Asymmetric synthesis mediated by chiral ligands

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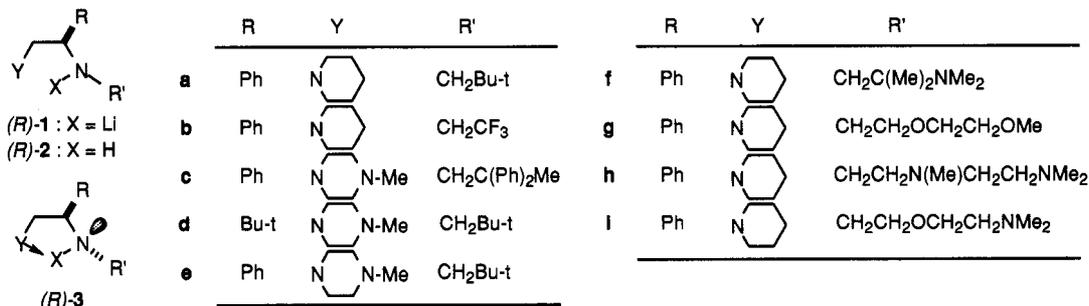
Abstract - Chiral chelated lithium amides were designed and synthesized. Studies have been done to explore the use of these lithium amides or their corresponding amines for enantioselective reactions such as deprotonation of prochiral cyclic ketones, kinetic resolution of racemic 2-substituted cyclohexanones by deprotonation, regioselective deprotonation of optically active 3-keto steroids, alkylation of achiral ketones, and deracemization of chiral ketones by protonation. Approaches to catalytic asymmetric deprotonation and alkylation are also attempted.

INTRODUCTION

Conversion of a carbonyl compound to an enolate anion by deprotonation and the reaction of an enolate anion with an electrophile to give the corresponding α-substituted carbonyl compound constitute the fundamental and widely used processes in synthetic organaic chemistry. Studies have been carried out to make these processes enantioselective, by employing chiral chelated lithium amides or their corresponding chiral amines. The ubiquitous use of lithium amides in organic synthesis promises potentialities of chiral lithium amides in enantioselective asymmetric synthesis.

DESIGN OF CHIRAL CHELATED LITHIUM AMIDES

Based on our earlier studies on diastereoselective asymmetric synthesis using chiral chelated lithioenamines (ref. 1), we designed chiral chelated lithium amides (**1a~i**) having the structures shown. The amides (**1a~e**) are structurally similar to lithium diisopropylamide (LDA) in that they have two bulky alkyl groups on the amide nitrogen, but incorporate a chiral carbon and a substituent (Y) on one of the alkyl groups. The substituent (Y) is a tertiary amino group and is expected to function as an internal ligation site for the lithium. We designed these bidentate-type chiral lithium amides as chiral versions of LDA based on the following four working hypotheses: 1) they exist as five-membered chelated forms that are stable during the reaction; 2) the amide nitrogen in these lithium amides is chiral, because the substituent R' on amide nitrogen will orient itself exclusively trans to the substituent R on the chiral carbon, as shown in **3**; 3) they form aggregates in solution to satisfy the valency of lithium, the degree of aggregation being dependent on the solvent used; 4) strongly coordinating additives such as hexamethylphosphoric triamide (HMPA) will promote deaggregation in solution. The amides (**1f~i**) were designed as chiral chelated lithium amides having additional ligation site(s) for the lithium.

	R	Y	R'		R	Y	R'
a	Ph	N☐	CH$_2$Bu-t	f	Ph	N☐	CH$_2$C(Me)$_2$NMe$_2$
b	Ph	N☐	CH$_2$CF$_3$	g	Ph	N☐	CH$_2$CH$_2$OCH$_2$CH$_2$OMe
c	Ph	N☐N-Me	CH$_2$C(Ph)$_2$Me	h	Ph	N☐	CH$_2$CH$_2$N(Me)CH$_2$CH$_2$NMe$_2$
d	Bu-t	N☐N-Me	CH$_2$Bu-t	i	Ph	N☐	CH$_2$CH$_2$OCH$_2$CH$_2$NMe$_2$
e	Ph	N☐N-Me	CH$_2$Bu-t				

(R)-1 : X = Li
(R)-2 : X = H
(R)-3

These chiral lithium amides (**1a~i**) can be prepared in both enantiomeric forms starting from the corresponding optically active amino acids that are available commercially.
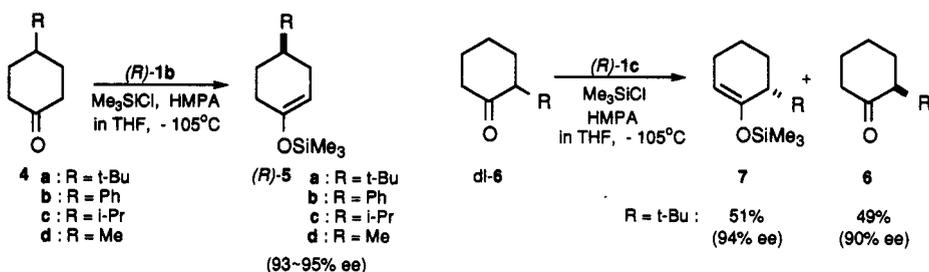
Since it is known that lithium amide is actively involved at the transition state of deprotonation reaction of a carbonyl compound (ref. 2), and that the lithium enolate forms a complex in solution with the amine coming from the lithium amide used (ref. 3), we expected that the use of the chiral lithium amide (1) or the corresponding amine (2) in the preparation and the reactions of lithium enolate might show enantioselectivities under kinetically controlled conditions.

ENANTIOSELECTIVE DEPROTONATION

One of the first successful examples of enantioselective deprotonation using chiral lithium amides was reported by Whitesell, who studied the conversion of prochiral cyclohexene oxide to chiral 2-cyclohexenol (ref. 4). Although enantiomeric excess (ee) of the product is not high, this result clearly demonstrates that chiral lithium amide can recognize enantiotopic protons of a prochiral molecule under kinetically controlled conditions.

Enantioselective deprotonation of prochiral cyclic ketones
Deprotonation of prochiral 4-substituted cyclohexanones (4a~d) by chiral lithium amides ((R)-1a,b) in the presence of excess trimethylsilyl chloride (TMSCl) (internal quench method (ref. 5)) was examined to give the corresponding chiral silyl enol ethers ((R)-5a~d) (ref. 6a, d~f). It is shown that asymmetric induction actually occurs. It is also shown that the chemical and optical yields of the products are dependent on the solvent used, but become nearly solvent-independent in the presence of HMPA (2 equivalents to 1 used). The stereochemical course of the reaction is generalized as shown.
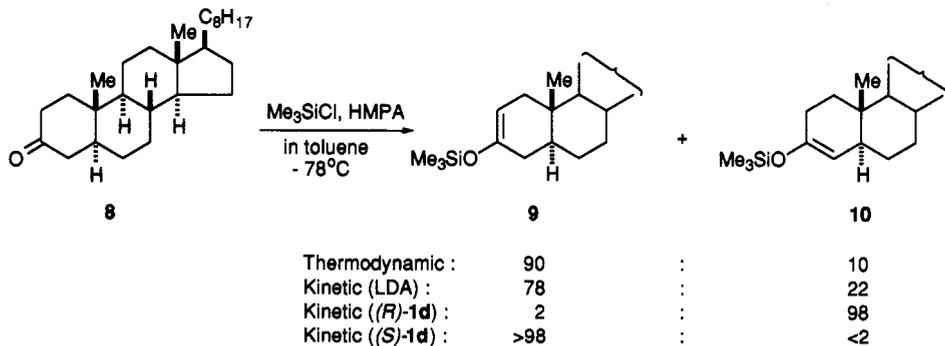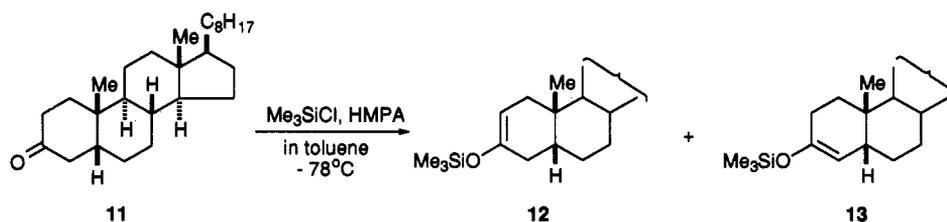

Kinetic resolution of racemic 2-substituted cyclohexanones
It is known that deprotonation of 2-substituted cyclohexanones (6) by hindered lithium amides such as LDA occurs highly selectively on methylene protons over methine protons under kinetically controlled conditions (ref. 2b). Incomplete deprotonation of dl-6 by (R)-1c in the presence of excess TMSCl gives the corresponding silyl enol ether (7) and the unreacted ketone (6) in reasonably high ee (ref. 7). They can be separated readily, and the undesired enantiomer can be recycled after desilylation followed by racemization or after racemization. The stereochemical course of the reaction is generalized as shown.
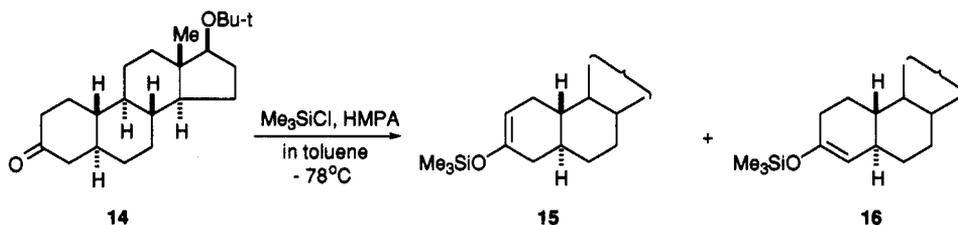
Regioselective deprotonation of optically active 3-keto steroids
It is known that under either kinetically or thermodynamically controlled conditions, enolization of cholestan-3-one (8) gives Δ^2-isomer of the enolate as the major product, while coprostan-3-one (11) furnishes largely the Δ^3-isomer. It was not possible to obtain Δ^3-isomer as the major product directly from 8, or the Δ^2-isomer as the major product directly from 11. It is found that the regioselectivity of these reactions can be efficiently increased or reversed, simply by the use of either enantiomer of the chiral lithium amides (ref. 8). Examples are shown below.

Thermodynamic :	90	: 10
Kinetic (LDA) :	78	: 22
Kinetic ((R)-1d) :	2	: 98
Kinetic ((S)-1d) :	>98	: <2

11   Me₃SiCl, HMPA / in toluene / -78°C   **12** + **13**

Thermodynamic :	7	:	93
Kinetic (LDA) :	16	:	84
Kinetic ((R)-1d) :	96	:	4
Kinetic ((S)-1d) :	<2	:	>98

14   Me₃SiCl, HMPA / in toluene / -78°C   **15** + **16**

Thermodynamic :	80	:	20
Kinetic (LDA) :	64	:	36
Kinetic ((R)-1e) :	95	:	5
Kinetic ((S)-1e) :	24	:	76

Although this strategy is restricted to optically active substrates, it should be useful as a new approach to achieve regioselective chemical transformations of optically active cyclohexanone derivatives.

Solution structures of (R)-1a

Labelled lithium amide ([^{6}Li,^{15}N₂]-(R)-1a) was prepared in order to elucidate its solution structures in relation to the effects of solvent and HMPA on the enantioselectivity of deprotonation reaction. The ^{6}Li and ^{15}N NMR spectra gave information on the connectivity between ^{6}Li and ^{15}N of this amide in solution. In THF-d_8, the ^{15}N NMR spectrum shows two kinds of nitrogen, each appearing as a triplet, while the ^{6}Li NMR spectrum shows one signal as a doublet of doublets. This indicates that (R)-1a exists as a chelated monomer (17) in THF. In toluene-d_8 or in ether containing toluene-d_8, the ^{15}N NMR spectrum shows two kinds of nitrogen, one of which appears as a triplet, the other as a quintet, while the ^{6}Li NMR spectrum shows a signal as a double triplet. This indicates that (R)-1a exists as a chelated dimer (18) in these solvents. Indeed, air-sensitive crystals of (R)-1a were isolated as colorless prisms from ether containing toluene, and X-ray analysis confirmed the dimeric structure as 18 (ref. 6d).

17   **18**
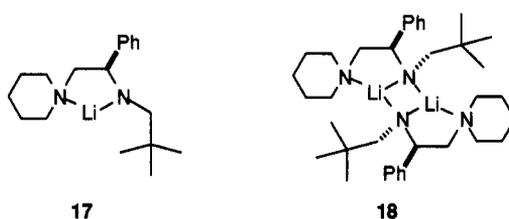
Addition of HMPA (2 equivalents) to a solution of [^{6}Li,^{15}N₂]-(R)-1a in THF-d_8 produces virtually no change in the NMR spectra, reflecting its chelated monomeric nature in this solvent system. By contrast, addition of HMPA (2 equivalents) to a solution of this amide in toluene-d_8 or in ether containing toluene-d_8 causes a change in the pattern of the NMR signals to that corresponding to the chelated monomer (17). These results support our working hypotheses discussed above and indicate that the chelated monomeric form of 1a is more reactive and gives higher enantioselectivity than the chelated dimeric form in deprotonation reaction.

An approach to catalytic asymmetric deprotonation

To investigate the possibility of a chiral tridentate-type lithium amide as a chiral base, (R)-1f having a dimethylamino group instead of one of the methyl groups in (R)-1a was prepared. Deprotonation reaction of 4a by (R)-1a and (R)-1f was examined in the presence of excess TMSCl at -78°C (Table 1).

TABLE 1. Deprotonation of **4a** by *(R)*-**1a** and *(R)*-**1f** to give *(R)*-**5a**

Base	Solvent	Without HMPA		With HMPA (2 equiv.)	
		Chem. y. (%)	E.e. (%)	Chem. y. (%)	E.e. (%)
(R)-**1a**	THF	86	84	82	82
(R)-**1a**	toluene	12	58	87	82
(R)-**1f**	THF	14	50	28	58
(R)-**1f**	toluene	2	26	34	57
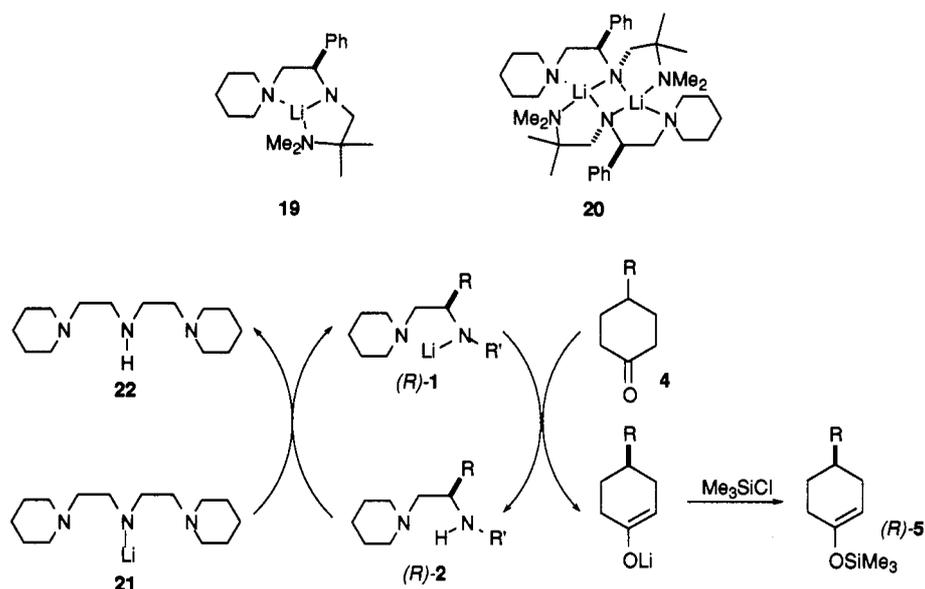
It is shown that chemical and optical yields of the product (*(R)*-**5a**) become reasonably lower by using *(R)*-**1f** having an additional internal ligation site for the lithium. By ⁶Li and ¹⁵N NMR spectral studies on [⁶Li,¹⁵N₃]-*(R)*-**1f**, it is indicated that this lithium amide exists almost entirely in THF in the presence of HMPA (2 equivalents) as a chelated monomer (**19**) in which lithium is tri-coordinated, in toluene as a chelated dimer (**20**) in which lithium is tetra-coordinated, and as a mixture of **19** and **20** in THF alone and in toluene in the presence of HMPA (2 equivalents). This result suggests that additional internal ligation to the lithium makes the lithium amide less reactive (and less stereoselective), probably due to the decrease in Lewis acidity of the lithium. This further suggests the possibility of carrying out the present enantioselective deprotonation reaction by employing less than a stoichiometric amout of a chiral bidentate-type amine in the presence of a sufficient amount of an achiral tridentate-type lithium amide (such as **21**) as shown below, provided that lithium-hydrogen interchange reaction (ref. 9) between the former and the latter occurs rapidly, favoring the formation of the chiral lithium amide.

¹H NMR spectral analysis was carried out on lithium-hydrogen interchange between lithium amides and amines in THF-*d₈* in the presence and in the absence of HMPA-*d₁₈* (2 equivalents to the lithium amide). It is shown that lithium-hydrogen interchange occurs, and that the formation of *(R)*-**1a** is not observed by mixing *(R)*-**2a** and **21**, while the formation of *(R)*-**1b** is favored exclusively by mixing *(R)*-**2b** with **21**. These opposite results may be due to the increased acidity of the amine proton of *(R)*-**2b** induced by the electron-withdrawing nature of the trifluoroethyl group.
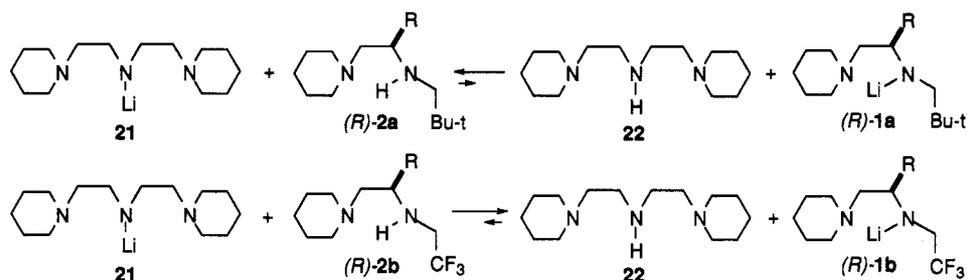
Deprotonation experiments agree with these findings. It is now possible to carry out the present deprotonation reaction of **4a~d** by the use of 0.3 equivalent of *(R)*-**2b** in the presence of excess **21** in the

presence of HMPA and dia;zabicyclo[2.2.2]octane (DABCO) followed by treatment with TMSCl (external quench method), as summarized in Table 2.

TABLE 2. An approach to catalytic asymmetric deprotonation of **4** by external quench method
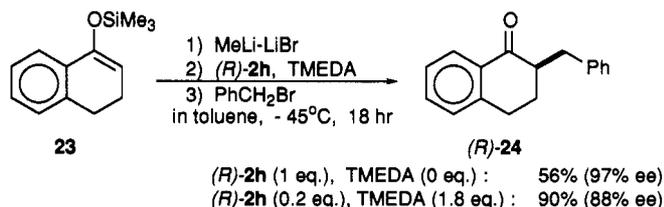

1) (R)-**1b**, (R)-**2b**, **21**
   HMPA (2.4 eq.), DABCO in THF, - 78°C
2) Me₃SiCl

Ketone		(R)-**1b**	(R)-**2b**	**21**	DABCO	Time	Product	
4	R	(eq.)	(eq.)	(eq.)	(eq.)	(hr)	Chem. y. (%)	E.e. (%)
4a	t-Bu	1.2	0	0	0	1.0	85	81
4a	t-Bu	0	0.3	2.4	1.5	1.5	83	79
4b	Ph	1.2	0	0	0	1.0	77	80
4b	Ph	0	0.3	2.4	1.5	1.5	77	76
4c	i-Pr	1.2	0	0	0	1.0	75	79
4c	i-Pr	0	0.3	2.4	1.5	1.5	80	76
4d	Me	1.2	0	0	0	1.0	82	78
4d	Me	0	0.3	2.4	1.5	1.5	70	75

ENANTIOSELECTIVE REACTIONS OF ACHIRAL LITHIUM ENOLATES WITH ACHIRAL ELECTROPHILES

Examples are known in which the lithium enolate prepared from a carbonyl compound and lithium amide exists in solution as a complex with the amine coming from the lithium amide used (ref. 3). This means that, by the use of a chiral lithium amide, symmetrical π–system of an achiral lithium enolate possibly exists in chiral environment in solution, reacting with an achiral electrophile enantioselectively.

Enantioselective alkylation

Enantioselective alkylation of cyclohexanone and 1-tetralone was realized in up to 97% ee by first forming their lithium enolates using a chiral lithium amide ((R)-**1g** or (R)-**1h**) followed by treatment with alkyl halides. The degree of asymmetric induction was found to be dependent on the solvent used, high in toluene, while very low in THF. It is also observed that lithium bromide enhances greatly the enantioselectivity of the reaction. Thus, the degree of asymmetric induction in the alkylation of the lithium enolate of cyclohexanone with benzyl bromide in toluene solution by this procedure was found to increase as the reaction proceeded. This is attributable to the increase in the concentration of lithium bromide, which is liberated as the alkylation proceeds. Furthermore, the extent of asymmetric induction increases greatly upon addition of the lithium bromide to the system from the beginning. The reaction can be conveniently carried out by the use of silyl enol ether as a starting material. It was treated with methyllithium-lithium bromide complex to give the corresponding lithium enolate containing lithium bromide. After addition of a chiral amine, alkylation was carried out similarly as shown below. Such results support the hypothesis that a lithium enolate-chiral secondary amine-lithium bromide complex is responsible for this highly enantioselective alkylation (ref. 10).


1) MeLi-LiBr
2) (R)-**2h**, TMEDA
3) PhCH₂Br
in toluene, - 45°C, 18 hr

23   (R)-**24**

(R)-**2h** (1 eq.), TMEDA (0 eq.) :   56% (97% ee)
(R)-**2h** (0.2 eq.), TMEDA (1.8 eq.) : 90% (88% ee)

An approach to catalytic asymmetric alkylation was examined under similar conditions using 0.2 equivalent of a chiral amine ((R)-**2h**) in the presence of excess tetramethylethylenediamine (TMEDA) as shown above. The product ((R)-**24**) was obtained in 88% ee (90% yield), indicating that (R)-**1h** is recycled efficiently *in situ* by ligand exchange.

Enantioselective protonation

By the same strategy, enantioselective protonation was examined. An example is shown below. An achiral silyl enol ether (**26**), prepared from the racemic ketone (dl-**25**), was treated with methyllithium-lithium bromide complex to give the corresponding lithium enolate containing lithium bromide. After addition of

(R)-**1i**, protonation by acetic acid gave *(S)*-**25** in 91% ee as shown below. This means a new method is available for deracemization of ketones having a chiral center at α-position of a carbonyl group (ref. 11).
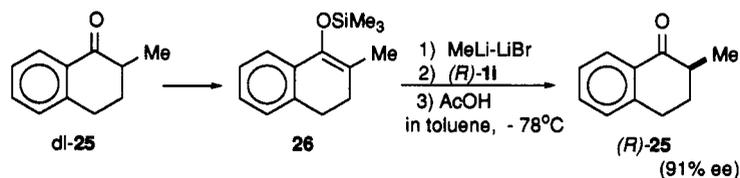
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