Highly Diastereoselective Aldol Reactions of Chiral Methyl Ketones

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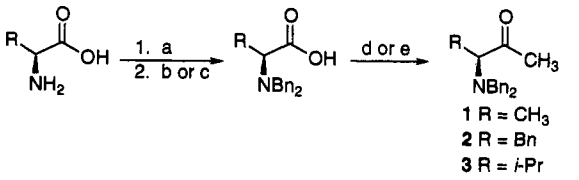
Summary: Highly diastereoselective aldol reactions of lithium enolates of α-(*N*,*N*-dibenzylamino)alkyl methyl ketones with a variety of aldehydes are reported.

Diastereoselective aldol additions have emerged as one of the most efficient and versatile methods available for preparing a wide range of optically active compounds.[1] Very high diastereoselectivities have been reported for aldol reactions involving chiral enolates derived from α-ethyl- or higher alkyl-substituted ketone derivatives. By contrast, relatively few examples of highly diastereoselective aldol reactions of chiral methyl ketones[2,3] or aldol reactions of methyl ketones with chiral catalysts have been reported.[4-7] Of these, most do not involve methyl ketones *per se* but instead utilize chiral acetate equivalents ($XC(O)CH_3$ where X is a chiral auxiliary[8-17]) in which the rotamer population around the C–X bond can be controlled by stereoelectronic factors.

In general, metal enolates of chiral methyl ketones, especially the lithium enolates, give poor diastereoselectivity, largely because these systems lack any inherent control of the rotamer population around the nonreacting C–C(O) bond.[3-11] In this paper we report the results of a study on aldol reactions of lithium enolates of α-(*N*,*N*-dibenzylamino)alkyl methyl ketones which proceed with exceptionally high diastereoselectivity, presumably due to the unique ability of the dibenzylamino group to participate in lithium chelation and simultaneously control the facial selectivity of the approaching aldehyde.

Scheme I[a]



[a] Key: (a) BnBr, K_2CO_3, EtOH; (b) LiOH, H_2O–THF (4:1); (c) cyclohexadiene, 10% Pd–C, EtOH; (d) Me_3CCOCl, Et_3N, THF, then MeMgCl; (e) MeLi (3.0 equiv), Et_2O.

The α-amino ketones used in this study were synthesized from α-amino acids using a minor modification of the procedure reported by Reetz *et al.*[18] as shown in Scheme I. The amino acids, L-alanine, L-phenylalanine, and L-valine (R = CH_3, Bn, and *i*-Pr, respectively), were first converted into their *N*,*N*-dibenzylaminobenzyl esters.[19] Hydrolysis or selective catalytic transfer hydrogenolysis[20] of the benzyl esters yielded the corresponding carboxylic acids which were subsequently converted to ketones **1–3** using either the Mukaiyama[21] or Jorgenson–Gilman[22] protocols. The yields for this four-step sequence ranged from 50% to 60%, based on recovered starting materials.[23]

Aldol reactions of kinetically-generated lithium enolates, derived from ketones **1–3**, were carried out with various aldehydes. On the basis of the results summarized in Table I, several noteworthy observations can be made. First, the aldol products could all be obtained in good yields. Second, as is commonly observed with aldol reactions, bulkier aldehydes generally exhibited higher diastereofacial selectivity than their less sterically encumbered counterparts (*e.g.*, compare entries 1 and 2 *vs* 3 and 4). Third, even the modest diastereoselectivities observed with the alanine-derived ketone, **1**, compared favorably to previous literature reports with other methyl ketone derivatives. Finally, in contrast with the small increase in the diastereoselectivity observed when increasing the size of the R group of the ketone from R = CH_3 to R = Bn (entries 5 and 6), the diastereoselectivity increased

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(23) The enantiomeric purity of the ketones was determined by chiral HPLC analysis using an IBM 9533 HPLC, equipped with a Diacel Chiralpak AS column (UV detector 254 nm; flow rate: 1 mL/min; solvent system: 98% hexane–2% 2-propanol; retention times: **1**, 10.14 min; **2**, 5.65 min; **3**, 4.68 min). Using this assay, the purity of amino ketones **2** and **3** was determined to be >99%, while the purity of **1** was approximately 96%. The partial racemization appears to have occurred at the ester hydrolysis step. For example, when the hydrolysis was carried out in refluxing 50% aqueous KOH/THF solution for 16 h, complete loss of optical activity for the corresponding ketone was observed.

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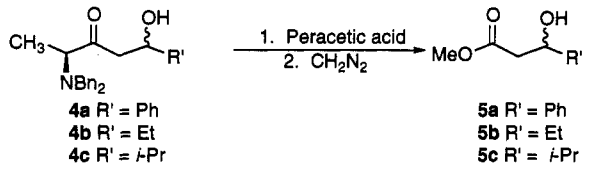
Table I. Diastereoselective Aldol Reactions of Preformed Lithium Enolates of α-Amino Ketones 1–3 with Different Aldehydes in THF

entry	ketone	aldehyde	% yield[a]	selectivity[b]	abs config[c]
1	1 (R = CH_3)	PhCHO	84	80:20	*R*
2	1 (R = CH_3)	C_2H_5CHO	85	82:18	*S*
3	1 (R = CH_3)	$(CH_3)_2CHCHO$	91	88:12[d]	*R*
4	1 (R = CH_3)	$(CH_3)_3CCHO$	81	89:11	*R*
5	2 (R = Bn)	$(CH_3)_2CHCHO$	78	90:10	*R*
6	2 (R = Bn)	$(CH_3)_3CCHO$	76	92:7	*R*
7	3 (R = *i*-Pr)	PhCHO	90	>98:2[e]	*R*
8	3 (R = *i*-Pr)	$(CH_3)_2CHCHO$	64	>98:2[e]	*R*
9	3 (R = *i*-Pr)	$(CH_3)_3CCHO$	88	>98:2[e]	*R*

[a] Isolated yields. [b] The diastereomeric ratios were determined by ^{13}C NMR of the aldol product prior to purification. [c] The absolute configuration of the newly formed stereogenic center (see Scheme II). Methyl ketones 1–3 possessed the *S* configuration. [d] An 86:14 ratio was determined using ^1H NMR. [e] The other isomer was not detected by either ^1H or ^{13}C NMR.

Scheme II

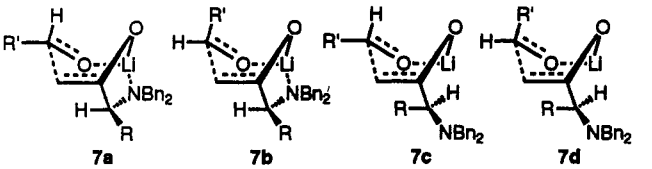


dramatically for the cases of R = *i*-Pr (entries 7–9). *To our knowledge, these cases represent the first examples of highly diastereoselective aldol reactions involving the lithium enolates of chiral methyl ketones.*

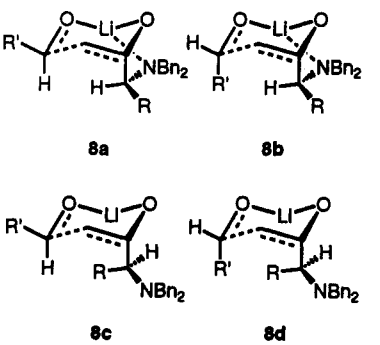
The absolute configuration of the new stereogenic center was unequivocally established by conversion of the crude aldol products into their corresponding 3-hydroxy methyl esters *via* known procedures[9] (see Scheme II). Eu(hfc)$_3$-induced ^1H NMR shifts of the methoxy group of the two enantiomers were significantly different [20 mol % Eu(hfc)$_3$, 4.20 (*R*), 4.01(*S*); 40 mol %, 4.80 (*R*), 4.52 (*S*)], and comparison with the values reported in the literature[3,24] confirmed the absolute configuration. Since the conversion of aldol products **4a–c** into their corresponding hydroxy esters proceeded in excellent overall yield, the integration of the well-separated methoxy groups of the two enantiomers could be correlated to the ratio of two diastereomers. This ratio was in close agreement (±1%) with the original diastereomeric ratio assigned to the aldol product based on ^{13}C NMR.[25]

Unless the rotamer population around the unreactive C–C(O) bond is heavily skewed toward a single preferred conformation, there would be little reason to expect any significant diastereoselectivity. In this case there are two alternative ways of achieving this end, *i.e.*, a purely steric model, dominated by the bulky *N,N*-dibenzylamino group,[19,26] or a chelation model, where the *N,N*-dibenzylamino group lies in the plane of the lithium enolate and the derived facial selectivity results from the difference in size between R′ and H.[27,28] The former model predicts that the *S*-starting ketone will produce the *S,S*-product, while the latter predicts the observed *S,R*-product.

As a consequence of this, we propose the chelated boat transition state model, **7**. Presumably, transition states **7b** and **7d**, which experience substantial destabilization from placing the R′-group in the sterically-encumbered "flagpole" position, do not make any meaningful contribution to the product distribution. Of the two remaining possibilities, **7a** or **7c**, **7a** is preferred since **7c** suffers from inherent $A_{1,3}$-strain not present in its diastereomeric counterpart. Moreover, this model nicely accommodates the parallel increase in diastereoselectivity with the size of R.



A distorted chair conformation of the general type depicted by **8** has been proposed to rationalize the observed selectivity in boron-[11] and titanium-mediated[16] aldol reactions of methyl ketones. However, on the basis of preliminary molecular modeling studies on the lithiated products, the boat transition states (**7**) appear to be intrinsically favored over the alternative chair forms (**8**).[29]



Thus, we have shown that lithium enolates of α-(*N,N*-dibenzylamino)alkyl methyl ketones undergo highly stereoselective aldol reactions with a number of aldehydes and that the observed selectivity can be rationalized in terms of transition-state model **7a**. In addition, since the presence of the *N,N*-dibenzylamino group can control the reduction stereochemistry of adjacent keto groups *via* a nonchelation mechanism, a tandem aldol/reduction sequence could prove to be useful in the synthesis of

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biologically-active amino diols.[18,31] Further studies to elucidate the synthetic potential of these aldol reactions are currently underway and will be reported in due course.

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Supplementary Material Available: Typical experimental procedure, as well as physical and spectroscopic data (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.