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Base-Controlled Diastereoselective Synthesis of Either *anti*- or *syn*-*β*-Aminonitriles

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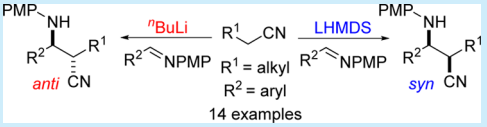
Supporting Information

ABSTRACT: Deprotonation of secondary alkane nitriles with nBuLi and addition to aryl imines gives kinetic anti-*β*-aminonitriles. Use of LHMDS allows reversible protonation of the reaction intermediate to give *syn*-*β*-aminonitriles. The pure diastereosiomers can be isolated in good yields, and the mechanism was elucidated.



The nitrile functional group is ubiquitous in synthesis due to its ease of incorporation, ability to facilitate the formation of new bonds, and interconversion into a myriad of other functional groups.[1] It is present in biologically active natural products, and its use as a pharmacophore has also been recognized.[2] The *β*-aminonitrile functional group is an under-investigated subset of alkanenitriles.[3] There are many naturally occurring *β*-aminonitriles and pharmaceuticals.[4−6] The *β*-aminonitrile is also a precursor to 1,3-diamines[7] and *β*-amino acid derivatives.

Routes to the *β*-aminonitrile functional group include ring opening of aziridines with cyanide,[8] conjugate addition of amines to acrylonitriles,[9] hydrocyanation of nitroalkenes,[10] and Thorpe−Ziegler reaction between two nitriles followed by conjugate reduction.[11] The most efficient method, and that which has led to many enantioselective syntheses through asymmetric transition metal catalysis, is the addition of alkanenitriles to imines.[12] Deprotonation of alkyl nitriles (CH_3CN, pK_a 31.3, $PhCH_2CN$, pK_a 21.9 in DMSO)[13] and subsequent reaction with electrophiles[3a] requires strong bases, such as LDA[14,15] and proazaphosphatranes,[16] which can trigger undesired side reactions such as epimerization[15] or elimination.[16] Increasing the acidity of alkylnitriles through coordination with catalytic transition-metal complexes has allowed the use of weaker bases for this reaction.[12] Examples of alkanenitriles other than acetonitrile often give poor diastereoselectivities.[17] Good enantioselectivities and in some cases good diastereoselectivities have been obtained in asymmetric catalyzed reactions, and the major diastereoisomer isolated from these can be either *anti* or *syn* depending upon the type of nitrile and catalyst used.[18] A rare and recent example of the addition of a lithio nitrile anion, generated by treatment with LHMDS, to an imine as part of a complex natural product synthesis gave no diastereoselectivity.[19] The same reaction using Ellman's auxiliary[20] on the imine gave a diastereoselectivity of ∼15:85 *anti*/*syn* for the product *β*-aminonitrile.[21] There is a clear need to be able to synthesize *β*-aminonitriles from longer alkanenitriles than acetonitrile and to understand how to access either *anti* or *syn* diastereoisomers to complement existing stereoselective methodology. We communicate here a synthesis of *β*-aminonitriles which by judicious choice of base can give either *anti*- or *syn*-*β*-aminonitriles with alkanenitriles and offer some mechanistic understanding of this.

We recently developed conjugate addition nitro-Mannich reactions where a nitronate anion generated by conjugate addition to a nitroalkene underwent addition to an imine.[22] We attempted an analogous reaction with cyanoalkenes. Although conjugate reduction using Superhydride proceeded cleanly, disappointingly, no 1,2-addition to the imine was observed with or without Brønsted or Lewis acids in a range of solvents.

To confirm that 1,2-addition could occur, we generated the corresponding *α*-cyano carbanion from 3-phenylpropanenitrile with a range of bases and then added imine (Scheme 1, R^1 = Bn, R^2 = 2-BrC_6H_5). The 2-bromophenyl imine was used in preparation for a possible Pd-catalyzed intramolecular amination.[22c,g,j] We observed that the diastereomeric ratio of the product *β*-aminonitriles was dependent on the nature of the base and temperature (Table 1). With the base *n*BuLi, the *anti*-*β*-aminonitrile was observed with a diastereomeric ratio (dr) = 85:15 at −78 °C (entry 1).[23] A repeat reaction with warming to rt for 5 min switched the diastereoselectivity to favor the *syn*-*β*-aminonitrile 15:85 (entry 2). In the case of LHMDS, the *syn*-*β*-aminonitrile was observed with dr = 10:90 at −78 °C (entry 3). Warming to room temperature as before gave no change in the sense or extent of diastereoselectivity (entry 4). LDA gave essentially the same results as *n*BuLi (compare entries 1 and 2 with 5 and 6). This similarity of *n*BuLi and LDA had been

Scheme 1. 1,2-Addition of Alkane Nitriles to Aldimines

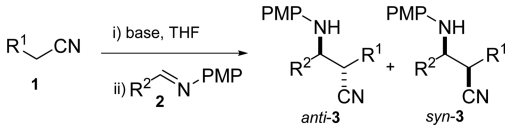


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Table 1. Effect of Base and Temperature for R^1 = Bn and R^2 = 2-BrC_6H_4[a]

entry	base	conditions	conv (%)[b]	*anti*/*syn*[c]
1	^{n}BuLi	−78 °C, 1 h	90	85:15
2	^{n}BuLi	−78 °C, 1 h; rt, 5 min	80	15:85
3	LHMDS	−78 °C, 1 h	100	10:90
4	LHMDS	−78 °C, 1 h; rt, 5 min	80	10:90
5	LDA	−78 °C, 1 h	90	80:20
6	LDA	−78 °C, 1 h; rt, 5 min	80	15:85

[a]All reactions were carried out on a 0.5 mmol scale, nitrile (1.0 equiv), base (1.1 equiv in hexane), imine (1.1 equiv) in THF (6 mL) at −78 °C for 1 h. [b]By ^{1}H NMR. [c]Determined by comparison of the ^{1}H NMR signals for the CH_2CHCN protons (~2.5−3.5 ppm) of the crude reaction mixture (to nearest 5).

noted before in the reaction of α-amidoalkylphenyl sulfones (generating the corresponding *N*-Boc-imine in situ) with lithiated nitriles and gave variable yields and diastereoselectivities of the *anti*-β-aminonitrile.[14]

We were intrigued by the fact that the judicious choice of base could prepare either *anti*- or *syn*-β-aminonitriles. A survey of the reaction of different lithiated alkane nitriles (from **1**), generated with either ^{n}BuLi or LHMDS at −78 °C for 1 h, with a variety of imines **2** was performed (Scheme 1, Table 2). A reaction with a secondary alkyl nitrile isobutyronitrile with either base gave only ~7% yield and was not further optimized. With primary alkyl nitriles, the base-controlled diastereoselectivity was observed across a range of substrates. There was a marginal gain in diastereoselectivity with aromatic imines if there was an *ortho*-substituent (compare entries 1, 2, 5−11 with entries 3 and 4). The beneficial effect of *ortho*-substituents was only replicated on the nitrile partner 3-(2-chlorophenyl)-propylnitrile for the *syn*-diastereoisomer generated with LHMDS (entries 21, 90% yield). Other nitriles of simple alkyl derivatives gave no clear trend in diastereoselectivities but gave some examples of good selectivity (entries 13, 14, and 21) and many others where the major isomers could be isolated diastereomerically pure. Alkyl imines derived from cyclohexanecarboxaldehyde and *n*-hexanal both gave the same diastereoselection with each base favoring the *anti*-diastereoisomer (entries 30−33). Other aromatic imines gave moderate to good yields of pure major diastereoisomers (entries 24−29).

To elucidate the mechanism for this diastereoselectivity, the reaction (Scheme 1, R^1 = Bn and R^2 = *o*-BrC_6H_4) was performed at −78 °C at varying reaction times and the crude material analyzed by ^{1}H NMR (Table 3). The results suggest that the initial 1,2-addition favors the *anti*-diastereoisomer in an 85:15 ratio after 1 min at −78 °C with both ^{n}BuLi and LHMDS. The initial *anti*-selectivity for LHMDS was quickly eroded over time (<30 min), and as the conversion increased

Table 2. Scope of Diastereoselectivity[a]

entry	R^1	R^2	base	*anti*-**3**:*syn*-**3**[b]	yield of major (%)[c]
1	Bn	2-Br-C_6H_5	^{n}BuLi	85:15	62
2	Bn	2-Br-C_6H_5	LHMDS	10:90	76
3	Bn	C_6H_5	^{n}BuLi	70:30	44
4	Bn	C_6H_5	LHMDS	20:80	68
5	Bn	2-Me-C_6H_5	^{n}BuLi	85:15	67
6	Bn	2-Me-C_6H_5	LHMDS	10:90	80
7	Bn	2-Br-3-Pyridyl	^{n}BuLi	85:15	65
8	Bn	2-Br-3-Pyridyl	LHMDS	40:60	40
9	Bn	2-Br-3-Pyridyl	LHMDS[d]	15:85	62
10	Bn	2-Cl-C_6H_5	^{n}BuLi	85:15	58
11	Bn	2-Cl-C_6H_5	LHMDS	15:85	70
12	Me	C_6H_5	^{n}BuLi	50:50	50
13	Me	C_6H_5	LHMDS	25:75	75
14	^{i}Pr	C_6H_5	^{n}BuLi	70:30	50
15	^{i}Pr	C_6H_5	LHMDS	40:60	47
16		C_6H_5	^{n}BuLi	55:45	54
17		C_6H_5	LHMDS	40:60	59
18		C_6H_5	^{n}BuLi	-	<10[e]
19		C_6H_5	LHMDS	40:60	63[f]
20	$PhCH_2CH_2$	C_6H_5	^{n}BuLi	60:40	56
21	$PhCH_2CH_2$	C_6H_5	LHMDS	20:80	82
22	2-Cl-$PhCH_2$	C_6H_5	^{n}BuLi	50:50	35
23	2-Cl-$PhCH_2$	C_6H_5	LHMDS	5:95	90
24	Bn	4-Cl-C_6H_5	^{n}BuLi	55:45	43
25	Bn	4-Cl-C_6H_5	LHMDS	10:90	70
26	Bn	4-MeO-C_6H_5	^{n}BuLi	65:35	48
27	Bn	4-MeO-C_6H_5	LHMDS	20:80	53
28	Bn	3-furyl	^{n}BuLi	60:40	43
29	Bn	3-furyl	LHMDS	35:65	50
30	Bn	cyclohexyl	^{n}BuLi	>95:5	53
31	Bn	cyclohexyl	LHMDS	>95:5	50
32	Bn	^{n}Pn	^{n}BuLi	70:30	48
33	Bn	^{n}Pn	LHMDS	70:30	45(17)[g]

[a]All reactions were carried out on a 0.5 mmol scale, nitrile (1.0 equiv), base (1.1 equiv in hexane), imine (1.1 equiv) in THF (6 mL) at −78 °C for 1 h. [b]Assigned by ^{1}H NMR comparison with compounds *anti*-**3** and *syn*-**3** R^1 = Bn, R^2 = 2-BrC_6H_5 and determined by comparison of the ^{1}H NMR signals for the CH_2CHCN protons (~2.5−3.5 ppm) of the crude reaction mixture (to nearest 5). [c]Isolated yield of pure major diastereoisomer. [d]−78 °C, 4.5 h. [e]Conversion by ^{1}H NMR. [f]Yield of inseparable diastereomeric mixture. [g]Yield of minor *syn*-diastereoisomer in parentheses.

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Table 3. Effect of Base and Temperature on Diastereoselectivity[a]

	^{n}BuLi		LHMDS	
time at −78 °C	*anti*/*syn*[b]	conv[c] (%)	*anti*/*syn*[b]	conv[c] (%)
1 min	85:15	80	85:15	30
5 min	85:15	90	70:30	50
30 min	85:15	90	25:75	90
1 h	85:15	90	10:90	100
3 h	50:50	>95	10:90	100
6 h	25:75	>95	10:90	100

[a]All reactions were carried out on a 0.5 mmol scale, nitrile (1.0 equiv), base (1.1 equiv in hexane), imine (1.1 equiv) in THF (6 mL) at −78 °C for 1 h. [b]Determined by comparison of the ^{1}H NMR signals for the CH_2CHCN protons (~2.5−3.5 ppm) of the crude reaction mixture (to nearest 5). [c]By ^{1}H NMR.

with time, the selectivity for the *syn*-diastereoisomer also increased to a maximum 10:90 (~60 min). For ^{n}BuLi, the initial and rapid *anti*-selectivity (85:15) was maintained and did not start to erode until after 1 h. After 6 h, the ^{n}BuLi reaction was *syn*-selective, but only to the extent of 25:75. These results suggest that the *anti*-diastereoisomer is the kinetic product and the *syn*-diastereoisomer is the thermodynamic product. The reason why the *syn*-diastereoisomer is the thermodynamically more stable product is not obvious to us.

To probe the mechanism of isomerization a crossover experiment was conducted. The initial product **3** (R^1 = Bn, R^2 = 2-BrC_6H_5), formed in situ from addition to PMP-protected imine **2** (R^2 = 2-BrC_6H_5) after 1 h at −78 °C, was treated with 1 equiv of the corresponding *N*-*p*-ethoxyphenyl-protected imine **4** and left to stir for a further 1 h at −78 °C (Scheme 2). The crude ^{1}H NMR did not show any incorporation of the second imine with either base. Repeating the crossover experiment, but warming to rt for 5 min directly after the addition of 1 equiv of **4**, showed a statistical 50:50 mixture of both β-aminonitriles, again for both bases. As there is no crossover at −78 °C, we can conclude that the equilibration of the LHMDS system at −78 °C is not due to a retro- then readdition pathway. Crossover was observed at rt; therefore, a retro-/readdition mechanism can take place on warming, which accounts for the formation of the thermodynamic *syn*-diastereoisomer for ^{n}BuLi as the reaction warms to rt. A key control experiment was treatment of *anti*-**3** with LHMDS (1.1 equiv) in the presence of **4** at −78 °C. After 1 h, there was again no incorporation of imine **4**, but the original *anti*-diastereoselectivity (85:15) had epimerized to the *syn*-diastereoisomer (15:85), within experimental error virtually identical to the original LHMDS *syn*-diastereoseletion (10:90). Additionally treatment of *anti*-**3** with ^{n}BuLi at −78 °C for 1 h led to no change in diastereoeslectivity, and treatment of *syn*-**3** with either *n*BuLi or LHMDS at −78 °C for 1 h also led to no change in diastereoselectivity. This enables the conversion of *anti*-β-aminonitriles to *syn*-β-aminonitriles.

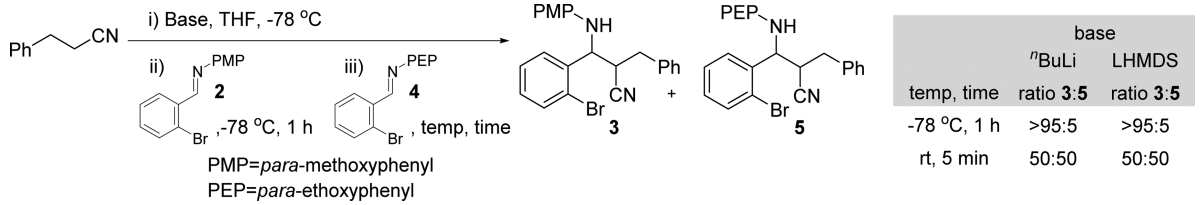
The pK_a of HMDS (26) is similar to that of *H*CCN (22−31).[13] We propose at −78 °C that equilibration occurs by deprotonation and reprotonation of the *H*CCN of **3** by HMDS (Scheme 3). Using LHMDS as base, the original kinetic *anti*-**3**-rich mixture is reprotonated by HMDS, and the regenerated LHMDS equilibrates the *H*CCN center to the thermodynamic mixture with *syn*-**3** as the major diastereoisomer. With ^{n}BuLi the initial kinetic *anti*-**3** rich mixture is stable at −78 °C for at least 1 h. Additional proof was provided by a series of other experiments (R^1 = Bn, R^2 = 2-BrC_6H_5). Addition of an equimolar quantity of HMDS to an ^{n}BuLi deprotonation directly before or after addition of imine favored the thermodynamic *syn*-**3** (25:75). Addition of an equimolar quantity of ^{n}BuLi to a LHMDS deprotonation followed by imine favored the kinetic *anti*-**3** (75:25). Allowing a LHMDS experiment to stir for 30 min after addition of imine and then adding an equimolar quantity of ^{n}BuLi favored the thermodynamic *syn*-**3** (20:80), implying that the equilibration was interrupted by irreversible deprotonation with ^{n}BuLi. Circumstantially commercial LHMDS led to the formation of *syn*-**3** more efficiently than freshly prepared LHMDS.[24] This explanation (Scheme 3) satisfactorily accounts for the diastereoselectivities of all the aromatic imines investigated, but an anomaly is the two examples of alkyl imines derived from cyclohexane carboxaldehyde and *n*-hexanal (entries 30−33). An equal amount of *anti*-diastereoisomer prevailed with both bases in each case, suggesting that the initial kinetic diastereoisomer does not undergo equilibration.

A previous literature report of lithium cyanoate additions to benzaldehyde imines using LDA suggests some epimerization via both retro-/readdition and deprotonation/reprotonation of *H*CCN.[15] The paper also goes on to show that addition of a variety of alkyl halides gives good to moderate yields of quaternary nitriles. In our case, it would not be unreasonable to assume that a small equilibrium exists between aza-anion **3** and **6** (Scheme 3) and that this is only significantly perturbed in the presence of a suitable reversible proton donor, such as HMDS.

To show the synthetic versatility of the β-aminonitriles, *syn*-**3** was reduced to the corresponding 1,3-diamine with $LiAlH_4$/H_2SO_4 in 92% yield and hydrolyzed with basic hydrogen peroxide to the β-amino acid in 65% yield, with no erosion in diastereoselectivity (see the Supporting Information).

The judicious choice of either irreversible conditions with ^{n}BuLi to give *anti*-diastereoselectivity or reversible conditions with LHMDS to give *syn*-diastereoselectivity provides an operationally simple method for the isolation of diastereomerically pure β-aminonitriles derived from substituted primary acetonitriles and aryl imines. The characterization of the thermodynamic equilibration process with HMDS offers the opportunity for the products from enantioselective syntheses

Scheme 2. Crossover Experiment



	base	
	^{n}BuLi	LHMDS
temp, time	ratio **3**:**5**	ratio **3**:**5**
-78 °C, 1 h	>95:5	>95:5
rt, 5 min	50:50	50:50

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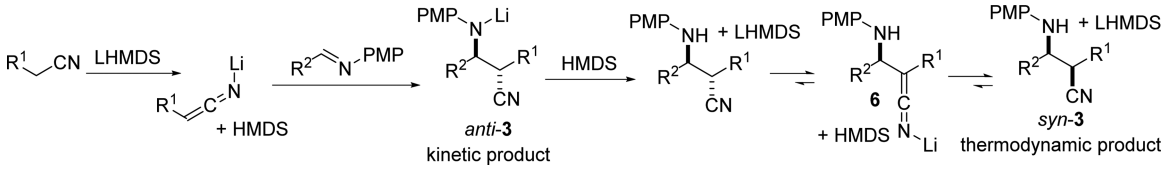
Scheme 3. Proposed Mechanism



that are *anti*-diastereoselective to be converted into *syn*-diastereoisomers. The methodology described provides a direct method for the stereoselective synthesis of *β*-aminonitriles, which will widen their use as chiral building blocks in target synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00679.

Experimental procedures, characterization data and NMR spectra for all compounds; representation of X-ray structure for *syn*-**3** (PDF)

Crystallographic data for *syn*-**3** (CIF)

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Notes

The authors declare no competing financial interest.

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(23) Unambiguous assignment of relative stereochemistry was achieved through single-crystal X-ray crystallography of the prevailing *syn*-diastereoisomer (*syn*-**3**) from a reaction using LHMDS. See the SI and CCDC 1531946.

(24) Possible quenching of LHMDS by adventitious water over time during use could increase the concentration of HMDS.

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