New methods for the synthesis of substituted nitriles

Venugopal Gudipati

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New Methods for the Synthesis of Substituted Nitriles

A Thesis presented to the Graduate School of Duquesne University

As partial fulfillment of the requirements for the degree of
Master of Science

By
Venugopal Gudipati
December 2002

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<table>
<thead>
<tr>
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<td>Master of Science</td>
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<td>Date</td>
<td>__________________________, 2002</td>
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<tr>
<td>Approved</td>
<td>Dr. Fraser F. Fleming</td>
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<td>Approved</td>
<td>Dr. Omar W. Steward</td>
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<td>Approved</td>
<td>Dr. Bruce Beaver</td>
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<td>Dr. Jeffry Madura – Chair</td>
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<td>Dr. David Seybert - Dean</td>
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Acknowledgements

I would like to sincerely thank Dr. Fraser F. Fleming, for being so much helpful to me as an advisor, teacher and friend. It’s been a great joy and experience working under your guidance. I am indebted to you for your kind help and understanding during critical times in my graduate studies. Thank you very much Dr. Fleming for everything.

I would like to thank Drs. Omar W. Steward and Bruce Beaver for their immense help by being on my committee. My thanks are due to Dr. Basu and Write who actually brought me here without whom I wouldn’t have had this wonderful experience.

I also want to thank co-workers of our research group for helping me a lot with their friendly discussions (Pravin, Qunzhao, Brian, Zhang, Lee and Kristin). My thanks are due to Tamanna, Sejal and Lisa for helping me in various ways.

Finally, I want to thank my parents and brothers for always being there for me with their encouragement and support during my times at Duquesne.

Thank all you again.
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Abstract

Part I of this thesis describes stereoselective conjugate additions of Grignard reagents to γ-hydroxy alkynenitriles. Grignard reagents readily add to γ-hydroxy alkynenitriles in an efficient chelation-controlled conjugate addition. t-BuMgCl-initiated deprotonation followed by addition of a second Grignard reagent triggers a conjugate addition leading to a cyclic magnesium chelate. Protonation of the resulting magnesium chelate stereoselectively generates tri-substituted alkenenitriles. Alternatively, addition of t-BuLi activates the magnesium chelate by conversion to the corresponding ate complex, permitting alkylation with aromatic and aliphatic aldehydes with complete stereochemical fidelity. Collectively the chelation-controlled conjugate addition-alkylation generates a range of tri and tetra-substituted alkenenitriles that are otherwise difficult to synthesize.

Part II of the thesis describes exploratory routes to nitrile-substituted carbocycles and oxacycles. t-BuOK readily deprotonates ω-haloalkynenitriles generating remarkably stable potassiated nitriles. Intercepting the potassiated nitriles with aldehyde electrophiles generates potassium alkoxide intermediates that rapidly cyclize to nitrile-substituted furan and pyran nitriles whereas alkylation with ester and alkyl halide electrophiles generates substituted halonitriles. Redirecting the cyclization manifold to carbonitrile formation is achieved simply with the corresponding iodonitrile and an appropriate ketone, triggering in situ enolate alkylation, deprotonation, and cyclization. The complementary cyclization manifolds provide rapid assembly of nitrile-substituted
furans, pyrans, and cyclohexanes and demonstrates the viability of metallated \(\omega\)-halonitriles in domino alkylation-cyclizations.
### List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Meaning</th>
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<tbody>
<tr>
<td>Ac</td>
<td>acetate</td>
</tr>
<tr>
<td>br</td>
<td>broad</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
</tr>
<tr>
<td>BuLi</td>
<td>butyllithium</td>
</tr>
<tr>
<td>(^{13}\text{C} \text{ NMR})</td>
<td>carbon nuclear magnetic resonance</td>
</tr>
<tr>
<td>d</td>
<td>doublet</td>
</tr>
<tr>
<td>dd</td>
<td>doublet of doublets</td>
</tr>
<tr>
<td>DMF</td>
<td>(N, N)-dimethlyformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>equiv</td>
<td>equivalent</td>
</tr>
<tr>
<td>Et</td>
<td>Ethyl</td>
</tr>
<tr>
<td>GC-MS</td>
<td>gas chromatography-mass spectrometry</td>
</tr>
<tr>
<td>h</td>
<td>hour(s)</td>
</tr>
<tr>
<td>(^1\text{H} \text{ NMR})</td>
<td>proton nuclear magnetic resonance</td>
</tr>
<tr>
<td>(\text{H}_2\text{SO}_4)</td>
<td>sulfuric acid</td>
</tr>
<tr>
<td>i</td>
<td>iso</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>m</td>
<td>multiplet</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>min</td>
<td>minute(s)</td>
</tr>
<tr>
<td>Ms</td>
<td>mesylate</td>
</tr>
<tr>
<td>Symbol</td>
<td>Definition</td>
</tr>
<tr>
<td>--------</td>
<td>------------------------------------</td>
</tr>
<tr>
<td>Ph</td>
<td>Phenyl</td>
</tr>
<tr>
<td>q</td>
<td>quartet</td>
</tr>
<tr>
<td>R</td>
<td>alkyl, aryl, or hydrogen</td>
</tr>
<tr>
<td>s</td>
<td>singlet</td>
</tr>
<tr>
<td>t</td>
<td>triplet</td>
</tr>
<tr>
<td>t</td>
<td>tertiary</td>
</tr>
<tr>
<td>t-BuOK</td>
<td>Potassium tertiary butoxide</td>
</tr>
<tr>
<td>Tf</td>
<td>triflate</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
</tbody>
</table>
1. Introduction: Synthesis of Alkynenitriles

Conjugate addition reactions rank as one of the most fundamental bond forming reactions.\(^1\) The centrality of conjugate addition stems from installing an alkyl constituent two carbons away from an electron withdrawing group while forming a reactive anion that can potentially be alkylated.\(^2\) Conjugate additions are typically performed with carbonyl substituted alkenes whereas less well-known are electron deficient alkynes, particularly alkynes activated with electron withdrawing groups other carbonyl derivatives.

Alkynenitriles are a poorly explored family of Michael acceptors. Electronically, the combination of linear alkyne and nitrile groups is significantly different from alkenes conjugated with carbonyl groups, potentially giving rise to complementary reactivity patterns in the two series. Exploring the chemical reactivity of alkynenitriles requires a rapid synthesis of these Michael acceptors that has been achieved by four different strategies. The following survey aims to illustrate the advantage of different alkynenitrile syntheses while cataloging the diverse structural types contained within this unusual class of Michael acceptors.

1.1 Dehydration of Acetylenic Carboxamides:

Dehydration of carboxamides\(^3\) provides saturated and unsaturated nitriles although far fewer alkynamides have been converted to alkynenitriles. Mechanistically a strongly oxophilic reagent is required to preferentially activate the carbonyl oxygen for subsequent elimination (Scheme 1, 2 $\rightarrow$ 3). Complexation with the carbonyl oxygen is facilitated by the electron donation from the nitrogen lone pair (Scheme 1).
Deprotonation of the activated complex 3, either from the conjugate or added base, triggers deprotonation and simultaneous deoxygenation to generate the alkynenitrile 4.

Historically, the dehydration of alkyneamides, propiolamid in particular, has employed P₂O₅.⁴ Dehydration with P₂O₅ gives excellent yields, for volatile alkynenitriles although the experiment is technically demanding and reliant on the availability of the amide precursors.⁵ More recently trichloromethyl chloroformate⁶ (liquid diphosgene) and Swern oxidation conditions⁷ have emerged as efficient reagents for the dehydration of carboxamides to nitriles (Equation 1).

\[
\begin{align*}
\text{Ph} & \quad \text{CONH}_2 & \quad \text{A. ClCO}_2\text{CCl}_3, (\text{MeO})_2\text{PO}, 90\% \\
\text{CONH}_2 & \quad \text{Ph} & \quad \text{B. (COCl)}_2, \text{DMSO}, \text{Et}_3\text{N}, 84\%
\end{align*}
\]

\[
\text{Ph} \quad \text{CONH}_2 \quad \text{P}_2\text{O}_5 \quad 83\% \quad \text{Ph} \quad \text{CN}
\]

1.2 Elimination of Alkynenitriles:

Significantly less common are eliminations of substituted alkenenitriles. Mechanistically an alkenenitrile containing a proton and a leaving group can be induced to eliminate to the corresponding alkynenitrile as is the case for the t-BuONa-induced dehydrohalogenation of 6 to alkynenitrile 4c (Equation 2).⁸
Alternatively, pyrolysis of oxoylids causes elimination to the corresponding acetylenic nitrile (Table 1). The driving force is the concerted elimination of triphenyl phosphine oxide, with high temperatures being required for the syn elimination because of the 120° bond angles enforced by $sp^2$ hybridization.

Table 1. Pyrolytic Oxoylid Synthesis of Alkynenitriles.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Yield</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Entry 1 R" /></td>
<td>75%</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2" alt="Entry 2 R" /></td>
<td>83%</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3" alt="Entry 3 R" /></td>
<td>94%</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4" alt="Entry 4 R" /></td>
<td>87%</td>
</tr>
<tr>
<td>5</td>
<td><img src="image5" alt="Entry 5 R" /></td>
<td>95%</td>
</tr>
<tr>
<td>6</td>
<td><img src="image6" alt="Entry 6 R" /></td>
<td>54%</td>
</tr>
</tbody>
</table>
1.3 CuCN-Cyanation of Terminal Acetylenes:

Several CuCN-based reagent combinations have been developed for the conversion of alkynes to the corresponding alkynenitriles. Copper has a propensity to complex alkynes, significantly increasing the acidity of terminal alkynes and allowing deprotonation by relatively weak bases. Deprotonation of the copper-complexed alkene 10 generates the copper (II) acetylide 11 that presumably undergoes reductive elimination to generate the alkynenitrile 4 (Scheme 2).

The combination of bis-(trimethylsilyl) peroxide and CuCN has been used to synthesize alkynenitrile 4a under neutral, mild conditions (Equation 3). A more extensively developed reagent system is cuprous cyanide in the presence of trimethylsilyl chloride, water and catalytic sodium iodide in DMSO/CH₃CN (Scheme 7). Although
the exact mechanisms are unknown, both reactions generate some dimeric alkyne, presumably by homocoupling of an organocopper intermediate (11, Scheme 2). The DMSO/CH₃CN solvent ratio appears to play an important role, with a 3:1 ratio producing optimal results. Addition of catalytic NaI, CuI, ZnI₂ or KI, facilitates the cyanation whereas addition of stoichiometric NaI gave a low yield.

**Equation 3**

\[
\text{Me}_3\text{SiOOSiMe}_3 + \text{CuCN} \xrightarrow{\text{THF}} \xrightarrow{\text{DMSO/CH}_3\text{CN (3:1); Cat NaI 50°C}} \xrightarrow{\text{CuCN, TMSCl, H}_2\text{O}} \xrightarrow{\text{4a}} \text{Ph} = \equiv \equiv \text{CN}
\]

**Table 2**

<table>
<thead>
<tr>
<th>Entr</th>
<th>R</th>
<th>Alkynenitilre</th>
<th>Yield(^{14})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>Ph = \equiv CN</td>
<td>72%</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>\equiv CN</td>
<td>76%</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>\equiv CN</td>
<td>72%</td>
</tr>
<tr>
<td>4</td>
<td>MeO</td>
<td>MeO = \equiv CN</td>
<td>84%</td>
</tr>
<tr>
<td>5</td>
<td>OMe</td>
<td>OMe = \equiv CN</td>
<td>78%</td>
</tr>
<tr>
<td>6</td>
<td>Cl</td>
<td>Cl = \equiv CN</td>
<td>51%</td>
</tr>
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</table>
Hydroxyalkynenitriles are prepared in moderate yields (60-62%) with CuCN complexes and 1-bromopropyn-3-ols (Table 3). The mechanism has been studied in some detail suggesting two competitive processes that depend on the exact nature of the copper complex. Aqueous DMF gives 4-hydroxybutynenitrile as the major product whereas polymeric copper species cause complexation with the alkyne, expulsion of bromide ion, and formation of a radical species capable of coupling to form dimers. However, aqueous DMF or hydroxylamine disrupts polymer formation minimizing dimerization, and allowing the formation of hydroxyalkynenitriles as the major product.

Table 3

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Alkynenitrile</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>Me&lt;sub&gt;2&lt;/sub&gt;C≡CN</td>
<td>60 %</td>
</tr>
<tr>
<td>2</td>
<td>Et</td>
<td>Me&lt;sub&gt;2&lt;/sub&gt;E≡CN</td>
<td>62 %</td>
</tr>
<tr>
<td>3</td>
<td>Pr</td>
<td>Me&lt;sub&gt;2&lt;/sub&gt;P≡CN</td>
<td>62 %</td>
</tr>
<tr>
<td>4</td>
<td>t-Bu</td>
<td>Me&lt;sub&gt;2&lt;/sub&gt;t-Bu≡CN</td>
<td>60 %</td>
</tr>
</tbody>
</table>
1.4 Electrophilic Cyanation of Terminal Alkynes

Several electrophilic cyanating reagents allow cyanation of metal acetylidies (Table 4). Cyanogen and ClCN are effective sources of electrophilic cyanide but are generally avoided due to their toxicity. Solid BrCN been used for cyanating copper acetylidies (Table 4, entry 2)\textsuperscript{16} but is unsuitable for most alkylolithiums since BrCN acts as a source of electrophilic bromine. A more convenient reagent is phenylcyanate that is conveniently prepared from BrCN and phenol.\textsuperscript{17} Recently two related reagents, cyanoimidazole and cyanobenzotriazole\textsuperscript{18} have been developed for the same purpose and unlike PhOCN, cyanoimidazole is commercially available.

Table 4

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkyne</th>
<th>Cyanating Agent</th>
<th>Alkynenitrile</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R≡H</td>
<td>BuLi[X-CN]</td>
<td>R≡CN</td>
<td>85%–</td>
</tr>
<tr>
<td></td>
<td>R: Me, Ethyl, n-Propyl, n-Butyl</td>
<td>ClCN</td>
<td>R≡CN</td>
<td>92%\textsuperscript{19}</td>
</tr>
<tr>
<td>2</td>
<td>C≡CCu</td>
<td>BrCN</td>
<td>C≡C-CN</td>
<td>60%\textsuperscript{16}</td>
</tr>
<tr>
<td>3</td>
<td>MeH</td>
<td>PhOCN</td>
<td>MeH-CN</td>
<td>91%\textsuperscript{20}</td>
</tr>
<tr>
<td>4</td>
<td>THPO</td>
<td>PhOCN</td>
<td>THPO-CN</td>
<td>96%\textsuperscript{21}</td>
</tr>
</tbody>
</table>
1.5 Conclusion:

Alkynenitriles are unusual Michael acceptors that are synthesized by four general methods. Dehydration of alkynylamides provides the corresponding nitriles by a dehydration that is suited for synthesizing small, volatile alkynenitriles. Similarly,
eliminations of alkenenitriles by pyrolysis is also of limited value. Conversion of terminal alkynes to alkynenitriles with CuCN, or electrophilic cyanide, is significantly milder and more versatile. Various copper complexes convert terminal alkynes and halo alkynes to the corresponding nitriles, although formation of dimers as side products is often problematic. The most attractive synthesis of alkynenitriles is by deprotonating terminal alkynes, followed by cyanation with an electrophilic cyanide source. Phenylcyanate in particular, is an excellent electrophilic cyanating agent, although the commercially available cyanating agent, cyanoimidazole may prove to be even more attractive.
2 Hydroxy Alkynenitriles: Stereoselective Chelation-Controlled Conjugate
Addition-Alkylations:

Chelation provides a powerful conjugate addition strategy that complements the
reactivity of organocopper and silver reagents.\textsuperscript{24} Chelation-controlled conjugate additions
are dramatically accelerated by positioning the two reactive centers in close proximity,
essentially harnessing the inherent entropic advantages of intramolecular reactions in a
formal intermolecular reaction.\textsuperscript{25} The increased reactivity obtained by chelation is
successfully illustrated by the facile addition of Grignard reagents to the
hydroxyalkenenitrile \textsuperscript{1} and the inability of cuprates\textsuperscript{27} to react with
cyclohexanecarbonitrile (1, HO = H).

\begin{center}
\textbf{Scheme.1 Chelation-Controlled Conjugate Addition to Alkenenitriles.}
\end{center}

Exploratory conjugate additions to hydroxy alkynenitriles demonstrate the viability of
using chelation for conjugate additions to alkynyl Michael acceptors.\textsuperscript{28} The significance
lies not only in extending chelation to activated alkyne Michael acceptors but in
stereoselectively synthesizing \textit{tri}-substituted alkenes that are difficult to synthesize with
other reagents. Remaining is the unmet challenge\textsuperscript{28} of performing chelation-controlled
conjugate addition-alkylations to alkynenitriles to generate *tetra*-substituted alkene – alkenes that are after particularly challenging to synthesize. Described below is a full account of a chelation –controlled conjugate addition to alkynenitriles leading to tri- and tetra-substituted alkenes.

**Results and Discussion**

A prerequisite for chelation controlled conjugate addition is an efficient route to substituted hydroxy alkynenitriles. Synthesizing hydroxy alkynenitriles is complicated by a rapid base-initiated polymerization, a challenge overcome with the corresponding ester, by employing THP-protected propynol allowing unmasking of the hydroxyl group under acidic conditions. Following this precedent the THP-protected alkyne **4a** was lithiated and exposed to phenyl cyanate to efficiently generate the THP-protected nitrile **6a**. Purification by silica gel chromatography prior to THP deprotection is essential since the desired 4-hydroxybutynenitrile **5a** is unstable to silica gel chromatography but is clearly and quantitatively synthesized by THP removal with Dowex. Sequential cyanation and THP removal of the homologous alkyne affords the more stable nitrile **5b** that is amenable to silica gel chromatography. Gem-dimethyl substitution similarly diminishes the propensity of alkynenitriles toward polymerization allowing direct formation of by deprotonating hydroxyalkyne **4c** with excess BuLi followed by cyanation with phenylcyanate (80%).

---

Table 1. Hydroxy Alkynenitrile Synthesis

---
<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkyne</th>
<th>Alkynenitrile</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{THPO} \equiv \equiv)</td>
<td>(\text{HO} \equiv \equiv \text{CN})</td>
<td>84%</td>
</tr>
<tr>
<td>2</td>
<td>(\text{THPO} \equiv \equiv)</td>
<td>(\text{HO} \equiv \equiv \text{CN})</td>
<td>76%</td>
</tr>
<tr>
<td>3</td>
<td>(\text{HO} \equiv \equiv)</td>
<td>(\text{HO} \equiv \equiv \text{CN})</td>
<td>80%</td>
</tr>
</tbody>
</table>

Hydroxy alkynenitriles \(5a\) and \(5c\) are excellent Michael acceptors for chelation-controlled conjugate additions. \(t\)-BuMgCl-initiated deprotonation of alkynenitriles \(5a\) or \(5c\) followed by a slight excess of a second potentially more valuable Grignard reagent triggers a particularly efficient conjugate addition (Table 2). \(t\)-BuMgCl is a particularly effective base since no transfer of the \(t\)-butyl group occurs during deprotonation at \(-78^\circ\) C whereas warming to ambient temperature with excess \(t\)-BuMgCl efficiently induces conjugate addition of the \(t\)-butyl group (Table 2, entry 4). Sterically-demanding \(t\)-Bu and \(n\)-Bu\(_3\)Sn groups react less efficiently than MeMgCl (Table 2, compare entries 1, 4 and 10) with an analogous steric compression reducing the efficiency gem-dimethyl substituted nitrile \(5c\) (compare Table 2 entries 1, 2, 5, and 6).
Alkyl, vinyl, aryl, and alkynyl Grignards add conjugatively to 5a and 5c, selectively generating E-alkenenitriles. Addition of the functionalized Grignard chlorobutylmagnesium bormide proceeds without interference of the halogen whereas the Grignard prepared from 3-chloropropyl phenylsulfide \( \text{(Table 2, entry 11)} \) generates the expected nitrile 7k as well as 7l, presumably through conjugate addition of \( \text{PhSMgCl} \) formed by cyclization of the Grignard reagent.

Table 2. Chelation-Controlled Conjugate Additions to Alkynenitriles

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkynenitrile</th>
<th>Grignard</th>
<th>Compound</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( \text{HO} - \equiv \text{CN} )</td>
<td>MeMgCl</td>
<td>( \text{HO} - \equiv \text{CN} )</td>
<td>92%</td>
</tr>
<tr>
<td></td>
<td>( 5a )</td>
<td></td>
<td>( 7a )</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>( \text{HO} - \equiv \text{CN} )</td>
<td>MeMgCl</td>
<td>( \text{HO} - \equiv \text{CN} )</td>
<td>70%</td>
</tr>
<tr>
<td></td>
<td>( 5c )</td>
<td></td>
<td>( 7b )</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>( \text{HO} - \equiv \text{CN} )</td>
<td>i-PrMgBr</td>
<td>( \text{HO} - \equiv \text{CN} )</td>
<td>87%</td>
</tr>
<tr>
<td></td>
<td>( 5a )</td>
<td></td>
<td>( 7c )</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>( \text{HO} - \equiv \text{CN} )</td>
<td>t-BuMgCl</td>
<td>( \text{HO} - \equiv \text{CN} )</td>
<td>60%</td>
</tr>
<tr>
<td></td>
<td>( 5a )</td>
<td></td>
<td>( 7d )</td>
<td></td>
</tr>
</tbody>
</table>
5  \[ \text{HO} \equiv \equiv \text{CN} \text{ PhMgCl} \]

5a

7e

6  \[ \text{HO} \equiv \equiv \text{CN} \text{ PhMgCl} \]

5c

7f

7  \[ \text{HO} \equiv \equiv \text{CN} \text{ MgBr} \]

5a

7g

8  \[ \text{HO} \equiv \equiv \text{CN} \text{ Ph} \]

5a

MgBr

7h

9  \[ \text{HO} \equiv \equiv \text{CN} \text{ BrMg}\text{CHCl} \]

5a

7i

10  \[ \text{HO} \equiv \equiv \text{CN} \text{ (n-Bu)}_3\text{SnMgCl} \]

5a

7j

11  \[ \text{HO} \equiv \equiv \text{CN} \text{ ClMg} \text{CHSPh}^{34} \]

5a

7k

7l
The conjugate addition with Me$_3$SiCH$_2$MgCl provides valuable insight into reaction mechanism (Table 2, entry 12). Mechanistically, deprotonation and halogen-alkyl exchange leads to an alkylmagnesium alkoxide that triggers the key anionic conjugate addition. Alkyl transfer requires overlap of the C-Mg HOMO with the $\pi^*$ LUMO where the $\pi^*$ node precludes a concerted addition$^{36}$ in favor of a stepwise alkyl transfer (8b to 9a). Equilibration of 9a to the chelate 9b parallels related allenolate equilibria$^{37}$ and is consistent with analogous chelates generated during carboxymagnesiation of alkynes. Chelate 9b is deactivated toward further addition with 8a except with the silicon-containing Grignard Me$_3$SiCH$_2$MgCl where silicate formation 10$^{38}$ unmasks a more reactive C-Mg bond$^{39}$ that reacts further with 8a.
Chelation is essential for the conjugate addition. Control experiment in which the THP-protected alkynenitrile 6a is exposed to BuMgCl leads to 90% recovery of unreacted nitrile. Similarly, over positioning the hydroxy group two atoms removed from the alkynenitrile prevents the conjugate addition. The inability of alkynenitrile 5b to undergo chelation controlled conjugate addition is surprising given the facile organocopper and alkylargentate.

Consistent with formation of a stable chelate is the surprising inability to alkylate 9 with benzaldehyde. Activation of the chelate 9 is achieved by addition of t-BuLi to initiate conversion to the more reactive ate complex (Scheme 3). Subsequent alkylation with PhCHO, or the potentially enolizable phenylpropionaldehyde, efficiently generates the tetra-substituted alkenenitriles 12 as single stereoisomers (Table 2). The alkylation
stereochemistry is consistent with a retentive alkylation through a cyclic “ate” complex is equally successful for the gem-dimethyl nitrile 5c as for 5a with a range of Grignard reagents (Table 2).\textsuperscript{45} Overall the stereo selective conjugate addition-alkylation assembles tetra-substituted alkenes that are otherwise difficult to synthesize.

**Scheme 3 Chelation-Controlled Conjugate Addition-Alkylation**

- **Table 2 Conjugate addition-alkylation to alkylenitrile**
Grignard reagents readily add to γ-hydroxy alkynenitriles in an efficient chelation controlled conjugate addition. t-BuMgCl initiated deprotonation followed by addition of a second Grignard reagent triggers conjugate addition leading to a cyclic magnesium chelate. Protonation of the chelate stereoselectively generates tri-substituted alkenenitriles. Alternatively, addition of t-BuLi activates the intermediate chelate by conversion to the corresponding ate complex permitting alkylation with aromatic and aliphatic aldehydes with complete stereochemical fidelity. Collectively the chelation-
controlled conjugate addition-alkylation generates a range of tetra-substituted alkenenitriles that are difficult to synthesize.
3 Metallated α-Halonitriles: Domino Cyclizations to Oxacycles and Carbocycles

Halogen-containing organometallic reagents are extremely versatile reagents.\textsuperscript{46} The value of haloalkylorganometallics lies in incorporating two reactive centers of opposite polarity for installing two new bonds through sequential alkylations.\textsuperscript{47} Sequential addition-alkylations of haloalkylorganometallics to imines, aldehydes, and ketones efficiently assembles diverse heterocycles whereas conjugate addition-alkylation forms the basis of several particularly efficient annulations.\textsuperscript{48} Collectively these efficient cyclizations continues the impetus for developing halogen-containing organometallics (Scheme 1).

\begin{center}
\begin{tikzpicture}
\node (1) at (0,0) {\text{Scheme 1}};
\node (2) at (-2,-1.5) {1};
\node (3) at (2,-1.5) {3};
\node (4) at (0,-1.5) {2};
\draw[->] (1) -- (2); \draw[->] (1) -- (3); \draw[->] (1) -- (4);
\draw[->] (2) -- (1) node[above] {Cl\textsubscript{(l)1-2}};
\draw[->] (3) -- (1) node[above] {Cl\textsubscript{(l)1-2}};
\draw[->] (4) -- (1) node[above] {Cl\textsubscript{(l)1-2}};
\node at (-1,-2) {{\text{\textcolor{red}{M}}}};
\node at (1,-2) {{\text{\textcolor{red}{M}}}};
\node at (-1,-2.5) {{\text{\textcolor{red}{X}}}};
\node at (1,-2.5) {{\text{\textcolor{red}{X}}}};
\node at (0,-3) {{\text{\textcolor{red}{R}}\textsubscript{1}}};
\node at (-2,-3) {{\text{\textcolor{red}{R}}\textsubscript{1}}};
\node at (2,-3) {{\text{\textcolor{red}{R}}\textsubscript{1}}};
\node at (-2,-3.5) {{\text{\textcolor{red}{R}}\textsubscript{2}}};
\node at (2,-3.5) {{\text{\textcolor{red}{R}}\textsubscript{2}}};
\end{tikzpicture}
\end{center}

Significantly less common are haloalkyl organometallics generated by deprotonation. The challenge lies in generating the haloalkyl organometallic while avoiding cyclization,\textsuperscript{49} a requirement cleverly overcome in the metal iodide-induced cleavage of cyclopropanes since ring opening reversibly generates homoenolates for in situ alkylation with imine and aldehyde electrophiles (Scheme 2, 4 to 6).\textsuperscript{50} Alternatively, the unique reactivity of nitrile anions permits currently the only direct deprotonation route to haloalkylorganometallics and subsequent alkylation with aldehydes to generate nitrile-substituted tetrahydrofurans.\textsuperscript{51} Collectively these precedents establish the viability of generating haloalkylorganometallics and their potential in domino synthesis.
Haloalkylorganometallics have two reactive centers that can potentially be alkylated through two complementary strategies; sequential nucleophilic-electrophilic alkylations, or sequential electrophilic-nucleophilic alkylations. Conceptually, interchanging the alkylation order provides complementary strategies to heterocycles or carbocycles from the same haloalkylorganometallic reagent. Independent development of halonitrile anion alkylations has allowed these two objectives to be realized to provide an array of nitrile-substituted carbocycles and oxacycles in a single synthetic operation.
Results and Discussion
Exploratory deprotonations employed 5-chloropentanecarbonitrile (10) since cyclization is significantly slower than for other medium sized rings and several 4-chlorobutyl-substituted nitrile,\textsuperscript{52} ester,\textsuperscript{53} acylsilane,\textsuperscript{54} and aldehyde\textsuperscript{55} functionalities are efficiently deprotonated and alkylated.\textsuperscript{56} Deprotonation of chloronitrile 10 with \textit{t}-BuOK\textsuperscript{57} in the presence of benzaldehyde rapidly generates the pyran 13a (Scheme 4). Presumably the transient potassiated nitrile 11 rapidly intercepts benzaldehyde resulting in a nucleophilic potassium alkoxide, ideally predisposed toward internal displacement leading to pyran nitrile 13a.

Scheme 4. Domino Alkylation of \(\omega\)-chloronitrile 10

The facile annulation route to pyran 13a is typical of the reactivity exhibited for a range of aldehydes (Table 1). Aromatic and aliphatic aldehydes generate pyrans equally efficiently, even with the potentially enolizable cyclopropanecarboxaldehyde (Table 1, entry 4). The resulting pyran-nitriles are generated as diastereomers, consistent with small steric demand of the nitrile group imparting a minimal bias in kinetic aldehyde\textsuperscript{58} alkylation.\textsuperscript{59}
Alkylating potassiated chloropentanecarbonitrile is not limited to aldehyde electrophiles. Intercepting 11 with ethyl benzoate generates the corresponding chloroketonitrile 14 while alkylation with MeI affords the substituted chloropentanenitrile 15 (Table 1, entries 5-6, respectively). Deprotonating the methyl-substituted nitrile 15 with benzaldehyde similarly generates the more highly substituted pyran nitrile 16 directly analogous to the unsubstituted nitrile 10 (compare Table 1, entries 1 and 7). Formation of pyran diastereomers in similar ratios confirms that the diastereomeric mixture arises from poor facial selectivity by the nitrile anion rather than through equilibration of the initially formed pyran nitriles.

Table 1: Oxacycle Cyclizations of α-Chloronitriles

<table>
<thead>
<tr>
<th>Entry</th>
<th>Halonitrile</th>
<th>Electrophile</th>
<th>Nitrile</th>
<th>Yield*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cl-CN CN</td>
<td>PhCHO</td>
<td>O-Ph-CN</td>
<td>88% (1:1)</td>
</tr>
<tr>
<td>2</td>
<td>Cl-CN CN</td>
<td>O=CH</td>
<td>O-Ph-CN</td>
<td>75% (1:5:1)</td>
</tr>
<tr>
<td>3</td>
<td>Cl-CN CN</td>
<td>t-BuCHO</td>
<td>O-Ph-CN</td>
<td>88% (2:5:1)</td>
</tr>
<tr>
<td>4</td>
<td>Cl-CN CN</td>
<td>O=CH</td>
<td>O-Ph-CN</td>
<td>85% (1:1)</td>
</tr>
<tr>
<td>5</td>
<td>Cl-CN CN</td>
<td>O=Et</td>
<td>Ph-Ph-CN</td>
<td>58%</td>
</tr>
</tbody>
</table>
Remarkably, 4-chlorocyclobutanenitrile (7) triggers an analogous cyclization to nitrile-substituted furans 17. Despite the seemingly increased propensity of the intermediate nitrile anion toward internal cyclization to a cyclopropane, in situ trapping is efficient with aryl and alkyl-substituted aldehydes.

Control experiments at 0 °C indicate that, in the absence of an electrophile, complete cyclization of 10 occurs within 3h whereas 7 cyclizes within 10 min. The remarkably slow internal cyclization prompted analogous in situ alkylations with ω-chlorohexane- and ω-chloroheptanecarbonitriles, 7a and 7b, which can potentially cyclize to 5- and 6-membered carbonitriles 5 (Scheme 5). Remarkably, no observable intramolecular
cyclization to a 5- or 6-membered carbonitrile occurs on deprotonating 18a and 18b in the presence of benzaldehyde. Exclusive *intermolecular* alkylation generates intermediate alkoxides without cyclization, presumably reflecting the increased steric demands associated with medium-ring formation (Scheme 5).

Collectively the sequential nucleophilic-electrophilic alkylations of chloronitriles demonstrate the viability and utility of metallated ω-halonitriles. The remaining challenge of reversing the alkylation sequence through sequential electrophilic-nucleophilic alkylation was probed with the more electrophilic bromopentanenitrile 20 and ketone 21 (Scheme 6). Sequential addition of ketone 21 and nitrile 20 to an excess of t-BuOK (5 equiv), in an effort to minimize equilibration with the more acid ketone (ΔpKa = 5-10), generates a mixture of nitriles 26, 28, and 29. Formation of the pyran nitrile 28 is surprising since the propensity toward cyclization is considerably enhanced with an alkylbromide. The co-generated alkenenitrile 29 arises by t-BuOK-initiated ring opening of the first-formed pyran 28 since resubjecting the pyran 28 to t-BuOK generates 29. In addition, substituting chloropentanenitrile 23 (X = Cl) for bromopentanenitrile 23 (X = Br) diverts the cascade sequence entirely toward formation of pyran nitrile 28 and alkenenitrile 29 with no detectable formation of carbonitrile 26.

Formation of the nitriles 28 and 29 provided key mechanistic insight for optimizing the electrophilic-nucleophilic alkylation sequence. Formation of the pyran nitrile 28 requires facile proton transfer between the ketone enolate 22 and nitrile 20, followed by nitrile
anion-ketone condensation prior to enolate alkylation. Although moderating the rate of proton transfer is difficult, diverting the reaction mode toward enolate alkylation simply requires a more reactive electrophile. Collectively these cascade sequences imply a requirement for a more reactive leaving group for diverting the reaction manifold from the pyran nitrile to carbonitrile 26.

Repeating the electrophilic-nucleophilic alkylation cascade with the more electrophilic iodonitrile 23 (X = I) redirects the cyclization cascade toward the carbonitrile 26 with minimal pyran nitrile formation (Scheme 5). Mechanistically the reaction is remarkably efficient given the series of proton transfers and alkylations involved during formation of the two new bonds.

**Conclusion**

*t*-BuOK readily deprotonates \(\omega\)-haloalkynitriles generating remarkably stable potassiated nitriles. Intercepting the potassiated nitriles with aldehyde electrophiles generates potassium alkoxide intermediates that rapidly cyclize to nitrile-substituted furan and
pyran nitriles whereas alkylation with ester and alkyl halide electrophiles generates substituted halonitriles. Redirecting the cyclization manifold to carbonitrile formation is achieved simply with the corresponding iodonitrile and an appropriate ketone, triggering in situ enolate alkylation, deprotonation, and cyclization. The complementary cyclization manifolds provide rapid assembly of nitrile-substituted furans, pyrans, and cyclohexanes and demonstrates the viability of metallated ω-halonitriles in domino alkylation-cyclizations.
EXPERIMENTAL

Proton nuclear magnetic resonance ($^1$H NMR) spectra and carbon nuclear magnetic resonance ($^{13}$C NMR) spectra were recorded on a Bruker 300 MHz spectrometer using deuteriochloroform as the solvent. Signal positions are given in parts per million (δ) and were determined relative to the residual proton signal for CHCl₃ (δ 7.26) and the carbon signal for CDCl₃ (δ 77.0). The $^1$H NMR coupling constants (J-values) are given in Hz. Spectral content is listed in the following order: chemical shift (δ), multiplicity, coupling constants (Hz), number of protons.

Infrared (IR) spectra were recorded on a Perkin Elmer model 1600 Fourier transform spectrophotometer with internal calibration. The IR spectra of solids and liquids were recorded as films on sodium chloride plates. Mass spectra were recorded on a Varian 3400 series gas chromatograph interfaced to a Saturn II mass spectrometer.

Preparative silica gel thin layer chromatography was performed on commercially available (PF-254), glass backed plates (25 x 25 cm), precoated with silica gel 60 to a thickness of 0.5 mm. Visualization of the chromatograms was accomplished with an ultraviolet light (254 nm), heating the chromatogram after staining with commercially available (Aldrich Chemical Co., Inc.) phosphomolybdic acid in ethanol (1:4 ratio), a 5% aqueous solution of ammonium molybdate in 10% aqueous sulfuric acid (w/v), or with an aqueous 5% potassium permanganate solution. Conventional flash chromatography was performed with 230-400 mesh silica gel (E. Merck, Silica gel 60). Radial
chromatography was performed on a Chromatotron® with plates prepared in-house with silica gel 60 PF254 containing gypsum.

Sonication was performed with a Bransonic® ultrasonic cleaner. Melting points were measured on a Mel-Temp II® apparatus and are uncorrected.

All dry solvents were obtained by refluxing over an appropriate drying agent. Distilled solvents were used immediately or stored over molecular sieves where appropriate. Diethyl ether and tetrahydrofuran were dried over sodium benzophenone ketyl.

Unless stated otherwise, all reactions were carried out under an atmosphere of dry nitrogen using glassware that had been thoroughly dried under vacuum.

4-(Tetrahydro-pyran-2-yloxy)-but-2-yenitrile: A hexanes solution of n-BuLi (5.4 mL, 8.6 mmol) was added to a -78 °C, THF solution of 4a (1.2 g, 8.6 mmol) followed, after 15 min, by a THF solution of PhOCN (1.3 equiv). The cooling bath was removed and, after 15 min, aqueous NaOH (6M) was added and followed by ether extraction. The combined extracts were washed sequentially with NaOH (6M), and saturated NaCl, passed through a short plug of silica gel (5 x 1 cm column), dried over NaSO₄, concentrated, and purified by radial chromatography (1:9 EtOAc/hexanes) to yield 1.3 g (92%) of 4-(Tetrahydro-pyran-2-yloxy)-but-2-yenitrile as oil: IR (film) 2304, 2265 cm⁻¹; ¹H NMR 1.52-1.84 (m, 6H), 3.54-3.58 (m, 1H), 3.75-3.83 (m, 1H), 4.37 (s, 2H), 4.76
(s, 1H); $^{13}$C NMR δ 18.6, 25.0, 29.9, 53.6, 59.7, 62.0, 81.6, 97.7, 104.6; MS m/e 164 (M-H).

**5-(Tetrahydro-pyran-2-yloxy)-pent-2-ynenitrile:** A hexanes solution (1.6 M) of n-BuLi (0.52mL, 0.84 mmol) was added to a -78 °C, THF solution of 4b (0.13g, 0.84mmol) followed, after 15 min, by a THF solution of PhOCN (1.3 equiv). The cooling bath was removed and, after 15 min, aqueous NaOH (6M) was added and followed by ether extraction. The combined extracts were washed sequentially with NaOH (6M), and saturated NaCl, passed through a short plug of silica gel (5 x 1 cm column), dried over NaSO$_4$, concentrated and, purified by radial chromatography (1:10 EtOAc/hexanes) to yield 0.12 g (80%) of 5-(Tetrahydro-pyran-2-yloxy)-pent-2-ynenitrile as oil: IR (film) 2314, 2261 cm$^{-1}$; $^1$H NMR δ 1.57-1.84 (m, 6H), 2.65-2.69 (m, 2H), 3.52-3.65 (m, 2H), 3.81-3.92 (m, 2H), 4.64 (brs, 1H); $^{13}$C NMR δ 19.2, 20.6, 25.3, 30.4, 55.9, 62.3, 63.7, 84.7, 99.0, 105.1; MS m/e 178 (M-H).

**4-Hydroxy-but-2-ynenitrile (5a):** An anhydrous methanolic solution (15 mL) of 5-(Tetrahydro-pyran-2-yloxy)-pent-2-ynenitrile (0.6 g) and Dowex (pre washed with anhydrous methanol) was stirred at room temperature for 1.5 h. The reaction was then filtered, the residue concentrated, and retreated with Dowex for 1.5 h to yield 295 mg (100%) of 5a as oil: IR (film) 3447, 2308, 2245 cm$^{-1}$; $^1$H NMR δ 2.39 (br, 1H), 4.40 (s, 2H), 2.38 (s, 1H); $^{13}$C NMR δ 50.6, 59.6, 83.1, 104.6.

**5-Hydroxy-pent-2-yntenitrile (5b):** A methanolic solution (10 mL) of 5-(Tetrahydro-pyran-2-yloxy)-pent-2-yntenitrile (0.12 g) and Dowex (prewashed with anhydrous methanol) was stirred at room temperature for 1.5 h. The reaction was then filtered, the residue concentrated, and retreated with Dowex for 1.5 h to yield 63 mg (100%) of 5b as
an oil: IR (film) 3434, 2315, 2263 cm$^{-1}$; $^1$H NMR $\delta$ 2.12 (s, 1H), 2.65-2.61 (s, $J = 6.0$ Hz, 2H), 3.82 (s, 2H); $^{13}$C NMR $\delta$ 23.0, 56.1, 59.3, 85.0, 105.0 MS $m/e$ 95 (M+H).

4-Hydroxy-4-methyl-pent-2ynenitrile (5c): A hexanes solution (1.6 M) of n-BuLi (2.96 mL, 4.75 mmol) was added to a -78 °C, THF solution of 4c (0.4 g, 4.75 mmol) followed, after 15 min, by a THF solution of PhOCN (1.3 equiv). The cooling bath was removed and, after 15 min, aqueous NaOH (6M) was added and followed by ether extraction. The combined extracts were washed sequentially with NaOH (6M), and saturated NaCl, dried over NaSO$_4$, concentrated and, purified by radial chromatography (1:9 EtOAc/hexanes) to yield 0.41 g (80%) of 7c as oil, identical to material previously synthesized$^1$.

General conjugate addition procedure: A THF solution of $t$-BuMgCl (1.0 equiv, 1-2M) was added to a -78 °C, THF solution of the $\gamma$-hydroxyalkynenitrile (1 equiv) followed, after 5 min, by a THF solution of the appropriate Grignard reagent (1.1 equiv, 1- 3 M). After 45 min, the reaction mixture was allowed to warm to room temperature (15 min) and then saturated aqueous NH$_4$Cl was added. The crude reaction mixture was extracted with EtOAc the combined organic extracts were dried (Na$_2$SO$_4$), passed through a short plug of silica gel (2 x 1 cm column), concentrated, and purified by radial chromatography.

4-Hydroxy-3-but-2-enenitrile (7a): Performing the general conjugate addition procedure with a THF solution (5 mL) of 5a (20 mg) and MeMgCl provided, after purification by radial chromatography (1:4 EtOAc/hexanes), 22 mg (92%) of 7a spectrally identical to material previously synthesized.$^2$


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(2E)-4-hydroxy-3,4-dimethylpent-2-enenitrile (7b): Performing the general conjugate addition procedure with a THF solution (5 mL) of 7c (20 mg) and MeMgCl provided, after purification by radial chromatography (1:4 EtOAc/hexanes), 16.1 mg (70%) of 7b as an oil: IR (film) 3410, 2932, 2215, 1601 cm⁻¹; ¹H NMR δ 1.37 (s, 6H), 2.08 (s, 3H), 5.63(s, 1H); ¹³C NMR δ 17.8, 28.5, 73.6, 94.1, 117.5, 169.6; MS e/m 126 (M+H).

(2E)-3-(hydroxymethyl)-4-methylpent-2-enenitrile (7c): Performing the general conjugate addition procedure with a THF solution (5 mL) of 5a (12.9 mg) and i-PrMgBr provided, after purification by radial chromatography (3:7 EtOAc/hexanes), 17.3 mg (87%) of 7c as an oil: IR (film) 3447, 2221, 1628 cm⁻¹; ¹H NMR δ 1.16 (d, J = 7.2Hz, 6H), 1.21 (br s, 1H), 3.10 (sept, J = 7 Hz, 1H), 4.30 (s, 2H), 5.53 (s, 1H); ¹³C NMR δ 20.5, 32.2, 61.0, 91.9, 116.9, 172.1; MS m/e 126 (M+ H).

(2E)-3-(hydroxymethyl)-4,4-dimethylpent-2-enenitrile (7d): Performing the general conjugate addition procedure with a THF solution (5 mL) of 5a (16.2 mg) and t-BuMgCl provided, after purification by radial chromatography (1:4 EtOAc/hexanes), 16.5 mg (60%) of 7d as an oil: IR (film) 3483, 2219, 1636 cm⁻¹; ¹H NMR δ 1.32 (s, 9H), 1.75 (s, 1H), 4.32 (s, 2H), 5.72 (s, 1H); ¹³C NMR δ 28.9, 36.2, 62.4, 91.4, 118.0, 173.2; MS m/e 140 (M + H).

(2E)-4-hydroxy-3-phenylbut-2-enenitrile (7e): Performing the general conjugate addition procedure with a THF solution (5 mL) of 5a (15 mg) and PhMgCl provided, after purification by radial chromatography (3:7 EtOAc/hexanes), 27 mg (92%) of 7e as an oil: IR (Film) 3446, 3060, 2221, 1623 cm⁻¹; ¹H NMR δ 2.37 (br s, 1H), 4.52 (s, 2H), 3.19 An unusually high C=N frequency and minor discrepancies in NMR shifts were previously reported for nitrile 7e: Tanyeli, C.; Demir, A.S.; Akhmedov, I. M.; Ozgiil, E.; Kandemir, C. G. Synth. Commun. 1996, 26, 2967.
5.78 (s, 1H), 7.43 (s, 5H); ¹³C NMR δ 64.6, 94.2, 117.4, 127.2, 128.9, 130.1, 134.7, 163.6; MS m/e 159.

(2E)-4-hydroxy-4-methyl-3-phenylpent-2-enenitrile (7f): Performing the general conjugate addition procedure with a THF solution (5 mL) of 5c (20 mg) and PhMgCl, provided after purification by radial chromatography (1:4 EtOAc/hexanes), 22.6 mg (66%) of 7f as a light brown solid. IR (film) 3440, 3060, 2229, 1614 cm⁻¹; ¹H NMR δ 1.39 (s, 6H), 1.86 (s, 1H), 5.97 (s, 1H), 7.19-7.44 (m, 5H); ¹³C NMR δ 28.7, 73.6, 97.1, 116.9, 127.7, 128.4, 128.7; HRMS (ESI) calcd for (M+Na⁺) C₁₂H₁₃NONa⁺ 210.0889, found 210.08933

(2E)-3-(hydroxymethyl) penta-2, 4-dienenitrile (7g): Performing the general conjugate addition procedure with a THF solution (5mL) of 5a (21.3 mg) and vinyl magnesium bromide provided, after purification by radial chromatography (1:4 EtOAc/hexanes), 25 mg (87%) of 7g as an oil: IR (film) 3423, 2218, 1635, 1582 cm⁻¹, ¹H NMR δ 2.08 (s, 1H), 4.51 (s, 2H), 5.54 (d, J = 11 Hz, 1H), 5.58 (d, J = 17 Hz, 1H), 5.69 (s, 1H), 6.87 (dd, J = 17, 11 Hz, 1H); ¹³C NMR: 61.0, 95.7, 116.6, 120.9, 131.4, 158.0; MS m/e 109.

(2E)-3-(hydroxymethyl)-5-phenylpent-2-en-4-ynenitrile (7h): Performing the general conjugate addition procedure with a THF solution (5 mL) of 5a (30 mg) and PhC≡CMgCl⁴ provided, after purification by radial chromatography (1:3 EtOAc/hexanes), 57.6 (85%) mg of 7h as an oil: IR (film) 3347, 3067, 2224, 2192, 1589 cm⁻¹; ¹H NMR δ 2.36 (s, 1H), 4.39 (s, 2H), 5.93 (s, 2H), 7.36-8.74 (m, 5H); ¹³C NMR: 64.1, 83.2, 100.9, 102, 116.7, 121.2, 128.5, 129.9, 132.3, 145.8 MS m/e 183 (M⁺).

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⁴ Prepared by reacting 1.5 equiv of phenylacetylene with 1.5 equiv of MeMgCl at 0°C for 15 min.
(2E)-7-chloro-3-(hydroxymethyl)-hept-2-enenitrile (7i): Performing the general conjugate addition procedure with a THF solution (5 mL) of 5a (15 mg) and chlorobutylmagnesium bromide provided, after purification by radial chromatography (3:7 EtOAc/hexanes), 25 mg (78%) of 7i as an oil: IR (Film) 3435, 2220, 1639 cm⁻¹, ¹H NMR δ 1.63–1.73 (m, 2H), 1.80–1.89 (m, 2H), 2.42 (t, J = 7.5 Hz, 2H), 3.57 (t, J = 6.0 Hz, 2H), 4.26 (s, 2H), 5.59 (s, 1H); ¹³C NMR: 25.3, 31.2, 31.6, 44.3, 63.9, 94.3, 116.8, 166.2; MS m/e 173 (M + H).

(2Z)-4,4-dibutyl-3-(hydroxymethyl)-4-stannaoct-2-enenitrile (7j): Performing the general conjugate addition procedure with a THF solution (5 mL) of 5a (10 mg) and (Bu)₃SnMgCl⁵ provided, after purification by radial chromatography (1:4 EtOAc/hexanes), 32 mg (70%) of 7j as oil: IR (film) 3422, 2217, 1654 cm⁻¹; ¹H NMR δ 0.91 (t, J = 7.0 Hz, 9H), 1.12-1.64 (m, 18H), 4.42 (s, 2H), 6.26 (s, 1H); ¹³C NMR δ 10.1, 13.6, 27.2, 29.0, 68.1, 105.5, 118.9, 176.7; MS m/e 373 (M⁺).

(2E)-3-(hydroxymethyl)-6-phenylthiohex-2-enenitrile (7k) and (2Z)-4-hydroxy-3-phenylthiobut-2-enenitrile (11l): Performing the general conjugate addition procedure with a THF solution (5 mL) of 5a (16 mg) and PhS(CH₂)₃MgCl provided, after purification by radial chromatography (3:7 EtOAc/hexanes), 19.3 mg (42%) of 7k and 20 mg (53%) of 7l as an oils. For 7k IR (film) 3426, 3060, 2219, 1632, 1584 cm⁻¹; ¹H NMR δ 1.60 (br s, 1H), 1.78-1.88 (m, 2H), 2.51 (dd, J = 8 Hz, 2H), 2.95 (t, J = 7.3 Hz, 2H), 4.20 (s, 2H), 5.57 (s, 1H), 7.17-7.60 (m, 5H); ¹³C NMR δ 27.6, 31.0, 33.5, 64.0, 94.6, 126.4, 129.0, 129.8, 165.7; MS e/m 233. For 7l IR (film) 3438, 3058, 2216, 1579 cm⁻¹;

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⁵ Prepared by reacting (Bu)₃SnH (1.3 equiv) with MeMgCl (1.3 equiv) at 0 °C for 10 min
\(^{1}\text{H NMR}\) \(\delta\) 2.03 (s, 1H), 4.07 (s, 2H), 5.81 (s, 1H), 7.27- 7.55 (m, 5H); \(^{13}\text{C NMR}\) \(\delta\) 64.1, 93.6, 127.9, 129.9, 134.7, 162; \(\text{MS}\) \(m/e\) 191 (M\(^{+}\)).

(2Z)-3-(hydroxymethyl)-5,5-dimethyl-5-silahex-2-enenitrile (7m) and (2E)-1-[1-(2,2-dimethyl-2-silapropyl)-2-hydroxyethylidene]-2-(hydroxymethyl)prop-2-ene-1,3-dicarbonitrile (7n): Performing the general conjugate addition procedure with a THF solution (5 mL) of 5a (20 mg) and (CH\(_3\))\(_3\)SiCH\(_2\)MgCl provided, after purification by radial chromatography (3:7 EtOAc/hexanes), 16 mg (38.3%) of 7m and 14 mg (19.4) of 7n as an oils. For 7m: \(\text{IR (Film)}\) 3456, 2215, 1620; \(^{1}\text{H NMR}\) \(\delta\) 0.12 (s, 9H), 1.94 (s, 2H), 4.13 (s, 2H), 5.39 (s, 1H); \(^{13}\text{C NMR}\) \(\delta\) - 1.0, 24.6, 65.3, 89.2, 118.1, 166.7; \(\text{MS}\) \(m/e\) 169.

For 7n: \(\text{IR (Film)}\) 3456, 2221, 1630 cm\(^{-1}\); \(^{1}\text{H NMR}\) \(\delta\) 0.22 (s, 9H), 2.38 (s, 2H), 4.27 (s, 2H), 4.36 (s, 2H), 5.84 (s, 1H); \(^{13}\text{C NMR}\) \(\delta\) -0.8, 28.0, 62.4, 63.3, 100.2, 100.6, 116.3, 157.1, 167.5; \(\text{MS}\) \(m/e\) 250 (M\(^{+}\)).

**General conjugate addition-alkylation procedure:** A THF solution of \(t\)-BuMgCl (1.0 equiv, 1-2 M) was added to a \(-78\) °C, THF solution of the \(\gamma\)-hydroxyalkynenitrile (1 equiv) followed, after 5 min, by a THF solution of the appropriate Grignard reagent (1.1 equiv, 1-3 M). After 45 min, the reaction mixture was allowed to warm to room temperature (15 min), re-cooled to \(-78\) °C, and then a hexanes solution of \(t\)-BuLi (1.2 equiv, 1.5 M) was added. The cooling bath was then removed, and after 15 min neat aldehyde (1.5 equiv) was added, followed, after a further 30 min, by aqueous saturated NH\(_4\)Cl. The crude reaction mixture was extracted with EtOAc, the combined extracts were passed through a short plug of silica gel (2 x 1 cm column), concentrated, and purified by radial chromatography.
(2Z)-4-hydroxy-2-(hydroxyphenylmethyl)-3-phenylbut-2-enenitrile (12a):
Performing the general conjugate addition - alkylation procedure with a THF solution (5 mL) of 5a (10 mg), PhMgCl and PhCHO provided, after purification by radial chromatography (3:7 EtOAc/hexanes), 19.6 mg (60%) of 12a as a light brown solid (mp 123-125): IR (film) 3388, 2219, 1595 cm\(^{-1}\); \(^1\)H NMR \(\delta\) 4.55-4.57 (m, 2H), 5.40-5.42 (m, 1H, exchanges with D\(_2\)O), 5.94-5.96 (m, 1H), 6.21 (d, \(J = 4.0\) Hz, 1H, exchanges with D\(_2\)O), 7.26-7.50 (m, 10H); \(^13\)C NMR \(\delta\) 60.6, 67.6, 117.4, 118.2, 125.9, 127.3, 128.1, 138.5, 141.6, 156.0 MS \(m/e\) 247 (M-H\(_2\)O).

(2Z)-3-(hydroxymethyl)-2-(1-hydroxy-3-phenylpropyl)-4-methylpent-2-enenitrile (12b): Performing the general conjugate addition - alkylation procedure with a THF solution (5 mL) of 5a (12 mg), i-PrMgCl and 3-phenylpropanal provided, after purification by radial chromatography (3:7 EtOAc/hexanes), 24.9 mg (65%) of 12b as an oil: IR (film) 3410, 2214, 1603 cm\(^{-1}\); \(^1\)H NMR \(\delta\) 1.07 (d, \(J = 6.4\) Hz, 3H), 1.15 (d, \(J = 6.3\) Hz, 3H), 1.70 (br s, 1H), 1.97-2.21 (m, 2H), 2.32 (br s, 1H), 2.74 (t, \(J = 7.5\) Hz, 2H), 3.14-3.23 (m, 1H), 4.14 (s, 2H), 4.55 (t, \(J = 6.8\), 1H), 7.12-7.31 (m, 5H); \(^13\)C NMR \(\delta\) 20.2, 20.4, 31.8, 35.1, 36.8, 57.0, 67.4, 116.3, 117.1, 126.2, 128.4, 128.5, 140.8, 164.3.

(2Z)-3-(hydroxymethyl)-2-(hydroxyphenylmethyl)-4-methylpent-2-enenitrile (12c): Performing the general conjugate addition - alkylation procedure with a THF solution (5 mL) of 5a (20 mg), i-PrMgCl and PhCHO provided, after purification by radial chromatography (4:6 EtOAc/hexanes), 41.1 mg (72%) of 12c as an oil: IR (Film) 3414, 2217, 1603 cm\(^{-1}\); \(^1\)H NMR \(\delta\) 1.09 (d, \(J = 6.7\) Hz, 3H), 1.15 (d, \(J = 7.1\) Hz, 3H), 2.64 (s, 1H), 3.13-3.22 (m, 1H), 3.45 (s, 1H), 4.30 (ABq, \(\Delta v = 31.5\) Hz, \(J = 12.3\) Hz, 2H), 5.79 (s,
1H), 7.32-7.45 (m, 5H); 13C NMR δ 20.2, 20.3, 35.2, 57.0, 70.0, 116.5, 117.0, 126.0, 128.7, 140.1, 163.4 MS m/e 231 (M-H).

(2E)-4-hydroxy-2-(1-hydroxy-3-phenylpropyl)-3-phenylbut-2-enenitrile (12d):
Performing the general conjugate addition - alkylation procedure with a THF solution (5 mL) of 5a (15 mg), PhMgCl and 3-phenylpropanal provided, after purification by radial chromatography (3:7 EtOAc/hexanes), 30.9 mg (57%) of 12d as an oil. IR (film) 3386, 2216, 1602 cm⁻¹; 1H NMR δ 2.1-2.24 (m, 2H), 2.74-2.78 (m, 2H), 3.20 (brs, 2H), 4.39 (ABq, Δν = 40.0 Hz, J = 13.4, 2H), 4.69 (t, J = 7 Hz, 1H), 7.20-7.38 (m, 10H); 13C NMR: 31.7, 37.1, 62.3, 67.6, 116.9, 118.2, 126.3, 127.8, 128.4, 128.6, 128.8, 129.6, 137.5, 140.6, 157.4.

(2Z)-4-hydroxy-2-(1-hydroxy-3-phenylpropyl)-4-methyl-3-phenylpent-2-enenitrile (12e): Performing the general conjugate addition - alkylation procedure with a THF solution (5 mL) of 5c (17 mg), PhMgCl and 3-phenylpropanal provided, after purification by radial chromatography (3:7 EtOAc/hexanes), 28.5 mg (57%) of 12e as an oil; IR (film) 3434, 2215, 1602 cm⁻¹; 1H NMR δ 1.25 (s, 3H), 1.36 (s, 3H), 1.40-1.60 (m, 2H), 2.01-2.27 (m, 2H), 2.72-2.92 (s, 2H), 5.22-5.27 (m, 1H), 7.20-7.71 (m, 10H); 13C NMR: 30.6, 31.4, 32.1, 37.2, 67.1, 74.9, 116.8, 120.1, 126.1, 127.1, 127.9, 128.5, 139.4, 141.2, 165.1; HRMS (ESI) calcd for (M+Na⁺) C21H23NO2 344.1621, found 344.1611.

(2Z)-4-hydroxy-2-(1-hydroxy-3-phenylpropyl)-3,4-dimethylpent-2-enenitrile (12f): Performing the general conjugate addition - alkylation procedure with a THF solution (5 mL) of 5c (20 mg), MeMgCl and 3-phenylpropanal, provided after purification by radial chromatography (3:7 EtOAc/hexanes), 29 mg (61%) of 12f as an oil; IR (film) 3433, 2211, 1602 cm⁻¹; 1H NMR δ 1.21-1.37 (m, 1H), 1.34 (s, 3H), 1.42 (s, 3H), 1.94-2.20 (m,
2H), 2.09 (s, 3H), 2.65-2.85 (m, 3H), 5.07-5.12 (m, 1H), 7.18-7.46 (m, 5H); $^{13}$C NMR: 22.0, 29.7, 30.3, 32.0, 37.3, 66.8, 75.2, 116.5, 117.7, 125.9, 128.4 (doubled), 141.3, 161.8; MS m/e 259 (M-OH).

**Experimental**

**General procedure for oxacycles formation:** To a 0 $^\circ$C THF solution of i-BuOK (1 equiv), neat RCHO (1equiv) was added followed by the addition of o-chloronitile. After 3 h, the reaction mixture was allowed to warm to the room temperature, quenched with saturated NH$_4$Cl, extracted with EtOAc, passed through short plug of silica (3 x 1), concentrated, and purified by radial chromatography.

**2-Phenyl-tetrahydro-pyran-3-carbonitrile (13a):** Performing the general procedure with a THF solution (5 mL) of 10 (144 mg, 1.23 mmol) and PhCHO (131 mg, 1.23 mmol) provided, after purification by radial chromatography (2:8 EtOAc/hexanes), 202.5 mg (88%, 1:1$^{65}$) of 13a as oils. For 13a trans: IR (film) 2239 cm$^{-1}$; $^1$H NMR $\delta$ 1.72-2.05 (m, 3H), 2.36-2.42 (m, 1H), 2.63-2.72 (m, 1H), 3.56-3.66 (m, 1H), 4.13-4.18 (m, 1H), 4.34 (d, J = 9.5 Hz, 1H), 7.31-7.48 (m, 5H); $^{13}$C NMR $\delta$ 24.0, 28.0, 35.2, 68.2, 80.6, 119.3, 126.5, 128.3, 128.6, 138.7; HRMS (ESI) calcd for (M+Na$^+$) C$_{12}$H$_{13}$NONa 210.0889, found 210.0889. For 13a cis: IR (film) 2238 cm$^{-1}$; $^1$H NMR $\delta$ 1.35-1.42 (m, 1H), 1.70-2.04 (m, 3H), 2.75 (br s, 1H), 3.36-3.44 (m, 1H), 4.00-4.05 (m, 1H), 4.23 (d, J = 1.9 Hz, 1H), 7.02-7.41 (m, 5H); $^{13}$C NMR $\delta$ 21.6, 27.0, 35.4, 68.8, 78.5, 118.8, 125.4, 128.0, 128.2, 139.0; HRMS (ESI) calcd for (M+Na$^+$) C$_{12}$H$_{13}$NONa 210.0889, found 210.0900.

**2-Furan-2-y1-tetrahydro-pyran-3-carbonitrile (13b):** Performing the general procedure with a THF solution (5 mL) of 10 (144 mg, 1.23 mmol) and furan-2-
carbaldehyde (119 mg, 1.23 mmol) provided, after purification by radial chromatography (2:8 EtOAc/hexanes), 164 mg (75%, 1.5:1\(^67\)) of 13b as oils. For 13b \textit{trans}: IR (film) 2236 cm\(^{-1}\); \(^1\text{H NMR} \delta 1.86-2.41 (m, 4H), 3.56-3.68 (m, 1H), 4.09 (d, \(J = 12.3\) Hz, 1H), 4.48 (d, \(J = 10.2\) Hz, 1H), 6.39 (br s, 1H), 6.46 (d, \(J = 3.1\) Hz, 1H), 7.44 (br s, 1H); \(^{13}\text{C NMR} \delta 23.9, 27.7, 31.6, 68.2, 73.5, 109.1, 110.4, 114.0, 143.1, 150.7; \text{MS m/e } 178 (M + H); \text{HRMS(ESI) calcd for (M+Na\(^+\)}, \text{C}_{10}\text{H}_{11}\text{NO}_2\text{Na} 200.0682 \text{found: 200.0698.}

For 13b \textit{cis}: IR (film) 2241 cm\(^{-1}\); \(^1\text{H NMR} \delta 1.59-2.09 (m, 4H), 2.26 (d, \(J = 13.3\) Hz, 2H), 3.15-2.16 (m, 1H), 3.56-3.65 (m, 1H), 4.19 (dd, \(J = 11, 4\) Hz, 1H), 4.54 (d, \(J = 2\)Hz, 1H), 6.39 (s, 1H), 6.52 (d, \(J = 2.9\) Hz, 1H), 7.39 (br s, 1H); \(^{13}\text{C NMR} \delta 21.8, 26.5, 32.1, 68.6, 73.3, 107.3, 110.3, 118.9, 142.1, 151.3; \text{MS m/e } 178 (M + H); \text{HRMS (ESI) calcd for (M+Na\(^+\)}, \text{C}_{10}\text{H}_{11}\text{NO}_2\text{Na} 200.0682 \text{found: 200.0698.}

2-\text{tert-Butyl-tetrahydro-pyran-3-carbonitrile (13c):} \text{Performing the general procedure with a THF solution (5 mL) of \textit{t}-BuOK (195 mg, 1.74 mmol), 10 (136 mg, 1.16 mmol) and excess 2,2-dimethylpropionaldehyde}\(^66\) provided, after purification by radial chromatography (2:8 EtOAc/hexanes), 170 mg (88%, 2.5:1\(^67\)) of 13c as oils. For 13c \textit{trans}: IR (film) 2235 cm\(^{-1}\); \(^1\text{H NMR} \delta 1.04 (s, 9H), 1.53-1.59 (m, 1H), 1.81 (dd, \(J = 12, 5\) Hz, 1H), 1.89 (dd, \(J = 12, 5\) Hz, 1H), 2.26-2.31 (m, 1H), 2.41-2.51 (m, 1H), 3.07 (d, \(J = 9.4\) Hz, 1H), 3.32-3.41 (m, 1H), 3.97-4.00 (m, 1H); \(^{13}\text{C NMR} \delta 24.5, 26.6, 28.0, 29.7, 35.7, 61.8, 68.2, 85.1, 121.5; \text{MS m/e } 168 (M + H). \text{HRMS (ESI) calcd for (M+Na\(^+\)}, \text{C}_{10}\text{H}_{17}\text{NONa} 190.1202 \text{found 190.1206. For 13c \textit{cis}: IR (film) 2236 cm\(^{-1}\); \(^1\text{H NMR} \delta 1.03 (s, 9H), 1.54 (d, \(J = 13.4\) Hz, 1H), 1.60-1.79 (m, 1H), 1.83-2.07 (m, 1H), 2.17 (d, \(J = 13.1\) 1H), 2.84 (s, 1H), 2.90 (s, 1H), 3.45 (t, \(J = 11.7\) Hz, 1H), 4.14 (dd, \(J = 11, 4\) Hz, 1H); \(^{13}\text{C NMR} \delta 22.1, 26.2, 27.5, 28.7, 34.6, 69.3, 85.3, 120.6; \text{MS m/e } 168 (M + H).}
2-Cyclopropyl-tetrahydro-pyran-3-carbonitrile (13d): Performing the general procedure with a THF solution (5 mL) of 10 (145 mg, 1.23 mmol) and cyclopropanecarbaldehyde (87 mg, 1.23 mmol) provided, after purification by radial chromatography (1:9 EtOAc/hexanes), 157 mg (85%, 1:1) of 13d as oils. For 13d trans:

IR (film) 2237 cm⁻¹; ¹H NMR δ 0.36-0.77 (m, 4H), 0.99-1.06 (m, 1H), 1.58-1.85 (m, 3H), 2.26 (d, J = 13.2 Hz, 1H), 2.54-2.62 (m, 1H), 2.73-2.78 (m, 1H), 3.34-3.43 (m, 1H), 3.99 (d, J = 11.9 Hz, 1H); ¹³C NMR δ 1.7, 3.2, 14.9, 24.2, 27.9, 33.6, 67.8, 81.0, 119.9; HRMS(ESI) calcd for (M+Na⁺) C₁₉C₁₃NONa 174.0889 found 174.0894. For 13d isomer:

IR (film) 2236 cm⁻¹; ¹H NMR δ 0.17-0.24 (m, 1H), 0.73 (m, 3H), 1.15-1.26 (m, 1H), 1.55 (d, J = 13 Hz, 1H), 1.71-2.10 (m, 2H), 2.17 (d, J = 13 Hz, 1H), 2.58-2.61 (m, 1H), 2.91 (br s, 1H), 3.40 (t, J = 11.6 Hz, 1H), 4.06-4.10 (m, 1H); ¹³C NMR δ 1.4, 3.7, 14.3, 15.0, 21.9, 26.7, 32.8, 68.4, 81.0, 119.7; HRMS (ESI) calcd for (M+Na⁺) C₉H₁₃NONa 174.0889 found 174.08957.

2-Phenyl-tetrahydro-furan-3-carbonitrile (17a): Performing the general procedure with a THF solution (5 mL) of 7 (128mg, 1.23 mmol) and PhCHO (130 mg, 1.23 mmol) provided, after purification by radial chromatography (3:7 EtOAc/hexanes), 160 mg (75%, 2.5:1) of 17a as oils. For 17a trans:

IR (film) 2240 cm⁻¹; ¹H NMR δ 2.31-2.50 (m 2H), 3.30-3.41 (m, 1H), 3.93-4.07 (m, 1H), 4.27-4.38 (m, 1H), 4.91-5.01 (d, J = 7.6 Hz, 1H), 7.48-7.51 (m, 5H); ¹³C NMR δ 31.3, 36.5, 67.3, 81.5, 118.9, 126.0, 128.4, 128.5, 137.1; HRMS(ESI) calcd for (M+Na⁺) C₁₁H₁₁NONa 196.0733 found 196.0747. For 17a cis:

IR (film) 2242 cm⁻¹; ¹H NMR δ 2.32-2.57 (m, 2H), 2.87 (dd, J = 16, 8 Hz, 1H), 4.09 (dd, J = 16, 8 Hz,1H), 4.20-4.28 (m, 1H), 4.95 (d, J = 7.7 Hz, 1H), 7.33-7.39 (m, 5H); ¹³C
NMR δ 30.9, 36.9, 67.8, 83.5, 119.7, 125.3, 128.4, 128.6, 138.6; HRMS (ESI) calcd for (M+Na⁺), C₁₁H₁₁NONa 196.0733, found 196.0725.

2,3,4,5-Tetrahydro-[2,2']bifuranyl-3-carbonitrile (17b): Performing the general procedure with a THF solution (5 mL) of 7 (127 mg, 1.23 mmol) and furan-2-carbaldehyde (119 mg, 1.23 mmol) provided, after purification by radial chromatography (2:8 EtOAc/hexanes), 162 mg (81%, 2:1⁶⁷) of 17b as oils. For 17b trans: IR (film) 2245 cm⁻¹; ¹H NMR δ 2.35 (ddd, J = 13, 13, 7 Hz, 1H), 2.46-2.58 (m, 1H), 3.28-3.35 (m, 1H), 4.00-4.17 (m, 2H), 5.03 (d, J = 7.0 Hz, 1H), 6.37-6.42 (m, 2H), 7.42 (s, 1H); ¹³C NMR δ 31.0, 33.1, 67.8, 109.1, 110.4, 119.5, 143.2, 150.3; HRMS (EI) calcd for C₉H₉NO_{2} 163.0630 found 163.0620. For 17b cis: IR (Film) 2244 cm⁻¹; ¹H NMR δ 2.42-2.58 (m, 2H), 3.38 (dd, J = 15, 7 Hz, 1H), 3.96 (dd, J = 16, 8 Hz, 1H), 4.24-4.32 (m, 1H), 5.12 (d, J = 6.8 Hz, 1H), 6.34-6.40 (m, 1H) 6.48 (d, J = 3.0 Hz, 1H), 7.45 (br s, 1H); ¹³C NMR δ 30.8, 33.8, 67.4, 75.2, 108.8, 110.4, 118.2, 143.0, 150.7; HRMS (EI) calcd for (M⁺) 163.0628, found 163.0617.

2-tert-Butyl-tetrahydro-furan-3-carbonitrile (17c): Performing the general procedure with a THF solution (5 mL) of 7 (128 mg, 1.23 mmol) and excess 2,2-dimethylpropionaldehyde⁶⁶ provided, without requiring further purification, 175.2 mg (93%, 1:0) of 17c as spectrally pure oil. For 17c trans: IR (film): 2240cm⁻¹; ¹H NMR δ 1.01 (s, 9H), 2.20-2.26 (m, 2H), 2.76 (dd, J = 16, 8 Hz, 1H), 3.70 (d, J = 7.4 Hz, 1H), 3.82 (dd, J = 16, 8 Hz, 1H), 3.94-4.01 (m, 1H); ¹³C NMR δ 25.5, 28.6, 31.9, 34.1, 67.7, 90.5, 121.4; HRMS (EI) calcd for C₉H₁₅NO 153.1150 found: 153.1132.

2-Cyclopropyl-tetrahydro-furan-3-carbonitrile (17d): Performing the general procedure with a THF solution (5 mL) of 7 (127 mg, 1.23 mmol) and
cyclopropanecarbaldehyde (86 mg, 1.23 mmol) provided, after purification by radial chromatography (2:8 EtOAc/hexanes), 121 mg (72%, 1:1) of 17d as oils. For 17d trans: IR (film) 2243 cm\(^{-1}\); \(^1\)H NMR \(\delta \): 0.44-0.68 (m, 4H), 0.91-1.02 (m, 1H), 2.14-2.45 (m, 2H), 2.79-2.88 (m, 1H), 3.37 (t, \(J = 8\) Hz, 1H), 3.83-3.91 (dd, \(J = 15, 8\) Hz, 1H), 4.02 (dd, \(J = 14, 8\) Hz, 1H); \(^{13}\)C NMR \(\delta \): 1.5, 2.7, 13.8, 30.8, 33.8, 67.2, 86.3, 120.2; HRMS (EI) calcd for C\(_8\)H\(_{11}\)NO 137.0835 found 137.0850;

For 17d cis: IR (film) 2241 cm\(^{-1}\); \(^1\)H NMR \(\delta \): 0.22-0.28 (m, 1H), 0.45-0.50 (m, 1H), 0.62-0.76 (m, 2H), 1.12-1.24 (m, 1H), 2.02-2.34 (m, 2H), 3.13-3.21 (m, 2H), 3.75 (dd, \(J = 16, 7\) Hz, 1H), 4.09 (dd, \(J = 15, 7\) Hz, 1H); \(^{13}\)C NMR \(\delta \): 1.8, 3.6, 12.1, 31.0, 33.6, 66.7, 84.0, 119.5; MS m/e 138 (M + H); HRMS(EI) calcd for C\(_8\)H\(_{11}\)NO 137.0835 found 137.0850.

6-Chloro-2-(hydroxy-phenyl-methyl)-hexanenitrile (19a): Performing the general procedure with a THF solution (5 mL) of 18a (131 mg, 1 mmol) and PhCHO (106 mg, 1 mmol) provided, after purification by radial chromatography (3:7 EtOAc/hexanes), 175 mg (74%, 1:1) of 19a as oils. For diastereomeric mixture of 19a: IR (film) 2244 cm\(^{-1}\); \(^1\)H NMR \(\delta \): 1.49-1.76 (m, 12H), 2.48 (br s, 2H), 2.78-2.92 (m, 2H), 3.47-3.53 (m, 4H), 4.75 (d, \(J = 5.9\) Hz, 1H), 4.80 (d, \(J = 5.9\) Hz, 1H), 7.37 (s, 5H), 7.39 (s, 5H); \(^{13}\)C NMR \(\delta \): 24.5, 27.2, 28.3, 31.9, 32.0, 40.3, 40.9, 44.3, 119.8, 126.1, 126.4, 128.9; GCMS e/m 238 (M + H).

7-Chloro-2-(hydroxy-phenyl-methyl)-heptanenitrile (19b): Performing the general procedure with a THF solution (5 mL) of 18b (180 mg, 1.23 mmol) and PhCHO (131 mg, 1.23 mmol) provided, after purification by radial chromatography (3:7 EtOAc/hexanes), 222 mg (72%, 1:1) of 19b as solid. For 19b: IR (film) 2053 cm\(^{-1}\); \(^1\)H NMR \(\delta \): 1.42-1.67 (m, 5H), 1.75 (pent, \(J = 7\) Hz, 2H), 2.35-2.40 (m, 2H), 2.80-2.87 (m,
1H), 3.51 (t, J = 6Hz, 2H), 4.78 (d, J = 6, 3 Hz, 1H), 7.38 (s, 5H); $^{13}$C NMR δ 26.2, 26.4, 28.8, 32.1, 40.9, 44.7, 73.9, 120.0, 126.1, 128.7, 140.3; HRMS(EI) calcd for C$_{14}$H$_{18}$ClNONa 274.0969 found 274.0971; For diastereomeric mixture of 19b: IR (film) 2242 cm$^{-1}$; $^1$H NMR δ 1.42-1.76 (m, 16H), 2.78-2.84 (m, 4H), 3.49-3.53 (m, 4H), 4.75 (d, J = 5.97 Hz, 1H), 4.81 (d, J = 5.97 Hz, 1H), 7.38 (s, 5H), 7.39 (s, 5H); HRMS calcd for C$_{14}$H$_{18}$ClNONa 274.0969 found 274.0961.

2-Benzoyl-5-chloro-pentanenitrile (14): Performing the general procedure with a THF solution (5 mL) of t-BuOK (290 mg, 2.58mmol), 10 (144 mg, 1.23 mmol), and ethyl benzoate (185 mg, 1.23 mmol) provided, after purification by radial chromatography (1:9 EtOAc/hexanes), 158 mg (58%) of 14 as an oil; IR (film) 2249, 1694, 1596 cm$^{-1}$; $^1$H NMR δ 1.96-2.31 (m, 4H), 3.62 (t, J = 6 Hz, 2H), 4.41-4.46 (m, 1H), 7.50-7.99 (m, 5H); $^{13}$C NMR δ 26.9, 29.4, 39.0, 43.6, 116.9, 128.7, 129.1, 133.8, 134.6, 190.2; HRMS (ESI) calcd for (M+Na$^+$) C$_{12}$H$_{12}$ClNONa 244.0500, found 244.0507.

5-Chloro-2-methyl-pentanenitrile (15): To a 0 °C THF solution of t-BuOK (1.38 g, 12.3 mmol), neat 10 (144 mg, 1.23 mmol) was added followed by (with in 3 min) the addition of MeI (1.4, 9.8 mmol). After 10 min, the reaction mixture was allowed to warm to the room temperature, quenched with saturated NH$_4$Cl, extracted with EtOAc, passed through short plug of silica (3 x 1), and concentrated to yield 150 mg (93%) of 15 as oil. IR (film): 2237 cm$^{-1}$; $^1$H NMR δ 1.34 (d, J = 7.5 Hz, 3H), 1.72-1.80 (m, 2H), 1.84-2.02 (m, 2H), 2.60-2.72 (m, 2H), 3.58 (t, J = 5.9 Hz, 2H); $^{13}$C NMR δ 18.0, 25.0, 29.7, 31.2, 43.9, 122.4.

3-Methyl-2-phenyl-tetrahydro-pyran-3-carbonitrile (16): Performing the general procedure with a THF solution (5 mL) of (110 mg, 0.83 mmol) 15 and PhCHO (88.7 mg,
0.83 mmol) provided, after purification by radial chromatography (2:8 EtOAc/hexanes), 120.2 mg (72%, 1:1 ratio of trans : cis isomers) of 16 as a solid. For 16 trans isomer: IR (film) 2234 cm\(^{-1}\); \(^1\)H NMR δ 1.02 (s, 3H), 1.51-1.60 (m, 2H), 2.04-2.18 (m, 2H), 3.46 (t, \(J = 11.7\) Hz, 1H), 3.89 (s, 1H), 4.10-4.14 (m, 1H), 7.13-7.33 (m, 5H); \(^{13}\)C NMR δ 23.2, 23.6, 36.5, 39.5, 46.8, 69.0, 85.8, 121.7, 126.6, 127.5, 128.1, 128.7, 137.0; MS m/e 202.

2-Hydroxy-2, 3, 3-trimethyl-cyclohexanecarbonitrile (26), 2-Isopropyl-2-methyl-tetrahydro-pyran-3-carbonitrile (28), and 2-(3-Hydroxy-propyl)-3,4-dimethyl-pent-2-enenitrile (29): Neat ketone 21 (322 mg, 3.72 mmol) was added to a 0 °C, THF solution of \(t\)-BuOK (700 mg, 6.23 mmol) followed, after 15 min, by neat 20 (200 mg, 1.24 mmol). The reaction mixture was allowed to warm to room temperature (1 h) and saturated aqueous NH\(_4\)Cl was added. The crude reaction mixture was extracted with EtOAc, and the combined organic extracts were passed through a short plug of silica gel (2 x 1 cm column), concentrated, and purified by radial chromatography (2:8 EtOAc/hexanes) to afford 66.3 mg (32%) of 26 as solid, 16.6 mg (8%) of 28 as oil, and 42 mg (20%) of 29 as oil.

Repeating the procedure with the chloronitrile 5a afforded 31.1 mg (15%) of 28, and 64.4 mg (31%) of 29.

Repeating the procedure with iodonitrile 30 afforded 100.1 mg (63%, 1.5:1 ratio of equitorial and axial nitrile epimers) of 26 as solids.

For 26 equitorial CN: IR (film) 3467, 2242 cm\(^{-1}\); \(^1\)H NMR δ 0.94 (s, 3H), 1.01 (s, 3H), 1.38 (s, 3H), 1.13-1.61 (m, 5H), 1.75 (td, \(J = 13, 4.1\) Hz, 1H), 1.87-2.18 (m, 1H), 2.66 (dd, \(J = 12, 5\) Hz, 1H); \(^{13}\)C NMR δ 20.4, 23.3, 24.8, 26.1, 27.9, 35.0, 37.1, 37.7, 73.2, 121.3; HRMS (ESI) calcd for (M+Na\(^+\)) C\(_{10}\)H\(_{17}\)NONa 190.1202, found 190.1196. For 26
axial CN: IR (film) 3485, 2241 cm\(^{-1}\); \(^1\)H NMR \(\delta\) 1.00 (s, 6H), 1.41 (s, 3H), 1.44-1.75 (m, 6H), 2.00-2.07 (m, 1H), 2.93 (dd, \(J = 12\), 4 Hz, 1H); \(^13\)C NMR \(\delta\) 20.2, 20.3, 21.5, 25.0, 27.9, 36.8, 38.0, 38.5, 74.2, 121.5; HRMS (ESI) calcd for (M+Na\(^+\)) C\(_{10}\)H\(_{17}\)NO\(_2\)Na 190.1202, found 190.1211; for 28: IR (film) 2236 cm\(^{-1}\); \(^1\)H NMR \(\delta\) 0.94-0.98 (m, 6H), 1.31 (s, 3H), 1.38-1.58 (m, 1H), 1.68-1.74 (m, 1H), 1.89-2.10 (m, 3H), 2.80 (dd, \(J = 9\), 4 Hz, 1H), 3.62-3.65 (m, 2H); \(^13\)C NMR \(\delta\) 16.2, 17.0, 17.3, 23.4, 23.6, 23.5, 33.1, 34.2, 60.4, 75.3, 120.9. For 29 Z- isomer: IR (film) 3441, 2208, 1622 cm\(^{-1}\); \(^1\)H NMR \(\delta\) 1.05 (d, \(J = 6\) Hz, 6H), 1.62-1.84 (m, 2H), 1.74 (s, 3H), 2.30 (t, \(J = 7\) Hz, 2H), 3.15-3.24 (m, 1H), 3.68 (t, \(J = 6\) Hz, 2H); \(^13\)C NMR \(\delta\) 12.6, 20.4, 26.1, 30.9, 35.7, 61.4, 107.1, 118.9, 161.5 MS m/e Mass spec (M+H) 168. For 29 E- isomer: IR (film) 3446, 2209, 1618 cm\(^{-1}\); \(^1\)H NMR \(\delta\) 1.02 (d, \(J = 6.7\) Hz, 6H), 1.75-1.84 (m, 3H), 1.98 (s, 3H), 2.34-2.39 (m, 2H), 2.95 (sept, \(J = 7\) Hz, 1H), 3.69 (t, \(J = 6\) Hz, 2H); \(^13\)C NMR \(\delta\) 16.9, 20.2, 25.4, 30.0, 31.4, 60.4, 107.9, 119.5, 161.1 MS m/e (M+H) 168.
References


28 For a preliminary account see ref. 1b.


35 19\% of the double addition product is obtained (Scheme 3)

36 A concerted addition requires simultaneous overlap of magnesium with $\alpha$ and $\beta$ carbons which have opposite phases.


X-ray crystallography confirmed the stereochemical assignment.

No alkylation was observed with MeI, allyl bromide, TMSCl, PhCOCl or MeOCOCl although alkylation of related α-magnesioalkenenitrile is possible by conversion to the corresponding cuprate.


59 The use of exactly an equivalent of base may prevent equilibration of the pyranonitrile diastereomers, since the presence of excess base causes diastereomeric ring-opening to the \( \alpha \)-substituted cinnaminitrile.

60 Alkylation was performed with excess of \( t \)-BuOK (10 equiv) and MeI (10 equiv) since formation of MTBE competes with the alkylation.


62 The pKa of acetone and acetonitrile are 20 and 25,\textsuperscript{a} respectively, with the pKa of acetonitrile being recently revised upward to ~30.\textsuperscript{b} (a) Bordwell, F. G.; Matthews, W. S. *J. Am. Chem. Soc.* **1974**, *96*, 1214. (b) Richard, J. P.; Williams, G.; Gao, J. *J. Am. Chem. Soc.* **1999**, *121*, 715.

63 Formation of alkenenitrile 24 is accompanied by considerable formation of polymeric material that presumably arises by conjugate addition.

64 For general experimental procedures see reference 49. The high-resolution mass spectra were recorded at The Ohio State University Campus Chemical Instrumentation Center.

65 Ratio of isomers

66 2,2-dimethyl propionaldehyde in \( t \)-BuOH was passed through a short plug of silica immediately before using in the reaction.
Ratio of *tran:* *cis* isomers

Repetitive chromatography afforded a sample of pure 14-trans

Repetitive chromatography afforded a pure, crystalline solid allowing conclusive identification of *trans* 16.