Nickel-Catalyzed Cyanation of Benzylic and Allylic Pivalates

by

Alexandria Daria Maria Jeanneret

A thesis submitted in conformity with the requirements for the degree of Master of Science
Department of Chemistry
University of Toronto

© Copyright by Alexandria Daria Maria Jeanneret 2018
Nickel-Catalyzed Cyanation of Benzylic and Allylic Pivalates

Alexandria Daria Maria Jeanneret

Master of Science
Department of Chemistry
University of Toronto
2018

Abstract

Nitriles are considered very versatile functional groups due to their ability to easily be transformed into a variety of other functional groups in one or two steps. In particular, the synthesis of α-arylnitriles is of interest to organic chemists due to their presence in pharmaceuticals and their value as synthetic intermediates. Taking advantage of nickel’s unique ability to insert into a C‒O bond, the focus of this thesis is on the nickel-catalyzed cyanation of benzylic and allylic pivalates, exploring the use of inorganic and organic cyanide sources for this transformation. The substrate scope for the synthesis of benzylic and allylic nitriles will be presented as well as studies examining the functional group tolerance of this cyanation reaction, which led to further insights into the mechanism and applicability of this chemistry.
Acknowledgments

First and foremost, I would like to thank Professor Sophie Rousseaux for the opportunity to work to work in her lab over the last year. Her passion for chemistry is beyond contagious and her guidance has been invaluable. I would also like to thank Professor Mark Taylor for his help with this thesis.

Secondly, I would like to thank all the staff at the NMR and AIMS facility for all their hard-work and dedication to ensuring the instruments run smoothly and for always taking the time to answer questions.

Thirdly, I want to thank everyone in the Rousseaux group during my time in the group. I know our time together was shorter than expected but I won’t forget the support and encouragement you all gave me during my time here. I hope that after I leave, pub nights at Red Room and board game nights in the group room will happen regularly. A special thanks goes out to Mike and Seb who’s constant bickering about just about everything, put me in hysterics on a daily basis. I wish everyone in the group best of luck in their future endeavours and hope that we will all stay in touch in the future.
Table of Contents

Acknowledgments .......................................................................................................................... iii
Table of Contents ........................................................................................................................... iv
List of Tables ................................................................................................................................. vi
List of Schemes .............................................................................................................................. vii
List of Figures ................................................................................................................................ ix
List of Abbreviations ...................................................................................................................... x
Chapter 1 ......................................................................................................................................... 1
  1 An Introduction to Benzylic Nitriles – Utility and Synthesis .................................................... 1
    1.1 Importance of the Nitrile Moiety ........................................................................................ 1
    1.2 Synthesis of α-Arylnitriles .............................................................................................. 3
      1.2.1 Functionalization of the α-Position of Alkyl Nitriles ............................................. 4
      1.2.2 Installation of the Nitrile Functional Group ............................................................ 8
    1.3 Nickel-Catalyzed C‒O Activation ...................................................................................... 9
    1.4 Our Strategy ...................................................................................................................... 11
Chapter 2 ....................................................................................................................................... 13
  2 Synthesis of α-Arylnitriles using Organic Cyanide Sources .................................................... 13
    2.1 Introduction ....................................................................................................................... 13
      2.1.1 Acetone Cyanohydrin ............................................................................................... 14
      2.1.2 Aminoacetonitriles ................................................................................................... 15
      2.1.3 Trimethylsilyl Cyanide ............................................................................................. 16
    2.2 Results and Discussion ..................................................................................................... 17
      2.2.1 Early Optimization with TMS-CN ........................................................................ 17
      2.2.2 Incremental Addition of TMS-CN ........................................................................ 18
      2.2.3 Substrate Scope ......................................................................................................... 21
List of Tables

Table 2.1 Early optimization attempts with TMS-CN ............................................................ 18
Table 2.2 Initial results with the incremental addition of TMS-CN ................................. 19
Table 2.3 Optimization of the concentration and incremental addition of TMS-CN .. 20
Table 2.4 Final optimization attempts ............................................................................. 21
Table 2.5 Substrate comparison with Zn(CN)$_2$ and TMS-CN ..................................... 22
Table 2.6 Scope of aminoacetonitriles ............................................................................. 23
Table 3.1 Sample of Glorius' robustness screen ............................................................. 32
Table 3.2 Robustness screen for the synthesis of α-arylnitriles ................................... 33
Table 4.1 Robustness screen for the synthesis of allylic nitriles ................................... 39
List of Schemes

Scheme 1.1 Strategies towards the synthesis of α-arylnitriles: a) functionalization of the α-position of an alkyl nitrile and b) installation of the nitrile group at the benzylic position... 4

Scheme 1.2 Methylation of benzylic nitriles. ................................................................................................................. 4

Scheme 1.3 Strategies for the arylation of alkyl nitriles: a) coupling of an aryl halide with a metallated alkyl nitrile and b) coupling of an aryl organometallic with an electrophilic alkyl nitrile. ............................................................................................................................................. 5

Scheme 1.4 α-Arylation of silylnitriles with aryl bromides........................................................................................................ 6

Scheme 1.5 Enantiospecific arylation of alkyl α-cyanohydrin triflates. ................................................................. 6

Scheme 1.6 Enantioselective Negishi cross-coupling of bromoacetonitriles..................................................................... 7

Scheme 1.7 Nickel-catalyzed hydrocyanation of styrene derivatives................................................................. 8

Scheme 1.8 Kolbe nitrile synthesis from benzyl halides.............................................................................................. 8

Scheme 1.9 Nickel-catalyzed Kumada, Negishi and Suzuki cross-coupling of activated alcohols............................................................ 10

Scheme 1.10 Reaction conditions established by N. Michel and H. Kim for the synthesis of α-arylnitriles................................................................. 11

Scheme 2.1 Cyanation of benzylic pivalates as developed by N. Michel and H. Kim.................. 13

Scheme 2.2 Equilibrium of acetone cyanohydrin to acetone and hydrogen cyanide......... 14

Scheme 2.3 Cyanation of aryl halides with acetone cyanohydrin. ...................................................... 14

Scheme 2.4 Cyanation of aryl pivalates with morpholinoacetonitrile. ........................................... 15

Scheme 2.5 Palladium-catalyzed cyanation of aryl iodides with TMS-CN. ......................... 16

Scheme 2.6 Nickel-catalyzed cyanation of benzyl chlorides................................................................. 17
Scheme 3.1 Substrate scope of α-arylnitriles................................................................. 26

Scheme 3.2 Unsuccessful cyanation of phenyl derivatives. .............................................. 27

Scheme 3.3 Synthesis of pyrrole derivatives................................................................. 28

Scheme 3.4 Synthesis of protected naphthyl derivatives from 6-bromo-2-naphthol........... 29

Scheme 3.5 Cyanation results of the protected naphthyl derivatives. .......................... 30

Scheme 4.1 General reaction scheme of a Tsuji-Trost reaction. ...................................... 35

Scheme 4.2 Nickel-catalyzed Suzuki cross-coupling of allylic pivalates........................... 36

Scheme 4.3 Substrate scope for the synthesis of allylic nitriles. ....................................... 37

Scheme 4.4 Enantiospecificity of our nickel-catalyzed cyanation reactions: a) cyanation of enantioenriched allylic pivalate 12a and b) cyanation of enantioenriched benzylic pivalate 1a.................................................................................................................................................. 40
List of Figures

Figure 1.1 Functional group interconversions of the nitrile moiety................................. 1

Figure 1.2 Additional chemical transformations of the nitrile moiety............................... 2

Figure 1.3 FDA-approved pharmaceuticals that incorporate the α-arylnitrile moiety......... 3
# List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Å</td>
<td>Angstroms</td>
</tr>
<tr>
<td>Ac</td>
<td>Acetyl</td>
</tr>
<tr>
<td>Ar</td>
<td>Aryl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-Butyloxycarbonyl</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl</td>
</tr>
<tr>
<td>°C</td>
<td>Degree Celsius</td>
</tr>
<tr>
<td>cod</td>
<td>Cyclooctadiene</td>
</tr>
<tr>
<td>Cy</td>
<td>Cyclohexyl</td>
</tr>
<tr>
<td>DART</td>
<td>Direct Analysis in Real Time</td>
</tr>
<tr>
<td>dba</td>
<td>Dibenzylideneacetone</td>
</tr>
<tr>
<td>DCE</td>
<td>Dichloroethane</td>
</tr>
<tr>
<td>dcypt</td>
<td>Dicyclohexylphosphinothiophene</td>
</tr>
<tr>
<td>DIBAL-H</td>
<td>Diisobutylaluminum hydride</td>
</tr>
<tr>
<td>DIPEA</td>
<td>Diisopropylethylamine</td>
</tr>
<tr>
<td>DMA</td>
<td>Dimethylacetamide</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-dimethylaminopyridine</td>
</tr>
<tr>
<td>DME</td>
<td>Dimethoxyethane</td>
</tr>
<tr>
<td>DMF</td>
<td>Dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethylsulfoxide</td>
</tr>
<tr>
<td>dppb</td>
<td>Diphosphinobutane</td>
</tr>
<tr>
<td>dppf</td>
<td>Diphosphinoferrocene</td>
</tr>
<tr>
<td>dppp</td>
<td>Diphosphinopropane</td>
</tr>
<tr>
<td>EI</td>
<td>Electron Ionization</td>
</tr>
<tr>
<td>ESI</td>
<td>Electrospray Ionization</td>
</tr>
<tr>
<td>Et</td>
<td>Ethyl</td>
</tr>
<tr>
<td>EtOAc</td>
<td>Ethyl acetate</td>
</tr>
<tr>
<td>equiv</td>
<td>Equivalents</td>
</tr>
<tr>
<td>FDA</td>
<td>U.S. Food and Drug Administration</td>
</tr>
<tr>
<td>g</td>
<td>Gram</td>
</tr>
<tr>
<td>GC-MS</td>
<td>Gas Chromatography Mass Spectrometry</td>
</tr>
<tr>
<td>HRMS</td>
<td>High Resolution Mass Spectrometry</td>
</tr>
<tr>
<td>h</td>
<td>Hour</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz</td>
</tr>
<tr>
<td>³Pr</td>
<td>Isopropyl</td>
</tr>
<tr>
<td>IR</td>
<td>Infrared</td>
</tr>
<tr>
<td>K</td>
<td>Kelvin</td>
</tr>
<tr>
<td>LG</td>
<td>Leaving group</td>
</tr>
</tbody>
</table>
M – mol/L
MeCN – Acetonitrile
mg – Miligram
MHz – Megahertz
min – Minute
mL – Millilitre
Ms – Mesylate
nm – Nanometers
NMR – Nuclear Magnetic Resonance
NSAIDs – Non-Steroidal Anti-Inflammatory Drugs
Ph – Phenyl
Ph.D. – Doctor of Philosophy
Me – Methyl
Piv – Pivalate
ppm – Parts per million
r.t. – Room temperature
'Butyl – tert-butyl
Temp. – Temperature
Tf – Trifluoromethanesulfonyl
THF – Tetrahydrofuran
TIPS – Triisopropylsilyl
TLC – Thin Layer Chromatography
TMEDA – Tetramethylethylenediamine
TMS – Trimethylsilyl
TOF – Time of Flight
UV – Ultra-Violet
Xantphos – 4,5-Bis(diphenylphosphino)-9,9-
dimethylxanthene
1 An Introduction to Benzylic Nitriles – Utility and Synthesis

1.1 Importance of the Nitrile Moiety

The nitrile functional group is a unique synthetic handle as it can be easily converted into a wide range of functional groups in one or two steps (Figure 1.1).\(^1\) A reduction reaction with DIBAL-H at -78 °C gives the corresponding aldehyde while addition of a Grignard reagent gives the corresponding ketone. Hydrolysis of the nitrile with aqueous acid gives the carboxylic acid while partial hydrolysis with NaOH, gives the amide.

![Functional group interconversions of the nitrile moiety.](image)

Beyond synthesizing various carbonyl functional groups, the nitrile moiety can be completely reduced to give the free amine product, or the nitrile can also be converted into various heterocycles such as tetrazoles (Figure 1.2).  

![Figure 1.2 Additional chemical transformations of the nitrile moiety.](image)

Aside from being a versatile synthetic intermediate, the nitrile functional group possesses unique properties, such as its hydrogen bond accepting properties, that are valuable in pharmaceuticals. It has also been reported that the inclusion of the nitrile moiety into drug-like compounds aids in the metabolic stability of the compound through inductive polarization.

As the nitrile moiety is a crucial intermediate that can easily be transformed into other functional groups, it is advantageous to install the nitrile group onto various molecular scaffolds to synthesize compounds such as α-arylnitriles. This particular class of compounds is useful in the synthesis of pharmaceuticals. For example, phenylacetic acid is a core structure commonly found in many non-steroidal anti-inflammatory drugs (NSAIDs) that can be easily accessed by the hydrolysis of phenylacetonitrile. Aside from being used as an intermediate towards the synthesis of pharmaceuticals, the α-arylnitrile motif itself is present in a range of pharmaceuticals. Figure 1.3 below demonstrates selected examples of FDA-approved pharmaceuticals that contain this structural motif, highlighted in blue.

---

The drugs shown above are used to treat a variety of ailments: verapamil treats hypertension, anastrozole is an anti-cancer drug, cilomilast is used in the treatment of chronic obstructive pulmonary disease and diphenoxylate is an opioid for the treatment of diarrhea. Due to the synthetic utility of the nitrile group as well as the abundance of α-arylnitriles in pharmaceuticals, the development of methods to prepare these compounds is of synthetic interest.

### 1.2 Synthesis of α-Arylnitriles

An abundance of research has been applied towards the synthesis of arylnitriles mainly through the use of aryl halides or pseudohalides, a source of cyanide and a transition-metal catalyst. More recently, research efforts have gone into the synthesis of alkyl nitriles. To prepare α-arylnitriles, current reports involve two different approaches (Scheme 1.1). The first strategy involves the functionalization of the α-position of an alkyl nitrile. This includes installing an alkyl group onto a benzyl nitrile, as well as the arylation of an alkyl nitrile. The second strategy entails the installation of the nitrile moiety at the benzylic position of a molecule. The discussion

---


in the next section will begin by looking at methods for the functionalization of the \( \alpha \)-position of alkyl nitriles.

**Scheme 1.1 Strategies towards the synthesis of \( \alpha \)-arylnitriles: a) functionalization of the \( \alpha \)-position of an alkyl nitrile and b) installation of the nitrile group at the benzylic position.**

### 1.2.1 Functionalization of the \( \alpha \)-Position of Alkyl Nitriles

The most straightforward strategy towards the functionalization of benzylic nitriles is achieved by deprotonation and subsequent alkylation, typically using alkyl iodides. Scheme 1.2 demonstrates that under basic conditions, the \( \alpha \)-position of benzyl nitriles can be deprotonated then methylated using methyl iodide to give the secondary benzylic nitrile product.\(^8\)

\[
\begin{align*}
\text{Ar-CN} & \quad \xrightarrow{1) \text{NaH}} \quad \text{Ar-CN} \\
& \quad \xrightarrow{2) \text{MeI}} \quad \text{Ar-CN} + \text{Ar-CN}
\end{align*}
\]

**Scheme 1.2 Methylation of benzylic nitriles.**

Despite the simplicity of this method, over-alkylation and the separation of the mono and di-alkylated products can be problematic. Furthermore, the need for a strong base to deprotonate the benzylic position severely limits the functional group tolerance and stereo-control is also a challenge in this reaction.

Recent metal-catalyzed cross-coupling reactions for the synthesis of \( \alpha \)-arylnitriles involve the arylation of alkyl nitriles.\(^9\) The arylation of alkyl nitriles can be further divided into two


strategies where the alkyl nitrile can play the role of either the nucleophile (Scheme 1.3a) or the electrophile (Scheme 1.3b).

\[
a) \quad \text{Ar}-X + \begin{array}{c} \text{CN} \\ \text{N} \end{array} R \xrightarrow{\text{Pd or Ni catalyst}} \begin{array}{c} \text{CN} \\ \text{N} \end{array} \text{Ar} R \\
b) \quad \text{Ar}-N + \begin{array}{c} X \\ \text{CN} \end{array} R \xrightarrow{\text{Pd or Ni catalyst}} \begin{array}{c} \text{CN} \\ \text{N} \end{array} \text{Ar} R
\]

Scheme 1.3 Strategies for the arylation of alkyl nitriles: a) coupling of an aryl halide with a metallated alkyl nitrile and b) coupling of an aryl organometallic with an electrophilic alkyl nitrile.

For example, a nucleophilic metallated nitrile species can be coupled with an aryl halide under palladium catalysis. Wu and Hartwig have demonstrated that α-silylnitriles can be α-arylated using aryl bromides to synthesize various α-arylnitrile derivatives (Scheme 1.4).\(^\text{10}\) While silylacetonitrile is a commercially available reactant, the formation of secondary and tertiary α-arylnitriles requires the synthesis of more functionalized silylnitriles. Unfortunately, despite the synthesis of tertiary α-arylnitriles, the products are racemic. Since the α-arylnitrile motif is a prevalent scaffold in pharmaceuticals, it is advantageous to be able to achieve asymmetric synthesis of α-arylnitriles.

Scheme 1.4 α-Arylation of silylnitriles with aryl bromides.

An alternative strategy for the synthesis of α-arylnitriles consists of coupling α-cyanohydrin derived electrophiles with an organometallic cross-coupling partner. Scheme 1.5 illustrates an example reported by He and Falck who accomplished the asymmetric synthesis of secondary α-arylnitriles using enantioenriched alkyl α-cyanohydrin triflates and aryl boronic acids.\textsuperscript{11}

Scheme 1.5 Enantiospecific arylation of alkyl α-cyanohydrin triflates.

The use of secondary alkyl α-cyanohydrin triflates often leads to the formation of the corresponding alkene as a result of β-hydride elimination. This side product was avoided through the use of bulky, electron-rich ligands coordinated to the palladium catalyst to favour reductive elimination over β-hydride elimination.\textsuperscript{11} The reaction scope includes various aryl boronic acids, giving secondary α-arylnitriles with inversion of stereochemistry with respect to the cyanohydrin triflate. The enantioenriched alkyl α-cyanohydrin triflates are synthesized via an asymmetric cyanosilylation followed by desilylation and addition of the triflate group. The

asymmetric cyanosilylation is achieved using a chiral ligand that requires a six-step synthesis to synthesize.\textsuperscript{12} As the synthesis of enantioenriched starting materials requires several synthetic steps, it would be advantageous to synthesize enantioenriched $\alpha$-arylnitriles from racemic starting materials.

Choi and Fu achieved a Negishi cross-coupling method to synthesize $\alpha$-arylnitriles (Scheme 1.6).\textsuperscript{13} While Falck used enantioenriched $\alpha$-cyanohydrin derived electrophiles for arylation with inversion of stereochemistry,\textsuperscript{11} Choi and Fu developed an enantioselective synthesis of $\alpha$-arylnitriles from more readily accessible racemic bromoacetonitriles. Thus, they have eliminated the need to synthesize enantioenriched nitrile starting materials.\textsuperscript{13}

\begin{center}
\begin{tikzpicture}
  \node (a) at (0,0) {\text{CN}};
  \node (b) at (-1,0) {\text{R_1Br}};
  \node (c) at (1,0) {\text{CN}};
  \node (d) at (0,1) {\text{Ar-ZnR_2}};
  \node (e) at (-1,1) {\text{NiCl_2(glyme)} (10 mol \%)};
  \node (f) at (1,1) {\text{TMEDA (20 mol \%)}};
  \node (g) at (0,-1) {\text{THF, -78 °C}};
  \draw [->] (a) -- (b);
  \draw [->] (b) -- (c);
  \draw [->] (c) -- (d);
  \draw [->] (d) -- (e);
  \draw [->] (e) -- (f);
  \draw [->] (f) -- (g);
\end{tikzpicture}
\end{center}

Scheme 1.6 Enantioselective Negishi cross-coupling of bromoacetonitriles.

The enantioselectivity of this reaction is controlled through the use of an easily accessible bis(oxazoline) chiral ligand (S,S)-1.2, allowing for racemic bromoacetonitriles to yield enantioenriched $\alpha$-arylnitriles. A major advantage in preparing enantioenriched $\alpha$-arylnitriles is that it allows for further transformations of the nitrile group into other functional groups with retention of stereochemistry.\textsuperscript{11}

As mentioned previously, there are two approaches towards the synthesis of $\alpha$-arylnitriles. Aside from functionalizing the $\alpha$-position of an alkyl nitrile, installation of the nitrile moiety at the

\textsuperscript{13} Choi, J.; Fu, G. J. Am. Chem. Soc. 2012, 134, 9102-9105.
benzylic position is another alternative. This approach allows for the synthesis of benzylic nitriles from more readily accessible starting materials and a commercially available cyanide source.

1.2.2 Installation of the Nitrile Functional Group

A classic strategy towards the synthesis of benzylic nitriles is through the nickel-catalyzed hydrocyanation of styrene derivatives (Scheme 1.7).\textsuperscript{14} Although, a straightforward method, hydrocyanation has several drawbacks mainly due to the use of hydrogen cyanide as the cyanide source. This toxic and highly volatile reagent is difficult to handle safely in a laboratory setting and is typically avoided.\textsuperscript{15} Furthermore, this reaction often suffers from poor regioselectivity and gives rise to a mixture of branched and linear nitrile products that are difficult to separate.\textsuperscript{14}

![Scheme 1.7 Nickel-catalyzed hydrocyanation of styrene derivatives.](image)

Safer alternatives to HCN are inorganic cyanide salts such as NaCN or KCN, which are the source of cyanide used in the Kolbe nitrile synthesis (Scheme 1.8).\textsuperscript{16} This synthesis of benzylic nitriles is accomplished using benzylic halides that undergo an S\textsubscript{N}2 reaction with an inorganic cyanide salt. The Kolbe nitrile synthesis is mostly limited to primary substrates as secondary and tertiary benzylic halides show an increase in the formation of the elimination product.

![Scheme 1.8 Kolbe nitrile synthesis from benzyl halides.](image)


Recently, there has been a push to move away from the use of organic halides in organic synthesis as they are harmful to the environment due to their toxicity towards plant and animal life.\textsuperscript{17} Benzyl halides are synthesized from radical halogenation of toluene using the corresponding diatomic halide whereas alkyl halides are typically synthesized from the corresponding alcohols using the Appel reaction and other related transformations.\textsuperscript{18, 19} In order to avoid the use of organic halides, alcohols can be activated to become pseudohalides. Activation occurs by such methods as esterification (\textendash OCOR), sulfonylation (\textendash OTf) or methylation (\textendash OMe) to mimic the leaving group ability of halides. Nickel catalysis has expanded the use of activated alcohols as pseudohalides due to nickel’s unique ability to insert into aryl and alkyl C\textendash O bonds and to undergo various cross-coupling reactions.\textsuperscript{20}

1.3 Nickel-Catalyzed C\textendash O Activation

An increasing amount of work has been done in the area of nickel-catalyzed C\textendash O activation, allowing for cross-coupling reactions with phenol derivatives such as pivalates, carbamates, sulfamates or methyl ethers.\textsuperscript{21} To date, there have been a multitude of examples in the literature regarding nickel-catalyzed C\textendash O activation of phenol derivatives using a variety of nucleophiles such as amines, organozincs, organoboron reagents, Grignards and other carbon nucleophiles.\textsuperscript{21} Examples are mostly limited to cross-coupling with phenol derivatives although examples of cross-coupling with C(sp\textsuperscript{3})\textendash O electrophiles have recently emerged.\textsuperscript{22}

Jarvo et al. have reported examples of nickel-catalyzed cross-coupling reactions using benzylic methyl ethers and pivalate esters as electrophiles (Scheme 1.9).\textsuperscript{20} Beyond achieving insertion into an alkyl C–O bond, they also demonstrate that this process occurs with inversion of stereochemistry. This enantiospecific strategy for carbon-carbon bond formation is applicable to Kumada, Negishi and Suzuki cross-coupling reactions to give the corresponding enantioenriched cross-coupled products.\textsuperscript{23}

\[
\begin{align*}
\text{OR}^1 & \quad \text{Ni Catalyst} \\
\text{Ar}^1 & \quad \text{R}^3 \text{MgBr, Me}_2\text{Zn or Ar}_3(\text{OR})_2 \\
\text{R}^1 = \text{Me or Piv} \\
\end{align*}
\]

\[
\begin{align*}
\text{From } ^{19}\text{PrMgBr:} & \quad 40\% \text{ yield} \quad 90\% \text{ ee} \\
\text{From } \text{Me}_2\text{Zn:} & \quad 84\% \text{ yield} \quad 94\% \text{ ee} \\
\text{From } \text{ArB(OR)}_2: & \quad 55\% \text{ yield} \quad 83\% \text{ ee}
\end{align*}
\]

Scheme 1.9 Nickel-catalyzed Kumada, Negishi and Suzuki cross-coupling of activated alcohols.

The broad range of cross-coupling partners applicable to this methodology highlights the synthetic utility of nickel-catalyzed C–O activation. However, the electrophile is often limited to substrates containing an extended \(\pi\)–system, such as naphthyl derivatives. Oxidative addition into the C–O bond breaks the aromaticity of the electrophile, forming a \(\pi\)–benzylnickel complex, therefore substrates containing an extended \(\pi\)–system are less destabilized as they maintain aromaticity.\textsuperscript{20} Despite this requirement of the electrophile to possess an extended \(\pi\)–system, the

beneficial use of ethers or esters in place of organic halides is further highlighted by the ease of synthesizing enantioenriched alcohols as starting materials.\textsuperscript{24}

1.4 Our Strategy

Further expansion of the scope of nucleophiles that can be used in stereospecific nickel-catalyzed C–O activation reactions would provide a wider range of enantioenriched products that could be used as intermediates in drug syntheses. Aware of the versatility of the nitrile moiety as well as the presence of the α-arylnitrile scaffold in various pharmaceuticals, we wondered if Jarvo’s C(sp\textsuperscript{3})–O bond functionalization strategy could be applied towards the synthesis of α-arylnitriles from benzylic pivalates. Based on previous results suggesting that naphthyl derivatives\textsuperscript{20} were ideal substrates for benzylic C–O activation, we began our studies using 1-(naphthalen-2-yl)ethyl pivalate 1a. This work was initiated by a Ph.D. candidate, Nicholas Michel, assisted by undergraduate student, Hyehwang Kim, who together established the two sets of optimal reaction conditions (Scheme 1.10). Starting material 1a was mixed with NiCl\textsubscript{2}(dpff), Zn(CN)\textsubscript{2} and ZnEt\textsubscript{2} in DMF at 110 °C for 16 hours with either K\textsubscript{3}PO\textsubscript{4} or Zn\textsubscript{5}(CO\textsubscript{3})\textsubscript{2}(OH)\textsubscript{6} as an additive. It is unclear what role the additive is playing in the reaction, but it appears to limit the amount of β-hydride elimination products that are observed. Conditions A include using 30 mol % of K\textsubscript{3}PO\textsubscript{4} as an additive which gave 2a in 94% and conditions B include using 15 mol % of Zn\textsubscript{5}(CO\textsubscript{3})\textsubscript{2}(OH)\textsubscript{6} to form 2a in 86% yield.

\begin{equation}
\text{1a} \quad \text{NiCl}_{2}(dpff; (10 \text{ mol} \%) \quad \text{Zn(CN)}_{2} \quad \text{A: K}_{3}\text{PO}_{4} \text{ (30} \text{ mol} \%) \quad \text{ZnEt}_{2} \text{ (15} \text{ mol} \%) \quad \text{DMF (0.1 M), 110 °C, 16 h} + \quad \text{Zn(CN)}_{2} \quad \text{(0.55 equiv)} \quad \rightarrow \quad \text{2a} \quad \text{B: Zn}_{5}(\text{CO}_{3})_{2}(\text{OH})_{6} \text{ (15 mol %)}
\end{equation}

**Scheme 1.10 Reaction conditions established by N. Michel and H. Kim for the synthesis of α-arylnitriles.**

After establishing the optimized reaction conditions, it was found that the poor solubility of Zn(CN)$_2$ was an issue when exploring the substrate scope. Several substrates tested under the reaction conditions gave poor conversion to the nitrile product and it was hypothesized that the heterogeneity of the reaction mixture was responsible this limitation. To overcome this obstacle, I decided to explore alternative cyanide sources in this reaction. More specifically, we hypothesized that organic cyanide sources would lead to a more homogeneous reaction mixture and would alleviate the substrate limitations imposed by inorganic cyanide salts. My initial role in this project was to explore organic cyanide sources that would allow for the synthesis of a broader scope of α-arylnitriles.
Chapter 2

2 Synthesis of α-Arylnitriles using Organic Cyanide Sources

2.1 Introduction

The use of inorganic cyanide salts as a reagent in metal-catalyzed cross-coupling reactions raises several concerns. These concerns include the potential for catalyst poisoning and the poor solubility of inorganic cyanide salts in organic solvents.\(^\text{15}\) In the context of our nickel-catalyzed cyanation of benzylic pivalates (Scheme 2.1), we hypothesized that the poor solubility of Zn(CN)\(_2\) and the heterogeneous nature of the reaction mixture was limiting the substrate scope of this reaction. As organic cyanide reagents could lead to a more homogeneous reaction mixture, this was hypothesized to be a solution to the limited substrate applicability of our cyanation reaction.

\[
\begin{align*}
\text{Ar-CH}_{2}\text{Piv} + \text{Zn(CN)}_2 \rightarrow & \text{NiCl}_2(\text{dpf}) \text{ (10 mol %)} \\
\text{K}_2\text{PO}_4 \text{ (30 mol %)} & \\
\text{Zr}_5\text{(CO}_3)_2\text{(OH)}_6 \text{ (15 mol %)} & \\
\text{ZnE}_2 \text{ (15 mol %)} & \\
\text{DMF (0.1 M), 110 °C, 16 h} & \\
\end{align*}
\]

Scheme 2.1 Cyanation of benzylic pivalates as developed by N. Michel and H. Kim.

There are many different organic cyanide reagents that are either commercially available or easily synthesized.\(^\text{25}\) Three classes were considered for this study: cyanohydrins, aminoacetonitriles and trialkylsilyl cyanides. More specifically, focus was applied to acetone cyanohydrin, morpholinoacetonitrile and trimethylsilyl cyanide.

2.1.1 Acetone Cyanohydrin

Acetone cyanohydrin is an organic cyanating reagent that readily releases acetone and hydrogen cyanide in solution, as illustrated in Scheme 2.2.\textsuperscript{25}

\[ \text{HO-CN} \rightleftarrows \text{C} + \text{HCN} \]

**Scheme 2.2 Equilibrium of acetone cyanohydrin to acetone and hydrogen cyanide.**

As HCN is generated \textit{in situ}, acetone cyanohydrin is often used as a safer alternative to HCN gas in nickel-catalyzed hydrocyanation reactions.\textsuperscript{15} A drawback of this reagent is the concern of catalyst poisoning if too much HCN is in solution prior to initiation of the catalytic cycle. This problem is easily circumvented by the slow addition of acetone cyanohydrin to ensure a slow release of cyanide. The slow addition of acetone cyanohydrin was demonstrated in the cyanation of aryl halides by the Chemical Development Department at Bayer Pharma (Scheme 2.3).\textsuperscript{26}

\[ \begin{array}{c}
\text{R}^1 \text{Br} \\
\text{X = Cl, Br}
\end{array} \xrightarrow{\text{1.2 equiv added over 2 hours}} \begin{array}{c}
\text{HO-CN} \\
\end{array} \xrightarrow{\text{1PrOH (0.38 M), DIPEA (2 equiv)}} \begin{array}{c}
\text{R}^1 \text{CN} \\
\end{array} \left\langle \begin{array}{c}
\text{(TMEDA)}\text{NiCl(\text{-toly}) (5 mol %)} \\
\text{dpf (7.5 mol %)}
\end{array} \right\rangle \]  

\text{8 examples 53 - 94%}

**Scheme 2.3 Cyanation of aryl halides with acetone cyanohydrin.**

This organic cyanide source was considered as a replacement for Zn(CN)\textsubscript{2} in our cyanation of benzylic pivalates but there was a concern regarding its boiling point. The boiling point of acetone cyanohydrin is 95 °C and the cyanation reactions are typically conducted at 110 °C. Therefore, acetone cyanohydrin was no longer considered as a potential alternative to inorganic cyanide salts and aminoacetonitriles were the next class of organic cyanide reagents that were explored.

2.1.2 Aminoacetonitriles

Aminoacetonitriles consist of a tertiary amine where the azomethine carbon acts as a carrier for the cyanide anion. The release of the cyanide anion is initiated upon the formation of an iminium species which can be further encouraged by using a more sterically congested tertiary amine. Aminoacetonitriles are more stable and less moisture sensitive cyanide reagents as heat is required to promote iminium formation. Prior to being considered as a source of cyanide, aminoacetonitriles were utilized as an imine precursor that is formed upon the displacement of the nitrile group to furnish mono- or difunctionalized products. Using aminoacetonitriles as organic cyanide sources was not recognized until Kotani et al. established their use in the cyanation of acetals and orthoesters. Itami et al. recently extended the application of aminoacetonitriles to the nickel-catalyzed cyanation of aryl pivalates. Several aminoacetonitriles were examined and the highest yield was obtained using morpholinoacetonitrile (Scheme 2.4).

\[
\begin{align*}
\text{R}^1\text{OPiv} + \text{N}^\text{CN} \xrightarrow{\text{NiBr}_2 (5 \text{ mol } \%), \text{ dcypt (10 \text{ mol } \%), Zr (30 \text{ mol } %)} } \text{R}^1\text{CN} \\
\text{K}_3\text{PC}_4 (2.0 \text{ equiv}) \text{ toluene} \ 150 ^\circ\text{C}, 18 \text{ h} \\
15 \text{ examples} \ 44 - 87\%
\end{align*}
\]

Scheme 2.4 Cyanation of aryl pivalates with morpholinoacetonitrile.

This report demonstrated that aminoacetonitriles could be used as successful cyanide reagents in nickel-catalyzed cross-coupling via C–O activation and it was thought that aminoacetonitriles could be a suitable alternative to Zn(CN)$_2$ in our synthesis of benzylic nitrile derivatives.

---

2.1.3 Trimethylsilyl Cyanide

Trimethylsilyl cyanide (TMS-CN) is commonly reported in the literature as a cyanide source in transition metal-catalyzed and organocatalyzed asymmetric synthesis of cyanohydrins. Aside from its reactivity with imines, aldehydes and ketones, there are select examples of its use in palladium-catalyzed cyanation of aryl halides. Scheme 2.5 below demonstrates early work completed by Hanafusa and Chatani, establishing the use of TMS-CN in the palladium-catalyzed cyanation of aryl iodides. This work was further extended by Beller et al. towards the cyanation of aryl bromides and aryl chlorides.

Scheme 2.5 Palladium-catalyzed cyanation of aryl iodides with TMS-CN.

The use of TMS-CN in the synthesis of alkyl nitriles was first established by Zieger and Wo using TiCl₄ in the cyanation of benzyl chlorides to construct a modest scope of benzylic nitriles. In the context of transition metal-catalyzed cyanation reactions, Tsuji et al. synthesized allylic nitriles from allylic carbonates and acetates under palladium catalysis. Of more relevance to our goal of achieving nickel-catalyzed cyanation of benzylic nitriles, Satoh and Obora reported the use of TMS-CN in the nickel-catalyzed synthesis of benzylic nitriles as illustrated in Scheme 2.6. This report inspired my initial exploration of TMS-CN as an alternative to Zn(CN)₂, in the hopes of broadening the substrate scope of benzylic nitriles that could be prepared from benzylic pivalates using our method.

---

Although optimistic towards using TMS-CN in our nickel-catalyzed cyanation reaction, we became aware of the challenges associated with this organic cyanide source. It was hypothesized that the limited reports of the use of TMS-CN in transition metal-catalyzed synthesis of aryl/alkyl nitriles was due to the high potential for catalyst poisoning when adding the cyanide reagent in one portion. In terms of our cyanation conditions, the use of basic additives, $\text{K}_3\text{PO}_4$ or $\text{Zn}_5(\text{CO}_3)_2(\text{OH})_6$, could cause TMS-CN to release the cyanide anion in solution. If TMS-CN is added in one portion, the large release of cyanide anions could displace the ligands on the metal catalyst, leading to catalyst poisoning prior to initiation of the catalytic cycle. A solution to this problem would be to control the release of cyanide anions in solution which can be accomplished through slow addition, an approach frequently used with acetone cyanohydrin. With this approach in mind, we proceeded to explore the use of TMS-CN as an alternative to Zn(CN)$_2$.

2.2 Results and Discussion

2.2.1 Early Optimization with TMS-CN

To begin the exploration into organic cyanide sources, TMS-CN was probed in the nickel-catalyzed cyanation of benzylic pivalates. As discussed in the previous chapter, Nicholas Michel found that substrate 1a gave the corresponding nitrile product in 94% yield with Zn(CN)$_2$. Therefore, 1a was chosen as the model substrate for optimization with TMS-CN. As demonstrated in Scheme 1.10, the previously optimized reaction conditions used with Zn(CN)$_2$ were considered a starting point into investigating the reactivity using TMS-CN (Table 2.1).
Table 2.1 Early optimization attempts with TMS-CN.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mol %)</th>
<th>Additive (mol %)</th>
<th>Solvent (M)</th>
<th>Temp. (°C)</th>
<th>Conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NiCl₂(dppf) (10)</td>
<td>K₃PO₄ (30)</td>
<td>DMF (0.1)</td>
<td>110</td>
<td>0%</td>
</tr>
<tr>
<td>2</td>
<td>NiCl₂(dppf) (10)</td>
<td>Zn₅(CO₃)₂(OH)₆ (15)</td>
<td>DMF (0.1)</td>
<td>110</td>
<td>0%</td>
</tr>
<tr>
<td>3ᵇ</td>
<td>NiCl₂(dppf) (10)</td>
<td>K₃PO₄ (30)</td>
<td>DMF (0.1)</td>
<td>110</td>
<td>0%</td>
</tr>
<tr>
<td>4</td>
<td>NiCl₂(dppf) (10)</td>
<td>K₃PO₄ (30)</td>
<td>DMF (0.1)</td>
<td>80</td>
<td>0%</td>
</tr>
<tr>
<td>5ᶜ</td>
<td>Ni(cod)₂ (20)</td>
<td>K₃PO₄ (30)</td>
<td>DMF (0.1)</td>
<td>110</td>
<td>0%</td>
</tr>
<tr>
<td>6</td>
<td>NiCl₂(dppf) (10)</td>
<td>K₃PO₄ (30)</td>
<td>DMF (1.0)</td>
<td>110</td>
<td>0%</td>
</tr>
<tr>
<td>7</td>
<td>NiCl₂(dppf) (10)</td>
<td>K₃PO₄ (30)</td>
<td>Toluene (1.0)</td>
<td>100</td>
<td>0%</td>
</tr>
</tbody>
</table>

*Yields determined by GC-MS using dodecane as an internal standard.
ᵇ10 mol % CsF.
ᶜRun in the absence of ZnEt₂.

Under the conditions previously developed by N. Michel but replacing Zn(CN)₂ with TMS-CN (Table 2.1, entries 1 and 2), the nitrile product was not observed. Therefore, each of the reaction parameters were altered to try to induce the formation of 2a. It was initially thought that TMS-CN may need an activator to release the cyanide anion but the addition of 10 mol % CsF did not yield the desired product (entry 3). Modifications to the nickel catalyst, temperature, solvent and concentration were examined but all reactions resulted in recovery of the starting material. A consistent result of 0% conversion of starting material suggested an inactive catalyst as it was expected that there would be some formation of the β-hydride elimination product if oxidative addition had taken place. It was hypothesized that the basic additives were triggering the immediate release of cyanide anions from TMS-CN, poisoning the catalyst and inhibiting oxidative addition. To overcome catalyst poisoning, TMS-CN was added in increments to control the amount of free cyanide anions present in solution.

### 2.2.2 Incremental Addition of TMS-CN

Incremental addition was carried out on a 0.2 mmol scale by diluting 4.0 equivalents of TMS-CN in 1 mL of DMF to give a concentration of 0.8 M. Arbitrarily, 0.1 mL of TMS-CN was
manually added every 30 minutes (Table 2.2) which equates to adding 0.08 mmol of TMS-CN with each addition.

Table 2.2 Initial results with the incremental addition of TMS-CN.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Changes to Above Reaction Conditions</th>
<th>Temp. (°C)</th>
<th>Incremental Addition of 0.08 mmol of TMS-CN</th>
<th>2a</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>110</td>
<td>30 min</td>
<td>24%</td>
<td>7%</td>
</tr>
<tr>
<td>2</td>
<td>None</td>
<td>110</td>
<td>1 hr</td>
<td>8%</td>
<td>34%</td>
</tr>
<tr>
<td>3</td>
<td>None</td>
<td>80</td>
<td>30 min</td>
<td>43%</td>
<td>8%</td>
</tr>
<tr>
<td>4</td>
<td>None</td>
<td>60</td>
<td>30 min</td>
<td>11%</td>
<td>3%</td>
</tr>
<tr>
<td>5</td>
<td>Toluene</td>
<td>80</td>
<td>30 min</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>6</td>
<td>MeCN</td>
<td>80</td>
<td>30 min</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>7</td>
<td>DMSO</td>
<td>80</td>
<td>30 min</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>8</td>
<td>DMA</td>
<td>80</td>
<td>30 min</td>
<td>4%</td>
<td>0%</td>
</tr>
</tbody>
</table>

*Yields determined by GC-MS using dodecane as an internal standard.

Once again, using the optimized conditions established by N. Michel for the reactions with Zn(CN)₂ as a starting point, TMS-CN was added in increments of 0.08 mmol every 30 min over a period of 5 hours and provided 24% yield of 2a (Table 2.2, entry 1). A slower addition of TMS-CN to 0.08 mmol every hour over a period of 10 hours appeared to be too slow of an addition as it favoured the formation of the β-hydride elimination product 3 over the nitrile product 2a (entry 2). Furthermore, lowering the temperature from 110 °C to 80 °C increased the yield of 2a to 43% (entry 1 vs 3). After lowering the temperature further, it was determined that 80 °C was the optimal temperature for this reaction (entries 1, 3, 4). As well, the use of either non-polar solvents or other polar aprotic solvents was detrimental to product formation (entries 5-8). From this point forward, focus was applied towards adjusting the frequency of incremental addition as well as the concentration of TMS-CN (Table 2.3) to further increase the yield of nitrile product above 43%.
Table 2.3 Optimization of the concentration and incremental addition of TMS-CN.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Incremental Addition of 0.08 mmol of TMS-CN</th>
<th>Concentration of TMS-CN (M)</th>
<th>2a</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30 min</td>
<td>0.8</td>
<td>43%</td>
<td>8%</td>
</tr>
<tr>
<td>2</td>
<td>30 min</td>
<td>1.0</td>
<td>25%</td>
<td>5%</td>
</tr>
<tr>
<td>3</td>
<td>1 hr</td>
<td>0.8</td>
<td>10%</td>
<td>20%</td>
</tr>
<tr>
<td>4</td>
<td>1 hr</td>
<td>1.0</td>
<td>15%</td>
<td>12%</td>
</tr>
</tbody>
</table>

*Yields determined by GC-MS using dodecane as an internal standard.

A few attempts revealed that neither increasing or decreasing the frequency of the incremental addition was beneficial (Table 2.3, entries 1 and 3) nor was increasing the concentration of the stock solution of TMS-CN used (entries 1 and 2). Therefore, the optimized addition conditions consisted of using 4.0 equivalents of TMS-CN in 1 mL DMF (0.8 M) and addition of the solution to the reaction in increments of 0.08 mmol every 30 minutes. Using these optimal addition conditions, further aspects of the reaction conditions were altered such as increasing the catalyst loading as well as altering the overall reaction concentration (Table 2.4).
Table 2.4 Final optimization attempts.

As shown in entry 2 (Table 2.4), doubling the catalyst loading of nickel increased the yield to 53%. The use of 20 mol % NiCl₂(dppf), along with dilution of the reaction mixture from 0.1 M to 0.04 M, caused a significant increase in nitrile formation to 82% and the product was isolated by silica gel column chromatography in 70% yield (entry 3). Diluting the reaction mixture further appeared to aid in preventing catalyst poisoning caused by the free cyanide released from TMS-CN. Finally, a syringe pump was used to add TMS-CN as opposed to manual addition but the slowest rate of addition for the syringe pump was 0.03 mL/min (entry 4). Using this rate of addition, the TMS-CN stock solution was added over 40 minutes (instead of over 5 hours as achieved by incremental addition) to give 9% of 2a, therefore the use of a syringe pump was not further explored. Thereby, the use of 20 mol % NiCl₂(dppf) in 0.04 M DMF became the newly optimized reaction conditions. With these conditions in hand, an initial investigation of the substrate scope was completed to determine if TMS-CN could overcome the limited substrate applicability that presented a large obstacle to α-arylnitrile synthesis when using Zn(CN)₂.

2.2.3 Substrate Scope

Table 2.5 below shows the substrates chosen to test the reaction conditions using TMS-CN. The yields of those are compared to the yields obtained with Zn(CN)₂. Although, TMS-CN provided a high yield of the secondary benzylic nitrile 2a, subjecting either a primary benzylic ester or a
secondary benzylic ester with an extended alkyl chain resulted in poor yields of the corresponding nitrile products, 2b and 2l respectively. This suggested that the incremental addition of TMS-CN may need to be optimized for each individual substrate to achieve high yields of the nitrile product which is undesirable as it limits the generality of the reaction.

Table 2.5 Substrate comparison with Zn(CN)$_2$ and TMS-CN.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nitrile Product</th>
<th>Zn(CN)$_2$</th>
<th>TMS-CN</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="2a" /></td>
<td>98%</td>
<td>82%</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="2b" /></td>
<td>90%</td>
<td>25%</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="2l" /></td>
<td>10%</td>
<td>0%</td>
</tr>
</tbody>
</table>

*aYields determined by GC-MS using dodecane as an internal standard.

As TMS-CN demonstrated more limited substrate scope than Zn(CN)$_2$, its use as an alternative cyanide source was discontinued and aminoacetonitriles were explored in the hopes of finding reaction conditions that would lead to broader substrate applicability.

2.2.4 Aminoacetonitriles

As demonstrated by Itami et al. in Scheme 2.4, aminoacetonitriles are a viable cyanide source in the nickel-catalyzed formation of aryl nitriles.$^{29}$ Their work showed that, amongst the aminoacetonitriles tested, morpholinoacetonitrile provided the desired product in the highest yield. Nevertheless, the four aminoacetonitriles investigated in their paper were tested as
cyanide sources with the model substrate 1a under the same reaction conditions previously developed by N. Michel for cyanation using Zn(CN)₂ (Table 2.6).

Table 2.6 Scope of aminoacetonitriles.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aminoacetonitrile</th>
<th>Conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Piperidinoacetonitrile (A1)</td>
<td>0%</td>
</tr>
<tr>
<td>2</td>
<td>Morpholinoacetonitrile (A2)</td>
<td>0%</td>
</tr>
<tr>
<td>3</td>
<td>Diisopropylaminoacetonitrile (A3)</td>
<td>0%</td>
</tr>
<tr>
<td>4</td>
<td>Diethylaminoacetonitrile (A4)</td>
<td>0%</td>
</tr>
</tbody>
</table>

Yields determined by GC-MS using dodecane as an internal standard.

Each of the four aminoacetonitriles were synthesized using bromoacetonitrile and the corresponding amine³⁶ and were tested under the previously optimized reaction conditions. All four of the aminoacetonitriles tested showed only starting material and no other by-products were observed. The consistent result of 0% conversion suggested that the aminoacetonitriles were potentially poisoning the nickel catalyst, as was hypothesized with the initial results using TMS-CN (Table 2.1). The slow addition of aminoacetonitriles could be a solution to avoiding catalyst poisoning but due to the impracticality of this method and the concern of aminoacetonitriles demonstrating limited substrate applicability, the use of aminoacetonitriles as an alternative cyanide source was discontinued.

2.3 Conclusion and Future Work

The use of acetone cyanohydrin, trimethylsilyl cyanide and aminoacetonitriles as alternatives to Zn(CN)₂ in our nickel-catalyzed cyanation of benzylic pivalates were each examined. After preliminary optimization studies on the use of TMS-CN, it quickly became apparent that the reagent led to catalyst inactivation if added in one portion. Therefore, an incremental addition of

³⁶ See experimental procedure in Chapter 5.
TMS-CN was employed to alleviate this problem. The frequency of addition and the overall reaction conditions were optimized but applying these conditions to other substrates did not lead to the formation of the corresponding nitrile products. We hypothesized that the incremental addition would need to be optimized for each individual substrate and as this would limit the generality of the reaction, the use of TMS-CN was discontinued.

Aminoacetonitriles were also unsuccessful for the formation of the α-arylnitrile product. Results suggested catalyst poisoning was occurring and although the slow addition of aminoacetonitriles was a possible solution, there was a concern for limited substrate applicability as previously demonstrated with TMS-CN.

The use of acetone cyanohydrin was initially disregarded as its boiling point is 95 °C and the optimized cyanation reactions with Zn(CN)$_2$ were performed at 110 °C. After discovering that TMS-CN was a more efficient cyanide source when the reaction temperature was lowered to 80 °C, future efforts should go into exploring optimizing the reaction conditions using acetone cyanohydrin as an alternative cyanide source.
Chapter 3

3 Cyanation of Benzylic Pivalates with Zn(CN)$_2$

3.1 Introduction

As discussed in Chapter 1, Nicholas Michel and Hyehwang Kim identified the optimal reaction conditions (Scheme 1.10) for the nickel-catalyzed cyanation of benzylic pivalates to synthesize the corresponding benzylic nitriles. Despite the initial substrate scope limitations, extensive efforts were made by the three of us to explore the substrate scope of other naphthyl derivatives in this reaction.

3.2 Results and Discussion

3.2.1 α-Arylnitrile Scope with Zn(CN)$_2$

The benzylic pivalate starting materials are generally synthesized by reduction of the aryl aldehyde or ketone followed by esterification of the free alcohol with trimethylacetyle chloride. The simplicity of the starting material synthesis allowed for the construction of several benzylic pivalate substrates that were subjected to the cyanation reaction. Scheme 3.1 below demonstrates the substrates that gave the highest yields of the corresponding nitrile product. All substrates were tested with both K$_3$PO$_4$ and Zn$_5$(CO$_3$)$_2$(OH)$_6$, and the additive that provided the highest yield of product was reported. Furthermore, to ensure reproducibility of the isolated yields, two trials were completed for each substrate and the average of the two yields was taken to be the final yield.
**Scheme 3.1 Substrate scope of α-arylnitriles.**

These reaction conditions allowed for the installation of a nitrile functional group at the benzylic position of naphthyl rings. They were also applicable to both benzofuran (2f) and thiophene (2g) heterocycles, although a higher catalyst loading was required to synthesize 2f in acceptable yield. Furthermore, the reaction allowed for benzylic cyanation when electron donating groups were present at C6 of the naphthyl ring (2d and 2e) but these were the only successful examples of substrates with substituents on the naphthyl ring. Furthermore, it is important to highlight the selectivity of this reaction as demonstrated by the formation of 2h. Since the arylnitrile product...
was not observed, this illustrates that oxidative addition occurs preferentially into the benzylic C(sp<sup>3</sup>)‒O bond over the C(sp<sup>2</sup>)‒O bond.<sup>37</sup>

Generally speaking, this reaction was restricted to substrates with an extended π–system, a trend that had been previously noted for other nickel-catalyzed C‒O activation at C(sp<sup>3</sup>)‒O bonds.<sup>20</sup>

To overcome the need for an extended π–system, it was hypothesized that altering the electronic properties of a phenyl ring could allow for oxidative addition to occur. Three α-aryl pivalates with either electron-donating or electron-withdrawing substituents (3a-3c) were synthesized via reduction of the corresponding aldehyde<sup>38</sup> and esterification with trimethylacetyl chloride (Scheme 3.2).<sup>39</sup> Subjecting 3a-3c to the cyanation reaction conditions resulted in <10% yield of the corresponding nitrile product for all three substrates. These results confirmed the need for the benzylic pivalates to have an extended π–system to form the nitrile product.

Scheme 3.2 Unsuccessful cyanation of phenyl derivatives.

The only substrate presented in the benzylic nitrile scope that is not a π–extended derivative is 1g which afforded the nitrile product 2g in 48% yield (average of two trials). Thiophene has a lower degree of aromaticity compared to a phenyl ring,<sup>40</sup> therefore, there could be less of an energetic penalty when aromaticity is broken during insertion into the C‒O bond allowing for the

---

formation of 2g despite the absence of an extended π-system. Based on this result, efforts were focused on the synthesis of a related pyrrole system. Scheme 3.3 illustrates the four-step synthesis towards two pyrrole substrates with different nitrogen protecting groups which were subjected to the cyanation reaction conditions.

Scheme 3.3 Synthesis of pyrrole derivatives.

Starting with pyrrole, Vilsmeier-Haack conditions were used to install an aldehyde at C2 of the pyrrole ring.\textsuperscript{41} Next, the free nitrogen atom was either Boc–protected or methylated to give intermediates 5a and 5b respectively.\textsuperscript{42,43} Both intermediates were subjected to reduction of the aldehyde by NaBH\textsubscript{4} followed by esterification of the primary alcohol with trimethylacetyl chloride\textsuperscript{38,39} to give pivalates 3d and 3e. Compound 3d was tested under the cyanation reaction conditions with both additives. Upon analysis of the \textsuperscript{1}H NMR spectrum of the crude reaction mixtures, removal of the Boc protecting group was observed, possibly due to the high reaction temperatures. This obstacle was eliminated with the use of the methylated pyrrole 3e, but this substrate resulted in the recovery of starting material under both sets of cyanation reaction conditions.

The results of using phenyl derivatives as well as pyrrole derivatives as substrates were all unsuccessful under the cyanation reaction conditions. This demonstrated how crucial the

\begin{thebibliography}{9}
\end{thebibliography}
presence of an extended π–system was to the success of this reaction. Therefore, research efforts were focused on synthesizing naphthyl derivatives with various substituents on the ring to further expand the substrate scope of benzylic nitriles.

### 3.2.2 Derivatization of 6-Bromo-2-naphthol

In an attempt to further broaden the substrate scope in our synthesis of α-arylnitriles, several starting materials were synthesized with different substituents on the naphthyl ring (Scheme 3.4). To explore the selectivity of the reaction, substrates 8a and 8b were synthesized to determine the selectivity of the reaction towards insertion into the C(sp^2)–O bond or the C(sp^3)–O bond. To further test the compatibility of the reaction, substrates 10a and 10b, bearing a TIPS–protected alcohol, were also prepared.

![Scheme 3.4 Synthesis of protected naphthyl derivatives from 6-bromo-2-naphthol.](image-url)

The synthesis began with 6-bromo-2-naphthol which when treated with 2.0 equivalents of n-butyl lithium, undergoes a lithium-halogen exchange. Upon the addition of either
dimethylformamide or dimethylacetamide, the corresponding aldehyde or methyl ketone was formed. Route 1 entailed the reduction of the carbonyl to give either the primary or secondary alcohol which underwent esterification of both the phenol and aliphatic alcohol to give substrates 8a and 8b. Route 2 required the TIPS protection of the hydroxyl group at C2, followed by reduction of the carbonyl to give the corresponding alcohol. In the last step, 9a and 9b underwent esterification to give substrates 10a and 10b. The four potential scope entries were subjected to the cyanation reaction conditions, the results of which are demonstrated in Scheme 3.5.

Scheme 3.5 Cyanation results of the protected naphthyl derivatives.

---

Subjecting the four substrates to the cyanation conditions A and B gave unexpected results as we anticipated that the presence of a protected alcohol substituent at a remote location would have minimal impact on the yield of the nitrile product. The use of Zn₅(CO₃)₂(OH)₆ with 8a gave the product 2h in an isolated yield of 40%, which was a significant decrease in yield when compared to the unsubstituted ring, 1b, that gave the nitrile product in 79% yield. Furthermore, it was observed that the yield only decreased further when K₃PO₄ was used as the additive. Despite the low yield of 2h, this substrate demonstrated the selectivity of the reaction for cyanation at the C(sp³)‒OPiv over the C(sp²)‒OPiv. The secondary substrate 8b under conditions B was unsuccessful in forming the nitrile product 2i while the use of K₃PO₄ only gave trace amounts of the nitrile product. A similar trend was observed for substrates 10a and 10b with the TIPS‒protected alcohol product. Product 2j was isolated in 37% yield with Zn₅(CO₃)₂(OH)₆ but no product was formed using K₃PO₄. The secondary substrate 10b resulted in recovery of the starting material under both sets of reaction conditions.

It was intriguing that derivation of the naphthyl ring with relatively inert substituents would have such a detrimental effect on product formation. We also wondered about the general functional group tolerance of this cyanation reaction. To further explore the effect of various functional groups, a robustness screen was performed on model substrate 1a to establish which functional groups were incompatible with the reaction.

3.2.3 Robustness Screen

Rather than undertake multi-step syntheses to prepare additional substrates, we were inspired by the concept of a robustness screen, a term coined by Prof. Frank Glorius. Table 3.1 illustrates an example of a robustness screen performed by the Glorius group for a Buchwald-Hartwig amination. By spiking the reaction with a series of additives, the authors gained insight into the functional group tolerance of the reaction. The purpose was to simulate the impact of a specific functional group present on the molecule and to determine if that functional group would react under the reaction conditions, inhibit reactivity all together or have no impact on the yield of

---

product. A conclusion was reached by comparing the product yield to that of the reaction without additive, along with the yield of additive remaining at the end of the reaction.

For simplicity, the data is assessed by colour coding, where red = <34%, yellow = 34-66% and green = >66%. If both the additive recovered and the product yield are in red, this would be evidence that the additive is reacting under the reaction conditions. The opposite, where both yields are green, indicates that the additive had no impact on the reaction. The last situation, where the product yield is red but most of the additive is recovered, implies that the additive is inhibiting catalysis and preventing product formation but is not being consumed in the reaction.

Table 3.1 Sample of Glorius' robustness screen.46

![Chemical Reaction Image]

<table>
<thead>
<tr>
<th>Additive (1.0 equiv)</th>
<th>Product</th>
<th>Additive remaining</th>
<th>SM remaining</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Image of Benzyl Acetate]</td>
<td>49%</td>
<td>60%</td>
<td>0%</td>
</tr>
<tr>
<td>![Image of Toluene]</td>
<td>75%</td>
<td>100%</td>
<td>0%</td>
</tr>
<tr>
<td>![Image of Benzylamine]</td>
<td>20%</td>
<td>95%</td>
<td>75%</td>
</tr>
</tbody>
</table>

*Yields determined by GC-MS using dodecane as an internal standard; green = >66%, yellow = 34-66%, red = <34%.

The reaction of 3-methoxyphenyl bromide and morpholine under standard Buchwald-Hartwig amination conditions gave the cross-coupled product in 89% yield. The robustness screen was conducted using the same reaction, but the reaction mixture was spiked with 1.0 equivalent of a chosen additive. The results in Table 3.1, taken from the Glorius publication46 demonstrated that an external alkene was well tolerated under the reaction conditions, but an arylnitrile functional group provides only 20% of the cross-coupled product while most of the additive was
recovered. This concludes that the nitrile functional group significantly interferes with the catalytic cycle without reacting itself.

This concept was applied to our nickel-catalyzed cyanation of benzylic pivalates. The robustness screen was performed using model substrate 1a and spiking the reaction with a series of selected additives. As a control reaction, with no additives present, 1a gave the nitrile product in 90% yield (K₃PO₄ conditions). Table 3.2 demonstrates the results of the additive screen under the cyanation reaction conditions.

**Table 3.2 Robustness screen for the synthesis of α-arylnitriles.**

\[
\begin{align*}
1a & \quad \text{OPiv} + \text{Zn(CN)}_2 \quad \text{(0.55 equiv)} \quad \text{NiCl}_2(\text{dppf}) \quad (10 \text{ mol } \%); \\
& \quad \text{K}_3\text{PO}_4 \quad (30 \text{ mol } \%); \\
& \quad \text{ZnE}l_2 \quad (15 \text{ mol } \%); \\
& \quad \text{DMF} \quad (0.1 \text{ M}), 110 \degree \text{C}, 16 \text{ h} \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>Additive (1.0 equiv)</th>
<th>Product</th>
<th>Additive remaining</th>
<th>SM remaining</th>
</tr>
</thead>
<tbody>
<tr>
<td>11a</td>
<td>Cl</td>
<td>0%</td>
<td>30%</td>
</tr>
<tr>
<td>11b</td>
<td>OPiv</td>
<td>46%</td>
<td>47%</td>
</tr>
<tr>
<td>11c</td>
<td>OTIPS</td>
<td>58%</td>
<td>41%</td>
</tr>
<tr>
<td>11d</td>
<td>OAc</td>
<td>38%</td>
<td>46%</td>
</tr>
</tbody>
</table>

*a* Isolated yields; green = >66%, yellow = 34-66%, red = <34%.

The addition of 2-chloronaphthalene resulted in 0% of 2a, and almost complete recovery of the starting material. Interestingly, 72% of 2-naphthalencarbonitrile was isolated suggesting that
oxidative addition into the C–Cl bond is faster than into the C–O bond. This indicates that a chlorine substituent on the naphthyl ring would not be tolerated under these reaction conditions.

In an attempt to explain why substrates having protected alcohols on the naphthyl ring demonstrated such poor reactivity, three protected naphthol derivatives, –OPiv (11b), –OTIPS (11c) and –OAc (11d) were synthesized. All three additives showed a similar impact on product formation, reducing the yield of product by 30-50%, yet most of the additive was recovered. These experiments suggest that the additives are inhibiting catalysis although the mechanism of inhibition is unclear at this point.

3.3 Conclusion and Future Work

In conclusion, Nicholas Michel, Hyehwang Kim and I were able to construct a scope of eight benzylic nitriles. Efforts were put forth to expand the substrate scope to include phenyl derivatives and heterocycles, but all resulted in trace amounts of the corresponding nitrile product. Acknowledging the need for an extended π–system to be present in the benzylic pivalates, other naphthyl derivatives were synthesized containing either a pivalate or a TIPS–protected alcohol substituent at C2 of the naphthyl ring. Subjecting the substrates to the cyanation reaction conditions resulted in poor yields of the nitrile products but we were able to demonstrate that oxidative addition occurs preferentially into the benzylic C(sp³)–O bond over the C(sp²)–OPiv bond.

To understand the poor reactivity with substrates containing relatively inert substituents, a robustness screen was performed. The results mirrored those obtained in the reaction scope where the yield of the nitrile product was reduced by half in the presence of a protected alcohol. This led to the conclusion that a protected alcohol functional group inhibits catalysis.

Future research could be dedicated towards a more in-depth exploration as to the functional group tolerance of the reaction as well as conducting mechanistic studies to explain the need for the extended π–system for the nickel catalyst to undergo oxidative addition into the benzylic C–O bond.
Chapter 4

4 Cyanation of Allylic Pivalates with Zn(CN)$_2$

4.1 Introduction

As previously observed, our nickel-catalyzed cyanation reaction is generally restricted to substrates possessing an extended π–system, therefore we were interested in exploring allylic pivalates as a potential class of substrates. Insertion into allylic C–O bonds with palladium catalysts is known as the Tsuji-Trost reaction.$^{47}$ This reaction has been expanded to include electrophiles such as esters, carbonates and alcohols with both carbon and heteroatom nucleophiles and can be accomplished asymmetrically (Scheme 4.1).$^{48,49}$ More importantly, by using TMS-CN as the nucleophile, the Tsuji-Trost reaction has been used to synthesize enantioenriched allylic nitriles from allylic acetates and carbonates.$^{50}$

\[
\begin{align*}
R\equiv\overset{\text{Pc Catalyst}}{\text{Nu-H}} & \rightarrow R\equiv\overset{\text{Nu}}{\text{Nu}} \\
X &= \text{OH, OAc, OCO}_2\text{Me}
\end{align*}
\]

Scheme 4.1 General reaction scheme of a Tsuji-Trost reaction.

Nickel-catalyzed cross-coupling with allylic C–O electrophiles has been previously established and is also known to occur stereospecifically.$^{51}$ Of particular interest to us was the report by Watson et al. on the enantiospecific nickel-catalyzed Suzuki cross-coupling of allylic pivalates.


with arylboroxines (Scheme 4.2).\textsuperscript{52} Taking advantage of readily prepared enantioenriched secondary allylic alcohol derivatives, the cross-coupled products are obtained with both high stereospecificity and regioselectivity. This chemistry has also been extended to the borylation of allylic pivalates where the retention or inversion of stereochemistry is controlled by the choice of solvent.\textsuperscript{53}

\begin{center}
\begin{tikzpicture}
  ...reaction conditions established NiCl\textsubscript{2} as the optimal nickel catalyst...\end{tikzpicture}
\end{center}

\textbf{Scheme 4.2 Nickel-catalyzed Suzuki cross-coupling of allylic pivalates.}

To the best of my knowledge, there are no reports of nickel-catalyzed cyanation of allylic electrophiles and we hypothesized that allylic pivalates may be suitable substrates in our cyanation reaction. Nicholas Michel tested allylic pivalate 12a under the cyanation reaction conditions and the corresponding nitrile product 13a was formed (Scheme 4.3). Using 12a to re-examine the reaction conditions, it was found that a combination of NiCl\textsubscript{2}(DME) with dppb as the external ligand enabled the room temperature cyanation of allylic pivalates. Using these milder optimized reaction conditions, Nicholas Michel and I explored the substrate scope.

\section*{4.2 Results and Discussion}

\subsection*{4.2.1 Scope of Allylic Nitriles}

Re-examination of the reaction conditions established NiCl\textsubscript{2}(DME) as the optimal nickel catalyst but this catalyst has a disadvantage of being more sensitive to moisture than NiCl\textsubscript{2}(dppf). The increased sensitivity of the nickel catalyst initially caused reproducibility issues due to our inability to control the humidity in the lab. After much trial and error, we found that submerging the reaction vial into an oil bath set at 23 °C, along with sealing the septum with vacuum grease,

\begin{thebibliography}{99}
\end{thebibliography}
helped to prevent moisture from the environment from deactivating the catalyst. This alteration in the reaction set-up allowed for each scope entry to be represented as the isolated yields of two trials and the average of the two were taken to be the final yields (Scheme 4.3).

Scheme 4.3 Substrate scope for the synthesis of allylic nitriles.

Subjecting either an α-aryl allylic pivalate (branched) or a γ-aryl allylic pivalate (linear) to the cyanation reaction conditions generates the linear nitrile product. This is further illustrated with

*Isolated yields obtained by Nicholas Michel.
substrates 12c and 12c’, as both give the γ–allylic nitrile product 13c in similar yields. This observation was also reported by Watson et al. in their Suzuki cross-coupling of allylic pivalates (Scheme 4.2) and they propose the occurrence is due to the formation of a π–allylnickel intermediate.\textsuperscript{52} With substrates 12a and 12b, competitive β-hydride elimination is a challenge, but both afforded the corresponding nitrile products in moderate yields. Additionally, substituents at the para position were well tolerated including alkyl groups (13d, 13e), a methoxy group (12f) and a fluoro group (12i). Surprisingly, chloro-substituted derivative 12j, gave 51% yield of the nitrile product 13j with no indication of oxidative addition into the C‒Cl bond. Performing the reaction at room temperature may have prevented the formation of the arylnitrile product, giving preference for the formation of the allylic nitrile product. Similar to the results using benzylic pivalate 8a, substrate 12g demonstrated high selectivity for oxidative addition into the C(sp\textsuperscript{3})‒OPiv bond over the C(sp\textsuperscript{2})‒OPiv bond as the arylnitrile product was not observed. Furthermore, as the yield of 13g was higher than the yield of 12a, the pivalate protected alcohol substituent does not reduce reactivity as previously demonstrated with the benzylic substrates. Overall, the scope of allylic nitriles demonstrates increased diversity in comparison to the scope of benzylic nitriles, this could be due to the increased ease of oxidative addition into an allylic C‒O bond than a benzylic C‒O bond.\textsuperscript{21}

4.2.2 Robustness Screen

To further understand the difference in functional group tolerance in the cyanation of benzylic and allylic pivalates, a robustness screen (Table 4.1) was performed with the same four additives that were previously used in Table 3.2. Using 12a as the model substrate under the cyanation reaction conditions without any additives, the corresponding nitrile product was isolated in 54% yield. Due to the lower yield of the nitrile product obtained from the model substrate, the colour coding used by Glorius was adjusted to more accurately represent the yield of product, while the original colour coding established by Glorius was used to represent the yield of additive recovered.\textsuperscript{46}
Table 4.1 Robustness screen for the synthesis of allylic nitriles.\textsuperscript{a,b}

\[ \text{OPiv} \quad + \quad \text{Zn(CN)}_2 \quad \text{(0.8 equiv)} \quad \xrightarrow{\text{NiCl}_2(\text{DME}) (10 \text{ mol \%}), \text{dppf (20 mol \%)}, \text{K}_3\text{PO}_4 (30 \text{ mol \%)}, \text{ZnEt}_2 (15 \text{ mol \%})} \quad \text{DMF (0.1 M)} \quad 23 \degree \text{C, 16 h}} \]

\begin{tabular}{|c|c|c|c|}
\hline
Additive & Product & Additive remaining & SM remaining \\
(1.0 equiv) & & & \\
\hline
11a & 53\% & 52\%\textsuperscript{c} & 30\% \\
11b & 28\% & 95\% & 57\% \\
11c & 38\% & 73\% & 37\% \\
11d & 46\% & 90\% & 32\% \\
\hline
\end{tabular}

\textsuperscript{a}Isolated yield of product; green = >33\%, yellow = 17-33\%, red = <17\%.
\textsuperscript{b}Isolated yield of additive; green = >66\%, yellow = 34-66\%, red = <34\%.
\textsuperscript{c}5\% of 2-naphthalenecarbonitrile was isolated.

Spiking the reaction with 2-chloronaphthalene (1.0 equiv) had no impact on product formation. In this case, only 5\% of 2-naphthalenecarbonitrile was isolated, although the mass balance for the remaining additive cannot be accounted for. This result does not reflect the isolation of 72\% of 2-naphthalenecarbonitrile in the robustness screen with 1a (Table 3.2). The reasoning behind this observation could be that the allylic C–O bond undergoes oxidative addition more readily than the benzylic C–O bond.\textsuperscript{21} Furthermore, the addition of protected napthalols (11b – 11d) into the reaction mixture did not lead to the dramatic decrease in yield of nitrile product that was initially observed with 1a, and most of the additive was recovered in each case.
4.3 Conclusion and Future Work

In conclusion, despite the limited substrate scope of naphthyl derivatives that can be prepared using our nickel-catalyzed cyanation reaction, the reaction conditions were found to also be applicable to diverse allylic pivalates. A robustness screen demonstrated that product formation is not inhibited by chlorine substituents or protected alcohols. We believe that the increased ease of oxidative addition into an allylic C–O bond over a benzylic C–O bond allowed for the higher functional group tolerance observed with allylic pivalates.

Further work completed by Nicholas Michel demonstrated that this reaction occurs with a high degree of stereospecificity. By synthesizing enantioenriched 12a in 99% ee and subjecting it to the cyanation reaction conditions, albeit with the use of KHCO₃ instead of K₃PO₄, the enantioenriched nitrile product was obtained in 87% ee (Scheme 4.4a). Unfortunately, using enantioenriched 1a under the cyanation reaction conditions led to complete racemization of the nitrile product (Scheme 4.4b).

![Scheme 4.4](image_url)

Scheme 4.4 Enantiospecificity of our nickel-catalyzed cyanation reactions: a) cyanation of enantioenriched allylic pivalate 12a and b) cyanation of enantioenriched benzylic pivalate 1a.
The future direction of this project will go into extending the applicability of alkyl C–O activation towards nucleophiles, such as amines. It would also be advantageous to expand the C–O electrophiles to other esters and ethers. Additionally, further studies will need to be conducted to be able to accomplish nickel-catalyzed alkyl C–O activation on substrates without an extended π–system to maximize the synthetic utility of this unique property of nickel.
Chapter 5

5 Experimental Procedure

5.1 Methods

Unless otherwise noted, all reactions were set up on benchtop and run under an atmosphere of argon or nitrogen using flame-dried glassware and anhydrous solvents. Anhydrous solvents were purchased from Sigma–Aldrich in Sure/Seal bottles and were used as received. Dimethylformamide (extra-dry, over molecular sieves, Acros Organics) was degassed by sonicating under vacuum for 2 minutes before use. Diethylzinc was purchased from Sigma–Aldrich as a 1.0 M solution in hexanes and was titrated according to Knochel’s protocol.\textsuperscript{54} Potassium phosphate was dried under vacuum at 150 °C for 12 hours and stored in a desiccator before use. All other commercial reagents were used as received. Cyanation reactions were performed in 8-mL Fisherbrand threaded tubes (manufacturer no. FB7377013100; Fisher catalog no. 14-957-76A) whose ends were sealed with size-19 rubber septa and electrical tape. All heated reactions were done in a temperature-controlled oil bath. Compounds were purified by flash column chromatography using SiliCycle SilicaFlash P60. Analytical thin layer chromatography was done on aluminum plates precoated with 60 Å F\textsubscript{254} silica gel and visualization of the TLC plates was completed using either UV light (254 nm) or potassium permanganate followed by heating.

\textsuperscript{1}H and \textsuperscript{13}C NMR spectra were recorded on Varian MercuryPlus 400 MHz or Bruker AvanceIII 400 MHz spectrometers at ambient temperature. Spectra were internally referenced to the residual solvent signal (CDCl\textsubscript{3} = 7.26 ppm, DMSO-\textsubscript{d}\textsubscript{6} = 2.50 ppm for \textsuperscript{1}H NMR and CDCl\textsubscript{3} = 77.16 ppm, DMSO-\textsubscript{d}\textsubscript{6} = 39.5 ppm for \textsuperscript{13}C NMR). Data for \textsuperscript{1}H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, p = pentet, m = multiplet, br = broad), coupling constants in Hz and integration. IR spectra were obtained on a Perkin-Elmer Spectrum 100 instrument equipped with a single-bounce diamond/ZnSe ATR accessory as solids or thin films. High-resolution mass spectra (HRMS) were recorded on a JEOL AccuTOF JMS-T1000LV mass spectrometer equipped with a Direct Analysis in Real Time (DART) ion source.

\textsuperscript{54} Krasovskiy, A.; Knochel, P. Synthesis (Stuttg) 2006, 5, 890-891.
5.2 General Procedure

General procedure A for the synthesis of benzylic and allylic alcohols

This procedure was adapted from a literature protocol.\textsuperscript{55}

Ketone or aldehyde (1.0 equiv) was added to a roundbottom flask and dissolved in anhydrous MeOH (0.70 M) and the solution was cooled to 0 °C. To the solution, sodium borohydride (0.50 equiv) was added portionwise and the mixture was left to stir at 0 °C for 5 minutes then warmed to room temperature and left to stir for 16 hours. The crude reaction mixture was dissolved in EtOAc and washed with water, NaHCO\textsubscript{3}, and brine then dried with MgSO\textsubscript{4}, filtered and concentrated under reduced pressure to afford the corresponding alcohol. Unless otherwise noted, the crude alcohol was of sufficient purity for use in the next step.

General procedure B for the synthesis of benzylic and allylic pivalates

This procedure was adapted from a literature protocol.\textsuperscript{56}

The alcohol (1.0 equiv) was added to a roundbottom flask and dissolved in anhydrous CH\textsubscript{2}Cl\textsubscript{2} (0.60 M). 4-Dimethylaminopyridine (0.10 equiv), triethylamine (1.2 equiv) and trimethylacetyl chloride (1.2 equiv) were added sequentially and the mixture was left to stir at room temperature for 16 hours. The crude reaction mixture was washed with NaHCO\textsubscript{3} and brine then dried with MgSO\textsubscript{4}, filtered and concentrated under reduced pressure. The product was purified by silica gel column chromatography.

General procedure C for the synthesis of aminoacetonitriles

This procedure was adapted from a literature protocol.\textsuperscript{57}

The amine (1.00 equiv) was dissolved in anhydrous MeCN (5.0 mL, 3.0 M) and the flask was cooled to 0 °C. Bromoacetonitrile (0.35 mL, 5.0 mmol, 0.33 equiv) was added dropwise and the flask was warmed to room temperature and left to stir for 16 hours. The reaction was quenched with NaHCO\textsubscript{3} and left to stir for 30 minutes. The crude reaction mixture was filtered over a pad of Celite and extracted with CH\textsubscript{2}Cl\textsubscript{2}, washed with brine, dried over Na\textsubscript{2}SO\textsubscript{4}, filtered and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography to afford the pure compound.


General procedure D for the synthesis of benzylic nitriles

An 8 mL vial charged with a small stir bar was flame dried under vacuum. When cooled, α-aryl pivalate (0.20 mmol, 1.0 equiv), NiCl$_2$(dppf) (0.014 g, 0.020 mmol, 0.10 equiv), Zn(CN)$_2$ (0.013 g, 0.11 mmol, 0.55 equiv) and either K$_3$PO$_4$ (0.013 g, 0.060 mmol, 0.30 equiv) or Zn$_5$(CO$_3$)$_2$(OH)$_6$ (0.017 g, 0.030 mmol, 0.15 equiv) were added under an argon atmosphere. The vial was evacuated and put under a nitrogen atmosphere three times, then purged with argon. To a flame dried 25 mL roundbottom flask, dry DMF (5.0 mL) was added and the solvent was degassed by bubbling with nitrogen gas and sonicated under vacuum, twice. DMF (2.0 mL, 0.10 M) was added to the vial under argon followed by ZnEt$_2$ (1.0 M solution in hexanes, 0.030 mL, 0.030 mmol, 0.15 equiv) and the vial was placed in an oil bath at 110 °C for 16 hours. The reaction mixture was cooled to room temperature, filtered over silica and Celite and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography to afford the corresponding benzylic nitrile.

General procedure E for the synthesis of allylic nitriles

An 8 mL vial charged with a small stir bar was flame dried under vacuum. When cooled, allylic pivalate (0.20 mmol, 1.0 equiv), NiCl$_2$(DME) (0.0040 g, 0.020 mmol, 0.10 equiv), dppb (0.017 g, 0.040 mmol, 0.20 equiv), Zn(CN)$_2$ (0.019 g, 0.16 mmol, 0.80 equiv) and K$_3$PO$_4$ (0.013 g, 0.060 mmol, 0.30 equiv) were added under an argon atmosphere. The vial was evacuated and put under a nitrogen atmosphere three times then purged with argon. To a flame dried 25 mL roundbottom flask, dry DMF (5.0 mL) was added and the solvent was degassed by bubbling with nitrogen gas and sonicated under vacuum, twice. DMF (2.0 mL, 0.10 M) was added to the vial under argon followed by ZnEt$_2$ (1.0 M solution in hexanes, 0.030 mL, 0.030 mmol, 0.15 equiv) and the vial was placed in an oil bath at 23 °C for 16 hours. The reaction mixture was cooled to room temperature, filtered over silica and Celite and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography to afford the corresponding allylic nitrile.
General procedure for the robustness screen with benzylic nitriles

An 8 mL vial charged with a small stir bar was flame dried under vacuum. When cooled, benzylic pivalate 1a (0.051 g, 0.20 mmol, 1.0 equiv), additive (0.20 mmol, 1.0 equiv), NiCl₂(dppf) (0.014 g, 0.020 mmol, 0.10 equiv), Zn(CN)₂ (0.013 g, 0.11 mmol, 0.55 equiv) and K₃PO₄ (0.013 g, 0.060 mmol, 0.30 equiv) were added under an argon atmosphere. The vial was evacuated and put under a nitrogen atmosphere three times, then purged with argon. To a flame dried 25 mL roundbottom flask, dry DMF (5.0 mL) was added and the solvent was degassed by bubbling with nitrogen gas and sonicated under vacuum, twice. DMF (2.0 mL, 0.10 M) was added to the vial under argon followed by ZnEt₂ (1.0 M solution in hexanes, 0.030 mL, 0.030 mmol, 0.15 equiv) and the vial was placed in an oil bath at 110 °C for 16 hours. The reaction mixture was cooled to room temperature, filtered over silica and Celite and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography using a gradient of 0-10% EtOAc/hexanes to isolate remaining 1a, the nitrile product 2a and the remaining additive.

General procedure for the robustness screen with allylic nitriles

An 8 mL vial charged with a small stir bar was flame dried under vacuum. When cooled, allylic pivalate 12a (0.046 g, 0.20 mmol, 1.0 equiv), additive (0.2 mmol, 1.0 equiv), NiCl₂(DME) (0.0040 g, 0.020 mmol, 0.10 equiv), dppb (0.017 g, 0.040 mmol, 0.20 equiv), Zn(CN)₂ (0.019 g, 0.16 mmol, 0.80 equiv) and K₃PO₄ (0.013 g, 0.060 mmol, 0.30 equiv) were added under an argon atmosphere. The vial was evacuated and put under a nitrogen atmosphere three times then purged with argon. To a flame dried 25 mL roundbottom flask, dry DMF (5.0 mL) was added and the solvent was degassed by bubbling with nitrogen gas and sonicated under vacuum, twice. DMF (2.0 mL, 0.10 M) was added to the vial under argon followed by ZnEt₂ (1.0 M solution in hexanes, 0.030 mL, 0.030 mmol, 0.15 equiv) and the vial was placed in an oil bath at 23 °C for 16 hours. The reaction mixture was cooled to room temperature, filtered over silica and Celite and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography using a gradient of 0-10% EtOAc/hexanes to isolate remaining 12a, the nitrile product 13a and the remaining additive.
5.3 Specific Procedure

Synthesis of benzylic pivalates:

Synthesized according to general procedure A using 2-acetonaphthone (2.55 g, 15.0 mmol, 1.00 equiv) and sodium borohydride (0.280 g, 7.50 mmol, 0.500 equiv) followed by general procedure B, using the crude alcohol (2.40 g, 14.0 mmol, 1.00 equiv), 4-dimethylaminopyridine (0.100 g, 1.00 mmol, 0.100 equiv), triethylamine (2.30 mL, 17.0 mmol, 1.20 equiv) and trimethylacetyl chloride (2.10 mL, 17.0 mmol, 1.20 equiv). The crude reaction mixture was purified by silica gel column chromatography using 10% EtOAc/hexanes to afford the pure compound as a white powder (2.27 g, 63% over two steps). $^1$H NMR (400 MHz, CDCl$_3$, 298 K) $\delta$ = 7.85-7.77 (m, 4H), 7.51-7.41 (m, 3H), 6.02 (q, $J$ = 6.6 Hz, 1H), 1.60 (d, $J$ = 6.6 Hz, 3H), 1.23 (s, 9H) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$, 298 K) $\delta$ = 178.0, 140.0, 133.2, 133.0, 128.3, 128.0, 127.7, 126.2, 126.0, 124.7, 124.0, 72.1, 38.8, 27.2, 22.3 ppm.

Experimental spectra match a literature report.$^{58}$

Synthesized according to general procedure A using 2-naphthaldehyde (4.68 g, 30.0 mmol, 1.00 equiv) and sodium borohydride (0.570 g, 15.0 mmol, 0.500 equiv) followed by general procedure B, using the crude alcohol (1.00 g, 6.30 mmol, 1.00 equiv), 4-dimethylaminopyridine (0.080 g, 0.63 mmol, 0.10 equiv), triethylamine (1.10 mL, 7.60 mmol, 1.20 equiv) and trimethylacetyl chloride (0.91 mL, 7.6 mmol, 1.2 equiv). The crude mixture was purified by silica gel column chromatography using 10% EtOAc/hexanes to afford the pure compound as a white powder (0.48 g, 32% over two steps). $^1$H NMR (400 MHz, CDCl$_3$, 298 K) $\delta$ = 7.87-7.82 (m, 4H), 7.54-7.45 (m, 3H), 5.29 (s, 2H), 1.28 (s, 9H) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$, 298 K) $\delta$ = 178.3, 133.9, 133.2, 133.0, 128.3, 128.0, 127.7, 126.8, 126.2, 126.0, 124.1, 125.6, 66.2, 38.9, 27.2 ppm.

Experimental spectra match a literature report.$^{59}$

---


Synthesized according to general procedure A, using 4-methoxybenzaldehyde (1.82 mL, 15.0 mmol, 1.00 equiv) and sodium borohydride (0.280 g, 7.50 mmol, 0.500 equiv) followed by general procedure B, using the crude alcohol (0.62 mL, 5.0 mmol, 1.0 equiv), triethylamine (0.84 mL, 6.0 mmol, 1.2 equiv), 4-dimethylaminopyridine (0.0600 g, 0.500 mmol, 0.100 equiv) and trimethylacetyl chloride (0.74 mL, 6.0 mmol, 1.2 equiv). The crude mixture was purified by silica gel column chromatography using 10% EtOAc/hexanes to afford the pure compound as a clear oil (0.43 g, 55% yield over two steps).  

\[ ^1H \text{NMR} (400 \text{ MHz, CDCl}_3, 298 K) \delta = 7.29-7.25 (m, 2H), 6.91-6.87 (m, 2H), 5.04 (s, 2H), 3.81 (s, 3H), 1.20 (s, 9H) \text{ ppm.} \]

\[ ^{13}C \text{NMR} (101 \text{ MHz, CDCl}_3, 298 K) \delta = 178.4, 159.4, 129.5, 128.6, 113.9, 65.9, 55.3, 38.8, 27.2 \text{ ppm.} \]

Experimental spectra match a literature report.\(^\text{60}\)

\[ \text{3a} \]

\[ \text{MeO} \]

\[ \text{OPiv} \]

Synthesized according to general procedure A, using 2,4-dimethoxybenzaldehyde (2.49 g, 15.0 mmol, 1.00 equiv) and sodium borohydride (0.280 g, 7.50 mmol, 0.500 equiv) followed by general procedure B, using the crude alcohol (1.29 mL, 8.90 mmol, 1.00 equiv), triethylamine (1.49 mL, 10.7 mmol, 1.20 equiv), 4-dimethylaminopyridine (0.120 g, 0.890 mmol, 0.100 equiv) and trimethylacetyl chloride (1.32 mL, 10.7 mmol, 1.20 equiv). The crude mixture was purified by silica gel column chromatography using 10% EtOAc/hexanes to afford the pure compound as a clear oil (1.23 g, 58% yield over two steps).  

\[ ^1H \text{NMR} (400 \text{ MHz, CDCl}_3, 298 K) \delta = 7.23-7.19 (m, 1H), 6.48-6.44 (m, 2H), 5.07 (s, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 1.20 (s, 9H) \text{ ppm.} \]

\[ ^{13}C \text{NMR} (101 \text{ MHz, CDCl}_3, 298 K) \delta = 178.5, 160.9, 158.8, 130.4, 117.4, 103.9, 98.5, 61.6, 55.4, 55.4, 38.8, 27.2 \text{ ppm.} \]

\[ \text{3b} \]

\[ \text{MeO} \]

\[ \text{OPiv} \]

\[ \text{OMe} \]


\[ \text{60 Quasdorf, K.; Tian, X.; Garg, N. J. Am. Chem. Soc. 2008, 130, 14422-14423.} \]
Synthesized according to general procedure A, using 2-(trifluoromethyl)benzaldehyde (2.05 mL, 15.0 mmol, 1.00 equiv) and sodium borohydride (0.280 g, 7.50 mmol, 0.500 equiv) followed by general procedure B, using the crude alcohol (1.50 g, 8.50 mmol, 1.00 equiv), triethylamine (1.42 mL, 10.2 mmol, 1.20 equiv), 4-dimethylaminopyridine (0.100 g, 0.850 mmol, 0.100 equiv) and trimethylacetyl chloride (1.26 mL, 10.2 mmol, 1.20 equiv). The crude mixture was purified by silica gel column chromatography using 10% EtOAc/hexanes to afford the pure compound as a clear oil (1.08 g, 53% yield over two steps).  

$^{1}$H NMR (400 MHz, CDCl$_3$, 298 K) $\delta =$ 7.66-7.62 (m, 1H), 7.56-7.48 (m, 2H), 7.42-7.37 (m, 1H), 5.24 (s, 2H), 1.20 (s, 9H) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$, 298 K) $\delta =$ 178.0, 134.7 (q, $J = 1.4$ Hz), 132.0, 129.6, 128.2 (q, $J = 30.9$ Hz), 128.1, 126.2 (q, $J = 5.6$ Hz), 122.8 (q, $J = 273.9$ Hz), 62.7, 38.9, 27.2 ppm.

Experimental spectra match a literature report.  

This compound was prepared according to a literature procedure.  

Dichloroethane (45 mL, 0.30 M) was added to a 250 mL roundbottom flask, and the flask was purged with argon. Added sequentially were phosphoryl chloride (1.40 mL, 15.0 mmol, 1.00 equiv), dimethylformamide (1.20 mL, 15.0 mmol, 1.00 equiv) and pyrrole (1.00 mL, 15.0 mmol, 1.00 equiv) and the reaction was left to stir for 16 hours at 60 °C. The reaction was quenched with NaHCO$_3$ and extracted with EtOAc, washed with brine, dried with MgSO$_4$, filtered and concentrated under reduced pressure. The crude reaction mixture was purified by silica gel column chromatography using 50% hexanes/EtOAc to afford a yellow solid (0.77 g, 54% yield).  

$^{1}$H NMR (400 MHz, CDCl$_3$, 298 K) $\delta =$ 9.53 (s, 1H), 7.16-7.13 (m, 1H), 7.01-6.98 (m, 1H), 6.37-6.34 (m, 1H) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$, 298 K) $\delta =$ 179.4, 132.9, 126.5, 121.4, 111.4 ppm.

Experimental spectra match a literature report.  

This compound was prepared according to a literature protocol. In a 250 mL roundbottom flask, sodium hydride (0.370 g, 11.2 mmol, 1.20 equiv) was suspended in 56 mL THF under an argon atmosphere. Pyrrole 4 (0.880 g, 9.30 mmol, 1.00 equiv) was dissolved in 9.0 mL THF and added over a period of 10 minutes to the stirring suspension at room temperature. After 1 hour, di-tert-butyl dicarbonate (2.20 g, 10.0 mmol, 1.10 equiv) was added and the reaction was left to stir for 13 hours at room temperature. The reaction was quenched with NH₄Cl, diluted with water, extracted with Et₂O, washed with brine, dried with Na₂SO₄, filtered and concentrated under reduced pressure. The crude reaction mixture was purified by silica gel column chromatography using 30% EtOAc/hexanes to afford an orange oil (1.66 g, 91% yield). ¹H NMR (400 MHz, CDCl₃, 298 K) δ = 10.28 (s, 1H), 7.44 (dd, J = 3.1, 1.8 Hz, 1H), 7.18 (dd, J = 3.7, 1.8 Hz, 1H), 6.29-6.26 (m, 1H), 1.64 (s, 9H) ppm. ¹³C NMR (101 MHz, CDCl₃, 298 K) δ = 182.3, 148.4, 134.8, 127.3, 121.2, 111.7, 85.8, 28.0 ppm.

Experimental spectra match a literature report.⁶³

Synthesized according to general procedure A, using 5a (1.66 g, 8.50 mmol, 1.00 equiv) and sodium borohydride (0.160 g, 4.30 mmol, 0.500 equiv) followed by general procedure B, using the crude alcohol (0.950 g, 4.80 mmol, 1.00 equiv), triethylamine (0.73 mL, 5.8 mmol, 1.2 equiv), 4-dimethylaminopyridine (0.0600 g, 0.480 mmol, 0.100 equiv) and trimethylacetyl chloride (0.71 mL, 5.8 mmol, 1.2 equiv). The crude mixture was purified by silica gel column chromatography using 30% EtOAc/hexanes to afford the pure compound as a clear oil (0.50 g, 47% yield over 2 steps). ¹H NMR (400 MHz, CDCl₃, 298 K) δ = 7.28 (dd, J = 3.4, 1.8 Hz, 1H), 6.27-6.24 (m, 1H), 6.13 (t, J = 3.3 Hz, 1H), 5.25 (d, J = 0.8 Hz, 2H), 1.59 (s, 9H), 1.21 (s, 9H) ppm. ¹³C NMR (101 MHz, CDCl₃, 298 K) δ = 178.1, 148.4, 129.3, 122.5, 114.7, 110.1, 84.0, 59.8, 38.8, 28.0, 27.2 ppm.

This compound was prepared according to a literature protocol. To a 500 mL roundbottom flask, 4 (1.46 g, 15.4 mmol, 1.00 equiv), K$_3$PO$_4$ (3.27 g, 15.4 mmol, 1.00 equiv) and DMF (154 mL, 0.100 M) were added and stirred at room temperature for 15 minutes then iodomethane (1.92 mL, 30.8 mmol, 2.00 equiv) was added dropwise. The reaction was left to stir at room temperature for another 8 hours. The mixture was quenched with water and extracted with EtOAc, dried with MgSO$_4$ and concentrated under reduced pressure to afford a clear oil (0.58 g, 35% yield). $^1$H NMR (400 MHz, CDCl$_3$, 298 K) $\delta$ = 9.52 (s, 1H), 6.91 (dd, $J$ = 4.0, 1.7 Hz, 1H), 6.88-6.86 (m, 1H), 6.21 (dd, $J$ = 4.0, 2.4 Hz, 1H), 3.93 (s, 3H) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$, 298 K) $\delta$ = 179.6, 132.0, 124.1, 109.5, 36.5 ppm. Experimental spectra match a literature report.

Synthesized according to general procedure A, using 5b (0.58 g, 5.3 mmol, 1.0 equiv) and sodium borohydride (0.10 g, 2.7 mmol, 0.50 equiv) followed by general procedure B, using the crude alcohol (0.20 g, 1.8 mmol, 1.0 equiv), triethylamine (0.31 mL, 2.2 mmol, 1.2 equiv), 4-dimethylaminopyridine (0.022 g, 0.18 mmol, 0.10 equiv) and trimethylacetyl chloride (0.27 mL, 2.2 mmol, 1.2 equiv). The crude mixture was purified by silica gel column chromatography using 20% EtOAc/hexanes to afford the pure compound as a clear oil (0.075 g, 42% yield over 2 steps). $^1$H NMR (400 MHz, CDCl$_3$, 298 K) $\delta$ = 6.66-6.64 (m, 1H), 6.21 (dd, $J$ = 3.7, 1.8 Hz, 1H), 6.09-6.06 (m, 1H), 5.05 (s, 2H), 3.61 (s, 3H), 1.19 (s, 9H) ppm.

---


$^{65}$ Not enough material for $^{13}$C spectra.
This compound was prepared according to a literature procedure. In a 100 mL round-bottom flask, 6-bromo-2-naphthol (0.500 g, 2.24 mmol, 1.00 equiv) is dissolved in anhydrous THF (27 mL, 0.080 M) under an argon atmosphere. The flask was cooled to -78 °C and n-butyl lithium (6.2 mL, 9.9 mmol, 1.6 M in hexanes) was added slowly. After 5 hours of stirring at -78 °C, anhydrous dimethylformamide (1.27 mL, 16.4 mmol) was added slowly and left to stir for 45 minutes. The reaction mixture was then poured into HCl/ice (pH < 1) under vigorous stirring and left to warm to room temperature overnight. The crude reaction mixture was extracted with CH₂Cl₂, the organic layers were combined and washed with H₂O, dried with MgSO₄, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography using 30% EtOAc/hexanes to afford a brown solid (0.30 g, 78% yield).

¹H NMR (400 MHz, DMSO-d₆, 298 K) δ = 10.34 (s, 1H), 10.05 (s, 1H), 8.44 (dd, J = 1.6, 0.7 Hz, 1H), 8.02 (dt, J = 8.5, 0.8 Hz, 1H), 7.83 (dd, J = 8.6, 1.6 Hz, 1H), 7.79 (dd, J = 8.6, 1.6 Hz, 1H), 7.25-7.21 (m, 2H) ppm. ¹³C NMR (101 MHz, DMSO-d₆, 298 K) δ = 192.4, 158.4, 138.1, 134.7, 131.6, 131.3, 127.0, 126.6, 122.7, 119.8, 109.2 ppm.

Experimental spectra match a literature report.

Synthesized according to general procedure A using 6a (0.25 g, 1.5 mmol, 1.0 equiv) and sodium borohydride (0.028 g, 0.75 mmol, 0.50 equiv). The product was obtained as a white powder (0.22 g, 86% yield). ¹H NMR (400 MHz, DMSO-d₆, 298 K) δ = 9.63 (s, 1H), 7.75-7.63 (m, 3H), 7.36 (dd, J = 8.5, 1.7 Hz, 1H), 7.12-7.05 (m, 2H), 5.20 (t, J = 5.2, 1H), 4.63-4.58 (m, 2H) ppm. ¹³C NMR (101 MHz, DMSO-d₆, 298 K) δ = 154.9, 136.7, 133.7, 129.1, 127.5, 125.8, 125.6, 124.5, 118.5, 108.6, 63.1 ppm.

Experimental spectra match a literature report.

---

Synthesized according to procedure B using 7a (0.20 g, 1.1 mmol, 1.0 equiv), 4-dimethylaminopyridine (0.027 g, 0.20 mmol, 0.10 equiv), triethylamine (0.37 mL, 2.6 mmol, 1.2 equiv) and trimethylacetyl chloride (0.33 mL, 2.6 mmol, 1.2 equiv). The crude mixture was purified by silica gel column chromatography in 20% EtOAc/hexanes to afford the pure compound as a white powder (0.27 g, 72%). $^{1}$H NMR (400 MHz, DMSO-d$_6$, 298 K) $\delta$ = 8.02-7.93 (m, 3H), 7.66 (d, $J$ = 2.3 Hz, 1H), 7.51 (dd, $J$ = 8.5, 1.8 Hz, 1H), 7.29 (dd, $J$ = 8.8, 2.4 Hz, 1H), 5.27 (s, 2H), 1.37 (s, 9H), 1.21 (s, 9H) ppm. $^{13}$C NMR (101 MHz, DMSO-d$_6$, 298 K) $\delta$ = 177.2, 176.5, 148.6, 133.9, 132.9, 130.6, 129.3, 127.8, 126.3, 121.9, 118.3, 65.4, 38.6, 38.3, 26.9, 26.8 ppm. HRMS (DART-TOF+) $m/z$: [M]$^+$ calcd for C$_{21}$H$_{26}$O$_3$ 342.18311; found 342.18386. IR (neat): 2975, 2934, 2879, 1749, 1727 cm$^{-1}$.

This procedure was adapted from a literature protocol.$^{66}$ In a 250 mL round-bottom flask, 6-bromo-2-naphthol (1.00 g, 4.48 mmol, 1.00 equiv) was dissolved in anhydrous THF (54 mL, 0.080 M) under an argon atmosphere. The flask was cooled to -78 °C and n-butyl lithium (12.3 mL, 19.7 mmol, 1.60 M in hexanes) was added slowly. After 5 hours of stirring at -78 °C, anhydrous dimethylacetamide (3.00 mL, 32.8 mmol) was added slowly and left to stir for 45 minutes. The reaction mixture was then poured into HCl/ice (pH < 1) under vigorous stirring and left to warm to room temperature overnight. The crude reaction mixture was extracted with CH$_2$Cl$_2$, the organic layers were combined and washed with H$_2$O, dried with MgSO$_4$, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography using 30% EtOAc/hexanes to afford a brown solid (0.68 g, 81% yield). $^{1}$H NMR (400 MHz, DMSO-d$_6$, 298 K) $\delta$ = 10.14 (s, 1H), 8.50 (s, 1H), 7.95 (d, $J$ = 9.3 Hz, 1H), 7.84 (d, $J$ = 8.6 Hz, 1H), 7.73 (d, $J$ = 8.7 Hz, 1H), 7.15 (d, $J$ = 7.1 Hz, 2H), 2.62 (s, 3H) ppm. $^{13}$C NMR (101 MHz, DMSO-d$_6$, 298 K) $\delta$ = 197.3, 157.8, 152.8, 137.1, 131.5, 130.5, 127.5, 126.5, 123.9, 119.5, 108.8, 26.5 ppm. Experimental spectra match a literature report.$^{66}$
Synthesized according to general procedure A using 6b (0.67 g, 3.6 mmol, 1.0 equiv) and sodium borohydride (0.14 g, 3.6 mmol, 1.0 equiv). The product was obtained as a white powder (0.58 g, 86% yield). $^1$H NMR (400 MHz, DMSO-$d_6$, 298 K) $\delta = 7.71-7.65$ (m, 2H), 7.58 (d, $J = 8.5$ Hz, 1H), 7.35 (dd, $J = 8.5$, 1.8 Hz, 1H), 7.07-7.02 (m, 2H), 4.78 (q, $J = 6.4$ Hz, 1H), 1.35 (d, $J = 6.4$ Hz, 3H) ppm. $^{13}$C NMR (101 MHz, DMSO-$d_6$, 298 K) $\delta = 206.4$, 154.9, 141.5, 133.6, 129.1, 127.4, 125.8, 124.6, 123.1, 118.5, 108.5, 68.2, 30.6, 25.8 ppm.

Experimental spectra match a literature report.  

Synthesized according to general procedure B using 7b (0.16 g, 0.60 mmol, 1.0 equiv), 4-dimethylaminopyridine (0.015 g, 0.12 mmol, 0.10 equiv), triethylamine (0.20 mL, 1.4 mmol, 1.2 equiv) and trimethylacetyl chloride (0.18 mL, 1.4 mmol, 1.2 equiv). The crude mixture was purified by silica gel column chromatography in 20% EtOAc/hexanes to afford the pure compound as a white powder (0.15 g, 73%). $^1$H NMR (400 MHz, DMSO-$d_6$, 298 K) $\delta = 7.99-7.90$ (m, 3H), 7.66 (d, $J = 2.4$ Hz, 1H), 7.56 (dd, $J = 8.6$, 1.8 Hz, 1H), 7.29 (dd, $J = 8.8$, 2.4 Hz, 1H), 5.94 (q, $J = 6.5$ Hz, 1H), 1.56 (d, $J = 6.5$ Hz, 3H), 1.35 (s, 9H), 1.20 (s, 9H) ppm. $^{13}$C NMR (101 MHz, DMSO-$d_6$, 298 K) $\delta = 176.6$, 176.5, 148.5, 139.3, 132.8, 130.7, 129.4, 127.8, 124.6, 124.2, 121.9, 118.2, 71.5, 38.6, 38.2, 26.8, 22.1 ppm. HRMS (DART-TOF+) $m/z$: [M]$^+$ calcd for C$_{22}$H$_{28}$O$_4$ 356.19876; found 356.20074. IR (neat): 2979, 2936, 2908, 1756, 1712 cm$^{-1}$.

---

This procedure was adapted from a literature protocol. In a 25 mL round-bottom flask, \(6b\) (0.560 g, 3.25 mmol, 1.00 equiv), imidazole (0.440 g, 6.50 mmol, 2.00 equiv) and anhydrous DMF (6.0 mL, 0.56 M) were added under an argon atmosphere. The flask was cooled to 0 °C, chlorotrisopropylsilane (0.83 mL, 3.9 mmol, 1.2 equiv) was added. The mixture was left to stir at room temperature for 16 hours. The reaction mixture was quenched with H\(_2\)O and extracted with EtOAc. The organic layers were combined, washed with H\(_2\)O and brine then dried over MgSO\(_4\), filtered and concentrated under reduced pressure.

Following general procedure A, the crude oil and sodium borohydride (0.080 g, 2.10 mmol, 0.600 equiv). The crude mixture was purified by silica gel column chromatography using 20% EtOAc/hexanes to afford the pure compound as a yellow oil (0.48 g, 69% yield over 2 steps). 1H NMR (400 MHz, CDCl\(_3\), 298 K) \(\delta = 7.57-7.52\) (m, 3H), 7.27 (dd, \(J = 8.5, 1.7\) Hz, 1H), 7.09 (d, \(J = 2.4\) Hz, 1H), 7.00 (dd, \(J = 8.8, 2.4\) Hz, 1H), 4.64 (s, 2H), 1.24-1.14 (m, 3H), 1.01 (d, \(J = 7.4\) Hz, 18H) ppm. 13C NMR (101 MHz, CDCl\(_3\), 298 K) \(\delta = 154.1, 136.1, 134.2, 129.3, 129.0, 127.1, 125.7, 125.5, 122.4, 114.5, 65.6, 18.0, 12.8\) ppm. Experimental spectra match a literature report.

Synthesized according to general procedure B using, \(9a\) (0.45 g, 1.3 mmol, 1.0 equiv), 4-dimethylaminopyridine (0.016 g, 0.13 mmol, 0.10 equiv), triethylamine (0.22 mL, 1.6 mmol, 1.2 equiv) and trimethylacetyl chloride (0.19 mL, 1.6 mmol, 1.2 equiv). The crude mixture was purified by silica gel column chromatography in 10% EtOAc/hexanes to afford the pure compound as a clear oil (0.35 g, 66%). 1H NMR (400 MHz, CDCl\(_3\), 298 K) \(\delta = 7.73-7.67\) (m, 3H), 7.39 (dd, \(J = 8.4, 1.8\) Hz, 1H), 7.22 (d, \(J = 2.4\) Hz, 1H), 7.15 (dd, \(J = 8.8, 2.5\) Hz, 1H), 5.23 (s, 2H), 1.38-1.28 (m, 3H), 1.25 (s, 9H), 1.14 (d, \(J = 7.4\) Hz, 18H) ppm. 13C NMR (101 MHz, CDCl\(_3\), 298 K) \(\delta = 178.4, 154.3, 134.3, 131.6, 129.4, 128.8, 127.1, 126.9, 126.1, 122.4, 114.4, 66.4, 38.9, 27.3, 18.0, 12.8\) ppm. HRMS (ESI) \(m/z\): [M+Na]\(^+\) calcd for C\(_{25}\)H\(_{38}\)O\(_3\)Si 414.25902; found 414.24860. IR (neat): 2945, 2867, 1729 cm\(^{-1}\).

---

This procedure was adapted from a literature protocol. In a 25 mL roundbottom flask, 6b (0.40 g, 2.1 mmol, 1.0 equiv), imidazole (0.29 g, 4.2 mmol, 2.0 equiv) and anhydrous DMF (4.0 mL, 0.56 M) were added under an argon atmosphere. The flask was cooled to 0 °C, and chlorotriisopropylsilane (0.54 mL, 2.5 mmol, 1.2 equiv) was added. The mixture was left to stir at room temperature for 16 hours. The reaction mixture was quenched with H₂O and extracted with EtOAc. The organic layers were combined, washed with H₂O and brine then dried over MgSO₄, filtered and concentrated under reduced pressure.

Following general procedure A, using the crude oil and sodium borohydride (0.030 g, 0.75 mmol, 0.30 equiv). The crude oil was purified by silica gel column chromatography using 20% EtOAc/hexanes to afford the pure compound as a clear oil (0.13 g, 48% yield over 2 steps). ¹H NMR (400 MHz, CDCl₃, 298 K) δ = 7.74-7.67 (m, 3H), 7.45 (dd, J = 8.5, 1.8 Hz, 1H), 7.22-7.20 (m, 1H), 7.13 (dd, J = 8.8, 2.4, 1H), 5.03 (qd, J = 6.4, 3.2 Hz, 1H), 1.84 (d, J = 3.5 Hz, 1H), 1.57 (d, J = 6.5 Hz, 3H), 1.37-1.27 (m, 3H), 1.13 (d, J = 7.3 Hz, 18H) ppm. ¹³C NMR (101 MHz, CDCl₃, 298 K) δ = 154.0, 140.9, 134.2, 129.3, 128.9, 127.1, 124.1, 123.7, 122.3, 114.4, 70.6, 25.0, 18.0, 12.8 ppm. HRMS (ESI) m/z: [M]+ calcld for C₂₁H₃₂O₂Si 344.21716; found 344.21478. IR (neat): 3348, 2944, 2892, 2866 cm⁻¹.

Synthesized according to general procedure B, using 9b (0.12 g, 0.35 mmol, 1.0 equiv), 4-dimethylaminopyridine (0.0050 g, 0.040 mmol, 0.10 equiv), triethylamine (0.06 mL, 0.36 mmol, 1.2 equiv) and trimethylacetyl chloride (0.050 mL, 0.36 mmol, 1.20 equiv). The crude mixture was purified by silica gel column chromatography in 10% EtOAc/hexanes to afford the pure compound as a clear oil (0.088 g, 59%). TLC Rf = 0.60 in 10% EtOAc/hexanes. ¹H NMR (400 MHz, CDCl₃, 298 K) δ = 7.71-7.65 (m, 3H), 7.40 (dd, J = 8.5, 1.8 Hz, 1H), 7.19 (d, J = 2.4 Hz, 1H), 7.12 (dd, J = 8.8, 2.4 Hz, 1H), 5.98 (q, J = 6.6 Hz, 1H), 1.58 (d, J = 6.6, 3H), 1.36-1.30 (m, 3H), 1.22 (s, 9H), 1.13 (d, J = 7.3 Hz, 18H) ppm. ¹³C NMR (101 MHz, CDCl₃, 298 K) δ = 177.7, 154.1, 137.2, 134.2, 129.4, 128.7, 127.0, 124.6, 124.3, 122.3, 114.3, 72.1, 38.8, 27.2, 22.3, 18.0, 12.8 ppm. HRMS (ESI) m/z: [M+Na]+ calcld for C₂₆H₄₀O₃Si 428.27467; found 428.26440. IR (neat): 2943, 2867, 1729 cm⁻¹.
Synthesis of aminoacetonitriles:

Synthesized according to general procedure C using piperidine (1.5 mL, 15 mmol, 1.0 equiv). The crude mixture was purified by silica gel column chromatography using 30% EtOAc/hexanes to afford a clear oil (0.17 g, 30% yield). \( ^1 \text{H NMR (400 MHz, CDCl}_3, 298 \text{ K)} \delta = 3.47 (s, 2H), 2.53-2.48 (m, 4H), 1.64-1.57 (m, 4H), 1.47-1.40 (m, 2H) \text{ ppm.} \)

\( ^{13} \text{C NMR (101 MHz. CDCl}_3, 298 \text{ K)} \delta = 114.9, 53.0, 46.9, 25.6, 23.2 \text{ ppm.} \)

Experimental spectra match a literature report.\(^{57}\)

Synthesized according to general procedure C using morpholine (1.3 mL, 15 mmol, 1.0 equiv). The crude mixture was purified by silica gel column chromatography using 30% hexanes/EtOAc to afford a white solid (0.54 g, 86% yield). \( ^1 \text{H NMR (400 MHz, CDCl}_3, 298 \text{ K)} \delta = 3.77-3.73 (m, 4H), 3.51 (s, 2H), 2.62-2.58 (m, 4H) \text{ ppm.} \)

\( ^{13} \text{C NMR (101 MHz. CDCl}_3, 298 \text{ K)} \delta = 114.5, 66.5, 51.9, 46.2 \text{ ppm.} \)

Experimental spectra match a literature report.\(^{57}\)

Synthesized according to general procedure C using diisopropylamine (2.1 mL, 15 mmol, 1.0 equiv). The crude mixture was purified by silica gel column chromatography using 20% hexanes/EtOAc to afford a clear oil (0.31 g, 44% yield). \( ^1 \text{H NMR (400 MHz, CDCl}_3, 298 \text{ K)} \delta = 3.54 (s, 2H), 3.19-3.12 (m, 2H), 1.11 (d, \text{J} = 6.5 \text{ Hz, 12H) ppm.} \)

\( ^{13} \text{C NMR (101 MHz. CDCl}_3, 298 \text{ K)} \delta = 119.1, 49.0, 33.3, 20.4 \text{ ppm.} \)

Experimental spectra match a literature report.\(^{57}\)
Synthesized according to general procedure C using diethylamine (1.6 mL, 15 mmol, 1.0 equiv). The crude mixture was purified by silica gel column chromatography using 30% hexanes/EtOAc to afford the pure compound as a clear oil (0.33 g, 59% yield). $^1$H NMR (400 MHz, CDCl₃, 298 K) $\delta = 3.59$ (s, 2H), 2.58 (q, $J = 7.2$ Hz, 4H), 1.09 (t, $J = 7.2$, 6H) ppm. $^{13}$C NMR (101 MHz, CDCl₃, 298 K) $\delta = 114.8$, 47.9, 40.6, 12.6 ppm.

Experimental spectra match a literature report.\(^{57}\)
Synthesis of benzylic nitriles:

\[
\begin{align*}
2a & & \text{Synthesized according to general procedure D using 1a (0.056 g, 0.20 mmol, 1.0 equiv) and K_3PO_4 (0.013 g, 0.060 mmol, 0.30 equiv). The crude mixture was purified by silica gel column chromatography using a gradient of 2%-20\% EtOAc/hexanes to afford the pure compound as a white powder (31 mg, 86\% yield).} \\
& & \text{\textit{^1}H NMR (400 MHz, CDCl}_3, 298 K) \delta = 7.90-7.82 (m, 4H), 7.55-7.49 (m, 2H), 7.43 (dd, J = 8.5, 1.9 Hz, 1H), 4.07 (q, J = 7.3 Hz, 1H), 1.73 (d, J = 7.3 Hz, 3H) ppm.} \\
& & \text{\textit{^{13}C NMR (101 MHz, CDCl}_3, 298 K) \delta = 134.3, 133.4, 132.8, 129.2, 127.9, 127.8, 127.7, 126.8, 125.6, 124.4, 121.6, 31.5, 21.5 \text{ ppm.}} \\
\end{align*}
\]

Experimental spectra match a literature report.\(^{70}\)

\[
\begin{align*}
2b & & \text{Synthesized according to general procedure D using 1b, (0.051 g, 0.20 mmol, 1.0 equiv) and K_3PO_4 (0.013 g, 0.060 mmol, 0.30 equiv). The crude mixture was purified by silica gel column chromatography using a gradient of 2%-10\% EtOAc/hexanes to afford the pure compound as a white powder (27 mg, 82\% yield) } \\
& & \text{\textit{^1}H NMR (400 MHz, CDCl}_3, 298 K) \delta = 7.90-7.82 (m, 4H), 7.56-7.50 (m, 2H), 7.39 (dd, J = 8.4, 1.9 Hz, 1H), 3.92 (s, 2H) ppm.} \\
& & \text{\textit{^{13}C NMR (101 MHz, CDCl}_3, 298 K) \delta = 133.3, 132.7, 129.1, 127.7, 127.7, 127.2, 126.8, 126.8, 126.5, 125.4, 117.8, 23.8 \text{ ppm.}} \\
\end{align*}
\]

Experimental spectra match a literature report.\(^ {71}\)


Synthesized according to general procedure D using 1f (0.049 g, 0.20 mmol, 1.0 equiv), NiCl\(_2\)(dppf) (0.027 g, 0.040 mmol, 0.20 equiv), Zn(CN)\(_2\) (0.013 g, 0.11 mmol, 0.55 equiv), Zn\(_5\)(CO\(_3\))\(_2\)(OH)\(_6\) (0.028 g, 0.050 mmol, 0.25 equiv) and ZnEt\(_2\) (0.050 mL, 0.050 mmol, 0.25 equiv). The crude mixture was purified by silica gel column chromatography using a gradient of 2% - 20% EtOAc/hexanes to afford the pure compound as a white powder (20 mg, 59% yield). \(^1\)H NMR (400 MHz, CDCl\(_3\), 298 K) δ = 7.56 (ddd, \(J = 7.5, 1.5, 1.0\) Hz, 1H), 7.47 (dq, \(J = 8.3, 1.0, 1H\), 7.34-7.28 (m, 1H), 7.27-7.22 (m, 1H), 6.72 (t, \(J = 1.0\) Hz, 1H), 4.13 (qd, \(J = 7.2, 1.1\) Hz, 1H), 1.78 (d, \(J = 7.3\) Hz, 3H) ppm. \(^{13}\)C NMR (101 MHz, CDCl\(_3\), 298 K) δ = 155.1, 151.7, 127.7, 124.8, 123.2, 121.1, 118.9, 111.3, 103.9, 25.7, 17.5 ppm.

Experimental spectra match a literature report.\(^72\)

Synthesized according to general procedure D using 8a (0.068 g, 0.20 mmol, 1.0 equiv) and Zn\(_5\)(CO\(_3\))\(_2\)(OH)\(_6\) (0.016 g, 0.030 mmol, 0.15 equiv). The crude mixture was purified by silica gel column chromatography using a gradient of 2% - 20% EtOAc/hexanes to afford the pure compound as a white powder (trial 1 : 19 mg, 40% yield; trial 2 : 22 mg, 42% yield). \(^1\)H NMR (400 MHz, CDCl\(_3\), 298 K) δ = 7.86-7.80 (m, 3H), 7.54 (d, \(J = 2.3\) Hz, 1H), 7.39 (dd, \(J = 8.5, 1.9\) Hz, 1H), 7.24 (d, \(J = 2.3\) Hz, 1H), 3.92 (s, 2H), 1.41 (s, 9H) ppm. \(^{13}\)C NMR (101 MHz, CDCl\(_3\), 298 K) δ = 177.2, 149.3, 133.2, 131.3, 129.1, 128.7, 127.0, 126.8, 126.2, 122.2, 118.4, 117.7, 39.2, 27.2, 23.8 ppm. HRMS (ESI) \(m/z\): [M]\(^+\) calcd for C\(_{17}\)H\(_{17}\)NO\(_2\) 268.19523; found 268.19562. IR (neat): 2972, 2944, 2890, 2283 cm\(^{-1}\).

Synthesized according to general procedure D using 10a (0.082 g, 0.20 mmol, 1.0 equiv) and Zn₅(CO₃)₂(OH)₆ (0.016 g, 0.030 mmol, 0.15 equiv). The crude mixture was purified by silica gel column chromatography using a gradient of 2% - 20% EtOAc/hexanes to afford the pure compound as a white powder (25 mg, 37% yield). 

**1H NMR (400 MHz, CDCl₃, 298 K)** δ = 7.74-7.68 (m, 3H), 7.32 (dd, J = 8.5, 2.0 Hz, 1H), 7.21 (d, J = 2.5 Hz, 1H), 7.16 (dd, J = 8.8, 2.4 Hz, 1H), 3.87 (s, 2H), 1.36-1.26 (m, 3H), 1.13 (d, J = 7.3 Hz, 18H) ppm.

**13C NMR (101 MHz, CDCl₃, 298 K)** δ = 154.5, 134.0, 129.1, 128.9, 127.7, 125.7, 124.8, 122.9, 118.0, 114.4, 23.7, 17.9, 12.7 ppm. **HRMS (ESI) m/z**: [M]+ calcd for C₂₁H₂₉NOSi 339.20184; found 339.21260. **IR** (neat): 2944, 2892, 2864, 2251 cm⁻¹.
Synthesis of additives for robustness screen:

Synthesized according to general procedure B using 2-naphthol (0.72 g, 5.0 mmol, 1.0 equiv), 4-dimethylaminopyridine (0.060 g, 0.50 mmol, 0.10 equiv), triethylamine (0.84 mL, 6.0 mmol, 1.2 equiv) and trimethylacetyl chloride (0.74 mL, 6.0 mmol, 1.2 equiv). The crude mixture was purified by silica gel column chromatography using 10% EtOAc/hexanes to afford the pure compound as a clear oil (0.79 g, 70%). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}, 298 K) \(\delta = 7.91-7.83\) (m, 3H), 7.55 (d, \(J = 2.3\) Hz, 1H), 7.56-7.45 (m, 2H), 7.22 (dd, \(J = 8.9, 2.3\) Hz, 1H), 1.43 (s, 9H) ppm. \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}, 298 K) \(\delta = 177.3, 148.8, 133.8, 131.4, 129.3, 129.3, 127.8, 127.6, 125.6, 121.2, 118.4, 39.2, 27.2\) ppm.

Experimental spectra match a literature report.\textsuperscript{73}

This procedure was adapted from a literature protocol.\textsuperscript{68} In a 25 mL round-bottom flask, 2-naphthol (0.72 g, 5.0 mmol, 1.0 equiv), imidazole (0.68 g, 10 mmol, 2.0 equiv) and anhydrous DMF (10 mL, 0.56 M) were added under an argon atmosphere. The flask was cooled to 0 °C, and chlorotriisopropylsilane (1.0 mL, 5.0 mmol, 1.2 equiv) was added. The mixture was left to stir at room temperature for 16 hours. The reaction mixture was quenched with H\textsubscript{2}O and extracted with EtOAc. The organic layers were combined, washed with H\textsubscript{2}O and brine then dried over MgSO\textsubscript{4}, filtered and concentrated under reduced pressure. The crude oil was purified by silica gel column chromatography using 100% hexanes to afford a clear oil (0.78 g, 52%). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}, 298 K) \(\delta = 7.78-7.68\) (m, 3H), 7.42 (ddd, \(J = 8.2, 6.8, 1.3\) Hz, 1H), 7.33 (ddd, \(J = 8.1, 6.8, 1.3\) Hz, 1H), 7.24-7.21 (m, 1H), 7.15 (dd, \(J = 8.8, 2.5\) Hz, 1H), 1.38-1.30 (m, 3H), 1.16 (d, \(J = 7.4\) Hz, 18H) ppm. \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}, 298 K) \(\delta = 153.9, 134.7, 129.3, 129.1, 127.6, 126.7, 126.1, 123.6, 122.1, 114.5, 18.0, 12.8\) ppm.

Experimental spectra match a literature report.\textsuperscript{74}

This procedure was adapted from a literature protocol. In a 50 mL roundbottom flask, 2-naphthol (0.72 g, 5.0 mmol, 1.0 equiv) was dissolved in anhydrous CH$_2$Cl$_2$ (20 mL, 0.25 M). 4-Dimethylaminopyridine (0.060 g, 0.50 mmol, 0.10 equiv), triethylamine (0.84 mL, 6.0 mmol, 1.2 equiv) and acetyl chloride (0.43 mL, 6.0 mmol, 1.2 equiv) were added to the flask sequentially and the mixture was left to stir at room temperature for 16 hours. The crude reaction mixture was extracted with NaHCO$_3$, washed with brine, dried with MgSO$_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography in 10% EtOAc/hexanes to afford the pure compound as a clear oil (0.71g, 76%). $^1$H NMR (400 MHz, CDCl$_3$, 298 K) $\delta$ = 7.87-7.79 (m, 3H), 7.56 (d, $J$ = 2.3 Hz, 1H), 7.52-7.44 (m, 2H), 7.23 (dd, $J$ = 8.9, 2.3 Hz, 1H), 2.36 (s, 3H) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$, 298 K) $\delta$ = 169.7, 148.3, 133.8, 131.5, 129.4, 127.8, 127.7, 126.6, 125.7, 121.1, 118.5, 21.2 ppm.

Experimental spectra match a literature protocol.  

---

Synthesis of allylic pivalates:

Synthesized according to general procedure A using 4-phenyl-3-buten-2-one (7.3 g, 50 mmol, 1.0 equiv) and sodium borohydride (1.1 g, 30 mmol, 0.60 equiv) followed by general procedure B, using the crude alcohol (3.0 g, 20 mmol, 1.0 equiv), triethylamine (3.9 mL, 28 mmol, 1.4 equiv), 4-dimethylaminopyridine (0.24 g, 2.0 mmol, 0.10 equiv) and trimethylacetyl chloride (3.2 mL, 26 mmol, 1.3 equiv). The crude mixture was purified by silica gel column chromatography using a gradient of 0-10% EtOAc/hexanes to afford the pure compound as a white solid (2.90 g, 63% yield over 2 steps).  

$^1$H NMR (400 MHz, CDCl$_3$, 298 K) δ = 7.45-7.36 (m, 2H), 7.35-7.29 (m, 2H), 7.28-7.22 (m, 1H), 6.59 (dd, $J = 16.0, 1.1$ Hz, 1H), 6.19 (dd, $J = 16.0, 6.4$ Hz, 1H), 5.51 (qdd, $J = 6.5, 6.5, 1.3$ Hz, 1H), 1.39 (d, $J = 6.5$ Hz, 3H), 1.22 (s, 9H) ppm.  

$^{13}$C NMR (101 MHz, CDCl$_3$, 298 K) δ = 177.7, 136.5, 131.0, 129.1, 128.5, 127.8, 126.5, 70.5, 38.8, 27.1, 20.3 ppm.

Experimental spectra match a literature report.\textsuperscript{76}

\textsuperscript{76} Srinivas, H.; Zhou, Q.; Watson, M. Org. Lett. 2014, 16, 3596-3599
Synthesis of allylic nitriles:

Synthesized according to general procedure E using \( \text{12a} \) (0.046 g, 0.20 mmol, 1.0 equiv). The crude mixture was purified by silica gel column chromatography using a gradient of 2\% - 10\% EtOAc/hexanes to afford the pure compound as a white powder (16 mg, 52\% yield). \(^1\)H NMR (400 MHz, \( \text{CDCl}_3 \), 298 K) \( \delta = 7.39-7.27 \) (m, 5H), 6.72 (dd, \( J = 15.9, 1.5 \) Hz, 1H), 6.07 (dd, \( J = 15.8, 6.1 \) Hz, 1H), 3.54-3.47 (m, 1H), 1.52 (d, \( J = 7.2 \) Hz, 3H) ppm. \(^{13}\)C NMR (101 MHz, \( \text{CDCl}_3 \), 298 K) \( \delta = 135.7, 132.5, 128.7, 128.2, 126.5, 124.3, 120.8, 28.4, 19.0 \) ppm.

Experimental spectra match a literature report.\(^{77}\)

Synthesized according to general procedure E using \( \text{12b} \) (0.049 g, 0.20 mmol, 1.0 equiv). The crude mixture was purified by silica gel column chromatography using a gradient of 1\% - 9\% EtOAc/hexanes to afford the pure compound as a white powder (14 mg, 41\% yield). \(^1\)H NMR (400 MHz, \( \text{CDCl}_3 \), 298 K) \( \delta = 7.32-7.18 \) (m, 5H), 6.66 (dd, \( J = 15.9, 1.4 \) Hz, 1H), 5.98 (dd, \( J = 15.9, 6.4 \) Hz, 1H), 3.31 (ddtd, \( J = 7.7, 6.3, 1.5 \) Hz, 1H), 1.83-1.67 (m, 2H), 1.05 (t, \( J = 7.4 \) Hz, 3H) ppm. \(^{13}\)C NMR (101 MHz, \( \text{CDCl}_3 \), 298 K) \( \delta = 135.8, 133.4, 128.7, 128.3, 126.5, 123.0, 120.1, 35.9, 26.7, 11.2 \) ppm. HRMS (DART-TOF+) \( m/z \) [M+NH\(_4\)]\(^+\) caled for C\(_{12}\)H\(_{17}\)N\(_2\) 189.1392; found 189.1390. IR (neat): 3028, 2970, 2935, 2878, 2241 cm\(^{-1}\).

Synthesized according to general procedure E using 12d (0.055 g, 0.20 mmol, 1.0 equiv). The crude mixture was purified by silica gel column chromatography using a gradient of 1% - 9% EtOAc/hexanes to afford the pure compound as a white powder (26 mg, 66% yield). \( ^1H \text{NMR} (400 \text{ MHz, CDCl}_3, 298 \text{ K}) \) \( \delta = 7.39-7.28 (m, 4H), 6.72 (dt, J = 15.8, 1.8 Hz, 1H), 6.01 (dt, J = 15.9, 5.7 Hz, 1H), 3.29 (dd, J = 5.7, 1.8 Hz, 2H), 1.32 (s, 9H) \) ppm. \( ^{13}C \text{NMR} (101 \text{ MHz, CDCl}_3, 298 \text{ K}) \) \( \delta = 151.5, 134.4, 132.9, 126.2, 125.7, 117.4, 115.9, 34.7, 31.3, 20.8 \) ppm. HRMS (DART-TOF+) \( m/z: [\text{M+NH}_4]^+ \) calcd for C\(_{14}\)H\(_{21}\)N\(_2\) 217.1705; found 217.1702. IR (neat): 2961, 2922, 2872, 2250 cm\(^{-1}\).

Synthesized according to general procedure E using 12h (0.053 g, 0.20 mmol, 1.0 equiv). The crude mixture was purified by silica gel column chromatography using a gradient of 4-20% EtOAc/hexanes to afford the pure compound as a yellow solid (21 mg, 57% yield). \( ^1H \text{NMR} (400 \text{ MHz, CDCl}_3, 298 \text{ K}) \) \( \delta = 6.89 (d, J = 1.6 Hz, 1H), 6.81 (dd, J = 8.0, 1.7 Hz, 1H), 6.77 (d, J = 8.0 Hz, 1H), 6.63 (dt, J = 15.7, 1.8 Hz, 1H), 5.97 (s, 2H), 5.88 (dt, J = 15.7, 5.7 Hz, 1H), 3.26 (dd, J = 5.7, 1.8 Hz, 2H) \) ppm. \( ^{13}C \text{NMR} (101 \text{ MHz, CDCl}_3, 298 \text{ K}) \) \( \delta = 148.3, 147.9, 134.4, 130.2, 121.5, 117.5, 115.0, 108.5, 105.8, 101.4, 20.8 \) ppm. HRMS (DART-TOF+) \( m/z: [\text{M+NH}_4]^+ \) calcd for C\(_{11}\)H\(_{13}\)N\(_2\)O\(_2\) 205.0977; found 205.0977. IR (neat): 2922, 2910, 2851, 2254 cm\(^{-1}\).

Synthesized according to general procedure E using 12j (0.050 g, 0.20 mmol, 1.0 equiv). The crude mixture was purified by silica gel column chromatography using a gradient of 0-14% EtOAc/hexanes to afford the pure compound as an off-white solid (19 mg, 54% yield). \( ^1H \text{NMR} (400 \text{ MHz, CDCl}_3, 298 \text{ K}) \) \( \delta = 7.30 (d, J = 0.9 Hz, 4H), 6.70 (dt, J = 15.8, 1.9 Hz, 1H), 6.04 (dt, J = 15.8, 5.6 Hz, 1H), 3.29 (dd, J = 5.6, 1.8 Hz, 2H) \) ppm. \( ^{13}C \text{NMR} (101 \text{ MHz, CDCl}_3, 298 \text{ K}) \) \( \delta = 134.2, 134.1, 133.5, 129.0, 127.9, 117.4, 117.1, 20.8 \) ppm. HRMS (DART-TOF+) \( m/z: [\text{M+NH}_4]^+ \) calcd for C\(_{10}\)H\(_{12}\)ClN\(_2\) 195.0689; found 195.0686. IR (neat): 3046, 2920, 2851, 2249 cm\(^{-1}\).
5.4 Spectra

400 MHz CDC\textsubscript{3}

1a

101 MHz CDC\textsubscript{3}

1a
*Not enough material for $^{13}$C spectra.
400 MHz, DMSO-d$_6$

101 MHz, DMSO-d$_6$
400 MHz, CDCl$_3$