Tetrahedron Letters, Vol.29, No.3, pp 337-338, 1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

ENANTIOSELECTIVE ALDOL REACTION MEDIATED BY CHIRAL LITHIUM AMIDE BASES

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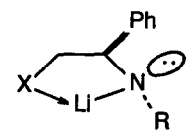
Summary: Highly enantioselective aldol reaction mediated by chiral lithium amide bases was achieved between some methylketones and aldehydes .

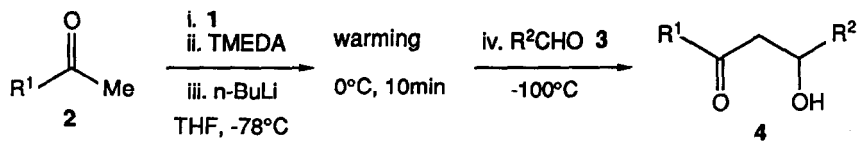
Asymmetric aldol reaction is a current focus in organic synthetic reactions.[1] Employing chiral auxiliaries that are not covalently bound to one of the reactants, there have been a few cases in which high enantiomeric excesses had been obtained. The most successful asymmetric induction has been realized in reactions of tin(II) enolates.[2] In the cases of employing readily accessible lithium enolates, the asymmetric inductions are usually low.[1,3] The highest ee that has been recorded is 85%.[4]

We have reported an efficient enantioselective deprotonation reaction using chiral lithium amide bases.[5] Five membered chelated structures are expected to be formed for these lithium amide bases as shown in Fig. 1. We applied these lithium amide bases as chiral reagents for enantioselective aldol reaction.[6]

Fig. 1



1a ; R = isopropyl, X = 1-piperidyl
b ; R = cyclohexyl, X = N-methyl piperazinyl



A typical experimental procedure (entry 2 in Table I) is as follows. A solution of lithium amide (**1b**) was prepared under argon atmosphere by adding a solution of n-butyllithium (1.8 mmol) in hexane (1.5 M solution) to a solution of the corresponding amine (2.0 mmol) in THF (10 ml) under stirring at -78°C. Tetramethylethylenediamine (TMEDA)(2.0 mmol) in THF (5 ml) was added. After 5 min acetophenone (1.6 mmol) in THF (5 ml) was added and the whole was stirred for 5 min. n-Butyllithium (1.8 mmol) in hexane was added and the mixture was warmed to 0°C for 10 min and was then recooled to -100°C. Benzaldehyde (2.0 mmol) in THF (8 ml)(-100°C) was added in one portion and stirring was continued at -100°C for 0.5 min. After addition of saturated aqueous ammonium chloride (10 ml), the product was isolated by the usual work up and purification (column chromatography (silica gel, AcOEt : hexane = 1:9~2:8)) to give R-(+)-4 (R^1=R^2=Ph) in 74% chemical yield. Enantiomeric excess (82%) of the product was determined by ^{1}H-NMR spectrum of its acetate in the presence of (+)-Eu-DPPM.

The reaction of **2** (R^1=Ph) by lithiation with **1a** followed by the addition of **3** (R^2=Ph) at -78°C gave the product in 2% ee. It is noteworthy that the stereoselectivity of the reaction is highly dependent on the reaction conditions. Thus, additional one equivalent of n-butyllithim is essential to the effective asymmetric induction (33% ee).[4,7,8] Warming process raised optical yield dramatically (61% ee). The addition of TMEDA raised the ee (65% ee). The reaction at -100°C (entry 1 in Table I) also raised the ee (73%).

The results of various methyl ketones and aldehydes in optimized conditions are summarized in Table I. Up to 86% ee was achieved.

Further studies on the stereochemical mechanisms are underway.

Table I. Asymmetric Aldol Reaction Mediated by Chiral Base (**1**)

entry	Base	R^1	R^2	isolated yield (%)	$[\alpha]_D$ (temp, solvent)	ee (%)[a]	config.
1	**1a**	Ph	Ph	74	+25.2° (25, MeOH)	73	R[c]
2	**1b**	Ph	Ph	74	+28.5° (25, MeOH)	82	R[c]
3[b]	**1b**	Ph	1-Naph	80	+119.9° (25, $CHCl_3$)	86	-[d]
4	**1b**	Ph	2-Naph	70	+32.6° (25, MeOH)	85	-[d]
5	**1b**	Ph	t-Bu	55	+59.9° (19, $CHCl_3$)	74	R[e]
6	**1b**	Ph	c-hexyl	65	+40.4° (20, $CHCl_3$)	65	R[e]
7	**1b**	Ph	n-Pr	52	+29.8° (25, $CHCl_3$)	50	S[e]
8	**1b**	t-Bu	t-Bu	73	+38.8° (19, $CHCl_3$)	62	R[e]
9	**1b**	t-Bu	Ph	76	+45.9° (25, $CHCl_3$)	75	-[d]

a) Enantiomeric excesses were determined by ^{1}H-NMR spectra in the presence of (+)-Eu-DPPM. (For entries 1~7, the corresponding acetates were used.) b) TMEDA was absent. c) ref. 9. d) Not yet determined. e) ref. 10

References and Notes

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(Received in Japan 8 October 1987)