DOI: 10.1002/ejoc.200801053

Metalated Nitriles: Internal 1,3-Asymmetric Induction

Fraser F. Fleming*[a] and Wang Liu[a]

Keywords: Nitrile / Conformation analysis / Alkylation / Diastereoselectivity

Stereoselective alkylations of acyclic, metalated nitriles are intimately controlled by a remote stereocenter. Probing the optimal steric demand through alkylations with a series of substituted pentanenitriles reveal the fundamental requirements for 1,3-asymmetric induction. Relaying these requirements into a predictive model suggests that the stereoselectivity arises from a preferential electrophilic attack on the more stable diamond lattice conformation of the metalated nitrile. Using this strategy a series of metalated alkanenitriles selectively intercept a diverse range of electrophiles in alkylations that efficiently install new quaternary centers. The metalated nitrile alkylations provide fundamental insight for remote stereoinduction and a solid foundation for further advances in stereoselective alkylations of flexible nucleophiles having a defined shape.

1.Introduction

Conformational control is a central prerequisite for stereoselective asymmetric synthesis.[1] A time-proven stereocontrol strategy, whose origin is often equated with the beginning of stereoselective synthesis,[2] is to employ conformationally constrained cyclic enolates that bias electrophile trajectories.[3] Underpinning stereoselective transformations within carbocycles is the ability to accurately predict the reactive conformation, a concept whose seminal importance was recognized in the 1969 Nobel Prize for "The Principles of Conformational Analysis."[4]

The conformational bias in six-membered rings usually rests on a preference for avoiding steric compression. 1,3-Diaxial interactions,[5] the steric compression between two axial substituents on a cyclohexane ring, is essentially the cyclic equivalent of the destabilizing *syn*-pentane interaction encountered in linear hydrocarbons (Figure 1, compare **1** and **2**). The centrality of the *syn*-pentane interaction is readily appreciated by imposing the carbon backbone of pentane onto a diamond lattice, a carbon scaffold in which the dihedral angles around carbon–carbon bonds are assumed to approximate the ideal found in diamond. Overlaying conformationally mobile chains onto a diamond lattice provides a valuable concept for readily identifying the low-energy conformations of acyclic chains without recourse to computational methods.[6]

Figure 1. Conformational analogies between cyclic and acyclic alkanes.

Seminal advances in acyclic conformational analysis reveal how substituents on flexible hydrocarbon chains can favor surprisingly few well-defined conformations.[7] For example, the *syn*-2,4-dimethylpentane motif, **3** (Figure 2), has facile rotation around the two core bonds but exhibits a strong substituent-dependent preference for one of two conformations **3′** or **3′′′** to avoid conformations with *syn*-pentane interactions (**3′′** or **3′′′′**).[8] The preference for conformer **3′** or **3′′′** depends on the relative steric demand of the substituents R^1, R^2, and Me. Although a precise measure of the interactions between these substituents and the *syn*-axial-like methine proton (see symbols in Figure 2) is compromised by the facile relaxation of substituents away from a perfect diamond lattice conformation, the steric interactions approximate the corresponding *A* values determined for substituted cyclohexanes (Figure 1).[9]

Numerous natural products incorporate the 2,4-dimethylpentane structural motif leading to one favored solution conformation.[7b] For example, in solution the nitrile-containing natural product calyculin C (**4**)[10] adopts conformation **4′** in the C29–C32 segment (Figure 3, inset) which minimizes the potential *syn*-pentane interactions.[11]

Internal asymmetric induction in alkylations with acyclic nucleophiles is a significant challenge. The challenge for metalated nitrile alkylations lies in taming the flexibility in-

[a] Department of Chemistry and Biochemistry,
Mellon Hall, Duquesne University, Pittsburgh PA 15282-1530, USA
Fax: +1-412-396-5683
E-mail: flemingf@duq.edu

Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.

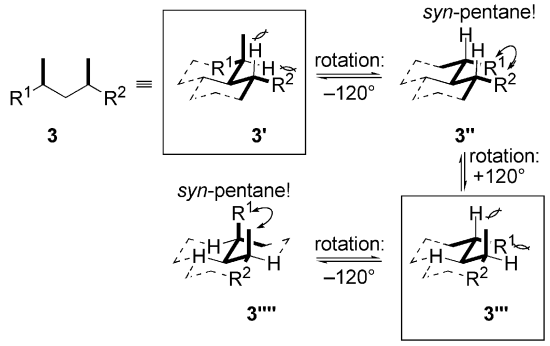


Figure 2. Acyclic conformational preferences in substituted 2,4-dialkylpentanes.

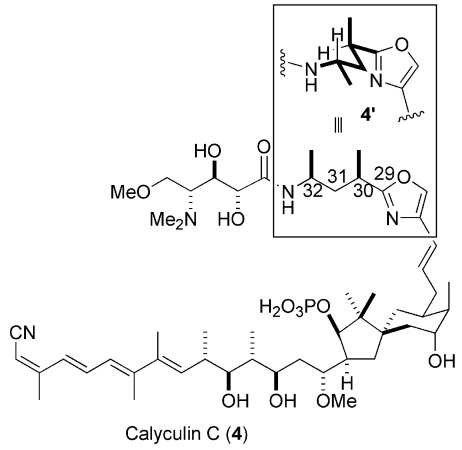


Figure 3. Structure and conformation of calyculin C.

herent in the intervening single bonds while concurrently propagating high asymmetry along the carbon chain. Pentanenitrile **5a**, bearing 2-methyl and 4-(1-naphthyl) substituents (Figure 4), appeared to fulfill the requirements because of a projected preference for a single diamond-lattice conformation.[12] Extensive conformational analyses of ibuprofen analogs,[13] such as **6**, demonstrate that the 1-naphthyl substituent prefers a conformation[14] with the methine proton almost eclipsing the naphthyl ring (Figure 4).[15] While the precise rotation angle depends intimately on the nature of the substituents, the eclipsed conformation avoids inherent allylic strain[16] that would otherwise ensue between one of the carbon substituents and the aromatic ring.

Planar aromatic substituents, such as the naphthyl ring, exert a surprisingly small steric demand in conformationally mobile hydrocarbons.[17] In fact, NMR analyses indicate that a phenyl ring exerts a smaller steric demand than a methyl group as a consequence of the planar "edge on" topology.[18] Embedding a naphthyl substituent at carbon 4 of pentanenitrile **5a** was therefore envisaged to create a highly asymmetric environment because of the different steric demand of the three substituents; a "large" methyl group, a medium-sized naphthyl group, and a small proton. Assuming that the pentane chain adopts a diamond lattice conformation (Figure 4, bonds printed in bold) with the

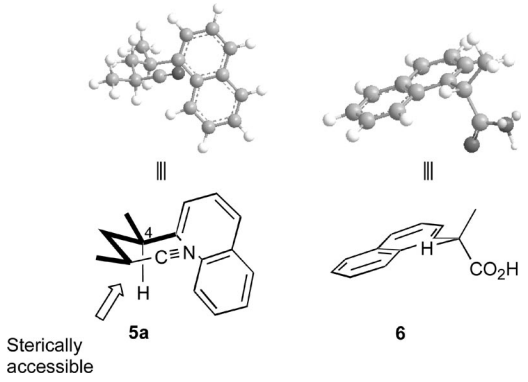


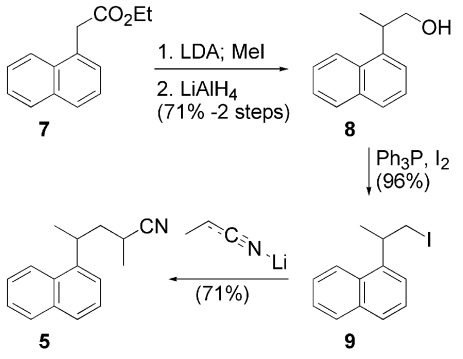
Figure 4. Conformational minima with (1-naphthyl) substituents.

naphthalene ring in a "methine-eclipsed" conformation, then any reagent approach to the nitrile should occur opposite the naphthalene ring. If the conformational integrity is maintained on deprotonation then any electrophilic approach to the metalated nitrile should experience significant stereodiscrimination.

2. Results and Discussion

2.1 First Generation

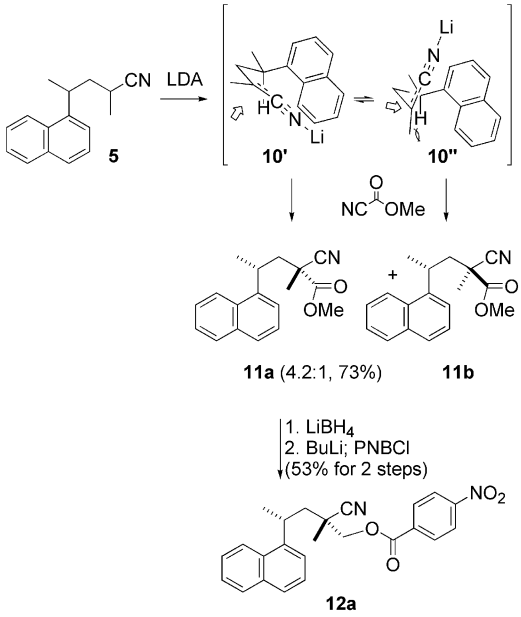
Facile and efficient access to the naphthyl-substituted nitrile **5** provided a valuable prototype for probing the asymmetric 1,3-induction strategy. Successive methylation and reduction of commercial ethyl 1-naphthylacetate (**7**) afforded alcohol **8** that was efficiently iodinated to provide **9** (Scheme 1). Despite the potential for dehydrohalogenation, alkylating **9** with lithiated propionitrile occurred smoothly to provide the requisite nitrile **5** as a mixture of diastereomers.



Scheme 1. Synthesis of a naphthyl-substituted nitrile prototype.

The diastereoselective alkylation of the metalated nitrile derived from **5** was probed with methyl cyanoformate as a test electrophile. Deprotonating **5** and acylating with methyl cyanoformate at –78 °C provided a 4.2:1 ratio of diastereomers **11a** and **11b** (Scheme 2). The stereochemical course of the reaction was determined by selectively reducing the carbonyl group of **11a** and esterifying the resulting alcohol with *p*-nitrobenzoyl chloride (PNBCl). X-ray crys-

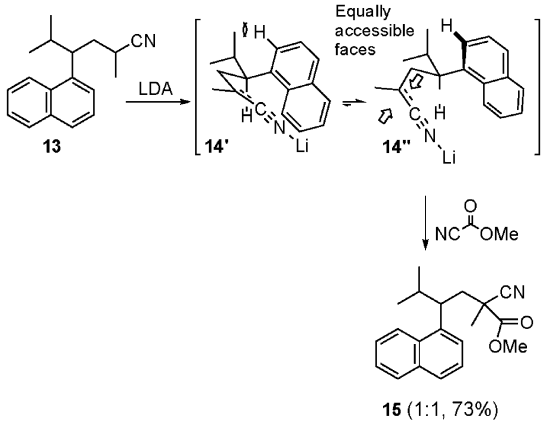
tallographic analysis of the resulting crystalline nitrile ester **12a** unequivocally established the relative configuration of the two chiral centers.[19] Relaying the stereochemistry of **12a** to the alkylation event is consistent with preferential electrophilic attack on the planar[20] *N*-lithiated nitrile conformer **10′** from the face opposite the naphthyl group.



Scheme 2. Stereoselective metalated nitrile acylation.

Conformers **10′** and **10′′** assume a common diamond-lattice conformation with the naphthylene ring eclipsing the methine proton (Scheme 2). The main point of difference between **10′** and **10′′** lies in the position of the 2-methyl substituent and, correspondingly, the preferred orientation of the lithiated nitrile. The stereoselective alkylation of **5** is consistent with **10′** being the preferred conformation with the small lithiated nitrile[21] eclipsing the naphthalene ring in the sterically more demanding position. Preferential alkylation of **10′** opposite the naphthyl ring leads to the major diastereomer whereas a similar attack on rotamer **10′′** having a *gauche*-type methyl-proton interaction, leads to the minor diastereomer.

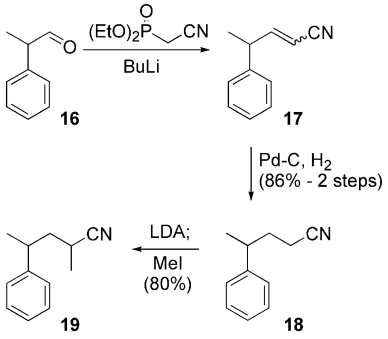
Scrutinizing the crystallographic structure of the nitrile ester **12a** identified a rotation of the aliphatic methine proton away from planarity with the naphthylene ring. Naively assuming that a larger substituent would correct this distortion stimulated the synthesis[22] and acylation of the isopropyl-substituted nitrile **13** (Scheme 3). Unfortunately, sequential deprotonation and acylation of **13** was completely non-selective. Although speculative, an eclipsing interaction in **14′** may cause a rotation away from the diamond lattice conformation rendering the faces in **14′′** equally accessible. The practical lesson from the alkylations of **5** and **13** is the requirement for a terminal methyl group with an adjacent aromatic ring.



Scheme 3. Non-selective alkylation of an isopropyl-substituted nitrile.

2.2 Second Generation

Armed with a rudimentary appreciation for the substitution requirements, attention was focused on determining if the nature of the electrophile or the metalated nitrile influences the stereoselectivity.[23] Employing the nitrile prototype **19** with a phenyl for naphthyl substitution appeared particularly attractive because of a more direct synthesis (Scheme 4) and the potential availability of both enantiomers of **16** through the chiral hydroformylation of styrene.[24] Efficient access to the requisite nitrile **19** was achieved by cyanomethylenation of aldehyde **16**, reduction of the resulting alkenenitrile **17** to **18** with magnesium in methanol[25] or by hydrogenation,[26] and subsequent methylation.

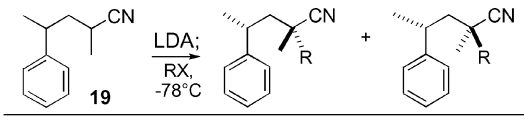


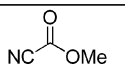
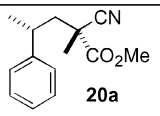
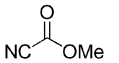
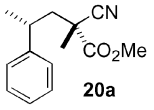
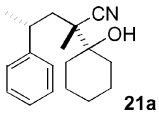
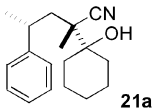
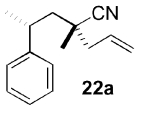
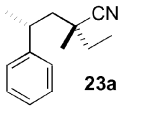
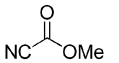
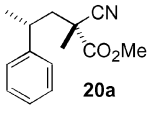
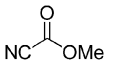
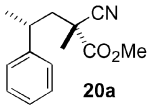
Scheme 4. Synthesis of phenyl-substituted nitrile prototype.

Alkylating the metalated nitrile derived from **19** proceeded with diastereoselectivities comparable to those of the naphthyl analogue (Table 1). As a point of comparison, deprotonating **19** with LDA and intercepting the lithiated nitrile with methyl cyanoformate preferentially affords two diastereomers in a 3.2:1 ratio (Table 1, Entry 1) whereas the naphthyl analog **5** afforded a 4.2:1 ratio of diastereomers (Scheme 2). For alkylations of **19**, the addition of TMEDA exerts a decline in selectivity (Table 1, Entry 2) and in comparable alkylations with cyclohexanone, lowering the temperature from –78 °C to –96 °C does not improve the stereo-

selectivity (Table 1, Entries 3 and 4). Alkylations with carbonyl, allylic bromide and alkyl iodide electrophiles occur with comparable levels of selectivity (Table 1).

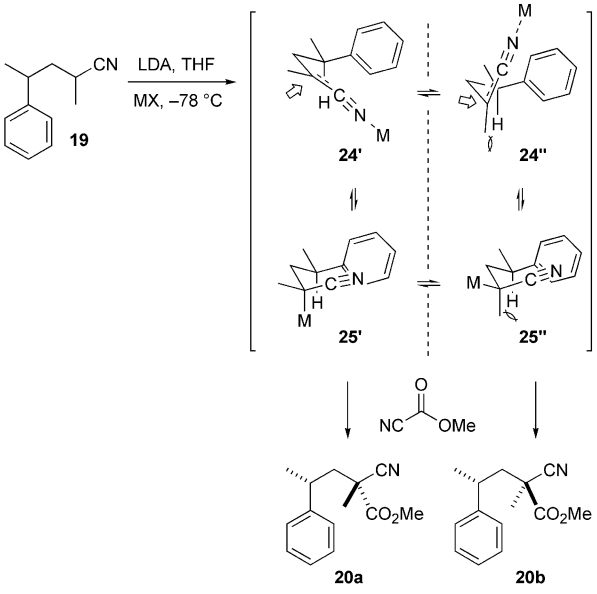
Table 1. Diastereoselective metalated nitrile alkylations.



Entry	RX, Conditions	Quaternary nitrile	Ratio[a]	Yield [%]
1		 **20a**	3.2:1[b]	65
2	 TMEDA	 **20a**	2.0:1	62
3		 **21a**	3.9:1[c]	75
4	 -98 °C	 **21a**	4.0:1[c]	68
5		 **22a**	3.8:1[d]	86
6		 **23a**	4.2:1[d]	56
7	 $ZnBr_2$	 **20a**	4.5:1	68
8	 $ZnCl_2$[e]	 **20a**	4.3:1	70

[a] The major diastereomer is that depicted. [b] The stereochemistry of **20a** is based on X-ray crystallography[27] of a derivative. [c] The configuration is assigned by analogy. [d] The configurations of **22a** and **23a** are based on chemical correlations. [e] The alkylation was performed at –50 °C.

Chemical correlations establish that the alkylations of nitrile **19** all occur with the same relative diastereoselectivity (see Supporting Information). In addition, the sense of asymmetric induction for **19** parallels that of the naphthyl-substituted nitrile **5**. Collectively, the alkylations of the lithiated nitrile derived from **19** are consistent with electrophilic attack onto the more accessible face of the *N*-lithiated nitrile conformer **24′** (Scheme 5).

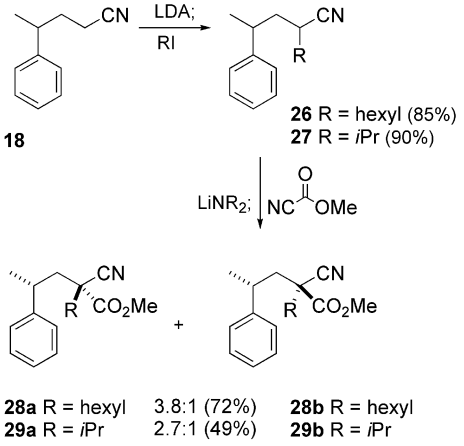


Scheme 5. Stereoselectivity model for metalated nitrile alkylations.

Having established the diastereoselectivity in alkylations of the *N*-lithiated nitrile **24** (Scheme 5), a series of metal additives were used to screen the selectivity preferences of a range of *N*- and *C*-metalated nitriles.[28] Sequentially deprotonating **19** with LDA, adding a metal halide, and then methyl cyanoformate generally led to complex reaction mixtures.[29] The cleanest reactions of highest selectivity were achieved with zinc halides which are known to favor transmetallation to *C*-zincated nitriles (**24**→**25**).[30] Rapid, conducted tour equilibration[31] interconverts these diastereomeric *C*-metalated nitriles through a sequence of *C*- to *N*-metal migration (**25′**→**24′**), rotation (**24′**→**24′′**), and migration of the metal back to carbon (**24′′**→**25′′**). Acylating the intermediate zincated nitriles affords predominantly **20a** (Table 1, Entries 7 and 8) consistent with retentive alkylation from the *C*-zincated nitrile conformer **25′** (M = ZnBr) which assumes that the long zinc–carbon bond places the steric demand of ZnBr between that of the methyl and nitrile groups.[9] The similar acylation stereoselectivity of the *C*-zincated nitrile offers no advantage over the corresponding acylation with an *N*-lithiated nitrile, particularly because zincated nitriles are generally considerably less nucleophilic.[32]

Changing the steric demand of the α-substituent in the metalated nitrile from methyl to hexyl or isopropyl has only a small influence on the stereoselectivity. Comparable acylations of hexyl nitrile **26** and isopropyl nitrile **27**, prepared by alkylations of **18** (Scheme 6), affords the nitrile diastereomers **28a** and **28b** in a 3.8:1 ratio and diastereomers **29a** and **29b** with a 2.7: selectivity preference.[33] The diastereomer ratios are only slightly different from that ob-

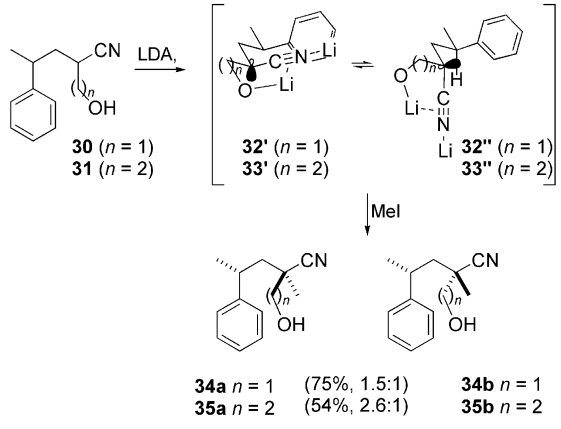
served for the α-methyl-bearing nitrile **19** (Scheme 5) suggesting that the alkylations proceed through similar conformations (cf. **24′** Scheme 5).



Scheme 6. Stereoselectivities of α-substituted metalated nitrile alkylations.

2.3 Third Generation

The comparable diastereoselectivity for alkylations of *N*- and *C*-metalated nitriles **24** and **25** (Scheme 5) stimulated alkylations with another type of metalated nitrile, a nitrile anion. The strategy was based on the highly selective alkylations of cyclic nitrile anions in which the anion geometry is enforced by internal complexation.[34] Experimentally, sequentially deprotonating the hydroxy nitriles **30** and **31**[35] with excess LDA, followed by addition of methyl iodide installs the quaternary center with a modest preference for **34a** and **35a**.[36] The diastereoselectivity is consistent with preferential alkylation from the nitrile anions **32′** and **33′** in which the alkoxy lithium is complexed to the nitrile[37] π-electrons with an additional lithium-π interaction with the benzene ring[38] (Scheme 7). Although the alkylations proceed with a consistent preference for the same diastereomer, the modest diastereoselectivity stimulated a fourth approach to impart greater stereocontrol.

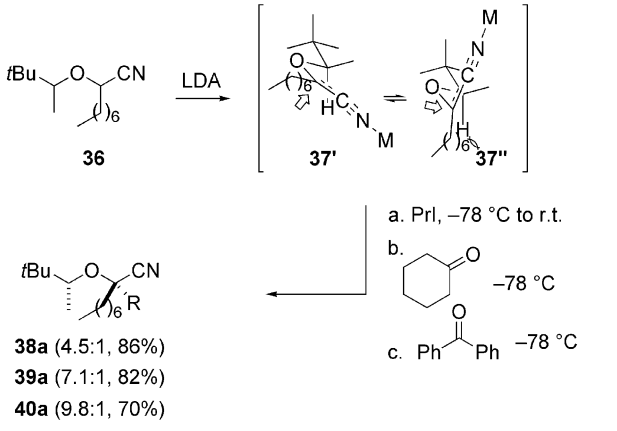


Scheme 7. Diastereoselective alkylations with dilithiated nitrile "anions.".

2.4 Fourth Generation

Designing a more efficient transfer of stereochemical information in metalated alkanenitrile alkylations focused on maximizing the difference in the steric demand of the terminal substituents. Replacing the γ-aromatic substituent with a *tert*-butyl group appeared particularly attractive because the chiral carbon would bear *t*Bu, Me, and H groups having disparate A values (4.7, 1.7, 0 kcal mol^{-1}).[9] Substituting an oxygen atom for the intervening methylene unit was envisaged to enhance the asymmetric induction through two complementary effects. The shorter C–O bond length (1.53 Å and 1.43 Å for C–C and C–O bonds, respectively)[39] should accentuate the internal relay of asymmetry and the n → σ^*_{C-H} stereoelectronic effect[40] should increase the preference for the diamond lattice conformation.

The requisite nitrile **36** was readily prepared in four-steps (Supporting Information). Sequentially deprotonating nitrile **36** and alkylating with several electrophiles selectively installs the new quaternary center with improved stereoselectivity (Scheme 8).[41] Alkylating with propyl iodide afforded **38a** with a slightly higher diastereoselectivity than for any other nitrile. By employing the carbonyl electrophiles, cyclohexanone and benzophenone and performing the alkylation at –78 °C, the hydroxynitriles **39a** and **40a** were obtained with the highest diastereoselectivity of any acyclic, metalated nitrile.



Scheme 8. Diastereoselective alkylations of an oxygen-containing nitrile.

Conclusions

Alkylations of acyclic metalated nitriles containing a remote stereocenter predictably install new quaternary centers through an internal relay of chiral information. The asymmetric environment was specifically designed using principles of allylic strain and *syn*-pentane interactions to favor one diamond lattice conformation with different steric demands for electrophilic attack on the diastereotopic faces of the metalated nitrile. Screening a series of substituted alkanenitriles reveals a dependable diastereoselectivity preference consistent with the diamond-lattice alkylation model.

The strategy is equally selective for *N*- or *C*-metalated nitriles. Quaternary centers are effectively installed in alkylations with carbonyl and alkyl halide electrophiles. Aromatic phenyl and naphthyl substituents at C-3 and primary alkyl substituents at C-1 are equally effective whereas secondary alkyl and hydroxyalkyl substituents at C-1 diminish the stereoselectivity. Optimal stereoselectivity is achieved with an oxygen-containing alkanenitrile in which the chiral center bears *tert*-butyl, methyl, and hydrogen substituents.

The value of the alkylations lie partly in the stereoselective installation of quaternary centers, but more in exploring the conceptual use of conformational control in hydrocarbon chains during stereoselective bond formation. The modest, but usable, diastereoselectivity likely reflects the dynamic nature of conformationally mobile systems; bond angles greater than the ideal of 109°, and small distortions of the carbon backbone that prevent an exact correspondence to one diamond lattice conformation. What is remarkable is the consistency of the diamond lattice model to predict the sense of stereoinduction. Collectively the alkylations provide fundamental insight for internal asymmetric induction with metalated nitriles and provide a solid foundation for stereoselective alkylations with acyclic nucleophiles.

Experimental Section

General Deprotonation–Alkylation Procedure: A THF solution of the nitrile (1.0 equiv.) was added to a –78 °C cold THF solution of LDA, generated from butyllithium (1.05 equiv.) and diisopropylamine (1.15 equiv.). After 50 min at –78 °C, neat electrophile (1.2 equiv.) was added. After 3 h at –78 °C, saturated, aqueous NH_4Cl was added, the crude product was extracted with EtOAc, dried ($MgSO_4$), concentrated, and purified by radial chromatography to afford analytically pure material.

Ethyl 2-Naphthalen-1-ylpropionate (i): The general procedure was employed with ethyl 1-naphthylacetate (1.07 g, 5 mmol) and methyl iodide (852 mg, 6 mmol) with the exception of allowing the reaction to warm to room temp. over 16 h before addition of saturated, aqueous NH_4Cl. The crude product was purified by radial chromatography (EtOAc/hexanes, 1:20) to afford 958 mg (84%) of **i** as an oil: IR (film): $\tilde{\nu}$ = 2980, 1727 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.14 (t, J = 7.2 Hz, 3 H), 1.65 (d, J = 7.3 Hz, 3 H), 4.07–4.19 (m, 2 H), 4.49 (q, J = 7.3 Hz, 1 H), 7.43–7.55 (m, 4 H), 7.75–7.78 (m, 1 H), 7.85–7.88 (m, 1 H), 8.09 (d, J = 8.5 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 18.2, 41.4, 60.8, 123.1, 124.4, 125.6, 126.2, 127.6, 128.9, 131.3, 133.9, 174.9 ppm. MS (CI): m/z = 229 [M + H^+]. HRMS (EI): calcd. for $C_{15}H_{16}O_2Na^+$ 251.1043; found 251.1043.

2-Naphthalen-1-ylpropan-1-ol (8): Solid $LiBH_4$ (367 mg, 16.8 mmol) was added to a THF solution (20 mL) of **i** (479 mg, 2.1 mmol). After 18 h, saturated, aqueous $NaHCO_3$ was added, and after 15 min, the layers were separated, and the aqueous phase was then extracted with diethyl ether (3 ×). The combined organic phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure and the residue was purified by radial chromatography (EtOAc/hexanes, 1:5) to afford 378 mg (90%) of **8** as an oil. IR (film): $\tilde{\nu}$ = 3408, 1736 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.35 (d, J = 6.3 Hz, 3 H), 2.02 (br. s, 1 H), 3.63–3.83 (m, 3 H), 7.31–7.48 (m, 4 H), 7.67 (d, J = 8.0 Hz, 1 H), 7.79–7.81 (m, 1 H), 8.07 (d, J = 8.1 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.7, 36.2, 67.8, 122.9, 123.0, 125.4, 125.4, 125.9, 126.9, 128.8, 131.8, 133.8, 139.5 ppm. MS (CI): m/z = 187 [M + H^+]. HRMS (EI): calcd. for $C_{13}H_{14}ONa^+$ 209.0937; found 209.0935.

1-(2-Iodo-1-methylethyl)naphthalene (9): Solid PPh_3 (124 mg, 0.47 mmol), imidazole (32 mg, 0.47 mmol), and iodine (120 mg, 0.47 mmol) were added to a dichloromethane solution (8 mL) of **8** (87 mg, 0.47 mmol). After 4 h, the solvent was removed and the crude iodide was purified by radial chromatography (EtOAc/hexanes, 1:30) to afford 134 mg (96%) of **9** as an oil. IR (film): $\tilde{\nu}$ = 2965, 795, 773 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.59 (d, J = 6.8 Hz, 1 H), 3.34–3.38 (m, 1 H), 3.60 (dd, J = 9.8, 4.5 Hz, 1 H), 3.84–3.93 (m, 1 H), 7.40 (d, J = 7.1 Hz, 1 H), 7.44–7.58 (m, 3 H), 7.76 (d, J = 8.0 Hz, 1 H), 7.88 (d, J = 8.8 Hz, 1 H), 8.03 (d, J = 8.5 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.4, 20.9, 36.7, 122.5, 122.6, 125.4, 125.5, 126.3, 127.4, 129.1, 131.0, 133.9, 140.0 ppm. MS (CI): m/z = 296 [M^+].

2-Methyl-4-naphthalen-1-ylpentanenitrile (5): The general alkylation procedure was employed with propionitrile (33 mg, 0.6 mmol) and **9** (178 mg, 0.6 mmol) with the modification of allowing the reaction mixture to warm to room temp. over 2 h before the addition of saturated, aqueous NH_4Cl. The crude product was purified by radial chromatography (EtOAc/hexanes, 1:30) to afford 107 mg (71%) of **5** as an oil. IR (film): $\tilde{\nu}$ = 2238 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.21 (d, J = 7.1 Hz, 3 H), 1.24 (d, J = 7.0 Hz, 3 H), 1.38 (d, J = 7.8 Hz, 3 H), 1.40 (d, J = 7.3 Hz, 3 H), 1.71–1.79 (m, 1 H), 1.95–2.06 (m, 2 H), 2.27–2.36 (m, 1 H), 2.62–2.70 (m, 1 H), 3.81–3.92 (m, 1 H each), 7.30–7.34 (m, 1 H each), 7.40–7.48 (m, 2 H each), 7.51–7.54 (m, 1 H each), 7.71 (d, J = 8.2 Hz, 1 H), 7.71 (d, J = 8.2 Hz, 1 H), 7.83 (d, J = 8.0 Hz, 1 H), 7.83 (d, J = 8.0 Hz, 1 H), 8.15 (d, J = 8.6 Hz, 1 H), 8.22 (d, J = 8.5 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.0 (18.4), 20.5, 22.8, 23.5 (23.9), 41.8 (42.4), 122.3, (122.5), 122.8, (122.8), 123.1, (125.4), 125.4, (125.5), 125.6, (126.1), 126.1 (126.9), 128.9 (128.9), 131.0 (131.6), 133.9 (133.9), 141.2 (141.4) ppm. MS (CI): m/z = 224 [M + H^+]. HRMS (EI): calcd. for $C_{16}H_{17}NNa^+$ 246.1253; found 246.1251.

Methyl (2*R,4*R**)-2-Cyano-2-methyl-4-(naphthalen-1-yl)pentanoate (11a) and Methyl (2*S**,4*R**)-2-Cyano-2-methyl-4-(naphthalen-1-yl)-pentanoate (11b):** The general procedure was employed with **5** (85 mg, 0.38 mmol) and methyl cyanoformate (40 mg, 0.47 mmol) to afford, after purification by radial chromatography (EtOAc/hexanes, stepped gradient 1:19, 1:9), 78 mg (73%) of **11a** and **11b** as an oily 4.2:1 mixture of diastereomers. IR (film): $\tilde{\nu}$ = 2954, 2244, 1730 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.40 (d, J = 7.0 Hz, 3 H), 1.48 (d, J = 7.0 Hz, 3 H), 1.53 (s, 3 H), 1.60 (s, 3 H), 2.18 (dd, J = 14.2, 4.9 Hz, 1 H), 2.30 (dd, J = 5.4, 14.2 Hz, 1 H), 2.41 (dd, J = 14.2, 8.7 Hz, 1 H), 2.65–2.71 (m, 1 H), 2.96 (s, 3 H), 3.77 (m, 3 H), 3.97–4.04 (m, 1 H each), 7.24–7.47 (m, 4 H each), 7.71 (d, J = 8.2 Hz, 1 H), 7.74 (d, J = 7.8 Hz, 1 H), 7.83–7.88 (m, 1 H each), 8.16 (d, J = 8.5 Hz, 1 H), 8.21 (d, J = 8.6 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.1, 24.8, 25.4, 43.3, 45.2, (52.6), 53.5, 119.7, (120.3), 122.6, (123.1), (125.4), 125.4, (125.5), 125.6, (126.1), 126.3, (127.0), 127.1, (128.8), 129.1, 130.8, (131.1), (133.9), 133.9, 141.8, (169.3), 170.3 ppm. MS (CI): m/z = 281 [M + H].

(2*R,4*R**)-2-Cyano-2-methyl-4-(naphthalen-1-yl)pentyl 4-Nitrobenzoate (12a) and (2*S**,4*R**)-2-Cyano-2-methyl-4-(naphthalen-1-yl)-pentyl 4-Nitrobenzoate (12b):** Solid $LiBH_4$ (18 mg, 0.8 mmol) was added to a THF solution (8 mL) of **11** (56 mg, 0.20 mmol). After 18 h, saturated, aqueous $NaHCO_3$ (5 mL) was added, the mixture was stirred for 15 min and then the phases were separated. The

aqueous phase was extracted with diethyl ether (3 ×) and then the combined organic extract was dried ($MgSO_4$), filtered, and concentrated under reduced pressure and the residue was purified by radial chromatography (EtOAc/hexanes, 1:5) to afford 36 mg (72%) of a mixture of diastereomeric alcohols. A hexanes solution of butyllithium (0.15 mmol) was added to a –78 °C, THF solution (5 mL) of this mixture of diastereomers (36 mg, 0.14 mmol), followed after 10 min, by neat *p*-nitrobenzoyl chloride (29.4 mg, 0.16 mmol). The resulting solution was warmed to room temp. and, after 1 h, water was added. The product was extracted with EtOAc (3 ×), dried ($MgSO_4$), concentrated and purified by radial chromatography (EtOAc/hexanes, 1:8) to provide 43.9 mg (78%) of a mixture of diastereomers from which a pure sample of the major diastereomer **12a** was obtained. The major diastereomer **12a** is a crystalline solid (m.p. 146–147 °C, CCDC-689493) whose structure was solved by X-ray diffraction: IR (film): $\tilde{\nu}$ = 2238, 1730 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.29 (s, 3 H), 1.57 (d, J = 7.0 Hz, 3 H), 2.22–2.30 (m, 2 H), 3.99 (br.s, 1 H), 4.24 (d, J = 11.0 Hz, 1 H), 4.29 (d, J = 11.0 Hz, 1 H), 7.41–7.44 (m, 2 H), 7.48–7.51 (m, 1 H), 7.54–7.57 (m, 1 H), 7.73–7.74 (m, 1 H), 7.87 (d, J = 7.9 Hz, 1 H), 8.17–8.20 (m, 2 H), 8.29–8.31 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.3, 23.8, 37.2, 43.5, 69.7, 122.1, 123.7, 125.5, 125.7, 126.4, 127.2, 129.3, 130.7, 130.9, 134.1, 134.4, 142.2, 150.8, 163.8 ppm. MS (CI): m/z = 403 [M + H^+]. HRMS (EI): calcd. for [M + Na], $C_{24}H_{22}N_2O_4Na^+$ 425.1477; found 425.1456. For the minor diastereomer **12b**: 1.50 (s, 3 H), 1.55 (d, J = 6 Hz, 3 H), 2.09 (dd, J = 14.4 Hz, 5.7 Hz, 1 H), 2.48 (dd, J = 13.3 Hz, 7.9 Hz, 1 H), 3.96–4.02 (m, 1 H), 4.11–4.19 (m, 2 H), 7.39–8.31 (m, 11 H). MS (CI): m/z = 403 [M + H^+].

Methyl 2-Cyano-2,5-dimethyl-4-naphthalen-1-ylhexanoate (15): The general deprotonation–alkylation procedure was employed with **13** (63 mg, 0.25 mmol) and methyl cyanoformate (232 mg, 0.27 mmol) to afford, after purification by radial chromatography (EtOAc/hexanes, stepped gradient 1:19, 1:9), 56 mg (73%) of **15** as an oily, 1:1 mixture of diastereomers. IR (film): $\tilde{\nu}$ = 2241, 1745 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.80 (d, J = 7.0 Hz, 3 H), 0.82 (d, J = 7.3 Hz, 3 H), 0.98 (d, J = 4.1 Hz, 3 H), 1.00 (d, J = 3.8 Hz, 3 H), 1.18–1.36 (m, 1 H), 1.29 (s, 3 H), 1.58 (s, 3 H), 1.88–1.99 (m, 1 H), 2.36 (dd, J = 14.1, 1.9 Hz, 1 H), 2.51–2.63 (m, 1 H), 2.56 (s, 3 H), 3.54 (s, 3 H), 3.48–3.62 (m, 1 H), 3.76–3.81 (m, 1 H), 7.29–7.56 (m, 4 H each), 7.71 (d, J = 8.2 Hz, 1 H), 7.75 (d, J = 8.0 Hz, 1 H), 7.83 (d, J = 8.3 Hz, 1 H), 7.86 (d, J = 8.0 Hz, 1 H), 8.12 (d, J = 8.5 Hz, 1 H), 8.25 (d, J = 9 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.0, (20.0), 20.4, (20.5), 23.7, (25.2), 34.9, (35.0), 40.1, (41.3), (41.9), 42.3, (43.4), 43.7, (52.2), 53.3, 119.9, (120.2), (123.0), 123.7, (124.3), 124.3, 124.9, (125.0), 125.4, (126.1), 127.0, (127.2), 128.6, (129.1), 132.6, (132.8), (133.8), 133.9, (137.9), 138.9, 169.3, (169.8) ppm. MS (CI): m/z = 310 [M + H^+]. HRMS (EI): calcd. for $C_{20}H_{24}NO_2^+$ 310.1802; found 310.1791.

4-Phenylpentanenitrile (18): A hexanes solution of BuLi (3.1 mL, 6.8 mmol) was added to a 0 °C, THF solution of diethyl (cyanomethyl)phosphonate (0.12 mL, 7.4 mmol). After 20 min, the reaction mixture was warmed to room temp. After 20 min the mixture was re-cooled to 0 °C and a THF solution (2.0 mL) of aldehyde **16** (804 mg, 6 mmol) was added. The solution was warmed to room temp. and after 2 h, saturated aqueous $NaHCO_3$ was added, and then the mixture was diluted with EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extract was washed with brine, dried (Na_2SO_4), and concentrated to afford essentially pure alkenenitrile **17** as judged by NMR analysis. The alkenenitrile was redissolved in MeOH (15 mL), solid Pd/C (10%, 200 mg) was added and then the suspension was stirred under 30 atm of H_2 for 6 h. The crude alkanenitrile was filtered through a plug of Celite, the filtrate was concentrated and the residue was purified by radial chromatography (EtOAC/hexanes, 1:30) to provide 820 mg (86%) of **18** as an oil: IR (film): $\tilde{\nu}$ = 2246 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.31 (d, J = 6.8 Hz, 3 H), 1.87–2.28 (m, 4 H), 2.84–2.88 (m, 1 H), 7.20–7.37 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.2, 21.6, 33.3, 38.6, 119.4, 126.5, 126.7, 128.5, 144.4 ppm. MS (CI): m/z = 160 [M + H^+]. HRMS (EI): calcd. for $C_{11}H_{13}NNa^+$ 182.0946; found 182.0951.

2-Methyl-4-phenylpentanenitrile (19a and 19b): Performing the general deprotonation–alkylation procedure with a THF solution (10 mL) of **18** (795 mg, 5 mmol) and MeI (852 mg, 6 mmol), provided, after purification by radial chromatography (EtOAc/hexanes, 1:30) 692 mg (80%) of pure **19** as an oily mixture of diastereomers in the ratio of 1:1.3. Careful chromatography provided pure samples of two diastereomers for characterization. For the first eluting diastereomer **19a**: IR (film): $\tilde{\nu}$ = 3026, 2237 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.23 (d, J = 7.4 Hz, 3 H), 1.31 (d, J = 7.3 Hz, 3 H), 1.67–1.73 (m, 1 H), 1.88–1.94 (m, 1 H), 2.19–2.27 (m, 1 H), 2.96–3.03 (m, 1 H), 7.21–7.34 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.5, 22.7, 24.1, 38.3, 42.9, 122.8, 126.7, 126.9, 128.8, 144.9 ppm. MS (CI): m/z = 174 [M + H^+]. For the second eluting diastereomer **19b**: IR (film): $\tilde{\nu}$ = 2238 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.32 (d, J = 7.3 Hz, 3 H), 1.33 (d, J = 6.9 Hz, 3 H), 1.75–1.81 (m, 1 H), 2.00–2.06 (m, 1 H), 2.52–2.57 (m, 1 H), 2.93–2.97 (m, 1 H), 7.21–7.36 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.6, 21.5, 23.3, 37.2, 42.2, 122.9, 126.6, 126.8, 128.7, 145.3 ppm. MS (CI): m/z = 174 [M + H^+].

Methyl (2*R,4*R**)-2-Cyano-2-methyl-4-phenylpentanoate (20a and 20b):** The general deprotonation–alkylation procedure was employed with **19** (450 mg, 2.6 mmol) and methyl cyanoformate (232 mg, 2.7 mmol) to afford, after purification by radial chromatography (EtOAc/hexanes, stepped gradient 1:19, 1:9), 390 mg (65%) of **20a and 20b** as an oily, 3.2:1 mixture of diastereomers. For the major diastereomer **20a**: ^1H NMR (400 MHz, $CDCl_3$): δ = 1.20 (d, J = 7.1 Hz, 3 H), 1.41 (s, 3 H), 2.08 (dd, J = 14.2, 7 Hz, 1 H), 2.19 (dd, J = 14.2, 7 Hz, 1 H), 2.93–3.00 (m, 1 H), 3.68 (s, 3 H), 7.10–7.24 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.5, 25.7, 37.4, 43.5, 45.5, 52.9, 119.6, 126.8, 127.7, 128.6, 145.5, 170.1 ppm. HRMS (EI): calcd. for $C_{14}H_{17}NO_2Na^+$ 254.1152; found 254.1148; For the minor diastereomer **20b**: ^1H NMR (400 MHz, $CDCl_3$): δ = 1.26 (d, J = 7.0 Hz, 3 H), 1.50 (s, 3 H), 1.92 (dd, J = 14, 4 Hz, 1 H), 2.35 (dd, J = 14, 10 Hz, 1 H), 2.93–3.00 (m, 1 H), 3.14 (s, 3 H), 7.10–7.24 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.7, 24.2, 38.0, 43.0, 46.0, 53.4, 119.9, 126.7, 127.0, 128.3, 143.7, 169.4 ppm.

(2*R,4*R**)-2-(1-Hydroxycyclohexyl)-2-methyl-4-phenylpentanenitrile (21a) and (2*S**,4*R**)-2-(1-Hydroxycyclohexyl)-2-methyl-4-phenylpentanenitrile (21b):** The general deprotonation–alkylation procedure was employed with **19** (104 mg, 0.6 mmol) and cyclohexanone (69 mg, 0.70 mmol) to afford, after purification by radial chromatography (EtOAc/hexanes, 1:5), 111 mg (68%) of **21** as an oily 3.9:1 mixture of diastereomers. For the major diastereomer **21a**: IR (film): $\tilde{\nu}$ = 3470, 2232 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.02 (s, 3 H), 1.39 (d, J = 7.0 Hz, 3 H), 1.42–1.80 (m, 12 H), 2.15 (dd, J = 13.8, 5.5 Hz, 1 H), 3.01–3.09 (m, 1 H), 7.18–7.32 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.8, 21.5, 21.5, 24.3, 25.3, 31.1, 31.6, 37.8, 40.8, 47.4, 74.6, 123.8, 126.3, 127.1, 128.7, 147.5 ppm. MS (CI): m/z = 272 [M + H^+]. HRMS (EI): calcd. for $C_{18}H_{25}NOK$ 310.1573; found 310.1587. For the minor diastereomer **21b**: IR (film): $\tilde{\nu}$ = 3472, 2231 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.35 (d, J = 7.0 Hz, 3 H), 1.42 (s, 3 H), 1.47–1.77 (m,

12 H), 2.26 (dd, *J* = 14.0, 7.2 Hz, 1 H), 3.00–3.05 (m, 1 H), 7.20–7.34 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.3, 21.5, 21.5, 24.5, 25.3, 31.4, 31.4, 37.3, 41.1, 46.5, 74.6, 122.9, 126.5, 127.1, 128.5, 146.5 ppm. MS (CI): *m*/*z* = 272 [M + H$^+$]. HRMS (EI): calcd. for $C_{18}H_{25}NONa$ 294.1828; found 294.1811.

(*R)-2-Methyl-2-[(*R**)-2-phenylpropyl]pent-4-enenitrile (22a) and (*S**)-2-Methyl-2-[(*R**)-2-phenylpropyl]pent-4-enenitrile (22b):** The general deprotonation–alkylation procedure was employed with **19** (450 mg, 2.6 mmol) and allyl bromide (327 mg, 2.7 mmol) to afford, after purification by radial chromatography (EtOAc/hexanes, 1:30), 476 mg (86%) of **22** as an oily, 3.8:1 mixture of diastereomers. For the major diastereomer **22a**: IR (film): $\tilde{\nu}$ = 2232, 1642 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.07 (s, 3 H), 1.37 (d, *J* = 7.3 Hz, 3 H), 1.82 (dd, *J* = 14.2, 7.8 Hz, 1 H), 1.95 (dd, *J* = 14.2, 5.2 Hz, 1 H), 2.24 (dd, *J* = 13.7, 7.3 Hz), 2.33 (dd, *J* = 13.7, 7.3 Hz, 1 H), 3.06 (sextet, *J* = 7.3 Hz, 1 H), 5.16 (d, *J* = 16.6 Hz, 1 H), 5.22 (d, *J* = 10.2 Hz, 1 H), 5.81–5.90 (m, 1 H), 7.20–7.33 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.9, 24.1, 36.2, 37.3, 45.3, 46.6, 120.0, 123.9, 126.4, 127.0, 128.6, 131.9, 146.9 ppm. MS (CI): *m*/*z* = 281 [M + H$^+$]. HRMS (EI): calcd. for $C_{15}H_{19}NNa^+$ 236.1410; found 236.1418. For the minor diastereomer **22b**: IR (film): $\tilde{\nu}$ = 2232 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.30 (s, 3 H), 1.37 (d, *J* = 6.8 Hz, 3 H), 2.08–2.21 (m, 4 H), 3.02–3.11 (m, 1 H), 5.06–5.19 (m, 1 H), 5.71–5.85 (m, 1 H), 7.21–7.35 (m, 5 H) ppm. HRMS (EI): calcd. for $C_{15}H_{19}NNa^+$ 236.1410; found 236.1398.

(2*R,4*R**)-2-Ethyl-2-methyl-4-phenylpentanenitrile (23a) and (2*S**,4*R**)-2-Ethyl-2-methyl-4-phenylpentanenitrile (23b):** The general procedure was employed with **19** (87 mg, 0.5 mmol) and ethyl iodide (94 mg, 0.6 mmol) to afford, after purification by radial chromatography (EtOAc/hexanes, 1:30), 56 mg (56%) of **23** as a 4.2:1 mixture of diastereomers as an oil. For the major diastereomer **23a** IR (film): $\tilde{\nu}$ = 2232 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.03 (t, *J* = 7.4 Hz, 3 H), 1.06 (s, 3 H), 1.36 (d, *J* = 7.1 Hz, 3 H), 1.45–1.54 (m, 1 H), 1.57–1.66 (m, 1 H), 1.80 (dd, *J* = 14.2, 8.0 Hz, 1 H), 1.92 (dd, *J* = 14.2, 5.4 Hz, 1 H), 2.99–3.07 (m, 1 H), 7.19–7.32 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.1, 23.5, 24.1, 34.0, 37.0, 37.3, 46.7, 124.1, 126.4, 127.0, 128.6, 147.1 ppm. MS (CI): *m*/*z* = 201 [M + H$^+$]. HRMS (EI): calcd. for $C_{14}H_{19}NNa^+$ 224.1415; found 224.1436. For the minor diastereomer **23b**: IR (film): $\tilde{\nu}$ = 2231 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 7.4 Hz, 3 H), 1.27 (s, 3 H), 1.35 (d, *J* = 7.0 Hz, 3 H), 1.55–1.63 (m, 1 H), 1.78 (dd, *J* = 14.2, 5.5 Hz, 1 H), 2.00 (dd, *J* = 14.2, 7.6 Hz, 1 H), 2.96–3.03 (m, 1 H), 7.20–7.32 (m, 5 H) ppm. MS (CI): *m*/*z* = 201 [M + H$^+$]. HRMS (EI): calcd. for $C_{14}H_{19}NK^+$ 240.1149; found 240.1153.

2-(2-Phenylpropyl)nonanenitrile (26): The general deprotonation–alkylation procedure was employed with **18** (191 mg, 1.2 mmol) and iodoheptane (315 mg, 1.4 mmol) to afford, after purification by radial chromatography (EtOAc/hexanes, 1:50), 262 mg (85%) of **26** as an oily mixture of diastereomers. For the first eluting diastereomer **26a**: IR (film): $\tilde{\nu}$ = 2235 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.8 Hz, 3 H), 1.29 (d, *J* = 7.0 Hz, 3 H), 1.27–1.59 (m, 12 H), 1.72–1.80 (m, 1 H), 1.93–2.00 (m, 1 H), 2.45–2.51 (m, 1 H), 2.90–2.99 (m, 1 H), 7.18–7.34 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 21.3, 22.6, 27.0, 29.0, 29.0, 29.5, 31.7, 31.9, 37.3, 40.6, 122.2, 126.6, 126.8, 128.7, 145.6 ppm. MS (CI): *m*/*z* = 258 [M + H$^+$]. HRMS (EI): calcd. for $C_{18}H_{27}NNa^+$ 280.2041; found 280.2011. For the second eluting diastereomer **26b**: IR (film): $\tilde{\nu}$ = 2235 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 6.9 Hz, 3 H), 1.31 (d, *J* = 7.0 Hz, 3 H), 1.19–1.58 (m, 12 H), 1.68–1.75 (m, 1 H), 1.86–1.93 (m, 1 H), 2.10–2.17 (m, 1 H), 2.96–3.05 (m, 1 H), 7.18–7.34 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3, 22.6, 22.9, 27.0, 28.9, 29.0, 30.2, 31.6, 32.7, 38.2, 40.9, 122.3, 126.7, 126.9, 128.8, 144.9 ppm. MS (CI): *m*/*z* = 258 [M + H$^+$]. HRMS (EI): calcd. for $C_{18}H_{27}NNa^+$ 280.2041; found 280.2015.

Methyl (*R)-2-Cyano-2-[(*R**)-2-phenylpropyl]nonanoate (28a) and Methyl (*S**)-2-Cyano-2-[(*R**)-2-phenylpropyl]nonanoate (28b):** The general deprotonation–alkylation procedure was employed with **26** (103 mg, 0.4 mmol) and methyl cyanoformate (41 mg, 0.48 mmol) to afford, after purification by radial chromatography (EtOAc/hexanes, 1:9), 91 mg (72%) of **28** as an oily mixture of diastereomers in the ratio of 3.8:1: IR (film): $\tilde{\nu}$ = 2241, 1744 cm^{-1}. MS (CI): *m*/*z* = 316 [M + H$^+$]. For the major diastereomer **28a**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 7.8 Hz, 3 H), 1.24 (d, *J* = 6.9 Hz, 3 H), 1.48–1.89 (m, 10 H), 2.12 (dd, *J* = 14.1, 6.3 Hz, 1 H), 2.24 (dd, *J* = 14.1, 6.3 Hz, 1 H), 3.02–3.04 (m, 1 H), 3.80 (s, 3 H), 7.22–7.34 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 21.8, 22.5, 25.2, 28.8, 29.1, 31.6, 37.4, 38.5, 44.9, 48.8, 53.3, 118.8, 126.9, 128.6, 145.8, 170.1 ppm. MS (CI): *m*/*z* = 316 [M + H$^+$]. HRMS (EI): calcd. for $C_{20}H_{29}NO_2K^+$ 354.1830; found 354.1808. For the minor diastereomer **28b**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 7.8 Hz, 3 H), 1.24 (d, *J* = 6.9 Hz, 3 H), 1.48–1.89 (m, 10 H), 1.98–2.02 (m, 1 H), 2.36–2.41 (m, 1 H), 3.05–3.08 (m, 1 H), 3.16 (s, 3 H), 7.22–7.34 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.8, 25.1, 28.8, 38.0, 39.5, 45.1, 49.3, 52.7, 119.3, 126.7, 127.8, 128.3, 143.8, 169.1 ppm. MS (CI): *m*/*z* = 316 [M + H$^+$].

2-Isopropyl-4-phenylpentanenitrile (27): The general procedure was employed with **18** (239 mg, 1.5 mmol) and isopropyl iodide (153 mg, 1.8 mmol) to afford, after purification by radial chromatography (EtOAc/hexanes, 1:30), 271 mg (90%) of **27** as an oily mixture of diastereomers. For the first eluting diastereomer **27a**: IR (film): $\tilde{\nu}$ = 2235 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.03 (d, *J* = 6.5 Hz, 3 H), 1.05 (d, *J* = 6.5 Hz, 3 H), 1.30 (d, *J* = 6.8 Hz, 3 H), 1.70–1.77 (m, 1 H), 1.82–1.89 (m, 1 H), 1.90–1.98 (m, 1 H), 2.43–2.48 (m, 1 H), 2.89–2.98 (m, 1 H), 7.19–7.34 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.2, 20.9, 21.2, 29.5, 36.9, 37.4, 38.5, 120.8, 126.5, 126.8, 128.7, 145.8 ppm. HRMS (EI): calcd. for $C_{14}H_{19}NK^+$ 240.1155; found 240.1169. For the second eluting diastereomer **27b**: IR (film): $\tilde{\nu}$ = 2235 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.96 (d, *J* = 6.8 Hz, 3 H), 1.00 (d, *J* = 6.8 Hz, 3 H), 1.32 (d, *J* = 6.8 Hz, 3 H), 1.67–1.70 (m, 2 H), 1.87–1.93 (m, 1 H), 2.04–2.18 (m, 1 H), 2.89–3.03 (m, 1 H), 7.19–7.33 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.7, 20.8, 23.1, 30.4, 37.3, 38.3, 38.4, 121.1, 126.6, 126.9, 128.8, 144.9 ppm. HRMS (EI): calcd. for $C_{14}H_{19}NNa^+$ 224.1415; found 224.1463.

Methyl (2*S,4*R**)-2-Cyano-2-isopropyl-4-phenylpentanoate (29a) and Methyl (2*R**,4*R**)-2-Cyano-2-isopropyl-4-phenylpentanoate (29b):** The general deprotonation–alkylation procedure was employed with **27** (80 mg, 0.4 mmol) and methyl cyanoformate (41 mg, 0.48 mmol) and with the modification of substituting Li-NEt_2 for LDA, to afford, after purification by radial chromatography (EtOAc/hexanes, 1:9), 51 mg (49%) of **29** as an oily 2.7:1 mixture of diastereomers: IR (film): $\tilde{\nu}$ = 2241, 1743 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.94 (d, *J* = 6.5 Hz, 3 H each), 0.99 (d, *J* = 6.7 Hz, 3 H each), 1.09 (d, *J* = 6.8 Hz, 3 H each), 1.12 (d, *J* = 6.7 Hz, 3 H each), 1.22 (d, *J* = 7.0 Hz, 3 H each), 1.34 (d, *J* = 7.0 Hz, 3 H each), 2.03–2.31 (m, 3 H each), 2.93–3.07 (m, 1 H each), 3.18 (s, 3 H each), 3.82 (s, 3 H each), 7.21–7.34 (m, 5 H each) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = (17.9), 18.7, 21.5, (23.7), 36.2, (36.3), 37.7, (38.1), (42.6), 42.8, (52.5), 53.0, 54.3, (54.9), 117.4, (118.2), (126.6), (126.7), 127.0, (127.8), (128.2), 128.6,

(144.0), 145.8, 170.1 ppm. MS (CI): *m*/*z* = 260 [M + H$^+$]. HRMS (EI): calcd. for $C_{16}H_{21}NO_2K^+$ 298.1204; found 298.1189.

(2*S,4*R**)-2-(Hydroxymethyl)-2-methyl-4-phenylpentanenitrile (34a) and (2*R**,4*R**)-2-(Hydroxymethyl)-2-methyl-4-phenylpentanenitrile (34b):** The general deprotonation–alkylation procedure was employed except with 2.2 equiv. of LDA and with **30** (76 mg, 0.4 mmol) and methyl iodide (62 mg, 0.44 mmol) to afford, after purification by radial chromatography (EtOAc/hexanes, 1:8), 61 mg (75%) of **34** as an oily, 1.5:1 mixture of diastereomers. For **34a**: IR (film): $\tilde{\nu}$ = 3451, 2236 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.07 (s, 3 H), 1.38 (d, *J* = 6.8 Hz, 3 H), 1.78–1.85 (m, 1 H), 2.07 (dd, *J* = 14.1, 5.3 Hz, 1 H), 3.03–3.08 (m, 1 H), 3.52 (d, *J* = 6.8 Hz, 2 H), 7.23–7.34 (m, 5 H) ppm; (100 MHz, $CDCl_3$): δ = 22.6, 24.7, 37.3, 39.2, 43.3, 67.2, 122.8, 126.9, 126.9, 128.9, 146.2 ppm. HRMS (EI): calcd. for $C_{13}H_{17}NONa^+$ 226.1202; found 226.1196. For **34b**: IR (film): $\tilde{\nu}$ = 3479, 2239 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.34 (d, *J* = 7.0 Hz, 3 H), 1.35 (s, 3 H), 1.44 (t, *J* = 6.8 Hz, 1 H), 1.75–1.80 (m, 1 H), 2.07–2.13 (m, 1 H), 3.03–3.10 (m, 1 H), 3.26–3.41 (m, 2 H), 7.23–7.34 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.8, 24.1, 37.2, 39.6, 43.1, 69.0, 123.2, 126.6, 127.0, 128.7, 146.7 ppm. MS (CI): *m*/*z* = 204 [M + H$^+$]. HRMS (EI): calcd. for $C_{13}H_{17}NONa^+$ 226.1202; found 226.1212.

(2*R,4*R**)-2-(2-Hydroxyethyl)-2-methyl-4-phenylpentanenitrile (35a) and (2*S**,4*R**)-2-(2-Hydroxyethyl)-2-methyl-4-phenylpentanenitrile (35b):** The general deprotonation–alkylation procedure was employed except with 2.2 equiv. of LDA and with **31** (81 mg, 0.4 mmol) and methyl iodide (62 mg, 0.44 mmol) to afford, after purification by radial chromatography (EtOAc/hexanes, 1:8), 47 mg (54%) of **35** as an oily 2.6:1 mixture of diastereomers: IR (film): $\tilde{\nu}$ = 3421, 2238 cm^{-1}. Although the major diastereomer was not separable, enriched fractions allowed complete NMR assignments. For the major diastereomer **35a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.33 (s, 3 H), 1.35 (d, *J* = 6.8 Hz, 3 H), 1.54–1.60 (m, 1 H), 1.70–1.90 (m, 2 H), 2.05 (dd, *J* = 14.3, 8.1 Hz, 1 H), 2.98–3.05 (m, 1 H), 3.69–3.78 (m, 2 H), 7.20–7.32 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.3, 25.4, 34.6, 37.0, 41.1, 47.5, 59.0, 124.0, 126.5, 127.0, 128.6, 146.5 ppm. HRMS (EI): calcd. for $C_{14}H_{19}NOK^+$ 256.1104; found 256.1154. For the minor diastereomer **35b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.13 (s, 3 H), 1.36 (d, *J* = 7.3 Hz, 3 H), 1.70–1.90 (m, 3 H), 1.97 (dd, *J* = 14.2, 5.4 Hz, 1 H), 3.01 (br. s, 1 H), 3.81 (t, *J* = 6.9 Hz, 2 H), 7.20–7.32 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.2, 24.4, 34.7, 37.1, 42.7, 47.3, 59.0, 124.1, 126.4, 126.9, 128.6, 146.8 ppm.

2-Propyl-2-(1,2,2-trimethylpropoxy)nonanenitrile (38a and 38b): The general procedure was employed with **36** (96 mg, 0.4 mmol) and 1-iodopropane (82 mg, 0.48 mmol) to afford, after purification by radial chromatography (EtOAc/hexanes, 1:50), 97 mg (86%) of **38a** and **38b** as a inseparable mixture of diastereomers in the ratio of 4.5:1 as an oil: IR (film): $\tilde{\nu}$ = 2959, 2928, 2872, 1082 cm^{-1}. ^{1}H NMR: δ = 0.88 (t, *J* = 6.6 Hz, 3 H)$^{\#}$, 0.88 (t, *J* = 6.6 Hz, 3 H)*, 0.89 (s, 9 H)$^{\#}$, 0.89 (s, 9 H)*, 0.95 (t, *J* = 7.4 Hz, 3 H)$^{\#}$, 0.95 (t, *J* = 7.4 Hz, 3 H)*, 1.17 (d, *J* = 6.3 Hz, 3 H)$^{\#}$, 1.17 (d, *J* = 6.3 Hz, 3 H)*, 1.40–1.79 (m, 16 H)$^{\#}$, 1.40–1.79 (m, 16 H)*, 3.50 (q, *J* = 6.2 Hz, 1 H)$^{\#}$, 3.50 (q, *J* = 6.2 Hz, 1 H)* ppm. ^{13}C NMR: δ = 14.0, 14.1, 16.5, (16.6), 17.1, (17.6), 22.6, (23.7), 24.2, 26.2, (26.2), 29.1, 29.6, 31.7, (31.7), 35.5, (35.5), 37.9, (38.6), 40.0, (40.7), 77.4, (77.5), 79.6, (79.6), 121.1, (121.1) ppm.

2-(1-Hydroxycyclohexyl)-2-(1,2,2-trimethylpropoxy)nonanenitrile (39a and 39b): The general procedure was employed with **36** (76 mg, 0.32 mmol) and cyclohexanone (34 mg, 0.35 mmol) to afford, after purification by radial chromatography (EtOAc/hexanes, 1:10), 88 mg (82%) of **39a** and **39b** as a inseparable mixture of diastereomers in the ratio of 7.1:1 as an oil: ^{1}H NMR: δ = 0.90$^{\#}$ (s, 9 H), 0.95* (s, 9 H), 0.88–0.93$^{\#}$ (m, 3 H), 0.88–0.93* (m, 3 H), 1.17* (d, *J* = 6.4 Hz, 3 H), 1.30$^{\#}$ (d, *J* = 6.4 Hz, 3 H), 1.31–1.95* (m, 23 H), 1.31–1.95$^{\#}$ (m, 23 H), 3.63* (q, *J* = 6.4 Hz, 1 H), 3.63$^{\#}$ (q, *J* = 6.4 Hz, 1 H) ppm. ^{13}C NMR: δ = 14.0, 15.3, (17.2), 21.4, (21.4), (21.4), 21.5, 22.6, (25.5), 25.6, (25.9), 26.3, (26.4), 26.4, 29.0, (29.0), 30.2, (30.3), 31.7, 31.8, 31.8, (32.0), (32.0), 33.8, (34.4), 35.5, (36.0), 76.1, (76.6), 80.5, (81.0), 82.3, (84.6), (119.3), 119.5 ppm.

2-(Hydroxydiphenylmethyl)-2-(1,2,2-trimethylpropoxy)nonanenitrile (40a and 40b): The general procedure was employed with **36** (105 mg, 0.44 mmol) and benzophenone (89 mg, 0.49 mmol) to afford, after purification by radial chromatography (EtOAc/hexanes, 1:10), 130 mg (70%) of **40a** and **40b** as a inseparable mixture of diastereomers in the ratio 9.8:1 of as an oil: ^{1}H NMR: δ = 0.64$^{\#}$ (s, 9 H), 0.88–0.93*$^{\#}$ (m, 3 H), 0.88* (s, 9 H), 1.05*$^{\#}$ (d, *J* = 6.0 Hz, 3 H), 1.10–2.10*$^{\#}$ (m, 12 H), 3.18* (br. s, 1 H), 3.27$^{\#}$ (br. s, 1 H), 3.69*$^{\#}$ (q, *J* = 6.4 Hz, 3 H), 7.25–7.40*$^{\#}$ (m, 3 H), 7.60–7.72*$^{\#}$ (m, 2 H), 7.75–7.82*$^{\#}$ (m, 12 H) ppm. ^{13}C NMR: δ = 14.0, 14.6, 17.2, 22.5, 25.8, (25.8), (26.1), 26.4, 28.8, (28.8), 29.8, (29.9), 31.6, (31.6), 35.6, (35.6), (77.2), 77.3, 81.4, (81.5), (81.8), 82.1, (119.0), 119.5, 127.5, 127.6, (127.6), 127.7, 127.7, 127.8, 127.8, 127.9, 128.2 ppm. MS (CI): *m*/*z* = 421 [M$^+$].

Supporting Information (see also the footnote on the first page of this article): ^{1}H NMR and ^{13}C NMR spectra for all new compounds, experimental procedures for chemical correlation of intermediates, and procedures for the synthesis of **13**, **30**, **31** and **36**.

Acknowledgments

Financial support for this research from the National Science Foundation (NSF) (CHE 0515715, CRIF 024872 for X-ray facilities, CHE 0421252 for HRMS instrumentation, and CHE 0614785 for NMR facilities) is gratefully acknowledged.

[1] a) M. Christmann, S. Bräse (Ed.), *Asymmetric Synthesis – The Essentials*, Wiley-VCH, Weinheim, **2007**; b) G. Q. Lin, Y. M. Li, A. S. C. Chan, *Principles and Applications of Asymmetric Synthesis*, Wiley-Interscience, Chichester, **2001**.
[2] O. T. Benfrey, P. J. T. Morris (Eds.) in *Robert Burns Woodward: Architect and Artist in the World of Molecules*, Chemical Heritage Foundation, Philadelphia, **2001**.
[3] A. H. Hoveyda, D. A. Evans, G. C. Fu, *Chem. Rev.* **1993**, *93*, 1307–1370.
[4] *Nobel Lectures, Chemistry 1963–1970*, Elsevier Publishing Company, Amsterdam, **1972**.
[5] E. L. Eliel, S. H.Wilen, L. N. Mander in *Stereochemistry of Organic Compounds*, Wiley, NY, **1994**, pp. 597–606.
[6] S. A. Babirad, Y. Wang, P. G. Goekjian, Y. Kishi, *J. Org. Chem.* **1987**, *52*, 4825–4827.
[7] a) R. W. Hoffmann, *Angew. Chem. Int. Ed.* **2000**, *39*, 2054–2070; b) R. W. Hoffmann, *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1124–1134.
[8] For correlations of density functional and molecular mechanics calculations of conformer populations with ^{13}C NMR coupling constants see: a) R. W. Hoffmann, M. Stahl, U. Schopfer, G. Frenking, *Chem. Eur. J.* **1998**, *4*, 559–566; b) M. Stahl, U. Schopfer, G. Frenking, R. W. Hoffmann, *J. Org. Chem.* **1997**, *62*, 3702–3704; c) M. Stahl, U. Schopfer, *J. Chem. Soc. Perkin Trans. 2* **1997**, 905–908.
[9] E. L. Eliel, S. H.Wilen, L. N. Mander in *Stereochemistry of Organic Compounds*, Wiley, NY, **1994**, pp. 696–697.
[10] F. F. Fleming, *Nat. Prod. Rep.* **1999**, *16*, 597–606.
[11] Y. Kato, N. Fusetani, S. Matsunaga, K. Hashimoto, K. Koseki, *J. Org. Chem.* **1988**, *53*, 3930–3932.

[12] The conformation shown for **5a** was determined from molecular mechanics calculations using Chem3D Pro. 11.0.

[13] a) N. Okulik, A. H. Jubert, *THEOCHEM* **2006**, *769*, 135–141; b) Y. G. Smeyers, S. Cuellare-Rodriguez, E. Galvez-Ruano, M. S. Arias-Perez, *J. Pharm. Sci.* **1985**, *74*, 47–49.

[14] a) E. Riis, S. Larsen, *Acta Crystallogr., Sect. E: Struct. Rep. Online* **2005**, *61*, 1396; b) L. Dupont, O. Diderberg, G. Dive, J. J. Godfroid, E. Steiner, *Acta Crystallogr., Sect. B: Struct. Sci.* **1982**, *38*, 2409–2411.

[15] The conformation depicted for **6** is a ChemDraw representation of the crystallographic structure.

[16] R. W. Hoffmann, *Chem. Rev.* **1989**, *89*, 1841–1860.

[17] The thickness of the benzene ring is estimated to be 1.7 Å: J. H. Brewster in *Conformational and chiroptical properties of alkyl halides* (Eds.: S. Patai, Z. Rappoport) *Supplement D2: The Chemistry of halides, pseudo-halides and azides*, John Wiley & Sons, Chichester, **1995**, chapter 3, pp. 85–121. Complementary evidence is provided by nucleophilic Me/Ph additions to Me/Ph-bearing aldehydes: a) A. Mengel, O. Reiser, *Chem. Rev.* **1999**, *99*, 1191; b) R. Göttlich, B. C. Kahrs, J. Krüger, R. W. Hoffmann, *Chem. Commun.* **1997**, 247–251; c) W. R. Roush, *J. Org. Chem.* **1991**, *56*, 4151–4157.

[18] For an insightful discussion in phenyl cyclohexane see: E. L. Eliel, S. H.Wilen, L. N. Mander in *Stereochemistry of Organic Compounds*, Wiley, NY, **1994**, p. 698.

[19] The authors have deposited the crystallographic data with the Cambridge Crystallographic Data Center (CCDC-689493). The data can be obtained, on request, from the Director, Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, UK.

[20] *N*-Metalated nitriles generally, and *N*-lithiated nitriles in particular, are planar at the nucleophilic carbon: G. Boche, *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 277.

[21] Nitriles have an exceedingly small steric demand, a mere 0.2 kcal mol^{-1}, and while the corresponding A value for an *N*-lithiated nitrile has not been determined, the steric demand is likely to be similar; a) F. R. Jensen, C. H. Bushweller, B. H. Beck, *J. Am. Chem. Soc.* **1969**, *91*, 344–351; b) B. Rickborn, F. R. Jensen, *J. Org. Chem.* **1962**, *27*, 4606–4608; c) N. L. Allinger, W. Szkrybalo, *J. Org. Chem.* **1962**, *27*, 4601–4603.

[22] Performing the alkylation of **7** (Scheme 1) with *i*PrI followed by the same reduction, iodination and alkylation sequence provided the isopropyl-bearing nitrile **13**. A detailed Scheme is provided in the Supporting Information

[23] For an overview of metalated nitrile structures and alkylation preferences see: F. F. Fleming, S. Gudipati, *Eur. J. Org. Chem.* **2008**, *29*, 5365–5374.

[24] For leading references see: a) C. J. Cobley, R. D. J. Froese, J. Klosin, C. Qin, G. T. Whiteker, K. A. Abboud, *Organometallics* **2007**, *26*, 2986–2999; b) M. Kuil, P. E. Goudriaan, P. W. N. M. Van Leeuwen, J. N. H. Reek, *Chem. Commun.* **2006**, 4679–4681; c) Y. Yan, X. Zhang, *J. Am. Chem. Soc.* **2006**, *128*, 7198–7202.

[25] J. A. Profitt, D. S. Watt, E. J. Corey, *J. Org. Chem.* **1975**, *40*, 127–128.

[26] a) C.-m. Zeng, M. Han, D. F. Covey, *J. Org. Chem.* **2000**, *65*, 2264–2266; b) C. Mellin, U. Hacksell, *Tetrahedron* **1987**, *43*, 5443–5446; c) S. K. Boyer, J. Bach, J. McKenna, E. Jagdmann Jr., *J. Org. Chem.* **1985**, *50*, 3408–3411; d) R. Sala, G. Peria, C. Passarotti, *Tetrahedron Lett.* **1984**, *25*, 4565–4568.

[27] The configuration of the major diastereomer was determined by chemoselectively reducing the ester functionality in **20a**, esterifying the resulting alcohol with *para*-nitrobenzoyl chloride (PNBCl), and using X-ray crystallographic analysis to unequivocally assign the stereochemistry in the resulting ester (CCDC-689492). Experimental details and spectroscopic data are provided in the Supporting Information.

[28] Differentiating between *C*- and *N*-metalated transition structures is experimentally challenging. Evolution of the ground state *C*-magnesiated nitrile to an *N*-magnesiated transition structure is virtually impossible to detect without recourse to computational modeling but seems highly unlikely given the divergent reactivity preferences of *C*- and *N*-metalated nitriles: a) F. F. Fleming, Z. Zhang, W. Liu, P. Knochel, *J. Org. Chem.* **2005**, *70*, 2200–2205; b) F. F. Fleming, S. Gudipati, Z. Zhiyu, W. Liu, O. W. Steward, *J. Org. Chem.* **2005**, *70*, 3845–3849.

[29] Ratios were obtained by analyzing the crude reaction mixtures by ^{1}H NMR (Scheme 4 in the Supporting Information). Isolated yields were only obtained for the cases shown in Table 1 for which the isolated ratios were essentially identical to those obtained by ^{1}H NMR integration of the crude reaction mixture.

[30] a) F. Orsini, *Synthesis* **1985**, 500–503; b) N. Goasdoue, M. Gaudemar, *J. Organomet. Chem.* **1972**, *39*, 17–27.

[31] a) P. R. Carlier, *Chirality* **2003**, *15*, 340–347; b) R. Koch, B. Wiedel, E. Anders, *J. Org. Chem.* **1996**, *61*, 2523–2529.

[32] Alkylations of (bromozinco)acetonitrile require reactive electrophiles and HMPT for efficient conversion.[30a]

[33] LDA was unable to completely deprotonate this more sterically hindered nitrile necessitating the use of $LiNEt_2$.

[34] Alkylations of cyclic internally chelated nitriles are highly selective: a) F. F. Fleming, Y. Wei, W. Liu, Z. Zhang, *Tetrahedron* **2008**, *64*, 7477–7488; b) F. F. Fleming, V. A. Vu, B. C. Shook, M. Raman, O. W. Steward, *J. Org. Chem.* **2007**, *72*, 1431–1436; c) F. F. Fleming, Y. Wei, W. Liu, Z. Zhang, *Org. Lett.* **2007**, *9*, 2733–2736.

[35] The synthesis of **30** and **31** is described in the Supporting Information.

[36] The configurations of **34a** and **35a** were determined by chemical correlation (Supporting Information).

[37] a) F. A. Davis, P. K. Mohanty, *J. Org. Chem.* **2002**, *67*, 1290–1296; b) F. A. Davis, P. K. Mohanty, D. M. Burns, Y. W. Andemichael, *Org. Lett.* **2000**, *2*, 3901–3903; c) T. Schrader, C. Kirsten, M. Herm, *Phosphorous, Sulfur Silicon Relat. Elem.* **1999**, *144–146*, 161; d) P. Gmeiner, E. Hummel, C. Haubmann, *Liebigs Ann.* **1995**, 1987–1992; e) A. W. Murray, N. D. Murray, R. G. Reid, *J. Chem. Soc., Chem. Commun.* **1986**, 1230–1232.

[38] Lithium cations complex with proximal alkenes and aromatic π systems: a) C. R. Harris, S. J. Danishefsky, *J. Org. Chem.* **1999**, *64*, 8434–8456; b) T. Rölle, R. W. Hoffmann, *J. Chem. Soc. Perkin Trans. 2* **1995**, 1953–1958; c) W. F. Bailey, A. D. Khanolkar, K. Gavaskar, T. V. Ovaska, K. Rossi, Y. Thiel, K. B. Wiberg, *J. Am. Chem. Soc.* **1991**, *113*, 5720–5727.

[39] F. H. Allen, O. Kennard, D. G. Watson, L. Brammer, A. G. Orpen, R. Taylor, *J. Chem. Soc., Perkin Trans. 2* **1987**, S1–19.

[40] a) S. Chandrasekhar, *ARKIVOC* **2005**, *13*, 37–66; b) *Stereoelectronic Effects* (Ed. A. J. Kirby), Oxford University Press, Bath, UK, **1998**.

[41] The sense of diastereoselectivity is made by analogy to prior alkylations as attempts to prepare crystalline derivatives were unsuccessful.

Received: October 27, 2008
Published Online: December 19, 2008

