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FACTORS CONTROLLING THE DIASTEREOFACE SELECTIVITY IN THE COMPLEMENTARY ASYMMETRIC ALKYLATION OF α-ALKYL β-KETO ESTERS

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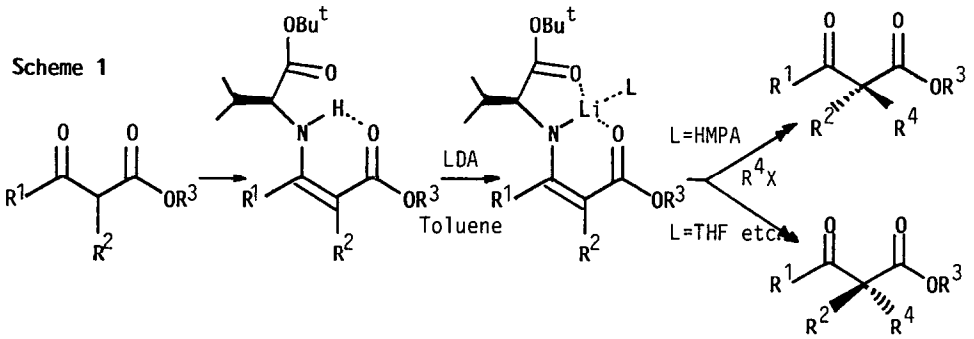
summary: Complementary asymmetric alkylation reaction of the lithioenamine derived from 2-methoxycarbonylcyclohexanone and (S)-valine tert-butyl ester was examined by employing the various electron pair donating additives in a toluene solvent, in order to clarify the factors controlling the diastereoface selectivity.

Development of the asymmetric reactions producing either enantiomers is of great importance since the chiral auxiliaries available are usually limited to one enantiomer.[1] Some sophisticated methodologies have been devised to produce either enantiomers in the formation of the chiral tertiary carbon center.[2] However, there has been only few reliable methods to produce either enantiomers bearing the chiral quaternary carbon center.[3] We have recently reported a complementary asymmetric synthesis of α,α-dialkyl β-keto esters via the alkylation of the lithioenamines derived from α-alkyl β-keto esters and (S)-valine tert-butyl ester (Scheme 1).[4] The crucial features of the method rely on the dependence of the diastereoface selection on the set of external ligand-toluene solvent systems. When toluene is used as a solvent, the use of one equivalent of HMPA as a ligand[5] leads to top side attack on the one hand, while the use of one to three equivalents of THF, NMe_3, or dioxolane leads to bottom side attack on the other hand. The purpose of the present communication is to report a further insight on this phenomena and to provide a mechanistic consideration on this intriguing reaction.

Scheme 1



The reaction of the lithioenamine **1** with methyl iodide in toluene was examined.[6] In the absence of HMPA the reaction did not proceed below -50°C. However, in the presence of one equivalent of HMPA, the reaction did proceed at -55°C to give the methylated product (**2** (R=Me)) in the enantiomeric purity of over 99% as shown in Table I. Even an addition of a catalytic amount of HMPA (0.1 eq) led to the formation of **2** in 85% ee. Both acceleration of

the reaction rate and enhancement of the diastereoface selection caused by the addition of HMPA imply the possibility that upon an addition of HMPA, the lithioenamine, existing probably in a mixture of aggregates (**4**) in a toluene solvent,[7] might be converted to the definitely organized reactive species similar to **5** bearing HMPA as the ligand (L in **5**) for the lithium cation.[5]

On the other hand, an addition of THF resulted in the bottom side attack to afford **3** (R=Me) as shown in Table II. An addition of two equivalents of THF led to the production of **3** in 92% ee. The more THF was added, the lower % ee of **3** became. When fifteen equivalents of THF was added, **3** of 67% ee was obtained. In THF solvent without an additive, **3** of 58% ee was obtained. These behaviors also imply the possibility that, upon an addition of THF, a mixture of aggregates (**4**) was converted to the real reactive species similar to **5** bearing THF as a coordinated ligand (L in **5**), which effects the high and reversed diastereoface selection.

Effects of some electron pair donating additives other than HMPA and THF in the methylation with methyl iodide and allylation with allyl bromide of **1** were also examined (Table III). There is a clear tendency that the powerful ligand afforded **2** resulting from the top side attack and the weaker ligand afforded **3** resulting from the bottom side attack. The importance of the chelated structure is evident from the data obtained by the use of [2.1.1]-cryptand. Although the crown ethers, 12-crown-4 and 18-crown-6, did not affect the diastereoface selectivity, the addition of [2.1.1]-cryptand did affect both reaction rate and diastereoface selection to afford **3** (R=Me) in 14% ee.[8] Since [2.1.1]-cryptand is known to be the powerful capture for the lithium cation,[5a,9] generation of a species of the disorganized free anion (**6**) should be responsible for the great acceleration of the reaction rate and the significant loss of the diastereoface selection.

Furthermore, the alkylation of the lithioenamine[10] derived from cyclohexanone and (S)-valine tert-butyl ester was carried out under the similar conditions (MeI/ HMPA, TMEDA, or THF in toluene, and in THF) and the diastereoface selection was found to be not so much sensitive to the solvent systems, giving (S)-methylcyclohexanone in 68∿98% ee. These data also suggest that the chelated structure shown in **5** was essential for the reversal of the diastereoface selection.

In all the alkylation reactions of the lithioenamine (**1**) carried out during the course of this study, the sense of asymmetric induction can be interpreted by assuming a trans-fused chelated structure in which the unshared electron pair of nitrogen retains a conjugation with an enamine double bond as shown in Figure 1.[11] The bulky and strongly ligating HMPA[12] (L in Fig. 1) would coordinate to the lithium cation to satisfy the tetravalency and result in both the increasing the negative charge in enamine system and suppressing the bottom side attack, leading to the top side attack. On the other hand, a weakly ligating ether or amine ligand (L in Fig. 1) would not activate the enamine system enough to simply react with alkyl halide and be replaced by alkyl halide[13] to result in the increase of the actual concentration of alkyl halide in the bottom side, leading to the preferential bottom side attack.[14]

Fundamental understanding on the factors controlling the diastereoface selection discussed here will open the new way to the development of the effective asymmetric reactions. Further studies are in progress in our laboratory.

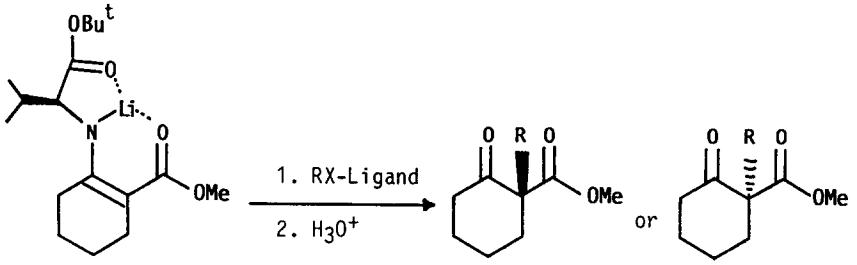


Table I. Effect of HMPA in Toluene[a)]

Run	HMPA(eq)	Temp(°C)	Isolated Yield(%)	%ee[b)] (Conf'n)
1	none	-5	57	50(R)
2	0.1	-78 to -20	55	85(R)
3	0.5	-78 to -20	62	91(R)
4	1.0	-55	57	99(R)
5	3.0	-78 to 0	64	91(R)

a) **1** →**2** (R=Me). b) See reference 4.

Table II. Effect of THF in Toluene[a)]

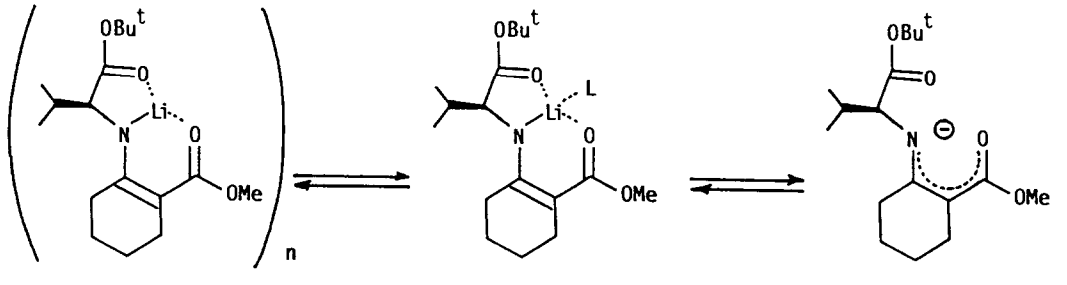
Run	THF(eq)	Temp(°C)	Isolated yield(%)	%ee[b)] (Conf'n)
1	none	-5	57	50(R)[c)]
2	2	-78	63	92(S)
3	4	-78	67	78(S)
4	6	-78	74	75(S)
5	15	-78	67	67(S)
6	in THF	-78	77	58(S)

a) **1** →**3** (R=Me). b) See reference 4.
c) **2** (R=Me).

Table III. Effect of Some Additives (Ligands) in Toluene (**1** →**2** or **3**)

Additives (eq)[a)]	**2** or **3** (R=Me) Temp (°C)	Isolated Yields(%)	%ee (Conf'n)[b)]	**2** or **3** (R=Allyl) Temp (°C)	Isolated Yields(%)	%ee (Conf'n)[b)]
None	-5	57	50(R)			
HMPA(1)	-55	57	99(R)	-55	71	76(S)
DMPU(3)				-20	65	51(S)
18-Crown-6(3)	-78 to -20	78	53(R)			
12-Crown-4(3)	-78 to -20	65	52(R)			
TMANO(3)	-78 to -20	52	7(R)			
TMA(3)	-78	27	3(R)	-55	11	20(S)
[2.1.1]-Cryptand(3)	-78	69	14(S)			
TMEDA(3)	-78 to -20	70	49(S)	-78	31	7(S)
1,4-Dioxane(2)	-78	20	59(S)			
1,3-Dioxolane(2)	-78	37	91(S)	-78	56	56(R)
THF(2)	-78	63	92(S)	-78	52	30(R)

a) HMPA: hexamethylphosphoramide; DMPU: N,N'-dimethylpropyleneurea; TMANO: trimethylamine N-oxide; TMA: trimethylamine; TMEDA: tetramethylethylenediamine. b) See reference 4.



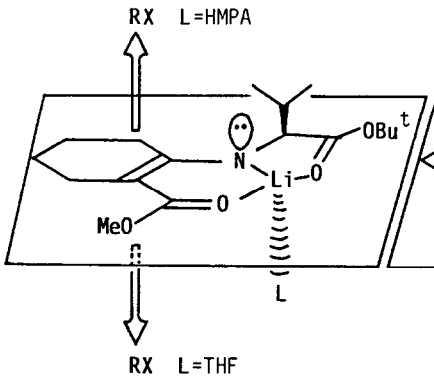


Figure 1

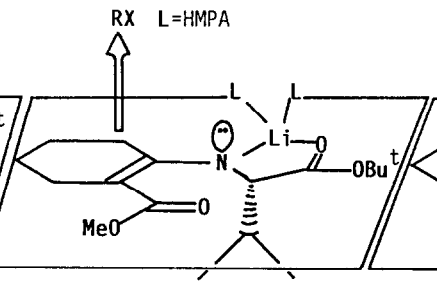


Figure 2[14)]

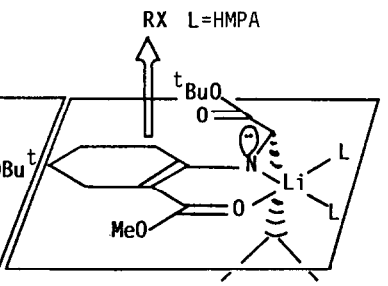


Figure 3[14)]

Acknowledgment. The authors express their sincere thanks to Prof. A. I. Meyers for his suggestion on the reaction mechanism.[14)]

References and Notes

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6. For the reaction procedure carried out in this paper, see reference 4.
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8. The reaction was completed within 30 min at -78°C upon an addition of [2.1.1]-cryptand.
9. D. Moras and R. Weiss, Acta Crystallog. Sec. B, 29, 400 (1973).
10. a) S. Hashimoto, Yakugaku Zasshi, 102, 1103 (1982); b) S. Hashimoto and K. Koga, Chem. Pharm. Bull, 27, 2760 (1979).
11. The cis-fused chelated structure is also possible. However, a constant overlap of the unshared electron pair of the nitrogen with an enamine double bond seems to be difficult by the inspection of the molecular model.
12. C. Reichardt, "Solvent Effects in Organic Chemistry," H. F. Ebel ed., Verlag Chemie, Weinheim, 1979.
13. The interaction of the lithium cation with alkyl halide has been suggested. cf. A. I. Meyers, D. R. Williams, and M. Druelinger, J. Am. Chem. Soc., 98, 3032 (1976) and references cited therein.
14. Although the above mechanistic interpretation (Fig. 1) seems to be plausible, alternatives for the top side attack caused by HMPA might be possible. Only partial breaking of the chelate by HMPA results to form the species shown in Fig. 2 or in Fig. 3. These would put the bulky isopropyl group in the bottom side, so attack comes from top side. We are grateful to Prof. Meyers for his suggestion on the mechanistic interpretation shown in Fig. 3.

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