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Developing Efficient Transition Metal Catalyzed C-C & C-X Bond Construction

Chiyu Wei
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Developing Efficient Transition Metal Catalyzed C-C & C-X Bond Construction

by

Chiyu Wei

A dissertation submitted in partial fulfillment of the requirement for the degree of Doctor of Philosophy Department of Chemistry College of Arts and Sciences University of South Florida

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Keywords: Pd/Amine catalysis, asymmetric, Au (I/III) catalysis, mild oxidant, HFIP

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Dedication

Dedicated to my parents and friends who understand and support me all the time.
Acknowledgements

First, I sincerely appreciate Dr. Shi for giving me the chance to study with him and guiding me through the last several years. Dr. Shi has encyclopedic knowledge and extensive interest, which always and will continue to inspire me. Dr. Shi always has high standards for us and would like to help us to be better chemists with better personality. He never hesitates to offer us his passionate help and always does his best to support us.

I am grateful when I came to the USF, Dr. Shi gave me a whole year RA due to my poor spoken English. I will never forget the great memory the Shi group spent together in Dr. Shi’s house playing poker or games. I will always remember that Dr. Shi leads us to enjoy Tampa bay’s scene even at the hard time during Covid-19.

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Finally, I appreciate my parents’ selfless love and continuous support in my life. I also want to thank my girlfriend for her support in the last several years. Without them, I can accomplish nothing.
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Abstract

This dissertation mainly contains three parts: 1) The synergistic Pd/enamine catalysis for asymmetric hydrocarbon functionalization of unactivated alkenes with ketones; 2) Gold redox catalysis with a selenium cation as mild oxidant; 3) HFIP promoted disulfidation and diselenation of alkyne, alkene, and allene.

Palladium-catalyzed alkene activation has its intrinsic limitation: 1) the requirement of a pre-functionalized alkene to form a Pd π-allyl complex; 2) problematic reversible β-H elimination. It always leads to limited reaction scope and losing of the stereochemical control. Synergistic palladium and enamine catalysis was conducted to promote ketone addition to unactivated olefins. A secondary amine-based organocatalyst was identified as the optimal co-catalyst for the directed Pd-catalyzed alkene activation. Furthermore, asymmetric hydrocarbofunctionalization of unactivated alkenes was also achieved with good to excellent yield and stereoselectivity.

Au redox catalysis always requires strong oxidants or delicate ligand design, which largely limits the reaction scope. In this part, we utilized selenide cation as mild oxidant to achieve Au oxidation. Excellent regioselectivity (trans) and good to excellent yields were achieved (up to 98% with 2% catalyst loading) with a wide range of substrates. Mechanistic investigation revealed a gold (I/III) redox process was successfully implemented under mild conditions.
Among various factors that can affect reactions, the solvent is the one that can dramatically impact the reaction performance. We accidentally observed Hexafluoro-2-propanol (HFIP), as a unique polar organic solvent that can promote the diselenation and disulfidation of C-C unsaturated bonds successfully. In contrast, other solvents, such as isopropanol and dichloroethane, could not promote the same reaction. This method revealed an example of HFIP promoted transformations under mild conditions, which greatly highlighted the unique reactivity of this special solvent.

In sum, the combination of transition metal catalyst and organic catalyst can promote a reaction in a highly efficient process and greatly extend the reaction scope, even providing stereoselectivity successfully. Applying mild oxidant in Au redox catalysis is able to achieve Au (III) and holds promise for generating synthetically valuable building blocks, which also enhance the basic understand of this rapidly growing field. HFIP as a magic solvent exhibits the stability to activate diselenides and disulfides to accomplish addition to C-C unsaturated bonds.
Chapter 1: Introduction of Transition Metal Catalysis

1.1 Introduction of organometallic chemistry

Chemistry is a science with a long history focused on materials synthesis. Today, two major branches of chemistry, organic chemistry, and supramolecular chemistry, provide various approaches to synthesize materials successfully and efficiently. Supramolecular chemistry utilizes non-covalent interactions to assemble pre-functionalized small molecules forming giant and highly organized structures.\(^1\) Due to the weak coordination, the self-assembling process goes through a dynamic interaction achieving thermodynamic product eventually.\(^2\) Supramolecular chemistry provides an efficient and straightforward route to obtain hundreds of thousands of giant and complicated structures. However, just because of its unique assembling way, it still faces two intrinsic challenges: lack of diversity and selectivity.

In 1824, the German chemist Wohler received oxalic acid from cyanogen by hydrolysis and in 1828, he inadvertently converted ammonium cyanate into urea by heating.\(^3\) These results become a key to lead human beings into organic chemistry. Compared with supramolecular chemistry, organic chemistry cannot achieve a huge framework in a simple step but furnishes many different methods to tune the selectivity and install disparate functional groups on a delicate small molecule. In a traditional organic reaction, nucleophiles and electrophiles are both necessary to make one reaction happen, which greatly limited the reactions scope.
To break through this restriction, organometallic chemistry plays an essential role in this effort. Organometallic chemistry is a study of metal/organic ligand complexes and employs them as the catalyst to accelerate reaction rate, enhance efficiency, and improve selectivity. The fundamental advancement of organometallic is converting the reaction types. In the past, reaction always needs one electrophile and one nucleophile, while organometallic chemistry can cause a reaction to occur between two nucleophiles or electrophiles. For example, aryl halide and carbonyl compound cannot react with each other directly, but magnesium is able to make the reaction happen by converting aryl halide to Grignard reagent.

1.2 Pd catalyzed alkene functionalization

Alkylation is a process of transferring an alkyl group to a substrate. In the petroleum-refining process, isobutane will be added in low-molecular-weight alkenes to form alkanes (mainly composed of propylene and butene). These alkanes are very efficient antiknock agent. Previously, tetraethyllead was used as the major antiknock agent, but it could pollute the environment by lead. Therefore, after 1970 tetraethyllead was gradually out of order. As a result, methyl tert-butyl ether was used as an alternative antiknock agent. After that, more and more alkanes were developed as better additives.

To achieve these functionalized alkanes, alkylation is a very useful method. Some common alkylating reagents include alkenes, alkyl bromides, and alkyl iodides. Compared with alkyl halides, alkenes usually are much cheaper. For example, ethylene is about $0.028/mol, while vinyl bromide is $6/mol and vinyl iodide is much more expensive. Besides, alkylation does not generate byproducts due to its 100% atom
economy. Because of these advantages, alkene has been applied broadly in organic synthesis (Figure 1). Although alkene possesses these benefits, it is still facing two main challenges: (1) low reactivity; (2) regioselectivity.

Figure 1. Reaction involving alkenes

Pd were used in organometallic chemistry since 1947. By that time, Lindlar's catalyst was employed in alkyne hydrogenation as a heterogeneous catalyst. It was the first time chemist realized the Pd activation to C-C unsaturated bonds. In 1972, the very famous Heck reaction published (Figure 2). Palladium catalyst could promote alkene substitution with aryl halides in high efficiency and pure trans selectivity with broad substrate scope under mild condition. This is a terrific transformation to build C<sub>sp2</sub>-C<sub>sp2</sub> bond as a perfect complement to Friedel-Crafts reaction achieving alkene or aryl functionalization. Due to this excellent performance, Richard F. Heck shared 2010 Nobel prize with Negishii and Suzuki. Although Heck reaction is epoch-making development, there are three limitations: 1) Nu must be strong Nu, like carbon or nitrogen nucleophile;
2) the reaction cannot avoid β-H elimination, which cause the losing of stereoselectivity;

3) Alkene must be activated alkene, so it limited the reaction scope.

![Figure 2. Heck reactions]

Except for the Heck reaction, there are many other typical Pd catalyzed alkene alkylation. Tsuji-Trost reaction uses Pd to catalyze alkyl Nu to attack allylic compound (Figure 3A). X should be a good leaving group, such as halides, or acetates. The mechanism is shown in the figure. Because of the requirement of mechanism, the allyl compound has to be functionalized prior to reaction, which largely limited the reaction scope.

Palladium catalyzed C-H activation is a very attractive research area in the past decades (Figure 3 B). A great advantage of C-H activation is no need to pre-functionalize the substrate (late-stage functionalization), which makes this methodology a green and atom-economical synthetic route. However, based on the mechanism, it also
requires extra oxidant, such as Ag salts or naphthoquinone. This will generate unfavored waste and narrow the substrates scope. What’s more, allyl compound is considered as active substrates and normal alkenes are inappropriate for this transformation.

Figure 3. Other Pd catalyzed alkene alkylation
Allene can be catalyzed by palladium to furnish alkylation. Allene does not require extra oxidants and exhibits better activity to this transformation, but it has the same issue with allyl-X compound, namely, pre-functionalization. Allene must be synthesized previously and consumed as soon as possible due to its instability even in the refrigerator. In conclusion, Pd is able to activate the alkene, but it faces many limitations, such as pre-functionalization, extra oxidant, limited substrate scope, and so on. To avoid these limitations and expand the reaction scope is an exciting direction in the next decades.

1.3 Au (I/III) redox catalysis with strong oxidant and gold reduction

The past two decades have witnessed tremendous growth in homogeneous gold catalysis. The unique capability of the gold cation as a carbophilic Lewis acid has rendered it a superior catalyst in nucleophilic addition reactions towards alkenes, allenes, and alkynes. On the other hand, the redox chemistry of gold(I) catalyst is largely neglected, mainly due to the high oxidation potential (AuI/III = 1.4 eV). Thanks to the pioneering work from Zhang, Hashmi, Toste and other groups, this challenge has been successfully overcome by utilizing external strong oxidants such as selectfluor, hypervalent iodine reagents, arylidiazonium salts.

Zhang and co-worker’s used PPh₃AuCl as the initial catalyst and selectfluor as the oxidant to form Au (III) intermediate (Figure 4A). The reaction mechanism was the combination of Au (I) π-acid and Au (I/III) redox catalysis. Au (I) would activate the internal alkyne to achieve vinyl gold intermediate via rearrangement, followed by oxidation of selectfluor. After the transmetalation with boronic acid, the Au (III) intermediate could form the product through reductive elimination. This reaction showed excellent
stereoselectivity and only E-isomer was formed. Based on a similar concept, Russell evolved PIDA oxidized Au catalyzed aryl cross-coupling (Figure 4B).\(^{17j}\) Due to the utilizing of strong oxidants, the reaction scopes have been largely limited. Many electron-rich substrates were not suitable for this transformation.

**Figure 4. Au redox catalysis with strong oxidants**

**Figure 5. Gold redox catalysis via photo condition**
Since the strong oxidant can oxidize Au and the mechanism probably go through single electron process, it gives photocatalysis good chance to participate in Au redox chemistry. In 2013, Glorius reported Au/photocatalyst catalyzed alkene difunctionalization (Figure 5).\textsuperscript{18} Diazonium salts were applied as oxidant and coupling partners. The reaction happened under room temperature, which is much milder compared to selectfluor condition. Based on the authors, the reaction went through a radical process. The photocatalyst would generate phenyl radical to oxidize Au (I) to Au (II), followed by single electron transfer (SET) to form Au (III) intermediate. Due to the Au (III) $\pi$-acidity to double bond, alkene would be activated, and the product formed via reductive elimination.

Since the Au oxidation potential is higher than 1.4 eV, it makes the reductive elimination faster. After oxidation of Au (I) complex, four coordination Au (III) intermediate formed (Figure 6).\textsuperscript{19} In this scenario, the Au complexes are very stable that can even be purified by column. Under high temperature, the ligand will dissociate to generate active three coordination complex, followed by the reductive elimination to form C-halide product. Using Ag salts to extract the halides generating Y-shape intermediate will push the reaction to form C-CF$_3$ bond reductive elimination.

![Figure 6. Au (III) reductive elimination](image-url)
Chapter 2: Pd/enamine Catalyzed Unactivated Alkenes Asymmetric Functionalization

2.1 Synergistic palladium/enamine catalysis and its challenges

As the previous chapter mentioned, transition metals are able to provide efficient activation to various electrophiles. Therefore, they have been considered as a greatly successful tool to active electrophiles, especially C-C unsaturated bonds, like alkenes or alkynes. Lewis acid catalyzed nucleophilic addition of alkenes has become a powerful synthetic approach for C–C and C–X bond construction.\(^2\) However, palladium is considered as a weak π-acid towards alkene activation, and therefore, a strong nucleophile is required to attack the Pd-activated alkene.\(^2\) Meanwhile, just like this year's Nobel prize introduced, organocatalysis is an ingenious tool for building molecules. The secondary amine, as one kind of organocatalysis, has also used widely in ketones or aldehydes activation as powerful nucleophiles. The combination of metal and enamine catalysis will provide very notable property in catalytic chemistry.\(^2\)

![Figure 7. Pd/enamine co-catalyzed alkylation of carbonyl compound](image_url)
In particular, Pd/enamine co-catalytic system offered an extremely powerful toolbox for C-C bond building.\textsuperscript{23} One of most common way of this chemistry is that enamine serves a nucleophile to attack the palladium activated carbon electrophile.

For instance, in 2006, Cordova and co-author developed the method using the combination of palladium and enamine catalysis to obtain the modified α-allylic carbonyl (\textbf{Figure 7}).\textsuperscript{24} In this work, Pd activated allylic ester to form Pd allylic complex as an electrophile, and second amine activated carbonyl compound to get enamine as the nucleophile. This transformation provided highly chemo- and regioselectivities with high yield under mild condition. The result also prompted the possibility of asymmetric synergistic metal/organocatalysis. Although it was a successful strategy, it still faced some limitations, such as limited substrate scope. For example, only allyl compound could participate in, and allyl compound usually required to be synthesized by several steps previously.

To expand the reaction scope into a broader scope, other carbon electrophiles are expected to be applied in to this dual-catalysis mode, like alkene. However, palladium is considered as a weak π-acid towards alkene activation, and therefore, a strong nucleophile is required to achieve this transformation. Hegedus group reported a very early example palladium activated terminal alkene alkylation (\textbf{Figure 8}).\textsuperscript{21c} In this reaction, strong carbon nucleophile was required and harsh reaction condition, which clearly illustrated the limitation. Furthermore, most of the product was β-elimination. It is also consistent with the palladium natural property and prevent to achieve a broader reaction scope.
To overcome the β-elimination, 2016 Engle and co-authors developed the bis-chelating directing group (DG) strategy to activate alkene via palladium (Figure 9). This novel methodology could inhibit the undesired β-elimination due the four-coordination intermediate. With the help of acidic environment, the reaction would go through very fast proto-depalladation to form the products. Since the product contained a chiral center, it offered a possibility to set up a chiral carbon on the product. What’s more, this strategy can make the metal center more electron rich, so it could activate inactivated alkene, such as normal terminal alkenes. However, this seminal work did not achieve enantioselective addition and only strong nucleophile was suitable.

Inspired by these findings, we noticed that via the combination of the bis-chelating DG coordinated palladium activation and secondary amine co-catalyst, we would achieve asymmetric unactivated alkene hydrocarbon functionalization with ketones. What’s more, developing new reaction partners that can facilitate transformation in this dual-catalysts mode will not only offer practical synthetic utility but also foster mechanistic insight to further advance this intriguing reaction pattern.
2.2. Unactivated alkenes asymmetric hydrocarbon functionalization catalyzed Pd/enamine system.

To test our design, we firstly employed acetophenone as the substrate. The results showed that without the secondary amine co-catalyst, no product was formed even using different directing groups (entry 1, Table 1), which was consistent with the Engle’s conclusion. With the employment of L-proline, the desired addition product 3a could be achieved with 60% yield, which means the activation of ketone is very essential. As our expectation, after testing five different directing groups, only bis-chelating directing group 1a (8-aminoquinoline) could promote this reaction, while other DGs failed. This result
emphasized the special role of DG in this transformation. After screening a series of conditions, pyrrolidine was identified as the best co-catalyst and toluene is optimal solvent, because it is lack of coordination with palladium. Due to the change of co-catalyst and solvent, the reaction temperature could be decreased to 80 °C with a nearly quantitative yield. Therefore, the optimal condition is using 20% pyrrolidine as the co-catalyst, toluene as the solvent under 80 °C. Inspired by this result, we then turned our attention to a more challenging asymmetric addition with the assistance of chiral secondary amines. Representative conditions screened are summarized in Table 2.

Table 1. Screen directing groups and amine catalysts

<table>
<thead>
<tr>
<th>DGs</th>
<th>Conditions</th>
<th>Conv.⁵</th>
<th>Yield⁵</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a-1e</td>
<td>MeCN, 120 °C</td>
<td>&lt;5%</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>1a</td>
<td>L-Proline 20%, MeCN, 120 °C</td>
<td>70%</td>
<td>60%</td>
</tr>
<tr>
<td>1b-1e</td>
<td>L-Proline 20%, MeCN, 120 °C</td>
<td>&lt;10%</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>1a</td>
<td>Pyrrolidine 20%, Tol, 80 °C</td>
<td>100%</td>
<td>99%(94%e)</td>
</tr>
</tbody>
</table>

⁵ Reaction conditions: 1a (1 eq.), 2a (3 eq.), Pd(OAc)₂ (10 mol%), amine cat. (20 mol%), AcOH (1 eq.), solvent (0.5 M), 36 h. ⁵ Conversion and yield were determined by 1H NMR using 1,3,5-trimethoxybenzene as internal standard. ⁵ Isolated yield.
With the optimal condition in hand, the reaction scope was evaluated. Substrates 3 from methyl-ketone is shown in Table 2. In most of cases, over 90% yields were received with almost all tested acetophenone derivatives. This transformation can tolerate both EDG (3b–3d) and EWG (3e and 3f) modified ketones with excellent yields. Slightly reduced yields were obtained with the ortho-substituted substrate (3j 89%, 3k, 82%) due to steric hindrance. Interestingly, aryl halide substrates (3g, 3h, and 3i) worked very well for this reaction without observation of Pd catalyzed oxidative addition of C-X bond, revealing an orthogonal reactivity compared with typical Pd(0) involved coupling reactions. Finally, amino acid modified derivative (3n) was also suitable for this reaction, suggesting the potential application of this method in bio-compatible compound preparation. Moreover, compound 3a was synthesized in a gram scale, which further indicated its practical synthetic value.

Table 2. Substrate scope of compound 3a,b

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Yield (%)</th>
<th>Isolated yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a, R=H</td>
<td>94%</td>
<td>1.27g</td>
</tr>
<tr>
<td>3b, R=Me</td>
<td>96%</td>
<td></td>
</tr>
<tr>
<td>3c, R=OMe</td>
<td>94%</td>
<td></td>
</tr>
<tr>
<td>3d, R=tBu</td>
<td>93%</td>
<td></td>
</tr>
<tr>
<td>3e, R=NO2</td>
<td>91%</td>
<td></td>
</tr>
<tr>
<td>3f, R=CF3</td>
<td>91%</td>
<td></td>
</tr>
<tr>
<td>3g, R=F</td>
<td>92%</td>
<td></td>
</tr>
<tr>
<td>3h, R=Cl</td>
<td>91%</td>
<td></td>
</tr>
<tr>
<td>3i, R=Br</td>
<td>92%</td>
<td></td>
</tr>
<tr>
<td>3j, R=o-Me</td>
<td>89%</td>
<td></td>
</tr>
<tr>
<td>3k, R=o-Cl</td>
<td>82%</td>
<td></td>
</tr>
<tr>
<td>3l, R=m-Me</td>
<td>94%</td>
<td></td>
</tr>
<tr>
<td>3m, R=m-NO2</td>
<td>82%</td>
<td></td>
</tr>
<tr>
<td>3n, R=NH Boc</td>
<td>95%</td>
<td></td>
</tr>
</tbody>
</table>

a Reaction condition: Pd(OAc)$_2$ (10 mol%), pyrrolidine (20 mol%), AcOH (1 eq.), solvent (0.5 M), 36 h. b Isolated yield.
Table 3. Optimization of amines for palladium/enamine catalysis

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd cat.</th>
<th>Amine</th>
<th>Sol.</th>
<th>Conv.</th>
<th>Yield</th>
<th>ee%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Pd(OAc)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>n/a</td>
<td>MeCN</td>
<td>&lt;5%</td>
<td>&lt;5%</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>A1</td>
<td>Tol</td>
<td>100%</td>
<td>95%</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>A2 or A3</td>
<td>Tol</td>
<td>&gt;20%</td>
<td>&lt;20%</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Pd(OAc)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>A4</td>
<td>Tol</td>
<td>62%</td>
<td>54%</td>
<td>11%</td>
</tr>
<tr>
<td>5</td>
<td>Pd(CH&lt;sub&gt;3&lt;/sub&gt;CN)&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>A4</td>
<td>Tol</td>
<td>79%</td>
<td>77%</td>
<td>15%</td>
</tr>
<tr>
<td>6</td>
<td>Pd(CH&lt;sub&gt;3&lt;/sub&gt;CN)&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>A5</td>
<td>Tol</td>
<td>100%</td>
<td>90%</td>
<td>33%</td>
</tr>
<tr>
<td>7</td>
<td>Pd(CH&lt;sub&gt;3&lt;/sub&gt;CN)&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>A6</td>
<td>Tol</td>
<td>100%</td>
<td>91%</td>
<td>63%</td>
</tr>
<tr>
<td>8</td>
<td>Pd(CH&lt;sub&gt;3&lt;/sub&gt;CN)&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>A7</td>
<td>Tol</td>
<td>100%</td>
<td>57%</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>9</td>
<td>Pd(CH&lt;sub&gt;3&lt;/sub&gt;CN)&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>A8</td>
<td>Tol</td>
<td>100%</td>
<td>96%</td>
<td>65%</td>
</tr>
<tr>
<td>10</td>
<td>Pd(CH&lt;sub&gt;3&lt;/sub&gt;CN)&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>A9</td>
<td>Tol</td>
<td>100%</td>
<td>97%</td>
<td>71%</td>
</tr>
<tr>
<td>11&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Pd(CH&lt;sub&gt;3&lt;/sub&gt;CN)&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>A9</td>
<td>Tol</td>
<td>100%</td>
<td>97%</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>12&lt;sup&gt;f&lt;/sup&gt;</td>
<td>Pd(CH&lt;sub&gt;3&lt;/sub&gt;CN)&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>A9</td>
<td>Tol</td>
<td>60%</td>
<td>55%</td>
<td>93%</td>
</tr>
<tr>
<td>13&lt;sup&gt;f&lt;/sup&gt;</td>
<td>Pd(CH&lt;sub&gt;3&lt;/sub&gt;CN)&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>A9</td>
<td>neat</td>
<td>100%</td>
<td>99%</td>
<td>(95%)&lt;sup&gt;g&lt;/sup&gt; 88%</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction conditions: Pd cat. (10 mol%), amine cat. (30 mol%), AcOH (1 eq.), solvent (0.5 M), under 80 °C, 24 h. <sup>b</sup> Conversion and yield were determined by 1H NMR using 1,3,5-trimethoxybenzene as internal standard. <sup>c</sup> ee value was determined by HPLC. <sup>d</sup> 120 °C, 36 h. <sup>e</sup> 72 h. <sup>f</sup> 60 °C, 24 h. <sup>g</sup> Isolated yield.

To screen the optimal asymmetric condition, compound 1a was treated with cyclohexanone 2b under Pd/pyrrolidine conditions giving addition product 4a with 95% yield, as expected (entry 2, Table 3). Macmillan catalysts A2/A3 were failed to activate the ketone with less than 20% conversion might due to its low reactivity to ketone<sup>26</sup> L-
proline could promote this transformation with moderate yield but low enantioselectivity. Clearly, a tight transition state with Pd and amine is crucial for good stereoselectivity. To avoid competitive OAc binding, Pd(CH$_3$CN)$_2$Cl$_2$ was then employed. An increasing ee (15%) was obtained with L-proline as co-catalyst (entry 5).

When Jorgensen catalyst A$_6$ was treated in, product 4a was obtained in 97% yield with 71% ee (entry 10). Based on the LC-MS data after the reaction, the TMS protecting group was gone. Therefore non-protecting co-catalyst A$_8$ was treated and gave the product in 65% ee. As a comparison, the OMe protected ligand A$_7$ gave almost no stereoselectivity (<5% ee). This result clearly suggested the importance of the hydroxyl group in promoting the stereoselectivity of the transformation. This is likely due to the coordination of OH with Pd intermediate, which not only accelerates the overall reaction rate by rendering the enamine addition into an intramolecular fashion, but also provides a good stereochemistry control. One challenge that prevented further improvement of the enantioselectivity is the racemization of product 4a. Extending reaction time resulted in a decreased ee value under the reaction condition (entry 11). To further fine-tuning the reaction, we conducted the reaction at lower temperature (60 °C). Lower conversion (60%) and yield (55%) were observed, though higher ee was received (93%). To increase the reaction rate at a lower temperature, the neat condition was applied. The reaction gave 100% conversion and 95% isolated yield with 88% ee of 4a.

With the optimal asymmetric condition in hand, we than explored the reaction scope by using cyclic ketones as the substrates (Table 4). In most of cases, the yields were excellent. Comparing with non-substituted cyclohexanone (4a), 4-substituted cyclohexanone derivatives (4b-4d) required a elevated temperature (80 °C) to achieve
the full conversion due to their increased steric hindrance. To our delight, because of the same reason, in these cases the previous problematic racemization was also inhibited, providing higher enantioselectivity. On the other hand, modest $dr$ value were observed. Ketal derivative (4e) was also tolerated under this acidic condition without deprotection, excellent yield and $ee$ were obtained.

Table 4. Substrate scope for asymmetric ketone alkylation$^{a,b,c}$

$^{a}$ Reaction conditions: Pd(MeCN)$_2$Cl$_2$ (10 mol%), A9 (30 mol%), AcOH (1 eq.), 24 h. $^b$ Isolated yield. $^c$ The $dr$ and $ee$ was determined by HPLC. $^d$ 80 °C.
Next, both heteroatom containing cyclohexanone (4f-4h) were tested. 4-oxotertrahydropyran (4f) provided 90% yield and 88% ee, while 4-oxopiperdine (4g) failed to observe any enantioselectivity possibly because of a quick epimerization. By switching to Boc protection, 3-oxopoperdine (4h) was achieved with modest ee, resulting from resonance of amide group to lock the conformation. 1-Trtralone (4i) showed excellent yields with 0% ee due to the more acidic α-proton. Smaller cyclic ketones such as cyclopentanone (4j) and cyclobutanone (4k) gave excellent yields with no ee, likely because of the highly-strained enamine intermediate, which offered no chiral differentiation in energy. As a result, introduction of an ester on cyclobutanone (4l) to increase steric bulkiness not only resulted in moderate enantioselectivity (45% ee) but also delivered excellent dr value (> 20:1), which was consistent with the previous result.

In addition to cyclic ketones, other carbonyl substrates were also explored. First, aldehyde was tested and proved not suitable for this transformation due to the undesired rapid aldol condensation side reaction. Other readily available ketone derivatives such as 1,3-diketones and β-keto-esters were tested as well. The reason why we chose α-substituted 1,3-dicarbonyl compounds for further study was it could form product with a quaternary stereocenter to prevent racemization. Instead of secondary amine, we tested amino acid first, it gave moderate conversion and yield, but almost no entioselectivity (Table 5). As a comparison, amino alcohol gave very similar conversion and yield, but moderate ee (entry 1 & 2). These results suggested the coordination to Pd intermediate was crucial in this transformation and it was consistent with our previous argument.
Table 5. Extensive screening of catalysts for dicarbonyl compounds.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid</th>
<th>Amine</th>
<th>Conv.</th>
<th>Yield</th>
<th>ee%</th>
<th>B/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HOAc</td>
<td></td>
<td>52%</td>
<td>46%</td>
<td>&lt;5%</td>
<td>86 : 14</td>
</tr>
<tr>
<td>2</td>
<td>HOAc</td>
<td></td>
<td>47%</td>
<td>43%</td>
<td>40%</td>
<td>50 : 50</td>
</tr>
<tr>
<td>3</td>
<td>HOAc</td>
<td></td>
<td>64%</td>
<td>61%</td>
<td>62%</td>
<td>47 : 53</td>
</tr>
<tr>
<td>4</td>
<td>HOAc</td>
<td></td>
<td>&lt;10%</td>
<td>&lt;10%</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>3-COOH</td>
<td></td>
<td>69%</td>
<td>63%</td>
<td>48%</td>
<td>43 : 57</td>
</tr>
<tr>
<td>6</td>
<td>HOAc (2 eq.)</td>
<td></td>
<td>62%</td>
<td>60%</td>
<td>52%</td>
<td>45 : 55</td>
</tr>
<tr>
<td>7b</td>
<td>HOAc</td>
<td></td>
<td>100%</td>
<td>99%</td>
<td>63%</td>
<td>47 : 53</td>
</tr>
</tbody>
</table>

Reaction conditions: Reaction conditions: Pd(CH$_3$CN)$_2$Cl$_2$ (10 mol%), amine (30 mol%), AcOH (1 eq.), 36 hours. Yield and conversion were determined by 1H NMR using 1,3,5-trimethoxybenzene as internal standard. The dr and ee was determined by HPLC. b neat.
After the extensive screening of catalysts, primary amine A9 was identified as an effective catalyst in promoting condensation of β-keto-ester with AQ-modified olefin. Benzoic acid was treated as the additive, however lower enantioselectivity was obtained. Increased the amount of acid lead to the decrease of ee%.

Although all β-ketone esters (5a, 5b, and 5c) showed excellent yield (95%), a regioselectivity issue (linear vs branch selectivity) was revealed as well, due to the formation of two possible enamine intermediates (Figure 4). All of these three substrates gave similar regioselectivity ratio (from 53:47 to 48:52). With the increasing size of substituted group R, the enantioselectivity would be increased from 63% to 74% ee. We also demonstrated that AQ directing group could be removed by a Boc protection-basic hydrolysis sequence, yielding the ε-keto acids 6 with 86% yield over two steps (Figure 4B).27

![Chemical structures](image)

**Figure 10.** Substrate scope of β-keto-ester and the removal of AQ
2.3 Conclusion

In summary, we reported a synergistic palladium/enamine catalyzed asymmetric addition of ketone to non-activated alkene under mild conditions. Using this protocol, asymmetric α-alkylation of ketone derivatives were successfully achieved by combining the chiral enamine formation and directed Pd-catalyzed alkene activation, which offered an efficient and cooperative catalysis system. Furthermore, this study revealed a novel approach towards α-branched ketones derivatives, highlighting its valuable synthetic utility.

2.4 Experimental data

2.4.1 General methods and materials

All of the reactions dealing with air and/or moisture-sensitive compounds were carried out under an atmosphere of argon using oven/flame-dried glassware and standard syringe/septa techniques. Unless otherwise noted, all commercial reagents and solvents were obtained from the commercial provider and used without further purification. 1H NMR and 13C NMR spectra were recorded on Varian 400 MHz spectrometers. Chemical shifts were reported relative to internal tetramethylsilane (δ 0.00 ppm) or CDCl3 (δ 7.26 ppm) or DMSO (δ 2.50 ppm) for 1H and CDCl3 (δ 77.16 ppm), DMSO (δ 40.00 ppm) for 13C. Flash column chromatography was performed on 230-430 mesh silica gel. Analytical thin layer chromatography was performed with precoated glass baked plates (250 μ) and visualized by fluorescence and by charring after treatment with potassium permanganate stain. HRMS were recorded on Agilent 6540 LC/QTOF spectrometer.
2.4.2 General procedure to synthesize 3a-3n:

\[
\begin{align*}
\text{AQ} - \text{alkene} + \text{ketone} &\rightarrow \text{3a-3n} \quad \text{Figure 11. Synthesis of 3a-3n}
\end{align*}
\]

An oven-dried vial was charged with Pd(OAc)\(_2\) (10 mol\%, 0.02 mmol), HOAc (1 equiv., 0.2 mmol), alkene (1 equiv., 0.2 mmol), ketone (3 equiv., 0.6 mmol), pyrrolidine (20 mol\%, 0.04 mmol) and toluene (1M, 0.2 mL). The vial was placed under vacuum and charged with Ar. The reaction was run under 80 °C. Once the reaction completed, the crude mixture was purified by flash chromatography (Hexane: Ethyl Acetate = 3:1) on silica gel to give desired product.

2.4.3 General procedure to synthesize 4a-4l:

\[
\begin{align*}
\text{AQ} - \text{alkene} + \text{ketone} &\rightarrow \text{4a-4m} \quad \text{Figure 12. Synthesis of 4a-4l}
\end{align*}
\]

An oven-dried vial was charged with Pd(MeCN)\(_2\)Cl\(_2\) (10 mol\%, 0.02 mmol), HOAc (1 equiv., 0.2 mmol), alkene (1 equiv., 0.2 mmol), ketone (4 equiv., 0.8 mmol) and A9 (30 mol\%, 0.06 mmol). The vial was placed under vacuum and charged with Ar (three times). The reaction was run under 60 °C. Once the reaction completed, the crude mixture was purified by flash chromatography (Hexane: Ethyl Acetate = 3:1) on silica gel to give desired product.
2.4.4 General procedure to synthesize 5a-5c:

An oven-dried vial was charged with Pd(MeCN)$_2$Cl$_2$ (10 mol%, 0.02 mmol), HOAc (1 equiv., 0.2 mmol), alkene (1 equiv., 0.2 mmol), ketone ester (3 equiv., 0.6 mmol) and A10 (30 mol %, 0.6 mmol). The vial was placed under vacuum and charged with Ar (three times). The reaction was run under 60 °C. Once the reaction completed, the crude mixture was purified by flash chromatography (Hexane: Ethyl Acetate = 3:1) on silica gel to give desired product.

2.4.5 Removal of directing group:

An oven-dried flask was added compound 3a (1 mmol), Boc$_2$O (4 equiv., 4 mmol), DMAP (1.5 equiv., 1.5 mmol), and dry acetonitrile (15 mL) then placed under vacuum and charged with Ar. The reaction was run under room temperature for 24 hours. Once the
reaction completed, the crude mixture was purified by flash chromatography (Hexane: Ethyl Acetate = 3:1) on silica gel and the product was used in the next step.

The product from the previous step was employed in THF/H2O (13 mL : 4.5 mL) and cooled to 0 °C, followed by the addition of LiOH (1.1 eq.) and H2O2 (9 eq.). The reaction was run at 0 °C until the reaction was done, then Na2S2O3 solution (aq., 1.5 M, 10 mL) was added. The solution was washed with DCM 20 mL twice. The aqueous phase was extracted with EA (25 mL) three times. The organic phase was combined, washed with brine (20 mL) and dried with Na2SO4, then the solvent was evaporated under vacuum. The crude mixture was purified by flash chromatography (DCM : MeOH = 10:1) to give the desired product 6 with 86% overall yield for two steps.

2.4.6 Synthesis of N(quinoline-8-yl)-but-3-enamide 1a:

\[
\text{N\textsubscript{NH}}_2^+ \text{HO}
\]

8-Aminoquinoline (10 mmol), vinyl acetic acid (1.3 eq., 13 mmol), and DCM (30 mL) were added in a 100 mL round bottom flask. 2,6-Lutidine (2 eq., 20 mmol) and HATU (1.3 eq., 1.3 mmol) were charged sequentially at r.t. The reaction was monitored by TLC. Upon the reaction completed, H2O (80 mL) was added into the mixture and extracted by DCM (3*40 mL). The organic layer was combined, washed with sat. NaHCO3 and brine, and then dried over Na2SO4. The solvent was evaporated under vacuum. The crude mixture was purified by flash chromatography (ethyl acetate: hexanes = 3:1) to give the
desired product 1a (1.87 g, 88% yield) as a yellow oil. The physical and spectroscopic data matched with literature.\textsuperscript{25b}

2.4.7 Compounds characterization

3a

\[
\text{\begin{center}
\begin{tikzpicture}
\node[draw,shape=circle] (A) at (0,0) {N};
\node[draw,shape=circle] (B) at (1,0) {O};
\draw[->] (A) -- (B);\end{tikzpicture}
\end{center}}
\]

6-oxo-6-phenyl-\textit{N}-(quinolin-8-yl)hexanamide

3a was prepared following the General Procedure 1.1 and purified by flash Chromatography. 94% yield. \textbf{\textsuperscript{1}H NMR} (400 MHz, CDCl\textsubscript{3}) δ 9.83 (s, 1H), 8.96 – 8.62 (m, 2H), 8.16 (dd, J = 8.2, 1.8 Hz, 1H), 8.02 – 7.91 (m, 2H), 7.69 – 7.35 (m, 6H), 3.07 (t, J = 6.5 Hz, 2H), 2.64 (t, J = 6.8 Hz, 2H), 2.00 – 1.81 (m, 4H). \textbf{\textsuperscript{13}C NMR} (101 MHz, CDCl\textsubscript{3}) δ 200.00, 171.45, 148.26, 138.39, 137.03, 136.45, 134.57, 133.10, 128.69, 128.07, 127.48, 121.61, 121.51, 116.54, 56.35, 38.35, 38.06, 25.35, 23.92. \textbf{HRMS} (ESI): Calculated for C\textsubscript{21}H\textsubscript{21}N\textsubscript{2}O\textsubscript{2} (M+H)+: 333.1598, found: 333.1601.

3b

\[
\text{\begin{center}
\begin{tikzpicture}
\node[draw,shape=circle] (A) at (0,0) {N};
\node[draw,shape=circle] (B) at (1,0) {O};
\draw[->] (A) -- (B);
\node[draw,shape=circle] (C) at (2,0) {Me};\end{tikzpicture}
\end{center}}
\]

6-oxo-\textit{N}-(quinolin-8-yl)-6-(p-tolyl)hexanamide

3b was prepared following the General Procedure 1.1 and purified by flash Chromatography. 96% yield. \textbf{\textsuperscript{1}H NMR} (400 MHz, CDCl\textsubscript{3}) δ 9.82 (s, 1H), 8.78 (m, 2H),
8.15 (d, J = 8.2 Hz, 1H), 7.85 (d, J = 7.8 Hz, 2H), 7.58 – 7.38 (m, 3H), 7.23 (d, J = 7.8 Hz, 2H), 3.03 (t, J = 6.6 Hz, 2H), 2.62 (t, J = 6.8 Hz, 2H), 2.39 (s, 3H), 2.08 – 1.78 (m, 4H).

**13C NMR (101 MHz, CDCl₃)** δ 199.74, 171.53, 148.25, 143.82, 138.44, 136.46, 134.61, 129.36, 128.28, 128.04, 127.52, 121.70, 121.51, 116.55, 38.28, 38.13, 25.43, 24.07, 21.74. **HRMS (ESI):** Calculated for C₂₂H₂₃N₂O₂ (M+H)⁺: 347.1754, found: 347.1762.

**3c**

![Chemical Structure](image)

6-(4-methoxyphenyl)-6-oxo-N-(quinolin-8-yl)hexanamide

**3c** was prepared following the General Procedure 1.1 and purified by flash Chromatography. 94% yield. **¹H NMR (400 MHz, CDCl₃)** δ 9.81 (s, 1H), 8.82 – 8.71 (m, 2H), 8.13 (d, J = 8.2 Hz, 1H), 7.92 (d, J = 8.4 Hz, 2H), 7.57 – 7.36 (m, 3H), 6.89 (d, J = 8.4 Hz, 2H), 3.83 (s, 3H), 2.99 (t, J = 6.5 Hz, 2H), 2.61 (t, J = 6.8 Hz, 2H), 1.98 – 1.81 (m, 4H). **¹³C NMR (101 MHz, CDCl₃)** δ 198.62, 171.50, 163.44, 148.21, 138.39, 136.42, 134.57, 130.37, 130.13, 128.00, 127.46, 121.67, 121.48, 116.49, 113.76, 55.52, 38.08, 38.00, 25.42, 24.16. **HRMS (ESI):** Calculated for C₂₂H₂₁N₂O₃ (M+H)⁺: 363.1703, found: 363.1707
6-(4-(tert-butyl)phenyl)-6-oxo-N-(quinolin-8-yl)hexanamide

3d was prepared following the General Procedure 1.1 and purified by flash Chromatography. 93% yield. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.83 (s, 1H), 8.79 (m, 2H), 8.19 – 8.11 (m, 1H), 7.90 (d, $J$ = 8.2 Hz, 2H), 7.60 – 7.38 (m, 5H), 3.04 (t, $J$ = 6.5 Hz, 2H), 2.63 (t, $J$ = 6.8 Hz, 2H), 2.05 – 1.85 (m, 4H), 1.33 (s, 9H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 199.67, 171.45, 156.69, 148.18, 138.36, 136.39, 134.55, 134.44, 128.07, 127.97, 127.43, 125.55, 121.64, 121.46, 116.47, 38.23, 38.05, 35.12, 31.15, 25.37, 24.03. HRMS (ESI): Calculated for C$_{25}$H$_{29}$N$_2$O$_2$ (M+H)$^+$: 389.2224, found: 389.2228.

6-(4-nitrophenyl)-6-oxo-N-(quinolin-8-yl)hexanamide

3e was prepared following the General Procedure 1.1 and purified by flash Chromatography. 91% yield. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.82 (s, 1H), 8.81 (d, $J$ = 4.1 Hz, 1H), 8.76 (d, $J$ = 6.8 Hz, 1H), 8.27 (d, $J$ = 8.5 Hz, 2H), 8.17 (d, $J$ = 8.2 Hz, 1H), 8.09 (d, $J$ = 8.4 Hz, 2H), 7.60 – 7.40 (m, 3H), 3.17 – 3.05 (m, 2H), 2.64 (d, $J$ = 6.6 Hz, 2H), 2.00 – 1.87 (m, 4H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 198.34, 171.27, 150.32, 148.32, 148.19, 141.38, 138.37, 136.53, 134.50, 129.08, 128.03, 127.40, 123.90, 121.65, 116.46,
38.91, 37.89, 25.10, 23.59. **HRMS** (ESI): Calculated for C\textsubscript{21}H\textsubscript{20}N\textsubscript{3}O\textsubscript{4} (M+H): 378.1448, found: 378.1454

**3f**

![Chemical structure of 3f](image)

6-oxo-N-(quinolin-8-yl)-6-(4-(trifluoromethyl)phenyl)hexanamide

**3f** was prepared following the General Procedure 1.1 and purified by flash Chromatography. 91% yield. **\textsuperscript{1}H NMR** (400 MHz, CDCl\textsubscript{3}) δ 9.82 (s, 1H), 8.84 – 8.69 (m, 2H), 8.16 (d, J = 8.3 Hz, 1H), 8.04 (d, J = 8.0 Hz, 2H), 7.70 (d, J = 8.1 Hz, 2H), 7.57 – 7.40 (m, 3H), 3.08 (t, J = 6.3 Hz, 2H), 2.63 (t, J = 6.8 Hz, 2H), 2.01 – 1.85 (m, 4H). **\textsuperscript{13}C NMR** (101 MHz, CDCl\textsubscript{3}) δ 198.88, 171.31, 148.17, 139.59, 138.34, 136.44, 134.50, 134.26 (q, J = 32.6 Hz), 128.37, 127.99, 127.44, 125.65, 123.69 (q, J = 274.0 Hz), 121.72, 121.62, 116.45, 38.61, 37.91, 25.15, 23.64. **\textsuperscript{19}F NMR** (376 MHz, CDCl\textsubscript{3}) δ -63.16. **HRMS** (ESI): Calculated for C\textsubscript{22}H\textsubscript{20}N\textsubscript{2}O\textsubscript{2}F\textsubscript{3} (M+H): 401.1471, found: 401.1477

**3g**

![Chemical structure of 3g](image)

6-(4-fluorophenyl)-6-oxo-N-(quinolin-8-yl)hexanamide

**3g** was prepared following the General Procedure 1.1 and purified by flash Chromatography. 92% yield. **\textsuperscript{1}H NMR** (400 MHz, CDCl\textsubscript{3}) δ 9.82 (s, 1H), 8.85 – 8.71 (m,
2H), 8.16 (d, J = 8.2 Hz, 1H), 7.98 (dd, J = 8.7, 5.5 Hz, 2H), 7.58 – 7.39 (m, 3H), 7.11 (t, J = 8.6 Hz, 2H), 3.03 (t, J = 6.6 Hz, 2H), 2.63 (t, J = 6.8 Hz, 2H), 1.98 – 1.82 (m, 4H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 198.31, 171.37, 165.69 (d, J = 254.3 Hz), 148.16, 138.34, 136.40, 134.51, 133.40, 130.71 (d, J = 7.4 Hz), 127.97, 127.44, 121.61, 121.52 (d, J = 4.0 Hz), 116.44, 115.65 (d, J = 21.4 Hz), 38.22, 37.97, 25.26, 23.85. $^{19}$F NMR (376 MHz, CDCl$_3$) δ -105.56, -105.57, -105.58, -105.60, -105.60, -105.61, -105.62, -105.63. HRMS (ESI): Calculated for C$_{21}$H$_{20}$N$_2$O$_2$F (M+H)$^+$: 351.1503, found: 351.1509

3h

6-(4-chlorophenyl)-6-oxo-N-(quinolin-8-yl)hexanamide

3h was prepared following the General Procedure 1.1 and purified by flash Chromatography. 91% yield. $^1$H NMR (400 MHz, CDCl$_3$) δ 9.82 (s, 1H), 8.84 – 8.71 (m, 2H), 8.17 (d, J = 8.2 Hz, 1H), 7.89 (d, J = 8.5 Hz, 2H), 7.58 – 7.35 (m, 5H), 3.03 (t, J = 6.6 Hz, 2H), 2.63 (t, J = 6.6 Hz, 2H), 1.97 – 1.84 (m, 4H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 198.67, 171.34, 148.27, 139.41, 138.35, 136.45, 135.28, 134.52, 129.58, 129.01, 127.98, 127.56, 121.76, 121.57, 116.54, 38.29, 37.97, 25.24, 23.80. HRMS (ESI): Calculated for C$_{21}$H$_{20}$N$_2$O$_2$Cl (M+H)$^+$: 367.1208, found: 367.1215
3i

![Chemical structure of 3i](image)

6-(4-bromophenyl)-6-oxo-N-(quinolin-8-yl)hexanamide

3i was prepared following the General Procedure 1.1 and purified by flash Chromatography. 92% yield. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.81 (s, 1H), 8.92 – 8.63 (m, 2H), 8.16 (d, $J = 7.8$ Hz, 1H), 7.81 (d, $J = 5.5$ Hz, 2H), 7.62 – 7.39 (m, 4H), 3.02 (t, $J = 5.2$ Hz, 2H), 2.62 (t, $J = 5.5$ Hz, 2H), 1.97 – 1.81 (m, 4H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 198.83, 171.32, 148.21, 138.32, 135.65, 134.49, 131.83, 129.64, 128.12, 127.96, 127.43, 121.70, 121.60, 116.49, 38.25, 37.94, 25.20, 23.75. HRMS (ESI): Calculated for C$_{21}$H$_{20}$N$_2$O$_2$Br (M+H)$^+$: 411.0703, found: 411.0706

3j

![Chemical structure of 3j](image)

6-oxo-N-(quinolin-8-yl)-6-(o-toly)hexanamide

3j was prepared following the General Procedure 1.1 and purified by flash Chromatography. 89% yield. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.82 (s, 1H), 8.83 – 8.74 (m, 2H), 8.16 (d, $J = 8.2$ Hz, 1H), 7.62 (d, $J = 7.6$ Hz, 1H), 7.58 – 7.40 (m, 3H), 7.35 (t, $J = 7.4$ Hz, 1H), 7.24 (t, $J = 8.7$ Hz, 2H), 2.98 (t, $J = 6.6$ Hz, 2H), 2.62 (t, $J = 6.8$ Hz, 2H), 2.48 (s, 3H), 1.96 – 1.81 (m, 4H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 204.24, 171.44, 148.18, 138.40, 138.18, 137.97, 136.42, 134.57, 131.99, 131.21, 128.48, 128.36, 128.01, 127.49, 125.75,
121.62, 116.47, 41.35, 38.08, 25.33, 24.05, 21.40. **HRMS** (ESI): Calculated for C_{22}H_{23}N_{2}O_{2} (M+H)^+: 347.1754, found: 347.1759.

3k

![Chemical structure of 3k]

6-(2-chlorophenyl)-6-oxo-N-(quinolin-8-yl)hexanamide

3k was prepared following the General Procedure 1.1 and purified by flash Chromatography. 82% yield. **1H NMR** (400 MHz, CDCl₃) δ 9.82 (s, 1H), 8.85 – 8.72 (m, 2H), 8.16 (d, J = 8.3, 1H), 7.61 – 7.22 (m, 7H), 3.03 (t, J = 6.7 Hz, 2H), 2.62 (t, J = 6.8 Hz, 2H), 1.97 – 1.81 (m, 4H). **13C NMR** (101 MHz, CDCl₃) δ 203.20, 171.27, 148.13, 139.57, 138.30, 136.35, 134.48, 131.56, 130.73, 130.47, 128.70, 127.92, 127.33, 126.93, 121.57, 121.49, 116.38, 42.67, 37.90, 25.09, 23.73. **HRMS** (ESI): Calculated for C_{21}H_{20}N_{2}O_{2}Cl (M+H)^+: 367.1208, found: 367.1216

3l

![Chemical structure of 3l]

6-oxo-N-(quinolin-8-yl)-6-(m-tolyl)hexanamide

3l was prepared following the General Procedure 1.1 and purified by flash Chromatography. 94% yield. **1H NMR** (400 MHz, CDCl₃) δ 9.82 (s, 1H), 8.90 – 8.64 (m,
2H), 8.15 (d, J = 8.1 Hz, 1H), 7.75 (d, J = 8.5 Hz, 2H), 7.58 – 7.40 (m, 3H), 7.33 (d, J = 8.0 Hz, 2H), 3.05 (t, J = 7.6 Hz, 2H), 2.62 (t, J = 8.0 Hz, 2H), 2.40 (s, 2H), 1.99 – 1.83 (m, 4H). \(^{13}\)C NMR (101 MHz, CDCl₃) δ 204.24, 171.44, 148.18, 138.40, 138.18, 137.97, 136.42, 134.57, 131.99, 131.21, 128.48, 128.36, 128.01, 127.49, 125.75, 121.62, 116.47, 41.35, 38.08, 25.33, 24.05, 21.40. HRMS (ESI): Calculated for C\(_{22}\)H\(_{23}\)N\(_2\)O\(_2\) (M+H)^+: 347.1754, found: 347.1763

3m

![Chemical structure of 3m](image)

6-(3-nitrophenyl)-6-oxo-N-(quinolin-8-yl)hexanamide

3m was prepared following the General Procedure 1.1 and purified by flash Chromatography. 82% yield. \(^1\)H NMR (400 MHz, CDCl₃) δ 9.83 (s, 1H), 8.88 – 8.69 (m, 3H), 8.40 (d, J = 8.3 Hz, 1H), 8.28 (d, J = 7.8 Hz, 1H), 8.17 (d, J = 7.5 Hz, 1H), 7.65 (t, J = 8.0 Hz, 1H), 7.58 – 7.42 (m, 3H), 3.14 (t, J = 6.8 Hz, 2H), 2.65 (t, J = 6.4 Hz, 2H), 2.02 – 1.86 (m, 4H), 1.56 (s, 3H). \(^{13}\)C NMR (101 MHz, CDCl₃) δ 197.64, 171.30, 148.56, 148.29, 138.41, 138.25, 136.51, 134.54, 133.69, 129.97, 128.06, 127.52, 127.37, 123.03, 121.75, 121.61, 116.55, 38.62, 37.95, 25.14, 23.58. HRMS (ESI): Calculated for C\(_{23}\)H\(_{20}\)N\(_3\)O\(_4\) (M+H)^+: 378.1448, found: 378.1455
Tert-butyl (2-oxo-2-((4-(6-oxo-6-(quinolin-8-ylamino)hexanoyl)phenyl)amino)ethyl) carbamate

3n was prepared following the General Procedure 1.1 and purified by flash Chromatography. 95% yield. $^1$H NMR (400 MHz, CDCl$_3$) δ 9.82 (s, 1H), 8.94 (s, 1H), 8.82 – 8.65 (m, 2H), 8.12 (d, $J = 8.2$ Hz, 1H), 7.87 (d, $J = 8.3$ Hz, 2H), 7.59 (d, $J = 8.3$ Hz, 2H), 7.53 – 7.37 (m, 3H), 5.59 (t, $J = 5.8$ Hz, 1H), 3.97 (d, $J = 5.9$ Hz, 2H), 2.96 (t, $J = 6.6$ Hz, 2H), 2.60 (t, $J = 6.8$ Hz, 2H), 1.97 – 1.76 (m, 3H), 1.45 (s, 9H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 198.81, 171.63, 168.43, 156.72, 148.27, 142.06, 138.40, 136.44, 134.47, 132.75, 129.45, 128.01, 127.43, 121.71, 121.61, 119.19, 116.54, 80.83, 45.62, 38.08, 28.40, 25.37, 23.96. HRMS (ESI): Calculated for C$_{28}$H$_{33}$N$_{4}$O$_{5}$ (M+H)$^+$: 505.2445, found: 505.2474

4a

6-cyclohexyl-6-oxo-N-(quinolin-8-yl)hexanamide

4a was prepared following the General Procedure 1.1 and purified by flash Chromatography. 95% yield. $^1$H NMR (400 MHz, CDCl$_3$) δ 9.80 (s, 1H), 8.81 (dd, $J = 4.2$, 1.7 Hz, 1H), 8.77 (d, $J = 7.2$ Hz, 1H), 8.16 (dd, $J = 8.2$, 1.7 Hz, 1H), 7.60 – 7.41 (m, 3H),
2.67 – 2.49 (m, 2H), 2.45 – 2.24 (m, 3H), 2.22 – 2.12 (m, 1H), 2.10 – 1.99 (m, 1H), 1.98 – 1.75 (m, 4H), 1.72 – 1.62 (m, 2H), 1.48 – 1.30 (m, 2H). \(^\text{13C NMR}\) (101 MHz, CDCl\textsubscript{3}) \(\delta\) 213.25, 171.69, 148.27, 138.47, 136.49, 134.66, 128.07, 127.56, 121.72, 121.51, 116.56, 50.78, 42.23, 38.38, 34.09, 29.16, 28.20, 25.14, 23.43. \(^\text{HRMS}\) (ESI): Calculated for C\textsubscript{19}H\textsubscript{23}N\textsubscript{2}O\textsubscript{3} (M+H\textsuperscript{+}): 311.1754, found: 311.1754.

The enantiomeric excess was determined by chiral HPLC: 88% \(ee\), (CHIRALPAK AS-H, hexane/i-PrOH = 80:20, flow rate 1 mL/min, \(T = 25\) °C, 254 nm), \(t_R\) (major) = 19.317 min, \(t_R\) (minor) = 15.009 min. The absolute configuration was assigned tentatively based on analogy.

\[4b\]

4-(2-oxo-5-phenylcyclohexyl)-N-(quinolin-8-yl)butanamide

\(4b\) was prepared following the General Procedure 1.2 and purified by flash Chromatography. 91% yield. \(^1\text{H NMR}\) (400 MHz, CDCl\textsubscript{3}) \(\delta\) 9.80 (s, 1H), 8.92 – 8.64 (m, 2H), 8.23 – 8.09 (m, 1H), 7.65 – 7.38 (m, 3H), 7.35 – 7.11 (m, 5H), 3.25 – 3.05 (m, 1H), 2.69 – 2.48 (m, 4H), 2.46 – 2.31 (m, 1H), 2.28 – 2.12 (m, 2H), 2.11 – 1.61 (m, 6H). \(^\text{13C NMR}\) (101 MHz, CDCl\textsubscript{3}) \(\delta\) 214.04, 171.16, 148.22, 144.44, 138.36, 136.43, 128.66, 127.45, 126.82, 126.74, 121.68, 121.52, 116.49, 49.28, 43.50, 41.91, 41.38, 38.44, 38.30, 33.42, 28.74, 23.28. \(^\text{HRMS}\) (ESI): Calculated for C\textsubscript{25}H\textsubscript{27}N\textsubscript{2}O\textsubscript{2} (M+H\textsuperscript{+}): 387.2067, found: 387.2086.
The enantiomeric excess was determined by chiral HPLC: **Major:** 93% ee, **Minor:** 73% ee (CHIRALPAK AS-H, hexane/i-PrOH = 85/15, flow rate 1 mL/min, T = 25 °C, 254 nm), **Minor:** \( t_R \) (major) = 19.853 min, \( t_R \) (minor) = 34.417 min; **Major:** \( t_R \) (major) = 40.780 min, \( t_R \) (minor) = 60.310 min; **dr:** 3.5/1. The absolute configuration was determined based on the comparison of the literature.

![Structure of 4c](image)

4c was prepared following the General Procedure 1.2 and purified by flash Chromatography. 96% yield. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 9.80 (s, 1H), 8.92 – 8.64 (m, 2H), 8.23 – 8.09 (m, 1H), 7.65 – 7.38 (m, 3H), 7.35 – 7.11 (m, 5H), 3.25 – 3.05 (m, 1H), 2.69 – 2.48 (m, 4H), 2.46 – 2.31 (m, 1H), 2.28 – 2.12 (m, 2H), 2.11 – 1.61 (m, 6H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) 213.93, 171.04, 148.10, 141.27, 138.22, 136.30, 135.88, 134.41, 129.22, 127.87, 127.31, 126.57, 121.57, 121.41, 116.37, 49.15, 38.44, 38.34, 37.48, 36.83, 33.38, 30.65, 23.18, 20.95. HRMS (ESI): Calculated for C\(_{26}\)H\(_{29}\)N\(_2\)O\(_2\) (M+H): 401.2224, found: 401.2247.

The enantiomeric excess was determined by chiral HPLC: **Major:** 93% ee, **Minor:** 70% ee (CHIRALPAK OJ-H, hexane/i-PrOH = 70:30, flow rate 1 mL/min, T = 25 °C, 254 nm), **Major:** \( t_R \) (major) = 25.653 min, \( t_R \) (minor) = 41.974 min; **Minor:** \( t_R \) (major) = 33.155 min,
t_R (minor) = 57.709 min; dr: 8.2/1. The absolute configuration was determined based on the comparison of the literature.

4d

Methyl 4-oxo-3-(4-oxo-4-(quinolin-8-ylamino)butyl)cyclohexane-1-carboxylate

4d was prepared following the General Procedure 1.2 and purified by flash Chromatography. 95% yield. ^1H NMR (400 MHz, CDCl_3) δ 9.80 (s, 1H), 8.86 – 8.72 (m, 2H), 8.16 (dd, J = 8.2, 1.7 Hz, 1H), 7.59 – 7.41 (m, 3H), 3.75 (s, 3H), 2.94 – 2.80 (m, 1H), 2.66 – 2.26 (m, 7H), 2.04 – 1.95 (m, 1H), 1.93 – 1.71 (m, 4H), 1.50 – 1.37 (m, 1H). ^13C NMR (101 MHz, CDCl_3) δ 212.21, 174.80, 171.45, 148.27, 138.46, 136.50, 134.62, 128.07, 127.54, 121.73, 121.55, 116.57, 52.18, 47.49, 38.69, 38.36, 38.07, 34.28, 29.30, 28.76, 23.19. HRMS (ESI): Calculated for C_{21}H_{25}N_{2}O_{4} (M+H)^+: 369.1809, found: 369.1829.

The enantiomeric excess was determined by chiral HPLC: Major: 96% ee, Minor: 43% ee (CHIRALPAK AS-H, hexane/i-PrOH = 82/18, flow rate 1 mL/min, T = 25 °C, 254 nm), Minor: t_R (major) = 45.983 min, t_R (minor) = 105.002 min; Major: t_R (major) = 66.030 min, t_R (minor) = 59.002 min; dr: 2.6/1. The absolute configuration was determined based on the comparison of the literature. ^28
4e was prepared following the General Procedure 1.2 and purified by flash Chromatography. 88% yield. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 9.80 (s, 1H), 8.88 – 8.69 (m, 2H), 8.16 (dd, \(J = 8.3, 1.6\) Hz, 1H), 7.58 – 7.42 (m, 3H), 4.12 – 3.90 (m, 4H), 2.76 – 2.48 (m, 4H), 2.43 – 2.32 (m, 1H), 2.22 – 2.12 (m, 1H), 2.09 – 1.87 (m, 3H), 1.87 – 1.69 (m, 3H), 1.41 – 1.30 (m, 1H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 211.41, 171.51, 148.21, 138.39, 136.42, 134.58, 128.00, 127.47, 121.67, 121.47, 116.49, 107.46, 64.84, 64.68, 46.32, 40.60, 38.36, 38.21, 34.85, 28.62, 23.12. HRMS (ESI): Calculated for C\(_{21}\)H\(_{25}\)N\(_2\)O\(_4\) (M+H): 369.1809, found: 369.1826.

The enantiomeric excess was determined by chiral HPLC: 87% ee, (CHIRALPAK OJ-H, hexane/i-PrOH = 90:10, flow rate 1 mL/min, \(T = 25^\circ\)C, 254 nm), \(t_R\) (major) = 104.713 min, \(t_R\) (minor) = 117.955 min. The absolute configuration was assigned tentatively based on analogy.
4-(4-oxotetrahydro-2H-pyran-3-yl)-N-(quinolin-8-yl)butanamide

**4f** was prepared following the General Procedure 1.2 and purified by flash Chromatography. 90% yield. 

**1H NMR** (400 MHz, CDCl₃) δ 9.80 (s, 1H), 8.85 – 8.68 (m, 2H), 8.15 (d, J = 8.2 Hz, 1H), 7.58 – 7.37 (m, 3H), 4.26 – 4.09 (m, 2H), 3.75 (td, J = 10.8, 3.7 Hz, 1H), 3.46 (t, J = 10.4 Hz, 1H), 2.68 – 2.50 (m, 4H), 2.43 – 2.37 (m, 1H), 1.99 – 1.75 (m, 3H), 1.43 – 1.30 (m, 1H). 

**13C NMR** (101 MHz, CDCl₃) δ 208.24, 171.17, 148.18, 138.38, 136.47, 136.43, 134.51, 128.01, 127.46, 121.63, 116.48, 72.75, 68.75, 51.58, 42.55, 38.01, 25.41, 23.19. 

**HRMS (ESI):** Calculated for C₁₈H₂₁N₂O₃ (M+H)+: 313.1547, found: 313.1565. 

The enantiomeric excess was determined by chiral HPLC: 88% ee, (CHIRALPAK OJ-H, hexane/i-PrOH = 70:30, flow rate 1 mL/min, T = 25 °C, 254 nm), tᵣ (major) = 35.458 min, tᵣ (minor) = 43.327 min. The absolute configuration was assigned tentatively based on analogy.

**4g**

4-(1-benzyl-4-oxopiperidin-3-yl)-N-(quinolin-8-yl)butanamide

**4g** was prepared following the General Procedure 1.2 and purified by flash Chromatography. 72% yield. 

**1H NMR** (400 MHz, CDCl₃) δ 9.78 (s, 1H), 8.84 – 8.68 (m, 2H), 8.15 (d, J = 8.2 Hz, 1H), 7.58 – 7.37 (m, 3H), 4.26 – 4.09 (m, 2H), 3.75 (td, J = 10.8, 3.7 Hz, 1H), 3.46 (t, J = 10.4 Hz, 1H), 2.68 – 2.50 (m, 4H), 2.43 – 2.37 (m, 1H), 1.99 – 1.75 (m, 3H), 1.43 – 1.30 (m, 1H).
2H), 8.13 (d, J = 8.1 Hz, 1H), 7.56 – 7.39 (m, 3H), 7.38 – 7.20 (m, 5H), 3.64 (d, J = 13.2 Hz, 1H), 3.54 (d, J = 13.2 Hz, 1H), 3.14 – 3.04 (m, 1H), 3.02 – 2.92 (m, 1H), 2.65 – 2.49 (m, 4H), 2.48 – 2.32 (m, 2H), 2.25 (t, J = 10.6 Hz, 1H), 1.99 – 1.84 (m, 1H), 1.84 – 1.71 (m, 2H), 1.44 – 1.31 (m, 1H). 13C NMR (101 MHz, CDCl3) δ 210.72, 171.43, 148.24, 138.42, 138.20, 136.47, 136.43, 134.59, 128.96, 128.50, 128.03, 127.45, 121.75, 121.63, 121.50, 116.53, 61.96, 59.03, 58.95, 53.61, 49.79, 41.11, 38.20, 27.11, 23.34. HRMS (ESI): Calculated for C25H28N3O2 (M+H)+: 402.2176, found: 402.2196.

The enantiomeric excess was determined by chiral HPLC: 0% ee, (CHIRALPAK OJ-H, hexane/i-PrOH = 75:25, flow rate 1 mL/min, T = 25 °C, 254 nm), tR = 33.561 min, tR = 51.758 min.

4h

Tert-butyl 3-oxo-4-(4-oxo-4-(quinolin-8-ylamino)butyl)piperidine-1-carboxylate

4h was prepared following the General Procedure 1.2 and purified by flash Chromatography. 80% yield. 1H NMR (400 MHz, CDCl3) δ 9.80 (s, 1H), 8.85 – 8.70 (m, 2H), 8.16 (d, J = 8.2 Hz, 1H), 7.58 – 7.41 (m, 3H), 4.80 -4.39 (m, 1H), 4.27 – 3.86 (m, 1H), 3.27 – 3.02 (s, 1H), 2.76 – 2.55 (m, 2H), 2.53 – 2.37 (m, 2H), 2.06 – 1.73 (m, 7H), 1.47 (s, 9H). 13C NMR (101 MHz, CDCl3) δ 208.64, 148.39, 148.11, 138.41, 136.44, 134.53, 128.03, 127.66, 127.30, 121.88, 121.54, 116.66, 116.41, 80.61, 37.31, 36.96, 30.42, 28.57, 28.39, 23.37, 23.29, 21.82. HRMS (ESI): Calculated for C23H30N3O4 (M+H)+: 412.2231, found: 412.2252.
The enantiomeric excess was determined by chiral HPLC: 47% ee, (CHIRALPAK OD-H, hexane/i-PrOH = 85:15, flow rate 1 mL/min, T = 25 °C, 254 nm), \( t_R \) (minor) = 30.184 min, \( t_R \) (major) = 34.668 min. The absolute configuration was assigned tentatively based on analogy.

4i

Tert-butyl 3-oxo-4-(4-oxo-4-(quinolin-8-ylamino)butyl)piperidine-1-carboxylate

4i was prepared following the General Procedure 1.2 and purified by flash Chromatography. 95% yield. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 9.83 (s, 1H), 8.87 – 8.71 (m, 2H), 8.15 (d, \( J = 8.2 \) Hz, 1H), 8.02 (d, \( J = 7.8 \) Hz, 1H), 7.58 – 7.40 (m, 4H), 7.26 (dt, \( J = 21.0, 7.6 \) Hz, 2H), 3.07 – 2.93 (m, 5H), 2.72 – 2.48 (m, 3H), 2.36 – 2.25 (m, 1H), 2.15 - 2.05 (m, 1H), 2.03 - 1.84(m, 3H), 1.73 – 1.61 (m, 1H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) 200.15, 171.61, 148.27, 144.10, 138.47, 136.47, 134.65, 133.29, 132.62, 128.81, 128.06, 127.56, 126.69, 121.69, 121.52, 116.56, 47.58, 38.35, 29.26, 28.64, 28.44, 23.28. HRMS (ESI): Calculated for C\(_{23}\)H\(_{23}\)N\(_3\)O\(_2\) (M+H): 359.1754, found: 359.1767.

The enantiomeric excess was determined by chiral HPLC: 0% ee, (CHIRALPAK OD-H, hexane/i-PrOH = 80:20, flow rate 1 mL/min, T = 25 °C, 254 nm), \( t_R \) = 50.978 min, \( t_R \) = 70.594 min.
4j

Tert-butyl 3-oxo-4-(4-oxo-4-(quinolin-8-ylamino)butyl)piperidine-1-carboxylate

4j was prepared following the General Procedure 1.2 and purified by flash Chromatography. 92% yield. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 9.80 (s, 1H), 8.85 – 8.72 (m, 2H), 8.16 (d, \(J = 8.3\) Hz, 1H), 7.57 – 7.42 (m, 3H), 2.66 – 2.50 (m, 2H), 2.37 – 2.22 (m, 2H), 2.18 – 1.96 (m, 3H), 1.95 – 1.71 (m, 4H), 1.61 – 1.52 (m, 1H), 1.49 – 1.35 (m, 1H).

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 221.17, 171.43, 148.23, 138.41, 136.46, 134.57, 128.03, 127.49, 121.69, 121.52, 116.52, 49.15, 38.22, 38.17, 29.65, 29.43, 23.75, 20.85. HRMS (ESI): Calculated for C\(_{18}\)H\(_{21}\)N\(_2\)O\(_2\) (M+H): 297.1598, found: 297.1597.

The enantiomeric excess was determined by chiral HPLC: 0% ee, (CHIRALPAK OD-H, hexane/i-PrOH = 80:20, flow rate 1 mL/min, T = 25 °C, 254 nm), \(t_R = 16.946\) min, \(t_R = 23.041\) min

4k

4-(2-oxocyclobutyl)-N-(quinolin-8-yl)butanamide

4k was prepared following the General Procedure 1.2 and purified by flash Chromatography. 95% yield. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 9.81 (s, 1H), 8.06 – 8.07 (m, 2H), 8.16 (d, \(J = 8.2\) Hz, 1H), 7.59 – 7.40 (m, 3H), 3.43 – 3.29 (m, 1H), 3.12-2.99 (m, 1H),
2.96 – 2.84 (m, 1H), 2.66 – 2.50 (m, 2H), 2.30 – 2.15 (m, 1H), 1.97 - 1.77 (m, 3H), 1.76 – 1.64 (m, 2H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 211.82, 171.31, 148.24, 138.45, 136.50, 134.57, 128.07, 127.52, 121.79, 121.68, 116.54, 60.42, 60.36, 44.67, 37.87, 29.19, 23.26, 17.02. HRMS (ESI): Calculated for C\(_{17}\)H\(_{19}\)N\(_2\)O\(_2\) (M+H): 283.1441, found: 283.1447.

The enantiomeric excess was determined by chiral HPLC: 0% ee, (CHIRALPAK AS-H, hexane/i-PrOH = 80/20, flow rate 1 mL/min, T = 25 °C, 254 nm), \(t_R\) (major) = 18.859 min, \(t_R\) (minor) = 25.859 min.

4l

![Ethyl 3-oxo-2-(4-oxo-4-(quinolin-8-ylamino)butyl)cyclobutane-1-carboxylate](image)

Ethyl 3-oxo-2-(4-oxo-4-(quinolin-8-ylamino)butyl)cyclobutane-1-carboxylate

4l was prepared following the General Procedure 1.2 and purified by flash Chromatography. 72% yield. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 9.78 (s, 1H), 8.83 – 8.68 (m, 2H), 8.15 (d, \(J = 8.2\) Hz, 1H), 7.56 – 7.39 (m, 3H), 4.20 (q, \(J = 7.1\) Hz, 2H), 3.65 – 3.56 (m, 1H), 3.38 (ddd, \(J = 17.4, 7.8, 3.1\) Hz, 1H), 3.10 (ddd, \(J = 17.4, 8.8, 2.4\) Hz, 1H), 2.90 (q, \(J = 8.0\) Hz, 1H), 2.65 – 2.48 (m, 2H), 1.97 – 1.81 (m, 3H), 1.78 – 1.65 (m, 1H), 1.27 (t, \(J = 7.1\) Hz, 3H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 206.18, 173.77, 170.92, 148.18, 138.30, 136.39, 134.45, 127.95, 127.36, 121.66, 121.50, 116.39, 64.99, 61.36, 53.55, 48.32, 37.46, 34.34, 28.21, 22.73, 14.20. HRMS (ESI): Calculated for C\(_{20}\)H\(_{23}\)N\(_2\)O\(_4\) (M+H): 355.1652, found: 355.1674.
The enantiomeric excess was determined by chiral HPLC: 45% ee, (CHIRALPAK OD-H, hexane/i-PrOH = 85:15, flow rate 1 mL/min, T = 25 °C, 254 nm), \( t_R \) (minor) = 40.1 min, \( t_R \) (major) = 44.1 min. The absolute configuration was assigned tentatively based on analogy.

**5a-B**

![Ethyl 2-acetyl-2-methyl-6-oxo-6-(quinolin-8-ylamino)hexanoate](image)

**5a-L**

![Ethyl 2-methyl-3,8-dioxo-8-(quinolin-8-ylamino)octanoate](image)

5a-B and 5a-L were prepared following the General Procedure 1.3 and purified by flash Chromatography as an inseparable mixture with 47:53 ratio. 95% yield. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 9.80 (s, 1H), 8.87 – 8.71 (m, 2H), 8.17 (d, \( J = 8.2 \) Hz, 1H), 7.59 – 7.40 (m, 3H), 4.26 – 4.11 (m, 2H), 3.57 – 3.47 (m, 0.5H), 2.74 – 2.52 (m, 3H), 2.18 (s, 1H), 2.07 – 1.65 (m, 4H), 1.57 (s, 1H), 1.40 (s, 1H), 1.34 (d, \( J = 7.2 \) Hz, 2H), 1.26 (t, \( J = 7.2 \) Hz, 3H).

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) 205.67, 172.92, 171.36, 170.96, 170.67, 148.24, 138.41, 136.48, 134.56, 128.04, 127.50, 121.72, 121.55, 116.52, 61.47, 59.68, 52.98, 41.20, 38.09, 37.95, 34.37, 26.27, 25.06, 23.22, 20.45, 18.92, 14.21, 12.90. HRMS (ESI): Calculated for \( \text{C}_{20}\text{H}_{24}\text{N}_2\text{O}_4 \) (M+H)\(^+\): 357.1809, found: 357.1831.
The enantiomeric excess was determined by chiral HPLC: 5a-B: 63% ee, (CHIRALPAK OD-H, hexane/i-PrOH = 90:10, flow rate 1 mL/min, T = 25 °C, 254 nm), tR (major) = 38.724 min, tR (minor) = 44.544 min. 5a-L: tR = 54.610 min. 5a-B:5a-L = 47:53.

5b-B

\[
\begin{align*}
\text{Isopropyl 2-acetyl-2-methyl-6-oxo-6-(quinolin-8-ylamino)hexanoate}
\end{align*}
\]

5b-L

\[
\begin{align*}
\text{Isopropyl 2-methyl-3,8-dioxo-8-(quinolin-8-ylamino)octanoate}
\end{align*}
\]

5b-B and 5b-L were prepared following the General Procedure 1.3 and purified by flash Chromatography as an inseparable mixture with 52:48 ratio. 95% yield. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 9.78\) (s, 1H), 8.86 – 8.71 (m, 2H), 8.16 (dd, \(J = 8.3, 1.6\) Hz, 1H), 7.59 – 7.39 (m, 3H), 5.13 – 4.97 (dp, \(J = 12.4, 6.3\) Hz, 2H), 3.48 (q, \(J = 7.1\) Hz, 0.5H), 2.73 – 2.49 (m, 3H), 2.17 (s, 1.5H), 2.06 – 1.58 (m, 5H), 1.38 (s, 1.5H), 1.32 (d, \(J = 7.1\) Hz, 1.5H), 1.24 (t, \(J = 5.4, 2.6\) Hz, 6H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta 205.45, 205.35, 172.12, 171.10, 170.71, 169.96, 148.01, 138.11, 136.22, 134.33, 134.30, 127.78, 127.18, 121.50, 121.34, 116.24, 68.75, 59.45, 52.91, 40.95, 37.83, 37.68, 34.07, 26.00, 24.85, 23.01, 21.56, 21.45, 20.17, 18.63, 12.61. HRMS (ESI): Calculated for \(C_{21}H_{27}N_2O_4\) (M+H): 371.1965, found: 357.1987.
The enantiomeric excess was determined by chiral HPLC: 5b-B: 74% ee, (CHIRALPAK OD-H, hexane/i-PrOH = 92:08, flow rate 1 mL/min, T = 25 °C, 254 nm), tR (major) = 30.231 min, tR (minor) = 36.600 min. 5b-L: tR = 41.909 min. 5b-B:5b-L = 52:48.

5c-B

Tert-butyl 2-acetyl-2-methyl-6-oxo-6-(quinolin-8-ylamino)hexanoate

5c-L

Tert-butyl 2-methyl-3,8-dioxo-8-(quinolin-8-ylamino)octanoate

5c-B and 5c-L were prepared following the General Procedure 1.3 and purified by flash Chromatography as an inseparable mixture with 51:49 ratio. 95% yield. 1H NMR (400 MHz, CDCl₃) δ 9.79 (s, 1H), 8.85 – 8.71 (m, 2H), 8.16 (d, J = 8.2 Hz, 1H), 7.59 – 7.40 (m, 3H), 3.43 (q, J = 7.1 Hz, 0.5H), 2.73 – 2.50 (m, 3H), 2.17 (s, 1.6H), 2.02 – 1.67 (m, 4H), 1.46 (s, 4.5H), 1.45 (s, 4.5H), 1.35 (s, 1.5H), 1.29 (d, J = 7.1 Hz, 1.5H). 13C NMR (101 MHz, CDCl₃) δ 215.60, 171.15, 148.12, 138.27, 136.33, 134.43, 127.90, 127.35, 121.58, 121.40, 116.38, 48.88, 41.29, 38.43, 37.57, 32.37, 31.48, 30.79, 27.41, 26.80, 23.22. HRMS (ESI): Calculated for C_{22}H_{28}NaN_{2}O_{4} (M+Na)^+: 407.1941, found: 407.1941.
The enantiomeric excess was determined by chiral HPLC: 5c-B: 74% ee, (CHIRALPAK OJ-H, hexane/i-PrOH = 95:05, flow rate 1 mL/min, T = 25 °C, 254 nm), \( t_R \) (major) = 31.039 min, \( t_R \) (minor) = 41.822 min. 5c-L: \( t_R \) = 54.620 min, \( t_R \) = 66.851 min. 5c-B:5c-L = 51:49

6

\[
\text{HO-}
\begin{array}{c}
| \text{C} | \\
\end{array}
\text{-CH-}
\begin{array}{c}
| \text{O} | \\
\end{array}
\text{-CO-}
\begin{array}{c}
| \text{C} | \\
\end{array}
\text{-O-}
\begin{array}{c}
| \text{H} | \\
\end{array}
\text{6-oxo-6-phenylhexanoic acid}
\]

6 were prepared following the General Procedure 1.4 and purified by flash Chromatography. 86% yield. \(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)) \( \delta \) 7.96 (d, \( J = 7.3 \) Hz, 1H), 7.56 (t, \( J = 7.4 \) Hz, 1H), 7.46 (t, \( J = 7.5 \) Hz, 1H), 3.01 (t, \( J = 7.0 \) Hz, 1H), 2.43 (t, \( J = 7.1 \) Hz, 1H), 1.87 – 1.68 (m, 2H). \(^{13}\text{C NMR}\) (101 MHz, CDCl\(_3\)) \( \delta \) 200.00, 179.67, 136.91, 133.11, 128.65, 128.22, 128.08, 38.12, 33.95, 24.34, 23.59. \text{HRMS} (ESI): Calculated for \( \text{C}_{25}\text{H}_{28}\text{N}_3\text{O}_2 \) (M+H): 207.1016, found: 207.1017
3.1 Gold redox catalysis without using strong oxidant

3.1.1 Introduction

As the chapter 1 introduced, strong oxidants are always required in Au redox catalysis, which impedes its further application due to limited substrate scope. Therefore, developing new methodology without using strong oxidant is necessary and meaningful. More recently, direct oxidative addition of Au (I) intermediate appeared. However, compared with the isoelectronic Pd (0) complexes, Au (I) called for either well-designed phosphine ligand or highly-strained substrates to achieve oxidative addition.

In 2014, Toste group revealed a formal gold oxidative addition toward to CF$_3$-I bond under photo condition (Figure 16). The mechanism study showed the reaction went through a radical process started from UV-initiated CF$_3$I excitation, followed by the single-electron transfer to achieve Au (III) from Au (I). The Au(III) intermediate was very stable could even be purified by column. However, only C-I bond reductive elimination could happen at high temperature instead of the C-C bond formation, likely due to the C-I bond faster reductive elimination rate.

Figure 16. Au oxidative addition to CF$_3$I bond
Treatment with Ag salt to abstract iodide would lead to CF$_3$-Ar reductive elimination in less than 1 min. This result suggested the formation of three coordination intermediate was the essential step of Au (III) intermediate.

In the same year, the Toste group published a bis gold catalyst involved oxidative addition toward to alkyl bromide forming C$_{sp2}$-C$_{sp3}$ bond (**Figure 17**). The orthogonal experiment showed that the reactivity and selectivity of gold catalysis was very similar to traditional palladium catalyzed cross coupling. Due to the bis-gold system, the oxidative addition was accelerated because of the formation of Au$^{II}$-Au$^{II}$ species. The key intermediate could go through fast reductive elimination without using Ag salts. Compared with monogold catalyst, bis metallic catalyst gave much better yield (up to 95% yield), which indicated necessary of the bis-gold intermediate.

![Orthogonal experiment](image)

**Figure 17. Bis-gold involved oxidative addition**
What’s more, the authors confirmed the gold (III) intermediates by X-ray, followed by Ag associated bromide abstraction triggered reductive elimination.

As mentioned before, rational designed ligand could promote gold oxidative addition. Amgoune and Bourissou reported a strategy using phosphine directed oxidative addition to aryl halide. This was the first example demonstrated monogold involved facile oxidative addition (Figure 18). Due to the phosphine chelation, the activation occurred much easier than Toste’s example (based on the DFT calculation). It could finish at room temperature without using UV to initiate. However, this methodology is still an intramolecular process, and it requires delicate ligand design, which limits its further application.

![Figure 18. Phosphine directed Au oxidative addition](image)

The same group revealed another gold facile oxidative addition using a special bisphosphine ligand later in the same year (Figure 19). In this methodology, the authors developed a bisphosphine ligand, carborane diphosphines (DPCb). Compared with normal dischelating ligand of Au, DPCb has unique bite angle (100°), while usually it should be 180° owing to the Au (I) geometry. What’s more, with this small bite angle, bisgold intermediate is preferred to form instead of this unique stable Au (I) complexes. This unusual property allowed the oxidative addition to arise at room temperature without the halide abstract and it could active various aryl iodides with both EDG and EWG. The only issue this method facing is still the requirement of a special ligand.
After these results, Bourissou reported Au oxidative addition using Me-Daphos (Figure 20). Because of the high redox potential of the Au (I)/Au(III) (1.4 eV), the reluctance of Au oxidative addition is an intrinsic property. To achieve the C-X bond activation, previously, virous strategies, such as harsh reaction condition (like UV), bisgold catalyst, or fancy designed ligand, were employed. However, they all have very limited reaction scopes, and they are hard to be applied widely. In this case, based on the DFT calculation result, the hemilabile P-N bischelating ligand can achieve oxidative addition under mild condition and the hemilabile coordination play an essential role. This is the first example utilizing a commercially available ligand to implement gold catalyzed cross coupling via oxidative addition to C-X bond.

Figure 19. Au oxidative addition using bisphosphine ligand

Figure 20. Me-Daphos Au (I) catalyzed cross coupling via O.A.
Although the above methods can perform Au (I/III) redox catalysis without using external oxidant, but they still require well-designed ligand, harsh condition, highly strained starting materials or stoichiometric amount Ag salt. It leads to limited substrate scope and prevents the further application. Therefore, developing a novel and effective approach to accomplish gold redox catalysis is not only important for enhancing the basic understanding of this rapidly growing field, but also holds promise for generating synthetically valuable building blocks. Recently, our group developed a mild oxidant to perform Au (I/III) redox catalysis to thioallylation without those limitations (Figure 21). This methodology is very efficient and stereoselective. The mass spectrometry has detected the Au (III) species in the reaction and the cross-over experiment double confirmed the Au redox process. This transformation was started from sulfur attack to Au (I) activated electron-deficient alkyne to achieve a vinyl gold intermediate. Then this intermediate went through a sequential intermolecular allyl transfer via Au (I/III) cycle. In particular, it was the first time that allyl sulfonium cation served as mild oxidant to complete Au (I/III) oxidation. The result suggested this method could be a robust strategy to combine Au (I) π-acid activation and gold redox catalysis.

Concerns: 1) only works for EWG activated alkenes; 2) plausible 3,3-rearrangement, not gold redox catalysis?

Figure 21. Our group recent example: alkyne thioallylation
3.1.2 Gold redox catalysis with a mild oxidant

Although mechanism study confirmed the exist of the Au (III) species via MS and cross-over experiments, the potential [3,3]-rearrangement mechanism pathway cannot be totally rule out.\(^{32}\) Moreover, that methodology only worked with electron-deficient alkynes, which limited the reaction scope greatly. There was no product obtained with other normal alkyne or allene as the substrates. Therefore, it is important to conduct a more detailed study of the detailed reaction mechanism and further expand the reaction to a wider range.

In this chapter, I discussed RXXR addition to virous alkynes and allenes via Au redox catalysis (Figure 22A). The conversion is carried out with high efficiency under mild conditions, and the desired product with good to excellent yield and excellent regioselectivity is obtained. Mechanism studies confirmed the Au(I/III) redox cycle, which confirmed the great potential of using selenium cations as an effective mild oxidant to promote gold redox catalysis in the future. More importantly, diselenation products can be further derived into high value-added synthetic intermediates.\(^{33}\)

As shown in Figure 22B, compounds with RXXR moieties may be interested in sequential nucleophilic addition and redox chemistry using a single Au(I) catalyst. Unlike thioallylation, the [3,3]-rearrangement pathway is not available in this alkyne difunctionalization reaction, which gives us an excellent chance to study gold redox catalysis in a simple case. Because of the weak bond dissociation energy of RXXR, it could form RX radicals in a transform and perform the above reaction via a free radical process.\(^{34}\) It results in poor regioselectivity in many cases. If the proposed gold catalytic route is successful, it will not only provide an alternative method for RXXR activation, but
also may complete the reaction with a better stereo result. But there are two potential challenges: 1) XR anion may coordinate with Au cation and reduce its reactivity; 2) slow reduction and elimination of C-X (relative to C-C), which may lead to competitive pro-dehydrogenation as a major by-product. To start our research, we first tried to use ROOR, RNNR and RSSR as nucleophiles to react with alkynes.

A) Exploring RX-XR as plausible Nu and oxidant for gold redox catalysis

Tasks: 1) developing new alkyne/allene difunctionalization under mild conditions; 2) evaluating choice of RXXR (X=O,N,S etc.); 3) confirming gold redox process.

b) RXXR addition to alkynes

Treating the alkyne 7a with peroxide or peracid gives 100% conversion, but no desired product 9 or by-product 9' was formed based on crude NMR. Because of the catalyst poisoning, there is no conversion when tetramethylhydrazine is treated in the reaction. Interestingly, the disulfide did show similar properties. Instead, 80% conversion and 58% yield were obtained. As expected, the byproduct, hydrothiolation product 9a', was observed in a 22% yield. It is worth noting that both 9a and 9a' are achieved with excellent
stereoselectivity (E/Z > 100:1). Later, X-ray crystallography (see below) confirmed the olefin geometry. These exciting results just exhibit our proposed mechanism (combination of gold pi-acid activation and redox catalysis) is valid.

Theoretically, the protodeauration can occur on gold (I) intermediates (vinyl gold) or gold (III) intermediates. Based on the discussion on chapter 1, the reductive elimination of gold (III) is a fast process. Therefore, we hypothesized that if a strong oxidant can foster a quick gold oxidation, it will go through a rapid reductive elimination to prevent protodeauration in the catalytic cycle. Then we focused on diselenide, because of two reasons: 1) Se is a better nucleophile than S, so it will help the formation vinyl gold formation; 2) selenium cation is a stronger oxidant that can promote fast oxidation. Table 6 summarizes the comparison between the best conditions and some alternative conditions. To our delight, the desired deselenium product 9b was formed with an excellent yield. Electron-deficient gold catalyst ((PhO)$_3$PAuNTf$_2$, entry 3) gave the lowest yield, while Ph$_3$PAuNTf$_2$ obtained better yield and IPrAuNTf$_2$ showed the best results (92% yield). The electron-rich gold catalyst could promote this transformation and it suggested the rate determining step was oxidation. It further proved our choice (strong oxidant can prevent protodeauration) was correct. DCE was identified as the best solvent. Without sacrificing yield or regioselectivity, the catalyst loading can be reduced to 2%. The results of other metal catalysts, including Pt, Ag, Cu, Fe, are poor. A decrease in yield was observed when using PhTeTePh (9c), which may be due to the stronger coordination between Te and the gold catalyst compared to Se or S, resulting in slow reaction rate.
Table 6. Gold-catalyzed alkyne diselenation: condition screening

<table>
<thead>
<tr>
<th>entry</th>
<th>Variation from standard conditions</th>
<th>conv.</th>
<th>9b (E/Z)</th>
<th>9b'</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>100%</td>
<td>92% (&gt;100:1)</td>
<td>5%</td>
</tr>
<tr>
<td>2</td>
<td>5% Ph3PAuNTf2</td>
<td>60%</td>
<td>46%</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>5% (PhO)2PAuNTf2</td>
<td>60%</td>
<td>31%</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>5% XPhosAuNTf2</td>
<td>100%</td>
<td>72% (40:1)</td>
<td>14%</td>
</tr>
<tr>
<td>5</td>
<td>2% IPrAuNTf2 (0.5 M)</td>
<td>100%</td>
<td>85% (32:1)</td>
<td>7%</td>
</tr>
<tr>
<td>6</td>
<td>1% IPrAuNTf2 (0.5 M)</td>
<td>100%</td>
<td>85% (20:1)</td>
<td>8%</td>
</tr>
<tr>
<td>7</td>
<td>Other 4 catalyst</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>10% PtCl2</td>
<td>80%</td>
<td>67%</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>other metal catalysts (Ag, Cu, Fe, etc)</td>
<td>&lt;60%</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>other solvents</td>
<td>&lt;80%</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>10% HOTf</td>
<td>&lt;5%</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>12</td>
<td>no catalyst</td>
<td>&lt;5%</td>
<td>nd</td>
<td>-</td>
</tr>
</tbody>
</table>

Reaction conditions: the catalyst (2%) was added into a DCE solution of alkyne (0.3 mmol) and diselenide (0.2 mmol). Run the reaction at 60 °C for 24 h. Conversion and yield were determined by 1H NMR spectroscopy with dimethyl sulfone as the internal standard.

With the optimal conditions in hand, we next explored the reaction scope, as shown in Table 7. In this transformation, it could tolerate many EDG and EWG on the aryl diselenides with good to excellent yield (9a-9g). However, CF3 substituted aryl diselenides only provide a moderate yield likely due to its slow nucleophilic addition. Alkyl diselenide also participated in the reaction smoothly, achieving 9j and 9k with satisfactory yields. Other carbonyl-activated alkynes, including esters (9l and 9m), ketones (9q), and acetylene diesters (9r), have been successfully diselenation with high yields. On the other hand, amides (9n-9p) gave low yield, which may be due to the coordination of the substrate.
Table 7. Substrate scope for diselenation of alkynes

<table>
<thead>
<tr>
<th>R</th>
<th>R’</th>
<th>R”Se-SeR”</th>
<th>2-5% IPrAuNTf₂</th>
<th>DCE, 0.2 M, temp., 24 h</th>
<th>R”Se-SeR”</th>
</tr>
</thead>
<tbody>
<tr>
<td>[56]</td>
<td>7</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

carbonyl-activated alkynes, 2% IPrAuNTf₂, 60 °C:

9b, R = H, 94%  
9d, R = 4-OMe, 92%  
9e, R = 4-Me, 88%  
9f, R = 4-Br, 86%  
9g, R = 4-F, 94%  
9h, R = 4-CF₃, 66%  
9i, R = 3-F, 80%

haloalkynes, ynamides and simple alkynes, 5% IPrAuNTf₂, rt:

9s, R = H, 82%  
9t, R = 4-Br, 86%  
9u, R = 4-F, 94%  
9v, R = 3-Me, 65%  
9w, R = 3-F, 69%  
9x, R = 2-Me, 60%

9aa, R = 4-OMeC₆H₄, 90%  
9ab, R = 4-MeC₆H₄, 96%  
9ac, R = 4-CF₃C₆H₄, 84%  
9ad, R = 4-CF₃C₆H₄, 72%  
9ae, R = Bn, 98%

Reaction conditions: the catalyst was added into a DCE solution of alkyne (0.3 mmol) and diselenide (0.2 mmol), and reacted at given temperature for 24 h. Isolated yield. ¹ 0.2 mmol alkyne and 0.3 mmol diselenide were used for the ease of purification. ² React at 80 °C.
Since EWG-activated alkynes could participate in this transformation successfully, we then turn our attention to some inactivated alkynes. First, various bromo attached internal alkynes were tested with phenyl diselenenides and provided the desired product in moderate to excellent yields (9s-9z).

The steric hindrance on the alkyne aryl group would lead to moderate yield (9v-9x) while the electron density did not affect the reaction. The radical clock substrate 9z could also show moderate yield and no cyclopropyl ring-opened product was observed. It suggested the reaction went through a radical free mechanism. Other diaryl selenides also react with internal Bromo-alkynes (9aa-9ae) compatibly. As expected, chloroalkyne was an effective substrate for this reaction (9af). We were very pleased to find that even electron-rich alkynes (such as ynamides) have done diselenation successfully to obtain the desired product with a moderate yield (9ag). Encouraged by this result, we tested the terminal and internal alkynes without electronic bias. To our delight, the desired products 9ah and 9ai were formed in moderate yields under gold catalyzed conditions, which further demonstrates the wide range of this conversion. Notably, in all cases, the diselenation products were formed as one alkene isomer, and their E-geometry was identified by the X-ray crystallography of the product 9t.

Encouraged by the previous successful results, we wondered whether this transformation can be further extended to allenes, which were not suitable substrates in previous thioallylation studies. After detailed reaction optimization, we are pleased to find that the diselenation products of allene can also be formed successfully through this protocol. As shown in Table 8, when 1,1-diphenyl allene was treated with different diselenenides, the desired products (11a-11e) were formed in good to excellent yields. Both
EDG and EWG were tolerated in this transformation, but benzyl diselenide gave only moderate yield due to the slow oxidation. 1,1-Dimethyl allene could also obtain the desired product (11f) in an excellent yield. The more steric tri-substituted allene smoothly undergoes the diselenation, providing the desired product 11g with a moderate yield. Although only moderate E/Z selectivity (11h-11i) was observed, the monosubstituted allene also provided an excellent yield. The structure of the E/Z isomer is clearly specified by X-ray crystallography (E-11i).

**Table 8. Substrate scope for diselenation of allenes**

<table>
<thead>
<tr>
<th>Reaction conditions: the catalyst (2%) was added into a DCE solution of allene (0.6 mmol) and diselenide (0.2 mmol) and reacted at rt for 24 h. Isolated yield.</th>
</tr>
</thead>
<tbody>
<tr>
<td>11a, R = H, 82%</td>
</tr>
<tr>
<td>11b, R = 4-OMe, 94%</td>
</tr>
<tr>
<td>11c, R = 4-F, 82%</td>
</tr>
<tr>
<td>11d, R = 4-Me, 91%</td>
</tr>
<tr>
<td>11e, 67%</td>
</tr>
<tr>
<td>11f, 84%</td>
</tr>
<tr>
<td>11g, 40%</td>
</tr>
<tr>
<td>11h, 96%, Z:E = 1.7:1</td>
</tr>
<tr>
<td>11i, Ar = 4-Methylphenyl 94%, E:Z = 2:1</td>
</tr>
</tbody>
</table>

In order to better clarify its mechanism, a series of experiments were conducted. First, the cross-over experiment clearly supports the intermolecular selenium transfer mechanism (Figure 23A). In addition, no direct oxidative addition of phenyl diselenide to
the gold(I) catalyst was observed by $^{31}$P NMR (Figure 23B). When more electron-rich styrene was treated, this reaction did not occur, which excludes the formation of selenium cations assisted by Au(I). We proposed a mechanism including gold-catalyzed nucleophilic addition of diselenide and subsequent selenium cation transfer by gold redox catalysis and attempted to capture key intermediates by mass spectrometry (Figure 23C).

**A**) Cross-over coupling confirmed intermolecular reaction

\[
\text{H} = \text{CO}_2\text{Me} + \begin{cases} \text{PhSe-SePh} & \text{1 equiv} \\ \text{TolSe-SeTol} & \text{1 equiv.} \end{cases} \xrightarrow{5\% \text{[Au]}} \text{DCE, 60}^\circ\text{C} \text{1:1:1 by NMR} \\
\text{PhSe} \quad \text{CO}_2\text{Me} \\
\text{H} \quad \text{SePh} \\
\text{TolSe} \quad \text{CO}_2\text{Me} \\
\text{H} \quad \text{SeTol} \\
\text{PhSe} \quad \text{H} \quad \text{TolSe} \\
\text{SeTol} \quad \text{SePh} \\
\text{H} \quad \text{SePh} \\
\text{CO}_2\text{Me} \quad \text{H} \quad \text{SeTol} \\
\text{H} \quad \text{SePh} \\
\text{PhSe} \quad \text{H} \quad \text{TolSe} \\
\text{SeTol} \quad \text{SePh} \]

**B**) $^{31}$P NMR experiment

- [Au], 60 °C
- [Au] + PhSeSePh, 60 °C
- [Au] + PhSeSePh, rt
- [Au], rt

**C**) In-situ MS-MS confirmed Au(III) mechanism

\[
\text{CO}_2\text{Me} + \text{PhSe-SePh} \xrightarrow{\text{Au(I)-IPr}} \begin{cases} \text{PhSe}^+ \cdot \text{SePh} & \text{oxidation} \\ \text{H} \quad \text{IPr-Au(III)-SePh} \end{cases} \xrightarrow{\text{R.E.}} \begin{cases} \text{SePh} & \text{m/z = 983 detected; consistent with CID} \\ \text{H} \quad \text{IPr} \quad \text{Au(III)-SePh} \end{cases} + \begin{cases} \text{PhSe}^+ \cdot \text{SePh} & \text{m/z = 1193 detected; consistent with CID} \\ \text{H} \quad \text{IPr} \quad \text{Au(III)-SePh} \end{cases}
\]

*Figure 23. Mechanism investigation*
The mass corresponding to the vinyl gold intermediate A was clearly detected. In addition, the m/z CID experiment of Intermediate A shows that there was a Au(II)-SePh+ fragment, which likely came from Au(III) Intermediate B which had the same Another Au(III) intermediate C which contains a similar composition as in the thioallylation case was also observed, and CID confirmed the existence of a Au(III) fragment too. Therefore, the mass study strongly supported that the Au(I/III) redox cycle is reasonable for this transformation.

Since 1,2-diselenide products 9 were interesting building blocks, they could be easily converted into other compounds through simple conversions. As shown in Figure 24, processing 9r under standard Suzuki coupling condition gave the undesired coupling product 12 with 75% yield. Despite the use of an excess of ArB(OH)$_2$, only a single isomer with a mono-substituted product was obtained, the structure of which has been confirmed by X-ray crystallography. This result indicates that this substrate may undergo a Heck-type mechanism instead of the direct C-Se bond oxidative addition proposed in the literature. This excellent chemical and stereoselectivity greatly highlights these 1,2-diselenide compounds under this new mild gold redox condition.

![Figure 24. Further conversion of diselenation product](image)

**3.2 Conclusion**

In summary, we reported a gold-catalyzed deselenium reaction of alkynes and allenes. This conversion achieves excellent yield and stereoselectivity as well as a wide range of
reactions. Terminal, internal, unactivated, and steric substrates were suitable in this transformation. Based on the results of crossover experiments, $^{31}\text{P}$ NMR, control experiments and in-situ mass spectrometry, the Au(I/III) mechanism was proposed. Our laboratory is currently studying other mild oxidants.

3.3 Experimental data

3.3.1 General Methods and Materials

All of the reactions dealing with air and/or moisture-sensitive compounds were carried out under an atmosphere of argon using oven/flame-dried glassware and standard syringe/septa techniques. Unless otherwise noted, all commercial reagents and solvents were obtained from the commercial provider and used without further purification. Diselenides and allenes were synthesized according to literature reports.

$^1\text{H}$ NMR, $^{13}\text{C}$ NMR and $^{19}\text{F}$ NMR spectra were recorded on a Varian Inova 400 MHz spectrometer. Chemical shifts were reported relative to internal tetramethylsilane (δ 0.00 ppm) for $^1\text{H}$ and CDCl$_3$ (δ 77.0 ppm) for $^{13}\text{C}$. Flash column chromatography was performed on 230-430 mesh silica gel. Analytical thin layer chromatography was performed with pre-coated glass baked plates (250μ) and visualized by fluorescence and by charring after treatment with potassium permanganate stain. HRMS data for substrates were collected on an Agilent 6540 LC/QTOF spectrometer in the mass-spec facility in the University of South Florida. For mechanistic studies using ESI-MS, the same MS instrument in Ohio University was used, and the samples were infused with a flow rate of 10 μL/min and sprayed at a high voltage of 5 kV. The X-ray diffraction data for 9t and 11i was measured on Bruker D8 Venture PHOTON 100 CMOS system.
3.3.2 General Procedure for Disulfidation, Diselenation or Ditelluration of Alkynes

To a DCE solution (1 mL) of diselenide 8 (0.2 mmol, 1 eq) and alkyne 7 (0.3 mmol, 1.5 eq) was added IPrAuNTf₂ catalyst (0.004 mmol, 0.02 eq or 0.01 mmol, 0.05 eq) in one portion. The reaction was flashed with Ar and allowed to stir at 60 °C or rt for 24 h. The reaction mixture was then concentrated by rot-vap and purified by flash chromatography (20:1 hexane/EtOAc) to obtain pure product 9.

3.3.3 General Procedure for Diselenation of Allenes

To a DCE solution (1 mL) of diselenide 8 (0.2 mmol, 1 eq) and allene 10 (0.6 mmol, 3 eq) was added IPrAuNTf₂ catalyst (0.004 mmol, 0.02 eq) in one portion. The reaction was flashed with Ar and allowed to stir at rt for 24 h in dark. The reaction mixture was then concentrated by rot-vap, and purified by flash chromatography (DCM:hexane = 1:10) to obtain pure product 11.

3.3.4 Synthetic procedure for Suzuki coupling of 6

An oven-dried vial was added 9r (273 mg, 0.6 mmol, 1 eq), boronic acid (324 mg, 1.8 mmol, 1.3 eq), Pd(PPh₃)₄ (70 mg, 0.06 mmol, 0.1 eq) and Cu(OAc)₂H₂O (144 mg, 0.72 mmol, 1.2 eq) sequentially. The reaction mixture was placed under vacuum and recharged with Ar. Then DMF 3 mL was added, and the reaction was flashed with Ar.
After reacting for 2 h at 80 °C, the reaction was quenched with NH₄Cl (sat.) 20 mL and extracted with DCM 10 mL three times. The three organic layers was combined and washed with H₂O twice. The organic layer was dried with Na₂SO₄ and concentrated under vacuum. Crude mixture was purified by flash chromatography (hexane:DCM = 10:1) to yield the desired product 12 (195 mg, 75%).

3.3.5 ³¹P NMR experiment

A series of control experiments were carried out to investigate if direct oxidative addition occurred with diselenide. First, gold catalyst (5.2 mg, 0.017 mmol) in CDCl₃ showed the same ³¹P NMR peak both at rt and after stirring at 60 °C for 0.5 h. Next, when treating the gold catalyst (5.2 mg, 0.017 mmol) with equal molar of diselenide (5.2 mg, 0.017 mmol) both at rt and 60 °C for 0.5 h, no change in ³¹P NMR was detected, which indicated a direct oxidative addition is unlikely for this system.

3.3.6 Cross-over experiment.

Figure 26. Cross-over experiment

To a DCE solution (0.6 mL) of two different diselenide (0.1 mmol for each, 1 eq) and alkyne 7a (0.6 mmol, 3 eq) was added IPrAuNTf₂ catalyst (0.004 mmol, 0.02 eq) in one
portion. The reaction was flashed with Ar and allowed to stir at 60 °C for 24 h. The ratio of four different product was determined by NMR.

![Figure 27. \(^1\)H NMR of cross-over experiment](image)

### 3.3.7 ORTEP Drawing for Crystal Structures

The X-ray diffraction data were measured on Bruker D8 Venture PHOTON 100 CMOS system equipped with a Cu K\(_\alpha\) INCOATEC ImuS micro-focus source (\(\lambda = 1.54178 \text{ Å}\)). Indexing was performed using Apex3. Data integration and reduction were performed using SaintPlus 6.01. Absorption correction was performed by multi-scan method implemented in SADABS. Space group was determined using XPREP implemented in APEX3. Structure was solved using SHELXT and refined using SHELXL-2017 (full-matrix
least-squares on $F^2$) through OLEX2 interface program. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed in geometrically calculated positions and were included in the refinement process using riding model with isotropic thermal parameters. Crystal data and refinement conditions are shown in Table 1.

Table 9. Crystal data and structure refinement for Z1_6_4

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#### 3.3.8 Mass Spectrometry Study

ESI-MS spectra were collected using a Thermo scientific Orbitrap Q Extractive Plus (Bremen, Germany) in the positive ion mode. Samples were infused at a flow rate of 10 μL/min and ionized at a high voltage of +5 kV.
3.3.9 ESI-MS analysis of 7a and 8b

General procedure: 200 µM IPrAuNTf₂ was added to 20 mM of diselenide and 30 mM methyl propiolate in 3 mL of DCE, and the reaction mixture was stirred at 60 °C for 24 h. The reaction mixture was diluted in 1:20 ratio with acetonitrile, and tested on 5 min, 1 h, 2.5 h and 5 h using ESI-MS (2 uL/min, +2.5 kV).

Three key intermediates were detected. Intermediate A (m/z = 983) which represents a vinyl Au(I) complex has the same mass as a possible Au(III) intermediate B. CID experiment at 983 revealed a Au(II)-SePh fragment, which strongly supported the existence of the Au(III) intermediate B. Another intermediate C (m/z = 1137), which had a similar formula as the Au(III) intermediate we observed in the thioallylation studies, provided a Au(II)-SePh fragment in the CID experiment too. All three intermediates existed at a noticeable concentration since 5 min. Thus, we propose a Au(I/III) redox cycle could be viable for this transformation.
Figure 29. ESI-MS results
Figure 29. ESI-MS results (continued)
3.3.10 Compound Characterization

This compound was prepared following general procedure 2.2, and crude mixture was purified using flash chromatography (20:1 hexane/EtOAc) to yield the unseparated mixture products with $9a/9a’ = 3:1$ as colorless oil (96%). $^1H$ NMR (400 MHz; CDCl$_3$): $\delta$ 7.90 (s, 1H), 7.50 – 7.45 (m, 4H), 7.32 – 7.25 (m, 6H), 3.81 (s, 3H). $^{13}C$ NMR (100 MHz; CDCl$_3$): $\delta$ 166.5, 151.9, 132.9, 132.8, 132.8, 130.2, 129.4, 128.2, 127.7, 114.3, 52.8. HRMS: $m/z$ (ESI) calculated for C$_{16}$H$_{14}$O$_2$Se$_2$ (M+H)$^+$: 398.9397, found 398.9392.
methyl (E)-2,3-bis(phenylselanyl)acrylate (9b)

This compound was prepared following general procedure 2.2, and crude mixture was purified using flash chromatography (20:1 hexane/EtOAc) to yield the desired product as colorless oil (94%). $^1$H NMR (400 MHz; CDCl$_3$): δ 7.90 (s, 1H), 7.50 – 7.45 (m, 4H), 7.32 – 7.25 (m, 6H), 3.81 (s, 3H). $^{13}$C NMR (100 MHz; CDCl$_3$): δ 166.5, 151.9, 132.9, 132.8, 132.8, 130.2, 129.4, 128.2, 127.7, 114.3, 52.8. HRMS: m/z (ESI) calculated for C$_{16}$H$_{14}$O$_2$Se$_2$ (M+H)$^+$: 398.9397, found 398.9392.

methyl (E)-2,3-bis(phenyltelluryl)acrylate (9c)

This compound was prepared following general procedure 2.2, and crude mixture was purified using flash chromatography (20:1 hexane/EtOAc) to yield the desired product as colorless oil (94%). $^1$H NMR (400 MHz; CDCl$_3$): δ 8.27 (s, 1H), 7.80 (d, 2H, $J = 7.2$ Hz), 7.49 (d, $J = 6.8$ Hz, 2H), 7.33 (t, $J = 7.2$ Hz, 1H), 7.24 (t, $J = 7.2$ Hz, 3H). $^{13}$C NMR (100 MHz; CDCl$_3$): δ 168.4, 140.2, 139.3, 136.9, 129.8, 129.1, 128.7, 127.8, 120.5, 113.9,
methyl (E)-2,3-bis((4-methoxyphenyl)selanyl)acrylate (9d)

This compound was prepared following general procedure 2.2, and crude mixture was purified using flash chromatography (20:1 hexane/EtOAc) to yield the desired product as colorless oil (92%). $^1$H NMR (400 MHz; CDCl$_3$): $\delta$ 7.56 (s, 1H), 7.45 (d, $J = 8.8$ Hz, 2H), 7.36 (d, $J = 8.8$ Hz, 2H), 6.82 (d, $J = 8.8$ Hz, 2H), 6.80 (d, $J = 8.8$ Hz, 2H), 3.81 (s, 3H), 3.78 (s, 3H), 3.77 (s, 3H). $^{13}$C NMR (100 MHz; CDCl$_3$): $\delta$ 166.2, 159.8, 159.8, 149.5, 136.1, 134.6, 123.2, 119.3, 115.1, 115.0, 114.8, 55.2, 55.2, 52.6. HRMS: $m/z$ (ESI) calculated for C$_{18}$H$_{18}$O$_4$Se$_2$ (M+Na)$^+$: 480.9428, found: 480.9449.

methyl (E)-2,3-bis($\rho$-tolylselanyl)acrylate (9e)

This compound was prepared following general procedure 2.2, and crude mixture was purified using flash chromatography (20:1 hexane/EtOAc) to yield the desired product as
colorless oil (88%). $^1$H NMR (400 MHz; CDCl$_3$): $\delta$ 7.78 (s, 1H), 7.37 (d, $J = 8.0$ Hz, 2H), 7.33 (d, $J = 8.0$ Hz, 2H), 7.10 – 7.06 (m, 4H), 3.80 (s, 3H), 2.32 (s, 3H), 2.31 (s, 3H). $^{13}$C NMR (100 MHz; CDCl$_3$): $\delta$ 166.4, 155.1, 138.2, 137.8, 133.4, 132.7, 130.2, 130.0, 129.2, 126.2, 114.5, 52.7, 21.1, 21.1. HRMS: $m/z$ (ESI) calculated for C$_{18}$H$_{18}$O$_2$Se$_2$ (M+Na)$^+$: 448.9529, found 448.9525.

![Chemical structure](image)

methyl (E)-2,3-bis((4-bromophenyl)selanyl)acrylate ($9f$)

This compound was prepared following general procedure 2.2, and crude mixture was purified using flash chromatography (20:1 hexane/EtOAc) to yield the desired product as colorless oil (86%). $^1$H NMR (400 MHz; CDCl$_3$): $\delta$ 7.88 (s, 1H), 7.44 (d, $J = 8.4$ Hz, 2H), 7.40 (d, $J = 8.4$ Hz, 2H), 7.35 (d, $J = 8.4$ Hz, 2H), 7.31 (d, $J = 8.4$ Hz, 2H), 3.80 (s, 3H). $^{13}$C NMR (100 MHz; CDCl$_3$): $\delta$ 166.3, 152.4, 134.5, 134.1, 132.5, 132.5, 131.4, 129.2, 122.9, 122.0, 114.3, 53.0. HRMS: $m/z$ (ESI) calculated for C$_{16}$H$_{12}$Br$_2$O$_2$Se$_2$ (M+H)$^+$: 556.7587, found 556.7589.
methyl (E)-2,3-bis((4-fluorophenyl)selanyl)acrylate (9g)

This compound was prepared following general procedure 2.2, and crude mixture was purified using flash chromatography (20:1 hexane/EtOAc) to yield the desired product as colorless oil (86%). \(^1\)H NMR (400 MHz; CDCl\(_3\)): δ 7.70 (s, 1H), 7.50 – 7.43 (m, 4H), 7.03 – 6.96 (m, 4H), 3.81 (s, 3H). \(^{13}\)C NMR (100 MHz; CDCl\(_3\)): δ 166.2, 162.9 (d, \(J = 244\) Hz), 162.7 (d, \(J = 247\) Hz), 150.8 (d, \(J = 0.9\) Hz), 135.7 (d, \(J = 8.0\) Hz), 135.2 (d, \(J = 8.0\) Hz), 127.4 (d, \(J = 3.5\) Hz), 124.2 (d, \(J = 3.5\) Hz), 116.6 (d, \(J = 21.5\) Hz), 116.5 (d, \(J = 21.5\) Hz), 114.8 (d, \(J = 0.7\) Hz), 52.8. \(^{19}\)F NMR (376 MHz; CDCl\(_3\)): δ -112.6, -113.1. HRMS: m/z (ESI) calculated for C\(_{16}\)H\(_{13}\)F\(_2\)O\(_2\)Se\(_2\) (M+H): 434.9214, found: 434.9205.

methyl (E)-2,3-bis((4-(trifluoromethyl)phenyl)selanyl)acrylate (9h)

This compound was prepared following general procedure 2.2, and crude mixture was purified using flash chromatography (20:1 hexane/EtOAc) to yield the desired product as colorless oil (66%). \(^1\)H NMR (400 MHz; CDCl\(_3\)): δ 7.70 (s, 1H), 7.58 – 7.36 (m, 4H), 7.03 – 6.96 (m, 4H), 3.81 (s, 3H). \(^{13}\)C NMR (100 MHz; CDCl\(_3\)): δ 166.4, 154.3, 148.1, 137.2,
$136.2, 133.1, 132.9, 131.3, 130.7$ ($q, \, J = 320$ Hz), $129.4$ ($q, \, J = 325$ Hz), $126.2$ ($d, \, J = 37$ Hz), $126.0$ ($d, \, J = 37$ Hz), $125.2$ ($d, \, J = 152$ Hz), $122.5$ ($d, \, J = 163$ Hz), $117.2, 113.8, 53.1$. 

$^{19}$F NMR (376 MHz; CDCl$_3$): δ $-62.8, -62.9$. HRMS: $m/z$ (ESI) calculated for C$_{18}$H$_{12}$F$_6$O$_2$Se$_2$ (M+H)$^+$: 534.9145, found 534.9148.

methyl (E)-2,3-bis((3-fluorophenyl)selanyl)acrylate (9i)

This compound was prepared following general procedure 2.2, and crude mixture was purified using flash chromatography (20:1 hexane/EtOAc) to yield the desired product as colorless oil (80%). $^1$H NMR (400 MHz; CDCl$_3$): δ 7.99 (s, 1H), 7.31 – 7.20 (m, 5H), 7.19 – 7.14 (m, 1H), 7.07 – 7.00 (m, 1H), 6.99 – 6.93 (m, 1H), 3.81 (s, 3H). $^{13}$C NMR (100 MHz; CDCl$_3$): δ 166.3, 162.8 ($d, \, J = 249$ Hz), 162.8 ($d, \, J = 249$ Hz), 152.9, 134.2 ($d, \, J = 6.5$ Hz), 132.2 ($d, \, J = 6.6$ Hz), 130.8 ($d, \, J = 8.0$ Hz), 130.6 ($d, \, J = 8.0$ Hz), 128.5 ($d, \, J = 3.2$ Hz), 127.8 ($d, \, J = 3.1$ Hz), 119.9 ($d, \, J = 21.9$ Hz), 119.5 ($d, \, J = 22.3$ Hz), 115.5 ($d, \, J = 20.9$ Hz), 114.6 ($d, \, J = 21.0$ Hz), 114.0, 53.0. $^{19}$F NMR (376 MHz; CDCl$_3$): δ $-111.0, -111.4$. HRMS: $m/z$ (ESI) calculated for C$_{16}$H$_{12}$F$_2$O$_2$Se$_2$ (M+H)$^+$: 734.9209, found 734.9205.
methyl (E)-2,3-bis(methylselanyl)acrylate (9j)

This compound was prepared following general procedure 2.2, and crude mixture was purified using flash chromatography (20:1 hexane/EtOAc) to yield the desired product as colorless oil (86%). $^1\text{H NMR}$ (400 MHz; CDCl$_3$): $\delta$ 7.66 (s, 1H), 3.83 (s, 3H), 2.24 (s, 3H), 2.21 (s, 3H). $^{13}\text{C NMR}$ (100 MHz; CDCl$_3$): $\delta$ 166.5, 147.1, 113.9, 52.6, 9.6, 7.9. **HRMS: m/z** (ESI) calculated for C$_6$H$_{10}$O$_2$Se$_2$ (M+Na)$^+$: 296.8905, found 296.8895.

methyl (E)-2,3-bis(benzylselanyl)acrylate (9k)

This compound was prepared following general procedure 2.2, and crude mixture was purified using flash chromatography (20:1 hexane/EtOAc) to yield the desired product as colorless oil (85%). $^1\text{H NMR}$ (400 MHz; CDCl$_3$): $\delta$ 7.74 (s, 1H), 7.32 – 7.12 (m, 10H), 3.89 (s, 2H), 3.84 (s, 2H), 3.76 (s, 3H). $^{13}\text{C NMR}$ (100 MHz; CDCl$_3$): $\delta$ 166.8, 152.1, 138.1, 138.1, 129.0, 128.8, 128.7, 128.4, 127.0, 126.8, 112.9, 52.6, 32.3, 32.0. **HRMS: m/z** (ESI) calculated for C$_{18}$H$_{18}$O$_2$Se$_2$ (M+Na)$^+$: 448.9520, found 448.9525.
benzyl (E)-2,3-bis(phenylselanyl)acrylate (9I)

This compound was prepared following general procedure 2.2, and crude mixture was purified using flash chromatography (20:1 hexane/EtOAc) to yield the desired product as colorless oil (87%). \(^1\)H NMR (400 MHz; CDCl\(_3\)): δ 7.98 (s, 1H), 7.51 – 7.41 (m, 4H), 7.32 – 7.18 (m, 11H), 5.23 (s, 2H). \(^{13}\)C NMR (100 MHz; CDCl\(_3\)): δ 165.8, 152.6, 135.4, 132.9, 132.8, 132.8, 132.8, 132.8, 130.4, 129.4, 128.4, 128.3, 128.1, 127.9, 127.6, 114.5, 67.4. HRMS: m/z (ESI) calculated for C\(_{22}\)H\(_{18}\)O\(_2\)Se\(_2\) (M+H): 474.9710, found 474.9707.

benzyl (E)-2,3-bis(phenylselanyl)acrylate (9m)

This compound was prepared following general procedure 2.2, and crude mixture was purified using flash chromatography (20:1 hexane/EtOAc) to yield the desired product as colorless oil (95%). \(^1\)H NMR (400 MHz; CDCl\(_3\)): δ 7.70 (s, 1H), 7.51 – 7.42 (m, 4H), 7.30 – 7.22 (m, 6H), 1.44 (s, 9H). \(^{13}\)C NMR (100 MHz; CDCl\(_3\)): δ 164.8, 147.4, 133.2, 133.2, 133.1, 132.6, 130.5, 129.2, 128.0, 127.5, 117.1, 82.7, 27.9. HRMS: m/z (ESI) calculated for C\(_{19}\)H\(_{20}\)O\(_2\)Se\(_2\) (M+Na): 462.9686, found 462.9675.
(E)-N-phenethyl-2,3-bis(phenylselanyl)acrylamide (9n)

This compound was prepared following general procedure 2.2, and crude mixture was purified using flash chromatography (20:1 hexane/EtOAc) to yield the desired product as colorless oil (82%). $^1$H NMR (400 MHz; CDCl$_3$): $\delta$ 8.31 (s, 1H), 7.66 – 7.60 (m, 2H), 7.38 – 7.32 (m, 3H), 7.28 – 7.18 (m, 8H), 7.12 (br, 1H), 7.07 – 7.01 (m, 2H), 3.54 (q, $J = 6.8$ Hz, 2H), 2.73 (t, $J = 6.8$ Hz, 2H). $^{13}$C NMR (100 MHz; CDCl$_3$): $\delta$ 165.6, 156.8, 138.5, 134.1, 133.2, 131.3, 129.4, 129.2, 129.1, 128.6, 128.5, 128.1, 126.8, 126.3, 113.5, 41.4, 35.5. HRMS: m/z (ESI) calculated for C$_{23}$H$_{21}$NOSe$_2$ (M+H)$^+$: 488.0027, found 488.0029.

(E)-N-phenyl-2,3-bis(phenylselanyl)acrylamide (9o)

This compound was prepared following general procedure 2.2, and crude mixture was purified using flash chromatography (20:1 hexane/EtOAc) to yield the desired product as colorless oil (48%). $^1$H NMR (400 MHz; CDCl$_3$): $\delta$ 8.92 (br, 1H), 8.47 (s, 1H), 7.67 – 7.61 (m, 2H), 7.52 – 7.47 (m, 2H), 7.42 – 7.20 (m, 10H), 7.12 – 7.06 (m, 1H). $^{13}$C NMR (100 MHz; CDCl$_3$): $\delta$ 163.8, 158.6, 137.5, 134.0, 133.2, 130.9, 129.7, 129.5, 129.4, 128.9, 128.3, 127.3, 124.5, 119.8, 113.7. HRMS: m/z (ESI) calculated for C$_{21}$H$_{17}$NOSe$_2$ (M+H)$^+$: 459.9687, found 459.9710.
methyl (E)-(2,3-bis(phenylselanyl)acryloyl)-D-phenylalaninate (9p)

This compound was prepared following general procedure 2.2, and crude mixture was purified using flash chromatography (20:1 hexane/EtOAc) to yield the desired product as colorless oil (55%). \( ^1H \text{NMR} \) (400 MHz; CDCl\(_3\)): \( \delta \) 8.36 (s, 1H), 7.65 – 7.59 (m, 2H), 7.54 (broad d, \( J = 8.0 \) Hz, 1H), 7.37 – 7.32 (m, 3H), 7.30 – 7.21 (m, 5H), 7.18 – 7.09 (m, 3H), 6.93 – 6.88 (m, 2H), 4.89 (dt, \( J = 8.0, 5.6 \) Hz, 1H), 3.63 (s, 3H), 3.06 (t, \( J = 5.6 \) Hz, 2H). \( ^{13}C \text{NMR} \) (100 MHz; CDCl\(_3\)): \( \delta \) 171.3, 165.4, 157.9, 135.5, 133.9, 133.2, 131.2, 129.7, 129.4, 129.3, 129.1, 128.5, 128.3, 127.0, 113.3, 53.9, 52.3, 37.9. \text{HRMS}: m/z (ESI) calculated for C\(_{25}\)H\(_{23}\)NO\(_3\)Se\(_2\) (M+H\(^+\)): 546.0081, found 546.0087.

(E)-3,4-bis(phenylselanyl)but-3-en-2-one (9q)

This compound was prepared following general procedure 2.2, and crude mixture was purified using flash chromatography (20:1 hexane/EtOAc) to yield the desired product as colorless oil (85%). \( ^1H \text{NMR} \) (400 MHz; CDCl\(_3\)): \( \delta \) 8.46 (s, 1H), 7.62 – 7.57 (m, 2H), 7.37 – 7.30 (m, 5H), 7.30 – 7.19 (m, 3H), 2.42 (m, 3H). \( ^{13}C \text{NMR} \) (100 MHz; CDCl\(_3\)): \( \delta \) 198.8, 159.3, 134.1, 132.9, 132.0, 129.9, 129.5, 129.4, 128.4, 126.8, 119.9, 18.8. \text{HRMS}: m/z (ESI) calculated for C\(_{16}\)H\(_{14}\)OSe\(_2\) (M+H\(^+\)): 382.9446, found 382.9450.
Dimethyl 2,3-bis(phenylselanyl)fumarate (9r)

This compound was prepared following general procedure 2.2, and crude mixture was purified using flash chromatography (20:1 hexane/EtOAc) to yield the desired product as colorless oil (93%). $^1$H NMR (400 MHz; CDCl$_3$): $\delta$ 7.60 – 7.56 (m, 4H), 7.34 – 7.27 (m, 6H), 3.45 (s, 6H). $^{13}$C NMR (100 MHz; CDCl$_3$): $\delta$ 165.3, 134.9, 134.7, 129.5, 128.9, 128.6, 52.4. HRMS: $m/z$ (ESI) calculated for C$_{18}$H$_{16}$O$_4$Se$_2$ (M+H)$^+$: 456.9452, found 456.9455.

(Z)-(1-bromo-2-phenylethene-1,2-diyl)bis(phenylselane) (9s)

This compound was prepared following general procedure 2.2, and crude mixture was purified using flash chromatography (pure hexane) to yield the desired product as colorless oil (93%). $^1$H NMR (400 MHz; CDCl$_3$): $\delta$ 7.47 – 7.42 (m, 2H), 7.33 – 7.23 (m, 5H), 7.13 – 7.07 (m, 1H), 7.05 – 6.97 (m, 5H), 6.96 – 6.91 (m, 2H). $^{13}$C NMR (100 MHz; CDCl$_3$): $\delta$ 147.0, 139.1, 136.5, 132.7, 131.6, 129.5, 129.1, 129.0, 128.4, 128.3, 127.8, 127.6, 127.5, 101.5. HRMS: $m/z$ (ESI) calculated for C$_{20}$H$_{16}$BrSe$_2$ (M+Na)$^+$: 494.8761, found 494.8748.
(Z)-(1-bromo-2-(4-bromophenyl)ethene-1,2-diyl)bis(phenylselane) (9t)

This compound was prepared following general procedure 2.2, and crude mixture was purified using flash chromatography (pure hexane) to yield the desired product as colorless oil (93%). $^1$H NMR (400 MHz; CDCl$_3$): $\delta$ 7.45 – 7.40 (m, 2H), 7.32 – 7.28 (m, 3H), 7.27 – 7.23 (m, 2H), 7.18 – 7.12 (m, 3H), 7.07 – 7.01 (m, 2H), 6.82 – 6.77 (d, $J = 8.4$ Hz, 2H). $^{13}$C NMR (100 MHz; CDCl$_3$): $\delta$ 145.5, 138.2, 136.5, 132.8, 131.3, 130.7, 130.6, 129.2, 129.2, 128.7, 128.7, 128.0, 121.8, 102.5. HRMS: m/z (ESI) calculated for C$_{20}$H$_{14}$Br$_2$Se$_2$ (M+H)$^+$: 572.7866, found 572.7837.

(Z)-(1-bromo-2-(4-fluorophenyl)ethene-1,2-diyl)bis(phenylselane) (9u)

This compound was prepared following general procedure 2.2, and crude mixture was purified using flash chromatography (pure hexane) to yield the desired product as colorless oil (93%). $^1$H NMR (400 MHz; CDCl$_3$): $\delta$ 7.45 – 7.40 (m, 2H), 7.32 – 7.27 (m, 3H), 7.27 – 7.23 (m, 2H), 7.15 – 7.10 (m, 1H), 7.04 – 6.99 (m, 2H), 6.91 – 6.86 (m, 2H), 6.73 – 6.68 (m, 2H). $^{13}$C NMR (100 MHz; CDCl$_3$): $\delta$ 161.8 (d, $J = 247$ Hz), 145.8, 136.6, 135.1 (d, $J = 3.4$ Hz), 132.7, 131.4, 130.7 (d, $J = 8.3$ Hz) 129.3, 129.2, 128.6, 128.5, 127.9, 114.6 (d, $J = 21.7$ Hz) 102.1 (d, $J = 1.7$ Hz). $^{19}$F NMR (376 MHz; CDCl$_3$): $\delta$ -113.2. HRMS: m/z (ESI) calculated for C$_{20}$H$_{14}$BrFSe$_2$ (M+H)$^+$: 512.8666, found 512.8667.
(Z)-(1-bromo-5-chloropent-1-ene-1,2-diyl)bis(phenylselane) (9v)

This compound was prepared following general procedure 2.2, and crude mixture was purified using flash chromatography (pure hexane) to yield the desired product as colorless oil (93%). $^1$H NMR (400 MHz; CDCl$_3$): δ 7.47 – 7.43 (m, 2H), 7.31 – 7.22 (m, 5H), 7.13 – 7.07 (m, 1H), 7.00 – 6.92 (m, 3H), 6.90 – 6.80 (m, 3H), 2.18 (m, 3H). $^{13}$C NMR (100 MHz; CDCl$_3$): δ 145.9, 138.3, 136.8, 135.2, 133.1, 131.1, 129.6, 129.3, 129.1, 128.6, 128.5, 128.2, 128.0, 127.9, 125.0, 100.5, 19.6. HRMS: $m/z$ (ESI) calculated for C$_{21}$H$_{17}$BrSe$_2$ (M+H)$^+$: 508.8917, found 508.8909.

(Z)-(1-bromo-2-cyclopropylethene-1,2-diyl)bis(phenylselane) (9w)

This compound was prepared following general procedure 2.2, and crude mixture was purified using flash chromatography (pure hexane) to yield the desired product as colorless oil (93%). $^1$H NMR (400 MHz; CDCl$_3$): δ 7.46 – 7.42 (m, 2H), 7.33 – 7.26 (m, 5H), 7.16 – 7.11 (m, 1H), 7.06 – 6.96 (m, 3H), 6.74 – 6.70 (m, 2H), 6.65 – 6.61 (m, 1H). $^{13}$C NMR (100 MHz; CDCl$_3$): δ 161.9 (d, $J$ = 245 Hz), 145.2 (d, $J$ = 2.0 Hz), 141.1 (d, $J$ = 8.1 Hz), 136.7, 133.0, 131.3, 129.3, 129.2, 129.1, 128.7, 128.6, 128.0, 124.9 (d, $J$ = 3.0 Hz)
Hz), 116.1 (d, J = 22.1 Hz), 114.5 (d, J = 20.9 Hz). ¹⁹F NMR (376 MHz; CDCl₃): δ -131.5.

HRMS: m/z (ESI) calculated for C₂₀H₁₄BrFSe₂ (M+H)^+: 512.8666, found 512.8675.

(Z)-(1-bromo-2-(o-tolyl)ethene-1,2-diyl)bis(phenylselane) (9x)

This compound was prepared following general procedure 2.2, and crude mixture was purified using flash chromatography (pure hexane) to yield the desired product as colorless oil (93%). ¹H NMR (400 MHz; CDCl₃): δ 7.47 – 7.42 (m, 2H), 7.31 – 7.26 (m, 3H), 7.26 – 7.22 (n, 2H), 7.12 – 7.07 (m, 1H), 6.99 – 6.91 (m, 3H), 6.90 – 6.80 (m, 3H), 2.18 (s, 3H). ¹³C NMR (100 MHz; CDCl₃): δ 145.8, 138.3, 136.8, 135.2, 133.1, 131.1, 129.6, 129.3, 129.1, 128.6, 128.5, 128.2, 128.0, 127.9, 125.0, 100.5, 19.6. HRMS: m/z (ESI) calculated for C₂₁H₁₇BrSe₂ (M+H)^+: 508.8917, found 508.8896.

(Z)-(1-bromo-5-chloropent-1-ene-1,2-diyl)bis(phenylselane) (9y)

This compound was prepared following general procedure 2.2, and crude mixture was purified using flash chromatography (pure hexane) to yield the desired product as colorless oil (93%). ¹H NMR (400 MHz; CDCl₃): δ 7.69 – 7.65 (m, 2H), 7.50 – 7.46 (m, 2H), 7.43 – 7.30 (m, 6H), 3.17 (t, J = 6.4 Hz, 2H), 2.64 – 2.58 (m, 2H), 1.81 – 1.73 (m, 2H). ¹³C NMR (100 MHz; CDCl₃): δ 147.7, 126.8, 131.6, 131.2, 129.4, 129.4, 129.4, 128.6,
127.6, 100.2, 43.7, 34.9, 32.0. **HRMS**: m/z (ESI) calculated for C$_{17}$H$_{16}$BrClSe$_{2}$ (M+H)$^{+}$: 494.8527, found 494.8516.

(Z)-(1-bromo-2-cyclopropylethene-1,2-diyl)bis(phenylselane) (9z)

This compound was prepared following general procedure 2.2, and crude mixture was purified using flash chromatography (pure hexane) to yield the desired product as colorless oil (93%). **$^{1}$H NMR** (400 MHz; CDCl$_{3}$): $\delta$ 7.55 – 7.51 (m, 2H), 7.51 – 7.47 (m, 2H), 7.35 – 7.32 (m, 3H), 7.30 – 7.26 (m, 3H), 1.85 – 1.77 (m, 1H), 0.76 – 0.68 (m, 4H). **$^{13}$C NMR** (100 MHz; CDCl$_{3}$): $\delta$ 145.5, 133.0, 131.5, 130.8, 129.2, 129.1, 127.9, 127.4, 109.0, 20.0, 10.4. **HRMS**: m/z (ESI) calculated for C$_{17}$H$_{15}$BrSe$_{2}$ (M+H)$^{+}$: 458.8761, found 458.8748.

(Z)-(1-bromo-2-phenylethene-1,2-diyl)bis((4-methoxyphenyl)selane) (9aa)

This compound was prepared following general procedure 2.2, and crude mixture was purified using flash chromatography (pure hexane) to yield the desired product as colorless oil (93%). **$^{1}$H NMR** (400 MHz; CDCl$_{3}$): $\delta$ 7.40 (d, $J = 8.8$ Hz, 2H), 7.14 (d, $J =$
8.4 Hz, 2H), 7.10 – 7.04 (m, 3H), 6.95 – 6.90 (m, 2H), 6.83 (d, J = 8.8 Hz, 2H), 6.51 (d, J = 8.8 Hz, 2H), 3.80 (s, 3H), 3.68 (s, 3H). $^{13}$C NMR (100 MHz; CDCl$_3$): δ 159.9, 159.8, 144.6, 139.2, 138.2, 136.0, 129.0, 127.6, 127.5, 121.5, 120.1, 114.7, 113.0, 102.8, 55.2, 55.1. HRMS: m/z (ESI) calculated for C$_{22}$H$_{19}$BrO$_2$Se$_2$ (M+Na)$^+$: 554.8972, found: 554.8971.

(Z)-(1-bromo-2-phenylethene-1,2-diyl)bis((4-fluorophenyl)selane) (9ab)

This compound was prepared following general procedure 2.2, and crude mixture was purified using flash chromatography (pure hexane) to yield the desired product as colorless oil (93%). $^1$H NMR (400 MHz; CDCl$_3$): δ 7.36 – 7.33 (m, 2H), 7.14 – 7.10 (m, 4H), 7.06 – 7.03 (m, 3H), 6.96 – 6.92 (m, 2H), 6.82 – 6.78 (m, 2H). $^{13}$C NMR (100 MHz; CDCl$_3$): δ 145.9, 139.2, 138.3, 138.0, 136.4, 133.3, 129.9, 129.2, 129.0, 127.8, 127.5, 125.9, 102.1, 21.2, 21.1. HRMS: m/z (ESI) calculated for C$_{22}$H$_{19}$BrSe$_2$ (M+H)$^+$: 522.9074, found 522.9057.
(Z)-(1-bromo-2-phenylethene-1,2-diyl)bis(p-tolylselane) (9ac)

This compound was prepared following general procedure 2.2, and crude mixture was purified using flash chromatography (pure hexane) to yield the desired product as colorless oil (93%). $^1$H NMR (400 MHz; CDCl$_3$): δ 7.45 – 7.41 (m, 2H), 7.23 – 7.18 (m, 2H), 7.09 – 7.09 (m, 3H), 7.03 – 6.98 (m, 2H), 6.92 – 6.99 (m, 2H), 6.69 (t, J = 8.8 Hz, 2H). $^{13}$C NMR (100 MHz; CDCl$_3$): δ 162.9 (d, J = 248 Hz), 145.6, 138.8, 138.7 (d, J = 8.2 Hz), 135.8 (d, J = 7.5 Hz), 128.9, 127.8, 127.7, 125.8 (d, J = 2.2 Hz), 124.3 (d, J = 2.2 Hz), 116.3 (d, J = 21.7 Hz), 115.6 (d, J = 21.5 Hz), 102.0. $^{19}$F NMR (376 MHz; CDCl$_3$): δ -112.1, -112.9. HRMS: m/z (ESI) calculated for C$_{20}$H$_{13}$BrF$_2$Se$_2$ (M+H)$^+$: 530.8572, found 530.8563.

(Z)-(1-bromo-2-phenylethene-1,2-diyl)bis((4-(trifluoromethyl)phenyl)selane) (9ad)

This compound was prepared following general procedure 2.2, and crude mixture was purified using flash chromatography (pure hexane) to yield the desired product as colorless oil (93%). $^1$H NMR (400 MHz; CDCl$_3$): δ 7.54 (d, J = 8.4 Hz, 2H), 7.51 (d, J =
8.0 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 8.0 Hz, 2H), 7.07 – 7.00 (m, 3H), 6.93 – 6.89 (m, 2H). $^{13}$C NMR (100 MHz; CDCl$_3$): $\delta$ 148.5, 138.6, 136.5, 133.9, 131.8, 130.5 (q, J = 216 Hz), 130.7 (q, J = 217 Hz), 128.8, 128.2, 127.9, 126.0 (q, J = 24 Hz), 125.2 (q, J = 24 Hz), 124.7 (q, J = 267 Hz), 122.9 (q, J = 267 Hz), 100.7, 77.0. $^{19}$F NMR (376 MHz; CDCl$_3$): $\delta$ -62.7, -63.0. HRMS: $m/z$ (ESI) calculated for C$_{22}$H$_{13}$BrF$_6$Se$_2$ (M+H)$^+$: 630.8508, found: 630.8507.

(Z)-(1-bromo-2-phenylethene-1,2-diyl)bis(benzylselane) (9af)

This compound was prepared following general procedure 2.2, and crude mixture was purified using flash chromatography (pure hexane) to yield the desired product as colorless oil (93%). $^1$H NMR (400 MHz; CDCl$_3$): $\delta$ 7.30 – 7.13 (m, 11H), 7.01 – 6.97 (m, 2H), 6.66 – 6.62 (m, 2H), 4.00 (s, 2H), 3.34 (s, 2H). $^{13}$C NMR (100 MHz; CDCl$_3$): $\delta$ 146.6, 139.5, 138.0, 136.9, 129.0, 128.9, 128.5, 128.4, 128.3, 128.1, 127.8, 126.9, 101.8, 34.0, 32.9. HRMS: $m/z$ (ESI) calculated for C$_{22}$H$_{19}$BrSe$_2$ (M+H)$^+$: 522.9074, found 522.9059.

(E)-((1-phenyl)-2-chloroethene-1,2-diyl)bis(phenylselane) (9ag)

This compound was prepared following general procedure 2.2, and crude mixture was purified using flash chromatography (pure hexane) to yield the desired product as
colorless oil (93%). $^1$H NMR (400 MHz; CDCl$_3$): δ 7.48 – 7.45 (m, 2H), 7.32 – 7.29 (m, 3H), 7.28 – 7.24 (m, 2H), 7.14 – 7.08 (m, 1H), 7.07 – 6.94 (m, 7H). $^{13}$C NMR (100 MHz; CDCl$_3$): δ 142.4, 138.3, 136.4, 133.1, 130.3, 129.3, 129.1, 128.6, 128.4, 128.2, 127.9, 127.7, 127.5, 113.4. HRMS: $m/z$ (ESI) calculated for C$_{20}$H$_{14}$BrClSe$_2$ (M+H)$^+$: 450.9266, found 450.9265.

$\text{(E)-3-(2-phenyl-1,2-bis(phenylselanyl)vinyl)oxazolidin-2-one (9ah)}$

This compound was prepared following general procedure 2.2, and crude mixture was purified using flash chromatography (pure hexane) to yield the desired product as colorless oil (93%). $^1$H NMR (400 MHz; CDCl$_3$): δ 7.94 – 7.91 (m, 2H), 7.50 – 7.46 (m, 2H), 7.41 – 7.33 (m, 3H), 7.27 – 7.22 (m, 6H), 7.22 – 7.18 (m, 2H), 3.91 (t, $J = 8.0$ Hz, 2H), 2.99 (t, $J = 8.0$ Hz, 2H). $^{13}$C NMR (100 MHz; CDCl$_3$): δ 154.0, 143.8, 132.7, 129.9, 129.2, 129.1, 129.0, 128.6, 128.5, 127.7, 127.2, 127.1, 125.7, 107.7, 43.2, 24.3. HRMS: $m/z$ (ESI) calculated for C$_{23}$H$_{19}$NO$_2$Se$_2$ (M+H)$^+$: 501.9819, found 501.9823.

$\text{(E)-(1-(p-tolyl)ethene-1,2-diyl)bis(phenylselane) (9ai)}$

This compound was prepared following general procedure 2.2, and crude mixture was purified using flash chromatography (pure hexane) to yield the desired product as
colorless oil (93%). $^1$H NMR (400 MHz; CDCl$_3$): δ 7.49 – 7.46 (m, 2H), 7.43 – 7.37 (m, 4H), 7.25 – 7.18 (m, 8H), 7.12 (d, $J$ = 8.0 Hz, 2H), 2.31 (s, 3H). $^{13}$C NMR (100 MHz; CDCl$_3$): δ 138.23, 136.60, 132.94, 132.02, 131.30, 130.84, 130.65, 129.20,129.15, 128.96, 128.51, 127.35, 127.32, 125.31, 21.31. HRMS: $m/z$ (ESI) calculated for C$_{21}$H$_{18}$Se$_2$ (M+H)$^+$: 430.9812, found: 430.9825.

(E)-(1-phenylprop-1-ene-1,2-diyl)bis(phenylselane) (9aj)

This compound was prepared following general procedure 2.2, and crude mixture was purified using flash chromatography (pure hexane) to yield the desired product as colorless oil (93%). $^1$H NMR (400 MHz; CDCl$_3$): δ 7.52 – 7.48 (m, 2H), 7.32 – 7.22 (m, 5H), 7.18 – 7.07 (m, 8H), 2.30 (s, 3H). $^{13}$C NMR (100 MHz; CDCl$_3$): δ 141.9, 135.1, 133.3, 132.4, 130.6, 129.9, 129.6, 129.3, 129.0, 128.7, 127.9, 127.7, 127.3, 127.0, 25.8. HRMS: $m/z$ (ESI) calculated for C$_{21}$H$_{18}$Se$_2$ (M+H)$^+$: 430.9812, found: 430.9815.

(3,3-diphenylprop-2-ene-1,2-diyl)bis(phenylselane) (11a)

This compound was prepared following general procedure 2.3, and crude mixture was purified using flash chromatography (Hexanes/DCM = 10:1) to yield the desired product...
as colorless oil (82%). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.49 – 7.54 (m, 2H), 7.28 – 7.34 (m, 2H), 7.17 – 7.26 (m, 10H), 7.11 – 7.16 (m, 2H), 7.05 – 7.10 (m, 2H), 6.96 – 7.02 (m, 2H), 3.87 (s, 2H).  $^{13}$C NMR (101 MHz, CDCl$_3$) δ 146.57, 143.01, 141.13, 134.42, 130.95, 130.11, 129.67, 129.26, 129.22, 128.96, 128.75, 128.10, 128.10, 127.84, 127.54, 127.38, 127.28, 127.13, 34.11. HRMS: m/z (ESI) calculated for C$_{27}$H$_{22}$Se$_2$ (M+H)$^+$: 528.9944, found: 528.9949.

(3,3-diphenylprop-2-ene-1,2-diyl)bis(phenylselane) (11b)

This compound was prepared following general procedure 2.3, and crude mixture was purified using flash chromatography (Hexanes/DCM = 10:1) to yield the desired product as colorless oil (94%). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.50 (d, J = 8.7 Hz, 2H), 7.32 – 7.31 (m, 6H), 7.19 – 7.14 (m, 3H), 7.10 (dd, J = 7.9, 1.7 Hz, 2H), 6.90 (dd, J = 6.6, 2.9 Hz, 2H), 6.77 (d, J = 8.7 Hz, 2H), 6.69 (d, J = 8.7 Hz, 2H), 3.79 (s, 3H), 3.77 (s, 3H), 3.70 (s, 2H).  $^{13}$C NMR (101 MHz, CDCl$_3$) δ 159.73, 159.57, 144.36, 143.04, 141.34, 137.27, 137.01, 131.98, 129.29, 127.95, 127.91, 127.50, 127.36, 126.84, 119.80, 119.59, 114.62, 114.42, 55.26, 33.89. HRMS: m/z (ESI) calculated for C$_{29}$H$_{26}$O$_2$Se$_2$ (M+H)$^+$: 567.0336, found: 527.0342.
This compound was prepared following general procedure 2.3, and crude mixture was purified using flash chromatography (Hexanes/DCM = 10:1) to yield the desired product as colorless oil (82%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.48 (dd, $J = 8.4$, 5.6 Hz, 2H), 7.35 – 7.29 (m, 2H), 7.27 – 7.17 (m, 6H), 7.04 (dd, $J = 7.3$, 2.2 Hz, 2H), 6.95 – 6.89 (m, 4H), 6.85 (t, $J = 8.7$ Hz, 2H), 3.79 (s, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 163.9 (d, $J = 11$ Hz), 161.5 (d, $J = 16$ Hz), 147.6, 142.8, 141.0, 137.0 (d, $J = 37$ Hz), 136.9 (d, $J = 37$ Hz), 131.1, 129.24, 129.17, 128.10, 127.94, 127.5, 127.2, 124.4 (d, $J = 35$ Hz), 123.8 (d, $J = 33$ Hz), 116.1 (d, $J = 217$ Hz), 115.9 (d, $J = 216$ Hz), 34.4. $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -113.40, -113.42, -113.43, -113.44, -113.45, -113.46, -113.47, -113.48, -114.00, -114.01, -114.02, -114.03, -114.04, -114.05, -114.06, -114.07. HRMS: $m/z$ (ESI) calculated for C$_{27}$H$_{20}$F$_2$Se$_2$ (M+H)$^+$: 542.9936, found: 542.9941.
This compound was prepared following general procedure 2.3, and crude mixture was purified using flash chromatography (Hexanes/DCM = 10:1) to yield the desired product as colorless oil (91%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.46 (d, J = 8.1 Hz, 2H), 7.30 – 7.17 (m, 9H), 7.12 (dd, J = 7.9, 1.8 Hz, 2H), 7.05 (d, J = 7.8 Hz, 2H), 7.01 – 6.91 (m, 4H), 3.81 (s, 2H), 2.32 (s, 3H), 2.30 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 145.42, 143.07, 141.24, 137.73, 137.25, 135.00, 134.75, 131.41, 129.76, 129.48, 129.25, 128.10, 127.96, 127.83, 127.33, 126.93, 126.07, 125.93, 33.88, 21.16, 21.10. HRMS: m/z (ESI) calculated for C$_{29}$H$_{26}$Se$_2$ (M+H)$^+$: 535.0438, found: 535.0443.

This compound was prepared following general procedure 2.3, and crude mixture was purified using flash chromatography (Hexanes/DCM = 10:1) to yield the desired product as colorless oil (84%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.52 – 7.46 (m, 2H), 7.44 – 7.37 (m, 2H), 7.28 – 7.17 (m, 6H), 3.88 (s, 2H), 1.98 (s, 3H), 1.65 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 141.89, 134.55, 131.57, 131.29, 130.11, 129.05, 128.70, 127.35, 126.46,
122.06, 34.66, 25.78, 20.57. **HRMS:** \( m/z \) (ESI) calculated for \( \text{C}_{17}\text{H}_{18}\text{Se}_2 \) (M): 381.9739, found: 381.9719.

(3-methyl-1-phenylbut-2-ene-1,2-diyl)bis(phenylselane) (11g)

This compound was prepared following general procedure 2.3, and crude mixture was purified using flash chromatography (Hexanes/DCM = 10:1) to yield the desired product as colorless oil (40%). \( ^1\text{H NMR} \) (400 MHz, CDCl\(_3\)) \( \delta \) 7.55 – 7.45 (m, 4H), 7.28 – 7.13 (m, 6H), 7.10 – 7.02 (m, 5H), 5.81 (s, 1H), 1.83 (s, 3H), 1.74 (s, 3H). \( ^{13}\text{C NMR} \) (101 MHz, CDCl\(_3\)) \( \delta \) 141.27, 140.42, 135.20, 133.08, 131.50, 130.51, 129.68, 129.16, 128.89, 128.79, 128.66, 128.62, 128.23, 128.09, 127.77, 127.06, 125.53, 54.40, 26.38, 20.99. **HRMS:** \( m/z \) (ESI) calculated for \( \text{C}_{23}\text{H}_{22}\text{Se}_2 \) (M+H): 459.0125, found: 459.0129.

(Z)-((5,6-bis(phenylselanyl)hex-4-en-1-yl)oxy)(tert-butyldimethylsilane) (11h)

This compound was prepared following general procedure 2.3, and crude mixture was purified using flash chromatography (Hexanes/DCM = 10:1) to yield the unseparated mixture products with Z/E = 1.7:1 as colorless oil (96%). \( ^1\text{H NMR} \) (400 MHz, CDCl\(_3\)) \( \delta \) 7.55 – 7.51 (m, 1H), 7.50 – 7.46 (m, 1H), 7.46 – 7.40 (m, 2H), 7.31 – 7.14 (m, 6H), 5.94 (t, J = 7.5 Hz, 0.39H), 5.77 (t, J = 7.1 Hz, 0.66H), 3.77 (s, 0.82H), 3.69 (s, 1.34H), 3.51 (t,
J = 6.4 Hz, 2H), 2.25 (q, J = 7.4 Hz, 1.28H), 1.92 (q, J = 7.5 Hz, 0.85H), 1.51 – 1.40 (m, 2H), 0.88 (s, 9H), 0.02 (s, 6H). 13C NMR (101 MHz, CDCl3) δ 139.87, 137.61, 134.55, 134.08, 132.82, 132.59, 129.06, 128.77, 127.26, 126.90, 62.42, 37.83, 32.15, 28.48, 25.91, 18.24, -5.30. HRMS: m/z (ESI) calculated for C24H34OSe2Si (M+H)+: 527.0782, found: 527.0787.

(Z)-(3-(4-bromophenyl)prop-2-ene-1,2-diyl)bis(p-tolylselane) (11i)

This compound was prepared following general procedure 2.3, and crude mixture was purified using flash chromatography (Hexanes/DCM = 10:1) to yield the unseparated mixture products with E/Z = 2:1 as white solid (94%). 1H NMR (400 MHz, CDCl3) δ 7.54 (d, J = 8.0 Hz, 0.7H), 7.48 (d, J = 8.0 Hz, 1.4H), 7.44 (d, J = 8.4 Hz, 1.5H), 7.39 (t, J = 8.2 Hz, 2.9H), 7.20 (d, J = 8.4 Hz, 1.3H), 7.15 (d, J = 7.9 Hz, 0.9H), 7.10 (d, J = 7.9 Hz, 1.5H), 7.07–7.05 (m, 1.8H), 7.02 (t, J = 7.7 Hz, 1.2H), 6.65 (s, 0.33H), 6.52 (s, 0.64H), 3.94 (s, 0.68H), 3.68 (s, 1.3H), 2.37 (s, 1.3H), 2.36 (s, 2.0H), 2.35 (s, 1.2H), 2.34 (s, 2.0H). 13C NMR (101 MHz, CDCl3) δ 138.27, 138.22, 137.68, 137.61, 135.8, 135.5, 135.11, 135.10, 135.04, 134.2, 133.0, 131.9, 131.3, 131.0, 130.7, 130.4, 130.15, 129.99, 129.76, 129.74, 129.61, 125.9, 125.1, 124.1, 121.1, 120.9, 77.0, 38.0, 31.7, 21.16, 21.11. HRMS: m/z (ESI) calculated for C23H21BrSe2 (M+H)+: 536.9230, found: 536.9229.
Dimethyl 2-(4-(methoxycarbonyl)phenyl)-3-(phenylselanyl)fumarate (12)

This compound was prepared following general procedure 2.4, and crude mixture was purified using flash chromatography (Hexanes/DCM = 10:1) to yield the desired product as colorless oil (75%). $^1$H NMR (400 MHz, CDCl3) δ 7.96 (d, J = 8.3 Hz, 2H), 7.67 (d, J = 7.0 Hz, 2H), 7.43 – 7.35 (m, 1H), 7.35 – 7.27 (m, 4H), 3.90 (s, 3H), 3.79 (s, 3H), 2.84 (s, 3H). $^{13}$C NMR (101 MHz, CDCl3) δ 166.70, 166.51, 164.43, 150.83, 140.53, 137.50, 132.58, 129.69, 129.66, 129.13, 128.78, 128.03, 126.33, 52.72, 52.15, 51.55. HRMS: m/z (ESI) calculated for C20H18O6Se (M)+: 434.0269, found: 434.0285.
3.4 HFIP promoted disulfidation and diselenation of C-C unsaturated bond

3.4.1 Introduction

Organic reaction always pursues valuable synthetic products from simple and commercial-available starting materials under mild conditions with high efficiency and excellent yields. Many factors will impact one reaction, including temperature, pressure, ratio of the reagents, solvent and so on. As one of the crucial tuning factors, solvent did not draw a lot attention. Surprisingly, with the discovery of ionic liquid and fluorinated solvents, abundant unexpected results emerged, which greatly enriched the synthetic box.

Ionic liquid is a kind of salt with very week coordination between ions and will be liquid at a certain temperature. For example, liquid KCl or KOH are ionic liquid under high temperature. Usually, it is restricted to the salt with melting points below 100 °C. Normal liquid is made by neutral molecule, but ionic liquid is made by salt. Because of this unique property, ionic liquid exhibits many numerous potential applications. They are great solvents to be electrolytes and very crucial for battery application. Since the ionic liquid has high boiling points, it will not pollute the environment via evaporation, so it is considered as a green solvent. Ionic liquids are also treated as a safer microwave synthesis method, because sudden pressure surges are not possible. Despite ionic liquids show these great properties, it only has limited application examples and most ionic liquids only work for some specific reactions, which prevent its further application.

Fluorinated solvents are another kind of magic solvents and have received tremendous attention in chemical, medicinal, and material research. The high electronegativity and good hydrophobicity of fluorine atom give fluorinated compounds unique chemical
properties. Recently, as one of these fluorinated solvents, hexafluoroisopropanol (HFIP) has been employed as an alternative solvent in substituting Lewis acid or Brønsted acid in promoting chemical transformations through H-bond networks under very mild conditions. The basic physical and chemical properties of HFIP have been summarized in the Figure 30. Compared with similar structure, isopropanol, HFIP exhibits much lower boiling point and pka, due to the attached strong electron-withdrawing group CF3. Due to the low boiling point, HFIP is a promising solvent in industrial processing, owing to its recyclability and low cost.

**Figure 30. Basic physical and chemical properties of HFIP**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>α value</th>
<th>β value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HFIP</td>
<td>1.96</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>EtOH</td>
<td>0.86</td>
<td>0.75</td>
</tr>
<tr>
<td>3</td>
<td>DMSO</td>
<td>0</td>
<td>0.76</td>
</tr>
<tr>
<td>4</td>
<td>THF</td>
<td>0</td>
<td>0.55</td>
</tr>
<tr>
<td>5</td>
<td>Toluene</td>
<td>0</td>
<td>0.12</td>
</tr>
</tbody>
</table>

The higher α value, the better hydrogen bond donor. The higher β value, the better hydrogen bond acceptor.
Using water and tetramethylsilane (TMS) as standards, HFIP presents more polar than water. The solvent nucleophilicity parameter $N$ constant showed the how strong nucleophile a solvent is. HFIP is a much weaker Nu than ethanol. Compared with other solvent, HFIP is great H-bond donor but very poor H-bond acceptor. Based on the DFT and X-ray crystallography, HFIP shows aggregation H-bond network, which will enhance the final H-bond to activate substrate or stabilize a cation. Since the exist of H-bond network and low nucleophilicity, HFIP has extremely strong effect on stabilization of benzylic cations. What’s more, due to the electron deficiency of HFIP, it is fairly stable under strong oxidative condition making HFIPP an ideal solvent for electrochemical investigations.

**Friedel crafts reaction**

$$\text{Ar-Cl} \xrightarrow{\text{Solvent, r.t.}} \text{ArCH}_2^+ \xrightarrow{\text{Anisole}} \text{Ar-CH}_2\text{Ar}$$

$\text{Ar} = 4\text{-OMeC}_6\text{H}_4$  

Yield: i-PrOH, 0%.  HFIP, 79%

**Polyene cyclization**

$$\begin{align*}
\text{NBS, morpholine, 0 }^\circ\text{C} \\
\text{Yield: i-PrOH, } <5\% \\
\text{HFIP, 78%}
\end{align*}$$

**Schmidt reaction**

$$\text{Yield: i-PrOH: trace} \quad \text{HFIP: 89%}$$

Figure 31. HFIP as a special solvent promoted challenging reactions

Some representative HFIP promoted transformations, including Friedel-Craft reaction, polyene cyclization, and Schmidt reaction, are shown in Figure 31. In comparison with other solvents which failed to produce the desired products, HFIP significantly promoted the reaction to obtain good to excellent yields. These results
greatly highlighted the unique reactivity of HFIP in facilitating organic transformations under mild conditions.

In the last chapter, we reported diselenation of alkynes under gold redox catalysis. Based on the solvent screening, we observed that HFIP could greatly promote the reaction of even more challenging unactivated internal alkyne without gold catalysts. Herein, we report this interesting solvent effect of HFIP on diselenation and disulfidation of the C-C unsaturated bond. Good to excellent yields were achieved with broad reaction substrate scope under metal-free condition, which demonstrated the unique reactivity of the HFIP solvent in promoting challenging organic transformations.

3.4.2 HFIP promoted disulfidation and diselenation

Disulfidation\textsuperscript{47} and diselenation\textsuperscript{34a, 48} of C-C unsaturated bonds are the basic organic transformations with many chemical and medicinal applications. Great progress has been made regarding these transformations by using transition metal promoters/catalysts, Lewis acid, and photocatalysts to achieve the desired products. Our interest in this reaction was originated from our continuous efforts in gold-catalyzed alkyne activation.\textsuperscript{17c, 31, 49} As shown in Figure 32A, we recently reported the diselenation of alkynes through a gold(I)-gold(III) redox catalytic cycle, giving diselenation products in excellent yields with high stereoselectivity (trans-addition only). However, this transformation did not work well on simple internal alkynes, even with an increased catalyst loading (10%) at 60 °C.

As shown in Figure 32B, treating internal alkyne 13a with diselenide 14a under previous gold catalytic conditions (DCE, 60 °C, 24 h) gave diselenation product 14a in poor conversion (15%) and low yield (14%) associated with completed gold catalyst
decomposition. Interestingly, switching solvent to HFIP greatly enhanced the reaction performance, giving 3a in nearly quantitative yield (93%). Control reaction using HFIP as solvent without gold catalyst was then carried out, achieving 3a in 78% yield with 80% conversion of 1a in 24 h. Extending the reaction time to 36 h gave a full conversion of 1a, and the desired product 3a was obtained in excellent yield (95%). In addition, applying hexafluoroacetone (HFA) as additive could accelerate the reaction with comparable yield in 30 hours.

![Diagram of reaction mechanism](image)

**Figure 32. HFIP promoted internal alkyne diselenation**

Other solvents, including iPrOH, DMSO, DMF, CH$_3$CN, acetone, chlorobenzene, and nitromethane, could not promote this reaction, resulting in less than 5% yield in all cases. Lowering temperature to 40 °C led to decreasing of conversion due to slower reaction kinetic. Notably, only trans-isomer 14a was observed under this metal-free condition,
suggesting a concerted bi-molecular trans-addition of diselenides to the plausible selenium cation intermediate formed from alkyne addition toward HFIP activated diselenides. Encouraged by these results, we evaluated the reaction scope of this metal-free HFIP promoted transformations.

Table 10. HFIP promoted alkyne diselenation substrate scope

| Reaction condition: alkyne (0.4 mmol) and diselenide (0.2 mmol) were added into HFIP:HFA = 19:1 (1 mL), and the mixture was stirred at 60 °C for 24 h. Isolated yield. |
|---|---|---|
| R=Ph | R''SeSeR'' | 14b, R = 4-Me, 96%, 14c, R = 3-Me, 96% |
| PhSe | 14d, R = 2-Me, 95% |
| PhSe | 14e, R = 4-F, 95% |
| PhSe | 14f, R = 3-F, 95% |
| PhSe | 14g, R = 2-F, 94% |
| PhSe | 14h, R = 4-CF3, 86% |
| PhSe | 14i, R = H, 96% |
| PhSe | 14j, R = 4-Me, 94% |
| PhSe | 14k, R = 3-Me, 95% |
| PhSe | 14l, R = 2-Me, 95% |
| PhSe | 14m, R = 4-F, 92% |
| PhSe | 14n, R = 3-F, 92% |
| PhSe | 14o, R = 2-F, 94% |
| PhSe | 14p, R = 4-OMe, 96% |
| PhSe | 14q, 60% |
| PhSe | 14r, R = 4-OMe, 82% |
| PhSe | 14s, R = 4-Me, 96% |
| PhSe | 14t, R = 4-F, 95% |
| PhSe | 14u, R = 3-F, 90% |
| PhSe | 14v, R = 2-F, 94% |
| PhSe | 14w, R = 4-OMe, 96% |
| PhSe | 14x, trace [Au/HFIP], 93% [Au/DCE], 55% |
| PhSe | 14y, trace [Au/HFIP], 80% [Au/DCE], 48% |

Various substituted alkynes were evaluated in this HFIP “boosted” transformation (Table 9). First, several diaryl acetylenes with different substituents on the aromatic rings were tested. Both electron-donating group (EDG) and electron-withdrawing group (EWG) substituted aromatic rings worked well in this reaction, giving the desired products (14a-14h) in excellent yields. Second, aliphatic alkynes (14i-14q) gave similar results with
desired products obtained mostly in excellent yields. The cyclopropyl substituted alkyne (14q) gave no ring-opening product, ruling out the potential radical mechanism. Third, a series of diselenides were also employed for this transformation (14r-14r), giving the expected products in good to excellent yields. A lower yield was observed with dibenzylselenide 14w due to the slow reaction rate. The terminal alkynes (14x, 14y) did not work under this HFIP condition. After switching the conditions to Au catalysis, significantly improved yields were obtained. Notably, employing HFIP as solvent instead of DCE, the reaction performance could be improved to 93% and 80%, respectively. This result high-lighted the great promoting effects of HFIP solvent in gold redox catalysis.

Since the Au/HFIP combination could generate products in good to excellent yield. We than tested the Au/HFIP condition with all the other alkynes substrates as a comparison. To our delight, in most cases, pure HFIP condition gave very similar or even better yields. However, Au catalysis was sensitive to electron deficient alkyne and steric hindrance yielding less desired products (3g, 3n, 3o). These results suggested the potential broad application of HFIP as crucial solvent.

Although the detailed mechanism of this HFIP promoting effect remains to be explored, one plausible reason behind this “boosting effect” is that HFIP activates RSeSeR to form a selenium species as a good leaving group through H-bond network. Therefore, under gold catalytic pathway, this HFIP boosting effect could help the oxidation of gold(I) to gold (III) with the activated selenium, which is likely the turn-over limiting step. Similarly, in the non-metal catalytic conditions, diselenides are good electrophiles, which form an equilibrium with alkyne addition. Overall, through the formation of H-bond, HFIP could greatly assist diselenides activation and increase the reactivity of this diselenation. Based
on this hypothesis, we wondered if this activation mode could be applied to similar transformations using alkene and allene as the substrate. To confirm this idea, reactions of diselenides with alkenes and allenes were performed.

**Table 11. Diselenation of alkyne under Au/HFIP condition**

<table>
<thead>
<tr>
<th>R</th>
<th>R'</th>
<th>5% IPrAuNTf₂</th>
<th>HFIP, 0.2 M, 60 °C, 24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>8a</td>
<td>R&quot;Se-SeR&quot;</td>
<td>R&quot;Se-SeR&quot;</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14a</td>
<td>R = 4-Me</td>
<td>89%</td>
</tr>
<tr>
<td>14b</td>
<td>R = 3-Me</td>
<td>87%</td>
</tr>
<tr>
<td>14c</td>
<td>R = 2-Me</td>
<td>90%</td>
</tr>
<tr>
<td>14d</td>
<td>R = 4-F</td>
<td>96%</td>
</tr>
<tr>
<td>14e</td>
<td>R = 3-F</td>
<td>94%</td>
</tr>
<tr>
<td>14f</td>
<td>R = 2-F</td>
<td>70%</td>
</tr>
<tr>
<td>14g</td>
<td>R = 4-CF₃</td>
<td>69%</td>
</tr>
<tr>
<td>14h</td>
<td>R = 4-OMe</td>
<td>92%</td>
</tr>
<tr>
<td>14i</td>
<td>R = H</td>
<td>89%</td>
</tr>
<tr>
<td>14j</td>
<td>R = 4-Me</td>
<td>93%</td>
</tr>
<tr>
<td>14k</td>
<td>R = 3-Me</td>
<td>86%</td>
</tr>
<tr>
<td>14l</td>
<td>R = 2-Me</td>
<td>82%</td>
</tr>
<tr>
<td>14m</td>
<td>R = 4-F</td>
<td>80%</td>
</tr>
<tr>
<td>14n</td>
<td>R = 3-F</td>
<td>51%</td>
</tr>
<tr>
<td>14o</td>
<td>R = 2-F</td>
<td>50%</td>
</tr>
<tr>
<td>14p</td>
<td>R = 4-OMe</td>
<td>95%</td>
</tr>
</tbody>
</table>

Reaction condition: to a HFIP solution (1 mL) of diselenide 8 (0.2 mmol, 1 eq) and alkyne 1 (0.4 mmol, 2 eq), IPrAuNTf₂ (0.01 mmol, 0.05 eq.) was added in one portion. The reaction was flashed with Ar and allowed to stir at 60 °C. Isolated yield.

As shown in **Figure 33A**, styrene failed to give diselenation product with the formation of complex reaction mixtures without diselenation product. With allene substrates, lower yields were observed. Monitoring the reactions with NMR revealed the decompositions...
of products overtime under the reaction conditions. The addition of gold catalyst in the allene case could give a faster reaction. As a result, improved yields were observed.

(A) Diselenation of alkenes and allenes

(B) Disulfidation of alkynes, alkenes, and allenes

Figure 33. Disulfidation and diselenation reaction

Considering that HFIP might provide a similar H-bond activation effect toward disulfide (RSSR), we started out our investigations on disulfidation with various unsaturated C-C
bonds under Au/HFIP condition. For alkyne substrates (Figure 33B), HFIP could not promote this transformation, giving desired disulfide products in low yield. In comparison, the combination of gold and HFIP afforded the desired products in good yield (72%), while DCE solvent gave only a trace amount of product. Different internal and terminal alkynes were tested with desired products observed in good to excellent yields (16a-16e). This result, again, greatly highlighted the boosting effect of HFIP solvent applied in gold catalysis, which was critical for alkyne activations.

Furthermore, reactions of disulfide with alkene under the HFIP condition gave the desired product 17a in 91% yield with gram-scale synthesis. Some representative alkenes were tested with the desired disulfidation products obtained in good to excellent yields (17b-17e). Notably, the sterically hindered 1,2-disubstituted alkene (cis-stilbene) accomplished the reaction in excellent yield (6e, 93%). Notably, other solvents, such as isopropanol and DCE, gave almost no reaction (<5%). Allene was also tested under the HFIP conditions, with or without gold catalyst presented. Moderate yield was observed using non-metal condition. With gold catalyst presented, no significantly improved yield was observed in HFIP comparing with DCE solvents due to the decomposition of product in HFIP. Nevertheless, HFIP presented a solvent promoting effect over other solvents, suggesting this boosting effect could also be applied in C-C unsaturated bonds disulfidation reaction under mild conditions.

3.5 Conclusion

In conclusion, the diselenation and disulfidation of C-C unsaturated bonds were reported using HFIP as the promoting solvent. Compared with other common organic
solvents, HFIP greatly enhanced the reaction performance by activating the diselenide and disulfide through H-bond networks. The desired products were achieved under mild conditions with good to excellent yield and high stereoselectivity. These results offered another prospective of using HFIP as the solvent to boost reactivity of substrates and achieve challenging transformations.

3.6 Experimental section

3.6.1 General Methods and Materials

All of the reactions dealing with air and/or moisture-sensitive compounds were carried out under an atmosphere of argon using oven/flame-dried glassware and standard syringe/septa techniques. Unless otherwise noted, all commercial reagents and solvents were obtained from the commercial provider and used without further purification. Diselenides and allenes were synthesized according to literature reports.

$^1$H NMR, $^{13}$C NMR and $^{19}$F NMR spectra were recorded on a Varian Inova 400 MHz and dd600 MHz spectrometer. Chemical shifts were reported relative to internal tetramethylsilane (δ 0.00 ppm) for $^1$H and CDCl$_3$ (δ 77.0 ppm) for $^{13}$C. Flash column chromatography was performed on 230-430 mesh silica gel. Analytical thin layer chromatography was performed with pre-coated glass baked plates (250μ) and visualized by fluorescence and by charring after treatment with potassium permanganate stain. HRMS data for substrates were collected on an Agilent 7890 GC-MS QTOF 7200 and 6540 LC/QTOF spectrometer in the mass-spec facility in the University of South Florida. The X-ray diffraction data for 3a, 3e was measured on Bruker D8 Venture PHOTON 100 CMOS system.
3.6.2 General Procedure for Diselenation of Alkynes

![Figure 34. Diselenation of Alkynes](image)

Diselenide 8 (0.2 mmol, 1 eq) and alkyne 13 (0.4 mmol, 2 eq) were added in a solution of HFIP/HFA (19:1, 1 mL). The reaction was allowed to stir at 60 °C for 30 h. The reaction mixture was then concentrated by rot-vap, and purified by flash chromatography to obtain pure product 14.

3.6.3 Procedure for Diselenation of Alkene

![Figure 35. Diselenation of Alkene](image)

Diselenide (0.2 mmol, 1 eq) and alkene (0.4 mmol, 2 eq) were added in a solution of HFIP/HFA (19:1, 1 mL). The reaction was allowed to stir at r.t. for 24 h. The desired product was not obtained.

3.6.4 Procedure for Diselenation of Allenes

![Figure 36. Diselenation of Allenes](image)
To a HFIP solution (1 mL) of diselenide (0.2 mmol, 1eq) and allene (0.4 mmol, 2 eq), IPrAuNTf₂ (0.01 mmol, 0.05 eq) was added in one portion. The reaction was flashed with Ar and allowed to stir at r.t. for 24 h in dark. The reaction mixture was then concentrated by rot-vap and purified by flash chromatography to obtain pure product 15.

3.6.5 General Procedure for Disulfidation of Alkynes:

\[
\text{Ph} = \equiv \text{R} + \text{PhS-SPh} \xrightarrow{5\% \text{ IPrAuNTf}_2, \text{HFIP, 0.2 M, 60 }^\circ\text{C, 24 h}} \text{Ph} \begin{array}{c} \text{S} \\ \text{Ph} \\ \text{SPh} \end{array} \text{Ph}\begin{array}{c} \text{S} \\ \text{R} \\ \text{SPh} \end{array}
\]

Figure 37. Disulfidation of Alkynes

To a HFIP solution (1 mL) of disulfide (0.2 mmol, 1 eq) and alkyne (0.4 mmol, 2 eq), IPrAuNTf₂ (0.01 mmol, 0.05 eq) was added in one portion. The reaction was flashed with Ar and allowed to stir at 60 °C for 24 h. The reaction mixture was then concentrated by rot-vap and purified by flash chromatography to obtain pure product 16.

3.6.6 Procedure for Disulfidation of Alkenes:

\[
\text{Ar} = \equiv \text{R} + \text{PhS-SPh} \xrightarrow{\text{HFIP/HFA = 19:1, 0.2 M, r.t.}} \text{PhS} \begin{array}{c} \text{S} \\ \text{Ar} \\ \text{SPh} \end{array} \text{R}
\]

Figure 38. Disulfidation of Allenes

Disulfide (0.2 mmol, 1eq) and alkene (0.4 mmol, 2 eq) were added in a solution of HFIP/HFA (19:1, 1 mL). The reaction was allowed to stir at r.t. for 48 h. The reaction
mixture was then concentrated by rot-vap, and purified by flash chromatography to obtain pure product 17.

3.6.7 General Procedure for Disulfidation of Allenes:

\[
\begin{array}{c}
\text{Ph} \equiv \text{Ph} + \text{PhS-SPh} \\
\xrightarrow{5\% \text{IPrAuNTf}_2} \\
\text{HFIP, 0.2 M, 60 °C, 24 h} \\
\text{Ph} \equiv \text{Ph} \equiv \text{SPh}
\end{array}
\]

Figure 39. Disulfidation of Allenes

To a HFIP solution (1 mL) of disulfide (0.2 mmol, 1eq) and allene (0.4 mmol, 2 eq), IPrAuNTf$_2$ (0.01 mmol, 0.05 eq) was added in one portion. The reaction was flashed with Ar and allowed to stir at 60 °C for 24 h in dark. The reaction mixture was then concentrated by rot-vap, and purified by flash chromatography (DCM:hexanes = 1:10) to obtain pure product 18.

3.6.8 ORTEP Drawing for Crystal Structures

X-ray diffraction data were measured on Bruker D8 Venture PHOTON II CPAD diffractometer equipped with a Cu Kα INCOATEC ImuS micro-focus source (λ = 1.54178 Å). Indexing was performed using APEX3 (Difference Vectors method). Data integration and reduction were performed using SaintPlus. Absorption correction was performed by multi-scan method implemented in SADABS. Space group was determined using XPREP implemented in APEX3. Structure(s) was (were) solved using SHELXT and refined using SHELXL-2018 (full-matrix least-squares on F2) through OLEX2 interface program.
Ellipsoid plot(s) was(were) drawn with Platon. Crystal data and refinement conditions are shown in Tables 1 and 2.

**Table 12. Crystal data and structure refinement for 3a.**

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<td>Radiation</td>
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Table 12. (Continued)

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Table 13. Crystal data and structure refinement for 3e

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</table>
3.6.9 Compound Characterization

(E)-1,2-diphenyl-1,2-bis(phenylselanyl)ethene (14a)

This compound was prepared following general procedure 2.3, and crude mixture was purified using flash chromatography (DCM:hexanes = 1:10) to yield the desired products as white solid (94.1 mg, 96%). $^1H$ NMR (400 MHz, CDCl$_3$) δ 7.26 – 7.21 (m, 4H), 7.21 – 7.14 (m, 8H), 7.13 – 7.08 (m, 2H), 7.08 – 7.03 (m, 2H), 7.02 – 6.95 (m, 4H). $^{13}C$ NMR (101 MHz, CDCl$_3$) δ 140.56, 135.03, 133.12, 130.4, 129.48, 128.34, 127.64, 127.38. HRMS (ESI) m/z: $^{1+}$ Calcd. for C$_{26}$H$_{20}$Se$_2$: 491.9895, found: 491.9903.

(E)-1,2-bis(phenylselanyl)-1,2-di-p-tolylethene (14b)

This compound was prepared following general procedure 2.3, and crude mixture was purified using flash chromatography (DCM:hexanes = 1:10) to yield the desired products as white solid (99.8 mg, 96%). $^1H$ NMR (600 MHz, CDCl$_3$) δ 7.18 (d, $J = 8.1$ Hz, 4H), 7.13 (d, $J = 8.0$ Hz, 4H), 7.07 (t, $J = 6.8$ Hz, 2H), 7.00 (t, $J = 7.4$ Hz, 4H), 6.98 (d, $J = 7.7$ Hz, 4H), 2.25 (s, 6H). $^{13}C$ NMR (151 MHz, CDCl$_3$) δ 137.92, 137.19, 134.79, 133.79, 133.36, 130.49, 129.45, 128.42, 127.29, 21.37. HRMS (ESI) m/z: $^{1+}$ Calcd. for C$_{28}$H$_{24}$Se$_2$: 520.0208, found: 520.0199.
(E)-1,2-bis(phenylselanyl)-1,2-di-<i>m</i>-tolylethene (14c)

This compound was prepared following general procedure 2.3, and crude mixture was purified using flash chromatography (DCM:hexanes = 1:10) to yield the desired products as white solid (99.7 mg, 96%). <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 7.20 – 7.17 (m, 4H), 7.09 – 7.03 (m, 6H), 7.02 – 6.97 (m, 6H), 6.93 – 6.89 (m, 2H), 2.21 (s, 6H). <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>) δ 140.32, 137.12, 135.06, 132.80, 130.24, 130.18, 128.21, 128.05, 127.48, 127.33, 126.48, 21.26. HRMS (ESI) m/z: <sup>1</sup>Calcd. for C<sub>28</sub>H<sub>24</sub>Se<sub>2</sub>: 520.0208, found: 520.0198.

(E)-1,2-bis(phenylselanyl)-1,2-di-<i>o</i>-tolylethene (14d)

This compound was prepared following general procedure 2.3, and crude mixture was purified using flash chromatography (DCM:hexanes = 1:10) to yield the desired products as white solid (98.5 mg, 95%). <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 7.18 – 7.13 (m, 4H), 7.13 – 7.03 (m, 7H), 7.02 – 6.94 (m, 6H), 6.87 (d, J = 7.5 Hz, 1H), 2.41 (s, 3H), 2.30 (s, 3H). <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>) δ 141.42, 140.01, 135.58, 134.84, 133.30, 133.29, 133.19, 130.63, 130.05, 129.79, 129.52, 129.28, 129.16, 128.76, 128.45, 128.22, 127.49, 127.38, 127.15, 126.74, 126.33, 126.03, 19.13, 9.03. HRMS (ESI) m/z: <sup>1</sup>Calcd. for C<sub>28</sub>H<sub>24</sub>Se<sub>2</sub>: 520.0208, found: 520.0208.
(E)-1,2-bis(4-fluorophenyl)-1,2-bis(phenylselanyl)ethene (14e)

This compound was prepared following general procedure 2.3, and crude mixture was purified using flash chromatography (DCM:hexanes = 1:10) to yield the desired products as yellow solid (100.1 mg, 95%). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.22 – 7.14 (m, 8H), 7.10 (t, $J = 7.3$ Hz, 2H), 7.03 (t, $J = 7.4$ Hz, 4H), 6.86 (t, $J = 8.6$ Hz, 4H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 161.84 (d, $J = 247.4$ Hz), 136.43 (d, $J = 3.3$ Hz), 135.13, 132.49, 131.22 (d, $J = 8.2$ Hz), 129.67, 128.56, 127.73, 114.71 (d, $J = 21.6$ Hz). $^{19}$F NMR (564 MHz, CDCl$_3$) δ -113.71, -113.72, -113.73, -113.74, -113.75, -113.76. HRMS (ESI) m/z: $^{+}$ Calcd. for C$_{26}$H$_{18}$F$_2$Se$_2$: 527.9707, found: 527.9699.

(E)-1,2-bis(3-fluorophenyl)-1,2-bis(phenylselanyl)ethene (14f)

This compound was prepared following general procedure 2.3, and crude mixture was purified using flash chromatography (DCM:hexanes = 1:10) to yield the desired products as yellow solid (100.2 mg, 95%). $^1$H NMR (600 MHz, CDCl$_3$) δ 7.25 (t, $J = 8.3$ Hz, 4H), 7.19 – 6.98 (m, 11H), 6.93 (t, $J = 7.5$ Hz, 1H), 6.89 – 6.80 (m, 2H). $^{13}$C NMR (151 MHz, CDCl$_3$) δ 162.18 (d, $J = 246.3$ Hz), 158.65 (d, $J = 247.4$ Hz), 142.35 (d, $J = 8.0$ Hz), 135.73, 134.79, 132.56, 131.16 (d, $J = 2.7$ Hz), 129.57 (d, $J = 8.0$ Hz), 129.33, 129.26, 129.21, 128.88 (d, $J = 15.1$ Hz), 128.60, 128.44, 128.15 (d, $J = 15.4$ Hz), 128.00, 127.69, 125.28 (d, $J = 2.8$ Hz), 123.44 (d, $J = 3.4$ Hz), 116.41 (d, $J = 21.9$ Hz), 115.25 (d, $J = 21.8$ Hz),
114.54 (d, J = 21.0 Hz). 19F NMR (564 MHz, CDCl3) δ -113.14, -113.15, -113.16, -113.17, -113.18, -113.45, -113.46, -113.47, -113.48, -113.48, -113.49. HRMS (ESI) m/z: 1+ Calcd. for C26H18F2Se2: 527.9707, found: 527.9704.

(E)-1,2-bis(2-fluorophenyl)-1,2-bis(phenylselanyl)ethene (14g)

This compound was prepared following general procedure 2.3, and crude mixture was purified using flash chromatography (DCM:hexanes = 1:10) to yield the desired products as yellow solid (99.3 mg, 94%). 1H NMR (600 MHz, CDCl3) δ 7.29 (d, J = 7.5 Hz, 4H), 7.19 – 7.15 (m, 2H), 7.15 – 7.10 (m, 4H), 7.04 (t, J = 7.6 Hz, 4H), 6.96 (t, J = 7.6 Hz, 2H), 6.89 (t, J = 9.0 Hz, 2H). 13C NMR (151 MHz, CDCl3) δ 158.79 (d, J = 247.6 Hz), 135.44, 135.24, 131.42, 131.07, 129.63 (d, J = 7.9 Hz), 128.92, 128.44, 127.83, 123.49, 115.33. 19F NMR (564 MHz, CDCl3) δ -112.17, -113.23. HRMS (ESI) m/z: 1+ Calcd. for C26H18F2Se2: 527.9707, found: 527.9708.

(E)-1,2-bis(phenylselanyl)-1,2-di-p-tolylethene (14h)

This compound was prepared following general procedure 2.3, and crude mixture was purified using flash chromatography (DCM:hexanes = 1:10) to yield the desired products as yellow solid (108 mg, 86%). 1H NMR (600 MHz, CDCl3) δ 7.44 (d, J = 8.1 Hz, 4H), 7.33
(d, J = 8.0 Hz, 4H), 7.17 – 7.14 (m, 4H), 7.14 – 7.11 (m, 2H), 7.03 (t, J = 7.5 Hz, 4H). \( ^{13}C \) NMR (151 MHz, CDCl\(_3\)) \( \delta \) 143.89, 135.12, 132.95, 129.67, 129.41 (d, J = 32.3 Hz), 129.04, 128.74, 128.06, 124.80 (q, J = 3.7 Hz), 123.92 (q, J = 273 Hz). \( ^{19}F \) NMR (376 MHz, cdcl\(_3\)) \( \delta \) -62.68. HRMS (ESI) m/z: \(^{1+}\) Calcd. for C\(_{28}\)H\(_{18}\)F\(_6\)Se\(_2\): 627.9643, found: 627.9638.

\[
\text{(E)-(1-phenylhex-1-ene-1,2-diyl)bis(phenylselane) (14i)}
\]

This compound was prepared following general procedure 2.3, and crude mixture was purified using flash chromatography (DCM:hexanes = 1:10) to yield the desired products as colorless oil (90.6 mg, 96%). \(^1H\) NMR (600 MHz, CDCl\(_3\)) \( \delta \) 7.49 – 7.43 (m, 2H), 7.29 – 7.25 (m, 2H), 7.24 – 7.17 (m, 3H), 7.12 – 7.00 (m, 8H), 2.71 – 2.60 (m, 2H), 1.63 – 1.50 (m, 2H), 1.25 (h, J = 7.4 Hz, 2H), 0.82 (t, J = 7.4 Hz, 3H). \( ^{13}C \) NMR (151 MHz, CDCl\(_3\)) \( \delta \) 141.60, 137.21, 134.53, 133.94, 130.94, 130.18, 130.11, 129.30, 128.86, 128.51, 127.56, 127.47, 127.15, 127.03, 37.20, 31.37, 22.13, 13.86. HRMS (ESI) m/z: \(^{1+}\) Calcd. for C\(_{24}\)H\(_{24}\)Se\(_2\): 472.0208, found: 472.0205.

\[
\text{(E)-(1-(p-tolyl)hex-1-ene-1,2-diyl)bis(phenylselane) (14j)}
\]

This compound was prepared following general procedure 2.3, and crude mixture was purified using flash chromatography (DCM:hexanes = 1:10) to yield the desired products as colorless oil (91.5 mg, 94%). \(^1H\) NMR (600 MHz, CDCl\(_3\)) \( \delta \) 7.50 – 7.46 (m, 2H), 7.32 –
7.23 (m, 5H), 7.15 – 7.07 (m, 3H), 7.02 (d, J = 8.1 Hz, 2H), 6.95 (d, J = 7.9 Hz, 2H), 2.66 – 2.58 (m, 2H), 2.24 (s, 3H), 1.57 – 1.49 (m, 2H), 1.27 – 1.20 (m, 2H), 0.81 (t, J = 7.3 Hz, 3H). \(^{13}\text{C NMR}\) (151 MHz, CDCl\(_3\)) δ 138.94, 137.97, 136.89, 134.72, 133.44, 130.60, 130.38, 130.19, 129.16, 128.89, 128.60, 128.30, 127.65, 126.99, 37.23, 31.49, 22.17, 21.23, 13.87. \(\text{HRMS (ESI)}\) m/z: \(^{1+}\) Calcd. for C\(_{25}\)H\(_{26}\)Se\(_2\): 486.0365, found: 486.0363.

(E)-(1-((m-tolyl)hex-1-ene-1,2-diyl)bis(phenylselane) (14k)

This compound was prepared following general procedure 2.3, and crude mixture was purified using flash chromatography (DCM:hexanes = 1:10) to yield the desired products as colorless oil (92.2 mg, 95%). \(^{1}\text{H NMR}\) (600 MHz, CDCl\(_3\)) δ 7.48 (dd, J = 7.0, 2.2 Hz, 2H), 7.30 – 7.22 (m, 5H), 7.15 – 7.06 (m, 3H), 7.02 (t, J = 7.6 Hz, 1H), 6.92 – 6.88 (m, 2H), 6.87 (s, 1H), 2.66 – 2.58 (m, 2H), 2.19 (s, 3H), 1.58 – 1.52 (m, 2H), 1.30 – 1.20 (m, 2H), 0.82 (t, J = 7.4 Hz, 3H). \(^{13}\text{C NMR}\) (151 MHz, CDCl\(_3\)) δ 141.55, 137.30, 137.06, 134.71, 133.87, 130.66, 130.39, 130.24, 129.98, 128.89, 128.52, 127.88, 127.63, 127.40, 127.15, 126.35, 37.13, 31.42, 22.19, 21.27, 13.89. \(\text{HRMS (ESI)}\) m/z: \(^{1+}\) Calcd. for C\(_{25}\)H\(_{26}\)Se\(_2\): 486.0365, found: 486.0367.
(E)-(1-(o-tolyl)hex-1-ene-1,2-diyl)bis(phenylselane) (14I)

This compound was prepared following general procedure 2.3, and crude mixture was purified using flash chromatography (DCM:hexanes = 1:10) to yield the desired products as colorless oil (92.5 mg, 95%). $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.49 – 7.44 (m, 2H), 7.30 – 7.22 (m, 5H), 7.16 (t, $J$ = 7.4 Hz, 1H), 7.05 (t, $J$ = 7.6 Hz, 2H), 7.03 – 6.97 (m, 2H), 6.90 (t, $J$ = 7.8 Hz, 1H), 6.76 (d, $J$ = 7.5 Hz, 1H), 2.66 – 2.52 (m, 2H), 2.17 (s, 3H), 1.63 – 1.49 (m, 2H), 1.33 – 1.23 (m, 2H), 0.85 (t, $J$ = 7.3 Hz, 3H). $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 140.05, 136.01, 135.47, 134.78, 134.52, 130.05, 129.82, 129.60, 129.50, 128.89, 128.45, 128.31, 127.89, 127.63, 127.36, 125.04, 35.84, 31.09, 22.21, 19.45, 13.92. HRMS (ESI) m/z: $^{1+}$ Calcd. for C$_{25}$H$_{26}$Se$_2$: 486.0365, found: 486.0364.

(F)-1-(4-fluorophenyl)hex-1-ene-1,2-diyl)bis(phenylselane) (14m)

This compound was prepared following general procedure 2.3, and crude mixture was purified using flash chromatography (DCM:hexanes = 1:10) to yield the desired products as colorless oil (90.1 mg, 92%). $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.47 – 7.41 (m, 2H), 7.29 – 7.24 (m, 2H), 7.24 – 7.19 (m, 3H), 7.13 – 7.09 (m, 1H), 7.08 – 7.01 (m, 4H), 6.76 (t, $J$ = 8.7 Hz, 2H), 2.69 – 2.61 (m, 2H), 1.61 – 1.51 (m, 2H), 1.31 – 1.21 (m, 2H), 0.83 (t, $J$ = 7.4 Hz, 3H). $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 161.56 (d, $J$ = 246.8 Hz), 137.57 (d, $J$ = 3.3 Hz),
137.45, 134.53, 134.20, 131.12, 131.06, 130.06, 129.84, 128.94, 128.65, 127.68, 127.41, 114.42 (d, J = 21.7 Hz), 37.34, 31.35, 22.17, 13.85. $^{19}$F NMR (376 MHz, cdcl$_3$) δ -114.48, -114.49, -114.50, -114.51, -114.52, -114.54. HRMS (ESI) m/z: $^{1+}$ Calcd. for C$_{24}$H$_{23}$FSe$_2$: 490.0114, found: 490.0116.

$$\text{(E)-(1-(3-fluorophenyl)hex-1-ene-1,2-diyl)bis(phenylselane) (14n)}$$

This compound was prepared following general procedure 2.3, and crude mixture was purified using flash chromatography (DCM:hexanes = 1:10) to yield the desired products as colorless oil (90.2 mg, 92%). $^1$H NMR (600 MHz, CDCl$_3$) δ 7.46 (d, J = 7.8, 2H), 7.31 – 7.23 (m, 5H), 7.18 – 7.13 (m, 1H), 7.13 – 7.09 (m, 2H), 7.09 – 7.03 (m, 1H), 6.85 (d, J = 7.7, 1H), 6.81 – 6.74 (m, 2H), 2.66 – 2.59 (m, 2H), 1.60 – 1.51 (m, 3H), 1.32 – 1.20 (m, 2H), 0.84 (t, J = 7.3 Hz, 3H). $^{13}$C NMR (151 MHz, CDCl$_3$) δ 162.03 (d, J = 246.0 Hz), 143.70, 143.65, 137.97, 134.67, 134.20, 129.89, 129.67, 129.51, 129.00, 128.97, 128.91, 128.71, 127.80, 127.52, 125.22 (d, J = 2.8 Hz), 116.32 (d, J = 21.8 Hz), 113.95 (d, J = 21.2 Hz), 37.28, 31.36, 22.19, 13.88. $^{19}$F NMR (564 MHz, CDCl$_3$) δ -113.94, -113.95, -113.95, -113.97, -113.97, -113.98. HRMS (ESI) m/z: $^{1+}$ Calcd. for C$_{24}$H$_{23}$FSe$_2$: 490.0114, found: 490.0112.
(E)-(1-(2-fluorophenyl)hex-1-ene-1,2-diy)bis(phenylselane) (14o)

This compound was prepared following general procedure 2.3, and crude mixture was purified using flash chromatography (DCM:hexanes = 1:10) to yield the desired products as colorless oil (92.2 mg, 94%). $^1$H NMR (600 MHz, CDCl$_3$) δ 7.50 – 7.45 (m, 2H), 7.35 – 7.31 (m, 2H), 7.29 – 7.23 (m, 3H), 7.17 – 7.13 (m, 1H), 7.11 – 7.07 (m, 2H), 7.07 – 7.03 (m, 1H), 6.98 (td, $J$ = 7.5, 1.8 Hz, 1H), 6.87 (td, $J$ = 7.5, 1.1 Hz, 1H), 6.80 (t, $J$ = 8.2, 1H), 2.68 (ddd, $J$ = 13.6, 9.6, 6.0 Hz, 1H), 2.58 (ddd, $J$ = 13.6, 9.6, 5.8 Hz, 1H), 1.66 – 1.57 (m, 2H), 1.35 – 1.27 (m, 2H), 0.87 (t, $J$ = 7.3 Hz, 3H). $^{13}$C NMR (151 MHz, CDCl$_3$) δ 158.75 (d, $J$ = 246.8 Hz), 138.26, 134.87, 134.25, 131.24 (d, $J$ = 2.8 Hz), 129.97, 129.27 (d, $J$ = 15.5 Hz), 129.19, 129.07, 129.02, 128.97, 128.54, 127.61 (d, $J$ = 15.5 Hz), 125.66, 123.27 (d, $J$ = 3.4 Hz), 115.11 (d, $J$ = 22.0 Hz), 36.89, 31.13, 22.16, 13.95. $^{19}$F NMR (564 MHz, CDCl$_3$) δ -113.22, -113.23, -113.23, -113.23, -113.23, -113.24, -113.24, -113.26. HRMS (ESI) m/z: $^{1+}$ Calcd. for C$_{24}$H$_{23}$FSe$_2$: 490.0114, found: 490.0112.

(E)-(1-(4-methoxyphenyl)hex-1-ene-1,2-diy)bis(phenylselane) (14p)

This compound was prepared following general procedure 2.3, and crude mixture was purified using flash chromatography (EA:hexanes = 1:10) to yield the desired products as colorless oil (96.4 mg, 96%). $^1$H NMR (600 MHz, CDCl$_3$) δ 7.48 (dd, $J$ = 7.3, 2.1 Hz, 2H),
7.30 – 7.23 (m, 5H), 7.15 – 7.07 (m, 3H), 7.05 (d, J = 8.4 Hz, 2H), 6.66 (d, J = 8.4 Hz, 2H), 3.72 (s, 3H), 2.66 – 2.58 (m, 2H), 1.57 – 1.51 (m, 2H), 1.26 – 1.19 (m, 2H), 0.82 (t, J = 7.3 Hz, 3H). 13C NMR (151 MHz, CDCl3) δ 158.56, 137.52, 134.72, 134.31, 133.66, 130.67, 130.59, 130.37, 130.30, 128.92, 128.62, 127.66, 127.07, 112.93, 55.09, 37.33, 31.51, 22.20, 13.87. HRMS (ESI) m/z: 1+ Calcd. for C25H26OSe2: 502.0314, found: 502.0291.

(E)-(1-cyclopropyl-2-phenylethene-1,2-diyl)bis(phenylselane) (14q)

This compound was prepared following general procedure 2.3, and crude mixture was purified using flash chromatography (DCM:hexanes = 1:10) to yield the desired products as yellow oil (54.7 mg, 60%). 1H NMR (600 MHz, CDCl3) δ 7.31 – 7.28 (m, 2H), 7.28 – 7.24 (m, 2H), 7.22 – 7.14 (m, 3H), 7.14 – 7.08 (m, 1H), 7.08 – 7.04 (m, 2H), 7.01 – 6.97 (m, 3H), 6.98 – 6.94 (m, 2H), 2.14 (m, J = 6.7 Hz, 1H), 0.80 (d, J = 7.8 Hz, 4H). 13C NMR (151 MHz, CDCl3) δ 141.56, 140.15, 134.98, 133.44, 133.33, 130.77, 129.93, 129.42, 128.90, 128.59, 127.52, 127.29, 126.88, 126.16, 19.26, 9.17. HRMS (ESI) m/z: 1+ Calcd. for C23H20Se2: 455.9895, found: 455.9889.
(E)-1,2-bis((4-methoxyphenyl)selanyl)-1,2-diphenylethene (14r)

This compound was prepared following general procedure 2.3, and crude mixture was purified using flash chromatography (EA:hexanes = 1:10) to yield the desired products as white solid (90.5 mg, 82%). $^1$H NMR (600 MHz, CDCl$_3$) δ 7.22 – 7.16 (m, 8H), 7.15 – 7.10 (m, 2H), 7.07 (d, $J$ = 8.7 Hz, 4H), 6.52 (d, $J$ = 8.8 Hz, 4H), 3.66 (s, 6H). $^{13}$C NMR (151 MHz, CDCl$_3$) δ 159.27, 140.46, 137.18, 132.46, 129.40, 127.65, 127.24, 120.23, 113.94, 55.07. HRMS (ESI) m/z: $^{+}$ Calcd. for C$_{28}$H$_{24}$O$_2$Se$_2$: 552.0107, found: 552.0094.

(E)-1,2-diphenyl-1,2-bis(p-tolylselanyl)ethene (14s)

This compound was prepared following general procedure 2.3, and crude mixture was purified using flash chromatography (DCM:hexanes = 1:10) to yield the desired products as white solid (99.8 mg, 96%). $^1$H NMR (600 MHz, CDCl$_3$) δ 7.22 (d, $J$ = 7.5 Hz, 4H), 7.18 (t, $J$ = 7.5 Hz, 4H), 7.12 (t, $J$ = 7.3 Hz, 2H), 7.05 (d, $J$ = 8.1 Hz, 4H), 6.80 (d, $J$ = 7.8 Hz, 4H), 2.18 (s, 6H). $^{13}$C NMR (151 MHz, CDCl$_3$) δ 140.67, 137.32, 135.07, 132.97, 129.45, 129.14, 127.58, 127.26, 126.30, 21.06. HRMS (ESI) m/z: $^{+}$ Calcd. for C$_{28}$H$_{24}$Se$_2$: 520.0208, found:520.0210.
(E)-1,2-bis((4-fluorophenyl)selanyl)-1,2-diphenylethene (14t)

This compound was prepared following general procedure 2.3, and crude mixture was purified using flash chromatography (DCM:hexanes = 1:10) to yield the desired products as yellow solid (100.1 mg, 95%). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.23 – 7.09 (m, 14H), 6.73 – 6.64 (m, 4H). $^{13}$C NMR (151 MHz, CDCl$_3$) δ 162.47 (d, $J = 248.0$ Hz), 140.11, 137.45 (d, $J = 8.0$ Hz), 132.58, 129.38, 127.81, 127.57, 124.48 (d, $J = 3.6$ Hz), 115.52 (d, $J = 21.6$ Hz). $^{19}$F NMR (564 MHz, CDCl$_3$) δ -113.60, -113.61, -113.61, -113.62, -113.63, -113.64, -113.65. HRMS (ESI) m/z: $^{1+}$ Calcd. for C$_{26}$H$_{18}$F$_2$Se$_2$: 527.9707, found: 527.9695.

(E)-1,2-diphenyl-1,2-bis((4-(trifluoromethyl)phenyl)selanyl)ethene (14u)

This compound was prepared following general procedure 2.3, and crude mixture was purified using flash chromatography (DCM:hexanes = 1:10) to yield the desired products as yellow solid (119.3 mg, 95%). $^1$H NMR (600 MHz, CDCl$_3$) δ 7.30 – 7.23 (m, 12H), 7.22 – 7.18 (m, 4H), 7.18 – 7.14 (m, 2H). $^{13}$C NMR (151 MHz, Chloroform-d) δ 140.01, 134.96 (d, $J = 1.7$ Hz), 134.38, 133.63, 129.37 (q, $J = 32.5$ Hz), 129.36, 128.00, 127.94, 125.11 (q, $J = 3.7$ Hz), 123.89 (q, $J = 272.2$ Hz). $^{19}$F NMR (564 MHz, CDCl$_3$) δ -62.77. HRMS (ESI) m/z: $^{1+}$ Calcd. for C$_{28}$H$_{18}$F$_6$Se$_2$: 627.9643, found: 627.9638.
(E)-1,2-bis((3-fluorophenyl)selanyl)-1,2-diphenylethene (14v)

This compound was prepared following general procedure 2.3, and crude mixture was purified using flash chromatography (DCM:hexanes = 1:10) to yield the desired products as yellow solid (94.7 mg, 90%). $^1$H NMR (600 MHz, CDCl$_3$) δ 7.28 – 7.23 (m, 4H), 7.23 – 7.17 (m, 4H), 7.17 – 7.11 (m, 2H), 6.99 – 6.93 (m, 4H), 6.92 – 6.86 (m, 2H), 6.78 – 6.72 (m, 2H). $^{13}$C NMR (151 MHz, CDCl$_3$) δ 161.88 (d, $J$ = 249.6 Hz), 133.38, 131.54 (d, $J$ = 6.8 Hz), 130.43 (d, $J$ = 3.1 Hz), 129.55 (d, $J$ = 7.8 Hz), 129.39, 127.82, 127.75, 121.59 (d, $J$ = 21.8 Hz), 114.52 (d, $J$ = 21.0 Hz). $^{19}$F NMR (564 MHz, CDCl$_3$) δ -112.79, -112.80, -112.80, -112.80, -112.81, -112.81, -112.82. HRMS (ESI) m/z: $^{1+}$ Calcd. for C$_{26}$H$_{18}$F$_2$Se$_2$: 527.9707, found: 527.9706.

(E)-1,2-bis(benzylselanyl)-1,2-diphenylethene (14w)

This compound was prepared following general procedure 2.3, and crude mixture was purified using flash chromatography (DCM:hexanes = 1:10) to yield the desired products as yellow solid (68.3 mg, 66%). $^1$H NMR (600 MHz, CDCl$_3$) δ 7.37 (t, $J$ = 7.5 Hz, 4H), 7.33 – 7.27 (m, 6H), 7.17 – 7.10 (m, 6H), 6.97 – 6.91 (m, 4H), 3.38 (s, 4H). $^{13}$C NMR (151 MHz, CDCl$_3$) δ 140.75, 138.19, 131.62, 129.45, 128.90, 128.22, 127.80, 126.56, 31.25. HRMS (ESI) m/z: $^{1+}$ Calcd. for C$_{28}$H$_{24}$Se$_2$: 520.0208, found: 520.0213.
methyl (E)-(2,3-bis(phenylselanyl)acyroyl)-D-phenylalaninate (14x)

This compound was prepared by using Au/HFIP condition: to a HFIP solution (1 mL) of diselenide (0.2 mmol, 1eq) and alkyne (0.4 mmol, 2 eq), IPrAuNTf$_2$ (0.01 mmol, 0.05 eq) was added in one portion. The reaction was flashed with Ar and allowed to stir at 60 °C. The reaction mixture was then concentrated by rot-vap, and purified by flash chromatography (EA:hexanes = 1:3) to yield the desired products as yellow oil (101.4 mg, 93%). $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 8.36 (s, 1H), 7.65 – 7.59 (m, 2H), 7.54 (d, $J$ = 8.1 Hz, 1H), 7.37 – 7.31 (m, 3H), 7.30 – 7.20 (m, 6H), 7.20 – 7.10 (m, 3H), 6.91 (d, $J$ = 6.7 Hz, 1H), 4.89 (dt, $J$ = 8.1, 5.7 Hz, 1H), 3.63 (s, 3H), 3.06(qd, $J$ = 9.4, 5.82 Hz, 2H). $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 171.31, 165.35, 157.91, 135.50, 133.91, 133.23, 131.19, 129.64, 129.43, 129.34, 129.12, 128.49, 128.27, 126.95, 126.94, 113.34, 53.95, 52.23, 37.84.

HRMS (ESI) m/z: $^{1+}$ Calcd. for C$_{25}$H$_{23}$NO$_3$Se$_2$: 545.0008, found: 545.0011.

(E)-N-phenyl-2,3-bis(phenylselanyl)acrylamide (14y)

This compound was prepared by using Au/HFIP condition: to a HFIP solution (1 mL) of diselenide (0.2 mmol, 1eq) and alkyne (0.4 mmol, 2 eq), IPrAuNTf$_2$ (0.01 mmol, 0.05 eq) was added in one portion. The reaction was flashed with Ar and allowed to stir at 60 °C. The reaction mixture was then concentrated by rot-vap, and purified by flash
chromatography (EA: hexanes = 1:3) to yield the desired products as yellow oil (73.4 mg, 80%). $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 8.92 (s, 1H), 8.48 (s, 1H), 7.68 – 7.62 (m, 2H), 7.52 – 7.47 (m, 2H), 7.43 – 7.39 (m, 2H), 7.38 – 7.34 (m, 3H), 7.32 – 7.26 (m, 4H), 7.25 – 7.21 (m, 1H), 7.12 – 7.07 (m, 1H). $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 163.94, 158.69, 137.69, 134.18, 133.32, 131.13, 129.86, 129.68, 129.54, 129.06, 128.48, 127.40, 124.68, 119.87, 113.96, 77.13. HRMS (ESI) m/z: $^{1+}$ Calcd. for C$_{21}$H$_{17}$NOSe$_2$: 458.9641, found: 458.9636.

(3,3-diphenylprop-2-ene-1,2-diyl)bis(phenylselane) (15)

This compound was prepared following general procedure 2.5, and crude mixture was purified using flash chromatography (DCM: hexanes = 1:10) to yield the desired products as colorless oil (62.7 mg, 62%). $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.50 (dd, $J = 7.5$, 1.9 Hz, 2H), 7.32 – 7.28 (m, 2H), 7.22 – 7.13 (m, 10H), 7.11 – 7.05 (m, 4H), 6.98 (dd, $J = 7.6$, 1.9 Hz, 2H), 3.87 (s, 2H). $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 146.42, 142.92, 141.05, 134.34, 134.33, 130.90, 130.02, 129.59, 129.17, 129.14, 128.88, 128.67, 128.02, 127.75, 127.47, 127.29, 127.19, 127.04, 77.00, 34.05. HRMS (ESI) m/z: $^{1+}$ Calcd. for C$_{27}$H$_{22}$Se$_2$: 506.0052, found: 506.0049.

(E)-(1-phenylhex-1-ene-1,2-diyl)bis(phenylsulfane) (16a)

This compound was prepared following general procedure 2.6, and crude mixture was purified using flash chromatography (DCM: hexanes = 1:10) to yield the desired products
as colorless oil (54.2 mg, 72%). $^1$H NMR (600 MHz, CDCl$_3$) δ 7.31 – 7.23 (m, 6H), 7.23 – 7.16 (m, 3H), 7.12 (q, $J = 7.2$ Hz, 4H), 7.09 – 7.04 (m, 2H), 2.69 (dd, $J = 9.1$, 6.4 Hz, 2H), 1.66 – 1.58 (m, 2H), 1.36 – 1.28 (m, 2H), 0.87 (t, $J = 7.4$ Hz, 3H). $^{13}$C NMR (151 MHz, CDCl$_3$) δ 139.44, 139.36, 136.42, 135.14, 134.42, 131.23, 131.05, 129.83, 128.83, 128.49, 127.42, 127.26, 126.76, 126.65, 34.29, 31.22, 22.36, 13.92. HRMS (ESI) m/z: $^{1+}$ Calcd. for C$_{24}$H$_{24}$S$_2$: 376.1319, found: 376.1306.

(E)-(1-(p-tolyl)hex-1-ene-1,2-diyl)bis(phenylsulfane) (5b)

This compound was prepared following general procedure 2.6, and crude mixture was purified using flash chromatography (DCM:hexanes = 1:10) to yield the desired products as colorless oil (57 mg, 73%). $^1$H NMR (600 MHz, CDCl$_3$) δ 7.33 – 7.24 (m, 4H), 7.24 – 7.04 (m, 8H), 6.95 (d, $J = 7.8$ Hz, 2H), 2.71 – 2.63 (m, 2H), 2.22 (s, 3H), 1.66 – 1.54 (m, 2H), 1.35 – 1.25 (m, 2H), 0.85 (t, $J = 7.3$ Hz, 3H). $^{13}$C NMR (151 MHz, CDCl$_3$) δ 139.73, 137.07, 136.51, 136.01, 135.16, 134.85, 131.13, 130.73, 129.69, 128.81, 128.50, 128.20, 126.76, 126.42, 34.31, 31.28, 22.35, 21.22, 13.90. HRMS (ESI) m/z: $^{1+}$ Calcd. for C$_{25}$H$_{26}$S$_2$: 390.1476, found: 390.1466.
(E)-(1-(m-tolyl)hex-1-ene-1,2-diyl)bis(phenylsulfane) (16c)

This compound was prepared following general procedure 2.6, and crude mixture was purified using flash chromatography (DCM:hexanes = 1:10) to yield the desired product as colorless oil (50 mg, 64%). \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 7.33 – 7.26 (m, 4H), 7.24 – 7.03 (m, 8H), 6.95 (d, \(J = 7.8\) Hz, 2H), 2.71 – 2.63 (m, 2H), 2.22 (s, 3H), 1.66 – 1.56 (m, 2H), 1.34 – 1.27 (m, 2H), 0.85 (t, \(J = 7.3\) Hz, 3H). \(^{13}\)C NMR (151 MHz, CDCl\(_3\)) \(\delta\) 139.73, 137.07, 136.50, 136.01, 135.15, 134.85, 131.13, 130.72, 129.69, 128.81, 128.50, 128.20, 126.77, 126.42, 34.30, 31.28, 22.35, 21.22, 13.90. HRMS (ESI) m/z: \(^1\)Calcd. for C\(_{25}\)H\(_{26}\)S\(_2\): 390.1476, found: 390.1465.

(PhS)nBu(PhS) n-Bu-

(E)-(1-(o-tolyl)hex-1-ene-1,2-diyl)bis(phenylsulfane) (16d)

This compound was prepared following general procedure 2.6, and crude mixture was purified using flash chromatography (DCM:hexanes = 1:10) to yield the desired product as colorless oil (72.6 mg, 93%). \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 7.31 – 7.23 (m, 4H), 7.22 – 7.17 (m, 3H), 7.15 – 7.07 (m, 2H), 7.05 – 6.97 (m, 2H), 6.90 (td, \(J = 6.6, 5.5, 2.9\) Hz, 1H), 6.84 (d, \(J = 7.5\) Hz, 1H), 2.76 (ddd, \(J = 13.6, 8.9, 6.6\) Hz, 1H), 2.58 (ddd, \(J = 13.6, 8.6, 6.4\) Hz, 1H), 2.22 (s, 3H), 1.68 – 1.58 (m, 2H), 1.40 – 1.30 (m, 2H), 0.89 (t, \(J = 7.3\) Hz, 3H). \(^{13}\)C NMR (151 MHz, CDCl\(_3\)) \(\delta\) 138.51, 136.89, 135.96, 135.94, 134.78, 134.05,

![Chemical Structure](PhS=H PhS=H)

(E)-(1-phenylethene-1,2-diyl)bis(phenylsulfane) (16e)

This compound was prepared following general procedure 2.6, and crude mixture was purified using flash chromatography (DCM:hexanes = 1:10) to yield the desired products as colorless oil (51.8 mg, 81%). $^1$H NMR (600 MHz, CDCl$_3$) δ 7.59 (d, $J = 7.7$ Hz, 2H), 7.38 – 7.29 (m, 8H), 7.26 – 7.19 (m, 4H), 7.13 (t, $J = 7.4$ Hz, 1H), 6.89 (s, 1H). $^{13}$C NMR (151 MHz, CDCl$_3$) δ 137.18, 135.72, 135.13, 132.49, 130.08, 129.52, 129.38, 129.16, 129.09, 128.92, 128.29, 128.13, 127.08, 126.75. **HRMS** (ESI) m/z: $^1+$ Calcd. for C$_{20}$H$_{16}$S$_2$: 320.0693, found: 320.0690

![Chemical Structure](PhS=H PhS=H)

(1-phenylethane-1,2-diyl)bis(phenylsulfane) (17a)

This compound was prepared following general procedure 2.7, and crude mixture was purified using flash chromatography (DCM:hexanes = 1:10) to yield the desired products as colorless oil (58.6 mg, 91%). $^1$H NMR (600 MHz, CDCl$_3$) δ 7.35 – 7.20 (m, 11H), 7.20 – 7.13 (m, 4H), 4.25 (dd, $J = 10.1$, 4.9 Hz, 1H), 3.49 (dd, $J = 13.6$, 4.9 Hz, 1H), 3.35 (dd, $J = 13.5$, 10.1 Hz, 1H). $^{13}$C NMR (151 MHz, CDCl$_3$) δ 139.55, 135.42, 134.10, 132.87,
129.94, 128.91, 128.51, 128.06, 127.76, 127.63, 126.39, 52.32, 39.61. **HRMS (ESI)** m/z: 1+ Calcd. for C_{20}H_{18}S_2: 322.0850, found: 322.0847.

![Structure of 1-(4-chlorophenyl)ethane-1,2-diylbis(phenylsulfane) (17b)](image)

(1-(4-chlorophenyl)ethane-1,2-diylbis(phenylsulfane) (17b)

This compound was prepared following general procedure 2.7, and crude mixture was purified using flash chromatography (DCM:hexanes = 1:10) to yield the desired products as colorless oil (66.9 mg, 94%). **^1H NMR** (600 MHz, CDCl$_3$) δ 7.29 – 7.17 (m, 10H), 7.17 – 7.10 (m, 4H), 4.19 (dd, $J = 10.3$, 4.8 Hz, 1H), 3.47 (dd, $J = 13.7$, 4.8 Hz, 1H), 3.26 (dd, $J = 13.6$, 10.3 Hz, 1H). **^13C NMR** (151 MHz, CDCl$_3$) δ 138.15, 135.08, 133.56, 133.42, 133.09, 130.09, 129.42, 128.99, 128.64, 127.90, 126.57, 51.79, 39.52. **HRMS (ESI)** m/z: 1+ Calcd. for C$_{20}$H$_{17}$ClS$_2$: 356.0455, found: 356.0460.

![Structure of 1-(m-tolyl)ethane-1,2-diylbis(phenylsulfane) (17c)](image)

(1-(m-tolyl)ethane-1,2-diylbis(phenylsulfane) (17c)

This compound was prepared following general procedure 2.7, and crude mixture was purified using flash chromatography (DCM:hexanes = 1:10) to yield the desired products as colorless oil (52.4 mg, 78%). **^1H NMR** (600 MHz, CDCl$_3$) δ 7.32 – 7.27 (m, 2H), 7.26 – 7.22 (m, 3H), 7.22 – 7.13 (m, 6H), 7.09 – 7.02 (m, 3H), 4.22 (dd, $J = 10.2$, 4.9 Hz, 1H), 3.47 (dd, $J = 13.6$, 4.9 Hz, 1H), 3.35 (dd, $J = 13.5$, 10.2 Hz, 1H), 2.31 (s, 3H). **^13C NMR** (151 MHz, CDCl$_3$) δ 139.34, 138.16, 135.53, 134.28, 132.78, 129.90, 128.90, 128.88,
128.69, 128.60, 128.38, 127.57, 126.33, 125.13, 52.30, 39.56, 21.42. **HRMS** (ESI) m/z: 

1+ Calcd. for C$_{21}$H$_{20}$S$_2$: 336.1001, found: 336.0996.

(1-(o-tolyl)ethane-1,2-diyl)bis(phenylsulfane) (**17d**)

This compound was prepared following general procedure **2.7**, and crude mixture was purified using flash chromatography (DCM:hexanes = 1:10) to yield the desired products as colorless oil (45.7 mg, 68%). **$^1$H NMR** (600 MHz, CDCl$_3$) $\delta$ 7.34 – 7.29 (m, 2H), 7.29 – 7.23 (m, 4H), 7.22 – 7.08 (m, 8H), 4.49 (dd, $J$ = 10.1, 5.1 Hz, 1H), 3.51 (dd, $J$ = 13.6, 5.1 Hz, 1H), 3.44 (dd, $J$ = 13.6, 10.1 Hz, 1H), 2.23 (s, 3H). **$^{13}$C NMR** (151 MHz, CDCl$_3$) $\delta$ 137.28, 136.60, 135.53, 134.16, 133.26, 130.48, 129.73, 128.95, 128.89, 127.81, 127.50, 126.62, 126.32, 47.72, 38.88, 19.40. **HRMS** (ESI) m/z: 1+ Calcd. for C$_{21}$H$_{20}$S$_2$: 336.1001, found: 336.0998.

1,2-diphenyl-1,2-bis(phenylthio)ethane (**17e**)

This compound was prepared following general procedure **2.7**, and crude mixture was purified using flash chromatography (DCM:hexanes = 1:10) to yield the desired products as colorless oil (74 mg, 93%). **$^1$H NMR** (600 MHz, CDCl$_3$) $\delta$ 7.28 – 7.21 (m, 4H), 7.21 – 7.13 (m, 6H), 7.13 – 7.05 (m, 6H), 7.03 – 6.97 (m, 4H), 4.67 (s, 2H). **$^{13}$C NMR** (151 MHz,
CDCl$_3$ $\delta$ 138.36, 134.59, 132.46, 129.23, 128.78, 127.56, 127.28, 127.22, 58.24. **HRMS** (ESI) m/z: $^{1+}$ Calcd. for C$_{26}$H$_{22}$S$_2$: 398.1157, found: 398.1150

This compound was prepared following general procedure 2.8, and crude mixture was purified using flash chromatography (DCM:hexanes = 1:10) to yield the desired products as colorless oil (45.1 mg, 55%). **$^1$H NMR** (600 MHz, CDCl$_3$) $\delta$ 7.36 (d, $J$ = 7.7 Hz, 2H), 7.29 – 7.14 (m, 14H), 7.12 (d, $J$ = 7.4 Hz, 2H), 7.08 – 7.03 (m, 2H), 3.76 (s, 2H). **$^{13}$C NMR** (151 MHz, CDCl$_3$) $\delta$ 148.78, 141.85, 141.09, 135.44, 134.84, 131.60, 131.11, 130.29, 129.34, 129.26, 128.88, 128.64, 128.15, 127.81, 127.43, 127.40, 126.77, 126.72, 77.00, 38.75. **HRMS** (ESI) m/z: $^{1+}$ Calcd. for C$_{27}$H$_{22}$S$_2$: 410.1157, found: 410.1164.
References


