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Electrophile-Dependent Alkylations of Lithiated 4-Alkoxyalk-4-enenitriles

Bhaskar R. Pitta,[a] *Omar W. Steward,*[b] *and Fraser F. Fleming*[c] *

[a] Biophore India, Hyderabad, Telangana 500033, India.

[b] Department of Chemistry and Biochemistry, Duquesne University, Pittsburgh, PA 15282, USA

[c] Department of Chemistry, Drexel University, Philadelphia, PA 19104, USA

flemingf@duq.edu

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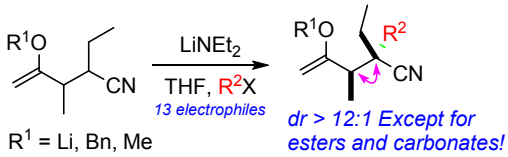
Abstract. Alkylations of acyclic, lithiated 4-alkoxyalk-4-enenitriles are highly diastereoselective with an unusual electrophile-dependent preference. Alkyl halides, sulfur, chlorine, and acyl cyanide electrophiles intercept a series of lithiated 4-alkoxyalk-4-enenitriles to install contiguous tertiary-quaternary stereocenters with high diastereoselectivity whereas acylations with ester and carbonate electrophiles are modestly selective. The diastereoselectivity is consistent with electrophilic attack on the most accessible face of the lithated nitrile for most electrophiles except ester and carbonate electrophiles which likely pre-coordinate the lithiated nitrile before acylation. Intercepting the lithiated 4-alkoxyalk-4-enenitriles with a range of

electrophiles provide insight into the criteria for otherwise challenging diastereoselective alkylations and acylations of acyclic nitriles.



Introduction

Metalated nitriles are exceptional nucleophiles capable of forging new carbon-carbon bonds in sterically demanding environments.[1] Two unusual characteristics lie at the heart of the extraordinary nucleophilicity, the minuscule steric demand of the nitrile unit,[2] roughly eight times smaller than a methyl group,[3] and an inductive charge stabilization that localizes electron density on the nucleophilic carbon atom.[4] Harnessing the exceptional nucleophilicity in stereoselective alkylations is largely confined to cyclic, conformationally constrained nitriles where the electrophile trajectory is dictated by a sterically biased topology.[1]

Stereoselective alkylations of *acyclic* nitriles are significantly more challenging.[5] The difficulty lies partly in constraining rotatable single bonds[6] and partly from the inherent bonding of metalated nitriles.[7] Asymmetric induction from chiral ligands complexed to lithium locates the chirality remote from the site of electrophilic attack because lithiated nitriles favor planar, nitrogen-coordinated dimers in the solid state[8] and solution[9] (**1a**, Figure 1). Consequently, highly selective asymmetric alkylations of lithiated nitriles are challenging[10] unless a proximal ligand redirects metal coordination to the nucleophilic carbon (**1b**, Figure 1).[11]

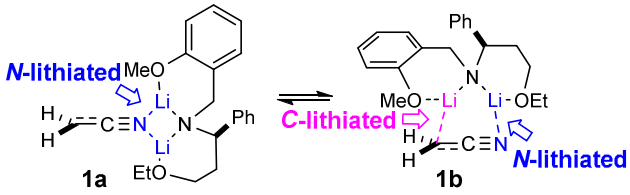
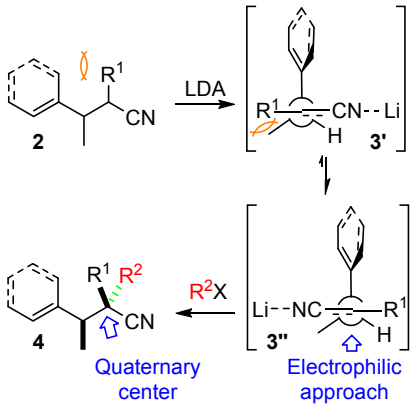


Figure 1. Equilibrating *N*- and *C*-Lithiated Nitrile Structures

One strategy for the stereoselective alkylation of acyclic metalated nitriles is to constrain the flexible backbone to bias electrophilic attack from one reactive conformation. The approach is illustrated in the alkylations of lithiated nitriles derived from **2** for which the diastereoselectivities are well above 20:1 (Scheme 1).[12] Allylic strain between R^1 and the aromatic ring favors an orthogonal orientation of the two groups; the metalated nitrile preferentially adopts the perpendicular arrangement **3''** with the small nitrile gauche to the C-3 methyl group to avoid the larger R^1-Me eclipsing interaction (**3'**). Electrophilic attack on the more accessible face of **3''** installs the quaternary center in **4** as essentially one diastereomer (Scheme 1).

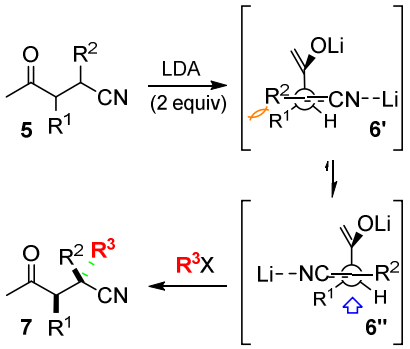
Scheme 1. Diastereoselective Alkylation of Acyclic Nitriles



Conceptually, a similar topology is anticipated upon double deprotonation of oxonitriles **5** because the resulting dianion should have a similar substitution and hybridization pattern (Scheme 2, cf. **6** with **3**).[13] Although the alkylations of oxonitriles **5** proved to be modestly

diastereoselective, alkylations of analogous oxygen-substituted alk-4-enenitriles were generally efficient and highly diastereoselective. Surveying an array of electrophiles revealed an unusual electrophile-dependent diastereoselectivity not previously observed with lithiated nitriles while defining conditions for selectively installing contiguous tertiary-quaternary stereocenters.

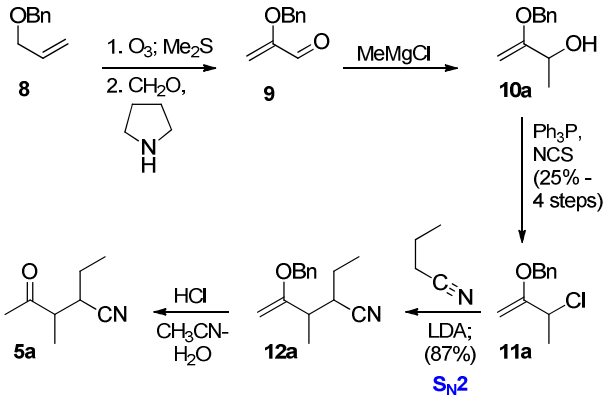
Scheme 2. Alkylation of Dilithiated Ketonitriles



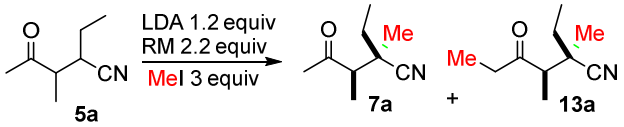
Results and Discussion

Exploring diastereoselective alkylations of acyclic γ-oxonitriles required a readily accessible prototype with easily varied substituents. Oxonitrile **5a** proved to be an ideal prototype whose synthesis was rapid and modular: ozonolysis of **8** and α-methylenation[14] provided enal **9** which reacted with MeMgCl to afford the rather labile[15] alcohol **10a** that was immediately chlorinated with *N*-chlorosuccinimide to provide the more stable chloride **11a** (Scheme 1).[16] The allylic chloride **11a** was then united with lithiobutyronitrile in a relatively rare S_N2 displacement at a secondary center (Scheme 3).[17] Subsequent hydrolysis of the enol ether-nitrile **12a** afforded oxonitrile **5a**.

Scheme 3. Synthesis of Oxonitrile **5a**



Exploratory alkylations of oxonitrile **5a** were frustrated by difficulties in forming the dianion and by over alkylation. The dilithiated nitrile, best prepared from LDA (1.2 equivalents) and excess BuLi (2.2 equivalents), was extremely reactive, affording a 2.0:1 diastereomeric mixture of the methylated oxonitriles **7a** within 5 minutes at -78 °C (Eq. 1).[18] An analogous mixed lithium-magnesium species prepared by sequential deprotonation with LDA followed by addition of *i*-PrMgCl, was significantly less nucleophilic; methylation with MeI required temperatures of at least -40 °C which afforded **7a** as a 2.8:1 ratio of diastereomers accompanied by the dimethylated nitrile **13a**.[19]



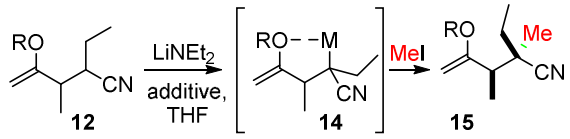
RM	yield, dr	yield, dr
BuLi	(87%, dr 2.0:1)	-
i-PrMgCl	(72%, dr 2.8:1)	(21%, dr 2.9:1)

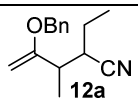
(eq. 1)

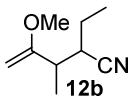
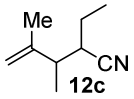
The low alkylation diastereoselectivity of oxonitrile **5a** stimulated a series of comparative methylations with structurally related 4-alkoxyalk-4-enenitriles **12**. The $LiNEt_2$[20] deprotonation of nitrile **12a** in THF and methylation with MeI afforded **15a** in higher diastereomeric ratios than

for the analogous methylation of the oxonitrile **5a** (Table 1).[21] The diastereoselectivity increased in moving from Et_2O to THF with minimal influence in performing the methylation in THF with added HMPA (5 equiv, Table 1, compare entries 1, 3, and 4). As expected, the diasteroselectivity increased when the reaction temperature was lowered from -78 to -98 °C (Table 1, compare entries 4 and 7). Methylation of the corresponding magnesiated nitrile prepared by chlorine-magnesium exchange[22], through addition of *i*-PrMgCl to the lithiated nitrile, or by metathesis afforded **15a** in very similar ratios to methylation of the lithiated nitrile (compare Table 1, entries 2, 5, 6, with entry 4). The similar diastereoselectivity with magnesium and lithium cations implies alkylation through the same type of intermediate, most likely a *C*-metalated nitrile **14** favored by internal complexation.[11,23]

Table 1. Comparative Alk-4-enenitrile Methylations[a]

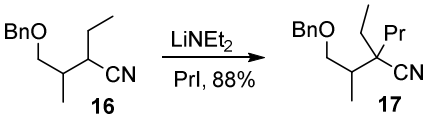


entry		conditions	yield (%)	ratio
1	 **12a**	Et_2O	79	4.3:1
2	**12a**	*i*-PrMgCl[b]	78	6.1:1
3	**12a**	HMPA	85	6.4:1
4	**12a**	-	88	6.5:1
5	**12a**	*i*-PrMgCl[c]	86	6.6:1
6	**12a**	$MgBr_2.OEt_2$[c]	87	6.7:1
7	**12a**	(-98 °C)	85	8.3:1

8	 **12b**	-	84	8.5:1
9	 **12c**	-	82	>19:1

[a] The alkylations were performed by adding the electrophile at -78 °C and allowing the reaction mixture to slowly warm to rt overnight. [b] The magnesiated nitrile was generated by an *i*-PrMgCl exchange of the corresponding chloronitrile **15e** (See Table 2, entry 3). [c] Added after the initial deprotonation.

Alkylations with the nitrile analogs **12b-c** were performed to probe the structural requirements for high selectivity. The size of the alkyl ether has a minimal influence on the methylation diastereoselectivity (Table 1, compare entry 4 with 8) whereas the replacement of the alkoxy substituent (A value = 0.55 kcal mol^{-1}) with a more sterically demanding methyl group (A value = 1.74 kcal mol^{-1})[3] afforded only one detectable diastereomer (Table 1, entry 9; cf. Scheme 1) .[24] The olefin is essential for the diastereoselective alkylation; the deprotonation of **16** and trapping with iodopropane afforded a 1.7:1 ratio of diastereomers (compare **17** eq 2 with **12a**, Table 1, entry 4).



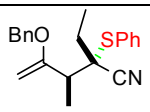
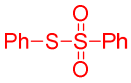
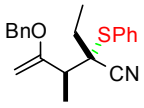
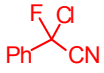
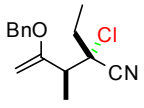
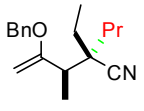
(eq 2)

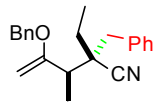
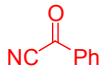
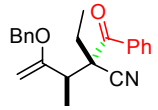
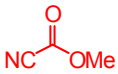
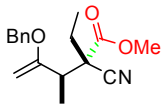
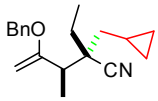
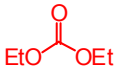
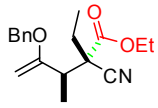
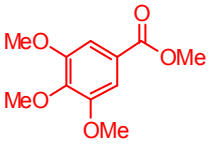
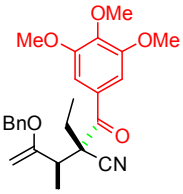
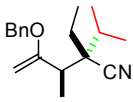
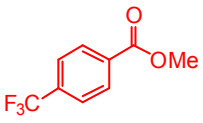
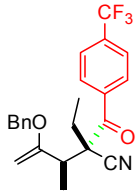
The stereoselectivity trends for the *methylations* of **12a-c** implied that trapping with electrophiles having a steric demand greater than that of MeI would increase the diastereoselectivity (Table 2). Surprisingly, the diastereoselectivity exhibited an unusual electrophile dependency. Intercepting the lithiated nitrile derived from **12a** with the heteroatom electrophiles diphenyl disulfide, S-phenyl benzenesulfonothioate, 2-chloro-2-fluoro-2-phenylacetonitrile[22] (Table 2, entries 1-3), and primary alkyl halides (Table 2, entries 4, 5, 8, and 9) proceeded with high diastereoselectivity. Diastereoselective alkylations with BnBr and

cyclopropylmethyl iodide (Table 2, entries 5 and 8) implicate alkylation via S_N2 displacement rather than through single electron transfer processes.[25] Alkylation of **12a** with isopropyl iodide, a secondary electrophile, was reasonably efficient but not selective (Table 2, entry 11).

In contrast to the diastereoselective alkylations, the *acylations* of **12a** exhibited variable diastereoselectivities. Acylations with benzoyl cyanide and methyl cyanoformate were highly selective (Table 2, entries 6 and 7, respectively) whereas analogous acylations with diethyl carbonate and electron rich or electron deficient methyl benzoates (Table 2, entries 9 and 10 and 12, respectively) were relatively unselective. For the diastereoselective synthesis of oxonitriles or ester-nitriles with this substitution pattern, electrophilic trapping with acyl cyanides is far superior than the use of the corresponding carbonates or esters (Table 2, compare entries 6 and 7 with entries 9-10 and 12). Understanding the conditions required for stereoselectively accessing quaternary acylnitriles is important because of their use in the synthesis of bioactive targets.[26]

Table 2. Alkylations of **12a** with Diverse Electrophiles[a]

entry	electrophile	quaternary nitrile	Yield (%)	ratio
1	PhSSPh	 **15d**	89	>19:1
2		 **15d**	78	>19:1
3		 **15e**	88	>19:1
4		 **15f**	87	>19:1

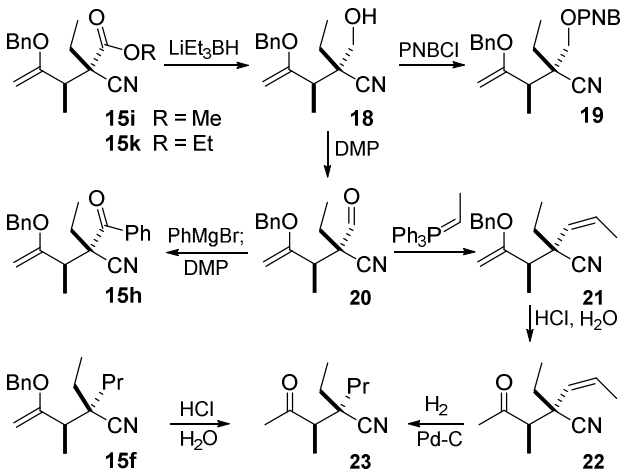
5		 **15g**	89	>19:1
6		 **15h**	88	>19:1
7		 **15i**	87	16.6:1[b]
8		 **15j**	79	12.0:1
9		 **15k**	87	3.2:1[c]
10		 **15l**	84	2.7:1
11		 **15m**	66	2.3:1[c]
12		 **15n**	76	2.2:1

[a] The alkylations were performed by adding the electrophile at -78 °C and allowing the reaction mixture to slowly warm to rt overnight.[27] [b] Sequentially adding MeCu and methyl cyanoformate at -78 °C affords a 17.2:1 ratio of diastereomers (88% yield). Allowing the reaction mixture to warm to 0 °C prior to adding methyl cyanoformate afforded a 1.1:1 ratio of diastereomers (62% yield). [c] The same ratio was obtained when the reaction temperature was maintained at -78 °C for 6 h.

The configurational assignments were made through a series of chemical correlations to the crystalline benzoate **19** whose structure was determined by x-ray crystallography (Scheme 4).

Reduction of the ester-nitriles **15i** and **15k**, to alcohol **18**, followed by treatment with *p*-nitrobenzoyl chloride (PNBCl) provided the crystalline benzoate **19**. Oxidation of **18** with Dess-Martin periodinane (DMP) afforded aldehyde-nitrile **20** which allowed correlation with **15h** through sequential phenyl addition and oxidation. Aldehyde-nitrile **20** was subjected to a three-step olefination, hydrolysis, hydrogenation (**20** → **21** → **22** → **23**) to provide **23**, the same ketonitrile obtained from hydrolysis of **15f**.

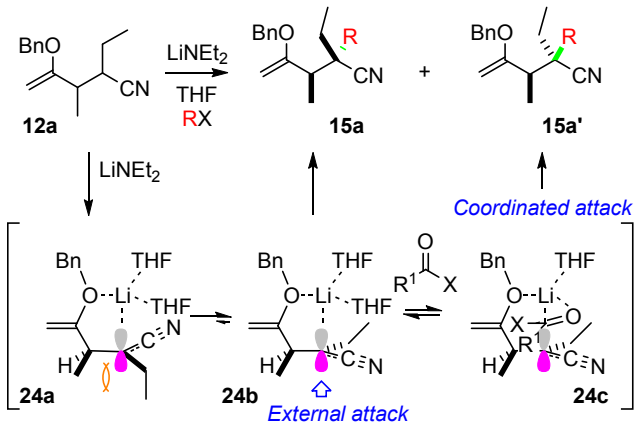
Scheme 4. Chemical Correlation of Configuration



A tentative rationale for the selectivity trends is that primary alkyl halides and highly reactive electrophiles attack the lithiated nitrile at the most sterically accessible carbon whereas carbonate and ester electrophiles competitively coordinate to the lithiated nitrile leading to some alkylation through electrophilic attack on the opposite face. Electrophilic attack is most likely on the more accessible face of lithiated nitrile conformer **24b** where the steric compression is minimized by instead eclipsing the small nitrile with the vicinal methyl group rather than eclipsing the two alkyl groups as in **24a** (Scheme 5). Acyl cyanides likely follow the same trajectory. Carbonates

and esters may competitively chelate to the lithium cation by displacing ligated THF leading to internal delivery of the electrophile to the opposite face of the lithiated nitrile (Scheme 5, **24c** → **15a'**). Coordination of carbonyl electrophiles to metalated nitriles in similar contexts is sufficiently strong to control both stereoselectivity[28] and chemoselectivity.[29]

Scheme 5. Tentative Alkylation Mechanism



Conclusion

Diastereoselective alkylations with a series of 4-oxygenated alkenenitriles-4- revealed unusual electrophile-dependent stereoselectivity preferences. Whereas the alkylations of a dilithiated enolate-nitrile were relatively unselective, the alkylations of the corresponding 4-alkoxy alk-4-enenitriles with primary alkyl halides, and sulfur, chlorine, and acyl cyanide electrophiles were highly selective. Analogous *acyl*ations with acyl cyanides were highly selective whereas trapping with carbonate and ester electrophiles was modestly selective. The stereoselectivity trends are consistent with an approach-controlled electrophilic attack on the most accessible face of a *C*-lithiated nitrile and a less selective alkylation of esters and carbonates caused by electrophile

coordination prior to acylation. Collectively, these represent the first electrophile-dependent trapping of lithiated nitriles and define conditions for installing an array of vicinal tertiary-quaternary centers with high diastereoselectivity.

Experimental Section

General Experimental Procedures. All non-aqueous reactions were performed in oven- or flame-dried glassware under a nitrogen atmosphere. All chemicals were purchased from commercial vendors and used as received unless otherwise specified. Anhydrous tetrahydrofuran (THF) and diethyl ether were distilled from benzophenone-sodium under N_2 before use. Reactions were magnetically stirred and monitored by thin layer chromatography (TLC) with 250 μm precoated silica gel plates. Preparative radial chromatography was performed on 1 or 2 mm plates prepared in-house that were coated with silica (PGF-Prep TLC w/Gypsum UV/254, 5-50 μm). ^{1}H NMR and ^{13}C NMR high resolution nuclear magnetic resonance spectra were recorded on a Varian Inova 300 (300 MHz/75 MHz) or Varian Inova 500 (500 MHz/126 MHz spectrometers at 25 °C. Chemical shifts are reported relative to TMS (δ 0.00) for ^{1}H NMR and chloroform (δ 77.16) for ^{13}C NMR. IR spectra were recorded as thin films (PerkinElmer Spectrum 100 FT-IR Spectrometer). High resolution mass spectra (HRMS) were recorded on an Agilent 6200 TOF LC MS system using a nano ESI and APCI-TOF interface.

(((3-Chlorobut-1-en-2-yl)oxy)methyl)benzene (11a): A stream of ozone was bubbled through a -78 °C, CH_2Cl_2 solution (15 mL) of the allyl benzyl ether (1.5 g, 10.12 mmol, 1.0 equiv) until the distinctive blue color of ozone was clearly observed. Ozonolysis was then terminated and excess

ozone was displaced by passing a stream of nitrogen through the solution for 5 min. Neat dimethyl sulfide (0.94 g, 15.2 mmol, 1.5 equiv) was added, the solution was allowed to warm to room temperature and then stirred overnight. The crude reaction mixture was washed twice with water and brine, and was then dried (Na_2SO_4), and concentrated to afford the crude aldehyde (1.52 g). Propionic acid (0.075 g, 1.01 mmol, 0.1 equiv) and pyrrolidine (72.0 mg, 1.01 mmol, 0.1 equiv) were added to a mixture of *i*-PrOH (1.0 mL), aqueous formaldehydehyde solution (10.1 mmol, 37% formaldehyde in water, 1.0 equiv) and the crude 2-(benzyloxy)acetaldehyde[14] (1.52 g, 10.62 mmol, 1.05 equiv) and then the reaction mixture was stirred at 45 °C. After 24 h saturated, aqueous $NaHCO_3$ was added and then the mixture was extracted with Et_2O (3 x 15 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated to afford 1.61 g of crude 2-(benzyloxy)acrylaldehyde (**9**).[14] A THF solution of methylmagnesium bromide solution (5.46 mL, 10.9 mmol, 1.1 equiv) was added dropwise to a THF solution (15 mL) of the crude 2-(benzyloxy)acrylaldehyde (1.61 g, 9.93 mmol, 1 equiv). After 15 minutes, a solution of saturated, aqueous NH_4Cl was added (5 mL), the phases were separated and the aqueous phase was extracted with ethyl acetate (2 x 20 mL). The combined organic phase was washed with brine, dried (Na_2SO_4), and concentrated to afford 1.73 g of crude 3-(benzyloxy)but-3-en-2-ol (**10a**). Triphenyl phosphine (7.68 g, 29.3 mmol, 3.0 equiv), and NCS (3.91 g, 29.3 mmol, 3.0 equiv) were added sequentially to a 0 °C, THF solution (100 mL) of crude 3-(benzyloxy)but-3-en-2-ol (1.74 g, 9.76 mmol, 1.0 equiv). After 2 h, the reaction mixture was allowed to warm to room temperature. After 16 h, the reaction mixture was poured in to a flask containing a solution of saturated, aqueous $NaHCO_3$ (25 mL) and diethyl ether (30 mL). The phases were separated and the aqueous phase was then extracted with ether (2 x 20 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated to afford a

crude product that was purified by silica gel column chromatography (pure hexanes to 1:49, EtOAc/hexanes) to afford 0.5 g (25% for 4 steps) of pure chloride **11a** as an oil: IR (film) 1629, 2930 cm^{-1}; ^{1}H NMR: δ 1.71 (d, *J* = 6.9 Hz, 3H), 4.14 (d, *J* = 2.9 Hz, 1H), 4.35 (d, *J* = 2.9 Hz, 1H), 4.54 (q, *J* = 6.9 Hz, 1H), 4.87 (s, 2H), 7.32-7.42 (m, 5H); ^{13}C NMR: δ 22.90, 57.2, 69.8, 84.1, 127.2, 127.85, 128.5, 136.7, 161.5; HRMS(EI) $[M+Na]^+$ calcd for $C_{11}H_{13}ClONa$ 219.0553; found 219.0547.

4-(Benzyloxy)-2-ethyl-3-methylpent-4-enenitrile (12a): A THF solution (0.3 M) of butyronitrile (527 mg, 7.63 mmol, 3.0 equiv) was added to a -78 °C, THF solution (0.1 M) of LDA, generated from butyllithium (3.05 equiv) and diisopropylamine (3.15 equiv). After 30 minutes at -78 °C, a THF (3.0 mL) solution of (((3-chlorobut-1-en-2-yl)oxy)methyl)benzene (**11a**, 500 mg, 2.54 mmol, 1.0 equiv) was added and then the reaction was allowed to warm to rt. After 16h, saturated, aqueous NH_4Cl (5 mL) was added, the phases were separated and the crude product was extracted with EtOAc (2 x 15 mL). The combined organic phase was dried (Na_2SO_4), and concentrated to afford a crude product that was purified by radial chromatography (4 mm plate, 3:97, EtOAc/hexanes) to afford 507 mg (87%, dr = 1.3:1) of 4-(benzyloxy)-2-ethyl-3-methylpent-4-enenitrile (**12a**) as an oily liquid: For the major diastereomer: IR (film) 1628, 2236, 2278, 2936, 2972 cm^{-1}; ^{1}H NMR: δ 1.11-1.13 (m, 3H), 1.36 (d, *J* = 7.2 Hz, 3H), 1.60-1.68 (m, 2H), 2.48-2.52 (m, 1H), 2.78-2.82 (m, 1H), 4.13 (s, 2H), 4.78 (ABq, Δν =14.5 Hz, *J* =12.0 Hz, 2H), 7.34-7.43 (m, 5H); ^{13}C NMR: δ 11.8, 16.9, 23.9, 37.4, 41.3, 69.5, 83.9, 121.3, 127.4, 128.0, 128.6, 136.8, 162.0; HRMS(EI) m/z $[M+Na]^+$ calcd for $C_{15}H_{19}NONa$ 252.1364; found 252.1356. For the minor diastereomer: IR (film) 1627, 2236, 2278, 2936, 2971 cm^{-1}; ^{1}H NMR: δ 1.10-1.13 (m, 3H), 1.27 (d, *J* = 7.2 Hz, 3H), 1.56-1.69 (m, 2H), 2.56-2.61 (m, 1H), 2.73-2.77 (m, 1H), 4.14 (d, *J* = 2.8 Hz, 1H), 4.16 (d, *J* = 2.8 Hz, 1H), 4.76-4.83 (ABq, Δν = 20.4 Hz, *J* = 11.6

Hz, 2H), 7.34-7.41 (m, 5H); ^{13}C NMR: δ 12.0, 16.2, 22.4, 37.5, 40.8, 69.6, 83.8, 121.4, 127.5, 127.9, 128.5, 136.9, 162.5; HRMS(EI) m/z $[M+Na]^+$ calcd for $C_{15}H_{19}NONa$ 252.1364; found 252.1362.

2-Ethyl-3-methyl-4-oxopentanenitrile (5a): An aqueous solution of HCl (0.24 µl, 0.0065 mmol, 0.01 equiv) was added to an acetonitrile solution (3 mL) of 4-(benzyloxy)-2-ethyl-2,3-dimethylpent-4-enenitrile (150 mg, 0.654 mmol, 1.0 equiv) and then H_2O (59 mg, 3.27 mmol, 5 equiv) was added. After 30 min, a solution (5 mL) of saturated, aqueous $NaHCO_3$ was added, the phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 x 15 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated to afford the crude nitrile that was purified by radial chromatography (2 mm plate, 4:96 to 8:92, EtOAc/hexanes) to afford 84.6 mg (93%) of pure 2-ethyl-3-methyl-4-oxopentanenitrile as a colorless mixture of diastereomers: For the major diastereomer: IR (film) 1711, 2237 cm^{-1}; ^{1}H NMR: δ 1.08-1.11 (m, 3H), 1.34 (d, J = 7.2 Hz, 3H), 1.53-1.59 (m, 2H), 2.22 (s, 3H), 2.69-2.75 (m, 1H), 2.92-2.96 (m, 1H); ^{13}C NMR: δ 11.8, 15.2, 24.2, 28.9, 35.3, 47.8, 120.6, 208.2; HRMS(EI) m/z $[M+H]^+$ calcd for $C_8H_{14}NO$ 140.1075; found 140.1063. For the minor diastereomer: IR (film) 1712, 2237 cm^{-1}; ^{1}H NMR: δ 1.12-1.14 (m, 3H), 1.28 (d, J = 6.6 Hz, 3H), 1.59-1.66 (m, 2H), 2.26 (s, 3H), 2.79-2.86 (m, 2H); ^{13}C NMR: δ 11.8, 14.0, 21.9, 28.7, 34.8, 47.8, 121.0, 208.1; HRMS(EI) m/z $[M+H]^+$ calcd for $C_8H_{14}NO$ 140.1075; found 140.1062.

(2*R, 3*R**)- and (2*R**, 3*S**)-2-Ethyl-2,3-dimethyl-4-oxopentanenitrile (7a).** A THF solution (0.3 M) of 2-ethyl-3-methyl-4-oxopentanenitrile (25 mg, 0.18 mmol, 1.0 eq) was added to a -78 °C, THF solution (0.1 M) of LDA, generated from butyllithium (1.2 equiv) and diisopropylamine (1.25 equiv). After 30 min a hexanes solution (2.5 M) of butyllithium (0.395 mmol, 2.2 equiv) in hexne was added and then the reaction was allowed to warm to rt. After 30 min the solution was

cooled -78 °C and then neat iodomethane (76 mg, 0.539 mmol, 3.0 equiv) was added. After 5 minutes, a solution (4 mL) of saturated, aqueous NH_4Cl was added. The phases were separated and then the crude product was extracted with EtOAc (2 x 10 mL), dried (Na_2SO_4), concentrated, and purified by radial chromatography (2 mm plate, 4:96 to 8:92, EtOAc/hexanes) to afford 24 mg (87%, dr 2.0:1) of analytically pure 2-ethyl-2,3-dimethyl-4-oxopentanenitrile as a colorless mixture of diastereomers. For **(2*R***, 3*R** 7a**): IR (film) 1713, 2233 cm^{-1}; ^1H NMR: δ 1.07-1.11 (m, 3H), 1.27 (d, *J* = 7.0 Hz, 3H), 1.36 (s, 3H), 1.57-1.64 (m, 1H), 1.69-1.76 (m, 1H), 2.29 (s, 3H), 2.73 (q, *J* = 7.0 Hz, 1H); ^{13}C NMR: δ 9.2, 12.4, 21.1, 30.0, 30.1, 38.7, 52.4, 123.0, 208.9; HRMS(EI) calcd for (M + H^+), $C_9H_{15}NOH^+$ 154.1232, found 154.1224. For **(2*R***, 3*S** 7a**): IR (film) 1712, 2233 cm^{-1}; ^1H NMR: δ 1.09-1.12 (m, 3H), 1.34 (d, *J* = 7.2 Hz, 3H), 1.37 (s, 3H), 1.52-1.59 (m, 1H), 1.83-1.90 (m, 1H), 2.26 (s, 3H), 2.73 (q, *J* = 7.2 Hz, 1H).; ^{13}C NMR: δ 9.2, 12.4, 21.0, 30.0, 30.2, 38.7, 52.3, 123.0, 208.8; HRMS(EI) m/z $[M + Na]^+$ calcd for $C_9H_{15}NONa$ 176.1051; found 176.1038. Preparation of **(2*R***, 3*R**)-7a** by ozonolysis for configurational correlation: A stream of ozone was bubbled through a -78 °C, dichloromethane solution (10 mL) of **(2*R***, 3*R**)-15c** (45 mg, 0.297 mmol, 1.0 equiv) until the distinctive blue color of ozone was clearly observed. Ozonolysis was then terminated and the excess ozone was purged by passing a stream of nitrogen through the solution for 5-10 min. Neat dimethyl sulfide (28 mg, 0.446 mmol, 1.5 equiv) was added and then the reaction was allowed to warm to rt. After 16 h the solution was washed with water and then brine. The organic phase was dried (Na_2SO_4), concentrated, and then purified by radial chromatography (1 mm plate, 8:92, EtOAc/hexanes) to afford 42.4 mg (93%) of **(2*R***, 3*R**)-7a** spectrally identical to material previously isolated.

(2*R*, 3*R**)-2-ethyl-2,3-dimethyl-4-oxohexanenitrile (13a).** A THF solution (0.3 M) of 2-ethyl-3-methyl-4-oxopentanenitrile (25 mg, 0.18 mmol, 1.0 eq) was added to a -78 °C, THF

solution (0.1 M) of LDA, generated from butyllithium (1.2 equiv) and diisopropylamine (1.25 equiv). After 30 min, a THF solution (2.0 M) of *i*-PrMgCl solution (0.395 mmol, 2.2 equiv) was added and then the reaction was allowed to warm to rt. After 30 min the reaction was cooled to -78 °C, neat iodomethane (38 mg, 0.269 mmol, 1.5 equiv) was added, and then the reaction was allowed to warm slowly to -45 °C. After 5 h, a solution (4 mL) of saturated, aqueous NH_4Cl was added and then the phases were separated. The organic phase was extracted with EtOAc (2 x 10 mL), dried (Na_2SO_4), and concentrated and purified by radial chromatography (2 mm plate, 4:96 to 8:92, EtOAc/hexanes) to afford 19.5 mg (72%, dr 2.8:1) of analytically pure 2-ethyl-2,3-dimethyl-4-oxopentanenitrile and 6 mg (21%, dr 2.9:1) of 2-ethyl-2,3-dimethyl-4-oxohexanenitrile (**13a**) as a colorless mixture of diastereomers. For **(2*R**, 3*R**)-13a**: IR (film) 1714, 2233 cm^{-1}; ^1H NMR: δ 1.05-1.08 (m, 6H), 1.21 (d, J = 7.3 Hz, 3H), 1.33 (s, 3H), 1.53-1.59 (m, 1H), 1.65-1.72 (m, 1H), 2.53-2.60 (m, 2H), 2.72 (q, J = 7.3 Hz, 1H); ^{13}C NMR: δ 7.6, 9.3, 12.6, 21.0, 29.9, 36.4, 38.9, 51.3, 123.0, 211.6; HRMS(EI) m/z $[M + Na]^+$ calcd for $C_{10}H_{17}NONa$ 190.1208; found 190.1196. For **(2*R**, 3*S**)-13a**: IR (film) 1715, 2233 cm^{-1}; ^1H NMR: δ 1.04-1.07 (m, 6H), 1.29 (d, J = 7.3 Hz, 3H), 1.34 (s, 3H), 1.47-1.84 (m, 2H), 2.53-2.71 (m, 2H), 2.74 (q, J = 7.3 Hz, 1H); ^{13}C NMR: δ 7.6, 9.2, 13.7, 20.2, 29.9, 36.5, 39.7, 50.9, 123.0, 211.6; HRMS(EI) m/z $[M + Na]^+$ calcd for $C_{10}H_{17}NONa$ 190.1208; found 190.1196.

General alk-4-enenitrile deprotonation and alkylation procedure: A THF solution (0.3 M) of the alk-4-enenitrile (1.0 equiv) was added to a -78 °C, THF solution (0.1 M) of lithium diethylamide, generated from butyllithium (1.05 equiv) and diethylamine (1.15 equiv). The reaction was allowed to warm to rt over 30 min and then cooled to -78 °C. Neat electrophile (1.15 equiv) was added and then the reaction was allowed to slowly warm to rt. After 16 h, a solution (3 mL) of saturated, aqueous NH_4Cl was added, the phases were separated, and the

aqueous phase was extracted with EtOAc (2 x 10 mL). The combined organic extract was dried (Na_2SO_4), concentrated, and purified by radial chromatography to afford analytically pure material.

(2*R, 3*R**)- and (2*R**, 3*S**)-4-(Benzyloxy)-2-ethyl-2,3-dimethylpent-4-enenitrile (15a):** Following the general procedure with the variation of performing the reaction in diethyl ether in place of THF, and with lithium diethylamide (0.115 mmol), **12a** (25 mg, 0.109 mmol) and iodomethane (16 mg, 0.115 mmol), afforded, after purification on a Chromatotron (1 mm plate, 1:99 to 3:97 hexanes: ethyl acetate), 21 mg (79%, 4.3:1 dr) of **15a** as an oil: For **(2*R**, 3*R**)-15a**: IR (film) 1628, 2233 cm^{-1}; ^1H NMR: δ 1.09-1.11 (m, 3H), 1.32 (s, 3H), 1.37 (d, *J* = 7.2 Hz, 3H), 1.49-1.56 (m, 1H), 1.82-1.89 (m, 1H), 2.41 (q, *J* = 7.2 Hz, 1H), 4.10 (d, *J* = 2.5 Hz, 1H), 4.14 (d, *J* = 2.5 Hz, 1H), 4.77 (ABq, Δν = 18.5 Hz, *J* = 11.6 Hz, 2H), 7.32-7.40 (m, 5H); ^{13}C NMR: δ 9.3, 15.4, 20.9, 31.3, 40.8, 45.7, 69.4, 84.7, 123.9, 127.2, 127.8, 128.5, 136.9, 162.4; HRMS(EI) calcd for ($M+H^+$), $C_{16}H_{22}NO^+$ 244.1701, found 244.1684. For **(2*R**, 3*S**)-15a**: IR (film) 696, 739, 811, 1286, 1626, 2233, 2881, 2940, 2976 cm^{-1}; ^1H NMR: δ 1.07-1.10 (m, 3H), 1.33 (d, *J* = 7.2 Hz, 3H), 1.36 (s, 3H), 1.49-1.54 (m, 1H), 1.76-1.81 (m, 1H), 2.37 (q, *J* = 7.2 Hz, 1H), 4.12 (d, *J* = 2.5 Hz, 1H), 4.14 (d, *J* = 2.5 Hz, 1H), 4.79 (ABq, Δν = 20.7 Hz, *J* = 11.9 Hz, 2H), 7.32-7.43 (m, 5H); ^{13}C NMR: δ 9.4, 14.8, 22.2, 30.1, 40.7, 46.6, 69.4, 84.6, 123.7, 127.2, 127.7, 128.4, 136.9, 162.6; HRMS(EI) m/z $[M+H]^+$ calcd for $C_{16}H_{22}NO$ 244.1701; found 244.1698. From **15f**, (Table 1. Entry 2). A THF solution of *i*-PrMgCl (0.327 mmol, 3.0 equiv) was added to a -78 °C, THF (2.0 mL) solution of **15f** (25 mg, 0.109 mmol, 1.0 equiv) and then the cooling bath was removed. After 30 min, the solution was cooled to -78 °C, neat iodomethane (46 mg, 0.327 mmol, 3.0 equiv) was added, and then the reaction was allowed to slowly warm to rt. Saturated, aqueous NH_4Cl (3 mL) was added, the phases were separated, and the aqueous phase

was extracted with EtOAc (2 x 10 mL). The combined organic extracts were dried (Na_2SO_4), concentrated, and purified on a Chromatotron (1 mm plate, 1:99 to 3:97 hexanes: ethyl acetate), to afford 20.7 mg (78%, 6.1:1 dr) of **15a**. (Table 1. Entry 3). Performing the general procedure with lithium diethylamide (0.115 mmol), **12a** (25 mg, 0.109 mmol) with the variation of adding HMPA (0.545 mmol) and stirring for 5 min at -78 °C prior to the addition of iodomethane (16 mg, 0.115 mmol), afforded, after purification on a Chromatotron (1 mm plate, 1:99 to 3:97 hexanes: ethyl acetate), 22.6 mg (85%, 6.4:1 dr) of **15a**. (Table 1, Entry 4): Performing the general procedure with lithium diethylamide (0.115 mmol), **12a** (25 mg, 0.109 mmol) and iodomethane (16 mg, 0.115 mmol), afforded, after purification on a Chromatotron (1 mm plate, 1:99 to 3:97 hexanes: ethyl acetate), 23.3 mg (88%, 6.5:1 dr) of **15a**. (Table 1. Entry 5). Performing the general procedure with lithium diethylamide (0.115 mmol), **12a** (25 mg, 0.109 mmol) with the variation of adding *i*-PrMgCl solution (0.115 mmol) in THF (2.0 M) and stirring for 1.0 h prior to the addition of iodomethane (16 mg, 0.115 mmol), afforded, after purification on a Chromatotron (1 mm plate, 1:99 to 3:97 hexanes: ethyl acetate), 22.8 mg (86%, 6.6:1 dr) of **15a**. (Table 1. Entry 6). Performing the general procedure with lithium diethylamide (0.115 mmol), **12a** (25 mg, 0.109 mmol) with the variation of adding $MgBr_2.OEt_2$ (0.115 mmol) and stirring for 1.0 h prior to the addition of iodomethane (16 mg, 0.115 mmol), afforded, after purification on a Chromatotron (1 mm plate, 1:99 to 3:97 hexanes: ethyl acetate), 23 mg (87%, de ratio 6.7:1) of **15a**. (Table 1. entry 7): Performing the general procedure with lithium diethylamide (0.115 mmol), **12a** (25 mg, 0.109 mmol) with the variation of cooling the reaction to -98 °C prior to the addition of iodomethane (16 mg, 0.115 mmol), afforded, after purification on a Chromatotron (1 mm plate, 1:99 to 3:97 hexanes: ethyl acetate), 22.5 mg (85%, 8.3:1 dr) of **15a**.

2-Ethyl-4-methoxy-3-methylpent-4-enenitrile (12b): A THF solution (0.3 M) of butyronitrile (527 mg, 7.63 mmol, 3.0 equiv) was added to a -78 °C, THF solution (0.1 M) of LDA, generated from butyllithium (3.05 equiv) and diisopropylamine (3.15 equiv). After 30 minutes, a THF solution (3.0 mL) of 3-bromo-2-methoxybut-1-ene[17b] (306 mg, 2.54 mmol, 1.0 equiv) was added and then the reaction was allowed to warm to rt. Saturated, aqueous NH_4Cl (5 mL) was added, the phases were separated, and the aqueous phase was extracted with EtOAc (2 x 15 mL). The combined organic extracts were dried (Na_2SO_4), and concentrated to afford a crude product that was purified by radial chromatography (4 mm plate, 3:97, EtOAc/hexanes) to afford 338 mg (87%, 1.3:1 dr) of **12b** as an oil. For the major diastereomer: IR (film) 1624, 1659, 2236 cm^{-1}; ^1H NMR: δ 1.07 (t, *J* = 7.3 Hz, 3H), 1.26 (d, *J* = 7.0 Hz, 3H), 1.54-1.60 (m, 2H), 2.36-2.43 (m, 1H), 2.67-2.72 (m, 1H), 3.53 (s, 3H), 3.97 (d, *J* = 9.0 Hz 1H), 3.99 (d, *J* = 9.0 Hz, 1H); ^{13}C NMR: δ 11.7, 16.7, 23.9, 37.4, 41.0, 54.9, 82.3, 121.3, 163.2; HRMS(EI) m/z $[M+Na]^+$ calcd for $C_9H_{15}NONa$ 176.1051; found 176.1041. For the minor diastereomer: IR (film) 1624, 1658, 2236 cm^{-1}; ^1H NMR: δ 1.06-1.10 (m, 3H), 1.20 (d, *J* = 7.0 Hz, 3H), 1.50-1.63 (m, 2H), 2.45-2.52 (m, 1H), 2.63-2.68 (m, 1H), 3.55 (s, 3H), 4.00 (d, *J* = 3.8 Hz, 1H), 4.02 (d, *J* = 3.8 Hz, 1H; ^{13}C NMR: δ 11.9, 16.1, 22.3, 37.5, 40.5, 54.9, 82.2, 121.3, 163.5; HRMS(EI) $[M+Na]^+$ calcd for $C_9H_{15}NONa$ 176.1051; found 176.1041.

(2*R,3*R**)-2-ethyl-4-methoxy-2,3-dimethylpent-4-enenitrile (15b).** Performing the general procedure with lithium diethylamide (0.115 mmol), **12b** (25 mg, 0.163 mmol) and iodomethane (24 mg, 0.170mmol), afforded, after purification on a Chromatotron (1 mm plate, 1:99 to 3:97 hexanes: ethyl acetate), 22.9 mg (84%, 8.5:1 dr) of **(2*R**, 3*R**)-15b** as an oil: IR (film) 1623, 1655, 2233 cm^{-1}; ^1H NMR: δ 1.07-1.07 (m, 3H), 1.25 (d, *J* = 7.0 Hz, 3H), 1.30 (s, 3H), 1.36-1.49 (m, 1H), 1.68-1.87 (m, 1H), 2.28 (q, *J* = 7.0 Hz, 1H), 3.54 (s, 3H), 4.00 (s, 2H); ^{13}C NMR: δ 9.4,

14.8, 22.1, 30.0, 40.5, 46.4, 54.7, 83.1, 123.7, 163.7; HRMS(EI) $[M+Na]^+$ calcd for $C_{10}H_{17}NONa$ 190.1208; found 190.1196.

2-Ethyl-3,4-dimethylpent-4-enenitrile (12c). A hexanes solution (2.5 M) of butyllithium (1.03 mmol, 1.19 equiv) was added to a -78 °C, THF suspension (5.0 mL) of methyltriphenylphosphonium iodide (418 mg, 1.03 mmol, 1.2 equiv). After 30 min, a THF solution of **5a** (120 mg, 0.862 mmol, 1.0 equiv) was added dropwise and then the solution was allowed to warm to rt. After 12 h, saturated, aqueous NH_4Cl (3 mL) was added, the phases were separated, and the aqueous phase was extracted with diethyl ether (2 x 10 mL). The combined organic phase was dried (Na_2SO_4) and concentrated to give crude nitrile that was purified by radial chromatography (1 mm plate, 2:98, EtOAc/hexanes) to afford 79 mg (67%) of pure nitrile: IR (film) 1648, 2235 cm^{-1}; HRMS(EI) m/z $[M + H]^+$ calcd for $C_9H_{15}NH$ 138.1283; found 138.1272. For the major diastereomer: ^1H NMR: δ 1.08-1.12 (m, 3H), 1.24 (d, J = 6.9 Hz, 3H), 1.52-1.65 (m, 2H), 1.68 (s, 3H), 2.35-2.52 (m, 2H), 4.84-4.90 (m, 2H); ^{13}C NMR: δ 11.7, 17.4, 18.8, 24.1, 37.9, 42.7, 113.0, 121.4, 145.4. For the minor diastereomer: ^1H NMR: δ 1.08-1.12 (m, 3H), 1.17 (d, J = 6.9 Hz, 3H), 1.52-1.65 (m, 2H), 1.77 (s, 3H), 2.35-2.52 (m, 2H), 4.84-4.90 (m, 2H); ^{13}C NMR: δ 11.9, 17.0, 19.8, 22.6, 38.0, 42.3, 113.2, 121.5, 145.5.

(2*R, 3*R**)-2-ethyl-2,3,4-trimethylpent-4-enenitrile (15c)**: A THF solution (0.3 M) of **12c** (70 mg, 510 mmol, 1.0 equiv) was added to a -78 °C, THF solution (0.1 M) of $LiNEt_2$, generated from butyllithium (1.05 equiv) and diethylamine (1.15 equiv). The solution was warmed to rt and after 30 min the solution was cooled to -78 °C, and neat iodomethane (83 mg, 587 mmol, 1.15 equiv) was then added. After 5 minutes, saturated, aqueous NH_4Cl (2 mL) was added, the phases were separated, and the aqueous phase was extracted with EtOAc (2 x 10 mL). The combined organic extracts were dried (Na_2SO_4), concentrated, and purified by radial chromatography (1

mm plate, 2:98, EtOAc/hexanes) to afford 63 mg (82%) of **(2*R**, 3*R**)-15c** as an oil: IR (film) 1646, 2232 cm^{-1}; ^1H NMR: δ 1.06-1.09 (m, 3H), 1.26 (d, *J* = 7.0 Hz, 3H), 1.33 (s, 3H), 1.31-1.43 (m, 1H), 1.70-1.80 (m, 1H), 1.84-1.85 (m, 3H), 2.22 (q, *J* = 7.0 Hz, 1H), 4.85-4.89 (m, 2H); ^{13}C NMR: δ 9.3, 15.7, 20.2, 22.4, 30.6, 40.0, 48.5, 114.3, 123.9, 146.0; HRMS(EI) m/z $[M + H]^+$ calcd for $C_{10}H_{17}NH$ 152.1439; found 152.1428.

(2*S, 3*S**)-4-(Benzyloxy)-2-ethyl-3-methyl-2-(phenylthio)pent-4-enenitrile (15d).** Performing the general procedure with lithium diethylamide (0.115 mmol), **12a** (25 mg, 0.109 mmol) and diphenyl disulfide (25 mg, 0.115 mmol), afforded, after purification on a Chromatotron (1 mm plate, 1:99 to 3:97 hexanes: ethyl acetate), 32 mg (89%) of **(2*S**, 3*S**)-15d** as an oil: IR (film) 1624, 2229 cm^{-1}; ^1H NMR: δ 1.13-1.16 (m, 3H), 1.55 (d, *J* = 7.2 Hz, 3H), 1.71-1.80 (m, 2H), 2.62 (q, *J* = 7.2 Hz, 1H), 4.15 (d, *J* = 2.8 Hz, 1H), 4.18 (d, *J* = 2.8 Hz, 1H), 4.81 (ABq, Δν = 22.0 Hz, *J* = 11.9 Hz, 2H), 7.27-7.48 (m, 8H), 7.68-7.70 (m, 2H); ^{13}C NMR: δ 8.9, 16.4, 28.5, 44.6, 54.4, 69.6, 85.3, 120.3, 127.2, 127.7, 128.4, 129.2, 129.5, 130.1, 136.6, 137.2, 161.5; HRMS(EI) m/z $[M+Na]^+$ calcd for $C_{21}H_{23}NOSNa$ 360.1398, found 360.1404. Performing the general procedure with lithium diethylamide (0.115 mmol), **12a** (25 mg, 0.109 mmol) and S-phenyl benzenethiosulfonate (28.6 mg, 0.115 mmol), afforded, after purification on a Chromatotron (1 mm plate, 1:99 to 3:97 hexanes: ethyl acetate), 28.7 mg (78%) of **15d** as an oil identical to material previously synthesized.

(2*S, 3*S**)-4-(Benzyloxy)-2-chloro-2-ethyl-3-methylpent-4-enenitrile (15e).** Performing the general procedure with lithium diethylamide (0.115 mmol), **12a** (25 mg, 0.109 mmol) and 2-chloro-2-fluoro-2-phenylacetonitrile (19.5 mg, 0.115 mmol), afforded, after purification on a Chromatotron (1 mm plate, 1:99 to 3:97 hexanes: ethyl acetate), 25 mg (88%) of **(2*S**, 3*S**)-15e** as an oil: IR (film) 1625, 2237 cm^{-1}; ^1H NMR: δ 1.25 (t, *J* = 7.4 Hz, 3H), 1.56 (d, *J* = 6.9 Hz,

3H), 1.94-1.98 (m, 1H), 2.11-2.15 (m, 1H), 2.75 (q, *J* = 6.9 Hz, 1H), 4.20-4.22 (m, 2H), 4.80 (ABq, Δν = 5.0 Hz, *J* = 12.0 Hz, 2H), 7.32-7.46 (m, 5H); ^{13}C NMR: δ 9.7, 16.0, 33.8, 50.2, 66.4, 69.6, 85.9, 117.9, 127.2, 127.9, 128.5, 136.4, 160.4. HRMS(EI) m/z $[M + H]^+$ calcd for $C_{15}H_{18}ClNOH$ 264.1155; found 264.1142.

(2*S, 3*R**)-4-(Benzyloxy)-2-ethyl-3-methyl-2-propylpent-4-enenitrile (15f).** Performing the general procedure with lithium diethylamide (0.115 mmol), **12a** (25 mg, 0.109 mmol) and 1-iodopropane (19.5 mg, 0.115 mmol), afforded, after purification on a Chromatotron (1 mm plate, 1:99 to 3:97 hexanes: ethyl acetate), 25.7 mg (87%) of **(2*S**, 3*R**)-15f** as an oil: IR (film) 1621, 2230 cm^{-1}; ^{1}H NMR: δ 0.94 (t, *J* = 7.2 Hz, 3H), 0.98-1.10 (m, 3H), 1.31 (d, *J* = 7.2 Hz, 3H), 1.38-1.48 (m, 2H), 1.54-1.76 (m, 4H), 2.48 (q, *J* = 7.2 Hz, 1H), 4.11 (d, *J* = 2.8 Hz, 1H), 4.13 (d, *J* = 2.8 Hz, 1H), 4.73-4.80 (ABq, Δν = 21.7 Hz, *J* = 11.9 Hz, 2H), 7.29-7.41 (m, 5H); ^{13}C NMR: δ 9.0, 14.2, 15.2, 17.4, 26.4, 35.7, 43.4, 44.6, 69.4, 84.6, 123.3, 127.3, 127.7, 128.4, 136.9, 162.7; HRMS(EI) m/z $[M+H]^+$ calcd for $C_{18}H_{26}NO$ 272.2014; found 272.2005.

(2*S, 3*R**)-2-Benzyl-2-ethyl-3-methyl-4-oxopentanenitrile (15g')**. Performing the general procedure with lithium diethylamide (0.115 mmol), **12a** (25 mg, 0.109 mmol) and benzyl bromide (19.6 mg, 0.115 mmol), afforded crude **15g** that hydrolyzed to the corresponding ketone upon purification on a Chromatotron (1 mm plate, 1:99 to 3:97 hexanes: ethyl acetate) affording 21 mg (89%) of **(2*S**, 3*R**)-15g'** as an oil: IR (film) 1712, 2232 cm^{-1}; ^{1}H NMR: δ 1.09-1.12 (m, 3H), 1.32 (d, *J* = 7.2 Hz, 3H), 1.66-1.74 (m, 1H), 1.86-1.92 (m, 1H), 2.16 (s, 3H), 2.73 (q, *J* = 7.2 Hz, 1H), 2.91 (d, *J* = 13.9 Hz, 1H), 3.09 (d, *J* = 13.9 Hz, 1H), 7.27-7.35 (m, 5H); ^{13}C NMR: δ 9.4, 12.9, 25.9, 30.0, 38.7, 44.8, 48.8, 122.4, 127.4, 128.6, 130.3, 135.4, 208.9; HRMS(EI) m/z $[M+Na]^+$ calcd for $C_{15}H_{19}NONa$ 252.1364, found 252.1357.

(2*S, 3*R**)-2-Benzoyl-4-(benzyloxy)-2-ethyl-3-methylpent-4-enenitrile (15h).** Performing the general procedure with lithium diethylamide (0.115 mmol), **12a** (25 mg, 0.109 mmol) and benzoyl cyanide (15 mg, 0.115 mmol), afforded, after purification on a Chromatotron (1 mm plate, 1:99 to 3:97 hexanes: ethyl acetate), 32 mg (88%) of **(2*S**, 3*R**)-15h** as an oil: IR (film) 1625, 1685, 2234 cm^{-1}; ^1H NMR: δ 0.99-1.03 (m, 3H), 1.35 (d, *J* = 7.0 Hz, 3H), 1.96-2.03 (m, 1H), 2.20-2.27 (m, 1H), 3.14 (q, *J* = 7.0 Hz, 1H), 4.20-4.22 (m, 2H), 4.74 (ABq, Δν = 3.5 Hz, *J* = 11.8 Hz, 2H), 7.26-7.38 (m, 5H), 7.44-7.47 (m, 2H), 7.55-7.59 (m, 1H), 8.00-8.02 (m, 2H); ^{13}C NMR: δ 10.1, 16.2, 30.0, 45.7, 57.0, 69.5, 85.8, 120.9, 127.3, 127.7, 128.4, 128.4, 128.9, 133.1, 136.5, 136.8, 161.1, 196.2; HRMS(EI) m/z $[M + H]^+$ calcd for $C_{22}H_{23}NO_2H$ 334.1807; found 334.1827. Prepared from **iv**: A THF solution (2.0 M) of PhMgBr (0.184 mmol, 1.05 equiv) was added dropwise to a rt, THF solution (1 mL) of **(2*S**, 3*R**)-iv** (45 mg, 0.175 mmol, 1.0 equiv). After 15 min, saturated aqueous NH_4Cl solution was added (5 mL), the phases were separated, and the aqueous phase was extracted with ethyl acetate (2 x 10 mL). The combined organic extract was washed with brine, dried (Na_2SO_4), and concentrated to afford crude (2*S**, 3*R**)-4-(benzyloxy)-2-ethyl-2-((R)-hydroxy(phenyl)methyl)-3-methylpent-4-enenitrile (58 mg) that was oxidized without purification. A CH_2Cl_2 solution (15% wt solution) of Dess-Martin periodinane (0.190 mmol, 1.1 equiv) was added to a CH_2Cl_2 solution (3.0 mL) of (2*S**, 3*R**)-4-(benzyloxy)-2-ethyl-2-((R)-hydroxy(phenyl)methyl)-3-methylpent-4-enenitrile (58 mg, 0.173 mmol, 1.0 equiv). After 1 h, the mixture was filtered through Celite, the solid was washed with CH_2Cl_2 (5 mL), and then the solvent was removed. Purification of the crude ketone by radial chromatography (1 mm plate, 4:96, EtOAc/hexanes) provided 42 mg (72%) of **(2*S**, 3*S**)-15h** as a light yellow oil spectrally identical to material previously characterized.

(2*S, 3*R**)-methyl 4-(benzyloxy)-2-cyano-2-ethyl-3-methylpent-4-enoate (15i).** Performing the general procedure with lithium diethylamide (0.115 mmol), **12a** (25 mg, 0.109 mmol) and methyl cyanoformate (10 mg, 0.115 mmol), afforded, after purification on a Chromatotron (1 mm plate, 1:99 to 3:97 hexanes: ethyl acetate), 27.3 mg (87%) of **15i** as an oily mixture of diastereomers.[30] For **(2*S**, 3*R**)-15i** IR (film) 1628, 1742, 2230 cm^{-1}; ^1H NMR: δ 1.01-1.04 (m, 3H), 1.31 (d, *J* = 6.9 Hz, 3H), 1.82-1.88 (m, 1H), 1.92-1.97 (m, 1H), 2.82 (q, *J* = 6.9 Hz, 1H), 3.75 (s, 3H), 4.18 (d, *J* = 2.8 Hz, 1H), 4.19 (d, *J* = 2.8 Hz, 1H), 4.77 (ABq, Δν = 17.1 Hz, *J* = 12.2 Hz, 2H), 7.29-7.41 (m, 5H); ^{13}C NMR: δ 10.1, 15.9, 29.2, 45.7, 53.2, 54.7, 69.5, 85.6, 118.2, 127.3, 127.8, 128.4, 136.6, 160.6, 169.5; HRMS(EI) m/z $[M+Na]^+$ calcd for $C_{17}H_{21}NO_3Na$ 310.1419; found 310.1444.

(2*S, 3*R**)-4-(benzyloxy)-2-(cyclopropylmethyl)-2-ethyl-3-methylpent-4-enenitrile (15j).** Performing the general procedure with lithium diethylamide (0.115 mmol), **12a** (25 mg, 0.109 mmol) and (iodomethyl)cyclopropane (21 mg, 0.115 mmol), afforded a 12.0:1 ratio of diastereomers which, after purification on a Chromatotron (1 mm plate, 1:99 to 3:97 hexanes: ethyl acetate), afforded 24.4 mg (79%) of a single isomer[30] of **(2*S**, 3*R**)-15j** as an oil: IR (film) 1621, 2230 cm^{-1}; ^1H NMR: δ 0.14-0.23 (m, 2H), 0.52-0.56 (m, 2H), 0.75-0.81 (m, 1H), 1.01-1.05 (m, 3H), 1.30 (d, *J* = 7.0 Hz, 3H), 1.43-1.49 (m, 1H), 1.75-1.81 (m, 3H), 2.62 (q, *J* = 7.0 Hz, 1H), 4.12-4.14 (m, 2H), 4.77 (ABq, Δν = 5.5 Hz, *J* = 12.0 Hz, 2H), 7.29-7.41 (m, 5H); ^{13}C NMR: δ 4.2, 5.0, 6.2, 9.3, 15.1, 26.8, 38.0, 43.4, 45.2, 69.4, 84.7, 123.3, 127.3, 127.7, 128.4, 136.9, 162.8; HRMS(EI) m/z $[M+H]^+$ calcd for $C_{19}H_{25}NOH$ 284.2014; found 284.1998.

Ethyl (2*S, 3*R**)- and (2*R**, 3*R**)-4-(benzyloxy)-2-cyano-2-ethyl-3-methylpent-4-enoate (15k)**: Using the general procedure with lithium diethylamide (0.115 mmol), **12a** (25 mg, 0.109 mmol) and diethyl carbonate (13.5 mg, 0.115 mmol), afforded, after purification on a

Chromatotron (1 mm plate, 1:99 to 3:97 hexanes: ethyl acetate), 28.6 mg (87%) of **15k** as an oily mixture of diastereomers (3.2:1 dr). For **(2*S**, 3*R**)-15k**: IR (film) 1738, 2230 cm^{-1}; ^1H NMR: δ 1.01-1.04 (m, 3H), 1.30-1.32 (m, 6H), 1.81-1.88 (m, 1H), 1.91-1.98 (m, 1H), 2.80 (q, *J* = 7.2 Hz, 1H), 4.15-4.29 (m, 4H), 4.78 (ABq, Δν = 17.6 Hz, *J* = 11.9 Hz, 2H), 7.29-7.42 (m, 5H); ^{13}C NMR: δ 10.0, 14.1, 16.0, 29.3, 45.6, 54.8, 62.7, 69.5, 85.6, 118.3, 127.8, 127.2, 128.4, 136.6, 160.7, 169.0; HRMS(EI) m/z $[M+H]^+$ calcd for $C_{18}H_{24}NO_3$ 302.1756, found 302.1759. For **(2*S**, 3*S**)-15k**: IR (film) 1738, 2230 cm^{-1}; ^1H NMR: δ 1.05-1.08 (m, 3H), 1.16 (t, *J* = 7.2 Hz, 3H), 1.36 (d, *J* = 7.2 Hz, 3H), 1.91-1.99 (m, 2H), 2.80 (q, *J* = 7.2 Hz, 1H), 3.95-4.04 (m, 2H), 4.11 (d, *J* = 2.8 Hz, 1H), 4.13 (d, *J* = 2.8 Hz, 1H), 4.68-4.76 (ABq, Δν = 28.6 Hz, *J* = 11.6 Hz, 2H), 7.28-7.42 (m, 5H); ^{13}C NMR: δ 10.0, 14.0, 14.4, 29.7, 45.4, 54.9, 62.2, 69.8, 84.5, 118.2, 127.5, 127.8, 128.4, 136.6, 161.7, 168.4; HRMS(EI) m/z $[M+H]^+$ calcd for $C_{18}H_{24}NO_3$ 302.1756; found 302.1761.

(2*S, 3*R**)- and (2*R**, 3*R**)-4-(Benzyloxy)-2-ethyl-3-methyl-2-(3,4,5-trimethoxybenzoyl)-pent-4-enenitrile (15l)**: Performing the general procedure with lithium diethylamide (0.115 mmol), **12a** (25 mg, 0.109 mmol) and methyl 3,4,5-trimethoxybenzoate (26 mg, 0.115 mmol), afforded, after purification on a Chromatotron (1 mm plate, 1:99 to 3:97 hexanes: ethyl acetate), 38.8 mg (84%) of 4-(benzyloxy)-2-ethyl-3-methyl-2-(3,4,5-trimethoxybenzoyl)pent-4-enenitrile as on oily mixture of diastereomers: IR (film) 1590, 1676, 2938 cm^{-1}; HRMS(EI) m/z $[M + H]^+$ calcd for $C_{25}H_{29}NO_5H$ 424.2124; found 424. 2113. For **(2*S**, 3*R**)-15l**: ^1H NMR: δ 0.99-1.05 (m, 3H), 1.35 (d, *J* = 7.0 Hz, 3H), 1.98-2.08 (m, 1H), 2.18-2.31 (m, 1H), 3.14 (q, *J* = 7.0 Hz, 1H), 3.74 (s, 3H), 3.89 (s, 6H), 4.14-4.25 (m, 2H), 4.71 (s, 2H), 7.18-7.44 (m, 7H); ^{13}C NMR: δ 10.1, 14.5, 30.2, 46.0, 53.5, 56.2, 60.9, 69.5, 85.1, 107.0, 121.1, 127.2, 127.4, 128.4, 131.4, 136.5, 152.6, 161.1, 193.8. For **(2*S**, 3*S**)-15l**: ^1H NMR: δ 0.99-1.05 (m, 3H), 1.41 (d, J = 7.3 Hz, 3H),

1.98-2.08 (m, 1H), 2.18-2.31 (m, 1H), 3.03 (q, *J* = 7.3 Hz, 1H), 3.88 (s, 3H), 3.93 (s, 6H), 4.14-4.25 (m, 2H), 4.54 (ABq, Δν = 4.5 Hz, *J* = 11.8 Hz, 2H), 7.18-7.44 (m, 7H); ^{13}C NMR: δ 10.3, 16.0, 30.8, 46.8, 56.3, 56.5, 61.0, 69.5, 85.8, 106.8, 121.4, 127.1, 127.7, 128.3, 131.9, 136.1, 152.7, 161.8, 194.1.

(2*S, 3*R**)- and (2*S**, 3*S**)-4-(Benzyloxy)-2-ethyl-2-isopropyl-3-methylpent-4-enenitrile (15m).** Using the general procedure with lithium diethylamide (0.115 mmol), **12a** (25 mg, 0.109 mmol) and isopropyl iodide (19.5 mg, 0.115 mmol), afforded, after purification on a Chromatotron (1 mm plate, 1:99 to 3:97 hexanes: ethyl acetate), 19.5 mg (66%) of **15m** as an oily mixture of diastereomers (2.3:1): IR (film) 1621, 2228, 2882, 2941, 2972 cm^{-1}; HRMS(EI) m/z [M+H]$^+$ calcd for $C_{18}H_{26}NO$ 272.2014; found 272.2007. For **(2*S**, 3*R**)-15m**: ^{1}H NMR: δ 1.02 (d, *J* = 6.9 Hz, 3H), 1.04-1.07 (m, 3H), 1.12 (d, *J* = 6.9 Hz, 3H), 1.35 (d, *J* = 7.2 Hz, 3H), 1.63-1.76 (m, 2H), 2.10-2.16 (m, 1H), 2.55-2.60 (m, 1H), 4.10-4.16 (m, 2H), 4.71-4.78 (m, 2H), 7.30-7.43 (m, 5H); ^{13}C NMR: δ 11.6, 16.6, 17.5, 18.6, 24.0, 32.8, 43.2, 49.0, 69.4, 84.7, 122.5, 127.2, 127.7, 128.4, 136.8, 163.3. For **(2*S**, 3*S**)-15m**: ^{1}H NMR: δ 1.01 (d, *J* = 6.9 Hz, 3H), 1.07 (d, *J* = 6.9 Hz, 3H), 1.10-1.12 (m, 3H), 1.35 (d, *J* = 7.2 Hz, 3H), 1.63-1.76 (m, 2H), 2.10-2.16 (m, 1H), 2.55-2.60 (m, 1H), 4.10-4.16 (m, 2H), 4.71-4.78 (m, 2H), 7.30-7.43 (m, 5H); ^{13}C NMR: δ 11.6, 16.6, 17.5, 19.2, 25.1, 32.2, 43.2, 48.8, 69.4, 84.7, 122.5, 127.3, 127.6, 128.4, 136.9, 163.3.

(2*S, 3*R**)-and (2*S**, 3*S**)-4-(Benzyloxy)-2-ethyl-3-methyl-2-(4-(trifluoromethyl)benzoyl)-pent-4-enenitrile (15n).** Using the general procedure with lithium diethylamide (0.115 mmol), **12a** (25 mg, 0.109 mmol) and methyl 4-(trifluoromethyl)benzoate (23.37 mg, 0.115 mmol), afforded, after purification on a Chromatotron (1 mm plate, 1:99 to 3:97 hexanes: ethyl acetate), 33.3 mg (76%) of **15n** as an oily mixture of diastereomers (2.2:1). For **(2*S**, 3*R**)-15n**: IR (film)

1690, 2940 cm^{-1}; ^1H NMR: δ 1.02-1.06 (m, 3H), 1.44 (d, *J* = 7.3 Hz, 3H), 2.04-2.13 (m, 1H), 2.17-2.25 (m, 1H), 3.08 (q, *J* = 7.3 Hz, 1H), 4.14 (m, 2H), 4.52 (s, 2H), 7.11-7.26 (m, 6H), 7.55 (d, *J* = 8.2 Hz, 2H), 7.96 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR: δ 10.2, 14.8, 31.3, 46.7, 57.5, 69.6, 85.4, 120.3, 125.1, 127.2, 127.8, 128.3, 129.0, 132.5, 133.7, 135.7, 140.2, 161.3, 196.0; HRMS(EI) m/z $[M + H]^+$ calcd for $C_{23}H_{22}F_3NO_2H$ 402.1681; found 402.1675. For **(2*S**, 3*S**)-15n**: IR (film) 1692, 2938 cm^{-1}; ^1H NMR: δ 1.01-1.05 (m, 3H), 1.37 (d, *J* = 7.3 Hz, 3H), 1.92-2.01 (m, 1H), 2.20-2.29 (m, 1H), 3.12 (q, *J* = 7.3 Hz, 1H), 4.22 (s, 2H), 4.69 (s, 2H), 7.26-7.34 (m, 6H), 7.68 (d, *J* = 8.3, 2H), 8.05 (d, *J* = 8. 3 Hz, 2H); ^{13}C NMR: δ 10.1, 15.8, 29.5, 45.9, 56.9, 69.6, 86.0, 120.6, 125.4, 127.3, 127.8, 128.4, 129.2, 134.1, 134.4, 136.2, 139.6, 160.6, 195.4; HRMS(EI) m/z $[M + H]^+$ calcd for $C_{23}H_{22}F_3NO_2H$ 402.1681; found 402.1675.

(2*S, 3*R**)- and (2*S**, 3*S**)-2-ethyl-4-methoxy-3-methyl-2-(4-(trifluoromethyl)benzoyl)pent-4-enenitrile (15o)**: Performing the general procedure with lithium diethylamide (0.115 mmol), **12b** (25 mg, 0.163 mmol) and methyl 4-(trifluoromethyl)benzoate (35 mg, 0.171 mmol), afforded, after purification on a Chromatotron (1 mm plate, 1:99 to 3:97 hexanes: ethyl acetate), 41 mg (77 %, 1.6:1 dr) of **15o** as an oily mixture of diastereomers (1.6:1 dr). For **(2*S**, 3*R**)-15o**: IR (film) 1692, 1727, 2973 cm^{-1}; ^1H NMR: δ 1.01-1.05 (m, 3H), 1.31 (d, *J* = 7.0 Hz, 3H), 1.89-1.98 (m, 1H), 2.17-2.26 (m, 1H), 3.05 (q, *J* = 7.0 Hz, 1H), 3.49 (s, 3H), 4.10 (d, *J* = 2.5 Hz, 1H), 4.14 (d, *J* = 2.5 Hz, 1H), 7.75 (d, *J* = 8.3, 2H), 7.96 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR: δ 10.1, 15.9, 29.9, 45.9, 54.7, 57.0, 84.5, 120.5, 125.5, 129.1, 130.0, 134.4, 139.8, 161.8, 195.8; HRMS(EI) m/z $[M + Na]^+$ calcd for $C_{17}H_{18}F_3NO_2Na$ 348.1187; found 348.1178. For **(2*S**, 3*S**)-15o**: IR (film) 1691, 1727 2942 cm^{-1}; ^1H NMR: δ 1.04 (t, *J* = 7.3 Hz, 3H), 1.38 (d, *J* = 7.0 Hz, 3H), 2.03-2.09 (m, 1H), 2.15-2.22 (m, 1H), 2.98 (q, *J* = 7.0 Hz, 1H), 3.32 (s, 3H), 4.00 (d, *J* = 3.0 Hz, 1H), 4.08 (d, *J* = 3.0 Hz, 1H), 7.73 (d, *J* = 8.3 Hz, 2H), 8.06 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR: δ 10.2,

14.4, 31.3, 46.6, 54.6, 57.4, 84.0, 120.2, 125.2, 128.9, 134.1, 140.5, 162.3, 196.4; HRMS(EI) m/z $[M + Na]^+$ calcd for $C_{17}H_{18}F_3NO_2Na$ 348.1187; found 348.1178.

4-(Benzyloxy)-2-ethyl-3-methylbutanenitrile (16): A THF solution (0.3 M) of butyronitrile (2.5 g, 36.2 mmol, 1.0 equiv) was added to a -78 °C, THF solution (0.1 M) of LDA, generated from butyllithium (1.05 equiv) and diisopropylamine (1.15 equiv). After 30 min, 3-benzyloxy-2-bromopropane[31] (8.70 g, 37.98 mmol, 1.05 equiv.) was added, and then the reaction was allowed to warm to rt. After 16 h, saturated aqueous NH_4Cl was added (5 mL), the phases were separated, and the aqueous phase was extracted with EtOAc (2 x 20 mL). The combined organic extract was dried (Na_2SO_4), and concentrated to afford a crude nitrile that was purified by silica gel column chromatography (5:95, EtOAc/hexanes) to afford 7.0 g (85 %) **16** as a colorless oil: IR (film) 2234, 2877, 2968 cm^{-1}; HRMS(EI) m/z $[M + Na]^+$ calcd for $C_{14}H_{19}NONa$ 240.1364, found 240.1355. Diastereomer 1: ^1H NMR: δ 1.05 (d, J = 7.03 Hz, 3H), 1.09-1.13 (m, 3H), 1.52-1.179 (m, 2H), 1.99-2.05 (m, 1H), 2.88-2.93 (m, 1H), 3.39-3.52 (m, 2H), 4.50-4.59 (m, 2H), 7.31-7.41 (m, 5H); ^{13}C NMR: δ 12.26, 12.89, 23.69, 35.32, 35.78, 72.97, 73.39, 120.71, 127.74, 127.82, 128.46, 138.05. Diastereoisomer 2: ^1H NMR: δ 1.09 (d, J = 7.03 Hz, 3H), 1.09-1.13 (m, 3H), 1.52-1.179 (m, 2H), 2.09-2.15 (m, 1H), 2.63-2.68 (m, 1H), 3.39-3.52 (m, 2H), 4.50-4.59 (m, 2H), 7.31-7.41 (m, 5H); ^{13}C NMR: δ 12.06, 15.01, 21.86, 35.24, 36.41, 72.39, 73.30, 121.58, 127.64, 127.69, 128.51, 138.17.

2-(1-(Benzyloxy)propan-2-yl)-2-ethylpentanenitrile (17): A THF solution (0.3 M) of **i** (25 mg, 0.115 mmol, 1.0 equiv.) was added to a -78 °C, THF (0.1 M) solution of $LiNEt_2$, generated from butyllithium (1.05 equiv) and diethylamine (1.15 equiv). The reaction was allowed to warm to rt and after 30 min the solution was cooled to -78 °C and then neat 1-iodopropane (20.5 mg, 0.121 mmol, 1.05 equiv) was added. After 15 min, saturated aqueous NH_4Cl was added (5 mL), the phases were separated, and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried (Na_2SO_4), concentrated, and purified by radial chromatography (1 mm plate, 2:98, EtOAc/hexanes) to afford 26.0 mg (88%) of **17** as an oily mixture of diastereomers (1.7:1). IR (film) 2230, 2875, 2967 cm^{-1}; HRMS(EI) m/z $[M + H]^+$ calcd for $C_{17}H_{25}NOH$ 260.2009; found 260.2003. For diastereomer 1: ^1H NMR: δ 0.95-0.98 (m, 3H), 1.01-1.05 (m, 3H), 1.12 (d,

J = 6.8 Hz, 3H), 1.39-1.75 (m, 6H), 2.08-2.13 (m, 1H), 3.38-3.42 (m, 1H), 3.66-3.70 (m, 1H), 4.50-4.57 (m, 2H), 7.28-7.40 (m, 5H); ^{13}C NMR: δ 8.97, 13.07, 14.31, 17.65, 26.43, 35.08, 37.03, 44.00, 72.34, 73.31, 123.36, 127.57, 128.43, 138.20. For diastereomer 2: ^{1}H NMR: δ 0.95-0.98 (m, 3H), 1.00-1.04 (m, 3H), 1.12 (d, *J* = 6.8 Hz, 3H), 1.39-1.75 (m, 6H), 2.08-2.13 (m, 1H), 3.38-3.42 (m, 1H), 3.66-3.70 (m, 1H), 4.50-4.57 (m, 2H), 7.28-7.40 (m, 5H); ^{13}C NMR: δ 8.74, 13.16, 14.28, 17.81, 26.27, 35.18, 37.09, 44.02, 72.30, 73.31, 123.36, 127.59, 127.66, 138.20.

(2*S, 3*R**)-4-(benzyloxy)-2-ethyl-2-(hydroxymethyl)-3-methylpent-4-enenitrile (18)**: Preparation from **(2*S**, 3*R**)-15i**: A THF solution (1 M) of lithium triethylborohydride (1.19 mL, 1.183 mmol, 2.0 equiv) was added to a 0 °C, THF solution (1 mL) of **(2*S**, 3*R**)-15i** (170 mg, 0.592 mmol, 1.0 equiv). After 30 min, the reaction was allowed to warm to rt. After 16h, saturated, aqueous NH_4Cl was added (4 mL), the phases were separated, and the aqueous phase was extracted with EtOAc (2 x 15 mL). The combined organic extract was dried (Na_2SO_4), concentrated, and purified by radial chromatography (2 mm plate, 10:90 hexanes: ethyl acetate) to afford 123 mg (80%) of analytically pure **18**: IR (film) 1622, 1656, 2236, 2882, 2973, 3454 cm^{-1}; ^{1}H NMR: δ 1.07-1.11 (m, 3H), 1.35 (d, *J* = 7.3 Hz, 3H), 1.61-1.81 (m, 2H), 2.23 (*br*, s, 1H), 2.78 (q, J = 7.3 Hz, 1H), 3.73-3.80 (m, 2H), 4.19-4.23 (m, 2H), 4.79 (ABq, Δn = 7.0 Hz, *J* = 11.5 Hz, 2H), 7.34-7.43 (m, 5H); ^{13}C NMR: δ 9.4, 14.8, 23.9, 41.7, 47.4, 63.8, 69.8, 85.6, 121.8, 127.5, 128.1, 128.6, 136.3, 161.7; HRMS(EI) m/z $[M + Na]^+$ calcd for $C_{16}H_{21}NO_2Na$ 282.1470; found 282.1471. Preparation from **(2*S**, 3*R**)-15k**: A THF solution (1M) of lithium triethylborohydride (0.2 mL, 0.199 mmol, 2.0 equiv) was added to a 0 °C, THF solution (1 mL) of **(2*S**, 3*R**)-15k** (30 mg, 0.0995 mmol, 1.0 equiv). After 30 min, the reaction was allowed to warm to rt. After 16 h, saturated, aqueous NH_4Cl was added (3 mL), the phases were separated and the aqueous phase was extracted with EtOAc (2 x 15 mL). The combined organic extract was dried (Na_2SO_4), concentrated, and purified by radial chromatography (2 mm plate, 10:90 hexanes: ethyl acetate) to afford 20 mg (78%) of analytically pure **18**.

(2*S, 3*R**)-4-(Benzyloxy)-2-cyano-2-ethyl-3-methylpent-4-en-1-yl 4-nitrobenzoate (19)**: A hexanes solution (1.6 M) of BuLi (0.135 mmol, 1.0 equiv) was added, dropwise, to a -78 °C,

THF solution (2.0 mL) of **(2*S**, 3*R**)-18** (35 mg, 0.135 mmol, 1.0 equiv). After 10 min, a THF solution (1.0 mL) of PNBCl (0.25 mg, 0.135 mmol, 1.0 equiv) was added and then the reaction mixture was allowed to warm to rt. After 16 h, saturated, aqueous NH_4Cl (2 mL) was added, the phases were separated, and the aqueous phase was extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and then concentrated. Purification of the concentrated material by radial chromatography (1 mm plate, 8:92, EtOAc/hexanes) afforded 45.8 mg (83%) of **(2*S**, 3*R**)-19** as a solid (mp 78.5-80 °C), whose structure was unequivocally determined by X-ray diffraction: IR (film) 1607, 1732, 2237, 2925, 2976 cm^{-1}; ^1H NMR: δ 1.13-1.50 (m, 3H), 1.40 (d, *J* = 7.3 Hz, 3H), 1.72-1.82 (m, 1H), 1.86-1.93 (m, 1H), 2.79 (q, *J* = 7.3 Hz, 1H), 4.13 (d, *J* = 2.8 Hz, 1H), 4.19 (d, *J* = 2.8 Hz, 1H), 4.46-4.52 (m, 2H), 4.75 (ABq, Δν = 6.3 Hz, *J* = 11.5 Hz, 2H), 7.29-7.34 (m, 5H), 8.18 (d, *J* = 8.8 Hz, 2H), 8.29 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR: δ 9.6, 14.8, 25.0, 42.6, 45.4, 65.8, 69.7, 85.9, 120.6, 123.7, 127.4, 127.9, 128.5, 130.9, 134.7, 136.4, 150.8, 161.0, 164.0; HRMS(EI) m/z $[M + H]^+$ calcd for $C_{23}H_{24}N_2O_5H$ 409.1763; found 409.1746.

(2*S, 3*R**)-4-(Benzyloxy)-2-ethyl-2-formyl-3-methylpent-4-enenitrile (20)**: A CH_2Cl_2 solution (15% wt) of the Dess-Martin periodinane (0.339 mmol, 1.1 equiv) was added to a rt, CH_2Cl_2 solution (3.0 mL) of **(2*S**, 3*R**)-18** (80 mg, 0.308 mmol, 1.0 equiv). After 1 h, the mixture was filtered through Celite, the solid was washed with CH_2Cl_2 (5 mL), and then the filtrate was evaporated. The resultant crude aldehyde was purified by radial chromatography (2:98, EtOAc/Hexane) to provide **(2*S**, 3*R**)-20** 67.5 mg (85%) as a light yellow, oily liquid: IR (film) 1630, 1733, 2244, 2880, 2974 cm^{-1}; ^1H NMR: δ 1.02-1.06 (m, 3H), 1.29 (d, *J* = 7.0 Hz, 3H), 1.80-1.96 (m, 2H), 2.76 (q, *J* = 7.0 Hz, 1H), 4.20-4.22 (m, 2H), 4.79 (ABq, Δν = 7.3 Hz, *J* = 11.8 Hz, 2H), 7.32-7.38 (m, 5H), 9.41 (s, 1H); ^{13}C NMR: δ 9.6, 15.2, 25.3, 43.6, 57.9, 69.8, 85.8, 117.8, 127.4, 127.9, 128.5, 136.3, 160.2, 194.4; HRMS(EI) m/z $[M + H]^+$ calcd for $C_{16}H_{19}NO_2H$ 258.1494; found 258.1491.

(*S, Z)-2-((*R**)-3-(Benzyloxy)but-3-en-2-yl)-2-ethylpent-3-enenitrile (21)**: A hexanes solution (2.2 M) of butyllithium (0.30 mmol, 1.19 equiv) was added to a -78 °C, THF suspension (3 mL) of ethyltriphenylphosphonium iodide (127 mg, 0.303 mmol, 1.2 equiv). After 30 min, a THF solution of **(2*S**, 3*R**)-20** (65 mg, 0.252 mmol, 1.0 equiv.) was added and then the reaction was allowed to warm to rt. After 12 h, saturated aqueous NH_4Cl (3.0 mL) was added, the phases were separated, and then the aqueous phase was extracted with diethyl ether (2 x 15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated to give the crude olefin that was purified by radial chromatography (1 mm plate, 2:98 to 4:96, EtOAc/hexanes) to afford 50.0 mg (74%) of pure **(*S**, Z)-21** as an oil: IR (film) 1624, 1657, 1728, 2235, 2855, 2927 cm^{-1}; ^1H NMR: δ 1.02-1.06 (m, 3H), 1.34 (d, J = 7.0 Hz, 3H), 1.52-1.61 (m, 1H), 1.82-1.91 (m, 1H), 1.95 (dd, J = 7.5, 1.8, 3H), 2.35 (q, J = 7.0 Hz, 1H), 4.14-4.16 (m, 2H), 4.77 (ABq, Δν = 4.3 Hz, J = 11.8 Hz, 2H), 4.89-4.93 (m, 1H), 5.70-5.78 (m, 1H), 7.26-7.46 (m, 5H); ^{13}C NMR: δ 9.7, 13.4, 15.7, 31.1, 45.8, 47.4, 69.3, 84.7, 122.2, 127.3, 128.4, 128.7, 129.4, 136.9, 162.2; HRMS(EI) m/z $[M + H]^+$ calcd for $C_{18}H_{23}NOH$ 270.1858; found 270.1848.

(*S, *Z*)-2-Ethyl-2-((R*)-3-oxobutan-2-yl)pent-3-enenitrile (22)**: Water (17 mg, 0.928 mmol, 5 equiv), and aqueous HCl (1.86 μmol, 0.01 equiv) were added to a rt, acetonitrile solution (2.0 mL) of **(*S**, Z)-21** (50 mg, 0.1856 mmol, 1.0 equiv.) After 30 min, saturated aqueous $NaHCO_3$ (5 mL) was added, the phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated to afford a crude ketonitrile that was purified by radial chromatography (1 mm

plate, 5:95 to 8:92, EtOAc/hexanes) to afford 29 mg (87%) of pure **(*S**, *Z*)-22** as a pale yellow oil: IR (film) 1714, 2234, 2882, 2938, 2974 cm^{-1}; ^1H NMR: δ 1.04-1.02 (m, 3H), 1.32 (d, *J* = 7.3 Hz, 3H), 1.67-1.70 (m, 1H), 1.80-1.84 (m, 1H), 1.96 (dd, *J* = 7.3, 1.8 Hz, 3H), 2.24 (s, 3H), 2.79 (q, *J* = 7.3 Hz, 1H), 4.93-4.97 (m, 1H), 5.76-5.81 (m, 1H); ^{13}C NMR: δ 9.5, 13.3, 13.5, 29.8, 30.2, 43.5, 53.4, 121.5, 127.1, 130.4, 208.5; HRMS(EI) m/z $[M + H]^+$ calcd for $C_{11}H_{17}NOH$ 180.1388; found 180.1380.

(2*S, 3*R**)-2-Ethyl-3-methyl-4-oxo-2-propylpentanenitrile (23)**: Preparation by hydrogenation of **(*S**, *Z*)-22**: Solid Pd/C (5%, 0.011 mmol, 0.1 equiv) was added to a rt, methanolic solution (5 mL) of **(*S**, *Z*)-22** (20 mg, 0.111 mmol, 1.0 equiv). The solution was sequentially purged with argon and hydrogen, and then maintained under a positive pressure of hydrogen using a balloon. After 3h, the mixture was filtered, the filtrate was evaporated, and the crude nitrile was purified by radial chromatography (1 mm plate, 8:92, EtOAc/hexanes) to afford 19.0 mg (95%) of **(2*S**, 3*R**)-23** as a pale yellow oil: IR (film) 1715, 2230, 2877, 2965 cm^{-1}; ^1H NMR: δ 0.95-0.99 (m, 3H), 1.00-1.03 (m, 3H), 1.26 (d, *J* = 7.0 Hz, 3H), 1.34-1.57 (m, 3H), 1.64-1.74 (m, 3H), 2.26 (s, 3H), 2.80 (q, *J* = 7.0 Hz, 1H); ^{13}C NMR: δ 8.9, 12.7, 14.2, 17.5, 26.3, 29.84, 35.1, 42.9, 49.8, 122.6, 208.9; HRMS(EI) m/z $[M + Na]^+$ calcd for $C_{11}H_{19}NONa$ 204.1364; found 204.1361. Preparation by hydrolysis of **(2*R**, 3*R**)-15f**: Water (10 mg, 0.55 mmol, 5 equiv) and aqueous HCl (0.24 μL, 6.5 μmol, 0.01 equiv) were added to a rt, acetonitrile solution (3 mL) of **(2*R**, 3*R**)-15f** (30 mg, 0.110 mmol, 1.0 equiv). After 30 min, saturated aqueous $NaHCO_3$ (5 mL) was added, the phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated to afford a crude oxonitrile that was purified by radial

chromatography (2 mm plate, 4:96 to 8:92, EtOAc/hexanes) to afford 18 mg (91%) of **(2*S**, 3*R**)-23** spectrally identical to material previously isolated.

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Supporting Information Available. Experimental procedures and schemes for stereochemical correlations, analyticalAnalytical data for all new compounds, and a CIF file for a crystalline derivative prepared for configurational analysis. This material is available free of charge via internet at http://pubs.acs.orghttp://pubs.acs.org.

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[19] Adding HMPA to the mixed metal species exacerbates the over-alkylation increasing the amount of **13a** and an isopropyl ketone resulting from methylation of **13a**.

[20] $LiNEt_2$ has a modest steric demand and is often more effective than LDA in deprotonating tertiary nitriles embedded near adjacent stereocenters.

[21] No deprotonation was observed with LiHMDS in toluene, perhaps because of the difficulty in abstracting the hindered proton.

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[24] No trace of the diastereomer was detected in the crude ^{1}H NMR of the reaction mixture. Ozonolysis of **12c** afforded **7a** indicating the same sense of stereoselectivity.

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