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Alkenenitrile Transmissive Olefination: Synthesis of the Putative Lignan "Morinol I"

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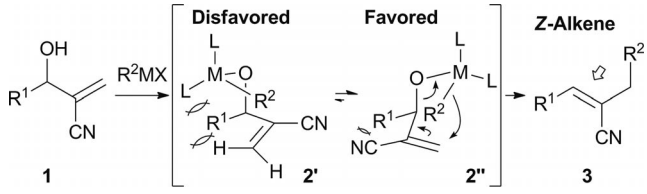
Grignard reagents trigger an addition–elimination with α′-hydroxy acrylonitriles to selectively generate *Z*-alkenenitriles. The modular assembly of *Z*-alkenenitriles from a Grignard reagent, acrylonitrile, and an aldehyde is ideal for stereoselectively synthesizing alkenes, as illustrated in the synthesis of the putative lignan morinol I.

Introduction

Six-electron transition structures undergird many extremely powerful synthetic methods.[1] Diels–Alder cycloadditions, electrocyclic reactions, and [3,3] sigmatropic rearrangements all proceed through privileged six-electron, six-atom transition structures. A remarkable diversity of atom substitutions are tolerated within the six-membered ring; Cope, Claisen, and aza-Cope reactions incorporate carbon, oxygen, and nitrogen ring atoms, respectively. Equally powerful are heteroatom–metal combinations proceeding through six-membered Zimmerman–Traxler transition structures that efficiently and stereoselectively allow aldol condensations, allylations, and intramolecular hydride reductions.[2]

Harnessing the facility of six-electron reactions to drive the formal displacement of hydroxide is rare – only high-valent titanium and cerium promote the elimination.[3] Typically, allylic alcohols require activation prior to displacement because hydroxide is a poor leaving group.[4] Conceptually, hydroxide ejection from hydroxyalkenenitrile **1** (Scheme 1) could be promoted through a concerted, six-electron, anionic rearrangement (**2** → **3**) and by forming a particularly stable metal oxide. Preferential rearrangement through conformer **2′′** would assemble α-substituted *Z*-alkenenitrile **3**, whose stereoselective synthesis is challenging.[4a,5] The value of alkenenitriles lies in their versatility as synthetic intermediates[6] and as potent pharmacophores embedded within numerous bioactive natural products[7] and pharmaceuticals.[8] Generally, only one *E*/*Z* stereoisomer is bioactive, or at least significantly more active, underscoring the need for rapid, modular, stereoselective syntheses of alkenenitriles.[9]



Scheme 1. Transmissive olefination route to *Z*-alkenenitriles.

Results and Discussion

Exploratory forays focused on a magnesium oxide driven rearrangement because of the strength of the Mg=O bond,[10] the prevalence of commercial Grignard reagents, and ready access to activated allylic alcohols through Baylis–Hillman condensations.[11] After some optimization of temperature and stoichiometry, the addition of an excess amount of *i*PrMgCl to hydroxyalkenenitrile **1a** was found to readily afford *Z*-alkenenitrile **3a** as a single diastereomer[12] (Table 1, Entry 1).

The transmissive olefination smoothly generates an array of *Z*-alkenenitriles **3** from the corresponding hydroxyalkenenitriles **1** (Table 1). The extremely compact nitrile group resists nucleophilic attack by the proximal Grignard reagent, instead channeling a stereoselective[12] alkyl addition–elimination to alkenenitrile **3**. For example, addition of BuMgCl to nitrile **1a** forms perfumery agent **3c** as a single stereoisomer (Table 1, Entry 3).[13] Sterically demanding, secondary, and tertiary Grignard reagents add with efficacies comparable to those of primary Grignard reagents (Table 1, Entries 2 and 3 vs. 1, 4, and 5). Similarly, no significant difference in efficiency is observed between

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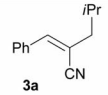
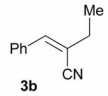
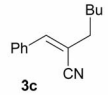
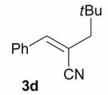
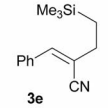
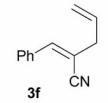
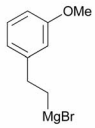
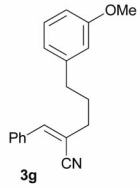
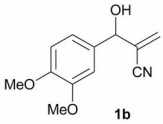
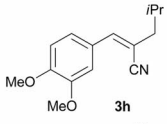
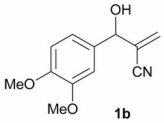
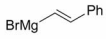
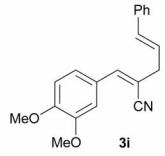
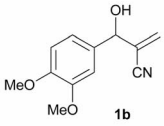
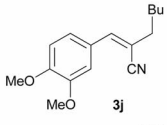
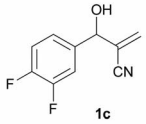
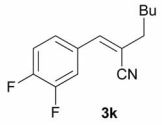
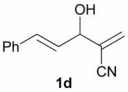
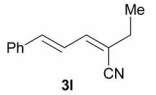
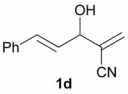
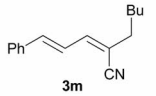
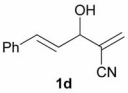
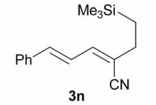
Table 1. α′-Hydroxy alkenenitrile transmissive olefination.[a]

Entry	Hydroxynitrile	Grignard	Alkenenitrile	Yield [%]
1	 **1a**	*i*PrMgCl	 **3a**	56
2	 **1a**	MeMgCl	 **3b**	62
3	 **1a**	BuMgCl	 **3c**	77
4	 **1a**	*t*BuMgCl	 **3d**	54
5	 **1a**	Me_3SiCH_2MgCl	 **3e**	52
6	 **1a**		 **3f**	66
7	 **1a**		 **3g**	62
8	 **1b**	*i*PrMgCl	 **3h**	60
9	 **1b**		 **3i**	63
10	 **1b**	BuMgCl	 **3j**	83
11	 **1c**	BuMgCl	 **3k**	68
12	 **1d**	MeMgCl	 **3l**	54 (4:1)
13	 **1d**	BuMgCl	 **3m**	50 (6:1)
14	 **1d**	Me_3SiCH_2MgCl	 **3n**	52 (6:1)

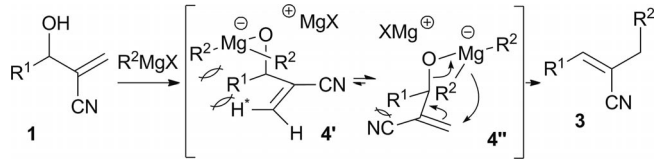
[a] An excess amount of the Grignard reagent was added to hydroxynitrile **1** at 0 °C and after 50 min saturated, aqueous NH_4Cl was added.

electron-rich and electron-deficient aryl hydroxynitriles (Table 1, compare Entries 3, 10, and 11). Although acetylenic Grignard reagents do not engage in the rearrangement, vinylmagnesium halides effectively generate skipped dienes without detectable olefin isomerization (Table 1, Entries 6 and 9).

Modest oxygenation within the Grignard reagent is tolerated (Table 1, Entry 7), although attempts to use (1,3-dioxan-2-ylethyl)magnesium bromide were unsuccessful. The transmissive olefination with (3-methoxyphenethyl)magnesium bromide employed one equivalent of *i*PrMgBr as a sacrificial base (Table 1, Entry 7), reducing the amount of the Grignard reagent required for alkyl transfer to two equivalents. Using this procedure, alkenenitrile **3g** was prepared in 62% yield.

A carbinol substituent capable of stabilizing charge is required for the rearrangement.[14] Presumably the sp^2 center promotes the rearrangement by aligning a p orbital with the C–O bond undergoing cleavage. In addition to benzylic alcohols (Table 1, Entries 1–11), cinnamyl alcohol **1d** readily affords conjugated dienenitriles[9,15] **3l**–**n** (Table 1, Entries 12–14).

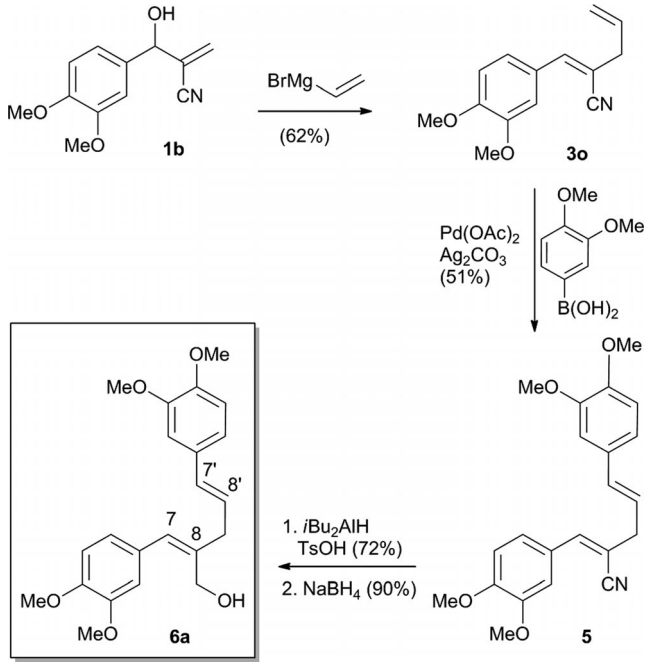
The addition–elimination requires 3.5 equiv. of Grignard reagent suggesting rearrangement via the more nucleophilic magnesiate **4** (Scheme 2) rather than an alkylmagnesium alkoxide (cf. **2**, M = Mg; Scheme 1).[16] Consistent with the intermediacy of a magnesiate, no rearrangement is observed on treating **1a** with one equivalent of dibutylmagnesium. Magnesium cations appear essential, as the sequential addition of one equivalent of RMgX followed by an excess amount of RLi affords only trace amounts of alkenenitrile **3**. Formation of *Z*-alkenenitrile **3** is consistent with a concerted,[17] exocyclic intramolecular rearrangement through magnesiate **4′′** in which the sterically miniscule nitrile group[18] eclipses the carbinol substituent R^1. The model also accounts for the higher selectivity of aryl over alkenyl substituents R^1 assuming that the latter orients[14] to position a proton toward the eclipsing inside substituent (H* in **4′** and CN in **4′′**).



Scheme 2. Transmissive olefination mechanism.

Rapid access to *Z*-alkenenitriles stimulated applying the transmissive olefination to the synthesis of the neolignan morinol I. Isolated during a bioactivity guided isolation of the Chinese medicinal herb *Morina chinensis*,[19] morinol I possesses a skipped diene unique among this class of neolignan metabolites (**6a**, Scheme 3).[20] Vinylmagnesium bromide initiated transmissive olefination with veratraldehyde-derived nitrile **1b** effectively provided requisite *Z*-dienenitrile **3o** as a single stereoisomer.[11b] Subsequent exposure of **3o** to 3,4-dimethoxyboronic acid in the presence of

$Pd(OAc)_2$ and Ag_2CO_3 affords dienenitrile **5** with full control over the olefin stereochemistry (Scheme 3). Conventional iBu$_2$AlH reduction of nitrile **5**,[21] hydrolysis, and aldehyde reduction afforded an 8:1 ratio of *E*/*Z* enal diastereomers that were reduced to target alcohol (7*Z*,7′*E*)-**6a** and diastereomer (7*E*,7′*E*)-**6b**. Neither alcohol (7*Z*,7′*E*)-**6a** nor C7–C8 *E*-diastereomer (7*E*,7′*E*)-**6b** exhibit spectroscopic data matching the reported spectral listing of the natural product. Unfortunately, samples and copies of the spectroscopic data exhibited by the natural lignin are not available to resolve the ambiguous HMBC and NOE data that are inconsistent with the skipped diene structure proposed for morinol I.[22] Although the precise structure of morinol I is elusive, the five-step synthesis of the putative structure of morinol I demonstrates the ability of the transmissive olefination strategy to rapidly assemble this type of molecular scaffold.



Scheme 3. Transmissive olefination route to morinol I.

Conclusions

The transmissive olefination of hydroxy alkenenitriles efficiently and stereoselectively assembles *Z*-alkenenitriles from three readily available components: an aldehyde, acrylonitrile, and a Grignard reagent. The strategy directly employs Baylis–Hillman alcohols without prior hydroxyl activation by harnessing a unique elimination of magnesium oxide. Simply adding excess Grignard reagent to an α′-hydroxyalkenenitrile triggers a transmissive olefination to efficiently provide a diverse array of *Z*-alkenenitriles. The versatility of the transmissive olefination is illustrated in the rapid synthesis of the structure proposed for the lignan morinol I.

Experimental Section

General Transmissive Olefination Procedure: An ethereal solution of the Grignard reagent (3.5 equiv.) was slowly added to a stirred 0 °C, THF solution of **1**. After 50 min, the mixture was quenched with 0.1 M HCl solution, and then the resulting mixture was stirred vigorously for 5 min. The crude product was extracted with diethyl ether, dried ($MgSO_4$), concentrated, and purified by radial chromatography to afford analytically pure material.

Supporting Information (see footnote on the first page of this article): Experimental procedures, spectroscopic and analytical data, and copies of the NMR spectra for all new compounds.

Acknowledgments

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[22] Although other metabolites appear to be derivatives of a precursor having the structure proposed for morinol I, the HMBC and NOE data are inconsistent with the skipped diene structure of **6a**. The ambiguities and the lack of further reports leave synthesis as the best avenue for determining the correct structure. Full details of the transmissive olefination approach to morinol I alkene diastereomers and structural isomers will be published in a separate account.

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