Transmissive Olefination of Alkenenitrile and Allylic Halides

Lihua Yao
TRANSMISSIVE OLEFINATION OF ALKENENITRILES AND
ALLYLIC HALIDES

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the Degree of Master of Science

By
Lihua Yao

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ABSTRACT

TRANSMISSIVE OLEFINATION OF ALKENENITRILES AND ALLYLIC HALIDES

By
Lihua Yao
May, 2011

Thesis supervised by Dr. Fraser Fleming

Part 1. Grignard reagents readily add to alkenenitriles bearing an adjacent hydroxyl group to afford Z-alkenenitriles with transmissive relocation of the C=C bond. Mechanistically the transmissive olefination is consistent with rearrangement through a cyclic 6-membered transition structure in which the formal displacement of hydroxide occurs by forming magnesium oxide.

Part 2. Addition of niobium halides to a series of allylic or propargylic alkoxides directly provides allylic or allenic halides. Halogenation formally occurs through a metalla-halo-[3, 3] rearrangement although at least these different mechanisms may operate competitively. Transposition of the olefin is equally effective for allylic alkoxides prepared by nucleophilic addition, deprotonation, or reduction.
ACKNOWLEDGEMENT

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2. Fraser F. Fleming; P. C. Ravikumar; Lihua Yao “Direct Conversion of Aldehydes and Ketones to Allylic Halides by a NbX$_5$-[3, 3] Rearrangement” Synlett **2009**, *1077*.


4. Fraser F. Fleming; Wang Liu; Lihua Yao; P. C. Ravikumar “Alkeneitriles: Transmissive Olefination via Conjugate Addition-MgO Elimination” *Manuscript in preparation*
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1. Introduction (Taken in part from the Journal of Medicinal Chemistry\textsuperscript{1})

1.1 Background

Over 30 nitrile-containing pharmaceuticals are prescribed for a diverse variety of medicinal indications with almost 20 nitrile-containing leads in clinical development. Trends identifying the roles of the nitrile in medical agents have emerged as the number of nitrile-containing pharmaceuticals has increased. Coupled with the increasing number of nitrile-containing agents have been structural advances that provide insight into the binding of small molecule inhibitors. X-ray crystallography in particular is providing key insight into small molecule-protein interactions through an increasing number of structures with inhibitors bound in the active site. Augmenting the available interactions with current nitrile-containing pharmaceuticals are details from clinical candidates no longer under development.

The prevalence of nitrile-containing pharmaceuticals, and the continued stream of potential agents in the pipeline, attests to the biocompatibility of the nitrile functionality.\textsuperscript{2} The nitrile group is not particularly electrophilic, even toward thiols such as glutathione,\textsuperscript{3} unless activated by adjacent functionalities such as an electron withdrawing group.\textsuperscript{4} Several new amino nitriles for diabetes treatment feature a reversible electrophilic attack, but involve a tightly orchestrated activation-electrophilic addition that is not otherwise readily achieved.

The nitrile group is relatively robust and not readily metabolized.\textsuperscript{5} Metabolically, the nitrile group in most nitrile-containing pharmaceuticals is passed through the body
unchanged. In cases of drug metabolism prior to elimination, the formation of glucuronides, conjugation with glutathione, N-dealkylation, N-acetylation, hydrolysis, and oxidation typically occurs at sites remote from the nitrile and without modification of the nitrile group.

Release of cyanide from aromatic or fully substituted carbons is not observed, whereas alkylnitriles bearing an adjacent proton can be oxidized in the liver to cyanohydrins with subsequent cyanide release. Mandelonitrile, a cyanohydrin produced by ingesting almonds or some fruit pits, releases cyanide as the main degradation pathway and is responsible for the toxicity of cyanogenic glycosides. The potential oxidation and cyanide ejection likely explains why only four of the bioactive nitriles in the review contain an adjacent C-H bond. Epoxidation of alkenenitriles and ring opening can potentially liberate cyanide, but the epoxidation is synthetically difficult and metabolism at other sites appears more likely given the success of several alkenenitrile-containing pharmaceuticals.

Vildagliptin is a recently released aminonitrile-containing antidiabetic drug in which the nitrile bearing carbon is not fully substituted (Figure 1). Perhaps because of a concern for cyanide release, the metabolism has been closely examined in humans. The main metabolite comes from hydrolysis of the nitrile which likely stems from the covalent intermediate formed from this carboxyl transition structure analogue. Nitrile hydrolysis is rather rare and, when observed, is a very minor metabolic pathway.
Nitriles are unusual functionalities by virtue of the short, polarized triple bond. The linear, rodlike geometry has a cylindrical diameter of 3.6 Å for the π-system resulting in a minuscule steric demand along the axis. For comparison, the C≡N unit is essentially 8 times smaller than a methyl group! Several crystal structures show the nitrile projecting into narrow clefts to make polar interactions or hydrogen bonds in stERICALLY congested environments.

Nitriles often play a key role as hydrogen bond acceptors. Several crystal structures show hydrogen bonding between the nitrile nitrogen and amino acids or to water which in turn is bound to the protein backbone. Many hydrogen bonds are between the nitrile and serine or arginine as expected for these hydrogen bond donors. In other clinical candidates, the strong dipole facilitates polar interactions in which the nitrile acts as a hydroxyl or carboxyl isostere.

1.2 Alkenenitrile Pharmaceuticals

Drugs containing the unsaturated nitrile functionality are conjugated either with additional electron withdrawing groups or heteroatoms (Figure 2). Often the nitrile is
positioned adjacent to a hydrogen bond donor or acceptor implying an electronic role for the nitrile group. Conjugation of the nitrile with an additional electron withdrawing group facilitates Michael additions as in 2 (entacapone).

2 is a potent inhibitor of catechol-O-methyltransferase and used for treating Parkinson’s disease by facilitating passage of dopaminergic agents across the blood-brain barrier. Molecular docking reveals a series of hydrogen bonds with the nitrocatechol ring but no specific interactions for the nitrile. (trilostane) is an inhibitor of 3β-hydroxysteroid dehydrogenase that was used to treat Cushing's syndrome in humans but is now licensed only for treating dogs. has been successfully used in treating post-menopausal women for breast cancer by inhibiting 3-hydroxysteroid dehydrogenase. Molecular modeling and mutant studies demonstrate the necessity of the nitrile group and identifies an interaction with a serine residue as being critical.

**Figure 2.** Alkenenitrile-Containing Pharmaceuticals
4 (lanoconazole)\textsuperscript{31} and 5 (luliconazole)\textsuperscript{32} are topical antifungal drugs developed and marketed in Japan. Both 4 and 5 inhibit sterol 14-methylase in fungi\textsuperscript{31} and although marketed as a racemate the activity resides in the S-enantiomer. An interaction is proposed between the enzyme and the dichlorobenzene ring\textsuperscript{33} with the dithioalkenenitrile acting as a Michael acceptor.\textsuperscript{34} 6 (nilvadipine) is a calcium channel blocker used to treat hypertension and cerebral artery occlusion,\textsuperscript{35} and recently entered trials to treat Alzheimer's disease.\textsuperscript{36} The role of the nitrile is unknown.

Celgene Corp.'s antitumor agent 7 (CC-5079) prevents tubulin polymerization but remains active against multi-drug resistant cells.\textsuperscript{37} Subsequent assays identified the Z-diastereomner as being more active with molecular modeling suggesting a key hydrogen bond between the nitrile nitrogen and a tyrosine hydroxyl group in tubulin.\textsuperscript{38} 8 (levosimendan, Simdax) is a novel inodilator used to manage acute or chronic heart failure.\textsuperscript{39} As with many Ca\textsuperscript{2+} sensitization and K\textsuperscript{+} channel-mediators, the enzyme-inhibitor interactions are not fully resolved. Development of a related dinitrile inhibitor, 9 (KW-5092), suggests that the dinitrile creates a rigid, polar moiety comparable to a nitro group.\textsuperscript{40}

1.3 Conclusion

Structurally diverse nitrile-containing drugs are in use for a variety of medical treatments. These range from blockbuster drugs to numerous candidates currently being pursued in clinical trials. Surveying the interactions of the nitrile within these pharmaceuticals and drug candidates reveals that the biological function of the nitrile group varies
considerably. In some instances the nitrile merely polarizes the adjacent electron density whereas in other cases the nitrile is a key component for molecular recognition.

Recent advances in molecular recognition, through crystallography, NMR, and modeling, is providing an increased understanding of the interactions between small molecule inhibitors and their targets. By surveying a range of pharmaceuticals and clinical candidates, several roles of the nitrile group have been identified.

1.) Carbonyl bioisostere. In several non-steroidal inhibitors arylnitriles function as a carbonyl equivalent. These inhibitors have the advantage of minimizing interference with other steroid receptors and improving bioavailability. The homology is evident in the overlay of progesterone and the nitrile-inhibitor 10 in the progesterone receptor site (Figure 3). The nitrile nitrogen occupies virtually the same position as the carbonyl oxygen of progesterone and engages in the same polar interactions.

Figure 3. Nitrile Inhibitor 10 and Progesterone Overlay
2.) **Hydroxyl and carboxyl surrogate.** The small, polar nitrile is a strong hydrogen bond acceptor with a significant solvation shell. The combination allows the nitrile to function as hydroxyl and carboxyl surrogates. Hydrogen bonding is particularly common to the protein backbone, amino acid side chains, or water molecules enclosed within the binding domain. The relationship is exemplified by functional group replacements performed using the anti-cancer drug 13 (etoposide) as a lead structure. Replacing the glycoside with a nitrile 11 was significantly more efficacious than the acid 12.

![Comparative Nitrile and Acid Etoposide Analogs](image)

**Figure 4.** Comparative Nitrile and Acid Etoposide Analogs.

3.) **Non–Specific Dipole Interaction.** The powerful electron-withdrawing nature of the CN unit allows non-specific dipole interactions with amino acids and metal ions. In cyanoguanidines, and related structures, nitrile substitution allows tuning of the guanidine basicity and hydrogen bonding properties.

4.) **Azomethine-Water Bioisostere.** Cyanoquinolines and cyanopyridines 15 can act as more potent azomethine-water 14 bioisosteres. Interchanging a water-
bound quinazoline with a 3-cyano quinoline or pyridine effectively exchanges the mobile hydrogen-bonded pyrimidine-water complex for a direct hydrogen bond between the nitrile and the protein. Expulsion of water from the binding domain adds an additional entropic component to the binding affinity (Figure 5).

![Figure 5. Cyanoquinolines and Cyanopyridines as Azomethine-Water Bioisosteres](image)

5.) **Carboxyl Transition State Analog.** Several amino nitriles function as proline peptidases by reversibly forming covalently bound imino esters at the active site. Conversion of the nitrile to the imino ester appears choreographed through activation of the nitrile and addition of serine or cysteine.

6.) **Halogen Bioisostere.** The nitrile mimics the polarization of the halides and is often an excellent halogen bioisostere. Being smaller than bromine or iodine, the nitrile is often capable of achieving better contact with amino acids lining an active site.

7.) **Improving ADME-Toxicology Profiles.** Computational properties and empirical rules such as Lipinski’s rules are routinely employed to guide structure-based drug design. While a potent molecule is essential for drug discovery, ultimately ADME-Tox properties decide which molecule is advanced into clinical trials. During optimization, leads tend to increase in size and lipophilicity which can be offset by introducing the sterically
insignificant nitrile group. Replacing a hydrogen with a nitrile can roughly lower cLogP\textsuperscript{47} by half an order of magnitude and nearly an order of magnitude reduction for LogD.\textsuperscript{48} A more dramatic decrease in lipophilicity by over a full order of magnitude for cLogP/LogD often occurs when replacing a halogen or methyl group by a nitrile. The development of 16 from 17 (capravirine) provides an excellent case study in modulating ADME properties through nitrile substitution. Refining 17 led to the truncated analog 17 that was evaluated and found to be less potent and more lipophilic. Consistent with the nitrile being a halogen bioisostere, interchanging the chlorine with a nitrile (18 \rightarrow 19) reduced the lipophilicity by an order of magnitude and increased the lipophilic-ligand efficiency (LLE).\textsuperscript{49} Introduction of a second nitrile led to 16 with similar activity to 17, 141 mass units smaller, a decreased lipophilicity, and a much improved half-life in human liver microsomes (HLM); 7.5 minutes for 17 compared to 73 minutes for 16 (Figure 6).
A comprehensive survey of the interactions between the nitrile group and a diverse range of bioactive receptors has been studied. Collating the nitrile-containing drugs and clinical candidates by their structural similarities, reveals at least seven different modes by which nitrile substituents accentuate binding to receptor targets. A greater understanding of these specific functions is likely to facilitate lead optimizations with nitrile-containing candidates and will, optimistically, increase the number of nitrile-containing pharmaceuticals.
2. Transmissive Olefination via Conjugate Addition-MgO Elimination (Taken in part from a manuscript in preparation for Angew Chem)\textsuperscript{50}

2.1 Introduction

Six-membered transition structures are an essential motif in many powerful synthetic methods. \textsuperscript{51} [4+2] Cycloadditions, electrocyclic reactions, and [3,3]-sigmatropic rearrangements proceed through privileged six-electron, six-atom transition structures because the electron delocalization allows a low-energy pathway for the reaction.

[3,3]-Sigmatropic rearrangements comprise a subset of six-electron reactions which generally favor rearrangement through a chair-like transition structure. [3,3]-Sigmatropic rearrangements exhibit a remarkable diversity of atom substitutions within the six-membered ring (Figure 7). Cope, Claisen, and aza-Cope-Mannich reactions incorporate carbon, oxygen, and nitrogen ring atoms respectively. Related aldol, metal allylation, and intramolecular hydride reductions proceeding through Zimmerman-Traxler transition structures\textsuperscript{52} similarly proceed through 6 membered TS’s that incorporate a metal and a heteroatom.

\[ A^\cdot \cdot B^\cdot \rightarrow A^\cdot \cdot B^\cdot \rightarrow A^\cdot \cdot B^\cdot \]

\[ {^{20}} \quad {^{21}} \quad {^{22}} \]

\textbf{Figure 7.} Generalized [3,3]-Sigmatropic Rearrangement.
The facility of these diverse, six-electron reactions hints at the possibility of new reaction modes. A conceptually intriguing variation of this six electron strategy is the anionic rearrangement driven by formation of a metal oxide (Scheme 1).\textsuperscript{53} Specifically, the addition of a Grignard reagent to a hydroxymethylacrylonitrile was anticipated to generate the alkylmagnesium alkoxide \textit{24} whose [3,3]-sigmatropic rearrangement to the \textit{Z}-alkenenitrile \textit{25} would be aided by formation of magnesium oxide.\textsuperscript{54} Rearrangement through the chair transition structure \textit{24b} avoids the allylic strain present in \textit{24a} and would serve to efficiently favor the \textit{Z} diastereomer.\textsuperscript{55,56}

\begin{center}
\textit{Scheme 1. Transmissive Olefination Route to Alkenenitriles.}
\end{center}

Alkenenitriles are versatile synthetic intermediates\textsuperscript{57} that are readily transformed into an array of carbocycles\textsuperscript{58} and heterocycles.\textsuperscript{59} The alkenenitrile structural motif is also a key functionality embedded within several bioactive natural products\textsuperscript{60} and pharmaceuticals\textsuperscript{61} which typically require selective access to one olefin geometry for bioactivity. The increasing isolation of alkenenitriles from natural sources,\textsuperscript{62} and their incorporation
within drug targets underscores the need for rapid, modular stereoselective syntheses of alkenenitriles.\textsuperscript{63}

\textbf{2.2 Results and discussion}

The precursor hydroxy alkenenitriles are readily generated through ultrasound assisted\textsuperscript{64} Bayliss-Hillman condensation.\textsuperscript{65} In a related strategy\textsuperscript{66}, activation of the hydroxyl group, typically by acetylation, and allylic displacement affords \(\alpha\)-substituted alkenenitriles.\textsuperscript{67}

Experimentally, the viability of initiating the magnesium oxide-driven rearrangement was explored through the addition of excess \(i\)-PrMgCl to hydroxynitrile \textbf{23a}. Gratifyingly, the \(Z\)-alkenenitrile \textbf{25a} was afforded in 56\% yield (Table 1, entry 1) consistent with a concerted intramolecular rearrangement through the alkylmagnesium alkoxide \textbf{24}. The addition-elimination requires three equivalents of Grignard reagent implying that the rearrangement proceeds via the more nucleophilic magnesiate \textbf{24b} rather than an alkylmagnesium alkoxide.\textsuperscript{68} The incipient steric compression present in \textbf{24a} is anticipated to favor rearrangement through \textbf{24b} in which the small nitrile group is located in the more sterically demanding position. The extremely compact \(\pi\)-system of the nitrile resists nucleophilic attack by the proximal Grignard reagent, instead channeling the alkylmagnesium alkoxide to engage in a 6-electron transmissive olefination. Driven by the irreversible formation of magnesium oxide,\textsuperscript{69} the intramolecular rearrangement is remarkably facile and extremely selective\textsuperscript{70} for the \(Z\)-alkenenitrile \textbf{25a}.\textsuperscript{71}
Table 1. Transmissive Olefination of α-Hydroxy Alkenenitriles

<table>
<thead>
<tr>
<th>Entry</th>
<th>Hydroxynitrile</th>
<th>Grignard</th>
<th>Alkenenitrile</th>
<th>yield</th>
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<tr>
<td>1</td>
<td>Ph(\text{OH})(\text{CN})(\text{CN}) (23\text{a})</td>
<td>(i)-PrMgCl</td>
<td>Ph(\text{CN})(\text{CN}) (25\text{a})</td>
<td>56%</td>
</tr>
<tr>
<td>2</td>
<td>Ph(\text{OH})(\text{CN})(\text{CN}) (23\text{a})</td>
<td>MeMgCl</td>
<td>Ph(\text{CN})(\text{CN}) (25\text{b})</td>
<td>62%</td>
</tr>
<tr>
<td>3</td>
<td>Ph(\text{OH})(\text{CN})(\text{CN}) (23\text{a})</td>
<td>BuMgCl</td>
<td>Ph(\text{CN})(\text{CN}) (25\text{c})</td>
<td>77%</td>
</tr>
<tr>
<td>4</td>
<td>Ph(\text{OH})(\text{CN})(\text{CN}) (23\text{a})</td>
<td>(t)-BuMgCl</td>
<td>Ph(\text{CN})(\text{CN}) (25\text{d})</td>
<td>54%</td>
</tr>
<tr>
<td>5</td>
<td>Ph(\text{OH})(\text{CN})(\text{CN}) (23\text{a})</td>
<td>Me(_3\text{SiCH}_2)MgCl</td>
<td>Ph(\text{CN})(\text{CN}) (\text{SiMe}_3) (25\text{e})</td>
<td>52%</td>
</tr>
<tr>
<td>6</td>
<td>Ph(\text{OH})(\text{CN})(\text{CN}) (23\text{a})</td>
<td>BrMg</td>
<td>Ph(\text{CN})(\text{CN}) (25\text{f})</td>
<td>66%</td>
</tr>
</tbody>
</table>
7. \( \text{Ph} = \text{CN} \quad 23a \quad \text{BrMg} \quad \text{Ph} = \text{CN} \quad 25g \quad 62\% \\
\text{MeO} \quad \text{OH} \quad \text{MeO} \quad \text{OH} \quad \text{MeO} \quad \text{OH} \\
\text{MeO} \quad \text{MeO} \quad \text{MeO} \quad \text{MeO} \quad \text{MeO} \quad \text{MeO} \\
8. \text{i-PrMgCl} \quad 25h \quad 60\% \\
9. \text{BrMg} \quad \text{SiMe}_{3} \quad 25i \quad 52\% \\
10. \text{BrMg} \quad \text{Ph} \quad \text{Ph} \quad 25j \quad 63\% \\
11. \text{BuMgCl} \quad 25k \quad 83\% \\
12. \text{BuMgCl} \quad 25l \quad 68\% \\
13. \text{Me}_{3}\text{SiCH}_{2}\text{MgCl} \quad 25m \quad 52\% \quad (6:1)
The transmissive olefination is remarkably facile for an array of hydroxynitriles (Table 1). Aliphatic and olefinic Grignard reagents add with equal efficacy, with the skipped dienes 25f, and 25i-j being generated without isomerization (Table 1, entry 6 and entries 9, 10). Addition of BuMgCl to nitrile 23a stereoselectively forms the perfumery agent 25c\(^{72}\) (Table 1, entry 3). Modest oxygenation within the Grignard reagent is tolerated (Table 1, entry 7) although attempts to use the internally chelated, less nucleophilic bromomagnesium dioxolane were unsuccessful. Sterically demanding secondary (Table 1, entries 1 and 8) and tertiary Grignards (Table 1, entry 4) are as stereoselective as MeMgCl, the smallest nucleophilic Grignard reagent. The stereoselectivity is consistent with the size of the carbinol substituent determining the stereoselectivity rather than the alkyl group engaging in the transfer (Scheme 2).

The utility of dienenitriles\(^{73}\) stimulated the transmissive olefination with the hydroxy dienenitrile 23d (Table 1, entries 13, 14 and 15). Addition of MeMgCl affords the dienenitrile 25n with a 4:1 preference for the Z stereochemistry whereas BuMgCl affords the dienenitrile 25o as a 6:1 Z:E mixture of diastereomers. Although the stereoselectivity is modest, this currently represents one of the most selective routes to this functionality.
The transmissive olefination of hydroxy nitriles rapidly assembles Z-alkenenitriles from three readily available components: an aldehyde, acrylonitrile, and a Grignard reagent. The operational simplicity of the method stimulated applying the transmissive olefination to the synthesis of the neolignan morinol I. Morinol I is one of a series of neolignans that was isolated during a bioactivity guided isolation of extracts from the roots of the traditional Chinese medicinal herb *Morina Chinensis*. For such a relatively simple molecule, morinol I is rather remarkable. Morinol I is the only neoligan among the entire family of morinol metabolites to have a skipped diene. Other morinols are formally those having water added to the C7-C8 bond. Intriguingly, although Morinol I is drawn in the isolation report as having a skipped diene structure, the NMR data are more consistent with having a conjugated diene. Unfortunately a sample or spectral data is unavailable to resolve the structure of morinol I leaving synthesis as the most promising method for determining the correct structure of this metabolite. The structural assignment of the remaining family members appears secure, in part because morinol C and D have been synthesized.

Access to the putative structure of morinol I began with the ultrasound-promoted DABCO condensation of veratraldehyde 24 with acrylonitrile (Scheme 2). Transmissive olefination of the resulting nitrile 23b initiated with vinylmagnesium bromide, readily installed the requisite Z-stereochemistry to afford the alkenenitrile 25p as a single stereoisomer. Mizoroki Heck addition of 3, 4-dimethoxyboronic acid to 25p selectively appended the second aromatic ring favoring the E-geometry by 8:1. Reduction of the nitrile to the corresponding alcohol via conventional i-Bu₂AlH reduction, hydrolysis, and aldehyde reduction was irreproducible and gave an aldehyde that was extremely
prone to isomerization. Consequently an alternative reduction sequence was developed involving hydrolysis to amide, imide formation, and reduction (26→30). Using this sequence the putative morinol I was obtained without the formation of olefin isomers. Unfortunately alcohol 30 exhibits spectral data distinctly different for that reported from Morinol I.

Scheme 2. Transmissive Olefination Route to 30

Acess to the vinylsilane 25p provided a unique opportunity to prepare the Z-isomer of morinol I, a potential candidate for the natural product. Iodination of the vinylsilane 25i with NIS in hexafluoroisopropanol\(^\text{79}\) provided the Z-vinyliodide 31 that was engaged in a Suzuki coupling to give 32 as a single isomer. Nitrile reduction via the hydrolysis, imide, and reduction sequence provided alcohol 35 again exhibiting spectral data different from that of morinol I\(^\text{80}\) (Scheme 3).
2.3 Conclusion

The transmissive olefination of hydroxy alkenenitriles efficiently assembles $Z$-alkenenitriles from three readily available components: an aldehyde, acrylonitrile, and a Grignard reagent. Adding excess Grignard reagent to an hydroxyl alkenenitrile triggers a 6-electron transmissive olefination driven by formation of magnesium oxide. The versatility of the stereoselective $Z$-alkenenitrile synthesis is illustrated in a 5-step synthesis of several morinol lignans in an effort to determine the structure of the nature product. Collectively these syntheses establish the structure of morinol I as the only member of the morinol family having a conjugated diene.
3. Allylic and Allenic Halide Synthesis via NbCl$_5$- and NbBr$_5$-Mediated Alkoxide Rearrangements (Taken in part from Journal of Organic Chemistry$^{81}$)

3.1 Introduction

Allylic halides are powerful, versatile electrophiles.$^{82}$ The excellent electrophilicity stems from stereoelectronic interactions between the $\sigma^{*}_{C-X}$ orbital and the adjacent $\pi$ system,$^{83}$ facilitating a range of efficient and predictable displacements.$^{84}$ Numerous natural product syntheses have harnessed the excellent electrophilicity of allylic halides to overcome difficult displacements and challenging cyclizations.$^{85}$

Allylic halide intermediates in total synthesis campaigns are frequently synthesized from aldehydes through olefination-reduction-halogenation sequences (Scheme 4,$^{36}$ $36\rightarrow37\rightarrow38\rightarrow39$).$^{86}$ The three-step sequence is necessitated in part because the requisite Wittig reagents suffer facile halide ejection,$^{87}$ preventing a direct "halo-olefination," and partly because of the predictable conversion of primary allylic alcohols $38$ to allylic halides $39$ without rearrangement.$^{88}$ In contrast, regioselective halogenation of secondary allylic alcohols is reagent$^{89}$ and structure$^{90}$ dependent with many reactions channeling through both $S_N2$ and $S_N2'$ displacement manifolds.$^{91}$

Scheme 4. Typical Allylic Halide Synthesis
Direct halogenation of propargylic alcohols similarly affords mixtures of regioisomeric halides. Consequently a two steps sequence of alcohol activation, usually sulfonylation, followed by $S_N2'$ halide displacement is typically employed to convert propargylic alcohols $40$ to terminal allenic halides $42$ (Scheme 5, $40 \rightarrow 41 \rightarrow 42$). Subsequent transition metal catalyzed coupling allows a diverse range of bond constructions on these valuable synthetic partners.

\[
\begin{align*}
\text{Scheme 5. Typical Allenic Halide Synthesis}
\end{align*}
\]

The inherent utility of allylic and allenic halides stimulated a direct synthesis from carbonyl and alcoholic precursors. Conceptually the transformation centers on a metalla-halo-[3,3] rearrangement predicated on metal oxide elimination and the privileged nature of six-membered transition structures (Scheme 6). Addition of a vinyl metal bearing an appropriate halide was envisaged to access the allylic alkoxide $44$ and trigger a concerted rearrangement to the corresponding allylic halide $45$. As sporadically happens in chemical research, the same concept was being simultaneously pursued with allylic chlorotitanium alkoxides ($44$ MX=TiCl$_3$). Mechanistic experiments with these titanium alkoxides implicated a stepwise ionization-halogenation sequence rather than a concerted rearrangement, although in principle tuning the metal oxophilicity and halogen nucleophilicity should favor a concerted halogen transfer.
Publication of the pioneering titanium-based allylic chloride synthesis was closely followed by communication\textsuperscript{103} of a complementary niobium pentahalide procedure. Although preliminary, the use of niobium broadened the substrate scope and offered the promise of a general approach to both allylic and allenic halides through a concerted rearrangement. Complete details of these niobium pentachloride and pentabromide rearrangements are provided with an emphasis on: mechanistic insight; extended substrate scope to include allylic alcohols, aldehydes, enals, ketones, and enones; cascade reduction-halogenation and addition-halogenation strategies; and the synthesis of allenic bromides.

**3.2 Results and discussion**

The metalla-halo-[3,3]-rearrangement strategy requires a metal halide capable of simultaneously activating the allylic alcohol, delivering a halogen in an $S\text{N}_2'$ displacement, and forming a stable metal oxide.

The ability to chlorinate benzyl alcohol stimulated a direct nucleophilic addition-chlorination with aldehydes (Scheme 7). Adding BuMgCl or BuLi to benzaldehyde affords metal alkoxides $46$ that are readily transformed into the secondary benzylic chloride $47$ upon exposure to NbCl$_5$. An analogous addition of the chlorine-containing
Grignard reagent 48<sup>104</sup> efficiently provides the dichloride 49 indicating that NbCl<sub>5</sub> tolerates additional chlorination in the substrate (Scheme 5).

![Scheme 7](image)

Scheme 7. Organometallic Addition-Chlorination with NbCl<sub>5</sub>

The sequential addition-chlorinations with benzaldehyde (Scheme 8) provided an excellent foundation for the direct halo-olefination of aldehydes and ketones.<sup>105</sup> In the optimized procedure, vinylmagnesium bromide<sup>106</sup> was added to a THF solution<sup>107</sup> of the aldehyde and then four volumes of dioxane and solid NbCl<sub>5</sub> were added. After 10 min the crude chloride<sup>108</sup> was isolated and subjected to phenylsulfenylate displacement in THF to afford, in the case of 3-methoxybenzaldehyde 43b, an excellent yield of the corresponding sulfide 51.

![Scheme 8](image)

Scheme 8. Direct Halo-Olefination-Sulfide Displacement of Aldehyde

The niobium-mediated halogenation of metal alkoxides is equally effective for the addition of organometallics to unsaturated carbonyl compounds (Scheme 9). Reducing ketone 52 with LiBH<sub>4</sub> and adding NbCl<sub>5</sub> affords the corresponding chloride that was
displaced with sulenate in an overall reductive-selenylation with translocation of the double bond. Collectively these addition-chlorination and reduction-chlorination sequences imply significant scope for halogenating allylic alkoxides generated as intermediates from different reactions.

Scheme 9. Organometallic-Addition- NbCl₅ Chlorination.

The proclivity of allylic alcohols to participate in the formal metalla-halo-[3,3]-rearrangement stimulated expanding the substrate scope to include propargylic alcohols (Table 2). Sequential deprotonation and chlorination of the propargylic alcohol 54a afforded only a trace of the allenyl chloride at room temperature, whereas coaxing the reaction with heating led to considerable decomposition. NbBr₅ proved to be a more efficient halogenating agent triggering a smooth rearrangement at room temperature (Table 2, entry 1).

The NbBr₅ rearrangement is of reasonably broad scope and provides rapid access to synthetically versatile bromoallenes (Table 2). Secondary and tertiary propargylic alcohols react with similar efficiency (Table 2, entries 1-4, respectively). The bromination is equally applicable to alcohols with adjacent aromatic substitution as with aliphatic substituents (Table 2, compare entry 1 with entries 2-4). Although speculative, the allenyl bromide synthesis is envisaged through the hexacoordinate niobiate 55 formed
through expansion of niobium's coordination sphere. Concomitant internal delivery of the halogen to the olefin terminus is likely promoted by forming trichloroniobium oxide.\textsuperscript{110}

Table 2. Metala-halo-[3, 3] rearrangement of Propargylic Alcohols

<table>
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</table>
3.3 Conclusion

Allylic and allenic halides are readily generated by adding NbCl$_5$ or NbBr$_5$ to allylic or propargylic alkoxides. The halogenation formally occurs through a metalla-halo [3,3] rearrangement although ionization and direct displacement mechanisms appear to compete in some cases. The intermediate allylic alkoxides can be prepared by deprotonation or, equally as effectively, through an organometallic addition or reduction allowing the direct conversion of an aldehyde or ketone to the corresponding allylic chloride. Particularly useful is the direct "halo-olefination" of aromatic and aliphatic aldehydes by sequential addition of vinylmagnesium bromide and NbCl$_5$ or NbBr$_5$ which overcomes the current multi-step sequences. Secondary or tertiary propargylic alcohols react similarly with NbBr$_5$ to afford allenylic bromides. The halides are readily isolated in pure form through simple extraction and can be used in subsequent displacements without prior purification.
4. Experimentals

General Procedure A for Baylis-Hillman Reaction: To a stirred solution of aldehyde (1 mmol) and DABCO (1, 4-diazabicyclo[2,2,2]octane) (10 mmol) in a mixture solvent of 1,4-dioxane (4 ml) and water (1 ml), was added acrylonitrile (10 mmol). The resulting clear mixture was stirred at room temperature for 48 h. Then 1N HCl was added to the mixture until an acidic mixture (PH = 6) is formed. After ethyl acetate (30 ml) was added, the organic phase was separated and the water phase was extracted with ethyl acetate (2×10 ml). The combined organic phase was washed with brine and dried over anhydrous magnesium sulfate. After removing of the solvent and low bolting-point substance, the crude product was purified by radial chromatography to afford analytically pure material.

General Procedure B for Baylis-Hillman Reaction: To a stirred solution of aldehyde (1 mmol) and DABCO (1,4-diazabicyclo[2,2,2]octane) (0.6 mmol) in a mixture solvent of 1,4-dioxane (4 ml) and water (1 ml), was added acrylonitrile (2.0 mmol). The resulting clear mixture vibrates with ultrasonic at room temperature for 5h. Then 1N HCl was added to the mixture until an acidic mixture (PH = 6) is formed. After ethyl acetate (30 ml) was added, the organic phase was separated and the water phase was extracted with ethyl acetate (2×10 ml). The combined organic phase was washed with brine and dried over anhydrous magnesium sulfate. After recrystallization, the crude product was purified to afford analytically pure material.

General Procedure C for Transmissive Olefination via Conjugate Addition-MgO Elimination: To a stirred THF solution of 23 at a -20°C was added a Gringard reagent (3.0 equiv) slowly. After 3 h, the mixture was quenched with 0.1 M HCl solution, the
resulting mixture was stirred vigorously for 5 min. The crude product was extracted with ether, dried (MgSO₄), concentrated, and purified by radial chromatography to afford analytically pure material.

2-(Hydroxy-phenyl-methyl)-acrylonitrile (23a): General Procedure A for Baylis-Hillman Reaction was employed with benzyl aldehyde (1.06 g, 10 mmol) to afford, after purification by radial chromatography (25% EtOAc in hexanes), 1.45 g (91%) of 23a as an oil: \[ ^1H \text{NMR (CDCl}_3, 400 MHz): \delta 3.36 \text{ (s, 1H)}, 5.22 \text{ (s, 1H)}, 5.98 \text{ (s, 1H)}, 6.05 \text{ (s, 1H)}, 7.35 – 7.42 \text{ (m, 5H)}; \]
\[ ^{13}C \text{NMR (CDCl}_3, 100 MHz): \delta 73.9; 116.9; 126.0; 126.4; 128.8; 130.0; 139.0 \text{ ppm}. \]

2-[(3, 4-Dimethoxy-phenyl)-hydroxy-methyl]-acrylonitrile (23b): General Procedure B for Baylis-Hillman Reaction was employed with 3, 4-dimeoxy benzyl aldehyde (1.66 g, 10 mmol) to afford, after purification by radial chromatography (35% EtOAc in hexanes), 2.06g (95%) of 23b as an oil: \[ ^1H \text{NMR (CDCl}_3, 400 MHz): \delta 3.78 \text{ (s, 1H)}, 3.81 \text{ (s, 3H)}, 3.81 \text{ (s, 3H)}, 5.15 \text{ (s, 1H)}, 5.94 \text{ (s, 1H)}, 6.80 – 6.87 \text{ (m, 3H)}; \]
\[ ^{13}C \text{NMR (CDCl}_3, 100 MHz): \delta 55.5, 73.2, 109.1, 110.8, 116.8, 118.8, 126.1, 129.4, 131.6, 148.6, 148.7 \text{ ppm}. \]

2-((3,4-difluorophenyl)(hydroxy)methyl)acrylonitrile (23c): General Procedure A for Baylis-Hillman Reaction was employed with 3,4-difluorobenzaldehyde (1.42 g, 10 mmol) to afford, after purification by radial chromatography (25% EtOAc in hexanes), 1.46 g (75%) of 23c as an oil: \[ \text{IR (neat) 2231 cm}^{-1}; \]
\[ ^1H \text{NMR (CDCl}_3, 400 MHz): \delta 3.98 \text{ (s, 1H)}, 5.25 \text{ (s, 1H)}, 6.01 \text{ (s, 1H)}, 6.12 \text{ (s, 1H)}, 7.01 – 7.25 \text{ (m, 3H)}; \]
\[ ^{13}C \text{NMR (CDCl}_3, 100 MHz): \delta 3.98 \text{ (s, 1H)}, 5.25 \text{ (s, 1H)}, 6.01 \text{ (s, 1H)}, 6.12 \text{ (s, 1H)}, 7.01 – 7.25 \text{ (m, 3H)}; \]
\[ ^{13}C \text{NMR (CDCl}_3, 100 MHz): \delta 3.98 \text{ (s, 1H)}, 5.25 \text{ (s, 1H)}, 6.01 \text{ (s, 1H)}, 6.12 \text{ (s, 1H)}, 7.01 – 7.25 \text{ (m, 3H)}; \]
100 MHz): δ 72.8, 115.5 (d, J = 18 Hz), 116.7, 117.6 (d, J = 17 Hz), 122.7 (d, J = 4 Hz), 125.6, 131.1, 136.4 (d, J = 9 Hz), 150.3 (d, J = 248 Hz), 150.4 (d, J = 248 Hz) ppm.

3-Hydroxy-2-methylene-5-phenyl-pent-4-enenitrile (23d): General Procedure A for Baylis-Hillman Reaction was employed with cinnamyl aldehyde (1.32 g, 10 mmol) to afford, after purification by radial chromatography (25% EtOAc in hexanes), 1.35 g (73%) of 23d as an oil: ¹H NMR (CDCl₃, 400 MHz): δ 3.59 (s, 1H), 4.84 (d, J = 7 Hz), 5.93 (s, 3H), 6.02 (s, 3H), 6.14 (dd, J = 16 Hz, 7 Hz, 1H), 6.66 (d, J = 16 Hz, 1H), 7.24 – 7.36 (m, 5H); ¹³C NMR (CDCl₃, 100 MHz): δ 72.5, 116.9, 125.1, 126.4, 126.6, 128.2, 128.5, 130.3, 133.3, 135.5 ppm.

(Z)-2-Benzylidene-4-methyl-pentanenitrile (25a): General Procedure C was employed with 23a (40.0mg, 0.25mmol) and isopropyl magnesium bromide (0.43ml, 0.75mmol) to afford, after purification by radial chromatography (hexanes), 25.9 mg (56%) of 25a as an oil: IR (neat) 2209, 2957 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 0.99 (d, J = 6.8 Hz, 6H), 2.00 – 2.06 (m, 1H), 2.27 (d, J = 7.3 Hz, 2H), 6.90 (s, 1H), 7.38 – 7.74 (m, 5H); ¹³C NMR (CDCl₃, 100 MHz): δ 24.8, 30.4, 48.3, 113.5, 121.8, 131.4, 131.6, 132.7, 136.3, 147.1 ppm; HRMS for C₁₃H₁₅N: [M+Na⁺] calculated: 208.1102, found: 208.1093.

(Z)-2-Benzylidene-butyronitrile (25b): General Procedure C was employed with 23a (40.0mg, 0.25mmol) and methyl magnesium bromide (0.33ml, 0.75mmol) to afford, after purification by radial chromatography (hexanes), 24.3 mg (62%) of 25b as an oil: IR (neat) 2972, 2209 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 1.26 (t, J = 7.0 Hz, 3H), 2.45 (q, J
= 7.0 Hz, 2H), 6.94 (s, 1H), 7.38 - 7.43 (m, 3H), 7.70 - 7.73 (m, 2H); $^{13}$C NMR(CDCl$_3$, 100 MHz): $\delta$ 13.0, 29.6, 113.0, 118.7, 128.5, 128.8, 129.8, 133.8, 142.5 ppm.

(Z)-2-Benzylidene-heptanenitrile (25c): General Procedure C was employed with 23a (40.0 mg, 0.25 mmol) and butyl magnesium chloride (0.43ml, 0.75mmol) to afford, after purification by radial chromatography (hexanes), 38.5 mg (77%) of 25c as an oil: IR (neat) 2928, 2209 cm$^{-1}$; $^1$H NMR(CDCl$_3$, 400 MHz): $\delta$ 0.92 (t, $J$ = 7.0 Hz, 3H), 1.33 - 1.38 (m, 4H), 164 - 1.70 (m, 2H), 2.40 (t, $J$ = 7.7 Hz, 2H), 6.92 (s, 1H), 7.39 - 7.42 (m, 3H), 7.71 - 7.73 (m, 2H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 14.0, 22.3, 27.9, 30.8, 36.2, 111.6, 118.8, 128.5, 128.8, 129.8, 133.8, 143.2 ppm.

(Z)-2-Benzylidene-4,4-dimethyl-pentanenitrile (25d): General Procedure C was employed with 23a (40.0mg, 0.25mmol) and t-butyl magnesium chloride (0.75ml, 0.75mmol) to afford, after purification by radial chromatography (hexanes), 27.0 mg (54%) of 25d as an oil: IR (neat) 2959, 2209 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 1.05 (s, 9H), 2.30 (s, 2H), 6.88 (s, 1H), 7.39 - 7.75 (m, 5H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 32.1, 35.4, 52.7, 111.5, 122.9, 131.5, 131.6, 132.8, 136.7, 149.3 ppm; HRMS C$_{14}$H$_{17}$N: [M+Na$^+$] calculated: 222.1259, found: 222.1245.

(Z)-2-Benzylidene-4-trimethylsilyl-butyronitrile (25e): General Procedure C was employed with 23a (40.0 mg, 0.25mmol) and trimethylsilyl methyl magnesium chloride (0.75 ml, 0.75mmol) to afford, after purification by radial chromatography (hexanes), 31.6 mg (52%) of 25e as an oil: IR (neat) 2953, 2209 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 0.06 (s, 9H), 0.86 – 0.91 (m, 2H), 2.38 – 2.43 (m, 2H), 6.94 (s, 1H), 7.34 – 7.72 (m,
(Z)-2-Benzylidene-pent-4-enenitrile (25f): General Procedure C was employed with 23a (40.0 mg, 0.25 mmol) and vinyl magnesium bromide (1.1 ml, 0.75 mmol) to afford, after purification by radial chromatography (hexanes), 27.9 mg (66%) of 25f as an oil: IR (neat) 2926, 2209, 1641 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz): δ 3.11 (dd, \(J = 1.0\) Hz, 6.4 Hz, 2H), 5.21 – 5.25 (m, 2H), 5.82 – 5.90 (m, 1H), 6.93 (s, 1H), 7.34 – 7.71 (m, 5H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): δ 42.9, 112.3, 121.5, 121.7, 131.5, 131.7, 132.9, 135.6, 136.7, 146.8 ppm; HRMS C\(_{12}\)H\(_{11}\)N: [M+Na\(^+\)] calculated: 192.0789, found: 192.0794.

(Z)-2-Benzylidene-5-(3-methoxy-phenyl)-pentanenitrile (25g): General Procedure B was employed with 23a (48 mg, 0.3 mmol) and 3-methoxy phenethyl magnesium bromide (1.8 ml, 0.90 mmol) to afford, after purification by radial chromatography (10% EtOAc in hexanes), 51.5 mg (62%) of 25g as an oil: IR (neat) 2936, 2209, 1736 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz): δ 1.96 – 2.04 (m, 2H), 2.40 – 2.45 (m, 2H), 2.68 (t, \(J = 7.5\) Hz, 2H), 3.80 (s, 3H), 6.74 (s, 1H), 6.76 – 6.80 (m, 2H), 6.91 (s, 1H), 7.20 – 7.25 (m, 2H), 7.35 – 7.43 (m, 3H), 7.71 – 7.42 (m, 2H); \(^{13}\)C NMR(CDCl\(_3\), 100 MHz): δ 29.5, 34.8, 35.5, 55.1, 111.0, 111.3, 114.2, ,118.7, 120.8, 128.5, 128.8, 129.4, 129.9, 133.7, 142.8, 143.7, 159.7 ppm; HRMS C\(_{12}\)H\(_{11}\)N: [M+Na\(^+\)] calculated: 300.1365, found: 300.1373.

(Z)-2-(3,4-Dimethoxy-benzylidene)-4-methyl-pentanenitrile (25h): General Procedure C was employed with 23b (66 mg, 0.3 mmol) and isopropyl magnesium bromide (0.55
ml, 1.1 mmol) to afford, after purification by radial chromatography (15% EtOAc in hexanes), 44.0 mg (60%) of 25h as an oil: IR (neat) 2957, 2205 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 0.99 (d, \(J = 6.5\) Hz, 6H), 1.96 – 2.06 (m, 1H), 2.23 – 2.25 (m, 1H), 3.92 (s, 3H), 3.94 (s, 3H), 6.81 (s, 1H), 6.86 (d, \(J = 8.6\) Hz, 1H), 7.19 (dd, \(J = 8.2\) Hz, 2.0 Hz, 1H), 7.54 (d, \(J = 2.0\) Hz, 1H); \(^1\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 21.9, 27.6, 45.3, 55.9, 107.6, 110.3, 110.8, 119.6, 123.1, 126.8, 144.0, 148.9, 150.5 ppm; HRMS C\(_{15}\)H\(_{19}\)NO\(_2\): [M+Na\(^+\)] calculated: 284.1053, found: 284.1054.

(2Z, 4E)-2-(3, 4-Dimethoxybenzylidene)-5-(trimethylsilyl)pent-4-enenitrile (25i):

Neat 1, 2-dibromoethane (0.01 mL, 0.07 mmol) was added to a suspension of Mg (22.4 mg, 0.89 mmol) in cold (0°C) THF (0.8 mL). Neat (E)-(2-(trimethylsilyl)vinyl) bromide (0.09 mL, 0.69 mmol) was added dropwise and after 1 h at 0 °C the THF solution of the resulting Grignard reagent was added to a -20 °C, THF solution (3 mL) of 2-((3, 4-dimethoxyphenyl)(hydroxy)methyl) acrylonitrile 23b (50 mg, 0.23 mmol). After 3 h, the reaction mixture was poured into aqueous, saturated NH\(_4\)Cl (2 mL). The aqueous phase was extracted with EtOAc (3 x 10 mL), the combined organic phase was washed with brine, dried (Na\(_2\)SO\(_4\)), concentrated and purified by radial chromatography (15% EtOAc in hexanes) to afford 36.8 mg (52%) of nitrile 25i as a light yellow oil: IR (neat) 2954, 2206, 1600 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) -0.01 (s, 9H), 3.16 (d, \(J = 6.6\) Hz, 2H), 3.92 (s, 3H), 3.94 (s, 3H), 5.88 (d, \(J = 18.0\) Hz, 1H), 6.04 (dt, \(J = 18.0, 6.6\) Hz, 1H), 6.84 (s, 1H), 6.87 (d, \(J = 7.8\) Hz, 1H), 7.19 (dd, \(J = 7.8, 1.8\) Hz, 1H), 7.56 (d, \(J = 1.8\) Hz, 1H); \(^1\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) -1.32, 42.7, 55.9, 106.2, 110.1, 110.7, 119.4, 123.3, 126.6, 134.7, 140.3, 143.9, 148.8, 150.5 ppm; HRMS for C\(_{17}\)H\(_{23}\)NO\(_2\)Si: [M+H\(^+\)] calculated 302.1577, found 302.1563.
(2Z,4E)-2-(3,4-Dimethoxybenzylidene)-5-phenylpent-4-enenitrile (25j): A cold (0 °C) suspension of Mg (22.4 mg, 0.89 mmol) in THF (0.8 mL) was activated by adding 1,2-dibromoethane (0.01 mL, 0.07 mmol) and after 5 min. β-bromostyrene (0.09 mL, 0.69 mmol) was added dropwise. After 1 h at 0 °C the THF solution of the Grignard reagent was added to a -20 °C THF solution (3 mL) of 2-((3,4-dimethoxyphenyl)(hydroxy)methyl)acrylonitrile 23b (50 mg, 0.23 mmol). After 3 h the reaction mixture was poured into an aqueous saturated NH₄Cl solution (2 mL). The aqueous phase was extracted with EtOAc (3 x 10 mL), the combined organic phase was washed with brine, dried (Na₂SO₄), concentrated, and purified by radial chromatography (15% EtOAc in hexanes) to afford 44.5 mg (63%) of nitrile 25j as a light yellow oil: IR (neat) 2934, 2206, 1599 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 3.28 (d, J = 6.6 Hz, 2H), 3.92 (s, 3H), 3.93 (s, 3H), 6.25 (td, J = 15.6, 7.2 Hz, 1H), 6.58 (d, J = 15.6 Hz, 1H), 6.88 (d, J = 8.4 Hz, 1H), 6.92 (s, 1H), 7.21 (d, J = 8.4 Hz, 1H), 7.26 (d, J = 7.8 Hz, 2H), 7.33 (t, J = 7.8 Hz, 1H), 7.40 (d, J = 7.8 Hz, 2H), 7.53 (s, 1H); ¹³C NMR (CDCl₃, 100 MHz): δ 39.2, 56.0, 106.6, 110.4, 110.8, 119.4, 123.2, 124.4, 126.4, 126.6, 127.7, 128.6, 133.6, 136.7, 143.8, 148.9, 150.7 ppm; HRMS for C₂₀H₁₉NO₂ [M+Na⁺] Calculated 328.1314, found 328.1321.

(Z)-2-(3,4-dimethoxybenzylidene)heptanenitrile (25k): General Procedure C was employed with 23b (40 mg, 0.18 mmol) and butylmagnesium chloride (0.27 mL, 0.55 mmol) to afford, after purification by radial chromatography (15% EtOAc in hexanes), 64.7 mg (83%) of 25k as an oil: IR (neat) 2930, 2204, 1599 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 0.92 (t, J = 6.8 Hz, 3H), 1.30-1.40 (m, 4H), 1.60-1.70 (m, 2H), 2.37 (td, J = 8.0,
1.2 Hz, 2H), 6.84 (s, 1H), 6.87 (d, J = 8.4 Hz, 1H), 7.18 (dd, J = 8.4, 2.0 Hz, 1H), 7.53 (d, J = 2.4 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 14.0, 22.4, 28.1, 30.9, 36.2, 55.9, 108.7, 110.3, 110.8, 119.5, 123.0, 126.9, 143.1, 148.9, 150.4 ppm; HRMS for C$_{16}$H$_{21}$NO$_2$ [M+Na$^+$] calculated 282.1470, found 282.1481.

(Z)-2-(3,4-Difluorobenzylidene)heptanenitrile (25l): General Procedure C was employed with 23e (40 mg, 0.20 mmol) and butylmagnesium bromide (0.30 mL, 0.60 mmol) to afford, after purification by radial chromatography (hexanes), 33 mg (68%) of 25l as an oil: IR (neat) 2930, 2205, 1599 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz): δ 0.92 (t, J = 5.5 Hz, 3H), 1.33-1.38 (m, 4H), 1.60-1.68 (m, 2H), 2.39 (t, J = 7.5 Hz, 2H), 6.83 (s, 1H), 7.18 (q, J = 9.0 Hz, 1H), 7.42-7.46 (m, 1H), 7.56-7.62 (m, 1H); $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 13.9, 22.3, 27.8, 30.8, 36.1, 113.0 (d, J = 3 Hz), 117.3 (d, J = 18 Hz), 117.7 (dd, J = 18, 1 Hz), 118.2, 125.2 (dd, J = 7, 4 Hz), 130.9 (dd, J = 6, 4 Hz), 140.7 (d, J = 2 Hz), 150.3 (dd, J = 248, 12 Hz), 151.0 (dd, J = 252, 13 Hz) ppm; HRMS for C$_{14}$H$_{15}$NF$_2$ [M+Na$^+$] calculated:258.1071, found:258.1075.

(2Z,4E)-5-Phenyl-2-(2-(trimethylsilyl)ethyl)penta-2,4-dienenitrile(25m) and (2E,4E)-5-phenyl-2-(2-(trimethylsilyl)ethyl)penta-2,4-dienenitrile (25m'): General Procedure A was employed with 23d (40 mg, 0.22 mmol) and ((trimethylsilyl) methyl)magnesium chloride (0.65 mL, 0.65 mmol, 1 M in THF) to afford, after purification by radial chromatography (hexanes), 28.8 mg (52%) of 25m and 25m' as a 6:1 mixture of oils. For 25m: IR (neat) 2952, 2204 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz): δ 0.04 (s, 9H), 0.73-0.82 (m, 2H), 2.26-2.32 (m, 2H), 6.74 (dd, J = 11.0, 1.0 Hz, 1H), 6.78 (d, J = 15.5 Hz, 1H),
7.15 (dd, J = 15.5, 11.0 Hz, 1H), 7.30 (t, J = 7.5 Hz, 1H), 7.36 (t, J = 7.5 Hz, 2H), 7.48 (d, J = 7.0 Hz, 2H); 13C NMR (CDCl3, 100 MHz): δ -1.8, 15.6, 29.2, 116.4, 118.2, 124.7, 127.2, 128.8, 129.1, 135.9, 138.5, 142.5 ppm. For 25m*: IR (neat) 2953, 2204 cm⁻¹; 1H NMR (CDCl3, 500 MHz): δ 0.08 (s, 9H), 0.79-0.87 (m, 2H), 2.37-2.42 (m, 2H), 6.80 (d, J = 2.0 Hz, 1H), 6.83 (d, J = 4.4 Hz, 1H), 6.92-7.00 (m, 1H), 7.33 (t, J = 7.5 Hz, 1H), 7.38 (t, J = 7.5 Hz, 2H), 7.46 (d, J = 7.0 Hz, 2H); 13C NMR (CDCl3, 125 MHz): δ -1.8, 16.0, 23.7, 116.4, 121.7, 127.2, 128.9, 129.3, 139.7, 141.8 ppm; HRMS for C16H21NSi [M+Na⁺] calculated: 278.1341, found: 278.1345.

(2E, 4Z)-2-ethyl-5-phenylpenta-2,4-dienenitrile (25n) and (2E, 4E)-2-ethyl-5-phenylpenta-2,4-dienenitrile (25n’): General Procedure C was employed with 23d (40 mg, 0.22 mmol) and methyl magnesium bromide (0.23 mL, 0.66 mmol) to afford, after purification by radial chromatography (hexanes), 21.7mg (54%) of 25n and 25n’ as a 4:1 mixture of oils. For 25n: IR (neat) 2205; 1H NMR (CDCl3, 400 MHz): δ 1.22 (t, J = 7.5 Hz, 3H), 2.35 (q, J = 7.5 Hz, 2H), 6.75 (d, J = 11.1 Hz, 1H), 6.79 (d, J = 15 Hz, 1H), 7.15 (dd, J = 11.1 Hz, 15 Hz, 1H), 7.29 – 7.49 (m, 5H); 13C NMR(CDCl3, 100 MHz): δ 12.9, 22.5, 114.7, 120.6, 121.7, 127.2, 128.9, 129.3, 135.8, 140.0, 142.7 ppm. For 25n’: IR (neat) 2920, 2203cm⁻¹; 1H NMR (CDCl3, 400 MHz): δ 1.23 (t, J = 7.5 Hz, 3H), 2.44 (q, J = 7.5 Hz, 2H), 6.81 – 6.87 (m, 2H), 6.99 (dd, J = 11.2 Hz, 15.3 Hz, 1H), 7.32 – 7.50 (m, 5H); 13C NMR (CDCl3, 100 MHz): δ 12.8, 27.6, 114.8, 118.0, 124.6, 127.2, 128.8, 129.1, 135.8, 138.7, 143.1 ppm. HRMS for C13H13N: [M+Na⁺] calculated: 206.0946, found: 206.0940.
(2E, 4Z)-2-(3-Phenyl-allylidene)-heptanenitrile (25o) and (2E, 4E)-2-(3-Phenyl-allylidene)-heptanenitrile (25o’): General Procedure C was employed with 23d (40 mg, 0.22 mmol) and butyl magnesium bromide (0.35 ml, 0.66 mmol) to afford, after purification by radial chromatography (hexanes), 25.7 mg (50%) of 25o and 25o’ as a 6:1 mixture of oils. For 25o: IR (neat) 2930, 2208, 1451 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 0.84 (t, J = 6.6 Hz, 3H), 1.22 – 1.32 (m, 4H), 1.48 – 1.56 (m, 2H), 2.24 (t, J = 7.6 Hz, 2H), 6.66 (d, J = 11 Hz, 1H), 6.71 (d, J = 15.6 Hz, 1H), 7.08 (dd, J = 11 Hz, 15.6 Hz, 1H), 7.19 – 7.42 (m, 5H); ¹³C NMR (CDCl₃, 400 MHz): δ 13.9, 22.3, 27.9, 30.9, 34.3, 113.6, 118.1, 124.7, 127.2, 128.8, 129.1, 135.9, 138.7, 143.9 ppm; For 25o’: IR (neat) 2926, 2204, 1443 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 0.92 (t, J = 7.0 Hz, 3H), 1.35 – 1.38 (m, 4H), 1.59 – 1.66 (m, 2H), 2.40 (t, J = 7.0 Hz, 2H), 6.81 – 7.02 (m, 3H), 7.130 – 7.48 (m, 5H); ¹³C NMR (CDCl₃, 100 MHz): δ 14.0, 22.4, 28.0, 29.0, 31.4, 113.5, 120.9, 121.9, 127.2, 128.9, 129.3, 135.8, 139.9, 143.3 ppm. HRMS for C₁₆H₁₉N: [M+K⁺] calculated: 264.1155, found: 264.1188.

(Z)-2-(3,4-dimethoxybenzylidene)pent-4-enenitrile (25p): General Procedure C was employed with 23b (1095.0 mg, 5.0 mmol) and vinyl magnesium bromide (21.4 ml, 15.0 mmol) to afford, after purification by radial chromatography (15% EtOAc in hexanes), 756.8 mg (62%) of 25p as an oil: IR (film) 2938, 2200, 1512 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 3.11 – 3.13 (m, 2H), 3.92 (s, 3H), 3.93 (s, 3H), 5.22 – 5.28 (m, 2H), 5.85 – 5.92 (m, 1H), 6.87 (d, J = 8.6 Hz, 1H), 6.87 (s, 1H), 7.20 (dd, J = 8.6 Hz, 2 Hz), 7.54 (d, J = 2 Hz, 1H); ¹³C NMR (CDCl₃, 100 MHz): δ 39.9, 55.9, 106.4, 110.3, 110.8, 118.6, 119.3, 123.2, 126.6, 133.1, 143.8, 148.9, 150.6 ppm; HRMS C₁₄H₁₃NO₂: [M+Na⁺] calculated: 252.1001, found: 252.0974.
(2Z, 4E)-2-(3,4-Dimethoxybenzylidene)-5-(3,4-dimethoxyphenyl)pent-4-enenitrile (27): A DMF solution (8 mL) of (3,4-dimethoxyphenyl) boronic acid (124.7 mg, 0.66 mmol), palladium acetate (9.8 mg, 0.04 mmol), silver carbonate (87.3 mg, 0.87 mmol) and (Z)-2-(3,4-dimethoxybenzylidene)pent-4-enenitrile (100.0 mg, 0.44 mmol) was heated at 50 °C. After 12 h, the mixture was cooled and then the reaction mixture was poured into water (2 mL). The aqueous phase was extracted with EtOAc (3 x 10 mL), the combined organic phase was washed with brine, dried (Na₂SO₄), concentrated, and purified by radial chromatography (30% EtOAc in hexanes) to afford 81.5 mg (51%) of nitrile 27 as a yellow solid (mp: 88-89 °C): IR (neat) 2931, 2206 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 3.26 (d, J = 7.2 Hz, 2H), 3.89 (s, 3H), 3.91 (s, 3H), 3.92 (s, 3H), 3.93 (s, 3H), 6.11 (dt, J = 16.0, 6.8 Hz, 1H), 6.51 (d, J = 16.0 Hz, 1H), 6.88 (d, J = 8.4 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 6.93 (d, J = 2.0 Hz, 1H), 6.93 (s, 1H), 6.95 (s, 1H), 7.21 (dd, J = 8.4, 2.0 Hz, 1H), 7.54 (d, J = 2.0 Hz, 1H); ¹³C NMR (CDCl₃, 100 MHz) : δ 39.2, 55.9 (2), 56.0, 106.8, 108.8, 110.4, 110.8, 111.1, 119.5, 119.53, 122.5, 123.2, 126.6, 129.8, 133.2, 143.7, 148.90, 148.95, 149.03, 150.7 ppm; HRMS for C₂₂H₂₃NO₄ [M+Na⁺] calculated: 388.1525, found: 388.1517.

(2Z, 4E)-2-(3, 4-Dimethoxybenzylidene)-5-(3,4-dimethoxyphenyl)pent-4-enamide (28): Solid Parkins catalyst [bis(dimethylphosphinous acid-kP)dimethylphosphinyl-kP-hydridoplatinum(II)] (0.5 mg, 0.0075 mmol) was added to an ethanol/water solution (1:1, 20 mL) of (2Z, 4E)-2-(3,4-dimethoxybenzylidene)-5-(3,4-dimethoxyphenyl)pent-4-enenitrile (54.8 mg, 0.15 mmol) and then the reaction mixture was heated to reflux. After 15 h, the solution was cooled, the solvent was evaporated, and then the residue was
purified by radial chromatography (70% EtOAc in hexanes) to afford 50.0 mg (87%) of the amide 28 as a white solid (mp: 108-109 °C): IR (solid) 3416, 3338, 2935, 1672, 1518 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 3.31 (d, J = 7.2 Hz, 2H), 3.86 (s, 3H), 3.88 (s, 6H), 3.91 (s, 3H), 5.42 (s, 2H), 6.14 (dt, J = 16.0, 7.2 Hz, 1H), 6.47 (d, J = 16.0 Hz, 1H), 6.57 (s, 1H), 6.82 (dd, J = 8.4, 2.0 Hz, 2H), 6.90-6.97 (m, 4H); ¹³C NMR (CDCl₃, 100 MHz): δ 39.8, 55.9, 56.0, 108.7, 111.0, 111.1, 111.3, 119.3, 121.3, 124.3, 128.3, 130.2, 130.3, 132.3, 135.3, 148.7, 148.9, 149.0, 172.1 ppm; HRMS for C₂₂H₂₅NO₅ [M+Na⁺] calculated: 406.1631 found: 406.1619.

tert-Butyl(2Z,4E)-2-(3,4-dimethoxybenzylidene)-5-(3,4-dimethoxyphenyl)pent-4-enoylcarbamate (29): Solid di-tert-butyldicarbonate (43.4 mg, 0.20 mmol) and 4-dimethyaminopyridine (1.2 mg, 0.01 mmol) were added to a rt, CH₂Cl₂ solution (5mL) of (2Z, 4E)-2-(3,4-dimethoxybenzylidene)-5-(3,4-dimethoxyphenyl)pent-4-enamide (40 mg, 0.10 mmol). After 20 h, the reaction mixture was poured into dichloromethane (10 mL), the phases were separated, the organic phase was combined and was then washed sequentially with 1M HCl (10 mL) and water (10 mL). The solvent was evaporated and the residue was then purified by radial chromatography (30% EtOAc in hexanes) to afford 35.3 mg (73 %) of imide 29 as a light yellow oil: IR (neat) 2979, 1777, 1601 cm⁻¹, ¹H NMR (CDCl₃, 500 MHz): δ 1.43 (s, 9H), 3.31 (d, J = 7.2 Hz, 2H), 3.87 (s, 3H), 3.88 (s, 3H), 3.89 (s, 3H), 3.90 (s, 3H), 6.22 (dt, J = 11.6, 7.2 Hz, 1H), 6.51 (d, J = 11.6 Hz, 1H), 6.51 (s, 1H), 6.80-7.02 (m, 7H); ¹³C NMR (CDCl₃, 100 MHz): δ 27.8, 38.4, 55.8, 55.9, 84.6, 108.7, 110.8, 111.0, 111.1, 119.4, 124.0, 128.1, 130.5, 130.7, 132.7, 133.5,
(2Z, 4E)-2-(3,4-Dimethoxybenzylidene)-5-(3,4-dimethoxyphenyl)pent-4-en-1-ol (30):
A THF solution (0.13 mL) of lithium triethylborohydride (0.13 mmol, 1 M) was added to a rt, THF solution (5 mL) of tert-butyldi(2Z,4E)-2-(3,4-dimethoxybenzylidene)-5-(3,4-dimethoxyphenyl)pent-4-enoyl)carbamate (30 mg, 0.06 mmol). After 2 h, an aqueous solution (10 mL) of 30% H₂O₂ was added. After 30 min, the aqueous phase was extracted with EtOAc (3 x 10 mL), the combined organic phase was washed with brine, dried (Na₂SO₄), concentrated, and purified by radial chromatography (30% EtOAc in hexanes) to afford 16.0 mg (72%) of alcohol 30 as a light yellow oil: IR (neat) 3520, 2935, 1598 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 1.59 (broad s, 1H), 3.20 (d, J = 7.0 Hz, 2H), 3.88 (s, 6H), 3.89 (s, 3H), 3.91 (s, 3H), 4.34 (s, 2H), 6.20 (dt, J = 15.8 Hz, 7.2 Hz, 1H), 6.47 (d, J = 15.8 Hz, 2H), 6.81–6.96 (m, 6H); ¹³C NMR (CDCl₃, 100 MHz): δ 39.5, 55.8, 55.9, 55.9, 61.3, 108.6, 110.9, 111.1, 112.0, 119.1, 121.2, 126.0, 129.4, 129.8, 130.4, 131.7, 138.5, 148.1, 148.5, 148.6, 149.0 ppm; HRMS for C₂₂H₂₆O₅ [M+H⁺] calculated: 393.1678, found: 393.1696.

(2Z,4Z)-2-(3,4-Dimethoxybenzylidene)-5-iodopent-4-enitrile (31): Solid N-iodosuccinimide (146.3 mg, 0.65 mmol) was added to a 0 °C 1,1,1,3,3,3-hexafluoroisopropanol and dichloromethane (1:1) solution (1.6 mL) of (2Z,4E)-2-(3,4-dimethoxybenzylidene)-5-(trimethylsilyl)pent-4-enitrile (130 mg, 0.43 mmol). After 10 min, the reaction mixture was poured into an aqueous, saturated NH₄Cl solution (2mL). The aqueous phase was extracted with EtOAc (3 x10 mL), the combined organic phase
was washed with brine, dried (Na$_2$SO$_4$), concentrated, and purified by radial chromatography (15% EtOAc in hexanes) to afford 125 mg (82%) of nitrile 31 as a light yellow oil. IR (neat) 2934, 2206, 1597 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz): δ 3.26 (d, $J = 6.6$ Hz, 2H), 3.93 (s, 3H), 3.94 (s, 3H), 6.39 (dt, $J = 7.6$, 7.6 Hz, 1H), 6.57 (dt, $J = 7.6$ Hz, 1.4 Hz, 1H), 6.89 (d, $J = 8.4$ Hz, 1H), 6.95 (s, 1H), 7.21 (dd, $J = 8.4$, 2.4 Hz, 1H), 7.52 (d, $J = 2.4$ Hz, 1H); $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 40.8, 55.9 (2), 86.6, 104.0, 110.2, 110.7, 119.2, 123.4, 126.3, 135.6, 144.3, 148.8, 150.7 ppm; HRMS for C$_{14}$H$_{14}$NO$_2$I [M+Na$^+$] calculated: 377.9967, found: 377.9944.

(2Z, 4Z)-2-(3,4-Dimethoxybenzylidene)-5-(3,4-dimethoxyphenyl)pent-4-enenitrile (32): Solid (3,4-dimethoxyphenyl) boronic acid (87.8 mg, 0.46 mmol), palladium acetate (14.0 mg, 0.06 mmol) and triphenyl phosphine (32.5 mg, 0.12 mmol) were added to a rt, THF solution (8 mL) of (2Z,4E)-2-(3,4-dimethoxybenzylidene)-5-iodopent-4-enenitrile (100.0 mg, 0.31 mmol). After 12 h, the reaction mixture was poured into water (2 mL). The aqueous phase was extracted with EtOAc (3 x 10 mL), the combined organic phase was washed with brine, dried (Na$_2$SO$_4$), concentrated, and purified by radial chromatography (30% EtOAc in hexanes) to afford 88.3 mg (78%) of nitrile 32 as a light yellow oil: IR (neat) 2931, 2206 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz): δ 3.39 (d, $J = 7.8$ Hz, 2H), 3.89 (s, 3H), 3.90 (s, 3H), 3.92 (s, 3H), 3.93 (s, 3H), 5.72 (dt, $J = 11.4$, 7.2 Hz, 1H), 6.67 (d, $J = 11.4$ Hz, 1H), 6.83 (s, 1H), 6.85-6.89 (m, 3H), 6.91 (s, 1H), 7.19 (dd, $J = 8.4$, 1.8 Hz, 1H), 7.53 (d, $J = 1.8$ Hz, 1H); $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 34.7, 55.9 (2), 106.8, 110.3, 110.8, 111.0, 111.9, 119.5, 121.1, 123.2, 124.9, 126.6, 129.3, 132.5, 143.6, 148.3, 148.7, 149.0, 150.7 ppm; HRMS for C$_{22}$H$_{23}$NO$_4$ [M+Na$^+$] calculated:388.1525, found:388.1512.
(2Z, 4Z)-2-(3, 4-Dimethoxybenzylidene)-5-(3, 4-dimethoxyphenyl)pent-4-enamide (33): Solid Parkins catalyst [bis(dimethylphosphinous acid-P)dimethylphosphinyl-P-hydridoplatinum(II)] (0.6 mg, 0.01 mmol) was added to an ethanol/water solution (1:1, 20 mL) of (2Z, 4Z)-2-(3,4-dimethoxybenzylidene)-5-(3,4-dimethoxyphenyl)pent-4-enenitrile (80 mg, 0.22 mmol) and then the reaction was heated to reflux. After 15 h, the solvent was evaporated and the residue was purified by radial chromatography (70% EtOAc in hexanes) to afford 95.1 mg (92%) of amide 33 as a white solid (mp: 101-102 °C): IR (solid) 3411, 3339, 2934, 2836, 1677, 1601 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 3.48 (d, J = 7.6 Hz, 2H), 3.88 (s, 3H), 3.90 (s, 3H), 3.91 (s, 3H), 3.92 (s, 3H), 5.43 (s, 2H), 5.75 (dt, J = 11.6, 7.6 Hz, 1H), 6.59 (s, 1H), 6.61 (d, J = 11.6 Hz, 1H), 6.80-7.00 (m, 6H); ¹³C NMR (CDCl₃, 100 MHz): δ 34.1, 55.9 (2), 111.0, 111.3, 111.9, 121.2 (2), 126.3, 128.3, 129.8 (2), 131.4, 135.2, 148.1, 148.7, 148.8, 172.3 ppm; HRMS for C₂₂H₂₅NO₅ [M+Na⁺] calculated: 406.1631, found: 406.1618.

tert-Butyl((2Z,4Z)-2-(3,4-dimethoxybenzylidene)-5-(3,4-dimethoxyphenyl)pent-4-enoyl)carbamate (34): Solid di-tert-butyl dicarbonate (136.8 mg, 0.63 mmol) and 4-dimethyamino pyridine (2.9 mg, 0.02 mmol) were added to a CH₂Cl₂, rt, solution (5 mL) of (2Z, 4Z)-2-(3,4-dimethoxybenzylidene)-5-(3,4-dimethoxyphenyl)pent-4-enamide (90 mg, 0.24 mmol). After 20 h the reaction mixture was poured into dichloromethane (10 mL) and washed sequentially with 1M HCl (10 mL) and water (10 mL). The solvent was evaporated and the residue was then purified by radial chromatography (30% EtOAc in hexanes) to afford 88.3 mg (76 %) of imide 34 as a light yellow oil: IR (neat) 3296, 2930,
1766, 1686 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 1.38 (s, 9H), 3.45 (d, \(J = 7.8\) Hz, 2H), 3.85 (s, 3H), 3.88 (s, 3H), 3.89 (s, 3H), 3.91 (s, 3H), 5.73 (dt, \(J = 11.4, 7.2\) Hz, 1H), 6.61 (d, \(J = 6.0\) Hz, 1H), 6.62 (d, \(J = 6.0\) Hz, 1H), 6.80-6.92 (m, 7H); \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 27.8, 33.6, 55.8, 55.9 (2), 82.7, 110.7, 110.8, 110.9, 111.6, 121.2, 125.6, 127.8, 129.6, 131.8, 134.6, 148.1, 148.6, 148.8, 149.0, 149.1 ppm; HRMS for C\(_{27}\)H\(_{33}\)NO\(_7\) \([M+Na^+]\) calculated: 506.2155, found: 506.2155.

\((1Z, 4Z)-1.5\)-Bis(3,4-dimethoxyphenyl)penta-1,4-dien-2-ol (35): A THF solution (0.34 mL) of lithium triethylborohydride (0.34 mmol, 1 M) was added to a rt, THF solution (5 mL) of tert-butyl((2\(Z,3E\))-2-(3,4-dimethoxybenzylidene)-5-(3,4-dimethoxyphenyl)penta-4-enoyl)carbamate (80 mg, 0.17 mmol). After 2 h, an aqueous 30% solution (10 mL) of H\(_2\)O\(_2\) was added. After 30 min, the aqueous phase was extracted with EtOAc (3 x 10 mL), the combined organic phase was washed with brine, dried (Na\(_2\)SO\(_4\)), concentrated and purified by radial chromatography (30% EtOAc in hexanes) to afford 43.4 mg (69%) of alcohol 35 as a light yellow oil: IR (neat) 3517, 2925, 1514 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 1.28 (s, 1H), 3.36 (d, \(J = 7.0\) Hz, 2H), 3.88 (s, 6H), 3.89 (s, 3H), 3.91 (s, 3H), 4.35 (s, 2H), 5.82 (dt, \(J = 11.6\) Hz, 7.6 Hz, 1H), 6.51(s, 1H), 6.66 (d, \(J = 11.6\) Hz, 1H), 6.81–6.96 (m, 6H); \(^1\)C NMR (CDCl\(_3\), 400 MHz): \(\delta\) 34.7, 55.9 (3), 77.2, 110.9, 111.9, 112.0, 121.1, 121.2, 128.0, 129.0, 130.0, 131.0, 138.7, 148.0 ppm; HRMS for C\(_{22}\)H\(_{26}\)O\(_5\) \([M+Na^+]\) calculated: 393.1678, found: 393.1691.

Rearrangement to allylic halides and sulfide
(1-chloropentyl) benzene (47): Butylmagnesium bromide (0.62ml, 1.24mmol) was added dropwise to a 0 °C, THF (0.8ml) solution of benzaldehyde(0.095ml, 0.94mmol) and the solution was then allowed to react in 0°C for 1h. Dry niobium chloride (634.5mg, 2.35mmol) and dioxane (8ml) was added, and then the solution was allowed to warm to room temperature. After 1h, the reaction mixture was poured into HCl (2M), and the phases were separated. The aqueous phase was extracted with EtOAc, and then the combined organic phase was washed with brine, dried (NaSO₄), and concentrated to provide an oil which was purified by radical chromatography (hexanes) afforded 132.2 mg (77%) of chloride 47 as an oil: IR (neat) 1713, 1494, 1454 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 0.89 (t, J= 7.2Hz, 3H), 1.31-1.36 (m, 4H), 2.04-2.14 (m, 2H), 4.84 (dd, J= 8.0Hz, J= 7.0Hz, 1H), 7.29-7.38 (m, 5H); ¹³C NMR (CDCl₃, 100MHz) δ 13.9, 22.1, 29.2, 39.7, 63.9, 126.9, 128.2, 128.6, 142.0 ppm.

(1-chloropentyl) benzene (47): Butyl lithium (0.49ml, 1.13mmol) was added dropwise to a -78°C, THF (0.8ML) solution of benzaldehyde (0.095ml, 0.94mmol) and the solution were then allowed to react in 0°C for 1h. Dry niobium chloride (634.5mg, 2.35mmol) and dioxane (8ml) was added, and then the solution was allowed to warm to room temperature. After 1h, the reaction mixture was poured into HCl (2M), and the phases were separated. The aqueous phase was extracted with EtOAc, and then the combined organic phase was washed with brine, dried (NaSO₄), and concentrated to provide an oil which was purified by radical chromatography (hexanes) afforded 89.3 mg (52%) of chloride 47 as an oil: IR (neat) 1713, 1494, 1454 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 0.89 (t, J= 7.2Hz, 3H), 1.31-1.36 (m, 4H), 2.04-2.14 (m, 2H), 4.84 (dd, J= 8.0Hz, J= 7.0Hz, J= 1.0Hz, 1H), 7.29-7.38 (m, 5H); ¹³C NMR (CDCl₃, 100MHz) δ 13.9, 22.1, 29.2, 39.7, 63.9, 126.9, 128.2, 128.6, 142.0 ppm.
7.0Hz, 1H), 7.29-7.38 (m, 5H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 13.9, 22.1, 29.2, 39.7, 63.9, 126.9, 128.2, 128.6, 142.0 ppm.

**(1,5-dichloropentyl)benzene (49):** (4-chlorobutyl) bromide (0.145ml, 1.23mmol) was added dropwise to a 0°C, THF (0.8ml) suspension of Mg (45.2mg, 1.89mmol), activated by addition of 1, 2-dibromoethane (0.01ml, 0.2mmol) and allowed to react at 0 for 1h. Then benzaldehyde (0.095ml, 0.94mmol) was added to the mixture and the solution was then allowed to react in 0°C for 1h. Dry niobium chloride (634.5mg, 2.35mmol) and dioxane (8ml) was added, and then the solution was allowed to warm to room temperature. After 1h, the reaction mixture was poured into HCl (2M), and the phases were separated. The aqueous phase was extracted with EtOAc, and then the combined organic phase was washed with brine, dried (Na$_2$SO$_4$), and concentrated to provide an oil which was purified by radical chromatography (hexanes) afforded 146.9 mg (72%) of dichloride 49 as an oil: IR (neat) 2944, 1454 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 1.56 (m, 1H), 1.77-1.83(m, 1H), 2.05-2.17 (m, 2H), 3.52 (t, $J$= 6.4Hz, 2H), 4.85 (dd, $J$= 8.0Hz, $J$= 6.4Hz, 1H), 7.32-7.39 (m, 5H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 24.5, 32.0, 39.3, 44.6, 63.4, 126.9, 128.3, 128.7, 141.6 ppm.

**(E)-(3-(3-methoxyphenyl)allyl)(phenyl)sulfane (51):** Vinyl magnesium bromide (0.7M, 1.2mmol) was added dropwise to a 0°C, THF solution (0.5ml) of 3-methoxybenzaldehyde (136.15mg, 1.0 mmol). After 1 h, the solid niobium chloride (325.08mg, 1.2mmol) and dioxane (5ml) was added at 0°C. After 1h, the reaction
mixture was poured into HCl (2M), and the phases were separated. The aqueous phase
was extracted with EtOAc, and then the combined organic phase was washed with brine,
dried (NaSO₄), and concentrated to provide an oil. A THF solution (0.2M) of the crude
allylic chloride was added to a 10°C, THF suspension of NaH and thiophenol. The
reaction mixture was allowed to warm to r.t. Over 16h, the reaction mixture was poured
into an aq NaOH solution (2%) and then extracted with EtOAc, and then the combined
organic phase was washed with brine, dried (NaSO₄), and concentrated to provide an oil
which can be purified by radical chromatography (hexanes) to provide the pure sulfide
146.2 mg (57%): IR (neat) 3517, 2925, 1514 cm⁻¹, ¹H NMR (CDCl₃, 500 MHz) δ 3.69
(d, J=1.0Hz, 1H), 3.71 (d, J=1.0Hz, 1H), 3.79 (s, 3H), 6.25 (dt, J=15.5Hz, J=7.0Hz, 1H),
6.38 (d, J=15.5Hz, 1H), 6.84 (ddd, J=8.0Hz, J=2.0Hz, J=0.5Hz, 1H), 6.89 (t, J=2.0Hz,
1H), 6.91 (d, J=8.0Hz, 1H), 7.18-7.39 (m, 6H); ¹³C NMR (CDCl₃, 100 MHz) δ 37.1,
55.3, 111.7, 113.2, 119.1, 125.5, 126.5, 128.9, 129.5, 130.3, 132.7, 138.2, 159.8 ppm.
HRMS for C₁₆H₁₆OS [M+Na⁺] calculated: 257.0995, found: 257.1021;

**Cinnamyl (phenyl) sulfane (53):** Solid LiBH₄ (2mg, 0.09mmol) was added to a rt, THF
solution (1.0ml) of 1-phenylprop-2-en-1-one (24mg, 0.18 mmol). After 1h the mixture
was cooled to 0°C, and then dioxane (5.0ml) and solid NbCl₅ (56.9mg, 0.22mmol) were
added. The cooling bath was removed and the reaction was allowed to warm to rt. After
1h aqueous HCl (1M, 1ml) was added, the aqueous phase was extracted with EtOAc, the
combined organic extracts were sequentially washed with water and brine, and then dried
(Na₂SO₄) and concentrated to afford 17.8 mg of (E)-(3-chloroprop-1-enyl) benzene as an
oil spectally identical to the material previously identified¹¹¹. A portion of crude (E)-(3-
chloroprop-1-enyl) benzene (5.8mg, 0.04mmol) was dissolved in THF (2ml) and then added to a rt, THF (3ml) solution containing NaH (3.8mg, 0.1mmol) and benzenethiol (0.01ml, 0.1mmol). After 16h water was added, the aqueous phase was extracted with EtOAc, and the combined organic extracts were washed with brine, dried (Na$_2$SO$_4$) and concentrated. Purification by radical chromatography (hexanes) provided 4.7 mg (54%) of pure cinnamyl (phenyl) sulfane 53 as an oil.

**General procedure of Propargylic alcohol:**

A THF solution of ethynyl magnesium chloride (0.6M, 3.6 mmol) was added dropwise to a 0 °C THF solution of aldehyde (3.0mmol). After 2 h, saturated, aqueous, NH$_4$Cl (10ml) was added, the aqueous phase was extracted with EtOAc, and the combined organic extracts were washed with brine, dried (NaSO$_4$), and concentrated. Purification by radical chromatography afforded propargillic alcohol as an oil.

**1-phenylprop-2-yn-1-ol (54a):** Following the general procedure with a THF solution of ethynyl magnesium chloride (6.0 ml, 3.6 mmol), benzaldehyde (318.3 mg, 3.0 mmol) and purification by radical chromatography (10% EtOAc in hexanes) afforded 297.1 mg (75%) of 1-phenylprop-2-yn-1-ol as an oil: $^1$H NMR (CDCl$_3$, 400 MHz) δ 2.61 (d, $J$ = 2.4Hz, 1H), 3.00 (s, 1H), 5.37 (s, 1H), 7.29-7.50 (m, 5H); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ 64.3, 75.0, 84.7, 127.0, 129.0, 129.0, 140.1 ppm.

**non-1-yn-3-ol (54b):** Following the general procedure with a THF solution of ethynyl magnesium chloride (6.0 ml, 3.6 mmol), heptanal (342.6 mg, 3.0 mmol) and purification
by radical chromatography (10% EtOAc in hexanes) afforded 239.6 mg (57%) of non-1-yn-3-ol as an oil: $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 0.87 (t, $J$= 7.2Hz, 3H), 1.21-1.40 (m, 6H), 1.42-1.46 (m, 2H), 1.66-1.73 (m, 2H), 2.46 (d, $J$= 2.0 Hz, 1H), 4.35 (td, $J$= 6.4Hz, $J$= 2.0Hz, 1H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 14.1, 22.6, 25.0, 28.9, 31.7, 37.6, 62.2, 72.7, 85.1 ppm.

5-phenylpent-1-yn-3-ol (54c): Following the general procedure with a THF solution of ethynyl magnesium chloride (6.0 ml, 3.6 mmol), 3-phenylpropanal (402.5 mg, 3.0 mmol) and purification by radical chromatography (10% EtOAc in hexanes) afforded 381 mg (79%) of 5-phenylpent-1-yn-3-ol as an oil: $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 1.84 (d, $J$=5.5 Hz, 1H), 2.01-2.07 (m, 2H), 2.50 (d, $J$=2.0 Hz, 1H), 2.81 (t, $J$=7.5 Hz, 2H), 4.37 (q, $J$=6.5 Hz, 1H), 7.20-7.30 (m, 5H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 31.3, 39.1, 61.6, 73.4, 84.6, 126.1, 128.5, 141.1 ppm.

2-cyclohexylbut-3-yn-2-ol (54d): Following the general procedure with a THF solution of ethynyl magnesium chloride (6.0 ml, 3.6 mmol), 1-cyclohexylethanone (378.3 mg, 3.0 mmol) and purification by radical chromatography (10% EtOAc in hexanes) afforded 218.3 mg (48%) of 2-cyclohexylbut-3-yn-2-ol as an oil: $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$1.14-1.24 (m, 6H), 1.45 (s, 3H), 1.79-1.80 (m, 1H), 1.82 (m, 3H), 1.93 (m, 2H) 2.42 (s, 1H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 26.2, 26.3, 27.2, 27.3, 27.7, 48.5, 71.0, 71.9, 87.2 ppm.

**General procedure of rearrangement to allenyl bromide:** A dioxane solution of the propargylic alcohol (0.58 mmol) was added to a dioxane solution of potassium hydride
(0.70 mmol). After 10 min, the solid niobium bromide (0.70 mmol) was added. After 2 h, the reaction mixture was poured into HCl (2M), and the phases were separated. The aqueous phase was extracted with EtOAc, and then the combined organic phase was washed with brine, dried (NaSO₄), and concentrated to provide an oil which was purified by radical chromatography.

(3-bromoprop-1,2-diennyl)benzene(56a): Following the general procedure with a dioxane solution (3ml) of 1-phenylprop-2-yn-1-ol (20.0 mg, 0.15 mmol), potassium hydride (7.2 mg, 0.18 mmol), niobium bromide (88.6 mg, 0.18 mmol) and purification by radical chromatography (hexanes) afforded 15.4 mg (53%) of (3-bromoprop-1,2-dienyl)benzene as an oil: IR (neat) 1953, 1496, 1453 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 6.32 (d, J=5.6 Hz, 1 H), 6.36 (d, J=5.6 Hz, 1H), 7.26-7.36 (m, 5H); ¹³C NMR (CDCl₃, 100 MHz) δ 74.8, 102.6, 127.9, 128.6, 128.8, 131.7, 203.0 ppm.

1-bromonona-1,2-diene (56b): Following the general procedure with a dioxane solution (10ml) of non-1-yn-3-ol (220.0 mg, 1.57 mmol), potassium hydride (75.2 mg, 1.88 mmol), niobium bromide (925.0 mg, 1.88 mmol) and purification by radical chromatography (hexanes) afforded 197.7 mg (62%) of 1-bromonona-1, 2-diene as an oil: IR (neat) 1978, 1621, 1451 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 0.89 (t, J=6.8Hz, 3H), 1.26-1.45 (m, 9H), 2.15 (qd, J=6.4 Hz, J=2.4 Hz, 2H), 5.39 (q, J=6.4 Hz, 1H), 5.93 (dt, J=5.2 Hz, J=2.4 Hz, J=0.4 Hz, 1H); ¹³C NMR (CDCl₃, 400 MHz) δ 14.1, 22.6, 28.3, 28.7, 29.7, 31.6, 72.1, 101.1, 202.1 ppm.
(5-bromopenta-3, 4-diene) benzene (56c): Following the general procedure with a dioxane solution (6 ml) of 5-phenylpent-1-yn-3-ol 54a (93 mg, 0.58 mmol), potassium hydride (27.8 mg, 0.70 mmol), niobium bromide (343.2 mg, 0.70 mmol), and purification by radical chromatography (hexanes) afforded 83.3 mg (65%) of (5-bromopenta-3, 4-diene) benzene as an oil: IR (neat) 1980, 1451 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 2.47-2.49 (m, 2H), 2.78 (t, $J$=7.0 Hz, 2H), 5.43 (q, $J$=6.5 Hz, $J$=5.5 Hz, 1H), 5.95 (dt, $J$=5.5 Hz, $J$=2.0 Hz, 1H), 7.19-7.31 (m, 5H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 29.9, 34.6, 72.7, 100.1, 126.1, 128.4, 140.9, 202.2 ppm.

(4-bromobuta-2,3-dien-2-yl)cyclohexane(56d): Following the general procedure with a dioxane solution (3 ml) of 2-cyclohexylbut-3-yn-2-ol (37.0 mg, 0.24 mmol), potassium hydride (11.7 mg, 0.29 mmol), niobium bromide (141.7 mg, 0.29 mmol) and purification by radical chromatography (10% EtOAc in hexanes) afforded 29.3 mg (57%) of (4-bromobuta-2,3-dien-2-yl)cyclohexane as an oil: IR (neat) 1986, 1716 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 0.96-1.01 (m, 2H), 1.12 (m, 1H), 1.20-1.23 (m, 2H), 1.26 (S, 3H), 1.31-1.37 (m, 2H), 1.65 (d, $J$= 7.0 Hz, 1H), 1.78 (d, $J$=10.0 Hz, 3H) 6.26 (d, $J$=1.5 Hz, ,1H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 25.4, 26.3, 26.4, 26.5, 27.0, 27.4, 48.1, 105.0, 143.38, 192.7 ppm.
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9 For N-dealkylation of verapamil see the following: (a) Borlak, J.; Walles, M.; Elend, M.; Thum, T.; Preiss, A.; Levens, K. Xenobiotica. 2003, 33, 655. (b) McIlhenny, H. M. J. Med. Chem. 1971, 14, 1178. For N-dealkylation of zaleplon see the following: (c)

10 For N-acetylation of alogliptin see the following: Christopher, R.; Covington, P.; Davenport, M.; Fleck, P.; Mekki, Q. A; Wann E. R; Karim, A. *Clin. Ther.* **2008**, 30, 513.


17 (a) Sakamoto, K.; Nakamura, Y. *Xenobiotica* **1993**, 23, 649. (b) Sakamoto, K.; Nakamura, Y. *Xenobiotica* **1993**, 23, 391. For an example where nitrile hydrolysis may be present or an artifact of the analysis technique see ref 10h. An extensive metabolic profiling of lersivirine identified less than two percent of metabolites arising from nitrile hydrolysis. **6e**


ADME is an acronym describing the pharmacokinetics and pharmacology of an active pharmaceutical ingredient within an organism: absorption, distribution, metabolism, and excretion.


LogP is the ratio of an unionized drug distributed between octanol and water phases at equilibrium. High logP ratios correlate with increased lipophilicity.

LogD is the 1-octanol-water coefficient at different pH values.


68 No rearrangement is observed with one equivalent of dibutylmagnesium. For the enhanced reactivity of magnesiates over alkylmagnesium halides see: Knochel, P.

70$^1$H NMR analysis of the crude reaction mixture failed to identify any of the $E$-alkenenitrile.


78Winterfeldt E. Synthesis. 1975, 10, 617.


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105 Addition of the Grignard reagent prior to the addition of NbCl₅ or NbBr₅ is required to avoid transmetallation to an organoniobium species because these organoniobiums are weak nucleophiles that do not react with ketones: Kauffmann, T.; Antfang, E.; Ennen, B.; Klas, N. *Tetrahedron Lett.* **1982**, 23, 2301.

106 Vinylmagnesium chloride in THF is significantly less efficient in contrast to the related procedure employing TiCl₄.

107 Optimization experiments revealed the necessity of THF in the Grignard addition as the use of dioxane caused incomplete addition.

108 Close scrutiny of the intermediate chloride revealed the presence of less than 5% of a closely related material that was eventually identified as the corresponding allylic bromide. The naphthyl bromide could arise by in situ displacement of the chloride by the bromide present from the Grignard reagent or potentially through a mixed Mg-Nb species.
