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Enantioselective Protonation of Lithium Enolates with Chiral Imides Possessing a Chiral Amide

Akira Yanagisawa, Tetsuo Kikuchi, Tsuyoshi Watanabe, and Hisashi Yamamoto[*,#]

Graduate School of Engineering, Nagoya University, Chikusa-ku, Nagoya 464-8603

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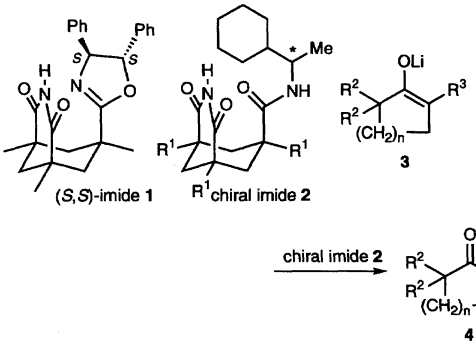
New chiral imides possessing a chiral amide can be prepared from 1,3,5-trimethyl-*r*-1,*c*-3,*c*-5-cyclohexanetricarboxylic acid or related triacids and optically active amines. These imides are superior to 1,3,5-trimethyl-*c*-5-[(4*S*,5*S*)-4,5-diphenyl-2-oxazolin-2-yl]-*r*-1,*c*-3-cyclohexanedicarboximide reported previously as a chiral proton source for enantioselective protonation of lithium enolates of 2-alkylcycloalkanones.

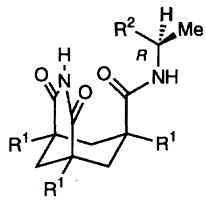
A large number of chiral proton sources have been developed for the asymmetric protonation of prochiral metal enolates.[1—3] The majority of these proton sources are effective for the reaction of enolates possessing polar functional groups such as amino, hydroxy, or aryl groups, while there have been few successful examples of asymmetric induction of enolates derived from simple ketones.[4] We have previously shown that 1,3,5-trimethyl-*c*-5-[(4*S*,5*S*)-4,5-diphenyl-2-oxazolin-2-yl]-*r*-1,*c*-3-cyclohexanedicarboximide ((*S*,*S*)-imide **1**), a chiral imide with an asymmetric 2-oxazoline, is an efficient chiral proton source for asymmetric protonation of simple metal enolates.[5] With this imide **1**, some lithium enolates of α-monoalkylated cycloalkanones can be protonated with nearly 90%ee; however, the protonation of the lithium enolates possessing a long alkyl substituent or phenyl group at the C-2 position results in low enantiomeric excesses or no asymmetric induction. We report here a new enantioselective protonation of lithium enolates **3** of α-monoalkylated cycloalkanones with chiral imide **2** having a chiral amide portion (Eq. 1). We were interested in using the chiral amide group as a chiral auxiliary of chiral imide **2**, because the amide was anticipated to form a transition-state structure similar to that for 2-oxazoline group of (*S*,*S*)-imide **1** in the protonation, and the flexible structure of the amide moiety seemed more beneficial for the enantioface discrimination.



(1)

Results and Discussion

Chiral imide **2** was synthesized from (*R*)- or (*S*)-1-cyclohexylethylamine **6** and imide acid chloride **5**[6] in the presence of triethylamine in CH_2Cl_2 (Eq. 2). Treatment of lithium enolate **8**, generated from silyl enol ether **7** and *n*-BuLi/hexane (1.1 molar amounts) in THF at 0 °C,[7] with a solution of (*R*)-imide **2a** (1.1 molar amounts) in THF at −78 °C for 2 h, followed by quenching with Me_3SiCl (to remove unreacted **8**) at −78 °C, gave (*S*)-enriched 2-methylcyclohexanone **9** in 98% yield with 85%ee, which is higher than that given by (*S*,*S*)-imide **1**[5] (Table 1, compare Entry 1 with Entry 5). Using various chiral imides, we studied the enantioselectivity of this protonation; yields and enantiomeric excesses of the product **9** obtained by reactions with other chiral imides **2b—2g** and **10—12** in THF at −78 °C are shown in Table 1 and Chart 1. Substitution of the cyclohexyl group of **2a** by an aryl group or bulkier *t*-butyl group resulted in lower enantioselectivities, while the chemical yields were satisfactory (Entries 2—4). Among the chiral imides derived from 1,3,5-trimethyl-*r*-1,*c*-3,*c*-5-cyclohexanetricarboxylic acid (Kemp's triacid) and different optically active amines, 1,3,5-trimethyl-*c*-5-[(*R*)-(1-cyclohexylethyl)aminocarbonyl-*r*-1,*c*-3-cyclohexanedicarboximide ((*R*)-imide **2a**) was the most effective chiral proton source for the protonation of **8**. Then we noted the effect of R^1 group of the imide on the enantioselectivity. When the three methyl groups of **2a** were replaced with propyl groups, the opposite enantioface dis-

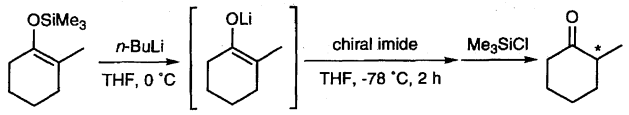


10, R^1 = Me; R^2 = Ph
11, R^1 = Me; R^2 = 1-naphthyl
12, R^1 = Me; R^2 = *t*-Bu
2a, R^1 = Me; R^2 = *c*-C_6H_{11}
2b, R^1 = *n*-Pr; R^2 = *c*-C_6H_{11}
2c, R^1 = benzyl; R^2 = *c*-C_6H_{11}
2d, R^1 = *i*-Bu; R^2 = *c*-C_6H_{11}
2e, R^1 = *i*-Pr; R^2 = *c*-C_6H_{11}
2f, R^1 = *c*-C_5H_9; R^2 = *c*-C_6H_{11}
2g, R^1 = *c*-C_6H_{11}; R^2 = *c*-C_6H_{11}

Chart 1.

CREST, Japan Science and Technology Corporation (JST).

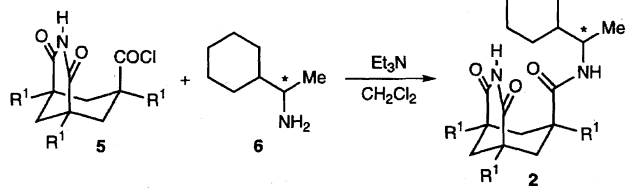
Table 1. Protonation of Lithium Enolate **8** with Chiral Imides **1**, **2a**—**2g**, and **10**—**12**[a]



Entry	Chiral imide	Yield/%[c]	ee%[d]	Configuration[e]
1[f]	**1**	89	23 (24)	*R*
2	**10**	86	47 (48)	*S*
3	**11**	92	25	*S*
4	**12**[g]	95	49 (53)[h]	*S*
5	**2a**	98	82 (85)	*S*
6	**2b**	97	24 (25)	*R*
7	**2c**	99	42 (44)	*R*
8	**2d**	86	70 (73)	*R*
9	**2e**	89	76 (79)	*R*
10	**2f**	98	77 (80)	*R*
11	**2g**	89	87 (91)	*R*

a) Unless otherwise noted, the lithium enolate **8** was generated from the corresponding silyl enol ether **7** and a solution of *n*-BuLi/hexane (1.1 molar amounts) in THF at 0 °C for 2 h. The following protonation was carried out using a chiral imide (1.1 molar amounts) in THF at −78 °C for 2 h. The reaction was quenched by TMSCl at −78 °C to exclude the unreacted enolate **8**. b) Parenthesis indicate the regioisomeric ratios of the starting silyl enol ether **7**. c) Isolated yield. d) Determined by GC analysis with chiral column (Chiraldex™ B-TA or G-TA, astec). Parentheses indicate the corrected values based on the regioisomeric ratio of the starting silyl enol ether **7**. e) The absolute cofiguration was determined by comparison of the $[\alpha]_D$ value with reported data (Ref. 8). f) Ref. 5. g) The enantiomeric excess of **12** is 95%. h) Corrected values based on the regioisomeric ratio of the starting silyl enol ether **7** and on the enantiomeric excess of the chiral imide **12**.

crimination occurred preferentially and (*R*)-enriched product **9** was formed with 25%ee (Entry 6). Furthermore, the enantiomeric excess of (*R*)-**9** was found to increase as the steric hindrance of R^1 group became larger (Entries 6—11). As a consequence, chiral imide **2g** gave the best enantioselectivity (Entry 11).

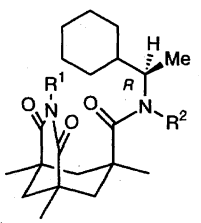


(2)

This asymmetric protonation can be applied to various lithium enolates **14** of cyclic ketones; the results with chiral imides **1**, **2a**, and **2g** are summarized in Table 2. These reactions have the following characteristics: (1) All of the reactions proceeded to give a satisfactory yield at −78 °C for 2 h. (2) Higher enantioselectivity was observed for every substrate using chiral imide **2a** or **2g** than that by (*S*,*S*)-imide **1**[5] (compare Entries 3, 5, and 8 with Entries 1, 4, and 7). (3) The highest enantioselectivity (97%ee) was obtained in the reaction of lithium enolate **16** with chiral imide **2g** (Entry 3). Two methyl groups at the C-6 position of the enolate **16** are necessary for a high level of asymmetric induction. (4) Use of (*R*)-imide **2g** gave an (*R*)-enriched product, whereas (*S*)-ketone was predominantly formed by (*R*)-imide **2a**, except for the case of lithium enolate **16**, which showed the opposite *R*-selectivity (Entry 2).

As to the present protonation with new chiral imides **2a** and **2g**, two reaction pathways are possible: (1) protonation by an imide proton and (2) protonation by an amide proton. To elucidate the reaction mechanism, we synthesized differently *N*-methylated chiral imides **2a-amide-*N*-Me** and **2a-imide-*N*-Me** (Chart 2), and applied them to protonation of lithium enolate **8** under the reaction conditions described in Table 1. When the imide **2a-amide-*N*-Me** was used as a proton source, the reaction proceeded smoothly to provide (*S*)-enriched ketone **9** in 98% yield, though with very low enantioselectivity (4%ee). In marked contrast, almost no protonation (less than 1% yield) took place with 1.1 molar amounts of the imide **2a-imide-*N*-Me** in THF at −78 °C for 2 h. These results suggest that the imide proton of chiral imide **2a** or **2g** is preferentially transferred to an enolate and the remaining amide proton plays an important role in the asymmetric induction.

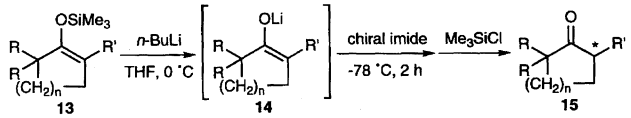
Proposed transition-state structures of the asymmetric pro-

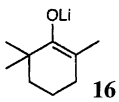
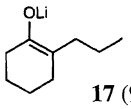


2a-amide-*N*-Me, R^1 = H; R^2 = Me
2a-imide-*N*-Me, R^1 = Me; R^2 = H

Chart 2.

Table 2. Enantioselective Protonation of Various Enolates with Chiral Imides **1**, **2a**, and **2g**[a]



Entry	Lithium enolate	Chiral imide	Yield/%[b]	ee%	Configuration[c]
1[d]	 **16**	**1**	98	88[e]	*R*[f]
2		**2a**	88	58[e]	*R*[f]
3		**2g**	80	97[e]	*R*[f]
4[d]	 **17** (97 : 3)[g]	**1**	98	51[h] (52)[h,i]	*R*[j]
5		**2a**	97	54[h] (56)[h,i]	*S*[j]
6		**2g**	90	17[h] (18)[h,i]	*R*[j]
7[d]	 **18**	**1**	95	59[e]	*R*[k]
8		**2a**	64	73[e]	*S*[k]
9		**2g**	89	35[e]	*R*[k]

a) Unless otherwise specified, a lithium enolate **14** was generated from the corresponding silyl enol ether **13** and a solution of *n*-BuLi/hexane (1.1 molar amounts) in THF at 0 °C for 2 h. The following protonation was carrried out using chiral imide **1**, **2a**, or **2g** (1.1 molar amounts) in THF at −78 °C for 2 h. The reaction was quenched by TMSCl at −78 °C to exclude the unreacted enolate **14**. b) Isolated yield. c) The absolute configuration was determined by comparison of the $[\alpha]_D$ value with reported data. d) Ref. 5. e) Determined by GC analysis with chiral column (Chiraldex™ G-TA, astec). f) Ref. 4b. g) Parenthesis indicates the regioisomeric ratio of the starting silyl enol ether **17**. h) Determined by HPLC analysis (Chiralcel OB-H, Daicel Chemical Industries, Ltd.). i) Corrected value based on the regioisomeric ratio of the starting silyl enol ether **17**. j) Refs. 8b and 9. k) Ref. 9.

tonation of lithium enolate **16** with (*R*)-imide **2a** are shown in Fig. 1. Two favorable conformational isomers **A** and **B** are possible for the imide **2a** in which two hydrogen bonds exist between an amide group and an imide group. Structure **A** is estimated to be more stable than structure **B**, since the latter has an amide methyl group oriented to the inside. Both oxygen atoms of the amide and of the imide can be coordinated to the lithium atom of the enolate **16**, providing probable transition-state structures **C** and **D** derived from **A** and **B**, respectively. Structure **C** avoids steric repulsion between a methyl group of the amide portion and the alkyl ring of the enolate. Thus, the imide **2a** protonates the enolate **16** selectively at the *Si* face. Two methyl groups at the C-6 position of the enolate **16** seem indispensable to a high level of enantioface discrimination. Further studies on asymmetric protonation with these chiral imides and on the precise reaction mechanism are currently underway.

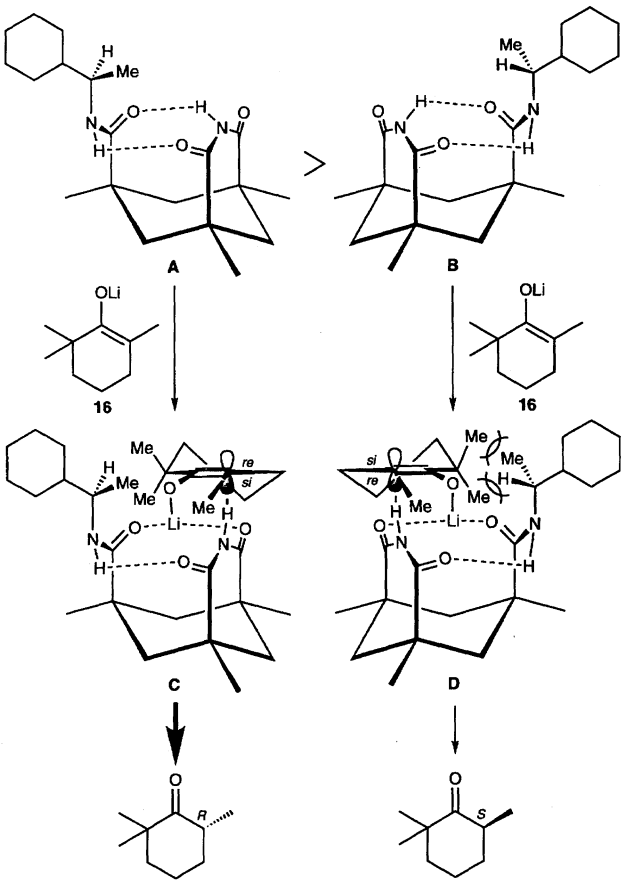


Fig. 1. Proposed transition state structures of the asymmetric protonation of lithium enolate **16** with (*R*)-imide **2a**.

Experimental

General. Analytical TLC was done on E. Merck precoated (0.25 mm) silica gel 60 F_{254} plates. Column chromatography was conducted using silica gel 60 (E. Merck 9385, 230—400 mesh). Infrared (IR) spectra were recorded on a Shimadzu FTIR-8100 spectrometer. ^{1}H NMR spectra were measured on a Varian Gemini-300 (300 MHz) spectrometer. Chemical shifts of ^{1}H NMR spectra were reported relative to tetramethylsilane ($\delta = 0$). Splitting patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Mass spectra were recorded with a JEOR JMS-AX505HA mass spectrometer. Analytical gas–liquid phase chromatography (GC) was performed on a Shimadzu GC-8A instrument equipped with a flame ionization detector and a chiral column (astec, Chiraldex™ G-TA or B-TA) using nitrogen as carrier gas. Analytical high-performance liquid chromatography (HPLC) was

done with a Shimadzu LC-6A or 10A instrument using a chiral column (Chiralcel OB-H, 4.6 mm×25 cm, Daicel Chemical Industries, Ltd.). Optical rotation was measured on a JASCO DIP-140 or DIP-1000 polarimeter. Microanalyses were accomplished at the Faculty of Agriculture, Nagoya University. All experiments were carried out under an atmosphere of standard grade argon gas (oxygen < 10 ppm). In experiments requiring dry solvents, Et_2O and THF were freshly distilled from sodium metal using benzophenone ketyl as indicator. Dry Et_2O and THF were also used as purchased from Wako (dehydrated, > 99.5%, water: < 0.005%). Dichloromethane (CH_2Cl_2) was stored over 4-Å molecular sieves. Triethylamine (Et_3N) was stored over KOH pellets. Silyl enol ether **7** and that of **17** were prepared by treating the corresponding ketones with bromomagnesium diisopropylamide in ether, followed by silylation (TMSCl, Et_3N, HMPA).[10] Silyl enol ether of **16** was prepared by treating 2,2,6-trimethylcyclohexanone with LDA in THF, followed by silylation (TMSCl, Et_3N). Silyl enol ether of **18** was prepared by treating 2-methyl-2-cyclopentenone with L-Selectride® in THF, followed by silylation (TMSCl, Et_3N).[11] Other chemicals were used as purchased.

Typical Procedure for Synthesis of Chiral Imides from Kemp's Triacid: (*R*)-Imide 2a. A mixture of Kemp's triacid (2.0 g, 7.75 mmol) and urea (1.0 g, 16.7 mmol) in diglyme (10 ml) was stirred at 170—180 °C for 2 h. The reaction mixture was cooled to room temperature and acidified with 2 mol dm^{-3} HCl solution. The resulting white precipitate was filtered off and dried at 110 °C under the reduced pressure for 4 h to give the crude imide acid (1.84 g, 7.69 mmol, > 99% yield). To this compound (1.44 g, 6.02 mmol), $SOCl_2$ (6.0 ml, 82.3 mmol) was added slowly and the resulting solution was refluxed at 110 °C for 2 h. The solution was concentrated to give the imide acid chloride **5** (R^1 = Me, 1.53 g, 5.94 mmol, 99% yield) as a pale yellow solid. To a solution of (*R*)-1-cyclohexylethylamine (**6**, 280 mg, 2.20 mmol) and triethylamine (418 µl, 3.00 mmol) in dry CH_2Cl_2 (5 ml) was added a solution of the resulting imide acid chloride **5** (R^1 = Me, 515 mg, 2.00 mmol) in dry CH_2Cl_2 (7 ml) dropwise at 0 °C. The reaction mixture was stirred at this temperature for 2 h. To this mixture was added a saturated NaCl solution (10 ml) and the aqueous layer was extracted with ether (10 ml). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (2:1 hexane/ethyl acetate as the eluant) to afford the imide **2a** (655 mg, 1.88 mmol, 94% yield) as a white solid: Mp 170—174 °C; TLC R_f 0.41 (2:1 ethyl acetate/hexane); IR (KBr) 3390, 3218, 3106, 2930, 2855, 1725, 1695, 1650, 1522, 1464, 1426, 1381, 1364, 1325, 1242, 1208, 891, 878, 863, 848, 801, 666 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.81—1.02 (m, 2 H, CH_2), 1.02 (d, 3 H, J = 6.9 Hz, CH_3), 1.05—1.37 (m, 4 H, 2 CH_2), 1.10 (d, 1 H, J = 14.1 Hz, one proton of CH_2), 1.21 (s, 3 H, CH_3), 1.27 (s, 6 H, 2 CH_3), 1.36 (d, 1 H, J = 14.4 Hz, one proton of CH_2), 1.37 (d, 1 H, J = 13.2 Hz, one proton of CH_2), 1.55—1.79 (m, 5 H, CH and 2 CH_2), 2.00 (d, 1 H, J = 13.2 Hz, one proton of CH_2), 2.33 (d, 1 H, J = 14.4 Hz, one proton of CH_2), 2.77 (d, 1 H, J = 14.1 Hz, one proton of CH_2), 3.71—3.89 (m, 1 H, CHN), 5.26 (d, 1 H, J = 8.7 Hz, amide NH), 7.47 (s, 1 H, imide NH); $[\alpha]_D^{26}$ +2.7 (*c* 2.2, $CHCl_3$). Found: C, 68.94; H, 9.39; N, 7.99%. Calcd for $C_{20}H_{32}N_2O_3$: C, 68.93; H, 9.25; N, 8.04%. Other chiral imides **10**—**12** and **2a-amide-*N*-Me** were prepared by a similar procedure using the imide acid chloride **5** (R^1 = Me) and the corresponding optically active amines.

(*R*)-Imide 10. Mp 112—114 °C; TLC R_f 0.35 (2:1 ethyl acetate/hexane); IR (KBr) 3381, 3244, 2969, 2932, 1698, 1653, 1647, 1541, 1523, 1509, 1375, 1362, 1320, 1204, 763, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.12—1.32 (m, 11 H, including 1.18 [s, 3 H, CH_3], 1.25 [s, 6 H, 2 CH_3]), 1.36 (d, 1 H, J = 13.4 Hz, one proton of CH_2), 1.47 (d, 3 H, J = 6.9 Hz, CH_3), 1.97 (d, 1 H, J = 13.2 Hz, one proton of CH_2), 2.45 (d, 1 H, J = 13.4 Hz, one proton of CH_2), 2.68 (d, 1 H, J = 14.1 Hz, one proton of CH_2), 4.96—5.09 (m, 1 H, CHN), 5.64 (d, 1 H, J = 6.9 Hz, amide NH), 7.14 (s, 1 H, imide NH), 7.22—7.41 (m, 5 H, aromatic); $[\alpha]_D^{24}$ +53.4 (*c* 2.1, $CHCl_3$). Found: C, 70.09; H, 7.83; N, 8.21%. Calcd for $C_{20}H_{26}N_2O_3$: C, 70.15; H, 7.65; N, 8.18%.

(*R*)-Imide 11. Mp 116—119 °C; TLC R_f 0.48 (2:1 ethyl acetate/hexane); IR (KBr) 3387, 3225, 3100, 3056, 1700, 1653, 1509, 1464, 1460, 1426, 1381, 1362, 1325, 1238, 1194, 801, 779 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.02—1.40 (m, 12 H, including 1.11 [s, 3 H, CH_3], 1.24 [s, 3 H, CH_3], 1.25 [s, 3 H, CH_3]), 1.64 (d, 3 H, J = 6.7 Hz, CH_3), 1.98 (d, 1 H, J = 13.4 Hz, one proton of CH_2), 2.24 (d, 1 H, J = 14.4 Hz, one proton of CH_2), 2.84 (d, 1 H, J = 13.8 Hz, one proton of CH_2), 5.64 (d, 1 H, J = 8.0 Hz, amide NH), 5.82—5.97 (m, 1 H, CHN), 7.38—8.07 (m, 8 H, aromatic and imide NH); $[\alpha]_D^{25}$ +24.0 (*c* 2.0, $CHCl_3$). Found: C, 73.36; H, 7.37; N, 7.17%. Calcd for $C_{24}H_{28}N_2O_3$: C, 73.44; H, 7.19; N, 7.14%.

(*R*)-Imide 12. Mp 194—198 °C; TLC R_f 0.38 (2:1 ethyl acetate/hexane); IR (KBr) 3414, 3238, 3106, 2965, 2934, 2870, 1719, 1698, 1509, 1458, 1381, 1372, 1306, 1213, 1134, 865, 803 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.84 (s, 9 H, 3 CH_3), 1.00 (d, 3 H, J = 6.9 Hz, CH_3), 1.06 (d, 1 H, J = 13.8 Hz, one proton of CH_2), 1.22 (s, 3 H, CH_3), 1.27 (s, 3 H, CH_3), 1.28 (s, 3 H, CH_3), 1.38 (d, 1 H, J = 13.3 Hz, one proton of CH_2), 1.42 (d, 1 H, J = 14.8 Hz, one proton of CH_2), 2.01 (d, 1 H, J = 13.3 Hz, one proton of CH_2), 2.26 (d, 1 H, J = 14.8 Hz, one proton of CH_2), 2.84 (d, 1 H, J = 13.8 Hz, one proton of CH_2), 3.79—3.92 (m, 1 H, CHN), 5.25 (d, 1 H, J = 9.2 Hz, amide NH), 7.50 (s, 1 H, imide NH); $[\alpha]_D^{30}$ −13.6 (*c* 2.1, $CHCl_3$). Found: C, 66.90; H, 9.46; N, 8.65%. Calcd for $C_{18}H_{30}N_2O_3$: C, 67.05; H, 9.38; N, 8.69%. Optical purity of this imide was 95%.

(*R*)-Imide 2a-amide-*N*-Me. Mp 90—93 °C; TLC R_f 0.27 (1:1 ethyl acetate/hexane); IR (KBr) 3230, 3110, 2967, 2930, 2853, 1727, 1698, 1464, 1397, 1381, 1325, 1208, 1119, 1080, 1065, 754 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.77—1.49 (m, 21 H, 4 CH_2, one proton of CH_2, and 4 CH_3), 1.50—1.80 (m, 5 H, CH and 2 CH_2), 1.97 (d, 1 H, J = 13.2 Hz, one proton of CH_2), 2.67—3.00 (m, 2 H, CH_2), 2.83 (s, 3 H, CH_3), 4.30—4.54 (m, 1 H, CHN), 7.39 (s, 1 H, imide NH); $[\alpha]_D^{29}$ +20.2 (*c* 2.2, $CHCl_3$). Found: C, 69.57; H, 9.54; N, 7.67%. Calcd for $C_{21}H_{34}N_2O_3$: C, 69.58; H, 9.45; N, 7.73%.

Typical Procedure for Synthesis of Chiral Imides from Kemp's Triacid Derivatives: (*R*)-Imide 2e. To a solution of diisopropylamine (3.20 ml, 22.5 mmol) in THF (20 ml) was added a solution of *n*-BuLi (1.53 mol dm^{-3}, 14.0 ml, 21.4 mmol) in hexane at 0 °C, and the mixture was stirred for 30 min at this temperature. After addition of a solution of trimethyl 1,3,5-cyclohexanetricarboxylate (1.29 g, 4.99 mmol) in THF (10 ml), the resulting orange mixture was vigorously stirred at 0 °C for 2 h and then cooled to −78 °C. A solution of isopropyl iodide (2.40 ml, 23.6 mmol) and HMPA (2.24 ml, 12.9 mmol) in THF (10 ml) was added and the mixture was stirred at −78 °C for 1 h and then at room temperature for 23 h. The reaction mixture was treated with 2 mol dm^{-3} HCl solution (50 ml) at 0 °C and the aqueous layer was extracted with ether. The combined organic extracts were washed with a saturated $Na_2S_2O_3$ solution and then with saturated brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo after filtration. The crude product was finally purified by flush-column

chromatography on silica gel (1:5 to 1:3 ethyl acetate/hexane as the eluant) to give the triisopropylated *cis,cis*-trimethyl ester (1.08 g, 2.81 mmol, 56% yield) as a colorless solid: Mp 61—65 °C; TLC R_f 0.37 (1:3 ethyl acetate/hexane); IR (KBr) 2969, 1740, 1474, 1441, 1314, 1266, 1229, 1181, 1154, 1142, 1115, 1019, 988, 889, 731 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ = 0.89 (d, 18 H, J = 6.9 Hz, 6 CH_3), 1.12 (d, 3 H, J = 14.5 Hz, three protons of 3 CH_2), 1.87 (septet, 3 H, J = 6.9 Hz, 3 CH), 2.48 (d, 3 H, J = 14.5 Hz, three protons of 3 CH_2), 3.66 (s, 9 H, 3 CH_3). A mixture of the triisopropylated *cis,cis*-trimethyl ester (800 mg, 2.08 mmol) and lithium iodide (2.54 g, 19.0 mmol) in pyridine (14 ml) was refluxed for 64 h. Then, pyridine was removed in vacuo and the residue was diluted with CH_2Cl_2 (50 ml). After addition of 2 mol dm^{-3} HCl solution (50 ml) at 0 °C, the resulting mixture was filtered by a glass filter funnel filled with Celite® and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with a saturated $Na_2S_2O_3$ solution, dried over anhydrous Na_2SO_4, and concentrated in vacuo to give the crude triacid (850 mg). A mixture of the crude Kemp's triacid derivative (850 mg, 2.49 mmol) and urea (300 mg, 5.00 mmol) in diglyme (8 ml) was stirred at 170—180 °C for 14 h. The reaction mixture was cooled to room temperature and acidified with 2 mol dm^{-3} HCl solution. The resulting white precipitate was filtered off and dried at 110 °C under the reduced pressure for 4 h to give the crude imide acid (714 mg). To this compound (714 mg, 2.21 mmol), $SOCl_2$ (5.0 ml, 68.5 mmol) was added slowly and the resulting mixture was refluxed at 110 °C for 3 h. The solution was concentrated to give the imide acid chloride **5** (R^1 = *i*-Pr, 754 mg, 2.21 mmol) as a pale yellow solid. To a solution of (*R*)-1-cyclohexylethylamine (**6**, 305 mg, 2.40 mmol) and 4-dimethylaminopyridine (54.0 mg, 0.442 mmol) and triethylamine (460 μl, 3.30 mmol) in dry CH_2Cl_2 (4 ml) was added a solution of the resulting imide acid chloride **5** (R^1 = *i*-Pr, 754 mg, 2.21 mmol) in dry CH_2Cl_2 (12 ml) dropwise at 0 °C. The reaction mixture was stirred at room temperature for 12 h. To this mixture was added a saturated NaCl solution (10 ml) and the aqueous layer was extracted with ether (10 ml). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (2:1 hexane/ethyl acetate as the eluant) to afford the imide **2e** (833 mg, 1.93 mmol, 88% yield based on the triisopropylated *cis,cis*-trimethyl ester) as a white solid: Mp 190—199 °C; TLC R_f 0.36 (1:3 ethyl acetate/hexane); IR (KBr) 3397, 3233, 3112, 2970, 2929, 2849, 1702, 1651, 1522, 1462, 1447, 1389, 1345, 1320, 1279, 1231, 1210, 1196, 1173, 837, 791, 745 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ = 0.82—1.45 (m, 7 H, CH and 3 CH_2), 0.90 (d, 6 H, J = 5.2 Hz, 2 CH_3), 0.94 (d, 6 H, J = 6.9 Hz, 2 CH_3), 0.95 (d, 6 H, J = 7.1 Hz, 2 CH_3), 1.04 (d, 3 H, J = 6.8 Hz, CH_3), 1.30 (d, 1 H, J = 14.1 Hz, one proton of CH_2), 1.48—1.80 (m, 7 H, CH and 3 CH_2), 1.92 (d, 1 H, J = 13.0 Hz, one proton of CH_2), 2.10 (d, 1 H, J = 14.5 Hz, one proton of CH_2), 2.24—2.43 (m, 2 H, 2 CH), 2.54 (d, 1 H, J = 14.1 Hz, one proton of CH_2), 3.71—3.88 (m, 1 H, CHN), 5.23 (d, 1 H, J = 7.5 Hz, amide NH), 7.48 (s, 1 H, imide NH); $[\alpha]_D^{29}$ −1.9 (*c* 2.0, $CHCl_3$). Found: C, 72.05; H, 10.31; N, 6.38%. Calcd for $C_{26}H_{44}N_2O_3$: C, 72.18; H, 10.25; N, 6.47%. Other chiral imides **2b**—**2d**, **2f**, and **2g** were prepared by a similar procedure using (*R*)-1-cyclohexylethylamine (**6**) and the corresponding imide acid chloride **5**.

(*R*)-Imide 2b. Mp 72—75 °C; TLC R_f 0.33 (1:2 ethyl acetate/hexane); IR (KBr) 3386, 3240, 2959, 2932, 2860, 2853, 1700, 1650, 1541, 1509, 1458, 1376, 1341, 1248, 1198 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ = 0.79—0.99 (m, 2 H, CH_2), 0.83 (t, 3 H, J = 7.2 Hz, CH_3), 0.93 (t, 6 H, J = 7.1 Hz, 2 CH_3), 1.02 (d, 3 H, J = 6.8 Hz, CH_3), 1.05—1.44 (m, 17 H, 8 CH_2 and one proton of CH_2), 1.52—1.79 (m, 5 H, CH and 2 CH_2), 1.86—2.00 (m, 2 H, CH_2), 2.18 (d, 1 H, J = 13.1 Hz, one proton of CH_2), 2.21 (d, 1 H, J = 14.5 Hz, one proton of CH_2), 2.66 (d, 1 H, J = 14.0 Hz, one proton of CH_2), 3.72—3.87 (m, 1 H, CHN), 5.26 (d, 1 H, J = 8.2 Hz, amide NH), 7.47 (s, 1 H, imide NH); $[\alpha]_D^{30}$ −3.0 (*c* 2.2, $CHCl_3$). Found: C, 72.18; H, 10.55; N, 6.46%. Calcd for $C_{26}H_{44}N_2O_3$: C, 72.18; H, 10.25; N, 6.47%.

(*R*)-Imide 2c. Mp 104—108 °C; TLC R_f 0.17 (1:3 ethyl acetate/hexane); IR (KBr) 3459, 3384, 3087, 3061, 3029, 2926, 2851, 1952, 1889, 1700, 1655, 1603, 1584, 1509, 1495, 1464, 1452, 1383, 1306, 1194, 1181, 1073, 1032, 916, 889, 804, 766, 741, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ = 0.77—1.79 (m, 18 H, including 0.96 [d, 3 H, J = 6.9 Hz, CH_3]), 2.27 (d, 1 H, J = 14.7 Hz, one proton of CH_2), 2.60 (m, 5 H, 2 CH_2 and one proton of CH_2), 3.13 (d, 1 H, J = 17.7 Hz, one proton of CH_2), 3.18 (d, 1 H, J = 18.0 Hz, one proton of CH_2), 3.66 (m, 1 H, CHN), 5.11 (d, 1 H, J = 7.5 Hz, amide NH), 6.95—7.00 (m, 2 H, aromatic), 7.05—7.11 (m, 4 H, aromatic), 7.18—7.34 (m, 9 H, aromatic), 7.40 (s, 1 H, imide NH); $[\alpha]_D^{25}$ +4.0 (*c* 1.0, $CHCl_3$). Found: C, 79.12; H, 7.68; N, 5.17%. Calcd for $C_{38}H_{44}N_2O_3$: C, 79.13; H, 7.69; N, 4.86%.

(*R*)-Imide 2d. Mp 69—71 °C; TLC R_f 0.34 (1:3 ethyl acetate/hexane); IR (KBr) 3386, 3238, 2955, 2928, 2870, 2853, 1701, 1649, 1522, 1509, 1466, 1451, 1387, 1368, 1320, 1252, 1198, 891, 803, 765, 683 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ = 0.72—1.44 (m, 34 H, including 0.95 [d, 6 H, J = 5.7 Hz, 2 CH_3], 1.02 [d, 3 H, J = 6.7 Hz, CH_3]), 1.51—1.80 (m, 8 H, 4 CH and 2 CH_2), 2.02—2.14 (m, 2 H, CH_2), 2.21 (d, 1 H, J = 14.7 Hz, one proton of CH_2), 2.28 (d, 1 H, J = 13.2 Hz, one proton of CH_2), 2.73 (d, 1 H, J = 13.7 Hz, one proton of CH_2), 3.65—3.81 (m, 1 H, CHN), 5.27 (d, 1 H, J = 8.4 Hz, amide NH), 7.49 (s, 1 H, imide NH); $[\alpha]_D^{24}$ −3.0 (*c* 2.0, $CHCl_3$). Found: C, 73.21; H, 11.05; N, 5.92%. Calcd for $C_{29}H_{50}N_2O_3$: C, 73.37; H, 10.62; N, 5.90%.

(*R*)-Imide 2f. Mp 91—94 °C; TLC R_f 0.23 (1:3 ethyl acetate/hexane); IR (KBr) 3384, 3230, 2950, 2869, 1701, 1650, 1509, 1451, 1385, 1327, 1304, 1206, 1190, 764, 681 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ = 0.82—1.88 (m, 39 H), 1.03 (d, 3 H, J = 6.8 Hz, CH_3), 1.93 (d, 1 H, J = 13.0 Hz, one proton of CH_2), 2.14 (d, 1 H, J = 14.6 Hz, one proton of CH_2), 2.33—2.52 (m, 2 H, 2 CH), 2.62 (d, 1 H, J = 14.0 Hz, one proton of CH_2), 3.71—3.87 (m, 1 H, CHN), 5.31 (d, 1 H, J = 7.9 Hz, amide NH), 7.45 (s, 1 H, imide NH); $[\alpha]_D^{30}$ +0.50 (*c* 2.3, $CHCl_3$). Found: C, 75.25; H, 10.05; N, 5.37%. Calcd for $C_{32}H_{50}N_2O_3$: C, 75.25; H, 9.87; N, 5.48%.

(*R*)-Imide 2g. Mp 118—122 °C; TLC R_f 0.28 (1:3 ethyl acetate/hexane); IR (KBr) 3378, 2928, 2853, 1705, 1509, 1451, 1206, 1179, 851, 766 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ = 0.80—2.06 (m, 52 H, including 1.04 [d, 3 H, J = 6.9 Hz, CH_3]), 2.53 (d, 1 H, J = 14.1 Hz, one proton of CH_2), 3.72—3.89 (m, 1 H, CHN), 5.21 (d, 1 H, J = 7.9 Hz, amide NH), 7.49 (s, 1 H, imide NH); $[\alpha]_D^{30}$ −1.5 (*c* 1.6, $CHCl_3$). Found: C, 75.82; H, 10.24; N, 5.19%. Calcd for $C_{35}H_{56}N_2O_3$: C, 76.04; H, 10.21; N, 5.07%.

(*R*)-Imide 2a-imide-*N*-Me. Suspension of Kemp's triacid (1.0 g, 3.87 mmol) in xylene (30 ml) was heated at 180—200 °C for 7.5 h with a Dean–Stark trap under argon. Concentration of the mixture afforded a crude acid anhydride. To this anhydride was added 40% $MeNH_2$ solution in water (25 ml) and 4-dimethylaminopyridine (100 mg, 0.819 mmol). The resulting mixture was stirred at 110 °C for 14 h and then concentrated to ca. 10 ml. The mixture was cooled to 0 °C and acidified to pH 1 with concentrated HCl. The resulting precipitate was filtered off and washed with cold water. The solid was dried at 110 °C under reduced pressure for 2 h to

give the crude imide acid (900 mg, 3.55 mmol, 91% yield based on Kemp's triacid). To this compound, $SOCl_2$ (7.0 ml, 96.0 mmol) was added slowly and the resulting solution was refluxed at 110 °C for 2 h. The solution was concentrated to give the corresponding imide acid chloride (966 mg, 3.55 mmol, > 99% yield) as a pale yellow solid. To a solution of (*R*)-1-cyclohexylethylamine (**6**, 497 mg, 3.91 mmol) and triethylamine (740 µl, 5.31 mmol) in dry CH_2Cl_2 (7 ml) was added a solution of the resulting imide acid chloride (966 mg, 3.55 mmol) in dry CH_2Cl_2 (10 ml) dropwise at 0 °C. The reaction mixture was stirred at this temperature for 6 h. To this mixture was added a saturated NaCl solution (10 ml) and the aqueous layer was extracted with ether (10 ml). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (1:1 hexane/ethyl acetate as the eluant) to give the imide **2a-imide-*N*-Me** (1.24 g, 3.42 mmol, 87% yield) as a white solid: Mp 175—178 °C; TLC R_f 0.44 (1:1 ethyl acetate/hexane); IR (KBr) 3411, 2971, 2938, 2874, 2851, 1717, 1671, 1526, 1460, 1453, 1418, 1381, 1360, 1337, 1316, 1291, 1273, 1211, 1115, 1046, 984, 890, 841, 756 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ = 0.80—1.40 (m, 21 H, 4 CH_2, one proton of CH_2, and 4 CH_3), 1.50—1.79 (m, 5 H, CH and 2 CH_2), 1.94 (d, 1 H, J = 13.1 Hz, one proton of CH_2), 2.32 (d, 1 H, J = 14.1 Hz, one proton of CH_2), 2.69 (d, 1 H, J = 14.2 Hz, one proton of CH_2), 2.97 (s, 3 H, CH_3), 3.63—3.78 (m, 1 H, CHN), 5.14 (d, 1 H, J = 8.3 Hz, amide NH); $[\alpha]_D^{27}$ +0.24 (*c* 2.2, $CHCl_3$). Found: C, 69.32; H, 9.74; N, 7.70%. Calcd for $C_{21}H_{34}N_2O_3$: C, 69.58; H, 9.45; N, 7.73%.

Typical Procedure for Protonation of Lithium Enolates with Chiral Imides: Synthesis of (*S*)-2-Methylcyclohexanone (9) (Entry 5 in Table 1). To a solution of trimethylsilyl enol ether **7** (184 mg, 1.0 mmol, 96.3:3.7 regioisomeric ratio) in dry THF (5 ml) at 0 °C was added a solution of *n*-BuLi (1.54 mol dm^{-3}, 0.71 ml, 1.1 mmol) in hexane under an argon atmosphere.[7] After the reaction mixture had been stirred for 2 h at 0 °C, a solution of (*R*)-imide **2a** (383 mg, 1.1 mmol) in dry THF (5 ml) was added dropwise at −78 °C. After the mixture was stirred for 2 h, TMSCl (0.13 ml, 1.0 mmol) was added to exclude the unreacted lithium enolate **8**, and stirring continued for another 30 min at this temperature. The reaction mixture was treated with saturated aqueous NH_4Cl (10 ml) and the aqueous layer was extracted twice with ether (10 ml each). The combined organic extracts were washed with saturated brine (20 ml), dried over anhydrous Na_2SO_4, and concentrated in vacuo after filtration. The crude product was finally purified by flush-column chromatography on silica gel (1:5 ether/pentane and then ethyl acetate as the eluants) to give (*S*)-enriched 2-methylcyclohexanone (**9**, 110 mg, 98% yield) with 85%ee. The enantiomeric ratio was determined by GC analysis using a chiral column (astec Chiraldex™ B-TA, 60 °C, 50 Pa): t_R = 21.7 min (*R*-isomer); t_R = 22.6 min (*S*-isomer). The absolute configuration was determined by comparison of its optical rotation with published data.[8] The (*R*)-imide **2a** was recovered (> 90% yield) without a noticeable loss of optical purity.

The enantiomeric ratio of other ketones summarized in Table 2 (Entries 1—3 and 7—9) was determined by GC analysis using a chiral column (astec, Chiraldex™ G-TA). That of 2-propylcyclohexanone (Entries 4—6) was determined by HPLC analysis with a chiral column (Chiralcel OB-H, Daicel Chemical Industries, Ltd.). The absolute configuration of these ketones was determined by comparison of the $[\alpha]_D$ value with published data.[4b,8b,9]

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