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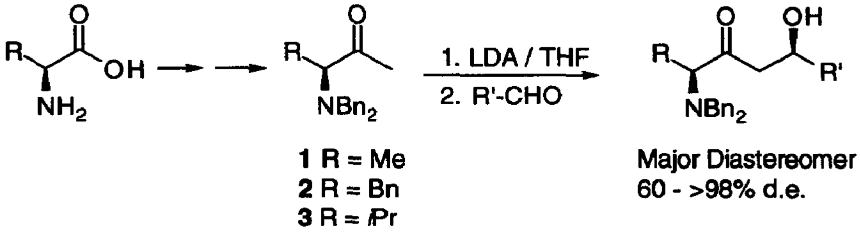
Surprisingly High Diastereoselection in the Aldol Reactions of Sodium Enolates of α-Amino Methyl Ketones

Bharat R. Lagu[1] and Dennis C. Liotta*

Department of Chemistry, Emory University, Atlanta, GA 30322

Abstract: Kinetic enolates of a number of α-(N,N-dibenzyl)amino methyl ketones were allowed to react with a variety of aldehydes. High diastereoselectivity was observed for sodium enolates compared to their lithium counterparts.

Diastereoselective aldol reactions are widely used for the rapid construction of a number of important classes of organic compounds.[2] Although many reports have appeared in the literature describing high diastereoselectivity for aldol reactions of ethyl or substituted ketones or acetate equivalents, relatively few examples can be found for highly diastereoselective aldol reactions of chiral methyl ketones.[3] We have recently reported that the lithium enolates of α-N,N-dibenzylamino methyl ketones undergo aldol reaction with good stereocontrol as shown below.[4] A twist-boat transition state involving internal chelation of the amino group was proposed as a working model to rationalize the observed selectivity (see **Figure 1**, **A**). In this communication we present the results of a study which demonstrates that the stereoselectivity of these reactions can be further enhanced by judicious alteration of several of the reaction parameters.



1 R = Me
2 R = Bn
3 R = *i*Pr

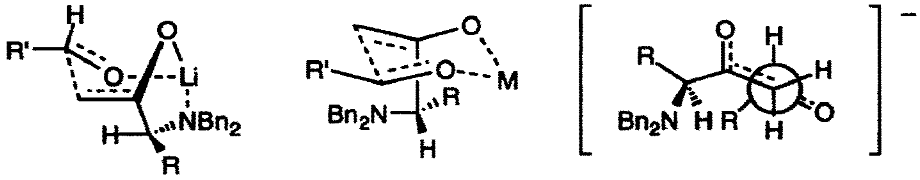
Major Diastereomer
60 - >98% d.e.

The α-(N,N-dibenzyl)amino methyl ketones **1-3** were readily synthesized by following the Reetz protocol.[5] The kinetic enolates of these ketones were allowed to react with pivalaldehyde under a variety of conditions which are summarized in **Table 1**. Several of our observations are noteworthy. Changing the base from LDA to LiHMDS did not result in any change in the diastereoselectivity of the reaction. Based on the working model **A**, it was anticipated that counterions, such as Na or K, which generally form ionic bonds with oxygen, would disrupt the chelation, resulting in lower diastereoselectivity.[6] In the event, the potassium enolate of **1** surprisingly gave the aldol product with only slightly lower selectivity compared to that observed with the lithium enolate (**Table 1**, entries 3 and 2). Even more surprisingly, when the sodium enolate of **1** was allowed to react with pivalaldehyde, only a single diastereomeric aldol product was produced (**Table 1**, entry 4). In order to determine if this observation with sodium enolates was general and not restricted to only sterically demanding aldehydes, a study was initiated involving a number of aldehydes and ketones. The results of this study are summarized in **Table 2**.

It is evident from **Table 2** that some of the trends that were observed with the lithium enolates of **1-3** are maintained with their sodium counterparts. These include the following: (1) bulkier aldehydes give better selectivities (**Table 2**, entries 1-4); (2) sterically hindered ketones give higher diastereoselectivities than unhindered ketones; (3) the configuration of the newly generated chiral center was always 'R' for the major diastereomer. Importantly, in all the cases that were examined, sodium enolates exhibited higher selectivities and chemical yields than their lithium counterparts. For example, a dramatic increase in the diastereoselectivity was observed in the reaction of acrolein with sodium enolate of **1** (90:10) compared to its corresponding lithium enolate (63:37) (**Table 2**, entry 4). These results are reproducible and constant within the experimental limits.[7]

Since these new results are not easily explained using the transition state model **A**, a refinement of the model was necessary. A possible model is exemplified in transition state **B**, which is very similar to one proposed by Masamune[8] and Thornton[9] involving a chair transition state in which the oxygen and the amino group of the enolate are oriented to minimize dipole moment. The aldehyde then approaches from the less hindered side. Another possible model is the open transition state model, depicted in **C**, which is similar to one proposed by Noyori and coworkers.[10] In this model, the aldehyde is thought to approach from the less hindered *si* face of the enolate. The two oxygen atoms are oriented in opposite directions for electrostatic reasons. Attack on the *re* face of the enolate would not occur for steric reasons. In principle, any of these models could account for the high diastereoselectivity observed with sodium enolates.

In order to differentiate between these alternatives, the kinetic enolate of **1** was generated with LDA and then transmetalated with $ZnCl_2$[11] and $ClTi(O^iPr)_3$[12] (**Table 1**, entries 5 and 6). If either three-point or two-point chelation was an important factor in controlling diastereoselectivity (*i. e.*, either transition states **A** or **B**, respectively), these enolates would be expected to result in enhanced d. e.'s relative to the corresponding lithium enolates. However, this proved to be contrary to our observations.[13] Moreover, addition of triisopropylborane[14] in the reaction of the lithium enolate of **1** (**Table 1**, entry 7) with pivalaldehyde gave the aldol product with essentially the same diastereoselectivity. Finally, we have found that the inclusion of additives, such as TMEDA or HMPA (**Table 1**, entries 8 and 9), did not result in diminution of diastereoselectivity.[15] While these results are not easily rationalized using either our originally proposed model **A** or the Masamune / Thornton model **B**, they are in excellent agreement with the open transition state model **C**.



A **B** **C**

Figure 1

Table 1: Effects of Different Reaction Conditions on Diastereoselectivity of the Aldol Reaction of Kinetic Enolates of 1 with Trimethylacetaldehyde.

Entry	Base / Conditions	% Yield[a]	Selectivity[b](R:S)[c]
1	LDA	84	89 : 11
2	LHMDS	81	90 :10
3	KHMDS	78	82 : 18
4	**NaHMDS**	**90**	**> 98 : 2**[d]
5	LDA / $ZnCl_2$	64	86 : 14
6	LDA / $ClTi(O\textit{i}\text{-}Pr)_3$[e]	73	58 : 42
7	LDA / $\textit{i}\text{-}Pr_3B$	79	91 : 9
8	LDA / HMPA	78	90 : 10
9	LDA / TMEDA	90	92 : 8
10	LDA / 12-C-4[f]	78	94 : 6

a. Isolated yields. b. Determined by ^{13}C NMR of the crude aldol product. c. See footnote 16. d. No other diastereomer observed by ^1H, ^{13}C NMR. e. 3.0 equiv. of $ClTi(OiPr)_3$ was used. f. 1.0 equiv. of 12-C-4 was used.

Table 2: Aldol Reactions of α-Amino Ketones 1-3 with Different Aldehydes.

Entry	Ketone	Aldehyde	Selectivity[a] (% Yield)[b] LDA	NaHMDS
1	**1**	^{t}BuCHO	89 : 11 (81)	> 98 : 2 (90)
2	**1**	^{i}PrCHO	88 : 12 (91)	> 98 : 2 (83)
3	**1**	PhCHO	80 : 20 (81)	92 : 8 (90)
4	**1**	**Vinyl-CHO**	**63 : 37 (90)**	**90 : 10 (94)**
5	**2**	^{i}PrCHO	90 : 10 (78)	> 98 : 2 (82)
6	**2**	^{t}BuCHO	93 : 7 (76)	> 98 : 2 (82)
7	**3**	^{t}BuCHO	> 98 : 2 (64)	> 98 : 2 (72)

a. The absolute configuration at the newly formed center was 'R' in all cases.[16] b. All products have been fully characterized (^1H, ^{13}C, IR, LRMS, HRMS and combustion analysis).

These results also raise the question of whether the observed increase in diastereoselectivity for the aldol reactions with sodium enolates is the result of kinetic or thermodynamic control. In order to probe this, two aldol reactions were run simultaneously with the lithium and sodium enolates of **1** and benzaldehyde to give aldol products with 80:20 and 92:8 ratios of diastereomers, respectively. The mixtures were then isolated and re-exposed to NaHMDS in THF at -78°C. The products obtained after equilibration showed a diminution in the diastereomeric ratio (from 80:20 to 68:32 for the lithium case and from 92:8 to 88:12 for the sodium case). Since the magnitude of these changes exceed the magnitude of the experimental error, it suggests that the observed diastereoselectivity results from kinetic control.

In summary, we have shown that sodium enolates of α-(N,N-dibenzyl)amino methyl ketones undergo aldol reactions with very high diastereoselectivity (> 98:2).[17] Preliminary experiments suggest that the product is obtained *via* kinetic control and the results are best rationalized by invoking an open transition state model such as **C**.

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15. Addition of 12-C-4 to the kinetic lithium enolate of **1**, which was expected to enhance the degree of dissociation of the lithium from the enolate oxygen, resulted in only a modest increase in the observed d. e. (**Table 1**, entry 10). These experiments have also been carried out by using benzaldehyde as the aldehyde and similar trends were observed (*i. e.*, almost no change in the diastereoselectivity). We rationalize these observations by noting that while 12-C-4 can effectively solvate one hemisphere of the lithium solvation shell, its presence in no way precludes extensive interactions between lithium and the enolate oxygen.
16. For a discussion of the assignment of absolute configuration, see Ref. 4.
17. **General Experimental Procedures:** To a -78°C, THF solution of NaHMDS (0.1M, 1.3 equiv.) was added 1.0 equiv. of ketone **1**, **2** or **3** as a THF solution. After one hour, the aldhedye was added *via* a syringe and the reaction was immediately quenched with a saturated ammonium chloride solution. The reaction products were isolated using standard work-up procedures. Similar protocols were used for reactions involving lithium enolates. Reactions involving boron, titanium and zinc enolates employed experimental procedures given in the cited references.

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