Pure & Appl. Chem., Vol. 57, No. 12, pp. 1883–1886, 1985.
Printed in Great Britain.

Asymmetric induction in acyclic systems utilizing metal compounds

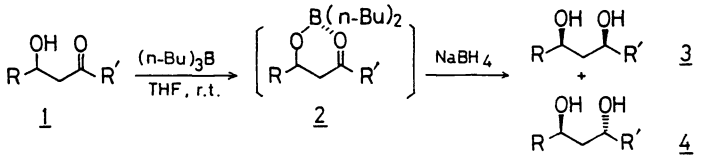
Koichi Narasaka

Department of Chemistry, Faculty of Science, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113, JAPAN

Abstract - Stereochemistry of the reduction of acyclic β-hydroxy ketones and their O-benzyloximes is well directed by a hydroxyl group to give *syn*-1,3-diols and *syn*-1,3-amino alcohols respectively. Furthermore, a highly enantioselective aldol reaction is achieved starting from chiral 1,3-oxazolidines prepared from ketones and chiral norephedrine. Generation of stannous azaenolate from the oxazolidines and the successive reaction with aldehydes lead to the aldol products in high level of enantiomeric purity even from methyl ketones. The asymmetric aldol reaction between 3-pentanone and aldehydes gives *anti*-aldols of high enantiomeric purity.

The subtle problem of selectivity in organic synthesis has presented itself as a formidable challenge to the synthetic organic chemist, and in recent years the control of stereochemistry in acyclic systems is one area which has attracted the efforts of many organic chemists. The problem is especially acute when chiral centers are not adjacent to each other, and remote chiral control is therefore particularly challenging.

Concerning the remote chiral induction in acyclic systems, first the stereoselective reduction of β-hydroxy ketones 1 was investigated by using a hydroxyl group for control of stereoselection. The formation of boron chelate intermediates 2 has been found to be effective to realize the high 1,3-asymmetric induction in the reduction of hydroxy ketones 1. Treatment of 1 with tributylborane or triisobutylborane and the successive reduction with sodium borohydride afforded stereoselectively the corresponding *syn*-1,3-diols 3.[1,2] As various β-hydroxy ketones are nowadays readily prepared by directed aldol reactions, the present method is expected to be used for the preparation of a wide variety of *syn*-1,3-diols.



1 2

Since high 1,3-asymmetric induction was observed in the reduction of β-hydroxy ketones directed by the hydroxyl group, the stereoselective formation of 1,3-amino alcohols[3] has been examined by the reduction of β-hydroxy ketone O-benzyloximes 5 which are easily derived from β-hydroxy ketones 1 and O-benzylhydroxylamine.

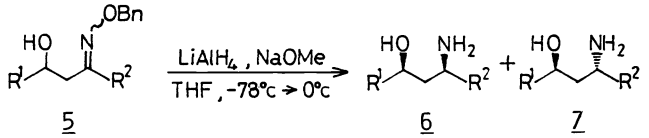


Table 1. Preparation of *syn*-1,3-diols

R	R	Reaction Temp. (Reaction time)	Ratio of *syn*(3):*anti*(4) (Total yield)
C_6H_5	C_6H_5	-78 °C (2h)	98: 2 (94%)
n-C_4H_9	n-C_4H_9	-100 °C (5h)	96: 4 (74%)
C-C_6H_{11}	C-C_6H_{11}	-100 °C (6h)	84:16 (90%)
		-78 °C (36h)	88:12 (85%)*
Me	CH_2=CH(CH_2)$_2$	-100 °C (6h)	95: 5 (93%)

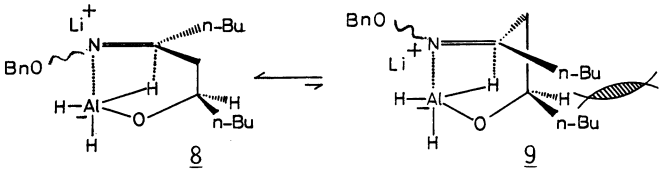
* (iso-Bu)$_3$B was used instead of (n-Bu)$_3$B.

Table 2. Preparation of *syn*-1,3-amino alcohols

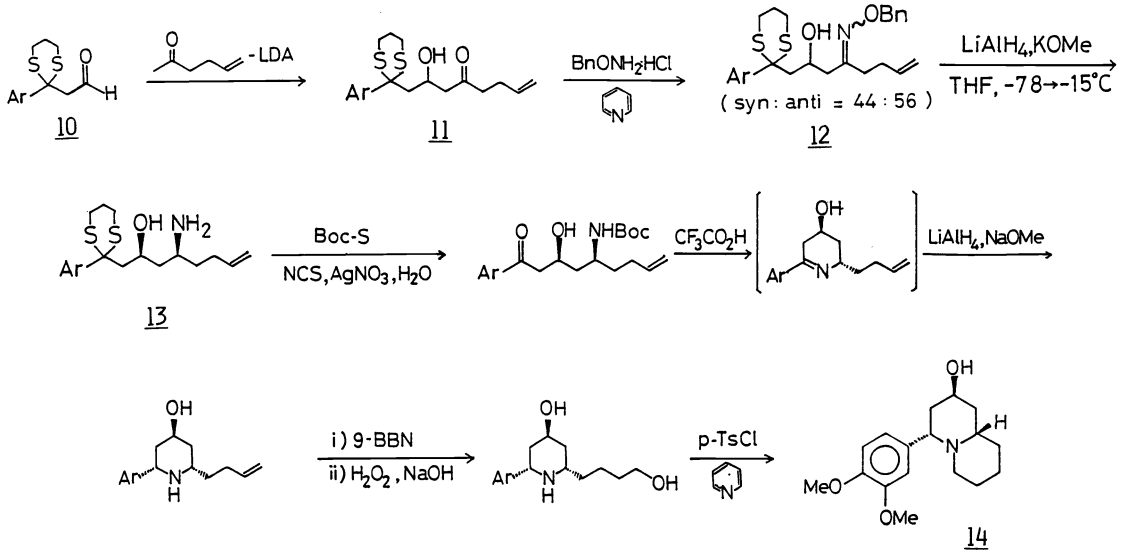
R^1	R^2	*syn*:*anti* of 5	Ratio of 6:7 (Total yield)
n-Bu	n-Bu	(48:52)	96: 4 (92%)
			97: 3 (92%)*
i-Bu	i-Bu	(45:55)	95: 5 (92%)
$PhCH_2CH_2$	$PhCH_2CH_2$	(49:51)	94: 6 (89%)
$PhCH_2CH_2$	CH_3	(66:34)	97: 3 (94%)
Ph	CH_3	(72:28)	92: 8 (93%)*

* Potassium methoxide was used.

The reduction of O-benzyloximes 5 with lithium aluminumhydride in the presence of sodium or potassium methoxide was found to result in the stereoselective formation of *syn*-1,3-amino alcohols 6 presumably by intramolecular reduction via the preferable transition state 8.[4]



Having established the stereoselective method for the preparation of *syn*-amino alcohols 6, we diverted our interest toward the application of this method to the synthesis of alkaloids, particularly a quinolizidine alkaloid. Quinolizidine alkaloids have been generally synthesized starting from cyclic precursors. By applying the present method, an alternative approach was provided in which the cyclic alkaliod, lasubine II (14),[5] is formed from a stereoselectively derived acyclic intermediate 13.
The aldol reaction of 5-hexen-2-one with an aldehyde 10 gave the corresponding adduct 11 in which the whole carbon skeleton for lasubine II was arranged. Conversion of 11 into the O-benzyloxime 12 and the successive reduction with $LiAlH_4$-CH_3OK produced stereoselectively the key intermediate, *syn*-amino alcohol 13. After the cyclization steps as shown in the following scheme, the synthesis of lasubine II (14) was completed in a stereoselective manner.[6]



Thus, these stereoselective reductions directed by a hydroxyl group would provide useful methods for preparation of acyclic 1,3-diols and amino alcohols. We next turned our attention to preparing these compounds in optically active forms and considered the possibility of developing an enantioselective aldol reaction. Recently, various efficient asymmetric aldol reactions have been established by using chiral metal enolates or by employing a chiral ligand and a prochiral enolate.[7] Although β-hydroxy carboxylic acid

derivatives have been prepared in high enantiomeric excess by these methods, the asymmetric aldol reactions between ketones and aldehydes have scarcely shown good enantioselectivity.[8] Furthermore, achievement of high enantiomeric induction in aldol reactions of methyl ketones and acetic acid equivalents has been considered to be difficult, so we first investigated the enantioselective aldol reaction utilizing a chiral oxazolidine 15 as a starting material.

The chiral oxazolidine 15 was easily prepared from chiral norephedrine and acetone. It was considered that the treatment of 15 with 2 molar equiv. of LDA followed by the addition of stannous chloride would generate the chiral stannous azaenolate 16 which forms a five membered chelate. When the stannous azaenolate 16 was treated with aldehydes at 0°C and the successive cleavage of a chiral auxiliary was carried out on silica gel, the corresponding aldol products 17 were obtained in good optical purities.[9]

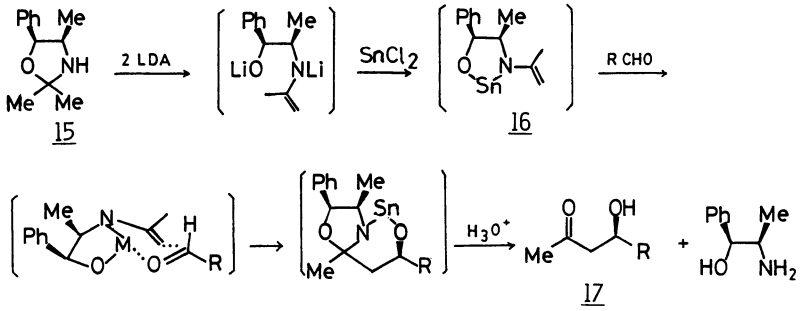


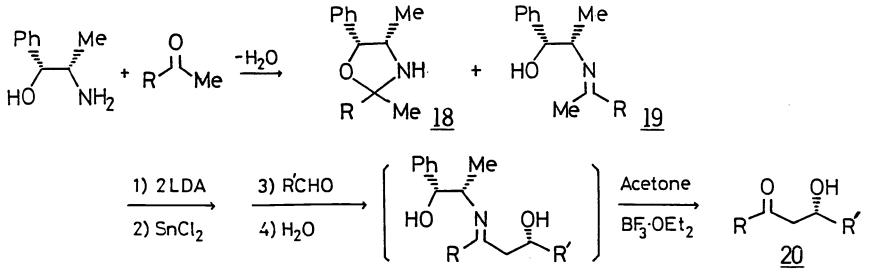
Table 3. Asymmetric aldol reaction of acetone

RCHO	Yield(%)	e.e.(%)
Ph⌒CHO	59	58
⌒CHO	60	58
⟨H⟩—CHO	65	73
t-BuCHO	65	86

Table 4. Asymmetric aldol reaction of methyl ketones

RCOMe	R'CHO	Yield(%)	e.e.(%)
PhCOMe	⌒CHO	69	76
	⟨H⟩—CHO	64	77
	t-BuCHO	66	93
t-BuCOMe	Ph⌒CHO	64	85
	⟨H⟩—CHO	54	92
	t-BuCHO	56	>95

The satisfactory asymmetric induction observed even in the aldol reaction of acetone prompted us to investigate the enantioselective aldol reaction of some methyl ketones. Condensation of a methyl ketone with (-)-norephedrine was carried out azeotropically to give a mixture of the corresponding oxazolidine 18 and imine 19 quantitatively. The reaction with aldehydes was undertaken by the above procedure and the results are shown in Table 4.[9]



Thus, an efficient method was accomplished for the overall asymmetric aldol reaction of methyl ketones with aldehydes providing aldol products with high degree of enantioselectivity. This method was then further applied to the asymmetric aldol reaction of 3-pentanone. The chiral oxazolidine of 3-pentanone 21 was lithiated and converted to a stannous azaenolate, and was employed in the reaction with aldehydes. As is depicted in Table 5, *anti*-aldols 22 were obtained predominantly in excellent optical purity.[10]

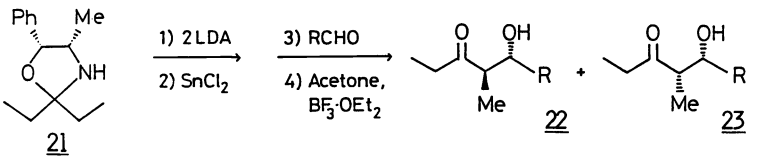
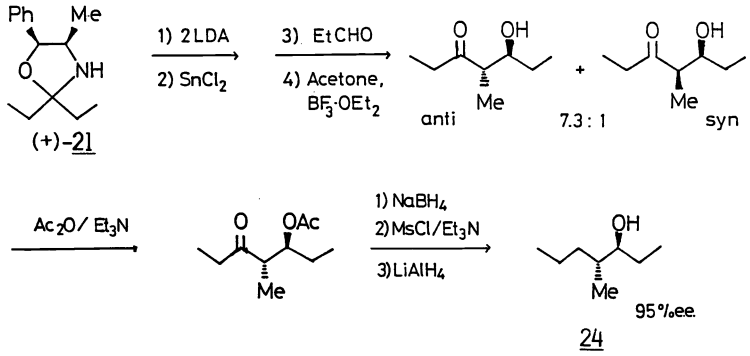


Table 5. Asymmetric aldol Reaction of 3-pentanone

RCHO	yield(%)	anti:syn	e.e.(%)
Ph⌒CHO	77	7:1	92
⟨H⟩—CHO	75	9:1	92
t-BuCHO	56	6:1	>95

Although several selective asymmetric reactions have been reported for the preparation of optically active *syn*-β-hydroxy acid derivatives, highly enantioselective synthesis of the diastereomer, the *anti*-β-hydroxy carboxylic acid derivatives, has still been difficult.[11] On the other hand, *anti*-aldols 22 were thus prepared in high enantioselectivity by this aldol reaction utilizing a cyclic stannous azaenolate.

Furthermore, an isomer of an insect pheromone, (3S,4R)-4-methylheptan-3-ol(24), was synthesized from (+)-oxazolidine 21 in almost optically pure form.[10]



ACKNOWLEDGEMENTS

It is a great pleasure to acknowledge the valuable contributions of my co-workers whose names appear in the references. I thank Professor T. Mukaiyama for valuable discussions and suggestions. Financial support of this work by the Education Ministry, Japanese Government (Grant 58470018) is gratefully appreciated.

REFERENCES

1. a) K. Narasaka and F. C. Pai, Chem. Lett., 1415 (1980); b) idem, Tetrahedron, 40, 2233, (1984).
2. Recent topics in stereoselective synthesis of 1,3-diols; T. Matsumoto, F. Matsuda, K. Hasegawa, and M. Yanagiya, Tetrahedron, 40, 2337 (1984); M. T. Reetz, Angew. Chem. Int. Ed. Engl. 23, 556 (1984); and references cited in the ref. 1b.
3. For recent progress of preparation of acyclic 1,3-amino alcohols; V. Jäger and R. Schohe, Tetrahedron, 40, 2199 (1984); M. Hirama, T. Shigemoto, Y. Yamazaki, and S. Ito, J. Am. Chem. Soc., 107, 1797 (1985); and references cited therein and in the ref. 4a.
4. a) K. Narasaka and Y. Ukaji, Chem. Lett., 147 (1984); b) K. Narasaka, S. Yamazaki, and Y. Ukaji, ibid., 2068 (1984).
5. K. Fuji, T. Yamada, E. Fujita, and H. Murata, Chem. Pharm. Bull., 26, 2515 (1978).
6. K. Narasaka, S. Yamazaki, and Y. Ukaji, unpublished results.
7. 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, Wiley-Interscience, New York (1984), Vol. 13, p. 1; C. H. Heathcock, "The Aldol Addition Reaction," in "Asymmetric Synthesis," ed by J. D. Morrison, Academic Press Inc., Orland (1984), Vol. 3, p. 111; N. Iwasawa and T. Mukaiyama, Chem. Lett., 297 (1983).
8. T. Mukaiyama, N. Iwasawa, R. W. Stevens, and T. Haga, Tetrahedron, 40, 1381 (1984); and references cited in the ref. 9.
9. K. Narasaka, T. Miwa, H. Hayashi, and M. Ohta, Chem. Lett., 1399 (1984).
10. K. Narasaka and T. Miwa, submitted to Chem. Lett..
11. A. I. Meyers and Y. Yamamoto, J. Am. Chem. Soc., 103, 4278 (1981).