UC Riverside
UCR Honors Capstones 2018-2019

Title
New Methods for the Synthesis of Novel Triazoles as Ligands and Potential Drugs

Permalink
https://escholarship.org/uc/item/6gb3v4zj

Author
Richards, William

Publication Date
2019-04-01

eScholarship.org Powered by the California Digital Library
University of California

NEW METHODS FOR THE SYNTHESIS OF NOVEL TRIAZOLES AS LIGAND AND POTENTIAL DRUGS

By

William John Richards

A capstone project submitted for
Graduation with University Honors

May 9, 2019

University Honors
University of California, Riverside

APPROVED

_____
Dr. Catharine Larsen
Department of Chemistry

_____
Dr. Richard Cardullo, Howard H Hays Jr. Chair, University Honors

Abstract

More than half of the top 100 pharmaceuticals contain nitrogen heteroaromatics in their structures. Triazoles have become more prevalent in medicinal chemistry due to their wide substrate tolerability and synthetic utility as intermediates and lead compounds. However, new methods for their synthesis are necessary to access the full range of compounds desired to study the relationship between structure and therapeutic activity. Changing the substituents on either end of the pyridyl triazole will allow us to study how electronics and physical features can affect the catalytic activity as well as biological activity of the triazoles. The pyridyl triazoles can further be modified through exploring a more efficient process for the synthesis of iodinated triazoles. By synthesizing iodinated triazoles, a wide array of alternate functional groups could be added to the core triazole structure. As the chemical composition of these ligands change, this will alter their physical characteristics and pharmacological efficacy, which are related to basicity and binding ability. These triazole analogs will be tested as ligands for catalysis and as drug candidates. The catalytic activity of the pyridyl triazoles palladium complexes was found by running simple suzuki cross coupling reactions and screening how well the complexes perform in varying conditions. Conditions for the addition of various nucleophile classes to triazoles bearing an iodine atom were developed. Examples of the target nucleophiles are alcohols, thiols, and amines bearing alkyl and other functional groups. The size and composition of each substituent attached to these nucleophiles will be varied to test the extent of what can be added to the triazole through these nucleophilic additions. Initial conditions will mimic those under which we initially discovered the reaction: an excess of nucleophile will be added to the iodinated triazole in the presence of potassium carbonate as the base. Products will be purified by column chromatography and characterized by 1H and 13C NMR, MS, and other standard means.

Table of Contents

Table of Schemes

Table of Figures

Table of Tables

Introduction:

The Triazole scaffold has become a very important aspect of pharmaceutical research with many applications within medicinal chemistry.[10] Triazoles have been found to be good heterocyclic pharmacophore with anti-viral, anti-cancer, and antibiotic agents.[1-5] Pyridyl triazoles specifically have become more relevant due to their potential biological activity[8-9] and catalytic potential in performing cross-coupling reactions[6] which is one of the most popular reactions used in the pharmaceutical industry[7] due to their robustness, versatility, and availability of starting materials. Due to this biologically activity and ability to act as catalysts, the synthesis of new triazoles with different substituent coming off of them has been highly desired. The copper-catalyzed azide-alkyne cycloaddition (CuAAC) is a very good method of making the triazoels. The CuAAC method is very versatile and easy to run.[11-14] The method is also very substrate tolerant meaning that the triazoles produced through this method can be varied quite heavily allowing for the study of different conditions. This leads to the ability to see how modifying the pyridyl triazole can affect the catalytic activity as well as biological activity.

Background:

Substituted pyrydyl triazoles are useful target molecules and methodologies to synthesize them are highly desired as a result. This is because substituted pyridyl triazoles have been found to be fairly biologically active as well as good ligands for complexation which are then fairly efficient catalysts for cross coupling reactions.

Studies for the biological activity of pyridyl triazoles have found that substituted pyridyl triazoles have pretty good biological activity as anti cancer as well as anti inflammatory drugs. Its anti cancer activity comes from its ability to inhibit nicotinamide phosphoribosyltransferase (NMPRTase).[8] It was thought that by inhibiting the production of NAD could be a way of

stopping cancer cells. The idea was that affecting NAD(p) levels could result in cell death in cells that used pyridine nucleotides. The main way that cells make regulate NAD levels is through NMPRTase which turns nicotinamide to NAD after a few steps.[15] This lead to NMPRTase being studied as a target for anti cancer drugs. For the study over 100 pyridyl triazole derivatives were tested and 4 had IC_{50} values in nanomolar concentrations (Figure 1).

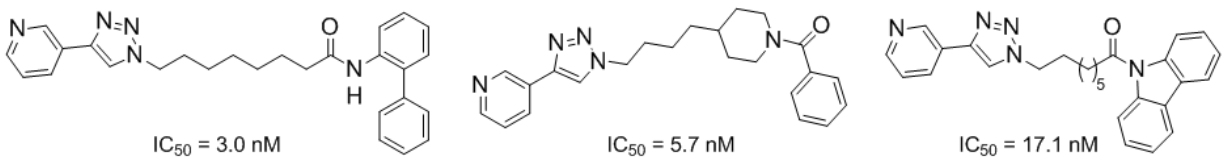


Figure 1: Pyridyl triazoles shown to be NMPRTase inhibitors.

The anti inflammatory activity stems from pyridyl triazoles ability to inhibit tautomerase activity of human macrophage migration inhibitory factor (MIF).[9] MIF inhibition has become a very interesting topic considering how many diseases are linked to MIF. A few examples are Crohn's disease, rheumatoid arthritis, and in some cases cancer[16]. Developing molecules that can improve inhibition of the MIF will be invaluable due to the number of people it will be able to help.

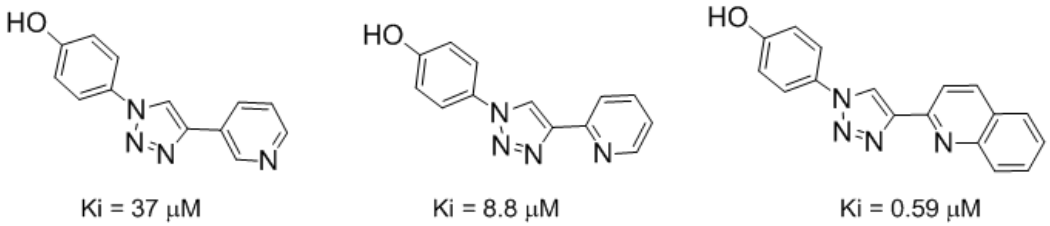


Figure 2: Pyridyl triazoles shown to be MIF inhibitors.

Suzuki cross coupling reactions have become a staple of pharmaceutical chemistry and drug development. Carbon-carbon bonds are some of the hardest bonds to form in organic synthesis and reactions that can form them efficiently are sought after. Cross coupling reaction have

gained prominence in the synthesis of organic molecules as the reactions are pretty robust and substrate tolerable. This allows for very complicated starting materials to be joined together in one step. Even though multiple types of cross coupling reactions exist such as Heck and Stille, Suzuki reactions have gained in popularity due to the benign byproducts and large pool of reagents available allowing for great variability in what can be produced. Due to this the Suzuki reaction remains one of the most convenient ways to connect two aromatic rings together with a carbon-carbon bond.

Chapter One: Substituted Pyridyl Triazole Synthesis

1.1: Synthesis of Pyridyl Triazole:

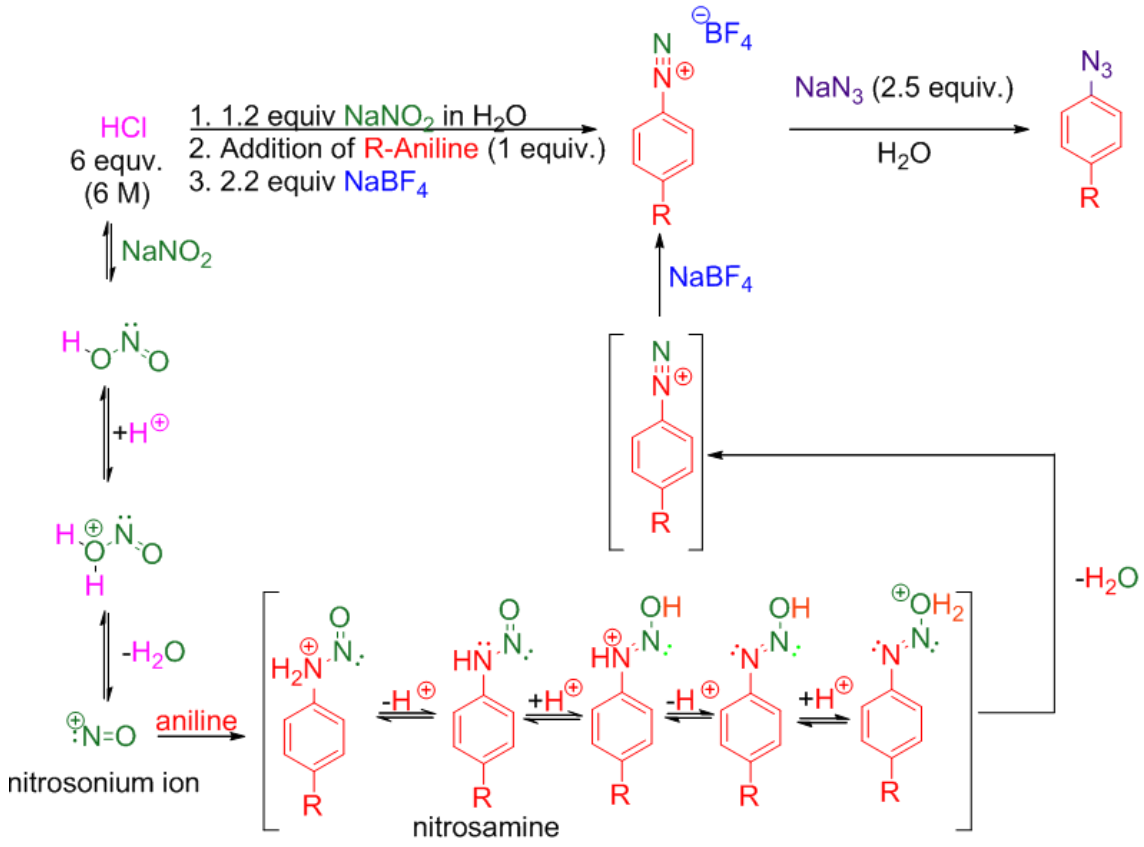
The versatility and ease of the copper-catalyzed azide-alkyne cycloaddition (CuAAC) allows for easy variation to the core triazole structure through adding different functional groups to either the alkyne or azide. In order to study the pyridyl triazole as drug candidates and catalysts, a electronically diverse scope of aryl azides were utilized in the CuAAC reaction while the alkyne was always 2-ethynylpyridine. This allowed for the study of the pyridyl triazole to be done under different electronic conditions.

To do this a diverse set of azides needed to be synthesized with functional groups ranging in electron donating or withdrawing ability. This was done by turning a range of aryl anilines with different functional groups in the para position into their respective azides (Scheme 1).[17-18] To do this a water/brine solution was cooled to 0 °C. Then water and hydrochloric acid were mixed to form a 6 M hydrochloric acid solution after which sodium nitrite is added drop wise. The nitrite then gets protonated to form nitrous acid. The nitrous acid then gets protonated giving

the conjugate acid of nitrous acid which has a water group which can act as a leaving group. The resulting water group then leaves the molecule causing the formation of a nitrosonium ion. The sodium nitrite was dissolved in a minimal amount of water before being added and was added drop wise to the 6 M hydrochloric acid solution which minimized the amount of nitrous acid that fumed off as a redish vapor. The solution should become a blue/green color as the nitrosonium is formed. Aniline is then introduced to the system which results in the nitrosonium ion adding to the aniline which is then deprotonated to form a nitrosamine. The addition of the aniline causes the solution to turn a dark orangey red color nearly immediately and the aniline should be dropped as close to the solution's surface as possible since it can react with the nitrous acid vapor in the round bottom flask. The nitrosamine then tautomerizes which forms another water group which subsequently leaves forming a diazonuim ion. The use of a sodium tetrafuoroborate causes the diazonium ion to form a terafluoroborate salt which proceeds to precipitate out of the water as a orange solid. The hydrophobic nature of fluorine is what causes the resulting diazonium salt to precipitate out of the water. This allows for the diazonium to be isolated from any excess aniline which could cause purity issues later when the azide is formed. The diazonium salt if very unstable and is not dried fully during the vacuum filtration process due to a risk of spontaneous fissure of the carbon-N2 bond which can result in an explosion. Metal utensils is also not used since even small amounts of metal azides are very unstable and even a small amount being formed can result in explosions.

Sodium azide is dissolved in water to form a solution in which the diazonium salt is added which results in the formation of the desired aryl azide. This mechanism is thought to occur through aromatic nucleophilic substitution since gas is evolved from the solution when the diazonium salt is added. The azide can act as a nucleophile which displaces the N_2 of the

diazonium causing nitrogen gas to be evolved. While the diazonium salt is added to the sodium azide solution, a yellow oil was formed which was likely the azide since the final azide is an orange oil but appears yellow when diluted. The solution is left to stir for 18 h before the azide is extracted from the water using diethyl ether and concentrated down after being dried with sodium sulfate. One thing of note for the concentration process is that the phenyl azide can evaporate under low pressure so the phenylazide should not be held under vacuum for too long or the yields will be low.



Scheme 1: Mechanism for synthesizing aryl azide.

Using this method a range of substituted phenyl azides (**1**-**5**) were able to be made (Table 1). For this research only parasubstituted aryl azides were focused on having substituents ranging from electron donating groups such as methoxy to electron withdrawing groups such as

trifluoromethyl. This allowed for us to test the biologic activity as well as catalytic activity of the pyridyl triazole under differing electronic conditions. This is because adding an aryl azide leads to the entire molecule being conjugated meaning that by changing the electronics of the aryl azide, the electronics of the entire resulting triazole can be changed. For example the trifluoromethyl substituted phenylazide (**5**) makes the resulting pyridyl triazole electron deficient while the methoxy substituted phenylazide (**1**) makes the pyridyl triazole electron rich. This makes it possible to control the electronics in an easy way that doesn't really affect the overall sterics of the pyridyl triazole which could also change the cataylitic activity and biological activity. In other words this was a convenient way to test for primarily how only the electronic conditions affect the pyridyl triazoles.

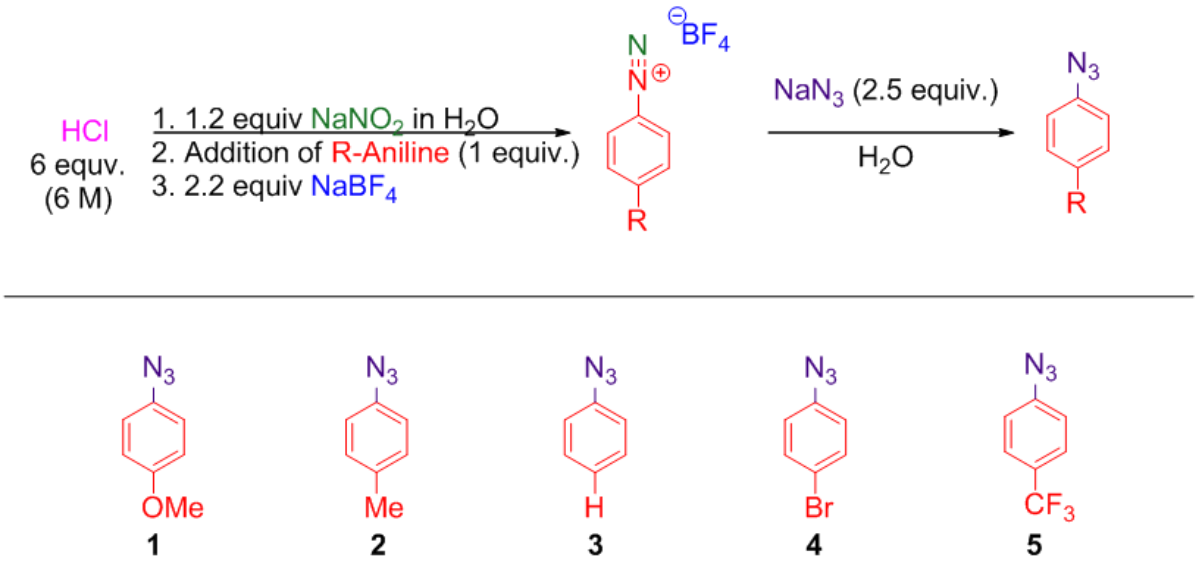
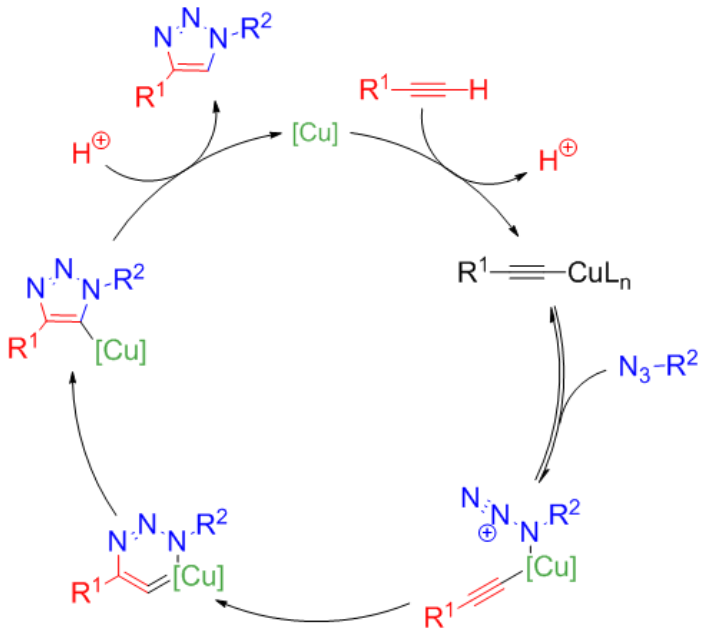


Table 1: Synthesis of electronically divers aryl azides.

After forming the aryl azides the CuAAC reaction was utilized to actually form the pyridyl triazole by reacting the aryl azide with the desired substituent with the 2-ethynylpyridine which results in the formation of the desired pyridyl triazoles (**6-10**). To do this,

copper sulfate pentahydrate was added to a round bottom flask before being purged with argon for about 5 minutes. Fallowing this a 7:3 ethanol with water mixture was added to the round bottom flask. Sodium ascorbate was then added and the mixture was mixed for about 5 minutes. After this the aryl azide is then added to the solution drop wise in which the solution turns a orange color likely due to the fact that the azide is an orange oil. Following the addition of the aryl azide the 2-ethynylpyridine was added drop wise. The solution eventual turns a black color and the reaction mixture is extracted using water and ethyl acetate. The organic layer is then isolated and dried using sodium sulfate before being concentrated down to be purified through column chromatography. By changing the substituent on the aryl azide a electronically diverse set of pyridyl triazoles were formed (Table 2).

This reaction proceeds by first the copper (II) being reduced to copper (I) through the excess of sodium acrorbate.[19-20] Then the terminal alkyne undergoes oxidative addition being added to the copper. The azide then coordinates to the copper setting up the interaction between alkyne and azide. This results in a oxidative metallacycle formation which also defines the regioselectivity for the reaction. Reductive ring contraction of the metallacycle occurs forming a cuprous triazole which is then protonated to reform the Cu(I) and put out the triazole (Scheme 16). There is some debate on whether this reaction actually utilizes two copper atoms in the synthesis and new evidence seems to confirm that to be the case.[21-23]



Scheme 16: Proposed mechanism for CuAAC reaction.

This method was able to produce a large range of substituted pyridyl triazoles (**6-10**) from the aryl azides (**1-5**) with pretty respectable yields (Table 2). The more electron donating substituent on the triazole lead to higher conversion being shown by how the methoxy and methyl versions (**6-7**) had about 30 to 40 percent better yields than the trifluoromethyl and bromine versions (**9-10**). This could have been explained through the columns being harder to run for the more electron poor pyridyl triazoles and how the azide has to coordinate with the copper which would be easier to do with more electron density.

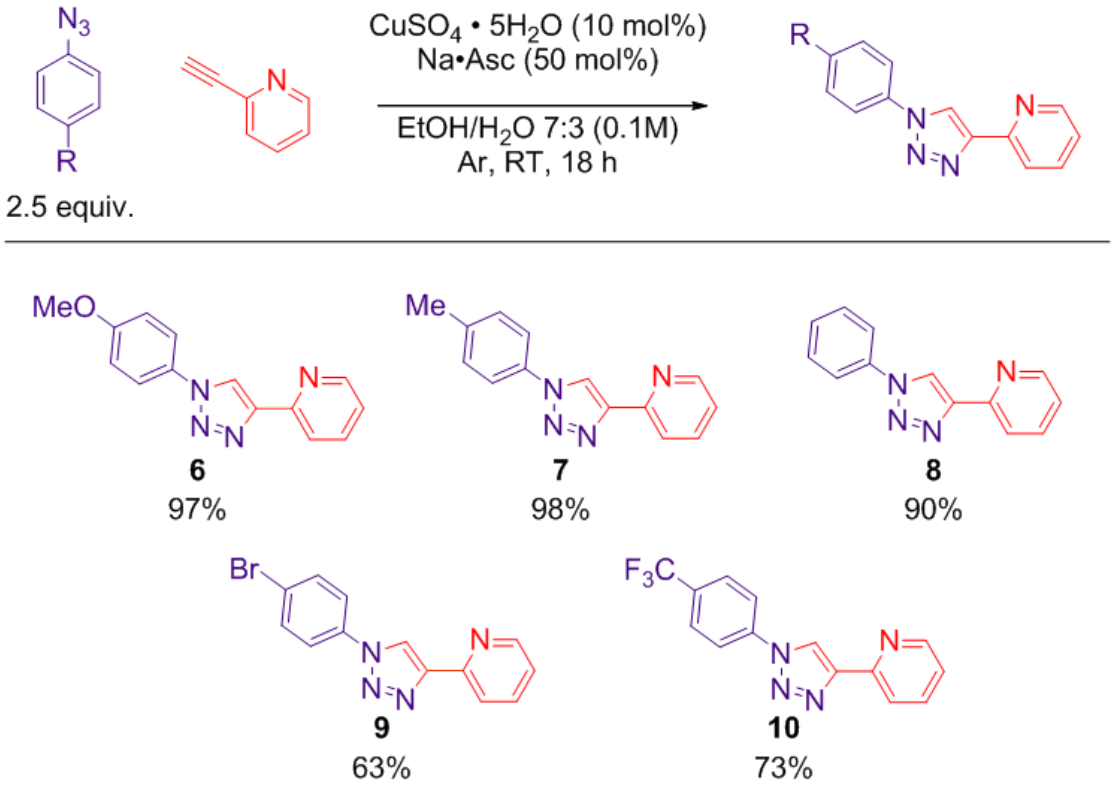


Table 2: Synthesis of electronically diverse pyridyl triazoles.

1.2 Pyridyl Triazoles as catalysts:

With the success of synthesizing the substituted pyridyl triazoles (Table 2), the next step in the study was to test the catalytic activity of the pyridyl triazole ligands with different electronic conditions. To do this, the first step was to form metal complexes and since Suzuki–Miyaura coupling is one of the most versatile and popular reactions as well as usually uses palladium catalysts it made sense to pursue making palladium complexes.

In order to make the palladium complexes $PdCl_2(MeCN)_2$ was used as a palladium source. The pyridyl triazole is dissolved in dichloromethane before having the $PdCl_2(MeCN)_2$ added to the solution. The palladium source undergoes ligand exchange at room temperature without the need of an inert atmosphere with the pyridyl triazole which results in a complex. The

complex is not soluble in dichloromethane which results in it precipitating out of solution. The fact that the $PdCl_2(MeCN)_2$ and pyridyl triazole ligand were soluble in dichloromethane while the metal complex between the palladium and pyridyl triazole were not soluble in dichloromethane made the purification process pretty straight forward. The product was purified by centrifuging the reaction mixture in order to push the complex to the bottom of the tube allowing for the supernatant to be removed. Small portions of the reaction mixture was added to the centrifuge tubes at a time due to the small size of the centrifuge tubes but all of the complex easily fit into the centrifuge tubes. The supernatant contained all of the soluble impurities and was discolored. Once all of the complex was transferred to the centrifuge tube, the complex was washed about 3 to 4 times with dichloromethane by adding the dichloromethane to the complex and shaking the tube. The mixture was then put into the centrifuge for about 40 seconds so that all of the solid went to the bottom of the tube. After this, the supernatant was pipetted off and the process was repeated. By the end the supernatant should be clear indicating that the complex was pure since none of the soluble starting materials were present. The complex was then dried under vacuum and stored in the freezer for later use. This method was able to be used with the pyridyl triazole ligands (**6-10**) producing electronically diverse complexes with excellent yields (Table 3). They were all pretty insoluble in dichloromethane so the purification method worked for all of them.

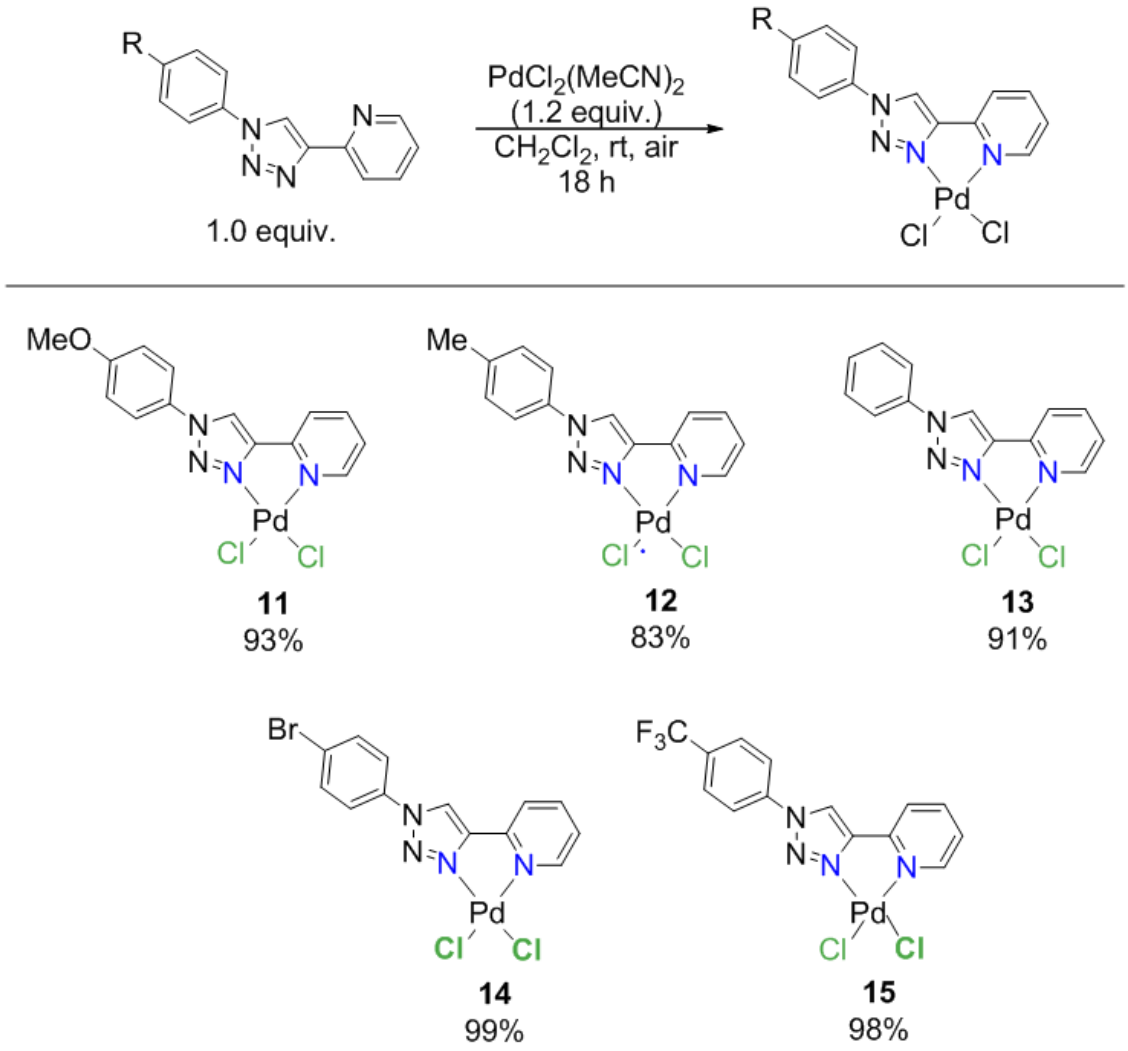
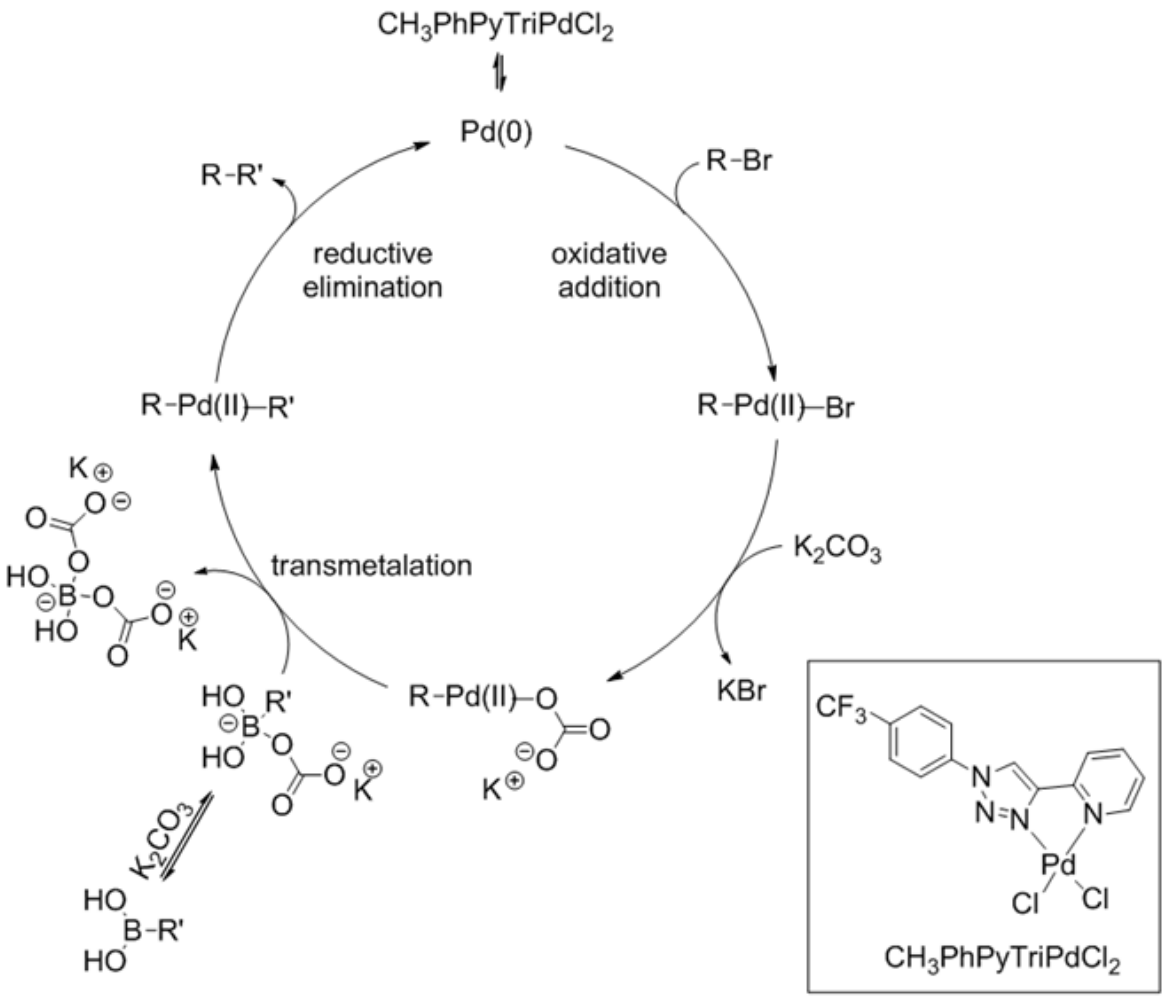


Table 3: Synthesis palladium complexes from electronically diverse pyridyl triazoles.

After successfully making the desired palladium complexes (**11-15**), the complexes were screened for catalytic activity to see which one was the best for use as a catalyst as well as what were optimal conditions for performing the Suzuki coupling reactions. After many trials it was found that the trifluoromethyl pyridyl triazole palladium complex (**15**) was the best catalyst and was actually very good. It was many times more efficient than the president with a catalytic turnover of about 10,000.

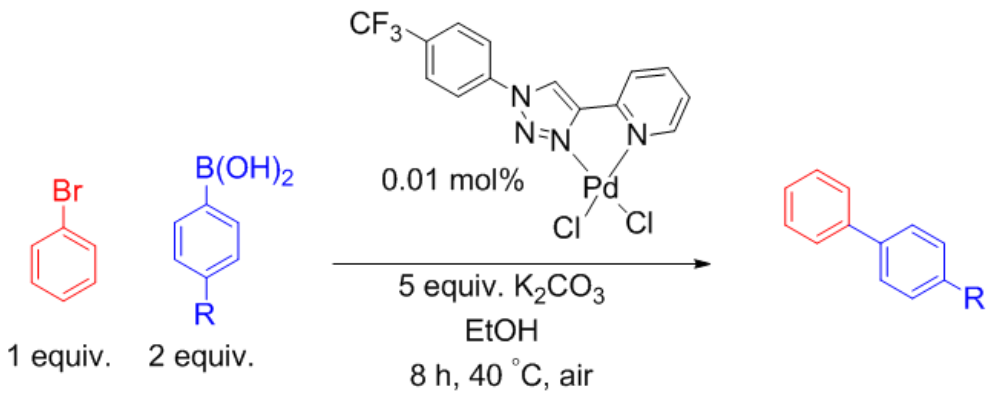


Scheme 2: Mechanism for Suzuki cross coupling to be used in this study.

In order to further find catalytic potential of $CF_3PhPyTriPdCl_2$ (**15**), a boronic acid screen was done with varying electronic condition to see how the electronic conditions of the boronic acid affect reactivity (Table 4). Like the aryl azides, aryl bornic acids were used since the substituent on a aromatic ring could be used to affect the electronics of the whole molecule which can more accurately show how electronics affects the reactivity in the Suzuki reaction. In order to do this, bromobenzene was used as the aryl halide and the optimized conditions found earlier were used. 5 equivalences of potassium carbonate and 2 equivalences of aryl boronic acid was added to a vial followed by ethanol and the bromobenzene. A stir bar was added before 0.01

mol% of $CF_3PhPyTriPdCl_2$ (**15)** was added to the mixture. The reaction was let run for 8 h at 40 degrees Celsius without an inert atmosphere. The product was then extracted using ethyl acetate and water in order to isolated the organic aspects of the reaction before being dried with sodium sulfate and concentrated down. The crude product was purified through column chromatography using hexanes as the eluent since the products were very non-polar and traveled readily even with nonpolar eluents.

The yields ranged from about 60% to 99% depending on the boronic acid being used (Table 4). The electron rich aryl boronic acids such as from **17** and **18** preformed much better than the electron poor boronic acids such as from **16** and **19**. This can be explained through the fact that the boronic acid is the nucleophile of the reaction. The boronic acid takes part in the transmetalation (Scheme 2) in which the boronic acid takes the bormine and gives its aromatic group to the palladium. The more electron rich boronic acid will be the most efficient at this leading to the trend seen.



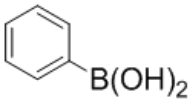
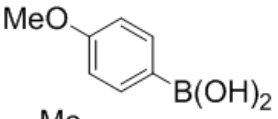
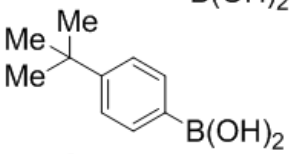
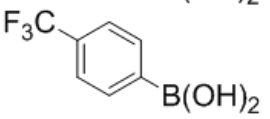
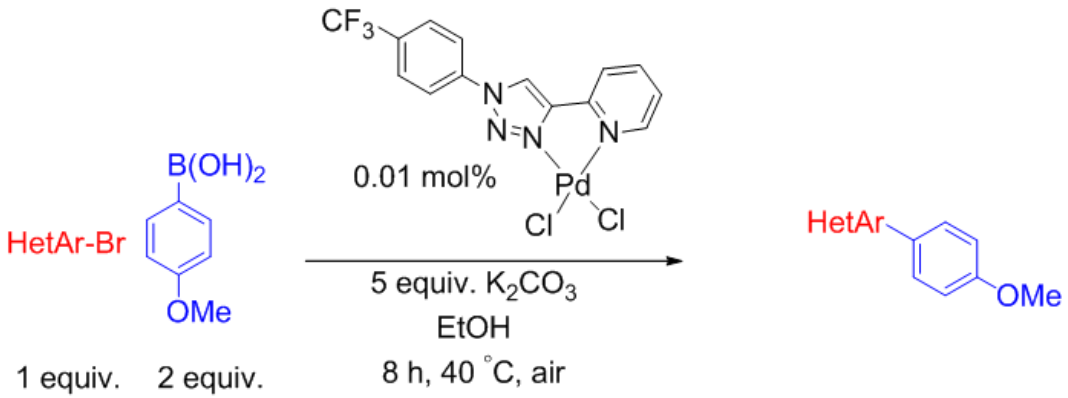
Ar-B(OH$_2$)	Yield (%)	
	73	**16**
	98	**17**
	99	**18**
	60	**19**

Table 4: Electronically diverse boronic acid screen for Suzuki cross coupling reaction showing that electron rich boronic acids preform better than electron poor boronic acids.

Due to how many pharmaceuticals contain heterocyclic rings and the potential the pyridyl triazole complexes have shown in efficiently performing Suzuki reactions, heterocyclic halides were also screened (Table 5) to further expand the scope of the catalytic activity for $CF_3PhPyTriPdCl_2$ (**15**). To do this, 4-methoxyphenylboronic acid was used as the aryl boronic acid as that showed to produce one of the better yields during the boronic acid screen as well as had the easier purification process. The 4-tertbutylphenylboronic acid despite leading to an equally excellent yield during the boronic acid screen had issues separating from the impurities while being columned likely due to how nonpolar it was making it travel through the column with everything else leading to virtually no separation. The reactions done for this heterocycle

screen involved adding 5 equivalences of potassium carbonate with 2 equivalences of the 4-methoxyphenylboronic acid. Ethanol was then added and the heterocycle was added fallowed by the addition of a stir bar. 0.01 mol% of the $CF_3PhPyTriPdCl_2$ (**15**) was then added and the reaction was let run for 8 h at 40 degrees Celsius while not needing an inert atmosphere. The reaction mixture was then extracted using water and ethyl acetate and purified using column chromatography with a mixture of diethyl ether and hexanes. The product was concentrated down without adding heat and in the dark as the product seemed to be light and heat sensitive. This method produced a wide range of heterocyclic products (**20-23**) with modest to excellent yields.



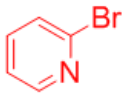
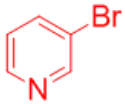
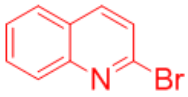
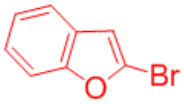
HetAr-Br	Yield (%)	
	53	**20**
	99	**21**
	89	**22**
	99	**23**

Table 5: Heterocycle screen for Suzuki cross coupling reaction.

The first time isolating the desired hetercycle products (**20-23**) seemed to be working at first since the product solutions were clean by both TLC as well GC after coming out of the column. However, after being concentrated down and dried under vacuum, the NMR showed that there was an impurity. This did not make sense since the sample was pure only hours earlier and nothing was done that could have introduced the new impurity. Since the impurity was not likely introduced between the column and NMR sample, it was thought that the impurity could be resulting from degradation of the heterocyclic products (**20-23**). The main ways a product can degrade is through being light sensitive, heat sensitive, and or air sensitive. Correcting for heat

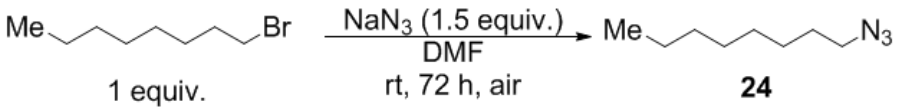
and light sensitivity was done by concentrating the product containing solutions down with the lights off and no added heat. By doing this, the heterocyclic products (**20-23**) were clean by NMR showing that heterocyclic products were light and or heat sensitive and that the impurity was a result of the product degrading.

1.3 Synthesis of n-octyl Pyridyl Triazole:

With the success of the phenyl pyridyl triazole palladium complexes as catalysts for Suzuki cross coupling, it was interesting to see how alkyl pyridyl triazoles could perform as catalysts for the Suzuki reaction since the alkyl group would make it more oily allowing it to be more soluble in organic media. That could allow for the alkyl pyridyl triazole to be more versatile in different scenarios. The alkyl pyridyl triazole could also have interesting biological activity since the alkyl chain would allow for it to go in places that the less hydrophobic phyridyl triazoles could go as well as introduce new electronic conditions that could affect its binding ability to target sights.

In order to make the n-octyl pryidyl triazole (**25**) the alkyl azide had to be synthesized. In this case 1-azidooctane (**24**) was synthesized since smaller alkyl azides are very unstable. In order to do this 1.5 equivalences of sodium azide was added to round bottom flask. At first THF was tried as the solvent due to how it is easy to evaporate off and is very uncreative with most reagents. Followed by the addition of THF, 1-bromooctane was added to the reaction solution drop wise which lead to an off color red/orange solution. This reaction was shown to not have the best conversion to the desired azide (**24**) though meaning that THF was not a good solvent to use. Instead of THF, DMF was used as the solvent. The reaction was then run again using DMF (Scheme 3) and following the drop wise addition of 1-bromooctane to the reaction mixture the solution gained a redish tint. The 1-azidooctane (**24**) was concentrated resulting in a redish oil

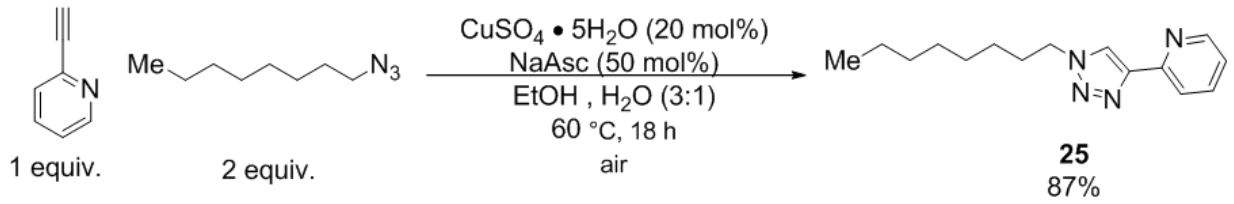
which was used in the n-octyl pyridyl triazole (**25**) forming reaction without any further purification.



Scheme 3: Synthesis of 1-azidooctane using DMF as solvent.

This reaction was also tried with water as the solvent since as seen in other azide reactions, halogenated alkyl groups can be reacted with sodium azide while in water. Since water is an ionic solvent, the non-polar azide products is an oil that does not mix with the water. This leads to easy separation since the azide just needs to be extracted from the water. This idea lead to virtually no conversion to 1-azidooctane (**24**) though.

To make the alkyl pyridyl triazole (Scheme 4), a very similar methodology was used as the one used in forming the phenyl pyridyl triazoles synthesis. Copper sulfate pentahydrate was added to a round bottom flask before being purged with argon for about 5 minutes. Fallowing this a 3:1 ethanol with water mixture was added to the round bottom flask. Sodium ascorbate was then added and the mixture was mixed for about 5 minutes. After this the 1-azidooctane (**24**) is then added to the solution drop wise in which the solution turns a yellow. Following the addition of the 1-azidooctane (**24**), the 2-ethynylpyridine was added drop wise. The reaction solution was extracted using diethyl ether and water and the organic layer was concentrated down. The crude product was then purified using a column chromatography with silica a diethyl ether in hexanes eluent yielding the desired alkyl pyridyl triazole (**25**) as a white solid with a respectable yield of 87%.

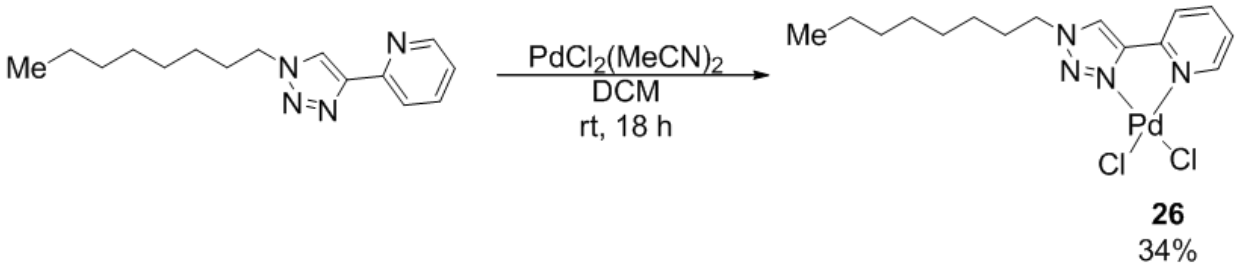


Scheme 4: Synthesis of alkyl pyridyl triazole using 1-azidooctane.

The main difference between this methodology (Scheme 4) when compared to the previous for triazole formation (Table 2) is that the n-octyl pyridyl triazole had a larger ratio of ethanol in the solvent and was also run at 60 degrees Celsius rather than at room temperature. This was done to help the alkyl azide go into solution being that it was more hydrophobic. This is because by increasing the amount of ethanol and heat lead to a higher solubility of the alkyl azide. The catalyst loading was also increased from 10 mol% to 20 mol% to promote triazole formation since less azide would be able to go into solution and interact with the catalyst.

With the successful synthesis of the n-octyl pyridyl triazole, the next step was to check its catalytic activity in the Suzuki reaction by forming the palladium complex. The process to form the palladium complex with the alkyl pyridyl triazole (**25**) is shown in Scheme 5. The procedure was virtually the same as the procedure used to form the phenyl pyridyl triazoles palladium complexes (**11-15**). The pyridyl triazole is dissolved in dichloromethane before having the $PdCl_2(MeCN)_2$ added to the solution. The palladium source undergoes ligand exchange at room temperature without the need of an inert atmosphere with the alkyl pyridyl triazole (**25**) which results in the desired complex (**26**). The n-octyl pyridyl triazole (**25**) is more non polar than the phenyl pyridyl triazoles (**6-10**) due to the added alkyl group which complicated the isolation process. Like before, the precipitate was separated from the supernatant through the use of a centrifuge. The supernatant was then pipetted off and more DCM was added and the mixed with the precipitate. This was repeated until the resulting supernatant was clear, however, it resulted

in a poor yield. The poor yield was thought to be due to the fact that the desired complex (**26**) was somewhat dissolved in the DCM due to the more oily nature of the triazole ligand being used (**25**) which would increase its solubility in DCM. To check this, the supernatant was put into the freezer to see if any dissolved desired complex (**26**) could be precipitated out as the temperature would lower its solubility in the DCM. After about 18 hours the supernatant had precipitate at the bottom showing that some of the n-octyl pyridyl triazole palladium complex (**26**) was in fact dissolved in the DCM resulting in a 34% yield.



Scheme 5: Formation of the alkyl pyridyl triazole palladium complex for Suzuki reaction.

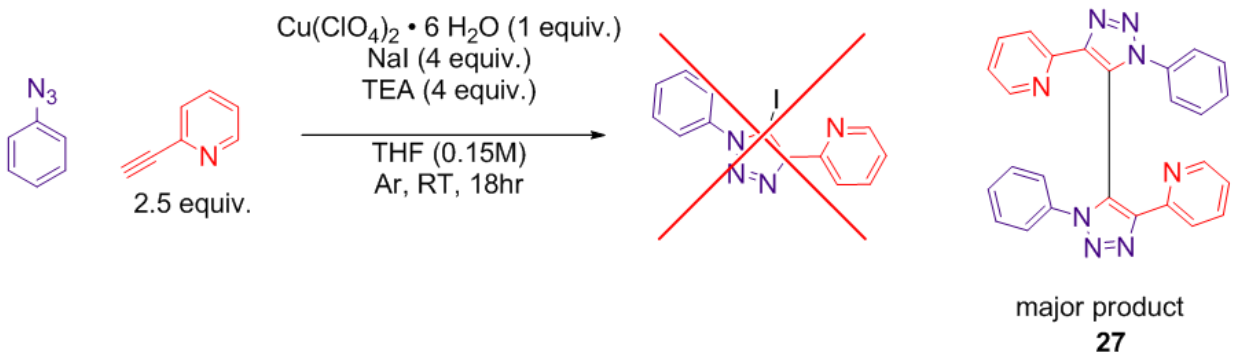
In order to test the catalytic activity of this alkyl pyridyl triazole, it was used as the catalyst a suzuki reaction. The reaction being used was 4-bromoanisole with phenyl boronic acid. This is because that reaction was one of the ones used while testing the trifluoromethyl phenyl pyridyl triazole palladium complex (**15**) and was therefore a good reaction to use as a comparison. Unfortunately while using the n-octyl pyridyl triazole palladium complex (**26**), the conversion to desired product was not very good showing that it was not a better catalyst. Because of that, this complex was not further tested for catalytic activity and the idea of making alkyl triazoles was dropped to give more time to developing

Chapter 2: Iodinated PyTri Expanding the Functionalization of the Molecule

2.1 Synthesis of Iodinated PyTri

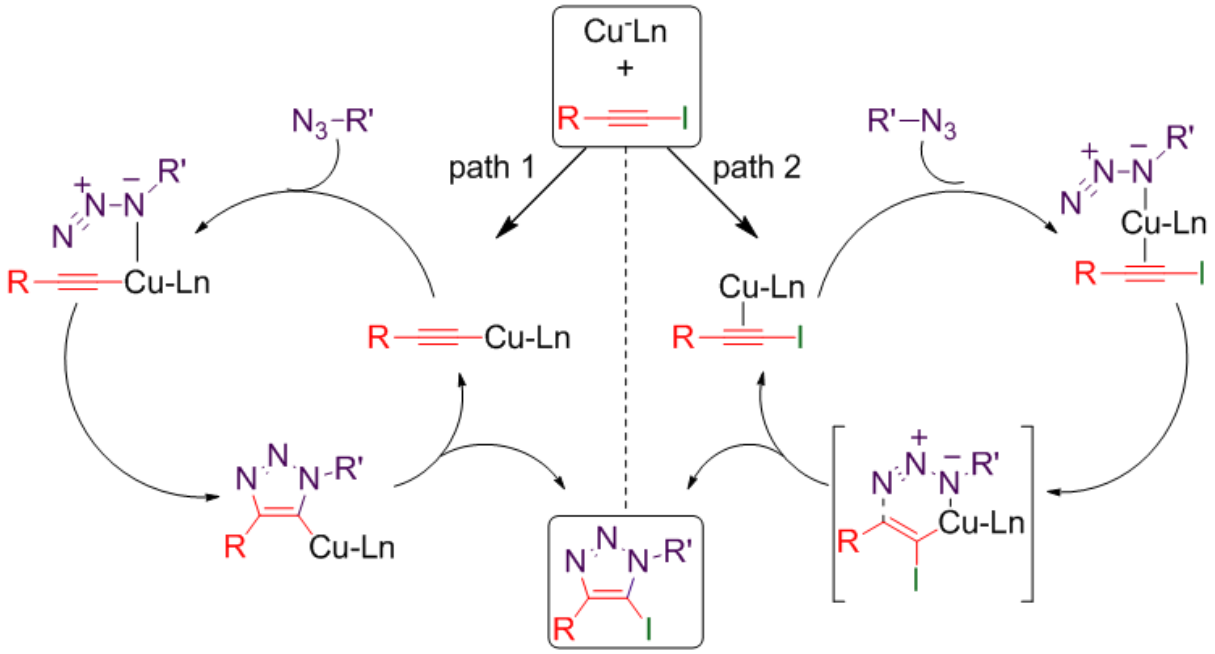
As shown before, the CuAAC reaction is very versatile and allows for a lot of variation to be done to it which makes the triazole formation to be very substrate tolerable. Just by changing the azide or alkyne being used produces different triazole products. This does not allow for complete functionalization to the core triazole structure though. Previous work has shown that producing iodinated triazoles are possible and allow for further functionalization to the triazole which can alter the catalytic as well as pharmaceutical affects by changing the electronics and sterics of the molecule. Due to this, iodinating the pyridyl triazoles was pursued as if possible would allow for a larger scope for pyridyl triazole structures.

The first attempt at synthesizing the iodinated pyridyl triazole was to make the pyridyl triazole and then iodinating in the same reaction (Scheme 6). This was desired as it would mean that only the phenyl azide (**3**) would have to made before making the iodinated triazole as the other reagents were commercially available. This was done by putting 1 equiv. of copper dichlorate hexahydrate into a round bottom flask and purging it with argon for about 5 minutes before THF was added. Fallowing the addition of THF, 4 equivalence of both sodium iodide and triethylamine was added to the solution and allowed to stir for about 5 minutes. Then 1 equivalence of phenyl azide (**3**) was added to the solution drop wise which was then followed by the addition of 2.5 equivalence of 2-ethynylpyridine drop wise. The reaction was then let run for 18 hours and the reaction mixture was then extracted using ethyl acetate and water. Unfortunately this reaction did not produce any iodinated pyridyl triazole and actually produced the dimerized product (**27**). Despite this method being effective in forming other iodinated triazoles[24], this mythology did not work with forming iodinated phenyl pyrydyl triazoles in one step.



Scheme 6: Attempted synthesis of iodininated pyridyl triazole in a one step reaction that resulted in the production of dimerized product.

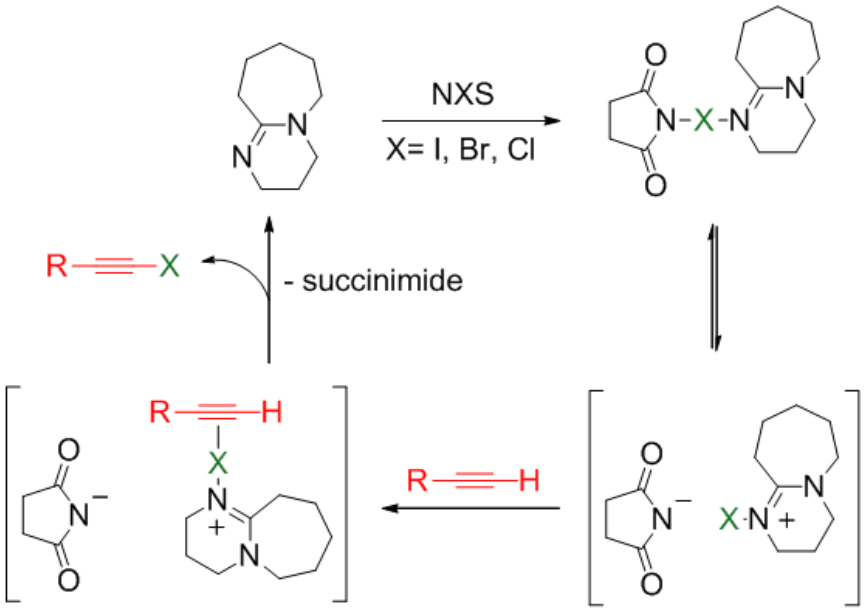
Due to how the triazole formation and iodination being done in one step was not possible for the pyridyl triazoles a different apporach had to be done. It has been found that iodinated triazoles could be formed by reacting a pre iodinated alkyne with azides during the CuAAC reaction.[25] As shown in scheme 7 this reaction has 2 similar possible reactions pathways. Path 1 starts off with the iodinated alkyne being added to the copper catalyst through oxidative addition. The next step is that the azide coordinates to the copper. This is done by the nitrogen bearing the negative charge using its lone pair to attach to the copper. Then a cyclization can occur with the adjacent nitrogen to the alkyne yielding a cupric triazolide. An equivalent of the iodinated alkyne then reacts with the cupric triazolide and causes the copper to be replaced forming the desired iodinated triazole product. Path 2 is where the copper forms a pi-complex with the akyne which intern activates the alkyne. The azide then cooridinates just like before which puts the now activated alkyne and azide together allowing them to undergo the cyclization. This occurs through a vinylidene-type transition state which produces the desired iodinated triazole. The interesting thing about this proposed pathway is that the iodine carbon bond is never broken and is maintained throughout the entire catalytic cycle.



Scheme 7: Two proposed pathways that the synthesis of iodinated triazole can follow starting with iodinated alkyne.

Knowing this a method for forming iodinated 2-ethynylpyridine had to be found in order to be used in the synthesis of iodinated pyridyl triazoles. As it turns out a methodology was developed that allowed for the rapid formation of halogenated 2-ethynylpyridine.[26] The methodology utilized 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and N-halosuccinimides to halogenated alkynes (Scheme 8). To do this 2-ethnylpyridine and N-iodosuccinimide was added to solution using tetrahydrofuran as a solvent. DBU was then added to the reaction in order to activate the system. When the DBU was added it reacts with the N-iodosuccinimide to form a very electrophilic iodine species through a halogen bond adduct. This iodine species then interacts with the 2-ethynylpyridine to form a pi-coordinated complex. The iodinated 2-ethynylpyridine is then formed through the terminal alkyne being deprotanated to form succinimide and iodinated alkyne (**28**). This reaction was then extracted using ethyl acetate and

water and then the organic layer was concentrated down and the crude was purified through column chromatography to yield a white solid.



Scheme 8: Mechanism for forming iodinated alkyne using N-halosuccinimide and to activate the system.

By substituting different halogens in the N-halosuccinimide, different halogens were able to be put onto the 2-ethynylpyridine (Table 6). Doing this both chlorinated 2-ethynylpyridine (**30**) as well as brominated 2-ethynylpyridine (**29**) were able to be made. Both the iodinated alkyne (**28**) as well as the brominated alkyne (**29**) were able to be formed in exceptional yields. The chlorinated alkyne (**30**) did not have a good yield. The halogenated alkynes (**28-30**) were all purified in the same method of column chromatography.

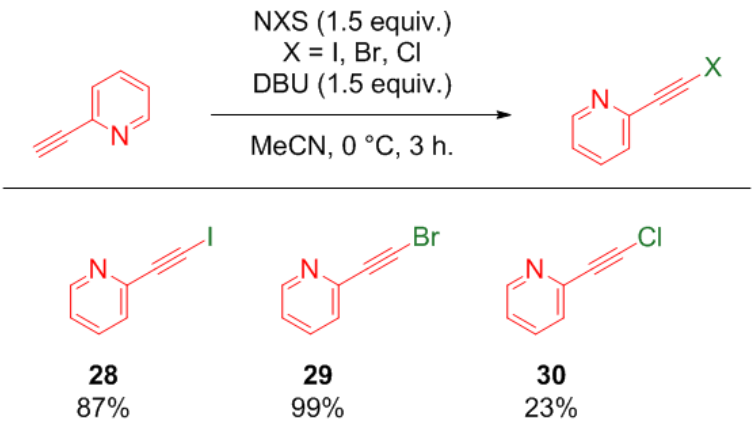
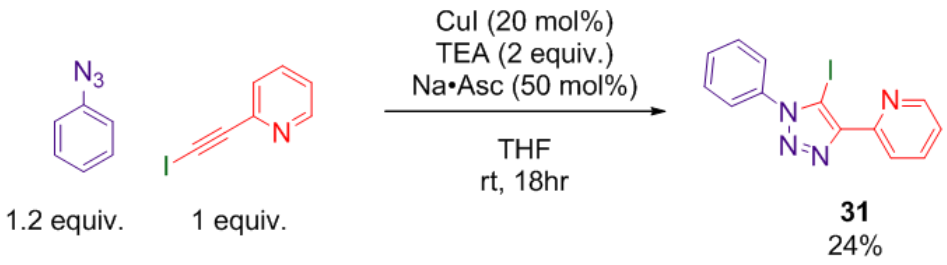


Table 6: Using the N-halosuccinimide and DBU reaction methodology to produce different halogenated 2-ethynylpyridines.

Although the iodinated 2-ethynylpryidine (**28**) is a white solid directly after being purified, when not used immediately it starts to turn black. Originally this color change was thought to be a problem since when products turn black it normally indicates that it is no longer pure as a some sort of side reaction occurred. In order to see if the iodinated 2-ethynylpyridine (**28**) was still useable an NMR was taken which showed that it was still pure meaning that whatever was causing the black color did not affect purity all that much.

After successfully forming the iodonated alkyne (**28**), the CuAAC type reaction shown in Scheme 7 was utilized to actually form the iodinated pyridyl triazole (Scheme 9). To do this, copper iodide was added to a round bottom flask before being purged with argon for about 5 minutes. tetrahydrofuran is then added to the round bottom flask fallowed by sodium ascorbate and triethylamine which is added drop wise. This mixture is then stirred together for about 5 minutes in which the solution gains a slight bluish green tint. This bluish tint is fairly hard to notice though. The aryl azide (**4**) is then added to the solution drop wise in which the solution turns a orange color likely due to the fact that the azide (**4**) is an orange oil. The iodinated 2-ethynylpryidine (**28**) was then added drop wise after being dissolved in minimal tetrahydrofuran

in which the reaction turns a mud color before ultimately becoming a black solution. This was let run for 18 h before being run through an alumina plug and then running a silica column with a ratio of ethyl acetate and hexanes as the eluent. The product (**31**) after being purified is a tan solid with a yield of about 20 percent.



Scheme 9: Successful synthesis of iodinated triazole using triethylamine and iodinated 2-ethynylpyridine.

Originally for the iodinated triazole synthesis, instead of an alumina plug the reaction mixture, was extracted using ethyl acetate and water. The columns for this reaction however were very long and it was thought that maybe it was due to a lot of impurities that are not taken out through the extraction and that maybe plugs would remove more. To test this a plug screen was done by taking 1 mL aliquots of the reaction mixture and running them through different types plugs. The plugs tried were celite, fluorocile, silica, alumina, and sodium sulfate. After running the aliquots through one of the plugs, TLCs of the resulting solutions were taken before being dried for NMR analysis (Figure 3). Both the NMR data and TLC data showed that alumina, fluorocile, and silica plugs actually made the reaction solution cleaner than what an extraction was able to do and that the alumina lead to the cleanest reaction solution albeit still dirty. The sodium sulfate also seemed to trap some of the triazole product (**31**) showing that performing an extraction is not a very good idea since product is likely lost during the drying process. Due to alumina plugs showing the most potential different eluent polarities where tried with the alumina plugs but the eluent did not affect the purity. Following this discovery the

iodinated triazole synthesis from Scheme 9 was run again but having the entire reaction mixture put through an alumina plug and purified through column chromatography like before. This reduced the time required for the column and since the extraction was also really hard to do with the two layers not separating easily made just running an alumina plug more efficient.

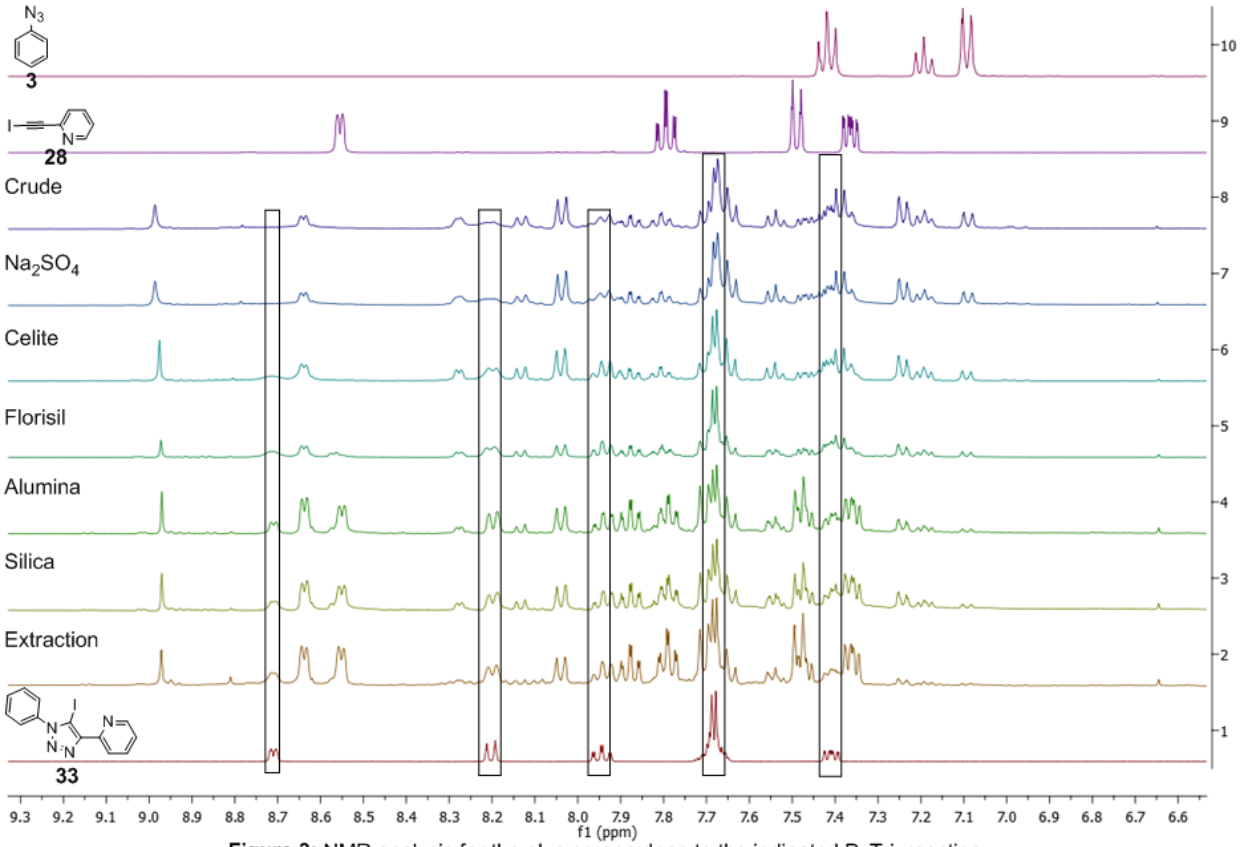


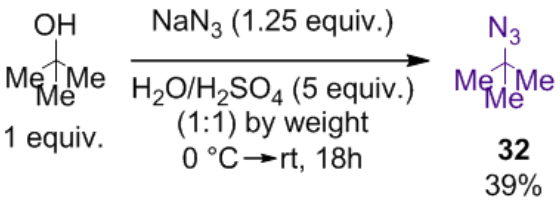
Figure 3: NMR analysis for the plug screen done to the iodinated PyTri reaction mixture showing that alumina had worked the best.

The method used for iodinated triazole formation (Scheme 9) produces a lot of impurities that could not be removed through the use of a plug as shown by thin layer chromatography where the product peak is one of about 5 major spots that are UV active. This was not ideal considering that the yields were not very high to begin with and the presence of all of the impurities made the column harder as some of the impurities moved through the columns at

similar speeds leading to poor separation and impure fractions lowering the yield further. Because of this, a way of making the reaction more efficient was sought after.

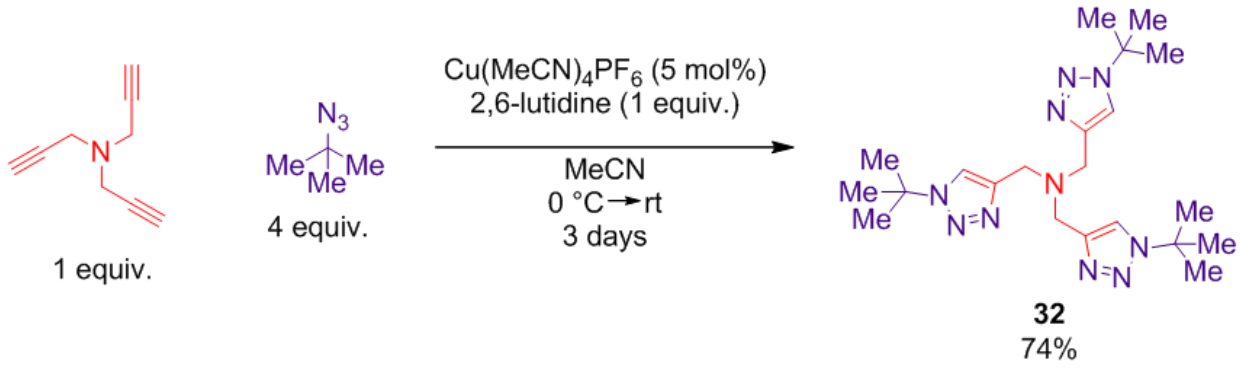
Previous work has shown that using larger tertiary amines increases the yield of the iodinated triazole formation as well as leads to less byproducts.[28] This is because the larger amine adds steric bulk to the copper catalyst and reduces the ability for dimerization to occur as well as other side reactions. The study where larger amines were shown to lead to better yields also showed that tris((1-tert-butyl-1H-1,2,3-triazolyl)methyl)amine (TTTA) was the better of the larger amines to be used in the reaction.

The process of forming TTTA is pretty straight forward. The first part of the reaction starts out with *t*-butanol and then creates *t*-butyl azide (Scheme 10).[27] The process for this is making a 1:1 ratio by weight solution of sulfuric acid in water. Then 1.25 equivalence of sodium azide was dissolved in the acidic solution. Following this, 1 equivalence of *t*-butanol was added to the solution drop wise which results in the formation of *t*-butylazide (**32**) in the water/acid solution with a Sn1 type reaction mechanism. Unlike in the synthesis of phenylazide (**4**), the *t*-butylazide (**32**) was not at all miscible with the water solution which made purification much easier. This purification was done by just putting the reaction mixture into a separatory funnel and separating the aqueous layer from the organic layer. In this case the organic layer was the *t*-butylazide (**32**) which was then dried using sodium sulfate and run though a plug without any further purification before being used in the TTTA formation.



Scheme 10: Creation of *t*-butyl azide for TTTA synthesis using acidic solvent and sodium azide.

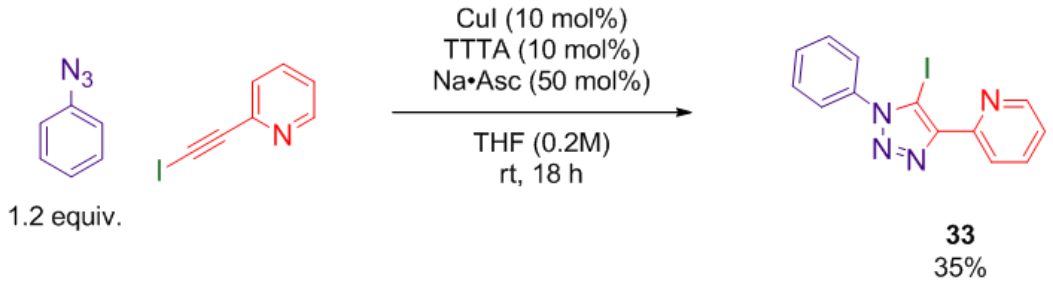
The next step was to make the TTTA (Scheme 11).[29] This was done by putting Copper(I) tetrakis(acetonitrile) hexafluorophosphate into a vial and purging it with argon for about 5 minutes. Acetonitrile was added to the vial as the solvent and 2,6-lutidine was then added to the solution drop wise. The reaction solution was then placed into a ice/brine bath and was let stir for about 5 minutes. Then 4 equivalence of *t*-butylazide (**31**) was added to the solution drop wise followed by 1 equivalence of tripropargylamine being added drop wise. The reaction was let run for 3 days and warm to ambient temperature. After 3 days the TTTA (**32**) had formed as a white precipitate in the solution and was filtered out of solution. The TTTA (**32**) was then rinsed with cold acetonitrile affording the desired product as a white solid with a yield of 74%.



Scheme 11: Synthesis of TTTA to help with the formation of iodinated triazole.

Once the TTTA (**32**) was synthesized, the iodinated triazole was formed again (Scheme 12). Like before, copper iodide was added to a round bottom flask before being purged with argon for about 5 minutes. Tetrahydrofuran is then added to the round bottom flask fallowed by

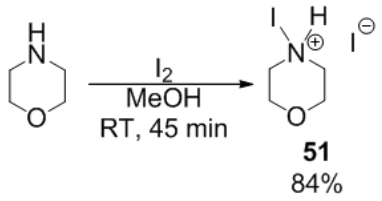
sodium ascorbate. This time TTTA (**32**) was added instead of triethylamine. This mixture is then stirred together for about 5 minutes in which the solution gains a slight bluish green tint. This bluish tint is fairly hard to notice though. The aryl azide (**4**) is then added to the solution drop wise in which the solution turns a orange color likely due to the fact that the phenylazide (**4**) is an orange oil. The iodinated 2-ethynylpryidine (**28**) was then added drop wise after being dissolved in minimal tetrahydrofuran in which the reaction turns a mud color before ultimately becoming a black solution. This was let run for 18 h before being extracted using ethyl acetate and then running a column with a ratio of ethyl acetate and hexanes as the eluent. The product (**33**) after being purified is a tan solid with a yield of about 30 percent.



Scheme 12: The use of TTTA instead of triethylamine in the formation of the iodinated pyridyl triazole produces about a 10% better yield then when triethylamine was used.

The method using TTTA (**32**) rather than triethylamine did produce a better yield as well as had a cleaner reaction solution. Before the TLC plate of the crude product had about 5 different major spots. However, with the TTTA (**32**) being used there were only 2 major spots. One of them corresponded to the iodinated pyridyl triazole (**33**) while the other corresponded to unreacted iodinated 2-ethynylpyridine (**28**). This was a major improvement and made the purification much easier since there were not a lot of byproducts that moved at a similar speed through the column. The yield was also about 10 percent better making the reaction just overall better as well.

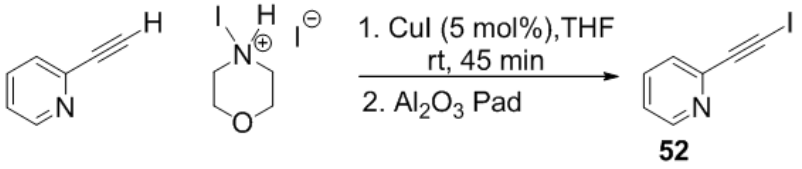
Due to the low yields and long reaction times as well as purification methods required in producing iodinated pyridyl triazole (**33**) the main bottleneck for studying them is making enough to use. One of the most time consuming steps is preparing the iodinated 2-ethynylpyridine (**28**). This reaction only has a 3 h reaction time but requires a column that takes about 4 to 5 hours to do. When this is coupled with the pyridyl triazole synthesis (Scheme 12) that takes 18 h to run and then another 4 to 5 hour column the amount of time required to make iodinated pyridyl triazole (**33**) becomes very limiting. Because of this, alternate ways of forming the iodinated 2-ethynylpyridine that does not require as much time to purify was wanted. It has been reported that iodinated alkynes could be formed with the use of iodomorpholine iodide and then put directly into the iodinated triazole formation after only being run through an alumina pad. This has the potential of saving a lot of time and making the iodinated pyridyl triazole synthesis much more efficient and faster.



51
84%

Scheme 14: Synthesis of iodomorpholine iodide.

The process of making iodomorpholine iodide is very easy (Scheme 14). Elemental iodide is added to a vial after which methanol is put in. Morpholine is then added to the reaction drop wise and nearly immediately some orange solid starts to form and the solution goes from a dark purple/black to an orange color after about 45 minutes. The iodomorpholine iodide (**51**) is then collected through filtration and no further purification is needed.



52

Scheme 15: Synthesis of iodinated 2-ethynylpyridine using iodomorpholine iodide lessen the purification process requried for iodinated triazole synthesis.

Iodinated 2-ethynylpyridine is then made using the alternate method (Scheme 15). Copper iodide is added to a vial followed by dry tetrahydrofuran. Then iodomorpholine iodide (**51**) is added before adding 2-ethynylpyridine drop wise. This mixture is then let stir for 45 minutes at room temperature before affording 2-ethynylpyridine (**52**). The NMR taken of the crude mixture actually showed that the product was decently clean considering it was only run through alumina (Figure 4). The major peaks in the alkyl region was likely from morpholine by products. When this was put into the iodinated triazole formation reaction it did form some of the product (**33**) showing that this is a viable alternative that can save several hours.

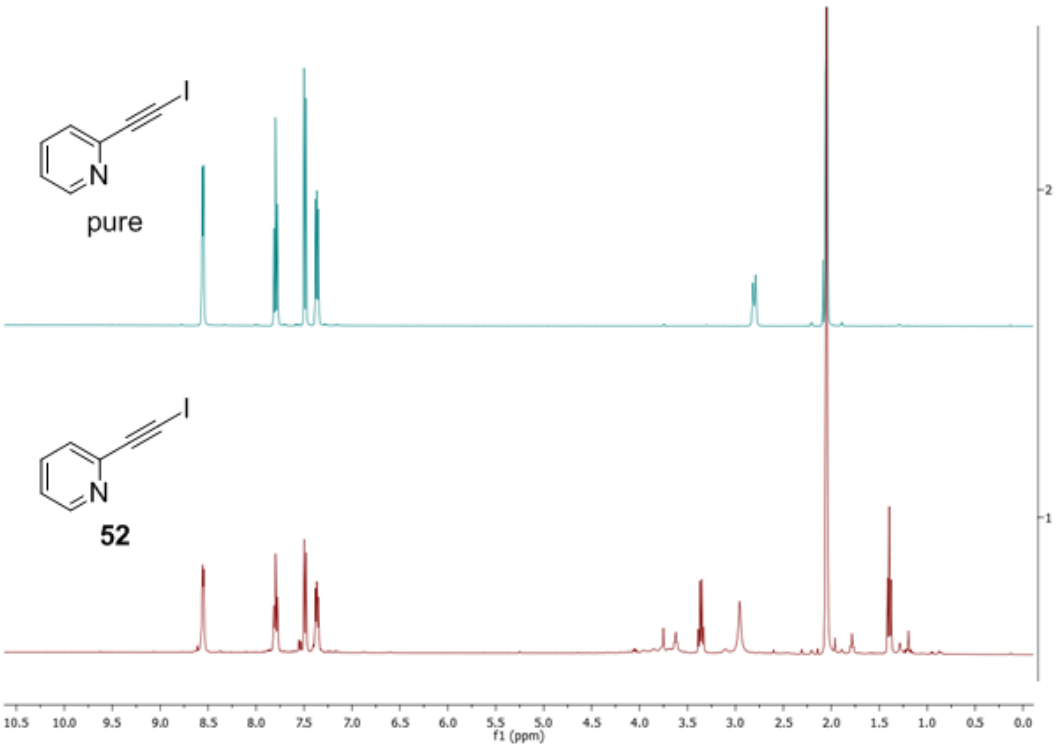
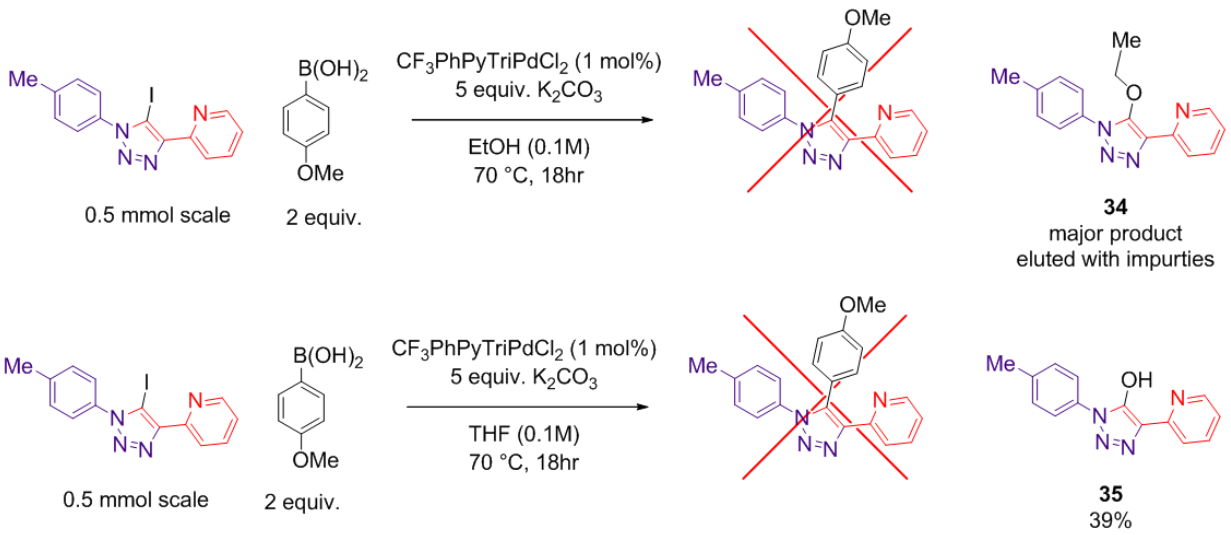


Figure 4: NMR showing how crude iodinated 2-ethynylpyridine from the iodomorpholine iodide method gave a surprisingly clean product.

2.2 Nucleophilic Substitution of the Iodinated Triazole:

Due to previous work showing that Suzuki coupling was possible[30] with triazoles bearing a iodine made us pursue that path of further functionalizing the triazole first. Since the $CF_3PhPyTriPdCl_2$ (**15**) had shown promise as a catalyst for Suzuki reactions that catalyst was used in the optimized conditions found previously which involved ethanol as the solvent, potassium carbonate, and 4-methoxyphenylboronic acid (Scheme 13). 1 equivalence of iodinated triazole, 2 equivalence of 4-methoxyphenylboronic acid, and 5 equivalence of potassium carbonate was added to a vile. Then ethanol was added as the solvent and 1 mol% of the catalyst (**15**) was added. The reaction was ran for 18 h at 70 degrees Celsius. This reaction did not produce the desired product but did produce the ethoxylated product (**34**). The reaction was

attempted again using tetrahydrofuran as the solvent instead of ethanol to see if Suzuki coupling could be done without hafting to compete with the ethanol. This however did not work either producing the hydroxylated product (**35**) with a OH group coming from the boronic acid.



Scheme 13: Attempted use of a Suzuki reaction with the iodinated pyridyl triazole that did not produce the desired result but did show that nucleophilic substitution was possible.

Even though the attempts to perform Suzuki reactions did not work with the iodinated pyridyl triazoles, this did show that nucleophilic substitution could be done instead. Since alkoxylations were shown to be possible from the attempts at performing a Suzuki reaction the nucleophilic substitutions were tried with various alcohols first (Table 7). In order to test the extent of the reactivity for the alcohols in the nucleophilic addition alcohols of different sizes where used. For this study methanol, ethanol, isopropanol, and *t*-butanol was used. The method of performing this reaction was taking 1 equivalence of iodinated pyridyl triazole (**33**) and 5 equivalence of potassium carbonate and mixing it with some of the alcohol being used as the nucleophile. Then the reaction was heated to 70 degrees Celsius for 18 h. The reaction mixture is then extracted using ethylacetate and then purified using column chromatography with a ethyl acetate in hexanes eluent. When using the alcohols it was found that *t*-butylalcohol is too bulky

to perform the nucleophilic substitution and the reaction using *t*-butylalcohol actually preduced the hydroxylated product (**36**). When the t-butanol being used was dry no product was observed to form.

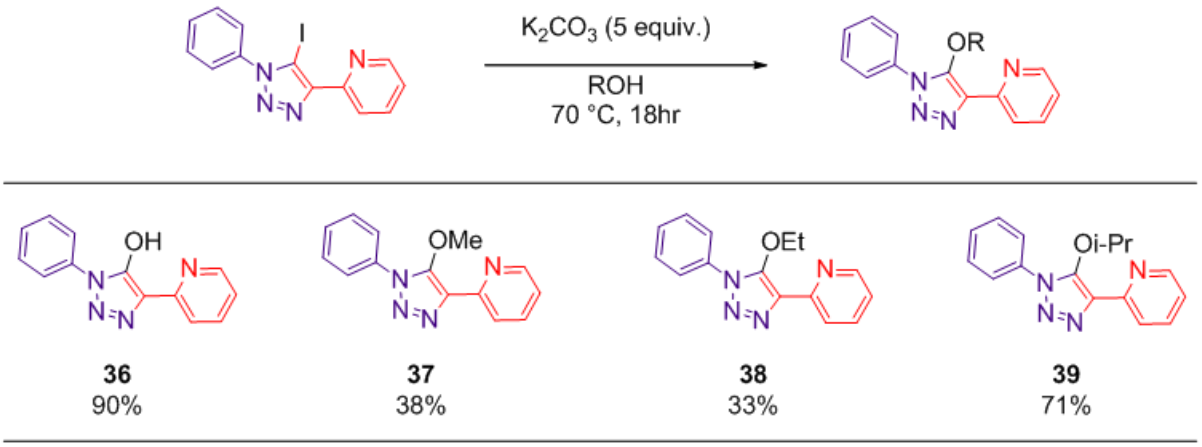


Table 7: Alkoxylation of iodinated pyridyl triazole using sterically diverse alcohols showing the extent of alcohol reactivity with respect to sterics.

The only thiol available to be used was n-propanethiol. The method of performing this reaction was taking 1 equivalence of iodinated pyridyl triazole (**33**) and 5 equivalence of potassium carbonate and mixing it with some of the thiol being used as the nucleophile and heating it at 70 degrees Celsius for 18 h. The reaction mixture is then extracted using ethylacetate and then purified with column chromatography. This showed that thiols were possible nucleophiles to be used however further analysis would have to be performed in order know the true extent of the reactivity thiols hold with the iodinated pyridyls tiazoles. Ideally some secondary as well as tertiary thiols would be tried like what was done with the alcohols.

The number of amines used were much larger than thiols and alcohols used due to the larger availability for amines. Because of this the reactivity of amines as the nucleophile was able to be explored much more being expanded to many different types of primary, secondary, and tertiary amines (Table 8). The method for performing the aminations is primarily the same for the amines as it was for the alcohols and thiols. 1 equivalence of iodinated pyridyl triazole

(**33**) and 5 equivalence of potassium carbonate was mixed with some of the amine being used as the nucleophile. The reaction was then heated to 70 degrees Celsius for 18 h. The reaction mixture is then extracted using ethylacetate and then purified with column chromatography. In the cases where the amines were a solid the reaction was run with tetrahydrofuran as the solvent and then 5 equivalence of amine was put into the reaction mixture. The temperature was also varied depending on the boiling point of the amine. Different amines gave different levels of success however the trend seemed to be that lower boiling point amines did not work very well in the given condition as the reactions tended to dry up prematurely not allowing them to go to completion as a result. Secondary amines also tended to give the best yields. This could be due to how they are better nucleophiles than primary amines but it also could be that the added steric bulk protects the formed aminated triazole from further reactions.

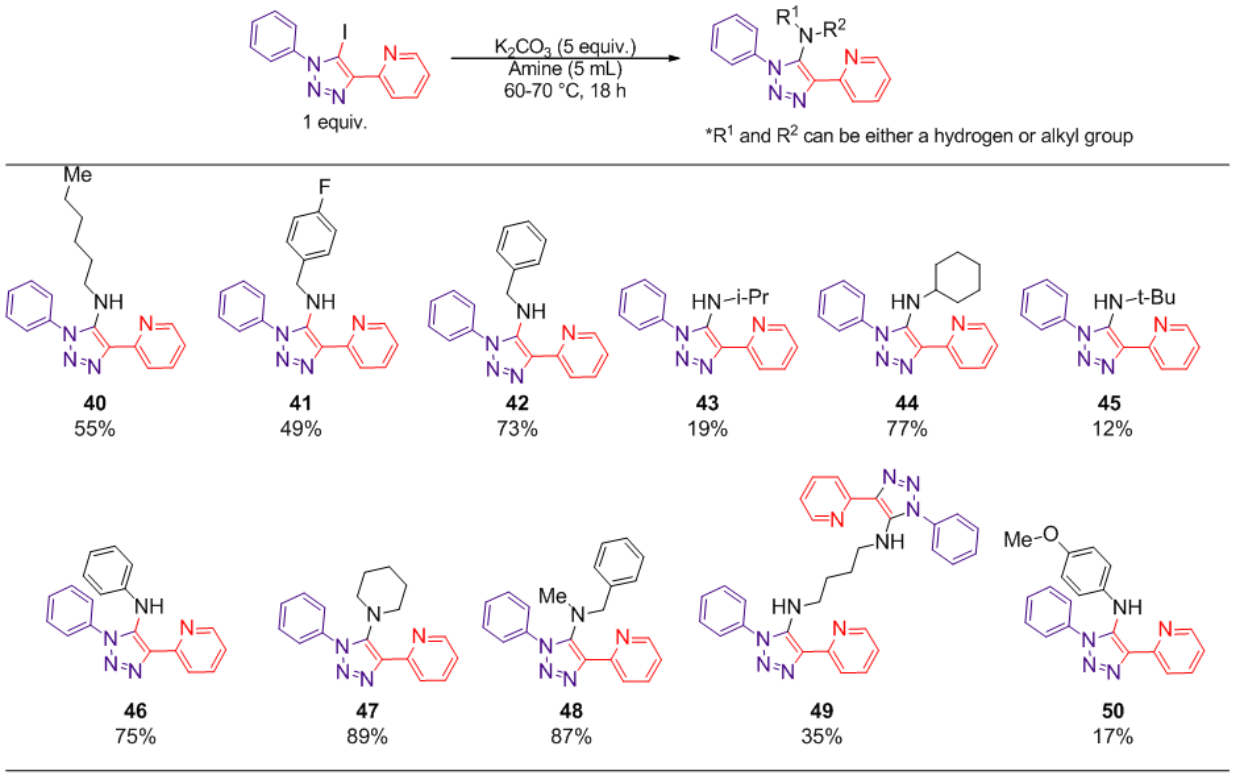


Table 8: Amination of iodinated pyridyl triazoles showing how secondary amines seem to work better than primary amines and that sterics is not the primary condition that affects yield.

Temperature seemed to be a very important factor for the reaction to precede since the reactions that were ran at lower temperature did not perform as well as reaction with higher temperature. The temperature the reaction was run at also seemed to be more important than the sterics of the nucleophile. The clearest example for this was how temperature mattered more was how isopropyl amine (**43**) lead to a very poor yield of 19% however cyclohexylamine (**44**) lead to a decent yield of 77%. Both amines are secondary amines and cyclohexylamine is even arguably more hindered but still had a better yield. The main difference was that isopropylamine dried out before the reaction was over and then was ran at a lower temperature showing that higher temperature are needed to get the optimal yields for the aminations.

In the cases where the amines used had large boiling points that made concentrating the crude product challenging, the amine could actually be distilled off since the aminated products (**40-50**) do not seem to be heat sensitive and are a solid that will not evaporate off. This is important because if the column is attempted while everything is still dissolved in the amine everything is pulled through the silica in the amine and there is very little separation and the product is very impure and the product needs to be columned twice as result. The fact that the amine can be removed through distillation is a very useful fact since it is a relatively quick way of solving the issue of needing two columns which reduces the yield and makes the process very time consuming.

References:

1) Cho, J. H.; Bernard, D. L.; Sidwell, R .W.; Kernand, E. R.; Chu, C. K. *J. Med. Chem.*, **2006**, 49, 1140

2) Brik, A.; Alexandratos, J.; Lin, Y.-C.; Elder, J. H.; Olson, A. J.; Wlodawer, A.; Goodsell, D. S.; Wong, C.-H. *ChemBioChem*, **2005**, 6, 1167

3) Brik, A.; Muldoon, J.; Lin, Y.-C.; Elder, J. H.; Goodsell, D. S.; Olson, A. J.; Fokin, V. V.; Sharpless, K. B.; Wong, C.-H. *ChemBioChem*, **2003**, 4, 1246.

4) Pagliai, F.; Pirali, T.; Del Grosso, E.; Di Brisco, R.; Tron, G. C.; Sorba, G.; Genazzani, A. A. *J. Med. Chem.*, **2006**, 49, 467.

5) Romero, A.; Liang, C.-H.; Chiu, Y.-H.; Yao, S.; Duffield, J.; Sucheck, S. J.; Marby, K.; Rabuka, D.; Leung, P. Y.; Shue, Y.-K.; Ichikawa, Y.; Hwang, C.-K. *Tetrahedron Lett.* **2005**, 46, 1483.

6) Jindabot, S.; Teerachanan, K.; Thonkam, P.; Kiatisevi, S.; Khamnaen, T.; Phiriyawirut, P.; Charoenchaidet, S.; Sooksimuang, T.; Kongsaeree, P.;
Sangtrirutnugul, P. J. *Organomet. Chem.* **2014**, 750, 35.

7) Nicolaou, K.C.; Bulger, P.G.; Sarlah, D. *Angew*. *Chem. Int. Ed*. **2005**, 44,
4442.

8) Colombano, G.; Travelli, C.; Galli, U.; Caldarelli, A.; Chini, M. G.; Canonico, P. L.; Sorba, G.; Bifulco, G.; Tron, G. C.; Genazzi, A. A. *J. Med. Chem.* **2010,** 616.

9) Dziedzic, P.; Cisneros, J. A.; Robertson, M. J.; Hare, A. A.; Danford, N. E.; Baxter, R. H. G.; Jorgensen, W. L. *J. Am. Chem. Soc.* **2015**, 2996.

10) Kharb, R.; Chander, P.; Shahar Yar, S.; Shahar Yar, M. *Journal of Enzyme Inhibition and Medicinal Chemistry*, **2011,** 26:1, 1-21

11) Fokin, V. V.; Sharpless, K. B.; Rostovtsev, V. V.; Green, L. G. *Angew. Chem.* **2002**, 114, Nr. 14

12) Hein, J.; Fokin, V. *Chem. Soc. Rev.*, **2010** ,39, 1302–131

13) Meldal, M.; Tornoe, C. W. *Chem. Rev.* **2008**, 108, 2952.

14) Wu, P.; Fokin, V. V. Aldrichim. *Acta* **2007**, 40, 7.

15) Khan, J. A.; Forouhar, F.; Tao, X.; Tong, L. Expert Opin. Ther. Targets. 2007, 11, 695.

16) Conroy, H.; Mawhinney, L.; Donnelly, S. C. Q. *J. Med.* **2010**, 103, 831.

17) Lucas, H. J.; Kennedy, E. R. *Org. Synth.* **1939**, 19, 55.

18) Lindsay, R. O.; Allen, C. F. H. *Org, Synth.* **1942**, 22, 96.

19) Davies, M. B. *Polyhedron* **1992**, 11, 285 - 321.

20) Creutz, C. *Inorg.Chem.***1981**,20, 4449.

21) Worrell, B. T.; Malik J. A.; Fokin, V. V. *Science* **2013,** 340, 457-460.

22) Makarem M. *et al*, *Angew. Chem., Int. Ed.*, 2015, **54**, 7431.

23) Jin, L.; Tolentino, D. R.; Melaimi, M.; Bertrand, G. *Sci. Adv.* **2015**, 1

24) Brotherton, S. W.; Clark, J. R.; Zhu, L. *J. Org. Chem.* **2012**, 77, 6443-6455

25) Hein, E. J.; Tripp, C. J.; Krasnavo, B. L.; Sharpless, K. B.; Fokin, V. V. *Angew. Chem. Int. Ed*. **2009**, 48, 8018 –8021

26) Li, M.; Li, Y.; Zhoa, B.; Liang, F.; Jin, L. *RSC Adv.* **2014**, 4, 30046–30049

27) Bottaro, J.; Penwell, P.; Schmitt, R. *Synthetic Communications* **1997**, 27:8, 1465-1467

28) Hein, J.; Tripp, J.; Krasnova, L.; Sharpless K.; Fokin, V. Angew. Chem. Int. Ed. **2009**, 48, 8018 –8021

29) Chan, T. R.; Hilgraf, R.; Sharpless, K. B.; Fokin, V. V. *Org. Lett.* **2004**, 6,

2853.

30) Deng, J.; Yong-Ming, W. *Synthesis* **2005**, No. 16, 2730–2738