Unsaturated Nitriles: Stereoselective MgO Eliminations

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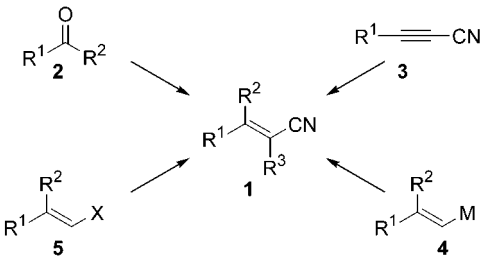
α,β-Unsaturated nitriles are readily synthesized by eliminating MgO from β-hydroxynitriles. Deprotonating acyclic, and cyclic, β-hydroxynitriles with excess MeMgCl smoothly generates dianion intermediates that eject MgO with concurrent formation of α,β-unsaturated nitriles. Alternatively, sequential addition of lithioacetonitrile and $MgBr_2$ to aldehydes and ketones generates magnesium alkoxides in situ that eliminate MgO upon addition of MeMgCl. The MeMgCl-induced MgO eliminations smoothly generate α,β-unsaturated nitriles from hindered ketones that are otherwise difficult to synthesize.

Introduction

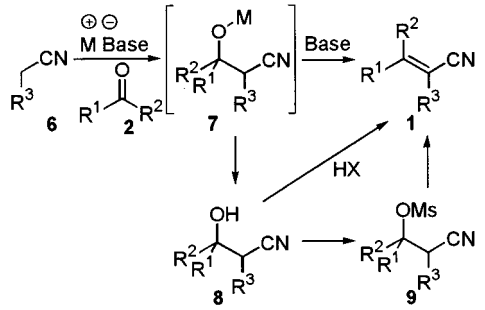
α,β-Unsaturated nitriles occupy a unique niche as synthetic intermediates.[1] Unsaturated nitriles are highly polarized by virtue of the exceptional inductive electron withdrawal of the nitrile unit,[2] and yet the nitrile group is a relatively poor electrophile that has been incorporated within organolithium[3] and Grignard[4] reagents. The unique reactivity of α,β-unsaturated nitriles, and the continued isolation of nitrile-containing natural products,[5] requires increasingly versatile syntheses to augment the current methods of assembling unsaturated nitriles.[6]

Four general strategies have emerged for synthesizing α,β-unsaturated nitriles (Scheme 1):[6] condensations with carbonyl compounds (**2** → **1**);[7] conjugate additions, or reductions, of alkynenitriles (**3** → **1**);[8] cyanide coupling of vinyl halides and triflates (**4** → **1**);[9] and cyanation of vinyl anions (**5** → **1**).[10] Of these four strategies, the availability of carbonyl precursors has predisposed most α,β-unsaturated nitrile syntheses to condensations of nitrile anions with aldehydes and ketones.

Scheme 1



Scheme 2



Nitrile anions rapidly react with carbonyl electrophiles to generate β-alkoxy nitriles (**7**, Scheme 2).[11] Intermediate β-alkoxy nitriles[12] containing phosphorus[13] (**7**, R = PPh_3) and silicon[14] (**7**, $R^3 = SiMe_3$) substituents directly eliminate the corresponding oxides, providing α,β-unsaturated nitriles in a single synthetic operation.

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(2) (a) Bradamante, S.; Pagani, G. A. *J. Chem. Soc., Perkin Trans. 2* **1986**, 1035. (b) Dayal, S. K.; Ehrenson, S.; Taft, R. W. *J. Am. Chem. Soc.* **1972**, *94*, 9113.

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(5) Fleming, F. F. *Nat. Prod. Rep.* **1999**, *16*, 597.

(6) Kiefel, M. J. In *Comprehensive Organic Functional Group Transformations*; Katritzky, A. R., Meth-Cohn, O., Rees, C. W. Eds.; Pergamon: Cambridge, U.K., 1995; Vol. 3, pp 641−676.

(7) For leading references see: (a) Kisanga, P.; D'Sa, B.; Verkade, J. *J. Org. Chem.* **1998**, *63*, 10057. (b) DiBiase, S. A.; Lipisko, B. A.; Haag, A.; Wolak, R. A.; Gokel, G. W. *J. Org. Chem.* **1979**, *44*, 4640.

(8) (a) Kleijn, H.; Westmijze, H.; Meijer, J.; Vermeer, P. *J. Organomet. Chem.* **1981**, *206*, 257. (b) Westmijze, H.; Kleijn, H.; Vermeer, P. *Tetrahedron Lett.* **1979**, 3327. (c) Westmijze, H.; Kleijn, H.; Vermeer, P. *Synthesis* **1979**, 430. (d) Westmijze, H.; Kleijn, H.; Vermeer, P. *Synthesis* **1978**, 454.

(9) For leading references see: (a) Sakakibara, Y.; Enami, H.; Ogawa, H.; Fujimoto, S.; Kato, H.; Kunitake, K.; Sasaki, K.; Sakai, M. *Bull. Chem. Soc. J.* **1995**, *68*, 3137. (b) Piers, E.; Fleming, F. F. *Can. J. Chem.* **1993**, *71*, 1867.

(10) (a) Hughes, T. V.; Cava, M. P. *J. Org. Chem.* **1999**, *64*, 313. (b) Klement, I.; Lennick, K.; Tucker, C. E.; Knochel, P. *Tetrahedron Lett.* **1993**, *34*, 4623. (c) Murray, R. E.; Zweifel, G. *Synthesis* **1980**, 150.

(11) In some instances the condensation is reversible: (a) Carlier, P. R.; Lo, C. W.-S.; Lo, M. M.-C.; Wan, N. C.; Williams, I. D. *Org. Lett.* **2000**, *2*, 2443. (b) Carlier, P. R.; Lam, W. W.-F.; Wan, N. C.; Williams, I. D. *Angew. Chem.* **1998**, *37*, 2252.

(12) For leading references to the synthesis of β-hydroxy nitriles see: (a) Xiao, Z.; Timberlake, J. W. *Tetrahedron* **1998**, *54*, 4211. (b) Reference 11.

(13) (a) Guita, E.-M.; Seyden-Penne, J. *Synth. Commun.* **1984**, *14*, 565. (b) Loupy, A.; Sogadji, K.; Seyden-Penne, J. *Synthesis* **1977**, 126. (c) D'Incan, E.; Seyden-Penne, J. *Synthesis* **1975**, 516. For an excellent *cis*-selective synthesis see: Takayanagi, H. *Tetrahedron Lett.* **1994**, *35*, 1581.

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Condensations of nitrile anions with aromatic aldehydes and ketones similarly generate unsaturated nitriles in a single operation since the intermediate β-hydroxynitriles **8** readily dehydrate upon exposure to mild acid or base (**8** → **1**, Scheme 2).[15] Aliphatic β-hydroxynitriles dehydrate less readily[16] and require conversion to the corresponding mesylate[17] (**9**) to promote the elimination (Scheme 2).

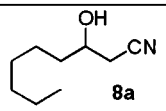
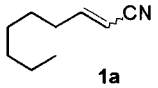
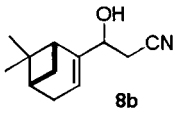
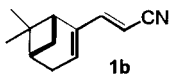
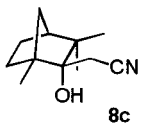
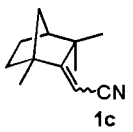
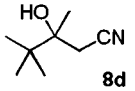
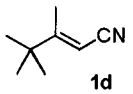
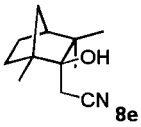
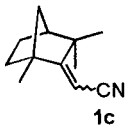
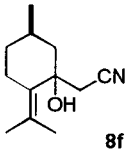
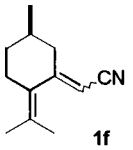
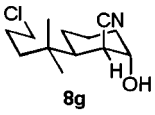
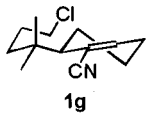
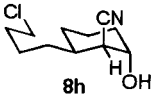
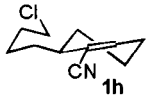
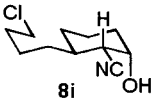
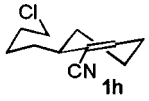
Results and Discussion

Conceptually, the simplest α,β-unsaturated nitrile synthesis is the consecutive nitrile anion addition−metal oxide[18] elimination (**7** → **1**, Scheme 2). The idealistic conception of ejecting metal oxides is well precedented,[18] particularly for dianion-induced eliminations of magnesium oxide.[19] The predominance of MgO eliminations likely reflects the highly covalent character of the Mg−O bond[20] that facilitates alkene formation.

Elimination of MgO from β-hydroxynitriles provides an attractive synthesis of α,β-unsaturated nitriles.[21] β-Hydroxynitriles are readily synthesized[12] and the robust nitrile group is well-suited to vigorous treatment with strong base. The low electrophilicity of nitriles, combined with the ease of magnesium oxide elimination, suggests Grignard reagents as ideal bases for the sequential deprotonation of hydroxy nitriles and the subsequent MgO elimination.

Preparative MeMgCl-induced elimination of MgO from β-hydroxynitriles provides a general, high-yielding synthesis of α,β-unsaturated nitriles (Table 1). The MgO elimination effectively assembles a variety of acyclic (Table 1, entries 1 and 4), exocyclic (Table 1, entries 3, 5, and 6) and endocyclic unsaturated nitriles[22] (Table 1, entries 7−9). Addition of MeMgCl at −78 °C followed by warming to room temperature smoothly generates the unsaturated nitriles with only the more demanding eliminations requiring higher reaction temperatures (Table 1, entries 3, 5, 8, and 9). Eliminations of the less-substituted secondary β-hydroxynitriles **8a** and **8b**, require 12 and 4 h, respectively, at −78 °C prior to warming, presumably allowing formation of the dianion without simultaneously generating any unsaturated nitrile that otherwise participates in deleterious conjugate additions.[23]

Table 1. MgO Elimination of β-Hydroxy Nitriles

Entry	β-Hydroxynitrile	Unsaturated Nitrile	Yield
1	 **8a**	 **1a**	71% 1:1 E:Z
2	 **8b**	 **1b**	84%
3[a]	 **8c**	 **1c**	91% 5:1 E:Z
4	 **8d**	 **1d**	81%
5[a, b]	 **8e**	 **1c**	86% 5:1 E:Z
6[c]	 **8f**	 **1f**	87% 2:1 E:Z
7	 **8g**	 **1g**	92%
8[a]	 **8h**	 **1h**	90%
9[a]	 **8i**	 **1h**	87%

[a] Performed in refluxing THF. [b] Performed with a 5:1 ratio of **8c**:**8e**. [c] Performed with a 2:1 ratio of diastereomeric alcohols **8f**.

The MgO eliminations preferentially afford the more stable α,β-unsaturated nitrile. Unsaturated nitriles with large β-substituents form the *E*-isomers exclusively (Table 1, entries 2 and 4) while the fenchone-derived hydroxy nitriles **8c** and **8e** preferentially eliminate to stagger the nitrile between the two methyl groups, avoiding $A^{1,3}$ strain with the angular methyl group (Table 1, entries 3 and 5). Collectively, the MgO eliminations efficiently provide di- and trisubstituted α,β-unsaturated nitriles, even in hindered environments, that are frequently challenging to construct with conventional Wittig-type reagents.

The successful MgO elimination from β-hydroxynitriles stimulated pursuing a direct conversion of aldehydes and ketones to the corresponding α,β-unsaturated nitriles. Conceptually, formation of the intermediate magnesium alkoxide **11** requires only addition of magnesiated aceto-

(14) (a) Palomo, C.; Aizpurua, J. M.; Aurrekoetxea, N. *Tetrahedron Lett.* **1990**, *31*, 2209. (b) Haruta, R.; Ishiguro, M.; Furuta, K.; Mori, A.; Ikeda, N.; Yamamoto, H. *Chem. Lett.* **1982**, 1093. (c) Matsuda, I.; Murata, S.; Ishii, Y. *J. Chem. Soc., Perkin Trans. 1* **1979**, 26.

(15) Alberghina, G.; Amato, M. E.; Bottino, F. A.; Corsaro, A.; Fisichella, S. *J. Heterocycl. Chem.* **1986**, *23*, 1747. And references therein.

(16) An exception is found in two excellent methods for condensing acetonitrile with aliphatic ketones: Reference 7.

(17) (a) Palomo, C.; Aizpurua, J. M.; López, M. C.; Aurrekoetxea, N. *Tetrahedron Lett.* **1990**, *31*, 2205. (b) Takahashi, A.; Kirio, Y.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1989**, *111*, 643.

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(20) Simanek, E.; Huang, N. L. *Phys. Rev. Lett.* **1966**, *17*, 699.

(21) For a preliminary account see: Fleming, F. F.; Shook, B. C. *Tetrahedron Lett.* **2000**, *41*, 8847.

(22) Fleming, F. F.; Shook, B. C.; Jiang, T.; Steward, O. W. *Org. Lett.* **1999**, *1*, 1547.

(23) Bergmann, E. D.; Ginsburg, D.; Pappo, R. *Org. React.* **1959**, *10*, 179.

Scheme 3

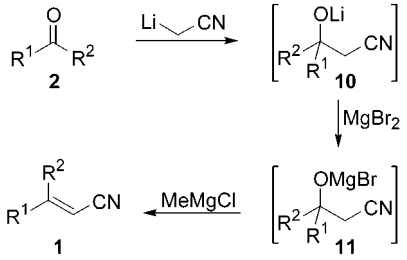
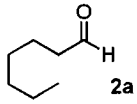
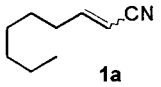
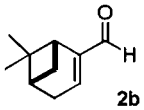
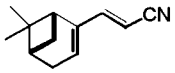
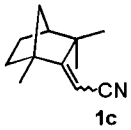
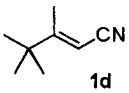
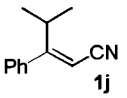


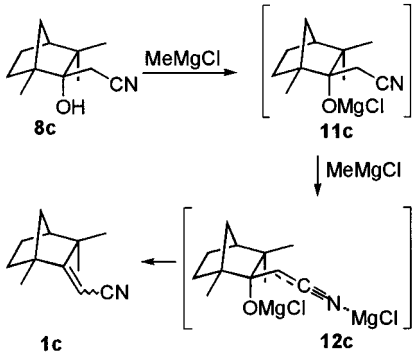
Table 2. Direct Synthesis of Unsaturated Nitriles

Entry	Carbonyl	Product	Yield
1	 **2a**	 **1a**	64% 1:1 E:Z
2	 **2b**	 **1b**	63%
3	 **2c**	 **1c**	67% 1:1 E:Z
4	 **2d**	 **1d**	61%
5	 **2j**	 **1j**	70%

nitrile to an aldehyde or ketone (Scheme 3). Several attempts to employ magnesiated acetonitrile[24] eventually led to a preparatively more expedient method where lithioacetonitrile, prepared from *n*-BuLi and acetonitrile,[25] is added to the aldehyde or ketone, followed by transmetalation of the resulting lithium alkoxide with anhydrous $MgBr_2$.[26] Subsequent addition of MeMgCl (1.1 equiv) to the intermediate alkoxide triggers the elimination, generating the corresponding α,*β*-unsaturated nitrile (Scheme 3).

Direct cyanomethylenation with lithioacetonitrile, $MgBr_2$, and MeMgCl provides a valuable conversion of aldehydes and ketones to the corresponding α,*β*-unsaturated nitriles (Table 2). The method is particularly useful for hindered ketones, such as fenchone (**2c**) where the carbonyl group is flanked by two quaternary centers, and provides unsaturated nitriles with higher stereoselectivities than often observed in Wittig reactions.[13a−c] The one-pot MgO elimination is a valuable complement to KOH-induced condensations of CH_3CN[7b] in allowing cyanomethylation of aldehydes that are prone to self-condensation (Table 2, entry 1). The direct condensations with metalated acetonitrile effectively span aldehyde, enal, ketone, and aryl ketone carbonyls, indicating the method's potential for assembling a diverse range of α,*β*-unsaturated nitriles.

Scheme 4



Several reaction features point to an E1cb mechanism. Slow addition of MeMgCl (2.1 equiv) to **8c** (Scheme 4) causes continuous effervescence, indicating that two sequential deprotonations occur to form a discrete dimetalated nitrile **12c**. Removal of an aliquot delivers recovered hydroxy nitrile **8c**, suggesting the formation of an intermediate dianion followed by ejection of MgO upon warming, rather than an E_2 elimination. Corroborating evidence for dianion intermediates are the eliminations of *β*-hydroxynitriles **8h** and **8i** (Table 1, entries 8 and 9) that converge to a common alkene in the same time period and with the same yield, reaction features consistent with dianion intermediates and not with a concerted elimination from a cyclic transition state.[18]

Conclusion

α,*β*-Unsaturated nitriles are readily synthesized through an elimination of magnesium oxide. The precursor *β*-alkoxy nitriles are readily accessed, either by MeMgCl-induced deprotonation of *β*-hydroxy nitriles, or through addition of lithioacetonitrile to aldehydes and ketones, followed by $MgBr_2$ transmetalation. Deprotonation of the resulting *β*-alkoxy nitriles with MeMgCl generates a dianion that ejects MgO to efficiently provide the corresponding α,*β*-unsaturated nitriles. The method is particularly advantageous for hindered ketones, providing a versatile route to diverse α,*β*-unsaturated nitriles with stereoselectivities comparable to, or higher than, those obtained with Wittig reagents.

Experimental Section[27]

General procedure for the Synthesis of *β*-Hydroxynitriles. Neat CH_3CN (1.25 equiv) was added to a −78 °C, THF solution (0.1 M) of *n*-BuLi (1.20 equiv). After 15 min, neat aldehyde or ketone (1.0 equiv) was added, the −78 °C bath was removed, and the mixture was allowed to warm to room temperature. After 2 h saturated, aqueous NH_4Cl was added and the aqueous phase extracted with EtOAc. The extracts were combined, washed with brine, dried (Na_2SO_4), concentrated, and purified by radial chromatography (1 mm plate, 3:7 EtOAc:hexanes) to afford the corresponding *β*-hydroxynitrile.

(±)-3-Hydroxynonanenitrile (8a).[28] The general procedure was employed with heptanal (**2a**) (100 mg, 0.88 mmol) to afford, after radial chromatography, 125 mg (92%) of **8a** as an oil: IR (film) 3450, 2251 cm^{-1}; ^1H NMR δ 0.85 (t, J = 6.8 Hz, 3H), 1.15−1.60 (m, 10H), 2.44 (dd, J = 17, 6 Hz, 1H), 2.53 (dd, J = 17, 5 Hz, 1H), 2.98 (br s, 1H), 3.88 (p, J = 6 Hz, 1H);

(24) Direct formation with magnesium and bromoacetonitrile is complicated by an electron transfer from the metal to the nitrile[4f] whereas the direct deprotonation of acetonitrile with Grignard reagents causes significant 1,2-addition to the nitrile: Hauser, C. R.; Humphlett, W. J. *J. Org. Chem.* **1950**, *15*, 359.

(25) Arseniyadis, S.; Kyler, K. S.; Watt, D. S. *Org. React.* **1984**, *31*, 1.

(26) Kaiser, E. M.; Hauser, C. R. *J. Am. Chem. Soc.* **1967**, *89*, 4566.

^{13}C NMR δ 13.8, 22.4, 25.2, 25.9, 28.8, 31.5, 36.4, 67.4, 117.8; MS *m/e* 154 (M − H).

3-[(1*S*,5*S*)-6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl]-3-hydroxypropanenitrile (8b). The general procedure was employed with (−)-myrtenal (**2b**) (57 mg, 0.38 mmol) to afford, after radial chromatography, 63 mg (87%) of **8b** as an oily mixture of two diastereomers: IR (film) 3458, 3034, 2252, 1653 cm^{-1}; ^{1}H NMR δ 0.81, 0.82 (s, 3H each), 1.14 (d, *J* = 8. Hz, 1H), 1.28 (s, 3H), 2.00−2.59 (m, 8H), 4.30 (t, *J* = 6 Hz, 1H), 5.56−5.62 (m, 1H); ^{13}C NMR δ 21.1 (co-incident), 23.9 and 24.0, 25.9 (co-incident), 30.9 (coincident), 31.5 and 31.6, 37.7 and 37.8, 40.6 and 40.7, 41.6 and 41.8, 69.8 and 70.0, 117.5 (coincident), 120.0 and 120.1, 146.9 and 147.1; MS *m/e* 192 (M + H) for each isomer.

(1*R*,2*R*,4*S*)-2-(2-Hydroxy-1,3,3-trimethylbicyclo[2.2.1]-hept-2-yl)acetoenitrile (8c) and (1*R*,2*S*,4*S*) -2-(2-Hydroxy-1,3,3-trimethylbicyclo[2.2.1]hept-2-yl)acetoenitrile (8e). The general procedure was employed with (−)-fenchone **(2c)** (150 mg, 0.99 mmol) to afford, after radial chromatography, 177 mg (93%) of **8c** and **8e** in a 5.8:1 ratio.[29] Repetitive chromatography afforded an enriched sample of **8e**, as a 1:1 mixture of diastereomers, and pure **8c** as a white crystalline solid (mp 84−86 °C): IR (NaCl) 3464, 2253 cm^{-1}; ^{1}H NMR δ 1.05 (s, 3H), 1.07 (s, 3H), 1.18 (s, 3H), 1.05−1.60 (m, 4H), 1.65−1.79 (m, 2H), 1.88−2.01 (m, 2H), 2.50 (s, 2H); ^{13}C NMR δ 17.3, 21.7, 24.8, 25.8, 26.7, 29.9, 40.8, 44.2, 49.4, 52.3, 79.9, 119.3; MS *m/e* 194 (M + H). Comparing spectra of pure **8c** with the enriched mixture reveals **8e** to exhibit: ^{1}H NMR δ 1.02 (s, 3H), 1.07 (s, 3H), 1.09 (s, 3H), 1.05−2.01 (m, 8H), 2.50 (s, 2H); ^{13}C NMR δ 15.8, 22.2, 23.4, 24.8, 25.4, 30.8, 40.9, 45.0, 46.7, 52.7, 80.3, 119.0; MS *m/e* 194 (M + H).

(±)-3-Hydroxy-3,4,4-trimethylpentanenitrile (8d). The general procedure was employed with 3,3-dimethylbutan-2-one (200 mg, 2.00 mmol) to afford, after radial chromatography, 236 mg (84%) of **8d** as a white crystalline solid (mp 38−40 °C): IR (NaCl) 3484, 2249 cm^{-1}; ^{1}H NMR δ 0.98 (s, 9H), 1.40 (s, 3H), 1.77 (s, 1H), 2.59 (ABq, *J* = 16, $\Delta\nu_{AB}$ = 62 Hz, 2H); ^{13}C NMR δ 22.7, 25.1, 27.5, 37.6, 74.9, 118.6; MS *m/e* 142 (M + H).

2-[(5S)-1-Hydroxy-5-methyl-2-(methylethylidene)cyclohexyl]acetonitrile (8f). The general procedure was employed with (+)-pulegone (150 mg, 0.99 mmol) to afford, after radial chromatography, 169 mg (89%) of **8f** as an oily mixture of diastereomers, spectroscopically identical to material previously reported.[30]

General Procedure for the MgO Elimination of Hydroxynitriles. A THF solution of MeMgCl (2.1 equiv) was added to a room temperature, THF solution (0.1 M) of the appropriate β-hydroxynitrile (1 equiv). After 12 h, saturated, aqueous NH_4Cl was added, and the aqueous phase was extracted with EtOAc. The organic extracts were combined, dried (Na_2SO_4), concentrated, and purified by radial chromatography (1 mm plate, 1:9 EtOAc:hexanes) to afford the corresponding unsaturated nitrile.

Non-2-enenitrile (1a). The general procedure was employed with **8a** (68 mg, 0.44 mmol) but adding the MeMgCl to a cold (−78 °C), THF solution of **8a** and maintaining the temperature at −78 °C for 12 h prior to warming to room temperature for 12 h. This modification afforded, after radial chromatography, 43 mg (71%) of (*E*)-**1a**[31] and (*Z*)-**1a**[32] as a 1:1 mixture of oils. Repetitive radial chromatography provided pure samples of each isomer: (*Z*)-**1a**: IR (film) 3064, 2220, 1620 cm^{-1}; ^{1}H NMR δ 1.20−1.30 (m, 3H), 1.55−1.90 (m, 8H), 2.65−2.78 (m, 2H), 5.54−5.60 (m, 1H), 6.71 (dt, *J* = 10.9, 7.7 Hz, 1H); ^{13}C NMR of a 1:1 mixture δ 13.9, 22.4, 27.5, 28.1, 28.5, 28.6, 31.4, 31.8, 33.2, 99.4, 99.6, 115.9, 117.5, 155.1, 156.0; MS *m/e* 138 (M + H).

(2*E*)-3-((1*S*,5*S*)-6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl)prop-2-enenitrile (1b). The general procedure was employed with **8b** (34 mg, 0.18 mmol) but adding the MeMgCl to a cold (−78 °C), THF solution of **8b** and maintaining the temperature at −78 °C for 4 h prior to warming to room temperature for 12 h. This modification afforded, after radial chromatography, 26 mg (84%) of **1b** as an oil with ^{1}H NMR and IR data identical to that reported previously:[33] ^{13}C NMR δ 20.7, 26.1, 31.0, 32.5, 37.9, 40.5, 40.6, 92.3, 119.0, 135.1, 145.3, 150.7; MS *m/e* 174 (M + H).

2-(1,3,3-Trimethylbicyclo[2.2.1]hept-2-ylideneacetonitrile (1c). The general procedure was employed with **8c** (87 mg, 0.45 mmol) but refluxing the solution for 2 h immediately following the addition of MeMgCl. This modification afforded, after radial chromatography, 61 mg (77%) of (*E*)-**1c** and 11 mg (14%) of (*Z*)-**1c** as oils. (*E*)-**1c**: IR (film): 3050, 2213, 1631 cm^{-1};^{1}H NMR δ 1.17 (s, 3H), 1.26 (s, 3H), 1.34 (s, 3H), 1.54−1.66 (m, 4H), 1.72 (dd, *J* = 8.7, 2.5 Hz, 1H), 1.75 (dd, *J* = 9.2, 2.5 Hz, 1H), 1.89 (br s, 1H), 4.94 (s, 1H); ^{13}C NMR δ 17.8, 23.4, 25.0, 25.5, 34.9, 43.4, 44.6, 48.1, 52.2, 84.3, 117.5, 186.6; MS 176 (M + H). (*Z*)-**1c**: IR (film): 3040, 2211, 1631 cm^{-1}; ^{1}H NMR δ 1.05 (s, 3H), 1.08 (s, 3H), 1.17−1.42 (m, 3H), 1.59 (s, 3H), 1.60−1.83 (m, 3H), 1.88 (br s, 1H), 4.94 (s, 1H); ^{13}C NMR δ 18.7, 25.0, 25.8, 28.6, 35.2, 45.3, 46.0, 46.6, 52.7, 85.0, 117.4, 185.7; MS *m/e* 176 (M + H). An analogous elimination using a 5:1 ratio of **8c**:**8e** (76 mg, 0.39 mmol) afforded 59 mg (86%) of (*E*)-**1c** and (*Z*)-**1c** in a 5:1 ratio.

(2*E*)-3,4,4-Trimethylpent-2-enenitrile (1d). The general procedure was employed with **8d** (105 mg, 0.74 mmol) using Et_2O, rather than EtOAc, to extract the aqueous phase to afford, after radial chromatography (1 mm plate, 1:9 Et_2O:pentane), 74 mg (81%) of **1d**[34] as a volatile oil: IR (film) 2219, 1613 cm^{-1}; ^{1}H NMR δ 1.09 (s, 9H), 2.06 (d, *J* = 0.7 Hz, 3H), 5.17 (br s, 1H); ^{13}C NMR δ 17.8, 28.3, 37.4, 93.4, 117.8, 172.8; MS *m/e* 124 (M + H).

2-[5-Methyl-2-(propan-2-ylidene)cyclohexylidene]-1-carbonitrile (1f). The general procedure was employed with **8f** (80 mg, 0.42 mmol) to afford, after radial chromatography, 43 mg (59%) of (*E*)-**1f** and 20 mg (28%) of (*Z*)-**1f** as oils. (*E*)-**1f**: IR (film) 3050, 2213, 1605 cm^{-1}; ^{1}H NMR δ 1.11−1.35 (m, 1H), 1.38 (d, *J* = 6.0 Hz, 3H), 1.46−1.65 (m, 2H), 2.08 (s, 3H), 2.11 (s, 3H), 2.13−2.40 (m, 2H), 2.98 (dt, *J* = 13.8, 4 Hz, 1H), 3.14−3.21 (m, 1H), 5.18 (s, 1H); ^{13}C NMR δ 20.3, 21.5, 21.9, 30.1, 34.0, 34.5, 42.5, 94.5, 117.3, 128.2, 132.2, 165.7; MS *m/e* 176 (M + H). (*Z*)-**1f**: IR (film) 3040, 2213, 1611 cm^{-1}; ^{1}H NMR δ 1.34 (d, *J* = 6.3 Hz, 3H), 2.07 (d, *J* = 1.4 Hz, 3H), 2.11 (s, 3H), 2.00−2.20 (m, 5H), 2.60−2.71 (m, 1H), 3.02−3.18 (m, 1H), 5.38 (s, 1H); MS *m/e* 176 (M + H).

6-(4-Chloro-1,1-dimethylbutyl)cyclohex-1-enecarbonitrile (1g). The general procedure was employed with **8g**[22] (21 mg, 86 mmol) to afford, after radial chromatography, 18 mg (92%) of **1g** as a colorless oil: IR (film) 2959, 2855, 2210, 1615 cm^{-1}; ^{1}H NMR δ 1.01 (s, 3H), 1.07 (s, 3H), 1.44−1.90 (m, 9H), 2.09−2.27 (m, 2H), 3.49 (dt, *J* = 13.7, 6.9 Hz, 1H), 3.57 (dt, *J* = 13, 6 Hz, 1H), 6.81−6.84 (m, 1H); ^{13}C NMR δ 20.4, 24.1, 25.7, 26.0, 27.5, 36.4, 37.9, 43.4, 45.6, 114.7, 121.5, 150.4; MS *m/e* 226 (M + H).

6-(4-Chlorobutyl)cyclohex-1-enecarbonitrile (1h). The general procedure was employed with **8h**[22] (11 mg, 51 mmol) but refluxing the solution for 2 h immediately following the addition of MeMgCl. This modification afforded, after radial chromatography, 9 mg (90%) of **1h** as a colorless oil spectro-

(27) For general experimental procedures, see: Fleming, F. F.; Hussain, Z.; Weaver, D.; Norman, R. E. *J. Org. Chem.* **1997**, *62*, 1305.

(28) β-hydroxynitrile **8a** has been prepared previously and partial ^{1}H NMR data reported: Barhdadi, R.; Gal, J.; Heintz, M.; Troupel, M.; Périchon, J. *Tetrahedron* **1993**, *49*, 5091.

(29) Nucleophilic additions to fenchone generate predominantly the endo-alcohol corresponding to **8c**: Gosselin, P.; Joulain, D.; Laurin, P.; Rouessac, F. *Tetrahedron Lett.* **1990**, *31*, 3151.

(30) Trost, B. M.; Florez, J.; Jebaratnam, D. J. *J. Am. Chem. Soc.* **1987**, *109*, 613.

(31) *E*-**1a** exhibited spectral data identical to that reported previously: Röttlander, M.; Boymond, L.; Cahiez, G.; Knochel, P. *J. Org. Chem.* **1999**, *64*, 1080.

(32) Nitrile *Z*-**1a** has been reported previously although the ^{1}H NMR data appears to be incorrectly referenced and is therefore shifted compared to the stated values: Crowe, W. E.; Goldberg, D. R. *J. Am. Chem. Soc.* **1995**, *117*, 5162.

(33) ^{1}H NMR data for nitrile **1b** has been reported previously.[13a]

(34) Nitrile **1d** has been prepared previously although no spectral data were reported: Palomo, C.; Aizpurua, J. M.; Garcia, J. M.; Ganboa, I.; Cossio, F. P.; Lecea, B.; López, C. *J. Org. Chem.* **1990**, *55*, 2498.

scopically identical to material previously reported.[35] An analogous elimination with **8i** (10 mg, 47 mmol) afforded, after radial chromatography, 8 mg (87%) of **1h** as a colorless oil.

General Procedure for the Direct Conversion of Carbonyl Compounds to Unsaturated Nitriles. Neat CH_3CN (1.25 equiv) was added to a −78 °C, THF solution (0.1 M) of BuLi (1.20 equiv). After 15 min, neat aldehyde or ketone was added, the −78 °C bath was removed, and the mixture was allowed to warm to room temperature. After 2 h a THF suspension of $MgBr_2$ (1.1 equiv) was added, followed after 15 min by a THF solution of MeMgCl (1.1 equiv). After 12 h saturated, aqueous NH_4Cl was added, and the aqueous phase was extracted with EtOAc. The organic extracts were combined, dried (Na_2SO_4), concentrated, and purified by radial chromatography (1 mm plate, 1:9 EtOAc:hexanes) to afford the corresponding unsaturated nitrile.

Non-2-enenitrile (1a). The general procedure was employed with heptanal (**2a**) (100 mg, 0.88 mmol) but adding the MeMgCl to a cold (−78 °C), THF solution and maintaining the temperature at −78 °C for 12 h prior to warming to room temperature for 12 h. This modification afforded, after radial chromatography, 77 mg (64%) of (*E*)-**1a** and (*Z*)-**1a** as a 1:1 mixture.

(2*E*)-3-((1*S*,5*S*)-6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl)prop-2-enenitrile (1b). The general procedure was employed with (−)-myrtenal **2b** (110 mg, 0.73 mmol) but adding the MeMgCl to a cold (−78 °C), THF solution and maintaining the temperature at −78 °C for 4 h prior to warming to room temperature for 12 h. This modification afforded, after radial chromatography, 79 mg (63%) of **1b**.

2-(1, 3, 3-Trimethylbicyclo[2.2.1]hept-2-ylideneethanenitrile (1c). The general procedure was employed with (−)-fenchone **2c** (50 mg, 0.33 mmol) but refluxing the solution for 2 h immediately following the addition of MeMgCl. This modification afforded, after radial chromatography, 39 mg (67%) of (*E*)-**1c** and (*Z*)-**1c** as a 1:1 mixture.

(2*E*)-3,4,4-Trimethylpent-2-enenitrile (1d). The general procedure was employed with 3,3-dimethylbutan-2-one **2d** (100 mg, 1.00 mmol) using Et_2O, rather than EtOAc, to extract the aqueous phase to afford, after radial chromatography (1 mm plate, 1:9 Et_2O:pentane), 75 mg (61%) of relatively volatile **1d**.

(2*E*)-4-Methyl-3-phenylpent-2-enenitrile (1j). The general procedure was employed with 2-methyl-1-phenylpropan-1-one (**2j**, 100 mg, 0.67 mmol) to afford, after radial chromatography, 81 mg (70%) of **1j**[36] as an oil: IR (film) 3060, 2218, 1659, 1613 cm^{-1}; ^1H NMR δ: 1.10 (d, J = 7.7 Hz, 6H), 2.85 (sept, J = 7 Hz, 1H), 5.35 (s, 1H), 7.30−7.45 (m, 5H); ^{13}C NMR δ: 21.1, 35.7, 94.2, 117.6, 127.2, 128.5, 129.1, 138.1, 172.3; MS *m/e* 171 (M^+).

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Supporting Information Available: ^1H NMR and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0162944

(35) Fleming, F. F.; Shook, B. C. *J. Org. Chem.* **2002**, *67*, 2885.

(36) Nitrile **1j** has been prepared previously although no spectral data were reported: Atwal, K. S.; O'Reilly, B, C.; Ruby, E. P.; Turk, C. F.; Aberg, G.; Asaad, M. M.; Bergey, J. L.; Moreland, S.; Powell, J. R. *J. Med. Chem.* **1987**, *30*, 627.