CHEMISTRY LETTERS, pp. 1399 - 1402, 1984.

HIGHLY ENANTIOSELECTIVE ALDOL REACTION OF METHYL KETONES VIA CHIRAL STANNOUS AZAENOLATES

Koichi NARASAKA, Tetsuo MIWA, Hiroki HAYASHI, and Masako OHTA Department of Chemistry, Faculty of Science, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113

Chiral 1,3-oxazolidines are readily prepared from methyl ketones and chiral norephedrine. Formation of stannous azaenolates from the oxazolidines and reaction with aldehydes followed by removal of the chiral auxiliary lead to the aldol products in high level of enantiomeric purity.

In recent several years, the development of enantioselective aldol reactions have been widely studied in conjunction with the synthesis of natural products, and highly enantioselective aldol reactions have been established by employing chiral enolates of ethyl ketones and propionic acid derivatives.¹⁾ On the other hand, it has still remained as a problem to achieve high asymmetric induction in aldol reactions of methyl ketones and acetic acid derivatives.²⁾ To our knowledge, the Sn(II) enolate-chiral diamine method is only applied successfully to the enantioselective aldol reaction of an acetic acid derivative.³⁾

In this communication, we wish to report a convenient and highly enantioselective aldol reaction of methyl ketones <u>via</u> readily available chiral 1,3-oxazolidines. The general pathway of this aldol reaction is outlined in the following scheme. That is, when a chiral oxazolidine (<u>1</u>) which is prepared from a chiral 1,2-amino alcohol (for example, chiral norephedrine) and a methyl ketone is treated with 2 molar equiv. of lithium diisopropylamide (LDA), the lithium azaenolate (<u>2</u>) would be generated. Then by the addition of a metal salt, the



lithium azaenolate (2) would be converted to a chiral azaenolate (3) which would exist in the rigid conformation by forming a five membered metal chelate.⁴⁾ Therefore, high asymmetric induction would be expected in the successive aldol reaction between 3 and an aldehyde. The adduct (4) thus formed would be readily hydrolyzed under mild acid conditions to afford an optically active β -hydroxy ketones along with the chiral auxiliary.

First, we examined the enantioselective aldol reaction employing acetone as a starting methyl ketone.⁵⁾ The reactions of chiral oxazolidines derived from acetone and various chiral 1,2-amino alcohols with 3-phenylpropanal were precisely investigated to find out the suitable chiral auxiliary and additive metal salt. And, in conclusion, it was noted that when norephedrine and stannous chloride were employed as a chiral auxiliary and an additive metal salt respectively, 4-hydroxy-6-phenyl-2-hexanone was obtained in good optical purity.

The experimental procedure is as follows: The oxazolidine of acetone (la) was prepared quantitatively by stirring a dry acetone solution of (+)-norephedrine overnight and following distillation.⁶⁾ To a THF (2 ml) solution of LDA (2.1 mmol) was added a THF (2 ml) solution of la (1 mmol) at 0 °C and the mixture was stirred for 2 h. Then a THF (4 ml) solution of SnCl₂ (1.05 mmol) was added at 0 $^\circ C$ and stirred for 30 min. To this mixture was added a THF (2 ml) solution of 3phenylpropanal (1.2 mmol). After being stirred for 20 min at 0 °C, the mixture was quenched with aqueous 4% NaHCO3. Filtration through a Celite pad, extraction with ether and evaporation of the solvent gave an oily residue, which was purified by column chromatography on silica gel. The resulting adduct ($\underline{4}$, M=H,H) was easily hydrolyzed during the chromatographic separation and (+)-4-hydroxy-6phenyl-2-hexanone was obtained in 59% yield (58% e.e.). According to the same procedure, the reaction between <u>la</u> and various aldehydes were examined, and the results are summarized in Table 1. The aldol products with primary and secondary aldehydes were obtained in 58-73% e.e., which means that the present procedure is the most efficient method for the enantioselective aldol reaction of acetone as

Ph Me	1) 2LDA / THF	3) RCH0 / 0 °C	0 0H 八 I
X Me Me	2) SnCl ₂	4) H ₃ 0 ⁺	Me R
1α			

Table 1.

RCHO	Yield/%	Optical purity/% e.e.	[α] _D
Ph(CH ₂) ₂ CHO	59	58 ⁷⁾	$[\alpha]_{D}^{20}+9.9^{\circ}$ (c 1.9, CHCl ₃)
n-PrCHO	60	58 ^{7),8)}	$[\alpha]_{D}^{25}+35.1^{\circ}$ (c 2.1, CHCl ₃)
(Et) ₂ CHCHO	60	69 ⁷)	$[\alpha]_{D}^{\overline{1}2}+23.2^{\circ}$ (c 1.3, CHCl ₃)
с-С ₆ н ₁₁ Сно	65	737)	$[\alpha]_{D}^{\bar{1}8}+45.0^{\circ}$ (c 1.0, CHCl ₃)
t-BuCHO	65	86 ⁹⁾	$[\alpha]_{D}^{24}+43.9^{\circ}$ (c 0.81, EtOH)

1400

compared with the conventional methods.⁵⁾ And furthermore, the high enantiomeric excess (86% e.e.) was observed in the reaction with pivalaldehyde.

As the high level of the asymmetric induction was observed even in the aldol reaction of acetone, we were prompted to investigate the enantioselective aldol reaction of some methyl ketones. Condensation of acetophenone (or 3,3-dimethyl-2-butanone) with (-)-norephedrine was carried out azeotropically in the presence of a catalytic amount of $\text{Et}_2\text{O}^{\circ}\text{BF}_3$ to give a mixture of the corresponding oxazolidine (<u>1b</u>) and imine (<u>5b</u>) quantitatively. The reactions with aldehydes were investigated using this mixture according to the same reaction procedure. As the resulting adducts (<u>6</u>) were found to resist to be hydrolyzed with silica gel, the transformation to the corresponding β -hydroxy ketones was performed by treatment of <u>6</u> with acetone in the presence of a catalytic amount of $\text{Et}_2^{\circ}\text{BF}_3$. The yield and the optical purity of these products are summarized in Table 2, and it is apparent that the aldol products of methyl ketones were obtained in high to excellent optical purity.



RCOCH ₃	R ´CHO	Yield/%	Optical purity/% e.e.	[α] _D (CHCl ₃)
PhCOCH ₃	Ph(CH ₂) ₂ CHO	68 69	70 ⁷⁾ 76 ⁷⁾ ,8)	$[\alpha]_{D}^{21}$ -37.0° (c 2.8) $[\alpha]_{2}^{26}$ -4].1° (c 1.4)
	с-С ₆ н ₁₁ Сно	64	77 ⁷)	$[\alpha]_{D}^{20} - 49.9^{\circ}$ (c 2.4)
t-BuCOCH ₃	t-BuCHO Ph(CH ₂) ₂ CHO	66 64	85 ⁷)	$[\alpha]_{D}^{29} - 71.1^{\circ}$ (c 1.4) $[\alpha]_{D}^{24} - 14.5^{\circ}$ (c 1.7)
	c-C ₆ H ₁₁ CHO t-BuCHO	54 56	84 ⁷⁾ ,92 ¹⁰⁾ >95 ⁹⁾	$ [\alpha]_{D}^{22}-43.6^{\circ} (c \ 1.6) \\ [\alpha]_{D}^{21}-65.8^{\circ} (c \ 1.4) $

In summary, we have shown an efficient method that accomplished overall the aldol reaction of a methyl ketone with an aldehlyde, providing an aldol product with a high degree of enantioselectivity. It is also noted that the introduction and the recovery of the chiral auxiliary (norephedrine) are carried out by simple procedures, and particularly, the high asymmetric induction is achieved even at ice-cooling reaction temperature. The authors are grateful to Professor Teruaki Mukaiyama for valuable discussion during this work. This research was supported by the Ministry of Education, Japanese Government (Grant-In-Aid, 58470018).

References

- Reviews; D. A. Evans, J. V. Nelson, and T. R. Taber, "Stereoselective Aldol Condensations," in "Topics in Stereochemistry," ed by N. L. Allinger, E. L. Eliel, and S. H. Wielen, John Wiley and Sons, Inc., New York (1982), Vol. 13, p.1; C. H. Heathcock, "The Aldol Addition Reaction," in "Asymmetric Synthesis," ed by J. D. Morrison, Academic Press, Inc., New York (1984), Vol. 3, p. 111.
- 2) a) D. Seebach, V. Ehrig, and M. Teschner, Jestus Liebigs Ann. Chem., <u>1976</u>, 1357; b) H. Eichenauer, E. Friedrich, W. Lutz, and D. Enders, Angew. Chem., Int. Ed. Engl., <u>17</u>, 206 (1978); c) T. Sugasawa and T. Toyoda, Tetrahedron Lett., <u>1979</u>, 1423; d) C. H. Heathcock and C. T. White, J. Am. Chem. Soc., <u>101</u>, 7076 (1979); e) D. A. Evans and T. R. Taber, Tetrahedron Lett., <u>21</u>, 4675 (1980); f) C. H. Heathcock, C. T. White, J. J. Morrison, and D. VanDerveer, J. Org. Chem., <u>46</u>, 1296 (1981); g) C. H. Heathcock, M. C. Pirrung, J. Lampe, C. T. Buse, and S. D. Young, ibid., 46, 2290 (1981).
- 3) N. Iwasawa and T. Mukaiyama, Chem. Lett., 1983, 297.
- 4) A similar type of a five membered organotin(IV) azaenolate of cyclohexanone was used for the enantioselective Michael reaction; B. De Jeso and J-C.
 Pommier, Tetrahedron Lett., 21, 4511 (1980).
- 5) The enantioselectivity (48% e.e.) displayed in the aldol reaction using a chiral hydroazone of acetone is actually the best result for the aldol reaction of acetone.^{2b)}
- 6) <u>la</u>: bp 100 °C (0.2 mmHg, bath temp); ¹H NMR (CDCl₃) δ 0.73 (3H, d, J=6 Hz) 1.4 (3H, s) 1.63 (3H, s) 1.87 (1H, s) 3.83 (1H, m) 5.00 (1H, d, J=7 Hz) 7.22 (5H, s); IR (Neat) 3300, 1605, 1495 cm⁻¹; $[\alpha]_D^{23}$ +32.5° (c 4.95, CHCl₃).
- 7) Determined by ¹H NMR or ¹⁹F NMR measurement of its MTPA ester in the presence of Eu(fod)₃. S. Yamaguchi and H. S. Mosher, J. Org. Chem., <u>38</u>, 1870 (1973).
- 8) The absolute configuration was determined for 4-hydroxy-2-heptanone or 3hydroxy-1-phenyl-1-hexanone by the derivation reaction from optically active 3-hydroxy-hexanoic acid; See D. A. Evans, J. Bartroli, and T. L. Shih, J. Am. Chem. Soc., 103, 2127 (1981); and Ref. 3.
- 9) Determined by ¹H NMR measurement in the presence of $Eu(hfc)_3$.
- 10) Determined by the specific rotation.^{2b)}

(Received June 2, 1984)