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Alkenenitriles: Annulations with ω-Chloro Grignard Reagents

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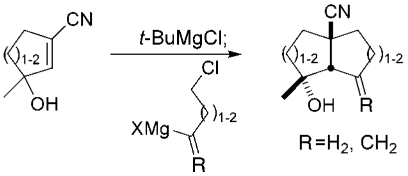
ABSTRACT

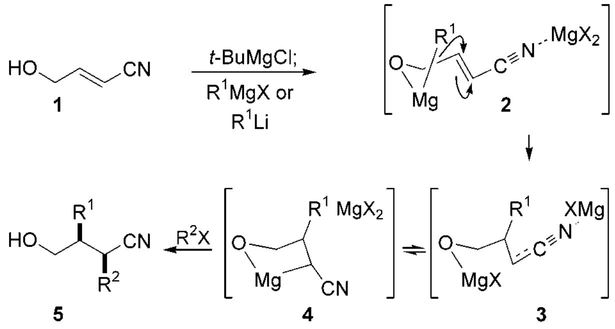


ω-Chloro Grignard reagents chelate with cyclic γ-hydroxy-α,β-alkenenitriles to trigger a conjugate addition–alkylation annulation. The chelation-controlled conjugate addition–alkylation is the first anionic annulation with α, β-alkenenitriles, providing *cis* bicyclo[3.3.0]octane, hydrindane, and decalin ring systems in a single synthetic operation.

Multicomponent reactions are extremely powerful for installing high levels of molecular complexity in a single synthetic operation.[1] Historically, conjugate addition−alkylations[2] have long harnessed the intrinsic efficiency of installing multiple bonds in a single operation, typically by intercepting intermediate enolates with reactive alkyl halides.[3] Pioneering syntheses of halogen-containing organocopper reagents, derived from ω-chloro Grignard reagents,[4] transforms conjugate addition−alkylations into a versatile annulation with carbonyl-based Michael acceptors, efficiently providing a diverse array of bicyclic ring systems.[5]

Anionic conjugate addition−alkylation annulations with alkenenitriles constitute a significant challenge.[6] The challenge lies in overcoming the inherent difficulty in performing anionic conjugate additions to a recalcitrant Michael acceptor.[7] Conjugate addition is dramatically enhanced by temporarily chelating reactive Grignard[8] and organolithium[9] derived nucleophiles directly adjacent to the β-carbon of alkenenitriles (Scheme 1). Transient formation of the alkylmagnesium alkoxide **2**, by sequential deprotonation and halogen−alkyl exchange,[10] promotes the otherwise difficult conjugate addition that does not occur in the absence of an

Scheme 1. Chelation-Controlled Addition Mechanism



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(1) Ho, T.-L. In *Tandem Organic Reagents*; Wiley: New York, 1992.

(2) Taylor, R. J. K. *Synthesis* **1985**, 364.

(3) Hulce, M.; Chapdelaine, M. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, pp 237−268.

(4) (a) Piers, E.; Yeung, B. W. A.; Fleming, F. F. *Can. J. Chem.* **1993**, *71*, 280. (b) Piers, E.; Karunaratne, V. *Tetrahedron* **1989**, *45*, 1089.

(5) (a) Varner, M. A.; Grossman, R. B. *Tetrahedron* **1999**, *55*, 13867. (b) Vandewalle, M.; DeClerq, P. *Tetrahedron* **1985**, *41*, 1767.

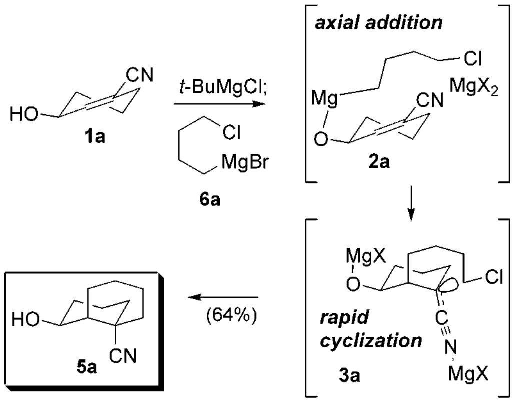
(6) No anionic annulations exist for alkenenitriles, although a clever Heck-based annulation was recently reported: Lautens, M.; Paquin, J.-F.; Piguel, S.; Dahlmann, M. *J. Org. Chem.* **2001**, *66*, 8127. For Diels−Alder annulations see: (a) Zhu, J.-L.; Liu, H.-J.; Shia, K.-S. *Chem. Commun.* **2000**, *17*, 1599. (b) Seth, P. P.; Totah, N. I. *Org. Lett.* **1999**, *1*, 1411. (c) De Lucchi, O.; Piccolrovazzi, N.; Modena, G. *Tetrahedron Lett.* **1986**, *27*, 4347.

(7) Fleming, F. F.; Hussain, Z.; Weaver, D.; Norman, R. E. *J. Org. Chem.* **1997**, *62*, 1305 and references therein.

10.1021/ol0261175 CCC: $22.00

adjacent hydroxyl group.[9] Alkylative interception of the intermediate nitrile anion **4** installs an additional C−C bond, with modest stereoselectivity, in an efficient intermolecular conjugate addition−alkylation.[8b]

Scheme 2. ω-Chloro Grignard Annulation



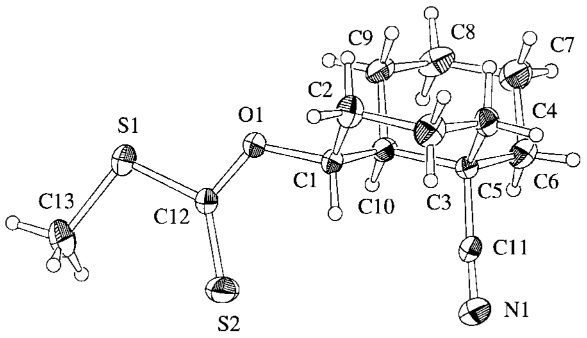


Figure 1. ORTEP of *cis*-decalin xanthate **7a**.

Conceptually, *intramolecular* conjugate addition-alkylation with an ω-chloro Grignard reagent constitutes a viable annulation for alkenenitriles. Experimentally, sequential addition of *t*-BuMgCl and chlorobutylmagnesium bromide (**6a**)[11] triggers a smooth four-carbon annulation with the hydroxy alkenenitrile **1a**[12] (Scheme 2). Mechanistically, deprotonation and alkyl transfer from a modest excess of **6a** generates the key alkylmagnesium alkoxide **2a**. Preferential equatorial disposition of the magnesium alkoxide **2a** favorably positions the nucleophile for a stereoelectronically favored axial delivery[13] of the alkyl chain, directly generating the nitrile anion **3a**. Rapid cyclization[14] from the ensuing conformation, prior to ring-flipping, directs cyclization to the *cis*-decalin **5a**, whose stereochemistry was secured by conversion to the crystalline xanthate **7a**[15] (Figure 1).

The rapid annulation of ω-chloro Grignard **6a** with cyclic alkenenitrile **1a** is in stark contrast to the analogous reaction of **6a** with acyclic alkenenitrile **1** (Scheme 1) where no cyclization occurs. Presumably stable chelates[16] **4** form with acyclic alkenenitriles, preventing cyclization, whereas axial addition through **2a** leads to conformation **3a** where chelation is geometrically precluded. The ensuing rapid cyclization, from an uncomplexed, reactive nitrile anion, is typical of the reactivity exhibited for a variety of cyclic five- and six-membered alkenenitriles (Table 1).

ω-Chloro Grignard initiated annulations to cyclic alkenenitriles efficiently provide a diverse array of bicyclic nitriles (Table 1).[17] Chelation of chlorobutylmagnesium bromide with secondary and tertiary alkoxides, from **1a**,[12] **1b**,[18] and **1c**[18] (Table 1, entries 1, 2, and 5, respectively), are equally effective in alkenenitrile annulations, exhibiting complete control over the two newly formed stereocenters.[19] Similarly, sp^2 hybridized Grignard reagents **6b**[20] and **6c**[20] assemble exomethylene decalin and hydrindanes **5c**, **5d**, and **5f** (Table 1, entries 3, 4, and 6, respectively). Annulations to the five-membered nitrile **1c** provides hydrindanes **5e** and **5f** (Table 1, entries 5 and 6) with substitution patterns complementing those obtained by annulation to the cyclohexanecarbonitrile **1b** (Table 1, entry 4). Collectively, conjugate addition−alkylations provide an efficient annulation route to octaline-, hydrindane-, and decalin-containing bicyclic nitriles.

Annulations with **6b** and **6c** reveal key mechanistic insight for the alkyl transfer. Grignard **6b** (Table 1, entries 3 and 6), prepared by MgBr$_2$ transmetalation of the corresponding organolithium,[4a] is unstable above −50 °C, whereas the chelation-controlled conjugate addition to alkenenitriles requires temperatures in excess of −20 °C. Despite annulations being unsuccessful with the colloidal solutions of **6b**, generated by sequential iodine−lithium exchange and MgBr$_2$ transmetalation, the Grignard reagent derived by direct iodine−magnesium ate exchange[20] affords a homogeneous

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(8) (a) Fleming, F. F.; Gudipati, V.; Steward, O. W. *Org. Lett.* **2002,** *4*, 659. (b) Fleming, F. F.; Wang, Q.; Steward, O. W. *Org. Lett.* **2000**, *2*, 1477.

(9) Fleming, F. F.; Wang, Q.; Zhang, Z.; Steward, O. W. *J. Org. Chem.* **2002**, *67*, in press.

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

(11) Bernady, K. F.; Poletto, J. F.; Nocera, J.; Mirando, P.; Schaub, R. E.; Weiss, M. J. *J. Org. Chem.* **1980**, *45*, 4702.

(12) Fleming, F. F.; Wang, Q.; Steward, O. W. *J. Org. Chem.* **2001**, *66*, 2171.

(13) Deslongchamps, P. In *Stereoelectronic Effects in Organic Chemistry*; Pergamon: Exeter, 1983; pp 221−242.

(14) Attemps to intercept **3a** by premature protonation afforded only recovered **1a** and decalin **5a**.

(15) The authors have deposited atomic coordinates with the Cambridge Crystallographic Data Center (CCDC 185837). The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, U.K.

(16) Analogous chelates exhibit poor nucleophility. See: (a) Fallis, A. G.; Forgione, P. *Tetrahedron* **2001**, *57*, 5899. (b) Reference 8a.

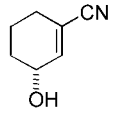
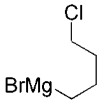
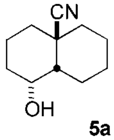
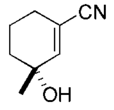
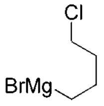
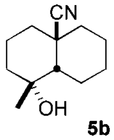
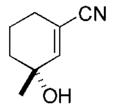
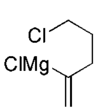
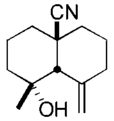
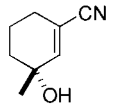
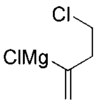
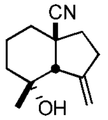
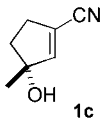
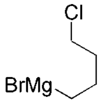
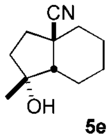
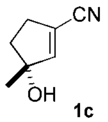
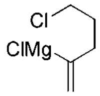
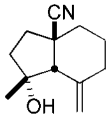
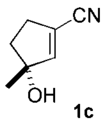
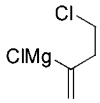
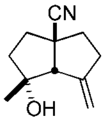
(17) **Standard Procedure.** A THF solution of *t*-BuMgCl (1.2 equiv) was added to a −78 °C THF solution (0.6 M) of the alkenenitrile. After 10 min, a THF solution of the chloroalkyl Grignard reagent (1.5 equiv) was added, and after 10 min, the solution was allowed to warm to room temperature over a 2 h period. Subsequent addition of saturated, aqueous NH$_4$Cl, extraction, and radial chromatography afforded the spectroscopically pure bicyclic nitriles, characterized by ^{1}H and ^{13}C NMR, IR, and MS.

(18) Cyclic nitriles **1b** and **1c** are readily available via a sulfoxide-induced cyanohydrin rearrangement: Fleming, F. F.; Zhang, Z. Unpublished results.

(19) No diastereomers were detected by ^{1}H NMR analysis of the crude reaction mixture.

(20) Obtained by iodine−magnesium ate exchange[a] of the corresponding vinyl iodides[b]: (a) Inoue, A.; Kitagawa, K.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **2001**, *66*, 4333. (b) Kamiya, N.; Chikami, Y.; Ishii, Y. *Synlett* **1990**, 675.

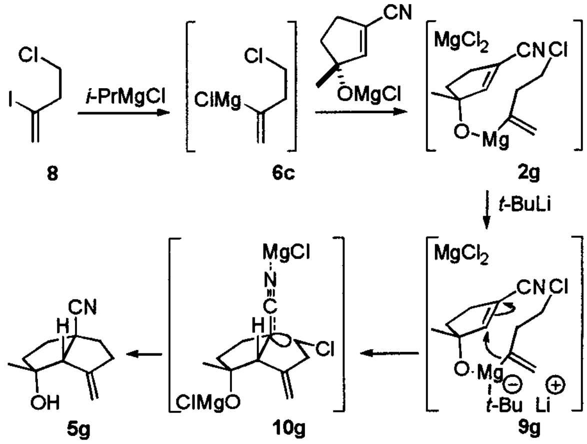
Table 1. Annulations of Alkenenitriles with ω-Chloro Grignards[a]

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

[a] The hydroxynitiles were sequentially treated with *t*-BuMgCl followed by the ω-chloro Grignard indicated. [b] Prepared by *i*-PrMgCl exchange.

solution of **6b** that triggers efficient annulations (Table 1, entries 3 and 6). Curiously, the homologous Grignard **6c** successfully annulates the six-membered nitrile **1b** (Table 1, entry 4) but not the five-membered nitrile **1c** (Table 1, entry 7). Suspecting formation of chelate **2g** (Scheme 3), where alkyl transfer is geometrically retarded, Grignard **6c** was prepared by *i*-PrMgCl[21] exchange followed by addition of *tert*-butyllithium to the chelate to stimulate conjugate addition from the more nucleophilic ate complex **9g**.[9] Synthetically, *t*-BuLi addition stimulates the conjugate addition−alkylation with **6c** resulting in the smooth assembly of bicyclo[3.3.0]nitrile **5g**.

Scheme 3. Chelation-Controlled Annulation



ω-Chloro Grignard reagents trigger efficient chelation-controlled conjugate addition−alkylations to cyclic alkenenitriles. Chelation is essential for conjugate addition, either through an alkylmagnesium alkoxide or from the more reactive ate complexes. Rapid cyclization of the resulting nitrile anions establishes the *cis*-ring junction with complete stereochemical fidelity. Collectively, ω-chloro Grignard annulations to cyclic alkenenitriles efficiently provide the ubiquitous decalin, hydrindane, and octaline ring systems, installing two new stereocenters and two new bonds, in a single synthetic operation.

Acknowledgment. Financial support from NIH is gratefully acknowledged.

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(21) Abarbri, M.; Thibonnet, J.; Bérillon, L.; Dehmel, R.; Rottländer, M.; Knochel, P. *J. Org. Chem.* **2000**, *65*, 4618.