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Enantioselective Protonation of Prochiral Enolates with Chiral Imides

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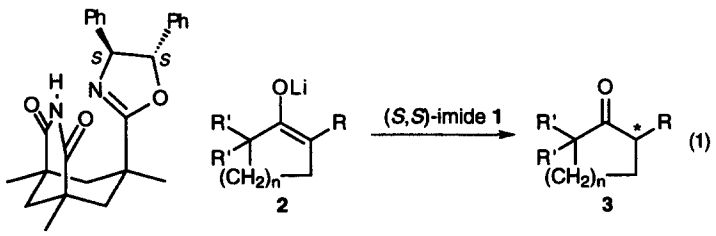
Abstract: New chiral proton sources possessing an asymmetric 2-oxazoline ring, (*S,S*)-imide **1** and related imides, were synthesized from Kemp's triacid and optically active 2-amino alcohols. With these chiral imides, various lithium enolates of α-monoalkylated cycloalkanones were effectively protonated with excellent to moderate enantioselectivity. An increase in enantioselectivity was observed in the asymmetric protonation of prochiral enolates with (*S,S*)-imide **1** using lithium salt as an additive. For example, (*R*)-enriched 2-*n*-pentylcyclopentanone **35** was obtained in high yield with 90% ee when the silyl enol ether **33** was treated with *n*-BuLi in the presence of 5 equiv of LiBr in Et_2O, and the resulting lithium enolate **34** was then protonated by a solution of (*S,S*)-imide **1** in THF. In contrast, the product **35** obtained without LiBr exhibited a lower enantiomeric excess (74% ee).

Asymmetric protonation of prochiral metal enolates is an effective route to optically active carbonyl compounds. Although a number of groups have made important contributions to the continuing progress in this process,[1-3] most of these are the reactions of enolates having polar groups including amino, hydroxyl, or phenyl groups, and there have been few satisfactory reports on the asymmetric induction of enolates of simple ketones such as 2-methylcyclohexanone.[4] We describe here that (*S,S*)-imide **1** and related imides, chiral imides with an asymmetric 2-oxazoline ring, are efficient chiral proton sources for enantioselective protonation of prochiral metal enolates **2** derived from α-monoalkylated cycloalkanones (eq 1), and that the enantioselectivity can be remarkably improved using lithium bromide as an additive.[5]



(1)

(*S,S*)-imide **1**

Selective *C*-protonation of an enolate is required for achieving high enantioselectivity. We anticipated that an imide would react with an enolate preferentially at the C-2 position due to the relatively weak acidity of the imide proton.[6] The chiral imide **1** was easily synthesized from Kemp's triacid **4**[7] in more than 90% overall yield (Scheme 1). The imide acid chloride **5**[8] was reacted with (1*R*, 2*S*)-2-amino-1,2-diphenylethanol (**6**)

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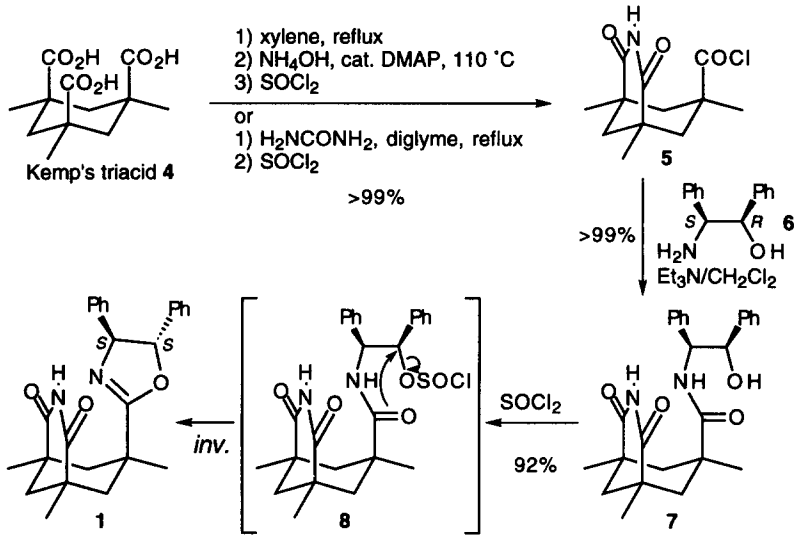
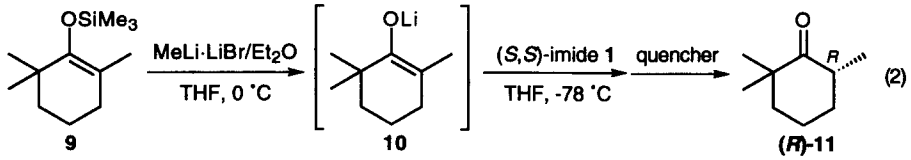
leading to the amide **7** quantitatively, and the subsequent cyclization with thionyl chloride to form a 2-oxazoline ring via **8** furnished (*S,S*)-imide **1** in 92% yield. The mechanism of the cyclization in which the 2-oxazoline is formed with inversion at the carbon atom possessing the hydroxyl group is known.[9] The structure and absolute configuration of **1** have been established by X-ray analysis.[10]



Scheme 1. Synthesis of (*S,S*)-imide **1**.

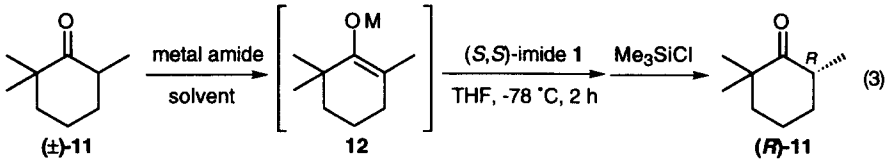
Treatment of the lithium enolate **10**, prepared from the silyl enol ether **9** and methyllithium-lithium bromide complex/diethyl ether[11] in THF at 0 °C, with (*S,S*)-imide **1** (1 equiv) in THF at -78 °C for 30 min followed by quenching with Me_3SiCl at -78 °C gave (*R*)-enriched 2,2,6-trimethylcyclohexanone [(*R*)-**11**] in 63% yield with 86% ee (eq 2). Unreacted enolate **10** was, however, recovered as the silyl enol ether **9** in 27% yield. The high level of asymmetric induction by the chiral imide **1** is quite fascinating to synthetic chemists, and thus we studied the reaction conditions of this protonation. At least two hours of stirring was found to be required to complete the reaction (eq 2). When the protonation was quenched after 2 h with sat. NH_4Cl aqueous solution, a satisfactory yield of the product (*R*)-**11** was obtained without any loss of enantioselectivity.



		(*R*)-11		recovered 9
reaction time, h	quencher	yield, %	% ee	yield, %
0.5	Me_3SiCl	63	86	27
2	Me_3SiCl	96	87	3
17	Me_3SiCl	93	87	3
2	NH_4Cl/H_2O	86	87	5

From a practical point of view, it is more beneficial to use metal enolate **12**, generated directly from racemic ketone **11**, for asymmetric protonation. Although various metal amides of alkali and alkaline-earth metals were tested, no better results were obtained (eq 3). For example, 82% ee of (*R*)-**11** was produced by

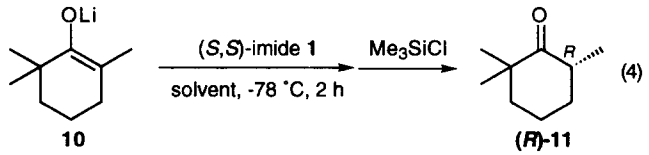
protonation of the lithium enolate **12** (M = Li) derived from (±)-**11** and LDA. The decrease in enantioselectivity is probably due to the coexisting amine which might be coordinated to a lithium metal of the enolate **12** and affect the transition state. In fact, an addition of one extra equivalent of diisopropylamine to the enolate **12** further decreased the enantiomeric excess.



(±)-**11** **12** (*R*)-**11**

metal amide	solvent	reaction conditions	yield, %	% ee
LDA	THF	-78 ~ 0 °C, 0.5 h	72	82
LDA + *i*-Pr_2NH (1 eq)	THF	-78 ~ 0 °C, 0.5 h	76	73
NaHMDS	THF	-78 ~ 0 °C, 2 h	78	5
KHMDS	THF	-78 ~ 0 °C, 2 h	74	42
i-Pr_2NMgI	Et_2O	0 °C ~ r.t., 6 h	79	5

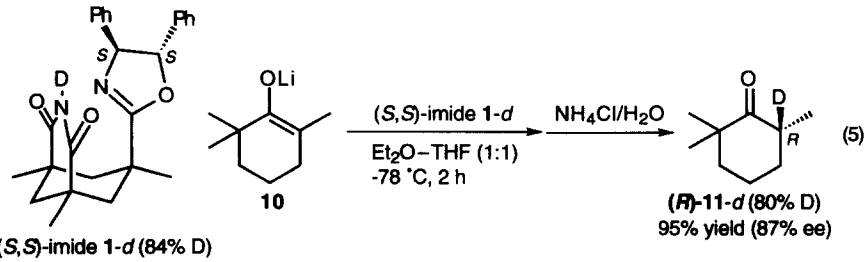
Diethyl ether or THF is generally a convenient solvent for preparation of a lithium enolate from the corresponding silyl enol ether and methyllithium, however, it is not clear whether these relatively polar solvents have a positive influence on the enantioselectivity of the subsequent reaction or not. Although several less polar solvents including dichloromethane and toluene were examined for the protonation of lithium enolate **10** with (*S*,*S*)-imide **1**, better results were not obtained than that with a mixture of Et_2O and THF or THF alone (eq 4).



10 (*R*)-**11**

solvent	yield, %	% ee
Et_2O–THF (1:1)	86	87
THF	96	87
CH_2Cl_2	61	32
toluene	74	23

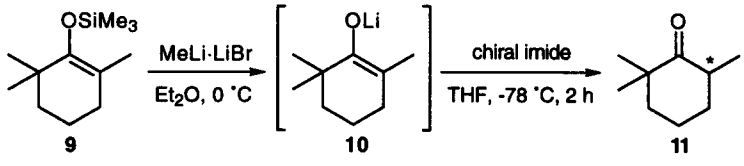
If a deuterium-labelled chiral imide is used as a proton source for the protonation of enolates, it is possible to prepare α-deuteriated chiral ketones. For example, the lithium enolate **10** was treated with (*S*,*S*)-imide **1**-*d* (84% deuterium incorporation) followed by quenching with sat. NH_4Cl aqueous solution to give deuteriated product (*R*)-**11**-*d* in 95% yield with 87% ee and 80% deuterium incorporation (eq 5). This result clearly showed that the imide proton was directly transferred to the C-2 position of the enolate **10**.

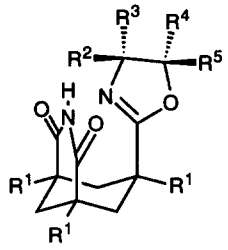


(*S*,*S*)-imide **1**-*d* (84% D) **10** (*R*)-**11**-*d* (80% D)
95% yield (87% ee)

With the chiral imides **1** and **13–22** derived from a variety of amino alcohols, we examined the protonation of the lithium enolate **10** under optimum reaction conditions (Table 1). Use of (*R*,*R*)-imide **13**, the enantiomer of (*S*,*S*)-imide **1**, gave (*S*)-**11** with an enantioselectivity similar to that for **1** (entry 2). Substitution of the three methyl groups on the cyclohexane ring of **1** by *n*-propyl groups[8b,12] did not affect the enantiomeric ratio (entry 3). The imide **15** having a *cis* stereochemistry showed an enantioselectivity lower than that for the *trans*-isomers (compare entries 1-4). The configuration of product **11** was found to be determined by the absolute configuration of the C-4 asymmetric carbon atom of the oxazoline (entries 2 and 4-6). Consequently, although other chiral imides **18–22** which possess a bulky alkyl group or methoxymethyl group on the oxazoline ring were also tested, (*S*,*S*)-imide **1** and (*R*,*R*)-imide **13** were the most effective chiral proton sources for the protonation of **10**.

Table 1. Protonation of the lithium enolate **10** with chiral imides **1** and **13-22**[a]





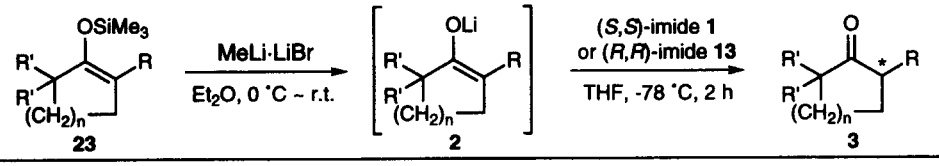
13, R^1 = Me; R^2 = R^4 = H; R^3 = R^5 = Ph
14, R^1 = *n*-Pr; R^2 = R^4 = Ph; R^3 = R^5 = H
15, R^1 = *n*-Pr; R^2 = R^5 = H; R^3 = R^4 = Ph
16, R^1 = Me; R^2 = R^4 = R^5 = H; R^3 = Ph
17, R^1 = Me; R^2 = H; R^3 = R^4 = R^5 = Ph
18, R^1 = Me; R^2 = *i*-Pr; R^3 = R^4 = R^5 = H
19, R^1 = Me; R^2 = *t*-Bu; R^3 = R^4 = R^5 = H
20, R^1 = Me; R^2 = R^4 = R^5 = H; R^3 = $MeOCH_2$
21, R^1 = Me; R^2 = H; R^3 = *i*-Pr; R^4 = R^5 = Ph
22, R^1 = Me; R^2 = $MeOCH_2$; R^3 = R^4 = H; R^5 = Ph

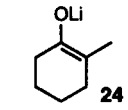
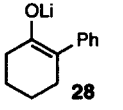
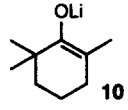
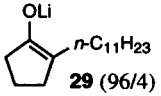
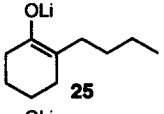
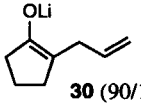
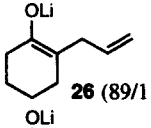
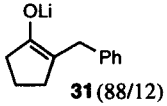
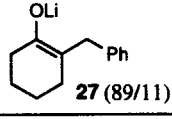
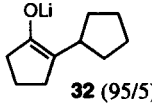
entry	chiral imide	yield, %[b]	% ee[c]	config[d]	entry	chiral imide	yield, %[b]	% ee[c]	config[d]
1	**1**	86	87	*R*	7	**18**	86	66	*R*
2	**13**	86	88	*S*	8	**19**	75	54	*R*
3[e]	**14**	75	88	*R*	9	**20**	87	44	*S*
4[e]	**15**	76	60	*S*	10	**21**	79	7	*S*
5	**16**	90	54	*S*	11[e]	**22**	97	82	*R*
6	**17**	97	85	*S*					

[a] Unless otherwise noted, the lithium enolate **10** was generated from the corresponding silyl enol ether (**9**, 1 equiv) and MeLi·LiBr (1.5 M solution in Et_2O, 1.2 equiv) in Et_2O at 0°C. The following protonation was carried out using a chiral imide (1.2 equiv) in THF at -78 °C for 2 h. The reaction was quenched by a saturated NH_4Cl aqueous solution at -78 °C. [b] Isolated yield. [c] Determined by GC analysis with chiral column (CHROMPACK). [d] The absolute configuration was determined by comparison of the $[\alpha]_D$ value with reported data. [e] The reaction was quenched by TMSCl at -78 °C to exclude the unreacted enolate **10**.

This asymmetric protonation can be applied to a variety of enolates of ketones and the results using (*S*,*S*)-imide **1** or (*R*,*R*)-imide **13** are summarized in Table 2. These reactions have the following characteristics: (1) the (*R*)- and (*S*)-enriched ketones could be prepared with almost equal optical purity by (*S*,*S*)-imide **1** and (*R*,*R*)-imide **13**; (2) two methyl groups at the C-6 position of the enolate **10** were effective for attaining higher enantioselectivities (entries 3 and 4); (3) introduction of a longer or bulky alkyl substituent at C-2 position of cyclohexanone derived lithium enolate **2** (n = 2) resulted in low enantiomeric excesses with the exception of 2-allyl derivative **26** (entries 5-7). Almost no asymmetric induction occurred in the

Table 2. Enantioselective protonation of various lithium enolates with **1** and **13**[a]



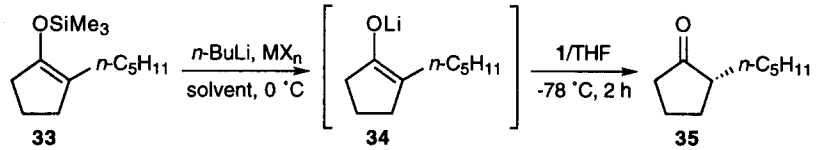
			ketone						ketone		
entry	lithium enolate[b]	chiral imide	yield, %[c]	% ee	config[d]	entry	lithium enolate[b]	chiral imide	yield, %[c]	% ee	config[d]
1	 **24** (96/4)	**1**	77	66[e] (68)[f]	*R*	8[g]	 **28**	**1**	92	4[j]	*S*
2		**13**	60	67[e] (70)[f]	*S*						
3[g]	 **10**	**1**	86	87[h]	*R*	9	 **29** (96/4)	**1**	95	92[e] (96)[f]	*R*
4[g]		**13**	86	88[h]	*S*	10		**13**	91	93[e] (97)[f]	*S*
5	 **25**	**1**	68	29[e]	*R*	11	 **30** (90/10)	**1**	45	71[e] (78)[f]	*S*
6	 **26** (89/11)	**1**	98	64[i] (72)[f]	*S*	12	 **31** (88/12)	**1**	71	57[e] (65)[f]	*S*
7	 **27** (89/11)	**1**	91	34[e] (39)[f]	*S*	13	 **32** (95/5)	**1**	70	51[e] (53)[f]	*R*

[a] Unless otherwise noted, lithium enolate **2** was generated from the corresponding silyl enol ether **23** (1 equiv) and MeLi·LiBr (1.5 M solution in Et_2O, 1.2 equiv) in Et_2O at 0 °C ~ r.t. The following protonation was carried out using a chiral imide (1.2 equiv) in THF at -78 °C for 2 h. The reaction was quenched by a saturated NH_4Cl aqueous solution. [b] Parentheses indicate the regioisomeric ratio of the starting silyl enol ethers **23**. [c] Isolated yield. Unreacted silyl enol ethers **23** were separated from the ketones **3**. [d] The absolute configuration was determined by comparison of the $[\alpha]_D$ value with reported data. [e] Determined by HPLC analysis of the MTPA ester of alcohol derived from the corresponding ketone by reduction ($NaBH_4/CH_3OH$ or L-Selectride®/THF) and the subsequent esterification (MTPACl, DMAP, Et_3N/CH_2Cl_2). [f] Corrected value based on the regioisomeric ratio of the starting silyl enol ether **23**. [g] Lithium enolate **2** was generated in THF at 0 °C. [h] Determined by GC analysis with chiral column (CHROMPACK). [i] Determined by GC analysis with chiral column (Chiraldex™ B-TA, astec). [j] Determined by HPLC analysis (Chiralcel OD-H, Daicel Chemical Industries, Ltd.).

protonation of the lithium enolate **28** prepared from 2-phenylcyclohexanone (entry 8); (4) a cyclopentanone derived lithium enolate **2** (n = 1) offered, in general, an enantioselectivity better than that for the corresponding enolate of cyclohexanone (compare entries 6, 7, 11, and 12). The highest ee was obtained with the enolate of cyclopentanone **29** which bears a long alkyl group (entries 9 and 10). Interestingly, protonation of the lithium enolate of 2-cyclopentylcyclopentanone **32** with (*S*,*S*)-imide **1** gave (*R*)-enriched ketone with 53% ee (entry 13). This reversal of the absolute configuration of the product is probably owing to the steric bulkiness of the cyclopentyl group.

It is well established that a lithium halide is incorporated into a lithium enolate to form mixed aggregates[13] and often increases the enantioselectivity of asymmetric reaction.[14] Thus, we investigated the salt effect on the enantioselective protonation with (*S*,*S*)-imide **1** (Table 3). Treatment of the silyl enol ether **33** with a solution of *n*-BuLi/hexane[15] (1.1 equiv) in the presence of a metal salt in THF or ether at 0 °C for 2 h followed by protonation of the resulting lithium enolate **34** with (*S*,*S*)-imide **1** (1.1 equiv) in THF at -78 °C for 2 h gave (*R*)-enriched 2-*n*-pentylcyclopentanone (**35**). When metal salts were absent, the reaction took place in THF or a mixture of ether and THF with moderate enantioselectivity (entries 1 and 2). In contrast, higher enantiomeric excesses were observed in the presence of more than one equivalent of lithium bromide (entries 3-10). Among them, the use of 5 equiv of the salt in ether resulted in the highest optical purity (90% ee, entry 8). In general, the protonation gave better results in a mixture of ether and THF than in THF alone (entries 1-10).[16] Other metal salts and solvents were less effective for the asymmetric induction (entries 11-19).

Table 3. Influence of salts on the enantioselectivity of protonation of the lithium enolate **34** with (*S*,*S*)-imide **1**[a]



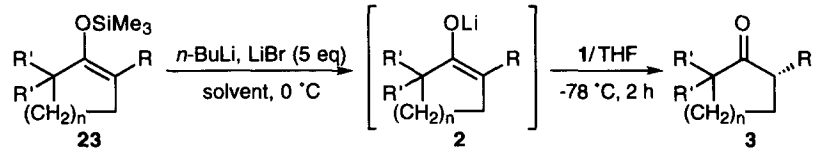
33 **34** **35**

entry	MX_n (equiv)	solvent[b]	yield, %[c]	% ee[d]	entry	MX_n (equiv)	solvent[b]	yield, %[c]	% ee[d]
1	—	THF	54	63	11	LiCl (5)	THF	>99	80
2	—	Et_2O	79	74	12	LiCl (5)	Et_2O	97	77
3	LiBr (1)	THF	82	79	13	$LiClO_4$ (5)	THF	99	58
4	LiBr (1)	Et_2O	90	83	14	$LiClO_4$ (5)	Et_2O	>99	72
5	LiBr (2)	THF	>99	79	15	LiI (5)	THF	78	40
6	LiBr (2)	Et_2O	99	85	16	NaBr (5)	THF	>99	65
7	LiBr (5)	THF	86	77	17	$MgBr_2$ (5)	THF	86	1[e]
8	LiBr (5)	Et_2O	>99	90	18[f]	LiBr (5)	Et_2O	97	60
9	LiBr (10)	THF	97	78	19[g]	LiBr (5)	MeO^nPr	>99	71
10	LiBr (10)	Et_2O	82	88					

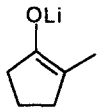
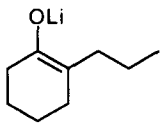
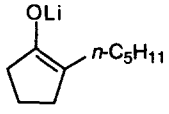
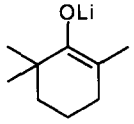
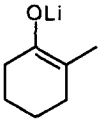
[a] Unless otherwise specified, the lithium enolate **34** was generated from the silyl enol ether **33** (1 equiv) and a solution of *n*-BuLi/hexane (1.1 equiv) in the presence of metal salt in the specified solvent at 0 °C for 2 h. The enolate **34** was then protonated with (*S*,*S*)-imide **1** (1.1 equiv) in THF at -78 °C for 2 h. The reaction was quenched by TMSCl at -78 °C to exclude the unreacted enolate **34**. [b] A small amount of hexane (ca. 3%) was contained in each solvent. [c] Isolated yield. [d] Determined by GC analysis with chiral column (Chiraldex™ B-TA, astec). (*R*)-Enriched ketone **35** was obtained in each case except for entry 17. [e] (*S*)-Enriched product was obtained. [f] A solution of (*S*,*S*)-imide **1** in CH_2Cl_2 was used. [g] A solution of (*S*,*S*)-imide **1** in MeO^nPr was used.

Findings on the enantioselective protonation of various enolates **10**, **24**, **34**, **36**, and **37** with (*S*,*S*)-imide **1** in the presence of 5 equiv of LiBr are summarized in Table 4. These examples have the following characteristics: (1) a positive salt effect has been seen for all enolates examined, except for **10** (entries 9 and 10); (2) higher enantioselectivity was observed when lithium enolate **24**, **34**, **36**, and **37** were generated in ether than in THF;[16] and (3) a lithium enolate of 2-alkylcyclopentanone is superior to that of 2-alkylcyclohexanone with respect to enantioselectivity (compare entries 1, 2, 5, and 6).

Table 4. Enantioselective protonation of various enolates with (*S*,*S*)-imide **1** in the presence of LiBr[a]

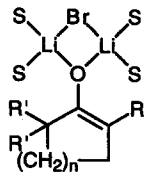


23 **2** **3**

entry	lithium enolate[b]	solvent[c]	yield, %[d]	% ee[e]	entry	lithium enolate[b]	solvent[c]	yield, %[d]	% ee[e]
1		THF	73 (95)	86[f] (59)[f]	7		THF	91 (98)	63, 65[g] (51, 52[g])
2	**36**	Et_2O	93 (91)	92[f] (51)[f]	8	**37** (97/3)	Et_2O	98 (98)	71, 73[g] (60, 62[g])
3		THF	86 (54)	77 (63)	9		THF	95 (98)	88[h] (88)[h]
4	**34**	Et_2O	>99 (79)	90 (74)	10	**10**	Et_2O	84 (88)	79[h] (87)[h]
5		THF	92 (89)	48, 50[g] (23, 24[g])					
6	**24** (96/4)	Et_2O	98 (85)	66, 68[g] (32, 33[g])					

[a] Unless otherwise specified, a lithium enolate **2** was generated from the corresponding silyl enol ether **23** (1 equiv) and a solution of *n*-BuLi/hexane (1.1 equiv) in the presence of LiBr (5 equiv) in THF or Et_2O at 0 °C for 2 h. The following protonation was carried out using (*S*,*S*)-imide **1** (1.1 equiv) in THF at -78 °C for 2 h. The reaction was quenched by TMSCl at -78 °C to exclude the unreacted enolate **2**. [b] Parentheses indicate the regioisomeric ratio of the starting silyl enol ethers **23**. [c] A small amount of hexane (ca. 3%) was contained in each solvent. [d] Isolated yield. Parentheses indicate the yields of the reaction in the absence of LiBr. [e] Determined by GC analysis with chiral column (Chiraldex™ B-TA, astec). Parentheses indicate the enantioselectivities of the reaction in the absence of LiBr. (*R*)-Enriched ketone was obtained in each case. [f] Determined by GC analysis with chiral column (Chiraldex™ B-TA, astec) of the acetate ester of *cis*-2-methylcyclopentanol derived from the corresponding ketone by reduction (L-Selectride®/THF, -78 °C) and acetylation (Ac_2O, Et_3N/CH_2Cl_2, r.t.). [g] Corrected value based on the regioisomeric ratio of the starting silyl enol ether **23**. [h] Determined by GC analysis with chiral column (Chiraldex™ G-TA, astec).

It is not obvious why LiBr increases the enantioselectivity of protonation. However, a mixed aggregate such as **38** might be formed consisting of a lithium enolate and LiBr, and this could take part in the reaction.[13] In fact, it has been shown that the salt suppresses the concentration of a monomeric lithium enolate, and that a lithium enolate-LiBr mixed aggregate is the dominant reactant at higher concentrations of LiBr.[17]



38 (S = THF or Et_2O)

A proposed transition state of this protonation is shown in Figure 1. The lithium atom of the enolate **10** coordinates to both the nitrogen atom of the 2-oxazoline ring and the oxygen atom of (*S*,*S*)-imide **1**. An eight-membered ring that avoids steric repulsion between a phenyl substituent of oxazoline ring and the alkyl ring of the enolate is formed. Thus, the imide **1** protonates selectively at the *si* face of the lithium enolate **10**. In addition, steric bulkiness of alkyl substituents at the C-6 position seems beneficial for the enantioface discrimination. Further study on asymmetric protonation with this chiral imide and its precise reaction mechanism is currently underway.

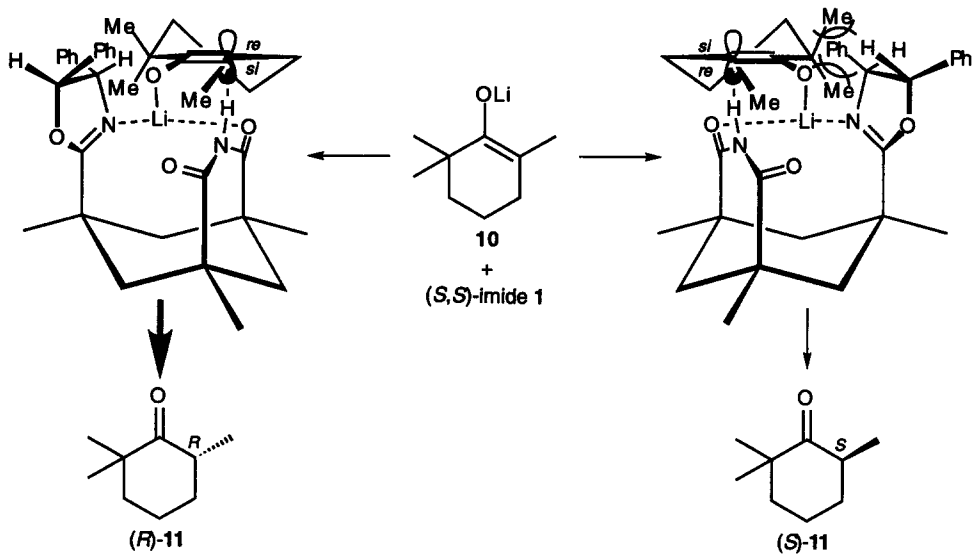


Figure 1. Proposed transition state structures of the asymmetric protonation of lithium enolate **10** with (*S*,*S*)-imide **1**

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). Infrared (IR) spectra were recorded on a Shimadzu FTIR-8100 spectrometer. ^{1}H NMR spectra were measured on a Varian Gemini-200 (200 MHz) or Gemini-300 (300 MHz) spectrometer. Chemical shifts of ^{1}H NMR spectra were reported relative to tetramethylsilane (δ 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 capillary column of PEG-HT (0.25 × 25000 mm) using nitrogen as carrier gas. Analytical high-performance liquid chromatography (HPLC) was done with a Shimadzu LC-6A or 10A instrument using 4.6 mm × 25 cm Daicel CHIRALCEL AD, OB, OB-H, OD, or OD-H. 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 **9** was prepared by treating 2,2,6-trimethylcyclohexanone (**11**) with LDA in THF followed by silylation (TMSCl, Et_3N). Silyl enol ethers of **24-32** and **37** were prepared by treating the corresponding ketones with bromomagnesium diisopropylamide in ether followed by silylation (TMSCl, Et_3N, HMPA).[18] Silyl enol ether **33** and silyl enol ether of **36** were prepared by treating 2-*n*-pentyl-2-cyclopentenone and 2-methyl-2-cyclopentenone, respectively, with L-Selectride® in THF followed by silylation (TMSCl, Et_3N).[19] Other chemicals were used as purchased.

Acid chloride 5[8] (Scheme 1). Suspension of Kemp's triacid **4** (5.84 g, 22.6 mmol, Aldrich) in xylene (100 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 anhyride was added concentrated NH_4OH (150 mL) and 4-(dimethylamino)pyridine (550 mg, 4.50 mmol). The resulting homogeneous solution was stirred at 110 °C for 12 h and then concentrated to ca. 20 mL. The resulting mixture was cooled to 0 °C and acidified to pH 1 with 2 N HCl solution. After 1 h, the solid was filtered off and washed with cold water. The solid was dried at 110 °C under reduced pressure for 4 h to afford the crude imide acid. To this compound $SOCl_2$ (80.0 mL, 1.10 mol) was added slowly and the resulting solution was refluxed at 110 °C for 3 h. The solution was concentrated to give the acid chloride **5** (5.80 g, 22.5 mmol, >99% yield) as a pale yellow solid. The spectral data were identical with those in the literature.[8]

The intermediate imide acid can also be prepared from Kemp's triacid **4** by the following procedure: A mixture of **4** (2.0 g, 7.74 mmol) and urea (1.0 mg, 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 as above to give the crude imide acid (1.84 g, 7.69 mmol, >99% yield).

Amide 7 (Scheme 1). To a solution of (1*R*,2*S*)-2-amino-1,2-diphenylethanol (**6**, 8.53 g, 40 mmol) and triethylamine (5.6 mL, 40.2 mmol) in dry CH_2Cl_2 (15 mL) was added a solution of the imide acid chloride **5** (5.71 g, 22.2 mmol) in dry CH_2Cl_2 (30 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 (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 amide **7** (9.61 g, 22.1 mmol, >99% yield) as a white solid: mp 110 ~ 114 °C; TLC R_f 0.65 (ethyl acetate); IR ($CHCl_3$) 3457, 3357, 3021, 1730, 1701, 1497, 1464, 1219, 1211, 1188 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.05-1.47 (m, 12 H, including 1.11 [s, 3 H, CH_3], 1.26 [s, 3 H, CH_3], 1.33 [s, 3 H, CH_3]), 2.02 (d, 1 H, J = 12.2 Hz), 2.33 (d, 1 H, J = 14.7 Hz), 2.80 (d, 1 H, J = 13.9 Hz), 3.61 (d, 1 H, J = 6.2 Hz, OH), 5.20 (m, 2 H, CHO and CHN), 6.17 (d, 1 H, J = 7.1 Hz, amide NH), 6.98-7.27 (m, 10 H, aromatic), 7.96 (s, 1 H, imide NH); $[\alpha]^{20}_D$ -35.8 (*c* 1.7, EtOH); FDMS, *m/z* calcd for $C_{26}H_{31}N_2O_4$ (M^+ + H) 435.2, found 435.4. Enantiomer of the amide **7**: $[\alpha]^{20}_D$ +36.1 (*c* 1.9, EtOH). Other physical and spectral data (mp, TLC, IR, and ^1H NMR) were identical with those of the amide **7**.

(*S,S*)-Imide 1 (Scheme 1). To the amide **7** (9.60 g, 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 (*S,S*)-imide **1** (8.46 g, 20.3 mmol, 92% yield) as a white solid: mp 183 ~ 184 °C; TLC R_f 0.42 (ethyl acetate/hexane 1:1); IR ($CHCl_3$) 3357, 3021, 1729, 1711, 1650, 1461, 1210, 1188 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.23-1.47 (m, 12 H, including 1.27 [s, 3 H, CH_3], 1.32 [s, 3 H, CH_3], 1.45 [s, 3 H, CH_3]), 2.03 (d, 1 H, J = 13.3 Hz), 2.84 (d, 1 H, J = 13.6 Hz), 2.91 (d, 1 H, J = 15.6 Hz), 5.01 (d, 1 H, J = 10.0 Hz, CHO), 5.15 (d, 1 H, J = 10.0 Hz, CHN), 7.20-7.46 (m, 11 H, aromatic and imide NH); $[\alpha]^{26}_D$ -21.9 (*c* 0.73, $CHCl_3$). Anal. Calcd for $C_{26}H_{28}N_2O_3$: C, 74.98; H, 6.77; N, 6.73. Found: C, 75.03; H, 6.74; N, 6.77. Optical purity of (*S,S*)-imide **1** was determined to be >99% by HPLC analysis with chiral column. Other imides were prepared by a similar procedure.

(*R,R*)-Imide 13. $[\alpha]^{26}_D$ +24.7 (*c* 0.73, $CHCl_3$). Other physical and spectral data (mp, TLC, IR, and ^1H NMR) were identical with those of (*S,S*)-imide **1**.

Imide 14. mp 193~195 °C; TLC R_f 0.44 (ethyl acetate/hexane 1:3); IR ($CHCl_3$) 3364, 3033, 2963, 2936, 2876, 1705, 1456, 1217, 1211 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.89-0.96 (m, 9 H), 1.21-2.10 (m, 18 H), 2.24 (d, 1 H, J = 12.0 Hz), 2.74 (d, 1 H, J = 13.8 Hz), 2.80 (d, 1 H, J = 14.4 Hz), 5.01 (d, 1 H, J = 10.5 Hz, CHO),

5.12 (d, 1 H, J = 10.7 Hz, CHN), 7.22-7.42 (m, 11 H, aromatic and imide NH); $[\alpha]^{26}_{D}$ -3.3 (c 1.39, $CHCl_3$). Anal. Calcd for $C_{32}H_{40}N_2O_3$: C, 76.77; H, 8.05; N, 5.60. Found: C, 76.72; H, 8.02; N, 5.54.

Imide 15. mp 196~198 °C; TLC R_f 0.38 (ethyl acetate/hexane 1:3); IR ($CHCl_3$) 3434, 3362, 3024, 3009, 2963, 2936, 2876, 1707, 1636, 1497, 1480, 1211 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.79 (t, 6 H, J = 7.0 Hz), 0.94 (t, 6 H, J = 6.9 Hz), 1.06-1.38 (m, 13 H), 1.83-1.91 (m, 2 H), 2.16 (d, 1 H, J = 13.1 Hz), 2.24 (d, 2 H, J = 14.0 Hz), 7.20-7.57 (m, 13 H, aromatic, imide NH, CHO, and CHN); $[\alpha]^{23}_{D}$ -0.9 (c 2.35, $CHCl_3$). Anal. Calcd for $C_{32}H_{40}N_2O_3$: C, 76.77; H, 8.05; N, 5.60. Found: C, 76.79; H, 8.04; N, 5.56.

Imide 16. mp 154~157 °C; TLC R_f 0.58 (ethyl acetate); IR ($CHCl_3$) 3625, 3366, 2974, 2934, 1728, 1709, 1462, 1393, 1325, 1213, 1210 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.23-1.44 (m, 12 H, including 1.26 [s, 3 H], 1.28 [s, 3 H], 1.36 [s, 3 H]), 2.01 (d, 1 H, J =14.0 Hz), 2.77 (d, 1 H, J = 14.0 Hz), 2.84 (d, 1 H, J = 14.6 Hz), 4.02 (t, 1 H, J = 8.6 Hz, CHN), 4.54 (dd, 1 H, J = 8.4, 10.4 Hz, CHO), 5.13 (dd, 1 H, J = 8.6, 10.2 Hz, CHO), 7.18-7.40 (m, 5 H, aromatic); $[\alpha]^{20}_{D}$ +27.5 (c 1.05, $CHCl_3$); FDMS, m/z calcd for $C_{20}H_{24}N_2O_3$ (M^+) 340.2, found 340.4.

Imide 17. mp 101~106 °C; TLC R_f 0.36 (ethyl acetate/hexane 1:1); IR ($CHCl_3$) 3625, 3362, 3021, 2975, 2940, 1730, 1713, 1462, 1393, 1325 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.24 (s, 3 H), 1.27 (s, 3 H), 1.34 (d, 1 H, J = 14.0 Hz), 1.37 (d, 1 H, J = 14.4 Hz), 1.41 (d, 1 H, J = 12.0 Hz), 1.95 (d, 1 H, J = 13.4 Hz), 2.87 (d, 1 H, J = 14.6 Hz), 3.07 (d, 1 H, J = 14.4 Hz), 5.99 (s, 1 H, CHN), 6.78-7.59 (m, 16 H, aromatic and imide NH); $[\alpha]^{24}_{D}$ +220.0 (c 1.34, $CHCl_3$). Anal. Calcd for $C_{32}H_{32}N_2O_3$: C, 78.03; H, 6.54; N, 5.69. Found: C, 78.02; H, 6.54; N, 5.77.

Imide 18. mp 208~209 °C; TLC R_f 0.46 (ethyl acetate); IR ($CHCl_3$) 3625, 3370, 3029, 2971, 2934, 1728, 1709, 1655, 1462, 1391, 1213, 1180 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.78 (d, 3 H, J = 6.7 Hz), 0.96 (d, 3 H, J = 6.8 Hz), 1.16-1.25 (m,11 H, including 1.24 [s, 3 H], 1.25 [s, 6 H]), 1.36 (d, 1 H, J = 13.3 Hz), 1.69 (m, 1 H), 1.98 (d, 1 H, J = 13.2 Hz), 2.70 (d, 1 H, J = 14.1 Hz), 2.74 (d, 1 H, J = 14.1 Hz), 3.71-3.88 (m, 2 H, CHO and CHN), 4.15 (dd, 1 H, J =8.0, 9.2 Hz), 7.44 (s, 1 H, imide NH); $[\alpha]^{20}_{D}$ -29.6 (c 1.26, $CHCl_3$). Anal. Calcd for $C_{17}H_{26}N_2O_3$: C, 66.64; H, 8.55; N, 9.14. Found: C, 66.56; H, 8.47; N, 9.19.

Imide 19. mp 198~200 °C; TLC R_f 0.65 (ethyl acetate); IR ($CHCl_3$) 3368, 3031, 2969, 2934, 1728, 1709, 1462, 1393, 1364, 1327 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.84 (s, 3 H), 1.16-1.40 (m, 12 H, including 1.24 [s, 3 H], 1.25 [s, 3 H], 1.26 [s, 3 H]), 1.98 (d, 1 H, J = 13.2 Hz) 2.65 (d, 1 H, J = 13.9 Hz) 2.85 (d, 1 H, J = 13.8 Hz), 3.71 (dd, 1 H, J =10.0, 8.4 Hz, CHO), 3.91 (t, 1 H, J =8.6 Hz, CHN), 4.07 (dd, 1 H, J =10.2, 8.6 Hz, CHO), 7.43 (s, 1 H, imide NH); $[\alpha]^{22}_{D}$ -42.0 (c 1.2, $CHCl_3$). Anal. Calcd for $C_{18}H_{28}N_2O_3$: C, 67.47; H, 8.80; N, 8.74. Found: C, 67.48; H, 8.82; N, 8.65.

Imide 20. mp 105~106 °C; TLC R_f 0.42 (ethyl acetate/MeOH 10:1); IR ($CHCl_3$) 3625, 3363, 3009, 2975, 2934, 1727, 1707, 1655, 1462, 1221, 1217, 1211 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.15-1.25 (m, 11 H, including 1.22 [s, 3 H], 1.24 [s, 3 H], 1.25 [s, 3 H]), 1.36 (d, 1 H, J = 13.2 Hz), 1.98 (d, 1 H, J = 15.5 Hz), 2.63 (d, 1 H, J = 13.9 Hz), 2.73 (d, 1 H, J = 13.9 Hz), 3.42 (s, 3 H), 3.51 (m, 2 H), 4.10-4.20 (m, 3 H), 8.01 (s, 1 H, imide NH); $[\alpha]^{20}_{D}$ +19.0 (c 1.21, $CHCl_3$). Anal. Calcd for $C_{16}H_{24}N_2O_4$: C, 62.32; H, 7.84; N, 9.08. Found: C, 62.33; H, 7.64; N, 9.31.

Imide 21. mp 209~210 °C; TLC R_f 0.47 (ethyl acetate/hexane 1:1); IR ($CHCl_3$) 3375, 2980, 2939, 1730, 1709, 1462, 1389, 1325, 1221, 1211, 1192 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.64 (d, 3 H, J = 6.5 Hz), 0.77 (d, 3H, J = 6.6 Hz), 1.21-1.29 (m, 11 H, including 1.21 [s,3 H], 1.24 [s, 3 H], 1.29 [s, 3 H]), 1.39 (d, 1 H, J = 13.3 Hz), 1.58 (m, 1 H) 1.99 (d, 1 H, J = 13.4 Hz), 2.79 (d, 1 H, J = 14.1 Hz), 2.93 (d, 1 H, J = 14.3 Hz), 4.37 (d, 1 H, J = 7.4 Hz, CHN), 7.10-7.40 (m, 11 H, aromatic and imide NH); $[\alpha]^{22}_{D}$ -248.0 (c 1.03, $CHCl_3$). Anal. Calcd for $C_{29}H_{34}N_2O_3$: C, 75.96; H, 7.47; N, 6.11. Found: C, 75.23; H, 7.13; N, 5.98.

Imide 22. mp 63~66 °C; TLC R_f 0.56 (ethyl acetate); IR ($CHCl_3$) 3625, 3375, 3300, 2973, 2934, 1727, 1705, 1659, 1223, 1210 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.17-1.42 (m, 12 H, including 1.24 [s, 3 H], 1.28 [s, 3 H], 1.35 [s, 3 H]), 2.10 (d, 1 H, J = 15.0 Hz), 2.65 (d, 1 H, J = 13.9 Hz), 2.74 (d, 1 H, J = 14.0 Hz), 3.49 (dd, 1 H, J = 10.0, 3.4 Hz, CH_2OMe), 3.51 (s, 3 H), 3.77 (dd, 1 H, J = 10.0, 3.4 Hz, CH_2OMe), 3.97 (dt, 1 H, J =3.4, 8.6 Hz, CHN), 5.35 (d, 1 H, J = 8.6 Hz, CHO), 7.19-7.36 (m, 5 H, aromatic), 8.24 (s, 1 H, imide NH); $[\alpha]^{20}_{D}$ +7.0 (c 1.47, $CHCl_3$); FDMS, m/z calcd for $C_{22}H_{28}N_2O_4$ (M^+) 384.2, found 384.0.

Typical Procedure for Enantioselective Protonation of Lithium Enolate with Chiral Imide (Entry 1 in Table 1, Entry 3 in Table 2). To a solution of **9** (104 mg, 0.49 mmol) in dry Et_2O (2.5 mL) at 0 °C was added a solution of MeLi (1.5 M, 0.35 mL, 0.53 mmol) in Et_2O under argon atmosphere.[11] After the reaction mixture had been stirred for 2 h at 20 to 25 °C, protonation was carried out at -78 °C by adding a solution of (*S,S*)-imide **1** (211 mg, 0.51 mmol) in dry THF (2.5 mL). The reaction solution was held at -78 °C for 2 h. Then a saturated NH_4Cl aqueous solution (10 mL) was added, and the organic material was extracted twice with Et_2O (2 × 10 mL). The combined extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was

purified by column chromatography on silica gel (hexane/Et_2O, 5:1) to afford (*R*)-2,2,6-trimethylcyclohexanone (**11**, 59 mg, 86% yield) with 87% ee. The enantiomeric ratio was determined by GC analysis using a chiral column (CHROMPACK, 130 °C): t_R = 10.5 min (*R*-isomer); t_R = 10.9 min (*S*-isomer). The absolute configuration was determined by comparison of its optical rotation with published data; (*R*)-isomer (46% ee): $[\alpha]^n_{578}$ -36.3 (*c* 1.8, $CHCl_3$).[4b] Observed $[\alpha]_D$ value of (*R*)-isomer (69% ee): $[\alpha]^{22}_D$ -41.0 (*c* 3.1, $CHCl_3$). The imide **1** was recovered (>90% yield) without a noticeable loss of optical purity.

The enantiomeric ratio of other ketones summarized in Table 2 (entries 1, 2, 5-7, 9-13) was determined by HPLC analysis of the MTPA ester of alcohol derived from the corresponding ketone by reduction ($NaBH_4$/CH_3OH or L-Selectride®/THF) and subsequent esterification (MTPACl, DMAP, Et_3N/CH_2Cl_2). The absolute configuration of these ketones was determined by comparison with published data. Observed $[\alpha]_D$ value of ketones in Table 2: (*R*)-2-methylcyclohexanone (36% ee), $[\alpha]^{24}_D$ -5.9 (*c* 0.5, MeOH);[20] (*R*)-2-*n*-butylcyclohexanone (29% ee), $[\alpha]^{26}_D$ -6.6 (*c* 1.6, $CHCl_3$);[21] (*S*)-2-allylcyclohexanone (64% ee), $[\alpha]^{26}_D$ -7.4 (*c* 3.2, MeOH);[20b,22] (*S*)-2-benzylcyclohexanone (39% ee), $[\alpha]^{25}_D$ -11.3 (*c* 1.5, MeOH);[20b,22] (*S*)-2-*n*-undecanylcyclopentanone (93% ee), $[\alpha]^{25}_D$ +77.3 (*c* 1.2, Et_2O);[23] (*S*)-2-allylcyclopentanone (78% ee), $[\alpha]^{24}_D$ -149.4 (*c* 1.2, $CHCl_3$);[24] (*S*)-2-benzylcyclopentanone (65% ee), $[\alpha]^{24}_D$ -95.7 (*c* 1.5, $CHCl_3$);[4c,25] (*R*)-2-cyclopentylcyclopentanone (53% ee), $[\alpha]^{23}_D$ +86.6 (*c* 1.1, $CHCl_3$).[26]

Typical Procedure for Enantioselective Protonation of Lithium Enolate with (*S,S*)-Imide 1 in the Presence of LiBr (Entry 8 in Table 3, Entry 4 in Table 4). To a mixture of **33** (226 mg, 1.0 mmol) and LiBr (434 mg, 5.0 mmol) in dry Et_2O (5 mL) at 0 °C was added a solution of *n*-BuLi (1.65 M, 0.67 mL, 1.1 mmol) in hexane under argon.[15] After the reaction mixture had been stirred for 2 h at 0 °C, a solution of (*S,S*)-imide **1** (443 mg, 1.1 mmol) in dry THF (5 mL) was added dropwise at -78 °C. After being stirred for 2 h, TMSCl (0.13 mL, 1.0 mmol) was added to exclude the unreacted lithium enolate **34**, and stirring continued for another 30 min at this temperature. A saturated NH_4Cl solution (10 mL) was then added, and the organic material was extracted twice with Et_2O (2 × 10 mL). The combined organic extracts were washed with saturated brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (pentane/Et_2O, 5/1 to hexane/ EtOAc, 1:2) to give the (*R*)-enriched 2-*n*-pentylcyclopentanone (**35**, 155 mg, >99% isolated yield) with 90% ee as a colorless oil which showed the appropriate spectral data: TLC R_f 0.28 (1:10 ethyl acetate/hexane); IR (neat) 2959, 2930, 2872, 2859, 1740, 1468, 1456, 1408, 1379, 1333, 1271, 1154, 1092, 1003, 930, 831, 727 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, 3 H, *J* = 6.9 Hz, CH_3), 1.16-1.41 (m, 7 H, one proton of CH_2 and 3 CH_2), 1.42-1.60 (m, 1 H, one proton of CH_2), 1.67-1.89 (m, 2 H, CH_2), 1.92-2.37 (m, 5 H, CH and 2 CH_2); $[\alpha]^{24}_D$ -114.9 (*c* 2.1, MeOH). The absolute configuration was determined by comparison of its optical rotation with published data.[27] The enantiomeric ratio was determined by GC analysis using a chiral column (astec, Chiraldex™ B-TA, 80 °C, 70 Pa): t_R = 23.9 min (*R*-isomer); t_R = 24.7 min (*S*-isomer). The imide **1** was recovered (>90% yield) without a noticeable loss of optical purity.

The enantiomeric ratio of other ketones summarized in Table 4 (entries 5-8) was determined by GC analysis using a chiral column (astec, Chiraldex™ B-TA). That of 2-methylcyclopentanone (entries 1 and 2) was determined by GC analysis with chiral column (astec, Chiraldex™ B-TA) of the acetate ester of *cis*-2-methylcyclopentanol derived from the ketone by reduction (L-Selectride®/THF, -78 °C) and acetylation (Ac_2O, Et_3N/CH_2Cl_2, r.t.). The enantiomeric ratio of 2,2,6-trimethylcyclohexanone (entries 9 and 10) was determined by GC analysis with chiral column (astec, Chiraldex™ G-TA). The absolute configuration of these ketones was determined by comparison with published data. Observed $[\alpha]_D$ value of ketones in Table 4: (*R*)-2-methylcyclopentanone (86% ee), $[\alpha]^{27}_D$ -65.0 (*c* 1.57, MeOH);[22] (*R*)-2-*n*-propylcyclohexanone (73% ee), $[\alpha]^{27}_D$ -18.2 (*c* 4.2, MeOH).[20b,22]

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