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New methods for the synthesis of substituted nitriles

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New Methods for the Synthesis of Substituted Nitriles

A Thesis presented to the Graduate School of Duquesne University

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Master of Science

By
Venugopal Gudipati
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Approved	Dr. David Seybert - Dean
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	(Signature)

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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-haloalkylnitriles 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.

List of Abbreviations

Ac	-	acetate
br	-	broad
Bu	-	butyl
BuLi	-	butyllithium
^{13}C NMR	-	carbon nuclear magnetic resonance
d	-	doublet
dd	-	doublet of doublets
DMF	-	*N, N*-dimethlyformamide
DMSO	-	dimethylsulfoxide
equiv	-	equivalent
Et	-	Ethyl
GC-MS	-	gas chromatography-mass spectrometry
h	-	hour(s)
^{1}H NMR	-	proton nuclear magnetic resonance
H_2SO_4	-	sulfuric acid
i	-	iso
IR	-	infrared
LDA	-	lithium diisopropylamide
m	-	multiplet
Me	-	methyl
min	-	minute(s)
Ms	-	mesylate

Ph	-	Phenyl
q	-	quartet
R	-	alkyl, aryl, or hydrogen
s	-	singlet
t	-	triplet
t	-	tertiary
t-BuOK	-	Potassium tertiary butoxide
Tf	-	triflate
THF	-	tetrahydrofuran
TMS	-	trimethylsilyl

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.

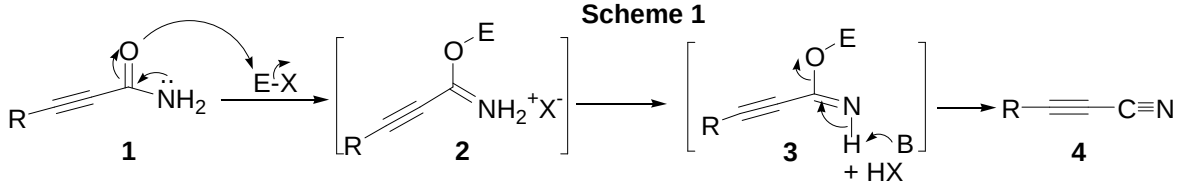
Alkynenitriles are a poorly explored family of Michael acceptors. Electronically, the combination of linear alkyne and nitrile groups is significantly different from alkynes conjugated with carbonyl groups, potentially giving rise to complementary reactivity patterns in the two series. Exploring the 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** → **3**). Complexation with the carbonyl oxygen is facilitated by the electron donation from the nitrogen lone pair (Scheme 1).

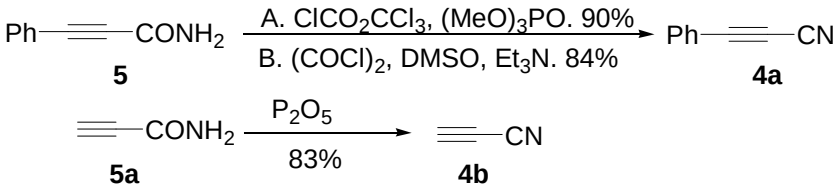
Deprotonation of the activated complex **3**, either from the conjugate or added base, triggers deprotonation and simultaneous deoxygenation to generate the alkynenitrile **4**.

Scheme 1



Historically, the dehydration of alkyneamides, propiolamide in particular, has employed P_2O_5.[4] Dehydration with P_2O_5 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 chloroformate[6] (liquid diphosgene) and Swern oxidation conditions[7] have emerged as efficient reagents for the dehydration of carboxamides to nitriles (Equation 1).

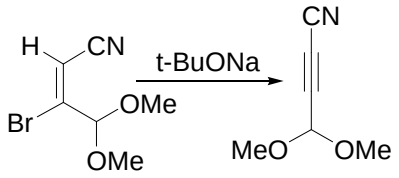
Equation 1



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]

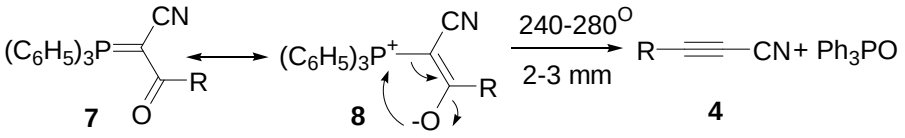
Equation 2



6 **4c** 65%

Alternatively, pyrolysis of oxoylids **7**[9] 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^{o} bond angles enforced by sp^{2} hybridization.

Table 1. Pyrolitic Oxoylid Synthesis of Alkynenitriles.



7 **8** **4**

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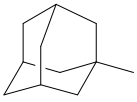
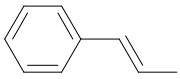
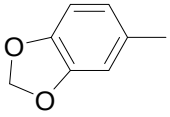
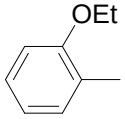
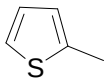
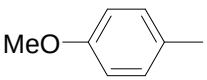
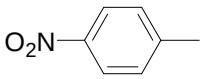
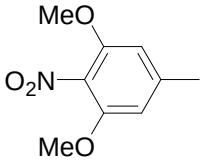
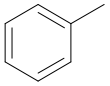
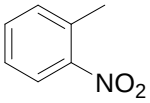
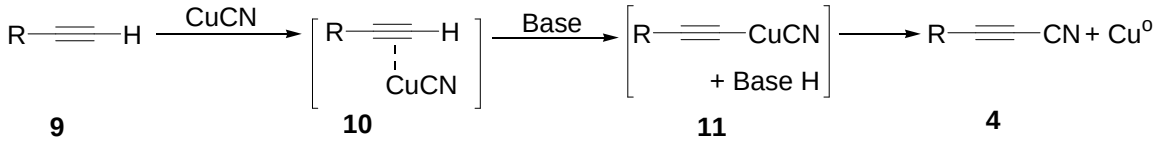
1		75%
2		83%
3		94%
4		87%
5		95%
6		54%

7		45%
8		34%
9		83%[10]
10		18%[11]

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).

Scheme 2



The combination of *bis*-(trimethylsilyl) peroxide and CuCN has been used to synthesize alkynenitrile **4a** under neutral, mild conditions (Equation 3).[12] A more extensively developed reagent system is cuprous cyanide in the presence of trimethylsilyl chloride, water and catalytic sodium iodide in DMSO/CH_3CN (Scheme 7).[13] Although

the exact mechanisms are unknown, both reactions generate some dimeric alkyne, presumably by homocoupling of an organocopper intermediate (**11**, Scheme 2). The DMSO/CH_3CN solvent ratio appears to play an important role, with a 3:1 ratio producing optimal results. Addition of catalytic NaI, CuI, ZnI_2 or KI, facilitates the cyanation whereas addition of stoichiometric NaI gave a low yield.

Equation 3

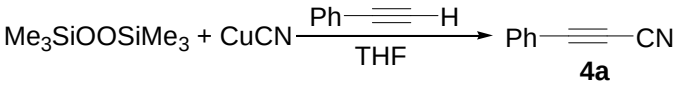
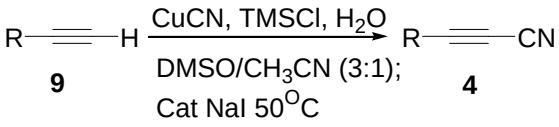


Table 2



Entry	R	Alkynenitilre	Yield[14]
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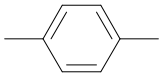
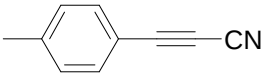
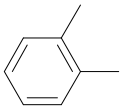
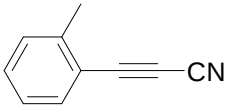
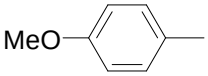
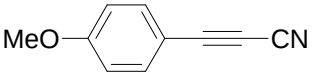
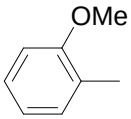
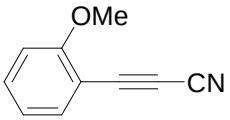
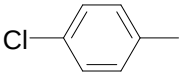
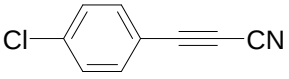
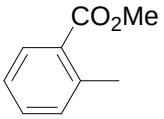
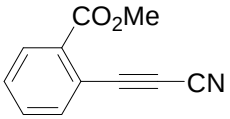
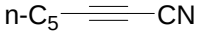
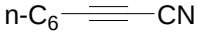
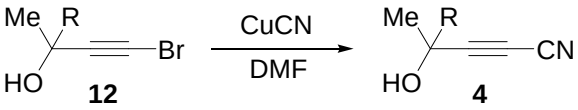
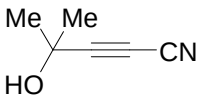
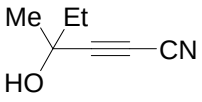
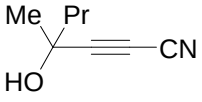
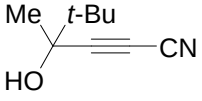
2			76%
3			72%
4			84%
5			78%
6			51%

7			74%
8	n-C5		56%
9			53%

Hydroxyalkynenitriles are prepared in moderate yields (60-62%) with CuCN complexes[15] 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-hydroxybuytynenitrile 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

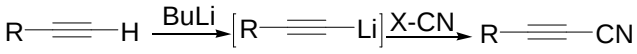


Entry	R	Alkynenitrile	Yield
1	Me		60 %
2	Et		62 %
3	Pr		62 %
4	*t*-Bu		60 %

1.4 Electrophilic Cyanation of Terminal Alkynes

Several electrophilic cyanating reagents allow cyanation of metal acetylides (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 acetylides (Table 4, entry 2)[16] but is unsuitable for most alkyllithiums since BrCN acts as a source of electrophilic bromine. A more convenient reagent is phenylcyanate that is conveniently prepared from BrCN and phenol.[17] Recently two related reagents, cyanoimidazole and cyanobenzotriazole[18] have been developed for the same purpose and unlike PhOCN, cyanoimidazole is commercially available.

Table 4



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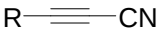
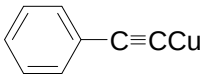
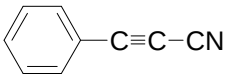
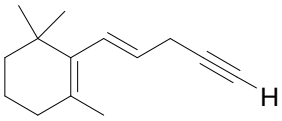
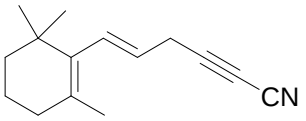
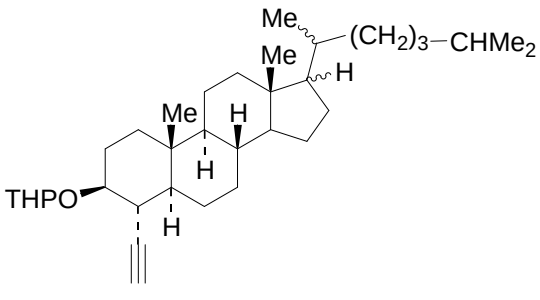
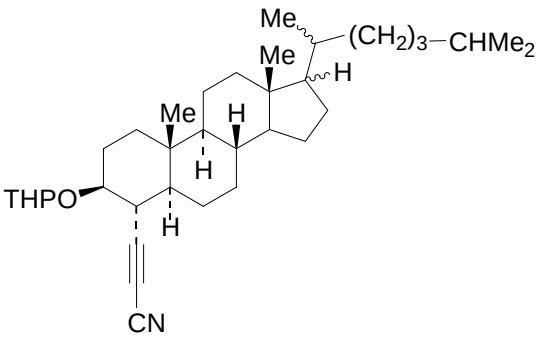
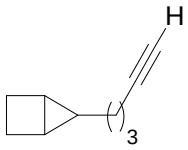
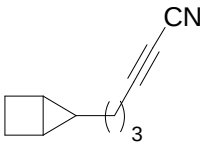
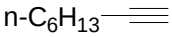
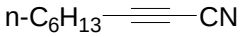
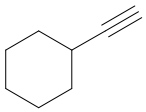
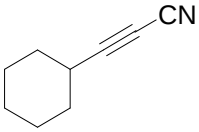
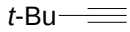
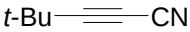
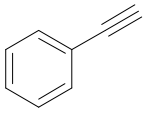
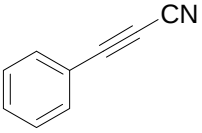
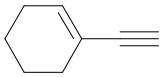
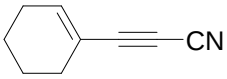
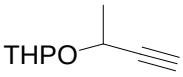
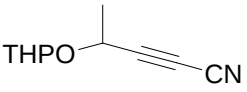
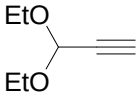
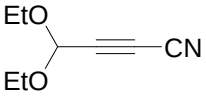
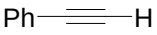
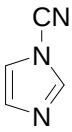
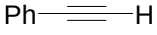
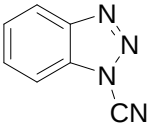
1	 R: Me, Ethyl, n-Propyl, n-Butyl	ClCN		85-92%[19]
2		BrCN		60%[16]
3		PhOCN		91%[20]
4		PhOCN		96%[21]

5		PhOCN		75%[22]
6		PhOCN		94%[17]
7		PhOCN		92%[17]
8		PhOCN		87%[17]
9		PhOCN		95%[17]
10		PhOCN		94%[17]
11		PhOCN		76%[17]
12		PhOCN		70%[17]
13				94%[23]
14				83%[18]

1.5 Conclusion:

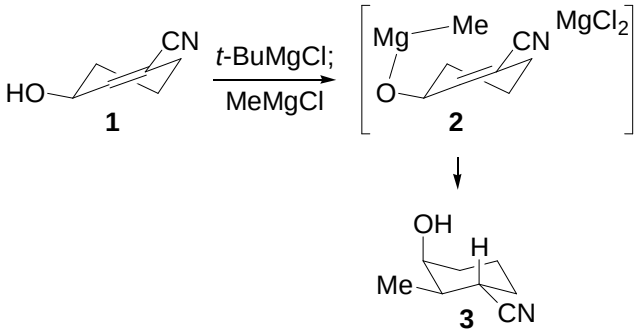
Alkynenitriles are unusual Michael acceptors that are synthesized by four general methods. Dehydration of alkynylamides provides the corresponding nitriles by a dehydration that is suited for synthesizing small, volatile alkynenitriles. Similarly,

eliminations of alkenenitriles by pyrolysis is also of limited value. Conversion of terminal alkynes to alkynenitilres 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.[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.[25] The increased reactivity obtained by chelation is successfully illustrated by the facile addition of Grignard reagents to the hydroxyalkenenitrile **1**[26] and the inability of cuprates[27] to react with cyclohexanecarbonitrile (1, HO = H).

Scheme.1Chelation-Controlled Conjugate Addition to Alkenenitrles.



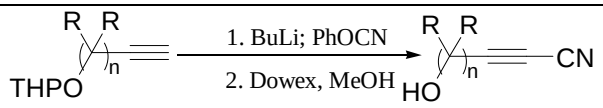
Exploratory conjugate additions to hydroxy alkynenitriles demonstrate the viability of using chelation for conjugate additions to alkynyl Michael acceptors.[28] The significance lies not only in extending chelation to activated alkyne Michael acceptors but in stereoselectively synthesizing *tri*-substituted alkenes that are difficult to synthesize with other reagents. Remaining is the unmet challenge[28] of performing chelation-controlled

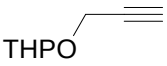
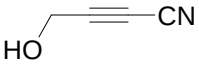
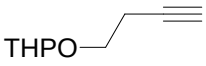
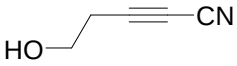
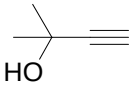
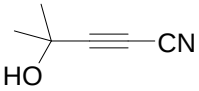
conjugate addition-alkylations to alkynenitriles to generate *tetra*-substituted alkene – alkenes that are after particularly challenging to synthesize.[29] Described below is a full account of a chelation –controlled conjugate addition to alkynenitriles leading to tri- and tetra-substituted alkenes.

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,[30] a challenge overcome with the corresponding ester,[31] 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[32] 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

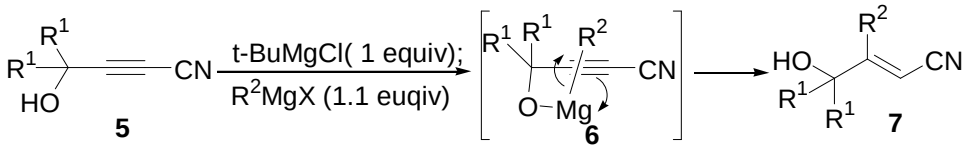


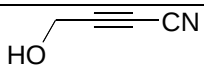
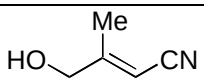
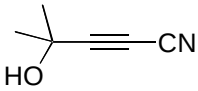
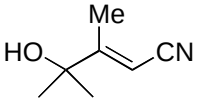
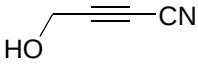
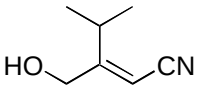
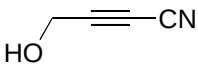
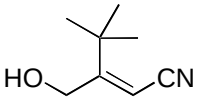
Entry	Alkyne	Alkynenitrile	Yield
1	 **4a**	 **5a**	84%
2	 **4b**	 **5b**	76%
3	 **4c**	 **5c**	80%

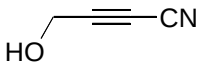
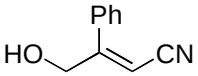
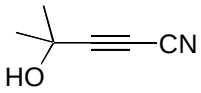
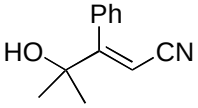
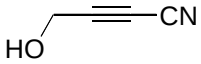
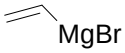
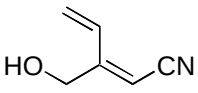
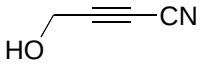
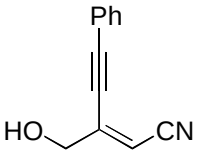
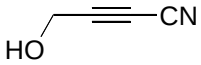
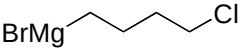
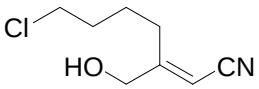
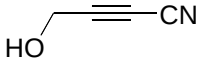
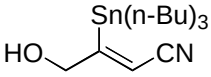
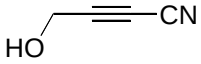
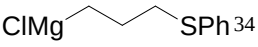
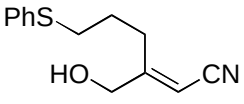
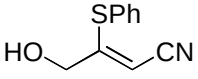
Hydroxy alkynenitriles **5a** and **5c** are excellent Michael acceptors for chelation-controlled conjugate additions. *t*-BuMgCl-initiated deprotonation of alkynenitriles **5a** or **5c** followed by a slight excess of a second potentially more valuable Grignard reagent triggers a particularly efficient conjugate addition (Table 2). *t*-BuMgCl is a particularly effective base since no transfer of the *t*-butyl group occurs during deprotonation at -78^{o} 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_3Sn 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).

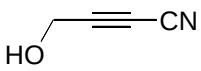
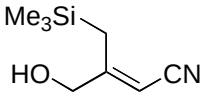
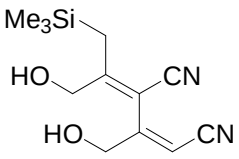
Alkyl, vinyl, aryl, and alkynyl Grignards add conjugatively to **5a** and **5c**, selectively generating E-alkenenitriles. Addition of the functionalized Grignard chlorobutylmagnesium bormide proceeds without interference of the halogen whereas the Grignard prepared from 3-chloropropyl phenylsulfide[33] (Table 2, entry 11) generates the expected nitrile **7k** as well as **7l,** presumably through conjugate addition of of PhSMgCl formed by cyclization of the Grignard reagent.

Table 2. Chelation-Controlled Conjugate Additions to Alkynenitriles



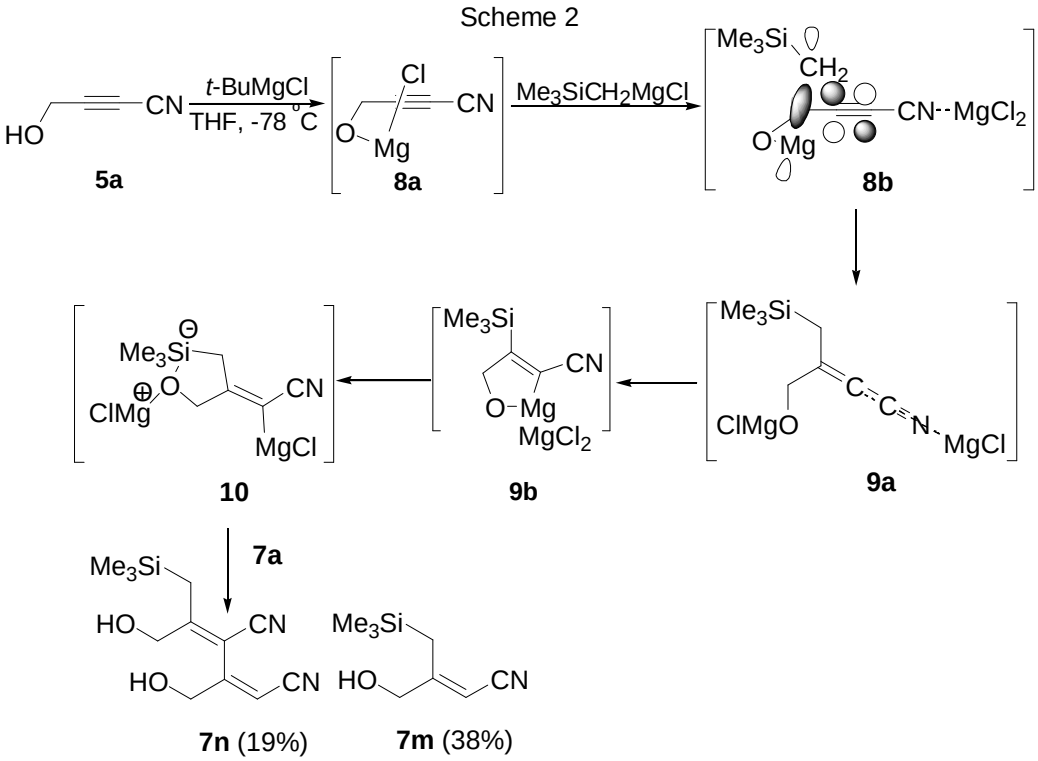
Entry	Alkynenitrile	Grignard	Compound	Yield
1	 **5a**	MeMgCl	 **7a**	92%
2	 **5c**	MeMgCl	 **7b**	70%
3	 **5a**	i-PrMgBr	 **7c**	87%
4	 **5a**	t-BuMgCl	 **7d**	60%

5	 **5a**	PhMgCl	 **7e**	92%
6	 **5c**	PhMgCl	 **7f**	66%
7	 **5a**		 **7g**	87%
8	 **5a**		 **7h**	85%
9	 **5a**		 **7i**	78%
10	 **5a**	$(n\text{-}Bu)_3SnMgCl$	 **7j**	70%
11	 **5a**		 **7k**	42%
			 **7l**	53%

12	 **5a**	Me_3SiCH_2MgCl	 **7m**	38%[35]
			 **7n**	19%

The conjugate addition with Me_3SiCH_2MgCl 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 π^* LUMO where the π^* 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 carbomagnesiation of alkynes. Chelate **9b** is deactivated toward further addition with **8a** except with the silicon-containing Grignard Me_3SiCH_2MgCl where silicate formation **10**[38] unmasks a more reactive C-Mg bond[39] that reacts further with **8a.**

Scheme 2



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[40] and alkylargentate.[41]

Consistent with formation of a stable chelate is the surprising inability to alkylate **9** with benzaldehyde[42]. 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[43] **12** as single stereoisomers (Table 2).[44] 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).[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

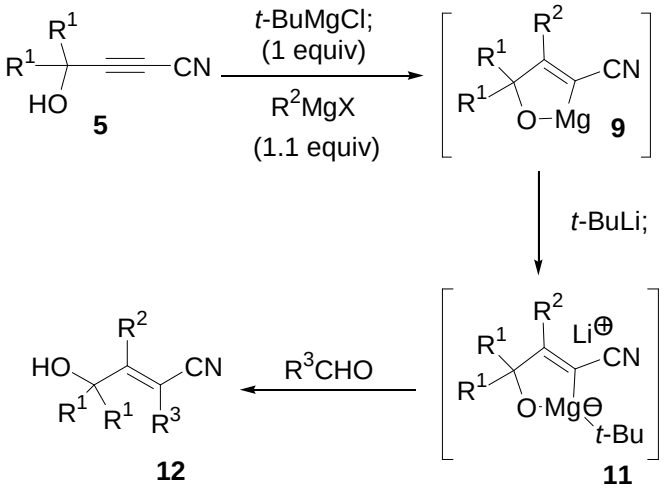
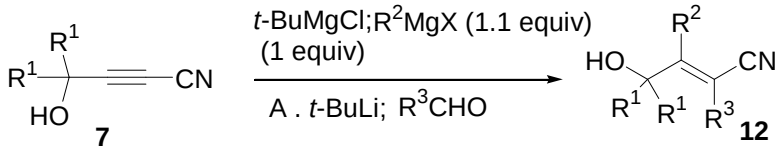
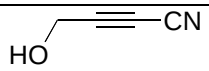
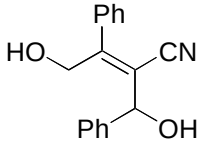
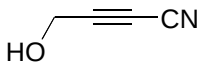
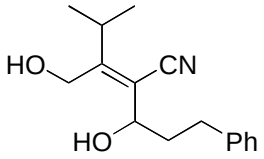
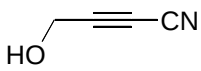
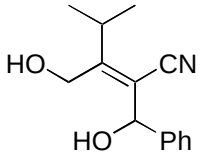
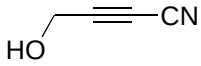
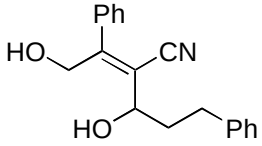
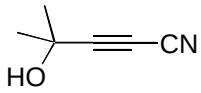
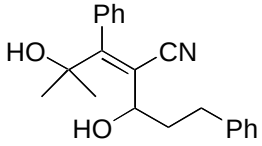
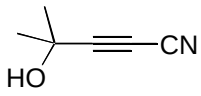
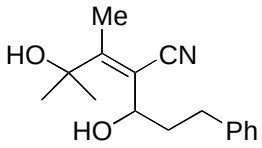


Table 2 Conjugate addition-alkylation to alkynenitrile



Entry	Alkynenitrile	Grignard	Aldehyde	Product	Yield
1	 **5a**	PhMgCl	PhCHO	 **12a**	60%
2	 **5a**	*i*-PrMgBr	$PhCH_2CH_2CHO$	 **12b**	65%

3	 **5a**	*i*-PrMgBr	PhCHO	 **12c**	72%
4	 **5a**	PhMgCl	$PhCH_2CH_2CHO$	 **12d**	57%
5	 **5c**	PhMgCl	$PhCH_2CH_2CHO$	 **12e**	57%
6	 **5c**	MeMgCl	$PhCH_2CH_2CHO$	 **12f**	61%

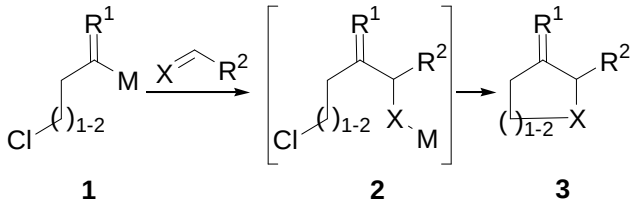
Grignard reagents readily add to γ-hydroxy alkynenitriles in an efficient chelation controlled conjugate addition. *t*-BuMgCl initiated deprotonation followed by addition of a second Grignard reagent triggers conjugate addition leading to a cyclic magnesium chelate. Protonation of the chelate stereoselectively generates tri-substituted alkenenitriles. Alternatively, addition of *t*-BuLi activates the intermediate chelate by conversion to the corresponding ate complex permiting 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 ω-Halonitriles: Domino Cyclizations to Oxacycles and Carbocycles

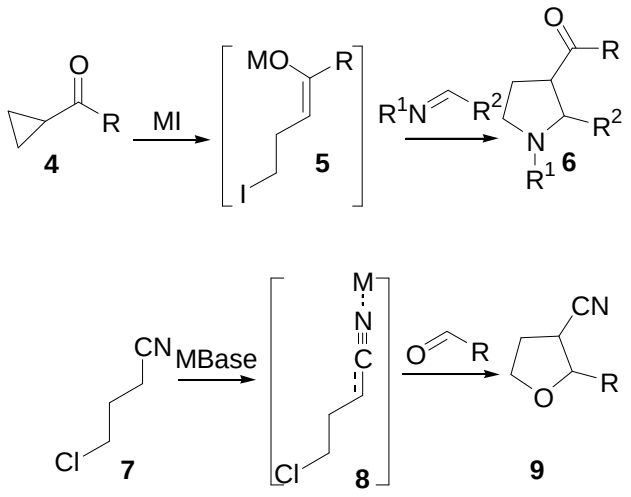
Halogen-containing organometallic reagents are extremely versatile reagents.[46] The value of haloalkylorganometallics lies in incorporating two reactive centers of opposite polarity for installating two new bonds through sequential alkylations.[47] Sequential addition-alkylations of haloalkylorganometallics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

Scheme 1



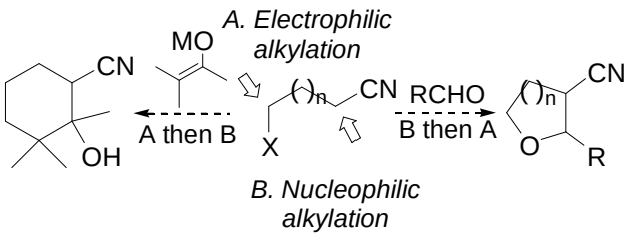
Significantly less common are haloalkyl organometallics generated by deprotonation. The challenge lies in generating the haloalkyl organometallic while avoiding cyclization,[49] a requirement cleverly overcome in the metal iodide-induced cleavage of cyclopropanes since ring opening reversibly generates homoenolates for in situ alkylation with imine and aldehyde electrophiles (Scheme 2, **4** to **6**).[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.[51] Collectively these precedents establish the viability of generating haloalkylorganometallics and their potential in domino synthesis.

Scheme 2: ω-Halogen-containing Organometallics



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 heterocyclces 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-subsituted carbocycles and oxacycles in a single synthetic operation.

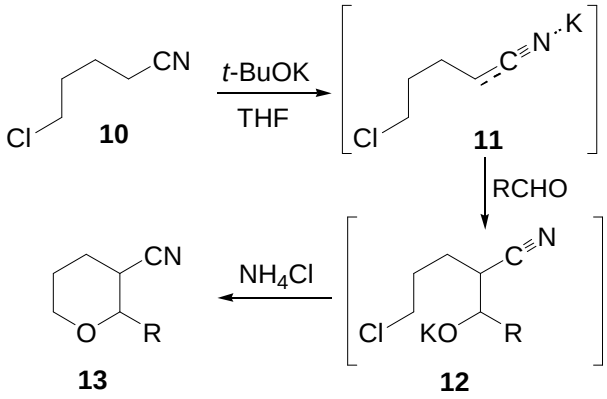
Scheme 3



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,[52] ester,[53] acylsilane,[54] and aldehyde[55] functionalities are efficiently deprotonated and alkylated.[56] Deprotonation of chloronitrile **10** with *t*-BuOK[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**.

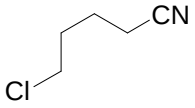
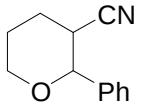
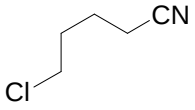
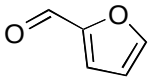
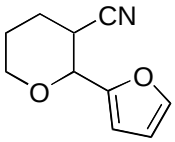
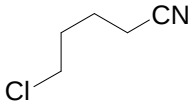
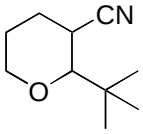
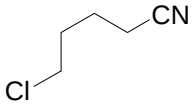
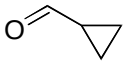
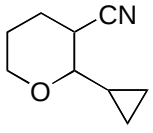
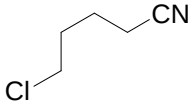
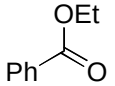
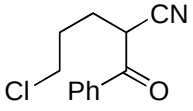
Scheme 4. Domino Alkylation of ω-chloronitrile **10**

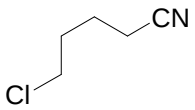
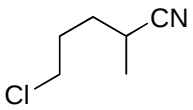
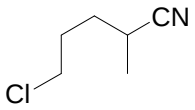
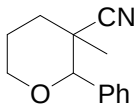
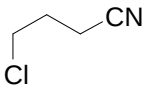
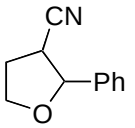
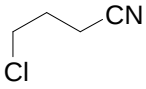
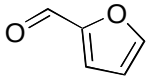
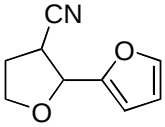
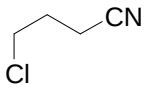
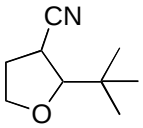
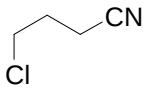
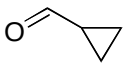
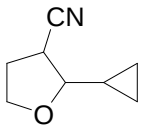


The facile annulation route to pyran **13a** is typical of the reactivity exhibited for a range of aldehydes (Table 1). Aromatic and aliphatic aldehydes generate pyrans equally efficiently, even with the potentially enolizable cyclopropanecarboxaldehyde (Table 1, entry 4). The resulting pyran-nitriles are generated as diastereomers, consistent with small steric demand of the nitrile group imparting a minimal bias in kinetic aldehyde[58] alkylation.[59]

Alkylating potassiated chloropentanecarbonitrile is not limited to aldehyde electrophiles. Intercepting **11** with ethyl benzoate generates the corresponding chloroketonitrile **14** while alkylation with MeI[60] 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 ω–Chloronitriles

Entry	Halonitrile	Electrophile	Nitrile	Yield[a]
1	 **10**	PhCHO	 **13a**	88% (1:1)
2	 **10**		 **13b**	75% (1.5:1)
3	 **10**	*t*-BuCHO	 **13c**	88% (2.5:1)
4	 **10**		 **13d**	85% (1:1)
5	 **10**		 **14**	58%

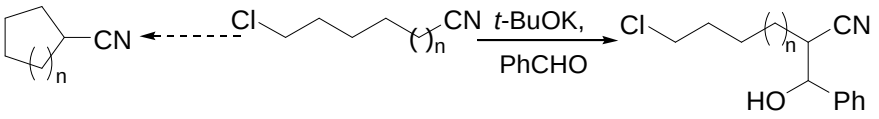
6	 **10**	MeI	 **15**	93%
7	 **15**	PhCHO	 **16**	72%
8	 **7**	PhCHO	 **17a**	75% (2.5:1)
9	 **7**		 **17b**	81% (2:1)
10	 **7**	*t*-BuCHO	 **17c**	93% (1:0)
11	 **7**		 **17d**	72% (1:1)

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).

Scheme 5. Alkylation of Homologus ω-Halonitriles



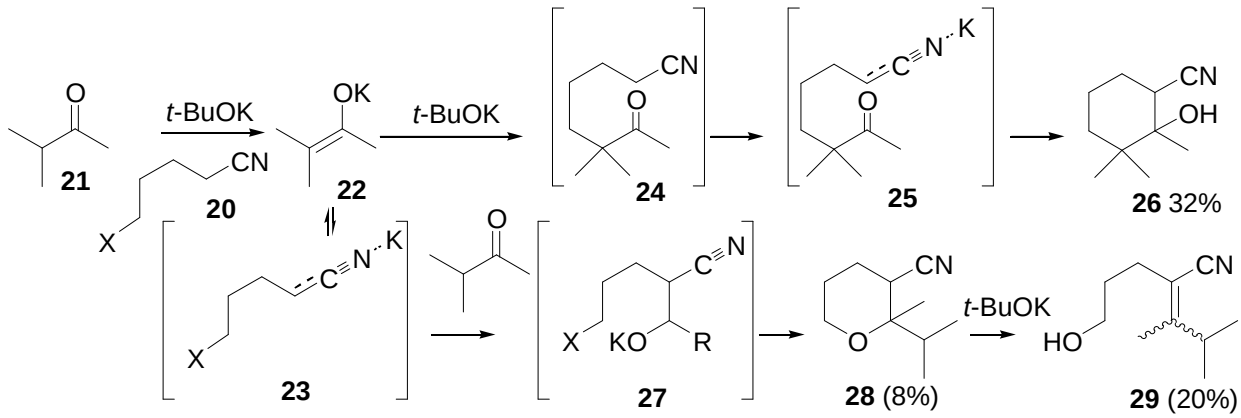
18a n=1 **19a** n=1 (74%, 1:1)
18b n=2 **19b** n=2 (72%, 1:1)

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[61] with the more acid ketone (ΔpK_a = 5-10),[62] 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**.[63] 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**.

Scheme 6



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 ω-haloalkylnitriles 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 $CHCl_3$ (δ 7.26) and the carbon signal for $CDCl_3$ (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 PF_{254} 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-ynenitrile: A hexanes solution of n-BuLi (5.4 mL, 8.6 mmol) was added to a -78 ^{o}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 $NaSO_4$, concentrated, and purified by radial chromatography (1:9 EtOAc/hexanes) to yield 1.3 g (92%) of 4-(Tetrahydro-pyran-2-yloxy)-but-2-ynenitrile as oil: IR (film) 2304, 2265 cm^{-1}; ^{1}H 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 ^{o}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 *e/m* 178 (M-H).

4-Hydroxy-but-2-tynenitrile (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-ynenitrile (5b): A methanolic solution (10 mL) of 5-(Tetrahydro-pyran-2-yloxy)-pent-2-ynenitrile (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, 2263cm^{-1}; ^{1}H NMR δ 2.12 (s, 1H), 2.65-2.61 (s, *J* = 6.0 Hz, 2H), 3.82 (s, 2H); ^{13}C NMR δ 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 ^{o}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 ^{o}C, THF solution of the γ–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_4Cl was added. The crude reaction mixture was extracted with EtOAc the combined organic extracts were dried (Na_2SO_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]

[1] Landor, S. R.; Demetrion, B.; Grzeskowiak, R.; Pavey, D. F. *J. Organomet. Chem*. **1975**, *93*, 129.
[2] Fleming, F. F.; Wang, Q.; Steward, O. W. *J. Org. Chem*. **2001**, *66*, 2171.

(2*E*)-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}; ^{1}H NMR δ 1.37 (s, 6H), 2.08 (s, 3H), 5.63(s, 1H); ^{13}C NMR δ 17.8, 28.5, 73.6, 94.1, 117.5, 169.6; MS *e/m* 126 (M+H).

(2*E*)-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}; ^{1}H 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); ^{13}C NMR δ 20.5, 32.2, 61.0, 91.9, 116.9, 172.1; MS *m/e* 126 (M+ H).

(2*E*)-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}; ^{1}H NMR δ 1.32 (s, 9H), 1.75 (s, 1H), 4.32 (s, 2H), 5.72 (s, 1H); ^{13}C NMR δ 28.9, 36.2, 62.4, 91.4, 118.0, 173.2; MS *m/e* 140 (M + H).

(2*E*)-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:[3] IR (Film) 3446, 3060, 2221, 1623 cm^{-1}; ^{1}H NMR δ 2.37 (br s, 1H), 4.52 (s, 2H),

[3] 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); ^{13}C NMR δ 64.6, 94.2, 117.4, 127.2, 128.9, 130.1, 134.7, 163.6; MS *m/e* 159.

(2*E*)-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}; ^{1}H NMR δ 1.39 (s, 6H), 1.86 (s, 1H), 5.97 (s, 1H), 7.19-7.44 (m, 5H); ^{13}C NMR δ 28.7, 73.6, 97.1, 116.9, 127.7, 128.4, 128.7; HRMS (ESI) calcd for (M+Na^{+}) $C_{12}H_{13}NONa^{+}$ 210.0889, found 210.08933

(2*E*)-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}, ^{1}H 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); ^{13}C NMR: 61.0, 95.7, 116.6, 120.9, 131.4, 158.0; MS *m/e* 109.

(2*E*)-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≡CMgCl[4] 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}; ^{1}H NMR δ 2.36 (s, 1H), 4.39 (s, 2H), 5.93 (s, 2H), 7.36-8.74 (m, 5H); ^{13}C 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^{+}).

[4] Prepared by reacting 1.5 equiv of phenylacetylene with 1.5 equiv of MeMgCl at 0^{O}C for 15 min.

(2*E*)-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}, ^{1}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); ^{13}C NMR: 25.3, 31.2, 31.6, 44.3, 63.9, 94.3, 116.8, 166.2; MS *m/e* 173 (M + H).

(2*Z*)-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 $(Bu)_3SnMgCl$[5] provided, after purification by radial chromatography (1:4 EtOAc/hexanes), 32 mg (70%) of **7j** as oil: IR (film) 3422, 2217, 1654 cm^{-1}; ^{1}H NMR δ 0.91 (t, *J* = 7.0 Hz, 9H), 1.12-1.64 (m, 18H), 4.42 (s, 2H), 6.26 (s, 1H); ^{13}C NMR δ 10.1, 13.6, 27.2, 29.0, 68.1, 105.5, 118.9, 176.7; MS *m/e* 373 (M^{+}).

(2*E*)-3-(hydroxymethyl)-6-phenylthiohex-2-enenitrile (7k) and (2*Z*)-4-hydroxy-3-phenylthiobut-2-enenitrile (11l): Performing the general conjugate addition procedure with a THF solution (5 mL) of **5a** (16 mg) and $PhS(CH_2)_3MgCl$ 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}; ^{1}H 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); ^{13}C 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};

[5] Prepared by reacting $(Bu)_3SnH$ (1.3 equiv) with MeMgCl (1.3 equiv) at 0 ^{o}C for 10 min

^{1}H NMR δ 2.03 (s, 1H), 4.07 (s, 2H), 5.81 (s, 1H), 7.27- 7.55 (m, 5H); ^{13}C NMR δ 64.1, 93.6, 127.9, 129.9, 134.7, 162; MS *m/e* 191 (M^{+}).

(2*Z*)-3-(hydroxymethyl)-5,5-dimethyl-5-silahex-2-enenitrile (7m) and (2*E*)-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 $(CH_3)_3SiCH_2MgCl$ 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:** IR (Film) 3456, 2215, 1620; ^{1}H NMR δ 0.12 (s, 9H), 1.94 (s, 2H), 4.13 (s, 2H), 5.39 (s, 1H); ^{13}C NMR δ - 1.0, 24.6, 65.3, 89.2, 118.1, 166.7; MS *m/e* 169. For **7n:** IR (Film) 3456, 2221, 1630 cm^{-1}; ^{1}H NMR δ 0.22 (s, 9H), 2.38 (s, 2H), 4.27 (s, 2H), 4.36 (s, 2H), 5.84 (s, 1H); ^{13}C NMR δ -0.8, 28.0, 62.4, 63.3, 100.2, 100.6, 116.3, 157.1, 167.5; MS *m/e* 250 (M+H).

General conjugate addition-alkylation procedure: A THF solution of *t*-BuMgCl (1.0 equiv, 1-2 M) was added to a – 78 ^{o}C, THF solution of the γ–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 ^{o}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_4Cl. 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.

(2*Z*)-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 δ 4.55-4.57 (m, 2H), 5.40-5.42 (m, 1H, exchanges with D_2O), 5.94-5.96 (m, 1H), 6.21 (d, *J* = 4.0 Hz, 1H, exchanges with D_2O), 7.26-7.50 (m, 10H); ^{13}C NMR δ 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_2O).

(2*Z*)-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 δ 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 δ 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.

(2*Z*)-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 δ 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, Δν = 31.5 Hz, *J* = 12.3 Hz, 2H), 5.79 (s,

1H), 7.32-7.45 (m, 5H); ^{13}C 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).

(2*E*)-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}; ^{1}H NMR δ 2.1-2.24 (m, 2H), 2.74-2.78 (m, 2H), 3.20 (brs, 2H), 4.39 (AB_q, Δν = 40.0 Hz, *J* = 13.4, 2H), 4.69 (t, *J* = 7 Hz, 1H), 7.20-7.38 (m, 10H); ^{13}C 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.

(2*Z*)-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}; ^{1}H 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); ^{13}C 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 ($M+Na^+$) $C_{21}H_{23}NO_2$ 344.1621, found 344.1611.

(2*Z*)-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}; ^{1}H 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[64]

General procedure for oxacycles formation: To a 0 ^{o}C THF solution of *t*-BuOK (1 equiv), neat RCHO (1equiv) was added followed by the addition of ω-chloronitile. After 3 h, the reaction mixture was allowed to warm to the room temperature, quenched with saturated NH_4Cl, 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 δ 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 δ 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 δ 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 δ 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-yl-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** *trans*: IR (film) 2236 cm^{-1}; ^{1}H NMR δ 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}C NMR δ 23.9, 27.7, 31.6, 68.2, 73.5, 109.1, 110.4, 119.0, 143.1, 150.7; MS m/e 178 (M + H); HRMS(ESI) calcd for ($M+Na^{+}$), $C_{10}H_{11}NO_2Na$ 200.0682 found: 200.0698. For **13b** *cis*: IR (film) 2241 cm^{-1}; ^{1}H NMR δ 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* = 2Hz, 1H), 6.39 (s, 1H), 6.52 (d, *J* = 2.9 Hz, 1H), 7.39 (br s, 1H); ^{13}C NMR δ 21.8, 26.5, 32.1, 68.6, 73.3, 107.3, 110.3, 118.9, 142.1, 151.3; MS m/e 178 (M + H); HRMS (ESI) calcd for ($M+Na^{+}$), $C_{10}H_{11}NO_2Na$ 200.0682 found: 200.0698.

2-*tert*-Butyl-tetrahydro-pyran-3-carbonitrile (13c): Performing the general procedure with a THF solution (5 mL) of *t*-BuOK (195 mg, 1.74 mmol), **10** (136 mg, 1.16 mmol) and **e**xcess 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** *trans:* IR (film) 2235 cm^{-1}; ^{1}H NMR δ 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}C NMR δ 24.5, 26.6, 28.0, 29.7, 35.7, 61.8, 68.2, 85.1, 121.5; MS m/e 168 (M + H). HRMS (ESI) calcd for ($M+Na^{+}$): $C_{10}H_{17}NONa$ 190.1202 found 190.1206. For **13c** *cis*: IR (film) 2236 cm^{-1}; ^{1}H NMR δ 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}C NMR δ 22.1, 26.2, 27.5, 28.7, 34.6, 69.3, 85.3, 120.6; 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[65]) of **13d** as oils. For 13d *trans*: IR (film) 2237 cm^{-1}; ^{1}H 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); ^{13}C NMR δ 1.7, 3.2, 14.9, 24.2, 27.9, 33.6, 67.8, 81.0, 119.9; HRMS(ESI) calcd for ($M+Na^{+}$) $C_{19}C_{13}NONa$ 174.0889 found 174.0894. For **13d** *isomer*: IR (film) 2236 cm^{-1}; ^{1}H 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); ^{13}C 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 ($M+Na^{+}$) $C_9H_{13}NONa$ 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[67]) of **17a** as oils. For **17a** *trans*: IR (film) 2240 cm^{-1}; ^{1}H 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);^{13}C NMR δ ; 31.3, 36.5, 67.3, 81.5, 118.9, 126.0, 128.4, 128.5, 137.1; HRMS(ESI) calcd for ($M+Na^{+}$) $C_{11}H_{11}NONa$ 196.0733 found 196.0747. For **17a** *cis*: IR (film) 2242 cm^{-1}; ^{1}H 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); ^{13}C

NMR δ 30.9, 36.9, 67.8, 83.5, 119.7, 125.3, 128.4, 128.6, 138.6; HRMS (ESI) calcd for ($M+Na^+$), $C_{11}H_{11}NONa$ 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%, 2:1[67]) 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); ^{13}C NMR δ 31.0, 33.1, 67.8, 109.1, 110.4, 119.5, 143.2, 150.3; HRMS (EI) calcd for $C_9H_9NO_2$ 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).; ^{13}C 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-dimethylpropionaldehyde[66] 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); ^{13}C NMR δ 25.5, 28.6, 31.9, 34.1, 67.7, 90.5, 121.4; HRMS (EI) calcd for $C_9H_{15}NO$ 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[67]) of **17d** as oils. For **17d** *trans*: IR (film) 2243 cm^{-1}; ^1H NMR δ ; 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 δ 1.5, 2.7, 13.8, 30.8, 33.8, 67.2, 86.3, 120.2; HRMS (EI) calcd for $C_8H_{11}NO$ 137.0835 found 137.0850; For **17d** *cis*: IR (film) 2241 cm^{-1}; ^1H NMR δ 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 δ 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 $C_8H_{11}NO$ 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[65]) of **19a** as oils. For diastereomeric mixture of **19a:** IR (film) 2244 cm^{-1}; ^1H NMR δ 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 δ 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}; ^1H NMR δ 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 ^{o}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_4Cl, 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**[68] as a solid.[69] 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 ^{o}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_4Cl 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 δ 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 δ 20.2, 20.3, 21.5, 25.0, 27.9, 36.8, 38.0, 38.5, 74.2, 121.5; HRMS (ESI) calcd for ($M+Na^{+}$) $C_{10}H_{17}NONa$ 190.1202, found 190.1211; for **28**: IR (film) 2236 cm^{-1}; ^{1}H NMR δ 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 δ 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 δ 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 δ 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 δ 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 δ 16.9, 20.2, 25.4, 30.0, 31.4, 60.4, 107.9, 119.5, 161.1 MS *m/e* (M+H) 168.

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[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.

[67] Ratio of *tran: cis* isomers

[68] Repetitive chromatography afforded a sample of pure **14**-trans

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