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Alkynenitriles: Chelation-Controlled Conjugate Additions

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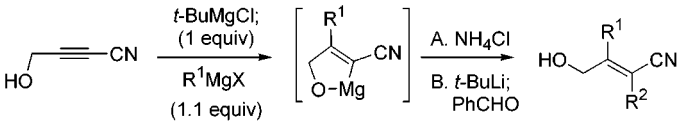
ABSTRACT

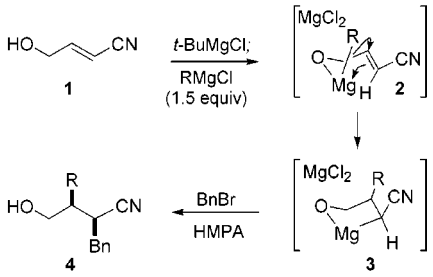


Chelation between γ-hydroxybutynenitrile and Grignard reagents triggers a particularly facile anionic conjugate addition reaction. Structurally diverse Grignard reagents add with equal efficiency, providing an intermediate anion that stereoselectively alkylates benzaldehyde in an overall addition–alkylation reaction.

Anionic conjugate additions are among the most fundamental of carbon−carbon bond forming reactions.[1] Conjugate additions to unsaturated carbonyl compounds occur with excellent chemo- and stereoselectivity[1] for a diverse array of stabilized and organometallic nucleophiles. Unsaturated nitriles, in contrast, are recalcitrant Michael acceptors,[2] requiring activation[3] or powerful nucleophiles[4] to coax otherwise difficult or impossible conjugate additions.

A particularly expedient solution for conjugate addition to alkenenitriles[5] is to temporarily chelate[6] the nucleophile proximal to the Michael acceptor (Scheme 1). Deprotonating **1**, followed by addition of a second Grignard reagent, generates a transient alkylmagnesium alkoxide **2**, triggering a smooth conjugate addition. Protonation or alkylation of the resulting chelate **3** efficiently provides substituted nitriles with two new bonds and the controlled formation of up to two new stereocenters.

Scheme 1



The enhanced Michael acceptor properties of alkynenitriles suggested an analogous chelation-controlled addition as a means of extending chelation strategies to encompass conjugate additions to activated alkynes.[7] Particularly appealing is the possibility of intercepting the intermediate chelate in a sequential addition−alkylation route to stereodefined, tetra-substituted alkenes that are otherwise difficult to synthesize.[8] Achieving this goal would extend current conjugate addition of organocopper reagents[9] and alkyl-

(1) Perlmutter, P. In *Conjugate Addition Reactions in Organic Synthesis*; Pergamon: New York, 1992.
(2) Fleming, F. F.; Hussain, Z.; Weaver, D.; Norman, R. E. *J. Org. Chem.* **1997**, *62*, 1305.
(3) (a) Morales-Rios, M. S.; Suarez-Castillo, O. R.; Trujillo-Serrato, J. J.; Joseph-Nathan, P. *J. Org. Chem.* **2001**, *66*, 1186. (b) Fleming, F. F.; Pu, Y.; Tercek, F. *J. Org. Chem.* **1997**, *62*, 4883. (c) Wallenfels, K.; Friedrich, K.; Rieser, J.; Ertel, W.; Thieme, H. K. *Angew. Chem.* **1976**, *15*, 261.
(4) Fleming, F. F.; Pak, J. J. *J. Org. Chem.* **1995**, *60*, 4299.
(5) Fleming, F. F.; Wang, Q.; Steward, O. W. *Org. Lett.* **2000**, *2*, 1477.
(6) (a) Fallis, A. G.; Forgione, P. *Tetrahedron* **2001**, *57*, 5899. (b) Normant, J. F.; Alexakis, A. *Synthesis* **1981**, 841.
(7) Chelation-controlled conjugate additions to activated alkenes are effective with several electron-withdrawing groups, with analogous additions to activated alkynes appearing not to have been investigated: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.
(8) Ojima, I.; Kumagai, M. *Tetrahedron Lett.* **1974**, 4005.
(9) (a) Kleijn, H.; Westmijze, H.; Meijer, J.; Vermeer, P. *J. Organomet. Chem.* **1981,** *206*, 257. (b) Westmijze, H.; Kleijn, H.; Vermeer, P. *Synthesis* **1978**, 454.

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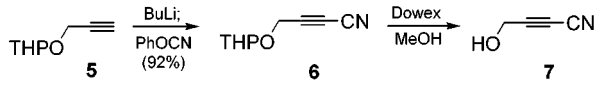
argentates[10] to alkynenitriles and generate hydroxyalkenenitriles for further conjugate additions.[5]

Essential for this venture is a rapid, efficient synthesis of hydroxybutynenitrile (**7**). The tendency of **7** toward base-initiated polymerization[11] stimulated adapting the synthesis of the corresponding ester[12] where unmasking of the hydroxyl group is performed under acidic conditions. Deprotonating THP-protected propargyl alcohol **5**,[12] (Scheme 2) followed

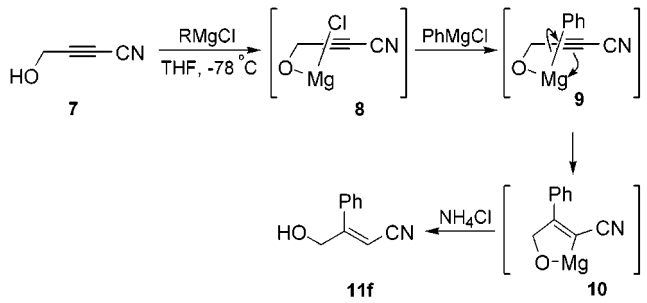
Scheme 2



by cyanation with phenylcyanate,[13] smoothly affords gram quantities of the chromatographically stable alkynenitrile **6**. THP removal with acidic Dowex quantitatively generates alkynenitrile **7**, which is simply isolated, spectroscopically pure, by filtration.

Conjugate additions to **7** were initially probed with PhMgBr. Addition of excess PhMgCl at −78 °C, followed by warming to room temperature, initiates a smooth conjugate addition reaction generating **11f** in 96% yield (Scheme 3). Mechanistically, the reaction most likely proceeds through

Scheme 3

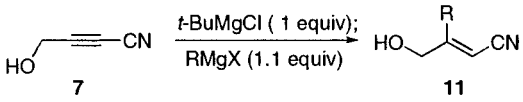


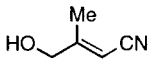
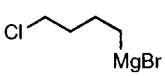
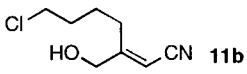
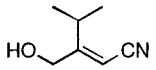
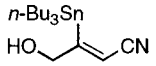
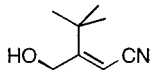
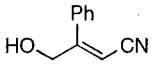
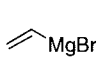
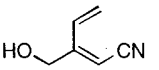
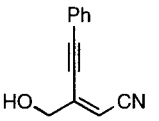
initial formation of the chloromagnesium alkoxide **8**[14] followed by halogen−alkyl exchange.[15] Alkyl transfer[16] from the resulting alkylmagnesium alkoxide **9** leads to an intermediate chelate **10**[6] that, upon protonation, affords the conjugate addition product **11f**. The heightened reactivity of the alkynenitrile **7** is apparent from the smooth conjugate addition at −78 °C, whereas the corresponding alkenenitrile requires ambient temperature to initiate the addition.[5]

Despite the fact that the chelation-controlled conjugate addition is significantly more facile than with alkenenitriles, *t*-BuMgCl serves as an excellent sacrificial base for selective deprotonation, without prematurely engaging in a potentially deleterious conjugate addition reaction. Deprotonating **7** with *t*-BuMgCl, followed by addition of PhMgCl, triggers phenyl transfer at −78 °C (Scheme 3) to afford the conjugate addition product **11f** in 92% yield.[17] Use of *t*-BuMgCl as a sacrificial base effectively allows conjugate addition with only a slight excess of a second, potentially more valuable, Grignard reagent.

The chelation-controlled conjugate additions are effective with a diverse range of Grignard reagents (Table 1). Alkyl

Table 1. Chelation-Controlled Conjugate Additions to **7**



entry	Grignard	nitrile	yield
1	MeMgCl	 **11a**	92%
2		 **11b**	78%
3	*i*-PrMgBr	 **11c**	87%
4	*n*-$Bu_3SnMgCl$	 **11d**	70%
5	*t*-BuMgCl	 **11e**	60%
6	PhMgCl	 **11f**	92%
7		 **11g**	87%
8		 **11h**	85%

and aryl Grignard reagents add with equal efficiency, even installing hindered tri-*n*-butylstannyl and *tert*-butyl groups without difficulty (Table 1, entries 4 and 5). The reaction tolerates sp^3, sp^2, and sp hybridized Grignard reagents (Table

(10) (a) Westmijze, H.; Kleijn, H.; Vermeer, P. *Tetrahedron Lett.* **1979**, *35*, 3327 and (b) ref 9a.
(11) Matsumura, K.; Saraie, T.; Hashimoto, N. *J. Takeda Res. Lab.* **1971**, *30*, 682.
(12) Earl, R. A.; Townsend, L. B. I. *Org. Synth.* **1982**, *60*, 81.
(13) Murray, R. E.; Zweifel, G. *Synthesis* **1980**, 150.
(14) Turova, N. Y.; Turevskaya, E. P. *J. Organomet. Chem.* **1972**, *42*, 9.
(15) Swiss, K. A.; Liotta, D. C.; Maryanoff, C. A. *J. Am. Chem. Soc.* **1980**, *112*, 9393.
(16) Forgione, P.; Fallis, A. G. *Tetrahedron Lett.* **2000**, *41*, 11.

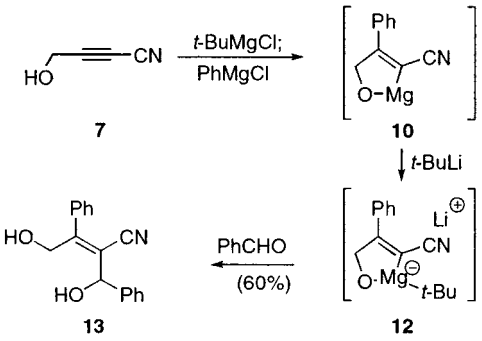
(17) **Representative Procedure.** A THF solution of *t*-BuMgCl (1.0 equiv) is added to a cold (−78 °C), THF solution of **7** (1 equiv), followed after 5 min by a THF solution of PhMgCl (1.1 equiv). After 45 min the reaction mixture is allowed to warm to room temperature, followed by addition of saturated, aqueous NH_4Cl. Extraction followed by filtration of the organic extract through a short plug of silica, drying (Na_2SO_4), and radial chromatography of the resulting crude nitrile affords pure **11f** (92%).

1, entries 1−5, 6 and 7, and 8, respectively) and even proceeds smoothly with chlorobutylmagnesium bromide[18] (Table 1, entry 2). In all cases the *trans*-hydroxybutenenitrile is the exclusive stereoisomer, suggesting that protonation of the chelate occurs with retention of stereochemistry (Scheme 3).

The chelation-controlled conjugate addition generates a chelate for potential alkylation with electrophiles. Addition of chlorobutylmagnesium bromide[18] to **7** (Table 1, entry 2), without subsequent intramolecular alkylation, indicates a particularly low nucleophilicity of the formal "dianion." Surprisingly, the intermediate chelate is even unreactive toward PhCHO![19]

With the presumption that a tightly bound alkylmagnesium alkoxide prevents alkylation with PhCHO, *t*-BuLi (1.2 equiv) was added to chelate **10** in an attempt to generate the corresponding magnesium ate complex[20] (Scheme 4). Addition of *t*-BuLi effectively transforms the unreactive chelate **10** into a reactive species that stereoselectively reacts with PhCHO to form the tetra-substituted alkenenitrile **13**.

Scheme 4



Although speculative, addition of *t*-BuLi may generate the ate complex **12** (Scheme 4) with enhanced nucleophilicity for an efficient alkylation[21] with benzaldehyde. Stereochemical assignment of the resulting tetra-substituted alkene **13** was unequivocally determined by X-ray analysis[22] (Figure 1). Alkylation and protonation of **10** and **12** proceed with the same stereochemical preference, consistent with the intermediacy of cyclic chelates.[6]

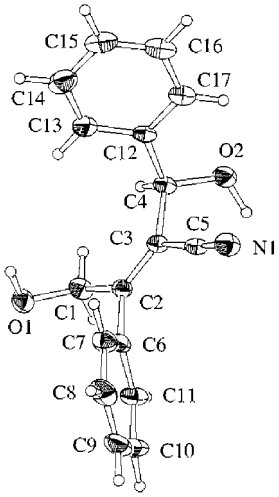


Figure 1. ORTEP drawing of **13**.

Chelation-controlled conjugate addition of Grignard reagents to γ-hydroxybutynenitrile efficiently generates a diverse array of tri-substituted alkenenitriles. Exclusive formation of one stereoisomer stems from preferential protonation of a particularly stable chelate that does not directly alkylate aldehyde electrophiles. Alkylation of the chelate requires activation with an equivalent of *t*-BuLi prior to the addition of PhCHO, presumably allowing alkylation through the more reactive ate complex. Collectively, the sequential conjugate addition−alkylation stereoselectively generates a tetra-substituted alkenenitrile in one synthetic operation.

Acknowledgment. Financial support from NIH is gratefully acknowledged.

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

(19) Presumably the nitrile decreases the nucleophilicity of the organometallic since related alkyl-substituted chelates (**10** CN=Me) do react with aldehydes at ambient temperature.[16]

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

(21) Related, nonchelated magnesiated acrylonitriles react directly with aldehydes: Thibonnet, J.; Knochel, P. *Tetrahedron Lett.* **2000**, *41*, 3319.

(22) The authors have deposited the crystallographic data for **13** with the Cambridge Crystallographic Data Center (CCDC 177267). The data can be obtained, on request, from the Director, Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, U.K.