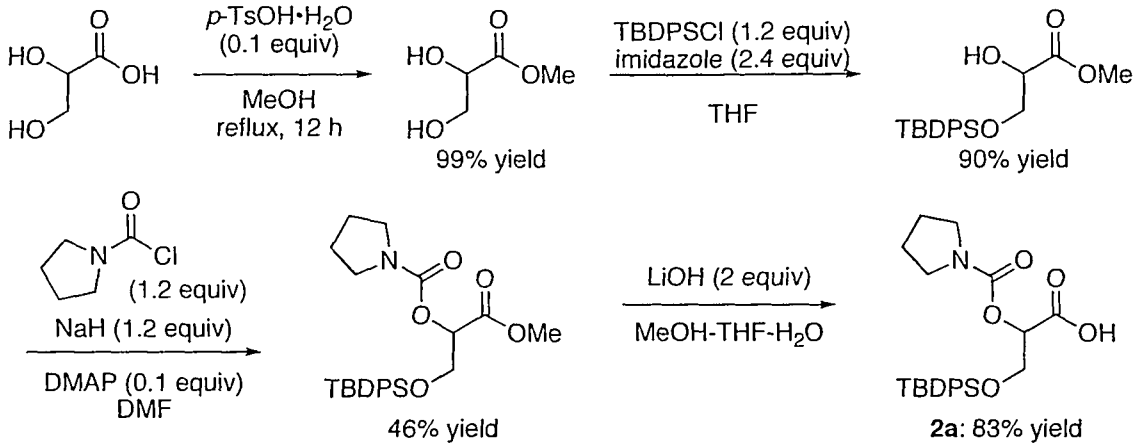
Figure 1. Proposed transition-state assembly.

In summary, we have described the first method for the synthesis of chiral carboxylic acid via the kinetic resolution of racemic carboxylic acids using histidine-derived nucleophilic catalyst **1**. This catalyst could recognize the substrate by hydrogen bonding interaction. Further investigations of histidine-derived catalysts are underway in our laboratory.

Experimental Section

General. Infrared (IR) spectra were recorded on a JASCO FT/IR 460 plus spectrometer. 1H NMR spectra were measured on a Varian Gemini-2000 spectrometer (300 MHz) at ambient temperature. Data were recorded as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (s = singlet; d = doublet; t = triplet; m = multiplet), coupling constant (Hz), integration, and assignment. 13C NMR spectra were measured on Varian Gemini-2000 (75 MHz) spectrometer. Chemical shifts were recorded in ppm 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 x 25 cm), AD-H (4.6 mm x 25 cm), or Daicel CHIRALPAK AS-H (4.6 mm x 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. x 20 m x 0.125 μ m). 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 GF254 0.25 mm or silica gel NH2 F254S 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 tetrahydorofuran (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 analytical-grade and obtained commercially.

Preparation of (±)-3-(*tert*-butyldiphenylsilyloxy)-2-(pyrrolidine-1-carbonyloxy)-propanoic acid (2a).



Preparation of (±)-methyl 2,3-dihydroxypropanoate.

To the stirred solution of glyceric acid (65% in water) (4.08 g, 25 mmol) and *p*-TsOH•H_2O (95 mg, 1 mmol) in MeOH (10 ml) was reflux for 12 h. The reaction solution was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (eluent: EtOAc-MeOH = 50:1~10:1) to give 3.00 g (99% yield) of product as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.16-2.25 (m, 1H), 3.15-3.21 (m, 1H), 3.84 (s, 1H), 3.85 (ddd, J = 3.6, 5.4, 11.7 Hz, 1H), 3.92 (ddd, J = 3.3, 5.4, 11.7 Hz, 1H) 4.29 (q, J = 4.2 Hz, 1H).

Preparation of (±)-methyl 3-(*tert*-butyldiphenylsilyloxy)-2-hydroxypropanoate.

To the solution of (±)-methyl 2,3-dihydroxypropanoate (2.88 g, 24 mmol) and imidazole (3.59 g, 52.8 mmol) in THF (80 ml) was added dropwise TBDPSCl (6.87 ml, 26.4 mmol) at 0 °C. The white solid precipitated. The reaction mixture was diluted with Et_2O, washed with brine and water. The organic layer was dried over $MgSO_4$ and evaporated. The residue was purified by flash column chromatography on silica gel (eluent: Hexane-EtOAc = 10:1~2:1) to give 7.73 g (90% yield) of product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (s, 9H), 3.16 (d, J = 7.8 Hz, 1H), 3.80 (s, 3H), 3.92 (dd, J = 3.0, 10.2 Hz, 1H), 3.98 (dd, J = 3.0, 10.5 Hz, 1H), 4.25 (dt, J = 3.0, 5.1 Hz, 1H), 7.35-7.48 (m, 6H), 7.60-7.68 (m, 4H).

Preparation of (±)-3-(*tert*-butyldiphenylsilyloxy)-1-methoxy-1-oxopropan-2-yl pyrrolidine-1-carboxylate.

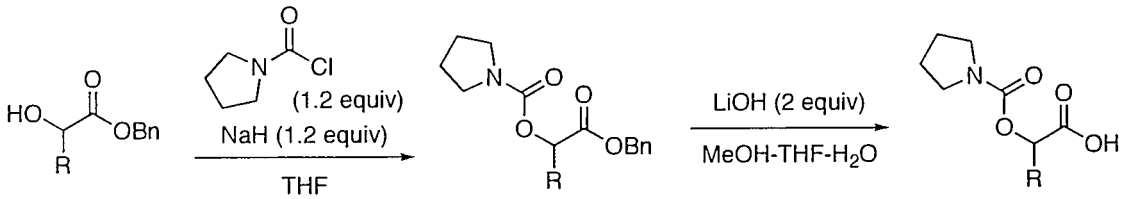
To the solution of (±)-methyl 3-(*tert*-butyldiphenylsilyloxy)-2-hydroxypropanoate (8.01 g, 22 mmol), DMAP (244 mg, 2 mmol) and 1-pyrrolidinecarbonyl chloride (2.96 ml, 26.8

mmol) in DMF (50 ml) was added NaH (60% in oil, 1.07 g, 26.8 mmol) slowly at 0 °C. The reaction mixture was stirred at room temperature for overnight, cooled to 0 °C, poured onto 1 M HCl aqueous solution and extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by flash column chromatography on silica gel (eluent: Hexane-EtOAc = 10:1~1:1) to give 4.63 g (46% yield) of product. ^1H NMR (300 MHz, $CDCl_3$) δ 1.03 (s, 9H), 1.80-1.98 (s, 4H) 3.30-3.48 (m, 3H), 3.48-3.59 (m, 1H), 3.77 (s, 3H) 3.98 (dd, *J* = 3.0, 11.1 Hz, 1H), 4,11 (dd, *J* = 5.1, 11.1 Hz, 1H), 5.19 (dd, *J* = 3.0, 5.1 Hz, 1H), 7.34-7.47 (m, 6H), 7.62-7.71 (m, 4H).

Preparation of (±)-3-(*tert*-butyldiphenylsilyloxy)-2-(pyrrolidine-1-carbonyloxy)-propanoic acid (2a).

To the solution of (±)-3-(*tert*-butyldiphenylsilyloxy)-1-methoxy-1-oxopropan-2-yl pyrrolidine-1-carboxylate (2.53 g, 5.6 mmol) in THF (5 ml) and MeOH (5 ml) was added slowly the solution of LiOH (470 mg, 11 mmol) in H_2O (5 ml) at 0 °C. After 3 h, the reaction mixture was diluted with Et_2O and brine, washed with Et_2O, acidified by 1 M HCl aqueous solution, extracted with Et_2O. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and evaporated. The residue was recrystallized from $CHCl_3$-hexane to give 2.05 g (83% yield) of product as white solid: ^1H NMR (300 MHz, $CDCl_3$) δ 1.03 (s, 9H), 1.79-1.97 (m, 4H), 3.38-3.56 (m, 4H), 4.01 (dd, *J* = 3.0, 11.1 Hz, 1H), 4.13 (dd, *J* = 5.1, 11.1 Hz, 1H), 5.22 (dd, J = 3.0, 5.4 Hz, 1H), 7.32-7.46 (m, 6H), 7.62-7.72 (m, 4H), 8.58-9.02 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.4, 25.1, 25.9, 26.7(3C), 46.1, 46.5, 63.6, 74.0, 127.9 (4C), 129.9 (4C), 133.1 (2C), 135.7, 135.7, 154.4, 173.3; IR (KBr) 3650-3300 (br), 2959, 2931, 1660, 1447, 1209, 1114, 707 cm^{-1}; HRMS(FAB) calcd for $C_{24}H_{32}NO_5Si_4$ $[(M+H)^+]$ 442.2050, found 442.2047.

General preparation of (±)-2-(pyrrolidine-1-carbonyloxy)carboxylic acid (2b-c).



R = Ph: 86% yield
R = Bn: 94% yield
R = *i*-Pr: 58% yield

R = Ph: 94% yield
R = Bn: 95% yield
R = *i*-Pr: 30% yield

To the solution of (±)-benzyl 2-hydroxy-carboxylate (5 mmol) and 1-pyrrolidinecarbonyl

chloride (6 mmol) in THF was added NaH (6 mmol) carefully at 0 °C. The reaction mixture was stirred at room temperature for 12 h, cooled to 0 °C, poured onto 1 M HCl aqueous solution and extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by flash column chromatography on silica gel (eluent: Hexane-EtOAc = 40:1~2:1) to give (±)-benzyl 2-(pyrrolidine-1-carbonyloxy)carboxylate in good yield.

2-(benzyloxy)-2-oxo-1-phenylethyl pyrrolidine-1-carboxylate. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.78-1.98 (m, 4H), 3.32-3.52 (m, 3H), 3.52-3.65 (m, 1H), 5.16 (s, 2H), 5.98 (s, 1H), 7.17-7.25 (m, 2H) 7.25-7.42 (m, 6H), 7.44-7.52 (m, 2H).

1-(benzyloxy)-1-oxo-3-phenylpropan-2-yl pyrrolidine-1-carboxylate. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.70-1.99 (m, 4H), 3.09 (dd. J = 8.3, 14.1 Hz, 1H), 3.17 (dd, J = 5.0, 14.1 Hz, 1H), 3.18, 3.56 (m, 4H), 5.11 (d, J = 12.5 Hz, 1H), 5.19 (t, J = 3.3 Hz, 1H), 4.21 (d, J = 12.5 Hz, 1H), 7.15-7.45 (m, 10H).

1-(benzyloxy)-3-methyl-1-oxobutan-2-yl pyrrolidine-1-carboxylate. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (d, J = 5.1 Hz, 3H), 1.00 (d, J = 5.1 Hz, 1H), 1.78-1.96 (m, 4H), 2.24 (dsept, J = 4.5, 6.9 Hz, 1H), 3.30- 3.58 (m, 4H), 4.86 (d, J = 4.5 Hz, 2H), 4.13 (d, J = 12.3 Hz, 1H), 5.24 (d, J = 12.3 Hz, 1H), 7.28-7.44 (m, 5H).

To the solution of (±)-benzyl 2-(pyrrolidine-1-carbonyloxy)carboxylate (4.3 mmol) in THF (5 ml) and MeOH (5 ml) was added slowly the solution of LiOH (10 mmol) in H_2O (5 ml) at 0 °C. After 3 h, the reaction mixture was diluted with Et_2O and brine, washed with Et_2O, acidified by 1 M HCl aqueous solution, extracted with Et_2O. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and evaporated. The residue was recrystallized from $CHCl_3$-hexane or purified by flash column chromatography on silica gel to give (±)-2-(pyrrolidine-1-carbonyloxy)carboxylic acid (2b-c). The corresponding physical and spectroscopic data for the carboxylic acid follow.

(±)-2-Phenyl-2-(pyrrolidine-1-carbonyloxy)acetic acid (2b). White solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.78-2.00 (m, 4H), 3.33-3.50 (m, 3H), 3.52-3.64 (m, 1H), 5.92 (s, 1H), 7.34-7.42 (m, 3H), 7.45-7.55 (m, 2H), 8.64-9.04 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.0, 25.8, 46.1, 46.5, 74.7, 127.7 (2C), 128.8 (2C), 129.2, 134.2, 154.2, 174.0; IR (KBr)

3650-3350 (br), 2964, 2896, 1757, 1661, 1437, 1207, 1168, 1135, 1114, 766, 727 cm^{-1}; HRMS(FAB) calcd for $C_{13}H_{16}NO_4$ [(M+H)$^+$] 250.1079, found 250.1080.

(±)-3-Phenyl-2-(pyrrolidine-1-carbonyloxy)propanoic acid (2c). White solid: ^1H NMR (300 MHz, $CDCl_3$) δ 1.75-1.93 (m, 4H), 3.11 (dd, *J* = 9.0, 14.1 Hz, 1H), 3.20-3.50 (m, 4H), 3.25 (dd, J = 3.5, 14.1 Hz, 1H), 5.15 (dd, *J* = 3.9, 9.3 Hz, 1H), 7.20-7.34 (m, 5H), 9.26-9.60 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.0, 25.7, 37.5, 46.0, 46.4, 73.7, 127.0, 128.5 (2C), 129.6 (2C), 136.4, 154.5, 174.7; IR (KBr) 3650-3350 (br), 2937, 2884, 1762, 1656, 1441, 1253, 1216, 1195, 1129, 760, 700 cm^{-1}; HRMS(FAB) calcd for $C_{14}H_{18}NO_4$ [(M+H)$^+$] 264.1236, found 264.1237.

(±)-3-Methyl-2-(pyrrolidine-1-carbonyloxy)butanoic acid (2d). Colorless liquid: ^1H NMR (300 MHz, $CDCl_3$) δ 1.01 (d, *J* = 6.9 Hz, 3H), 1.05 (d, *J* = 6.9 Hz, 3H), 2.27 (d, septet, *J* = 3.9, 6.9 Hz, 1H), 3.33-3.57 (m, 4H), 4.83 (4d, *J* = 4.2 Hz, 1H), 6.70-7.43 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.3, 19.2, 25.1, 25.8, 30.3, 45.9, 46.4, 77.1, 154.7, 175.0; IR (neat) 2969, 2879, 1714, 1441, 1335, 1182, 1135, 1111, 768 cm^{-1}; HRMS(FAB) calcd for $C_{10}H_{18}NO_4$ [(M+H)$^+$] 216.1237, found 216.1235.

Preparation of cis-6-(pyrrolidine-1-carbonyl)cyclohex-3-enecarboxylic acid (5).

To the solution of cis-Δ^4-tetrahydrophthalic anhydride (1.52 g, 10 mmol) in CH2Cl2 (100 ml) was added pyrrolidine (1.67 ml, 20 mmol) at room temperature. After 5 h, the solution was concentrated in vacuo. The residue was diluted with Et_20, washed with 1 M HCl aqueous solution, extracted with Et2O. The combined organic layer was dried overt Na_2SO_4, filtered, and evaporated. The residue was recrystallized from $CHCl_3$-hexane to give 1.40 mg (90% yield) of product as brown solid: ^1H NMR (300 MHz, $CDCl_3$) δ 1.99-2.48 (m, 7H), 2.80-2.92 (m, 1H), 3.08-3.16 (m, 2H), 3.45-3.66 (m, 4H), 5.64-5.73 (m, 1H), 5.76-5.84 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.5, 26.0, 26.2, 29.4, 40.6, 41.2, 47.0, 47.5, 124.7, 127.3, 173.0, 175.4; IR (neat) 3600-3300 (br), 3025, 2981, 2888, 2333, 2256, 1935, 1713, 1563, 1514, 1457, 1377,1339, 1287, 1256, 1217, 1054, 764 cm^{-1}; HRMS(FAB) calcd for $C_{12}H_{18}NO_3$ [(M+H)$^+$] 224.1287, found 224.1282.

General procedure for the kinetic resolution of racemic carboxylic acids induced by 1

To a suspension of racemic carboxylic acid (0.5 mmol), 2,4,6-collidine (1.0 mmol) and anhydrous MS 4A in CCl_4 (1 ml) was added trimethylacetyl chloride (74 μl, 0.6 mmol) at

room temperature. After the 1 h, the reaction mixture was cooled at -20 °C, added the solution of **1** (16.5 mg, 0.025 ml), trimethylacetic acid (11.5 μl, 0.1 mmol) and *tert*-butanol (28.6 μl, 0.3 mmol) in CCl_4. After being stirred for 48 h at -20 °C, the reaction mixture was treated with 0.1 M HCl aqueous solution, diluted with EtOAc, washed with 0.1 M HCl aqueous solution and brine. The aqueous layer was extracted with EtOAc. The extracted organic layer was washed with 0.1 M HCl aqueous solution and brine. The combined organic layer was dried over $MgSO_4$, filtered, and evaporated. The residue was purified by flash column chromatography on Cromatorex® NH-DM1020 (eluent: hexane-EtOAc = 20:1-5:1) to give a product. The ee value of Ester was determined by HPLC analysis. The *S* value was estimated by the following equation, $S = \ln[(1-c)(1+ee_{ester})]/\ln[(1-c)(1-ee_{ester})]$. The corresponding physical and spectroscopic data for the products follow.

(+)-1-(Benzyloxy)-3-(*tert*-butyldiphenylsilyloxy)-1-oxopropan-2-yl pyrrolidine-1-carboxylate. TLC (hexane–EtOAc = 2:1) R_f = 0.32; $[\alpha]_D^{22}$ = 0.7 (*c* = 2.7, $CHCl_3$) f or 6% ee; HPLC (Daicel Chiralpack OD-H, hexane:2-propanol = 20:1, flow rate = 1.0 mL/min) t_R = 11.6 (minor), 20.2 (major) min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00 (s, 9H), 1.80-1.94 (m, 4H), 3.28-3.48 (m, 3H), 3.48-3.59 (m, 1H), 4.07 (dd, *J* = 2.9, 11.1 Hz, 1H), 4.16 (dd, *J* = 4.4, 11.1 Hz, 1H), 5.17 (d, *J* = 12.3 Hz, 1H), 5.23 (t, *J* = 3.5 Hz, 1H), 5.25 (dd, *J* = 12.3 Hz, 1H), 7.25-7.47 (m, 11H), 7.57-7.72 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ19.4, 25.1, 25.9, 26.7 (3C), 46.0, 46.4, 63.8, 67.1, 74.1, 127.8, 128.3, 128.4, 128.6, 129.9, 133.0, 133.2 ,135.6, 135.7, 154.2, 169.1; IR (KBr) 3650-3300 (br), 2952, 2879, 1763, 1714, 1421, 1196, 1117, 701 cm^{-1}; HRMS(FAB) calcd for $C_{31}H_{38}NO_5Si$ [(M+H)$^+$] 532.2519, found 224.1282.

(+)-3-(*tert*-Butyldiphenylsilyloxy)-1-isopropoxy-1-oxopropan-2-yl pyrrolidine-1-carboxylate. TLC (hexane–EtOAc = 2:1) R_f = 0.32; $[\alpha]_D^{22}$ = 8.6 (*c* = 2.1, $CHCl_3$) f or 69% ee; HPLC (Daicel Chiralpack AD-H, hexane:2-propanol = 20:1, flow rate = 1. 0 mL/min) t_R = 13.5 (major), 16.3 (minor) min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (s, 9H,), 1.26 (d, *J* = 6.3 Hz, 3H), 1.29 (d, *J* = 6.3 Hz, 3H), 1.82-1.94 (m, 4H), 3.2 8-3.50 (m, 3H), 3.50-3.60 (m, 1H), 3.96 (dd, *J* = 3.0, 11.1 Hz, 1H), 4.14 (dd, *J* = 4. 8, 11.1 Hz, 1H), 5.10 (septet, *J* = 6.3 Hz, 1H), 5.12 (dd, *J* = 3.0, 4.2 Hz, 1H), 7.34-7.48 (m, 6H), 7.64-7.73 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.4, 22.0 (2C), 25.1, 25.9, 26.7 (3C), 46.0, 46.4, 63.9, 69.1, 74.2, 127.8 (2C), 127.8 (2C), 129.9 (2C), 13 3.2, 133.4, 135.6 (2C), 135.7 (2C), 154.3, 168.7; IR (film) 2982, 2933, 2883, 1701, 1

428, 1113, 704 cm^{-1}; HRMS(FAB) calcd for $C_{27}H_{38}NO_5Si$ [(M+H)$^+$] 484.2519, found 4 84.2520.

(+)-1-*tert*-Butoxy-3-(*tert*-butyldiphenylsilyloxy)-1-oxopropan-2-yl pyrrolidine-1-carboxylate. TLC (hexane–EtOAc = 2:1) R_f = 0.37; $[\alpha]_D^{22}$ = 9.4 (*c* = 1.1, $CHCl_3$) f or 83% ee; HPLC (Daicel Chiralpack AD-Hx2, hexane:2-propanol = 20:1, flow rate = 0.5 mL/min) t_R = 22.1 (major), 24.4 (minor) min; ^1H NMR (300 MHz, $CDCl_3$) δ 1. 04 (s, 9H), 1.49 (s, 9H), 1.79-1.96 (m, 4H), 3.28-3.30 (m, 3H), 3.30-3.60 (m, 1H), 3. 94 (dd, *J* = 28.5, 11.0 Hz, 1H), 4.13 (dd, *J* = 4.4, 11.0 Hz, 1H), 5.06 (dd, *J* = 2.7, 4.5 Hz, 1H), 7.34-7.47 (m, 10H), 7.65-7.73 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 1 9.4, 25.1, 25.9, 26.7 (3C), 28.2 (3C), 46.0, 46.4, 64.1, 74.3, 82.0, 127.8 (2C), 127.8 (2C), 129.8 (2C), 133.2, 133.5, 135.6 (2C), 135.8 (2C), 154.3, 168.2; IR (neat) 2955, 2932, 2878, 1754, 1713, 1426, 1368, 1254, 1226, 1163, 1114, 823, 704 cm^{-1}; HRMS (FAB) calcd for $C_{28}H_{40}NO_5Si$ [(M+H)$^+$] 498.2676, found 498.2676.

(*R*)-2-*tert*-Butoxy-2-oxo-1-phenylethyl pyrrolidine-1-carboxylate. TLC (hexane–EtOAc = 2:1) R_f = 0.37; $[\alpha]_D^{22}$ = –53.0 (*c* = 1.6, $CHCl_3$) for 61% ee; HPLC (Daicel Chiralpack AD-Hx2, hexane:2-propanol = 20:1, flow rate = 0.5 mL/min) t_R = 28.3 ((*R*) major), 31.7 ((*S*) minor) min; ^1H NMR (300 MHz, $CDCl_3$) δ 1.40 (s, 3H), 1.77-1.99 (m, 4H), 3.33-3.53 (m, 3H), 3.53-3.68 (m, 1H), 5.81 (s, 1H), 7.30-7.42 (m, 3H), 7.44-5.72 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.1, 25.8, 28.0, 46.0, 46.3, 75.1, 82.1, 127.4 (2C), 128.6 (2C), 128.7, 135.3, 154.0, 169.0; IR (KBr) 3600-3300 (br), 2979, 2874, 1744, 1704, 1427, 1343, 1276, 1226, 1153, 1127, 1110 cm^{-1}; HRMS(FAB) calcd for $C_{17}H_{24}NO_4$ [(M+H)$^+$] 306.1705, found 306.1702. The absolute configuration was determined by reduction with $LiAlH_4$ to corresponding diol and comparison with commercially available (*R*)-2-Phenyl-1,2-ethanediol by chiral-GC analysis.

(+)-1-*tert*-Butoxy-1-oxo-3-phenylpropan-2-yl pyrrolidine-1-carboxylate. TLC (hexane–EtOAc = 2:1) R_f = 0.37; $[\alpha]_D^{22}$ = 0.9 (*c* = 1.1, $CHCl_3$) for 86% ee; HPLC (Daicel Chiralpack AD-Hx2, hexane:2-propanol = 20:1, flow rate = 0.5 mL/min) t_R = 52.0 (minor), 55.6 (major) min; ^1H NMR (300 MHz, $CDCl_3$) δ 1.41 (s, 9H), 1.74-1.94 (m, 4H), 3.07 (dd, *J* = 8.0, 13.9 Hz, 1H), 3.13 (dd, *J* = 4.8, 13.9 Hz, 1H), 3.23-3.41 (m, 3H), 3.41-3.52 (m, 1H), 5.04 (dd, *J* = 5.3, 8.0, 1H), 7.18-7.33 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.0, 25.8, 28.0 (3C), 37.8, 45.9, 46.2, 73.6, 81.9, 126.8, 128.3 (2C), 129.6 (2C), 136.7, 154.1, 169.8; IR (film) 2981, 1742, 1702, 1429, 1370, 1209, 1156, 1348, 1217 cm^{-1}; HRMS(FAB) calcd for

$C_{18}H_{26}NO_4$ [(M+H)$^+$] 320.1862, found 320.1862.

(—)-1-*tert*-Butoxy-3-methyl-1-oxobutan-2-yl pyrrolidine-1-carboxylate. TLC (hexane–EtOAc = 2:1) R_f = 0.41; $[\alpha]_D^{23}$ = —5.3 (*c* = 0.9, $CHCl_3$) for 83% ee; HPLC (Daicel Chiralpack AD-Hx2, hexane:2-propanol = 20:1, flow rate = 0.5 mL/min) t_R = 40.1 (major), 42.8 (minor) min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (d, *J* = 6.9 Hz, 3H), 1.01 (d, *J* = 6.9 Hz, 3H), 1.47 (s, 9H), 1.80-1.95 (m, 4H), 2.21 (d, septet, *J* = 4.2, 6.9 Hz, 1H), 3.33-3.46 (m, 3H), 3.46-3.58 (m, 1H), 4.70 (d, *J* = 4.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.3, 19.1, 25.1, 25.8, 28.2, 30.5, 45.9, 46.3, 77.2, 81.6, 154.6, 170.0; IR (film) 2973, 2933, 2878, 1739, 1697, 1431, 1370, 1162, 1131, 1348 cm^{-1}; HRMS(FAB) calcd for $C_{14}H_{26}NO_4$ [(M+H)$^+$] 272.1862, found 272.1867.

***(R)*-*tert*-Butyl 2-(*tert*-butoxycarbonylamino)-3-phenylpropanoate.** TLC (hexane–EtOAc = 2:1) R_f = 0.12; $[\alpha]_D^{21}$ = —24.3 (*c* = 0.9, $CHCl_3$) for 83% ee; HPLC (Daicel Chiralpack AD-Hx2, hexane:2-propanol = 9:1, flow rate = 1 mL/min) t_R = 10.3 (major), 16.3 (minor) min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40 (s, 9H), 1.42 (s, 9H), 3.05 (d, *J* = 6.0 Hz, 2H), 4.45 (dd, *J* = 6.2, 14.3 Hz, 1H), 5.00 (8.4 Hz, 1H), 7.18-7.34 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.1 (3C), 28.4 (3C), 38.7, 54.9, 79.8, 82.1, 126.9, 128.4 (2C), 130.0 (2C), 136.5, 155.2, 171.1. The absolute chemistry was determined by comparing the optical rotation of this material with that reported in the literature (Lit: N-Boc-L-Phe-O*t*-Bu $[\alpha]_D^{24}$ = 32.04 (*c* = 1.08, $CHCl_3$)[11]

(+)-Isopropyl 6-(pyrrolidine-1-carbonyl)cyclohex-3-enecarboxylate. $[\alpha]_D^{22}$ = 9.5 (*c* = 2.4, $CHCl_3$) for 58% ee; HPLC (Daicel Chiralpack OD-H, hexane:2-propanol = 20:1, flow rate = 1.0 mL/min) t_R = 20.5 (major), 24.3 (minor) min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (d, *J* = 3.3 Hz, 3H), 1.23 (d, *J* = 3.3 Hz, 3H), 1.78-2.20 (m, 4H), 2.32-2.46 (m, 3H), 2.50-2.89 (m, 2H), 3.12-3.20 (m, 1H), 3.37-3.62 (m, 4H), 5.01 (septet, *J* = 6.3 Hz, 1H), 5.62-5.73 (m, 1H), 5.73-5.82 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.8, 21.9, 24.3, 26.0, 26.1, 26.4, 37.4, 39.7, 45.8, 46.6, 67.6, 123.7, 125.9, 172.7, 173.6; IR (film) 2981, 2877, 1722, 1627, 1447, 1374, 1344, 1293, 1249, 1184, 1108 cm^{-1}; HRMS(FAB) calcd for $C_{15}H_{24}NO_3$ [(M+H)$^+$] 266.1756, found 266.1754.

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Appendix 1

Enantioselective Epoxidation of Allylic Alcohols by a Chiral Complex of Vanadium: An Effective Controller System and A Rational Mechanistic Model**

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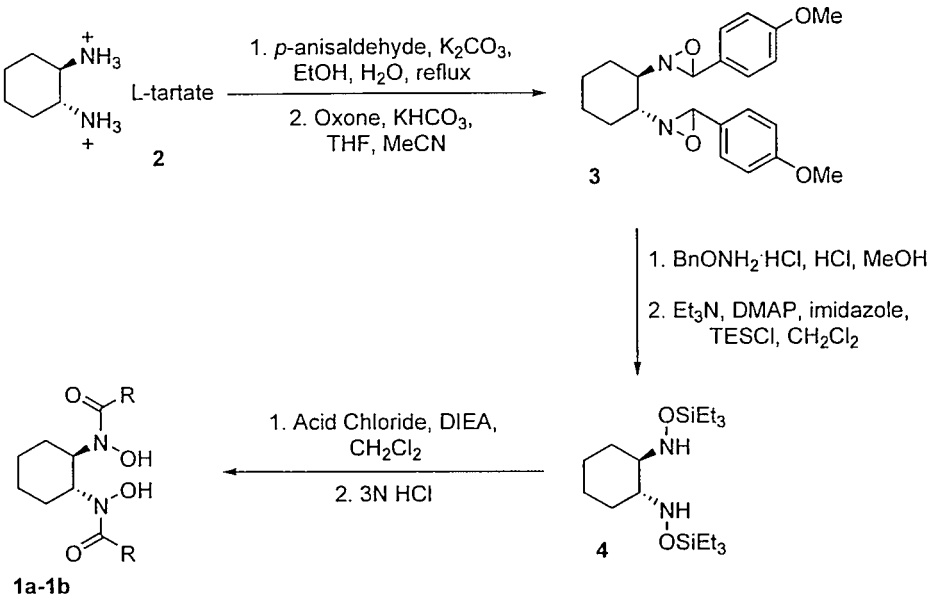
The asymmetric epoxidation of allylic alcohols by metal catalysts,[1] though a widely used synthetic method, would be even more practical if the following conditions could be achieved: 1) ligand design to achieve high enantioselectivity for Z-olefins, 2) less than 1 mol% catalyst loading, 3) reaction conditions at 0 °C to RT for fewer hours, 4) use of aqueous TBHP (*tert*-butyl hydroperoxide) as an achiral oxidant instead of anhydrous TBHP, and 5) easy work-up procedure for small epoxy alcohols. Many groups have made important contributions to the steady improvement of Sharpless' methodology for the titanium-tartarate catalyzed asymmetric epoxidation.[2-4] Nonetheless, each of these approaches fails to fulfill the above criteria.[1-5] In this communication, we report our recent progress on all five fronts.

Recently, we developed a series of hydroxamic acid ligands and demonstrated that they were effective for the vanadium-catalyzed asymmetric epoxidation of allylic alcohols.[6,7] These results suggested that several structural features of the hydroxamic acid significantly enhanced the rate and enantioselectivity. However, the ligand deceleration effect was still observed in these cases.[6-8] To exclude this effect, we planned to design a new C_2-symmetric bishydroxamic acid **1** incorporating several features: 1) with an additional binding site, **1** is capable of chelating as an bi-dentate ligand to the metal center to complete the generation of chiral vanadium-ligand complex more efficiently than monohydroxamic acid; 2) when the R group of amide in **1** is sufficiently large, it will direct the amide carbonyl oxygen towards the cyclohexane ring to minimize steric interaction and restrict its coordination with the metal. A second aspect is that the attachment of additional ligands to vanadium will also be restricted for steric reasons. Thus, doubly or triply coordinated species, which are believed to be inactive, should not be generated with this bishydroxamic acid ligand, and consequently the ligand deceleration effect with the vanadium-**1** catalyst system should not be problematic.[8]

To prove the veracity of our hypothesis, we devised a synthetic protocol for **1** from readily available diamine tartrate salt (Scheme 1).[9] These reaction sequences can be conducted with satisfactory yields and without any purification to provide **4**, and we have prepared a wide array of diverse ligands **1.**

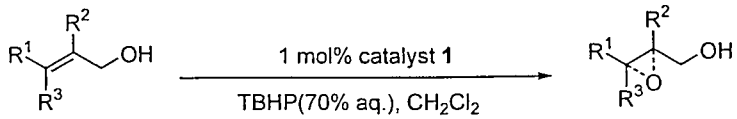


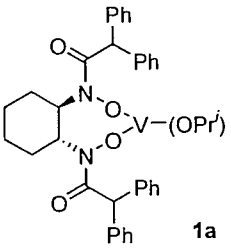
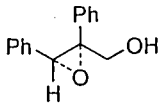
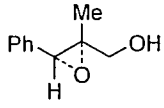
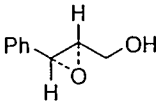
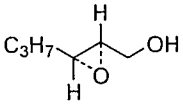
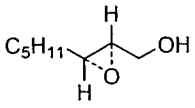
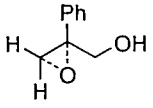
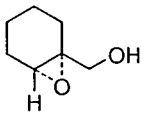
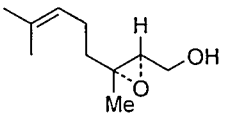
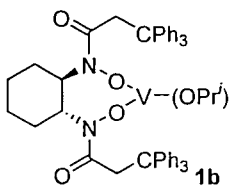
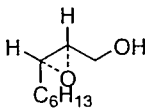
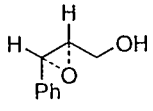
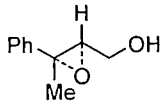
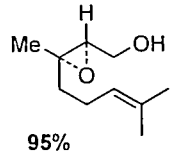
(**1a**, R = $CHPh_2$), (**1a*** R = CH(3,5-dimethylphenyl)$_2$), (**1b** R = CH_2CPh_3)

Scheme 1. Preparation of bishydroxamic acid.

As expected, the complex of vanadium with **1** provided epoxy alcohols with both high enantioselectivities and good yields (Scheme 2).[9] The catalyst **1a** derived from vanadium and **1a** invariably induced excellent enantioselectivity during the epoxidation of *trans*-disubstituted and trisubstituted allylic alcohols. The most gratifying aspect of this catalyst system was the excellent enantioselectivity during epoxidation of *cis*-substituted allylic alcohols with catalyst **1b** derived from vanadium and **1b.** Some additional comments are: 1) slow reactivity of some substrates were surmounted by performing the epoxidation at 0°C or RT without significant loss of enantioselectivity; 2) catalyst loading could be as low as 0.2 mol%; 3) reactions were performed under air with aqueous solution of TBHP to obtain all the above results. Use of anhydrous TBHP increased neither yield nor ee value.[9] Also as expected, the negative effect of dynamic ligand exchange was not observed in the vanadium-bis-hydroxamic acid catalyst system. The high reactivity of the vanadium-ligand complex was maintained even if the ratio of ligand to vanadium was increased to more than 3:1.[9]

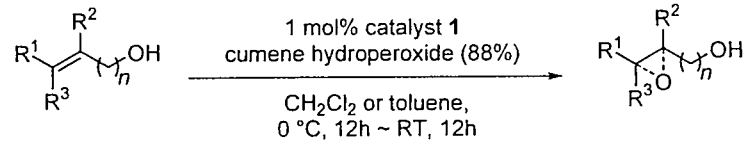
Scheme 2. Enantioselective epoxidation of allylic alcohols.

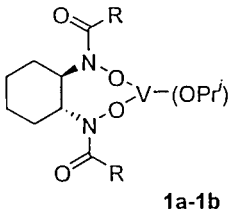
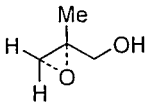
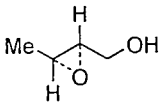
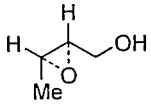
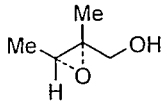
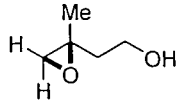


catalyst	ee (temp.(°C); t(h); yield(%))			
 **1a**	 **97%** (-20; 48; 91)	 **97%** (-20; 48; 84)	 **97%** (-20; 60h; 53)	 **95%** (-20; 72; 56)
	 **95%** (-20; 72; 51)	 **95%** (0; 48h; 73)	 **95%** (-20; 48; 79)	 **95%** (cat. **1a***) (-20; 48h; 68)
 **1b**	 **95%** (0; 72; 60)	 **97%** (-20; 120; 24)	 **96%** (-20; 48; 64)	 **95%** (-20; 48h; 62)

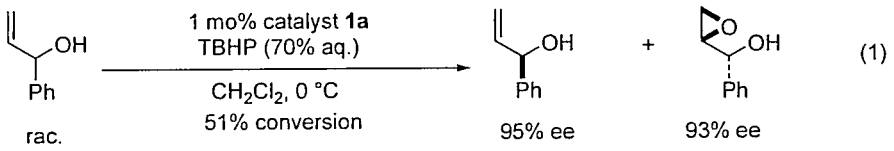
This method was next applied to asymmetric synthesis of small epoxy alcohols, a long-standing problem for asymmetric oxidation. Thus, after the reaction, the product was extracted with water to give the enantiopure epoxy alcohols (Scheme 3).[2,9]

Scheme 3. Enantioselective epoxidation of small allylic alcohols.



catalyst	ee (catalyst; yield(%))		
 **1a-1b**	 **97%** (**1a***; 78)	 **93%** (**1a**; 50)	 **92%** (**1b**; 71)
	 **95%** (**1a**; 68)	 **94%** (**1a***; 73)	

Finally, the method was also applied to kinetic resolution of secondary allylic alcohol. As expected, both the epoxy alcohol and the allylic alcohol were isolated with high enantioselectivities after the reaction [Eq. (1)].[9]



(1)

To explain the enantioselectivity, we propose the following possible intermediate during epoxidation (Figure 1).[10] As shown in the left model, the second and fourth quadrants are more crowded than the first and third quadrants because of the structural features of chiral cyclohexyl diamine, especially when vanadium is assembled. As shown in the right model, $VO(OPr^i)_3$ coordinates with **1a** by displacement of two *i*PrOH by two hydroxyl groups from bis-hydroxamic acid. Another *i*PrOH of $VO(OPr^i)_3$ is then displaced by TBHP, which occupies the less crowded third quadrant. Finally, when the allylic alcohol assembles, it will coordinate with vanadium by its oxygen from the top. During the reaction, the oxygen of TBHP is spiro overlapped with the olefin and attacks it from the bottom. The steric bulk at the alpha position of the carboxylate plays an important role, which is greater in case **1a**, and suitable for trans-substituted allylic alcohols. On the other hand, the additional flexibility of ligand **1b** allows the cis- substituted allylic alcohols enough space to fit in the chiral pocket resulting in high selectivity.

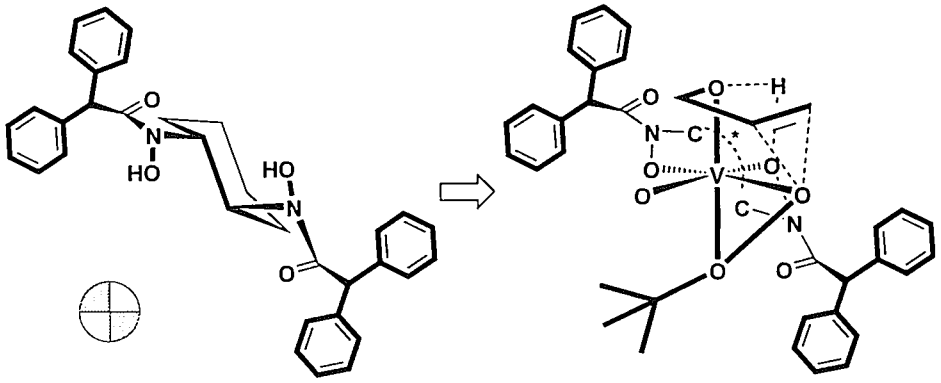


Figure 1. Postulated model of epoxidation of allylic alcohol catalyzed by vanadium-**1a** complex.

In conclusion, we developed a new catalyst system for the asymmetric epoxidation of allylic alcohols. Mechanistic understanding and study of further applications of bishydroxamic acid ligands in asymmetric catalysis is in progress.

Experimental Section

Representative experimental procedure: to a solution of **1a** (11.2 mg, 0.0210 mmol) in dichloromethane or toluene (1 mL) was added $VO(OPr^i)_3$ (0.0025 mL, 0.0104 mmol), and the mixture was stirred for 1 h at RT. The resulting solution was cooled to 0 °C, and then 70% aqueous tert-butylhydroperoxide (TBHP) (0.22 mL, 1.59 mmol) and α-phenylcinnamic alcohol (220 mg, 1.05 mmol) were added and stirring was continued at the same temperature for 12 hours. The process of epoxidation was monitored by TLC. Saturated aqueous Na_2SO_3 was then added, and the mixture was stirred for 1 h at 0 °C. The mixture was then allowed to warm to RT, extracted with Et_2O, dried over Na_2SO_4 and concentrated under reduced pressure. The remaining residue was purified by flash column chromatography on silica gel to provide epoxy alcohol in 93% yield with 94% ee. Detailed information on determining the ee values of epoxy alcohols is provided in the support information.

References

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Synlett **2000**, 899-901; b) B. Traber, Y. G. Jung, T. K. Park, J. I. Hong, *Bull. Korean Chem. Soc.* **2001**, *22*, 547-548; c) H. L. Wu, B. J. Uang, *Tetrahedron: Asymmetry* **2002**, *13*, 2625-2628.

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[8] D. J. Berrisford, C. Bolm, K. B. Sharpless, *Angew. Chem.* **1995**, *107*, 1159-1171; *Angew. Chem. Int. Ed.* **1995**, *34*, 1059-1070.

[9] See supporting information for detailed experimental procedure.

[10] For mechanistic study on vanadium-hydroxamic acid oxidation see, a) K. P. Bryliakov, E. P. Talsi, *Kinetics and Catalysis (Translation of Kinetika i Kataliz)* **2003**, *44*, 334-346; b) K. P. Bryliakov, E. P. Talsi, T. Kühn, C. Bolm, *New Journal of Chemistry* **2003**, *27*, 609-614

Keywords: epoxidation. asymmetric catalysis. vanadium. chirality. ligand design

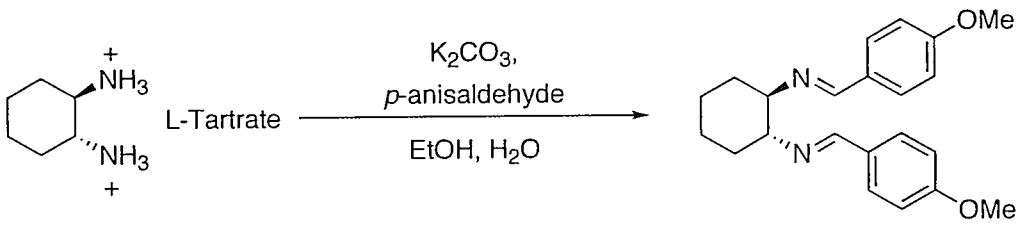
General.

Infrared (IR) spectra were recorded on a Nicolet 20 SXB FTIR. ^{1}H NMR spectra were recorded on a Bruker Avance 400 (400 MHz) spectrometer. Chemical shift values (δ) are expressed in ppm downfield relative to internal standard (tetramethylsilane at 0 ppm). Multiplicities are indicated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). ^{13}C NMR spectra were recorded on a Bruker Avance 400 (100 MHz), a Bruker Avance 500 (125 MHz) spectrometer and are expressed in ppm using solvent as the internal standard ($CDCl_3$ at 77.0 ppm). Analytical gas-liquid chromatography (GLC) was performed on a Shimadzu GC-17A instrument equipped with a flame ionization detector and a capillary column of β-TA (0.25 mm × 25m) using nitrogen as carrier gas. High-performance liquid chromatography (HPLC) was performed on a Varian ProStar Series equipped with a variable wavelength detector using chiral stationary columns (Chiracel, OB-H or OD-H, 0.46 cm x 25

cm) from Daicel. Optical rotations were measured on a JASCO DIP-1000 digital polarimeter. High-resolution electro spray ionization (HRMS-ESI) mass spectra were obtained on a Micromass Q-Tof-2, Quadrupole Time of Flight mass spectrometer at the University of Illinois Research Resources Center in positive mode.

All reactions were carried out in oven-dried glassware with magnetic stirring unless otherwise noted. Analytical thin-layer chromatography (TLC) was performed on Merck pre-coated TLC plates (silica gel 60 GF254, 0.25mm). Flash chromatography was performed on silica gel E. Merck 9385 or silica gel 60 extra pure (for all the *bis*-hydroxamic acids). Dichloromethane (CH_2Cl_2) and toluene ($PhCH_3$) were purchased from Acros as anhydrous solvents. *N,N*-diisopropylethylamine and triethylamine were stored over KOH pellets. Allylic alcohols and products in Table 1 have been previously isolated and characterized. References can be found elsewhere.[1] Anhydrous *tert*-butyl hydroperoxide (TBHP) solution in CH_2Cl_2 was prepared according to the literature procedure.[2] All other reagents and starting materials, unless otherwise noted, were purchased from commercial vendors and used without further purification.

Preparation of (*R,R*)-*N,N'*-*Bis*-(4-methoxybenzylidene)-cyclohexane-1,2-diimine.

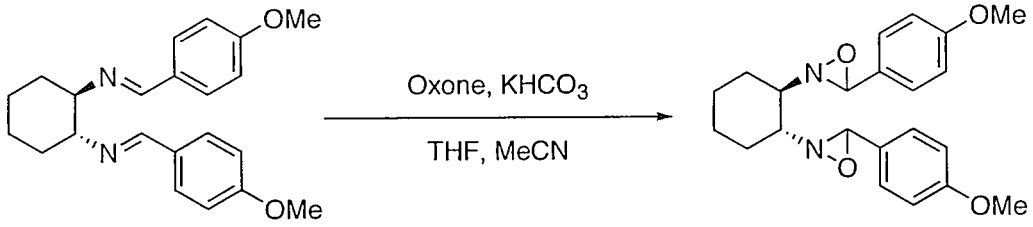


2

A mixture of diammonium salt (**2**) (26.4 g, 100 mmol), K_2CO_3 (27.6 g, 200 mmol), and de-ionized water (130 mL) was stirred until dissolution was achieved, and then ethanol (420 mL) was added. The resulting cloudy mixture was heated to reflux, and a solution of *p*-anisaldehyde (27.5 g, 200 mmol) in ethanol (40 mL) was added in a steady stream over 30 min. The yellow slurry was stirred at reflux for 5 h before heating was discontinued. The reaction mixture was cooled to room temperature, and the water phase was separated and discarded. The organic phase was concentrated and dissolved in dichloromethane. It was then removed any trace of water, dried over Na_2SO_4 and filtered. The filtrate was removed solvent to provide crude diimine as light yellow solid (34.8 g, 99% yield), which was used in the following step without further purification. Pure product, which was applied to determine the structure, was obtained by recrystalization from dichloromethane and hexanes as white solid: R_f 0.6 (EtOAc/hexanes, 3:7); FTIR (film) υ_{max} 2929, 2855, 1643, 1606, 1579, 1512, 1463,

1303, 1250, 1165, 1032, 831 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 2 H), 7.52 (d, J = 8.8 Hz, 4 H), 6.82 (d, J = 8.8 Hz, 4 H), 3.78 (s, 6 H), 3.37-3.32 (m, 2 H), 1.87-1.77 (m, 6 H), 1.49-1.46 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5 (C), 160.5 (CH), 129.7 (CH), 114.0 (CH), 74.0 (CH_3), 55.5 (CH), 33.3 (CH_2), 24.8 (CH_2); HRMS-ESI calcd for $C_{22}H_{27}O_6N_2$ $[M+H]^+$ 351.2073, found 351.2076.

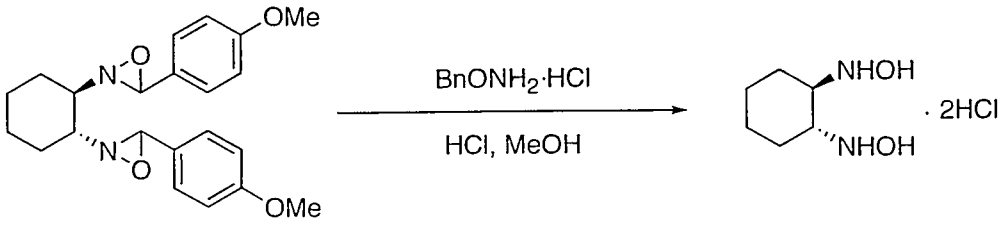
Preparation of Dioxaziridine 3.



3

To a stirred solution of diimine (10.5 g, 30.0 mmol) in MeCN (180 mL) and THF (360 mL), at room temperature, was added an aqueous solution (300 mL) of $KHCO_3$ (50.5 g, 504 mmol) followed by an aqueous solution (300 mL) of Oxone (44 g, 72 mmol). After stirring for 2 h 15 min, the reaction mixture was diluted with CH_2Cl_2 (600 mL). The biphasic mixture was separated and the aqueous portion was extracted with CH_2Cl_2 (2 x 300 mL) and the combined organic extracts was dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure to provide crude dioxaziridine **3** (10.7 g, 93% yield) as light yellow solid, which was used in the following step without further purification. Pure product, which was applied to determine the structure, was obtained by recrystalization from dichloromethane and hexane as white solid: FTIR (film) υ_{max} 2935, 1615, 1517, 1309, 1456, 1437, 1310, 1252, 1171, 1031, 821 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.81-6.78 (m, 4 H), 6.58-6.54 (m, 4 H), 4.37 (s, 2 H), 3.78 (s, 6 H), 2.39-2.37(m, 2 H), 2.21-2.18 (m, 2 H), 1.83-1.80 (m, 2 H), 1.58-1.51 (m, 2 H), 1.31-1.27 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.7 (C), 129.0 (CH), 126.5 (C), 113.8 (CH), 81.6 (CH), 72.4 (CH_3/CH), 55.4 (CH_3/CH), 30.3 (CH_2), 24.1 (CH_2); HRMS-ESI calcd for $C_{22}H_{26}O_4N_2Na$ $[M+Na]^+$ 405.1788, found 405.1790.

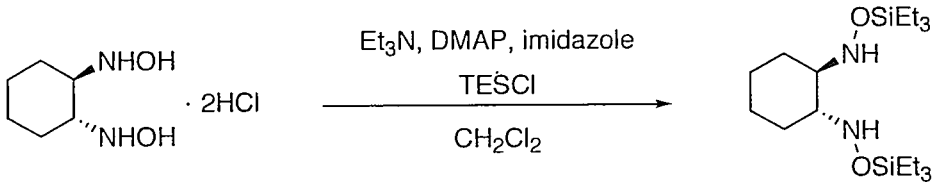
Preparation of Dihydroxylamine dihydrochloride.



3

To a mixture of the unpurified product **3** (10.7 g) obtained from the previous oxidation reaction and benzyloxyhydroxyl amine hydrochloride (8.8 g, 55.1 mmol) was treated with anhydrous methanol (250 mL), and then 1 M HCl in MeOH (94 mL, 94 mmol) was added immediately. The resulting mixture was stirred for 20 minutes. The reaction mixture was then concentrated under reduced pressure to dryness. Et_2O (200 mL) and de-ionized water (100 mL) was added. The bi-layer was separated and the organic part was extracted with de-ionized water (20 mL). Combined aqueous portion was washed with Et_2O (2 x 100 mL). The aqueous portion was concentrated to 60-75 mL and the resulting white solid ($BnONH_2$.HCl) was filtered off, then filtrate was concentrated under reduced pressure to provide *bis*-hydroxylamine dihydrochloride (6.1 g) as an oily solid, which contained 5-10% of $BnONH_2$.HCl. This material was utilized in the next step without any purification: ^1H NMR (400 MHz, D_2O) δ 3.66-3.62 (m, 2 H), 2.02-1.98 (m, 2 H), 1.69-1.66 (m, 2 H), 1.41-1.37 (m, 4 H), 1.20-1.15 (m, 2 H); ^{13}C NMR (100 MHz, D_2O) δ 58.6 (CH), 25.1 (CH_2), 22.1 (CH_2).

Preparation of (*R,R*)-*O,O'*-bistriethylsilylcyclohexyl-1,2-dihydroxylamine 4.

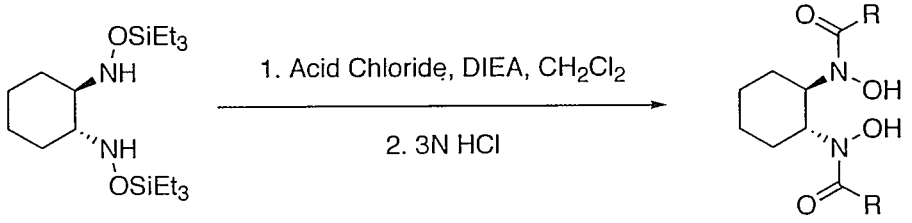


4

To a stirred suspension of *bis*-hydroxylamine dihydrochloride (2.24 g, 10.2 mmol) in CH_2Cl_2 (40 mL) under nitrogen at room temperature was added Et_3N (3.70 mL, 25.6 mmol). After 1 h, to the resulting cloudy white suspension, DMAP (374 mg, 3.06 mmol), imidazole (4.17 g, 61.4 mmol) followed by triethylsilyl chloride (6.90 mL, 40.9 mmol) were added and stirring was continued 16 h, and then poured into an aqueous solution of $NaHCO_3$ (5.16 g, 61.4 mmol) and extracted with EtOAc (2 x 100 mL). The combined organic extracts was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was dissolved in a small amount of dichloromethane and filtered through a small plug of silica gel by

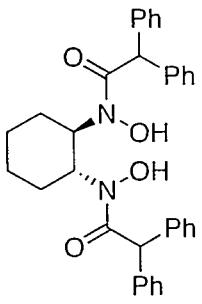
washing with the mixture of EtOAc/hexanes (0.5:99.5) to provide **4** (4.23 g), which contained diethylsilyl ether as about 1:1 mixture and was used in the following step without further purification: R_f 0.6 (EtOAc/hexanes, 1:9); FTIR (film) υ_{max} 2954, 2876, 1557, 1540, 1458, 1417, 1238, 1072, 1008, 883, 841, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.46 (br s, 2 H), 2.66-2.63 (m, 2 H), 2.19-2.18 (m, 2 H), 1.71-170 (m, 2 H), 0.98 (t, J = 8.0 Hz, 18 H), 0.67 (q, J = 8.0 Hz, 12 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 63.1 (CH), 30.6 (CH_2), 24.8 (CH_2), 7.11 (CH_3), 4.3 (CH_2); HRMS-ESI calcd for $C_{18}H_{42}O_2N_2Si_2Na$ $[M+Na]^+$ 397.2683, found 397.2690.

General procedure for preparation of *Bis*-hydroxamic acids (1a, 1b, 1a*).



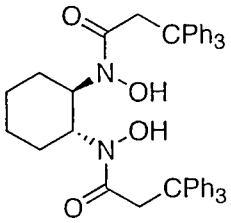
4 **1**

To a stirred solution of **4** (1 mmol) and DIEA (1.04 mL, 6 mmol) in CH_2Cl_2 (20 mL) was added acid chloride (3 mmol, dissolved in 5 mL CH_2Cl_2) under nitrogen. After 24-72 h, the reaction mixture was treated with 3N HCl (or 1M HCl/MeOH). After stirring for 30 min the reaction mixture was extracted with CH_2Cl_2, washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel 60 extra pure to provide the *bis*-hydroxamic acid.



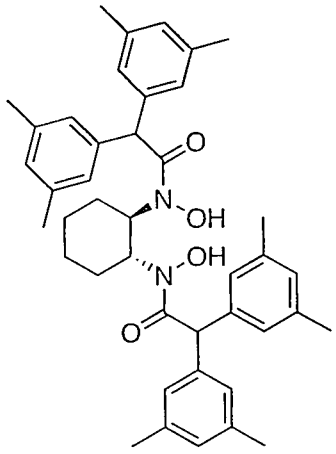
1a

(*R,R*)-*N*-[2-(Diphenylacetylhydroxyamino)-cyclohexyl]-*N*-hydroxy-2,2-diphenyl-acetamide 1a. Yield, 55%; white solid: R_f 0.5 (EtOAc/hexanes, 3:7); FTIR (film) υ_{max} 3195, 3062, 3029, 2961, 2940, 2862, 1750, 1687, 1658, 1620, 1600, 1495, 1451, 1401, 1309, 1251, 1166, 1079, 1032, 909, 733, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.04 (s, 2 H), 7.32-7.04 (m, 20 H), 5.50 (s, 2 H), 4.56-4.55 (m 2 H), 1.78 (m, 6 H), 1.24 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.2 (C=O), 139.4 (C), 139.2 (C), 129.5 (CH), 128.9 (CH), 128.8 (CH), 128.7 (CH), 127.3 (CH), 127.1 (CH), 56.7 (CH), 53.4 (CH), 27.9 (CH_2), 24.6 (CH_2). HRMS-ESI calcd for $C_{34}H_{34}O_4N_2Na$ $[M+Na]^+$ 557.2416, found 557.2438; $[\alpha]_D^{28.4}$ +93.47 (*c* 1.0, $CHCl_3$).



1b

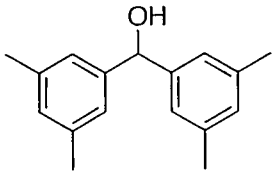
(*R,R*)-*N*-Hydroxy-*N*-{2-[hydroxy-(3,3,3-triphenylpropionyl)-amino]-cyclohexyl}-3,3,3-triphenylpropionamide 1b. Yield, 72%; white solid: R_f 0.63 (EtOAc/hexanes, 1:3); FTIR (film) υ_{max} 3150, 2938, 2859, 1616, 1493, 1446, 1419, 1170, 769, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 2 H), 7.28-7.17(m, 30 H), 4.19 (d, *J* = 16.1 Hz, 2 H), 3.94-3.92 (m, 2 H), 3.55 (d, *J* = 16.1 Hz, 2 H), 1.68-1.65 (m, 2 H), 1.50-1.38 (m, 4 H), 1.12-1.07 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6 (C=O), 147.2 (C), 129.6 (CH), 127.8 (CH), 126.3 (CH), 56.2 (C), 55.2 (CH), 42.5 (CH_2), 27.5 (CH_2), 24.6 (CH_2); HRMS-ESI calcd for $C_{48}H_{46}O_4N_2Na$ $[M+Na]^+$ 737.3355, found 737.3379; $[\alpha]_D^{28.4}$ +22.12 (*c* 1.0, $CHCl_3$).



1a*

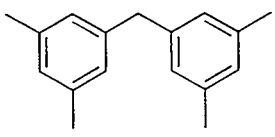
(*R,R*)-*N*-(2-{[2,2-Bis-(3,5-dimethylphenyl)-acetyl] hydroxyamino}-cyclohexyl)-2,2-bis-(3,5-dimethylphenyl)-*N*-hydroxyacetamide 1a*. Yield, 20%: *Rf* 0.5 (EtOAc/hexane, 1:4); FTIR (film) υ_{max} 3172, 3007, 2919, 2861, 1621, 1602, 1452, 1404, 1309, 1264, 1233, 1166, 1132, 1037, 958, 897, 851, 823, 790, 770, 736, 710, 688, 660 cm-1; ^1H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 2 H), 6.87-6.72 (m, 12 H), 5.35 (s, 2 H), 4.52-4.50 (m 2 H), 2.27 (s, 12 H), 2.14 (s, 12 H), 1.89-1.77 (m, 6 H), 1.26 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0 (C=O), 139.2 (C), 139.0 (C), 137.9 (C), 137.5 (C), 128.6 (CH), 128.5 (CH), 126.8 (CH), 126.4 (CH), 56.5 (CH), 53.0 (CH), 27.7 (CH_2), 24.5, (CH_2), 21.4 (CH_3), 21.3 (CH_3); HRMS-ESI calcd for $C_{42}H_{50}O_4N_2Na$ $[M+Na]^+$ 669.3668, found 669.3668.

Preparation of Alcohol for Ligand 1a*.



The corresponding alcohol of ligand **1a*** was prepared according to the general method to prepare alcohol. ^1H NMR (400 MHz, CDCl3) δ 7.00 (s, 4 H), 6.90 (s, 2 H), 5.70 (d, *J* = 3.2 Hz, 1 H), 2.30 (s, 12 H), 2.12 (d, *J* = 3.4 Hz, 1H).

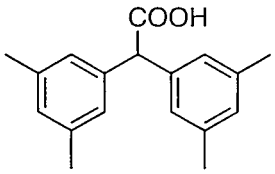
Reduction of Alcohol.[3]



To a stirred suspension of NaI (18g, 120 mmol) in MeCN (10 mL), under an atmosphere of nitrogen at room temperature, was added trimethylsilylchloride (15 mL, 115 mmol). After stirring for 20 min,

the reaction mixture was cooled to 0 °C. A solution of alcohol (4.8 g, 20 mmol) in CH_2Cl_2 (20 mL) and MeCN (10 mL) was added slowly to maintain the reaction temperature below 10 °C. The reaction mixture was allowed to warm to room temperature and the conversion was monitored by TLC. It was recooled to 5 °C prior to work-up. A solution of NaOH was added and the reaction mixture was cooled to room temperature. The biphasic mixture was extracted with diclromethane (3 times) and the combined organic portions was washed with saturated $Na_2S_2O_3$ to remove iodine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by the flash column chromatography on silica gel to provide the alkane (2.42 g). Yield, 54%; colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (s, 2 H), 6.81 (s, 4 H), 3.82 (s, 2 H), 2.27 (s, 12 H).

Preparation of Carboxylic Acid:



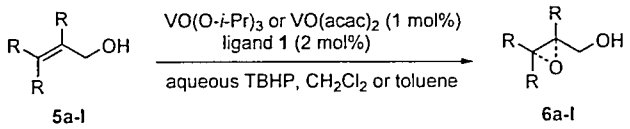
To a stirred solution of the alkane (2.42 g, 10.8 mmol) in freshly distilled anhydrous THF, under an atmosphere of nitrogen at 0 °C, was added *n*-butyl lithium (5 mL, 12.5 mmol). After stirring for 15 min at 0 °C, the reaction mixture was allowed to warm to room temperature. After another 1 h, anhydrous CO_2 was bubbled through. The inlet of CO_2 was continued for several minutes after the color change of the reaction mixture. Water was added followed by saturated NaOH solution to achieve pH 12-14. The aqueous solution was washed with ether and separated, acidified with 1 M HCl to achieve pH 2-3, which was extracted with EtOAc (3 times). The combined organic extracts were then dried over Na_2SO_4, filtered and concentrated under reduced pressure to provide crude acid (1.68 g), which was used to prepare the corresponding acid chloride by general procedure without further purification. Yield, 58%; light yellow solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.57 (bs, 1 H), 6.90 (s, 4 H), 6.86 (s, 2 H), 4.85 (s, 1 H), 2.23 (s, 12 H).

General procedure for asymmetric epoxidation of allylic alcohols in the presence of $VO(OPr^i)_3$ and ligand 1.

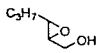
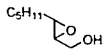
To a solution of **1** (0.0210 mmol) in dichloromethane or toluene (1 mL) was added $VO(OPr^i)_3$ (0.0025 mL, 0.0104 mmol), and the mixture was stirred for 1 h at room temperature. The resulting solution was cooled to 0 °C, and then 70% aqueous *tert*-butylhydroperoxide (TBHP) (0.22 mL, 1.59 mmol) and allylic alcohol **5** (1.05 mmol) were added and stirring was continued at the same temperature for several hours. The process of epoxidation was monitored by TLC. Saturated aqueous Na_2SO_3 was added, and the mixture was stirred for 1 h

at 0 °C. The mixture was then allowed to warm to room temperature, extracted with Et_2O, dried over Na_2SO_4 and concentrated under reduced pressure. The remaining residue was purified by flash column chromatography on silica gel to provide epoxy alcohol **6**. Detailed information of determining the ee values of epoxy alcohols was provided in Table 3-a.

Table 1: Enantioselective Epoxidation of Allylic Alcohols



5a-l 6a-l

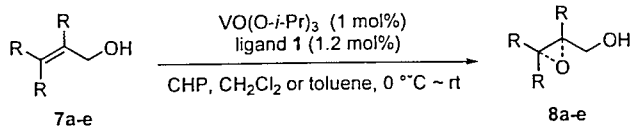
entry[a]	epoxy alcohol	ligand	temp, time	yield[b] (%)	ee[c], config.[d] (%)
1[e]		**1a**	0 °C, 15 h	87	94, (*2R, 3R*)
2		**1a**	0 °C, 12 h	93	94, (*2R, 3R*)
3[f]		**1a**	0 °C ~ rt	95	93, (*2R, 3R*)
4[g]		**1a**	0 °C, 12 h	91	94, (*2R, 3R*)
5[h]		**1a**	0 °C, 12 h	90	95, (*2R, 3R*)
6		**1a**	-20 °C, 48 h	91	97, (*2R, 3R*)
7		**1a**	0 °C, 12 h	87	94, (*2R, 3R*)
8		**1a**	-20 °C, 48 h	84	97, (*2R, 3R*)
9		**1a**	0 °C, 12 h	55	94, (*2R, 3R*)
10		**1a**	-20 °C, 60 h	53	97, (*2R, 3R*)
11		**1a**	0 °C, 12 h	51	92, (*2R, 3R*)
12		**1a**	-20 °C, 72 h	56	95, (*2R, 3R*)
13		**1a**	0 °C, 18 h	58	92, (*2R, 3R*)
14		**1a**	-20 °C, 72 h	51	95, (*2R, 3R*)
15		**1a**	0 °C, 12 h	73	95, (*R*)
16		**1a**	0 °C, 12 h	84	92, (*2R, 3R*)
17		**1a**	-20 °C, 48 h	79	95, (*2R, 3R*)
18		**1b**	0 °C, 72 h	60	95, (*2R, 3S*)
19[g]		**1b**	0 °C, 72 h	57	95, (*2R, 3S*)
20		**1b**	0 °C, 5 d	64	93, (*2R, 3S*)
21		**1b**	-20 °C, 5 d	24	97, (*2R, 3S*)

[a] All reactions were carried out in dichloromethane in the presence of 1.5 equiv of *tert*-butylhydroperoxide (TBHP) (70% aqueous solution) unless otherwise indicated. [b] Isolated yield after chromatographic purification. [c] Ee values were determined by either chiral HPLC or chiral GC and the detailed information was provided in (Table 3-a). [d] Determined by comparison of reported optical rotation. [e] Toluene was used as solvent. [f] 0.2 mol% $VO(O\text{-}i\text{-}Pr)_3$ and 0.4 mol% ligand was used, reaction was performed at 0 °C for 6 h and then warmed to rt to complete the conversion. [g] 3.5 M TBHP in dichloromethane was used. [h] $VO(acac)_2$ was used.

General procedure for asymmetric epoxidation of small allylic alcohols in the presence of $VO(OPr^i)_3$ and ligand 1.

To a solution of **1** (0.0125 mmol) in dichloromethane or toluene (1 mL; for the case of **7e**, only 0.25 mL of toluene was used as solvent) was added $VO(OPr^i)_3$ (0.0025 mL, 0.0104 mmol), and the mixture was stirred for 1 h at room temperature. The resulting solution was cooled to 0 °C, and then 88% cumene hydroperoxide (CHP) (0.25 mL, 1.50 mmol) and small allylic alcohol **7** (0.086 mL, 1.00 mmol) were added and stirring was continued at the same temperature for 12 h. Reaction mixture was then allowed to warm to room temperature and stirring was continued at room temperature for another 12 h to make sure that the epoxidation was complete. It was then extracted with deionized water (3 x 0.5 mL). To the combined aqueous portion, saturated aqueous $NaHCO_3$ (0.010 mL) was added to prevent the hydrolysis of the epoxy alcohol **8** and the mixture was extracted with toluene (3 x 1.0 mL) to remove residual cumene hydroperoxide and 2-phenyl-2-propanol. All the above extractions were performed by utilizing the vortex mixer to achieve efficient mixing and at 0 °C to prevent the hydrolysis of epoxy alcohol **8**. To the aqueous portion, fresh distilled anhydrous THF (5 mL) was added and concentrated under reduced pressure with rotary evaporator at room temperature. To the concentrate (~2 mL), additional THF (5 mL) was added and solvent was removed under the same conditions. This process was repeated for 8 times and all the solvent was removed at the final time to provide the product as colorless liquid, which contained a mixture of epoxy alcohol **8** and THF (mole ratio was determined by ^1H NMR). GC analysis: distribution of the product was above 97% epoxy alcohol **8**. Detailed information of determining the ee values of epoxy alcohol **8** was provided in Table 3-b.

Table 2: Enantioselective Epoxidation of Small Allylic Alcohols.



7a-e 8a-e

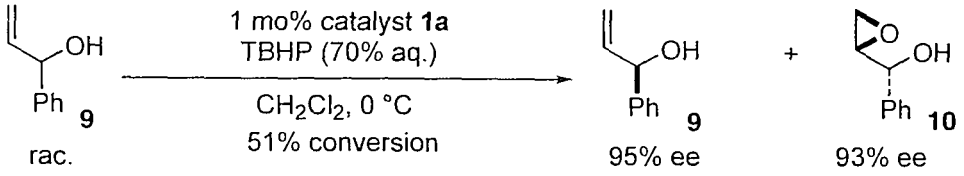
entry[a]	epoxy alcohol	ligand		temp, time	yield[b] (%)	ee[c], config.[d] (%)
1[e]		**8a**	**1a***	0 °C, 12 h ~rt, 12 h	78	97, (*R*)
2[e, f]			**1a***	0 °C, 24 h ~ rt, 24 h	70	96, (*R*)
3		**8b**	**1a**	0 °C, 12 h ~rt, 12 h	50	93, (*2R, 3R*)
4		**8c**	**1b**	0 °C, 12 h ~rt, 12 h	71	92, (*2R, 3S*)
5		**8d**	**1a**	0 °C, 12 h ~rt, 12 h	68	95, (*2R, 3R*)
6[e]		**8e**	**1a***	0 °C, 12 h ~rt, 12 h	73	94, (*S*)

[a] All reactions were carried out in dichloromethane in the presence of 1.5 equiv of cumene hydroperoxide (CHP) (88%) unless otherwise indicated. [b] See experimental procedure. [c] Ee values were determined by chiral GC and the detailed information was provided in (Table 3-b). [d] Determined by comparison of reported optical rotation. [e] Toluene was used as solvent. [f] 0.5 mol% $VO(O\text{-}i\text{-}Pr)_3$ and 0.6 mol% ligand was used.

Procedure for kinetic resolution of secondary allylic alcohols in the presence of $VO(OPr^i)_3$ and ligand 1a.

To a solution of **1a** (0.0420 mmol) in dichloromethane (1 mL) was added $VO(OPr^i)_3$ (0.0050 mL, 0.0208 mmol), and the mixture was stirred for 1 h at room temperature. The resulting solution was cooled to 0 °C, and then 70% aqueous *tert*-butylhydroperoxide (TBHP) (0.44 mL, 3.18 mmol) and secondary allylic alcohol **9** (2.10 mmol) were added and stirring was continued at the same temperature for 12 d. [The process of conversion was monitored by HPLC: saturated aqueous Na_2SO_3 was added to a small portion of reaction mixture (0.05 mL), and the mixture was stirred for 30 min at 0 °C. The mixture was then allowed to warm to room temperature, extracted with Et_2O, dried over Na_2SO_4 and concentrated under reduced pressure. Detailed information of determining the conversion and ee values of the secondary allylic alcohol **9** and the epoxy alcohol **10** was provided in Table 3-c.] Saturated aqueous Na_2SO_3 was added when the conversion was over 51%, and the mixture was stirred for 1 h at

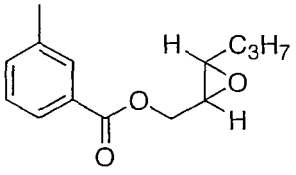
0 °C. The mixture was then allowed to warm to room temperature, extracted with Et_2O, dried over Na_2SO_4 and concentrated under reduced pressure. The remaining residue was purified by flash column chromatography on silica gel to provide the secondary allylic alcohol **9** and the epoxy alcohol **10**. Ee values of **9** and **10** were determined by HPLC.



(1)

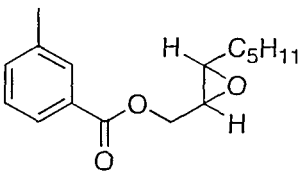
General procedure for preparation of the 3-methylbenzoate derivatives.

To a stirred solution of epoxy alcohol (0.5 mmol) in CH_2Cl_2 (2 mL) was added Et_3N (0.1 mL, 0.6 mmol) followed by *m*-Toluoyl chloride (0.066 mL, 0.5 mmol). The resulting mixture was stirred for 2 h and then concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel to provide the ester.



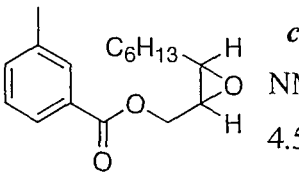
11 d

***trans*-3-Methyl-benzoic acid 3-propyloxiranylmethyl ester 11d:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88-7.85 (m, 2 H), 7.38-7.30 (m, 2 H), 4.59 (dd, *J* = 12.2, 3.3 Hz, 1 H), 4.17 (dd, *J* = 12.2, 6.2 Hz, 1 H), 3.11-3.08 (m, 1 H), 2.95-2.91 (m, 1 H), 2.40 (s, 3 H), 1.61-1.44 (m, 4 H), 0.97 (t, *J* = 7.3 Hz, 3 H).



11 e

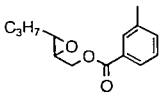
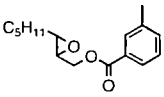
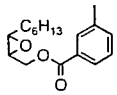
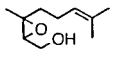
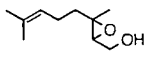
***trans*-3-Methyl-benzoic acid 3-pentyloxiranylmethyl ester 11e:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89-7.86 (m, 2 H), 7.40-7.32 (m, 2 H), 4.60 (dd, *J* = 12.2, 3.3 Hz, 1 H), 4.18 (dd, *J* = 12.1, 6.2 Hz, 1 H), 3.12-3.09 (m, 1 H), 2.95-2.92 (m, 1 H), 2.41 (s, 3 H), 1.63-1.58 (m, 2 H), 1.52-1.42 (m, 2 H), 1.37-1.31 (m, 4 H), 0.90 (t, *J* = 7.0 Hz, 3 H).



11 h

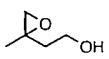
***cis*-3-Methyl-benzoic acid 3-hexyloxiranylmethyl ester 11h:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90-7.88 (m, 2 H), 7.40-7.33 (m, 2 H), 4.58 (dd, *J* = 12.1, 4.3 Hz, 1 H), 4.29 (dd, *J* = 12.1, 7.0 Hz, 1 H), 3.35-3.31 (m, 1 H), 3.10-3.06 (m, 1 H), 2.42 (s, 3 H), 1.65-1.30 (m, 10 H), 0.90 (t, *J* = 6.9 Hz, 3 H).

Table 3-a. **Conditions for Determination of Enantiomeric Excess of Epoxy Alcohols**

entry	substrate	Ee determined on		method	conditions	retention time	config.
1	**5a**	**6a**		chiral HPLC	OD-H, 95:5 H/*i*-P[a] 1 mL/min, 210 nm	12.9 min (major) 11.3 min (minor)	(2*R*,3*R*)
2	**5b**	**6b**		chiral HPLC	OD-H, 95:5 H/*i*-P[a] 0.4 mL/min, 210 nm	30.4 min (major) 23.8 min (minor)	(2*R*,3*R*)
3	**5c**	**6c**		chiral HPLC	OD-H, 90:10 H/*i*-P[a] 0.5 mL/min, 210 nm	22.7 min (major) 20.9 min (minor)	(2*R*,3*R*)
4	**5d**	**11d**		chiral HPLC	OB-H, 98:2 H/*i*-P[a] 0.5 mL/min, 230 nm	23.2 min (major) 26.7 min (minor)	(2*R*,3*R*)
5	**5e**	**11e**		chiral HPLC	OB-H, 99.8:0.2 H/*i*-P[a] 1 mL/min, 230 nm	22.0 min (major) 19.4 min (minor)	(2*R*,3*R*)
6	**5f**	**6f**		chiral HPLC	OD-H, 98:2 H/*i*-P[a] 1 mL/min, 210 nm	25.7 min (major) 20.1 min (minor)	(2*R*)
7	**5g**	**6g**		chiral GC	β-TA, 100 kpa 80 °C (C)[b]; 100 °C (I)[c]	23.8 min (major) 20.2 min (minor)	(2*R*,3*R*)
8	**5h**	**11h**		chiral HPLC	OB-H, 99.8:0.2 H/*i*-P[a] 1 mL/min, 230 nm	25.0 min (major) 13.7 min (minor)	(2*R*,3*S*)
9	**5i**	**6i**		chiral HPLC	OD-H, 90:10 H/*i*-P[a] 0.5 mL/min, 210 nm	17.9 min (major) 21.6 min (minor)	(2*R*,3*S*)
10	**5j**	**6j**		chiral HPLC	OD-H, 95:5 H/*i*-P[a] 0.4 mL/min, 210 nm	36.2 min (major) 41.1 min (minor)	(2*R*,3*R*)
11	**5k**	**6k**		chiral GC	β-TA, 100 kpa 90 °C (C)[b]; 110 °C (I)[c]	42.9 min (major) 50.6 min (minor)	(2*R*,3*S*)
12	**5l**	**6l**		chiral GC	β-TA, 85 kpa 90 °C (C)[b]; 110 °C (I)[c]	58.2 min (major) 62.5 min (minor)	(2*R*,3*R*)

[a] H/*i*-P : Hexane/2-propanol. [b] (C) : column. [c] (I) : injection.

Table 3-b. **Conditions for Determination of Enantiomeric Excess of Small Epoxy Alcohols**

entry	substrate	Ee determined on		method	conditions	retention time	config.
1	**7a**	**8a**		chiral GC	β-TA, 100 kpa 70 °C (C)[b]; 100 °C (I)[c]	6.3 min (major) 5.6 min (minor)	(2*R*)
2	**7b**	**8b**		chiral GC	β-TA, 100 kpa 70 °C (C)[b]; 100 °C (I)[c]	4.6 min (major) 5.3 min (minor)	(2*R*,3*R*)
3	**7c**	**8c**		chiral GC	β-TA, 100 kpa 70 °C (C)[b]; 100 °C (I)[c]	13.2 min (major) 10.2 min (minor)	(2*R*,3*S*)
4	**7d**	**8d**		chiral GC	β-TA, 100 kpa 70 °C (C)[b]; 100 °C (I)[c]	10.5 min (major) 7.0 min (minor)	(2*R*,3*R*)
5	**7e**	**8e**		chiral GC	β-TA, 100 kpa 70 °C (C)[b]; 100 °C (I)[c]	12.1 min (major) 14.0 min (minor)	(2*S*)

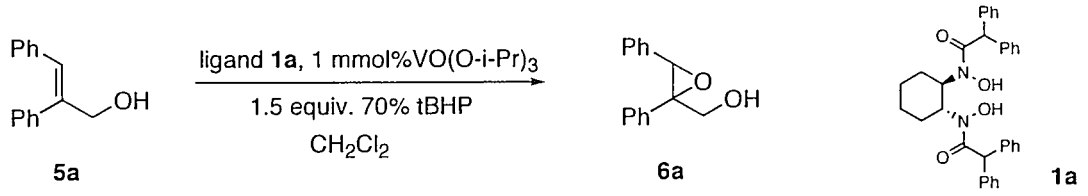
[a] H/*i*-P : Hexane/2-propanol. [b] (C) : column. [c] (I) : injection.

Table 3-c. **Conditions for Determination of Enantiomeric Excess of 9 and 10.**

entry	substrate	Ee determined on		method	conditions	retention time	config.
1	**9**			chiral HPLC	OD-H, 95:5 H/*i*-P[a] 1 mL/min, 210 nm	8.6 min (major) 10.5 min (minor)	(*R*)
		10		chiral HPLC	OD-H, 95:5 H/*i*-P[a] 1 mL/min, 210 nm	15.7 min (major) 13.9 min (minor)	

[a] H/*i*-P : Hexane/2-propanol.

Table 4. Differentiation of Yields and Ee values with the Increase of the Ratio of Ligand to Vanadium



Ligand:VO(O-i-Pr)$_3$	Temp.	yield: 1h	4h	6h	2d	ee
1:1	-20°C	20%	54%	67%	>95%	95%
2:1	-20°C	17%	50%	62%	95%	97%
3:1	-20°C	17%	50%	61%	95%	97%

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Appendix 2

New Insights into the Classical DMAP-Catalyzed Acylation of Alcohols: Auxiliary Base- and Solvent-Free Conditions

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The acylation of alcohols is one of the most fundamental reactions in organic synthesis.[1] 4-(*N*,*N*-Dimethylamino)pyridine (DMAP, **1**) is a very effective catalyst for the esterification of alcohols with acid anhydrides[2–4] and other related reactions.[5] The classical DMAP-catalyzed acylation with acid anhydrides is generally conducted in the presence of more than one equivalent of an auxiliary base as a scavenger of the carboxylic acid. From the perspective of green chemistry, the acylation of alcohols in the presence of only a catalytic amount of DMAP would be more desirable than that with more than one equivalent of an additional base.[6] Recently, Zipse and coworkers proposed a mechanism for the DMAP-catalyzed acetylation of alcohols (Figure 1).[7] The reaction proceeds via acetylpyridinium intermediate **2a**. In the nucleophilic addition of alcohols (ROH) toward **2a**, acetate anion (AcO^-) abstracts the proton of alcohols. The reaction of **2a** with alcohols produces acetates (ROAc) and the acetate salt of DMAP **4a** via transition state **3a**. This step is thought to be the rate-determining step. In the presence of an auxiliary base such as triethylamine, DMAP **1** is effectively regenerated (**4** → **1**). Hassner and coworkers reported that in $CDCl_3$–CCl_4 without any added base, the 4-pyrrolidinopyridine (PPY)-catalyzed acetylation of *tert*-butyl alcohol was much slower than that with an auxiliary base, especially toward the completion of the reaction.[8] This is probably due to the catalyst (DMAP and PPY) being largely protonated by acetic acid in the reaction mixture.

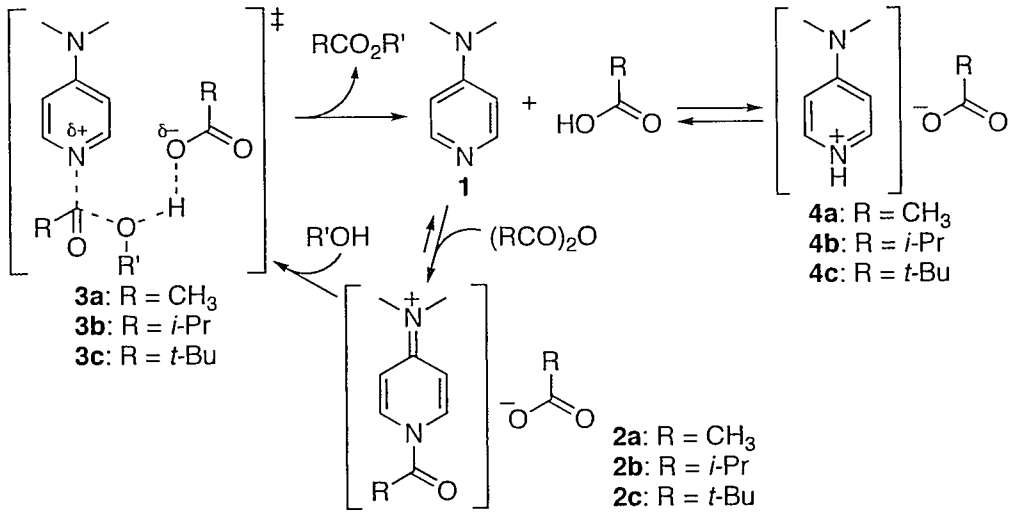


Figure 1. Proposed mechanism of the DMAP-catalyzed acylation.[7]

In principle, DMAP-catalyzed acylation should proceed even in the absence of an auxiliary base, since carboxylate anions rather than auxiliary bases deprotonate alcohols (Figure 1).[9] We considered that the solvent effect must play a key role in the effective regeneration of DMAP without an auxiliary base. We first examined the solvent effect in

the DMAP-catalyzed isobutyrylation of *l*-menthol (Figure 2). The reaction was conducted with isobutyric anhydride (1.0 equiv) in the presence of DMAP (0.1 mol %) with or without *i*-Pr_2NEt (1.0 equiv). As reported by Hassner and coworkers,[8] in the presence of *i*-Pr_2NEt (graph A), the reaction proceeded more smoothly in a less-polar solvent such as heptane (red line) than in a polar solvent such as acetonitrile (orange line) or dichloromethane (black line). Interestingly, the reaction proceeded rapidly even without solvent (green line).[10] The rate-accelerating effect of less-polar solvents was explained by the easy collapse of the charged intermediate **2b** to the ester and **1**. In contrast, polar solvents raise the reaction barrier by solvating the charged intermediate **2b**. As expected, the reactivity of DMAP-catalyzed isobutyrylation without an auxiliary base largely depended on the solvent (graph B). The reaction proceeded very rapidly in no solvent (green line) or heptane (red line) under auxiliary base-free conditions. In contrast, the reaction in acetonitrile (orange line) or dichloromethane (black line) under base-free conditions exhibited much lower reactivity than that in the presence of *i*-Pr_2NEt. The effective regeneration of free DMAP (**1**) in no solvent or less-polar solvent might result in excellent reactivities, while polar solvent caused preferential formation of the ammonium salt **4** under base-free conditions and decreased the reactivity.

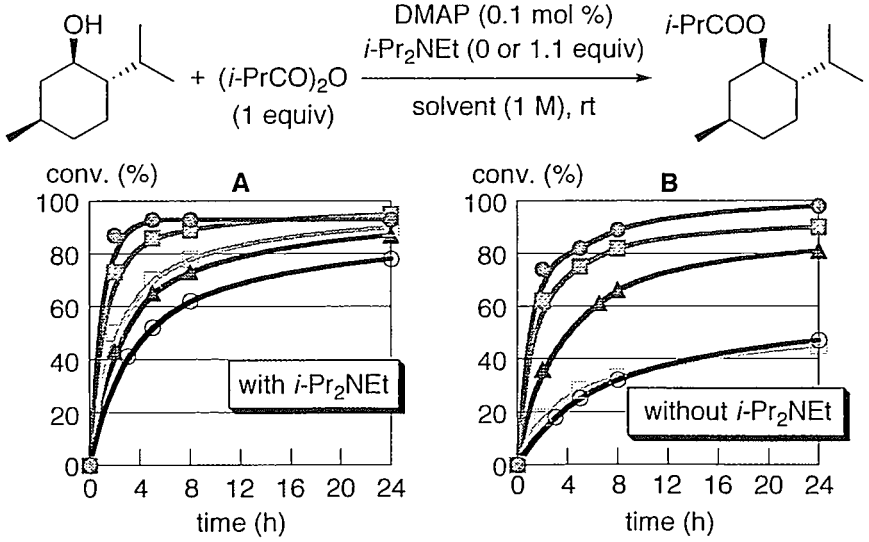


Figure 2. Solvent effect in the DMAP-catalyzed isobutyrylation of *l*-menthol. The reaction of *l*-menthol (5 mmol) was conducted with $(i\text{-PrCO})_2O$ (5 mmol) in the presence of DMAP (0.1 mol %) in solvent (5 mL). Green line, no solvent; red line, heptane; blue line, THF; orange line, CH_3CN; black line, CH_2Cl_2.

Next, the DMAP-catalyzed acetylation, isobutyrylation and pivaloylation of *l*-menthol were examined in no solvent (Figure 3). Solvent-free acetylation in the absence of an auxiliary base showed lower reactivity than that in the presence of *i*-Pr_2NEt (graph C). The high reactivity of DMAP-catalyzed acetylation under solvent-free conditions should be primarily attributed to the effective promotion by *i*-Pr_2NEt. The use of heptane as solvent efficiently promoted the acetylation under the base-free conditions.[11] The reactivity of isobutyrylation was almost independent of the presence of *i*-Pr_2NEt (graph D). Interestingly, pivaloylation under base- and solvent-free conditions gave better results than with *i*-Pr_2NEt (graph E). Since pivalic acid (pK_a 5.03) is a weaker acid than acetic acid (pK_a 4.76), free DMAP (**1**) would regenerate more efficiently in pivaloylation than in acetylation under base-free conditions. Furthermore, *i*-Pr_2NEt decelerated pivaloylation in no solvent, probably due to the generated salt of *i*-Pr_2NEt and pivalic acid, which served as a polar solvent. More basic pivalate anion acted as a base to efficiently promote pivaloylation under base-free conditions. On the other hand, less-basic acetate anion did not work as a very efficient base, and the reactivity of acetylation largely depended on auxiliary bases.

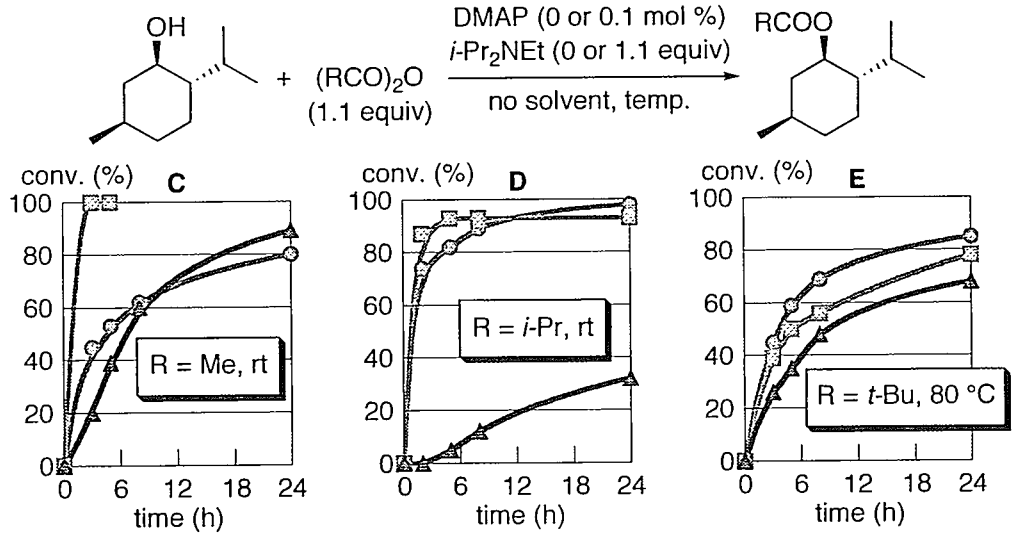


Figure 3. Effect of auxiliary base on the DMAP-catalyzed acetylation, isobutyrylation and pivaloylation of *l*-menthol. Green line, DMAP (0.1 mol %) without *i*-Pr_2NEt; red line, DMAP (0.1 mol %) and *i*-Pr_2NEt (1.1 equiv); blue line, *i*-Pr_2NEt (1.1 equiv) without DMAP.

To explore the generality and scope of DMAP-catalyzed acylation under base- and solvent-free conditions, the reaction was examined with various alcohols (Table 1). Acylations of not only primary alcohols but also secondary alcohols proceeded well (entries

1–11). The present protocol could be easily applied to a large-scale process, and the reaction of *l*-menthol (100 mmol) with isobutyric anhydride (1.1 equiv) catalyzed by DMAP (0.05 mol %) gave the corresponding ester in quantitative yield (entry 9). Acetylation of a,a-dimethylbenzyl alcohol gave a-methylstyrene as an elimination byproduct in no solvent (entry 11).[6a,6b] Interestingly, when the reaction was conducted in heptane, the acetylation product was obtained in 88% yield along with no elimination byproduct (entry 12). The lower polarity of heptane might suppress the formation of the tertiary carbocation. The isobutyrylation of a,a-dimethylbenzyl alcohol under solvent-free conditions gave the product in good yield (entry 13). The acylations of aromatic alcohols also proceeded smoothly under base- and solvent-free conditions (entries 14–16).

Table 1. DMAP-catalyzed acylation of alcohols with acid anhydrides[a]

$$R^1OH + (R^2CO)_2O \xrightarrow[\text{no solvent}]{\text{DMAP (0.5 mol \%)}} R^1OCOR^2$$
(1.1 equiv)

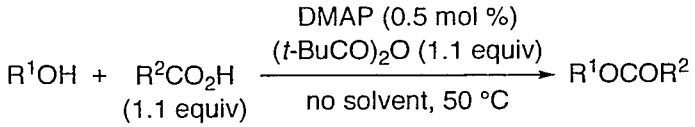
entry	R^1OH	$(R^2CO)_2O$	conditions (°C, h)	yield[b] (%)
1	$Ph(CH_2)_3OH$	Ac_2O	rt, 6	94
2	$Ph(CH_2)_3OH$	$(i\text{-PrCO})_2O$	rt, 2	93
3	$Ph(CH_2)_3OH$	$(t\text{-BuCO})_2O$	100, 3	96 (95)[c]
4[d]	$PhCH(OH)CH_3$	Ac_2O	rt, 9	90
5[d]	$PhCH(OH)CH_3$	$(i\text{-PrCO})_2O$	rt, 5	99
6	$PhCH(OH)CH_3$	$(t\text{-BuCO})_2O$	100, 5	92 (89)[c]
7	*l*-menthol	Ac_2O	rt, 9	84
8	*l*-menthol	$(i\text{-PrCO})_2O$	rt, 5	93
9[e]	*l*-menthol	$(i\text{-PrCO})_2O$	50, 19	100[f]
10	*l*-menthol	$(t\text{-BuCO})_2O$	100, 8	90
11[g]	$PhC(OH)(CH_3)_2$	Ac_2O	100, 24	0 (53)[i]
12[g,h]	$PhC(OH)(CH_3)_2$	Ac_2O	reflux, 24	88 (0)[i]
13[g]	$PhC(OH)(CH_3)_2$	$(i\text{-PrCO})_2O$	100, 24	88
14	$2,4,6\text{-}(CH_3)_3C_6H_2OH$	Ac_2O	rt, 24	88
15	$2,4,6\text{-}(CH_3)_3C_6H_2OH$	$(i\text{-PrCO})_2O$	rt, 24	91
16	$4\text{-}(CH_3O)C_6H_4OH$	$(i\text{-PrCO})_2O$	rt, 2	96

[a] Unless otherwise noted, the reaction of alcohol (5 mmol) and acid anhydride (5.5 mmol) was conducted with DMAP (0.5 mol %) at rt. [b] Isolated yield. [c] The reaction was conducted with *i*-Pr_2NEt (1.1 equiv). [d] 1.3 equiv of acid anhydride were used. [e] The reaction of *l*-menthol (100 mmol) and isobutyric anhydride (110 mmol) was conducted with DMAP (0.05 mol %) at 50 °C. [f] Established by ^1H NMR analysis. [g] 5 mol % of

DMAP was used. [h] The reaction was conducted in heptane (1 M). [i] Isolated yield of a-methylstyrene.

We examined esterification between alcohols and carboxylic acids using pivalic anhydride under base- and solvent-free conditions (Table 2).[6a,6b,12] The reaction was thought to proceed via the corresponding mixed anhydrides. Since the counter anion of the acylpyridinium intermediate was pivalate, the reaction should proceed well even under base- and solvent-free conditions. As expected, in the presence of pivalic anhydride (1.1 equiv) and DMAP (0.5 mol %), the reaction proceeded smoothly under base- and solvent-free conditions, and the corresponding esters were obtained in high yield (entries 1–3). Esterification of *N*-Boc-phenylalanine with 1-octanol gave the corresponding ester in 92% yield with complete retention of its chiral center (entry 4).

Table 2. DMAP-catalyzed esterification of alcohols and carboxylic acids in the absence of base[a]



entry	R^1OH	R^2CO_2H	time (h)	yield[b] (%)
1	$Ph(CH_2)_3OH$	$Ph(CH_2)_2CO_2H$	24	80
2	*l*-menthol	$Ph(CH_2)_2CO_2H$	24	90
3	*l*-menthol	*c*-$C_6H_{11}CO_2H$	15	92
4	*n*-$C_{18}H_{37}OH$	Boc-L-Phe-OH	24	92 (>99)[c]

[a] The reaction of alcohol (1 mmol) and carboxylic acid (1.1 mmol) was conducted with DMAP (0.5 mol%) and pivalic anhydride (1.1 mmol) at 50 °C. [b] Isolated yield. [c] Optical purity (% ee) of the product.

In conclusion, we have demonstrated that only 0.05–0.5 mol % of DMAP was needed to efficiently catalyze acylation of alcohols with acid anhydrides (1.0–1.3 equiv) under auxiliary base- and solvent-free conditions. Especially, pivaloylation proceeded more smoothly than that with *i*-Pr_2NEt. Recover and reuse of commercially available polystyrene-supported DMAP was also achieved without any loss of catalytic activity.[11]

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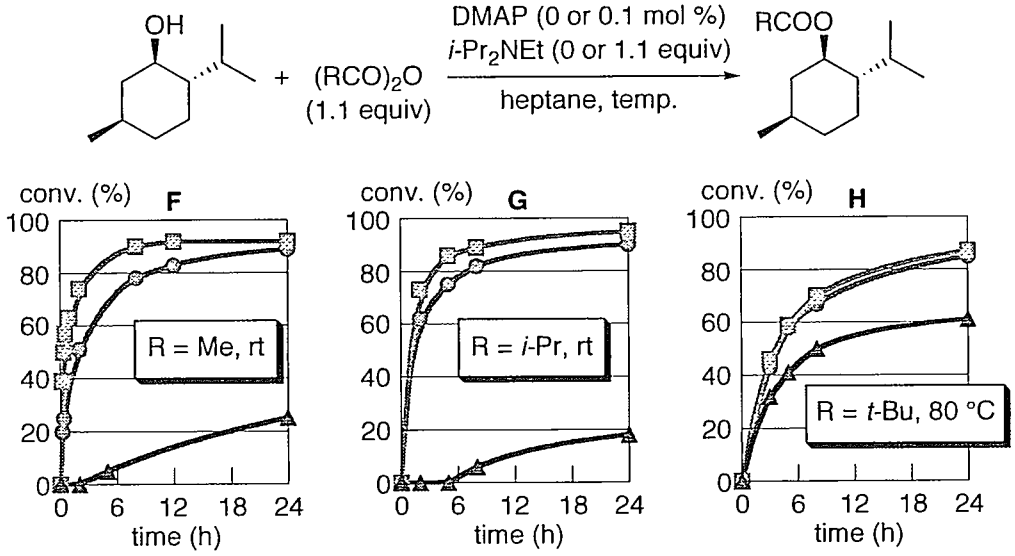
General Method. IR spectra were recorded on a JASCO FT/IR-460 plus spectrometer. ^1H spectra were measured on a Varian Gemini-2000 spectrometer (300 MHz) at ambient temperature. Data were recorded as follows: chemical shift in ppm from internal tetramethysilane on the δ scale, multiplicity (s = singlet; d = doublet; t = triplet; m = multiplet), coupling constant (Hz), and integration. ^{13}C NMR spectra were measured on a Varian Gemini-2000 spectrometer (75 MHz) at ambient temperature. Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard ($CDCl_3$ at 77.0 ppm). All experiments were carried out under an atmosphere of dry nitrogen. For TLC analysis, Merck precoated TLC plates (silica gel 60 F_{254} 0.25 mm) were used. For preparative column chromatography, Merck silica gel 60 (0.040–0.063 mm) was used. Chemical materials were obtained from commercial supplies and used without further purification. All products in the present work are known compounds as shown below.

Effect of Auxiliary Base on the DMAP-Catalyzed Acetylation, Isobutyrylation and Pivaloylation of *l*-Menthol in Heptane. Green line, DMAP (0.1 mol %) without *i*-Pr_2NEt; red line, DMAP (0.1 mol %) and *i*-Pr_2NEt (1.1 equiv); blue line, *i*-Pr_2NEt (1.1 equiv) without DMAP.



Typical Procedure for Acylation of Alcohols with Acid Anhydrides (Table 1, entry 8). To a mixture of *l*-menthol (781 mg, 5.0 mmol) and DMAP (**1**) (3.1 mg, 0.025 mmol) was added isobutyric anhydride (912 mL, 5.5 mmol) at ambient temperature. After being stirred at ambient temperature for 5 h, the reaction mixture was diluted with EtOAc, washed with 1 M HCl and brine successively, dried with Na_2SO_4, and concentrated. The residue was

purified by column chromatography on silica gel eluted with a mixture of hexane and ethyl acetate, to give (1*R*,2*S*,5*R*)-5-methyl-2-(1-methylethyl)cyclohexyl 2-methylpropanoate (1.05 g, 93% yield).

3-Phenylpropyl acetate (Table 1, entry 1):[1,2] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.90–2.01 (m, 2H), 2.05 (s, 3H), 2.69 (t, *J* = 7.4 Hz, 2H), 4.09 (t, *J* = 6.5 Hz, 2H), 7.11–7.33 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0, 30.1, 32.1, 63.8, 126.0, 128.4, 128.4, 141.2, 171.2.

3-Phenylpropyl 2-methylpropanoate (Table 1, entry 2):[1,3] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (d, *J* = 7.0 Hz, 6H), 1.90–2.02 (m, 2H), 2.55 (septet, *J* = 7.0 Hz, 1H), 2.69 (t, *J* = 7.8 Hz, 2H), 4.09 (t, J = 6.5 Hz, 2H), 7.11–7.34 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.0, 30.2, 32.1, 34.5, 63.5, 126.0, 128.4, 128.4, 141.2, 177.2.

3-Phenylpropyl 2,2-dimethylpropanoate (Table 1, entry 3):[1,3] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (s, 9H), 1.97–2.03 (m, 2H), 2.74 (t, *J* = 7.6 Hz, 2H), 4.12 (t, J = 6.3 Hz, 2H), 7.21–7.34 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.2, 30.3, 32.1, 38.7, 63.5, 126.0, 128.4, 128.4, 141.2, 178.5.

1-Phenyethyl acetate (Table 1, entry 4):[1,4] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.53 (d, *J* = 6.6 Hz, 3H), 2.07 (s, 3H), 5.88 (q, *J* = 6.6 Hz, 1H), 7.26–7.41 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4, 22.2, 72.3, 126.1, 127.8, 128.5, 141.6, 170.3.

1-Phenyethyl 2-methylpropanoate (Table 1, entry 5):[5] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16 (d, *J* = 7.0 Hz, 6H), 1.52 (d, *J* = 6.6 Hz, 3H), 2.56 (septet, *J* = 6.9 Hz, 1H), 5.87 (q, *J* = 6.6 Hz, 1H), 7.22–7.36 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.9, 22.3, 34.1, 71.9, 125.9, 127.7, 128.4, 141.9, 176.3.

1-Phenyethyl 2,2-dimethylpropanoate (Table 1, entry 5):[6] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (s, 9H), 1.51 (d, *J* = 6.6 Hz, 3H), 5.87 (q, *J* = 6.6 Hz, 1H), 7.30–7.39 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.3, 27.0, 38.6, 71.0, 125.7, 127.5, 128.3, 177.5.

(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methylethyl)cyclohexyl acetate (Table 1, entry 7):[1,7] ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.76 (d, *J* = 7.0 Hz, 3H), 0.89 (d, *J* = 7.0 Hz, 3H), 0.90 (d, *J* = 6.6 Hz, 3H), 0.84–1.14 (m, 3H), 1.30–1.60 (m, 2H), 1.79–1.93 (m, 2H), 1.93–2.04 (m, 2H), 2.03 (s,

3H), 4.67 (dt, J = 4.4, 10.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.3, 20.7, 21.3, 22.0, 23.4, 26.3, 31.3, 34.2, 40.9, 47.0, 74.1, 170.7.

(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methylethyl)cyclohexyl 2-methylpropanoate (Table 1, entries 8 and 9):[1,8] ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.75 (d, J = 6.9 Hz, 3H), 0.89 (d, J = 7.1 Hz, 3H), 0.90 (d, J = 6.4 Hz, 3H), 0.81–1.10 (m, 3H), 1.15 (d, J = 6.9 Hz, 3H), 1.16 (d, J = 6.9 Hz, 3H), 1.32–1.59 (m, 2H), 1.62–1.74 (m, 2H), 1.82–2.02 (m, 2H), 2.51 (septet, J = 6.9 Hz, 1H), 4.65 (dt, J = 4.4, 10.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.1, 19.0, 20.8, 22.0, 23.3, 26.1, 31.3, 34.2, 40.4, 47.0, 73.7, 176.7.

(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methylethyl)cyclohexyl 2,2-dimethylpropanoate (Table 1, entry 10):[1,9] ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.75 (d, J = 7.0 Hz, 3H), 0.80–1.11 (m, 3H), 0.89 (d, J = 6.8 Hz, 3H), 0.90 (d, J = 6.8 Hz, 3H), 1.19 (s, 9H), 1.30–1.44 (m, 1H), 1.44–1.56 (m, 1H), 1.62–1.72 (m, 2H), 1.82–2.00 (m, 2H), 4.62 (dt, J = 4.4, 10.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.0, 20.8, 22.0, 23.2, 26.1, 27.1, 31.3, 34.3, 38.7, 40.7, 47.0, 73.7, 178.0.

a,a-Dimethylbenzyl acetate (Table 1, entries 11 and 12):[1,10] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.77 (s, 6H), 2.04 (s, 3H), 7.20–7.40 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.3, 28.6, 81.4, 124.2, 126.9, 128.2, 145.8, 169.7.

a,a-Dimethylbenzyl 2-methylpropanoate (Table 1, entry 13):[11] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (d, J = 6.9 Hz, 6H), 1.76 (s, 6H), 2.53 (septet, J = 6.9 Hz, 1H), 7.20–7.38 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.9, 28.5, 34.7, 80.9, 124.1, 126.8, 128.2, 146.0, 175.6.

2,4,6-Trimethylphenyl acetate (Table 1, entry 14):[12] ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.15 (s, 6H), 2.30 (s, 3H), 2.36 (s, 3H), 6.91 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.7, 21.0, 21.3, 129.7, 130.1, 135.8, 146.4, 169.6.

2,4,6-Trimethylphenyl 2-methylpropanoate (Table 1, entry 15):[13] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (d, J = 6.9 Hz, 6H), 2.09 (s, 6H), 2.26 (s, 3H), 2.86 (septet, J = 6.9 Hz, 1H), 6.86 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.1, 19.1, 20.7, 34.2, 129.1, 129.6, 135.0, 145.7, 174.8.

***p*-Methoxyphenyl acetate** (Table 1, entry 16):[14] ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.26 (s,

3H), 3.77 (s, 3H), 6.87 (d, J = 9.0 Hz, 2H), 6.99 (d, J = 9.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0, 55.5, 114.4, 122.3, 144.1, 157.2, 169.9.

Typical Procedure for Esterification between Alcohols and Carboxylic Acids (Table 2, entry 2). To a mixture of *l*-menthol (156 mg, 1.0 mmol), 3-phenylpropionic acid (165 mg, 1.1 mmol) and DMAP (**1**) (6.1 mg, 0.005 mmol) was added pivalic anhydride (223 mL, 1.1 mmol) at ambient temperature. After being stirred at 50 °C for 24 h, the reaction mixture was diluted with EtOAc, washed with 1 M HCl and brine successively, dried with Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel eluted with a mixture of hexane and ethyl acetate, to give (1*R*,2*S*,5*R*)-5-methyl-2-(1-methylethyl)cyclohexyl 3-phenylpropanoate (259 mg, 90% yield).

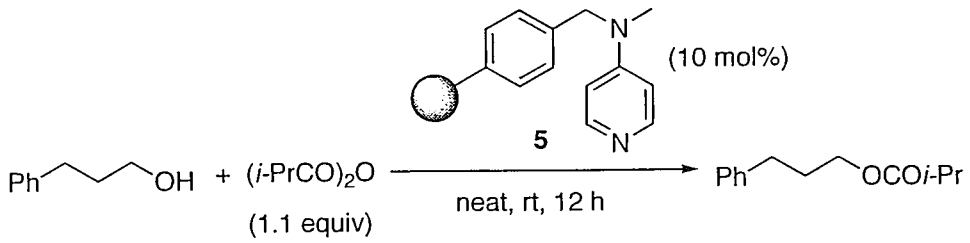
3-Phenylpropyl 3-phenylpropionate (Table 2, entry 1):[3] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.91 (m, 2H), 2.62 (m, 4H), 2.95 (t, J = 7.8 Hz, 2H), 4.08 (t, J = 6.6 Hz, 2H), 7.13–7.31 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.9, 30.0, 32.0, 35.8, 63.7, 125.9, 126.2, 128.2, 128.3, 128.3, 128.4, 140.4, 141.0, 172.9.

(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methylethyl)cyclohexyl 3-phenylpropionate (Table 2, entry 2):[15] ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.62 (d, J = 6.9 Hz, 3H), 0.68–1.75 (m, 14H), 1.78–1.93 (m, 1H), 2.53 (t, J = 7.8 Hz, 2H), 2.87 (t, J = 7.8 Hz, 2H), 4.59 (dt, J = 4.6, 10.9 Hz, 1H), 7.05–7.26 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.2, 20.7, 22.0, 23.3, 26.0, 31.0, 31.3, 34.1, 36.1, 40.8, 46.9, 74.1, 126.1, 128.2, 128.3, 140.4, 172.4.

(1*R*,2*S*,5*R*)-5-Methyl-2-(1-methylethyl)cyclohexyl cyclohexanecarboxylate (Table 3, entry 3):[16] ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.74 (d, J = 7.0 Hz, 3H), 0.80–2.00 (m, 19H), 0.89 (d, J = 7.0 Hz, 3H), 0.90 (d, J = 6.4 Hz, 3H), 2.26 (tt, J = 3.7, 11.0 Hz, 1H), 4.65 (tt, J = 4.2, 10.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.1, 22.0, 23.3, 24.2, 25.4, 25.5, 25.8, 26.1, 29.0, 29.1, 31.3, 34.3, 40.9, 43.5, 47.1, 73.5, 175.7.

(Boc-Phe-O-*n*-C_8H_{17}) (Table 3, entries 4 and 5):[17] ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, J = 6.9 Hz, 3H), 1.18–1.46 (m, 10H), 1.42 (s, 9H), 1.51–1.65 (m, 2H), 3.01–3.16 (m, 2H), 4.08 (t, J = 6.9 Hz, 2H), 4.57 (q, J = 8.4 Hz, 1H), 4.98 (br d, , J = 8.7 Hz, 1H), 7.10–7.33 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 22.6, 25.8, 27.0, 28.2, 28.4, 29.1, 31.7, 38.4, 54.4, 65.5, 79.8, 126.9, 128.4, 129.3, 136.0, 155.0, 171.2.

Isobutyrylation of 3-Phenyl-1-propanol Using Polystyrene-Supported DMAP as a Recyclable Catalyst. The reaction of 3-phenyl-1-propanol (5 mmol) and acid anhydride (5.5 mmol) was conducted with polystyrene-supported DMAP **5** (10 mol %) at rt for 12 h.



run	0	1	2	3	4	5
yield (%)	100	100	100	100	100	100

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Pulication List

1. Rational Design of an L-Histidine-Derived Minimal Artificial Acylase for the Kinetic Resolution of Racemic Alcohols
   Kazuaki Ishihara, Yuji Kosugi, Matsujiro Akakura
   J. Am. Chem. Soc. **2004**, *126*, 12212-12213

2. Design of Small Molecular Artificial Enzyme using Histidine frame
   Yuji Kosugi, Kazuaki Ishihara
   Kagaku **2005**, *60*, 72-73.

3. Enantioselective Epoxidation of Allylic Alcohols by a Chiral Complex of Vanadium: An Effective Controller System and a Rational Mechanistic Model
   Wei Zhang, Arindrajit Basak, Yuji Kosugi, Yujiro Hoshino, Hisashi Yamamoto
   Angew. Chem. Int. Ed. **2005**, *44*, 4389-4391

4. Kinetic Resolution of Racemic Alcohols Catalyzed by Minimal Artificial Acylases Derived from L-Histidine
   Yuji Kosugi, Matsujiro Akakura, Kazuaki Ishihara
   Tetrahedron in press.

5. New Insights into the Classical DMAP-Catalyzed Acylation of Alcohols: Auxiliary Base- and Solvent-Free Conditions
   Akira Sakakura, Kimio Kawajiri, Yuji Kosugi and Kazuaki Ishihara
   J. Am. Chem. Soc. to be submitted.

6. Kinetic Resolution of Racemic Carboxylic Acids Catalyzed by an L-Histidine-derived Minimal Artificial Acylase
   Kazuaki Ishihara, Yuji Kosugi
   In preparation

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