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Alkynenitriles: stereoselective chelation controlled conjugate addition–alkylations

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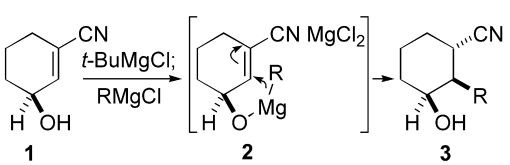
Abstract—Chelation-controlled conjugate addition of Grignard reagents to γ-hydroxyalkynenitriles stereoselectively generates tri- and tetra-substituted alkenenitriles. *t*-BuMgCl-initiated deprotonation of hydroxyalkynenitriles followed by addition of a second Grignard reagents triggers a facile conjugate addition leading to a cyclic magnesium chelate. Protonation of the chelate stereoselectively generates trisubstituted nitriles whereas the addition of *t*-BuLi causes conversion to an 'ate' complex that allows alkylation with aldehyde electrophiles. The chelation-controlled conjugate addition–alkylation generates tri- and tetra-substituted alkenenitriles that are otherwise difficult to synthesize.

1. Introduction

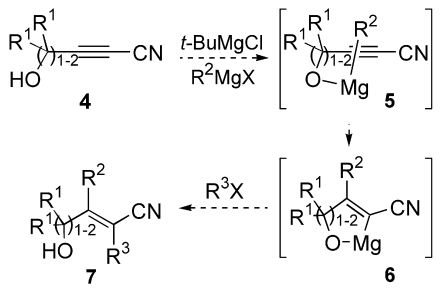
Chelation provides a powerful means of bond construction.[1] Temporary chelation dramatically accelerates many reactions by virtue of the close proximity imparted on the two reactive centers, essentially harnessing the inherent entropic advantages of intramolecular reactions[2] in a formal intermolecular process. Tethering the two reacting centers generally imposes precise geometric constraints on the transition state resulting in high stereoselectivity during bond formation,[3] in some cases affording stereoisomers that are otherwise difficult to access.[4]

Conjugate addition[5] and carbometallation[6] reactions, especially, are dramatically enhanced by chelation. The enhanced reactivity is readily apparent by comparing chelation-controlled[7] and organocopper[8] conjugate additions to alkenenitriles—substrates that are generally recalcitrant acceptors in anionic conjugate addition reactions.[9] For example, sequential deprotonation of **1** with *t*-BuMgCl (Scheme 1) and alkyl exchange from a variety of Grignard reagents triggers a stereoselective conjugate addition through chelate **2** whereas cuprates are unreactive toward cyclohexenecarbonitrile (**1**, HO═H).



Scheme 1. Chelation-controlled conjugate addition.

The enhanced reactivity, and high stereoselectivity, of chelation-controlled conjugate additions to alkenenitriles suggested extending the strategy to alkynenitriles. The attraction lies not only in enlarging chelation-controlled conjugate additions to incorporate sp-hybridized acceptors,[10] but in stereoselectively assembling tri-substituted alkenenitriles (Scheme 2, R^3=H).[11] Conceptually, chelation-controlled conjugate addition, followed by intercepting the intermediate vinyl organometallic **6** with carbon electrophiles,[12] provides a concise route to tetra-substituted alkenenitriles **7** for which few syntheses exist.[13] This account describes the scope of chelation-controlled conjugate additions to hydroxyalkynenitriles[14] and the first series of conjugate addition–alkylation reactions with alkynenitriles. Collectively these chelation-controlled conjugate addition reactions stereoselectively assemble tri- and tetra-substituted alkenenitriles that are otherwise challenging synthetic targets.



Scheme 2. Chelation-controlled conjugate addition–alkylation of alkynenitriles.

Keywords: conjugate addition; alkynenitriles.

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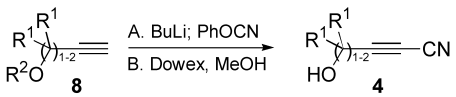
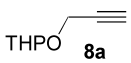
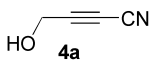
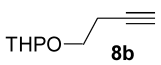
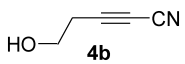
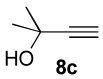
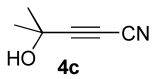
Table 1. Hydroxyalkynenitrile synthesis



Entry	Alkyne	Method	Alkynenitrile	Yield (%)
1	 **8a**	A+B	 **4a**	84
2	 **8b**	A+B	 **4b**	76
3	 **8c**	A	 **4c**	80

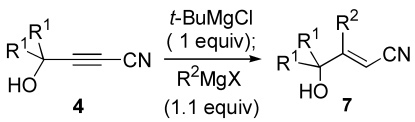
2. Results and discussion

A prerequisite for chelation-controlled conjugate addition reactions is an efficient synthesis of diverse hydroxyalkynenitriles. A general route to hydroxyalkynenitriles must overcome the instability of the parent 4-hydroxybutynenitrile (**4a**) toward base[15] and silica gel chromatography[16] that stems partly from the enhanced electrophilicity imparted by the proximal hydroxyl group,[17] and partly from the accessibility of the electrophilic β-carbon. Moderating the reactivity by THP protection of the hydroxyl group[18] proved admirable in allowing a high yielding deprotonation–cyanation[19] route to the chromatographically stable THP-protected alkynenitrile that was subsequently converted to spectroscopically pure **4a** on exposure to Dowex 50-X4 (Table 1, entry 1). Analogous lithiation–cyanations of alkynes **8b** and **8c** generate the chromatographically stable alkynenitriles **4b** and **4c** (Table 1, entries 2–3), with the sterically hindered nitrile **4c** imparting sufficient stability for direct double lithiation–cyanation of the hydroxyalkyne **8c** (Table 1, entry 3).

Hydroxyalkynenitriles **4a** and **4c** react with a range of Grignard reagents in an efficient chelation-controlled conjugate addition (Table 2). Experimentally, *t*-BuMgCl deprotonates the γ-hydroxyalkynenitriles permitting conjugate addition upon addition of a slight excess of a second, potentially more valuable, Grignard reagent. *t*-BuMgCl is an excellent sacrificial base for the initial deprotonation[20] since no transfer of the *t*-butyl group occurs during deprotonation at −78°C, whereas warming to ambient temperature with excess *t*-BuMgCl efficiently induces conjugate addition of the *t*-butyl group (Table 2, entry 4). High steric demand is tolerated in the Grignard reagent and in the alkynenitrile, although the reaction efficiency is reduced relative to reactions with less-substituted counterparts (compare Table 2, entry 1 with entries 4 and 9; entry 1 with entry 2; and entry 5 with entry 6).

Chelation-controlled conjugate additions of alkyl, vinyl, aryl, and alkynyl Grignards exclusively generate *E*-alkenenitriles.[21] Modest halogen, silicon, and sulfur functionality is tolerated in the Grignard reagent (Table 2, entries 10–12) although the instability[22] of the Grignard prepared from 3-chloropropyl phenylsulfide[23] (Table 2, entry 11) causes concomitant formation of **7l**, presumably through conjugate addition of PhSMgCl formed by cyclization of the Grignard reagent.

Table 2. Conjugate additions to alkynenitriles



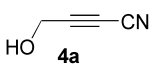
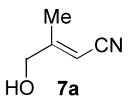
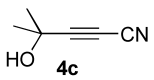
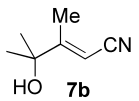
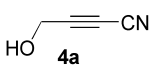
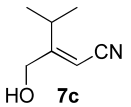
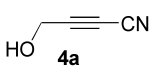
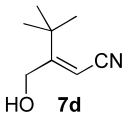
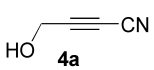
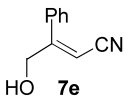
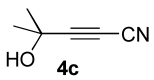
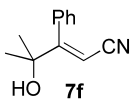
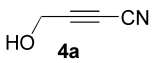
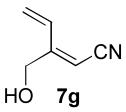
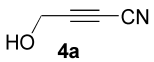
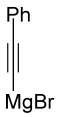
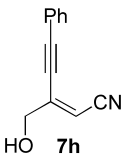
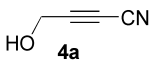
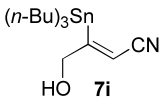
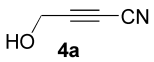
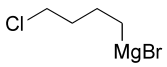
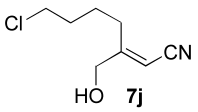
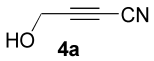
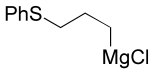
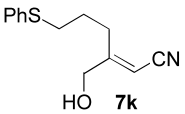
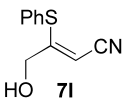
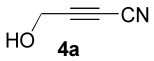
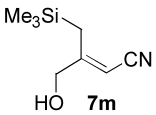
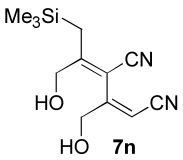
Entry	Alkynenitrile	Grignard reagent	Alkenenitrile	Yield (%)
1	 **4a**	MeMgCl	 **7a**	92
2	 **4c**	MeMgCl	 **7b**	70
3	 **4a**	*i*-PrMgBr	 **7c**	87
4	 **4a**	*t*-BuMgCl	 **7d**	60
5	 **4a**	PhMgCl	 **7e**	92

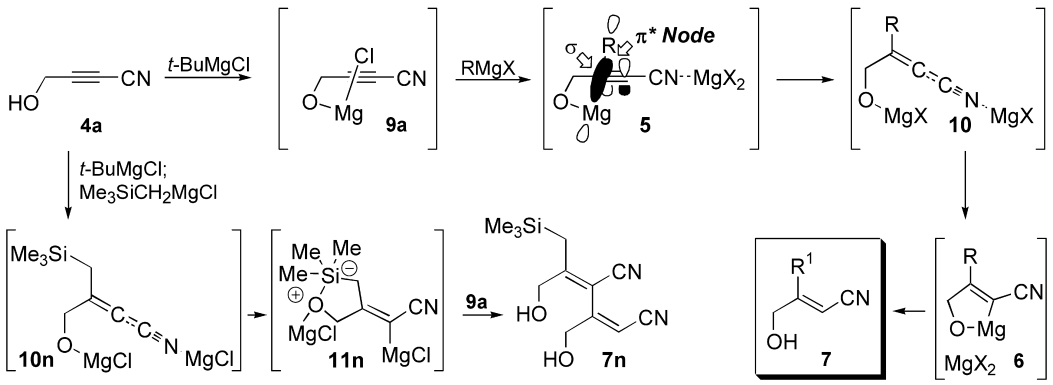
Table 2 (*continued*)

Entry	Alkynenitrile	Grignard reagent	Alkenenitrile	Yield (%)
6	 **4c**	PhMgCl	 **7f**	66
7	 **4a**		 **7g**	87
8	 **4a**		 **7h**	85
9	 **4a**	$(n\text{-Bu})_3SnMgCl$	 **7i**	70
10	 **4a**		 **7j**	78
11	 **4a**		 **7k**	42
			 **7l**	53
12	 **4a**	Me_3SiCH_2MgCl	 **7m**	38
			 **7n**	19

Chelate **6** is surprisingly unreactive toward alkylation—even being unreactive toward benzaldehyde![24] The low nucleophicity of chelate **6** is consistent with the inability of **6** to act as a vinyl Grignard reagent in a second chelation-controlled conjugate addition with alkynenitrile **9a** (Scheme 3). Competitive conjugate addition of the chelate **6** is only observed with Me_3SiCH_2MgCl (Table 1, entry 12), presumably reflecting formation of the silicate **11n**[25] from **10n** which unmasks a more reactive C–Mg bond[26] that competes with the hindered Me_3SiCH_2MgCl for **9a**.

Mechanistically, the stepwise chelation controlled conjugate addition directly parallels the analogous reactions of hydroxyalkenenitriles.[7] *t*-BuMgCl-induced deprotonation of the γ-hydroxyalkynenitrile followed by halogen–alkyl exchange[5b] (Scheme 3), leads to the alkylmagnesium alkoxide **5** that triggers the key anionic conjugate addition. Alkyl transfer from **5** requires overlap of the σ carbon–magnesium bond with the π^*-LUMO where the π^*-node precludes a concerted addition[27] as does the large distance between the magnesium and α-carbon atoms. Alkyl transfer from **5**, with activation of the nitrile by MgX_2, leads directly to the magnesiated alkenenitrile **10** that will equilibrate[28] to the cyclic chelate **6**.[29] Subsequent protonation of **6** generates the corresponding alkenenitrile **7** with retention of stereochemistry.[6]

Chelation is essential for the conjugate addition. A control experiment in which the THP-protected alkynenitrile **4a** HO═OTHP is exposed to *n*-BuMgCl leads to 90% recovery of unreacted nitrile. Similarly, positioning the hydroxyl group two atoms removed from the alkynenitrile prevents

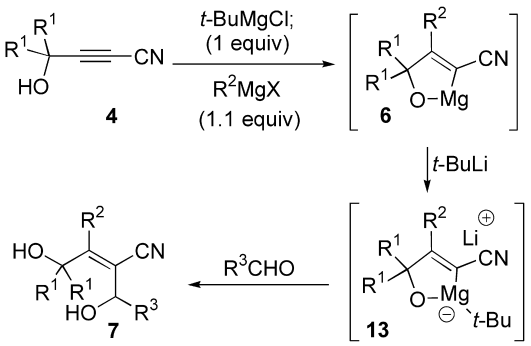


Scheme 3. Chelation-controlled conjugate addition mechanism.

the conjugate addition. The inability of alkynenitrile **4b** to undergo chelation controlled conjugate addition is surprising given the related carbometallation of butynols with Grignard reagents,[6] and the apparently more favorable proximity achieved by increasing the length of the tether (Eq. (1)). Although speculative, the inability of a chelation-controlled conjugate addition with **4b** may stem from an interaction[30] between magnesium and the π-bond[31] which positions the alkyl group away from the alkyne and deactivates the alkynenitrile nitrogen toward complexation with magnesium dihalide.

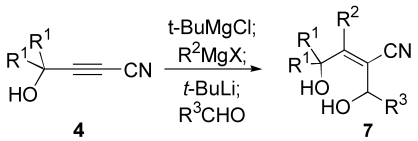
(1)

The poor nucleophilicity of the chelate **6** is surprising for a formal 'dianion.' Efforts to activate the chelate **6** by weakening the Mg-sp^2 bond focused on the addition of *t*-BuLi for conversion to the more reactive magnesium ate species **13** (Scheme 4).[32] Although not proof for the intermediacy of an ate complex, the addition of *t*-BuLi sufficiently activates **6** for a stereoselective[33] alkylation with aldehydes[34] that is consistent with a retentive alkylation[6a] through a cyclic ate complex (Table 3). The overall sequence of *t*-BuMgBr deprotonation, RMgX conjugate addition, *t*-BuLi ate activation, and alkylation is remarkably efficient for several Grignard reagents and even with the potentially enolizable aldehyde 3-phenylpropanal (Table 3, entries 3–6). Collectively, the three component coupling stereoselectively generates tetrasubstituted alkenenitriles that are otherwise difficult to synthesize.



Scheme 4. Chelation-controlled conjugate addition–alkylations.

Table 3. Alkynenitrile conjugate addition–alkylations



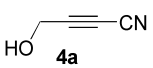
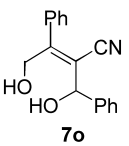
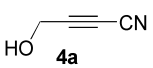
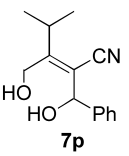
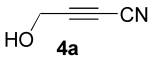
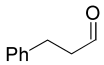
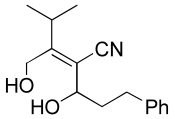
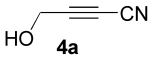
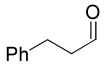
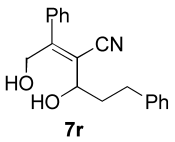
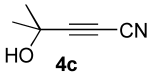
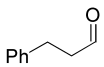
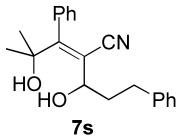
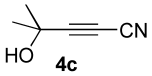
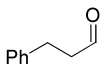
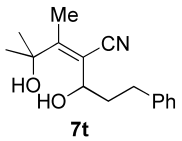
Entry	Alkynenitrile	Grignard Reagent	Aldehyde	Alkenenitrile	Yield (%)
1	 **4a**	PhMgCl	PhCHO	 **7o**	60
2	 **4a**	*i*-PrMgBr	PhCHO	 **7p**	72

Table 3 (*continued*)

Entry	Alkynenitrile	Grignard Reagent	Aldehyde	Alkenenitrile	Yield (%)
3	 **4a**	*i*-PrMgBr		 **7q**	65
4	 **4a**	PhMgCl		 **7r**	57
5	 **4c**	PhMgCl		 **7s**	57
6	 **4c**	MeMgCl		 **7t**	61

Temporary chelation of Grignard reagents to γ-hydroxyalkynenitriles triggers a facile conjugate addition reaction. *t*-BuMgCl-initiated deprotonation of γ-hydroxyalkynenitriles and addition of a slight excess of a second Grignard reagent causes a stepwise conjugate addition resulting in the formation of a cyclic magnesium chelate. Protonation of the chelate stereoselectively generates tri-substituted alkenenitriles whereas addition of *t*-BuLi generates a more reactive ate complex that alkylates aromatic and aliphatic aldehydes with complete stereochemical fidelity. Collectively the chelation-controlled conjugate addition–alkylation generates a range of tri- and tetra-substituted alkenenitriles that are otherwise difficult to synthesize.

3. Experimental[35]

3.1. Data for compounds

3.1.1. 4-(Tetrahydro-pyran-2-yloxy)-but-2-ynenitrile. A hexanes solution of *n*-BuLi (5.4 mL, 8.6 mmol) was added to a −78°C, THF solution of **8a**[18] (1.2 g, 8.6 mmol) followed, after 15 min, by a THF solution of PhOCN[19] (1.3 equiv.). The cooling bath was removed and, after 15 min, aqueous NaOH (6 M) was added and followed by ether extraction. The combined extracts were washed sequentially with NaOH (6 M), and saturated NaCl, passed through a short plug of silica gel (5×1 cm column), dried over $NaSO_4$, concentrated, and purified by radial chromatography (1:9 EtOAc/hexanes) to yield 1.3 g (92%) of 4-(tetrahydro-pyran-2-yloxy)-but-2-ynenitrile as oil: IR (film) 2304, 2265 cm^{-1}; ^1H NMR 1.52–1.84 (m, 6H), 3.54–3.58 (m, 1H), 3.75–3.83 (m, 1H), 4.37 (s, 2H), 4.76 (s, 1H); ^{13}C NMR δ 18.6, 25.0, 29.9, 53.6, 59.7, 62.0, 81.6, 97.7, 104.6; MS *m/e* 164 (M−H).

3.1.2. 4-Hydroxy-but-2-ynenitrile (4a). An anhydrous methanolic solution (15 mL) of 5-(tetrahydro-pyran-2-yloxy)-pent-2-ynenitrile (0.6 g) and Dowex (pre washed with anhydrous methanol) was stirred at room temperature for 1.5 h. The reaction was then filtered, the residue concentrated, and retreated with Dowex for 1.5 h to yield 295 mg (100%) of **4a** as oil: IR (film) 3447, 2308, 2245 cm^{-1}; ^1H NMR δ 2.39 (br, 1H), 4.40 (s, 2H), 2.38 (s, 1H); ^{13}C NMR δ 50.6, 59.6, 83.1, 104.6.

3.1.3. 5-(Tetrahydro-pyran-2-yloxy)-pent-2-ynenitrile. A hexanes solution (1.6 M) of *n*-BuLi (0.52 mL, 0.84 mmol) was added to a −78°C, THF solution of **8b**[36] (0.13 g, 0.84 mmol) followed, after 15 min, by a THF solution of PhOCN (1.3 equiv.). The cooling bath was removed and, after 15 min, aqueous NaOH (6 M) was added and followed by ether extraction. The combined extracts were washed sequentially with NaOH (6 M), and saturated NaCl, passed through a short plug of silica gel (5×1 cm column), dried over $NaSO_4$, concentrated and, purified by radial chromatography (1:10 EtOAc/hexanes) to yield 0.12 g (80%) of 5-(tetrahydro-pyran-2-yloxy)-pent-2-ynenitrile as oil: IR (film) 2314, 2261 cm^{-1}; ^1H NMR δ 1.57–1.84 (m, 6H), 2.65–2.69 (m, 2H), 3.52–3.65 (m, 2H), 3.81–3.92 (m, 2H), 4.64 (brs, 1H); ^{13}C NMR δ 19.2, 20.6, 25.3, 30.4, 55.9, 62.3, 63.7, 84.7, 99.0, 105.1; MS *e/m* 178 (M−H).

3.1.4. 5-Hydroxy-pent-2-ynenitrile (4b). A methanolic solution (10 mL) of 5-(Tetrahydro-pyran-2-yloxy)-pent-2-ynenitrile (0.12 g) and Dowex (pre-washed with anhydrous methanol) was stirred at room temperature for 1.5 h. The reaction was then filtered, the residue concentrated, and retreated with Dowex for 1.5 h to yield 63 mg (100%) of **4b** as an oil: IR (film) 3434, 2315, 2263 cm^{-1}; ^1H NMR δ 2.12 (s, 1H), 2.65–2.61 (s, *J*=6.0 Hz, 2H), 3.82 (s,

2H); ^{13}C NMR δ 23.0, 56.1, 59.3, 85.0, 105.0 MS *m/e* 95 (M+H).

3.1.5. 4-Hydroxy-4-methyl-pent-2ynenitrile (4c). A hexanes solution (1.6 M) of *n*-BuLi (2.96 mL, 4.75 mmol) was added to a −78°C, THF solution of **8c** (0.4 g, 4.75 mmol) followed, after 15 min, by a THF solution of PhOCN (1.3 equiv.). The cooling bath was removed and, after 15 min, aqueous NaOH (6 M) was added and followed by ether extraction. The combined extracts were washed sequentially with NaOH (6 M), and saturated NaCl, dried over $NaSO_4$, concentrated and, purified by radial chromatography (1:9 EtOAc/hexanes) to yield 0.41 g (80%) of **4c** as oil, identical to material previously synthesized.[37]

3.2. General conjugate addition procedure

A THF solution of *t*-BuMgCl (1.0 equiv., 1–2 M) was added to a −78°C, THF solution of the γ-hydroxyalkynenitrile (1 equiv.) followed, after 5 min, by a THF solution of the appropriate Grignard reagent (1.1 equiv., 1–3 M). After 45 min, the reaction mixture was allowed to warm to room temperature (15 min) and then saturated aqueous NH_4Cl was added. The crude reaction mixture was extracted with EtOAc the combined organic extracts were dried (Na_2SO_4), passed through a short plug of silica gel (2×1 cm column), concentrated, and purified by radial chromatography.

3.2.1. 4-Hydroxy-3-but-2-enenitrile (7a). Performing the general conjugate addition procedure with a THF solution (5 mL) of **4a** (20 mg) and MeMgCl provided, after purification by radial chromatography (1:4 EtOAc/hexanes), 22 mg (92%) of **7a** spectrally identical to material previously synthesized.[21a]

3.2.2. (2*E*)-4-Hydroxy-3,4-dimethylpent-2-enenitrile (7b). Performing the general conjugate addition procedure with a THF solution (5 mL) of **4c** (20 mg) and MeMgCl provided, after purification by radial chromatography (1:4 EtOAc/hexanes), 16.1 mg (70%) of **7b** as an oil: IR (film) 3410, 2932, 2215, 1601 cm^{-1}; ^{1}H NMR δ 1.37 (s, 6H), 2.08 (s, 3H), 5.63 (s, 1H); ^{13}C NMR δ 17.8, 28.5, 73.6, 94.1, 117.5, 169.6; MS *e/m* 126 (M+H).

3.2.3. (2*E*)-3-(Hydroxymethyl)-4-methylpent-2-enenitrile (7c). Performing the general conjugate addition procedure with a THF solution (5 mL) of **4a** (12.9 mg) and *i*-PrMgBr provided, after purification by radial chromatography (3:7 EtOAc/hexanes), 17.3 mg (87%) of **7c** as an oil: IR (film) 3447, 2221, 1628 cm^{-1}; ^{1}H NMR δ 1.16 (d, *J*=7.2 Hz, 6H), 1.21 (br s, 1H), 3.10 (sept, *J*=7 Hz, 1H), 4.30 (s, 2H), 5.53 (s, 1H); ^{13}C NMR δ 20.5, 32.2, 61.0, 91.9, 116.9, 172.1; MS *m/e* 126 (M+H).

3.2.4. (2*E*)-3-(Hydroxymethyl)-4,4-dimethylpent-2-enenitrile (7d). Performing the general conjugate addition procedure with a THF solution (5 mL) of **4a** (16.2 mg) and *t*-BuMgCl provided, after purification by radial chromatography (1:4 EtOAc/hexanes), 16.5 mg (60%) of **7d** as an oil: IR (film) 3483, 2219, 1636 cm^{-1}; ^{1}H NMR δ 1.32 (s, 9H), 1.75 (s, 1H), 4.32 (s, 2H), 5.72 (s, 1H); ^{13}C NMR δ 28.9, 36.2, 62.4, 91.4, 118.0, 173.2; MS *m/e* 140 (M+H).

3.2.5. (2*E*)-4-Hydroxy-3-phenylbut-2-enenitrile (7e). Performing the general conjugate addition procedure with a THF solution (5 mL) of **4a** (15 mg) and PhMgCl provided, after purification by radial chromatography (3:7 EtOAc/hexanes), 27 mg (92%) of **7e** as an oil:[38] IR (Film) 3446, 3060, 2221, 1623 cm^{-1}; ^{1}H NMR δ 2.37 (br s, 1H), 4.52 (s, 2H), 5.78 (s, 1H), 7.43 (s, 5H); ^{13}C NMR δ 64.6, 94.2, 117.4, 127.2, 128.9, 130.1, 134.7, 163.6; MS *m/e* 159.

3.2.6. (2*E*)-4-Hydroxy-4-methyl-3-phenylpent-2-enenitrile (7f). Performing the general conjugate addition procedure with a THF solution (5 mL) of **4c** (20 mg) and PhMgCl, provided after purification by radial chromatography (1:4 EtOAc/hexanes), 22.6 mg (66%) of **7f** as a light brown solid: IR (film) 3440, 3060, 2229, 1614 cm^{-1}; ^{1}H NMR δ 1.39 (s, 6H), 1.86 (s, 1H), 5.97 (s, 1H), 7.19–7.44 (m, 5H); ^{13}C NMR δ 28.7, 73.6, 97.1, 116.9, 127.7, 128.4, 128.7; HRMS (ESI) calcd for (M+Na$^+$) $C_{12}H_{13}NONa^+$ 210.0889, found 210.08933.

3.2.7. (2*E*)-3-(Hydroxymethyl) penta-2, 4-dienenitrile (7g). Performing the general conjugate addition procedure with a THF solution (5 mL) of **4a** (21.3 mg) and vinyl magnesium bromide provided, after purification by radial chromatography (1:4 EtOAc/hexanes), 25 mg (87%) of **7g** as an oil: IR (film) 3423, 2218, 1635, 1582 cm^{-1}, ^{1}H NMR δ 2.08 (s, 1H), 4.51 (s, 2H), 5.54 (d, *J*=11 Hz, 1H), 5.58 (d, *J*=17 Hz, 1H), 5.69 (s, 1H), 6.87 (dd, *J*=17, 11 Hz, 1H); ^{13}C NMR: 61.0, 95.7, 116.6, 120.9, 131.4, 158.0; MS *m/e* 109.

3.2.8. (2*E*)-3-(Hydroxymethyl)-5-phenylpent-2-en-4-ynenitrile (7h). Performing the general conjugate addition procedure with a THF solution (5 mL) of **4a** (30 mg) and PhC≡CMgCl[39] provided, after purification by radial chromatography (1:3 EtOAc/hexanes), 57.6 (85%) mg of **7h** as an oil: IR (film) 3347, 3067, 2224, 2192, 1589 cm^{-1}; ^{1}H NMR δ 2.36 (s, 1H), 4.39 (s, 2H), 5.93 (s, 2H), 7.36–8.74 (m, 5H); ^{13}C NMR: 64.1, 83.2, 100.9, 102, 116.7, 121.2, 128.5, 129.9, 132.3, 145.8 MS *m/e* 183 (M$^+$).

3.2.9. (2*Z*)-4,4-Dibutyl-3-(hydroxymethyl)-4-stannaoct-2-enenitrile (7i). Performing the general conjugate addition procedure with a THF solution (5 mL) of **4a** (10 mg) and $(Bu)_3SnMgCl$[40] provided, after purification by radial chromatography (1:4 EtOAc/hexanes), 32 mg (70%) of **7i** as oil: IR (film) 3422, 2217, 1654 cm^{-1}; ^{1}H NMR δ 0.91 (t, *J*=7.0 Hz, 9H), 1.12–1.64 (m, 18H), 4.42 (s, 2H), 6.26 (s, 1H); ^{13}C NMR δ 10.1, 13.6, 27.2, 29.0, 68.1, 105.5, 118.9, 176.7; MS *m/e* 373 (M$^+$).

3.2.10. (2*E*)-7-Chloro-3-(hydroxymethyl)-hept-2-enenitrile (7j). Performing the general conjugate addition procedure with a THF solution (5 mL) of **4a** (15 mg) and chlorobutylmagnesium bromide[41] provided, after purification by radial chromatography (3:7 EtOAc/hexanes), 25 mg (78%) of **7j** as an oil: IR (Film) 3435, 2220, 1639 cm^{-1}, ^{1}H NMR δ 1.63–1.73 (m, 2H), 1.80–1.89 (m, 2H), 2.42 (t, *J*=7.5 Hz, 2H), 3.57 (t, *J*=6.0 Hz, 2H), 4.26 (s, 2H), 5.59 (s, 1H); ^{13}C NMR: 25.3, 31.2, 31.6, 44.3, 63.9, 94.3, 116.8, 166.2; MS *m/e* 173 (M+H).

3.2.11. (2*E*)-3-(Hydroxymethyl)-6-phenylthiohex-2-enenitrile (7k) and (2*Z*)-4-hydroxy-3-phenylthiobut-2-enenitrile (7l). Performing the general conjugate addition

procedure with a THF solution (5 mL) of **4a** (16 mg) and $PhS(CH_2)_3MgCl$[22] provided, after purification by radial chromatography (3:7 EtOAc/hexanes), 19.3 mg (42%) of **7k** and 20 mg (53%) of **7l** as an oils. For **7k** IR (film) 3426, 3060, 2219, 1632, 1584 cm^{-1}; ^1H NMR δ 1.60 (br s, 1H), 1.78–1.88 (m, 2H), 2.51 (dd, J=8 Hz, 2H), 2.95 (t, J=7.3 Hz, 2H), 4.20 (s, 2H), 5.57 (s, 1H), 7.17–7.60 (m, 5H); ^{13}C NMR δ 27.6, 31.0, 33.5, 64.0, 94.6, 126.4, 129.0, 129.8, 165.7; MS *e*/*m* 233. For **7l** IR (film) 3438, 3058, 2216, 1579 cm^{-1}; ^1H NMR δ 2.03 (s, 1H), 4.07 (s, 2H), 5.81 (s, 1H), 7.27- 7.55 (m, 5H); ^{13}C NMR δ 64.1, 93.6, 127.9, 129.9, 134.7, 162; MS *m*/*e* 191 (M^+).

3.2.12. (2*Z*)-3-(Hydroxymethyl)-5,5-dimethyl-5-silahex-2-enenitrile (7m) and (2*E*)-1-[1-(2,2-dimethyl-2-silapropyl)-2-hydroxyethylidene]-2-(hydroxymethyl)prop-2-ene-1,3-dicarbonitrile (7n). Performing the general conjugate addition procedure with a THF solution (5 mL) of **4a** (20 mg) and $(CH_3)_3SiCH_2MgCl$ provided, after purification by radial chromatography (3:7 EtOAc/hexanes), 16 mg (38.3%) of **7m** and 14 mg (19.4) of **7n** as an oils. For **7m**: IR (Film) 3456, 2215, 1620; ^1H NMR δ 0.12 (s, 9H), 1.94 (s, 2H), 4.13 (s, 2H), 5.39 (s, 1H); ^{13}C NMR δ −1.0, 24.6, 65.3, 89.2, 118.1, 166.7; MS *m*/*e* 169. For **7n**: IR (Film) 3456, 2221, 1630 cm^{-1}; ^1H NMR δ 0.22 (s, 9H), 2.38 (s, 2H), 4.27 (s, 2H), 4.36 (s, 2H), 5.84 (s, 1H); ^{13}C NMR δ-0.8, 28.0, 62.4, 63.3, 100.2, 100.6, 116.3, 157.1, 167.5; MS *m*/*e* 250 (M+H).

3.3. General conjugate addition–alkylation procedure

A THF solution of *t*-BuMgCl (1.0 equiv., 1–2 M) was added to a −78°C, THF solution of the γ-hydroxyalkynenitrile (1 equiv.) followed, after 5 min, by a THF solution of the appropriate Grignard reagent (1.1 equiv., 1–3 M). After 45 min, the reaction mixture was allowed to warm to room temperature (15 min), re-cooled to −78°C, and then a hexanes solution of *t*-BuLi (1.2 equiv., 1.5 M) was added. The cooling bath was then removed, and after 15 min neat aldehyde (1.5 equiv.) was added, followed, after a further 30 min, by aqueous saturated NH_4Cl. The crude reaction mixture was extracted with EtOAc, the combined extracts were passed through a short plug of silica gel (2×1 cm column), concentrated, and purified by radial chromatography.

3.3.1. (2*Z*)-4-Hydroxy-2-(hydroxyphenylmethyl)-3-phenylbut-2-enenitrile (7o). Performing the general conjugate addition–alkylation procedure with a THF solution (5 mL) of **4a** (10 mg), PhMgCl and PhCHO provided, after purification by radial chromatography (3:7 EtOAc/hexanes), 19.6 mg (60%) of **7o** as a light brown solid (mp 123–125°C): IR (film) 3388, 2219, 1595 cm^{-1}; ^1H NMR δ 4.55–4.57 (m, 2H), 5.40–5.42 (m, 1H, exchanges with D_2O), 5.94–5.96 (m, 1H), 6.21 (d, J=4.0 Hz, 1H, exchanges with D_2O), 7.26–7.50 (m, 10H); ^{13}C NMR δ 60.6, 67.6, 117.4, 118.2, 125.9, 127.3, 128.1, 138.5, 141.6, 156.0 MS *m*/*e* 247 ($M-H_2O$).

3.3.2. (2*Z*)-3-(Hydroxymethyl)-2-(hydroxyphenylmethyl)-4-methylpent-2-enenitrile (7p). Performing the general conjugate addition–alkylation procedure with a THF solution (5 mL) of **4a** (20 mg), *i*-PrMgCl and PhCHO provided, after purification by radial chromatography (4:6 EtOAc/hexanes), 41.1 mg (72%) of **7p** as an oil: IR (Film) 3414, 2217, 1603 cm^{-1}; ^1H NMR δ 1.09 (d, J=6.7 Hz, 3H), 1.15 (d, J=7.1 Hz, 3H), 2.64 (s, 1H), 3.13–3.22 (m, 1H), 3.45 (s, 1H), 4.30 (ABq, $\Delta\nu$=31.5 Hz, J=12.3 Hz, 2H), 5.79 (s, 1H), 7.32–7.45 (m, 5H); ^{13}C NMR δ 20.2, 20.3, 35.2, 57.0, 70.0, 116.5, 117.0 126.0, 128.7, 140.1, 163.4 MS *m*/*e* 231 (M−H).

3.3.3. (2*Z*)-3-(Hydroxymethyl)-2-(1-hydroxy-3-phenylpropyl)-4-methylpent-2-enenitrile (7q). Performing the general conjugate addition–alkylation procedure with a THF solution (5 mL) of **4a** (12 mg), *i*-PrMgCl and 3-phenylpropanal provided, after purification by radial chromatography (3:7 EtOAc/hexanes), 24.9 mg (65%) of **7q** as an oil: IR (film) 3410, 2214, 1603 cm^{-1}; ^1H NMR δ 1.07 (d, J=6.4 Hz, 3H), 1.15 (d, J=6.3 Hz, 3H), 1.70 (br s, 1H), 1.97–2.21 (m, 2H), 2.32 (br s, 1H), 2.74 (t, J=7.5 Hz, 2H), 3.14–3.23 (m, 1H), 4.14 (s, 2H), 4.55 (t, J=6.8 Hz, 1H), 7.12–7.31 (m, 5H); ^{13}C NMR δ 20.2, 20.4, 31.8, 35.1, 36.8, 57.0, 67.4, 116.3, 117.1, 126.2, 128.4, 128.5, 140.8, 164.3.

3.3.4. (2*E*)-4-Hydroxy-2-(1-hydroxy-3-phenylpropyl)-3-phenylbut-2-enenitrile (7r). Performing the general conjugate addition–alkylation procedure with a THF solution (5 mL) of **4a** (15 mg), PhMgCl and 3-phenylpropanal provided, after purification by radial chromatography (3:7 EtOAc/hexanes), 30.9 mg (57%) of **7r** as an oil. IR (film) 3386, 2216, 1602 cm^{-1}; ^1H NMR δ 2.1–2.24 (m, 2H), 2.74–2.78 (m, 2H), 3.20 (brs, 2H), 4.39 (AB_q, $\Delta\nu$=40.0 Hz, J=13.4 Hz, 2H), 4.69 (t, J=7 Hz, 1H), 7.20–7.38 (m, 10H); ^{13}C NMR: 31.7, 37.1, 62.3, 67.6, 116.9, 118.2, 126.3, 127.8, 128.4, 128.6, 128.8, 129.6, 137.5, 140.6, 157.4.

3.3.5. (2*Z*)-4-Hydroxy-2-(1-hydroxy-3-phenylpropyl)-4-methyl-3-phenylpent-2-enenitrile (7s). Performing the general conjugate addition–alkylation procedure with a THF solution (5 mL) of **4c** (17 mg), PhMgCl and 3-phenylpropanal provided, after purification by radial chromatography (3:7 EtOAc/hexanes), 28.5 mg (57%) of **7s** as an oil; IR (film) 3434, 2215, 1602 cm^{-1}; ^1H NMR δ 1.25 (s, 3H), 1.36 (s, 3H), 1.40–1.60 (m, 2H), 2.01–2.27 (m, 2H), 2.72–2.92 (s, 2H), 5.22–5.27 (m, 1H), 7.20–7.71 (m, 10H); ^{13}C NMR: 30.6, 31.4, 32.1, 37.2, 67.1, 74.9, 116.8, 120.1, 126.1, 127.1, 127.9, 128.5, 139.4, 141.2, 165.1; HRMS (ESI) calcd for ($M+Na^+$) $C_{21}H_{23}NO_2$ 344.1621, found 344.1611.

3.3.6. (2*Z*)-4-Hydroxy-2-(1-hydroxy-3-phenylpropyl)-3,4-dimethylpent-2-enenitrile (7t). Performing the general conjugate addition–alkylation procedure with a THF solution (5 mL) of **4c** (20 mg), MeMgCl and 3-phenylpropanal, provided after purification by radial chromatography (3:7 EtOAc/hexanes), 29 mg (61%) of **7t** as an oil: IR (film) 3433, 2211, 1602 cm^{-1}; ^1H NMR δ 1.21–1.37 (m, 1H), 1.34 (s, 3H), 1.42 (s, 3H), 1.94–2.20 (m, 2H), 2.09 (s, 3H), 2.65–2.85 (m, 3H), 5.07–5.12 (m, 1H), 7.18–7.46 (m, 5H); ^{13}C NMR: 22.0, 29.7, 30.3, 32.0, 37.3, 66.8, 75.2, 116.5, 117.7, 125.9, 128.4 (doubled), 141.3, 161.8; MS *m*/*e* 259 (M−OH).

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