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Inter- and Intramolecular Cobalt (I)-Catalyzed [2+2+2] Cyclizations of Bisnitriles

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Inter- and Intramolecular Cobalt (I)-Catalyzed 
[2+2+2] Cyclizations of Bisnitriles

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Acknowledgements

I would like to thank all those who helped to support my research, both academically and financially. In particular, I would like to thank Dr. John K. Snyder for his insight and counsel for the years that I have been able to work in his group. I would also like to thank Cuifang Cai for her help in this research, along with the other members of the Snyder group, who have provided me with great insight and support throughout my research. I would also like to thank the Undergraduate Research Opportunities Program at BU for awarding me the Clare Boothe Luce Award to support my research over the summer of 2013, as well as for awarding me a FROG grant for the spring of 2014. Finally, I would like to thank the Boston University Chemistry Department and the Mason Fund for providing me with the funding to present my research at the ACS National Meeting in Dallas, Texas.
Abstract

The cobalt (I)-catalyzed intramolecular [2+2+2] cyclization reactions previously investigated by Vollhardt were successfully applied to alkynylbisnitrile species in the formation of novel annulated pyridazines. This chemistry demonstrates the first successful formation of an N,N bond through a [2+2+2] cyclization pathway. Nitrogen linkers with different protecting groups were incorporated into the alkynylbisnitrile species, and were used as a site of selective deprotection and diversification of the cyclized scaffold. Using this methodology, two novel ureas were formed from the annulated pyridazines with high yields (88-93%), indicating the feasibility of the development of a diverse small molecule library using this chemistry. Expanding upon the success in the intramolecular cyclizations, the intermolecular incorporation of alkynes and nitriles with arylbisnitriles was examined. Although the intermolecular incorporation of diphenylacetylene was found to only provide trace amounts of the desired product, favoring the trimerization product, benzonitrile was found to incorporate well, forming the corresponding 1,2,4-triazine regioselectively (44%).
Introduction

Since their discovery in 1952, interest in [2+2+2] cyclizations has been growing due to their applications in preparing substituted heterocyclic and carbocyclic aromatic systems.\textsuperscript{1,2} The first discovery of this [2+2+2] cyclization chemistry by Christoph Grundmann was reported in 1952, where three nitriles were found to trimerize to form the 1,3,5-triazine with catalytic acid (Scheme 1).\textsuperscript{3} As this novel reaction type was investigated, transition metals such as lanthanide (III) were found to activate the nitriles and catalyze the [2+2+2] cyclization.\textsuperscript{4}

Much of the pioneering work on the synthetic applications of these transition metal catalyzed [2+2+2] cyclizations was preformed by Peter Vollhardt with alkyne systems.\textsuperscript{5,6} In 1977, he reported the application of the catalyst CpCo(CO)\textsubscript{2} in transition-metal-catalyzed acetylene cyclizations. In particular, he demonstrated the efficacy of this catalyst in the synthesis of indans and tetralins, although with variable yields (n = 3, 4, respectively, Scheme 2 Equation 1). He reported that most of the variability in the yield came from the formation of a byproduct due to the trimerization of the acetylene. As a result, he found that bulky groups in the R\textsubscript{1} and R\textsubscript{2} positions, such as trimethylsilyl groups, provided higher yields. Developing this chemistry, Vollhardt successfully demonstrated the applications of this chemistry to purely intramolecular systems, linking the π systems through a carbon chain, which resulted in a significant increase in yield (Scheme 2 Equation 2, 84%).\textsuperscript{6}
Expanding on Vollhardt’s research, other groups began to examine the incorporation of heteroatom linkers in the tethers to prepare a number of heterocycles. In 2003, Yamamoto examined applying intramolecular cyclization techniques to a similar group of heteroatom-tethered triynes in inter- and intramolecular cyclizations (Scheme 3). Interestingly, Yamamoto chose to employ a different catalyst, Cp*Ru(COD)Cl, in these cyclizations, as he found that the COD ligand can be easily replaced by an alkyne to initiate the cyclization, and the bulky Cp* ligand provided a compact coordinate space which may have aided in regio- and chemoselectivity. The intramolecular cyclizations of these heteroatom-tethered triynes was found to achieve very high yields with mild conditions, with the highest yields corresponding to the products with the smaller ring size in the annulated carbocyclic aromatic cyclization product (n = 0, Scheme 3).7

Similarly, recent research has investigated the incorporation of nitriles as one of the π-components to form annulated pyridine derivatives. Similar to the investigation of the triyne cyclizations, a number of different transition metal catalysts have been successfully used for these cyclizations, including CpCo(CO)₂ and [Ir(cod)Cl]₂.8-10 Although the transition metal catalysts used in these cyclizations are diverse, all of the catalysts can be defined as soft, π-Lewis acids. Nitriles have been found to be successfully incorporated into these cyclizations both intramolecularly, which has allowed a significant expansion of the scope of these reactions. As the scope of these reactions has increased, many groups have recently begun to examine applications to the syntheses of aromatic compounds.11,12 Currently, these cyclizations have been successfully incorporated into the synthesis of various biologically active natural
products. In particular, Vollhardt demonstrated the successful utilization of [2+2+2] cyclizations in the novel synthesis of a steroid-like core (Scheme 4). He proposed that this core molecule, synthesized in only three steps using a [2+2+2] cyclization pathway (48% yield overall), could be easily transformed into the steroid estrone. Other groups have also demonstrated applications to the synthesis of various natural products such as (+)-complanadine A, a neurotrophic factor inducer, and herbindoles A-C, which have antifeedant activity against fishes.

Previously in the Snyder group, the application of these cyclizations to heteroatom-tethered bisalkynylnitriles has been examined, leading to the formation of tetrahydro-1,6-naphthyridines, utilizing the CpCo(CO)$_2$ catalyst first reported by Vollhardt (Scheme 5). Through the incorporation of two different heteroatom tethers (nitrogen and oxygen) in a single bisalkynylnitrile cyclization precursor, Snyder was able to achieve the synthesis of these tricyclic bisheterocycles. Selective deprotection of the PMB group allowed for scaffold diversification, forming a variety of ureas, amides, amines and sulfonamides with variations at the R and R’ positions to make an expansive small molecule library.

The synthesis of pyridazines (1,2-diazines) has been of great interest to the pharmaceutical industry, as these substructures are present in a number of molecules that have
been found to possess biological activity. A variety of drugs, such as hydralazine (an antihypertensive), minaprine and pipofezine (antidepressants), possess these pyridazine cores (Scheme 6).\textsuperscript{16-18} Furthermore, a number of these pyridazine-based molecules are currently being investigated in screenings for binding affinity to the liver X receptor beta (LXRβ) and in the development of naproxen, an anti-inflammatory drug.\textsuperscript{17,19}

Based on a recent analysis of the GSK database, pyridazines have been characterized as one of the most “developable” scaffolds.\textsuperscript{20} However, useful synthetic routes to these pyridazines as substructures in larger molecules have been difficult, with most strategies incorporating the dinitrogen unit with the N,N bond already intact in the form of a hydrazine or hydrazone.\textsuperscript{21} The methodologies for achieving these pyridazine systems previously occurred by two mechanisms. These involved either the incorporation of hydrazine to a \(\alpha,\delta\)-dicarbonyl system (Scheme 7)\textsuperscript{22,23}, or cyclizations of a diazonium ion(Scheme 8).\textsuperscript{24} These syntheses are rather complex, due to the necessity of the incorporation of an already intact nitrogen-nitrogen bond. As a result, the syntheses do not allow for an extensive variety in the number of pyridazines that can be easily created.

The development of new methodologies for pyridazine synthesis may allow not only for the formation of known biological targets with greater ease and efficiency, but it may enhance the number of molecules with a known substructure for
incorporation into diversified screening libraries. The goal of this research was to apply [2+2+2] cyclization chemistry to synthesize these pyridazines in an intramolecular fashion from alkynylbisnitriles, which would prove to be the first successful formation of an N,N bond in a [2+2+2] cyclization pathway (Scheme 9). Future work could then greatly expand upon the number of pyridazines that can be easily synthesized.

Scheme 9. Intramolecular approach to the cyclizations of alkynylbisnitriles to form annulated pyridazines, where X= N, O and n= 1, 2
Results and Discussion

Preparation of the N,N-Linked Bisnitrile (1a-c):

The application of intramolecular [2+2+2] cyclizations to the synthesis of pyridines from alkynylbisnitriles was initially examined. The alkynylbisnitrile cyclization precursors were successfully synthesized, following a similar procedure as demonstrated by our group in the formation of bisalkynylnitriles (Scheme 10).\(^9\) Nitrogen tethers were incorporated as potential sites for diversification after cyclization to the pyridazine scaffold. The synthesis of the N,N-linked alkynylbisnitrile species 1a was straight-forward, incorporating two different protecting groups onto each linking nitrogen in order to allow for selective diversification (Scheme 10). A second addition of \(\alpha\)-bromoacetonitrile to form the tertiary amine in the \(S_N2\) reaction of the aminonitrile was avoided through the use of dropwise addition of the bromoacetonitrile reagent, along with decreased reaction times from 10 hours to 6 hours. A similar synthesis was pursued to achieve related alkynylbisnitrile species with varying protecting groups and carbon chain lengths (1b-c, Scheme 11).

Cyclization of the N,N-Linked Bisnitriles (1a-c) to Form the Pyridazine (2a-c):
Utilizing the CpCo(CO)$_2$ catalytic conditions that had been previously used in the synthesis of tetrahydronaphthyridines in our group, the bisalkynylnitrile 1d was cyclized by Cuifang Cai to form the corresponding pyridazine (2d, Scheme 12)$^9$.

Cuifang Cai preformed a brief optimization study on the cyclization reaction for the formation of the pyridazine 2d (Table 1). Entries 1-4 of Table 1 demonstrate the efficacy of related catalysts for the [2+2+2] cyclization reaction. However, only the CpCo(CO)$_2$ catalyst used by Vollhardt was found to provide promising yields of the desired product 2d, with the other catalysts providing either very low yields of 2d, or returning the uncyclized starting material (Entries 1-3, Table 4). Consequently, the cyclization reaction was optimized for the duration and temperature with the CpCo(CO)$_2$ catalyst (Entries 4-7, 10-11, Table 1). For this substrate 1d, increasing the duration of the reaction led to a decrease in yield, due an increase in the formation of a byproduct corresponding to elimination of the tosyl group (Entries 4-6, Table 1). Additionally, increasing the catalyst loading of the Co (I) catalyst (30 mol %, Entry 8) was found to have no effect on the yield of the desired product 2d. Conversely, a decrease in the catalyst loading of the Co (I) catalyst resulted in a slight decrease in the yield of the cyclization reaction (10 mol %, Table 1). Optimizations Studies for the Cyclization of 1d.$^{a,b}$

<table>
<thead>
<tr>
<th>Catalyst (eq)</th>
<th>Time (min)</th>
<th>Temp (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 CoCp(CO)(MeO)$_2$CC=CCO)$_2$Me</td>
<td>15</td>
<td>180</td>
<td>9</td>
</tr>
<tr>
<td>2 Rh(COD)$_2$BF$_4$</td>
<td>10</td>
<td>180</td>
<td>0</td>
</tr>
<tr>
<td>3 RhCl(PPh$_3$)$_3$</td>
<td>15</td>
<td>180</td>
<td>0</td>
</tr>
<tr>
<td>4 CoCp(CO)$_2$</td>
<td>5</td>
<td>180</td>
<td>65</td>
</tr>
<tr>
<td>5 CoCp(CO)$_2$</td>
<td>10</td>
<td>180</td>
<td>50</td>
</tr>
<tr>
<td>6 CoCp(CO)$_2$</td>
<td>15</td>
<td>180</td>
<td>50</td>
</tr>
<tr>
<td>7 CoCp(CO)$_2$</td>
<td>30</td>
<td>180</td>
<td>25</td>
</tr>
<tr>
<td>8 CoCp(CO)$_2$</td>
<td>10</td>
<td>180</td>
<td>60</td>
</tr>
<tr>
<td>9 CoCp(CO)$_2$</td>
<td>10</td>
<td>180</td>
<td>50</td>
</tr>
<tr>
<td>10 CoCp(CO)$_2$</td>
<td>5</td>
<td>160</td>
<td>70</td>
</tr>
<tr>
<td>11 CoCp(CO)$_2$</td>
<td>10</td>
<td>160</td>
<td>54</td>
</tr>
</tbody>
</table>

a) All reactions were performed under microwave irradiation: 160 °C at 200 Watts, 180 °C at 300 Watts, 0.05 M in chlorobenzene, 30-40 mg scale.
b) Data provided by the work of Cuifang Cai.

Scheme 12. Intramolecular [2+2+2] Cyclization of 1d to form the Pyridazine 2d.
Entry 9). Furthermore, Cuifang Cai found that the thermal conditions resulted in a significant decrease in yield in comparison to the typical microwave irradiation conditions (20% yield of 2d). Entry 10 was found to provide the optimized conditions for the cyclization of 1d. The optimized conditions from Table 1 were then applied to the bisalkynylnitriles 1a-c to form the respective pyridazines 2a-c (Scheme 13). Unfortunately, due to the necessity of the microwave in this cyclization reaction, the reaction could not be run at a scale of greater than 50 mg without a significant decrease in the yield for the reaction. Alternative methodologies to scale up the cyclization reaction, such as the utilization of flow chemistry, were considered, however they could not be applied to this scheme due to the extreme sensitivity of the CpCo(CO)$_2$ catalyst to air.

Selective Diversification in the Preparation of Ureas (4a-b):

Following the facile synthesis of pyridazines 2a-c through the [2+2+2] cyclization strategy, the selective diversification of these pyridazines for incorporation into small molecule libraries was examined. The pyridazine 2a was chosen to demonstrate the feasibility of this chemistry,

<table>
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<tr>
<th>Reagent</th>
<th>Conditions</th>
<th>Yield (%)</th>
<th>Notes</th>
</tr>
</thead>
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<tr>
<td>1a</td>
<td>TFA</td>
<td>0</td>
<td>Decomposition products</td>
</tr>
<tr>
<td>2</td>
<td>SCX-3</td>
<td>0</td>
<td>Starting material Isolated</td>
</tr>
<tr>
<td>3</td>
<td>TMSI (2.0 eq)</td>
<td>87</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Deprotection of Pyridazine 2a.

a) Data provided by the work of Cuifang Cai
as the removal of the BOC-protecting group typically requires only mild conditions. Initially, Cuifang Cai examined the application of TFA, a common reagent in BOC-deprotection reactions (Entry 1, Table 2). However, the deprotection with TFA was proven to be very messy and none of the desired deprotected pyridazine 2a was isolated, due to the acid-sensitive nature of the pyridazine.

For this reason, alternative methodologies to achieve BOC-deprotection were examined (Entries 2 and 3, Table 2). Entry 2 employed SCX-3, the resin-bound p-toluenesulfonic acid (Figure 1), in a catch-and-release type methodology. The catch-and-release method should allow SCX-3 to selectively bind the BOC-protected pyridazine, allowing impurities to be rinsed off before deprotecting the pyridazine and isolating the pure, deprotected product. However, only the starting material was isolated from this reaction, most likely due to association between the resin and the pyridazine without reacting with the bound p-TsOH. The use of TMSI was subsequently examined, as it had been previously shown to quench the removed tert-butyl carbocation produced from the BOC group (Table 2, Entry 3). Fortunately, this methodology was found to provide the desired deprotected pyridazine 3a in good purity with high yields while also utilizing mild reaction conditions (87%, Table 2). This methodology was determined to be the ideal deprotection methodology for our scaffold, and was used for all subsequent deprotection reactions in the process of selective diversification.

Following the deprotection of the pyridazine 3a, diversification of the scaffold for incorporation into a small molecule library was demonstrated through the formation of

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**Figure 1.** SCX-3, the resin-bound para-toluenesulfonic acid

**Scheme 14.** Selective deprotection of the pyridazine 2a
two unique ureas **4a-b** (Scheme 14). The synthesis of these ureas was standard, following a similar procedure as was used in the synthesis of the tetrahydronaphthrydine library. These reactions demonstrated the feasibility of the formation of a small molecule library of annulated pyridazines through the formation of ureas on the deprotected scaffold.

The intramolecular [2+2+2] cyclization conditions were thus successfully applied to form pyridazine molecules from alkynylbisnitriles in fairly high yields, providing the first example of N,N-bond formation in a [2+2+2] cyclization strategy. This offers both a new methodology to access known pyridazines and also expands upon the number of molecules with pyridazine cores that can be easily synthesized. Furthermore, this chemistry establishes that these novel pyridazine scaffolds can be easily diversified in only two steps to form a complex small molecule library.

**Attempted Reductive Ring Contraction of the Pyridazine:**

Following the demonstration of the successful application of an intramolecular [2+2+2] cyclization strategy to the formation of novel, diverse annulated pyridazines, we became interested in the using these pyridazines to create a pathway to access additional novel molecules. In particular, a reductive ring contraction of the pyridazine **2c** to form the corresponding pyrrole was briefly examined (Scheme 15). The typical reaction conditions for these ring contraction reactions was initially employed. Unfortunately, due to the sensitivity of the annulated pyridazine to acid, the pyridazine substrate would begin to decompose immediately. As a result, only trace amounts of product were found. In order to slow down the competing decomposition
of the pyridazine 2a, the acetic acid was added dropwise to the reaction, as opposed to its previous use as a solvent. However, this only produced trace amounts of desired product. This chemistry was suspended due to these initial discouraging results.

**Intermolecular Incorporations of Alkynes and Nitriles:**

Instead of pursuing the formation of a small molecule library of pyridazines resulting from the intramolecular [2+2+2] cyclization, the expansion of this chemistry to the incorporation of various alkynes and nitriles was examined through an intermolecular pathway. The O-linked arylbisnitrile species 5 was prepared for these intermolecular cyclization studies; the synthesis was routine and provided high yields (5, Scheme 16).

Initially, the intermolecular cyclization of the arylbisnitrile 5 with an alkyne was examined. Diphenylacetylene was chosen as the ideal alkyne to initially examine this reaction in hopes that the bulky phenyl groups would prevent dimerizations or trimerizations of the acetylene, while also allowing for simplicity in terms of the regioselectivity of the reaction. However, cyclization of the arylbisnitrile 5 proved to exclusively form the pyridine product from the trimerization of two acetylenes and the single aryl nitrile of the arylbisnitrile 5 (6b, Scheme 17). The reaction was repeated at
80\(^\circ\) C in an attempt to favor the dimerization reaction, however the cyclization reaction was still found to provide the trimerization product 6b (21\%) with only trace amounts of the minor desired product 6a.

Similarly, intermolecular cyclizations of 5 with nitriles were examined for the formation of the 1,2,4-triazine (Scheme 18). Initially, the cyclization reactions were examined utilizing the CpCo(CO)\(_2\) catalyst at 80\(^\circ\) C under microwave irradiation (Entries 1 and 2, Table 3). However, none of the desired product was able to be isolated; the unknown major product of these reactions was found to correspond to a molecular weight of 188. Increasing the temperature of the reaction to 180\(^\circ\) C, the bisnitrile 5 successfully cyclized with the solvent, benzonitrile, to form the 1,2,4-triazine 6a (44\%, Entry 3, Table 3).

Additionally, the cyclization was found to provide one regioisomer selectively, however which regioisomer was formed is still to be determined.

<table>
<thead>
<tr>
<th>Table 3. Intermolecular Nitrile Incorporation to the Bisnitrile 5a.</th>
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<tbody>
<tr>
<td>Nitrile</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
</tbody>
</table>

\(a\) All reactions were preformed under microwave irradiation: 50 mg scale, 1 M concentration in the nitrile, for 15 minutes.
Future Work

Upon additional examination of the major product for the intermolecular incorporation of nitriles at 80° C, the major product was believed to have been the result of incorporation of carbon monoxide from the CpCo(CO)₂ catalyst, resulting in the formation of the cyclic urea through a hetero-Pauson Khand-type pathway (Scheme 19).²⁷-²⁹ A 4% yield of the unknown product was isolated (Entry 1, Table 4). In an attempt to increase the yield of the cyclic urea product without increasing the amount of catalyst used, a CO atmosphere was employed (Entries 2 and 3, Table 4). However, no noticeable effect in the yield was seen. Entry 3 demonstrates a substitution of benzene as the solvent for this reaction, as the low yield for Entry 2 was initially thought to be a result of the low solubility of CO in benzonitrile. Interestingly, the use of benzene as the solvent only resulted in the recovery of starting material. This may be due to the excess of CO in the solution, which could prevent the dissociation of the CO ligand from the CpCo(CO)₂, a required step for the catalysis of the reaction. For this reason, the application of the typical Pauson Khand catalyst, Co₂(CO)₈, was examined both under microwave irradiation and thermal conditions (Entries 4 and 5, Table 4, respectively).²⁷-²⁹ The use of microwave irradiation was found to provide product in considerable yield (32%), in addition to returned starting material (Entry 4, Table 4). An additional catalyst, cyclohexylamine, was applied in the microwave irradiation

<table>
<thead>
<tr>
<th>Table 4. Formation of the Cyclic Urea.</th>
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<tbody>
<tr>
<td>Catalyst (eq)</td>
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<tr>
<td>--------------</td>
</tr>
<tr>
<td>1* CoCp(CO)₂ (0.2)</td>
</tr>
<tr>
<td>2* CoCp(CO)₂ (0.2)</td>
</tr>
<tr>
<td>3* CoCp(CO)₂ (0.2)</td>
</tr>
<tr>
<td>4* Co₂(CO)₈ (0.2), CyNH₂ (1.2)</td>
</tr>
<tr>
<td>5 Co₂(CO)₈ (1.2)</td>
</tr>
</tbody>
</table>

a) Reactions were performed under microwave irradiation: 80 °C, 50 mg scale.
reaction to promote liberation of the CO ligand.\textsuperscript{28} When this reaction was examined thermally, only starting material was returned (Entry 5, Table 4). However, future studies involving the use of the cyclohexylamine catalyst in the thermal reaction are suspected to provide some amount of desired product.

Surprisingly, the Co\textsubscript{2}(CO)\textsubscript{8} catalyst was found to afford a different product than the CpCo(CO)\textsubscript{2} catalyst, suggesting that the product of the CpCo(CO)\textsubscript{2} catalyzed reaction is not in fact the cyclic urea. In our future work, identity of the product of the Co\textsubscript{2}(CO)\textsubscript{8} catalyzed reaction will be confirmed, and the identity of the product of CpCo(CO)\textsubscript{2} catalyzed reaction will be determined. Furthermore, related catalysts such as Fe\textsubscript{2}(CO)\textsubscript{9} will be applied to this chemistry, and additional substrates such as the nitrogen-tethered arylbisnitrile will be examined. Based on preliminary results, however, it is apparent that the chemistry being examined is very promising, due to the high yields of these reactions before optimization of the reaction conditions. Once these products have been identified, this will most likely prove to be a very interesting application of the previously studied [2+2+2] cyclization reactions.
Experimental

**General Methods:** All reactions were preformed in anhydrous solvents under an atmosphere of argon, unless otherwise noted. All solvents and reagents used are commercially available, and were not purified further. THF was obtained from a still to ensure dryness. All microwave reactions were preformed on a CEM microwave, and all NMR spectra were recorded on Varian NMR (400 MHz or 500 MHz) in deuterated chloroform.

**Synthesis of the N,N-Linked Bisnitrile 1a Through the Alkynyl-Mannich Reaction**

The PMB-aminonitrile (0.19 g, 1 eq) was dissolved in DCM (1.7 mL, 0.6 M) combined with n-formaldehyde (0.12 g, 1 eq) and p-toluene sulfonic acid (0.19 g, 1 eq) in the reaction vessel. The reaction was stirred and heated to 60°C for 8 hours before slowly removing the DCM from the reaction through a rotovap. The resulting product was combined with the BOC-alkynyl nitrile (0.19 g, 1 eq) and copper (I) bromide (0.082 g, 0.5 eq) before redissolving the mixture in a solution of 2:1 THF:DMF (0.75 mL:0.375 mL, 0.9 M). The resulting solution was heated to 70°C for 18 hours. The solvent was then removed, followed by an extraction with ethyl acetate and brine three times, combining the organic layers and drying it over sodium sulfate. The residue was purified using silica-gel chromatography [ethyl acetate: petroleum ether (1:10) to (1:1)] to return purified product 2a (230 mg, 68%). Bisnitrile 1a: $^1$H NMR (500MHz, CDCl$_3$) δ 7.26 (d, J= 8.7 Hz, 2H), 6.86 (d, $J_{ab}$= 8.7 Hz, 2H), 4.23 (s, 2H), 4.22 (s, 2H), 3.80 (s, 3H), 3.61 (br s, 2H), 3.40 (br s, 2H), 2.86 (t, J= 6.8 Hz, 2H), 2.48 (t, J= 6.8, 2H), 1.51 (s, 9H). $^{13}$C NMR (500MHz, CDCl$_3$) δ: 159.04, 130.07, 129.60, 118.60, 115.66, 113.86, 82.51, 79.09, 57.39, 55.26, 48.52, 41.67, 28.19, 16.96. Bisnitrile 1b: $^1$H NMR (500MHz, CDCl$_3$) δ 7.24 (d, J= 8.6 Hz, 2H), 6.85 (d,
$J= 8.6 \text{ Hz}, 2H), 4.16 (\text{br s}, 2H), 3.78 (s, 3H), 4.16 (\text{br s}, 2H), 3.78 (s, 3H), 3.65-3.56 (\text{overlap, 4H}), 3.36 (s, 2H), 2.84 (t, J= 6.8 \text{ Hz}, 2H), 2.65 (\text{br s}, 2H), 2.47 (t, J= 6.8 \text{ Hz}, 2H), 1.48 (s, 9H).

Bisnitrile 1c: $^1$H NMR (400MHz, CDCl$_3$) $\delta$ 7.39-7.33 (overlap, 8H), 7.29 (tt, J= 7.0, 1.7 Hz, 2H), 3.72 (s, 4H), 3.45 (s, 4H), 2.91 (t, J= 6.9 Hz, 4H), 2.52 (t, J= 6.9 Hz, 4H). $^{13}$C NMR (400MHz, CDCl$_3$) $\delta$: 137.72, 128.87, 127.58, 118.54, 79.53, 60.37, 58.05, 48.80, 41.92, 16.98.

**Synthesis of the Annulated Pyridazine 2a**

The alkynylbisnitrile 1a (45.4 mg, 0.115 mmol) was added to an oven-dried microwave vessel equipped with a stir bar and purged with argon. An anhydrous solution of CpCo(CO)$_2$ in chlorobenzene (85.7 mg of CpCo(CO)$_2$ in 10.7 mL PhCl, 8.009 mg/mL) was created in an oven-dried scintillation vial. From this CpCo(CO)$_2$ stock solution, 0.52 mL was added to the microwave vessel (4.1 mg, 0.2 eq CpCo(CO)$_2$), along with an additional 1.48 mL of PhCl (0.06 M). The microwave vessel was then capped and subjected to 180$^\circ$C in the microwave for 15 minutes at 300 W. The solvent was removed in vacuo, and the residue was purified by flash chromatography on silica gel to yield the annulated pyridazine 2a (DCM/MeOH 20:1, 27 mg, 60%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 7.21 (d, J= 8.1 Hz, 2H), 6.83 (d, J= 8.1 Hz, 2H), 4.81 (s, 1H), 4.75 (s, 1H), 4.46 (s, 1H), 4.44 (s, 1H), 3.76 (s, 3H), 3.61 (br s, 2H), 3.42 (s, 2H), 3.20 (dd, J= 5.7, 4.5 Hz, 2H), 2.84 (dd, J= 5.7, 4.5 Hz, 2H), 1.45 (s, 9H). $^{13}$C NMR (400 MHz, CDCl$_3$) $\delta$: 159.08, 154.34, 131.99, 130.23, 113.91, 80.72, 77.22, 76.49, 61.78, 55.29, 51.20, 50.99, 49.77, 48.53, 30.07, 29.72, 28.48, 28.39. Pyridazine 2b: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.19 (d, J= 8.5, 2H), 6.82 (d, J= 8.5, 2H), 4.31 (br s, 2H), 3.75 (s, 3H), 3.66 (dd, J= 5.9, 5.5, 2H), 3.61 (br s, 2H), 3.16 (dd, J= 5.9, 5.5, 2H), 3.10 (dd, J= 5.7, 5.3, 2H), 2.77 (dd, J= 5.7, 5.3, 2H), 1.42 (s, 9H).
Pyridazine 2c: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.31-7.18 (overlap, 10H), 3.64 (s, 4H), 3.37 (s, 4H), 3.13 (dd, $J$= 5.8, 5.8 Hz, 4H), 2.74 (dd, $J$= 5.8, 5.8 Hz, 4H).

**Synthesis of the Deprotected Pyridazine 3**

To a solution of 1,2 diazine 2a (22.0 mg, 0.056 mmol) in acetonitrile (0.56 mL), TMSI (0.0223 g, 2 equiv) was added at 0 °C. The solution was stirred under an argon atmosphere at 0 °C. After completion of the reaction (30 min), NaHCO$_3$ (aq) (1.11 mL) was added, and the solution was stirred for 30 minutes at rt. The resulting solution was extracted with DCM (3 x 100 mL). The combined organic layers were washed once with saturated brine and dried over sodium sulfate, and the solvent was removed invacuo. The residue was purified by flash chromatography on silica gel to yield the deprotected 1,2 diazine (DCM/MeOH, 5:1; 14.3 mg, 87% yield): $^1$H NMR (400MHz, CDCl$_3$) $\delta$: 7.21 (d, $J$=7.4, 2H), 6.83 (d, $J$=7.4, 2H), 4.36 (s, 2H), 4.07 (s, 2H), 3.76 (s, 3H), 3.61 (s, 2H), 3.47 (s, 2H), 3.19 (dd, $J$= 3.9, 3.0 Hz, 2H), 2.82 (dd, $J$= 3.9, 3.0 Hz, 2H).

**Synthesis of the Urea 4a**

A solution of deprotected 1,2 diazine (10.7 mg, 0.036 mmol) in DCM (2.14 mL) was prepared, followed by addition of cyclohexylisocyanate (4.98 mg, 1.1 equiv). The solution was stirred at 65 °C for 4 hours. PS-Trisamine (1.0 equiv, 8.1 mg, 4.46 mmol/g) was then added, and the solution was stirred at 50 °C for 12 hours. The PS-trisamine resin was removed through filtration. The solvent was removed from the filtrate in vacuo, and the residue was purified by flash chromatography on silica gel to yield the urea 4a (DCM/MeOH, 20:1; 15.2 mg, 88% yield).
Urea 4b: $^{13}$C NMR (400MHz, CDCl$_3$) δ: 159.20, 158.69, 155.63, 132.35, 130.34, 113.98, 77.23, 77.23, 76.51, 61.65, 55.30, 51.09, 50.44, 49.62, 49.50, 48.71, 34.05, 29.88, 29.71, 25.57, 25.05.

**Synthesis of the Arylbisnitrile 5.**

A 0.6183 g portion of hydroxybenzonitrile (5.196 mmol, 1 eq) was dissolved in 5.196 mL of DCE (1 M) in a round bottom flask equipped with a stir bar. A 0.86 g portion of K$_2$CO$_3$ (6.235 mmol, 1.2 eq) was added to the solution, and the resulting mixture was stirred at room temperature for 30 minutes before adding a 0.431 mL portion of bromoacetonitrile dropwise (6.235 mmol, 1.2 eq). A reflux condenser was attached to the round bottom flask, and the resulting mixture was refluxed for 20 hours. The solvent was removed in vacuo before extracting the product with brine and ethyl acetate (3 x 100 mL). The organic layers were combined and dried over sodium sulfate, and the solvent was removed in vacuo. The residue was purified by flash chromatography on silica gel to yield the arylbisnitrile 5 (Pet. Ether/EtOAc, 3:1; 0.7101 g, 86% yield): $^1$H NMR (500MHz, CDCl$_3$) δ: 7.62-7.68 (overlap, 2H), 7.20 (ddd, $J= 7.6, 7.6, 0.9$ Hz, 1H), 7.12 (br d, $J= 8.4, 1H$), 4.92 (s, 2H). $^{13}$C NMR (500MHz, CDCl$_3$) δ: 157.60, 134.56, 134.44, 123.36, 115.26, 113.93, 112.54, 103.20, 53.81.

**Synthesis of the Triazine 6a**

The arylbisnitrile 5 (55.9 mg, 0.3538 mmol) was added to an oven dried microwave vessel equipped with a stir bar and purged with argon. An anhydrous solution of CpCo(CO)$_2$ in benzonitrile (24.9 mg of CpCo(CO)$_2$ in 0.69 mL PhCl, 36.1 mg/mL) was created in an oven-dried scintillation vial. From this CpCo(CO)$_2$ stock solution, 0.35 mL was added to the microwave vessel (12.7 mg, 0.2 eq CpCo(CO)$_2$, 1 M). The microwave vessel was then capped
and subjected to $180^\circ$ C in the microwave for 10 minutes at 300 W. The solvent was removed in vacuo, and the residue was purified by flash chromatography on silica gel to yield the triazine 6a (Pet. Ether/EtOAc, 10:1, 41 mg, 44% yield): $^1$H NMR (500MHz, CDCl$_3$) $\delta$: 8.40 (d, $J= 6.0$ Hz, 2H), 8.20 (ddd, $J= 7.8$, 1.2, 1.1 Hz, 1H), 7.55 (dd, $J= 1.7$, 1.2 Hz, 1H), 7.54 (d, $J= 1.1$ Hz, 1H), 7.45-7.55 (overlap, 4H), 5.25 (br s, 2H). $^{13}$C NMR (500MHz, CDCl$_3$) $\delta$: 160.14, 157.17, 148.99, 148.27, 138.31, 133.97, 130.10, 129.76, 128.41, 128.17, 123.75, 122.96, 122.22, 112.49, 29.71.
References


Appendix

1: N,N-Linked Alkynylbisnitrile 1a $^1$H NMR Spectrum
2: N,N-Linked Alkynylbisnitrile 1a $^{13}$C NMR Spectrum
3: N,N-Linked Alkynylbisnitrile 1b $^1$H NMR Spectrum
4: N,N-Linked Alkynylbisnitrile 1c $^1$H NMR Spectrum
5: N,N-Linked Alkynylbisnitrile 1c $^{13}$C NMR Spectrum
6: Annulated Pyridazine 2a $^1$H NMR Spectrum
7: Annulated Pyridazine 2a $^{13}$C NMR Spectrum
8: Annulated Pyridazine 2b $^1$H NMR Spectrum
9: Annulated Pyridazine 2c $^1$H NMR Spectrum
10: Deprotected Pyridazine 3 $^1$H NMR Spectrum
11: Urea 4b $^{13}$C NMR Spectrum
12: O-Linked Arylbisnitrile 5 $^1$H NMR Spectrum
13: O-Linked Arylbisnitrile 5 $^{13}$C NMR Spectrum
14: 1,2,4-Triazine 6a $^1$H NMR Spectrum
15: 1,2,4-Triazine 6a $^{13}$C NMR Spectrum