JOC Article

# Cyclic Alkenenitriles: Synthesis, Conjugate Addition, and Stereoselective Annulation

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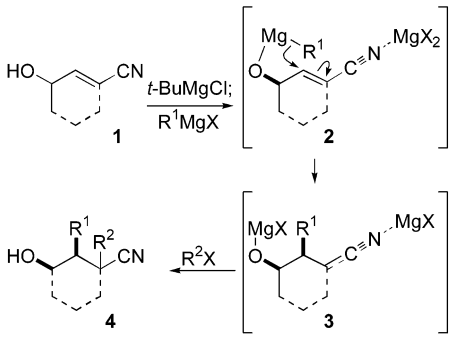
*O*-Alkylation of unsaturated silyl cyanohydrins with DMSO−$Ac_2O$ triggers a rearrangement to methylthiomethyl-protected hydroxyalkenenitriles that are easily hydrolyzed for subsequent annulations with $\omega$-chloroalkyl Grignard reagents. Deprotonating the $\gamma$-hydroxyalkenenitriles with *t*-BuMgCl followed by addition of $\omega$-chloroalkyl Grignard reagents triggers a conjugate addition−alkylation sequence leading exclusively to *cis*-octalins, hydrindanes, and decalins. Stereoelectronic control favors an axial conjugate addition leading to a particularly reactive conformer that rapidly cyclizes to *cis*-fused bicyclic nitriles, whereas generating the ring-flipped conformer, through a stepwise sequence, allows access to the diastereomeric *trans*-decalin. Collectively, the rearrangement−annulation sequence represents the first general annulation of alkenenitriles to assemble diverse bicyclic nitriles with complete control over the two newly installed stereocenters.

## Introduction

Annulations feature prominently as key bond-forming reactions in natural product syntheses.[1] The centrality of annulation reactions stems from numerous reliable strategies for elaborating monocyclic precursors into complex, biologically active, multicyclic targets.[2] Originally, the power of annulation-based synthesis was first demonstrated in Robinson annulation routes to steroids,[3] initiating an enduring search for annulations of increasing complexity, stereoselectivity, and efficiency.[4] Fulfilling these criteria has inspired syntheses of several exceptionally versatile bifunctional reagents, containing nucleophilic and electrophilic centers, for sequential conjugate addition−alkylation annulations to unsaturated carbonyl compounds.[5]

Annulation reactions with unsaturated nitriles are inherently more difficult than analogous annulations with unsaturated carbonyl compounds. The challenge stems from the paucity of anionic conjugate additions to unsaturated nitriles which, despite being highly polarized,[6] are recalcitrant Michael acceptors that react poorly with many conventional nucleophiles.[7] A particularly effective method for promoting conjugate additions to alkenenitriles[8] is to temporarily chelate Grignard reagents to $\gamma$-hydroxy unsaturated nitriles,[9] effectively harnessing the inherent entropic advantages[10] of intramolecular reactions in promoting a formal intermolecular conjugate addition (Scheme 1). Mechanistically, sequential deprotonation of hydroxyalkenenitriles **1** followed by alkyl exchange[11] from a modest excess of a

**SCHEME 1. Chelation-Controlled Conjugate Addition−Alkylation of Alkenenitriles**




* Corresponding author.

(1) (a) Tokoroyama, T. *Synthesis* **2000**, 611. (b) Vandewalle, M.; De Clercq, P. *Tetrahedron* **1985**, *41*, 1767.

(2) Varner, M. A.; Grossman, R. B. *Tetrahedron* **1999**, *55*, 13867.

(3) (a) Gawley, R. E. *Synthesis* **1976**, 777. (b) Jung, M. E. *Tetrahedron* **1976**, *32*, 3.

(4) For recent annulation reviews, see: (a) Reference 1. (b) McCarroll, A. J.; Walton, J. C. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3215. (c) Grossman, R. B. *Synlett* **2001**, 13. (c) Larock, R. C. *J. Organomet. Chem.* **1999**, *576*, 111. (d) Davies, H. M. L. *Adv. Cycloaddition* **1999**, *5*, 119.

(5) Piers, E. *Pure Appl. Chem.* **1988**, *60*, 107.

(6) Reddy, G. S.; Mandell, L.; Goldstein, J. H. *J. Am. Chem. Soc.* **1961**, *83*, 3, 1300.

(7) Fleming, F. F.; Wang, Q. *Chem. Rev.* **2003**, *103*, 2035.

(8) (a) Jamison, T. F.; Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 4353. (b) Molander, G. A.; Harris, C. R. *J. Org. Chem.* **1997**, *62*, 7418. (c) Fleming, F. F.; Hussain, Z.; Weaver, D.; Norman, R. E. *J. Org. Chem.* **1997**, *62*, 1305. (d) Cooke, M. P., Jr.; Parlman, R. M. *J. Am. Chem. Soc.* **1977**, *99*, 5222. (e) Brattesani, D. N.; Heathcock, C. H. *J. Org. Chem.* **1975**, *40*, 2165.

(9) For hydroxy alkenenitriles, see: (a) Fleming, F. F.; Wang, Q.; Zhang, Z.; Steward, O. W. *J. Org. Chem.* **2002**, *67*, 5953. For hydroxy alkynenitriles, see: (b) Fleming, F. F.; Gudipati, V.; Steward, O. W. *Tetrahedron* **2003**, *59*, 5585.

(10) Eliel, E. L.; Wilen, S. H.; Mander, L. N. In *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; pp 676−682.

(11) Swiss, K. A.; Liotta, D. C.; Maryanoff, C. A. *J. Am. Chem. Soc.* **1990**, *112*, 9393.

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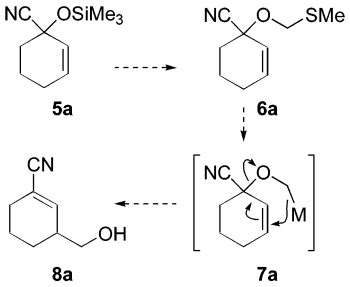
second Grignard reagent generates the alkylmagnesium alkoxide **2** that triggers a stereoselective conjugate addition. Alkylating the resulting magnesiated nitrile **3** with electrophiles installs two new stereocenters in one synthetic operation.[12]

Conceptually, the sequential conjugate addition−alkylation of $\omega$-chloroalkyl Grignard reagents[5,13] to cyclic hydroxyalkenenitriles provides an annulation route to bicyclic nitriles. Developing this annulation strategy requires an expedient synthesis of cyclic hydroxyalkenenitriles for which few syntheses currently exist.[14] Addressing this deficiency suggested accessing the requisite cyclic hydroxyalkenenitriles from an unsaturated silyl cyanohydrin since chiral silyl cyanohydrins are readily available in high enantiomeric ratios.[15] The strategy envisages conversion of an unsaturated trimethylsilyl cyanohydrin to the corresponding methylthiomethyl ether followed by halogen−SMe exchange and [2,3] Wittig rearrangement (Scheme 2). The 2-fold appeal of this sequence lies in transposing the cyanohydrin chirality into the hydroxyalkenenitrile[16] for stereoselective chelation-controlled conjugate additions and in concurrently expanding the versatility of silyl cyanohydrins through an oxygen functional group interchange rather than the more typical addition to, or hydrolysis of, the nitrile group.[15]

**SCHEME 2. Cyanohydrin−Alkenenitrile Rearrangement Strategy**

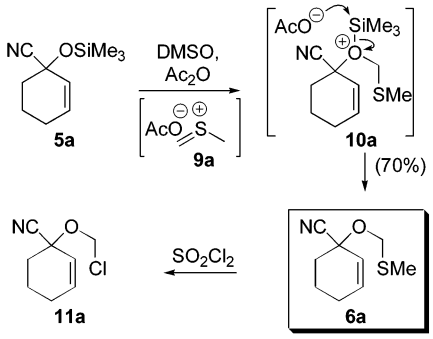



Pursuing this strategy identified an unusual silyl cyanohydrin rearrangement for synthesizing several cyclic alkenenitriles. Chelation-controlled conjugate addition of $\omega$-chloroalkyl Grignard reagents to the resulting cyclic hydroxyalkenenitriles generates intermediate magnesiated nitriles that cyclize to *cis*-octalins, hydrindanes, and decalins in the first general annulation of alkenenitriles. Collectively, the rearrangement-annulation reactions generate a diverse array of bicyclic nitriles providing insight into the stereoelectronically controlled conjugate addition and cyclization reactions.

## Results and Discussion

A key lead for *O*-alkylating the trimethylsiloxyl group of enone-derived[17] cyanohydrins stems from two *O*-alkylations of trimethylsilyl cyanohydrins with $ClCH_2OCH_3$.[18] Presuming the alkylation to require a particularly reactive electrophile, the cyanohydrin **5a**[17a,b] was treated with the sulfonium ylide **9a**[19] to directly generate the methylthiomethyl cyanohydrin **6a** (Scheme 3). The trimethylsilyl−methylthiomethyl interchange proceeds by an *O*-alkylation of **5a** with ylide **9a**,[20] formed in situ from DMSO and acetic anhydride,[19] followed by desilylation to generate **6a**. Unfortunately, chlorination of **6a** with $SO_2Cl_2$[21] followed by numerous metalation strategies failed to promote the desired Wittig rearrangement[22] of **11a** but rather caused significant degradation and formation of ketone-containing ethers arising from attack on the nitrile group.[23] Attempts to deprotonate and rearrange the corresponding nitrile (**11a**, CN═Cl),[24] were similarly fruitless despite close precedent in the rearrangement of cyanomethyl enamines.[25]

**SCHEME 3. *O*-Alkylation of Silylcyanohydrin 5a**




Although the [2,3] Wittig strategy proved unmanageable, concurrent alkylations of the methyl-substituted

(12) Fleming, F. F.; Wang, Q.; Steward, O. W. *J. Org. Chem.* **2003**, *68*, 4235.

(13) (a) Boudier, A.; Bromm, L. O.; Lotz, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 4415. (b) Bernady, K. F.; Poletto, J. F.; Nocera, J.; Mirando, P.; Schaub, R. E.; Weiss, M. J. *J. Org. Chem.* **1980**, *45*, 4702.

(14) (a) Fleming, F. F.; Wang, Q.; Steward, O. W. *J. Org. Chem.* **2001**, *66*, 2171. (b) Kurihara, T.; Miki, M.; Yoneda, R.; Harusawa, S. *Chem. Pharm. Bull.* **1986**, *34*, 2747. (c) Nokami, J.; Mandai, T. Nishimura, A.; Takeda, T.; Wakabayashi, S.; Kunieda, N. *Tetrahedron Lett.* **1986**, *27*, 5109. (d) Nokami, J.; Mandai, T.; Imakura, Y.; Nishiuchi, K.; Kawada, M.; Wakabayashi, S. *Tetrahedron Lett.* **1981**, *22*, 4489.

(15) (a) Gregory, R. J. H. *Chem. Rev.* **1999**, *99*, 3649. (b) Effenberger, F. *Enantiomer* **1996**, *1*, 359. (c) North, M. *Synlett* **1993**, 807.

(16) Schrader, T.; Kirsten, C.; Herm, M. *Phosp. Sulf. Silicon* **1999**, *144−146*, 161.

(17) (a) Higuchi, K.; Onaka, M.; Izumi, Y. *Bull. Chem. Soc. J.* **1993**, *66*, 2016. (b) Wada, M.; Takahashi, T.; Domae, T.; Fukuma, T.; Miyoshi, N.; Smith, K. *Tetrahedron: Asymmetry* **1997**, *8*, 3939. (c) Agami, C.; Fadlallah, M. *Tetrahedron* **1983**, *39*, 777.

(18) Kabalka, G. W.; Mathur, S. B.; Gai, Y. Z. *Org. Prep. Proc. Intl.* **1990**, *22*, 87.

(19) (a) Lee, T. V. In *Comprehensive Organic Synthesis*; Fleming, I., Trost, B. M., Eds.; Pergamon: Oxford, 1991; Vol. 7, pp 291−303. (b) Yamada, K.; Kato, K.; Nagase, H.; Hirata, Y. *Tetrahedron Lett.* **1976**, *17*, 65.

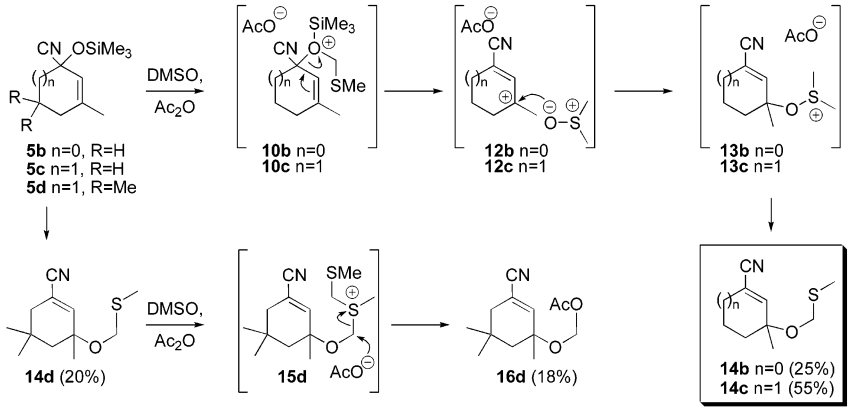
(20) O-Alkylation of the TMS cyanohydrin by the sulfonium ylide, rather than $Ac_2O$, is required by the recovery of unreacted **5c** from refluxing $Ac_2O$.

(21) Okada, Y.; Wang, J.; Yamamoto, T.; Mu, Y.; Yokoi, T. *J. Chem. Soc., Perkin Trans. 1* **1996,** 2139.

(22) Davidsen, S. K. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: Chichester, U.K., 1995; pp 5005−5006.

(23) The poor electrophilicity of the nitrile functionality and the viability of several nitrile-containing alkyllithium[a,b] and Grignard[c−h] reagents implied the viability of forming and rearranging the metalated cyanohydrin **7a**. (a) Tucker, C. E.; Majid, T. N.; Knochel, P. *J. Am. Chem. Soc.* **1992**, *114*, 3983. (b) Parham, W. E.; Jones, L. D. *J. Org. Chem.* **1976**, *41*, 1187. (c) Inoue, A.; Kitagawa, K.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **2001**, *66*, 4333. (d) Lee, J.-s.; Velarde-Ortiz, R.; Guijarro, A.; Wurst, J. R.; Rieke, R. D. *J. Org. Chem.* **2000**, *65*, 5428. (e) Abarbri, M.; Thibonnet, J.; Bérillon, L.; Dehmel, F.; Rottländer, M.; Knochel, P. *J. Org. Chem.* **2000**, *65*, 4618. (f) Thibonnet, J.; Knochel, P. *Tetrahedron Lett.* **2000**, *41*, 3319. (g) Kitagawa, K.; Inoue, A.; Shinokubo, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 2481. (h) Burns, T. P.; Rieke, R. D. *J. Org. Chem.* **1987**, *52*, 3674.

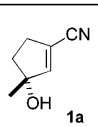
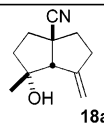
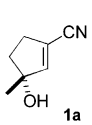
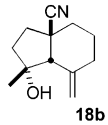
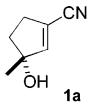
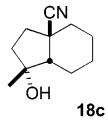
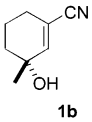
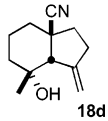
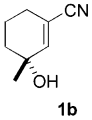
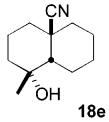
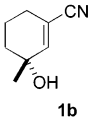
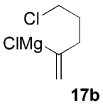
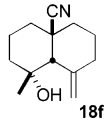
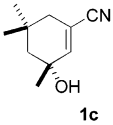
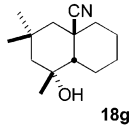
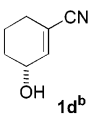
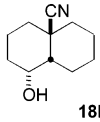
**SCHEME 4. Rearrangement of Trimethylsilyl Cyanohydrins to Cyclic Alkenenitriles**




analogue **5c** were rewarded with an unanticipated rearrangement to the synthetically valuable cyclic alkenenitrile **14c** (Scheme 4). Mechanistically, alkylation of **5c** with the sulfonium salt **9a** affords the oxonium ion **10c**[26] that, unlike **10a**, fragments to the more stable methyl-substituted carbocation[27] **12c** (Scheme 4). Subsequent DMSO attack[28] on carbocation **12c** generates the sulfonium nitrile[29] **13c** that suffers a Pummerer-type rearrangement[30] to afford the rearranged nitrile **14c** (55% yield). The relatively facile rearrangement of **5c** contrasts with the significantly less efficient rearrangement of the cyanohydrins **5b** and **5d** (24% and 20% yield, respectively)[31] that rearrange more slowly[32] allowing the initially formed alkenenitriles to react further, as implied by concurrent formation of the unusual ester−nitrile **16d** with **14d**.[30e]

Mercury-assisted hydrolyses[33] of **14b**−**d** efficiently provides a series of $\gamma$-hydroxyalkenenitriles for chelation-controlled conjugate addition−alkylations (Table 1).[34] *t*-BuMgCl-initiated deprotonation of the 5-membered nitrile **1a** and addition of a slight excess of the chloroalkyl Grignard reagents **17a**−**c** trigger sequential conjugate addition−alkylations generating the octaline- and hydrindane-substituted nitriles **18a**−**c** (Table 1, entries

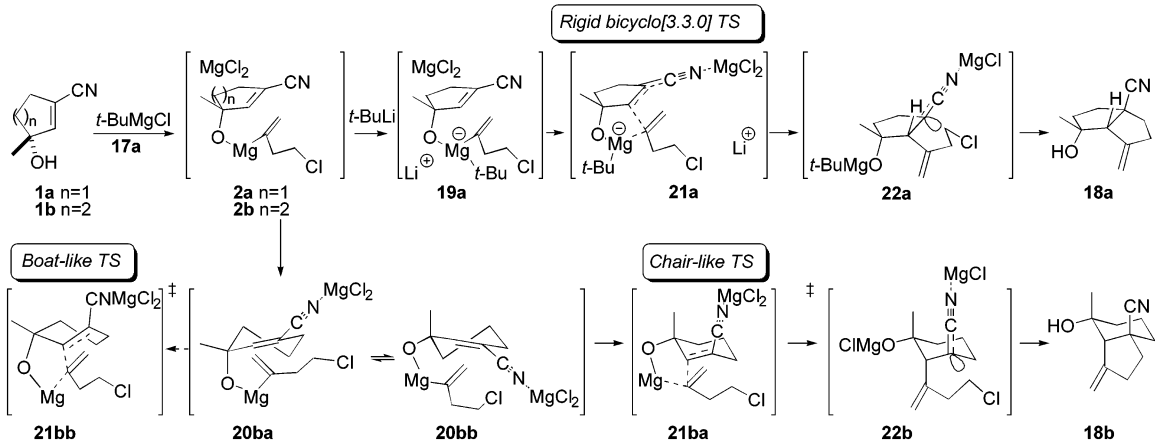
**TABLE 1. Hydroxyalkenenitrile Annulations with $\omega$-Chloroalkyl Grignard Reagents**

| entry | alkenenitrile | Grignard | bicyclic nitrile | yield |
|---|---|---|---|---|
| 1 |  **1a** |  **17a**[a] |  **18a** | 62% |
| 2 |  **1a** |  **17b** |  **18b** | 68% |
| 3 |  **1a** |  **17c** |  **18c** | 56% |
| 4 |  **1b** |  **17a** |  **18d** | 65% |
| 5 |  **1b** |  **17c** |  **18e** | 58% |
| 6 |  **1b** |  **17b** |  **18f** | 75% |
| 7 |  **1c** |  **17c** |  **18g** | 54% |
| 8 |  **1d**[b] |  **17c** |  **18h** | 64% |

[a] One equivalent of *t*-BuLi is added after addition of **17a** to promote conjugate addition through the ate complex (Scheme 5). [b] **1d** was synthesized by ring opening of the corresponding epoxide.[14a]

(24) Soli, E. D.; Manoso, A. S.; Patterson, M. C.; DeShong, P.; Favor, D. A.; Hirschmann, R.; Smith, A. B., III. *J. Org. Chem.* **1999**, *64*, 3171.
(25) Mander, L. N.; Turner, J. V. *J. Org. Chem.* **1973**, *38*, 2915.
(26) Prior cleavage of the TMS group to the corresponding cyanohydrin (**5c**, $Me_3Si$=H), by adventitious acetic acid, appears unlikely since subjecting the cyanohydrin (**5c**, $Me_3Si$=H) to the reaction conditions affords **14c** in only 7% yield.
(27) Stabilization of carbocations by nitriles rests on dramatically enhanced ionization rates in generating carbocations adjacent to nitriles, relative to trifluoromethyl groups,[a] although recent evidence suggests that the rate differences are due to ground state effects and that nitriles do not significantly stabilize adjacent carbocations.[b] The divergent reactivity between **5a** and **5c** is more consistent with formation of a carbocation, rather than a concerted displacement, with modest stabilization from the nitrile and a greater inductive stabilization from the methyl group for **5c**. (a) Creary, X. *Chem. Rev.* **1991**, *91*, 1625. (b) Tekeuchi, K.; Kitagawa, T.; Ohga, Y.; Nakakimura, A.; Munakata, M. *Tetrahedron* **1997**, *53*, 8155.
(28) Addition of sodium acetate suppresses the yield for the analogous 5-membered ring cyanohydrin implying that DMSO is the nuleophile rather that acetate.
(29) For a comprehensive analysis of carbocation interception by DMSO, see: Creary, X.; Burtch, E. A.; Jiang, Z. *J. Org. Chem.* **2003**, *68*, 1117.
(30) (a) Kennedy, M.; McKervey, M. A. In *Comprehensive Organic Synthesis*; Fleming, I., Trost, B. M., Eds.; Pergamon: Oxford, 1991; Vol. 7, pp 193−216. (b) Abe, H.; Fujii, H.; Masunari, C.; Itani, J.; Kashino, S.; Shibaike, K.; Harayama, T. *Chem. Pharm. Bull.* **1997**, *45*, 778. (c) Williams, D. R.; Klingler, F. D.; Dabral, V. *Tetrahedron Lett.* **1988**, *29*, 3415. (d) Hendrickson, J. B.; Schwartzman, S. M. *Tetrahedron Lett.* **1975**, *16*, 273. (e) Corey, E. J.; Kim, C. U. *J. Am. Chem. Soc.* **1972**, *94*, 7586. (f) Johnson, C. R.; Phillips, W. G. *J. Am. Chem. Soc.* **1969**, *91*, 682. (g) Pfitzner, K. E.; Moffatt, J. G. *J. Am. Chem. Soc.* **1965**, *87*, 5670.

**SCHEME 5. Stereoelectronic Control in Chelation-Controlled Conjugate Addition−Alkylations**



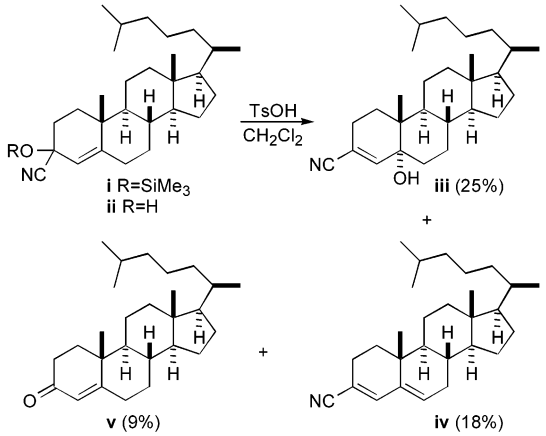

1−3). An analogous annulation of **1b** with **17a** generates the hydrindane **18d** with a complementary substitution pattern (compare Table 1, entries 2 and 3 with 4) whereas the annulations of **1b**−**d** with **17b**,**c** afford decalin-containing nitriles (Table 1, entries 5−8). In each instance, the chelation-controlled conjugate addition of $\omega$-haloalkyl Grignard reagents rapidly assembles the corresponding bicyclic nitriles with complete control over the two newly installed stereocenters.

Several fascinating mechanistic details emerge by comparing the annulations of the chloroalkyl Grignard **17a** with the 5- and 6-membered alkenenitriles **1a** and **1b** (Table 1, entries 1 and 4, respectively). In each case, sequential deprotonation of the alkenenitriles with *t*-BuMgCl, and halogen−alkyl exchange[11] with **17a**, generates the key alkylmagnesium alkoxides **2a** and **2b** (Scheme 5). Intramolecular delivery of the chloroalkyl group is facile from **2b**, and for every other conjugate addition (Table 1, entries 2−8), whereas **2a** requires the addition of *t*-BuLi to coax conjugate addition through the more nucleophilic ate complex[9a] **19a** (Scheme 5). Critical for the conjugate additions is the pyramidalization of the $\beta$-carbon during the alkyl transfer, creating two potential addition modes for the more flexible 6-membered alkenenitriles: axial delivery of the alkyl group through a stereoelectronically favored chairlike transition state **21ba** or equatorial alkyl delivery through a less favorable, boatlike transition state **21bb**.[35] An analogous pyramidalization of the $\beta$-carbon in the 5-membered alkenenitrile requires a more significant distortion of the bicyclo[3.3.0] transition state **21a** potentially explaining the requirement for conjugate addition through the more nucleophilic ate complex **19a**.[36]

Preferential formation of the *cis*-decalins **18e**−**h** (Table 1, entries 5−8) is highly unusual since analogous metalated nitriles preferentially cyclize to *trans*-decalins.[37] An extensive series of cyclizations with **23** reveals that pyramidalization of the metalated nitrile in THF directs cyclization to the *trans*-decalin **25** through the least sterically congested transition state **24** (Scheme 6). The contrasting annulations to *cis*-decalins suggests that the conjugate addition generates particularly reactive dimagnesiated nitriles, such as **22e**, poised for a rapid cyclization from the conformation directly ensuing from an axial conjugate addition (Scheme 7)—assuming that internal alkylation is faster[38] than equilibration to the more stable chair conformation and subsequent cyclization to a *trans*-decalin.

**SCHEME 6. Trans-Selective Nitrile Anion Cyclizations**


(31) No rearrangement of the trimethylsilyl cyanohydrin **i** (R = $Me_3$-Si)[17c] occurs under identical conditions whereas exposure of the cyanohydrin **ii** (R = H) to TsOH causes rearrangement to **iii**, dehydration to the corresponding diene **iv**, hydrolysis to 4-cholesten-3-one **v**, and recovery of unreacted cyanohydrin **ii** (48%).



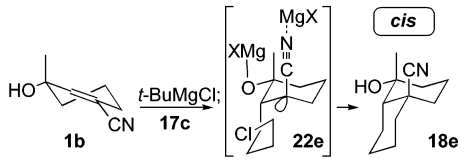

(32) Only 60% conversion of **5d** occurs in 40 h, the time required for complete conversion of **5c** to **14c**.

(33) Corey, E. J.; Bock, M. G. *Tetrahedron Lett.* **1975,** *16*, 3269.

(34) For a preliminary communication, see: Fleming, F. F.; Zhang, Z.; Wang, Q.; Steward, O. W. *Org. Lett.* **2002**, *4*, 2493.

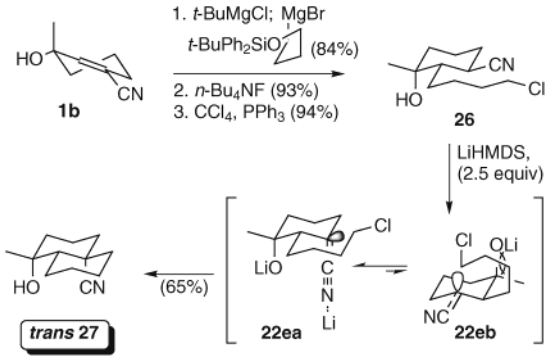
(35) An excellent stereoelectronic analysis rationalizes the preference for axial conjugate addition of endocyclic enones,[a] whereas the stereoelectronic analysis for an exocyclic electron-withdrawing group does not appear to have been examined previously. (a) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: Exeter, 1983; pp 221−242. Consistent with a stereoelectronically favored axial addition is the inability to react **17c** with the steroidal nitrile **ii**[31] where the rigid steroidal *trans*-ring junction enforces the more difficult equatorial conjugate addition from an axially oriented alkylmagnesium alkoxide.

**SCHEME 7. Cis-Selective Nitrile Anion Annulations**




Key evidence supporting the rapid cyclization of **22e** rests on cyclizing the analogous dilithiated nitrile to a *trans*-decalin (Scheme 8). Accessing the desired equatorial precursor **26** was achieved through the conjugate addition of a TBDPS-containing Grignard reagent to **1b** where the TBDPSO-substituent allows a conformational equilibration after the conjugate addition without premature cyclization.[39] Subsequent silyl ether cleavage and chlorination provides the chloride **26** with the chlorobutyl group in the requisite equatorial conformation. Deprotonating **26** with excess LiHMDS generates the conformationally biased dilithiated nitrile **22ea**[40] that cyclizes exclusively to the *trans*-decalin **27**. Exclusive cyclization to the *trans*-decalin is consistent with alkylation through the less sterically congested conformer **22ea**, strongly implying[41] that the *cis*-selective annulations of **18e**−**h** result from a rapid cyclization of the axial conformation formed directly following the conjugate addition (**22e**, Scheme 7).

**SCHEME 8. Trans-Selective Nitrile Anion "Annulation"**




Mechanistically the annulations of chloroalkyl Grignard reagents with 6-membered hydroxyalkenenitriles exhibit a high degree of stereoelectronic control. The initial formation of an equatorially oriented alkylmagnesium alkoxide, generated by *t*-BuMgCl deprotonation and halogen-alkyl exchange (**20bb**, Scheme 5), preferentially triggers an axial conjugate addition to alkenenitriles through a chairlike transition state (**21ba**, Scheme 5). Conjugate addition installs an axially oriented chlorobutyl side chain that is rapidly alkylated by the particularly reactive dimagnesiated nitrile, irreversibly establishing the *cis*-ring junction stereochemistry in decalins **18e**−**h**.

## Conclusion

*ω*-Haloalkyl Grignard reagents trigger chelation-controlled annulations with 5- and 6-membered cyclic alkenenitriles that are derived from an unusual rearrangement of unsaturated silyl cyanohydrins. The annulation generates *cis*-fused octalins, hydrindanes, and decalins with complete control over the two newly installed stereocenters. Collectively, the conjugate addition−alkylation provides the first general annulation of alkenenitriles, affording substituted bicyclic nitriles that are ideal precursors for terpenoid syntheses.

**Acknowledgment.** Financial support of this research from NIH and travel funds from NSF are gratefully acknowledged.

**Supporting Information Available:** Experimental procedures, $^1$H NMR and $^{13}$C NMR spectra for all new compounds, and an ORTEP for **18f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(36) Presumably addition of the homologous Grignard **17b** to **1a** does not require conjugate addition through the ate complex since **17b** is more reactive than **17a**. The greater nucleophilicity of **17b** could stem from better internal chelation[a] with the pendant chloride that increases the electron density on magnesium[b] that is relayed into a greater nucleophilicity of the adjacent carbon−magnesium bond. (a) For internal chelation of Grignard reagents, see: Bickelhaupt, F. In *Grignard Reagents: New Developments*; Richey, H. G., Jr., Ed.; Wiley: Chichester, 2000; Chapter 9. (b) For an analogous activation of dialkylzincs by ligation, see: Reddy, C. K.; Devasagayaraj. A.; Knochel, P. *Tetrahedron Lett.* **1996**, *37*, 4495.

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

(38) Attempts to intercept **22e** by premature protonation afforded only recovered **1b** and decalin **18e**.

(39) The stereochemical assignment is based on a $^1$H NMR coupling constant analysis and by analogy to the conformational preferences of closely related nitriles.[9a]

(40) Fleming, F. F.; Shook, B. C.; Jiang, T.; Steward, O. W. *Tetrahedron* **2003**, *59*,737.

(41) Cyclization of the experimentally more accessible dilithiated nitrile **22e**, rather than the dimagnesiated nitrile **22e** (Li = MgX), does not rule out the possible influence of different aggregation effects that may influence the stereoselectivity.