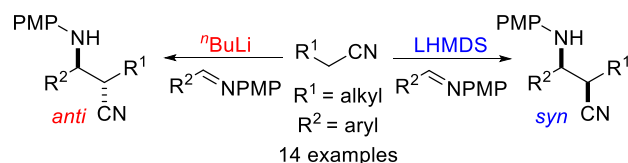


Base controlled diastereoselective synthesis of either *anti*- or *syn*- β -aminonitriles

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Supporting Information Placeholder



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 diastereoisomers can be isolated in good yields and the mechanism was elucidated.

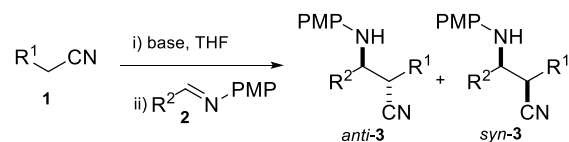
The nitrile functional group is ubiquitous in synthesis due to its ease of incorporation, ability to facilitate the formation of new bonds and interconversion into a myriad of other functional groups.¹ It is present in biologically active natural products and its use as a pharmacophore has also been recognised.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-diamines⁷ 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 nitroalkenes¹⁰ 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 (CH₃CN, pK_a 31.3, PhCH₂CN, 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 epimerisation¹⁵ 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 catalysed reactions, 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 auxiliary²⁰ on the imine gave a diastereoselectivity ~15:85 *anti*:*syn* for the prod-

uct β -aminonitrile.²¹ There is a clear need to be able to synthesise 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.

Scheme 1. 1,2-addition of alkane nitriles to aldimines



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, R¹=Bn, R²=2-Br-C₆H₅). The 2-bromophenyl imine was used in preparation for a possible Pd catalysed 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 nBuLi 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 favour the *syn*- β -aminonitrile 15:85 (entry 2). In the case of LHMDS the

syn- β -aminonitrile was observed with *dr* = 90:10 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 ⁿBuLi (compare entries 1 and 2 with 5 and 6). This similarity of ⁿBuLi and LDA had been 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

Table 1. Effect of base and temperature for R¹=Bn and R²=2-BrC₆H₄^a

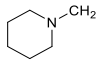
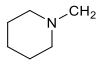


entry	base	conditions	conversion (%) ^b	<i>anti</i> : <i>syn</i> ^c
1	ⁿ BuLi	-78 °C, 1 h	90	85:15
2	ⁿ BuLi	-78 °C, 1 h; rt, 5 min	80	15:85
3	LHMDS	-78 °C, 1 h	100	10:90
4	LHMDS	-78 °C, 1 h; rt, 5 min	80	10:90
5	LDA	-78 °C, 1 h	90	80:20
6	LDA	-78 °C, 1 h; rt, 5 min	80	15:85

^aAll 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. ^bBy ¹H NMR. ^cDetermined by comparison of the ¹H NMR signals for the CH₂CHCN protons (~2.5-3.5 ppm) of the crude reaction mixture (to nearest 5).

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 ⁿBuLi 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 *iso*-butyronitrile with either base gave only ~7% yield and was not further optimised. 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)propyl nitrile for the *syn*-diastereoisomer generated with LHMDS (entries 21, 90% yield). Other nitriles of simple alkyl derivatives gave no clear trend in diastereoselectivities,

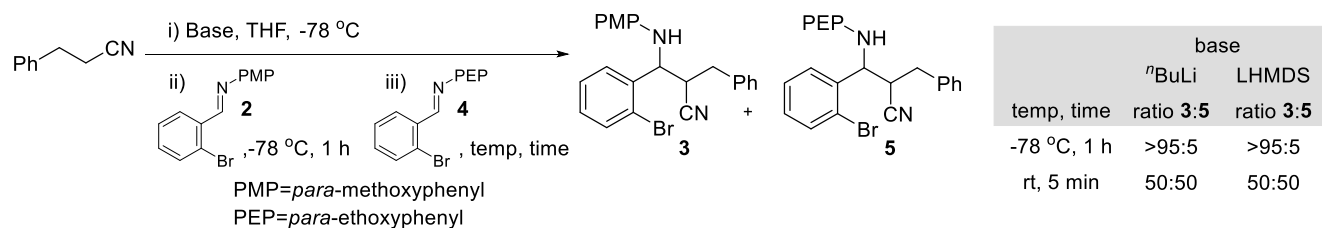
Table 2. Scope of diastereoselectivity^a

entry	R ¹	R ²	base	<i>anti</i> - 3 : <i>syn</i> - 3 ^b	yield of major (%) ^c
1	Bn	2-Br-C ₆ H ₅	ⁿ BuLi	85:15	62
2	Bn	2-Br-C ₆ H ₅	LHMDS	10:90	76
3	Bn	C ₆ H ₅	ⁿ BuLi	70:30	44
4	Bn	C ₆ H ₅	LHMDS	20:80	68
5	Bn	2-Me-C ₆ H ₅	ⁿ BuLi	85:15	67
6	Bn	2-Me-C ₆ H ₅	LHMDS	10:90	80

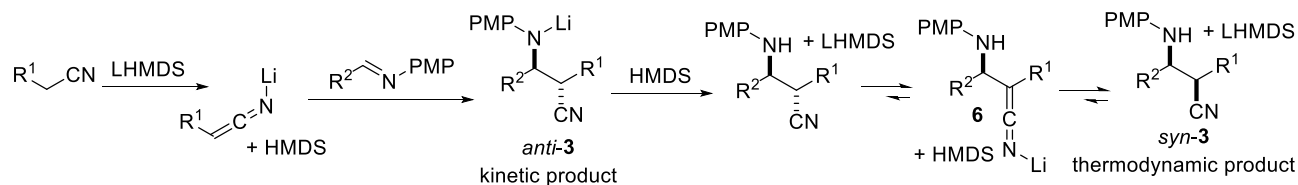
7	Bn	2-Br-3-Pyridyl	ⁿ BuLi	85:15	65
8	Bn	2-Br-3-Pyridyl	LHMDS	40:60	40
9	Bn	2-Br-3-Pyridyl	LHMDS ^d	15:85	62
10	Bn	2-Cl-C ₆ H ₅	ⁿ BuLi	85:15	58
11	Bn	2-Cl-C ₆ H ₅	LHMDS	15:85	70
12	Me	C ₆ H ₅	ⁿ BuLi	50:50	50
13	Me	C ₆ H ₅	LHMDS	25:75	75
14	ⁱ Pr	C ₆ H ₅	ⁿ BuLi	70:30	50
15	ⁱ Pr	C ₆ H ₅	LHMDS	40:60	47
16		C ₆ H ₅	ⁿ BuLi	55:45	54
17		C ₆ H ₅	LHMDS	40:60	59
18		C ₆ H ₅	ⁿ BuLi	-	<10 ^e
19		C ₆ H ₅	LHMDS	40:60	63 ^f
20	PhCH ₂ CH ₂	C ₆ H ₅	ⁿ BuLi	60:40	56
21	PhCH ₂ CH ₂	C ₆ H ₅	LHMDS	20:80	82
22	2-Cl-PhCH ₂	C ₆ H ₅	ⁿ BuLi	50:50	35
23	2-Cl-PhCH ₂	C ₆ H ₅	LHMDS	5:95	90
24	Bn	4-Cl-C ₆ H ₅	ⁿ BuLi	55:45	43
25	Bn	4-Cl-C ₆ H ₅	LHMDS	10:90	70
26	Bn	4-MeO-C ₆ H ₅	ⁿ BuLi	65:35	48
27	Bn	4-MeO-C ₆ H 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

^aAll 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. ^bAssigned by ¹H NMR comparison with compounds *anti*-**3** and *syn*-**3** R¹=Bn, R²=2-Br-C₆H₅ and determined by comparison of the ¹H NMR signals for the CH₂CHCN protons (~2.5-3.5 ppm) of the crude reaction mixture (to nearest 5). ^cIsolated yield of pure major diastereoisomer. ^d-78 °C, 4.5 h. ^eConversion by ¹H NMR. ^fYield of inseparable diastereomeric mixture. ^gYield of minor *syn*-diastereoisomer in parenthesis.

Scheme 2. Crossover experiment



Scheme 3. Proposed mechanism



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 favouring 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, $\text{R}^1=\text{Bn}$ and $\text{R}^2=o\text{-BrC}_6\text{H}_4$) was performed at -78 °C at varying reaction times and the crude material analysed by ^1H NMR (Table 3). The results suggest that the initial 1,2-addition favours the *anti*-diastereoisomer in an 85:15 ratio after 1 min at -78 °C with both $^n\text{BuLi}$ and LHMDS. The initial *anti*-selectivity for LHMDS was quickly eroded over time (<30 min) and as the conversion increased with time, the selectivity for the *syn*-diastereoisomer also increased to a maximum 10:90 (~60 min). For $^n\text{BuLi}$ the initial and rapid *anti*-selectivity (85:15) was maintained and did not start to be eroded until after 1 h. After 6 h the $^n\text{BuLi}$ 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. Quite why the *syn*-diastereoisomer is the thermodynamically more stable product is not obvious to us.

Table 3. Effect of base and temperature on diastereoselectivity^a

time at -78 °C	$^n\text{BuLi}$		LHMDS	
	<i>anti</i> : <i>syn</i> ^b	conversion (%) ^c	<i>anti</i> : <i>syn</i> ^b	conversion (%) ^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

^aAll 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. ^bDetermined by comparison of the ^1H NMR signals for the CH_2CHCN protons (~2.5-3.5 ppm) of the crude reaction mixture (to nearest 5). ^cBy ^1H NMR.

To probe the mechanism of isomerisation a crossover experiment was conducted. The initial product **3** ($\text{R}^1=\text{Bn}$, $\text{R}^2=2\text{-Br-C}_6\text{H}_5$), formed *in situ* from addition to PMP protected imine **2** ($\text{R}^2=2\text{-Br-C}_6\text{H}_5$) after 1 h at -78 °C, was treated with an equivalent of the corresponding *N*-*para*-ethoxyphenyl protected imine **4** and left to stir for a further 1 h at -78 °C (Scheme 2). The crude ^1H 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 an equivalent 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 re-addition pathway. Crossover was observed at rt, therefore a retro- / re-addition mechanism can take place on warming, which accounts for the formation of the thermodynamic *syn*-diastereoisomer for $^n\text{BuLi}$ as the reaction warms to rt.

A key control experiment was treatment of *anti*-**3** ($\text{R}^1=\text{Bn}$, $\text{R}^2=2\text{-Br-C}_6\text{H}_5$) 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 epimerised to the *syn*-diastereoisomer (15:85), within experimental error virtually identical to the original LHMDS *syn*-diastereoselection (10:90). Additionally treatment of *anti*-**3** ($\text{R}^1=\text{Bn}$, $\text{R}^2=2\text{-Br-C}_6\text{H}_5$) with $^n\text{BuLi}$ at -78 °C for 1 h led to no change in diastereoselectivity, and treatment of *syn*-**3** ($\text{R}^1=\text{Bn}$, $\text{R}^2=2\text{-Br-C}_6\text{H}_5$) with either $^n\text{BuLi}$ 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 pKa of HMDS (26) is similar to that of HCCN (22-31).¹³ We propose at -78 °C that equilibration occurs by deprotonation and reprotonation of the HCCN of **3** by HMDS (Scheme 2). Using LHMDS as base the original kinetic *anti*-**3** rich mixture is reprotonated by HMDS and the regenerated LHMDS equilibrates the HCCN centre to the thermodynamic mixture, with *syn*-**3** as the major diastereoisomer. With $^n\text{BuLi}$ 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 ($\text{R}^1=\text{Bn}$, $\text{R}^2=2\text{-Br-C}_6\text{H}_5$). Addition of an equimolar quantity of HMDS to a $^n\text{BuLi}$ deprotonation directly before or after addition of imine favoured the thermodynamic *syn*-**3** (25:75). Addition of an equimolar quantity of $^n\text{BuLi}$ to a LHMDS deprotonation, followed by imine favoured 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 ⁿBuLi favoured the thermodynamic *syn*-3 (20:80), implying that the equilibration was interrupted by irreversible deprotonation with ⁿBuLi. 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 epimerisation *via* both retro-/re-addition and deprotonation/reprotonation of HCCN.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 (R¹=Bn, R²=2-Br-C₆H₅) was reduced to the corresponding 1,3-diamine with LiAlH₄/H₂SO₄ in 92% yield and hydrolysed with basic hydrogen peroxide to the β-amino acid in 65% yield, with no erosion in diastereoselectivity (see Supportin Information (SI)).

The judicious choice of either irreversible conditions with ⁿBuLi 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 characterisation of the thermodynamic equilibration process with HMDS offers the opportunity for the products from enantioselective syntheses 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.

Experimental procedures, characterisation data and NMR spectra for all compounds. Representation of X-ray structure for *syn*-3 R¹=Bn, R²=2-Br-C₆H₅ (PDF)

Crystallographic data for *syn*-3 R¹=Bn, R²=2-Br-C₆H₅ (CIF)

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Notes

The authors declare no competing interest.

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REFERENCES

- (1) (a) *Chemistry of the Cyano Group*; Rappoport, Z.; Patai, S., Eds.; Wiley: London, 1970. (b) Fatiadi, A. J. Supplement C. In *The Chemistry of Triple Bonded Functional Groups, Part 2*; Rappoport, Z.; Patai, S., Eds.; Wiley: London, 1983; pp 1057-1303.
- (2) Fleming, F. F.; Yao, L.; Ravikumar, P. C.; Funk, L.; Shook, B. C. *J. Med. Chem.* **2010**, *53*, 7902.
- (3) (a) Arseniyadis, S.; Kyler, K. S.; Watt, D. S. *Org. React.* **1984**, *31*, 1. (b) Fleming, F. F. *Nat. Prod. Rep.* **1999**, *16*, 597.
- (4) Naruse, N.; Yamamoto, S.; Yamamoto, H.; Kondo, S.; Masuyoshi, S.; Numata, K.-I.; Fukagawa, Y.; Oki, T. *J. Antibiot.* **1993**, *46*, 685.
- (5) Zeches, M.; Ravao, T.; Richard, B.; Massiot, G.; Le Men-Olivier, L.; Verpoorte, R. *J. Nat. Prod.* **1987**, *50*, 714.
- (6) Mesa, R. A.; Yasothan, U.; Kirkpatrick, P. *Nature Reviews Drug Discovery* **2012**, *11*, 103.
- (7) For a recent review, see: Xiaolei J.; Huang, H. *Org. Biomol. Chem.* **2016**, *14*, 10557.
- (8) For example: Saika, M.; Deka, D. C.; Karmakar, S. *Current Microwave Chemistry* **2016**, *3*, 47 and references therein.
- (9) For example: Yadav, J. S.; Reddy, B. V. S.; Parincala, G.; Reddy, P. V. *Synthesis* **2002**, 2383 and references therein.
- (10) Anderson, J. C.; Blake, A. J.; Mills, M.; Ratcliffe, P. D. *Org. Lett.* **2008**, *10*, 4141.
- (11) For example: Chhiba, V.; Bode, M. L.; Mathiba, K.; Kwezi, W.; Brady, D. *J. Mol. Cat. B: Enzymatic* **2012**, *76*, 68.
- (12) For a review of catalytic cyanoalkylation, see: López, R.; Palomo, C. *Angew. Chem. Int. Ed.* **2015**, *54*, 13170.
- (13) (a) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456. (b) Richard, J. P.; Williams, G.; Gao, J. *J. Am. Chem. Soc.* **1999**, *121*, 715.
- (14) Mecozzi, T.; Petrini, M.; Profeta, R. *J. Org. Chem.* **2001**, *66*, 8264.
- (15) Viteva, L.; Gospodova, T.; Stefanovsky, Y.; Simova, S. *Tetrahedron* **2005**, *61*, 5855.
- (16) (a) D'Sa, B. A.; Kisanga, P.; Verkade, J. G. *J. Org. Chem.* **1998**, *63*, 3961. (b) Kisanga, P.; McLeod, D.; D'Sa, B.; Verkade, J. G. *J. Org. Chem.* **1999**, *64*, 3090.
- (17) (a) Poisson, T.; Gembus, V.; Oudeyer, S.; Marsais, F.; Levacher, V. *J. Org. Chem.* **2009**, *74*, 3516. (b) Hyodo, K.; Kondo, M.; Funahashi, Y.; Nakamura, S. *Chem. Eur. J.* **2013**, *19*, 4128.
- (18) (a) Aydin, J.; Conrad, C. S.; Szabó, K. J. *Org. Lett.* **2008**, *10*, 5175. (b) Hyodo, K.; Nakamura, S.; Tsuji, K.; Ogawa, T.; Funahashi, Y.; Shibata, N. *Adv. Synth. Catal.* **2011**, *353*, 3385. (c) Zhao, J.; Liu, X.; Luo, W.; Xie, M.; Lin, L.; Feng, X. *Angew. Chem. Int. Ed.* **2013**, *52*, 3473.
- (19) Tian, M.; Yan, M.; Baran, P. S. *J. Am. Chem. Soc.* **2016**, *138*, 14234.
- (20) Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600.
- (21) The terms *anti* and *syn* are defined in this paper according to that forwarded by Masamune. Masamune, S.; Ali, S. A.; Smitman, D. L.; Garvey, D. S. *Angew. Chem. Int. Ed.*, **1980**, *19*, 557.
- (22) (a) Anderson, J. C.; Blake, A. J.; Koovits, P. J.; Stepney, G. J. *J. Org. Chem.* **2012**, *77*, 4711. (b) Anderson, J. C.; Horsfall, L. R.; Kalogirou, A. S.; Mills, M. R.; Stepney, G. R.; Tizzard, G. *J. Org. Chem.* **2012**, *77*, 6186. (c) Anderson, J. C.; Noble, A.; Tocher, D. A. *J. Org. Chem.* **2012**, *77*, 6703. (d) Anderson, J. C.; Koovits, P. J. *Chem. Sci.*, **2013**, *4*, 2897. (e) Anderson, J. C.; Kalogirou, A. S.; Porter, M. J.; Tizzard, G. *J. Beil. J. Org. Chem.* **2013**, *9*, 1737. (f) Anderson, J. C.; Kalogirou, A. S.; Tizzard, G. *J. Tetrahedron* **2014**, *17*, 9337. (g) Anderson, J. C.; Campbell, I. B.; Campos, S.; Shannon, J.; Tocher, D. A. *Org. Biomol. Chem.* **2015**, *13*, 170. (h) Anderson, J. C.; Barham, J. P.; Rundell, C. D. *Org. Lett.* **2015**, *17*, 4090. (i) Anderson, J. C.; Rundell, C.

D. *Synlett* **2016**, 27, 41. (j) Anderson, J. C.; Campbell, I. B.; Campos, S.; Reid, I. H.; Rundell, C. D.; Shannon, J.; Tizzard, G. J. *Org. Biomol. Chem.* **2016**, *14*, 8270

(23) Unambiguous assignment of relative stereochemistry was achieved through single crystal X-ray crystallography of the prevailing

syn-diastereoisomer (*syn*-**3** R¹=Bn, R²=2-Br-C₆H₅) from a reaction using LHMDS. See SI and CCDC 1531946

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