To the Graduate Council:

I am submitting herewith a dissertation written by Ashleigh Lauren Prince entitled "Homogeneous and Heterogeneous Approaches to 1,2,4-Triazine-Accelerated Copper-Catalyzed Azide-Alkyne Cycloadditions." I have examined the final electronic copy of this dissertation for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, with a major in Chemistry.

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Homogenoeous and Heterogeneous Approaches to 1,2,4-Triazine-Accelerated Copper-Catalyzed Azide-Alkyne Cycloadditions

A Dissertation Presented for
the Doctor of Philosophy
Degree
The University of Tennessee, Knoxville

Ashleigh Lauren Prince
August 2011

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For my Granny

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Abstract

Over the last decade, the domain of click chemistry has grown exponentially and has significantly impacted the fields of organic synthesis, medicinal chemistry, molecular biology, and materials science. The ideal model of a click reaction has become the copper-catalyzed azide-alkyne cycloaddition (CuAAC). Inherent limitations of CuAAC, including high temperatures, long reaction times, and difficult purifications, have been minimized by the development of nitrogen-based ligands. Herein, we present a novel application of 1,2,4-triazines by investigating their use as accelerants for CuAAC.

A diverse library of 1,2,4-triazines were synthesized in order to examine the molecular determinants of their catalytic activity. These ligands were found to be potent accelerants, at catalytic concentrations, in the presence of both copper(I) and copper(II) salts. Remarkably, these catalyzed reactions proceeded at room temperature, generating high isolated yields, in both polar and nonpolar solvents. 5,6-Diphenyl-3-(pyridin-2-yl)1,2,4-triazine was the most active ligand studied, producing an 89% yield in a model click reaction within one hour. Additional experiments with an array of azides and alkynes yielded similar results, defining a broad substrate scope for 1,2,4-triazines as catalysts for click chemistry.

Heterogeneous 1,2,4-triazines were designed using different solid supports and different sites of attachment with respect to the 1,2,4-triazine ligand. The primary advantages offered by these immobilized catalysts are the

prevention of metal contamination in 1,2,3-triazole products and the recyclability of the catalyst. Results indicated that 1,2,4-triazine-functionalized silica was a more effective accelerant of CuAAC, whereas polystyrene-supported 1,2,4-triazines displayed modest activity. In coordination with copper(II), 1,2,4-triazines appended onto silica generated isolated yields greater than 90% after four consecutive reaction cycles with minimal copper leaching. Further research will utilize both homogeneous and heterogeneous 1,2,4-triazine-accelerated CuAAC in the derivatization of solid supports for energy-related chemical processes and in the synthesis of novel enzyme inhibitors.

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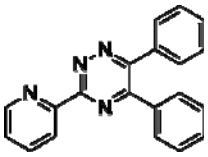
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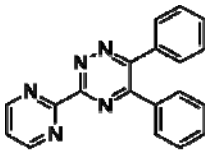
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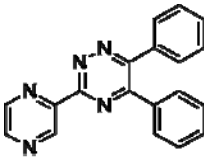
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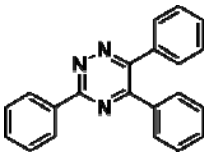
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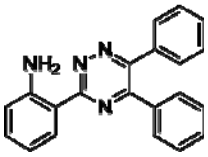
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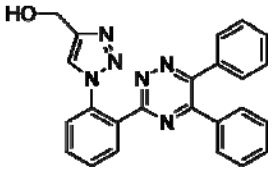
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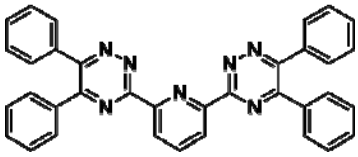
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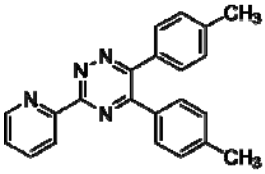
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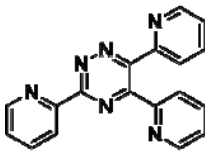
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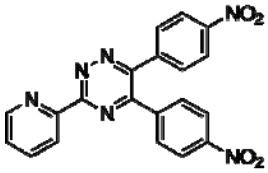
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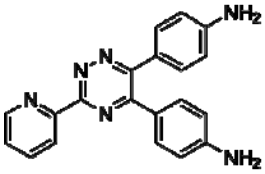
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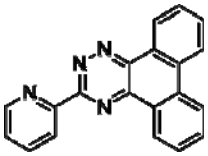
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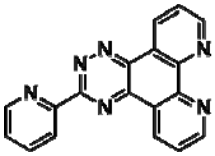
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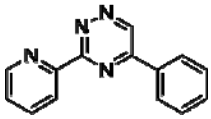
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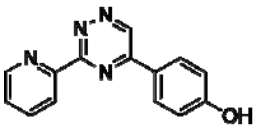
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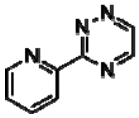
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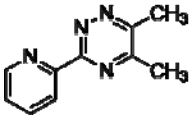
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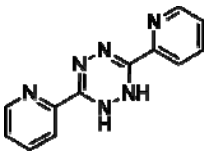
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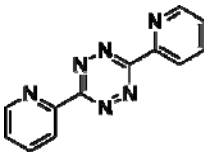
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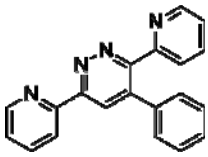
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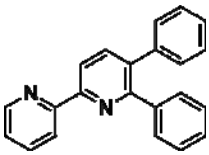
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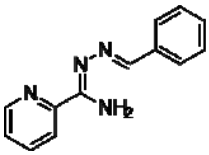
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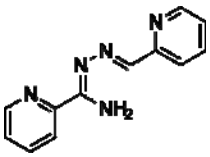
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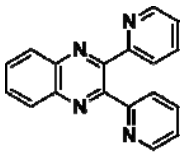
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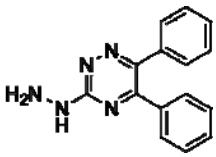
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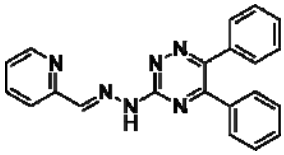
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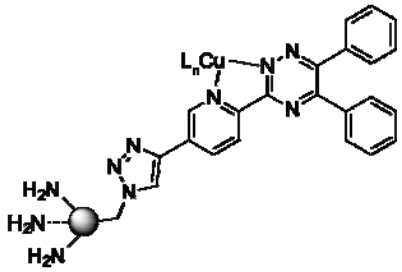


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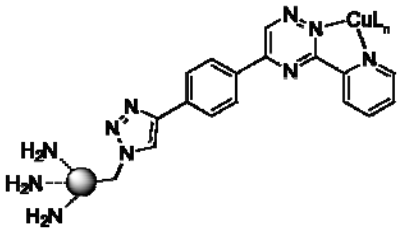


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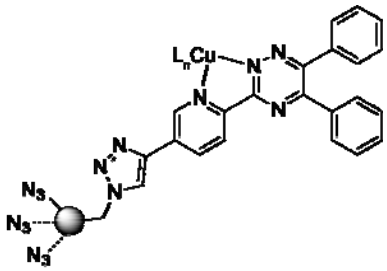
Summary of Heterogeneous Polystyrene Catalysts



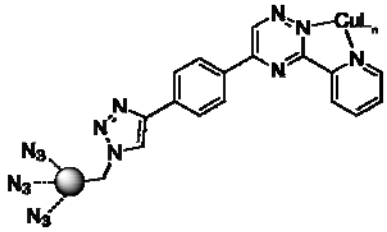
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4-24 Cu(II)
4-42 Cu(II) (Low Loading)



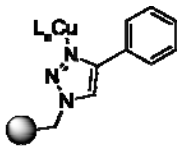
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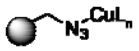
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4-28 Cu(II)



4-29 Cu(I)
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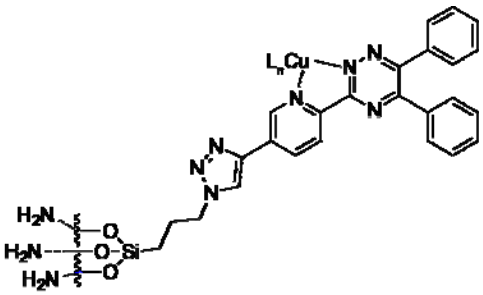


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4-46 Cu(II) (Low Loading)

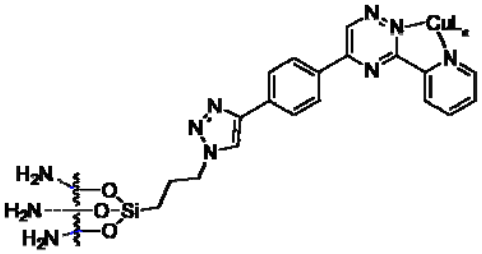


4-36 Cu(I)
4-37 Cu(II)

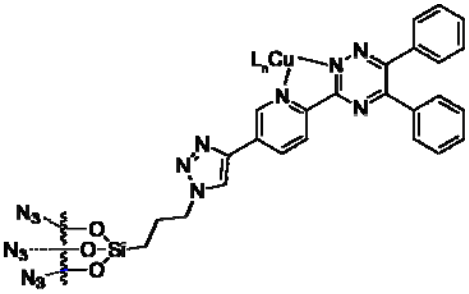
Summary of Heterogeneous Silica Catalysts



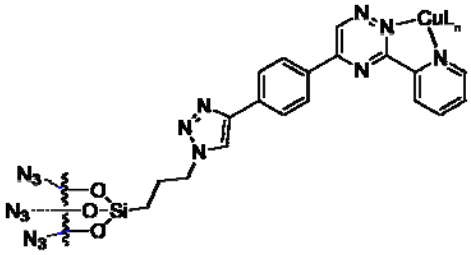
4-54 Cu(I)
4-55 Cu(II)



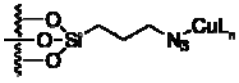
4-56 Cu(I)
4-57 Cu(II)



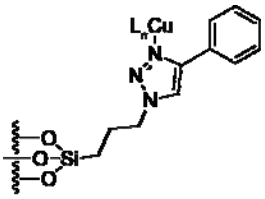
4-58 Cu(I)
4-59 Cu(II)



4-60 Cu(I)
4-61 Cu(II)



4-64 Cu(I)
4-65 Cu(II)



4-66 Cu(I)
4-67 Cu(II)

Abbreviations and Acronyms

ACN	Acetonitrile
AcOH	Acetic Acid
Br_2	Bromine
$CHCl_3$	Chloroform
DCE	Dichloroethane
DCM	Dichloromethane
DMF	N,N-Dimethylfomamide
CuAAC	Copper-Catalyzed Azide-Alkyne Cycloaddition
$Cu(BF_4)_2 \bullet 6H_2O$	Copper tetrafluoroborate hexahydrate
CuCN	Copper nitrate
CuI	Copper iodide
$[Cu(MeCN)_4]^+BF_4^-$	Tetrakis(acetonitrile-N)copper(I) tetrafluoroborate
$CuSO_4 \bullet 5H_2O$	Copper sulfate pentahydrate
Et_2O	Diethyl ether
Et_3N	Triethylamine
EtOAc	Ethyl acetate
EtOH	Ethanol
GC-MS	Gas chromatography – mass spectroscopy
H_2SO_4	Sulfuric acid
HBTU	O-Benzotriazole-N,N,N',N'-tetramethyl-uronium-hexafluoro-phosphate
HCl	Hydrochloric acid
HDAC	Histone deacetylase
HNO_3	Nitric acid
HOBt	1-Hydroxybenzotriazole hydrate
HPLC	High-pressure liquid chromatography
ICP-OES	Inductively coupled plasma – optical emission spectroscopy
IR	Infrared spectroscopy
KBr	Potassium bromide
KCN	Potassium cyanide
$KMnO_4$	Potassium permanganate
KOH	Potassium hydroxide
LC/MS	Liquid chromatography-mass spectroscopy
MeCN	Acetonitrile
MeOH	Methanol
MMP	Matrix metalloproteinase
MOF	Metal-organic framework
MW	Microwave
$NaHCO_3$	Sodium bicarbonate
NaN_3	Sodium azide
$NaNO_2$	Sodium nitrite

NH_4OAc	Ammonium acetate
NMP	N-Methylpyrolidinone
NMR	Nuclear magnetic resonance
NPM	Non-precious metal
ORR	Oxygen reduction reaction
$Pd(OAc)_2$	Palladium(II) acetate
$Pd(PPh_3)_2Cl_2$	Bis(triphenylphosphine)palladium(II) chloride
SeO_2	Selenium dioxide
TBAB	Tetrabutylammonium bromide
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBTA	Tris(benzyltriazolylmethyl)amine
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
$SnCl_2 \cdot 2H_2O$	Tin(II) chloride dihydrate
UV-Vis	Ultraviolet – visible spectroscopy

Chapter 1

Fundamentals of Click Chemistry and Azide-Alkyne Cycloadditions

1.1 The "Click Chemistry" Philosophy

An examination of molecules synthesized by nature reveals numerous examples of carbon-heteroatom linkages, including nucleic acids, proteins, and polysaccharides. This remarkable paradigm of combinatorial chemistry is simply nature's way of generating large, diverse oligomers. Following nature's lead, the term "click chemistry" was coined and described by K.B. Sharpless *et al.*,[1] as being "*modular, wide in scope, high yielding, creating only inoffensive by-products (that can be removed without chromatography), stereospecific, simple to perform, and requiring benign or easily removed solvent*" and click chemistry has recently been the subject of numerous reviews.[2-5] In other words, the term is meant to signify that joining molecular building blocks is as easy to execute as "clicking" together two pieces of a jigsaw puzzle (Figure 1.1). The two puzzle pieces can only make a connection with each other when in a specific orientation and must link together regardless of what other pieces are already attached to them.

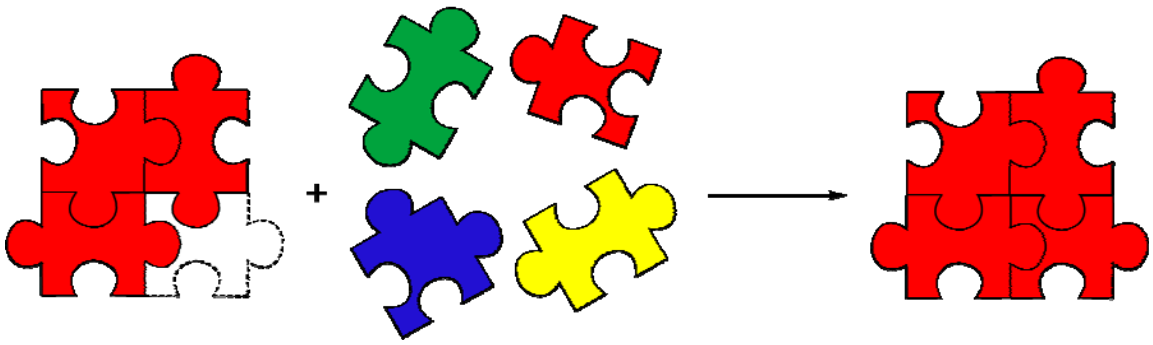


Figure 1.1 Figurative Illustration of "Click Chemistry."

Meeting the requirements of click chemistry is undoubtedly a tall order. Nevertheless, several reactions have proven to meet, or exceed, all the necessary requirements. Examples include additions to carbon-carbon bonds, such as oxidative addition, nucleophilic ring opening, including those of aziridines and epoxides, carbonyl chemistry, and several cycloaddition reactions (Figure 1.2).[1,6] However, it is the copper-catalyzed azide-alkyne cycloaddition (CuAAC) yielding 1,2,3-triazoles that has risen to the occasion and became the ideal model of a click reaction.

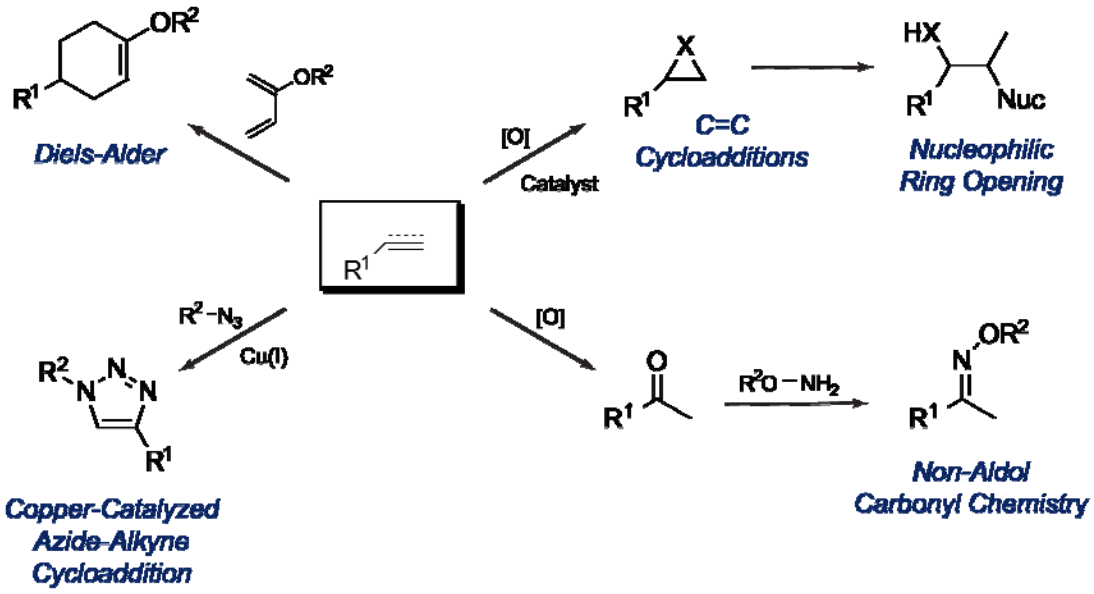


Figure 1.2 Reactions Meeting the Criteria of Click Chemistry.
Adapted from Moses *et al.*[6]

1.2 Importance of 1,2,3-Triazoles

The 1,2,3-triazole heterocycle has attracted a considerable amount of attention from a drug discovery standpoint due to its high chemical stability (generally inert to severe hydrolytic, reducing, and oxidizing conditions), strong dipole moment, aromatic character, and hydrogen bond accepting capabilities.[3] These characteristics allow 1,2,3-triazoles to effectively interact in numerous ways with biological molecules, such as serving as a mimic for peptide bonds.[7] The development of click chemistry has sped up the process of drug discovery, resulting in numerous drug compounds containing 1,2,3-triazoles (Figure 1.3). Examples of such drugs include tazobactam[8] (**1-1**), a penicillin derivative, resveratrol analogue[9] **1-2**, and histone deacetylase inhibitor[10] **1-3**. In addition to drug discovery, 1,2,3-triazoles been successfully utilized as components of polymers and metal coatings[11] due to their strong affinity for metal ions and therefore have utilized in materials science applications.[12,13]

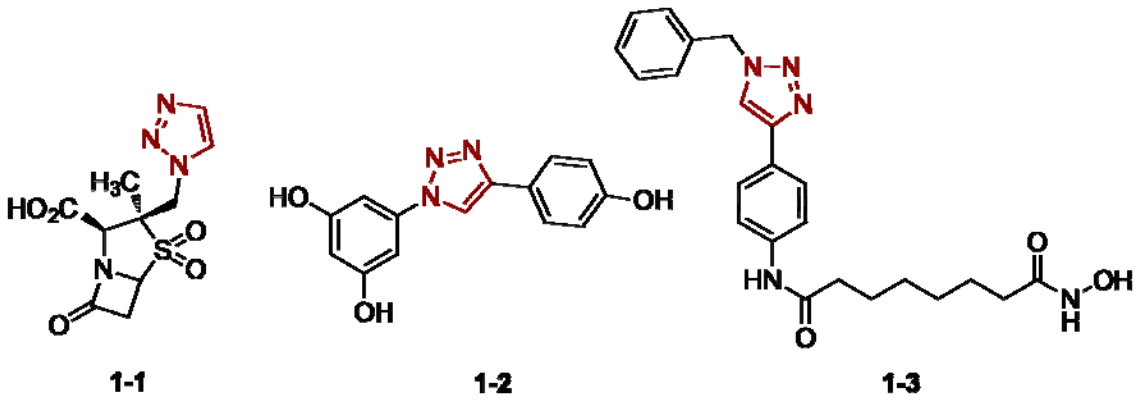


Figure 1.3 Drug Compounds Containing the 1,2,3-Triazole Scaffold.

1.3 Azide-Alkyne Cycloadditions

Azide-alkyne cycloadditions were first studied by Rolf Huisgen and coworkers during the course of their studies of 1,3-dipolar cycloadditions.[14] At first, the cycloaddition of azides with olefins received greater attention from synthetic chemists than the corresponding reaction with alkynes. However, the azide-alkyne cycloaddition has many unique and appealing characteristics. First, the product 1,2,3-triazole is a stable aromatic compound. Second, azides and alkynes are both relatively nonpolar, neither acidic nor basic, and incapable of forming hydrogen bonds. Therefore, they are nearly "invisible" to and unreactive with a majority of other functional groups, which allows them to be incorporated into a synthetic scheme when convenient and without concern of their stability if additional transformations are required. Because of this kinetic stability, the cycloaddition reaction of azides and alkynes typically require long reaction times and elevated temperatures to overcome the high activation energy.

The thermal reaction of azides and alkynes results in a mixture of 1,2,3-triazole regioisomers (Figure 1.4). This result can be explained by differences in HOMO-LUMO energy levels of both reactants being of similar magnitude, thus producing an equal ratio of 1,4- and 1,5-disubstituted-1,2,3-triazole. Most recently, research has been focused on selectively generating one regioisomer over the other by employing transition metal catalysts. When copper(I) is used, the 1,4-disubstituted-1,2,3-triazole is synthesized, whereas ruthenium(II)

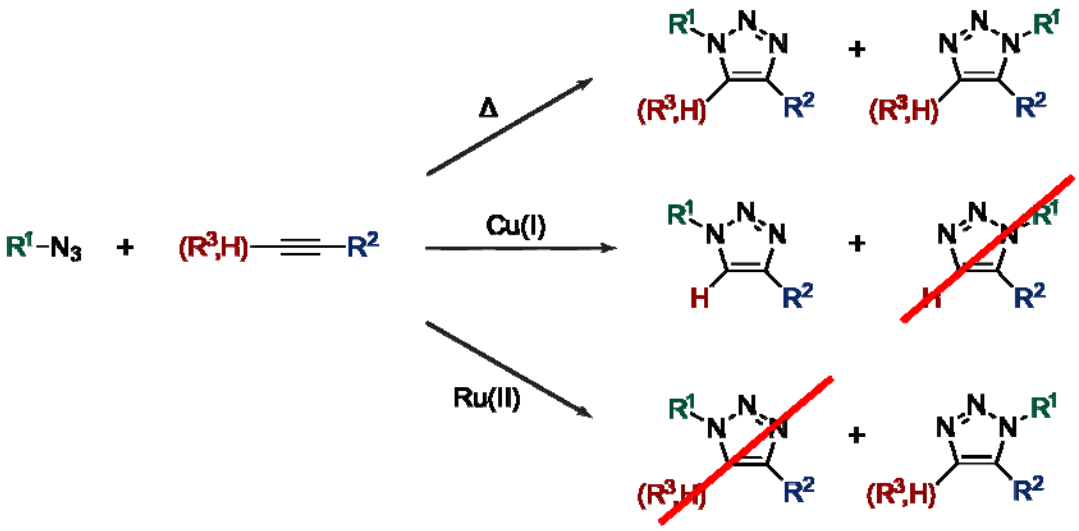


Figure 1.4 Cycloaddition Reactions of Azides and Alkynes.

produces only the 1,5-disubstituted-1,2,3-triazole[15] (or the 1,4,5-trisubstituted-1,2,3-triazole if internal alkynes are used).

1.4 Copper-Catalyzed Azide-Alkyne Cycloadditions (CuAAC)

In addition to generating only the 1,4-disubstituted regioisomer, copper(I) also accelerates the reaction by a factor of 10^6 relative to the uncatalyzed version resulting in tremendously fast reactions that generally proceed at room temperature.[16] The CuAAC reaction is also not significantly affected by electronic and steric properties of the groups attached to the substrates and as a result permits the synthesis of a diverse library of 1,2,3-triazole analogs. Another

advantage is that it can proceed in numerous protic and aprotic solvents and is unaffected by most organic functional groups thereby eliminating the need for protecting groups.[17] The wide substrate scope, high regioselectivity, and readily available starting materials have expanded the array of applications of CuAAC and thus triggered a demand for additional synthetic methods yielding 1,2,3-triazoles under a wider range of conditions.

The synthesis of 1,2,3-triazoles is an extraordinarily robust reaction and can therefore be accomplished with a variety of copper(I) sources, as extensively summarized by Meldal *et al.*[5] The most important factor to bear in mind is maintaining the copper(I) oxidation state at a high level throughout the course of the reaction. For that reason, the most common protocol involves the *in situ* generation of copper(I) from the reduction of copper(II) sulfate with sodium ascorbate in aqueous environments.[18] Alternative aqueous reaction conditions include utilizing copper(0) in the form copper turnings[7] or nanoparticles[19], with or without the addition of a copper(II) source, have also been reported. These reactions usually require longer reaction times due to the slow formation of the active copper(I) species, but the solid copper facilitates the purification of 1,2,3-triazole.

Not all reactions are amenable to aqueous environments; as a result, the development of protocols using organic solvents has also been thoroughly documented. The use of copper(I) halide salts have become prevalent, with copper iodide being preferred because of its increased solubility.[5,20] Another

commonly used copper(I) source with a high solubility in organic solvent includes tetrakis(acetonitrile-N)copper(I) hexafluorophosphate.[21] Finally, various heterogeneous copper(I) sources have developed as click catalysts using a diverse array of insoluble supports such as zeolite[22], charcoal[23], polystyrene[24], and silica[25]. Although many diverse procedures for CuAAC have been established, unraveling the mechanism of this notable organic reaction has proven to be a much more difficult process.

1.5 Mechanistic Considerations of CuAAC

Any proposed mechanism of CuAAC should successfully explain the distinctive body of experimental evidence collected thus far: it is highly regioselective, tolerates most functional groups, has a wide substrate and solvent scope, and can proceed at room temperature. Numerous research groups have published reports containing mechanistic studies of CuAAC,[16,26-31] but the role of the copper catalyst has led to many disputes and revisions of the mechanism. The following stepwise mechanism is a result of multiple calculations and kinetic studies found within the literature and represents the most current view of the mechanism of CuAAC (Figure 1.5). The catalytic cycle begins by formation of π-alkyne copper complex **1-5** in step A. Calculations have indicated that this copper coordination lowers the pK_a of the alkyne by approximately 10 units, therefore allowing it to be easily deprotonated resulting in copper acetylide **1-6**

(step B). It is worth noting that using an excess of copper may result in the formation of insoluble metal aggregates, which may impede the reaction.

Upon coordination of the azide to copper (step C), dinuclear intermediates **1-7** and **1-8** have both been proposed. Recent kinetic studies have indicated the rate of the catalytic process is second order with respect to copper. These results, along with additional evidence discussed below, support the belief that two copper centers are most likely involved in the catalytic cycle. The key bond-forming event occurs in step D. The complexation of the azide activates it toward nucleophilic attack from acetylene carbon C4 at the N3 position of the azide (numbers are from traditional triazole nomenclature) resulting in metallocycle **1-9**. This is consistent with experimental results that illustrate an acceleration of the reaction when electron-withdrawing substituents are on the alkyne. The barrier for ring contraction, step E, is very low and therefore triazole-copper derivative **1-10** is generated very rapidly. Proteolysis, step F, releases the 1,2,3-triazole product and regenerates the copper catalyst, **1-4**, thereby completing the cycle.

A recent report analyzing and comparing all of the proposed mechanistic intermediates of CuAAC has been published (Table 1.1).[31] The thermal, uncatalyzed reaction resulting in regioisomers is explained by their nearly analogous energy barriers (entry 1). All proposed intermediates containing copper (entries 2-6) clearly indicate a preference for the 1,4-triazole, illustrating the importance of the copper to regioselectivity. The mononuclear (entries 2-3) and tetranuclear (entry 5) copper complexes do show a substantial decrease in

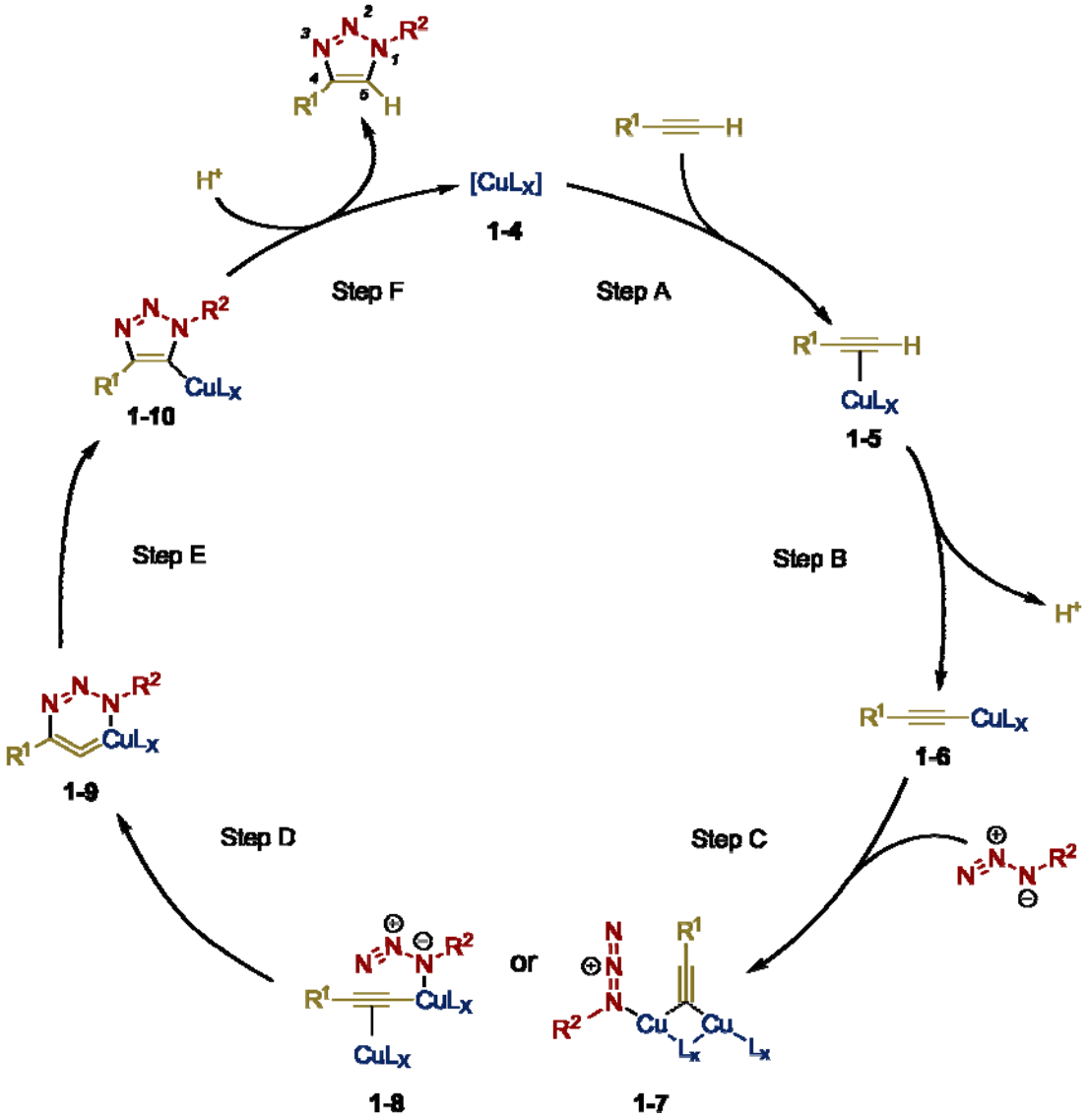


Figure 1.5 Proposed Catalytic Cycle of CuAAC.

Table 1.1 Activation Energies of Several Proposed Intermediates of CuAAC.[31]

Entry	Proposed Intermediate	Activation Energy (kcal/mol) 1,4-triazole	1,5-triazole
1	uncatalyzed	36.1	35.6
2	mononuclear copper acetylide	27.1	40.1
3	mononuclear π-complex	29.1	34.0
4	dinuclear π-complex	21.7	27.6
5	tetranuclear copper acetylide	28.5	38.7
6	dinuclear copper acetylide	16.0	20.4

the activation barrier compared to the uncatalyzed process. However, it is the dinuclear copper species (entries 4 and 6) that posses the lowest activation energies, with the dinuclear acetylide being the lowest at 16.0 kcal/mol. These results clearly explain the observed regioselectivity, rate acceleration, and second order kinetics of the copper species.

The common byproducts of CuAAC result from oxidative acetylenic couplings[3] also catalyzed by copper(I) (Figure 1.6), with the Glaser coupling being the most studied example (**1-11**).[32] These side reactions result from the thermodynamic instability of the copper(I) oxidation state.[3] However, several methods can be used to minimize oxidative byproducts, such as the addition of a reducing agent, using an oxygen-free atmosphere, and employing a copper-binding ligand.

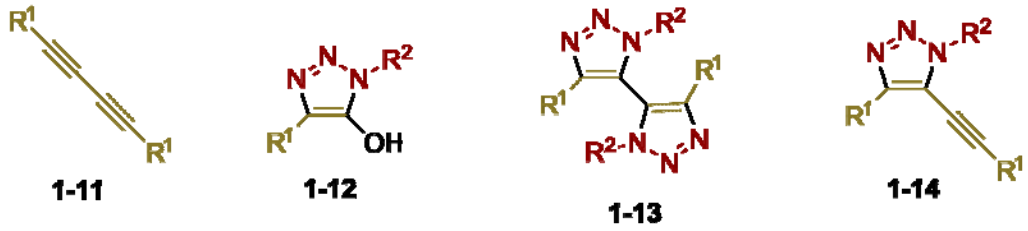


Figure 1.6 Common Oxidative Coupling Byproducts Observed in CuAAC Reactions.

1.6 Ligand-Accelerated CuAAC

Although ligands are not required to achieve the catalytic effect of copper(I) in CuAAC, they are often utilized to enhance the rate of the reaction and protect the copper(I) from oxidation. Undoubtedly, nitrogen ligands are the most popular class of ligands for CuAAC.[4] Not only do amines act as ligands, but other potential roles include assisting in the deprotonation of the alkyne, facilitating ligand exchange, and preventing the formation of unreactive copper aggregates. Triamine ligand **1-15** and copper bromide are commonly used in CuAAC reactions and polymerization processes such as ATRP (Figure 1.7). A solid supported version of this catalytic system was also developed, but when reused displayed a gradual decrease in activity resulting from either oxidation of the copper(I) centers or metal leaching.[33] However, better results were obtained using the tripodal complex **1-16**, which can more efficiently protect the copper center from oxidation.[34]

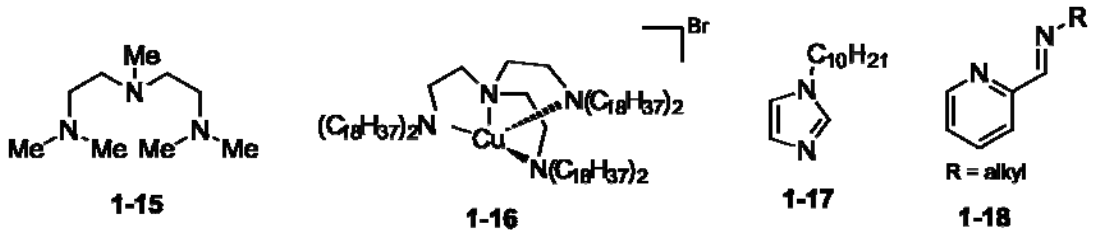


Figure 1.7 Nitrogen-based Accelerants used in CuAAC Reactions.

Imidazole derivatives have also been used as click catalysts. Recently, it was reported that the long alkyl chain of **1-17** was essential to its activity[35] (Figure 1.7). Multiple 1,2,3-triazoles were prepared in high yield using **1-17**; however, reaction conditions were limited to being performed either on water or neat. The first simple imine ligands studied were pyridylimines, such as **1-18**, and were applied to one-pot, simultaneous CuAAC/polymerizations.[36] One inherent drawback to imine ligands is their instability (they must be stored at 0°C under an inert atmosphere).

As early as 2003, polytriazoles were discovered to accelerate CuAAC reactions, and have since become one of most widely utilized ligands for click chemistry. Their application has been focused on bioconjugation reactions in aqueous environments.[37] However, not long after their first application as a CuAAC additive, a comparative study examining different polytriazole architectures was published (Figure 1.8).[38] Remarkably, different trends in activity were observed depending on the type of copper(I) source employed. Amino-triazole **1-19** was the most active ligand used in conjunction with

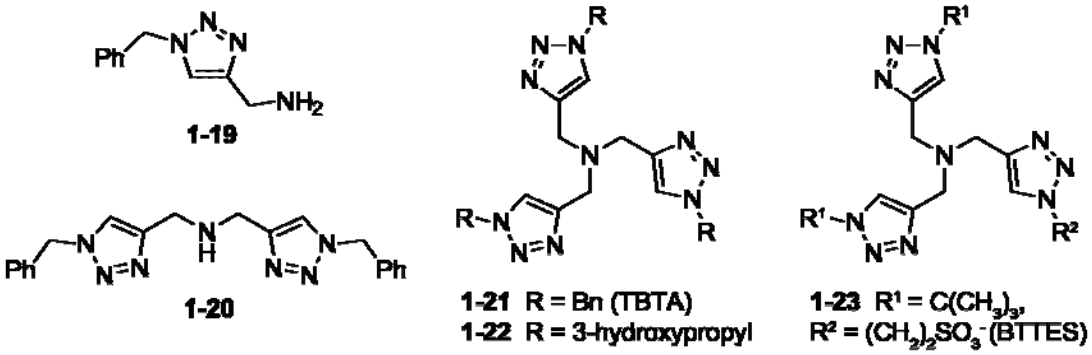


Figure 1.8 Triazole Ligands used in CuAAC Reactions.

copper(II)sulfate and sodium ascorbate, while bis-triazole **1-20** had the highest activity when used with tetrakis(acetonitrile-N)copper(I) hexafluorophosphate. Still, tris-triazoles, tris-(benzyltriazolylmethyl)amine (**1-21**) in particular, have virtually become the only triazole ligands used to accelerate CuAAC reactions.[38-40] A water-soluble derivative of TBTA (**1-22**) containing multiple hydroxy groups, was also synthesized and studied as an accelerant of CuAAC[41], in addition to **2-23** which has demonstrated efficiency *in vivo*.[42] Furthermore, a heterogeneous version of **1-21** has also been reported and can be reused up to nine consecutive times without loss of activity, although long reaction times were required in order to ensure high yields.[24]

Most recently, in search of a more active catalyst and additional mechanistic insight, the polydentate trimethylamine scaffold was extended to include “hybrid” ligands.[40] These ligands contain a range of functionalities on the ligand “arms”, including benzimidazole, 2-pyridyl, and 1,2,3-triazole (Figure 1.9). Notably, the catalytic activity of each ligand varied according to the reaction

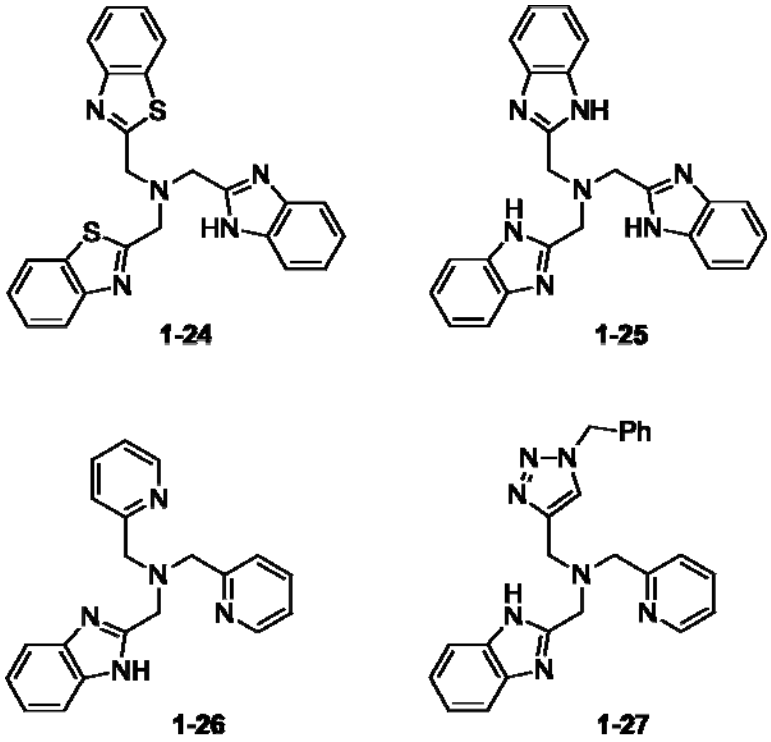
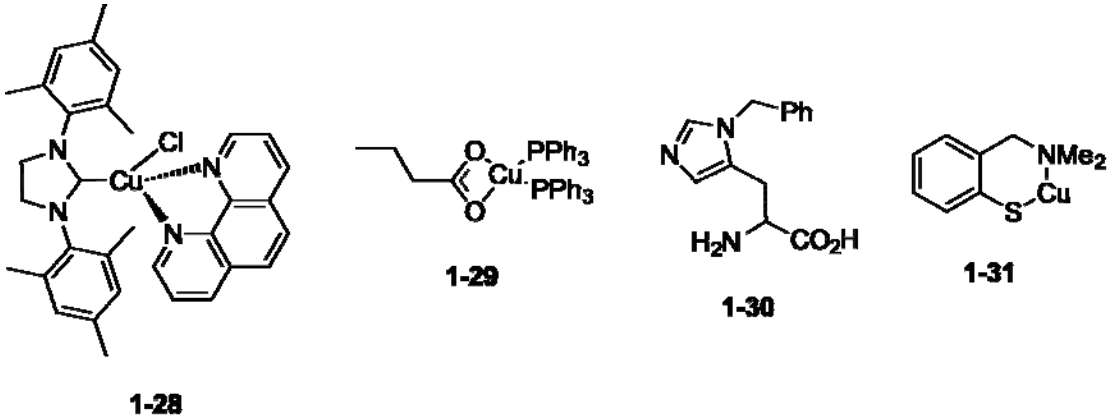


Figure 1.9 Hybrid Ligands used in CuAAC Reactions.

conditions. Hence, whereas **1-24** best performed under dilute reaction conditions, **1-25** was found to be an optimal ligand under concentrated conditions. Ligand **1-26**, a strongly coordinating ligand, was found be the most superior under organic conditions; although, high ligand:metal ratios must be avoided so as to prevent catalyst deactivation.

Additional types of accelerants for CuAAC have also been explored, although not as extensively as nitrogen ligands. N-heterocyclic carbene (NHC) ligand **1-28** has displayed remarkable activity producing 1,2,3-triazoles in high yield under ambient conditions (Figure 1.10). In addition, unlike most NHC

ligands which can only be used under neat or “on water” conditions, **1-28** remains highly active in multiple solvents.[43] Despite the popularity of phosphorous-based ligands in modern organic chemistry, only a very limited number exist for CuAAC.[44,45] One such example is **1-29**, in which triphenylphosphine was shown to improve the catalytic activity of copper carboxylate complexes.[45] Finally, oxygen- and sulfur-based ligands, such as **1-30**[46] and **1-31**[47], represent additional classes of ligands that have scarcely been investigated as CuAAC accelerants due to their requirements for inert reaction conditions. In summary, even though several ligands have been determined to accelerate CuAAC reactions, catalytic activities have been shown to vary extensively depending upon reaction conditions. Because the majority of research involving click chemistry has centered on the application of these ligands toward increasingly complex systems, the identification and investigation of additional CuAAC ligands must continue to move forward in order to keep pace with the increasing demand of modern organic synthesis.



1-28 **1-29** **1-30** **1-31**

Figure 1.10 Less Commonly used Ligands in CuAAC Reactions.

1.7 1,2,4-Triazines as Ligands for CuAAC

In spite of the recognition ligand-accelerated CuAAC has received, common shortcomings have included poor solubility of ligands, isolation of 1,2,3-triazoles, and extended reaction times. As a result, the pursuit of ligands containing novel scaffolds capable of improving the efficiency of click reactions is an ongoing project. Some of the most common heterocyclic scaffolds contained within CuAAC ligands are 1,2,3-triazoles, along with pyridines and benzimidazoles. However, 1,2,4-triazines are also known to coordinate various transition metals, including copper, and their complexes have been studied in great detail.[48-51]

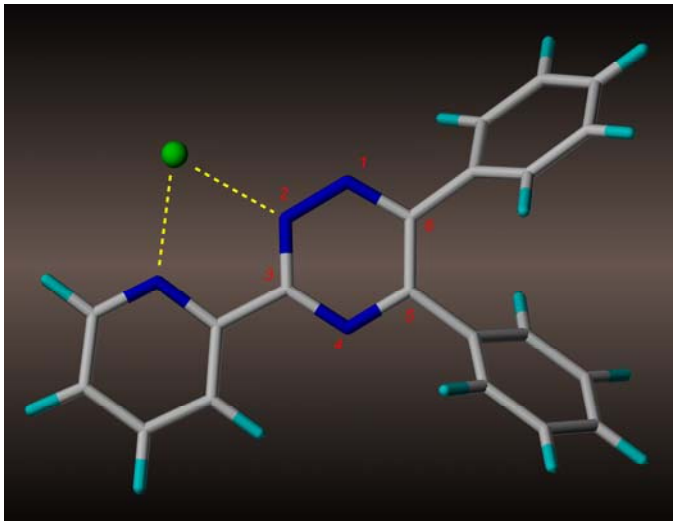


Figure 1.11 Coordination of Copper with 3-(pyridin-2-yl)-1,2,4-triazines.

The complexation of copper by 3-(pyridin-2-yl)-1,2,4-triazines has been shown to occur via coordination with N2 of the triazine and the nitrogen of the 2-pyridyl ring (Figure 1.11).[52,53] Coordination by N2 of the triazine ring is more favorable than coordination through N4 owing to the lack of steric bulk afforded by N1 as opposed the 5-substituent. Furthermore, the electrochemical properties of triazine-copper(II) complexes have been documented and are known to posses increased and positive Cu(II)/Cu(I) reduction potentials.[54] Triazine complexation is also thought to stabilize the copper(I) species by disfavoring disproportionation.[53,54]

From a synthetic viewpoint, 1,2,4-triazines are easily accessible from the same common precursors as 1,2,4-triazoles[55-57] (Figure 1.12), which have been

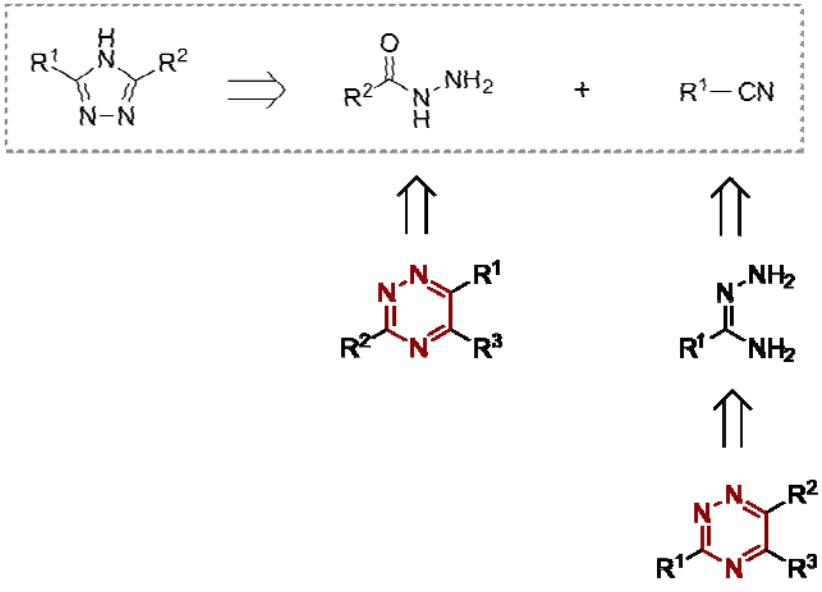


Figure 1.12 Retrosynthetic Analysis of 1,2,4-Triazines and 1,2,4-Triazoles.

the focus of numerous projects within our research group. The most basic 1,2,4-triazines can easily be synthesized in 2 steps from either a nitrile or hydrazide. It is this straightforward synthesis of 1,2,4-triazines, in combination with their propensity to bind copper and stabilize the required copper(I) species, that make them logical candidates as CuAAC accelerants.

1.8 Applications of 1,2,4-Triazine-Accelerated Catalysis

While the number of applications involving CuAAC are immense, we have chosen to narrow the focus of 1,2,4-triazine-accelerated CuAAC to a few select topics of interest to our research group, all of which highlight various advantages of 1,2,4-triazine-accelerated CuAAC. First, the derivatization of solid surfaces will not only allow us to synthesize an insoluble, recyclable version of our own triazine catalyst, but permit the functionalization of energy-related chemical surfaces as well. Both homogeneous and heterogeneous versions of 1,2,4-triazine-accelerated CuAAC have become primary methods in the synthesis of a library of 1,2,3-triazoles with activities ranging from histone deacetylase (HDAC) inhibitors to oxidation catalysts. Finally, the catalytic efficiency of 1,2,4-triazines as ligands in other organometallic transformations is currently under investigation.

1.8.1 Derivatization of Solid Surfaces

One of the prime advantages of utilizing 1,2,4-triazine ligands is their tight coordination of copper, thereby not contaminating the 1,2,3-triazole products with residual copper. This potential contamination is especially of concern when attempting to modify surfaces that will ultimately be used to coordinate other transition metals. As a result, 1,2,4-triazine-accelerated CuAAC has successfully been applied to the modification of several solid supports. Heterogeneous 1,2,4-triazine catalysts have been immobilized on both polystyrene and silica supports, hence generating a reusable version of its homogeneous counterpart. (Figure 1.13A). Current research efforts are focused on the synthesis of ligand-modified carbon surfaces (Figure 1.13B), which have immediate applications as catalysts in the oxygen reduction reaction (ORR).

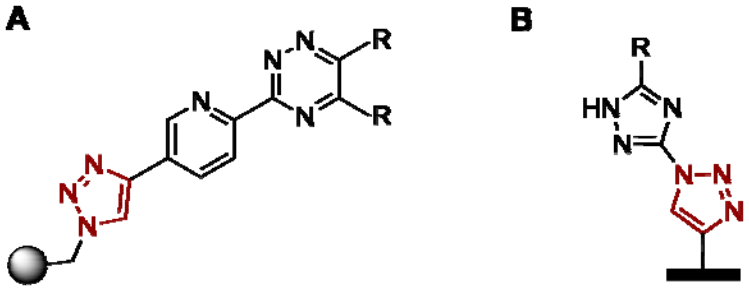


Figure 1.13 Examples of Surface Modification using CuAAC. **(A)** Heterogeneous 1,2,4-Triazine Catalysts. **(B)** Derivatization of Carbon Surfaces.

1.8.2 Synthesis of Small Molecules: Medicinal Targets and Catalysts

Immobilized 1,2,4-triazine ligands also provide several benefits, one of which is simplifying the purification of products. By taking advantage of this and using a combinatorial approach, a library of 1,2,3-triazole -containing compounds can be generated quickly. Due to our interest in both medicinal chemistry and catalysis, we have designed numerous scaffolds incorporating both 1,2,3- and 1,2,4-triazoles that have dual functions (Figure 1.14). By appending a hydroxamic acid zinc-binding-group (ZBG) and aromatic cap group to these scaffolds, potential HDAC inhibitors will be synthesized. However, modification of R^1 and R^2 to include additional nitrogen heterocycles will result in novel ligands for catalysis and their activity for various energy-related processes, such as hydrocarbon oxidation and biomass conversion, will then be determined.

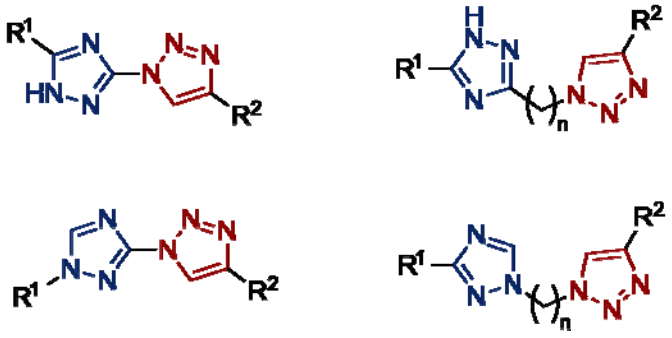


Figure 1.14 Molecular Scaffolds Containing 1,2,3-Triazole and 1,2,4-Triazole Heterocycles.

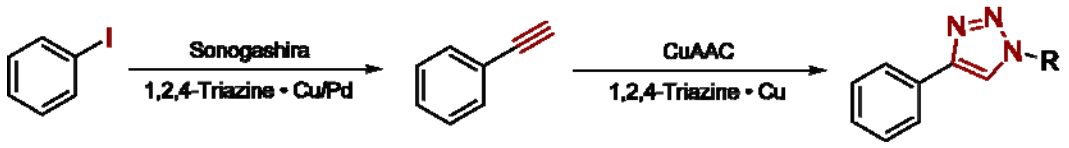


Figure 1.15 1,2,4-Triazine-Accelerated Catalysis of Sonogashira Reaction and CuAAC.

1.8.3 1,2,4-Triazine-Accelerated Sonogashira Reaction

In addition to copper, 1,2,4-triazines are well-known for coordinating a wide array of transition metals. Among those metals is palladium, which can be used in combination with copper, to catalyze Sonogashia Reactions. Because the synthesis of aromatic alkynes via Sonogashira Reactions is a common precursor reaction in combination with CuAAC, we chose to investigate 1,2,4-triazine-accelerated Sonogashira Reactions (Figure 1.16). The most common drawback of this popular reaction is metal contamination of products, which may perhaps be alleviated by the addition of 1,2,4-triazine ligands. By identifying other organometallic reactions in which 1,2,4-triazines demonstrate activity, their synthetic value as ligands will ultimately increase.

1.9 Scope of This Work

This dissertation describes research directed toward the application of 1,2,4-triazines as catalysts for copper-catalyzed azide-alkyne cycloadditions

(CuAAC). Chapters 2 and 3 are focused on homogeneous 1,2,4-triazines. Chapter 2 discusses the design and synthesis of 1,2,4-triazine ligands and derivatives thereof, while chapter 3 summarizes the catalytic activity of 1,2,4-triazines toward CuAAC reactions.

Heterogeneous 1,2,4-triazines are the focal point of chapters 4 and 5. Chapter 4 presents the synthesis of 1,2,4-triazines on various insoluble supports, including polystyrene and silica. Chapter 5 then compares the catalytic activity of heterogeneous 1,2,4-triazines in regard to CuAAC and the Sonogashira Reaction. Finally, chapter 6 describes ongoing efforts of CuAAC towards the derivatization of solid surfaces for energy-related chemical processes.

Chapter 2

Design and Synthesis of 1,2,4-Triazine Ligands

2.1 Background and Significance

Since the first 1,2,4-triazine was synthesized in 1889,[58] countless descriptions of their synthesis, physical properties, and biological activities have been published, including a recent review by Lindsley *et al*.[57] The 1,2,4-triazine scaffold can be found embedded in molecules with a wide variety of applications (Figure 2.1). However, only a scarcity of isolated natural products, such as **2-1**, contain the 1,2,4-triazine ring system.[59] 1,2,4-Triazines are most frequently utilized in commercial applications, including metal chelators[60] (**2-2**), dyes (**2-3**), and pesticides[61] (**2-4**). In addition, the 1,2,4-triazine scaffold can also function as a pharmacophore in drugs used to treat cancer[62] (**2-5**) and epilepsy[63] (**2-6**). Most recently, 1,2,4-triazine-copper complexes have been isolated and thoroughly characterized.[48-50]

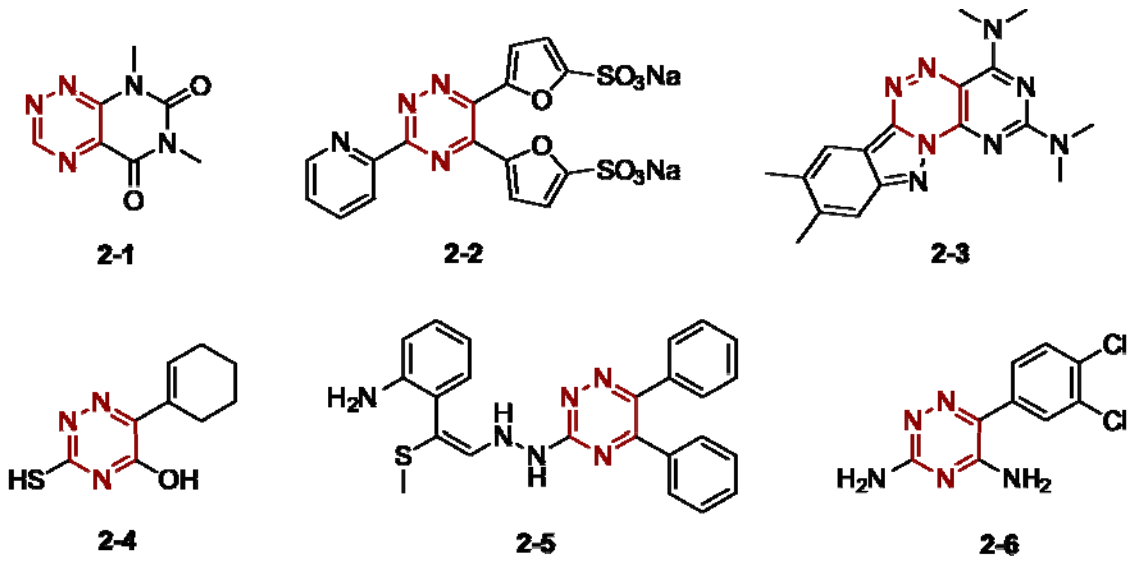


Figure 2.1 Common Molecules Containing the 1,2,4-Triazine Scaffold.

While 1,2,4-triazine copper-complexes have been the subject of numerous manuscripts and the field of click chemistry is continuously growing exponentially, these two subjects have yet to share a common bond. Since CuAAC has emerged over the last decade as an indispensable tool of choice for the connection of highly-functionalized molecules, ligands that accelerate this reaction have become an active area of research, both in our lab and around the world. Chapter 2 summarizes the synthesis of structurally distinct 1,2,4-triazines, while Chapter 3 discusses their immediate application as ligands for CuAAC.

2.2 Strategies for 1,2,4-Triazine Synthesis

The synthesis of 1,2,4-triazines can be best summarized by five basic types of reactions (Figure 2.2).[57] The most commonly employed method is ring closure reactions, which involve the formation of either two or three N-C bonds. Ring transformations can generate 1,2,4-triazines by the reaction of 1,2,4,5-tetrazines with electron-rich dienophiles in a Diels-Alder reaction. Although not explored in this manuscript, aromatization reactions of 1,2,4-triazinones followed by elimination will also yield 1,2,4-triazines. Substituent modification of 1,2,4-triazines can be accomplished using numerous methods, including lithiation, grignard reactions, and nucleophilic substitution. Finally, cyclization reactions of appropriately substituted 1,2,4-triazines will result in the formation of a second heterocyclic ring.

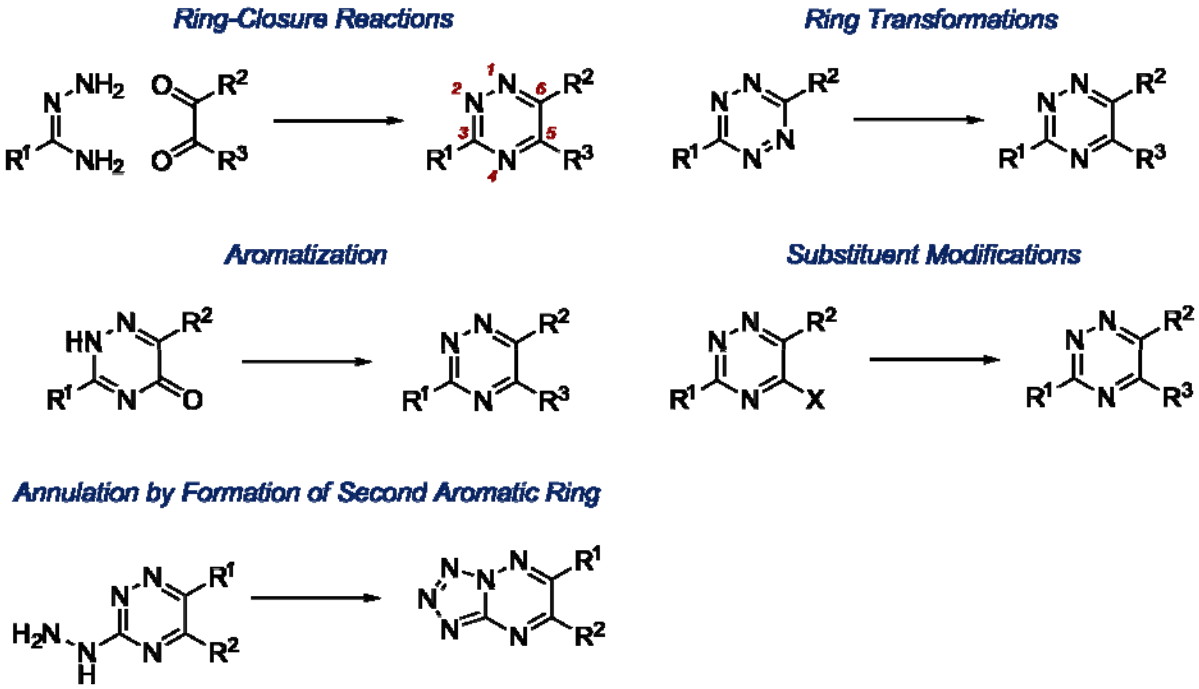


Figure 2.2 Synthetic Strategies for the Synthesis of 1,2,4-Triazines.

The synthetic strategies and structure of 1,2,4-triazines present three regions suitable for modification: the 3-position, the 5- and 6- positions, and the 1,2,4-triazine scaffold itself. By synthesizing a library of 1,2,4-triazines with different stereoelectronic features, it will be possible to determine which characteristics are responsible for the catalytic activity of 1,2,4-triazines in the CuAAC reaction.

2.3 Ring-Closure Reactions

Ring-closure reactions represent the most straightforward method for the synthesis of 1,2,4-triazines. This synthetic route allows various substituents to be installed at the 3-, 5-, and 6-positions of the 1,2,4-triazine ring, beginning from either an amidrazone[55] or a hydrazide[56] and a 1,2-diketone. The major advantage of this synthetic method is that the two necessary building blocks can be combined systematically to quickly generate a combinatorial library of 1,2,4-triazines.

2.3.1 3-Substituted-5,6-Diphenyl-1,2,4-Triazines

The reaction of amidrazones with 1,2-diketones has been among the most studied methods for assembly of 1,2,4-triazines (Figure 2.3A). Amidrazone **2-10** is easily accessible by a reaction of the corresponding nitrile, **2-7**, with hydrazine hydrate at room temperature. The isolated amidrazone **2-10** can then undergo reaction with benzil thereby yielding 1,2,4-triazine **2-13** in a 75% overall yield. Additional nitriles appended to nitrogen-based heterocycles were also successfully converted to 1,2,4-triazines in good overall yields. This synthetic sequence can be carried out with minimal purification as both the intermediate amidrazone and product 1,2,4-triazine can typically be isolated by filtration.

Another robust synthetic method toward 1,2,4-triazines involves the reaction of a hydrazide intermediate, **2-18**, with benzil and ammonium acetate

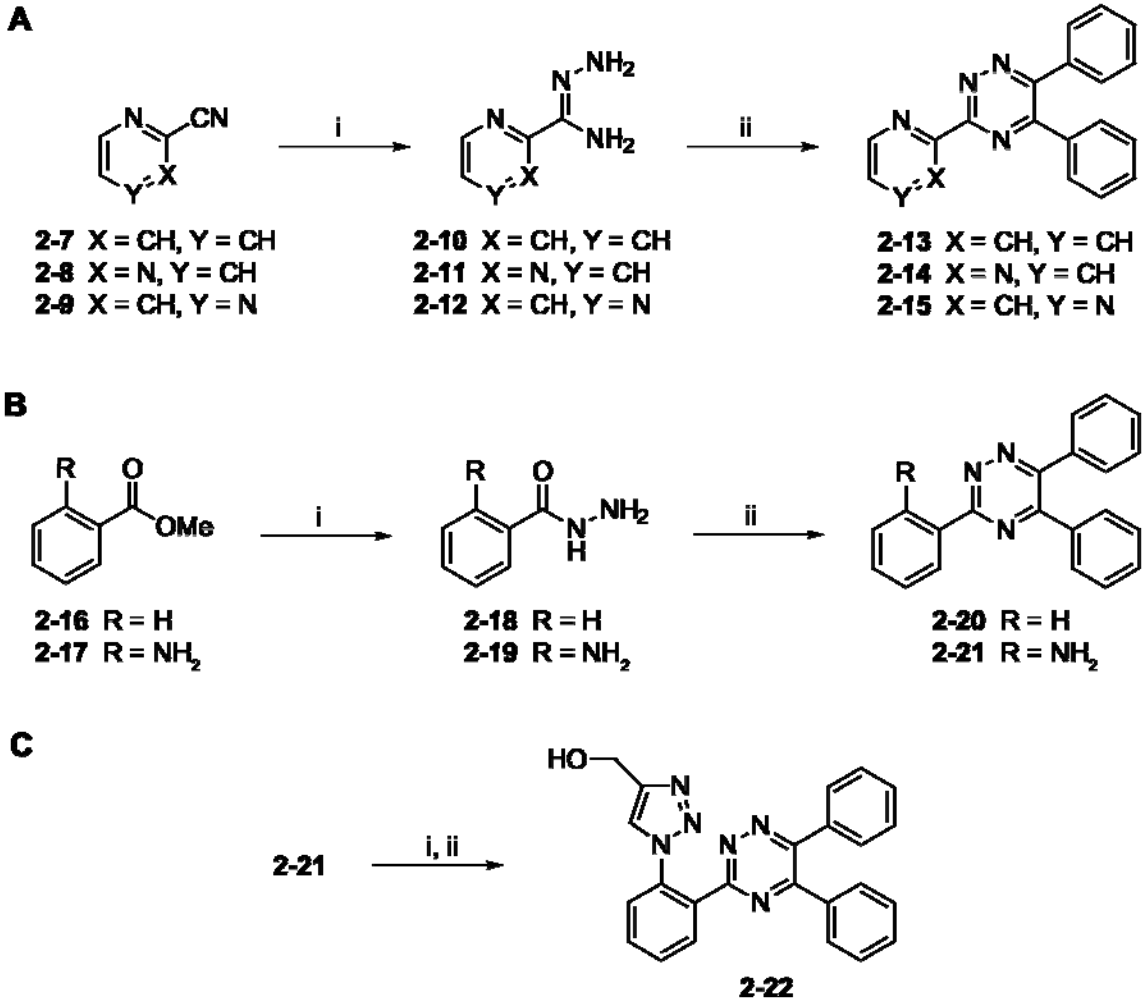
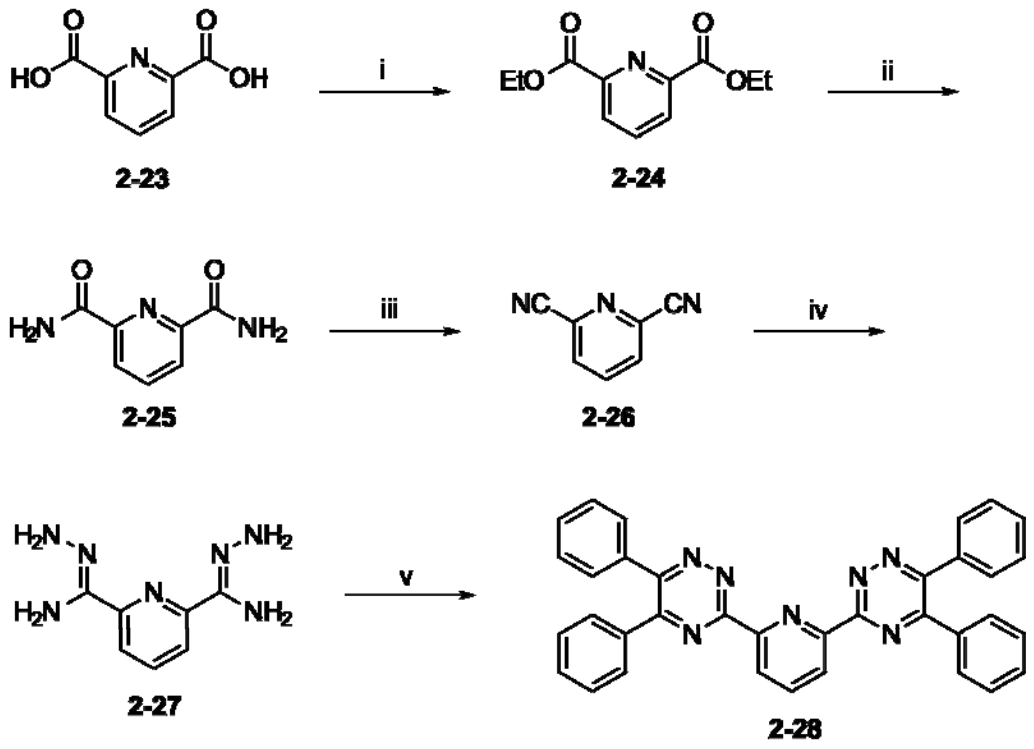


Figure 2.3 Synthesis of 3-Substituted-1,2,4-Triazines. **(A)** (i) hydrazine hydrate, EtOH; (ii) benzil, EtOH, 80°C. **(B)** (i) hydrazine hydrate, MeOH, reflux; (ii) benzil, NH_4OAc, AcOH, MW, 750W. **(C)** (i) $NaNO_2$, NaN_3, EtOAc, HCl, 0°C; (ii) propargyl alcohol, Et_3N, **2-13**, $[Cu(MeCN)_4]^+BF_4^-$, ACN.

(Figure 2.3B). This method generates the 1,2,4-triazine by the formation of three N-C bonds and as a result is best accomplished using microwave irradiation. The formation of the 1,2,4-triazine is usually complete within 10 min, but typical yields only reached 50% most likely due to the use of a conventional microwave and the formation of multiple by-products.

Additional transformation of the amine functional group of 1,2,4-triazine **2-21** was successful (Figure 2.3C). By first converting this aromatic amine into an azide by means of typical Sandmeyer Reaction conditions, we were able to synthesis a 1,2,3-triazole using CuAAC. This 1,2,3-triazole-1,2,4-triazine **2-22**



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Figure 2.4 Synthesis of a Bis-Triazine Derivative. (i) EtOH, HCl, MW, 750W; (ii) NH_4OH, 35°C; (iii) TFAA, Et_3N, THF, 0°C; (iv) hydrazine hydrate, EtOH; (v) benzil, EtOH, 80°C

was successfully isolated by column chromatography in 57% over the two steps and resulted in the attachment of an additional copper-binding functional group to the 1,2,4-triazine.

Due to our success in the synthesis of 1,2,3-triazole-1,2,4-triazine, we next attempted the synthesis of bis-triazine compound **2-28**, which could potentially be a tridentate ligand (Figure 2.4). After formation of bis-ester **2-24**, reaction with ammonium hydroxide resulted in bis-amide **2-25**. Subjecting the bis-amide to dehydrating conditions using trifluoroacetic anhydride yielded bis-nitrile **2-26**, followed by conversion to bis-triazine **2-28** via the intermediate bis-amidrazone, **2-27**. Even though the yield was 16% over the 5 steps, each intermediate could easily be isolated by filtration which eliminated the need for column chromatography and thus allowed the scheme to be completed relatively quickly.

2.3.2 3-Pyridine-5,6-Disubstituted-1,2,4-Triazines

In order to instill diversity into the 5- and 6-positions of the 1,2,4-triazine, substituted 1,2-diketones were synthesized via a Benzoin Condensation (Figure 2.5). Aldehyde **2-29**, after conversion to the intermediate alpha-hydroxy ketone, was oxidized yielding benzil derivative **2-31**, albeit in low yield. Reaction with amidrazone **2-10**, yielded the corresponding 1,2,4-triazine **2-33**. Pyridine aldehydes can also be converted into 1,2,-diketones using the same reaction scheme, thereby synthesizing tripyridine-1,2,4-triazine **2-34**. This addition of

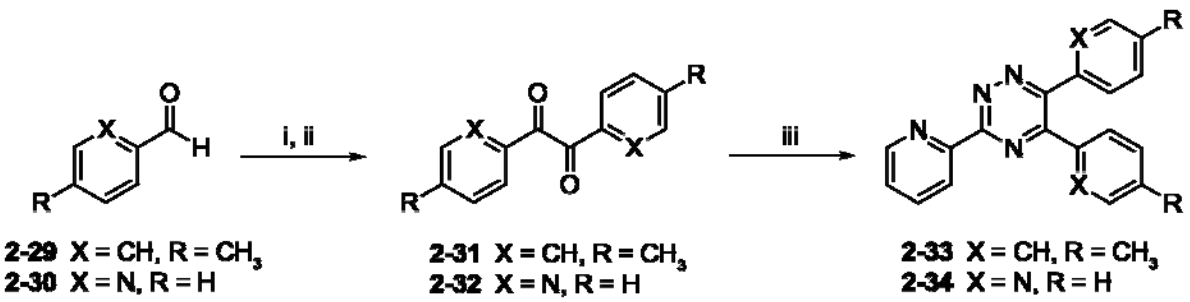


Figure 2.5 Synthesis of 5,6-Disubstituted-1,2,4-Triazines. (i) KCN, EtOH, H_2O, reflux; (ii) HNO_3, reflux; (iii) **2-10**, EtOH, 80°C.

nitrogen atoms within the 5- and 6- substituents will not only alter the electron density of the 1,2,4-triazine, but could also modify the preferred binding site for copper metal.

In order to compliment the electron-donating nature of the methyl substituent on **2-33**, a 1,2,4-triazine containing electron-withdrawing groups was desired. However, aldehydes with strong electron-withdrawing groups, such as nitro groups, are not amenable to the Benzoin Condensation. Instead, Figure 2.6 illustrates the synthesis of a nitro-substituted diketone via an oxazole intermediate. Benzoin, **2-35**, was first acetylated then reacted with ammonium acetate to generate an oxazole. Nitration of this intermediate resulted in **2-37**, which could then be oxidized to yield the nitro-substituted 1,2-diketone **2-38**. Finally, this 1,2-diketone was easily reacted with amidrazone **2-10,** generating 1,2,4-triazine **2-39** in an overall yield of 35%. After multiple attempts to reduce the nitro groups to amines, Pd/C was the found to be the preferred method but difficulties in the isolation resulted in 80% purity of **2-40**.

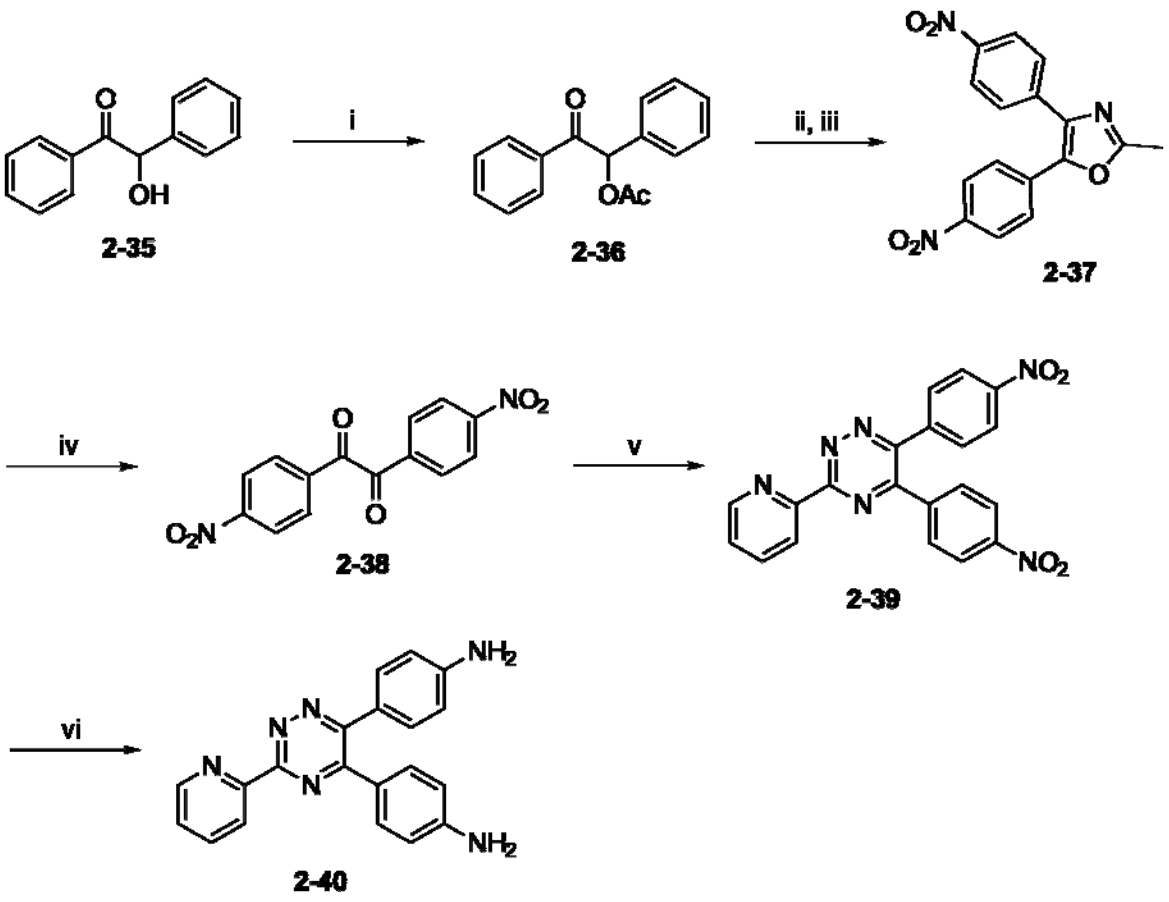


Figure 2.6 Synthesis of Nitro and Amine Containing 1,2,4-Triazines. (i) acetic anhydride, AcOH, HCl, 100°C; (ii) NH_4OAc, AcOH, reflux; (iii) HNO_3, H_2SO_4, 55°C; (iv) NaOAc, Br_2, AcOH, H_2O, reflux; (v) **2-10**, EtOH, 80°C; (vi) hydrazine hydrate, Pd/C, EtOH, reflux.

At first glance, the 1,2,4-triazines discussed thus far may appear to be entirely planar. While the aromatic 3-substituent does in fact lie in the same plane as the 1,2,4-triazine, the 5- and 6-substituents are slightly twisted.[52] In order to determine if this "twisted" orientation is necessary for activity, we successfully synthesized multiple 1,2,4-triazines that are entirely planar by fusing the 5- and 6-substituents together (Figure 2.7A-C). By reacting amidrazone **2-10** with phenanthrene-9,10-dione (**2-41**), 1,10-phenanthroline-5,6-dione (**2-44**), or isatin (**2-46**) the corresponding 1,2,4-triazine can be generated with an average yield of 70% after isolation by filtration.

With the intention of identifying which substituent, the 5- or 6-, played a larger role in activity, attempts were made to synthesize 1,2,4-triazines with only one of these two substituents. The most straightforward route to these 1,2,4-triazines is through unsymmetrical 1,2-diones, which can be synthesized from the oxidation of acetophenone derivatives using selenium dioxide (Figure 2.8A). 1,2,4-Triazine formation under neutral conditions will yield only the 5-substituted-1,2,4-triazine.[64] A single stereoisomer is formed because the terminal nitrogen of the hydrazono group of the amidrazone is the most nucleophilic nitrogen. It is this nitrogen atom that will attack the most electrophilic carbon, which in this case is the aldehyde carbon, producing an intermediate diazene and thus generating only the 5-substituted product.[57] It has been reported that 6-substituted-1,2,4-triazines can be synthesized under acidic conditions[65], but all attempts were unsuccessful (Figure 2.8B).

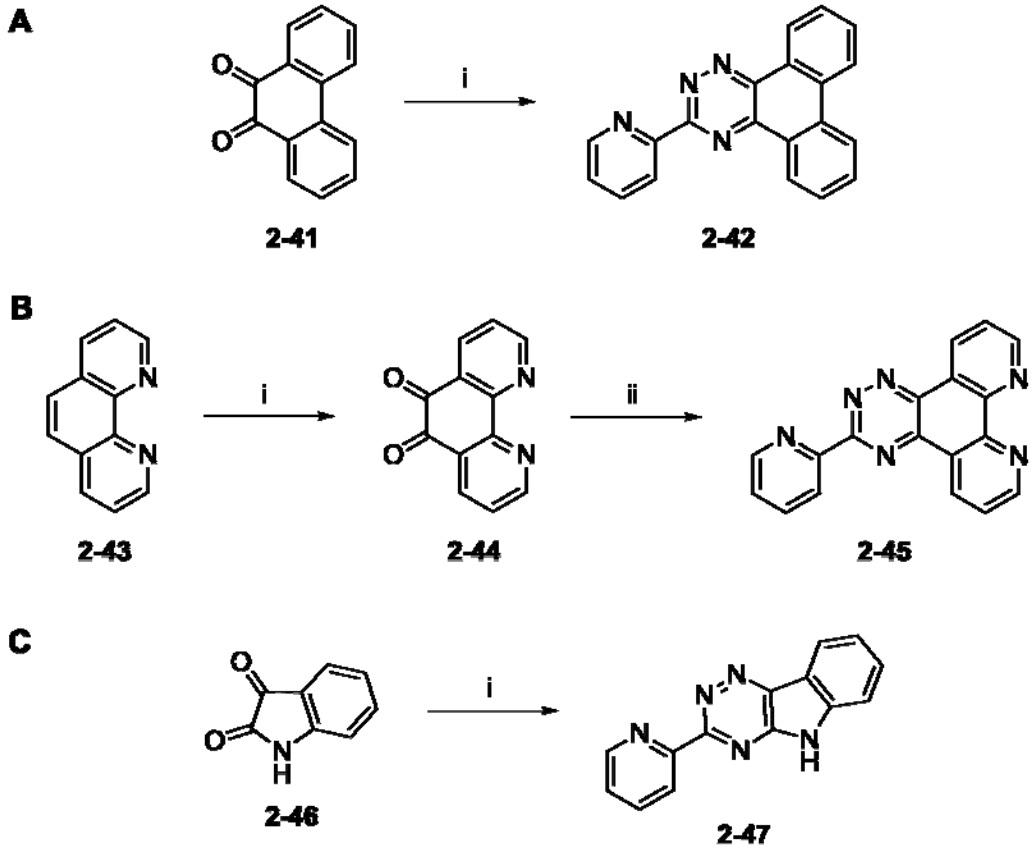


Figure 2.7 Synthesis of 1,2,4-Triazines from Fused-1,2-Dione Derivatives. **(A)** (i) **2-10**, ACN, 80°C. **(B)** (i) KBr, HNO_3, H_2SO_4, reflux; (ii) **2-10**, DMF, 80°C. **(C)** (i) **2-10**, EtOH, 80°C.

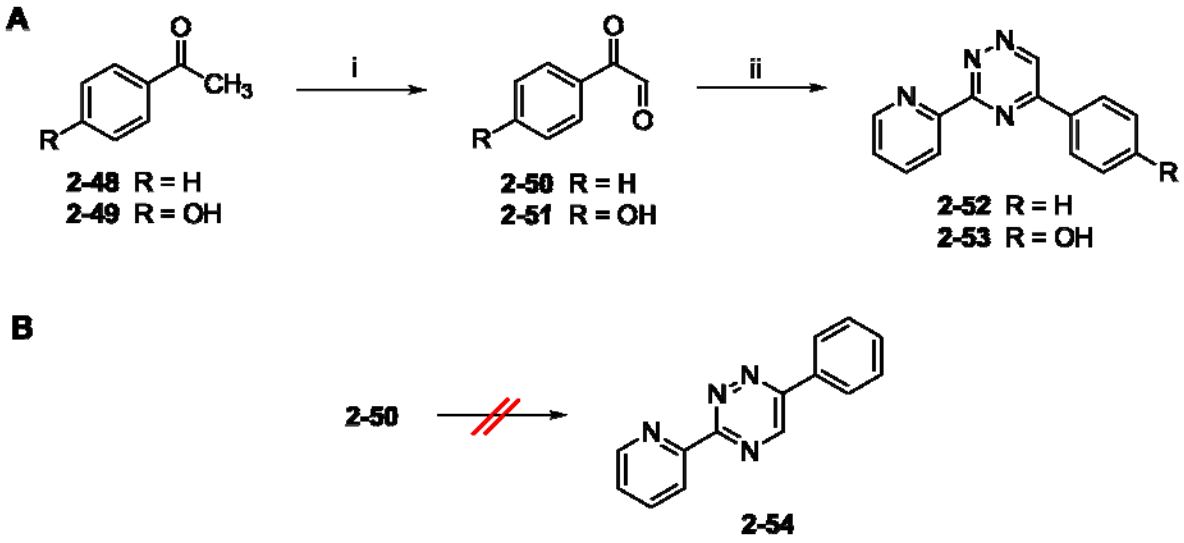


Figure 2.8 Synthesis of 1,2,4-Triazines from Unsymmetrical 1,2-Diones. **(A)** (i) SeO_2, dioxane, H_2O, reflux; (ii) **2-10**, EtOH, 80°C.

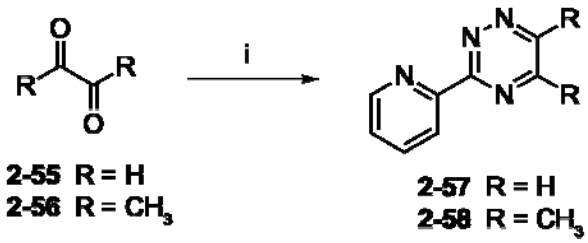


Figure 2.9 Synthesis of 5,6-Nonaromatic-1,2,4-Triazines. (i) **2-10**, EtOH, 80°C.

In order to determine to what extent steric bulk at the 5- and 6-positions influenced activity of the 1,2,4-triazine ligands, aromatic groups were replaced with methyl groups and protons (Figure 2.9). These 1,2,4-triazines were easily synthesized from commercial dialdehyde, glyoxal (**2-55**) and 2,3-butadione (**2-56**), with a percent yield greater than 85%.

2.4 Ring Transformations

A more indirect method for the synthesis of 1,2,4-triazines and derivatives thereof is through 1,2,4,5-tetrazine intermediates. As mentioned before, when 2-cyanopyridine (**2-7**) is reacted with hydrazine hydrate at room temperature, the product generated is amidrazone **2-10**. Alternatively, when heated, this reaction will yield **2-59** and oxidation then results in 1,2,4,5-tetrazine **2-60** (Figure 2.10). 1,2,4,5-Tetrazines are highly reactive dienes in inverse electron demand Diels-Alder and will react readily with alkynes, alkenes, nitriles, and related compounds.[57] For example, **2-60** reacts with phenylacetylene to yield the pyridazine derivative **2-61** in 77% yield. However, the low yield of the 1,2,4,5-tetrazine results in a 23% overall yield for **2-61**.

The 1,2,4-triazine scaffold, due to its electron deficient pi system, can also serve as a versatile building block for the synthesis of additional heterocycles. Typically, a diene reacts across the C3/C6 followed by expulsion of N_2, providing synthetic routes to a range of heterocycles such as pyridines, pyrimidines, and

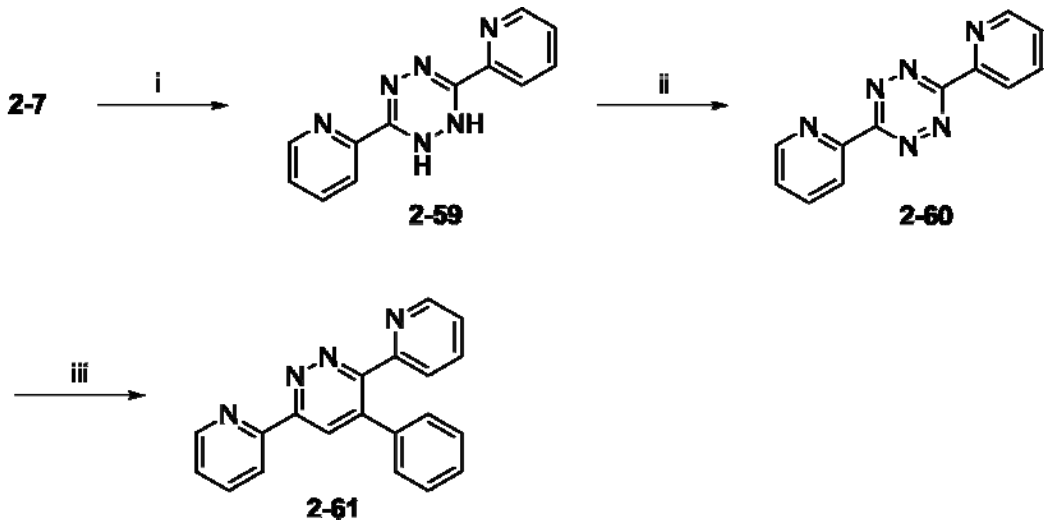


Figure 2.10 Synthesis of 1,2,4,5-Tetrazines and 1,2-Pyridazine Ligands. (i) hydrazine hydrate, EtOH, reflux; (ii) AcOH, HNO_3, 0°C; (iii) phenylacetylene, toluene, reflux.

pyrazines.[66] 1,2,4-Triazine **2-13** was reacted with 2,5-norbornadiene to yield bipyridine derivative **2-62** in 66% yield (Figure 2.11).

When amidrazones are reacted with aldehydes, as opposed to 1,2-diones, only the hydrazono group of the amidrazone is nucleophilic enough to attack the aldehyde therefore generating an non-cyclic triazine derivative. The amine remains unreactive, even under conditions employing excess aldehyde. Therefore substituted amidrazone ligands **2-64** and **2-65** were successfully synthesized in greater than 80% yield (Figure 2.12).

In addition to heterocycles such as triazines, tetrazines, bipyridines, and pyridazines, we synthesized a quinoxaline derivative by reacting diaminopyridine (2-66) with 1,2-diketone **2-32** in a quantitative yield (Figure 2.13). With an

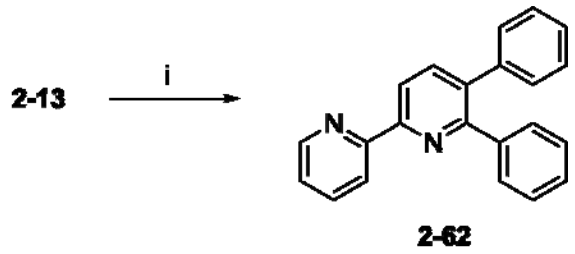


Figure 2.11 Synthesis of Bipyridine Ligand. (i) 2,5-norbornadiene, EtOH, reflux.

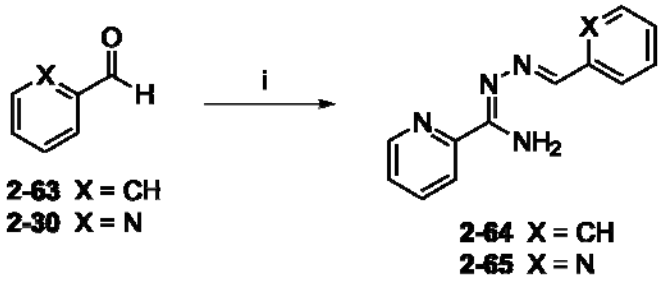


Figure 2.12 Synthesis of Substituted Amidrazone Ligands. (i) **2-10**, EtOH, 80°C.

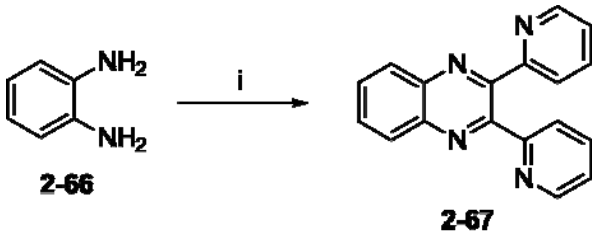


Figure 2.13 Synthesis of Quinoxaline Ligand. (i) **2-32**, EtOH, reflux.

extensive variety of heterocyclic scaffolds in place to potentially mimic the 1,2,4-triazine region of our ligand, our attention shifted to synthesizing additional analogs of the 2-pyridine at the 3-position of the 1,2,4-triazine in hope of producing “hybrid ligands.”

2.5 Substituent Modifications

Typically, reactivity decreases in the order of C5 > C3 > C6 for substitution reactions of 1,2,4-triazines due to the electron deficiency of the 1,2,4-triazines.[57,67] This preference for substitution at the 5-position can be explained by the 1,4-quinonoid contribution to the intermediate anion when a formal charge

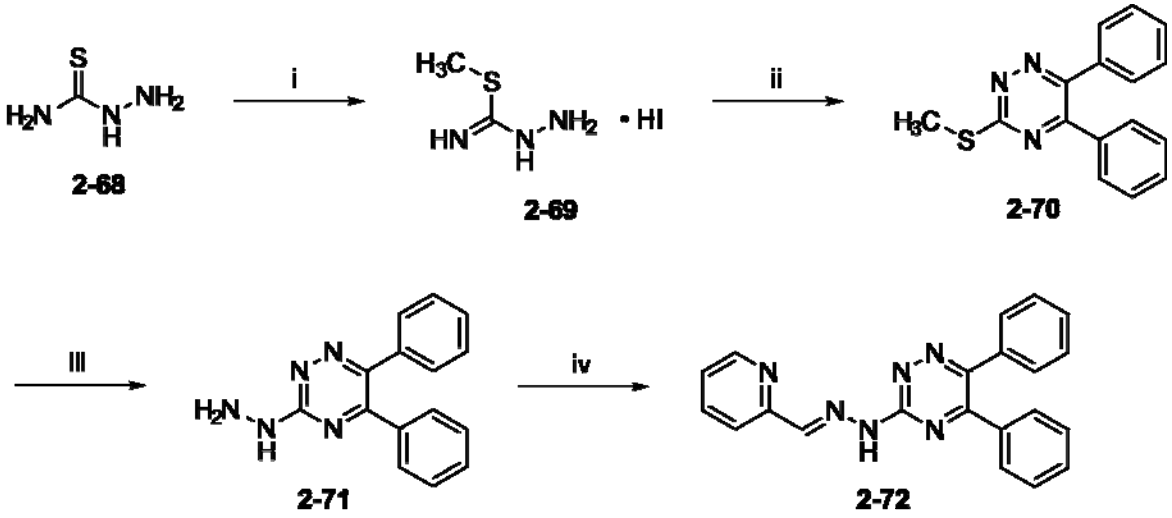


Figure 2.14 Synthesis of 3-Substituted-1,2,4-Triazines. (i) iodomethane, EtOH, 60°C; (ii) benzil, EtOH; (iii) hydrazine hydrate, EtOH, 80°C; (iv) **2-30**, EtOH, 80°C.

can be placed at N2. However once the 5-position is substituted, nucleophilic attack will occur at the 3-position, while reaction at the 6-position is rarely observed.

Recent work by Finn and colleagues has shown that by utilizing two or more different metal-binding heterocycles, one can tailor a ligand to have higher activity in a specific environment.[40] Therefore, we began to design synthetic routes that focused on analogs of the 2-pyridine ring in the 3-position of the 1,2,4-triazine by taking advantage of substituent modification reactions. In order to position a leaving group at the C3 position, methyl hydrazinecarbimiodthioate hydroiodide (**2-69**) is synthesized and reacted with benzil to yield **2-70** in 89% yield (Figure 2.14). The methylthio group is then displaced by hydrazine hydrate generating **2-71**, which can be reacted with an aldehyde thereby yielding imine **2-72**.

In an attempt to put a 1,2,3-triazole in the 3-position, **2-71** was first converted into azide **2-73** (Figrue 2.15). Nevertheless, all attempts to click with propargyl alcohol resulted in only the recovery of starting materials. It was only then that we determined the equilibrium between azide **2-73** and tetrazole **2-75** favors the tetrazole and as a result prevents the click reaction from occurring.[68]

With the inability to place a 1,2,3-triazole at the 3-position, our focus then shifted to a 1,2,4-triazole and 1,2,4-triazine. Oxidation of **2-70** yielded a better leaving group at the 3-position, which then permitted substitution using cyanide as a nucleophile, to synthesize **2-77** in an overall 58% yield (Figure 2.16A).

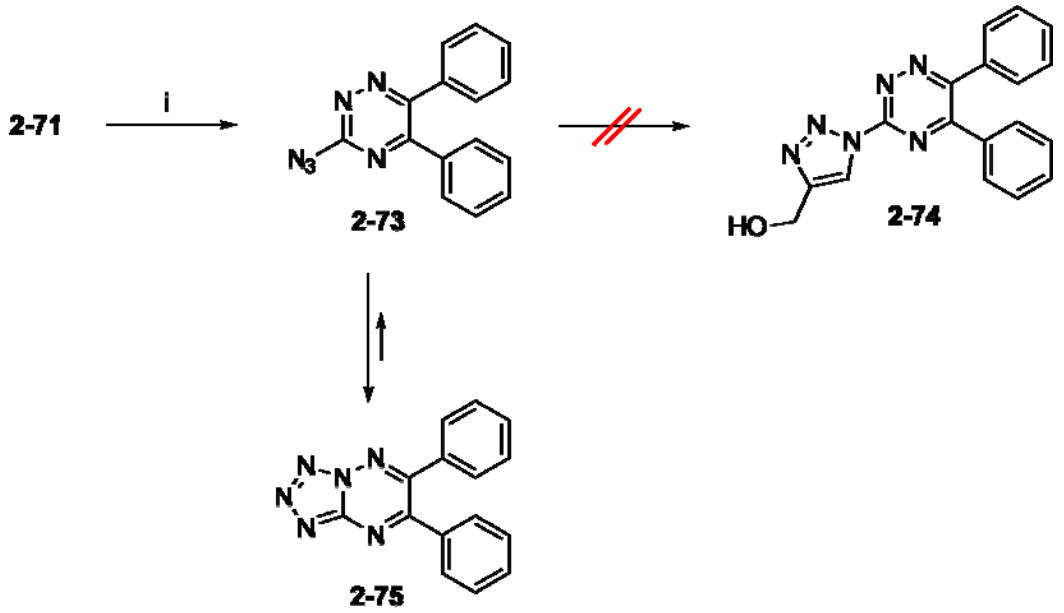


Figure 2.15 Synthesis of 3-Azido-1,2,4-Triazine. (i) $NaNO_2$, AcOH, water.

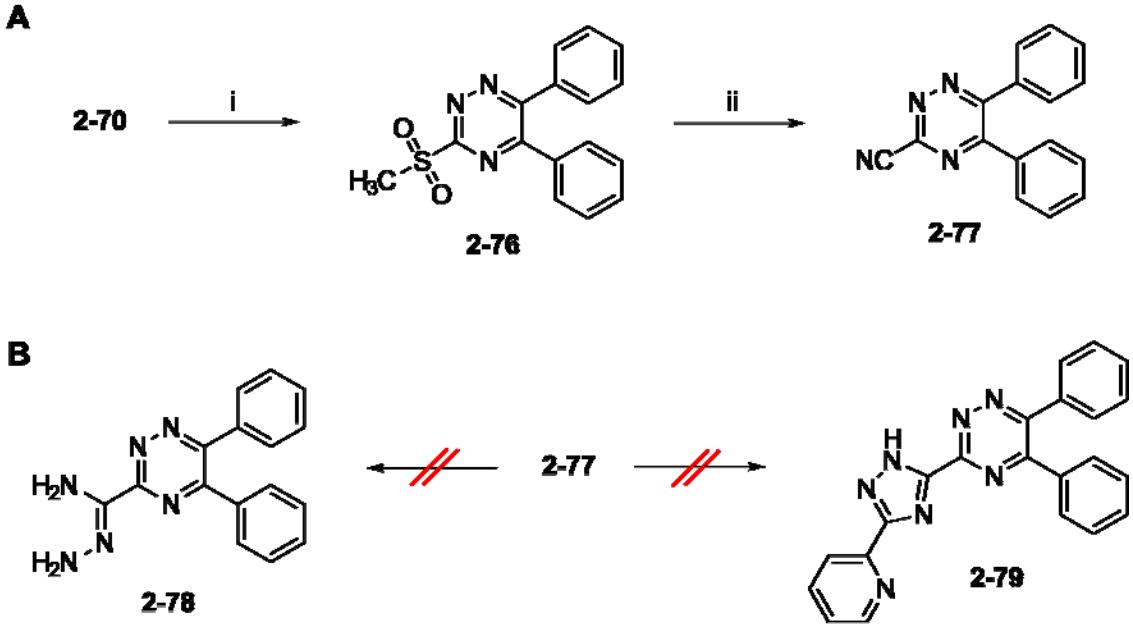


Figure 2.16 Synthesis of 3-Cyano-1,2,4-Triazine. **(A)** (i) $KMnO_4$, TBAB, AcOH, benzene, water; (ii) KCN, DMF.

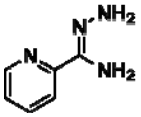
Surprisingly, nitrile **2-77** did not react in the manner we expected. The nitrile at the 3-position, behaves as a leaving group even in the presence of weaker nucleophiles.[57,69] The isolated products from Figure 2.16B include various unintended substituents at the 3-position stemming from nucleophiles such as n-butanol, 2-pyridyl hydrazide, and hydrazine hydrate.

2.6 Conclusions

In summary, a library of 1,2,4-triazines was synthesized using a multitude of synthetic schemes, particularly ring-closure reactions. Three regions were focused upon for modification: the 3-position, the 5- and 6- positions, and the core 1,2,4-triazine scaffold. The catalytic activity of these 1,2,4-triazines will be presented in chapter 3, along with an investigation of the reaction scope.

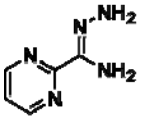
2.7 Experimental

Materials and General Methods. Reagents and solvents were purchased from various commercial sources and used without further purification unless otherwise stated. Anhydrous solvents were purified using a Grubbs solvent system. Analytical thin-layer chromatography (TLC) was performed using aluminum backed silica gel TLC plates with UV indicator from Sorbent Technologies. Flash column chromatography was performed using 40-63 μm (230 x 400 mesh) silica gel from Sorbent Technologies. ^{1}H and ^{13}C NMR were recorded at 600 MHz and 151 MHz, respectfully, on a Varian Inova spectrometer. All chemical shifts were reported in δ units relative to tetramethylsilane or the corresponding deuterated solvent. High resolution mass spectra (ESI) were obtained on a JEOL AccuTOF DART spectrometer. Infrared spectra were recorded on a Varian 4100 FT-IR using KBr pellets or KBr salt plates. Absorption spectra were collected on a Thermo Scientific Evolution 600. High pressure liquid chromatography (HPLC) was performed using a Beckman Coulter System equipped with a UV-Vis detector, autosampler, Varian C18 column, and a mobile phase composed of acetonitrile and trifluoroacetic acid.

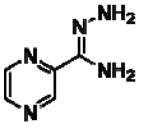


picolinohydrazonamide (2-10). 2-7 (5g, 48 mmol) was dissolved in EtOH (6mL) and hydrazine hydrate (3.26 mL, 67 mmol) and stirred at room temperature overnight. The pale white precipitate was filtered and washed with Et_2O in 94% yield. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.52 (m, 1H),

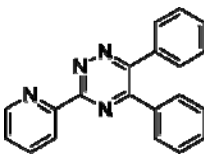
8.01 (d, 1H, J = 7.8 Hz), 7.69 (t, 1H, J = 7.8 Hz), 7.26 (m, 1H), 5.27 (br, 2H), 4.59 (b, 2H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 150.8, 148.7, 147.9, 136.4, 123.8, 119.7. HRMS (ESI) m/z calculated 137.08272 ($C_6H_9N_4$, $[M+H]^+$), m/z observed 137.08324 ($C_6H_9N_4$, $[M+H]^+$).



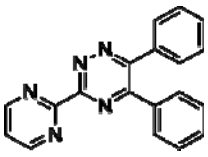
pyrimidine-2-carbohydrazonamide (2-11). **2-8** (250 mg, 2.38 mmol) was dissolved in EtOH (0.3 mL) and hydrazine hydrate (0.163 mL, 3.33 mmol) and stirred overnight at room temperature. Reaction was monitored by TLC. The reaction was concentrated *in vacuo* to yield a yellow oil in quantitative yield. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.77 (d, 2H, J = 4.8 Hz), 7.26 (t, 1H, J = 4.8 Hz), 5.17 (b, 2H), 4.83 (b, 2H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 158.8, 157.2, 146.6, 120.6. HRMS (ESI) m/z calculated 138.07797 ($C_5H_8N_5$, $[M+H]^+$), m/z observed 138.07782 ($C_5H_8N_5$, $[M+H]^+$).



pyrazine-2-carbohydrazonamide (2-12). **2-9** (250 mg, 2.38 mmol) was dissolved in EtOH (0.3 mL) and hydrazine hydrate (0.163 mL, 3.33 mmol) and stirred overnight at room temperature. Reaction was monitored by TLC. The pale white precipitate was filtered and washed with EtOH resulting in a 60% yield. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 9.27 (s, 1H), 8.51 (m, 1H), 8.44 (m, 1H), 5.12 (b, 2H), 4.72 (b, 2H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 146.6, 146.4, 144.1, 142.8, 142.3. HRMS (ESI) m/z calculated 138.07797 ($C_5H_8N_5$, $[M+H]^+$), m/z observed 138.07783 ($C_5H_8N_5$, $[M+H]^+$).

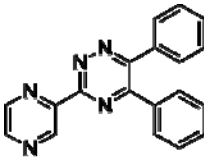


5,6-diphenyl-3-(pyridin-2-yl)-1,2,4-triazine (2-13). 2-10 (500 mg, 3.67 mmol) and benzil (772 mg, 3.67 mmol) were added to 10 mL of EtOH. The slurry was heated at 80°C for 6 h with complete dissolution. Progress of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature and the resulting precipitate was filtered and washed with EtOH and Et_2O resulting in a 76% yield. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.91 (d, 1H, J = 4.2 Hz), 8.70 (d, 1H, J = 7.8 Hz), 7.91 (t, 1H, J = 7.8 Hz), 7.68 (d, 2H, J = 7.8 Hz), 7.64 (d, 2H, J = 7.8 Hz), 7.46 (t, 1H, J = 6.6 Hz), 7.43-7.31 (m, 6H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 160.7, 156.5, 156.3, 152.9, 150.5, 137.0, 135.6, 135.3, 130.7, 129.9, 129.7, 129.6, 128.6. 128.5, 125.4, 124.1. UV-Vis (MeCN) λ_{max} nm (ε M^{-1} cm^{-1}): 387 (454.7). HRMS (ESI) m/z calculated 311.12967 ($C_{20}H_{15}N_4$, $[M+H]^+$), m/z observed 311.12831 ($C_{20}H_{15}N_4$, $[M+H]^+$).



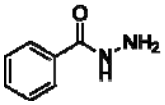
5,6-diphenyl-3-(pyrimidin-2-yl)-1,2,4-triazine (2-14). 2-11 (100 mg, 0.730 mmol) and benzil (153 mg, 0.730 mmol) were added to 2 mL of EtOH. The slurry was heated for 6 h at 80°C. Progress of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature and the resulting yellow precipitate was filtered and washed with EtOH resulting in a 75% yield. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 9.10 (d, 2H, J = 4.8 Hz), 7.68-7.64 (m, 4H), 7.51 (t, 1H, J = 4.8 Hz), 7.46-7.43 (m, 2H), 7.41-7.39 (m, 2H), 7.38-7.35 (m, 2H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 161.8,

160.2, 158.3, 157.4, 156.7, 135.5, 135.2, 131.0, 130.1, 129.9, 128.8, 121.9. UV-Vis (MeCN) λ_{max} nm (ε M^{-1} cm^{-1}): 386 (460.4). HRMS (ESI) m/z calculated 312.12492 ($C_{19}H_{14}N_5$, $[M+H]^+$), m/z observed 312.12414 ($C_{19}H_{14}N_5$, $[M+H]^+$).

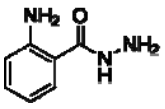


5,6-diphenyl-3-(pyrazin-2-yl)-1,2,4-triazine (2-15). 2-12 (100 mg, 0.730 mmol) and benzil (153 mg, 0.730 mmol) were added to 2 mL of EtOH. The slurry was heated overnight at 80°C. Progress of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature and concentrated *in vacuo* to quantitatively yield the product as a yellow solid. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 9.91 (s, 1H), 8.87 (s, 1H), 8.78 (s, 1H), 7.69 (d, 2H, J = 7.2 Hz), 7.65 (d, 2H, J = 7.8 Hz), 7.48-7.45 (m, 2H), 7.42-7.37 (m, 4H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 159.6, 157.2, 156.7, 148.6, 146.3, 145.7, 145.0, 135.4, 135.1, 131.2, 130.2, 130.1, 129.8, 128.9, 128.8. UV-Vis (MeCN) λ_{max} nm (ε M^{-1} cm^{-1}): 386 (523.6). HRMS (ESI) m/z calculated 312.12492 ($C_{19}H_{14}N_5$, $[M+H]^+$), m/z observed 312.12346 ($C_{19}H_{14}N_5$, $[M+H]^+$).

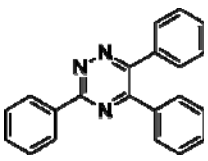
General Hydrazide Method: Methyl ester (1 eq) was dissolved in hydrazine hydrate (2.5 eq) and MeOH (3.5 M) and refluxed overnight. MeOH and excess hydrazine hydrate were removed *in vacuo*. The precipitated product was dried under vacuum.



benzohydrazide (2-18). Prepared using general hydrazide method and isolated as a white solid. ^{1}H NMR (CD_3CN, 600 MHz) δ 8.23 (br), 7.76 (d, 2H, J = 7.2 Hz), 7.52 (m, 1H), 7.45 (t, 2H, J = 7.2 Hz) ^{13}C NMR (CD_3CN, 151 MHz) δ 168.3, 134.3, 132.3, 129.4, 127.8. HRMS (ESI) m/z calculated 137.07149 ($C_7H_9N_2O$, $[M+H]^+$), m/z observed 137.07190 ($C_7H_9N_2O$, $[M+H]^+$).

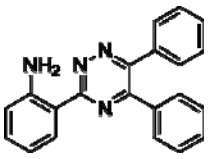


2-aminobenzohydrazide (2-19). Prepared using general hydrazide method and isolated as a pale brown solid. ^{1}H NMR (CD_3CN, 600 MHz) δ 8.04 (br) 7.34 (d, 2H, J = 7.8 Hz), 7.18 (t, 1H, J = 7.2 Hz). 6.71 (d, 1H, J = 7.2 Hz), 6.59 (t, 1H, J = 7.2 Hz), 4.79 (br). ^{13}C NMR (D_2O, 151 MHz) δ 170.8, 146.5, 132.8, 128.3, 118.5, 117.9, 117.3. HRMS (ESI) m/z calculated 152.08239 ($C_7H_{10}N_3O$, $[M+H]^+$), m/z observed 152.08191 ($C_7H_{10}N_3O$, $[M+H]^+$).

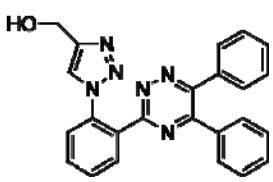


3,5,6-triphenyl-1,2,4-triazine (2-20). 2-16 (142 mg, 1.05 mmol), benzil (200 mg, 0.95 mmol), and ammonium acetate (732 mg, 9.50 mmol) were suspended in AcOH (2 mL). The suspension was heated in a conventional microwave at 750W and monitored by TLC until benzil no longer remained. The reaction mixture was concentrated *in vacuo* and precipitated out of EtOH. The product was isolated as a pale yellow solid in 51% yield. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.67 (s, 1H), 7.67 (d, 2H, J = 7.2 Hz), 7.62

(d, 2H, J = 7.2 Hz), 7.55-7.54 (m, 3H), 7.44-7.34 (m, 6H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 161.3, 155.48, 155.46, 135.9, 135.5, 134.8, 131.5, 130.7, 129.8, 129.5, 129.4, 128.8, 128.6, 128.5, 128.3. UV-Vis (MeCN) λ_{max} nm (ε M^{-1} cm^{-1}): 385 (480.9). HRMS (ESI) m/z calculated 310.13442 ($C_{21}H_{16,}N_3$, $[M+H]^+$), m/z observed 310.13349 ($C_{21}H_{16}N_3$, $[M+H]^+$).

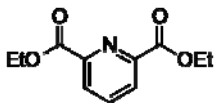


2-(5,6-diphenyl-1,2,4-triazin-3-yl)aniline (2-21). 2-17 (230 mg, 1.52 mmol), benzil (306 mg, 1.46 mmol), and ammonium acetate (1.02 g, 13.2 mmol) were suspended in AcOH (3 mL). The suspension was heated in a conventional microwave at 750W and monitored by TLC until benzil no longer remained. The reaction mixture was concentrated *in vacuo* and precipitated out of EtOH. The product was isolated as an orange solid in 42% yield. ^1H NMR ($CDCl_3$, 600 MHz) δ 8.61 (d, 1H, J = 7.8 Hz), 7.66 (d, 2H, J = 7.8 Hz), 7.60 (d, 2H, J = 7.2 Hz), 7.46-7.35 (m, 6H), 7.29 (t, 1H, J = 7.2 Hz), 6.84-6.79 (m, 2H), 6.39 (s, 2H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 163.3, 155.3, 154.0, 149.3, 136.2, 135.8, 132.3, 131.0, 130.9, 130.0, 129.7, 129.6, 128.8, 128.7, 117.5, 117.2, 115.8. UV-Vis (MeCN) λ_{max} nm (ε M^{-1} cm^{-1}): 373 (5762.7). HRMS (ESI) m/z calculated 325.14532 ($C_{21}H_{17}N_4$, $[M+H]^+$), m/z observed 325.14438 ($C_{21}H_{17}N_4$, $[M+H]^+$).

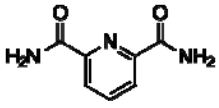


(1-2-(5,6-diphenyl-1,2,4-triazin-3-yl)phenyl)-1H-1,2,3-triazol-4-yl)methanol (2-22). 2-21 (50 mg, 0.154 mmol) was dissolved in 2 mL EtOAc. 1 mL of 1.5 M HCl was added and the solution was cooled to 0°C in an ice bath. Sodium nitrite (21 mg, 0.308 mmol) was dissolved in 0.5 mL water and added dropwise to the reaction solution while stirring at 0°C. After 15 min, sodium azide (40 mg, 0.616 mmol) was dissolved in 0.5 mL water and added dropwise to the reaction solution while stirring at 0°C. After slowly warming to room temperature, the reaction was monitored by TLC. Upon completion, the reaction was extracted with EtOAc (x3), washed with 1 M HCl, water, and brine, and dried with sodium sulfate. After concentration *in vacuo*, the crude material was dissolved in 0.4 mL ACN. Propargyl alcohol (4.3 mg, 0.077 mmol) and triethylamine (10.7 µL, 0.077 mmol) were added to the reaction solution. 5,6-diphenyl-3-(pyridin-2-yl)-1,2,4-triazine (0.2 mg, 0.77 µmol) and tetrakis(acetonitrile-N)copper(I) tetrafluoroborate (0.2 mg, 0.77 µmol) were then added to the reaction solution. The reaction was stirred at room temperature overnight. After concentration *in vacuo*, the crude product was purified by silica gel chromatography with gradient elution using EtOAc and hexanes to yield a pale yellow solid in 57% yield. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.47 (d, 1H, J = 7.2), 7.83 (s, 1H), 7.77-7.72 (m, 2H), 7.59-7.56 (m, 3H), 7.41-7.29 (m, 9H), 4.73 (s, 2H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 161.1, 155.4, 155.3, 136.1, 135.1, 135.0, 132.2, 131.9, 131.5, 130.9, 130.4, 129.8, 129.7,

129.5, 128.6, 128.4, 127.0, 56.5. HRMS (ESI) m/z calculated 407.16203 ($C_{24}H_{19}N_6O$, $[M+H]^+$), m/z observed 407.16117 ($C_{24}H_{19}N_6O$, $[M+H]^+$).

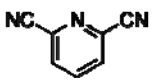


diethyl pyridine-2,6-dicarboxylate (2-24). 2-23 (2 g, 11.97 mmol) was suspended in EtOH (5 mL) and HCl (0.5 mL). The suspension was heated in a conventional microwave oven at 750W and monitored by TLC until starting material no longer remained. The reaction mixture was concentrated *in vacuo* and redissolved in water. After adjusting the pH to 8 with 10 M sodium hydroxide, the reaction was extracted with EtOAc (x3) and rinsed with brine. The solution was dried with sodium sulfate and concentrated *in vacuo* to yield a white solid in 56% yield. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.28 (d, 2H, J = 6.6 Hz), 8.00 (t, 1H, J = 6.6 Hz), 4.48 (d, 4H, J = 6.0 Hz), 1.45 (s, 6 H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 164.8, 148.8, 138.3, 128.0, 62.5, 14.4. HRMS (ESI) m/z calculated 224.09228 ($C_{11}H_{14}NO_4$, $[M+H]^+$), m/z observed 224.09179 ($C_{11}H_{14}NO_4$, $[M+H]^+$).

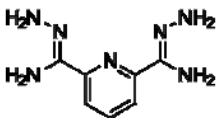


pyridine,2-6-dicarboxamide (2-25). Ammonium hydroxide (2.5 mL) was added to **2-24** (1.5 g, 6.72 mmol) and warmed at 35°C for 1 h with vigorous stirring. After cooling to 0°C, the precipitate was filtered and washed with water. The resulting white solid was dried under vacuum in an 80% yield. ^{1}H NMR (d_6-DMSO, 600 MHz) δ 8.87 (s, 2H), 8.19-8.14 (m, 3H), 7.70 (s, 2H). ^{13}C NMR (d_6-DMSO, 151 MHz) δ 165.4, 149.1, 139.1,

124.1. HRMS (ESI) m/z calculated 166.06165 ($C_7H_8N_3O_2$, $[M+H]^+$), m/z observed 166.06152 ($C_7H_8N_3O_2$, $[M+H]^+$).

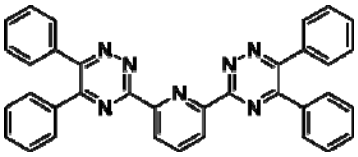


pyridine-2,6-dicarbonitrile (2-26). Anhydrous THF (5 mL) and triethylamine (1.58 mL, 11.31 mmol) were added to **2-25** (850 mg, 5.14 mmol) under nitrogen atmosphere. The suspension was cooled to 0°C and trifluoroacetic anhydride (1.57 mL, 11.31 mmol) was added dropwise. After 10 min, the solution was allowed to stir at room temperature for 3 h. The reaction was then quenched with 5 mL of saturated sodium bicarbonate. The resulting precipitate was filtered and washed with water. The resulting white solid was dried under vacuum in a 52% yield. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.06 (t, 1H, J = 7.8 Hz), 7.92 (d, 2H, J = 7.8 Hz) ^{13}C NMR ($CDCl_3$, 151 MHz) δ 138.7, 135.4, 131.0, 115.4. HRMS (ESI) m/z calculated 130.04052 ($C_7H_4N_3$, $[M+H]^+$), m/z observed 130.03995 ($C_7H_4N_3$, $[M+H]^+$).

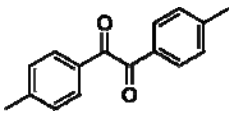


pyridine-2,6-bis(carbohydrazonamide) (2-27). 2-26 (288 mg, 2.23 mmol) was dissolved in EtOH (0.5 mL) and hydrazine hydrate (0.5 mL, 8.93 mmol) and stirred overnight at room temperature. EtOH and excess hydrazine hydrate were removed *in vacuo*. The white solid was dried under vacuum and then stored at 0°C in a 73% yield. ^{1}H NMR (d_6-DMSO, 600 MHz) δ 7.93 (d, 2H, J = 7.8 Hz), 7.66 (t, 1H, J = 7.8 Hz), 6.18 (br), 3.29 (br). ^{13}C NMR (d_6-DMSO, 151 MHz) δ 149.6, 146.0, 136.0, 119.1.

HRMS (ESI) m/z calculated 194.11542 ($C_7H_{12}N_7$, $[M+H]^+$), m/z observed 194.11599 ($C_7H_{12}N_7$, $[M+H]^+$).

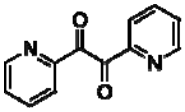


2,6-bis(5,6-diphenyl-1,2,4-triazin-3-yl)pyridine (2-28). **2-27** (288 mg, 1.49 mmol) and benzil (642 mg, 3.05 mmol) were added to 4 mL of EtOH. The slurry was heated overnight at 80°C with complete dissolution. Progress of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature and the resulting precipitate was filtered and washed with EtOH and Et_2O resulting in a 92% yield. ^1H NMR (CD_2Cl_2, 600 MHz) δ 8.86 (d, 2H, J = 7.8 Hz), 8.23 (t, 1H, J = 7.8 Hz), 7.73 (d, 4H, J = 7.2 Hz), 7.66 (d, 4H, J = 7.2 Hz), 7.51-7.48 (m, 4 H), 7.47-7.40 (m, 8H). ^{13}C NMR (CD_2Cl_2, 151 MHz) δ 160.9, 156.9, 156.5, 153.8, 138.5, 135.9, 135.7, 131.0, 130.1, 130.0, 129.8, 128.84, 128.75, 125.9. UV-Vis (9:1 DCE:MeOH) λ_{max} nm (ε M^{-1} cm^{-1}): 394 (1039.0). HRMS (ESI) m/z calculated 542.20932 ($C_{35}H_{24}N_7$, $[M+H]^+$), m/z observed 542.21167 ($C_{35}H_{24}N_7$, $[M+H]^+$).



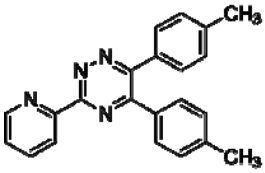
1,2-di-p-tolylethane-1,2-dione (2-31). **2-29** (5 g, 41.6 mmol) and KCN (1.35 g, 20.8 mmol) was dissolved in EtOH (8 mL) and water (4 mL). The mixture was heated under reflux for 0.5 h. After cooling to room temperature, the reaction mixture was poured into an ice bath and the crude benzoin intermediate was precipitated. The solid was then filtered and

further washed with water. The crude benzoin intermediate was then refluxed in nitric acid (8 mL) for 2 h. The reaction mixture was poured into an ice bath and the crude benzil derivative was precipitated and filtered. Recrystallization from EtOH yielded a yellow solid in 39% yield. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.86 (d, 4H, J = 7.8 Hz), 7.30 (d, 4H, J = 7.8 Hz), 2.42 (s, 6H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 194.6, 146.2, 130.9, 130.2, 129.8, 22.1. HRMS (ESI) m/z calculated 239.10720 ($C_{16}H_{15}O_2$, $[M+H]^+$), m/z observed 152.08191 239.10710 ($C_{16}H_{15}O_2$, $[M+H]^+$).

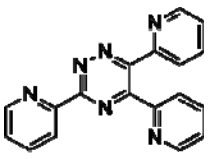


1,2-di(pyridin-2-yl)ethane-1,2-dione (2-32). **2-30** (1 g, 9.34 mmol) and KCN (304 mg, 4.66 mmol) were dissolved in water (10 mL) which immediately formed an orange precipitate. The slurry was heated at 80°C for 0.5 h. After cooling to room temperature, the reaction was filtered and rinsed with additional water. The intermediate precipitate was then cooled to 0°C and 5 mL of concentrated nitric acid was added dropwise. The solution was again heated at 80°C for 0.5 h. The reaction was then cooled to 0°C and neutralized with 10 M sodium hydroxide. The resulting precipitate was filtered and purified by silica gel chromatography with gradient elution using EtOAc and hexanes to yield a pale white solid in 45% yield. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.58 (d, 2H, J = 4.2 Hz), 8.21 (d, 2H, J = 7.8 Hz), 7.92 (dt, 2H, J = 7.8, 1.8 Hz), 7.49-7.47 (m, 2H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 197.1, 151.8, 149.6, 137.3,

128.0, 122.5. HRMS (ESI) m/z calculated 213.06640 ($C_{12}H_9N_2O_2$, $[M+H]^+$), m/z observed 213.06625 ($C_{12}H_9N_2O_2$, $[M+H]^+$).

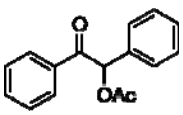


3-(pyridin-2-yl)-5,6-di-p-tolyl-1,2,4-triazine (2-33). 2-10 (284 mg, 2.10 mmol) and **2-31** (500 mg, 2.10 mmol) were added to EtOH (12 mL). The slurry was heated at 80°C for 6 h with complete dissolution. Progress of the reaction was monitored by TLC. After concentration *in vacuo*, the crude product was purified by silica gel chromatography with gradient elution using EtOAc and hexanes to yield a pale yellow solid in 41.1% yield. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.92 (d, 1H, J = 4.8 Hz), 8.70 (d, 1H, J = 7.8 Hz), 7.93 (t, 1H, J = 7.8 Hz), 7.62 (d, 2H, J = 8.4 Hz), 7.54 (d, 2H, J = 8.4 Hz), (m, 1H), 7.21 (d, 2H, J = 7.8 Hz), 7.19 (d, 2H, J = 7.8 Hz), 2.40 (s, 3H), 2.38 (s, 3H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 160.6, 156.5, 156.3, 153.2, 150.6, 141.3, 140.0, 137.2, 133.1, 132.8, 130.1, 129.6, 129.5, 129.4, 125.4, 124.2, 21.7, 21.6. UV-Vis (MeCN) λ_{max} nm (ε M^{-1} cm^{-1}): 400 (445.5). HRMS (ESI) m/z calculated 339.16097 ($C_{22}H_{19}N_4$, $[M+H]^+$), m/z observed 339.15939 ($C_{22}H_{19}N_4$, $[M+H]^+$).



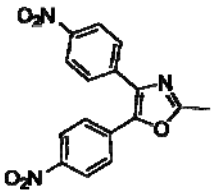
3,5,6-tri(pyridin-2-yl)-1,2,4-triazine (2-34). 2-10 (100 mg, 0.730 mmol) and **2-32** (150 mg, 0.730 mmol) were added to 2 mL of EtOH. The slurry was heated overnight at 80°C with complete dissolution. Progress of the reaction was monitored by TLC. The reaction

mixture was cooled to room temperature and the resulting precipitate was filtered and washed with EtOH resulting in a 95% yield. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.94 (d, 1H, J = 3.6 Hz), 8.75 (d, 1H, J = 7.8 Hz), 8.36-8.35 (m, 2H), 8.27-8.25 (m, 2H), 7.96 (dt, 1H, J = 7.8, 1.8 Hz), 7.93-7.87 (m, 2H), 7.52-7.49 (m, 1H), 7.32-7.29 (m, 2H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 161.5, 156.37, 156.35, 154.9, 154.8, 152.8, 150.8, 148.93, 148.92, 137.4, 137.21, 137.19, 125.9, 125.1, 124.70, 124.66, 124.5, 124.0. UV-Vis (MeCN) λ_{max} nm (ε M^{-1} cm^{-1}): 382 (495.9). HRMS (ESI) m/z calculated 313.12017 ($C_{18}H_{13}N_6$, $[M+H]^+$), m/z observed 313.11959 ($C_{18}H_{13}N_6$, $[M+H]^+$).

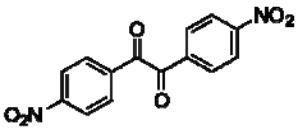


2-oxo-1,2-diphenylethyl acetate (2-36). 2-35 (4 g, 18.84 mmol) and acetic anhydride (4.33g, 42.40 mmol) were dissolved in AcOH (4 mL). Concentrated HCl (0.4 mL) was added dropwise at room temperature. The reaction was then heated at 100°C for 30 min. After cooling to room temperature, 50 mL of water was added and the reaction continued to stir at room temperature for an additional 2 h. The precipitate was filtered and purified by silica gel chromatography with gradient elution using EtOAc and hexanes to yield a white solid in 63% yield. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.93 (d, 2H, J = 7.8 Hz), 7.51 (t, 1H, J = 7.8 Hz), 7.47 (d, 2H, J = 7.8 Hz), 7.41-7.34 (m, 5H), 6.87 (s, 1H), 2.21 (s, 3H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 193.8, 170.6, 134.7, 133.7, 133.6, 129.5, 129.3, 128.9, 128.83, 128.76, 77.8, 20.9. HRMS (ESI) m/z

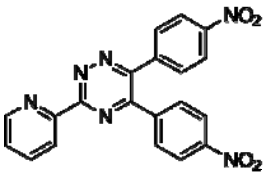
calculated 255.10212 ($C_{16}H_{15}O_3$, $[M+H]^+$), m/z observed 255.10306 ($C_{16}H_{15}O_3$, $[M+H]^+$).



2-methyl-4,5-bis(4-nitrophenyl)oxazole (2-37). **2-36** (1 g, 3.93 mmol) and ammonium acetate (454 mg, 5.90 mol) were dissolved in AcOH (1.3 mL) and refluxed for 2 h. After warming to room temperature, the crude reaction was poured over ice and extracted with Et_2O. The organic layer was washed with water and brine, then dried with sodium sulfate. Concentration *in vacuo* produced the intermediate oxazole as a brown oil. This oil was dissolved in sulfuric acid (3 mL) and nitric acid (3 mL) was added dropwise at room temperature. The reaction was then heated at 55°C for 15 min. Progress of the reaction was monitored by TLC. After warming to room temperature, ice was added to precipitate the product. Recrystalization from AcOH producted yellow solid in 59% yield. ^1H NMR ($CDCl_3$, 600 MHz) δ 8.26 (t, 4H, J = 8.4 Hz), 7.82 (d, 2H, J = 8.4 Hz), 7.74 (d, 2H, J = 8.4 Hz), 2.62 (s, 3H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 162.4, 147.9, 147.7, 145.0, 138.3, 136.3, 134.3, 128.9, 127.2, 124.5, 124.3, 14.2. HRMS (ESI) m/z calculated 326.07770 ($C_{16}H_{12}N_3O_5$, $[M+H]^+$), m/z observed 326.07637 ($C_{16}H_{12}N_3O_5$, $[M+H]^+$).

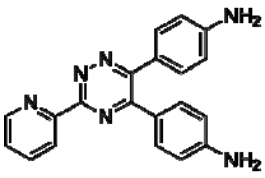


1,2-bis(4-nitrophenyl)ethane-1,2-dione (2-38). **2-37** (600 mg, 1.85 mmol) and sodium acetate (1.2 g, 14.8 mmol) were dissolved in a combination of AcOH (6.6 mL) and water (0.67 mL). Bromine (591 mg, 7.4 mmol) was then added and the reaction was refluxed for 2 h. Progress of the reaction was monitored by TLC. After cooling to room temperature, the reaction was poured over ice and filtered. Recrystalization from AcOH produced a yellow solid in 42% yield. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.39 (d, 4H, J = 8.4 Hz), 8.21 (d, 4H, J = 8.4 Hz). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 190.4, 151.7, 136.9, 131.4, 124.4. HRMS (ESI) m/z calculated 301.04606 ($C_{14}H_9N_2O_6$, $[M+H]^+$), m/z observed 301.04552 ($C_{14}H_9N_2O_6$, $[M+H]^+$).

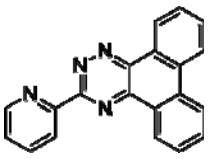


5,6-bis(4-nitrophenyl)-3-(pyridin-2-yl)-1,2,4-triazine (2-39). **2-10** (136 mg, 1.0 mmol) and **2-38** (300 mg, 1.0 mmol) were added to 6 mL of EtOH. The slurry was heated overnight at 80°C with complete dissolution. Progress of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature and the resulting precipitate was filtered and washed with EtOH resulting in a 93% yield. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.96 (d, 1H, J = 4.2 Hz), 8.75 (d, 1H, J = 7.8 Hz), 8.30-8.27 (m, 4H), 7.99 (dt, 1H, J = 7.8, 1.2 Hz), 7.86 (d, 2H, J = 7.2 Hz), 7.82 (d, 2H, J = 6.6 Hz), 7.56-7.54 (m, 1H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 161.6, 154.7, 154.6, 152.0, 151.0, 149.5, 149.1, 141.1, 140.7, 137.5, 131.2, 130.8, 126.3, 124.8, 124.33, 124.28. UV-Vis (MeCN) λ_{max} nm (ε M^{-1} cm^{-1}): 404 (546.5).

HRMS (ESI) m/z calculated 401.09983 ($C_{20}H_{13}N_6O_4$, $[M+H]^+$), m/z observed 401.09918 ($C_{20}H_{13}N_6O_4$, $[M+H]^+$).

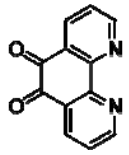


4,4'-(3-(pyridin-2-yl)-1,2,4-triazine-5,6-diyl)dianiline (2-40). **2-39** (200 mg, 0.5 mmol), and 5% palladium/carbon (2 mg), and hydrazine hydrate (1 mL) were added to 2.5 mL of EtOH. The reaction was refluxed for 6 h and progress was monitored by TLC. Upon completion, reaction was filtered through celite and eluted with MeOH. Concentration *in vacuo* yielded the crude product as an orange solid in 85% yield. HPLC purity: 80%. UV-Vis (9:1 MeCN:DMSO) λ_{max} nm (ε M^{-1} cm^{-1}): 475 (483.0). HRMS (ESI) m/z calculated 341.15147 ($C_{20}H_{17}N_6$, $[M+H]^+$), m/z observed 341.15043 ($C_{20}H_{17}N_6$, $[M+H]^+$).

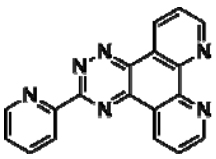


3-(pyridin-2-yl)phenanthro[9,10-e][1,2,4]triazine (2-42). **2-10** (500 mg, 3.67 mmol) and **2-41** (764 mg, 3.67 mmol) were added to 10 mL of ACN. The slurry was heated at 80°C overnight with complete dissolution. Progress of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature and the resulting precipitate was filtered and washed with ACN and Et_2O resulting in a 75% yield. ^1H NMR ($CDCl_3$, 600 MHz) δ 9.55 (d, 1H, J = 7.8 Hz), 9.49 (d, 1H, J = 7.8 Hz), 9.01 (d, 1H, J = 4.8 Hz), 8.90 (d, 1H, J = 7.8 Hz), 8.61 (d, 2H, J = 7.8 Hz), 8.01 (t, 1H, J = 7.8 Hz), 7.91 (t, 1H, J = 7.8 Hz), 7.86 (t, 1H, J = 7.8 Hz), 7.82 (t, 1H, J = 7.2 Hz),

7.78 (t, 1H, J = 7.2 Hz), 7.53 (m, 1H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 160.67, 153.7, 150.6, 145.6, 143.3, 137.2, 133.9, 132.6, 131.4, 131.1, 128.7, 128.1, 127.9, 127.5, 127.2, 125.31, 125.28, 124.3, 123.1, 123.0. UV-Vis (DCE) λ_{max} nm (ε M^{-1} cm^{-1}): 424 (381.7). HRMS (ESI) m/z calculated 309.11402 ($C_{20}H_{13}N_4$, $[M+H]^+$), m/z observed 309.11249 ($C_{20}H_{13}N_4$, $[M+H]^+$).

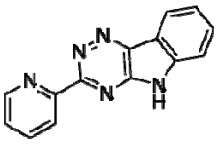


1,10-phenanthroline-5,6-dione (2-44). 2-43 (500 mg, 2.78 mmol) and KBr (700 mg, 5.88 mmol) was added to a mixture of concentrated sulfuric acid (5 mL) and nitric acid (2.5 mL) at -5°C. The mixture was stirred at that temperature for 15 min and then brought to reflux and heated for 4 h. The yellow solution was allowed to cool and poured over 50 g of ice and carefully brought to pH 9 by addition of 5 M sodium hydroxide. The suspension was extracted with $CHCl_3$, dried over anhydrous sodium sulfate, and concentrated *in vacuo* to yield fine yellow needles in 84% yield. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 9.14 (d, 2H, J = 4.8 Hz), 8.52 (d, 2H, J = 7.8 Hz), 7.60 (dd, 2H, J = 7.8, 4.8 Hz). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 178.7, 156.4, 152.9, 137.3, 128.1, 125.6. HRMS (ESI) m/z calculated 211.05075 ($C_{12}H_7N_2O_2$, $[M+H]^+$), m/z observed 211.05055 ($C_{12}H_7N_2O_2$, $[M+H]^+$).



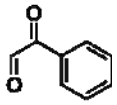
3-(pyridin-2-yl)-[1,2,4]triazino[5,6-f][1,10]phenanthroline (2-45). 2-10 (64 mg, 0.476 mmol) and **2-44** (100 mg, 0.476 mmol) were added to 4 mL of DMF. The slurry was heated at

80°C overnight with complete dissolution. Progress of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature and the resulting precipitate was filtered and washed with DMF and Et_2O resulting in a 74% yield. ^1H NMR (d_6-DMSO, 600 MHz) δ 9.71 (d, 1H, J = 7.8 Hz), 9.66 (d, 1H, J = 7.2 Hz), 9.35 (s, 1H), 9.31 (s, 1H), 8.96 (s, 1H), 8.84 (d, 1H, J = 7.8 Hz), 8.17 (t, 1H, J = 7.2 Hz), 8.05 (s, 2H), 7.72 (s, 1H). ^{13}C NMR (d_6-DMSO, 151 MHz) δ 160.9, 154.4, 153.2, 152.8, 150.4, 149.3, 147.1, 144.5, 142.6, 137.6, 133.9, 132.1, 126.0, 125.4, 125.1, 124.84, 124.78, 124.5. UV-Vis (9:1 DCE:MeOH) λ_{max} nm (ε M^{-1} cm^{-1}): 423 (376.6). HRMS (ESI) m/z calculated 311.10452 ($C_{18}H_{11}N_6$, $[M+H]^+$), m/z observed 311.10452 ($C_{18}H_{11}N_6$, $[M+H]^+$).

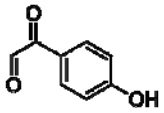


3-(pyridin-2-yl)-5H-[1,2,4]triazino[5,6-b]indole (2-47). **2-10** (500 mg, 3.67 mmol) and **2-46** (540 mg, 3.67 mmol) were added to 10 mL of EtOH. The slurry was heated at 80°C overnight with complete dissolution. Progress of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature and the resulting orange precipitate was filtered and washed with EtOH and Et_2O resulting in a 59% yield. ^1H NMR ($CDCl_3$, 600 MHz) δ 8.67 (d, 1H, J = 4.2 Hz), 8.50-8.47 (m, 2H), 8.02 (bs, 1H), 7.90 (dt, 1H, J = 9, 1.8 Hz), 7.50 (m, 1H), 7.32 (t, 1H, J = 7.8 Hz), 7.11 (t, 1H, J = 7.8 Hz), 6.90 (d, 1H, J = 7.8 Hz). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 166.9, 160.6, 149.6, 148.9, 146.3, 142.4, 137.0, 131.8, 128.9, 126.1, 123.0, 122.7, 118.5,

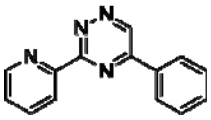
110.3 MS (ESI) m/z calculated 248.09362 ($C_{14}H_{10}N_5$, $[M+H]^+$), m/z observed 248.09721 ($C_{14}H_{10}N_5$, $[M+H]^+$).



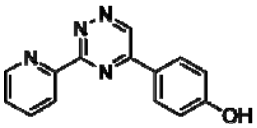
2-oxo-2-phenylacetaldehyde (2-50). Selenium dioxide (924 mg, 8.32 mmol) was suspended in dioxane (4.2 mL) and water (0.20 mL) and heated at 55°C until mostly dissolved. **2-48** (1 g, 8.32 mmol) was then added and the reaction was refluxed for 4 h. After cooling to room temperature, the reaction was filtered and the filtrate was concentrated *in vacuo*. Purification via silica gel chromatography with gradient elution using EtOAc and hexanes was used to further purify the reaction mixture. The crude product was used in further reactions. MS (ESI) m/z calculated 135.04460 ($C_8H_7O_2$, $[M+H]^+$), m/z observed 135.042 ($C_8H_7O_2$, $[M+H]^+$).



2-(4-hydroxyphenyl)-2-oxoacetaldehyde (2-51). Selenium dioxide (814 mg, 7.34 mmol) was suspended in dioxane (3.7 mL) and water (0.18 mL) and heated at 55°C until mostly dissolved. **2-49** (3 g, 15.0 mmol) was then added and the reaction was refluxed for 4 h. After cooling to room temperature, the reaction was filtered and the filtrate was concentrated *in vacuo*. Purification via silica gel chromatography with gradient elution using EtOAc and hexanes was used to further purify the reaction mixture. The crude product was used in further reactions. MS (ESI) m/z calculated 151.03952 ($C_8H_7O_3$, $[M+H]^+$), m/z observed 151.038 ($C_8H_7O_3$, $[M+H]^+$).

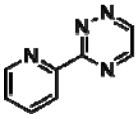


5-phenyl-3-(pyridin-2-yl)-1,2,4-triazine (2-52). **2-50** (246 mg, 1.84 mmol) and **2-10** (250 mg, 1.84 mmol) were added to 5 mL of EtOH. The slurry was heated for 4 h at 80°C with complete dissolution. Progress of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature and purified by silica gel chromatography with gradient elution using EtOAc and hexanes to yield a white solid in 82% yield. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 9.72 (s, 1H), 8.94 (d, 1H, J = 4.2 Hz), 8.68 (d, 1H, J = 7.8 Hz), 8.31 (d, 2H, J = 8.4 Hz), 7.95 (t, 1H, J = 7.8 Hz), 7.63-7.59 (m, 3H), 7.50 (m, 1H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 162.9, 156.0, 153.2, 150.7, 145.5, 137.3, 133.6, 132.8, 129.6, 128.0, 125.7, 124.3. UV-Vis (MeCN) λ_{max} nm (ε M^{-1} cm^{-1}): 382 (486.2). HRMS (ESI) m/z calculated 235.09837 ($C_{14}H_{11}N_4$, $[M+H]^+$), m/z observed 235.09829 ($C_{14}H_{11}N_4$, $[M+H]^+$).

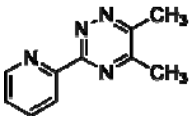


4-(3-(pyridin-2-yl)-1,2,4-triazin-5-yl)phenol (2-53). **2-51** (150 mg, 1.0 mmol) and **2-10** (136 mg, 1.0 mmol) were added to 3 mL of EtOH. The slurry was heated overnight at 80°C with complete dissolution. Progress of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature and concentrated *in vacuo* yielding an orange solid in 90% yield. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 9.56 (s, 1H), 8.89 (d, 1H, J = 4.2 Hz), 8.72 (d, 1H, J = 7.8 Hz), 8.10 (d, 2H, J = 8.4 Hz), 8.00 (t, 1H, J = 8.4 Hz), 7.56 (m, 1H), 6.96 (d, 2H, J = 4.8 Hz), 3.49 (s, 1H). ^{13}C NMR ($CDCl_3$, 151

MHz) δ 162.5, 161.6, 156.1, 153.1, 149.9, 145.1, 130.2, 126.0, 124.8, 124.7, 116.9. UV-Vis (MeCN) λ_{max} nm (ε M^{-1} cm^{-1}): 385 (1054.7). HRMS (ESI) m/z calculated 251.09329 ($C_{14}H_{11}N_4O$, $[M+H]^+$), m/z observed 251.09254 ($C_{14}H_{11}N_4O$, $[M+H]^+$).

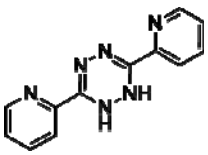


3-(pyridin-2-yl)-1,2,4-triazine (2-57). **2-10** (500 mg, 3.67 mmol) and **2-55** (40% by wt in water, 533 mg, 3.67 mmol) were added to 10 mL of EtOH. The slurry was heated overnight at 60°C with complete dissolution. Progress of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature and filtered. The filtrate was concentrated *in vacuo* to yield an orange-brown solid in 83% yield. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 9.29 (s, 1H), 8.89 (d, 1H, J = 4.2 Hz), 8.82 (s, 1H), 8.68 (d, 1H, J = 7.8 Hz), 7.93 (m, 1H), 7.49 (t, 1H, J = 6.6 Hz) ^{13}C NMR ($CDCl_3$, 151 MHz) δ 163.6, 152.5, 150.7, 149.5, 148.8, 137.4, 126.0, 124.2. UV-Vis (MeCN) λ_{max} nm (ε M^{-1} cm^{-1}): 388 (376.0). HRMS (ESI) m/z calculated 159.06707 ($C_8H_7N_4$, $[M+H]^+$), m/z observed 159.06661 ($C_8H_7N_4$, $[M+H]^+$).

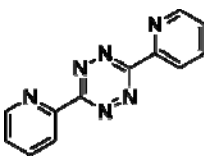


5,6-dimethyl-3-(pyridin-2-yl)-1,2,4-triazine (2-58). **2-10** (600 mg, 4.17 mmol) and **2-56** (377 mg, 4.38 mmol) were added to 10 mL of EtOH. The slurry was heated at 80°C overnight with complete dissolution. Progress of the reaction was monitored by TLC. After concentration *in vacuo*, the crude product was purified by silica gel chromatography with

gradient elution using EtOAc and hexanes to yield a pale brown solid in 90.0% yield. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.88 (m, 1H), 8.65 (d, 1H, J = 8.4 Hz), 7.90 (t, 1H, J = 7.8 Hz), 7.46-7.44 (m, 1H), 2.78 (s, 3H), 2.70 (s, 3H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 161.5, 159.6, 157.0, 153.0, 150.3, 137.1, 125.2, 123.8, 22.1, 19.7. UV-Vis (MeCN) λ_{max} nm (ε M^{-1} cm^{-1}): 372 (378.1). HRMS (ESI) m/z calculated 187.09782 ($C_{10}H_{11}N_4$, $[M+H]^+$), m/z observed 187.09857 ($C_{10}H_{11}N_4$, $[M+H]^+$).

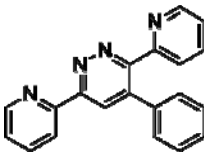


3,6-di(pyridin-2-yl)-1,2-dihydro-1,2,4,5-tetrazine (2-59). **2-7** (1.0 g, 10.5 mmol) and hydrazine hydrate (2 mL, 42 mmol) was dissolved in 8 mL of EtOH and refluxed overnight. Progress of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature and the resulting orange precipitate was filtered and washed with Et_2O resulting in a 42% yield. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.58-8.57 (m, 4H), 8.05 (d, 2H, J = 7.8 Hz), 7.75 (dt, 2H, J = 7.2, 1.8 Hz), 7.40-7.34 (m, 2H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 148.5, 147.7, 146.7, 136.9, 125.0, 121.4. UV-Vis (MeCN) λ_{max} nm (ε M^{-1} cm^{-1}): 382 (350.3). HRMS (ESI) m/z calculated 239.10452 ($C_{12}H_{11}N_6$, $[M+H]^+$), m/z observed 239.10400 ($C_{12}H_{11}N_6$, $[M+H]^+$).



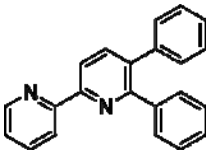
3,6-di(pyridin-2-yl)-1,2,4,5-tetrazine (2-60). To a stirring suspension of **2-59** (500 mg, 2.1 mmol) in 2.5 mL of AcOH at 0°C was added dropwise 0.4 mL of concentrated nitric acid. The

slurry was allowed to warm to room temperature overnight. The mixture was poured over cold water and made alkaline by addition of sodium carbonate solution. The resulting purple precipitate was filtered, washed with water, and dried under vacuum in 66% yield. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 9.00 (d, 2H, J = 3.6 Hz), 8.76 (d, 2H, J = 8.4 Hz), 8.02 (dt, 2H, J = 8.4, 1.8 Hz), 7.60-7.58 (m, 2H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 164.0, 151.2, 150.3, 137.6, 126.7, 124.7. UV-Vis (MeCN) λ_{max} nm (ε M^{-1} cm^{-1}): 539 (351.9). HRMS (ESI) m/z calculated 237.08887 ($C_{12}H_9N_6$, $[M+H]^+$), m/z observed 237.08985 ($C_{12}H_9N_6$, $[M+H]^+$).

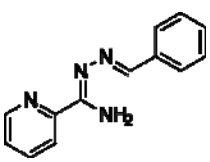


4-phenyl-3,6-di(pyridin-2-yl)pyridazine (2-61). 2-60 (260 mg, 0.85 mmol) and phenylacetylene (173 mg, 1.69 mmol) was dissolved in 5 mL of toluene. The reaction was refluxed for 8 h with progress of the reaction monitored by TLC. Upon disappearance of the starting materials, the reaction was concentrated *in vacuo* and purified by silica gel chromatography with gradient elution using EtOAc and hexanes to yield a pale brown solid in 77% yield. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.81 (d, 1H, J = 8.4 Hz), 8.74 (d, 1H, J = 4.8 Hz), 8.67 (s, 1H), 8.48 (d, 1H, J = 4.8 Hz), 7.94-7.89 (m, 2H), 7.80 (dt, 1H, J = 9.0, 1.8 Hz), 7.43-7.41 (m, 1H), 7.34-7.30 (m, 3H), 7.29-7.26 (m, 3H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 158.5, 157.9, 156.0, 153.6, 149.6, 149.2, 140.7, 137.4, 137.1, 136.7, 129.1, 128.57, 128.55, 125.8, 125.04, 124.95, 123.5, 122.1. UV-Vis (MeCN) λ_{max} nm (ε M^{-1} cm^{-1}): 350 (344.8). HRMS (ESI)

m/z calculated 311.12967 ($C_{20}H_{15}N_4$, $[M+H]^+$), m/z observed 311.12827 ($C_{20}H_{15}N_4$, $[M+H]^+$).

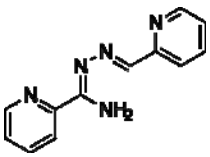


5,6-diphenyl-2,2'-bipyridine (2-62). 2-13 (250 mg, 0.81 mmol) and 2,5-norbornadiene (746 mg, 8.1 mmol) were added to 5.4 mL EtOH and refluxed overnight. Progress of the reaction was monitored by TLC. After concentration *in vacuo*, the crude product was purified by silica gel chromatography with gradient elution using EtOAc and hexanes to yield a white solid in 66% yield. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.71 (d, 1H, J = 4.8 Hz), 8.60 (d, 1H, J = 7.8 Hz), 8.45 (d, 1H, J = 7.8 Hz), 7.87 (d, 1H, J = 8.4 Hz), 7.82 (dt, 1H, J = 7.8, 1.2 Hz), 7.49-7.48 (m, 2H), 7.33-7.27 (m, 7H), 7.25-7.23 (m, 2H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 156.4, 156.2, 154.7, 149.2, 140.5, 140.1, 139.7, 137.0, 136.2, 130.3, 129.7, 128.5, 127.97, 127.96, 127.4, 123.9, 121.6, 119.3. UV-Vis (DCE) λ_{max} nm (ε M^{-1} cm^{-1}): 350 (240.5). HRMS (ESI) m/z calculated 309.13917 ($C_{22}H_{17}N_2$, $[M+H]^+$), m/z observed 309.13781 ($C_{22}H_{17}N_2$, $[M+H]^+$).

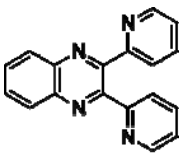


benzylidenepicolinohydrazonamide (2-64). 2-10 (250 mg, 1.84 mmol) and **2-63** (390 mg, 3.67 mmol) were added to 5 mL of EtOH. The reaction was heated overnight at 80°C with progress of the reaction monitored by TLC. The reaction mixture was cooled to room temperature and concentrated *in vacuo.* Purification by silica gel

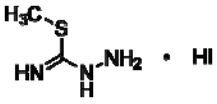
chromatography with gradient elution using EtOAc and hexanes yielded a yellow solid in 87% yield. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.61 (d, 1H, J = 4.8 Hz), 8.57 (s, 1H), 8.35 (d, 1H, J = 8.4 Hz), 7.84-7.82 (m, 2H), 7.80-7.78 (m, 1H), 7.44-7.40 (m, 3H), 7.40-7.37 (m, 1H), 6.57 (br, 2H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 157.2, 156.1, 150.4, 148.5, 136.7, 135.4, 130.3, 128.8, 128.1, 125.3, 121.5. UV-Vis (MeCN) λ_{max} nm (ε M^{-1} cm^{-1}): 332 (26568). HRMS (ESI) m/z calculated 225.11402 ($C_{13}H_{13}N_4$, $[M+H]^+$), m/z observed 225.11336 ($C_{13}H_{13}N_4$, $[M+H]^+$).



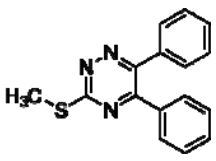
(pyridin-2-ylmethylene)picolinohydrazonamide (2-65). 2-10 (250 mg, 1.84 mmol) and **2-30** (394 mg, 3.67 mmol) were added to 5 mL of EtOH. The reaction was heated overnight at 80°C with progress of the reaction monitored by TLC. The reaction mixture was cooled to room temperature and concentrated *in vacuo.* Purification by silica gel chromatography with gradient elution using EtOAc and hexanes yielded a yellow solid in 84% yield. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.67 (d, 1H, J = 4.2 Hz), 8.63 (s, 1H), 8.60 (d, 1H, J = 4.2 Hz), 8.38 (d, 1H, J = 8.4 Hz), 8.08 (d, 1H, J = 8.4 Hz), 7.80 (dt, 1H, J = 7.2, 1.2 Hz), 7.31 (dt, 1H, J = 7.2, 1.8 Hz), 7.40-7.38 (m, 1H), 7.29-7.27 (m, 1H), 7. 6.63 (br, 2H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 157.9, 156.3, 154.4, 150.2, 149.8, 148.5, 136.8, 136.4, 125.5, 124.7, 121.8, 121.7. UV-Vis (MeCN) λ_{max} nm (ε M^{-1} cm^{-1}): 332 (32452). HRMS (ESI) m/z calculated 226.10927 ($C_{12}H_{12}N_5$, $[M+H]^+$), m/z observed 226.11020 ($C_{12}H_{12}N_5$, $[M+H]^+$).



2,3-di(pyridin-2-yl)quinoxaline (2-67). 2-66 (50 mg, 0.472 mmol) and 1,2-di(pyridin-2-yl)ethane-1,2-dione (100 mg, 0.472 mmol) were dissolved in 2.4 mL of EtOH and refluxed for 6 h. After cooling to room temperature, the reaction mixture was concentrated *in vacuo* yielding a pale brown solid in quantitative yield. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.38 (d, 2H, J = 4.8 Hz), 8.23 (dd, 2H, J = 3.6, 2.4 Hz), 7.96 (d, 2H, J = 7.8 Hz), 7.84-7.80 (m, 4H), 7.24 (m, 2H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 157.6, 152.6, 148.8, 141.3, 136.8, 130.6, 129.6, 124.4, 123.1. UV-Vis (MeCN) λ_{max} nm (ε M^{-1} cm^{-1}): 332 (8345). HRMS (ESI) m/z calculated 285.11402 ($C_{18}H_{13}N_4$, $[M+H]^+$), m/z observed 285.11511 ($C_{18}H_{13}N_4$, $[M+H]^+$).

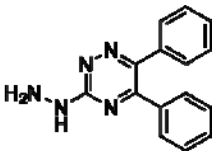


methyl hydrazinecarbimiodthioate hydroiodide (2-69). 2-68 (500 mg, 5.49 mmol) was dissolved in 10 mL EtOH and heated at 60°C for 30 min. Iodomethane (0.38 mL, 6.06 mmol) was added portion wise and continue stirring at 60°C for an additional 30 min. After cooling to room temperature, the mixture was concentrated *in vacuo* resulting in a pale brown solid in quantitative yield. The recovered solid was used in further reactions without additional purification.

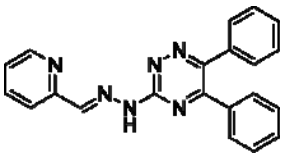


3-(methylthio)-5,6-diphenyl-1,2,4-triazine (2-70). 2-69 (500 mg, 2.15 mmol) and benzil (451 mg, 2.15 mmol) were dissolved in 10 mL of EtOH and stirred overnight at room temperature.

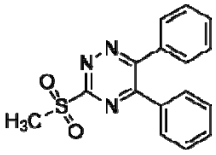
Progress of the reaction was monitored by TLC. The reaction was quenched by addition of saturated sodium bicarbonate and solid sodium sulfate and stirring 30 min. The mixture was filtered and DCM was added to the resulting precipitate. The DCM solution was filtered and the corresponding filtrate concentrated *in vacuo*. The product was isolated as a yellow solid in 89% yield. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.55 (d, 2H, J = 8.4 Hz), 7.52 (d, 2H, J = 7.8 Hz), 7.44-7.39 (m, 2H), 7.37-7.32 (m, 4H), 2.76 (s, 3H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 171.3, 155.6, 153.9, 135.54, 135.52, 131.0, 130.0, 129.57, 129.56, 128.8, 128.7, 14.2. HRMS (ESI) m/z calculated 280.09084 ($C_{16}H_{14}N_3S$, $[M+H]^+$), m/z observed 280.08966 ($C_{16}H_{14}N_3S$, $[M+H]^+$).



3-hydrazinyl-5,6-diphenyl-1,2,4-triazine (2-71). 2-70 (200 mg, 0.717 mmol) and hydrazine hydrate (336 mg, 4.30 mmol) were dissolved in 2 mL of EtOH and heated at 80°C overnight. Progress of the reaction was monitored by TLC. The reaction mixture was concentrated *in vacuo* and dried under vacuum yielding a green-yellow solid in 84% yield. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.49-7.48 (m, 2H), 7.43-7.41 (m, 3H), 7.36-7.32 (m, 5H), 6.60 (br, 1H), 4.17 (br, 2H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 162.42, 157.3, 151.4, 136.2, 136.1, 130.7, 129.8, 129.5, 128.8, 128.6. UV-Vis (MeCN) λ_{max} nm (ε M^{-1} cm^{-1}): 353 (2894). HRMS (ESI) m/z calculated 264.12492 ($C_{15}H_{14}N_5$, $[M+H]^+$), m/z observed 264.12513 ($C_{15}H_{14}N_5$, $[M+H]^+$).

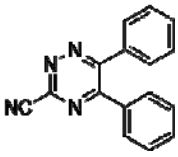


5,6-diphenyl-3-(2-(pyridin-2-ylmethylene)hydrazinyl)-1,2,4-triazine (2-72). **2-71** (75 mg, 0.285 mmol) and **2-30** (31 mg, 0.285 mmol) were dissolved in 3 mL of EtOH and refluxed for 4 h. After cooling to room temperature, the resulting precipitate was filtered and rinsed with EtOH yielding a yellow solid in 80% yield. ^{1}H NMR (d_6-DMSO, 600 MHz) δ 8.60 (d, 1H, J = 4.8 Hz), 8.34 (s, 1H), 8.00 (d, 1H, J = 8.4 Hz), 7.87 (t, 1H, J = 7.8 Hz), 7.05-7.36 (m, 12H). ^{13}C NMR (d_6-DMSO, 151 MHz) δ 158.4, 156.6, 153.6, 151.4, 149.4, 144.3, 136.8, 136.0, 135.8, 130.3, 129.5, 129.1, 128.5, 128.30, 128.29, 123.8, 119.5. UV-Vis (9:1 DCE/MeOH) λ_{max} nm (ε M^{-1} cm^{-1}): 376 (13290). HRMS (ESI) m/z calculated 353.15147 ($C_{21}H_{17}N_6$, $[M+H]^+$), m/z observed 353.14993 ($C_{21}H_{17}N_6$, $[M+H]^+$).



3-(methylsulfonyl)-5,6-diphenyl-1,2,4-triazine (2-76). Dissolved **2-70** (2.5 g, 8.9 mmol) and tetrabutylammonium bromide (287 mg, 0.89 mmol) in 60 mL of benzene and 18 mL of AcOH. Added potassium permanganate (2.8 g, 17.9 mmol) as a solution in 90 mL of water to the reaction and stirred at room temperature overnight. Added saturated sodium bisulfite (approx 5 mL) until color disappeared. Neutralized solution with solid potassium carbonate. Dried organic layer with anhydrous sodium sulfate and concentrated *in vacuo* yielding a yellow solid in 77% yield. Compound was used immediately or carefully stored away from light and in the freezer to prevent decomposition. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.68 (d, 2H, J =

7.2 Hz), 7.62 (d, 2H, J = 7.2 Hz), 7.52-7.49 (m, 2H), 7.43 (t, 2H, J = 7.8 Hz), 7.37 (t, 2H, J = 7.8 Hz). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 164.5, 159.7, 158.1, 134.2, 133.8, 132.33, 131.0, 130.4, 129.7, 129.4, 129.0, 128.5. HRMS (ESI) m/z calculated 312.08067 ($C_{16}H_{14}N_3O_2S$, $[M+H]^+$), m/z observed 312.08136 ($C_{16}H_{14}N_3O_2S$, $[M+H]^+$).



5,6-diphenyl-1,2,4-triazine-3-carbonitrile (2-77). Dissolved **2-76** (500 mg, 1.61 mmol) and finely crushed KCN (210 mg, 3.22 mmol) in 16 mL of DMF and stirred at room temperature. Progress of the reaction was closely monitored by TLC and not allowed to stir overnight. When reaction reached completion, added a small amount of water and extracted with DCM. Purification by alumina chromatography with gradient elution using EtOAc and hexanes yielded a yellow solid in 75% yield. ^1H NMR ($CDCl_3$, 600 MHz) δ 7.63 (d, 4H, J = 7.8 Hz), 7.51 (t, 2H, J = 7.8 Hz), 7.43 (t, 2H, J = 7.8 Hz), 7.39 (t, 2H, J = 7.8 Hz). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 158.3, 156.5, 144.8, 134.1, 133.6, 132.3, 131.2, 130.1, 129.8, 129.2, 129.1. MS (ESI) m/z calculated 259.09837 ($C_{16}H_{11}N_4$, $[M+H]^+$), m/z observed 259.09377 ($C_{16}H_{11}N_4$, $[M+H]^+$).

Chapter 3

Catalytic Activity of 1,2,4-Triazine Ligands

The text of Chapter 3 was taken in part from a manuscript coauthored with Belinda Lady and Professor Shane Foister (University of Tennessee, Knoxville).

Prince, A. L.; Lady, B. S.; Elgammal, R. A.; Foister, S. “1,2,4-Triazine-Accelerated CuAAC.” *Chem. Eur. J.*, **in submission**.

3.1 Background and Significance

Since its discovery in 2002, the copper-catalyzed azide-alkyne cycloaddition (CuAAC) has become a fundamental reaction in routine organic synthesis.[18,20] As a result, "click chemistry" has found success in an array of applications, spanning the fields of medicinal chemistry,[70,71] biological chemistry,[72-74] and materials science.[12,13] This expanding array of applications has driven the demand for additional synthetic methods yielding 1,2,3-triazoles, including the addition of nitrogen-based ligands that stabilize the active copper(I) species. Despite the interest that ligand-accelerated CuAAC has received, challenges such as ligand solubility, prolonged reaction times, and difficulties in product purification remain.

Motivated by the necessity to develop a simplified procedure for the synthesis of 1,2,3-triazoles, a series of 1,2,4-triazines were synthesized and their propensity to accelerate the CuAAC reaction has been examined in detail. These ligands were found to be potent accelerants, at catalytic concentrations, in the presence of either copper(I) or copper(II) salts. 1,2,4-Triazine acceleration of CuAAC was observed in both polar and nonpolar solvents, requiring one equivalent of triethylamine for optimal results. Additional experiments employing a diverse selection of azides and alkynes were also examined, thus defining a broad substrate scope for 1,2,4-triazines as catalysts for CuAAC. The structural requirements for 1,2,4-triazines were outlined using a diverse library of ligands,

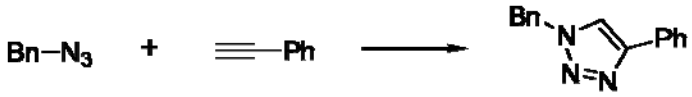
while preliminary mechanistic studies suggested a novel mode of action for 1,2,4-triazines as CuAAc catalysts.

3.2 Optimization of Reaction Conditions for 1,2,4-Triazine-Accelerated CuAAC

We began our investigation of 1,2,4-triazine-accelerated CuAAC in the context of the model reaction between benzyl azide and phenylacetylene in acetonitrile. Reactions were performed by sequential addition of **2-13**, followed by a copper salt, to a 0.2 M solution of azide and alkyne, in the presence of triethylamine. After one hour under ambient conditions, percent yields were determined by quantification of the 1,2,3-triazole product using LC-MS. Initial experiments examined the relative stoichiometries of ligand **2-13** and tetrakis(acetonitrile-N)copper(I) tetrafluoroborate relative to a control reaction (Table 3.1, entries 1-6). While ligand **2-13** significantly enhances the percent yield in all cases, an equimolar mixture of ligand and copper at 1 mol% was found to be optimal. The control reaction, using the same standard conditions without ligand **2-13** resulted in a considerably diminished yield of 12%.

In light of these results and recent reports in the chemical literature[75,76], copper(II) salts were then examined in combination of ligand **2-13** (entries 7-8). Surprisingly, percent yields using copper(II) salts were found to be comparable to reactions containing copper(I) salts. These reactions proceed without the

Table 3.1 Optimization of Reaction Conditions for 1,2,4-Triazine-Accelerated CuAAC.[a]



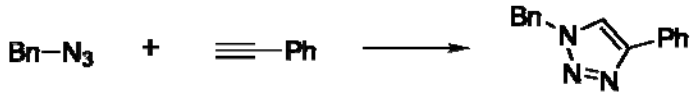
Entry	Copper Source	mol% Copper	mol% Triazine	Percent Yield after 1 h
1	$[Cu(MeCN)_4]^+BF_4^-$	2	2	66.6 ± 5.7
2	$[Cu(MeCN)_4]^+BF_4^-$	1	2	65.5 ± 3.5
3	$[Cu(MeCN)_4]^+BF_4^-$	1	1	75.1 ± 1.4
4	$[Cu(MeCN)_4]^+BF_4^-$	1	0.5	44.0 ± 2.8
5	$[Cu(MeCN)_4]^+BF_4^-$	0.5	0.5	25.1 ± 1.3
6	$[Cu(MeCN)_4]^+BF_4^-$	1	0	12.0 ± 0.6[b]
7	$Cu(OAc)_2 \cdot H_2O$	1	1	62.4 ± 8.2
8	$Cu(BF_4)_2 \cdot 6H_2O$	1	1	72.0 ± 3.2

[a]General conditions: benzyl azide (1 eq), phenylacetylene (1 eq), triethylamine (2 eq), copper source, and 5,6-diphenyl-3-(pyridin-2-yl)-1,2,4-triazine (**2-13**). Reactions were run at room temperature in 0.2 M acetonitrile with respect to substrates.
[b]General conditions with following exception: triethylamine (1 eq)

addition of excessive reducing agents, such as sodium ascorbate. CuAAC acceleration with ligand **2-13** and copper(II) acetate is comparable to that reported for copper(II) acetate alone, though occurring at lower loading (1 mol% vs. 5 mol%), and in shorter time intervals (1 hour vs. 18 hours).[75,76] In addition, regardless of the copper salt employed with **2-13**, no byproducts resulting from Glaser coupling were observed.

The role of organic base on CuAAC acceleration by **2-13** was next investigated. Of the three bases studied, only triethylamine produced satisfactory yields (Table 3.2, entries 1-4). Since the pyridine functional group is known to bind metal, this observation may be a result of the heterocyclic bases saturating the copper species thereby halting the progress of the reaction. It was

Table 3.2 Optimization of Organic Base in 1,2,4-Triazine-Accelerated CuAAC.[a]



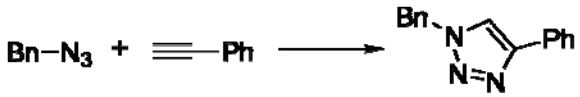
Entry	Base	Equivalents of Base	Percent Yield after 1 h
1	None	N/A	< 5
2	Pyridine	2	< 5
3	2,6-Lutidine	2	11.2 ± 0.5
4	Triethylamine	2	75.0 ± 1.4
5	Triethylamine	1	89.3 ± 2.4
6	Triethylamine	5	59.4 ± 0.8

[a]General conditions: benzyl azide (1 eq), phenylacetylene (1 eq), organic base, and tetrakis(acetonitrile-N)copper(I) tetrafluoroborate (0.01 eq), and 5,6-diphenyl-3-(pyridin-2-yl)-1,2,4-triazine (**2-13**) (0.01 eq). Reactions were run at room temperature in 0.2 M acetonitrile with respect to substrates.

determined that an optimal yield of 89% was reached when 1 equivalent of triethylamine was added, relative to azide and alkyne substrates (entries 4-6). Trialkylamines are often employed to stabilize copper(I) species during organic reactions and also required for 1,2,4-triazine-accelerated CuAAC; however, triethylamine alone, in the absence of **2-13**, resulted in an insignificant percent yield of 1,2,3-triazole (Table 3.1, entry 6).

The concentration of click reactions is also of importance, especially in regards to biological systems. Therefore, further experiments were applied to the model reaction in order to determine the effective substrate concentration range (Table 3.3). The relative concentrations of triazine ligand **2-13** and copper were maintained at 1 mol% with respect to the substrates. The maximum activity was

Table 3.3. Evaluation of Substrate Concentration in 1,2,4-Triazine-Accelerated CuAAC.[a]



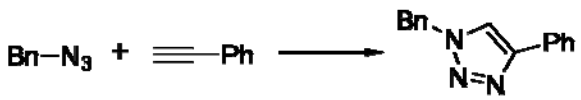
Entry	Substrate Concentration	Percent Yield after 1 h
1	0.2 M	89.3 ± 2.4
2	0.1 M	72.9 ± 2.9
3	0.05 M	24.8 ± 1.7

[a]General conditions: benzyl azide (1 eq), phenylacetylene (1 eq), triethylamine (1 eq), and tetrakis(acetonitrile-N)copper(I) tetrafluoroborate (0.01 eq), and 5,6-diphenyl-3-(pyridin-2-yl)-1,2,4-triazine (**2-13**) (0.01 eq). Reactions were run at room temperature in acetonitrile at concentrations listed with respect to substrates.

observed at a substrate concentration of 0.2 M, although appreciable activity was still seen after one hour at substrate concentrations of 0.1 M.

Having a choice of multiple solvents greatly enhances the toolbox of a synthetic chemist and also expands the potential applications of 1,2,4-triazine-accelerated CuAAC. For that reason, additional experiments were conducted to explore the ability of triazine **2-13** to function efficiently in a variety of organic solvents. The obtained isolated yields revealed that **2-13** functions efficiently in solvents with different polarity. Among the solvents studied, dichloromethane, toluene, and ethyl acetate all resulted in isolated percent yields above 90% within one hour (Table 3.4). The least effective solvents examined included dimethylsulfoxide, isopropyl alcohol, and tetrahydrofuran, although the latter did produce reasonable yields after prolonged reaction times.

Table 3.4 Evaluation of Solvent in 1,2,4-Triazine-Accelerated CuAAC.[a]



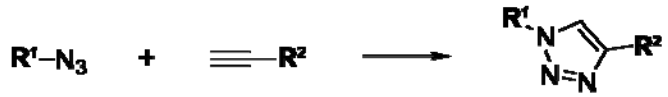
Entry	Solvent	Isolated Percent Yield
1	Dichloromethane	92
2	Toluene	91
3	Ethyl Acetate	90
4	Acetone	79
5	Dimethylformamide	61
6	Dioxane	83
7	Cyclohexane	85
8	Tetrahydrofuran	86[b]
9	Dimethylsulfoxide	13
10	Isopropanol	45

[a]General conditions: azide (1 eq), alkyne (1 eq), triethylamine (1 eq), tetrakis(acetonitrile-N)copper(I) tetrafluoroborate (0.01 eq), and 5,6-diphenyl-3-(pyridin-2-yl)-1,2,4-triazine (2-13) (0.01 eq) in 20% ACN: 80% solvent at room temperature for 1 hr. Isolated by flash chromatography and percent yields are an average of two reactions.
[b]No reaction after 1 hr. Yield represents reaction after 24 hrs.

3.3 Substrate Scope of 1,2,4-Triazine-Accelerated CuAAC

The acceleration of CuAAC by triazine ligand **2-13** was next evaluated with azide and alkyne substrates having different stereoelectronic features (Table 3.5). In addition to benzyl azide, electron rich and electron poor aromatic azides, as well as primary and secondary alkyl azides were found to be compatible with 1,2,4-triazine-accelerated CuAAC. Sterically hindered aromatic azides also resulted in high percent yields; however, tertiary azide substrates were unreactive even at long reaction intervals.

Table 3.5 Substrate Scope of 1,2,4-Triazine-Accelerated CuAAC.[a]



3-1 3-2 3-3

Entry	R^1	R^2	Product	Isolated Percent Yield
1	Bn (3-1a)	Ph (3-2a)	3-3a	87
2	Ph (3-1b)	Ph (3-2a)	3-3b	95[b]
3	4-OMePh (3-1c)	Ph (3-2a)	3-3c	83[b]
4	4-CO_2MePh (3-1d)	Ph (3-2a)	3-3d	91[b]
5	2,4-diMePh (3-1e)	Ph (3-2a)	3-3e	90
6	2,6-diMePh (3-1f)	Ph (3-2a)	3-3f	83
7	$CH_3(CH_2)_6$ (3-1g)	Ph (3-2a)	3-3g	88
8	$CH_3(CH_2)_4CHCH_3$ (3-1h)	Ph (3-2a)	3-3h	80
9	1-adamantyl (3-1i)	Ph (3-2a)	3-3i	5
10	Bn (3-1a)	CH_2OH (3-2b)	3-3j	76
11	Bn (3-1a)	$C(CH_3)_2OH$ (3-2c)	3-3k	80
12	Bn (3-1a)	1-OHC_6H_{10} (3-2d)	3-3l	79
13	Bn (3-1a)	2,4-diMePh (3-2e)	3-3m	68
14	Bn (3-1a)	4-OMePh (3-2f)	3-3n	87[c]
15	Bn (3-1a)	4-CO_2MePh (3-2g)	3-3o	86[c]
16	Bn (3-1a)	2-CO_2MePh (3-2h)	3-3p	89[c]

[a]General conditions: azide (1 eq), alkyne (1 eq), triethylamine (1 eq), tetrakis(acetonitrile-N)copper(I) tetrafluoroborate (0.01 eq), and 5,6-diphenyl-3-(pyridin-2-yl)-1,2,4-triazine (1) (0.01 eq). Reactions were run at room temperature for 18 h in 0.2 M acetonitrile with respect to substrates. Products were isolated by flash chromatography and percent yields are an average of two reactions.

[b]Isolated by filtration and percent yields are an average of two reactions

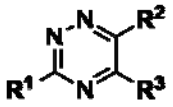
[c]General conditions with the following exception: Rxn carried out in dichloromethane using copper(II) tetrafluoroborate hexahydrate to avoid bis-triazole formation.

Alkyne substrates proved to be more sensitive to the reaction conditions employed, especially when the alkyne was present on an aromatic ring also containing an ether or ester functional group. In these cases, when the reaction was run in acetonitrile, a bis-triazole byproduct[77] (**3-4**), not easily separated from the desired 1,2,3-triazole product, was formed. The formation of this byproduct was prevented by using dichloromethane as a solvent, thereby allowing isolation of the intended 1,2,4-triazole product. Overall, varying the alkyne substituent resulted in a greater variation from the percent yield of the model system using phenylacetylene. Nevertheless, alkyl and sterically hindered alkynes were also found to be amenable with 1,2,4-triazine-accelerated CuAAC in moderate yields.

3.4 Ligand Scope of 1,2,4-Triazine-Accelerated CuAAC

With an increased understanding of the optimal reaction conditions, we proceeded to synthesize a library of 1,2,4-triazine ligands to further analyze the structural requirements necessary for activity. While the most active 1,2,4-triazine ligand (**2-13**) was used for previous optimization studies, additional ligands also showed high activity for the acceleration of CuAAC (Table 3.6). It quickly became evident that the 3-pyridin-2-yl substituent is critical for activity, as additional nitrogen heterocycles, such as 2-pyrimidine (**2-14**) and 2-pyrazine (**2-15**), resulted in a drastic decrease in activity. In accord with this observation, other nitrogen-containing functional groups proved to be inactive as well,

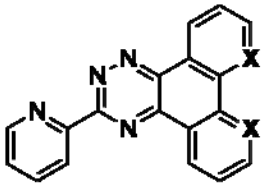
Table 3.6 CuAAC Reactions with Various 1,2,4-Triazines and Derivatives.[a]



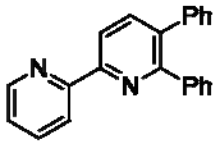
2-13 R^1 = 2-pyr, R^2 = R^3 = Ph
2-57 R^1 = 2-pyr, R^2 = R^3 = H
2-58 R^1 = 2-pyr, R^2 = R^3 = CH_3
2-34 R^1 = R^2 = R^3 = 2-pyr
2-20 R^1 = R^2 = R^3 = Ph

2-33 R^1 = 2-pyr, R^2 = R^3 = 4-CH_3-Ph
2-39 R^1 = 2-pyr, R^2 = R^3 = 4-NO_2-Ph
2-40 R^1 = 2-pyr, R^2 = R^3 = 4-NH_2-Ph
2-52 R^1 = 2-pyr, R^2 = H, R^3 = Ph
2-53 R^1 = 2-pyr, R^2 = H, R^3 = 2-OH-Ph

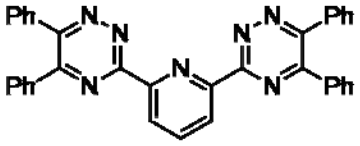
2-21 R^1 = 2-aniline, R^2 = R^3 = Ph
2-14 R^1 = 2-pyrimidine, R^2 = R^3 = Ph
2-15 R^1 = 2-pyrazine, R^2 = R^3 = Ph
2-71 R^1 = $NHNH_2$, R^2 = R^3 = Ph
2-72 R^1 = NHNCH-(2-pyr), R^2 = R^3 = Ph



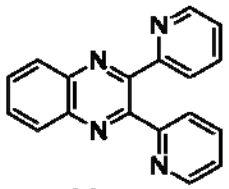
2-42 X = CH
2-45 X = N



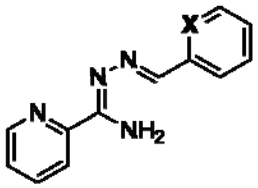
2-62



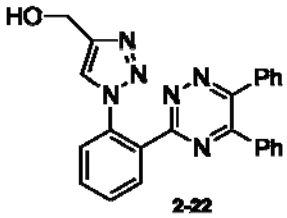
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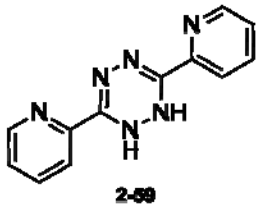
2-67



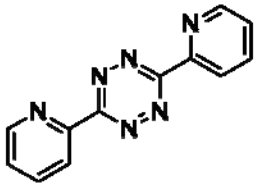
2-64 X = CH
2-65 X = N



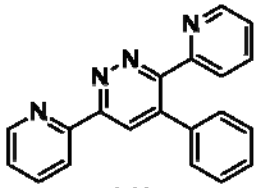
2-22



2-59



2-60



2-61

Entry	Ligand	Percent Yield after 1 h	Entry	Ligand	Percent Yield after 1 h	Entry	Ligand	Percent Yield after 1 h
1	2-13	89.3 ± 2.4	10	2-39	60.9 ± 2.5	19	2-60	19.4 ± 0.4
2	2-14	28.5 ± 1.1	11	2-40	60.5 ± 0.9	20	2-61	26.7 ± 0.4
3	2-15	24.4 ± 0.5	12	2-42	75.3 ± 3.1	21	2-62	19.2 ± 0.2
4	2-20	13.2 ± 1.1	13	2-45	79.6 ± 4.6	22	2-64	19.3 ± 0.3
5	2-21	12.1 ± 0.4	14	2-52	71.7 ± 0.6	23	2-65	17.8 ± 0.2
6	2-22	10.3	15	2-53	44.9 ± 1.3	24	2-67	27.6 ± 0.7
7	2-28	15.1 ± 1.1	16	2-57	41.8 ± 5.5	25	2-71	26.2 ± 0.9
8	2-33	85.6 ± 2.8	17	2-58	57.1 ± 3.3	26	2-72	19.4 ± 0.5
9	2-34	20.4 ± 0.2	18	2-59	23.0 ± 0.3			

[a]General conditions: benzyl azide (1 eq), phenylacetylene (1 eq), triethylamine (1 eq), tetrakis(acetonitrile-N)copper(I) tetrafluoroborate (0.01 eq), and triazine (0.01 eq). Reactions were run at room temperature in 0.2 M acetonitrile with respect to substrates.

including 2-aniline (**2-21**), hydrazine (**2-71**), and imine (**2-72**). To date, the 3-pyridin-2-yl group has proven to be irreplaceable; however, based on recent literature results[40] other heterocycles may also prove to be active in future studies.

Alterations to the 5- and 6-positions of the 1,2,4-triazine scaffold provided additional structural information as well. As the phenyl rings of **2-13** are replaced with hydrogen atoms, activity begins to decrease thus resulting in a direct correlation between the phenyl rings at 5- and 6-position and activity (**2-52**, **2-57**). Removal of the 6-phenyl substituent of **2-13** results in a ligand with appreciable activity, suggesting that the 5-substituent may exert a greater influence on copper coordination. Furthermore, a 1,2,4-triazine containing methyl groups at the 5- and 6-positions (**2-58**) showed a significant increase in activity compared to having only protons at these positions (**2-57**), thereby highlighting the significant affect that substituents at the 5- and 6-positions play in overall activity. Although aromatic rings resulted in higher activity than alkyl substituents, having 2-pyridyl rings at positions 5 and 6 (**2-34**) resulted in a considerable decrease in activity, possibly due to the electron-withdrawing nature of the pyridine ring.

The addition of groups to the para-position of the phenyl rings at 5 and 6 not only increased solubility of the ligands, but revealed an electrostatic preference for 1,2,4-triazine ligands. The slightly electron-donating methyl groups (**2-33**) still retained a high activity, whereas the stronger electron-donating amine groups (**2-40**) and electron-withdrawing nitro (**2-39**) groups caused a

predominant decrease in activity. In addition to electrostatic effects, we also examined consequences of altering the three-dimensional conformation of **2-13** by fusion of the phenyl rings at the 5- and 6-positions. The phenyl rings of **2-13** are slightly twisted in relation to the 1,2,4-triazine, while 1,2,4-triazine ligands **2-42** and **2-45** are entirely flat. This observation, in combination with decreased solubility, may contribute to the slight reduction in activity of ligands **2-42** and **2-45**.

The importance of the core 1,2,4-triazine scaffold was investigated by replacing the 1,2,4-triazine with various other heterocycles. All attempts to replace the 1,2,4-triazine proved to be detrimental to the CuAAC activity of the

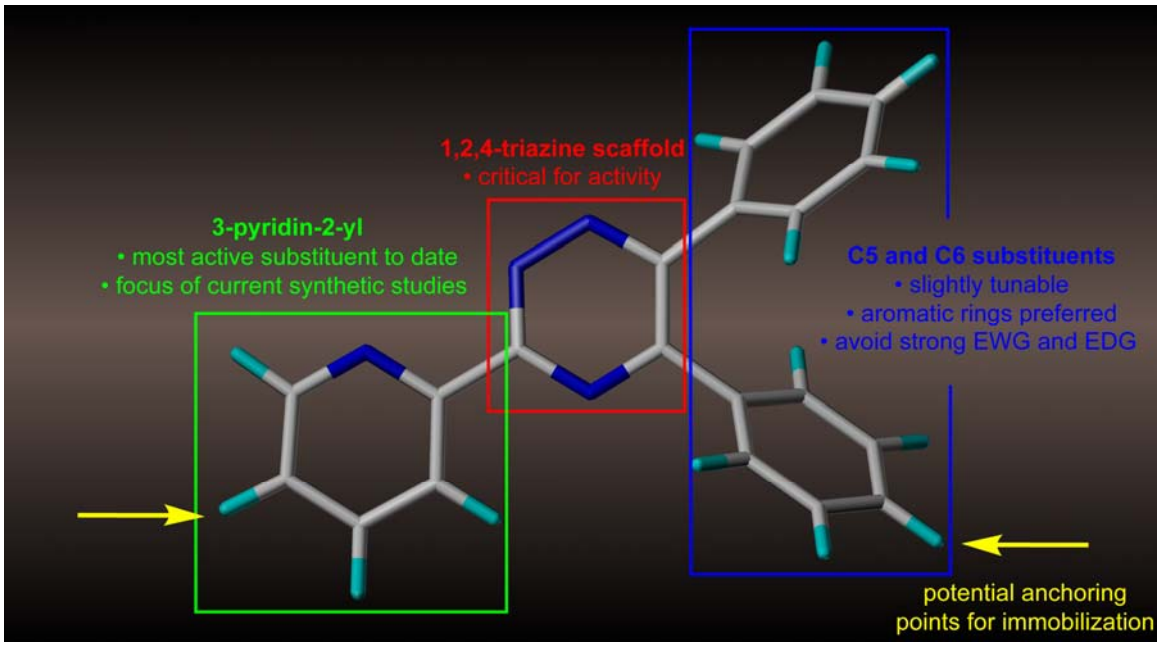


Figure 3.1 Structural Features of 1,2,4-Triazine Ligands.

ligand as heterocycles such as pyridine (**2-62**), pyridazine (**2-61**), quinoxaline (**2-67**), and tetrazine (**2-60**) groups all resulted in percent yields lower than thirty percent. Likewise, the 2,6-bis-1,2,4-triazine (**2-28**) also proved to be inactive, possibly owing to the introduction of steric bulk vicinal to the pyridine nitrogen. Therefore, the structure-activity relationships presented in Table 3.6 correlate well with the details of triazine-copper complexes presented in the chemical literature.[52,53]

In conclusion, the structural features of 1,2,4-triazine ligands as accelerants for CuAAC have been studied (Figure 3.1). While the 2-pyridine is the most active substituent to date at the 3-position, current synthetic methods are underway to synthesize "hybrid ligands" containing various other metal binding heterocycles at the 3-position. The catalytic activity of 1,2,4-triazines is highest when the 5- and 6-positions are occupied by bulky, aromatic rings, although avoidance of strong electron-withdrawing and electron-donating groups is advised. Finally, it was determined that the 1,2,4-triazine scaffold was irreplaceable and thus required to maintain activity. All considered, in order to avoid interference with the copper-binding face of the 1,2,4-triazine, all strategies for immobilization of the triazine ligand (further discussed in chapter 4) were attempted from the opposite face.

3.5 Mechanistic Investigations of 1,2,4-Triazine-Accelerated CuAAC

In efforts to explore the copper dependence of 1,2,4-triazine-accelerated CuAAC, UV-Vis spectroscopy was examined in the presence of both copper(I) and copper(II) sources. Absorption spectra of mixtures of ligand **2-13** with copper(I) and copper(II) salts, in the presence and absence of triethylamine, suggest that 1,2,4-triazine ligands do stabilize copper(I) species (Figure 3.2A). The long wavelength absorption, characteristic of d-d transitions in copper(II) complexes (>700 nm), is diminished in the presence of ligand **2-13** and base. Furthermore, the absorption spectrum of a solution of ligand **2-13**, triethylamine, and a copper(II) salt is essentially superimposable with the corresponding absorption spectrum of a solution containing a copper(I) salt. The presence of

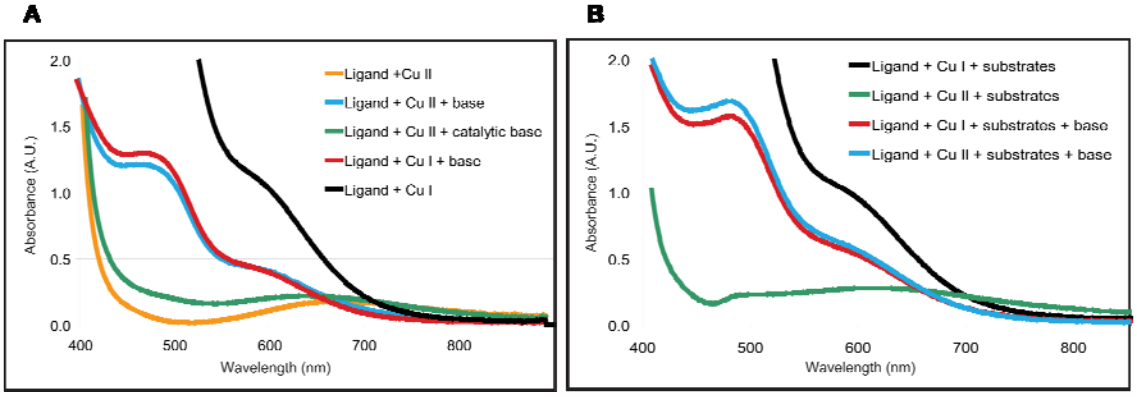
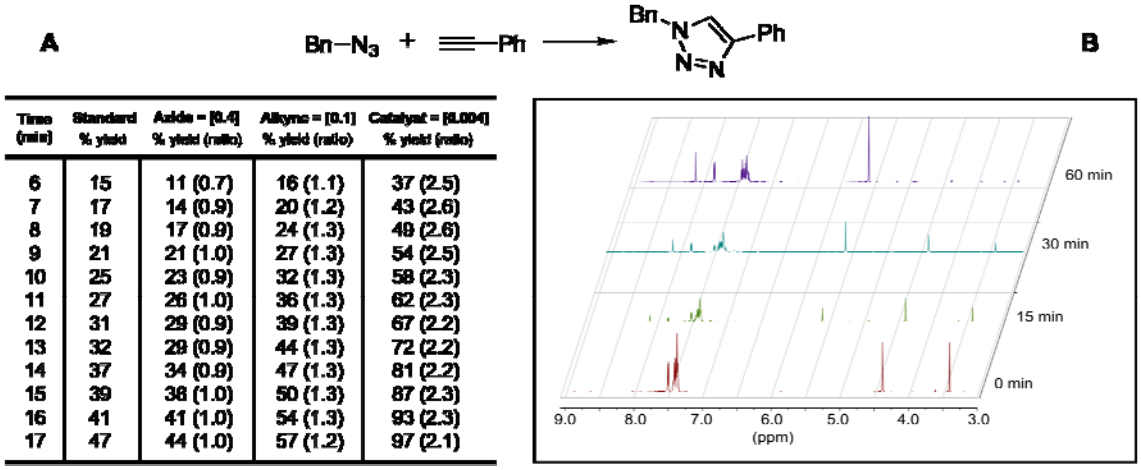


Figure 3.2 UV-Vis spectra of 1,2,4-triazine-accelerated CuAAC. 5,6-diphenyl-3-(pyridin-2-yl)-1,2,4-triazine (0.01 eq) (**2-13**) in acetonitrile with either tetrakis(acetonitrile-N)copper(I) tetrafluoroborate (0.01 eq) or copper(II) tetrafluoroborate hexahydrate (0.01 eq). The addition of triethylamine (0.01 eq or 1.0 eq) was studied without (**A**) and with (**B**) benzyl azide (1.0 eq) and phenylacetylene (1.0 eq).

azide and alkyne substrates does not affect this feature of the absorption spectra (Figure 3.2B).

A preliminary investigation of the kinetics of 1,2,4-triazine-accelerated CuAAC in the model reaction between benzyl azide and phenylacetylene was undertaken using ^{1}H NMR (Figure 3.3). Based upon these initial observations, the reaction rate appears to be zero order with respect to the azide substrate and approximately first order with respect to 1,2,4-triazine ligand **2-13** and tetrakis(acetonitrile-N)copper(I) tetrafluoroborate. The reaction order with respect to the alkyne substrate is more complex as higher concentrations of



Time (min)	Standard % yield	Azide = [0.4] % yield (ratio)	Alkyne = [0.1] % yield (ratio)	Catalyst = [0.004] % yield (ratio)
6	15	11 (0.7)	16 (1.1)	37 (2.5)
7	17	14 (0.9)	20 (1.2)	43 (2.6)
8	19	17 (0.9)	24 (1.3)	49 (2.6)
9	21	21 (1.0)	27 (1.3)	54 (2.5)
10	25	23 (0.9)	32 (1.3)	58 (2.3)
11	27	26 (1.0)	36 (1.3)	62 (2.3)
12	31	29 (0.9)	39 (1.3)	67 (2.2)
13	32	29 (0.9)	44 (1.3)	72 (2.2)
14	37	34 (0.9)	47 (1.3)	81 (2.2)
15	39	38 (1.0)	50 (1.3)	87 (2.3)
16	41	41 (1.0)	54 (1.3)	93 (2.3)
17	47	44 (1.0)	57 (1.2)	97 (2.1)

Figure 3.3 Kinetic NMR Data of 1,2,4-Triazine-Accelerated CuAAC Reaction. (**A**) Standard conditions: benzyl azide (0.2 M), phenylacetylene (0.2 M), triethylamine (0.4 M), tetrakis(acetonitrile-N)copper(I) tetrafluoroborate (0.002 M), and 5,6-diphenyl-3-(pyridin-2-yl)-1,2,4-triazine (**2-13**) (0.002 M) in deuterated acetonitrile. Concentrations for additional reactions were altered as indicated above. Ratio is percent yield of the indicated reaction divided by that of the standard reaction. (**B**) Kinetic array for 1,2,4-triazine-accelerated CuAAC reaction under standard conditions. Disappearance of alkyne (3.4 ppm) and benzylic azide protons (4.4 ppm) as benzylic triazole protons (5.6 ppm) appear over time.

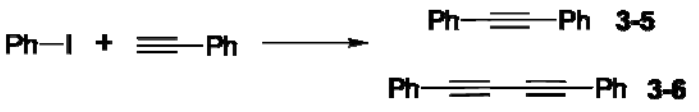
phenylacetylene appear to slow the rate of reaction. More detailed kinetic studies, such as electrochemistry experiments, are needed to draw any further conclusions and fully access the mechanistic details of this reaction.

3.6 1,2,4-Triazine-Accelerated Sonogashira Reactions

The synthesis of aromatic alkynes is also of interest to our group, due to their large role in CuAAC reactions. Therefore, we have begun to investigate 1,2,4-triazines as accelerants in the Sonogashira Reaction, which employs both copper and palladium as transition metal catalysts. The most commonly utilized palladium source is bis(triphenylphosphine)palladium(II),[78] wherein reactions typically reach completion within a few hours at room temperature (Table 3.7, entry 1). However, 1,3-diynes, oxidative byproducts resulting from the Glaser Reaction, are also observed.

When used as accelerants in CuAAC, 1,2,4-triazines prohibit the formation of oxidative byproducts. While their use as ligands in Sonogashira Reactions does require mild heat and results in a slightly lower overall yield, the ratio of product to 1,3-diyne is double that of typical reaction conditions (Table 3.8, entry 2). Encouraged by these initial results, a thorough investigation of 1,2,4-triazine-accelerated Sonogashira Reactions is currently underway. Although, CuAAC reactions with *in-situ* formation of azides are relatively common[79,80], there are few

Table 3.7 1,2,4-Triazine-Accelerated Sonogashira Reaction.



Entry	Percent Yield of 3-5	Percent Yield of 3-6	Ratio of 3-5 : 3-6
1[a]	85	15	5.7
2[b]	77	6	12.8

[a]General conditions: iodobenzene (1 eq), phenylacetylene (1.25 eq), triethylamine (1.25 eq), copper iodide (0.015 eq), and bis(triphenylphosphine)palladium(II) (0.025 eq) in 0.4 M tetrahydrofuran at room temperature after 5.5 h. Percent yields determined by HPLC.
[b]General conditions: iodobenzene (1 eq), phenylacetylene (1.25 eq), triethylamine (1.25 eq), copper iodide (0.015 eq), palladium acetate (0.025 eq), and 5,6-diphenyl-3-(pyridin-2-yl)-1,2,4-triazine (**2-13**) (0.08 eq) in 0.4 M acetonitrile at 60°C after 5.5 h. Percent yields determined by HPLC.

examples of one-pot Sonogashira-CuAAC reactions.[81] As a result, we intend to fully investigate the potential of 1,2,4-triazine ligands as accelerants of this one-pot reaction in detail.

3.7 Conclusions

In summary, the ability of 1,2,4-triazine ligands as accelerants for CuAAC reactions have been discussed. These ligands operate in the presence of copper(I) or copper(II) salts and give high isolated yields of product 1,2,3-triazoles in short reaction times under ambient conditions. Excessive reducing agents, such as sodium ascorbate, are not necessary and products are not contaminated by diyne by-products or trace amounts of copper. 1,2,4-Triazine ligands are very practical synthetic targets and function at millimolar

concentrations. The value of these ligands as accelerants for CuAAC is enhanced by the finding that they operate effectively in numerous solvents, which gives synthetic chemists a wide variety of conditions which can be tailored to particular azide and alkyne starting materials. Finally, 1,2,4-triazine-accelerated CuAAC has been successfully applied to numerous azide and alkyne starting materials, such as electron rich, electron poor, primary, secondary, and sterically hindered substrates.

Essential structural requirements of 1,2,4-triazine ligands have been detailed, while preliminary mechanistic evidence has been collected. Further research efforts are focused toward improving homogeneous acceleration of CuAAC by synthesizing hybrid ligands containing additional heterocycles appended to the 3-position of the core 1,2,4-triazine scaffold. Initial results of a 1,2,4-triazine-accelerated Sonogashira Reactions have been established and detailed studies are underway. In addition, the development of synthetic methods to immobilize 1,2,4-triazines on polystyrene and silica supports have been completed and are the subject of chapters 4 and 5.

3.8 Experimental

Materials and General Methods. Reagents and solvents were purchased from various commercial sources and used without further purification unless otherwise stated. Anhydrous solvents were purified using a Grubbs solvent system. Analytical thin-layer chromatography (TLC) was performed using aluminum backed silica gel TLC plates with UV indicator from Sorbent Technologies. Flash column chromatography was performed using 40-63 μm (230 x 400 mesh) silica gel from Sorbent Technologies. ^{1}H and ^{13}C NMR were recorded at 600 MHz and 151 MHz, respectfully, on a Varian Inova spectrometer. All chemical shifts were reported in δ units relative to tetramethylsilane or the corresponding deuterated solvent. High resolution mass spectra (ESI) were obtained on a JEOL AccuTOF DART spectrometer. Liquid chromatography mass spectra were obtained on a QSTAR XL Hybrid LC/MS/MS equipped with a Vydac C18 column and a mobile phase composed of acetonitrile and formic acid. Infrared spectra were recorded on a Varian 4100 FT-IR using KBr pellets or KBr salt plates. Absorption spectra were collected on a Thermo Scientific Evolution 600. High pressure liquid chromatography (HPLC) was performed using a Beckman Coulter System equipped with a UV-Vis detector, autosampler, Varian C18 column, and a mobile phase composed of acetonitrile and trifluoroacetic acid.

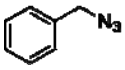
WARNING: Low molecular weight azides are potentially explosive. Appropriate safety measures should always be taken when handling these compounds.

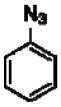
LC/MS Methodology. All reactants and reagents were added as stock solutions unless otherwise noted. The concentrations of these stock solutions were determined by UV-Vis spectroscopy. Reactants and reagents were added in the following order: excess solvent, azide, alkyne, base, ligand and copper source. After 1 h the reactions were diluted in acetonitrile to a final concentration range of 15 – 25 μM and analyzed by LC-MS using a Vydac C18 column. The isocratic mobile phase was composed of 45% acetonitrile and 0.5% formic acid. Percent yields were determined based on product formation using an external calibration curve. All reactions containing a standard deviation were run in triplicate unless otherwise noted.

General Azide Method A: Aromatic Azides. The aniline derivative (approx 2 g, 16.24 mmol) was dissolved in 80 mL of EtOAc. 40 mL of 1.5 M HCl was added and the solution cooled to 0 °C in an ice bath. Sodium nitrite (1.68 g, 24.36 mmol) was dissolved in 20 mL water and added dropwise to the reaction solution while stirring at 0°C. After 15 min, sodium azide (3.17 g, 48.72 mmol) was dissolved in 20 mL water and added dropwise to the reaction solution while stirring at 0°C. After slowly warming to room temperature, the reaction was

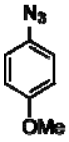
monitored by TLC. Upon completion, the reaction was extracted with EtOAc (x3) and washed with 1 M HCl, water, and brine. The solution was then dried with sodium sulfate and concentrated *in vacuo* to yield the corresponding aromatic azide. Yields: 80 – 94%.

General Azide Method B: Aliphatic/Benzylic Azides. The bromine derivative (approx 2 g, 11.17 mmol) was dissolved in 25 mL of dimethylformamide. Sodium azide (799 mg, 12.28 mmol) was added and the reaction was stirred overnight at room temperature. Progress of the reaction was monitored by TLC and GC-MS. Upon completion, the reaction was quenched with 50 mL of water (exothermic) and stirred until reaching room temperature. The solution was then extracted with diethyl ether (x3) and washed with water (x2) and brine. The solution was then dried with sodium sulfate and concentrated *in vacuo* to yield the corresponding aliphatic azide. Yields: 79 – 98%.

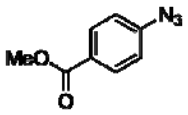
 **(azidomethyl)benzene (3-1a).** Prepared using general azide method B and isolated as a colorless oil. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.40-7.37 (m, 2H), 7.35-7.31 (m, 3H), 4.33 (s, 2H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 135.5, 129.0, 128.44, 128.35, 54.9. IR (film) ν_{max} 2099 cm^{-1}. MS (ESI) m/z calculated 106.066 (C_7H_8N, $[M-N_2+H]^+$), m/z observed 106.064 (C_7H_8N, $[M-N_2+H]^+$).



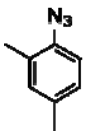
azidobenzene (3-1b). Prepared using general azide method A and isolated as a brown oil. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.35 (t, 2H, J = 7.8 Hz), 7.14 (t, 1H, J = 7.8 Hz), 7.03 (d, 2H, J = 7.8 Hz). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 140.0, 129.8, 124.9, 119.1. IR (film) ν_{max} 2129 cm^{-1}. MS (ESI) m/z calculated 92.050 (C_6H_6N, $[M\text{-}N_2+H]^+$), m/z observed 92.048 (C_6H_6N, $[M\text{-}N_2+H]^+$).



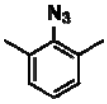
1-azido-4-methoxybenzene (3-1c). Prepared using general azide method A and isolated as a brown solid. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 6.95 (d, 2H, J = 9 Hz), 6.89 (d, 2H, J = 9 Hz). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 157.0, 132.3, 120.0, 115.1, 55.6. IR (film) ν_{max} 2110 cm^{-1}. MS (ESI) m/z calculated 122.061 (C_7H_8NO, $[M\text{-}N_2+H]^+$), m/z observed 122.060 (C_7H_8NO, $[M\text{-}N_2+H]^+$).



methyl 4-azidobenzoate (3-1d). Prepared using general azide method A and isolated as an orange-brown solid. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.05 (d, 2H, J = 7.4 Hz), 7.07 (d, 2H, J = 7.4 Hz), 3.91 (s, 3H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 166.4, 144.9, 131.6, 126.8, 119.0, 52.3. IR (film) ν_{max} 2125 cm^{-1}. MS (ESI) m/z calculated 150.056 ($C_8H_8NO_2$, $[M\text{-}N_2+H]^+$), m/z observed 150.056 (C_7H_7NO, $[M\text{-}N_2+H]^+$).



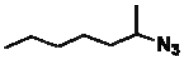
1-azido-2,4-dimethylbenzene (3-1e). Prepared using general azide method A and isolated as a brown oil. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.03-6.97 (m, 3H), 2.29 (s, 3H), 2.17 (s, 3H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 135.6, 134.2, 131.9, 129.3, 127.6, 117.8, 20.8, 17.2. IR (film) v_{max} 2122 cm^{-1}. MS (ESI) m/z calculated 120.081 ($C_8H_{10}N$, $[M-N_2+H]^+$), m/z observed 120.081 ($C_8H_{10}N$, $[M-N_2+H]^+$).



2-azido-1,3-dimethylbenzene (3-1f). Prepared using general azide method A and isolated as a brown oil. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.02-7.00 (m, 3H), 2.36 (s, 6H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 137.0, 132.1, 128.9, 125.7, 18.2. IR (film) v_{max} 2129 cm^{-1}. MS (ESI) m/z calculated 120.081 ($C_8H_{10}N$, $[M-N_2+H]^+$), m/z observed 120.081 ($C_8H_{10}N$, $[M-N_2+H]^+$).



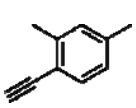
1-azidoheptane (3-1g). Prepared using general azide method B and isolated as a clear oil. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 3.26 (t, 2H, J = 6.6 Hz), 1.62-1.58 (m, 2H), 1.38-1.27 (m, 8H), 0.89 (t, 3H, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 51.5, 31.7, 28.8, 26.7, 22.6, 14.1, 14.0. IR (film) v_{max} 2099 cm^{-1}. MS (ESI) m/z calculated 114.128 ($C_7H_{16}N$, $[M-N_2+H]^+$), m/z observed 114.128 ($C_7H_{16}N$, $[M-N_2+H]^+$).



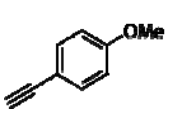
2-azidoheptane (3-1h). Prepared using general azide method B and isolated as a clear oil. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 3.43-3.40 (m, 1H), 1.52-

1.27 (m, 8H), 1.25 (d, 3H, J = 6 Hz), 0.89 (t, 3H, J = 6 Hz). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 58.2, 36.3, 31.7, 25.9, 22.7, 19.6, 14.1. IR (film) v_{max} 2110 cm^{-1}. MS (ESI) m/z calculated 114.128 ($C_7H_{16}N$, $[M-N_2+H]^+$), m/z observed 114.129 ($C_7H_{16}N$, $[M-N_2+H]^+$).

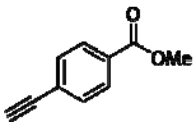
General Alkyne Method. Aryl iodide (10 mmol), dichlorobis-(triphenylphosphine)palladium(II) (0.25 mmol), and CuI (0.15 mmol) were combined in a round bottom flask and flushed with N_2. Anhydrous THF was added (12.5 mL) followed by a dropwise addition of triethylamine (15 mmol) and trimethylsilylacetylene (15 mmol) in anhydrous THF (12.5 mL). Reaction was stirred at room temperature and monitored by TLC. Upon completion, solvent was removed *in vacuo* and purified by silica gel chromatography to yield the corresponding trimethylsilyl protected alkyne. To the protected alkyne (10 mmol) in MeOH (20 mL) was added solid K_2CO_3 (1.5 mmol) and the resulting suspension stirred at room temperature, with reaction progress monitored by TLC. Upon completion, the reaction was concentrated *in vacuo*, and the residue brought up in DCM and water. The aqueous layer was extracted with DCM (x3). The combined organic layers were washed with water (x1), sat'd $NaHCO_3$, and brine. The solution was dried with sodium sulfate, concentrated *in vacuo* and purified by silica column chromatography to yield corresponding terminal alkyne.



1-ethynyl-2,4-dimethylbenzene (3-2e). Prepared using general alkyne method from 1-iodo 2,4-dimethylbenzene. Purified by silica chromatography using gradient elution of hexanes and ethyl acetate to yield a red oil in 61% yield. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.35 (d, 1H, J = 7.8 Hz), 7.02 (s, 1H), 6.95 (d, 1H, J = 7.8 Hz), 3.22 (s, 1H), 2.42 (s, 3H), 2.32 (s, 3H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 140.7, 139.0, 132.6, 130.4, 126.5, 119.0, 82.9, 80.3, 21.6, 20.6. HRMS (ESI) m/z calculated 131.08608 ($C_{10}H_{11}$, $[M+H]^+$), m/z observed 131.08606. ($C_{10}H_{11}$, $[M+H]^+$).

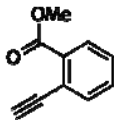


1-ethynyl-4-methoxybenzene (3-2f). Prepared using general alkyne method from 4-iodoanisole. Purified by silica chromatography using gradient elution of hexanes and ethyl acetate to yield a yellow oil in 65% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.43 (d, 2H, J = 7 Hz), 6.85 (d, 2H, J = 7 Hz), 3.82 (s, 3H), 2.99 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 160.1, 133.7, 114.3, 114.1, 83.8, 75.9, 55.4. HRMS (ESI) m/z calculated 133.06534 (C_9H_9O, $[M+H]^+$), m/z observed 133.06486. (C_9H_9O, $[M+H]^+$).



methyl 4-ethynylbenzoate (3-2g). Prepared using general alkyne method from methyl-4-iodobenzoate. Purified by silica column chromatography using gradient elution of hexanes and ethyl acetate to yield an off-white solid in 91% yield. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.00 (d, 2H, J = 8.4 Hz), 7.55 (d, 2H, J = 8.4 Hz), 3.92 (s, 3H), 3.23, (s, 1H). ^{13}C NMR ($CDCl_3$,

151 MHz) δ 166.6, 132.2, 130.3, 129.6, 126.9, 82.9, 80.2, 52.4. HRMS (ESI) m/z calculated 161.06025 ($C_{10}H_9O_2$, $[M+H]^+$), m/z observed 161.05971. ($C_{10}H_9O_2$, $[M+H]^+$).

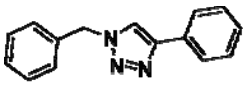


methyl 2-ethynylbenzoate (3-2h). Prepared using general alkyne method from methyl-2-iodobenzoate. Purified by silica column chromatography using gradient elution of hexanes and ethyl acetate to yield an orange oil in 88% yield. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.94 (dd, 1H, J = 7.8, 1.2 Hz), 7.63 (dd, 1H, J = 7.8, 1.2 Hz), 7.48 (td, 1H, J = 7.8, 1.2 Hz), 7.41 (td, 1H, J = 7.8, 1.2 Hz), 3.94 (s, 3H), 3.40 (s, 1H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 166.6, 135.1, 132.6, 131.9, 130.4, 128.6, 122.8, 82.4, 82.2, 52.3. HRMS (ESI) m/z calculated 161.06025 ($C_{10}H_9O_2$, $[M+H]^+$), m/z observed 161.06039. ($C_{10}H_9O_2$, $[M+H]^+$).

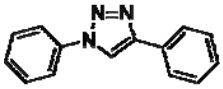
General Triazole Method A: Azide (1 mmol), alkyne (1 mmol), and triethylamine (1 mmol) were dissolved in acetonitrile (5 mL). **(1)** (10 μmol) and tetrakis(acetonitrile-N)copper(I) tetrafluoroborate (10 μmol) were added to the reaction solution and stirred at room temperature for 18 hours. Concentration *in vacuo* and purification yielded desired 1,2,3-triazole product.

General Triazole Method B: Azide (1 mmol), alkyne (1 mmol), and triethylamine (1 mmol) were dissolved in dichloromethane (5 mL). **(1)** (10 μmol) and copper(II) tetrafluoroborate hexahydrate (10 μmol) were added to the

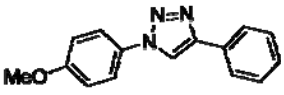
reaction solution and stirred at room temperature for 18 hours. Concentration *in vacuo* and purification yielded desired 1,2,3-triazole product.



1-benzyl-4-phenyl-1H-1,2,3-triazole (3-3a). Prepared using general triazole method A. Purified by silica column chromatography using gradient elution of hexanes and ethyl acetate as a white solid in 87% yield. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.80 (d, 2H, J = 8.4 Hz), 7.66 (s, 1H), 7.41-7.37 (m, 5H), 7.32-7.31 (m, 3H), 5.58 (s, 2H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 148.4, 134.8, 130.7, 129.3, 128.9, 128.3, 128.2, 125.8, 119.6, 54.4. HRMS (ESI) m/z calculated 236.11877 ($C_{15}H_{14}N_3$, $[M+H]^+$), m/z observed 236.11898 ($C_{15}H_{14}N_3$, $[M+H]^+$).

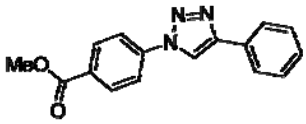


1,4-diphenyl-1H-1,2,3-triazole (3-3b). Prepared using general triazole method A. Precipitated from 5% nitric acid as a brown solid in 95% yield. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.20 (s, 1H), 7.93 (d, 2H, J = 6.6 Hz), 7.81 (d, 2H, J = 7.8 Hz), 7.55 (t, 2H, J = 7.8 Hz), 7.48-7.46 (m, 3H), 7.38 (t, 1H, J = 7.8 Hz). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 148.6, 137.2, 130.4, 129.9, 129.1, 128.9, 128.6, 126.0, 120.7, 117.7 . HRMS (ESI) m/z calculated 222.10312 ($C_{14}H_{12}N_3$, $[M+H]^+$), m/z observed 222.10280 ($C_{14}H_{12}N_3$, $[M+H]^+$).

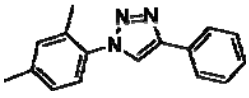


1-(4-methoxyphenyl)-4-phenyl-1H-1,2,3-triazole (3-3c). Prepared using general triazole method A. Precipitated

from 5% nitric acid as a brown solid in 83% yield. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.11 (s, 1H), 7.91 (d, 2H, J = 7.2 Hz), 7.69 (d, 2H, J = 7.8 Hz), 7.46 (t, 2H, J = 7.2 Hz), 7.37 (t, 1H, J = 7.2 Hz), 7.05 (d, 2H, J = 7.8 Hz) 3.88 (s, 3H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 160.0, 148.4, 130.7, 130.5, 129.0, 128.5, 126.0, 122.3, 118.0, 115.0, 55.8. HRMS (ESI) m/z calculated 252.11369 ($C_{15}H_{14}N_3O$, $[M+H]^+$), m/z observed 252.11371 ($C_{15}H_{14}N_3O$, $[M+H]^+$).

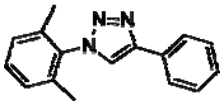


methyl 4-(4-phenyl)-1H-1,2,3-triazol-1-yl)benzoate (3-3d). Prepared using general triazole method A. Precipitated from 5% nitric acid as a yellow solid in 91% yield. ^{1}H NMR (d_6-DMSO, 600 MHz) δ 9.46 (s, 1H), 8.21 (d, 2H, J = 9 Hz), 8.15 (d, 2H, J = 8.4 Hz), 7.97 (d, 2H, J = 7.8 Hz), 7.52 (t, 2H, J = 7.8 Hz), 7.41 (t, 1H, J = 7.8 Hz), 3.91 (s, 1H). ^{13}C NMR (d_6-DMSO, 151 MHz) δ 165.4, 147.6, 139.8, 131.1, 130.0, 129.4, 129.1, 128.4, 125.4, 119.8, 119.7, 52.4. HRMS (ESI) m/z calculated 280.10860 ($C_{16}H_{14}N_3O_2$, $[M+H]^+$), m/z observed 280.10883 ($C_{16}H_{14}N_3O_2$, $[M+H]^+$).

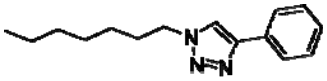


1-(2,4-dimethylphenyl)-4-phenyl-1H-1,2,3-triazole (3-3e). Prepared using general triazole method A. Purified by silica column chromatography using gradient elution of hexanes and ethyl acetate as a white solid in 90% yield. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.92 (d, 3H, J = 9 Hz), 7.46 (t, 2H, J = 7.8 Hz), 7.36 (t, 1H, J = 7.2 Hz) 7.27 (d, 1H, J = 7.8 Hz), 7.20 (s, 1H), 7.15 (d, 1H, J = 7.8 Hz), 2.41 (s, 3H), 2.23 (s, 3H). ^{13}C NMR ($CDCl_3$, 151

MHz) δ 147.6, 140.1, 134.3, 133.6, 132.2, 130.6, 129.0, 128.4, 127.6, 125.92, 125.91, 121.3, 21.3, 18.0. HRMS (ESI) m/z calculated 250.13442 ($C_{16}H_{16}N_3$, $[M+H]^+$), m/z observed 250.13462 ($C_{16}H_{16}N_3$, $[M+H]^+$).

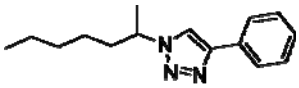


1-(2,6-dimethylphenyl)-4-phenyl-1H-1,2,3-triazole (3-3f). Prepared using general triazole method A. Purified by silica column chromatography using a gradient elution of hexanes and ethyl acetate as a white solid in 83% yield. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.94 (d, 2H, J = 8.4 Hz), 7.87 (s, 1H), 7.47 (t, 2H, J = 7.2 Hz), 7.37 (t, 1H, J = 7.8 Hz), 7.34 (t, 1H, J = 7.2 Hz), 7.21 (d, 2H, J = 7.8 Hz), 2.07 (s, 6H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 147.8, 136.1, 135.6, 130.6, 130.2, 129.1, 128.6, 128.5, 125.9, 121.4, 17.6. HRMS (ESI) m/z calculated 250.13442 ($C_{16}H_{16}N_3$, $[M+H]^+$), m/z observed 250.13497 ($C_{16}H_{16}N_3$, $[M+H]^+$).

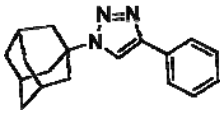


1-heptyl-4-phenyl-1H-1,2,3-triazole (3-3g). Prepared using general triazole method A. Purified by silica column chromatography using gradient elution of hexanes and ethyl acetate as a white solid in 88% yield. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.84 (d, 2H, J = 7.8 Hz), 7.74 (s, 1H), 7.42 (t, 2H, J = 7.8 Hz), 7.33 (t, 1H, J = 7.8 Hz), 4.39 (t, 2H, J = 7.2 Hz), 1.97-1.92 (m, 2H,), 1.35-1.27 (m, 8H), 0.88 (t, 3H, J = 7.2 Hz). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 147.9, 130.9, 128.9, 128.2, 125.8, 119.5, 50.6, 31.7, 30.5,

28.8, 26.6, 22.7, 14.2. HRMS (ESI) m/z calculated 244.18137 ($C_{15}H_{22}N_3$, $[M+H]^+$), m/z observed 244.18152 ($C_{15}H_{22}N_3$, $[M+H]^+$).



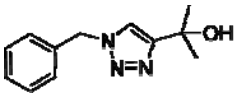
1-(heptan-2-yl)-4-phenyl-1H-1,2,3-triazole (3-3h). Prepared using general triazole method A. Purified by silica column chromatography using gradient elution of hexanes and ethyl acetate as a white solid in 80% yield. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.85 (d, 2H, J = 7.8 Hz), 7.74 (s, 1H), 7.42 (t, 2H, J = 7.8 Hz), 7.32 (t, 1H, J = 7.2 Hz), 4.74-4.68 (m, 1H), 1.97-1.92 (m, 1H), 1.86-1.82 (m, 1H), 1.60 (d, 3H, J = 6.6 Hz), 1.28-1.18 (m, 6H), 0.86 (t, 3H, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 147.7, 131.0, 128.9, 128.1, 125.8, 117.4, 57.7, 37.4, 31.5, 25.8, 22.6, 21.6, 14.1. HRMS (ESI) m/z calculated 244.18137 ($C_{15}H_{22}N_3$, $[M+H]^+$), m/z observed 244.18197 ($C_{15}H_{22}N_3$, $[M+H]^+$).



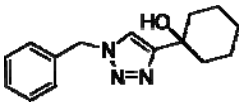
1-(adamantan-1-yl)-4-phenyl-1H-1,2,3-triazole (3-3i). Prepared using general triazole method A. Purified by silica column chromatography using gradient elution of hexanes and ethyl acetate as a white solid in 5% yield. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.85-7.82 (m, 3H), 7.41 (t, 2H, J = 6.0 Hz), 7.31 (t, 1H, J = 6.0 Hz), 2.30 (s, 9 H), 1.82 (s, 6 H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 146.9, 131.3, 128.9, 128.0, 125.8, 116.1, 59.7, 43.2, 36.1, 29.6. HRMS (ESI) m/z calculated 280.18137 ($C_{10}H_{20}N_3O$, $[M+H]^+$), m/z observed 280.18240 ($C_{10}H_{20}N_3O$, $[M+H]^+$).



(1-benzyl-1H-1,2,3-triazol-4-yl)methanol (3-3j) Prepared using general triazole method A. Purified by silica column chromatography using gradient elution of ethyl acetate and methanol to yield a white solid in 76% yield. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.44 (s, 1H), 7.37 (m, 3H), 7.27 (d, 2H, J = 9 Hz), 5.51 (s, 2H), 4.76 (s, 2H), 2.49 (s, 1H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 148.2, 134.6, 128.3, 129.0, 128.3, 121.7, 56.7, 54.4. HRMS (ESI) m/z calculated 190.09804 ($C_{10}H_{12}N_3O$, $[M+H]^+$), m/z observed 190.09876. ($C_{10}H_{12}N_3O$, $[M+H]^+$).

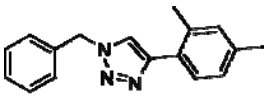


2-(1-benzyl-1H-1,2,3-triazol-4-yl)propan-2-ol (3-3k) Prepared using general triazole method A. Purified by silica column chromatography using gradient elution of hexanes and ethyl acetate to yield a white solid in 80.0% yield. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.39-7.36 (m, 3H), 7.34 (s, 1H), 7.28 (d, 2H, J = 7.2 Hz), 5.50 (s, 2H), 2.41 (s, 1H), 1.61 (s, 6H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 156.1, 134.7, 129.3, 128.9, 128.3, 119.0, 68.7, 54.3, 30.6. HRMS (ESI) m/z calculated 218.12934 ($C_{12}H_{16}N_3O$, $[M+H]^+$), m/z observed 218.13039. ($C_{12}H_{16}N_3O$, $[M+H]^+$).

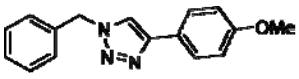


1-(1-benzyl-1*H*-1,2,3-triazol-4-yl)cyclohexanol (3-3l) Prepared using general triazole method A. Purified by silica column chromatography using gradient elution of hexanes and ethyl acetate to yield a white solid in 79% yield. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.37 (d, 3H, J = 9

Hz), 7.34 (s, 1H), 7.27 (d, 2H, J = 9 Hz), 5.50 (s, 2H), 2.24 (s, 1H), 1.94 (t, 2H, J = 10.8 Hz), 1.85 (d, 2H, J = 13.2 Hz), 1.69-1.75 (m, 2H), 1.59-1.65 (m, 1H), 1.53-1.55 (m, 2H), 1.31-1.37 (m, 1H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 156.2, 134.8, 129.3, 128.9, 128.3, 119.5, 69.8, 54.3, 38.3, 25.5, 22.1. HRMS (ESI) m/z calculated 258.16064 ($C_{15}H_{20}N_3O$, $[M+H]^+$), m/z observed 258.16137. ($C_{15}H_{20}N_3O$, $[M+H]^+$).

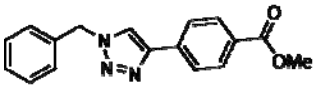


1-benzyl-4-(2,4-dimethylphenyl)-1H-1,2,3-triazole (3-3m) Prepared using general triazole method A. Purified by silica column chromatography using gradient elution with hexanes and ethyl acetate to yield a white solid in 68.4% yield. ^1H NMR ($CDCl_3$, 600 MHz) δ 7.63 (d, 1H, J = 7.8 Hz), 7.52 (s, 1H), 7.36-7.40 (m, 3H), 7.31 (d, 2H, J = 7.8 Hz), 7.1 (m, 2H), 5.60 (s, 2H), 2.39 (s, 3H), 2.34 (s, 3H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 147.8, 135.4, 135.0, 131.7, 129.3, 128.9, 128.8, 128.1, 127.2, 126.9, 121.5, 54.3, 21.4, 21.3. HRMS (ESI) m/z calculated 264.15007 ($C_{17}H_{18}N_3$, $[M+H]^+$), m/z observed 264.15016. ($C_{17}H_{18}N_3$, $[M+H]^+$).

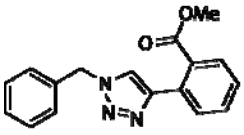


1-benzyl-4-(4-methoxyphenyl)-1*H*-1,2,3-triazole (3-3n) Prepared using general triazole method B. Purified by silica column chromatography using gradient elution of hexanes and ethyl acetate to yield a white solid in 87% yield. ^1H NMR ($CDCl_3$, 600 MHz) δ 7.72 (d, 2H, J = 8.4 Hz), 7.57 (s, 1H), 7.35-7.41 (m, 3H), 7.30-7.32 (m, 2H), 6.93 (d, 2H, J

= 9 Hz), 5.57 (s, 2H), 3.83 (s, 3H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 159.7, 148.3, 134.9, 129.3, 128.9, 128.2, 127.2, 123,4, 118.8, 114.3, 55.5, 54.4. HRMS (ESI) m/z calculated 266.12934 ($C_{16}H_{16}N_3O$, $[M+H]^+$), m/z observed 266.13042. ($C_{16}H_{16}N_3O$, $[M+H]^+$).

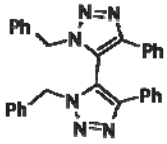


methyl 4-(1-benzyl-1H-1,2,3-triazol-4-yl) benzoate (3-3o) Prepared using general triazole method B. Purified by silica column chromatography using gradient elution of hexanes and ethyl acetate to yield a white solid in 86% yield. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.07 (d, 2H, J = 8.4 Hz), 7.88 (d, 2H, J = 8.4 Hz), 7.74 (s, 1H), 7.36-7.42 (m, 3H), 7.32-7.33 (m, 2H), 5.59 (s, 2H), 3.92 (s, 3H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 166.9, 147.3, 135.0, 134.6, 130.3, 129.7, 129.4, 129.1, 128.3, 125.6, 120.5, 54.5, 52.3. HRMS (ESI) m/z calculated 294.12425 ($C_{17}H_{16}N_3O_2$, $[M+H]^+$), m/z observed 294.12490. ($C_{17}H_{16}N_3O_2$, $[M+H]^+$).



methyl 2-(1-benzyl-1H-1,2,3-triazol-4-yl)benzoate (3-3p) Prepared using general triazole method B. Purified by silica column chromatography using gradient elution of hexanes and ethyl acetate to yield an off-white solid in 89% yield. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.81 (d, 1H, J = 7.8 Hz), 7.77 (d, 1H, J = 7.8 Hz), 7.72 (s, 1H), 7.54 (td, 1H, J = 7.8, 1.2 Hz), 7.35-7.41 (m, 4H), 7.31-7.32 (m, 2H), 5.59 (s, 2H), 3.72 (s, 3H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 168.9, 146.3, 135.0, 131.6, 130.5, 130.4, 130.3, 129.3,

128.9, 128.2, 122.7, 54.3, 52.3. HRMS (ESI) m/z calculated 294.12425 ($C_{17}H_{16}N_3O_2$, $[M+H]^+$), m/z observed 294.12508. ($C_{17}H_{16}N_3O_2$, $[M+H]^+$).



3,3'-dibenzyl-5,5'-diphenyl-3H,3'H-4,4'-bi(1,2,3-triazole) (3-4). Isolated as by-product when using general triazole method A. Purified by silica column chromatography using gradient elution of hexanes and ethyl acetate to yield a white solid in 3% yield. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.42–7.46 (m, 4H), 7.22–7.25 (m, 2H), 7.18–7.22 (m, 4H), 7.11–7.16 (m, 2H), 7.08 (t, 4H, J = 7.2 Hz), 6.80 (d, 4H, J = 7.2 Hz), 4.69 (d, 2H, J = 15 Hz), 4.62 (d, 2H, J = 15 Hz). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 148.0, 133.1, 129.4, 129.1, 129.0, 128.92, 128.86, 128.3, 126.0, 120.0, 52.8. HRMS (ESI) m/z calculated 469.21407 ($C_{30}H_{25}N_6$, $[M+H]^+$), m/z observed 469.21239. ($C_{30}H_{25}N_6$, $[M+H]^+$).

Chapter 4

Design and Synthesis of Heterogeneous 1,2,4-Triazine Catalysts

4.1 Background and Significance

Transition metal catalytic systems generally rely on homogeneous catalysts because of their high catalytic activity, selectivity, and more straightforward synthesis.[82] However, homogeneous catalysts are known to suffer from significant drawbacks. The major drawback is metal contamination of the product resulting from inefficient separation and therefore requiring column chromatography, which is highly undesirable from an industrial or biological standpoint. In addition, the homogeneous metal catalyst can not be reused, which is a serious economical drawback due to the loss of expensive metals.

The aforementioned disadvantages of homogeneous catalytic systems have caused the development of heterogeneous catalysts to gain enormous attention in recent years. The primary advantages of heterogeneous supported catalysts are the ease of separation of product and reusability of catalyst. Numerous materials, including alumina,[83] silica,[25,84] zeolite,[22] and polystyrene,[24,85,86] have successfully been utilized as insoluble supports and thus provide these advantages. Furthermore, one additional benefit is the improved efficiency commonly resulting from a more stable active site and better steric control of reaction intermediates. This comparatively higher stability of a solid supported catalyst often results in the reaction being less sensitive, such as no longer requiring anhydrous conditions, and more tolerable to a wide range of solvents.

Not only does immobilization of the metal present a chemist with synthetic and financial advantages, but also offers an environmentally benign approach toward organometallic reactions, as many reactions proceed using water as the reaction medium.[24,25,87] Recovery of the heterogeneous catalyst usually only requires a simple filtration or decantation and can be reused without additional treatment. These simple work-up protocols, easy handling of catalysts, metal-free products, and recyclability advantages make heterogeneous catalysts a valuable alternative to their homogeneous counterparts. Chapter 4 describes the synthesis of heterogeneous 1,2,4-triazine catalysts, while chapter 5 summarizes their activity as accelerants of CuAAC.

4.2 Synthetic Strategies for Heterogeneous 1,2,4-Triazine Catalysts

Covalently bonded heterogeneous catalysts are composed of three distinct components: the insoluble support, the active catalyst, and a linker joining the two (Figure 4.1A). With the successful development and optimization of 1,2,4-triazine-accelerated CuAAC, the most plausible choice of linker is a 1,2,3-triazole. Not only would this 1,2,3-triazole linker provide a highly stable connection, but would also highlight a practical application of homogeneous 1,2,4-triazine-accelerated CuAAC as a method of derivatizing solid surfaces. With the linker determined, two possible synthetic routes were considered. The first scheme involves attachment of the alkyne substrate to the insoluble support

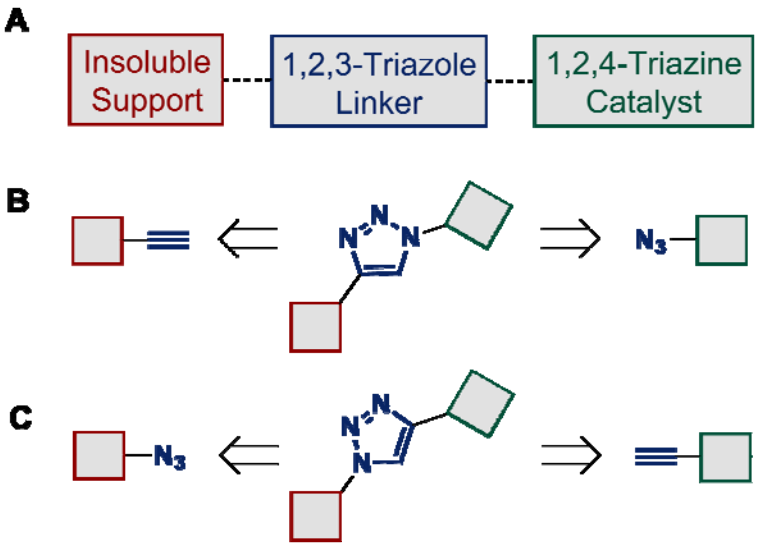


Figure 4.1 Synthetic Strategies for the Synthesis of Heterogeneous 1,2,4-Triazine Catalysts.

and the synthesis of an azide-substituted-1,2,4-triazine (Figure 4.1B). The alternative is to append the azide to the support and synthesize an alkyne-substituted-1,2,4-triazine (Figure 4.1C). While both routes appear viable, the deciding factor of the "best" route was based upon the synthetic feasibility of the subsituted-1,2,4-triazine.

4.3 Substituted-1,2,4-Triazine Building Blocks

Due to our previous success of synthesizing aromatic azides, we began by attempting the synthesis of **4-1** from amine-substituted **2-40** (Figure 4.2). However, after numerous attempts, this route proved to be more difficult than expected and was thus abandoned. Our unsuccessful attempt at synthesizing an

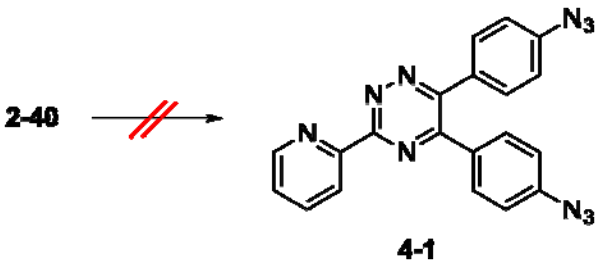


Figure 4.2 Attempted Synthesis of a Diazido-1,2,4-Triazine.

azide-substituted 1,2,4-triazine, combined with the low overall yield of **2-40** (30%), led us to next consider a more concise synthetic route to an alkyne-substituted 1,2,4-triazine.

The Benzoin Condensation was again utilized to synthesize **4-3** in moderate yield (Figure 4.3). Reaction with amidrazone **2-10**, yielded the corresponding 1,2,4-triazine. Using standard Sonogoshira Reaction conditions, we attempted the synthesis of **4-5**, containing two alkyne substituents. Although all of the starting material was consumed, the reaction yielded multiple products that were inseparable by column chromatography. However, we were encouraged by this result and subsequently established a synthetic scheme to alleviate this isolation problem.

Even though previous results have shown that the catalytic activity of 1,2,4-triazines slightly decrease with the removal of the phenyl ring at the 6-position, we were confident that we could now efficiently synthesize **4-11** (Figure 4.4). Unsymmetrical 1,2-dione **4-9**, was generated from oxidation of the

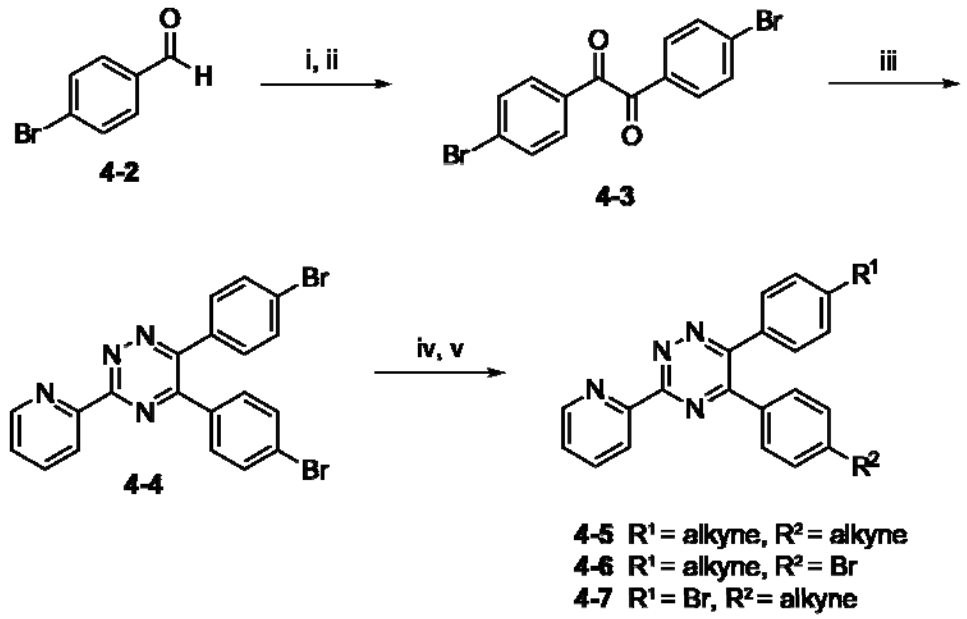


Figure 4.3 Attempted Synthesis of a Diethynyl-1,2,4-Triazine. (i) KCN, EtOH, H_2O, reflux; (ii) HNO_3, reflux; (iii) **2-10**, EtOH, THF, 80°C; (iv) trimethylsilylacetylene, NEt_3, CuI, $Pd(PPh_3)_2Cl_2$, THF, reflux; (v) K_2CO_3, MeOH, EtOH.

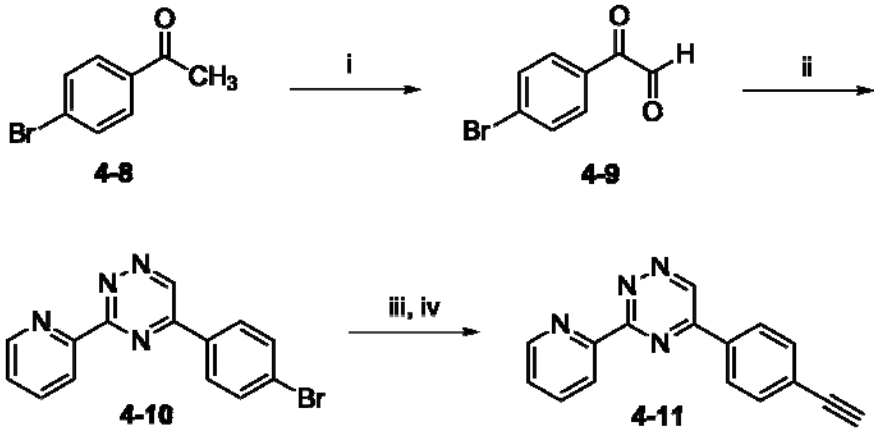


Figure 4.4 Synthesis of the 5-(4-ethynylphenyl)-substituted 1,2,4-Triazine Building Block. (i) SeO_2, dioxane, H_2O, reflux; (ii) **2-10**, EtOH, 80°C; (iii) trimethylsilylacetylene, NEt_3, CuI, $Pd(PPh_3)_2Cl_2$, THF, reflux; (iv) K_2CO_3, MeOH, EtOH.

acetophenone derivative using selenium dioxide. Synthesis of 1,2,4-triazine **4-10** proceeded by reaction with amidrazone **2-10** under neutral conditions. The Sonogashira Reaction with a mono-bromide derivative was successful and yielded alkyne **4-11** in an overall yield of 20%.

We initially selected the para-position of the 5-substituted-1,2,4-triazine as an anchoring point for immobilization because we believed it would not interfere with the copper-binding face of the 1,2,4-triazine. However, in concern that the absence of the phenyl ring at the 6-position may decrease the activity more than anticipated; we simultaneously designed a scheme that would retain both phenyl rings at the 5- and 6-position by installing the alkyne on the 2-pyridyl substituent. 5-Bromo-2-cyano-pyridine, **4-13**, was initially synthesized from 2,5-dibromo-pyridine, but this low-yielding, initial step ultimately resulted in the purchase of **4-13** from a commercial source (Figure 4.5). Conversion of the nitrile to amidrazone **4-14** was accomplished in 79% yield using hydrazine hydrate in ethanol, although the reaction took 72 h at room temperature to reach completion. Reaction with amidrazone **2-10**, yielded 1,2,4-triazine **4-15** in high yield, followed by conversion of the bromide to an alkyne which resulted in 1,2,4-triazine **4-16** with a 45% overall yield.

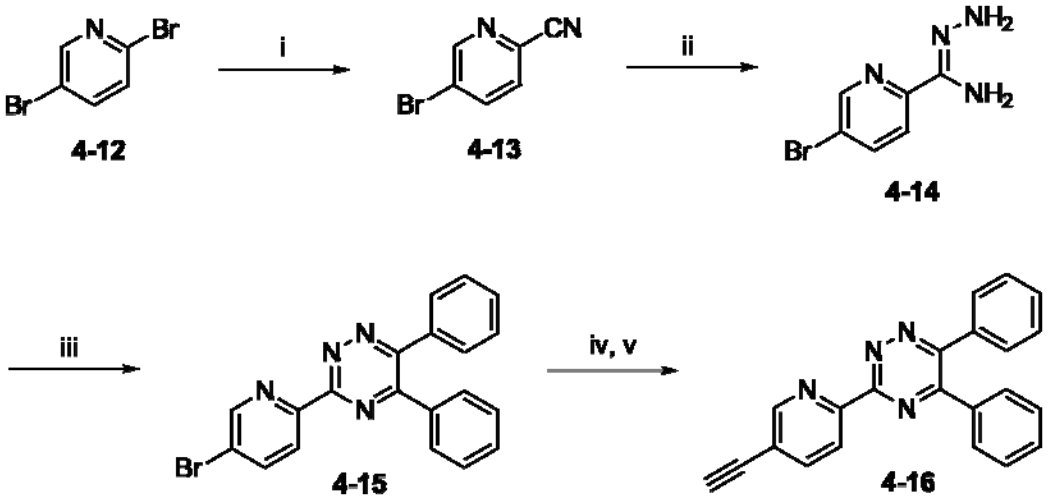


Figure 4.5 Synthesis of the 3-(5-ethynylpyridin-2-yl)-substituted 1,2,4-Triazine Building Block. (i) CuCN, NaCN, DMF, reflux; (ii) hydrazine hydrate, EtOH; (iii) benzil, EtOH, 80°C; (iv) trimethylsilylacetylene, NEt_3, CuI, $Pd(PPh_3)_2Cl_2$, THF, reflux; (v) K_2CO_3, MeOH, EtOH, DCM.

4.4 Polystyrene-Supported 1,2,4-Triazines

Merrifield resin, a polystyrene support, was selected as a solid support of interest for its excellent swelling properties in a wide range of organic solvents and its inexpensive, widespread availability. The initial synthesis of polystyrene-supported 1,2,4-triazines began with a high-loading resin (1.4 mmol/g), but a low-loading resin (0.5 mmol/g) was later used for comparison. Since two alkyne-substituted 1,2,4-triazine derivatives were successfully synthesized, the synthesis on the polystyrene support was focused on immobilization of the essential azide substrate.

4.4.1 High-Loading Polystyrene

Polystyrene-supported azide (**4-18**) was synthesized from Merrifield resin (**4-17**) by reaction with sodium azide at 80°C (Figure 4.6A). Infrared spectroscopy (FT-IR) was used to qualitatively confirm substitution of the azide by the appearance of a characteristic absorption at approximately 2100 cm^{-1} (Figure 4.7A). The alkyne-substituted 1,2,4-triazines (**4-11** and **4-16**) were immobilized using previously optimized 1,2,4-triazine-accelerated CuAAC conditions at 60°C. Approximate loading of the 1,2,4-triazine was determined by HPLC analysis of the reaction filtrate and resulted in a loading of 1.19 and 1.15 mmol/g for **4-19** and **4-20**, respectfully. However, it was determined that the 1,2,4-triazine-accelerated CuAAC reaction did not reach completion due to high-loading of the Merrifield resin and remaining presence of an azide absorption (Figure 4.7B). In order to prevent the support from further reaction with alkyne substrates, any remaining azide was reduced by means of tin chloride (Figure 4.7C). Since most CuAAC reactions are performed under basic conditions, the presence of amine functional groups on the support should not adversely affect the catalyst, and may even prove beneficial. Lastly, **4-21** and **4-22** were each treated with solutions of copper(I) and copper(II), then analyzed by IR spectroscopy, where a broad, new absorption band in the spectra could be observed (Figure 4.7D). Copper loading of **4-23 – 4-26** was then quantified using ICP where results ranged from 0.46 – 0.59 mmol/g. In order to determine the necessity and/or potential benefit of reducing excess azide, **4-19** and **4-20**, still

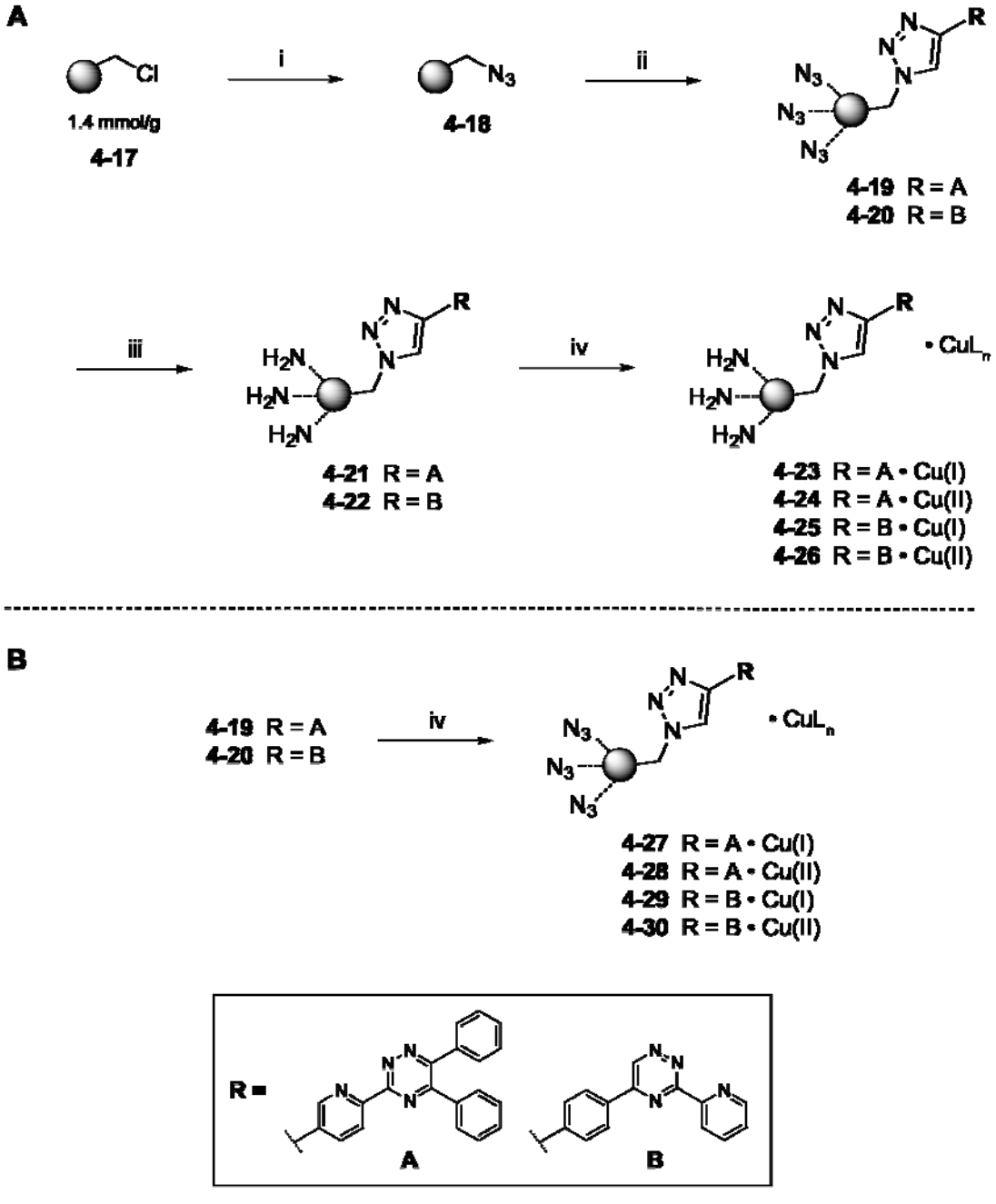


Figure 4.6 Synthesis of Polystyrene-Supported 1,2,4-Triazine Catalysts. (i) NaN_3, TBAI, NMP, H_2O, 80°C; (ii) alkyne-substituted 1,2,4-triazine (**4-11** or **4-16**), Et_3N, $[Cu(MeCN)_4]^+BF_4^-$, **2-13**, ACN, DCE, 60°C; (iii) $SnCl_2 \cdot 2H_2O$, thiophenol, Et_3N, ACN; (iv) copper source ($[Cu(MeCN)_4]^+BF_4^-$ or $Cu(BF_4)_2 \cdot 6H_2O$), ACN, DCE, 60°C.

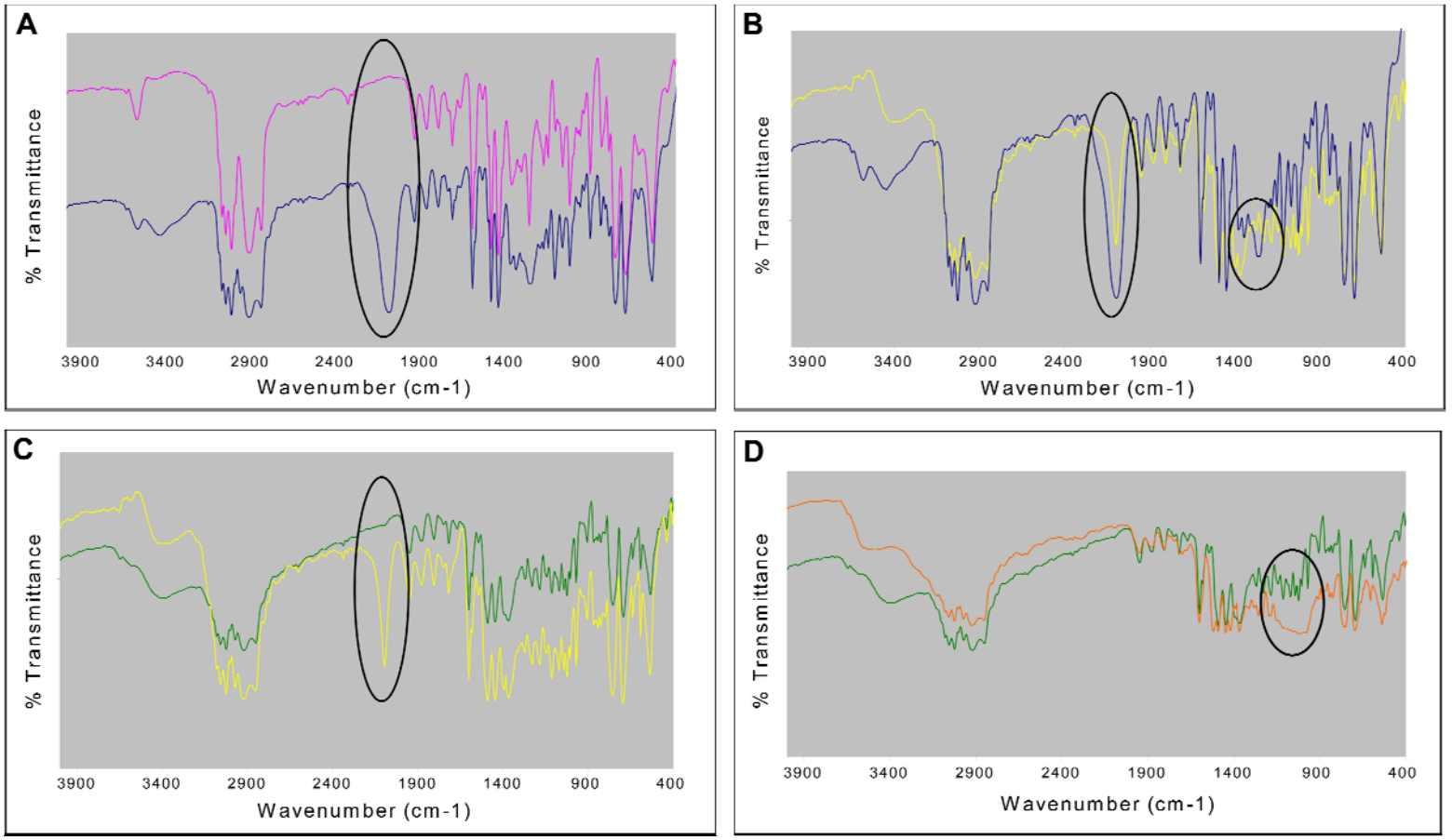


Figure 4.7 Infrared Spectra of Polystyrene-Supported 1,2,4-Triazine Catalysts. **(A)** Figure 4.6A, rxn i. **(B)** Figure 4.6A, rxn ii. **(C)** Figure 4.6A, rxn iii. **(D)** Figure 4.6A, rxn iv.

containing residual azide, were also complexed under the same conditions resulting in **4-27 – 4-30** and a copper loading ranging from 0.38 – 0.45 mmol/g (Figure 4.6B).

In order to attribute the catalytic activity of the polystyrene support to the appended 1,2,4-triazine, several controls were also synthesized. First, the initial azide-forming reaction would need to be quantified in order to fully verify the azide attachment. By reduction of **4-18**, followed by standard peptide coupling conditions, **4-32** was synthesized and subjected to an Fmoc-Assay as published

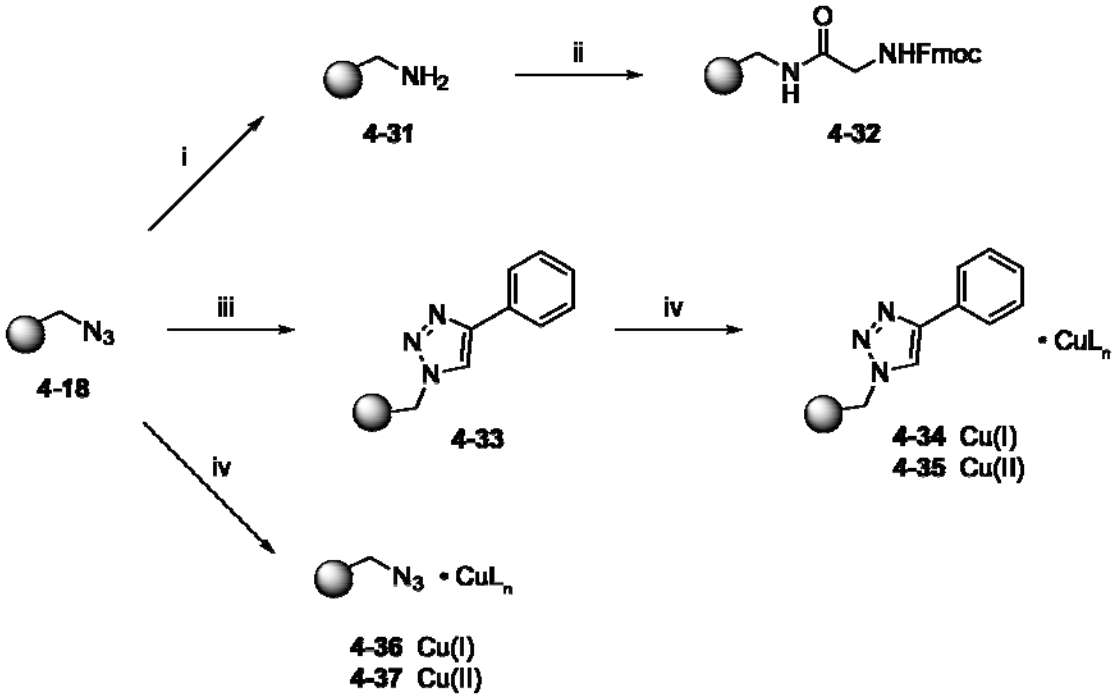


Figure 4.8 Synthesis of Polystyrene-Supported Controls. (i) $SnCl_2 \bullet 2H_2O$, thiophenol, Et_3N, THF; (ii) Fmoc-Gly, HBTU, HOBt, DIEA, NMP; (iii) phenylacetylene, Et_3N, $[Cu(MeCN)_4]^+BF_4^-$, **2-13**, ACN, DCE, 60°C; (iv) copper source ($[Cu(MeCN)_4]^+BF_4^-$ or $Cu(BF_4)_2 \bullet 6H_2O$), ACN, DCE, 60°C.

by Gude, *et al*.[88] (Figure 4.8). The azide loading was determined to be 1.08 mmol/g, slightly lower than anticipated, possibly owing to the steric bulk of the Fmoc group. Since 1,2,3-triazoles are known to bind copper and often used in the synthesis of accelerants for CuAAC,[24,38] a 1,2,3-triazole was synthesized on polystyrene, without incorporation of a 1,2,4-triazine, by reacting **4-18** with phenylacetylene. Afterward, complexation with copper(I) and copper(II) resulted in **4-34** and **4-35**, respectfully, with copper loading values of 0.00 and 0.16 mmol/g. Azides are also capable of coordinating copper, as can be seen in all proposed CuAAC mechanisms, and therefore azide coordination with copper(I) (**4-36**) and copper(II) (**4-37**) was also attempted, followed by ICP determination of copper loading values of 0.08 and 0.00 mmol/g, respectfully.

4.4.2 Low-Loading Polystyrene

In response to both the incomplete CuAAC reaction of the high-loading polystyrene azide (**4-18**) and the unexpected activity of 1,2,3-triazole **4-35** (discussed in detail within chapter 5), we decided to also synthesize a lower-loading polystyrene-supported 1,2,4-triazine. As before, azide **4-39** was synthesized from Merrifield resin and sodium azide (Figure 4.9). Azide **4-39** was then reacted with alkyne **4-16**, yielding **4-40** with a 1,2,4-triazine loading of 0.38 mmol/g. However, an azide absorption could still be detected by IR spectroscopy, resulting in the reduction of residual azide yielding **4-41.** Lastly,

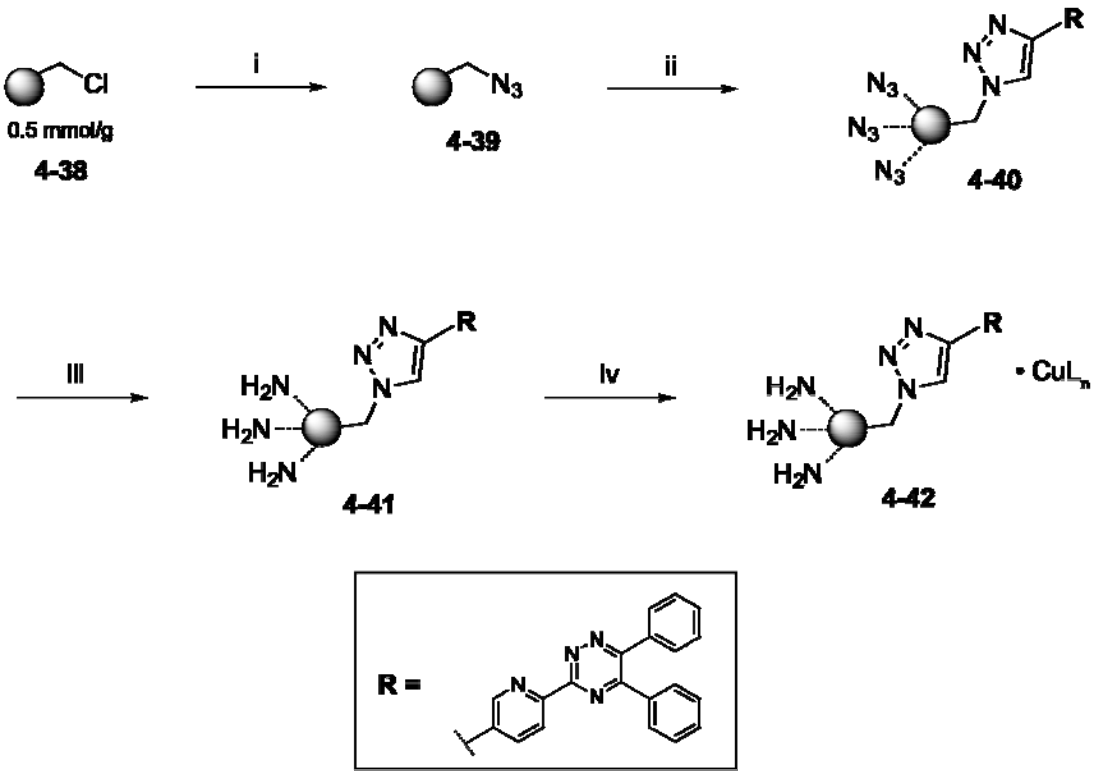


Figure 4.9 Synthesis of Low-Loading Polystyrene-Supported 1,2,4-Triazine Catalysts. (i) NaN_3, TBAI, NMP, H_2O, 80°C; (ii) alkyne-substituted 1,2,4-triazine **4-16**, Et_3N, $[Cu(MeCN)_4]^+BF_4^-$, **2-13**, ACN, DCE, 60°C; (iii) $SnCl_2 \cdot 2H_2O$, thiophenol, **Et_3N**, ACN; (iv) $Cu(BF_4)_2 \cdot 6H_2O$, ACN, DCE, 60°C.

complexation with copper(II) generated **4-42** with a copper loading of 0.12 mmol/g.

The appropriate controls were also synthesized using the lower-loading polystyrene support. Reduction of **4-39**, then coupling of Fmoc-glycine resulted in **4-44** (Figure 4.10). The Fmoc-Assay[88] determined the azide loading to be 0.35 mmol/g, again slightly lower than anticipated. Azide **4-39** was also reacted with phenylacetylene using 1,2,4-triazine-accelerated CuAAC yielding 1,2,3-triazole **4-45**, which had a copper loading of 0.01 mmol/g after complexation with

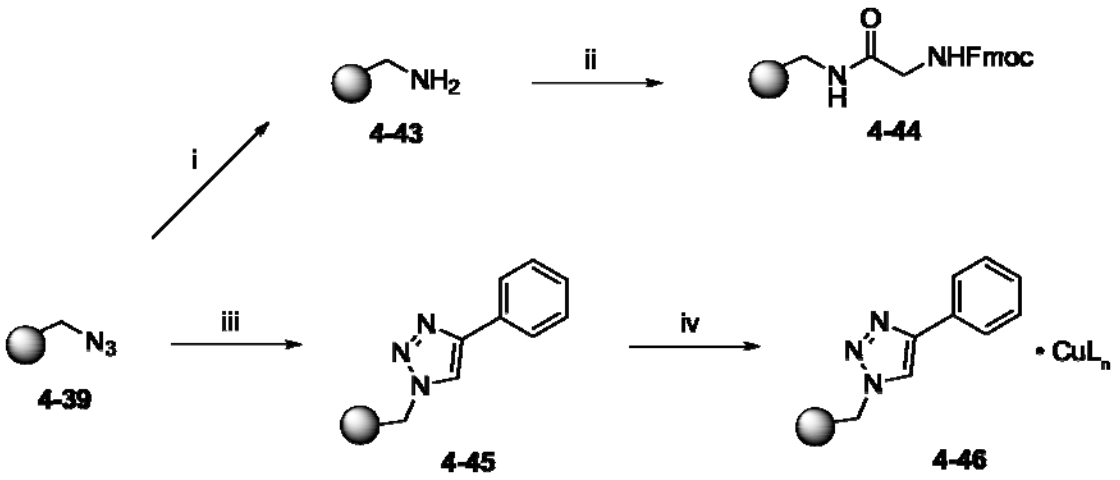


Figure 4.10 Synthesis of Low-Loading Polystyrene-Supported Controls. (i) $SnCl_2 \bullet 2H_2O$, thiophenol, Et_3N, THF; (ii) Fmoc-Gly, HBTU, HOBt, DIEA, NMP; (iii) phenylacetylene, Et_3N, $[Cu(MeCN)_4]^+BF_4^-$, **2-13**, ACN, DCE, 60°C; (iv) $Cu(BF_4)_2 \bullet 6H_2O$, ACN, DCE, 60°C.

copper(II) (**4-46**). This 1,2,3-triazole synthesized on low-loading Merrifield resin had a significantly lower copper(II) loading when compared to the corresponding high-loading 1,2,3-triazole **4-35** (0.16 mmol/g).

4.5 Silica-Supported 1,2,4-Triazines

Silica exhibits many different chemical properties when compared to polystyrene and therefore offers an alternative in circumstances when polystyrene supports may be inadequate, such as aqueous reaction conditions and high temperatures. The primary advantages of silica are its high surface area, exceptional chemical and thermal stability, and inexpensive cost.[25] In order to anchor the alkyne-substituted 1,2,4-triazines onto the silica support, an azide-functionalized silica was first synthesized.

Activated silica gel (**4-47**) was first treated with 3-aminopropyltriethoxysilane at 90°C, followed by reaction with triflic azide resulting in azide **4-49** (Figure 4.11A). The alkyne-substituted 1,2,4-triazines (**4-11** and **4-16**) could then be immobilized using 1,2,4-triazine-accelerated CuAAC conditions at 60°C yielding **4-50** and **4-51**, respectfully. Analysis of the reaction filtrate was analyzed by HPLC, resulting in a 1,2,4-triazine loading of 0.46 mmol/g for **4-50** and 0.45 mmol/g for **4-51**. As before, residual azide was reduced, then silica was complexed with either copper(I) or copper(II) generating **4-54 – 4-57** with copper loading values ranging from 0.15 – 0.29 mmol/g as determined by ICP analysis. 1,2,4-Triazine-functionalized silica **4-58 – 4-61** was also synthesized, still containing residual azide, by complexation with solutions of copper(I) and copper(II) (Figure 4.11B). Copper loading varied from 0.06 – 0.17 mmol/g, slightly lower than their amine-functionalized counterparts.

The amine-functionalized silica was reacted with Fmoc-glycine and analyzed according to previously published Fmoc-Assay conditions[88], which revealed a loading of 0.41 mmol/g of 3-aminopropyltriethoxysilane (Figure 4.12A). Azide-functionalized silica **4-49** was reacted with phenylacetylene, generating **4-63** (Figure 4.12B). Afterward, both azide **4-49** and 1,2,3-triazole **4-63** were complexed with copper(I) and copper(II) solutions and copper loading results are as follows: 0.05 mmol/g (**4-64**); 0.06 mmol/g (**4-65**); 0.02 mmol/g (**4-65**); 0.10 mmol/g (**4-67**).

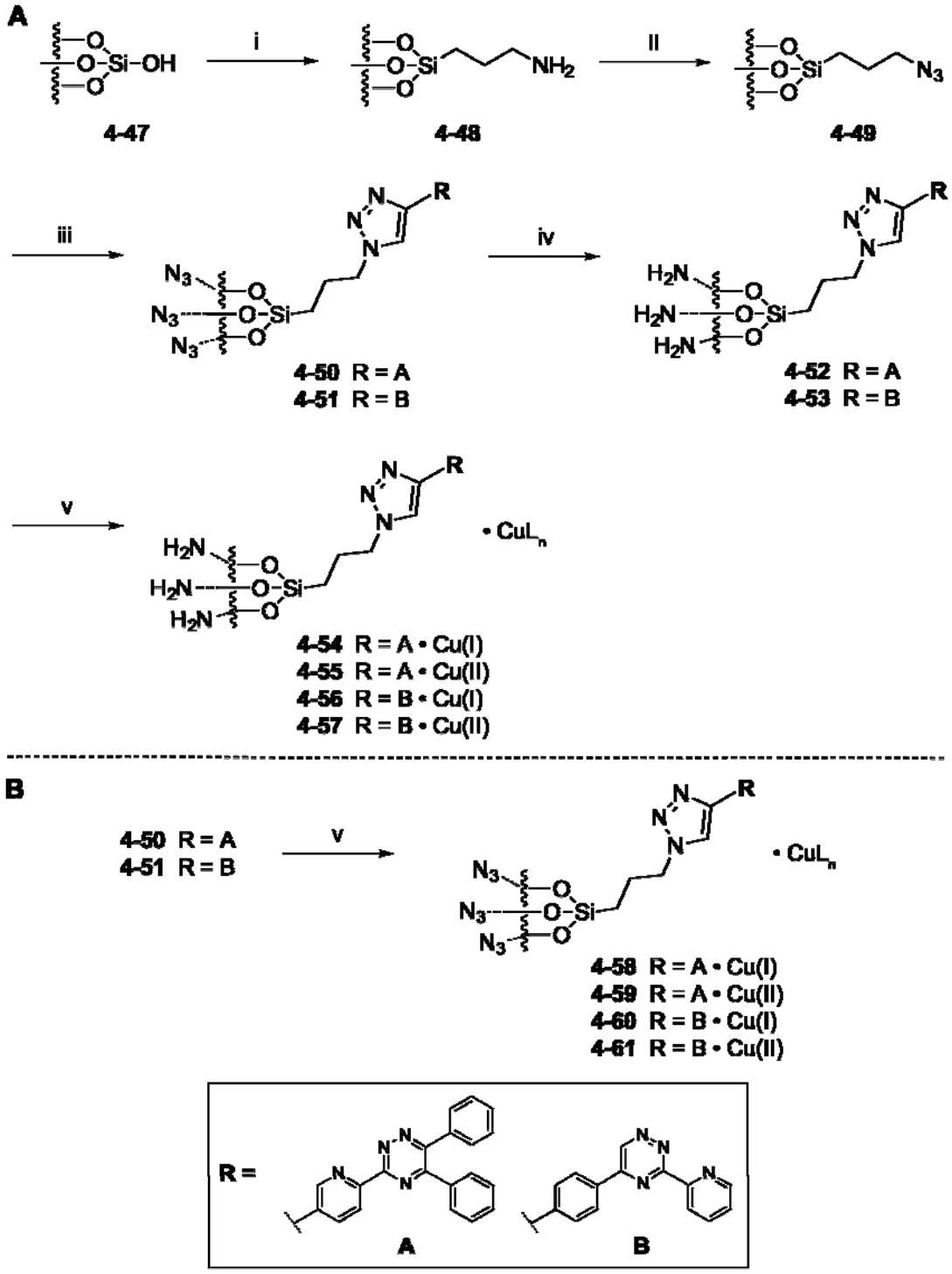


Figure 4.11 Synthesis of Silica-Supported 1,2,4-Triazine Catalysts. (i) 3-aminopropyltriethoxysilane, toluene, 90°C; (ii) triflic azide, $CuSO_4$•$5H_2O$, Et_3N, DMF, MeOH; (iii) alkyne-substituted 1,2,4-triazine (**4-11** or **4-16**), Et_3N, $[Cu(MeCN)_4]^+BF_4^-$, **2-13**, ACN, DCE, 60°C; (iv) $SnCl_2$•$2H_2O$, thiophenol, Et_3N, ACN; (v) copper source ($[Cu(MeCN)_4]^+BF_4^-$ or $Cu(BF_4)_2$ •$6H_2O$), ACN, DCE, 60°C.

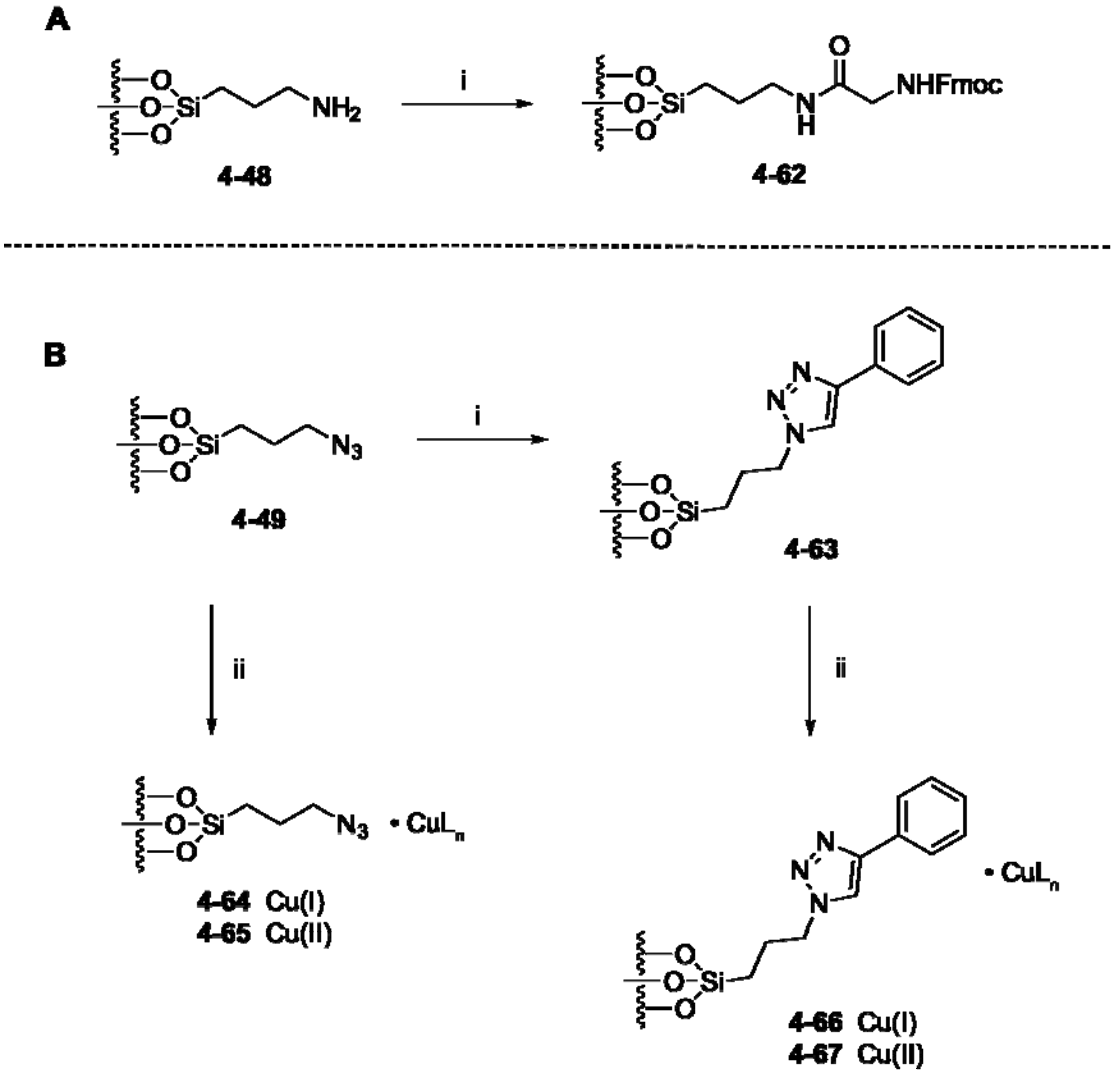


Figure 4.12 Synthesis of Silica-Supported 1,2,4-Triazine Controls. **(A)** (i) Fmoc-Gly, HBTU, HOBt, DIEA, NMP. **(B)** (i) phenylacetylene, Et_3N, $[Cu(MeCN)_4]^+BF_4^-$, **2-13**, ACN, DCE, 60°C; (ii) copper source ($[Cu(MeCN)_4]^+BF_4^-$ or $Cu(BF_4)_2 \cdot 6H_2O$), ACN, DCE, 60°C.

4.6 Synthesis and Cleavage of 1,2,4-Triazine from Knorr Resin

While Merrifield resin and silica are exceptional insoluble supports since they can only be cleaved under extreme circumstances, this attribute does make characterization more difficult. Therefore, in order to verify that our 1,2,4-triazine was being appended onto the solid-support, we designed a scheme using Knorr resin, a polystyrene-based support cleaved under acidic conditions. 4-bromobutanoic acid was coupled to Knorr resin (**4-68**) after removal of the Fmoc

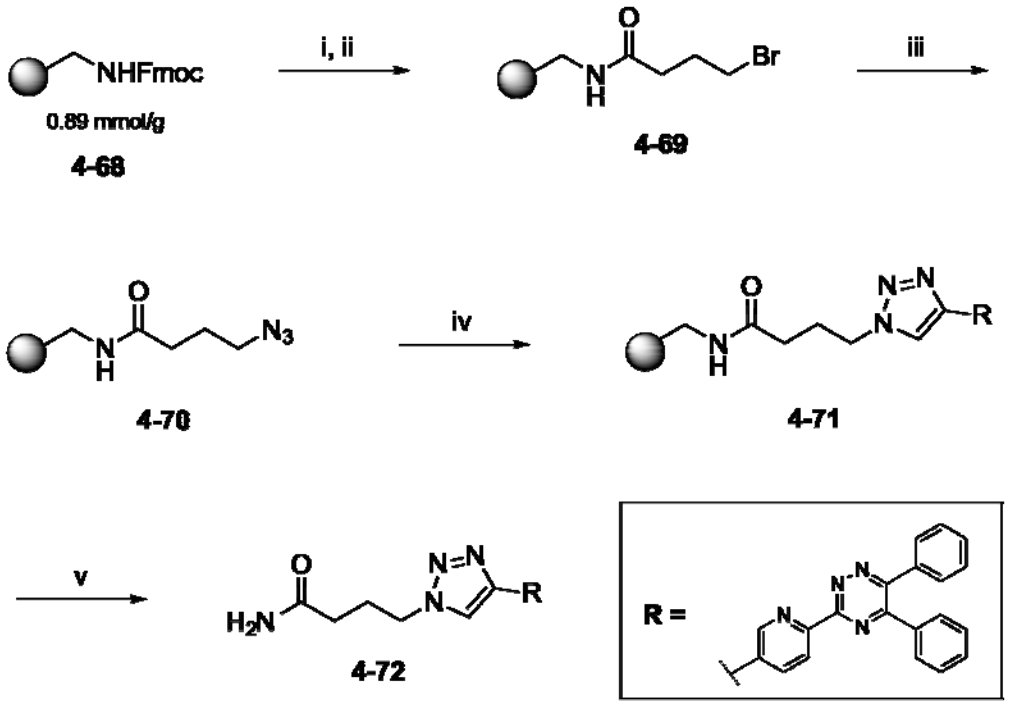


Figure 4.13 Synthesis and Cleavage of 1,2,4-Triazine Ligand from Knorr Resin. (i) piperidine, NMP; (ii) 4-bromobutanoic acid, HBTU, HOBt, DIEA, NMP; (iii) NaN_3, TBAI, NMP, H_2O, 60°C; (iv) alkyne-substituted 1,2,4-triazine **4-16**, Et_3N, $[Cu(MeCN)_4]^+BF_4^-$, **2-13**, ACN, DCE, 60°C; (v) 20% TFA in DCM.

protecting group (Figure 4.13). Next, sodium azide was reacted with **4-69**, yielding azide-functionalized Knorr resin (**4-70**). 1,2,4-Triazine-accelerated CuAAC was then utilized once again to click triazine **4-16** to the solid support. After cleavage from the resin using TFA, **4-72** was recovered and characterized by mass spectroscopy, fortifying that 1,2,4-triazine-accelerated CuAAC can be used to derivatize solid surfaces.

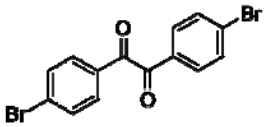
4.7 Conclusions

In conclusion, two alkyne-substituted 1,2,4-triazine derivatives were appended to two different types of solid supports, polystyrene and silica. Reaction progress on the solid support was monitored using various techniques including IR spectroscopy, HPLC, and an Fmoc-Assay, while synthesis on Knorr resin validated our synthetic methodology. After coordintation of copper metal to the support, copper loading was quantified using ICP-OES. Several controls were also synthesized in order to properly attribute the catalytic activity of these heterogeneous catalysts to the covalently attached 1,2,4-triazine. The copper loading of all the aforementioned supports will be compared to their catalytic activity in chapter 5, along with a discussion of optimizing CuAAC reaction conditions using heterogeneous 1,2,4-triazines.

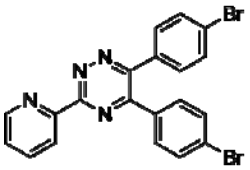
4.8 Experimental

Materials and General Methods. Reagents and solvents were purchased from various commercial sources and used without further purification unless otherwise stated. Anhydrous solvents were purified using a Grubbs solvent system. Analytical thin-layer chromatography (TLC) was performed using aluminum backed silica gel TLC plates with UV indicator from Sorbent Technologies. Flash column chromatography was performed using 40-63 μm (230 x 400 mesh) silica gel from Sorbent Technologies. ^{1}H and ^{13}C NMR were recorded at 600 MHz and 151 MHz, respectfully, on a Varian Inova spectrometer. All chemical shifts were reported in δ units relative to tetramethylsilane or the corresponding deuterated solvent. High resolution mass spectra (ESI) were obtained on a JEOL AccuTOF DART spectrometer. Infrared spectra were recorded on a Varian 4100 FT-IR using KBr pellets or KBr salt plates. While frequencies from the polystyrene or silica support were considered background and disregarded, all significant frequencies were reported in cm^{-1} units. Copper was quantified by inductively coupled plasma – optical emission spectroscopy (ICP-OES) using a Perkin Elmer Optima 2100 DV. High pressure liquid chromatography (HPLC) was performed using a Beckman Coulter System equipped with a UV-Vis detector, autosampler, Varian C18 column, and a mobile phase composed of acetonitrile and trifluoroacetic acid.

4.8.1 Alkyne-Substituted 1,2,4-Triazine Building Blocks

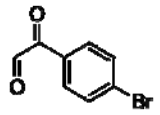


1,2-bis(4-bromophenyl)ethane-1,2-dione (4-3). p-Bromoaldehyde (435 mg, 2.35 mmol) and KCN (77 mg, 1.18 mmol) were dissolved in EtOH (0.6 mL) and water (0.4 mL). The mixture was heated under reflux for 0.5 h. After cooling to room temperature, the reaction mixture was poured into an ice bath and the crude benzoin intermediate was extracted with $CHCl_3$ and concentrated *in vacuo*. The crude benzoin intermediate was then refluxed in nitric acid (2 mL) for 2 h. The reaction mixture was poured into an ice bath and the crude benzil product was precipitated and filtered. Recrystallization from EtOH yielded a yellow solid in 65% yield. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.84 (d, 4H, J = 7.8 Hz), 7.68 (d, 4 H, J = 7.8 Hz). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 192.8, 132.7, 131.7, 131.5, 131.0. HRMS (ESI) m/z calculated 366.89693 ($C_{14}H_9Br_2O_2$, $[M+H]^+$), m/z observed 366.89757 ($C_{14}H_9Br_2O_2$, $[M+H]^+$).

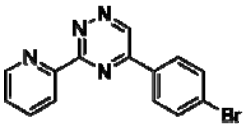


5,6-bis(4-bromophenyl)-3-(pyridin-2-yl)-1,2,4-triazine (4-4). Picolinohydrazonamide (73.5 mg, 0.54 mmol) and **4-3** (200 mg, 0.54 mmol) were added to EtOH (3.5 mL) and THF (1.5 mL). The slurry was heated at 80°C overnight with complete dissolution. Progress of the reaction was monitored by TLC. The reaction mixture was concentrated *in vacuo* and precipitated out of EtOH. The product

was isolated as an yellow solid in 29.7% yield. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.93 (m, 1H), 8.71 (d, 1H, J = 7.8 Hz), 7.96 (t, 1H, J = 7.8 Hz), 7.58-7.52 (m, 9H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 161.1, 155.5, 155.3, 152.7, 150.8, 137.3, 134.4, 134.0, 132.3, 132.3, 131.6, 131.2, 126.1, 125.8, 125.0, 124.4. HRMS (ESI) m/z calculated 466.95070 ($C_{20}H_{13}Br_2N_4$, $[M+H]^+$), m/z observed 466.94999 ($C_{20}H_{13}Br_2N_4$, $[M+H]^+$).

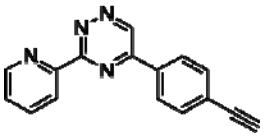


2-(4-bromophenyl)-2-oxoacetaldehyde (4-9). Selenium dioxide (1.67 g, 15 mmol) was suspended in dioxane (7.5 mL) and water (0.36 mL) and heated at 55°C until mostly dissolved. 1-(4-bromophenyl)ethanone (3 g, 15.0 mmol) was then added and the reaction was refluxed for 3 h. After cooling to room temperature, the reaction was filtered and the filtrate was concentrated *in vacuo*. The crude product was used in further reactions. MS (ESI) m/z calculated 212.95512 ($C_8H_6BrO_2$, $[M+H]^+$), m/z observed 212.986 ($C_8H_6BrO_2$, $[M+H]^+$).



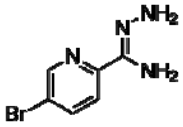
5-(4-bromophenyl)-3-(pyridin-2-yl)-1,2,4-triazine (4-10). **4-9** (782 mg, 3.7 mmol) and picolinohydrazonamide (500 mg, 3.7 mmol) were added to 14 mL of EtOH. The slurry was heated overnight at 80°C with complete dissolution. Progress of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature and the resulting precipitate was filtered and washed with EtOH resulting in a 46% yield. ^{1}H NMR

($CDCl_3$, 600 MHz) δ 9.70 (s, 1H), 8.94 (d, 1H, J = 4.2 Hz), 8.68 (d, 1H, J = 7.8 Hz), 8.20 (d, 2H, J = 7.8 Hz), 7.96 (t, 1H, J = 7.8 Hz), 7.75 (d, 2H, J = 6.6 Hz), 7.51 (t, 1H, J = 6.0 Hz). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 132.6, 132.48, 132.45, 132.1, 131.7, 131.5, 131.2, 130.2, 88.9, 87.5. MS (ESI) m/z calculated 313.00888 ($C_{14}H_{10}BrN_4$, $[M+H]^+$), m/z observed 313.00791 ($C_{14}H_{10}BrN_4$, $[M+H]^+$).

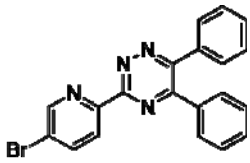


5-(4-ethynylphenyl)-3-(pyridin-2-yl)-1,2,4-triaizne (4-11). **4-10** (594 mg, 1.9 mmol), dichlorobis(triphenylphosphine)palladium(II) (67 mg, 0.1 mmol), copper iodide (18 mg, 0.1 mmol), and anhydrous THF (7.5 mL) were combined and placed under nitrogen. Triethylamine (577 mg, 5.7 mmol) and ethynyltrimethylsilane (560 mg, 5.7 mmol) were added and the reaction refluxed overnight. Reaction progress was monitored by TLC. After concentration *in vacuo*, the crude intermediate was purified by silica gel chromatography with gradient elution using EtOAc and hexanes. The intermediate was then dissolved in a 0.5 M alcohol solution (2 EtOH : 1 MeOH) and 0.1 eq of potassium carbonate was added. The reaction was allowed to stir at room temperature and reaction progress was monitored by TLC. Upon completion, the reaction was concentrated *in vacuo* and purified by silica gel chromatography with gradient elution using EtOAc and hexanes to yield a pale brown solid in 44% yield. ^1H NMR ($CDCl_3$, 600 MHz) δ 9.72 (s, 1H), 8.95 (d, 1H, J = 4.8 Hz), 8.69 (d, 1H, J = 7.8 Hz), 8.30 (d, 2H, J = 8.4 Hz), 7.96 (dt, 1H, J = 7.8, 1.8 Hz), 7.71 (d, 2H, J = 8.4 Hz), 7.52–7.50 (m,

1H), 3.3 (s, 1H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 163.0, 155.1, 153.1, 150.7, 145.3, 137.3, 133.7, 133.2, 127.9, 126.8, 125.9, 124.4, 82.9, 80.8. HRMS (ESI) m/z calculated 259.09837 ($C_{16}H_{11}N_4$, $[M+H]^+$), m/z observed 259.09788 ($C_{16}H_{11}N_4$, $[M+H]^+$).

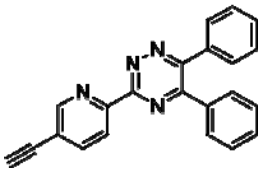


5-bromopicolinohydrazonamide (4-14). To a stirring suspension of **4-13** (1.0 g, 5.5 mmol) in 5 mL of EtOH was added hydrazine hydrate (0.584 mL, 7.7 mmol). The suspension was stirred at room temperature for 72 h and progress of the reaction was monitored by TLC. The pale yellow precipitate was then filtered and washed with Et_2O in 79% yield. ^1H NMR ($CDCl_3$, 600 MHz) δ 8.57 (s, 1H), 7.91 (dd, 1H, J = 8.4, 2.4 Hz), 7.81 (dt, 1H, J = 9.0, 2.4 Hz), 5.16 (bs, 1H), 4.60 (bs, 1H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 149.6, 149.0, 147.9, 139.2, 121.14, 121.08. HRMS (ESI) m/z calculated 214.99323 ($C_6H_8BrN_4$, $[M+H]^+$), m/z observed 214.99251 ($C_6H_8BrN_4$, $[M+H]^+$).



3-(5-bromopyridin-2-yl)-5,6-diphenyl-1,2,4-triazine (4-15). **4-14** (800 mg, 3.72 mmol) and benzil (782 mg, 3.72) were added to 15 mL of EtOH. The slurry was heated overnight at 80°C with complete dissolution. Progress of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature and the resulting precipitate was filtered and washed with EtOH and Et_2O resulting in a 91% yield. ^1H NMR ($CDCl_3$, 600 MHz) δ 8.97 (s, 1H), 8.62 (dd, 1H, J = 9.0,1.8 Hz), 8.07 (dt,

1H, J = 8.4, 3.0 Hz), 7.67 (d, 2H, J = 6.6 Hz), 7.64 (d, 2H, J = 7.2 Hz), 7.47-7.44 (m, 2H), 7.41-7.36 (m, 4H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 160.4, 156.8, 156.6, 151.8, 151.5, 139.9, 135.6, 135.3, 131.0, 130.1, 130.0, 129.7, 128.81, 128.79, 125.4, 123.6. MS (ESI) m/z calculated 389.04018 ($C_{20}H_{14}BrN_4$, $[M+H]^+$), m/z observed 389.02638 ($C_{20}H_{14}BrN_4$, $[M+H]^+$).



3-(5-ethynylpyridin-2-yl)-5,6-diphenyl-1,2,4-triazine (4-16). **4-15** (1.0 g, 2.57 mmol), dichlorobis(triphenylphosphine)palladium(II) (90 mg, 0.13 mmol), copper iodide (24 mg, 0.13 mmol), and anhydrous THF (13 mL) were combined and placed under nitrogen. Triethylamine (780 mg, 7.71 mmol) and ethynyltrimethylsilane (757 mg, 7.71 mmol) were added and the reaction was heated overnight at 80°C. Reaction progress was monitored by TLC. After concentration *in vacuo*, the crude intermediate was purified by silica gel chromatography with gradient elution using EtOAc and hexanes. The intermediate was then dissolved in 8 mL of EtOH, 4 mL of MeOH, and 4 mL DCM. Potassium carbonate (0.1 eq) was added the reaction was allowed to stir overnight at room temperature with reaction progress monitored by TLC. Upon completion, the reaction was concentrated *in vacuo* and purified by silica gel chromatography with gradient elution using EtOAc and hexanes to yield a yellow solid in 62% yield. ^1H NMR ($CDCl_3$, 600 MHz) δ 9.00 (s, 1H), 8.70 (d, 1H, J = 8.4 Hz), 8.01 (dd, 1H, J = 8.4, 1.8 Hz), 7.67 (d, 2H, J = 7.2 Hz), 7.63 (d, 2H, J = 7.2

Hz), 7.47-7.44 (m, 2H), 7.41-7.36 (m, 4H), 3.38 (s, 1H). ^{13}C NMR ($CDCl_3$, 151 MHz) δ 160.4, 156.7, 156.6, 153.5, 152.2, 140.3, 135.7, 135.3, 131.0, 130.1, 130.0, 129.8, 128.80, 128.78, 123.5, 121.2, 82.8, 80.5. MS (ESI) m/z calculated 335.12967 ($C_{22}H_{15}N_4$, $[M+H]^+$), m/z observed 335.12451 ($C_{22}H_{15}N_4$, $[M+H]^+$).

4.8.2 Heterogeneous 1,2,4-Triazine Catalysts

Polystyrene-Supported Azide Method. Merrifield resin (14 mmol), sodium azide (42 mmol), tetrabutylammonium iodide (14 mmol) were added to 60 mL of NMP and 10 mL of water. Reaction was heated at 80°C overnight. After cooling to room temperature, the resin was filtered, washed with NMP, water, DCM, MeOH, and Et_2O, and air dried.

Heterogeneous CuAAC Method A. A solution of phenylacetylene (1.07 mmol), triethylamine (1.07 mmol), **2-13** (9.72 μmol), and tetrakis(acetonitrile-N)copper(I) tetrafluoroborate (9.72 μmol) dissolved in 1 mL of ACN and 4 mL of DCE was added to the supported azide (0.972 mmol). Reaction was heated at 60°C for 4 h. After cooling to room temperature, the support was filtered and washed with DCE, water, MeOH, and Et_2O and air dried.

Heterogeneous CuAAC Method B. The corresponding alkyne-substituted 1,2,4-triazine (2.38 mmol), triethylamine (2.38 mmol), **2-13** (22.0 μmol), and

tetrakis(acetonitrile-N)copper(I) tetrafluoroborate (22.0 μmol) were dissolved in 4.4 mL of ACN and 8.8 mL of DCE and added to the supported azide (2.16 mmol). Reaction was heated at 60°C for 18 h. After cooling to room temperature, an aliquot of the reaction solution was appropriately diluted and analyzed by HPLC to determine loading of the 1,2,4-triazine. The support was then filtered, washed with DCE, water, MeOH, and Et_2O and air dried.

HPLC Methodology. The CuAAC reactions involving 1,2,4-triazine **4-11** were diluted in acetonitrile to a final concentration range of 0.4 – 4 mM and analyzed by HPLC at a wavelength of 317 nm. The CuAAC reactions involving 1,2,4-triazine **4-16** were diluted in acetonitrile to a final concentration range of 0.3 – 3 mM and analyzed by HPLC at a wavelength of 301 nm. In all cases, the isocratic mobile phase was composed of 80% acetonitrile and 0.1% trifluoroacetic acid. Loading of the 1,2,4-triazine was determined based on percent difference using the aforementioned external calibration curves.

Heterogeneous Reduction Method. A solution of tin chloride dihydrate (1.62 mmol), triethylamine (4.86 mmol), and thiophenol (6.48 mmol) in 15 mL of solvent (ACN or THF) was added to the supported azide (1.62 mmol). The reaction was stirred at room temperature for 4 h – 8 h. The support was then filtered, washed with ACN, water, DCM, MeOH, and Et_2O and air dried. Kaiser test was positive, indicating free amine was present.

Polystyrene-Supported Complexation Method. A 10 mM stock solution of the corresponding copper source in 1:1 ACN:DCE was prepared. Copper (0.0594 mmol) was added to the resin (0.054 mmol) and heated at 60°C for 2 h. An equivalent volume of copper stock solution was concentrated and analyzed by ICP-OES as a control. After cooling to room temperature, the resin was filtered, washed with ACN, DCM, MeOH, and Et_2O and air dried. The filtrate was concentrated *in vacuo*, analyzed by ICP-OES, and compared to the ICP-OES value of the aforementioned control solution.

Silica-Supported Complexation Method. A 10 mM stock solution of the corresponding copper source in ACN was prepared. Copper (0.0226 mmol) was added to the silica (0.0205 mmol) and heated at 60°C for 2 h. An equivalent volume of copper stock solution was concentrated and analyzed by ICP-OES as a control. After cooling to room temperature, the silica was filtered, washed with ACN, DCM, MeOH, and Et_2O and air dried. The filtrate was concentrated *in vacuo*, analyzed by ICP-OES, and compared to the ICP-OES value of the aforementioned control solution.

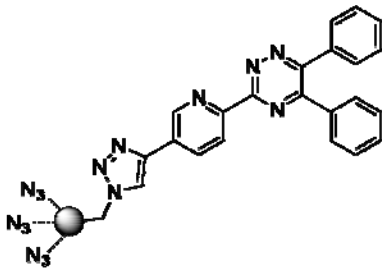
ICP-OES Methodology. The filtrate recovered from complexation reactions was redissolved in 2% nitric acid and 1% MeOH to a final concentration of 75 ppm copper (assuming all copper from the reaction was still present). Samples from the initial 10 mM copper stock solutions were treated in the same manner. All

samples were heated at 60°C for 10 min and left undisturbed at room temperature overnight to ensure all copper was dissolved. Quantification of copper was determined using an external calibration curve ranging from 75 ppm – 1 ppm at a wavelength of 324.75 nm.

Heterogeneous Fmoc-Glycine Method. Fmoc-glycine (3.5 mmol), HBTU (3.47 mmol), HOBt (1.75 mmol), and DIEA (5.95 mmol) were dissolved in 10 mL of NMP and allowed to stir at room temperature for 15 min before addition to solid support (0.35 mmol). The reaction was stirred at room temperature for 8 h. The support was then filtered, washed with NMP, water, DCM, MeOH, and Et_2O, and air dried. Kaiser test was negative, indicating no amine was present. Support was then analyzed according to previously published Fmoc Assay conditions.

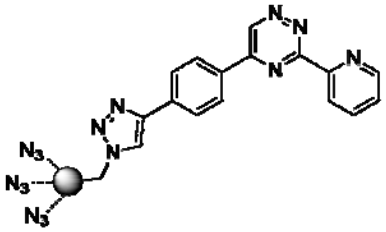


polystyrene-supported azide (4-18). Synthesized according to Polystyrene-Supported Azide Method and isolated as a white solid. IR (KBr) ν_{max} 3456, 2974, 2102, 1381, 1346, 1115 cm^{-1}.

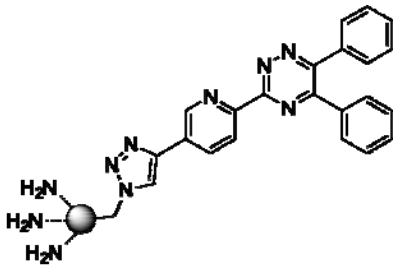


polystyrene-supported 5,6-diphenyl-3-(pyridin-2-yl)-1,2,4-triazine with residual azide (4-19). Synthesized according to Heterogeneous CuAAC Method B and isolated as a red-brown solid. 1,2,4-

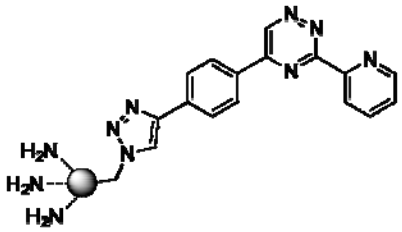
Triazine loading as determined by HPLC was 1.19 mmol/g. IR (KBr) v_{max} 2098, 1951, 1890, 1809, 1400, 1369, 1281, 1232, 1188, 1045, 1007, 972 cm^{-1}.



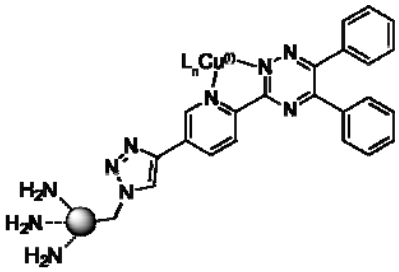
polystyrene-supported 5-phenyl-3-(pyridin-2-yl)-1,2,4-triazine with residual azide (4-20). Synthesized according to Heterogeneous CuAAC Method B and isolated as a dark brown solid. 1,2,4-Triazine loading as determined by HPLC was 1.15 mmol/g. IR (KBr) v_{max} 3414, 2099, 1948, 1878, 1809, 1612, 1539, 1362, 1319, 1188, 1119, 1045 cm^{-1}.



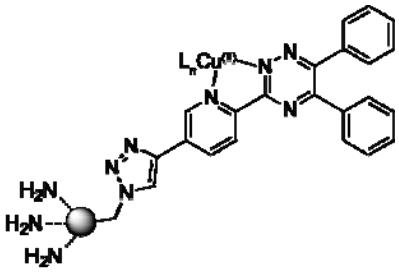
polystyrene-supported 5,6-diphenyl-3-(pyridin-2-yl)-1,2,4-triazine with residual amine (4-21). Synthesized according to Heterogeneous Reduction Method and isolated as a brown solid. IR (KBr) v_{max} 3410, 1951, 1886, 1813, 1381, 1273, 1230, 1188, 1119, 1076, 1026, 972 cm^{-1}.



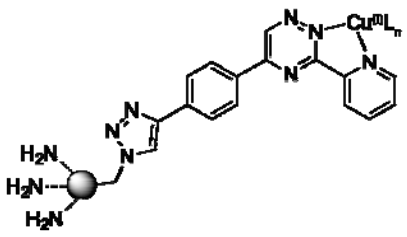
polystyrene-supported 5-phenyl-3-(pyridin-2-yl)-1,2,4-triazine with residual amine (4-22). Synthesized according to Heterogeneous Reduction Method and isolated as a brown solid. IR (KBr) v_{max} 3379, 1948, 1878, 1809, 1612, 1539, 1362, 1319, 1188, 1045 cm^{-1}.



polystyrene-supported 5,6-diphenyl-3-(pyridin-2-yl)-1,2,4-triazine with residual amine copper(I) complex (4-23). Synthesized according to Polystyrene-Supported Complexation Method using tetrakis(acetonitrile-N)copper(I) tetrafluoroborate and isolated as a black solid. Copper loading as determined by ICP-OES was 0.46 mmol/g. IR (KBr) v_{max} 1960, 1898, 1813, 1370, 1192, 1140-990 (br) cm^{-1}.

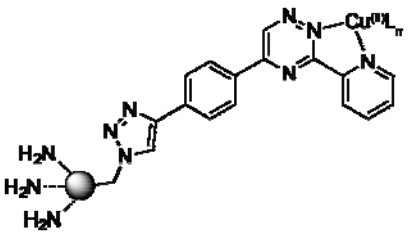


polystyrene-supported 5,6-diphenyl-3-(pyridin-2-yl)-1,2,4-triazine with residual amine copper(II) complex (4-24). Synthesized according to Polystyrene-Supported Complexation Method using copper(II) tetrafluoroborate hexahydrate and isolated as a dark green solid. Copper loading as determined by ICP-OES was 0.48 mmol/g. IR (KBr) v_{max} 1963, 1897, 1813, 1373, 1196, 1175-925 (br) cm^{-1}.

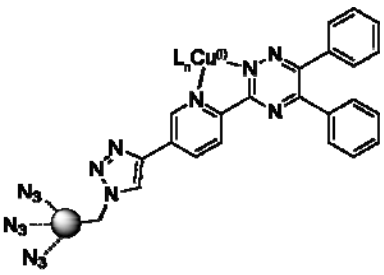


polystyrene-supported 5-phenyl-3-(pyridin-2-yl)-1,2,4-triazine with residual amine copper(I) complex (4-25). Synthesized according to Polystyrene-Supported Complexation Method using tetrakis(acetonitrile-N)copper(I) tetrafluoroborate and isolated as a black solid. Copper loading as determined by ICP-OES was

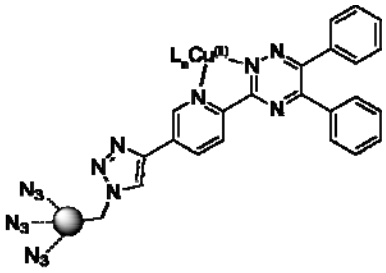
0.47 mmol/g. IR (KBr) ν_{max} 3596, 1951, 1886, 1813, 1624, 1547, 1366, 1331, 1192, 1150-990 (br) cm^{-1}.



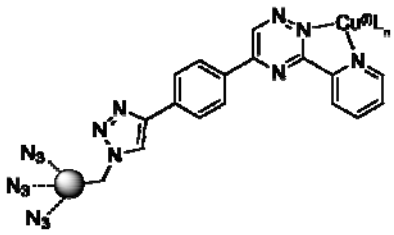
polystyrene-supported 5-phenyl-3-(pyridin-2-yl)-1,2,4-triazine with residual amine copper(II) complex (4-26). Synthesized according to Polystyrene-Supported Complexation Method using copper(II) tetrafluoroborate hexahydrate and isolated as a dark green solid. Copper loading as determined by ICP-OES was 0.59 mmol/g. IR (KBr) ν_{max} 3549, 1952, 1886, 1813, 1612, 1550, 1377, 1331, 1192, 1175-925 cm^{-1}.



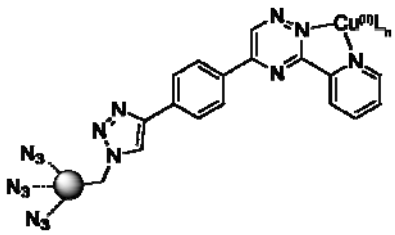
polystyrene-supported 5,6-diphenyl-3-(pyridin-2-yl)-1,2,4-triazine with residual azide copper(I) complex (4-27). Synthesized according to Polystyrene-Supported Complexation Method using tetrakis(acetonitrile-N)copper(I) tetrafluoroborate and isolated as black solid. Copper loading as determined by ICP-OES was 0.41 mmol/g. IR (KBr) ν_{max} 2102, 1963, 1890, 1820, 1415, 1369, 1238, 1110-990 (br) cm^{-1}.



polystyrene-supported 5,6-diphenyl-3-(pyridin-2-yl)-1,2,4-triazine with residual azide copper(II) complex (4-28). Synthesized according to Polystyrene-Supported Complexation Method using copper(II) tetrafluoroborate hexahydrate and isolated as a green solid. Copper loading as determined by ICP-OES was 0.43 mmol/g. IR (KBr) v_{max} 2098, 1956, 1894, 1820, 1419, 1377, 1234, 1140-920 (br) cm^{-1}.



polystyrene-supported 5-phenyl-3-(pyridin-2-yl)-1,2,4-triazine with residual azide copper(I) complex (4-29). Synthesized according to Polystyrene-Supported Complexation Method using tetrakis(acetonitrile-N)copper(I) tetrafluoroborate and isolated as a black solid. Copper loading as determined by ICP-OES was 0.38 mmol/g. IR (KBr) v_{max} 2099, 1952, 1890, 1813, 1609, 1539, 1362, 1327, 1192, 1145-980 (br) cm^{-1}.

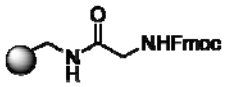


polystyrene-supported 5-phenyl-3-(pyridin-2-yl)-1,2,4-triazine with residual azide copper(II) complex (4-30). Synthesized according to Polystyrene-Supported Complexation Method

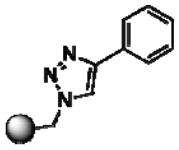
using copper(II) tetrafluoroborate hexahydrate and isolated as a green solid. Copper loading as determined by ICP-OES was 0.45 mmol/g. IR (KBr) ν_{max} 2102, 1955, 1890, 1813, 1612, 1555, 1377, 1335, 1196, 1160-930 (br) cm^{-1}.



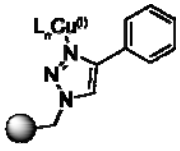
polystyrene-supported amine (4-31). Synthesized by Heterogeneous Reduction Method and isolated as a pale white solid. IR (KBr) ν_{max} 3426, 3321, 1670, 1277 cm^{-1}.



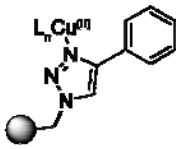
polystyrene-supported fmoc-glycine (4-32). Synthesized according to Heterogeneous Fmoc-Glycine Method and isolated as a light brown solid. Fmoc loading as determined by Fmoc Assay was 1.08 mmol/g. IR (KBr) ν_{max} 3422, 3348, 1952, 1879, 1813, 1732, 1690, 1520, 1354, 1250, 1196 cm^{-1}.



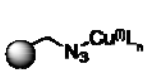
polystyrene-supported triazole (4-33). Synthesized according to Heterogeneous CuAAC Method A and isolated as a light brown solid. IR (KBr) ν_{max} 3406, 3136, 1354, 1227, 1184, 1045, 972, 910 cm^{-1}.



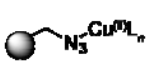
polystyrene-supported triazole copper(I) complex (4-34). Synthesized according to Polystyrene-Supported Complexation Method using tetrakis(acetonitrile-N)copper(I) tetrafluoroborate and isolated as a pale white solid. Copper loading as determined by ICP-OES was 0.00 mmol/g. IR (KBr) ν_{max} 3406, 3136, 1354, 1227, 1184, 1045, 972, 910 cm^{-1}.



polystyrene-supported triazole copper(II) complex (4-35). Synthesized according to Polystyrene-Supported Complexation Method using copper(II) tetrafluoroborate hexahydrate and isolated as a pale green solid. Copper loading as determined by ICP-OES was 0.16 mmol/g. IR (KBr) v_{max} 3406, 3136, 1354, 1227, 1184, 1120-930 (br) cm^{-1}.



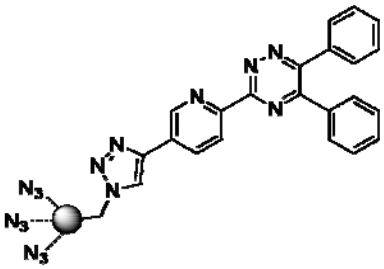
polystyrene-supported azide copper(I) complex (4-36). Synthesized according to Polystyrene-Supported Complexation Method using tetrakis(acetonitrile-N)copper(I) tetrafluoroborate and isolated as a white solid. Copper loading as determined by ICP-OES was 0.08 mmol/g. IR (KBr) v_{max} 3456, 2974, 2102, 1381, 1346, 1115 cm^{-1}.



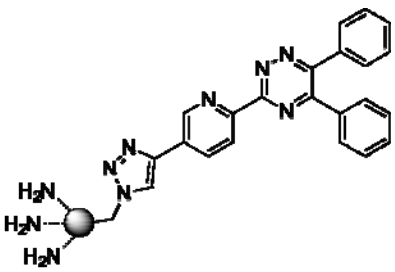
polystyrene-supported azide copper(II) complex (4-37). Synthesized according to Polystyrene-Supported Complexation Method using copper(II) tetrafluoroborate hexahydrate and isolated as a white solid. Copper loading as determined by ICP-OES was 0.00 mmol/g. IR (KBr) v_{max} 3456, 2974, 2102, 1381, 1346, 1115 cm^{-1}.



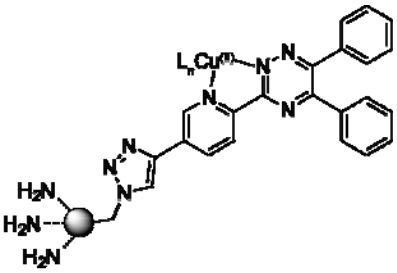
low-loading polystyrene-supported azide (4-39). Synthesized by Polystyrene-Supported Azide Method and isolated as a white solid. IR (KBr) v_{max} 2099, 1119 cm^{-1}.



low-loading polystyrene-supported 5,6-diphenyl-3-(pyridin-2-yl)-1,2,4-triazine with residual azide (4-40). Synthesized by Heterogeneous CuAAC Method B and isolated as a brown solid. 1,2,4-Triazine loading as determined by HPLC was 0.38 mmol/g. IR (KBr) v_{max} 2099, 1277, 1119 cm^{-1}.

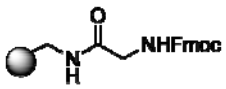


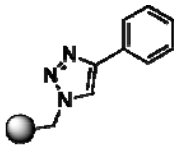
low-loading polystyrene-supported 5,6-diphenyl-3-(pyridin-2-yl)-1,2,4-triazine with residual amine (4-41). Synthesized by Heterogeneous Reduction Method and isolated as a light brown solid. IR (KBr) v_{max} 2099, 1277, 1119 cm^{-1}.

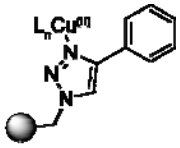


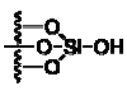
low-loading polystyrene-supported 5,6-diphenyl-3-(pyridin-2-yl)-1,2,4-triazine with residual amine copper(II) complex (4-42). Synthesized according to Polystyrene-Supported Complexation Method using copper(II) tetrafluoroborate hexahydrate and isolated as a green solid. Copper loading as determined by ICP-OES was 0.12 mmol/g. IR (KBr) v_{max} 2099, 1281, 1175-930 (br) cm^{-1}.

 **low-loading polystyrene-supported amine (4-43).** Synthesized by Heterogeneous Reduction Method and isolated as a pale white solid. IR (KBr) v_{max} 3456, 3337, 1276, 1119 cm^{-1}.

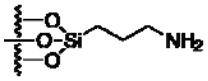
 **low-loading polystyrene-supported fmoc-glycine (4-44).** Synthesized according to Heterogeneous Fmoc-Glycine Method and isolated as a light brown solid. Fmoc loading as determined by Fmoc Assay was 0.35 mmol/g. IR (KBr) v_{max} 3421, 3352, 1735, 1693, 1384, 1119 cm^{-1}.

 **low-loading polystyrene-supported triazole (4-45).** Synthesized according to Heterogeneous CuAAC Method A and isolated as a white solid. IR (KBr) v_{max} 3472, 2098, 1273, 1119 cm^{-1}.

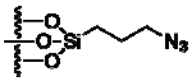
 **low-loading polystyrene-supported triazole copper(II) complex (4-46).** Synthesized according to Polystyrene-Supported Complexation Method using copper(II) tetrafluoroborate hexahydrate and isolated as a white solid. Copper loading as determined by ICP-OES was 0.01 mmol/g. IR (KBr) v_{max} 2099, 1277, 1119 cm^{-1}.

 **activated silica (4-47).** Silica gel (10 g) was refluxed overnight in 1.2 M HCL (100 mL). The suspension was cooled to room temperature, filtered, and rinsed with deionized water until filtrate reached a

neutral pH. The silica was then washed with MeOH (30 mL), acetone (15 mL), DCM (15 mL), toluene (15 mL), MeOH, (15 mL) and Et_2O (15 mL). After air drying ON, silica was spread onto a petri dish and dried overnight in an oven at approx 180°C then further dried under high vacuum for 24-48 h. Isolated as a white solid.

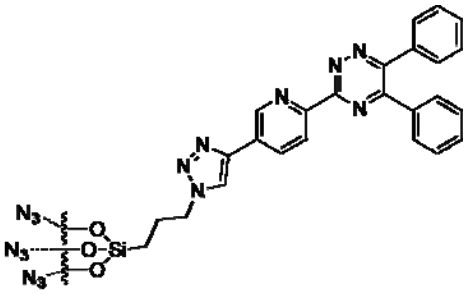


silica-supported amine (4-48). 3-aminopropyl triethoxysilane (8.0 mmol) was added to a suspension of (**4-47**) (8.0 g) in toluene (80 mL) and heated overnight at 90°C. The suspension was cooled to room temperature, filtered, and rinsed with toluene, MeOH, water, DCM, acetone, and Et_2O. The silica was dried under high vacuum overnight with a recovery of 8.75 g. Isolated as a white solid. Kaiser test was positive, indicating free amine was present. IR (KBr) ν_{max} 2990, 2951, 2878 cm^{-1}.

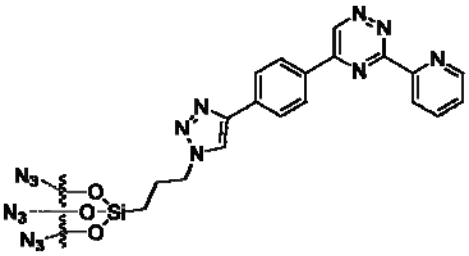


silica-supported azide (4-49). **4-48** (8g, 3.28 mmol) was suspended in 60 mL of DMF and 6 mL of MeOH. Triethylamine (13.1 mmol) and copper sulfate pentahydrate (1 M solution in water, 3.28 mmol) were added to reaction. Triflic azide (1M solution in toluene, 26.2 mmol) was then added drop wise to the reaction. After stirring, at room temperature overnight, the silica was filtered and washed with DCM, MeOH, water, toluene, acetone, and Et_2O with a recovery of 8.45 g. Isolated as a light blue solid.

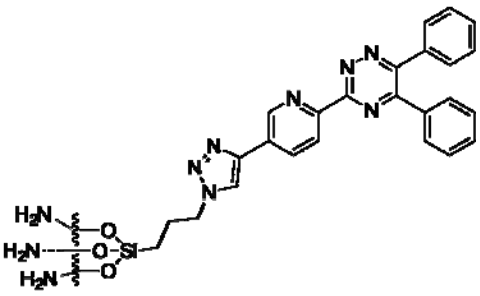
Kaiser test was negative, indicating no free amine was present. IR (KBr) v_{max} 2990, 2947, 2900, 2110, 1458, 1412 cm^{-1}.



silica-supported 5,6-diphenyl-3-(pyridin-2-yl)-1,2,4-triazine with residual azide (4-50). Synthesized by Heterogeneous CuAAC Method B and isolated as a brown solid. 1,2,4-Triazine loading as determined by HPLC was 0.46 mmol/g. IR (KBr) v_{max} 2990, 2955, 2900, 2110, 1605, 1516, 1447, 1415, 1369 cm^{-1}.

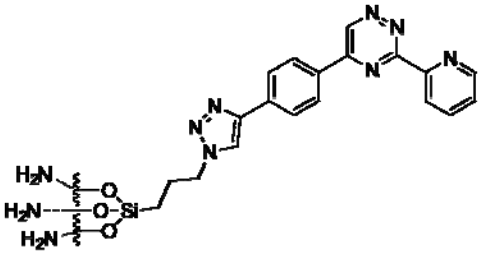


silica-supported 5-phenyl-3-(pyridin-2-yl)-1,2,4-triazine with residual azide (4-51). Synthesized by Heterogeneous CuAAC Method B and solid as a brown solid. 1,2,4-Triazine loading as determined by HPLC was 0.45 mmol/g. IR (KBr) v_{max} 3660, 2956, 2106, 1612, 1547, 1501, 1362, 1327 cm^{-1}.

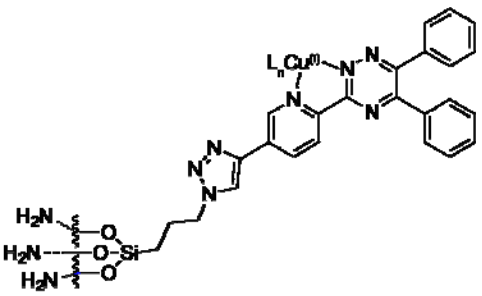


silica-supported 5,6-diphenyl-3-(pyridin-2-yl)-1,2,4-triazine with residual amine (4-52). Synthesized by Heterogeneous Reduction Method and isolated as a dark

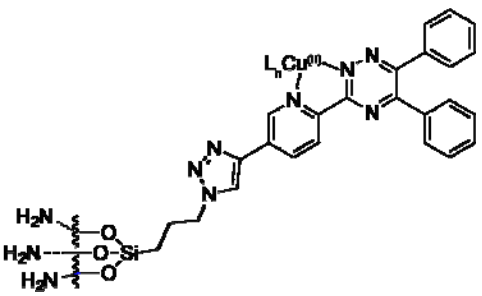
brown solid. IR (KBr) ν_{max} 3078, 2955, 2106, 1651, 1578, 1508, 1446, 1404, 1373 cm^{-1}.



silica-supported 5-phenyl-3-(pyridin-2-yl)-1,2,4-triazine with residual amine (4-53). Synthesized by Heterogeneous Reduction Method and isolated as a dark brown solid. IR (KBr) ν_{max} 3665, 2955, 2110, 1616, 1543, 1504, 1415, 1365, 1323 cm^{-1}.

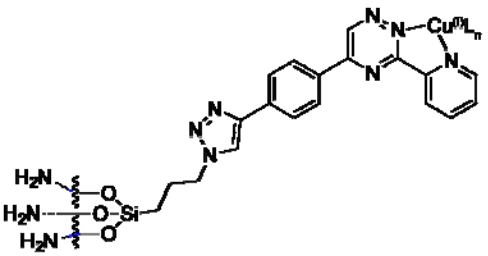


silica-supported 5,6-diphenyl-3-(pyridin-2-yl)-1,2,4-triazine with residual amine copper(I) complex (4-54). Synthesized according to Silica-Supported Complexation Method using tetrakis(acetonitrile-N)copper(I) tetrafluoroborate and isolated as a brown solid. Copper loading as determined by ICP-OES was 0.22 mmol/g. IR (KBr) ν_{max} 3078, 2955, 2106, 1651, 1578, 1508, 1446, 1404, 1373 cm^{-1}.

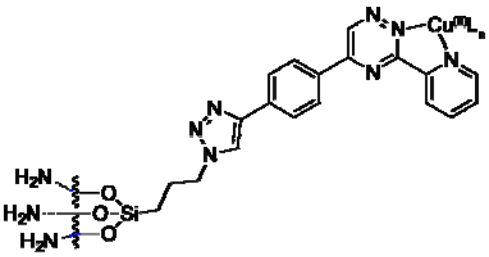


silica-supported 5,6-diphenyl-3-(pyridin-2-yl)-1,2,4-triazine with residual amine copper(II) complex (4-55). Synthesized

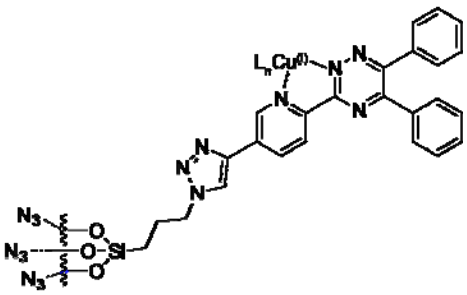
according to Silica-Supported Complexation Method using copper(II) tetrafluoroborate hexahydrate and isolated as a green-brown. Copper loading as determined by ICP-OES was 0.29 mmol/g. IR (KBr) ν_{max} 3078, 2955, 2106, 1651, 1578, 1508, 1446, 1404, 1373 cm^{-1}.



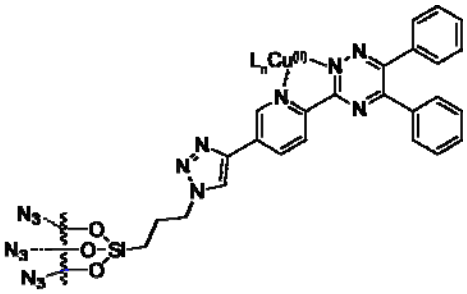
silica-supported 5-phenyl-3-(pyridin-2-yl)-1,2,4-triazine with residual amine copper(I) complex (4-56). Synthesized according to Silica-Supported Complexation Method using tetrakis(acetonitrile-N)copper(I) tetrafluoroborate and isolated as a brown solid. Copper loading as determined by ICP-OES was 0.15 mmol/g. IR (KBr) ν_{max} 3665, 2955, 2110, 1616, 1543, 1504, 1415, 1365, 1323 cm^{-1}.



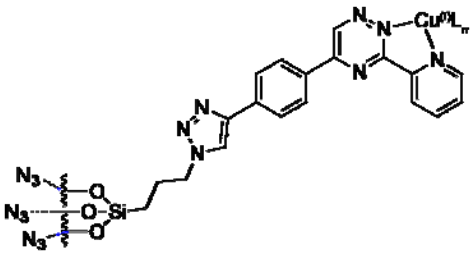
silica-supported 5-phenyl-3-(pyridin-2-yl)-1,2,4-triazine with residual amine copper(II) complex (4-57). Synthesized according to Silica-Supported Complexation Method using copper(II) tetrafluoroborate hexahydrate and isolated as a green-yellow solid. Copper loading as determined by ICP-OES was 0.23 mmol/g. IR (KBr) ν_{max} 3665, 2955, 2110, 1616, 1543, 1504, 1415, 1365, 1323 cm^{-1}.



silica-supported 5,6-diphenyl-3-(pyridin-2-yl)-1,2,4-triazine with residual azide copper(I) complex (4-58). Synthesized according to Silica-Supported Complexation Method using tetrakis(acetonitrile-N)copper(I) tetrafluoroborate and isolated as a brown solid. Copper loading as determined by ICP-OES was 0.07 mmol/g. IR (KBr) v_{max} 2990, 2955, 2900, 2110, 1605, 1516, 1447, 1415, 1369 cm^{-1}.

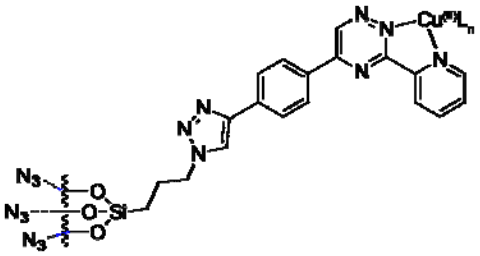


silica-supported 5,6-diphenyl-3-(pyridin-2-yl)-1,2,4-triazine with residual azide copper(II) complex (4-59). Synthesized according to Silica-Supported Complexation Method using copper(II) tetrafluoroborate hexahydrate and isolated as a green solid. Copper loading as determined by ICP-OES was 0.13 mmol/g. IR (KBr) v_{max} 2990, 2955, 2900, 2110, 1605, 1516, 1447, 1415, 1369 cm^{-1}.

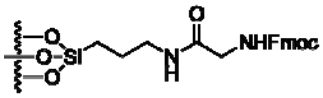


silica-supported 5-phenyl-3-(pyridin-2-yl)-1,2,4-triazine with residual azide copper(I) complex (4-60). Synthesized according to Silica-Supported Complexation Method using tetrakis(acetonitrile-N)copper(I) tetrafluoroborate

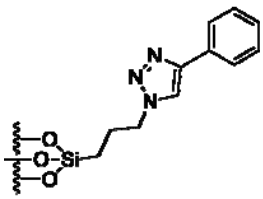
and isolated as a brown solid. Copper loading as determined by ICP-OES was 0.06 mmol/g. IR (KBr) ν_{max} 3660, 2956, 2106, 1612, 1547, 1501, 1362, 1327 cm^{-1}.



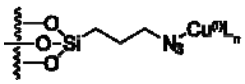
silica-supported 5-phenyl-3-(pyridin-2-yl)-1,2,4-triazine with residual azide copper(II) complex (4-61). Synthesized according to Silica-Supported Complexation Method using copper(II) tetrafluoroborate hexahydrate and isolated as a green-yellow solid. Copper loading as determined by ICP-OES was 0.17 mmol/g. IR (KBr) ν_{max} 3660, 2956, 2106, 1612, 1547, 1501, 1362, 1327 cm^{-1}.



silica-supported fmoc-glycine (4-62). Synthesized according to Heterogeneous Fmoc-Glycine Method and isolated as a light brown solid. Fmoc loading as determined by Fmoc Assay was 0.41 mmol/g. IR (KBr) ν_{max} 2950, 1717, 1674, 1535, 1450 cm^{-1}.

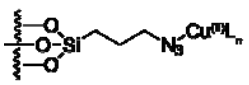


silica-supported triazole (4-63). Synthesized according to Heterogeneous CuAAC Method A and isolated as a light blue solid. IR (KBr) ν_{max} 2955, 2114, 1465, 1450 cm^{-1}.

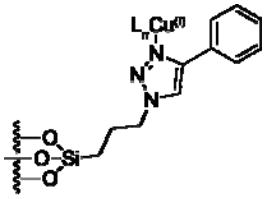


silica-supported azide copper(I) complex (4-64). Synthesized according to Silica-Supported Complexation Method using tetrakis(acetonitrile-N)copper(I) tetrafluoroborate and isolated as a

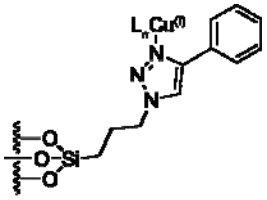
light blue solid. Copper loading as determined by ICP-OES was 0.05 mmol/g. IR (KBr) ν_{max} 2990, 2947, 2900, 2110, 1458, 1412 cm^{-1}.



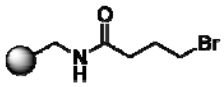
silica-supported azide copper(II) complex (4-65). Synthesized according to Silica-Supported Complexation Method using copper(II) tetrafluoroborate hexahydrate and isolated as a light blue solid. Copper loading as determined by ICP-OES was 0.06 mmol/g. IR (KBr) ν_{max} 2990, 2947, 2900, 2110, 1458, 1412 cm^{-1}.



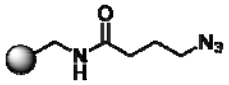
silica-supported triazole copper(I) complex (4-66). Synthesized according to Silica-Supported Complexation Method using tetrakis(acetonitrile-N)copper(I) tetrafluoroborate and isolated as a light green-blue solid. Copper loading as determined by ICP-OES was 0.02 mmol/g. IR (KBr) ν_{max} 2955, 2114, 1465, 1450 cm^{-1}.



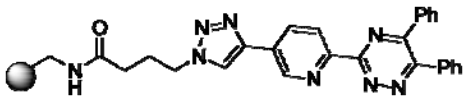
silica-supported triazole copper(II) complex (4-67). Synthesized according to Silica-Supported Complexation Method using copper(II) tetrafluoroborate hexahydrate and isolated as a light blue solid. Copper loading as determined by ICP-OES was 0.10 mmol/g. IR (KBr) ν_{max} 2955, 2114, 1465, 1450 cm^{-1}.



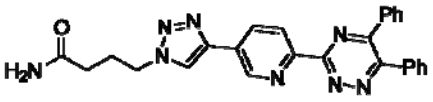
polystyrene-supported 4-bromobutanoic acid (4-69). 4-68 was rinsed with a solution of 20% piperidine in NMP (1 x 1min and 1 x 20min). 4-Bromobuytric acid (1.34 mmol), HBTU (1.29 mmol), HOBt (0.668 mmol), and DIEA (3.12 mmol) were dissolved in 3 mL of NMP and allowed to stir at room temperature for 15 min before addition to amine resin (0.445 mmol). The reaction was stirred overnight at room temperature. The support was then filtered, washed with NMP, water, DCM, MeOH, and Et_2O, and air dried. Kaiser test was approximately 25% positive, indicating some amine was present. Reaction was reset a second time and stirred overnight at room temperature. Isolated as an orange solid. Kaiser test was negative, indicating no free amine was present. IR (KBr) ν_{max} 3669, 3438, 3318 cm^{-1}.



polystyrene-supported 4-azidobutanoic acid (4-70). 4-69 (0.40 mmol), sodium azide (1.2 mmol), tetrabutylammonium iodide (0.40 mmol) were added to 2.5 mL of NMP and 0.5 mL of water. Reaction was heated at 60°C overnight. After cooling to room temperature, the resin was filtered, washed with NMP, water, DCM, MeOH, and Et_2O, and air dried. Isolated as a light brown solid. IR (KBr) ν_{max} 3437, 3325, 3028, 2931, 2862, 2102, 1682, 1612, 1508, 1450, 1300, 1211, 1119, 1038 cm^{-1}.



polystyrene-supported 5,6-diphenyl-3-(pyridin-2-yl)-1,2,4-triazine (4-71). Alkyne-substituted 1,2,4-Triazine **4-16** (0.343 mmol), triethylamine (0.312 mmol), **2-13** (3.12 µmol), and tetrakis(acetonitrile-N)copper(I) tetrafluoroborate (3.12 µmol) were dissolved in 2.0 mL of ACN and 2.0 mL of DCE and added to the supported azide (**4-70**) (0.312 mmol). Reaction was heated at 60°C overnight. The support was then filtered, washed with DCE, water, MeOH, and Et_2O and air dried. Isolated as a brown solid. IR (KBr) ν_{max} 3437, 3325, 3028, 2931, 2862, 1678, 1612, 1508, 1454, 1296, 1211, 1119, 1038 cm^{-1}.



4-(4-(6-(5,6-diphenyl-1,2,4-triazin-3-yl)pyridin-3-yl)-1H-1,2,3-triazol-1-yl)butanamide (4-72). A solution of 20% TFA in DCM (5 mL) was added to **4-71** (300mg, 0.267 mmol) and let stand at room temperature for 15 min. After filtration, the filtrate was concentrated *in vacuo* and triturated with Et_2O to yield the product amide. MS (ESI) m/z calculated 463.20 ($C_{26}H_{23}N_8O$, $[M+H]^+$), m/z observed 463.16 ($C_{26}H_{23}N_8O$, $[M+H]^+$).

Chapter 5

Catalytic Activity of Heterogeneous 1,2,4-Triazines

The text of Chapter 5 was taken in part from a manuscript coauthored with Belinda Lady and Professor Shane Foister (University of Tennessee, Knoxville).

Prince, A. L.; Lady, B. S.; Foister, S. “Heterogeneous Approaches to 1,2,4-Triazine-Accelerated CuAAC.” *J. Catal.*, **in preparation**.

5.1 Background and Significance

The copper-catalyzed azide-alkyne cycloaddition (CuAAC) is considered one of the most notable synthetic trends during the last decade, as indicated by the numerous review articles.[1,3,5,6,89,90] As a result, the number of synthetic procedures for CuAAC has also expanded and now includes various copper sources and ligand accelerants. While the tremendous success of CuAAC lies in the use of copper, the presence of transition metals is generally undesirable for most applications. Consequently, metal-free strategies have generated a lot of interest,[91-93] especially in biorelated applications. However, the required use of strained cycloalkynes has prevented this method from achieving widespread success in other disciplines employing CuAAC, such as synthetic chemistry and materials science. An alternative strategy to prevent metal contamination in reaction products is immobilization of the catalyst to an insoluble, heterogeneous support, which also facilitates easy removal and reusability of the catalyst.[24,25,33,84,85]

In continuation of our previous studies of 1,2,4-triazine-accelerated CuAAC, herein we report the catalytic activity of heterogeneous 1,2,4-triazines. 1,2,4-Triazine ligands were covalently immobilized onto polystyrene and silica supports and found to be effective accelerants of CuAAC at catalytic concentrations when complexed to either copper(I) or copper(II). Certain catalysts were active in multiple organic solvents, while others remained active without the addition of triethylamine. Recyclability and copper retention indicated

that 1,2,4-triazine-functionalized silica could be reused up to three times without loss of activity or copper leaching. Finally, a substrate scope was examined, along with microwave applications of heterogeneous 1,2,4-triazine catalysts.

5.2 Heterogeneous Catalysts Currently Used for CuAAC

Previous reports involving the development of heterogeneous CuAAC catalysts include the non-covalent immobilization of copper onto various types of solid supports, such as zeolite,[22] charcoal,[94] hydrotalcite,[95] and titanium oxide.[96] Other reports however, have focused on the covalent attachment of nitrogen-based ligands to insoluble supports (Figure 5.1), which are then used to complex copper. A pioneering study by Girald *et al.* detailed the activity of copper(I) immobilized on Amberlyst A-21 (**5-1**) resin in CuAAC reactions.[86] Unfortunately, the weak coordination of copper resulted in leaching of the catalyst and oxidation of the copper(I) source. Amine-functionalized silica **5-2** has also been reported to complex copper and accelerate CuAAC.[84] Although high yields were achieved and the catalyst could be recycled, solvents were limited to ethanol and dimethylsulfoxide. Chan and Fokin have described an efficient heterogeneous catalyst based on the tris(benzyltriazolylmethyl)amine (TBTA) ligand appended to a swellable Tenta-Gel support (**5-3**).[24] While very efficient, chemists must choose between the lengthy synthesis of immobilized TBTA or its expensive purchase price (Table 5.1).

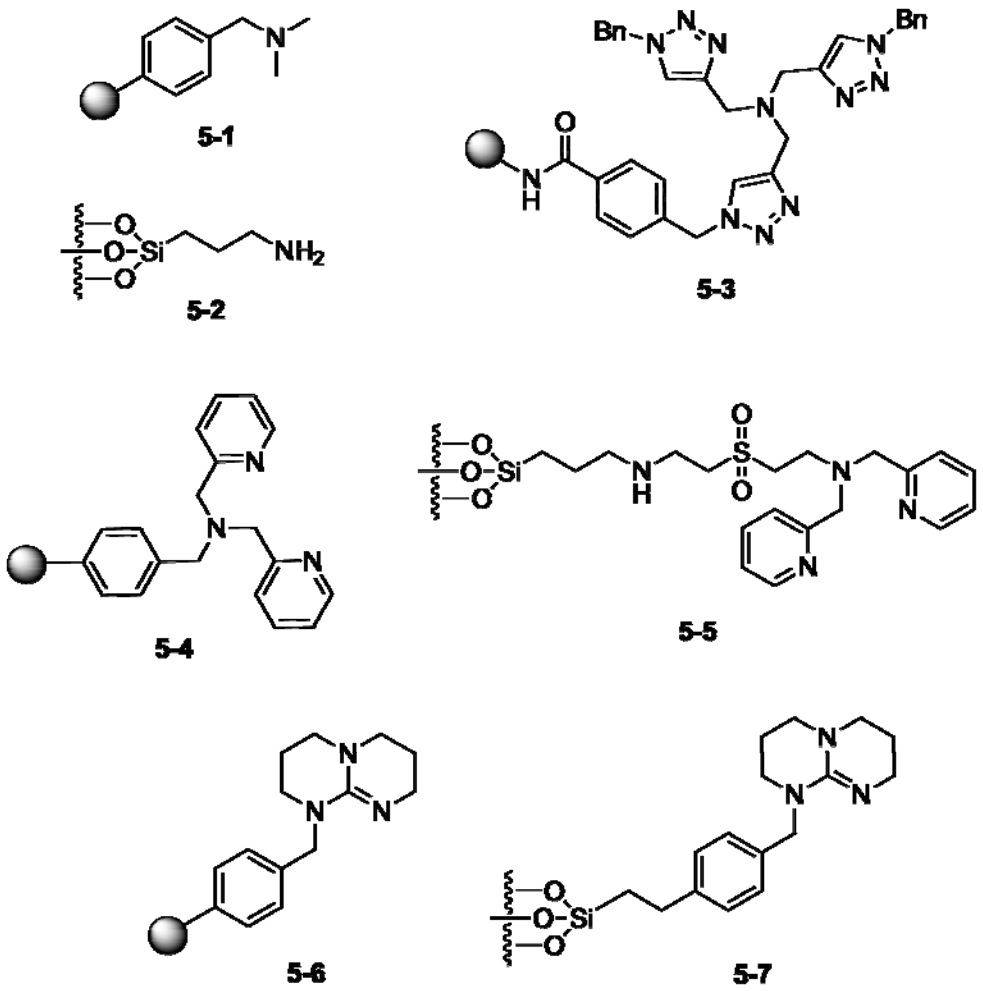


Figure 5.1 Heterogeneous Nitrogen-based Accelerants of CuAAC.

Table 5.1 Assessment of Heterogeneous Nitrogen-based Catalysts for CuAAC.

Catalyst	Purchase Price[a]	Copper Loading	Typical Reaction Conditions & Purification
Amberlyst-21 **(5-1)**	$3.04	CuI - 1.23 mmol/g (wt)	24h at RT using 8 mol% Cu filtration followed by chromatography
Si-APTS **(5-2)**	$4.32	CuI - 2.76% (AAS)	24h at 78°C using 5 mol% Cu filtration followed by chromatography
TG-TBTA **(5-3)**	$510.00	$[Cu(MeCN)_4]^+PF_6^-$ - 1.23 mmol/g (ICP)	24h at 50°C using 1 mol% Cu filtration
Dw-BPMA **(5-4)**	$0.80	CuCl - 7.08% (AAS)	neet or MW irradiation using 20 mg cat/mmol substrate filtration followed by chromatography
Si-BPMA **(5-5)**	—	CuCl - 2.44% (AAS)	neet or MW irradiation using 20 mg cat/mmol substrate filtration
PS-TBD **(5-6)**	$65.20	CuI - 0.28% (WD-XRF)	12h at 40°C using 3 mol% Cu filtration followed by recrystallization
Si-TBD **(5-7)**	$36.90	CuI - 0.30% (WD-WRF)	12h at 40°C using 3 mol% Cu filtration followed by recrystallization

[a]Price per gram of nitrogen-based ligand from Sigma Aldrich.

Additional nitrogen-based ligands, such as bispicolylamine (BPMA, **5-4**, **5-5**)[25] and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD, **5-6**, **5-7**)[85] have been attached to both polystyrene and silica and subsequently examined as CuAAC accelerants. Even though **5-4** and **5-5** must both be used under neat reaction conditions or in a microwave reactor, the authors concluded that the silica supported catalyst (**5-5**) displayed a superior performance based upon increased yields and decreased reaction times. From the advantages and disadvantages of several nitrogen-based, heterogeneous catalysts summarized above and listed in Table 5.1, it is apparent that significant advances have been made, yet the pursuit of improved, reusable CuAAC catalysts is a continually developing area of research.

5.3 Loading and Catalytic Activity of Heterogeneous 1,2,4-Triazine-Accelerated CuAAC

Our analysis of heterogeneous catalysts began with a comparison of copper loading values for covalently bonded 1,2,4-triazines, 1,2,3-triazoles, and azides. The functionalized-support was heated in a solution of either tetrakis(acetonitrile-N)copper(I) tetrafluoroborate or copper(II) tetrafluoroborate hexahydrate for two hours and the filtrate was used to quantify the copper loading by difference using ICP-OES. It was determined 1,2,4-triazine-functionalized polystyrenes (Table 5.2, entries 1-4) coordinate significantly more copper than their triazole (entry 5) and azide (entry 6) counterparts.

Table 5.2 Evaluation of Copper Loading and Catalytic Activity of Various Polystyrene-Supported Catalysts for CuAAC Reactions.

Entry	Catalyst	Cu(I) loading[a]	Cu(I) Percent Yield[b]	Catalyst	Cu(II) loading[a]	Cu(II) Percent Yield[b]
1	4-23	0.46	80	4-24	0.48	87
2	4-25	0.47	67	4-26	0.59	88
3	4-27	0.41	75	4-28	0.43	88
4	4-29	0.38	65	4-30	0.45	79
5	4-34	0.00	0	4-35	0.16	73
6	4-36	0.08	0	4-37	0.00	0

[a]General conditions: Polystyrene resin (1 equiv) and copper source (1.1 equiv) were heated at 60°C for 2 h in a 1:1 mixure of ACN:DCE at 0.01 M. The resin was filtered and washed thoroughly. The filtrate was used to calculate loading (mmol/g) by difference using ICP-OES.
[b]*General Conditions:* Percent yield determined from the reaction of benzyl azide (0.25 mmol, 1 equiv), phenylacetylene (1 equiv), triethylamine (1 equiv), and resin (5 mg) in DCE at 0.2 M. The reactions were heated at 60°C for 4 h, filtered, and concentrated *in vacuo*. Percent yield was determined based on mass of isolated 1,2,3-triazole.

Furthermore, copper(II) catalysts had a higher loading value than the corresponding copper(I) catalysts in most all cases (entries 1-5), with the azide being the only exception (entry 6). Comparing the 1,2,4-triazine-functionalized polystyrene catalysts, supports with residual amine (entries 1-2) had a slightly higher loading than those containing residual azide (entries 3-4).

Various functionalized supports were then screened for activity in a model click reaction between benzyl azide and phenylacetylene. Reactions were performed by sequential addition of azide, alkyne, and triethylamine to the corresponding polystyrene (~1mol% copper) at 0.2M in acetonitrile with respect to substrates. After four hours at 60°C, percent yields were determined based on the recovered mass of the isolated 1,2,3-triazole, following filtration and concentration *in vacuo*. In accord with the copper loading, 1,2,4-triazines complexed with copper(II) generated a higher percent yield than their copper(I)

counterparts (Table 5.2, entries 1-4), with the 1,2,4-triazine appended at the 3-postion (entries 1, 3) being slightly more active than the 1,2,4-triazine appended at the 5-position (entries 2, 4). Surprisingly, 1,2,3-triazole-functionalized polystyrene complexed with copper(II) (**4-35**), initially synthesized as a control, had comparable activity to the 1,2,4-triazine-functionalized supports.

Since 1,2,3-triazoles are a common scaffold found within click catalysts,[24,38] we speculated that this result may be due to the high density of 1,2,3-triazoles on the support. In order to verify this hypothesis, 1,2,4-triazines and 1,2,3-triazoles were both appended on a lower-loading polystyrene resin. As seen in Table 5.3, the 1,2,4-triazine (entry 1) is able to maintain its catalytic activity on lower-loading polystyrene, however the 1,2,3-triazole (entry 2) is no longer active, thereby confirming our conclusion. Furthermore, this observed acceleration of CuAAC can now fully be attributed to the 1,2,4-triazine portion of the catalyst.

Table 5.3 Evaluation of Copper Loading and Catalytic Activity of Low-Loading Polystyrene-Supported Catalysts for CuAAC Reactions.

Entry	Catalyst	Cu(II) loading[a]	Isolated Percent Yield[b]
1	4-42	0.12	83
2	4-46	0.01	3

[a]General conditions: Polystyrene resin (1 equiv) and copper source (1.1 equiv) were heated at 60°C for 2 h in a 1:1 mixture of ACN:DCE at 0.01 M. The resin was filtered and washed thoroughly. The filtrate was used to calculate loading (mmol/g) by difference using ICP-OES.
[b]General Conditions: Percent yield determined from the reaction of benzyl azide (0.25 mmol, 1 equiv), phenylacetylene (1 equiv), triethylamine (1 equiv), and resin (5 mg) in DCE at 0.2 M. The reactions were heated at 60°C for 4 h, filtered, and concentrated *in vacuo*. Percent yield was determined based on mass of isolated 1,2,3-triazole.

In addition to polystyrene, we were also interested in utilizing a silica support since the two have very distinctive properties. A polystyrene support will swell in several organic solvents and typically has a higher loading, whereas silica is more appropriate for aqueous conditions, does not swell, and usually has a lower loading than that of polystyrene.[25] Equivalent experiments to determine copper loading and catalytic activity of silica-supported catalysts were completed and compared with polystyrene catalysts. While the overall copper loading of silica catalysts was lower than polystyrene, similar trends were observed. Once again, copper(II) catalysts achieved a higher loading value than the corresponding copper(I) catalysts (Table 5.4), and 1,2,4-triazine-functionalized silica with residual amines (entries 1-2) resulted in the highest copper loading. While all 1,2,4-triazine-functionalized silica catalysts (Table 5.4, entries 1-4)

Table 5.4 Evaluation of Copper Loading and Catalytic Activity of Various Silica-Supported Catalysts for CuAAC Reactions.

Entry	Catalyst	Cu(I) loading[a]	Cu(I) Percent Yield[b]	Catalyst	Cu(II) loading[a]	Cu(II) Percent Yield[b]
1	4-54	0.22	87	4-55	0.29	88
2	4-56	0.15	90	4-57	0.23	90
3	4-58	0.07	85	4-59	0.13	89
4	4-60	0.06	86	4-61	0.17	87
5	4-64	0.05	79	4-65	0.06	79
6	4-66	0.02	64	4-67	0.10	71

[a]General conditions: Silica (1 equiv) and copper (1.1 equiv) were heated at 60°C for 2 h in ACN at 0.01 M. The silica was filtered and washed thoroughly. The filtrate was used to calculate loading (mmol/g) by difference using ICP-OES.
[b]General Conditions: Percent yield determined from the reaction of benzyl azide (0.25 mmol, 1 equiv), phenylacetylene (1 equiv), triethylamine (1 equiv), and silica (10 mg) in ACN at 0.2 M. The reactions were heated at 60°C for 4 h, filtered, and concentrated *in vacuo*. Percent yield was determined based on mass of isolated 1,2,3-triazole.

achieved percent yields greater than 85% and were more active than silica functionalized with azides (entry 5) and 1,2,3-triazoles (entry 6), the azide- and 1,2,3-triazole-functionalized silica catalysts were active after one reaction cycle.

Given that most heterogeneous CuAAC catalysts are operable without the addition of organic base,[24,33,85] we next investigated the role of triethylamine in our heterogeneous 1,2,4-triazine reaction conditions. Initially, 1,2,4-triazines appended to both polystyrene and silica, coordinated with both copper(I) and copper(II), were screened for activity in our model reaction without the addition of triethylamine (Table 5.5, entries 1-4). Of the four catalysts studied, only a combination of silica and copper(I) produced satisfactory yields (entry 3). In light

Table 5.5 CuAAC Reactions with1,2,4-Triazine-Functionalized Polystyrene and Silica Catalysts without the Addition of Organic Base.

Entry	Catalyst	Isolated Percent Yield[a]
1	4-23	3[b]
2	4-24	2[b]
3	4-54	84
4	4-55	4
5	4-56	84
6	4-58	18
7	4-60	31
8	4-64	7
9	4-66	11

[a]General conditions: Percent yield determined from the reaction of benzyl azide (0.25 mmol, 1 equiv), phenylacetylene (1 equiv), and silica (10 mg) in ACN at 0.2 M. The reactions were heated at 60°C for 4 h, filtered, and concentrated *in vacuo*. Percent yield was determined based on mass of isolated 1,2,3-triazole.
[b]General conditions with the following exceptions: resin (5 mg) and DCE at 0.2 M.

of these results, all silica catalysts coordinated with copper(I) were screened without the presence of triethylamine (entries 5-9), but it was concluded that only the 1,2,4-triazine-functionalized silica catalysts with residual amine coordinated with copper(I) (entries 3, 5) were capable of accelerating CuAAC without the addition of triethylamine.

5.4 Recyclability and Copper Retention of Heterogeneous 1,2,4-Triazine-Accelerated CuAAC

With an increased understanding of the activity of heterogeneous 1,2,4-triazines, we next proceeded in determining the recyclability, and hence copper retention of various catalysts. After each click reaction cycle, the heterogeneous catalyst was rinsed and reused without additional treatment. In addition, the only 1,2,4-triazine support used in further studies was the 1,2,4-triazine appended at the 3-postion. Not only does this heterogeneous 1,2,4-triazine produce higher

Table 5.6 Recyclability of Polystyrene-Supported Catalysts for CuAAC Reactions.[a]

Entry	Catalyst	Cycle 1 % yield	Cycle 2 % yield	Cycle 3 % yield	Cycle 4 % yield
1	4-23	81	72	54	29
2	4-24	76	83	77	50
3	4-35	60	4	2	N.D.

[a]General conditions: Percent yield determined from the reaction of benzyl azide (1.0 mmol, 1 equiv), phenylacetylene (1 equiv), triethylamine (1 equiv), and resin (20 mg) in DCE at 0.2 M. The reactions were heated at 60°C for 4 h, filtered, and concentrated *in vacuo*. Percent yield was determined based on mass of isolated 1,2,3-triazole. Resin was collected, dried, and re-used without additional treatment.

yields, but the alkyne-substituted 1,2,4-triazine building block can be prepared in an overall higher yield. Results indicate that after four reaction cycles using 1,2,4-triazine-functionalized polystyrene coordinated with copper(I) (Table 5.6, entry 1) the percent yield of 1,2,3-triazole has decreased by 52%, whereas the corresponding copper(II) polystyrene (entry 2) has only lost 26% of its initial activity. 1,2,3-Triazole-functionalized polystyrene coordinated with copper(II) (**4-35**) was previously shown to be active after one cycle; however, attempts to recycle this resin were unsuccessful (entry 3), thus conveying the superior performance of 1,2,4-triazine catalysts.

In accord with recyclability, copper retention is another key property to the viability of heterogeneous catalysts. The crude 1,2,3-triazole products were dissolved in a nitric acid solution and copper retention was calculated by difference using ICP-OES. Evaluation of Tables 5.6 and 5.7 indicate that as the 1,2,4-triazine-functionalized polystyrene catalyst leaches copper, the ability of the

Table 5.7 Copper Retention of Polystyrene-Supported Catalysts after Consecutive CuAAC Reactions.[a]

Entry	Catalyst	Cycle 1 % copper	Cycle 2 % copper	Cycle 3 % copper	Cycle 4 % copper
1	4-23	84	71	53	28
2	4-24	95	82	64	45
3	4-35	48	34	24	N.D.

[a]General conditions: Benzyl azide (1.0 mmol, 1 equiv), phenylacetylene (1 equiv), triethylamine (1 equiv), and resin (20 mg) were heated at 60°C for 4 h in DCE at 0.2 M. The reactions were filtered, and concentrated *in vacuo*. The isolated 1,2,3-triazoles were dissolved in 2% nitric acid (4 mL), heated to 60°C for 10 min, and left undisturbed overnight. The suspension was then filtered and the filtrate used to calculate the percent of copper retained by the resin using ICP-OES.

catalyst to accelerate CuAAC also decreases accordingly. Even though catalytic activity and copper retention decrease to approximately 50% after four reaction cycles, the most recyclable polystyrene catalysts studied were 1,2,4-triazines complexed with copper(II) (Table 5.7, entry 2).

Analogous recyclability and copper retention studies were also carried out for silica-supported catalysts. We are pleased to report that the 1,2,4-triazine-functionalized silica coordinated with copper(II) (Table 5.8, entry 2) maintained its original activity after four reaction cycles. In addition, the percent yield using 1,2,4-triazine-functionalized silica coordinated with copper(I) (entry 1) only slightly decreased after four reaction cycles even without the addition of triethylamine.

Copper retention studies of silica-supported catalysts revealed that the 1,2,4-triazine-functionalized silica coordinated with copper(II) (Table 5.9, entry 2) is the superior choice of heterogeneous 1,2,4-triazine catalyst. While copper(I)

Table 5.8 Recyclability of Silica-Supported Catalysts for CuAAC Reactions.[a]

Entry	Catalyst	Cycle 1 % yield	Cycle 2 % yield	Cycle 3 % yield	Cycle 4 % yield
1	4-54	86*	86*	74*	72*
2	4-55	88	91	88	90
3	4-67	76	69	52	59

[a]General conditions: Percent yield determined from the reaction of benzyl azide (0.5 mmol, 1 equiv), phenylacetylene (1 equiv), triethylamine (1 equiv), and silica (20 mg) in ACN at 0.2 M. The reactions were heated at 60°C for 4 h, filtered, and concentrated *in vacuo*. Percent yield was determined based on mass of isolated 1,2,3-triazole. Silica was collected, dried, and re-used without additional treatment.
*Reactions without triethylamine.

Table 5.9 Copper Retention of Silica-Supported Catalysts after Consecutive CuAAC Reactions.[a]

Entry	Catalyst	Cycle 1 % copper	Cycle 2 % copper	Cycle 3 % copper	Cycle 4 % copper
1	4-54	98*	94*	84*	77*
2	4-55	98	95	93	91
3	4-67	88	77	51	13

[a]General condtions: Benzyl azide (0.5 mmol, 1 equiv), phenylacetylene (1 equiv), triethylamine (1 equiv), and silica (20 mg) were heated at 60°C for 4 h in ACN at 0.2 M. The reactions were filtered, and concentrated *in vacuo*. The isolated 1,2,3-triazoles were dissolved in 2% nitric acid (4 mL), heated to 60°C for 10 min, and left undisturbed overnight. The suspension was then filtered and the filtrate used to calculate the percent of copper retained by the silica using ICP-OES.
*Reactions without triethylamine.

coordinated 1,2,4-triazine (entry 1) displayed modest copper retention, 1,2,3-triazole-functionaled silica complexed with copper(II) leached a significant amount of copper after four reaction cycles (entry 3).

5.5 Solvent and Substrate Scope of Heterogeneous 1,2,4-Triazine-Accelerated CuAAC

A solvent scope was investigated in order to increase the potential applications of heterogeneous 1,2,4-triazine-accelerated CuAAC and determine the limitations of each catalyst. Isolated percent yields indicate that 1,2,4-triazine-functionalized polystyrene **4-24** works best in acetonitrile and moderately well in dichloroethane (Table 5.10). However, reactions in tert-butanol and toluene failed to yield any significant amount of 1,2,3-triazole. In contrast, the 1,2,4-triazine-functionalized silica catalyst **4-55** functioned quite efficiently in all solvents analyzed.

Table 5.10 Solvent Scope of 1,2,4-Triazine-Functionalized Polystyrene and Silica Catalysts for CuAAC Reactions.

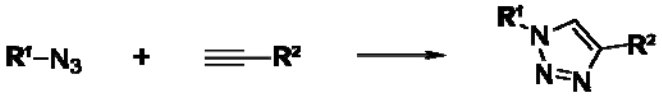
Entry	Solvent	Isolated Percent Yield[a]	Isolated Percent Yield[b]
1	acetonitrile	89	88
2	dichloroethane	69	86
3	tert-butanol	5	79
4	toluene	3	83

[a]General conditions: Percent yield determined from the reaction of benzyl azide (0.25 mmol, 1 equiv), phenylacetylene (1 equiv), triethylamine (1 equiv), and polystyrene catalyst 4-24 (5 mg) at 0.2 M. The reactions were heated at 60°C for 4 h, filtered, and concentrated *in vacuo*. Percent yield was determined based on mass of isolated 1,2,3-triazole.
[b]General conditions with the following exception: silica catalyst 4-55 (10 mg)

The acceleration of heterogeneous 1,2,4-triazine-accelerated CuAAC by silica-supported catalysts was next evaluated with various azide and alkyne substrates and compared to percent yields obtained using homogeneous 1,2,4-triazine-accelerated CuAAC. In addition to benzyl azide, aromatic and aliphatic were found to be compatible with heterogeneous 1,2,4-triazines (Table 5.11, entries 1-3). Alkyl alkynes were also successfully converted to 1,2,3-triazoles (entry 4). Furthermore, aromatic alkynes containing ether functional groups (entry 5), did not generate a bis-triazole product as previously seen using homogeneous 1,2,4-triazine-accelerated CuAAC.

With the high success of previous substrates, we then attempted a more challenging substrate scope. Various alkyne substrates containing functional groups common to medicinal chemistry were found compatible with heterogeneous 1,2,4-triazine-accerlated CuAAC,[90] including nitriles, amines, and

Table 5.11 Substrate Scope of 1,2,4-Triazine-Functionalized Silica Catalysts in Comparison with Homogeneous 1,2,4-Triazine-Accelerated CuAAC.[a]



3-1 3-2 3-3

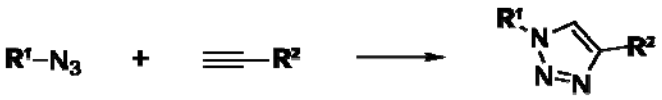
Entry	R^1	R^2	Product	Isolated Percent Yield
1	Bn (3-1a)	Ph (3-2a)	3-3a	88 (87)
2	2,6-diMePh (3-1f)	Ph (3-2a)	3-3f	77 (83)
3	$CH_3(CH_2)_6$ (3-1g)	Ph (3-2a)	3-3g	75 (88)
4	Bn (3-1a)	CH_2OH (3-2b)	3-3j	89 (76)
5	Bn (3-1a)	4-OMePh (3-2f)	3-3n	84 (87)

[a]General conditions: Percent yield determined from the reaction of azide 3-1 (0.25 mmol, 1 equiv), alkyne 3-2 (1 equiv), triethylamine (1 equiv) and catalyst 4-55 (10 mg) in ACN at 0.2 M. The reactions were heated at 60°C for 4 h, filtered, and concentrated *in vacuo*. Percent yield was determined based on mass of isolated 1,2,3-triazole.
( ) Indicate the isolated percent yield when using the homogeneous 1,2,4-triazine ligand 2-13 (Table 3.5).

pyridines (Table 5.12, entries 1-3). Dialkyne substrates were also produced in high yield (entry 4); however, the diazide substrate resulted in a lower yield due to the poor solubility of the mono-triazole intermediate (entry 5). Thus far, the only substrates found to be incompatible with heterogeneous 1,2,4-triazine-accelerated CuAAC are those containing metal-binding functionalities, such as 1,2,4-triazoles.

Microwave reactors are becoming more popular in synthetic chemistry labs due to the acceleration of numerous reactions through the use of microwave irradiation.[97] Since heterogeneous 1,2,4-triazine-accelerated CuAAC reactions do not proceed in a timely fashion at room temperature but produce high yields at 60°C within four hours, we decided to investigate the use of these catalysts

Table 5.12 Challenging Substrate Scope of 1,2,4-Triazine-Functionalized Silica Catalysts for CuAAC Reactions.[a]



5-8 5-9 5-10

Entry	R^1	R^2	Product	Isolated Percent Yield
1	Bn (3-1a)	4-CN-Ph (5-2a)	5-3a	76
2	Bn (3-1a)	4-NH_2-Ph (5-2b)	5-3b	70
3	Bn (3-1a)	2-Pyr (5-2c)	5-3c	85
4	Bn (3-1a)	1,7-octadiyne (5-2d)	5-3d	78[b]
5	1,4-diazidobutane (5-1a)	Ph (3-2a)	5-3e	47[c]

[a]General conditions: Percent yield determined from the reaction of azide 5-1 (0.25 mmol, 1 equiv), alkyne 5-2 (1 equiv), triethylamine (1 equiv) and catalyst 4-55 (10 mg) in ACN at 0.2 M. The reactions were heated at 80°C for 4 h, filtered, and concentrated *in vacuo*. Percent yield was determined based on mass of isolated 1,2,3-triazole.
[b]General conditions with the following exception: benzyl azide (2 equiv).
[c]General conditions with the following exception: phenylacetylene (2 equiv).

in the microwave in hopes of decreasing the reaction time even further. Results show that both polystyrene- and silica-supported 1,2,4-triazines equally accelerated CuAAC reactions in the microwave within fifteen minutes (Table 5.13, entries 1-2). In addition, trimethylsilyl-protected phenylacetylene was successfully deprotected *in situ* and reacted with benzyl azide in high yield (entry 3). Therefore, our focus next shifted to 1,2,4-triazine-accelerated Sonogashira Reactions, with the goal of developing a one-pot procedure consisting of both reactions using a heterogeneous catalyst.

Table 5.13 Microwave CuAAC Reactions using 1,2,4-Triazine-Functionalized Polystyrene and Silica Catalysts.

Entry	Catalyst	Isolated Percent Yield
1	4-24	86[a]
2	4-55	88[b]
3	4-55	87[c]

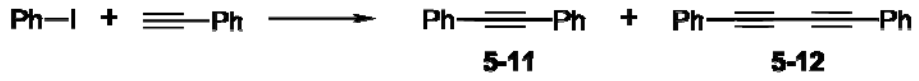
[a]General conditions: Percent yield determined from the reaction of benzyl azide (0.25 mmol, 1 equiv), phenylacetylene (1 equiv), and resin (5 mg) in ACN at 0.2 M. The reactions were microwaved at 120°C for 15 min, filtered, and concentrated *in vacuo*. Percent yield was determined based on mass of isolated 1,2,3-triazole.
[b]General conditions with the following exception: silica (10 mg).
[c]General conditions with the following exceptions: silica (10 mg), TMS-protected phenylacetylene (1 equiv), and potassium carbonate (0.1 eq) in 4:1 ACN:MeOH at 0.2 M.

5.6 Heterogeneous 1,2,4-Triazine-Accelerated Sonogashira Reactions

While palladium has successfully been attached to both polysytrene[98,99] and silica[100] supports, phosphine ligands are generally the ligand of choice. Given that leaching of palladium from these phosphate-functionalized supports is a common problem, Cai *et al.* chose to alter the type of support.[101] Alternatively, we choose to investigate 1,2,4-triazine-accelerated Sonogashira Reactions using our silica-supported catalysts. Since Sonogashira Reactions typically employ both copper and palladium,[78] our analysis of silica-supported, 1,2,4-triazine-accelerated Sonogashira Reactions began by optimizing the coordination ratio of these two metals. 1,2,4-Triazine-functionalized silica **4-52** was coordinated to varying ratios of copper(II) tetrafluoroborate hexahydrate and palladium acetate,

while loading was calculated by ICP-OES. Sonogashira Reactions were heated at 60°C overnight using a model system of iodobenzene and phenylacetylene and percent yields were monitored by HPLC. The highest percent yield of diphenylacetylene (**5-11**) was achieved with silica catalyst **5-15**, containing approximately equal loading of copper and palladium (Table 5.13, entry 4). In addition, the yield of glaser byproduct (**5-12**) decreased as the copper loading decreased. However, Sonogashira reactions also proceeded without the addition of copper (entry 7), most likely due to a minor copper contamination of palladium acetate.

Table 5.14 Sonogashira Reactions using 1,2,4-Triazine-Functionalized Silica Catalysts.



Entry	Catalyst	mol % of Cu : Pd	Cu(II) loading[a]	Pd(II) loading[a]	Percent Yield of 5-11[b]	Percent Yield of 5-12[b]
1	4-55	100 : 0	0.21	0.00	1	9
2	5-13	95 : 5	0.23	0.02	45	33
3	5-14	85 : 15	0.20	0.07	57	28
4	5-15	75 : 25	0.14	0.12	63	25
5	5-16	50 : 50	0.05	0.24	59	24
6	5-17	25 : 75	0.00	0.36	56	18
7	5-18	0 : 100	0.00	0.47	50	14
8	4-55 + 5-19	NA	NA	NA	55	23
9	none	NA	NA	NA	1	0

[a]General conditions: 1,2,4-Triazine-functionalized silica 4-52 (1 eq) was heated for 2 h at 60°C in the presence of copper tetrafluoroborate hexahydrate and palladium acetate (1.1 eq of total metal) in anhydrous ACN at 0.01 M. The silica was filtered and washed thoroughly. The filtrate was used to calculate loading (mmol/g) by difference using ICP-OES.
[b]General Conditions: Percent yields determined from the reaction of iodobenzene (0.1 mmol, 1 equiv), phenylacetylene (1 equiv), and triethylamine (1 equiv), with silica catalyst (10 mg) in ACN at 0.2 M. The reactions were heated overnight at 60°C and percent yields were quantified by HPLC.

Further optimization of 1,2,4-triazine-accelerated Sonogashira Reaction with silica-supported catalysts included increasing the equivalents of triethylamine, using copper(I) as opposed to copper(II), and the addition of soluble 1,2,4-triazine **2-13** to the complexation reaction. In spite of these attempts, the yield of **5-11** remained at 63%, thus not improving (Table 5.14). The solvent was the remaining aspect of the reaction left to optimize. Various solvents commonly used for Sonogashira Reactions were screened; unfortunately, results show lower yields of **5-11** as well as higher yields of **5-12** in comparison to acetonitrile. With optimization studies complete, multiple attempts at the rare one-pot Sonogashira-CuAAC reaction[81] employing 1,2,4-triazine-functionalized silica catalysts were undertaken without success. Remaining optimistic, additional studies of this 1,2,4-triazine-accelerated one-pot reaction are currently underway.

Table 5.15 Solvent Scope of Sonogashira Reactions using 1,2,4-Triazine-Functionalized Silica Catalysts.

Entry	Solvent	Percent Yield of 5-11[a]	Percent Yield of 5-12[a]
1	acetonitrile	56	23
2	methanol	54	18
3	dimethylformamide	42	31
4	toluene	15	47

[a]General Conditions: Percent yields determined from the reaction of iodobenzene (0.1 mmol, 1 equiv), phenylacetylene (1 equiv), and triethylamine (1 equiv), with silica catalysts 4-24 (5 mg) and 5-18 (5 mg) in anhydrous solvent at 0.2 M. The reactions were heated overnight at 60°C and percent yields were quantified by HPLC.

5.7 Conclusions

In summary, 1,2,4-triazine-functionalized silica was found to be a potent accelerant of CuAAC, while polystyrene-supported 1,2,4-triazines displayed modest activity. After synthesizing the alkyne-substituted 1,2,4-triazine building block **4-16** in an overall yield of 45%, standard silica gel was transformed into the aforementioned silica catalysts in four steps. These catalysts produce high yields of isolated 1,2,3-triazoles in short reaction times requiring only minimal work-up. Copper(II) coordinated catalysts are superior to their copper(I) counterparts in areas of copper loading, catalytic activity, and recyclability. 1,2,4-Triazine-functionalized silica coordinated with copper(II) (**4-55**) generated percent yields greater than 90% after four consecutive reaction cycles with minimal copper leaching, while the corresponding copper(I) catalyst (**4-54**) was operable without the addition of triethylamine.

The value of heterogeneous 1,2,4-triazine catalysts is enhanced by their capacity to operate effectively in various solvents at copper concentrations as low as 1 mol%. In addition, the activity of silica-supported catalysts were comparable to previously reported homogeneous 1,2,4-triazine, **2-13**. Results also illustrated that 1,2,4-triazine-functionalized silica could be applied to medicinal targets containing additional functional groups such as amines and pyridines. 1,2,4-Triazine-accelerated Sonogashira Reactions were optimized and more detailed experiments of a one-pot Sonogashira-CuAAC reaction are currently in progress.

5.8 Experimental

Materials and General Methods. Reagents and solvents were purchased from various commercial sources and used without further purification unless otherwise stated. Anhydrous solvents were purified using a Grubbs solvent system. Analytical thin-layer chromatography (TLC) was performed using aluminum backed silica gel TLC plates with UV indicator from Sorbent Technologies. Flash column chromatography was Copper was quantified by inductively coupled plasma – optical emission spectroscopy (ICP-OES) using a Perkin Elmer Optima 2100 DV. High pressure liquid chromatography (HPLC) was performed using a Beckman Coulter System equipped with a UV-Vis detector, autosampler, Varian C18 column, and a mobile phase composed of acetonitrile and trifluoroacetic acid.

General Heterogeneous 1,2,4-Triazine-Accelerated CuAAC Reaction. Benzyl azide (0.25 mmol), phenylacetylene (0.25 mmol), and triethylamine (0.25 mmol) were added to the heterogeneous catalyst (1 mol% copper) at 0.2 M, with respect to substrates, in acetonitrile. Reactions were heated at 60°C for 4 h, cooled to room temperature, and filtered to remove catalyst. The filtrate was concentrated *in vacuo* to yield 1,2,3-triazole as a white solid.

Recyclability of Heterogeneous Catalysts. After CuAAC reaction was complete and filtered, the catalyst was rinsed with dichloromethane, methanol, and ether. Catalyst was air dried and reused without additional treatment.

Copper Retention of Heterogeneous Catalysts. A solution of 2% HNO_3 (4 mL) and MeOH (0.04 mL) were added to isolated 1,2,3-triazole products. After heating at 60°C for approximately 10 min, the suspension was left standing at room temperature overnight. After filtration, the filtrate was analyzed by ICP-OES in order to calculate the percent of copper retained by the catalyst. Copper was quantified using an external calibration curve ranging from 75 ppm – 1 ppm at a wavelength of 324.75 nm.

Sonogashira Complexation Method. A 10 mM stock solution of copper(II) tetrafluoroborate hexahydrate in ACN was prepared, along with a 3.34 mM stock solution of palladium acetate. A combination of copper and palladium (0.0253 mmol of total metal) were added to 1,2,4-triazine-functionalized silica **4-52** (0.0230 mmol) and heated at 60°C for 2 h. An equivalent amount of copper and palladium were combined, concentrated, and analyzed by ICP-OES as a control. After cooling to room temperature, the silica was filtered, washed with ACN, DCM, MeOH, and Et_2O and air dried. The filtrate was concentrated *in vacuo*, analyzed by ICP-OES, and compared to the ICP-OES value of the aforementioned control solution.

General Heterogeneous 1,2,4-Triazine-Accelerated Sonogashira Reaction. Iodobenzene (0.10 mmol), phenylacetylene (0.10 mmol), and triethylamine (0.10 mmol) were added to the heterogeneous catalyst (10 mg) at 0.2 M, with respect to substrates, in acetonitrile. Reactions were heated overnight at 60°C, cooled to room temperature, and analyzed by HPLC using a c18 column with an isocratic mobile phase of 80% acetonitrile. Percent yields were determined using an external calibration curve.

Chapter 6

Approaches toward the Derivatization of Solid Surfaces for Energy-Related Chemical Processes

6.1 *Progression of 1,2,4-Triazine Catalysis*

An ongoing focus of research in our group is the catalytic activity of 1,2,4-triazoles in combination with non-precious metals (NPMs). This research has led to the development of several scaffolds with selective activities in complementary chemical processes such as the conversion of biomass, the reduction of oxygen, and the oxidation of hydrocarbons. The structural similarity between 1,2,4-triazoles and 1,2,4-triazines and their synthetic accessibility from common precursors[55-57] made 1,2,4-triazines logical candidates for catalyst discovery in

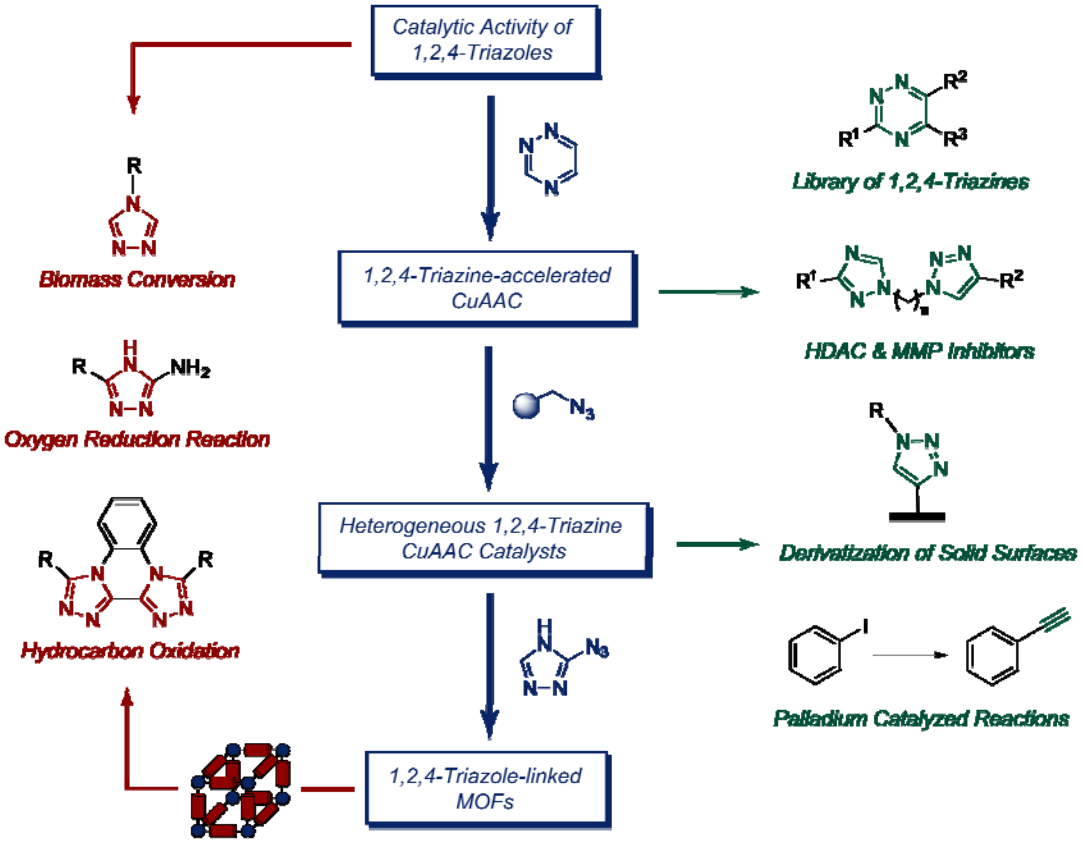


Figure 6.1 Progression and Applications of 1,2,4-Triazine Catalysis

our group. In spite of their structural similarity, complexes of 1,2,4-triazines did not display any activity for the aforementioned chemical processes; however, unlike 1,2,4-triazoles, they were found to display activities as potent accelerants of CuAAC reactions (Figure 6.1).

After the activity of 1,2,4-triazines was optimized for CuAAC reactions, it was demonstrated that these reaction conditions were amenable to a broad substrate scope, including heterogeneous azides. By taking full advantage of this discovery, we successfully utilized homogeneous 1,2,4-triazines to synthesize multiple heterogeneous 1,2,4-triazine catalysts on both polystyrene and silica supports. The catalytic activity of heterogeneous 1,2,4-triazines were subsequently investigated, which led to various applications of these catalysts, including synthesizing potential inhibitors of histone deacetylase (HDAC) and matrix metalloproteinase (MMP) enzymes, as well as exploration into palladium catalyzed reactions. Results illustrated that silica-supported catalysts demonstrated superior activity and recyclability; however, it was their *inability* to click triazole substrates that ultimately launched an innovative, new project.

6.2 Introduction to Metal-Organic Frameworks (MOFs)

Both 1,2,3- and 1,2,4-triazoles are notorious for their ability to form metal-organic framworks (MOFs) when coordinated with NPM, including copper.[102-104] Additional examples of ligands include nitriles, carboxylates, and nitrogen-containing heterocycles such as pyridine, imidazole, and 1,3,5-triazine (Figure

6.2). In theory, the synthesis of a MOF only requires a potentially bridging ligand and metal ion containing more than one vacant site. In reality, these macromolecular structures are very sensitive to the reaction conditions employed during their synthesis;[105] nonetheless, they have become attractive targets for applications such as gas storage,[106] drug-delivery systems,[107] and catalysis.[108] More specifically, MOFs containing copper have been used as catalysts for the oxidation of olefins,[109] ring-opening of epoxides,[110] and even azide-alkyne cycloadditions.[111]

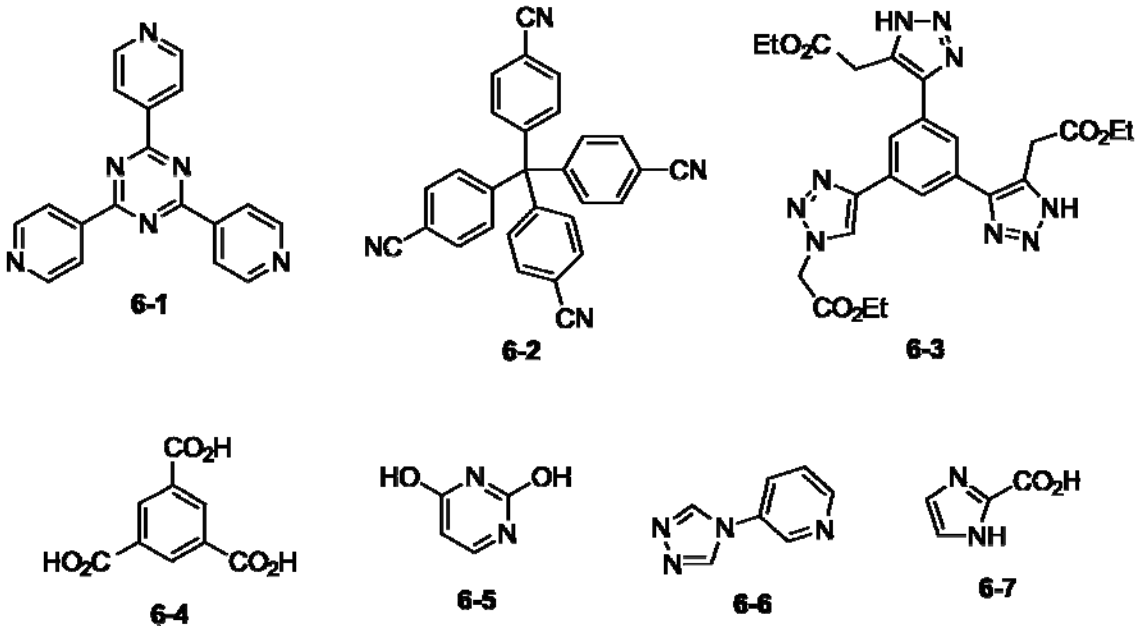


Figure 6.2 Examples of Ligands used in the Synthesis of MOFs.

6.3 Probable Evidence of MOFs

Probable evidence of MOFs were first observed with 1,2,3-triazoles during the synthesis of heterogeneous catalysts. High-loading polystyrene appended with 1,2,3-triazole (**4-35**) was able to coordinate enough copper(II) to catalyze an azide-alkyne cycloaddition, albeit, only once (Table 6.1, entry 1). Conversely, the lower-loading counterpart (**4-46**) was proven to be inactive (entry 2). Hence, 1,2,3-triazoles are capable of coordinating copper(II) and forming catalysts only when densely-packed, similar to the packing of coordination polymers or MOFs.

After numerous attempts, the reaction of **6-8** with phenylacetylene using the optimized 1,2,4-triazine-accelerated CuAAC reaction conditions proved unsuccessful using homogeneous and heterogeneous catalysts. While numerous azides and alkynes were found to be compatible with 1,2,4-triazines, this failed reaction was especially disappointing and thus sparked a more detailed investigation. Review of the literature revealed that 3-azido-1,2,4-triazoles could undergo CuAAC with standard conditions using copper(II) sulfate

Table 6.1 Comparison of 1,2,3-Triazole-Functionalized Polystyrene Catalysts for CuAAC Reactions.

Entry	Catalyst	Commercial Resin Loading[a]	Cu(II) Loading[a]	Isolated Percent Yield[b]
1	4-35	1.4	0.16	73
2	4-46	0.5	0.01	3

[a]Loading is reported in mmol/g
[b]Isolated product is 1-benzyl-4-phenyl-1,2,3-triazole

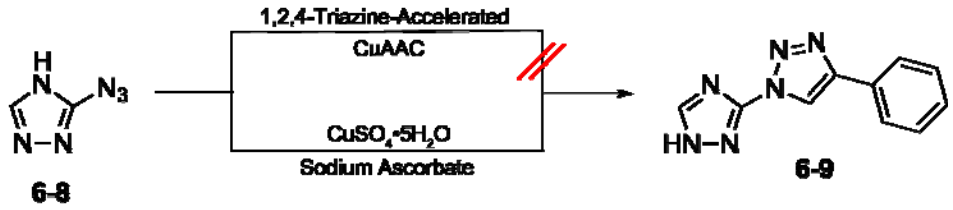


Figure 6.3 CuAAC Reaction of 3-Azido-1,2,4-Triazole.

and sodium ascorbate (Figure 6.3).[112,113] Therefore, we hypothesize that there may be an interaction taking place between the 1,2,4-triazine catalyst and the 1,2,4-triazole substrate in the presence of copper, i.e. a metal-organic framework.

6.4 Current Approaches toward the Synthesis of 1,2,4-Triazole-Containing Catalysts using CuAAC

There are examples of 1,2,4-triazole-based MOFs containing mixed ligand sets.[114] In these cases, the overall macromolecular architecture created depends upon the non-covalent interactions of the ligands and available modes of metal coordination. Consequently, we have chosen to utilize this proposed MOF to our advantage by synthesizing highly-ordered molecular scaffolds incorporating catalysts with known activity. One of those catalysts, 3,5-diamo-1,2,4-triazole, is a known catalyst for the oxygen reduction reaction (ORR) and has been examined in the context of an alkaline fuel cell.[115,116] In replacing one

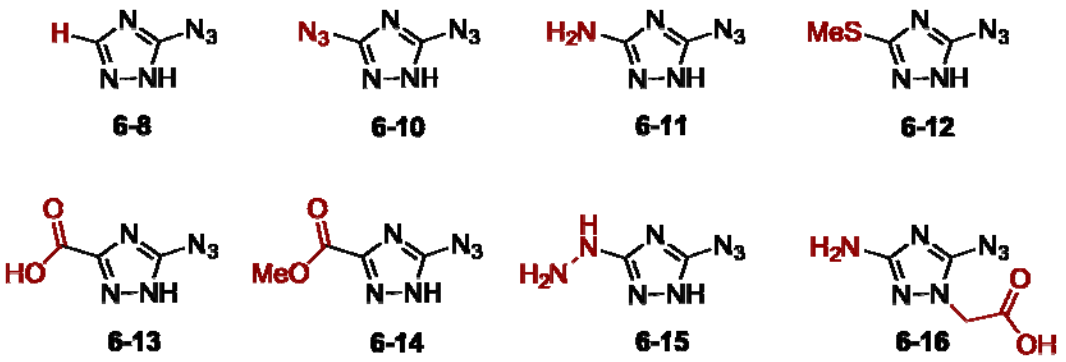


Figure 6.4 3-Azido-1,2,4-Triazole Derivatives.

of the amine groups with an azide, we can generate "clickable" substrates. Thus our synthetic strategy incorporates a diverse collection of 3-substituted-5-azido-1,2,4-triazoles as bridging ligands in the synthesis of MOFs (Figure 6.4).

The 3-substituted-5-azido-1,2,4-triazoles ligands, such as **6-11**, will first be coordinated to copper, either in solution (**6-17**) or in the presence of oxidized carbon black (**6-19**) (Figure 6.5). The addition of an alkyne should initiate a click reaction in expectation that a noncovalent assembly of bis-triazoles will be produced (**6-18**). Post-synthesis modification of MOFs using CuAAC have been reported,[117,118] as well as the synthesis of MOFs using 1,2,3-triazole linkers. However, no reports could be found of a simultaneous click reaction and MOF formation. If MOFs are produced in the presence of carbon blacks (**6-20**), the chemical features of the carbon surfaces may function as co-ligands either by participation in metal coordination or by pre-organizing a network of ligands for metal binding.[119] Furthermore, while studies of composite mixtures have shown

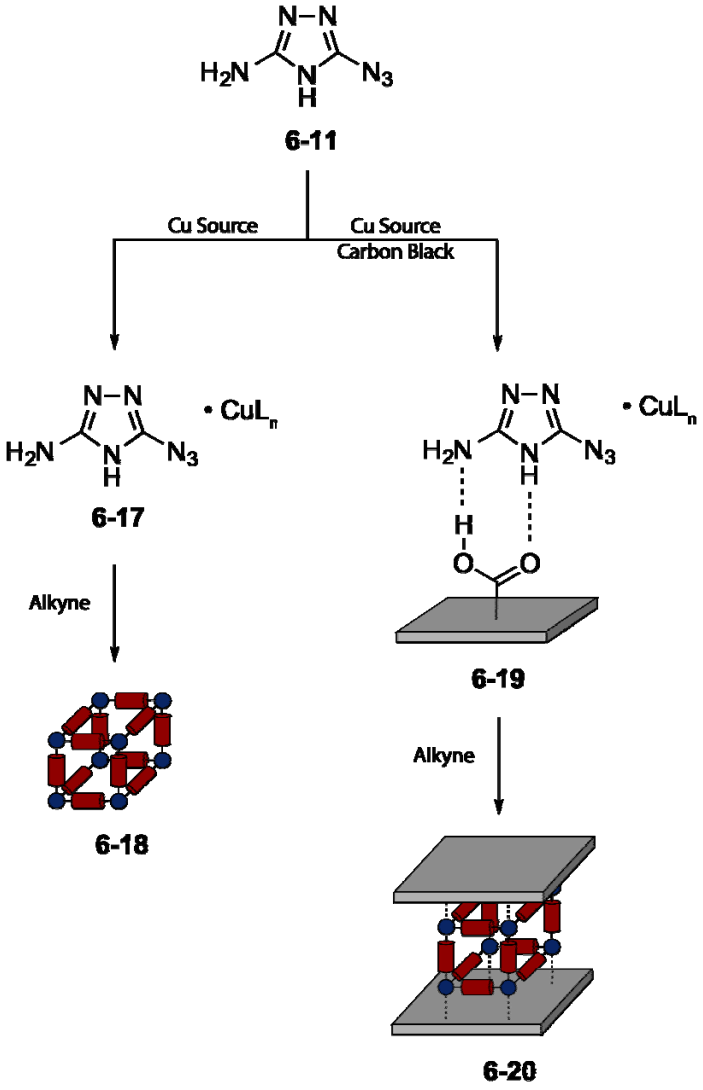


Figure 6.5 Proposed Synthetic Routes toward 1,2,3-1,2,4-Triazole-Containing MOFs.

that the carbon component enhances the dispersive forces; features of the MOF component are dominant and thus responsible for expanding the porosity and increasing adsorbance. Scanning electron microscopy (SEM) has been used to analyze these composite materials and has revealed the formation of "sandwichlike sturctures" with the carbon material acting as a divider between the thin platelets of the MOF.[120,121]

In addition to adsorbing copper complexes of 1,2,4-triazoles onto carbon, we have sought to covalently attach them as well. This primary advantage of this method is elimination of ambiguity in determining the chemical structure of the catalytically active surfaces. Oxidation of the carbon is a proven method for generating oxygen-containing functional groups, including carboxylic acids (**6-22**) (Figure 6.6).[122,123] 4-Ethynylanailine can then be appended by formation of an amide via an acid chloride intermediate (**6-23**). A CuAAC reaction using 3,5-diazido-1,2,4-triazole (**6-10**) will result in the immobilization of the bis-triazole scaffold along with an unreacted azide (**6-24**). The conditions of additional CuAAC reactions with di-alkynes can be tailored to synthesize heterogeneous surfaces with various chemical properties depending upon the structure of the appended alkyne. In addition to alkyl alkynes, the success of silica-supported 1,2,4-triazine catalysts have also led us to append alkyne-substituted 1,2,4-triazines in anticipation of further improving heterogeneous 1,2,4-triazine catalysis.

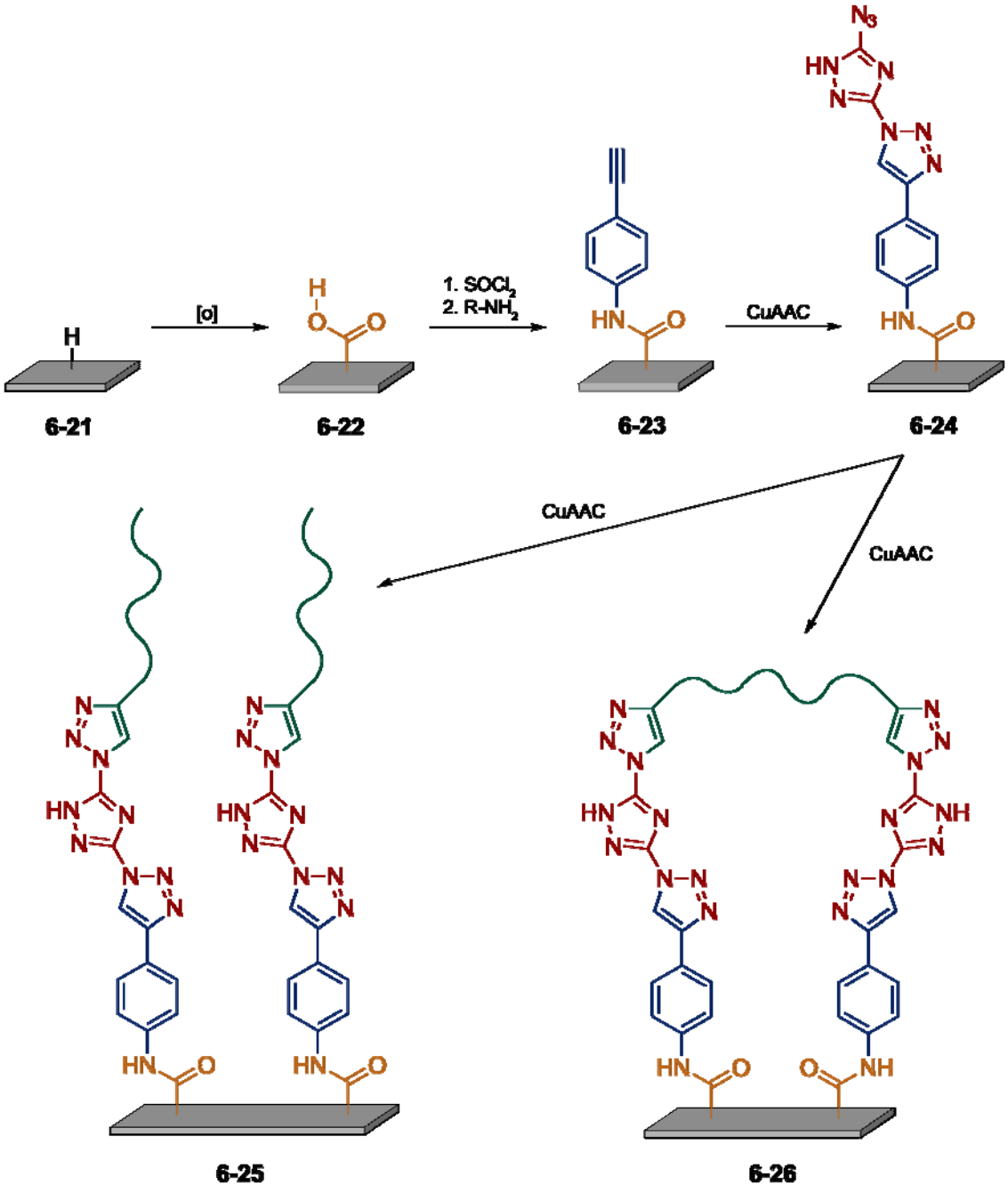


Figure 6.6 Synthesis of Covalently-Modified Carbon Blacks.

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