JOC Article

γ-Hydroxy-α,β-alkenenitriles: Chelation-Controlled Conjugate Additions[1]

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Temporarily anchoring Grignard and organolithium reagents to γ-hydroxy-α,β-alkenenitriles promotes efficient conjugate additions to what are otherwise recalcitrant Michael acceptors. Sequential deprotonation and addition of a modest excess of a second Grignard reagent allows effective conjugate delivery of alkyl groups to cyclic and acyclic alkenenitriles. Mechanistically, conjugate additions proceed through alkylmagnesium alkoxide complexes for all but the more substituted alkenenitriles that require alkyl transfers from the more reactive ate complexes. Synthetically, chelation-controlled conjugate additions rapidly, and stereoselectively, assemble substituted nitriles, installing up to two new stereocenters in a single synthetic operation.

Introduction

Anionic conjugate additions occupy a central niche for creating carbon−carbon bonds.[2] The centrality of anionic conjugate additions stems from installing a new bond two carbons removed from an electron-withdrawing group, with the potential for additional C−C bond formation through α-alkylation.[3] Numerous Michael additions to enones and enoates are featured as key steps in natural product syntheses,[4] attesting to the versatility and reliability of conjugate additions for the stereoselective[5] installation of strategic carbon−carbon bonds.

In contrast to unsaturated carbonyl compounds, anionic conjugate additions to alkenenitriles are significantly more demanding.[6] Efforts to elucidate the fundamental requirements for conjugate additions to these recalcitrant acceptors stimulated three approaches with a biased proclivity toward conjugate addition: intramolecular additions with dithiane anions,[6b] intermolecular additions with highly nucleophilic sulfur and selenium anions,[7] and conjugate addition of Grignard reagents[8] to oxonitriles[9] where the alkenenitrile is further activated by conjugation with a ketone. Collectively, these reactions exhibit a distinct correlation between reaction efficiency and increasing electron density on the nucleophile.[6b]

Conjugate addition of carbon nucleophiles to unactivated alkenenitriles is particularly demanding. The challenge lies in overcoming the inherent propensity of highly electron-rich organolithium and Grignard nucleophiles toward 1,2-addition,[10] caused by the greater polarization of the C≡N group over the β-carbon of alkenenitriles. Redirecting the addition to the β-carbon by chelation, as pioneered with enones,[11] potentially overcomes 1,2-addition by temporarily anchoring a highly charged nucleophile in close proximity to the poor acceptor and geometrically precludes intramolecular attack on the nitrile group.

Exploratory reactions[12] establish the viability of chelation-controlled conjugate additions to alkenenitriles. In seeking to develop this strategy, a diverse array of alkenenitriles have been subjected to additions with various Grignard reagents. Collectively, these reactions demonstrate a broad generality for chelation-controlled conjugate additions, effectively installing quaternary carbons, and up to two new stereocenters with virtually complete stereocontrol, to provide a robust method for rapidly assembling complex molecular fragments.

Results and Discussion

The exploratory addition of excess methylmagnesium chloride to 4-hydroxybutenenitrile (**1a**) triggers an ef-

† Present address: Department of Chemistry, Cornell University, Ithaca, NY.

(1) Taken in part from Wang, Q. Ph.D. Thesis, Duquesne University, Pittsburgh, PA, 2001.

(2) Perlmutter, P. In *Conjugate Addition Reactions in Organic Synthesis*; Pergamon: New York, 1992.

(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) Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135.

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

(6) (a) Rakita, P. E. In *Handbook of Grignard Reagents*; Silverman, G. S., Rakita, P. E., Eds.; Marcel Dekker: New York, 1996; pp 381−389. (b) Fleming, F. F.; Hussain, Z.; Weaver, D.; Norman, R. E. *J. Org. Chem.* **1997**, *62*, 1305.

(7) Fleming, F. F.; Pak, J. J. *J. Org. Chem.* **1995**, *60*, 4299.

(8) Fleming, F. F.; Pu, Y.; Tercek, F. *J. Org. Chem.* **1997**, *62*, 4883.

(9) (a) Fleming, F. F.; Guo, J.; Wang, Q.; Weaver, D. *J. Org. Chem.* **1999**, *64*, 8568. (b) Fleming, F. F.; Huang, A.; Sharief, V.; Pu, Y. *J. Org. Chem.* **1999**, *64*, 2830.

(10) For a summary of 1,2- vs 1,4-additions to alkenenitriles, see: *Grignard Reactions of Nonmetallic Substances*; Kharasch, M. S., Reinmuth, O., Eds.; Prentice Hall: New York, 1954; pp 782−783.

(11) For pioneering chelation-controlled additions to enones, see: (a) Swiss, K. A.; Hinkley, W.; Maryanoff, C. A.; Liotta, D. C. *Synthesis* **1992**, 127. (b) Solomon, M.; Jamison, W. C. L.; McCormick, M.; Liotta, D.; Cherry, D. A.; Mills, J. E.; Shah, R. D.; Rodgers, J. D.; Maryanoff, C. A. *J. Am. Chem. Soc.* **1988**, *110*, 3702.

(12) For a preliminary account, see: Fleming, F. F.; Wang, Q.; Steward, O. W. *Org. Lett.* **2000**, *2*, 1477.

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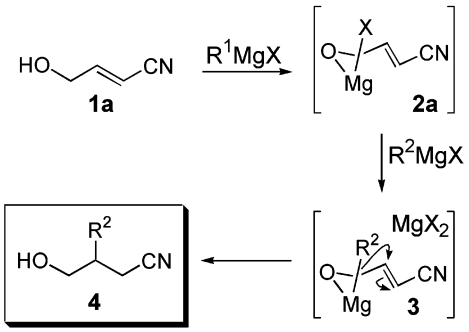
SCHEME 1. Chelation-Controlled Conjugate Addition

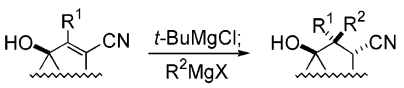


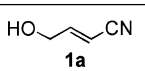
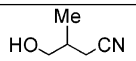
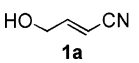
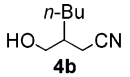
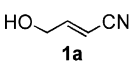
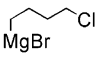
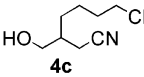
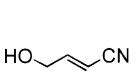
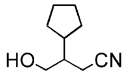
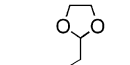
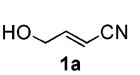
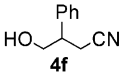
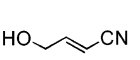
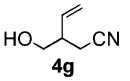
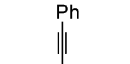
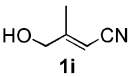
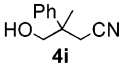
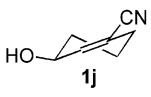
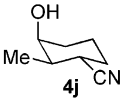
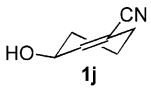
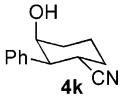
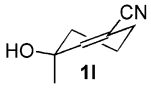
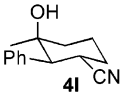
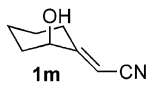
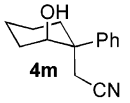
ficient chelation-controlled conjugate addition (Scheme 1). Mechanistically, deprotonation at −78 °C generates the chloromagnesium alkoxide **2a**[13] that rapidly engages in a halogen−methyl exchange[14] with the excess MeMgCl. The resulting alkylmagnesium alkoxide **3** initiates a smooth conjugate addition upon warming to room temperature, ultimately generating the conjugate adduct **4**.

The substantial rate difference between deprotonation and conjugate addition at −78 °C allows *t*-BuMgCl or PhMgCl[15] to be employed as sacrificial bases. *t*-BuMgCl is a particularly convenient base, effectively deprotonating a range of hydroxy alkenenitriles prior to an alkyl transfer from a modest excess of a second, potentially more valuable, Grignard reagent (Table 1). Sequential deprotonation with *t*-BuMgCl and addition of sp-, sp^2-, and sp^3-hybridized Grignard reagents triggers alkyl transfer to variously substituted alkenenitriles, tolerating alkyl chloride and acetal functionality despite internal complexation of the Grignard reagent.[16] Sterically demanding Grignard reagents add efficiently to acyclic and cyclic alkenenitriles (Table 1, entries 1−9 and 10−13, respectively) even with trisubstituted alkenenitriles where alkyl substitution generally retards conjugate addition.[17] Particularly significant are the conjugate additions to *β*,*β*-disubstituted nitriles, permitting installation of quaternary centers with complete stereocontrol (Table 1, entries 9 and 13, respectively).

Conjugate additions to cyclic alkenenitriles are exquisitely stereoselective. Alkyl transfers to endocyclic and exocyclic alkenenitriles (Table 1, entries 10−12 and 13, respectively) install the new carbon bond from the same face as the hydroxyl group,[18] consistent with a stereoelectronically controlled axial[5] addition from an alkylmagnesium alkoxide (**5**). Highly selective axial protonation of the resulting metalated nitrile **6** is particularly unusual[19] (Table 1, entries 10−12), perhaps transpiring

TABLE 1. Chelation-Controlled Conjugate Additions to *γ*-Hydroxy-α,*β*-alkenenitriles[a]

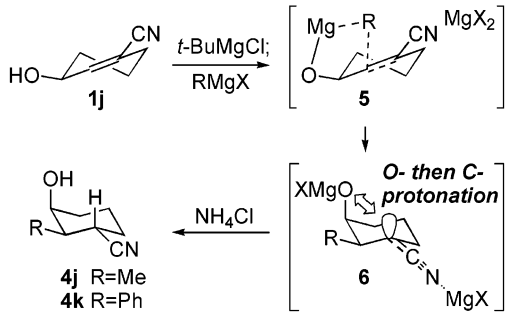


Entry	Alkenenitrile	Grignard	Nitrile	Yield
1	 **1a**	MeMgCl	 **4a**	74%
2	 **1a**	BuMgCl	 **4b**	80%
3	 **1a**		 **4c**	51%[b]
4	 **1a**		 **4d**	79%
5	**1a**		 **4e**	78%
6	 **1a**	PhMgCl	 **4f**	76%
7	 **1a**		 **4g**	63%
8	**1a**		 **4h**	62%
9	 **1i**	PhMgCl[c]	 **4i**	63%
10	 **1j**	MeMgCl[c]	 **4j**	60%
11	 **1j**	PhMgCl	 **4k**	86%
12	 **1l**	PhMgCl	 **4l**	72%[d]
13	 **1m**	PhMgCl[c]	 **4m**	57%

[a] Typically, 1.0 equiv of *t*-BuMgCl was added at −78 °C followed, after 5 min, by the Grignard reagent (1.0−1.1 equiv) and warming to room temperature. [b] Compound **4b** (11%) is also obtained, resulting from the addition of $ClMg(CH_2)_4MgBr$ formed during Grignard formation. [c] Performed with 2.1−2.5 equiv of the Grignard reagent. [d] Obtained as a 9:1 ratio of stereoisomers at the nitrile-bearing carbon.

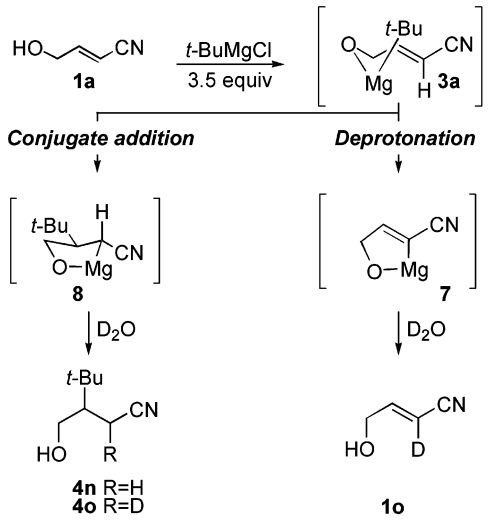
(13) Turova, N. Y.; Turevskaya, E. P. *J. Organomet. Chem.* **1972**, *42*, 9.
(14) Swiss, K. A.; Liotta, D. C.; Maryanoff, C. A. *J. Am. Chem. Soc.* **1990**, *112*, 9393.
(15) For comparison, deprotonation of **1a** with PhMgCl and conjugate addition of MeMgCl provided the methyl transfer product in 63% yield, whereas *t*-BuMgCl provided a 74% yield.
(16) Sworin, M.; Neumann, W. L. *Tetrahedron Lett.* **1987**, *28*, 3217.
(17) Krief, A. *Tetrahedron* **1980**, *36*, 2531.
(18) The stereochemistry of **4k** was secured by X-ray analysis with the crystallographic data being deposited with the Cambridge Crystallographic Data Center (CCDC 184135). The data can be obtained, upon request, from the Director, Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, UK.
(19) Gerlach, U.; Haubenreich, T.; Hünig, S.; Keita, Y. *Chem. Ber.* **1993**, *126*, 1205.

from initial protonation on oxygen followed by intramolecular delivery to the pyramidal[20] nitrile anion. Synthetically, the chelation-controlled conjugate addition relays the alcohol stereochemistry into the controlled installation of adjacent carbon−carbon and carbon−hydrogen bonds with almost complete stereoselectivity.



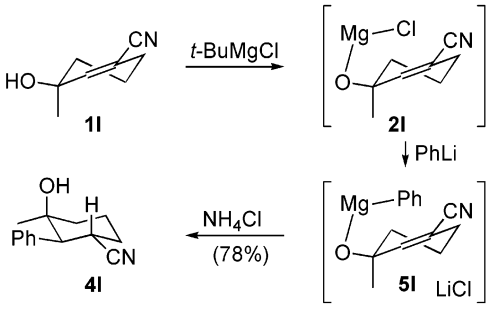
Initial attempts to add sterically demanding *t*-BuMgBr to alkenenitriles afforded primarily recovered nitrile. The inefficient conjugate addition culminates from a facile α-deprotonation, reflecting the increased basicity of the tertiary Grignard reagent,[21] as confirmed by sequential addition of excess *t*-BuMgCl and deuteriolysis (**1a** → **3a** → **1o**, Scheme 2). Presumably, α-deprotonation from

SCHEME 2. Addition of Tertiary Grignard Reagents



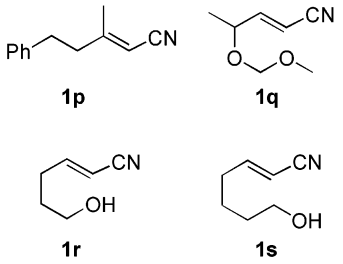
alkylmagnesium alkoxide **3a** occurs at −78 °C or prior to obtaining the more moderate temperatures (0−25 °C) required for the conjugate addition, since simply performing the reaction at ambient temperature largely overcomes deleterious deprotonation (59% of conjugate adduct **4o** and 18% of **1o**). The preference for conjugate addition over deprotonation is remarkable given the demanding installation of adjacent quaternary−tertiary stereocenters during the conjugate addition.

Chelation provides an effective method for the conjugate addition of alkyllithiums to alkenenitriles, as well as Grignard reagents. Sequential deprotonation of **1l** with *t*-BuMgCl and addition of phenyllithium generates the requisite alkylmagnesium alkoxide **5l**, culminating in a 78% yield of the substituted nitrile **4l**. The requirement for a magnesium chelate is underscored by the lack of conjugate addition upon exposure of **1l** to excess PhLi.



Mechanism

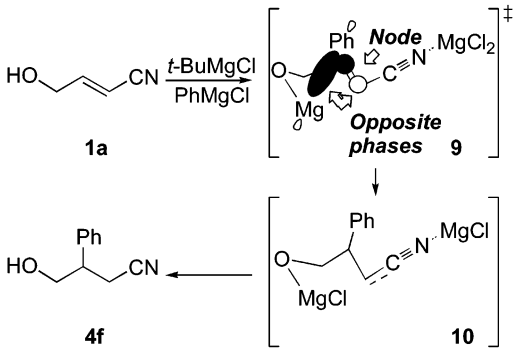
Chelation is essential for the conjugate addition of Grignard reagents to alkenenitriles. Control experiments involving addition of BuMgCl to **1p**, and the MOM-containing alkenenitrile **1q**, afford only recovered starting material.[22] Similarly, exposure of **1p** to MeMgOMe, mimicking the reactivity of the intermediate chelates **3**, leads only to recovery of the nitrile. Chelation apparently requires hydroxylation adjacent to the alkenenitrile since relocating the hydroxyl group three or four carbons away, as in **1r**[23] and **1s**,[23] precludes conjugate addition.



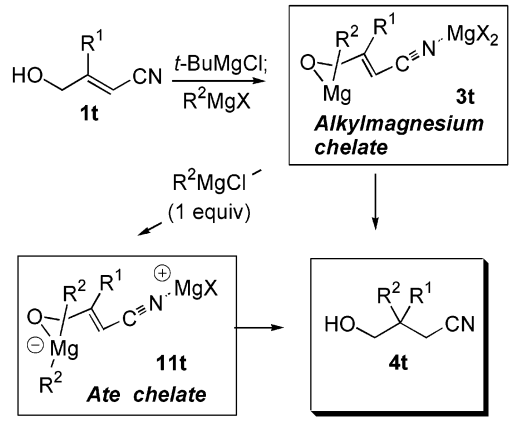
Chelation-controlled additions to alkenenitriles are consistent with an intramolecular alkyl transfer[24] from an alkylmagnesium alkoxide.[25] Although the exact mechanism remains speculative, an orbital symmetry analysis[26] favors a stepwise, anionic[27] mechanism since the node of the alkenenitrile π^* LUMO prohibits a concerted

(20) Fleming, F. F.; Shook, B. C. *Tetrahedron* **2002**, *58*, 1.
(21) (a) González, B.; González, A. M.; Pulido, F. J. *Synth. Commun.* **1995**, *25*, 1005. (b) Melamed, U.; Feit, B.-A. *J. Org. Chem.* **1983**, *48*, 1928. (c) Schmidt, R. R.; Hirsenkorn, R. *Tetrahedron* **1983**, *39*, 2043. (d) Feit, B. A.; Melamed, U.; Schmidt, R. R.; Speer, H. *Tetrahedron* **1981**, *37*, 2143. (e) Schmidt, R. R.; Speer, H. *Synthesis* **1979**, 797. (f) Melamed, U.; Feit, B. A. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1228. (g) Schmidt, R. R.; Talbiersky, J. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 853.
(22) Addition of BuMgCl to **1p** using the general conjugate addition procedure afforded 69% of the recovered nitrile and 11% of deconjugated isomers resulting from δ-deprotonation.
(23) Fleming, F. F.; Wang, Q.; Steward, O. W. *J. Org. Chem.* **2001**, *66*, 2171.
(24) Richey, H. G., Jr.; Wilkins, C. W., Jr.; Brown, B. S.; Moore, R. E. *Tetrahedron Lett.* **1976**, 723.
(25) (a) Fallis, A. G.; Forgione, P. *Tetrahedron* **2001**, *57*, 5899. (b) Normant, J. F.; Alexakis, A. *Synthesis* **1981**, 841.
(26) Kirby, A. J. In *Stereoelectronic Effects*; Oxford University Press: Bath, UK, 1996; pp 46−47.
(27) The addition of PhMgCl and the more facile alkyl transfer from MeMgCl over *t*-BuMgCl are consistent with an anionic mechanism and not a radical mechanism: Blomberg, C. In *Handbook of Grignard Reagents*; Silverman, G. S., Rakita, P. E., Eds.; Marcel Dekker: New York, 1996; Chapters 11−12.

SCHEME 3. Mechanism: Stepwise, Anionic Alkyl Transfer



SCHEME 4. Alkyl- and Ate-Conjugate Addition Mechanisms



orbital overlap[28] between the Mg−Ph σ bond and the α- and β-carbons during the alkyl transfer (**9**, Scheme 3). Association of the nitrile with the Lewis-acidic metal salt, MgX_2 or LiCl, likely promotes the anionic addition in directly generating the metalated nitrile anion **10**.

Two distinct anionic mechanisms operate in chelation-controlled conjugate additions to alkenenitriles: alkyl transfer from an alkylmagnesium alkoxide **3t** or through the corresponding ate[29] chelate **11t** (Scheme 4). The key signature for the intermediacy of an ate complex is the necessity for 2 equiv of the Grignard reagent, a requirement observed with additions to the more demanding β,β-disubstituted alkenenitriles (compare entries 6 and 9 in Table 1). The trend parallels Michael additions to unsaturated carbonyls where increasing substitution retards conjugate addition through a combination of steric and electronic effects.[17]

Comparative additions to the α-substituted nitrile **1j** reveal an unusual reactivity difference between PhMgCl and MeMgCl (Table 1, entries 10 and 11). PhMgCl is sufficiently reactive to stimulate conjugate addition to **1j** with 1.1 equiv through an alkylmagnesium alkoxide, whereas 2.5 equiv of the less reactive MeMgCl are required for alkyl transfer through the more reactive ate complex (compare entries 10 and 11 in Table 1). Conceivably, all alkyl transfers could occur through catalytic quantities of the ate complex, since the general procedure employs a slight excess of the Grignard reagent; however, the minimal methylation of **1j** under the standard conditions is more consistent with only the substituted alkenenitrile additions requiring alkyl transfers through the more reactive ate complex.

Conclusion

Chelation provides a practical solution to the long-standing difficulty of performing conjugate additions to α,β-alkenenitriles. Cyclic and acyclic alkenenitriles efficiently participate in alkyl transfers from organolithium and Grignard reagents, affording a diverse array of substituted nitriles. Conjugate addition occurs through alkylmagnesium alkoxides for modestly substituted alkenenitriles, whereas more highly substituted nitriles participate in similarly efficient alkyl transfers from more reactive ate complexes. Collectively, the chelation-controlled conjugate additions demonstrate the rapid, stereoselective assembly of substituted nitriles, installing up to two new stereogenic centers in a single synthetic operation.

Experimental Section[30]

General Conjugate Addition Procedure. A THF solution of *t*-BuMgCl (1.0 equiv, 1−2 M) was added to a cold (−78 °C) THF solution (0.5−1 M) of the γ-hydroxy-α,β-alkenenitrile under nitrogen. After 5 min, a THF solution of RMgX (1.1 equiv, 1−3 M) was added, and the cooling bath was removed. After 1.5 h, saturated, aqueous NH_4Cl was added, and the aqueous phase was extracted with EtOAc. The combined extracts were dried (Na_2SO_4), concentrated, and then purified by radial chromatography. A modified workup procedure was developed for water-soluble products where HOAc (3.2 equiv) was added after 1.5 h rather than saturated, aqueous NH_4Cl. The solution was then diluted with EtOAc and the resulting mixture filtered through silica gel. The crude product was concentrated and purified by radial chromatography.

Acknowledgment. Financial support from NIH is gratefully acknowledged.

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

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(28) For a related analysis, see: Gawley, R. E. *Tetrahedron Lett.* **1999**, *40*, 4297.

(29) Inoue, A.; Kitagawa, K.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **2001**, *66*, 4333.

(30) For general experimental procedures, see ref 6b. The high-resolution mass spectra were recorded at The Ohio State University Campus Chemical Instrumentation Center.