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Enantioselective Methylation of the Lithium Enolate of 1-Tetralone Mediated by Chiral C_2-Symmetric DMEU Derivatives

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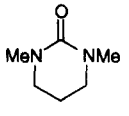
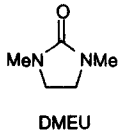
Abstract: Chiral C_2-symmetric DMEU derivatives were designed and synthesized as chiral ligands for lithium. The reaction of the lithium enolate (**2**) of 1-tetralone (**1**) with methyl iodide in toluene in the presence of a DMEU derivative (**11**) and hexamethyldisilazane gave (*S*)-2-methyl-1-tetralone ((*S*)-**3**) in up to 92% ee.

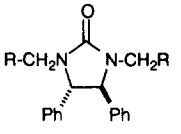
Hexamethylphosphoric triamide (HMPA) has been used widely in organic synthesis for its unique properties as a dipolar aprotic solvent and as a monodentate ligand to form complexes with metal cations.[2] Since the industrial use of HMPA is not recommended in view of its possible carcinogenicity, cyclic urea derivatives, such as DMPU (*N,N'*-dimethyl-*N,N'*-propyleneurea[3]) and DMEU (*N,N'*-dimethyl-*N,N'*-ethyleneurea[4]), were developed as safe substitutes having similar properties.[5]



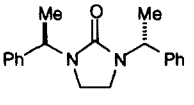
DMPU



DMEU



4: R = Bu^t
5: R = Ph
6: R = H
7: R = α-naphthyl
8: R = 1-adamantyl



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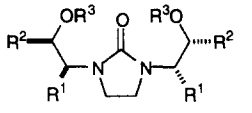
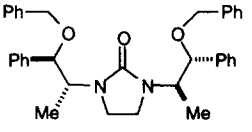


10: R^1 = Me, R^2 = Ph, R^3 = Me
11: R^1 = Me, R^2 = Ph, R^3 = CH_2Ph
12: R^1 = Me, R^2 = Ph, R^3 = CH_2-$C_6H_2Me_3$-2,4,6
13: R^1 = H, R^2 = Ph, R^3 = CH_2Ph
14: R^1 = Me, R^2 = H, R^3 = CH_2Ph
15: R^1 = Ph, R^2 = Ph, R^3 = CH_2Ph



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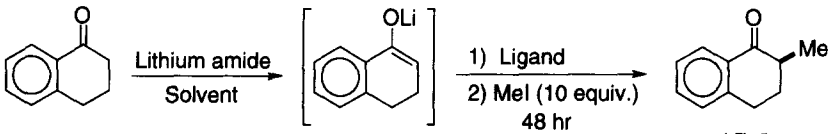
In the course of our studies on enantioselective alkylation of achiral lithium enolates with achiral alkyl halides mediated by chiral amines as ligands for the lithium,[6] we became interested in designing chiral versions of these cyclic urea derivatives as chiral ligands. Since we expected by model studies that 5-membered and C_2-symmetric chiral urea derivatives would give better chiral environment than the corresponding 6-membered

ones, we prepared various chiral C_2-symmetric derivatives (**4**~**16**)[7] of DMEU, and examined their effects on the stereochemical course of the reaction of the lithium enolate (**2**) of 1-tetralone (**1**) with methyl iodide to give 2-methyl-1-tetralone (**3**).[8] The results are summarized in Table 1.

Table 1 Enantioselective Methylation of 2



1 **2** (*S*)-**3**

Run	Lithium Amide[a]	Ligand (1.1 eq.)	Additive (eq.)	Solvent	Temp (°C)	**3** Chem. Y. (%)	**3** E. E. (%)[b]	**3** Config.
1	LDA	none	none	toluene	-45	10	-	-
2	LDA	DMPU	none	toluene	-45	27	-	-
3	LDA	DMEU	none	toluene	-45	45	-	-
4	LDA	**4**	none	toluene	-45	13	45	*S*
5	LDA	**4**	none	ether	-45	4	19	*S*
6	LDA	**4**	none	THF	-45	52	0	-
7	LDA	**4**	none	DME	-45	57	0	-
8	LDA	**5**	none	toluene	-45	13	19	*S*
9	LDA	**6**	none	toluene	-45	48	0	-
10	LDA	**7**	none	toluene	-45	9	9	*S*
11	LDA	**8**	none	toluene	-45	0	-	-
12	LDA	**9**	none	toluene	-45	30	11	*R*
13	LDA	**10**	none	toluene	-45	40	8	*S*
14	LDA	**11**	none	toluene	-45	38	40	*S*
15	LDA	**11**[c]	none	toluene	-45	47	39	*S*
16	LDA	**12**	none	toluene	-45	12	2	-
17	LDA	**13**	none	toluene	-45	22	4	-
18	LDA	**14**	none	toluene	-45	24	0	-
19	LDA	**15**	none	toluene	-45	16	0	-
20	LDA	**16**	none	toluene	-45	32	0	-
21	LTMP	**11**	none	toluene	-45	36	29	*S*
22	LHMDS	**11**	none	toluene	-45	41	50	*S*
23	LHMDS	**11**	none	toluene	-78	34	82	*S*
24	LHMDS	**11**	HMDS (4.0)	toluene	-78	49	92	*S*
25[d]	LHMDS	**11**	HMDS (4.0)	toluene	-78	66	90	*S*

a) In all cases, lithium amide (1.1 eq.) in hexane solution was used. b) The ee values of the product were determined by HPLC analysis using a chiral column (Daicel OD-H). c) Three equivalents of **11** were used. d) The reaction was carried out for one week.

We first examined the effects of DMPU and DMEU on the chemical yields of the reaction in toluene. Under the same reaction conditions, it is shown that the chemical yields of **3** were increased in the presence of 1.1 equivalents of these cyclic urea derivatives (runs 1~3). This fact suggests the possibility that chiral DMEU derivatives may work as chiral auxiliaries to render the reaction enantioselective. Encouraged by these data, we designed chiral DMEU derivatives in two ways.

In the first approach, a cyclic urea derivative (**4**) was synthesized having two chiral centers in the ring and CH_2-Bu^t group on both nitrogens. We designed this compound as a chiral ligand based on the assumption that the Bu^t group in **4** will orient itself exclusively in the other side of the nearest phenyl group on the chiral carbon.[9,10] In the presence of 1.1 equivalents of **4**, it is shown that chemical yield and ee of the product (**3**) are dependent on the solvent used under the same reaction time (48 hr) at -45°C (runs 4~7). Thus, in less polar solvents such as toluene (run 4) and ether (run 5), the reaction gave an optically active product in lower chemical yields, while in more polar solvents such as THF (run 6) and DME (run 7), a racemic product was obtained in higher chemical yields. From these data, toluene was selected as the solvent of choice. Among the compounds (**4~8**) having an R group of different sizes, **4** was found to be most efficient as a chiral ligand to give the product in 45% ee. It is also shown that chemical yield of the product becomes lower as the bulkiness of the R group increases, presumably due to the steric hindrance for coordination of the urea carbonyl group to the lithium.

In the second approach, a cyclic urea derivative (**9**) was examined having a chiral center at the substituent on both nitrogens. Although ee of the product was low, **9** gave the product in higher chemical yield (run 12) than **4** (run 4). It is interesting to note that this cyclic urea derivative having an α-branched alkyl group on both nitrogens can also work as a ligand to the lithium to enhance the reaction. Therefore, several derivatives (**10~16**) having chiral center(s) and an alkoxy group as an additional ligation site at the substituent on both nigrogens were synthesized from the corresponding optically active β-amino alcohols. Among them, only **11** gave the product in moderate chemical and optical yields (run 14). The substituent on oxygen (runs 13, 14, and 16) and relative configuration of the two chiral centers on the substituent (runs 14 vs. 20) are found to be important for asymmetric induction, while cyclic urea derivatives (**14**, **15**) having one chiral center on the substituent on both nitrogens did not work as a chiral ligand (runs 17 and 18). Moreover, the use of a 3-fold excess of **11** did not improve the optical yield of the product (run 15).

We have also found that the lithium amide used as a base for the preparation of the lithium enolate of **1** also affects the reaction. Thus, in the reaction using **11** as a chiral ligand, the use of lithium tetramethylpiperidide (LTMP) reduced enantioselectivity of the reaction (run 21), while the use of lithium hexamethyldisilazide (LHMDS) improved it (run 22). It is also shown that the presence of excess hexamethyldisilazane (HMDS) increased the enantioselectivity of the reaction (runs 23 vs. 24). Racemization of the product during the reaction was found to be minimal, because elongation of the reaction time increased the chemical yield of the product in almost the same enantioselectivity (run 24 vs. 25).

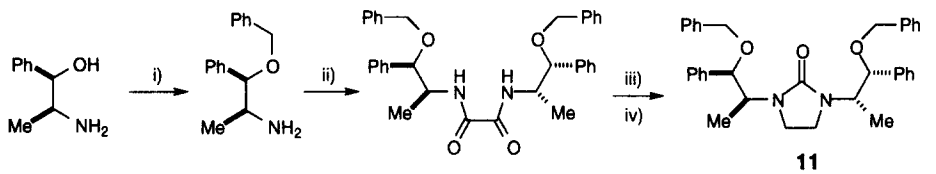
A typical experimental procedure is as follows (run 24). Under argon atmosphere, a solution of n-butyllithium in hexane (1.71 *N*, 0.64 ml, 1.1 mmol) was added to a solution of HMDS (1.08 ml, 5.1 mmol) in toluene (6 ml) at -78°C. After stirring for 10 min, a solution of **11** (589 mg, 1.1 mmol) in toluene (3 ml) was added, and the whole was stirred at -78°C for 10 min. A solution of **1** (146 mg, 1.0 mmol) in toluene (3 ml) was added. After stirring for another 20 min, methyl iodide (0.62 ml, 10 mmol) in toluene (3 ml) was added, and the whole was stirred at -78°C for 48 hr. The reaction mixture was quenched with 10% aqueous citric acid, and the whole was extracted with ethyl acetate. The organic extracts were combined, washed successively with 20% aqueous $Na_2S_2O_3$, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl, and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gave a residue, which was purified by column chromatography (silica gel, hexane-ether (50:3)) to give (*S*)-**3** (78.8 mg, 49%), $[\alpha]_D^{25}$ -48.1 (*c*, 2.1, dioxane),

as a pale yellow oil. Enantiomeric excess of this product was determined to be 92% by HPLC using a chiral column. The starting material (**1**) (64.0 mg, 44%) was recovered.

Although rate enhancement of this reaction is still moderate, the present results clearly show that a chiral C_2-symmetric cyclic urea derivative (**11**) can work efficiently as a chiral ligand for enantioselective reaction of achiral lithium enolate (**2**).

REFERENCES AND NOTES

1. Present addresses: a) Central Research Institute, Zeria Pharmaceutical Co., Ltd., Konan-cho, Ohsato-gun, Saitama 360-01, Japan. b) Department of Medicinal Chemistry, School of Medicine, Hiroshima University, Kasumi, Minami-ku, Hiroshima 734, Japan.
2. a) Normant, H. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 1046-1067. b) Gilkerson, W. R.; Jackson, M. D. *J. Am. Chem. Soc.* **1979**, *101*, 4096-4100. c) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624-1654.
3. Systematic IUPAC name is 1,3-dimethyl-2-oxo-hexahydropyrimidine.
4. Systematic IUPAC name is 1,3-dimethyl-2-imidazolidinone.
5. a) Mukhopadhyay, T.; Seebach, D. *Helv. Chim. Acta* **1982**, *65*, 385-391. b) Seebach, D.; Henning, R.; Mukhopadhyay, T. *Chem. Ber.* **1982**, *115*, 1705-1720. c) Seebach, D.; Beck, A. K.; Studer, A. in *Modern Synthetic Methods 1995*, Vol. 7, ed. by Ernst, B.; Leumann, C: VCH, 1995, p. 1-178.
6. a) Murakata, M.; Nakajima, M.; Koga, K. *J. Chem. Soc., Chem. Commun.* **1990**, 1657-1658. b) Imai, M.; Hagihara, A.; Kawasaki, H.; Manabe, K.; Koga, K. *J. Am. Chem. Soc.* **1994**, *116*, 8829-8830. c) Koga, K.; Shindo, M. *J. Synth. Org. Chem., Jpn.* **1995**, *53*, 1021-1032.
7. a) All compounds were fully characterized by ^{1}H-NMR, MS, and elemental analyses. b) As an example, **11** was synthesized from (1*R*,2*S*)-norephedrine as shown below.



11

i) NaH, $PhCH_2Br$ in THF; ii) oxalyl chloride in CH_2Cl_2; iii) $LiAlH_4$ in THF; iv) $(CCl_3O)_2CO$, Et_3N in CH_2Cl_2.

8. The absolute configuration of optically active **3** is known: Jaouen, G.; Meyer, A. *J. Am. Chem. Soc.* **1975**, *97*, 4667-4672.
9. For example, see: Corey, E. J.; Yu, C.-M.; Kim, S. S. *J. Am. Chem. Soc.* **1989**, *111*, 5495-5496.
10. It is shown by X-ray analysis that the conformation of **5** in a solid state is as expected. Details will be reported elsewhere.

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