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γ- and δ-Hydroxynitriles: diastereoselective electrophile-dependent alkylations

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ABSTRACT

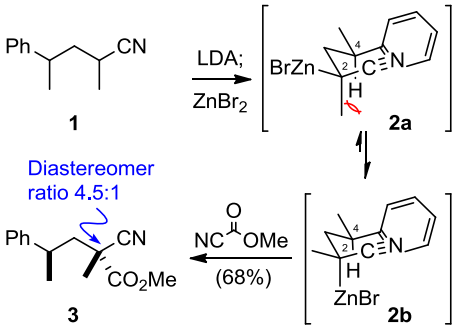
Deprotonating γ- and δ-hydroxynitriles with *i*-PrMgCl allows highly diastereoselective alkylations controlled by the asymmetry of the remote carbinol stereocenter. Mechanistic experiments are consistent with γ-hydroxynitriles alkylating via a chelated magnesiated nitrile whereas δ-hydroxynitriles favor alkylation from acyclic magnesiated nitriles. Collectively these alkylations; are the first electrophile-dependent alkylations of *acyclic* nitriles, exhibit a unique influence on the nature of the Grignard used for the deprotonation, and address the challenge of installing quaternary centers in conformationally mobile, acyclic nitriles.

1. Introduction

Metalated nitriles are exceptional nucleophiles.[1] The nitrile's compact, cylindrical geometry,[2] combined with the strong inductive stabilization,[3] localizes a high charge density on an extremely small,[4] nucleophilic carbon. Attack from the small, charged nucleophile permits the facile installation of quaternary centers,[5] even in cases where comparable enolate alkylations are unsuccessful.[6]

Diastereoselective alkylations of *acyclic* nitriles are challenging because; chiral auxiliaries are not readily incorporated on or near the nitrile unit,[7] chiral ligands complexed to *N*-lithiated-nitriles lie in a remote position from the nucleophilic carbon and poorly relay the chiral asymmetry,[8] *C*-metalated nitriles rapidly epimerize,[9] and inherently flexible, rotatable, single bonds in alkanenitriles make access to one reactive conformer difficult.[10] Highly stereoselective alkylations of acyclic, metalated nitriles require restricting conformational mobility. An effective strategy for 1,2-asymmetric induction is to install a sterically biased stereocenter immediately adjacent to the nucleophilic carbon in combination with judiciously positioned alkyl substituents and unsaturation.[11] More remote 1,3-asymmetric induction with the chiral center *two* carbons removed from the metalated center diminishes the selectivity into the range of 3–5:1 (**1**→**3**, Scheme 1),[12] reflecting the difficulty of selectively accessing and alkylating one diamond lattice conformation (cf. **2a**⇄**2b**).

Temporary chelation provides a robust method for restricting conformational mobility for diastereoselective alkylations.[13]



Scheme 1. 1,3-Induction in the alkylation of an acyclic nitrile.

Applying the strategy to acyclic, γ-hydroxynitriles **4**, by deprotonating with a Grignard reagent, generates a magnesiated nitrile tentatively identified as the chiral, racemic, cyclic magnesiate **5** (Scheme 2).[14] Alkylations of **5** exhibit a highly unusual diastereoselectivity dependence on the nature of the electrophile;[15] alkyl halides afford *syn*-diastereomers **6′**, reactive carbonyl electrophiles alkylate non-selectively (**6″**), and less reactive ester and carbonate electrophiles alkylate to afford *anti*-diastereomers (**6‴**).[16]

The present manuscript describes mechanistic experiments to probe the structure and reactivity of the intermediate magnesiated nitrile, additional alkylations of γ-hydroxynitriles with a series of substituted alkyl halides, an application to the synthesis of an antitussive agent, and alkylations with homologous δ-hydroxynitriles. In addition, a series of ester acylations are described where the intermediate ketones are *reduced* to the corresponding dihydroxynitriles by a stereoselective hydride transfer from the Grignard-derived *iso*-

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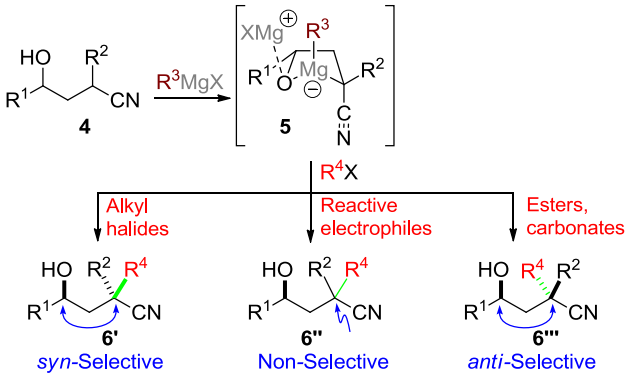


Scheme 2. Diastereoselective chelation-controlled alkylations of δ-hydroxynitriles.

propyl group. Collectively these studies define the limits of this hydroxynitrile chelation strategy, address the long-standing challenge of installing quaternary centers in conformationally mobile, acyclic nitriles, and provides a robust, predictive model that accounts for the unusual electrophile-dependent stereoselectivity in alkylations of γ-hydroxynitriles.

2. Results and discussion

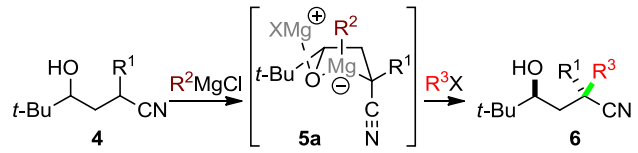
Preliminary alkylations of δ-hydroxynitriles employed the *tert*-butyl-substituted nitrile **4a**[17] as a prototype to accentuate the emerging stereoselectivity trends (Table 1). Screening several base-additive combinations[18] identified *i*-PrMgCl as the most effective base for doubly deprotonating hydroxynitrile **4a**. Directly deprotonating alkylnitriles with Grignard reagents is unusual because nucleophilic addition to the nitrile group typically competes with proton abstraction.[19] In the present case, the hydroxyl group serves to direct internal deprotonation without detectable attack on the nitrile.

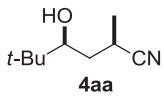
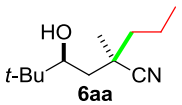
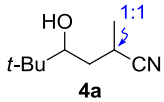
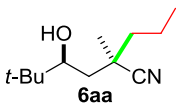
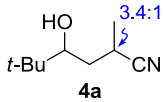
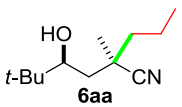
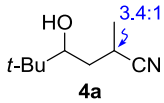
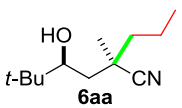
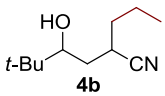
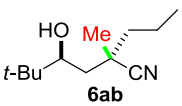
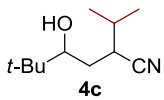
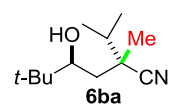
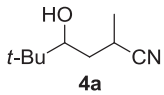
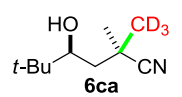
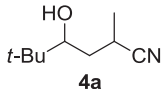
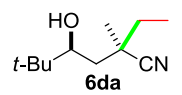
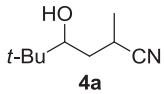
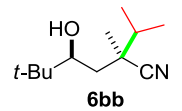
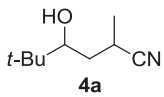
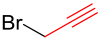
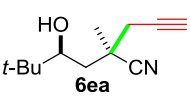
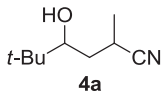
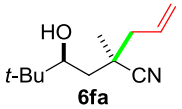
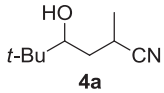
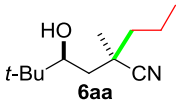
Operationally, *i*-PrMgCl is added to a −78 °C, THF solution of the hydroxynitrile, which is warmed to rt for 30 min and then re-cooled to −78 °C before addition of the electrophile. Although the double deprotonation formally requires 2 equiv of *i*-PrMgCl, virtually no deprotonation is observed until 4 equiv of *i*-PrMgCl is added.[20] Increasing the amount of *i*-PrMgCl to 5 equiv improves the conversion by at least 25% and was therefore employed in all subsequent deprotonations (Table 1, compare the yield for entry 4 with entries 1–3).

The alkylation diastereoselectivity of **4a** is independent of the stereochemistry at the nitrile-bearing carbon. Sequentially deprotonating and alkylating diastereomerically pure **4aa**, a 1:1, or a 3.4:1 ratio of diastereomers **4a** and alkylating with propyl iodide, affords the quaternary nitrile **6aa** with essentially the same diastereoselectivity and in comparable yield (Table 1, entries 1–3). Forming the same ratio of diastereomers **6aa**, independent of the starting configuration of **4a**, implies forming a common magnesiated nitrile having the same configuration at the nucleophilic carbon. Presumably deprotonation provides a facile epimerization mechanism, consistent with the rapid equilibration of cyclic magnesiated nitriles[9b] and the configurational lability of *C*-lithiated cyanohydrin-derived carbamates.[21]

Large variations in the size of the alkyl substituent at the nitrile-bearing carbon have only a modest influence on the alkylation diastereoselectivity. Substituting the prototypical α-methyl substituent of **4a** with a propyl- or *iso*-propyl-substituent, in **4b** and **4c** (Table 1, entries 5 and 6, respectively), and alkylating with MeI, or CD_3I for **4a** (Table 1, entry 7), allows the diastereoselectivity to be compared with electrophiles having virtually the same steric demand. Despite the *A* values varying from 1.70 to 2.15 kcal mol^{-1}, for methyl, propyl, and *iso*-propyl groups, the diastereoselectivity remains very similar.[4] Presumably the C-2 substituent is positioned

Table 1
Diastereoselective alkylations of γ-hydroxynitriles



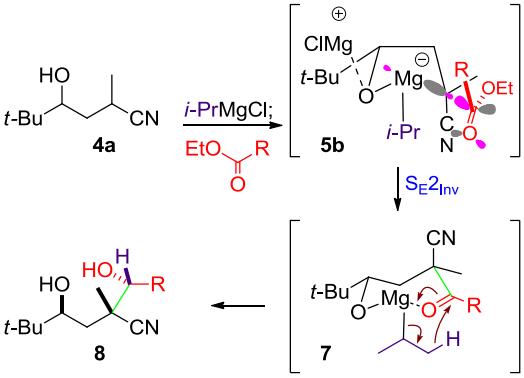
Entry	Hydroxynitrile[a]	Electrophile	Quaternary nitrile	Yield % (dr)
1	 **4aa**		 **6aa**	79 (16.0:1)
2	 **4a**		 **6aa**	91 (16.2:1)
3	 **4a**		 **6aa**	91[b] (16.2:1)
4	 **4a**		 **6aa**	64 (16.2:1)[c]
5	 **4b**	MeI	 **6ab**	95[b] (9.4:1)
6	 **4c**	MeI	 **6ba**	95 (8.0:1)
7	 **4a**	CD_3I	 **6ca**	96 (7.5:1)
8	 **4a**		 **6da**	82 (6.5:1)
9	 **4a**		 **6bb**	47[d] (5.5:1)
10	 **4a**		 **6ea**	75[b] (5.0:1)
11	 **4a**		 **6fa**	93[b] (4.7:1)
12	 **4a**		 **6aa**	56 (2.5:1)[b,e]

[a] Unless otherwise specified, the hydroxynitriles are mixtures of diastereomers.
[b] Previously reported.[16]
[c] *i*-PrMgCl of 4 equiv was employed.
[d] Recovered 42% starting hydroxynitrile.
[e] MeMgCl was employed as the base in place of *i*-PrMgCl.

away from the incoming electrophile in the magnesiated nitrile complex, consistent with a retentive alkylation (S_E2_{Ret})[22] from the nucleophilic C–Mg bond in magnesiate **5a**.

Among the alkyl halide electrophiles, no clear correlation emerges between the steric demand of the alkyl group and the diastereoselectivity; PrI (16.2:1)>EtI (6.5:1)>*i*-PrI (5.5:1)>HC≡CCH$_2$Br (5.0:1)>H$_2$C=CHCH$_2$Br (4.7:1).[23] Propyl iodide alkylates significantly more selectively than the sterically similar, but more reactive, allyl and propargyl bromides (Table 1, compare entry 3 with entries 10 and 11). Collectively, the alkylation trends with alkyl halides are not consistent with steric approach control and suggest that the diastereoselectivity results from stereoelectronic controlled[24] S_E2 substitutions.[22]

Unlike most metalated nitrile alkylations where the diastereoselectivity depends only on the steric trajectory,[5] the alkylations of **4** exhibit an unusual dependence on the nature of the electrophile. Intercepting the magnesiated nitrile derived from **4a** with esters affords dihydroxynitriles **8** in which the stereochemistry at the nitrile-bearing carbon is inverted relative to that obtained from alkylations of **4a** with alkyl halides (Scheme 3). Deprotonating **4a** with *i*-PrMgCl and adding ethyl isobutyrate affords the dihydroxynitrile **8aa** in 87% yield and as a single diastereomer. The relative configuration of the two new stereocenters was determined by X-ray crystallography (Fig. 1).[25]



Scheme 3. Sequential acylation–reductions with ester electrophiles.

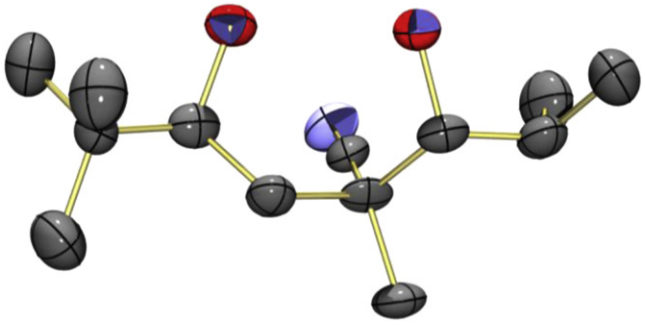
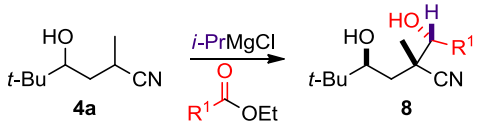


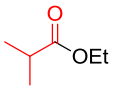
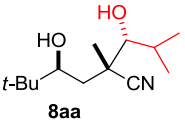
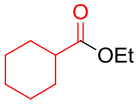
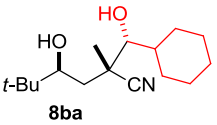
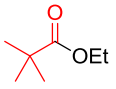
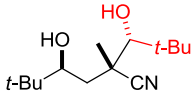
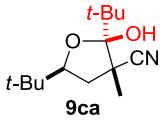
Fig. 1. ORTEP of the dihydroxynitrile **8aa**.

The formation of dihydroxynitriles **8** is consistent with an initial, invertive acylation (S_E2_{Inv})[22] of the magnesiated nitrile **5b** (Scheme 3). Preferential attack by the ester on the small nucleophilic orbital allows a collinear orbital overlap. Subsequent selective[26] reduction of the intermediate ketone **7** through internal hydride delivery[27] is favored by the close proximity of the Grignard-derived *iso*-propyl group.

The ester acylation–reduction sequence is effective with alkylesters bearing one or two α-substituents (Table 2). The

Table 2
Diastereoselective ester acylations of **4a**



entry	Electrophile	Quaternary nitrile	Yield (%)
1		 **8aa**	87
2		 **8ba**	84
3		 **8ca**	64[a]
		 **9ca**	17

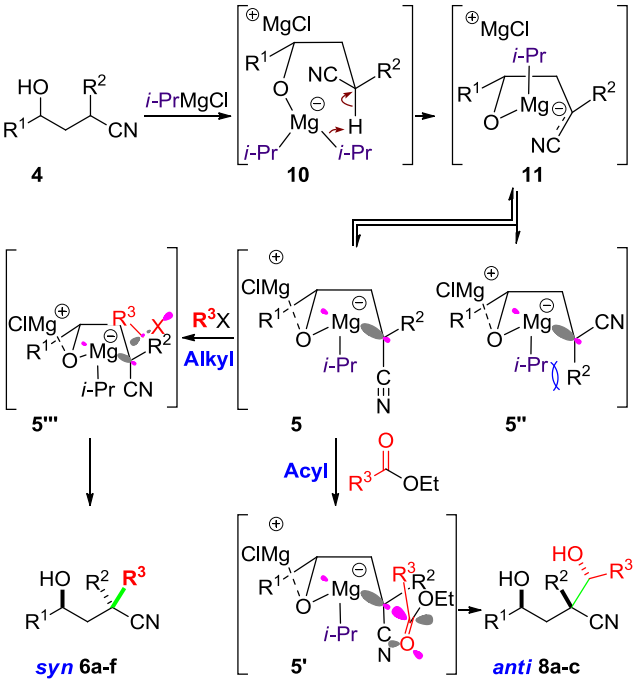
[a] Requires 10 equiv of *i*-PrMgCl.

diastereoselectivity of the acylation and the reduction is excellent with only one diastereomer detected in the ^{1}H NMR of the crude reaction mixture. The acylation of **5b** with the sterically encumbered ester, ethyl pivalate, is delicately poised between reduction to **8ca** and intramolecular cyclization to lactol **9ca** (Table 2, entry 3). Using 5 equiv of *i*-PrMgCl for the deprotonation–acylation results in cyclization to lactol **9ca**[16] whereas 10 equiv of *i*-PrMgCl allows reduction to diol **8ca** (Table 2, entry 3). The ability of an additional 5 equiv of *i*-PrMgCl to cause complete reduction of the intermediate lactol **9ca** to the corresponding diol nitrile **8ca** again identifies the Grignard reagent as the hydride source in these reductions.

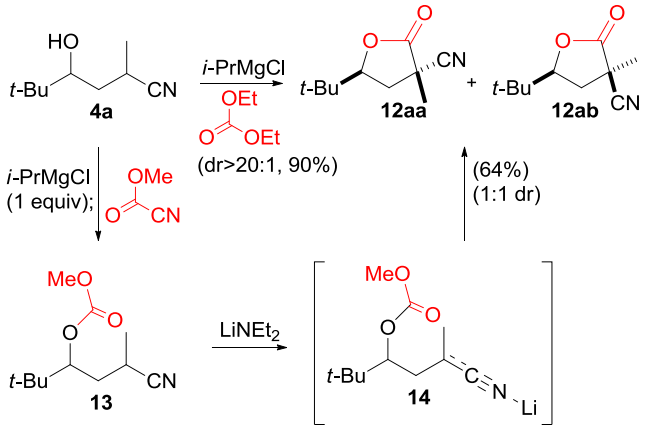
2.1. Mechanism

Insight into the nature of the intermediate magnesiated nitrile came from otherwise identical alkylations of **4a** with PrI in which deprotonations with MeMgCl or *i*-PrMgCl give dramatically different diastereoselectivities. Deprotonating **4a** with *i*-PrMgCl is significantly more selective than deprotonating with MeMgCl (Table 1, compare entries 3 and 12; 16.2:1 vs 2.5:1, respectively), suggesting that a Grignard-derived alkyl group is incorporated within the magnesiated nitrile. Incorporation of an *iso*-propyl group within **5** is consistent with the reduction of ester electrophiles and the reactivity and stereoselectivity differences of related *C*-magnesiated nitriles.[28] A working mechanism that accounts for the structure of the Grignard reagent, the electrophile-dependent alkylations, the acylation–reduction sequence with ester electrophiles, and the requirement for an excess of the Grignard reagent is for alkylation via the cyclic, nitrile-stabilized magnesiate **5** (Scheme 4).

Five equivalents of Grignard reagent is optimal for deprotonating the hydroxynitriles **4** (Scheme 4). In addition to the 2 equiv consumed in the deprotonation, one additional equivalent of *i*-PrMgCl is likely required to form the magnesiate **10** and facilitate the deprotonation to the doubly deprotonated nitrile **11**. Although



Scheme 4. Tentative alkylation mechanism.



Scheme 5. Lithiated nitrile diastereoselectivity probe.

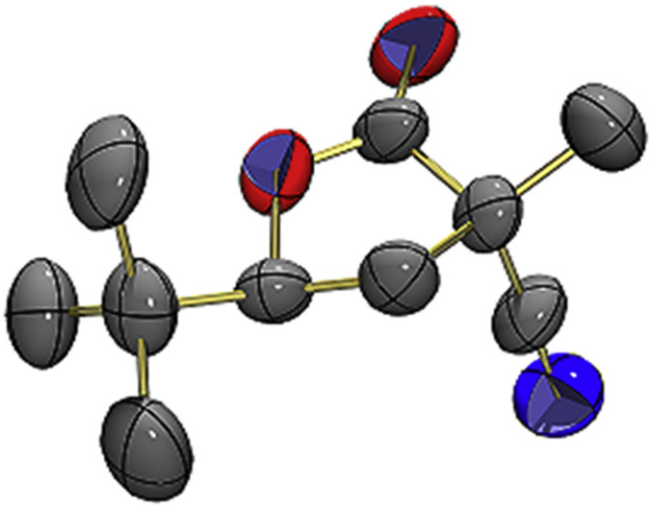


Fig. 2. ORTEP of the lactone-nitrile **12aa**.

the requirement for 4 equiv, ideally five, of *i*-PrMgCl is uncertain, the related formation of an oxygenated, magnesiated nitrile required 5 equiv of EtMgCl.[29] Possibly, *i*-PrMgCl is sequestered in an association with the alkoxide oxygen (see **5**, Scheme 4). Significantly, the diastereoselectivity is the same with 4 or 5 equiv of *i*-PrMgCl (Table 1, entries 4 and 3, respectively).

After the double deprotonation, **11** should preferentially cyclize to the sterically less congested *iso*-propyl-containing magnesiate **5**. Assuming a chloromagnesium cation[30] complexes the most accessible face of the electron rich alkyloxy oxygen in **5**, then the adjacent *iso*-propyl group should lie on the opposite side of the five-membered ring and preferentially eclipse the small nitrile group rather than the larger R^2 group (cf. **5** and **5″**, Scheme 4).

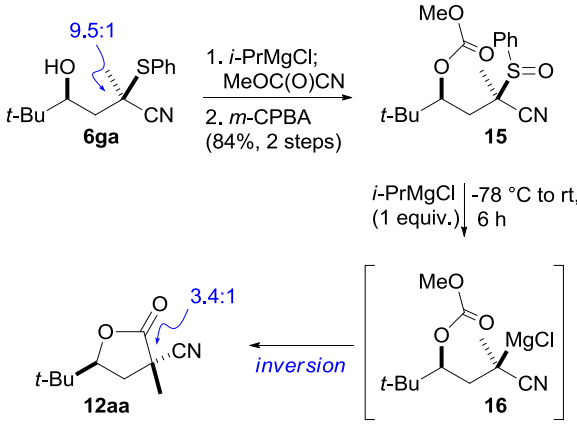
Assuming alkylations from the cyclic magnesiate **5** explains the unusual electrophile-dependent alkylations of δ-hydroxynitriles, although other mechanistic scenarios cannot be excluded.[31] The retentive alkylations of alkyl halides are consistent with a side-on overlap of the carbon-magnesium bond (**5‴**→*syn* **6a**–**f**, Scheme 4). An electrophilic approach to the C–Mg bond is relatively remote from the alkyl substituent R^2, whose steric demand has minimal influence on the diastereoselectivity (Table 1, entries 5–7). The alternative, invertive attack on **5‴** with an sp^3 hybridized electrophile would impose severe steric compression in the transition structure and should be strongly correlated with the steric demand of the adjacent substituent R^2, which is not the case. Carbonyl electrophiles have a diminished steric demand and larger anti-bonding orbitals that should facilitate backside attack onto the small nucleophilic orbital of the C–Mg bond. Alkylations of carbonyl electrophiles progressing through **5′** benefit from progression through a co-linear, two-center, two-electron transition structure whereas a retentive alkylation requires a three-center, two-electron transition structure.

The invertive alkylation of carbonyl electrophiles is evident from the acylation of **4a** with diethylcarbonate (Scheme 5). The highly selective (>20:1 dr) invertive acylation of **4a** is followed by an attack of the alkoxide onto the carbonyl to form the lactone **12aa**.[32] The relative stereochemistry of **12aa** was secured by X-ray diffraction (Fig. 2).[33]

Diethyl carbonate could potentially acylate first on carbon and then lactonize or through a reversed O- then C-acylation sequence (**13**→**14**→**12a**, Scheme 5). The potential acylation sequences were discriminated by independently preparing **13** and deprotonating the nitrile with lithium diethylamide. The absence of any diastereoselectivity in the cyclization of **13** with $LiNEt_2$, implies that the acylation of **4a** with diethyl carbonate[16] occurs first on carbon in a stereoelectronically controlled acylation.

Although the *N*-lithiated nitrile **14** cyclizes non-selectively, the corresponding *C*-magnesiated nitrile could potentially impart greater internal asymmetric induction. Only recently has methodology become available to access the requisite *C*-magnesiated nitrile[34] to test whether this is a viable intermediate. Sequentially acylating and oxidizing a 9.5:1 ratio[35] of nitrile diastereomers with **6ga** predominating (Scheme 6), provides sulfinyl nitrile **15** that was engaged in a rapid sulfinyl–magnesium exchange.[34] Adding *i*-PrMgCl to **15** generates the lactone **12aa** in a 3.4:1 ratio,[36] which is significantly lower than the acylation of **4a** with diethylcarbonate (>20:1, Scheme 5). Consequently the *C*-magnesiated nitrile **16** seems unlikely as an intermediate,[37] again supporting stereoelectronically controlled acylation of **4a** from magnesiate **5**.

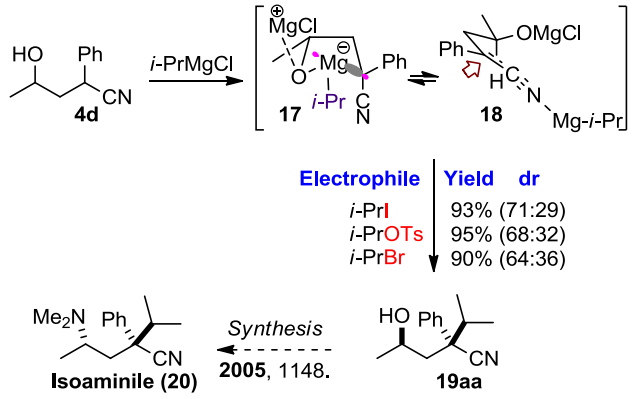
The predominant lactone diastereomer **12aa** is that expected from a retentive sulfinyl–magnesium exchange **15**→**16** followed by an invertive acylation **16**→**12aa**, consistent with the general trend of magnesiated nitriles to acylate with inversion. Presumably the



Scheme 6. Intramolecular acylation of a *C*-magnesiated nitrile.

3.4:1 ratio of lactone diastereomers arises because of transient configurational stability of the *C*-magnesiated nitrile **16**.[9,21] Collectively the intramolecular acylations of **13** (Scheme 5) and **15** (Scheme 6) imply that the diastereoselective alkylations of the magnesiated nitriles are stereoelectronically controlled.

The diastereoselective γ-hydroxynitrile alkylations stimulated synthesizing hydroxynitrile **19aa** in a formal synthesis of the cough suppressant isoaminile (**20**, Scheme 7).[38] Adding excess *i*-PrMgCl to hydroxynitrile **4d**[17] affords a magnesiated nitrile intermediate that very efficiently alkylates *i*-PrI, *i*-PrBr, and *i*-PrOTs (**17**/**18**→**19aa**). The modest diastereoselectivity could arise from alkylation from two different chelates (cf. **5** and **5″**, Scheme 4) because of the small steric demand of the methyl carbinol substituent. Alternatively, the strong resonance delocalization of charge into the adjacent phenyl group[3b] may favor the non-chelated conformer[12] **18** from which alkylation is only modestly selective. Hydroxynitrile **19aa** has previously been converted into isoaminile (**20**) by activating the hydroxyl group and displacing with dimethylamine.[38]



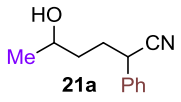
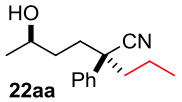
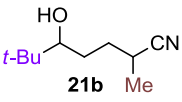
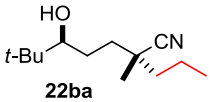
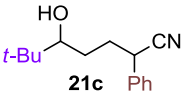
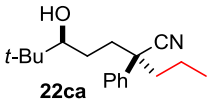
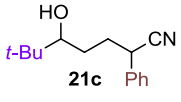
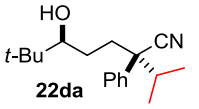
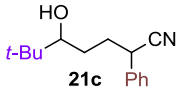
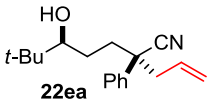
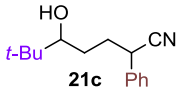
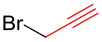
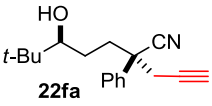
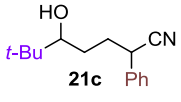
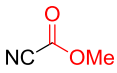
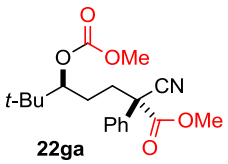
Scheme 7. Formal synthesis of isoaminile.

2.2. Homologous alkylations

A series of hydroxyl-directed deprotonation–alkylations were performed with homologous δ-hydroxynitriles to determine the viability of 1,4-asymmetric induction. Compared to γ-hydroxynitriles, positioning the carbinol center four carbons removed from the nucleophile leads to significantly lower diastereoselectivity (Table 3). Surprisingly, increasing the steric demand of the δ-hydroxynitrile carbinol group from methyl to *tert*-butyl, only marginally increases the diastereoselectivity (2.5:1 compared to 2.7:1, Table 3, entries 1 and 3, respectively). The enormous difference in steric demand between Me and *t*-Bu groups (1.7 and 4.7 kcal mol^{-1})[4] implies that a cyclic chelate is not formed and that the diastereoselectivity arises from modest diastereofacial differences in electrophilic attack on an acyclic conformer. A modest decrease in stereoselectivity occurs as the steric demand of the α-substituent changes from a methyl to phenyl group (Table 3, compare entries 2 and 3).

Alkylations of the *tert*-butyl δ-hydroxynitrile **21c** are increasingly selective in the series *iso*-propyl iodide, propyl iodide, propargyl bromide, allyl bromide (Table 3, entries 3–6)—almost opposite the order for the γ-hydroxynitrile **4a** (Table 1). Acylating **21c** with methyl cyanoformate affords a 3.5:1 ratio of bis-acylated nitrile diastereomers with acylation on both oxygen and carbon,

Table 3
Diastereoselective alkylations of δ-hydroxynitriles

Entry	δ-Hydroxyl nitrile	Electrophile	Quaternary nitrile	Yield % (dr)
1				93 (2.5:1)
2				64 (4.0:1)
3				90 (2.7:1)
4				88 (1.4:1)
5				85 (5.9:1)
6				86 (3.7:1)
7				62 (3.5:1)

favoring **22ga** with the same relative configuration as for alkylations with alkyl halides. The bis-acylation of **21c** and the absence of electrophile-dependent diastereoselectivity, are consistent with reaction from an acyclic magnesiated nitrile rather than a cyclic magnesiate.[39] At a minimum, the modest selectivities suggest that the magnesiated nitriles derived from γ- and δ-hydroxynitriles have significantly different structural integrity.

3. Conclusion

γ- and δ-Hydroxynitriles undergo double deprotonation–alkylations that efficiently install nitrile-bearing, quaternary centers. The alkylations of δ-hydroxynitriles are typically highly diastereoselective with the stereochemistry being dependent on the nature of the electrophile; alkyl halides install the alkyl group *syn* to the hydroxyl whereas reactive carbonyl electrophiles alkylate nonselectively. In contrast, less reactive ester and carbonate electrophiles selectively install the carbonyl *anti* to the hydroxyl group.

Mechanistically the alkylations of γ-hydroxynitriles are consistent with forming a highly unusual, nitrile-stabilized magnesiate that incorporates a Grignard-derived alkyl group. Alkylations with ester electrophiles afford dihydroxynitriles arising from an extremely selective reduction of the intermediate ketones triggered by β-hydride elimination within the magnesiate. Comparable alkylations and acylations of the homologous δ-hydroxynitriles exhibit modest stereoselectivities that suggest alkylation through an acyclic conformation with significantly different structural integrity to that derived from γ-hydroxynitriles. Collectively these alkylations are the first electrophile-dependent alkylations of *acyclic* nitriles, exhibit a unique influence on the nature of the Grignard used for the deprotonation, demonstrate an unusual acylation–reduction in acylations with esters, and address the challenge of installing quaternary centers in conformationally mobile, acyclic nitriles.

4. Experimental

4.1. (2*RS*,4*SR*)- and (2*SR*,4*SR*)-4-Hydroxy-5,5-dimethyl-2-propylhexanenitrile (4b)

Modifying a known procedure,[17] neat pentanenitrile (2.75 mL, 31.5 mmol) was added to a −78 °C THF solution (30 mL) of LDA prepared from diisopropylamine (4.52 mL, 32.3 mmol) and butyllithium (32.1 mmol). After 45 min, neat 3,3-dimethyl-1,2-epoxybutane (4.00 mL, 32.5 mmol) was added and then the cooling bath was removed. After 1 h, the solution was cooled to −78 °C, solid NH_4Cl (2.21 g, 41.3 mmol) was added, followed after 20 min, by an aqueous solution of 2 M HCl (50 mL). The resultant solution was allowed to warm to rt overnight, the phases were separated, and then the aqueous phase was extracted with ether. The combined organic phase was dried (Na_2SO_4) and then the solvent was removed under reduced pressure to yield an oil that was purified by flash chromatography (95:5, hexanes/EtOAc) to yield 3.35 g (58% yield) of **4b** as an oily mixture of diastereomers: IR (neat): 3471, 2240 cm^{-1}. Careful chromatography provided a small, pure, sample of each diastereomer for ^1H NMR analysis. Major isomer: ^1H NMR (500 MHz, $CDCl_3$): δ 3.52 (br d, J=10.5 Hz, 1H), 3.30 (m, 1H), 2.96–2.90 (m, 1H), 1.76–1.48 (m, 12H), 0.99–0.95 (m, 6H), 0.92 (s, 9H). Minor isomer: ^1H NMR (500 MHz, $CDCl_3$): δ 3.30 (m, 1H), 2.82–2.79 (m, 1H), 1.76–1.48 (m, 12H), 0.99–0.95 (m, 6H), 0.91 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 123.13, 122.40, 77.15, 76.80, 34.94, 34.82, 34.24, 33.90, 33.11, 28.96, 28.43, 25.40, 20.47, 20.32, 13.62, 13.58. HRMS (ESI) m/z calcd for $C_{11}H_{21}NONa$ (M+Na) 206.1521, found 206.1532.

4.2. General alkylation procedure

A THF solution of *i*-PrMgCl (5.0 equiv, 2.0 M solution) was added to a −78 °C, THF solution of the hydroxynitrile (1 equiv). After 5 min, the cold bath was removed and the reaction mixture was allowed to warm up to rt. After 30 min, the reaction mixture was cooled to −78 °C, neat electrophile (5–10 equiv) was added, and then the cooling bath was removed. After 16 h a saturated, aqueous solution of NH_4Cl was added, the phases were separated, and the aqueous phase was extracted three times with EtOAc. The combined organic extracts were dried over Na_2SO_4, concentrated, and purified by either silica gel column chromatography (230–400 mesh) or radial chromatography, to afford analytically pure material.

*4.2.1. (2RS,4SR)- and (2RS,4RS)-4-Hydroxy-2,5,5-trimethyl-2-propylhexanenitrile (**6aa** and **6ab**, respectively).* Performing the general procedure using nitrile **4a**[17] (57.1 mg, 0.368 mmol), *i*-PrMgCl (0.92 mL, 1.84 mmol), and PrI (0.36 mL, 3.70 mmol) gave a crude product that was purified by radial chromatography (95:5, hexanes/EtOAc) to afford 66.1 mg (91% yield) of **6a** (16.2:1 ratio of diastereomers **6aa** and **6ab**, respectively) as a colorless oil spectrally identical to material previously isolated.[16] Alternate procedure using MeMgCl as the base: performing the general procedure with nitrile **4a**[17] (65.1 mg, 0.419 mmol), MeMgCl (0.70 mL, 2.10 mmol), and PrI (0.50 mL, 5.14 mmol) gave a crude product that was purified by radial chromatography (95:5, hexanes/EtOAc) to afford 46.1 mg (56% yield) of pure **6a** as an oily mixture of diastereomers in a 2.5:1 ratio of **6aa** and **6ab**, respectively. Preparation of **6aa** by hydrogenating **6ea**: a methanolic solution (15 mL) of hydroxynitrile **6ea** (44.2 mg, 0.229 mmol) was hydrogenated for 4 h in a Parr shaker at 50 psi using 5% Pd/C (6.3 mg, 0.059 mmol). The reaction mixture was then concentrated, the crude product was redissolved in EtOAc, and then passed through a short pad of silica gel to afford 42.5 mg (94% yield) of pure **6aa** as a colorless oil. Preparation of **6aa** by hydrogenating **6fa**: a MeOH solution (15 mL) of hydroxynitrile **6fa** (75.4 mg, 0.386 mmol) was hydrogenated for 4 h in a Parr shaker at 50 psi using 5% Pd/C (5.1 mg, 0.048 mmol). The reaction mixture was then concentrated, the residue redissolved in EtOAc, and then passed through a short pad of silica gel to afford 67.1 mg (88% yield) of pure **6aa**.

*4.2.2. (2RS,4SR)-4-Hydroxy-2,5,5-trimethyl-2-propylhexanenitrile (**6aa** and **6ab**, respectively).* Performing the general procedure with nitrile **4b**[17] (101.5 mg, 0.554 mmol), *i*-PrMgCl (1.39 mL, 2.78 mmol), and methyl iodide (0.35 mL, 5.62 mmol) gave a crude product that was purified by radial chromatography (90:10, hexanes/EtOAc) to afford 103.9 mg (95% yield) of **6a** (9.4:1 ratio of diastereomers **6aa** and **6ab**, respectively) spectrally identical to material previously isolated.[16]

*4.2.3. (2RS,4SR)- and (2RS,4RS)-4-Hydroxy-2-isopropyl-2,5,5-trimethylhexanenitrile (**6ba** and **6bb**, respectively).* Performing the general procedure using nitrile **4c**[17] (94.5 mg, 0.52 mmol), *i*-PrMgCl (1.29 mL, 2.58 mmol), and methyl iodide (1.00 mL, 16.1 mmol) gave a crude product that was purified by radial chromatography employing (90:10, hexanes/EtOAc) to afford 96.6 mg (95% yield) of **6b** (8.0:1 ratio of diastereomers **6ba** and **6bb**, respectively) as a colorless oil: IR (neat): 3489, 2254 cm^{-1}.[40] Careful chromatography provided a small, pure, sample of each diastereomer for ^1H NMR analysis. For **6ba**: ^1H NMR (500 MHz, $CDCl_3$): δ 3.58–3.55 (m, 1H), 1.95–1.87 (m, 1H), 1.84–1.82 (m, 1H), 1.72 (dd, J=8.5, 14.0 Hz, 1H), 1.59–1.58 (m, 2H), 1.38 (s, 3H), 1.08 (d, J=6.5 Hz, 3H), 1.03 (d, J=6.5 Hz, 3H), 0.92 (s, 9H). For **6bb**: ^1H NMR (500 MHz, $CDCl_3$): δ 3.51–3.47 (m, 1H), 1.95–1.87 (m, 1H), 1.84–1.82 (m, 1H), 1.72 (dd,

J=8.5, 14.0 Hz, 1H), 1.59–1.58 (m, 2H), 1.38 (s, 3H), 1.08 (d, J=6.5 Hz, 3H), 1.03 (d, J=6.5 Hz, 3H), 0.92 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 124.8, 124.6, 77.3, 76.3, 40.7, 39.5, 38.8, 38.1, 35.4, 35.3, 25.4, 25.4, 21.2, 20.9, 18.3, 17.4, 17.2. HRMS (ESI)[40] m/z calcd for $C_{12}H_{23}NONa$ (M+Na) 220.1677, found 220.1682. Performing the general procedure using nitrile **4a**[17] (128.0 mg, 0.83 mmol), *i*-PrMgCl (2.06 mL, 4.12 mmol), and *iso*-propyl iodide (1.00 mL, 10.0 mmol) gave a crude product that was purified by radial chromatography (95:5, hexanes/EtOAc) to afford 76.5 mg (47% yield) of **6b** (5.5:1 ratio of diastereomers **6bb** and **6ba**, respectively) as a colorless oil.

*4.2.4. (2RS,4SR)- and (2SR,4SR)-4-Hydroxy-2,5,5-trimethyl-2-(trideuteromethyl)hexanenitrile (**6ca** and **6cb**, respectively).* Performing the general procedure using nitrile **4a**[17] (128.4 mg, 0.83 mmol), *i*-PrMgCl (2.07 mL, 4.14 mmol), and CD_3I (1.00 mL, 16.1 mmol) gave a crude product that was purified by radial chromatography (90:10, hexanes/EtOAc) to afford 136.8 mg (96% yield) of **6ca** (7.5:1 ratio of diastereomers **6ca** and **6cb**, respectively) as a colorless oil: IR (neat): 3499, 2235 cm^{-1}.[40] For **6ca**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.51 (dd, J=9.3, 2.0 Hz, 1H), 1.72 (dd, J=14.5, 2.0 Hz, 1H), 1.68 (d, J=4.5 Hz, 1H), 1.55 (dd, J=14.5, 9.3 Hz, 1H), 1.45 (s, 3H), 0.92 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 125.6, 76.9, 42.4, 35.1, 31.2, 27.5, 25.3. For (2*SR*,4*SR*)-**6c**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.51 (dd, J=9.3, 2.0 Hz, 1H), 1.72 (dd, J=14.5, 2.0 Hz, 1H), 1.68 (d, J=4.5 Hz, 1H), 1.55 (dd, J=14.5, 9.3 Hz, 1H), 1.39 (s, 3H), 0.92 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 125.6, 76.9, 42.4, 35.1, 31.2, 27.5, 25.3. HRMS (ESI)[40] m/z calcd for $C_{10}H_{16}D_3NONa$ (M+Na) 195.1553, found 195.1542.

*4.2.5. (2RS,4SR)- and (2SR,4SR)-2-Ethyl-4-hydroxy-2,5,5-trimethylhexanenitrile (**6da** and **6db**, respectively).* Performing the general procedure with nitrile **4a**[17] (76.4 mg, 0.492 mmol), *i*-PrMgCl (1.24 mL, 2.48 mmol), and ethyl iodide (1.00 mL, 12.5 mmol) gave a crude product that was purified by radial chromatography (95:5, hexanes/EtOAc) to afford 73.9 mg (82% yield) of **6d** (6.5:1 ratio of diastereomers **6da** and **6db**, respectively) as a light yellow oil: IR (neat): 3462, 2235 cm^{-1}.[40] For **6da**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.56–3.52 (m, 1H), 1.82–1.70 (m, 3H), 1.54 (dd, J=7.6, 14.0 Hz, 1H), 1.48–1.41 (m, 1H), 1.41 (s, 3H), 1.08 (t, J=7.4 Hz, 3H), 0.92 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 124.7, 76.9, 40.6, 36.7, 35.3, 33.0, 25.3, 24.3, 9.2. For (2*SR*,4*SR*)-**6d**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.50–3.48 (m, 1H), 1.82–1.70 (m, 3H),1.66–1.60 (m, 1H), 1.48–1.41 (m, 1H), 1.35 (s, 3H), 1.08 (t, J=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 124.9, 76.4, 40.9, 36.0, 35.2, 33.0, 25.4, 23.8, 9.2. HRMS (ESI)[40] m/z calcd for $C_{11}H_{21}NONa$ (M+Na) 206.1521, found 206.1533.

*4.2.6. (2SR,4SR)-4-Hydroxy-2-((RS)-1-hydroxy-2-methylpropyl)-2,5,5-trimethylhexanenitrile (**8aa**).* Performing the general procedure with nitrile **4a**[17] (112.1 mg, 0.722 mmol), *i*-PrMgCl (1.80 mL, 3.60 mmol), and ethyl isobutyrate (0.49 mL, 3.66 mmol) gave a crude product that was purified by column chromatography (90:10, hexanes/EtOAc) to afford 154.8 mg (90%) of **8aa** as a white crystalline solid (mp 65–67 °C) whose structure was determined by X-ray crystallography:[16] IR (mull): 3385, 3294, 2245 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.12 (br s, 1H), 3.72 (d, J=8.5 Hz, 1H), 3.36 (d, J=2.2 Hz, 1H), 2.53 (br s, 1H), 1.97–2.06 (m, 1H), 1.88 (dd, J=13.5, 1.3 Hz, 1H), 1.69 (dd, J=13.5, 8.5 Hz, 1H), 1.35 (s, 3H), 1.10 (d, J=6.9 Hz), 1.06 (d, J=6.9 Hz, 1H), 0.94 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 123.0, 79.7, 77.0, 43.8, 41.3, 35.1, 30.0, 25.5, 23.7, 21.8, 14.6. HRMS (ESI) m/z calcd for $C_{13}H_{25}NO_2Na$ (M+Na) 250.1783, found 250.1790.

*4.2.7. (2SR,4SR)-2-((RS)-Cyclohexyl(hydroxy)methyl)-4-hydroxy-2,5,5-trimethylhexanenitrile (**8ba**).* Performing the general procedure with nitrile **4a**[17] (78.9 mg, 0.508 mmol), *i*-PrMgCl (1.28 mL, 2.56 mmol), and distilled ethyl cyclohexanecarboxylate (0.43 mL, 2.58 mmol) gave a crude product that was purified by column chromatography (95:5, hexanes/EtOAc) to afford 114.0 mg (84% yield) of **8ba** as a gel: IR (neat): 3359, 3270, 2250 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.16 (br s, 1H), 3.70 (d, J=8.5 Hz, 1H), 3.30 (s, 1H), 2.72 (br s, 1H), 2.03–1.99 (m, 1H), 1.86 (dd, J=14.8, 1.0 Hz, 1H), 1.83–1.76 (m, 2H), 1.68 (dd, J=14.8, 9.5 Hz, 1H), 1.67–1.60 (m, 1H), 1.51 (td, J=8.5, 3.0 Hz, 2H), 1.35 (s, 3H), 1.33–1.15 (m, 5H), 0.94 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 123.2, 80.0, 76.8, 43.7, 41.0, 40.3, 35.1, 31.6, 26.7, 26.1, 26.1, 25.5, 25.1, 23.7. HRMS (ESI) m/z calcd for $C_{16}H_{29}NO_2Na$ (M+Na) 290.2096, found 290.2106.

*4.2.8. (2SR,4SR)-4-Hydroxy-2-((RS)-1-hydroxy-2,2-dimethylpropyl)-2,5,5-trimethylhexanenitrile (**8ca**).* Performing the general procedure with nitrile **4a**[17] (60.1 mg, 0.508 mmol), *i*-PrMgCl (0.97 mL, 1.94 mmol), and distilled ethyl trimethylacetate (0.30 mL, 1.97 mmol) gave a crude product that was purified by column chromatography employing (95:5, hexanes/EtOAc) to afford 22.6 mg (17%) of **9ca**, spectrally identical to material previously isolated,[16] and 59.8 mg (64% yield) of **8ca** as a white powder (mp 83–84 °C): IR (neat): 3296, 2242 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.57 (br d, J=8.8 Hz, 1H), 3.51 (br s, 1H), 2.62 (br s, 1H), 2.06 (dd, J=14.6, 1.2 Hz, 1H), 1.87 (br s, 1H), 1.67 (dd, J=14.6, 9.6 Hz, 1H), 1.50 (s, 3H), 1.14 (s, 9H), 0.94 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 125.2, 80.4, 76.4, 42.3, 39.6, 37.2, 35.4, 28.0, 25.4, 20.5. HRMS (ESI) m/z calcd for $C_{14}H_{27}NO_2Na$ (M+Na) 264.1939, found 264.1948.

*4.2.9. (3SR,5SR)- and (3SR,5RS)-5-(tert-Butyl)-3-methyl-2-oxotetrahydrofuran-3-carbonitrile (**12aa** and **12ab**, respectively).* A THF solution of *i*-PrMgCl (0.38 mL, 0.76 mmol) was added to a −78 °C, THF solution (5 mL) of nitrile **6g**[16] (166.4 mg, 0.632 mmol). After 5 min, neat methyl cyanoformate (0.05 mL, 0.630 mmol) was added and the cooling bath was then removed. After 5 min, saturated, aqueous NH_4Cl was added, the phases separated, and the aqueous phase was then extracted with EtOAc. The combined organic phase was dried (Na_2SO_4), filtered through a short pad of silica gel, and concentrated to afford a crude oil that was used without further purification. The crude nitrile was added to a −40 °C, CH_2Cl_2 solution (3 mL) containing *m*-CPBA (268.7 mg, 1.20 mmol) previously dried over Na_2SO_4[41] and the cooling bath was then removed. After 4 h, saturated, aqueous NH_4Cl was added, the crude mixture was extracted with CH_2Cl_2, the combined organic phase was dried (Na_2SO_4), filtered through a short pad of silica gel, and concentrated to afford 178.4 mg of crude sulfinyl nitrile **15** that was used without further purification. A THF solution of *i*-PrMgCl (0.15 mL, 0.30 mmol) was added to a −78 °C, THF solution (2 mL) of **15** (96.4 mg, 0.286 mmol) and then the cooling bath was removed. After 16 h, saturated, aqueous NH_4Cl was added and the phases were separated. The aqueous phase was extracted with EtOAc, the combined organic phase was dried (Na_2SO_4), and then the mixture was evaporated under reduced pressure to afford an oil. The crude oil was then purified by radial chromatography (98:2, hexanes/EtOAc) to afford 28.9 mg (56% yield) of **12a** (3.4:1 ratio of diastereomers **12aa** and **12ab**, respectively) as a colorless oil spectrally identical to material previously isolated.[16]

*4.2.10. (2RS,4RS) and (2SR,4RS)-4-Hydroxy-2-isopropyl-2-phenylpentanenitrile (**19aa** and **19ab**, respectively).* Performing the general procedure with nitrile **4d**[17] (101.3 mg, 0.578 mmol), *i*-PrMgCl (1.45 mL, 2.90 mmol), and *i*-PrI (1 mL, 10.02 mmol) gave a crude product that was purified by column chromatography (90:10, hexanes/EtOAc) to afford 116.2 mg (93% yield) of **19a** (2.45:1 ratio of diastereomers **19aa** and **19ab**, respectively) as a colorless oil exhibiting spectral data analogous to that reported previously.[38] Performing the general procedure with nitrile **4d**[17] (150.0 mg, 0.856 mmol), *i*-PrMgCl (2.14 mL, 4.28 mmol), and *i*-PrOTs[42] (1.28 g, 5.97 mmol) gave a crude product that was purified by column chromatography (90:10, hexanes/EtOAc) to afford 185.7 mg (95%

yield) of **19a** (2.13:1 ratio of diastereomers **19aa** and **19ab**, respectively) as a colorless oil exhibiting spectral data analogous to that reported previously.[38] Performing the general procedure with nitrile **4d** (205.0 mg, 1.170 mmol), *i*-PrMgCl (2.92 mL, 5.84 mmol), and *i*-PrBr (1 mL, 10.7 mmol) gave a crude product that was purified by column chromatography (90:10, hexanes/EtOAc) to afford 229.6 mg (90% yield) of **19a** (1.78:1 ratio of diastereomers **19aa** and **19ab**, respectively) as a colorless oil exhibiting spectral data analogous to that reported previously.[38]

*4.2.11. (2RS,5RS)- and (2SR,5RS)-5-Hydroxy-2-phenylhexanenitrile (**21a**).*[43] Solid $NaBH_4$ (1.52 g, 40.18 mmol) was added in four portions over 30 min to a 0 °C, methanolic solution (15 mL) of 5-oxo-2-phenylhexanenitrile[44] After 1 h, the solvent was removed under reduced pressure, the resultant crude material was dissolved in EtOAc, and then the solution was extracted with saturated, aqueous NH_4Cl. The organic layer was dried (Na_2SO_4), evaporated under reduced pressure to give a crude oil, and the resulting material was purified by column chromatography (70:30, hexanes/EtOAc) to afford 1.86 g of **21a** (98% yield, 1:1 ratio of diastereomers)[45] as a light yellow oil: IR (neat): 3397, 2241 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.37–7.30 (m, 5H), 3.86–3.74 (m, 2H), 2.11–1.91 (m, 3H), 1.61–1.52 (m, 2H), 1.18 (d, J=7.5 Hz, 3H), 1.17 (d, J=7.5 Hz, 3H)*; ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.7, 135.6*, 129.0, 127.9, 127.1*, 127.1, 120.8*, 120.7, 67.3, 66.8*, 37.2, 36.9*, 36.1, 35.8*, 32.3, 31.8*, 23.6, 23.5*. HRMS (ESI) m/z calcd for $C_{12}H_{15}NONa$ (M+Na) 212.1051, found 212.1065.

*4.2.12. (2RS,5SR)- and (2SR,5SR)-5-Hydroxy-6,6-dimethyl-2-phenylheptanenitrile (**21c**).*[46] A THF solution (3 mL) of 4-iodo-2-phenylbutanenitrile (**i**)[47] (1.57 g, 5.80 mmol) was added to a rt, THF suspension (1 mL) of activated zinc[48] (0.488 g, 7.46 mmol). After consumption of the iodide, approximately 4 h, the solution was cooled to 0 °C and a 1 M THF solution of $CuCN\cdot 2LiCl$[48] (7.0 mL, 7.0 mmol) was added. After 5 min, neat pivaloyl chloride (0.86 mL, 6.99 mmol) was added followed, after 1 h, by saturated, aqueous NH_4Cl (50 mL). After 30 min, the phases were separated, the aqueous phase was extracted with Et_2O, the organic phase was combined and then successively washed with saturated, aqueous NaOAc and saturated, aqueous $NaHCO_3$. The organic phase was dried (Na_2SO_4), and then the solvent was removed under reduced pressure to give a crude ketone **ii** that was dissolved in 20 mL of methanol and cooled to 0 °C and then solid $NaBH_4$ (0.88 g, 23.3 mmol) was added in one portion. After 1 h, the methanol was evaporated, the residue was dissolved in EtOAc, and the organic phase was then washed with saturated, aqueous NH_4Cl. The organic phase was dried (Na_2SO_4), the solvent was removed under reduced pressure, and the resulting crude oil was purified by column chromatography (90:10, hexanes/EtOAc) to afford 912.5 mg (68% overall yield) of **21c** (1:1 ratio of diastereomers) as a light yellow oil: IR (neat): 3502, 2234 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.41–7.31 (m, 5H), 3.91–3.84 (m, 1H), 3.22 (m, 1H), 2.26–2.15 (m, 1H), 1.99–1.87 (m, 1H), 1.82–1.65 (m, 1H), 1.52–1.33 (m, 2H), 0.90 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$):47 δ 136.0, 135.9*, 129.0, 127.9*, 127.2, 127.1*, 121.0, 120.8*, 79.5, 78.8*, 37.5, 36.9*, 35.0, 33.8, 33.2*, 28.9, 28.4*, 25.5. HRMS (ESI) m/z calcd for $C_{15}H_{21}NONa$ (M+Na) 254.1521, found 254.1509.

*4.2.13. (2RS,5RS)- and (2SR,5RS)-5-Hydroxy-2-phenyl-2-propylhexanenitrile (**22aa** and **22ab**, respectively).* Performing the general procedure with nitrile **21a** (206.0 mg, 1.09 mmol), *i*-PrMgCl (2.72 mL, 5.54 mmol), and PrI (1.0 mL, 10.3 mmol) gave a crude product that was purified by column chromatography (70:30, hexanes/EtOAc) to afford 234.7 mg (93% yield) of **22a** (2.5:1 ratio of diastereomers **22aa** and **22ab**, respectively)[49] as a colorless oil: IR (neat): 3478, 2253 cm^{-1}.[40] For **22aa**: ^1H NMR (500 MHz, $CDCl_3$): δ 7.41–7.35 (m, 3H), 7.32–7.27 (m, 2H), 3.81–3.74 (m, 1H), 2.14–1.85 (m, 6H), 1.63–1.42 (m, 2H), 1.34–1.16 (m, 1H), 1.14 (d, J=6.5 Hz, 3H), 0.88 (t, J=7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.2, 128.8, 127.5, 125.8, 122.5, 67.5, 47.9, 43.5, 37.0, 34.5, 23.5, 18.5, 13.8. For **22ab**: ^1H NMR (500 MHz, $CDCl_3$): δ 7.41–7.35 (m, 4H), 7.32–7.27 (m, 1H), 3.73–3.68 (m, 1H), 2.21 (ddd, J=13.5, 5.0, 4.5 Hz, 1H), 1.14 (d, J=6.5 Hz, 3H), 0.88 (t, J=7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.4, 128.8, 127.5, 125.8, 122.4, 67.4, 47.9, 43.1, 36.9, 34.6, 23.4, 18.5, 13.8. HRMS (ESI) m/z calcd for $C_{14}H_{21}NONa$ (M+Na) 254.1521, found 254.1527.

*4.2.14. (2RS,5SR)- and (2SR,5SR)-5-Hydroxy-2,6,6-trimethyl-2-propylheptanenitrile (**22ba** and **22bb**, respectively).* Performing the general procedure with nitrile **vi**[50] (76.9 mg, 0.495 mmol), *i*-PrMgCl (1.24 mL, 2.48 mmol), and MeI (0.04 mL, 0.643 mmol) afforded crude **21b** that was filtered through a small plug of silica and used without further purification. Employing the general procedure with nitrile **21b** (85.6 mg, 0.506 mmol), *i*-PrMgCl (1.27 mL, 2.54 mmol), and PrI (1 mL, 10.3 mmol) afforded a crude product that was purified by column chromatography (95:5, hexanes/EtOAc) to give 68.6 mg (64% yield based on **21b**) of **22b** (4.0:1 ratio of diastereomers **22ba** and **22bb**, respectively)[51] as a colorless oil: IR (neat): 3486, 2234 cm^{-1}. For **22ba**: ^1H NMR (500 MHz, $CDCl_3$): δ 3.19 (br d, J=10.5 Hz, 1H), 1.81 (ddd, J=12.5, 4.5, 4.5 Hz, 1H), 1.74–1.65 (m, 1H), 1.63–1.36 (m, 7H), 1.30 (s, 3H), 0.97 (t, J=7.0 Hz, 3H), 0.92 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 124.6, 80.0, 42.2, 37.2, 36.6, 35.1, 25.6, 23.7, 18.2, 14.1. For **22bb**: ^1H NMR (500 MHz, $CDCl_3$): δ 3.17–3.14 (m, 1H), 1.98 (ddd, J=12.5, 4.5, 4.0 Hz, 1H), 1.74–1.36 (m, 8H), 1.32 (s, 3H), 0.97 (t, J=7.0 Hz, 3H), 0.92 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 124.5, 80.0, 41.3, 37.3, 36.7, 35.1, 26.7, 24.3, 18.1, 14.1. HRMS (ESI)[40] m/z calcd for $C_{13}H_{25}NONa$ (M+Na) 234.1834, found 234.1823.

*4.2.15. (2RS,5SR)- and (2RS,5RS)-5-Hydroxy-6,6-dimethyl-2-phenyl-2-propylheptanenitrile (**22ca** and **22cb**, respectively).* Performing the general procedure with nitrile **21c** (119.8 mg, 0.518 mmol), *i*-PrMgCl (1.30 mL, 2.60 mmol), and PrI (1.00 mL, 10.3 mmol) gave a crude product that was purified by column chromatography (85:15, hexanes/EtOAc) to afford 127.6 mg (90% yield) of **22c** (2.7:1 ratio of diastereomers **22ca** and **22cb**, respectively) as a colorless oil: IR (neat): 3481, 2240 cm^{-1}.[40] For **22ca**: ^1H NMR (500 MHz, $CDCl_3$): δ 7.42–7.26 (m, 5H), 3.20 (d, J=13.5 Hz, 1H), 2.30 (ddd, J=18.5, 5.5, 2.0 Hz, 1H), 2.03–1.39 (m, 4H), 1.21–0.96 (m, 2H), 0.88 (t, J=9.3 Hz, 3H), 0.81 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.3, 128.8, 127.6, 125.9, 122.8, 79.8, 48.1, 43.9, 38.4, 35.0, 27.1, 25.5, 18.6, 13.9. For **22cb**: ^1H NMR (500 MHz, $CDCl_3$): δ 7.42–7.26 (m, 5H), 3.03–2.98 (m, 1H), 2.43–2.35 (m, 1H), 2.03–0.99 (m, 8H), 0.88 (t, J=9.3 Hz, 3H), 0.80 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.8, 128.8, 127.6, 125.8, 122.5, 80.0, 48.2, 43.0, 38.7, 35.0, 27.3, 25.5, 18.6, 13.9. HRMS (ESI)[40] m/z calcd for $C_{17}H_{27}NONa$ (M+Na) 296.1990, found 296.1974. Preparation of **22ca** by hydrogenation of **22ea**: a methanolic solution (15 mL) of hydroxynitrile **22ea** (75.6 mg, 0.279 mmol) was hydrogenated for 4 h in a Parr shaker at 50 psi using 5% Pd/C (7.0 mg, 0.066 mmol). The reaction mixture was then concentrated, the crude product was redissolved in EtOAc, and then passed through a short pad of silica gel to afford 73.3 mg (96% yield) of pure **22ca** as a colorless oil. Preparation of **22ca** by hydrogenation of **22fa**: a methanolic solution (15 mL) of hydroxynitrile **22fa** (95.5 mg, 0.355 mmol) was hydrogenated for 4 h in a Parr shaker at 50 psi using 5% Pd/C (8.1 mg, 0.076 mmol). The reaction mixture was then concentrated, the crude product was redissolved in EtOAc, and then passed through a short pad of silica gel to afford 92.4 mg (95% yield) of pure **22ca** as a colorless oil.

*4.2.16. (2SR,5SR)- and (2SR,5RS)-5-Hydroxy-2-isopropyl-6,6-dimethyl-2-phenylheptanenitrile (**22da** and **22db**, respectively).* Performing the

general procedure with nitrile **21c** (105.1 mg, 0.454 mmol), *i*-PrMgCl (1.14 mL, 2.28 mmol), and *i*-PrI (1 mL, 10.0 mmol) gave a crude product that was purified by column chromatography (90:10, hexanes/EtOAc) to afford 109.8 mg (88% yield) of **22d** (1.4:1 ratio of diastereomers **22da** and **22db**, respectively)[51] as a colorless oil: IR (neat): 3472, 2236 cm^{-1}. For **22da**: ^1H NMR (500 MHz, $CDCl_3$): δ 7.40–7.27 (m, 5H), 3.21 (dd, J=5.5, 2.0 Hz, 1H), 2.59–2.49 (m, 1H), 2.16–2.08 (m, 3H), 1.81 (ddd, J=11.0, 4.5, 2.5 Hz, 1H), 1.36–1.21 (m, 2H), 1.21 (d, J=7.5 Hz, 3H), 0.96–0.85 (m, 2H), 0.78 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.1, 128.7, 127.5, 126.4, 121.5, 80.1, 53.7, 38.2, 35.2, 27.7, 25.5, 18.9, 18.60. For **22db**: ^1H NMR (500 MHz, $CDCl_3$): δ 7.40–7.27 (m, 5H), 2.96 (dd, J=7.5, 2.0 Hz, 1H), 2.26 (ddd, J=11.0, 4.0, 2.0 Hz, 1H), 1.60–1.52 (m, 1H), 1.36–1.21 (m, 2H), 1.19 (d, J=7.5 Hz, 3H), 0.75 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.9, 128.7, 121.3, 79.8, 53.5, 37.8, 35.0, 27.4, 18.8, 18.5. HRMS (ESI)[40] m/z calcd for $C_{17}H_{27}NONa$ (M+Na) 296.1990, found 296.1984.

*4.2.17. (2SR,5SR)- and (2SR,5RS)-2-Allyl-5-hydroxy-6,6-dimethyl-2-phenylheptanenitrile (**22ea** and **22eb**, respectively).* Performing the general procedure with nitrile **21c** (74.8 mg, 0.323 mmol), *i*-PrMgCl (0.81 mL, 1.62 mmol), and allyl bromide (1 mL, 11.6 mmol) gave a crude product that was purified by column chromatography (85:15, hexanes/EtOAc) to afford 75.0 mg (85% yield) of **22e** (5.9:1 ratio of diastereomers **22ea** and **22eb**, respectively)[52] as a colorless oil: IR (neat): 3479, 2237 cm^{-1}.[40] For **22ea**: ^1H NMR (500 MHz, $CDCl_3$): δ 7.43–7.36 (m, 4H), 7.32–7.28 (m, 1H), 5.70–5.59 (m, 1H), 5.14–5.09 (m, 2H), 3.20 (dd, J=11.0, 2.0 Hz, 1H), 2.67 (d, J=7.0 Hz, 2H), 2.33 (ddd, J=12.5, 4.5, 1.5 Hz, 1H), 2.00 (ddd, J=14.0, 4.5, 2.0 Hz, 1H), 1.69–1.62 (m, 1H), 1.37 (br s, 1H), 1.11–1.02 (m, 1H), 0.82 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.7, 131.8, 128.9, 127.7, 126.1, 122.2, 112.0, 79.7, 47.8, 46.1, 37.2, 35.0, 27.0, 25.5. For **22eb**: ^1H NMR (500 MHz, $CDCl_3$): δ 7.43–7.36 (m, 4H), 7.32–7.28 (m, 1H), 5.70–5.59 (m, 1H), 5.14–5.09 (m, 2H), 3.04–3.00 (m, 1H), 2.44–2.39 (m, 1H), 1.92–1.86 (m, 1H), 1.46–1.00 (m, 5H), 0.81 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.1, 131.7, 128.8, 127.8, 126.0, 122.0, 119.9, 79.9, 47.9, 45.2, 37.6, 35.0, 27.2, 25.5. HRMS (ESI)[40] m/z calcd for $C_{17}H_{25}NONa$ (M+Na) 294.1834, found 294.1863.

*4.2.18. (2SR,5SR)- and (2SR,5RS)-5-Hydroxy-6,6-dimethyl-2-phenyl-2-(prop-2-yn-1-yl)heptanenitrile (**22fa** and **22fb**, respectively).* Performing the general procedure with nitrile **21c** (103.4 mg, 0.447 mmol), *i*-PrMgCl (1.12 mL, 2.24 mmol), and neat propargyl bromide (1 mL, 13.3 mmol) gave a crude product that was purified by column chromatography (90:10, hexanes/EtOAc) to afford 103.2 mg (86% yield) of **22f** (3.7:1 ratio of diastereomers **22fa** and **22fb**, respectively)[52] as a colorless oil: IR (neat): 3495, 3295, 2241, 2226.[40] For **22fa**: ^1H NMR (500 MHz, $CDCl_3$): δ 7.50–7.45 (m, 2H), 7.43–7.31 (m, 2H), 7.36–7.31 (m, 1H), 3.24 (dd, J=10.5, 2.3 Hz, 1H), 2.82 (d, J=2.5 Hz, 2H), 2.42 (ddd, J=12.0, 4.5, 1.5 Hz, 1H), 2.18 (ddd, J=11.5, 4.5, 2.7 Hz, 1H), 2.13 (t, J=2.5 Hz, 1H), 1.72–1.64 (m, 1H), 1.16–1.09 (m, 1H), 0.83 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.0, 129.0, 128.2, 126.0, 121.6, 80.0, 78.1, 72.7, 47.1, 36.2, 35.0, 32.3, 27.1, 25.5. For **22fb**: ^1H NMR (500 MHz, $CDCl_3$): δ 7.50–7.45 (m, 2H), 7.43–7.31 (m, 2H), 7.36–7.31 (m, 1H), 3.09–3.05 (m, 1H), 2.85 (AB_q $\Delta\nu$=27.5 Hz, J=17.0, 2.5 Hz, 1H), 2.60–2.52 (m, 1H), 2.11 (t, J=2.5 Hz, 1H), 2.01–1.94 (m, 3H), 1.52–1.40 (m, 2H), 1.16–1.09 (m, 1H), 0.82 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.7, 128.9, 128.2, 125.9, 121.4, 79.8, 78.2, 72.7, 47.2, 36.6, 35.0, 31.5, 27.3, 25.5. HRMS (ESI)[40] m/z calcd for $C_{17}H_{23}NONa$ (M+Na) 292.1677, found 292.1667.

*4.2.19. (2SR,5SR)- and (2SR,5RS)-Methyl-2-cyano-5-((methoxycarbonyl)oxy)-6,6-dimethyl-2-phenylheptanoate (**22ga** and **22gb**, respectively).* Performing the general procedure with nitrile **21c** (97.5 mg, 0.421 mmol), *i*-PrMgCl (1.05 mL, 2.10 mmol), and methyl cyanoformate (0.27 mL, 3.40 mmol) gave a crude product that was purified by column chromatography (98:2, hexanes/EtOAc) to afford 6.2 mg of **vii** (3.4:1 ratio of diastereomers)[53] as a yellow oil and 91.1 mg (62% yield) of **22g** (3.5:1 ratio of diastereomers **22ga** and **22gb**, respectively) as a colorless oil: IR (neat): 2245, 1719 cm^{-1}. For **22ga**: ^1H NMR (500 MHz, $CDCl_3$): δ 7.55–7.50 (m, 2H), 7.45–7.35 (m, 3H), 4.57 (dd, J=7.5, 3.0 Hz, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 2.39 (m, 1H), 2.26–2.16 (m, 1H), 1.79–1.58 (m, 2H), 0.90 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.9, 156.3, 134.0, 129.3, 129.0, 126.0, 118.1, 85.0, 54.9, 54.0, 53.7, 35.0, 25.9, 25.7. For **22gb**: ^1H NMR (500 MHz, $CDCl_3$): δ 7.55–7.50 (m, 2H), 7.45–7.35 (m, 3H), 4.51–4.45 (m, 1H), 3.80 (s, 3H), 2.51–2.44 (m, 1H), 2.16–2.11 (m, 1H), 1.79–1.58 (m, 2H), 0.90 0.87 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.8, 156.3, 134.0, 129.3, 129.0, 126.0, 118.1, 85.1, 54.9, 54.0, 53.8, 35.1, 35.0, 25.8, 25.6. For *(3RS,6SR)-methyl 6-(tert-butyl)-2-oxo-3-phenyltetrahydro-2H-pyran-3-carboxylate (**vii**)*: ^1H NMR (500 MHz, $CDCl_3$): δ 7.35–7.26 (m, 5H), 4.54 (dd, J=10.5, 2.8 Hz, 1H), 3.81 (s, 3H), 2.78–2.73 (m, 1H), 2.71–2.64 (m, 1H), 1.73–1.58 (m, 2H), 0.85 (s, 9H).

*4.2.20. (3SR,6SR)-6-Methyl-3-phenyl-3-propyltetrahydro-2H-pyran-2-one (**iii**).*[43] A diethylene glycol solution of (2*RS*,5*RS*)- and (2*SR*,5*RS*)-5-hydroxy-2-phenyl-2-propylhexanenitrile (2.5:1 ratio of diastereomers, 448.0 mg, 1.94 mmol) and KOH (548.7 mg, 9.77 mmol) was heated to 250 °C. After 6 h, the mixture was allowed to cool to rt, diluted with ether, and then aqueous 6M HCl (100 mL) was added. The phases were separated, the aqueous phase was extracted with ether, the combined aqueous phase was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure to yield a crude oil that was purified by column chromatography (90:10, hexanes/EtOAc) to afford 360.4 mg (80% yield) of (**iii**) as a yellow oil (2.5:1 ratio of diastereomers): IR (neat): 1725 cm^{-1}. For (3*SR*,6*SR*)-**iii**: ^1H NMR (500 MHz, $CDCl_3$): δ 7.45–7.10 (m, 5H), 4.01–3.94 (m, 1H), 2.58–2.52 (m, 1H), 2.14 (td, J=3.5, 14.0 Hz, 1H), 2.05–1.60 (m, 9H), 1.44–1.33 (m, 1H), 1.31–1.23 (m, 2H), 1.20 (d, J=6.0 Hz, 3H), 1.19–1.05 (m, 3H), 0.89 (t, J=7.0 Hz, 3H), 0.82 (t, J=7.0, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.6, 142.8, 140.2, 128.9, 127.1, 126.3, 78.8, 72.7, 51.8, 44.0, 27.6, 26.4, 22.2, 17.5, 14.4. For (3*SR*,6*RS*)-**iii**: ^1H NMR (500 MHz, $CDCl_3$): δ 7.45–7.10 (m, 5H), 4.51–4.48 (m, 1H), 2.27 (dt, J=14.5, 3.5 Hz, 1H), 1.52–1.45 (m, 1H), 1.27 (d, J=6.0 Hz, 3 H), 0.89 (t, J=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.1, 142.7, 140.0, 128.6, 126.8, 126.0, 50.4, 27.3, 21.5.

*4.2.21. 6,6-Dimethyl-5-oxoheptanenitrile (**v**).* A THF solution (5 mL) of 4-iodobutyronitrile[54] (2.90 g, 14.87 mmol) was added to a rt THF suspension (1 mL) of activated zinc[48] (1.21 g, 18.51 mmol). After consumption of the iodide, approximately 1 h, the solution was cooled to 0 °C and 1 M CuCN·2LiCl[48] (18.50 mL, 18.5 mmol) was added. After 5 min, neat pivaloyl chloride (2.00 mL, 16.3 mmol) was added followed, after 1 h, by saturated, aqueous NH_4Cl (100 mL). After 30 min, the phases were separated, the aqueous phase was extracted with Et_2O, and the combined organic phase was successively washed with saturated, aqueous NaOAc and saturated, aqueous $NaHCO_3$. The organic phase was dried (Na_2SO_4), the solvent was removed under reduced pressure, and the crude ketone was purified by column chromatography (90:10, hexanes/EtOAc) to afford 2.10 g (92% yield) of **(v)** as a pale yellow colored oil: IR (neat): 2246, 1709 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 2.69 (t, J=6.9 Hz, 2H), 2.42 (t, J=6.9 Hz, 2H), 1.92 (quintet, J=6.9 Hz, 2 H), 1.16 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 214.3, 119.3, 44.0, 34.3, 26.3, 19.5, 16.3. HRMS (ESI) m/z calcd for $C_9H_{15}NONa$ (M+Na) 176.1051, found 176.1002.

*4.2.22. 5-Hydroxy-6,6-dimethylheptanenitrile (**vi**).* Solid $NaBH_4$ (1.37 g, 36.2 mmol) was added to a 0 °C methanolic solution (15 mL) of 6,6-dimethyl-5-oxoheptanenitrile (**v**, 1.385 g, 9.04 mmol). After 30 min, the methanol was evaporated under reduced pressure, the crude alcohol was dissolved in EtOAc and then washed with

a saturated, aqueous solution of NH_4Cl. The organic phase was dried (Na_2SO_4), concentrated under reduced pressure, and the resulting crude oil was purified by column chromatography (70:30, hexanes/EtOAc) to afford 1.40 g (>99% yield) of (**vi**) as a light yellow colored oil: IR (neat): 3458, 2248 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 3.22 (br d, J=11 Hz, 1H), 2.46–2.37 (m, 2H), 1.98–1.94 (m, 1H), 1.74–1.68 (m, 2H), 1.43–1.38 (m, 2H), 0.91 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 119.8, 79.1, 35.0, 30.1, 25.5, 23.0, 17.1. HRMS (ESI) m/z calcd for $C_9H_{17}NONa$ (M+Na): 178.1208, found 178.1246.

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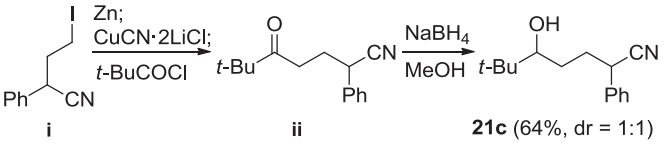
Supplementary data

Experimental procedures, ^1H NMR, and ^{13}C NMR spectra for all new compounds and ORTEPs for all of the crystal structures. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.10.016.

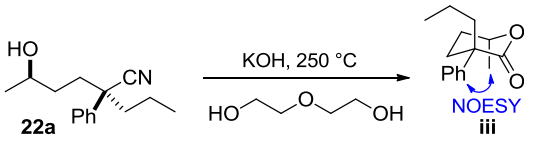
References and notes

1. Kaumanns, O.; Appel, R.; Lemek, T.; Seeliger, F.; Mayr, H. *J. Org. Chem.* **2009**, *74*, 75.
2. The cylindrical diameter of the π-system is only 3.6 Å: Sheppard, W. A. In *The Chemistry of the Cyano Group*; Rappoport, Ed.; Interscience Pub., The University of Virginia: Virginia, 1970, Chapter 5.
3. (a) Richard, J. P.; Williams, G.; Gao, J. *J. Am. Chem. Soc.* **1999**, *121*, 715; (b) Bradamante, S.; Pagani, G. A. *J. Chem. Soc., Perkin Trans. 2* **1986**, 1035; (c) Dayal, S. K.; Ehrenson, S.; Taft, R. W. *J. Am. Chem. Soc.* **1972**, *94*, 9113.
4. The *A* value of a nitrile is a mere 0.2 kcal mol^{-1}: Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley: New York, NY, 1994, pp 696–697.
5. (a) Fleming, F. F.; Shook, B. C. *Tetrahedron* **2002**, *58*, 1; (b) Arseniyadis, S.; Kyler, K. S.; Watt, D. S. *Organic Reactions: Addition and Substitution Reactions of Nitrile-stabilized Carbanions*; Wiley: New York, NY, 1984.
6. (a) Pellissier, H.; Michellys, P. Y.; Santelli, M. *Steroids* **2007**, *72*, 297; (b) Barton, D. H. R.; Bringmann, G.; Motherwell, W. B. *Synthesis* **1980**, 68.
7. For chiral auxiliaries bearing an adjacent nitrile group see: (a) Partogyan-Halim, K.; Besson, L.; Aitken, D. J.; Husson, H.-P. *Eur. J. Org. Chem.* **2003**, 268; (b) Cativiela, C.; Díaz-de-Villegas, D. M.; Galvez, A. J.; Lapena, Y. *Tetrahedron* **1995**, *51*, 5921; (c) Cativiela, C.; Diaz-de-Villegas, D. M.; Galvez, A. J. *J. Org. Chem.* **1994**, *59*, 2497; (d) Hanamoto, T.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 2463; (e) Maigrot, N.; Mazaleyrat, J.-P.; Welvart, Z. *J. Org. Chem.* **1985**, *50*, 3916.
8. (a) Carlier, P. R.; Lam, F. W.; Wan, C. N.; Williams, D. I. *Angew. Chem., Int. Ed.* **1998**, *37*, 2252; (b) Brunner, H.; Zintl, H. *Monatsh. Chem.* **1991**, *122*, 841; (c) Suto, Y.; Kumagai, N.; Matsunaga, S.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2003**, *5*, 3147; (d) Mi, Q. A.; Wang, Y. Z.; Jiang, Z. Y. *Tetrahedron: Asymmetry* **1993**, *4*, 1957; (e) Soai, K.; Hirose, Y.; Sakata, S. *Tetrahedron: Asymmetry* **1992**, *3*, 677; (f) Soai, K.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 3371.
9. (a) Carlier, P. R.; Zhang, Y. *Org. Lett.* **2007**, *9*, 1319; (b) Fleming, F. F.; Gudipati, S.; Zhang, Z.; Liu, W.; Steward, O. W. *J. Org. Chem.* **2005**, *70*, 3845.
10. (a) Hoffmann, R. W. *Angew. Chem., Int. Ed.* **2000**, *39*, 2054; (b) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1124.
11. (a) Fleming, F. F.; Liu, W.; Ghosh, S.; Steward, O. W. *J. Org. Chem.* **2008**, *73*, 2803; (b) Fleming, F. F.; Liu, W.; Ghosh, S.; Steward, O. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 7098.
12. Fleming, F. F.; Liu, W. *Eur. J. Org. Chem.* **2009**, 699.
13. Mikami, K.; Shimizu, M.; Zhang, H.-C.; Maryanoff, B. E. *Tetrahedron* **2001**, *57*, 2917.
14. For an excellent discussion of related alkylations with chiral organolithiums see: Clayden, J. *Organolithiums: Selectivity for Synthesis*; Pergamon: Amsterdam, 2002, Chapter 6.
15. For the electrophile-dependent alkylations of a related, but cyclic, nitrile see: Fleming, F. F.; Zhang, Z.; Wei, G.; Steward, O. W. *J. Org. Chem.* **2006**, *71*, 1430.
16. For a preliminary account see: Mycka, R. J.; Steward, O. W.; Fleming, F. F. *Org. Lett.* **2010**, *12*, 3030.
17. The hydroxynitriles were prepared by condensing the appropriate lithiated nitrile with an epoxide: Taylor, S. K.; De Young, D.; Simons, L. J.; Vyvyan, J. R.; Wemple, M. A.; Wood, N. K. *Synth. Commun.* **1998**, *28*, 1691; When the reaction was complete, solid NH_4Cl was added, followed after 20 min, by an aqueous solution of 2 M HCl. The latter modification prevents cyclization to the corresponding lactone: Larcheveque, M.; Debal, A. *Synth. Commun.* **1980**, *10*, 49.
18. Deprotonating with LDA or BuLi in different solvents and in the presence or absence of HMPA afforded dianions that less efficiently alkylated allyl bromide as a test electrophile.
19. (a) Hauser, C. R.; Humphlett, W. J. *J. Org. Chem.* **1950**, *15*, 359; Deprotonating alkylnitriles is favored in a few situations, particularly for the more acidic phenyl acetonitrile: (b) Fauvarque, J.-F.; Meklati, B.; Dearing, C. *C.R. Chim.* **1968**, *267*, 1162; (c) Ivanov, C.; Markov, P.; Arnaudov, M. *Chem. Ber.* **1967**, *100*, 690; (d) Ivanov, C.; Markov, P.; Arnaudov, M. *Chem. Ber.* **1964**, *97*, 2987.
20. Prior to the deprotonation, the molarity of *i*-PrMgCl was determined by titration: Krasovskiy, A.; Knochel, P. *Synthesis* **2006**, 890.
21. Sasaki, M.; Takegawa, T.; Ikemoto, H.; Kawahata, M.; Yamaguchi, K.; Takeda, K. *Chem. Commun.* **2012**, 2897.
22. For an excellent overview of terms, steric constraints, and orbital overlap see: Gawley, R. E. *Tetrahedron Lett.* **1999**, *40*, 4297.
23. The relative configurations of the hydroxynitriles **6** were determined through a combination of NOE, NOESY, and chemical correlation as described in detail in Supplementary data.
24. Kirby, A. J. *Stereoelectronic Effects*; Oxford University Press: Oxford, 1996, pp 38–40.
25. The authors have deposited the crystallographic data for **8aa** with the Cambridge Crystallographic Data Center (CCDC# 814019). The data can be obtained, on request, from the Director, Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, UK
26. No diastereomers were discernable in the ^1H NMR of the crude reaction mixture.
27. Dunn, G. E.; Warkentin, J. *Can. J. Chem.* **1956**, *34*, 75.
28. Cyclic alkylmagnesium alkoxides react selectively with benzaldehyde, whereas **5** reacts non-selectively, but are not reactive toward activated allylic or benzylic halides unless in the presence of HMPA: Fleming, F. F.; Wang, Q.; Steward, O. W. *J. Org. Chem.* **2003**, *68*, 4235.
29. Cruz, D. C.; Yuste, F.; Díaz, E.; Ortiz, B.; Sánchez-Obregón; Walls, F.; García Ruano, J. L. *Arkivoc* **2005**, *vi*, 211.
30. (a) Layfield, R. A.; Bullock, T. H.; Garcia, F.; Humphrey, S. M.; Schueler, P. *Chem. Commun.* **2006**, 2039; (b) Sakamoto, S.; Imamoto, T.; Yamaguchi, K. *Org. Lett.* **2001**, *3*, 1793.
31. As carbonyl electrophiles react non-selectively or with the opposite sense of diastereoselectivity to alkyl halides,[16] the possibility exists that carbonyl electrophiles react by precoordination whereas alkyl halides react through a non-coordinated process that occurs with opposite diastereoselectivity.
32. Vu, V. A.; Marek, I.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 351.
33. The authors have deposited the crystallographic data for **12aa** with the Cambridge Crystallographic Data Center (CCDC# 814018). The data can be obtained, on request, from the Director, Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, UK.
34. Nath, D.; Fleming, F. F. *Angew. Chem., Int. Ed.* **2011**, *50*, 11790.
35. The diastereomeric ratio refers to the *syn*/*anti* ratio of hydroxyl and phenylsulfide groups. No effort was made to separate the sulfoxide diastereomers resulting from *m*-CPBA oxidation because this stereocenter is cleaved during the magnesium exchange procedure.
36. Presumably, the epimerization of magnesiated nitrile **16** competes with the internal acylation to form **12aa**.
37. The sulfinyl–magnesium exchange of **23** employed 1 equiv of *i*-PrMgCl to avoid *iso*-propyl addition to the lactone by excess *i*-PrMgCl. Consequently **24** is an acylated magnesiated nitrile rather than an acylated nitrile-stabilized magnesiate that would ideally correlate with O-acylation of **18a**.
38. Sold as the isoaminile-cyclamate salt under the name Peracon® Antoneitti, F.; Brenna, E.; Fuganti, C.; Gatti, F. G.; Giovenzana, T.; Grande, V.; Malpezzi, L. *Synthesis* **2005**, 1148.
39. No mechanistic work was pursued after obtaining modest diastereoselectivity in these optimized alkylations.
40. Obtained from a mixture of diastereomers.
41. Kopp, F.; Sklute, G.; Polborn, K.; Marek, I.; Knochel, P. *Org. Lett.* **2005**, *7*, 3789 The procedure is described in Supplementary data SI51.
42. Granander, J.; Sott, R.; Hilmersson, G. *Tetrahedron* **2002**, *58*, 4717.
43. Adjoran, I.; Frobel, K. Process for preparation of tetrahydropyranone derivatives. World Patent WO 2010144937 A2 20101223, Appl., 2010.
44. Protiva, M.; Novak, L.; Borovicka, M. *Collect. Czech. Chem. Commun.* **1962**, *27*, 559.
45. The signals for the individual diastereomers were not unequivocally distinguished and therefore the signals assigned to one diastereomer are designated with an asterisk.
46. The following sequence was used to prepare **21c** from 4-iodo-2-phenylbutanenitrile (i):[47]

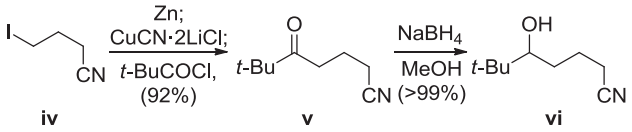


47. Cheng, C. Y.; Lu, H. Y.; Lee, F. M.; Tam, S. W. *J. Pharm. Sci.* **1990**, *79*, 758.
48. Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390.

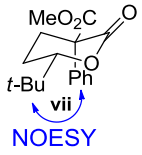
49. The relative configuration was determined by cyclizing, and hydrolyzing hydroxynitrile **22a** to the corresponding lactone **iii** whose configuration was assigned from NOESY correlations.



50. Nitrile **vi** was prepared from 4-iodobutanenitrile (**iv**) by sequentially reacting the mixed cuprate derived from **iv** with pivaloyl chloride and reducing the resulting halonitrile with $NaBH_4$ to afford **vi**.[48]



51. The configuration is based on a correlation with diagnostic spectral patterns in the diastereomers of **22c** and **22c′**.
52. Hydrogenation of the major diastereomer afforded **32c** allowing the configuration to be assigned.
53. Lactone **vii** likely arises through acylation and cyclization of hydroxynitrile **21c** followed by hydrolysis. Separation of the major lactone diastereomer provided a sample for NOSEY from which the relative stereochemistry was obtained.



54. Powell, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 7788.