C-Metalated Nitriles: Diastereoselective Alkylations and Arylations

Robert John Mycka

Duquesne University

Follow this and additional works at: https://dsc.duq.edu/etd

Part of the Organic Chemistry Commons

Recommended Citation

This Immediate Access is brought to you for free and open access by Duquesne Scholarship Collection. It has been accepted for inclusion in Electronic Theses and Dissertations by an authorized administrator of Duquesne Scholarship Collection.
C-METALED NITRILES: DIASTEREOSELECTIVE ALKYLATIONS AND ARYLAATIONS

A Dissertation
Submitted to the Bayer School of Natural and Environmental Sciences

Duquesne University

In partial fulfillment of the requirements for the degree of Doctor of Philosophy

By
Robert J. Mycka

December 2019
C-METALATED NITRILES: DIASTEREOSELECTIVE ALKYLATIONS AND ARYLATIONS

By

Robert J. Mycka

Approved November 13, 2019

Dr. Bruce D. Beaver
Professor of Chemistry and Biochemistry
(Committee Chair)

Dr. Jeffrey D. Evanseck
Professor of Chemistry and Biochemistry
(Committee Member)

Dr. Shahed U. M. Khan
Associate Professor of Chemistry and Biochemistry
(Committee Member)

Dr. Patrick T. Flaherty
Associate Professor of Pharmacy
(Committee Member)

Dr. Fraser F. Fleming
Chair, Department of Chemistry, Drexel University
Professor of Chemistry
(Committee Member)

Dr. Ellen S. Gawalt
Chair, Department of Chemistry and Biochemistry
Professor of Chemistry and Biochemistry

Dr. Philip Reeder
Dean, Bayer School of Natural and Environmental Sciences
ABSTRACT

C-METALATED NITRILES: DIASTEREOSELECTIVE ALKYLATIONS AND ARYLATIONS

By

Robert J. Mycka

December 2019

Dissertation supervised by Professor Fraser F. Fleming

Development of an sp$^3$ hybridized halogen-magnesium exchange route to Grignard reagents, chelation-controlled asymmetric induction of $\gamma$- and $\delta$-hydroxynitriles as well as a diastereoselective arylation procedure for C-zincated nitriles have been explored. Sequential addition of $i$-PrMgCl and $n$-BuLi to 3- and 4-carbon iodoalcohols triggers a facile halogen-metal exchange to generate cyclic magnesium alkoxides capable of intercepting electrophiles to produce a diverse range of substituted alcohols. This work advances progress toward the synthesis of highly desirable chiral Grignard reagents.

Double deprotonation of $\gamma$- and $\delta$-acyclic hydroxynitriles with $i$-PrMgCl effects highly diastereoselective alkylations via a singly-chelated magnesiated nitriles. These alkylations are electrophile-dependent with either syn- or anti-addition occurring depending upon the electronic properties of the electrophile. These alkylations are the first electrophile-dependent alkylations of acyclic nitriles and exhibit a unique reactivity
depending upon the nature of the Grignard reagent used for deprotonation. The work presented here addresses the long-standing challenge of stereoselective installation of quaternary carbons in conformationally mobile, acyclic nitriles.

Lastly, deprotonating substituted cyclohexancarbonitriles with the TMPZnCl·LiCl complex affords C-zincated nitriles that can couple in a diastereoselective manner with aryl bromides in the presence of catalytic Pd(OAc)$_2$ and S-Phos. Ring substituents displaying a wide range of steric and stereoelectronic effects have been examined. Selectivity ranges from null to high depending upon the size and location of the substituent. The diastereoselectivity trends discovered here present an immense potential for the synthesis of substituted cyclohexancarbonitriles, key intermediates and targets in active pharmaceutical agent synthesis.
DEDICATION

For my parents, who taught me from a young age that I could achieve anything!
ACKNOWLEDGEMENT

First and foremost, I wish to thank my advisor and mentor Professor Fraser Fleming. I also wish to thank Dr. Fleming, not just for the chemistry knowledge, but also all of the life lessons, both philosophical and religious that you have taught me over the years. Our excursion to Munich really helped me to learn about myself. I appreciate all of your help and patience throughout our chemistry endeavors, as not all compounds were revealed as easily as we would have hoped. Nonetheless, we were able to overcome a lot of challenges and achieve a lot of good work that we hope people can use in the future.

Next I would like to thank Dr. Bruce Beaver for all of your mentorship throughout this Ph.D. endeavor. I could never have become the chemist I am today if you hadn’t made me push arrows and learn mechanisms the way that you did. All of your lunches and talks where you provided me with both chemical and life guidance will be cherished forever. I couldn’t have achieved this without you. Thank you again!

I especially need to thank Professor Patrick Flaherty. You are a wealth of knowledge about chemistry, reactions and life. I appreciate all of your help throughout this endeavor. I undoubtedly could not have achieved this degree without you. I absolutely appreciate everything that you have done for me throughout the past several years!

I would like to thank the other people that have served on my dissertation committee at various times. These people include Dr. Tomislav Pintauer and Dr. Jeffrey D. Evanseck and Dr. Shahed U. M. Khan. I am ever grateful to the three of you for your help and support you gave me to help achieve this degree.
Other professors I wish to thank include Professor Paul Knochel ("Uncle Paul") for all of your help and mentorship in Munich. It was an absolute honor to work for you. I also would like to thank Professor Paul Floreancig for mentorship during this process. After all, “it was just chromatography.” Lastly, I would like to thank the late Dr. Mitchell E. Johnson. We had a lot of fun, and I learned a lot about academics from you. You may have passed away too soon; however, the memories we had talking football and otherwise will be cherished forever!

I would also like to thank the various lab mates over the years that always made me feel like we were an unstoppable team for Dr. Fleming. These lab mates include Dr. Viet Anh Vu, Dr. Wang Liu, Dr. Guoqing Wei, Yunjing Wei, Subbu Gudipati, Som Ghosh, Dr. Pitta Bhaskar Reddy, Dr. Ponneri Chandrababu Ravikumar, Lihua Yao, Jenna Daggett, Brian Zlobecki, Kristen Carlisle and Kenny Drombosky. My lab mates in Munich were also gratefully acknowledged for all of the fun that we had. These people include: Dr. Andreas Wagner, Dr. Ben Haag, Dr. Tobias Thaler, Dr. Milica Jaric, Dr. Matthias Schade, Dr. Stéphanie Duez, Dr. Tobias Blümke, Dr. Sebastian Bernhardt, Simon Matthe, and last but not least, Vladimir Malakhov.

Support from Dr. William Eckenhoff for X-Ray studies as well as HRMS measurements Dr. Timothy Fahrenholz are also gratefully acknowledged. In tandem with the measurements, I would like to thank Dave Hardesty, Danny Bodnar and Lance Crosby for keeping the instruments running, especially the NMRs.

Lastly, I would like to thank Dean Philip Reeder. I appreciate all of your help in making the final step of this process come to fruition.
# TABLE OF CONTENTS

ABSTRACT ........................................................................................................................................ iv

DEDICATION ....................................................................................................................................... vi

ACKNOWLEDGEMENT .................................................................................................................. vii

LIST OF TABLES ............................................................................................................................ xii

LIST OF FIGURES ........................................................................................................................... xiii

LIST OF ABBREVIATIONS ............................................................................................................. xiv

Chapter 1 ........................................................................................................................................... 1

Prologue ........................................................................................................................................... 1

1.1 Introduction ............................................................................................................................... 1

1.2 Objectives .................................................................................................................................. 6

1.3 Organization .............................................................................................................................. 7

Chapter 2 ........................................................................................................................................... 9

NMR Studies of Nitrile Ions and Metalated Nitriles ................................................................. 9

2.1 Introduction to Metalated Nitriles ............................................................................................ 9

2.2 $^{13}$C NMR of Nitrile Stabilized Anions ................................................................................ 12

2.3 $^{13}$C NMR of $N$-metalated Nitriles ...................................................................................... 18

2.4 $^{13}$C NMR of $C$-Metalated Nitriles ....................................................................................... 20

2.5 $^{13}$C NMR of $C$-Palladated Nitriles ....................................................................................... 24

Chapter 3 ......................................................................................................................................... 29
Grignard Reagents: Alkoxide-Directed Iodine-Magnesium Exchange at sp³ Centers ....29

3.1 Introduction ..........................................................................................................................29
3.2 Iodine-Magnesium Exchange at sp³ Centers .......................................................................30
3.3 Mechanism of the Iodine-Magnesium Exchange at sp³ Centers ........................................32
3.4 Conclusion ............................................................................................................................34

Chapter 4 .....................................................................................................................................35

γ- and δ-Hydroxynitrile-Derived Dianions: Diastereoselective Electrophile-Dependent
Alkylations ..................................................................................................................................35

4.1 Introduction ............................................................................................................................35
4.2 Alkylations of γ-Hydroxynitriles .......................................................................................38
4.3 Probing the Steric Minimum for Alkylations .....................................................................43
4.4 Changing the Alkylation Stereochemistry .........................................................................44
4.5 Mechanism of Alkylation ......................................................................................................44
4.6 Formal Synthesis of Isoaminile ..............................................................................................51
4.7 Homologous Alkylations ........................................................................................................52
4.8 Conclusion ...............................................................................................................................57
4.9 Stereochemical Proof for the 1,3-Induction Products ...........................................................58
4.10 Stereochemical Proof for the 1,4-Alkylation Products .........................................................60

Chapter 5 .....................................................................................................................................62

Cyclohexylcarbonitriles: Diastereoselective Arylations with TMPZnCl·LiCl ...................62
### LIST OF TABLES

<table>
<thead>
<tr>
<th>Table</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Table 1</td>
<td>$^{13}$C NMR shifts of Nitriles Bearing $\alpha$-Stabilized Substituents</td>
<td>13</td>
</tr>
<tr>
<td>Table 2</td>
<td>$^{13}$C NMR shifts of N-Metalated Nitriles</td>
<td>19</td>
</tr>
<tr>
<td>Table 3</td>
<td>$^{13}$C NMR shifts of C-Metalated Nitriles</td>
<td>22</td>
</tr>
<tr>
<td>Table 4</td>
<td>$^{13}$C NMR Shifts of C-Palladated Nitriles</td>
<td>25</td>
</tr>
<tr>
<td>Table 5</td>
<td>Iodine-Magnesium Exchange and Alkylation of Iodoalcohols</td>
<td>31</td>
</tr>
<tr>
<td>Table 6</td>
<td>Optimization of the Reaction of 60a with n-PrI</td>
<td>39</td>
</tr>
<tr>
<td>Table 7</td>
<td>Reaction of 60a with Various Electrophiles</td>
<td>40</td>
</tr>
<tr>
<td>Table 8</td>
<td>Diastereoselective Ester Acylations of 60a</td>
<td>50</td>
</tr>
<tr>
<td>Table 9</td>
<td>Diastereoselective Isopropyl Additions to 60f</td>
<td>52</td>
</tr>
<tr>
<td>Table 10</td>
<td>Diastereoselective Alkylations of $\delta$–hydroxynitriles 73</td>
<td>56</td>
</tr>
<tr>
<td>Table 11</td>
<td>Diastereoselective Cyclohexanecarbonitrile Coupling</td>
<td>66</td>
</tr>
</tbody>
</table>
## LIST OF FIGURES

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Figure 1</td>
<td>Representative Natural Products Containing a Nitrile Functionality.</td>
<td>1</td>
</tr>
<tr>
<td>Figure 2</td>
<td>Representative Nitrile-Containing Pharmaceuticals.</td>
<td>2</td>
</tr>
<tr>
<td>Figure 3</td>
<td>Continuum of Metalated-Nitrile Geometries.</td>
<td>3</td>
</tr>
<tr>
<td>Figure 4</td>
<td>Selected $^{13}$C and $^{15}$N NMR Solution Structure Data.</td>
<td>11</td>
</tr>
<tr>
<td>Figure 5</td>
<td>Comparison of N- and C-Metalated Nitrile Structures.</td>
<td>12</td>
</tr>
<tr>
<td>Figure 6</td>
<td>Stereochemical Determinations for 1,3-Induction.</td>
<td>58</td>
</tr>
<tr>
<td>Figure 7</td>
<td>ORTEP of dihydroxynitrile $61m$.</td>
<td>60</td>
</tr>
<tr>
<td>Figure 8</td>
<td>Stereochemical Determinations for 1,4-Induction.</td>
<td>61</td>
</tr>
<tr>
<td>Figure 9</td>
<td>Arylacetonitrile Pharmaceuticals.</td>
<td>64</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Meaning</td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>---------</td>
<td></td>
</tr>
<tr>
<td>Ac</td>
<td>acetate</td>
<td></td>
</tr>
<tr>
<td>br</td>
<td>broad</td>
<td></td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
<td></td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
<td></td>
</tr>
<tr>
<td>$^{13}$C NMR</td>
<td>carbon nuclear magnetic resonance</td>
<td></td>
</tr>
<tr>
<td>d</td>
<td>doublet</td>
<td></td>
</tr>
<tr>
<td>dd</td>
<td>doublet of doublets</td>
<td></td>
</tr>
<tr>
<td>ddd</td>
<td>doublet of doublet of doublets</td>
<td></td>
</tr>
<tr>
<td>dddd</td>
<td>doublet of doublet of doublet of doublets</td>
<td></td>
</tr>
<tr>
<td>DMF</td>
<td>$N,N$-dimethylformamide</td>
<td></td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
<td></td>
</tr>
<tr>
<td>dt</td>
<td>doublet of triplets</td>
<td></td>
</tr>
<tr>
<td>dr</td>
<td>diastereomeric ratio</td>
<td></td>
</tr>
<tr>
<td>equiv.</td>
<td>equivalents</td>
<td></td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
<td></td>
</tr>
<tr>
<td>Et$_2$O</td>
<td>diethyl ether</td>
<td></td>
</tr>
<tr>
<td>EtOAc</td>
<td>ethyl acetate</td>
<td></td>
</tr>
<tr>
<td>GC-MS</td>
<td>gas chromatography-mass spectrometry</td>
<td></td>
</tr>
<tr>
<td>h</td>
<td>hour(s)</td>
<td></td>
</tr>
<tr>
<td>HMDS</td>
<td>bis(trimethylsilyl)amide</td>
<td></td>
</tr>
<tr>
<td>$^1$H NMR</td>
<td>proton nuclear magnetic resonance</td>
<td></td>
</tr>
<tr>
<td>HRMS</td>
<td>high resolution mass spectra</td>
<td></td>
</tr>
<tr>
<td>H$_2$SO$_4$</td>
<td>sulfuric acid</td>
<td></td>
</tr>
<tr>
<td>i</td>
<td>iso</td>
<td></td>
</tr>
<tr>
<td>IR</td>
<td>infrared spectroscopy</td>
<td></td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
<td></td>
</tr>
<tr>
<td>m</td>
<td>multiplet</td>
<td></td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
<td></td>
</tr>
<tr>
<td>min.</td>
<td>minutes</td>
<td></td>
</tr>
<tr>
<td>MPt.</td>
<td>melting point</td>
<td></td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
<td></td>
</tr>
<tr>
<td>Ms</td>
<td>mesylate</td>
<td></td>
</tr>
<tr>
<td>nOe</td>
<td>nuclear Overhauser effect</td>
<td></td>
</tr>
<tr>
<td>NOESY</td>
<td>Nuclear Overhauser Spectroscopy</td>
<td></td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
<td></td>
</tr>
<tr>
<td>Pr</td>
<td>propyl</td>
<td></td>
</tr>
<tr>
<td>q</td>
<td>quartet</td>
<td></td>
</tr>
<tr>
<td>R</td>
<td>alkyl, aryl, or hydrogen</td>
<td></td>
</tr>
<tr>
<td>r.t.</td>
<td>room temperature</td>
<td></td>
</tr>
<tr>
<td>s</td>
<td>singlet</td>
<td></td>
</tr>
<tr>
<td>t</td>
<td>triplet</td>
<td></td>
</tr>
<tr>
<td>t or tert</td>
<td>tertiary</td>
<td></td>
</tr>
<tr>
<td>td</td>
<td>triplet of doublets</td>
<td></td>
</tr>
<tr>
<td>Tf</td>
<td>triflate</td>
<td></td>
</tr>
<tr>
<td>TBS</td>
<td>tert-butyl dimethyl silyl</td>
<td></td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
<td></td>
</tr>
<tr>
<td>TMEDA</td>
<td>$N, N, N', N'$-tetramethylethane-1,2-diamine</td>
<td></td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
<td></td>
</tr>
<tr>
<td>Tos</td>
<td>tosylate</td>
<td></td>
</tr>
<tr>
<td>tt</td>
<td>triplet of triplets</td>
<td></td>
</tr>
</tbody>
</table>
Chapter 1

Prologue

1.1 Introduction

The nitrile group is one of the most fundamental functional groups studied in organic chemistry. The nitrile is an important functional group contained in scores of natural products derived from terrestrial, marine, plant, and animal sources. These structures can vary from simple 1, to more complex 2, and can also resemble carbohydrates 3. With more structurally complex nitrile containing natural products being characterized, the need for advancement of nitrile chemistry becomes necessary.

Figure 1. Representative Natural Products Containing a Nitrile Functionality.

<table>
<thead>
<tr>
<th>β-cyanoglutamic acid (1)</th>
<th>Cyanopuupehenone (2)</th>
<th>A cyanogenic glucoside (3)</th>
</tr>
</thead>
</table>

Nitriles are also an important component of pharmaceutical chemistry present both in synthetic intermediates as well as final targets. Currently, there are well over thirty nitrile-containing pharmaceuticals approved by the FDA, with many more in clinical trials. The use of nitriles in pharmaceutical continues to grow as more researchers become aware that the nitrile is not readily metabolized, the release of toxic cyanide anion is rare, and that nitrile hydrolysis is rare, usually representing a minor metabolic contribution.
Shown below is a representative set of nitrile-containing pharmaceuticals. Anastrazole 4, a blockbuster non-steroidal aromatase inhibitor from AstraZeneca, is the drug of choice for the treatment of advanced breast cancer.\(^\text{10}\) Escitalopram 5,\(^\text{11}\) is a multi-million dollar SSRI antidepressant released by Lundbeck, and Primacor\(^\text{12}\) 6 is a peak III cAMP phosphodiesterase inhibitor prescribed for heart failure. The nitrile can mimic enzyme substrates, and often used to increase water solubility and decrease susceptibility to oxidative metabolism in the liver.\(^\text{6}\)

**Figure 2. Representative Nitrile-Containing Pharmaceuticals.**

![Image of Anastrazole, Escitalopram, and Primacore](image)

The synthetic necessity for nitrile-containing natural products and pharmaceuticals demands creation of new methods to generate these complex scaffolds. While discovery of carbon-carbon bond forming reactions remains a fundamental goal in organic chemistry, carbonyl-based carbon-carbon bond formation methodology remains disproportionally represented. Nitrile ions are emerging as important intermediates with an entire volume of *Organic Reactions* dedicated to their chemistry.\(^\text{13}\) Nitrile anions and metalated nitriles are powerful nucleophiles capable of efficiently installing hindered quaternary carbons.\(^\text{13}\) Both C- and N-metalated nitriles benefit from having strong nucleophilicity that correlates directly with the pK\(_a\) of the conjugate acid (approximately 29 – 31, in DMSO).\(^\text{14}\)
The nitrile group itself possesses a relatively small C≡N bond length that is on average of approximately 1.14 Å, and only possesses an A-value of approximately 0.2 kcal/mol. Also, the nitrile acts as a strong electron withdrawing group that allows for a high charge density to be placed on the nucleophilic carbanion with almost no delocalization into the nitrile group. Analysis of several X-Ray studies on metalated nitriles and nitrile based ions reveal a continuum of geometries at the nucleophilic carbon. These structures can be placed into four distinct categories (c.f. Figure 3): the planar N-metalated ketenimine 7a, the partially pyramidal N-metalated nitrile 7b, the tetrahedral-like C-metalated nitrile 7c and the free nitrile carbanion 7d. Generation of 7a–d can be achieved by judicious selection of solvent, counter ion, and temperature used in the reaction enabling regio- and stereoselectivity.

Figure 3. Continuum of Metalated-Nitrile Geometries.

The geometries shown in Figure 3 consistently reveal both N- and C-metalated nitriles 7b and 7c respectively possess partial double bond character for the C – CN bond with only a slight weakening of the C≡N bond (1.15 – 1.20 Å) relative to neutral nitriles (1.14 Å). Less common metalated ketenimines, 7a analyzed by X-Ray crystallography, exhibit significant structural diversity with respect to bond length and angles when compared to metalated nitriles. The partial X-Ray structure of the palladated ketenimine reveals a C≡C≡N bond angle of that is nearly linear (176°) with
a bent C=N-Pd bond geometry (131°) analogous to an sp² hybridized imine nitrogen geometry. The ketenimine C=C bond approximates normal double bond length (1.35 Å), while the C=N bond considerably shorter (1.20 Å) implying a significant contribution from resonance to the overall structure. This geometry is most significantly different from those of metalated nitriles.¹⁷

Despite the fact that nitrile alkylation reactions are well-documented,¹³,²⁰ development of new alkylation strategies are still required. Often, these traditional alkylation reactions (See Scheme 1) require the use of a strong base to abstract the proton α to the nitrile, which precludes additional acidic functionality on the molecule. Also, problems with double alkylation often ensue if the nitrile contains more than one α-proton as rapid proton transfer between the substituted product and the metalated nitrile or nitrile anion can be rapid.

**Scheme 1. Traditional Nitrile Alkylation Strategies.**

Pioneering attempts to provide better functional group tolerance and reduced double alkylation can be seen in Scheme 2. The use of a rapid halogen metal exchange (11 → 9a or 9c),²¹ or a sulfoxide-metal exchange²² (12 → 9a or 9c) as employed in Scheme 2, can correct the double alkylation problem; however, the use of aggressive reagent combinations (PBr₃/Br₂) and the extra steps required to synthesize the sulfoxide make these reactions problematic.
Scheme 2. Alternative Nitrile Alkylation Strategies.

Stereoselective alkylation of metalated nitriles is a highly desirable synthetic conversion. Deprotonation of 4-tert-butylcyclohexanecarbonitrile 13 with the use of a lithium amide base\textsuperscript{21ab} smoothly furnishes the \(N\)-metalated nitrile 14 that can be trapped with methyl iodide to form 15 (major product) and 15\(^\prime\) (minor products) as a mixture of diastereomers. Bromination of 4-tert-butylcyclohexanecarbonitrile to the \(\alpha\)-bromonitrile 16 reacts by either a halogen-magnesium or a halogen-copper exchange to give intermediate 17 that can smoothly react with methyl iodide to yield isomer 15 \textit{exclusively}! (See Scheme 3)

A remaining caveat is the use strong lithium amide bases and aggressive reagents does preclude acidic protons and sensitive functionality on the starting compound. Stereoselective reactions have been performed on cyclic nitriles; however, the development of a new strategy allowing for both the stereoselective alkylation of *acyclic* nitriles with other functionality was initially an unrealized opportunity.

1.2 Objectives

The work presented has three specific goals. The first specific goal is to develop an sp³ halogen-magnesium exchange taking advantage of a proximal alkoxide in the γ- or δ-position as seen in Scheme 4. This methodology will be developed and explored for three reasons. The first reason is that *functionalized* sp³ hybridized Grignard reagents are difficult to access. Secondly, the development of this strategy would allow the construction of valuable polyfunctional synthetic intermediates that organic chemists can use towards their respective synthetic targets. Third, the development of these sp³ hybridized Grignard reagents enables development of yet unrealized “chiral” Grignard reagents.

![Scheme 4. Alkoxide-Directed Halogen-Magnesium Exchange at sp³ Centers.](image)

The second specific goal set forth in this dissertation is the development of internal 1,3- and 1,4-internal asymmetric induction employing γ- and δ-hydroxynitriles as seen in Scheme 5. Hydroxynitriles are envisioned to undergo double deprotonation with equilibration to a single intermediate 21 that can react with various electrophiles to efficiently produce products of the type 22 capable of installing hindered quaternary
centers at the α-carbon to the nitrile. Development and exploration of this methodology is anticipated to yield improved methodology to relay chirality over a distance of three or four carbons in acyclic, conformationally mobile nitriles.

**Scheme 5. Asymmetric Induction of γ- and δ-Hydroxynitiles.**

![Scheme 5 Diagram]

The third and final specific goal of this research is to develop a new method for stereoselectively installing quaternary centers at the carbon α to the nitrile by stereoselectively coupling metalated nitriles of type 24 with an aromatic ring stereoselectively using palladium coupling. In turn, this methodology allows for the synthesis of diverse polyfunctional, substituted arylacetonitriles shown as 25.

**Scheme 6. Diastereoselective Arylations of Cyclohexanecarbonitiles.**

![Scheme 6 Diagram]

1.3 Organization

This dissertation describes two new methods for generating sp³ hybridized Grignard reagents and one new method for the stereoselective addition of aromatic rings to metalated nitriles. The first method of generating the sp³ hybridized Grignard reagents employs the use of a proximal deprotonated hydroxyl group that facilitates the exchange on an alkyl iodide. The second method generates sp³ Grignard reagents again makes use
of a proximal deprotonated hydroxyl to abstract an acidic proton $\alpha$ to the nitrile where a cyclic intermediate can stereoselectively react with electrophiles to access fully-substituted nitriles. Lastly, the diastereoselective arylation of metalated-cyclohexanecarbonitriles via palladium catalysis is described.

Chapter 2 provides a literature review and tabulation of $^{13}$C NMR shifts of nitrile anions, $N$-metalated nitriles and $C$-metalated nitriles. This chapter essentially reinforces methodology to determine the metalation site of nitriles in the solution state by means of $^{13}$C NMR Spectroscopy.

Chapter 3 describes the development of a novel means of performing a halogen-magnesium exchange at an sp$^3$ center. This strategy allows for the construction of versatile intermediates that can be used towards synthetic targets of interest and helps to address a means towards the generation of a “chiral” Grignard reagent.

Chapter 4 provides a new approach for stereoselectively generating fully-substituted nitriles making use of a deprotonated hydroxyl group proximal to the nitrile. This methodology solves the long-standing problem of diastereoselectively alkylating acyclic nitriles.

Chapter 5 yields an attractive procedure for coupling aryl rings to the $\alpha$ carbon to the nitrile stereoselectively. Prior to this work, coupling aromatic rings to the $\alpha$ position of the nitrile was notoriously difficult. The work in this contribution, not only addresses this difficulty, but also provides a means of stereoselectively coupling nitriles to aromatic rings.

Lastly, Chapter 6 provides a summary of the work performed and a how it has impacted the field of synthetic organic chemistry.
Chapter 2

NMR Studies of Nitrile Ions and Metalated Nitriles

2.1 Introduction to Metalated Nitriles

Metalated nitriles are exceptional nucleophiles. Their nucleophilicity stems from the powerful inductive stabilization of the nitrile group that stabilizes an adjacent negative charge without significantly delocalizing the carbanion electron density. Traditionally, reactive nitrile intermediates can be classified into four different categories: nitrile anions, $N$-metalated nitriles, $C$-metalated nitriles, and metalated ketene imines. This chapter focuses on the $^{13}$C NMR studies of nitrile anions, $N$-metalated and $C$-metalated nitriles and how their respective nitrile resonance correlates their structure.

Pioneering structural studies of lithiated acetonitriles provide an essential of understanding the general structures metalated nitriles. Lithiated phenyl acetonitrile has been widely studied, partly because the organometallic is easily generated by deprotonating phenyl acetonitrile with an alkyl lithium or a metalamide. Lithiated phenylacetonitrile favors a dimeric structure in THF solution, and is consistent with solution and the solid-state analyses. In solution, the $^{13}$C resonance of the nitrile carbon shifts modestly from $\delta = 146.2$ to $\delta = 152.7$ ppm depending upon the solvent. On the other hand, deprotonating phenyl acetonitrile with lithium amide bases in the presence of TMEDA, generates the corresponding monomer whose structure is consistent with that identified by X-Ray diffraction.
Extensive NMR studies have been performed on N-lithiated phenyl acetonitrile intermediates. As seen in Figure 4, Carlier and co-workers\textsuperscript{24} we able to generate 26a, by deprotonating phenyl acetonitrile with $n$-BuLi. The resonance of the nitrile for 26a exhibited a peak downfield to $\delta = 147.0$ ppm in $d_8$-toluene and $\delta = 149.7$ ppm in a 1:1 $d_8$-toluene:$d_8$-THF mixture.\textsuperscript{24} Deprotonation of phenyl acetonitrile followed by the addition of one equivalent of TMEDA, affords 28 which exhibits an even further downfield shift of $\delta = 153.7$ ppm. Lastly, 29 can be generated by LiHMDS deprotonation of phenyl acetonitrile followed by addition of TMEDA. The resonance of the nitrile then drops slightly to $\delta = 146.2$ ppm. This data is significant because all three compounds exhibit a much farther downfield shift from the anion of phenyl acetonitrile $\delta = 134.4$ ppm (DMSO) and $\delta = 137.4$ ppm (THF/HMPA). The compilation of data implies that the lithium is more tightly bound to the nitrogen of the nitrile and is pulling more electron density from the nitrile bearing carbon, whereas the anion allows for more localization of the electron density of the nitrile bearing carbon. Further evidence to support this claim can be seen through the coupling constants. The coupling constants...
between nitrogen (\(^{15}\text{N}\)) and lithium are 3.5, 3.4 and 3.1 Hz for 28, 26a, and 29 respectively. On the other hand, \(^1J_{\text{Li}-\text{N}}\) for the anion 30 was shown to be 6.1 Hz - virtually double that of the metalated nitriles!\(^{26}\) This conclusively shows that the lithium is tightly bound to the nitrogen in the nitriles, which is consistent with the X-Ray Structure of 27 and 26a.

**Figure 4. Selected \(^{13}\text{C}\) and \(^{15}\text{N}\) NMR Solution Structure Data.**

<table>
<thead>
<tr>
<th>Compound</th>
<th>(\delta)</th>
<th>(^1J_{\text{Li}-\text{N}})</th>
</tr>
</thead>
<tbody>
<tr>
<td>28</td>
<td>153.7</td>
<td>3.5 Hz</td>
</tr>
<tr>
<td>29</td>
<td>146.2</td>
<td>3.1 Hz</td>
</tr>
<tr>
<td>26a</td>
<td>149.7</td>
<td>3.4 Hz</td>
</tr>
<tr>
<td>30</td>
<td>Microscopic Data</td>
<td></td>
</tr>
</tbody>
</table>

Importantly, the general trend of lithium bonding to nitrogen holds true for almost all compounds except in the cases of lithiated cyclopropanecarbonitriles\(^{18c}\) or the presence of proximal, strong donor ligands,\(^{27}\) where the lithium cation coordinates with the nucleophilic carbon and the nitrile nitrogen.\(^{28}\) Lithiated nitriles typically aggregate in both solution and the solid state. The extent of aggregation in solution is highly dependent of the nature of the solvent as well as the overall size and steric constraints of the nitrile. Lithiated phenyl acetonitrile exists as a dimer in both DMSO and DME; however, in THF at \(-108\) °C, it exists as a monomer. Alternatively, lithioacetonitrile
exists as a tetramer\textsuperscript{29} in DMSO and DME, but exists as a dimer in THF.\textsuperscript{30} N-metalated nitriles, containing transition metals are generally monomeric.

Distinguishing between $N$- and $C$-metalated nitriles is readily achieved by $^{13}$C NMR spectroscopy because the chemical shift of the nitrile is sensitive to the local environment.\textsuperscript{31} $N$-metalated nitriles resonate within a range of $\delta = 140 – 157$ ppm (see Figure 5, structures 26, 31 and 32),\textsuperscript{24,32} whereas, $C$-metalated nitriles resonate between $\delta = 115 – 138$ ppm (Figure 5, structures 33 - 35).\textsuperscript{33} Nitrile anions resonate in the downfield region (see Table 1).\textsuperscript{34}

**Figure 5. Comparison of $N$- and $C$-Metalated Nitrile Structures.**

![Diagram showing N- and C-metalated nitriles and their chemical shifts](image)

2.2 $^{13}$C NMR of Nitrile Stabilized Anions

Alkane nitriles bearing a strong electron withdrawing group on the $\alpha$-carbon are readily deprotonated. Many alkylation of metalated nitriles are performed in etheral solvents, such as THF or Et\textsubscript{2}O. NMR studies of nitrile-stabilized carbanions are performed in highly polar solvents, or solvents with polar additives to help solvate the
ionic intermediates. A series of acetonitriles bearing electron-withdrawing groups were deprotonated and the $^{13}$C NMR chemical shifts of the nitrile carbon were recorded (Table 1). Despite a variety of substituents, the $^{13}$C chemical shift of the nitrile carbon only varies from $\delta = 125.2$ to 139.0 ppm. Chemical shifts of the nitrile carbon are only modestly affected by changes in the solvent (see entries 36, 41, 43 and 49).\textsuperscript{34} The anion of phenylsulfonylacetonitrile with lithium or sodium counter ions\textsuperscript{34-35} (entries 49 and 51, respectively) resonate at almost the same chemical shift. Comparing the chemical shift of the nitrile carbon in phenylacetonitrile ($\delta = 134.4$ ppm, entry 23) with diphenylacetonitrile ($\delta = 133.1$ ppm, entry 27) and malonitrile ($\delta = 130.4$ ppm, entry 36) reveals the greater influence of the nitrile over the benzene ring.\textsuperscript{34} Nitriles are powerful electron withdrawing groups that inductively stabilize electron density. Interestingly, the work on lithiated nitriles containing sulfones and phosphonates\textsuperscript{36} exhibit different structural properties both in the solution and in the solid state. In solution, the structures are anticipated to be solvent-separated ion pairs; however, in the solid state X-Ray studies reveal the metal often times is bound to an oxygen and the geometry at the nitrile bearing carbon is pyramidal.

**Table 1.** $^{13}$C NMR Shifts of Nitriles Bearing $\alpha$-Stabilized Substituents.

<table>
<thead>
<tr>
<th>entry</th>
<th>nitrile</th>
<th>solvent, $^{13}$C NMR shift (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1$^{37,*}$</td>
<td><img src="image" alt="Structure 1" /></td>
<td>$d_6$-benzene 154.0</td>
</tr>
<tr>
<td>2$^{37}$</td>
<td><img src="image" alt="Structure 2" /></td>
<td>$d_6$-benzene 152.7</td>
</tr>
<tr>
<td>3$^{37,*}$</td>
<td><img src="image" alt="Structure 3" /></td>
<td>$d_6$-benzene 152.7</td>
</tr>
<tr>
<td>Compound</td>
<td>Formula</td>
<td>Chemical Shift (ppm)</td>
</tr>
<tr>
<td>----------</td>
<td>---------</td>
<td>---------------------</td>
</tr>
<tr>
<td>4&lt;sup&gt;37&lt;/sup&gt;</td>
<td>$\text{Ph}_2\text{RuNNEC}^+\text{SO}_2\text{Ph}$</td>
<td>152.5</td>
</tr>
<tr>
<td>5&lt;sup&gt;37&lt;/sup&gt;</td>
<td>$\text{CO}_2\text{Ph}$</td>
<td>152.5</td>
</tr>
<tr>
<td>6&lt;sup&gt;37,*&lt;/sup&gt;</td>
<td>$\text{i-Pr}_2\text{NNEC}^+\text{SO}_2\text{Ph}$</td>
<td>152.0</td>
</tr>
<tr>
<td>7&lt;sup&gt;37,*&lt;/sup&gt;</td>
<td>$\text{Me}_{2}\text{P}-\text{RuNNEC}^+\text{SO}_2\text{Ph}$</td>
<td>151.7</td>
</tr>
<tr>
<td>8&lt;sup&gt;37&lt;/sup&gt;</td>
<td>$\text{Ph}_2\text{RuCN}$</td>
<td>125.5</td>
</tr>
<tr>
<td>9&lt;sup&gt;37&lt;/sup&gt;</td>
<td>$\text{Me}_2\text{P}^-\text{RuCN}$</td>
<td>125.4</td>
</tr>
<tr>
<td>10&lt;sup&gt;37&lt;/sup&gt;</td>
<td>$\text{Ph}<em>{2}\text{Me}</em>{2}\text{P}-\text{RuCN}$</td>
<td>125.4</td>
</tr>
<tr>
<td>11&lt;sup&gt;37,37&lt;/sup&gt;</td>
<td>$\text{Ph}_2\text{RuCN}$</td>
<td>125.2</td>
</tr>
<tr>
<td>12&lt;sup&gt;38&lt;/sup&gt;</td>
<td>$\text{CDCl}_3$</td>
<td>143.5</td>
</tr>
<tr>
<td>13&lt;sup&gt;37,*&lt;/sup&gt;</td>
<td>$\text{Ph}_{2}\text{P}-\text{RuNNEC}^+\text{H}$</td>
<td>143.4</td>
</tr>
<tr>
<td>14&lt;sup&gt;33&lt;/sup&gt;</td>
<td>$\text{Ph}_{2}\text{RuNNEC}^+\text{CO}_2\text{Bu}$</td>
<td>143.2</td>
</tr>
<tr>
<td>15&lt;sup&gt;38&lt;/sup&gt;</td>
<td>$\text{CDCl}_3$</td>
<td>144.0</td>
</tr>
<tr>
<td>16&lt;sup&gt;33&lt;/sup&gt;</td>
<td>$\text{Ph}_{2}\text{RuNNEC}^+\text{SO}_2\text{Ph}$</td>
<td>143.7</td>
</tr>
<tr>
<td>17&lt;sup&gt;37&lt;/sup&gt;</td>
<td>$\text{Ph}<em>{2}\text{Me}</em>{2}\text{P}-\text{RuCN}$</td>
<td>126.0</td>
</tr>
</tbody>
</table>
18\textsuperscript{37} \begin{align*} \text{Ph}_3\text{P} & \cdot \text{Ru} \\ \text{Ph}_3\text{P} & \cdot \text{CN} \end{align*} \quad d_0\text{-benzene} \quad 125.9

19\textsuperscript{37} \begin{align*} \text{Ph}_3\text{P} & \cdot \text{Ru} \\ \text{t-BuNC} & \cdot \text{CN} \end{align*} \quad d_0\text{-benzene} \quad 124.06, 124.09

20\textsuperscript{37} \begin{align*} \text{OC} & \cdot \text{Ru} \\ \text{Ph}_3\text{P} & \cdot \text{CN} \end{align*} \quad d_0\text{-benzene} \quad 123.6

21\textsuperscript{39} \begin{align*} \text{N} & \cdot \text{Cu} \\ \text{Ph}_3\text{P} & \cdot \text{CN} \end{align*} \quad \text{CD}_2\text{Cl}_2 \quad 137.8

22\textsuperscript{34,\dagger} \begin{align*} \text{PhS} & \cdot \text{Na}^+ \\ \text{Ph} & \cdot \text{C} & \text{N} \end{align*} \quad \text{DMSO} \quad 139.0

23\textsuperscript{34,\dagger} \begin{align*} \text{Ph} & \cdot \text{Na}^+ \\ \text{Ph} & \cdot \text{C} & \text{N} \end{align*} \quad \text{THF/HMPA} \quad 134.4

24\textsuperscript{36,*} \begin{align*} \text{i-PrO} & \cdot \text{Li}^+ \\ \text{i-PrO} & \cdot \text{C} & \text{N} \end{align*} \quad d_5\text{-pyridine} \quad 133.6

25\textsuperscript{36,*} \begin{align*} \text{EtO} & \cdot \text{Li}^+ \\ \text{EtO} & \cdot \text{C} & \text{N} \end{align*} \quad d_5\text{-pyridine} \quad 133.3

26\textsuperscript{34} \begin{align*} \text{EtO} & \cdot \text{Na}^+ \\ \text{EtO} & \cdot \text{C} & \text{N} \end{align*} \quad \text{DMSO} \quad 131.4

27\textsuperscript{34,\dagger} \begin{align*} \text{Ph} & \cdot \text{Na}^+ \\ \text{Ph} & \cdot \text{C} & \text{N} \end{align*} \quad \text{DMSO} \quad 133.1

28\textsuperscript{34,\dagger} \begin{align*} \text{Me}_3\text{N} & \cdot \text{Na}^+ \\ \text{Me}_3\text{N} & \cdot \text{C} & \text{N} \end{align*} \quad \text{DMSO} \quad 132.8
\[ \begin{align*}
29^{34,\dagger} & : \text{DMSO} \quad 131.3 \\
30^{34,\dagger} & : \text{DMSO} \quad 129.7 \\
31^{34,\dagger} & : \text{DMSO} \quad 129.5 \\
32^{34,\dagger} & : \text{DMSO} \quad 130.79 \\
33^{34,\dagger} & : \text{DMSO} \quad 129.4 \\
34^{34,\dagger} & : \text{DMSO} \quad 128.8 \\
35^{34,\dagger} & : \text{DMSO} \quad 127.7 \\
36^{34,\dagger} & : \text{DMSO} \quad 130.4 \quad \text{MeOH} \quad 130.3 \quad \text{THF/HMPA} \quad 130.3 \\
37^{34,\dagger} & : \text{DMSO} \quad 126.24 \\
38^{40} & : \text{\(d_6\)-DMSO} \quad 130.2
\end{align*} \]
39$^{40}$

\[
\begin{array}{c}
\text{MeO} \quad \text{Na}^+ \\
\text{Ph} \\
\end{array}
\]

$^1$H NMR (DMSO, 130.1)

40$^{34,†}$

\[
\begin{array}{c}
\text{Me} \\
\text{O} \\
\text{Ph} \\
\end{array}
\]

$^1$H NMR (DMSO, 129.3)

41$^{34,†}$

\[
\begin{array}{c}
\text{MeO} \quad \text{Na}^+ \\
\text{Ph} \\
\end{array}
\]

$^1$H NMR (DMSO, MeOH, 127.3, 126.6)

42$^{34,†}$

\[
\begin{array}{c}
\text{MeO} \quad \text{Na}^+ \\
\text{Ph} \\
\end{array}
\]

$^1$H NMR (DMSO, 128.6)

43$^{34,†}$

\[
\begin{array}{c}
\text{MeO} \quad \text{Na}^+ \\
\text{Ph} \\
\end{array}
\]

$^1$H NMR (DMSO, MeOH, 129.3, 129.4)

44$^{34,†}$

\[
\begin{array}{c}
\text{MeO} \quad \text{Na}^+ \\
\text{Ph} \\
\end{array}
\]

$^1$H NMR (DMSO, 127.4)

45$^{34,†}$

\[
\begin{array}{c}
\text{MeO} \quad \text{Na}^+ \\
\text{Ph} \\
\end{array}
\]

$^1$H NMR (DMSO, 128.6)

46$^{34,†}$

\[
\begin{array}{c}
\text{MeO} \quad \text{Na}^+ \\
\text{Ph} \\
\end{array}
\]

$^1$H NMR (DMSO, 128.6)

47$^{36,*a}$

\[
\begin{array}{c}
t\text{-BuSO}_2 \quad \text{Li}^+ \\
\text{O} \\
\end{array}
\]

$^1$H NMR (DMSO, $de$-DMSO, 128.46, 128.53)

48$^{34,†}$

\[
\begin{array}{c}
\text{MeO} \quad \text{Na}^+ \\
\text{Ph} \\
\end{array}
\]

$^1$H NMR (DMSO, 127.4)

49$^{34,†}$

\[
\begin{array}{c}
\text{PhSO} \quad \text{Na}^+ \\
\text{O} \\
\end{array}
\]

$^1$H NMR (DMSO, MeOH, 126.3, 127.1)
2.3 $^{13}$C NMR of $N$-metalated Nitriles

The structure of $N$-lithiated phenylacetonitrile has been intensively analyzed by IR, NMR, and X-Ray crystallography.\(^{17}\) The methylene protons are significantly more acidic than aliphatic nitriles and are readily abstracted by lithium amides and alkyl lithiums. Also, $^{13}$C NMR studies on lithioacetonitrile (Table 2, entries 2 – 5) and other aliphatic nitriles revealed more of the same downfield resonance shifts (Table 2, entries 1 and 6 – 15).

Recently, some very interesting $^{13}$C NMR data has been obtained with $N$-metalated nitriles.\(^{32}\) Deprotonating phenyl acetonitrile with $i$-PrMgCl, was originally thought to generate a $C$-metalated nitrite as observed previously\(^{27-29}\) but surprisingly, the $N$-magesiated nitrite was observed (Table 2, entry 10).\(^{32}\) Attempts to coax both lithium and magnesium into generating a $C$-metalated nitrite by placing a chelating ortho-
methoxy group were futile as only the \(N\)-metalated nitriles (entries 11 and 12) were observed.\(^{32}\)

### Table 2. \(^{13}\)C NMR Shifts of \(N\)-Metalated Nitriles.

<table>
<thead>
<tr>
<th>entry</th>
<th>Nitrile</th>
<th>solvent</th>
<th>(^{13})C NMR shift</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^{32})</td>
<td><img src="image1" alt="Nitrile 1" /></td>
<td>(d_8)-THF</td>
<td>163.6</td>
</tr>
<tr>
<td>2(^{26,28})</td>
<td><img src="image2" alt="Nitrile 2" /></td>
<td>(d_8)-THF</td>
<td>157.3</td>
</tr>
<tr>
<td>3(^{28})</td>
<td><img src="image3" alt="Nitrile 3" /></td>
<td>(d_8)-THF</td>
<td>156.5</td>
</tr>
<tr>
<td>4(^{28})</td>
<td><img src="image4" alt="Nitrile 4" /></td>
<td>(d_8)-THF</td>
<td>155.3</td>
</tr>
<tr>
<td>5(^{28})</td>
<td><img src="image5" alt="Nitrile 5" /></td>
<td>(d_{10})-Et(_2)O</td>
<td>149.5</td>
</tr>
<tr>
<td>6(^{24b,a,*})</td>
<td><img src="image6" alt="Nitrile 6" /></td>
<td>1:1, (d_8)-toluene: (d_8)-THF</td>
<td>153.7</td>
</tr>
<tr>
<td>7(^{24})</td>
<td><img src="image7" alt="Nitrile 7" /></td>
<td>(d_8)-toluene</td>
<td>149.7</td>
</tr>
<tr>
<td>8(^{24a,*})</td>
<td><img src="image8" alt="Nitrile 8" /></td>
<td>(d_8)-toluene</td>
<td>147.0</td>
</tr>
<tr>
<td>9(^{24c})</td>
<td><img src="image9" alt="Nitrile 9" /></td>
<td>THF</td>
<td>146.2</td>
</tr>
</tbody>
</table>
2.4 $^{13}$C NMR of C-Metalated Nitriles

$^{13}$C NMR analysis of zincated acetonitrile in different solvents reveals essentially no change in the nitrile resonance indicating that the C-zincated structure is maintained (entries 15 – 17). Adding chromium and tungsten to acrylonitriles generates C-metalated nitriles which the carbanion is bound to chromium or tungsten. The C-cuprated nitrile in entries 18 and 25 prepared by halogen-metal exchange, shows a $^{13}$C resonance at $\delta = 131.2$ and 123.5 ppm respectively. This resonance is quite different. The highly aliphatic nitrile displays a lower chemical shift than that of the cuprated dinitrile (Table 1, entry 21) prepared by decarboxylation and the benzyl nitrile. This shielding effect of the carbon atom of the nitrile of entries 18 and 25 arises from a closer proximity to protons then the dinitrile of entry 1. C-Rhenium metalated nitriles have been...
examined with several alkylation studies (Table 3, entries 4 – 12), revealing that possessing the metal α to the nitrile does lower the pKₐ of the nitrile and allows for a facile generation of mono alkylation products. In seeking dinuclear iron species, the C-metalated ferrous-nitriles were synthesized as intermediates by means of deprotonating aliphatic nitriles with LDA and adding to iron as seen in entries 20 and 21. Interestingly, dinuclear iron species containing two nonequivalent nitriles have been shown to resonate in the same region as well (Table 3, entry 21). Making use of the halogen-metal exchange, C-magnesiated nitriles can be formed by as depicted in entry 23. Interestingly, C-ruthenium complexes can be made by reacting the appropriate diruthenium precursor with (n-Bu)₄N⁺CN⁻ in dichloromethane (entry 22). New intermediates generating C-borylated nitriles (entry 24) have proven useful in the synthesis of acrylonitriles. Hydrophosphonation using platinum catalysts generate C-platinated nitriles. Deprotonating acetonitrile and adding iridium triflates capitulates intermediates (entry 26) that can be further hydrolyzed to the corresponding amides. Adding Au(I) to triphenylphosphoranylidene acetonitrile produces a nucleophilic C-auralated acetonitrile as an ylide complex shown as entry 29. C-Germylated nitriles can easily be achieved by means of coupling phenyl acetonitrile with geranium-triflates (entries 27 and 30) or C-H insertions of acetonitrile (entry 66). Lastly, in studying the activation of C – CN bonds, the intermediate Ni complex of entry 70 was detected, and fully characterized by both spectroscopy and X-Ray diffraction.
Table 3. $^{13}$C NMR Shifts of C-Metalated Nitriles.

<table>
<thead>
<tr>
<th>entry</th>
<th>Nitrile</th>
<th>solvent</th>
<th>$^{13}$C NMR shift</th>
</tr>
</thead>
</table>
| 1$^{47}$ | \[
\text{OC} \text{CN} \\
\text{OC} - \text{W} \text{CN} \\
\text{OC} 
\] | $d_6$-acetone | 140.6 |
| 2$^{48}$ | \[
\text{Cp}_2\text{W} \text{CN} \\
\text{CN} 
\] | $d_6$-benzene | 133.7 |
| 3$^{47}$ | \[
\text{OC} - \text{Cr} \text{CN} \\
\text{OC} 
\] | $d_6$-acetone | 136.1 |
| 4$^{49}$ | \[
\text{ON} \cdot \text{Re} \cdot \text{PPh} \\
\text{Cp} \text{N} \text{C} \text{Me} \\
\text{H} 
\] | CD$_2$Cl$_2$ | 135.9 |
| 5$^{49}$ | \[
\text{ON} \cdot \text{Re} \cdot \text{PPh} \\
\text{Cp} \text{N} \text{C} \text{Me} \\
\text{H} 
\] | CD$_2$Cl$_2$ | 135.0 |
| 6$^{49}$ | \[
\text{ON} \cdot \text{Re} \cdot \text{PPh} \\
\text{Cp} \text{N} \text{C} \text{n-Bu} \\
\text{H} 
\] | CD$_2$Cl$_2$ | 134.7 |
| 7$^{49}$ | \[
\text{ON} \cdot \text{Re} \cdot \text{PPh} \\
\text{Cp} \text{n-Bu} \text{C} \text{CN} \\
\text{H} 
\] | CD$_2$Cl$_2$ | 134.7 |
| 8$^{49}$ | \[
\text{ON} \cdot \text{Re} \cdot \text{PPh} \\
\text{Cp} \text{Me} \text{C} \text{CN} \\
\text{H} 
\] | CD$_2$Cl$_2$ | 134.3 |
| 9$^{49}$ | \[
\text{ON} \cdot \text{Re} \cdot \text{PPh} \\
\text{Cp} \text{Me} \text{C} \text{CN} \\
\text{H} 
\] | CD$_2$Cl$_2$ | 134.1 |
| 10$^{49}$ | \[
\text{ON} \cdot \text{Re} \cdot \text{PPh} \\
\text{Cp} \text{N} \text{C} \text{Me} \\
\text{H} 
\] | CD$_2$Cl$_2$ | 133.2 |
| 11$^{49}$ | \[
\text{ON} \cdot \text{Re} \cdot \text{PPh}_3 \\
\text{CN} 
\] | CD$_2$Cl$_2$ | 133.0 |
<table>
<thead>
<tr>
<th>No.</th>
<th>Entry</th>
<th>Structure</th>
<th>Solvent</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>OC\textsuperscript{50}Re\textsuperscript{50}OC</td>
<td>CDCl\textsubscript{3}</td>
<td>130.1</td>
</tr>
<tr>
<td>13</td>
<td>$d_8$-THF</td>
<td>133.2</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>$d_6$-benzene</td>
<td>132.6</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>BrZn-CN</td>
<td>THF</td>
<td>131.8</td>
</tr>
<tr>
<td>16</td>
<td>BrZn-CN</td>
<td>Pyridine</td>
<td>130.3</td>
</tr>
<tr>
<td>17</td>
<td>BrZn-CN</td>
<td>DMSO</td>
<td>128.1</td>
</tr>
<tr>
<td>18</td>
<td>CuMe-CN</td>
<td>$d_8$-THF</td>
<td>131.2</td>
</tr>
<tr>
<td>19</td>
<td><em>Cp-Fe-Fe-Cp</em></td>
<td>CD\textsubscript{2}Cl\textsubscript{2}</td>
<td>130, 133</td>
</tr>
<tr>
<td>20</td>
<td>(OC\textsubscript{3})Fe-CN</td>
<td>CDCl\textsubscript{3}</td>
<td>128.7</td>
</tr>
<tr>
<td>21</td>
<td>(OC\textsubscript{3})Fe-CN</td>
<td>CDCl\textsubscript{3}</td>
<td>128.0</td>
</tr>
<tr>
<td>22</td>
<td>*Ru-Ru-CN</td>
<td>CD\textsubscript{2}Cl\textsubscript{2}</td>
<td>127.7</td>
</tr>
<tr>
<td>23</td>
<td>MgBr-CN</td>
<td>$d_8$-THF</td>
<td>126.6</td>
</tr>
<tr>
<td>24</td>
<td>(i-PrN)\textsubscript{2}B-CN</td>
<td>CDCl\textsubscript{3}</td>
<td>125.7</td>
</tr>
<tr>
<td>No.</td>
<td>Structure</td>
<td>solvent</td>
<td>δ (ppm)</td>
</tr>
<tr>
<td>-----</td>
<td>-----------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>25</td>
<td><img src="image" alt="CuMe CN" /></td>
<td>d$_6$-THF</td>
<td>123.5</td>
</tr>
<tr>
<td>26</td>
<td><img src="image" alt="Ir Me CN" /></td>
<td>d$_6$-benzene</td>
<td>122.1</td>
</tr>
<tr>
<td>27</td>
<td><img src="image" alt="Ph CN" /></td>
<td>CDCl$_3$</td>
<td>121.4</td>
</tr>
<tr>
<td>28</td>
<td><img src="image" alt="Et$_3$Ge H CN" /></td>
<td>d$_6$-benzene</td>
<td>119.8</td>
</tr>
<tr>
<td>29</td>
<td><img src="image" alt="ClAu PPh$_3$ CN" /></td>
<td>CDCl$_3$</td>
<td>118.5</td>
</tr>
<tr>
<td>30</td>
<td><img src="image" alt="Et$_3$Ge CO$_2$Et CN" /></td>
<td>CDCl$_3$</td>
<td>116.8</td>
</tr>
<tr>
<td>31</td>
<td><img src="image" alt="Ni i-Pr Cl i-Pr i-Pr CN" /></td>
<td>d$_6$-benzene</td>
<td>115.9</td>
</tr>
</tbody>
</table>

(*) Indicates that the structure was solved by X-Ray Crystallography.

### 2.5 ¹³C NMR of C-Palladated Nitriles

Lastly, and perhaps most importantly, are C-palladated nitriles. This subset of C-metalated nitriles are placed into a separate table (Table 4) to emphasize their utility. These metalated nitriles possess a variety of properties including α-arylation catalysis (entries 10, 11, 28),¹⁶⁰ polymerization (entries 3–7, 9, 13, 14, 19–21, 24–26, 28–29),¹⁶¹,¹⁶² CO insertion (entry 2),¹⁶³ ligand design (entry 8, 12, 15–18, 22, 30),¹⁶⁴ alkylation of Cp rings (entry 1),¹⁶⁵ enolate coupling (entry 23),¹⁶⁸ and ylide chemistry (entries 62 and 68).¹⁶²
Table 4. $^{13}$C NMR Shifts of C-Palladated Nitriles.

<table>
<thead>
<tr>
<th>entry</th>
<th>Nitrile</th>
<th>solvent</th>
<th>$^{13}$C NMR shift</th>
</tr>
</thead>
<tbody>
<tr>
<td>1$^{65}$</td>
<td><img src="image" alt="Cp$_2$TaP(OMe)$_3$" /></td>
<td>$d_6$-benzene</td>
<td>130.2</td>
</tr>
<tr>
<td>2$^{63}$</td>
<td><img src="image" alt="BrMe$_3$Pd" /></td>
<td>$d_6$-acetone</td>
<td>130.2</td>
</tr>
<tr>
<td>3$^{62}$</td>
<td><img src="image" alt="F$2$C${18}$-C$_6$-PM$_3$" /></td>
<td>CD$_2$Cl$_2$</td>
<td>129.3</td>
</tr>
<tr>
<td>4$^{62}$</td>
<td><img src="image" alt="O-t-Bu" /></td>
<td>CD$_2$Cl$_2$</td>
<td>128.9</td>
</tr>
<tr>
<td>5$^{61}$</td>
<td><img src="image" alt="PhPdMe$_3$" /></td>
<td>CD$_2$Cl$_2$</td>
<td>128.0</td>
</tr>
<tr>
<td>6$^{61}$</td>
<td><img src="image" alt="p-TolPd" /></td>
<td>CD$_2$Cl$_2$</td>
<td>126.5, 127.3</td>
</tr>
<tr>
<td>7$^{61}$</td>
<td><img src="image" alt="B(C$_6$F$_5$)$_4$" /></td>
<td>CD$_2$Cl$_2$</td>
<td>126.2</td>
</tr>
<tr>
<td>8$^{64}$</td>
<td><img src="image" alt="B(C$_6$F$_5$)$_4$" /></td>
<td>CDCl$_3$</td>
<td>126.2</td>
</tr>
<tr>
<td>9$^{61}$</td>
<td><img src="image" alt="p-TolPd" /></td>
<td>CD$_2$Cl$_2$</td>
<td>125.9</td>
</tr>
<tr>
<td>10$^{60,*}$</td>
<td><img src="image" alt="PhPdMe$_3$" /></td>
<td>CD$_2$Cl$_2$</td>
<td>125.8</td>
</tr>
<tr>
<td>22&lt;sup&gt;64&lt;/sup&gt;</td>
<td><img src="image" alt="Structure" /></td>
<td>CDCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>124.0</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>23&lt;sup&gt;38&lt;/sup&gt;</td>
<td><img src="image" alt="Structure" /></td>
<td>CDCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>123.9</td>
</tr>
<tr>
<td>24&lt;sup&gt;61&lt;/sup&gt;</td>
<td><img src="image" alt="Structure" /></td>
<td>CD&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>123.8</td>
</tr>
<tr>
<td>25&lt;sup&gt;61&lt;/sup&gt;</td>
<td><img src="image" alt="Structure" /></td>
<td>CD&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>123.8</td>
</tr>
<tr>
<td>26&lt;sup&gt;61&lt;/sup&gt;</td>
<td><img src="image" alt="Structure" /></td>
<td>CD&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>122.6</td>
</tr>
<tr>
<td>27&lt;sup&gt;56&lt;/sup&gt;</td>
<td><img src="image" alt="Structure" /></td>
<td>CDCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>122.0, 122.1</td>
</tr>
<tr>
<td>28&lt;sup&gt;60&lt;/sup&gt;</td>
<td><img src="image" alt="Structure" /></td>
<td>d&lt;sup&gt;8&lt;/sup&gt;-THF</td>
<td>121.84</td>
</tr>
<tr>
<td>29&lt;sup&gt;61&lt;/sup&gt;</td>
<td><img src="image" alt="Structure" /></td>
<td>CD&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>121.6</td>
</tr>
<tr>
<td>30&lt;sup&gt;64&lt;/sup&gt;</td>
<td><img src="image" alt="Structure" /></td>
<td>CD&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>118.7 – 120.7</td>
</tr>
</tbody>
</table>

(*)&nbsp;Indicates that the structure was solved by X-Ray Crystallography.
2.6 Conclusion

Collectively, structural analysis of metalated nitriles display complex, yet well characterized geometries. Hence, the study of the inherent reactivity of metalated nitriles, especially $^{13}$C NMR provides an empirical basis to greatly enhance the field of organic synthesis by increasing the reactivity of the versatile nitrile group by metalation.
Chapter 3

Grignard Reagents: Alkoxide-Directed Iodine-Magnesium Exchange at \(sp^3\) Centers

[Taken in part from Org. Lett. 2007, 9, 4507.][66,67]

3.1 Introduction

Organometallic reagents are central to the realm of organic chemistry.\(^{68}\) Within the vast range of reagents, organomagnesium reagents, more commonly known as Grignard reagents have remained among the most important organometallics since their discovery in 1900.\(^{69}\) Traditionally, Grignard reagents are prepared by the direct insertion of magnesium into carbon-halogen bonds in aprotic solvents.\(^{70}\) Due to the temperature required for insertion, these reagents readily react with most sensitive functionality.

Knochel and co-workers have pioneered a renaissance in Grignard chemistry using low temperature halogen-magnesium\(^{71}\) and sulfoxide-magnesium exchange\(^{72}\) to allow functional group tolerance. The halogen-magnesium exchange often employs electron deficient alkenes, or directing groups on aromatic systems to promote the exchange. A remaining challenge is an exchange process on an \(sp^3\) hybridized carbon.

Several ingenious strategies have recently arisen; intramolecular magnesium delivery to form benzylic Grignard reagents,\(^{73}\) use of metal directing groups on cyclopropyl systems,\(^{74}\) sulfoxide exchange on chiral secondary chlorides,\(^{75}\) halogen-magnesium exchange on \(\alpha\)-halo nitriles,\(^{21,42}\) functionalized magnesium carbenoids,\(^{76}\) and more recently the use of a self-collapsing Grignard reagent.\(^{77}\)
3.2 Iodine-Magnesium Exchange at sp³ Centers

A conceptually appealing route to sp³ hybridized Grignard reagents makes use of a proximal hydroxyl group to promote an intramolecular halogen-metal exchange by means of an alkoxide delivery to form what are considered to be Normant-like reagents.

Initial research, focused on the alkoxide-directed halogen-magnesium exchange of commercially available 3-iodo-1-propanol 36a. Intensive optimization with different combinations of Grignard reagents and organolithiums found that deprotonating 36a with an equimolar equivalent of i-PrMgCl followed by two equivalents of n-BuLi allowed for the formation of a species tentatively assigned as a cyclic magnesium alkoxide 39a. Intercepting 39a with cyclohexanone yielded 71% of 1-(3-hydroxypropyl)cyclohexanol 40a accompanied by 14% of 1-butylcyclohexanol 41 (Scheme 8).

Scheme 8. Intramolecular Exchange Route to sp³ Hybridized Grignard Reagents.

During optimization, the competitive cyclization of 36a to oxetane 38 was identified as a serious problematic reaction. Apparently, the corresponding magnesium
alkoxide is less susceptible to cyclization to the oxetane than the lithium alkoxide. Exploring the generality of the reaction, Grignard reagent 39 was intercepted with other carbonyl and sulfur electrophiles including benzophenone and S-phenyl benzenethiosulfonate (Table 1, entries 2 – 3) to furnish the diol 40b and thio-ether 40c respectively.

Table 5. Iodine-Magnesium Exchange and Alkylation of Iodoalcohols.

<table>
<thead>
<tr>
<th>entry</th>
<th>alkyl-iodide</th>
<th>electrophile</th>
<th>product</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>36a</td>
<td>cyclohexanone</td>
<td>40a</td>
<td>71</td>
</tr>
<tr>
<td>2</td>
<td>36a</td>
<td>benzophenone</td>
<td>40b</td>
<td>64</td>
</tr>
<tr>
<td>3</td>
<td>36a</td>
<td>benzothiosulfonate</td>
<td>40c</td>
<td>64</td>
</tr>
<tr>
<td>4</td>
<td>36b</td>
<td>benzothiosulfonate</td>
<td>40d</td>
<td>54</td>
</tr>
</tbody>
</table>
This reaction methodology was extended to a substituted iodopropanol (entry 4). The requisite substrate, 36b, was synthesized by converting 3-iodopropanoic acid to the corresponding acid chloride with oxalyl chloride and catalytic DMF, followed by the addition of two equivalents of allylmagnesium bromide (78% yield). The iodoalcohol 36b undergoes the standard exchange alkylating S-phenyl benzenethiosulfonate to yield the corresponding thio-ether 40d (entry 4). The strategy works with 4-iodo-1-butanol\textsuperscript{81} affording an intermediate that reacts with cyclohexanone to furnish the diol 40e (entry 5) and S-phenyl benzenethiosulfonate to yield the corresponding thio-ether 40f (entry 6). Trapping the Grignard derived from 36c with and S-phenyl benzenethiosulfonate required 2.5 equivalents of the electrophile for complete conversion for reasons not immediately apparent.

3.3 Mechanism of the Iodine-Magnesium Exchange at sp\textsuperscript{3} Centers

Mechanistically, this exchange process is envisioned to proceed through the magnesium alkoxide intermediate 37 (Scheme 9). Subsequent addition of \textit{n}-BuLi, can conceivably generate Grignard 43 by two alternative pathways. The first pathway 37 $\rightarrow$ 43 involves, a chlorine-butyl exchange\textsuperscript{82} followed by butyl addition to afford an electron
rich magnesiate 41. Subsequent iodine-magnesium exchange would afford the magnesiate 43 possibly in equilibrium with the cyclic magnesium alkoxide 39 and a free equivalent of \( n\text{-BuLi} \). Alternatively internal complexation of \( n\text{-BuLi} \) and the magnesium alkoxide might facilitate a directed iodine-lithium exchange\(^{83} \) to afford the Normant-like reagent 42 that can subsequently form the ate complex 43 (37 → 43, Scheme 9).

**Scheme 9. Iodine-Magnesium Exchange of sp\(^3\) Hybridized Alkyliodides.**

Conceptually, the more basic butyl group in the ate complex 43 might be selectively consumed by deprotonating the co-generated 1-iodobutane in an \( E_2 \) elimination reaction. Alternatively, an equilibrium between the magnesiate 43 and the cyclic Grignard reagent might be displaced in favor of the Grignard reagent 39 by consumption of the 1-iodobutane by the \( n\text{-BuLi} \) released from the ate complex.

Intercepting the cyclic Grignard reagents with electrophiles is in some cases compromised by a competitive butyl addition to the electrophile suggesting that either the equilibrium does not lie exclusively on the right (43 ↔ 39) or that the alkoxypropyl or alkoxybutyl group is selectively transferred.
3.4 Conclusion

Collectively, this alkoxide directed iodine-magnesium exchange of iodoalcohols provides a valuable strategy for accessing sp$^3$ hybridized Grignard reagents. This exchange process proceeds rapidly at $-78$ °C affording a cyclic magnesium alkoxide that intercepts electrophiles to afford a variety of functionalized alcohols. Potentially, this alkoxide-directed strategy provides a valuable synthetic strategy for accessing sp$^3$ hybridized Grignard reagents that might prove useful in the synthesis of chiral Grignard reagents.
Chapter 4

\(\gamma\)- and \(\delta\)-Hydroxynitrile-Derived Dianions: Diastereoselective Electrophile-Dependent Alkylations

[Taken in part from: Org. Lett. 2010, 12, 3030 and Tetrahedron 2013, 69, 366.]^{44a,b}

4.1 Introduction

Metalated nitriles are potent nucleophiles.\(^{84}\) The nitrile group is a compact, cylindrical electron withdrawing group\(^{85}\) that provides inductive stabilization\(^{86}\) and possesses the ability to localize a high charge density on a relatively small nucleophilic carbon.\(^{15}\) Alkylations of nitrile derived anions allows for the creation of difficult, nitrile-substituted\(^{20}\) ring systems, and sterically hindered quaternary centers,\(^{13}\) even in cases where comparable enolated alkylations are unsuccessful.\(^{87}\)

Cyclic, metalated nitriles offer the ability to install sterically congested quaternary centers with predictable stereochemistry.\(^{45b}\) For example, simply by judicious choice of base, cyclic nitrile \(44\) can easily be converted to either \(cis\)- or \(trans\)-decalins (\(c.f.\) Scheme 10, \(44 \rightarrow 47a\) and \(44 \rightarrow 47b\)).\(^{45b}\) Deprotonating the cyclic hydroxynitrile \(44\) with an excess of \(i\)-PrMgCl allows for the generation of the bicyclic magnesium alkoxide \(45\) which can then undergo cyclization to the \(cis\)-decalin \(47a\). However, adding an excess of \(n\)-BuLi affords the \(N\)-metalated nitrile \(46\) where another lithium atom possesses the ability to span the hydroxyl and the \(\pi\)–system of the axial nitrile directing the cyclization to the \(trans\)-decalin \(47b\).
Diastereoselective alkylations of *acyclic* nitriles are significantly more challenging.\(^{20}\) The challenge stems structural features of acyclic nitriles: the use of chiral auxiliaries on or near the nitrile are often difficult or even impossible to achieve,\(^ {88}\) the use of chiral ligands to complex *N*-metalated nitriles often relay chirality poorly due to the remote position of the nucleophilic carbon,\(^ {89}\) *C*-metalated nitriles rapidly epimerize,\(^ {90,45b}\) and the inherently flexible, rotatable single bonds in aliphatic nitriles make access to any one single conformer quite difficult.\(^ {91}\)

Highly stereoselective alkylations of acyclic nitriles can be achieved by restricting the conformational mobility of the molecule. One such method as seen in Scheme 11 allows for the placing of a sterically biased stereocenter adjacent to the nucleophilic carbon and judiciously positioning alkyl and unsaturated substituents allowing for a highly diastereoselective 1,2-asymmetric induction.\(^ {44c-e}\)
Moving the chiral center two carbons away from the metalated nitrile diminished the selectivity into the range of approximately 3 – 5:1 (Scheme 12), reflecting the difficulty of selectively accessing and alkylating one diamond lattice conformation (c.f. 53a $\leftrightarrow$ 53b) over the other.

Collectively, the above mentioned strategies imply a need for new selective strategies to selectively install quaternary centers within conformationally mobile, acyclic nitriles. Temporary chelation provides a tantalizing means of relaying chirality over 3 – 4 carbons when attempting to alkylate metalated nitriles. Prior attempts to test the configurational stability of C-metalated nitriles, began in our laboratory on both the $E$-
and Z-γ-hydroxy-α,β-alkenenitriles 55 as shown in Scheme 13. Use of t-BuMgCl was employed to deprotonate the hydroxyl group and a second equivalent of a Grignard reagent (R-MgX) was used to trigger a conjugate addition of the R group to generate the cyclic C-metalated nitriles 58a and 58b. Alkylation with benzaldehyde affords a 4:1 mixture of diastereomers 59a and 59b at the benzylic position in 64% yield. Stereochemical fidelity was maintained for both the conjugate addition and the configuration at the nitrile bearing carbon. This reaction is significant because it shows that chelation can be used to set the stereochemistry at the nitrile bearing carbon; however, the magnesium alkoxide was not particularly nucleophilic and the reaction only alkylated highly reactive electrophiles such as benzaldehyde and benzyl bromide and required the presence of HMPA.

**Scheme 13. Alkylation of a Chelated Acyclic γ-Hydroxy-α,β-alkenenitrile.**

4.2 Alkylations of γ-Hydroxynitriles

Through the course of our research we desired a direct means of generating cyclic magnesium alkoxides of type 58 for an efficient chiral relay to the nitrile bearing carbon without the use of a conjugate addition. γ-Hydroxynitriles are valuable precursors in the generation of carbocycles and heterocycles. Their latent use in total synthesis is also
well documented. \(^\text{95}\) \(\gamma\)-Hydroxynitriles of this type are most easily synthesized by means of generating a \(N\)-lithiated nitrile, quenching with an epoxide, followed by addition of dilute acid. \(^\text{96}\) In exploratory experiments, a range of Grignard reagents were screened to doubly deprotonate \(60a\) followed by alkylation with \(n\)-PrI as an electrophile (c.f. Table 6).

**Table 6. Optimization of the Reaction of 60a with \(n\)-PrI.**

<table>
<thead>
<tr>
<th>entry</th>
<th>Grignard</th>
<th>yield (%)</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.0 equiv. MeMgBr</td>
<td>56</td>
<td>2.5:1</td>
</tr>
<tr>
<td>2</td>
<td>5.0 equiv. MeMgCl</td>
<td>52</td>
<td>2.5:1</td>
</tr>
<tr>
<td>3</td>
<td>5.0 equiv. PhMgBr</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>4</td>
<td>2.2 equiv. (i)-PrMgCl</td>
<td>91</td>
<td>16.6</td>
</tr>
<tr>
<td>5</td>
<td>3.2 equiv. (i)-PrMgCl</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>6</td>
<td>4.0 equiv. (i)-PrMgCl</td>
<td>64</td>
<td>16.0</td>
</tr>
<tr>
<td>7</td>
<td>5.0 equiv. (i)-PrMgCl</td>
<td>72</td>
<td>16.0</td>
</tr>
<tr>
<td>8</td>
<td>5.0 equiv. (i)-PrMgBr</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>9</td>
<td>5.0 equiv. (t)-BuMgCl</td>
<td>72</td>
<td>16.0</td>
</tr>
<tr>
<td>10</td>
<td>1.0 equiv. (t)-BuMgCl</td>
<td>0</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Optimization experiments clearly show that greater than 4 equivalents of RMgX is necessary for complete deprotonation \(\alpha\) to the nitrile and the use of \(i\)-PrMgCl is best for high diastereoselectivities. Use of less bulky Grignard reagents (c.f. entries 1 – 2) leads to diminished yields and diasteromeric ratios, while \(t\)-BuMgCl and combinations thereof
lead to no deprotonation in the $\alpha$-position of the nitrile (entries 9 – 10). This is significant because it suggests that the Grignard is incorporated in the structure of the intermediate.

Exploratory reactions employed the tert-butyl-substituted nitrile 60a using 5 equivalents of $i$-PrMgCl for the deprotonation. Alkylations with various electrophiles were performed with the expectation that the large, sterically demanding tert-butyl substituent would accentuate the emerging stereoselectivity trends. The results are shown in Table 7.

**Table 7. Reaction of 60a with Various Electrophiles.**

<table>
<thead>
<tr>
<th>entry</th>
<th>electrophile</th>
<th>nitrile</th>
<th>yield (%)</th>
<th>(dr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CD$_3$I</td>
<td>37a</td>
<td>96</td>
<td>(7.5:1)</td>
</tr>
<tr>
<td>2</td>
<td>I</td>
<td>61b</td>
<td>82</td>
<td>(6.5:1)</td>
</tr>
<tr>
<td>3</td>
<td>I</td>
<td>61c</td>
<td>91</td>
<td>(16.6:1)</td>
</tr>
<tr>
<td>4</td>
<td>Br</td>
<td>61d</td>
<td>93</td>
<td>(4.7:1)</td>
</tr>
<tr>
<td>5</td>
<td>Br</td>
<td>61e</td>
<td>75</td>
<td>(5.0:1)</td>
</tr>
<tr>
<td></td>
<td>Compound</td>
<td>Ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>----------</td>
<td>-------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td><img src="61f.png" alt="Structure" /></td>
<td>47&lt;sup&gt;b&lt;/sup&gt; (5.5:1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td><img src="61g.png" alt="Structure" /></td>
<td>86 (14.3:1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**non-Selective**

<table>
<thead>
<tr>
<th></th>
<th>Compound</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td><img src="61g.png" alt="Structure" /></td>
<td>95 (1.3:1)</td>
</tr>
<tr>
<td>9</td>
<td><img src="61h.png" alt="Structure" /></td>
<td>90 (1:1)</td>
</tr>
<tr>
<td>10</td>
<td><img src="61i.png" alt="Structure" /></td>
<td>92 (1:1)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**anti-Selective**

<table>
<thead>
<tr>
<th></th>
<th>Compound</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td><img src="61j.png" alt="Structure" /></td>
<td>62 (5.9:1)</td>
</tr>
<tr>
<td>12</td>
<td><img src="61h.png" alt="Structure" /></td>
<td>90 (&gt;20:1)</td>
</tr>
</tbody>
</table>

(a) All ratios were determined by 500 MHz <sup>1</sup>H NMR integration of well resolved, distinct signals. (b) 42% of the starting material 60a was recovered. (c) A ratio of 1:1 at the carbinol carbon of the two anti-selective isomers.

Reaction of 60a with 5 equivalents of i-PrMgCl generates a competent metalated nitrile that smoothly and cleanly reacts with electrophiles. The quaternary nitriles can be classified in three distinct categories: syn-selective (entries 1–7), non-selective (entries
8–10), and \textit{anti}-selective (entries 11–12). Intercepting the metalated intermediate with simple alkyl halides such as CD$_3$I, EtI, and \textit{n}-PrI efficiently affords \textit{syn} products. Alkylation with the slower, relatively less reactive \textit{n}-PrI affords the best selectivity (16.6:1). Interestingly, employing more reactive electrophiles, allyl bromide and propargyl bromide having essentially the same steric demand as \textit{n}-PrI, alkylate just as efficiently as the alkyl halides; however, the selectivity is much lower 4.7:1 and 5.0:1, respectively. The reaction of propargyl bromide, though seemingly trivial, allows for insight into the reaction. There was no detectible allene formed; only the acetylenic nitrile 61e was observed. This is significant because it shows that the reaction occurs via an S$_\text{N}2$ process and not S$_\text{N}2\text{'}. The difference in selectivities between alkylation with \textit{S}-phenyl benzenethiosulfonate and diphenyl disulfide are intriguing. \textit{S}-phenyl benzenethiosulfonate smoothly generates the corresponding thio-ether with poor selectivity (1.3:1, entry 8) as compared to the “relatively” less reactive diphenyl disulfide (entry 7) which generates the same thio-ether in a much improved ratio of 14.3:1.

Reaction with highly reactive electrophiles such as methyl cyanoformate (entry 9) allows for the acylation of the nucleophilic species which then undergoes spontaneous lactonization\textsuperscript{97} from the attack of the magnesium alkoxide onto the intermediate ester. This reaction, though high yielding, affords a 1:1 mixture of diastereomers. As well, reaction with benzaldehyde allows for the alkylation of the metalated intermediate efficiently, but again in a nonselective manner yielding a 1:1 mixture of diastereomers.
Intriguingly, the same lactone from methyl cyanoformate can be generated in a much more selective manner by using the less electrophilic diethyl carbonate to alkylate the intermediate metalated nitrile in an anti fashion with excellent selectivity (50:1) as determined by GCMS. Lastly, the use of ethyl pivalate generates the lactol 61j diastereoselectively in an anti manner.

4.3 Probing the Steric Minimum for Alkylations

Only a few pharmaceuticals and natural products possess tert-butyl substituents. Numerous bioactive molecules possess isopropyl and methyl substituents, so in the course of our research, we attempted to determine how small we can make the carbinol substituent and still achieve selectivity. With the isopropyl-bearing hydroxynitrile, alkylation under standard reaction conditions with n-PrI, affords a 5.8:1 ratio of diastereomers, down drastically from the tert-butyl ratio of 16.6:1. Not surprisingly, the diastereoselectivity with the methyl-substituted hydroxynitrile proceeds with a lower selectivity of 3.6:1 for alkylation with n-PrI. Collectively, these two experiments reveal that the increasing size of the carbinol substituent increases the selectivity.

Scheme 14. Probing the Steric Minimum for Chiral Relay.
4.4 Changing the Alkylation Stereochemistry

Synthetically, generation of the opposite diastereomer of the tert-butyl series can be achieved simply by changing the substituent α to the nitrile. For example, the α-propyl-nitrile 60d and the isopropyl α-isopropyl-nitrile 60e were both subjected to standard alkylation conditions, employing an excess of MeI as the electrophile. The n-propyl tether generates 61c’ in a ratio of 9.4:1 while the more sterically demanding isopropyl nitrile 60e generates 61f’ in an 8.0:1 ratio of diastereomers. The diastereoselectivity is opposite that of 61c and 61f with n-PrI and i-PrI, respectively (Table 7, entries 3 and 6).

Scheme 15. Changing the Configuration at the α Carbon to the Nitrile.

4.5 Mechanism of Alkylation

Insight into the nature of the intermediate magnesiated nitrile was obtained by comparing the alkylations of 60 employing the two different Grignard reagents MeMgCl and i-PrMgCl. Remarkably, deprotonating with the larger, more sterically demanding i-PrMgCl causes a significantly more selective alkylation than MeMgCl (Table 6, entries 1 and 2; 16.6:1 vs 2.5:1 respectively) which suggests that the Grignard-derived alkyl group is incorporated within the intermediate magnesiated nitrile. Negligible stereoselectivity
differences arise on changing the counter ion from chloride to bromide. Compared to the cyclic magnesium alkoxides shown in Scheme 13, the alkylation of 60 proceed via a much more nucleophilic intermediate and alkylate with less reactive electrophiles such as \( n\text{-PrI}, i\text{-PrI} \) and diethyl carbonate.

A working mechanism that accounts for the unique influence of the Grignard structure, the electrophile dependent alkylations, and the requirement for a large excess of the Grignard reagent assumes alkylation via the cyclic, nitrile-stabilized magnesiate 64 as depicted in Scheme 16. Subjecting 60 to an excess of \( i\text{-PrMgCl} \), allows the first equivalent of Grignard to deprotonate the hydroxyl group. A second equivalent of Grignard then facilitates an isopropyl-chlorine exchange, and a third equivalent of Grignard generates magnesiate 62. Magnesiate 62 is sufficiently basic to internally abstract the proximal acidic methine proton \( \alpha \) to the nitrile generating deprotonated nitrile 63 which should preferentially cyclize to the less sterically congested isopropyl-containing magnesiate 64'. Assuming a chloromagnesium cation\(^9\) complexes the electron rich alkoxy oxygen in 64 on the most accessible face opposite of the five-membered ring and preferentially eclipses the smaller, linear nitrile group rather than the larger substituent, \( R^2 \) (\textit{c.f.} 64' and 64", Scheme 16) then diastereomer 64' should be more stable than diastereomer 64".
Subsequent alkylation of the “chiral” nitrile-stabilized magnesiate 64 exhibits an unusual dependence on the nature of the electrophile. Although speculative, the retentive alkylations with alkyl halides are consistent with a side-on overlap with the carbon-magnesium bond 65. Invertive attack of 65 with an $sp^3$ hybridized electrophile would require drastic steric compression and should be strongly correlated with the steric demand of the adjacent substituent $R^2$, which is not the case (Table 7, entries 8 – 10). Carbonyl electrophiles have a diminished steric demand and larger anti-bonding orbitals.
that should allow backside attack onto the small nucleophilic orbital of the C – Mg bond. An alkylation progressing through 66 benefits from a two center, two electron transition structure whereas a retentive alkylation requires a three center, two electron TS. Non-selective electrophiles (entries 8 – 10) may react through both trajectories because of their high reactivity.

Support for the proposed mechanism was obtained through selective alkylations of an N-metalated nitrile and an analogous C-metalated nitrile. Although the different acylation selectivities of 60a with methyl cyanoformate and diethyl carbonate implicate stereoelectronic control, the two electrophiles could potentially react through different O, C- or C, O-acylation sequences having different selectivities. As a mechanistic test for internal asymmetric induction from an O, C-acylation sequence, the carbonate 43 was prepared from 60a by deprotonating the hydroxyl with an equimolar amount of i-PrMgCl and addition of methyl cyanoformate. The resulting carbonate 67, was treated with a slight excess of LiNEt$_2$ to generate the N-metalated nitrile which cyclized to a 1:1 mixture of lactones. This implies that there is no inherent conformational bias imparted by the remote chiral center in the N-lithiated nitrile 68.
Although the N-lithiated nitrile 68 cyclizes nonselectively, the corresponding O-acylated, C-magnesiated nitrile could conceivably react selectively. In order to generate the requisite C-magnesiated nitrile, carbonate 69 was formed in the same manner as described prior. m-CPBA oxidation of the thio-ether 61g yields the corresponding α-sulfinyl nitrile. Making use of a low temperature, sulfinyl-magnesium exchange,22b the C-magnesiated nitrile 70 was generated by adding i-PrMgCl which generated lactones 61h and 61h’ in a ratio of 3.4:1. Because diethyl carbonate alkylates 60a with a significantly higher diastereoselectivity (> 20:1), the C-magnesiated, O-acylated nitrile 70 seems unlikely as an intermediate. Consistent with an invertive acylation of magnesiated nitrile 70, the major lactone diastereomer 61h arises from a retentive sulfinyl-magnesium exchange followed by an invertive acylation (Table 7, entries 11 – 12).
Scheme 18. Intramolecular Acylation of a C-Magnesiated Nitrile.

Acylations with ester electrophiles provide excellent support for inclusion of an isopropyl group within the magnesiate $64'$. Acylations of $64'$ with large, more sterically demanding esters afford dihydroxynitriles $61m-o$ (Scheme 13). Formation of $61m-o$ likely arises via the corresponding ketones $71$, followed by a selective reduction through internal hydride delivery$^{100}$ from the Grignard derived isopropyl group (Scheme 19). This reduction of the hindered ketone, is presumably constrained by chelation which very selectively directs reduction from the $re$ face of the carbonyl. The mechanistic scenario is consistent with the relative configuration of the carbinol and quaternary nitrile-bearing centers in $37m-o$. The acylation of $60a$ with ethyl pivalate is delicately poised. Under the standard conditions, acylation is followed by cyclization to lactol $61j$; whereas, an excess of $i$-PrMgCl (10 equivalents) is required for reduction to the diol $61o$ (compare Table 7, entry 11 and Table 8, entry 3).
Scheme 19. Sequential Acylation-Reductions with Ester Electrophiles.

Table 8. Diastereoselective Ester Acylations of 60a.

<table>
<thead>
<tr>
<th>entry</th>
<th>electrophile</th>
<th>product</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EtCOO</td>
<td>61m</td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td>CcOEt</td>
<td>61n</td>
<td>84</td>
</tr>
<tr>
<td>3</td>
<td>t-BOEt</td>
<td>61o</td>
<td>64&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

(a) Accompanied by 17% of the lactol 61j and required 10 equiv. of i-PrMgCl.
4.6 Formal Synthesis of Isoaminile

The diastereoselective hydroxynitrile alkylations stimulated an attempt to rapidly synthesize the cough suppressant isoaminile 72.\textsuperscript{95c} Sold as the isoaminile-cyclamate salt under the name Peracon\textsuperscript{®}, a chiral synthesis of isoaminile 72, was previously achieved by means of a 12-step synthesis.\textsuperscript{95c} Making use of our reaction methodology, we made attempts to synthesize isoaminile by simple alkylation of 60f with an isopropyl group. Generation of 61p, followed by activation of the hydroxyl group and displacement with dimethylamine would complete the synthesis in only three steps from the known hydroxynitrile 61f.\textsuperscript{96}

Deprotonating 60f and alkylating with i-PrI efficiently installs the quaternary center in 93% yield. However, the selectivity was only a meager 2.4:1 ratio of diastereomers in favor of the syn-addition product.\textsuperscript{95c} In an attempt to improve the ratio, we used the less reactive electrophile i-PrBr. This alkylated efficiently to form 61p in 90% yield; however, the selectivity decreased to 1.8:1, again in favor of the syn-addition product. Lastly, in an attempt to react the intermediate at low temperatures, use of a much more reactive electrophile, i-PrOTos\textsuperscript{101} was employed. The reaction was high yielding (95% yield), but with a low selectivity of only 2.1:1, again in favor of the syn-isomer. Unfortunately, the α phenyl substituent appears deleterious, probably by delocalizing charge into the ring making a less stable chelate, and resulting in alkylation from an open structure.

![Scheme 20](image)

Table 9. Diastereoselective Isopropyl Additions to 60f.

<table>
<thead>
<tr>
<th>entry</th>
<th>electrophile</th>
<th>yield 61p (%)</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>i-PrI</td>
<td>93</td>
<td>2.4:1</td>
</tr>
<tr>
<td>2</td>
<td>i-PrBr</td>
<td>90</td>
<td>2.1:1</td>
</tr>
<tr>
<td>3</td>
<td>i-PrOTos</td>
<td>93</td>
<td>1.8:1</td>
</tr>
</tbody>
</table>

4.7 Homologous Alkylations

A series of hydroxyl-directed deprotonation-alkylations were performed with homologous δ-hydroxynitriles to determine the viability of a chelation-controlled 1,4-asymmetric induction. A minimum of four equivalents of Grignard is required to fully deprotonate the hydroxynitrile. Presumably the magnesiate 74 is sufficiently basic to abstract the proton α to the nitrile and generate 75 which collapses to 76 in which all substituents are in an equatorial position in a chair-like conformer. This 6-membered
chelate 76 was anticipated to exhibit greater conformational rigidity than for the 5-membered chelate 64$^\circ$.

Scheme 21. Chelation-Controlled 1,4-Asymmetric Induction.

The synthesis of requisite $\delta$-hydroxynitriles requires a multi-step synthesis. Conjugate addition of phenyl acetonitrile to methyl vinyl ketone in the presence of catalytic sodium methoxide according to a literature procedure affords 79.$^{102}$ Subsequent reduction of the resultant ketone 79 with NaBH$_4$ furnishes the corresponding $\delta$–hydroxynitrile 73a in almost quantitiative yield as a 1:1 ratio of diastereomers.


Synthesis of the methyl substituted $\delta$–hydroxynitrile 73b can be achieved from commercially available 4-chlorobutyronitrile. Facile halogen exchange of the chloride in 4-chlorobutyronitrile with NaI in refluxing acetone affords 80.$^{103}$ Activated zinc
insertion into the iodide of 80 furnished the organo-zinc intermediate which undergoes subsequent transmetallation to the corresponding Knochel cuprate and which smoothly reacts with pivaloyl chloride to form ketone 81 (92% yield, Scheme 23). Reduction of ketone 81 with an excess of NaBH₄ in MeOH generates the unsubstituted δ-hydroxynitrile 82 in 98% yield. The unsubstituted nitrile 82 was then methylated by deprotonating with five equivalents of i-PrMgCl and reacting with 1.05 equivalents of MeI.

Scheme 23. Synthesis of 5-hydroxy-2,6,6-trimethylheptanenitrile.

The synthesis of tert-butyl-α-phenyl hydroxynitrile 73c (Scheme 24), was accomplished from 4-iodo-2-phenylbutanenitrile 83 via a multi-step synthesis. Alkyl iodide 83 was reacted with activated zinc and the resulting organozinc was transmetallated to the Knochel cuprate and reacted with pivaloyl chloride to afford ketone 84. Ketone 84 proved exceedingly difficult to purify, and was not isolated, but rather was directly reduced with NaBH₄ to furnish hydroxynitrile 73c, in a 1:1 ratio of diastereomers in 64% overall yield.
Scheme 24. Synthesis of 5-hydroxy-6,6-dimethyl-2-phenylheptanenitrile.

Perhaps not surprisingly, positioning the carbinol center four carbons removed from the nucleophile leads to a significantly diminished diastereoselectivity when alkylating δ–hydroxynitriles of type 73 (Table 10). When the carbinol substituent is a methyl group (Table 10) deprotonation and alkylation with n-PrI as an electrophile affords 78a in a 2.5:1 ratio of diastereomers compared to a ratio of 3.3:1 for the γ–hydroxynitrile counterpart. Surprisingly, increasing the steric demand at the carbinol center, by employing 73b with a tert-butyl group, only modestly increased the selectivity for the alkylation with n-PrI (Table 10, entry 2, 4.0:1).

Reacting 73b, with other electrophiles proved exceedingly difficult, because of the difficulty of abstracting the proton α to the nitrile. In order to make the methine proton α to the nitrile more acidic, as well as simultaneously increase steric demand at that stereocenter, a series of alkylations with the α-phenyl hydroxynitrile 73c were performed. Unfortunately deprotonating 73c and adding n-PrI afforded 78c with a decreased selectivity to 2.7:1 (entry 3). However, alkylation with allyl bromide (entry 3) generated 78d with a diastereoselectivity of 5.9:1. Interestingly, deprotonating 73c and intercepting with methyl cyanoformate generates the bis-acylated product 78e in a ratio of 3.5:1 (entry 5). Alkylations with propargyl bromide and i-PrI, both proceed with lower stereoselectivities, 3.7:1 and 1.4:1 respectively, than that of the homolgous 1,3
alkylations (5.0:1 and 5.5:1 respectively; compare Table 7, entries 5 and 6 with Table 10, entries 6 and 7).

**Table 10. Diastereoselective Alkylations of δ–hydroxynitriles 73.**

<table>
<thead>
<tr>
<th>entry</th>
<th>nitrile</th>
<th>electrophile</th>
<th>product</th>
<th>yield (%) (dr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="73a" /></td>
<td><img src="image" alt="I-" /></td>
<td><img src="image" alt="78a" /></td>
<td>93 (2.5:1)</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="73b" /></td>
<td><img src="image" alt="I-" /></td>
<td><img src="image" alt="78b" /></td>
<td>64 (4.0:1)</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="73c" /></td>
<td><img src="image" alt="I-" /></td>
<td><img src="image" alt="78c" /></td>
<td>90 (2.7:1)</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="73c" /></td>
<td><img src="image" alt="Br" /></td>
<td><img src="image" alt="78d" /></td>
<td>85 (5.9:1)</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="73c" /></td>
<td><img src="image" alt="CN" /></td>
<td><img src="image" alt="78e" /></td>
<td>62 (3.5:1)</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="73c" /></td>
<td><img src="image" alt="Br" /></td>
<td><img src="image" alt="78f" /></td>
<td>86 (3.7:1)</td>
</tr>
</tbody>
</table>
Unfortunately, the modest selectivity in alkylations of δ-hydroxynitriles potentially limits their use. The lack of selectivity could emerge from competitive alkylation from an acyclic conformer or from an equilibrium between two diastereomeric complexes (Scheme 21). In light of the lack of selectivity, no effort was made to probe the mechanism for this reaction.

4.8 Conclusion

γ- and δ-hydroxynitriles undergo double deprotonation-alkylations that install quaternary centers. The alkylations of γ-hydroxynitriles are typically highly diastereoselective with the stereochemistry being dependent on the nature of the electrophile. Alkyl halides install the alkyl group syn to the hydroxyl; whereas, the reactive carbonyls alkylate non-selectively. In contrast, less reactive ester and carbonate electrophiles selectively install the carbonyl anti to the hydroxyl group.

Mechanistically, the alkylations are consistent with forming a highly unusual nitrile-stabilized magnesiate that incorporates an alkyl group derived from the Grignard reagent used for the deprotonation. Alkylations with ester electrophiles afford dihydroxynitriles arising from an extremely selective β-hydride elimination within the magnesiate. Comparable alkylations and acylations of the homologous δ-hydroxynitriles are only modestly selective, possibly due to the competitive alkylation from an acyclic, open chain conformation. Collectively, these alkylations are the first electrophile-dependent alkylations of acyclic nitriles, exhibit a unique influence on the nature of the
Grignard used for the deprotonation, and address the challenge of installing quaternary centers in conformationally mobile, acyclic nitriles.

4.9 Stereochemical Proof for the 1,3-Induction Products

Stereochemical proof of compounds 61a through 61o was determined by four different means: manipulation and correlation to that which was already known, X-Ray diffraction, cyclization in combination with nOe and/or NOESY experiments, and lastly by analogy. The results of all stereochemical conditions are shown in Figure 6.

Figure 6. Stereochemical Determinations for 1,3-Induction.
First, the allylated product 61d and the acetylene product 61e were both hydrogenated under standard conditions in a Paar shaker using 5% Pd/C as a catalyst and methanol as a solvent. The results indicate that both the both allyl bromide and propargyl bromide alkylate in the same sense that n-PrI alkylates. The minor isomer of the n-PrI alkylation, 61c, was subjected to a modified cyclization procedure of Larchevêque and Debal.\textsuperscript{96a} Quenching the intermediate sodium alkoxide generated by NaHMDS with absolute ethanol generated the anticipated imino-lactone as well as a sufficient amount of the corresponding lactone. This lactone was full characterized by various spectroscopic methods (\textsuperscript{1}H NMR, \textsuperscript{13}C NMR, IR, HRMS) and subjected to a NOESY experiment. NOESY clearly indicated that tert-butyl and n-propyl are cis on the ring convolutes structure 85 and allows for the unfolding of 61c‘. Subjecting the major isomer of 61g to the same cyclization conditions affords a sufficient amount of the corresponding lactone 86, which was also subjected to several nOe experiments. nOe experiments indicated that the tert-butyl and methyl are on the same side of the ring, which when unfolded yields structure 61g. Using a combination of nOe and NOESY experiments convoluted the structures of both lactols 61j and 61j‘. X-Ray diffraction unequivocally produced structures for the lactone 61h generated from diethyl carbonate as well as all three isomers generated from reaction with benzaldehyde. Lastly, by analogy, structures 61a, 61b, 61f, 61k, and 61l were made by comparison of the singlet produced in the \textsuperscript{1}H NMR spectrum by the methyl at the quaternary center of all of the alkyl halide products. In every case, the methyl singlet of each major isomer possesses a higher chemical shift then that of its minor counterpart.
Stereochemical proof of the products of this sequential acylation-reduction lies within the X-Ray structure of 61m as shown below. The other two products 61n and 61o were made by analogy to 61m.

**Figure 7. ORTEP of dihydroxynitrile 61m.**

4.10 Stereochemical Proof for the 1,4-Alkylation Products

Stereochemistry of the alkylation products was first determined by hydrogenating the alkene 78d and the acetylene nitrile 78f using catalytic Pd/C. The results of both reactions revealed the same major diastereomer that n-PrI yielded 78c. The stereochemistry of the propyl-substituted products were determined by alkaline hydrolysis of the δ-hydroxynitrile 78a to the lactone 87 whose structure was revealed by a NOESY experiment. Isolated as a side product from the reaction with methyl cyanoformate, lactone 88 was subjected to NOESY and revealed product 78e. The stereochemistry of alkylated product 78g resulting from i-PrI was made by analogy to the other alkyl halides. Lastly, and perhaps most importantly, the methine proton resulting from the secondary alcohol centers, shows a distinguishable pattern in the 1H NMR spectrums. Further evidence to support the stereochemistry of all of the products is that the major isomer occurs as a doublet, and the minor isomer yields a multiplet which is located at least 0.1 – 0.2 ppm upfield from the doublet. This trend and splitting pattern for both the major and minor isomers was universal with every electrophile.
Figure 8. Stereochemical Determinations for 1,4-Induction.

Chemical Correlation:

NOESY:

Analogy to 78c:
Chapter 5

Cyclohexylcarbonitriles: Diastereoselective Arylations with TMPZnCl·LiCl

[Taken in part from J. Org. Chem. 2012, 77, 7671.]

5.1 Introduction

Transition metal catalyzed cross-coupling reactions provide a powerful means for the formation of carbon-carbon bonds. More specifically, the Pd-catalyzed α-arylation of carbonyls and their derivatives has vastly expanded the field of enolate chemistry. However, the α-arylation of nitriles remains significantly unexplored. The development of a variety of TMP-bases have been developed to generate various organometallics. These bases not only exhibit a high kinetic basicity, but also their side product generated during the reaction, TMP-H does not hinder catalysis reactions like other amine bases.

Recently, in this lab, the use of TMPZnCl·LiCl has proven to efficiently generate C-zinacted nitriles from nitriles of type 94 which can undergo Negishi cross-coupling with aryl bromides in the presence of Pd(OAc)$_2$ and Buchwald’s S-Phos to generate α-arylated products of type 90 (Scheme 25).

Scheme 25. α-Arylation of C-Zincated Nitriles.
This work on racemic substrates is an excellent entry into diastereoselective Negishi-coupling reactions by means of remote control. Prior work on simple alkyl-substituted, aliphatic 5- and 6-membered ring systems have proven quite successful, exhibiting a high diastereoselectivity by means of the most thermodynamically favored Pd intermediate. Latent use of this methodology has recently been extended to substituted Piperidines.

Substituted arylacetonitriles are prevalent motifs embedded within diverse pharmaceuticals. Typically, the nitrile-bearing carbon is fully substituted, as in the blockbuster drug anastrazole and the well-studied antiarrhythmic agent verapamil. A more specific scaffold amongst these pharmaceuticals are aryl-substituted cyclohexanecarbonitriles such as the second-generation H1-receptor antagonist levocabastine and the phosphodiesterase inhibitor cilomilast. Continuing development of bioactive arylacetonitriles is stimulating numerous approaches to this pharmacophore, particularly via transition metal catalyzed cross coupling of metalated nitriles.
5.2 Arylation of Cyclohexylcarbonitriles

Through the course of our research, we found it necessary to extend this work to functionalized ring systems, namely cyclohexylcarbonitriles. Substituted cyclic C-metalated nitriles, have been shown to exhibit highly diastereoselective alkylations and acylations. These substituted cyclohexyl-ring systems are easily prepared according to literature prescient by means of the appropriate ketone and TosMIC. The resultant substrates of type 89 can then be deprotonated with TMPZnCl·LiCl generating the most stable zinc intermediate 94, which then undergoes transmetalation to palladium generating the Pd(II)-intermediates of type 95, which undergoes reductive elimination to capitulate products of type 90.

Continuing the TMP-based arylation of nitriles, cyclohexanecarbonitrile 89a has been couple with several aryl bromides as seen in Scheme 26. Deprotonating 89a with TMPZnCl·LiCl allows arylation with electron rich and electron deficient aryl bromides.
Extensive screening again identified the Pd(OAc)$_2$ as the proper palladium source and S-Phos the proper ligand with aryl bromides being optimal for coupling, allowing facile coupling even with the sterically demanding 2-bromoanisole. It is worth mentioning that coupling with esters could only be accomplished by using a hindered tert-butyl ester. Subsequent reactions with ethyl esters led to attack on the ester to form the corresponding ketone instead of the desired coupling product.

Scheme 26. α-Arylation of Cyclohexanecarbonitrile.

A significant challenge remaining in this area is the diastereoselective arylation of cyclic nitriles because of the importance of this structural motif in pharmaceuticals. 4-tert-butycyclohexanecarbonitrile 89b$^{118}$ was employed as a conformationally constrained prototype for the diastereoselective coupling with 4-bromobenzonitrile. During optimization, it was discovered that use of the corresponding iodide was explored; however, it produced significant amounts of [1,1’-biphenyl]-4,4’-dicarbonitrile
through homocoupling of the electrophile. The optimized procedure involves drop-wise addition of TMPZnCl-LiCl to a room temperature THF solution of 89. After 20 min., S-Phos, Pd(OAc)$_2$ and the electrophile were added and the resultant heated to 50 °C until completion. The results and scope of the diastereoselective coupling reactions employing substituted nitriles 89 with aryl bromides utilizing Pd(OAc)$_2$ (2 mol %) and S-Phos (4 mol %) as a catalyst system to generate products of type 90 are summarized in Table 11.

Table 11. Diastereoselective Cyclohexanecarbonitrile Coupling.

<table>
<thead>
<tr>
<th>entry</th>
<th>substituted nitrile</th>
<th>aryl bromide</th>
<th>product</th>
<th>yield (%) (dr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$t$-Bu-CN$_3$</td>
<td>Br-C$_6$H$_4$CN</td>
<td>90d</td>
<td>75% (&gt;20:1)$^a$</td>
</tr>
<tr>
<td>2</td>
<td>$t$-Bu-CN$_3$</td>
<td>Br-C$_6$H$_4$OMe</td>
<td>90e</td>
<td>60% (8.4:1)$^b$</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Structure 89c" /></td>
<td><img src="image" alt="Structure 90f" /></td>
<td>72% (2.3:1) (^c)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="Structure 89d" /></td>
<td><img src="image" alt="Structure 90g" /></td>
<td>68% (3.5:1) (^d)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="Structure 89d" /></td>
<td><img src="image" alt="Structure 90h" /></td>
<td>68% (4.8:1) (^d)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="Structure 89e" /></td>
<td><img src="image" alt="Structure 90i" /></td>
<td>70% (6.2:1) (^d)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td><img src="image" alt="Structure 89f" /></td>
<td><img src="image" alt="Structure 90j" /></td>
<td>51% (&gt;20:1) (^a)</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td><img src="image" alt="Structure 89g" /></td>
<td><img src="image" alt="Structure 90k" /></td>
<td>71% (&gt;20:1) (^a)</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td><img src="image" alt="Structure 89h" /></td>
<td><img src="image" alt="Structure 90l" /></td>
<td>72% (&gt;20:1) (^a)</td>
<td></td>
</tr>
</tbody>
</table>

(a) No other diastereomer could be detected. (b) Ratio determined by HPLC. (c) Ratio determined by \(^1\)H NMR Spectroscopy. (d) Ratio determined by GC.

Not surprisingly, the results appear to be related to the conformational mobility of the cyclohexane ring’s substituent and position. Making use of structure 89b, the large tert-butyl group appears to better anchor the ring and allows for the smooth coupling with
para-functionalized aromatic bromides (entry’s 1 – 2) making use of a nitrile (entry 1) and a methoxy group in excellent to good ratios of >20:1 and 8.4:1 for 90d and 90e respectively.

It was originally thought that a high diastereoselectivity could be achieved even with the use of a smaller methyl group in the 4-position of the cyclohexane ring. However, this was not the case as the diastereoselectivity dropped dramatically to 3.5:1 and 4.8:1 for 4-bromobenzonitrile and 4-bromoanisole respectively (entry’s 4 and 5) when coupled to 89d. This is not entirely unexpected, as the much smaller methyl group, can only generate 0.8 kcal mol\(^{-1}\), in diaxal strain. Although, somewhat unexpected is the case of the isopropyl group in the 4-position on the cyclohexane ring 89c. This reaction (entry 3) yielded a dr lower than the corresponding methyl, instead of a ratio between the tert-butyl (>20:1) and methyl (>3.5:1), for reasons not immediately apparent.

Importantly, moving the methyl substituent to the 3-position of the cyclohexane ring 89e, better locks the intermediate palladium-complex and generates a better ratio of 6.2:1 when coupled with 4-bromobenzonitrile (entry 6).

Interestingly, coupling can be achieved with the methyl in the 2-position of the cyclohexane ring 89f (entry 8). This reaction gives excellent selectivity (entry 9) of a dr >20:1; however, it comes at the cost of a lower yield. This is presumably due to side reactions because the deprotonation requires 12 hours at 50 °C for consumption of the proton α to the nitrile, and due to the long reaction time after addition of the 4-bromobenzonitrile (38 hours) which allowed for significant homo-coupling of 4-bromobenzonitrile.
A pleasant surprise arrived when utilizing the TBS functionality in 89g. This substrate can easily be prepared NaBH₄ reduction of the corresponding ketone followed by silylation. The resultant was then subjected to our coupling conditions, yielding 71% of 90k with excellent selectivity (>20:1). Additionally, coupling of an exceptionally rigid cholesterol derivative 89h was also found to give a selectivity >20:1 (entry 10).

**Scheme 27. Metalated Nitrile Coupling Mechanism.**

5.3 Mechanism

Mechanistically, the reaction most likely proceeds through zincation, transmetalation to palladium, and reductive elimination (Scheme 27). Deprotonating 89 with TMPZnCl-LiCl affords a C-zincated nitrile that proceeds through a conducted tour \( C \rightarrow N \rightarrow C \) metal migration sequence to 94 with the zinc in the equatorial orientation. Transmetallation of the zincated nitrile 94 with an arylpalladium bromide...
would afford the C-palladated nitrile $95^{124}$ with subsequent reductive elimination affording nitrile $90$. Variations in the diastereomeric ratio for the same carbonitrile with different aryl bromides (entries 1 – 2 and 4 – 5) implies that an equilibrium exists between axial and equatorial C-palladated nitriles $95$ and $95'$. An electronic influence on the equilibrium between $95$ and $95'$ is implied from the diastereomeric ratios of the tert-butyl- and isopropylcyclohexane carbonitriles (compare entries 1-3 with entry 9) which typically exert similar conformational restriction.\(^{15}\) The 4-tert-butylcarbonitrile $89b$, causes a bond angle distortion at C-4\(^{125}\) that decreases the $s$ character of the C – CN bond, consistent with the electronic influence of the remote substituent is the virtually exclusive diastereocontrol for the 4-OTBS cyclohexanecarbonitrile which has a significantly smaller steric demand than either a $t$-butyl or $i$-Pr substituent (0.7, 4.2, and 2.2 kcal mol\(^{-1}\) for OTBS, $t$-Bu, and $i$-Pr groups, respectively).

The diastereoselective coupling of 2-methylcyclohexanecarbonitrile $89f$ is highly selective entry 10). Presumably the C-palladated nitrile $95$ ($R =$ Me) exerts a strong preference for conformer $95$ where the small nitrile and vicinal methyl groups are gauche to avoid steric compression between a gauche methyl group and the sterically demanding palladium-SPhos complex $95'$.

5.4 Conclusions

Deprotonating cyclohexanecarbonitriles with TMPZnCl·LiCl and coupling with aryl bromides diastereoselectively affords substituted cyclohexanecarbonitriles. The diastereoselectivity trends are unusual in exhibiting a strong electronic dependence on the nature of the aryl bromide and the substituents on the cyclohexane ring. 4-$t$-Butyl- and 4-TBSO- substituents exert virtually complete stereocontrol whereas 4-$i$-Pr, 4-Me, and 3-
Me substituents are significantly less selective. In contrast, the coupling of 2-methylcyclohexanecarbonitrile, installing vicinal tertiary-quaternary centers, is highly stereoselective. Collectively these alkylations are the first diastereoselective arylations of cyclic nitriles and establish unusual stereoelectronic effects that should prove useful in synthesizing cyclohexanecarbonitrile-containing pharmaceuticals.
Chapter 6

Conclusions

6.1 Halogen-Magnesium Exchange at sp\textsuperscript{3} Centers

A facile halogen-magnesium exchange employing the advantage of a proximal alkoxide directing group has been explored and developed as seen in Scheme 28. Deprotonating iodoalcohols of type 36 with i-PrMgCl generates magnesium alkoxides 37 which are envisioned to undergo a halogen-metal exchange and form cyclic magnesium alkoxides 39 capable of intercepting carbonyl and sulfur electrophiles yielding products of type 40.


![Scheme 28](image)

This work was found to possess a few minor drawbacks. A slight excess of the electrophile was required to consume a small amount of the nucleophilic butyl group due the Schlenk equilibrium shown in Scheme 29. In any event, the alkoxide 39 or the magnesiate 39 was found to be more nucleophilic than the butyl group.

Scheme 29. Schlenk Equilibrium Associated with Alkoxide-Directed Exchanges.

![Scheme 29](image)
This work presented ultimately led to the development of other methodologies including development of an sp³ halogen-metal exchange bearing an oxygen in the γ-position via a self-collapsing Grignard reagent. This work has found its way into the total synthesis of Rhopaloic Acid. This methodology has several advantages: it allows for the generation of sp³ hybridized Grignard reagents bearing an alcohol functionality and facilitates the generation of polyfunctional products.

### 6.2 Electrophile-Dependent Alkylations of γ- and δ-Hydroxynitriles

Deprotonating γ-hydroxynitriles 60 with an excess of i-PrMgCl affords an unusual, nitrile-stabilized magnesiate 64 that incorporates a Grignard-derived alkyl group that can be intercepted with a wide-variety of electrophiles to yield products of type 61 (see Scheme 30).

**Scheme 30. Alkylations of γ-hydroxynitriles.**

The alkylations of γ-hydroxynitriles are typically highly diastereoselective with the stereochemistry dependent upon the electrophile: alkyl halides install the alkyl group syn to the hydroxyl whereas reactive carbonyl electrophiles alkylate non-selectively. In contrast, less reactive ester and carbonate electrophiles selectively install the carbonyl anti to the hydroxyl group!
Deprotonating \( \delta \)-hydroxynitriles 73 with an excess of \( i \)-PrMgCl affords intermediates of type 76 that can be intercepted with a wide-variety of electrophiles to yield products of type 78 as depicted in Scheme 31.

**Scheme 31. Alkylations of \( \delta \)-hydroxynitriles.**

Comparative alkylations and acylations of the homologous \( \delta \)-hydroxynitriles exhibit modest stereoselectivity that suggest alkylation through a nitrile anion that is significantly different with respect to the structural integrity to the \( \gamma \)-hydroxynitriles; perhaps an acyclic conformation such as 77.

Importantly, Coldham and co-workers have used our synthetic methology as a key intermediate in their synthesis of the tetracyclic core of *Daphiniphyllum* Alkaloids.\(^{95b}\) This application, as well as employment of our other synthetic transformations\(^{127-128}\) demonstrate the utility of this work.

### 6.3 Diastereoselective Coupling of Substituted Cyclohexanecarbonitriles

Deprotonation of cyclohexanecarbonitriles 89 with the powerful base system of TMPZnCl·LiCl generates C-zincated nitriles of the type 94 which can undergo stereoselective palladium catalysis with Pd(OAc)\(_2\) and S-Phos to generate products of type 90 *via* the stabilized palladium complex 95 (Scheme 32).
Scheme 32. Stereoselective Coupling of Substituted Cyclohexanecarbonitriles.

Steric and electronic effects influence the diastereoselectivity of 4-\textit{t}-butyl-, 4-TBSO-, and 2-Me-cyclohexanecarbonitriles with complete diastereocontrol. Only modest diastereoselectivity is seen with 4-\textit{i}-Pr-, 4-Me-, and 3-Me substituted cyclohexanecarbonitriles.

The uncommon, yet predictable diastereoselectivity trends detailed in this work should prove useful for practical synthesis of substituted cyclohexanecarbonitrile-containing pharmaceuticals.
Chapter 7

Experimental Section

7.1 General Considerations

All reactions were carried out with magnetic stirring in a flame-dried 50 mL round-bottom flask under argon. Use of other size round-bottom flasks gave diminished yields. Syringes used to transfer reagents and solvents were purged with argon prior to use. Benzaldehyde, allyl bromide, ethyl trimethylacetate and diethyl carbonate were freshly distilled. Propyl iodide and propargyl bromide were passed through basic alumina and silica successively prior to use. Lastly, i-PrMgCl, methyl cyanoformate, diphenyl disulfide and S-Phenyl benzenethiosulfonate were used as received prior to use. THF was distilled prior to use over sodium and benzophenone.

TLC was performed with Silicycle glass-backed Ultra Pure Silica Gel plates and visualized either by UV detection or Ceric Ammonium Molybdate (CAM) stain. Please note that all other stains for detection were found to be inferior to CAM due to the steric hinderance of the hydroxyl.

IR Spectra were recorded on a Nicolet 380 FT-IR neat. NMR spectra were recorded on either a 500 MHz for $^1$H NMRs or a 400 MHz (100 MHz) for $^{13}$C NMRs on Bruker Avance$^{II}$ NMR in CDCl$_3$ where chemical shifts are reported in parts per million (ppm) using TMS as an internal standard. High resolution mass spectra (HRMS) were recorded using electrospray ionization on an Agilent LC/MSD 1200 Series Nanoflow Time of Flight (TOF) mass spectrometer. X-Rays were taken on a Bruker Smart Apex II CCD Diffractometer.
7.2 General Procedures

**General Procedure for sp³ Exchanges:**

A THF solution of $i$-PrMgCl (1.1 equiv.) was added to a -78 °C, THF solution of the iodoalcohol (1 equiv.). After 5 min, a hexanes solution of $n$-BuLi (2.1 equiv.) was added and after 5 min the electrophile (1.1 equiv.) was added neat. After 30 min, saturated, aqueous NH$_4$Cl was added, the crude product was separated and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried (Na$_2$SO$_4$), concentrated, purified by silica gel (230 – 400 mesh) chromatography to afford analytically pure material.

**General Procedure for Hydroxynitrile Alkylations:**

A THF solution of $i$-PrMgCl (5.0 equiv., 2.0 M solution) was added to a -78 °C, THF solution of the hydroxynitrile (1 equiv.). After 5 min, the cold bath was removed and the reaction was allowed to warm up to room temperature. After 30 min the reaction was cooled to -78 °C, the electrophile (5 – 10 equiv.) was added neat, and then the cooling bath was removed. After 16 h a saturated, aqueous solution of NH$_4$Cl was added, the phases were separated, and the aqueous phase was extracted three times with EtOAc. The combined organic extracts were dried over Na$_2$SO$_4$, concentrated, and purified by either silica gel (230 – 400 mesh) or radial chromatography to afford analytically pure material.
**General Procedure for the Conversion of Ketones to Nitriles:**

Modifying a known procedure, solid $t$-BuOK (1.2 equiv.) was added to a vigorously stirred, THF solution (0.1 M) of the ketone (1 equiv.). After 20 min solid toluenesulfonylmethyl isocyanide (TosMIC, 1.2 equiv.) was added. After 4 h, a saturated, aqueous NH$_4$Cl solution was added, the phases were separated, and the aqueous phase was extracted with Et$_2$O (3x). The combined organic extracts were dried (Na$_2$SO$_4$), concentrated, and purified by silica gel (230 – 400 mesh) chromatography to afford analytically pure material.

**General Coupling Procedure:**

A THF solution of TMPZnCl·LiCl$^{109f}$ (1.5 equiv) was added drop-wise to a THF solution (2 mL) of the nitrile in a 25 mL Schlenk-tube. After 20 min complete deprotonation was checked by removing an aliquot and treating with allyl bromide and a catalytic amount CuCN·2LiCl solution (1 M in THF).$^{129}$ Upon complete metalation, SPhos (4 mol %), Pd(OAc)$_2$ (2 mol %) and the electrophile (0.6 equiv.) were added and then the reaction mixture was placed in an oil bath at 50 °C. Reaction progress was checked by GC analysis of aliquots quenched with a solution of NH$_4$Cl. Upon completion, saturated, aqueous NH$_4$Cl was added, the phases were separated, and the aqueous phase was extracted with ether. The combined organic phase was dried (Na$_2$SO$_4$), the solvent was evaporated under reduced pressure, and the crude nitrile was then purified by silica gel flash chromatography or radial chromatography.
7.3 Iodine-Magnesium Exchange Reactions

4-(2-iodoethyl)hepta-1,6-dien-4-ol (36b)

Oxalyl chloride (1.31 mL, 15.0 mmol) was added to a room temperature, CH₂Cl₂ solution (10 mL) containing two drops of DMF and 3-iodopropionic acid (2.03 g, 10.0 mmol). After stirring for 30 min at room temperature the solvent was removed, the residue was redissolved in 10 mL of THF and the resulting solution was cooled to – 42 °C. Then allylmagnesium bromide (32 mL, 20.4 mmol) was added. The solution was allowed to warm to ambient temperature over 1.5 h, then 50 mL of water was added. The crude product was poured into a separatory funnel containing aqueous 0.2 M HCl (75 mL) and shaken. The aqueous phase was separated, extracted with EtOAc and the combined organic extracts were washed with sequentially with water and NaHCO₃. The resultant was dried (Na₂SO₄), concentrated, purified by column chromatography and fractionally distilled under vacuum to afford 2.11 g (78% yield) of 36b as an oil.

IR (neat): 3444 (OH), 1638 (alkene) cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ 5.86 – 5.77 (m, 2H), 5.21 – 5.13 (m, 4H), 3.26 – 3.22 (m, 2H), 2.27 – 2.20 (m, 4H), 2.14 – 2.11 (m, 2H), 1.64 (s, 1H).

¹³C NMR (125 MHz, CDCl₃): δ 132.74, 119.59, 74.79, 44.39, 43.31, -1.29.

HRMS (ESI) m/z calcd. For C₉H₁₅IONa (M + Na) 267.0246, expt. 267.0240.
1-(3-hydroxypropyl)cyclohexanol (40a)

![Chemical Structure]

The general procedure was employed with i-PrMgCl (2.0 M, 0.45 mmol), n-BuLi (2.9 M, 0.85 mmol), 3-iodo-1-propanol (75.6 mg, 0.41 mmol) and cyclohexanone (50 μL, 0.48 mmol) to afford, after column chromatography 45.4 mg (71% yield) of 40a.

\[^{1}H\text{ NMR}\ (500\text{ MHz, CDCl}_3): \delta 3.67\ (t, J = 6.7\ Hz, 2\text{H}), 1.71 – 1.40\ (16\ \text{H}).\]

\[^{13}C\text{ NMR}\ (125\text{ MHz, CDCl}_3): \delta 71.08, 63.24, 38.82, 37.49, 26.09, 25.79, 22.24.\]

The above compound is in good agreement with that which was reported previously.\[^{130}\]

1,1-diphenylbutane-1,4-diol (40b)

![Chemical Structure]

The general procedure was employed with i-PrMgCl (2.0 M, 0.61 mmol), n-BuLi (2.9 M, 1.17 mmol), 3-iodo-1-propanol (103.5 mg, 0.556 mmol) and benzophenone (0.12 g, 0.07 mmol) to afford, after column chromatography 86.0 mg (64% yield) of 40b.

\[^{\text{IR\ (neat): 3404}\ (\text{OH}), 3351\ (\text{OH})\ cm^{-1}.}\]

\[^{1}H\text{ NMR}\ (500\text{ MHz, CDCl}_3): \delta 7.46 – 7.40\ (m, 4\text{H}), 7.35 – 7.28\ (m, 4\text{H}), 7.26 – 7.19\ (m, 2\text{H}), 3.72 – 3.65\ (m, 2\text{H}), 2.99\ (\text{br s, 1H}), 2.44\ (t, J = 7.3\ Hz, 2\text{H}), 1.57 – 1.64\ (m, 2\text{H}), 1.54\ (s, 1\text{H}).\]

\[^{13}C\text{ NMR}\ (125\text{ MHz, CDCl}_3): \delta 147.1, 128.1, 126.7, 126.1, 77.8, 63.0, 38.9, 27.1.\]

\[^{\text{HRMS\ (ESI) \text{m/z\ calcd.\ For\ C}_{16}\text{H}_{18}\text{O}_2\text{Na (M + Na)}\ 265.1204,}\ \text{expt.\ 265.1211.}}\]

80
3-(Phenylthio)propan-1-ol (40c)

\[
\text{HO} \quad \text{SPh}
\]

The general procedure was employed with \( i\text{-PrMgCl (2.0 M, 0.64 mmol), n-BuLi (2.0 M, 1.22 mmol), 3-iodo-1-propanol (115 mg, 0.556 mmol) and } S\text{-Phenylbenzenethiosulfonate (0.3874 g, 0.63 mmol) to afford, after radial chromatography 66.9 mg (64\% yield) of 40c.} \)

\(^1\text{H NMR (500 MHz, CDCl}_3\text{): } \delta 7.42 – 7.15 (m, 5H), 3.78 (t, J = 6 Hz, 2H), 3.05 (t, J = 7 Hz, 2H), 1.91 (quintet, J = , 2H), 1.65 (br s, 1H). \)

\(^{13}\text{C NMR (125 MHz, CDCl}_3\text{): } \delta 136.21, 129.18, 128.89, 126.97, 61.38, 31.67, 30.23. \)

The above compound is in good agreement with that which was reported previously.\(^{131}\)

4-(2-(Phenylthio)ethyl)hepta-1,6-dien-4-ol (40d)

\[
\text{HO} \quad \text{SPh}
\]

The general procedure was employed with \( i\text{-PrMgCl (2 M, 0.45 mmol), n-BuLi (2.0 M, 0.85 mmol), 4-(2-iodoethyl)hepta-1,6-dien-4-ol (107.4 mg, 0.40 mmol) and } S\text{-Phenylbenzenethiosulfonate (0.1214 g, 0.48 mmol) to afford, after radial chromatography 54.2 mg (64\% yield) of 40d.} \)

\(^\text{IR (neat): } 3460 (OH), 1636 (alkene) \text{ cm}^{-1}. \)

\(^1\text{H NMR (500 MHz, CDCl}_3\text{): } \delta 7.36 – 7.32 (m, 2H), 7.30 – 7.27 (m, 2H), 7.20 – 7.15 (m, 1H), 5.85 – 5.76 (m, 2H), 5.18 – 5.09 (m, 4H), 3.04 – 2.99 (m, 2H), 2.30 – 2.21 (m, 4H), 1.83 – 1.78 (m, 2H), 1.71 (br s, 1H). \)
$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 136.4, 133.1, 129.0, 119.3, 73.3, 43.7, 38.5, 27.9.

HRMS (ESI) $m/z$ calcd. For C$_{15}$H$_{20}$OSK (M + K) 287.0872, expt. 287.0849.

1-(4-hydroxybutyl)cyclohexanol (40e)

The general procedure was employed with $i$-PrMgCl (2 M, 0.59 mmol), $n$-BuLi (2.9 M, 1.08 mmol), 4-iodobutan-1-ol (106.6 mg, 0.53 mmol) and cyclohexanone (0.15 mL, 1.45 mmol) to afford, after column chromatography 49.4 mg (60% yield) of 40e.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 3.65 (t, $J = 6.7$ Hz, 2H), 1.80 – 1.20 (m, 18H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 71.71, 63.00, 41.95, 37.40, 33.20, 26.14, 22.45, 19.44.

The above compound is in good agreement with that which was reported previously.$^{130}$

4-(Phenylthio)butan-1-ol (40f)

The general procedure was employed with $i$-PrMgCl (2.0 M, 0.59 mmol), $n$-BuLi (2.9 M, 1.05 mmol), 4-iodobutan-1-ol (104.2 mg, 0.52 mmol) and S-Phenylbenzenethiosulfonate (0.3452 g, 1.4 mmol) to afford, after column chromatography 54.3 mg (57% yield) of 40f.
\( ^1 \)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.40 – 7.10 (m, 5H), 3.66 (t, \( J = 6.0 \) Hz, 2H), 2.96 (t, \( J = 7.0 \), 2H), 1.76 – 1.67 (m, 4H), 1.48 (br s, 1H).

\( ^{13} \)C NMR (125 MHz, CDCl\(_3\)): \( \delta \) 136.55, 129.15, 128.89, 125.85, 62.35, 33.46, 31.69, 25.48.

The above compound is in good agreement with that which was reported previously.\(^{132} \)

7.4 \( \gamma \)- and \( \delta \)-hydroxynitrile Alkylation Reactions

(\( 2RS,4SR \)) and (\( 2SR,4SR \)) 4-hydroxy-2,5-dimethylhexanenitrile (60c)

Modifying a known procedure,\(^96 \) neat propionitrile (2.75 mL, 31.51 mmol) was added to a -78°C THF solution (30 mL) of LDA solution prepared from 4.52 mL (32.25 mmol) diisopropylamine and (32.1 mmol) of butyllithium. After 45 minutes, neat 1,2-epoxy-3-methylbutane (5.0 g, 58.1 mmol) was added. The resulting solution was then allowed to warm to room temperature. After 1h, the solution was cooled to \(-78^\circ\) C and then 50 mL of aqueous 2 M HCl was added. The resultant was then allowed to warm up to room temperature overnight and then the phases were separated and the aqueous phase was extracted with ether. The combined organic phases dried (Na\(_2\)SO\(_4\)) and then evaporated under reduced pressure to yield an oil which was purified by flash chromatography (95:5, hexanes:EtOAc) to yield 3.40 g (76% yield) of 60b as an oily mixture of diastereomers.

Major Isomer:

\( ^1 \)H NMR (500 MHz, CDCl\(_3\)): \( \delta \) 3.61 - 3.56 (m, 1H), 3.04 – 2.96 (m, 1H), 2.60 (br s, 1H), 1.83 (dd, \( J = 5.6 \), 10 Hz, 1H), 1.80 (dd, \( J = 5.6 \), 10 Hz, 1H), 1.73 – 1.60 (m, 2H),
1.57 – 1.50 (m, 1H), 1.35 (d, \( J = 7.2 \), 3H), 1.34 (d, \( J = 7.2 \) Hz, 3H), 0.93 (d, \( J = 6.8 \) Hz, 6H), 0.92 (d, \( J = 6.8 \) Hz, 6H).

\( ^{13} \text{C NMR} \) (100 MHz, CDCl\(_3\)): \( \delta \) 123.69, 122.99, 73.68, 72.93, 38.30, 37.64, 33.87, 33.62, 22.67, 21.73, 18.40, 18.25, 17.22, 17.02.

**Minor Isomer:**

\( ^{1} \text{H NMR} \) (500 MHz, CDCl\(_3\)): \( \delta \) 3.49 – 3.39 (m, 1H), 2.89 - 2.86 (m, 1H), 2.36 (br s, 1H), 1.83 (dd, \( J = 5.6 \), 10 Hz, 1H), 1.80 (dd, \( J = 5.6 \), 10 Hz, 1H), 1.73 – 1.60 (m, 2H), 1.57 – 1.50 (m, 1H), 1.35 (d, \( J = 7.2 \), 3H), 1.34 (d, \( J = 7.2 \) Hz, 3H), 0.93 (d, \( J = 6.8 \) Hz, 6H), 0.92 (d, \( J = 6.8 \) Hz, 6H).

\( ^{13} \text{C NMR} \) (100 MHz, CDCl\(_3\)): \( \delta \) 123.69, 122.99, 73.68, 72.93, 38.30, 37.64, 33.87, 33.62, 22.67, 21.73, 18.40, 18.25, 17.22, 17.02.

**Mixture:**

\( \text{IR (neat): 3442 (OH), 2241 (CN) cm}^{-1}. \)

\( \text{HRMS m/z calcd. for C}_{8}\text{H}_{15}\text{NONa (M} + \text{Na): 164.1051; expt. 164.1052.} \)

\((2RS,4SR)-\text{and (2SR,4RS)-4-hydroxy-5,5-dimethyl-2-propylhexanenitrile (60d)}\)

This procedure was adapted from that Larchevêque and Debal,\(^{96}\) (2.75 mL, 31.51 mmol) propionitrile was added to an LDA solution containing 4.52 mL (32.25 mmol) diisopropylamine and 32.10 mmol of a butyllithium in THF at -78° C. The resulting
solution was allowed to deprotonate for 45 minutes and then 4.0 mL (32.5 mmol) of 3,3-dimethyl-1,2-epoxybutane was added. The resulting solution was then allowed to warm up to room temperature over the period of one hour. The solution was cooled back down to –78° and 50 mL of 2 M HCl was added. This resultant was then allowed to warm up to room temperature overnight. The resulting mixture was extracted with ether and dried over sodium sulfate and evaporated under reduced pressure to yield an oil which was purified by flash chromatography employing 95:5 (hexanes:EtOAc) to yield 3.35 g (58% yield) of the title compound as an oily mixture of diastereomers.

**Mixture:**

**IR** (neat): 3471 (OH), 2240 (CN) cm\(^{-1}\).

**\(^1\)H NMR** (500 MHz, CDCl\(_3\)): δ 3.52 (br d, J = 10.5 Hz, 1H), 3.30 (m, 1H), 2.96 - 2.90 (m, 1H), 2.82 - 2.79 (m, 1H), 1.76 - 1.48 (m, 12H), 0.99 - 0.95 (m, 6H), 0.92 (s, 9H), 0.91 (s, 9H).

**\(^{13}\)C NMR** (100 MHz, CDCl\(_3\)): δ 123.13, 122.40, 77.15, 76.80, 34.94, 34.82, 34.24, 33.90, 33.11, 28.96, 28.43, 25.40, 20.47, 20.32, 13.62, 13.58.

**HRMS** m/z calcd. for C\(_{11}\)H\(_{21}\)NONa (M + Na): 206.1521; expt. 206.1532.

\((2RS, 4SR)- and (2SR, 4SR)-4-hydroxy-2,5,5-trimethyl-2-(trideuteromethyl)hexanenitrile (61a)\)

\[
\text{OH} \quad \text{CD}_{3} \quad \text{CN} \quad \text{t-Bu}
\]

The reaction was carried out according to the general procedure using nitrile 60a (128.4 mg, 0.83 mmol), \(i\)-PrMgCl (2.07 mL, 4.14 mmol), and CD\(_3\)I (1.00 mL, 16.07 mmol) to
give a crude product that was purified by radial chromatography employing 90:10
(hexanes:EtOAc) to afford 136.8 mg (96% yield) of 61a in a 7.5:1 ratio of diastereomers
as a colorless oil.

**Major Isomer (2RS, 4SR):**

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 3.51 (dd, $J = 2, 9.3$ Hz, 1H), 1.72 (dd, $J = 2, 14.5$ Hz,
2H), 1.68 (d, $J = 4.5$ Hz, 2H), 1.55 (dd, $J = 9.3, 14.5$ Hz, 1H), 1.45 (s, 3H), 0.92 (s, 9H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 125.62, 76.93, 42.37, 35.13, 31.20, 27.49, 25.33.

**Minor Isomer (2SR, 4SR):**

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 3.51 (dd, $J = 2, 9.3$ Hz, 1H), 1.72 (dd, $J = 2, 14.5$ Hz,
2H), 1.68 (d, $J = 4.5$ Hz, 2H), 1.55 (dd, $J = 9.3, 14.5$ Hz, 1H), 1.39 (s, 3H), 0.92 (s, 9H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 125.62, 76.93, 42.37, 35.13, 31.20, 27.49, 25.33.

**Mixture:**

IR (neat): 3499 (OH), 2235 (CN) cm$^{-1}$.

HRMS m/z calcd. for C$_{10}$H$_{16}$D$_3$NONa (M + Na): 195.1553; expt. 195.1542.

**(2RS, 4SR) and (2SR, 4SR)-2-ethyl-4-hydroxy-2,5,5-trimethylhexanenitrile (61b)**

Performing the general procedure with nitrile 60a (76.4 mg, 0.492 mmol), $i$-PrMgCl
(1.24 mL, 2.48 mmol), and ethyl iodide (1.00 mL, 12.5 mmol) gave a crude product that
was purified by radial chromatography (95:5, hexanes:EtOAc) to afford 73.9 mg (82% yield) of 61b and 61b* (6.5:1 ratio of diastereomers) as a light yellow oil.

**Minor (2RS, 5SR):**

\[^1\mathrm{H}\text{ NMR}\] (400 MHz, CDCl\textsubscript{3}): $\delta$ 3.56 - 3.52 (m, 1H), 1.82 - 1.70 (m, 3H), 1.54 (dd, $J =$ 7.6, 14.0 Hz, 1H), 1.48 - 1.41 (m, 1H), 1.41 (s, 3H), 1.08 (t, $J =$ 7.4 Hz, 3H), 0.92 (s, 9H);
\[^{13}\text{C NMR}\] (100 MHz, CDCl\textsubscript{3}): $\delta$ 124.68, 76.94, 40.63, 36.69, 35.27, 33.03, 25.33, 24.28, 9.15.

**Minor Isomer (2SR, 5SR):**

\[^1\text{H NMR}\] (400 MHz, CDCl\textsubscript{3}): $\delta$ 3.50 - 3.48 (m, 1H), 1.82 - 1.70 (m, 3H), 1.66 - 1.60 (m, 1H), 1.48 - 1.41 (m, 1H), 1.35 (s, 3H), 1.08 (t, $J =$ 7.4 Hz, 3H).
\[^{13}\text{C NMR}\] (100 MHz, CDCl\textsubscript{3}): $\delta$ 124.89, 76.39, 40.91, 35.96, 35.16, 32.96, 25.37, 23.76, 9.15.

**Mixture:**

\[^{1}\text{IR}\text{ (neat): } 3462 (\text{OH}), 2235 (\text{CN}) \text{ cm}^{-1}.\]

\[^{1}\text{HRMS (ESI) } m/z \text{ calcd. for } \text{C}_{11}\text{H}_{21}\text{NONa (M + Na) } 206.1521, \text{ found } 206.1533.\]
(2RS, 4SR)-4-hydroxy-2,5,5-trimethyl-2-propylhexanenitrile (61c)

The reaction was performed according to the general procedure using nitrile 60a (57.1 mg, 0.368 mmol), i-PrMgCl (0.92 mL, 1.84 mmol), and PrI (0.36 mL, 3.70 mmol) to give a product residue that was purified by radial chromatography to afford 66.1 mg (91% yield) of 61c and 61c' (16.2:1 ratio) as a colorless oil.

Using MeMgCl as the base: The reaction was performed according to the general procedure using nitrile 60a (65.1 mg, 0.419 mmol), MeMgCl (0.70 mL, 2.10 mmol), and PrI (0.50 mL, 5.14 mmol) to give a crude product that was purified by radial chromatography to afford 46.1 mg (56% yield) of 61c as an oily mixture of diastereomers (2.5:1 ratio).

By hydrogenation of 61d: A MeOH solution (15 mL) of hydroxynitrile 61d (75.4 mg, 0.386 mmol) was hydrogenated for 4 h in a Parr shaker at 50 psi using 5% Pd/C (5.1 mg, 0.048 mmol). The methanol was then evaporated, the residue redissolved in EtOAc, and then passed through a short pad of silica gel to afford 67.1 mg (88%) of 61c.

By hydrogenation of 61e: A methanolic solution (15 mL) of hydroxynitrile 61e (44.2 mg, 0.229 mmol) was hydrogenated for 4 h in a Parr shaker at 50 psi using 5% Pd/C (6.3 mg, 0.059 mmol). The methanol was then evaporated, the crude product was redissolved in EtOAc, and then passed through a short pad of silica gel to afford 42.5 mg (94%) of 61c as a colorless oil.
IR (neat): 3498 (OH), 2234 (CN) cm\(^{-1}\).

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta 3.53\) (d, \(J = 9.3\) Hz, 1H), 1.81 (overlapping br s, 1H and d, \(J = 4.9\) Hz), 1.69 - 1.61 (m, 1H), 1.57 – 1.43 (m, 4H), 1.42 (s, 3H), 0.97 (t, \(J = 7.3\) Hz, 3H), 0.92 (s, 9H).

\(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta 124.88, 76.98, 42.29, 41.12, 36.15, 35.29, 25.35, 24.89, 18.17, 14.13\).

HRMS m/z calcd. for C\(_{12}\)H\(_{23}\)NONa (M + Na): 220.1677; expt. 220.1700.

(2\(SR\), 4\(SR\))-4-hydroxy-2,5,5-trimethyl-2-propylhexanenitrile (61c’)

Performing the general procedure with nitrile 60b (101.5 mg, 0.554 mmol), \(i\)-PrMgCl (1.39 mL, 2.78 mmol), and methyl iodide (0.35 mL, 5.62 mmol) gave a crude product that was purified by radial chromatography (90:10, hexanes:EtOAc) to afford 103.9 mg (95% yield) of 61c’ (9.4:1 ratio of diastereomers)\(^{133}\) as a colorless oil.

IR (neat): 3498, 2234 cm\(^{-1}\).

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta 3.53\) - 3.48 (br d, \(J = 9.3\) Hz, 1H), 1.81 (br s, 1H), 1.81 (d, \(J = 4.9\) Hz, 1H), 1.74 - 1.70 (m, 1H), 1.57 – 1.43 (m, 3H), 1.36 (s, 3H), 0.97 (t, \(J = 7.3\) Hz, 3H), 0.92 (s, 9H).

\(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta 124.88, 76.46, 42.35, 41.11, 35.31, 29.69, 25.35, 24.89, 24.14, 18.15\).
HRMS (ESI) \( m/z \) calcd. for \( \text{C}_{12}\text{H}_{23}\text{NONa} (\text{M} + \text{Na}) 220.1677 \), found 220.1700.

\((2\text{RS}, 4\text{SR})\)- and \((2\text{SR}, 4\text{SR})\)-2-allyl-4-hydroxy-2,5,5-trimethylhexanenitrile (61d and 61d’)

Performing the general procedure with nitrile 60a (72.8 mg, 0.469 mmol), \( \text{i-PrMgCl} \) (1.25 mL, 2.50 mmol), and allyl bromide (0.41 mL, 4.74 mmol) gave a crude product that was purified by radial chromatography (98:2, hexanes:EtOAc) to afford 85.2 mg (93\% yield) of 61d and 61d’ (4.7:1 ratio of diastereomers) as a light yellow oil.

**Major Isomer (2RS, 4SR):**

\(^1\text{H NMR}\) (500 MHz, CDCl\(_3\)): \( \delta 5.95 - 5.82 \) (m, 1H), \( 5.25 - 5.17 \) (m, 2H), 3.55 (d, \( J = 9.0 \) Hz, 1H), 2.43 (dd, \( J = 13.8, 7.4 \) Hz, 1H), 2.28 (dd, \( J = 13.8, 7.4 \) Hz, 1H), 1.92 (br s, 1H), 1.83 (d, \( J = 15.0 \) Hz, 1H), 1.46 (m, 1H), 1.43 (s, 3H), 0.91 (s, 9H).

\(^{13}\text{C NMR}\) (125 MHz, CDCl\(_3\)): \( \delta 132.05, 124.33, 120.01, 76.79, 44.16, 40.36, 35.84, 35.27, 25.31, 24.73. \)

**Minor Isomer (2SR, 4SR):**

\(^1\text{H NMR}\) (500 MHz, CDCl\(_3\)): \( \delta 5.95 - 5.82 \) (m, 1H), \( 5.25 - 5.17 \) (m, 2H), 3.52 (d, \( J = 5.8 \) Hz, 1H), 2.53 (dd, \( J = 14.3, 7.5 \) Hz, 1H), 2.32 (dd, \( J = 14.3, 7.5 \) Hz, 1H), 1.65 (d, \( J = 5.8 \) Hz, 1H), 1.35 (s, 3H), 0.91 (s, 9H).
\textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}): \( \delta \) 132.20, 124.53, 119.89, 76.43, 44.07, 40.68, 35.22, 35.17, 25.34, 24.17.

**Mixture:**

\textbf{IR (neat):} 3508 (OH), 2238 (CN), 1643 (alkene) cm\textsuperscript{-1}.

\textbf{HRMS (ESI) m/z} calcd. for formula: \( \text{C}_{12}\text{H}_{21}\text{NONa} (\text{M + Na}) \) 218.1521, found 218.1570.

\( (2\text{RS}, 4\text{SR})\)-4-hydroxy-2,5,5-trimethyl-2-(prop-2-ynyl)hexanenitrile (61e)

Performing the general procedure with nitrile 60a (108.1 mg, 0.70 mmol), \( i\)-PrMgCl (2.09 mL, 4.18 mmol), and propargyl bromide (1.00 mL, 13.3 mmol) gave a crude product that was purified by radial chromatography employing (98:2, hexanes:EtOAc) to afford 101.0 mg (75\% yield) of 61e (5.0:1 ratio of diastereomers) as an oil.

\textbf{IR (neat):} 3494 (OH), 3314 (alkyne), 2239 (CN), 2123 (alkyne) cm\textsuperscript{-1}.

\textbf{\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}):} \( \delta \) 3.54 (dd, \( J = 2.5, 9.5 \) Hz, 1H), 2.65 - 2.55 (m, 2H), 2.19 - 2.16 (m, 1H), 1.97 (br d, \( J = 15.0 \) Hz, 1H), 1.74 (very br d, \( J = 4.5 \) Hz, 1H), 1.61 (dd, \( J = 14.5, 9.5 \) Hz, 1H), 1.54 (s, 3H), 0.93 (s, 9H)

\textbf{\textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}):} \( \delta \) 123.83, 76.74, 72.58, 39.43, 35.28, 29.65, 25.33, 24.89.

\textbf{HRMS (ESI) m/z} calcd. for \( \text{C}_{12}\text{H}_{19}\text{NONa} (\text{M + Na}) \) 216.1364, found 216.1335.
(2RS, 4SR)-4-hydroxy-2-isopropyl-2,5,5-trimethylhexanenitrile (61f)

Performing the general procedure using nitrile 60a (128.0 mg, 0.83 mmol), i-PrMgCl (2.06 mL, 4.12 mmol), and isopropyl iodide (1.00 mL, 10.0 mmol) gave a crude product that was purified by radial chromatography (95:5, hexanes:EtOAc) to afford 76.5 mg (47% yield) of 61f and 61f' (5.5:1 ratio of diastereomers) as a colorless oil.

IR (neat): 3489 (OH), 2254 (CN) cm\(^{-1}\).

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta \) 3.58 - 3.55 (m, 1H), 1.95 - 1.87 (m, 1H), 1.84 - 1.82 (m, 1H), 1.72 (dd, \(J = 8.5, 14.0 \) Hz, 1H), 1.59 - 1.58 (m, 2H), 1.31 (s, 3H), 1.08 (d, \(J = 6.5 \) Hz, 3H), 1.03 (d, \(J = 6.5 \) Hz, 3H), 0.92 (s, 9H).

HRMS (ESI) \(m/z\) calcd. for C\(_{12}\)H\(_{23}\)NONa (M + Na) 220.1677, found 220.1682.

(2SR, 4SR)-4-hydroxy-2-isopropyl-2,5,5-trimethylhexanenitrile (61f')

Performing the general procedure using nitrile 60e (94.5 mg, 0.52 mmol), i-PrMgCl (1.29 mL, 2.58 mmol), and methyl iodide (1.00 mL, 16.1 mmol) gave a crude product that was purified by radial chromatography employing (90:10, hexanes:EtOAc) to afford 96.6 mg (95% yield) of 61f' and 61f (8.0:1 ratio of diastereomers) as a colorless oil.

IR (neat): 3494 (OH), 2238 (CN) cm\(^{-1}\).
$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 3.51 - 3.47 (m, 1H), 1.95 - 1.87 (m, 1H), 1.84 - 1.82 (m, 1H), 1.72 (dd, $J = 8.5$, 14.0 Hz, 1H), 1.59 - 1.58 (m, 2H), 1.31 (s, 3H), 1.08 (d, $J = 6.5$ Hz, 3H), 1.03 (d, $J = 6.5$ Hz, 3H), 0.92 (s, 9H).

HRMS (ESI) $m/z$ calcd. for C$_{12}$H$_{23}$NONa (M + Na) 220.1677, found 220.1694.

Mixture of (37f) and (37f'):

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 124.82, 124.59, 77.28, 76.29, 40.67, 39.47, 38.78, 38.12, 35.44, 35.32, 25.44, 25.36, 21.24, 20.92, 18.31, 17.35, 17.22.

**(2RS, 4SR)- and (2RS, 4RS)-4-hydroxy-2,5,5-trimethyl-2-(phenylthio)hexanenitrile (37g)**

**Method A:** Performing the general procedure with nitrile 60a (82.2 mg, 0.530 mmol), i-PrMgCl (1.32 mL, 2.64 mmol), and diphenyl disulfide (0.69 g, 2.65 mmol) gave a crude product that was purified by radial chromatography (90:10, hexanes:EtOAc) to afford 133.9 mg (96% yield) of 61g and 61g' (14.3:1 ratio of diastereomers) as a colorless oil.

**Method B:** Performing the general procedure with nitrile 60a (70.1 mg, 0.45 mmol), i-PrMgCl (1.13 mL, 2.26 mmol), and S-phenyl benzenethiosulfonate (0.567 g, 2.27 mmol) gave a crude product that was purified by column chromatography (90:10, hexanes:EtOAc) to afford 113.1 mg (95% yield) of 61g and 61g' (1.3:1 ratio of diastereomers) as a colorless oil.
For (2RS, 4SR):

**IR (neat):** 3503 (OH), 2231 (CN) cm⁻¹;

**¹H NMR (500 MHz, CDCl₃):** δ 7.70 (br d, J = 7.0 Hz, 2H), 7.49 – 7.40 (m, 3H), 3.66 (d, J = 9.5 Hz, 1H), 2.02 (br d, J = 14.5 Hz, 1H), 1.96 (br s, 1H), 1.81 (dd, J = 14.5, 9.5 Hz, 1H), 1.66 (s, 3H), 0.89 (s, 9H).

**¹³C NMR (100 MHz, CDCl₃):** δ 137.07, 130.34, 129.38, 129.23, 121.88, 77.06, 43.90, 41.40, 35.32, 26.73, 25.31.

**HRMS (ESI) m/z calcd. for C₁₅H₂₁NOSNa (M + Na) 286.1242, found 286.1209.**

For (2RS, 4RS):

**IR (neat):** 3503 (OH), 2231 (CN) cm⁻¹.

**¹H NMR (500 MHz, CDCl₃):** δ 7.70 (br d, J = 7.0 Hz, 2H), 7.49 – 7.40 (m, 3H), 3.66 (d, J = 9.5 Hz, 1H), 2.01 (d, J = 14.5 Hz, 1H), 1.92 (dd, J = 14.5, 9.5 Hz, 1H), 1.59 (s, 3H), 0.93 (s, 9H).

**¹³C NMR (100 MHz, CDCl₃):** δ 137.0, 130.32, 129.35, 129.24, 122.19, 76.2, 43.4, 41.9, 25.9, 25.4.

**HRMS (ESI) m/z calcd. for C₁₅H₂₁NOSNa (M + Na) 286.1242, found 286.1209.**

(3SR, 5SR)-5-(tert-buty)-3-methyl-2-oxotetrahydrofuran-3-carbonitrile (61h)

![Chemical structure](image)

**Method A:** Performing the general procedure with nitrile 60a (52.1 mg, 0.336 mmol), i-PrMgCl (0.84 mL, 1.68 mmol), and methyl cyanoformate (0.16 mL, 2.01 mmol) gave a
crude product that was purified by column chromatography (98:2, hexanes:EtOAc) to afford 54.8 mg (90% yield) of 61h and 61h' (1:1 ratio of diastereomers) as an oil.

**Method B:** Performing the general procedure with nitrile 60a (84.0 mg, 0.541 mmol), i-PrMgCl (1.35 mL, 2.70 mmol), and diethyl carbonate (0.33 mL, 2.72 mmol) gave a crude product that was purified by radial chromatography (98:2, hexanes:EtOAc) to afford 88.3 mg (90% yield) of 61h and 61h' (50.0:1 ratio, determined by GCMS) as a colorless oil.

**Method C:** Preparation of 61h via cyclization of 43: A THF solution of i-PrMgCl (0.16 mL, 0.32 mmol) was added to a -78 °C, THF solution (5 mL) of nitrile 60a (49.2 mg, 0.317 mmol). After 5 min neat methyl cyanoformate (0.03 mL, 0.378 mmol) was added and then the cooling bath was removed. After 5 min, saturated, aqueous NH₄Cl was added, the phases were separated, and the aqueous phase was then extracted with EtOAc. The combined organic phase was dried (Na₂SO₄), filtered through a short pad of silica gel, and concentrated to afford crude 43 that was used without further purification. A THF solution (2 mL) of 43 (65.6 mg, 0.308 mmol) was added to a -42 °C, THF solution of LiNEt₂ (0.369 mmol). After 45 min, saturated, aqueous NH₄Cl was added, the phases were separated, and the aqueous phase was extracted with EtOAc. The combined organic phase was dried (Na₂SO₄), and concentrated to afford a crude product that was purified by column chromatography (98:2, hexanes:EtOAc) to afford 36.2 mg (64% yield) of 37h and 37h' (1:1 mixture of diastereomers) as an oil.
**Method D:** A THF solution of \( i\)-PrMgCl (0.38 mL, 0.76 mmol) was added to a -78 °C, THF solution (5 mL) of nitrile \( 61g \) (166.4 mg, 0.632 mmol). After 5 min neat methyl cyanoformate (0.05 mL, 0.630 mmol) was added and the cooling bath was then removed. After 5 min, saturated, aqueous NH\(_4\)Cl was added, the phases separated, and the aqueous phase was then extracted with EtOAc. The combined organic phase was dried (Na\(_2\)SO\(_4\)), filtered through a short pad of silica gel, and concentrated to afford a crude oil that was used without further purification. The crude nitrile was added to a -40 °C, CH\(_2\)Cl\(_2\) solution (3 mL) containing \( m\)-CPBA (268.7 mg, 1.20 mmol) previously dried over Na\(_2\)SO\(_4\) and the cooling bath was then removed. After 4 h, saturated, aqueous NH\(_4\)Cl was added, the crude mixture was extracted with CH\(_2\)Cl\(_2\), the combined organic phase was dried (Na\(_2\)SO\(_4\)), filtered through a short pad of silica gel, and concentrated to afford 178.4 mg of crude sulfinyl nitrile \( 45 \) that was used without further purification. A THF solution of \( i\)-PrMgCl (0.15 mL, 0.30 mmol) was added to a -78 °C, THF solution (2 mL) of \( 45 \) (96.4 mg, 0.286 mmol) and then the cooling bath was removed. After 16 h, saturated, aqueous NH\(_4\)Cl was added and the phases were separated. The aqueous phase was extracted with EtOAc, the combined organic phase was dried (Na\(_2\)SO\(_4\)), and then the mixture was evaporated under reduced pressure to afford an oil. The crude oil was then purified by radial chromatography (98:2, hexanes:EtOAc) to afford 28.9 mg (56% yield) of \( 61h \) and \( 61h' \) (3.4:1 ratio of diastereomers) as a colorless oil.
For (3SR, 5SR), a white solid, whose structure was solved by X-Ray crystallography:

**MPt.** 68 – 69 °C.

**IR** (neat): 2240 (CN), 1783 (lactone) cm\(^{-1}\);

**\(^1\)H NMR** (500 MHz, CDCl\(_3\)): \(\delta\) 4.39 (dd, \(J = 11.2, 5.2\) Hz, 1H), 2.66 (dd, \(J = 13.2, 5.2\) Hz, 1H), 1.97 (dd, \(J = 13.2, 11.2\) Hz, 1H), 1.68 (s, 3H), 0.98 (s, 9H).

**\(^{13}\)C NMR** (100 MHz, CDCl\(_3\)): \(\delta\) 170.49, 118.07, 85.51, 39.77, 37.46, 33.10, 24.84, 21.48.

**HRMS** (ESI) \(m/z\) calcd. for C\(_{10}\)H\(_{15}\)NO\(_2\)Na (M + Na) 204.1000, found 204.1012.

\(\text{(3RS,5SR)-5-(tert-butyl)-3-methyl-2-oxotetrahydrofuran-3-carbonitrile (61h')}\)

**IR** (neat): 2248 (CN), 1774 (lactone) cm\(^{-1}\).

**\(^1\)H NMR** (500 MHz, CDCl\(_3\)): \(\delta\) 4.24 (dd, \(J = 6.2, 10.4\) Hz, 1H), 2.52 (dd, \(J = 10.4, 13.3\) Hz, 1H), 2.27 (dd, \(J = 6.2, 13.3\) Hz, 1H), 1.72 (s, 3H), 0.99 (s, 9H).

**\(^{13}\)C NMR** (100 MHz, CDCl\(_3\)): \(\delta\) 171.41, 118.68, 85.41, 39.90, 36.01, 33.52, 24.74, 22.09.

**HRMS** \(m/z\) calcd. for formula: C\(_{10}\)H\(_{15}\)NO\(_2\)Na (M + Na); 204.1000; expt. 204.1020.

Performing the general procedure with nitrile 60a (76.1 mg, 0.490 mmol), \(i\)-PrMgCl (1.23 mL, 2.46 mmol), and benzaldehyde (0.25 mL, 2.45 mmol) with the exception of
maintaining the reaction at -78 °C before addition of saturated, aqueous NH₄Cl, afforded a crude product that was purified by radial chromatography to afford 117.8 mg (92% yield) of 61i as an oily mixture of three diastereomers (61i': 61i'': 61i''', 1.0:1.0:2.0 ratio). The diastereomers were separated by preparative HPLC.

(2SR,4SR)-4-hydroxy-2-((SR)-hydroxy(phenyl)methyl)-2,5,5-trimethylhexanenitrile

(61i')

MPt. 154 – 157 °C.

^{1}H NMR (500 MHz, CDCl₃): δ 7.48 (br d, J = 7.8 Hz, 2H), 7.40 – 7.29 (m, 3H), 5.12 (s, 1H), 4.20 (s, 1H), 3.83 (d, J = 8.3 Hz, 1H), 2.34 (s, 1H), 1.89 (d, J = 15.2 Hz, 1H), 1.83 (dd, J = 8.3, 15.2 Hz, 1H), 1.12 (s, 3H), 0.98 (s, 9H).

^{13}C NMR (125 MHz, CDCl₃): δ 138.38, 128.00, 127.97, 127.26, 127.00, 77.44, 73.83, 42.31, 38.72, 35.18, 25.15, 20.11.

IR (neat): 3397 (OH), 2238 (CN) cm⁻¹.

HRMS m/z calcd. for formula: C_{16}H_{23}NO_{2}Na (M + Na); 284.1626; expt. 284.1664.
(2SR,4SR)-4-hydroxy-2-((RS)-hydroxy(phenyl)methyl)-2,5,5-trimethylhexanenitrile

(61i")

**Mpt.** 118 – 120 °C.

**¹H NMR** (500 MHz, CDCl₃):  δ 7.52 – 7.48 (m, 2H), 7.39 – 7.34 (m, 3H), 4.66 (d, J = 2.4 Hz, 1H), 4.59 (d, J = 1.9 Hz, 1H), 3.80-3.83 (m, 1H), 2.66 (d, J = 2.8 Hz, 1H), 1.95 (d, J = 14.6 Hz, 1H), 1.81 (dd, J = 9.4, 14.6 Hz, 1H), 1.12 (s, 3H), 0.97 (s, 9H).

**¹³C NMR** (100 MHz, CDCl₃): δ 139.38, 128.67, 128.34, 127.57, 122.09, 79.30, 77.09, 43.40, 42.02, 35.15, 25.45, 24.53.

**IR** (neat): 3311 (OH), 3111 (OH), 2237 (CN) cm⁻¹.

**HRMS** m/z calcd. for formula: C₁₆H₂₃NO₂Na (M + Na); 284.1626; expt. 284.1625.
(2RS,4SR)-4-hydroxy-2-((SR)-hydroxy(phenyl)methyl)-2,5,5-trimethylhexanenitrile

(61i’’)

\[
\text{MPt. } 108 – 110 \degree C.
\]

\[^1\text{H NMR}\ (500 \text{ MHz, CDCl}_3): \delta 7.51 – 7.47 (m, 2H), 7.40 – 7.34 (m, 3H), 4.66 (d, } J = 3.3 \text{ Hz, 1H), 3.60 (m, 1H), 3.47 (d, } J = 4 \text{ Hz, 1H), 2.11 (overlapping s, 1H and d, } J = 14.9 \text{ Hz, 1H), 1.99 (dd, } J = 9.5, 14.9 \text{ Hz, 1H), 1.25 (s, 3H), 0.95 (s, 9H).}
\]

\[^{13}\text{C NMR}\ (100 \text{ MHz, CDCl}_3): \delta 138.70, 128.71, 128.30, 127.60, 122.98, 77.20, 76.03, 43.15, 38.41, 35.35, 25.24, 21.48.
\]

\[\text{IR (neat): } 3421 (\text{OH}), 3376 (\text{OH}), 3239 (\text{CN}) \text{ cm}^{-1}.
\]

\[\text{HRMS } m/z \text{ calcd. for formula: } C_{16}H_{23}NO_2Na (M + Na); 284.1626; \text{ expt. } 284.1648.
\]
Performing the general procedure with nitrile 60a (62.1 mg, 0.400 mmol), i-PrMgCl (1.00 mL, 2.00 mmol), and ethyl trimethylacetate (0.31 mL, 2.03 mmol) gave a crude product that was purified by column chromatography employing 95:5 (hexanes:EtOAc) to afford 59.2 mg (62% yield) of 61j and 61j' in a 5.9:1 ratio of diastereomers as a gel-like precipitate.

**Major Isomer:**

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 3.80 (dd, $J = 6.6$, 8.2 Hz, 1H), 2.32 (dd, $J = 5.6$, 6.6 Hz, 1H), 2.09 (dd, $J = 5.6$, 8.2 Hz, 1H), 2.00 (s, 1H), 1.61 (s, 3H), 1.23 (s, 9H), 0.93 (s, 9H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 125.24, 107.77, 82.37, 43.34, 42.09, 39.60, 33.22, 25.86, 25.65, 23.82.

**Minor Isomer:**

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 3.87 (dd, $J = 5.6$, 6 Hz, 1H), 2.66 - 2.71 (m, 1H), 1.81 (dd, $J = 5.6$, 6.3 Hz, 1H), 1.56 (s, 3H), 1.16 (s, 9H), 0.89 (s, 9H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 122.78, 108.28, 86.02, 46.19, 40.17, 39.75, 33.26, 26.13, 25.73, 22.34.
Mixture:

IR (neat): 3443 (OH), 2254 (CN) cm\(^{-1}\).

HRMS \(m/z\) calcd. for formula: C\(_{14}\)H\(_{25}\)NO\(_2\)Na (M + Na); 262.1783; expt. 262.1788.

\((2RS, 4SR)-\) and \((2SR,4SR)-4\)-Hydroxy-2-methyl-2-propyl-pentanenitrile (61k)

The reaction was carried out according to the general procedure using nitrile 60b (107.8 mg, 0.95 mmol), \(i\)-PrMgCl (2.02 mL, 4.04 mmol), and \(n\)-PrI (1.00 mL, 10.28 mmol) to give a crude product that was purified by radial chromatography employing 90:10 (hexanes:EtOAc) to afford 140.4 mg (95% yield) of 61k and 61k' in a 3.6:1 ratio of diastereomers as a colorless oil.

Major Isomer:

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 4.15 – 4.05 (m, 1H), 2.18 br s, 1H), 1.69 – 1.59 (m, 2H), 1.53 - 1.42 (m, 2H), 1.39 (s, 3H), 1.25 (d, \(J = 6\) Hz, 3H), 0.95 (t, \(J = 7.3\) Hz, 3H).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 124.67, 65.20, 47.47, 42.24, 35.41, 25.03, 24.60, 17.93, 13.97.

Minor Isomer:

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 1.82 (dd, \(J = 5.5, 9.5\) Hz, 1H), 1.35 (s, 3H), 1.25 (d, \(J = 6.1\) Hz, 3H), 0.95 (t, \(J = 7.3\) Hz, 3H).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 124.67, 64.72, 47.63, 42.19, 34.80, 24.57, 24.09, 17.93, 13.97.
Mixture:

IR (neat): 3443 (OH), 2234 (CN) cm$^{-1}$.

HRMS $m/z$ calcd. for C$_9$H$_{17}$NONa (M + Na): 178.1208; expt. 178.1230.

(2RS,4SR)- and (2SR,4SR)-4-Hydroxy-2,5-dimethyl-2-propyl-hexanenitrile (611)

The reaction was performed according to the general procedure using nitrile 60b (75.2 mg, 0.533 mmol), i-PrMgCl (1.33 mL, 2.66 mmol), and n-PrI (1.00 mL, 10.28 mmol) to give a crude product that was purified by radial chromatography employing 90:10 (hexanes:EtOAc) to afford 92.5 mg (95% yield) of 611 and 611' in a 5.8:1 ratio of diastereomers as a colorless oil.

Major Isomer:

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 3.72 (ddd, $J$ = 1.5, 5, 9.5 Hz, 1H), 1.79 (very br s, 1H), 1.74 - 1.63 (m, 2H), 1.59 - 1.45 (m, 4H), 1.42 (s, 3H), 0.97 (t, $J$ = 7.5 Hz, 3H), 0.93 (dd, $J$ = 2.5, 11 Hz, 6H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 124.82, 73.66, 43.17, 42.28, 35.90, 35.20, 24.79, 18.33, 18.09, 16.77, 14.07.

Minor Isomer:

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 3.68 (ddd, $J$ = 1.5, 4.5, 9.5 Hz, 1H), 1.36 (s, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 124.82, 73.21, 42.26, 34.70, 24.79, 24.25, 17.00.
Mixture:

IR (neat): 3456 (OH), 2234 (CN) cm\(^{-1}\).

HRMS \(m/z\) calcd. for \(\text{C}_{11}\text{H}_{21}\text{NONa} (M + Na)\): 206.1521; expt. 206.1526.

\((2SR,4SR)-4\text{-hydroxy-2-}\{(RS)-1\text{-hydroxy-2-methylpropyl}\}-2,5,5\text{-trimethylhexanenitrile (61m)}\)

Performing the general procedure with nitrile 60a (112.1 mg, 0.722 mmol), \(i\)-PrMgCl (1.80 mL, 3.60 mmol), and ethyl isobutyrate (0.49 mL, 3.66 mmol) gave a crude product that was purified by column chromatography employing 90:10 (hexanes:EtOAc) to afford 154.8 mg (90%) of 61m as white crystals.

\textbf{MPt.} 65 – 67\(^\circ\)C.

\(^1\text{H NMR}\ (500\ MHz, \text{CDCl}_3): \delta\ 4.12\ (\text{br s, 1H}),\ 3.72\ (d, J = 8.5\ Hz, 1H),\ 3.36\ (d, J = 2.2\ Hz, 1H),\ 2.53\ (\text{br s, 1H}),\ 1.97 - 2.06\ (m, 1H),\ 1.88\ (dd, J = 1.3, 13.5\ Hz, 1H),\ 1.69\ (dd, J = 13.5, 8.5\ Hz, 1H),\ 1.35\ (s, 3H),\ 1.10\ (d, J = 6.9\ Hz),\ 1.06\ (d, J = 6.9\ Hz, 1H),\ 0.94\ (s, 9H)\).  

\(^{13}\text{C NMR}\ (100\ MHz, \text{CDCl}_3): \delta\ 123.01,\ 79.73,\ 76.97,\ 43.76,\ 41.33,\ 35.11,\ 30.01,\ 25.46,\ 23.74,\ 21.75,\ 14.62\).

\(\text{IR (neat): 3385 (OH), 3294 (OH), 2245 (CN) cm}^{-1}\).

HRMS \(m/z\) calcd. for formula: \(\text{C}_{13}\text{H}_{25}\text{NO}_2\text{Na} (M + Na)\); 250.1783; expt. 250.1790.
Performing the general procedure with nitrile 60a (78.9 mg, 0.508 mmol), i-PrMgCl (1.28 mL, 2.56 mmol), and distilled ethyl cyclohexanecarboxylate (0.43 mL, 2.58 mmol) gave a crude product that was purified by column chromatography employing 95:5 (hexanes:EtOAc) to afford 114.0 mg (84% yield) of 61n as a gel like precipitate.

**IR** (neat): 3359 (OH), 3270 (OH), 2250 (CN) cm$^{-1}$.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 4.16 (br s, 1H), 3.70 (d, $J = 8.5$ Hz, 1H), 3.30 (s, 1H), 2.72 (br s, 1H), 2.03 - 1.99 (m, 1H), 1.86 (dd, $J = 1, 14.8$ Hz, 1H), 1.83 - 1.76 (m, 2H), 1.68 (dd, $J = 9.5, 14.8$ Hz, 1H), 1.67 - 1.60 (m, 1H), 1.51 (td, $J = 3, 8.5$ Hz, 2H), 1.35 (s, 3H), 1.33 - 1.15 (m, 5H), 0.94 (s, 9H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 123.20, 80.00, 76.83, 43.70, 41.02, 40.31, 35.09, 31.56, 26.68, 26.14, 26.09, 25.49, 25.14, 23.73.

HRMS $m/z$ calcd. for C$_{16}$H$_{29}$NO$_2$Na (M + Na): 290.2096; expt. 290.2106.
Performing the general procedure with nitrile 60c (60.1 mg, 0.508 mmol), \(i\)-PrMgCl (0.97 mL, 1.94 mmol), and distilled ethyl trimethylacetate (0.30 mL, 1.97 mmol) gave a crude product that was purified by column chromatography employing 95:5 (hexanes:EtOAc) to afford 59.8 mg (64% yield) of 61o as a white powder.

**MPt.** 83 – 84°C.

\(^1\text{H}\) NMR (400 MHz, CDCl\(_3\)): \(\delta\) 3.57 (br d, \(J = 8.8\) Hz, 1H), 3.51 (br s, 1H), 2.62 (br s, 1H), 2.06 (dd, \(J = 1.2, 14.6\) Hz, 1H), 1.87 (br s, 1H), 1.67 (dd, \(J = 9.6, 14.6\) Hz, 1H), 1.50 (s, 3H), 1.14 (s, 9H), 0.94 (s, 9H).

\(^{13}\text{C}\) NMR (100 MHz, CDCl\(_3\)): \(\delta\) 125.17, 80.43, 76.36, 42.29, 39.63, 37.16, 35.37, 28.02, 25.39, 20.51.

IR (neat): cm\(^{-1}\).

HRMS \(m/z\) calcd. for C\(_{14}\)H\(_{27}\)NO\(_2\)Na (M + Na): 264.1939; expt. 264.1948.

\(\text{(2SR,4SR)-4-hydroxy-2-} (\text{RS})\text{-1-hydroxy-2,2-dimethylpropyl)-2,5,5-}
\text{trimethylhexanenitrile (61o)}\)

\(\text{(2RS,4RS)- and (2SR,4RS)-4-hydroxy-2-isopropyl-2-phenylpentanenitrile (61p)}\)

Using \(i\)-PrI as the electrophile: Performing the general procedure with nitrile 60f (101.3 mg, 0.578 mmol), \(i\)-PrMgCl (1.45 mL, 2.90 mmol), and \(i\)-PrI (1 mL, 10.02 mmol)
gave a crude product that was purified by column chromatography employing 90:10 (hexanes:EtOAc) to afford 116.2 mg (93% yield) of $61p$ and $61p'$ in a 2.45:1 ratio of diastereomers as a colorless oil.

**Using $i$-PrOTos$^{101}$ as the electrophile:** Performing the general procedure with nitrile $60f$ (150.0 mg, 0.856 mmol), $i$-PrMgCl (2.14 mL, 4.28 mmol), and $i$-PrOTos (1.28 g, 5.97 mmol) gave a crude product that was purified by column chromatography employing 90:10 (hexanes:EtOAc) to afford 185.7 mg (95% yield) of $61p$ and $61p'$ in a 2.13:1 ratio of diastereomers as a colorless oil.

**Using $i$-PrBr as the electrophile:** Performing the general procedure with nitrile $60f$ (205.0 mg, 1.170 mmol), $i$-PrMgCl (2.92 mL, 5.84 mmol), and $i$-PrBr (1 mL, 10.65 mmol) gave a crude product that was purified by column chromatography 90:10 (hexanes:EtOAc) to afford 229.6 mg (90% yield) of $61p$ and $61p'$ in a 1.78:1 ratio of diastereomers as a colorless oil.

**$(2RS,4RS)$-4-hydroxy-2-isopropyl-2-phenylpentanenitrile ($61p$)**

\[
\begin{align*}
\text{OH} & \quad \text{Ph} \\
\text{CN} & \\
\end{align*}
\]

$^1H$ NMR (500 MHz, CDCl$_3$): $\delta$ 7.75 - 7.33 (m, 5H), 3.53 - 3.43 (m, 1H), 2.35 (dd, $J = 9.5$, 14.5 Hz, 1H), 2.21 - 2.10 (m, 2H), 1.93 (dd, $J = 3$, 14.5 Hz, 1H), 1.24 (d, $J = 6.5$ Hz, 3H), 1.07 (d, $J = 6.0$ Hz, 3H), 0.76 (d, $J = 6.0$ Hz, 3H).
(2SR,4RS)-4-hydroxy-2-isopropyl-2-phenylpentanenitrile (61p')

\[\text{OHPh} \quad \text{CN}\]

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.75 - 7.33 (m, 5H), 3.85 - 3.78 (m, 1H), 2.25 (dd, $J = 4.5, 14.5$ Hz, 1H), 2.21 - 2.10 (m, 2H), 1.22 (d, $J = 6.5$ Hz, 6H), 0.75 (d, $J = 7.0$ Hz, 3H).

Mixture:

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 137.79, 137.47, 128.96, 128.77, 127.92, 127.60, 126.34, 121.70, 120.84, 65.74, 64.90, 61.95, 50.98, 46.81, 46.61, 38.51, 38.31, 24.30, 23.73, 18.46, 18.42.

The above compounds are in good agreement with that which was reported previously.$^{95c}$

(2RS, 5RS) and (2SR, 5RS)-5-hydroxy-2-phenylhexanenitrile (73a)

\[\text{OH} \quad \text{CN} \quad \text{Ph}\]

Solid NaBH$_4$ (1.52 g, 40.18 mmol) was added in four portions over 30 min to a 0 °C, methanolic solution (15 mL) of 5-oxo-2-phenylhexanenitrile$^{102b}$ After 1 h, the solvent was removed under reduced pressure, the resultant crude material was dissolved in EtOAc, and then the solution was extracted with saturated, aqueous NH$_4$Cl. The organic layer was dried (Na$_2$SO$_4$), evaporated under reduced pressure to give a crude oil, and the resulting material was purified by column chromatography (70:30, hexanes:EtOAc) to afford 1.86 g of 73a and 73a' (98% yield, 1:1 ratio of diastereomers) as a light yellow oil.
Mixture:

**IR (neat):** 3397 (OH), 2241 (CN) cm$^{-1}$.

**$^1$H NMR (500 MHz, CDCl$_3$):** $\delta$ 7.37 - 7.30 (m, 5H), 3.86 - 3.74 (m, 2H), 2.11 - 1.91 (m, 3H), 1.61 - 1.52 (m, 2H), 1.18 (d, $J$ = 7.5 Hz, 3H), 1.17 (d, $J$ = 7.5 Hz, 3H).

**$^{13}$C NMR (100 MHz, CDCl$_3$):** $\delta$ 135.68, 135.62, 128.96, 127.94, 127.14, 127.10, 120.81, 120.73, 67.25, 66.83, 37.22, 36.93, 36.10, 35.80, 32.25, 31.79, 23.61, 23.50.

**HRMS (ESI) m/z calcd. for C$_{12}$H$_{15}$NONa (M + Na) 212.1051, found 212.1065.**

(2RS, 5SR)- and (2SR,5RS)-5-hydroxy-6,6-dimethyl-2-phenylheptanenitrile (73c)

![化合物结构图](image)

A THF solution (3 mL) containing 1.5717 g (5.80 mmol) of 4-iodo-2-phenylbutanenitrile was added to 0.4879 g (7.46 mmol) of activated zinc$^{104}$ in 1 mL of THF at room temperature. After consumption of the iodide, approximately 4 hours, the solution was cooled to 0 ºC and 7 mL of a 1 M solution of CuCN∙2LiCl$^{104}$ was added to the reaction mixture. After 5 min, the 0.86 mL (6.99 mmol) of pivaloyl chloride was added to the reaction mixture. This solution was maintained at 0 ºC for 1 hour. Then 50 mL of saturated NH$_4$Cl was added to the reaction and allowed to stir for another 30 min. The resultant was extracted with Et$_2$O, and the ether layer was successively washed with NaOAc and NaHCO$_3$. The organic layer was dried over sodium sulfate, evaporated under reduced pressure to give a crude product that was dissolved in 20 mL of methanol and cooled to 0 ºC. 0.88 g of solid NaBH$_4$ was then added in one portion to this solution and allowed to stir at 0 ºC. After 1 hour, the methanol was evaporated, and the residue
diluted with EtOAc and saturated NH₄Cl. The organic layer was extracted, dried over Na₂SO₄ and evaporated under reduced pressure to yield a crude oil which was purified by column chromatography employing 90:10 (hexanes:EtOAc) to afford 912.5 mg of 73c (68% overall yield) in a 1:1 ratio of diastereomers as a lightly colored oil.

**Mixture:**

**IR** (neat): 3502 (OH), 2234 (CN) cm⁻¹.

**¹H NMR** (500 MHz, CDCl₃): δ 7.41 - 7.31 (m, 5H), 3.91 - 3.84 (m, 1H), 3.22 (sextet of doublets, J = 2.5, 7.5 Hz, 1H), 2.26-2.15 (m, 1H), 1.99 - 1.87 (m, 1H), 1.82 - 1.65 (m, 1H), 1.52 - 1.33 (m, 2H), 0.90 (s, 9H).

**¹³C NMR** (100 MHz, CDCl₃): δ 136.00, 135.86, 128.98, 127.94, 127.18, 127.12, 121.01, 120.78, 79.52, 78.83, 37.53, 36.89, 35.02, 33.83, 33.17, 28.87, 28.40, 25.49.

**HRMS** m/z calcd. for C₁₅H₂₁NONa (M + Na): 254.1521; expt. 254.1509.

**{(2RS,5RS)- and (2SR,5SR)-5-hydroxy-2-phenyl-2-propylhexanenitrile (78a)}**

Performing the general procedure with nitrile 73a (206.0 mg, 1.09 mmol), i-PrMgCl (2.72 mL, 5.54 mmol), and n-PrI (1 mL, 10.28 mmol) gave a crude product that was purified by column chromatography 70:30 (hexanes:EtOAc) to afford 234.7 mg (93% yield) of 78a and 78a' in a 2.5:1 ratio of diastereomers as a colorless oil.
Major Isomer:

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.41 - 7.35 (m, 4H), 7.32 - 7.27 (m, 1H), 3.81 - 3.74 (m, 1H), 2.14 (dd, $J = 4.5, 5.0, 13.5$ Hz, 1H), 2.05 - 1.90 (m, 2H), 1.86 (ddd, $J = 4.5, 5.0, 12.5$ Hz, 1H), 1.63 - 1.42 (m, 2H), 1.34 - 1.16 (m, 1H), 1.14 (d, $J = 6.5$ Hz, 3H), 0.88 (t, $J = 7.3$ Hz, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 138.20, 128.78, 127.53, 125.80, 122.52, 67.45, 47.94, 43.47, 37.02, 34.51, 23.54, 18.52, 13.79.

Minor Isomer:

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.41 - 7.35 (m, 4H), 7.32 - 7.27 (m, 1H), 3.73 - 3.68 (m, 1H), 2.21 (ddd, $J = 4.5, 5.0, 13.5, 1H$), 1.14 (d, $J = 6.5$ Hz, 3H), 0.88 (t, $J = 7.3$ Hz, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 138.43, 128.78, 127.53, 125.76, 122.38, 67.35, 47.94, 43.10, 36.93, 34.56, 23.40, 18.52, 13.79.

Mixture:

IR (neat): 34.78 (OH), 2253 (CN) cm$^{-1}$.

HRMS m/z calcd. for C$_{14}$H$_{21}$NONa (M + Na): 254.1521; expt. 254.1527.

(2RS,5SR)- and (2SR,5RS)-5-hydroxy-2,6,6-trimethyl-2-propylheptanenitrile (78b)

Performing the general procedure with nitrile 82 (76.9 mg, 0.495 mmol), i-PrMgCl (1.24 mL, 2.48 mmol), and MeI (0.04 mL, 0.643 mmol) to yield crude 73b which was filtered
through a small plug of silica and used without further purification. Then the general procedure employing 73b (85.6 mg, 0.506 mmol), i-PrMgCl (1.27 mL, 2.54 mmol), and n-PrI (1 mL, 10.28 mmol) to yield crude 78b was performed with gave a crude product that was purified by column chromatography 95:5 (hexanes:EtOAc) to afford 68.6 mg (64% yield based on 73b) of 78b and 78b' in a 4.0:1 ratio of diastereomers as a colorless oil.

**Major:**

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 3.19 (br d, $J = 10.5$ Hz, 1H), 1.81 (ddd, $J = 4.5$, 4.5, 12.5 Hz, 1H), 1.74 – 1.65 (m, 1H), 1.63 – 1.36 (m, 7H), 1.30 (s, 3H), 0.97 (t, $J = 7.0$ Hz, 3H), 0.92 (s, 9H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 124.55, 80.04, 42.16, 37.18, 36.58, 35.13, 25.60, 23.74, 18.15, 14.14.

**Minor Isomer:**

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 3.17 – 3.14 (m, 1H), 1.98 (ddd, $J = 4.0$, 4.0, 12.5 Hz, 1H), 1.32 (s, 3H), 0.97 (t, $J = 7.0$ Hz, 3H), 0.92 (s, 9H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 124.55, 80.04, 41.26, 37.29, 36.66, 35.13, 26.72, 24.27, 18.11, 14.14.

**Mixture:**

IR (neat): 3486 (OH), 2234 (CN) cm$^{-1}$.

HRMS $m/z$ calcd. for C$_{13}$H$_{25}$NONa (M + Na): 234.1834; exp. 234.1823.
Performing the general procedure with nitrile 73c (119.8 mg, 0.518 mmol), i-PrMgCl (1.30 mL, 2.60 mmol), and n-PrI (1 mL, 10.28 mmol) gave a crude product that was purified by column chromatography 85:15 (hexanes:EtOAc) to afford 127.6 mg (90% yield) of 78c and 78c’ in a 2.7:1 ratio of diastereomers as a colorless oil.

**Major Isomer:**

$^1$H NMR (500 MHz, CDCl$_3$): δ 7.42 – 7.26 (m, 5H), 3.20 (d, $J = 13.5$ Hz, 1H), 2.30 (ddd, $J = 2.0$, 5.5, 18.5 Hz, 1H), 2.03 – 1.90 (m, 2H), 1.90 – 1.80 (m, 2H), 1.70 – 1.60 (m, 1H), 1.55 – 1.39 (m, 2H), 1.21 – 0.96 (m, 2H), 0.88 (t, $J = 9.3$ Hz, 0.81 (s, 9H).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 138.31, 128.84, 127.57, 125.91, 122.75, 79.79, 48.08, 43.90, 38.39, 35.03, 27.12, 25.51, 18.60, 13.88.

**Minor Isomer:**

$^1$H NMR (500 MHz, CDCl$_3$): δ 7.42 – 7.26 (m, 5H), 3.03 – 2.98 (m, H), 2.43 – 2.35 (m, 1H), 0.88 (t, $J = 9.3$ Hz, 3H), 0.80 (s, 9H).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 138.79, 128.81, 127.57, 125.84, 122.50, 79.96, 48.18, 43.02, 38.72, 35.0327.30, 25.49, 18.60, 13.88.
Mixture:

IR (neat): 3481 (OH), 2240 (CN) cm⁻¹.


(2SR,5SR)- and (2RS,5RS)-2-allyl-5-hydroxy-6,6-dimethyl-2-phenylheptanenitrile

(78d)

Performing the general procedure with nitrile 73c (74.8 mg, 0.323 mmol), i-PrMgCl (0.81 mL, 1.62 mmol), and allyl bromide (1 mL, 11.56 mmol) gave a crude product that was purified by column chromatography 85:15 (hexanes:EtOAc) to afford 75.0 mg (85% yield) of 78d and 78d' in a 5.9:1 ratio of diastereomers as a colorless oil.

Major Isomer:

¹H NMR (500 MHz, CDCl₃): δ 7.43 – 7.36 (m, 4H), 7.32 – 7.28 (m, 1H), 5.70 – 5.59 (m, 1H), 5.14 – 5.09 (m, 2H), 3.20 (dd, J = 2.0, 11.0 Hz, 1H), 2.67 (d, J = 7.0 Hz, 2H), 2.33 (ddd, J = 1.5, 4.5, 12.5 Hz, 1H), 2.00 (ddd, J = 2.0, 4.5, 14 Hz, 1H), 1.69 – 1.62 (m, 1H), 1.37 (br s, 1H), 1.11 – 1.02 (m, 1H), 0.82 (s, 9H).

¹³C NMR (100 MHz, CDCl₃): δ 137.74, 131.77, 128.86, 127.73, 126.06, 122.18, 119.96, 79.73, 47.82, 46.05, 37.20, 35.01, 27.03, 25.49.
Minor Isomer:

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.43 – 7.36 (m, 4H), 7.32 – 7.28 (m, 1H), 5.70 – 5.59 (m, 1H), 5.14 – 5.09 (m, 2H), 3.04 – 3.00 (m, 1H), 2.44 – 2.39 (m, 1H), 1.92 – 1.86 (m, 1H), 1.46 – 1.40 (m, 1H), 0.81 (s, 9H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 138.12, 131.74, 128.82, 127.75, 126.01, 121.97, 119.91, 79.88, 47.94, 45.17, 37.60, 35.01, 27.20, 25.47.

Mixture:

IR (neat): 3479 (OH), 2237 (CN) cm$^{-1}$.

HRMS m/z calcd. for C$_{17}$H$_{25}$NOna (M + Na): 294.1834; expt. 294.1863.

(2SR,5SR)- and (2RS,5RS)methyl 2-cyano-5-((methoxycarbonyl)oxy)-6,6-dimethyl-2-phenylheptanoate (78e)

Performing the general procedure with nitrile 73c (97.5 mg, 0.421 mmol), $i$-PrMgCl (1.05 mL, 2.10 mmol), and methyl cyanoformate (0.27 mL, 3.40 mmol) gave a crude product that was purified by column chromatography 98:2 (hexanes:EtOAc) to afford 91.1 mg (62% yield) of 73e and 73e’ in a 3.5:1 ratio of diastereomers as a colorless oil and 6.2 mg of 88 in a 3.4:1 ratio of diastereomers as a yellow oil.
Mixture:

IR (neat): 2245 (CN), 1719 (ester) cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ 7.55 – 7.50 (m, 2H), 7.45 – 7.35 (m, 3H), 4.57 (dd, J = 3.0, 7.5 Hz, 1H), 4.51 – 4.45 (m, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.78 (s, 3H), 2.51 – 2.44 (m, 1H), 2.39 (ddd, J = 1.5, 4.5, 28.0 Hz, 1H), 2.26 – 2.16 (m, 1H), 2.16 – 2.11 (m, 1H), 1.79 – 1.58 (m, 3H), 0.90 (s, 9H), 0.87 (s, 9H).

¹³C NMR (100 MHz, CDCl₃): δ 167.92, 167.77, 156.32, 156.25, 134.03, 133.95, 129.26, 129.03, 129.01, 126.03, 118.09, 118.05, 85.12, 85.04, 54.90, 54.89, 53.99, 53.97, 53.79, 53.72, 35.10, 35.03, 35.02, 25.89, 25.79, 25.67, 25.63.

(2SR,5SR)- and (2RS,5RS)-5-hydroxy-6,6-dimethyl-2-phenyl-2-(prop-2-yn-1-yl)heptanenitrile (78f)

Performing the general procedure with nitrile 73c (103.4 mg, 0.447 mmol), i-PrMgCl (1.12 mL, 2.24 mmol), and neat propargyl bromide (1 mL, 13.28 mmol) gave a crude product that was purified by column chromatography 90:10 (hexanes:EtOAc) to afford 103.2 mg (86% yield) of 78f and 78f* in a 3.7:1 ratio of diastereomers as a colorless oil.

Major Isomer:

¹H NMR (500 MHz, CDCl₃): δ 7.50 – 7.45 (m, 2H), 7.43 – 7.31 (m, 2H), 7.36 – 7.31 (m, 1H), 3.24 (dd, J = 2.3, 10.5 Hz, 1H), 2.85 (ddd, J = 2.5, 17, 27.5 Hz, 1H), 2.82 (d, J =
3Hz, 2H), 2.42 (ddd, $J = 1.5, 4.5, 12$ Hz, 1H), 2.18 (ddd, $J = 2.7, 4.5, 11.5$ Hz, 1H), 2.13 (t, $J = 2.5$ Hz, 1H), 1.72 – 1.64 (m, 1H), 1.16 – 1.09 (m, 1H), 0.83 (s, 9H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 137.04, 128.96, 128.22, 125.99, 121.62, 79.69, 78.07, 72.67, 47.13, 36.23, 35.02, 32.32, 27.11, 25.49.

**Minor Isomer:**

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.50 – 7.45 (m, 2H), 7.43 – 7.31 (m, 2H), 7.36 – 7.31 (m, 1H), 3.09 – 3.05 (m, 1H), 2.60 – 2.52 (m, 1H), 2.11 (t, $J = 2.5$ Hz, 1H), 2.01 – 1.94 (m, 1H), 1.52 – 1.40 (m, 2H), 0.82 (s, 9H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 137.74, 128.90, 128.22, 125.93, 121.43, 79.81, 78.15, 72.73, 47.15, 36.60, 35.02, 31.49, 27.30, 25.47.

**Mixture:**

IR (neat): 3495 (OH), 3295 (alkyne), 2241 (CN), 2226 (alkyne) cm$^{-1}$.

HRMS $m/z$ calcd. for $\text{C}_{17}\text{H}_{23}\text{NONa}$ (M + Na): 292.1677; expt. 292.1667.
Performing the general procedure with nitrile 73c (105.1 mg, 0.454 mmol), \(i\)-PrMgCl (1.14 mL, 2.28 mmol), and \(i\)-PrI (1 mL, 10.02 mmol) gave a crude product that was purified by column chromatography 90:10 (hexanes:EtOAc) to afford 109.8 mg (88% yield) of 78g and 78g’ in a 1.4:1 ratio of diastereomers as a colorless oil.

**Mixture:**

**IR** (neat): 3472 (OH), 2236 (CN) cm\(^{-1}\).

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 7.40 – 7.27 (m, 5H), 3.21 (dd, \(J = 2.0, 5.5\) Hz, 1H), 2.96 (dd, \(J = 2.0, 7.5\) Hz, 1H), 2.59 – 2.49 (m, 1H), 2.26 (ddd, \(J = 2.0, 4.0, 11.0\) Hz, 1H), 2.16 – 2.08 (m, 3H), 1.81 (dd, \(J = 2.5, 4.5, 11\) Hz, 1H), 1.60 – 1.52 (m, 1H), 1.36 – 1.21 (m, 2H), 1.21 (d, \(J = 7.5\) Hz, 3H), 1.19 (d, \(J = 7.5\) Hz, 3 H), 0.96-0.85 (m, 1H), 0.78 (s, 9H), 0.75 (s, 9H).

\(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 138.12, 137.89, 128.70, 128.65, 127.50, 126.39, 121.53, 121.27, 80.08, 79.82, 53.66, 53.49, 38.16, 37.77, 35.22, 34.98, 27.65, 27.42, 25.47, 18.90, 18.83, 18.60, 18.50.

**HRMS** m/z calcd. for C\(_{17}\)H\(_{27}\)NONa (M + Na): 296.1990; expt. 296.1984.
A THF solution (5 mL) containing 2.90 g (14.87 mmol) of 4-iodobutyronitrile was added to 1.21 g (18.51 mmol) of activated zinc in 1 mL THF at room temperature. After consumption of the iodide, approximately 1 hour, the solution was cooled to 0 °C and 18.50 mL of a 1M solution of CuCN·2LiCl was added to the reaction mixture. After 5 min, the 2.00 mL (16.25 mmol) of pivaloyl chloride was added to the reaction mixture. This solution was maintained at 0 °C for 1 hour. Then 100 mL of saturated NH₄Cl was added to the reaction and allowed to stir for another 30 min. The resultant was extracted with Et₂O, and the ether layer was successively washed with NaOAc and NaHCO₃. The organic layer was dried over sodium sulfate, evaporated under reduced pressure to give a crude product which was purified by column chromatography employing 90:10 (hexanes:EtOAc) to afford 2.10 g of 57 (92% yield) a pale colored oil.

**IR** (neat): 2246 (CN), 1709 (ketone).

**₁H NMR** (500 MHz, CDCl₃): δ 2.69 (t, J = 6.9 Hz, 2H), 2.42 (t, J = 6.9 Hz, 2H), 1.92 (quintet, J = 6.9 Hz, 2 H), 1.16 (s, 9H).

**¹³C NMR** (125 MHz, CDCl₃): δ 214.25, 119.27, 44.04, 34.26, 26.31, 19.49, 16.34.

**HRMS** m/z calcd. for C₉H₁₅NONa (M + Na): 176.1051; exp. 176.1002.
5-hydroxy-6,6-dimethylheptanenitrile (82)

A methanolic solution at 0 ºC of containing 1.385 g (9.04 mmol) of 6,6-dimethyl-5-oxoheptanenitrile 81 was added 1.370 g (36.21 mmol) of solid NaBH₄ in one portion and allowed to stir at 0 ºC for 30 min. The methanol was evaporated under reduced pressure and the resultant was diluted with EtOAc and extracted with a saturated solution of NH₄Cl. The organic layer was dried over sodium sulfate, evaporated under reduced pressure to give a crude oil which can be purified by column chromatography employing 70:30 (hexanes:EtOAc) to afford 1.4012 g of 82 (>99% yield) as a lightly colored oil.

IR (neat): 3458 (OH), 2248 (CN).

¹H NMR (500 MHz, CDCl₃): δ 3.22 (br d, 11 Hz, 1H), 2.46 – 2.37 (m, 2H), 1.98 – 1.94 (m, 1H), 1.74 – 1.68 (m, 2H), 1.43 – 1.38 (overlapping singlet and m, 2H), 0.91 (s, 9H).

¹³C NMR (100 MHz, CDCl₃): δ 119.83, 79.11, 34.95, 30.08, 25.49, 23.02, 17.10.

HRMS m/z calcd. for C₉H₁₇NONa (M + Na): 178.1208; exp. 178.1246.
(3RS,5SR)- and (3SR,5RS)-5-tert-butyl-3-methyl-3-(phenylthio)dihydrofuran-2(3H)-one (86)

\[
\text{O} \quad \text{SPh}
\]

A THF solution of NaHMDS (0.54 mL, 0.54 mmol) was added to a 0 °C, THF solution (5 mL) of 37g (70.7 mg, 0.268 mmol). After 30 min, 200 proof EtOH (3 mL) was added and then the mixture was concentrated to afford the crude lactone. Column chromatography afforded a mixture of the lactone (62) and an unstable imino lactone.

**IR** (neat): 1761 (lactone) cm\(^{-1}\).

**\(^1H\) NMR** (500 MHz, CDCl\(_3\)): \(\delta\) 7.58 – 7.54 (m, 2H), 7.46 – 7.41 (m, 2H), 7.38 – 7.34 (m, 2H), 4.21 (dd, \(J = 5.0, 10.7\) Hz, 1H), 2.24 (dd, \(J = 3.1, 5.0\) Hz, 1H), 2.09 (dd, \(J = 3.1, 10.7\) Hz, 1H), 1.48 (s, 3H), 0.93 (s, 9H).

**\(^13C\) NMR** (125 MHz, CDCl\(_3\)): \(\delta\) 176.09, 137.18, 130.02, 129.61, 128.91, 84.04, 51.52, 38.62, 33.05, 24.91, 23.46.

**HRMS** \(m/z\) calcd. for formula: C\(_{15}\)H\(_{20}\)SO\(_2\)Na (M + Na): 287.1082; expt. 287.1102.
A diethylene glycol mixture containing 448.0 (1.937 mmol) of 5-hydroxy-2-phenylhexanenitrile 78a and 548.7 mg of KOH and refluxed for 6 hours at 250° C. The mixture was then cooled to ambient temperature and diluted with ether and 100 mL of 6 M HCl was added. The resultant was extracted, the ether layer was washed with brine and the subsequent organic layer was dried over sodium sulfate, concentrated under reduced pressure to yield a crude oil which was purified by column chromatography employing 90:10 (hexanes:EtOAc) to afford 360.4 mg (80% yield) of 6387 as a yellow oil.

Mixture:

IR (neat): 1725 (lactone) cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ 7.45 – 7.10 (m, 5H), 4.51 – 4.48 (m, 1H), 4.01 – 3.94 (m, 1H), 2.58 – 2.52 (m, 1H), 2.27 (dt, J = 3.5 Hz, 14.5 Hz), 2.14 (td, J = 3.5, 14.0 Hz), 2.05 - 1.60 (m, 9H), 1.52 – 1.45 (m, 1H), 1.44 – 1.33 (m, 1H), 1.31 – 1.23 (m, 2H), 1.27 (d, J = 6.0 Hz, 3 H), 1.20 (d, J = 6.0 Hz, 3H), 1.19-1.05 (m, 3H), 0.89 (t, J = 7.0 Hz, 3H), 0.82 (t, J = 7.0, 3H).
$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 175.64, 174.12, 142.80, 142.69, 140.24, 140.02, 128.91, 128.59, 127.14, 126.81, 126.31, 126.04, 78.76, 77.60, 72.73, 51.77, 50.44, 43.95, 27.63, 27.33, 26.39, 22.24, 21.46, 17.46, 14.43.

$(3RS,6SR)$- and $(3SR,6RS)$-methyl 6-(tert-butyl)-2-oxo-3-phenyltetrahydro-2H-pyran-3-carboxylate (88)

Major:

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.35 – 7.26 (m, 5H), 4.54 (dd, $J$ = 2.8, 10.5 Hz, 1H), 3.81 (s, 3H), 2.78 – 2.73 (m, 1H), 2.71 – 2.64 (m, 1H), 1.73 – 1.58 (m, 2H), 0.85 (s, 9H).

Minor:

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.35 – 7.26 (m, 5H), 4.52 – 4.50 (m, 1H), 3.81 (s, 3H), 2.56 – 2.47 (m, 1H), 2.45 – 2.39 (m, 1H), 0.84 (s, 9H).

7.5 Arylation Reactions

4-isopropylcyclohexanecarbonitrile (89c)

Performing the general cyanation procedure with 4-isopropylcyclohexanone (1.00 g, 7.13 mmol), t-BuOK (0.96 g, 8.56 mmol), and TosMIC (1.67 g, 8.55 mmol) gave the crude nitrile that was purified by column chromatography (95:5, hexanes:EtOAc) to afford 0.865 g (80% yield) of 89c as an oily mixture of diastereomers.
IR (neat): 2230 (CN) cm\(^{-1}\).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 2.94-2.90 (m, 1H), 2.33 (tt, \(J = 4.0, 12.5\) Hz, 1H), 2.15-2.10 (m, 2H), 2.10-1.98 (m, 2H), 1.81-1.76 (m, 2H), 1.58-1.52 (m, 2H), 1.50-1.33 (m, 4H), 1.12-1.02 (m, 2H), 1.02-0.95 (m, 2H), 0.89 (d, \(J = 7.0\) Hz, 6H), 0.85 (d, \(J = 6.5\) Hz, 6H).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 122.84, 122.16, 43.22, 42.54, 32.39, 29.99, 28.51, 28.29, 27.14, 25.60, 19.60, 19.50.

HRMS (ESI) \(m/z\) calcd. for C\(_{10}\)H\(_{17}\)NNa (M+Na): 174.1259; found 174.1246.

4-methylcyclohexanecarbonitrile (89d)

Performing the general cyanation procedure with 4-methylcyclohexanone (1.00 g, 7.13 mmol), \(t\)-BuOK (1.20 g, 10.69 mmol), and TosMIC (2.09 g, 10.70 mmol) gave the crude nitrile that was purified by column chromatography (95:5, hexanes:EtOAc) to afford 0.829 g (75% yield) of 89d as an oily mixture of diastereomers.

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 2.99-2.94 (m, 1H), 2.43 (tt, \(J = 4.0, 12.4\) Hz, 1H), 2.09-2.04 (m, 3H), 1.91-1.86 (m, 3H), 1.84-1.75 (m, 3H), 1.75-1.64 (m, 3H), 1.48-1.32 (m, 4H), 1.32-1.15 (m, 4H), 0.93 (d, \(J = 6.8\) Hz, 3H), 0.92 (d, \(J = 6.4\) Hz, 3H).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 122.74, 122.45, 37.89, 36.41, 34.01, 33.65, 31.78, 29.54, 28.28, 28.25, 27.20, 25.02, 22.17, 22.13, 21.82.

HRMS (ESI) \(m/z\) calcd. for C\(_8\)H\(_{10}\)NNa (M - 3H+Na): 143.0694; found 143.0702.
3-methylcyclohexanecarbonitrile (89e)

Performing the reaction according to the general cyanation procedure using 3-methylcyclohexanone (1.00 g, 7.13 mmol), t-BuOK (1.20 g, 10.69 mmol), and TosMIC (2.09 g, 10.70 mmol) gave the crude nitrile that was purified by column chromatography (85:15, pentane:ether) to afford 0.847 g (77% yield) of the nitrile 89e as an oily mixture of diastereomers:135

\[ \text{H NMR (400 MHz, CDCl}_3\text{)}: \delta 2.98-2.94 (m, 1H), 2.43 (tt, J = 3.6, 12.4 Hz, 1 H), 2.11-2.00 (m, 3H), 1.95-1.87 (m, 2H), 1.85-1.75 (m, 3H), 1.74-1.65 (m, 4H), 1.50-1.40 (m, 2H), 1.30-1.14 (m, 4H), 0.93 (d, J = 6.8 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H). \]

\[ \text{C NMR (100 MHz, CDCl}_3\text{)}: \delta 122.73, 122.41, 37.92, 36.43, 36.43, 34.02, 33.66, 31.79, 29.56, 28.52, 2827, 25.03, 22.15, 21.79. \]

\[ \text{HRMS (ESI) m/z calcd. for C}_8\text{H}_{14}\text{N (M+H): 124.1126; found 124.1096.} \]

2-methylcyclohexanecarbonitrile (89f)

Performing the reaction according to the general cyanation procedure using 2-methylcyclohexanone (2.03 g, 18.10 mmol), t-BuOK (2.48 g, 22.10 mmol), and TosMIC (4.42 g, 22.64 mmol) gave the crude nitrile that was purified by column chromatography (85:15, pentane:ether) to afford 1.86 g (83% yield) of the nitrile 89f as an oily mixture of
diastereomers exhibiting spectral properties identical to that exhibited by previously isolated material.  

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 2.83-2.79 (m, 1H), 2.12-1.98 (m, 3H), 1.79-1.53 (m, 11H), 1.36-1.15 (m, 4H), 1.12 (d, $J$ = 6.4 Hz), 1.08 (d, $J$ = 6.4 Hz), 1.04-0.90 (m, 1H).

$^{13}$C NMR (100 MHz, CDCl$_3$): 122.28, 120.66, 36.18, 35.29, 34.65, 33.82, 33.50, 30.65, 29.98, 28.70, 25.11, 25.03, 24.88, 21.93, 20.79, 20.07.

4-((tert-butyldimethylsilyl)oxy)cyclohexanecarbonitrile (89g)

Two portions of solid NaBH$_4$ (360 mg, 9.51 mmol) were added to a 0 °C, methanolic solution (20 mL) of 4-oxocyclohexanecarbonitrile (585 mg, 4.75 mmol). After 30 min the ice bath was removed and after 1 h the solvent was under reduced pressure. The concentrate dissolved in EtOAc (100 mL), extracted with water (100 mL), dried (Na$_2$SO$_4$), and then the solvent was evaporated under reduced pressure. The crude hydroxynitrile 270.7 mg (2.16 mmol) was dissolved in DMF (5 mL) and then TBSCl (244.8 mg, 1.62 mmol) and imidazole (229.4 mg, 3.36 mmol) were added. After 16 h a solution of aqueous, saturated NH$_4$Cl (20 mL) was added, the phases were separated, and the aqueous phase extracted with ether (100 mL). The organic phase was dried (Na$_2$SO$_4$), the solvent was evaporated under reduced pressure, and the crude silyl ether nitrile was purified by column chromatography (hexanes) to afford 318.3 mg (82% yield) of 89g as a mixture of diastereomers.  

126
IR (neat) 2239 (CN) cm\(^{-1}\).

\(^{1}\)H NMR (400 MHz, CDCl\(_{3}\)): \(\delta\) 3.81-3.74 (m, 1H), 2.63 (m, 1H), 2.09-1.99 (m, 2H), 1.89-1.76 (m, 1H), 1.72-1.52 (m, 4H), 1.49-1.33 (m, 1H), 0.89 (s, 9H), 0.88 (s, 9H), 0.04 (s, 6H).

\(^{13}\)C NMR (100 MHz, CDCl\(_{3}\)): \(\delta\) 122.32, 122.25, 67.45, 66.69, 32.12, 27.13, 25.71, 17.99, -4.87.

HRMS (ESI) \(m/z\) calcd. for C\(_{13}\)H\(_{25}\)NOSiNa (M+Na): 262.1603; found 262.1615.

4-(1-cyanocyclohexyl)benzonitrile (90a)

\[\text{CN} \quad \text{CN} \]

\[\text{C} \quad \text{C} \]

The reaction was performed according to the general procedure using cyclohexanecarbonitrile (91.9 mg, 0.842 mmol), TMPZnCl·LiCl (1.30M, 0.81 mL, 1.26 mmol), SPhos (10.6 mg, 4 mol%), Pd(OAc)\(_{2}\) (2.9 mg, 2 mol %) and 4-bromobenzonitrile (117.8 mg, 0.647 mmol) to give a crude product that was purified by column chromatography employing 95:5 (pentane:ether) to afford 106.0 mg (80% yield) of 90a as an off-white solid.

**Mpt.** 61 – 63 °C.

IR (neat): 2230 (CN) cm\(^{-1}\).

\(^{1}\)H NMR (400 MHz, CDCl\(_{3}\)): \(\delta\) 7.70 (d, \(J = 8.8\) Hz, 2H), 7.62 (d, \(J = 8.8\) Hz, 2H), 2.15 (br d, \(J = 12.8\) Hz, 2H), 1.91-1.75 (m, 7H), 1.31-1.25 (m, 1H).
$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 146.46, 132.72, 126.55, 121.56, 118.20, 111.99, 44.73, 37.11, 24.75, 23.38.

HRMS $m/z$ calcd. for C$_{14}$H$_{14}$N$_2$ (M$^+$): 210.1157; expt. 210.1153.

**tert-butyl 4-(1-cyanocyclohexyl)benzoate (90b)**

Performing the general coupling procedure with cyclohexanecarbonitrile (91.9 mg, 0.842 mmol), TMPZnCl·LiCl (1.30 M, 0.81 mL, 1.26 mmol), SPhos (10.6 mg, 4 mol%), Pd(OAc)$_2$ (2.9 mg, 2 mol%) and tert-butyl 4-bromobenzoate (166.4 mg, 0.647 mmol) and purification of the crude nitrile by column chromatography (95:5, pentane:ether) afforded 128.1 mg (75% yield) of 90b as a white solid.

**Mpt.** 93 – 96 °C.

**IR** (neat): 2235 (CN), 1706 (ester) cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.00 (d, $J = 8.8$ Hz, 2H), 7.55 (d, $J = 8.8$ Hz, 2H), 2.18-2.13 (m, 2H), 1.93-1.73 (m, 6H), 1.59 (s, 9H), 1.35-1.24 (m, 2H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 165.09, 145.68, 131.61, 129.69, 125.48, 122.14, 81.22, 44.53, 37.20, 28.14, 24.86, 23.46.

HRMS (ESI) $m/z$ calcd. for C$_{18}$H$_{23}$NO$_2$ (M$^+$): 285.1728; found 285.1702.
1-(2-methoxyphenyl)cyclohexanecarbonitrile (90c)

The reaction was performed according to the general procedure using cyclohexanecarbonitrile (91.9 mg, 0.842 mmol), TMPZnCl·LiCl (1.30 M, 0.81 mL, 1.26 mmol), SPhos (10.6 mg, 4 mol%), Pd(OAc)$_2$ (2.9 mg, 2 mol%) and 2-bromoanisole (0.080 mL, 0.647 mmol) to give a crude product that was purified by column chromatography employing 95:5 (pentane:ether) to afford 88.5 mg (64% yield) of 90c as a gel-like precipitate.

**IR** (neat): 2229 (CN) cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.35-7.30 (m, 2H), 7.00-6.95 (m, 2H), 3.93 (s, 3H), 2.41-2.36 (m, 2H), 1.96-1.74 (m, 7H), 1.35-1.22 (m, 1H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 157.57, 129.14, 129.07, 125.94, 122.50, 120.80, 112.18, 55.57, 40.82, 34.55, 25.31, 23.34.

**HRMS** m/z calcd. for C$_{14}$H$_{17}$NO (M+Na): 238.1208; expt. 238.1210.

4-((1SR,4SR)-4-(tert-butyl)-1-cyanocyclohexyl)benzonitrile (90d)

Performing the general coupling procedure with 4-(tert-butyl)cyclohexanecarbonitrile (122 mg, 0.738 mmol),$^{118}$ TMPZnCl·LiCl (1.25 M, 0.89 mL, 1.11 mmol), SPhos (9.3 mg,
Performing the general coupling procedure with 4-\((\text{tert-butyl})\text{-cyclohexanecarbonitrile}\)\textsuperscript{118} (138 mg, 0.758 mmol), TMPZnCl·LiCl (1.25 M, 1.00 mL, 1.25 mmol), SPhos (10.5 mg, 4 mol%), Pd(OAc)\(_2\) (2.9 mg, 2 mol %) and 4-bromoanisole (0.08 mL, 0.637 mmol) gave the crude nitrile that was purified by column chromatography (97:3, pentane:ether) to afford 103.6 mg (60% yield) of \textbf{90e} and \textbf{90e}' as an oily mixture of diastereomers (8.4:1 ratio) that were separated by preparative HPLC.
Major Isomer (1SR,4SR):

IR (neat) 2239 (CN) cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ 7.41 (d, J = 9.2 Hz, 2H), 6.91 (d, J = 8.8 Hz, 2H), 3.82 (s, 3H), 2.22 (br d, J = 10.8 Hz, 2H), 1.93 (br d, J = 12.8 Hz, 2H), 1.75 (dt, J = 2.8, 12.8 Hz, 2H), 1.66-1.54 (m, 2H), 1.10 (tt, J = 3.2, 12 Hz, 1H), 0.93 (s, 9H).

¹³C NMR (100 MHz, CDCl₃): δ 158.99, 133.37, 126.67, 122.92, 114.10, 55.32, 47.10, 43.46, 37.89, 32.42, 27.49, 24.70.

HRMS (ESI) m/z calcd. for C₁₈H₂₅NONa (M+Na): 294.1834; found 294.1811.

Minor Isomer (1RS,4SR):

¹H NMR (400 MHz, CDCl₃): δ 7.39 (d, J = 9.2 Hz, 2H), 6.93 (d, J = 8.8 Hz, 2H), 3.84 (s, 3H), 2.75-2.67 (m, 2H), 2.13-2.03 (m, 2H), 1.72-1.63 (m, 2H), 1.17-1.05 (m, 2H), 0.93-0.85 (m, 1H), 0.77 (s, 9H).

¹³C NMR (100 MHz, CDCl₃): δ 158.85, 128.89, 128.42, 152.50, 114.35, 55.27, 47.21, 37.27, 35.27, 32.36, 27.27, 21.98.

HRMS (ESI) m/z calcd. for C₁₈H₂₅NONa (M+Na): 294.1834; found 294.1832.

4-((1SR,4SR)- and (1RS,4SR)-1-cyano-4-isopropylcyclohexyl)benzonitrile (90f)

Performing the general coupling procedure with 4-isopropylcyclohexanecarbonitrile (103.8 mg, 0.686 mmol), TMPZnCl·LiCl (1.04M, 1.00 mL, 1.04 mmol), SPhos (11.3 mg, 4 mol%), Pd(OAc)₂ (3.1 mg, 2 mol %) and 4-bromobenzonitrile (123.6 mg, 0.679 mmol)
gave the crude nitrile that was purified by column chromatography (95:5, pentane:ether) to afford 123.7 mg (72% yield) of 90f and 90f* as an oily mixture of diastereomers (2.3:1 ratio).

**Major Isomer (1SR,4SR):**

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.69 (d, $J = 8.5$ Hz, 2H), 7.62 (d, $J = 8.5$ Hz, 2H), 2.24-2.16 (m, 2H), 1.94-1.87 (m, 2H), 1.79 (dt, $J = 3.5$, 13.5 Hz, 2H), 1.64-1.52 (m, 3H), 1.21-1.11 (m, 1H), 0.94 (d, $J = 7$ Hz, 6H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 146.311, 132.70, 126.56, 118.23, 111.94, 44.78, 42.82, 37.24, 32.42, 26.74, 19.73.

**Minor Isomer (1RS,4SR):**

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 2.04-1.98 (m, 2H), 1.89-1.84 (m, 2H), 1.35-1.30 (m, 1H), 0.89 (d, $J = 6.5$, 6H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 146.38, 132.75, 127.19, 118.20, 111.98, 44.78, 42.82, 37.24, 32.89, 24.92.

**Mixture:**

IR (neat): 2230 (CN) cm$^{-1}$.

HRMS (ESI) $m/z$ calcd. for C$_{17}$H$_{20}$N$_2$Na (M+Na): 275.1524; found 275.1501.
Performing the general coupling procedure with 4-methylcyclohexanecarbonitrile (90.0 mg, 0.731 mmol), TMPZnCl·LiCl (1.25M, 0.88 mL, 1.10 mmol), SPhos (9.2 mg, 4 mol%), Pd(OAc)$_2$ (2.5 mg, 2 mol %) and 4-bromobenzonitrile (102.3 mg, 0.679 mmol) gave the crude nitrile that was purified by column chromatography (90:10, pentane:ether) to afford 85.8 mg (68% yield) of $90g$ and $90g'$ as a mixture of diastereomers (3.5:1 ratio).

**Major Isomer (1SR,4SR):**

$^1$H NMR (600 MHz, CDCl$_3$): δ 7.69 (d, $J = 9.0$ Hz, 2H), 7.62 (d, $J = 9.0$ Hz, 2H), 2.17-2.13 (m, 2H), 1.90-1.85 (m, 2H), 1.81 (dt, $J = 3.6$, 13.2 Hz, 2H), 1.03 (d, $J = 6.0$ Hz, 3H).

**Minor Isomer (1RS,4SR):**

$^1$H NMR (600 MHz, CDCl$_3$): δ 2.06-1.95 (m, 2H), 1.01 (d, $J = 6.6$, 3H).

**Mixture:**

IR (neat) 2231 (CN) cm$^{-1}$.

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 146.28, 132.67, 126.91, 126.55, 121.54, 118.16, 111.97, 111.95, 44.39, 37.13, 31.81, 31.52, 28.82, 21.95, 21.86.

**HRMS (ESI) m/z calcd.** for C$_{15}$H$_{16}$N$_2$Na (M+Na): 247.1211; found 247.1206.
Performing the general coupling procedure with 4-methylcyclohexanecarbonitrile (68.0 mg, 0.552 mmol), TMPZnCl·LiCl (1.25 M, 0.67 mL, 0.838 mmol), SPhos (7.9 mg, 4 mol%), Pd(OAc)$_2$ (2.2 mg, 2 mol %) and 4-bromoanisole (0.06 mL, 0.478 mmol) gave the crude nitrile that was purified by radial chromatography (95:5, hexanes:EtOAc) to afford 79.8 mg (68% yield) of 90h and 90h’ as a mixture of diastereomers (4.8:1 ratio) from which pure samples of each diastereomer were obtained for characterization.

**Major Isomer (1SR,4SR):**

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.40 (d, $J = 8.8$ Hz, 2H), 6.91 (d, $J = 8.8$ Hz, 2H), 3.81 (s, 3H), 2.62-2.30 (m, 2H), 1.86-1.79 (m, 4H), 1.57-1.47 (m, 2H), 1.46-1.39 (m, 1H), 1.00 (d, $J = 6.4$ Hz, 3H).

**Minor Isomer (1RS,4SR):**

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 3.82 (s, 3H), 2.00-1.95 (m, 2H), 0.98 (d, $J = 6.8$, 3H).

**Mixture:**

IR (neat) 2232 (CN) cm$^{-1}$. 
$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 158.98, 158.96, 133.44, 133.36, 127.70, 127.16, 126.68, 123.57, 122.96, 114.19, 114.10, 55.31, 43.16, 37.50, 32.13, 31.70, 29.06, 22.06.

HRMS (ESI) $m/z$ calcd. for C$_{15}$H$_{19}$N$_2$ONa (M+Na): 252.1364; found 252.1372.

4-((1SR,3SR)- and (1RS,3SR)-1-cyano-3-methylcyclohexyl)benzonitrile (90i).

Performing the general coupling procedure with 3-methylcyclohexanecarbonitrile (176 mg, 1.428 mmol), TMPZnCl·LiCl (1.25 M, 1.72 mL, 2.15 mmol), SPhos (18.1 mg, 4 mol%), Pd(OAc)$_2$ (4.9 mg, 2 mol%) and 4-bromobenzonitrile (198.9 mg, 1.093 mmol) gave the crude nitrile that was purified by column chromatography (90:10, pentane:ether) to afford 171 mg (70% yield) of 90i and 90i’ as a mixture of diastereomers (6.2:1 ratio).

Major Isomer (1SR,3SR):

IR (neat) 2230 (CN) cm$^{-1}$.

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 7.69 (d, $J$ = 8.4 Hz, 2H), 7.62 (d, $J$ = 7.8 Hz, 2H), 2.15-2.07 (m, 2H), 2.04-1.94 (m, 1H), 1.93-1.85 (m, 3H), 1.67 (dt, $J$ = 4.2, 12.6 Hz), 1.39 (dd, $J$ = 12.0, 12.6 Hz, 1H), 1.01 (d, $J$ = 6.4 Hz, 3H), 1.05-0.98 (m, 1H).

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 146.29, 132.64, 126.48, 121.70, 118.14, 111.89, 44.97, 36.68, 36.61, 33.47, 29.87, 23.32, 21.89.

HRMS (ESI) $m/z$ calcd. for C$_{13}$H$_{16}$N$_2$ (M+): 224.1313; found 224.1312.
Minor Isomer (1RS,3SR):

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 2.54-2.42 (m, 2H), 1.71-1.61 (m, 1H), 1.45-1.30 (m, 1H), 1.21-1.11 (m, 1H), 1.00 (d, $J = 6.3$ Hz, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 143.65, 132.79, 127.94, 123.8, 112.01, 42.60, 39.19, 34.69, 33.11, 27.26, 21.52, 20.57.

4-((1RS,2SR)-1-cyano-2-methylcyclohexyl)benzonitrile (90j).

Performing the general coupling procedure with 2-methylcyclohexanecarbonitrile (165.0 mg, 1.34 mmol), TMPZnCl·LiCl (1.40 M, 1.44 mL, 2.02 mmol), SPhos (5.0 mg, 4 mol%), Pd(OAc)$_2$ (17.0 mg, 2 mol %) and 4-bromobenzonitrile (187.7 mg, 1.031 mmol) gave the crude nitrile that was purified by column chromatography (90:10, pentane:ether) to afford 117.6 mg (51% yield) of 90j as the sole diastereomer.

IR (neat) 2230 (CN) cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.70 (d, $J = 8.4$ Hz, 2H), 7.61 (d, $J = 8.4$ Hz, 2H), 2.08-1.77 (m, 6H), 1.62-1.52 (m, 2H), 1.44-1.38 (m, 1H), 0.79 (d, $J = 6.8$ Hz, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 145.45, 132.68, 126.85, 119.79, 118.25, 111.80, 51.77, 40.12, 39.12, 31.81, 25.44, 23.41, 17.72.

HRMS (ESI) $m/z$ calcd. for C$_{15}$H$_{16}$N$_2$Na (M+Na): 247.1211; found 247.1200.
4-((1SR,4SR)-4-((tert-butyldimethylsilyl)oxy)-1-cyanocyclohexyl)benzonitrile (90k).

Performing the general coupling procedure with 4-((tert-butyldimethylsilyl)oxy)cyclohexanecarbonitrile (109.4 mg, 0.457 mmol), TMPZnCl·LiCl (0.86 M, 0.89 mL, 0.685 mmol), SPhos (7.5 mg, 4 mol%), Pd(OAc)$_2$ (2.1 mg, 2 mol %) and 4-bromobenzonitrile (55.3 mg, 0.304 mmol) gave the crude nitrile that was purified by radial chromatography (92:8, hexanes:EtOAc) to afford 73.5 mg (71% yield) of 90k as an off-white solid.

**IR** (neat) 2232 (CN) cm$^{-1}$.

**$^1$H NMR** (400 MHz, CDCl$_3$): $\delta$ 7.70 (d, $J = 8.8$ Hz, 2H), 7.62 (d, $J = 8.4$ Hz, 2H), 3.70-3.62 (m, 1H), 2.21-2.15 (m, 2H), 2.05-1.99 (m, 2H), 1.68-1.57 (m, 2H), 1.97-1.92 (m, 1H), 1.91-1.82 (m, 3H), 0.91 (s, 9H), 0.09 (s, 6H).

**$^{13}$C NMR** (100 MHz, CDCl$_3$): $\delta$ 145.49, 132.76, 126.60, 121.23, 118.12, 112.18, 69.51, 43.68, 35.59, 32.83, 25.76, 18.07, -4.63.

**HRMS** (ESI) $m/z$ calcd. for C$_{20}$H$_{28}$N$_2$OSiNa (M+Na): 363.1869; found 363.1852.
Performing the general coupling procedure with (5R,8S,9R,10R,13S,14R,17S)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)hexadecahydro-1H-cyclopenta[a]phenanthrene-3-carbonitrile\(^{118}\) (61.6 mg, 0.155 mmol), TMPZnCl·LiCl (2.0 M, 0.77 mL, mmol), SPhos (4.0 mg, 4 mol%), Pd(OAc)\(_2\) (1.2 mg, 2 mol%) and 4-bromobenzonitrile (29.1 mg, 0.160 mmol) gave the crude nitrile that was purified by column chromatography (97:3, pentane:ether) to afford 92.7 mg (72% yield) of \(90l\) as a single diastereomer.

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.70 (d, \(J = 8.0\) Hz, 2H), 7.62 (d, \(J = 8.0\) Hz, 2H), 2.05–0.97 (m, 31H), 0.91 (d, \(J = 8.0\) Hz, 3H), 0.88 (s, 3H), 0.89 × 2 (d, \(J = 8.0\) Hz, 3H), 0.67 (s, 3H).

\(^{13}\)C NMR (150 MHz, CDCl\(_3\)): \(\delta\) 146.32, 132.73, 126.59, 122.19, 118.27, 111.93, 56.25, 56.13, 53.65, 45.28, 43.42, 42.54, 39.78, 39.48, 38.81, 36.11, 35.79, 35.58, 35.44, 35.37, 32.93, 31.52, 28.19, 28.00, 27.99, 24.13, 23.81, 22.83, 22.55, 20.95, 18.64, 12.20, 12.07.

HRMS (ESI) \(m/z\) calcd. for C\(_{35}\)H\(_{50}\)N\(_2\)ONa (M+Na): 521.3872; found 521.3836.
Chapter 8

References


(a) δ = 146.2 in d8-THF. Crowley, P. J.; Leach, M. R., Meth-Cohn, O.; Wakefeild, B. J. Tetrahedron Lett. 1986, 27, 2909. (b) δ = 147.0 in d8-toluene containing two equivalents of THF, δ = 149.7 in a 1:1 mixture of d8-toluene: d8-THF, and δ = 152.7 in d8-toluene containing 1 equivalent of TMEDA, Personal Communication from Carlier, P. R. (c) Carlier, P. R.; Lo, C. W.-S. J. Am. Chem. Soc. 2000, 122, 12819.

140


42 See Reference 21.

(b) Mycka, R. J.; Steward, O. W.; Fleming, F. F. *Org. Lett.* 2010, 12, 3033.


(b) A copy of the 13C spectrum was obtained via personal communication.


57 Castany, M. H.; Lavayssière, H.; Dousse, G. Main Group Metal Chemistry 1999, 22, 133.


65 Butts, M. D.; Bergman, R. G. Organometallics 1993, 12, 4269.

66 Optimizing the alkoxide-directed exchange was a collaborative project developed with Dr. Viet Anh Vu and Subrahmanyam Gudipati.


72 (a) Satoh, T.; Takano, K.; Ota, H.; Someya, H.; Matsuda, K.; Koyama, M. Tetrahedron 1998, 54, 5557. (b) See References 22(a) and 22(b).

Sequential deprotonation and protodiation of 3-iodo-1-propanol at –78 °C leads to diminishing recovery with 1-iodo-2,2,4-trimethylpentan-3-ol affording only 2-isopropyl-3,3-dimethyloxetane.

The cylindrical diameter of the π-system is only 3.6 Å: Sheppard, W. A. in The Chemistry of the Cyano Group Rappoport, Ed. 1970, Ch. 5.


(a) Carlier, P. R.; Zhang, Y. Org. Lett. 2007, 9, 1319.


See Reference 74(a).


111 Glorius, F. Nature Chemistry 2010, 2, 78.

Nitriles have an exceedingly small steric demand, a mere 0.2 kcal mol⁻¹, and while the corresponding \( K \) value for an alkylzinc has not been determined, alkylations of zincated nitriles are consistent with the steric demand of the organozinc being greater: Fleming, F. F.; Liu, W. Eur. J. Org. Chem. 2009, 699.

Palladium coordinates to the formally anionic carbon of deprotonated nitriles unless the ligands on palladium have severe steric compression: Culkin, D. A.; Hartwig, J. F. Organometallics 2004, 23, 3398.


Complete consumption of the nitrile was monitored by GCMS.


The configuration was assigned by sequential cyclization and hydrolysis to the lactone 85 whose configuration was assigned through a NOESY correlation:


