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Hydroxy Alkenenitriles: Diastereoselective Conjugate Addition−Alkylations

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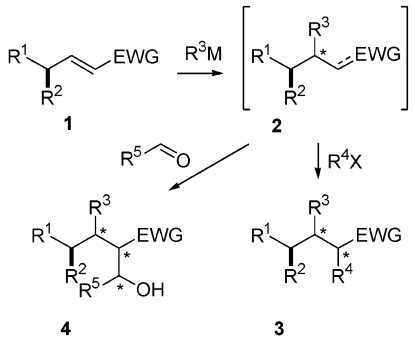
Chelation-controlled conjugate addition of Grignard reagents to cyclic and acyclic γ-hydroxyalkenenitriles stereoselectively generates β-substituted hydroxynitriles. *t*-BuMgCl-induced deprotonation of γ-hydroxyalkenenitriles followed by chloride−alkyl exchange from a second Grignard reagent, generates an alkylmagnesium alkoxide that triggers conjugate addition. Alkylation of the resulting magnesiated nitrile with alkyl halide and carbonyl electrophiles efficiently installs two new bonds and up to three stereocenters in a single synthetic operation.

Conjugate addition reactions rank among the most strategic carbon−carbon bond-forming reactions in organic synthesis.[1] The seminal importance of conjugate addition reactions stems from installing a new bond two or more carbons removed from an electron-withdrawing group with high substrate-induced stereoselectivity.[2] Alternatively, chiral nucleophiles allow enantioselective, reagent-controlled, conjugate additions to Michael acceptors with high stereoselectivity, even with acyclic Michael acceptors.[3]

Enantio- and diastereoselective conjugate additions generate chiral enolates[3] with the potential for α-alkylation (Scheme 1). Typically, sequential conjugate addition−alkylations[4] employ activated alkyl halide[5] or aldehyde[6] electrophiles to maximize the efficiency of sequentially forming two new bonds. The synthetically attractive formation of multiple bonds requires high stereoselectivity during each bond-forming event, effectively requiring close proximity between substrate and reagent.[7,2b,c]

SCHEME 1. Enantio- and Diastereoselective Conjugate Addition−Alkylation



The paragon for close proximity is chelation.[8] Typically, chelation-controlled conjugate additions are exquisitely stereoselective, accessing stereochemistries that are often inaccessible with conventional organocopper reagents.[9] In addition, chelation promotes conjugate additions with recalcitrant Michael acceptors since tethering the two reactive centers in close proximity essentially harnesses the inherent entropic advantages[10] of intramolecular reactions in promoting a formal intermolecular reaction. The enhanced reactivity of chelation-controlled additions is encapsulated in the facile conjugate addition of diverse Grignard reagents to **5a**[11] whereas most cuprates,[12] and many other anionic nucleophiles,[13] are unreactive toward unsaturated nitriles (eq 1).

Conceptually, hydroxy alkenenitriles represent ideal substrates for probing stereoselective conjugate addi-

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(9) (a) 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. (b) Swiss, K. A.; Hinkley, W.; Maryanoff, C. A.; Liotta, D. C. *Synthesis* **1992**, 127. (c) White, J. D.; Shin, H.; Kim, T.-S.; Cutshall, N. S. *J. Am. Chem. Soc.* **1997**, *119*, 2404.

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

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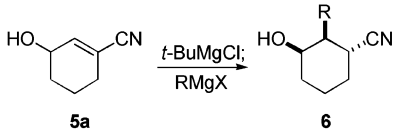


(1)

tion−alkylations, a powerful multicomponent strategy used in prostaglandin synthesis,[14] but relatively unexplored with *acyclic* chiral Michael acceptors. Indeed, conjugate additions to hydroxy alkenenitriles effectively relay the hydroxyl stereochemistry in sequential conjugate addition−alkylations, controlling the formation of two new bonds, and up to three stereocenters, in a single synthetic operation.

Results and Discussion

Diastereoselective Conjugate Additions to Acyclic Nitriles. Acyclic nitrile **5b** represents a particularly attractive substrate for probing stereoselective conjugate additions (Scheme 2). Nitrile **5b** is rapidly synthesized[15] with a small steric bias emanating from the methyl group that provides a measure of the *minimum* stereoselectivity expected in conjugate additions to acyclic γ-hydroxyalkenenitriles. Experimentally, *t*-BuMgCl-initiated deprotonation of **5b**[16] and addition of PhMgCl triggers a smooth phenyl transfer through the phenylmagnesium alkoxide **7a** to afford a single nitrile diastereomer **8a**[17] (Scheme 2). The excellent stereochemical fidelity requires internal delivery from **7a** that may be facilitated by the acute C−O−Mg bond angle (90−100°).[18] Alkyl transfer from the opposite face detrimentally positions the phenyl group close to the nitrile group in conformation **7b** whereas conformer **7c** suffers from significant allylic strain.[19]

SCHEME 2. Diastereoselective Conjugate Addition to 5b

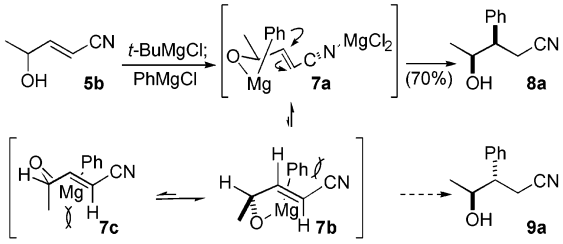
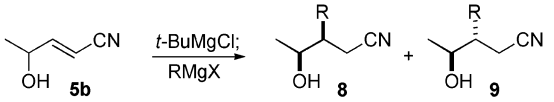


TABLE 1. Diastereoselective Conjugate Addition of RMgX to Alkenenitrile 5b[a]



entry	Grignard	solvent	alkanenitrile(s)	ratio **8**:**9**	yield, %
1	PhMgCl	THF	**8a**	1:0	70
2	*n*-BuMgCl	THF	**8b**/**9b**	9:1	70
3	$CH_2CHMgBr$	THF	**8c**/**9c**	4:1	67
4	MeMgCl	PhH	**8d**/**9d**	3.2:1	—[b]
5	MeMgCl	Et_2O	**8d**/**9d**	2.3:1	—[b]
6	MeMgCl	THF	**8d**/**9d**	2:1	61
7	MeMgCl	DME	**8d**/**9d**	1:1	—[b]

[a] Procedure: 1.0 equiv of *t*-BuMgCl was added at −78 °C followed, after 5 min, by the appropriate Grignard reagent and warming of the reaction to ambient temperature over a 2-h period. [b] Yield not determined.

Conjugate additions to **5b** are syn-selective for a range of Grignard reagents (Table 1). The syn-selectivity directly correlates with the size of the Grignard alkyl group, suggesting increasing alkyl transfer through conformation **7b** as the steric compression between the nitrile and alkyl groups is relieved. Performing the chelation-controlled addition in poor donor solvents, to favor a more compact transition state, modestly enhances the preference for the syn-isomer whereas DME, a good donor solvent, erodes the stereoselectivity (Table 1, entries 4−7).

Diastereoselective Conjugate Addition−Alkylations. The selective chelation-controlled additions to nitrile **5b** stimulated intercepting the intermediate magnesiated nitrile in a sequential conjugate addition−alkylation. *t*-BuMgCl-initiated conjugate addition of PhMgCl to **5b** followed by alkylation with benzaldehyde generates two diastereomers with complete stereocontrol at the β- and nitrile-bearing carbons. X-ray analysis[17] deconvoluted the two stereoisomers as arising from a 4:1 preference for the *si* face of benzaldehyde, a modest selectivity comparable to that of related alkylations[14] (Table 2, entry 1). Intercepting the same bis-magnesiated nitrile intermediate with benzyl bromide requires the addition of HMPA and leads predominantly to nitrile **11b**[17] (Table 2, entry 2), presumably through a different, more reactive, metallonitrile since benzylation occurs

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(13) For a discussion see: Fleming, F. F.; Hussain, Z.; Weaver, D.; Norman, R. E. *J. Org. Chem.* **1997**, *62*, 1305.

(14) For sequential conjugate addition−aldehyde alkylation routes to protaglandins see: (a) Arnold, L. A.; Naasz, R.; Minnaard, A. J.; Feringa, B. L. *J. Org. Chem.* **2002**, *67*, 7244. (b) Arnold, L. A.; Naasz, R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2001**, *123*, 5841. (c) Keller, E.; Maurer, J.; Naasz, R.; Schader, T.; Meetsma, A.; Feringa, B. L. *Tetrahedron*: *Asymmetry* **1998**, *9*, 2409. (d) Asai, T.; Morizawa, Y.; Shimada, T.; Nakayama, T.; Urushihara, M.; Matsumura, Y.; Yasuda, A. *Tetrahedron Lett.* **1995**, *36*, 273. (e) Suzuki, M.; Kiho, T.; Tomokiyo, K.; Furuta, K.; Fukushima, S.; Takeuchi, Y.; Nakanishi, M.; Noyori, R. *J. Med. Chem.* **1998**, *41*, 3084.

(15) For syntheses of **5b** see: (a) Tiecco, M.; Testaferri, L.; Marini, F.; Santi, C.; Bagnoli, L.; Temperini, A. *Tetrahedron*: *Asymmetry* **1999**, *10*, 747. (b) Tiecco, M.; Testaferri, L.; Tingoli, M.; Bagnoli, L.; Santi, C. *J. Chem. Soc., Chem. Commun.* **1993**, 637. (c) Fleming, F. F.; Wang, Q.; Steward, O. W. *J. Org. Chem.* **2001**, *66*, 2171. For other syntheses of hydroxyalkenenitriles see: (d) Kang, S.-K.; Lee, D.-H.; Kim, Y.-S.; Kang, S.-C. *Synth. Commun.* **1992**, *22*, 1109. (e) Kitano, Y.; Matsumoto, T.; Wakasa, T.; Okamoto, S.; Shimazaki, T.; Kobayashi, Y.; Sato, F.; Miyaji, K.; Arai, K. *Tetrahedron Lett.* **1987**, *28*, 6351. (f) Nokami, J.; Mandai, T. Nishimura, A.; Takeda, T.; Wakabayashi, S.; Kunieda, N. *Tetrahedron Lett.* **1986**, *27*, 5109.

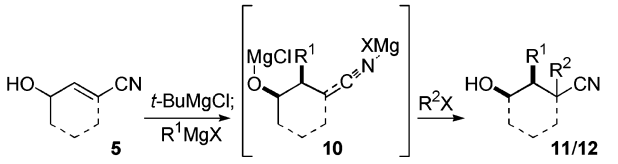
(16) The chelation-controlled conjugate additions were performed on readily available racemic hydroxy alkenenitriles.[15c]

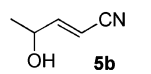
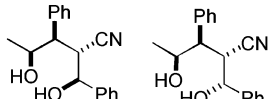
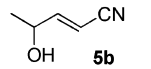
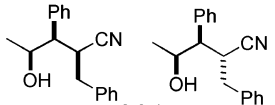
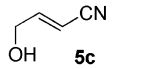
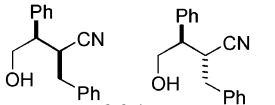
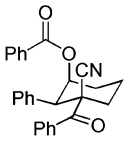
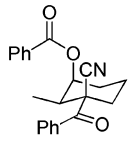
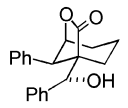
(17) X-ray crystallography of **11b** (CCDC# 198856), **11c** (CCDC# 143821), **11d** (CCDC# 198857), and **11f** (CCDC# 198858) and the 4-nitrobenzoate derivative for **8a** (CCDC# 198854) and di-4-nitrobenzoates for **11a** (CCDC# 198855) and **12a** (CCDC# 198859) confirmed the stereochemical assignment. The supplementary crystallographic data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, UK (fax +44 1223 336033; or deposit@ccdc.cam.ac.uk).

(18) Uhn, H. L. In *Handbook of Grignard Reagents*; Silverman, G. S., Rakita, P. E., Eds.; Marcel Dekker: New York, 1996; pp 117−144.

(19) Hoffman, R. W. *Chem. Rev.* **1989**, *89*, 1841.

TABLE 2. Sequential Conjugate Addition−Alkylations with γ-Hydroxy-α,β-alkenenitriles[a]



Entry	Alkenenitrile	Reagents	Alkylated Nitrile	Yield
1	 **5b**	PhMgCl; PhCHO	 **11a** 4:1 **12a**	64%
2	 **5b**	PhMgCl; BnBr, HMPA	 **11b** 2.3:1 **12b**	82%
3	 **5c**	PhMgCl; BnBr, HMPA	 **11c** 6.6:1 **12c**	63%
4	 **5a**	PhMgCl; PhCOCl	 **11d**	81%
5	 **5a**	MeMgCl; PhCOCl	 **11e**	77%
6	 **5a**	PhMgCl; PhCHO	 **11f**	48%[b]

[a] Typical procedure: 1.0 equiv of *t*-BuMgCl was added at −78 °C followed, after 5 min, by the appropriate RMgX, warming to room temperature, and addition of the appropriate electrophile. [b] Decomposition occurs during chromatography significantly reducing the high crude yield.

predominantly with the opposite stereochemical sense to that with PhCHO in the absence of HMPA. HMPA solvation likely causes alkylation from an open metallonitrile where the benzylation stereochemistry is influenced by the phenyl- and hydroxyl-bearing stereocenters as implied by the analogous PhMgCl conjugate addition−benzylation with **5c**. Sequential β-phenylation−α-benzylation of **5c** is more selective[17] (Table 2, entry 3), presumably reflecting the beneficial influence of the phenyl-bearing stereocenter that is mismatched with the hydroxyl stereocenter in the bis-magnesiated nitrile derived from **5b**.

Conjugate addition−alkylations with the cyclic alkenenitrile **5a** are completely stereoselective. Addition of either PhMgCl or MeMgCl to **5a** installs alkyl substituents on the same face as the hydroxyl group, generating bis-magnesiated nitriles for *C*- and *O*-benzoylation with PhCOCl (Table 2, entries 4 and 5). An analogous conjugate addition−alkylation with benzaldehyde as the electrophile generates a single diastereomeric lactone **11f**[17] resulting from alkoxide attack on the newly installed axial nitrile, installing three contiguous stereocenters in one operation (Table 2, entry 6).

Mechanism. Chelation-controlled conjugate additions to alkenenitriles occur through a stepwise, anionic mechanism.[11] *t*-BuMgCl-initiated deprotonation generates a halomagnesium alkoxide[20] that undergoes halogen−alkyl exchange[21] with a second Grignard reagent to generate the key alkylmagnesium alkoxide **7a** (Scheme 3). Stepwise conjugate addition from the alkylmagnesium alkoxide generates the bis-magnesiated nitrile **10a** that likely cyclizes to a magnesium chelate **13**.[22]

Comparative conjugate additions of PhMgCl to *E*-**5b** and a 1:1 *E:Z*-mixture of **5b** and **5d**[16] provide insight into the nature of the chelate **13**. Sequential conjugate addition−alkylation with PhMgCl and benzaldehyde gives **11a** and **12a** in a 4:1 ratio from **5b** and in a 3.3:1 ratio from a 1:1 *E:Z*-mixture of **5b** and **5d**, in 64% yield in each case. Generating virtually the same ratio of diastereomers **11a** and **12a**, independent of the *E:Z* stereochemistry, requires conjugate addition through conformers **7a** and **7d**, leading initially to the rotomers **10a** and **10d**.[23] Interconvertion of **10a** and **10d**, by single bond rotation, may occur before or after forming the chelates **13a** or **13d**, which subsequently direct alkylation with benzaldehyde.

Invertive alkylation from the chelate **13a** appears most likely based on the analogous conjugate addition−alkylation leading to **11f** (Scheme 4). Chelation-controlled conjugate addition of PhMgCl to nitrile **5a** can only generate chelate **13f** because the positions of the magnesium alkoxide and the anionic carbon are enforced by the rigid cyclohexane ring. Subsequent benzaldehyde alkylation from the chelate **13f** must occur with inversion, as determined by the stereochemistry of the crystalline lactone **11f**. Consequently, if the analogous benzaldehyde alkylation of **13** (Scheme 3) occurs with inversion the reactive chelate must be **13a**, which parallels examples of invertive carbonyl alkylations with heteroatom-stabilized organolithiums.[24]

Chelation-controlled conjugate additions to α,β-alkenenitriles are highly stereoselective. Acyclic alkenenitriles effectively relay the hydroxyl stereochemistry during installation of the β-substituent, leading to magne-

(20) Turova, N. Ya.; Turevskaya, E. P. *J. Organomet. Chem.* **1972**, *42*, 9.

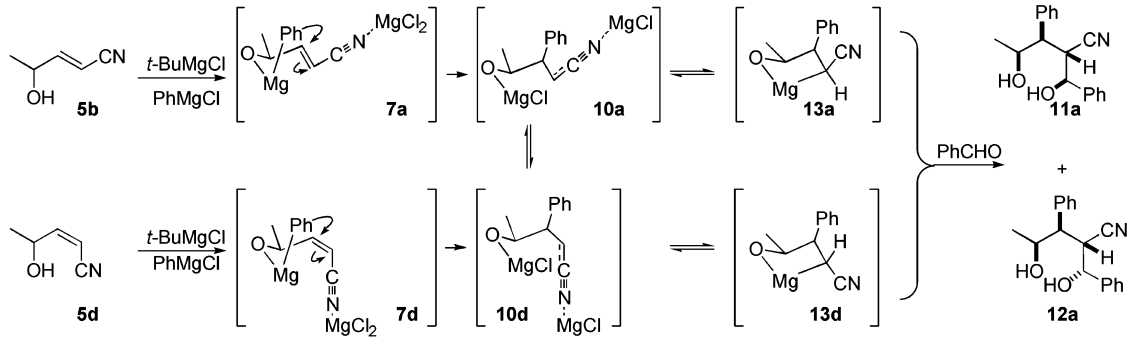
(21) Swiss, K. A.; Liotta, D. C.; Maryanoff, C. A. *J. Am. Chem. Soc.* **1990**, *112*, 9393.

(22) For related magnesium chelates see: (a) Fallis, A. G.; Forgione, P. *Tetrahedron* **2001**, *57*, 5899. (b) Normant, J. F.; Alexakis, A. *Synthesis* **1981**, 841.

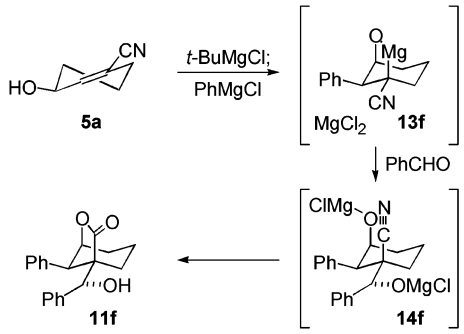
(23) Related carbomagnesiation of vinyl silanes is highly stereoselective[a,b] consistent with either the rapid, stepwise formation of the new carbon−magnesium bond[11] or a concerted carbomagnesiation where the asynchronous nature of the transition state permits this forbidden [2+2] addition.[c] (a) Hoffmann, R. W.; Knopff, O.; Faber, T. *J. Chem. Soc., Perkin Trans. 2* **2001**, 1785. (b) Utimoto, K.; Imi, H.; Shiragami, S.; Fujikura, S.; Nozaki, H. *Tetrahedron Lett.* **1985**, *26*, 2101. (c) Bundens, J. W.; Yudenfreund, J.; Francl, M. M. *Organometallics* **1999**, *18*, 3913.

(24) (a) Laumer, J. M.; Kim, D. D.; Beak, P. *J. Org. Chem.* **2002**, *67*, 6797. (b) Gawley, R. E. *Tetrahedron Lett.* **1999**, *40*, 4297. (c) Carstens, A.; Hoppe, D. *Tetrahedron* **1994**, *50*, 6097.

SCHEME 3. Chelation-Controlled Conjugate Addition Mechanism



SCHEME 4. Chelate Alkylation Stereochemistry



siated nitriles capable of alkylating carbonyl and alkyl halide electrophiles. Intercepting the magnesiated nitrile intermediate with benzaldehyde is completely selective at the nitrile-bearing carbon with a modest 4:1 selectivity arising from preferential attack on the *si* face of the carbonyl group. Analogous conjugate additions to cyclic alkenenitriles exhibit complete stereocontrol during conjugate addition and alkylation. Collectively the sequential conjugate addition−alkylations install two new bonds and up to three contiguous stereocenters in a single synthetic operation.

Acknowledgment. Financial support from NIH is gratefully acknowledged.

Supporting Information Available: Experimental procedures, ^{1}H NMR and ^{13}C NMR spectra for all new compounds, and ORTEP's for **11b**, **11c**, **11d**, and **11f**, the *p*-nitrobenzoate derivative of **8a**, and the dinitrobenzoates of **11a** and **12a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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