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HMPA Promotes Retro-Aldol Reaction, Resulting in Syn-Selective Addition of Lithiated 1-Naphthylacetonitrile to Aromatic Aldehydes

Paul R. Carlier,*,† Cedric W.-S. Lo, Michael M.-C. Lo, Nan Chi Wan, and Ian D. Williams

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

pcarlier@chemserver.chem.vt.edu

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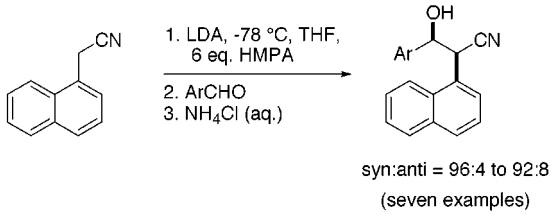
ABSTRACT



In HMPA–THF solution, lithiated 1-naphthylacetonitrile undergoes highly syn-selective addition to aromatic aldehydes, providing the first access to such syn-aldols. Syn-selectivity is also observed with two other arylacetonitriles. Aldolate equilibration and crossover experiments demonstrate that HMPA promotes retro-aldol reaction and that aldol diastereoselectivity under these conditions is *thermodynamically controlled*.

Despite its toxicity, HMPA remains a favorite additive for optimizing the rates and selectivities of organolithium reactions.[1] HMPA enhances the reactivity of carbanions, amides, and enolates and can help effect difficult metalations. Addition of HMPA changes the kinetic *E*:*Z* selectivity of enolate formation[2] and accelerates the rate of *E*- to *Z*-isomerization of ketone enolates (at 0 °C).[2c,3] It can also redirect the course of organolithium addition to α,β-unsaturated carbonyl compounds, favoring 1,4-addition by kinetic[4] or thermodynamic[5] control. In this report we describe the use of HMPA to achieve syn-selective aldol reaction of 1-naphthylacetonitrile and two other arylacetonitriles with aromatic aldehydes. The selectivity attained is traced to HMPA-facilitated retro-aldol reaction and the operation of thermodynamic control. To our knowledge this work provides the first example of the use of HMPA to promote retro-aldol reaction or to reverse diastereoselectivity of an aldol reaction.[6]

Arylacetonitriles generally undergo anti-selective aldol reaction with aldehydes, although the degree of selectivity attained depends on the steric bulk of the aldehyde.[7] With

† Current address: Department of Chemistry, Virginia Tech, Blacksburg, VA 24061.

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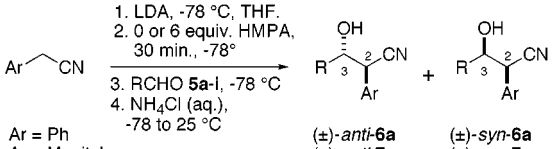
aromatic aldehydes selectivity is moderate to low, as can be seen for reactions of nitriles **1**−**4** with benzaldehyde **5a** (Table 1, aldols **6a**−**9a**, column 4). In an attempt to improve

Table 1. Effect of HMPA on Aldol Reaction Diastereoselectivity of Arylacetonitriles[a]



1: Ar = Ph
2: Ar = Mesityl
3: Ar = 2-Naphthyl
4: Ar = 1-Naphthyl

(±)-*anti*-**6a** (±)-*syn*-**6a**
(±)-*anti*-**7a** (±)-*syn*-**7a**
(±)-*anti*-**8a** (±)-*syn*-**8a**
(±)-*anti*-**9a-i** (±)-*syn*-**9a-i**

			anti:syn (% yield)	
aldol	Ar	R	0 equiv of HMPA	6 equiv of HMPA
6a	Ph	Ph	85:15 (70)[b,c]	42:58 (69)
7a	mesityl	Ph	88:12 (56)	90:10 (68)
8a	2-Naph	Ph	70:30 (89)[b,c]	36:64 (82)
9a	1-Naph	Ph	72:28 (75)[c]	**8:92** (76)
9b	1-Naph	1-Naph	58:42 (39)[c]	**8:92** (80)[d]
9c	1-Naph	2-Naph	69:31 (29)[c]	**5:95** (73)
9d	1-Naph	2-Me-C_6H_4	63:37 (55)[c]	**7:93** (81)
9e	1-Naph	4-Me-C_6H_4	57:43 (44)[c]	**4:96** (72)
9f	1-Naph	4-Cl-C_6H_4	50:50 (46)[c]	**8:92** (73)
9g	1-Naph	4-MeO-C_6H_4	38:62 (39)[c]	**4:96** (68)
9h	1-Naph	*t*-Bu	>98:2 (87)[c]	>98:2 (64)
9i	1-Naph	*c*-C_6H_{11}	88:12 (81)[c]	71:29 (83)

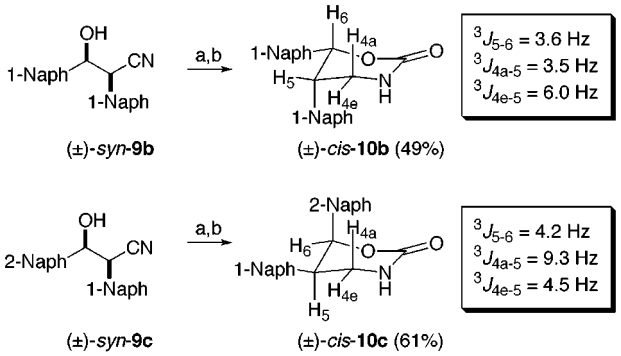
[a] Reactions were performed in THF at −78 °C at 0.025 M; 30 min after addition of the aldehyde, reactions were quenched at −78 °C by the addition of NH_4Cl (aq). For reactions with HMPA, aldehydes were added 30 min after addition of HMPA (6 equiv) to the lithiated nitrile. The yields reported are isolated yields after chromatography, unless otherwise noted. [b] Data from ref 7. [c] NMR yield. [d] The yield at 30 min was quite low; this reaction was quenched 4 h after addition of aldehyde.

the selectivity, a number of additives were examined, and HMPA was found to cause a reversal of diastereoselectivity in three of the four cases (Table 1, aldols **6a**−**9a**, cf. columns 4 and 5). Most striking were the reactions with 1-naphthylacetonitrile **4**. In pure THF, diastereoselectivities with aromatic aldehydes **5a**−**g** were very low. However, in the presence of 6 equiv of HMPA, anti:syn selectivities ranging from 8:92 to 4:96 were obtained (Table 1, aldols **9a**−**g**, column 5).[8] The addition of HMPA also led to significant increases in the yield of the aldol products. Experiments to determine how much HMPA is needed for high syn-selectivity were then carried out. For aldols **9e**,**g** use of 2 or 6 equiv of HMPA gave almost identical levels of syn-selectivity; for **9a**−**d**,**f** use of 2 equiv of HMPA gave slightly lower levels of syn-selectivity. To explore the generality of this HMPA-induced change in diastereoselectivity, reactions with aliphatic aldehydes **5h** and **5i** were performed. Unfortunately, in the presence of HMPA these reactions remained anti-selective (Table 1, aldols **9h**,**i**).

(8) Thus far HMPA is uniquely effective. In reactions of **4** and **5a**, LiCl, DMSO, TMEDA, and the HMPA substitutes DMPU and dimethylacetamide failed to induce syn-selectivity. Use of sodium hexamethylsilazide as base, with or without added HMPA, resulted in poor syn-selectivity.

The relative stereochemistry of the aldols was determined according to our previously described vicinal ($^3J_{2-3}$) coupling constant method,[7] or in the case of *anti*-**7a** by X-ray crystallography. In the cases of *syn*-**9b**,**c**, additional confirmation of the relative stereochemistry was obtained by conversion of the aldols to the cyclic carbamate derivatives *cis*-**10b**,**c** (Scheme 1).[7,9] ^{1}H NMR spectroscopy confirmed

Scheme 1[a]



[a] Reagents: (a)1:1 $LiAlH_4/AlCl_3$, Et_2O, rt, 6 h; (b) $(Cl_3CO)_2CO$, Et_3N, CH_2Cl_2, −78 to 0 °C.

the cis relationship of the ring substituents in each case. The preferred conformer of the *cis*-carbamates **10** depends on the relative steric demand of the C-5 and C-6 substituents.[9] If the C-5 and C-6 substituents have equal steric demand (as for *cis*-**10b**), then the C-5 axial conformer dominates, to minimize 1,3-diaxial interactions.

The syn-selectivity observed for arylacetonitriles **1**, **3**, and **4** with aromatic aldehydes in the presence of HMPA is quite unusual. Previously, syn-selectivity with benzaldehyde has been observed only for an aliphatic nitrile, valeronitrile.[9] As a first step toward determining the role of HMPA in reversing the selectivity of these aldol reactions, the extent of aldolate equilibration under the two reaction conditions was examined. We have previously used this technique to establish that the aldol reaction of **1** and cyclohexanecarboxaldehyde **5i** is essentially irreversible over 30 min at −78 °C.[10] Thus, diastereomerically enriched samples of aldols **7a**, **8a**, and **9c** were resubjected to 1 equiv of LDA at −78 °C for 30 min, in the presence or absence of HMPA, followed by the normal quench (Table 2). In the absence of HMPA, diastereomerically enriched samples of these aldols show little (≤5%) change, suggesting that aldol reaction under these conditions is predominantly kinetically controlled.

However, aldolate equilibration experiments in the presence of HMPA show significant change in the diastereomer ratio (15% (**7a**), 68% (**8a**), 88% (**9c**)). In the case of **8a** and **9a**, the final anti:syn ratios attained closely approximate those observed in the corresponding HMPA-mediated aldol reactions (cf. Table 1). This important observation indicates that

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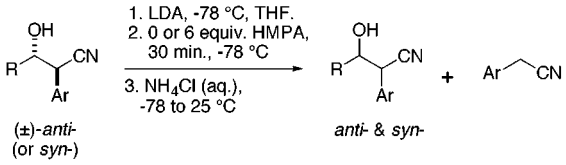
Table 2. Aldolate Equilibration Experiments[a]



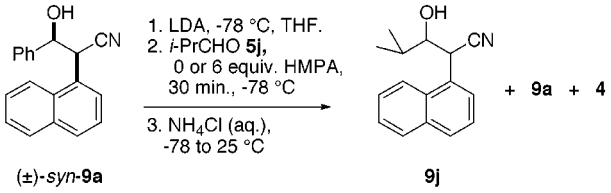
aldol	HMPA (equiv)	start anti:syn	end anti:syn	% change[b] (mol % of nitrile)
7a	0	0:100	0:100	0 (0)
7a	6	0:100	15:85	15 (6)
8a	0	6:94	10:90	4 (6)
8a	0	100:0	95:5	5 (6)
8a	6	100:0	32:68	68 (8)
9c	0	0:100	4:96	4 (2)
9c	6	100:0	12:88	88 (33)

[a] Diastereomerically enriched aldols were treated with 1 equiv of LDA at −78 °C in THF at 0.025 M for 30 min, in the presence or absence of HMPA, followed by the normal quench. Anti:syn ratios and mol % of nitrile were determined by ^{1}H NMR. Results reported represent the average of at least two experiments. [b] % change represents the difference (%) in the starting and final anti:syn ratios; mol % of nitrile refers to the amount of $ArCH_2CN$ detected after the aldolate equilibration experiment.

aldol diastereoselectivity in these HMPA-mediated reactions is *thermodynamically controlled*. Consistent with this hypothesis, increasing the HMPA-mediated aldol reaction times from 30 min to 24 h provides slightly improved syn-selectivities for aldols **6a** and **8a** (to 33:67 and 29:71, respectively; cf. Table 1). Thus, for reactions of lithiated **1**, **3**, and **4** with aromatic aldehydes in THF−HMPA, the *syn*-aldol is the thermodynamic product. In contrast, aldolate equilibration experiments demonstrate that HMPA-mediated formation of **7a** is *not* completely reversible within 30 min at −78 °C (cf. Tables 1 and 2). Slow aldolate equilibration may explain why HMPA-mediated aldol reactions to form **7a** remain anti-selective, even after 24 h at −78 °C (anti:syn = 86:14).

That aldolate equilibration occurs via retro-aldol reaction and not through epimerization of the α-nitrile carbon is supported by aldolate crossover experiments (Scheme 2). Deprotonation of *syn*-**9a** in the presence of isobutyraldehyde **5j** and in the absence of HMPA produced only a trace amount of aldolate crossover product **9j**. Thus, in pure THF, retro-aldol reaction (and thereby formation of lithiated 1-naphthylacetonitrile) is slow. However, in the presence of 6 equiv of HMPA, a considerable amount (27%) of crossover product **9j** is formed, indicating that retro-aldol reaction and

Scheme 2. Aldolate Crossover Experiments[a]



HMPA	mol% **9j** (anti:syn)	mol% **9a** (anti:syn)	mol% **4**
0 equiv.	2 (>95:5)	96 (<1:99)	2
6 equiv.	27 (72:28)	70 (5:95)	3

[a] Reactions were carried out at −78 °C in THF at 0.025 M for 30 min, in the presence or absence of HMPA, followed by the normal quench. Yields and anti:syn ratios were determined by ^{1}H NMR. Results reported represent the average of at least two experiments.

capture of the lithiated nitrile by **5j** are fast. Thus, we attribute the rapid aldolate equilibration observed in HMPA−THF solution (Table 2) to retro-aldol reaction.

How addition of HMPA improves reversibility of the aldol reaction is not yet clear. If the action of HMPA were catalytic, sub-stoichiometric application of chiral phosphoramides[6] in asymmetric nitrile aldol[11] and retro-nitrile aldol reactions could be envisioned. That HMPA does indeed act as a nucleophilic catalyst[6] of aldol/retro-aldol reaction (albeit an inefficient one) is suggested by the following observations: after 24 h at −78 °C, reaction of lithiated **4** and benzaldehyde in the presence of 0.2 equiv of HMPA gave aldol **9a** in a 34:66 ratio (NMR yield 91%). Repeating this experiment at −37 °C improves the anti:syn ratio of **9a** to 23:77 but decreases the NMR yield to 48%. These results also suggest that formation of the lithium aldolate of **9a** is not highly exothermic and thus highlight the usefulness of HMPA for promoting reversibility in low-temperature nitrile aldol reactions. Finally, these results stand in interesting contrast to those of ketone enolate aldol reactions, where aldolate equilibration was found to be faster in nonpolar solvents (pentane) than in diethyl ether,[12] and addition of HMPA did not cause any observable change in aldol stereoselectivity.[13]

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Supporting Information Available: Synthetic procedures and characterization data for all new compounds and the Ortep for X-ray structure determination of (±)-*anti*-**7a**. This material is available free of charge at http://pubs.acs.org.

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