Doctoral Thesis

Exploring the Potential of Shuttle Catalysis in Organic Synthesis

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Exploring the Potential of Shuttle Catalysis in Organic Synthesis

A thesis submitted to attain the degree of

DOCTOR OF SCIENCES of ETH ZURICH

(Dr. sc. ETH Zurich)

presented by

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Accepted on the recommendation of

Prof. Dr. Bill Morandi, examiner
Prof. Dr. Antonio Togni, co-examiner

2019
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Yu, Peng
30th May 2019
Zurich, Switzerland
Publications and Presentations

Publications

“Iridium-Catalyzed Hydrochlorination of Alkynes via Shuttle Catalysis”

“Nickel-Catalyzed Cyanation of Aryl Chlorides and Triflates Using Butyronitrile: Merging Retro-Hydrocyanation with Cross-coupling”

[3] Lian, Z.; Bhawal, B. N.; Yu, P.; Morandi B.

These authors contributed equally to this work)
“Unlocking Mizoroki-Heck-Type Reactions of Aryl Cyanides Using Transfer Hydrocyanation as a Turnover-Enabling Step”


Presentations

20/09/2018 Poster presentation (22nd International Conference on Organic Synthesis, Florence, Italy)
“A New Strategy to Access Aryl Nitriles”

12/12/2017 Poster presentation (Max-Planck-Institut für Kohlenforschung Institute Seminar, Mülheim an der Ruhr, Germany)
“Nickel-Catalyzed Cyanation of Aryl Chlorides and Triflates Using Butyronitrile: Merging Retro-Hydrocyanation with Cross-Coupling”

12/10/2017 Oral presentation (8th Young Chemists' Symposium Ruhr 2017, Mülheim an der Ruhr, Germany)
“A New Strategy to Access Aryl Nitriles”

13/06/2016 Poster presentation (Max-Planck-Institut für Kohlenforschung Institute Seminar, Mülheim an der Ruhr, Germany)
“Unlocking Mizoroki-Heck-Type Reactions of Aryl Cyanides Using Transfer
Hydrocyanation as a Turnover-Enabling Step”
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Abstract

Catalytic functional group transfer reactions have emerged as powerful and attractive methods for chemical synthesis. These reactions proceed through a chemical group transfer between a donor molecule and an acceptor molecule, enabling a distinct and powerful strategy for performing chemical reactions. This strategy was recently defined as “shuttle catalysis” by Morandi and co-workers. Shuttle catalysis strategy has two notable features: first, both functionalization (the forward reaction) and defunctionalization (the reverse reaction) can be achieved; second, the use of hazardous reagents can often be avoided. Based on this strategy, a variety of transfer reactions have been developed, such as transfer hydrogenation, transfer hydromagnesiation, transfer hydroformylation, transfer hydroacylation, transfer hydrocyanation, and transfer hydrochlorocarbonylation. Despite these advances, extending the application of shuttle catalysis in other hydrofunctionalization reactions or beyond remains of great interest and significance. This thesis describes the application of shuttle catalysis in several transformations, where the hydrofunctionalization is used for catalyst regeneration and the dehydrofunctionalization is used to transfer a toxic compound, and a hydrofunctionalization reaction.

First, we applied the shuttle catalysis strategy to the Mizoroki-Heck coupling reaction with aryl cyanides, which is otherwise challenging to realize under normal Heck conditions. In contrast to the traditional Mizoroki-Heck coupling reaction where a base is used to enable the regeneration of the metal catalyst, this reaction uses a transfer hydrocyanation step to regenerate the metal catalyst. Using an alkyne as the HCN acceptor, we developed a nickel-catalyzed intramolecular Mizoroki-Heck-type reaction of aryl cyanides (Scheme I a). A palladium-catalyzed intermolecular Mizoroki-Heck-type reaction of aryl cyanides was also developed using an alkene as the HCN acceptor (Scheme I b).
(a) Nickel-catalyzed intramolecular Mizoroki-Heck type reaction with aryl cyanides.

\[
\begin{align*}
\text{Ar} & \quad \begin{array}{c}
\text{H} \\
\text{CN}
\end{array} \quad + \quad \begin{array}{c}
\text{R} \\
\text{==}=\text{R}
\end{array} \quad \xrightarrow{\text{Ni(COD)}_2, \text{PPh}_3, \text{AlMe}_2\text{Cl}} \quad \begin{array}{c}
\text{Ar} \\
\text{R}
\end{array} \quad + \quad \begin{array}{c}
\text{R} \\
\text{NC} \\
\text{H}
\end{array} \\
\text{toluene, 60 °C, 16 h} & \quad \text{20 examples 45-92%}
\end{align*}
\]

(b) Palladium-catalyzed intermolecular Mizoroki-Heck type reaction with aryl cyanides.

\[
\begin{align*}
\text{R} & \quad \text{CN} \quad + \quad \text{Ar} \quad \xrightarrow{\text{Pd}_2(\text{dba})_3, \text{CyJohnPhos}, \text{AlMe}_2\text{Cl}} \quad \begin{array}{c}
\text{R} \\
\text{==}=\text{Ar}
\end{array} \quad + \quad \begin{array}{c}
\text{R} \\
\text{CN}
\end{array} \\
\text{toluene, 100 °C, 16 h} & \quad \text{16 examples 45-88%}
\end{align*}
\]

Scheme I. Shuttle catalysis-enabled Mizoroki-Heck-type reaction of aryl cyanides.

Next, we applied the strategy to the cyanation reaction of aryl (pseudo) halides. In the reaction, shuttle catalysis enables the use of an alkyl nitrile as the cyanating reagent, and the transfer of cyano groups is achieved by a dehydrocyanation process. Under nickel catalysis, we were able to realize this reaction using butyronitrile as a cyanating reagent (Scheme II).

(a) Nickel-catalyzed cyanation of aryl chlorides with butyronitrile.

\[
\begin{align*}
\text{R} \quad \text{Cl} & \quad + \quad \text{Me} \quad \xrightarrow{\text{Ni(acac)}_2, \text{Xanthos, Al(isobutyl)}_3} \quad \begin{array}{c}
\text{R} \\
\text{CN}
\end{array} \quad + \quad \text{Me} \\
\text{toluene, 120 °C, 12 h} & \quad \text{18 examples 51-87%}
\end{align*}
\]

(b) Nickel-catalyzed cyanation of aryl and vinyl triflates with butyronitrile.

\[
\begin{align*}
\text{R} \quad \text{OTf} & \quad + \quad \text{Me} \quad \xrightarrow{\text{Ni(COD)}_2, \text{Xanthos, AlCl}_3, \text{Et}_3\text{N}} \quad \begin{array}{c}
\text{R} \\
\text{CN}
\end{array} \quad + \quad \text{Me} \\
\text{toluene, 120 °C, 12 h} & \quad \text{23 examples 50-97%}
\end{align*}
\]

Scheme II. Shuttle catalysis-enabled cyanation of aryl chlorides and triflates with butyronitrile.
Finally, a hydrochlorination of alkynes was realized through shuttle catalysis. This strategy enables the use of an alkyl chloride as the hydrochlorinating reagent, leading to a broader functional group tolerance compared to previously reported methods using HCl or acid chlorides. In the presence of [IrCl(COD)] as the catalyst, we were able to use 4-chlorobutan-2-one as a HCl source to perform this transformation (Scheme III).

Scheme III. Shuttle catalysis-enabled hydrochlorination of alkynes with 4-chlorobutan-2-one.
Zusammenfassung


Die vorliegende Arbeit beschreibt die Anwendung der Shuttle-Katalyse anhand mehrerer Beispiele, wobei die Hydrofunktionalisierung einmal zur Katalysatorregenerierung eingesetzt wird und bei einem weiteren Beispiel die Dehydrofunktionalisierung die Übertragung einer toxischen Verbindung erlaubt. Des Weiteren wird eine neue Hydrofunktionalisierung gezeigt.


\[
\begin{align*}
\text{ArCN} + R \equiv \equiv R & \xrightarrow{\text{Ni(COD)}_2, \text{PPh}_3, \text{AlMe}_2\text{Cl}} \text{Ar} \equiv \equiv R + \text{NC} \equiv \equiv H \\
& \text{Toluol, } 60^\circ\text{C, } 16\text{ h} \\
20\text{ Beispiele} \quad 45-92%
\end{align*}
\]


(b) Palladium-katalysierte intermolekulare Mizoroki-Heck-artige Reaktion mit Arylcyaniden.

\[
\begin{align*}
\text{R-CN} + \text{Ar} \equiv \equiv \text{C} & \xrightarrow{\text{Pd}_2(\text{dba})_2, \text{CyJohnPhos}} \text{Ar} \equiv \equiv \text{C} + \text{R-CN} \\
& \text{Toluol, } 100^\circ\text{C, } 16\text{ h} \\
16\text{ Beispiele} \quad 45-88%
\end{align*}
\]

CyJohnPhos

Schließlich konnten wir die Hydrochlorierung von Alkinen anhand einer Shuttle-Katalyse verwirklichen. Diese Herangehensweise ermöglicht die Verwendung eines Alkylchlorids als Hydrochlorierungsreagenz und führt zu einer erweiterten Toleranz an funktionellen Gruppen gegenüber früheren Methoden mit HCl oder Säurechloriden. In der Gegenwart von $\text{[IrCl(cod)\textsubscript{2}]}$ als Katalysator konnten wir 4-Chlorobutan-2-on als die HCl-Quelle verwenden um diese Reaktion durchzuführen (Schema III).

Schema III. Hydrochlorierung von Alkinen mit 4-Chlorobutan-2-on ermöglicht durch Shuttle-Katalyse.
### List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>acac</td>
<td>acetylacetonate</td>
</tr>
<tr>
<td>aq</td>
<td>aqueous</td>
</tr>
<tr>
<td>Ar</td>
<td>argon</td>
</tr>
<tr>
<td>atm</td>
<td>atmosphere</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-butyloxycarbonyl</td>
</tr>
<tr>
<td>BTC</td>
<td>bis(trichloromethyl) carbonate</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
</tr>
<tr>
<td>Bz</td>
<td>benzoyl</td>
</tr>
<tr>
<td>COD</td>
<td>1,5-cyclooctadiene</td>
</tr>
<tr>
<td>Cp*</td>
<td>1,2,3,4,5-pentamethylcyclopentadienyl</td>
</tr>
<tr>
<td>CSA</td>
<td>camphorsulfonic acid</td>
</tr>
<tr>
<td>Cy</td>
<td>cyclohexyl</td>
</tr>
<tr>
<td>dba</td>
<td>dibenzylideneacetone</td>
</tr>
<tr>
<td>DCC</td>
<td>N,N'-dicyclohexylcarbodiimide</td>
</tr>
<tr>
<td>DCE</td>
<td>1,2-dichloroethane</td>
</tr>
<tr>
<td>DCM</td>
<td>dichloromethane</td>
</tr>
<tr>
<td>DIBAL-H</td>
<td>diisobutylaluminum hydride</td>
</tr>
<tr>
<td>DMAc</td>
<td>N,N-dimethylacetamide</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-dimethylaminopyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>dimethylformamide</td>
</tr>
<tr>
<td>DMPU</td>
<td>N,N'-dimethylpropyleneurea</td>
</tr>
<tr>
<td>DMSO</td>
<td>methyl sulfoxide</td>
</tr>
<tr>
<td>dppe</td>
<td>1,2-bis(diphenylphosphino)ethane</td>
</tr>
<tr>
<td>dpff</td>
<td>1,1'-ferrocenediyl-bis(diphenylphosphine)</td>
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<tr>
<td>dppp</td>
<td>1,3-bis(diphenylphosphino)propane</td>
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<tr>
<td>eq.</td>
<td>equivalent</td>
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<td>Et</td>
<td>ethyl</td>
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</table>
g
GC
h
HFIP
HRMS
Hz
i
Ir
J
LA
M
Me
mg
min
mL
mmol
Ms
MTBE
NBD
NBE
NBS
Ni
NMR
OMe
OTf
Pd
Ph
Phos
PIDA
ppm
Pr
gram
gas chromatography
hour
hexafluoroisopropanol
high resolution mass spectrometry
Herz
iso
iridium
coupling constant
Lewis acid
molar concentration
methyl
milligram
minute
milliliter
millimol
mesyl
methyl tert-butyl ether
norbornadiene
norbornene
N-bromosuccinimide
nickel
nuclear magnetic resonance
methoxyl
triflate
palladium
phenyl
phosphine
phenyliodonium diacetate
parts per million
propyl
<table>
<thead>
<tr>
<th>Abbreviation</th>
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<tr>
<td>Rh</td>
<td>rhodium</td>
</tr>
<tr>
<td>RT</td>
<td>room temperature</td>
</tr>
<tr>
<td>sat</td>
<td>saturated</td>
</tr>
<tr>
<td>t</td>
<td>tert</td>
</tr>
<tr>
<td>TBHP</td>
<td>tert-butyl hydroperoxide</td>
</tr>
<tr>
<td>TBS</td>
<td>tert-butyldimethylsilyl</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>thin-layer chromatography</td>
</tr>
<tr>
<td>TMDS</td>
<td>tetramethyldisiloxane</td>
</tr>
<tr>
<td>TMEDA</td>
<td>N,N,N',N'-tetramethylethylenediamine</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>Ts</td>
<td>toluenesulfonyl</td>
</tr>
<tr>
<td>UV</td>
<td>ultraviolet</td>
</tr>
<tr>
<td>µL</td>
<td>microliter</td>
</tr>
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1. Introduction: Shuttle Catalysis
1.1. The Concept of Shuttle Catalysis

Transfer hydrogenation refers to the reduction of unsaturated compounds, such as ketones and alkenes, using an organic molecule as the source of hydrogen.\(^1\) In contrast to traditional hydrogenation proceeding through direct addition of hydrogen, this reaction proceeds through a transfer of hydrogen equivalent from a sacrificial donor molecule to an acceptor molecule. For example, the transfer hydrogenation of ketones can be achieved using isopropanol as a hydrogen source, and the hydrogen equivalent is transferred to the ketone by a metal catalyst (equation 1.1).\(^2\)

\[
\begin{align*}
\text{O} & \quad \text{H} & \quad \text{H} & \quad \text{O} \\
R^1 & \quad R^2 & \quad \text{Me} & \quad \text{Me}
\end{align*}
\overset{[M]}{\longrightarrow}
\begin{align*}
\text{H} & \quad \text{H} & \quad \text{O} & \quad \text{Me} \\
R^1 & \quad R^2 & \quad \text{Me} & \quad \text{Me}
\end{align*}
\text{(equation 1.1)}
\]

A variety of transfer hydrogenation reactions\(^3\) including asymmetric variants\(^4\) have been established since the first discovery by Knoevenagel in 1903.\(^5\) These reactions are particularly useful in laboratory-scale synthesis because they possess several advantages over the direct hydrogenation, such as the avoidance of hazardous hydrogen gas and the elaborate equipment that comes with it, and the reverse reaction, dehydrogenation of alcohols, can be achieved due to their reversibility.

The development of transfer hydrogenation reactions has provided an underexplored concept for understanding and designing catalytic reversible transfer reactions. This concept was recently defined as “shuttle catalysis” by Morandi and co-workers.\(^6\) Through shuttle catalysis, a

---


chemical group beyond hydrogen (shuttled group) can be transferred between a donor molecule and an acceptor molecule to achieve a functionalization and defunctionalization (Scheme 1.1).

Scheme 1.1. Definition of the concept of shuttle catalysis.

In the functionalization process (forward reaction, Scheme 1.2a), the installation of a functional group is enabled by shuttle catalysis. In this transformation, a sacrificial donor is used, and the functional group (shuttled group) is transferred from this donor to an acceptor, which is the substrate in this case. In the defunctionalization process (reverse reaction, Scheme 1.2b), the removal of a functional group is achieved using shuttle catalysis. In this transformation, a sacrificial acceptor is required to trap the functional group (shuttled group) that is removed from the donor, which is the substrate in this case. Concerning the atom-economy and practicality of the reaction, the sacrificial donor should ideally be a small organic molecule with high availability, and the sacrificial acceptor should be an inexpensive and readily available chemical. Owing to the reversibility of shuttle catalysis reactions, a driving force is usually required to drive the equilibrium to favor either the forward or the reverse reaction. Generally, the formation of gaseous reagents, polymerized molecules, insoluble by-products, or the release of strain can be employed as a driving force.
Exploring the Potent ial of Shuttle Catalysis in Organic Synthesis

Scheme 1.2. Overview of the shuttle catalysis strategy: forward and reverse.

Remarkable benefits can be obtained from using shuttle catalysis in reactions, particularly the reaction that traditionally rely on the use of toxic, reactive, or unstable reagents such as hydrogen cyanide, Grignard reagents, and syngas. In this introduction, several shuttle catalysis reactions, where such a reagent is replaced with a donor molecule, are discussed.
1.2. Examples of Transfer Reactions Using Shuttle Catalysis

1.2.1. Transfer hydromagnesiation

An early example of shuttle catalysis reactions is the work on the transfer hydromagnesiation reported by Cooper and Finkbeiner in 1962 (Scheme 1.3).\(^7\) In this report, they demonstrated an approach for the synthesis of Grignard reagents via a titanium-catalyzed transfer hydromagnesiation of alkenes using an alkyl magnesium bromide as the source of HMgBr. In the reaction, several alkyl magnesium bromides (alkyl = \(n\)-propyl, \(iso\)-propyl or ethyl) could serve as sacrificial donor molecules. Methylmagnesium bromide without \(\beta\)-hydrogens is not able to transfer an HMgBr equivalent, demonstrating the involvement of a transfer process in the reaction. Compared with the conventional approach, where Grignard reagents are prepared by reacting magnesium metal with an alkyl or aryl halide, this transfer hydromagnesiation provides a more practical method for the synthesis of Grignard reagents despite the fact that only few substrates were shown in the report and the yields of products were poor.

\[ \text{Cooper and Finkbeiner, 1962} \]

\[ \text{substrate (acceptor)} + \text{sacrificial donor (1.0 eq.)} \xrightarrow{\text{TiCl}_4 (2.8 \text{ mol\%})} \text{Et}_2\text{O, reflux, 18 h}} \text{ HMgBr} + \text{R}^1\text{R}^2 \]

<table>
<thead>
<tr>
<th>Sacrificial donor (1.0 eq.)</th>
<th>Yields of alcohol (%)</th>
<th>Sacrificial donor (1.0 eq.)</th>
<th>Yields of alcohol (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{HMgBr})</td>
<td>41</td>
<td>(\text{HMgBr})</td>
<td>11</td>
</tr>
<tr>
<td>(\text{HMgBr})</td>
<td>18</td>
<td>(\text{MeMgBr})</td>
<td>0</td>
</tr>
</tbody>
</table>

Scheme 1.3. Titanium-catalyzed hydromagnesiation of alkenes through shuttle catalysis.

Following this report, a number of transfer hydromagnesiation reactions have been developed due to the great synthetic importance of Grignard reagents in organic synthesis. For example, in 2010 Thomas and co-workers reported a synthesis of α-aryl carboxylic acids via an iron-catalyzed transfer hydromagnesiation of styrenes followed by carboxylation with CO$_2$ (Scheme 1.4a). This reaction provides a practical and efficient route to access carboxylic acids through a two-step transformation: transfer hydromagnesiation and carboxylation. In the hydromagnesiation process, ethyl magnesium bromide is used as the sacrificial donor of HMgBr which is transferred to the aryl alkene acceptor in the presence of FeCl$_2$ as precatalyst and a bis(imino)pyridine ligand (L1). The formation of volatile ethene is believed to provide a driving force for the transformation. Concerning the mechanism, this transfer hydromagnesiation was proposed to proceed through an initial transmetallation between iron catalyst and the Grignard reagent, which gives an organoferrate complex 1-A (Scheme 1.4b). The subsequent coordination of styrene on this complex and β-hydride elimination generates an alkene ligated iron hydride species 1-C which could then undergo hydrometallation with styrene to form intermediate 1-D. Finally, transmetallation with another equivalent of Grignard reagent generates the new Grignard reagent which could be reacted with CO$_2$ to produce the carboxylic acid products. A wide range of aryl carboxylic acids can be prepared through this transfer hydromagnesiation strategy in high yields and with excellent regioselectivity.

---


Scheme 1.4. Iron-catalyzed hydromagnesiation of alkenes through shuttle catalysis.

In 2016, a similar work was reported by Xi and co-workers, where they demonstrated that the hydrocarboxylation of alkenes could also be achieved via a titanium-catalyzed transfer hydromagnesiation and the following carboxylation with CO$_2$ (Scheme 1.5).\textsuperscript{10} In this transfer hydromagnesiation process, an HMgBr or HMgCl equivalent is transferred from a simple donor, \textit{iso}-propylmagnesium bromide or chloride, to an alkene acceptor to produce a new Grignard reagent. This newly formed Grignard reagent is then trapped by CO$_2$ to form a carboxylic acid. A wide range of styrene derivatives and terminal alkyl alkenes were proved to be effective acceptors for the transfer hydrocarboxylation, with the former leading to the branched products and the latter leading to the linear products. Conjugated dienes could also be reacted efficiently, and the transfer hydromagnesiation occurs preferentially on the less substituted alkene, leading to the branched product after reaction with CO$_2$.

Exploring the Potential of Shuttle Catalysis in Organic Synthesis

Scheme 1.5. Ti-catalyzed hydromagnesiation of alkenes through shuttle catalysis.

The use of alkynes as an acceptor for the transfer hydromagnesiation has also been reported by Nakamura and co-workers (Scheme 1.6).\(^\text{11}\) In the report, the authors demonstrated a transfer of HMgBr from a sacrificial donor EtMgBr to the substrate using an iron catalyst under ligand-free conditions. A wide range of functional groups can be tolerated in this transformation, including bromide, iodide, amine, and alkene, enabling the preparation of various useful vinylmagnesium compounds. This reaction provides a method for facile preparation of vinylmagnesium compounds using a simple and ready available Grignard reagent even though the substrate scope of the current approach is limited to diarylalkynes and several 1,3-diynes.

---

1.2.2. Transfer Hydroformylation

Hydroformylation refers to the addition of syngas (a mixture of CO and H₂) across olefins to form an aldehyde. The reaction occupies an important position in organic chemistry, and has seen wide application in industrial synthesis. However, the direct use of syngas as the source of HCHO remains a significant drawback of this transformation due to the high toxicity of carbon monoxide and the flammability and explosiveness of hydrogen. Therefore, the discovery of new methods and hydroformylating reagents to avoid the use of hazardous syngas is in high demand. Shuttle catalysis would be an effective strategy to prevent the direct use of syngas in hydroformylation reactions. Through such a strategy, the syngas can be replaced with a donor molecule from which HCHO is transferred to the substrate.

---

The transfer hydroformylation was proved feasible by Brookhart and co-workers (Scheme 1.7).\textsuperscript{14} They demonstrated a hydroformylation reaction through a transfer of HCHO from isovaleroaldehyde to the alkene using a rhodium catalyst. The formation of gaseous isobutene and the use of excess of substrate are believed to drive the reaction to a high conversion.

\textit{Brookhart and co-workers, 1999}

\begin{equation*}
\begin{array}{c}
\text{Me} \quad \text{H} \quad \text{O} \\
\text{Me} \quad \text{H} \quad \text{O}
\end{array}
\quad 
\begin{array}{c}
\text{fBu} \quad \text{C} \\
\text{50 eq.}
\end{array}
\quad 
\begin{array}{c}
\text{catalyst 1 (2 mol\%)} \\
\text{60 °C, 24 h}
\end{array}
\quad 
\begin{array}{c}
\text{H} \quad \text{O} \\
\text{Me}
\end{array}
\quad 
\begin{array}{c}
\text{fBu} \quad \text{C} \\
\text{Me}
\end{array}
\quad 
\begin{array}{c}
\text{85 \% conversion}
\end{array}
\end{equation*}

\textbf{Scheme 1.7. Rh-catalyzed hydroformylation of alkenes through shuttle catalysis.}

Although the transfer hydroformylation represents an attractive strategy and was proved feasible, this field remained underdeveloped until a recent report by You and co-workers (Scheme 1.8a).\textsuperscript{15} In the report, a rhodium-catalyzed transfer hydroformylation of alkynes for the synthesis of $\alpha$, $\beta$-unsaturated aldehydes is disclosed. In the reaction, inexpensive and easy-to-handle $n$-butyraldehyde is used as a sacrificial HCOH donor and the formation of volatile propene provides a driving force. A wide range of functional groups can be tolerated in this transformation including tertiary alcohols, amines, amides, esters, aldehydes, and ketones. Moreover, some substrates derived from biologically relevant compounds can be converted to the corresponding $\alpha,\beta$-unsaturated aldehydes in high yields and selectivity. One notable advantage of this method compared with the traditional hydroformylation of alkynes using syngas is that side reactions such as hydrogenation of alkynes or the product can be completely suppressed. Concerning the mechanism (Scheme 1.8b), it is proposed to start with an oxidative addition of the aldehyde C–H bond to form an acyl–Rh(III)–hydride species 1-E. The subsequent


reductive elimination and CO de-insertion generates an intermediate \(1\-G\) which could undergo a \(\beta\)-hydride elimination to form an alkene-ligated rhodium hydride species \(1\-H\). A ligand exchange with an alkyne followed by a sequence of CO re-insertion, oxidative addition and reductive elimination leads to the aldehyde product and regenerates the rhodium catalyst. This transfer hydroformylation provides a powerful and operational method for the synthesis of \(\alpha,\beta\)-unsaturated aldehydes which are valuable building blocks. However, a critical limitation of this transformation is that the substrates scope is limited to internal alkynes.

\[(a) \text{ You and co-workers, 2019} \]

\[\begin{align*}
R^1\equiv& -R^2 + H\equiv O\equiv H & \xrightarrow{[\text{Rh(COD)OMe}]_2 (2 \text{ mol\%})} & \text{Xantphos (4 mol\%)} & 4\-NO_2\text{PhCO}_2\text{H (4 mol\%)} \\
& \text{THF, 80 °C, 24 h} & \text{37 examples} & \text{45-93\% yield}
\end{align*}\]

selected examples:

\[\begin{align*}
\text{Scheme 1.8. Rhodium-catalyzed hydroformylation of alkynes through shuttle catalysis.}
\end{align*}\]

In contrast to hydroformylation, the dehydroformylation (reverse reaction) remained challenging to realize until the establishment of the shuttle catalysis strategy. In 2015, the Dong
group demonstrated an approach based on shuttle catalysis for the efficient dehydroformylation of aldehydes (Scheme 1.9a). The reaction proceeds through a transfer process where the HCHO equivalent is transferred from an aldehyde to a sacrificial acceptor in the presence of a rhodium catalyst, leading to a variety of alkene products in high yields and with good selectivity. The strained alkene, norbornadiene or norbornene, is used as a sacrificial acceptor in this reaction and the release of strain is believed to provide the driving force. According to the proposed mechanism (Scheme 1.9b), this transfer dehydroformylation of aldehydes might proceed through a similar catalytic cycle to that for You’s hydroformylation of alkynes. An initial aldehyde C–H bond activation by the rhodium catalyst generates an acyl–Rh(III)–hydride species 1-M, which then undergoes reductive elimination, CO de-insertion and β-hydride elimination to produce an alkene-ligated rhodium hydride intermediate 1-P. Then a ligand exchange with norbornadiene or norbornene releases the alkene product and intermediate 1-Q which could undergo a similar process in reverse order to regenerate the rhodium catalyst.

1.2.3. Transfer hydroacylation

In addition to formaldehyde, other aldehydes can also be transferred by shuttle catalysis. In 1999, Jun and co-workers reported a transfer hydroacylation of alkenes using a combination of RhCl(PPh₃)₃ and 2-amino-3-picoline as catalyst (Scheme 1.10a). In this reaction, RCHO is transferred from a sacrificial ketone to the alkene, enabling a facile synthesis of ketones. An

Scheme 1.9. Rhodium-catalyzed dehydroformylation of aldehydes through shuttle catalysis.

---

excess of substrate is required to promote the reaction, but the polymerization of the alkene by-product can also provide a driving force. According to the proposed mechanism (Scheme 1.10b), this reaction might start with a chelation-assisted C–C bond activation with the aid of 2-amino-3-picoline,\textsuperscript{18} which could lead to a Rh(III) complex \textbf{1-V}. A $\beta$-hydride elimination of this complex gives rhodium hydride species \textbf{1-W} and the alkene by-product. Subsequent alkene exchange, reinsertion and reductive elimination regenerates the rhodium catalyst and form a ketamine \textbf{1-Y}, which could provide the hydroacylated product after hydrolysis. Traditionally, the hydroacylation proceeds through direct addition of an aldehyde across the alkene, an approach that can be problematic when the aldehyde is volatile or unstable.\textsuperscript{19} This problem can be addressed using this transfer hydroacylation strategy.


1.2.4. Transfer hydrocyanation

Direct hydrocyanation of alkenes represents an efficient and practical approach to access nitriles which are important synthetic intermediates and abundant in pharmaceuticals,
agrochemicals and organic materials.\textsuperscript{20} Despite its use in industry,\textsuperscript{21} this method is difficult to use in the laboratory due to the need for highly toxic and explosive HCN as the hydrocyanating reagent. Although safer HCN sources, such as acetone cyanohydrin\textsuperscript{22} and a combined source, TsCN/PhSiH\textsubscript{3},\textsuperscript{23} have been developed, the risk of generating HCN during the reaction remains. To address this problem, Morandi and co-workers recently developed a nickel-catalyzed transfer hydrocyanation of alkenes using a simple and less toxic alkyl nitrile as the source of HCN (Scheme 1.11).\textsuperscript{24} This shuttle catalysis reaction enables the transfer of HCN from a sacrificial donor, isovaleronitrile, to a wide range of alkenes including several drug precursors through shuttle catalysis, producing the corresponding nitrile products in high yields and with excellent regioselectivity. The formation and release of volatile isobutene as by-product is believed to provide the driving force for this reaction. Compared to the conventional hydrocyanation reactions using hazardous HCN as the hydrocyanating reagent, this transfer hydrocyanation of alkenes provides a safer method for the preparation of nitriles.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{scheme111.png}
\caption{Nickel-catalyzed transfer hydrocyanation through shuttle catalysis.}
\end{figure}

\textbf{Morandi and co-workers, 2016}

\begin{align*}
\text{Ni(COD)}_2 (5 \text{ mol\%}) & \quad \text{DPEphos (5 mol\%)} \\
\text{AlMe}_2\text{Cl (20 mol\%)} & \quad \text{toluene, 100-130 °C}
\end{align*}

\begin{align*}
\text{drug precursors and other examples:}
\end{align*}

\begin{align*}
\text{MeO} & \quad \text{CN} \\
\text{96\% (l/b = 80:20)} & \quad \text{Nabumetone prec.}
\end{align*}

\begin{align*}
\text{CN} & \quad \text{CN} \\
\text{47\% (>95:5)} & \quad \text{Pheniramine prec.}
\end{align*}

\begin{align*}
\text{CN} & \quad \text{CN} \\
\text{95\% (l/b > 95:5)} & \quad \text{(l/b > 95:5)}
\end{align*}

\begin{align*}
\text{CN} & \quad \text{CN} \\
\text{62\% (l/b > 95:5)} & \quad \text{(l/b > 95:5)}
\end{align*}

\textbf{Scheme 1.11. Nickel-catalyzed transfer hydrocyanation through shuttle catalysis.}


\textsuperscript{24} Fang, X.; Yu, P.; Morandi, B. \textit{Science} \textbf{2016}, \textit{351}, 832.
The reverse reaction, dehydrocyanation of alkyl nitriles, was also realized, enabling the transformation of a wide variety of aliphatic nitriles into the corresponding alkenes under the same reaction conditions (Scheme 1.12). Changing the direction of the reaction equilibrium was achieved through the use of the reactive and strained norbornadiene as a sacrificial acceptor of HCN, and the release of strain provides the driving force for the reaction.

Scheme 1.12. Nickel-catalyzed transfer dehydrocyanation through shuttle catalysis.

With respect to the mechanism for this transfer of HCN, a catalytic cycle consisting of dehydrocyanation of an alkyl nitrile and hydrocyanation of an alkene was proposed. As shown in Scheme 1.13, an oxidative addition of the C–CN bond of the alkyl nitrile followed by β-hydride elimination generates an alkene-ligated intermediate 1-B1 (dehydrocyanation). This intermediate then undergoes a ligand exchange with an alkene to form a new alkene-ligated intermediate 1-C1. Subsequent migratory insertion followed by reductive elimination leads to the product and regenerates the active nickel catalyst (hydrocyanation). The Al-Lewis acid is proposed to assist the oxidative addition by weakening the C–CN bond through coordination with the cyano group.25

---

1.2.5. Transfer hydrochlorocarbonylation

Encouraged by the development of transfer hydrocyanation reaction, the Morandi group also developed a transfer hydrochlorocarbonylation of unsaturated hydrocarbons using a palladium catalyst (Scheme 1.14a). In this reaction, butyryl chloride serves as a sacrificial donor of HCOCl and the formation of propene provides the driving force. This reaction offers a novel method for the synthesis of carbonyl compounds through the in situ derivatization of the acid chloride products. Compared with the traditional approach, the Reppe-type carbonyl reaction, where the synthesis of carbonyl compounds is achieved using CO in the presence of a nucleophile, this method avoids the use of toxic CO and does not require the elaborate equipment to handle pressurized gas. Moreover, some challenging nucleophiles, which are difficult to react in Reppe-type carbonyl reactions, such as indole, tertiary alcohol and bulky aniline, show high reactivity in this transformation. Under Pd\(_2\)(dba)\(_3\)/Xantphos catalysis, both alkenes and alkynes can react with the scope of alkynes being broader, affording a wide range of \(\alpha,\beta\)-unsaturated carbonyl compounds in high yields. The reverse reaction was also proved feasible by the achievement of a dehydrochlorocarbonylation of a complex aliphatic acid chloride using norbornene as a sacrificial acceptor (Scheme 1.14b).

---

**Scheme 1.14. Palladium-catalyzed transfer hydrochlorocarbonylation of alkynes and alkenes.**
1.3. Conclusion and Project Outline

Transfer hydrogenation represents a practical method for the reduction of unsaturated compounds, such as ketones and alkenes. Since its discovery over one century ago, it has been significantly developed and seen extensive application in industry. A notable feature of this reaction is that the direct use of explosive and flammable gaseous hydrogen can be avoided. Alternatively, an organic donor molecule is used as the source of hydrogen. Under metal catalysis, the hydrogen equivalent can be transferred to the substrate (acceptor) through a sequential process consisting of dehydrogenation and hydrogenation. Besides the transfer of hydrogen, the transfer strategy has also been used for the transfer of other chemical groups such as HMgBr, HCHO, and RCHO, enabling various functionalization and defunctionalization reactions without using toxic reagents. This transfer strategy was recently defined as “shuttle catalysis” by our group. And based on this strategy, we further developed a transfer hydrocyanation using a simple and low-toxic aliphatic nitrile as the alternative to highly toxic and explosive HCN. Following this work, our group also discovered a transfer hydrochlorocarbonylation using an inexpensive and easy-to-handle aliphatic acid chloride as the source of HCOCl, addressing the problems associated with the use of corrosive HCl and toxic CO in the traditional approach.

Despite the advances in transfer hydrofunctionalization and dehydrofunctionalization reactions, extending the application of shuttle catalysis in organic synthesis remains of great interest and significance. In this thesis, apart from a hydrofunctionalization reaction based on shuttle catalysis, some other transformations using this transfer strategy are also presented. In the second chapter, a Mizoroki-Heck-type reaction of aryl cyanides using the hydrocyanation as a catalyst-turnover step is discussed. In the third chapter, a cyanation of aryl chlorides and triflates using a simple aliphatic nitrile as the source of CN is described, wherein the transfer of CN is enabled by a dehydrocyanation process. Finally, a shuttle catalysis enabled hydrochlorination of alkynes using a similar aliphatic chloride as the hydrochlorinating reagent is presented.

2. Shuttle Catalysis-enabled Mizoroki–Heck-type Reactions of Aryl Cyanides
Abstract

The Mizoroki-Heck coupling reaction, as one of the most important methods for catalytic C–C bond formation, has seen the broad application in organic synthesis. Generally, aryl halides and their equivalents (e.g. aryl sulfonates) are used as electrophiles in this type of reaction. However, aryl cyanides have been rarely reported to serve as electrophiles in such a reaction despite their ubiquity and accessibility. In this chapter, a new approach for Mizoroki-Heck reaction that enables the use of aryl cyanides as electrophiles is presented. Unlike the traditional Mizoroki-Heck reaction, where a base is required for regeneration of the active catalyst, this method uses a transfer hydrocyanation strategy for catalyst turnover. A nickel-catalyzed intramolecular and a palladium-catalyzed intermolecular Mizoroki-Heck-type reactions of aryl cyanides under base-free conditions are reported here, and the details of the work, including optimization of reaction conditions, investigation of reaction scope and mechanistic study are further discussed.

(This work has been carried out in cooperation with Dr. Xianjie Fang)
2.1. Introduction

2.1.1. Mizoroki-Heck Reaction

In 1971, Mizoroki and co-workers reported a direct catalytic arylation reaction of alkenes with iodobenzene using palladium chloride as a catalyst, a reaction which led to the formation of aryl substituted alkenes (Scheme 2.1a).\textsuperscript{29} The use of a base was critical to the reaction, with potassium acetate being most effective. Under the reported conditions with methanol as solvent, alkenes including styrene, ethylene, propylene and methyl acrylate reacted to give the corresponding aryl substituted alkenes in good to excellent yields. Shortly after, Heck and coworkers demonstrated that such a transformation could also work with benzyl and styryl halides as electrophiles to form diverse functionalized alkenes in the presence of palladium acetate as a catalyst and tri-n-butylamine as a base under neat conditions (Scheme 2.1b).\textsuperscript{30} This alkene functionalization reaction between alkenes and halide electrophiles was later named the Mizoroki-Heck reaction, which has been significantly developed during the past several decades.

(a) \textit{Mizoroki and co-workers, 1971}

\[
\begin{align*}
\text{R} & \quad + \quad \text{Ph–I} \\
\text{2.0 eq.} & \\
(\text{R} = \text{Ph, CO}_2\text{Me, Me, H})
\end{align*}
\]

\[
\begin{align*}
PdCl_2 (1 \text{ mol\%}) & \\
\text{CH}_3\text{COOK (1.2 eq.)} & \\
\text{CH}_3\text{OH, 120 °C, 2 h} & \rightarrow \text{Ph} \quad \rightarrow \text{R} \\
73-97 \text{ yield}
\end{align*}
\]

(b) \textit{Heck and co-workers, 1972}

\[
\begin{align*}
\text{Ph–I} & \quad + \quad \text{Ph} \\
1.25 \text{ eq.} & \\
\text{n-Bu}_3\text{N (1.0 eq.)} & \text{solvent free, 100 °C, 2 h} \\
& \rightarrow \text{Ph} \quad \rightarrow \text{Ph} \\
75\% \text{ yield}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Electrophiles</th>
<th>Alkenes</th>
<th>Products (yields)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph\text{–}Cl</td>
<td>H\text{3}COOCH\text{C}=\text{CH}_2</td>
<td>Ph\text{–}\text{COOCH}_3 \text{ (67%)}</td>
</tr>
<tr>
<td>Ph\text{–}Br</td>
<td>H\text{3}COOCH\text{C}=\text{CH}_2</td>
<td>Ph\text{–}\text{COOCH}_3 \text{ (47%)}</td>
</tr>
</tbody>
</table>

Scheme 2.1. Seminal examples of Mizoroki-Heck reactions.


Since its discovery, the Mizoroki-Heck reaction has emerged as one of the most powerful tools for functionalizing alkenes. It has been widely used in organic synthesis to form vinylic C–C bonds both in academic and industrial research.\textsuperscript{31} For example, in the total synthesis of the natural product lasiodiplodin, Fürstner and co-workers used the Mizoroki-Heck reaction of an aryl triflate with ethylene to construct a styrene moiety (Scheme 2.2).\textsuperscript{32} Alternative approaches, such as the Still cross-coupling could also be used in this step, however, they led to lower yields.

\textit{Fürstner and co-workers, 2000}

![Scheme 2.2. An application of the Mizoroki-Heck reaction in total synthesis.](image)

A remarkable example of industrial application of Mizoroki-Heck reaction was demonstrated by Albemarle in the synthesis of anti-inflammatory drug Naproxen (Scheme 2.3).\textsuperscript{33} The reaction of 2-bromo-6-methoxynaphthalene with ethylene is employed as a key step in the formation of the intermediate 2-methoxy-6-vinylnaphthalene. Moreover, the Mizoroki-Heck reaction is also used in the industrial-scale production of many other fine chemicals,\textsuperscript{34} such as Prosulfuron (an herbicide), Singulair (an antiasthma agent), among others, demonstrating its great synthetic value on industrial scale.

\textsuperscript{31} Jagtap, S. Catalysis, 2017, 7, 267.
Scheme 2.3. An application of the Mizoroki-Heck reaction in industrial synthesis.

The Mizoroki-Heck reaction has become highly versatile over the past decades. Thanks to the development of catalysts and ligands, remarkable improvements have been achieved in aspects ranging from reactivity and selectivity to functional group tolerance and reaction scope. Palladium-based catalysts were originally developed for this transformation and are the most commonly used catalyst nowadays. Catalysts based on other transition metals such as copper, nickel, platinum, cobalt, ruthenium, and rhodium are also capable of catalyzing such reactions. Ligands, on the other hand, have a significant effect on not only the reactivity but also the selectivity of the Mizoroki-Heck reaction. Phosphine ligands represent the most effective


class and are used most frequently. Some chiral phosphine ligands have also been developed for asymmetric Mizoroki-Heck reactions.\(^{42}\)

With respect to the electrophile, aryl halides\(^{43}\) and triflates\(^{44}\) are most commonly used due to their wide availability (Equation 2.1). Among aryl halides, chlorides represent the most attractive electrophiles because they are more readily available and inexpensive. Aryl triflates are also common electrophiles for the Mizoroki-Heck reaction because of their high reactivity and easy accessibility from phenol derivatives.

\[
\text{Ar} \cdot \text{X} + \text{R} \xrightarrow{\text{transition metal, base}} \text{Ar} \cdot \text{R} \quad \text{(equation 2.1)}
\]

\((\text{X} = \text{halides, OTf})\)

In addition to aryl halides and triflates, transformations involving many other types of electrophiles have also been established, which has enormously expanded the scope of the Mizoroki-Heck reaction. One of them is alkyl halides, a class of substrate that was historically considered difficult to undergo transition metal-catalyzed cross-coupling reactions due to the facile β-hydride elimination of the intermediate generated from the oxidative addition.\(^{45}\) Additional electrophiles include diazonium salts,\(^{46}\) aryl chlorides,\(^{47}\) aryl sulfonyl chlorides,\(^{48}\) aryl phosphonic acids,\(^{49}\) hypervalent iodo compounds,\(^{50}\) hydrazines,\(^{51}\) aryl carboxylic acids,\(^{52}\) arenes,\(^{53}\) ethers,\(^{54}\) anhydrides,\(^{55}\) esters,\(^{56}\) and amides.\(^{57}\)


2.1.2. Cross-Coupling Reactions of Aryl Cyanides

Although the scope regarding electrophile has been greatly expanded, aryl cyanides have been rarely reported as electrophiles in the Mizoroki-Heck reaction even though they are widely found in diverse organic molecules and readily accessible synthetically. The following reasons are believed to account for this fact: 1) The inert aromatic C–CN bond is reluctant to undergo oxidative addition under classical Mizoroki-Heck reaction conditions. 2) The activation of aromatic C–CN bonds usually requires the assistance of a Lewis acid, which might be incompatible with the base required in the normal Mizoroki-Heck reaction for regenerating the catalyst. 3) HCN can be formed as a by-product after reaction of H–M–CN species with base causing safety issues.

The development of transition metal-catalyzed aromatic C–CN bond activation provides an opportunity to use aryl cyanides as an electrophile in the Mizoroki-Heck reaction. Several cross-coupling reactions of aryl cyanides based on catalytic C–CN bond activation have been disclosed. In 2001, Miller and co-workers for the first time reported the coupling of aryl cyanides with aromatic Grignard reagents via nickel-catalyzed C–CN bond activation. In the presence of NiCl₂(PMe₃)₂ and t-BuOLi, a number of aryl cyanides, including 2-, 3- or 4- cyanopyridines and 2-cyanofuran, were able to couple with diverse aromatic Grignard reagents to give biaryl products in excellent yields (Scheme 2.4).
Exploring the Potential of Shuttle Catalysis in Organic Synthesis

Scheme 2.4. First example of using aryl cyanides as substrates in cross-coupling reactions.

In addition to aromatic Grignard reagents, alkyl and alkenyl Grignard reagents were also found to be suitable coupling components for the cross-coupling with aryl cyanides. Using NiCl₂(PMe₃)₂ as a catalyst and t-BuOLi or PhSLi as a base, Dankwardt and co-workers were able to convert a host of aryl cyanides into the corresponding aryl alkanes and aryl alkenes. This method provides an efficient way to access styrene derivatives and alkyl arenes from aryl cyanides (Scheme 2.5).

\[
\begin{align*}
\text{Ar}^1\text{CN} + \text{Ar}^2\text{MgX} & \xrightarrow{\text{NiCl}_2(\text{PMe}_3)_2 \ (5 \text{ mol} \%) \quad t-\text{BuOLi} \ (2.2 \text{ eq.}) \quad \text{THF, 60 °C, 3 h}} \text{Ar}^1\text{–Ar}^2 \\
(X = \text{Cl or Br}) \quad 2.0 \text{ eq.} 
\end{align*}
\]

16 examples 69-97% yield

Scheme 2.5. A cross-coupling reaction of aryl cyanides with alkyl and alkenyl Grignard reagents.

Aryl cyanides were also reported to couple with secondary amines by Miller and co-workers in 2003. The authors demonstrated that the coupling could proceed smoothly in the presence of CsF and BuLi using Ni(CN)·4H₂O as a catalyst, leading to aromatic amines in moderate to good yields. This reaction represents the first amination of aryl cyanides via nickel-catalyzed C–CN activation (Scheme 2.6).

\[
\begin{align*}
\text{Ar–CN} + \text{RMgBr} & \xrightarrow{\text{NiCl}_2(\text{PMe}_3)_2 \ (5 \text{ mol} \%) \quad t-\text{BuOLi or PhSLi} \ (2.2 \text{ eq.}) \quad \text{THF, 0-60 °C, 16 h}} \text{Ar–R} \\
\text{R} = \text{alkyl or alkenyl} \quad 2.0 \text{ eq.} 
\end{align*}
\]

18 examples 33-80% yield

---

Miller and co-workers, 2003

\[
\text{Ar} = \text{CN} + \text{R} \equiv \text{NH} (\text{R} = \text{alkyl}) \xrightarrow{\text{Ni}(\text{CN}) \cdot \text{4H}_2\text{O} (5 \text{ mol\%})} \xrightarrow{\text{CsF (1.5 eq.), BuLi (2.0 eq.) THF, reflux, 8 h}} \text{Ar} = \text{NR}_2
\]

17 examples
42-77% yield

Scheme 2.6. Amination of aryl cyanides via C–CN activation.

Miller and co-workers further expanded the scope of organometallic compounds to alkynylzinc reagents, developing a method that enables the use of aryl cyanides as coupling partner in the Sonogashira reaction. In the presence of \( \text{NiCl}_2(\text{PMe}_3)_2 \) as a catalyst, several aryl cyanides were alkynylated efficiently to furnish the corresponding aryl alkynes in high yields (Scheme 2.7).\(^6\)

Miller and co-workers, 2004

\[
\text{Ar} = \text{CN} + \text{R} \equiv \text{ZnBr} (\text{R} = \text{aryl, alkyl, Me}_2\text{Si}) \xrightarrow{\text{NiCl}_2(\text{PMe}_3)_2 (10 \text{ mol\%})} \xrightarrow{\text{THF, 65 °C, 20 h}} \text{Ar} = \text{R}
\]

18 examples
45-98% yield

Scheme 2.7. An alkynylation of aryl cyanides via C–CN activation.

More recently, a nickel-catalyzed Suzuki-Miyaura coupling reaction of aryl cyanides has also been developed by Shi and co-workers using \( \text{NiCl}_2(\text{PMe}_3)_2 \) as a catalyst. Under their conditions, a variety of aryl cyanides bearing substituents including amides, esters, halides, and heterocycles could react smoothly with a diversity of boronic acid derivatives, giving the Suzuki products in good yields (Scheme 2.8).\(^7\)

---


2.1.3. Arylcyanation of Alkynes with Aryl Cyanides

In addition to these applications of aryl cyanides in the traditional cross-coupling reactions, aryl cyanides have also been reported to react efficiently with unsaturated hydrocarbons through C–CN bond activation. A pioneering work on arylcyanation of alkynes was disclosed by Hiyama and co-workers (Scheme 2.9).\(^{63}\) Using a Ni(cod)\(_2\)/PMe\(_3\) catalyst combination, a wide array of aryl cyanides could be activated and added on alkynes, leading to the corresponding vinyl cyanides in high yields. A nickel-catalyzed cleavage of the C–CN bond through an oxidative addition was proposed to initiate the reaction. The authors also pointed out that aryl cyanides bearing electron-donating groups reacted slower, suggesting that the oxidative addition of the C–CN bond might be the rate-determining step.

Subsequent studies on the arylcyanation of alkynes by the same group found that Lewis acids had a beneficial effect on the reactivity on the reaction. With the aid of catalytic amounts of AlMe₂Cl, a broad array of aryl cyanides could be activated efficiently under mild conditions (low temperature, low catalyst loading), including the ones bearing electron-rich substituents (Scheme 2.10).⁶⁴ Lewis acids were believed to function through coordination to the cyano group, thereby weakening the C–CN bond, which led to an acceleration of the oxidative addition step and therefore, the reaction.

**Hiyama and co-workers, 2007**

![Scheme 2.10. Nickel/LA-catalyzed arylcyanation of alkynes via C-CN activation.](image)

<table>
<thead>
<tr>
<th>Ar</th>
<th>R¹, R²</th>
<th>yield, reaction time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph-4-OMe</td>
<td>R¹, R² = Pr</td>
<td>96%, 16 h</td>
</tr>
<tr>
<td>Ph-4-CO₂Me</td>
<td>R¹, R² = Pr</td>
<td>93%, 25 h</td>
</tr>
</tbody>
</table>

In spite of these pioneering works using aryl cyanides as electrophiles, no example of Mizoroki Heck reaction of aryl cyanides has been reported under the classical reaction conditions. To the best of our knowledge, only one isolated example of Mizoroki Heck reaction using aryl cyanides as electrophiles under unusual conditions was reported by Chatani and co-workers in 2010 (Scheme 2.11).⁶⁵ In this reaction, the C–CN bond was activated by a rhodium catalyst under the assistance of an organosilicon reagent, and a base was not required for completing the catalytic cycle. However, under the conditions, this reaction has a limited substrate scope as it could only work with vinylsilanes. Furthermore, the reaction temperature was not ideal (130 °C). Two additional examples where the Mizoroki-Heck reaction of aryl cyanides have been found as a side reaction have been reported by Hiyama and co-workers while

---


attempting the carbocyanation of alkenes.\textsuperscript{66} However, the Heck products in both cases were only formed in low yields, and further study on this side reaction has not been reported.

*Chatani and co-workers, 2010*

\[
\begin{array}{c}
\text{Ar-CN} + \text{SiEt}_3 \quad \text{Rh(COD)Cl}_2 (5 \text{ mol\%}) \\
4.0 \text{ eq.} \quad \text{L3} (10 \text{ mol\%}) \quad \text{Me}_3\text{Si-SiMe}_3 (2.0 \text{ eq.}) \\
\text{ethylcyclohexane, 130 °C, 15 h} \quad \text{Ar-} \text{SiEt}_3 \\
\text{13 examples} \quad \text{40-88\% yield}
\end{array}
\]

Scheme 2.11. The Mizoroki-Heck reaction of aryl cyanides with vinylsilanes.

2.2. Nickel-Catalyzed Intramolecular MH-type Reaction of Aryl Cyanides Using an Alkyne as HCN Acceptor

2.2.1. Reaction Design

Owing to the high availability and synthetic accessibility of aryl cyanides, the development of methods that enable the use of aryl cyanides as electrophiles for the Mizoroki-Heck reaction would be of great significance from a synthetic point of view. Aryl cyanides have been rarely used as electrophiles in such a reaction partly because of the poor ability of traditional Heck conditions to activate the aromatic C–CN bonds. However, the development of traditional cross-coupling and addition reactions of aryl cyanides provides an opportunity to enable the use of aryl cyanides as electrophiles in the Mizoroki-Heck reaction.

In the generally accepted mechanism of the Mizoroki-Heck reaction, the base plays a pivotal role in catalyst regeneration (Scheme 2.12). The choice of a base can often have a significant effect on the outcome of the Mizoroki-Heck reaction. However, for the Mizoroki-Heck reaction using aryl cyanides as substrate, as discussed in the section 2.1, the use of base can be a problem for two reasons: 1) it might be incompatible with the Lewis acid which is usually required for assisting the activation of aryl C–CN bond; and 2) the byproduct that formed by the reaction of H–M–CN species with base can raise safety issues. Thus, the development of a new method that can complete the catalytic cycle without using a base would potentially provide a solution to the challenge of the Mizoroki-Heck reaction with aryl cyanides.

Scheme 2.12. General mechanism for the Mizoroki-Heck reaction.

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67 See reference 35f.
Inspired by the transfer hydrocyanation reaction developed recently by our group, we reasoned that a shuttle catalysis strategy could be used to regenerate the active metal catalyst via transfer hydrocyanation, and would thus circumvent the use of a base (Scheme 2.13). Through this strategy, the H–M–CN species generated would react with an acceptor, which can be an alkyne or an alkene, through a hydrocyanation to regenerate the active metal catalyst and release the byproduct which would be a nontoxic nitrile.

Scheme 2.13. A shuttle catalysis approach to the Mizoroki-Heck reaction.

Given the inherent reversibility of alkene hydrocyanation, we started to test our idea using an alkyne as the acceptor of HCN, which should be able to simplify the reaction system because the hydrocyanation of an alkyne is irreversible. On the other hand, an alkyne is more reactive than an alkene toward the hydrocyanation, which can avoid the hydrocyanation of an alkene as a side reaction. We selected a 2-cyanostyrene (S21) as the model substrate and 4-octyne (S22) as both reaction component and HCN acceptor to test our hypothesis (Scheme 2.14). We envisaged this intramolecular Mizoroki-Heck-type reaction would proceed through a tandem sequence composed of oxidative addition of the Ar–CN bond under the assistance of a Lewis acid, intermolecular alkyne insertion into the species generated from oxidative addition, further insertion of alkene intramolecularly, β-hydride elimination and alkyne hydrocyanation which could regenerate the metal catalyst.
2.2.2. Evaluation of The Reaction Conditions

We initially used the same catalytic system as in the previously developed transfer hydrocyanation, which consists of Ni(COD)$_2$ as a catalyst, DPEphos as a ligand and AlMe$_3$Cl as a co-catalyst. Encouragingly, 14% yield of product could be obtained under these conditions (Table 2.1, entry 6). Having this preliminary result, we then tried several different ligands. As shown in Table 2.1, triphenylphosphine was the most efficient ligand for this reaction and could lead to the desired product (21) in 77% yield (Entry 1). Importantly, the hydrocyanation product (22) was also formed in 63% yield under these conditions, which confirmed the involvement of a hydrocyanation process in the reaction. Electron-rich ligands such as triethylphosphine and tricyclohexylphosphine, which are more commonly used for promoting the activation of inert chemical bonds, only gave the product in yields lower than 10% (Entries 2 and 3). A Buchwald type ligand, RuPhos, performed even worse than trialkylphosphines, giving the product in 5% yield (Entry 4). Bidentate phosphine ligands such as dppe did not show any positive effect on the outcome of the reaction (Entries 5 and 6).
Table 2.1. Study of the ligand effects.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>21 (%)(^b)</th>
<th>22 (%)(^b) (E/Z) (^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PPh(_3) (20 mol%)</td>
<td>77</td>
<td>63 (96/4)</td>
</tr>
<tr>
<td>2</td>
<td>PEt(_3)</td>
<td>9</td>
<td>7 (78/42)</td>
</tr>
<tr>
<td>3</td>
<td>PCy(_3) (20 mol%)</td>
<td>6</td>
<td>Trace</td>
</tr>
<tr>
<td>4</td>
<td>RuPhos (20 mol%)</td>
<td>5</td>
<td>4 (32/68)</td>
</tr>
<tr>
<td>5</td>
<td>dppe (10 mol%)</td>
<td>8</td>
<td>8 (&gt;99/1)</td>
</tr>
<tr>
<td>6</td>
<td>DPEphos (10 mol%)</td>
<td>14</td>
<td>14 (&gt;99/1)</td>
</tr>
</tbody>
</table>

\(^a\)Reaction conditions: S\(_{21}\) (0.25 mmol), S\(_{22}\) (2.0 eq.), Ni(COD)\(_2\) (10 mol%), AlMe\(_2\)Cl (40 mol%), toluene (0.5 mL), 50 °C, 16 h. \(^b\)GC yields with isooctane as an internal standard. \(^c\)The ratio of E/Z was determined by GC analysis.

Having triphenylphosphine as the optimized ligand, we moved to screen the Lewis acid and reaction temperature. The results are summarized in Table 2.2, showing that a number of different Lewis acids were tested and a great effect on the reactivity of the reaction was observed. AlMe\(_2\)Cl was found to perform the best, delivering the desired product (21) in 77% yield (Entry 1). AlMe\(_3\) could also catalyze the reaction efficiently even though the product was formed in a slightly lower yield (Entry 2). Other Lewis acids such as AlCl\(_3\) and BPh\(_3\) were found inactive (Entries 3, 4). Decreasing the loading of AlMe\(_2\)Cl to 20 mol% lowered the yield of product from 77% to 70% (Entry 5). Gratifyingly, the yield of the product could be improved to 81% by increasing the temperature to 60 °C (Entry 6).
Table 2.2. Study of Lewis acid and temperature effects.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>LA</th>
<th>T</th>
<th>21 (%)(^b)</th>
<th>22 (%)(^b) (E/Z)(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AlMe(_2)Cl (40 mol%)</td>
<td>50 °C</td>
<td>77</td>
<td>63 (96/4)</td>
</tr>
<tr>
<td>2</td>
<td>AlMe(_3) (40 mol%)</td>
<td>50 °C</td>
<td>71</td>
<td>65 (&gt;99/1)</td>
</tr>
<tr>
<td>3</td>
<td>AlCl(_3) (40 mol%)</td>
<td>50 °C</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>BPh(_3) (40 mol%)</td>
<td>50 °C</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>AlMe(_2)Cl (20 mol%)</td>
<td>50 °C</td>
<td>70</td>
<td>53 (93/7)</td>
</tr>
<tr>
<td>6</td>
<td>AlMe(_2)Cl (40 mol%)</td>
<td>60 °C</td>
<td>81</td>
<td>67 (90/10)</td>
</tr>
</tbody>
</table>

\(^a\)Reaction conditions: S\(_{21}\) (0.25 mmol), S\(_{22}\) (2.0 eq.), Ni(COD)\(_2\) (10 mol\%), PPh\(_3\) (40 mol\%), toluene (0.5 mL), 16 h. \(^b\)GC yields with isooctane as an internal standard. \(^c\)The ratio of E/Z was determined by GC analysis.

Further optimization of catalyst loading and control experiments in the absence of catalyst, ligand or Lewis acid was carried out. As shown in Table 2.3, a lower yield was obtained when the reaction was performed with lower loading of Ni(COD)\(_2\), PPh\(_3\) and AlMe\(_2\)Cl, either at 50 °C or 100 °C (Entries 1, 2). The reaction was entirely halted when performed with Pd\(_2\)(dba)\(_3\) instead of Ni(COD)\(_2\) or in the absence of Ni(COD)\(_2\), revealing the critical role of the nickel catalyst in the reaction (Entries 3, 6). Likewise, no reactivity could be observed when AlMe\(_2\)Cl was replaced with Et\(_3\)N (Entry 4), which suggested that the reaction could not proceed through the traditional base-facilitated pathway. As shown in entry 5, a lower yield was obtained when Et\(_3\)N was added in the standard reaction. This result strongly supported our hypothesis that Lewis acids might not be compatible with the additional base. Moreover, the reaction did not occur when performed in the absence of AlMe\(_2\)Cl (Entry 8), demonstrating the importance of Lewis acid to the success of this intramolecular Mizoroki-Heck-type reaction of aryl cyanides. The ligand was also found to be crucial for the reaction since a much lower yield was obtained in the control experiment without triphenylphosphine (Entry 7).
Table 2.3. Further optimization and control experiments.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Deviation from standard conditions</th>
<th>21 (%)\textsuperscript{b}</th>
<th>22 (%)\textsuperscript{b} (E/Z)\textsuperscript{c}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ni(COD)\textsubscript{2} (5 mol%) / PPh\textsubscript{3} (10 mol%) / AlMe\textsubscript{2}Cl (20 mol%) at 50 °C</td>
<td>48</td>
<td>34 (&gt;99/1)</td>
</tr>
<tr>
<td>2</td>
<td>Ni(COD)\textsubscript{2} (5 mol%) / PPh\textsubscript{3} (10 mol%) / AlMe\textsubscript{2}Cl (20 mol%) at 100 °C</td>
<td>49</td>
<td>37 (60/40)</td>
</tr>
<tr>
<td>3</td>
<td>Pd\textsubscript{2}(dba)\textsubscript{3} (5 mol%) instead of Ni(COD)\textsubscript{2}</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Et\textsubscript{3}N (1.0 eq.) instead of AlMe\textsubscript{2}Cl</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>With Et\textsubscript{3}N (1.0 eq.)</td>
<td>36</td>
<td>32 (&gt;99/1)</td>
</tr>
<tr>
<td>6</td>
<td>Without Ni(COD)\textsubscript{2}</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>Without PPh\textsubscript{3}</td>
<td>17</td>
<td>12 (&gt;99/1)</td>
</tr>
<tr>
<td>8</td>
<td>Without AlMe\textsubscript{2}Cl</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Reaction conditions: S\textsubscript{21} (0.25 mmol), S\textsubscript{22} (2.0 eq.), toluene (0.5 mL), 16 h. \textsuperscript{b}GC yields with isoctane as an internal standard. \textsuperscript{c}The ratio of E/Z was determined by GC analysis.

2.2.3. Substrate Scope

After establishing the optimized conditions, we turned our attention to investigate the reaction scope. As shown in Table 2.4, electron-rich substrates were well tolerated under the conditions as the substrate bearing a methyl group could react well to afford the corresponding product in a good yield (Entry 2). Substrates bearing halogens or ethers showed good reactivity and no side products arising from the reaction of C–halogen or C–O bond was detected (Entries 3, 4, 5 and 8). Interestingly, a styrene or a diphenylacetylene on the substrate remained untouched under the reaction conditions and the desired products could be obtained in good yields (Entries 6 and 7). Heterocycles such as thiophene and benzofuran were also well tolerated (Entries 9 and 10). With respect to alkynes, both cyclic and acyclic aliphatic alkynes reacted efficiently under the standard conditions and led to the corresponding products in good to excellent yields (Entries 11 to 14, and 17). However, it should be pointed out that the regioselectivity originated from using asymmetric alkynes could only be obtained at a poor level.
In contrast to aliphatic alkynes, the aromatic alkyne diphenylacetylene was unreactive even at an elevated temperature (Entry 16). Finally, a strained alkene norbornene was also successfully applied to this transformation although a higher temperature was required, leading to the product in a high yield (Entry 15). Please note that along with the desired product the corresponding transfer hydrocyanation products were also produced in moderate to good yields which are given in the experimental section.

**Table 2.4. Substrate scope of the intramolecular MH-type reaction of aryl cyanides.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Entry</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Product 1" /></td>
<td>81%</td>
<td>10</td>
<td><img src="image10.png" alt="Product 10" /></td>
<td>45%</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2.png" alt="Product 2" /></td>
<td>70%</td>
<td>11</td>
<td><img src="image11.png" alt="Product 11" /></td>
<td>67%</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3.png" alt="Product 3" /></td>
<td>89%</td>
<td>12</td>
<td><img src="image12.png" alt="Product 12" /></td>
<td>73%</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4.png" alt="Product 4" /></td>
<td>88%</td>
<td>13</td>
<td><img src="image13.png" alt="Product 13" /></td>
<td>89%</td>
</tr>
<tr>
<td>5</td>
<td><img src="image5.png" alt="Product 5" /></td>
<td>60%</td>
<td>14</td>
<td><img src="image14.png" alt="Product 14" /></td>
<td>92%</td>
</tr>
</tbody>
</table>
To extend the substrate scope of this transformation, a benzyl nitrile derivative 2-(2-vinylphenyl)acetonitrile (S220) was subjected to the transformation (Scheme 2.15). Interestingly, it could react with both acyclic and cyclic aliphatic alkyne efficiently to give the corresponding substituted naphthalene products 219 and 220 in good yields, a result that demonstrated the robustness of this intramolecular MH-type reaction. With regard to the mechanism of this transformation, it is believed to proceed through an oxidative addition of the sp$^3$ C–CN bond on nickel catalyst under the assistance of Lewis acid, alkyne insertion into the species generated from the oxidative addition, further insertion of alkene, β-hydride elimination and alkyne hydrocyanation. Finally, a rapid isomerization of the initially formed products took place to form the thermodynamically more stable products 219 and 220.
2.2.4. Mechanistic Studies

According to the hypothesis, we were able to depict the proposed catalytic cycle for this intramolecular MH-type reaction of aryl cyanides as shown in Scheme 2.16. The intermediate 2-B, which is generated from oxidative addition of the aryl C–CN bond onto the nickel catalyst, undergoes insertion across an alkyne, leading to the intermediate 2-C. A further intramolecular insertion across the alkene followed by reductive elimination would lead to the product and species 2-E. This species could then react with the alkyne through a hydrocyanation to regenerate the catalyst and form the nontoxic side product.
To obtain experimental information to support this proposed catalytic cycle, several mechanistic experiments were performed. Initially, a reaction of substrate S21 and norbornene was conducted in an attempt to isolate the reductive elimination product of intermediate 2-C. Encouragingly, the product (221) could be isolated in 42% yield when the reaction was performed at 60 °C instead of 100 °C (Scheme 2.17a). This result confirmed the intermolecular alkyne insertion step. We next designed an experiment using a trans-β methyl styrene derivative S213 as starting material to react with 4-octyne under the standard conditions. The isolation of two alkene regioisomers, 222 and 223, which might be derived from a non-regioselective β-hydride elimination of a metal species bearing two different β-hydrogens, suggested the involvement of intermediate 2-D (Scheme 2.17b). Finally, a deuterium-labeling experiment using substrate S21-D as the starting material was performed. The observation of 79% deuterium
incorporation in the product 224 provided strong evidence for the involvement of the transfer hydrocyanation as a turnover-enabling step in the catalytic cycle (Scheme 2.17c).

Scheme 2.17. Mechanistic experiments.
2.3. **Palladium-Catalyzed Intermolecular MH-type Reaction of Aryl Cyanides Using an Alkene as HCN Acceptor**

2.3.1. **Studies of Reaction Conditions**

Encouraged by the result of the intramolecular MH-type reaction of aryl cyanides using an alkyne as the HCN acceptor, we moved to explore the reactivity of the intermolecular MH-type reaction of aryl cyanides using a less active alkene as the HCN acceptor. As an initial trial, we applied the catalytic system developed for the intramolecular MH-type reaction to a reaction of benzonitrile (S221) and styrene. Gratifyingly, 14% yield of the desired product (225) could be detected when the reaction was conducted at 100 °C (Table 2.5, entry 1). After a preliminary evaluation of the temperature and the loading of Lewis acid, we found that the reaction could also take place at 60 °C with lower loading of Lewis acid (20 mol%), affording the product in 16% yield (Table 2.5, entry 2). Based on these conditions, we then evaluated the effect of ligands on the reactivity of the reaction. As shown in entries 3-8, both electron-rich and electron-poor monophosphine ligands gave poor yields of product (Table 2.5, entries 3-8). Bidentate phosphine ligands also showed poor activity as all of them led to the products in yields less than 10% (Table 2.5, entries 9-15). Moreover, only trace amounts of transfer hydrocyanation product (226) could be detected by GC in all these reactions.
Table 2.5. Studies of the condition for the intermolecular MH-type reaction of aryl cyanides.\textsuperscript{a}

\begin{table}[h]
\centering
\begin{tabular}{lllll}
\hline
Entry & Ligand & Lewis acid (mol\%) & T. & 225 (\%)\textsuperscript{b} \\
\hline
1 & PPh\textsubscript{3} (20 mol\%) & AlMe\textsubscript{2}Cl (40) & 100 °C & 14\%
2 & PPh\textsubscript{3} (20 mol\%) & AlMe\textsubscript{2}Cl (20) & 60 °C & 16\%
3 & L\textsubscript{3} (20 mol\%) & AlMe\textsubscript{2}Cl (20) & 60 °C & 15\%
4 & L\textsubscript{4} (20 mol\%) & AlMe\textsubscript{2}Cl (20) & 60 °C & 7\%
5 & PCy\textsubscript{3} (20 mol\%) & AlMe\textsubscript{2}Cl (20) & 60 °C & 10\%
6 & XPhos (20 mol\%) & AlMe\textsubscript{2}Cl (20) & 60 °C & 11\%
7 & JohnPhos (20 mol\%) & AlMe\textsubscript{2}Cl (20) & 60 °C & <5\%
8 & DavePhos (20 mol\%) & AlMe\textsubscript{2}Cl (20) & 60 °C & <5\%
9 & L\textsubscript{5} (10 mol\%) & AlMe\textsubscript{2}Cl (20) & 60 °C & 0\%
10 & L\textsubscript{6} (10 mol\%) & AlMe\textsubscript{2}Cl (20) & 60 °C & <5\%
11 & L\textsubscript{7} (10 mol\%) & AlMe\textsubscript{2}Cl (20) & 60 °C & <5\%
12 & Xantphos (10 mol\%) & AlMe\textsubscript{2}Cl (20) & 60 °C & 0\%
13 & dppe (10 mol\%) & AlMe\textsubscript{2}Cl (20) & 60 °C & 0\%
14 & L\textsubscript{8} (10 mol\%) & AlMe\textsubscript{2}Cl (20) & 60 °C & <5\%
15 & dppp (10 mol\%) & AlMe\textsubscript{2}Cl (20) & 60 °C & <5\%
\hline
\end{tabular}
\end{table}

\textsuperscript{a}Reaction conditions: Ni(COD)\textsubscript{2} (5 mol\%), S221 (0.2 mmol), styrene (5.0 eq.), toluene (0.5 mL), Ar, 60 °C, 16 h. \textsuperscript{b}GC yields with dodecane as an internal standard.
We then turned our attention to evaluate the metal precatalyst and found that the use of Pd$_2$(dba)$_3$ as catalyst could effectively improve the product yield (Table 2.6). Moreover, significant amounts of the hydrocyanation product could also be detected, a result that provided clear evidence for the proposed alkene hydrocyanation-enabled catalyst regeneration process. In the presence of a Pd$_2$(dba)$_3$/AlMe$_2$Cl catalytic system, a group of phosphine ligands were then screened. The result showed that CyJohnPhos was the best ligand for the reaction, giving the product in 70% yield (Table 2.6, entry 1). However, this ligand was inactive when the reaction was performed at a temperature lower than 80 °C (Table 2.6, entry 10-12).

**Table 2.6. Study of conditions for the intermolecular MH-type reaction of aryl cyanides.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>T.</th>
<th>225 (%)</th>
<th>226 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CyJohnPhos (10 mol%)</td>
<td>100 °C</td>
<td>70</td>
<td>36</td>
</tr>
<tr>
<td>2</td>
<td>DavePhos (10 mol%)</td>
<td>100 °C</td>
<td>18</td>
<td>16</td>
</tr>
<tr>
<td>3</td>
<td>XPhos (10 mol%)</td>
<td>100 °C</td>
<td>30</td>
<td>27</td>
</tr>
<tr>
<td>4</td>
<td>RuPhos (10 mol%)</td>
<td>100 °C</td>
<td>19</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>BrettPhos (10 mol%)</td>
<td>100 °C</td>
<td>17</td>
<td>13</td>
</tr>
<tr>
<td>6</td>
<td>JohnPhos (10 mol%)</td>
<td>100 °C</td>
<td>21</td>
<td>25</td>
</tr>
<tr>
<td>7</td>
<td>SPhos (10 mol%)</td>
<td>100 °C</td>
<td>46</td>
<td>29</td>
</tr>
<tr>
<td>8</td>
<td>PPh$_3$ (10 mol%)</td>
<td>100 °C</td>
<td>17</td>
<td>13</td>
</tr>
<tr>
<td>9</td>
<td>PPhCy$_2$ (10 mol%)</td>
<td>100 °C</td>
<td>35</td>
<td>29</td>
</tr>
<tr>
<td>10</td>
<td>CyJohnPhos (10 mol%)</td>
<td>25 °C</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>CyJohnPhos (10 mol%)</td>
<td>60 °C</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>CyJohnPhos (10 mol%)</td>
<td>80 °C</td>
<td>63</td>
<td>50</td>
</tr>
</tbody>
</table>

*aReaction conditions: S221 (0.2 mmol), styrene (2.0 eq.), toluene (0.5 mL), Ar, 16 h. bGC yields with dodecane as an internal standard. cYields of the mixture of regioisomers.
With the optimized catalyst and ligand in hand, we continued to evaluate other factors that might have a significant effect on the reaction, such as the ratio of catalyst to ligand, the loading of reagents, the concentration of reaction mixture, and the solvent. As shown in Table 2.7, the highest yield of product could be obtained when the reaction was performed with a Pd$_2$(dba)$_3$/CyJohnPhos/AlMe$_2$Cl catalytic system with a ratio of 2.5/10/40 mol% (Entry 5). A higher concentration of reagents is beneficial to the reaction, leading to improved yields of both the desired product and hydrocyanation product (Entry 6). Finally, we found that toluene is the best solvent for this intermolecular MH-type reaction of cyanides as other solvents such as benzene, DCE and DCM gave the products in lower yields (Entries 6-9).

Table 2.7. Further optimization for the intermolecular MH-type reaction of aryl cyanides.$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd/P/Al (mol%)</th>
<th>Styrene (eq.)</th>
<th>Solvent (mL)</th>
<th>225 (%)$^b$</th>
<th>226 (%)$^b,c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5/20/40</td>
<td>2.0</td>
<td>Toluene (0.5)</td>
<td>39</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>2.5/20/20</td>
<td>2.0</td>
<td>Toluene (0.5)</td>
<td>48</td>
<td>43</td>
</tr>
<tr>
<td>3</td>
<td>2.5/10/10</td>
<td>2.0</td>
<td>Toluene (0.5)</td>
<td>44</td>
<td>41</td>
</tr>
<tr>
<td>4</td>
<td>2.5/10/40</td>
<td>2.0</td>
<td>Toluene (0.5)</td>
<td>60</td>
<td>48</td>
</tr>
<tr>
<td>5</td>
<td>2.5/10/20</td>
<td>2.0</td>
<td>Toluene (0.5)</td>
<td>70</td>
<td>36</td>
</tr>
<tr>
<td>6</td>
<td>2.5/10/20</td>
<td>5.0</td>
<td>Toluene (0.25)</td>
<td>76</td>
<td>70</td>
</tr>
<tr>
<td>7</td>
<td>2.5/10/20</td>
<td>5.0</td>
<td>Benzene (0.25)</td>
<td>65</td>
<td>45</td>
</tr>
<tr>
<td>8</td>
<td>2.5/10/20</td>
<td>5.0</td>
<td>DCE (0.25)</td>
<td>68</td>
<td>44</td>
</tr>
<tr>
<td>9</td>
<td>2.5/10/20</td>
<td>5.0</td>
<td>DCM (0.25)</td>
<td>72</td>
<td>47</td>
</tr>
</tbody>
</table>

$^a$Reaction conditions: S221 (0.2 mmol), Ar, 100 °C, 16 h. $^b$GC yields with dodecane as an internal standard. $^c$Yields of regioisomers.
2.3.2. Substrate Scope

Under the optimized reaction conditions, the scope of both aryl cyanide and alkene was then investigated. With respect to the aryl cyanides, functional groups such as ether, amine, fluoride, and chloride were well tolerated, leading to the corresponding products in high yields (Table 2.8, entries 4, 5, 8, 11 and 12). Substrates bearing substituents, whether it is electron-donating or electron-withdrawing, could react effectively under the optimized conditions to give the products in good yields (Table 2.8, entries 2, 11 and 12). Sterically hindered substrates such as 2-methoxybenzonitrile also showed good reactivity, affording the products in good yields (Table 2.8, entries 4 and 10). Regarding the alkenes, a number of styrene derivatives with diverse substituents such as methyl, phenyl, fluoride, and chloride were converted into the corresponding products in moderate to good yields (Table 2.8, entries 13-16).
Table 2.8. Substrate scope of the intermolecular MH-type reaction of aryl cyanides.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Yield\textsuperscript{b}</th>
<th>Entry</th>
<th>Product</th>
<th>Yield\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Image" /></td>
<td>82%</td>
<td>9</td>
<td><img src="image2" alt="Image" /></td>
<td>59%</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Image" /></td>
<td>65%</td>
<td>10</td>
<td><img src="image4" alt="Image" /></td>
<td>81%</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="Image" /></td>
<td>77%</td>
<td>11</td>
<td><img src="image6" alt="Image" /></td>
<td>61%</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7" alt="Image" /></td>
<td>71%</td>
<td>12</td>
<td><img src="image8" alt="Image" /></td>
<td>53%</td>
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<td>5</td>
<td><img src="image9" alt="Image" /></td>
<td>62%</td>
<td>13</td>
<td><img src="image10" alt="Image" /></td>
<td>73%</td>
</tr>
<tr>
<td>6</td>
<td><img src="image11" alt="Image" /></td>
<td>61%</td>
<td>14</td>
<td><img src="image12" alt="Image" /></td>
<td>45%</td>
</tr>
<tr>
<td>7</td>
<td><img src="image13" alt="Image" /></td>
<td>88%</td>
<td>15</td>
<td><img src="image14" alt="Image" /></td>
<td>48%</td>
</tr>
<tr>
<td>8</td>
<td><img src="image15" alt="Image" /></td>
<td>44%</td>
<td>16</td>
<td><img src="image16" alt="Image" /></td>
<td>50%</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Reaction conditions: aryl cyanide (0.2 mmol), alkene (5.0 eq.), Pd\textsubscript{2}(dba)\textsubscript{3} (2.5 mol\%), CyJohnPhos (10 mol\%), AlMe\textsubscript{2}Cl (20 mol\%), toluene (0.25 mL), Ar, 100 °C, 16 h.

\textsuperscript{b}isolated yields.

To seek applications of this intermolecular MH-type reaction of aryl cyanides in organic synthesis, we applied our method to the synthesis of a multi-conjugated compound via an
iterative coupling reaction which comprised two intermolecular MH-type reactions (Scheme 2.18). As illustrated in Table 2.8, the benzonitrile was able to couple with a chlorine-substituted styrene $S_{235}$ in a chemoselective manner under the standard conditions to afford a chlorine-substituted trans-stilbene product $230$. Using the product as an electrophile to react with a cyano-substituted styrene $S_{237}$ under reported traditional MH coupling conditions,$^{68}$ we could finally obtain a multi-conjugated aryl nitrile as the product $242$ in a high yield. The success of such a streamlined synthesis demonstrated the synthetic value of our approach to organic synthesis.

Scheme 2.18. An application in the synthesis of multi-conjugated molecule.

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2.4. Conclusion

In this chapter, a shuttle catalysis-based approach that enables the use of aryl cyanides as electrophiles in the Mizoroki-Heck reaction has been presented. In contrast to the traditional MH reaction, where a base is required for the regeneration of catalyst, our approach uses a transfer hydrofunctionalization strategy to regenerate the active metal catalyst. In this transfer hydrofunctionalization process, both alkynes and alkenes can be used as HCN acceptors.

A nickel-catalyzed intramolecular MH-type reaction of aryl cyanides using an alkyne as HCN acceptor was discussed firstly (Scheme 2.19). In this transformation, a wide range of aryl cyanides could couple with diverse alkynes to yield the corresponding densely functionalized benzofulvene with high efficiency. However, two challenges remain: 1) aromatic alkynes are difficult to react, 2) regioselectivity of the reaction using asymmetric aliphatic alkynes is poor.

An intermolecular MH-type reaction using an alkene as HCN acceptor was then discussed (Scheme 2.20). In contrast to the intramolecular MH-type reaction, where a nickel complex was used as catalyst, this reaction was catalyzed by a palladium catalyst. Under the optimized conditions, a diversity of trans stilbene products were obtained by coupling a range of aryl cyanides with styrene derivatives. It’s worth mentioning that the aryl C–Cl bond was efficiently tolerated under the conditions, enabling the synthesis of a multi-conjugated aromatic nitrile through an iterative coupling approach.

Scheme 2.19. Nickel-catalyzed intramolecular MH-type reaction of aryl cyanides.

Scheme 2.20. Palladium-catalyzed intermolecular MH-type reaction of aryl cyanides.

69 Fang*, X.; Yu*, P.; Cerai, G. P.; Morandi B. Chem. Eur. J. 2016, 22, 15629. ([*] These authors contributed equally to this work)
Scheme 2.20. Palladium-catalyzed intermolecular MH-type reaction of aryl cyanides.

Concerning the mechanism, a catalytic cycle involving a transfer hydrocyanation of alkynes or alkenes was proposed based on several mechanistic experiments. The hydrofunctionalization process was confirmed by both the isolation of hydrocyanation products and by a deuterium-labeling experiment.
3. Shuttle Catalysis-enabled Cyanation of Aryl Chlorides and Triflates Using Butyronitrile as a Cyanating Reagent
Abstract

Transition metal-catalyzed cyanation of aryl halides and their variants has been extensively studied during the past few decades. While remarkable achievement has been made in this field, the frequent use of highly toxic cyanide reagents often limits their broad application. In this chapter, a safe and practical method for the synthesis of aryl and vinyl nitriles via a nickel-catalyzed cyanation of aryl (pseudo)halides using butyronitrile as a cyanating reagent is described. The transfer of cyano groups between butyronitrile and substrates was achieved using shuttle catalysis through a dehydrocyanation process. Through this strategically distinct approach, a wide array of aryl chlorides and aryl triflates, including several natural product derivatives, were converted into the corresponding nitriles in moderate to excellent yields. A gram-scale synthesis was also achieved, demonstrating the scalability of this transformation. Regarding the mechanism, a dual catalytic cycle composed of dehydrocyanation and cross-coupling was proposed, which is supported by observations of experiments designed to discriminate several different mechanistic pathways. Optimization of reaction conditions, investigation of reaction scope, and mechanistic studies are discussed herein.
3.1. Introduction

3.1.1. Nitriles

Nitriles play an important role in various aspects of chemistry. For example, acetonitrile, the simplest organic nitrile, is among the most common solvent used for organic reactions. Nitriles are used as ligands for tuning the activity of metal complexes and also as an auxiliary group for directing C–H bond activation. Moreover, nitriles are widely present as a key unit in pharmaceuticals, agrochemicals, and organic materials.

Nitriles also serve as important building blocks in organic synthesis due to the synthetic versatility of the cyano group. They can be easily transformed into a wide variety of other functional groups, including carboxylic acids, amides, amines, aldehydes, ketones, and heterocycles (Figure 3.1).

![Figure 3.1. Transformation of nitriles.](image)

3.1.2. Synthesis of Aryl Nitriles

---

Aryl nitriles represent the largest class of nitriles that are encountered in pharmaceuticals (Figure 3.2).\(^7^4\) The development of methods for the synthesis of aryl nitriles has thus attracted the interest of chemists in both the academic and industrial community. The history of nitrile synthesis can be dated back in 1832 when Wöhler and Liebig successfully synthesized benzonitrile and benzoyl cyanide.\(^7^5\) While remarkable progress has been made,\(^7^6\) this field remains an active research area due to the high demand for safer cyanating reagents and practical procedures.

\[\text{Pericazine antipsychotic} \]
\[\text{Febuxostat treatment for gouty arthritis} \]
\[\text{Citalopram antidepressant} \]
\[\text{Letrozole aromatase inhibitor} \]
\[\text{Cromakalim treatment for hypertension} \]
\[\text{Dapivirine antiretroviral} \]

\textbf{Figure 3.2. Examples of aryl nitrile-containing pharmaceuticals.}

Traditionally, the most popular approach to access aryl nitriles has been the Sandmeyer reaction \(^7^7\) and the Rosenmund–von Braun reaction \(^7^8\) where aryl nitriles can be synthesized from

---


aryl diazonium salts and aryl halides, respectively (Scheme 3.1). However, both reactions have critical limitations: 1) The use of stoichiometric amounts of CuCN as a cyanating reagent, resulting in heavy metal waste; 2) The requirement of harsh reaction conditions such as high temperature leads to a limited reaction scope; 3) The cheapest and most readily available aryl halides (e.g., aryl chlorides) show very low reactivity under the conditions.

![Scheme 3.1. Previous approaches to access aryl nitriles.](image)

To overcome the limitations of these previous approaches, transitional metal-catalyzed cyanation reactions have been introduced, and have emerged as one of the most important tools for the synthesis of aryl nitriles in recent decades. Among those transition metals, palladium-based catalysts are most widely used due to their ability to tolerate various functional groups and high stability under atmospheric conditions. Nickel complexes represent attractive catalysts for cyanation reactions due to their high propensity to undergo oxidative addition with inert chemical bonds. Copper salts, which are lower in price and toxicity compared with palladium and nickel, are also used frequently to catalyze or mediate cyanation reactions.

Among existing methods, transition metal-catalyzed cyanation of aryl halides has proved to be the most popular for the synthesis of aryl nitriles even though the use of aryl halides as starting materials lacks atom and step efficiency (Scheme 3.2a). The pre-installation of halides is required for substrate preparation, and the halides turn into waste in the end of the reaction. In this context, the approach using arenes in direct cyanation reactions of C–H bonds is more promising because of its sustainability, and the high availability of substrates. A significant

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number of cyanation reactions through transition metal-catalyzed arene C–H bond activation have been developed (Scheme 3.2b).\textsuperscript{82} However, their limitations such as narrow reaction scope and the reliance on the directing group to ensure the site selectivity often reduce their synthetic value.

\[
\begin{align*}
(a) & \quad \begin{array}{c}
\text{R} \quad \text{X} \quad \text{+} \quad \text{CN} \\
\text{\textbullet} \quad \text{X = Cl, Br, I} \quad \text{\textbullet} \quad \text{CN = KCN, NaCN, Zn(CN)₂, etc.}
\end{array} \\
\text{transition metal} \\
\begin{array}{c}
\text{R} \quad \text{CN}
\end{array} \\
\hline
(b) & \quad \begin{array}{c}
\text{R} \quad \text{H} \quad \text{+} \quad \text{CN} \\
\text{\textbullet} \quad \text{CN = TMSCN, TsCN, MeNO₂, DMF, etc.}
\end{array} \\
\text{transition metal} \\
\begin{array}{c}
\text{R} \quad \text{CN}
\end{array}
\end{align*}
\]

Scheme 3.2. Synthesis of aryl nitriles from (a) aryl halides and (b) arenes.

In addition to arenes, other alternatives to aryl halides have also been developed for the transition metal-catalyzed preparation of aryl nitriles. They include aryl diazonium salts,\textsuperscript{83} aryl sulfonyl chlorides,\textsuperscript{84} aryl organometallic compounds,\textsuperscript{85} aryl carboxylic acids and their derivatives,\textsuperscript{86} as well as phenol derivatives such as aryl triflates,\textsuperscript{87} aryl tosylates,\textsuperscript{88} aryl mesylates\textsuperscript{89} (Scheme 3.3). Among these substrates, aryl triflates are most commonly used.

\textsuperscript{82} Ping, Y.; Ding, Q.; Peng, Y. \textit{ACS Catal.} 2016, 6, 5989.


Scheme 3.3. Synthesis of aryl nitriles from other precursors.

Toluene derivatives can be used as substrates for the synthesis of aryl nitriles. Traditionally, this synthesis was achieved via an ammoxidation using ammonia as a nitrogen source in the presence of a heterogeneous catalyst. However, the harsh conditions, such as high temperature and pressure, were required for the reaction, reducing its synthetic value. The use of harsh conditions can be avoided by using transition metal-catalysis. In 2009, Jiao and co-workers reported a copper-catalyzed direct cyanation of toluene derivatives using NaN$_3$ as a nitrogen source (Scheme 3.4). The reaction proceeds at ambient temperature in the presence phenyliodonium diacetate (PIDA) as an oxidant. However, the substrate scope of this reaction is limited to substrates bearing a heteroatom substituent at the para position, which is believed to play a role in the stabilization of the benzyllic cation which might be involved during the catalytic cycle.

More recently, Jiao and co-workers reported that aryl nitriles could also be accessed from styrenes or phenylacetylenes using TMSN$_3$ as a nitrogen source (Scheme 3.5). The cyanation of styrenes was achieved using a copper salt as catalyst in the presence of stoichiometric amount of NBS (Scheme 3.5a). This transformation has a broad functional group tolerance even though substrates bearing chloro and bromo substituents were converted to diazido compounds as the major product. The cyanation of phenylacetylene is catalyzed by a silver catalyst (Scheme 3.5b). This reaction also has a broad substrate scope. Alkynes bearing both electron-donating and -withdrawing functional groups can be well tolerated, producing the corresponding aryl nitrile products in high yields.

Scheme 3.5. Synthesis of aryl nitriles from styrene and phenylacetylene.

---

Aryl aldehydes were reported to serve as substrates in a CuBr₂-mediated synthesis of aryl nitriles by You and co-workers. In the reaction, they used K₃[Fe(CN)₆] as a source of nitrogen (Scheme 3.6). This transformation tolerates a wide array of functional groups and produces various aryl nitriles from inexpensive aldehydes in high yields. However, the use of stoichiometric amounts of the copper bromide limits its application.

**You and co-workers, 2016**

\[
\text{ArCHO} + \text{K₃[Fe(CN)₆]} \xrightarrow{0.5 \text{ eq.}} \xrightarrow{\text{CuBr₂ (1.0 eq.)}} \text{Ar-CN} \\
\text{DMF, O₂, 150 °C} \\
\text{22 examples} \\
\text{50-80% yield}
\]

**Scheme 3.6. Synthesis of aryl nitriles from aryl aldehydes.**

Aryl aldoximes, which can be readily prepared from the reaction of aryl aldehydes with hydroxylamine or ammonia, have also been utilized for the synthesis of aryl nitriles. Kim and co-workers described a palladium-catalyzed approach for the preparation of aryl nitriles using aryl aldoximes (Scheme 3.7a). Shortly after, Ragauskas and Lu reported a dehydration of aryl aldoximes to prepare aryl nitriles using CuCl₂ as a catalyst (Scheme 3.7b). This method allowed the authors to synthesize a number of aryl nitriles from aldehydes in a one-pot fashion, including a few heteroaryl nitriles as shown in the Scheme.

---

Additionally, aryl nitriles can also be produced from benzylalcohols, benzylamines, and benzylazides under transition metal-catalysis. Several transition metals, which are not commonly used for cyanation reactions, such as ruthenium, iron, and cobalt, have proved effective for the conversion of these benzylic compounds into aryl nitriles (Scheme 3.8).  

\[ \text{Scheme 3.7. Synthesis of aryl nitriles from aryl aldoximes.} \]

3.1.3. Cyanating Reagents: Metal Cyanides

As a key ingredient of cyanation reactions, cyanating reagents can have a significant effect on both the outcome and the application of the reaction. Thus, their properties, such as toxicity, availability, stability, reactivity, and price, must be considered when choosing a cyanating reagent for the preparation of nitriles. In the study of transition metal-catalyzed cyanation reactions, a large portion of effort has been devoted to the discovery of new and greener cyanating reagents.
Transition metal-catalyzed cyanation of aryl halides represents a popular and powerful methodology for the synthesis of aryl nitriles. In these reactions, metal cyanides, such as KCN,98 NaCN,99 TMSCN,100 Zn(CN)2 101 and K4[Fe(CN)6],102 are often used as a cyanating reagent. The common feature of these reagents is that cyanide ions can be released easily when dissolving the reagents in the reaction solvent, which can enable facile installation of a cyano group into the substrate. However, this also often leads to the deactivation of catalysts because the free cyanide ions can coordinate with the transition metal complexes. The ease of cyanide ion dissociation from the metal cyanide salts also raises safety issues due to the generation of extremely toxic and explosive HCN gas. Furthermore, the use of metal cyanide salts in the cyanation reactions produces metal waste, making these reactions uneconomical.

Among these metal cyanides, K4[Fe(CN)6] is usually considered more promising for two reasons: 1) Compared with other metal cyanide reagents, K4[Fe(CN)6] is less toxic and easier to handle; 2) An improved catalyst productivity can be achieved with K4[Fe(CN)6] due to its slow release of cyanide ions in the reaction mixture. However, problems associated with this reagent caused by the poor solubility of K4[Fe(CN)6] in organic solvents remain, such as poor reproducibility, lack of scalability and the generation of metal waste.

3.1.4. Cyanating Reagents: Nonmetallic Sources

To tackle such problems caused by the use of metal cyanide reagents, a number of non-metal cyano sources have been discovered and applied to the transition metal-catalyzed cyanation reactions. For example, Acetone cyanohydrin was initially employed as a cyanating reagent in a palladium-catalyzed cyanation of aryl halides by Beller and co-workers in 2003 (Scheme 3.9).\textsuperscript{103} In this work, the authors demonstrated that catalyst deactivation could be effectively prevented through careful control of the concentration of cyanide ions in the reaction mixture which was achieved by slow addition of the cyanating reagent using a syringe pump. Moreover, the slow addition of acetone cyanohydrin also allowed the catalyst turnover number to reach 1900. Despite these advantages, the substrate scope of this reaction is limited to unhindered aryl bromides and activated aryl chlorides.

\textit{Beller and co-workers, 2003}

\[
\begin{align*}
\text{R} & \quad \text{X} \quad \text{Acetone cyanohydrin (1.05 eq.)} \\
\text{(X = Br, Cl)} & \quad \text{Pd(OAc)}_2 (0.5 \text{ mol\%}) \\
& \quad \text{DPPPE (1 mol\%), TMEDA (10 mol\%)} \\
& \quad \text{Na}_2\text{CO}_3 (1.05 \text{ eq.}) \\
& \quad \text{DMAC, 100-140 °C, 21 h} \\
\rightarrow & \quad \text{R-CN} \\
& \quad \text{15 examples 21-99\%}
\end{align*}
\]

\textbf{selected examples}

\begin{itemize}
\item 46\% \text{S} - \text{CN}
\item 82\% \text{N} - \text{CN}
\item 96\% \text{F} - \text{CN}
\item 82\% \text{Cl} - \text{CN}
\item 95\% \text{MeO} - \text{CN}
\end{itemize}

\textbf{DPPPE}

\textbf{TMEDA}

Scheme 3.9. Palladium-catalyzed cyanation of aryl halides using acetone cyanohydrin.

Following the report, Beller and co-workers also disclosed a cyanation of aryl halides using a copper catalyst (Scheme 3.10a).\textsuperscript{104} Similarly, precise control of the concentration of


cyanide ions in the reaction mixture was achieved by slow addition of acetone cyanohydrin. This allowed for a wide variety of aryl nitriles to be produced in high yields. A limitation which has been overcome over the palladium-catalyzed approach described above is that aryl bromides bearing ortho substituents are well tolerated. Interestingly, a structurally similar compound, cyclohexanone cyanohydrin, can also be employed as a cyanating reagent for the preparation of aryl nitriles according to a report published by Taran and co-workers in 2010 (Scheme 3.10b).

In the report, they demonstrated a palladium-catalyzed approach to transform various aryl carboxylic acids into the aryl nitriles using cyclohexanone cyanohydrin as a cyanating reagent.

\[ \text{Scheme 3.10. Copper-catalyzed cyanation of aryl halides using acetone cyanohydrin.} \]

Despite the benefits from using cyanohydrin compounds as a cyanating reagent, careful handling is required to prevent the generation of HCN because of their facile decomposition under heating. To avoid the risk of generating hazardous HCN gas, some other nonmetallic cyano sources have been developed (Figure 3.4). However, they can only be utilized in limited examples.

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The use of alkyl nitriles as a cyanating reagent has attracted increasing attention due to their low toxicity and availability. In 1998, Cheng and co-workers disclosed a palladium cyanation of aryl halides wherein several alkyl nitriles served as cyanating reagents (Scheme 3.11). In this reaction, the authors could transfer the cyano group from alkyl nitriles, such as acetonitrile, propionitrile, \(n\)-butyronitrile, and benzyl nitrile, to the substrates using \(\text{Pd}[\text{P}(n\text{-Bu})_3]_2\text{Cl}_2\) as a catalyst in the presence of \(\text{PPh}_3\) and \(\text{Zn}\). According to the mechanistic study, this reaction might proceed through a palladoimine intermediate \(3\text{-A}\). The formation of \(\text{RZnX}\) was proposed based on the detection of \(\text{R}_2(\text{C}=\text{O})\), which can be formed by the reaction of \(\text{RZnX}\) with the alkyl nitrile. This method provides a safe route to aryl nitriles due to the use of non-toxic and stable alkyl nitriles as a cyanating reagent. However, it also possesses a few limitations: 1) The use of large excess of zinc metal; 2) The substrate scope is limited to \(\text{ortho}\)-substituted aryl bromides; 3) High temperature limits the functional group tolerance.

\[ \text{Ar}-\text{X} + \text{CN}^- \xrightarrow{\text{transition metal}} \text{Ar}-\text{CN} \]

<table>
<thead>
<tr>
<th>(\text{Ar}-\text{X})</th>
<th>'CN'</th>
<th>(\text{Ar}-\text{X})</th>
<th>'CN'</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{X} = \text{Li})</td>
<td>(\text{PhOCN})</td>
<td>(\text{X} = \text{H})</td>
<td>(\text{CHON(CH}_3)_2)</td>
</tr>
<tr>
<td>(\text{X} = \text{B(OH)}_2)</td>
<td>(\text{PhSCN})</td>
<td>(\text{X} = \text{Br, I})</td>
<td>(\text{CHONH}_2)</td>
</tr>
<tr>
<td>(\text{X} = \text{MgBr-LiCl})</td>
<td></td>
<td>(\text{X} = \text{H})</td>
<td>(\text{CHON(CH}_3)_2\text{NH}_3)</td>
</tr>
<tr>
<td>(\text{X} = \text{B(OH)}_2, \text{H})</td>
<td>(\text{N-Ts})</td>
<td>(\text{X} = \text{B(OH)}_2, \text{H})</td>
<td>(\text{CHON(CH}_3)_2\text{NH}_4\text{HCO}_3)</td>
</tr>
<tr>
<td>(\text{X} = \text{H})</td>
<td>(\text{CH}_3\text{NO}_2)</td>
<td>(\text{X} = \text{H})</td>
<td>(\text{SO(CH}_3)_2\text{NH}_4\text{HCO}_3)</td>
</tr>
</tbody>
</table>

Figure 3.4. Nonmetallic cyanide sources other than acetone cyanohydrin.

Scheme 3.11. Palladium-catalyzed cyanation of aryl halides with alkyl nitriles.

A more practical method using malononitrile as a cyanating reagent was developed by Zhou and co-workers (Scheme 3.12). Here, the transfer of a cyano group was achieved with a Cu(OAc)$_2$/1,10-phenanthroline catalytic system in the presence of KF and $t$-BuONa. Mechanistic studies suggested the reaction might proceed through the formation of a copper complex 3-B. A wide range of aryl iodides, including electron-rich and electron-poor, could be cyanated in this transformation, leading to the corresponding aryl nitriles in good yields. However, the cyanation of relative less reactive aryl bromides and chlorides was not demonstrated.

Scheme 3.12. Copper-catalyzed cyanation of aryl iodides with malononitrile.

---

3.2. Nickel-Catalyzed Cyanation of Aryl Chlorides with Butyronitrile

3.2.1. Reaction Design

As described in section 3.1, alkyl nitriles have served as cyanating reagents for the synthesis of aryl nitriles due to their low toxicity, high availability, and stability. The use of alkyl nitriles as a cyanating reagent can effectively prevent catalyst deactivation and reduce the risk of generating HCN. However, current methods using alkyl nitriles as cyanating reagents are limited in substrate scope and often produce metal wastes.\(^40\) Thus, the development of novel methods that can enable the use of alkyl nitriles as cyanating reagents is in high demand.

As discussed in section 1, we recently developed a shuttle catalysis approach for hydrocyanation of alkenes with an alkyl nitrile as the HCN source, avoiding the direct use of gaseous, hazardous HCN. The mechanism for this transfer hydrocyanation was proposed to proceed through an initial nickel-catalyzed oxidative addition of C–CN bond and subsequent β–H elimination, which generates an alkene-ligated H–Ni–CN intermediate. Ligand exchange of this intermediate with a new alkene followed by a classical hydrocyanation process complete the catalytic cycle and lead to the hydrocyanation product. Inspired by this transfer mechanism, we reasoned that the shuttle catalysis strategy could also enable the cyanation of aryl halides through the transfer of “CN” from a simple alkyl nitrile bearing β-hydrogens.

The dehalogenation of aryl halides is a valuable transformation in organic synthesis. Recently, Lipshutz and co-workers reported a palladium-catalyzed dehalogenation of aryl halides using tetramethyldisiloxane (TMDS) as the source of hydrogen.\(^110\) In the report, the authors proposed that the reaction could proceed through a catalytic cycle consisting of two processes. As shown in Scheme 3.13, two intermediate, Ar–Pd–X and H–Pd–H, could be generated independently from the oxidative addition of ArX and the reaction of tetramethyldisiloxane with Pd(0). A transmetallation between the two intermediates then occurs, leading to the intermediate Ar–Pd–H which could finally lead to the dehalogenated product by reductive elimination.

Inspired by the mechanism of this dehalogenation reaction, we hypothesized that the reaction could proceed with a nickel catalyst through a mechanism composed of two distinct catalytic cycles: (a) and (b) (Scheme 3.14). Through the cycle (a), an Ar–Ni–X intermediate (3-C) could be generated by oxidative addition of ArX. Through the cycle (b), an H–Ni–CN intermediate (3-D) could be generated by a sequence of oxidative addition of the C–CN bond and β-hydride elimination. A transmetallation between the intermediates 3-C and 3-D was envisaged to occur, which could lead to the formation of Ar–Ni–CN intermediate (3-F) and intermediate H–Ni–X (3-E). Then reductive elimination of Ar–Ni–CN would give the aryl nitrile product, and the reaction of H–Ni–X with a base would regenerate the active Ni(0) catalyst. However, to realize this hypothesis, several challenges would have to be overcome: 1) The catalyst must be carefully selected to enable all the elementary steps involved in the catalytic cycle to occur; 2) The efficient occurrence of the transmetallation between intermediate Ar–Ni–X and H–Ni–CN must be ensured by adjusting the rate of the catalytic cycle (a) and (b); 3) An appropriate base must be selected to avoid reaction with H–Ni–CN species or the Lewis acid which is usually required to assist the cleavage of C–CN bonds.
3.2.2. Evaluation of The Reaction Conditions

To test the hypothesis, we initially selected isovaleronitrile (R31) as the cyanating reagent to react with bromobenzene under similar conditions to that of the previously described transfer hydrocyanation: Ni(cod)₂ (10 mol%), dppf (10 mol%), AlMe₂Cl (20 mol%), K₃PO₄ (2.0 eq.) at 120 °C in toluene for 12 hours. Encouragingly, 12% yield of benzonitrile could be detected by GC in a reaction of bromobenzene with 1.5 equivalent of isovaleronitrile under these conditions (Table 3.1, entry 1). Optimization of the equivalent of isovaleronitrile showed that the best result could be obtained using 5.0 equivalent of isovaleronitrile. Interestingly, no product was observed when using isovaleronitrile as a solvent (Table 3.1, entries 3-5). Butyronitrile (R32) was also tested under the conditions, and a slightly higher yield of product could be obtained when 5.0 equivalent of this reagent was used (Table 3.1, entry 6). Because butyronitrile is cheaper than isovaleronitrile, it was used as the standard reagent for further optimization.
Table 3.1. Initial screen for the cyanation of bromobenzene with alkyl nitriles.\textsuperscript{a}

\begin{tabular}{|l|c|c|}
\hline
Entry & Cyanating reagent & S221 (\%)\textsuperscript{b} \\
\hline
1 & R31 (1.5 eq.) & 8 \\
2 & R31 (3.0 eq.) & 12 \\
3 & R31 (5.0 eq.) & 14 \\
4 & R31 (10.0 eq.) & 8 \\
5 & R31 (used as solvent) & 0 \\
6 & R32 (5.0 eq.) & 19 \\
\hline
\end{tabular}

\textsuperscript{a}Reaction conditions: S31 (0.1 mmol), Ni(cod)\textsubscript{2} (10 mol\%), dpff (10 mol\%), AlMe\textsubscript{2}Cl (20 mol\%), K\textsubscript{3}PO\textsubscript{4} (2.0 eq.), toluene (0.5 mL), 120 °C, 12 h. \textsuperscript{b}GC yields are given using \textit{n}-dodecane as an internal standard.

Using butyronitrile as a cyanating reagent, we first evaluated the effect of ligands on the outcome of the reaction (Table 3.2). A variety of bidentate phosphine ligands were first evaluated (Entries 1-11). Xantphos proved to be the most effective ligand, leading to the benzonitrile being formed in 27\% yield (Entry 10). Several nitrogen-based bidentate ligands were also screened. However, no reactivity could be observed (Entries 12-14). In contrast to bidentate ligands, monodentate ligands, including phosphines and NHCs, led to trace amount of product or less (Entries 15-23). It’s worth noting that side reactions, such as homodimerization of bromobenzene or Heck-type reactions, were not observed under these reaction conditions even though a small part of starting material was found to decompose during the reaction.
Table 3.2. Evaluation of ligands.  

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>S221 (%)</th>
<th>S31 (%)</th>
<th>Entry</th>
<th>Ligand</th>
<th>S221 (%)</th>
<th>S31 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L8</td>
<td>5</td>
<td>7</td>
<td>13</td>
<td>L15</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>dppp</td>
<td>4</td>
<td>9</td>
<td>14</td>
<td>L16</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>L5</td>
<td>trace</td>
<td>12</td>
<td>15</td>
<td>CyJohnPhos</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>L10</td>
<td>12</td>
<td>23</td>
<td>16</td>
<td>RuPhos</td>
<td>trace</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>L11</td>
<td>25</td>
<td>39</td>
<td>17</td>
<td>PCy3</td>
<td>trace</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>L6</td>
<td>0</td>
<td>0</td>
<td>18</td>
<td>L17</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>L12</td>
<td>8</td>
<td>9</td>
<td>19</td>
<td>L18</td>
<td>trace</td>
<td>30</td>
</tr>
<tr>
<td>8</td>
<td>L7</td>
<td>22</td>
<td>35</td>
<td>20</td>
<td>L19</td>
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<td>L13</td>
<td>19</td>
<td>26</td>
<td>21</td>
<td>DavePhos</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>Xantphos</td>
<td>27</td>
<td>35</td>
<td>22</td>
<td>L20</td>
<td>trace</td>
<td>18</td>
</tr>
<tr>
<td>11</td>
<td>DPEphos</td>
<td>trace</td>
<td>13</td>
<td>23</td>
<td>L21</td>
<td>trace</td>
<td>10</td>
</tr>
<tr>
<td>12</td>
<td>L14</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

*Reaction conditions: S31 (0.1 mmol), R32 (5.0 eq.), Ni(cod)₂ (10 mol%), bidentate ligand (10 mol%), monodentate ligand (20 mol%), AlMe₂Cl (20 mol%), K₃PO₄ (2.0 eq.), toluene (0.5 mL), 120 °C, 12 h. *GC yields are given using n-dodecane as an internal standard. *Conversions are given using n-dodecane as an internal standard.

The effect of the base on the reaction was then evaluated in the presence of Xantphos as a ligand. As shown in Table 3.3, several bases were evaluated. However, no product could be
detected in the reaction using bases such as K$_2$CO$_3$, KOAc, KOr-Bu, NaOr-Bu (Entries 1-4). Using Cs$_2$CO$_3$ as a base gave some product but in a low yield (Entry 5).

Table 3.3. Evaluation of the effect of bases.$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>S221 (%)$^b$</th>
<th>S31 (%)$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>K$_2$CO$_3$ (2.0 eq.)</td>
<td>0</td>
<td>27</td>
</tr>
<tr>
<td>2</td>
<td>KOAc (2.0 eq.)</td>
<td>0</td>
<td>48</td>
</tr>
<tr>
<td>3</td>
<td>NaOr-Bu (2.0 eq.)</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>KOr-Bu (2.0 eq.)</td>
<td>0</td>
<td>41</td>
</tr>
<tr>
<td>5</td>
<td>Cs$_2$CO$_3$ (2.0 eq.)</td>
<td>5</td>
<td>47</td>
</tr>
<tr>
<td>6</td>
<td>K$_3$PO$_4$ (2.0 eq.)</td>
<td>19</td>
<td>23</td>
</tr>
</tbody>
</table>

$^a$Reaction conditions: S31 (0.1 mmol), R32 (5.0 eq.), Ni(cod)$_2$ (10 mol%), Xantphos (10 mol%), AlMe$_2$Cl (20 mol%), toluene (0.5 mL), 120 °C, 12 h. $^b$GC yields are given using n-dodecane as an internal standard. $^c$Conversions are given using n-dodecane as an internal standard.

The Lewis acid can have a great effect on the reaction by affecting the C–CN activation step. A higher yield was obtained by using AlMe$_3$ instead of AlMe$_2$Cl (Table 3.4, entry 2). Increasing the loading of Lewis acid to 60 mol% resulted in a slight increase in the yield of product, giving benzonitrile in 36% yield (Table 3.4, entry 3). Nevertheless, the bromobenzene was fully consumed in this case, indicating that a large part of the starting material had decomposed or was consumed by the side reactions such as the coupling of bromobenzene with Lewis acids which can occur with high loadings of Lewis acid (Table 3.4, entry 3). In an attempt to avoid the side reactions or decomposition of the starting material, a variety of Lewis acids (Table 3.4, entries 5-8) were screened. The results showed that the use of a Lewis acid with heavy alkyl groups could suppress the side reaction or prevent decomposition of the starting material to some extent, and also led to the product in a higher yield (Table 3.4, entry 5). Although 63% yield of product could be obtained under the conditions, nearly 30% of starting material was still lost during the reaction. To this end, we moved our attention to the starting
material and hypothesized that the use of a less reactive aryl halide might solve this problem because the lower rate of oxidative addition can potentially reduce side reactions and be propitious to the transmetallation step. Therefore, we replaced the bromobenzene with a less reactive chlorobenzene and tested it in the reaction. Gratifyingly, a slightly higher yield of benzonitrile could be obtained (Table 3.4, entry 9). More importantly, less decomposition or side reaction of starting material was observed probably because the lower reactivity of chlorobenzene suppressed the side reaction, and therefore promoted the desired reaction. This exciting result showed that the use of aryl chlorides as starting materials could allow for a more economic transformation due to their lower price and higher availability compared to aryl bromides. Moreover, the transition metal-catalyzed cyanation of aryl chlorides is relatively less studied and often more challenging to realize.

Table 3.4. Evaluation of Lewis acids and equivalents of cyanating reagent.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis acid (mol%)</th>
<th>R32 (eq.)</th>
<th>S221 (%)(^b)</th>
<th>S31 (%)(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AlMe(_2)Cl (20)</td>
<td>5.0</td>
<td>27</td>
<td>35</td>
</tr>
<tr>
<td>2</td>
<td>AlMe(_3) (20)</td>
<td>5.0</td>
<td>34</td>
<td>49</td>
</tr>
<tr>
<td>3</td>
<td>AlMe(_3) (60)</td>
<td>5.0</td>
<td>36</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>AlMe(_3) (60)</td>
<td>10.0</td>
<td>49</td>
<td>89</td>
</tr>
<tr>
<td>5</td>
<td>Al(n-octyl)(_3) (60)</td>
<td>10.0</td>
<td>63</td>
<td>91</td>
</tr>
<tr>
<td>6</td>
<td>AlCl(_3) (60)</td>
<td>10.0</td>
<td>8</td>
<td>22</td>
</tr>
<tr>
<td>7</td>
<td>B(Ph-5F)(_3) (60)</td>
<td>10.0</td>
<td>5</td>
<td>16</td>
</tr>
<tr>
<td>8</td>
<td>BPh(_3) (60)</td>
<td>10.0</td>
<td>25</td>
<td>31</td>
</tr>
<tr>
<td>9</td>
<td>Al(n-octyl)(_3) (60)</td>
<td>10.0</td>
<td>66</td>
<td>83(^d)</td>
</tr>
</tbody>
</table>

\(^a\)Reaction conditions: S31 (0.1 mmol), Ni(cod)\(_2\) (10 mol\%), Xantphos (10 mol\%), K\(_3\)PO\(_4\) (2.0 eq.), toluene (0.5 mL), 120 °C, 12 h. \(^b\)Yields and conversions are determined by GC using \(n\)-dodecane as an internal standard. \(^c\)Conversions are determined by GC using \(n\)-dodecane as an internal standard. \(^d\)Chlorobenzene was used instead of bromobenzene.
Further optimization using chlorobenzene (S32) as a starting material was conducted. As shown in Table 3.5, the use of Ni(acac)\(_2\) instead of Ni(cod)\(_2\) as a catalyst in the presence of zinc gave the product in a slightly higher yield (Entry 2), and the use of the Lewis acid bearing a bulkier alkyl group resulted in an improved yield as well (Entry 3), probably preventing undesired cross-coupling. The loading of catalyst, ligand, Lewis acid and reductant as well as their ratio also have a considerable effect on the reactivity. After further investigation, we finally identified a combination of Ni(acac)\(_2\) (5 mol%), Zn (0.15 eq.), Xantphos (5 mol%), Al(isobutyl)\(_3\) (20 mol%) as the optimized conditions, which led to the formation of benzonitrile in 88% yield (Entry 3). The results of control experiments in the absence of Ni(acac)\(_2\), Xantphos or Al(isobutyl)\(_3\) revealed that each of them is required for the transformation to occur (Entries 4-6).

### Table 3.5. Further optimization with chlorobenzene.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Deviation from conditions shown in the Scheme</th>
<th>S221 (%)(^b)</th>
<th>S32 (%)(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>71</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>Al(n-octyl)(_3) instead of Al(isobutyl)(_3)</td>
<td>69</td>
<td>98</td>
</tr>
<tr>
<td>3</td>
<td>Ni(acac)(_2) (5 mol%), Zn (0.15 eq.), Xantphos (5 mol%), Al(isobutyl)(_3) (20 mol%)</td>
<td>88</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>Without Ni(acac)(_2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>without Xantphos</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>without Al(isobutyl)(_3)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

\(^a\)Reaction conditions: S32 (0.1 mmol), R32 (1.0 mmol, 10 eq.), toluene (0.5 mL), 120 °C, 12 h.  
\(^b\)Yields and conversions are determined by GC using n-dodecane as an internal standard.  
\(^c\)Conversions are determined by GC using n-dodecane as an internal standard.

### 3.2.3. Substrate Scope

After establishing the optimal reaction conditions, we began to investigate the reaction scope of this nickel-catalyzed cyanation of aryl chlorides with butyronitrile. As shown in Table 3.6, aryl chlorides bearing electron-donating alkyl or ether substituents reacted effectively to give the corresponding aryl nitriles in good yields (Entries 1-7). An electron-neutral phenyl
substituent and electron-withdrawing fluoro group were also well tolerated in this transformation (Entries 8-10). Some ortho substituted-substrates were converted into the desired products in high yields, revealing a good tolerance of this transformation to the steric hindrance (Entries 4, 9, 11, 12). Importantly, a group of useful nitrogen- and oxygen-containing heterocycles, such as pyrroles, morpholines, dioxoles and indoles were efficiently tolerated under the reaction conditions even though a higher loading of catalyst was required in some cases (Entries 13-18).
Table 3.6. Reaction scope of the nickel-catalyzed cyanation of aryl chlorides.\textsuperscript{a}

\begin{table}[h]
\centering
\begin{tabular}{clcc}
\hline
\textbf{Entry} & \textbf{Product} & \textbf{Yield}\textsuperscript{b} & \textbf{Entry} & \textbf{Product} & \textbf{Yield}\textsuperscript{b} \\
\hline
1 & \(\text{fBu-} \) & 75\% & 10 & Ph- & 62\% \\
2 & \(\text{nBu-} \) & 70\% & 11 & & 81\%\textsuperscript{c} \\
3 & & 76\% & 12 & & 71\%\textsuperscript{d} \\
4 & & 68\% & 13 & & 65\%\textsuperscript{e} \\
5 & MeO- & 51\% & 14 & & 65\% \\
6 & & 79\%\textsuperscript{c} & 15 & O- & 70\%\textsuperscript{d} \\
7 & & 70\%\textsuperscript{c} & 16 & & 71\% \\
8 & BnO- & 70\%\textsuperscript{d} & 17 & NC & 78\%\textsuperscript{f} \\
9 & & 75\%\textsuperscript{d} & 18 & & 87\%\textsuperscript{f} \\
\hline
\end{tabular}
\caption{Reaction scope of the nickel-catalyzed cyanation of aryl chlorides.\textsuperscript{a}}
\end{table}

\textsuperscript{a}Reaction conditions: aryl chlorides (0.2 mmol), \textbf{R32} (10.0 eq.), 120 °C, 12 h.
\textsuperscript{b}Yields of isolated products. \textsuperscript{c}n = 7.5. \textsuperscript{d}n = 10. \textsuperscript{e}n = 15. \textsuperscript{f}n = 12.5.

Although a broad substrate scope was obtained, the reaction also showed limitations. Substrates bearing electron withdrawing groups, particularly the ester group, ketone group, nitro
group and trifluoromethyl group, were difficult to react under the reaction conditions, leading to very low conversion of starting materials (Scheme 3.15).

Scheme 3.15. Unsuccessful examples.
3.3. Nickel-Catalyzed Cyanation of Aryl and Vinyl Triflates with Butyronitrile

3.3.1. Studies of Reaction Conditions

To demonstrate the robustness and generality of this method, we also applied it to other classes of electrophiles. In particular, we were interested by aryl and vinyl triflates, which are important precursors used in cross-coupling reactions. The development of methods enabling the conversion of aryl and vinyl triflates into the corresponding nitrile compounds is of great synthetic importance due to their easy preparation from phenols or aliphatic ketones. However, a literature survey showed that cyanation of aryl and vinyl triflates has not been sufficiently studied, particularly those catalyzed by transition metals. Moreover, among the reported transition metal-catalyzed cyanation reactions with aryl triflates or vinyl triflates, only limited examples have been reported using nickel salts as catalysts, and all these protocols relied on the use of highly toxic KCN as a cyanating reagent. Therefore, we aimed to apply our method to the cyanation of aryl triflates and vinyl triflates.

We initially performed the reaction of phenyl triflate with butyronitrile under the standard conditions for the cyanation of aryl chlorides. Unfortunately, no cyanation product could be detected. The same results were obtained when other Lewis acids, such as AlMe₃, AlMe₂Cl and AlCl₃, were used instead of Al(isobutyl)₃. Encouragingly, the reaction proceeded when it was performed using a Ni(COD)₂ as catalyst in the presence of AlMe₃, affording benzonitrile in 43% yield (Table 3.7, entry 1). The use of trimethylamine as a base had a positive effect on the reactivity of the reaction, improving the yield to 59% (Table 3.7, entry 2). Having this delightful result, we then optimized the reaction temperature. As shown in entries 3-6, lowering the temperature led to a considerable increase in the yield of product. A temperature lower than 50 °C, nevertheless, has a deleterious effect on the reactivity of the reaction, leading to a suppressed yield in the product (Table 3.7, entry 6). Further evaluation of the Lewis acid and its loading led us to achieve a set of optimal reaction conditions comprised of Ni(COD)₂ (10 mol%), Xantphos (10 mol%), AlCl₃ (60 mol%) and Et₃N (2.0 eq.), which could lead to the benzonitrile in 93% yield (Table 3.7, entry 9). As expected, no reactivity could be observed when the reaction was performed in the absence of Lewis acid (Table 3.7, entry 10). Finally, a control experiment under neat conditions was performed and the result indicated that this transformation could also proceed efficiently without a solvent (Table 3.7, entry 14).
Table 3.7. Optimization for the nickel-catalyzed cyanation of aryl and vinyl triflates.\(^a\)

![Reaction scheme]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis acid (mol%)</th>
<th>Base (eq.)</th>
<th>T (°C)</th>
<th>S221 (%)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AlMe(_3) (60)</td>
<td>K(_2)PO(_4) (2.0)</td>
<td>120</td>
<td>43</td>
</tr>
<tr>
<td>2</td>
<td>AlMe(_3) (60)</td>
<td>Et(_3)N (2.0)</td>
<td>120</td>
<td>59</td>
</tr>
<tr>
<td>3</td>
<td>AlMe(_3) (60)</td>
<td>Et(_3)N (2.0)</td>
<td>100</td>
<td>71</td>
</tr>
<tr>
<td>4</td>
<td>AlMe(_3) (60)</td>
<td>Et(_3)N (2.0)</td>
<td>80</td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td>AlMe(_3) (60)</td>
<td>Et(_3)N (2.0)</td>
<td>50</td>
<td>71</td>
</tr>
<tr>
<td>6</td>
<td>AlMe(_3) (60)</td>
<td>Et(_3)N (2.0)</td>
<td>40</td>
<td>17</td>
</tr>
<tr>
<td>7</td>
<td>Al(isobutyl)(_3) (60)</td>
<td>Et(_3)N (2.0)</td>
<td>50</td>
<td>87</td>
</tr>
<tr>
<td>8</td>
<td>Al(Et)(_3) (60)</td>
<td>Et(_3)N (2.0)</td>
<td>50</td>
<td>84</td>
</tr>
<tr>
<td>9</td>
<td>AlCl(_3) (60)</td>
<td>Et(_3)N (2.0)</td>
<td>50</td>
<td>93</td>
</tr>
<tr>
<td>10</td>
<td>Without LA</td>
<td>Et(_3)N (2.0)</td>
<td>50</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>AlCl(_3) (40)</td>
<td>Et(_3)N (2.0)</td>
<td>50</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>AlCl(_3) (20)</td>
<td>Et(_3)N (2.0)</td>
<td>50</td>
<td>0</td>
</tr>
<tr>
<td>13</td>
<td>AlCl(_3) (80)</td>
<td>Et(_3)N (2.0)</td>
<td>50</td>
<td>77</td>
</tr>
<tr>
<td>14</td>
<td>AlCl(_3) (60)</td>
<td>Et(_3)N (2.0)</td>
<td>50</td>
<td>84(^c)</td>
</tr>
</tbody>
</table>

\(^a\)Reaction conditions: S321 (22.6 mg, 0.1 mmol), R32 (69.1 mg, 10.0 eq.), toluene (0.5 mL), 12 h. \(^b\)GC yields are given using n-dodecane as an internal standard. \(^c\)neat condition.

3.3.2. Substrate Scope

With the optimal reaction conditions in hand, we investigated the substrate scope of this nickel-catalyzed cyanation of aryl and vinyl triflates with butyronitrile. During the investigation, we found that a controlled rate of addition of aryl triflates was critical for some substrates. For example, substrates bearing electron-withdrawing group such as trifluoromethyl or ester group,
which showed very low reactivity in the cyanation of aryl chlorides, reacted well through a slow addition of triflates with the aid of syringe pump, affording the products in 65% and 62% yield, respectively (Table 3.8, entries 2, 3). Moreover, the slow addition enabled the equivalents of butyronitrile to be reduced from 10 to 3. Several heterocycle substrates, including unprotected indoles and carbazoles, were also converted into the corresponding nitrile products in high yields (Table 3.8, entries 16-19). The reaction showed good tolerance to the steric effect as substrates containing an ortho substituent, such as the methyl group, reacted efficiently under the conditions (Table 3.8, entry 6). Interestingly, a multi-nitrile compound could be accessed by the simultaneous installation of multiple cyano groups using this nickel-catalyzed cyanation of triflate derivatives (Table 3.8, entry 10). Aryl halides were well tolerated under the conditions, providing an opportunity to access complex molecules through an iterative synthesis (Table 3.8, entries 11, 12). Finally, this method was also applied to the cyanation of the vinyl triflate, providing an efficient route to synthetically versatile vinyl nitriles (Table 3.8, entry 20).
Table 3.8. Reaction scope of the nickel-catalyzed cyanation of aryl triflates.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Yield(^b)</th>
<th>Entry</th>
<th>Product</th>
<th>Yield(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{Ph-CN})</td>
<td>93(^c)</td>
<td>11</td>
<td>(\text{Cl-CN})</td>
<td>65%</td>
</tr>
<tr>
<td>2</td>
<td>(\text{F-CN})</td>
<td>65(^d)</td>
<td>12</td>
<td>(\text{Cl-CN})</td>
<td>75(^e)</td>
</tr>
<tr>
<td>3</td>
<td>(\text{Me-CN})</td>
<td>62(^d)</td>
<td>13</td>
<td>(\text{N-CN})</td>
<td>76%</td>
</tr>
<tr>
<td>4</td>
<td>(\text{Me-CN})</td>
<td>91%</td>
<td>14</td>
<td>(\text{O-CN})</td>
<td>95%</td>
</tr>
<tr>
<td>5</td>
<td>(\text{nBu-CN})</td>
<td>92%</td>
<td>15</td>
<td>(\text{N-CN})</td>
<td>90%</td>
</tr>
<tr>
<td>6</td>
<td>(\text{Ph-CN})</td>
<td>78%</td>
<td>16</td>
<td>(\text{N-CN})</td>
<td>85(^b)</td>
</tr>
<tr>
<td>7</td>
<td>(\text{Ph-CN})</td>
<td>97%</td>
<td>17</td>
<td>(\text{N-CN})</td>
<td>72(^d)</td>
</tr>
<tr>
<td>8</td>
<td>(\text{N-CN})</td>
<td>96%</td>
<td>18</td>
<td>(\text{N-CN})</td>
<td>55(^b)</td>
</tr>
<tr>
<td>9</td>
<td>(\text{N-CN})</td>
<td>91(^c)</td>
<td>19</td>
<td>(\text{N-CN})</td>
<td>50(^d)</td>
</tr>
<tr>
<td>10</td>
<td>(\text{NC-CN})</td>
<td>82(^f)</td>
<td>20</td>
<td>(\text{N-CN})</td>
<td>93%</td>
</tr>
</tbody>
</table>

\(^a\)Reaction conditions: aryl triflate (0.2 mmol), \(\text{R32}\) (138.2 mg, 10.0 eq.), Ni(COD)\(_2\) (5.5 mg, 10 mol\%), Xantphos (11.6 mg, 10 mol\%), Et\(_3\)N (55.6 μL, 2.0 eq.), toluene (0.5 mL), 50 °C, 12 h. \(^b\)isolated yields. \(^c\)GC yields are given using \(n\)-dodecane as an internal
Owing to the significant role of cyano group in bioactive molecules, we were encouraged to apply this nickel-catalyzed cyanation of aryl and vinyl triflates to the cyanation of several substrates derived from natural products such as estrone (Scheme 3.16, 333), cholesterol (Scheme 3.16, 334) and tocopherol (Scheme 3.16, 335). To our delight, all of these natural product derivatives could be transformed into the corresponding nitriles in excellent yields (Scheme 3.16), demonstrating the synthetic value of this transformation.


To examine the practicality and scalability of our method, a cyanation of the tocopherol derivative on a preparative scale was performed. An open system was crucial to drive the reaction to completion through the release of the gaseous propene generated during decyanation. Gratifyingly, the desired nitrile product could be produced with an excellent yield under the optimized conditions, demonstrating the practicality and scalability of our method (Scheme 3.17). It is worth noting that only two equivalent of butyronitrile were required for this gram-scale synthesis.
3.3.3. Mechanistic Studies

We hypothesized that the reaction might proceed through a catalytic cycle comprised of a cross-coupling process and a dehydrocyanation process. The two processes were proposed to merge through a transmetallation between the two intermediates, 3-C and 3-D, which are generated independently from oxidative addition of ArX (Scheme 3.18, cycle a) and dehydrocyanation of butyronitrile (Scheme 3.18, cycle b). The transmetallation would lead to the formation of two new species 3-F and 3-E with the former species would give the nitrile product by a reductive elimination and the latter would regenerate the active Ni(0) catalyst with the aid of a base (Scheme 3.18).

Scheme 3.18. The proposed catalytic cycle.
To support our hypothesis, the reaction was mechanistically probed. The dehydrocyanation of butyronitrile to generate the key intermediate H–Ni–CN could be substantiated by the detection of undecene isomers in high yield in an experiment using a dodecanenitrile (R33) as the cyanating reagent (Scheme 3.19).

Scheme 3.19. The control experiment using a dodecanenitrile as the cyanating reagent.

One of the advantages of using butyronitrile as a cyanating reagent is that the risk of generating toxic HCN can be significantly reduced. However, necessary precaution has to be taken when using it in the presence of a transition metal catalyst because the toxic HCN can be generated through a transition metal-catalyzed dehydrocyanation. To exclude this possibility, we performed a control experiment with dodecanenitrile in the absence of the substrate (Scheme 3.20a). The detection of only small amount of undecene isomers suggested that the catalytic dehydrocyanation of an alkyl nitrile cannot proceed under our conditions, eliminating the possibility of generating toxic HCN gas in the presence of large excess amount of butyronitrile. Importantly, the cyanation reaction resumed when adding the phenyl triflate to the reaction mixture (Scheme 3.20b), suggesting that the transmetallation between Ar–Ni–X and H–Ni–CN is most likely involved. Furthermore, the slow addition of substrates in some cases is critical to the reactivity of the reaction, suggesting the need for a similar rate of the generation of Ar–Ni–X and H–Ni–CN.
**Scheme 3.20.** A control experiment in the absence of the substrate.

Additional experiments with cyanide ion sources, such as tetrabutylammonium cyanide and acetone cyanohydrin were also performed under the standard conditions (Scheme 3.21). As expected, no reactivity could be observed in both the two reactions, suggesting that the in situ generation of cyanide ion is unlikely to be involved.

**Scheme 3.21.** Control experiments with other cyanide sources.
3.5. Conclusion

In this chapter, a shuttle catalysis-based approach for the synthesis of aryl nitriles using butyronitrile as a cyanating reagent is described. Using a nickel catalyst and Lewis acid co-catalysis, a wide range of aryl chlorides and aryl triflates were converted to the corresponding aryl nitriles in high yields. First, a cyanation of aryl chlorides using Ni(acac)$_2$ as precatalyst, Xantphos as ligand, Al(isobutyl)$_3$ as co-catalyst, Zn as reductant and K$_3$PO$_4$ as base was discussed (Scheme 3.22). A group of aryl chlorides, including several substrates bearing heterocycles, were converted into aryl nitriles in this reaction.

![Scheme 3.22. Nickel-catalyzed cyanation of aryl chlorides.](image)

Then a cyanation of aryl and vinyl triflates using Ni(COD)$_2$, Xantphos, AlCl$_3$ and Et$_3$N system was discussed. (Scheme 3.23). This transformation proceeds under milder reaction conditions (50 °C) and tolerates a broad array of functional groups, including unprotected indoles, and carbazoles. Moreover, the electron-deficient substrates can react well to give the corresponding nitrile products in high yields, complementing the cyanation of aryl chlorides. A gram-scale synthesis of a tocopherol derivative was also demonstrated.

![Scheme 3.23. Nickel-catalyzed cyanation of aryl and vinyl triflates.](image)

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With regards to the mechanism, a dehydrocyanation and cross-coupling merged catalytic cycle, where a transmetallation was proposed to be crucial, was discussed. The dehydrocyanation process was substantiated by the detection of high yield of alkene derived from the corresponding alkyl nitrile, and the transmetallation was supported by the fact that no reactivity was observed in the control experiments with cyanide ions. More importantly, the catalytic dehydrocyanation of an alkyl nitrile cannot proceed in the absence of substrates under the conditions, eliminating the possibility of generating toxic HCN in the presence of large excess amount of butyronitrile.

In conclusion, this shuttle catalysis-enabled approach provides a safe route to aryl and vinyl nitriles. The concept of merging transfer hydrofunctionalization and cross-coupling provides a new strategy for reaction design in organic synthesis.
4. Shuttle Catalysis-enabled Hydrochlorination of Alkynes
Abstract

Vinyl halides are not only widely found in natural products and bioactive molecules, but also serve as versatile building blocks in organic synthesis. Thus, the development of methods for the synthesis of vinyl halides is of great significance. Transition metal-catalyzed hydrohalogenation of alkynes represents one of the most straightforward and efficient methods to synthesize vinyl halides. In this chapter, a shuttle catalysis approach to access vinyl chlorides via an iridium-catalyzed transfer hydrochlorination of unactivated alkynes is described. In contrast to previous methods using HCl or acid chlorides as the hydrochlorinating reagent, this reaction uses 4-chlorobutan-2-one as a HCl source. The transformation tolerates a broad range of functional groups, including several acid sensitive groups, such as tertiary alcohols, silyl ethers and acetals. Preliminary mechanistic study enabled us to propose a mechanism involving a H–Ir–Cl species which could undergo an insertion across the alkyne and the subsequent reductive elimination to form the product and regenerate the catalyst.
4.1. Introduction

4.1.1. Vinyl Chlorides

Vinyl halides serve as versatile building blocks in organic synthesis. Among those, vinyl chlorides have been frequently used as coupling partners in transition metal-catalyzed cross-coupling reactions for the formation of C–C bonds and C–heteroatom bonds, such as Suzuki-Miyaura, Sonogashira, Negishi, Stille and Buchwald-Hartwig reactions.

In addition to their great value in synthetic chemistry, vinyl chlorides are also widely found in natural products and bioactive compounds (Figure 4.1). Therefore, the development of methodologies for the synthesis of vinyl chlorides is of great significance to both chemistry and biology.

![Figure 4.1. Examples of vinyl chloride-containing natural products and bioactive compounds](image-url)

---

4.1.2. Synthesis of Vinyl Chlorides

Owing to the importance of vinyl chlorides in chemistry and biology, numerous efforts have been devoted to the development of methods for vinyl chlorides synthesis. A large number of approaches to access vinyl chlorides from various starting materials have been established so far. Among those starting materials, carbonyl compounds and alkynes are more commonly used in both traditional and modern protocols. Nevertheless, some drawbacks of these protocols remain, such as the need for strongly acidic conditions, the use of hazardous chlorinating reagents and the generation of undesired by-products.

Carbonyl compounds have been well studied as starting materials for the synthesis of vinyl chlorides, however, most of the established approaches are not catalytic and often require the use of toxic phosphorus reagents such as PCl₅, CrCl₂ or POCl₃. In 2007, Su and co-workers developed a catalytic approach for the synthesis of vinyl chlorides from ketone. In this reaction, a wide range of (Z)-vinyl chlorides were produced using BTC (Bis(trichloromethyl) carbonate) as a chlorinating reagent and a combination of Sc(OTf)₃, DMF and benzoyl chloride as the catalytic system (Scheme 4.1).124 Regarding the mechanism, the authors proposed a six-membered transition state to be involved in the catalytic cycle, which leads to the Z selectivity


121 See reference 119a, 119b.
122 See reference 119c.
123 See reference 119d.
124 See reference 119i.
through a *cis*-elimination. Advantages of this transformation are obvious, such as high stereoselectivity, the use of relatively safe chlorinating reagent and low catalyst loading. Nevertheless, the generation of CO\textsubscript{2} and HCl as by-products limits its application in preparative synthesis and results in a poor functional group tolerance.

\textit{Su and co-workers, 2007}

\begin{center}
\begin{tikzpicture}
\node[draw, text width=2cm] at (0,0) (a) {\(\text{R}^1\text{O}\text{R}^2\)}; \node[draw, text width=2cm] at (2,0) (b) {\(\text{Cl}\)}; \node[draw, text width=2cm] at (4,0) (c) {\(\text{R}^1\text{C}\text{H}\text{R}^2\)}; \node[draw, text width=2cm] at (6,0) (d) {\(\text{Cl}_{3}\text{C}O\text{OC}l_{3}\)}; \node[draw, text width=2cm] at (8,0) (e) {\text{BTC}};
\node[draw, text width=2cm] at (1,1.5) (f) {\text{Sc(OTf)}_3 (2 \text{ mol\%})}; \node[draw, text width=2cm] at (1,0.3) (g) {\text{DMF (1 \text{ mol\%})}}; \node[draw, text width=2cm] at (1,-0.7) (h) {\text{PhCOCl (5 \text{ mol\%})}}; \node[draw, text width=2cm] at (1,-2) (i) {\text{BTC (0.4 eq.), EtOAc, 8 h}}; \node[draw, text width=2cm] at (2,1.5) (j) {21 \text{ examples}}; \node[draw, text width=2cm] at (2,1) (k) {\text{up to 83\% yield}}; \node[draw, text width=2cm] at (2,0.5) (l) {\text{(Z)-isomer}};
\end{tikzpicture}
\end{center}

\textbf{Scheme 4.1. An example of catalytic preparation of vinyl chlorides from ketones.}

A metal-free approach towards vinyl chlorides from ketones using the same reagent (BTC) was reported more recently by Kartika and co-workers (Scheme 4.2).\textsuperscript{125} Using this approach, a group of aliphatic and aromatic ketones can be converted into the corresponding vinyl chlorides in moderate to good yields in the presence of an excess of pyridine. The reaction was proposed to proceed through a pyridinium carbamate intermediate which is formed through the activation of the carbonyl group with BTC and pyridine. While it is true that metal catalysts and toxic reagents are not required in this reaction, limitations such as narrow substrate scope and the formation of \textit{geminal}-dichloride by-product in some cases restrict its application.

\textsuperscript{125} See reference 119j.
The synthesis of vinyl chlorides from alkynes represents an attractive method due to the accessibility of alkynes and their frequent use in catalytic protocols. It can be mainly achieved by transition metal-catalyzed carbo- and hydrochlorination of alkynes. The carbochlorination is often used to prepare substituted vinyl chlorides. The mechanism for this reaction generally involves a chlorometalation step in which chloro and metal atoms add across an alkyne simultaneously to form a carbon–halogen and a carbon–metal bond, with the latter undergoing subsequent reductive elimination to generate a carbon–carbon bond. Transition metal-catalyzed carbochlorination reactions have been well studied, and a variety of molecules, including allyl chlorides, acid chlorides, chloroformates and chloroalkynes, can be used as reagents. However, the limited reaction scope in many cases often reduces their synthetic value.

The transition metal-catalyzed hydrochlorination of alkynes has been well developed over the past decades. A few transition metals could catalyze this reaction. A gold catalyst was discovered by Thomas and co-workers when they were studying the oxidation of phenlacetylene.\(^{131}\) The most recent example of gold-catalyzed hydrochlorination of alkynes was reported by Xu and co-workers (Scheme 4.3).\(^ {132}\) In this work, they demonstrate a highly selective and efficient approach for the synthesis of vinyl chlorides with HCl/DMPU. In the presence of AuCl and a phosphine ligand, a wide range of alkynes, including a peptide molecule and an estrone derivative, were hydrochlorinated to the corresponding vinyl chlorides. The main advantages associated with this method are exclusive \textit{anti}-selectivity, excellent compatibility of the cationic gold catalyst with chloride ions,\(^ {133}\) air tolerance and high functional group tolerance. However, the high cost of gold limits its broad application, particularly on a large-scale.

\textit{Xu and co-workers, 2017}

\[ \text{R}^1\equiv\text{R}^2 \xrightarrow{\begin{array}{c} \text{AuCl/L22 (2 mol\%)} \\ \text{HCl/DMPU (1.2 eq.)} \\ \text{HFIP/MeNO}_2 (1:1), \text{RT or 75 }^\circ\text{C} \end{array}} \text{Cl} \text{R}^2 \equiv\text{R}^2 \xrightarrow{\begin{array}{c} \text{anti-addition} \\ \text{22 examples} \\ \text{66-99\% yield} \end{array}} \]

\begin{align*}
\text{MeO}(\text{Me}) & \quad \text{Me}(\text{OMe}) \\
\text{i-Pr} & \quad \text{i-Pr} \\
\text{L22} & \quad \text{DMPU} \\
\text{HFIP} & \quad \text{Cl} \\
\text{H}_2\text{C} & \quad \text{NH} \\
\text{CH}_3 & \quad \text{F}_3\text{C} \\
\text{OH} & \quad \text{CF}_3 \\
\end{align*}

Scheme 4.3. Gold(I)-catalyzed \textit{anti}-hydrochlorination of alkynes using HCl/DMPU.

A ruthenium catalyst was also found effective to catalyze the hydrochlorination reaction. In 2012, Dérien and co-workers found that Cp*RuCl(COD) was able to catalyze the dimerization of alkynes to give chlorinated dienes through a hydrochlorination process with HCl.\(^ {134}\) Based on

\begin{itemize}
\end{itemize}
this result, they developed a ruthenium-catalyzed hydrochlorination of alkynes using HCl in the presence of the same precatalyst (Scheme 4.4a).\textsuperscript{135} Under the reported conditions with triphenylphosphine as a ligand, a number of terminal alkynes were converted to the vinyl chlorides in excellent yields and with exclusive Markovnikov selectivity. Interestingly, the reaction also works well using a combination of camphorsulfonic acid (CSA) and BnEt\textsubscript{3}NX as the source of HCl instead of an ethereal HCl solution under the standard conditions, leading to vinyl chlorides in excellent yields. Vinyl bromides or iodides could also be synthesized in high yields with the corresponding ammonium halide (Scheme 4.4b). However, the substrate scope of this reaction is limited to terminal alkynes and symmetric internal alkynes.

\textit{D\textregistered rien and co-workers, 2015}

\[ \text{R} \equiv \text{H} + \text{HCl (2 M in Et}_2\text{O)} \rightarrow \text{Cl} \text{R} \]

\text{(a) syn-addition 15 examples 75-100\% yield}

\[ \text{Cp*RuCl(cod) (2.5 mol\%) PPh}_3 \text{(2.5 mol\%) DCE, RT} \]

\[ \text{Cl} \text{R} \]

\[ \text{Ph} \equiv \text{H} + \text{CSA} + \text{BnEt}_3\text{NX} \]

\text{(b) X = Cl 1 h 97\%}

\text{X = Br 2 h 95\%}

\text{X = I 3 h 88\%}

\text{Scheme 4.4. Ruthenium-catalyzed syn-hydrochlorination of alkynes using HCl.}

Palladium catalysts have been used in several examples of alkyne hydrochlorination.\textsuperscript{136} The most recent example is the report by Engle and co-workers where they disclosed a palladium-catalyzed hydrochlorination of unactivated alkynes using in-situ generated HCl. This reaction proceeds with high regio- and stereoselectivity which are controlled through the


introduction of a removable directing group (Scheme 4.5). Although a wide array of substituted vinyl chlorides can be synthesized efficiently and selectively, the need for placing a directing group on the specific position of substrates before hydrochlorination and removing it after render the method non step-economic. Moreover, the use of acid chloride as the source of Cl can result in a poor functional group tolerance.

Scheme 4.5. Palladium-catalyzed directed anti-hydrochlorination of alkynes with in-situ generated HCl.

4.2. Iridium-catalyzed hydrochlorination of alkynes

4.2.1. Reaction Design

Based on the shuttle catalysis concept, our group recently developed several important transformations that could overcome challenges associated with the use of hazardous reagents. They include HCN-free hydrocyanation of alkenes, cyanide-free cyanation of aryl chlorides and triflates and CO/HCl-free hydrochlorocarbonylation of alkynes. In these reactions, shuttle catalysis enables the use of safe and stable organic molecules, such as alkyl nitriles and aliphatic acid chloride, as alternatives to the traditional hazardous reagents. Encouraged by these works, we aimed to develop a shuttle catalysis-enabled hydrochlorination of alkynes using alkyl chlorides as a HCl source. Compared with previously reported hydrochlorination reactions, such a reaction would provide a safer and milder method for the synthesis of vinyl chlorides and should be able to ensure a broader functional group tolerance due to the use of an alkyl chloride as the hydrochlorinating reagent.

4.2.2. Evaluation of The Reaction Conditions

We started to test the reactivity of the hydrochlorination reaction with alkyl chlorides that are structurally similar to the reagents used in the previously reported shuttle catalysis reactions,\textsuperscript{138} such as isobutyl chloride and butyl chloride. Several transition metal catalysts that are used in reported hydrochlorination or carbochlorination reactions were used for the test, such as Cp*RuCl(COD) and [IrCl(COD)]\textsubscript{2}. Unfortunately, both the reagents were found unreactive under any reaction conditions based on these catalysts probably because of the inertness of sp\textsuperscript{3} C–Cl bonds. Nickel catalysts, such as Ni(COD)\textsubscript{2}, were also used in the initial test due to their high propensity to activate sp\textsuperscript{3} C–Cl bonds. However, we obtained the same result as that with Cp*RuCl(COD) or [IrCl(COD)]\textsubscript{2}. We then reasoned that the reagent bearing a polar group at a neighboring position to the chlorine atom could be reactive because of directing or inductive effects. With this idea in mind, we tested a few reagents bearing a carbonyl group at the α, β, or γ position to the chloro group (Table 4.1). Gratifyingly, a reagent bearing a carbonyl group at the β position to the chlorine atom was found reactive in the hydrochlorination of 5-Phenyl-1-pentyne with a [IrCl(COD)]\textsubscript{2}/Cphos catalytic system and gave the product in 15% yield (Table 4.1, entry 3). Further evaluation enabled us to identify 4-Chloro-2-butanone as the most reactive reagent and afforded the product (41) as a single isomer in 85% yield (Table 4.1, entry 4). More importantly, methyl vinyl ketone, which was produced by the dehydrochlorination of 4-Chloro-2-butanone, could be obtained in 87% yield, clearly suggesting the involvement of a functional group transfer process. While the use of 1-chloropentan-3-one also led to a 75% yield of product, other reagents such as 1-chloroacetone, 3-chloro-2-butanone, ethyl 3-chloropropanoate, 3-chloro-1-phenyl-1-propanone, and 5-chloro-2-pentanone were found unreactive under the conditions.

\textsuperscript{138} See reference 6.
Table 4.1. Initial studies on the reagent.\(^{a}\)

![Image of the reaction scheme]

<table>
<thead>
<tr>
<th>Entry</th>
<th>‘Cl’</th>
<th>41 (%)(^{b})</th>
<th>Entry</th>
<th>‘Cl’</th>
<th>41 (%)(^{b})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cl</td>
<td>0</td>
<td>5</td>
<td>Cl</td>
<td>75</td>
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<td>6</td>
<td>Cl</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Cl</td>
<td>15</td>
<td>7</td>
<td>Cl</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Cl</td>
<td>85</td>
<td>8</td>
<td>Cl</td>
<td>trace</td>
</tr>
</tbody>
</table>

\(^{a}\)Reaction conditions: S41 (0.1 mmol), ‘Cl’ (0.2 mmol), [IrCl(COD)]\(_2\) (2.5 mol%), CPhos (7.5 mol%), toluene (0.25 mL) at 80 °C, 5 h. \(^{b}\)NMR yields using dibromomethane as an internal standard.

Using 4-chlorobutan-2-one as a HCl donor, we continued to optimize the reaction conditions for the hydrochlorination reaction. Several different transition metal catalysts other than [IrCl(COD)]\(_2\) were initially evaluated. Only Pd\(_2\)(dba)\(_3\) showed some activity, giving the product (41) in 10% yield (Table 4.2, entry 2). Both Ni(COD)\(_2\) and [RhCl(COD)]\(_2\) could not catalyze the reaction (Table 4.2, entries 3 and 4). The effect of ligand was next studied using [IrCl(COD)]\(_2\) as precatalyst. Electron-rich and neutral ligands were found to be beneficial (Table 4.2, entries 5-7) even though the bulky P(n-Bu)\(_3\) only gave the product in 10% yield (Table 4.2, entry 8). Some Buchwald type ligands were highly effective for the transformation, leading to the product in high yields (Table 4.2, entries 9-12). In contrast, bidentate phosphine ligands were generally not suitable for this iridium-catalyzed hydrochlorination, even though exceptions were
observed with Cy-Xantphos (L23) or t-Bu-Xantphos (L24), obtaining 85% and 83% yield, respectively (Table 4.2, entries 13-14). Others ligands such as Xantphos, DPEphos, L8 and dppe only gave the product in yields lower than 24% (Table 4.2, entries 15-18). Reducing the amount of 4-chlorobutan-2-one (R41) had a deleterious effect on the outcome of the hydrochlorination, leading to a decreased 68% yield (Table 4.2, entry 19). On the other hand, no reactivity was observed when performing the reaction at temperatures below 80 °C (Table 4.2, entry 20). Both the transition metal-catalyst and the ligand play a critical role in this reaction according to the results of control experiments performed in the absence of either [IrCl(COD)]2 or CPhos (Table 4.2, entries 21, 22). The effect of the solvent was also evaluated and the results enabled us to identify toluene as the optimal solvent for this transformation (Table 4.2, entry 23). Finally, we could establish the optimized catalytic system comprised of [IrCl(COD)]2 as a catalyst, CPhos as a ligand, and toluene as solvent at 80 °C, which led to 41 as a single isomer in 85% GC yield (Table 4.2, entry 1).
Table 4.2. Evaluation of catalyst, ligand, and solvent.a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Deviation from standard conditions</th>
<th>41 (%)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>Pd(_2)(dba)(_3) instead of [IrCl(COD)](_2)</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>Ni(COD)(_2) instead of [IrCl(COD)](_2)</td>
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</tr>
<tr>
<td>4</td>
<td>[RhCl(COD)](_2) instead of [IrCl(COD)](_2)</td>
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</tr>
<tr>
<td>5</td>
<td>PPh(_3) instead of Cphos</td>
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</tr>
<tr>
<td>6</td>
<td>PCy(_3) instead of Cphos</td>
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</tr>
<tr>
<td>7</td>
<td>PPhCy(_2) instead of Cphos</td>
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</tr>
<tr>
<td>8</td>
<td>P(n-Bu)(_3) instead of Cphos</td>
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</tr>
<tr>
<td>9</td>
<td>DavePhos instead of Cphos</td>
<td>80</td>
</tr>
<tr>
<td>10</td>
<td>RuPhos instead of Cphos</td>
<td>79</td>
</tr>
<tr>
<td>11</td>
<td>XPhos instead of Cphos</td>
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</tr>
<tr>
<td>12</td>
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<tr>
<td>15</td>
<td>XantPhos instead of Cphos</td>
<td>15</td>
</tr>
<tr>
<td>16</td>
<td>DPEPhos instead of Cphos</td>
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</tr>
<tr>
<td>17</td>
<td><strong>L8</strong> instead of Cphos</td>
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</tr>
<tr>
<td>18</td>
<td>dppe instead of Cphos</td>
<td>0</td>
</tr>
<tr>
<td>19</td>
<td>1.2 equivalent of <strong>I</strong></td>
<td>68</td>
</tr>
<tr>
<td>20</td>
<td>RT or 50 °C</td>
<td>0 (84°c)</td>
</tr>
<tr>
<td>21</td>
<td>no [IrCl(COD)](_2)</td>
<td>0</td>
</tr>
<tr>
<td>22</td>
<td>no Cphos</td>
<td>20</td>
</tr>
<tr>
<td>23</td>
<td>Dioxane, benzene, xylene, THF, DCM or DCE instead of toluene</td>
<td>62-80</td>
</tr>
</tbody>
</table>

---

aReaction conditions: S41 (0.1 mmol), R41 (0.2 mmol), [IrCl(COD)]\(_2\) (2.5 mol%), CPhos (7.5 mol%), toluene (0.25 mL) at 80 °C, 5 h. bNMR yields using dibromomethane as an internal standard. c100 °C.
4.2.3. Substrate Scope

After establishing the optimal conditions, we then studied the substrate scope of this iridium-catalyzed transfer hydrochlorination of alkynes. As shown in Table 4.3, a broad array of aliphatic terminal alkynes could undergo hydrochlorination to produce the corresponding vinyl chlorides in high yields. An aromatic terminal alkyne also reacted using Ruphos as the ligand (Entry 18). This transformation shows an excellent functional group tolerance as alkynes bearing a broad range of functional groups could react effectively, including nitriles (Entry 5), esters (Entry 7), amines (Entry 9), fluorides (Entry 12), chlorides (Entry 6), nitros (Entry 11), aldehydes (Entry 16) and aryl iodides (Entry 13). An important functional group α,β-unsaturated ester was also tolerated, leading to the product in good yield (Entry 10). Moreover, alkynes containing heterocycles such as pyridine and thiophene could be hydrochlorinated smoothly to produce the corresponding vinyl chlorides in high yields, demonstrating the potential of this transformation in the synthesis of bioactive molecules (Entries 14, 15). Interestingly, a product bearing multiple vinyl chlorides could be produced from a substrate bearing multiple terminal alkynes using our method (Entry 17).
Table 4.3. Substrate scope of iridium-catalyzed hydrochlorination of alkynes.$^a$

$$R_1\text{==}=\text{R}_2 + \text{Cl}\text{O} \quad \text{Cl}_{\text{R}_41, \text{2.0 eq.}} \quad \text{[IrCl(cod)]}_2 (2.5 \text{ mol\%})$$

\[
\text{Cphos (7.5 mol\%)} \quad \text{toluene, 80 °C, 5 h} \quad \text{R}_1\text{==}=\text{R}_2
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkyne</th>
<th>Product</th>
<th>Yields (%)$^b$</th>
</tr>
</thead>
<tbody>
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<td><img src="image2.png" alt="Product" /></td>
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</tr>
<tr>
<td>2</td>
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<td>67</td>
</tr>
<tr>
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<td><img src="image6.png" alt="Product" /></td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7.png" alt="Alkyne" /></td>
<td><img src="image8.png" alt="Product" /></td>
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</tr>
<tr>
<td>5</td>
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<td><img src="image10.png" alt="Product" /></td>
<td>78$^c$</td>
</tr>
<tr>
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</tr>
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</tr>
<tr>
<td>9</td>
<td><img src="image17.png" alt="Alkyne" /></td>
<td><img src="image18.png" alt="Product" /></td>
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</tr>
<tr>
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</tr>
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<td><img src="image22.png" alt="Product" /></td>
<td>87</td>
</tr>
<tr>
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<td><img src="image23.png" alt="Alkyne" /></td>
<td><img src="image24.png" alt="Product" /></td>
<td>88</td>
</tr>
</tbody>
</table>
The tolerance of acid-sensitive functional groups is a critical challenge in previous hydrochlorination reactions due to the use of acidic reagents such as HCl. In principle, our acid-free transfer hydrochlorination approach should be able to overcome the challenge. To test this, we subjected several alkynes bearing tertiary silyl ethers (Table 4.4, \textsuperscript{419}), acetals (Table 4.4, \textsuperscript{420}), or tertiary alcohols (Table 4.4, \textsuperscript{421}) to the conditions. Gratifyingly, all these functional groups could be well tolerated according to the results, further revealing the excellent functional group tolerance of our method.
Table 4.4. Tolerance of acid-sensitive functional groups.

| R1                  | R2                  | [IrCl(cod)]2 (2.5 mol%) | Cphos (7.5 mol%) | toluene, 80 ºC, 5 h | R1 | R2 |
|---------------------|---------------------|-------------------------|------------------|---------------------|-------------------|
| 419, 68%            |                    |                         |                  |                     |      |

| R1                  | R2                  | [IrCl(cod)]2 (5 mol%)  | t-Bu-Xanthos (20 mol%), toluene (0.5 mL) at 80 ºC, 12 h | R1 | R2 |
|---------------------|---------------------|-----------------------|--------------------------------------------------------|-------------------|
| 420, 60%            |                    | 421, 50%              |                                                         |      |

\(^a\)alkynes (0.2 mmol), \(\textbf{R41}\) (0.4 mmol), [IrCl(COD)]_2 (2.5 mol%), Cphos (7.5 mol%), toluene (0.5 mL) at 80 ºC, 5 h isolated yields. \(^b\)alkynes (0.2 mmol), \(\textbf{R41}\) (0.8 mmol), [IrCl(COD)]_2 (5 mol%), t-Bu-Xanthos (20 mol%), toluene (0.5 mL) at 80 ºC, 12 h isolated yield.

Furthermore, alkynes derived from natural products such as estrone (Scheme 4.6, 422) and cholic acid (Scheme 4.6, 423) were also converted efficiently to the corresponding vinyl chlorides in high yields, further demonstrating the synthetic value of this new iridium-catalyzed hydrochlorination reaction.


Internal alkynes were also evaluated. The results showed that both aliphatic and aromatic internal alkynes could react at a higher temperature. A symmetric diarylethyne could be converted to the corresponding vinyl chloride in excellent yield and with high stereoselectivity (Scheme 4.7, 424). A symmetric aliphatic internal alkyne also reacted smoothly under the conditions. However, the stereoselectivity is not ideal in this case (Scheme 4.7, 425). With respect to asymmetric internal alkynes, an ester-substituted substrate could be converted to the corresponding vinyl chloride as a single isomer in good yield (Scheme 4.7, 426).
Finally, a gram-scale synthesis was achieved with an aliphatic terminal alkyne (44) bearing an aryl chloride group with the product being formed in high yield, demonstrating the robustness and practicality of this iridium-catalyzed hydrochlorination approach (Scheme 4.8).

4.2.4. Mechanistic Studies

Preliminary studies were conducted to get insights into the mechanism of this iridium-catalyzed hydrochlorination of alkynes with 4-chloro-2-butanone. Initially, we carried out a reaction using HCl instead of 4-chloro-2-butanone as the hydrochlorinating reagent under the standard conditions (Scheme 4.9a). The reaction could proceed efficiently and lead to a similar result to that of the reaction with 4-chloro-2-butanone. Based on this result, we speculated that the reaction with 4-chloro-2-butanone might proceed through a Cl–Ir–H intermediate. In contrast to our standard system which is unreactive at room temperature or in the absence of phosphine ligand (Scheme 4.9b), the hydrochlorination with HCl could even proceed at room temperature.
without the need of any ligand, suggesting: 1) The speculative Cl–Ir–H intermediate is more likely generated through iridium-catalyzed activation of the reagent, 4-chloro-2-butanone, rather than by oxidative addition of in-situ generated HCl. 2) The activation of 4-chloro-2-butanone to generate Cl–Ir–H intermediate probably starts with the challenging oxidative addition of the inert C–Cl bond, which requires pushing conditions such as high temperature and electron-rich phosphine ligand or the assistance of a directing group, followed by β-Hydride elimination. However, an alternative pathway to the Cl–Ir–H intermediate through an initial C–H oxidative addition followed by β-chloride elimination cannot be excluded at the current stage.

(a) The control experiment with HCl

\[
\text{Scheme 4.9. Control experiments with HCl and 4-chloro-2-butanone under ligand or ligandless conditions.}
\]

(b) Reagent activation promoted by electron-rich ligand and elevated temperature

To rule out the involvement of in-situ generation of HCl in the reaction, experiments in the absence of alkyne were performed (Scheme 4.10). Decomposition of the reagent R41 was not observed in the reaction performed at 80 °C in the absence of catalyst and ligand (Scheme 4.10a).

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In addition, no significant conversion of 4-chloro-2-butanone could be detected in the reaction performed with catalyst and ligand (Scheme 4.10b). These results, combined with the fact that acid-sensitive functional groups are well tolerated in the transformation, suggest the in-situ generation of HCl is unlikely to occur.

![Scheme 4.10. Control experiments in the absence of alkyne or catalyst.](image)

To get insights into the alkyne insertion step, we initially performed two deuterium labeling experiments using DCl as chlorinating reagent (Scheme 4.11a) and a deuterium-labeled alkyne as substrate (Scheme 4.11b), respectively. Interestingly, we obtained similar results from the two experiments in terms of yield and selectivity. Both reactions led to high yields of product and nearly equimolar amount of the stereoisomers. We then performed an experiment in which an exogenous source of chloride ions was added. As expected, the ratio of products derived from \( \text{anti} \) - and \( \text{syn} \) - insertions was reversed. These observations, together with the fact that Rh(III)-Cl and Ir(III)-Cl species undergo rapid M-Cl insertion,\(^{141}\) suggest that the alkyne insertion step might proceed through chloroiridation in a competing \( \text{syn} \) - and \( \text{anti} \)-fashion.

Scheme 4.11. Control experiments with the deuterium-labelled reagents or alkyne.

Based on these observations, we are able to depict the catalytic cycle as below. Oxidative addition of C–Cl bond on the iridium catalyst, which might be assisted by the carbonyl group through chelation, and the subsequent β-hydride elimination generates the intermediate 4-C (Scheme 4.12, path 2). This intermediate then undergoes alkyne insertion through chloroiridation to form the intermediate 4-D, which could finally lead to the product and regenerate the iridium catalyst by reductive elimination. However, the formation of intermediate 4-C through oxidative addition of C–H bond on the iridium catalyst followed by β-chloride elimination cannot be excluded at the current stage (Scheme 4.12, path 1).
4.3. Conclusion

In this chapter, a shuttle catalysis-based method for the synthesis of vinyl chlorides via an iridium-catalyzed transfer hydrochlorination of alkynes is described. In contrast to previous transition metal catalyzed hydrochlorination reactions where corrosive reagents such as HCl or acid chlorides were used, this method uses chlorobutan-2-one as a HCl source. A broad range of functional groups can be tolerated in this transformation, enabling access to a wide diversity of vinyl chlorides. Notably, acid-sensitive groups such as tertiary alcohols, silyl ethers and acetals could also be efficiently tolerated, complementing the previously reported methods. Mechanistic studies were conducted and the results allowed us to propose a mechanism involving a Cl–Ir–H intermediate. This intermediate is likely generated through oxidative addition of the C–Cl bond of chlorobutan-2-one on the iridium catalyst and the subsequent β-hydride elimination. However, the other pathway through oxidative addition of the C–H bond followed by β-chloride elimination cannot be excluded at the current stage. We were also able to propose an alkyne insertion into the Cl–Ir–H intermediate through an unselective chloroiridation. However, more studies are absolutely required for getting deeper insights into the mechanism of this novel reaction.
5. Conclusion and Outlook
Shuttle catalysis has emerged as a useful strategy in organic synthesis for the (de)functionalization of molecules. Based on this strategy, our group recently developed a transfer hydrocyanation of alkenes using isovaleronitrile as a source of hydrogen cyanide and a dehydrocyanation of alkyl nitriles using norbornadiene as an acceptor of hydrogen cyanide. In this reaction, the transfer of HCN is facilitated by a nickel/aluminum Lewis acid co-catalyzed C–CN bond activation.

Inspired by this transfer hydrocyanation reaction, we first applied the shuttle catalysis in a Mizoroki-Heck-type reaction of aryl cyanides. In contrast to the traditional Mizoroki-Heck reaction, where a base is required to regenerate the catalyst, our reaction uses a transfer hydrocyanation as the catalyst turnover step, therefore precluding the requirement for a base. Using a combination of nickel and aluminum Lewis acid as catalyst, we developed an intramolecular Mizoroki-Heck-type reaction of aryl cyanides using an alkyne as HCN acceptor. In this transformation, a wide range of aryl cyanides could couple with alkynes, such as 4-octyne and cyclododecyn, to yield the corresponding benzofulvenes with high efficiency. We also realized an intermolecular Mizoroki-Heck-type reaction of aryl cyanides using an alkene as HCN acceptor in the presence of a palladium catalyst. Concerning the mechanism, the transfer hydrocyanation process was substantiated by the isolation of hydrocyanation products.

We next developed a transfer cyanation of aryl chlorides and triflates for the synthesis of aryl nitriles using butyronitrile as a cyanating reagent. With regards to the mechanism, a transfer dehydrocyanation and cross-coupling catalytic cycle were merged through a transmetallation step. The dehydrocyanation process was substantiated by the detection of high yield of alkene derived from the corresponding alkyl nitrile, and the transmetallation was supported by the fact that no reactivity was observed in the control experiments with cyanide ions. More importantly, the catalytic dehydrocyanation of an alkyl nitrile only proceeds in the presence of substrates, eliminating the possibility of generating toxic HCN when there is an excess amount of butyronitrile.

Finally, in the context of shuttle catalysis-enabled hydrofunctionalization, we developed an iridium-catalyzed transfer hydrochlorination of alkynes. In contrast to previous transition metal-catalyzed hydrochlorination reactions where corrosive reagents such as HCl or acid chlorides
were used, this method uses chlorobutane-2-one as a source of HCl. A notable feature of this transformation is that acid-sensitive functional groups such as tertiary alcohols, silyl ethers and acetals are tolerated. Regarding the mechanism for this HCl transfer, we proposed a Cl–Ir–H intermediate which could be generated through an iridium-catalyzed oxidative addition of the C–Cl bond of chlorobutane-2-one and subsequent β-hydride elimination. We also proposed an alkyne insertion into the Cl–Ir–H intermediate through an unselective chloroiridation. However, more studies are required to gain a deeper insight into the mechanism, and the discovery of a more sustainable hydrochlorinating reagent remains interesting.

The shuttle catalysis strategy has great potential to enable a broader range of transformations. First of all, besides our previously discussed hydrocyanation or hydrochlorination, we believe that this strategy can also be applied to a broader class of transfer hydrofunctionalization reactions such as transfer hydrofluorination or transfer hydroamination. These reactions would provide complementary routes to introduce functional groups into molecules. Moreover, to apply the shuttle catalysis to the asymmetric hydrofunctionalization is also of interest since it could allow a more practical approach to the synthesis of enantioenriched compounds. A particularly interesting example would be the asymmetric hydrocyanation, which may be achieved through the use of chiral ligands.

Besides hydrofunctionalization, we also believe that the shuttle catalysis strategy possesses potential in other types of transformations. As shown in the transfer cyanation of aryl chlorides and triflates, the transfer dehydrofunctionalization can be used in combination with cross-coupling reactions to achieve the functionalization of aromatics. This provides a new concept for chemists to design reactions by merging various reactions with the shuttle catalysis strategy. Based on the transfer cation reaction, we believe that this concept can also be applied to a broader class of aromatic functionalization reactions, such as acylation, formylation or chlorocarbonylation by using alkyl ketones, alkyl aldehydes or alkyl acid chlorides as donor molecules. Moreover, to extend the scope of these aromatic functionalization reactions from aromatic halides to simple arenes through C–H functionalization is also of significance.
6. Experimental Part
General Information

All the catalysts, ligands, Lewis acids, bases, zinc and manganese used during the study were purchased from commercial suppliers and used as received. Bis(1,5-cyclooctadiene)nickel(0) and Bis(1,5-cyclooctadiene)diiridium(I) dichloride was stored in the glovebox (LABmaster Pro SP, MBraun). Some substrates were purchased and used without any further purification. The others were synthesized following the reported procedures. Toluene was degassed before using and stored in the glovebox (LABmaster Pro SP, MBraun). $^1$H NMR and $^{13}$C NMR spectra were recorded at 500 MHz and at 125 MHz, respectively on a spectrometer in CDCl$_3$ at room temperature. $^1$H NMR was reported as follows: chemical shift, multiplicity ($s =$ singlet, $d =$ doublet, $t =$ triplet, $q =$ quadruplet, $m =$ multiplet and $br =$ broad signal), coupling constant ($J$ values) in Hz and integration. Chemical shifts ($\delta$) were reported with respect to the corresponding solvent residual peak at 7.26 ppm for CDCl$_3$ for $^1$H NMR. $^{13}$C NMR spectra ($^1$H-broadband decoupled) were reported in ppm using the central peak of CDCl$_3$ (77.16 ppm). High-resolution mass spectrometric measurements were provided by the Mass Spectrometry Department of the Max-Planck Institut für Kohlenforschung and ETH Zurich. The molecular ion [M]$^+$, [M+H]$^+$ and [M+Na]$^+$ are given in m/z units. For TLC analysis silica gel coated glass plates (0.25 mm) with fluorescence indicator UV$_{254}$ (Macherey-Nagel, TLC plates SIL G-25 UV$_{254}$), irradiation of UV light at 254 nm and oxidative staining using potassium permanganate solution (KMnO$_4$) were used. For flash column chromatography silica gel 60 (particle size 40–63 $\mu$m, Merck) was used and the technical grade solvents were used.
6.1. Experimental Part to Chapter 2

6.1.1. Substrates Preparation and Characterization

General procedure 2A: For the synthesis of S21, S23-S25, S27, S29, S212

A Schlenk tube equipped with a magnetic stirring bar was charged with 2-halidearylnitrile (1.5 mmol), Tetrakis(triphenylphosphin)palladium (86.7 mg, 0.075 mmol), sodium carbonate (349.8 mg, 3.3 mmol), potassium vinyltrifluoroborate (S21b, 301.4 mg, 2.25 mmol) and 1,4-dioxane/ethanol/water (5:3:2) (3.0 mL) under an argon atmosphere. The solution was then stirred at 120 °C in an oil bath. After stirring for 20 h, the solution was cooled to room temperature, diluted with water (3.0 mL) and extracted with MTBE (10.0 mL × 3). The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give crude product. Purification by flash column chromatography afforded the products.

Characterization of S21, S23-S25, S27, S29, S212

2-Vinylbenzonitrile (S21) (The spectral data are consistent with those reported in the literature.142)

Was produced from 2-bromobenzonitrile (S21a, 273.0 mg, 1.5 mmol) following the general procedure 2A. Purification by flash column chromatography (20:1 n-pentane/MTBE) afforded the product in 73% yield (S21, 123.0 mg).

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Exploring the Potential of Shuttle Catalysis in Organic Synthesis

\[ ^1H \text{ NMR (500 MHz, CDCl}_3 \delta 7.70 - 7.65 (m, 1H), 7.63 (ddd, } J = 7.7, 1.3, 0.5 \text{ Hz, 1H), 7.56 (tdd, } J = 8.0, 1.3, 0.5 \text{ Hz, 1H), 7.34 (td, } J = 7.6, 1.2 \text{ Hz, 1H), 7.08 (dd, } J = 17.4, 11.1 \text{ Hz, 1H), 5.95 (d, } J = 17.4 \text{ Hz, 1H), 5.54 (d, } J = 11.1 \text{ Hz, 1H).} \]

\[ ^13C \text{ NMR (125 MHz, CDCl}_3 \delta 140.79, 133.05, 133.02, 132.85, 128.08, 125.56, 119.06, 117.90, 111.30.} \]

HRMS-EI (m/z): [M]^+ calcd for C9H7N, 129.057299; found 129.057340.

4-Methyl-2-vinylbenzonitrile (S23):

Was produced from 2-bromo-4-methylbenzonitrile (S23a, 294.1 mg, 1.5 mmol) following the general procedure 2A. Purification by flash column chromatography (20:1 n-pentane/MTBE) afforded the product in 75% yield (S23, 161.1 mg).

\[ ^1H \text{ NMR (500 MHz, CDCl}_3 \delta 7.51 (d, } J = 7.9 \text{ Hz, 1H), 7.46 (s, 1H), 7.15 (d, } J = 7.9 \text{ Hz, 1H), 7.04 (dd, } J = 17.4, 11.0 \text{ Hz, 1H), 5.93 (d, } J = 17.4 \text{ Hz, 1H), 5.51 (d, } J = 11.0 \text{ Hz, 1H), 2.42 (s, 3H).} \]

\[ ^13C \text{ NMR (125 MHz, CDCl}_3 \delta 143.66, 140.65, 133.15, 132.95, 129.05, 126.19, 118.68, 118.24, 108.42, 22.03.} \]

HRMS-EI (m/z): [M]^+ calcd for C10H9N, 143.072949; found 143.073040.

4-Fluoro-2-vinylbenzonitrile (S24) (the spectral data are consistent with those reported in the literature.\(^{143}\))

Was produced from 2-chloro-4-fluorobenzonitrile (S24a, 233.3 mg, 1.5 mmol) following the general procedure 2A. Purification by flash column chromatography (20:1 n-pentane/MTBE) afforded the product in 77% yield (S24, 169.9 mg).

\[ ^1H \text{ NMR} \ (500 \text{ MHz, CDCl}_3) \delta 7.64 \text{ (dd, } J = 8.6, 5.5 \text{ Hz, 1H), 7.34 \text{ (dd, } J = 9.7, 2.5 \text{ Hz, 1H), 7.10} - 6.98 \text{ (m, 2H), 5.95 \text{ (d, } J = 17.3 \text{ Hz, 1H), 5.61 \text{ (d, } J = 10.9 \text{ Hz, 1H).} \]

\[ ^{13}C \text{ NMR} \ (125 \text{ MHz, CDCl}_3) \delta 165.24 \text{ (d, } J = 253.75 \text{ Hz), 143.88 \text{ (d, } J = 10.00 \text{ Hz), 135.36 \text{ (d, } J = 10.00 \text{ Hz), 132.18 \text{ (d, } J = 2.50 \text{ Hz), 120.36, 117.18, 115.94 \text{ (d, } J = 23.75 \text{ Hz), 112.66 \text{ (d, } J = 23.75 \text{ Hz), 107.46 \text{ (d, } J = 2.50 \text{ Hz).} \]

HRMS-EI (m/z): \[ [M]^+ \text{ calcd for C}_{9}H_{6}FN, 147.047877; \text{ found 147.048000.} \]

4,5-Difluoro-2-vinylbenzonitrile (S25):

![4,5-Difluoro-2-vinylbenzonitrile](image)

Was produced from 2-chloro-4,5-difluorobenzonitrile (S25a, 260.3 mg, 1.5 mmol) following the general procedure 2A. Purification by flash column chromatography (20:1 n-pentane/MTBE) afforded the product in 74% yield (S23, 183.3 mg).

\[ ^1H \text{ NMR} \ (500 \text{ MHz, CDCl}_3) \delta 7.46 \text{ (ddd, } J = 9.4, 7.5, 3.7 \text{ Hz, 2H), 7.00 \text{ (ddd, } J = 17.3, 11.0, 1.6 \text{ Hz, 1H), 5.88 \text{ (d, } J = 17.3 \text{ Hz, 1H), 5.60 \text{ (d, } J = 11.0 \text{ Hz, 1H).} \]

\[ ^{13}C \text{ NMR} \ (125 \text{ MHz, CDCl}_3) \delta 154.62, 154.52, 152.57, 152.46, 150.67, 150.56, 148.65, 148.54, 139.30, 139.27, 139.25, 139.21, 131.36, 131.35, 131.34, 121.81, 121.79, 121.65, 121.63, 120.26, 120.25, 116.03, 116.02, 116.01, 115.12, 114.82, 114.67, 107.47, 107.44, 107.41, 107.39. \]

HRMS-EI (m/z): \[ [M]^+ \text{ calcd for C}_{9}H_{5}F_{2}N, 165.038456; \text{ found 165.038560.} \]

2,5-Divinylbenzonitrile (S27) (the spectral data are consistent with those reported in the literature.\textsuperscript{144})

Was produced from 2,5-dichlorobenzonitrile (S27a, 258.0 mg, 1.5 mmol) following the general procedure 2A. Purification by flash column chromatography (20:1 n-pentane/MTBE) afforded the product in 72% yield (S27, 167.6 mg).

\[^1\text{H NMR}\] (500 MHz, CDCl\(_3\)) \(\delta\) 7.65 – 7.56 (m, 3H), 7.05 (dd, \(J = 17.3, 11.0\) Hz, 1H), 6.67 (dd, \(J = 17.6, 10.9\) Hz, 1H), 5.94 (d, \(J = 17.4\) Hz, 1H), 5.81 (d, \(J = 17.6\) Hz, 1H), 5.52 (d, \(J = 11.1\) Hz, 1H), 5.38 (d, \(J = 10.9\) Hz, 1H).

\[^{13}\text{C NMR}\] (125 MHz, CDCl\(_3\)) \(\delta\) 139.76, 137.70, 134.62, 132.69, 130.68, 130.34, 125.72, 118.80, 117.82, 116.47, 111.63.

\[^{1}\text{HRMS-EI (m/z)}\]: [M]\(^+\) calcd for C\(_{11}\)H\(_9\)N, 155.072949; found 155.073070.

6-Vinylbenzo[d][1,3]dioxole-5-carbonitrile (S29) (the spectral data are consistent with those reported in the literature.\(^2\))

Was produced from 6-bromobenzo[d][1,3]dioxole-5-carbonitrile (S29a, 339.0 mg, 1.5 mmol) following the general procedure 2A. Purification by flash column chromatography (10:1 n-pentane/MTBE) afforded the product in 72% yield (S29, 1837.0 mg).

\[^1\text{H NMR}\] (500 MHz, CDCl\(_3\)) \(\delta\) 7.09 (br, 1H), 7.05 – 6.95 (m, 2H), 6.06 (s, 2H), 5.77 (d, \(J = 17.3\) Hz, 1H), 5.44 (d, \(J = 10.8\) Hz, 1H).

\[^{13}\text{C NMR}\] (125 MHz, CDCl\(_3\)) \(\delta\) 152.02, 147.60, 137.72, 132.67, 117.97, 117.43, 111.21, 105.05, 104.21, 102.53.

\[^{1}\text{HRMS-EI (m/z)}\]: [M]\(^+\) calcd for C\(_{10}\)H\(_7\)NO\(_2\), 173.047129; found 173.047240.
2-(2-Vinylphenyl) acetonitrile (S212) (the spectral data are consistent with those reported in the literature.)

![Structure of 2-(2-Vinylphenyl) acetonitrile (S212)]

Was produced from 4-chloro-2-vinylbenzonitrile (S212a, 294.1 mg, 1.5 mmol) following the general procedure 2A. Purification by flash column chromatography (10:1 n-pentane/MTBE) afforded the product in 77% yield (S212, 152.5 mg).

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.51 (dd, $J = 7.5$, 1.6 Hz, 1H), 7.41 – 7.37 (m, 1H), 7.37 – 7.28 (m, 2H), 6.85 (dd, $J = 17.2$, 10.9 Hz, 1H), 5.70 (dd, $J = 17.2$, 1.1 Hz, 1H), 5.45 (dd, $J = 11.0$, 1.1 Hz, 1H), 3.76 (s, 2H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 137.00, 133.07, 128.97, 128.74, 128.54, 127.21, 126.83, 118.42, 117.70, 21.85.

HRMS-EI (m/z): [M+H]$^+$ calcld for C$_{10}$H$_{10}$N, 144.080774; found 144.080790.

Synthesis of 2-chloro-4-fluorobenzonitrile (S26)

![Synthesis of 2-chloro-4-fluorobenzonitrile (S26)]

To a stirred slurry of (Ph$_3$PCH$_3$)Br (6.4 g, 18 mmol) in anhydrous THF (40 mL) was added n-BuLi (7.2 mL, 18 mmol, 2.5M solution in hexane) at 0 °C under an argon atmosphere and the resulting solution was allowed to stir at room temperature for 1.5 hours. The solution was cooled to 0 °C and added dropwise to a solution of 2-bromo-5-chlorobenzaldehyde (S26a, 3.3 g, 15 mmol) in anhydrous THF (20 mL). The resulting solution was then stirred at room temperature for another 2 hours. After diluting with ethyl acetate and quenching with saturated aqueous NH$_4$Cl was added (40 mL). The resulting reaction mixture was then extracted with ethyl acetate (3 x 60 mL). The combined organic phase was washed with bine, dried over sodium sulfate,

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filtered and concentrated under reduced pressure. Purification by flash column chromatography (100% n-pentane) afforded 1-bromo-4-chloro-2-vinylbenzene in 60% yield (S26b, 1.96 g.).

To a solution of 1-bromo-4-chloro-2-vinylbenzene (S26b, 1.74 g, 8 mmol) in DMF (60 mL) was added CuCN (1.43 g, 16 mmol) at room temperature and the mixture was stirred at 150 °C for 16 hours. After cooling the reaction mixture to room temperature and diluting with MTBE, saturated aqueous solution of sodium carbonate was added to quench the reaction and the resulting mixture was extracted with MTBE (3 x 50 mL). The combined organic phase was washed several times with brine, dried over sodium sulfate and concentrated under reduced pressure. Purification of the crude product with flash column chromatography on silica gel (20:1 pentane/MTBE) afforded the product in 70% yield (S26, 916 mg).

Characterization of S26

\[ ^1H\text{ NMR}\ (500\text{ MHz, CDCl}_3) \delta\ 7.64\ (d,\ J = 2.0\ Hz,\ 1H),\ 7.57\ (d,\ J = 8.4\ Hz,\ 1H),\ 7.33\ (dd,\ J = 8.3,\ 2.0\ Hz,\ 1H),\ 7.02\ (dd,\ J = 17.4,\ 11.0\ Hz,\ 1H),\ 5.96\ (d,\ J = 17.4\ Hz,\ 1H),\ 5.61\ (d,\ J = 11.0\ Hz,\ 1H).\]

\[ ^13C\text{ NMR}\ (125\text{ MHz, CDCl}_3) \delta\ 142.44,\ 139.66,\ 134.13,\ 132.02,\ 128.47,\ 125.93,\ 120.47,\ 117.15,\ 109.66.\]

HRMS - EI (m/z): [M]+ calcd for C_{9}H_{6}ClN, 163.018327; found 163.018370.

Synthesis of 4-(phenylethynyl)-2-vinylbenzonitrile (S28)

\[ \text{S26} + \text{S28b} \rightarrow \text{S28} \]

A Schlenk tube equipped with a magnetic stirring bar was charged with 4-chloro-2-vinylbenzonitrile (S26, 245.4 mg, 1.5 mmol), Tetrakis(triphenylphosphin)palladium (86.7 mg, 0.075 mmol), sodium carbonate (349.8 mg, 3.3 mmol), 2-Phenyl-1-ethynylboronic acid pinacol ester (S28b, 513.2 mg, 2.25 mmol) and 1,4-dioxane/ethanol/water (5:3:2, 3.0 mL) under an argon atmosphere. The tube was then placed on the heating plate and the solution was stirred at
120 °C in an oil bath. After stirring for 20 h, the solution was cooled to room temperature, diluted with water (3.0 mL) and extracted with MTBE (10.0 mL × 3). The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give crude product. Purification of the crude product by flash column chromatography (20:1 n-pentane/MTBE) afforded the product in 72% yield (S28, 247.6 mg).

**Characterization of S28**

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.80 (d, $J = 1.5$ Hz, 1H), 7.61 (d, $J = 8.0$ Hz, 1H), 7.57 – 7.54 (m, 2H), 7.47 (dd, $J = 8.0, 1.6$ Hz, 1H), 7.41 – 7.36 (m, 3H), 7.06 (dd, $J = 17.4, 11.0$ Hz, 1H), 6.00 (d, $J = 17.4$ Hz, 1H), 5.59 (d, $J = 11.1$ Hz, 1H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 140.87, 132.94, 132.47, 131.94, 130.84, 129.26, 128.65, 128.59, 128.33, 122.37, 119.82, 117.66, 110.42, 93.57, 87.94.

HRMS-EI (m/z): [M]$^+$ calcd for C$_{17}$H$_{11}$N, 229.088599; found 229.088650.

**Synthesis of 2-vinylthiophene-3-carbonitrile (S210)**

\[
\begin{align*}
\text{S210a} & \xrightarrow{(PPh_3CH_3)Br (1.2 \text{ eq.})} \text{S210b} & \xrightarrow{\text{CuCN (2.0 eq.)}} \text{S210}
\end{align*}
\]

To a stirred slurry of (Ph$_3$PCH$_3$)Br (2.14 g, 6 mmol) in anhydrous THF (20 mL) was added $n$-BuLi (2.4 mL, 6 mmol, 2.5M solution in hexane) at 0 °C under an argon atmosphere and the resulting solution was allowed to stir at room temperature for 1.5 hours. After cooling to 0 °C, the solution was added dropwise a solution of 3-bromothiophene-2-carbaldehyde (S210a, 955 mg, 5 mmol) in anhydrous THF (10 mL). The resulting solution was then stirred at room temperature for another 2 hours. After diluting the with ethyl acetate and quenching with saturated aqueous NH$_4$Cl was added (20 mL). The reaction mixture was then extracted with ethyl acetate (3 x 60 mL). The combined organic phase was washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. Purification of the resulting crude
product by flash column chromatography (100% n-pentane) afforded 3-bromo-2-vinylthiophene in 68% yield (S210b, 642.8 mg).

To a solution of 3-bromo-2-vinylthiophene (S210b, 378 mg, 2 mmol) in DMF (15 mL) was added CuCN (358.2 mg, 4 mmol) at room temperature and the mixture was then allowed to stir at 150 °C for 16 hours. After cooling the reaction mixture to room temperature and diluting with MTBE, saturated aqueous solution of sodium carbonate was added to quench the reaction and the mixture was extracted with MTBE (3 x 30 mL). The combined organic phase was washed several times with brine, dried over sodium sulfate and concentrated under reduced pressure. Purification of the resulting crude product by flash column chromatography on silica gel (20:1 pentane/MTBE) afforded the product in 71% yield (S210, 192.0 mg).

Characterization of S210

^1H NMR (500 MHz, CDCl$_3$) δ 7.21 (d, $J = 5.3$ Hz, 1H), 7.15 (d, $J = 5.3$ Hz, 1H), 7.01 (ddd, $J = 17.4$, 10.9, 0.8 Hz, 1H), 5.85 (d, $J = 17.3$ Hz, 1H), 5.48 (d, $J = 11.0$ Hz, 1H).

^13C NMR (125 MHz, CDCl$_3$) δ 152.41, 129.01, 127.11, 125.03, 118.99, 114.82, 108.36.

HRMS-EI (m/z): [M]$^+$ calcd for C$_7$H$_5$NS, 135.013721; found 135.013750.

Synthesis of 4-(benzofuran-2-yl)-2-vinylbenzonitrile (S211)

A Schlenk tube equipped with a magnetic stirring bar was charged with 4-chloro-2-vinylbenzonitrile (S26, 245.4 mg, 1.5 mmol), Tetrakis(triphenylphosphin)palladium (86.7 mg, 0.075 mmol), sodium carbonate (349.8 mg, 3.3 mmol), benzofuran-2-ylboronic acid (S211a, 364.4 mg, 2.25 mmol) and 1,4-dioxane/ethanol/water (5:3:2, 3.0 mL) under an argon atmosphere. The solution was stirred at 120 °C in an oil bath. After stirring for 20 h, the solution was cooled to room temperature, diluted with water (3.0 mL) and extracted with MTBE (10.0 mL x 3). The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated.
under reduced pressure to give crude product. Purification of the crude product by flash column chromatography (20:1 n-pentane/MTBE) afforded the product in 57% yield (S211, 209.7 mg).

**Characterization of S211**

**1H NMR (500 MHz, CDCl₃)** δ 8.13 (d, J = 1.6 Hz, 1H), 7.80 (dd, J = 8.1, 1.6 Hz, 1H), 7.69 (d, J = 8.1 Hz, 1H), 7.63 (dt, J = 7.7, 1.1 Hz, 1H), 7.56 (dq, J = 8.3, 0.9 Hz, 1H), 7.36 (ddd, J = 8.4, 7.2, 1.3 Hz, 1H), 7.30 – 7.26 (m, 1H), 7.20 (d, J = 0.8 Hz, 1H), 7.12 (dd, J = 17.4, 11.0 Hz, 1H), 6.10 (d, J = 17.4 Hz, 1H), 5.63 (d, J = 11.0 Hz, 1H).

**13C NMR (125 MHz, CDCl₃)** δ 155.39, 153.73, 141.40, 141.40, 133.51, 132.89, 128.81, 125.70, 124.17, 123.59, 121.64, 121.53, 119.74, 117.88, 111.58, 110.45, 104.54.

**HRMS-EL (m/z):** [M+H]+ calcd for C₁₇H₁₂NO, 246.091339; found 246.091310.

**Synthesis of (E)-2-(prop-1-en-1-yl)benzonitrile (S213):**

A Schlenk tube equipped with a magnetic stirring bar was charged with 4-chloro-2-vinylbenzonitrile (S21a, 273.0 mg, 1.5 mmol), Tetrakis(triphenylphosphin)palladium (86.7 mg, 0.075 mmol), sodium carbonate (349.8 mg, 3.3 mmol), (E)-4,4,5,5-tetramethyl-2-(prop-1-en-1-y1)-1,3,2-dioxaborolane (S213a, 378.1 mg, 2.25 mmol) and 1,4-dioxane/ethanol/water (5:3:2, 3.0 mL) under an argon atmosphere. The solution was stirred at 120 °C in an oil bath. After stirring for 20 h, the solution was cooled to room temperature, diluted with water (3.0 mL) and extracted with MTBE (10.0 mL × 3). The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give crude product. Purification by flash column chromatography (20:1 n-pentane/MTBE) afforded the product in 74% yield (S213, 158.9 mg).
Characterization of S213 (the spectral data are consistent with those reported in the literature.\textsuperscript{146})

\textbf{\textsuperscript{1}H NMR} (500 MHz, CDCl\textsubscript{3}) \(\delta\) 7.62 – 7.56 (m, 2H), 7.50 (td, \(J = 8.8, 8.0, 1.0\) Hz, 1H), 7.31 – 7.21 (m, 1H), 6.76 (dd, \(J = 15.7, 1.7\) Hz, 1H), 6.45 (dq, \(J = 15.6, 6.7\) Hz, 1H), 1.96 (dd, \(J = 6.7, 1.8\) Hz, 3H);

\textbf{\textsuperscript{13}C NMR} (125 MHz, CDCl\textsubscript{3}) \(\delta\) 141.29, 132.98, 132.75, 131.60, 127.32, 127.00, 125.41, 118.28, 110.42, 18.91.

\textbf{HRMS-EI} (m/z): [M]\textsuperscript{+} calcd for C\textsubscript{10}H\textsubscript{9}N, 143.072949; found 143.073050.

**Synthesis of 2-(vinyl-1-\textit{d}) benzonitrile (S21-D) (the procedure was reported in the literature.\textsuperscript{147})**

\[
\begin{align*}
\text{S21-D1} & \xrightarrow{\text{Ni(dppp)Cl}_2 (3 \text{ mol\%})} \xrightarrow{\text{DIBAL-H (1.3 eq.)}} \text{DIBAL-H} (1.3 \text{ eq.}) \xrightarrow{\text{THF, 0 \text{°C to RT} D}_2\text{O}} \text{S21-D2} & \xrightarrow{\text{CuCN (2.0 eq.)}} \text{DMF, 150 \text{°C}} \rightarrow \text{S21-D}
\end{align*}
\]

To an oven-dried Schlenk tube equipped with a magnetic stirring bar was added commercial grade 1,3-bis(diphenylphosphino)propane nickel(II) chloride (162.6 mg, 0.3 mmol). The tube was sealed with a septum and purged with argon for about 10 minutes. Tetrahydrofuran (10 mL) was then added via a syringe, which was followed by dropwise addition of commercial grade di-\textit{iso}-butylaluminum hydride (13.0 mL, 13 mmol, 1M in THF) at 22 °C (gas evolution occurs as DIBAL-H was added). The resulting black solution was cooled to 0 °C and 1-bromo-2-ethynylbenzene (S21-D1, 1.2 mL, 10 mmol) was slowly added over 30 minutes (please note the reaction was exothermic). Upon completion of the addition, the solution was allowed to warm to 22 °C and stir at this temperature for additional two hours. Then the reaction mixture was cooled to 0 °C (ice bath) and Deuterium oxide (D\textsubscript{2}O, 1.0 mL) was added dropwise to the cool mixture. After stirring at 0 °C for additional 30 minutes, the mixture was extracted with MTBE (10.0 mL x 3) and the combined organic phases were dried over magnesium sulfate, filtered and concentrated under reduced pressure to afford the crude product as a yellow oil. Purification by


flash column chromatography (100% n-pentane) afforded 1-bromo-2-(vinyl-1-d) benzene in 98% yield (S21-D2, 1.8 g, deuteration level >98% based on 1HNMR).

To a solution of 1-bromo-2-(vinyl-1-d) benzene (S21-D2, 920 mg, 5.0 mmol) in DMF (35.0 mL) was added CuCN (895.6 mg, 10.0 mmol) at room temperature and the mixture was then allowed to stir at 150 °C for 16 hours. After cooling the reaction mixture to room temperature and diluting with MTBE, saturated aqueous solution of sodium carbonate was added to quench the reaction and the mixture was extracted with MTBE (50.0 mL x 3). The combined organic phase was washed several times with brine, dried over sodium sulfate and concentrated under reduced pressure. Purification of the resulting crude product by flash column chromatography on silica gel (20:1 pentane/MTBE) afforded 2-(vinyl-1-d) benzonitrile in 70% yield (S21-D, 455.6 mg, deuteration level >98% based on 1HNMR).

**Characterization of S21-D**

1H NMR (500 MHz, CDCl3) δ 7.69 – 7.65 (m, 1H), 7.63 (ddd, J = 7.8, 1.3, 0.5 Hz, 1H), 7.59 – 7.52 (m, 1H), 7.34 (td, J = 7.6, 1.1 Hz, 1H), 5.96 – 5.93 (m, 1H), 5.55 – 5.52 (m, 1H).

13C NMR (125 MHz, CDCl3) δ 140.72, 133.04, 132.85, 132.71 (t, J = 23.75 Hz), 128.08, 125.54, 118.90, 117.90, 111.27.

HRMS-EI (m/z): [M]+ calcd for C9H6DN, 130.063576; found 130.063720.

6.1.2. General Procedures for Nickel-Catalyzed Intramolecular MH-type Reaction of Aryl Cyanides

**General procedure 2B: For optimization of reaction conditions**

A catalyst and a ligand were placed in a 4 mL screw-cap vial equipped with a magnetic stirring bar under an argon atmosphere inside a glovebox. Solvent was added and the resulting mixture
was allowed to stir at room temperature in the glovebox for approximately 10 minutes till the catalyst and ligand were dissolved in the solvent, which resulted in an orange solution. To this solution 2-vinylbenzonitrile (S21, 0.25 mmol), 4-octyne (S22, 0.5 mmol) and the Lewis acid were then added and the vial was sealed tightly. The vial was moved out of the glovebox, placed on the heating plate and was allowed to heat and stir. Upon completion of the reaction, the mixture was cooled down to room temperature and isooctane (50.0 μL) was added as an internal standard, and the reaction mixture was analyzed by GC to determine the yield and ratio of isomers.

**General procedure 2C: For scope study**

![Chemical structure](image)

Bis(cycloocta-1,5-dien) nickel (6.9 mg, 10 mol%, 0.025 mmol) and triphenylphosphine (13.1 mg, 20 mol%, 0.05 mmol) were placed in a 4 mL screw-cap vial equipped with a magnetic stirring bar under an argon atmosphere inside a glovebox. Toluene (0.5 mL) was added and the resulting mixture was allowed to stir at room temperature in the glovebox for approximately 10 minutes till the catalyst and ligand were dissolved in the solvent, which resulted in an orange solution. To this solution arylnitrile (0.25 mmol), alkyne (0.5 mmol) and dimethylaluminum chloride (1.0 M solution in hexane, 100.0 μL, 40 mol%, 0.1 mmol) were then added subsequently and the vial was sealed tightly. The vial was moved out of the glovebox, placed on the heating plate and was then allowed to heat and stir at 60 °C. After reacting for 16 hours, the reaction was cooled to room temperature and isooctane (50.0 μL) was added as an internal standard to the solution for GC analysis. After completion of GC measurement, the crude reaction mixture was purified with flash column chromatography on silica gel to afford the desired products and the corresponding hydrocyanation products.

### 6.1.3. General Procedures for Palladium-Catalyzed Intermolecular MH-type Reaction of Aryl Cyanides
**General procedure 2D: For optimization of reaction conditions**

A catalyst and a ligand were placed in a 4 mL screw-cap vial equipped with a magnetic stirring bar under an argon atmosphere inside a glovebox. Solvent was added and the resulting mixture was allowed to stir at room temperature in the glovebox for approximately 10 minutes, which resulted in a brown solution. To this solution benzonitrile (S221, 0.2 mmol), styrene, the Lewis acid and additive were then added subsequently and the vial was sealed tightly. The vial was moved out of the glovebox, placed on the heating plate and was allowed to heat and stir. Upon completion of the reaction, the mixture was cooled to room temperature and n-dodecane (40.0 μL) was added as an internal standard, and the reaction mixture was analyzed by GC to determine the yield and ratio of isomers.

**General procedure 2E: For scope study**

To a 4.0 mL screw-cap vial equipped with a magnetic stirring bar was added tris(dibenzylidenaceton)dipalladium (4.6 mg, 2.5 mol%, 0.005 mmol) and 2-(Dicyclohexylphosphino)biphenyl (7.0 mg, 10 mol%, 0.02 mmol) inside a glovebox. Toluene (0.25 mL) was added and the resulting mixture was allowed to stir at room temperature in the glovebox for approximately 10 minutes, which resulted in a brown solution. To this solution aryl nitrile (0.2 mmol), alkene (1.0 mmol) and dimethylaluminum chloride (1.0 M solution in hexane, 40.0 μL, 20 mol%, 0.04 mmol) were then added and the vial was sealed tightly. The vial was moved out of the glovebox, placed on the heating plate and was then allowed to heat and stir at 100 °C. After reacting for 16 hours, the reaction was cooled to room temperature and diluted with MTBE (1.0 mL). After completion of TLC analysis, the solvent was removed with the aid...
of rotary evaporator under reduced pressure. Purification of the residue by flash column chromatography on silica gel afforded the desired products.

6.1.4. Characterization of Products

**Methylene-2,3-dipropyl-1H-indene** (21, Table 2.4, entry 1, 43.0 mg, 81% isolated yield)

![Methylene-2,3-dipropyl-1H-indene](image)

Was produced by reacting 2-vinylbenzonitrile with 4-octyne under the standard conditions. Following the general procedure 2C, the product was obtained after purification by flash column chromatography on silica gel using 100% n-pentane as eluent. The hydrocyanation product was formed as a mixture of stereoisomers (67%, E/Z = 90/10).

**1H NMR** (500 MHz, CDCl₃) δ 7.53 (dt, J = 7.3, 1.0 Hz, 1H), 7.24 (td, J = 7.4, 1.1 Hz, 1H), 7.18 (d, J = 7.3 Hz, 1H), 7.13 (td, J = 7.4, 1.2 Hz, 1H), 5.94 (s, 1H), 5.61 (s, 1H), 2.56 – 2.52 (m, 2H), 2.51 – 2.46 (m, 2H), 1.67 – 1.60 (m, 2H), 1.59 – 1.53 (m, 2H), 1.01 (t, J = 6.9 Hz, 3H), 0.98 (t, J = 6.9 Hz, 3H);

**13C NMR** (125 MHz, CDCl₃) δ 147.70, 143.91, 141.70, 136.53, 136.49, 127.94, 124.59, 119.16, 118.28, 108.92, 27.96, 26.94, 24.50, 22.21, 14.64, 14.56.

**HRMS-EI (m/z):** [M+H]+ calcd for C₁₁H₂₁, 213.163775; found 213.163930.

**6-Methyl-1-methylene-2,3-dipropyl-1H-indene** (23, Table 2.4, entry 2, 39.6 mg, 70% isolated yield)

![6-Methyl-1-methylene-2,3-dipropyl-1H-indene](image)

Was produced by reacting 4-methyl-2-vinylbenzonitrile with 4-octyne under the standard conditions. Following the general procedure 2C, the product was obtained after purification by
flash column chromatography on silica gel using 100% \( n \)-pentane as eluent. The hydrocyanation product was formed as a mixture of stereoisomers (60%, E/Z = 95/5).

\( ^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 7.36 – 7.33 (m, 1H), 7.08 – 7.01 (m, 2H), 5.90 (s, 1H), 5.56 (s, 1H), 2.54 – 2.43 (m, 4H), 2.38 (s, 3H), 1.66 – 1.58 (m, 2H), 1.58 – 1.50 (m, 2H), 0.99 (t, \( J = 6.8 \) Hz, 3H), 0.96 (t, \( J = 6.8 \) Hz, 3H);

\( ^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 147.82, 141.64, 141.38, 136.80, 135.74, 134.23, 128.39, 120.20, 118.01, 108.36, 28.02, 26.93, 24.45, 22.21, 21.60, 14.62, 14.52.

HRMS-EI (m/z): [M]+ calcd for C\(_{17}\)H\(_{22}\), 226.171600; found 226.171570.

6-Fluoro-1-methylene-2,3-dipropyl-1\( H \)-indene (24, Table 2.4, entry 3, 39.6 mg, 89% isolated yield)

\[ \text{Was produced by reacting 4-fluoro-2-vinylbenzonitrile with 4-octyne under the standard conditions. Following the general procedure 2C, the product was obtained after purification by flash column chromatography on silica gel using 100% \( n \)-pentane as eluent. In this case, the trans-hydrocyanation product was isolated by flash column chromatography on silica gel using 20:1 \( n \)-pentane/MTBE as eluent (27.1 mg, 79%). The NMR spectral data are consistent with those reported in the literature.}^{148} \]

6-Fluoro-1-methylene-2,3-dipropyl-1\( H \)-indene

\( ^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 7.20 (dd, \( J = 8.8, 2.3 \) Hz, 1H), 7.06 (dd, \( J = 8.1, 4.9 \) Hz, 1H), 6.91 (ddd, \( J = 9.5, 8.2, 2.4 \) Hz, 1H), 5.90 (s, 1H), 5.62 (s, 1H), 2.53 – 2.48 (m, 2H), 2.48 – 2.42 (m, 2H), 1.65 – 1.57 (m, 2H), 1.57 – 1.49 (m, 2H), 0.99 (t, \( J = 7.5 \) Hz, 3H), 0.97 (t, \( J = 7.5 \) Hz, 3H);

\( ^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 161.72 (d, \( J = 240.00 \) Hz), 147.02 (d, \( J = 2.50 \) Hz), 141.23, 139.71 (d, \( J = 2.50 \) Hz), 138.55 (d, \( J = 7.50 \) Hz), 136.39 (d, \( J = 3.75 \) Hz), 118.73 (d, \( J = 8.75 \) Hz),

113.99 (d, $J = 22.50$ Hz), 109.81, 107.25 (d, $J = 23.75$ Hz), 27.97, 26.98, 24.40, 22.13, 14.60, 14.53.

**HRMS-EI (m/z):** [M]$^+$ calcd for C$_{10}$H$_{19}$F, 230.146528; found 230.146700.

**$(E)$-2-Propylhex-2-enenitrile**

![Propylhex-2-enenitrile](image)

$^1$H NMR (500 MHz, CDCl$_3$) δ 6.35 (tt, $J = 7.6$, 1.2 Hz, 1H), 2.20 – 2.12 (m, 4H), 1.57 (h, $J = 7.4$ Hz, 2H), 1.45 (h, $J = 7.4$ Hz, 2H), 0.94 (q, $J = 7.3$ Hz, 6H);

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 148.28, 120.35, 115.03, 30.54, 30.51, 21.92, 21.43, 13.84, 13.49.

**HRMS-ESI (m/z):** [M+Na]$^+$ calcd for C$_9$H$_{15}$NNa, 160.109668; found 160.109800.

**5,6-Difluoro-1-methylene-2,3-dipropyl-1H-indene (25, Table 2.4, entry 4, 54.6 mg, 88% isolated yield)**

![5,6-Difluoro-1-methylene-2,3-dipropyl-1H-indene](image)

Was produced by reacting 4,5-difluoro-2-vinylbenzonitrile with 4-octyne under the standard conditions. Following the general procedure 2C, the product was obtained after purification by flash column chromatography on silica gel using 100% n-pentane as eluent. The hydrocyanation product was formed as a mixture of stereoisomers (82%, E/Z = 94/6).

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.31 – 7.24 (m, 1H), 6.92 (dd, $J = 10.3$, 7.2 Hz, 1H), 5.85 (s, 1H), 5.63 (s, 1H), 2.50 – 2.43 (m, 4H), 1.62 – 1.50 (m, 4H), 0.99 (t, $J = 7.5$ Hz, 3H), 0.96 (t, $J = 7.5$ Hz, 3H);

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 151.75, 151.64, 149.80, 149.76, 149.69, 149.65, 147.82, 147.71, 146.39, 140.39, 140.37, 140.36, 140.20, 140.18, 140.15, 140.12, 137.82, 137.78, 132.39, 132.37,

**HRMS-EI (m/z):** [M]$^+$ calcd for C$_{16}$H$_{18}$F$_2$, 248.137107; found 248.137180.

**6-Chloro-1-methylene-2,3-dipropyl-1H-indene (26, Table 2.4, entry 5, 37.0 mg, 60% isolated yield)**

![Chemical structure](image)

Was produced by reacting 4-chloro-2-vinylbenzonitrile with 4-octyne under the standard conditions. Following the general procedure 2C, the product was obtained after purification by flash column chromatography on silica gel using 100% n-pentane as eluent. The hydrocyanation product was formed as a mixture of stereoisomers (48%, E/Z = 51/49).

**$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.46 (d, $J$ = 1.9 Hz, 1H), 7.20 (dd, $J$ = 7.9, 1.9 Hz, 1H), 7.07 (d, $J$ = 7.9 Hz, 1H), 5.92 (s, 1H), 5.64 (s, 1H), 2.53 – 2.43 (m, 4H), 1.64 – 1.50 (m, 4H), 1.01 – 0.98 (m, 3H), 0.98 – 0.95 (m, 3H);

**$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 146.86, 142.27, 141.25, 138.21, 137.05, 130.59, 127.61, 119.80, 119.06, 110.16, 27.90, 26.97, 24.39, 22.15, 14.57, 14.52.

**HRMS-EI (m/z):** [M]$^+$ calcd for C$_{16}$H$_{19}$Cl, 246.116978; found 246.117110.

**1-Methylene-2,3-dipropyl-5-vinyl-1H-indene (27, Table 2.4, entry 6, 45.3 mg, 76% isolated yield)**

![Chemical structure](image)

Was produced by reacting 2,5-divinylbenzonitrile with 4-octyne under the standard conditions. Following the general procedure 2C, the product was obtained after purification by flash column
chromatography on silica gel using 100% n-pentane as eluent. The hydrocyanation product was formed as a mixture of stereoisomers (71%, E/Z >99/1).

**1H NMR** (500 MHz, CDCl₃) δ 7.47 (d, J = 7.6 Hz, 1H), 7.22 (d, J = 1.4 Hz, 1H), 7.17 (dd, J = 7.6, 1.2 Hz, 1H), 6.77 (dd, J = 17.6, 10.9 Hz, 1H), 5.91 (s, 1H), 5.76 (dd, J = 17.6, 0.9 Hz, 1H), 5.59 (s, 1H), 5.23 (dd, J = 10.9, 0.9 Hz, 1H), 2.58 – 2.52 (m, 2H), 2.51 – 2.45 (m, 2H), 1.68 – 1.60 (m, 2H), 1.59 – 1.52 (m, 2H), 1.01 (t, J = 7.4 Hz, 3H), 0.97 (t, J = 7.4 Hz, 3H);

**13C NMR** (125 MHz, CDCl₃) δ 147.41, 144.30, 141.44, 137.63, 137.55, 137.30, 136.27, 123.13, 119.24, 115.86, 113.14, 108.93, 27.90, 27.00, 24.43, 22.25, 14.64, 14.54.

**HRMS-EI (m/z):** [M]+ calcd for C₁₈H₂₂, 238.172150; found 238.172037.

1-Methylene-6-(phenylethenyl)-2,3-dipropyl-1H-indene (28, Table 2.4, entry 7, 45.3 mg, 58% isolated yield)

![Diagram of 1-Methylene-6-(phenylethenyl)-2,3-dipropyl-1H-indene](Image)

Was produced by reacting 4-(phenylethenyl)-2-vinylbenzonitrile with 4-octyne under the standard conditions. Following the general procedure 2C, the product was obtained after purification by flash column chromatography on silica gel using 100% n-pentane as eluent. The hydrocyanation product was formed as a mixture of stereoisomers (50%, E/Z >99/1).

**1H NMR** (500 MHz, CDCl₃) δ 7.68 (dd, J = 1.4, 0.5 Hz, 1H), 7.56 – 7.52 (m, 2H), 7.43 (dd, J = 7.7, 1.5 Hz, 1H), 7.38 – 7.31 (m, 3H), 7.17 – 7.13 (m, 1H), 5.98 (s, 1H), 5.65 (s, 1H), 2.57 – 2.44 (m, 4H), 1.66 – 1.52 (m, 4H), 1.01 (t, J = 7.5 Hz, 3H), 0.98 (t, J = 7.5 Hz, 3H);

**13C NMR** (125 MHz, CDCl₃) δ 147.10, 143.97, 141.77, 138.18, 136.54, 131.65, 131.58, 128.45, 128.08, 123.82, 122.39, 119.12, 118.21, 109.90, 90.75, 88.90, 27.91, 27.05, 24.45, 22.25, 14.61, 14.57.

**HRMS-EI (m/z):** [M]+ calcd for C₂₄H₂₄, 312.187250; found 312.187150.
5-Methylene-6,7-dipropyl-5H-indeno[5,6-d][1,3]dioxole (29, Table 2.4, entry 8, 44.9 mg, 70% isolated yield)

Was produced by reacting 6-vinylbenzo[d][1,3]dioxole-5-carbonitrile with 4-octyne under the standard conditions. Following the general procedure 2C, the product was obtained after purification by flash column chromatography on silica gel using 100% n-pentane as eluent. The hydrocyanation product was formed as a mixture of stereoisomers (70%, E/Z = 99/1).

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.03 (s, 1H), 6.68 (s, 1H), 5.93 (s, 2H), 5.78 (s, 1H), 5.53 (s, 1H), 2.49 – 2.39 (m, 4H), 1.63 – 1.48 (m, 4H), 0.97 (dt, $J = 14.9$, 7.4 Hz, 6H);

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 147.72, 147.35, 145.33, 140.96, 138.74, 135.29, 130.27, 108.44, 101.48, 101.01, 100.21, 28.01, 27.03, 24.67, 22.18, 14.60, 14.51.

HRMS-EI (m/z): [M+H]$^+$ calcd for C$_{17}$H$_{21}$O$_2$, 257.153605; found 257.153620.

6-Methylene-4,5-dipropyl-6H-cyclopenta[b]thiophene (210, Table 2.4, entry 9, 43.7 mg, 80% isolated yield)

Was produced by reacting 2-vinylthiophene-3-carbonitrile with 4-octyne under the standard conditions. Following the general procedure 2C, the product was obtained after purification by flash column chromatography on silica gel using 100% n-pentane as eluent. The hydrocyanation product was formed as a mixture of stereoisomers (68%, E/Z = 99/1).

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.19 (d, $J = 4.7$ Hz, 1H), 6.86 (d, $J = 4.7$ Hz, 1H), 5.73 (s, 1H), 5.56 (s, 1H), 2.47 – 2.43 (m, 2H), 2.42 – 2.37 (m, 2H), 1.67 – 1.59 (m, 2H), 1.57 – 1.48 (m, 2H), 1.01 – 0.97 (m, 3H), 0.97 – 0.94 (m, 3H);
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$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 151.25, 144.42, 138.48, 135.55, 134.98, 126.97, 118.91, 111.44, 29.33, 27.09, 25.12, 22.22, 14.47, 14.39.

HRMS-EI (m/z): [M]$^+$ calcd for C$_{14}$H$_{18}$S, 218.112923; found 218.112767.

2-(1-Methylene-2,3-dipropyl-1H-inden-6-yl)benzofuran (211, Table 2.4, entry 10, 37.0 mg, 45% isolated yield)

![2-(1-Methylene-2,3-dipropyl-1H-inden-6-yl)benzofuran](image)

Was produced by reacting 4-(benzofuran-2-yl)-2-vinylbenzonitrile with 4-octyne under the standard conditions. Following the general procedure, the product was obtained after purification by flash column chromatography on silica gel using 100% n-pentane as eluent. The hydrocyanation product was formed as a mixture of stereoisomers (32%, E/Z > 99/1).

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.02 (dd, $J = 1.6, 0.6$ Hz, 1H), 7.76 (dd, $J = 7.8, 1.6$ Hz, 1H), 7.59 – 7.56 (m, 1H), 7.53 (dq, $J = 8.1, 0.9$ Hz, 1H), 7.29 – 7.20 (m, 3H), 7.01 (d, $J = 1.0$ Hz, 1H), 6.08 (s, 1H), 5.69 (s, 1H), 2.59 – 2.49 (m, 4H), 1.69 – 1.62 (m, 2H), 1.62 – 1.54 (m, 2H), 1.02 (t, $J = 7.0$ Hz, 3H), 1.00 (t, $J = 7.0$ Hz, 3H);

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 157.01, 154.91, 147.34, 144.36, 141.79, 138.06, 137.06, 129.67, 127.00, 124.85, 123.99, 122.99, 120.76, 118.53, 115.96, 111.16, 109.78, 100.40, 27.95, 27.09, 24.46, 22.29, 14.62, 14.57.

HRMS-EI (m/z): calcd for C$_{24}$H$_{24}$O, 328.182715; found 328.182431.

2,3-Dimethyl-1-methylene-1H-indene (212, Table 2.4, entry 11, 26.2 mg, 67% isolated yield)

![2,3-Dimethyl-1-methylene-1H-indene](image)

Was produced by reacting 2-vinylbenzonitrile with 2-butyne under the standard conditions. Following the general procedure 2C, the product was obtained after purification by flash column
chromatography on silica gel using 100% \textit{n}-pentane as eluent. The spectral data are consistent with those reported in the literature.\textsuperscript{149}

\textbf{\textsuperscript{1}H NMR} (500 MHz, CDCl\textsubscript{3}) \( \delta \) 7.53 – 7.49 (m, 1H), 7.27 – 7.23 (m, 1H), 7.16 – 7.11 (m, 2H), 5.90 (s, 1H), 5.59 (s, 1H), 2.10 (d, \( J = 1.0 \) Hz, 3H), 2.08 (d, \( J = 1.1 \) Hz, 3H);

\textbf{\textsuperscript{13}C NMR} (125 MHz, CDCl\textsubscript{3}) \( \delta \) 148.61, 144.68, 137.22, 136.09, 131.91, 128.04, 124.71, 118.98, 117.70, 108.40, 10.67, 9.79.

\textbf{HRMS-EI ([m/z]}): [M]\textsuperscript{+} calcd for C\textsubscript{12}H\textsubscript{12}, 156.09350; found 156.093490.

\textbf{2,3-Diethyl-1-methylene-1H-indene (213, Table 2.4, entry 12, 33.6 mg, 73\% isolated yield)}

\[
\begin{array}{c}
\text{Et} \\
\text{Et}
\end{array}
\]

Was produced by reacting 2-vinylbenzonitrile with 3-hexyne under the standard conditions. Following the general procedure \textbf{2C}, the product was obtained after purification by flash column chromatography on silica gel using 100\% \textit{n}-pentane as eluent.

\textbf{\textsuperscript{1}H NMR} (500 MHz, CDCl\textsubscript{3}) \( \delta \) 7.53 (dt, \( J = 7.3, 1.0 \) Hz, 1H), 7.24 (dd, \( J = 7.4, 1.1 \) Hz, 1H), 7.19 (d, \( J = 7.3 \) Hz, 1H), 7.13 (td, \( J = 7.4, 1.2 \) Hz, 1H), 5.95 (s, 1H), 5.62 (s, 1H), 2.58 (q, \( J = 7.6 \) Hz, 2H), 2.53 (q, \( J = 7.6 \) Hz, 2H), 1.20 (t, \( J = 7.6 \) Hz, 3H), 1.15 (t, \( J = 7.6 \) Hz, 3H);

\textbf{\textsuperscript{13}C NMR} (125 MHz, CDCl\textsubscript{3}) \( \delta \) 147.27, 144.58, 142.64, 137.50, 136.52, 127.99, 124.65, 119.28, 118.13, 108.74, 18.83, 17.86, 15.99, 13.68.

\textbf{HRMS-EI ([m/z]}): [M]\textsuperscript{+} calcd for C\textsubscript{14}H\textsubscript{16}, 184.124650; found 184.124790.

\textbf{2,3-Dibutyl-1-methylene-1H-indene (214, Table 2.4, entry 13, 53.5 mg, 89\% isolated yield)}

\[
\begin{array}{c}
n\text{-Bu} \\
n\text{-Bu}
\end{array}
\]

Was produced by reacting 2-vinylbenzonitrile with 5-decyne under the standard conditions. Following the general procedure 2C, the product was obtained after purification by flash column chromatography on silica gel using 100% n-pentane as eluent. The trans-hydrocyanation product was isolated in this case by flash column chromatography on silica gel using 20:1 n-pentane/MTBE as eluent (33.5 mg, 81%).

2,3-Dibutyl-1-methylene-1H-indene

\[ ^1\text{H NMR} \ (500 \text{ MHz, CDCl}_3 \delta \ 7.52 \text{ (dt, } J = 7.3, 1.0 \text{ Hz, } 1\text{H}), 7.24 \text{ (td, } J = 7.4, 1.1 \text{ Hz, } 1\text{H}), 7.17 \text{ (d, } J = 7.3 \text{ Hz, } 1\text{H}), 7.12 \text{ (td, } J = 7.4, 1.2 \text{ Hz, } 1\text{H}), 5.93 \text{ (s, } 1\text{H}), 5.60 \text{ (s, } 1\text{H}), 2.57 – 2.52 \text{ (m, } 2\text{H}), 2.52 – 2.47 \text{ (m, } 2\text{H}), 1.61 – 1.54 \text{ (m, } 2\text{H}), 1.53 – 1.47 \text{ (m, } 2\text{H}), 1.47 – 1.36 \text{ (m, } 4\text{H}), 0.95 \text{ (q, } J = 7.2 \text{ Hz, } 6\text{H}); \]

\[ ^{13}\text{C NMR} \ (125 \text{ MHz, CDCl}_3 \delta \ 147.69, 143.92, 141.75, 136.55, 136.51, 127.94, 124.58, 119.16, 118.23, 108.81, 33.53, 31.13, 25.63, 24.62, 23.24, 23.16, 14.19. \]

**HRMS-EI (m/z): \ [M]^+ \text{ calcd for C}_{18}H_{24}, \ 240.087250; \text{ found } 240.187290.**

\((E)-2\)-Butylhept-2-enenitrile

\[ ^1\text{H NMR} \ (500 \text{ MHz, CDCl}_3 \delta \ 6.33 \text{ (tt, } J = 7.6, 1.2 \text{ Hz, } 1\text{H}), 2.24 – 2.12 \text{ (m, } 4\text{H}), 1.56 – 1.48 \text{ (m, } 2\text{H}), 1.44 – 1.30 \text{ (m, } 6\text{H}), 0.92 \text{ (dt, } J = 9.0, 7.2 \text{ Hz, } 6\text{H}); \]

\[ ^{13}\text{C NMR} \ (125 \text{ MHz, CDCl}_3 \delta \ 148.25, 120.41, 115.08, 30.73, 30.29, 28.34, 28.31, 22.43, 22.17, 13.94, 13.93. \]

**HRMS-EI (m/z): \ [M]^+ \text{ calcd for C}_{11}H_{19}N, \ 165.151749; \text{ found } 165.151574.**

2,3-Dibutyl-1-methylene-1H-indene (215, Table 2.4, entry 14, 61.3 mg, 92% isolated yield)
Was produced by reacting 2-vinylbenzonitrile with cyclododecyne under the standard conditions. Following the general procedure 2C, the product was obtained after purification by flash column chromatography on silica gel using 100% n-pentane as eluent. In this case, the trans hydrocyanation product was also isolated by flash column chromatography on silica gel using 20:1 n-pentane/MTBE as eluent (41.6 mg, 87%).

2,3-Dibutyl-1-methylene-1H-indene

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.52 (dt, \(J = 7.4, 1.0\) Hz, 1H), 7.25 – 7.19 (m, 2H), 7.13 (td, \(J = 7.2, 1.6\) Hz, 1H), 5.95 (s, 1H), 5.63 (s, 1H), 2.59 (t, \(J = 7.3\) Hz, 2H), 2.55 (t, \(J = 7.3\) Hz, 2H), 1.82 – 1.75 (m, 2H), 1.74 – 1.67 (m, 2H), 1.55 – 1.49 (m, 4H), 1.41 – 1.31 (m, 8H);

\(^1\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 147.73, 143.88, 142.03, 136.93, 136.59, 127.94, 124.63, 119.06, 118.78, 109.41, 28.87, 26.12, 25.75, 25.72, 24.83, 24.78, 23.16, 22.45, 22.41, 22.20.

HRMS-EI (m/z): [M]\(^+\) calcd for C\(_{20}\)H\(_{26}\), 266.202900; found 266.203010.

(E)-Cyclododec-1-ene-1-carbonitrile

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 6.30 (t, \(J = 8.1\) Hz, 1H), 2.29 (t, \(J = 6.7\) Hz, 2H), 2.25 (q, \(J = 7.2\) Hz, 2H), 1.67 (dt, \(J = 10.7, 6.6\) Hz, 2H), 1.57 – 1.49 (m, 2H), 1.37 – 1.25 (m, 12H);

\(^1\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 148.76, 120.21, 115.34, 26.08, 25.72, 25.35, 24.63, 24.56, 24.11, 24.10, 22.27, 22.05.

HRMS-EI (m/z): [M]\(^+\) calcd for C\(_{13}\)H\(_{21}\)N, 191.166849; found 191.166840.
(1R,4S,4aR,9aS)-9-methylene-2,3,4,4a,9,9a-hexahydro-1H-1,4-methanofluorene (216, Table 2.4, entry 15, 42.2 mg, 86% isolated yield)

![Chemical structure](image)

Was produced by reacting 2-vinylbenzonitrile with norbornene under the standard conditions. Following the general procedure 2C, the product was obtained after purification by flash column chromatography on silica gel using 100% n-pentane as eluent. The spectral data are consistent with those reported in the literature.\(^{150}\) In this case, the hydrocyanation product was also isolated by flash column chromatography on silica gel using 20:1 n-pentane/MTBE as eluent (23.3 mg, 77%).

(1R,4S,4aR,9aS)-9-methylene-2,3,4,4a,9,9a-hexahydro-1H-1,4-methanofluorene

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.44 (d, \(J = 7.6\) Hz, 1H), 7.25 – 7.15 (m, 3H), 5.50 (d, \(J = 2.4\) Hz, 1H), 5.03 (d, \(J = 1.9\) Hz, 1H), 3.06 (d, \(J = 7.0\) Hz, 1H), 2.82 (d, \(J = 7.0\) Hz, 1H), 2.26 (dd, \(J = 16.9, 4.0\) Hz, 2H), 1.68 – 1.61 (m, 1H), 1.61 – 1.54 (m, 1H), 1.46 – 1.40 (m, 1H), 1.39 – 1.33 (m, 1H), 1.02 (dp, \(J = 10.0, 1.9\) Hz, 1H), 0.95 (dp, \(J = 10.1, 1.4\) Hz, 1H);

\(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 154.60, 149.05, 142.73, 128.69, 126.72, 125.25, 120.10, 103.08, 52.35, 52.16, 44.74, 42.64, 32.48, 29.51, 28.77.

HRMS-ESI (m/z): [M+Na]\(^+\) calcd for C\(_{15}\)H\(_{16}\)NNa, 144.078368; found 144.078553.

(1R,2R,4S)-bicyclo [2.2.1] heptane-2-carbonitrile

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 2.59 (d, \(J = 3.5\) Hz, 1H), 2.39 (d, \(J = 3.6\) Hz, 1H), 2.35 (ddd, \(J = 9.1, 4.8, 1.6\) Hz, 1H), 1.85 – 1.76 (m, 1H), 1.73 – 1.66 (m, 1H), 1.64 – 1.50 (m, 3H), 1.41 – 1.34 (m, 1H), 1.27 – 1.14 (m, 2H);

\(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 123.71, 41.90, 37.30, 36.20, 36.13, 31.18, 28.63, 28.50.

HRMS-ESI (m/z): [M+Na]\(^+\) calcd for C\(_8\)H\(_{11}\)NNa, 144.078368; found 144.078553.

1-Methylene-2,3-diphenyl-1H-indene (217, Table 2.4, entry 16, 0 mg, 0% isolated yield)

In this case, a diphenylacetylene was used as reactant and HCN acceptor to react with 2-vinylbenzonitrile under the standard reaction conditions. As a result, 1-methylene-2,3-diphenyl-1H-indene was not detected by GC and the starting materials were recovered. The same result was obtained when the reaction was performed at 100 °C.

*a*: Ethyl 8-(3-methyl-1-methylene-1H-inden-2-yl)octanoate;  
*b*: Ethyl 8-(2-methyl-1-methylene-1H-inden-3-yl)octanoate (218, Table 2.4, entry 17, 47.0 mg, 63% isolated yield, *a/b* = 43/57)

Were produced by reacting 2-vinylbenzonitrile with methyl undec-9-ynoate under the standard conditions. Following the general procedure 2C, the product was obtained as a mixture of region-isomers after purification by flash column chromatography on silica gel using 20:1 *n*-pentane/MTBE as eluent. The hydrocyanation product was isolated in this case also as a mixture of region-isomers by flash column chromatography on silica gel using 2:1 *n*-pentane/MTBE as eluent (27.9 mg, 50%).

*a*: Ethyl 8-(3-methyl-1-methylene-1H-inden-2-yl)octanoate;  
*b*: Ethyl 8-(2-methyl-1-methylene-1H-inden-3-yl)octanoate


1H NMR (500 MHz, CDCl3) δ 7.53 – 7.49 (m, 1H), 7.27 – 7.20 (m, 1H), 7.16 – 7.08 (m, 2H), 5.91 (d, J = 8.0 Hz, 1H), 5.58 (d, J = 3.3 Hz, 1H), 3.66 (s, 3H), 2.52 (dt, J = 18.8, 7.6 Hz, 2H), 2.30 (t, J = 7.5 Hz, 2H), 2.08 (d, J = 18.1 Hz, 3H), 1.65 – 1.47 (m, 4H), 1.37 – 1.30 (m, 6H);

13C NMR (125 MHz, CDCl3) δ 174.42, 148.70, 147.55, 144.52, 143.99, 141.74, 137.24, 136.64, 136.36, 136.17, 131.81, 128.04, 127.96, 124.76, 124.57, 119.14, 119.04, 117.97, 117.82, 108.65, 108.57, 51.59, 34.23, 30.81, 29.72, 29.66, 29.35, 29.34, 29.28, 29.26, 28.60, 25.66, 25.10, 24.70, 10.77, 9.86.


Methyl (E)-10-cyanoundec-9-enoate and Methyl (E)-9-cyanoundec-9-enoate

1H NMR (500 MHz, CDCl3) δ 6.45 – 6.30 (m, 1H), 3.66 (s, 3H), 2.30 (t, J = 7.5 Hz, 2H), 2.22 – 2.11 (m, 2H), 1.87 – 1.77 (m, 3H), 1.65 – 1.59 (m, 2H), 1.56 – 1.49 (m, 1H), 1.44 – 1.36 (m, 1H), 1.35 – 1.29 (m, 6H);

13C NMR (125 MHz, CDCl3) δ 174.34, 174.31, 148.63, 142.69, 120.90, 120.25, 115.99, 109.27, 51.61, 34.17, 34.15, 29.11, 29.08, 28.79, 28.61, 28.26, 27.86, 25.00, 24.98, 14.93, 14.41.

HRMS-EI (m/z): [M+H]+ calcd for C13H22O2, 224.164504; found 224.164260.

1-Methyl-2,3-dipropynaphthalene (219, Table 2.4, 39.6 mg, 70% isolated yield)

\[ \text{Me} \]
\[ \text{n-Pr} \]
\[ \text{n-Pr} \]

In this case, 2-(2-vinylphenyl) acetonitrile (35.8 mg, 0.25 mmol) was used as starting material to react with 4-octyne (55.1 mg, 0.50 mmol) under the conditions consisting of bis(cycloocta-1,5-dien)nickel (6.9 mg, 10 mol%, 0.025 mmol), triphenylphosphine (13.1 mg, 20 mol%, 0.05 mmol) and dimethylaluminum chloride (1.0 M solution in hexane, 100 μL, 40 mol%, 0.1 mmol) in toluene (0.5 mL) at 100 °C for 16 hours following the general procedure 2C. The product was obtained after purification by flash column chromatography on silica gel using 100% n-pentane/MTBE as eluent.
1H NMR (500 MHz, CDCl₃) δ 8.01 (d, J = 8.4 Hz, 1H), 7.75 (d, J = 7.7 Hz, 1H), 7.52 (s, 1H), 7.47 – 7.37 (m, 2H), 2.86 – 2.80 (m, 2H), 2.80 – 2.75 (m, 2H), 2.67 (s, 3H), 1.73 (dq, J = 14.9, 7.4 Hz, 2H), 1.63 – 1.53 (m, 2H), 1.09 (t, J = 7.5 Hz, 3H), 1.07 (t, J = 7.5 Hz, 3H);

13C NMR (125 MHz, CDCl₃) δ 139.27, 137.55, 132.20, 131.82, 131.17, 127.96, 125.85, 125.03, 124.76, 123.99, 36.27, 32.11, 24.66, 24.17, 14.94, 14.86, 14.51.

HRMS-EI (m/z): [M]+ calcd for C₁₇H₂₂, 226.171580; found 226.171600.

5-Methyl-6,7,8,9,10,11,12,13,14,15-decahydrocyclododeca[b]naphthalene (220, Table 2.4, 54.0 mg, 77% isolated yield)

In this case, 2-(2-vinylphenyl) acetonitrile (35.8 mg, 0.25 mmol) was used as starting material to react with cyclododecyne (82.1 mg, 0.50 mmol) under the conditions consisting of bis(cycloocta-1,5-dien)nickel (6.9 mg, 10 mol%, 0.025 mmol), triphenylphosphine (13.1 mg, 20 mol%, 0.05 mmol) and dimethylaluminum chloride (1.0 M solution in hexane, 100 μL, 40 mol%, 0.1 mmol) in toluene (0.5 mL) at 100 °C for 16 hours following the general procedure 2C. The product was obtained after purification by flash column chromatography on silica gel using 100% n-pentane/MTBE as eluent.

1H NMR (500 MHz, CDCl₃) δ 7.99 (d, J = 8.4 Hz, 1H), 7.76 – 7.67 (m, 1H), 7.56 (s, 1H), 7.40 (dddd, J = 19.3, 7.9, 6.7, 1.4 Hz, 2H), 2.95 – 2.89 (m, 2H), 2.86 – 2.80 (m, 2H), 2.67 (s, 3H), 1.83 – 1.76 (m, 2H), 1.75 – 1.68 (m, 2H), 1.66 – 1.56 (m, 6H), 1.55 – 1.51 (m, 2H), 1.51 – 1.44 (m, 4H);

13C NMR (125 MHz, CDCl₃) δ 140.22, 137.65, 132.22, 131.79, 127.85, 126.53, 125.06, 124.82, 123.97, 32.27, 30.83, 28.33, 28.25, 27.86, 27.74, 27.16, 27.04, 23.20, 22.88, 15.18.

HRMS-EI (m/z): [M]+ calcd for C₂₁H₂₈, 280.218550; found 280.218650.

(E)-1,2-diphenylethene (225, Table 2.8, entry 1, 29.6 mg, 82% isolated yield)
Was produced by reacting benzonitrile (S221) with styrene under the standard conditions. Following the general procedure 2E, the product was obtained after purification by flash column chromatography on silica gel. The spectral data are consistent with those reported in the literature.\textsuperscript{151}

\textbf{1H NMR} (500 MHz, CDCl\textsubscript{3}) \(\delta\) 7.56 (d, \(J = 8.0\) Hz, 2H), 7.40 (t, \(J = 7.7\) Hz, 2H), 7.30 (t, \(J = 10.0\) Hz, 1H), 7.15 (s, 1H);
\textbf{13C NMR} (125 MHz, CDCl\textsubscript{3}) \(\delta\) 137.47, 128.84, 128.82, 127.76, 126.65.

\textit{(E)-1-methyl-4-styrylbenzene} (227, Table 2.8, entry 2, 25.3 mg, 65\% isolated yield)

Was produced by reacting 4-methylbenzonitrile (S222) with styrene under the standard conditions. Following the general procedure 2E, the product was obtained after purification by flash column chromatography on silica gel. The spectral data are consistent with those reported in the literature.\textsuperscript{152}

\textbf{1H NMR} (500 MHz, CDCl\textsubscript{3}) \(\delta\) 7.55 – 7.50 (m, 2H), 7.43 (d, \(J = 8.2\) Hz, 2H), 7.37 (t, \(J = 7.7\) Hz, 2H), 7.28 – 7.23 (m, 1H), 7.18 (d, \(J = 7.6\) Hz, 2H), 7.14 (d, \(J = 20.0\) Hz, 1H), 7.09 (d, \(J = 20.0\) Hz, 1H), 2.38 (s, 3H);
\textbf{13C NMR} (125 MHz, CDCl\textsubscript{3}) \(\delta\) 137.66, 134.70, 129.53, 128.79, 128.76, 127.84, 127.54, 126.57, 126.53, 21.40.

\textit{(E)-1-(tert-butyl)-4-styrylbenzene} (228, Table 2.8, entry 3, 36.4 mg, 77\% isolated yield)

Was produced by reacting 4-(tert-butyl)benzonitrile (S223) with styrene under the standard conditions. Following the general procedure 2E, the product was obtained after purification by flash column chromatography on silica gel. The spectral data are consistent with those reported in the literature.\textsuperscript{153}

\[ ^1\text{H NMR} \ (500 \text{ MHz, CDCl}_3) \ \delta \ 7.55 - 7.50 (m, 2H), 7.49 - 7.45 (m, 2H), 7.42 - 7.34 (m, 4H), 7.29 - 7.23 (m, 1H), 7.14 (d, J = 20.0 \text{ Hz}, 1H), 7.09 (d, J = 20.0 \text{ Hz}, 1H), 1.35 (s, 9H); \]
\[ ^{13}\text{C NMR} \ (125 \text{ MHz, CDCl}_3) \ \delta \ 150.93, 137.69, 134.71, 128.79, 128.65, 128.08, 127.55, 126.56, 126.39, 125.76, 34.78, 31.45. \]

(E)-1-methoxy-2-styrylbenzene (229, Table 2.8, entry 4, 29.9 mg, 71% isolated yield)

Was produced by reacting 2-methoxybenzonitrile (S224) with styrene under the standard conditions. Following the general procedure 2E, the product was obtained after purification by flash column chromatography on silica gel. The spectral data are consistent with those reported in the literature.\textsuperscript{154}

\[ ^1\text{H NMR} \ (500 \text{ MHz, CDCl}_3) \ \delta \ 7.61 (dd, J = 7.7, 1.5 \text{ Hz}, 1H), 7.55 (d, J = 7.7 \text{ Hz}, 2H), 7.50 (d, J = 16.5 \text{ Hz}, 1H), 7.36 (t, J = 7.7 \text{ Hz}, 2H), 7.28 - 7.23 (m, 2H), 7.12 (d, J = 16.5 \text{ Hz}, 1H), 6.98 (t, J = 7.5 \text{ Hz}, 1H), 6.91 (d, J = 7.6 \text{ Hz}, 1H), 3.90 (s, 3H); \]
\[ ^{13}\text{C NMR} \ (125 \text{ MHz, CDCl}_3) \ \delta \ 157.07, 138.11, 129.25, 128.79, 128.71, 127.48, 126.70, 126.60, 126.55, 123.65, 120.89, 111.09, 55.67. \]


(E)-1-methoxy-3-styrylbenzene (230, Table 2.8, entry 5, 26.1 mg, 62% isolated yield)

\[
\text{MeO} \quad \text{Ph} \\
\]

Was produced by reacting 3-methoxybenzonitrile (S225) with styrene under the standard conditions. Following the general procedure 2E, the product was obtained after purification by flash column chromatography on silica gel. The spectral data are consistent with those reported in the literature.\(^{155}\)

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta 7.54 \text{ (dd, } J = 8.2, 1.1 \text{ Hz, 2H}, 7.41 – 7.35 \text{ (m, 2H), 7.32 – 7.26 (m, 2H), 7.14 (dt, } J = 7.6, 1.3 \text{ Hz, 1H}, 7.12 \text{ (d, } J = 2.8 \text{ Hz, 2H), 7.09 – 7.06 \text{ (m, 1H), 6.85 (ddd, } J = 8.2, 2.6, 0.9 \text{ Hz, 1H), 3.87 (s, 3H);} \)

\(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta 160.03, 138.92, 137.36, 129.76, 129.14, 128.81, 128.72, 127.81, 126.68, 119.38, 113.43, 111.89, 55.38.

(E)-1,3-dimethyl-5-styrylbenzene (231, Table 2.8, entry 6, 25.4 mg, 61% isolated yield)

\[
\text{Me} \\
\text{Me} \\
\text{Ph} \\
\]

Was produced by reacting 3,5-dimethylbenzonitrile (S226) with styrene under the standard conditions. Following the general procedure 2E, the product was obtained after purification by flash column chromatography on silica gel. The spectral data are consistent with those reported in the literature.\(^{156}\)

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta 7.58 – 7.51 \text{ (m, 2H), 7.39 (t, } J = 7.7 \text{ Hz, 2H), 7.29 (t, } J = 7.4 \text{ Hz, 1H), 7.19 (s, 2H), 7.14 (d, } J = 16.3 \text{ Hz, 1H), 7.09 (d, } J = 16.3 \text{ Hz, 1H), 6.95 (s, 1H), 2.38 (s, 6H);} \)

\(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta 138.22, 137.65, 137.36, 129.56, 129.02, 128.78, 128.41, 127.58, 126.58, 124.56, 21.45.


(E)-4-styryl-1,1'-biphenyl (232, Table 2.8, entry 7, 19.7 mg, 44% isolated yield)

Was produced by reacting [1,1'-biphenyl]-4-carbonitrile (S227) with styrene under the standard conditions. Following the general procedure 2E, the product was obtained after purification by flash column chromatography on silica gel. The spectral data are consistent with those reported in the literature.\(^{157}\)

**\(^1\)H NMR** (500 MHz, CDCl\(_3\)) \(\delta\) 7.65 – 7.58 (m, 6H), 7.55 (dt, \(J = 8.1, 1.6\) Hz, 2H), 7.46 (t, \(J = 7.7\) Hz, 2H), 7.41 – 7.34 (m, 3H), 7.31 – 7.26 (m, 1H), 7.17 (s, 2H);

**\(^13\)C NMR** (125 MHz, CDCl\(_3\)) \(\delta\) 140.82, 140.49, 137.48, 136.53, 128.95, 128.90, 128.85, 128.34, 127.80, 127.50, 127.47, 127.08, 127.07, 126.68.

(E)-N,N-dimethyl-4-styrylaniline (233, Table 2.8, entry 8, 19.7 mg, 44% isolated yield)

Was produced by reacting 4-(dimethylamino)benzonitrile (S228) with styrene under the standard conditions. Following the general procedure 2E, the product was obtained after purification by flash column chromatography on silica gel. The spectral data are consistent with those reported in the literature.\(^{158}\)

**\(^1\)H NMR** (500 MHz, CDCl\(_3\)) \(\delta\) 7.48 (d, \(J = 7.2\) Hz, 2H), 7.42 (d, \(J = 8.8\) Hz, 2H), 7.33 (t, \(J = 7.7\) Hz, 2H), 7.20 (t, \(J = 7.4\) Hz, 1H), 7.06 (d, \(J = 16.2\) Hz, 1H), 6.92 (d, \(J = 16.2\) Hz, 1H), 6.73 (d, \(J = 8.8\) Hz, 2H), 2.99 (s, 6H);

**\(^13\)C NMR** (125 MHz, CDCl\(_3\)) \(\delta\) 150.28, 138.32, 128.93, 128.71, 127.70, 126.81, 126.15, 125.93, 124.54, 112.60, 40.63.


(E)-1-styrylnaphthalene (234, Table 2.8, Entry 9, 27.2 mg, 59% isolated yield)

\[
\text{Ph} \\
\text{Naphthalene ring}
\]

Was produced by reacting 1-naphthonitrile (S229) with styrene under the standard conditions. Following the general procedure 2E, the product was obtained after purification by flash column chromatography on silica gel. The spectral data are consistent with those reported in the literature.\(^\text{159}\)

\[^{\text{1H NMR}}\ (500 \text{ MHz, CDCl}_3) \delta 8.27 (d, J = 8.3 \text{ Hz, 1H}), 7.96 – 7.89 (m, 2H), 7.84 (d, J = 8.2 \text{ Hz, 1H}), 7.79 (d, J = 7.2 \text{ Hz, 1H}), 7.65 (d, J = 7.6 \text{ Hz, 2H}), 7.60 – 7.50 (m, 3H), 7.44 (t, J = 7.7 \text{ Hz, 2H}), 7.34 (t, J = 7.4 \text{ Hz, 1H}), 7.19 (d, J = 16.0 \text{ Hz, 1H});\]

\[^{\text{13C NMR}}\ (125 \text{ MHz, CDCl}_3) \delta 137.76, 135.15, 133.87, 131.90, 131.54, 128.88, 128.75, 128.17, 127.91, 126.82, 126.22, 125.96, 125.95, 125.83, 123.91, 123.76.\]

(E)-2-styrylnaphthalene (235, Table 2.8, entry 10, 37.3 mg, 81% isolated yield)

\[
\text{Ph} \\
\text{Naphthalene ring}
\]

Was produced by reacting 2-naphthonitrile (S230) with styrene under the standard conditions. Following the general procedure 2E, the product was obtained after purification by flash column chromatography on silica gel. The spectral data are consistent with those reported in the literature.\(^\text{160}\)

\[^{\text{1H NMR}}\ (500 \text{ MHz, CDCl}_3) \delta 7.89 – 7.81 (m, 4H), 7.76 (dd, J = 8.6, 1.7 \text{ Hz, 1H}), 7.60 – 7.56 (m, 2H), 7.52 – 7.44 (m, 2H), 7.40 (t, J = 7.7 \text{ Hz, 2H}), 7.32 – 7.22 (m, 3H);\]

\[^{\text{13C NMR}}\ (125 \text{ MHz, CDCl}_3) \delta 137.50, 134.96, 133.85, 133.18, 129.17, 128.92, 128.87, 128.45, 128.14, 127.84, 127.82, 126.76, 126.69, 126.47, 126.04, 123.66.\]


(E)-1-fluoro-3-styrylbenzene (236, Table 2.8, entry 11, 24.2 mg, 61% isolated yield)

\[
\begin{array}{c}
\text{F} \\
\text{C-} \\
\text{C} \\
\text{C} \\
\end{array}
\]

Was produced by reacting 3-fluorobenzonitrile (S231) with styrene under the standard conditions. Following the general procedure 2E, the product was obtained after purification by flash column chromatography on silica gel. The spectral data are consistent with those reported in the literature.\(^{161}\)

\[^{1}H\] NMR (500 MHz, CDCl\(_3\)) \(\delta 7.55 – 7.51\) (m, 2H), 7.39 (dd, \(J = 8.4, 6.9\) Hz, 2H), 7.35 – 7.26 (m, 3H), 7.23 (dt, \(J = 10.2, 2.0\) Hz, 1H), 7.13 (d, \(J = 16.3\) Hz, 1H), 7.07 (d, \(J = 16.3\) Hz, 1H), 6.97 (tdd, \(J = 8.2, 2.6, 1.2\) Hz, 1H).

\[^{13}C\] NMR (125 MHz, CDCl\(_3\)) \(\delta 163.33\) (d, \(J = 245.3\) Hz), 139.86 (d, \(J = 7.4\) Hz), 136.97, 130.25, 130.18, 130.16, 128.88, 128.14, 127.62 (d, \(J = 2.8\) Hz), 126.79, 122.59 (d, \(J = 2.6\) Hz), 114.51 (d, \(J = 21.4\) Hz), 112.91 (d, \(J = 22.1\) Hz).

(E)-1-chloro-3-styrylbenzene (237, Table 2.8, entry 12, 22.8 mg, 53% isolated yield)

\[
\begin{array}{c}
\text{Cl} \\
\text{C-} \\
\text{C} \\
\text{C} \\
\end{array}
\]

Was produced by reacting 3-chlorobenzonitrile (S232) with styrene under the standard conditions. Following the general procedure 2E, the product was obtained after purification by flash column chromatography on silica gel. The spectral data are consistent with those reported in the literature.\(^{162}\)

\[^{1}H\] NMR (500 MHz, CDCl\(_3\)) \(\delta 7.54 – 7.50\) (m, 3H), 7.41 – 7.36 (m, 3H), 7.32 – 7.27 (m, 2H), 7.24 (ddd, \(J = 7.9, 2.1, 1.2\) Hz, 1H), 7.12 (d, \(J = 16.3\) Hz, 1H), 7.04 (d, \(J = 16.3\) Hz, 1H).


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$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 139.37, 136.95, 134.78, 130.26, 130.01, 128.89, 128.17, 127.62, 127.35, 126.79, 126.43, 124.88.

\textit{(E)-1-methyl-4-styrylbenzene} (238, Table 2.8, entry 13, 28.4 mg, 73% isolated yield)

![E-1-methyl-4-styrylbenzene](image)

Was produced by reacting benzonitrile with 1-methyl-4-vinylbenzene (S233) under the standard conditions. Following the general procedure 2E, the product was obtained after purification by flash column chromatography on silica gel. The spectral data are consistent with those reported in the literature.$^{163}$

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.55 – 7.50 (m, 2H), 7.43 (d, $J$ = 8.2 Hz, 2H), 7.37 (t, $J$ = 7.7 Hz, 2H), 7.28 – 7.23 (m, 1H), 7.18 (d, $J$ = 7.6 Hz, 2H), 7.14 (d, $J$ = 20.0 Hz, 1H), 7.09 (d, $J$ = 20.0 Hz, 1H), 2.38 (s, 3H);

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 137.66, 134.70, 129.53, 128.79, 128.76, 127.84, 127.54, 126.57, 126.53, 21.40.

\textit{(E)-4-styryl-1,1'-biphenyl} (239, Table 2.8, entry 14, 23.1 mg, 45% isolated yield)

![E-4-styryl-1,1'-biphenyl](image)

Was produced by reacting benzonitrile with 4-vinyl-1,1'-biphenyl (S234) under the standard conditions. Following the general procedure 2E, the product was obtained after purification by flash column chromatography on silica gel. The spectral data are consistent with those reported in the literature.$^{164}$

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.65 – 7.58 (m, 6H), 7.55 (dt, $J$ = 8.1, 1.6 Hz, 2H), 7.46 (t, $J$ = 7.7 Hz, 2H), 7.41 – 7.34 (m, 3H), 7.31 – 7.26 (m, 1H), 7.17 (s, 2H);

$^{163}$ See reference 152.

$^{164}$ See reference 157
**Experimental Part**

\[\text{\textsuperscript{13}C NMR \ (125\ \text{MHz, CDCl}_3} \ \delta \ 140.82, 140.49, 137.48, 136.53, 128.95, 128.90, 128.85, 128.34, 127.80, 127.50, 127.47, 127.08, 127.07, 126.68.\]

\textbf{(E)-1-chloro-4-styrylbenzene (240, Table 2.8, entry 15, 20.6 mg, 48% isolated yield)}

\[
\begin{array}{c}
\text{Ph} \\
\text{Cl} \\
\text{C=C} \\
\text{Ph}
\end{array}
\]

Was produced by reacting benzonitrile with 1-chloro-4-vinylbenzene (S235) under the standard conditions. Following the general procedure 2E, the product was obtained after purification by flash column chromatography on silica gel. The spectral data are consistent with those reported in the literature.\textsuperscript{165}

\[\text{\textsuperscript{1}H NMR \ (500\ \text{MHz, CDCl}_3} \ \delta \ 7.54 - 7.49 \text{ (m, 2H)}, 7.46 - 7.43 \text{ (m, 2H)}, 7.38 \text{ (t, } J = 7.6 \text{ Hz, 2H)}, 7.35 - 7.32 \text{ (m, 2H)}, 7.31 - 7.26 \text{ (m, 1H)}, 7.08 \text{ (d, } J = 15.0 \text{ Hz, 1H)}, 7.07 \text{ (d, } J = 15.0 \text{ Hz, 1H)};\]

\[\text{\textsuperscript{13}C NMR \ (125\ \text{MHz, CDCl}_3} \ \delta \ 137.11, 135.98, 133.30, 129.45, 128.97, 128.87, 128.00, 127.79, 127.50, 126.69.\]

\textbf{(E)-1-fluoro-4-styrylbenzene (241, Table 2.8, entry 16, 19.8 mg, 50% isolated yield)}

\[
\begin{array}{c}
\text{Ph} \\
\text{F} \\
\text{C=C} \\
\text{Ph}
\end{array}
\]

Was produced by reacting benzonitrile with 1-fluoro-4-vinylbenzene (S236) under the standard conditions. Following the general procedure 2E, the product was obtained after purification by flash column chromatography on silica gel. The spectral data are consistent with those reported in the literature.\textsuperscript{166}

\[\text{\textsuperscript{1}H NMR \ (500\ \text{MHz, CDCl}_3} \ \delta \ 7.53 - 7.46 \text{ (m, 4H)}, 7.37 \text{ (t, } J = 7.7 \text{ Hz, 2H)}, 7.29 - 7.25 \text{ (m, 1H)}, 7.10 - 6.99 \text{ (m, 4H)};\]


\[^{13}\text{C} \text{NMR} (125 \text{ MHz, CDCl}_3) \delta 162.48 \text{ (d, } J = 247.3 \text{ Hz)}, 137.31, 133.66 \text{ (d, } J = 2.5 \text{ Hz)}, 128.85, 128.64 \text{ (d, } J = 2.6 \text{ Hz)}, 128.12 \text{ (d, } J = 8.0 \text{ Hz)}, 127.81, 127.62, 126.58, 115.76 \text{ (d, } J = 21.7 \text{ Hz)}.\]

6.1.5. Synthesis of a Multi-Conjugated Molecule

\[(E)-1\text{-chloro-4-styrylbenzene (240)}\] was prepared by reacting benzonitrile (S221) with 1-chloro-4-vinylbenzene (S235) following the general procedure 2E. \[242\] was produced by reacting 240 with 4-vinylbenzonitrile (S237) following previously reported conditions and procedure.\(^{167}\)

Synthesis of 4-((E)-4-((E)-styryl)styryl)benzonitrile (242)

Under an argon atmosphere inside a glovebox, an 8.0 mL screw-cap vial equipped with a magnetic stirring bar was charged with \(\text{Pd(OAc)}_2 \) (0.9 mg, 4 mol %), 2-dicyclohexylphosphino-2’-(N,N-dimethylamino)biphenyl (Dave-Phos, 4.5 mg, 8 mol %) and 1,4-dioxane (0.5 mL). The vial was sealed and allowed to stir at room temperature inside the glovebox. After stirring for approximately 10 minutes, \((E)-1\text{-chloro-4-styrylbenzene (240, 20.0 mg, 0.093 mmol)}\), 4-vinylbenzonitrile (S237, 18.1 mg, 0.1395 mmol) and tetrabutylammonium acetate (TBAE, 56.2 mg, 0.186 mmol) were added. The tube was sealed tightly and moved out of the glovebox, and the reaction mixture was allowed to stir at 100 °C for 24 hours. Upon completion of the reaction, the mixture was diluted with dichloromethane (2.0 mL) and the solid was removed through a filtration through silica gel (which was rinsed with dichloromethane) to afford a clear solution. The solvent was removed with the aid of a rotary evaporator under reduced pressure and the

residue was purified by flash column chromatography on silica gel to yield 4-((E)-4-((E)-styryl)styryl)benzonitrile (242) as a blue solid in 85% yield.

**Characterization of 242** (The spectral data of 242 are consistent with those reported in the literature.)

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.64 (d, \(J = 8.4\) Hz, 2H), 7.59 (d, \(J = 8.3\) Hz, 2H), 7.56 – 7.50 (m, 6H), 7.38 (t, \(J = 7.6\) Hz, 2H), 7.28 (t, \(J = 7.4\) Hz, 1H), 7.22 (d, \(J = 16.3\) Hz, 1H), 7.16 (d, \(J = 16.4\) Hz, 1H), 7.13 – 7.08 (m, 2H).

\(^13\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 142.01, 137.91, 137.28, 135.71, 132.65, 132.12, 129.45, 128.89, 128.13, 128.01, 127.45, 127.10, 126.98, 126.73, 126.65, 119.19, 110.68.

6.1.6. Mechanistic Experiments

**Experiment A:** To get insight into the step of alkyne insertion. (Scheme 2.17a)

This experiment was designed to get insight into the alkyne insertiona step of the proposed catalytic cycle (Step 2, Scheme 2.16). To carry out the experiment, norbornene (47.1 mg, 2.0 eq.) was choosed as both the reactant and HCN acceptor to react with 2-vinylbenzonitrile (32.3 mg, 0.25 mmol) under the standard conditios shown in the Scheme above. Following the general procedure 2C, 221 was obtained after putification by flash column chromatography on silica gel using n-pentane/MTBE (10:1) as eluent in 42% isolated yield (23.4 mg).

**Characterization of 221**

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.48 (dd, \(J = 7.5, 1.4\) Hz, 1H), 7.34 (dd, \(J = 7.8, 1.3\) Hz, 1H), 7.30 (td, \(J = 7.5, 1.5\) Hz, 1H), 7.25 (td, \(J = 7.5, 1.4\) Hz, 1H), 6.91 (dd, \(J = 17.2, 10.9\) Hz, 1H), 5.66 (dd,
$J = 17.2, 1.4$ Hz, $1H$), $5.36$ (dd, $J = 10.9, 1.5$ Hz, $1H$), $3.23$ (d, $J = 9.1$ Hz, $1H$), $3.00$ (dd, $J = 9.1, 1.6$ Hz, $1H$), $2.75$ (d, $J = 20.4$ Hz, $2H$), $2.08$ (dt, $J = 10.6, 1.8$ Hz, $1H$), $1.77 − 1.71$ (m, $2H$), $1.57$ (dt, $J = 10.6, 1.6$ Hz, $1H$), $1.41$ (dq, $J = 9.9, 2.1$ Hz, $2H$);

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 138.40, 137.71, 134.69, 128.16, 127.34, 126.86, 125.69, 120.08, 117.54, 46.64, 42.93, 41.30, 40.31, 37.16, 30.59, 27.92.

HRMS-El (m/z): [M]$^+$ calcd for C$_{16}$H$_{17}$N, 223.135548; found 223.135620.

**Experiment B:** To demonstrate the involvement of intermediate 2-D (Scheme 2.17b).

![Scheme 2.17b](image)

This experiment was designed to the involement of intermediate 2-D. In this experiment, $(E)$-2-(prop-1-en-1-yl)benzonitrile (S213, 35.8 mg, 0.25 mmol) was reacted with 4-octyne (55.1 mg, 0.50 mmol) under the standard reaction conditions shown in the Scheme above. Following the general procedure 2C, (Z)-1-ethylidene-2,3-dipropyl-1H-indene (222) and (S)-2,3-dipropyl-1-vinyl-1H-indene (223) were obtained after purification by flash column chromatography on silica gel using 100% n-pentane as eluent in 40% and 45% isolated yields, respectively (22.6 mg, 25.5 mg).

**Characterization of 222**

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.70 (d, $J = 7.5$ Hz, $1H$), 7.25 − 7.20 (m, $2H$), 7.14 (ddd, $J = 8.6, 6.2, 2.5$ Hz, $1H$), 6.33 (q, $J = 7.5$ Hz, $1H$), 2.55 − 2.50 (m, $2H$), 2.49 − 2.43 (m, $2H$), 2.34 (d, $J = 7.5$ Hz, $3H$), 1.64 − 1.58 (m, $2H$), 1.56 − 1.50 (m, $2H$), 1.01 (t, $J = 7.3$ Hz, $3H$), 0.98 (t, $J = 7.4$ Hz, $3H$);

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 144.82, 141.00, 137.81, 137.72, 135.80, 126.92, 126.39, 124.19, 123.47, 118.33, 27.81, 26.99, 24.76, 22.51, 15.58, 14.65, 14.61.

HRMS-El (m/z): [M]$^+$ calcd for C$_{17}$H$_{22}$, 226.171600; found 226.171690.
Characterization of 223

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.31 (dq, $J = 7.3$, 1.0 Hz, 1H), 7.30 – 7.24 (m, 2H), 7.15 (ddd, $J = 7.3$, 6.4, 2.2 Hz, 1H), 5.44 – 5.33 (m, 2H), 5.29 – 5.23 (m, 1H), 3.90 (d, $J = 7.6$ Hz, 1H), 2.54 – 2.49 (m, 2H), 2.44 (ddd, $J = 13.8$, 9.1, 7.2 Hz, 1H), 2.28 (ddd, $J = 14.1$, 9.2, 5.4 Hz, 1H), 1.67 – 1.56 (m, 3H), 1.46 (dddd, $J = 14.5$, 13.3, 7.2, 1.8 Hz, 1H), 0.98 (t, $J = 7.3$ Hz, 3H), 0.95 (t, $J = 7.4$ Hz, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 146.04, 145.80, 145.51, 137.78, 137.55, 126.78, 124.14, 123.70, 118.61, 117.62, 56.16, 29.03, 27.59, 23.19, 22.27, 14.43, 14.39.

HRMS-EI (m/z): [M]$^+$ calcd for C$_{17}$H$_{22}$, 226.171600; found 226.171690.

Experiment C: To illustrate the transfer hydrocyanation step (Scheme 2.17c).

This experiment was designed to illustrate the transfer hydrocyanation step. In this experiment, a deuterated substrate 2-(vinyl-$d$)benzonitrile ($S_{21}$-$D$, 98% D, 32.5 mg, 0.25 mmol) was reacted with cycloocta-1,5-diene ($S_{217}$, 82.1 mg, 0.50 mmol) under the standard conditions shown in the Scheme above. Following the general procedure $2C$, (E)-cycloocta-1-ene-1-carbonitrile-2-$d$ was obtained after purification by flash column chromatography on silica gel using n-pentane/MTBE (20:1) as eluent in 90% isolated yield ($224$, 79% D, 22.6 mg).

Characterization of 224

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.30 (t, $J = 8.1$ Hz, 0.21H), 2.29 (t, $J = 6.7$ Hz, 2H), 2.25 (t, $J = 6.6$ Hz, 2H), 1.71 – 1.64 (m, 2H), 1.56 – 1.49 (m, 2H), 1.39 – 1.23 (m, 12H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 148.79, 148.63, 148.44, 148.25, 120.23, 115.35, 115.23, 115.13, 77.41, 77.16, 76.91, 26.10, 26.07, 25.74, 25.63, 25.36, 25.32, 24.64, 24.58, 24.13, 24.11, 22.29, 22.06.
HRMS-EI (m/z): [M]⁺ calcd for C₁₃H₂₀DN, 192.173126; found 192.173260.
6.2. Experimental Part to Chapter 3

6.2.1. Substrates Preparation and Characterization

Synthesis of S39 and S310

\[
\begin{align*}
R & \quad \text{OH} & + & \quad \text{Br} & \quad \xrightarrow{\text{K}_2\text{CO}_3, \text{CH}_3\text{CN}, \text{reflux, overnight}} & \quad \text{OBn} \\
\text{S39, S310} & 
\end{align*}
\]

General procedure:

To a stirred solution of phenol (11.0 mmol) and \( \text{K}_2\text{CO}_3 \) (1.52 g, 11.0 mmol) in MeCN (20.0 mL), was added benzyl bromide (1.44 mL, 10.0 mmol). The resulting solution was heated to reflux overnight. After cooling to room temperature, aqueous NaOH (50.0 mL) was added to the reaction mixture. The mixture was then separated and the aqueous layer was extracted with \( \text{Et}_2\text{O} \) (3 \( \times \) 30 mL). The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give the crude product. Purification by flash column chromatography (ethyl acetate/hexane) afforded S39 and S310.

Characterization of S39 and S310

1-\( \text{Benzyloxy}\)-3-chlorobenzene (S39, 95% yield)

\[
\begin{align*}
\text{BnO} & \quad \text{Cl} \\
\text{S39} & 
\end{align*}
\]

\(^1\text{H NMR}\) (500 MHz, CDCl\(_3\)) \( \delta \) 7.45 – 7.39 (m, 4H), 7.37 – 7.34 (m, 1H), 7.23 – 7.19 (m, 1H), 7.02 – 6.95 (m, 1H), 6.98 – 6.95 (m, 1H), 6.89 – 6.86 (m, 1H), 5.06 (s, 2H).

\(^{13}\text{C NMR}\) (125 MHz, CDCl\(_3\)) \( \delta \) 159.63, 136.56, 135.02, 130.37, 128.79, 128.28, 127.62, 121.28, 115.45, 113.49, 70.34.

1-\( \text{Benzyloxy}\)-4-chloro-2-fluorobenzene (S310, 85% yield)

**Exploring the Potential of Shuttle Catalysis in Organic Synthesis**

1H NMR (500 MHz, CDCl₃) δ 7.44 – 7.37 (m, 4H), 7.36 – 7.32 (m, 1H), 7.12 (dd, J = 11.0, 2.5 Hz, 1H), 7.02 – 7.01 (m, 1H), 6.92 (t, J = 9.0 Hz, 1H), 5.12 (s, 2H).

13C NMR (125 MHz, CDCl₃) δ 152.86 (d, J_CF = 248.3 Hz), 145.70 (d, J_CF = 10.5 Hz), 136.26, 128.80, 128.40, 127.58, 126.01 (d, J_CF = 9.0 Hz), 124.34 (d, J_CF = 3.8 Hz), 117.22 (d, J_CF = 22.6 Hz), 116.70 (d, J_CF = 2.4 Hz), 71.82.

**Synthesis of 3-Chloro-4-fluoro-1,1'-biphenyl (S311)**

\[
\begin{array}{c}
\text{Cl} \quad \text{F} \\
\text{B(OH)}_2 \\
\text{Cl} \quad \text{F} \\
\text{I} \\
\text{Ph} \quad \text{Cl} \quad \text{F}
\end{array}
\]

Iodobenzene (408.0 mg, 2.0 mmol), (3-chloro-4-fluorophenyl)boronic acid (418.5 mg, 2.4 mmol), Pd(OAc)₂ (13.5 mg, 0.06 mmol), DABCO (13.5 mg, 0.12 mmol), K₂CO₃ (819.2 mg, 6.0 mmol) and acetone (10.0 mL) was added to a tube. The tube was sealed and stirred at 110 °C for 2 hours. The reaction mixture was then cooled to room temperature and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (ethyl acetate/hexane) to afford the product (S311, 72% yield).

**Characterization of S311**

1H NMR (500 MHz, CDCl₃) δ 7.62 (dd, J = 7.0, 2.0 Hz, 1H), 7.53 – 7.51 (m, 2H), 7.47 – 7.42 (m, 3H), 7.39 – 7.36 (m, 1H), 7.21 (t, J = 8.5 Hz, 1H).

13C NMR (125 MHz, CDCl₃) δ 157.79 (d, J_CF = 246.9 Hz), 139.17, 138.64 (d, J_CF = 3.8 Hz), 129.39, 129.09, 127.96, 127.13, 126.91 (d, J_CF = 7.3 Hz), 121.39 (d, J_CF = 17.8 Hz), 116.95 (d, J_CF = 20.6 Hz).

**Synthesis of 1-(4-chlorophenyl)piperidine (S315)**

Under argon, KOtBu (168.3 mg, 1.5 mmol), 1-chloro-4-iodobenzene (238.5 mg, 1.0 mmol), and piperidine (102.2 mg, 1.2 mmol) were added in a Schlenk tube charged with Pd$_2$(dba)$_3$ (9.2 mg, 0.01 mmol), IPr·HCl (17.0 mg, 0.04 mmol), 1,4-dioxane (3.0 mL) and a magnetic stirring bar. The Schlenk tube was then placed in a 100 °C Oil bath and stirred for 24 hours. After cooling to room temperature, the reaction mixture was diluted with water and extracted with diethyl ether (3 × 10 mL). The combined extracts were washed with brine, dried over anhydrous Na$_2$SO$_4$, filtered and concentrated under reduced pressure. Purification of the residue by flash silica chromatography (ethyl acetate/hexane) afforded the product (S315, 82% yield).

Characterization of S315

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.20 – 7.16 (m, 2H), 6.86 – 6.83 (m, 2H), 3.13 – 3.11 (m, 4H), 1.72 – 1.68 (m, 4H), 1.60 – 1.55 (m, 2H).

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 150.95, 128.97, 124.01, 117.78, 50.80, 25.85, 24.31.

Synthesis of 6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indole (S319)$^{172}$

To a stirred, ice-cooled solution of indole (303.2 mg, 2.0 mmol) in DMF (5.0 mL) under argon was added NaH (60% dispersion in mineral oil, 128.0 mg, 3.2 mmol) and the resulting mixture was stirred at room temperature for 45 min. After cooling to 0 °C, 2-(trimethylsilyl)ethoxymethyl chloride (500.2 mg, 3.0 mmol) was added dropwise. The reaction mixture was then stirred at room temperature for 5 h. The reaction was quenched with water and


the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Purification of the residue by flash silica chromatography (ethyl acetate/hexane) afforded the product (S319, 70% yield).

**Characterization of S319**

**¹H NMR** (500 MHz, CDCl₃) δ 7.52 (dd, J = 8.5, 0.5 Hz, 1H), 7.50 – 7.49 (m, 1H), 7.15 (d, J = 3.5 Hz, 1H), 7.11 (dd, J = 8.5, 2.0 Hz, 1H), 6.50 (dd, J = 3.0, 1.0 Hz, 1H), 5.43 (s, 2H), 3.48 – 3.45 (m, 2H), 0.91 – 0.88 (m, 2H), -0.05 (s, 9H).

**¹³C NMR** (125 MHz, CDCl₃) δ 136.88, 128.81, 128.24, 127.75, 121.88, 121.02, 110.31, 102.66, 75.85, 66.06, 17.84, -1.31.

**Synthesis of 6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indole (S320)**¹⁷³

To a stirred suspension of NaH (60% dispersion in mineral oil, 96.0 mg, 2.4 mmol) in DMF (5.0 mL) was added dropwise a solution of indole (303.2 mg, 2.0 mmol) in DMF (2.0 mL) at 0 °C, and the mixture was stirred at room temperature for 30 min. Then (bromomethyl)benzene (0.36 mL, 3.0 mmol) was added dropwise to the mixture at 0 °C, and the resulting mixture was stirred at room temperature overnight. The reaction was quenched with water and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. Purification of the residue by flash silica chromatography (ethyl acetate/hexane) afforded the product (S320, 86% yield).

**Characterization of S320**

¹⁷³ See reference 172.
Experimental Part

**1H NMR** (500 MHz, CDCl₃) δ 7.56 – 7.53 (m, 1H), 7.31 – 7.23 (m, 3H), 7.16 – 7.13 (m, 1H), 7.11 (dd, J = 3.5, 1.0 Hz, 1H), 7.05 – 7.00 (m, 3H), 6.58 (t, J = 3.0 Hz, 1H), 5.78 (s, 2H).

**13C NMR** (125 MHz, CDCl₃) δ 139.20, 131.98, 131.71, 131.14, 128.79, 127.48, 126.33, 123.74, 120.51, 119.98, 116.89, 102.63, 51.95.

**Synthesis of S322-S336, S343**

\[ \text{PhOH} + \text{F}_3\text{SO}_2\text{SO}_2\text{CF}_3 \rightarrow \text{PhTf} \]

**General procedure:**

Under argon, a 50 mL two-necked round-bottomed flask was charged with phenol (3.0 mmol), dry dichloromethane (10.0 mL) and analytical-grade pyridine (0.3 mL, 3.6 mmol). The solution was cooled to 0 °C in an ice bath, and treated with dropwise addition of triflic anhydride (0.76 mL, 4.5 mmol). The resulting mixture was slowly warmed up to room temperature and stirred for additional 2 hours. Upon completion of the reaction (monitored by TLC), the reaction mixture was diluted with Et₂O, quenched with 1.0 M aq. HCl and washed with sat. NaHCO₃ and brine. After drying over anhydrous Na₂SO₄ and concentrated under reduced pressure, the residue was purified by flash column chromatography on silica gel to afford the triflates.

**Characterization of S322-S336, S343**

4-(Trifluoromethyl)phenyl trifluoromethanesulfonate (S322, 85% yield)

**1H NMR** (500 MHz, CDCl₃) δ 7.75 (d, J = 9.0 Hz, 2H), 7.42 (d, J = 8.5 Hz, 2H).

**13C NMR** (125 MHz, CDCl₃) δ 151.72, 131.04 (q, JCF= 33.3 Hz), 127.91 (q, JCF= 3.6 Hz), 123.39 (q, JCF= 270.6 Hz), 122.18, 118.86 (q, JCF = 318.8 Hz).

---

Methyl 4-(((trifluoromethyl)sulfonyl)oxy)benzoate (S323, 90% yield)

![Methyl 4-(((trifluoromethyl)sulfonyl)oxy)benzoate](image)

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.16 – 8.13 (m, 2H), 7.37 – 7.34 (m, 2H), 3.94 (s, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 165.57, 152.63, 132.04, 130.51, 121.57, 118.84 (q, $J_{CF} = 318.3$ Hz), 52.69.

4-Methoxyphenyl trifluoromethanesulfonate (S324, 93% yield)

![4-Methoxyphenyl trifluoromethanesulfonate](image)

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.21 – 7.18 (m, 2H), 6.94 – 6.91 (m, 2H), 3.82 (s, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 159.25, 143.18, 122.47, 118.92 (q, $J_{CF} = 318.5$ Hz), 115.17, 55.80.

4-Butylphenyl trifluoromethanesulfonate (S325, 95% yield)

![4-Butylphenyl trifluoromethanesulfonate](image)

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.25 – 7.22 (m, 2H), 7.18 – 7.15 (m, 2H), 2.63 (t, $J = 8.0$ Hz, 2H), 1.63 – 1.57 (m, 2H), 1.39 – 1.32 (m, 2H), 0.93 (t, $J = 7.5$ Hz, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 147.81, 143.61, 130.17, 121.13, 118.70 (q, $J_{CF} = 318.3$ Hz), 35.14, 33.55, 22.40, 13.99.

2,4-Dimethylphenyl trifluoromethanesulfonate (S326, 90% yield)

![2,4-Dimethylphenyl trifluoromethanesulfonate](image)
**Experimental Part**

**1H NMR** (500 MHz, CDCl₃) δ 7.13 – 7.11 (m, 2H), 7.06 – 7.04 (m, 1H), 2.35 (s, 3H), 2.34 (s, 3H).

**13C NMR** (125 MHz, CDCl₃) δ 146.63, 138.40, 132.84, 130.55, 128.24, 121.04, 118.82 (q, J<sub>CF</sub> = 317.8 Hz), 20.88, 16.35.

[1,1'-Biphenyl]-4-yl trifluoromethanesulfonate (S327, 80% yield)

\[
\text{Ph} \begin{array}{c}
\end{array} \text{OTf}
\]

**1H NMR** (500 MHz, CDCl₃) δ 7.67 – 7.64 (m, 2H), 7.58 – 7.56 (m, 2H), 7.50 – 7.46 (m, 2H), 7.43 – 7.39 (m, 1H), 7.38 – 7.35 (m, 2H).

**13C NMR** (125 MHz, CDCl₃) δ 149.07, 141.83, 139.42, 129.12, 129.01, 128.20, 127.32, 121.76, 118.94 (q, J<sub>CF</sub> = 318.3 Hz).

**5,6,7,8-Tetrahydronaphthalen-2-yl trifluoromethanesulfonate (S328, 92% yield)**

\[
\text{OTf}
\]

**1H NMR** (500 MHz, CDCl₃) δ 7.12 (d, J = 8.0 Hz, 1H), 7.00 – 6.98 (m, 2H), 2.81 – 2.77 (m, 4H), 1.84 – 1.78 (m, 4H).

**13C NMR** (125 MHz, CDCl₃) δ 147.44, 139.76, 137.78, 130.77, 121.48, 118.23, 117.64 (q, J<sub>CF</sub> = 318.1 Hz), 29.56, 29.01, 22.89, 22.68.

**Naphthalen-2-yl trifluoromethanesulfonate (S329, 88% yield)**

\[
\text{OTf}
\]

**1H NMR** (500 MHz, CDCl₃) δ 7.93 (d, J = 9.0 Hz, 1H), 7.92 – 7.87 (m, 2H), 7.76 (d, J = 2.0 Hz, 1H), 7.61 – 7.56 (m, 2H), 7.38 (d, J = 9.0, 2.5 Hz, 1H).

**13C NMR** (125 MHz, CDCl₃) δ 147.24, 133.48, 132.50, 130.76, 128.17, 128.06, 127.71, 127.34, 119.68, 119.36, 118.97 (q, J<sub>CF</sub> = 318.5 Hz).
[1,1'-Biphenyl]-2,2'-diyl bis(trifluoromethanesulfonate) (S330, 75% yield)

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

\(^1\text{H NMR}\ (500 \text{ MHz, CDCl}_3) \delta 7.57 – 7.46 (m, 6H), 7.43 (dd, J = 8.5, 1.5 Hz, 2H).

\(^{13}\text{C NMR}\ (125 \text{ MHz, CDCl}_3) \delta 146.94, 132.72, 130.89, 129.49, 128.65, 121.83, 118.44 (q, J_{\text{CF}} = 317.8 \text{ Hz}).

4'-Chloro-[1,1'-biphenyl]-4-yl trifluoromethanesulfonate (S331, 70% yield)

\[
\begin{align*}
\text{Cl} & \quad \text{Ph} \\
\text{Ph} & \quad \text{Ph} \\
\text{OTf}
\end{align*}
\]

\(^1\text{H NMR}\ (500 \text{ MHz, CDCl}_3) \delta 7.63 – 7.60 (m, 2H), 7.50 – 7.47 (m, 2H), 7.45 – 7.42 (m, 2H), 7.37 – 7.34 (m, 2H).

\(^{13}\text{C NMR}\ (125 \text{ MHz, CDCl}_3) \delta 149.23, 140.61, 137.87, 134.48, 129.34, 128.91, 128.58, 121.95, 118.92 (q, J_{\text{CF}} = 318.1 \text{ Hz}).

4-Chloro-3-ethylphenyl trifluoromethanesulfonate (S332, 85% yield)

\[
\begin{align*}
\text{Cl} & \quad \text{Ph} \\
\text{Ph} & \quad \text{OTf}
\end{align*}
\]

\(^1\text{H NMR}\ (500 \text{ MHz, CDCl}_3) \delta 7.41 (d, J = 9.0 \text{ Hz, 1H}), 7.15 (d, J = 3.0 \text{ Hz, 1H}), 7.07 (dd, J = 9.0, 3.0 \text{ Hz, 1H}), 2.78 (q, J = 7.5 \text{ Hz, 2H}), 1.26 (t, J = 7.5 \text{ Hz, 3H}).

\(^{13}\text{C NMR}\ (125 \text{ MHz, CDCl}_3) \delta 148.15, 144.46, 133.87, 130.95, 122.25, 119.96, 118.87 (q, J_{\text{CF}} = 318.3 \text{ Hz}), 26.98, 13.58.

2-(Pyrrolidin-1-yl)phenyl trifluoromethanesulfonate (S333, 60% yield)
**Experimental Part**

1H NMR (500 MHz, CDCl₃) δ 7.23 – 7.19 (m, 1H), 7.16 (dd, J = 8.5, 2.0 Hz, 1H), 6.88 (dd, J = 8.5, 1.5 Hz, 1H), 6.79 – 6.76 (m, 1H), 3.36 – 3.34 (m, 4H), 1.98 – 1.95 (m, 4H).

13C NMR (125 MHz, CDCl₃) δ 142.59, 138.98, 128.91, 122.80, 118.78 (q, J_{CF} = 318.3 Hz), 118.32, 117.25, 50.41, 25.44.

**Benzo[d][1,3]dioxol-5-yl trifluoromethanesulfonate (S334, 95% yield)**

1H NMR (500 MHz, CDCl₃) δ 6.80 (d, J = 8.0 Hz, 1H), 6.77 (d, J = 2.0 Hz, 1H), 6.74 (dd, J = 8.0, 2.5 Hz, 1H), 6.05 (s, 2H).

13C NMR (125 MHz, CDCl₃) δ 148.69, 147.61, 143.63, 118.86 (q, J_{CF} = 318.6 Hz), 114.54, 108.34, 103.52, 102.62.

**4-(1H-Pyrazol-1-yl)phenyl trifluoromethanesulfonate (S335, 81% yield)**

1H NMR (500 MHz, CDCl₃) δ 7.93 (d, J = 2.5 Hz, 1H), 7.81 – 7.78 (m, 2H), 7.75 (d, J = 1.5 Hz, 1H), 7.39 – 7.36 (m, 2H), 6.50 (dd, J = 2.5, 2.0 Hz, 1H).

13C NMR (125 MHz, CDCl₃) δ 147.40, 142.02, 134.00, 126.96, 122.66, 120.60, 118.89 (q, J_{CF} = 318.63 Hz), 108.63.

**4-(1H-Pyrazol-1-yl)phenyl trifluoromethanesulfonate (S336, 80% yield)**
$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 9.00 (dd, $J = 4.0$, 1.5 Hz, 1H), 8.22 – 8.20 (m, 2H), 7.76 (d, $J = 2.5$ Hz, 1H), 7.61 (dd, $J = 9.5$, 3.0 Hz, 1H), 7.51 (dd, $J = 8.5$, 4.5 Hz, 1H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 151.85, 147.18, 136.26, 132.63, 128.45, 123.27, 122.75, 119.39, 118.92 (q, $J_{CF} = 318.4$ Hz).

**(R)-2,8-Dimethyl-2-((4R,8R)-4,8,12-trimethyltridecyl)chroman-6-yl trifluoromethanesulfonate (S343, 95% yield)**

\[ \text{TFO} \]
\[ \text{CH}_3 \]
\[ \text{CH}_3 \]
\[ \text{CH}_3 \]

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.85 (d, $J = 3.0$ Hz, 1H), 6.80 (d, $J = 3.5$ Hz, 1H), 2.79 – 2.71 (m, 2H), 2.16 (s, 3H), 1.85 – 1.73 (m, 2H), 1.62 – 1.02 (m, 24H), 0.88 – 0.84 (m, 12H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 151.83, 141.60, 128.52, 121.84, 120.88, 119.20, 118.92 (q, $J_{CF} = 318.5$ Hz), 77.00, 40.30, 39.53, 37.60, 37.55, 37.53, 37.44, 32.96, 32.83, 30.81, 28.14, 24.96, 24.60, 24.31, 22.87, 22.78, 22.60, 21.08, 19.90, 19.80, 16.33.

**Synthesis of 9-benzyl-9H-carbazol-1-yl trifluoromethanesulfonate (S337)**\(^{175}\)

\[ \text{TFO} \]
\[ \text{CH}_3 \]
\[ \text{CH}_3 \]
\[ \text{CH}_3 \]

To a stirred suspension of NaH (60% dispersion in mineral oil, 96.0 mg, 2.4 mmol) in DMF (5.0 mL) was added dropwise a solution of 9H-carbazol-1-yl trifluoromethanesulfonate (630.5 mg, 2.0 mmol) in DMF (2.0 mL) at 0 °C, and the mixture was stirred at room temperature for 30 min. Then (bromomethyl)benzene (0.36 mL, 3.0 mmol) was added dropwise to the mixture at 0 °C, and the resulting mixture was stirred at room temperature overnight. The reaction was quenched with water and the aqueous layer was extracted with ethyl acetate. The combined organic layer

\(^{175}\) See reference 172.
was dried over anhydrous Na$_2$SO$_4$ and concentrated in vacuo. purification by flash silica chromatography afforded the product (EtOAc: hexane, 76% yield).

$^1$H NMR (500 MHz, CDCl$_3$) δ 8.14 – 8.11 (m, 2H), 7.50 – 7.47 (m, 1H), 7.41 (dt, $J = 8.5$, 1.0 Hz, 1H), 7.32 – 7.26 (m, 4H), 7.25 (d, $J = 2.5$ Hz, 1H), 7.16 – 7.12 (m, 3H), 5.51 (s, 2H).

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 147.96, 141.77, 140.78, 136.25, 129.11, 127.99, 126.92, 126.54, 123.05, 122.22, 121.55, 120.82, 118.96 (q, $J_{CF} = 318.8$ Hz), 120.34, 112.44, 109.48, 102.50, 47.09.

**Synthesis of 1H-indol-4-yl trifluoromethanesulfonate (S338)**

Et$_3$N (1.6 mL, 11.3 mmol) was added to a solution of 4-hydroxyindole (1.0 g, 7.5 mmol) in DCM (20.0 mL) followed by addition of a solution of N-phenyltrifluoromethanesulfonimide (2.6 g, 7.5 mmol,) in DCM (5.0 mL) at 0 °C. Then the reaction mixture was stirred for 2 hour at room temperature. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (DCM/hexane, 60% yield) to give the product.

$^1$H NMR (500 MHz, CDCl$_3$) δ 8.37 (br s, 1H), 7.40 (d, $J = 8.5$ Hz, 1H), 7.40 (t, $J = 3.0$ Hz, 1H), 7.40 (t, $J = 8.0$ Hz, 1H), 7.06 (d, $J = 8.0$ Hz, 1H), 6.67 – 6.66 (m, 2H).

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 142.57, 138.18, 125.84, 122.28, 121.28, 118.98 (q, $J_{CF} = 318.13$ Hz), 112.13, 111.53, 99.48.

**Synthesis of 1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl trifluoromethanesulfonate (S340)**

KHMDS in toluene (5.00 mL of a 0.5 M solution, 2.5 mmol) was added slowly to a solution of 4-phenyl-1-cyclo-hexanone (0.4 g, 2.3 mmol) in THF (10.0 mL) at -78 °C under argon. The solution was allowed to warm to room temperature, and kept stirring for 1 hour. The reaction mixture was cooled to -78 °C and a solution of N-phenyl trifluoromethanesulfonimide (0.94 g, 2.63 mmol) in THF (5.0 mL) was added via syringe. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (DCM/hexane, 90% yield) to give the product.

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.38 – 7.34 (m, 2H), 7.29 – 7.24 (m, 3H), 5.89 (dt, \(J = 5.5, 3.0\) Hz, 1H), 2.92 – 2.86 (m, 1H), 2.63 – 2.34 (m, 4H), 2.14 – 2.09 (m, 1H), 2.04 – 1.96 (m, 1H).

\(^13\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 149.13, 144.69, 128.78, 126.89, 126.80, 118.23, 117.42 (q, \(J_{CF} = 317.8\) Hz), 38.88, 31.71, 29.82, 28.01.

**Synthesis of (8S,9S,10R,13R,14S,17R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-2,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-3-yl trifluoromethanesulfonate (S342)**

Under argon, a 50 mL two-necked round-bottomed flask was charged with 2,6-di-tert-butyl-4-methylpyridine (616.0 mg, 3.0 mmol) and dry dichloromethane (10.0 mL). Then trifluoromethanesulfonic anhydride (0.4 mL, 2.4 mmol) was added rapidly via a syringe and a

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solution of cholest-4-en-3-one (770.0 mg, 2.0 mmol) in dry dichloromethane (2.0 mL) was added through the dropping funnel, dropwise and with stirring, during 5–10 mins. The mixture was stirred for an additional 1 hour at room temperature. Then the solvent was removed under reduced pressure as soon as the solution turned slightly pink and a white precipitate separated, the residue was filtered and washed with diethyl ether (3 × 10 mL). The combined solution was washed 1.0 M aq. HCl and brine (3 × 10 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The product was obtained by flash column chromatography (MTBE/hexane, 83% yield).

**1H NMR** (500 MHz, CDCl₃) δ 5.98 (d, J = 2.5 Hz, 1H), 5.58 – 5.57 (m, 1H), 2.59 – 2.52 (m, 1H), 2.37 – 2.33 (m, 1H), 2.20 (dt, J = 18.5, 5.0 Hz, 1H), 2.03 (dt, J = 12.5, 3.5 Hz, 1H), 1.93 – 1.81 (m, 2H), 1.71 – 0.98 (m, 20H), 0.96 (s, 3H), 0.92 (d, J = 6.5 Hz, 3H), 0.87 (d, J = 2.0 Hz, 3H), 0.86 (d, J = 2.0 Hz, 3H), 0.71 (s, 3H).

**13C NMR** (125 MHz, CDCl₃) δ 147.07, 138.18, 128.52, 120.69, 118.70 (q, J_CF = 318.1 Hz), 56.87, 56.28, 47.90, 42.59, 39.78, 39.67, 36.33, 35.93, 34.92, 33.94, 32.13, 31.79, 28.37, 28.18, 25.73, 24.33, 23.98, 22.98, 22.72, 21.35, 18.86, 18.78, 12.12.

**Synthesis of (8R,9S,13S,14S)-3-methoxy-13-methyl-7,8,9,11,12,13,14,15-octahydro-6H-cyclopenta[a]phenanthren-17-yl trifluoromethanesulfonate (S341)**

Under argon, a 50 mL two-necked round-bottomed flask was charged with 2,6-di-tert-butyl-4-methylpyridine (616.0 mg, 3.0 mmol) and dry dichloromethane (10.0 mL). Then trifluoromethanesulfonic anhydride (0.4 mL, 2.4 mmol) was added rapidly via a syringe and a solution of 3-methoxyl Estrone (568.8 mg, 2.0 mmol) in dry dichloromethane (2.0 mL) was added through the dropping funnel, dropwise and with stirring, during 5–10 mins. The mixture

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178 See reference 177.
was stirred for an additional 1 hour at room temperature. Then the solvent was removed under reduced pressure as soon as the solution turned slightly pink and a white precipitate separated, and the residue was filtered and washed with diethyl ether (3 × 10 mL). The combined solution was washed 1.0 M aq. HCl and brine (3 × 10 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. Product **S341** was obtained by flash column chromatography (MTBE/Hexane, 88% yield).

**¹H NMR** (500 MHz, CDCl₃) δ 7.19 (d, J = 9.0 Hz, 1H), 6.74 (dd, J = 8.5, 2.5 Hz, 1H), 6.66 (d, J = 2.5 Hz, 1H), 5.63 (dd, J = 3.5, 1.5 Hz, 1H), 3.79 (s, 3H), 2.97 – 2.86 (m, 2H), 2.43 – 2.30 (m, 3H), 2.14 – 2.09 (m, 1H), 1.96 – 1.89 (m, 2H), 1.84 – 1.78 (m, 1H), 1.70 – 1.54 (m, 3H), 1.49 – 1.41 (m, 1H), 1.02 (s, 3H).

**¹³C NMR** (125 MHz, CDCl₃) δ 159.46, 157.76, 137.79, 132.26, 126.08, 118.75 (q, J₁C = 318.5), 114.61, 114.06, 111.64, 55.33, 53.71, 45.24, 44.34, 36.86, 32.89, 29.59, 28.51, 26.90, 25.97, 15.48.

### 6.2.2. General Procedures for Nickel-Catalyzed Cyanation of Aryl Chlorides

**General procedure 3A: For optimization of reaction conditions**

![Catalyst, Ligand, Reductant, Base, and Lewis Acid](image)

Under argon, to an 8.0 mL Screw-cap vial equipped with a magnetic stirring bar was added catalyst, ligand, reductant and toluene (0.5 mL). The mixture was allowed to stir for 5 min. Then butyronitrile (R32), chlorobenzene (S32, 0.1 mmol), base and Lewis acid were added sequentially to the resulting solution and the vial was sealed and placed on a heating plate. Upon completion of the reaction, the reaction mixture was cooled to room temperature and quenched by adding two drops of water. The reaction mixture was dried over anhydrous Na₂SO₄ and analyzed using GC or NMR.

**General procedure 3B: For scope study**
Under argon, to an 8.0 mL Screw-cap vial equipped with a magnetic stirring bar was added Ni(acac)$_2$ (2.6 mg, 5 mol%), Xantphos (5.8 mg, 5 mol%), Zn (2.0 mg, 15 mol%) and toluene (0.5 mL). The mixture was allowed to stir for 5 min. Then butyronitrile (138.2 mg, 2.0 mmol), aryl chloride (0.2 mmol), K$_3$PO$_4$ (84.9 mg, 0.4 mmol) and Al(isobutyl)$_3$ (25% in toluene, 31.7 mg, 20 mol%) were added sequentially to the resulting solution and the vial was sealed and placed on a heating plate (120 °C). After stirring for 12 hours, the reaction mixture was cooled to room temperature and quenched by adding two drops of water. The reaction mixture was dried over anhydrous Na$_2$SO$_4$ and concentrated under reduced pressure. The products were obtained after purification by flash column chromatography on silica gel.

### 6.2.3. General Procedures for Nickel-Catalyzed Cyanation of Aryl and Vinyl Triflates

**General procedure 3C: For optimization of reaction conditions**

Under argon, to an 8.0 mL Screw-cap vial equipped with a magnetic stirring bar was added catalyst, ligand, and toluene (0.5 mL). The mixture was allowed to stir for 5 min. Then butyronitrile (R32), phenyl triflate (S321), base and Lewis acid were added sequentially to the resulting solution and the vial was sealed and placed to a heating plate. Upon completion of the reaction, the reaction mixture was cooled to room temperature and quenched by adding two drops of water. The reaction mixture was dried over anhydrous Na$_2$SO$_4$ and analyzed using GC or NMR.

**General procedure 3D: For scope study**
Under argon, to a 16.0 mL Screw-cap vial equipped with a magnetic stirring bar was added Ni(COD)\(_2\) (13.8 mg, 10 mol%), Xantphos (29.2 mg, 10 mol%) and toluene (0.5 mL). The mixture was allowed to stir for 5 min. Then butyronitrile (103.7 mg, 1.0 mmol), Et\(_3\)N (139.0 µL, 1.0 mmol) and AlCl\(_3\) (40.0 mg, 60 mol%) were added sequentially to the resulting solution and the vial was sealed and placed to a heating plate (70 °C). Then a solution of aryl triflates (0.5 mmol) in toluene (1.5 mL) was slowly dosed into the stirring reaction mixture via syringe pump during 2-4 hours. After an additional stirring for 1 hour at 50-70 °C, the reaction mixture was cooled to room temperature and quenched by adding a few drops of water. The reaction mixture was dried over anhydrous Na\(_2\)SO\(_4\) and concentrated under reduced pressure. Products were obtained after purification by flash column chromatography on silica gel.

**General procedure 3E: For scope study**

Under argon, to an 8.0 mL Screw-cap vial equipped with a magnetic stirring bar was added Ni(COD)\(_2\) (5.5 mg, 10 mol%), Xantphos (11.6 mg, 10 mol%) and toluene (0.5 mL). The mixture was allowed to stir for 5 min. Then butyronitrile (138.2 mg, 2.0 mmol), aryl or vinyl triflates (0.2 mmol), Et\(_3\)N (55.6 µL, 0.4 mmol) and AlCl\(_3\) (16.0 mg, 60 mol%) were added sequentially to the resulting solution and the vial was sealed and placed on a heating plate (50 °C). After stirring for 12 hours, the reaction mixture was cooled to room temperature and quenched by two drops of water. The reaction mixture was dried over anhydrous Na\(_2\)SO\(_4\) and concentrated under reduced pressure. Products were obtained after purification by flash column chromatography on silica gel.
6.2.4. Characterization of Products

4-(tert-Butyl)benzonitrile (S223, Table 3.6, entry 1, 75% isolated yield)

![4-(tert-Butyl)benzonitrile](image)

Was produced by reacting 1-(tert-butyl)-4-chlorobenzene with butyronitrile (R32) following the general procedure 3B.

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.60-7.58 (m, 2H), 7.49-7.47 (m, 2H), 1.33 (s, 9H).

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 156.78, 132.12, 126.31, 119.31, 109.47, 35.43, 31.10.

HRMS-EI (m/z): [M]$^+$ calcd for C$_{11}$H$_{13}$N$_1$, 159.104249; found, 159.104260.

4-Butylbenzonitrile (33, Table 3.6, entry 2, 70% isolated yield)

![4-Butylbenzonitrile](image)

Was produced by reacting 1-butyl-4-chlorobenzene with butyronitrile (R32) following the general procedure 3B.

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.57 – 7.55 (m, 2H), 7.28 – 7.26 (m, 2H), 2.66 (t, $J = 8.0$ Hz, 2H), 1.64 – 1.57 (m, 2H), 1.39 – 1.31 (m, 2H), 0.93 (t, $J = 7.5$ Hz, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 148.70, 132.23, 129.33, 119.33, 109.62, 35.95, 33.22, 22.39, 13.99.

HRMS-EI (m/z): [M]$^+$ calcd for C$_{11}$H$_{13}$N$_1$, 159.104249; found, 159.104430.

3,4-Dimethylbenzonitrile (34, Table 3.6, entry 3, 76% isolated yield)

![3,4-Dimethylbenzonitrile](image)
Was produced by reacting 4-chloro-1,2-dimethylbenzene with butyronitrile following the general procedure 3B.

**1H NMR** (500 MHz, CDCl₃) δ 7.41 – 7.37 (m, 2H), 7.21 (d, J = 8.0 Hz, 1H), 2.32 (s, 3H), 2.29 (s, 3H).

**13C NMR** (125 MHz, CDCl₃) δ 142.58, 138.00, 132.98, 130.41, 129.78, 119.43, 109.68, 20.27, 19.69.

**HRMS-EI (m/z):** [M]⁺ calcd for C₉H₉N₁, 131.072949; found, 131.073040.

**2,4-Dimethylbenzonitrile (35, Table 3.6, entry 4, 68% isolated yield)**

![2,4-Dimethylbenzonitrile](image)

Was produced by reacting 1-chloro-2,4-dimethylbenzene with butyronitrile (R32) following the general procedure 3B.

**1H NMR** (500 MHz, CDCl₃) δ 7.40 (d, J = 1.5 Hz, 1H), 7.28 (dd, J = 7.5, 2.0 Hz, 1H), 7.19 (d, J = 7.5 Hz, 1H), 2.50 (s, 3H), 2.34 (s, 3H).

**13C NMR** (125 MHz, CDCl₃) δ 138.99, 136.18, 133.68, 132.85, 130.23, 118.48, 112.68, 20.77, 20.09.

**HRMS-ESI (m/z):** [M + Na]⁺ calcd for C₉H₉N₁Na₁, 154.062718; found, 154.062660.

**4-Methoxybenzonitrile (36, Table 3.6, entry 5, 51% isolated yield)**

![4-Methoxybenzonitrile](image)

Was produced by reacting 1-chloro-4-methoxybenzene with butyronitrile (R32) following the general procedure 3B.

**1H NMR** (500 MHz, CDCl₃) δ 7.60-7.57 (m, 2H), 6.96-6.93 (m, 2H), 3.86 (s, 3H).

**13C NMR** (125 MHz, CDCl₃) δ 162.96, 134.10, 119.34, 114.87, 104.10, 55.67.
**Experimental Part**

**HRMS-EI (m/z):** \([M]^+\) calcd for C_{8}H_{7}N_{1}O_{1}, 133.052214; found, 133.052270.

**3,5-Dimethoxybenzonitrile** (37, Table 3.6, entry 6, 79% isolated yield)

![3,5-Dimethoxybenzonitrile](image)

Was produced by reacting 1-chloro-3,5-dimethoxybenzene with butyronitrile (R32) following the general procedure 3B.

**\(^{1}\text{H NMR}\) (500 MHz, CDCl\(_3\)) δ 6.76 (dd, J = 2.5, 1.0 Hz, 2H), 6.65 (t, J = 2.5 Hz, 1H), 3.81 (s, 6H).**

**\(^{13}\text{C NMR}\) (125 MHz, CDCl\(_3\)) δ 161.12, 118.89, 113.56, 110.02, 105.79, 55.81.**

**HRMS-EI (m/z):** \([M]^+\) calcd for C_{9}H_{9}N_{1}O_{2}, 163.062779; found, 163.062880.

**3-(Benzyloxy)benzonitrile** (38, Table 3.6, entry 7, 70% isolated yield)

![3-(Benzyloxy)benzonitrile](image)

Was produced by reacting 1-(benzyloxy)-3-chlorobenzene with butyronitrile (R32) following the general procedure 3B.

**\(^{1}\text{H NMR}\) (500 MHz, CDCl\(_3\)) δ 7.45 – 7.34 (m, 6H), 7.27 – 7.25 (m, 1H), 7.22 – 7.19 (m, 2H), 5.09 (s, 2H).**

**\(^{13}\text{C NMR}\) (125 MHz, CDCl\(_3\)) δ 158.89, 135.96, 130.50, 128.87, 128.48, 127.58, 124.88, 120.25, 118.81, 117.97, 113.37, 70.47.**

**HRMS-EI (m/z):** \([M]^+\) calcd for C_{4}H_{11}N_{1}O_{1}, 209.083514; found, 209.083470.

**4-(Benzyloxy)-3-fluorobenzonitrile** (39, Table 3.6, entry 8, 70% isolated yield)
Was produced by reacting 1-(benzyloxy)-4-chloro-2-fluorobenzene with butyronitrile (R32) following the general procedure 3B.

\[^{1}\text{H NMR}\,(500\text{ MHz, CDCl}_3)\,\delta\,7.44\,–\,7.34\,(m,\,7H),\,7.07\,–\,7.03\,(m,\,1H),\,5.21\,(s,\,2H)\].

\[^{13}\text{C NMR}\,(125\text{ MHz, CDCl}_3)\,\delta\,152.18\,(d,\,J_{\text{CF}} = 248.6\text{ Hz}),\,151.17\,(d,\,J_{\text{CF}} = 10.5\text{ Hz}),\,135.27,\,129.67\,(d,\,J_{\text{CF}} = 4.0\text{ Hz}),\,128.96,\,128.72,\,127.51,\,119.93\,(d,\,J_{\text{CF}} = 21.1\text{ Hz}),\,118.08\,(d,\,J_{\text{CF}} = 2.3\text{ Hz}),\,115.43\,(d,\,J_{\text{CF}} = 2.6\text{ Hz}),\,104.44\,(d,\,J_{\text{CF}} = 8.1\text{ Hz}),\,77.39\].

\[^{\text{HRMS-ESI (m/z):}}\,[\text{M+Na}]^{+}\text{ calcd for } C_{14}H_{10}N_{1}O_{1}F_{1}Na_{1},\,250.063861;\text{ found, 250.064030.}\]

**4-Fluoro-[1,1''-biphenyl]-3-carbonitrile (310, Table 3.6, entry 9, 75% isolated yield)**

Was produced by reacting 3-chloro-4-fluoro-1,1''-biphenyl with butyronitrile (R32) following the general procedure 3B.

\[^{1}\text{H NMR}\,(500\text{ MHz, CDCl}_3)\,\delta\,7.82\,–\,7.78\,(m,\,2H),\,7.53\,–\,7.46\,(m,\,4H),\,7.44\,–\,7.40\,(m,\,1H),\,7.31\,–\,7.27\,(m,\,1H)\].

\[^{13}\text{C NMR}\,(125\text{ MHz, CDCl}_3)\,\delta\,162.62\,(d,\,J_{\text{CF}} = 257.5\text{ Hz}),\,138.68\,(d,\,J_{\text{CF}} = 3.6\text{ Hz}),\,138.08,\,133.78\,(d,\,J_{\text{CF}} = 8.1\text{ Hz}),\,131.97,\,129.32,\,128.53,\,127.09,\,116.96\,(d,\,J_{\text{CF}} = 19.6\text{ Hz}),\,114.08,\,101.99\,(d,\,J_{\text{CF}} = 15.6\text{ Hz})\].

\[^{\text{HRMS-EI (m/z):}}\,[\text{M}]^{+}\text{ calcd for } C_{13}H_{8}N_{1}F_{1},\,197.063527;\text{ found, 197.063640.}\]

**[1,1''-Biphenyl]-4-carbonitrile (S227, Table 3.6, entry 10, 62% isolated yield)**
Was produced by reacting 4-chloro-1,1'-biphenyl with butyronitrile (R32) following the general procedure 3B.

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.74 – 7.68 (m, 4H), 7.60 – 7.58 (m, 2H), 7.51 – 7.47 (m, 2H), 7.45 – 7.41 (m, 1H).

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 145.81, 139.31, 132.72, 129.24, 128.79, 127.87, 127.36, 119.07, 111.06.

HRMS-EI (m/z): [M]$^+$ calcd for C$_{13}$H$_9$N$_1$, 179.072949; found, 179.072710.

1-Naphthonitrile (S229, Table 3.6, entry 11, 81% isolated yield)

![Naphthonitrile](image)

Was produced by reacting 1-chloronaphthalene with butyronitrile (R32) following the general procedure 3B.

$^1$H NMR (500 MHz, CDCl$_3$) δ 8.25 (dd, $J$ = 8.5, 1.5 Hz, 1H), 8.08 (dt, $J$ = 8.5, 1.0 Hz, 1H), 7.94-7.91 (m, 2H), 7.72-7.69 (m, 1H), 7.64-7.61 (m, 1H), 7.54-7.51 (m, 1H);

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 133.41, 133.07, 132.77, 132.50, 128.79, 128.74, 127.69, 125.30, 125.06, 117.95, 110.35.

HRMS-EI (m/z): [M]$^+$ calcd for C$_{11}$H$_7$N$_1$, 153.057299; found, 153.057330.

Anthracene-9-carbonitrile (313, Table 3.6, entry 12, 71% isolated yield)

![Anthracene-9-carbonitrile](image)

Was produced by reacting 9-chloroanthracene with butyronitrile (R32) following the general procedure 3B.
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\[ ^1\text{H NMR (500 MHz, CDCl}_3 \] \( \delta \) 8.64 (s, 1H), 8.42-8.39 (m, 2H), 8.06 (dd, \( J = 8.5, 1.0 \) Hz, 2H), 7.72-7.69 (m, 2H), 7.59-7.56 (m, 2H).

\[ ^13\text{C NMR (125 MHz, CDCl}_3 \] \( \delta \) 133.45, 132.87, 130.76, 129.09, 129.07, 126.49, 125.43, 117.40, 105.58.

HRMS-EI \( (m/z) \): [M]+ calcd for C\(_{15}\)H\(_9\)N\(_1\), 203.072949; found, 203.073000.

4-(Piperidin-1-yl)benzonitrile (314, Table 3.6, entry 13, 65% isolated yield)

![Structure of 4-(Piperidin-1-yl)benzonitrile](image)

Was produced by reacting 1-(4-chlorophenyl)piperidine with butyronitrile (R32) following the general procedure 3B.

\[ ^1\text{H NMR (500 MHz, CDCl}_3 \] \( \delta \) 7.46 – 7.44 (m, 2H), 6.85 – 6.82 (m, 2H), 3.33 – 3.31 (m, 4H), 1.69 – 1.64 (m, 6H).

\[ ^13\text{C NMR (125 MHz, CDCl}_3 \] \( \delta \) 153.70, 133.59, 120.48, 114.17, 99.06, 48.56, 25.37, 24.38.

HRMS-EI \( (m/z) \): [M]+ calcd for C\(_{12}\)H\(_{14}\)N\(_2\), 186.115147; found, 186.114930.

4-(1H-pyrrol-1-yl)benzonitrile (315, Table 3.6, entry 14, 65% isolated yield)

![Structure of 4-(1H-pyrrol-1-yl)benzonitrile](image)

Was produced by reacting 1-(4-chlorophenyl)-1H-pyrrole with butyronitrile (R32) following the general procedure 3B.

\[ ^1\text{H NMR (500 MHz, CDCl}_3 \] \( \delta \) 7.73-7.70 (m, 2H), 7.50-7.47 (m, 2H), 7.14 (t, \( J = 2.5 \) Hz, 2H), 6.41 (t, \( J = 2.0 \) Hz, 2H).

\[ ^13\text{C NMR (125 MHz, CDCl}_3 \] \( \delta \) 143.80, 133.93, 120.08, 119.02, 118.60, 112.29, 108.75.

HRMS-EI \( (m/z) \): [M]+ calcd for C\(_{11}\)H\(_8\)N\(_2\), 168.068198; found, 168.068220.

4-Morpholinobenzonitrile (316, Table 3.6, entry 15, 70% isolated yield)

![Structure of 4-Morpholinobenzonitrile](image)
Experimental Part

Was produced by reacting 4-(4-chlorophenyl)morpholine with butyronitrile (R32) following the general procedure 3B.

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.53-750 (m, 2H), 6.88-6.85 (m, 2H), 3.86-3.84 (m, 4H), 3.29-3.27 (m, 4H).

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 153.62, 133.64, 119.98, 114.20, 101.12, 66.58, 47.45.

HRMS-EI (m/z): [M]$^+$ calcd for C$_{11}$H$_{12}$N$_2$O$_1$, 188.094412; found, 188.094740.

Benzo[d][1,3]dioxole-5-carbonitrile (317, Table 3.6, entry 16, 71% isolated yield)

Was produced by reacting 5-chlorobenzo[d][1,3]dioxole with butyronitrile (R32) following the general procedure 3B.

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.21 (dd, $J$ = 8.0, 1.5 Hz, 1H), 7.03 (d, $J$ = 1.5 Hz, 1H), 6.86 (d, $J$ = 8.0 Hz, 1H), 6.07 (s, 2H).

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 151.65, 148.16, 128.35, 119.01, 111.55, 109.26, 105.11, 102.34.

HRMS-EI (m/z): [M]$^+$ calcd for C$_8$H$_5$N$_1$O$_2$, 147.031479; found, 147.031480.

1-((2-(Trimethylsilyl)ethoxy)methyl)-1H-indole-6-carbonitrile (318, Table 3.6, entry 17, 78% isolated yield)

Was produced by reacting 6-chloro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indole with butyronitrile (R32) following the general procedure 3B.
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\[ ^1H \text{ NMR} \ (500 \text{ MHz, CDCl}_3) \delta 7.84 – 7.83 \ (m, 1H), 7.68 \ (dd, J = 8.5, 1.0 \text{ Hz, 1H}), 7.38 – 7.36 \ (m, 2H), 6.60 \ (dd, J = 3.5, 1.0 \text{ Hz, 1H}), 5.50 \ (s, 2H), 3.48 – 3.45 \ (m, 2H), 0.91 – 0.87 \ (m, 2H), 0.06 \ (s, 9H). \]

\[ ^13C \text{ NMR} \ (125 \text{ MHz, CDCl}_3) \delta 135.28, 132.44, 131.74, 123.26, 121.90, 120.66, 115.17, 104.81, 103.28, 76.06, 66.37, 17.83, -1.33. \]

HRMS-ESI (m/z): [M + Na]^+ calcd for C_{15}H_{20}N_2O_1Si_1Na_1, 295.123780; found, 295.123710.

1-Benzyl-1H-indole-7-carbonitrile (319, Table 3.6, entry 18, 87% isolated yield)

![1-Benzyl-1H-indole-7-carbonitrile](image)

Was produced by reacting 1-benzyl-7-chloro-1H-indole with butyronitrile (R32) following the general procedure 3B.

\[ ^1H \text{ NMR} \ (500 \text{ MHz, CDCl}_3) \delta 7.87 \ (dd, J = 8.0, 1.5 \text{ Hz, 1H}), 7.53 \ (dd, J = 7.5, 1.0 \text{ Hz, 1H}), 7.34 – 7.27 \ (m, 3H), 7.20 \ (d, J = 3.0 \text{ Hz, 1H}), 7.17 – 7.12 \ (m, 3H), 6.65 \ (dd, J = 3.5, 1.5 \text{ Hz, 1H}), 5.74 \ (s, 2H). \]

\[ ^13C \text{ NMR} \ (125 \text{ MHz, CDCl}_3) \delta 137.28, 134.38, 131.02, 130.51, 128.97, 128.88, 127.96, 126.93, 126.60, 119.51, 118.60, 103.11, 94.08, 50.77. \]

HRMS-ESI (m/z): [M + Na]^+ calcd for C_{16}H_{12}N_2Na_1, 255.089266; found, 255.089410.

4-(Trifluoromethyl)benzonitrile (320, Table 3.8, entry 2, 65% isolated yield)

![4-(Trifluoromethyl)benzonitrile](image)

Was produced by reacting 4-(trifluoromethyl)phenyl trifluoromethanesulfonate with butyronitrile (R32) following the general procedure 3D.

\[ ^1H \text{ NMR} \ (500 \text{ MHz, CDCl}_3) \delta 7.81 \ (d, J = 8.5 \text{ Hz, 2H}), 7.16 \ (d, J = 8.5 \text{ Hz, 2H}). \]

\[ ^13C \text{ NMR} \ (125 \text{ MHz, CDCl}_3) \delta 134.72 \ (q, J_{CF} = 33.1 \text{ Hz}), 132.83, 126.33 \ (q, J_{CF} = 3.8 \text{ Hz}), 123.18 \ (q, J_{CF} = 270.9 \text{ Hz}), 117.57, 116.22 \ (q, J_{CF} = 1.3 \text{ Hz}). \]
HRMS-ESI (m/z): [M]+ calcd for C_{8}H_{4}N_{1}F_{3}, 171.029070; found, 171.029034.

**Methyl 4-cyanobenzoate (321, Table 3.8, entry 3, 62% isolated yield)**

![Methyl 4-cyanobenzoate structure](image)

Was produced by reacting methyl 4-(((trifluoromethyl)sulfonyl)oxy)benzoate with butyronitrile (R32) following the general procedure 3D.

\[ \text{1H NMR (500 MHz, CDCl}_3\text{): } \delta 8.14 - 8.12 \text{ (m, 2H), 7.75 - 7.73 (m, 2H), 3.95 (s, 3H).} \]

\[ \text{13C NMR (125 MHz, CDCl}_3\text{): } \delta 165.52, 134.04, 132.33, 130.20, 118.06, 116.51, 52.83. \]

HRMS-ESI (m/z): [M+Na]+ calcd for C_{9}H_{7}N_{1}O_{2}Na_{1}, 184.036890; found, 184.036898.

**4-(1H-Pyrazol-1-yl)benzonitrile (327, Table 3.8, entry 16, 85% isolated yield)**

![4-(1H-Pyrazol-1-yl)benzonitrile structure](image)

Was produced by reacting methyl 4-((1H-pyrazol-1-yl)phenyl trifluoromethanesulfonate with butyronitrile (R32) following the general procedure 3D.

\[ \text{1H NMR (500 MHz, CDCl}_3\text{): } \delta 7.99 \text{ (d, } J = 2.5 \text{ Hz, 1H), 7.84 - 7.82 (m, 2H), 7.76 (d, } J = 1.5 \text{ Hz, 1H), 7.75 - 7.72 (m, 2H), 6.53 (dd, } J = 2.5, 1.5 \text{ Hz, 1H).} \]

\[ \text{13C NMR (125 MHz, CDCl}_3\text{): } \delta 143.06, 142.52, 133.75, 126.91, 119.03, 119.01, 118.49, 109.67, 109.14. \]

HRMS-EI (m/z): [M+H]+ calcd for C_{10}H_{8}N_{3}, 170.071330; found, 170.071271.

**Quinoline-6-carbonitrile (328, Table 3.8, entry 17, 72% isolated yield)**

![Quinoline-6-carbonitrile structure](image)
Was produced by reacting methyl quinolin-6-yl trifluoromethanesulfonate with butyronitrile (R32) following the general procedure 3D.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 9.06 (dd, $J = 4.5, 2.0$ Hz, 1H), 8.25 – 8.24 (m, 2H), 8.21 (d, $J = 8.5$Hz, 1H), 7.86 (dd, $J = 9.0, 2.0$ Hz, 1H), 7.55 (dd, $J = 8.5, 4.5$ Hz, 1H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 153.37, 149.24, 136.55, 134.25, 131.21, 130.30, 127.71, 122.87, 118.61, 110.60.

HRMS-EI (m/z): [M+H]$^+$ calcd for C$_{10}$H$_7$N$_2$, 155.060420; found, 155.060372.

$1H$-indole-4-carbonitrile (330, Table 3.8, entry 18, 55% isolated yield)

Was produced by reacting $1H$-indol-4-yl trifluoromethanesulfonate with butyronitrile (R32) following the general procedure 3D.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.69 (br s, 1H), 7.66 – 7.64 (m, 1H), 7.48 (dd, $J = 7.5, 1.0$ Hz, 1H), 7.40 (dd, $J = 3.0, 2.0$ Hz, 1H), 7.40 (dd, $J = 8.0, 7.5$ Hz, 1H), 6.77 – 6.76 (m, 1H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 135.65, 129.36, 127.10, 125.49, 121.72, 119.00, 116.09, 103.05, 101.76.

HRMS-EI (m/z): [M+Na]$^+$ calcd for C$_9$H$_6$N$_2$Na, 165.042340; found, 165.042317.

$9H$-carbazole-2-carbonitrile (331, Table 3.8, entry 19, 50% isolated yield)

Was produced by reacting $9H$-carbazol-1-yl trifluoromethanesulfonate with butyronitrile (R32) following the general procedure 3D.
**Experimental Part**

**1H NMR** (500 MHz, CDCl₃) δ 8.41 (br s, 1H), 8.14 – 8.10 (m, 2H), 7.76 – 7.75 (m, 1H), 7.55 – 7.49 (m, 3H), 7.33 – 7.30 (m, 1H).

**13C NMR** (125 MHz, CDCl₃) δ 140.73, 138.45, 128.05, 127.00, 122.87, 122.31, 121.31, 121.12, 120.61, 120.28, 114.94, 111.29, 108.24.


5,6,7,8-Tetrahydronaphthalene-2-carbonitrile (322, Table 3.8, entry 8, 96% isolated yield)

![5,6,7,8-Tetrahydronaphthalene-2-carbonitrile](image)

Was produced by reacting 5,6,7,8-tetrahydronaphthalen-2-yl trifluoromethanesulfonate with butyronitrile (R32) following the general procedure 3E.

**1H NMR** (500 MHz, CDCl₃) δ 7.34 – 7.33 (m, 2H), 7.13 (d, J = 8.0 Hz, 1H), 2.81 – 2.76 (m, 4H), 1.83 – 1.79 (m, 4H).

**13C NMR** (125 MHz, CDCl₃) δ 143.11, 138.56, 132.89, 129.97, 128.97, 119.49, 109.23, 29.74, 29.15, 22.70, 22.66.


2-Naphthonitrile (S230, Table 3.8, entry 9, 91% isolated yield)

![2-Naphthonitrile](image)

Was produced by reacting naphthalen-2-yl trifluoromethanesulfonate with butyronitrile (R32) following the general procedure 3E.

**1H NMR** (500 MHz, CDCl₃) δ 8.23 (d, J = 1.5 Hz, 1H), 7.92 – 7.88 (m, 3H), 7.66 – 7.59 (m, 3H). **13C NMR** (125 MHz, CDCl₃) δ 134.76, 134.26, 132.36, 129.97, 128.97, 119.49, 109.23, 29.74, 29.15, 22.70, 22.66.

HRMS-ESI (m/z): [M + Na]⁺ calcd for C₁₁H₇N₁Na₁, 176.047068; found, 176.047010.

[1,1'-Biphenyl]-2,2'-dicarbonitrile (323, Table 3.8, entry 10, 82% isolated yield)
Was produced by reacting [1,1'-biphenyl]-2,2'-diyl bis(trifluoromethanesulfonate) with butyronitrile (R32) following the general procedure 3E.

\( ^1\text{H NMR} \ (500 \text{ MHz, CDCl}_3) \delta \ 7.83 \ (dt, J = 7.5, 1.5 \text{ Hz, } 2\text{H}), \ 7.74 \ – \ 7.71 \ (m, \ 2\text{H}), \ 7.59 \ – \ 7.56 \ (m, \ 4\text{H}). \)

\( ^{13}\text{C NMR} \ (125 \text{ MHz, CDCl}_3) \delta \ 141.71, \ 133.70, \ 132.99, \ 130.70, \ 129.34, \ 117.68, \ 112.54. \)

HRMS-ESI (m/z): [M+Na]⁺ calcd for C\(_{14}\)H\(_8\)N\(_2\)Na, 227.057966; found, 227.057980.

**4'-Chloro-[1,1'-biphenyl]-4-carbonitrile (324)** (Table 3.8, entry 11, 65% isolated yield)

Was produced by reacting 4'-chloro-[1,1'-biphenyl]-4-yl trifluoromethanesulfonate with butyronitrile (R32) following the general procedure 3E.

\( ^1\text{H NMR} \ (500 \text{ MHz, CDCl}_3) \delta \ 7.74 \ – \ 7.72 \ (m, \ 2\text{H}), \ 7.66 \ – \ 7.64 \ (m, \ 2\text{H}), \ 7.53 \ – \ 7.51 \ (m, \ 2\text{H}), \ 7.47 \ – \ 7.44 \ (m, \ 2\text{H}). \)

\( ^{13}\text{C NMR} \ (125 \text{ MHz, CDCl}_3) \delta \ 144.51, \ 137.72, \ 135.10, \ 132.83, \ 129.45, \ 128.60, \ 127.70, \ 118.87, \ 111.43. \)

HRMS-ESI (m/z): [M+Na]⁺ calcd for C\(_{13}\)H\(_8\)N\(_1\)Na, 236.023746; found, 236.023830.

**4-Chloro-3-ethylbenzonitrile (325)** (Table 3.8, entry 12, 75% isolated yield)

Was produced by reacting 4-chloro-3-ethylphenyl trifluoromethanesulfonate with butyronitrile (R32) following the general procedure 3E.
1H NMR (500 MHz, CDCl₃) δ 7.53 (dd, J = 2.0, 1.0 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.42 (dd, J = 8.5, 3.0 Hz, 1H), 2.79 (q, J = 7.5 Hz, 2H), 1.25 (t, J = 8.0 Hz, 3H).

13C NMR (125 MHz, CDCl₃) δ 143.38, 139.32, 133.03, 130.67, 130.47, 118.42, 111.06, 26.67, 13.60.

HRMS-ESI (m/z): [M+Na]⁺ calcd for C₉H₈NClNa₁, 188.023746; found, 188.023820.

2-(Pyrrolidin-1-yl)benzonitrile (326, Table 3.8, entry 13, 76% isolated yield)

Was produced by reacting 2-(pyrrolidin-1-yl)phenyl trifluoromethanesulfonate with butyronitrile (R32) following the general procedure 3E.

1H NMR (500 MHz, CDCl₃) δ 7.45 – 7.41 (m, 1H), 7.33 – 7.30 (m, 1H), 6.65 – 6.62 (m, 2H), 3.61 – 3.58 (m, 4H), 2.01 – 1.99 (m, 4H).

13C NMR (125 MHz, CDCl₃) δ 150.19, 135.84, 133.47, 121.57, 115.97, 114.33, 94.49, 49.91, 25.85.

HRMS-ESI (m/z): [M + H]⁺ calcd for C₁₁H₁₃N₂, 173.107322; found, 173.107390.

9-Benzyl-9H-carbazole-2-carbonitrile (329, Table 3.8, entry 15, 90% isolated yield)

Was produced by reacting 9-benzyl-9H-carbazol-1-yl trifluoromethanesulfonate with butyronitrile (R32) following the general procedure 3E.

1H NMR (500 MHz, CDCl₃) δ 8.18 – 8.15 (m, 2H), 7.67 – 7.65 (m, 1H), 7.56 – 7.53 (m, 1H), 7.50 (dd, J = 8.0, 1.0 Hz, 1H), 7.46 – 7.44 (m, 1H), 7.35 – 7.32 (m, 1H), 7.31 – 7.27 (m, 3H), 7.13 – 7.11 (m, 2H), 5.53 (s, 2H).
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\[^{13}\text{C}\] NMR (125 MHz, CDCl\textsubscript{3}) δ 142.00, 139.63, 136.20, 129.14, 128.09, 128.05, 126.65, 126.44, 122.65, 122.07, 121.43, 121.14, 120.45, 120.28, 113.29, 109.59, 108.38, 46.94.

**HRMS-ESI (m/z):** [M+Na]\(^{+}\) calcd for C\textsubscript{20}H\textsubscript{14}N\textsubscript{2}Na\textsubscript{1}, 305.104916; found, 305.105100.

1,2,3,6-Tetrahydro-[1,1'-biphenyl]-4-carbonitrile (332, Table 3.8, entry 20, 50% isolated yield)

![1,2,3,6-Tetrahydro-[1,1'-biphenyl]-4-carbonitrile](image)

Was produced by reacting 1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl trifluoromethanesulfonate with butyronitrile (R32) following the general procedure 3E.

\[^{1}\text{H}\] NMR (500 MHz, CDCl\textsubscript{3}) δ 7.36 – 7.32 (m, 2H), 7.26 – 7.23 (m, 1H), 7.21 – 7.19 (m, 2H), 6.73 – 6.71 (m, 1H), 2.86 – 2.79 (m, 1H), 2.55 – 2.48 (m, 1H), 2.47 – 2.27 (m, 3H), 2.06 – 2.01 (m, 1H), 1.85 – 1.77 (m, 1H).

\[^{13}\text{C}\] NMR (125 MHz, CDCl\textsubscript{3}) δ 145.03, 144.68, 128.77, 126.78, 126.77, 119.61, 112.44, 38.45, 33.65, 28.73, 27.34.

**HRMS-ESI (m/z):** [M+Na]\(^{+}\) calcd for C\textsubscript{13}H\textsubscript{13}Na\textsubscript{1}, 206.094018; found, 206.093990.

(R)-2,8-Dimethyl-2-((4R,8R)-4,8,12-trimethyltridecyl)chromane-6-carbonitrile (335, Scheme 3.6, 50% isolated yield)

![R)-2,8-Dimethyl-2-((4R,8R)-4,8,12-trimethyltridecyl)chromane-6-carbonitrile](image)

Was produced by reacting (R)-2,8-dimethyl-2-((4R,8R)-4,8,12-trimethyltridecyl)chroman-6-yl trifluoromethanesulfonate with butyronitrile (R32) following the general procedure 3E.

\[^{1}\text{H}\] NMR (500 MHz, CDCl\textsubscript{3}) δ 7.23 – 7.22 (m, 2H), 2.80 – 2.70 (m, 2H), 2.15 (s, 3H), 1.87 – 1.75 (m, 2H), 1.60 – 1.01 (m, 24H), 0.87 – 0.83 (m, 12H).
**Experimental Part**

**13C NMR** (125 MHz, CDCl₃) δ 156.28, 131.91, 131.64, 127.82, 121.52, 120.08, 101.89, 77.87, 40.29, 39.51, 37.57, 37.51, 37.47, 37.42, 32.93, 32.78, 30.73, 28.12, 24.94, 24.57, 24.40, 22.86, 22.77, 22.08, 21.03, 19.89, 19.78, 16.04.

**HRMS-ESI (m/z):** [M + Na]⁺ calcd for C₂₈H₄₅N₁O₁Na₁, 434.339333; found, 434.339480.

(8S,9S,10R,13R,14S)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-2,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthrene-3-carbonitrile (334, Scheme 3.6, 50% isolated yield)

![Chemical structure](image)

Was produced by reacting (8S,9S,10R,13R,14S,17R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-2,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-3-yl trifluoromethanesulfonate with butyronitrile (R₃₂) following the general procedure 3E.

**1H NMR** (500 MHz, CDCl₃) δ 6.64 (d, J = 2.0 Hz, 1H), 5.77 (t, J = 4.0 Hz, 1H), 2.40 – 2.24 (m, 3H), 2.03 (dt, J = 13.0, 3.5 Hz, 1H), 1.89 – 1.81 (m, 2H), 1.77 – 1.70 (m, 1H), 1.68 – 1.48 (m, 4H), 1.45 – 1.25 (m, 5H), 1.21 – 0.96 (m, 10H), 0.92 – 0.91 (m, 6H), 0.86 (dd, J = 7.0, 2.5 Hz, 6H), 0.70 (s, 3H).

**13C NMR** (125 MHz, CDCl₃) δ 143.57, 140.03, 133.05, 120.56, 106.62, 56.82, 56.24, 47.97, 42.58, 39.70, 39.64, 36.30, 35.90, 34.60, 32.88, 32.34, 31.68, 28.32, 28.15, 24.51, 24.26, 23.97, 22.96, 22.70, 21.04, 19.11, 18.84, 12.10.

**HRMS-ESI (m/z):** [M+Na]⁺ calcd for C₂₈H₄₃N₁Na₁, 416.328767; found, 416.328860.

(8S,9S,13S,14S)-3-methoxy-13-methyl-7,8,9,11,12,13,14,15-octahydro-6H-cyclopenta[a]phenanthrene-17-carbonitrile (333, Scheme 3.6, 50% isolated yield)

![Chemical structure](image)
Was produced by reacting (8R,9S,13S,14S)-3-methoxy-13-methyl-7,8,9,11,12,13,14,15-octahydro-6H-cyclopenta[a]phenanthren-17-yl trifluoromethanesulfonate with butyronitrile (R32) following the general procedure.

**1H NMR** (500 MHz, CDCl₃) δ 7.19 (dd, J = 9.0, 1.5 Hz, 1H), 6.73 (dd, J = 8.5, 3.0 Hz, 1H), 6.67 (dd, J = 3.5, 2.0 Hz, 1H), 6.65 (dd, J = 3.5, 1.0 Hz, 1H), 3.78 (s, 3H), 2.96 – 2.85 (m, 2H), 2.48 – 2.40 (m, 2H), 2.34 – 2.29 (m, 1H), 2.25 – 2.19 (m, 1H), 2.10 – 2.06 (m, 1H), 1.95 – 1.90 (m, 1H), 1.73 – 1.58 (m, 4H), 1.52 – 1.43 (m, 1H), 0.96 (s, 3H).

**13C NMR** (125 MHz, CDCl₃) δ 157.75, 147.36, 137.70, 132.18, 127.75, 126.15, 115.99, 114.06, 111.65, 55.37, 55.35, 48.63, 44.27, 37.34, 34.21, 32.80, 29.65, 27.81, 26.33, 16.52.

**HRMS-ESI (m/z):** [M+Na]⁺ calcd for C₂₀H₂₃N₁O₁Na₁, 316.167182; found, 316.167120.

### 6.2.5. Procedure for the Gram-Scale Experiment

Under argon, to a 50 mL two-necked round-bottomed flask equipped with a magnetic stirring bar was added Ni(COD)₂ (110.0 mg, 10 mol%), Xantphos (231.0 mg, 10 mol%) and toluene (12.0 mL). The mixture was allowed to stir for 10 min. Then butyronitrile (R32, 2.7 g, 40 mmol), S399 (2.15 g, 4.0 mmol), Et₃N (809.0 mg, 8.0 mmol) and AlCl₃ (320.0 mg, 60 mol%) were added sequentially to the resulting solution. The flask was connected to an argon line and placed in a 70 °C oil bath. After stirring for 12 hours, the reaction mixture was cooled to room temperature and quenched by 1.0 mL of water. The reaction mixture was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. Product 335 (1.5 g, 91%) was obtained after purification by flash column chromatography on silica gel.
6.2.6. Mechanistic Experiments

**The control experiment using dodecanenitrile as a cyanating reagent (Scheme 3.19)**

Under argon, to an 8.0 mL Screw-cap vial equipped with a magnetic stirring bar was added Ni(COD)$_2$ (2.8 mg, 10 mol%), Xantphos (5.8 mg, 10 mol%) and toluene (0.5 mL). The mixture was allowed to stir for 5 min. Then dodecanenitrile (R33, 181.3 mg, 1.0 mmol), phenyl triflate (S321, 22.6 mg, 0.1 mmol), Et$_3$N (27.8 µL, 0.2 mmol) and AlCl$_3$ (8.0 mg, 60 mol%) were added sequentially to the resulting solution and the vial was sealed and placed on a heating plate (50 °C). After stirring for 12 hours, the reaction mixture was cooled to room temperature and diluted with DCM (2.0 mL). n-Dodecane (17.0 mg, 0.1 mmol) was then added to the diluted solution and the mixture was analyzed by GC. The result showed that 98% of S221 was formed and 125% of the corresponding alkene was formed as a mixture of isomers.

**The control experiment in the absence of the substrate (Scheme 3.20a)**

Under argon, to an 8.0 mL Screw-cap vial equipped with a magnetic stirring bar was added Ni(COD)$_2$ (2.8 mg, 10 mol%), Xantphos (5.8 mg, 10 mol%) and toluene (0.5 mL). The mixture was allowed to stir for 5 min. Then dodecanenitrile (R33, 181.3 mg, 1.0 mmol), Et$_3$N (27.8 µL, 0.2 mmol) and AlCl$_3$ (8.0 mg, 60 mol%) were added sequentially to the resulting solution and the vial was sealed and placed on a heating plate (50 °C). After stirring for 12 hours, the reaction mixture was cooled to room temperature and diluted with DCM (2.0 mL). n-Dodecane (17.0 mg, 0.1 mmol) was then added to the diluted solution and the mixture was analyzed by GC. The result showed that 98% of S221 was formed and 125% of the corresponding alkene was formed as a mixture of isomers.
0.1 mmol) was then added to the diluted solution and the mixture was analyzed by GC. The result showed that 23% of 337 the corresponding alkene was formed as a mixture of isomers.

The reaction resumed by adding the substrate after 12 h (Scheme 3.20b)

Under argon, to an 8.0 mL Screw-cap vial equipped with a magnetic stirring bar was added Ni(COD)$_2$ (2.8 mg, 10 mol%), Xantphos (5.8 mg, 10 mol%) and toluene (0.5 mL). The mixture was allowed to stir for 5 min. Then dodecanenitrile (R33, 181.3 mg, 1.0 mmol), Et$_3$N (27.8 µL, 0.2 mmol) and AlCl$_3$ (8.0 mg, 60 mol%) were added sequentially to the resulting solution and the vial was sealed and placed on a heating plate (50 °C). After stirring for 12 hours, the reaction mixture was cooled to room temperature and phenyl triflate (S321, 22.6 mg, 0.1 mmol) was added. After stirring for additional 12 hours at 50 °C, the reaction mixture was cooled to room temperature and diluted with DCM (2.0 mL). n-Dodecane (17.0 mg, 0.1 mmol) was then added to the diluted solution and the mixture was analyzed by GC. The result showed that 92% of S221 was formed and 125% of the corresponding alkene was formed as a mixture of isomers.

The control experiment using Bu$_4$NCN (Scheme 3.21a)

Under argon, to an 8.0 mL Screw-cap vial equipped with a magnetic stirring bar was added Ni(COD)$_2$ (2.8 mg, 10 mol%), Xantphos (5.8 mg, 10 mol%) and toluene (0.5 mL). The mixture was allowed to stir for 5 min. Then Bu$_4$NCN (53.7 mg, 0.2 mmol), phenyl triflate (S321, 22.6 mg, 0.1 mmol), Et$_3$N (27.8 µL, 0.2 mmol) and AlCl$_3$ (8.0 mg, 60 mol%) were added sequentially to
the resulting solution and the vial was sealed and placed to a heating plate (50 °C). After stirring for 12 hours, the reaction mixture was cooled to room temperature and diluted with DCM (2.0 mL). n-Dodecane (17.0 mg, 0.1 mmol) was then added to the diluted solution and the mixture was analyzed by GC. The result showed that no cyanation product was formed in the reaction.

The control experiment using acetone cyanohydrin (Scheme 3.21b)

Under argon, to an 8.0 mL Screw-cap vial equipped with a magnetic stirring bar was added Ni(COD)$_2$ (2.8 mg, 10 mol%), Xantphos (5.8 mg, 10 mol%) and toluene (0.5 mL). The mixture was allowed to stir for 5 min. Then acetone cyanohydrin (17.0 mg, 0.2 mmol), phenyl triflate (S321, 22.6 mg, 0.1 mmol), Et$_3$N (27.8 µL, 0.2 mmol) and AlCl$_3$ (8.0 mg, 60 mol%) were added sequentially to the resulting solution and the vial was sealed and placed to a heating plate (50 °C). After stirring for 12 hours, the reaction mixture was cooled to room temperature and diluted with DCM (2.0 mL). n-Dodecane (17.0 mg, 0.1 mmol) was then added to the diluted solution, and the mixture was analyzed by GC. The result showed that no cyanation product was formed in the reaction.
6.3. Experimental Part to Chapter 4
6.3.1. Substrates Preparation and Characterization

Synthesis of hex-5-yn-1-yl 4-methylbenzenesulfonate (S48)

\[
\begin{align*}
\text{hex-5-yn-1-ol} & \xrightarrow{\text{TsCl, Et}_3\text{N, DMAP, DCM, 0 °C to RT}} \text{S48} \\
\end{align*}
\]

To a 100 mL two-neck round-bottom flask containing 5-hexyn-1-ol (0.55 mL, 5.0 mmol, 1.00 equiv.) and anhydrous CH\(_2\)Cl\(_2\) (10 mL) were added successively DMAP (61 mg, 0.1 equiv.), Et\(_3\)N (1.1 mL, 1.5 equiv.) and TsCl (1.4 g, 1.5 equiv.) at 0 °C. The reaction mixture was allowed to warm up to room temperature and stirred for 24 hours. The solvent was removed under reduced pressure and the resulting residue was purified by flash column chromatography using silica gel (ethyl acetate/pentane) to give the product (1.0 g, 90% yield).

Characterization of S48

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.79 (d, \(J = 8.0\) Hz, 2H), 7.35 (d, \(J = 8.0\) Hz, 2H), 4.06 (t, \(J = 6.5\) Hz, 2H), 2.45 (s, 3H), 2.16 (td, \(J = 7.0, 2.5\) Hz, 2H), 1.92 (t, \(J = 3.0\) Hz, 1H), 1.81 – 1.75 (m, 2H), 1.59 – 1.53 (m, 2H).

\(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 144.88, 133.26, 129.99, 128.03, 83.53, 70.04, 69.10, 27.92, 24.37, 21.79, 17.88.

HRMS-ESI (m/z): \([M + Na]^+\) calcd for C\(_{13}\)H\(_{16}\)O\(_3\)S\(_1\)Na\(_1\), 275.071140; found, 275.071237.

Synthesis of \(N\)-(hex-5-yn-1-yl)-4-methylbenzenesulfonamide (S49)

\[
\begin{align*}
\text{hex-5-yn-1-ol} & \xrightarrow{1. \text{MsCl, Et}_3\text{N}} \text{NHTs} \\
\end{align*}
\]

To a flame-dried 100 mL flask containing 5-hexyn-1-ol (980.7 mg, 10.0 mmol), triethylamine (4.2 mL, 3.0 equiv.) and CH₂Cl₂ (40 mL) was added methanesulfonyl chloride (1.6 g, 1.4 equiv.) dropwise at 0 °C, causing the reaction mixture to turn from light yellow to a turbid orange. After stirring for 3 hours, water (15.0 mL) was added. The organic phase was separated by extraction with dichloromethane and the combined organic extracts were washed with brine, dried with Na₂SO₄ and concentrated under reduced pressure. The crude residue thus obtained was directly dissolved in DMF (20.0 mL) without purification. Then TsNH₂ (2.7 g, 1.6 equiv.) and Cs₂CO₃ (3.9 g, 1.2 equiv.) were sequentially added and the mixture was allowed to stir at 120° C. After completion (TLC monitoring), the reaction mixture was cooled down to room temperature and quenched by saturated aqueous NH₄Cl. Then the organic layer was separated by extraction with ether, washed with brine, dried with Na₂SO₄ and concentrated under reduced pressure. Purification of the resulting residue by flash column chromatography afforded the product (1.3 g, 50% yield).

Characterization of S49

¹H NMR (400 MHz, CDCl₃) δ: 7.75 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 4.77 (t, J = 6.5 Hz, 1H), 2.94 (q, J = 7.0 Hz, 2H), 2.42 (s, 3H), 2.13 (td, J = 7.0, 2.5 Hz, 2H), 1.91 (t, J = 3.0 Hz, 1H), 1.61 – 1.55 (m, 2H), 1.53 – 1.47 (m, 2H).

¹³C NMR (125 MHz, CDCl₃) δ 143.50, 137.00, 129.82, 127.20, 83.84, 68.91, 42.76, 28.61, 25.35, 21.63, 17.97.

HRMS-ESI (m/z): [M – H]⁻ calcd for C₁₃H₁₆N₁O₂S₁, 250.090920; found, 250.090726.

Synthesis of hex-5-yn-1-yl 4-nitrobenzoate (S411)¹⁸¹

To a 100 mL two-neck round-bottom flask containing 5-hexyn-1-ol (0.55 mL, 5.0 mmol, 1.00 equiv.) and anhydrous CH₂Cl₂ (10 mL) were added successively DMAP (61 mg, 0.1 equiv.),

pyridine (1.2 mL, 3.0 equiv.) and 4-nitrobenzoyl chloride (1.86 g, 2.0 equiv.) at 0 °C. The reaction mixture was allowed to warm up to room temperature and stirred for 1 hour. The solvent was removed under reduced pressure and the resulting residue was purified by flash column chromatography using silica gel (ethyl acetate/pentane) to give the product (1.01 g, 82 % yield).

**Characterization of S411**

$^1$H NMR (500 MHz, CDCl$_3$) δ 8.30 – 8.27 (m, 2H), 8.22 – 8.19 (m, 2H), 4.41 (t, $J = 6.5$ Hz, 2H), 2.29 (td, $J = 7.5, 3.0$ Hz, 2H), 1.98 (t, $J = 2.5$ Hz, 1H), 1.97 – 1.91 (m, 2H), 1.73 – 1.67 (m, 2H).

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 164.80, 150.67, 135.83, 130.81, 123.68, 83.77, 69.10, 65.58, 27.77, 25.11, 18.25.

HRMS-ESI (m/z): [M + Na]$^+$ calc’d for C$_{13}$H$_{13}$N$_1$O$_4$Na$_1$, 270.073710; found, 270.073678.

**Synthesis of hex-5-yn-1-yl 4-iodobenzoate (S413)$^{182}$**

To a 100 mL two-neck round-bottom flask containing 5-hexyn-1-ol (0.55 mL, 5.0 mmol, 1.00 equiv.) and anhydrous CH$_2$Cl$_2$ (10 mL) were added successively DMAP (61 mg, 0.1 equiv.), pyridine (1.2 mL, 3.0 equiv.) and 4-iodobenzoyl chloride (2.66 g, 2.0 equiv.) at 0 °C. The reaction mixture was allowed to warm up to room temperature and stirred for 1 hour. The solvent was removed under reduced pressure and the resulting residue was purified by flash column chromatography using silica gel (ethyl acetate/pentane) to give the product (1.48 g, 90 % yield).

**Characterization of S413**

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.81 – 7.79 (m, 2H), 7.75 – 7.73 (m, 2H), 4.34 (t, $J = 6.5$ Hz, 2H), 2.28 (td, $J = 7.0, 3.0$ Hz, 2H), 1.97 (t, $J = 2.5$ Hz, 1H), 1.93 – 1.87 (m, 2H), 1.71 – 1.66 (m, 2H).

$^{182}$ See reference 26.
Experimental Part

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 166.21, 137.85, 131.15, 129.95, 100.81, 83.92, 68.99, 64.86, 27.86, 25.16, 18.26.

HRMS-ESI (m/z): [M + Na]$^+$ calcd for C$_{13}$H$_{13}$O$_2$I$_1$Na$_1$, 350.985470; found, 350.985246.

Synthesis of hex-5-yn-1-yl 6-chloronicotinate (S414)$^{183}$

To a 100 mL two-neck round-bottom flask containing 5-hexyn-1-ol (0.55 mL, 5.0 mmol, 1.00 equiv.) and anhydrous CH$_2$Cl$_2$ (10 mL) were added successively DMAP (61 mg, 0.1 equiv.), pyridine (1.2 mL, 3.0 equiv.) and 6-chloronicotinoyl chloride (1.76 g, 2.0 equiv.) at 0 °C. The reaction mixture was allowed to warm up to room temperature and stirred for 1 hour. The solvent was removed under reduced pressure and the resulting residue was purified by flash column chromatography using silica gel (ethyl acetate/pentane) to give the product (1.1 g, 93 % yield).

Characterization of S414

$^1$H NMR (500 MHz, CDCl$_3$) δ 8.99 (d, $J = 2.5$ Hz, 1H), 8.23 (ddd, $J = 8.5$, 2.5, 1.0 Hz, 1H), 7.41 (d, $J = 8.0$ Hz, 1H), 4.38 (t, $J = 6.5$ Hz, 2H), 2.28 (td, $J = 7.0$, 2.5 Hz, 2H), 1.97 (t, $J = 2.5$ Hz, 1H), 1.95 – 1.89 (m, 2H), 1.71 – 1.65 (m, 2H).

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 164.54, 155.80, 151.30, 139.68, 125.30, 124.30, 83.75, 69.10, 65.34, 27.75, 25.07, 18.23.

HRMS-ESI (m/z): [M + H]$^+$ calcd for C$_{12}$H$_{13}$N$_1$O$_2$Cl$_1$, 238.062980; found, 238.062932.

Synthesis of hex-5-yn-1-yl thiophene-2-carboxylate (S415)$^{184}$

---

$^{183}$ See reference 26.
To a 100 mL two-neck round-bottom flask containing 5-hexyn-1-ol (0.55 mL, 5.0 mmol, 1.00 equiv.) and anhydrous CH₂Cl₂ (10 mL) were added successively DMAP (61 mg, 0.1 equiv.), pyridine (1.2 mL, 3.0 equiv.) and thiophene-2-carbonyl chloride (1.46 g, 2.0 equiv.) at 0 °C. The reaction mixture was allowed to warm up to room temperature and stirred for 1 hour. The solvent was removed under reduced pressure and the resulting residue was purified by flash column chromatography using silica gel (ethyl acetate/pentane) to give the product (937.4 mg, 90 % yield).

Characterization of S415

^1H NMR (500 MHz, CDCl₃) δ 7.80 (dd, J = 4.0, 1.5 Hz, 1H), 7.55 (dd, J = 5.0, 1.0 Hz, 1H), 7.10 (dd, J = 5.0, 1.0 Hz, 1H), 4.33 (t, J = 6.5 Hz, 2H), 2.28 (td, J = 7.0, 2.5 Hz, 2H), 1.97 (t, J = 3.0 Hz, 1H), 1.92 – 1.86 (m, 2H), 1.71 – 1.65 (m, 2H).

^13C NMR (125 MHz, CDCl₃) δ 162.39, 134.06, 133.48, 132.42, 127.87, 83.99, 68.92, 64.75, 27.90, 25.14, 18.26.

HRMS-ESI (m/z): [M + Na]^+ calcd for C₁₁H₁₂O₂SNa, 231.045200; found, 231.045022.

Synthesis of 4-formylphenyl 5-chlorohex-5-enoate (S416)^185

To an argon flushed one-necked flask equipped with a stirring bar containing hex-5-ynoic acid (560.0 mg, 5.0 mmol), 4-hydroxybenzaldehyde (732.6 mg, 6.0 mmol, 1.2 equiv.) and anhydrous CH₂Cl₂ (20 mL) were added DCC (1.1 g, 5.5 mmol, 1.10 equiv.) and DMAP (61.1 mg, 0.5 mmol, 0.1 equiv.) at 0 °C. Then the reaction mixture was warmed up to room temperature and stirred

^185 See reference 26.
overnight. Then the resulting mixture was filtered and the filtrate was concentrated under reduced pressure. Purification of the resulting residue by flash column chromatography using silica gel (MTBE/pentane) afforded the product (810.8 mg, 75% yield).

**Characterization of S416**

**^1^H NMR** (500 MHz, CDCl₃) δ 9.99 (s, 1H), 7.93 – 7.90 (m, 2H), 7.29 – 7.26 (m, 2H), 2.76 (t, J = 7.5 Hz, 2H), 2.76 (td, J = 7.0, 2.5 Hz, 2H), 2.02 (t, J = 2.5 Hz, 1H), 2.00 – 1.95 (m, 2H).

**^1^3^C NMR** (125 MHz, CDCl₃) δ 191.01, 171.01, 155.44, 134.12, 131.33, 122.45, 82.99, 69.71, 33.04, 23.47, 17.90.

**HRMS-ESI (m/z):** [M + H]^+ calcd for C₁₃H₁₃O₃, 217.086100; found, 217.085920.

**Synthesis of tert-Butyldimethyl(undec-10-yn-1-yloxy)silane (S419)**

![Synthesis of tert-Butyldimethyl(undec-10-yn-1-yloxy)silane (S419)](image)

To a 100 mL two-neck round-bottom flask containing imidazole (204.3 mg, 1.5 equiv.), undec-10-yn-1-ol (336.4 mg, 2.0 mmol), and CH₂Cl₂ (10 mL) was added TBSCI (331.6 mg, 1.1 equiv.) at 0 °C under argon. The reaction was warmed up to room temperature and stirred for 2 hours. Then the mixture was filtered through a plug of silica and the filtrate was concentrated under reduced pressure. Purification of the crude residue by flash column chromatography using silica gel (ethyl acetate/pentane) afforded the product (519.8 mg, 92% yield).

**Characterization of S419**

**^1^H NMR** (500 MHz, CDCl₃) δ 3.60 (t, J = 6.5 Hz, 2H), 2.18 (td, J = 7.0, 2.5 Hz, 2H), 1.93 (t, J = 2.5 Hz, 1H), 1.55-1.48 (m, 4H), 1.42-1.36 (m, 2H), 1.29 (br s, 8H), 0.89 (s, 9H), 0.05 (s, 6H).

**^1^3^C NMR** (125 MHz, CDCl₃) δ 84.94, 68.18, 63.47, 33.03, 29.63, 29.54, 29.21, 28.90, 28.65, 26.15, 25.94, 18.56, -5.09.

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HRMS-ESI (m/z): [M + H]^+ calcd for C_{17}H_{35}O_{1}Si_{1}, 283.245300; found, 283.245169.

Synthesis of 4-(5,5-dimethyl-1,3-dioxan-2-yl)phenyl hex-5-ynoate (S420)\textsuperscript{187}

\[
\begin{align*}
\text{CO}_2H & \quad \text{HOCH(OH)CH}_2\text{OH} \\
\text{In(OTf)}_3 & \quad \text{benzen, reflux} \\
\text{S420}
\end{align*}
\]

To a 50 mL round-bottomed flask fitted with a Dean-Stark trap were added aldehyde (432.4 mg, 2.0 mmol), benzene (10 mL), diol (416.4 mg, 2.0 equiv.) and the indium triflate (2.2 mg, 0.2 mol %). The resulting mixture was heated at reflux and monitored by TLC. Upon completion of the reaction, the reaction mixture was cooled down to room temperature and the solvent was removed under reduced pressure. Purification of the crude residue by flash column chromatography using silica gel (ethyl acetate/pentane) afforded the product (532.2 mg, 88% yield).

Characterization of S420

\textbf{\textsuperscript{1}H NMR} (500 MHz, CDCl\textsubscript{3}) \(\delta\) 7.53 – 7.51 (m, 2H), 7.11 – 7.08 (m, 2H), 5.39 (s, 1H), 3.78 – 3.75 (m, 2H), 3.65 (d, \(J = 10.5\) Hz, 2H), 2.71 (t, \(J = 7.5\) Hz, 2H), 2.35 (td, \(J = 7.5, 2.5\) Hz, 2H), 2.01 (t, \(J = 3.0\) Hz, 1H), 2.00 – 1.94 (m, 2H), 1.28 (s, 3H), 0.80 (s, 3H).

\textbf{\textsuperscript{13}C NMR} (125 MHz, CDCl\textsubscript{3}) \(\delta\) 171.47, 151.08, 136.31, 127.47, 121.47, 101.21, 83.22, 77.79, 69.52, 33.10, 30.36, 23.64, 23.19, 22.03, 17.97.

HRMS-ESI (m/z): [M + Na]^+ calcd for C\textsubscript{18}H\textsubscript{22}O\textsubscript{4}Na\textsubscript{1}, 325.141230; found, 325.141029.

Synthesis of hex-5-yn-1-yl (4R)-4-((10S,13R)-10,13-dimethyl-3,7,12-trioxohexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)pentanoate (S423)\textsuperscript{188}


\textsuperscript{188} See reference 26.
To an argon flushed one-necked flask equipped with a stirring bar containing dehydrocholic acid (2.0 g, 5.0 mmol), hex-5-yn-1-ol (589.2 mg, 6.0 mmol, 1.2 equiv.) and anhydrous CH₂Cl₂ (20 mL) were added DCC (1.1 g, 5.5 mmol, 1.10 equiv.) and DMAP (61.1 mg, 0.5 mmol, 0.1 equiv.) at 0 °C. The reaction mixture was warmed up to room temperature and stirred overnight. Then the resulting mixture was filtered and the filtrate was concentrated under reduced pressure. Purification of the resulting residue by flash column chromatography using silica gel (MTBE/pentane) afforded the product (810.8 mg, 75% yield).

Characterization of S423

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 4.08 (t, \(J = 1.5\) Hz, 2H), 2.93 – 2.81 (m, 3H), 2.41 – 2.19 (m, 10H), 2.15 – 2.09 (m, 2H), 2.06 – 1.99 (m, 3H), 1.98 – 1.93 (m, 2H), 1.87 – 1.80 (m, 2H), 1.78 – 1.72 (m, 2H), 1.64 – 1.56 (m, 3H), 1.42 – 1.21 (m, 7H), 1.06 (s, 3H), 0.84 (d, \(J = 6.5\) Hz, 3H).

\(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 212.00, 209.11, 208.78, 174.21, 83.99, 68.84, 63.87, 57.03, 51.89, 49.13, 46.98, 45.79, 45.68, 45.12, 42.93, 38.77, 36.62, 36.15, 35.64, 35.42, 31.63, 30.59, 27.84, 27.76, 25.28, 25.09, 22.05, 18.77, 18.22, 11.99.

HRMS-ESI (m/z): [M + Na]\(^+\) calcd for C\(_{30}\)H\(_{42}\)O\(_5\)Na\(_1\), 505.292490; found, 505.292444.

Synthesis of (pent-4-yn-1-yl-5-d)benzene (S41-D)

To a sealed flask were added 1 (0.58 g, 4 mmol) and dry THF (5 mL) via a syringe under argon. The solution was cooled down to -78 °C and \(n\)BuLi (2.5 M hexane solution; 2.0 mL, 1.25 equiv.)

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\(^{189}\) Huang, X.; Li, X.; Jiao, N. Chem. Sci., 2015, 6, 6355.
was added dropwise. Then the reaction mixture was allowed to warm up to -30 °C and stir for 1 hour. D$_2$O (99.9%-d; 10 mL) was carefully added to the resulting solution at -78 °C and the reaction mixture was stirred for 30 min at the same temperature. After dilution with diethyl ether (15 mL), the mixture was washed with HCl (2.0 M, 10 mL) and extracted with diethyl ether (10 mL x 3). The combined organic phases were dried with Na$_2$SO$_4$ and concentrated under reduced pressure. Purification by flash column chromatography afforded S41-D1 (0.46 g, 80%, 95% D).

**Characterization of S41-D**

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.31 – 7.28 (m, 2H), 7.21 – 7.18 (m, 3H), 2.75 (t, $J = 7.5$ Hz, 2H), 2.21 (t, $J = 7.0$ Hz, 2H), 2.00 (t, $J = 3.0$ Hz, 0.05H), 1.89 – 1.83 (m, 2H).

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 141.62, 128.66, 128.51, 126.07, 83.86 (t, $J_{C-D} = 7.6$ Hz), 68.57 (t, $J_{C-D} = 30.1$ Hz), 34.78, 30.20, 17.94.

HRMS-EI (m/z): [M]$^+$ calcd for C$_{11}$H$_{11}$D$_1$, 145.099700; found, 145.099627.

6.3.2. **General procedures for Iridium-Catalyzed Hydrochlorination of alkynes**

**General procedure 4A: For optimization of reaction conditions**

![Reaction Scheme](image)

Under argon, to an 8.0 mL Screw-cap vial equipped with a magnetic stirring bar were added catalyst, ligand and toluene (0.5 mL). After stirring for 5 min, the hydrochlorinating reagent and pent-4-yn-1-ylbenzene (S41) were added sequentially to the resulting solution and the vial was sealed and placed on a heating plate. After stirring for 5 hours, the reaction mixture was cooled down analyzed using GC or NMR.

**General procedure 4B: For hydrochlorination of aliphatic terminal alkynes**
Under argon, to an 8.0 mL Screw-cap vial equipped with a magnetic stirring bar were added [IrCl(COD)]$_2$ (3.4 mg, 2.5 mol%), Cphos (6.6 mg, 7.5 mol%) and toluene (0.5 mL). After stirring for 5 min, 4-chlorobutan-2-one (R41, 42.6 mg, 2.0 equiv.), alkyne substrate (0.2 mmol), were added sequentially to the resulting solution and the vial was sealed and placed on a heating plate (80 °C). After stirring for 5 hours, the reaction mixture was cooled down to room temperature and purified by flash column chromatography on silica gel to give the products.

**General procedure 4C: For hydrochlorination of aromatic terminal alkynes**

Under argon, to an 8.0 mL Screw-cap vial equipped with a magnetic stirring bar were added [IrCl(COD)]$_2$ (3.4 mg, 2.5 mol%), Ruphos (7.0 mg, 7.5 mol%) and toluene (0.5 mL). After stirring for 5 min, 4-chlorobutan-2-one (R41, 42.6 mg, 2.0 equiv.), alkyne substrate (0.2 mmol), were added sequentially to the resulting solution and the vial was sealed and placed on a heating plate (80 °C). After stirring for 12 hours, the reaction mixture was cooled down to room temperature and purified by flash column chromatography on silica gel to give the products.

**General procedure 4D: For hydrochlorination of internal alkynes**

Under argon, to an 8.0 mL Screw-cap vial equipped with a magnetic stirring bar were added [IrCl(COD)]$_2$ (3.4 mg, 2.5 mol%), Cphos (6.6 mg, 7.5 mol%) and toluene (0.5 mL). After stirring for 5 min, 4-chlorobutan-2-one (42.6 mg, 2.0 equiv.), alkyne substrate (0.2 mmol), were added sequentially to the resulting solution and the vial was sealed and placed on a heating plate (80 °C). After stirring for 12 hours, the reaction mixture was cooled down to room temperature and purified by flash column chromatography on silica gel to give the products.
added sequentially to the resulting solution and the vial was sealed and placed on a heating plate (110 °C). After stirring for 12 hours, the reaction mixture was cooled down to room temperature and purified by flash column chromatography on silica gel to give the products.

6.3.3. Characterization of Products

(4-Chloropent-4-en-1-yl)benzene (41, Table 4.3, entry 1, 79% isolated yield)

Was produced by reacting pent-4-yn-1-ylbenzene with 4-chlorobutan-2-one (R41) following the general procedure 4B.

\[ ^{1}H \text{ NMR} (500 \text{ MHz, CDCl}_3) \delta 7.31 – 7.28 (m, 2H), 7.22 – 7.19 (m, 3H), 5.18 (d, J = 0.5 Hz, 1H), 5.15 – 5.14 (m, 1H), 2.65 (t, J = 8.0 Hz, 2H), 2.38 (t, J = 7.5 Hz, 2H), 1.94 – 1.88 (m, 2H). \]

\[ ^{13}C \text{ NMR} (125 \text{ MHz, CDCl}_3) \delta 142.74, 141.86, 128.59, 128.52, 126.05, 112.43, 38.69, 34.76, 28.92. \text{ HRMS-EI (m/z): } [M]^+ \text{ calcd for C}_{11}H_{13}Cl_1, 180.070640; \text{ found, 180.070578.} \]

(3-Chlorobut-3-en-1-yl)benzene (42, Table 4.3, entry 2, 67% isolated yield)

Was produced by reacting but-3-yn-1-ylbenzene with 4-chlorobutan-2-one (R41) following the general procedure 4B.

\[ ^{1}H \text{ NMR} (500 \text{ MHz, CDCl}_3) \delta 7.32 – 7.28 (m, 2H), 7.23 – 7.20 (m, 3H), 5.15 (d, J = 1.0 Hz, 1H), 5.09 – 5.08 (m, 1H), 2.90 (t, J = 8.0 Hz, 2H), 2.66 – 2.63 (m, 2H). \]

\[ ^{13}C \text{ NMR} (125 \text{ MHz, CDCl}_3) \delta 142.07, 140.67, 128.59, 128.52, 126.05, 112.43, 38.69, 34.76, 28.92. \text{ HRMS-EI (m/z): } [M]^+ \text{ calcd for C}_{10}H_{11}Cl_1, 166.054759; \text{ found, 166.054928.} \]

(2-Chloroallyl)benzene (43, Table 4.3, entry 3, 75% isolated yield)
Experimental Part

2-Chlorodec-1-ene (44, Table 4.3, entry 4, 79% isolated yield)

5-Chlorohex-5-enenitrile (45, Table 4.3, entry 5, 78% isolated yield)
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$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 140.13, 119.14, 114.52, 37.66, 22.81, 15.94.

HRMS-EI (m/z): [M]$^+$ calcd for C$_8$H$_8$NCl, 129.033980; found, 129.033977.

**2,6-Dichlorohex-1-ene (46, Table 4.3, entry 6, 68% isolated yield)**

![2,6-Dichlorohex-1-ene](image)

Was produced by reacting 6-chlorohex-1-yne with 4-chlorobutan-2-one (R41) following the general procedure 4B.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.17 (d, $J = 1.0$ Hz, 1H), 5.15 – 5.14 (m, 1H), 3.56 (t, $J = 6.5$ Hz, 2H), 2.39 – 2.36 (m, 2H), 1.83 – 1.70 (m, 4H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 142.32, 112.64, 44.75, 38.46, 31.49, 24.55.

HRMS-EI (m/z): [M]$^+$ calcd for C$_6$H$_{10}$Cl$_2$, 152.015450; found, 152.015406.

**5-Chlorohex-5-enoate (47, Table 4.3, entry 7, 51% isolated yield)**

![5-Chlorohex-5-enoate](image)

Was produced by reacting methyl hex-5-ynoate with 4-chlorobutan-2-one (R41) following the general procedure 4B.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.18 (d, $J = 1.0$ Hz, 1H), 5.15 – 5.14 (m, 1H), 3.68 (s, 3H), 2.40 – 2.37 (m, 2H), 2.34 (t, $J = 7.5$ Hz, 2H), 1.93 – 1.87 (m, 2H).

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 173.69, 141.85, 113.00, 51.72, 38.40, 32.67, 22.43.

HRMS-ESI (m/z): [M + Na]$^+$ calcd for C$_7$H$_{11}$O$_2$Cl$_2$Na, 185.033960; found, 185.033977.

**5-Chlorohex-5-en-1-yl 4-methylbenzenesulfonate (48, Table 4.3, entry 8, 77% isolated yield)**

![5-Chlorohex-5-en-1-yl 4-methylbenzenesulfonate](image)
Was produced by reacting hex-5-yn-1-yl 4-methylbenzenesulfonate with 4-chlorobutan-2-one (R41) following the general procedure 4B.

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.80 – 7.77 (m, 2H), 7.35 (d, $J$ = 8.0 Hz, 2H), 5.13 (d, $J$ = 1.0 Hz, 1H), 5.08 – 5.07 (m, 1H), 4.04 (t, $J$ = 6.5 Hz, 2H), 2.45 (s, 3H), 2.30 – 2.27 (m, 2H), 1.69 – 1.55 (m, 4H).

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 144.90, 142.02, 133.21, 129.98, 128.00, 112.74, 70.18, 38.39, 27.76, 23.11, 21.77.

HRMS-ESI (m/z): [M + Na]$^+$ calcld for C$_{13}$H$_{17}$O$_3$Cl$_1$S$_1$Na$_1$, 311.048010; found, 311.047915.

$N$-(5-chlorohex-5-en-1-yl)-4-methylbenzenesulfonamide (49, Table 4.3, entry 9, 58% isolated yield)

Was produced by reacting $N$-(hex-5-yn-1-yl)-4-methylbenzenesulfonamide with 4-chlorobutan-2-one (R41) following the general procedure 4B.

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.76 – 7.74 (m, 2H), 7.31 (d, $J$ = 8.0 Hz, 2H), 5.11 (d, $J$ = 1.5 Hz, 1H), 5.07 – 5.06 (m, 1H), 4.69 (t, $J$ = 6.5 Hz, 1H), 2.96 – 2.92 (m, 2H), 2.42 (s, 3H), 2.28 – 2.25 (m, 2H), 1.56 – 1.44 (m, 4H).

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 143.54, 142.02, 137.03, 129.84, 127.21, 112.57, 42.97, 38.54, 28.53, 24.13, 21.64.

HRMS-ESI (m/z): [M]$^-$ calcld for C$_{13}$H$_{17}$Cl$_1$N$_1$O$_2$S$_1$, 286.067380; found, 286.067404.

5-Chlorohex-5-en-1-yl cinnamate (410, Table 4.3, entry 10, 82% isolated yield)
Was produced by reacting hex-5-yn-1-yl cinnamate with 4-chlorobutan-2-one (R41) following the general procedure 4B.

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.69 (d, $J = 16.0$ Hz, 1H), 7.55 – 7.51 (m, 2H), 7.40 – 7.37 (m, 3H), 6.45 (d, $J = 16.0$ Hz, 1H), 5.18 (d, $J = 1.5$ Hz, 1H), 5.16 – 5.15 (m, 1H), 4.23 (t, $J = 6.5$ Hz, 2H), 2.41 (t, $J = 7.0$ Hz, 2H), 1.77 – 1.67 (m, 4H).

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 167.12, 144.89, 142.48, 134.54, 130.40, 129.01, 128.20, 118.23, 112.56, 64.26, 38.80, 27.72, 23.74.

HRMS-ESI (m/z): [M + Na]$^+$ calcd for C$_{15}$H$_{17}$O$_2$ClNa, 287.080810; found, 287.080927.

5-Chlorohex-5-en-1-yl 4-nitrobenzoate (411, Table 4.3, entry 11, 87% isolated yield)

Was produced by reacting hex-5-yn-1-yl 4-nitrobenzoate with 4-chlorobutan-2-one (R41) following the general procedure 4B.

$^1$H NMR (500 MHz, CDCl$_3$) δ 8.30 – 8.27 (m, 2H), 8.22 – 8.19 (m, 2H), 5.19 (d, $J = 1.5$ Hz, 1H), 5.17 – 5.16 (m, 1H), 4.39 (t, $J = 6.5$ Hz, 2H), 2.44 – 2.41 (m, 2H), 1.85 – 1.79 (m, 2H), 1.77 – 1.71 (m, 2H).

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 164.81, 150.67, 142.25, 135.83, 130.81, 123.69, 112.81, 65.65, 38.73, 27.59, 23.68.

HRMS-ESI (m/z): [M + Na]$^+$ calcd for C$_{13}$H$_{14}$N$_1$O$_4$ClNa, 306.050160; found, 306.050356.

5-Chlorohex-5-en-1-yl 3,5-difluorobenzoate (412, Table 4.3, entry 12, 88% isolated yield)
Was produced by reacting hex-5-yn-1-yl 3,5-difluorobenzoate with 4-chlorobutan-2-one (R41) following the general procedure 4B.

\[ {^1}\text{H NMR} \ (500 \text{ MHz, CDCl}_3) \delta 7.57 - 7.52 \ (m, 2H), 7.01 \ (tt, J = 9.0, 2.5 \text{ Hz, 1H}), 5.19 \ (d, J = 1.0 \text{ Hz, 1H}), 5.17 - 5.16 \ (m, 1H), 4.35 \ (t, J = 6.5 \text{ Hz, 2H}), 2.43 - 2.40 \ (m, 2H), 1.83 - 1.69 \ (m, 4H). \\
{^{13}}\text{C NMR} \ (125 \text{ MHz, CDCl}_3) \delta 164.52 \ (t, J_{CF} = 3.6 \text{ Hz}), 162.90 \ (dd, J_{CF} = 248.3, 11.6 \text{ Hz}), 142.29, 133.69 \ (t, J_{CF} = 9.0 \text{ Hz}), 112.77, 112.73 \ (d, J_{CF} = 20.3, 6.5 \text{ Hz}), 108.49 \ (t, J_{CF} = 25.1 \text{ Hz}), 65.47, 38.74, 27.60, 23.66. \\
\text{HRMS-ESI (m/z)}: [M + Na]^+ \text{ calcd for } C_{13}H_{13}O_2F_2Cl, 297.046390; \text{ found, 297.046434}. \\
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5-Chlorohex-5-en-1-yl 4-iodobenzoate (413, Table 4.3, entry 13, 88% isolated yield)

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Was produced by reacting hex-5-yn-1-yl 4-iodobenzoate with 4-chlorobutan-2-one (R41) following the general procedure 4B.

\[ {^1}\text{H NMR} \ (500 \text{ MHz, CDCl}_3) \delta 7.81 - 7.79 \ (m, 2H), 7.75 - 7.73 \ (m, 2H), 5.18 \ (d, J = 1.5 \text{ Hz, 1H}), 5.16 - 5.15 \ (m, 1H), 4.33 \ (t, J = 1.5 \text{ Hz, 2H}), 2.41 \ (t, J = 7.5 \text{ Hz, 2H}), 1.82 - 1.69 \ (m, 4H). \\
{^{13}}\text{C NMR} \ (125 \text{ MHz, CDCl}_3) \delta 166.23, 142.38, 137.86, 131.14, 129.95, 112.68, 100.81, 64.94, 38.77, 27.66, 23.73. \\
\text{HRMS-ESI (m/z)}: [M + Na]^+ \text{ calcd for } C_{13}H_{14}O_2I_1Cl, 386.961790; \text{ found, 386.961924}. \\
\]

5-Chlorohex-5-en-1-yl 6-chloronicotinate (414, Table 4.3, entry 14, 83% isolated yield)

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Was produced by reacting hex-5-yn-1-yl 6-chloronicotinate with 4-chlorobutan-2-one (R41) following the general procedure 4B.
1H NMR (500 MHz, CDCl₃) δ 8.99 (dd, J = 2.5, 1.0 Hz, 1H), 8.23 (dd, J = 8.0, 2.5 Hz, 1H), 7.41 (dd, J = 8.5, 1.0 Hz, 1H), 5.18 (d, J = 1.0 Hz, 1H), 5.16 – 5.15 (m, 1H), 4.37 (t, J = 6.5 Hz, 2H), 2.43 – 2.40 (m, 2H), 1.83 – 1.69 (m, 4H).

13C NMR (125 MHz, CDCl₃) δ 164.53, 155.80, 151.29, 142.24, 139.68, 125.30, 124.31, 112.79, 65.40, 38.71, 27.58, 23.65.

HRMS-ESI (m/z): [M + H]+ calcd for C₁₂H₁₄N₁O₂Cl₂, 274.039520; found, 274.039610.

5-Chlorohex-5-en-1-yl thiophene-2-carboxylate (415, Table 4.3, entry 15, 78% isolated yield)

Was produced by reacting hex-5-yn-1-yl thiophene-2-carboxylate with 4-chlorobutan-2-one (R41) following the general procedure 4B.

1H NMR (500 MHz, CDCl₃) δ 7.80 (dd, J = 4.0, 1.5 Hz, 1H), 7.55 (dd, J = 5.0, 1.0 Hz, 1H), 7.10 (dd, J = 5.0, 3.5 Hz, 1H), 5.18 (d, J = 1.5 Hz, 1H), 5.16 – 5.15 (m, 1H), 4.32 (t, J = 6.5 Hz, 2H), 2.43 – 2.40 (m, 2H), 1.81 – 1.69 (m, 4H).

13C NMR (125 MHz, CDCl₃) δ 162.40, 142.45, 134.05, 133.49, 132.43, 127.88, 112.62, 64.86, 38.77, 27.69, 23.73.

HRMS-ESI (m/z): [M + Na]+ calcd for C₁₁H₁₃Cl₁O₂S₁Na₁, 267.021670; found, 267.021700.

4-Formylphenyl 5-chlorohex-5-enoate (416, Table 4.3, entry 16, 58% isolated yield)

Was produced by reacting 4-formylphenyl hex-5-ynoate with 4-chlorobutan-2-one (R41) following the general procedure 4B.
**1H NMR** (500 MHz, CDCl$_3$) δ 9.99 (s, 1H), 7.94 – 7.91 (m, 2H), 7.29 – 7.27 (m, 2H), 5.24 (d, $J = 1.0$ Hz, 1H), 5.21 – 5.20 (m, 1H), 2.64 (t, $J = 7.5$ Hz, 2H), 2.51 – 2.48 (m, 2H), 2.08 – 2.02 (m, 2H).

**13C NMR** (125 MHz, CDCl$_3$) δ 191.01, 171.05, 155.45, 141.54, 134.17, 131.37, 122.45, 113.46, 38.26, 32.94, 22.27.

**HRMS-ESI (m/z):** [M + Na]$^+$ calcd for C$_{13}$H$_{13}$Cl$_1$O$_3$Na$_1$, 275.044460; found, 275.044542.

**2,8-Dichloronona-1,8-diene** (417, Table 4.3, entry 17, 74% isolated yield)

Was produced by reacting nona-1,8-diyne with 4-chlorobutan-2-one (R41) following the general procedure 4B.

**1H NMR** (500 MHz, CDCl$_3$) δ 5.14 (d, $J = 1.0$ Hz, 2H), 5.12 – 5.11 (m, 2H), 2.36 – 2.33 (m, 4H), 1.62 – 1.56 (m, 4H), 1.37 – 1.31 (m, 2H).

**13C NMR** (125 MHz, CDCl$_3$) δ 142.97, 112.14, 39.13, 27.53, 26.97.

**HRMS-EI (m/z):** [M]$^+$ calcd for C$_9$H$_{14}$Cl$_2$, 192.047063; found, 192.047256.

**tert-Butyl((10-chloroundec-10-en-1-yl)oxy)dimethylsilane** (419, Table 4.4, entry 1, 68% isolated yield)

Was produced by reacting tert-butyldimethyl(undec-10-yn-1-yloxy)silane with 4-chlorobutan-2-one (R41) following the general procedure 4B.

**1H NMR** (500 MHz, CDCl$_3$) δ 5.13 (d, $J = 1.0$ Hz, 1H), 5.11 – 5.10 (m, 1H), 3.60 (t, $J = 7.0$ Hz, 2H), 2.34 – 2.31 (m, 2H), 1.58 – 1.48 (m, 4H), 1.29 (s, 10H), 0.90 (s, 9H), 0.05 (s, 6H).

**13C NMR** (125 MHz, CDCl$_3$) δ 143.32, 111.85, 63.47, 39.31, 33.03, 29.65, 29.54, 29.41, 28.69, 27.33, 26.15, 25.94, 18.54, -5.09.
HRMS-ESI (m/z): \([M + H]^+\) calcd for C\(_{17}\)H\(_{36}\)Cl\(_1\)O\(_1\)Si\(_1\), 319.221880; found, 319.221847.

4-(5,5-Dimethyl-1,3-dioxan-2-yl)phenyl 5-chlorohept-5-enoate (420, Table 4.4, entry 2, 60% isolated yield)

![4-(5,5-Dimethyl-1,3-dioxan-2-yl)phenyl 5-chlorohept-5-enoate](image)

Was produced by reacting 4-(5,5-dimethyl-1,3-dioxan-2-yl)phenyl hex-5-ynoate with 4-chlorobutan-2-one (R41) following the general procedure 4B.

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.54 – 7.51 (m, 2H), 7.10 – 7.07 (m, 2H), 5.39 (s, 1H), 5.22 (d, \(J = 1.0\) Hz, 1H), 5.20 – 5.19 (m, 1H), 3.77 (dd, \(J = 9.5, 1.5\) Hz, 2H), 3.65 (d, \(J = 10.5\) Hz, 2H), 2.59 (t, \(J = 7.5\) Hz, 2H), 2.49 – 2.46 (m, 2H), 2.06 – 2.00 (m, 2H), 1.28 (s, 3H), 0.80 (s, 3H).

\(^13\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 171.49, 151.06, 141.70, 136.34, 127.49, 121.44, 113.28, 101.19, 77.78, 38.32, 32.94, 30.36, 23.18, 22.36, 22.03.

HRMS-ESI (m/z): \([M + Na]^+\) calcd for C\(_{18}\)H\(_{23}\)Cl\(_1\)O\(_4\)Na\(_1\), 361.117590; found, 361.117707.

1-(1-Chlorovinyl)cyclohexan-1-ol (421, Table 4.4, entry 3, 50% isolated yield)

![1-(1-Chlorovinyl)cyclohexan-1-ol](image)

Was produced by reacting 1-ethynylcyclohexan-1-ol with 4-chlorobutan-2-one (R41) following the general procedure 4B.

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 5.47 (d, \(J = 2.0\) Hz, 1H), 5.29 (d, \(J = 1.5\) Hz, 1H), 1.81 – 1.56 (m, 10H), 1.29 – 1.20 (m, 1H).

\(^13\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 149.60, 111.04, 74.23, 35.62, 25.54, 21.92.

HRMS-EI (m/z): [M]^+ calcd for C\(_8\)H\(_{13}\)O\(_1\)Cl\(_1\), 160.064890; found, 160.064890.
(8R,9S,13S,14S)-3-((5-chloro-5-en-1-yl)oxo)-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17H-cyclopenta[a]phenanthren-17-one (422, Scheme 4.6, entry 1, 82% isolated yield)

\[
\text{Was produced by reacting (8R,9S,13S,14S)-3-(hex-5-yn-1-yloxy)-13-methyl-}
\]
\[
\text{6,7,8,9,11,12,13,14,15,16-decahydro-17H-cyclopenta[a]phenanthren-17-one with 4-chlorobutan-}
\]
\[
\text{2-one (R41) following the general procedure 4B.}
\]

\[^{1}H\text{ NMR (500 MHz, CDCl}_3\text{) } \delta 7.20 (d, J = 8.5 \text{ Hz}, 1 \text{H}), 6.71 (dd, J = 8.5, 2.5 \text{ Hz}, 1 \text{H}), 6.65 (d, J = 3.0 \text{ Hz}, 1 \text{H}), 5.17 (d, J = 1.0 \text{ Hz}, 1 \text{H}), 5.16 – 5.15 (m, 1 \text{H}), 3.95 (t, J = 6.0 \text{ Hz}, 2 \text{H}), 2.95 – 2.85 (m, 2 \text{H}), 2.53 – 2.48 (m, 1 \text{H}), 2.43 – 2.36 (m, 3 \text{H}), 2.28 – 2.23 (m, 1 \text{H}), 2.18 – 2.11 (m, 1 \text{H}), 2.08 – 1.93 (m, 3 \text{H}), 1.83 – 1.72 (m, 4 \text{H}), 1.67 – 1.40 (m, 6 \text{H}), 0.91 (m, 3 \text{H}).
\]

\[^{13}C\text{ NMR (125 MHz, CDCl}_3\text{) } \delta 221.01, 157.14, 142.69, 137.86, 132.12, 126.44, 114.67, 112.39, 112.22, 67.55, 50.55, 48.15, 44.12, 38.93, 38.52, 36.01, 31.73, 29.79, 28.34, 26.70, 26.07, 23.93, 21.73, 14.00.
\]

HRMS-ESI (m/z): [M + Na]^+ calcd for C_{24}H_{31}Cl_1O_2Na_1, 409.190560; found, 409.190477.

(8R,9S,13S,14S)-3-((5-chloro-5-en-1-yl)oxo)-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17H-cyclopenta[a]phenanthren-17-one (423, Scheme 4.6, entry 2, 72% isolated yield)
Was produced by reacting hex-5-yn-1-yl (R)-4-((5S,8R,9S,10S,13R,14S,17R)-10,13-dimethyl-3,7,12-trioxohexadecahydro-1H-cyclopenta[al]phenanthren-17-yl)pentanoate with 4-chlorobutan-2-one (R41) following the general procedure 4B.

\[ ^1H\text{ NMR} (500 \text{ MHz, CDCl}_3) \delta 5.15 (d, J = 1.0 \text{ Hz}, 1\text{H}), 5.13 - 5.12 (m, 1\text{H}), 4.08 - 4.06 (m, 2\text{H}), 2.93 - 2.81 (m, 3\text{H}), 2.41 - 2.18 (m, 10\text{H}), 2.15 - 2.11 (m, 2\text{H}), 2.06 - 1.93 (m, 4\text{H}), 1.87 - 1.80 (m, 2\text{H}), 1.65 - 1.61 (m, 5\text{H}), 1.42 - 1.21 (m, 7\text{H}), 1.06 (s, 3\text{H}), 0.84 (d, J = 6.5 \text{ Hz}, 3\text{H}). \]

\[ ^{13}\text{C NMR} (125 \text{ MHz, CDCl}_3) \delta 212.02, 209.13, 208.79, 174.23, 142.45, 112.52, 63.98, 57.02, 51.88, 49.12, 46.97, 45.79, 45.68, 45.12, 42.92, 38.76, 36.61, 35.14, 35.63, 35.41, 31.64, 30.60, 27.75, 27.64, 25.27, 23.71, 22.04, 18.76, 11.98. \]

**HRMS-ESI (m/z): [M + Na]^+ calcd for C\text{30H\text{43ClO5Na}}, 541.269220; found, 541.269122.**

1-(1-Chlorovinyl)-3-methoxybenzene (418, Table 4.3, entry 18, 50% isolated yield)

![1-(1-Chlorovinyl)-3-methoxybenzene](image)

Was produced by reacting 1-(1-chlorovinyl)-3-methoxybenzene with 4-chlorobutan-2-one (R41) following the general procedure 4C.

\[ ^1H\text{ NMR} (500 \text{ MHz, CDCl}_3) \delta 7.28 (t, J = 8.0 \text{ Hz}, 1\text{H}), 7.23 - 7.21 (m, 1\text{H}), 6.90 (ddd, J = 8.0, 2.5, 1.0 \text{ Hz}, 1\text{H}), 5.77 (d, J = 1.5 \text{ Hz}, 1\text{H}), 5.53 (d, J = 1.5 \text{ Hz}, 1\text{H}), 3.84 (s, 3\text{H}). \]

\[ ^{13}\text{C NMR} (125 \text{ MHz, CDCl}_3) \delta 159.64, 139.88, 138.52, 129.46, 119.00, 114.82, 113.11, 112.38, 55.49. \]

**HRMS-EI (m/z): [M]^+ calcd for C\text{9H\text{9OCl}}, 168.033770; found, 168.033643.**

\((E)-4,4'-(1-\text{Chloroethene}-1,2-diyl)bis(bromobenzene)\) (Scheme 4.7, 424, 88% isolated yield, E/Z = 87/13)
Was produced by reacting 1,2-bis(4-bromophenyl)ethyne with 4-chlorobutan-2-one (R41) following the general procedure 4D.

**1H NMR** (500 MHz, CDCl₃) δ 7.61 – 7.59 (m, 2H), 7.56 – 7.51 (m, 6H), 6.97 (s, 1H).

**13C NMR** (125 MHz, CDCl₃) δ 138.06, 133.98, 131.88, 131.76, 131.67, 131.11, 128.36, 125.47, 123.29, 122.34.

**HRMS-EI (m/z):** [M]+ calcd for C₁₄H₉Cl₁Br₂, 369.875450; found, 369.875429.

**5-Chlorodec-5-ene (425, Scheme 4.7, 92% isolated yield, E/Z = 36/64)**

Was produced by reacting dec-5-yne with 4-chlorobutan-2-one (R41) following the general procedure 4D.

**1H NMR** (500 MHz, CDCl₃) δ 5.58 (t, J = 8.0 Hz, 1H, =CH₆), 5.43 (tt, J = 7.0 Hz, 1H, =CH₂), 2.35 – 2.28 (m, 4H), 2.18 – 2.14 (m, 2H, CH₂₄), 2.06 – 2.01 (m, 2H, CH₂₆), 1.56 – 1.49 (m, 4H), 1.39 – 1.27 (m, 12H), 0.94 – 0.89 (m, 12H).

**13C NMR** (125 MHz, CDCl₃) δ 134.81, 134.12, 128.13, 125.51, 39.33, 33.50, 31.78, 31.06, 29.75, 29.70, 28.42, 28.36, 22.44, 22.36, 22.02, 21.82, 14.07, 14.03, 13.98.

**HRMS-EI (m/z):** [M]+ calcd for C₁₀H₁₉Cl₁, 174.117020; found, 174.116978.

**Methyl (E)-3-chlorooct-2-enoate (Scheme 4.7, 426, 60% isolated yield)**
Was produced by reacting methyl oct-2-ynoate with 4-chlorobutan-2-one (R41) following the general procedure 4D.

\[ ^1H \text{ NMR} \ (500 \text{ MHz, CDCl}_3) \delta 6.06 \text{ (s, 1H)}, \ 3.71 \text{ (s, 3H)}, \ 2.98 \text{ – 2.95 (m, 2H)}, \ 1.66\text{-1.60 (m, 2H)}, \ 1.35 \text{ – 1.32 (m, 4H)}, \ 0.91 \text{ – 0.89 (m, 3H).} \]

\[ ^{13}C \text{ NMR} \ (125 \text{ MHz, CDCl}_3) \delta 165.04, 158.05, 118.63, 51.60, 35.78, 31.07, 27.46, 22.53, 14.07. \]

\[ \text{HRMS-EI (m/z): [M]^+ calcd for C}_9\text{H}_{15}\text{O}_2\text{Cl}, 190.075610; \text{ found, 190.075508.} \]

6.3.4. Procedure for the Gram-Scale Experiment

Under argon, to a 50 mL two-necked round-bottomed flask equipped with a magnetic stirring bar were added \([\text{IrCl(COD)}]_2 \ (134.0 \text{ mg, 2.5 mol\%}), \text{ Cphos} \ (261.6 \text{ mg, 7.5 mol\%}) \text{ and toluene} \ (20.0 \text{ mL}). \) After stirring for 10 min, 4-chlorobutan-2-one \((1.7 \text{ g, 2.0 equiv.) and S427} \ (1.9 \text{ g, 8.0 mmol), were added sequentially to the resulting solution. Then the flask was connected to an argon line and placed in an 80 °C oil bath. After stirring for 5 hours, the reaction mixture was cooled down to room temperature and the product 427 \ (1.7 \text{ g, 78\%}) was obtained after purification by flash column chromatography on silica gel. \]

Characterization of 427

\[ ^1H \text{ NMR} \ (500 \text{ MHz, CDCl}_3) \delta 7.99 \text{ – 7.96 (m, 2H)}, \ 7.43 \text{ – 7.40 (m, 2H)}, \ 5.18 \text{ (d, J = 1.0 Hz, 1H)}, \ 5.16 \text{ – 5.15 (m, 1H)}, \ 4.33 \text{ (t, J = 6.5 Hz, 2H)}, \ 2.43 \text{ – 2.40 (m, 2H)}, \ 1.82 \text{ – 1.70 (m, 4H).} \]
**Experimental Part**

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 165.86, 142.39, 139.48, 131.08, 128.92, 128.85, 112.67, 64.93, 38.77, 27.68, 23.74.

**HRMS-ESI (m/z):** [M + Na]$^+$ calcd for C$_{13}$H$_{14}$O$_2$Cl$_2$Na$_1$, 295.026260; found, 295.026305.

### 6.3.5. Mechanistic Experiments

![Mechanistic Experiments Diagram]

Under argon, to an 8.0 mL Screw-cap vial equipped with a magnetic stirring bar were added [IrCl(COD)$_2$] (1.7 mg, 2.5 mol%), Cphos (3.3 mg, 7.5 mol%) and toluene (0.25 mL). After stirring for 5 min, 4-chlorobutan-2-one (R$_41$, 21.3 mg, 2.0 equiv.) and S$_{41}$ (0.1 mmol) were added sequentially to the resulting solution and the vial was sealed and placed on a heating plate (80 °C). After stirring for 5 hours, the reaction mixture was cooled down to room temperature and diluted with CDCl$_3$ (0.5 mL). The resulting solution was then analyzed by proton NMR using dibromomethane (17.4 mg, 0.1 mmol) as an internal standard to give the ratio of E/Z as 1.2:1, which was determined based on the NOESY and COSY NMR analysis.

![Mechanistic Experiments Diagram (Alternative)]

Under argon, to an 8.0 mL Screw-cap vial equipped with a magnetic stirring bar were added [IrCl(COD)$_2$] (1.7 mg, 2.5 mol%), Cphos (3.3 mg, 7.5 mol%) and toluene (0.25 mL). After stirring for 5 min, deuterium chloride (0.2 mL, 2.0 equiv., a 1.0 M solution in Et$_2$O) and S$_{41}$ (0.1 mmol) were added sequentially to the resulting solution and the vial was sealed and placed on a heating plate (80 °C). After stirring for 5 hours, the reaction mixture was cooled down to room temperature and diluted with CDCl$_3$ (0.5 mL). The resulting solution was then analyzed by proton NMR using dibromomethane (17.4 mg, 0.1 mmol) as an internal standard to give the ratio of E/Z as 0.7:1, which was determined based on the NOESY and COSY NMR analysis.
Under argon, to an 8.0 mL Screw-cap vial equipped with a magnetic stirring bar were added [IrCl(cod)]_2 (1.7 mg, 2.5 mol%), Cphos (3.3 mg, 7.5 mol%) and toluene (0.25 mL). After stirring for 5 min, 4-chlorobutan-2-one (R41, 21.3 mg, 2.0 equiv.), benzyltriethylammonium chloride (22.8 mg, 1.0 equiv.) and S41-D (0.1 mmol) were added sequentially to the resulting solution and the vial was sealed and placed on a heating plate (80 °C). After stirring for 5 hours, the reaction mixture was cooled down to room temperature and diluted with CDCl₃ (0.5 mL). The resulting solution was then analysed by proton NMR using dibromomethane (17.4 mg, 0.1 mmol) as an internal standard to give the ratio of E/Z as 1:1.8, which was determined based on the NOESY and COSY NMR analysis.