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γ-Hydroxy Unsaturated Nitriles: Chelation-Controlled Conjugate Additions

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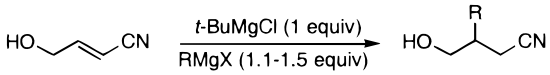
ABSTRACT

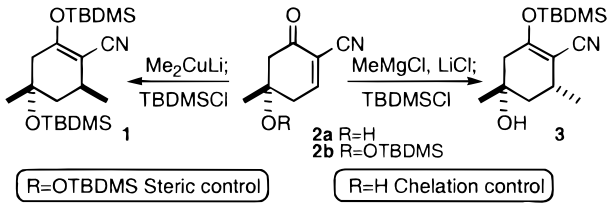


Chelation between γ-hydroxy unsaturated nitriles and Grignard reagents promotes an otherwise difficult anionic conjugate addition reaction. The intermediate chelate is readily generated by deprotonation with *t*-BuMgCl followed by the addition of a second Grignard reagent that triggers an intramolecular conjugate addition. Structurally diverse Grignard reagents add with equal efficiency, providing an intermediate anion that stereoselectively alkylates BnBr in an overall addition–alkylation reaction.

Anionic conjugate additions are one of the most important carbon−carbon bond-forming reactions.[1] While conjugate additions to α,β-unsaturated carbonyl compounds are often facile,[1] the corresponding reactions of α,β-unsaturated nitriles are significantly more demanding.[2] The paucity of conjugate additions to α,β-unsaturated nitriles limits strategies to the increasing number of nitrile-containing natural products[3] and prevents the unique properties of the nitrile group[4] from being fully realized. Our effort to probe the fundamental requirements of this reaction has resulted in the conjugate addition of sulfides,[5] selenides,[5] and dithiane anions[6] to α,β-unsaturated nitriles and of Grignard reagents to α,β-unsaturated oxonitriles.[7]

Anionic conjugate addition reactions are profoundly influenced by chelation.[8] The effect of chelation is succinctly illustrated in the addition of Grignard reagents to the hydroxylated α,β-unsaturated oxonitriles **2** (Scheme 1).[9]

Scheme 1



Chelation between the hydroxyl group of **2a** and MeMgCl stereoselectivity generates **3** while the conjugate addition with **2b**, without chelation, proceeds with the opposite stereoselectivity, affording **1**.

The high stereoselectivity and rapid reaction rate in Grignard reactions with **2a** suggests chelation as an effective method for promoting conjugate additions to otherwise unreactive α,β-unsaturated nitriles.[10] This strategy is par-

(1) Perlmutter, P. In *Conjugate Addition Reactions in Organic Synthesis*; Pergamon: New York, 1992.
(2) Rakita, P. E. In *Handbook of Grignard Reagents*; Silverman, G. S., Rakita, P. E., Eds.; Marcel Dekker: New York, 1996; pp 381−389.
(3) Fleming, F. F. *Nat. Prod. Rep.* **1999**, *16*, 597.
(4) Fatiadi, A. J. In *The Chemistry of Functional Groups, Supplement C*; Patai, S., Rappoport, Z., Eds. Wiley: New York, 1983; Chapter 26.
(5) Fleming, F. F.; Pak, J. J. *J. Org. Chem.* **1995**, *60*, 4299.
(6) Fleming, F. F.; Hussain, Z.; Weaver, D.; Norman, R. E. *J. Org. Chem.* **1997**, *62*, 1305.
(7) Fleming, F. F.; Pu, Y.; Tercek, F. *J. Org. Chem.* **1997**, *62*, 4883.
(8) For an excellent review see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.
(9) Fleming, F. F.; Guo, J.; Wang, Q.; Weaver, D. *J. Org. Chem.* **1999**, *64*, 8568.

(10) Conjugate additions with Grignard reagents have been observed with aryl-substituted α,β-unsaturated nitriles. (a) Kulp, S. S.; DiConcetto, J. A. *J. Chem. Educ.* **1990**, *67*, 271. (b) Kingsbury, C. A. *J. Org. Chem.* **1968**, *33*, 1128. (c) Prout, F. S.; Huang, E. P.-V.; Hartman, R. J.; Korpics, C. J.

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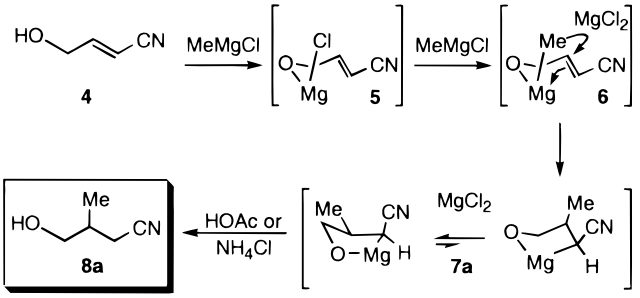
ticularly appealing since a successful conjugate addition leads, in principle, to nitrile anions[11] for sequential conjugate addition−alkylation reactions. Realization of this strategy is reported, representing the first example of chelation-controlled conjugate additions to α,β-unsaturated nitriles.

Rapid access to the α,β-unsaturated nitrile **4**[12] makes **4** an excellent prototype for examining the chelation-controlled conjugate addition reaction (Scheme 2). Addition of excess

Scheme 2

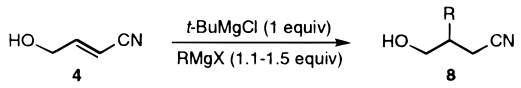


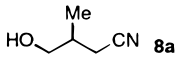
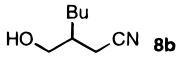
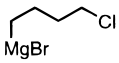
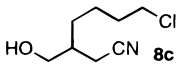
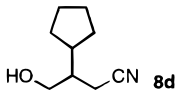
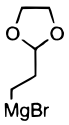
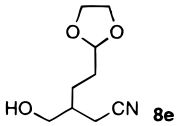
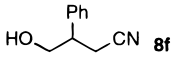
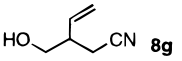
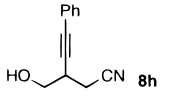
methylmagnesium chloride to **4** does indeed provide addition product **8a** after 2 h at room temperature. The reaction most likely proceeds via chloromagnesium alkoxide **5**[13] which reacts further with methylmagnesium chloride to generate methylmagnesium alkoxide **6**.[14] Alkyl transfer from complex **6** generates an intermediate dianion (**7a**) that is protonated to provide conjugate addition product **8a**. The importance of chelation is underscored by the inability of MeMgOMe[13] to react intermolecularly with an unsaturated nitrile.[15]

The conjugate addition is extremely clean, proceeding efficiently at room temperature and more slowly at dry ice temperatures. The slower rate at −78 °C is providential in allowing a sacrificial Grignard reagent (PhMgCl or *t*-BuMgCl) to be used for the deprotonation and only a slight excess of a second Grignard for the intramolecular addition. Using this strategy with either PhMgCl or *t*-BuMgCl for the initial deprotonation, and MeMgCl for the conjugate addition, provides the methyl transfer product in 63% and 74% yields, respectively.

The *t*-BuMgCl-initiated chelation-controlled conjugate addition is effective with a diverse range of Grignard reagents (Table 1).[16] Both alkyl and aryl Grignard reagents add

Table 1. Chelation-Controlled Conjugate Additions to **4**



Entry	Grignard	Product	Yield (%)
1	MeMgCl	 **8a**	74
2	BuMgCl	 **8b**	80
3		 **8c**	50[a]
4		 **8d**	78
5		 **8e**	78
6	PhMgCl	 **8f**	76
7		 **8g**	63
8		 **8h**	62

[a] 11% of **8b** is also obtained, resulting from the addition of $ClMg(CH_2)_4MgBr$ that is produced during the formation of the mono-Grignard reagent.

efficiently, with even the hindered cyclopentyl group being introduced without difficulty (Table 1, entry 4). Incorporating an acetal group within the Grignard reagent does not complicate the reaction (Table 1, entry 5), establishing that potential sites of additional chelation are readily tolerated. Further functional group tolerance is illustrated in the reaction with chlorobutylmagnesium bromide (Table 1, entry 3), and in reactions with sp, sp^2, and sp^3 hybridized Grignard reagents.

The chelation-controlled conjugate addition generates an intermediate anion that can potentially react with electrophiles. Addition of chlorobutylmagnesium bromide to **4** (Table 1, entry 3), without subsequent intramolecular alkylation, indicates that the formal dianion intermediate is not

J. Am. Chem. Soc. **1954**, *76*, 1911. (d) Kharasch, M. S.; Reinmuth, O. In *Grignard Reactions of Nonmetallic Substances*; Prentice Hall: New York, 1954; pp 782−783. (e) Wawzonek, S. *J. Am. Chem. Soc.* **1946**, *68*, 1157. (f) Reference 2.

(11) Arseniyadis, S.; Kyler, K. S.; Watt, D. S. *Org. React.* **1984**, *31*, 1.

(12) (a) Burrows, C. J.; Carpenter, B. K. *J. Am. Chem. Soc.* **1981**, *103*, 6983. (b) Burrows, C. J. Ph.D. Dissertation, Cornell University, Ithaca, NY, 1982. We are particularly grateful to Dr. Carpenter for providing experimental details from ref 12b.

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

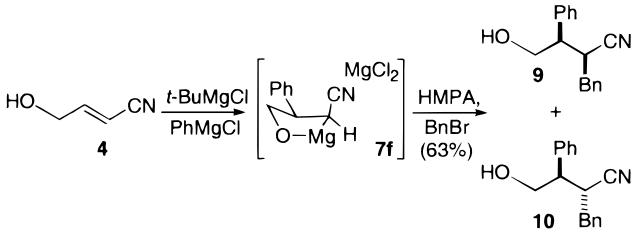
(14) Swiss, K. A.; Liotta, D. C.; Maryanoff, C. A. *J. Am. Chem. Soc.* **1990**, *112*, 9393.

(15) Addition of MeMgOMe to citronitrile (2h, rt) resulted in recoverey of citronitrile.

(16) **Representative procedure:** A THF solution of *tert*-butylmagnesium chloride (1.0 equiv) is added to a cold (−78 °C) THF solution (1.1 mM) of **4**. After 5 min, a THF solution of MeMgCl (1.1 equiv) is added, the cooling bath is removed, and the solution is allowed to stir for 1.5 h. The reaction mixture is cooled to 0 °C, neat AcOH (3.2 equiv) is added, followed by EtOAc (10 mL), and then the crude product is filtered through a short plug of silica gel. (This nonaqueous workup is only necessary for water-soluble γ-hydroxy nitriles.) Concentration followed by radial chromatography affords 74% of **8a**. The structural assignments are based on ^1H and ^{13}C NMR, IR, and GCMS analyses.

particularly nucleophilic.[17] Similarly, intermediate **7f**,[18] from the addition of PhMgCl to **4** (Scheme 3), is unreactive toward BnBr.

Scheme 3



The stability of intermediate dianion **7f** may reflect the high covalency of carbon−magnesium bonds,[19] suggesting that the addition of a strong oxygen donor will weaken the covalent C−Mg bond to allow alkylation. With this understanding, HMPA and BnBr were sequentially added to intermediate **7f**, providing dialkylated nitriles **9** and **10** with remarkable stereoselectivity (6.6:1, respectively). The stereochemical assignment of the major isomer **9** was unequivocally determined by X-ray analysis[20] (Figure 1).

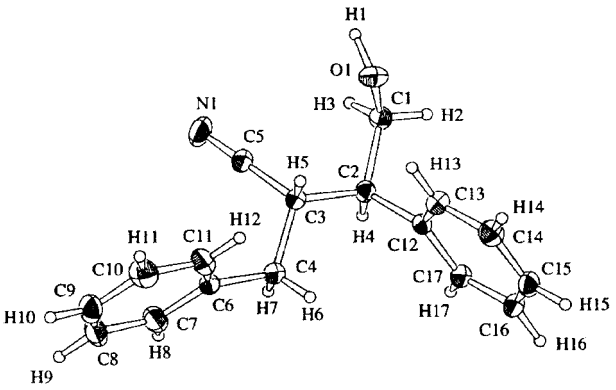
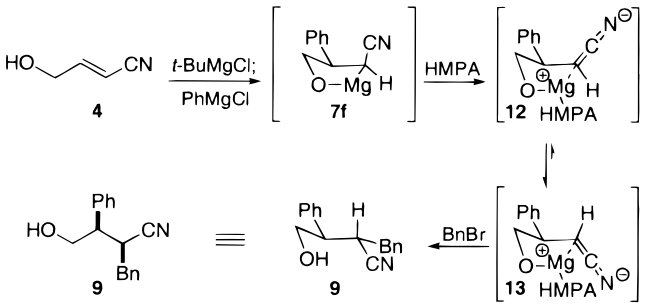


Figure 1. ORTEP of nitrile **9**.

The stereoselective alkylation of **7f** in the presence of HMPA is unusual. Formation of a "free" dianion with HMPA is expected to result in only modest levels of selectivity.[21] An alternative rationale envisages partial solvation by HMPA that weakens the C−Mg bond, allowing equilibration between two weakly coordinated[22] keteniminate anions **12** and **13** (Scheme 4).[23] Alkylation from the less sterically demanding keteniminate **13** is expected to occur from the backside of the keteniminate, leading preferentially to nitrile **9**.

Scheme 4



Chelation control overcomes the long-standing difficulty of anionic conjugate additions to α,β-unsaturated nitriles. Structurally diverse Grignard reagents add efficiently in this conjugate addition reaction, providing excellent access to β-substituted nitriles. Particularly significant is the sequential conjugate addition−alkylation with benzyl bromide that proceeds with remarkable stereoselectivity.

Acknowledgment. Financial support from NIH is gratefully acknowledged. Shih-Chi Chang is thanked for assistance with the X-ray structure determination.

OL005816J

(17) Normant, J. F.; Alexakis, A. *Synthesis* **1981**, 841.

(18) For related intermediates, see: (a) Eisch, J. J.; Merkley, J. H.; Galle, J. E. *J. Org. Chem.* **1979**, *44*, 587. (b) Chérest, M.; Felkin, H.; Frajerman, C.; Lion, C.; Roussi, G.; Swierczewski, G. *Tetrahedron Lett.* **1966**, 875.

(19) Clark, T.; Rohde, C.; Schleyer, P. V. R. *Organometallics* **1983**, *2*, 1344.

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

(21) Cainelli, G.; Cardillo, G.; Contento, M.; Trapani, G.; Umani Ronchi, A. *J. Chem. Soc., Perkin Trans. 1* **1973**, 400.

(22) Coordination between the magnesium alkoxide and the keteniminate is similar to the coordination observed between an enolate and an alkene: Harris, C. R.; Danishefsky, S. J. *J. Org. Chem.* **1999**, *64*, 8434.

(23) For leading references to the structure of nitrile anions, see: (a) Strzalko, T.; Seyden-Penne, J.; Wartski, L.; Corset, J.; Castella-Ventura, M.; Froment, F. *J. Org. Chem.* **1998**, *63*, 3287. (b) Koch, R.; Wiedel, B.; Anders, E. *J. Org. Chem.* **1996**, *61*, 2523. (c) Wiberg, K. B.; Castejon, H. *J. Org. Chem.* **1995**, *60*, 6327. (d) Carlier, P. R.; Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1994**, *116*, 11602. (e) Abbotto, A.; Bradamante, S.; Pagani, G. A. *J. Org. Chem.* **1993**, *58*, 449.