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Construction of Chiral Quaternary Carbon Centers by Asymmetric Alkylation of Achiral Lithium Enolates Mediated by Chiral Tetradentate Ligands: Stoichiometric and Catalytic Approaches

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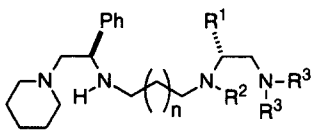
Abstract: Enantioselective asymmetric alkylation of achiral lithium enolates mediated by chiral tetradentate amine ligands is achieved to give chiral quaternary carbon centers. Turnover of a chiral tetradentate amine in the presence of an achiral bidentate amine during the reaction is also realized.

Keywords: *Asymmetric synthesis; Enantioselection; Quaternization; Catalysis*

Enantioselective reactions of achiral lithium enolates with achiral electrophiles using chiral ligands for the lithium provide a promising method for the construction of carbon stereocenters.[1] We have previously reported that some chiral multidentate amine ligands are efficient chiral auxiliaries for enantioselective alkylation,[2a-e] aldolization,[2f] Michael addition,[2g,h] and protonation[2i,j] by this strategy. In the alkylation of the lithium enolate (**4a**) of 1-tetralone with reactive alkyl halides in the presence of lithium bromide in toluene, the products having chiral tertiary carbon were obtained in good chemical and optical yields by using a stoichiometric amount of a chiral tetradentate amine (*(R)*-**1a**) (for example, run 1 in Table 1)[2c]. It is also shown that catalytic asymmetric alkylation is realized by using less than a stoichiometric amount of *(R)*-**1a** in the presence of 2 equivalents of achiral bidentate amine (**2b**).[2c] However, construction of chiral quaternary carbon center by asymmetric alkylation of the lithium enolate (**4b**) of 2-methyl-1-tetralone by the same strategy was not successful, even in the presence of a stoichiometric amount of *(R)*-**1a** (for example, run 2 in Table 1). A systematic survey focused on chiral tetradentate amine ligands for the construction of chiral quaternary carbon centers revealed that *(R,R)*-**1f** with C_2-symmetric nature was most effective for this purpose.

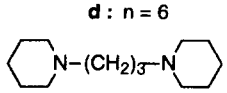


1

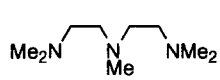
Me_2N-$(CH_2)_n$-NMe_2

2a : n = 2
b : n = 3
c : n = 4
d : n = 6

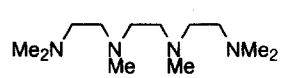
1	n	R^1	R^2	$(R^3)_2$
(R)-**1a**	0	H	Me	Me_2
(R)-**1b**	0	H	H	Me_2
(R)-**1c**	0	H	Me	-$(CH_2)_5$-
(R)-**1d**	0	H	H	-$(CH_2)_5$-
(R,R)-**1e**	0	Ph	H	-$(CH_2)_5$-
(R,R)-**1f**	1	Ph	H	-$(CH_2)_5$-
(R,R)-**1g**	2	Ph	H	-$(CH_2)_5$-



2e

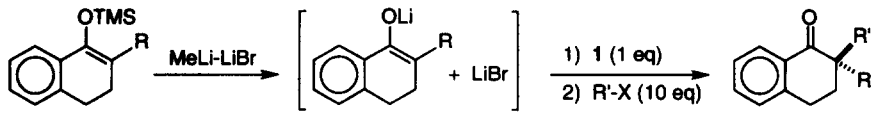


2f



2g

PII: S0040-4039(99)00299-3



3a : R = H
b : R = Me
c : R = CH_2Ph
d : R = Bu^n

4a : R = H
b : R = Me
c : R = CH_2Ph
d ; R = Bu^n

(R)-**5a** : R = H, R' = CH_2Ph
(R)-**5b** : R = Me, R' = CH_2Ph
(S)-**5b** : R = CH_2Ph, R' = Me
5c : R, R' = Bu^n, CH_2Ph
5d : R, R' = Me, CH_2-CH=CH_2
5e : R, R' = Me, Bu^n

Table 1 Enantioselective Alkylation of **4** Using **1** (1 equivalent) in the Presence of LiBr[a]

Run	Substrate 4	Ligand 1	R-X	Solvent	Temp. (°C)	Time (hr)	Product 5[c]	Yield (%)	E. e. (%)
1[b]	**4a**	*(R)*-**1a**	$PhCH_2Br$	toluene	-45	18	*(R)*-**5a**	56	97
2	**4b**	*(R)*-**1a**	$PhCH_2Br$	toluene	-18	48	*(R)*-**5b**	16	12
3	**4b**	*(R)*-**1b**	$PhCH_2Br$	toluene	-18	48	*(R)*-**5b**	60	13
4	**4b**	*(R)*-**1c**	$PhCH_2Br$	toluene	-18	48	*(R)*-**5b**	43	3
5	**4b**	*(R)*-**1d**	$PhCH_2Br$	toluene	-18	48	*(R)*-**5b**	64	31
6	**4b**	*(R,R)*-**1e**	$PhCH_2Br$	toluene	-18	48	*(R)*-**5b**	58	42
7	**4b**	*(R,R)*-**1f**	$PhCH_2Br$	toluene	-18	48	*(R)*-**5b**	97	85
8	**4b**	*(R,R)*-**1g**	$PhCH_2Br$	toluene	-18	48	*(R)*-**5b**	66	47
9	**4b**	*(R,R)*-**1f**	$PhCH_2Br$	toluene	-45	48	*(R)*-**5b**	93	94
10	**4b**	*(R,R)*-**1f**	$PhCH_2Br$	toluene	-45	18	*(R)*-**5b**	86	93
11	**4b**	*(R,R)*-**1f**	$PhCH_2Br$	toluene	-78	18	*(R)*-**5b**	8	97
12	**4b**	*(R,R)*-**1f**	$PhCH_2Br$	DME	-45	18	*(RS)*-**5b**	26	~0
13	**4b**	*(R,R)*-**1f**	$PhCH_2Br$	THF	-45	18	*(RS)*-**5b**	46	~0
14	**4b**	*(R,R)*-**1f**	$PhCH_2Br$	ether	-45	18	*(R)*-**5b**	17	30
15	**4b**	*(R,R)*-**1f**	$PhCH_2Br$	hexane	-45	18	*(R)*-**5b**	14	76
16	**4a**	*(R,R)*-**1f**	$PhCH_2Br$	toluene	-45	18	*(R)*-**5a**	57	84
17	**4b**	*(R,R)*-**1f**	CH_2=CH-CH_2Br	toluene	-45	18	**5d**	63	97
18	**4b**	*(R,R)*-**1f**	^nBuI	toluene	-45	18	**5e**	0	-
19	**4c**	*(R,R)*-**1f**	MeI	toluene	-45	18	*(S)*-**5b**	5	73
20	**4d**	*(R,R)*-**1f**	$PhCH_2Br$	toluene	-45	18	**5c**	14	51

[a] For general procedure, see note 3. [b] Data taken from ref. 2c. [c] Absolute configuration of *(S)*-**5b** was determined as shown in note 4. Absolute configurations of **5c**, **5d**, and **5e** are not yet determined.

Table 1 shows the results of a survey for chiral ligands and experimental conditions[3] using a stoichiometric amount of chiral tetradentate amines (*(R)*-**1a**~*(R,R)*-**1g**). For the benzylation of **4b**, *(R,R)*-**1f** was the best ligand among them, giving the product (*(R)*-**5b**)[4] in up to 93% yield and 94% ee in toluene (run 9). As was the case for the construction of chiral tertiary carbons by the same strategy,[2a-c,e] toluene is superior as a solvent to give the product in much higher ee than DME, THF, and ether (runs 10 vs 12-14), indicating that ligating solvents can compete with *(R,R)*-**1f** as the ligand for the lithium of lithium enolate. It is also shown that *(R,R)*-**1f** works efficiently for the reaction of **4a** and **4b** only with reactive alkylation reagents (runs 16,

10, and 17 vs. 18). For the substrates (**4c**, **4d**) having a bulkier substituent at 2-position, chemical yields and ee's of the products were found to be lower.

An approach to catalytic version of the above reaction as to the *(R,R)*-**1f** was made using the conditions reported previously.[2c] The results are summarized in Table 2. The reaction does not proceed practically in the absence of any ligand (run 1). In the presence of ligand(s), the reaction is enhanced greatly in the presence of 1 equivalent of *(R,R)*-**1f** (run 2), but not at all in the presence of 0.1 equivalent of *(R,R)*-**1f** (run 3), while it is enhanced to some extent in the presence of 2 equivalents of an achiral bidentate ligand (**2b**) (run 4). These results mean that one of the conditions for catalytic asymmetric alkylation to carry out in the presence of *(R,R)*-**1f** and **2** is fulfilled, expecting ligand exchange *in situ*.

Table 2 Catalytic Benzylation of **4b** with Benzyl Bromide (10 equivalents) Using *(R,R)*-**1f** in the Presence of Achiral Ligand to give *(R)*-**5b**[a]

Run	Chiral ligand *(R,R)*-**1f** (eq)	Achiral ligand **2** (eq)	Time (hr)	Product **5b**	Yield (%)	E. e. (%)
1	0	0	18	*(RS)*-**5b**	~0	-
2[b]	1.0	0	18	*(R)*-**5b**	86	93
3	0.1	0	18	*(R)*-**5b**	~0	-
4	0	**2b** (2.0)	18	*(RS)*-**5b**	12	-
5	0.1	**2a** (2.0)	48	*(R)*-**5b**	14	48
6	0.1	**2b** (1.0)	48	*(R)*-**5b**	28	86
7	0.1	**2b** (2.0)	48	*(R)*-**5b**	66	80
8	0.1	**2b** (2.0)	96	*(R)*-**5b**	69	77
9	0.1	**2c** (2.0)	48	*(R)*-**5b**	49	88
10	0.1	**2c** (3.0)	48	*(R)*-**5b**	33	77
11	0.1	**2d** (2.0)	48	*(R)*-**5b**	14	87
12	0.1	DME (2.0)	48	*(R)*-**5b**	4	18
13	0.1	**2e** (2.0)	48	*(R)*-**5b**	19	84
14	0.1	**2f** (2.0)	48	*(RS)*-**5b**	89	~0
15	0.1	**2g** (1.0)	48	*(R)*-**5b**	85	20

[a] All reactions were carried out in toluene at -45 °C. For general procedure, see note 3.
[b] Data taken from Table 1.

Using 0.1 equivalent of *(R,R)*-**1f**, the reaction was carried out in the presence of various achiral ligands (runs 5~15). Although catalytic efficiency is still unsatisfactory, the fact that the product (*(R)*-**5b**) was obtained in 66% yield and 80% ee using 2 equivalents of **2b** (run 7) clearly shows that turnover of *(R,R)*-**1f** is occurring during the reaction, and thus, provides the first example of catalytic asymmetric alkylation of achiral lithium enolates for the construction of chiral quaternary carbon centers.[6]

References and Notes

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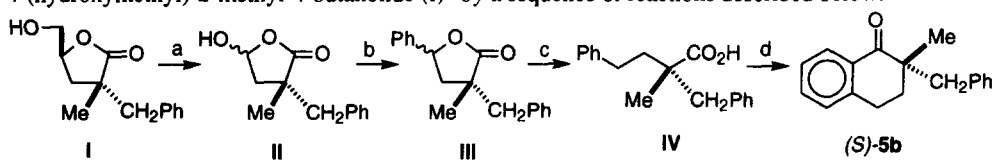
1. For reviews, see: a) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624-1654. b) Juaristi, E.; Beck, A. K.; Hansen, J.; Matt, T.; Mukhopadhyay, T.; Simson, M.; Seebach, D. *Synthesis* **1993**, 1271-

1290. c) Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis;* John Wiley & Sons: New York, 1995; Chapter 5.3 (pp 166-188). d) Berrisford, D. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 178-180. e) Koga, K. *Pure Appl. Chem.* **1994**, *66*, 1487-1492. f) Koga, K.; Shindo, M. *J. Synth. Org. Chem., Jpn.* **1995**, *53*, 1021-1032.

2. a) Murakata, M.; Nakajima, M.; Koga, K. *J. Chem. Soc., Chem. Commun.* **1990**, 1657-1658. b) Hasegawa, Y.; Kawasaki, H.; Koga, K. *Tetrahedron Lett.* **1993**, *34*, 1963-1966. c) Imai, M.; Hagihara, A.; Kawasaki, H.; Manabe, K.; Koga, K. *J. Am. Chem. Soc.* **1994**, *116*, 8829-8830. d) Matsuo, J.; Koga, K. *Chem. Pharm. Bull.* **1997**, *45*, 2122-2124. e) Murakata, M.; Yasukata, T.; Aoki, T.; Nakajima, M.; Koga, K. *Tetrahedron* **1998**, *54*, 2449-2458. f) Uragami, M.; Tomioka, K.; Koga, K. *Tetrahedron: Asymmetry* **1995**, *6*, 701-704. g) Yasuda, K.; Shindo, M.; Koga, K. *Tetrahedron Lett.* **1996**, *37*, 6343-6346. h) Yasuda, K.; Shindo, M.; Koga, K. *Tetrahedron Lett.* **1997**, *38*, 3531-3534. i) Yasukata, T.; Koga, K. *Tetrahedron: Asymmetry* **1993**, *4*, 35-38. j) Riviere, P.; Koga, K. *Tetrahedron Lett.* **1997**, *38*, 7589-7592.

3 The general procedure is as follows. Under argon atmosphere, a solution of TMS enol ether (**3**) (1.0 mmol) and DME (0.20 mmol) in a solvent (8.9 mL) was treated with a solution of MeLi (1.0 mmol) and LiBr (1.1 mmol) in ether (purchased from Kanto Chemical) at room temperature for 30 min. A solution of a chiral tetradentate amine (**1**) (0.10~1.0 mmol) in a solvent (3.0 mL) [and an achiral bidentate amine (**2**) or DME in the case of catalytic conditions] was added, and the whole was stirred at -20 °C for 40 min. Then, at -78 °C, a solution of alkyl or allyl halide (10 mmol) in a solvent (2.0 mL) was added dropwise within 2 min, and the whole was stirred at a desired temperature for a desired time. The reaction mixture was quenched by adding 10% aq citric acid (10 mL). After warmed to room temperature, the organic layer was separated and the aq layer was extracted with ether (20 mL x 2). The combined organic layers were washed successively with satd aq $NaHCO_3$ (20 mL x 2) and brine (20 mL x 1), dried over anhyd $MgSO_4$, filtered and evaporated to give the crude product, which was purified by column chromatography (silica gel, hexane-ether 50:1) to give a mixture of the target compound and the ketone derived from the starting TMS enol ether. The mixture was analyzed by HPLC using a chiral column (Daicel Chiralcel OJ® or OD-H®) to determine the enantiomeric excess and the chemical yield using naphthalene as an internal standard.

4. The absolute configuration of *(S)*-**5b** was determined by the synthesis from the known *(2S,4S)*-2-benzyl-4-(hydroxymethyl)-2-methyl-4-butanolide (I)[5] by a sequence of reactions described below.



[a] i) aq KOH, ii) KIO_4 in aq H_2SO_4. [b] i) PhMgBr, ii) H^+. [c] Pd-C/H_2. [d] Polyphosphoric acid.

5. Tomioka, K.; Cho, Y.-S.; Sato, F.; Koga, K. *J. Org. Chem.* **1988**, *53*, 4094-4098.

6. For reviews on diastereo- and enantioselective construction of chiral quaternary carbon centers, see: a) Martin, S. F. *Tetrahedron* **1980**, *36*, 419-460. b) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037-2066. c) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 388-401.