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Cyclic Alkenenitriles: Copper-Catalyzed Deconjugative α-Alkylation

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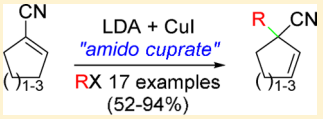
Supporting Information

ABSTRACT: An amido cuprate formed from CuCN and LDA allows a general deconjugative α-alkylation of cyclic alkenenitriles. Deprotonating cyclic alkenenitriles with LDA-CuCN avoids polymerization that otherwise plagues these alkylations and generates a reactive metalated nitrile for alkylations with a range of carbon and heteroatom electrophiles. The strategy provides an effective synthesis of quaternary 5-, 6-, and 7-membered cycloalk-1-enecarbonitriles substituted on the nitrile-bearing carbon.



INTRODUCTION

Nitriles occupy an unusual niche in natural products[1] and pharmaceuticals[2] due to the exquisitely small,[3] highly polar CN unit. Among cyclic nitriles, cyclohexanecarbonitriles with a ubiquitous six-membered ring are both versatile synthetic intermediates[4] and feature as a core pharmacophore in bioactive targets (Figure 1), such as the sponge metabolite

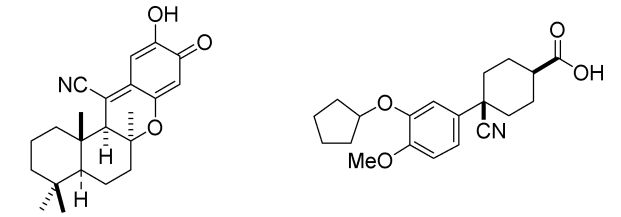


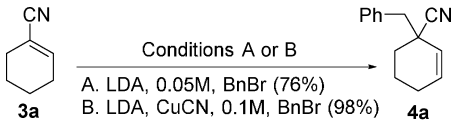
Figure 1. Bioactive cyclohexanecarbonitriles.

cyanopuupehenone (**1**)[5] and the antiasthmatic agent Cilomilast (**2**).[6] Consequently, numerous syntheses of cyclohexanecarbonitriles[7] have emerged to provide stereocontrolled methods for introducing a variety of substituents.[8]

The chemistry of cyclic alk-1-enecarbonitriles is significantly less developed than that of the saturated analogues.[9] Classical transformations such as conjugate addition[10] and deconjugative α-alkylation[11] are particularly challenging.[12] For example, the optimal deconjugative α-alkylation of cyclohex-1-enecarbonitrile requires HMPA and is reported only for alkyl iodides.[11,13] Performing the same procedure with cyclopent-1-enecarbonitrile generates oligomeric material arising from conjugate addition of the lithiated nitrile to the parent alkenenitrile prior to alkylation, a problem that plagues the alkylations of cyclic alkenenitriles.[11]

RESULTS AND DISCUSSION

Insight into the difficulty of alkylating cyclic alkenenitriles was probed by monitoring the reaction of cyclohex-1-enecarbonitrile (**3a**) with LDA. In preparing samples for NMR analysis, a strong concentration effect was observed in the deprotonation of cyclohex-1-enecarbonitrile (**3a**) with LDA; attempted deprotonation of a 0.14 M solution of cyclohex-1-enecarbonitrile (**3a**) caused rapid polymerization, whereas the slow deprotonation of a 0.05 M solution under otherwise identical conditions (1 h at −80 °C) permitted smooth formation of the corresponding lithiated nitrile. The subsequent alkylation with BnBr required less than 5 min at −80 °C (eq 1, condition A).



Eq. 1

The requirement for dilute solutions to effectively alkylate cyclohexanecarbonitrile and the inability to extend the procedure to cyclopent-1-enecarbonitrile (**3c**) stimulated a search for a more general deconjugative α-alkylation method for 5−7-membered cyclic alkenenitriles. Conceptually, nitrile complexation by a Lewis acid should facilitate a rapid deprotonation and minimize self-condensation provided the species is compatible with LDA. The choice of an activating agent was guided by the complexation of cyclohex-1-enecarbonitrile (**3a**) with copper(I) salts[14] and the diminished reactivity of cuprated nitriles relative to lithiated nitriles, which should decrease the propensity toward conjugate addition with

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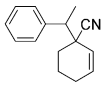
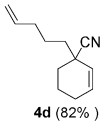
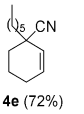
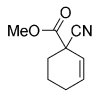
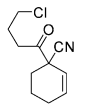
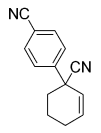
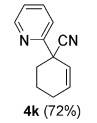
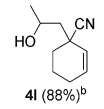
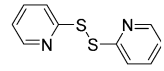
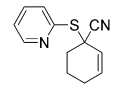
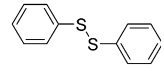
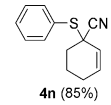
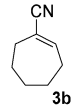
Table 1. Deconjugative α-Alkylation of Alkenenitriles[a]

entry	alkenenitrile	electrophile	alkylated nitrile
1	 **3a**		 **4b** (88%)
2	 **3a**		 **4c** (78%)[b]
3	 **3a**		 **4d** (82%)
4	 **3a**		 **4e** (72%)
5	 **3a**		 **4f** (92%)
6	 **3a**		 **4g** (88%)
7	 **3a**		 **4h** (90%)
8	 **3a**		 **4i** (73%)
9	 **3a**		 **4j** (94%)
10	 **3a**		 **4k** (72%)
11	 **3a**		 **4l** (88%)[b]
12	 **3a**		 **4m** (63%)
13	 **3a**		 **4n** (85%)
14	 **3b**		**4o** (78%)
15	**3c**		**4p** (92%)
16	**3c**		(**4q**, 52%)

[a]The general procedure employed 1.2 equiv of LDA at −78 °C with 0.1 equiv of CuCN. The alkenenitrile was added, and then the reaction was allowed to warm to −45 °C over 1 h. The solution was cooled to −78 °C, and then the electrophile was added. Reactive electrophiles were left at −78 °C for 2 h, whereas the less reactive electrophiles, such as alkyl halides, were allowed to warm to rt overnight. [b]Obtained as a 1:1 ratio of diastereomers.

the alkenenitrile.[15] After some optimization, an excellent procedure was developed[16] in which a THF solution of LDA was added to a −78 °C THF suspension of CuCN (10 mol %).[17] NMR monitoring of the resultant clear "amido cuprate"[18] solution revealed that deprotonation of cyclohex-1-enecarbonitrile was slow at −80 °C but was accelerated, without oligomerization, by allowing the solution to warm to −45 °C over 1 h. The metalated nitrile was subsequently cooled to −78 °C, and then BnBr was added to afford benzylnitrile **4a** in 98% yield (eq 1, condition B).[19]

The copper-catalyzed deprotonation procedure proved to be robust and effective with a variety of electrophiles and cyclic 5−7-membered alkenenitriles (Table 1).[20] Alkyl halides (entries 1−4), including a secondary bromide (entry 2), undergo efficient deconjugative α-alkylation with cyclohex-1-enecarbonitrile as do carbonyl-containing electrophiles (entries 5−8); the alkylation with chlorobutyroyl chloride is selective for acylation over alkylation (entry 8). The activated aromatics, 4-iodobenzonitrile (entry 9) and 2-chloropyridine[21] (entry 10), afforded α-arylnitriles that are structurally similar to several nitrile-containing pharmaceuticals.[2] Propylene oxide (entry 11) and two disulfides (entries 12 and 13) reacted efficiently to afford substituted, deconjugated alkenenitriles for further manipulation (vide infra). The homologous cyclohept-1-enecarbonitrile efficiently alkylated BnBr in 78% yield (entry 14). Modifying the protocol by using a 0.05 M solution and two equivalents of the amido cuprate[22] allowed alkylations of cyclopent-1-enecarbonitrile (entries 15 and 16). Collectively, these alkylations demonstrate the value of employing CuCN for the deconjugative α-alkylation of cyclic nitriles.

Access to arylthio-containing nitrile **4n** provided a second method for deconjugative α-alkylation. Nitriles bearing adjacent arylthio substituents react with BuLi to afford nucleophilic sulfidates[23] that, for **4n**, is presumed to generate **5** (Scheme 1). Subsequent alkylation with 2-chloropyridine provided the pyridyl nitrile **4k** in 74% yield, essentially the same as the

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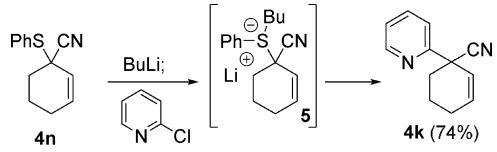
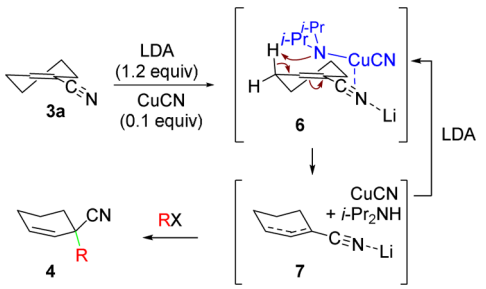
Scheme 1. Alternative Alkylation Route to Deconjugated α-Alkylated Nitriles



direct deconjugative α-alkylation (Table 1, entry 10). The sequence from **4n** to **4k** proceeds without CuCN, implying that the CuCN present from the amido cuprate facilitates only the deprotonation and not the arylation.

The role of the CuCN is intriguing. Interaction of the nitrile π-bond[24] with the amido cuprate may position the amide nitrogen close to the γ-proton for deprotonation (Scheme 2). Deprotonation would lead to lithiated nitrile **7** with release of CuCN that could react with LDA to reform the copper amide and complete the catalytic cycle.

Scheme 2. Tentative Deconjugative α-Alkylation Mechanism



The experimentally simple deconjugative α-alkylation of cyclic 5−7-membered alk-1-enecarbonitriles rests on employing an unusual amido cuprate for the deprotonation. The deconjugative α-alkylation is effective with a wide array of electrophiles, including alkyl bromides, avoids the polymerization that typically pervades these alkylations, and allows the previously inaccessable alkylation of cyclopent-1-enecarbonitrile. The alkylations efficiently access diverse quaternary nitriles, several of which contain a carbon scaffold found in bioactive nitriles.

EXPERIMENTAL SECTION

General Procedure for Copper-Catalyzed Alkenenitrile Alkylation. A THF solution (0.5−1.0 mM) of LDA [1.2 equiv, prepared from diisopropylamine (1.2 equiv) and BuLi (1.2 equiv)] was added to a stirred, −78 °C THF suspension of CuCN (0.1 equiv). After 5 min, neat alkenenitrile was added to the clear solution; the reaction was allowed to slowly warm to −45 °C over 1 h, and then the reaction mixture was cooled to −78 °C. Neat electrophile (1.2 equiv) was added to the reaction, and then the reaction was allowed to slowly warm to rt. After 2 h, saturated, aqueous NH_4Cl was added; the crude reaction mixture was extracted with EtOAc (3 × 10 mL), dried ($MgSO_4$), concentrated, and then purified by radial chromatography to afford analytically pure material.[25]

*1-Benzylcyclohex-2-enecarbonitrile (**4a**).* The general copper-catalyzed alkenenitrile alkylation procedure was employed with **3a** (50 mg, 0.47 mmol) and benzyl bromide (82 mg, 0.48 mmol) to afford, after purification by radial chromatography (1:10 EtOAc/hexanes), 96 mg (98%) of **4a** as a pale yellow oil: IR (film) 3058, 2230 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38−7.28 (m, 5H), 5.94 (dt, *J* = 9.5, 3.5 Hz, 1H), 5.59 (d, *J* = 9.8 Hz, 1H), 2.90 (ABq, Δν = 40 Hz, *J* = 15 Hz, 2H), 2.14−1.98 (m, 3H), 1.84−1.79 (m, 2H), 1.66−1.59 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.1, 131.4, 130.4, 128.4, 127.3, 126.1, 122.9, 45.4, 38.2, 32.8, 24.5, 19.0.; HRMS (+APCI) *m*/*z* [M + H^+] calcd for $C_{14}H_{16}N$ 198.1277; found 198.1277.

*1-Allylcyclohex-2-enecarbonitrile (**4b**).* The general copper-catalyzed alkenenitrile alkylation procedure was employed with **3a** (50 mg, 0.47 mmol) and allyl bromide (58 mg, 0.48 mmol) to afford, after purification by radial chromatography (1:10 EtOAc/hexanes), 65 mg (88%) of **4b** as an oil: IR (film) 3075, 2224, 1635 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.93−5.82 (m, 2H), 5.54 (d, *J* = 10.4 Hz, 1H), 5.25−5.14 (m, 2H), 2.42−2.27 (m, 2H), 2.13−1.92 (m, 3H), 1.86−1.74 (m, 2H), 1.53 (ddd, *J* = 13.4, 10.3, 4.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 131.8, 131.6, 126.0, 123.0, 120.1, 43.9, 36.8, 32.6, 24.5, 19.2. HRMS (+APCI) *m*/*z* [M + H^+] calcd for $C_{10}H_{14}N$ 148.1121; found 148.1121.

*1-(1-Phenylethyl)cyclohex-2-enecarbonitrile (**4c**).* The general copper-catalyzed alkenenitrile alkylation procedure was employed with **3a** (107 mg, 1.0 mmol) and (1-bromoethyl)benzene (205 mg, 1.2 mmol) to afford, after purification by silica gel flash chromatography (5:95 EtOAc/hexanes), 165 mg (78%) of **4c** as an oily, inseparable mixture of diastereomers (1:1): IR (film) 3031, 2937, 2227 cm^{-1}; ^{13}CNMR (101 MHz, $CDCl_3$) δ 141.6, (141.2), 131.9, (131.9), 128.9, (128.5), 128.5, (128.4), 127.5, 125.8, (125.5), 122.7, (122.6), 47.5, (47.1), 42.2, (42.1), 31.9, (31.8), 24.7, (24.6), 19.5, (19.2), 17.1, (16.7); HRMS(+APCI) *m*/*z* [M + H^+] calcd for $C_{15}H_{18}N$ 212.1434; found 212.1432. For diastereomer 1: ^1H NMR (500 MHz, $CDCl_3$) δ 7.34−7.27 (m, 5H), 5.89 (ddd, *J* = 10.1, 4.8, 2.7 Hz, 1H), 5.38 (ddt, *J* = 10.0, 3.0, 1.6 Hz, 1H), 2.84 (q, *J* = 7.1 Hz, 1H), 2.18−2.02 (m, 3H), 1.83−1.79 (m, 2H), 1.70−1.63 (m, 1H), 1.48 (d, *J* = 7.2 Hz, 3H). For diastereomer 2: ^1H NMR (500 MHz, $CDCl_3$) δ 7.34−7.27 (m, 5H), 5.95 (ddd, *J* = 10.1, 4.5, 2.9 Hz, 1H), 5.86−5.82 (m, 1H), 2.78 (q, *J* = 7.1 Hz, 1H), 2.01−1.94 (m, 3H), 1.77−1.71 (m, 2H), 1.63−1.58 (m, 1H), 1.55 (d, *J* = 7.1 Hz, 3H).

*1-(Pent-4-en-1-yl)cyclohex-2-enecarbonitrile (**4d**).* The general copper-catalyzed alkenenitrile alkylation procedure was employed with **3a** (107 mg, 1.0 mmol) and 5-bromo-1-pentene (179 mg, 1.2 mmol) to afford, after purification by silica gel flash chromatography (5:95 EtOAc/hexanes), 144 mg (82%) of **4d** as an oil: IR (film) 3030, 2942, 2865, 2229 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.91−5.87 (m, 1H), 5.79−5.75 (m, 1H), 5.54 (d, *J* = 9.9 Hz, 2H), 5.05−4.96 (m, 2H), 2.12−2.03 (m, 5H), 1.80−1.77 (m, 2H), 1.65−1.52 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.6, 130.9, 126.3, 123.0, 115.0, 38.9, 36.7, 33.4, 32.6, 24.4, 23.5, 19.1. HRMS (+APCI) *m*/*z* [M + H^+] calcd for $C_{12}H_{18}N$ 176.1434; found 176.1431.

*1-Hexylcyclohex-2-enecarbonitrile (**4e**).* The general copper-catalyzed alkenenitrile alkylation procedure was employed with **3a** (107 mg, 1.0 mmol) and 1-iodohexane (233 mg, 1.1 mmol) to afford, after purification by silica gel flash chromatography (5:95 EtOAc/hexanes), 138 mg (72%) of **4e** as an oil: IR (film) 2931, 2860, 2230 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.89−5.84 (m, 1H), 5.53 (d, *J* = 10.0 Hz, 1H), 2.11−1.99 (m, 3H), 1.82−1.75 (m, 2H), 1.62−1.44 (m, 5H), 1.37−1.26 (m, 6H), 0.91−0.85 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 131.0, 126.7, 123.5, 39.9, 37.1, 32.8, 31.6, 29.4, 24.6, 24.5, 22.6, 19.3, 14.1 ; HRMS (+APCI) *m*/*z* [M + H^+] calcd for $C_{13}H_{22}N$ 192.1747; found 192.1746.

*1-Pivaloylcyclohex-2-enecarbonitrile (**4f**).* The general copper-catalyzed alkenenitrile alkylation procedure was employed with **3a** (107 mg, 1.0 mmol) and pivaloyl chloride (145 mg, 1.2 mmol) to afford, after purification by flash chromatography (1:10 EtOAc/hexanes), 175 mg (92%) of **4f** as an oil; IR (film) 2938, 2880, 2236, 1710 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.08−6.04 (m, 1H), 5.63−5.59 (m, 1H), 2.19−2.00 (m, 3H), 2.03 (ddd, *J* = 12.9, 11.1, 3.6 Hz, 1H), 1.92−1.83 (m, 2H), 1.39 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.3, 132.5, 122.7, 120.9, 46.5, 46.4, 32.1, 26.9, 23.7, 18.4.; HRMS (+APCI) *m*/*z* [M + H^+] calcd for $C_{12}H_{18}NO$ 192.1383; found 192.1387.

*Methyl 1-Cyanocyclohex-2-enecarboxylate (**4g**).* The general copper-catalyzed alkenenitrile alkylation procedure was employed with **3a** (107 mg, 1.0 mmol) and methyl cyanoformate (102 mg, 1.2 mmol) to afford, after purification by flash chromatography (1:10 EtOAc/hexanes), 145 mg (88%) of **4g** as an oil: IR (film) 2957, 2244, 1747 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.11−6.07 (m, 1H), 5.75−

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5.71 (m, 1H), 3.84 (s, 3H), 2.23−2.10 (m, 4H), 1.89−1.84 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.9, 133.7, 121.2, 119.2, 53.9, 43.5, 30.9, 24.1, 18.7; HRMS (+APCI) m/z [M + H$^+$] calcd for $C_9H_{12}NO_2$ 166.0863; found 166.0866.

*1′-Hydroxy-[1,1′-bi(cyclohexan)]-2-ene-1-carbonitrile (**4h**).* The general copper-catalyzed alkenenitrile alkylation procedure was employed with **3a** (107 mg, 1.0 mmol) and cyclohexanone (118 mg, 1.2 mmol) to afford, after purification by flash chromatography (1:10 MTBE/hexanes), 150 mg (90%) of **4h** as a white solid (mp 87−88 °C): IR (film) 3464, 2934, 2235 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.07−6.03 (m, 1H), 5.78−5.75 (m, 1H), 2.16−1.94 (m, 3H), 1.89−1.81 (m, 3H), 1.73−1.56 (m, 8H), 1.51 (d, J = 1.4 Hz, 1H), 1.48−1.38 (m, 1H), 1.20−1.08 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.6, 123.0, 122.5, 74.4, 48.2, 32.5, 31.0, 28.0, 25.5, 24.6, 21.5, 19.9; HRMS (+APCI) m/z [M + H$^+$] calcd for $C_{13}H_{20}NO$ 206.1539; found 206.1545.

*1-(4-Chlorobutanoyl)cyclohex-2-enecarbonitrile (**4i**).* The general copper-catalyzed alkenenitrile alkylation procedure was employed with **3a** (107 mg, 1.0 mmol) and 4-chlorobutyryl chloride (280 mg, 1.20 mmol) to afford, after purification by silica gel flash chromatography (1:10 EtOAc/hexanes), 154 mg (73%) of **4i** as an oil: IR (film) 3031, 2934, 2240, 1722 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.15−6.10 (m, 1H), 5.66 (d, J = 9.9 Hz, 1H), 3.56 (t, J = 6.2 Hz, 2H), 2.94−2.90 (m, 2H), 2.15−1.97 (m, 6H), 1.86−1.80 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.2, 134.4, 120.5, 119.7, 49.6, 43.9, 35.4, 30.1, 26.3, 24.1, 18.7; HRMS (+APCI) m/z [M + H$^+$] calcd for $C_{11}H_{15}ClON$ 212.0837; found 212.0837.

*1,2,3,4-Tetrahydro-[1,1′-biphenyl]-1,4′-dicarbonitrile (**4j**).* The general copper-catalyzed alkenenitrile alkylation procedure was employed with **3a** (50 mg, 0.47 mmol) and 4-iodobenzonitrile (110 mg, 0.48 mmol) to afford, after purification by radial chromatography (1:10 EtOAc/hexanes), 98 mg (94%) of **4j** as an oil: IR (film) 2972, 2209 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 8.4 Hz, 2H), 7.59 (d, J = 8.4 Hz, 2H), 6.23 (dt, J = 9.8, 3.8 Hz, 1H), 5.71 (d, J = 9.9 Hz, 1H), 2.32−2.14 (m, 3H), 1.98−1.89 (m, 1H), 1.84−1.75 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.1, 133.8, 132.8, 127.3, 124.5, 121.5, 118.4, 112.1, 42.8, 37.9, 24.2, 19.3; HRMS (+APCI) m/z [M + H$^+$] calcd for $C_{14}H_{13}N_2$ 209.1073; found 209.1073.

*1-(Pyridin-2-yl)cyclohex-2-enecarbonitrile (**4k**).* The general copper-catalyzed alkenenitrile alkylation procedure was employed with **3a** (107 mg, 1.0 mmol) and 2-chloropyridine (125 mg, 1.2 mmol) to afford, after purification by silica gel flash chromatography (15:85 EtOAc/hexanes), 132 mg (72%) of **4k** as an oil: IR (film) 2932, 2865, 2237 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66−8.65 (m, 1H), 7.76−7.71 (m, 1H), 7.54−7.51 (m, 1H), 7.28−7.24 (m, 1H), 6.20−6.17 (m, 1H), 5.87−5.84 (m, 1H), 2.37−2.31 (m, 1H), 2.24−2.18 (m, 2H), 2.11 (ddd, J = 12.9, 11.5, 2.8 Hz, 1H), 2.00−1.96 (m, 1H), 1.85−1.81 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3, 150.0, 137.3, 132.7, 125.0, 122.9, 122.2, 121.0, 45.0, 35.8, 24.3, 19.4; HRMS (+APCI) m/z [M + H$^+$] calcd for $C_{12}H_{13}N_2$ 185.1073; found 185.1079.

*Preparation of **4k** by Sulfide-Lithium Exchange.* A hexanes solution of BuLi (0.55 mmol, 1.1 equiv) was added to a −78 °C THF solution (10 mL) of **4n** (107 mg, 0.5 mmol). After 5 min, neat 2-chloropyridine (68 mg, 0.6 mmol) was added, and then the reaction was allowed to slowly warm to room temperature. After 12 h, saturated aqueous NH_4Cl was added; the mixture was extracted with EtOAc, washed with brine and water, dried (Na_2SO_4), and concentrated. The residue was then purified by radial chromatography (1:10 EtOAc/hexanes) to afford 68 mg (74%) of **4k** as an oil spectrally identical to material previously isolated.

*1-(2-Hydroxypropyl)cyclohex-2-enecarbonitrile (**4l**).* The general copper-catalyzed alkenenitrile alkylation procedure was employed with **3a** (107 mg, 1.0 mmol) and propylene oxide (70 mg, 1.2 mmol) to afford, after purification by flash chromatography (1:10 EtOAc/hexanes), 146 mg (88%) of **4l** as an oily mixture of inseparable diastereomers (1:1 ratio): IR (film) 3440, 3029, 2933, 2838, 2230 cm^{-1}; ^{13}C NMR (101 MHz, $CDCl_3$) δ 131.6, (130.9), 127.0, (126.5), 123.75, (123.70), 65.35, (65.33), 48.2, 35.84, (35.75), 33.46, (33.37), 25.2, (25.1), 24.5, 19.3, (19.1); HRMS (+APCI) m/z [M + H+] calcd for $C_{10}H_{16}NO$ 166.1226; found 166.1230. For diastereomer 1: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.93−5.89 (m, 1H), 5.76−5.75 (m, 1H), 4.20−4.18 (m, 1H), 2.13−2.02 (m, 3H), 1.86−1.67 (m, 6H), 1.27 (d, J = 2.6 Hz, 3H). For diastereomer 2: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.93−5.89 (m, 1H), 5.61−5.58 (m, 1H), 4.20−4.18 (m, 1H), 2.13−2.02 (m, 3H), 1.86−1.67 (m, 6H), 1.26 (d, J = 2.6 Hz, 3H).

*1-(Pyridin-2-ylthio)cyclohex-2-enecarbonitrile (**4m**).* The general copper-catalyzed alkenenitrile alkylation procedure was employed with **3a** (321 mg, 3 mmol) and 2,2′-dipyridyldisulfide (748 mg, 3.4 mmol) to afford, after purification by silica gel flash chromatography (1:10 EtOAc/hexanes), 410 mg (63%) of **4m** as an oil: IR (film) 2932, 2867, 2842, 2229 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59−8.57 (m, 1H), 7.64−7.60 (m, 1H), 7.42−7.40 (m, 1H), 7.19−7.16 (m, 1H), 6.05−6.01 (m, 1H), 5.95−5.92 (m, 1H), 2.42−2.37 (m, 2H), 2.17−2.13 (m, 2H), 2.05−1.96 (m, 1H), 1.89−1.82 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.3, 150.1, 136.9, 133.2, 125.9, 123.7, 122.1, 121.0, 42.8, 33.3, 24.5, 18.4; HRMS (+APCI) m/z [M + H$^+$] calcd for $C_{12}H_{13}N_2S$ 217.0794; found 217.0795.

*1-(Phenylthio)cyclohex-2-enecarbonitrile (**4n**).* The general copper-catalyzed alkenenitrile alkylation procedure was employed with **3a** (877 mg, 8.2 mmol) and diphenyl disulfide (1962 mg, 9.0 mmol) to afford, after purification by silica gel flash chromatography (5:95 EtOAc/hexanes), 1.5 g (85%) of **4n** as an oil: IR (film) 2932, 2863, 2231 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71−7.68 (m, 2H), 7.47−7.39 (m, 3H), 6.00 (dt, J = 9.8, 3.7 Hz, 1H), 5.61 (dt, J = 9.8, 2.2 Hz, 1H), 2.15−1.93 (m, 5H), 1.79−1.75 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.3, 133.0, 130.5, 129.6, 129.4, 123.4, 120.9, 44.1, 32.9, 24.5, 18.2; HRMS (+APCI) m/z [M + H$^+$] calcd for $C_{13}H_{14}NS$ 216.0842; found 216.0839.

*Cyclohept-1-enecarbonitrile (**3b**).* A THF solution of cycloheptanecarbonitrile (1.00 g, 8.2 mmol) was added to a −78 °C THF solution of LDA (1.1 equiv). After 1 h, a THF (30 mL) solution of methyl phenylsulfinate[26] (1.40 g, 9.0 mmol) was added dropwise, and then the reaction was allowed to slowly warm to room temperature. After 13 h, saturated, aqueous NH_4Cl was added; the organic layer was separated, and then the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic extract was washed with brine, dried (Na_2SO_4), and concentrated to afford a crude product that was purified by silica gel flash column chromatography (1:99 EtOAc/hexanes) to afford 751.5 mg (69%) of pure **3b** as an oil: IR (film) 2932, 2862, 2215 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79- 6.76 (m, 1H), 2.41−2.38 (m, 2H), 2.32−2.27 (m, 2H), 1.79−1.74 (m, 2H), 1.63−1.53 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.7, 121.2, 117.8, 31.6, 31.5, 29.8, 26.3, 25.8; HRMS (+APCI) m/z [M + H$^+$] calcd for $C_8H_{12}N$ 122.0964; found 122.0963.

*1-Benzylcyclohept-2-enecarbonitrile (**4o**).* The general copper-catalyzed alkenenitrile alkylation procedure was employed with **3a** (121 mg, 1 mmol) and benzyl bromide (205 mg, 1.2 mmol) to afford, after purification by silica gel flash chromatography (5:95 EtOAc/hexanes), 165 mg (78%) of **4o** as an oil: IR (film) 3029, 2926, 2856, 2228 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.28 (m, 5H), 6.00−5.94 (m, 1H), 5.56−5.52 (m, 1H), 2.94 (ABq, $\Delta\nu$ = 50 Hz, J = 16 Hz, 2H), 2.31−2.20 (m, 2H), 1.96−1.89 (m, 3H), 1.85−1.74 (m, 1H), 1.58−1.52 (m, 1H), 1.43−1.36 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.2, 135.4, 130.9, 130.6, 128.4, 127.4, 121.7, 46.4, 42.5, 35.9, 27.7, 27.0, 26.3; HRMS (+APCI) m/z [M + H$^+$] calcd for $C_{15}H_{18}N$ 212.1434; found 212.1431.

*1-Hexylcyclopent-2-enecarbonitrile (**4p**).* A THF solution (10 mL) of LDA (2.2 mmol) was added to a −78 °C THF (5 mL) suspension of CuCN (180 mg, 2.0 mmol). After 5 min, a THF solution (5 mL) of alkenenitrile **3c** (93 mg, 1.0 mmol) and 1-iodohexane (466 mg, 2.2 mmol) was added to the clear solution, and then the reaction was allowed to slowly warm to rt. After 12 h, saturated, aqueous NH_4Cl was added; the crude reaction mixture was extracted with EtOAc (3 × 10 mL), dried (Na_2SO_4), and concentrated, and then the crude nitrile was purified by silica gel flash chromatography (5:95 EtOAc/hexanes) to afford 163 mg (92%) of **4p** as an oil: IR (film) 2956, 2932, 2859, 2227 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.95−5.93 (m, 1H), 5.67−5.64 (m, 1H), 2.50−2.36 (m, 3H), 1.96−1.91 (m, 1H), 1.66−1.46 (m, 4H), 1.33−1.26 (m, 6H), 0.94−0.81 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.7, 131.2, 123.8, 48.0, 39.1, 35.8, 31.7, 31.6, 29.4, 25.7,

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J. Org. Chem. 2016, 81, 4098−4102

22.7, 14.2; HRMS (+APCI) m/z [M + H$^+$] calcd for $C_{12}H_{20}N$ 178.1590; found 178.1588.

*1-(Pyridin-2-yl)cyclopent-2-enecarbonitrile (**4q**).* A THF solution (10 mL) of LDA (2.2 mmol) was added to a −78 °C THF (5 mL) suspension of CuCN (180 mg, 2.0 mmol). After 5 min, a THF solution (5 mL) of alkenenitrile **3c** (93 mg, 1.0 mmol) and 2-chloropyridine (251 mg, 2.2 mmol) was added to the clear solution, which was then allowed to slowly warm to rt. After 12 h, saturated, aqueous NH_4Cl was added; the crude reaction mixture was extracted with EtOAc (3 × 10 mL), dried (Na_2SO_4), and concentrated, and then the crude nitrile was purified by silica gel flash chromatography (10:90 EtOAc/hexanes) to afford 88 mg (52%) of **4q** as an oil: IR (film) 3060, 2946, 2856, 2236 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64−8.62 (m, 1H), 7.75−7.70 (m, 1H), 7.52−7.50 (m, 1H), 7.27−7.23 (m, 1H), 6.25−6.23 (m, 1H), 5.88−5.85 (m, 1H), 2.79−2.76 (m, 1H), 2.72−2.60 (m, 2H), 2.55−2.50 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8, 150.0, 137.3, 136.9, 130.3, 122.9, 122.2, 120.4, 55.0, 39.1, 32.2; HRMS (+APCI) m/z [M + H$^+$] calcd for $C_{11}H_{11}N_2$ 171.0917; found 171.0920.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00367.

^{1}H NMR and ^{13}C NMR FID files (ZIP)

Table of ^{1}H NMR and ^{13}C NMR spectra for all new compounds and a table showing optimization of the catalyst loading (PDF)

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Notes

The authors declare no competing financial interest.

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