

2,3-Anti Selective Aldol Reaction of Phenylacetoneitrile

Paul R. Carlier* and Kam Moon Lo

Department of Chemistry, Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong

Received May 19, 1994*

Summary: Diastereoselective (3.3:1 to >50:1) aldol reaction of nitriles and aldehydes is reported for the first time; concentration studies and the observed 2,3-*anti* selectivity suggest the intermediacy of a monomeric *N*-lithiated nitrile anion.

The stereochemistry of addition of ketone, ester, and amide enolates to aldehydes has been extensively investigated;¹ in contrast, very little attention has been given to the stereochemistry of addition of nitrile anions to aldehydes² (Scheme 1). This lack of attention is surprising, considering that enantiomerically pure β -hydroxy nitriles **5** would be versatile synthetic intermediates, given that the nitrile group is a synthetic precursor to the carbonyl and amino groups.³ Furthermore, despite the wide usage of nitrile anions in organic synthesis, little is known about their solution-state structure.⁴ Particularly controversial is the position of metalation; on the basis of ¹³C NMR, Bradamante and Pagani have concluded that the cyano group possesses a weak charge demand and propose that sodiated nitrile anions in *d*₆-DMSO are best described as α -cyano carbanions **2**.⁵ In this work we demonstrate for the first time diastereoselective addition of a nitrile anion to aldehydes and provide evidence for the intermediacy of a ketenimine-like *N*-lithiated-nitrile anion **3**.

To determine the optimum conditions for aldol reaction, we studied the effect of concentration on the diastereoselectivity of reaction of benzaldehyde **4b** with lithiated phenylacetoneitrile (generated from **1a** by treatment with LDA) in THF at -78 °C⁶ (Figure 1). Unambiguous assignment of 2,3-*anti* stereochemistry was made by comparison of the 400-MHz ¹H NMR spectra of the mixtures with those of the pure diastereomers.⁷ The

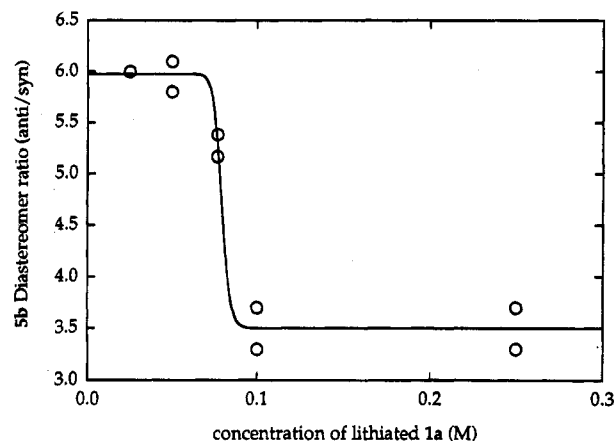
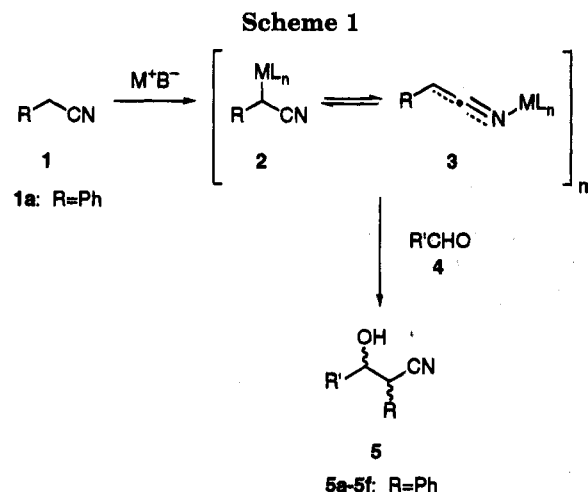


Figure 1. Diastereomer ratio of **5b** vs [lithiated-**1a**]. Diastereomer ratios measured by 400-MHz ¹H NMR; each point represents a separate aldol reaction.



* Abstract published in *Advance ACS Abstracts*, July 15, 1994.

(1) (a) Heathcock, C. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, Chapter 1.6. (b) Kim, B. M.; Williams, S. F.; Masamune, S. *Ibid.*, Chapter 1.7.

(2) To our knowledge no general studies of the diastereoselectivity of the nitrile aldol reaction have been reported. (a) Kasatkin reported that various titanated anions of phenylacetoneitrile reacted with benzaldehyde to give essentially a 1:1 mixture of diastereomers: Kasatkin, A. N.; Biktimirov, R. Kh.; Tolstikov, G. A.; Nikonenko, A. G. *J. Org. Chem. USSR* **1990**, *26*, 1037–1045. (b) Hamana reported that in the presence of (*n*-Bu)₂BOiPr and Et₃N, benzaldehyde and phenylacetoneitrile gave a 1:1 mixture of the diastereomeric aldol products: Hamana, H.; Sugawara, T. *Chem. Lett.* **1982**, 1401–1404. (c) Kauffman reported obtaining unassigned mixtures of diastereomers from various metalated propionitriles and benzaldehyde: Kauffmann, T.; Kieper, H.; Pieper, H. *Chem. Ber.* **1992**, 899.

(3) Existing methods for the preparation of optically active β -hydroxy nitriles include (a) addition of chirally-modified cyanomethyl zinc bromide to aldehydes (Soai, K.; Hirose, Y.; Sakata, S. *Tetrahedron Asymmetry* **1992**, *3*, 677–680), (b) lipase-catalyzed hydrolysis of acylated β -hydroxy nitriles (Itoh, T.; Takagi, Y.; Nishiyama, S. *J. Org. Chem.* **1991**, *56*, 1521–1524), and (c) yeast reduction of 3-oxoalkane-nitriles (Itoh, T.; Fukuda, T.; Fujisawa, T. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3851–3855).

(4) (a) Boche, G. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 277–297. (b) Kaneti, J.; Schleyer, P. v. R.; Clark, T.; Kos, A. J.; Spitznagel, G. W.; Andrade, J. G.; Moffat, J. B. *J. Am. Chem. Soc.* **1986**, *108*, 1481–1492. (c) Jorgensen, W. L.; Briggs, J. M. *J. Am. Chem. Soc.* **1989**, *111*, 4190–4197.

(5) Abboto, A.; Bradamante, S.; Pagani, G. A. *J. Org. Chem.* **1993**, *58*, 449–455.

small but reproducible change in diastereoselectivity observed with varying concentration was confirmed by HPLC and is quite significant; these results suggest that there are at least two kinetically active species present in the concentration range observed, which exhibit different diastereoselectivity. Furthermore, the overall sigmoid appearance of the *anti/syn* ratio versus concentration curve is suggestive of an aggregation equilibrium. *pK_a* determinations⁸ suggest that lithiated **1a** exists as

(6) **General Aldol Procedure.** The nitrile anions were generated at -78 °C by addition of nitrile to LDA or LiHMDS in the designated solvent; after 30 min, aldehyde was added, and after an additional 30 min the reaction was quenched by addition of saturated aqueous NH₄Cl. After workup, diastereomer ratios were measured by 400-MHz ¹H NMR or capillary GC. Control experiments (removal of solvent in Aldrich LDA solution *in vacuo*) confirmed that the small amounts of heptane and ethylbenzene present in commercial solutions of LDA did not affect the diastereoselectivity. All reactions were performed in oven-dried glassware under a nitrogen atmosphere. THF, Et₂O, and toluene were distilled from Na/benzophenone immediately prior to use. Both LDA and *n*-BuLi were titrated prior to use (2,2'-dipyridyl as indicator).

(7) Stereochemically pure *anti*-**5b** and *syn*-**5b** have been previously prepared by a 1,3-dipolar cycloaddition/reduction sequence: Wade, P. A.; Berezna, J. F. *J. Org. Chem.* **1987**, *52*, 2973–2977.

a monomeric tight ion pair in dilute THF solution (10^{-4} – 10^{-3} M); cryoscopic measurements⁹ confirm this finding. IR studies also suggest that lithiated **1a** is a monomeric tight ion pair at 0.025 M in THF but that solvated aggregates form at higher concentrations (0.25 M).¹⁰ Dimeric structures have been found in the solid state for lithiated **1a**.¹¹ Therefore, we propose that below 0.05 M the primary reactive species is monomeric, whereas above 0.1 M the dimer dominates the reaction manifold. The observation of optimum aldol diastereoselectivity in the monomeric concentration range is not surprising; monomeric species are likely to have more readily available coordination sites on lithium, and tight coordination of the aldehyde oxygen by the lithiated **1a** should enhance diastereoselectivity. A similar argument has been put forward to account for the regioselectivity of addition of lithiated **1a** to benzylidene acetone: in the monomeric concentration range (0.06 M) predominantly 1,2-addition occurs, and at higher concentrations (0.25 M) the predominant reaction is 1,4-addition.¹² Finally, it is worth noting that in the present case the use of LDA as base does not seem to significantly perturb the aggregation equilibrium observed previously using other lithium bases.

The diastereoselectivity of the aldol reaction was then explored at a nitrile anion concentration of 0.025 M, as a function of aldehyde substituent R', solvent, and amide base (Table 1). In THF for both LDA and LiHMDS there is a clear increase in diastereoselectivity with increasing R' group size (entries 1, 5, 17, 22 and 2, 10, 18, 23). In Et₂O the trend is less pronounced (entries 3, 7, 19, 24 and 4, 8, 20, 25). However, in both solvents, reaction with *tert*-alkyl-substituted aldehyde **4f** is extremely selective, showing only a single aldol diastereomer by 400-MHz ¹H NMR. For other substrates, optimum diastereoselectivity is generally obtained in THF; use of the nondonor solvent toluene does not improve the selectivity (entry 21). Finally, the nature of the amide base does not appear to significantly affect the diastereoselectivity.

At present, there is no general ¹H NMR method for determining relative stereochemistry of β -hydroxy nitriles—unlike the aldol products of ketones and esters, β -hydroxy nitriles cannot form an intramolecular hydrogen bond.¹³ Unambiguous ¹H NMR correlation of aldols **5a** was performed by conversion to the corresponding methyl esters.^{14,15} Correlation of aldols **5c** and **5d** was made by comparison of ¹H NMR chemical shifts and coupling constants to **5b**. We assign the major isomer of aldols **5e** and **5f** as 2,3-*anti* on the basis of coupling constants between the α -CN (H_a) and α -OH (H_b) proton. The favored conformations of both *syn* and *anti* diastereomers

Table 1

entry	aldehyde	R'	solvent	base	anti:syn ^a	yield ^b (%)
1	4a	<i>n</i> -Pr	THF	LDA	3.3:1 ^c	73
2			THF	LiHMDS	4.1:1 ^c	86
3			Et ₂ O	LDA	3.2:1 ^c	89
4			Et ₂ O	LiHMDS	3.6:1 ^c	51
5	4b	Ph	THF	LDA	6.0:1	86
6			THF	LiHMDS	5.5:1	86
7			Et ₂ O	LDA	3.2:1	80
8			Et ₂ O	LiHMDS	3.6:1	43
9	4c	4-MeC ₆ H ₄	THF	LDA	5.6:1	77
10			THF	LiHMDS	6.4:1	96
11			Et ₂ O	LDA	3.0:1	51
12			Et ₂ O	LiHMDS	4.2:1	42
13	4d	4-MeOC ₆ H ₄	THF	LDA	4.7:1	81
14			THF	LiHMDS	4.1:1	51
15			Et ₂ O	LDA	3.5:1	77
16			Et ₂ O	LiHMDS	3.2:1	42
17	4e	<i>c</i> -C ₆ H ₁₁	THF	LDA	8.4:1	89
18			THF	LiHMDS	6.8:1	73
19			Et ₂ O	LDA	5.3:1	79
20			Et ₂ O	LiHMDS	5.5:1	44
21			Toluene	LiHMDS	4.6:1	51
22	4f	<i>t</i> -Bu	THF	LDA	63:1 ^d	94
23			THF	LiHMDS	63:1 ^d	99
24			Et ₂ O	LDA	37:1 ^d	79
25			Et ₂ O	LiHMDS	53:1 ^d	61

^a Diastereomer ratios measured by 400-MHz ¹H NMR. All new compounds were fully characterized spectroscopically and gave correct elemental analyses. ^b Weight recovery in each case was greater than 90%. Yields were determined by NMR; only the aldol products and residual starting material could be detected. ^c The mixture of diastereomers cannot be resolved by 400-MHz ¹H NMR. Ratio measured by capillary GC. ^d *Syn* diastereomer could not be detected by 400-MHz ¹H NMR. Ratio measured by capillary GC.

should prefer to have the large Ph and cyclohexyl/*tert*-butyl groups in an *anti* (i.e., $\theta = 180^\circ$) relationship. In this conformation the 2,3-*anti* isomer will have a H_a–C–C–H_b dihedral angle of approximately 60°, giving rise to a small coupling constant (observed: R' = *c*-C₆H₁₁, 3.9 Hz; R' = *t*-Bu, 1.8 Hz). The 2,3-*syn* isomer would have a dihedral angle of approximately 180° in this conformation, giving rise to a large coupling constant (observed: R' = *c*-C₆H₁₁, 7.3 Hz; R' = *t*-Bu *syn* isomer cannot be detected by ¹H NMR). This correlation is also observed for aldols **5b**, **5c**, and **5d**. Thus, in each case, the major diastereomer is 2,3-*anti*.

That the observed 2,3-*anti* selectivity is *kinetic* in origin is confirmed by the following observation: subjection of *syn*-**5e** to the reaction conditions gave no detectable retro-aldol products and less than 3% *anti*-**5e** (presumably formed by epimerization). This selectivity is consistent with reaction via a cyclic-6-membered transition state of a monomeric *N*-lithiated-nitrile anion and aldehyde (Scheme 2). It is evident that eclipsing interactions would be minimized in transition structure **6a**, which gives rise to the favored 2,3-*anti* isomer. One would also expect that as the size of the R' group increases, the preference for transition structure **6a** would increase; we note in our work that as R' increases in size from *n*-Pr to Ph to cyclohexyl to *t*-Bu, the diastereoselectivity increases. Therefore, the transition-state model is consistent with both the absolute sense and trend of diastereoselection. The proposed intermediacy of an *N*-lithiated nitrile anion is consistent with the overwhelming preference for *N*-metalation observed in the solid state.^{16,17} The formulation of the reactive intermediate as an *N*-lithiated nitrile anion and not as a more traditional *N*-lithioketenimine is based on the very short CN bond length observed in the solid state of lithiated

(8) Lithiated anions generated by addition of diphenylmethyl-lithium: Kauffman, M. J.; Gronert, S.; Bors, D. A.; Streitwieser, A., Jr. *J. Am. Chem. Soc.* **1987**, *109*, 602–603.

(9) Bauer, W.; Seebach, D. *Helv. Chim. Acta* **1984**, *67*, 1972.

(10) Lithiated nitrile generated by treatment with *n*-BuLi or LiHMDS: Croisat, D.; Seyden-Penne, J.; Strzalko, T.; Wartski, L.; Corset, J.; Froment, F. *J. Org. Chem.* **1992**, *57*, 6435–6477.

(11) (a) [[PhCHCN–Li(tmeda)]₂·C₆H₆]: Boche, G.; Marsch, M.; Harms, K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 373–374. (b) [[PhCHCN–Li(tmeda)]Li(tmeda)N(*i*-Pr)₂]: Zarges, W.; Marsch, M.; Harms, K.; Boche, G. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1392–1393.

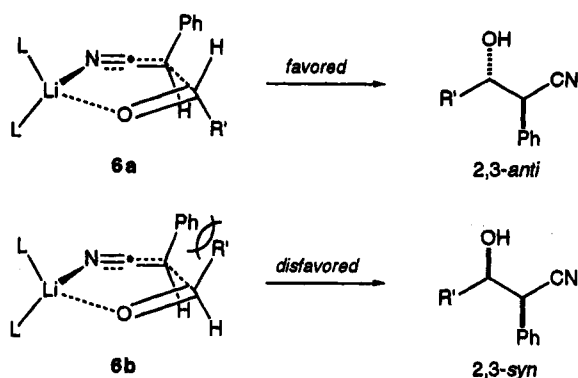
(12) See ref 10.

(13) Itoh has proposed a method based on the chemical shift of the α -CN proton, but it has been unambiguously demonstrated for only one substrate (see ref 3c).

(14) See ref 3c.

(15) The methyl ester derivatives of both *anti*-**5a** and *syn*-**5a** have been unambiguously synthesized by cuprate opening of the corresponding glycidic esters: Mulzer, J.; Lammer, O. *Chem. Ber.* **1986**, *119*, 2178–2190. No change in the *anti*/*syn* ratio of **5a** was observed during its conversion to the methyl ester.

Scheme 2



phenylacetonitrile and Bradamante and Paganì's observation of the relatively weak charge demand of the cyano group.

Clearly, the proposed transition-state model requires further study. Nevertheless, completely analogous transition states have previously been proposed to account for the high degree of *anti*-selectivity observed in the addition of isoelectronic allenic organometallics to aldehydes to give β -alkynic alcohols.^{18,19} Reaction via a 4-membered transition state involving an α -lithio nitrile

cannot be ruled out. However, it should be noted that the isoelectronic propargylic boranes react with aldehydes to give α -allenic alcohols, not propargylic alcohols.²⁰ Therefore, both the stereoselectivity and regioselectivity of the reaction support the intermediacy of an *N*-lithiated nitrile anion.

Finally, work continues toward optimization of the the diastereoselectivity with other nitriles, as well as toward asymmetric variants.

Acknowledgment. We wish to thank Mr. Hing Wai Cheng for performing some of the reactions in Et_2O listed in Table 1, Mr. Thomas Wong for mass spectral analysis, and Dr. Richard K. Haynes for helpful discussions. This research was sponsored by a Competitive Earmarked Research Grant from the Hong Kong Research Grants Council (HKUST203/93E). We also wish to thank the HKUST Department of Chemistry for financial support.

Supplementary Material Available: Experimental procedures, characterization data, and $^1\text{H}/^{13}\text{C}$ spectra for all new compounds (23 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.

(16) (a) See ref 4. (b) See ref 11a. (c) See ref 11b. (d) Hiller, W.; Frey, S.; Strähle, J.; Boche, G.; Zarges, W.; Harms, K.; Marsch, M.; Wollert, R.; Dehnicke, K. *Chem. Ber.* **1992**, *125*, 87–92. (e) Lambert, C.; Schleyer, P. v. R.; Pieper, U.; Stalke, D. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 77–79. (f) Barker, J.; Barnett, N. D. R.; Barr, D.; Clegg, W.; Mulvey, R. E.; O'Neil, P. A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1366–1368. (g) Note that C-lithiation is seen in a cyclopropyl nitrile: Boche, G.; Harms, K.; Marsch, M. *J. Am. Chem. Soc.* **1988**, *110*, 6925–6926.

(17) It should also be noted that ^{13}C NMR of lithiated **1a** in THF reveals a large $^1J_{\text{CH}}$ at the α -carbon (164 Hz), also suggesting *N*-metalation in this case (ref 10).

(18) (a) Ti: Furuta, K.; Ishiguro, M.; Haruta, R.; Ikeda, N.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2768–2776. (b) Zn: Zweifel, G.; Hahn, G. *J. Org. Chem.* **1984**, *49*, 4565–4567.

(19) *Anti*-selective carbonyl addition can also be inferred as a first step in the *Z*-selective olefination of aldehydes by lithiated (tri-alkylsilyl)acetonitriles: Yamakado, Y.; Ishiguro, M.; Ikeda, N.; Yamamoto, H. *J. Am. Chem. Soc.* **1981**, *103*, 5568–5570.

(20) (a) Zweifel, G.; Backlund, S. J.; Leung T. *J. Am. Chem. Soc.* **1978**, *100*, 5561–5562. (b) Wang, K. K.; Nikam, S. S.; Ho, C. D. *J. Org. Chem.* **1983**, *48*, 5376–5377.