Worcester Polytechnic Institute

Department of Chemistry and Biochemistry

Copper-Catalyzed Weak C-H Bond Amination

A Major Qualifying Project submitted for review to the faculty of

WORCESTER POLYTECHNIC INSTITUTE
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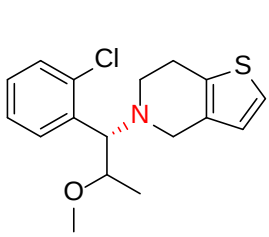
1 Introduction

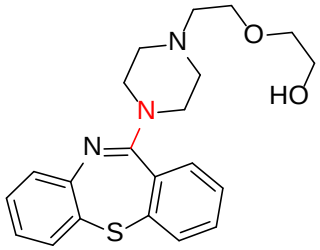
1.1 Motivation

Amines are one of the most important functional groups in chemistry with important applications for the synthesis of biologically active products.[1] The development of pathways that utilize the versatility of transition metal complexes to facilitate amine formation has been an area of interest in the pharmaceutical industry and academia in recent years.[2] In particular, metal catalyzed direct C-H amination provides an atom economical pathway to convert non-functionalized molecules into amines.

The project reported on herein focuses on the formation of benzylic amines by way of copper catalyzed C-H functionalization. Several top selling drugs have benzylic amine moieties in their structures. For example, Plavix and Seroquel (Figure 1) were the number 2 and 6 top selling pharmaceuticals in 2011, respectively, and both contain amine structures in benzylic positions.[3]



Plavix



Seroquel

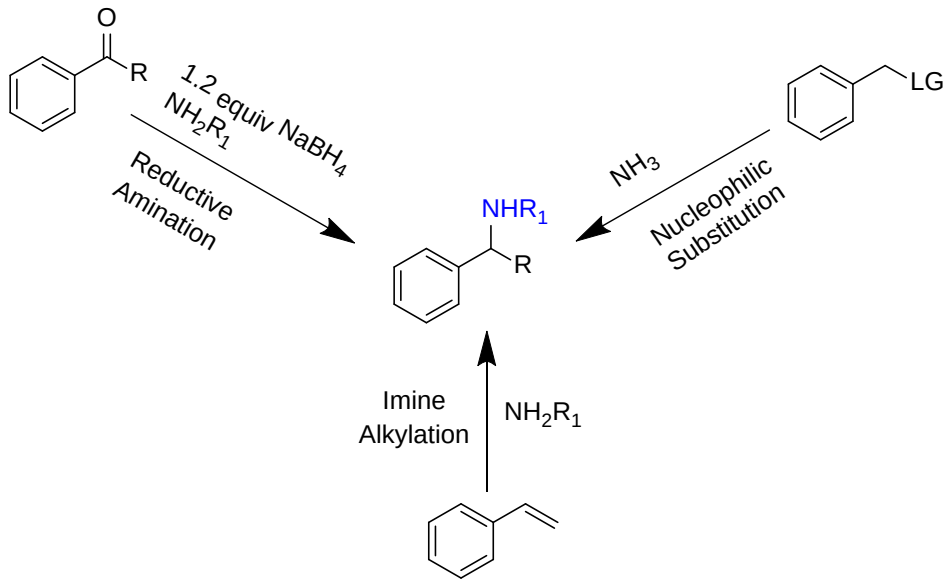
Figure 1. Benzylic amine containing top selling pharmaceuticals

Furthermore, there are many well-known antibacterial agents that contain benzylic sulfonamides functionalities.[4] Sulfonamides are used in a wide array of bioactive compounds and are being used as carbonic anhydrase inhibitors to help prevent disorders such as glaucoma, ulcers, and epilepsy.[5, 6]

The impressive amount of biologically active compounds containing benzylic amine structures makes benzylic amines attractive target molecules. Therefore, the continued development of direct aminations of benzylic C-H bonds can potentially contribute to future pharmaceutical syntheses.

1.2 Classical Methods of Benzylic Amine Formation

Classical methods of benzylic amine formation focus on functional group conversion reactions. These reactions typically involve substitutions of benzyl halogen or hydroxyl groups to produce amine functionalities.[7] Additionally, benzylic amines can be formed through reductive aminations of carbonyl groups as well as by hydrogenations of enamines. [8]



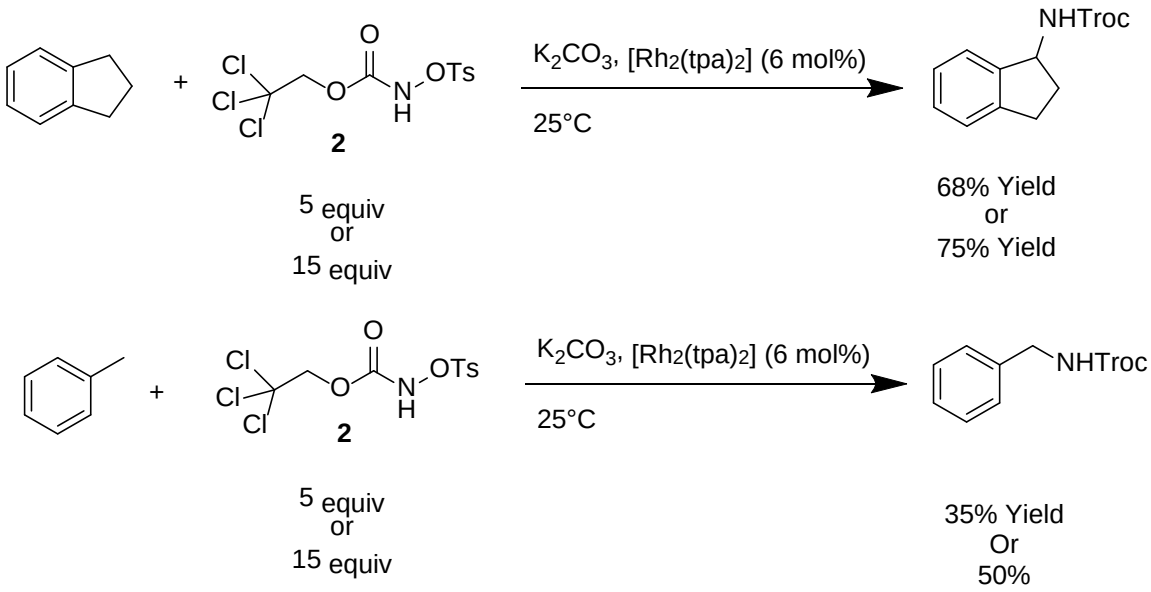
Scheme 1. Classical Amination Methods

1.3 Transition Metal Catalyzed C-H Functionalization

In contrast to the above described classical methods, which involve pre-functionalization with reactive groups at the benzylic position, a large amount of research in the last decades has developed an alternative, more direct approach: the one-step amination of benzylic C-H bonds. Direct C-H aminations typically cut down on the number of steps and reagents needed in syntheses adding to the overall atom economy and efficiency of a method.[9] This has been achieved by way of transition metal catalyzed reactions with rhodium [8], ruthenium[10], manganese[11], and copper [7, 12, 13, 14]. These transition metal catalyzed reactions require a nitrogen source for amination. Reagents that formally produce nitrenes, a reactive electron deficient nitrogen source, are typically used in these catalytic systems.[15] The following sections summarize several transition metal catalyzed methods available for direct benzylic C-H aminations.

1.3.1 Rh Catalyzed Benzylic C-H Amination

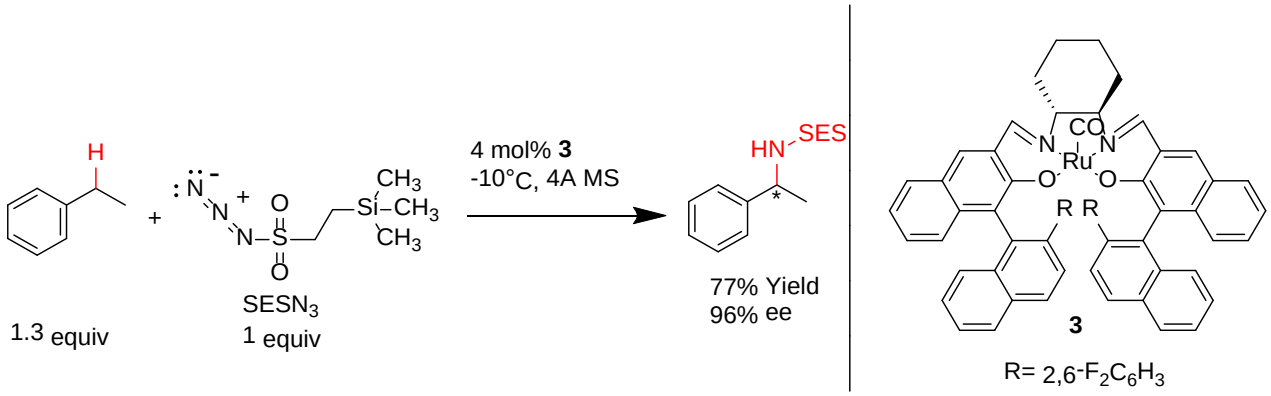
Research conducted by Huard and Lebel has shown that direct functionalization of benzylic C-H bonds can be achieved by utilizing the rhodium catalyzed system shown in Scheme 1. Their work reports yields of up to 75% in the case of indane as benzylic C-H substrate, when utilizing a [$Rh_2(tpa)_2$] catalyst and N-tosyloxycarbamates (**2**) as amination reagent and oxidant.[8] The ready availability of **2** and its ability to react under mild conditions makes it a very useful reagent. Despite the reaction shown in Scheme 1 being direct, versatile, high yielding, and possible under mild conditions, rhodium is an expensive transition metal and a cheaper, more abundant option would be favorable to create a more sustainable benzylic C-H amination method.



Scheme 2. Rh Catalyzed Benyzlic C-H Amination

1.3.2 Ru Catalyzed Benzylic C-H Amination

Another example of benzylic amination with precious metals is ruthenium catalyzed reactions. Work conducted by Nishioka and colleagues (Scheme 3) has shown that catalytic benzylic C-H amination can be accomplished using a Ru catalyst (**3**) alongside 2-(trimethylsilyl)ethanesulfonyl azide ($SESN_3$) as nitrene source.[10] Under optimized conditions, high yield and *ee*'s were reported for several substituted allylic and benzylic substrates. One particularly impressive example in this report was the amination of ethylbenzene in a reported yield of 77% and an *ee* of 96%. The paper further reports that only the C-H amination of ethyl, methyl, and cyclic groups in allylic or benzylic positions were possible with their catalyst system.



Scheme 3. Ruthenium Catalyzed Benzylic C-H Amination

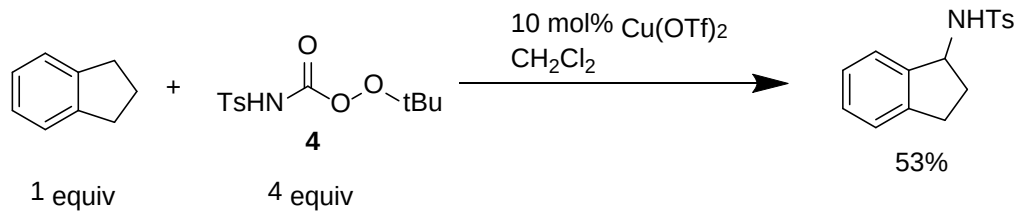
Although high yields and enantiomeric excesses were reported, the stability of the $SESN_3$ (Figure 2) as a nitrene source is questionable due to the tendency of azides to decompose spontaneously under loss of N_2. As such, $SESN_3$ is not thermodynamically stable and potentially explosive. For these reasons, $SESN_3$ must be handled carefully in the glovebox and cannot be prepared on a large scale. Overall, the hazardous nature of the amination reagent, as well as the high cost of ruthenium detracts from the usefulness of this method. Therefore, this method, while synthetically impressive, is not truly useful for general procedures.

1.3.3 Cu Catalyzed Benzylic C-H Amination

Due to the shortcomings of precious metal catalyzed benzylic C-H aminations, there is a growing body of research focusing on the catalytic formation of benzylic amines utilizing catalysts composed of more abundant transition metals. Copper catalysts have been shown to be particularly useful in facilitating the formation of benzylic amines through direct C-H amination. Due to its low cost and low impact on the environment, copper catalysts are excellent and more sustainable early transition metal alternatives to more precious metal catalysts.

Peroxycarbamate as C-H Amination Reagents

Work conducted by Kohmura (Scheme 3), employed peroxycarbamates (4) as amination reagents working alongside a $Cu(OTf)_2$ catalyst.[7] The reaction was able to catalytically aminate indane with yields ranging from 11-56%. N-tosyl variants of 4 were shown to afford the best yields. This method saw best yields with 10 mol % of the copper catalyst and a 1:4 ratio of substrate to 4.

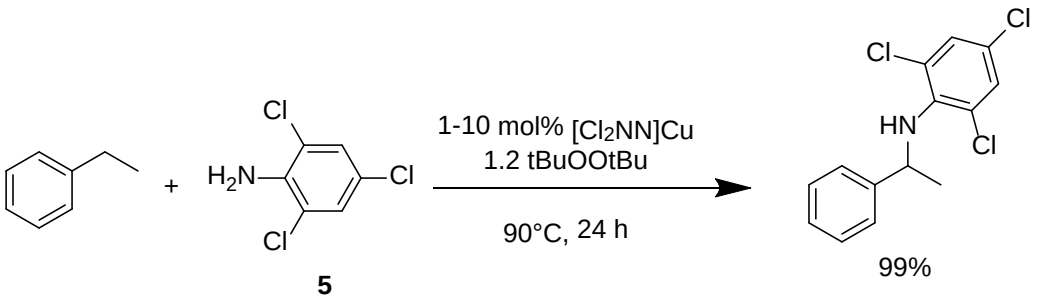


Scheme 4. Peroxycarbamate Nitrene Source

This method has two major drawbacks: The first challenge is the relatively high catalyst loading needed to see significant amination reactivity. Secondly, the thermal stability of the peroxycarbamate 4 is questionable. When scaled up, peroxycarbamates are potentially explosive and will degrade quickly; this limits use of peroxycarbamates to small scale preparation and use.[16]

Aromatic Amines and Peroxides

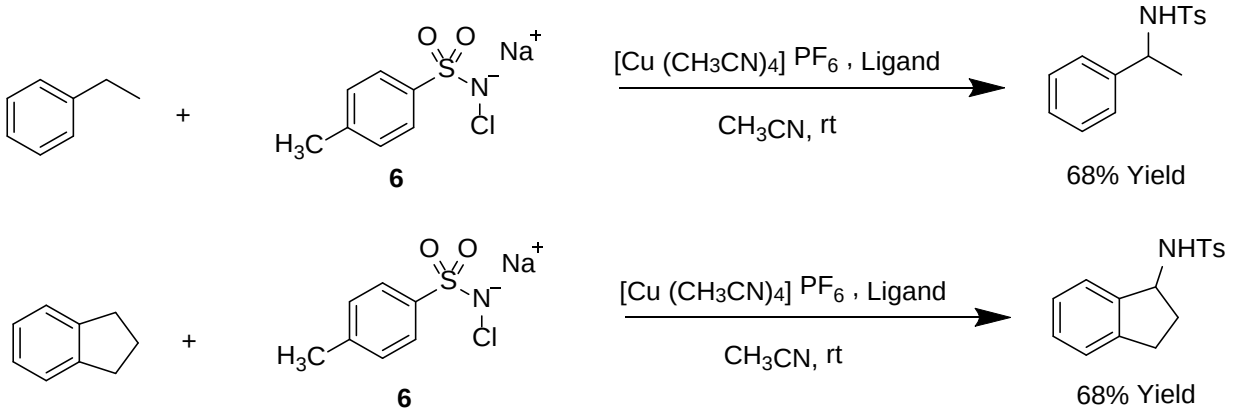
Another example of copper catalyzed benzylic C-H amination was published by Warren and coworkers. The study found that using a combination of aromatic amines and peroxides (Scheme 4) as nitrene source, effective benzylic amine formation could be achieved.[13] In the case of the amination of ethylbenzene with (5), an amination yield of 99% was reported with a catalyst loading of 1 mol%. However, these impressive yields are only observed with electron-deficient amines as reagents. When electron-rich substituted aromatic amines are employed, diazene byproduct formation is more prevalent and drastically reduces yields. For instance, the product yield when using 2,4,6-trimethylaniline is reduced to 47% because of diazene formation. Overall, the restricted amine substrate scope limits the versatility of this method, despite its impressive reactivity with electron-poor amine reactants. While this method is synthetically impressive, peroxides are not thermally stable. The thermal instability of peroxides makes their decomposition create heat and radicles resulting in catalytic decomposition. The risks associated with rapid peroxide decomposition are potentially dangerous, limiting the scalability of methods involving peroxides.[17]



Scheme 5. Aromatic Amine Nitrene Source Copper Catalyzed Benzylic C-H Amination

Chloroamine-T Amination Reagents

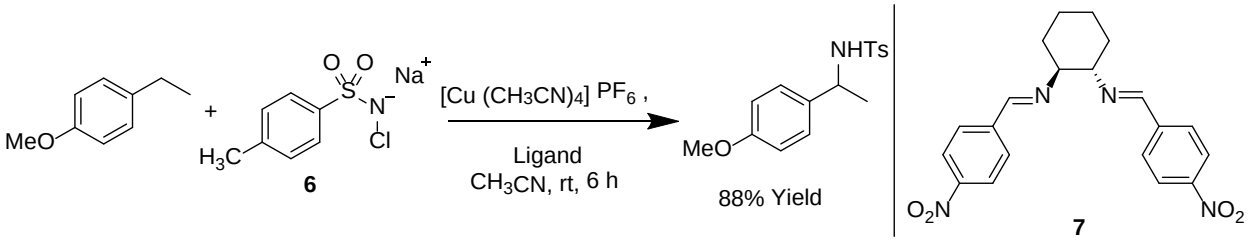
Nicholas found that by utilizing anhydrous chloramine-T (6) in conjunction with a commercially available Cu[I] source, $[Cu(NCMe)_4]PF_6$ in this case, produced good yields in forming benzylic amines (Scheme 5).[12] This method was successful with various benzylic substrates and different substitution patterns; ethylbenzene, triphenylmethane, and indane show yields of 68%, 66%, and 62% respectively. Contrary to many of the other methods established previously, Nicholas' method does not require peroxide additives for catalysis to take place. However, the study did not show any ability for variability in the amine source.



Scheme 6. Ligand Assisted Chloramine-T Copper C-H Amination

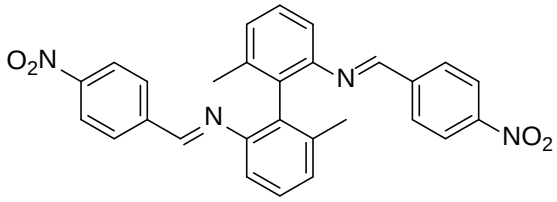
Ligand Assisted Copper Catalyzed Amination

Further studies by Nicholas highlighted that ligand enhancement of the copper catalyst can improve its effectiveness [12] and yields of benzylic amination product of up to 88% were reported when using 4-ethylanisole as the substrate. A ligand screen determined the dinitro-substituted diamine 7 to be the most promoting ligand (Scheme 6).



Scheme 7. Benzylic Amination of 4-ethylanisole using Dinitro-Substituted Diamne Ligand

Additionally, the work showed that ligand choice can aid in enantiomeric specificity. The study reported modest ee's in the amination of 4-Ethylanisole ranging from 3% to 39%. When 7 is used in the catalytic system an ee of 7% is seen. This can be compared to ligand 8 (Figure 2) which produces an *ee* of 39% without sacrificing yield (81%). While these enantioselectivities are not synthetically useful, the results suggest that chiral ligands may be able to allow enantioselective C-H aminations upon further optimization.

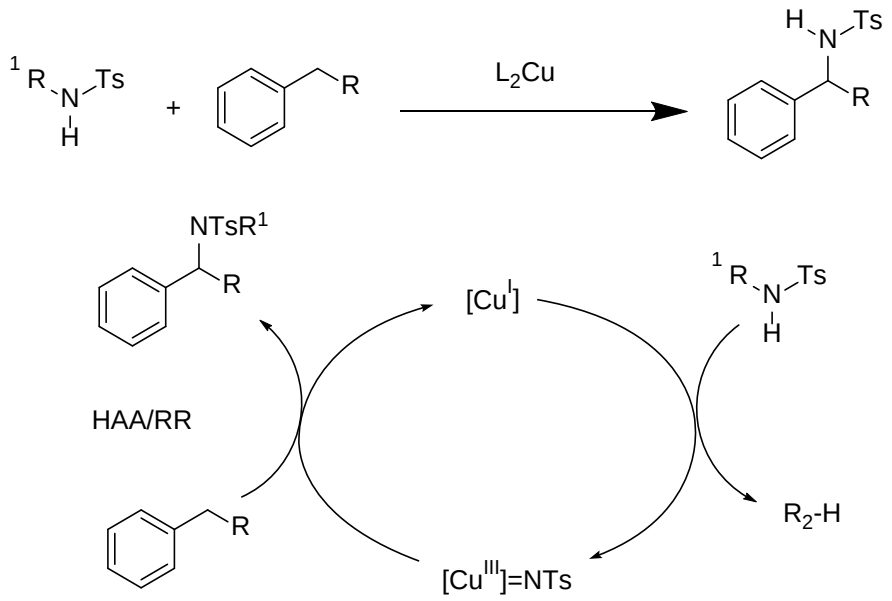


8

Figure 2. Dinitro-Substituted Biphenyldiamine Ligand

Mechanistic Studies

Due to the effectiveness of copper catalysis in benzylic amine formation, mechanistic aspects of the reactions were further investigated. A study conducted by Warren and Nicholas gave insight into the mechanism of copper catalyzed benzylic aminations.[18] The study determined that the amination reactions proceed through a hydrogen atom abstraction and radical rebound mechanism (HAA/RR), which abstracts a benzylic hydrogen from the substrate, followed by a radical rebound step between the respective amine creating the new C-N bond. Warren proposed the mechanism shown below (Scheme 8); support for their mechanistic proposal comes from isolating or synthesizing each key intermediate and testing their reactivity in stoichiometric reactions. Each cycle results in the regeneration of one amination reagent that is then reused in the subsequent cycle.



Scheme 8. Proposed Mechanism for Copper Catalyzed Amination

1.3.4 Issues to be Addressed

In summary, the issues with transition metal catalyzed benzylic C-H aminations described above provide the opportunity to add to the field. Many catalyzed methods involve expensive and scarce transition metals. In contrast, copper catalyzed aminations typically involve amination reagents that are not thermally stable, hazardous, show little variation in the introducible protecting groups, or are hydrolytically unstable. The lack of stability prevents large scale applications of these reagents. Additionally, many copper catalyzed systems have very limited substrate scopes and involve amination reagents that lack versatility.

1.4 Project Goal

The project reported on herein aims to utilize copper compounds to catalyze the direct amination of weak C-H bonds. The method developed should be versatile in the range of substrates it can aminate. Moreover, the amination reagent family developed should be able to install a wide variety of substituted amines. It would also be synthetically useful if the protecting group on the amination reagent is easily removable and potentially biologically active.

1.4.1 Approach

This project work is to expand the scope of amination reagents and substrates that can be employed for C-H amination with copper catalysts. A larger scope of amination reagents would provide insight into which aspects of the reagent structures lead to an

effective catalytic system. Additionally, a broader scope of substrates that can be aminated is needed to determine the versatility of the established C-H amination methodology.

Amination reagents for this project consist of a protecting group and a leaving group; the protecting group is bound to the N functionality of a hydroxylamine core, while the leaving group is bound to the respective O moiety (Figure 4). Desirable protecting groups must be either easily removable or biologically active – however, this research will also integrate if such a goal is achievable. Based on previous studies, an acetoxy leaving group and a tosyl protecting group are effective. Utilizing hydroxylamine-based amination reagents has shown improved thermal stability of the amination reagents.

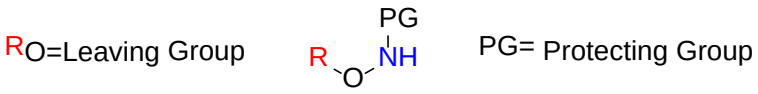
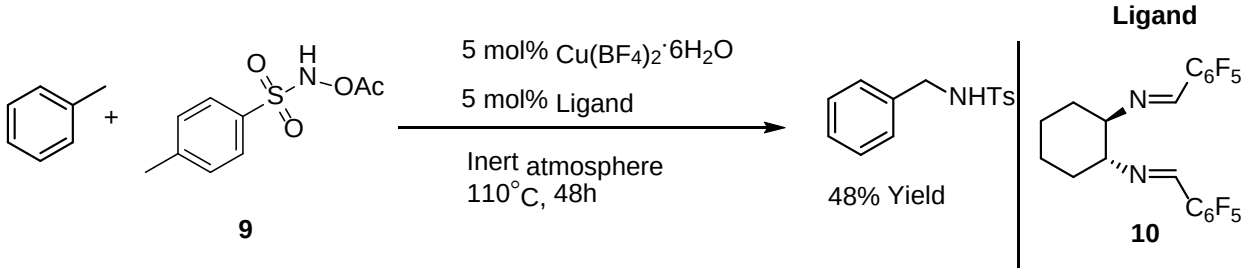


Figure 3. Amination Reagent Design

1.4.2 Knowledge at Project Start

At the start of this MQP project, research in the Emmert group had determined that the most effective benzylic C-H amination reaction conditions in hand produce yields of up to 48% (Scheme 9). The most widely employed amination reagent in the previous studies was N-acetoxy-4-methylbenzenesulfonamide (**9**), due to its ready availability. Additionally, through a screening of N-based ligands showed that diimine ligand (**10**) was superior at promoting benzylic C-H amination activity.



Scheme 9. Ligand Assisted Copper Catalyzed Benzylic Amination

With this knowledge as the starting point, the work reported herein focused on establishing a more comprehensive scope of amination reagents. Furthermore,

investigating steric and electronic effects of the amination reagent and substrates on the catalytic activity of the system was a goal for the reported studies together with establishing a general substrate scope of substrates with weak C-H bonds.

2. Results and Discussion

2.1 Results

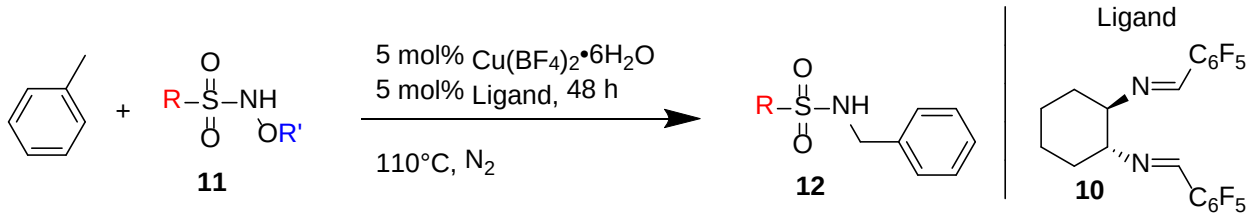
2.1.1 Amination Reagent Optimization

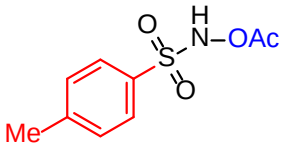
First, studies focused on determining structures of possible amination reagents for the amination of toluene. Work previously conducted by Anqi Wang in the Emmert group showed that running the reaction at 110 °C for 48 hours using ligand **10** has shown the highest yields of **2**. These conditions were employed for the herein described amination reagent screen.

Interestingly, yields were dependent on both the leaving group and the protecting group of the amination reagents (Table 1). The study shows that using pivalate or trifluoroacetate as the leaving groups decreases yields considerably when compared to the acetate leaving group. This suggests that the protecting group plays a major role in the catalytic activity of the amination reagents.

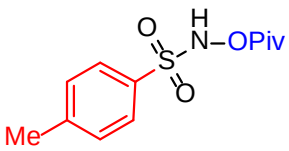
Additionally, replacing the protecting group with different substituents ultimately resulted in decreased yields in all cases. Particularly, both electron donating and withdrawing groups resulted in only decreases in yield. There are several possibilities for why this decrease in reactivity occurs. One possibility is that the catalytic activity of the system is not dependent on electronic donating and withdrawing effects and relies on other factors for reactivity. Also, other potential reason for this decrease in reactivity is lower stability of either the amination reagent or product formed when different electron donating or withdrawing substituents are added.

Table 1. Amination Reagent Scope.





48 ± 1%



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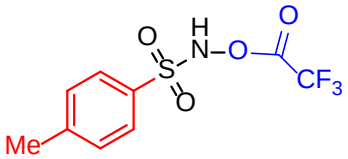

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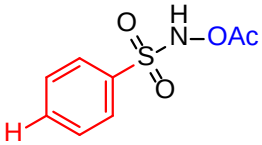
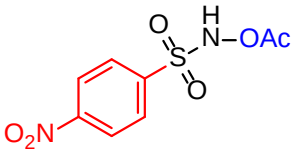


44 ± 1%



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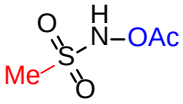

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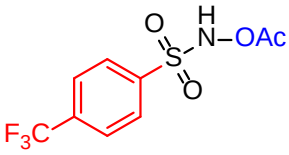

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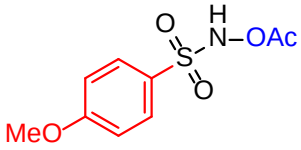

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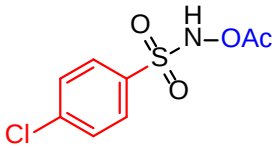


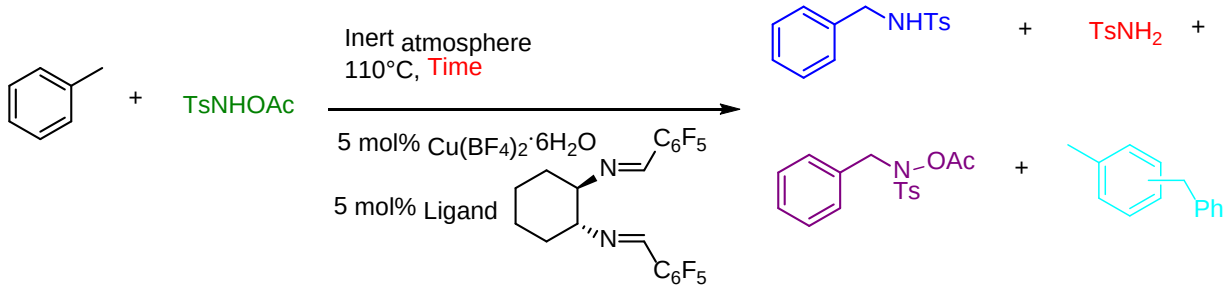
32 ± 2%

2.1.2 Time Study

To gain insight into the mechanism of the reaction, a time study was conducted (Figure 6). The formation and decomposition of the major reagents and products of our system were monitored over times ranging from 15 minutes to 48 hours. In the study the consumption of the amination reagent (TsNHOAc; grey line in Fig. 6) was nearly complete after the first 4 hours of reaction. In contrast, product formation (BnNHTs) was very slow for the first 4 hours. The rate of formation of BnNHTs increased from there until completion at 16 hours. This suggested that the reaction precedes an intermediate that was then converted into the product.

In independent studies[19], the intermediate in question was identified to be BnTsN-OAc; this intermediate formation and consumption is shown as a yellow trace in the time study: at about 4 hours into the reaction, intermediate formation had reached its peak, which correlates with the consumption of amination reagent observed previously. Additionally, from 4 to 16 hours the rate of formation of BnNHTs drastically increases.

Additionally, the rates of byproduct formation also proved to be interesting. The formation of $TsNH_2$ occurred on the same timeframe as the formation of intermediate (4 hours). This suggests that $TsNH_2$ is a byproduct of the formation of intermediate BnTsN-OAc. In contrast, the bitoyl sideproducts observed in the reaction are formed later on, concurrently with BnNHTs formation, suggesting that bitoyl formation occurs during the formation of BnNHTs from BnTsN-OAc.



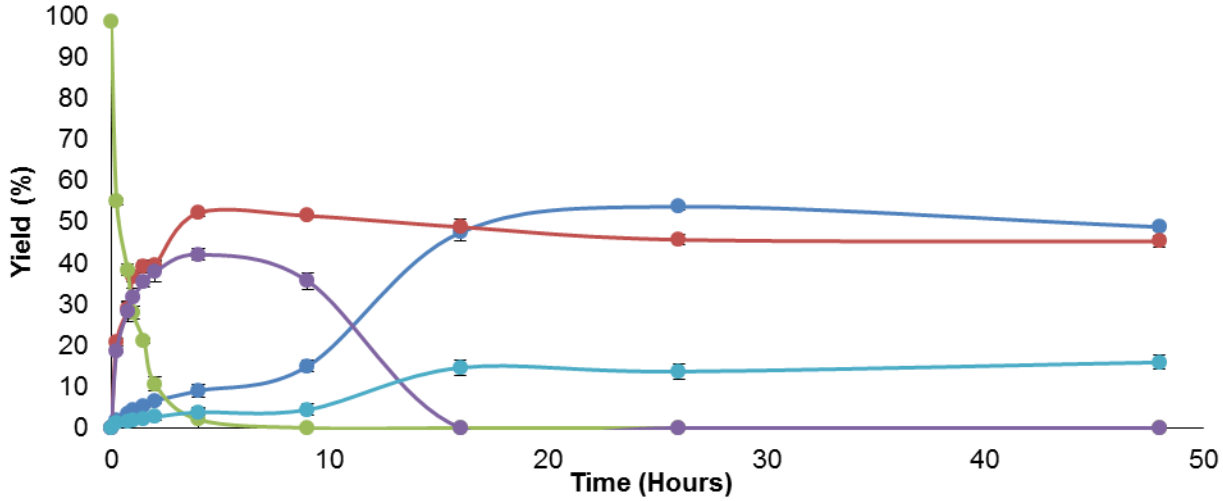


Figure 4. Time Study. Conditions: 5 mol% $Cu(BF_2)_2{\cdot}6H_2O$ (2.3 mg, 6.3 mmol), 5 mol% ligand (3.0 mg, 6.3 mmol), TsNHOAc (28.7 g, 0.125 mmol, 1 equivalent), and 2 ml (2 ml, 1.7 g, 18.8 mmol, 151 equivalent) dry toluene, heated at 110°C for X Time under nitrogen

2.1.3 Temperature Studies

Additionally, it was important to study the temperature dependences of the formation of BnNHTs, BnNTs-OAc, $TsNH_2$, and bitoyls (Figure 4). The reaction was run at several different temperatures keeping all other parameters constant. In this study, it was determined that the highest yield of product occurred at 110°C. However, the highest yield of intermediate (BnNTs-OAc) was seen at 90°C. From this data, questions about the activation barriers associated with the formation and consumption of intermediate were raised.

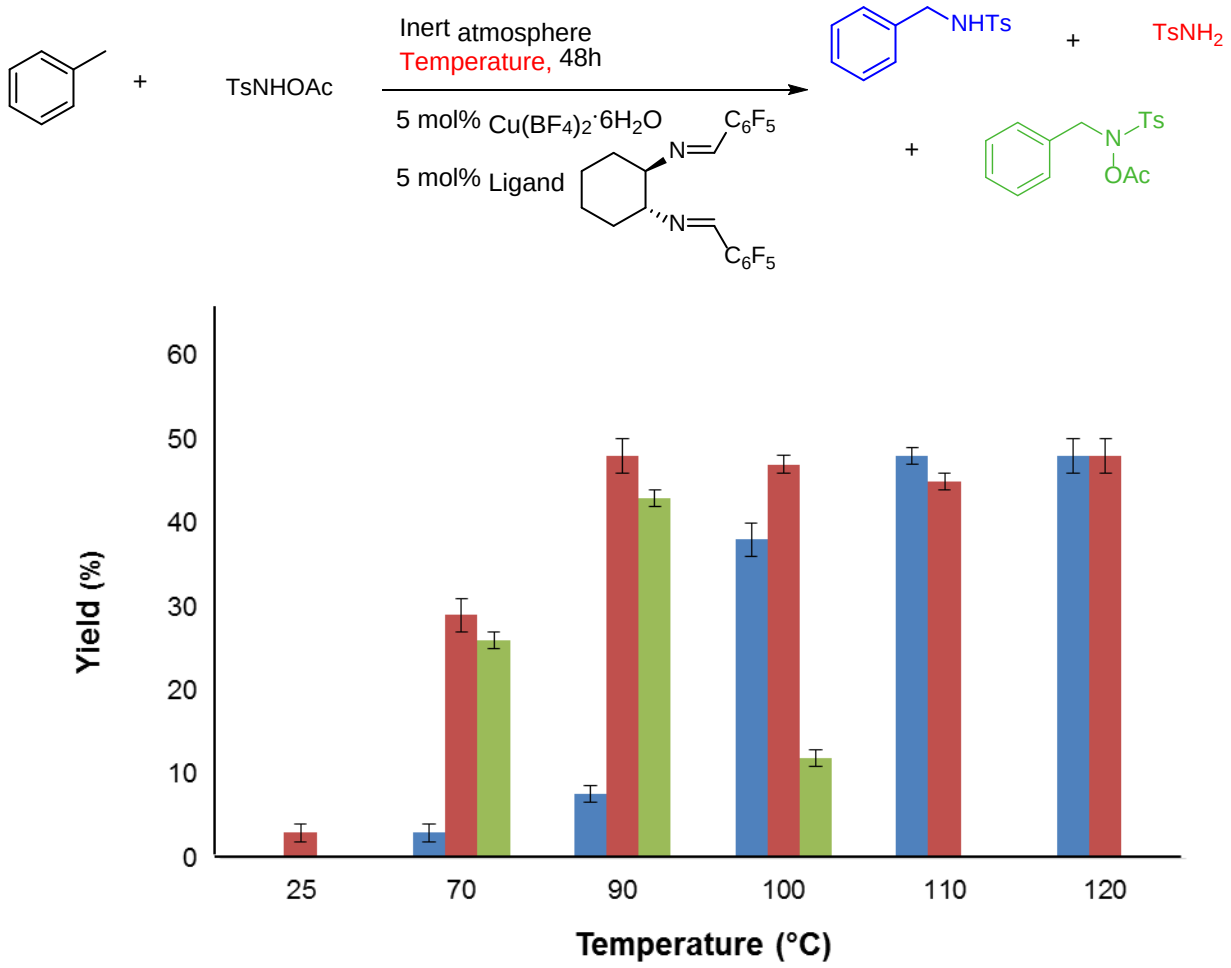


Figure 5. Catalytic Temperature Study. Conditions: 5 mol% $Cu(BF_2)_2 \cdot 6H_2O$ (2.3 mg, 6.3 mmol), 5 mol% ligand (3.0 mg, 6.3 mmol), TsNHOAc (28.7 g, 0.125 mmol, 1 equivalent), and 2 ml (2 ml, 1.7 g, 18.8 mmol, 151 equivalent) dry toluene, heated at the stated temperature for 48 hours under nitrogen.

2.1.4 Intermediate Studies

From here, we wanted to determine the relative activation barriers of both the formation and consumption of intermediate (Figure 5). Using an isolated batch of intermediate

BnTsn-OAc, a temperature study was performed under analogous conditions to Figure 4. It was observed that the highest yield of product BnNHTs was obtained at 110°C. This can be compared to the temperature study outlined above where the peak intermediate formation occurs at 90°C. The two studies described suggest that the formation of intermediate BnTsN-OAc has a significantly lower activation barrier than the conversion of -OAc to BnNHTs.

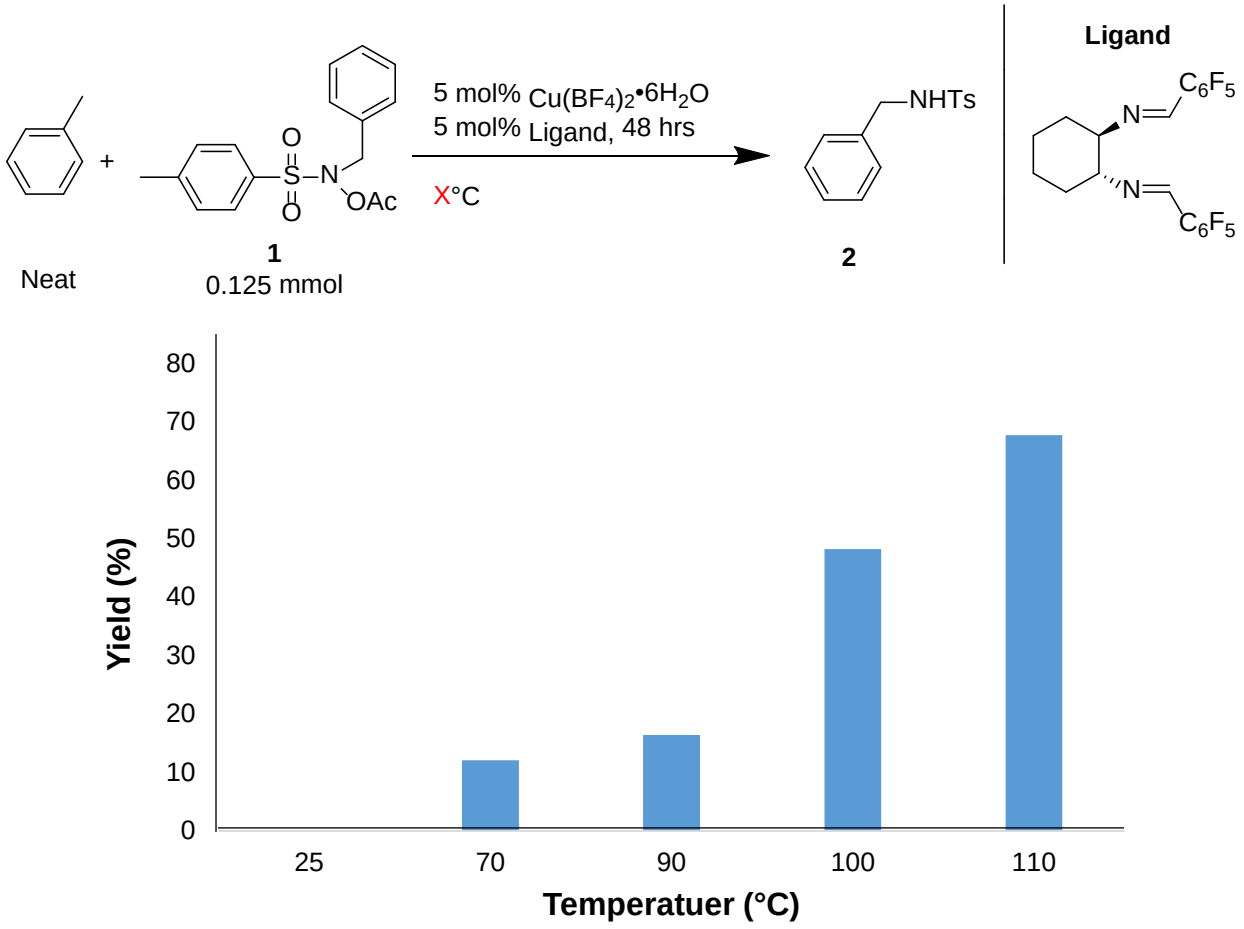
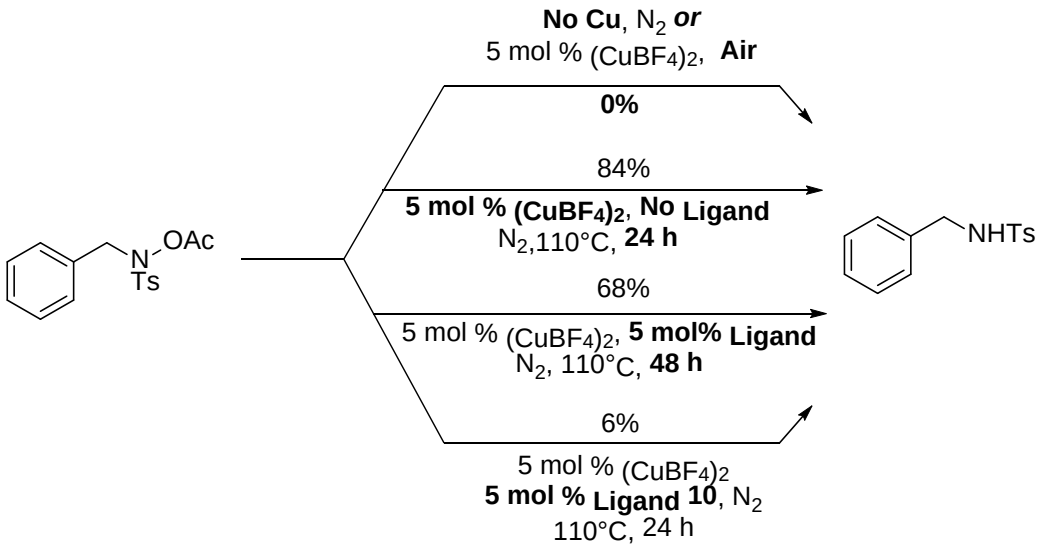


Figure 6. Intermediate Temperature Study. Conditions: 5 mol% $Cu(BF_4)_2 \cdot 6H_2O$ (2.3 mg, 6.3 mmol), 5 mol% ligand (3.0 mg, 6.3 mmol) and N-acetoxy-N-benzyl-4-methylbenzenesulfonamide (0.125 mmol, 38.1 mg), dry toluene (2 ml, 1.7 g, 18.8 mmol, 151 equivalent) stirred for 48 h X°C under N_2

Additionally, a study was conducted looking on the dependence of a catalyst for the conversion of BnTsN-OAc to BnTsNH (Scheme 10). The study tested the reaction over 24 hours. The study showed up to 84% conversion of BnTsN-OAc to BnTsNH in the presence of $Cu(BF_4)_2 \bullet 6H_2O$ and no ligand **10**. In contrast, in the presence of **10** the reaction had been restricted to just 6% conversion. This suggests that **10**, while necessary for the formation of BnTsN-OAc, actually inhibits formation of BnTsNH.

Also, since up to 67% conversion of BnNTs-OAc to BnNHTs occurs when the reaction is run for 48 hrs with **10**, it is believed that **10** decomposes during the course of the reaction. This allows for non-ligated copper to complete the formation of BnNHTs. This observation agrees with a ligand decomposition study conducted by Anqi that shows that **10** hydralizes over the course of the reaction.[19]



Scheme 10. BnNTs-OAc Intermediate Reactivity

2.1.5 Toluene Loading Studies

To see if the reaction is concentration dependent, a toluene loading study was conducted using several different equivalents of toluene ranging from 0.25 ml to 3.5 ml (Figure 7). In this study, it was observed that the reaction produces the most BnNHTs when 2 mL of toluene (146 equivalents) is used (48% BnNHTs). Slightly less yields were obtained at 1 ml, 2.5 ml, and 3.5 ml loadings (46 % BnNHTs for both). However, the yields decrease drastically when using 0.25 ml and 0.5 ml and there is a solid precipitate observed in the reaction vessel suggesting that the reaction may have solubility issues. The lower yields observed at low toluene loadings suggest that solubility of the reagents and/or catalyst may be an issue at lower loadings showing that the reaction is concentration dependent.

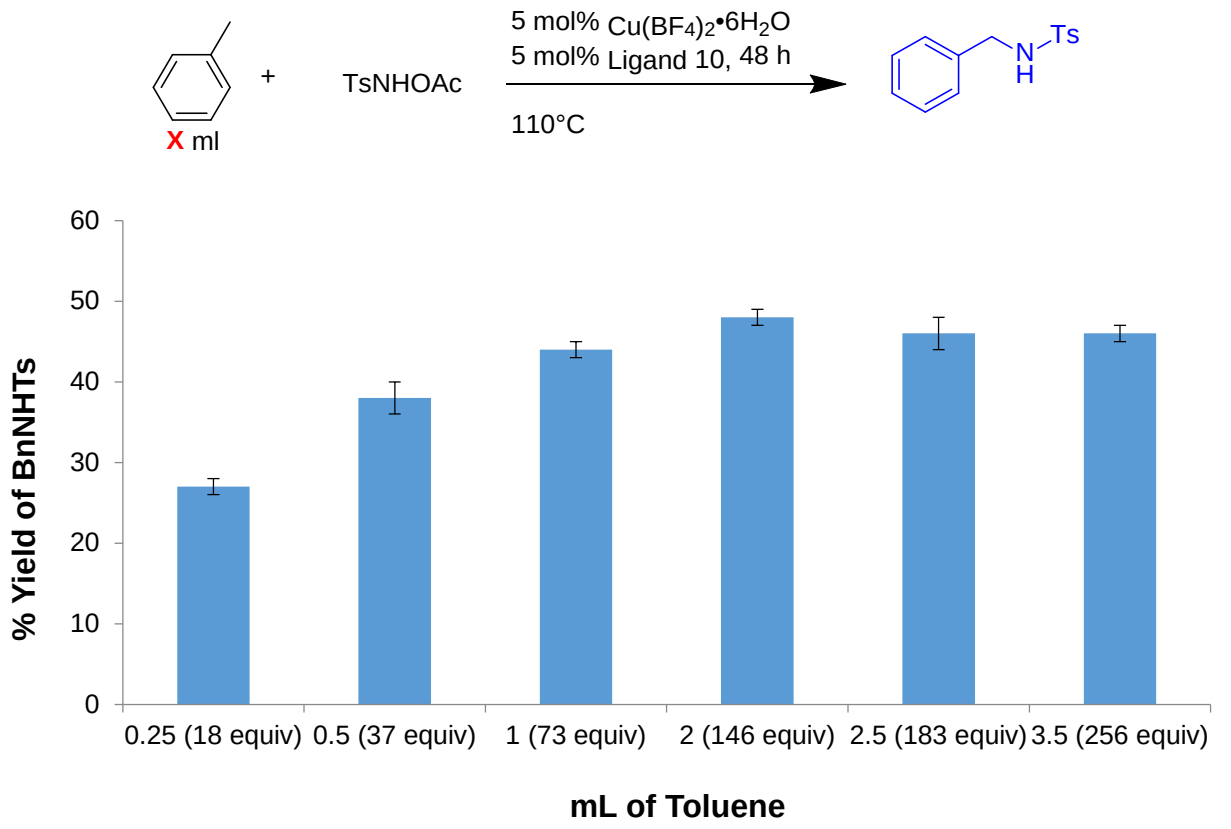


Figure 7. High Temperature Toluene Loading Study. Conditions: Toluene (0.25 - 3.50 mL, 0.22 - 3.03 g, 2.32 - 33.0 mmol, 18 - 146 equiv.), amination reagent 1 (28.7 mg, 0.125 mmol, 1.00 equiv), $Cu(BF_4)_2 \cdot 6H_2O$ (2.3 mg, 6.3 µmol, 5.0 mol%), ligand 3 (3.0 mg, 6.3 µmol, 5.0 mol), 48 h, 110°C, under N_2.

Additionally, a similar toluene loading study was run at 90°C too see if the conversion of intermediate (BnTsN-OAc) to product (BnTsNH) could be prohibited (Figure 8). It was observed in the study that lowering temperature allowed for relatively selective formation of BnTsN-OAc (6:1) when 2.0 ml of toluene was used. However, lower substrate loadings shows lower formation of BnTsN-OAc but similar formation of BnTsNH, showing lower intermediate selectivity. When toluene loading has been reduced to 0.5 ml, a selectivity of only 3.6:1 was observed. Additionally, the lowest loading resulted in high standard deviations and no reproducible data suggesting that solubility of the reagents and/or catalyst could be an issue that hinders reactivity.

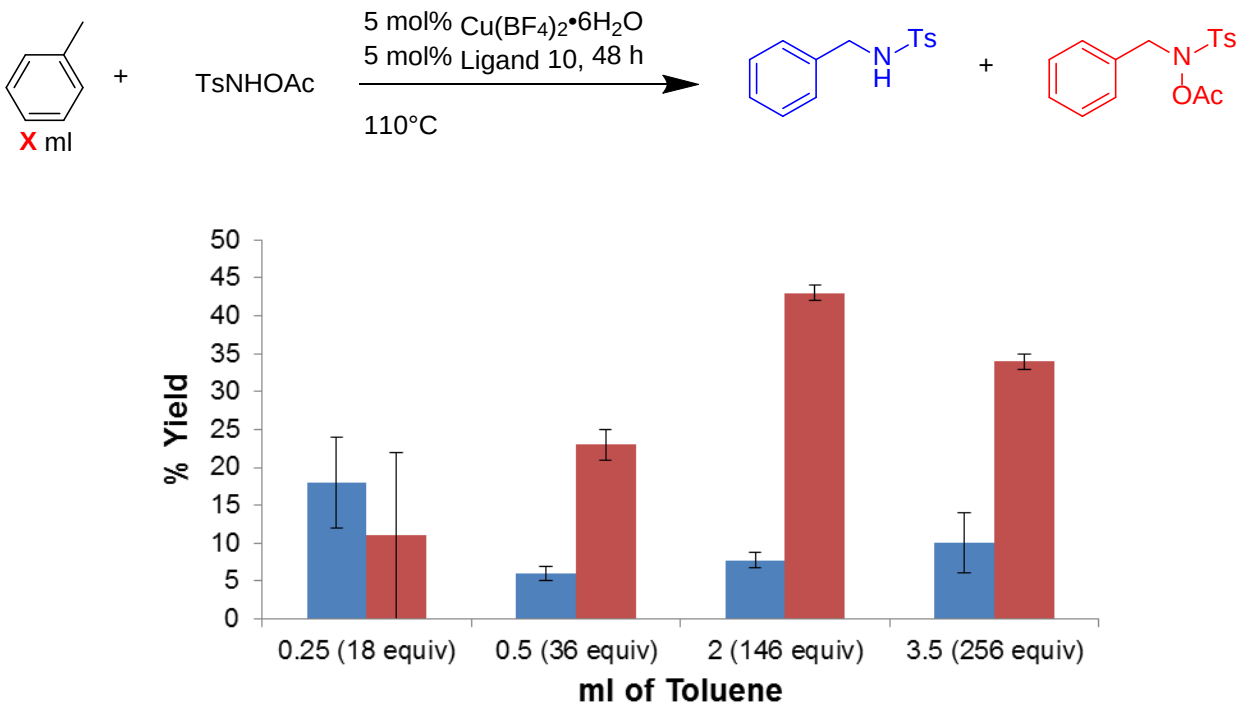


Figure 8. 90°C Toluene Loading Study. Conditions: Toluene (0.25 - 3.50 mL, 0.22 - 3.03 g, 2.32 - 33.0 mmol, 18 - 146 equiv.), amination reagent 1 (28.7 mg, 0.125 mmol, 1.00 equiv), $Cu(BF_4)_2 \cdot 6H_2O$ (2.3 mg, 6.3 µmol, 5.0 mol%), ligand 3 (3.0 mg, 6.3 µmol, 5.0 mol), 48 h at 90°C.

2.1.6 Hammett Study

In previous work conducted in the Emmert Group,[19] the inclusion of electron withdrawing and donating groups to the para-position of toluene only resulted in low to moderate decreases in yield with the exception of the methoxy substituted substrate. This suggests that electronic effects do not control the catalytic activity of the system and that there are more constraining underlying factors at work.

To further look into the possible stabilization effects of the electron-donating or electron withdrawing para-substituents, a Hammett study was conducted to look into how the initial rates of these reactions differed (Figure 9)**.**. However, the experiment resulted in no clear correlation between Hammett parameters or radical stabilization parameters (data on page 38). In each reaction, a blue or green precipitate formed quickly after heating. Due to the precipitation, of what is believed to be the copper catalyst because of the color, the kinetics of the reaction would have been heavily influenced. This solubility issue could have influenced the kinetic results and caused the discrepancies with the Hammett study.

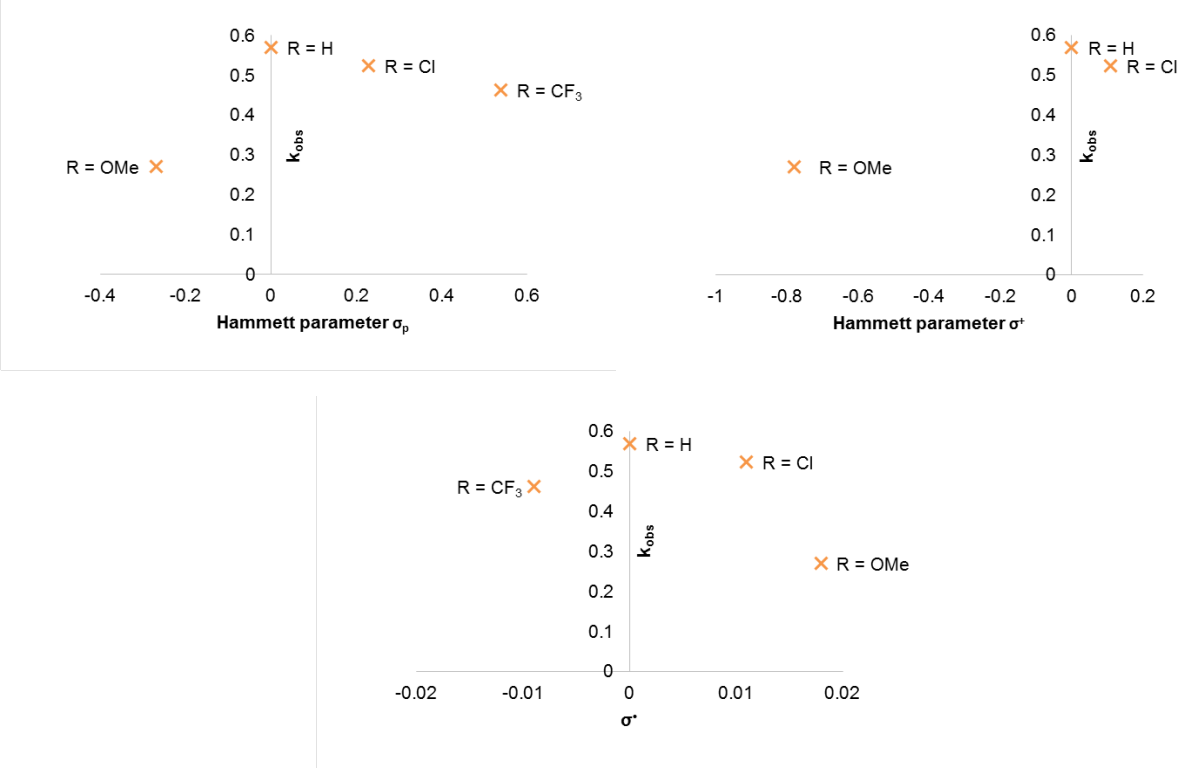


Figure 9: Plot of Initial Rates vs. Various Linear-Free-Energy-Relationship (LFER) Parameters.

2.1.7 Amination of THF

Under the same conditions as toluene amination, THF can be aminated as well, resulting in a yield of 67%.[19] To develop a more feasible reaction, the system must be able to run using much lower equivalents of substrate. To look into how the reactivity of THF differs when it is run in solvent, studies were run to see the effect of drastically lowering the substrate loading (Figure 10).

To start this study, reactions were run in benzene D-6 to determine if the amination of THF was possible with 1 to 1 ratios of THF to amination reagent. Benzene D-6 was chosen because it is easy solvent to analyses reactivity via NMR and does not have any benzylic C-H bonds that can interfere with the amination of THF. The experiment resulted in low yields of the aminated product of THF (6.4%). The same reaction run without copper or ligand **10** only showed trace amounts of the product via GC-MS. This suggests that the reaction is dependent on the copper catalyst. The same reaction was run using 4 equivalents of amination reagent, resulting in slightly higher yields of 17%. In contrast, when the reaction was run using 4 equivalents of THF and one equivalent of TsNHOAc the yield increased significantly to 32%.

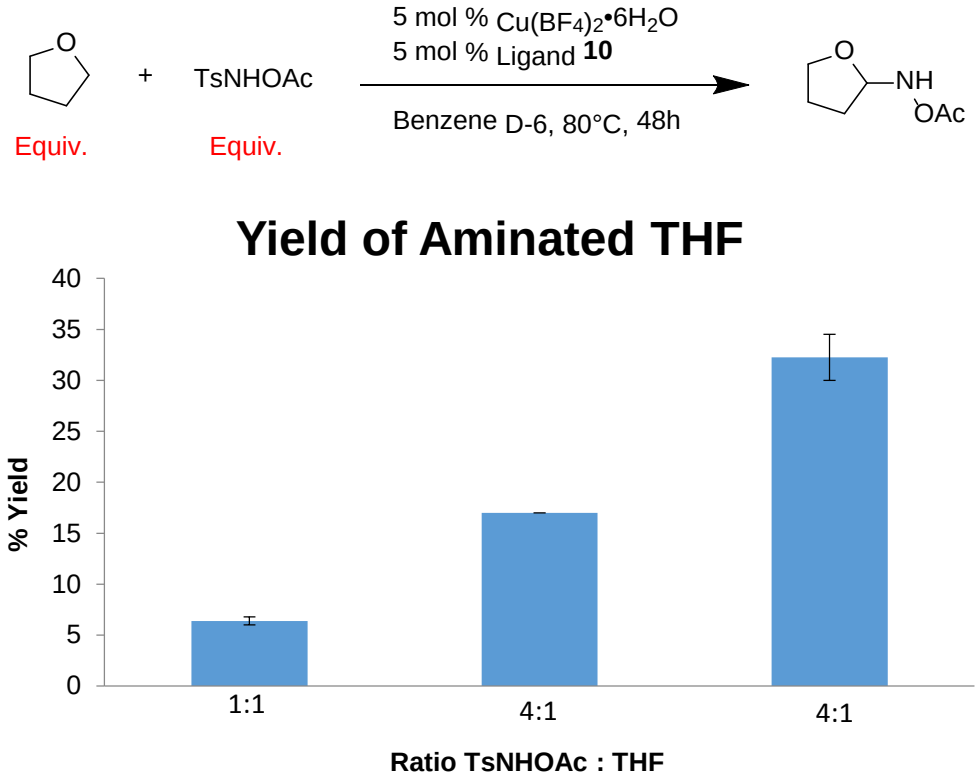


Figure 10. Low Loading THF Amination. Conditions: 5 mol% $Cu(BF_4)_2 \cdot 6H_2O$ (2.3 mg, 6.3 mmol), 5 mol% ligand (3.0 mg, 6.3 mmol), TsNHOAc, and 10 µl of THF in benzene D-6 (2ml) stirred for 48 hours at 80°C.

2.1.8 THF Amination Reagent Scope

To further optimize the low loading amination of THF, an amination reagent screen was conducted (Figure 10). The study was run at 80°C in benzene D-6 using a 1 to 1 ratio of amination reagent to THF. Interestingly, the best amination reagent for the amination of toluene (TsNHOAc) did not work as well as some other reagents with different protecting groups. While TsNHOAc only resulted in a 6.8% yield, $PhSO_2NHOAc$ and $MeSO_2NHOAc$ gave 23% and 18% yields respectively.

Of the amination reagents screened, only the reagents with a substituted sulfonyl protecting group and acetoxy leaving group showed any significant yields (full scope shown on page 40).

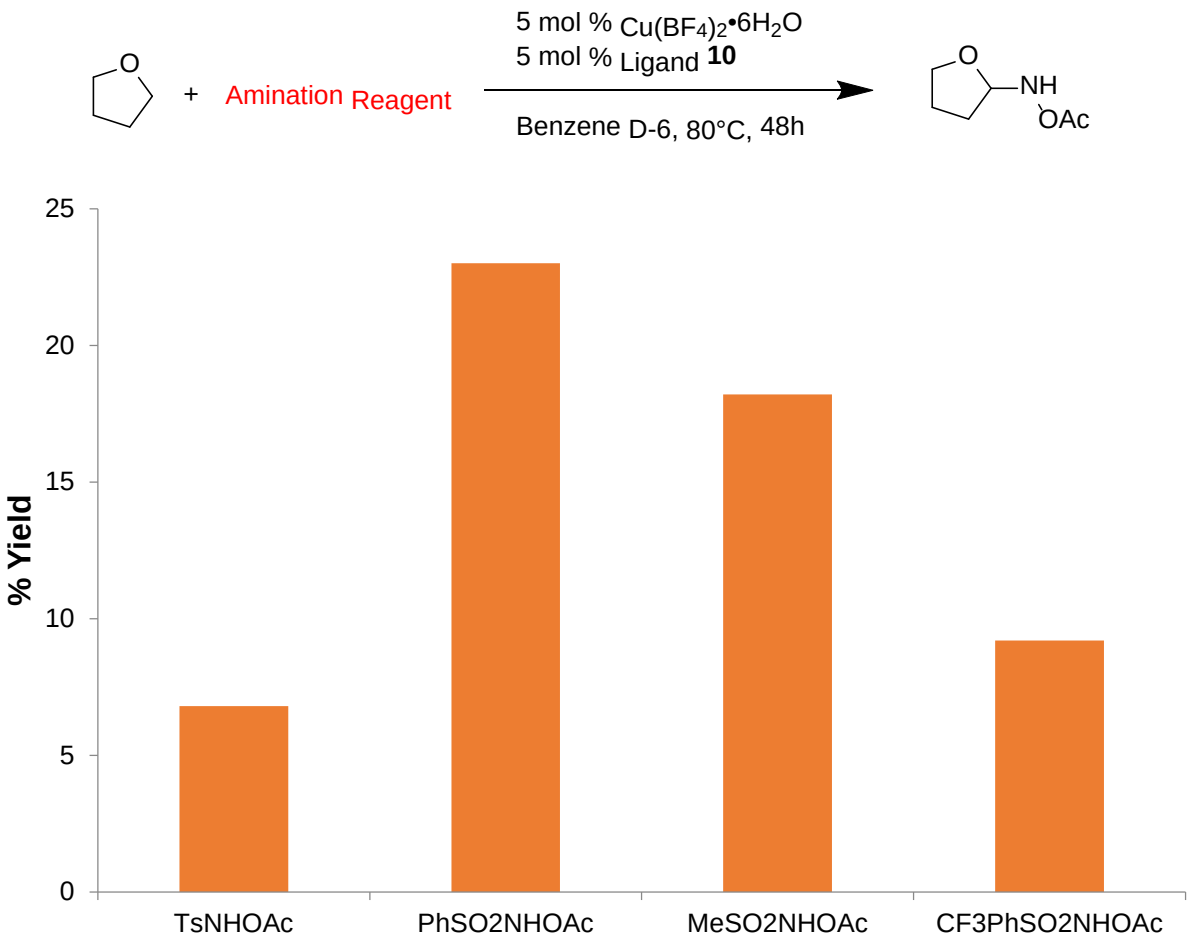
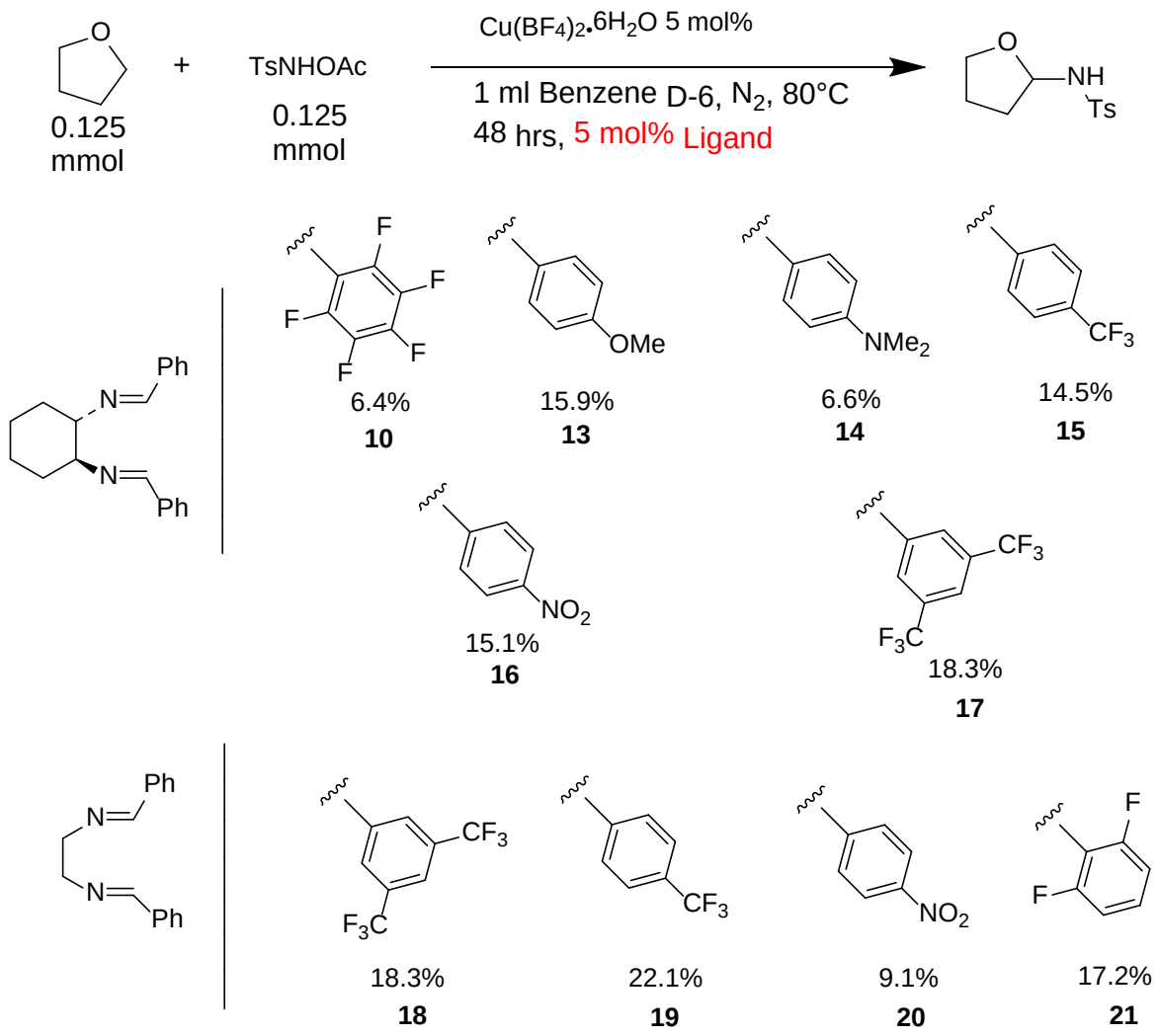


Figure 11. THF Amination Reagent Scope Conditions: 5 mol% $Cu(BF_4)_2 \cdot 6H_2O$ (2.3 mg, 6.3 mmol), 5 mol% ligand (3.0 mg, 6.3 mmol), 0.125 mmol of the designated amination reagent, and 10 µl of THF (8.9 mg, 0.125 mmol, 1 equivalent) in dry benzene-d_6 (1ml) stirred for 48 hours at 80°C

2.1.9 Amination of THF Ligand Screen

To continue the optimize THF amination a ligand screen was run in order to determine which ligand would be most reactive with our complex. From the study it was seen that ligand **10**, the best ligand for the amination of toluene, only produced a yield of about 6% when used for THF amination (Scheme 11). The highest yields of aminated THF were seen when using diimine ligands with trifluoromethyl electron withdrawing groups at various positions on the phenyl group. For instance, ligands **17**, **18**, and, **19** showed yields of 18% to 22%. Additionally, it appears that for the amination of THF the non-cyclic diimine ligands are more effective.



Scheme 11. Amination of THF Ligand Screen. Conditions: 5 mol% $Cu(BF_4)_2 \cdot 6H_2O$ (2.3 mg, 6.3 mmol), 5 mol% of the tested ligands (6.3 mmol), 0.125 mmol of the designated amination reagent, and 10 µl of THF (8.9 mg, 0.125 mmol, 1 equivalent) in dry benzene-d_6 (1ml) stirred for 48 hours at 80°C

3. Conclusions and Future Directions

Several conclusions can be drawn from the results shown above, the first being the role of the ligand in the amination process. Ligand **10** is vital for the formation of the BnNTs-OAc intermediate. However, ligand **10** inhibits the formation of BnNHTs from BnNTs-OAc as is shown above in the intermediate studies. Due to the inhibition from the ligand and the apparent reliance on un-ligated copper to transition from BnNTs-OAc to BnNHTs, it appears that developing a ligand that is more stable and produces more intermediate would increase the yields of this system.

Also, further research needs to be done to look into the enantiomeric specificity of the reaction. Ligand **10** is chiral so if any specificity can be determined the system can be optimized to be more selective. Additionally, the reaction has to be able to proceed without having an extreme excess of substrate, as it does now. Optimizing the ligand system to stop reacting once the intermediate has been formed can help with this, because then the reaction mechanism will not require three equivalents of substrate to react.[19]

4 Experimental

4.1 General Procedures: Techniques, Solvents, and Chemicals

Except for the indicated schemes, all reactions were run under air. All solvents used were technical grade. Solvents and other reagents used studies were purchased from Sigma Aldrich. All solvents used in catalytic reactions were dried over 4 Å molecular sieves and degassed. The molecular sieves were activated under vacuum at 150°C for 24 hours prior to use. To degas solvents, the freeze-pump-thaw method was used. The solvent was then moved into a glove box that was kept under N_2 atmosphere.

4.2 Analytical Methods

4.2.1 NMR Spectroscopy

^{1}H NMR spectra were measured on a Bruker BioSpin 500MHz Avance III Digital NMR spectrometer (^{1}H: 500MHz). Abbreviations to describe the amination reagent peaks are as follows: *s*: singlet, *d*: doublet, *t*: triplet, *q*: quartet, *quin*: quintet, *hex*: hextet, *sept*: septet, *br*: broad, *m*: multiplet. Yields were determined in catalytic reactions by utilizing an internal standard of 1,3-dinitrobenzene. The standard solution in $CDCl_3$ was calibrated to be 8.55 ppm.

^{13}C NMR spectra were measured on Bruker BioSpin 500MHz Avance III Digital NMR spectrometer (^{13}C: 125MHz). ^{19}F NMR spectra was sent to Clark University for analysis.

4.2.2 GC-MS

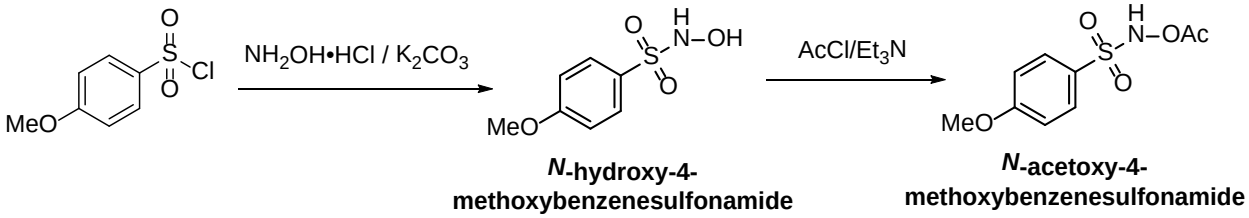
GC-MS was used to confirm product formation and to identity possible byproducts in catalytic reactions. GC-MS measurements were performed on a GC-MS System 5975 Series Quadrupole.

4.2.3 HRMS

HRMS data obtained from Notre Dame mass spectroscopy center.

4.3 Amination Reagent Synthesis

4.3.1 Synthesis of N-Acetoxy-4-methoxybenzenesulfonamide (2NJV Page 6)



Scheme 12. Synthesis of N-Acetoxy-4-methoxybenzenesulfonamide

4.17 g (60 mmol, 2.00 equiv) of hydroxylamine hydrochloride were added to 18 mL of water at 0 °C. A solution of 8.29 g (60 mmol, 2.00 equiv) K_2CO_3 was added to 12 mL of water and added to the hydroxylamine hydrochloride solution. The solution was allowed to stir for 15 minutes. THF (15 mL) and methanol (3.75 mL) were then added to the reaction vessel. Finally, 6.20 g (30 mmol, 1 equiv) of 4-methoxybenzenesulfonamide was added to the solution portion-wise. The solution was left to stir overnight at room temperature. The mixture was concentrate under vacuum to remove the organic solvents. The resulting aqueous suspension was extracted with 2 x 100 mL diethyl ether. The combined organic phases were dried over magnesium sulfate and filtered. The solvent of the filtrate was removed under vacuum to produce 3.90 g of crude *N*-hydroxy-4-methoxybenzenesulfanamide which was used in the next synthetic step without further purification.

3.90 g (19.2 mmol, 1 equiv) of crude *N*-hydroxy-4-methoxybenzenesulfanamide were dissolved in 150 mL of THF at -78°C. Then, 2.68 mL (1.64 g, 19.2 mmol, 1.00 equiv) of triethylamine was added dropwise to the solution. After stirring for 15 minutes, 1.36 mL (1.5 g, 19.2 mmol, 1.00 equiv) of acetyl chloride was added dropwise to the solution. The solution was left to stir at -78°C for four hours. Next, the organic solvents were removed under vacuum and 100 mL of DCM was added to the residue. The organic phase was washed with 2 x 30 mL of saturated potassium carbonate solution and the aqueous phases were combined. The combined aqueous phases were acidified with concentrated hydrochloric acid until pH 2. The product was extracted from the aqueous phase with dichloromethane (2 x 50 mL). The combined organic phases were dried over Magnesium Sulfate and filtered. The solvent of the resulting filtrate was removed under vacuum. The sample was then recrystallized using 2 ml of ethyl acetate and hexane dropwise until precipitate formed. The sample was allowed to cool in the freezer until all product crystallized. Solvent was removed using a pipet and the sample was dried under vacuum to afford 230 mg (4.9% yield) N-Acetoxy-4-methoxybenzenesulfonamide.

^{1}H NMR (500 MHz, $CDCl_3$, 25 ºC): δ [ppm] = 8.90 (s, 1H; NH), 7.86 (d, 2H; Ar-H), 7.01 (d, 2H; Ar-H), 3.89 (s, 3H, C*H*$_3$OPh-), 2.05 (s, 3H, -COC*H*$_3$);

^{13}C (NMR 125 MHz, $CDCl_3$, 25 ºC): δ [ppm] = 169.2, 164.6, 131.2, 126.5, 114.7, 55.9, 18.3 ;

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3375 (br), 3228 (s), 3193 (s), 1764 (s), 1595 (s), 1578 (s), 1497 (s), 1458 (s), 1438 (s), 1418 (s) 1369 (s), 1350 (s), 1325 (s), 1313 (s), 1257 (s), 1155 (s), 1092 (s), 1016 (s), 993 (s), 946 (s), 831 (s), 804 (s), 707 (s);

HRMS calc. 268.0250 (M+Na N-Acetoxy-4-methoxybenzenesulfonamide)., found 268.0260.

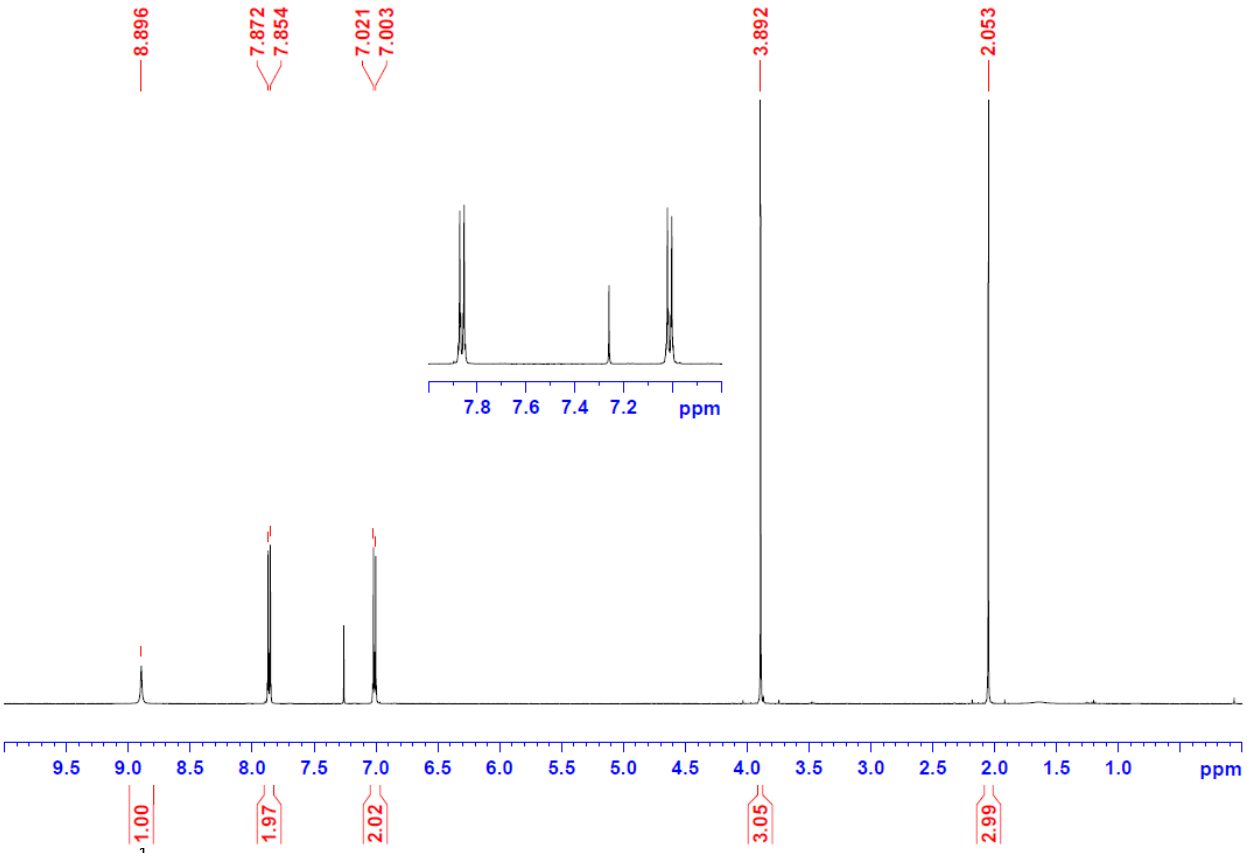


Figure 12. ^{1}H NMR of N-Acetoxy-4-methoxybenzenesulfonamide in $CDCl_3$

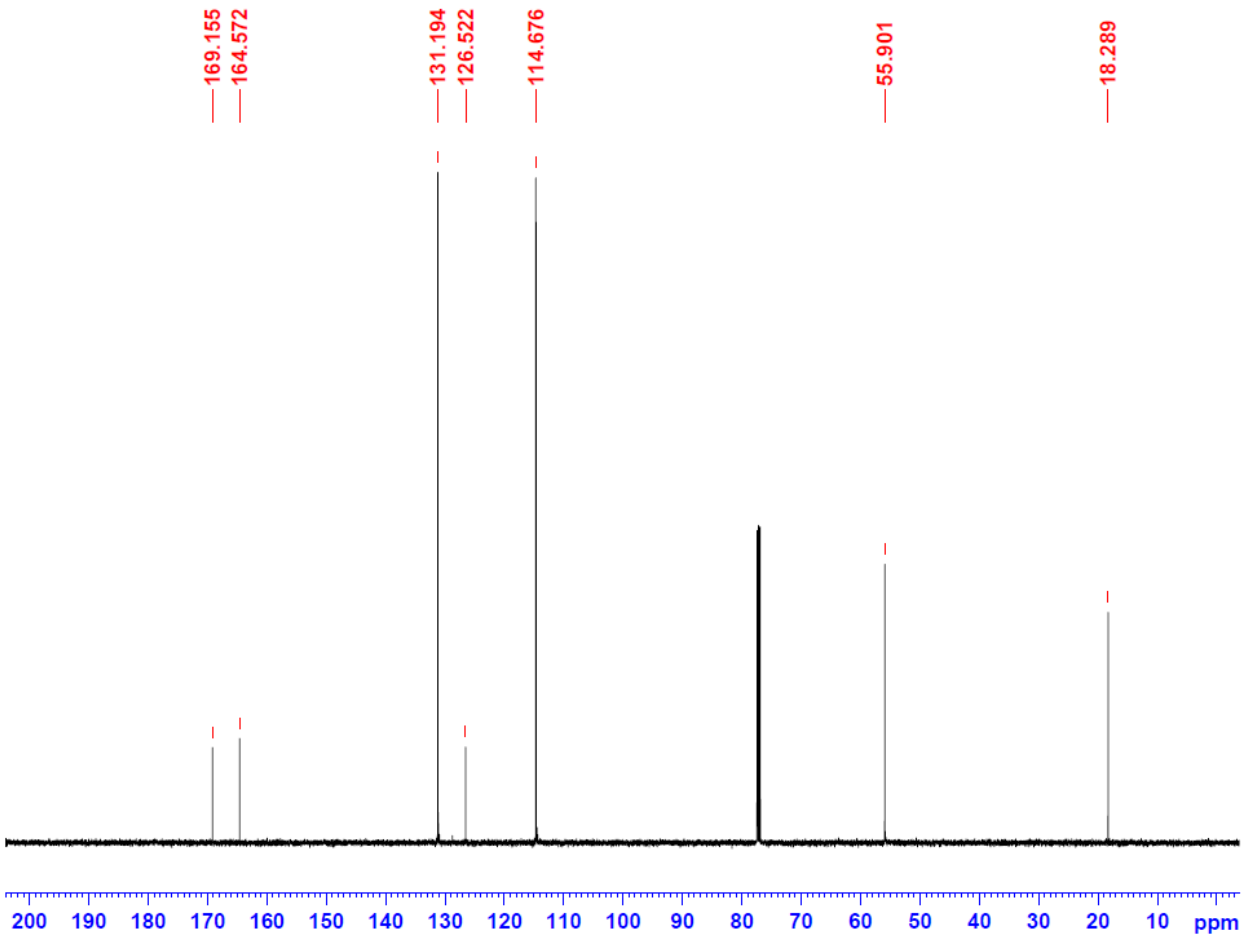
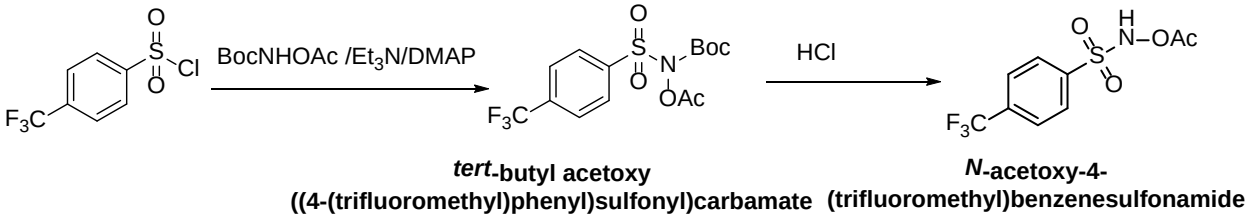


Figure 13. ^{13}C NMR of N-Acetoxy-4-methoxybenzenesulfonamide in $CDCl_3$

4.3.2 Synthesis of N-acetoxy-4-(trifluoromethyl)benzenesulfonamide (2NJV Page 9)



Scheme 13. Synthesis of N-acetoxy-4-(trifluoromethyl)benzenesulfonamide

First, 1.20 g (5.40 mmol, 0.95 equiv) of 4-(trifluoromethyl)benzenesulfonyl chloride, 1.0 g (5.7 mmol, 1 equiv) tert-butyl acetoxycarbamate, and 69.0 mg (0.57 mmol, 0.1 equiv) DMAP were dissolved in 20 mL of dichloromethane. Then, 1.6 mL (1.64g, 19.2 mmol, 1 equiv) of triethylamine was added dropwise and the reaction was left to stir overnight at room temperature. The solution washed with 30 mL of 1 M hydrochloric acid and then extracted using 100 mL of dichloromethane twice and dried over magnesium sulfate. The solvent of the filtrate was removed under vacuum. The crude product with a R_f value of was purified with a silica column using hexane and ethyl acetate (2:1). The solvent of the resulting solution was removed under vacuum. The resulting solid was then recrystallized using 2 ml of ethyl acetate and hexane dropwise until precipitate forms. The solution was then left in the freezer overnight and the solvent was removed using a pipet. The solid was then dried under vacuum resulting in 230 mg (15% yield) of N-acetoxy-4-(trifluoromethyl)benzenesulfonamide**.**

^{1}H NMR (500 MHz, $CDCl_3$, 25 ºC): δ [ppm] = 8.92 (s, 1H; NH), 7.88 (d, 2H; Ar-H), 7.55 (d, 2H; Ar-H), 2.09 (s, 3H, -COC$\underline{H_3}$);

^{13}C (NMR 125 MHz, $CDCl_3$, 25 ºC): δ [ppm] = 169.0, 136.2 (q), 129.4, 126.6 (q), 123.2 (q), 18.2 ppm;

IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3132 (s), 1770 (s), 1406 (s), 1377 (s), 1320 (s), 1169 (s), 1133 (s), 1109 (s), 1091 (s), 1062 (s), 1015 (s), 987 (s), 953 (s), 837 (s), 790 (s), 726 (s), 695 (s), 654 (s);

^{19}F (NMR 188.2 MHz, $CDCl_3$, 25 ºC): δ [ppm] =-63.32(s);

HRMS calc. 306.0018 (M+Na), found 306.0022.

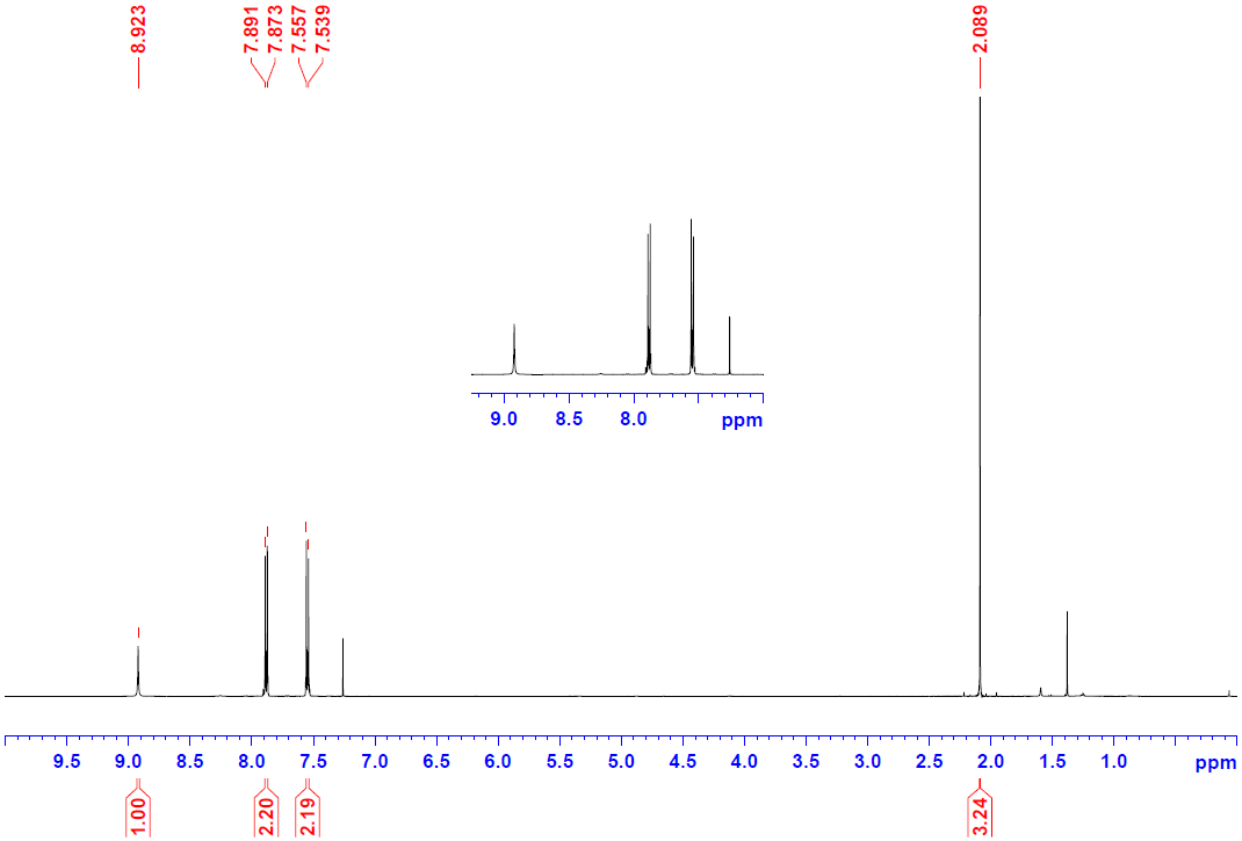


Figure 14. ^{1}H NMR of N-acetoxy-4-(trifluoromethyl)benzenesulfonamide in $CDCl_3$

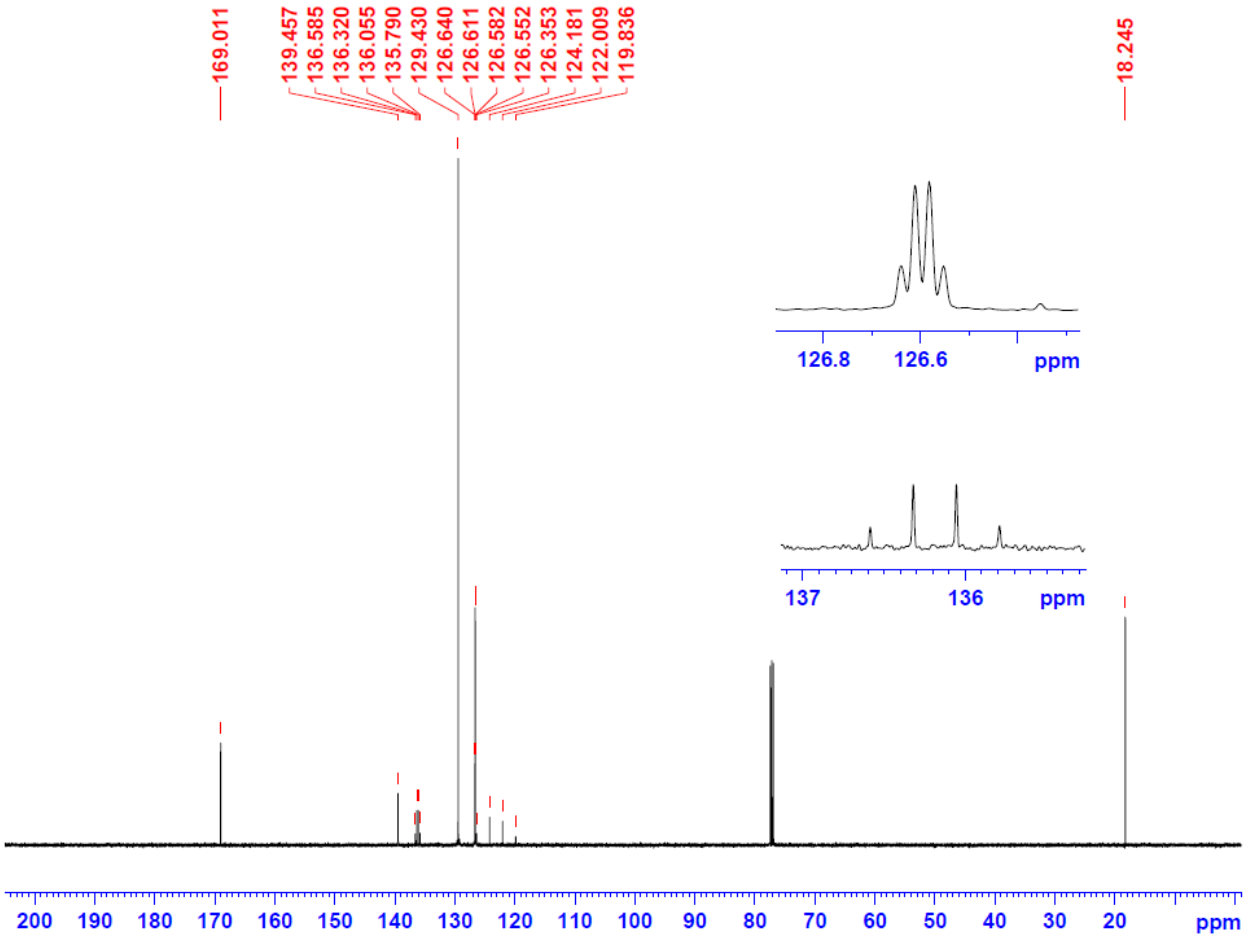


Figure 15. ^{13}C NMR of N-acetoxy-4-(trifluoromethyl)benzenesulfonamide in $CDCl_3$

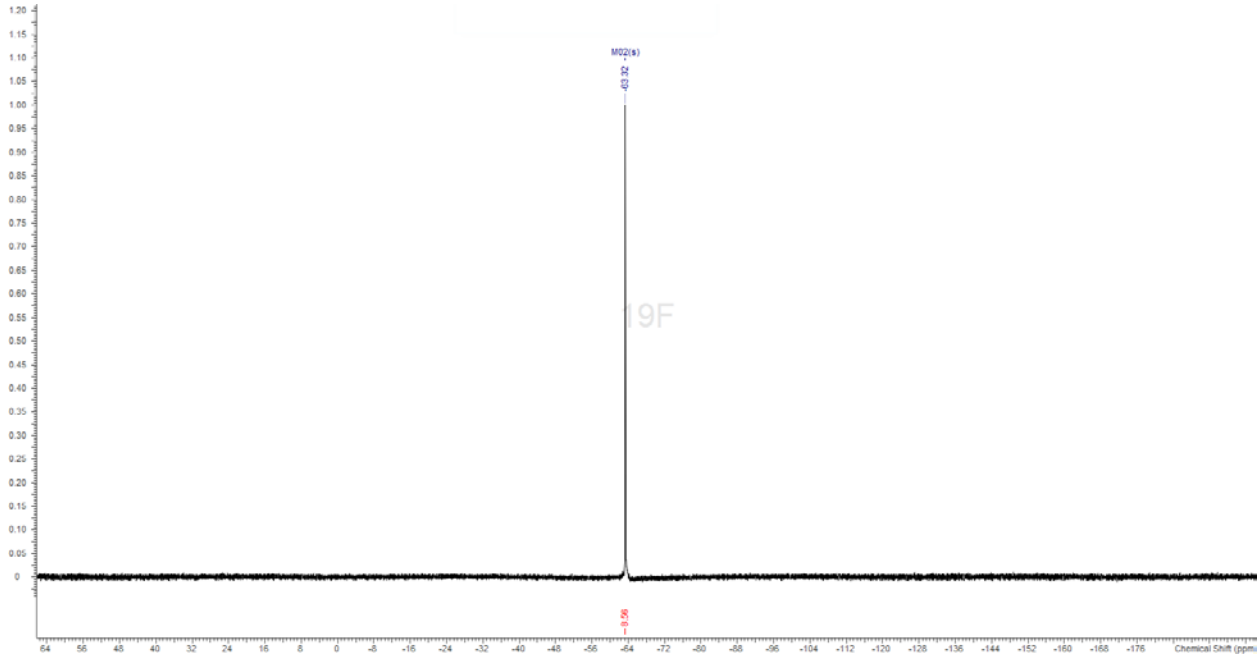
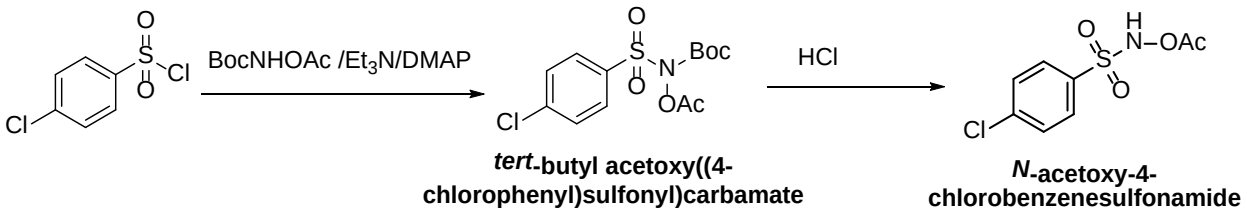


Figure 16. ^{19}F NMR of N-acetoxy-4-(trifluoromethyl)benzenesulfonamide in $CDCl_3$

4.3.3 Synthesis of N-Acetoxy-4-chlorobenzenesulfonamide (2NJV Page 17)



***tert*-butyl acetoxy((4-chlorophenyl)sulfonyl)carbamate** **N-acetoxy-4-chlorobenzenesulfonamide**

Scheme 14. Synthesis of N-Acetoxy-4-chlorobenzenesulfonamide

First, 2.29 g (10.8 mmol, 0.95 equiv) 4-chlorobenzenesulfonyl chloride, 2.0 g (11.4 mmol, 1 equiv) tert-butyl acetoxycarbamate, and 138.0 mg (1.14 mmol, 0.1 equiv) DMAP were dissolved in 40 mL of dichloromethane. Then, 3.2 mL (3.4 g, 38.4 mmol, 2 equiv) of triethylamine was added dropwise and the reaction was left to stir overnight at room temperature. The solution was washed with 30 mL of 1M hydrochloric acid and then extracted using 100 mL of dichloromethane twice and dried over magnesium sulfate. Solvent was removed using rotary evaporator. The crude product with a R_f value of 0.72 was purified with a silica column using hexane and ethyl acetate (2:1). The resulting solution was then recrystallized using 2 ml of ethyl acetate and hexane added dropwise until precipitate formed. It was then stored in the freezer overnight allowing crystallization. Solvent was then removed using a pipet and the remaining solid was dried under vacuum resulting in 167 mg (6.2% yield) of N-acetoxy-4-chlorobenzenesulfonamide**.**

^{1}H NMR (500 MHz, $CDCl_3$, 25 ºC): δ [ppm] = 8.92 (s, 1H; NH), 7.88 (d, 2H; Ar-H), 7.55 (d, 2H; Ar-H), 2.09 (s, 3H, -COC$\underline{H_3}$);

^{13}C (NMR 125 MHz, $CDCl_3$, 25 ºC): δ [ppm] = 169.0, 141.5, 134.0, 130.2, 129.8, 18.3;

IR (ATR): $\tilde{\nu}$ [cm^{-1}]= 3153 (s), 1773 (d), 1475 (s), 1417 (s), 1352 (s), 1197 (s), 1180 (s), 1165 (s), 1088 (s), 1012 (s), 824 (s), 764 (s), 734 (s), 648 (s);

HRMS calc. 249.9935 (M+H), found 249.9925.

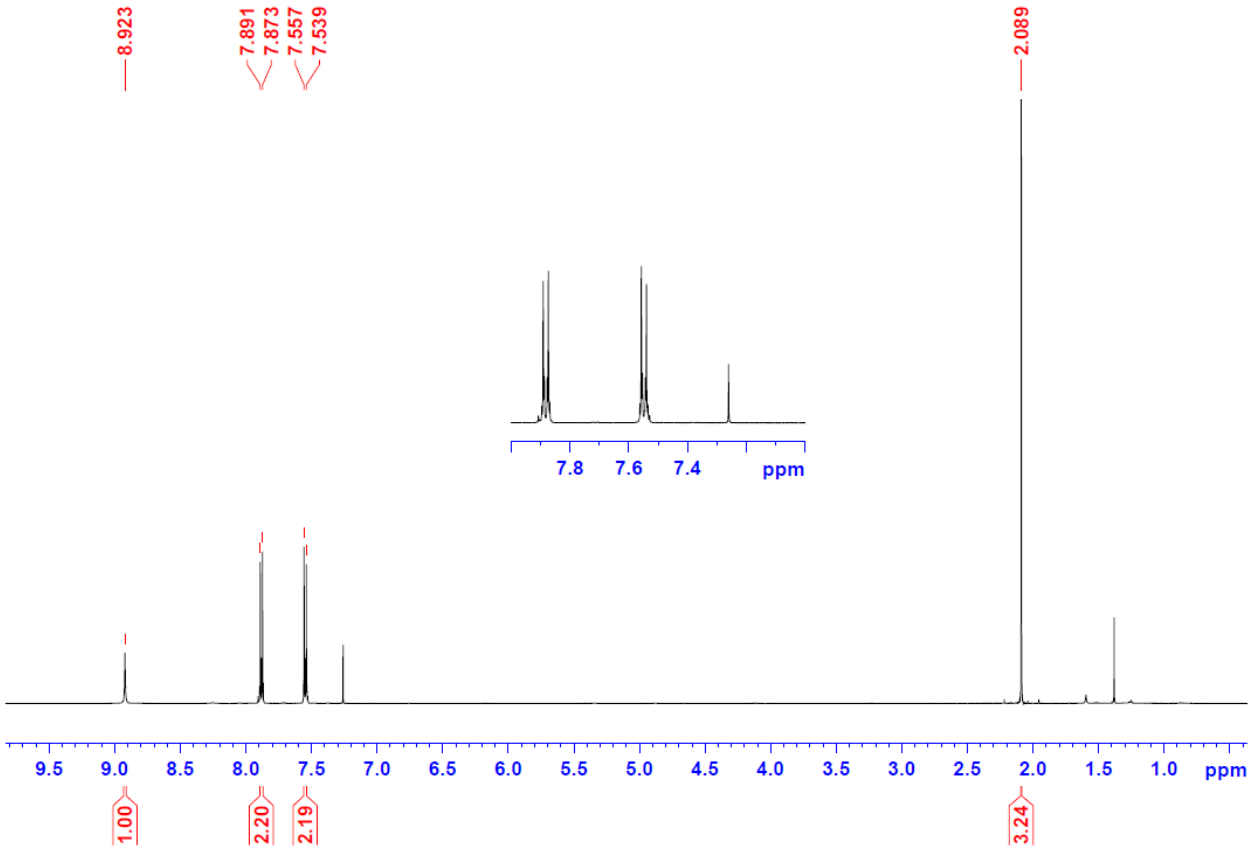


Figure 17. ^{1}H NMR of N-Acetoxy-4-chlorobenzenesulfonamide in $CDCl_3$

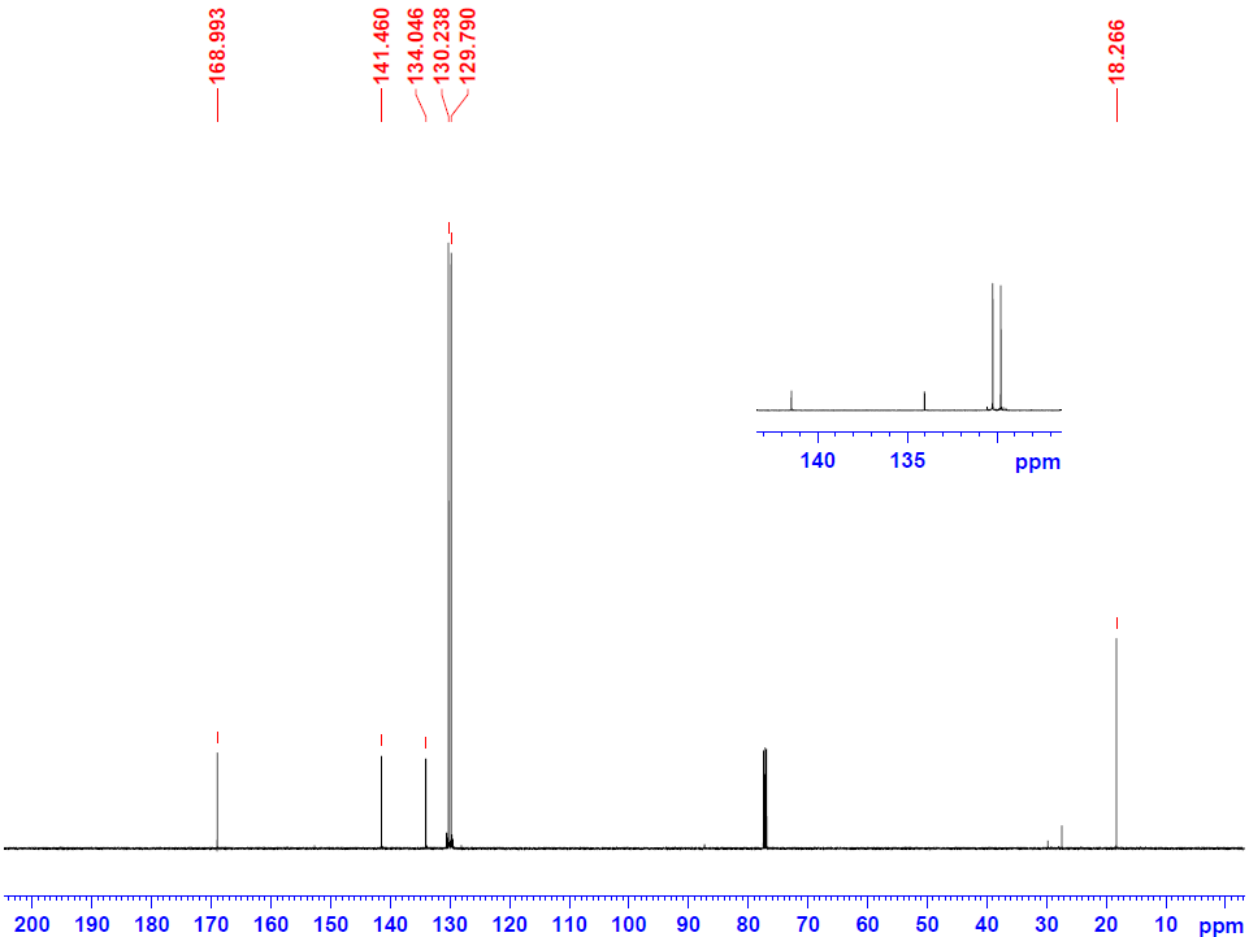
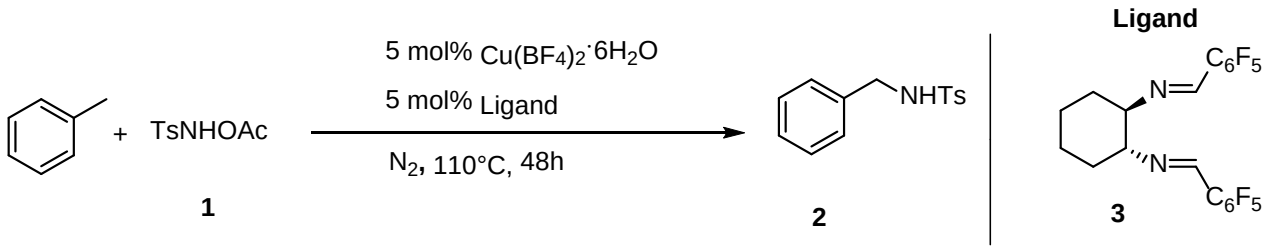


Figure 18. ^{13}C NMR of N-Acetoxy-4-chlorobenzenesulfonamide in $CDCl_3$

4.4 Catalytic Studies (Amination of Toluene)

4.4.1 Representative Catalytic Procedure



Scheme 15. General Catalytic Procedure

5 mol% $Cu(BF_2)_2 \cdot 6H_2O$ (2.3 mg, 6.3 mmol), 5 mol% **3** (3.0 mg, 6.3 mmol) and amination reagent **1** (28.7mg, 0.125 mmol, 1 equivalent) were added to a 4 ml vial under a N_2 atmosphere. Dry toluene (2.0 ml, 1.7 g, 18.8 mmol, 151 equivalent) was added to the vial and the vial was sealed tightly with a Teflon-lined vial cap. The resulting mixture was placed on a pre-heated hotplate and heated for 48 hours at 110 °C. The mixture was transferred to a 40 ml vial and the vial was rinsed with acetone (2 mL); the acetone phase was combined with the rest of the mixture. The solvents were removed under vacuum. The remaining solid was mixed with 0.5 mL of a 1H NMR standard solution of 1,3-dinitrobenzene (5.0 mg, 29 µmol) in $CDCl_{3;}$ after filtering through Celite, the filtrate was analyzed by quantitative 1H NMR to determine the crude catalytic yield. The yield of **2** was determined by comparing the integrals corresponding to the benzylic CH_2 group in **2** to the integral corresponding to the aromatic protons of 1,3-dinitrobenzene (8.55 ppm).

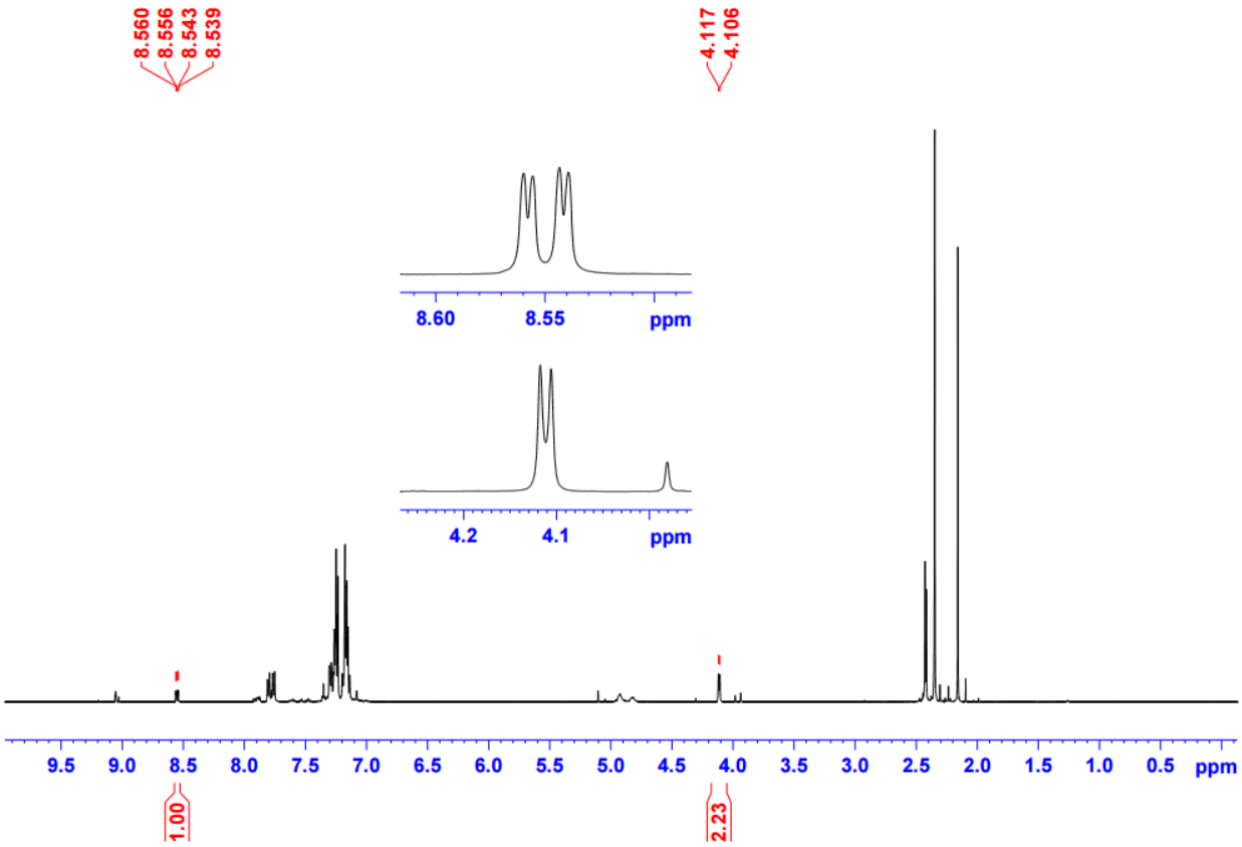
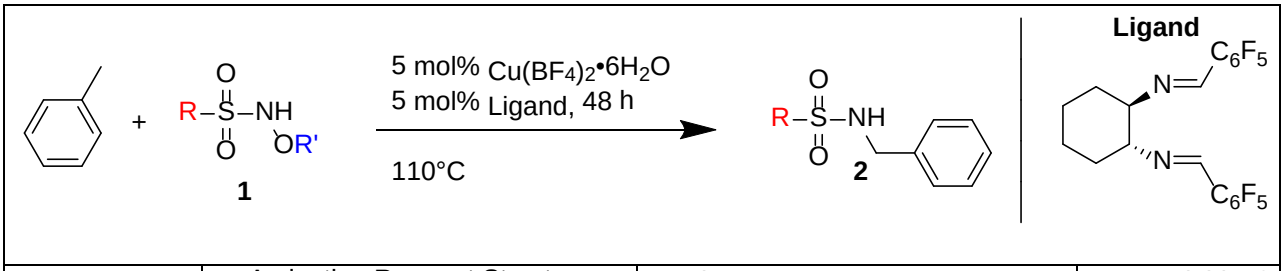
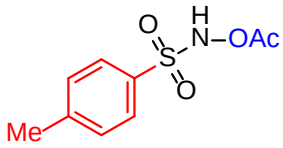
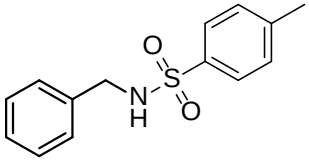
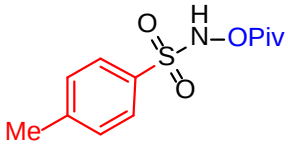
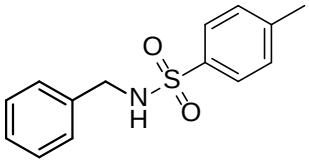
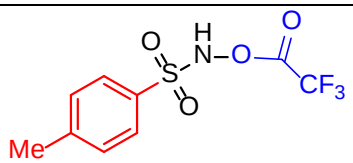
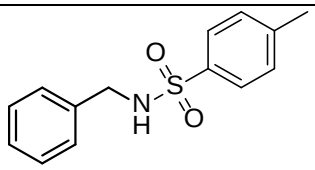
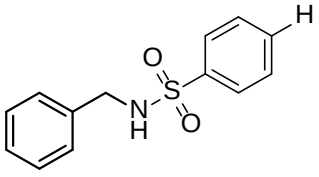
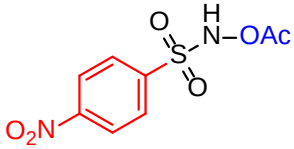
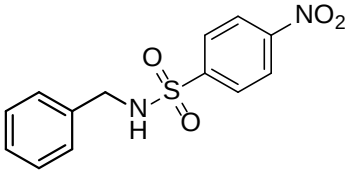


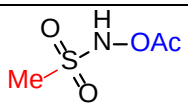
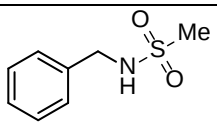
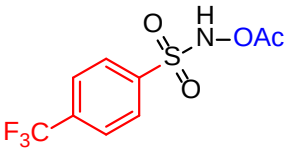
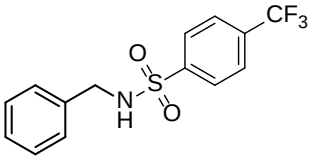
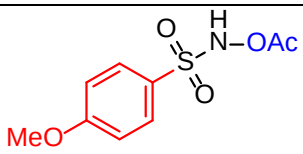
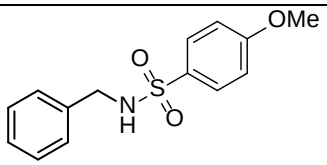
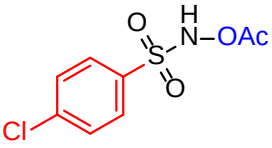
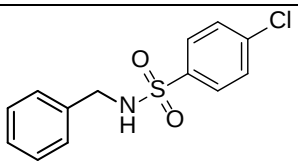
Figure 19. Example Spectrum of Crude Reaction Mixture with 1,3-Dinitrobenzene

4.4.2 Amination Reagent Screen (2NJV Pages 14, 15, and 23)

Table 2. Amination Reagent Screen: Conditions 5 mol% $Cu(BF_2)_2 \cdot 6H_2O$ (2.3 mg, 6.3 mmol), 5 mol% ligand (3.0 mg, 6.3 mmol), amination reagent **1** (0.125 mmol, 1 equivalent), and 2 ml (2 ml, 1.7 g, 18.8 mmol, 151 equivalent) dry toluene, heated at 110°C for 48 hours under nitrogen.

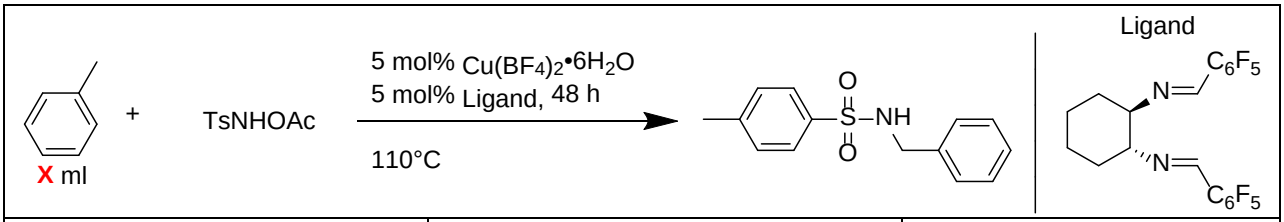


Entry	Amination Reagent Structure	Product Structure	NMR Yield of **2**
1			48 ± 1%
2			34± 1%
3			4 ± 1%
4			44 ± 1%
5			35 ± 1%

6			40 ± 1%
7			28 ± 2%
8			26 ± 1%
9			32 ± 2%

4.4.3 Toluene Loading Study

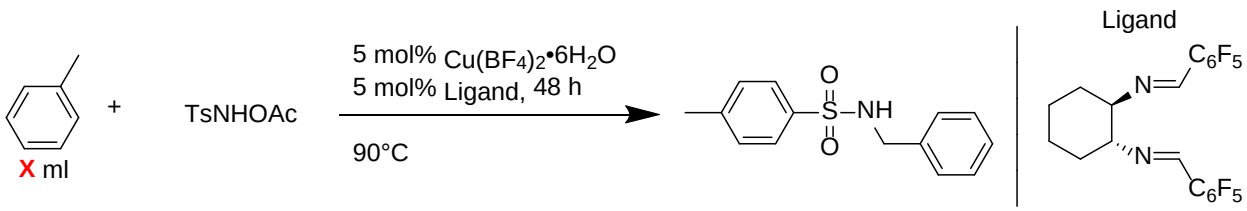
Table 3. Toluene Loading Study. Conditions: Toluene (0.25 - 3.50 mL, 0.22 - 3.03 g, 2.32 - 33.0 mmol, 18 - 146 equiv.), amination reagent 1 (28.7 mg, 0.125 mmol, 1.00 equiv), $Cu(BF_4)_2 \cdot 6H_2O$ (2.3 mg, 6.3 µmol, 5.0 mol%), ligand 3 (3.0 mg, 6.3 µmol, 5.0 mol), 48 h. The reactions were prepared according to the Representative Procedure for Catalytic Benzylic Amination Reactions



mL of Toluene	Equivalents of toluene to Amination Reagent	Yield
0.25	18	27 ± 1%
0.5	36	38 ± 2%
1	72	44 ± 1%
2	144	48 ± 1%
2.5	183	46 ± 2%
3.5	256	46 ± 1%

4.4.4 Toluene Loading Study 90°C (2NJV Page 31)

Table 4. Low Temperature Toluene Loading Study. Conditions: Toluene (0.25 - 3.50 mL, 0.22 - 3.03 g, 2.32 - 33.0 mmol, 18 - 146 equiv.), amination reagent 1 (28.7 mg, 0.125 mmol, 1.00 equiv), $Cu(BF_4)_2 \cdot 6H_2O$ (2.3 mg, 6.3 µmol, 5.0 mol%), ligand 3 (3.0 mg, 6.3 µmol, 5.0 mol), 48 h at 90°C. The reactions were prepared according to the Representative Procedure for Catalytic Benzylic Amination Reactions

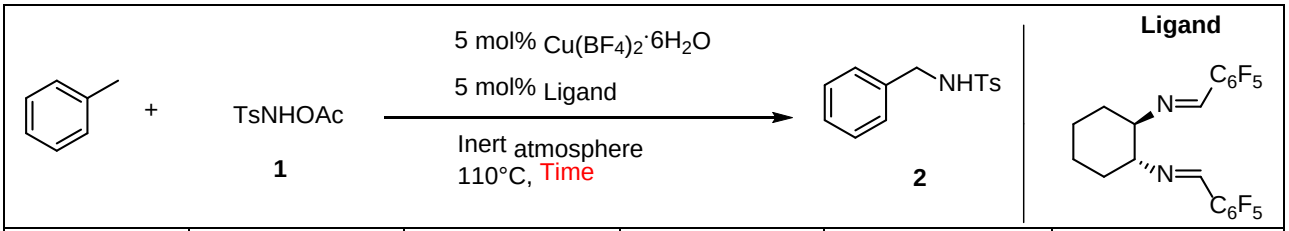


Entry	mL of Toluene	Yield of $TsNHCH_2Ph$	Intermediate Yield	$TsNH_2$	Bitoyl
1	0.25	18 ± 6%	11 ± 11%	32 ± 3%	3 ± 2%
2	0.5	6 ± 1%	23 ± 2%	32 ± 1%	3 ± 1%
3	2	7.7 ± 1%	43 ± 1%	48 ± 2%	5 ± 1%
4	3.5	10 ± 4%	34 ± 1%	35 ± 3%	4 ± 1%

4.4.5 Time Study (2NJV Page 27)

This time study followed the standard catalytic setup and workup procedures outlined above. The reactions were run over several different time intervals and the NMR analysis was used to determine the yields of product as well as, byproduct and intermediate yields.

Table 5. Time Study of amination of toluene with TsNHOAc Conditions 5 mol% $Cu(BF_2)_2 \cdot 6H_2O$ (2.3 mg, 6.3 mmol), 5 mol% ligand (3.0 mg, 6.3 mmol), TsNHOAc (28.7 g, 0.125 mmol, 1 equivalent), and 2 ml (2 ml, 1.7 g, 18.8 mmol, 151 equivalent) dry toluene, heated at 110°C for the stated time under nitrogen. Experiment found on 2NJV27C and 2NJV27D.



Time (hour)	$TsNHCH_2Ph$ Yield	$TsNH_2$ Yield	TsNHOAc Yield	bitol total Yield	Intermediate Yield
0.0	0.0 ± 0.0%	0.0 ± 0.0%	98.5 ± 0.1%	0.0 ± 0.0%	0.0 ± 0.0%
0.25	1.9 ± 0.2%	20.8 ± 0.9%	54.8 ± 0.9%	1.2 ± 0.1%	18.5 ± 0.2%
0.75	3.3 ± 0.2%	28.8 ± 1.5%	38.3 ± 1.5%	1.5 ± 0.1%	28.2 ± 2.4%
1.0	4.2 ± 0.1%	36.6 ± 1.2%	27.9 ± 1.6%	1.9 ± 0.1%	31.7 ± 2.2%
1.5	5.4 ± 0.3%	39.1 ± 1.5%	21.1 ± 0.5%	2.2 ± 0.2%	35.3 ± 1.0%
2.0	6.6 ± 0.7%	39.5 ± 1.2%	10.7 ± 1.8%	2.7 ± 0.7%	37.9 ± 2.6%
4.0	9.0 ± 1.6%	52.1 ± 0.8%	2.03 ± 2.9%	3.8 ± 0.8%	42.0 ± 1.3%
9.0	15.0 ± 1.3%	51.4 ± 0.46%	0.00 ± 0.0%	4.4 ± 1.4%	35.6 ± 2.0%
16.0	47.4 ± 2.1%	48.7 ± 1.8%	0.00 ± 0.0%	14.6 ± 1.8%	0.0 ± 0.0%
26.0	53.6 ± 0.8%	45.6 ± 1.2%	0.0 ± 0.0%	13.7 ± 1.8%	0.0 ± 0.0 %
48.0	48.7 ± 0.9%	45.2 ± 1.4%	0.0 ± .00%	15.9 ± 1.8%	0.0 ± 0.0%

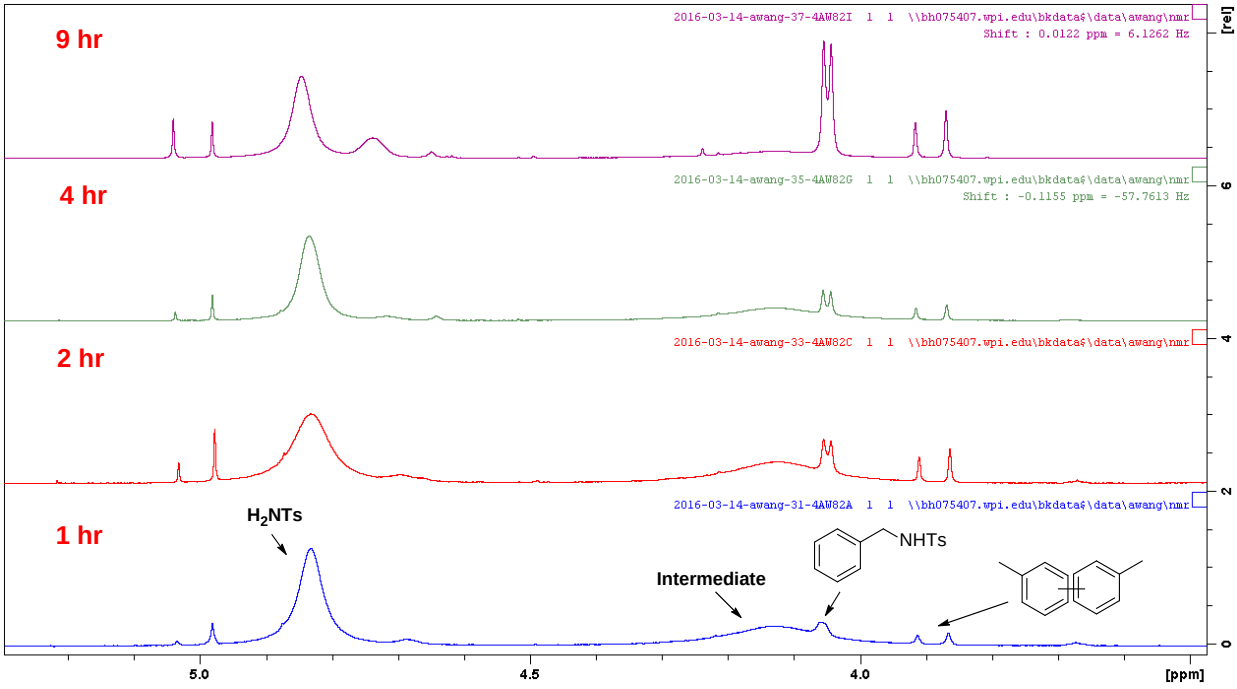
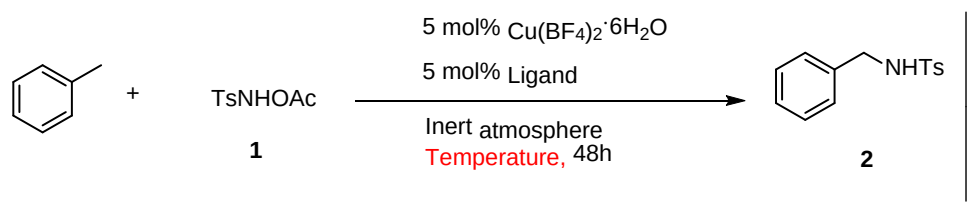


Figure 20. ^{1}H NMR comparison of time study

4.4.6 Temperature Study (2NJV Page 26)

Table 6. Temperature study conditions: 5 mol% $Cu(BF_2)_2 \cdot 6H_2O$ (2.3 mg, 6.3 mmol), 5 mol% ligand (3.0 mg, 6.3 mmol), TsNHOAc (28.7 g, 0.125 mmol, 1 equivalent), and 2 ml (2 ml, 1.7 g, 18.8 mmol, 151 equivalent) dry toluene, heated at the stated temperature for 48 hours under nitrogen. Reaction followed the general catalytic procedure listed above.

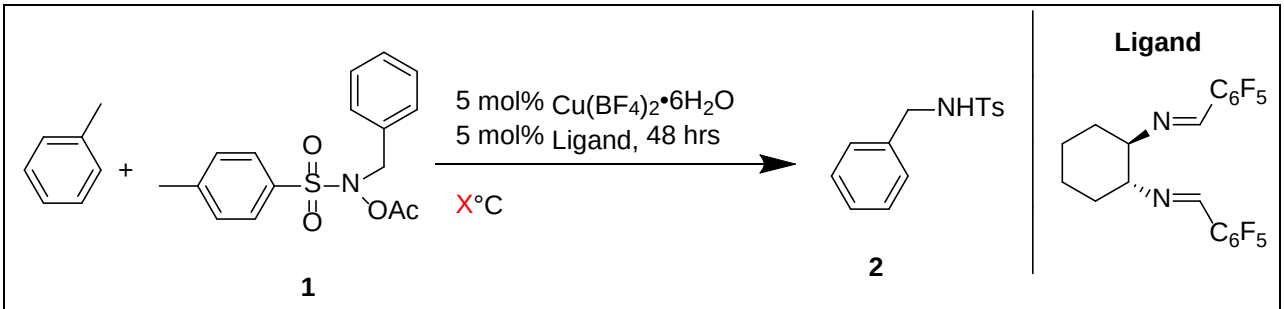


Entry	Temperature	NMR Yield of **2**	NMR Yield of **$TsNH_2$**	NMR Yield of **Intermediate**
1	Room Temperature	0%	3 ± 1%	0%
2	70 °C	3 ± 1%	29 ± 2%	26 ± 1%
3	90 °C	7.7 ± 1%	48 ±2%	43 ±1%
4	100 °C	38 ± 2%	47± 1%	12 ± 1%
5	110 °C	48 ± 1%	45 ± 1%	0%
6	120 °C	48 ± 2%	48 ± 2%	0%

4.4.7 Intermediate Temperature Study (2NJV Page 4)

5 mol% $Cu(BF_4)_2 \cdot 6H_2O$ (2.3 mg, 6.3 mmol), 5 mol% ligand (3.0 mg, 6.3 mmol) and N-acetoxy-N-benzyl-4-methylbenzenesulfonamide (**1**) (0.125 mmol, 38.1 mg) were added to a 5 ml vial under an inert atmosphere of nitrogen. Then, dry toluene (2 ml, 1.7 g, 18.8 mmol, 151 equivalents) was added to the vial. The resulting mixture was then stirred for 48 hours at the temperature being tested. The mixture was then transferred to a 40 ml vial and washed over using acetone. Solvent was then pulled using a rotary evaporator. The remaining solid was then dissolved in a standard solution of 1,3-dinitrobenzene (5.0 mg, 29 µmol) in 5 mL of $CDCl_3$ and filtered through Celite into an NMR tube. Yield of (**2**) was then determined using NMR.

Table 7. Intermediate Temperature Study Conditions: 5 mol% $Cu(BF_4)_2 \cdot 6H_2O$ (2.3 mg, 6.3 mmol), 5 mol% ligand (3.0 mg, 6.3 mmol) and N-acetoxy-N-benzyl-4-methylbenzenesulfonamide (1) (0.125 mmol, 38.1 mg), dry toluene (2 ml, 1.7 g, 18.8 mmol, 151 equivalent) stirred for 48 h at the stated temperature under nitrogen

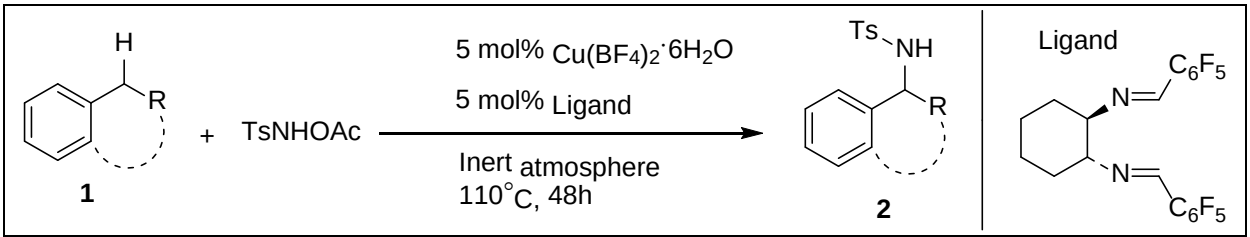


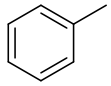
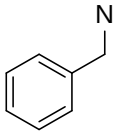
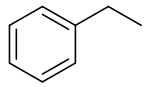
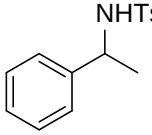
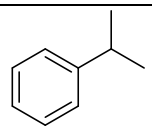
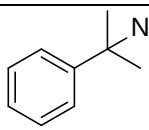
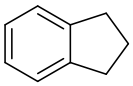
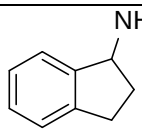
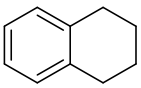
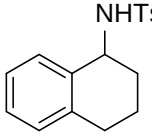
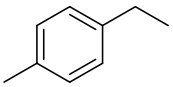
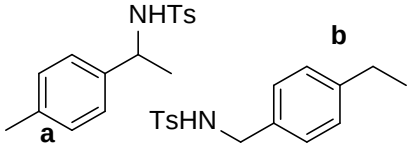
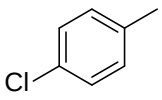
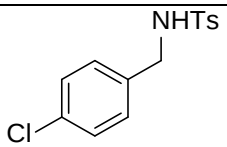
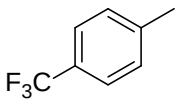
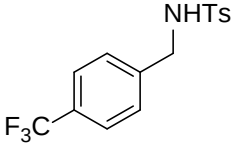
Entry	Ligand (mmol)	Temperature (°C)	Yield of **2**
1	6.3 mmol	Room Temperature	Trace
2	6.3 mmol	70°C	12.1 ± 0.2%
3	6.3 mmol	90°C	16.4 ± 0.1%
4	6.3 mmol	100°C	48.2 ± 0.8%
5	6.3 mmol	110°C	67.7± 2.3%
6	0 mmol	110°C	53.8± 0.6%

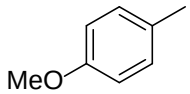
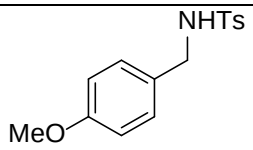
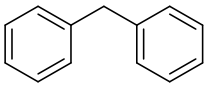
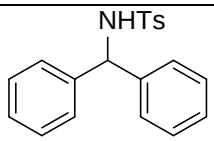
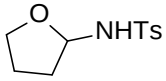
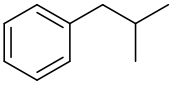
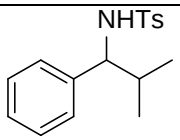
4.5 Catalytic Studies (Other Weak Bonds)

4.5.1 Substrate Scope

Table 8. Substrate Scope Conducted by Anqi Wang. Conditions: The reactions followed the general catalytic procedure outlined above. Each reaction was run using 2 ml of the designated substrate.



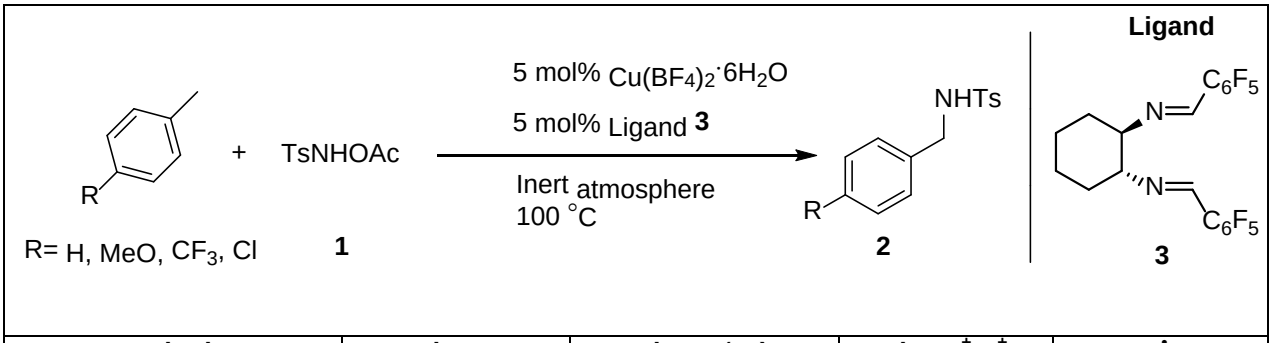
Substrate	Product Structure	NMR Yield of 2 (Isolated Yield)
		48 ± 1% (45%)
		45± 1% (42%)
		trace (75% $TsNH_2$)
		76 ± 2% (75%)
		64 ± 1% (56%)
		**a:** 55± 1% (43%); **b:** 12± 1%
		43 ± 2%
		40 ± 1%

		24 ± 2%
		86 ± 1% (72%)
		67 ± 2%
		3± 2%

4.5.2 Hammett Study (2NJV Page 33)

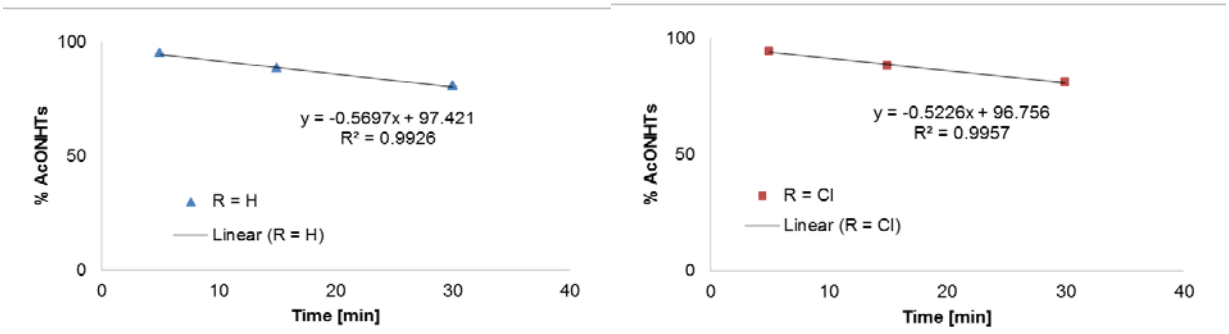
The Hammett Study was run following the general catalytic procedure, with the exception that the reactions were only run for 5, 15, and 20 minutes to observe the initial rates of consumption of TsNHOAc. Upon completion of each reaction, the reaction vessels were put into liquid nitrogen to stop the reaction completely.

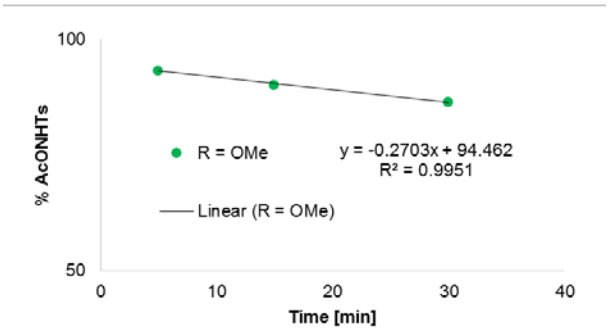
Table 9. Hammett Study Initial Rate Constant and other Parameters. Conditions: 5 mol% $Cu(BF_4)_2 \cdot 6H_2O$ (2.3 mg, 6.3 mmol), 5 mol% ligand (**3**) (3.0 mg, 6.3 mmol), TsNHOAc (**1**) (28.7 mg, 0.125 mmol, 1 equiv), and 2 ml of para-substituted toluene stirred for a time ranging from 5 min to 30 min at 100°C under an inert atmosphere. Experiment Number 2NJV33.

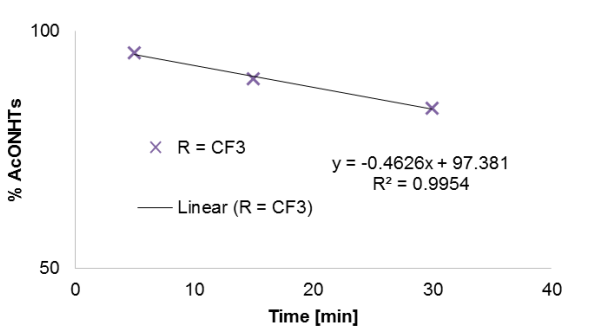


para-substituent	k_{obs}	sigma (σ_p)	sigma$^+$ σ^+	$\sigma^{\bullet}_{\alpha}$
CF_3	0.4626	0.54	n/a	-0.009
Cl	0.5226	0.23	0.11	0.011
H	0.5697	0	0	0
MeO	0.2703	-0.27	-0.78	0.018

Figure 21. Hammett Plot Determination of Initial Rate Constants

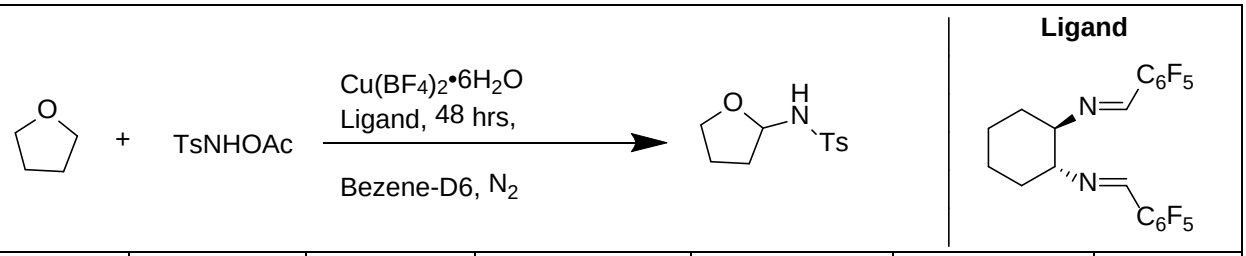



100
50
% AcONHTs
0
10
20
30
40
Time [min]
R = OMe
y = -0.2703x + 94.462
R² = 0.9951
Linear (R = OMe)


100
50
% AcONHTs
0
10
20
30
40
Time [min]
R = CF3
y = -0.4626x + 97.381
R² = 0.9954
Linear (R = CF3)

4.5.3 Amination Reagent Loading Study for Amination of THF (2NJV Pages 16, 19, and 36)

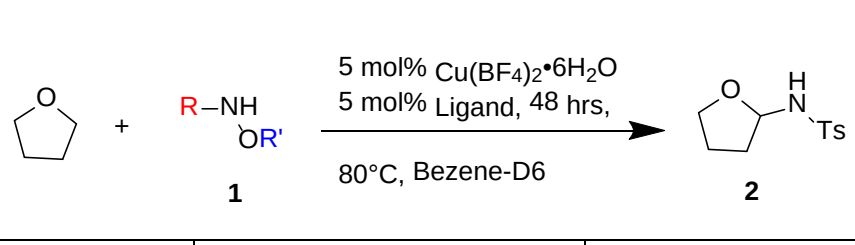
Table 10. Amination reagent and copper loading study, Conditions: 5 mol% $Cu(BF_4)_2 \cdot 6H_2O$ (2.3 mg, 6.3 mmol), 5 mol% ligand (3.0 mg, 6.3 mmol), TsNHOAc, and 10 µl of THF in benzene D-6 (2ml) stirred for 48 hours at 80°C.



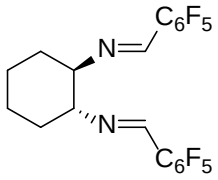
Entry	Copper (Mol %)	Ligand (Mol %)	Amination Reagent (Equivalents)	THF (Equivalents)	Temperature (°C)	Yield (%)
1	0	0	1	1	80	Trace
2	0	0	4	1	80	Trace
3	5	5	1	1	80	6 ± 1%
4	5	5	4	1	80	17.1
5	5	5	1	4	80	32 ± 2%

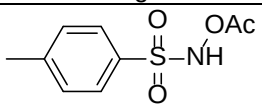
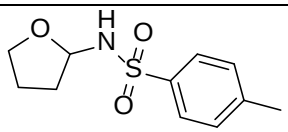
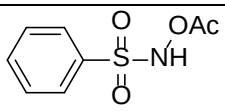
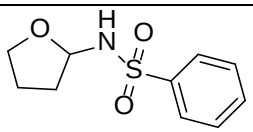
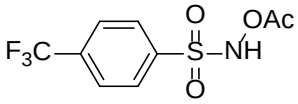
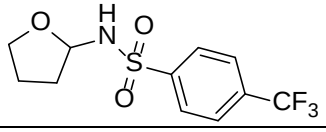
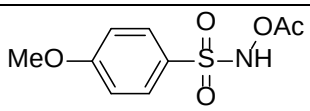
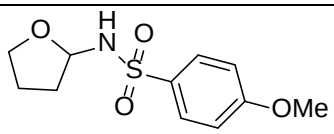
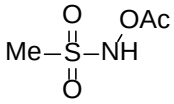
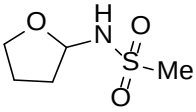
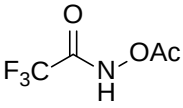
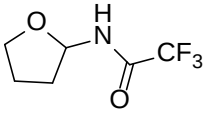
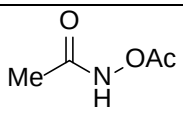
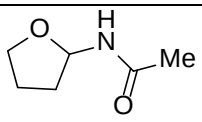
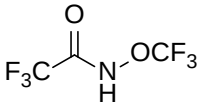
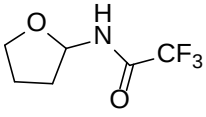
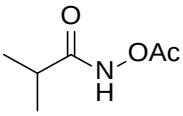
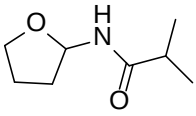
4.5.2 THF Amination Reagent Scope (2NJV Page 20)

Table 11. Amination Reagent Screen of THF. Conditions: 5 mol% $Cu(BF_4)_2 \cdot 6H_2O$ (2.3 mg, 6.3 mmol), 5 mol% ligand (3.0 mg, 6.3 mmol), 0.125 mmol of the designated amination reagent, and 10 µl of THF (8.9 mg, 0.125 mmol, 1 equivalent) in dry benzene-d_6 (1ml) stirred for 48 hours at 80°C



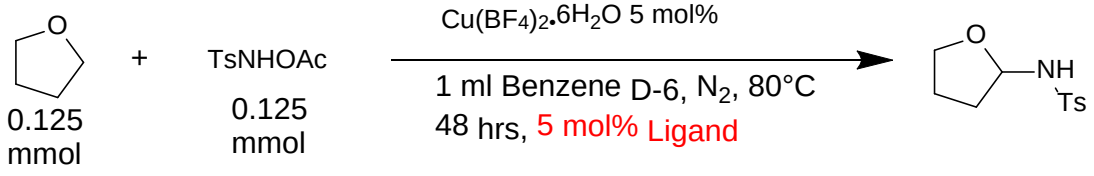
Ligand

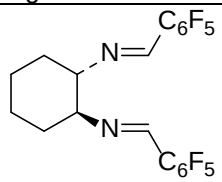
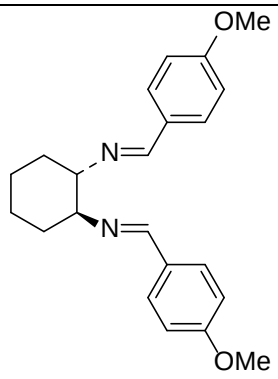
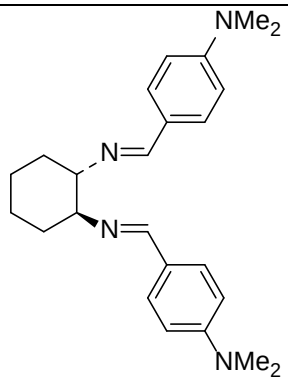


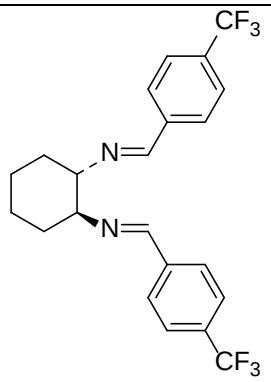
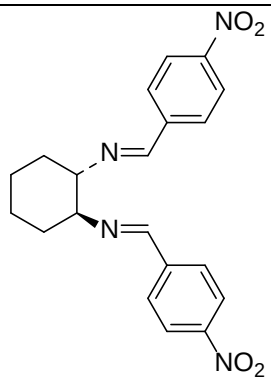
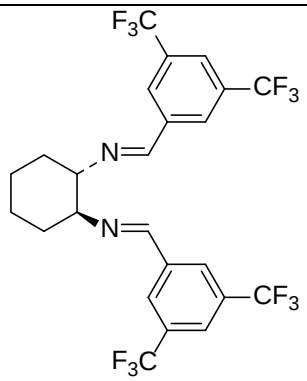
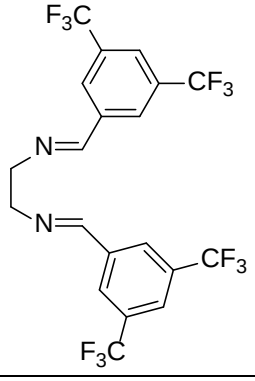
Entry	Amination Reagent Structure	Product Structure	Yield
1			6.8%
2			23%
3			9.2%
4			Trace
5			18.6%
6			Trace
7			Trace
8			Trace
9			Trace

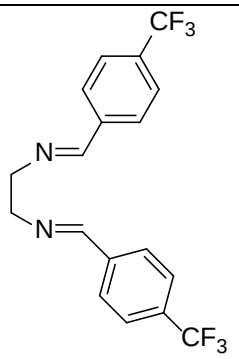
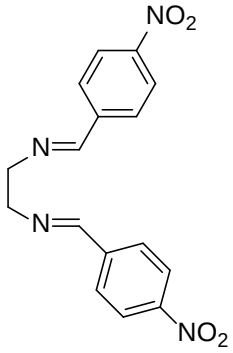
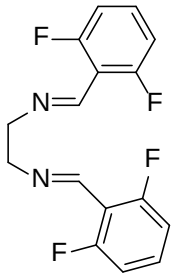
4.5.3 THF Amination Ligand Screen (2NJV Pages 38 and 39)

Table 12. Ligand Screen for the amination of THF. Conditions: 5 mol% $Cu(BF_4)_2 \cdot 6H_2O$ (2.3 mg, 6.3 mmol), 5 mol% of the tested ligands (6.3 mmol), 0.125 mmol of the designated amination reagent, and 10 µl of THF (8.9 mg, 0.125 mmol, 1 equivalent) in dry benzene-d_6 (1ml) stirred for 48 hours at 80°C



Entry	Ligand	% Yield
1		6.4
2		15.9
3		6.6

4		14.5
5		15.1
6		18.3
7		18.3

8		22.1
9		9.1
10		17.2

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