Enantioselective Aldol Reactions using Chiral Lithium Amides as a Chiral Auxiliary

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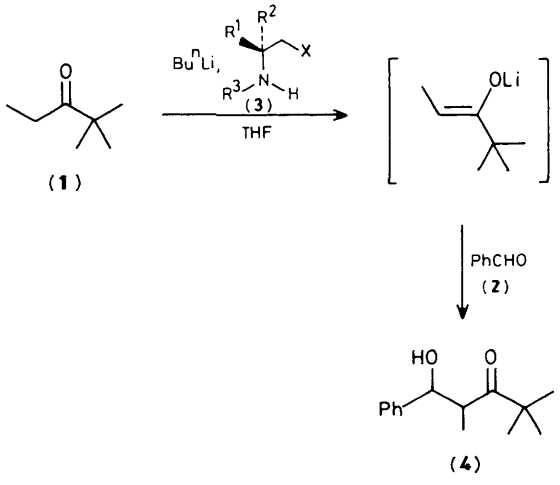
The enantioselective aldol reaction of ethyl t-butyl ketone with benzaldehyde in the presence of chiral ligands has been thoroughly investigated. With the lithium amide derived from 2-isopropylamino-1-methoxy-3-methylbutane (**3c**) as chiral ligand, a chemical yield of 93% and 68% enantiomeric excess were realized.

In connection with recent progress in stereocontrolled organic synthesis, chiral-base-mediated asymmetric syntheses have attracted much attention.[1] We have already reported[1] that carboxylic acids are enantioselectively α-alkylated by use of chiral lithium amides, which function as both strong base and chiral auxiliary. As an extension of this asymmetric reaction, we directed our attention to the enantioselective aldol reactions.

Although there are many reports of successful diastereoselective aldol reactions,[2] only a few reports of enantioselective ones have appeared.[3] We now report the enantioselective aldol reaction of ethyl t-butyl ketone (**1**) with benzaldehyde (**2**) in the presence of a chiral lithium amide derived from a chiral amine (**3**) and n-butyl-lithium, a reaction studied by Heathcock[4] with lithium di-isopropylamide (LDA) resulting in the racemic *erythro*-aldol *rac*-(**4**) (Scheme 1).

The chiral amines (**3a**—**l**) were prepared from readily available α-amino acids or α-phenylethylamine according to a method developed earlier.[1] The reaction conditions were investigated using (**3c**) as follows. To a solution of (**3c**) in tetrahydrofuran was added n-butyl-lithium to generate the lithium amide. Addition of the ketone (**1**) to the solution of the chiral lithium amide immediately produced the lithium enolate, which was treated with benzaldehyde (**2**) to give the *erythro*-aldol (**4**). The enantiomeric excess (% e.e.) of (**4**) was determined by h.p.l.c. on a chiral stationary phase column [Bakerbond™ (DNBPG) chiral column (RP-7103-0)]. The absolute configuration of the major isomer was tentatively assigned from the chiral recognition mechanism and the order of elution from the chiral column.[5]

As shown in Table 1, the amounts of n-butyl-lithium used to produce the chiral lithium amide seriously affected both the chemical yield and the enantiomeric excess in this reaction.



Scheme 1

Table 1. Effects of the amounts of n-butyl-lithium and lithiation temperatures in the use of the chiral amine (**3c**)

Reagent ratios										Lithiation temp/°C	Isolated yield/%	% e.e.	Configuration
(**1**)	:	(**3c**)	:	Bu^nLi	:	Pr^i_2NH							
1.0	:	1.2	:	0.6						−10	89[a]	2	*R,R*
1.0	:	1.2	:	1.2						−10	90	18	*S,S*
1.0	:	1.2	:	1.8						−10	52	57	*S,S*
1.0	:	1.2	:	2.2						−10	29	71	*S,S*
1.0	:	1.2	:	2.4	:	1.2				Room temp.	92	47	*S,S*
1.0	:	1.2	:	2.4	:	1.2				−10	93	68	*S,S*
1.0	:	1.2	:	2.4	:	1.2				−40	91	67	*S,S*
1.0	:	1.2	:	2.4	:	1.2				−70	88	33	*S,S*

[a]. Based on Bu^nLi.

Table 2. Enantioselective aldol reactions using various chiral lithium amides

(**3**)	R^1	R^2	R^3	X	Isolated yield/%	% e.e.	Configuration
(**3a**)	Me	H	Pr^i	OMe	85	45	*S,S*
(**3b**)	Pr^i	H	Me	OMe	77	5	*S,S*
(**3c**)	Pr^i	H	Pr^i	OMe	93	68	*S,S*
(**3d**)	Pr^i	H	Et_2CH	OMe	90	35	*S,S*
(**3e**)	Pr^i	H	cyclo-C_6H_{11}	OMe	89	57	*S,S*
(**3f**)	Pr^i	H	Bu^tCH_2	OMe	93	12	*S,S*
(**3g**)	H	Ph	Pr^i	H	80	66	*R,R*
(**3h**)	H	Ph	Pr^i	OMe	92	68	*R,R*
(**3i**)	H	Ph	Pr^i	OBu^t	85	54	*R,R*
(**3j**)	H	Ph	Pr^i	NMe_2	87	28	*R,R*
(**3k**)	H	Ph	Pr^i	$N[CH_2]_5$	84	30	*R,R*
(**3l**)	Bzl	H	Pr^i	OMe	80	44	*S,S*

When the ketone (**1**) was lithiated with 1.2 equiv. of the chiral lithium amide generated from (**3c**) and equimolar amounts of n-butyl-lithium, and then treated with benzaldehyde (**2**), the aldol (**4**) was obtained in 90% yield but the enantiomeric excess was only 18%. However, the enantiomeric excess was improved to 57% and further to 71% by increasing the amounts of n-butyl-lithium while the chemical yield was decreased due to the reaction of the excess of n-butyl-lithium with the ketone (**1**). This result suggested that the chiral lithium amide from (**3c**) was a more effective chiral ligand than the chiral amine (**3c**) itself in this aldol reaction. However, when (**1**) was lithiated at −10 °C by a combination of 1.2 equiv. of LDA and an equimolar amount of the lithium amide of (**3c**), the chemical yield increased to 93% and the enantiomeric excess was not affected (68%). Probably LDA acts as a strong base and the chiral lithium amide acts as a chiral auxiliary. Interestingly, both lowering the lithiation temperature to −70 °C and raising it to room temperature caused decrease of the enantiomeric excess to 33 and 47%, respectively. On the basis of the foregoing results, the procedure used subsequently comprised lithiation of the ketone (**1**) by a combination of 1.2 equiv. of LDA and 1.2 equiv. of the chiral lithium amide at −10 °C for 30 min, followed by treatment with benzaldehyde (**2**) at −70 °C for 5 min.

To find the most efficient chiral auxiliary, various chiral lithium amides were examined. Several noteworthy substituent effects were apparent (Table 2). Usually, the *S,S*-isomer of (**4**) was formed predominantly in the chiral environment produced by the (*S*)-amines (**3a**—**f** and **l**), which originated from L-α-amino acids. The use of (*R*)-amines (**3h**—**k**) derived from D-α-phenylglycine and the (*S*)-amine (**3g**) mainly gave the *R,R*-isomer of (**4**). As for the substituents attached to the chiral carbon atom, the use of isopropyl and phenyl groups gave the best result (68% e.e.); methyl and benzyl groups were less effective (*ca.* 45% e.e.). Among the *N*-substituents, the bulky isopropyl group showed the highest value for the enantiomeric excess; a striking decrease was observed when the methyl, 1-ethylpropyl and neopentyl groups were used. The methoxy group turned out to be the most effective substituent X, but the amino functions reduced the asymmetric efficiency (*ca.* 30% e.e.). Interestingly, when X was hydrogen, the enantiomeric excess was 66%, similar to that when the methoxy group was used.

Thus, in the aldol reaction of ethyl t-butyl ketone with benzaldehyde, both high chemical yield and high enantiomeric excess were attained by using LDA and the chiral lithium amide derived from (**3**) as a strong base and a chiral auxiliary, respectively.

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