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Enantioselective Synthesis of Cyclic, Quaternary Oxonitriles

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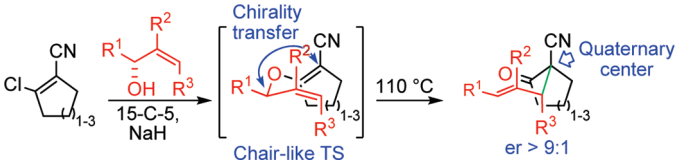

Quaternary oxonitriles are stereoselectively generated from the union of five-, six-, and seven-membered 2-chloroalkenecarbonitriles with chiral alcohols via a Claisen rearrangement. The strategy rests on a new conjugate addition−elimination of allylic alkoxides to 2-chlorocycloalkenecarbonitriles to afford substituted 2-alkoxyalkenenitriles. Subsequent thermolysis unmasks a cyclic oxonitrile while selectively forming a new quaternary center with enantiomeric ratios typically greater than 9:1. The overall alkylation strategy addresses the challenge of enantioselectively generating hindered, quaternary centers while simultaneously installing ketone, nitrile, and olefin functionalities.

Introduction

Installing hindered, quaternary centers remains one of the most challenging bond constructions in synthesis.[1] Forging quaternary centers with high enantiomeric ratios has stimulated diverse strategies, many of which harness intramolecular assistance to overcome the unfavorable steric compression of the central carbon atom.[2] Within several representative methods, asymmetric conjugate additions,[3] transition-metal-mediated coupling,[4] aldol condensation,[5] and allylic alkylation,[6] for example, the aim is not only to selectively install quaternary centers but to simultaneously install multiple, easily differentiated functional groups.

Mixed carbonyl-nitrile nucleophiles have featured in several quaternization methods.[7] The attraction lies in the nitrile's small steric demand,[8] which eases the steric compression, and the facile chemoselective descrimination between carbonyl and nitrile functionalities.[9] Chiral alkylations of cyclic ketonitriles are particularly attractive because of their rich history as synthetic intermediates.[10] For this reason, oxonitriles have been employed in alkylations with chiral auxiliaries[11] and chiral bases[12] and as pronucleophiles in chiral conjugate additions.[13]

Arguably the most robust method for installing hindered, quaternary centers is the Claisen rearrangement.[14] The predictability and efficiency of the Claisen rearrangement appeared

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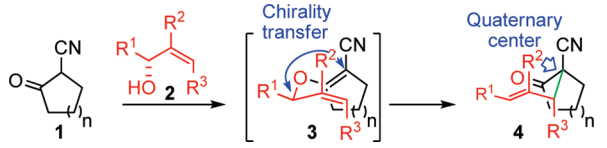
ideally matched with the versatility of oxonitriles[7] for installing functionalized quaternary centers. The strategy rests on condensing five-, six-, and seven-membered cyclic oxonitriles **1** with a chiral allylic alcohol **2** to afford an 2-alkoxyalkenenitrile **3** for a subsequent rearrangement (Scheme 1). The oxonitrile−Claisen strategy holds a 3-fold attraction: the predictable configuration of the quaternary center; the commercial availability of many chiral allylic alcohols as an inexpensive source of chirality; and installation of orthogonal ketone, nitrile, and alkene functionalities. Described here is the successful crafting of chiral quaternary oxonitriles through this efficient, stereoselective, and predictable strategy.

SCHEME 1. Oxonitrile−Claisen Rearrangement Strategy

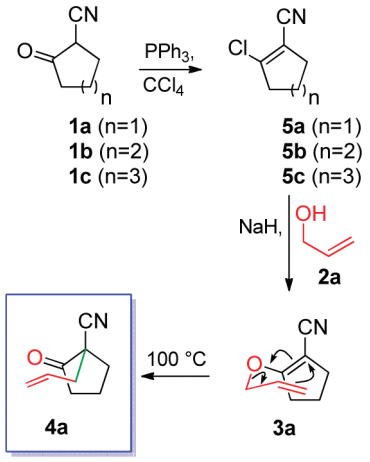


Results and Discussion

A major challenge in executing the oxonitrile Claisen strategy resides in accessing substituted 2-alkoxyalkenenitriles. *O*-Allylation of oxonitriles is often frustrated by competitive *C*-allylation and generally requires primary allylic electrophiles.[15] For assembling the more challenging *secondary* β-allyloxyalkenenitriles a conceptually different strategy was developed based on an addition−elimination of an alkoxide to 2-chlorocycloalkenecarbonitriles **5a**−**5c** (Scheme 2).[16] Facile access to 2-chlorocyclopentenecarbonitrile (**5a**) was readily achieved in 73% yield by halogenating **1a**[17] with Ph_3P and CCl_4.[18] Attemps to use PCl_5, $POCl_3$, triphosgene, and oxalyl chloride either afforded significantly lower yields or were completely ineffective. Although the chlorination of **5a** is relatively facile, the corresponding six- and seven-membered oxonitriles (**1b** and **1c**, respectively) are unreactive toward Ph_3P and CCl_4 under identical conditions. Access to the requisite six- and seven-membered chloroalkenenitriles was achieved by heating the reaction in a sealed tube at 110 °C, which effectively provides 2-chlorocyclohexenecarbonitrile (**5b**) and 2-chlorocycloheptenecarbonitrile (**5c**) in 82% and 76%, respectively.

Exploratory addition−eliminations to **5a** employed allyl alcohol and sodium hydride (Scheme 2). Although the desired 2-alkoxyalkenenitrile **3a** was obtained, the isolation was hampered by hydrolysis of the sensitive vinyl ether during silica gel chromatography.[19] An expedient solution was to simply perform the thermolysis on the crude 2-alkoxyalkenenitrile **3a** to directly access the allyl ketonitrile **4a** (40% yield, Scheme 2).

SCHEME 2. Claisen−Oxonitrile Alkylation Strategy



Close scrutiny of the crude reaction mixture before and after the Claisen rearrangement revealed the emergence of several side products during formation of the 2-alkoxyalkenenitrile, whereas the rearrangement faithfully generated oxonitrile **4a** of a similar purity. Consequently, subsequent optimization focused on improving the conjugate addition−elimination. Attempts to improve the alkoxide nucleophilicity through solvent[20] and temperature[21] changes met with minimal reward. The most efficacious conditions were to add 15-crown-5 to a room-temperature THF solution of the sodium alkoxide, which raised the overall yield of **4a** to 65%.[22]

Use of 15-crown-5 promotes the facile assembly of a variety of substituted 2-alkoxyalkenenitriles (Table 1, column 4).[23] Acyclic and cyclic primary and secondary allylic alcohols react equally well (Table 1, entries 1−8) with disubstituted olefins tolerating terminal or internal substituents (Table 1, compare entries 2, 3, and 8). Tertiary alcohols, not surprisingly, are unable to afford the 2-alkoxyalkenenitriles.[24] Remarkably, the addition−elimination proceeds with (*S*)-*cis*-verbenol (**2i**) to afford alkenenitrile **3i** despite the sterically hindered nature of

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(16) Under basic conditions, primary alcohols engage in a conjugate addition−elimination: (a) Redman, A. M.; Dumas, J.; Scott, W. J. *Org. Lett.* **2000**, *2*, 2061. (b) Friedrich, K.; Bechtold, L. W.; Fritz, H. *J. Pract. Chem.* **2000**, *342*, 819.

(17) Readily prepared from adiponitrile by a Thorpe−Ziegler cyclization: Schaefer, J. P.; Bloomfield, J. J. *Org. React.* **1967**, *15*, 1.

(18) The combination of Ph_3P, CCl_4 (a) was far superior than the previously described use of PCl_5 or $POCl_3$ for preparing 2-chlorocyclopentenecarbonitrile (b). (a) Kemp, D. S.; Carter, J. S. *J. Org. Chem.* **1989**, *54*, 109. (b) Cariou, M.; Lamont, M. *C. R. Chim. (C)* **1974**, *278*, 1457.

(19) Triethylamine was incorporated as a trace cosolvent during the isolation of several related Claisen substrates hinting at a general instability of these enol ethers.[15b]

(20) Use of DMF alone or THF/DMF mixtures did not improve the yield.

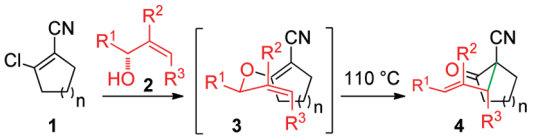
(21) Performing the reaction at reflux did not improve the overall yield.

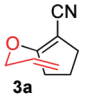
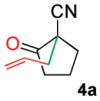
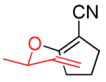
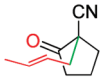
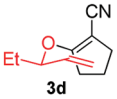
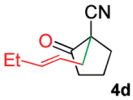
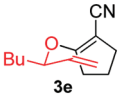
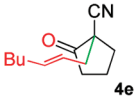
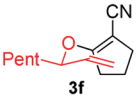
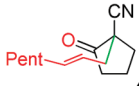
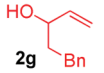
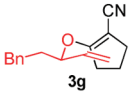
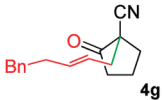
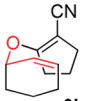
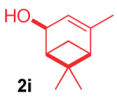
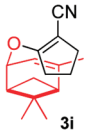
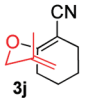
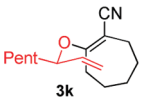
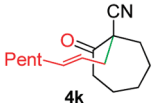
(22) KH with and without 18-C-6 yields similar results, but the lower cost and easier manipulation of NaH focused subsequent optimization on the latter base.

(23) The 2-alkoxyalkenenitriles were identified from ^1H NMR spectra of the crude reaction mixture and subjected to the Claisen rearrangement. Although the crude 2-alkoxyalkenenitriles from conjugate addition−elimination could be directly thermolyzed, in our experience the efficiency is improved through an aqueous work up prior to thermolysis.

(24) Use of linalool as a prototypical tertiary alcohol did not provide any enol ether even at elevated temperatures.

TABLE 1. Alkenenitrile Addition−Claisen Rearrangements



entry	nitrile	alcohol	alkenenitrile	quaternary nitrile	Yield[a]
1	**1a**	 **2a**	 **3a**	 **4a**	65%
2	**1a**	 **2b**	 **3b**	 **4b**	75%
3	**1a**	 **2c**	 **3c**	 **4c**	55%
4	**1a**	 **2d**	 **3d**	 **4d**	62%
5	**1a**	 **2e**	 **3e**	 **4e**	65%
6	**1a**	 **2f**	 **3f**	 **4f**	60%
7	**1a**	 **2g**	 **3g**	 **4g**	60%
8	**1a**	 **2h**	 **3h**	 **4h**	60%[b]
9	**1a**	 **2i**	 **3i**	-	70%[c]
10	**1b**	 **2b**	 **3j**	 **4j**	70%
11	**1c**	 **2f**	 **3k**	 **4k**	65%

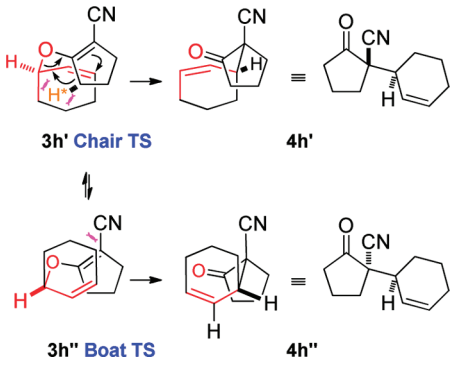
[a]Isolated as a single isomer unless otherwise indicated. [b]Isolated as a 1:1 mixture of diastereomers. [c]Yield of alkenenitrile.

the secondary alcohol (Table 1, entry 9). Unfortunately the steric compression that likely protects the acid sensitive enol ether of **3i** during chromatography also prevents Claisen rearrangement.

Despite the Claisen rearrangement of 2-alkyoxyalkenenitriles being retarded relative to the parent alkene,[15,25] the thermal sigmatropic bond relocation effectively generates a variety of quaternary oxonitriles (Table 1).[15,26] The diastereoselectivity is excellent for the rearrangement of the 2-alkoxyalkenenitriles derived from *acyclic* secondary allylic alcohols, with only the *trans*-alkene being observed (Table 1, entries 3−7 and 11). Thermolysis of **3h**, bearing a cyclic *cis*-alkene as part of the allyl ether, proceeds with the same efficiency but without any diastereofacial selectivity (Table 1, entry 8). Extending the strategy to six- and seven-membered alkenenitriles faithfully installs quaternary centers in the corresponding six- and seven-membered oxonitriles (Table 1, entries 10 and 11, respectively).

Diastereomers only arise in the rearrangement of **3h**, which most likely arises from the cyclic *Z*-alkene of the allylic ether moiety. Typically Claisen rearrangements occur through a chair-like transition structure,[14] as observed in closely related cyclic enol ethers,[27] which strongly suggests that the 2-alkoxyalkenenitriles typically rearrange through chairlike TSs. However, the chairlike transition structure emanating from **3h** thrusts the allylic proton H* directly into the face of the approaching cyclohexene ring (**3h′**, Scheme 3).[28] Bond migration from the opposite face, **3h″**, necessarily requires rearrangement through a boat-like TS. Although steric compression between the two rings is relieved in the exo arrangement **3h″**, the boat TS causes the nitrile to eclipse the cyclohexene methylene protons. The close interplay between these two different sets of steric interactions in **3h′** and **3h″** is reflected in the absence of diastereoselectivity (Table 1, entry 8) but suggests substitution patterns to improve the selectivity (vide infra).

SCHEME 3. Conformations Leading to Diastereomeric Oxonitriles



Excellent enantioselectivity is observed for addition−rearrangements with *chiral*, secondary, allylic alcohols (Table 2).[29]

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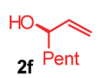
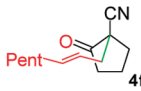
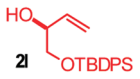
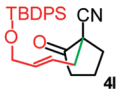
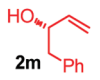
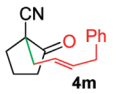
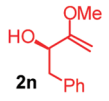
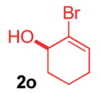
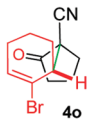
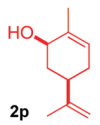
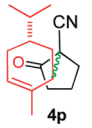
(26) Orsini, F.; Pelizzoni, F.; Forte, M. *Gazz. Chim. Ital.* **1986**, *116*, 115.
(27) Mikami, K.; Takahashi, K.; Nakai, T.; Uchimaru, T. *J. Am. Chem. Soc.* **1994**, *116*, 10948.
(28) For an excellent overview and computational analysis of chair and boat TSs in this type of system, see: (a) Gul, S.; Schoenebeck, F.; Aviyente, V.; Houk, K. N. *J. Org. Chem.* **2010**, *75*, 2115. (b) Khaledy, M. M.; Kalani, M. Y. S.; Khuong, K. S.; Houk, K. N.; Aviyente, V.; Neier, R.; Soldermann, N.; Velker, J. *J. Org. Chem.* **2003**, *68*, 572.
(29) An analogous rearrangement with chiral **3k** was successful but the enantiomeric ratio was unable to be determined using a variety of HPLC and GC methods.

TABLE 2. Enantioselective Oxonitrile Syntheses

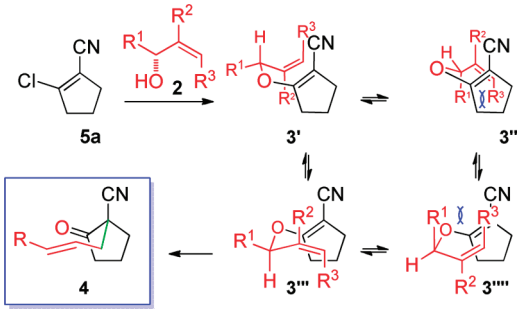
entry	alcohol	quaternary nitrile	yield	er/dr
1			60%	95:5
2			55%	93:7[a]
3			48%	95:5
4			72%	90:10[b]
5			55%	>99:1
6			73%	50:50

[a]The enantiomeric ratio was determined on the alcohol (**i**) obtained by cleaving the silyl ether. [b]The enantiomeric ratio was determined on the ketone (**ii**) obtained by hydrolysis of the enol ether.

Allylic alcohols **2f**, **2l**, and **2m** lacking olefinic substituents faithfully translate the carbinol stereochemistry with a *minimum* enantiomeric ratio of 93:7 (Table 2, entries 1−3). Substitution on the olefin slightly diminishes the ratio to 90:10 for **2n**, whereas with the cyclic, disubstituted allylic alcohol **2o** only a single enantiomer is detected (Table 2, entries 4 and 5, respectively). Introducing an additional stereocenter in the cyclohexenol ring, for **2p**, leads to a complete loss of stereoselectivity (Table 2, entry 6).

Effective translation of the allylic alcohol chirality to the quaternary center of the oxonitrile requires excellent discrimination between chair and boat transition structures (Scheme 4).

SCHEME 4. Claisen−Oxonitrile Alkylation Strategy

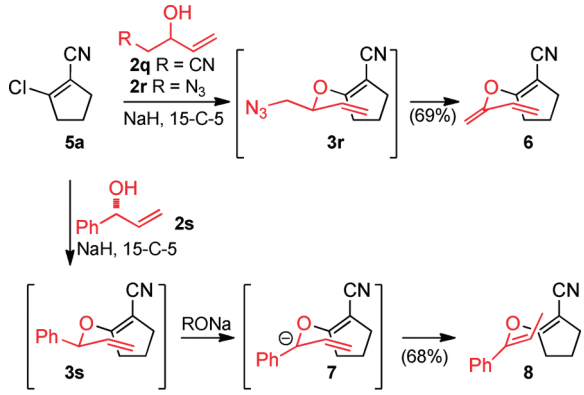


Comparing the four possible transition structures reveals severe allylic strain between the two alkyl substituents R^1 and R^3 in conformations **3′′** and **3′′′′**.[30] Of the two more favorable conformers **3′** and **3′′′**, the primary difference lies in **3′** progressing through a boat-like TS, whereas **3′′′** progresses through a chairlike TS. For the acyclic allylic alcohols the corresponding 2-alkoxyalkenenitriles exhibit a high preference for rearranging through chairlike transition structures corresponding to **3′′′** (Table 2, entries 1−4).[27]

Thermolysis of the nitrile derived from **2n**, in which the alkene bears a methoxy substituent, is less selective. Rearrangement via **3′′′** engenders a diaxial-type interaction, between R^2 and the nitrile, that is avoided in the boat TS **3′**. Despite the steric compression, the enantiomeric ratio remains relatively high at 90:10 (Table 2, entry 4).

Claisen rearrangement of the 2-alkoxyalkenenitriles derived from the cyclic allylic alcohols **2h**, **2o**, and **2p** can only proceed through the two transition structures **3′′** and/or **3′′′′** because of the *Z*-geometry of the allylic ether moiety. For the parent nitrile (**3h**, Table 1, entry 8) the transition structures must be of comparable energy because no selectivity is observed. Installing a bromine substituent proximal to the alcohol is anticipated to strongly destabilize conformer **3′′** (R^2 = Br) because of the steric compression between the bromine and nitrile groups *and* the alignment of their dipoles. Rearrangement via **3′′′′** places the dipoles in opposite directions and minimizes the steric interaction because the cyclopentene ring moves the ring methylene away from a true diaxial interaction with the proximal bromine substituent. Crystallization of **4o** allowed unequivocal determination of the absolute and relative configuration with the assignment being consistent with rearrangement via a boat-like transition structure.[31] Although carveol (**2p**) might be expected to exhibit a similar preference for bond translocation through a boat-like transition structure **3′′′′**, the isopropyl substituent projects into the cyclopentene ring in **3′′′′**, which is avoided in the chairlike TS **3′′**.[28] The consequence of the two competing effects is a lack of selectivity (Table 2, entry 6).

SCHEME 5. Divergent Addition−Eliminations



Investigating the structural diversity of the allylic alcohol identified two limitations of the addition−rearrangement strategy (Scheme 5). Attempts to condense the hydroxynitrile **2q**[32] with chloroalkenenitrile **5a** were not successful, possibly because of the lability of these "cyanoaldolates"

(30) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.

(31) Crystallographic details are provided in the Supporting Information.

(32) Prepared from (*S*)-3-buten-1,2-diol as described in the Supporting Information.

toward retroaldol fragmentation under basic conditions.[33] An analogous condensation with the azide **2r** afforded the diene **6**, presumably via elimination of hydroazoic acid from **3r**. The elimination appears delicately poised because the silyl ether-containing allylic alcohol **2l** (Table 2, entry 2) participates in the rearrangement without elimination.

Unexpectedly (*R*)-1-phenylprop-2-en-1-ol (**2s**) affords the bis-enol ether **8**. Mechanistically **8** likely arises through an initial conjugate addition−elimination to chloroalkenenitrile **5a** to afford **3s**. Presumably excess sodium alkoxide, whose basicity is enhanced through the addition of 15-crown-5, deprotonates **3s** to afford the delocalized anion **7**. Reprotonation affords the conjugated olefin **8** with the methyl eclipsing the smaller ether oxygen rather than the larger phenyl group.[34]

Conclusion

Installing quaternary centers in a diverse series of cyclic five-, six-, and seven-membered oxonitriles is readily accomplished by translating the stereochemistry of readily available chiral alcohols via a Claisen rearrangement. Key to this strategy is the union of *secondary* allylic alkoxides to 2-chlorocycloalkenecarbonitriles through a conjugate addition−elimination sequence. Subsequent thermolysis of the 2-alkoxyalkenenitriles selectively installs a new quaternary center with enantiomeric ratios typically greater than 9:1.

The strategy readily generates highly congested quaternary centers with substitution patterns that complement those available by asymmetric allylic alkylation methods. For example, transition metal coupling is ideal for the parent allylation, whereas the Claisen chirality transfer is excellent for the union of two cyclic substrates that forge a hindered quaternary-tertiary array. The sigmatropic rearrangement precludes formation of olefin regioisomers and always installs a *trans*-alkene unless constrained within a medium-sized ring.

Experimentally the reaction is a two-step operation in which an allylic alkoxide is condensed with a cyclic 2-chloroalkenecarbonitrile to afford a 2-alkoxyalkenenitrile that is directly thermolyzed. Diverse primary and secondary, cyclic and acyclic, allylic alcohols readily engage in the addition−rearrangement to give good yields of quaternary oxonitriles. Collectively the range of substituted allylic alcohols provide mechanistic insight and define the substitution patterns required for highly stereoselective rearrangements. The overall alkylation strategy addresses the challenge of enantioselectively installing hindered quaternary centers in cyclic hydroxynitriles while simultaneously installing orthogonal ketone, nitrile, and olefin functional groups.

Experimental Section

General Procedure for 2-Chlorocycloalkene-1-carbonitriles (5). Solid PPh_3 was added to a CH_2Cl_2 solution of the cyclic oxonitrile and CCl_4. The resulting reaction mixture was refluxed for 30 h or heated in a sealed tube for 48 h, the solvent was removed, and then the crude product was purified by silica gel column chromatography (1:4 EtOAc/hexanes) to afford the pure 2-chlorocycloalkene-1-carbonitriles.

2-Chlorocyclopent-1-enecarbonitrile (5a). The general procedure was employed with 2.00 g (18.34 mmol) of **1a** to afford 1.72 g (73%) of **5a**: IR (neat) 2220, 1622, 1434 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.76−2.60 (m, 4H), 2.17−2.01 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 152.0, 116.5, 112.7, 40.5, 35.2, 23.8.

2-Chlorocyclohex-1-enecarbonitrile (5b). The general procedure was employed with 1.50 g (12.18 mmol) of **1b** to afford 1.41 g (82%) of **5b**: IR (neat) 2217, 1631, 1450 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.50−2.45 (m, 2H), 2.37−2.33 (m, 2H), 1.81−1.75 (m, 2H), 1.73−1.66 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.5, 116.9, 109.9, 33.8, 28.4, 22.5, 20.8.

2-Chlorocyclohept-1-enecarbonitrile (5c). The general procedure was employed with 2.10 g (15.30 mmol) of **1c** to afford 1.81 g (76%) of **5c**: IR (neat) 2216, 1619, 1447 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.73−2.70 (m, 2H), 2.45−2.42 (m, 2H), 1.77−1.74 (m, 2H), 1.67−1.62 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5, 118.3, 114.3, 39.7, 31.6, 30.8, 25.8, 24.7; HRMS (ESI) [$M + H^+$] calcd for 156.0580 ($C_8H_{11}ClN$), found 156.0577.

General Conjugate Addition−Claisen Rearrangement Procedure. At rt, THF solutions of the allylic alcohol and neat 15-crown-5 were added sequentially to a suspension of NaH in THF or hexanes. After 3 h, a THF or hexanes solution of **5** was added, and after 40 h H_2O was added. The phases were separated, and the aqueous phase was then extracted with EtOAc. The combined organic phase was washed with brine, dried over Na_2SO_4 or $MgSO_4$, filtered, and then concentrated in vacuo. The crude 2-alkoxycycloalkenenitrile was dissolved in toluene and was then heated in a sealed tube at 110 °C for 20 h. After removal of the solvent in vacuo, the residue was purified by radial chromatography or column chromatography (EtOAc/Hexanes) to afford the pure oxonitrile.

1-Allyl-2-oxocyclopentanecarbonitrile (4a). The general procedure was employed in THF with 200.0 mg (1.57 mmol) of **5a** to give 152 mg (65%) of **4a**:[35] IR (neat) 2239, 1755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.85−5.74 (m, 1H), 5.26 (d, J = 9.0 Hz, 1H), 5.22 (d, J = 16.8 Hz, 1H), 2.61 (dd, J = 13.9, 7.0 Hz, 1H), 2.54−1.96 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.1, 130.9, 121.2, 119.0, 48.5, 38.1, 36.8, 33.7, 19.4; HRMS (ESI) [$M + H^+$] calcd for 150.0919 ($C_9H_{12}NO$), found 150.0913.

1-(2-Methylallyl)-2-oxocyclopentanecarbonitrile (4b). The general procedure was employed in THF with 500.0 mg (3.92 mmol) of **5a** to give 463 mg (75%) of **4b**: IR (neat) 2233, 1753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.98 (s, 1H), 4.85 (s, 1H), 2.60 (d, J = 14.4 Hz, 1H), 2.53−2.31 (m, 3H), 2.21 (d, J = 14.4 Hz, 1H), 2.13−1.98 (m, 3H), 1.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.3, 139.5, 119.5, 116.9, 47.9, 41.20, 36.4, 33.9 23.4, 19.4; HRMS (ESI) [$M + H^+$] calcd for 164.1075 ($C_{10}H_{14}NO$), found 164.1070.

(*E*)-1-(But-2-enyl)-2-oxocyclopentanecarbonitrile (4c). The general procedure was employed in THF with 200.0 mg (1.57 mmol) of **5a** to give 140 mg (55%) of **4c**: IR (neat) 2235, 1755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.64 (dq, J = 15.2, 4.0 Hz, 1H), 5.40 (dt, J = 15.2, 6.4 Hz, 1 H), 2.45 (dd, J = 14.0, 6.8 Hz, 1H), 2.46−2.27 (m, 3H), 2.25−2.19 (dd, J = 14.0, 7.6 Hz, 1H), 2.12−1.91 (m, 3H), 1.6 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.5, 132.2, 123.3, 119.3, 48.9, 37.0, 36.8, 33.5, 19.4, 18.2; HRMS (ESI) [$M + H^+$] calcd for 164.1075 ($C_{10}H_{14}NO$), found 164.1070.

(*E*)-2-Oxo-1-(pent-2-enyl)cyclopentanecarbonitrile (4d). The general procedure was employed in THF with 200.0 mg (1.57 mmol) of **5a** to give 171 mg (62%) of **4d**: IR (neat) 2235, 1770 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.75−5.16 (m, 1H), 5.46−5.31 (m, 1H), 2.60−1.94 (m, 10H), 0.99 (t, J = 7.5 Hz,

(33) (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.

(34) For an excellent compilation of steric compression based on A values see ref 8.

(35) Spectrally identical to material previously characterized: Levy, L. M.; Gotor, V. *J. Org. Chem.* **2004**, *69*, 2601.

3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 211.1, 141.0, 122.9, 121.0, 50.7, 38.8, 38.6, 35.33, 27.6, 21.1, 15.5; HRMS (ESI) [M + H^+] calcd for 178.1232 ($C_{11}H_{16}NO$), found 178.1226.

(*E*)-1-(Hept-2-enyl)-2-oxocyclopentanecarbonitrile (4e). The general procedure was employed in THF with 100.0 mg (0.78 mmol) of **5a** to give 107 mg (65%) of **4e**: IR (neat) 2235, 1753 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.71 (dtt, J = 15.4, 6.6, 1.5 Hz, 1H), 5.38 (dtt, J = 15.4, 6.6, 1.5 Hz, 1H), 2.54 (m, 10H), 1.40−1.24 (m, 4H), 0.87 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, CDCl3) δ 209.5, 137.8, 122.0, 119.3, 48.9, 37.0, 36.8, 33.5, 32.4, 31.5, 22.4, 19.4, 14.1; HRMS (ESI) [M + H^+] calcd for 206.1545 ($C_{13}H_{20}NO$), found 206.1539.

(+)-(*E*)-1-(Oct-2-enyl)-2-oxocyclopentanecarbonitrile (4f). The general procedure was employed in THF with 200.0 mg (1.57 mmol) of **5a** to give 192 mg (65%) of **4f**: 95:5 er was determined by HPLC (Daicel AS, 5% isopropanol/hexanes, 1.0 mL/min 295 nm, t_R (major) = 9.7 min, t_R (minor) = 8.6 min). $[\alpha]^{25}_D$ = +30.15 (c 1.26, ethyl acetate); IR (neat) 2236, 1755 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.63 (dt, J = 15.2, 7.3 Hz, 1H), 5.38 (dt, J = 15.2, 7.4 Hz, 1H), 2.55 (dd, J = 14.2, 7.2 Hz, 1H), 2.50−2.29 (m, 3H), 2.25 (dd, J = 14.2, 8.0 Hz, 1H), 2.16−1.93 (m, 5H), 1.40−1.20 (m, 6H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.4, 137.8, 122.0, 119.2, 49.0, 37.1, 37.0, 33.5, 32.7, 31.5, 29.0, 22.7, 19.4, 14.3; HRMS (ESI) [M + H^+] calcd for 220.1701 ($C_{14}H_{22}NO$), found 220.1696.

(*E*)-2-Oxo-1-(5-phenylpent-2-enyl)cyclopentanecarbonitrile (4g). The general procedure was employed in THF with 200.0 mg (1.57 mmol) of **5a** to give 119 mg (60%) of **4g**: IR (neat) 2234, 1753 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.33−7.16 (m, 5H), 5.65 (dt, J = 15.3, 6.3 Hz, 1H), 5.45−5.31 (dt, J = 15.3, 7.3 Hz, 1H), 2.72 (t, J = 7.5 Hz, 2H) 2.60−1.87 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 210.0, 142.4, 137.3, 129.5, 129.3, 126.9, 123.8, 120.0, 49.5, 37.7, 37.6, 36.4, 35.1, 34.1, 20.1; HRMS (ESI) [M + H^+] calcd for 254.1545 ($C_{17}H_{20}NO$), found 254.1539.

1-(Cyclohex-2-enyl)-2-oxocyclopentanecarbonitriles (4h). The general procedure was employed in THF with 200.0 mg (1.57 mmol) of **5a** to give 350 mg (60%) of **4h**. Careful chromatography gave two pure fractions of the first and second eluting isomers (85 mg and 45 mg, respectively). **First isomer**: light yellow oily liquid, R_f = 0.3 (1:9 EtOAc/hexanes). IR (neat) 2233, 1755 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91−5.88 (m, 1H), 5.13 (d, J = 10.4 Hz, 1H), 2.87−2.4 (m, 1H), 2.59−2.52 (m, 1H), 2.37−1.97 (m, 8H), 1.87−1.82 (m, 1H), 1.60−1.39 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.9, 133.0, 124.3, 119.0, 52.9, 39.5, 38.1, 31.1, 26.0, 25.1, 21.6, 19.8. **Second isomer**: colorless liquid, R_f = 0.23 (1:9 EtOAc/hexanes). IR (neat) 2234, 1750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.97−5.92 (m, 1H), 5.81 (d, J = 12.0 Hz, 1H), 2.70−2.65 (m, 1H), 2.55−2.49 (m, 1H), 2.37−2.25 (m, 2H), 2.18−1.98 (m, 5H), 1.89−1.72 (m, 2H), 1.58−1.47 (m, 1H), 1.37−1.23 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.4, 131.8, 125.2, 119.1, 52.4, 39.4, 37.7, 31.6, 24.9, 24.7, 22.8, 19.5; HRMS (ESI) [M + Na^+] calcd for 212.1051 ($C_{12}H_{15}NaNO$), found 212.1046.

1-(2-Methylallyl)-2-oxocyclohexanecarbonitrile (4j). The general procedure was employed in hexanes with 100.0 mg (0.71 mmol) of **5b** to give 88 mg (70%) of **4j**: IR (neat) 2218, 1730 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.98 (m, 1H), 4.85 (m, 1H), 2.84 (ddd, J = 13.7, 11.1, 5.7 Hz, 1H), 2.75 (d, J = 14.3 Hz, 1H), 2.49 (m, 1H), 2.38−2.32 (m, 2H), 2.13−1.98 (m, 2H), 1.93−1.66 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.9, 139.3, 120.2, 116.6, 50.3, 40.9, 39.0, 38.1, 28.4, 23.5, 21.9; HRMS (ESI) [M + H^+] calcd for 178.1232 ($C_{11}H_{16}NO$), found 178.1220.

(+)-(*E*)-1-(Oct-2-enyl)-2-oxocycloheptanecarbonitrile (4k). The general procedure was employed in hexanes with 185.0 mg (1.19 mmol) of **5c** to give 191 mg (65%) of **4k**: $[\alpha]^{20}_D$ = +13 (c 1.00; $CHCl_3$); IR (neat) 2239, 1715 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.60 (dt, J = 14.9, 6.8 Hz, 1H), 5.37 (m, 1H), 2.69 (dt, J = 12.5, 5.2 Hz, 1H), 2.61−2.53 (m, 2H), 2.35 (dd, J = 13.9, 7.9 Hz, 1H), 2.15 (m, 1H), 1.96−1.87 (m, 3H), 1.78−1.58 (m, 2H), 1.38−1.20 (m, 8H), 0.87 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.3, 137.7, 121.1, 120.4, 55.3, 41.2, 40.2, 35.3, 32.7 31.5, 29.1, 29.0, 26.0, 24.7, 22.7, 14.2; HRMS (ESI) [M + H^+] calcd for 248.2014 ($C_{16}H_{26}NO$), found 248.2010.

(+)-(*E*)-1-(4-Hydroxybut-2-enyl)-2-oxocyclopentanecarbonitrile (4l). The general procedure was employed in THF with 72.0 mg (0.56 mmol) of **5a** to give 133 mg (55%) of **4l**. The enantiomeric ratio was determined on the alcohol derived by deprotecting **4l** (260 mg, 0.62 mmol) with Bu_4NF, which afforded alcohol **i** (39.0 mg, 35%). 93:7 er was determined by HPLC (Daicel OB-H, 10% isopropanol/hexanes, 0.9 mL/min 207 nm, t_R (major) = 40.9 min, t_R (minor) = 32.9 min). $[\alpha]^{20}_D$ = +16.77 (c 1.55, $CHCl_3$); IR (neat) 3411, 2238, 1751 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.82−5.51 (m, 2H), 4.04 (dd, J = 4.9, 1.1 Hz, 2H), 2.66−1.88 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 210.9, 137.7, 125.2, 120.8, 64.4, 50.5, 38.4, 35.5, 21.0; HRMS (ESI) [M + H^+] calcd for 180.1025 ($C_{10}H_{14}NO_2$), found 180.1019.

(−)-(*E*)-2-Oxo-1-(4-phenylbut-2-enyl)cyclopentanecarbonitrile (4m). The general procedure was employed in THF with 167.0 mg (1.30 mmol) of **5a** to give 151 mg (48%) of **4m**: 95:5 er was determined by HPLC (Daicel OB-H, 20% isopropanol/hexanes, 1.0 mL/min 210 nm, t_R (major) = 17.8 min, t_R (minor) = 22.4 min); $[\alpha]^{20}_D$ = −10.4 (c 0.58; EtOAc); IR (neat) 2236, 1751 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.29 (m, 2H), 7.23−7.17 (m, 3H), 5.81 (dtt, J = 15.0, 6.8, 1.1 Hz, 1H), 5.53 (dddt, J = 15.0, 8.1, 6.8, 1.4 Hz, 1H), 3.41 (d, J = 6.8 Hz, 2H), 2.62−2.26 (m, 5H), 2.14−1.93 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.4, 140.0, 136.0, 128.8, 128.7, 126.5, 123.8, 119.2, 48.8, 39.2, 37.0, 36.8, 33.7, 19.4; HRMS (ESI) [M + H^+] calcd for 240.1388 ($C_{16}H_{18}NO$), found 240.1383.

(+)-2-Oxo-1-(2-oxo-4-phenylbutyl)cyclopentanecarbonitrile (4n). The general procedure was employed in THF with 210.0 mg (1.64 mmol) of **5a** to give 350 mg (72%) of **4n**. The enantiomeric ratio was determined on the corresponding ketone obtained by hydrolysis with 2 M HCl which afforded quantitatively **ii** (301.0 mg). 90:10 er was determined by HPLC (Daicel OC, 10% isopropanol/hexanes, 1.0 mL/min 206 nm, t_R (major) = 72.6 min, t_R (minor) = 66.2 min). $[\alpha]^{20}_D$ = +2.8 (c 2.86; EtOAc); IR (neat) 2230, 1755, 1716 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30−7.13 (m, 5H), 3.09 (s, 2H), 2.87 (t, J = 7.5 Hz, 2H), 2.74 (t, J = 7.5 Hz, 2H), 2.65−2.40 (m, 3H), 2.17−2.04 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.8, 204.8, 140.3, 128.9, 128.5, 126.6, 118.6, 46.2, 45.1, 44.1, 36.7, 33.7, 29.8, 20.1; HRMS (ESI) [M + H^+] calcd for 256.1338 ($C_{16}H_{18}NO_2$), found 256.1332.

(*S*)-(−)-1-((*S*)-2-Bromocyclohex-2-enyl)-2-oxocyclopentanecarbonitrile (4o). The general procedure was employed in THF with 69.0 mg (0.54 mmol) of **5a** to give 79 mg (55%) of **4o**: $[\alpha]^{20}_D$ = −124 (c 1.00; $CHCl_3$); IR (KBr) 2229, 1745 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.34−6.32 (m, 1H), 3.22−3.16 (m, 1H), 2.63−2.52 (m, 2H), 2.32 (m, 1H), 2.20−2.02 (m, 5H), 1.93 (m, 1H), 1.80 (m, 1H), 1.56 (m, 1H), 1.37 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.7, 136.3, 120.7, 119.6, 52.2, 45.3, 38.6, 31.5, 27.7, 27.2, 20.4,19.6; HRMS (ESI) [M + H^+] calcd for 268.0337 ($C_{12}H_{15}BrNO$), found 268.0332.

(+)-1-((5*S*)-2-Methyl-5-(prop-1-en-2-yl)cyclohex-2-enyl)-2-oxocyclopentanecarbonitrile (4p). The general procedure was employed in THF with 160.0 mg (1.26 mmol) of **5a** to give 224 mg (73%) of **4p**. The diastereomers were carefully separated to obtain pure first and second eluting isomers for characterization. **First isomer**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.68 (m, 1H), 4.75 (m, 1H), 4.70 (m, 1H), 3.08 (m, 1H), 2.66−1.80 (m, 10H), 1.74 (s, 3H), 1.40 (s, 3H). **Second isomer**: IR (neat) 2229, 1755 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.68 (m, 1H), 4.76 (s, 1H), 4.67 (s, 1H), 2.67 (m, 1H), 2.55 (m, 1H), 2.39−2.00 (m, 11H), 1.86 (s, 3H), 1.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

210.1, 209.9, 148.8, 132.0, 130.7, 130.2, 130.1, 128.9, 120.9, 118.8, 109.5, 109.4, 54.2, 50.5, 44.2, 42.5, 41.5, 40.8, 38.8, 36.9, 34.0, 31.2, 31.0, 30.5, 29.8, 29.7, 24.2, 23.2, 21.1, 21.0, 19.8, 19.2; HRMS (ESI) [$M + H^+$] calcd for 244.1701 ($C_{16}H_{22}NO$), found 244.1696.

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Supporting Information Available: Experimental procedures, analytical data for all new compounds, and a CIF file for **4o**. This material is available free of charge via the Internet at http://pubs.acs.org.