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Unsaturated Nitriles: Stereoselective Annulations and Alkylations

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Unsaturated Nitriles: Stereoselective Annulations and Alkylations

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Zhiyu Zhang

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To My Parents and My Wife!

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Title: Unsaturated Nitriles: Stereoselective Annulations and Alkylations

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Abstract

N-metallated nitriles are fundamental intermediate that have been used to generate new C-C bonds for over a century. C-metallated nitriles are new but equally important intermediates in being able to deliver complementary stereoselectivity. C-magnesiated nitriles are directly generated from chelation-controlled conjugated addition and can successfully furnish complete stereocontrol during installation of three new stereocenters (Section II-1).

The recent development of chiral organometallics has identified a remarkable series of electrophile-dependent alkylations that are significantly impacting organic synthesis. C-magnesiated nitriles from chelation-controlled conjugated addition are chiral nucleophiles that alkylate an array of electrophiles with retentive or invertive alkylation depending on the electrophiles. Specifically, alkyl halides and most carbonyl electrophiles afford one stereoisomer with the stereochemical assignments being confirmed by X-ray diffraction (Section II-2).

Multi-component reactions rapidly assemble complex targets. Sequential 1, 2 addition and chelation-controlled conjugate addition to oxonitriles efficiently generates highly substituted cyclic nitriles. ω-Haloalkyl Grignards trigger the same sequence with intramolecular alkylation to afford octalins, hydrindanes and decalins ideally suited for terpanoid synthesis. A complementary multicoponent addition-Friedel-Crafts alkylation has been employed for the total synthesis of *epi*-dehydroabietic acid (Section II-3).

The exchange of α-halonitriles with *i*-PrMgBr directly generates C-magnesiated nitriles. The rapid exchange allows *in situ* alkylations with aldehyde, ketone and acyl cyanide electrophiles without prior Grignard addition (Section II-4). Furthermore the exchange uses rapid equilibration allowing the diastereoselective alkylation of diastereomeric α-bromonitriles.

Acknowledgements

I would like to express my sincere gratitude to Dr. Fraser F. Fleming for teaching me through my coursework as well as in the lab. I have gained experience in several important courses, and my knowledge of organic chemistry has significantly advanced compared with when I first came to Duquesne five years ago. I am particularly grateful for finishing this dissertation with Dr. Fleming's help and direction.

I would like to thank Drs. David Seybert, Bruce Beaver and Paul Carlier for their significant effort in serving as my Ph. D. committee members. I also would like to thank Dr. Omar Steward for his excellent work in solving X-ray structures. The experience in Munich at Ludwig Maximilians University will remain with me throughout my lifetime and I offer my sincere gratitude to Dr. Paul Knochel and his group members.

I want to thank to my colleagues for helping me in various ways; Qunzhao, Yong, Brian, Lee, Wang, Guoqing, Pravin, Venu, Subbu and Som.

Finally, as the only son in the family, this dissertation is dedicated to my parents, Prof. Huimin Nie and Prof. Ji Zhang who I wish I could be with as they get old. I thank my sisters and brothers-in-laws for their support. Finally I specially want to thank my wife, Bing Yang, who supports me unconditionally and all the time.

List of Contents

List of Abbreviations

Ac	-	acetate
br	-	broad
Bn	-	benzyl
Bu	-	butyl
^{13}C NMR	-	carbon nuclear magnetic resonance
d	-	doublet
dd	-	doublet of doublets
ddd	-	doublet of doublet of doublets
dddd	-	doublet of doublet of doublet of doublets
DMF	-	*N,N*-dimethylformamide
DMSO	-	dimethylsulfoxide
equiv	-	equivalent
Et	-	ethyl
GC-MS	-	gas chromatography-mass spectrometry
h	-	hour(s)
HMDS	-	bis(trimethylsilyl)amide
^{1}H NMR	-	proton nuclear magnetic resonance
HR-MS	-	high resolution mass spectra
H_2SO_4	-	sulfuric acid
i	-	iso
IR	-	infrared
LDA	-	lithium diisopropylamine
m	-	multiplet
Me	-	methyl
min	-	minutes
MOM	-	methoxy methyl
m.p.	-	melting point
Ms	-	mesylate
Ph	-	phenyl
Pr	-	propyl

q	-	quartet
R	-	alkyl, aryl, or hydrogen
r.t.	-	room temperature
s	-	singlet
t	-	triplet
t or *tert*	-	tertiary
TBAF	-	tetra-n-butylammpnium fluoride
Tf	-	triflate
THF	-	tetrahydrofuran
TBDPS	-	tert-butyl diphenyl silyl
TMS	-	trimethylsilyl
TMSCN	-	trimethylsilyl cyanide

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I. Introduction: Cyclic Nitriles: Tactical Advantages in Synthesis

I-1. Introduction

Cyclic nitriles have a long and distinguished history as versatile synthetic intermediates.[1] The versatility stems from the nitriles extremely high polar-inductive effect,[2] the excellent hydrogen bond acceptor properties,[3] and the minimal steric demand of the

extremely small nitrile group – the A-value is only 0.2 kcal mol^{-1}![4] Nitriles are highly unusual among functional groups in stabilizing adjacent radicals, cations,[5] and anions[6] with the latter often exhibiting unique reactivity in providing chemo-, regio-, and stereo-selectivities that are practically inaccessible with carbonyl compounds.

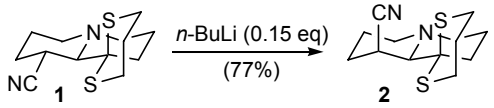
This review surveys the reactions of cyclic, aliphatic nitriles, in which the nitrile is directly bound to the ring. Among the myriad reations of nitriles the focus is on anionic reactions of nitriles that are significantly different from those of related electron withdrawing groups. The review is partitioned into five sections beginning with an overview of the structural features of nitriles as a prelude to understanding their unique properties (Section 2). Syntheses of cyclic nitriles are then surveyed (Section 3) followed by stereoselective alkylations (Section 4) and cyclizations (Section 5) of cyclic nitriles, and concluding with methods for removing the nitrile group (Section 6). The broad utility of nitriles in synthesis means that some sections are necessarily selective whereas some of the lesser known reactions are comprehensively surveyed. Highlighting the unique reactions of cyclic, aliphatic nitriles should enhance their use as synthetic intermediates, particularly in the total synthesis of nitrile-containing natural products.[7]

I-2. Unique Chemistry of Cyclic Nitriles

I-2-1. Stereoselectivity

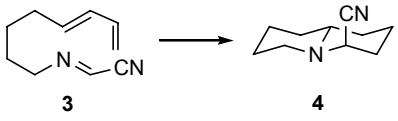
Nitriles exhibit unique stereoselectivity because of the exceptionally small size of the CN group. The linear, rod-like geometry localizes the strong dipole more than the triangular carbonyl electron withdrawing groups which, through bond rotation, spread the effective

charge over a larger surface area. The compact, cylindrical nature of the C≡N unit (3.6 Å cylindrical diameter of the π-system)[8] creates one of the smallest electron-withdrawing groups with an A value of 0.2 kcal·mol^{-1} compared to 0.6-2.0 kcal·mol^{-1} for carbonyl functionalities.[4] This difference gives rise to some surprising stereochemical preferences. For example, equilibration of quinolizidines causes epimerizable electron-withdrawing groups to favor an equatorial orientation[9] except for nitrile **1** where equilibration favors an axial orientation (Equation I-1).[10]



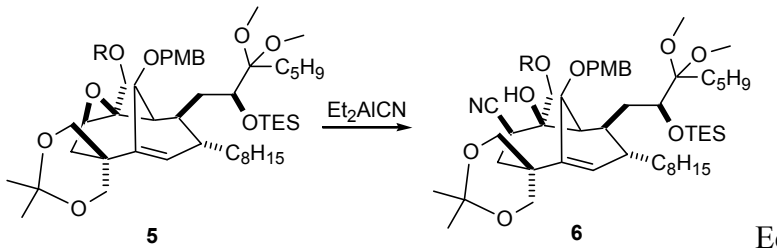
Eq. I-1

Similarly, intramolecular Diels-Alder cycloadditions generate cycloadducts that equilibrate in situ to install an axial nitrile[11] as a consequence of anomeric stabilization[12] (Equation I-2).



Eq. I-2

The small steric demand makes the CN unit ideal for installing a one-carbon unit in crowded environments. Historically the classical Nagata cyanation of enones has served as a particularly efficient introduction of nitriles into sterically congested enones.[13] Cyanation continues to serve as an incomparably efficient one-carbon installation in synthesis as featured in the synthesis of CP-263,114 where formation of the hindered hydroxyl nitrile was crucial for assembling the highly hindered and sensitive molecular architecture (Equation I-3).

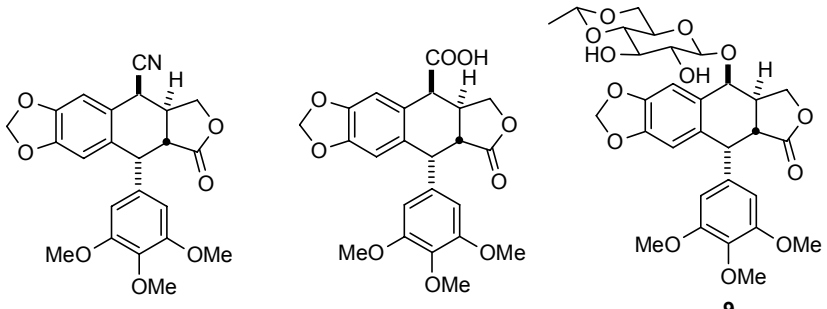


5 **6** Eq. I-3

I-2-2. Hydrogen Bonding

Nitriles have an exceptionally high dipole moment which, combined with the lone pair on nitrogen, is ideal for hydrogen bonding.[3] An extensive survey of x-ray structures reveals that electron donating substituents accentuate the super basicity of the CN unit thereby increasing the hydrogen bonding. The excellent hydrogen bond acceptor properties[14] of nitriles, combined with the extremely high polar-inductive effect[15] and minimal steric demand,[4] conspire to make the nitrile a particularly useful hydroxyl surrogate. An indication of the nitrile's efficacy is exemplified by the SAR development of the nitrile and acid podophylotoxin analogs (Figure I-1). Substituting a nitrile for the hydroxyl group of podophylotoxin gave **7** which retains a high bioactivity that exceeds the potency of the anti-cancer drug etoposide **9**.

Figure I-1. Podophylotoxin Analogs

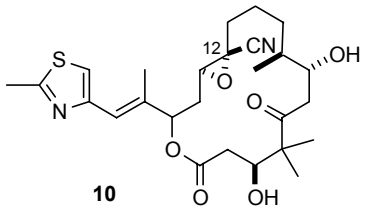


7 **8** **9**

Inhibition of L_{1210} IC_{50}(ng/mL)	3.48	164	155
Inhibition of KB IC_{50}(ng/mL)	155	10,000	308

Nitrile-substitution in potential drug leads has also been used to induce increased stability through inductive polarizarization. Nitrile substitution increases the stability of epothilone at low pH, which is posited as a critical issue for establishing oral dosing regimens for this potent anticancer agent.[16] Installing a nitrile substituent at C-12 of epothilone A (Figure I-2) not only retains excellent activity in *in vitro* assays but markedly improves the pH stability [pH 1 buffer (aq), T_{95} = 11 h].

Figure I-2. 12-Cyano-Epothilone A

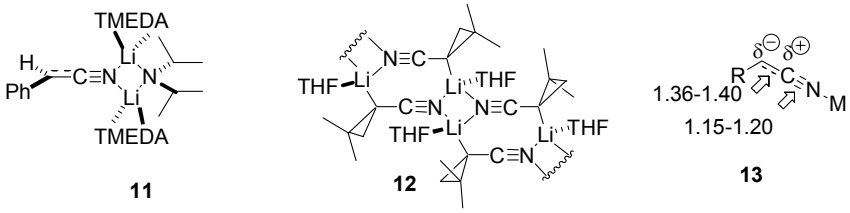


I-2-3. Exceptional Nucleophilicity

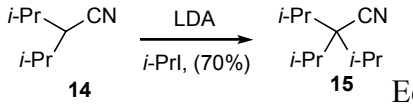
Metallated nitriles are powerful nucleophiles with an exceptional propensity for C-alkylation. Nitrile anions alkylate almost exclusively on carbon with silyl[17] and acetyl[18] chlorides being virtually the only electrophiles with a propensity for reaction on nitrogen. The exceptional nucleophilicity stems primarily from the powerful inductive stabilization of metallated nitriles rather than through resonance as is the case with enolates.[19] Pioneering x-ray structures of metallated nitriles have been instrumental in developing a coherent understanding of the reactivity and structure of metallated nitriles.[20] Surprisingly, metallated nitriles exhibit minimal elongation of the C≡N bond (1.15-1.20 Å, Figure I-3) when compared to C≡N the bond length of neutral nitriles (1.14A),[3] whereas the bond length between the nitrile carbon and the formal anionic carbon is typically intermediate between that of C-C double and single bonds (1.36-1.40 Å, **13**).

Essentially, the powerful inductive stabilization of the CN group[19,21] causes a strong, polarized attraction with the overall structure of metallated nitriles being akin to an ylide.

Figure I-3. X-ray Structures of Metallated Nitriles

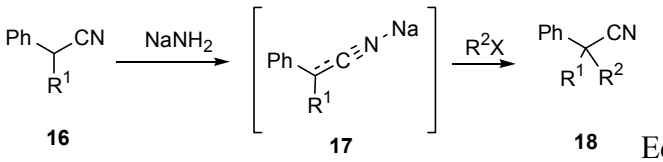


Consonant with the ylide-like structure of metallated nitriles is the high propensity for C-alkylation, even for sterically demanding alkylations. Comparative alkylations of sterically hindered nitriles, acids, and esters demonstrate the superior nucleophilicity of metallated nitriles.[22] The diisopropyl substituted nitrile **14** alkylates *i*-PrI in 70% yield whereas the corresponding acid (**14**, CN = COOH), which is more nucleophilic than the analogous ester, is unable to alkylate MeI (Equation I-4).



Eq. I-4

Consistent with the high nucleophilicity of sterically hindered metallated nitriles are a series of alkylations of sodiated α-substituted phenylacetonitriles (Equation I-5). Surprisingly, comparative methylations are increasingly efficient for substituents in the order butyl ~ ethyl > methyl > isopropyl > phenyl, consistent with a greater nucleophilicity being imparted from stronger electron donating substituents. Presumably the small methyl group confers a modest electron donation with minimal steric demand, when compared to the considerably larger, but better σ-donor, isopropyl substituent.[23]



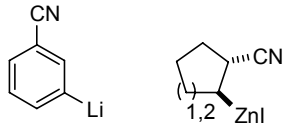
16 **17** **18** Eq. I-5

Comparative alkylations of malonates and malononitriles reiterate the exceptional nucleophilicity of nitriles.[24] Deprotonated malononitrile exhibits a particularly low instrinsic barrier, allowing facile hybridization changes during alkylation, consistent with the minimal resonance stabilization of nitriles.

I-2-4. High Reagent Compatibility

Unlike most carbonyl compounds, the nitrile group is inert to many nucleophilic reagents at low temperatures and has even been incorporated as a substituent within alkyllithium[25] and Grignard reagents.[26] Few examples of cyclic nitrile-substituted organometallics have been prepared despite the early incorporation within lithiated benzonitriles[27] and organozincs[28] (**19** and **20** respectively, Figure I-4).

Figure I-4. Cyclic Metallated Nitriles

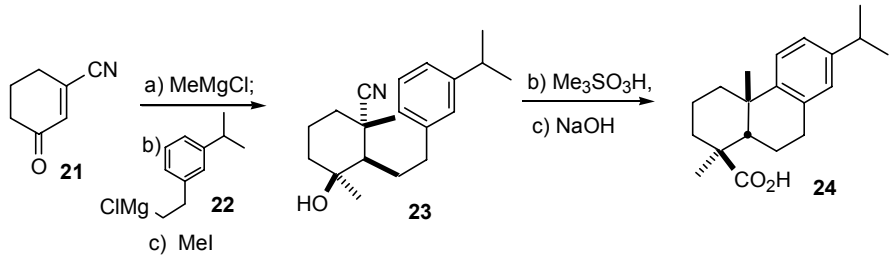


19 **20**

A direct benefit of the low electrophilicity of nitriles is that nitrile-containing intermediates are inert to many reagents and may be taken through many synthetic steps without the use of protecting groups.[29] Reduction of many carbonyl groups in the presence of nitriles has long exploited the modest electrophilicity of the C≡N functionality.[30] Similarly, despite a perception to the contrary, nitriles react slowly with Grignard reagents as illustrated in the preferential 1,2-addition, 1,4-addition of Grignard

reagents to the carbonyl and acrylonitrile groups of **21** (Scheme I-1) with no observable addition to the nitrile.[31] Furthermore, the cyclic nitrile **23** readily cyclizes to the abietane skeleton whereas the corresponding ester[32] instead reacts with the carbocation to generate a lactone which precludes Friedel-Crafts cyclization.

Scheme I-1. Oxonitrile to an Abietane Diterpanoid



I-2-5. Functional Group Interconversion.

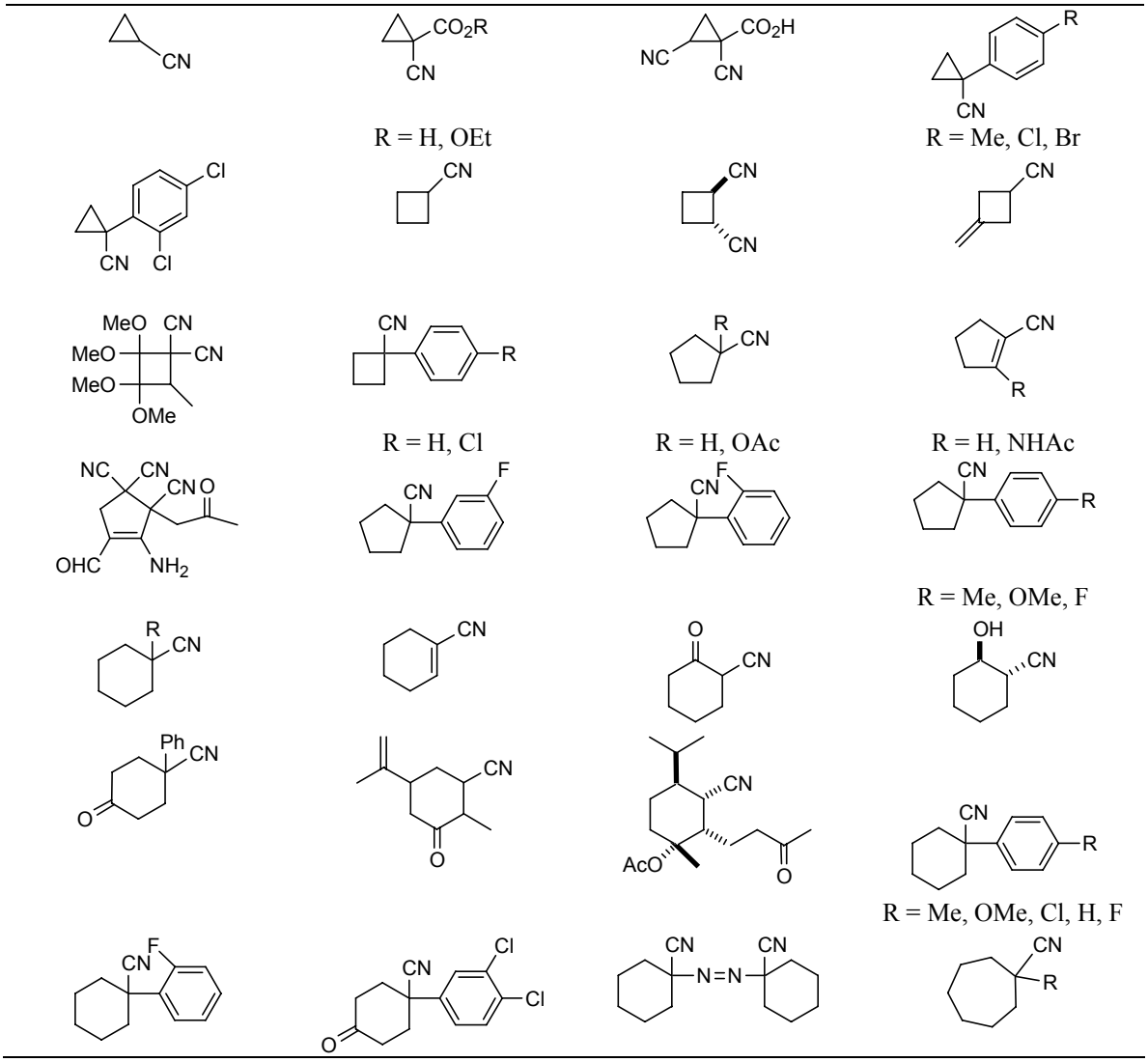
Nitriles are exquisitely positioned in terms of their reactivity; at low temperatures the nitrile can be incorporated within reactive intermediates like organolithium reagents[25] while at higher temperatures nucleophiles add to the nitrile group[1]. The classical addition of Grignard reagents to afford ketones is probably the best-known example, but the nitrile group is readily converted to a plethora of functionalities,[33] providing an excellent entry to carbocycles[20a] and heterocycles.[34]

I-3. Syntheses of Cyclic Nitriles

A surprising number of cyclic, aliphatic nitriles are commercially available (Chart I-1). The parent 3- through 7-membered carbonitriles and many with additional substituents at the nitrile bearing carbon, are available in 1g quantities or larger. In almost all instances

the nitriles are symmetrical with only one enantiomerically enriched nitrile being available.

Chart I-1. Commercial Available Cyclic Aliphatic Nitriles (≥ 1g listing)[a]



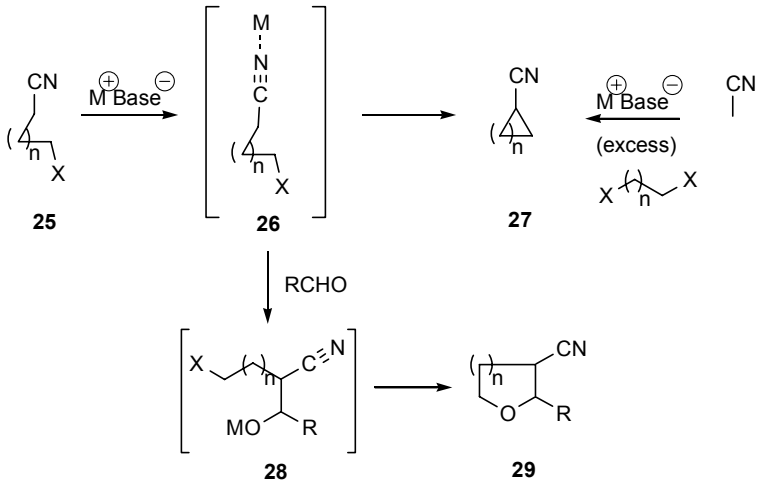
[a] The commercial availability was determined using a structure search with Scifinder (June 2004).

I-3-1. Alkanenitrile Syntheses

I-3-1-1. Cyclization

Cyclic alkanenitriles are readily prepared by intramolecular alkylation. A recent review[35] summarizes the two most prevalent alkylation strategies: cyclization of a metallated nitrile bearing a pendant electrophile (Scheme I-2, **25** → **27**) or, less commonly, two sequential deprotonation alkylation reactions performed in one synthetic operation (Scheme I-2, **27**). The direct dialkylation is particularly well suited to the formation of cyclopropanes[36] using slightly greater than two equivalents of BuLi and epi-bromohydrin.

Scheme I-2. Cyclic Nitrile Synthesis



An expedient variation for synthesizing nitrile-substituted furans[37] and pyrans[38] is to intercept the metallated nitrile **26** in situ with aldehyde electrophiles to generate alkoxides **28** that internally alkylate a pendent electrophile to deliver the corresponding nitrile-substituted furan or pyran.

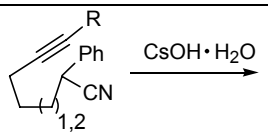
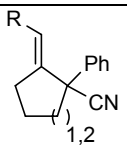
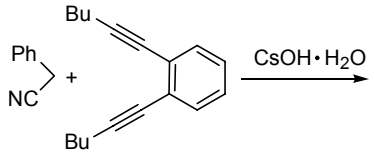
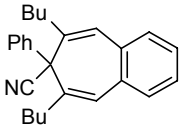
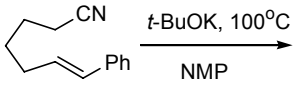
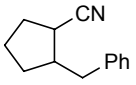
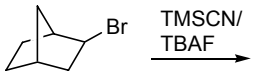
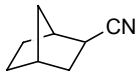
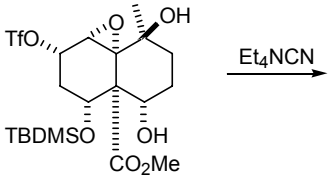
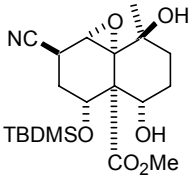
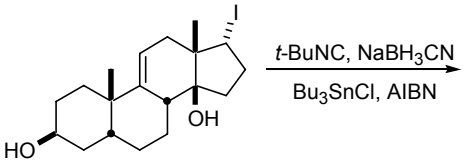
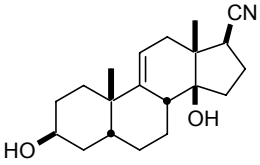
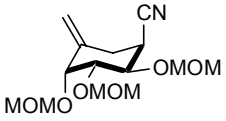
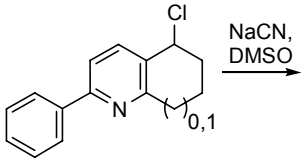
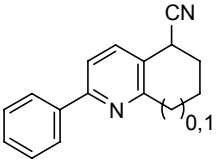
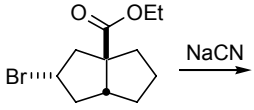
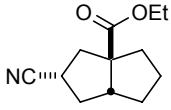
I-3-1-2. Syntheses from Cyclic Precursors

Cyclic nitriles are employed in myriad contexts. Syntheses of cyclic nitiriles are therefore focused on stereochemically complex transformations and are necessarily selective representations of the type of syntheses of cyclic nitriles.

The high nucleophilicity of metallated nitriles allows an unusual cyclization onto pendent alkenes and alkynes to generate cyclic nitriles (Table I-1, entries 1-3). The key to this unusual cyclization is the use of a relatively naked nitrile anion that is achieved through the use of CsOH or *t*-BuOK in highly polar solvents.

Cyclic nitriles are most commonly synthesized by S_N2 displacement of the corresponding cyclic halide or sulfonate.[39] The small, nucleophilic cyanide unit allows an efficient displacement with predictable stereochemical inversion (Table I-1, entries 4-15)[40] although neighboring group participation may redirect the usual displacement to meet retention (Table I-1, entries 14-15). Cyanide nucleophilicity can be enhanced with hypervalent silicates (Table I-1, entry 4) or with *t*-butyl ammonium cyanide (Table I-1, entry 5) which allows preferential displacement of a secondary triflate in the presence of an epoxide. In cases where cyanide displacement is unsuccessful the corresponding iodide can be converted to a radical and cyanated with tert-butyl isocyanide (Table I-1, entry 6). Direct cyanation of secondary alcohols can be performed *in situ* by a modified Mitsonobu inversion, avoiding the usual activation and cyanide displacement (Table I-1, entry 16). Benzylic and tertiary alcohols are conveniently converted to cyclic nitriles by intercepting the corresponding carbocation with cyanide (Table I-1, entries 17-20, respectively) in a reaction that has been extended to the cyanation of ethers and tertiary halides (Table I-1, entries 21-22).

Table I-1. Alkanenitrile Syntheses

Entry	Reaction	Cyclic Nitrile	Yield (%)
1			60-80[41]
2			75[41]
3			61(1:1)[42]
4			70[43]
5			74[44] for 2 steps
6			82[45]
7			90[46]
8			78[47]
9			74[48]

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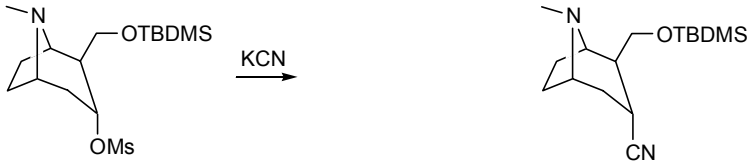
11			50[50]
12			85[51]
13			63[52]
14			74[53]
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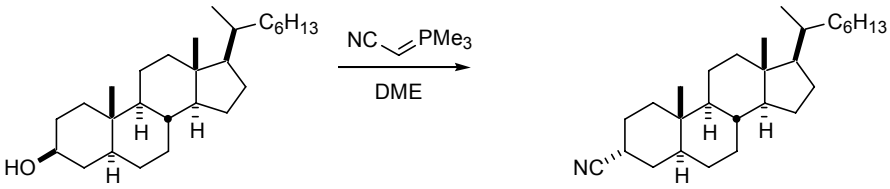
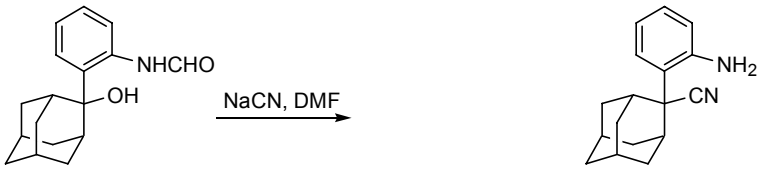
16			73[55]
17			82[56]
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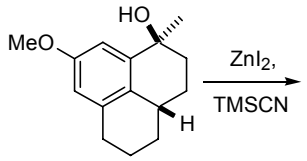
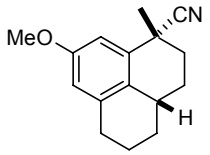
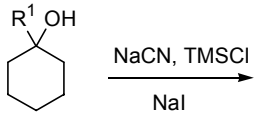
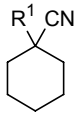
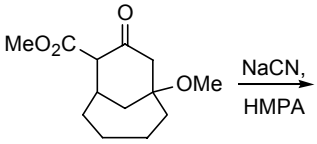
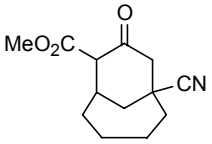
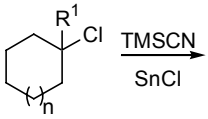
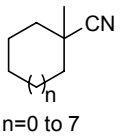
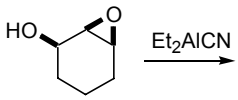
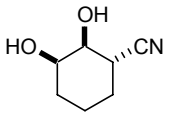
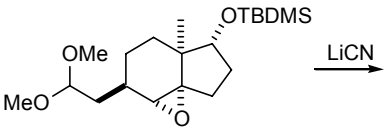
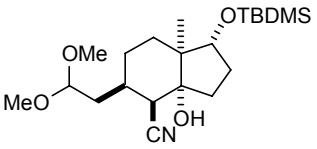
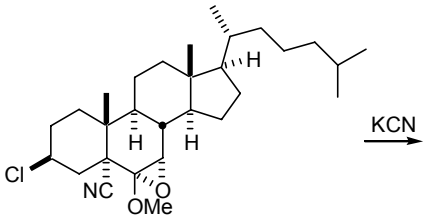
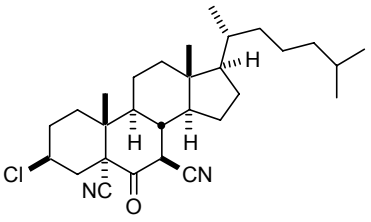
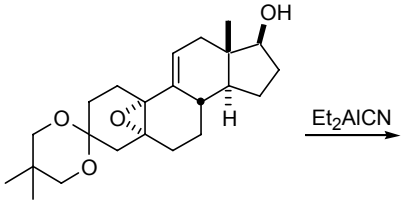
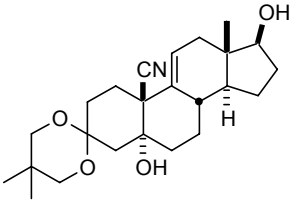
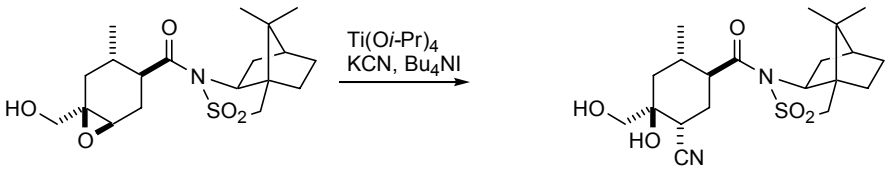
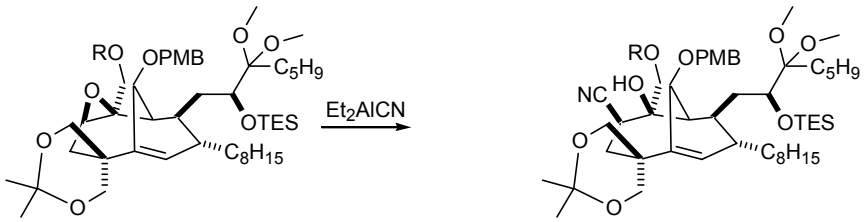
19			70[58]
20			64-91[59]
21			45[60]
22			75-90[61]
23			65[62]
24			84[63]
25			[64]
26			84[65]

27 

83[66]

28 

73[67]

29 

75[68]

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88[69]

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86[49]

32 

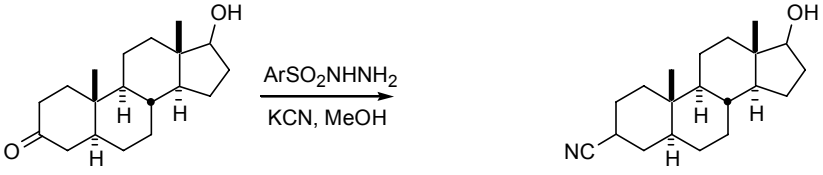
76[70]

33 

68[71]

34 

67-77[72]

35 

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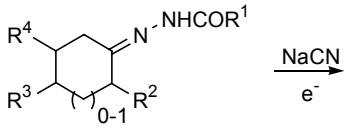
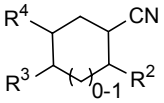
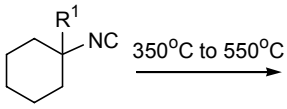
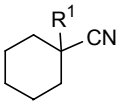
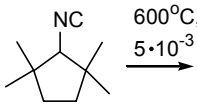
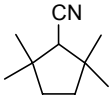
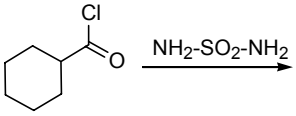
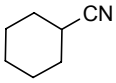
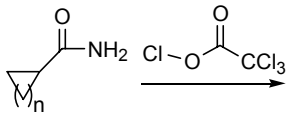
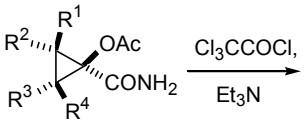
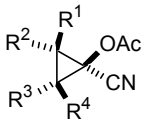
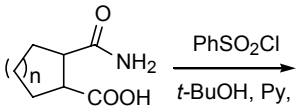
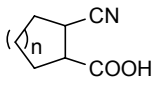
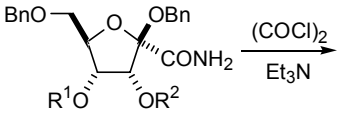
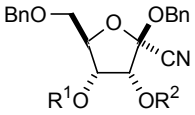
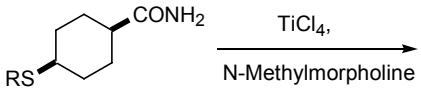
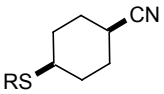
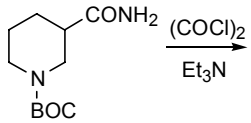
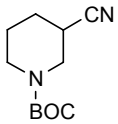
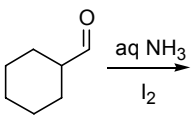
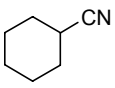
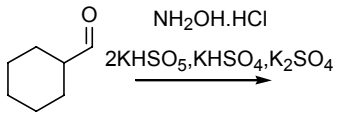
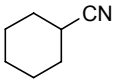
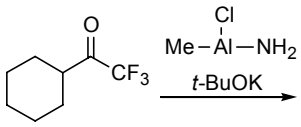
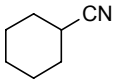
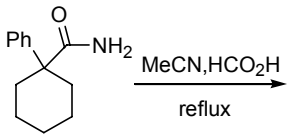
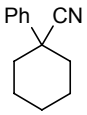
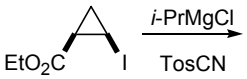
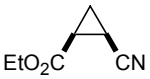
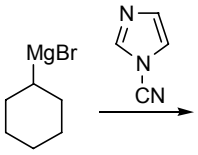
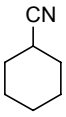
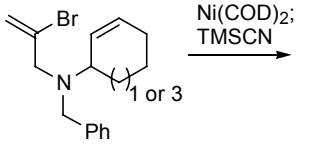
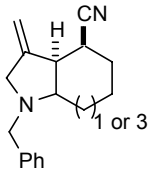
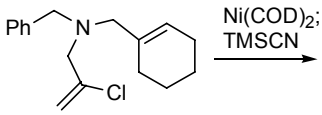
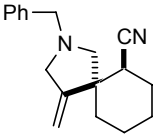
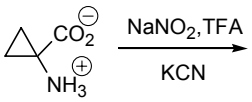
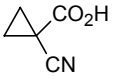
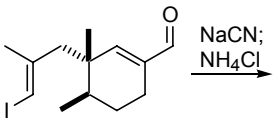
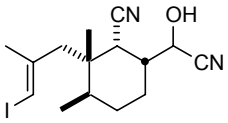
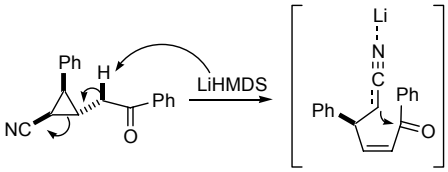
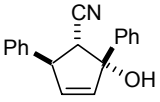
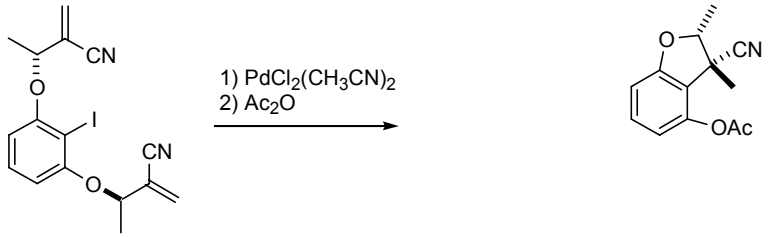
36			43-82[74]
37			80-100[75]
38			90[76]
39			95[77]
40			86-93[78]
41			81-94[79]
42			90[80]
43			94-95[81]
44			30-52[82]
45			89[81]
46			94[83]

47			70[84]
48			35[85]
49			92[86]
50			67[87]
51			90[83]
52			44-99[88]
53			84[88]
54			64[89]
55			60 for 2 steps[90]
56			45[91]

57 

51-86[92]

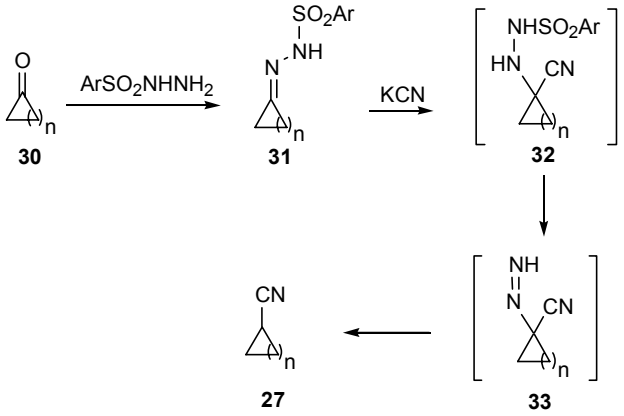
58 

81[93]

Nucleophilic cyanide cleanly opens epoxides to generate *trans*-diaxial hydroxy nitriles (Table I-1, entries 23-28). Diethyl aluminum cyanide is the reagent of choice (Table I-1, entry 23), presumably stemming from Lewis Acid-facilitated ring opening which can also be achieved with LiCN (Table I-1, entry 24). Et_2AlCN epoxide ring opening allows installation of quaternary nitriles even in the presence of acetals (Table I-1, entry 28).

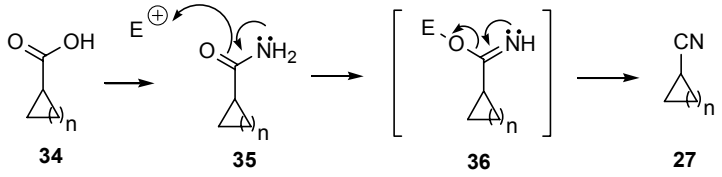
Cyclic ketones are readily homologated to nitriles with *t*-BuOK and p-toluenesulphonylmethyl isocyanide (TosMIC). The reaction is particularly effective with relatively hindered ketones (Table I-1, entries 29-33) although *t*-BuOK epimerizes substitutes adjacent to the ketone as well as the nitrile stereochemistry (Table I-1, entries 30-32). An earlier ketone homologation employs reversible addition of KCN to arylsulfonyl hydrazones giving an intermediate cyanohydrazine **32** that fragments to the nitrile via the diazo species **33** (Table I-1, entries 34 – 36, Scheme I-3). An analogous sequence is involved in the electrochemical cyanation of acyl hydrazones (Table I-1, entry 36). The rearrangement of isonitriles similarly constitutes an efficient synthesis of hindered nitriles (Table I-1, entries 37-38), although synthesizing the precursor isonitrile can require several steps.

Scheme I-3. Sulfonyl Hydrazone Cyanation of Ketones.



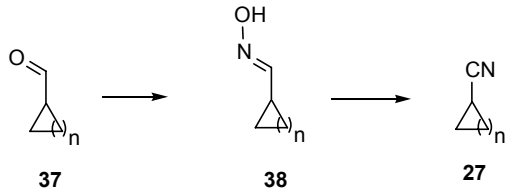
A variety of cyclic carboxylic acid derivatives are readily converted into the corresponding nitriles via amide intermediates in a reaction that tolerates numerous functional groups. The methods require conversion to the cyclic primary amide and subsequent dehydration by sequential O-activation and dehydration (**36** → **27**) (Scheme I-4).[94] An analogous sequence can be achieved with trifluromethyl ketones (**35,** OH = CF_3) where addition of methylchloroaluminum amide generates an imine (**36,** EO = CF_3) that ejects CF_3 to form the nitrile (Table I-1, entry 48).

Scheme I-4. Dehydation of Amides to Nitriles



Sequential amination and dehydration of cyclic aldehydes generates the corresponding nitriles. Conversion of the aldehyde to an intermediate oxime and dehydration is possible with a variety of mild reagents (Scheme I-5), even with ammonia through an in situ oxidation-dehydration (Table I-1, entry 46).

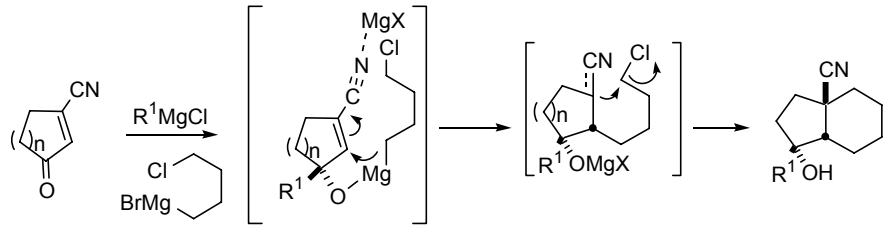
Scheme I-5. Dehydration of Aldehydes to Nitriles



37 **38** **27**

Alkyllithium and Grignard reagents react with a variety of electrophilic cyanide sources although only a few cyclic nitriles have been synthesized in this way (Table I-1, entries 50-51). In contrast, a series of nickel-induced cyclization-cyanations are particularly effective at generating an array of bicyclic nitriles. Alkylations to form bicyclic nitriles are uncommon because synthesizing the cyclization precursors often requires multiple steps. An exception is the chelation-controlled conjugate addition of ω-chloro Grignard reagents to oxoalkene nitriles **39** (Scheme I-6).[95]

Scheme I-6. Chelation-Controlled Conjugate Addition Based Annulations



39 **40** **41** **42** **43**

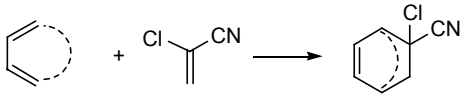
I-3-1-3. Diels-Alder Cycloaddition

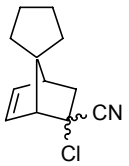
The venerable Diels-Alder reaction assembles an enormous number of cyclic nitriles. Less common, but particularly useful, are Diels-Alder reactions of α-chloroacrylonitriles that are the focus of this section. α-Chloroacrylonitrile is used extensively as a ketene equivalent in Diels-Alder reactions since ketenes are poor dienophiles.[96] A pioneering study revealed 2-chloroacrylonitrile cycloadditions to be more efficient, and more

regioselective than 2-acetoxyacrylonitrile, (Chart I-2, **51**), and with the added advantage of being commercially available. Generally 2-chloroacrylonitrile adds regioselectively (>20:1) to dienes placing the nitrile adjacent to the electron donating substitutent (Chart I-2, **52**, **54**, **57**). Typically mixtures of endo and exo isomers are obtained, although the stereochemistry of the nitrile-bearing carbon is inconsequential for subsequent hydrolyses to the corresponding ketone.

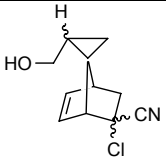
The Diels-Alder reaction between 2-chloroacrylonitrile and acyclic or exocyclic dienes affords high yields of cyclohexencarbonitriles even with sterically demanding dienes. The demanding reaction with vinyl furan to afford **64** required 1 day and 1.9 Gpa of pressure for an acceptable yield.[97] With lower pressures, or the use of 1-acetoxyacrylonitrile, lower yield with less regioselectivity was afforded. The reaction has been utilized in natural product synthesis including tabtoxinine-β-lactam and taxol (Chart I-2, **68**).

Chart I-2. Diels-Alder Reactions of α-Chloroacrylonitrile with Cyclic Dienes

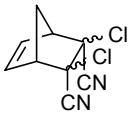




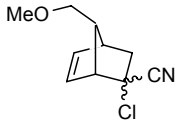
44 (90%)[98]



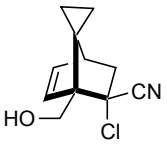
45 (98%)[99]



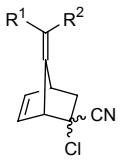
46 (100%)[100]



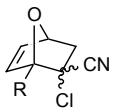
47 (90%)[101]



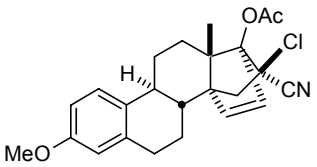
48 (60-91%)[102]



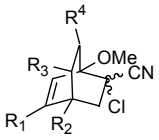
49[a] (92%)[103]



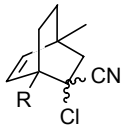
50 (55-100%)[104]



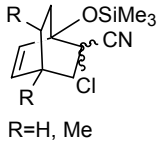
51 (83%)[105]



52 (67-81%)[106]

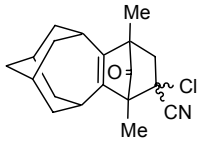


53 (71-90%)[107,108]

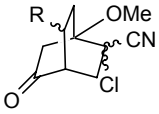


R=H, Me

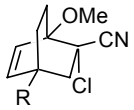
54 (97%)[109]



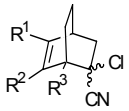
55 (88%)[110]



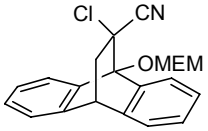
56 (48-60%)[111]



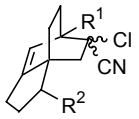
57 (50-96%)[112]



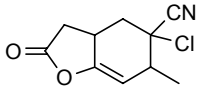
58 (82-96%)[113]



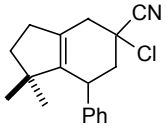
59 (98%)[114]



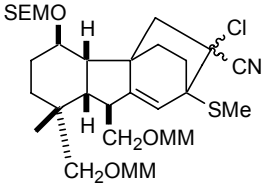
60[b] (43-93%)[115]



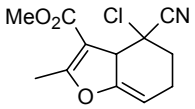
61 (60%)[116]



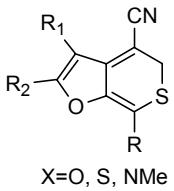
62 (85%)[117]



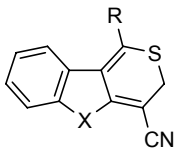
63 (65%)[118]



64 (70%)[119]



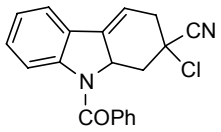
X=O, S, NMe



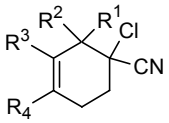
X=NMe, NCOPh

65 (44-93%)[120]

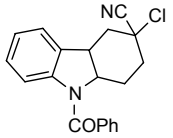
66 (48-52%)[120]



67 (69%)[121]



68 (85%)[122]



69[c] (45-51%)[123]

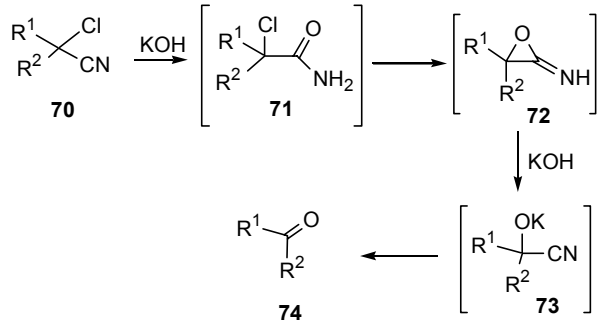
[a] A 3:1 ratio of regioisomers. [b] A mixture of regioisomers [c] A mixture of regioisomers

Furans are particularly challenging dienes that require either high pressures,[124] copper catalysts[125] or, more effectively, ZnI_2 catalysis[104] (Chart I-2, **50**), with complete conversion often requiring several weeks. Numerous cyclohexadienes react with α-chloroacrylonitrile to afford bicyclo-[2.2.0]-octenes (Chart I-2). The attraction of this

transformation stems from the prevalence of the bicyclo-[2.2.0]-octene unit in terpenoids and the rapid synthesis of alkoxycyclodienes through the Birch reduction of substituted anisoles. Unconjugated cyclohexadienes are rapidly isomerised to the conjugated dienes by base[126] and acid,[127] including the acidic silica sites on the surface glassware,[128] allowing sequential Birch reduction-Diels-Alder cycloaddition without prior isomerization.[129] Not surprisingly, the approach has been employed in total syntheses of several natural products: antheridic acid, modhephene and hinesol (Chart I-2, **57**, **60**, **63** respectively).

Cyclic 2-chloronitriles are usually hydrolyzed to the corresponding ketone with base,[130] although multi-step sequences are still sometimes required.[131] The KOH hydrolysis mechanism is highly unusual in proceeding through the α-chloroamide **71** (Scheme I-7) that most likely cyclizes to the imino oxirane **72**, fragments to the deprotonated cyanohydrin **73**, and ejects cyanide to form the ketone.[132] In some instances the α-chloroamide[133] **71** and the corresponding chloroacid have been isolated[131].

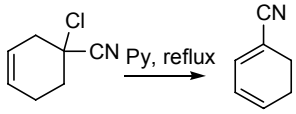
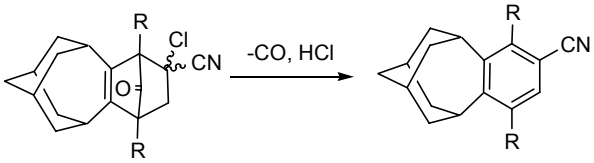
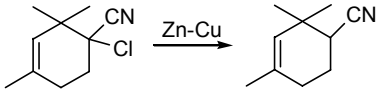
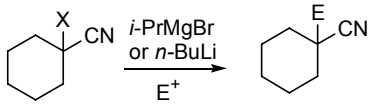
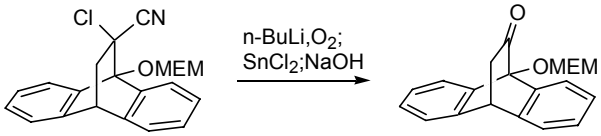
Scheme I-7. Hydrolysis Mechanism of α-Chloronitriles

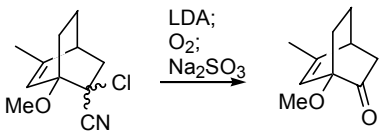
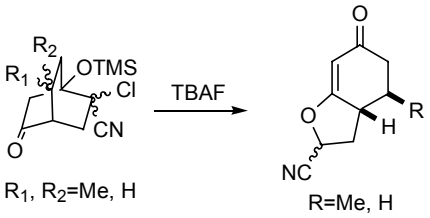
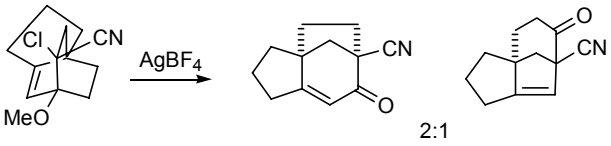
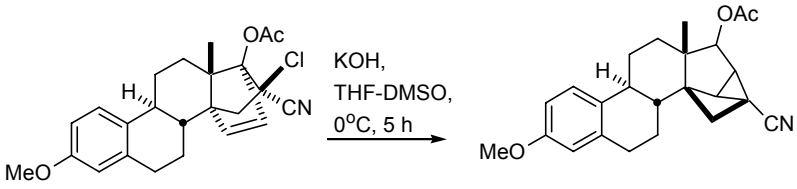
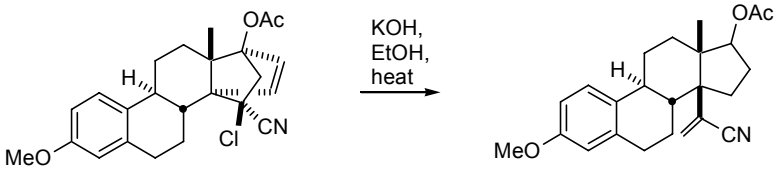


Cyclic α-halonitriles are generally precursors to ketones but also provide access to functionalized nitriles. Base- or CO-induced elimination affords the unsaturated nitriles (Table I-2, entries 1 and 2) while reduction with zinc-copper couple gives the parent

nitrile that may subsequently be deprotonated and exposed to oxygen in an indirect route to the corresponding ketone (Table I-2, entry 3). Alternatively treatment of α-chloro- or α-bromonitriles with BuLi, or more effectively, *i*-PrMgBr affords metallated nitriles that alkylate a range of electrophiles (Table I-2, entry 4) explaining the previously perplexing conversion of α-chloronitriles to ketones with BuLi[138] or LDA[139] (Table I-2, entries 5, 6) and oxygen. Several intriguing reactions cause structural reorganizations of α-chloronitriles (Table I-2, entries 7-10).

Table I-2. Miscellaneous Transformations of α-Chloronitriles

Entry	Reaction and Condition	Yield (%)
1		72[134]
2		76-86[135]
3		98[136]
4		52-82[137]
5		58[138]

6		70[139]
7		42-89[140]
8		95[141]
9		90[142]
10		69[142]

I-3-2. Alkenenitrile Syntheses

Cyclic alkenenitriles are ideal precursors to substituted alkanenitriles. Synthesizing cyclic alkenenitriles from acyclic precursors is attended by the inherent difficulty of performing an efficient cyclization-olefination sequence in a single synthetic operation. Intramolecular aldol-type reactions efficiently access cyclic alkenenitriles from aliphatic and aromatic oxonitriles (Table I-3, entries 1-5). A related strategy employs intramolecular Wittig condensation either by unmasking an aldehyde, or Wittig formation in situ (Table I-3, entries 6-8).

Most cyclic alkenenitriles are synthesized from cyclic ketone precursors by conversion to cyanohydrins and a subsequent elimination (Table I-3, entries 10-16). Although cyanohydrin, and related eliminations (Table I-3, entry 12) are not regioselective, the ketone can be regioselectively converted to an enol triflate, and coupled with LiCN (Table I-3, entry 20).

A diverse array of cyclic nitriles are generated from the corresponding nitro compounds (Table I-3, entry 22), that are prepared in a Knoevenagel condensation before nitromethane and a cyclic ketone. Mechanistically, deprotonation of the allylic nitro compound **75**, O-acylation of n-BuNCO, and elimination, generates the nitrile oxide **76** in situ, which is reduced with t-BuNC to afford the unsaturated nitrile **77** (Scheme I-8). Several isolated syntheses of cyclic alkenenitriles have emerged (Table I-3, entries 23-29) although the generality of these methods remains unexplored.

Scheme I-8. Nitrile Synthesis from Allylic Nitro Compounds

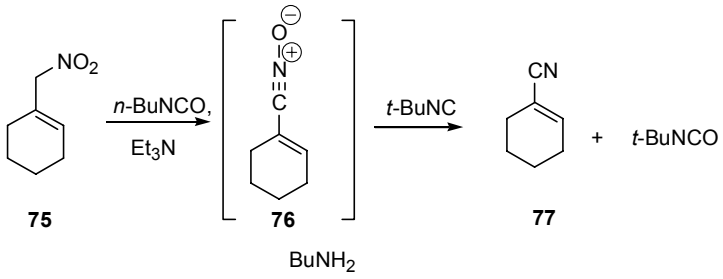
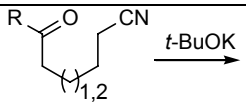
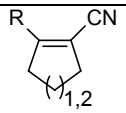
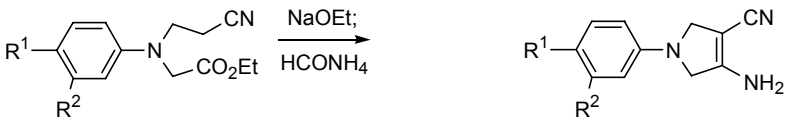
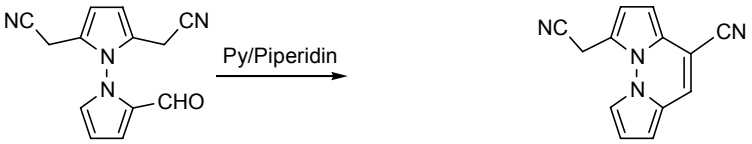
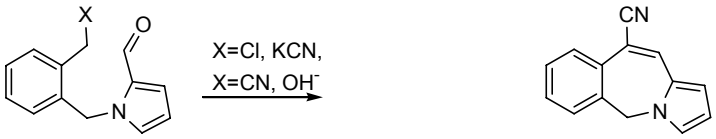
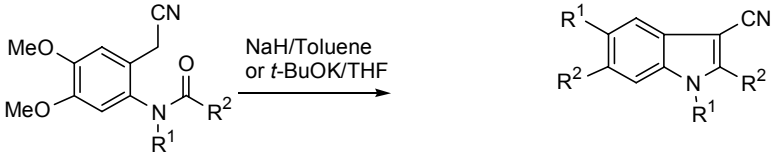
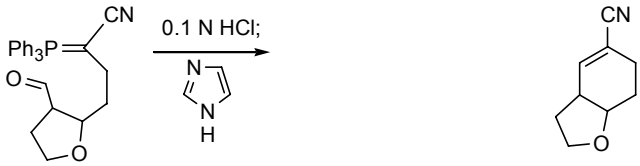
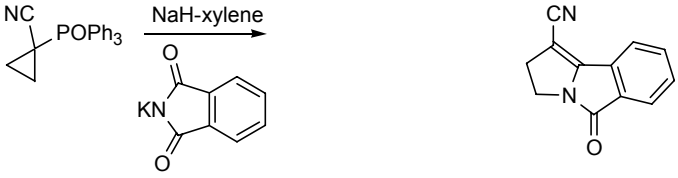
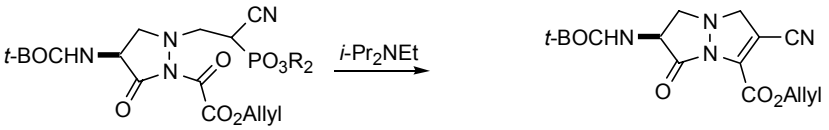
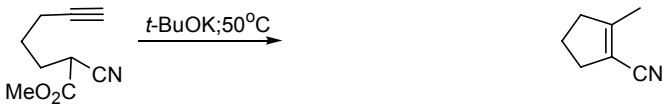
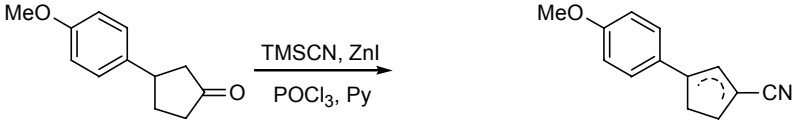
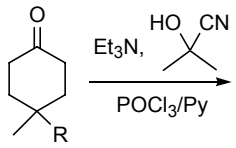
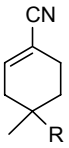
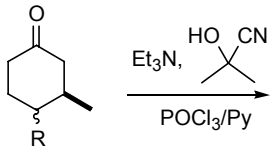
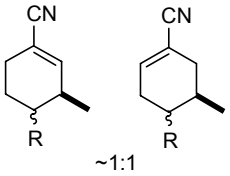
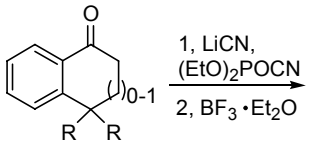
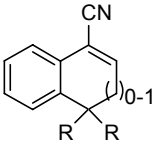
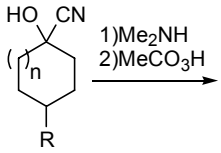
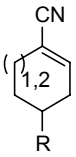
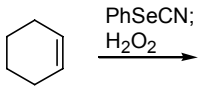
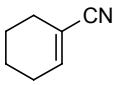
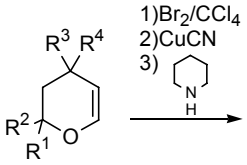
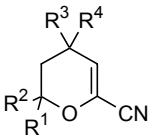
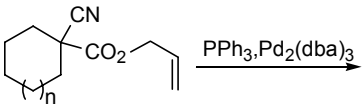
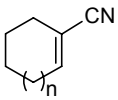
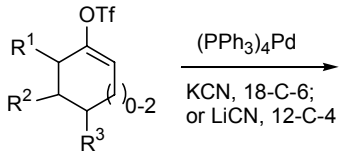
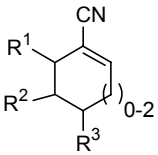
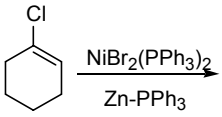
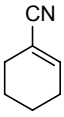
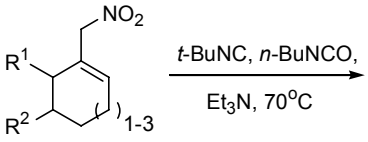
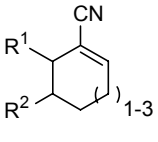
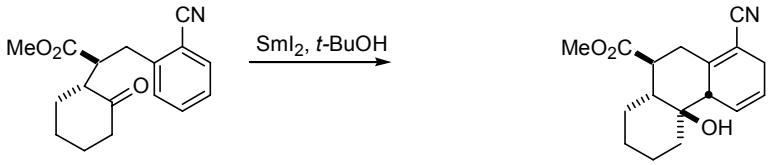
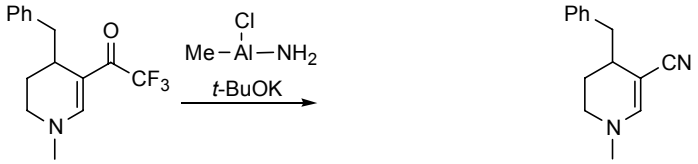
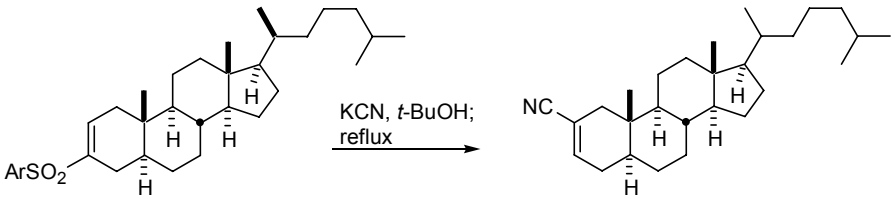
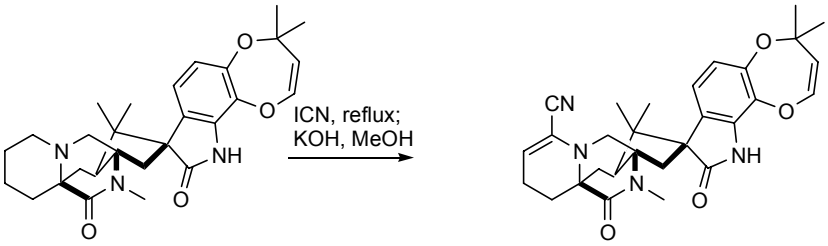


Table I-3. Alkenenitrile Syntheses

Entry	Reaction	Cyclic Alkenenitrile	Yield (%)
1			60-79[143]

2			50[144]
3			80[145]
4			44-88[146]
5			61-90[147]
6			71[148]
7			87[149]
8			25 for 2 steps[150]
9			86[151]
10			57-76[152]
11			92[153]
12			96[154]

13			80[155]
14		 ~1:1	52-89[156]
15			61-94[157]
16			38-56[158]
17			89[159]
18			63-93[160]
19			78-81[161]
20			59-89[162]
21			92[163]
22			57-82[164]

23			60[165]
24			91[166]
25			42[167]
26			58[168]
27			34-69[169]
28			60[170]
29			81[171]

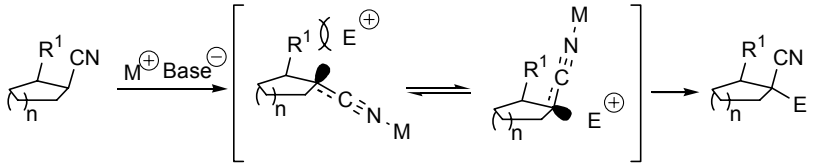
I-4. Alkylations of Cyclic Nitriles

I-4-1. Stereoselective Alkylations of Alkanenitriles

Metallated nitriles are powerful nucleophiles capable of forming new C-C bond in the most sterically demanding alkylations. In fact, alkylations of cyclic metallated nitriles

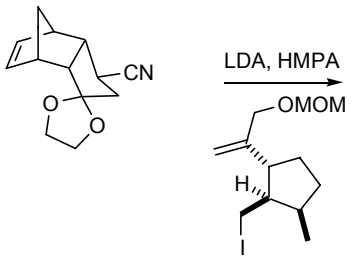
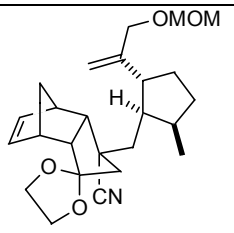
necessarily install a new quaternary center. Installation of hindered stereocenters is facilitated by the small size of the nitrile group that readily occupies the sterically most hindered position, eclipsing adjacent substituents (Scheme I-10, **80**), to provide the sterically most accessible trajectory for the incoming electrophile. The focus of this section, are the highly unusual stereoselectivities of cyclic nitrile alkylations attending formation of quaternary stereocenters.

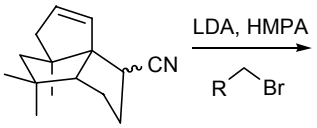
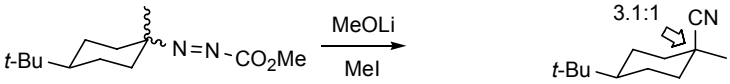
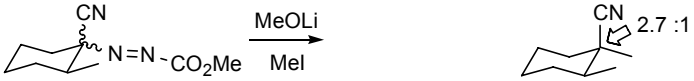
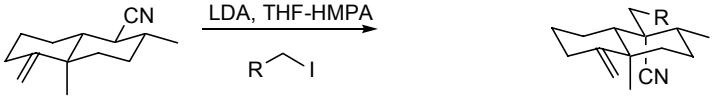
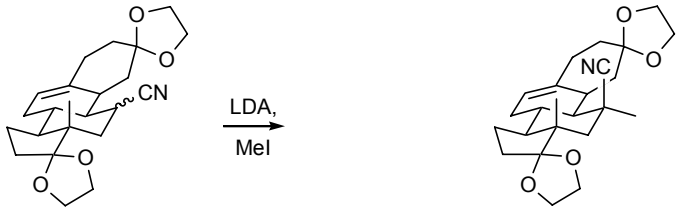
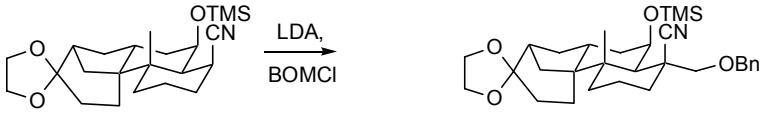
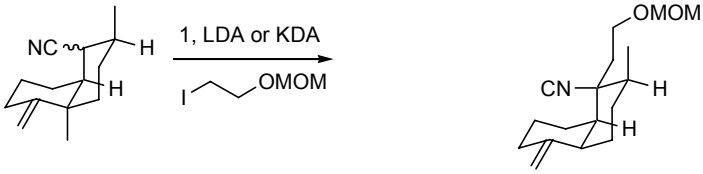
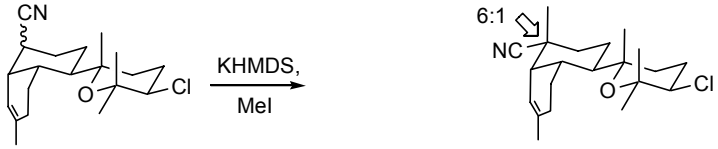
Scheme I-10. Stereoselective Alkylations of Cyclic Nitriles



Few stereoselective alkylations of cyclic 5-membered nitriles are known (Table I-4, entries 1-2). In each instance the electrophile approaches from the more accessible concave face concommitently installing the small nitrile group on the more sterically demanding convex face (Table I-4, entries 1 and 2). Forming the particularly hindered, contiguous quaternary-quaternary, stereocenters in the triquinane nitrile (Table I-4, entry 2) was a strategic step during the synthesis of (±) laurenene.[151]

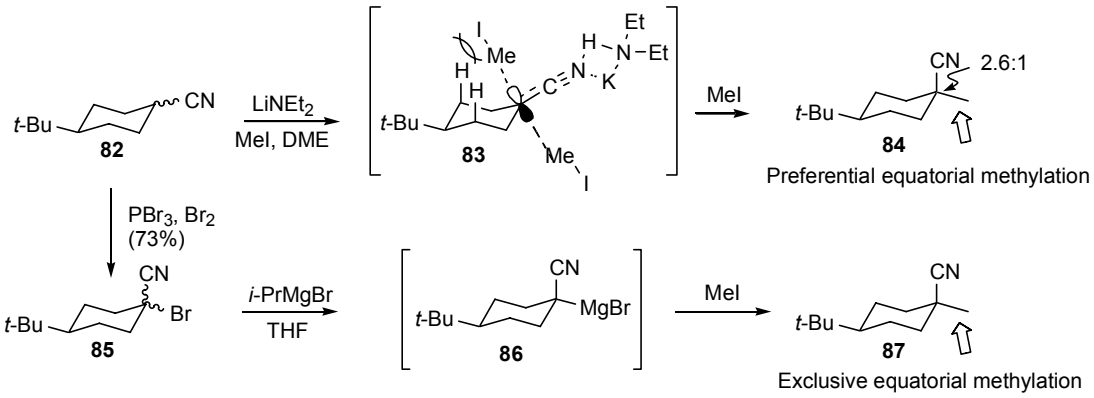
Table I- 4. Stereoselective Alkylation of Alkanenitriles

Entry	Reaction and Condition	Product	Yield (%)
1			55-67[172]

2		62-83[153]
3		82-96[173]
4		83[174]
5		84[175]
6		63[175]
7		97[176]
8		80[177]
9		90[178]
10		88[179]
11		91[180]
12		89[181]
13		79-93[182]
14		83[183]

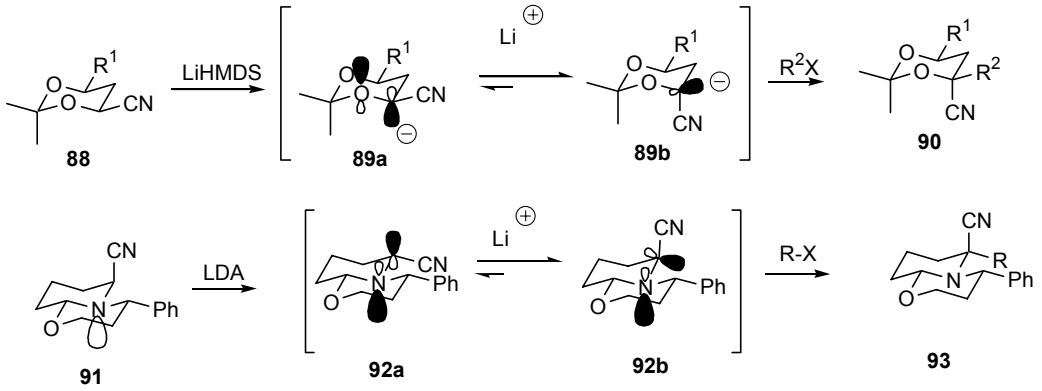
Pioneering alkylations with the conformationally constrained nitrile **82**[173] established a modest preference for equatorial alkylation in 6-membered carbonitriles (Scheme I-11, **82** → **84**). Deprotonating **82** with $LiNEt_2$ generates the N-metallated, planar nitrile **83** in which approach from the axial direction is modestly disfavored by steric interactions with the axial protons. Analogous levels of stereoselectivity are obtained in alkylations of constrained, unhindered nitriles (Table I-4, entry 6) and are comparable to the methylation selectivity of the corresponding planar enolate (5.7:1).[173] As the steric demand on the β-face increases, often from axial methyl substituents, alkylation occurs almost exclusively from the equatorial direction which has been extensively employed in terpenoid syntheses (Table I-4, entries 7-11). Analogously, α-substitution on relatively unhindered nitriles promotes alkylation from the axial direction (Table I-4, entry 14). Selective equatorial alkylation of sterically unbiased cyclohexanecarbonitriles occurs with C-metallated nitriles. Bromine-magnesium exchange of bromonitrile **85** causes equilibration to a single C-magnesiated nitrile that alkylates exclusively from the equatorial direction (**85** → **87**).[184]

Scheme I-11. Alkylation Preferences of C- and N-Metallated Nitriles



Extremely high preferences for equatorial alkylation are exhibited with cyano-1,3-dioxanes[185] and α-aminonitriles.[186] Cyano-1,3-dioxanes selectively alkylate a broad range of electrophiles from the equatorial direction (Scheme I-12) despite having minimal steric bias when compared to the carbon analog **82** (Scheme I-11). The stereoselectivity correlates with a distinct preference for a stereoelectronically controlled alkylation of the pyramidal nitrile anions **89b** and **92b** which avoids the anti-anomeric destabilization in **89a** and **92a** for alkylations of cyano-1,3-dioxanes and N-cyanomethyloxazolidines **91** respectively.

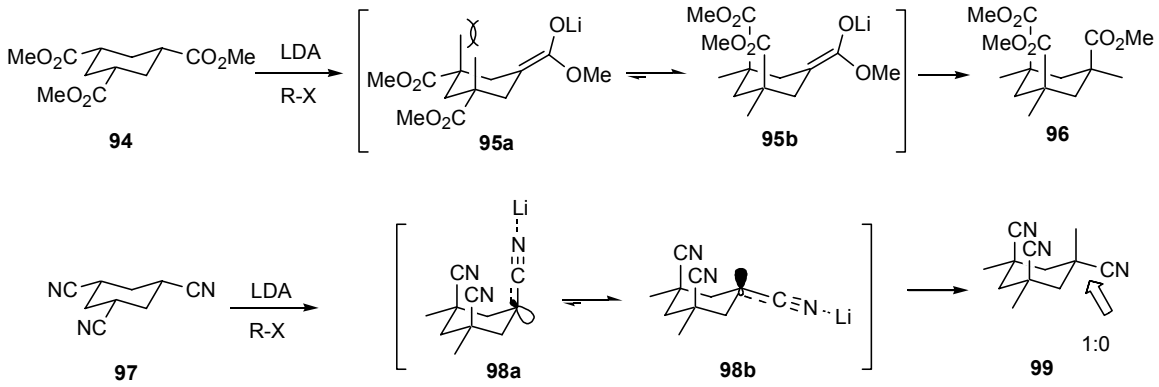
Scheme I-12. Stereoelectronically Controlled Nitrile Anion Alkylations



Distinct alkylation stereoselectivities for nitriles and carbonyl compounds are encapsulated in the comparative alkylations of trisubstituted cyclohexanes (Scheme I-13).[187] Exhaustive methylation of the tri-ester **94** affords the all *cis*-ester **96** whereas the corresponding nitrile **97** affords **99** where the final methylation occurs exclusively from the axial direction. Alkylation of the most stable ester enolate conformer **95b** preferentially occurs from an equatorial trajectory whereas the pyramidal, metallated nitrile **98** can readily access the two conformations **98a** and **98b,** because of the small

size of the nitrile group. Alkylation with small electrophiles, such as MeI, occurs from the axial direction to afford **99** whereas addition of a large electrophile, such as Ph_2PCl, experiences a severe steric interaction with the axial nitriles and therefore alkylates exclusively from the equatorial direction from **98a**.

Scheme I-13. Stereodivergent Nitrile and Ester Alkylations



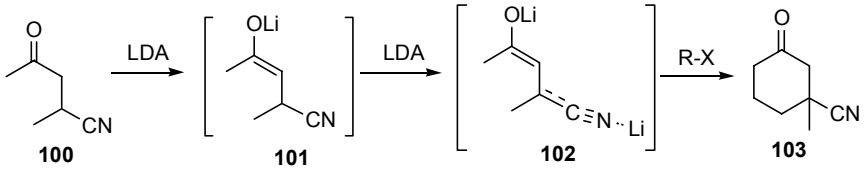
Deprotonating sterically hindered nitriles is often challenging with LDA (Table I-4, entry 13) For example, during the synthesis of palauolide,[176e,188] LDA was found to deprotonate the β-nitrile but not the β-epimer unless HMPA was added. Nitriles that are resistant to deprotonation[189] with LDA-HMPA combinations are often successfully deprotonated[190] with the base prepared from *t*-BuOK, *i*-Pr_2NH, and BuLi (KDA)[191] (Table I-4, entry 13).

I-4-2. Alkylations of Dianionic Nitriles

Nitriles containing additional protic functionality are smoothly deprotonated in the presence of excess base, affording formal dianions. Double deprotonation of this type was first demonstrated with β-ketonitriles[192] where deprotonation at -70 °C allows

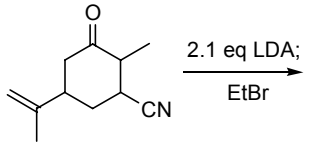
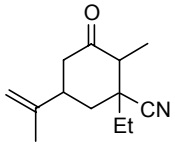
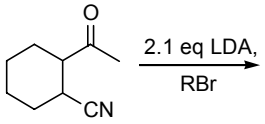
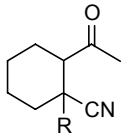
enolate formation without expulsion of cyanide prior to a second deprotonation adjacent to the nitrile (Scheme I-14). Monoalkylation of these dimetallated nitriles is highly selective with no double alkylation even in the presence of excess electrophile. The greater reactivity of the metallated nitrile correlates with the significantly higher pKa of nitriles as compared to ketones (ΔpKa = 5-10).[193] The remarkable regioselectivity in this alkylation has been harnessed in a route to bruceantin where the metallated nitrile controlls formation of two stereocenters[194] in a remarkably efficient installation of contiguous quaternary-tertiary stereocenters (Table I-5, entries 3 to 4).

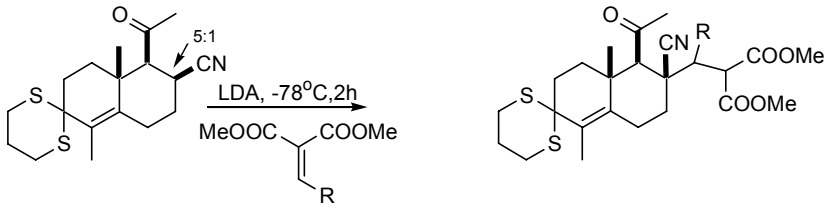
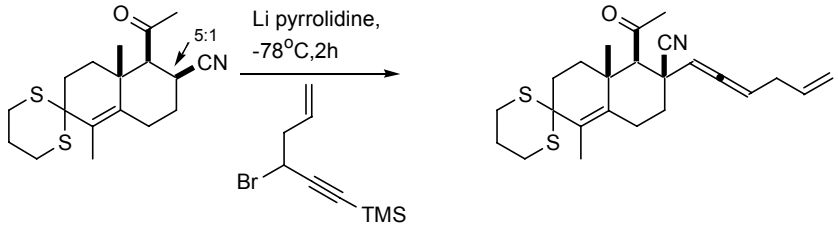
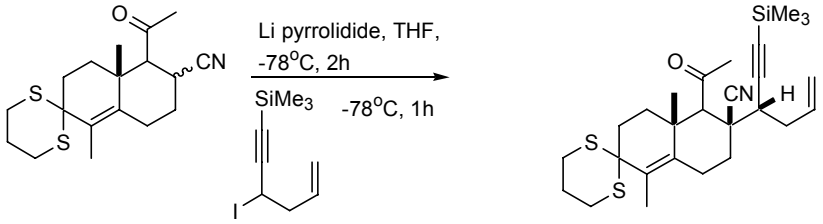
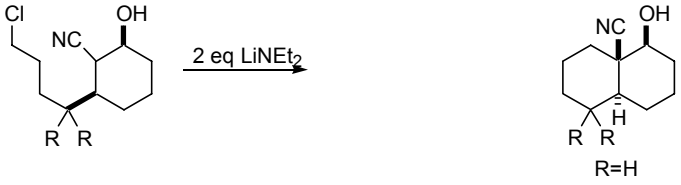
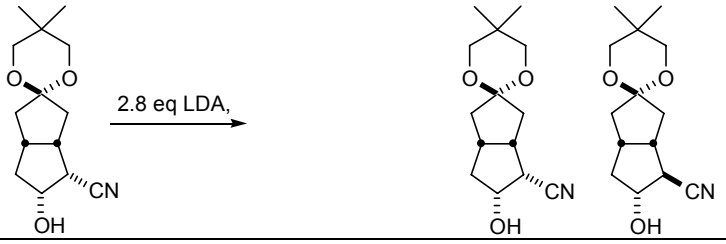
Scheme I-14. Dianionic Alkylations



The double deprotonation of hydroxynitriles generates particularly reactive metallated nitriles that selective cyclize to *trans*-decalins or reprotonate to provide a means for equilibrating the nitrile-bearing carbon (Table I-5, entries 6-7).

Table I-5. Alkylations of Dianionic Nitriles

Entry	Reaction and Condition	Product	Yield (%)
1			74[195]
2		 R=Et,Bu	85-86[195]

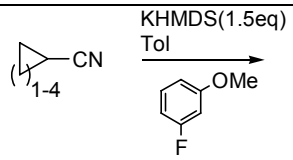
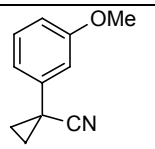
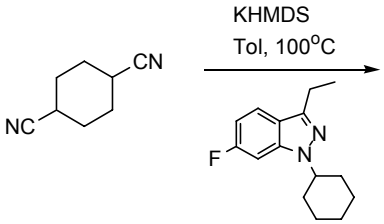
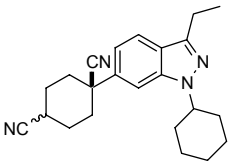
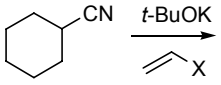
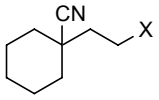
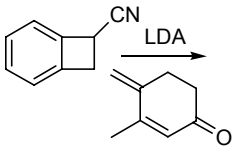
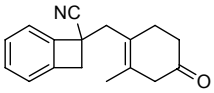
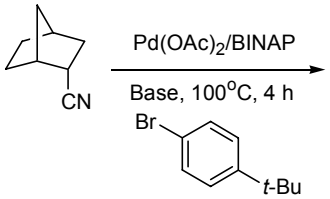
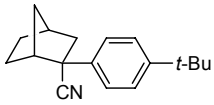
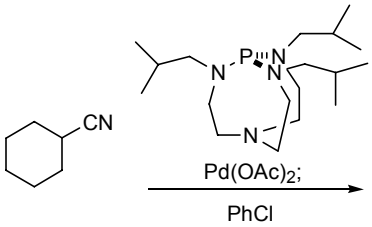
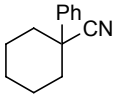
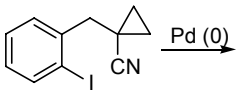
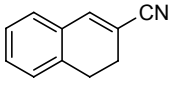
3			49-77[194]
4			80[194]
5			93[196]
6			78-85 [197]
7			90 (1:1)[198]

I-4-3. Alkylations with sp2-Hybridized Electrophiles

Nucleophilic additions of enolates to aryl- or vinyl halides are particularly challenging[199] reflecting the instability of enolates and the carbonyl derivative to the forcing conditions often required. Metallated nitriles are particularly well-suited since the nitriles tolerate alkyllithiums and are not prone to self condensation, traits that have been exploited in benzyne-based α-arylations. Recently a mechanistically distinct α-arylation of cyclic nitriles was achieved with fluorine-substituted aromatic electrophiles (Table I-6, entries 1- 2). The high nucleophilicity of metallated nitriles has been exploited in the direct

addition to activated alkenes (Table I-6, entries 3-4) and to aryl bromides with palladium catalysis (Table I-6, entries 5-7).

Table I-6. Nitrile Alkylations with sp2-Hybridized Electrophiles.

Entry	Reaction and Condition	Nitrile	Yield (%)
1			47[200]
2			77[201]
3		 X=Ph, $SiPh_3$, SPh	75-91[202]
4			81[203]
5			69[204]
6			81[205]
7			58[206]

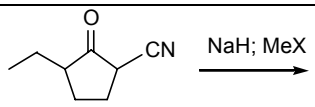
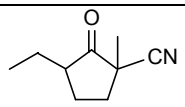
I-4-4. Alkylations of Oxonitriles

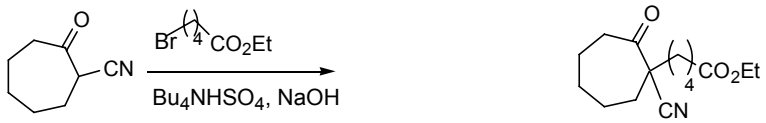
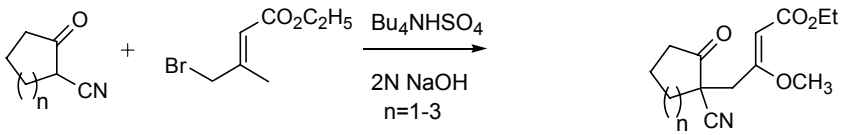
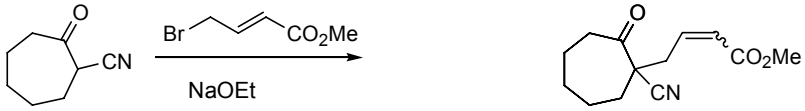
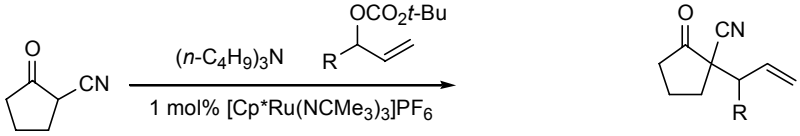
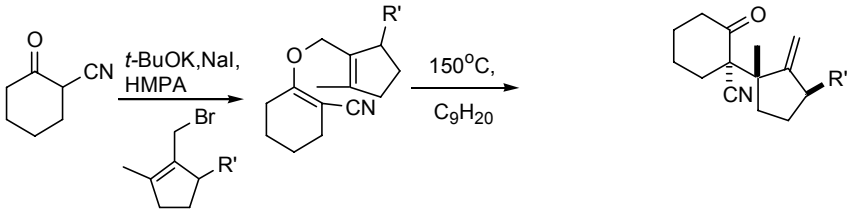
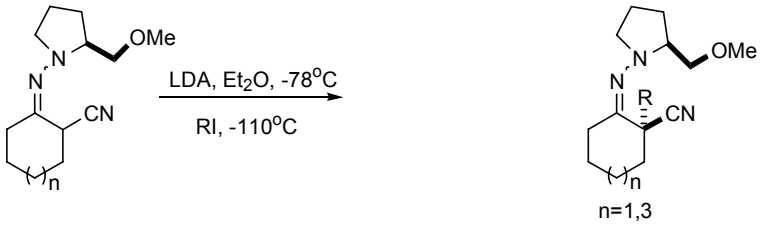
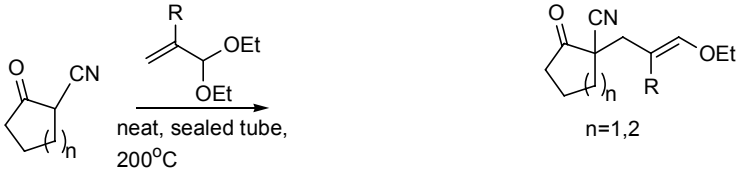
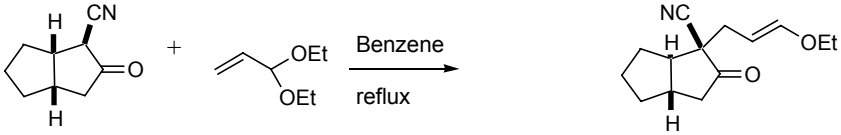
Oxonitrile alkylations were first developed during the emergence of modern synthesis. The high acidity of cyclic oxonitriles allows deprotonation with metal hydroxides[207] although many alkylations have employed stronger bases, presumably for convenience (Table I-7). Soft alkyl halides selectively alkylate on carbon even in the presence of electrophilic esters (Table I-7, entry 4). Allylic halides alkylate at the sterically less congested carbon through direct S_N2 displacement (Table I-7, entries 4-5) although the regioselectivity can be reversed with ruthenium catalysis (Table I-7, entry 6).

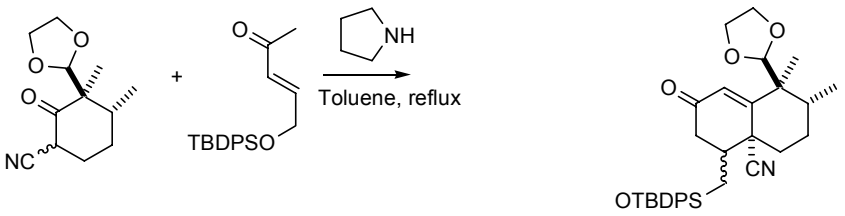
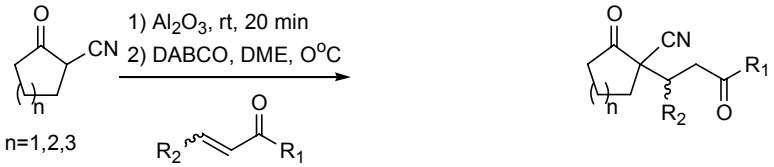
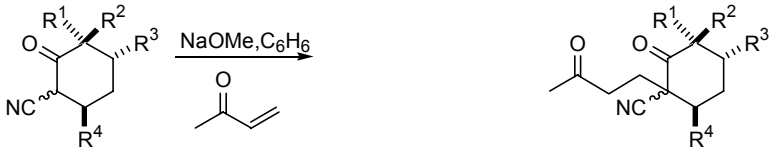
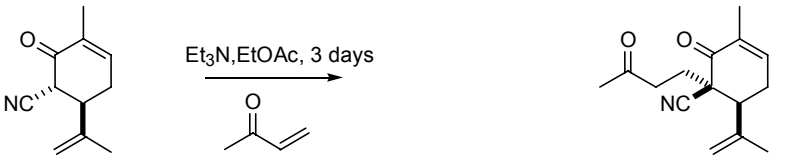
Alkylation of the ambident nucleophile is possible on oxygen or carbon, though for most endeavors C-alkylation is preferable. A clever exception was O-alkylation of an allylic electrophile to generate an alkyl vinyl ether en route to a stereoselective Claisen rearrangement (Table I-7, entry 7). Enantioselective alkylation is achieved by converting oxonitriles to the proline-derived hydrazone that alkylates with exceptional diastereoselectivity (Table I-7, entry 8).

Oxonitriles are excellent nucleophiles for conjugate additions and have been used extensively for Robinson annulations (Table I-7, entries 12-16). Detailed mechanistic studies indicate that the initial oxonitrile alkylation occurs from the axial direction with cyclization affording an axially oriented nitrile.

Table I-7. Oxonitrile Alkylations

Entry	Reaction and Condition	Product	Yield (%)
1			74[208]

2		80-85[209]
3		62[210]
4		80-82[211]
5		87[210]
6		85-98[212]
7		44-79[213]
8		52-80[214]
9		71-81[215]
10		68-71[216]
11		70[215]

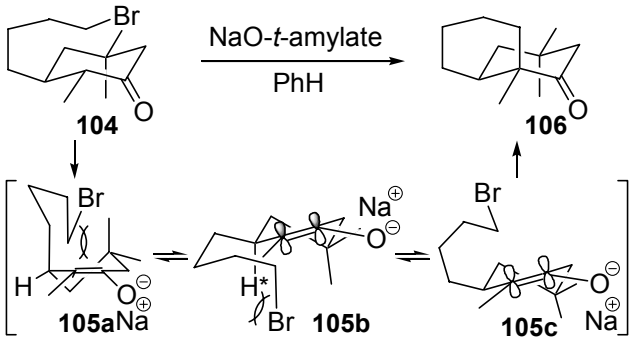
12			65[217]
13			74-98[218]
14			76-95[219]
15			78[218]
16			53[220]
17			94[221]
18			39-72[222]

I-5. Stereoselective Cyclizations

I-5-1. Alkanenitrile Cyclizations

Cyclic nitriles and ketones cyclize with very different stereoselectivities reflecting fundamental stabilization differences between metallated nitriles and enolates.[20a,] Cyclization of the ketone **104** to the *cis*-decalin **106** cleverly identified a required orientation of the nucleophilic enolates π-orbitals[223] directly toward the electrophilic carbon-bromine bond for an S_N2 displacement through conformer **105c** (Scheme I-15).

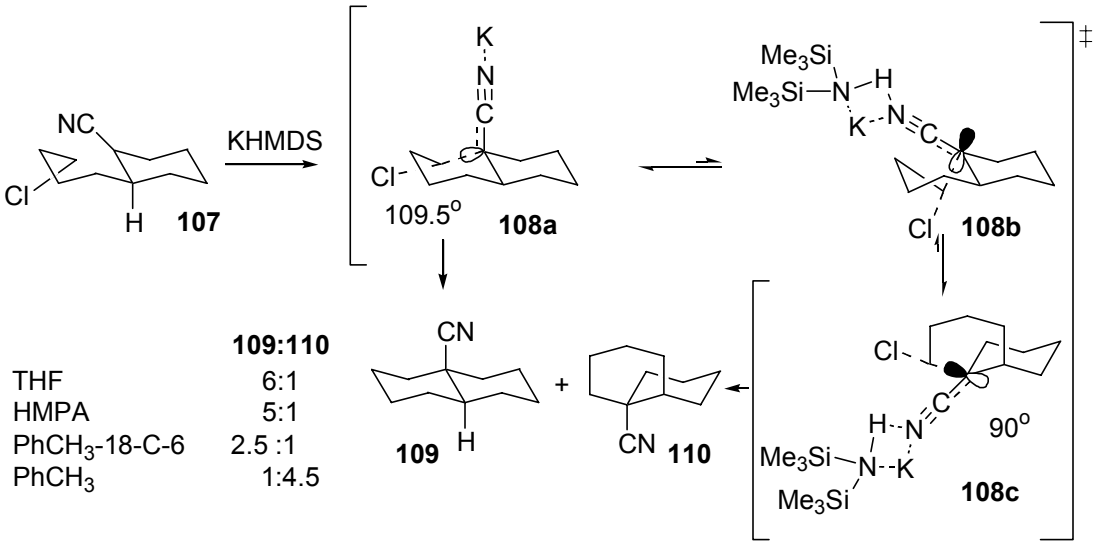
Scheme I-15. *cis*-Selective Enolate Cyclizations



The contrasting preference of metallated nitriles to cyclize to *trans*-decalins was first identified more than 30 years ago[224] and has been analyzed in detail for the parent decalin cyclization (Scheme I-16). The stereoselectivity in THF correlates with cyclization through a pyramidal transition state **108a** in which the metallated nitrile directly orients the pyramidal, nucleophilic orbital toward the electrophilic chloromethylene carbon. Changing the solvent from THF to toluene reverses the stereoselectivity by generating a planar amine-complexed metallated nitrile. Subsequent cyclization through transition state **108c** occurs in order to relieve the twisting induced in **108b** that accompanies the

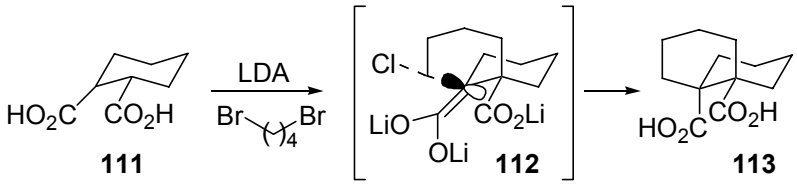
change in the metallated nitrile geometry from pyramidal to planar. Disrupting the complexation through the addition of 18-crown-6 restores the preference for the *trans*-decalin **109**, though the selectivity is not as high as in the better donor solvent THF (Scheme I-16).

Scheme I-16. Stereodivergent Cyclizations of Metallated Nitriles



Preferential cyclization of planar metallated nitriles to *cis*-decalins correlates with the cyclization of planar enolates derived from diacids (Scheme I-17).[225] Deprotonating the diacid **111**, in THF, affords exclusively the *cis*-decalin **112** through cyclization of the exocyclic enolate **113** that more closely parallels the exocyclic metallated nitrile **108** (Scheme I-16).

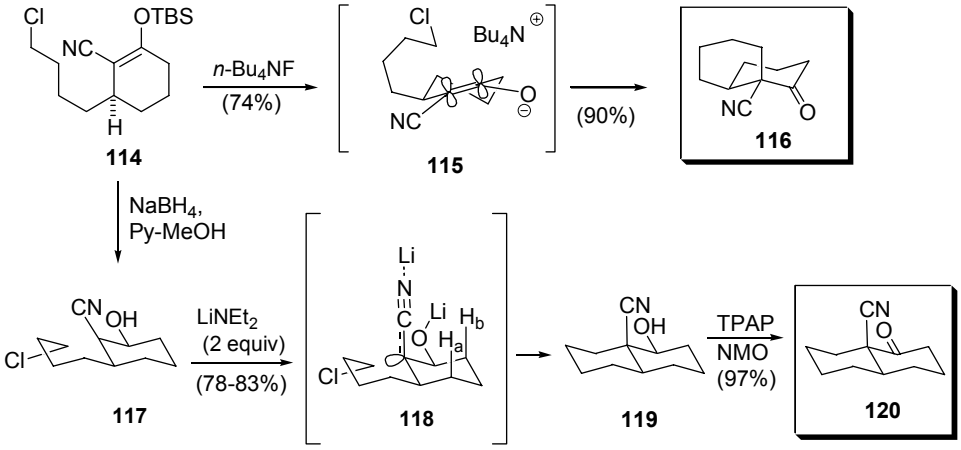
Scheme I-17. Cyclization of Diacids to *cis*-Decalins



I-5-2. Oxonitrile cyclizations

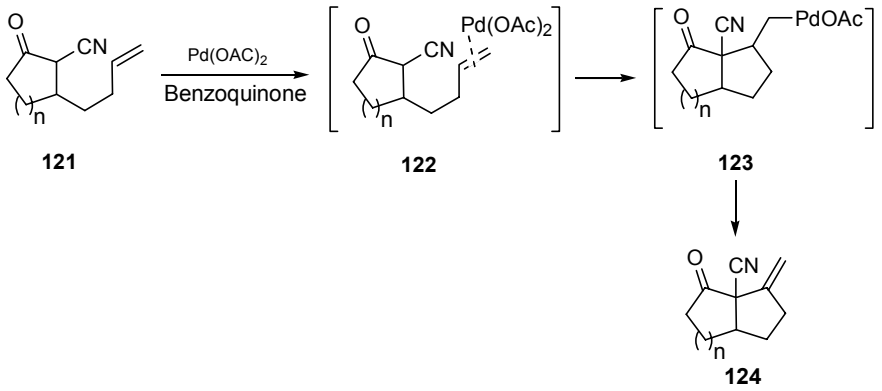
Oxonitrile cyclizations are particularly attractive since the opportunity exists for selective cyclization to *cis*- or *trans*- decalins from the same precursor. Cyclization of the oxonitrile enolate **115** generates the *cis*-decalin **116** exclusively (Scheme I-18). Reduction of **114** to the corresponding β-hydroxy nitrile **117,** and lithium diethylamide-induced cyclization, gives exclusively the *trans*-decalin **119** that was oxidized to the *trans*-decalone **120**, diastereomeric to **116**. The stereodivergent cyclizations stem from trajectory differences enforced by the planar enolate **115** and the pyramidal, metallated nitrile **118.** The selective cyclization of the same nitrile precursor **114** to both *cis* and *trans* decalins highlights the complimentarity of oxonitrile, and metallated nitrile cyclizations.

Scheme I-18. Stereodivergent Oxonitrile Cyclizations



Oxonitriles bearing a pendent δ-alkene are readily cyclized in an efficient oxidation cyclization (Scheme I-19).[226] Facile enolization followed by an intramolecular Heck reaction generates **123** that presumably undergoes reductive elimination to afford the bicyclic oxonitrile **124**.

Scheme I-19. Oxonitrile Cyclization



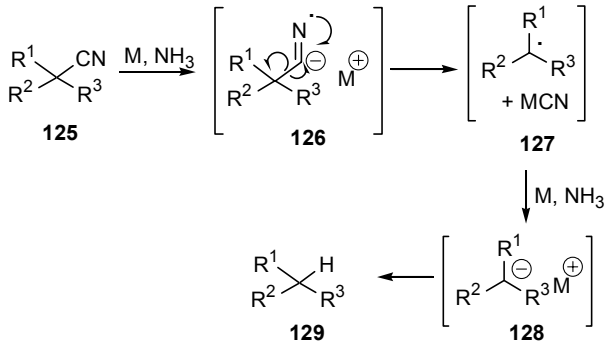
I-6. Decyanation of Cyclic Nitirles

The versatility of nitrile-based alkylations is enhanced through the facile removal of nitriles by several complementary strategies. Decyanation can be tuned to selectively give alkanes, alkenes, or, in instances where the nitrile is flanked by an adjacent electron-withdrawing group, a reactive nucleophile for subsequent alkylation.

I-6-1. Decyanation to Alkanes

Decyanation is most frequently achieved by dissolving metal reduction. The reaction is usually most efficient in the absence of a proton source and depends modestly on the reducing ability of the metal-ammonia combination, generally with increasing yields in the series Li, Na, K. Nitrile reduction proceeds through a series of electron transfers initially generating the free radical intermediate **126** that ejects cyanide with concommittant formation of radical **127** that is further reduced to a carbanion **128** and ultimately protonated (Scheme I-20).

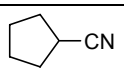
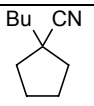
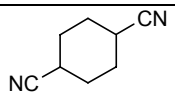
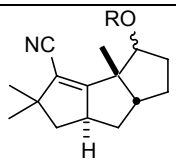
Scheme I-20. Dissolving Metal Decyanation Mechanism



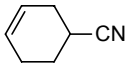
Decyanation by electrochemical reduction has the attendant advantage in affording hydrocarbons in 60-80% yield, even with secondary nitriles that generally react poorly with metals in ammonia. Alternatively, the use of potassium and dicyclohexyl-18-C-6 in toluene (Chart I-3, entry 10) or K in HMPA (Chart I-3, entry 15) is effective for the decyanation of primary and secondary nitriles.

Despite the attraction of decyanation, the reaction has only once been used in synthesis where electrolysis was found to trigger reduction and decyanation in 45% yield en route to hirsutene (Chart I-3, entry 11). Mechanistically distinct from the metal reduction and electrolysis reactions is the reduction with $Fe(acac)_3$-Na that is postulated to involve oxidative addition of reduced iron into the C-CN bond followed by proton abstraction from the ligand (Chart I-3, entries 5, 6).

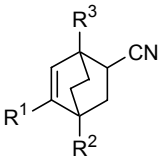
Chart I-3. Decyanation of Cyclic Nitriles to Alkanes[a]

			
1, (D. 77%)[227]	**2**, (G. 70%)[228]	**3**, (C. 49%)[229]	**4**, (E.28%)[230, b] (B.45)[231]

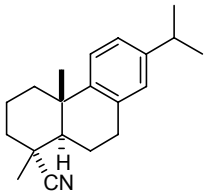
5, (B. 72)[231]



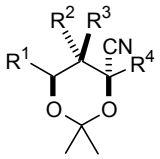
6, (D. 80%)[227]



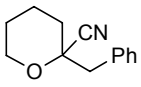
7, (E. 26-97%)[232]



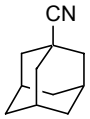
8, (A.95%)[233] (B. 60-80%)[234]



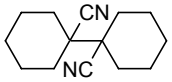
9, (A. 63-95%)[232]



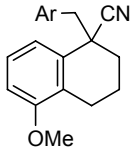
10, (B. 57%)[231]



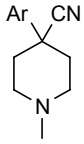
11, (F. quant)[232] (B.73%)[235]



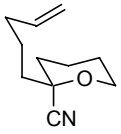
12, (A.95%)[234] (B.70%)[234] (C.80%)[234, 236] (D.76%)[236]



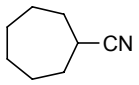
13, (I. 33-100%)[237]



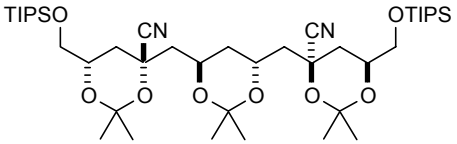
14, (H. 75%)[238]



15, (E. 76%)[239]



16, (B.60-80%)[234]



17, (E. 69%)[240]

[a]A)Na, NH_3; B)electrolysis; C)Li, $EtNH_2$; D)$Fe(acac)_3$, Na; E)Li, NH_3; F)K, PhMe, Dicyclohexyl-18-c-6; G)K, HMPA; H)Na, ROH; I)RLi; J)$LiAlH_4$; K) Bu_3SnH. [b] Conjugate reduction accompanies decyanation.

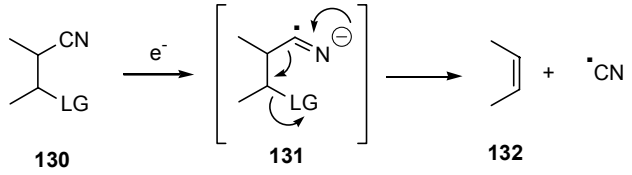
I-6-2. Decyanation of Cyclic Nitriles to Alkenes

Nitriles exhibit pseudohalide reactivity in being eliminated through loss of HCN. The elimination of cyanide is commonly encountered in the reversible formation of ketones from cyanohydrins which represents a valuable one-carbon cleavage of nitriles by prior

α-oxygeneration (Table I-8, entries 1-2). Elimination of HCN generally requires a carbonyl or olefinic group adjacent to the proton being abstracted, allowing elimination with modest bases *t*-BuOK, KOH, triethylamine, and DBU. A related elimination of β-trimethyl stannyl nitriles is triggered by addition of MeLi that most likely generates the stannate which ejects cyanide to install a methylene group.

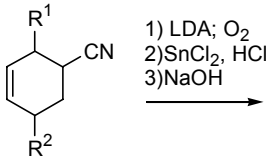
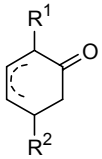
A mechanistically distinct decyanation to alkenes is possible by reducing nitriles containing β-leaving groups. Addition of an electron to the nitrile generates a radical anion that ejects an adjacent leaving group to form an alkene and a CN radical that is further reduced (Scheme I-21). Strong reducing agents such as sodium (Table I-8, entries 10, 11) or lithium (Table I-8, entry 9) in ammonia, or with naphthalene, efficiently allow a variety of leaving groups to be ejected. The reaction has been comprehensively examined for the elimination of β-mesyloxyl nitriles to afford an array of alkenes.

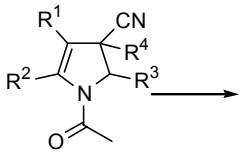
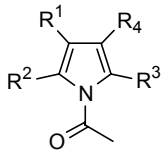
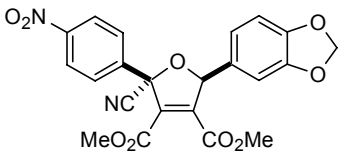
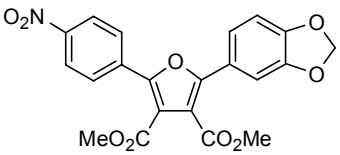
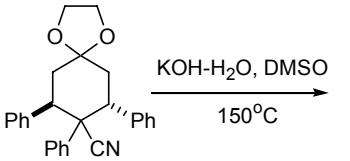
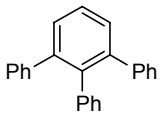
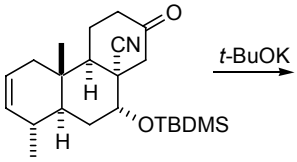
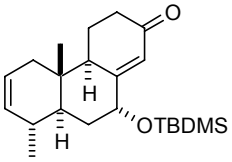
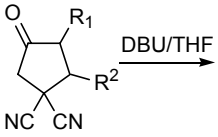
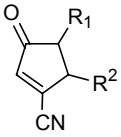
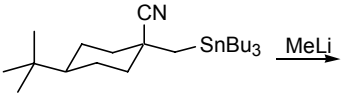
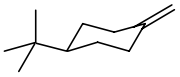
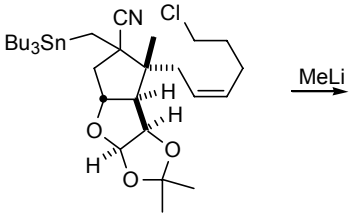
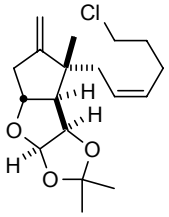
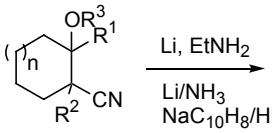
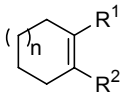
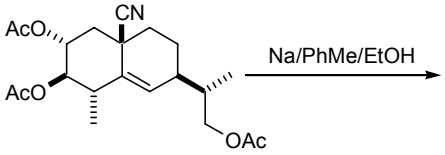
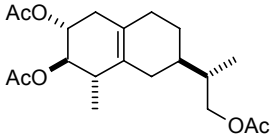
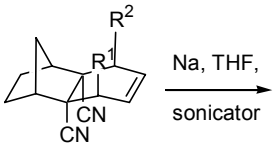
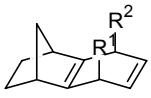
Scheme I-21. Reductive Decyanation to Alkenens



130 131 132

Table I-8. Decyanation to form Alkenes

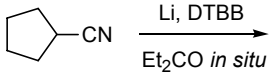
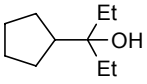
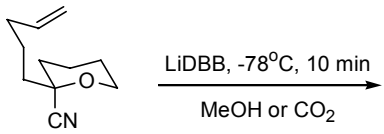
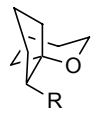
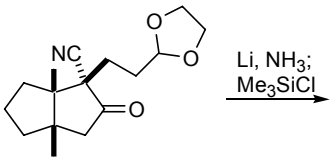
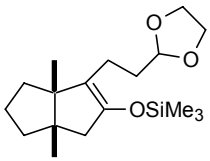
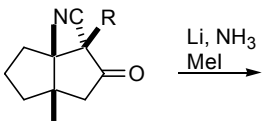
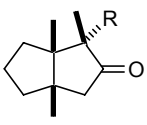
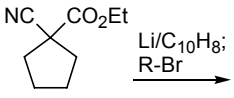
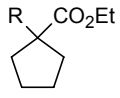
Entry	Reaction	Product	Yield (%)
1			56-65[241]

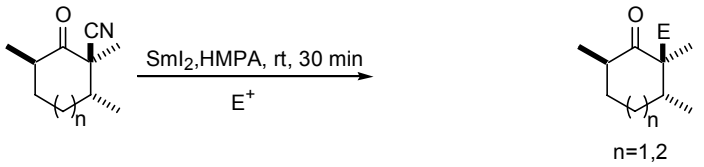
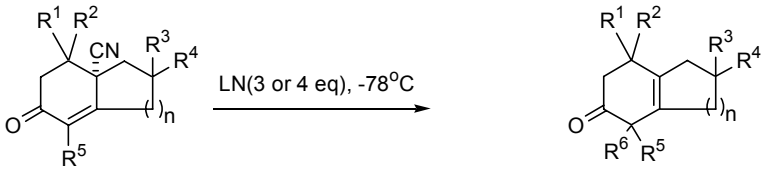
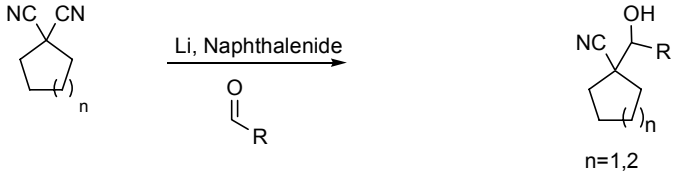
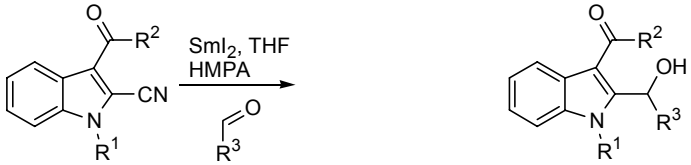
2			32-78[242]
3			81[243]
4			44[244]
5			57[245]
6			82-87(2 steps)[246]
7			64[247]
8			98[247]
9		 n=1 or 7, R^3=Ms,CH_2SO_4,CH_2SO_2Me, CH_2SMe, CH_2SO_2Me,	30-99[248]
10			71(2steps)[249]
11			30[250]

I-6-3. Sequential Decyanation-Alkylation

Reductive decyanation generates an anion for potential interception by electrophiles. Direct alkylation of the organolithium intermediates is rare (Table I-9, entry 1) although intramolecular cyclization of the organolithium is very efficient and demonstrates the potential for this chemistry (Table I-9, entry 2). The decyanation of ketonitriles readily generates reactive enolates (Table I-9, entries 3 and 4) and dienolates that stereoselectively alkylate a range of electrophiles. Historically, most decyanations have employed lithium-naphthalenide although the recent use of SmI_2 represents a significant advance in being particularly mild and ideally suited to use in total synthesis where the decyanation of highly functionalized intermediates is required.

Table I-9. Alkylation after Decyanation

Entry	Reaction and Conditions	Products	Yield (%)
1			47[251]
2		 R=H, CO_2Me	65-78[252]
3			86[253]
4			40-86[254]
5		 R=Bn R=$(CH_2)_4Br$	71 67[255]

6		60-80[256]
7		41-99[218]
8		76[257]
9		65-78[258]
10		51-85[259]

I-7. New Directions

Cyclic nitriles are versatile chameleons, providing potential electrophilic and nucleophilic reactivities. Nitriles tolerate a diverse array of organometallic reagents and yet, under more forcing conditions, are readily converted to a plethora of functional derivatives. The combination of these highly attractive attributes bodes well for the continued recurrence of nitriles as versatile synthetic intermediates.

Deprotonating cyclic nitriles affords powerful nucleophiles for stereoselective alkylation reactions. Alkylations of cyclic nitriles efficiently installs highly hindered quaternary stereocenters with virtually complete C-alkylation. Distinct reactivity differences

between C-metallated nitriles and the more common *N*-metallated nitriles are emerging which are particularly valuable for stereodivergent alkylations. The ability to selectively alkylate a single cyclic nitrile to the *R* or *S* diastereomer, by controlling the metal coordination site, is of fundamental importance and likely to stimulate future profitable developments in this area.

II. Discussion

II-1. Cyclic Alkenenitriles: Synthesis, Conjugate Addition, and Stereoselective Annulation

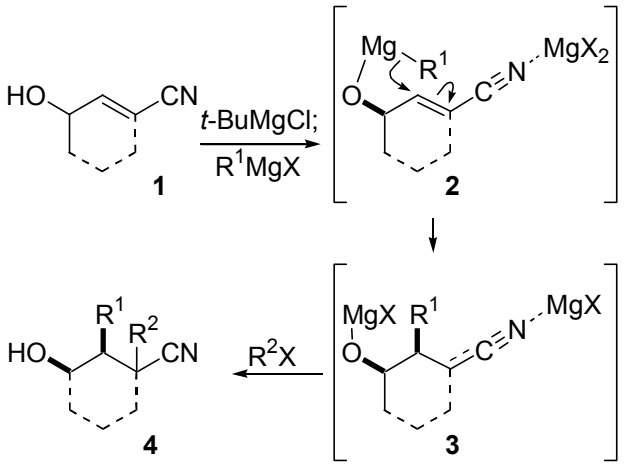
II-1-1. Introduction

Annulations feature prominently as key bond-forming reactions in natural product syntheses.[260] The centrality of annulation reactions stems from numerous reliable strategies for elaborating monocyclic precursors into complex, biologically active, multi-cyclic targets.[261] Originally the power of annulation-based synthesis was first demonstrated in Robinson annulation routes to steroids,[262] initiating an enduring search for annulations of increasing complexity, stereoselectivity, and efficiency.[263] Fulfilling these criteria has inspired syntheses of several exceptionally versatile bifunctional reagents, containing nucleophilic and electrophilic centers, for sequential conjugate addition-alkylation annulations to unsaturated carbonyl compounds.[264]

Annulation reactions with unsaturated nitriles are inherently more difficult than analogous annulations with unsaturated carbonyl compounds. The challenge stems from the paucity of anionic conjugate additions to unsaturated nitriles which, despite being highly polarized,[265] are recalcitrant Michael acceptors that react poorly with many conventional nucleophiles.[266] A particularly effective method for promoting conjugate additions to alkenenitriles[267] is to temporarily chelate Grignard reagents to γ-hydroxy unsaturated nitriles,[268] effectively harnessing the inherent entropic advantages[269] of intramolecular reactions in promoting a formal intermolecular conjugate addition (Scheme II-1-1). Mechanistically, sequential deprotonation of hydroxyalkenenitriles **1**

followed by alkyl exchange[270] from a modest excess of a second Grignard reagent, generates the alkylmagnesium alkoxide **2** that triggers a stereoselective conjugate addition. Alkylating the resulting magnesiated nitrile **3** with electrophiles installs two new stereocenters in one synthetic operation.[271]

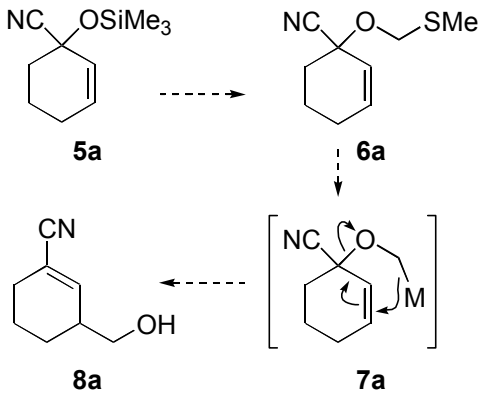
Scheme II-1-1. Chelation-Controlled Conjugate Addition-Alkylation of Alkenenitriles



Conceptually, the sequential conjugate addition-alkylation of ω-chloroalkyl Grignard reagents[264,272] to cyclic hydroxyalkenenitriles provides an annulation route to bicyclic nitriles. Developing this annulation strategy requires an expedient synthesis of cyclic hydroxyalkenenitriles for which few syntheses currently exist.[273] Addressing this deficiency suggested accessing the requisite cyclic hydroxyalkenenitriles from an unsaturated silyl cyanohydrin since chiral silyl cyanohydrins are readily available in high enantiomeric ratios.[274] The strategy envisages conversion of an unsaturated trimethylsilyl cyanohydrin to the corresponding methylthiomethyl ether followed by halogen-SMe exchange and [2,3] Wittig rearrangement (Scheme II-1-2). The two-fold appeal of this sequence lies in transposing the cyanohydrin chirality into the hydroxyalkenenitrile[275] for stereoselective chelation-controlled conjugate additions, and in concurrently expanding

the versatility of silyl cyanohydrins through an oxygen functional group interchange rather than the more typical addition to, or hydrolysis of, the nitrile group.[274]

Scheme II-1-2. Cyanohydrin-Alkenenitrile Rearrangement Strategy



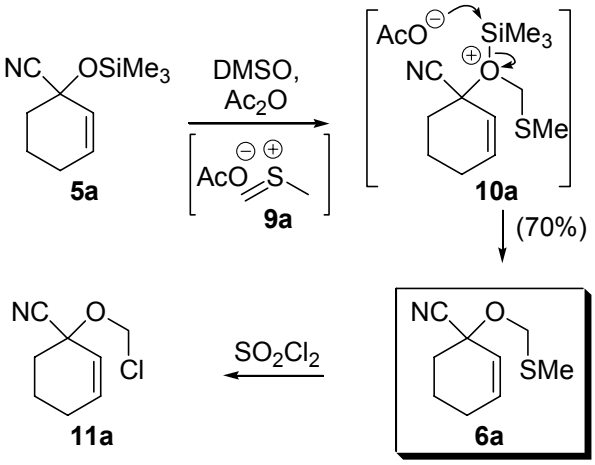
Pursuing this strategy identified an unusual silyl cyanohydrin rearrangement for synthesizing several cyclic alkenenitriles. Chelation-controlled conjugate addition of ω-chloroalkyl Grignard reagents to the resulting cyclic hydroxyalkenenitriles generates intermediate magnesiated nitriles that cyclize to *cis*-octalins, hydrindanes, and decalins in the first general annulation of alkenenitriles. Collectively the rearrangement-annulation reactions generate a diverse array of bicyclic nitriles providing insight into the stereoelectronically controlled conjugate addition and cyclization reactions.

II-1-2. Results and Discussion

A key lead for *O*-alkylating the trimethylsiloxyl group of enone-derived[276] cyanohydrins stems from two *O*-alkylations of trimethylsilyl cyanohydrins with $ClCH_2OCH_3$.[277] Presuming the alkylation to require a particularly reactive electrophile, the cyanohydrin **5a**[276a,b] was treated with the sulfonium ylide **9a**[278] to directly generate the methylthiomethyl cyanohydrin **6a** (Scheme II-1-3). The trimethylsilyl-methylthiomethyl

interchange proceeds by an *O*-alkylation of **5a** with ylide **9a**,[279] formed in situ from DMSO and acetic anhydride,[278] followed by desilylation to generate **6a**. Unfortunately chlorination of **6a** with SO_2Cl_2,[280] followed by numerous metalation strategies failed to promote the desired Wittig rearrangement[281] of **11a**, but rather caused significant degradation and formation of ketone-containing ethers arising from attack on the nitrile group.[282] Attempts to deprotonate and rearrange the corresponding nitrile (**11a** CN = Cl),[283] were similarly fruitless despite close precedent in the rearrangement of cyanomethyl enamines.[284]

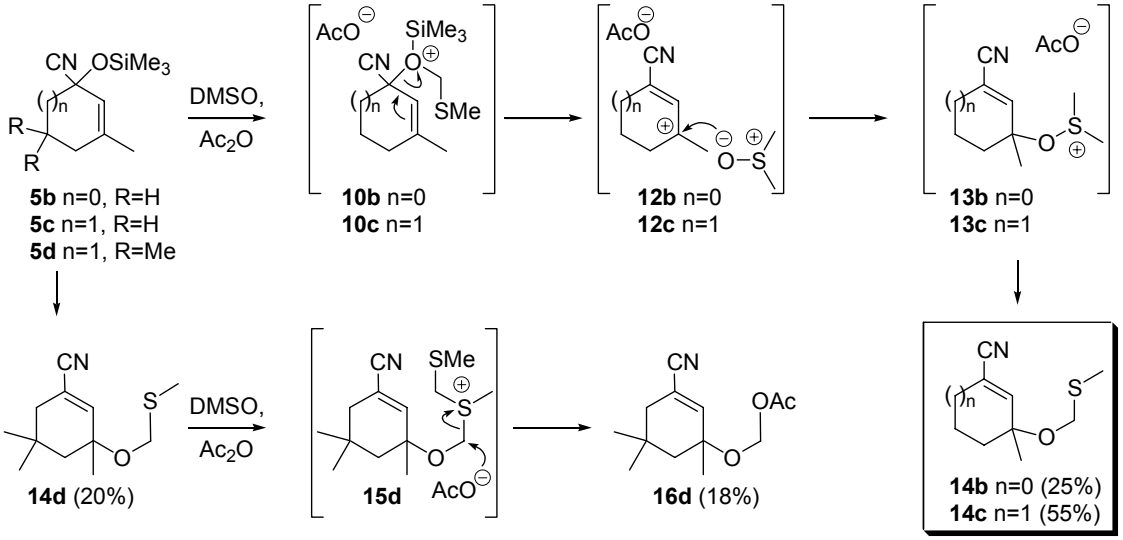
Scheme II-1-3. *O*-Alkylation of Silylcyanohydrin 5a



Although the [2,3] Wittig strategy proved unmanageable, concurrent alkylations of the methyl-substituted analog **5c** were rewarded with an unanticipated rearrangement to the synthetically valuable cyclic alkenenitrile **14c** (Scheme II-1-4). Mechanistically, alkylation of **5c** with the sulfonium salt **9a** affords the oxonium ion **10c**[285] that, unlike **10a**, fragments to the more stable methyl-substituted carbocation[286] **12c** (Scheme II-1-4). Subsequent DMSO attack[287] on carbocation **12c** generates the sulfonium nitrile[288] **13c** that suffers a Pummerer-type rearrangement[289] to afford the rearranged nitrile **14c** (55%

yield). The relatively facile rearrangement of **5c** contrasts with the significantly less efficient rearrangement of the cyanohydrins **5b** and **5d** (24% and 20% yield, respectively),[290] that rearrange more slowly[291] allowing the initially-formed alkenenitriles to react further, as implied by concurrent formation of the unusual ester-nitrile **16d** with **14d**.[289e]

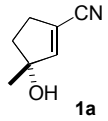
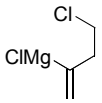
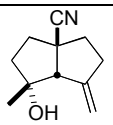
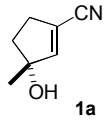
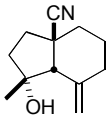
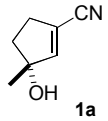
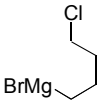
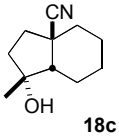
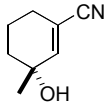
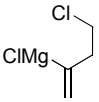
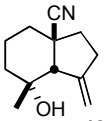
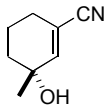
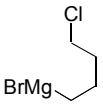
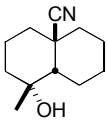
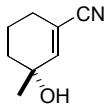
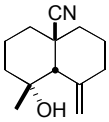
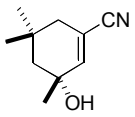
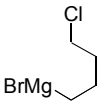
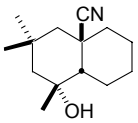
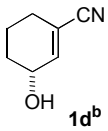
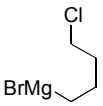
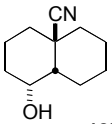
Scheme II-1-4. Rearrangement of Trimethylsilyl Cyanohydrins to Cyclic Alkenenitriles



Mercury-assisted hydrolyses[292] of **14b-d** efficiently provides a series of γ-hydroxyalkenenitriles for chelation-controlled conjugate addition-alkylations (Table II-1-1).[293] *t*-BuMgCl-initiated deprotonation of the 5-membered nitrile **1a**, and addition of a slight excess of the chloroalkyl Grignard reagents **17a-c**, trigger sequential conjugate addition-alkylations generating the octaline- and hydrindane-substituted nitriles **18a-c** (Table II-1-1, entries 1-3). An analogous annulation of **1b** with **17a** generates the hydrindane **18d** with a complementary substitution pattern (compare Table II-1-1, entries 2 and 3 with 4) whereas the annulations of **1b-d** with **17b-c** afford decalin-containing

nitriles (Table II-1-1, entries 5-8). In each instance the chelation-controlled conjugate addition of ω-haloalkyl Grignard reagents rapidly assembles the corresponding bicyclic nitriles with complete control over the two newly installed stereocenters.

Table II-1-1. Hydroxyalkenenitrile Annulations with ω-Chloroalkyl Grignard Reagents

Entry	Alkenenitrile	Grignard	Bicyclic nitrile	Yield
1	 **1a**	 **17a**[a]	 **18a**	62%
2	 **1a**	 **17b**	 **18b**	68%
3	 **1a**	 **17c**	 **18c**	56%
4	 **1b**	 **17a**	 **18d**	65%
5	 **1b**	 **17c**	 **18e**	58%
6	 **1b**	 **17b**	 **18f**	75%
7	 **1c**	 **17c**	 **18g**	54%
8	 **1d**[b]	 **17c**	 **18h**	64%

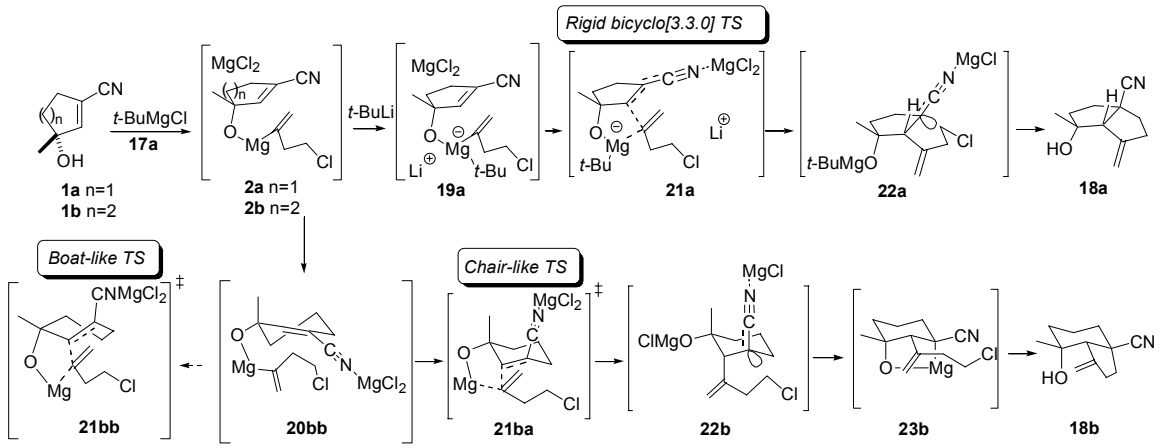
[a] An equivalent of *t*-BuLi is added after addition of **17a** to promote conjugate addition through the ate complex (Scheme 5). [b] **1d** was synthesized by ring opening of the corresponding epoxide.[273a]

Several fascinating mechanistic details emerge by comparing the annulations of the chloroalkyl Grignard **17a** with the 5- and 6-membered alkenenitriles **1a** and **1b** (Table II-

1-1, entries 1 and 4, respectively). In each case sequential deprotonation of the alkenenitriles with *t*-BuMgCl, and halogen-alkyl exchange[270] with **17a**, generates the key alkyl magnesium alkoxides **2a** and **2b** (Scheme II-1-5). Intramolecular delivery of the chloroalkyl group is facile from **2b**, and for every other conjugate addition (Table II-1-1, entries 2-8), whereas **2a** requires the addition of *t*-BuLi to coax conjugate addition through the more nucleophilic ate complex[268a] **19a** (Scheme II-1-5).

Critical for the conjugate additions is the pyramidalization of the β-carbon during the alkyl transfer, creating two potential addition modes for the more flexible 6-membered alkenenitriles: axial delivery of the alkyl group through a stereoelectronically-favored chair-like transition state **21ba**, or equatorial alkyl delivery through a less favorable, boat-like transition state **21bb**.[294] Axial conjugate addition leads to **22b** that is anticipated to ring-flip to the C-magnesiated nitrile **23b** and subsequently cyclize to deliver the *cis*-hydrindane **18b**. An analogous pyramidalization of the β-carbon in the 5-membered alkenenitrile **2a** requires a more significant distortion of the bicyclo[3.3.0] transition state **21a** potentially explaining the requirement for conjugate addition through the more nucleophilic ate complex **19a**.[295]

Scheme II-1-5. Stereoelectronic Control in Chelation-Controlled Conjugate Addition-Alkylations



Mechanistically the annulations of chloroalkyl Grignard reagents with 6-membered hydroxyalkenenitriles exhibit a high degree of stereoelectronic control. The initial formation of an equatorially oriented alkylmagnesium alkoxide, generated by *t*-BuMgCl deprotonation and halogen-alkyl exchange (**20bb**, Scheme II-1-5), preferentially triggers an axial conjugate addition to alkenenitriles through a chair-like transition state (**21ba**, Scheme II-1-5). Conjugate addition installs an axially oriented chlorobutyl side chain that ring flips prior to initial alkylation of a C-magnesiated nitrile, irreversibly establishing the *cis*-ring junction stereochemistry.

II-1-3. Conclusion

ω-Haloalkyl Grignard reagents trigger chelation-controlled annulations with 5- and 6-membered cyclic alkenenitriles that are derived from an unusual rearrangement of unsaturated silyl cyanohydrins. The annulation generates *cis*-fused octalins, hydrindanes, and decalins with complete control over the two newly installed stereocenters. Collectively, the conjugate addition-alkylation provides the first general annulation of

alkenenitriles, affording substituted bicyclic nitriles that are ideal precursors for terpenoid syntheses.

II-2. Metallated Nitriles: Electrophile-Dependent Alkylations

II-2-1. Introduction

Chiral organometallic reagents have tremendously impacted asymmetric synthesis.[296] Historically, chiral organometallics emerged with the appendage of chiral auxiliaries to sp^2-hybridized nucleophiles and later through the synthesis of chiral sp^3- hybridized organometallics. Particularly significant for the development of chiral sp^3 hybridized organometallics was the discovery of the greater configurational stability of α-alkoxyl alkylithiums[297] that facilitated sparteine-mediated syntheses of chiral organolithiums.[298]

An array of enantiomerically enriched organolithiums are now routinely synthesized by asymmetric deprotonation and metal exchange reactions.[299] Intercepting chiral, sp^3-hybridized organolithiums with electrophiles allows a virtually complete transfer of chirality from the carbon-lithium to a new stereogenic center. Generally chiral organolithiums alkylate with retention of the carbon-lithium bond configuration, although several configurationally stable, tertiary, benzyl- and allyllithiums alkylate alkylhalides with retention of configuration and carbonyl electrophiles with inversion of configuration.[300] Remarkably, reversals in the alkylation stereochemistry of chiral organolithiums can occur with different carbonyl electrophiles,[301] on changing from alkyl halide electrophiles to sulfonates[302] or phosphates,[303] and even upon substituting an alkyl chloride for an alkyl bromide![304]

The increasingly frequent electrophile-dependent alkylations of chiral organolithiums contrasts with the scarcity of electrophile-dependent alkylations of organometallics bearing an adjacent electron withdrawing group.[302b,305] Only in rare instances do chiral

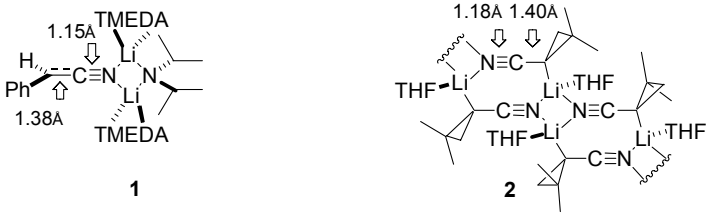
organometallics contain an adjacent electron-withdrawing group since delocalization promotes a loss of configurational stability. Chiral sulfoxides were the first stabilized nucleophiles exhibiting an electrophile-dependent stereoselectivity, with the discovery eliciting a flurry of mechanistic analyses.[306] Extensive alkylations revealed that the stereoselectivity depends not only on the electrophile,[306] but also on the solvent,[307] the presence of cryptands,[307] and even on the presence of lithium halide in the alkyllithium source,[308] with a complete understanding of the stereoselectivity languishing until almost 20 years after the original discovery.[306] In essence, the stereoselectivity stems from a combination of the chiral environment of the lithium cation and the strong inductive stabilization of the chiral sulfoxide.

Nitriles, like sulfoxides, are powerful electron withdrawing groups[309] that stabilize adjacent negative charge more by induction than resonance delocalization.[310] Experimentally, inductive stabilization of metallated nitriles was first identified during the retentive deprotonation of chiral cyclopropanecarbonitriles[311] and further substantiated in subsequent NMR analyses,[312] acidity measurements,[313] and nucleophilicity trends.[314] Inductive stabilization is apparent in the crystal structures of metallated nitriles where the C≡N bond length is virtually identical to the C≡N bond length in neutral nitriles.[315]

Solid state structures of metallated nitriles are generally planar and N-coordinated[316] **1** with C-coordination only being observed with cyclopropanecarbonitrile **2**[317] (Figure II-2-1). Li-NMR[318] similarly identifies the N-lithiated structure **1** as the dominant solution species, although cyclization studies point to the presence of amines as a key requirement in favoring N-coordination rather than C-coordination. Significantly, most metallated

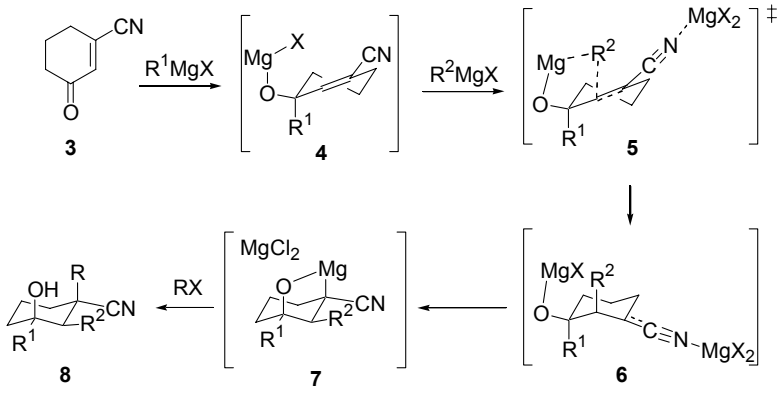
nitriles are synthesized by metal amide deprotonation that necessarily generates an equivalent of secondary amine.[319]

Figure II-2-1. X-Ray Structures of Metallated Nitriles



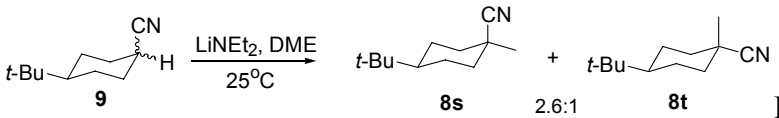
C-magnesiated nitriles are efficiently synthesized through the multicomponent Grignard 1,2-1,4-addition-alkylation to oxonitriles.[320] Mechanistically the C-magnesiated nitrile **7** is generated by the sequential 1,2-addition (**3→4)** and 1,4–addition (**5→6**) of Grignard reagents to oxonitrile **3** (Scheme II-2-1). The stereoelectronically-favored[321] axial addition **5** generates the dimagnesiated nitrile **6** that equilibrates to the conformationally more stable, C-magnesiated nitrile **7**[322] which is favored by internal magnesium coordination and the absence of an amine base. Alkylation of the C-magnesiated nitrile **7** with an array of electrophiles reveals an electrophile-dependent stereoselectivity that is unprecedented for metallated nitriles (Table II-2-1).

Scheme II-2-1. Multicomponent Addition-Alkylations to Oxonitrile 3



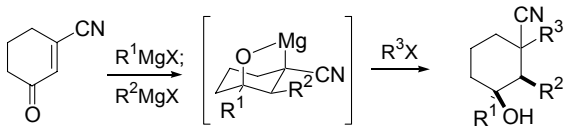
II-2-2. Results and Discussion

Probing the electrophile-dependent alkylations of C-magnesiated nitriles was pursued primarily with the dimethyl-substituted nitrile **7a** (Scheme II-2-1, R^1=R^2=Me).[323] Exclusive axial methylation of the magnesiated nitrile **7a** with Me_2SO_4, an electrophile capable of chelating prior to alkylation,[324] or MeI which is unlikely to chelate, affords the axial methylated nitrile **8a** (Table II-2-1, entries 1-2) implying that the preference for axial alkylation does not result from prior coordination with magnesium. The axial methylation is surprising since this installs a severe Me-OH diaxial interaction in **8a.** Increasing the steric demand of the alkylation, by installing a large adjacent phenyl group, through conjugate addition with PhMgCl, or by intercepting **7a** with the more sterically demanding *n*-propyliodide, maintains the preference for axial alkylation (Table II-2-1, entries 3-4). The stereoselective alkylations of **7** contrast with the analogous methylation of the conformationally locked nitrile **9** where methylation occurs with a modest preference for alkylation from the more accessible equatorial direction (equation II-2-1).[325]

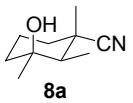
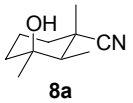
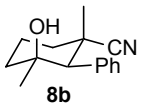
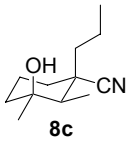
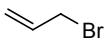
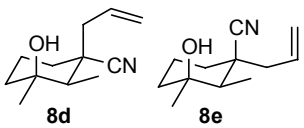
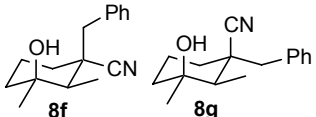
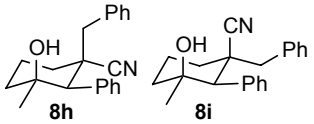
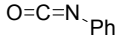
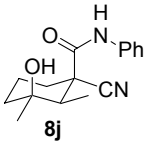
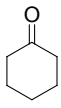
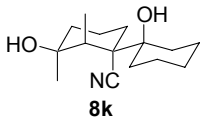
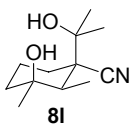


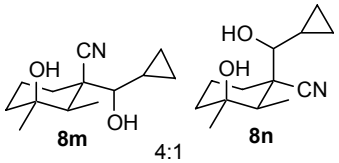
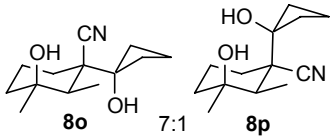
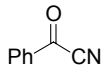
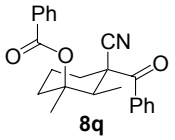
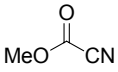
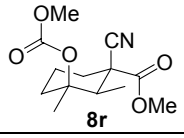
9 **8s** 2.6:1 **8t** Eq. II-2-1

Table II-2-1. Electrophile-Dependent Alkylations of C-Magnesiated Nitriles



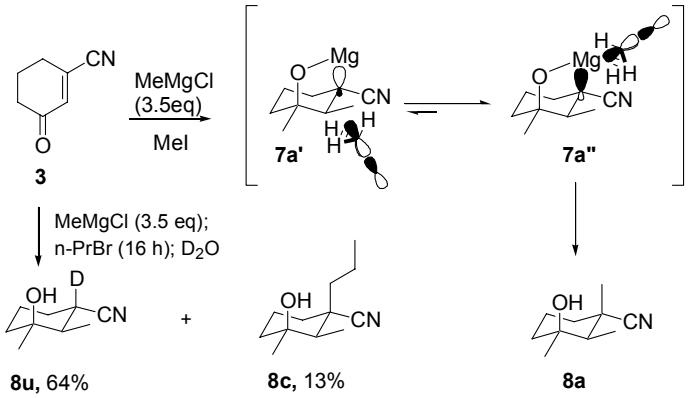
3 7 8

Entry	Grignard Reagent R^1MgX	Grignard Reagent R^2MgX	Electrophile	Nitrile	Yield
1	MeMgCl (excess)		Me_2SO_4	 **8a**	57%
2	MeMgCl (excess)		MeI	 **8a**	86%
3	MeMgCl	PhMgCl	MeI	 **8b**	71%
4	MeMgCl (excess)			 **8c**	70%
5	MeMgCl (excess)			 **8d** **8e** 1.7:1	71%
6	MeMgCl (excess)		BnBr	 **8f** **8g** 1.2:1	71%
7	MeMgCl	PhMgCl	BnBr	 **8h** **8i** 3.4:1	61%
8	MeMgCl (excess)			 **8j**	58%
9	MeMgCl (excess)			 **8k**	68%
10	MeMgCl (excess)			 **8l**	64%

11	MeMgCl (excess)		 **8m** 4:1 **8n**	65%
12	MeMgCl (excess)		 **8o** 7:1 **8p**	59%
13	MeMgCl (excess)		 **8q**	55%
14	MeMgCl (excess)		 **8r**	61%

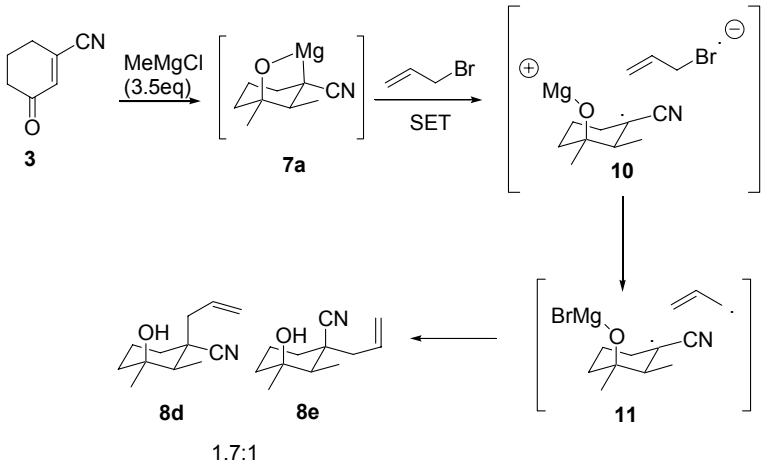
Collectively the axial alkylations of **7** with alkyl halides and sulfonates are consistent with a stereoelectronically controlled alkylation. Retentive alkylation of the C-magnesiated nitrile **7** requires a side-on overlap of the electrophilic σ^* orbital with the large lobe of metal carbon σ bond (Scheme II-2-2, **7a''**).[326] Although the side-on orbital overlap is far from optimal, the alternative co-linear approach of a sp^3 hybridized electrophile to the small σ lobe of the C-Mg bond is sterically prohibitive (Scheme II-2-2, **7a'**). Consistent with this analysis, the alkylation of **7a** with *n*-PrBr is considerably more difficult[327] than *n*-PrI which has a larger σ^* orbital. Alkylating the metallated nitrile **7a** with *n*-PrBr leads to incomplete conversion despite high deuteration requiring that a magnesiated nitrile, presumably **7a**, is still present (Scheme II-2-2)[328] and ruling out protonation of **7a**, by a preferential E_2 reaction, as the cause of incomplete alkylation.

Scheme II-2-2. Stereoelectronic S_E2 Alkylations of Metallated Nitriles



Contrasting the retentive alkylations of **7** with alkyl halide and sulfonate electrophiles are the non-selective alkylations of **7** with allyl and benzyl bromide. The disparate stereoselectivity is consistent with a mechanistic changeover to a single electron transfer reaction,[329] particularly since *n*-propyliodide and allylbromide have virtually identical steric demands (Table II-2-1, compare entry 4 with entries 5 and 6). Single electron transfer from **7a** to allyl bromide and expulsion of bromide (**10** → **11**), generates an allyl radical that is favored by proximity to radical couple from the axial direction (Scheme II-2-3),[330] with the 2:1 ratio suggesting that the allyl radical also migrates and couples from the sterically more open equatorial direction. Increasing the steric demand, by generating the magnesiated nitrile derived from conjugate addition of PhMgCl, similarly affords minimal selectivity for the nitrile diastereomers **8h** and **8i** in the alkylation with benzyl bromide (Table II-2-1, entry 7).

Scheme II-2-3. SET Alkylation of Magnesiated Nitriles

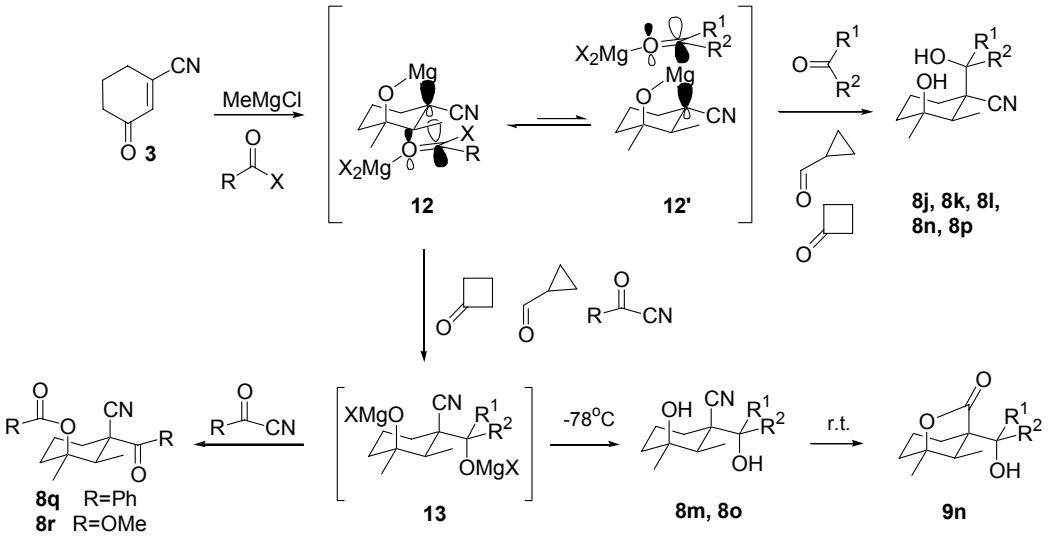


Carbonyl electrophiles exhibit an extremely delicate stereoselectivity dependence (Table II-2-1, entries 8-14). The C-magnesiated nitrile **7a** alkylates phenyl isocyanate, cyclohexanone, and acetone exclusively with retention of configuration (Table II-2-1, entries 8 - 10)[331] and, reiterating the high steric demand of the axial alkylation, X-ray diffraction shows that the resulting hydroxynitriles **8k** adopts a more stable ring-flipped conformation although not with **8l**. These axial alkylations are starkly contrasted by the equatorial acylations of **7a** with methyl cyanoformate and benzoyl cyanide that install 4 new bonds and 3 stereocenters in one synthetic operation (Table II-2-1, entries 13 and 14). Meanwhile, intercepting **7a** with cyclopropanecarboxaldehyde and cyclobutanone is unusual in alkylating with mainly inversion of configuration and accompanying amounts of the retentive alkylation product (Table II-2-1, entries 11-12).[331] Invertive alkylation of **7** with cyclopropanecarboxaldehyde installs an axial nitrile that is aligned for an internal attack by the axial alkoxide which does indeed occur if the reaction is allowed to warm to room temperature prior to protonation.

A tentative explanation for the stereoselectivity differences exhibited by the carbonyl electrophiles emerges by comparing the reactivity of the π^* orbitals (Scheme II-2-4).

Particularly reactive carbonyl electrophiles, such as methyl cyanoformate and benzoyl cyanide, have large, diffuse π^* orbitals, and are sufficiently small, planar electrophiles to allow a co-linear approach to the small σ lobe of the C-Mg bond. The equatorial trajectory, while more hindered than the side-on axial approach, benefits from co-linear orbital overlap which favors the invertive alkylation. Carbonyl electrophiles with a large steric demand, such as cyclohexanone, are unable to achieve sufficient proximity for overlap in a colinear equatorial approach and preferentially alkylate by side-on overlap, perhaps aided by complexation to magnesium.[332]

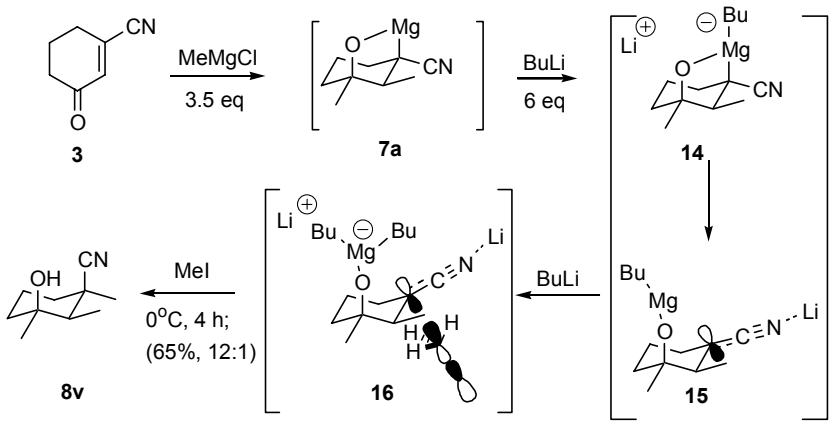
Scheme II-2-4. Electrophile-Dependent Alkylations of Magnesiated Nitrile



Conceptually, stereoelectronically controlled alkylation of C-magnesiated nitriles and sterically controlled alkylations of N-metallated nitriles can give different stereoselectivities with the same alkyl halide electrophile. Essentially, axial methylation of the C-magnesiated nitrile **7a** is stereoelectronically controlled whereas methylation of the corresponding N-metallated nitrile is anticipated from the sterically more accessible equatorial direction (Scheme II-2-5). After optimization this stereodivergent alkylation,

providing diastereomeric *R* and *S* stereocenters from a single metallated nitrile, was indeed realized.

Scheme II-2-5. Stereodivergent Alkylation of a C-Magnesiated Nitrile

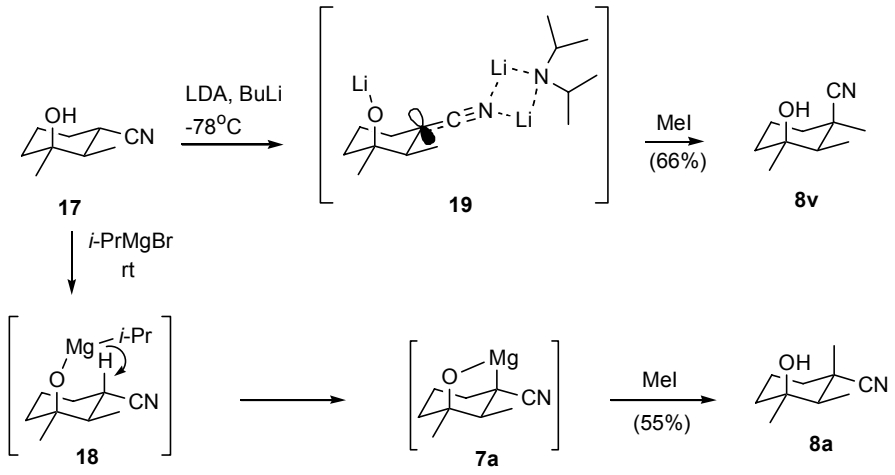


Conversion of the C-magnesiated nitrile **7a** to the putative N-metallated nitrile **15** was achieved through the addition of excess BuLi (Scheme II-2-5). Sequential addition of excess BuLi and methyl iodide to **7a**, completely reverses the stereochemical preference in favor of equatorial alkylation, preferentially affording **8v** and **8a** in 12:1 ratio (65% yield). The stereodivergent methylation is consistent with the conversion of the C-magnesiated nitrile **7a** to the ate complex **14**,[333] that is in equilibrium with the N-lithiated nitrile **15**. Further addition of BuLi generates the N-lithiated dibutyl magnesiate **16** which blocks alkylation from the axial direction and redirects methylation predominantly from an equatorial trajectory.

Alkylations of independently generated C- and N-metallated nitriles support the stereodivergent alkylations of **7a** and **16**. Deprotonating **17** with LDA and BuLi, to prevent an internal proton return from complexed *i*-Pr_2NH[334] (Scheme II-2-6), leads to

the N-lithiated nitrile **19** that is directly analogous to N-lithiated nitriles characterized in solution by lithium NMR.[335] Methylation of **19** occurs from the more sterically accessible equatorial direction to give **8v**[336] directly analogous to the methylation of **16** (Scheme II-2-5). As a control experiment, the corresponding C-magnesiated nitrile **7a** was synthesized in the absence of an amide base, through sequential inter- and intramolecular deprotonation of **17,** with 2 equivalents of *i*-PrMgBr, and methylated to afford **8a** as anticipated. Collectively, the equatorial alkylations of the N-metallated nitriles **16** (Scheme II-2-5) and **19** (Scheme II-2-6), and the axial alkylations of the C-magnesiated nitrile **7a**, provide stereodivergent alkylations through steric approach control and stereoelectronic control, respectively.

Scheme II-2-6. Stereodivergent Alkylations of N- and C-Magnesiated Nitriles.

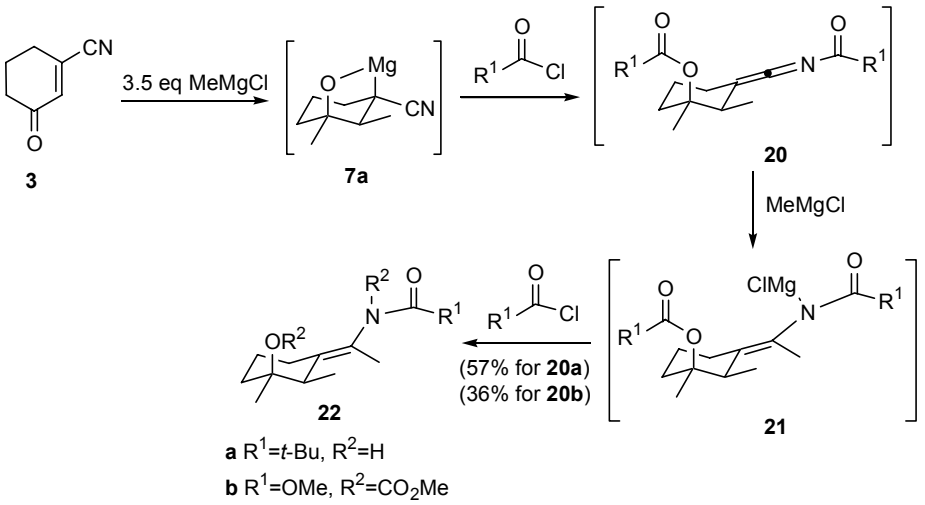


II-2-3. Novel Formation of Enamides

Intercepting the C-magnesiated nitrile **7a** with highly reactive, sterically hindered electrophiles causes a highly unusual N-acylation (Scheme II-2-7). Addition of excess MeMgCl to oxonitrile **3**, followed by methyl chloroformate or pivaloyl chloride,

generates the enamide **22**. Mechanistically, N-acylation of **7a** likely generates the activated imine **20** that is attacked by excess MeMgCl to afford **21** that is ultimately protonated or further acylated, in the case of methyl chloroformate, to form **22b**. Overall the sequence installs six new bonds and three stereocenters in one synthetic operation.[337]

Scheme II-2-7. Enamide Formation by N-Acylation



II-2-4. Conclusion

C-Magnesiated nitriles exhibit unprecedented electrophile-dependent alkylations. Alkyl halide and sulfonate electrophiles react with C-magnesiated nitriles with retention of stereochemistry whereas acylation with aldehyde and acyl cyanide electrophiles occurs with inversion of stereochemistry. The stereoelectronically controlled alkylations of C-magnesiated nitriles are stereochemically complementary to the alkylation of N-metallated nitriles where the stereochemistry is determined by steric approach control. Collectively, this represents the first stereodivergent alkylations of C-metallated nitriles, which provides a facile method for generating diasteroemeric quaternary centers from a single metallated nitrile.

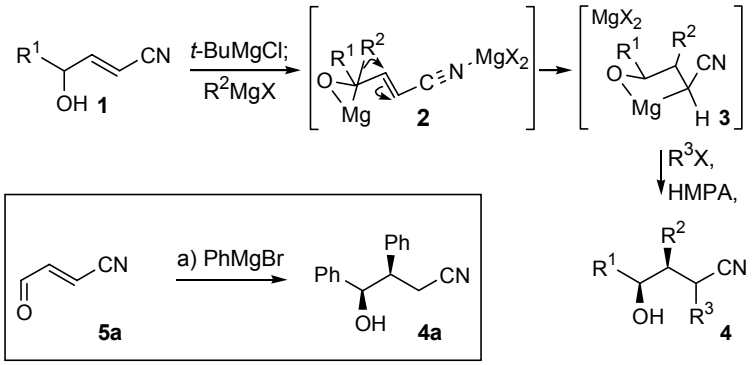
II-3. Multicomponent Grignard Addition-Alkylations

II-3-1. Introduction

Efficiently installing high molecular complexity is a fundamental pursuit in organic synthesis.[338] Several excellent strategies have emerged for installing multiple bonds in a single synthetic operation: bidirectional synthesis,[339] domino reactions,[340] biomimetic cascades,[341] and multicomponent reactions.[342] Each strategy exhibits complementary advantages, with multicomponent reactions benefiting from an inherent convergence that fulfills the synthetic criteria of assembling complex targets from fragments of similar size.[343]

As a subclass of multicomponent reactions, conjugate addition-alkylation reactions install two new bonds and up to three stereocenters in a single synthetic operation.[344] Chelation-controlled conjugate addition-alkylations exhibit the additional advantage of promoting conjugate additions with less reactive Michael acceptors. The strategy is particularly effective for γ-hydroxyalkenenitriles (Scheme II-3-1, **1** → **4)**[345] where chelation permits a facile conjugate addition-alkylation with a recalcitrant class of Michael acceptors that are unreactive toward many conventional nucleophiles.[346]

Scheme II-3-1. Chelation-Controlled Conjugate Additions to Alkenenitriles

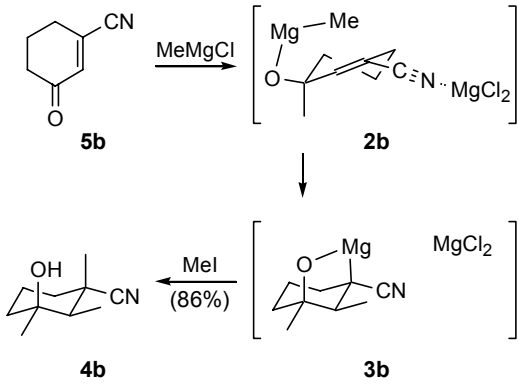


The highly efficient chelation-controlled conjugate additions to γ-hydroxyalkenenitriles stimulated a multicomponent variation with Grignard reagents and oxonitriles for potentially installing 3 new stereocenters in one operation (Inset, Scheme II-3-1). Conceptually, the addition of a Grignard reagent to the γ-oxonitrile **5a** was envisaged to directly generate an alkylmagnesium alkoxide intermediate **2** triggering conjugate addition and generating the magnesiated nitrile **3** for potential alkylation (Scheme II-3-1). Exploratory addition of excess PhMgBr to oxonitrile **5a**[347] triggers sequential carbonyl and conjugate addition generating **4a** as the sole stereoisomer.

II-3-2. Results and Discussions

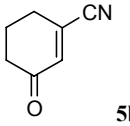
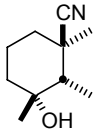
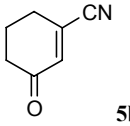
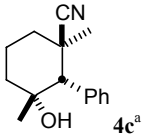
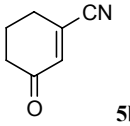
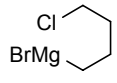
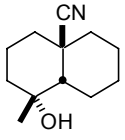
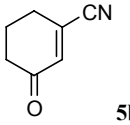
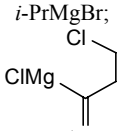
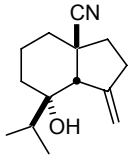
Although the formation of **4a** validates the multicomponent concept, optimizing the reaction was frustrated by the volatility and instability of **5a**.[347a] Attention was therefore redirected toward the more stable 6-membered oxonitrile **5b**[348] (Scheme II-3-2). Addition of excess methylmagnesium chloride to **5b** triggers the sequential carbonyl addition-conjugate addition affording the cyclic magnesiated nitrile **3b**.[345] Intercepting this formal dianion with methyl iodide installs a third stereocenter[349] generating **4b** as a single stereoisomer.[350]

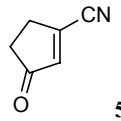
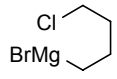
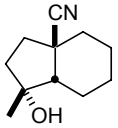
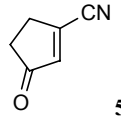
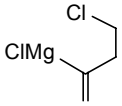
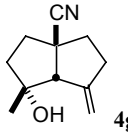
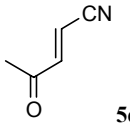
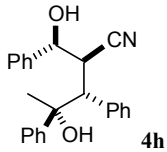
Scheme II-3-2. Multicomponent Addition-Alkylation with Oxonitrile 5b



The efficient three component addition-alkylation of **5b** is typical of the reactivity exhibited in a range of multi-component reactions (Table II-3-1). Grignard reagents react significantly faster with the carbonyl group than in the subsequent chelation-controlled conjugate addition, permitting the sequential addition of two different Grignard reagents, firstly to the ketone and secondly in the conjugate addition (Table II-3-1, entry 2). Employing ω-haloalkyl Grignard reagents, such as chlorobutylmagnesium bromide (**6a**)[351] or the related Grignard **6b**,[352] for the conjugate addition allows a smooth annulation route to the *cis*-fused decalin **4d** and hydrindane **4e** (Table II-3-1, entries 3-4, respectively). Similarly, carbonyl additions to the corresponding 5-membered oxonitrile **5c**,[348] followed by addition of the ω-haloalkyl Grignard reagents **6a** and **6b**, generates nitrile-substituted hydrindane and octalin rings in one synthetic operation (Table II-3-1, entries 5-6).

Table II-3-1. Multi-Component Oxonitrile Conjugate Addition-Alkylations

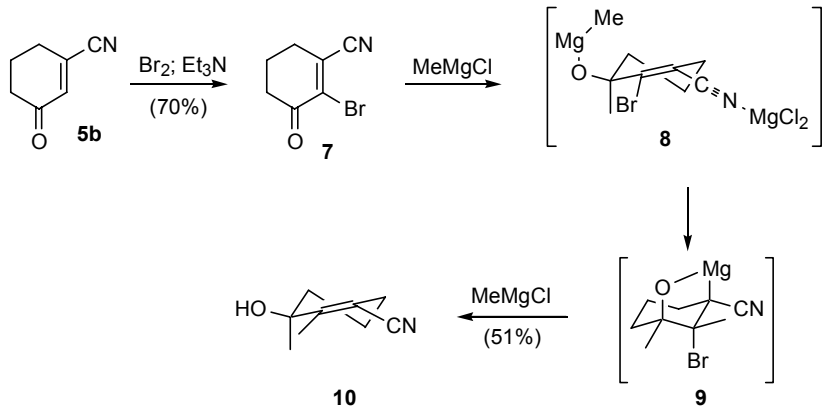
Entry	Oxonitrile	Reagents	Alkanenitrile	Yield
1	 **5b**	MeMgCl; MeI	 **4b**[a]	86%
2	 **5b**	MeMgCl; PhMgCl; MeI	 **4c**[a]	71%
3	 **5b**	MeMgCl;  **6a**	 **4d**	53%
4	 **5b**	*i*-PrMgBr;  **6b**[b]	 **4e**	58%

5	 **5c**	MeMgCl;  **6a**	 **4f**	53%
6	 **5c**	MeMgCl;  **6b**[c]	 **4g**	50%[b]
7	 **5d**	PhMgCl; PhCHO	 **4h**	52%[d]

[a] Stereochemistry assigned by x-ray crystallography.[353] [b] Prepared by *i*-PrMgCl exchange.[354] [c] An equivalent of *t*-BuLi is added after addition of **6b** to promote conjugate addition through the ate complex.[355] [d] The tentative stereochemical assignment is based on mechanistic implications.[8]

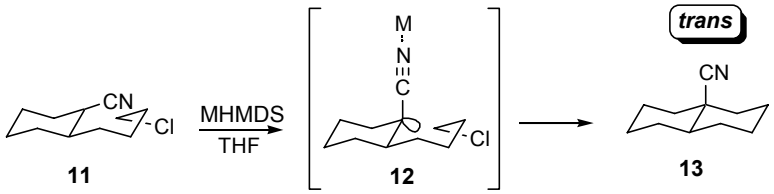
A key component of the multicomponent addition-alkylation is the formation of MgX_2 resulting from the Grignard exchange (Scheme II-3-3). Attempts to trigger the 1,2-1,4 addition by adding Bu_2Mg to **5b** resulted only in carbonyl addition, strongly implying that coordination of MgX_2 to the nitrile is required for the conjugate addition. Bromination of **5b** generates the more highly substituted oxonitrile **7** which reacts with excess MeMgCl to afford **10** (Scheme II-3-3). No conjugate addition occurs from **10,** unlike **5b,** indicating that β-alkyl substituents deactivate the unsaturated nitrile toward conjugate addition[9] whereas the bromine substituent sufficiently activated the acceptor to retain the reactivity.

Scheme II-3-3. Bromine-Subsituted Oxonitrile Multicomponent Additon



Preferential formation of the *cis*-octalin **4g** and *cis*-hydrindanes **4e**-**4f** (Table II-3-1, entries 4-6) are geometrically anticipated[356] whereas formation of the *cis*-decalin **4d** (Table II-3-1, entry 3) directly contrasts with analogous cyclizations of metallated nitriles.[357] Cyclization of the prototype nitrile **11** to the *trans*-decalin **13** is consistent with the cyclization of a pyramidalized, N-metallated nitrile through the least sterically congested transition state **12** (Scheme II-3-4). A critical distinction between the cyclization to **13** (Scheme II-3-4) and the formation of **4d** to **5b** lies in the structure of the metallated nitrile intermediates.

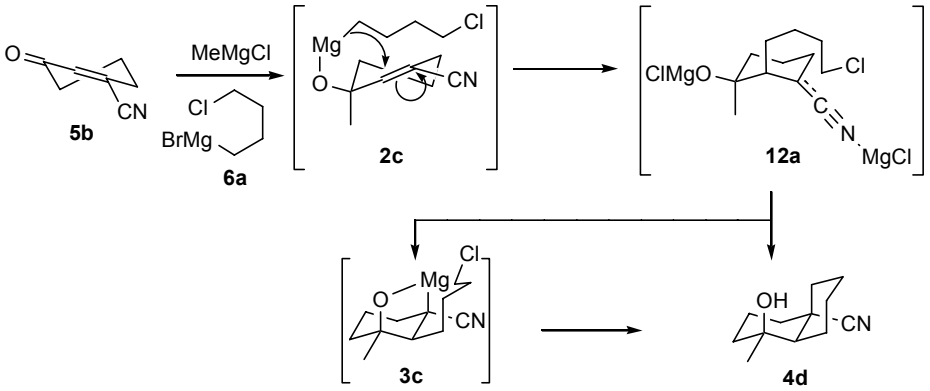
Scheme II-3-4. *trans*-Selective Nitrile Anion Cyclizations



The cyclization of **11** proceeds via a pyramidal N-metallated nitrile whereas the multicomponent annulation involves cyclization of a C-metallated nitrile. Sequential 1,2-

addition of MeMgCl to **5b** and a subsequent stereoelectronically controlled axial conjugate addition (**2c → 12a),**[358] leads to the bis-magnesiated nitrile **12a** (Scheme II-3-5). Conceptually, rapid cyclization of **12a**, prior to ring-flipping, leads directly to the *cis*-decalin **4d**, although equally plausible is the conversion of **12a** to the more stable C-magnesiated nitrile **3c**, followed by a stereoelectronically controlled cyclization to **4d**.

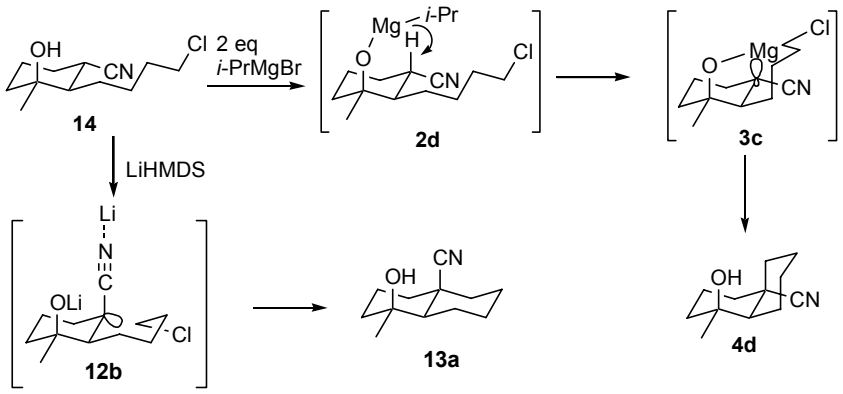
Scheme II-3-5. *cis* Decalin Cyclization Stereoselectivity



Elucidating the origin of the cyclization selectivity was achieved by independently generating the C-magnesiated nitrile **3c** and comparing the cyclization stereoselectivity with that from the corresponding N-metallated nitrile (Scheme II-3-6). Hydroxynitrile **14** with the pendant chlorobutyl side chain in an equatorial orientation, is known[358] to cyclize to the *trans*-decalin **13a** through a pyramidal, N-metallated nitrile directly analogous to the cyclization of **11** (Scheme II-3-4). Employing *i*-PrMgBr for deprotonation of **14** generates the C-magnesiated nitrile **3c** by an internal deprotonation of the alkylmagnesium alkoxide **2d**. Critically, the C-magnesiated nitrile **3c** has the electrophilic chlorobutyl side chain in the equatorial orientation and yet cyclizes exclusively to the *cis*-decalin **4d**, strongly implying that the multicomponent addition cyclization occurs by conversion of the *bis*-magnesiated nitrile **3c** to the C-magnesiated

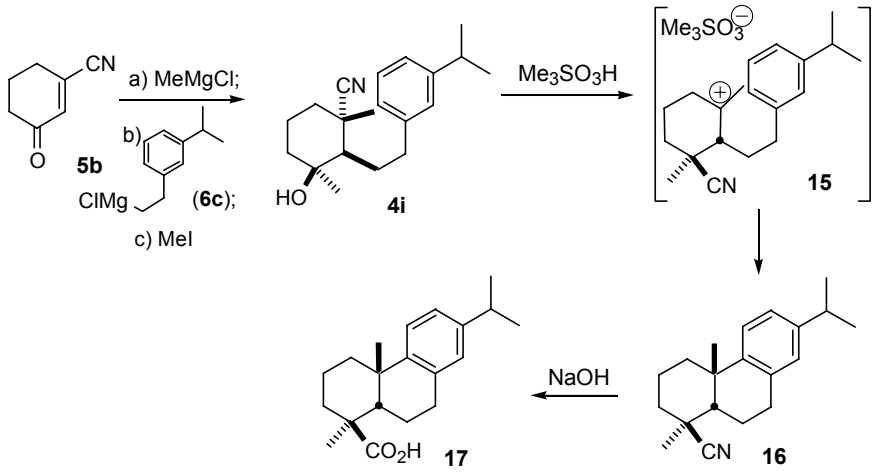
nitrile **4d**, followed by a stereoelectronically controlled cyclization (**12a→3c→4d,** Scheme II-3-5).

Scheme II-3-6. Chelation Controll Cyclization to *trans* Decalin



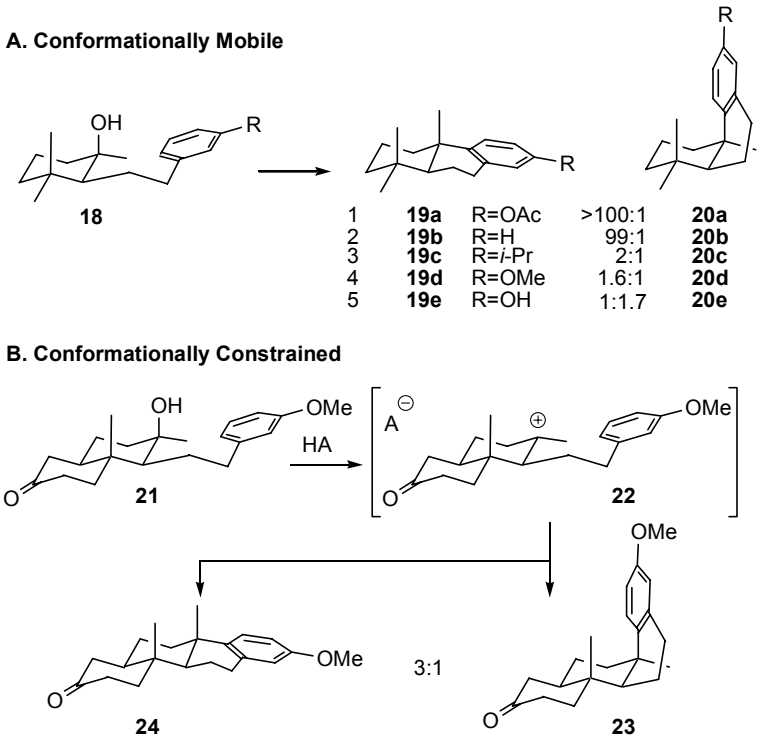
The rapid installation of 3 new stereocenters makes the multicomponent Grignard addition to oxonitriles ideally suited to terpenoid synthesis. Combining the multicomponent addition with cationic cyclization provides a particularly efficient entry to the dehydroabietic acid skeleton, several congeners of which exhibit antitumor, antibiotic, and cytotoxic actitvity.[359] Sequential addition of MeMgCl, Grignard **6c**,[360] and MeI, to **5b** installs the entire abietane carbon skeleton in one operation (Scheme II-3-7). Intramolecular Friedel-Crafts alkylation of **4i** affords predominantly[361] the *cis*-abietane **16,** illustrating the advantage of the small, non-nucleophilic nitrile that permits arylation without prior interception of the carbocation intermediate **15** that occurs with the corresponding ester.[362] Nitrile hydrolysis completes the synthesis of epi-dehydroabietic acid **17**.[363]

Scheme II-3-7. Multi-Component epi-Dehydroabietic Acid Synthesis



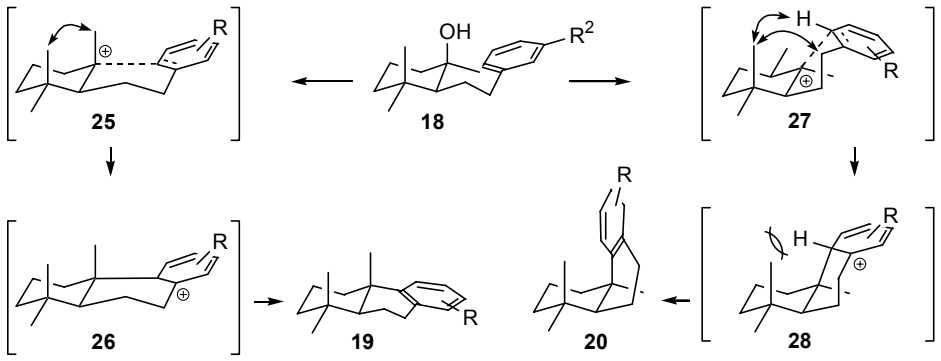
Friedel-Crafts alkylations of arylethylcyclohexanes are extremely well precedented despite the underlying principles governing the cyclization being poorly understood. Remarkably, the *cis*-*trans* stereoselectivity in Friedel-Crafts cyclizations (Scheme II-3-8, **18** → **19** + **20**) depends on the aromatic substituent in contrast to multicyclic polyene cyclizations that exhibit an inherent propensity for *trans*-fused carbocycles.[364] An empirical trend, gleaned from Friedel-Crafts cyclizations over the last 4 decades,[365] is for unsubstituted and electron-withdrawing arylethyl systems to favor *trans*-fused abietanes (Scheme II-3-8, entries 1-2)[366] whereas electron-donating substituents are typically non-selective (Scheme II-3-8, entries 3-5). Significantly the stereoselectivity does not depend on the geometry of the tertiary alcohol since cyclizations with diastereomeric alcohols, and alkenes whose protonation would afford the same carbocation, does not influence the cyclization stereoselectivity, suggesting the intermediacy of a fully dissociated carbocation.[367]

Scheme II-3-8. Carbocationic Cyclization Selectivities in Arylethylcyclohexanols



Particularly insightful were a series of cyclizations with conformationally locked cyclohexanols (Scheme II-3-8, **21** → **24** + **23**)[368] where the arylethyl side chain is constrained in the equatorial orientation for cyclization through a chair or twist[369] conformation (Scheme II-3-8, **22**). Furthermore, the similar stereoselectivities of the conformationally locked **21** and related conformationally mobile systems **18**, implies that these cyclizations proceed predominantly through conformations with the arylethyl group in an equatorial orientation.

Scheme II-3-9. *cis-trans*-Stereoselectivity in Friedel Crafts Cyclizations



A highly attractive explanation for the cyclization stereoselectivity is simply that the aromatic substituent changes the position of the transition state on the reaction coordinate. Implicit in this assertion is a degree of pyramidalization[370] of the carbocation in the transition state, a proposal first suggested over 25 years ago.[371] Two pyramidal transition states with axial- and equatorial-like methyl groups are possible, **25** and **27**, respectively, which differ significantly in their steric interactions (Scheme II-3-9) and which correlate directly with the two conformations proposed for pyramidal methylcyclohexane carbocations.[372] Cyclization through transition state **25** is impeded by a Me-Me 1,3-diaxial interaction, in early and late transition states since the ethyl tether imposes significant conformational constraints on the orientation required for approaching the carbocation. Alternatively, cyclization through transition state **27**, with the equatorial methyl group, relieves steric crowding, although at the expense of a severe interaction between the ortho proton of the aromatic ring and the axial methyl group, although the axial nitrile group present in the cyclization of **15** significantly relieve this steric interaction, explaining the 9:1 preference for the *cis*-fused abietane **16**.

II-3-3. Conclusion

Multicomponent Grignard addition-alkylations of oxonitriles rapidly assembles highly substituted mono- and bicyclic nitriles. Employing γ-haloalkyl Grignard reagents permits an efficient route to octalins, hydrindanes, and decalins with aryl-substituted Grignards being ideally suited for annulation via Friedel-Crafts alkylations. Collectively the strategy rapidly assembles a diverse array of cyclic nitriles, with complete control over the three stereogenic centers.

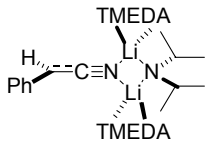
II-4. Halogen-Metal Exchange with α-Halonitriles**

II-4-1. Introduction

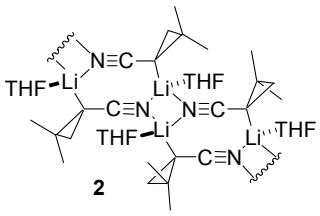
α-Metallated nitriles are particularly versatile synthetic intermediates.[373] The versatility stems from the high carbon nucleophilicity of metallated nitriles[373] and the ease of converting the nitrile group into a plethora of functional derivatives.[374] These synthetically valuable traits have led to metallated nitriles being featured in numerous sterically demanding alkylations.[373]

Metallated nitriles are typically generated by deprotonation with metal amide bases.[373b] Seminal X-ray structures of metallated nitriles,[375] generated with excess amide bases,[376] reveal a preference for N-metallation that is consistent with solution NMR and IR analyses[377] (Figure II-4-1, **1**). C-metallation is only observed with metallated cyclopropylnitriles where C-metallation is favored by the hybridization of the cyclopropane ring (Figure II-4-1, **2**).[378] Conceptually the site of metallation in nitriles could potentially relay into reactivity differences, as implied by intriguing stereoselectivity differences exhibited by metallated nitriles generated in the absence of amines.[379]

Figure II-4-1. X-Ray Structures of Metallated Nitriles



1



2

Historically, probing the reactivity of metallated nitriles in the absence of amines has been complicated by the difficulty in generating metallated nitriles without recourse to

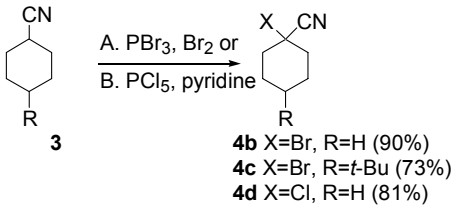
metal amides for deprotonation. Density functional calculations[380] reveal that deprotonation with lithium amide bases leads directly to N-metallated nitriles, precluding their use for kinetically accessing C-metallated nitriles. Alternatively, the metal hydrides NaH and KH, are generally ineffective for deprotonating aliphatic nitriles[373b] whereas *t*-BuOK, while excellent for deprotonating nitriles,[381] has the complication of establishing rapid prototropic equilibria.[382]

II-4-2. Results and Discussion

A potentially general route for generating metallated nitriles, without recourse to amide bases, is through halogen-metal exchange.[383] Halogen-metal exchange of related α-iodoketones[384] permits facile enolate formation, though the analogous formation of metallated nitriles is unknown, despite the opportunity for selectively generating elusive C-metallated nitriles. The opportunity for accessing C-metallated nitriles, with the added attraction of potentially generating metallated nitriles in the presence of more acidic functionality, stimulated the halogen-metal exchange of α-halonitriles.

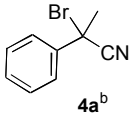
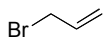
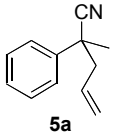
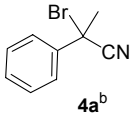
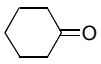
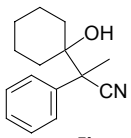
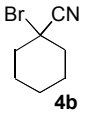
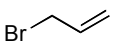
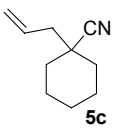
Diverse α-halonitriles are available by free radical halogenation, and from α-haloacrylonitriles by Diels-Alder cycloaddition[385] and organomercurial conjugate additions.[386] Direct halogenation is particularly robust, providing α-bromonitriles with PBr_3, Br_2[387] and α-chloronitriles with PCl_5, pyridine (Scheme II-4-1).[388] Collectively, these halogenations provide a range of α-halonitriles for probing the halogen-metal exchange.

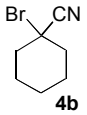
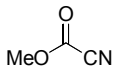
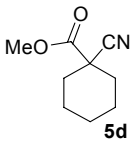
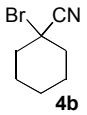
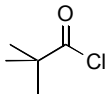
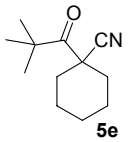
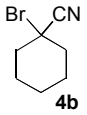
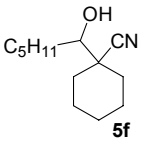
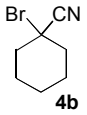
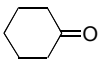
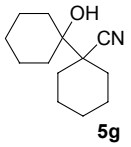
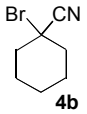
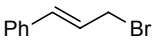
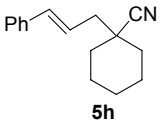
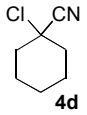
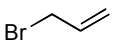
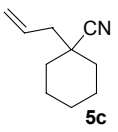
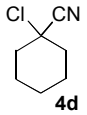
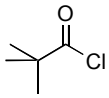
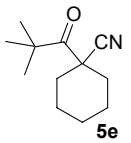
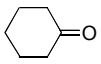
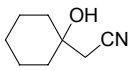
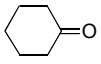
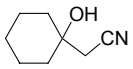
Scheme II-4-1. Synthesis of α-Halonitriles

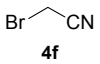
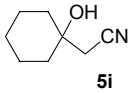


Halogen-metal exchange of α-halonitriles is extremely rapid. Exploratory exchange reactions with **4a** and *i*-PrMgBr causes an immediate color change that correlates with the virtually instantaneous exchange at -78 °C. Intercepting the metallated nitrile derived from **4a** with allyl bromide affords the corresponding quaternary nitrile **5a** (Table II-4-1, entry 1). The generality of the halogen-metal exchange was probed with **4b** and a range of electrophiles which affords a variety of alkylated nitriles (Table II-4-1, entries 2-8).

Table II-4-1. Halogen-Metal Exchange of α-Halonitriles

Entry	α-Halonitrile	Condition	Nitrile	Yield[a] a	Yield[a] b
1	 **4a**[b]	*i*-PrMgBr 	 **5a**	72%	
2	 **4a**[b]	*i*-PrMgBr 	 **5b**		71%
3	 **4b**	*i*-PrMgBr 	 **5c**	62%	82%

4	 **4b**	*i*-PrMgBr 	 **5d**	58%	80%
5	 **4b**	*i*-PrMgBr 	 **5e**	52%	70%
6	 **4b**	*i*-PrMgBr 	 **5f**		65%
7	 **4b**	*i*-PrMgBr 	 **5g**		73%
8	 **4b**	*i*-PrMgBr 	 **5h**		70%
9	 **4d**	BuLi 	 **5c**	72%	
10	 **4d**	BuLi 	 **5e**	54%	
11	 **4e**	*i*-PrMgBr 	 **5i**		79%
12	 **4e**	*n*-BuLi 	 **5i**		51%

13	 **4f**	*i*-PrMgBr	 **5i**	60%[c]

[a] Isolated yields for sequential metallation-alkylation, procedure A, and with an *in situ* metallation-alkylation, procedure B. [b] Prepared by free radical bromination with NBS.[389] [c] Contains 6% of the hydroxynitrile obtained by deprotonation and 1,2-addition.

The extremely rapid halogen-metal exchange suggested performing the exchange with the electrophile *in situ.*[390] Remarkably, the *in situ* electrophilic alkylation is successful with acyl cyanide, acid chloride, ketone and even aldehyde electrophiles (Table II-4-1, entries 2, 4-7). In no instance was prior addition of the organometallic to the electrophile observed, in fact the yield of reactions with *in situ* electrophilic alkylation was consistently 20% higher (Table II-4-1, column b). Alkylation with cinnamyl bromide (entry 8) reveals an exclusive preference for S_N2 displacement rather than S_N2' displacement as observed with arylacetonitrile alkylations.[391]

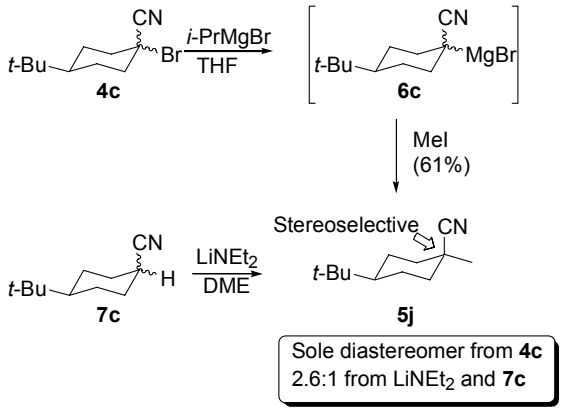
Significantly, the successful *in situ* metallation-alkylation of iodoacetonitrile with *i*-PrMgBr indicates that the metal halogen exchange is even faster than the potentially competitive deprotonation (entry 11).[392] An analogous exchange of bromoacetonitrile with nBuLi (entry 13) affords 6% of the hydroxynitrile resulting from deprotonation and 1,2 additon to cyclohexanone, indicating that the exchange with α-bromonitriles is slightly more difficult than with α-iodonitriles.

α-Chloronitriles are successfully metallated despite the difficulty generally observed in chlorine-metal exchange reactions.[393] Metal-halogen exchange of chloronitriles is best achieved with BuLi rather than *i*-PrMgBr, allowing sequential lithiation-alkylation (Table II-4-1, entries 9-10). Formation of lithiated nitriles from α-chloronitriles is particularly significant since numerous α-chloronitriles are readily available from Diels-Alder

cycloadditions.[385] Lithium-chlorine exchange explains the previously perplexing conversions of α-chloronitriles to ketones by sequential treatment with BuLi[394] or LDA,[395] and oxygen.

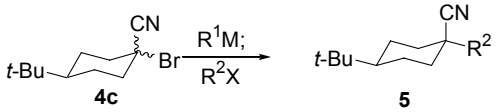
Mechanistically, halogen-metal exchange likely initially generates a C-metallated nitrile.[396] Configurational stability of the putative C-metallated nitrile was probed through the in situ methylation of a diastereomeric mixture[397] of nitriles **4c** (Scheme II-4-2). Formation of a single methylated nitrile **5j** indicates that the equilibration of the C-metallated nitriles is rapid, relative to methylation, presumably though a conducted tour mechanism.[380] Exclusive[398] formation of the equatorially-oriented methyl group suggests the intermediacy of a single C-metallated nitrile since the corresponding alkylation of **7c**, via an N-metallated nitrile,[399] affords a 2.6 to 1 ratio of diastereomers.[400] Although tentative, the stereoselective exchange-methylation is consistent with formation of an equatorial, C-magnesiated nitrile that alkylates methyl iodide with retention of configuration.[401]

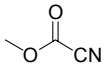
Scheme II-4-2. Stereoselective Nitrile Alkylations

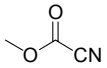


Probing the effect of temperature on the halogen-metal exchange proved to be particularly revealing. Surprisingly, *i*-PrMgBr exchange of bromonitrile **4c** and addition of MeI gives exclusively equatorial methylation regardless of the temperature (Table II-4-2, entries 1-3). Analogous *i*-PrMgBr exchange and alkylation with methyl cyanoformate similarly affords primarily the equatorially acylated nitrile regardless of the configurationa of the nitrile-bearing carbon (Table II-4-2, entries 4-5). The equatorial alkylation stereoselectivty directly contrasts with the BuLi exchange and methylation where the 3:1 ratio implies a constitutional change to an N-lithiated nitrile (compare to Scheme II-4-2, **7c** → **5j**). Collectively these alkylations indicate a rapid equilibration of the initially-formed metallated nitriles leading to equatorial, C-magnesiated nitriles that alkylate with retention of configuration, or an N-lithiated nitrile that alkylates with a modest preference for equatorial alkylation.

Table II-4-2. Stereoselectivity of Halo-Metal Exchange-Alkylations



Entry	Organometallic	T (^{o}C)	Electrophile	Selectivity[a]	Yield
1	*i*-PrMgBr	-78^{o}C	MeI	0:1	61%
2	*i*-PrMgBr	0^{o}C	MeI	0:1	75%
3	*i*-PrMgBr	r.t.	MeI	0:1	87%
4	*i*-PrMgBr[b]	-78^{o}C		1:12	62%

5	*i*-PrMgBr[c]	-78°C		1:17	71%
6	*n*-BuLi	-78°C	MeI	1:3	56%

[a]A diastereomeric mixture of bromonitriles was employed unless otherwise specified. [b]A single diastereomeric bromonitrile was employed. [c]A single bromonitrile diastereomeric to that in entry 4 was employed

II-4-3. Conclusion

Grignard and alkyllithium reagents trigger the rapid metal-halogen exchange of α-halonitriles. The resulting metallated nitriles alkylate a variety of electrophiles that are most efficiently intercepted *in situ*. Distinct stereoselectivity differences between metallated nitriles obtained by halogen-metal exchange and $LiNEt_2$ deprotonation suggest structural differences caused by the presence of the amine. Collectively the metal-halogen exchange provides a general route to metallated nitriles for probing the stereo- and regiochemical dependence of amines in metallated nitrile alkylations.

III. Summary

Cyclic nitriles are versatile precursors to numerous structural entities. γ-Hydroxyl-α, β-unsaturated nitriles, generated from α, β-unsaturated ketones through an unusual rearrangement, are ideal precursors to bicyclic nitriles. Chelation-controlled conjugated addition to these nitriles allows the first annulation to unsaturated nitriles and facilitated a more efficient 1, 2 addition - chelation-controlled conjugate addition to oxonitriles. Remarkably the resulting C-magnesiated nitriles alkylate alkyl halide, alkyl sulfonate, and ketone electrophiles with retention of stereochemistry whereas aldehyde and acyl cyanide electrophiles alkylate invertion of stereochemistry. Predictable alkylation trends provide a fast, effective method to furnish complex molecules in one synthetic operation with complete stereocontrol. The value of this in the synthesis of natural products is illustrated in the three-step synthesis of *epi*-dehydroabietic acid.

α-Halonitriles exchange with *i*-PrMgBr to deliver C-magnesiated nitriles whose stereoselective alkylations differ significantly from those of N-metallated nitirles. Alkylate with an array of electrophiles affords predominantly one diastereomer with the rapid exchange tolerating aldehyde, ketone and acyl cyanide electrophiles *in situ*.

Collectively these diverse alkyaltion strategies illustrate the versatility of cyclic nitriles. Rapid assembly of complex, cyclic nitriles provides an ideal synthesis of intermediates for synthesis that is likely to stimulate future development in this direction.

IV. Experimental[402]

IV-1. Cyclic Alkenenitriles: Synthesis, Conjugate Addition, and Stereoselective Annulation

General methylthiomethylation procedure.[403] An Ac_2O solution of the TMS cyanohydrin (4.6-1.1 mmol) was added to a room temperature, Ac_2O-DMSO solution (12 – 24 mM, 1:2), prepared 6 h in advance, followed by additional DMSO to maintain a 1:2 solvent ratio. After 40 h aqueous, 3M NaOH (26 mL) was added, and the reaction mixture extracted with hexane. The combined extracts were washed successively with 1M NaOH and water, dried (Na_2SO_4), and concentrated to afford a crude product that was then purified by radial chromatography.

1-(Methylthiomethoxy)cyclohex-2-enecarbonitrile (6a): Performing the general procedure with **5a**[404] (330 mg, 3.47mmol) provided, after purification by radial chromatography (1:19 EtOAc/hexanes), 250 mg (70%) of **6a** as an oil: IR (film) 3037, 1646 cm^{-1}; ^1H NMR δ 1.74-1.88 (m, 2H), 2.04-2.29 (m, 4H), 2.23 (s, 3H), 4.75 (s, 2H), 5.85(d, 1H, J = 9.9 Hz), 6.12 (dt,1H, J = 10, 3.7 Hz); ^{13}C NMR δ 14.6, 17.8, 24.5, 33.4, 70.5, 70.8, 119.8, 123.6, 135.1.

1-(Chloromethoxy)cyclohex-2-enecarbonitrile (11a): Neat thionyl chloride (12 μL, 0.15 mmol) was added to a room temperature CH_2Cl_2 solution (2 mL) of **6a** (31 mg, 0.145 mmol). After 10 min the solvent was removed to afford **11a** as an oil that was used

without purification: IR: 1652, 1096 cm^{-1}; ^{1}H NMR δ 1.78-1.95 (m, 2H), 2.02-2.14 (m, 4H), 5.65 (s, 2H), 5.87-5.95 (m, 1H), 6.18-6.26 (m, 1H); ^{13}C NMR δ 17.6, 24.3, 33.7, 72.3, 119.1, 122.6, 135.6.

1-(Cyanomethoxy)cyclohex-2-enecarbonitrile (vi): Standard[405] cyanide displacement was performed on the crude chloride **11a** with TMSCN (0.3 mmol, 30mg), TBAF (0.3mmol, 0.3mL) in MeCN at 80°C for 5 min to afford a light yellow mixture that was concentrated under vacuum to afford, after radial chromatography (3:17 EtOAc/Hexane), the dinitrile **vi** 48 mg (63%, from **6a**) as an oil: IR (film) 3039, 2234, 1646 cm^{-1}; ^{1}H NMR δ 1.72-1.91 (m, 2H), 2.09-2.19 (m, 4H), 4.41 (s, 3H), 5.75-5.84 (m, 1H), 6.19-6.27 (m, 1H): ^{13}C NMR δ 17.4, 24.4, 32.7, 51.2, 72.3, 115.6, 118.4, 121.7, 137.3.

1-Cyano-3-methyl-1-trimethylsilyloxy-cyclopent-2-ene (5b): Following the standard cyanosilylation procedure,[406] a CH_2Cl_2 solution (20 mL) of 3-methylcyclopent-2-en-1-one (0.49 mL, 4.32 mmol,) was added to dry ZnI_2 (850 mg, 2.6 mmol, dried at 120°C under high vacuum for 2 h) and the suspension cooled to 0 °C. Stirring was continued until a homogenous solution was obtained and then neat Me_3SiCN (792 mg, 8mmol) was added. After 40 min Et_3N (2.5 mL) and Et_2O (50 mL) were added, and then the mixture was poured into water in a well ventilated fume hood. The reaction mixture was extracted with Et_2O and the combined extract was then washed with brine, dried (Na_2SO_4), and concentrated to afford a crude product that was purified by radial chromatography (1:49 EtOAc/hexanes) to afford 610 mg (62%) of **5b** as a colorless oil: IR (film) 3061, 2226,

1654 cm^{-1}; ^1H NMR δ 0.21 (s, 9H), 1.80 (s, 3H), 2.13-2.66 (m, 4H), 5.46 (s, 1H); ^{13}C NMR δ 1.2, 16.6, 34.7, 41.3, 78.2, 121.8, 126.1, 149.0; MS: 195 (M^+).

1-(1,1-Dimethyl-1-silaethoxy)-3-methylcyclohex-2-enecarbonitrile (5c): Repeating the procedure for **5b** with ZnI_2 (530 mg, 1.63mmol), 3-methyl-cyclohexen-1-one (330 mg, 3.0 mmol), and Me_3SiCN (476 mg, 4.8 mmol) in CH_2Cl_2 (12 mL) afforded, after radial chromatography (1: 49 EtOAc/hexanes), 600 mg (95%) of **5c** as a colorless oil: IR (film) 2228, 1667 cm^{-1}; ^1H NMR δ 0.23 (s, 9H), 1.72 (s, 3H), 1.73-2.11 (m, 6H), 5.49 (s, 1H); ^{13}C NMR δ 1.4, 18.6, 23.3, 29.3, 36.7, 67.4, 122.1, 122.2, 141.1.

1-(1,1-Dimethyl-1-silaethoxy)-3,5,5-trimethylcyclohex-2-enecarbonitrile (5d): Repeating the procedure for **5b** with ZnI_2 (477 mg, 1.50mmol), 3,5,5-trimethylcyclohex-2-en-1-one (414 mg, 3.0 mmol), and Me_3SiCN (445 mg, 4.4 mmol) in CH_2Cl_2 (12 mL) afforded, after radial chromatography (1: 49 EtOAc/hexanes), 480 mg (68%) of **5d** as a colorless oil: IR (film) 2227, 1670 cm^{-1}; ^1H NMR δ 0.25 (s, 9H), 1.00 (s, 3H), 1.06 (s, 3H), 1.74 (s, 3H), 1.78-1.88 (m, 3H), 2.01 (d, J = 13.6 Hz, 1H), 5.48 (s, 1H); ^{13}C NMR δ 1.4, 23.6, 28.2, 29.3, 30.3, 43.5, 48.7, 67.1, 120.2, 122.1, 139.6; MS: 237 (M^+).

3-Cyano-3-trimethylsilyloxy-4-cholestene[407] (i): Repeating the procedure for **5b** with ZnI_2 (500 mg, 1.57 mmol), 4-cholesten-3-one (1.15 g, 3.0 mmol), and Me_3SiCN (445 mg, 4.50 mmol) in CH_2Cl_2 (12 mL) afforded, after radial chromatography (1: 49 EtOAc/hexanes), 1.08 g (75%) of **i** as a colorless oil: IR (film) 2225, 1655 cm^{-1}; ^1H NMR δ 0.24 (s, 9H), 0.67 (s, 3H), 0.86 (d, J = 6.6 Hz, 6H), 0.90 (d, J = 6.5 Hz, 3H), 1.04

(s, 3H); 0.73-2.23 (m, 26H), 5.30 (s, 1H) ^{13}C NMR δ 1.4, 11.8, 18.3, 18.5, 20.8, 22.4, 22.7,23.7, 24.0, 27.8, 28.0, 31.9, 32.4, 33.8, 34.1, 35.6, 36.0, 37.1, 39.4, 39.5, 42.3, 53.6, 55.7, 56.0, 68.4, 120.6, 121.4, 150.2; MS: 483 (M^+).

3-Methyl-3-(methylthiomethoxy)cyclopent-1-enecarbonitrile (14b): Performing the DMSO-Ac_2O general procedure with **5b** (610 mg, 3.13 mmol) provided, after purification by radial chromatography (1:19 EtOAc/hexanes), 140 mg (24%) of **14b** as an oil: IR (film) 2222, 1733 cm^{-1}; ^{1}H NMR δ 1.41 (s, 3H), 1.89-2.38 (m, 2H), 2.16 (s, 3H), 2.50-2.75 (m, 2H), 4.43(ABq, Δυ = 16.3, *J* = 11.0 Hz), 6.61 (s,1H); ^{13}C NMR δ 14.3, 25.0, 33.1, 35.3, 68.6, 88.7, 115.9, 116.8, 150.9; MS 183 (M^+).

3-Methyl-3-(1-methyl-1-thiavinyloxy)cyclohex-1-enecarbonitrile (14c): Performing the DMSO-Ac_2O general procedure with **5c** (370 mg, 1.77 mmol) provided, after purification by radial chromatography (1:19 EtOAc/hexanes), 210 mg (55 %) of **14c** as an oil: IR (film) 2220, 1632 cm^{-1}; ^{1}H NMR δ 1.35 (s, 3H), 2.18 (s, 3H), 1.41-2.32 (m, 6H), 4.51 (ABq, Δυ = 13.7, *J* = 10.7 Hz), 6.52 (s,1H); ^{13}C NMR δ 14.4, 18.8, 25.5, 26.8, 33.1, 67.9, 73.4, 115.1, 118.6, 147.1.

3,5,5-Trimethyl-3-(methylthiomethoxy)cyclohex-1-enecarbonitrile (14d): Performing the general procedure with **5d** (440 mg, 1.85 mmol) provided, after purification by radial chromatography (1:19 EtOAc/hexanes), 176 mg (40%) of recovered **5d**, 82.5 mg (20 %) of **14d**, and 78 mg (18%) of **16d** as oils. For **14d**: IR (film) 2222 cm^{-1}; ^{1}H NMR δ 0.99 (s, 3H), 1.05 (s, 3H), 1.35 (s, 3H), 1.20-2.09 (m, 4H), 4.49 (s, 2H), 6.55 (s,1H); ^{13}C NMR δ

14.5, 26.2, 27.8, 29.9, 30.0, 40.4, 45.9, 67.4, 73.8, 113.6, 118.9, 145.2; MS 225 (M^+). For **16d**: IR (film) 2222, 1748 cm^{-1}; ^1H NMR δ 1.00 (s, 3H), 1.01 (s, 3H), 1.35 (s, 3H), 1.15 (ABq, Δυ= 13.7, *J* = 14.5 Hz), 1.95-2.19 (m, 2H), 2.08 (s, 3H), 5.29-5.34 (m, 2H) 6.49 (s,1H); ^{13}C NMR δ 21.2, 26.7, 27.6, 30.0, 30.1, 40.3, 46.7, 74.5, 83.5, 114.0, 118.8, 144.7, 170.2; HRMS(ESI) calcd for ($M+Na^+$), $C_{13}H_{19}NO_3Na^+$ 260.1257, found 260.1282.

3-Hydroxy-3-methylcyclopent-1-enecarbonitrile (1a): Standard mercury-assisted hydrolysis[408] was performed by adding solid mercuric chloride (407 mg, 1.5 mmol) to an acetonitrile-water solution (4:1, 5 mL) of **14b** (180 mg, 0.98 mmol). After 8 h the reaction mixture was filtered through celite, washed with saturated, aqueous NH_4OAc and then the aqueous layer was re-extracted with ether. The combined extract was washed with brine, dried (Na_2SO_4), concentrated, and purified by radial chromatography (3:7 EtOAc/hexanes) to afford 110 mg (90%) of **1a** as an oil: IR (film) 3445, 2230, 1645 cm^{-1} ; ^1H NMR δ 1.44 (s, 3H), 1.58 (br s, 1H), 1.99-2.18 (m, 2H), 2.53-2.80 (m, 2H), 6.51 (t, *J* = 2.0 Hz, 1H); ^{13}C NMR δ 26.6, 32.8, 39.0, 82.9, 115.3, 116.0, 152.9; MS: 124 ($M+H^+$).

3-Hydroxy-3-methylcyclohex-1-enecarbonitrile (1b): Repeating the procedure for **1a** with **14c (**190 mg, 0.97 mmol) afforded, after radial chromatography (3:7 EtOAc/hexanes), 110 mg (92%) of **1b** as an oil: IR (film) 3425, 2226, 1631 cm^{-1}; ^1H NMR δ 1.34 (s, 3H), 1.62-2.28 (m, 7H), 6.42 (s, 1H); ^{13}C NMR δ 18.7, 26.6, 28.3, 36.1, 67.4, 113.1, 118.7, 148.8; MS 137 (M^+).

3-Hydroxy-3,5,5-trimethylcyclohex-1-enecarbonitrile (1c): Repeating the procedure for **1a** with **14d (**82.5 mg, 0.37 mmol) afforded, after radial chromatography (3:7 EtOAc/hexanes), 35 mg (59%) of **1c** as an oil: IR (film) 3439, 2223, 1636 cm^{-1}; ^{1}H NMR δ 1.01 (s, 3H), 1.06 (s, 3H), 1.33 (s, 3H), 1.53-1.73 (m, 2H), 1.95-2.08 (m, 2H), 6.43 (s, 1H) ; ^{13}C NMR δ 27.1, 29.8, 30.2, 40.1, 49.0, 68.1, 111.7, 119.0, 147.4; MS 166 (M+H).

5(*R*)-Hydroxycholest-3-ene-3-carbonitrile (iii): Aqueous, 1M HCl (3 mL) was added to a methanolic solution (6 mL) of **i** (2.24 mmol, 1.08g) at room temperature. After 1 h the solution was concentrated and dried under high vacuum to afford spectrally pure **ii** as a powder: IR (KBr) 3401, 2224, 1654 cm^{-1}; ^{1}H NMR δ 0.67 (s, 3H), 0.85 (s, 3H), 0.87 (s, 3H), 0.90 (d, J = 6.5 Hz, 3H); 1.05 (s, 3H), 0.97-2.20 (m, 29H), 5.30 (s, 1H) ; ^{13}C NMR δ 11.9, 18.5, 18.6, 21.0, 22.5, 22.8, 23.8, 24.1, 28.0, 28.2, 32.0, 32.5, 32.9, 34.1, 35.8, 36.1, 37.5, 39.5, 39.6, 42.4, 53.8, 55.8, 56.1, 67.4, 118.7, 121.7, 152.4. Solid $TsOH•H_2O$ (32 mg, 0.17 mmol) was added to a room temperature, CH_2Cl_2 solution (5 mL) of **ii** (70 mg, 0.17 mmol). After stirring at room temperature overnight, saturated, aqueous NH_4Cl was added, the mixture extracted with EtOAc, and the crude extracts concentrated and purified by radial chromatography (1:9 EtOAc/Hexanes) to afford 33.6 mg (48%) of recovered **ii,** 17.5 mg of **iii (25%)**, 11.4 mg (18%) of **iv**, and 5.9 mg (9%) of **v**. For **iii**:[409] IR (KBr) 3442, 2222, 1678 cm^{-1}; ^{1}H NMR δ 0.59 (s, 3H), 0.85 (s, 3H), 0.87(s, 3H), 0.90 (d, J = 6.6 Hz, 3H), 0.98 (s, 3H), 1.02-2.02 (m, 29H), 6.34 (s, 1H) ; ^{13}C NMR δ 11.9, 15.9, 18.6, 22.3, 22.5, 22.8, 23.8, 24.1, 26.8, 28.0, 28.1, 28.7, 34.7, 35.0, 35.7, 36.1, 38.4, 39.5, 39.7, 42.4, 43.5, 56.0, 56.1, 71.3, 115.1, 118.8, 148.7; MS 411 M^{+}; HRMS(ESI) calcd for ($M+Na^{+}$), $C_{28}H_{45}NONa^{+}$ 434.3393, found 434.3393 For **(iv):** IR (KBr) 2204,

1635 cm^{-1}; ^1H NMR δ 0.70 (s, 3H), 0.85 (s, 3H), 0.87(s, 3H), 0.90 (d, *J* = 4 Hz, 3H); 0.92 (s, 3H), 0.96-2.32 (m, 29H), 5.78 (s, 1H), 6.64 (s, 1H) ; ^{13}C NMR δ 12.0, 18.7, 18.9, 20.9, 22.6, 22.8, 23.8, 24.1, 24.4, 28.0, 28.2, 31.6, 32.2, 32.8, 34.5, 35.8, 36.2, 39.5, 39.6, 42.5, 47.9, 56.1, 56.7, 106.5, 120.4, 132.9, 139.9, 143.4; HRMS(ESI) calcd for ($M+Na^+$), $C_{28}H_{43}NNa^+$ 416.3288, found 416.3254.

General annulation procedure: A THF solution of *t*-BuMgCl (1.2 equiv) was added to a –78 °C, THF solution (0.6 M) of the alkenenitrile. After 10 min, a THF solution of the chloroalkyl Grignard reagent (1.5 equiv) was added and, after 10 min, the solution was allowed to warm to room temperature over a 2 h period. Subsequent addition of saturated, aqueous NH_4Cl, extraction, and radial chromatography afforded the spectroscopically pure bicyclic nitrile.

(1*R,5*S**,6*S**)-6-Hydroxy-6-methyl-4-methylenebicyclo[3.3.0]octanecarbonitrile** (**18a**): The Grignard reagent **17a** was prepared by standard[410] halogen-magnesium exchange as follows: A THF solution of *i*-PrMgCl (1.5 M, 0.20 mmol) was added to a -10 ^oC, THF solution (2 mL) of 1-chloro-3-iodo-4-butene[411] (0.17 mmol). After 1.5 h at -10 ^oC the solution was cooled to -78 ^oC followed by addition of a cold THF solution of the magnesium alkoxide prepared by deprotonation of nitrile **1a** (17 mg, 0.14 mmol) with 1.2 eq *t*-BuMgCl (1.2M) at –78 ^oC for 10 min. After 30 min at -78 ^oC a hexanes solution of *t*-BuLi (1.2 M, 0.40 mmol) was added. The resultant mixture was maintained at -78^oC for 30 min, the cooling bath was removed, and then the reaction allowed to warm to room temperature over a 2 h period. Subsequent addition of saturated NH_4Cl, extraction and

radial chromatography (1:4 EtOAc/Hexane) afforded the product 13.1 mg as a white solid (62%) (m.p. 73-74 ^{o}C) IR (KBr) 3497, 3074, 2233, 1658 cm^{-1}; ^{1}H NMR δ 0.94 (dd, *J* = 18.6, 6.7 Hz, 1H), 1.12 (dd, *J* = 20.3, 6.6 Hz, 1H), 1.42 (s, 3H), 1.87-2.50 (m, 7H), 3.06 (s, 1H), 4.98 (s, 1H), 5.17 (s, 1H); ^{13}C NMR δ 28.1, 34.5, 36.3, 37.2, 41.5, 47.5, 65.7, 80.0, 109.4, 126.0, 149.3; MS: 178 (M+H); HRMS(ESI) calcd for (M+Na^{+}), $C_{11}H_{15}NONa^{+}$ 200.1046, found 200.1055.

(1*R,6*S**,7*S**)-7-hydroxy-7-methyl-5-methylenebicyclo[4.3.0]nonanecarbonitrile (18b):** The Grignard reagent **17b** was prepared by standard halogen-magnesiate[412] exchange as follows: A hexanes solution of *n*-BuLi (1.2 M, 0.29 mmol) was added to a room temperature, THF solution of *i*-PrMgCl (2.0 M, 0.14 mmol). After 0.5 h the mixture was cooled to -78 ^{o}C and a THF solution (1 mL) of 1-chloro-4-iodo-5-pentene[411] (26 mg, 0.12 mmol) was added, maintaining the temperature at -78 ^{o}C for 1 h before using in the general procedure. Performing the general procedure with **1a (**15 mg, 0.12 mmol) and Grignard **17b** (0.12 mmol) afforded, after chromatography (1:4 EtOAc/Hexanes) 16 mg (68%) of **18b** as a white solid (m.p. 88-90 ^{o}C) IR (KBr) 3492, 3074, 2230, 1633 cm^{-1}; ^{1}H NMR δ 1.34 (s, 3H), 1.20-2.30 (m, 11H), 2.53 (s, 1H), 4.83 (s, 1H), 5.08 (s, 1H); ^{13}C NMR δ 23.6, 28.3, 32.8, 32.9, 35.9, 39.5, 42.6, 60.5, 81.5, 115.3, 125.2, 142.3; MS 192 (M+H^{+}); HRMS (ESI) calcd for (M+Na^{+}), $C_{12}H_{17}NONa^{+}$ 214.1202, found 244.1214.

(1*R,6*S**,7*S**)-7-Hydroxy-7-methylbicyclo[4.3.0]nonanecarbonitrile (18c) :** Performing the general procedure with **1a (**14 mg, 0.11 mmol) and a THF solution of chlorobutylmagnesium bromide[413] afforded, after radial chromatography (1:4

EtOAc/hexanes), 11.0 mg (56%) of **18c** as a white solid (m.p. 94-95 ^{o}C): IR (KBr) 3502, 2233 cm^{-1}; ^{1}H NMR δ 1.28 (s, 1H), 1.35 (s, 3H), 1.50-2.23 (m, 13H); ^{13}C NMR δ 20.7, 21.5, 21.8, 28.6, 32.5, 35.7, 40.1, 40.8, 51.6, 81.1, 126.0; MS 180 (M+H^{+}); HRMS(ESI) calcd for (M+Na^{+}), $C_{11}H_{17}NONa^{+}$ 202.1202, found 202.1200.

(1*S,5*S**,6*S**)-5-hydroxy-5-methyl-7-methylenebicyclo[4.3.0]nonanecarbonitrile (18d):** Performing the general procedure with **1b (**18mg, 0.13mmol) and Grignard **17a**, prepared as for **17b**[412] with 1-chloro-3-iodo-4-butene,[411] afforded, after chromatography (1:4 EtOAc/Hexanes) 17.7 mg (65%) of **18d** as a white solid (m.p. 109-110 ^{o}C): IR (KBr) 3492, 3079, 2235, 1657 cm^{-1}; ^{1}H NMR δ 1.30 (s, 1H), 0.88-2.09 (m, 11H), 2.21-2.82 (m, 3H), 5.19 (s, 1H), 5.23 (s, 1H); ^{13}C NMR δ 16.0, 30.2, 30.7, 32.8, 37.4, 42.9, 57.2, 70.2, 112.5, 126.0, 149.1; HRMS (ESI) calcd for (M+Na^{+}), $C_{12}H_{17}NONa^{+}$ 214.1202, found 244.1219.

(1*R,5*S**,6*S**)-5-hydroxy-5-methylbicyclo[4.4.0]decanecarbonitrile (18e):** Performing the general procedure with **1b (**17 mg, 0.12 mmol) and chlorobutylmagnesium bromide[413] afforded, after chromatography (1:4 EtOAc/Hexanes) 15.3 mg (58%) of **18e** as a white solid (m.p. 101-103^{o}C): IR (KBr) 3472, 2238 cm^{-1}; ^{1}H NMR δ 1.15 (s, 1H), 1.48 (s, 3H), 1.22-1.98 (m, 14H), 2.12-2.17 (m, 1H); MS 194 (M+H^{+}); HRMS (ESI) calcd for (M+Na^{+}), $C_{12}H_{19}NONa^{+}$ 216.1359, found 216.1373.

(1*R, 6*S**, 7*S**)-7-Hydroxy-7-methyl-5-methylenebicyclo[4.4.0]decanecarbonitrile (18f):** Performing the general procedure with **1b (**17 mg, 0.12 mmol) and Grignard **17b**

(0.15, mmol), prepared as for **18b**, afforded, after radial chromatography (1:4 EtOAc/hexane**s**), 19.0 mg (75%) of **18f** as a white solid[414] (m.p. 155-156 ^{o}C): IR (KBr) 3472, 3080, 2234, 1646 cm^{-1}; ^{1}H NMR δ 0.96 (s, 1H), 1.23 (s, 3H), 1.37-2.03 (m, 9H), 2.12-2.22 (m, 2H), 2.40-2.56 (m, 2H), 4.80 (s, 1H), 5.06 (s, 1H); ^{13}C NMR δ 16.7, 24.1, 28.9, 31.0, 31.8, 36.5, 40.4, 40.5, 54.5, 71.4, 115.5, 124.9, 144.4; MS 206 (M+H^{+}); HRMS (ESI) calcd for (M+Na^{+}), $C_{13}H_{19}NONa^{+}$ 228.1359, found 228.1353.

(1*R,5*S**,6*S**)-5-hydroxy-3,3,5-trimethylbicyclo[4.4.0]decanecarbonitrile (18g):** Performing the general procedure with **1c** (16.4 mg, 0.10 mmol) and chlorobutylmagnesium bromide[413] afforded, after chromatography (1:4 EtOAc/Hexanes) 12.0 mg (55%) of **18g** as a white solid (m.p. 118-119 ^{o}C): IR (KBr) 3489, 2228 cm^{-1}; ^{1}H NMR δ 1.12 (s, 3H), 1.14 (s, 3H), 1.51 (s, 3H), 0.93-1.98 (m, 13H), 2.22-2.30 (m, 1H); ^{13}C NMR δ 22.2, 22.5, 23.2, 31.0, 31.7, 31.9, 32.4, 35.1, 37.4, 44.0, 45.9, 50.1, 73.3, 126.9; HRMS (ESI) calcd for (M+Na^{+}), $C_{14}H_{23}NONa^{+}$ 244.1672, found 244.1683.

(1*R,5*S**,6S*)-5-Hydroxybicyclo[4.4.0]decanecarbonitrile (18h).** Performing the general procedure with **1d**[415] (45.3 mg, 0.37 mmol) and chlorobutylmagnesium bromide[413] (2.5 equiv) afforded, after radial chromatography (2:3 EtOAc/hexanes) 41.9 mg (64%) of **18h** as an oil:[416] IR (film) 3421, 2230 cm^{-1}; ^{1}H NMR δ 1.19-2.10 (m, 16H), 4.13 (dt, *J* = 11.7, 4.5 Hz, 1H); ^{13}C NMR δ 18.7, 20.8, 21.4, 24.8, 26.7, 28.4, 36.1, 38.4, 44.5, 69.9, 124.9; MS *m/e* 180 (M+1).

IV-2. Metallated Nitriles: Electrophile-Dependent Alkylations

General Multicomponent Addition-Alkylation procedure: A THF solution of the Grignard reagent (2 equiv) was added to a –78 ^{o}C, THF solution (0.1M) of the oxonitrile **3**. After 1 h at –78 ^{o}C, a THF solution of the second Grignard reagent (1.5 equiv) was added, or for reactions with only one Grignard reagent, 3.5 eq was added initially. The mixture was stirred at –78 ^{o}C for 10 min, and then warmed to room temperature. After 1.5 h, the electrophile (3 equiv) was added neat either at room temperature or with prior cooling to –78 ^{o}C. Subsequent addition of saturated NH_4Cl and extraction with EtOAc afforded a crude product that was washed with brine and dried ($MgSO_4$), concentrated and purified by radial chromatography to afford the pure nitrile.

(1*R*,2*S*,3*R*)-3-hydroxy-1,2,3-trimethylcyclohexanecarbonitrile (8a): The standard procedure was employed with oxonitrile **3** (130 mg, 1.06 mmol) and MeMgCl (1.9M, 2.12 mmol) except that 1.5 h after warming the reaction to room temperature, methyl iodide (452 mg, 3.18 mmol) was added to afford, after radial chromatography (stepped gradient 1:4, 1:5 EtOAc/hexanes), **8a** 154 mg (86%) as a crystalline solid (m.p. 100-103 ^{o}C) whose structure was confirmed by X-ray crystallography: IR (film) 3475, 2233 cm^{-1}; ^{1}H NMR: δ 1.19 (d, *J* = 7.4 Hz, 3H), 1.22 (s, 3H), 1.44 (s, 3H) 1.01-1.98 (m, 8H); ^{13}C NMR: δ 10.7, 16.5, 18.1, 30.1, 37.1, 37.4, 39.7, 44.0, 70.8, 126.4; HRMS(ESI) calcd for (M+Na^{+}), $C_{10}H_{17}NONa^{+}$ 190.1202, found 190.1202.

(1*R*,2*S*,3*R*)-3-hydroxy-1,3-dimethyl-2-phenylcyclohexanecarbonitrile (8b) : The standard procedure was employed with oxonitrile **3** (20.8 mg, 0.17 mmol), MeMgCl

(1.95M, 0.34mmol) and PhMgCl (1.6M, 0.26mmol) except that 1.5 h after warming the reaction to room temperature, methyl iodide (72 mg, 0.51 mmol) was added to afford, after radial chromatography (1:4 EtOAc/hexanes), **8b** 28 mg (71%) as a crystalline solid (m.p. 146-148 ^{o}C) whose structure was confirmed by X-ray crystallography: IR (film) 3460, 3049, 2226 cm^{-1}; ^{1}H NMR: δ 1.02 (s, 3 H), 1.28 (br s, 1H), 1.60 (s, 3 H), 1.37-1.75 (m, 3H), 1.97-2.11 (m, 3H), 2.71 (s, 1H), 7.26-7.54 (m, 5H); ^{13}C NMR: δ 17.0, 19.7, 31.2, 38.4, 38.4, 41.2, 56.9, 72.4, 125.4, 127.5, 128.0, 137.7; HRMS(ESI) calcd for (M+Na^{+}), $C_{15}H_{19}NONa^{+}$ 252.1359, found 252.1352.

(1*S*,2*R*,3*S*)-3-hydroxy-2,3-dimethyl-1-propylcyclohexanecarbonitrile (8c): The standard procedure was employed with oxonitrile **3** (95 mg, 0.79 mmol) and MeMgCl (3M, 2.75 mmol), alkylating with iodopropane (400 mg, 2.36 mmol) at room temperature overnight and terminating the reaction with D_2O rather than $NHCl_4$, to afford, after radial chromatography (stepped gradient 3:17, 1:4, 1:3 EtOAc/hexanes), 107 mg (70%) of **8c** as a crystalline solid (m.p. 125-126 ^{o}C) whose structure was confirmed by X-ray crystallography: IR (film) 3469, 2235 cm^{-1}; ^{1}H NMR: δ 0.91-0.95 (m, 3H), 1.15 (d, *J* = 5.9 Hz, 3 H), 1.19 (s, 3 H), 1.36-1.78 (m, 9H), 2.02-2.10 (m, 3H); ^{13}C NMR: δ 10.4, 14.3, 16.6, 18.8, 30.4, 30.5, 33.0, 39.7, 42.0, 45.3, 71.1, 125.3. HRMS(ESI) calcd for (M^{+}), $C_{12}H_{21}NONa^{+}$ 218.1515, found 218.1509.

(1*R*,2*R*,3*S*)-1-allyl-3-hydroxy-2,3-dimethylcyclohexanecarbonitrile (8d) and **(1*S*,2*R*,3*S*)-1-allyl-3-hydroxy-2,3-dimethylcyclohexanecarbonitrile (8e):** The standard procedure was employed with oxonitrile **3** (19 mg, 0.16 mmol) and MeMgCl (1.9M, 0.55

mmol) alkylating with allyl bromide (56 mg, 0.04 mmol) at room temperature for 1 h to afford, after radial chromatography (1:9 EtOAc/hexanes), 7.9 mg (26%) of **8e** as an oil and 13.5 mg (45%) of **8d** as a crystalline solid (m.p. 73-74^{o}C) whose structure was confirmed by X-ray crystallography: IR (film) 3490, 3077, 2230, 1641 cm^{-1}; ^{1}H NMR: δ 1.02 (s, 1H), 1.22 (d, *J* = 9.1 Hz, 3H), 1.24 (s, 3 H), 1.40 - 1.72 (m, 5H), 1.83 (q, *J* = 7.1 Hz, 1H), 2.13 (br d, *J* = 11.4 Hz, 1H), 2.36 (dd, *J* = 14.5, 5.6 Hz, 1H), 2.87 (dd, *J* = 14.5, 9.0 Hz, 1H), 5.16 (d, *J* = 5.5 Hz, 1H), 5.20 (s, 1H), 5.82-5.93 (m, 1H); ^{13}C NMR: δ 10.6, 16.3, 30.6, 33.0, 33.2, 39.9, 41.6, 45.0, 71.2, 119.1, 124.8, 133.8; HRMS(ESI) calcd for (M+Na^{+}), $C_{12}H_{19}NONa^{+}$ 216.1359, found 216.1354. For **8e**: IR (film) 3492, 3075, 2231, 1635 cm^{-1}; ^{1}H NMR: δ 1.20 (d, *J* = 4.3 Hz, 3H), 1.20 (s, 3 H), 1.14 – 2.03 (m, 8H), 2.19 (dd, *J* = 13.8, 8.3 Hz, 1H), 2.60 (dd, *J* = 13.8, 6.3 Hz, 1H), 5.14-5.22 (m, 2H), 5.73-5.87 (m, 1H); ^{13}C NMR: δ 9.8, 18.6, 29.6, 35.0, 39.9, 40.7, 43.1, 45.3, 71.1, 120.1, 123.2, 131.4; HRMS(ESI) calcd for (M+Na^{+}), $C_{12}H_{19}NONa^{+}$ 216.1359, found 216.1377.

(1*R*,2*R*,3*S*)-1-benzyl-3-hydroxy-2,3-dimethylcyclohexanecarbonitrile (8f) and **(1*S*,2*R*,3*S*)-1-benzyl-3-hydroxy-2,3-dimethylcyclohexanecarbonitrile (8g):** The standard procedure was employed with oxonitrile **3** (20 mg, 0.16 mmol) and MeMgCl (1.9M, 0.57mmol) alkylating with BnBr (34 mg, 0.3 mmol) at room temperature for 0.5 h to afford, after radial chromatography (1:3 EtOAc/hexanes), 13 mg (33%) of **8g** as a white solid (m.p.137-139^{o}C) and 15 mg (38%) of **8f** as a crystalline solid (m.p. 115-116^{o}C) whose structure was confirmed by X-ray crystallography: IR (film) 3498, 2229 cm^{-1}; ^{1}H NMR: δ 1.28 (s, 3H), 1.35 (d, *J* = 6.7 Hz, 3 H), 1.15 – 2.02 (m, 8H), 2.85 (d, *J* = 13.9 Hz, 1H), 3.49 (d, *J* = 14.5 Hz, 1H), 7.26-7.33 (m, 5H); ^{13}C NMR: δ 10.8, 16.6, 30.7,

32.5, 34.0, 40.2, 43.2, 45.8, 71.4, 125.0, 126.9, 128.2, 130.5, 137.0; HRMS(ESI) calcd for ($M+Na^+$), $C_{16}H_{21}NONa^+$ 266.1515, found 266.1521. For **8g**: IR (film) 3496, 3061, 2230 cm^{-1}; ^1H NMR: δ 1.22 (s, 3H), 1.37 (s, 3 H), 1.15 – 1.87 (m, 8H), 2.58 (d, *J* = 13.3 Hz, 1H), 3.25 (d, *J* = 13.3 Hz, 1H), 7.23-7.31 (m, 5H); ^{13}C NMR: δ 10.2, 18.4, 29.7, 34.9, 39.9, 41.8, 44.8, 46.3, 71.2, 123.0, 127.3, 128.3, 130.5, 135.1; HRMS(ESI) calcd for ($M+Na^+$), $C_{16}H_{21}NONa^+$ 266.1515, found 266.1521.

(1*R*,2*R*,3*S*)-1-benzyl-3-hydroxy-3-methyl-2-phenylcyclohexanecarbonitrile (8h) and **(1*S*,2*R*,3*S*)-1-benzyl-3-hydroxy-3-methyl-2-phenylcyclohexanecarbonitrile (8i) :** The standard procedure was employed with oxonitrile **3** (20 mg, 0.16 mmol) alkylating with BnBr (82 mg, 0.48 mmol) at room temperature overnight, to afford, after radial chromatography (stepped gradient 1:9, 1:4, 1:3 EtOAc/hexanes), 6.5 mg (14%) of **8i** as a white sold (m.p.134-135 ^oC) and 23 mg (47%) of **8h** as a crystalline solid (m.p. 158-159 ^oC) whose structure was confirmed by X-ray crystallography: IR (film) 3498, 3088, 2230 cm^{-1}; ^1H NMR: δ 1.09 (s, 3H), 1.30 (s, 1H), 1.50-1.85 (m, 4H), 2.00-2.23 (m, 2H), 2.90 (s, 1H), 2.96 (d, *J* = 14.7 Hz, 1H), 3.84 (d, *J* = 13.2 Hz, 1H), 7.21-7.41 (m, 10H); ^{13}C NMR: δ 16.9, 31.5, 32.9, 35.2, 41.6, 43.9, 58.2, 72.7, 123.9, 126.9, 127.6, 128.2, 130.5, 136.9, 137.2; HRMS(ESI) calcd for ($M+Na^+$), $C_{21}H_{23}NONa^+$ 328.1672, found 328.1685. For **8i**: IR (film) 3484, 3086, 2230 cm^{-1}; ^1H NMR: δ 0.95 (s, 3H), 0.85-2.17 (m, 7H), 2.38 (d, *J* = 4.5 Hz, 1H), 2.40 (s, 1H), 2.70 (d, *J* = 3.8 Hz, 1H), 7.05-7.53 (m, 9H), 8.27 (d, *J* = 7.7 Hz, 1H); ^{13}C NMR: δ 18.7, 30.4, 36.4, 40.1, 41.3, 45.6, 60.4, 71.5, 123.5, 127.1, 127.5, 127.6, 127.9, 128.0, 129.1, 130.5, 132.8, 134.9, 137.4; HRMS(ESI) calcd for ($M+Na^+$), $C_{21}H_{23}NONa^+$ 328.1672, found 328.1672.

(1*R*,2*R*,3*S*)-1-cyano-3-hydroxy-2,3-dimethyl-*N*-phenylcyclohexanecarboxamide (8j): The standard procedure was employed with oxonitrile **3** (120 mg, 1 mmol) and MeMgCl (3M, 3.5mmol) alkylating with phenylisocyanate (357 mg, 3 mmol) at –78 ^{o}C for 1 h, and then room temperature for 1 h to afford, after radial chromatography (stepped gradient 3:7, 1:2.5, 1:1 EtOAc/hexanes), 158 mg (58%) of **8j** as a crystalline solid (m.p. 164-165 ^{o}C) whose structure was confirmed by X-ray crystallography: IR (film) 3390, 2243, 1660 cm^{-1}; ^{1}H NMR: δ 1.30 (s, 3 H), 1.35 (d, *J* = 4.4 Hz, 3 H), 1.46-1.66 (m, 2H), 1.88-2.11 (m, 4H), 2.45 (br d, *J* = 10.9 Hz, 1H), 5.23 (s, 1H), 7.19-7.55 (m, 5H), 9.02 (s, 1 H); ^{13}C NMR: δ 11.3, 17.2, 29.1, 35.9, 39.9, 45.1, 51.4, 69.3, 121.0, 122.5, 125.8, 129.1, 136.4, 166.9; HRMS(ESI) calcd for (M+Na^{+}), $C_{16}H_{20}N_2O_2Na^{+}$ 295.1417, found 295.1417.

(1*R*,2*R*,3*S*)-1',3-dihydroxy-2,3-dimethyl-1,1'-bi(cyclohexyl)-1-carbonitrile (8k): The standard procedure was employed with oxonitrile **3** (100 mg, 0.82 mmol) and MeMgCl (3M, 2.87mmol) alkylating with cyclohexanone (242 mg, 2.46 mmol) at –78 ^{o}C for 1 h, to afford, after radial chromatography (stepped gradient 3:17, 1:4, 1:3 EtOAc/hexanes), 138 mg (68%) of **8k** as a crystalline solid (m.p.149-150 ^{o}C) whose structure was confirmed by X-ray crystallography: IR (film) 3436, 2230 cm^{-1}; ^{1}H NMR: δ 1.20 (s, 1H), 1.34 (s, 3H), 1.35 (d, *J* = 5.9 Hz, 3H), 1.13-2.15 (m, 17H), 2.39 (br d, *J* = 14.7 Hz, 1H); ^{13}C NMR: δ 13.8, 19.3, 21.7, 22.1, 25.0, 30.0, 31.3, 34.8, 35.6, 39.1, 48.5, 50.1, 71.5, 76.2, 125.5. HRMS(ESI) calcd for (M+Na^{+}), $C_{15}H_{25}NO_2Na^{+}$ 274.1777, found 274.1787.

(1*R*,2*R*,3*S*)-3-hydroxy-1-(1-hydroxy-1-methylethyl)-2,3-dimethylcyclohexanecarbonitrile (8l): The standard procedure was employed with

oxonitrile **3** (95 mg, 0.78 mmol) and MeMgCl (3M, 2.75) alkylating with acetone (136 mg, 2.34 mmol) at –78 ^{o}C for 1 h, to afford, after radial chromatography (stepped gradient 3:17, 1:4, 1:3 EtOAc/hexanes), 105 mg (64%) of **8l** as a crystalline solid (m.p. 109-111^{o}C) whose structure was confirmed by X-ray crystallography: IR (film) 3289, 2232 cm^{-1}; ^{1}H NMR: δ 1.46 (s, 3H), 1.51 (d, *J* = 7.4 Hz, 3H), 1.61 (s, 3H), 1.65 (s, 3H), 1.69 - 1.91 (m, 4H), 2.21 - 2.37 (m, 2H), 2.56 (br d, *J* = 13.2 Hz, 1H), 3.90 (br s, 1H), 5.15 (br s, 1H); ^{13}C NMR: δ 13.8, 19.0, 29.8, 30.4, 33.0, 39.4, 48.6, 48.9, 71.3, 75.2, 125.2. HRMS(ESI) calcd for (M+Na^{+}), $C_{12}H_{21}NO_2Na^{+}$ 234.1464, found 234.1464.

1-[cyclopropyl(hydroxy)methyl]-5,8-dimethyl-6-oxabicyclo[3.2.1]octan-7-one (8m):

The standard procedure was employed with oxonitrile **3** (121 mg, 0.83 mmol) and MeMgCl (3.0M, 2.9 mmol) alkylating with cyclopropane carbonitrile (203 mg, 2.9 mmol) at –78 ^{o}C for 1 h to afford, after radial chromatography (1:9 EtOAc/hexanes), 105 mg (55%) of **8m** and **8n** as a mixture. **8m** accounts for 45% as a crystalline solid (m.p. 124-125^{o}C) whose structure was confirmed by X-ray crystallography: IR (film) 3390, 2233 cm^{-1}; ^{1}H NMR: δ 0.34 (d, *J* = 11.1 Hz, 1H), 0.57 -0.77 (m, 4H), 1.15 (d, *J* = 14.7 Hz, 3 H), 1.30 (s, 3H), 1.10 – 2.13 (m, 9H), 3.20 (d, *J* = 7.4 Hz, 1H); ^{13}C NMR: δ 2.25, 4.27, 9.30, 13.4, 18.1, 28.0, 29.7, 39.5, 41.2, 45.7, 71.5, 75.6, 122.5. For **8n**: IR (film) 3390, 2233 cm^{-1}; ^{13}C NMR: δ 2.88, 4.99, 10.4, 14.4, 18.8, 29.6, 31.3, 40.0, 46.1, 46.8, 70.1, 73.9, 124.4.

3-hydroxy-1-(1-hydroxycyclobutyl)-2,3-dimethylcyclohexanecarbonitrile (8o): The standard procedure was employed with oxonitrile **3** (132 mg, 1.1 mmol) and MeMgCl

(3.0M, 3.85 mmol) alkylating with cyclobutanone (231 mg, 3.3 mmol) at –78°C for 4.5 h to afford, after radial chromatography (0:1, 1:99, 1:49, 3:97, 1:19 MeOH/CH_2Cl_2), 130 mg (53%) of **8o** as an oil and 15 mg (6%) of **8p** as a white solid. For **8o** IR (film) 3400, 2228 cm^{-1}; ^1H NMR: δ 0.80 – 0.85 (m, 1H), 1.07 (d, *J* = 7.3 Hz, 3H), 1.18 (s, 3 H), 1.23 – 2.23 (m, 12H), 2.44 – 2.54 (m, 1H), 2.73 – 2.83 (m, 1H); ^{13}C NMR: δ 10.6, 15.2, 18.5, 29.0, 29.4, 33.2, 36.4, 40.0, 41.6, 49.0, 71.7, 80.0, 122.9; HRMS(ESI) calcd for ($M+Na^+$), $C_{13}H_{21}NO_2Na^+$ 246.1464, found 246.1465. For **8p**: IR (film) 3446, 2232 cm^{-1}; ^1H NMR: δ 1.33 (d, *J* = 7.4 Hz, 3H), 1.38 (s, 3 H), 1.42 – 2.30 (m, 13H), 2.55 – 2.65 (m, 1H), 2.79 – 2.89 (m, 1H); ^{13}C NMR: δ 11.5, 15.5, 18.6, 29.8, 31.4, 35.0, 37.8, 39.9, 47.5, 48.6, 70.5, 80.2, 125.4; HRMS(ESI) calcd for ($M+Na^+$), $C_{13}H_{21}NO_2Na^+$ 246.1464, found 246.1462.

(1*S*,2*R*,3*S*)-3-benzoyl-3-cyano-1,2-dimethylcyclohexyl benzoate (8q): The standard procedure was employed with oxonitrile **3** (26 mg, 0.22 mmol) and MeMgCl (1.8M, 0.75 mmol), alkylating with benzoyl cyanide (85 mg, 0.65 mmol) at room temperature for 1 h to afford, after radial chromatography (stepped gradient 1:19, 1:9 EtOAc/hexanes), 42 mg (55%) of **8q** as a crystalline solid (m.p. 131-133 °C) whose structure was confirmed by X-ray crystallography: IR (film) 3060, 2235, 1710, 1686 cm^{-1}; ^1H NMR: δ 1.32 (d, *J* = 7.0 Hz, 3H), 1.46 (td, *J* = 14 Hz, 3 Hz, 2H), 1.76 (s, 3H), 1.56-1.91 (m, 1H), 1.95-1.99 (m, 1H), 2.48 (q, *J* = 3.3 Hz, 1H), 2.56 (br d, *J* = 2.58 Hz, 1H), 3.26 (dd, *J* = 14.5 Hz, 1.5 Hz, 1H), 7.41-7.61 (m, 6H), 8.06 (d, *J* = 7.5 Hz, 2H), 8.25 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR (C_6D_6): δ 12.5, 18.5, 24.9, 34.0, 36.4, 45.5, 53.1, 82.4, 121.4, 128.5, 129.3, 130.6, 131.9, 132.9, 133.2, 135.8, 165.8, 196.0; HRMS(EI) calcd for (M^+), $C_{23}H_{23}NO_3^+$ 361.1672, found 361.1656.

(1*S*,2*R*,3*S*)-3-acetyl-3-cyano-1,2-dimethylcyclohexyl acetate (8r): The standard procedure was employed with oxonitrile **3** (40 mg, 0.33 mmol) and MeMgCl (1.9M, 1.16mmol), alkylating with methyl cyanoformate (1.0 mmol, 85 mg) at –78 ^{o}C for 0.5 h, followed by warming to room temperature for 1 h, to afford, after radial chromatography (stepped gradient 1:19, 1:9 EtOAc/hexanes), 54 mg (61%) of **8r** as a crystalline solid (m.p. 89-90 ^{o}C) whose structure was confirmed by X-ray crystallography: IR (film) 2243,1742 cm^{-1}; ^{1}H NMR: δ 1.18 (d, *J* = 6.7 Hz, 3H), 1.57 (s, 3H), 1.25-1.90 (m, 4H), 2.02 (q, *J* = 7.0 Hz, 1H), 2.25 (br d, *J* = 10.4 Hz, 1H), 2.93 (br d, *J* = 5.5 Hz, 1H), 3.75 (s, 3H), 3.85 (s, 3H); ^{13}C NMR: δ 11.7, 18.0, 24.1, 33.6, 35.0, 45.0, 49.8, 53.7, 54.4, 81.8, 117.8, 153.7, 170.3; HRMS(ESI) calcd for (M+Na^{+}), $C_{13}H_{19}NO_5Na^{+}$ 292.1155, found 292.1157.

(1*R*,2*R*,3*S*)-3-hydroxy-1,2,3-trimethylcyclohexanecarbonitrile (8v): The standard procedure was employed with oxonitrile **3** (50 mg, 0.21 mmol), MeMgCl (3.0 M, 1.4 mmol), except after 1.5 h at rt, *n*-BuLi (2.4 M, 2.4 mmol) was added and 5 minutes later, MeI (483 mg, 3.4 mmol) was added followed by dropping the temperature to 0 ^{o}C. NH_4Cl was added in 4 h and workup as normal to provide a neat sample for radial chromatography (stepped gradient 1:199, 1:99 to 1:49 CH_2Cl_2/MeOH) to afford **8v** 40 mg and **8a** 3.4 mg (65%). **8v** is a light yellow solid (m.p.53-54 ^{o}C): IR (film) 3488, 2235 cm^{-1}; ^{1}H NMR: δ 1.20 (br s, 6H), 1.40 (s, 3H), 1.13-2.06 (m, 8H); ^{13}C NMR: δ 9.9, 18.8, 27.3, 29.4, 36.6, 38.7, 39.9, 47.6, 70.8, 124.0; HRMS(ESI) calcd for (M+Na^{+}), $C_{10}H_{17}NO^{+}$ 190.1202, found 190.1204.

***N*-{1-[(2*R*,3*S*)-3-hydroxy-2,3-dimethylcyclohexylidene]ethyl}-2,2-dimethylpropanamidem (22a):** The standard procedure was employed with oxonitrile **3** (20 mg, 0.017 mmol) and MeMgCl (1.5 M, 0.6mmol) alkylating with pivaloyl chloride (41 mg, 0.34 mmol) at room temperature overnight to afford, after radial chromatography (stepped gradient 1:4, 2:3, 1:1 EtOAc/hexanes), 24 mg (57%) of **22a** as a light brown oil: IR (film) 3450, 1666, 1650 cm^{-1}; ^{1}H NMR: δ 1.06 (d, J = 7.3 Hz, 3H), 1.16 (s, 3 H), 1.23 (s, 9H), 1.90 (s, 3H), 0.95 – 2.11 (m, 6H), 2.35 (br d, J = 14.0 Hz, 1H), 2.63 (q, J = 6.9 Hz, 1H), 6.51 (s, 1H); ^{13}C NMR: δ 13.3, 17.4, 23.3, 23.5, 27.6, 34.4, 38.9, 42.9, 73.0, 123.5, 134.9, 176.8; HRMS(EI) calcd for (M^+), $C_{15}H_{27}NO_2Na^+$ 276.1934, found 276.1959.

dimethyl 1-{(2*R*,3*S*)-3-[(methoxycarbonyl)oxy]-2,3-dimethylcyclohexylidene}ethylimidodicarbonate (22b): The standard procedure was employed with oxonitrile **3** (15 mg, 0.12 mmol) and MeMgCl (1.6M, 0.3mmol) alkylating with methyl chloroformate (28 mg, 0.3 mmol) at –78 ^{o}C for 1h and at room temperature for 1 h, to afford, after radial chromatography (stepped gradient 1:9, 1:4, 1:3 EtOAc/hexanes), 15 mg (37%) of **22b** as a white solid (m.p.143-135 ^{o}C): IR (film) 1787, 1745, 1711 cm^{-1}; ^{1}H NMR: δ 0.97 (d, J = 3.2 Hz, 3H), 1.41 (s, 3H), 1.87 (s, 3H), 1.75-2.05 (m, 5H), 2.40 (br d, J = 14.7 Hz, 1H), 3.15 (q, J = 6.9 Hz, 1H), 3.70 (s, 3H), 3.79 (s, 6H); ^{13}C NMR: δ 13.1, 17.7, 22.3, 22.7, 23.9, 30.5, 40.4, 53.5, 53.6, 54.0, 85.8, 125.9, 137.9, 152.9, 152.9, 153.6; HRMS(EI) calcd for (M^+), $C_{16}H_{25}NO_7Na^+$ 366.1523, found 366.1534.

IV-3. Multicomponent Grignard Addition-Alkylations

General Multicomponent Addition Procedure: A THF solution of the Grignard reagent (2 equiv) was added to a –78°C, THF solution (0.1M) of the oxonitrile. After 1 h at –78°C, a THF solution of the second Grignard reagent (1.5 equiv) was added. The mixture was stirred at –78°C for 10 min and then allowed to warm to room temperature over a 2 h period. Subsequent addition of saturated NH_4Cl and extraction with EtOAc afforded a crude solution that was washed with brine and dried. Concentration and radial chromatography afforded the pure nitrile.

(1*R*,2*S*,3*R*)-3-hydroxy-1,2,3-trimethylcyclohexanecarbonitrile (4b): The standard procedure was employed with oxonitrile **5b** (130 mg, 1.06 mmol) and MeMgCl (1.9M, 2.12 mmol) except that 1.5 h after warming the reaction to room temperature, methyl iodide (452 mg, 3.18 mmol) was added to afford, after radial chromatography (stepped gradient 1:4, 1:5 EtOAc/hexanes), **4b** 154 mg (86%) as a crystalline solid (m.p. 100-103 °C) whose structure was confirmed by X-ray crystallography: IR (film) 3475, 2233 cm^{-1}; ^1H NMR: δ 1.19 (d, J = 7.4 Hz, 3H), 1.22 (s, 3H), 1.44 (s, 3H) 1.01-1.98 (m, 8H); ^{13}C NMR: δ 10.7, 16.5, 18.1, 30.1, 37.1, 37.4, 39.7, 44.0, 70.8, 126.4; HRMS(ESI) calcd for ($M+Na^+$), $C_{10}H_{17}NONa^+$ 190.1202, found 190.1202. The intramolecular deprotonation procedure to get **4b**: A THF solution of the *i*-Pr Grignard reagent (0.9M, 0.73mL) was added to a room temperature, THF (3 mL) solution of the **14** (50mg, 0.33mmol). After 2 h at room temperature, MeI (94mg, 0.04 mL) was added. After 0.5 h, addition of saturated NH_4Cl and extraction with EtOAc afforded a crude solution that was washed

with brine and dried. Concentration and radial chromatography (stepped gradient 1:99, 1:49 MeOH/CH_2Cl_2), afforded the pure **4b** 30mg (55%) as a white solid.

(1*R*,2*S*,3*R*)-3-hydroxy-1,3-dimethyl-2-phenylcyclohexanecarbonitrile (4c) : The standard procedure was employed with oxonitrile **5b** (20.8 mg, 0.17 mmol), MeMgCl (1.95M, 0.34mmol) and PhMgCl (1.6M, 0.26mmol) except that 1.5 h after warming the reaction to room temperature, methyl iodide (72 mg, 0.51 mmol) was added to afford, after radial chromatography (1:4 EtOAc/hexanes), **4c** 28 mg (71%) as a crystalline solid (m.p. 146-148 ^oC) whose structure was confirmed by X-ray crystallography: IR (film) 3460, 3049, 2226 cm^{-1}; ^1H NMR: δ 1.02 (s, 3 H), 1.28 (br s, 1H), 1.60 (s, 3 H), 1.37-1.75 (m, 3H), 1.97-2.11 (m, 3H), 2.71 (s, 1H), 7.26-7.54 (m, 5H); ^{13}C NMR: δ 17.0, 19.7, 31.2, 38.4, 38.4, 41.2, 56.9, 72.4, 125.4, 127.5, 128.0, 137.7; HRMS(ESI) calcd for ($M+Na^+$), $C_{15}H_{19}NONa^+$ 252.1359, found 252.1352.

(1*R,5*S**,6*S**)-5-hydroxy-5-methylbicyclo[4.4.0]decanecarbonitrile (4d):** The standard procedure was employed with oxonitrile **5b** (25.9 mg, 0.21mmol) and a THF solution (1.3M, 1.5 eq) of chlorobutylmagnesium bromide solution to afford, after radial chromatography (1:4 EtOAc/hexanes) 22 mg (53%) of **4d** as a white solid (m.p. 101-103^oC): IR (KBr) 3472, 2238 cm^{-1}; ^1H NMR δ 1.15 (s, 1H), 1.48 (s, 3H), 1.22-1.98 (m, 14H), 2.12-2.17 (m, 1H); MS 194 ($M+H^+$); HRMS (ESI) calcd for ($M+Na^+$), $C_{12}H_{19}NONa^+$ 216.1359, found 216.1373. The intramolecular deprotonation procedure to get **4d**: A THF solution of the *i*-Pr Grignard reagent (0.7M, 0.2mL) was added to a room temperature, THF (2 mL) solution of the **14** (16mg, 0.07mmol). After 2 h at room

temperature, addition of saturated NH_4Cl and extraction with EtOAc afforded a crude solution that was washed with brine and dried. Concentration and radial chromatography afforded the pure **4d** 10mg (74%) as a white solid.

(3a*R*,7*R*,7a*R*)-7-hydroxy-7-isopropyl-1-methyleneoctahydro-3a*H*-indene-3a-carbonitrile (4e): Performing the general procedure with **5b** (22 mg, 0.18 mmol) and Grignard **6b** (0.20 mmol) {(prepared by standard halogen-magnesiate[417] exchange of *i*-$PrMgBu_2Li$ [addition of *n*-BuLi (1.2 M, 0.48 mmol) to a room temperature, THF solution of *i*-PrMgCl (1.5 M, 0.24 mmol) for 0.5 h] followed by cooling to -78°C} with a THF solution (1 mL) of 1-chloro-4-iodo-5-pentene[411] (43 mg, 0.20 mmol) at -78°C for 1 h afforded, after radial chromatography (1:4 EtOAc/Hexanes) 22 mg (58%) of **4e** as a white solid (m.p. 96-97 °C): IR (film) 3493, 3073, 2229, 1657 cm^{-1}; ^1H NMR: δ 0.90 (d, *J* = 6.8 Hz, 3H), 0.95 (d, *J* = 6.7 Hz, 3H), 1.04 (s, 1H), 1.19-1.27 (m, 1H), 1.51-1.89 (m, 5H), 2.04-2.16 (m, 2H), 2.40-2.65 (m, 3H), 2.81 (s, 1H), 5.09 (s, 1H), 5.22 (s, 1H); ^{13}C NMR: δ 15.3, 15.6, 18.3, 27.3, 30.6, 31.0, 33.0, 34.3, 43.3, 52.7, 74.5, 112.7, 126.3, 149.0; HRMS(ESI) calcd for ($M+Na^+$), $C_{14}H_{21}NONa^+$ 242.1515, found 242.1518.

(1*R,6*S**,7*S**)-7-Hydroxy-7-methylbicyclo[4.3.0]nonanecarbonitrile (4f) :** The standard procedure was employed with oxonitrile **5c** (9 mg, 0.084 mmol) and a (0.2 mL, 0.126 mmol) THF solution of chlorobutylmagnesium bromide[418] to afford, after radial chromatography (1:4 EtOAc/hexanes), 8.0 mg (53%) of **4f** as a white solid (m.p. 94-95 °C): IR (KBr) 3502, 2233 cm^{-1}; ^1H NMR δ 1.28 (s, 1H), 1.35 (s, 3H), 1.50-2.23 (m, 13H);

^{13}C NMR δ 20.7, 21.5, 21.8, 28.6, 32.5, 35.7, 40.1, 40.8, 51.6, 81.1, 126.0; MS 180 ($M+H^+$); HRMS(ESI) calcd for ($M+Na^+$), $C_{11}H_{17}NONa^+$ 202.1202, found 202.1200.

(1*R,5*S**,6*S**)-6-Hydroxy-6-methyl-4-methylenebicyclo[3.3.0]octanecarbonitrile** (**4g**): The Grignard reagent **6b** was prepared by standard[419] halogen-magnesium exchange by adding a THF solution of *i*-PrMgCl (1.6 M, 0.20 mmol) to a -10°C, THF solution (2 mL) of 1-chloro-3-iodo-4-butene[420] (0.20 mmol). After 1.5 h at -10°C the solution was cooled to -78°C followed by addition of a –78°C, THF solution of the magnesium alkoxide prepared by treatment of **5c** (20 mg, 0.17 mmol) with 2 equiv of MeMgCl (1.2M, 0.34 mmol) at –78°C for 1 h. After 30 min a hexanes solution of 2 equiv *t*-BuLi (1.2 M, 0.40 mmol) was added and after 30 minutes, the cooling bath was removed. The reaction was then allowed to warm to room temperature and after 2 h, saturated NH_4Cl was added. Extraction and radial chromatography (1:4 EtOAc/hexanes) afforded **4g** 15 mg (50%) as a white solid (m.p. 73-74 °C): IR (KBr) 3497, 3074, 2233, 1658 cm^{-1}; ^{1}H NMR δ 0.94 (dd, *J* = 18.6, 6.7 Hz, 1H), 1.12 (dd, *J* = 20.3, 6.6 Hz, 1H), 1.42 (s, 3H), 1.87-2.50 (m, 7H), 3.06 (s, 1H), 4.98 (s, 1H), 5.17 (s, 1H); ^{13}C NMR δ 28.1, 34.5, 36.3, 37.2, 41.5, 47.5, 65.7, 80.0, 109.4, 126.0, 149.3; MS: 178 (M+H); HRMS(ESI) calcd for ($M+Na^+$), $C_{11}H_{15}NONa^+$ 200.1046, found 200.1055.

(2*R*,3*R*,4*R*)-4-hydroxy-2-[hydroxy(phenyl)methyl]-3,4-diphenylpentanenitrile (4h) : The standard procedure was employed with oxonitrile **5d** (30 mg, 0.31 mmol) and PhMgCl (2.5M, 1.1 mmol) except that 1.5 h after warming the reaction to room temperature, benzaldehyde (127 mg, 1.2 mmol) was added and allowed to warm to room

temperature overnight to afford, after radial chromatography (stepped gradient 3:7, 1:2.5, 1:1 EtOAc/hexanes), **4h** 57 mg (52%) as a light yellow solid (m.p.139-140 ^{o}C): IR (film) 3442, 2248 cm^{-1}; ^{1}H NMR: δ 1.26 (s, 1H), 1.80 (s, 3H), 2.10 (br s, 1H), 3.30-3.34 (m, 1H), 3.68 (d, J = 3.0 Hz, 1H), 4.31 (d, J = 9.7 Hz, 1H), 7.04-7.42 (m, 15H); ^{13}C NMR: δ 28.1, 40.5, 54.0, 72.9, 76.2, 119.6, 125.4, 126.7, 127.1, 127.6, 128.0, 128.1, 128.6, 128.8, 130.8, 136.1, 140.5; HRMS(ESI) calcd for (M+Na^{+}), $C_{24}H_{23}NO_2Na^{+}$ 380.1621, found 380.1607.

2-bromo-3-oxocyclohex-1-ene-1-carbonitrile (7): A 1 mL CH_2Cl_2 solution of the bromine (240 mg, 1.5mmol) was added to a 0^{o}C, 4mL CH_2Cl_2 solution of **5b** (181 mg, 1.5 mmol). After 1.5 h at 0^{o}C, Et_3N (0.32 mL, 2.25 mmol) was added dropwise. The solution was stirred at rt for 1.5 h and was washed with 3% HCl twice and saturated brine once and dried over $MgSO_4$. Concentration and radial chromatography (stepped gradient 1:9, 3:17, 1:4, 1:3 EtOAc/hexanes) to afford **7** 210 mg (70%) as a light yellow oil: IR (film) 2221, 1706, 1692 cm^{-1}; ^{1}H NMR: δ 2.10 – 2.18 (m, 2H), 2.62 - 2.70 (m, 4H); ^{13}C NMR δ 21.9, 30.6, 37.4, 116.2, 131.1, 134.6, 188.7; HRMS(EI) calcd for (M^{+}), $C_7H_6BrNO^{+}$ 198.9627, found 198.9633.

3-hydroxy-2,3-dimethylcyclohex-1-ene-1-carbonitrile (10) : The standard procedure was employed with **7** (120 mg, 0.6mmol) and a THF solution of MeMgCl (3M, 3 mmol), except that MeI (1.8 mmol, 256mg) was added after rt 2.5 h, to afford, after radial chromatography (stepped gradient 1:4, 3:7 EtOAc/hexanes) 46 mg (51%) of **10** as a wax solid: IR (film) 3438, 2213, 1646 cm^{-1}; ^{1}H NMR: δ 1.31 (s, 3H), 1.60 - 1.75 (m, 4H), 2.06

(s, 3H), 2.20 - 2.22 (m, 2H); ^{13}C NMR δ 16.7, 19.0, 26.9, 27.8, 38.2, 70.0, 108.7, 118.7, 156.0.

2-butyl-3-hydroxy-3-methylcyclohexanecarbonitrile: A heptane solution of Bu_2Mg (1.0 M, 0.13 mmol) was added to a –78 ^{o}C, THF solution (2 mL) of nitrile alcohol (12 mg, 0.09 mmol). After 10 min, the reaction was allowed towarm to rt. After 1.5 h, saturated aqueous NH4Cl was added, the aqueous phase was extracted with EtOAc, washed with brine, concentration and radial chromatography (1:3 EtOAc/hexanes) to afford **2-butyl-3-hydroxy-3-methylcyclohexanecarbonitrile** 8 mg (63%) of as a wax solid: ^{1}H NMR δ 0.92 (t, *J* = 6.5 Hz, 3H), 1.26 (s, 3H), 1.08-1.95 (m, 13H), 2.09 (d, *J* = 11.1 Hz, 1H), 2.70 (m, 1H).

(1*S,6*S**,5*R**)-5-hydroxy-5-methylbicyclo[4.4.0]decanecarbonitrile (13a):** Addition of a toluene solution (2 mL) of **14** (15 mg, 65 mmol) to LiHMDS, prepared by addition of a hexanes solution of BuLi (1.6 M, 0.16 mmol) to a THF solution (2 mL) of 1,1,1,3,3,3-hexamethyldisilazane (0.04 mL**,** 0.164 mmol), was followed by heating to reflux. After 1 h the reaction was cooled, saturated, aqueous, NH_4Cl was added, and the organic phase separtated. The aqueous phase was extracted with EtOAc, the extracts combined, dried (Na_2SO_4), concentrated and purified by radial chromatography (1:4 EtOAc/hexanes) to afford 8.1 mg (65%) of **13a** as a white solid (m.p. 90-91^{o}C): IR (KBr) 3499, 2229 cm^{-1}; ^{1}H NMR δ 1.19 (s, 3H), 1.10-2.17 (m, 16H); ^{13}C NMR δ 18.8, 22.7, 23.0, 26.0, 28.8, 37.8, 39.0, 39.2, 40.2, 52.0, 70.4, 123.7; MS: 194 (M+H); HRMS (ESI) calcd for (M+Na^{+}), $C_{12}H_{19}NONa^{+}$ 216.1359, found 216.1370.

(1*R*,2*S*,3*R*)-3-hydroxy-1,3-dimethyl-2-(2-phenylethyl)cyclohexanecarbonitrile (4i) : The standard procedure was employed with oxonitrile **5b** (65 mg, 0.54 mmol) and MeMgCl (1.9M, 1.06mmol) and m-Isopropylphenethyl magnesiumbromide (0.5M, 0.79mmol) except that 1.5 h after warming the reaction to room temperature, methyl iodide (227 mg, 1.59 mmol) was added to afford, after radial chromatography (stepped gradient 1:9, 1:4 EtOAc/hexanes), **4i** 85 mg (54%) as a light yellow oil: IR (film) 3499, 2230, 1605 cm^{-1}; ^1H NMR: δ 1.26 (d, *J* = 6.6 Hz, 6H), 1.30 (s, 3H), 1.49 (s, 3H), 1.11-2.07 (m, 10H), 2.72-2.82 (m, 1H), 2.86-2.96 (m, 2H), 7.07-7.26 (m, 4H); ^{13}C NMR: δ 16.7,19.1, 24.1, 30.2, 31.0, 34.1, 37.1, 37.7, 38.2, 40.2, 49.8, 72.1, 124.0, 125.8, 126.6, 126.7, 128.4, 142.0, 149.1.

(1*S*,4a*S*,10a*S*)-7-isopropyl-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-1-carbonitrile (16): Neat methanesulfuric acid (0.4 mL) was added to a 0°C, $MeNO_2$ solution (2 mL) of **4i** (25 mg, 0.083 mmol). After 1.5 h, saturated aqueous NH_4Cl was added and the mixture extracted with ether. The combined extracts were washed with $NaHCO_3$, dried and concentrated to afford, after radial chromatography (1:49 EtOAc/hexanes), two diastereomers in a 1 to 10 ratio (^1H NMR integration). For the major isomer: IR (film) 2228 cm^{-1}; ^1H NMR: δ 1.22 (s, 3 H), 1.25 (s, 3 H), 1.33 (s, 3 H), 1.63 (s, 3 H), 1.16-2.07 (m, 9H), 2.80-2.89 (m, 3 H), 6.88 (s, 1H), 7.04 (br d, *J* = 7 Hz, 1H), 7.21 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR: δ 19.8, 20.0, 23.9, 26.0, 29.1, 29.6, 33.4, 33.4, 34.5, 35.7, 36.4, 38.3, 47.7, 124.4, 126.0, 126.4, 135.0, 142.8, 145.9; MS(EI) 281 m/e (M^+).

(1*S*,4a*S*,10a*S*)-7-isopropyl-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-1-carboxylic acid (17): A diethylene glycol solution (2mL) of **16** (34 mg, 0.12 mmol), NaOH (0.3 g, 7.5 mmol) and water (0.05mL) was heated at 170^{o}C for 16 h, and then heated to reflux for 6 h. After cooling the mixture was acidified and extracted with ether. The combined organic extract was dried and after radial chromatography (stepped gradient pure CH_2Cl_2, 1:49 MeOH/CH_2Cl_2, 1:24 MeOH/CH_2Cl_2), afforded 33 mg (90%) of **17** as a white solid (m.p.154-155 ^{o}C): IR (film) 3404 cm^{-1}; ^{1}H NMR: δ 1.11 (s, 3 H), 1.25 (d, *J* = 7.3 Hz, 6H), 1.29 (s, 3 H), 0.88-2.00 (m, 9H), 2.33 (d, *J* = 10.3 Hz, 1 H), 2.76-2.90 (m, 3H), 6.88 (s, 1H), 7.00 (d, *J* = 7.3 Hz, 1H), 7.18 (d, *J* = 7.3 Hz, 1H); ^{13}C NMR: δ 19.6, 19.8, 23.9, 26.3, 27.7, 30.1, 32.0, 32.8, 36.4, 36.7, 37.9, 44.2, 45.3, 123.7, 126.0, 135.3, 143.9, 144.7, 173.9; HRMS(EI) calcd for (M^+), $C_{20}H_{28}O_2^+$300.2084, found 300.2084.

IV-4. Halogen-Metal Exchange with α-Halonitriles

General bromination of tertiary nitriles: Neat bromine was added to ice-cooled PBr_3, then nitrile was injected one portion. The ice bath was taken away and the reaction was continued at 60^{o}C for 5 h until it was poured into ice chunks, extracted with ether for three times, washed the combined organic layer with $NaHCO_3$ (3 times), then water one time, dried over $MgSO_4$, concentrated and purified by radial chromatography to afford analytically pure material by IR, ^{1}H and ^{13}C NMR.

1-bromocyclohexanecarbonitrile (4b): The general procedure was employed with **3a** (3 g, 27.5 mmol), Br_2 (4.48 g, 28 mmol) and PBr_3 (7.56 g, 28 mmol) to afford, after purification by radial chromatography (1: 48 to 1:24 EtOAc/hexanes), 4.7 g of **4b** (yield: 90%) as an oil: IR (film) 2240, 802 cm^{-1}; ^1H NMR: δ 1.37 – 1.44 (m, 1H), 1.66-1.82 (m, 4H), 2.06 – 2.15 (m, 3H), 2.34 – 2.39 (m, 2H); ^{13}C NMR: δ 24.5, 24.5, 41.5, 46.3, 120.4.

1-bromo-4-*tert*-butylcyclohexanecarbonitrile (4c): The general procedure was employed with **3b** (1.22 g, 7.4 mmol), Br_2 (1.28 g, 8 mmol) and PBr_3 (2.16 g, 8 mmol), after purification by radial chromatography (1: 48 to 1:24 EtOAc/hexanes), to afford 1.32 g of **4c** (yield: 73%) as an oil (mixture about 1:1). For axial nitrile: IR (film) 2239 cm^{-1}; ^1H NMR: δ 0.89 (s, 9H), 1.04-1.11 (m, 1H), 1.45 – 1.55 (m, 2H), 1.74 – 1.79 (m, 2H), 1.90 – 2.01 (m, 2H), 2.37 – 2.42 (m, 2H); ^{13}C NMR: δ 21.7, 27.1, 32.3, 39.5, 46.2, 120.8. For equatorial nitrile: IR (film) 2234 cm^{-1}; ^1H NMR: δ 0.87 (s, 9H), 1.05-1.16 (m, 1H), 1.37 – 1.51 (m, 2H), 1.80 – 1.84 (m, 2H), 2.00 – 2.10 (m, 2H), 2.56 – 2.60 (m, 2H); ^{13}C NMR: 26.4, 27.2, 32.1, 42.0, 45.1, 46.0, 119.2.

General chloronation of tertiary nitriles:

1-chlorocyclohexanecarbonitrile (4d): Neat **3a** (3 g, 26.7 mmol) was added to PCl_5 (8.32 g, 40 mmol) and pyridine (4.22 g, 53.4 mmol) in 60 mL of CH_3Cl. The reaction was refluxed for 16 h until the mixture was poured into ice chunks, extracted with CH_2Cl_2 twice, washed organic layer with brine and 10% Na_2CO_3, dried over Mg_2SO_4 and removed solvent to afford, after purification by radial chromatography (1: 48 to 1:24 EtOAc/hexanes), 4.38 g (yield: 81%) of **4d** (two isomers) as an oil: IR (film) 2243, 815

cm^{-1}; ^1H NMR: δ 1.29 – 1.42 (m, 1H), 1.56-1.70 (m, 3H), 1.77 – 1.86 (m, 2H), 1.92 – 2.01 (m, 2H), 2.26 – 2.31 (m, 2H); ^{13}C NMR: δ 22.9, 23.7, 40.0, 57.2, 119.1. HRMS(EI) calcd for (M^+), $C_7H_{10}ClN^+$ 143.0496, found 143.0533.

General *in situ* alkylation procedure A: A THF solution of *i*-PrMgBr (1.05 equiv) was added to a -78 °C, THF (1 mmol) solution of **4b** (1.0 equiv) and the electrophile (1.05 equiv). After 2 h saturated, aqueous NH_4Cl solution was added, the crude product extracted with EtOAc, concentrated and purified by radial chromatography to afford analytically pure material by IR, HRMS, and ^1H and ^{13}C NMR.

General sequential alkylation procedure B: A THF solution of *i*-PrMgBr (1.05 equiv) was added to a -78 °C, THF (1 mmol) solution of **4b** (1.0 equiv) and after 1 minute the electrophile (1.05 equiv) was added neat. After 2 h saturated, aqueous NH_4Cl solution was added, the crude product extracted with EtOAc, concentrated and purified by radial chromatography to afford analytically pure material by IR, HRMS, and ^1H and ^{13}C NMR.

1-allylcyclohexanecarbonitrile (5c): The standard procedure A was employed with **4b** (175 mg, 0.93mmol) to afford, after purification by radial chromatography (1:39 to 1:19 EtOAc/hexanes), 113 mg (82%) of **5c** as an oil: IR (film) 3075, 2224, 1635 cm^{-1}; ^1H NMR: δ 1.02 (d, J = 6.5 Hz, 1H), 1.13-1.26 (m, 3H), 1.53 - 1.72 (m, 4H), 1.93 (d, J = 13.1 Hz, 1H), 2.05-2.50 (m, 2H), 2.15 (d, J = 10.9 Hz, 1H), 5.11 - 5.19 (m, 2H), 5.79 – 5.94 (m, 1H); ^{13}C NMR: δ 22.8, 25.1, 35.2, 38.7, 44.4, 119.4, 123.1, 131.8; HRMS(EI) calcd for (M^+), $C_{10}H_{15}N^+$ 149.1199, found 149.1182. Alkylation of **4b** (45 mg, 0.24

mmol), following general procedure B afforded 22 mg (62%) of **5c** as an oil. Alkylation of **4d** (40 mg, 0.28 mmol), following general procedure B, but substituting *n*-BuLi for *i*-PrMgBr, afforded 29 mg (72%) of **5c**.

methyl 1-cyanocyclohexanecarboxylate (5d): The standard procedure A was employed with **4b** (190 mg, 1.01 mmol) and methyl cyanoformate (94 mg, 1.1 mmol) to afford, after purification by radial chromatography (stepped gradient 1:19, 1:9 EtOAc/hexanes), **5d** 122 mg (72%) as an oil: IR (film) 2239, 1736 cm^{-1}; ^{1}H NMR: δ 1.13-1.25 (m, 1H), 1.52-1.73 (m, 7H), 1.99 (d, J = 13.3 Hz, 2H), 3.69 (s, 3H); ^{13}C NMR: δ 22.1, 24.5, 32.9, 45.2, 53.3, 119.0, 169.8; HRMS(EI) calcd for (M^+), $C_9H_{13}NO_2^+$ 167.0941, found 167.0938. Alkylation of **4b** (50 mg, 0.26 mmol) with methyl cyanoformate (44 mg, 0.52 mmol), following general procedure B, afforded 25 mg (58%) of **5d**.

1-(2,2-dimethylpropanoyl)cyclohexanecarbonitrile (5e): The standard procedure A was employed with **4b** (185 mg, 0.98 mmol) and pivaloyl chloride (120 mg, 1 mmol) to afford, after purification by radial chromatography (stepped gradient 1:39, 1:19 EtOAc/hexanes), **5e** 130 mg (70%) as a white solid (m.p.58-59 ^{o}C): IR (film) 2229, 1703 cm^{-1}; ^{1}H NMR: δ 1.23-1.30 (m, 2H), 1.37 (s, 9H), 1.72-1.85 (m, 6H), 1.91-1.94 (m, 2H); ^{13}C NMR: δ 21.9, 24.6, 26.5, 34.2, 46.3, 48.0, 121.6, 208.5; HRMS(ESI) calcd for ($M+Na^+$), $C_{12}H_{19}NONa^+$ 216.1359, found 216.1364. Alkylation of **4b** (50 mg, 0.26 mmol) with pivaloyl chloride (122 mg, 0.52 mmol), following general procedure B, afforded 26 mg (52%) of **5e** as an oil. Alkylation of **4d** (76 mg, 0.53 mmol) with pivaloyl

chloride (140 mg, 1.16 mmol), following general procedure B, but substituting *n*-BuLi for *i*-PrMgBr, afforded 55 mg (54%) of **5e**.

1-(1-hydroxyhexyl)cyclohexanecarbonitrile (5f): The standard procedure A was employed with **4b** (188 mg, 1.03 mmol) and hexanal (109 mg, 1.09 mmol) to afford, after purification by radial chromatography (stepped gradient 1:9, 3:17, 1:4 EtOAc/hexanes), **5f** 140 mg (65%) as an oil: IR (film) 3457, 2234 cm^{-1}; ^{1}H NMR: δ 0.84-0.99 (m, 3H), 1.07-1.88 (m, 17H), 2.15 (d, *J* = 11.8 Hz, 2H), 3.36-3.41 (m, 1H); ^{13}C NMR: δ 13.9, 22.5, 22.8, 22.9, 25.2, 25.8, 31.4, 31.5, 31.7, 32.1, 45.6, 76.4, 122.4; HRMS(ESI) calcd for ($M+Na^+$), $C_{13}H_{23}NONa^+$ 232.1672, found 232.1687.

1'-hydroxy-1,1'-bi(cyclohexyl)-1-carbonitrile (5g): The standard procedure A was employed with **4b** (50 mg, 0.27 mmol) and cyclohexanone (26 mg, 0.27 mmol) to afford, after purification by radial chromatography (stepped gradient 1:9, 3:17, 1:4 EtOAc/hexanes), **5g** 40 mg (73%) as a colorless solid (m.p.112-113^{o}C): IR (film) 3491, 2222 cm^{-1}; ^{1}H NMR: δ 1.05-1.15 (m, 1H), 1.35-1.76 (m, 19H), 1.96 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR: δ 21.5, 23.3, 25.2, 25.4, 28.8, 31.8, 49.7, 73.7, 123.0; HRMS(ESI) calcd for ($M+Na^+$), $C_{13}H_{21}NONa^+$ 230.1515, found 230.1522.

1-[(2*E*)-3-phenylprop-2-enyl]cyclohexanecarbonitrile (5h): The standard procedure A was employed with **4b** (148 mg, 0.79 mmol) and cinnamyl bromide (158 mg, 0.80 mmol) to afford, after purification by radial chromatography (stepped gradient 1:49, 1:24, 3:47 EtOAc/hexanes), **5h** 125 mg (70%) as a white solid (m.p. 62-63^{o}C): IR (film) 3055,

2226, 1597cm^{-1}; ^{1}H NMR: δ 1.13-1.34 (m, 3H),1.58-1.77 (m, 5H), 2.01(d, *J* = 11.8 Hz, 2H), 2.45 (d, *J* = 7.4 Hz, 2H), 6.24-6.35 (m, 1H), 6.51 (d, *J* = 16.1 Hz, 1H), 7.22-7.41 (m, 5H); ^{13}C NMR: δ 23.0, 25.3, 35.4, 39.2, 43.8, 123.4, 126.3, 127.5, 128.5, 134.5, 136.8; HRMS(EI) calcd for (M^+), $C_{16}H_{19}N^+$ 225.1512, found 225.1494.

(1-hydroxycyclohexyl)acetonitrile (5i): The standard procedure A was employed with iodoacetonitrile (322 mg, 1.93 mmol) and cyclohexanone (200 mg, 2.03 mmol) to afford, after purification by radial chromatography (stepped gradient 1:4, 3:7, 1:1 EtOAc/hexanes), **5i** 208 mg (79%) as an oil: IR (film) 3416, 2251 cm^{-1}; ^{1}H NMR: δ 1.20 - 1.34 (m, 2H), 1.52 - 1.74 (m, 9H), 2.51 (s, 2H); ^{13}C NMR: δ 21.5, 24.8, 31.4, 36.5, 69.7, 117.7; HRMS(EI) calcd for (M^+), $C_8H_{13}NO^+$ 139.0992, found 139.0987.

4-*tert*-butyl-1-methylcyclohexanecarbonitrile (5j): The standard procedure A was employed with **4b** (150 mg, 0.61 mmol, 2:1) and methyl iodide (173 mg, 1.22 mmol) to afford, after purification by radial chromatography (stepped gradient 2:49, 1:19 EtOAc/hexanes), **5j** 66 mg (61%) as an oil: IR (film) 2230 cm^{-1}; ^{1}H NMR: δ 0.84 (s, 9H), 0.89-1.03 (m, 1H), 1.30 (s, 3H), 1.16-1.42 (m, 4H), 1.74 (d, *J* = 11.8 Hz, 2H), 1.99 (d, *J* = 13.2 Hz, 2H); ^{13}C NMR: δ 24.4, 27.3, 27.4, 32.3, 34.5, 37.8, 47.2, 124.4; HRMS(EI) calcd for (M^+), $C_{12}H_{21}N^+$ 179.1669, found 179.1679.

V. List of Publications

1. “Alkenenitriles: Annulations with ω-Chloro Grignard Reagents” Fleming, F. F., Zhang, Z., Wang, Q., Steward, O. W. *Org. Lett.,* **2002**, *4*, 2493.

2. “γ-Hydroxyl-α,β-alkenenitriles: Chelation-Controlled Conjugate Additions” Fleming, F. F., Wang, Q., Zhang, Z., Steward, O. W. *J. Org. Chem.*, **2002**, *67*, 5953.

3. “Cyclic Alkenenitriels: Synthesis, Conjugate Addition, and Stereoselective Annulation” Fleming, F. F., Zhang, Z., Wang, Q., Steward, O. W. *J. Org. Chem.* **2003**, *68*, 7646.

4. “Oxonitriles: Multi-Component Grignard Addition-Alkylations” Fleming, F. F., Zhang, Z., Wang, Q., Steward, O. W. *Angew. Chem. Int. Ed.* **2004**, *43*, 1126.

5. “Metalated Nitriles: Holegen-Metal Exchange of α-Halonitriles” Fleming, F. F., Zhang, Z, Knochel, P. *Org. Lett.* **2004**, *6*, 501.

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[286] Stabilization of carbocations by nitriles rests on dramatically enhanced ionization rates in generating carbocations adjacent to nitriles, relative to trifluoromethyl groups,[a] although recent evidence suggests that the rate differences are due to ground state effects and that nitriles do not significantly stabilize adjacent carbocations.[b] The divergent reactivity between **5a** and **5c** is more consistent with formation of a carbocation, rather than a concerted displacement, with modest stabilization from the nitrile and a greater inductive stabilization from the methyl group for **5c**. (a) Creary, X. *Chem. Rev.* **1991**, *91*, 1625. (b) Tekeuchi, K.; Kitagawa, T.; Ohga, Y.; Nakakimura, A.; Munakata, M. *Tetrahedron* **1997**, *53*, 8155.

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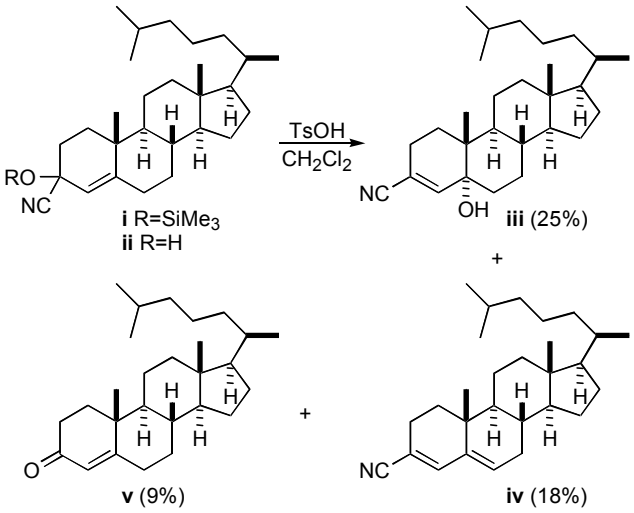

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[294] An excellent stereoelectronic analysis rationalizes the preference for axial conjugate addition of endocyclic enones[a] whereas the stereoelectronic analysis for an exocyclic electron withdrawing group does not appear to have been examined previously. (a) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*, Pergamon, Exeter, 1983, pp 221-242. Consistent with a stereoelectonically-favored axial addition is the inability to react **17c** with the steroidal nitrile **ii**[290] where the rigid steroidal *trans*-ring junction enforces the more difficult equatorial conjugate addition from an axially oriented alkylmagnesium alkoxide.

[295] Presumably addition of the homologous Grignard **17b** to **1a** does not require conjugate addition through the ate complex since **17b** is more reactive than **17a**. The greater nucleophilicity of **17b** could stem from better internal chelation[a] with the pendant chloride that increases the electron density on magnesium[b] that is relayed into a greater nucleophilicity of the adjacent carbon-magnesium bond. (a) For internal chelation of Grignard reagents see: Bickelhaupt, F. In *Grignard Reagents: New Developments* Richey, H. G. Jr. Ed; Wiley: Chichester, 2000; Chapter 9. (b) For an analogous activation of dialkylzincs by ligation see: Reddy, C. K.; Devasagayaraj. A.; Knochel, P. *Tetrahedron Lett.* **1996**, *37,* 4495.

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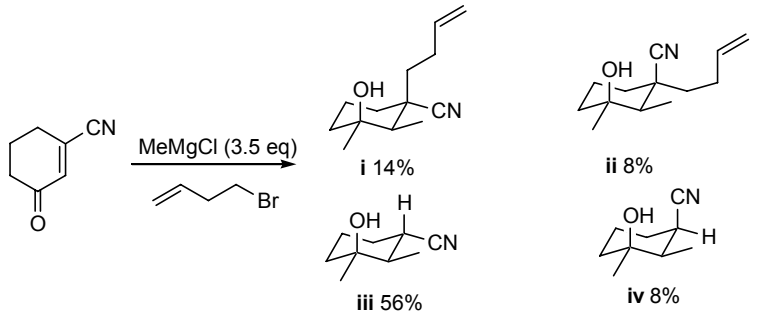

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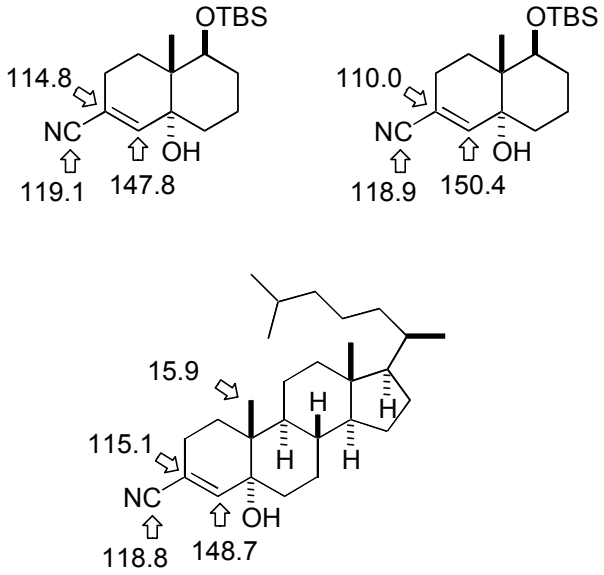

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