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Aldol Reactions of α-(N,N-Dibenzylamino) Ethyl Ketones

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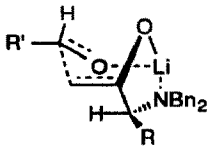
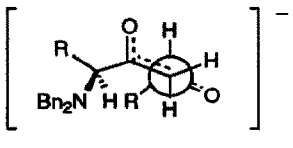
Abstract: Aldol reactions of the sodium enolates of α-(N,N-dibenzylamino) ethyl ketones proceed in a highly diastereoselective fashion and result in the formation of the all *syn* adduct. The observed stereoselectivities are most easily understood in the context of an open transition state.

We have recently reported that aldol reactions of α-(N,N-dibenzylamino) methyl ketones proceed in a highly diastereoselective manner.[3] This stereoselectivity is particularly striking for reactions involving sodium enolates which generally proceed with substantially better diastereoselectivities than their lithium counterparts.[4] In the initial report involving reactions of lithium enolates, we proposed a chelated twist boat transition state (**Scheme 1, A**) to explain both the observed stereoselectivities and the lack of solvent and additive effects. However, in a subsequent report involving reactions of sodium enolates, we concluded that an open transition state model (**Scheme 1, B**) could best accommodate the trends observed in that series. Unfortunately, the differences between the rationales employed in each of these reports creates an obvious conundrum. Either these two sets of apparently similar reactions are proceeding by fundamentally different pathways or (at least) one of the proposed models is incorrect. In order to differentiate between these alternatives, we have studied the aldol additions of α-(N,N-dibenzylamino) ethyl ketones.

Scheme 1



A

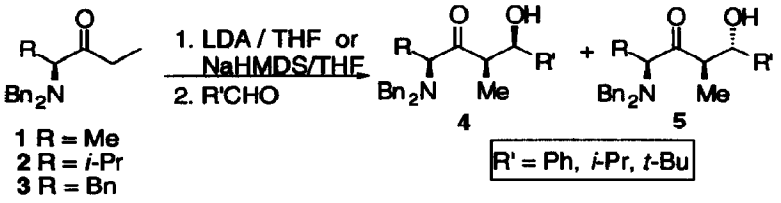


B

The α-(N,N-dibenzylamino) ethyl ketones[5] were synthesized from N,N-dibenzylamino acids[6] *via* the Mukaiyama protocol.[7] In the case of the valine-derived ketone,[8] the following synthetic sequence was employed: (i) oxidation of N,N-dibenzylvalinol to the corresponding aldehyde; (ii) addition of EtMgBr to the aldehyde, and; (iii) oxidation of the resulting secondary alcohol to the ketone. The kinetic enolates were generated by treatment of the ketone with lithium diisopropylamide (LDA) or sodium hexamethyldisilazide (NaHMDS) in THF at -78 °C for 1 hour and then allowed to react with a variety of aldehydes at -78 °C for 1-5 minutes. The results are summarized in **Table 1**.

For phenylalanine-derived ketones (R=Bn), only one diastereomer was observed for both lithium and sodium enolates (entries 6-8). Curiously, however, for the valine- (R=*i*-Pr) and alanine-

Table 1: Diastereoselective Aldol Reactions of Preformed Lithium and Sodium Enolates of α-Amino Ketones 1-3 with Different Aldehydes.



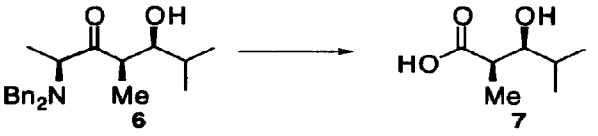
Entry	R	R'CHO	LDA d.r.[a] (% Yield)[b]	NaHMDS d.r.[a] (% Yield)[b]
1	Me	PhCHO	89:11(33)	94:6 (69)
2	Me	*t*-BuCHO	>95:5 (31)	>95:5 (55)
3	*i*-Pr	PhCHO	63:37 (56)	>95:5 (81)
4	*i*-Pr	*i*-PrCHO	47:32:21 (53)[c]	>95:5 (68)
5	*i*-Pr	*t*-BuCHO	>95:5 (54)	>95:5 (56)
6	Bn	PhCHO	>95:5 (51)	>95:5 (93)
7	Bn	*i*-PrCHO	>95:5 (56)	>95:5 (92)
8	Bn	*t*-BuCHO	>95:5 (40)	>95:5 (72)

[a] Diastereomeric ratios (**4** : **5**)were determined by ^{13}C NMR of the aldol product prior to purification. [b] Isolated yields. [c] The stereochemistry of the minor isomers has not been established in this case.

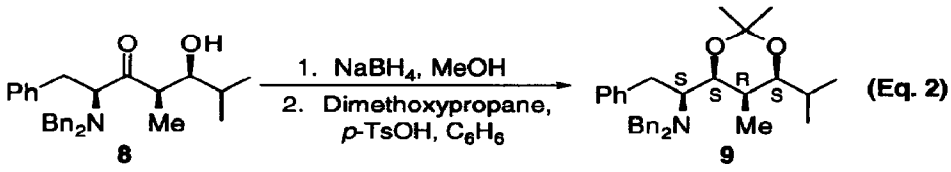
(R=Me) derived ketones, there was a marked difference in the stereoselectivities observed for the two different metal enolates (entries 1-5). In the reaction of the alanine-derived lithium enolate with benzaldehyde, two products were observed, the minor isomer of which was determined to be an *anti* aldol product **5**. The valine-derived lithium enolate also gave two aldol products with benzaldehyde and three aldol products with isobutyraldehyde without an overwhelming preference for any particular diastereomer. This is in stark contrast to our observations in the aldol reactions of the corresponding methyl ketones wherein the more sterically hindered ketones gave high diastereoselectivities. In all cases studied, however, sodium enolates consistently gave better yields and better diastereoselectivities than their lithium counterparts.

The structures of the major product formed in the reactions of either the sodium or lithium enolates were found to be the same. The relative and absolute stereochemistries of the products were established using the following protocols: (i) For each reaction the crude aldol product was subject to Baeyer-Villiger oxidation with peracetic acid as shown in **Eq. 1**.[9] The observed vicinal coupling constant between the protons at the newly-created stereocenters (~3.6 Hz) was consistent with the *syn*-stereochemistry. (ii) The absolute configuration of the newly generated stereocenters was determined by conversion of the aldol products to their corresponding diol acetonides (*i. e.*, stereoselective $NaBH_4$ reduction,[6] followed by acetonide formation) (see **Eq. 2**). Based on the ^{13}C NMR chemical shifts of the acetonide methyl groups, the configurations were assigned as shown.[10]

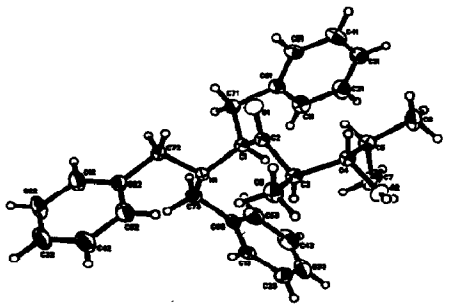
This assignment was later corroborated unequivocally by a single crystal X-ray structure determination of the aldol product where R=Bn and R'=i-Pr (*vide infra*).

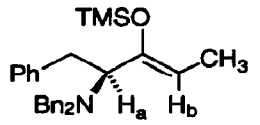


(Eq. 1)



(Eq. 2)





13 % NOE for H_a-H_b

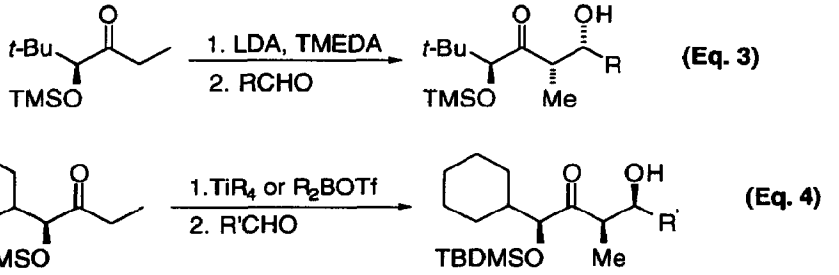
***X-Ray Crystal Structure of* 8**

The excellent stereoselectivities observed here suggest that only one enolate is being formed and, based on the *syn* stereochemistry of the newly generated stereocenters of the product, that it is likely to have a *Z*-geometry. Indeed, silylation of the sodium enolate of the phenylalanine-derived ketone with TMSCl gave the corresponding silyl enol ether which exhibited a 13% NOE enhancement of H_a upon irradiation of H_b (*vide infra*). However, since the boat-like transition state model (**Scheme 1, A**) originally proposed to explain the results for the methyl analogs requires an *E*-enolate geometry to produce the correct stereochemistry, it must now be rejected based on this new data.

A number of studies on the aldol reactions of similar substrates have been previously reported.[11] With chiral α-alkoxy ethyl ketones, Heathcock and co-workers[11a] obtained only the *anti, syn* aldol products with LDA, apparently *via* a chelation-controlled pathway (**Scheme 2, Eq. 3**). However, Thorton later demonstrated that the steric bulk of the α-alkoxy-substituent influences the reaction diastereoselectivity, with substrates containing bulkier α-alkoxy-substituents (which apparently disfavor chelation of the α-alkoxy-substituent to the lithium) exhibiting modest preferences for the *syn, syn*-stereochemistry.[12] Of course, this type of stereoselectivity could also be obtained quite cleanly by utilizing the titanium and boron enolates of analogous substrates, as demonstrated previously by Evans[11b], Thornton[11c] and Masamune[11d] (**Scheme 2, Eq. 4**). The results reported

here provide an interesting mechanistic and synthetic complement to these previous studies. Mechanistically, the very bulky α-(N,N-dibenzylamino)-substituent efficiently exploits the modest reversal of selectivity reported by Thorton. Moreover, since our sodium enolate reactions are unlikely to involve chelation-based pathways, we demonstrate the possibility of producing highly diastereoselective aldol reactions *via* pathways which most likely involve open transition states of the type shown in **Scheme 1, A**. Synthetically, the use of commercially-available NaHMDS provides a convenient and cost-effective alternative to the reagents required for generating the corresponding titanium and boron enolates.

Scheme 2



In conclusion, we have achieved excellent diastereoselectivities in the aldol reactions of α-(N,N-dibenzylamino) ethyl ketones by employing sodium enolates. The reactions produce the all *syn* adducts and are proposed to proceed *via* an open transition state involving the Z-enolate.

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1. Present address: Synaptic Pharmaceutical Corp., 215 College Road, Paramus, NJ 07652.
2. Address questions regarding the X-ray crystal structure to this author.
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5. The enantiomeric purity of the ketones were determined by chiral HPLC analysis using an IBM 9533 HPLC, equipped with a Daicel Chiralpak AS column (UV detector 254 nm; solvent system: 99.5% hexane / 0.5% isopropanol; flow rate: 1 mL/min). Retention times: Ketone **1**, 6.197 min; ketone **3** was reduced selectively to the secondary alcohol with $NaBH_4$, 7.5 min. The enantiomeric purities for these ketones were determined to be >95%. Ketone **2** was reduced to the secondary alcohol with $LiAlH_4$ and converted to its Mosher ester . The enatiomeric purity was determined to be 85% by ^1H NMR.
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