ASYMMETRIC MICHAEL REACTION OF α -ALKYL β -KETO ESTERS VIA CHIRAL ENAMINES

Kiyoshi Tomioka, Kaori Ando, Kōsuke Yasuda, and Kenji Koga* Faculty of Pharmaceutical Sciences, University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113, Japan

Summary: Depending on the combination of solvents and additives, Michael reaction of chiral lithioenamines generated from **1a,b** with di-tert-butyl methylenemalonate (2) affords, after hydrolysis, either enantiomers of α, α -disubstituted B-keto esters (3,4) in high enantiomeric excess.

Michael reaction is one of the most important procedures for the carbon-carbon bond forming reactions.¹ Asymmetric modifications of this procedure have been the current interests in synthetic organic chemistry.² However, there has been only few reliable asymmetric Michael reactions which provide either enantiomers from the same starting materials.³ We now report that asymmetric Michael reaction of chiral enamines (1a,b), prepared from α -alkyl B-keto esters and \underline{L} -valine \underline{tert} -butyl ester, with di- \underline{tert} -butyl methylenemalonate (2) provides either enantiomers of α , α -disubstituted B-keto esters (3,4) with high enantioselectivity.

Reaction of the chiral lithioenamine, generated by LDA-lithiation of 1a, 4^{4} with 2^{5} in toluene at -78°C afforded, after hydrolysis, (R)-4a in 33% enantiomeric excess (ee) as shown in the Table I.^{6,7} Addition of the 1 eq. of HMPA resulted in the reversal of the stereo-chemical course of the reaction to afford (S)-3a in 58% ee. Increase of the amount of HMPA was found to improve the stereoselectivity, providing 3a in 72% ee by the use of 4 eq. of HMPA at -78°C and 3a of 92% ee was obtained when the reaction was conducted at -95°C.

In striking contrast to these results, the reaction in toluene in the presence of THF dramatically changed the stereochemical course of the reaction to give 4a in 72% ee at -78°C and in 76% ee at -95°C. In the THF solvent at -105°C, 4a of 95% ee was obtained.



As summarized in the Table I the present reaction conditions are applicable to the asymmetric synthesis of both cyclic and acyclic α, α -disubstituted B-keto esters.

The results may be explained by the trans-fused chelated structure (5) proposed in the alkylation of the lithioenamines with alkyl halides.⁴ The ligand L would coordinate to lithium cation from the bottom side to satisfy its tetravalency.^{4b} The reaction in toluene in the presence of HMPA should proceed from the front side of 5 owing to the high coordinating ability of HMPA (L in ${f 5}$) to give ${f 3}$ and the reaction in the presence of THF should proceed from the bottom side via ligand exchange between THF (L in 5) and methylenemalonate of comparable coordinating ability to give 4. Further studies for mechanistic considerations are in progress in our laboratory.

0Bu-t

Ŕ²

5

0Et

Enamine	Solvent	Additive ^a	Temp °C	3/4	[a]° ^b	ee %	Yield % ^C
	Toluene	none	-78	4a	+16.4	33(R)	59
1a	Toluene	HMPA(1)	-78	3a	-28.3	58(S)	80
1a	Toluene	HMPA(2)	-78	3a	-33.3	68(S)	77
1a	Toluene	HMPA(4)	-78	3a	-35.3	72(S)	86
1a	Toluene	HMPA(4)	-95	3a	-45.1	92(S)	73
1a	Toluene	THF(2)	-78	4a	+35.2	72(R)	75
1a	Toluene	THF (8)	-78	4a	+35.5	72(R)	78
1a	Toluene	THF (8)	-95	4a	+37.5	76(R)	87
1a	THF	none	-78	4a	+39.6	80(R)	83
1a	THF	none	-105	4a	+46.6	95 (R)	86
1b	Toluene	HMPA(4)	-95	3b	+6.72	87 (S)	82
1b	Toluene	THF(8)	-95	4b	-5.08	66(R)	58
1b	THF	none	-105	4b	-6.48	84 (R)	86

Table I Asymmetric Michael Reaction of α -Alkyl B-Keto Esters

a) Numbers in parentheses are the equivalent of additive. b) Optical rotations were measured in CHCl₂ (25° C) at D line for **3,4a** and at 365 nm for **3,4b**. The maximum rotations were -49.2° for **3a** and +7.72° for **3b.** c) Isolated yield after chromatography on silica gel.

References and Notes

- 1) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., Menlo Park, California, 1972, p. 595.
- 2) For reviews, see: K. Tomioka and K. Koga, "Asymmetric Synthesis," ed. by J. D. Morrison, Academic Press, New York, 1983, Vol. 2, p. 201. For the leading references, see: K. Academic Press, New York, 1983, Vol. 2, p. 201. For the feading references, see: K. Hermann and H. Wynberg, J. Org. Chem., 44, 2238 (1979); M. Zuger, T. Weller, and D. Seebach, <u>Helv. Chim. Acta</u>, 63, 2005 (1980); T. Takeda, T. Hoshiko, and T. Mukaiyama, <u>Chemistry Lett.</u>, 1981, 797; D. J. Cram and G. D. Y. Sogah, J. Chem. Soc., <u>Chem. Commun.</u>, 1981, 625; D. Enders and K. Papadopoulos, <u>Tetrahedron Lett.</u>, 24, 4967 (1983); M. Pfau, G. Revial, A. Guingant, and J. d'Angelo, J. <u>Am. Chem. Soc.</u>, 107, 273 (1985).
 B. Nebout, B. de Jeso, and J.-C. Pommier, J. <u>Chem. Soc.</u>, <u>Chem. Commun.</u>, 1985, 504.
 A. Tomioka, K. Ando, Y. Takemasa, and K. Koga, J. <u>Am. Chem. Soc.</u>, 106, 2718 (1984); b)
- Idem, Tetrahedron Lett., 25, 5677 (1984). 5) P. Ballesteros, B. W. Roberts, and J. Wong, <u>J. Org. Chem.</u>, 48, 3603 (1983).
- 6) All new compounds described in this paper provided satisfactory spectroscopic and analytical data.
- The absolute configuration was determined by the chemical correlation. The ee was determined by the 'H NMR analysis in the presence of chiral shift reagent (Eu(hfc)₃). Details will be reported in due course.

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