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Kinetic Resolution of Racemic Alcohols Using Thioamide Modified 1-Methyl-histidine Methyl Ester

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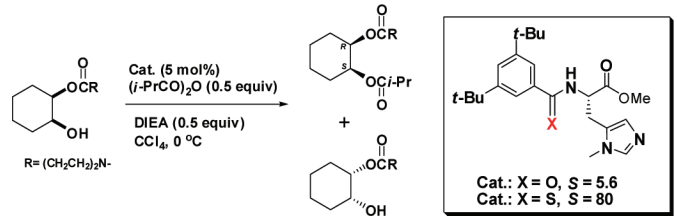
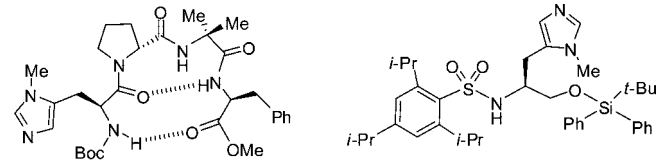


The low-molecular-weight and easily prepared *N*-thiobenzoyl 1-methyl-histidine methyl ester **3k** was utilized to efficiently catalyze the kinetic resolution of racemic secondary alcohols. Comparison of the conformations of amide catalyst **3c** and thioamide catalyst **3k** was made to understand the origin of the improvement of the enantioselectivity by thioamide modification.

Introduction

Owing to the great efforts of organic chemists, currently there are numerous chiral structures one may choose to use in enantioselective chemical reactions. Among them, some chiral molecules producing excellent asymmetric induction can be easily prepared from commercially available and inexpensive starting materials. These catalysts are practical for users who wish to prepare them in their own laboratories. Two typical examples are TADDOLs[1] (a group of versatile chiral auxiliaries) and fructose-derived ketone[2] (Shi epoxidation catalyst) that can be readily synthesized via simple two-step transformations from tartrate and fructose, respectively. Because of the good accessibility, they are among the most frequently used chiral inductive materials in organic chemistry laboratories. Our laboratory's long-term goal is to discover more such user-friendly chiral molecules and use them in enantioselective organocatalytic reactions.



1 2

FIGURE 1. Miller's *N*-methyl-histidine based β-hairpin-like tetrapeptide catalyst **1** and Ishihara's histidinol-derived catalyst **2**.

The catalysts that have been utilized for nonenzymatic enantioselective acylation[3] were chiral analogs of trialkylphosphine,[4] dialkylaminopyridine,[5] and recently discovered ring-fused imidazoline.[6] In particular, Miller's research group developed *N*-methyl-histidine containing oligopeptides (Figure 1) that successfully catalyze the kinetic resolution of secondary alcohols containing a hydrogen bond accepting auxiliary.[7a−h] The efficiency of this strategy was further demonstrated by Ishihara's research group. They reported that histidinol derivative **2**, containing only one chiral center, could catalyze the similar transformations with very impressive enantioselectivities.[7j,k]

In the X-ray structure of histidinol derivative **2**, the amide NH (H-bonding site) and the *N*-methyl imidazole ring (reactive

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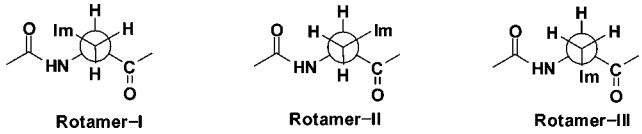


FIGURE 2. Newman projections of the three possible conformations by rotating the $C_\alpha-C_\beta$ bond of histidine derivatives: the imidazole ring and the amide NH are at the same side in rotamers **I** and **III**, whereas they are at the opposite side in rotamer **II**.

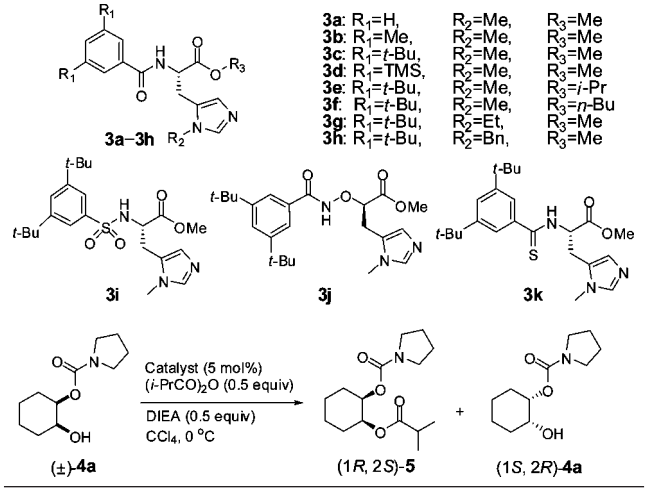
site) are at the same side and parallel to each other, which is probably forced by two very bulky groups at the N-terminal and the C-terminal.[7j,k] An analysis of the X-ray structure of **2** revealed that it adopts the conformation of rotamer **III** (Figure 2), which exhibits steric hindrance at imidazole ring site. In a series of studies about the side chain's orientation of aromatic amino acids using ^{1}H NMR spectroscopy,[8] it was found that rotamer **III** is strongly preferred for *N*-acylated histidine ester such as Ac-His-OMe in nonpolar solvent (the population of rotamer **III** is more than 50% in chloroform at room temperature). However, in polar organic solvent and aqueous solution, the less steric hindered rotamer **I** is the most stable conformation. We then questioned if an *N*-acylated histidine ester preferring the conformation of rotamer **III** might be directly used to catalyze asymmetric acylation in nonpolar solvents. In this paper, we wish to report our attempts to use *N*-thiobenzoyl 1-methylhistidine methyl ester as catalyst for kinetic resolution of racemic secondary alcohols.

Results and Discussion

The first compound we evaluated was the simple *N*-benzoyl 1-methyl-L-histidine methyl ester **3a** (Table 1), which gave an encouraging selectivity factor ($S = 2.3$) in the kinetic resolution of (±)-**4a** using $(i\text{-PrCO})_2O$ as acylation reagent. Variations of the group at the N-terminal, C-terminal, and imidazole ring of **3a** were applied, and the resulting compounds were tested under the same condition. Compounds **3a**−**3f** were readily prepared from the commercially available 1-methyl-L-histidine via standard N-terminal acylation and C-terminal esterification in high yield. Better enantioselectivities of **3b** and **3c** were observed by increasing the steric hindrance at the 3 and 5 positions of the benzoxy ring. However, further enlargement of the *tert*-butyl group in **3c** to the trimethylsilyl group in **3d** did not cause any significant improvement in selectivity. No noticeable benefit was observed by replacing the C-terminal methyl ester with a bulkier isopropyl ester (**3e**). Changing the methyl ester with an *n*-butyl ester (**3f**) made the resulting catalyst lose its selectivity. The steric factor of the *N*-alkyl group on the imidazole ring was also examined. The *N*-ethyl catalyst **3g** gave slightly lower selectivity and the *N*-benzyl catalyst **3h** gave similar selectivity as **3c**. All of these catalysts preferred selectively acylating the 1*R*,2*S* configuration of **4a**.

According to the conclusion of the Ishihara group's experiments,[7j,k] strengthening the H-bonding interaction between the catalyst and the substrate by changing amide functionality to sulfonamide dramatically enhanced the enantioselectivity because sulfonamide amide NH is a better hydrogen bond donor. Indeed, the sulfonamide **3i** provided considerably improved selectivity. Encouraged by this result, we decided to replace amide functionality in **3c** with amide isostere which was reported to present more acidic NH in literature. Catalyst **3j** bearing an aminoxy acid amide NH, which has been proved to be a good hydrogen bond donor,[9] was tested. Unfortunately, catalyst **3j** afforded almost no selectivity, which might be due to disturbance of the conformation of the catalyst by introduction of an extra oxygen atom. Thioamide NH was also found to be a better hydrogen bond donor compared with normal amide NH (in a similar way to thiourea compared with urea)[10] and for this reason, thioamide was frequently employed as an amide surrogate to obtain stronger hydrogen bonding in bioactive

TABLE 1. Kinetic Resolution of (±)-4a by 3a−3k[a]



catalyst	conv (%)	ee (%)[b] **5a**	ee (%)[b] **4a**	S[c]
3a	48	28	27	2.3
3b	49	44	42	3.8
3c	50	54	53	5.6
3d	51	53	56	5.7
3e	53	50	58	5.1
3f	50	5	4	1.1
3g	49	44	46	3.8
3h	51	53	55	5.7
3i	49	77	73	17
3j	48	13[d]	12	1.4
3k	52	90	97	80

[a] Conditions: racemic **4a** (0.25 mmol), catalyst (5 mol %), $(i\text{PrCO})_2O$ (0.125 mmol), DIEA (0.125 mmol), and CCl_4 (2.5 mL), 0 °C. [b] HPLC analysis. [c] Calculated according to the method of ref 3a. [d] The absolute configuration was 1*S*,2*R*.

(6) For recent examples of kinetic resolution employing ring-fused imidazoline catalysts, see: (a) Birman, V. B.; Uffman, E. W.; Jiang, H.; Li, X.; Kilbane, C. J. *J. Am. Chem. Soc.* **2004**, *126*, 12226. (b) Birman, V. B.; Jiang, H. *Org. Lett.* **2005**, *7*, 3445. (c) Birman, V. B.; Li, X. *Org. Lett.* **2006**, *8*, 1351. (d) Birman, V. B.; Guo, L. *Org. Lett.* **2006**, *8*, 4859. (e) Birman, V. B.; Li, X. *Org. Lett.* **2008**, *10*, 1115.

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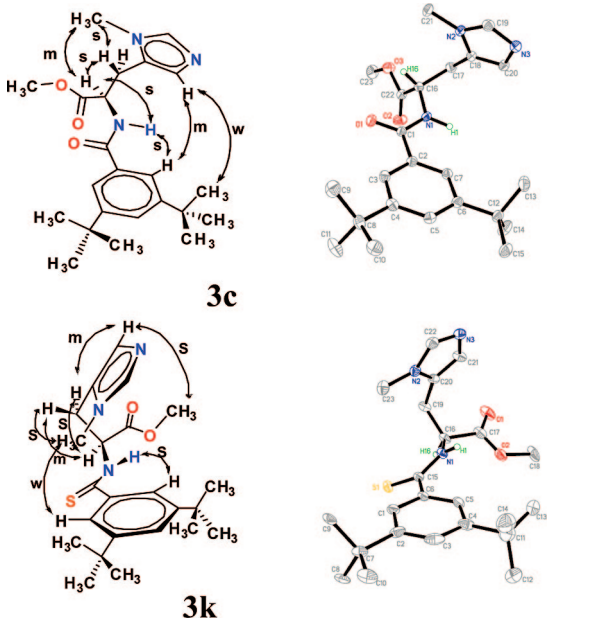


FIGURE 3. Summary of NOEs observed in the NOE difference spectroscopy of **3c** and **3k** (in the 3:1 solvent mixture of CCl_4 and $CDCl_3$, 5 mM at room temperature; s = strong NOE, m = medium NOE, w = weak NOE) and X-ray structures of **3c** and **3k**.

oligopeptides[11] and anion receptors.[12] The thioamide catalyst **3k** was prepared by selective thionation of **3c** using Lawesson's reagent.[13] There was a big improvement of the enantioselectivity when the acylation was performed using thioamide **3k** as catalyst, the enantioselectivity for recovered **4a** was 97% ee at 52% of conversion and the selectivity factor was 80.

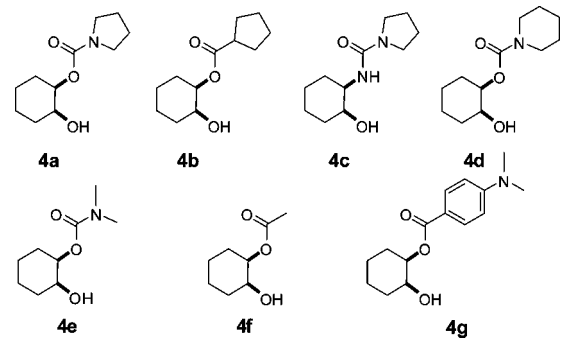
The reason for the big improvement of the selectivity for **3k** is worth considering. It was asked whether the thioamide modification only introduced a more acidic amide NH and thereby strengthened the hydrogen bond between the substrate and the catalyst or this modification caused subtle perturbation of the conformation of catalyst **3c**. The conformations of catalysts **3c** and **3k** were compared by the use of X-ray analysis and NMR spectroscopy. In the ^{1}H NMR spectrum of **3k**, the thioamide modification made the amide proton downfield-shifted to 8.1 ppm (the chemical shift of the amide NH in **3c** was 6.8 ppm), reflecting a more acidic thioamide NH. The single crystals grown in the mixture of carbon tetrachloride and *n*-hexane were subjected to X-ray analysis. NOE difference spectroscopy of **3c** and **3k** were taken using a mixed solvent of carbon tetrachloride and deuterochloroform, which was similar to the real solvent environment employed in the kinetic resolution reactions. The conformations found in solution coincided with that observed by X-ray analysis (Figure 3).

The imidazole side chain's orientation of catalyst **3c** resembles rotamer **I** rather than rotamer **III** (Figure 2) as suggested by early NMR studies,[8] probably owing to the presence of a large substituent at its N-terminal. Meanwhile, the imidazole ring is nearly perpendicular to the amide plane, although they are on the same side. However, the orientation of the imidazole side chain of catalyst **3k** resembles rotamer **III**, and the imidazole ring and the thioamide plane are parallel to each other on the same side. The relative steric positions of the imidazole ring and the amide NH are the same in **3k** and histidinol derivative **2**, though the other parts of the two molecules are rather different. It appears that the parallel relationship of the amide plane and the imidazole plane plus the rotamer **III**-like conformation are important for high enantioselective histidine-derived acylation catalysts.

The alteration of conformation by thioamide modification is possibly due to the larger van der Waals radius of sulfur. The imidazole side chain rotate 120° to adopt the conformation of rotamer **III** owing to the steric repulsion between the sulfur atom and the side chain. In the conformational studies of oligopeptides by single substitution of amide with thioamide along the peptide chain, it was found that the residues following a thioamide are more restricted because thioamide plane would be more difficult to rotate.[14] It is possible that the thioamide modification may also make **3k** more rigid than **3c**, and this was another factor that contributed to the high enantioselectivity observed for **3k**.

Subsequently, it was found that both electronic and steric factors of the auxiliary on alcohol substrates strongly influenced the selectivity of the kinetic resolution. Replacing *N*-pyrrolodinyl ring in **4a** (Table 2) with cyclopentyl ring in **4b**, both reactivity and selectivity decreased because the carbonyl oxygen atom of **4b** acts as a worse hydrogen bond acceptor and this weakens the interaction between the catalyst and the substrate. The carbonyl oxygen atom of **4c** is expected to be an even better hydrogen bond acceptor because it contains an urea type auxiliary. However, **4c** proved to be an inefficient substrate. In addition, it was found that either a slight increase (**4d**) or a slight

TABLE 2. Kinetic Resolution of Racemic 4a−4g by Catalyst 3k[a]



substrate	time (h)	conv (%)	ee of isobutyrate ester (%)[b]	ee of recovered alcohol (%)[b]	S[c]
4a	3	52	90	97	80
4b	10	48	64	60	9
4c	5	46	51	41	3
4d	4	52	65	73	11
4e	4	47	81	72	21
4f	6	58	56	78	8
4g	5	50	61	62	8

[a] Conditions: substrate alcohol (0.25 mmol), catalyst (5 mol %), $(i\text{PrCO})_2$O (0.125 mmol), DIEA (0.125 mmol), and CCl_4 (2.5 mL), 0 °C. [b] HPLC analysis. [c] Calculated according to the method of ref 3a.

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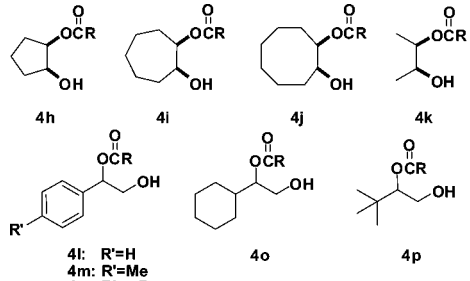
TABLE 3. Kinetic Resolution of Racemic 4h−4p (R = $(CH_2CH_2)_2N$-) by Catalyst 3k[a]



substrate	time (h)	conv (%)	ee of isobutyrate ester (%)[b]	ee of recovered alcohol (%)[b]	S[c]
4h	4	54	80 (1*R*,2*S*)	96	40
4i	4	53	84 (1*R*,2*S*)	98	65
4j	5	62	60 (1*R*,2*S*)	99.8	25
4k	2	44	86 (1*R*,2*S*)	68	28
4l	4	53	76 (*R*)	88	23
4m	3	43	83 (*R*)	63	21
4n	3	53	77 (*R*)	86	22
4o	1	53	78 (*R*)	92	32
4p	2	52	88 (*R*)	98	91

[a] Conditions: substrate alcohol (0.25 mmol), catalyst (5 mol %), $(i\text{PrCO})_2O$ (0.125 mmol), DIEA (0.125 mmol), and CCl_4 (2.5 mL), 0 °C. [b] HPLC analysis. [c] Calculated according to the method of ref 3a.

decrease (**4e**) of spacial hindrance of the auxiliary resulted in declined enantioselectivities. Employment of a simple methyl (**4f**) or *N, N*-dimethyl phenyl group (**4g**) led to lower enantioselectivities. These observations implied that the recognition site on the substrate was the carbamate auxiliary rather than the skeleton of the alcohol.

Several racemic alcohols were selected to test the asymmetric acyl transfer efficiency of catalyst **3k** (Table 3). Synthetically useful *S* values of 40 and 65 were obtained for acylation of **4h** and **4i**, though the enantioselectivities for **4h** and **4i** were even higher with histidinol derivative **2**. The ee value of the recovered alcohol **4j** was 99.8% at 62% conversion and the selectivity factor was 25. For an acylic substrate **4k**, the selectivity factor was 28. A new type of secondary alcohol (**4l**-**4p**) was resolved by **3k** in good to excellent selectivity. The best enantioselectivity was obtained for substrate **4p** (S = 91). This was the first example of effective kinetic resolution of protected secondary alcohol by acylating the adjacent primary alcohol.

In conclusion, the utilization of a thioamide as organocatalyst to catalyze asymmetric reaction has been described. The low-molecular-weight (MW = 415) and user-friendly catalyst **3k** was found to be an efficient catalyst for the kinetic resolution of monoprotected *cis*-diols and also the terminal vicinal diols. NMR and X-ray studies proved that the thioamide modification changes the conformation of the catalyst to the desired one and also that this conformation became more rigid owing to the relatively bulky sulfur atom. The current studies have shown the possibility of achieving high enantioselectivity through controlling the conformation of amino acid derivative by thionation of the amide carbonyl.

Experimental Section

Preparation of (*S*)-Methyl-2-(3,5-di-*tert*-butylphenylthioamido)-3-(1-methyl-1*H*-imidazol-5-yl) propanoate (3k). Step 1. To a solution of 3,5-di-*tert*-butylbenzoic acid (257 mg, 1.1 mmol) in DMF (10 mL) were added HOBt (150 mg, 1.1 mmol) and HBTU (417 mg, 1.1 mmol) at 0 °C under N_2 atmosphere. After stirring for 10 min, (*S*)-methyl-2- amino-3-(1-methyl-1*H*-imidazol-5-yl) propanoate dihydrochloride[15] (257 mg, 1 mmol) and DIEA (0.42 mL, 3.1 mmol) were added. The reaction was stirred at 0 °C for 1 h and at room temperature overnight. After removal of DMF under reduced pressure, the residue was dissolved in EtOAc and the mixture was washed with aqueous $NaHCO_3$, water and brine, respectively. The organic layer was separated and dried over anhydrous Na_2SO_4 and concentrated to give the crude product, which was then purified by flash column chromatography (eluent: 5% MeOH/EtOAc) to afford pure product **3c** as a white foam (339 mg, 85%). TLC (5% CH_3OH/EtOAc), R_f = 0.3; $[\alpha]^{20}_D$ = +30.5 (*c* 1.0, CH_2Cl_2); mp 191−193 °C; IR (KBr) 3258, 2960, 2905, 2869, 2479, 2004, 1637, 1536, 1438, 1250, 843 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.31 (s, 18H), 3.27−3.28 (m, 2H), 3.73 (s, 3H), 3.77 (s, 3H), 4.94 (dd, *J* = 9.0, 9.6 Hz, 1H), 7.02 (s, 1H), 7.07 (d, *J* = 4.2 Hz, 1H), 7.58 (s, 3H), 7.95 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 26.1, 31.3, 31.4, 32.6, 35.0, 52.1, 53.0, 121.2, 122.6, 126.5, 129.2, 132.6, 136.7, 151.6, 168.6, 171.3; LRMS (ESI) $[M + H]^+$ *m/z* 400.5. HRMS (ESI) for $C_{23}H_{33}N_3O_3$: calcd for $[M + H]^+$ 400.2595, found 400.2590.

Step 2. (*S*)-Methyl-2-(3,5-di-*tert*-butylbenzamido)-3-(1-methyl-1*H*-imidazol-5-yl)propanoate (**3c**, 200 mg, 0.5 mmol) was dissolved in a solvent mixture of CH_2Cl_2 (2 mL) and toluene (6 mL). Lawesson's reagent (2,4-bis(*p*-methoxyphenyl)-1,3-dithiaphosphetane 2,4-disulfide) (205 mg, 0.5 mmol) was added and the reaction mixture was heated at 80 °C for 4 h. After removal of solvent, the residue was dissolved in EtOAc and the mixture was washed with aqueous $NaHCO_3$, water and brine, respectively. The organic layer was separated and dried over anhydrous Na_2SO_4 and concentrated to give the crude product, which was then purified by flash column chromatography (eluent: 5% MeOH/CH_2Cl_2) to afford pure product **3k** as a light yellow foam (167 mg, 81%). TLC (5% CH_3OH/EtOAc), R_f = 0.5; $[\alpha]^{20}_D$ = +94.3 (*c* 1.0, CH_2Cl_2); mp 136−138 °C; IR (KBr) 3364, 3172, 2960, 2868, 1744, 1595, 1475, 1438, 1279, 1247, 1212, 1111, 1032, 981, 924, 897, 832, 762 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.33 (s, 18H), 3.36 (dd, *J* = 4.8, 10.8 Hz, 1H), 3.58 (s, 3H), 3.59 (dd, *J* = 6.6, 10.8 Hz, 1H), 3.84 (s, 3H), 5.49 (dd, *J* = 4.8, 6.6 Hz, 1H), 6.81 (s, 1H), 7.40 (s, 1H), 7.50 (s, 2H), 7.56 (s, 1H), 8.09 (d, *J* = 4.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 24.7, 31.3, 31.6, 35.0, 53.0, 57.7, 121.0, 126.1, 128.3, 138.6, 141.0, 151.4, 171.1, 200.6; LRMS (ESI) $[M + H]^+$ *m/z* 416.4. HRMS (ESI) for $C_{23}H_{33}N_3O_2S$: calcd for $[M+H]^+$ *m/z* 416.2366, found 416.2367.

Typical Procedure for the Kinetic Resolution of Racemic Secondary Alcohols Catalyzed by Histidine Derivatives. To the solution of (±)-**4a** (53 mg, 0.25 mmol) and catalyst **3k** (5 mg, 0.0125 mmol) in CCl_4 (2.5 mL) were added DIEA (22 μL, 0.125 mmol) and isobutyric anhydride (21 μL, 0.125 mmol) at 0 °C. After completion, the reaction mixture was quenched by water and extracted with EtOAc. The organic layer was washed with aqueous $NaHCO_3$, water and brine, respectively, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was then purified by flash column chromatography (eluent: 20% EtOAc/Petroleum ether). Enantiometic excess (ee) values of the acylated product **5a** (90%) and the recovered alcohol **4a** (97%) were determined by HPLC analysis. The conversion (*c* = 52%) and the *S* value (80) were estimated using the method of Kagan.[3a]

***cis*-*N*-(2-Isobutyryloxycyclohexanoxycarbonyl)pyrrolidine (5a).** $[\alpha]^{20}_D$ = −21.4 (*c* 1.0, $CHCl_3$) for 90% ee; ^1H NMR (600 MHz, $CDCl_3$) δ 1.16 (d, *J* = 4.2 Hz, 3H), 1.20 (d, *J* = 3.6 Hz, 3H), 1.34−1.50 (m, 2H), 1.51−1.72 (m, 4H), 1.78−1.95 (m, 6H), 2.57 (septet, *J* = 3.6 Hz, 1H), 3.31 (t, *J* = 6.6 Hz, 2H), 3.38 (t, *J* = 6.6 Hz, 2H), 4.85−4.92 (m, 1H), 5.01−5.08 (m, 1H); ^{13}C NMR (150 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; HPLC (Daicel Chiralpack AS-

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H, hexane/2-propanol = 90:10, flow rate = 0.8 mL/min) 210 nm, t_R = 7.0 min (1*S*,2*R*, minor), 7.5 min (1*R*,2*S*, major).

***cis*-*N*-(2-Hydroxycyclohexanoxycarbonyl)pyrrolidine (4a).** $[\alpha]^{20}_D$ = − 2.7 (*c* 1.0, $CHCl_3$) for 97% ee; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.33−1.34 (m, 2H), 1.55−1.58 (m, 2H), 1.65−1.70 (m, 3H), 1.85−1.93 (m, 5H), 2.62 (s, 1H), 3.40 (t, *J* = 6.6 Hz, 4H), 3.83−3.84 (m, 1H), 4.92 (dt, *J* = 3.6, 6.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.5, 22.0, 24.9, 25.6, 28.2, 30.0, 45.8, 46.2, 70.2, 74.3, 155.2; HPLC (Daicel Chiralpack AD-H, hexane/2-propanol = 92:8, flow rate = 1.0 mL/min) 210 nm, t_R = 14.1 min (1*S*,2*R*, major), 16.2 min (1*R*,2*S*, minor).

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Supporting Information Available: Experimental procedures, ^{1}H NMR, ^{13}C NMR, and HRMS spectra of catalyst **3a**−**3k**, secondary alcohols and their isopropyl esters in Table 2 and Table 3, HPLC data, X-ray structural analysis data of **3c** and **3k** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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