Catalytic Enantioselective Protonation of Lithium Enolates with Chiral Imides

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The catalytic enantioselective protonation of simple enolates was achieved using a catalytic amount of chiral imides and stoichiometric amount of achiral proton sources. Among the achiral proton sources examined in the protonation of the lithium enolate of 2,2,6-trimethylcyclohexanone catalyzed by (*S*,*S*)-imide **1**, 2,6-di-*tert*-butyl-*p*-cresol (BHT) and its derivatives gave the highest enantiomeric excess. For example, 90% ee of (*R*)-enriched ketone was obtained when (*S*,*S*)-imide **1** (0.1 equiv) and BHT (1 equiv) were used. Use of 0.01 equiv of the chiral catalyst still caused a high level of asymmetric induction. For catalytic protonation of the lithium enolate of 2-methylcyclohexanone, chiral imide **6** possessing a chiral amide portion was superior to (*S*,*S*)-imide **1** as a chiral proton source and the enolate was effectively protonated with up to 82% ee.

Introduction

Asymmetric protonation of enols or enolates is an efficient route as is asymmetric alkylation of enolates to prepare optically active carbonyl compounds that possess a tertiary asymmetric carbon at the α-position.[1] Examples have been reported of protonation of metal enolates by chiral proton sources,[2] chiral acid-promoted hydrolysis of enol ethers,[3] and hydrolysis of enol esters catalyzed by enzymes[4] or antibodies.[5] Although numerous chiral proton sources have been developed for the asymmetric protonation of metal enolates, most of these are valid for substrates bearing functional groups such as amino, hydroxy, or aryl groups, and few succeeded in the asymmetric induction of enolates of simple ketones.[6] We reported earlier that (*S*,*S*)-imide **1** and related imides are efficient chiral proton sources for enantioselective protonation of prochiral lithium enolates derived from 2-alkylcycloalkanones.[7] Furthermore, chiral imides such as **5** and **6** having a chiral amide portion were recently found to be superior to (*S*,*S*)-imide **1** as a chiral proton source for the protonation of simple enolates.[8] Reported herein is the catalytic process of this protonation with a catalytic amount of various imides and stoichiometric amount of achiral proton sources (eq 1).[9]

Results and Discussion

Asymmetric protonation of metal enolates fundamentally takes place catalytically if a coexisting achiral

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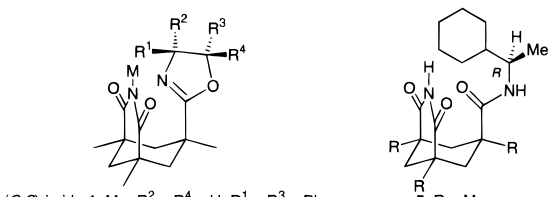
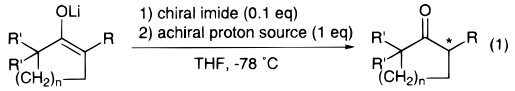
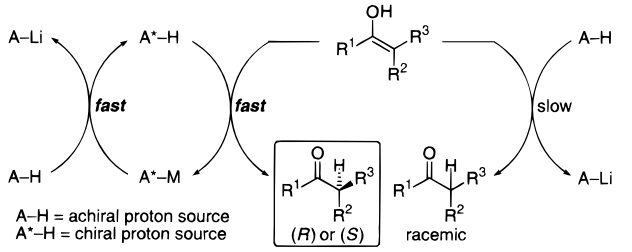




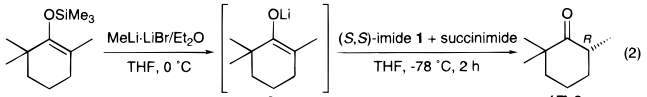
proton source A−H reacts with the deprotonated chiral proton source A*−M faster than with the metal enolate, a concept first introduced by Fehr and co-workers.[10] A hypothesis for the catalytic mechanism is shown in Scheme 1. Reaction of the metal enolate with the chiral proton source A*−H yields (*R*)- or (*S*)-ketone and the metalated chiral proton source A*−M. The chiral proton source A*−H can be reproduced by subsequent protonation of A*−M with the achiral proton source A−H. Higher reactivity of A*−M toward A−H than that of the metal enolate is the key to success in the catalytic cycle. If proton transfer from the achiral proton source A−H to the enolate occurs quickly at low temperature, selective deprotonation of one enantiomer of the resulting racemic ketone by A*−M is considered to be a possible alternative catalytic mechanism.

On the basis of this hypothesis, we envisaged that if a coexisting achiral proton source was selectively deprotonated by lithiated (*S*,*S*)-imide **2** and not by the lithium enolate **8**, a catalytic asymmetric protonation using (*S*,*S*)-imide **1** might be possible.[11] First, succinimide was employed as an achiral proton source since it was expected to possess a pK_a value similar to that of (*S*,*S*)-imide **1**.[12] Treatment of the lithium enolate **8**, generated from the silyl enol ether **7** and methyllithium in THF,[13] with a solution of (*S*,*S*)-imide **1** (1 equiv) and succinimide (1 equiv) in THF at −78 °C for 2 h afforded (*R*)-enriched ketone **9** in 83% yield with 87% ee, the same enantioselectivity as that given by (*S*,*S*)-imide **1**. This result

Scheme 1



showed that, despite the presence of an equimolar amount of succinimide, the enolate **8** was selectively reacted with (*S*,*S*)-imide **1** (eq 2). We then tested the catalytic process of this reaction. When a mixture of (*S*,*S*)-imide **1** (0.1 equiv) and succinimide (1 equiv) was used, (*R*)-**9** (72% yield) was obtained with 65% ee, which indicated the occurrence of the catalytic reaction (eq 2).



(*S*,*S*)-imide **1**	succinimide	yield, %	% ee
1 equiv	1 equiv	83	87
0.1 equiv	1 equiv	72	65

To diminish the competing reaction of an achiral proton source with the enolate **8**, it was very effective to add a catalytic amount of (*S*,*S*)-imide **1** to the enolate before the addition of a stoichiometric amount of an achiral imide. Actually, the enantioselectivity of (*R*)-**9** was improved to 83% ee employing this method (entry 2 in Table 1).

With various achiral proton sources, we studied the enantioselectivity of this catalytic protonation; yields and enantiomeric excesses of the product **9** obtained by the reaction using 0.1 equiv of (*S*,*S*)-imide **1** in THF at −78 °C are shown in Table 1. Among the achiral proton sources tested, glutarimide, phthalimide, phenol derivatives, and dipivaloylmethane provided higher enantiomeric excess than succinimide (entries 5−8, 10, 11, 13−15, and 20). The highest ee (90% ee) was achieved when 2,6-di-*tert*-butylphenol or 2,6-di-*tert*-butyl-*p*-cresol (BHT) was used (entries 10 and 11). In contrast, acyclic imides, phenol derivatives possessing an electron-withdrawing group, alcohols, and water were less effective achiral proton sources, and lower ee's were given with these compounds (entries 1, 9, and 22−24). Moderate acidity[14] and steric hindrance of the achiral proton source are required for obtaining high enantioselectivity in the catalytic protonation. We further attempted to reduce the amount of chiral catalyst and found that BHT and dipivaloylmethane still gave satisfactory chemical yield and ee, even when only 0.01 equiv of (*S*,*S*)-imide **1** was present (entries 12 and 21). In the reaction with succinimide or pentafluorophenol, use of less than 0.1 equiv of **1** resulted in significant loss of enantioselectivity (entries 3, 4, 16, and 17).

We next attempted the catalytic asymmetric protonation of the lithium enolate of 2-methylcyclohexanone **11**, which is a still more difficult substrate with which to

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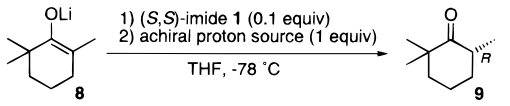
(11) Other studies on the catalytic enantioselective protonation of enolates: (a) Fehr, C.; Galindo, J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1888. (b) Fehr, C.; Galindo, J. *Helv. Chim. Acta* **1995**, *78*, 539. (c) Aboulhoda, S. J.; Létinois, S.; Wilken, J.; Reiners, I.; Hénin, F.; Martens, J.; Muzart, J. *Tetrahedron: Asymmetry* **1995**, *8*, 1865. (d) Nakamura, Y.; Takeuchi, S.; Ohira, A.; Ohgo, Y. *Tetrahedron Lett.* **1996**, *37*, 2805. (e) Ishihara, K.; Nakamura, S.; Kaneeda, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 12854. (f) Muzart, J.; Hénin, F.; Aboulhoda, S. J. *Tetrahedron*: Asymmetry **1997**, *8*, 381. (g) Sugiura, M.; Nakai, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2366. (h) Riviere, P.; Koga, K. *Tetrahedron Lett.* **1997**, *38*, 7589. (i) Vedejs, E.; Kruger, A. W. *J. Org. Chem.* **1998**, *63*, 2792. (j) Aboulhoda, S. J.; Reiners, I.; Wilken, J.; Hénin, F.; Martens, J.; Muzart, J. *Tetrahedron*: *Asymmetry* **1998**, *9*, 1847. (k) Ishihara, K.; Nakamura, H.; Nakamura, S.; Yamamoto, H. *J. Org. Chem.* **1998**, *63*, 6444. (l) Takeuchi, S.; Nakamura, Y.; Ohgo, Y.; Curran, D. P. *Tetrahedron Lett.* **1998**, *39*, 8691. See also: (m) Emori, E.; Arai, T.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1998**, *120*, 4043. (n) Hodous, B. L.; Ruble, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **1999**, *121*, 2637.

(12) For example, a pK_a value of succinimide is 9.5; see: *The Merck Index*, 12th ed.; Merck & Co. Inc.: Rahway, NJ, 1996; p 1515.

(13) *n*-BuLi can be used for cleavage of the Si−O bond of silyl enol ether **7** instead of MeLi. Generation of lithium enolates: Colvin, E. W. *Silicon in Organic Synthesis*; Butterworth: London, 1981; p 217.

(14) Vedejs and Kruger[11i] have reported that optimal pK_a value for the achiral proton source in their catalytic asymmetric protonation should be near that of the chiral proton source, but high enantioselectivity can be observed over a broad pK_a range (ΔpK_a = ca. 8).

Table 1. Enantioselective Protonation of the Lithium Enolate 8 Using a Catalytic Amount of (*S*,*S*)-Imide 1[a]

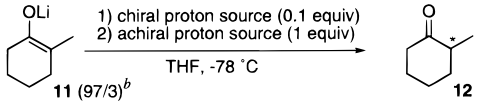


entry	equiv of **1**	achiral proton source	yield[b] (%)	ee[c] (%)
1	0.1	$(CH_3CO)_2NH$	69[d]	73
2	0.1	succinimide	76	83
3	0.05	succinimide	73	72
4	0.01	succinimide	80	60
5	0.1	glutarimide	76	87
6	0.1	phthalimide	76	87
7	0.1	PhOH	81	87
8	0.1	4-$MeOC_6H_4OH$	75	86
9	0.1	4-$O_2NC_6H_4OH$	68	80
10	0.1	2,6-(*t*-Bu)$_2$$C_6H_3OH$	>99	90
11	0.1	BHT[e]	85	90
12	0.01	BHT[e]	99	81
13	0.1	2,6-(*t*-Bu)$_2$-4-$MeOC_6H_2OH$	>99	90
14	0.1	2,6-(*t*-Bu)$_2$-4-BrC_6H_2OH	>99	88
15	0.1	C_6F_5OH	96	86
16	0.03	C_6F_5OH	95	78
17	0.01	C_6F_5OH	84	67
18	0.1	$MeCOCH_2CO_2Me$	85	75
19	0.1	$EtOCOCH_2CO_2Et$	77	77
20	0.1	$(t\text{-BuCO})_2CH_2$	>99	88
21	0.01	$(t\text{-BuCO})_2CH_2$	>99	80
22	0.1	*t*-BuOH	22[f]	73
23	0.1	CF_3CH_2OH	99	82
24	0.1	H_2O	>99	62

[a] Unless otherwise specified, lithium enolate **8** was generated from the corresponding silyl enol ether **7** (1 equiv) and MeLi·LiBr (1.2 equiv) or *n*-BuLi (1.1 equiv) in THF at 0 °C for 2 h. The enolate **8** was protonated with a catalytic amount of (*S*,*S*)-imide **1** in THF at −78 °C for 5−20 min followed by addition of achiral proton source (1 equiv) over a period of 2 h and stirring for 1 h in THF at −78 °C. Unreacted enolate **8** was recovered as silyl enol ether **7** by quenching with TMSCl at −78 °C. [b] Isolated yield. [c] Determined by HPLC analysis (Chiralcel OB, Daicel Chemical Industries, Ltd.) or GC analysis with chiral column (Chiraldex G-TA, astec). [d] The silyl enol ether **7** was obtained in 12% yield. [e] BHT = 2,6-(*t*-Bu)$_2$−4-MeC_6H_2OH. [f] The silyl enol ether **7** was obtained in 65% yield.

achieve a high level of asymmetric induction. The results are summarized in Table 2. Treatment of the lithium enolate **11** with a solution of chiral proton source (0.1 equiv) in THF at −78 °C for 5 min followed by addition of achiral proton source (1 equiv) over a period of 2 h and additional stirring for 1 h in THF at −78 °C gave optically active 2-methylcyclohexanone (**12**). When the enolate **11** was protonated with a stoichiometric amount (1.1 equiv) of (*S*,*S*)-imide **1** in the absence of achiral proton source, the ketone **12** was formed with 24% ee and *R*-configuration (entry 1).[15] Several achiral proton sources, which were effective for catalytic asymmetric protonation of lithium enolate **8** with (*S*,*S*)-imide **1**, were applied to the present catalytic protonation of the enolate **11**; however, the results were not satisfactory (entries 2−7). Although related imides **3**[7a,b,d] and **4** afforded higher enantiomeric excesses than (*S*,*S*)-imide **1** in the stoichiometric protonation of **11**, low enantioselectivity was observed for the catalytic process (entries 8−12).

Table 2. Enantioselective Protonation of the Lithium Enolate 11 Using a Catalytic Amount of Chiral Proton Sources[a]



entry	chiral proton source	achiral proton source	yield[c] (%)	ee[d] (%)
1	**1**[e]		89	24 (*R*)
2	**1**	succinimide	96	2 (*R*)
3	**1**	$(t\text{-BuCO})_2NH$	69	13 (*R*)
4	**1**	PhOH	>99	3 (*R*)
5	**1**	BHT[f]	>99	11 (*R*)
6	**1**	C_6F_5OH	>99	18 (*R*)
7	**1**	$(t\text{-BuCO})_2CH_2$	>99	17 (*R*)
8	**3**[e]		74	44 (*S*)
9	**3**	$(t\text{-BuCO})_2CH_2$	78	11 (*S*)
10	**4**[e]		71	53 (*R*)
11	**4**	BHT[f]	56	18 (*R*)
12	**4**	$(t\text{-BuCO})_2CH_2$	49	7 (*R*)
13	**5**[e]		98	85 (*S*)
14	**5**	BHT[f]	62	13 (*S*)
15	**5**	$(t\text{-BuCO})_2CH_2$	94	17 (*S*)
16	**6**[e]		89	91 (*R*)
17	**6**	2,6-$Me_2C_6H_3OH$	87	19 (*R*)
18	**6**	2,6-(*i*-Pr)$_2$$C_6H_3OH$	82	29 (*R*)
19	**6**	BHT[f]	80	79 (*R*)
20	**6**	4-Br-2,6-(*t*-Bu)$_2$$C_6H_2OH$	95	72 (*R*)
21	**6**	2-*t*-Bu-6-Et_3C-4-MeC_6H_2OH	82	82 (*R*)
22	**6**	C_6F_5OH	>99	6 (*R*)
23	**6**	$(t\text{-BuCO})_2CH_2$	92	55 (*R*)
24	**6**	CH_3COCMe_2OH	93	48 (*R*)

[a] Unless otherwise specified, lithium enolate **11** was generated from the corresponding silyl enol ether **10** (1 equiv) and *n*-BuLi (1.1 equiv) in THF at 0 °C for 2 h. The enolate **11** was protonated with a catalytic amount of chiral proton source in THF at −78 °C for 5 min followed by addition of achiral proton source (1 equiv) over a period of 2 h and stirring for 1 h in THF at −78 °C. Unreacted enolate **11** was recovered as silyl enol ether **10** by quenching with TMSCl at −78 °C. [b] The regioisomeric ratio of the starting silyl enol ether **10** is indicated in parentheses. [c] Isolated yield. [d] Determined by GC analysis with chiral column (Chiraldex B-TA, astec). Corrected value based on the regioisomeric ratio of the starting silyl enol ether **10**. [e] Stoichiometric amount (1.1 equiv) of chiral proton source was used. [f] BHT = 2,6-(*t*-Bu)$_2$−4-MeC_6H_2OH.

Chiral imides **5** and **6**, prepared from Kemp's triacid or its derivative and (*R*)-1-cyclohexylethylamine, are chiral proton sources of choice for protonation of the enolate **11**, and between them, the chiral imide **6** provided the best ee (91% ee, entry 16).[8] This chiral proton source was also quite effective for the catalytic protonation of the enolate **11** and gave (*R*)-enriched ketone **12** with 79% ee and 55% ee in combination with BHT and dipivaloylmethane, respectively (entries 19 and 23). We noted the steric bulkiness of BHT and thus investigated the effect of substituents of phenol derivatives on enantioselectivity (entries 17−22). As a consequence, further improvement of ee was achieved when 2-*tert*-butyl-6-(1,1-diethylpropyl)-4-methylphenol[16] was employed as an achiral proton source (entry 21). A bulky α-hydroxyketone also furnished moderate enantioselectivity (entry 24).

Summary and Conclusion

Described herein is a method of catalytic asymmetric protonation of lithium enolates with chiral imides. Main

(15) We have recently shown that the enantioselectivity of protonation of the enolate **11** is remarkably increased using LiBr as an additive.[7c,d] For example, when the enolate **11**, generated from the corresponding silyl enol ether **10** and MeLi·LiBr in Et_2O, is protonated with (*S*,*S*)-imide **1**, 68% ee of the (*R*)-enriched ketone **12** can be obtained as described in the previous reports.[7a,b] In contrast, the present protonation was performed in the absence of LiBr, and thus, a lower ee was observed.

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features of the present scheme are as follows: (1) chiral proton sources are readily prepared from Kemp's triacid or its derivatives and optically active 2-amino alcohols or optically active amines; (2) simple prochiral lithium enolates derived from the corresponding 2-methylcyclohexanones are efficiently protonated with high enantioselectivity; (3) sterically hindered phenol derivatives and β-diketone compounds are effective achiral proton sources for the catalytic protonation; (4) acceptable ee's are obtained in the protonation of lithium enolate of 2,2,6-trimethylcyclohexanone even when only 0.01 equiv of chiral catalyst is used. The high level of enantioselectivity and operational simplicity of the present catalytic procedure provide a practical route to optically active carbonyl compounds and are broadly applicable in organic synthesis. Further studies on catalytic asymmetric protonation with chiral imides and related chiral proton sources are currently underway.

Experimental Section

General Methods. 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). ^{1}H NMR spectra were recorded in $CDCl_3$ at 300 MHz, and chemical shifts are reported relative to tetramethylsilane (δ 0). Analytical gas−liquid-phase chromatography (GC) was performed using a flame ionization detector and a chiral column (astec, Chiraldex G-TA or B-TA) using nitrogen as carrier gas. 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** was prepared by treating 2,2,6-trimethylcyclohexanone with LDA in THF, followed by silylation (TMSCl, Et_3N). Silyl enol ether **10** was prepared by treating the corresponding ketone with bromomagnesium diisopropylamide in ether, followed by silylation (TMSCl, Et_3N, HMPA).[17] Other chemicals were used as purchased.

General Procedure for Synthesis of Chiral Imides 1, 3, and 4. 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 N HCl solution. The resulting white precipitate was filtered off and dried at 110 °C under 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) was added slowly $SOCl_2$ (6.0 mL, 82.3 mmol), and the resulting solution was refluxed at 110 °C for 2 h. The solution was concentrated to give the imide acid chloride (1.53 g, 5.94 mmol, 99% yield) as a pale yellow solid. The spectral data were identical with those in the literature.[18] To a solution of the corresponding 2-amino alcohol (40 mmol) and triethylamine (5.6 mL, 40.2 mmol) in dry CH_2Cl_2 (15 mL) was added dropwise a solution of the imide acid chloride (5.71 g, 22.2 mmol) in dry CH_2Cl_2 (30 mL) at 0 °C. The reaction mixture was stirred at this temperature for 2 h. To this mixture was added a saturated NaCl solution (20 mL), and the aqueous layer was extracted with ether (20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (hexane/ethyl acetate 2:1) to afford the corresponding amide. To this amide (22.1 mmol) was added $SOCl_2$ (15.0 mL, 206 mmol) dropwise at 20 °C. The resulting yellow solution was stirred at this temperature for 30 min. After evaporation of excess $SOCl_2$, the mixture was dissolved in CH_2Cl_2 (10 mL). This solution was neutralized with 2 N NaOH solution at 0 °C, and the aqueous layer was extracted with CH_2Cl_2 (10 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (hexane/ethyl acetate 1:1) to afford the desired chiral imide. The optical purities of imides **1**, **3**, and **4** were determined to be >99% by HPLC analysis with chiral column. Physical and spectral data (mp, TLC, IR, ^{1}H NMR, $[\alpha]_D$, and elementary analysis) of chiral imides **1** and **3** were reported previously.[7d]

Imide 4: mp 67−70 °C; TLC R_f 0.24 (1:1 ethyl acetate/hexane); IR (KBr) 3210, 3063, 2925, 1725, 1655, 1493, 1460, 1449, 1381, 1362, 1327, 1212, 1170, 961, 762, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.91 (s, 3 H), 1.18 (d, 1 H, J = 14.1 Hz), 1.22 (d, 1 H, J = 14.4 Hz), 1.27 (s, 3 H), 1.31 (s, 3 H), 1.38 (d, 1 H, J = 13.2 Hz), 2.02 (d, 1 H, J = 13.2 Hz), 2.43 (m, 1 H), 2.76 (d, 1 H, J = 13.8 Hz), 2.84 (d, 1 H, J = 13.8 Hz), 3.11−3.24 (m, 3 H), 3.27 (s, 3 H), 3.37 (m, 1 H), 3.58 (m, 1 H), 4.75 (t, 1 H, J = 3.6 Hz), 7.19−7.36 (m, 10 H), 9.22 (s, 1 H); $[\alpha]^{31}_D$ −277.9 (c 0.95, $CHCl_3$). Anal. Calcd for $C_{30}H_{36}N_2O_5$: C, 71.40; H, 7.19; N, 5.55. Found: C, 71.42; H, 7.19; N, 5.64.

General Procedure for Synthesis of Chiral Imides 5 and 6. To a solution of (*R*)-1-cyclohexylethylamine (305 mg, 2.40 mmol), 4-(dimethylamino)pyridine (54.0 mg, 0.442 mmol), and triethylamine (460 μL, 3.30 mmol) in dry CH_2Cl_2 (4 mL) was added dropwise a solution of the corresponding imide acid chloride (2.2 mmol) in dry CH_2Cl_2 (12 mL) 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 desired chiral imide. Physical and spectral data (mp, TLC, IR, ^{1}H NMR, $[\alpha]_D$, and elementary analysis) of chiral imides **5** and **6** were reported previously.[8]

Typical Procedure for Catalytic Protonation of Lithium Enolates with Chiral Imides: Synthesis of (*R*)-2,2,6-Trimethylcyclohexanone (9) (Entry 11, Table 1). To a solution of trimethylsilyl enol ether **7** (212 mg, 1.0 mmol) in dry THF (4 mL) at 0 °C was added a solution of *n*-BuLi (1.55 M, 0.70 mL, 1.1 mmol) in hexane under an argon atmosphere.[13] After the reaction mixture had been stirred for 2.5 h at 0 °C, a solution of (*S*,*S*)-imide **1** (40 mg, 0.1 mmol) in dry THF (1 mL) was added dropwise at −78 °C. The reaction solution was held at −78 °C for 5 min. Then, a solution of 2,6-di-*tert*-butyl-*p*-cresol (BHT, 220 mg, 1.0 mmol) in THF (5 mL) was added with a syringe pump (over a period of 2 h) at −78 °C. After the mixture was stirred for 1 h, TMSCl (0.13 mL, 1.0 mmol) was added to exclude the unreacted lithium enolate **8**, and stirring was 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 flash-column chromatography on silica gel (1:15 ether/hexane and then ethyl acetate as the eluants) to give (*R*)-enriched 2,2,6-trimethylcyclohexanone (**9**, 119 mg, 85% yield) with 90% ee. The enantiomeric ratio was determined by GC analysis using a chiral column (astec Chiraldex G-TA, 60 °C, 50 Pa): t_R = 24.7 min (*R*-isomer); t_R = 30.0 min (*S*-isomer). The absolute configuration was determined by comparison of its optical rotation with published data.[6b] The (*S*,*S*)-imide **1** was recovered (82% yield) without a noticeable loss of optical purity.

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The enantiomeric ratio of 2-methylcyclohexanone was determined by GC analysis using a chiral column (astec, Chiraldex B-TA). The absolute configuration was determined by comparison of the $[\alpha]_D$ value with published data.[19]

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