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## Synthesis of Alkyl Aryl Ethers Using a Halogen Exchange Coupled to an Ullmann Etherification

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Synthesis of Alkyl Aryl Ethers Using a Halogen  
Exchange Coupled to an Ullmann Etherification

By

Antonio Joseph Campedelli

\* \* \* \* \*

Submitted in partial fulfillment  
of the requirements for  
Honors in the Department of Chemistry

UNION COLLEGE

June, 2020

## Abstract

The Ullmann ether synthesis is a reaction that couples aryl halides to aliphatic alcohols. It works best with aryl iodides because the aryl bromides are much less reactive, and aryl chlorides are even more so. A Finkelstein type halogen exchange reaction has been shown to effectively substitute iodide for bromide on aryl bromides with high yields. The goal of this project is to develop a one pot halogen exchange, Ullmann coupling reaction to allow for aryl bromides to be coupled successfully to aliphatic alcohols. This is feasible because the reaction conditions of the two reactions are so similar. Several condition variables were tested to attempt to achieve the highest amount of conversion possible. Different solvent systems, such as pairing methanol with dioxane, dimethylformamide, toluene, and N-methyl-2-pyrrolidone, were tested as well as a number of ethylenediamine based ligands. The conditions that were best suited to produce the ether products used ethylenediamine as a ligand with a copper iodide catalyst in neat methanol. This data can be seen in further detail in Table 8, entry 6.

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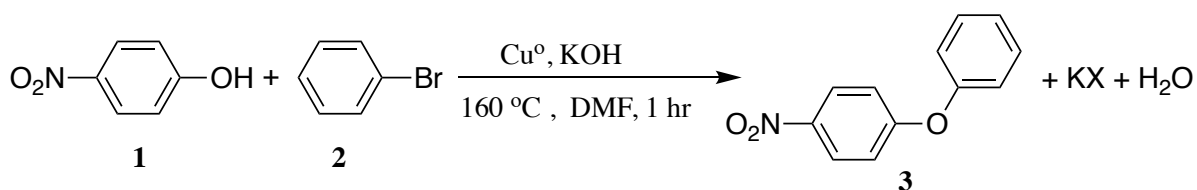
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## 1. Introduction

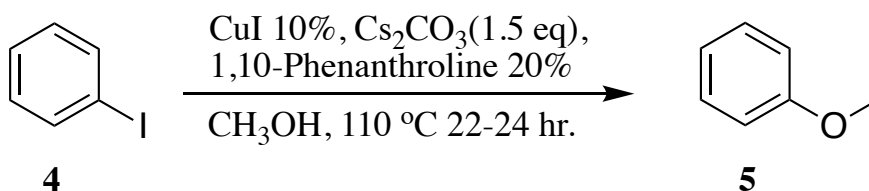
The Ullmann condensation was first reported in 1905 by Fritz Ullmann. As a method of coupling aryl halides with phenols to form diarylethers (Scheme 1), the method employs harsh conditions, and high temperatures as well as stoichiometric amounts of elemental copper.<sup>1</sup>

**Scheme 1.**



Interest in this coupling reaction gained traction in 2002 when the research group of Prof. Stephen L. Buchwald developed a method of coupling aryl iodides with primary alcohols using catalytic amounts of CuI as opposed to Cu<sup>0</sup> (Scheme 2).<sup>2</sup> Buchwald and co-workers showed that using bidentate aromatic diamine ligands, such as 1,10-phenanthroline, worked best for Cu<sup>I</sup> solubility and the overall success of the Cu<sup>I</sup> as a catalyst.<sup>2</sup>

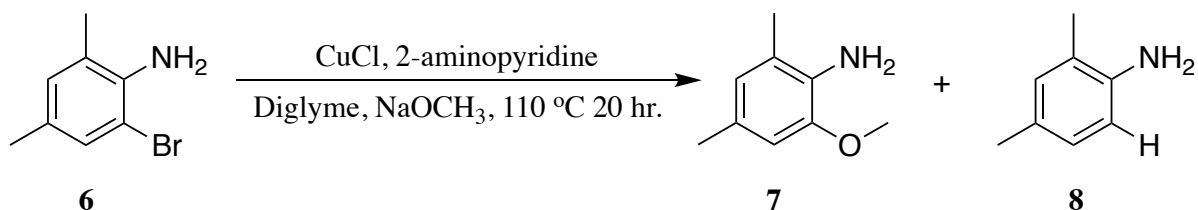
**Scheme 2.**





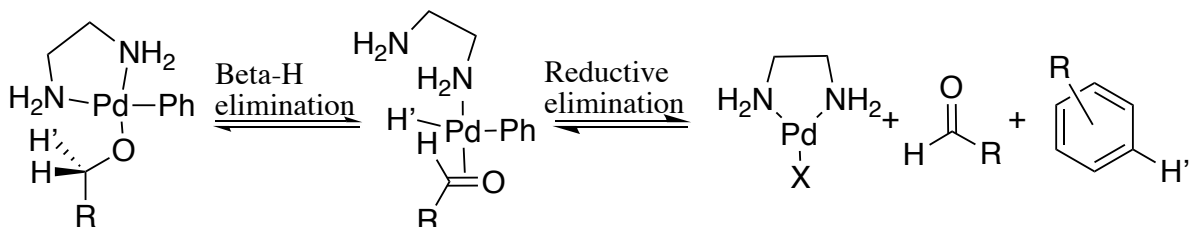
It has also been reported by the Buchwald group that this process is successful with primary alcohols as well as secondary alcohols.<sup>2</sup> For example, cyclopentanol and but-3-en-2-ol are two secondary alcohols that have been shown to react with 4-iodoanisole with yields of 75% and 54% respectively for each the products.<sup>2</sup> It was noted that the temperature had to be increased to 120 °C in order to achieve the 75% yield for cyclopentanol substrate.<sup>2</sup> Primary alcohols such as methanol, ethanol, propanol, and butanol have all been shown to work with a variety of aryl iodides with higher yields depending on the type of aryl iodide.<sup>2</sup> It has also been reported that this process can yield the reduced form of the aryl halide which is observable in Scheme 3.<sup>3</sup>

**Scheme 3.**

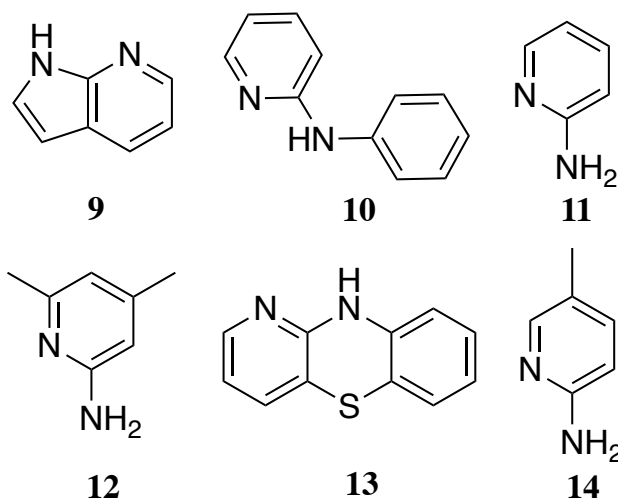


This additional reaction pathway has also been observed in palladium catalyzed coupling reactions, and is thought to be due to a  $\beta$ -Hydride transfer occurring prior to the reduction elimination step (Scheme 4).<sup>4,5</sup> It is thought that the  $\beta$ -Hydrogen of the alcohol, denoted H', undergoes an elimination reaction, in which the hydride becomes chelated to the metal center as well as the  $\pi$  orbitals of the newly oxidized carbonyl.<sup>4</sup> This is thought to lead to the reductive elimination of a reduced aryl ring, and an aldehyde or ketone depending on whether the alcohol used was primary or secondary.<sup>4</sup>

Scheme 4.

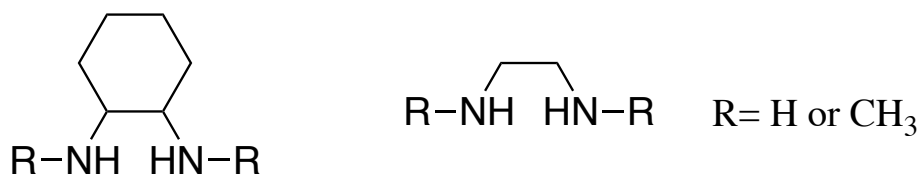


The problem of the presence of reduced side product was recognized by Paul J. Fagan and co-workers. It was addressed by screening a library of ligands to be used with the copper catalyst.<sup>3</sup> Scheme 3 is slightly different from Scheme 2, due to the fact that Scheme 3 is an alkoxylation which uses the deprotonated alcohol from the start. Using an alkoxide eliminates the need for a base to be present in the catalytic cycle. There were a few ligands that were successful in reducing the amount of  $\beta$ -Hydride elimination side product while affording high yields of the Ullmann ether products.<sup>3</sup>



**Figure 1.** Ligands capable of reducing  $\beta$ -Hydride elimination side product in Ullmann ether synthesis. Among these bidentate nitrogen-based ligands are 7-azaindole (**9**), *N*-phenylpyridin-2-amine (**10**), pyridin-2-amine (**11**), 4,6-dimethylpyridin-2-amine (**12**), 10*H*-benzo[*b*]pyrido[2,3-*e*][1,4]thiazine (**13**), 5-methylpyridin-2-amine (**14**).

There are a variety of viable ligand options for Scheme 1. It has been shown that phenanthrolines,  $\alpha$ -amino acids, imines, 1,3-diketones, and salicylamides are all suitable ligands for this process.<sup>6,7</sup> Diamine-based ligands such as ethylenediamine (en) and cyclohexane-1,2-diamine, shown in figure 2, tend to have greater success when being scaled up due to the fact that they are readily available in large quantities.<sup>6</sup>



**Figure 2.** Cyclohexane-1,2-diamine (a; R=H) and ethylenediamine (b; R=H).

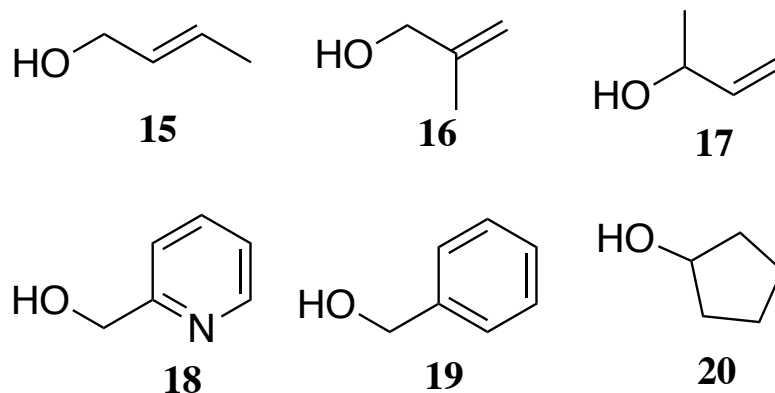
If the nitrogen atoms are disubstituted in the ligand, sterics becomes a factor in how well the ligand-catalyst system performs. The most effective ligands are less substituted because highly substituted Lewis bases have more steric bulk around the lone pair of the ligand, which can interfere with the ligand's ability to chelate to the  $\text{Cu}^{\text{I}}$  metal center.<sup>6,7</sup>

Another important factor in the success of this reaction is finding the best base. Buchwald hypothesized that it was important to match the rate of deprotonation of the nucleophile to the rate of bond formation between the nucleophile and the substrate.<sup>6</sup> This hypothesis was supported by the fact that strong bases such as KHMDS are ineffective unless added slowly.<sup>6</sup> Although it is true that  $\text{Cs}_2\text{CO}_3$  from Scheme 2 is a mild base, it is thought that its low solubility in aprotic solvents allows for a slow rate of deprotonation of the alcohol.<sup>2,6</sup> The need to match the rate of deprotonation to the rate of product formation is likely the reason why the  $\text{Cu}^{\text{I}}$  catalyzed amination of aryl halides requires a

different base than that of the alkoxylation of aryl halides.<sup>2,6</sup> For example, the Buchwald group reported that the bases  $K_2CO_3$  and  $K_3PO_4$  both work well for the amidation for aryl halides.<sup>6</sup> However, because aryl iodides are much more reactive than aryl bromides,  $K_3PO_4$  matches the rate of deprotonation to the formation of product better than  $K_2CO_3$ , but  $K_2CO_3$  matches the rates better for aryl bromides because  $K_2CO_3$  is thought to deprotonate the amide nucleophile more slowly than  $K_3PO_4$ .<sup>6</sup> In addition, neither one of these bases work as well as  $Cs_2CO_3$  in the alkoxylation of aryl iodides because alcohol has a different acidity than an amide.<sup>6</sup>

$Cu^I$  catalyzed ether formation reactions have been shown to work best in polar aprotic solvents, such as DMF, dioxane, diglyme and others.<sup>2,3,7</sup> It should be noted that Buchwald's synthesis of aryl ethers were successfully run in neat alcohol.<sup>2</sup> In cases when the alcohol was not a suitable solvent, such as benzyl alcohol, the reaction could also be run in toluene with an excess of the benzyl alcohol, or other large alcohols such as in Figure 3.<sup>2</sup>

Buchwald and co-workers have shown that a variety of alcohols can effectively interact with the  $Cu^I$  catalyst and act as a nucleophile in the reaction, successfully forming a variety of aryl ethers from alcohol variation alone.<sup>2</sup> Methanol up to butanol were shown to be suitable reactants, along with the six diverse alcohols shown in Figure 3.

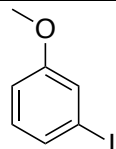
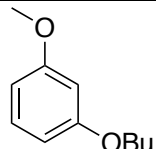
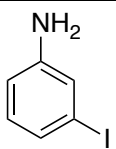
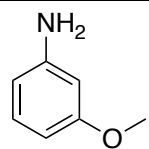
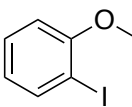
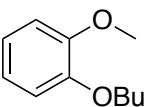
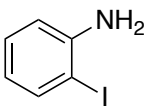
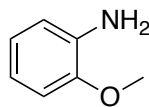


**Figure 3.** Additional alcohols that can be coupled to aryl iodides. Among these alcohols are (*E*)-but-2-en-1-ol (**15**), 2-methylprop-2-en-1-ol (**16**), but-3-en-2-ol (**17**), pyridin-2-ylmethanol (**18**), phenylmethanol (**19**), cyclopentanol (**20**).

The choice of catalyst is an important factor in success of this reaction. There is a wide variety of Cu catalysts available, varying in the oxidation state, or the anion that accompanies the metal. The most effective Cu catalysts in the Ullmann ether synthesis have been shown to be Cu<sup>I</sup> salts, paired with halogen anions.<sup>2,3</sup> CuI, CuBr, and CuCl have all been shown to be suitable catalysts with decreasing efficiency going from CuI to CuCl.<sup>2,3,8</sup> Additionally Henri-Jean Cristau and co-workers have found that Cu<sub>2</sub>O can also be a suitable catalyst for the Ullmann ether synthesis.<sup>8</sup>

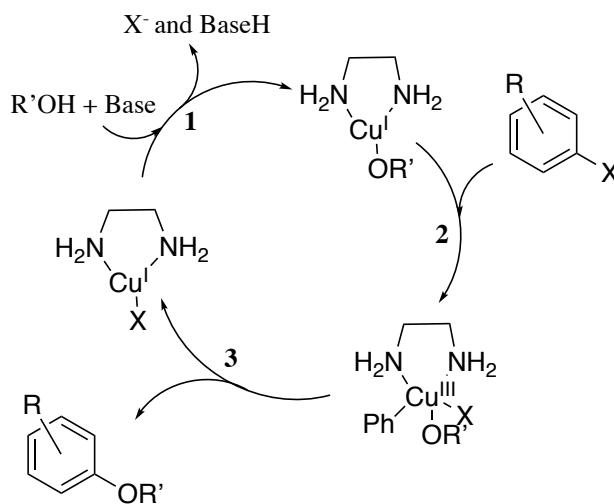
When varying the substituents, on the aryl halide, it has been reported that sterics as well as electronics have an effect on the reaction. As evidence by the observation that meta substituted aryl halides give higher yields than ortho substitute aryl halides, Table 1 summarizes some of the results put together by the Buchwald group displaying this trend.<sup>2</sup> It is unknown whether the electronic difference or steric difference between ortho and meta substituted aryl halides has a greater effect on the yields presented.

**Table 1.** A comparison of the yields of two sets of meta and ortho substituted aryl iodides.<sup>2</sup>

Aryl Iodide	Product	Yield %	Aryl Iodide	Product	Yield %
		94 <sup>a</sup>			78
		72			53

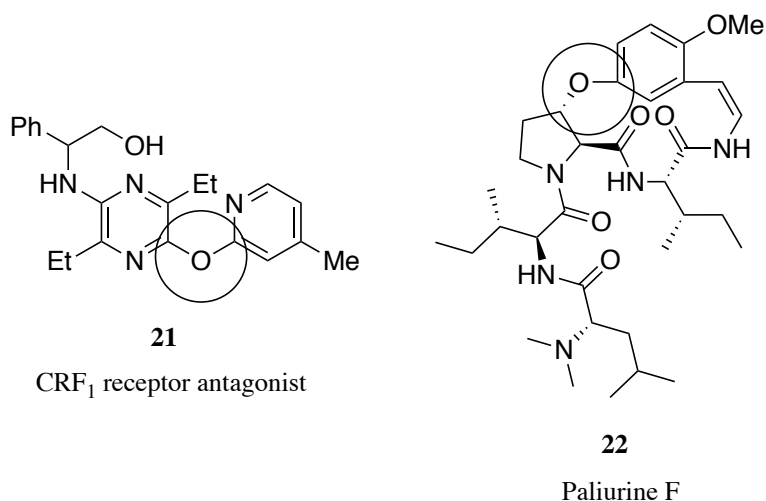
a. This reaction was run using 5 mol% catalyst as opposed to 10 mol% catalyst.

The mechanism of the Ullmann ether synthesis and N-arylation, which both use  $\text{Cu}^{\text{I}}$  salt as the catalyst, have been described similarly as redox catalytic cycles.<sup>7,9</sup> In these cycles, the nucleophile replaces the counter ion of the catalyst, shown as step 1 in the catalytic cycle of Figure 4. This step is followed by an oxidative addition of the aryl halide to the copper which yields a  $\text{Cu}^{\text{III}}$  complex, represented by step 2 in Figure 4. This is followed by a reductive elimination of the aryl ring now bound to the nucleophile which leaves the catalyst with its original counter ion, given by step 3 in Figure 4.<sup>7,9</sup>

**Figure 4.** The proposed catalytic cycle of the  $\text{Cu}^{\text{I}}$  catalyzed Ullmann coupling reaction, where X represents a halide.

The Ullmann ether synthesis by itself is very limited in scope. This is due to the fact that the aryl bromides are much less reactive than the aryl iodides and therefore give poor yields compared to aryl iodides. This is problematic because aryl bromides are more readily available and cheaper than their aryl iodide counterparts.<sup>6,10</sup>

Although the most effective reactions are limited to aryl iodide starting materials, the Ullmann ether synthesis is still a very useful coupling reaction and has a variety of applications, from pharmaceutical synthesis to natural product synthesis.<sup>6</sup> This coupling reaction was used by Pfizer to synthesize CRF<sub>1</sub> receptor antagonist (**21**) which could be used in the treatment of stress related disorders.<sup>6,11</sup> It was also used for the alkyl-aryl ether linkage of the natural product Paliurine-F (**22**), a bioactive natural product that has sedative, antibacterial, antifungal, and antiplasmodial (kills parasites) properties (Figure 5).<sup>12</sup> Paliurine-F could not be efficiently extracted from plants due to its low abundance and therefore needed to be synthesized.<sup>12</sup> The Cu<sup>I</sup> mediated linkage of the hydroxypyrrolidine to 5-iodo-2-methoxybenzaldehyde proved to be a key synthetic step in the total synthesis of Paliurine F.<sup>12</sup>



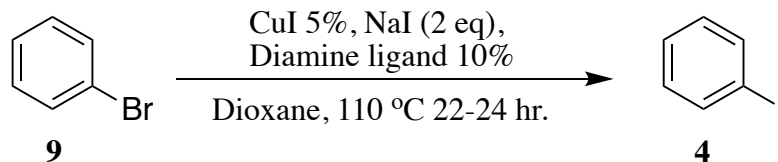
**Figure 5.** The structure of Paliurine F, a bioactive natural product, and CRF<sub>1</sub> receptor antagonist which could be used to reduce stress.

The lack of reactivity of the aryl bromides is a major drawback in the diversity of possible applications of the Ullmann ether synthesis. Fortunately, an aromatic halogen exchange reaction, coined an “aromatic Finkelstein” reaction has been reported by the Buchwald lab, and occurs under very similar conditions to the Ullmann ether synthesis.<sup>13</sup>

The aromatic Finkelstein reaction is a Cu<sup>I</sup> catalyzed halogen exchange reaction in which the bromide on aryl bromides can be exchanged with iodide to yield aryl iodide, which is the more reactive of the two species.<sup>13</sup> These reactions follow the conditions of Scheme 5. The reaction conditions of the aromatic Finkelstein reaction are almost identical to the Ullmann type coupling reactions, in that they utilize Cu<sup>I</sup> salts as catalysts and the ligands are very similar.<sup>13</sup> Both diamine ligands shown in Figure 2 are viable options for this reaction.<sup>13</sup>

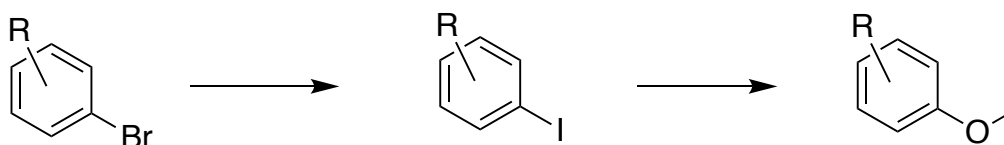


Scheme 5.



The aromatic Finkelstein reaction and the Ullmann ether synthesis both described previously, react under almost identical conditions, using the same catalyst with the same type of ligand system, in more or less the same types of solvents. Because the Ullmann coupling reaction is largely limited to aryl iodides due to the lack of reactivity of bromine, coupling the aromatic Finkelstein reaction with the Ullmann coupling reaction could be a powerful synthetic tool. It is hypothesized that by adding base and an alcoholic nucleophile to the conditions of the Finkelstein reaction shown in Scheme 5, an aryl ether will be formed from an aryl bromide, with an observable aryl iodide intermediate as seen in Scheme 6. This domino coupling reaction has already been shown to work for addition of a cyano group as well as amination of the aryl bromide via the aryl iodide intermediate.<sup>10,14</sup> The fact that this process worked for two other types of similar Cu<sup>I</sup> mediated coupling reactions suggests that it should also be a feasible pathway by which to achieve an aryl ether from an aryl bromide.

Scheme 6.



## 2. Experimental

### 2.1 General Experimental Methods

#### 2.1.1 Method A: Reduction of di-Schiff's base<sup>15</sup>

The di-Schiff's base (1.0 eq) was dissolved in a 3:1 MeOH: DCM (50 mL) solvent system. Sodium borohydride was added to a 1% sodium methoxide solution in methanol (13 mL). This mixture was added dropwise to the di-Schiff's base solution. The reaction mixture was stirred at in an ice bath, kept at approximately 18 °C for 16 h. The solvent was removed *in vacuo* to reveal the crude product as a yellow oil. The residue was diluted with water (30 mL) and extracted with methyl tertbutyl ether (MTBE) (3 × 30 mL). The organic layers were combined and dried (MgSO<sub>4</sub>), and concentrated *in vacuo* to reveal the crude product as white crystals at ~20 °C.

#### 2.1.2 Method B: Domino Reaction

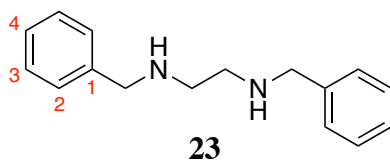
All solids were added to a sealable reaction vessel with a stir bar. Cs<sub>2</sub>CO<sub>3</sub> (1.75 eq) was added followed the halide salt (KI or NaI) (0.2-2.0 eq). Next the CuI catalyst was added (0.1 eq) followed by the aryl bromide if it was a solid, and if it was a liquid it was added after the solvent (1 eq). If the ligand was a solid it was added after the aryl halide, and if it was a liquid it was added after the solvent (0.2 eq). The solids were dissolved in 1 mL of total solvent for every mmol of aryl halide. If a solvent system was implemented, the order of addition was not focused on. As said before, any other liquid reagents were added after the solvents. The reaction tube was then sealed and allowed to stir at 110 °C for 24 h. The reaction contents were allowed to cool and 20 μL of the crude reaction contents were added to 1 mL of MeOH and analysed by GC-MS.

### 2.1.3 Method C: Ullmann Reaction

All solids were added to a sealable reaction vessel with a stir bar.  $\text{Cs}_2\text{CO}_3$  (1.75 eq) was added followed by the CuI catalyst (0.1 eq). Next, the aryl halide (Ar-Br or Ar-I) was added if it was a solid, and if it was a liquid it was added after the solvent (1 eq). If the ligand was a solid it was added after the aryl halide, and if it was a liquid it was added after the solvent (0.2 eq). The solids were dissolved in 1 mL of total solvent for every mmol of aryl halide. If a solvent system was implemented, the order of addition was not focused on. As said before, any other liquid reagents were added after the solvents. The reaction tube was then sealed and allowed to stir at 110 °C for 24 h. The reaction contents were allowed to cool and 20  $\mu\text{L}$  of the crude reaction contents were added to 1 mL of MeOH and analysed by GC-MS.

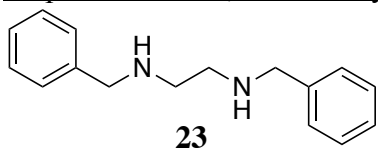
## 2.2 Compound Numbering

The compounds synthesized in this thesis are numbered in the following way.



## 2.3 Compounds

### Preparation of $N^1, N^2$ -dibenzylethane-1,2-diamine

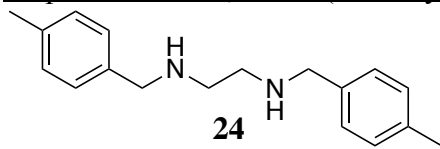


Synthesized using method A using (1*E*,1'*E*)- $N, N'$ -(ethane-1,2-diyl)bis(1-phenylmethanimine) (1.00 g, 4.17 mmol, 1.0 eq), Sodium Borohydride (649 mg, 17.1 mmol, 4.1 eq), MeOH (43 mL), DCM (10 mL), and Sodium Methoxide (1

mL) and the reaction stirred for overnight. The title compound 26 (1.00 g, 5.80 mmol, 99%) was collected as a yellow solid.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** 7.31-7.23 (10H, m, 2-H, 3-H, 4-H), 3.77 (4H, s, NHCH<sub>2</sub>Ar), 2.75 (4H, s, CH<sub>2</sub>CH<sub>2</sub>NH), 1.65 (2H, broad-s, NH); **<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** 140.5, 128.4, 128.1, 126.9, 54.0, 48.8, 27.0.

Preparation of *N*<sup>1</sup>, *N*<sup>2</sup>-bis(4-methylbenzyl)ethane-1,2-diamine

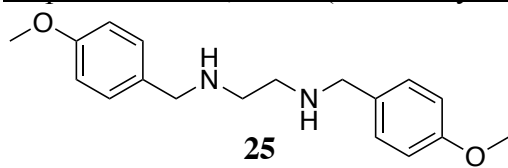


Synthesized using method A using (1*E*,1'*E*)-*N*, *N*'-

(ethane-1,2-diyl)bis(1-*p*-tolylmethanimine) (1.50 g, 5.68 mmol, 1.0 eq), Sodium Borohydride (885 mg, 23.3 mmol, 4.1 eq), MeOH (43 mL), DCM (10 mL), and Sodium Methoxide (1 mL) and the reaction stirred for overnight. The title compound 24 (1.36 g, 5.09 mmol, 90%) was collected as a white solid.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** 7.19 (4H, d, *J* 7.9, 2-H), 7.12 (4H, d, *J* 7.8, 3-H), 3.73 (4H, s, NHCH<sub>2</sub>Ar), 2.74 (4H, s, CH<sub>2</sub>CH<sub>2</sub>NH), 2.33 (6H, s, H<sub>3</sub>CAr), 1.66 (2H, broad-s, NH); **<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** 137.5, 136.5, 129.1, 128.1, 53.7, 48.8, 21.1.

Preparation of *N*<sup>1</sup>, *N*<sup>2</sup>-bis(4-methoxybenzyl)ethane-1,2-diamine



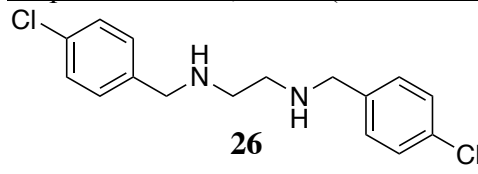
Synthesized using method A using (1*E*,1'*E*)-*N*,

*N*'-(ethane-1,2-diyl)bis(1-(4-methoxyphenyl)methanimine) (1.88 g, 6.35 mmol, 1.0 eq), Sodium Borohydride (1.00 g, 26.3 mmol, 4.1 eq), MeOH (43 mL), DCM (10 mL), and Sodium Methoxide (1 mL) and the reaction stirred for overnight. The title compound 23 (1.74 g, 5.80 mmol, 91%) was collected as a white solid.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** 7.21 (4H, d, *J* 8.7, 2-H), 6.84 (4H, d, *J* 8.7, 3-H), 3.79 (6H, s, H<sub>3</sub>COAr), 3.70 (4H, s, NHCH2Ar), 2.73 (4H, s, CH<sub>2</sub>CH2NH), 1.76 (2H, broad-s, NH);

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** 158.6, 132.5, 129.4, 113.8, 55.3, 53.3, 48.6.

Preparation of *N*<sup>1</sup>, *N*<sup>2</sup>-bis(4-chlorobenzyl)ethane-1,2-diamine



**26**

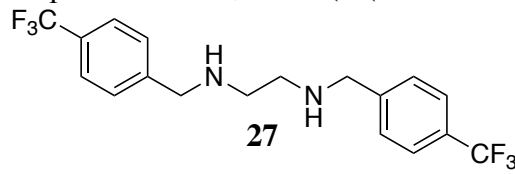
Synthesized using method A using (1*E*,1'*E*)-*N*, *N*'-

(ethane-1,2-diyl)bis(1-(4-chlorophenyl)methanimine) (1.00 g, 3.3 mmol, 1.0 eq), Sodium Borohydride (562 mg, 14.8 mmol, 4.5 eq), MeOH (43 mL), DCM (10 mL), and Sodium Methoxide (1 mL) and the reaction stirred for overnight. The title compound 28 (0.944 g, 3.06 mmol, 93%) was collected as a yellow oil.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** 7.28 (4H, d, *J* 8.6, 3-H), 7.23 (4H, d, *J* 8.6, 2-H), 3.76 (4H, s, NHCH2Ar), 2.75 (4H, s, CH<sub>2</sub>CH2NH), 1.63 (2H, broad-s, NH); **<sup>13</sup>C NMR (100 MHz,**

**CDCl<sub>3</sub>):** 139.0, 132.6, 129.4, 128.5, 53.2, 48.7.

Preparation of *N*<sup>1</sup>, *N*<sup>2</sup>-bis(4-(trifluoromethyl)benzyl)ethane-1,2-diamine



**27**

Synthesized using method A using (1*E*,1'*E*)-*N*,

*N*'-(ethane-1,2-diyl)bis(1-(4-(trifluoromethyl)phenyl)methanimine) (1.00 g, 2.69 mmol, 1.0 eq), Sodium Borohydride (419 mg, 11.0 mmol, 4.1 eq), MeOH (43 mL), DCM (10 mL), and Sodium Methoxide (1 mL) and the reaction stirred for overnight. The title compound 27 (0.91 g, 2.42 mmol, 90%) was collected as a yellow oil.

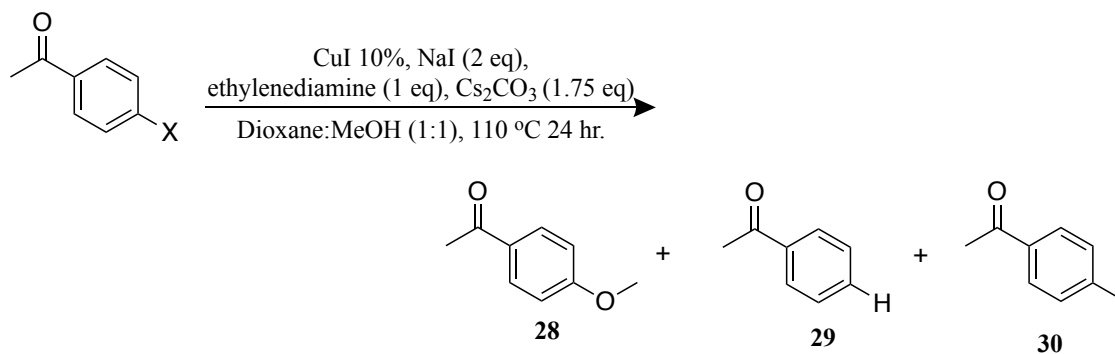
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** 7.57 (4H, d, *J* 8.0, 3-H), 7.43 (4H, d, *J* 8.0, 2-H), 3.84 (4H, s, NHCH2Ar), 2.76 (4H, s, CH<sub>2</sub>CH2NH), 1.76 (2H, broad-s, NH); **<sup>13</sup>C NMR (100 MHz,**

**CDCl<sub>3</sub>):** 144.5, 129.7, 128.6, 128.3, 125.3, 53.4, 48.8.

### 3. Results and Discussion

The conditions of the aromatic Finkelstein reaction developed by Buchwald and co-workers used dioxane as the solvent.<sup>13</sup> For this reason, a dioxane and methanol solvent system was tested in order to see if it was necessary for the dioxane to be a co-solvent in a domino reaction. The Ullmann reaction was tested by removing the NaI from Scheme 7. Both 4-bromoacetophenone and 4-iodoacetophenone were tested as starting materials to support the need for the domino process to obtain an aryl ether from an aryl bromide. The Ullmann reaction with an aryl bromide starting compound show only 40.7 % conversion compared to the Ullmann reaction with an aryl iodide starting compound with 94.0 % conversion which can be seen in Table 2 as entries **1** and **2** respectively. The domino reaction, entry **3**, showed 69.6 % conversion to the desired aryl ether (**28**). However, a significant 30.4 % of the starting material was converted to acetophenone, which is the product achieved when the aryl-halogen is reduced.

**Scheme 7.**

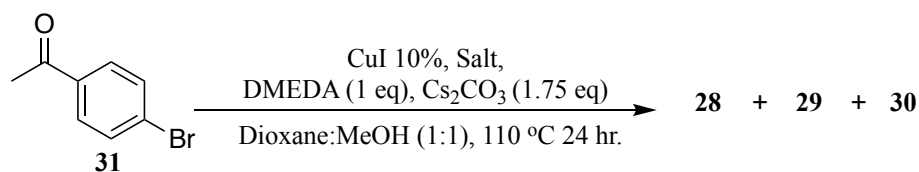


**Table 2.** A comparison of the Ullmann type reaction, the Finkelstein reaction and the proposed domino reaction that combines the two.

Entry	X	Salt	SM	<b>28</b>	<b>29</b>	<b>30</b>
1	Br	None	54.4	40.7	4.9	0
2	I	None	0	94.0	6.0	0
3	Br	NaI	0	69.6	30.4	0

The success of the aryl iodide reaction was expected because aryl iodide conversion to aryl ethers has been documented in the literature.<sup>2</sup> When the same Ullmann type reaction is run under the same conditions with 4-bromoacetophenone instead of 4-iodoacetophenone, the reaction only goes to 40.7 % completion, which suggests that the aryl bromides are less reactive than the aryl iodides, which is also consistent with previous reports.<sup>8</sup> Since the addition of NaI to the Ullmann reaction with 4-bromoacetophenone as a starting material almost doubles the reaction progress, this suggests that a more reactive aryl iodide intermediate could be formed before methoxylation occurs. It must be noted that because the conditions are so close to that of the Ullmann ether synthesis, it is possible that a percentage of conversion to the aryl ether could be due to a bromine-based Ullmann reaction. Because the aryl bromide is reported to be very unreactive to begin with, the amount is predicted to be very small.

The next set of experiments were run in order to see if the NaI needed to be added in stoichiometric amounts or if it could be added catalytically and achieve similar conversion. The optimization of the NaI then led to the testing of KI as an iodine source due to the fact that the literature shows evidence of both salts being a viable source of iodine.<sup>13</sup> The ligand dimethylethylenediamine (DMEDA) was also tested and shown to be more effective in the 1:1 dioxane-methanol solvent system so it was adopted for this set of reactions. The reaction shown in Scheme 8 produced 91.5 % conversion (Table 3.1, Entry 1), which is greater than the 69.6 % shown in Table 2 (Entry 3). The Scheme 8 reaction without NaI showed 35.8 % conversion, while the Scheme 8 reaction with 20 mol percent NaI produced 41.5% conversion. The Scheme 8 reaction with 20 mol percent of KI, substituted for NaI, produced 56.4% conversion.

**Scheme 8.****Table 3.** A comparison of different amounts of salt as well as different types of salt.

Entry	Salt	Eq <sup>a</sup>	<b>31</b>	<b>28</b>	<b>29</b>	<b>30</b>
1	NaI	2	0	91.5	8.5	0
2	None	0	64.2	35.8	0	0
3	NaI	0.2	58.5	41.5	0	0
4	KI	0.2	40.8	56.4	2.8	0

a. Equivalent of halide salt

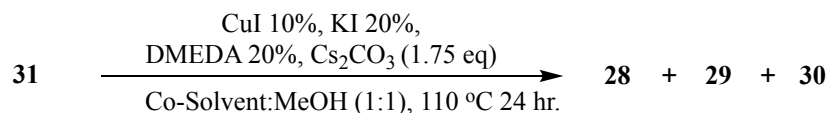
The amount of NaI was reduced to 20% mol to test whether or not the NaI could be catalytic. The results in Table 3 entries 1 and 2 support the results from Table 2. Entry 3 only works slightly better than entry 2, so no conclusions can be drawn from the data. Entry 4 on the other hand uses catalytic amounts of KI and shows more progress than entry 2 suggesting not only that the iodo salt can be added catalytically, but also that KI is a better source of I<sup>-</sup> than NaI. It is unknown why this is, but it is suspected to be related to the respective solubilities of each salt in the Dioxane-Methanol solvent system being used.

The Ullmann coupling uses aliphatic alcohols as the nucleophile and the solvent, so numerous co-solvents were tested to optimize both the halogen exchange step in the domino reaction as well as the Ullmann coupling reaction.<sup>2</sup> DMEDA was used as the ligand in this reaction set because it showed less reaction progress than ethylenediamine. If ethylenediamine was used and all of the reactions achieved close to 100% conversion, it would be harder to draw any conclusions from the data. The 1:1 solution of dioxane and methanol showed little conversion to the desired product with only 28.5 %



conversion. This is less than the 1:1 solution of dioxane and methanol results in Table 3, entry 4. because the amount of ligand was reduced from 1 eq to 20% mol. The toluene-methanol solvent system resulted in 47.0 % conversion to compound **28**. The DMF-methanol solvent system yielded only 27.2 % conversion to the aryl ether (**28**). The NMP-methanol solvent system produced 59.6 % conversion to the ether product (**28**), but also converted 31.1 % of the starting material to the reduced acetophenone side product (**29**). Neat methanol gave the best results with 92.2 % conversion to the desired aryl ether (**28**).

#### Scheme 9.



**Table 4.** A comparison of different co-solvents with methanol to find the best solvent system.

Entry	Co-solvent	<b>31</b>	<b>28</b>	<b>29</b>	<b>30</b>
1	Dioxane	67.4	28.5	4.1	0
2	Toluene	51.3	47.0	1.7	0
3	DMF	65.4	27.2	6.2	1.2
4	NMP	9.3	59.6	31.1	0
5	MeOH (neat)	7.8	92.2	0	0

The results from Table 4 suggest that the most effective solvent system at producing the desired product was the NMP: MeOH solvent system. It is interesting that DMF and NMP do not show similar results, given that the structure of the two solvents are so similar, with NMP having a slightly larger hydrophobic area in the carbon ring. It is possible that the salts such as KI and Cs<sub>2</sub>CO<sub>3</sub> are mostly soluble in the solvent system due to the presence of MeOH, and that when larger alcohols are used such as EtOH and propanol are used, the salts will be less soluble, affecting reaction progress.<sup>16</sup> None of the

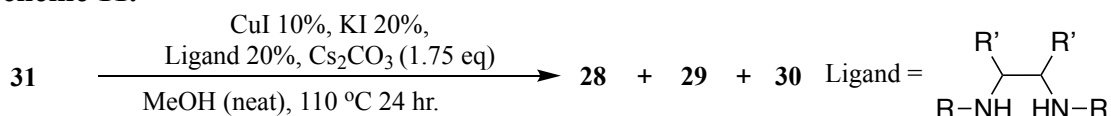
solvent system results show ether (**28**) production comparable to the neat MeOH results, which is expected because the MeOH, which is reactant, is so much more abundant when not diluted by another solvent.

Different solvent ratios were applied to the solvent systems tested in Table 5 in order to gain insight on which systems gave the best results and how each solvent affected the success of the reaction. The 4:1 dioxane-methanol system resulted in almost no conversion to the ether product (**28**) with only 2.7% conversion, while the 1:4 dioxane-methanol system, resulted in 75.8% conversion to compound **28**. The 4:1 toluene-methanol system showed almost no conversion to the aryl ether (**28**) with only 7.1 % conversion. The 1:4 toluene-methanol system, conversely, resulted in 74.7 % conversion to the compound **28**. The 4:1 DMF-methanol system resulted in 37.1 % conversion to compound **28**, with 20.7 % of the starting material converted to compound **29**. There was also evidence of a small amount of the 4-iodoacetophenone intermediate (**30**). The 1:4 DMF-methanol system converted 36.5 % of the starting material to the aryl ether (**28**) while also showing evidence of a small amount of the aryl iodide intermediate (**30**). The 4:1 NMP-methanol system resulted in 24.9 % conversion to the ether product with the majority of the starting material being converted to acetophenone (**29**) at 55.9 % conversion. The 1:4 NMP-methanol system converted 91.7 % of the starting material to the ether product (**28**) which is similar to the results of the neat methanol solvent conditions.



of ethylenediamine were tested in the domino reaction, and it seemed that adding substituents to both carbons or both nitrogens on ethylenediamine reduced the reaction's efficiency. All reactions were run for 24 hours with 20 mol percent ligand amounts and 10 mol percent of the catalyst. The ethylenediamine had shown the most reaction progress at the 24-hour mark with 97.8 % completion, with meso-1,2-diphenylethylenediamine (Meso-1,2) showing slightly less progress showing 92.6 % completion at 24 hours. The reaction using DMEDA also showed reduced reaction progress compared to the reaction that used ethylenediamine as the ligand, with only 92.2 % completion at 24 hours. The reaction using *N*<sup>1</sup>, *N*<sup>2</sup>-dibenzylethane-1,2-diamine (**23**) as a ligand showed the least reaction progress of the four ligand types, with 79.0% completion.

**Scheme 11.**



**Table 6.** A comparison of different ligands based on the basic ethylenediamine scaffold with varying substituent size.

Entry	R	R'	<b>31</b>	<b>28</b>	<b>29</b>	<b>30</b>
1	H	H	1.5	97.8	0.7	0
2	H	Ph	6.7	92.6	0.7	0
3	Me	H	7.8	92.2	0	0
4	CH <sub>2</sub> Ph	H	21.0	79.0	0	0

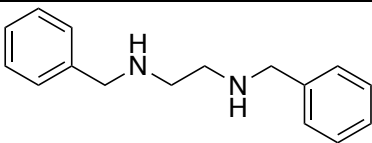
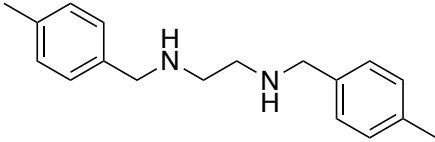
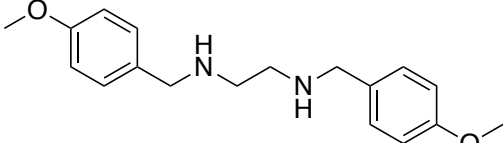
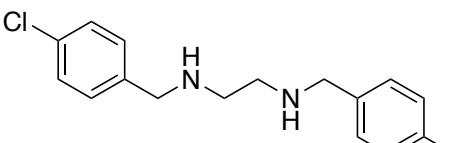
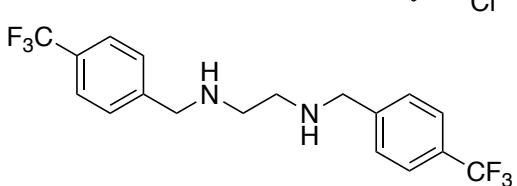
The results from Table 6 display a trend that produces more of compound **28** when the ligand being used has the smallest substituents in the nitrogens that chelate to the copper metal centre. It is possible that the large aromatic ring on either side of compound **26** is sterically hindering chelation to the metal centre, which could impede

reaction progress. Ethylenediamine on the other hand has hydrogen at both R and R' which is the least sterically hindering substituent and it shows almost 100% production of the aryl ether (**28**).

Five derivatives of ethylenediamine were prepared with the purpose of being used as ligands to test against ethylenediamine. These five ligands can be seen in Table 7.

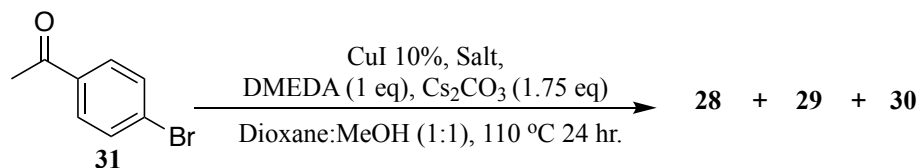
They all build off ethylenediamine's basic scaffold to include a mixture of both electron donating and withdrawing groups in the para position of the phenyl group.

**Table 7.** Five ligands that were synthesized for the purpose of being tested as possible ligands for the domino reaction.

Entry	Ligand
23	
24	
25	
26	
27	

The amount of ligand used was varied to look at the effect of small vs. large quantities of ligand has on reaction success. The reaction conditions used are based on Table 3, entry 4 which is an adaptation of Scheme 8 shown below. The only conditions that are varied from Table 3, entry 4, is the ligand concentration. The ligand used in this set of reactions was DMEDA. Both reactions were run using 10 mol percent of CuI catalyst, and the high ligand concentration reaction used 1 eq of ligand, which gave 56.3 % conversion, while the 20 mol percent ligand conditions gave 28.5 % conversion. Any less than a 2:1 ligand to catalyst ratio will reduce the catalyst efficiency given that the ligand is bidentate and two ligands are needed for each CuI species.<sup>2</sup>

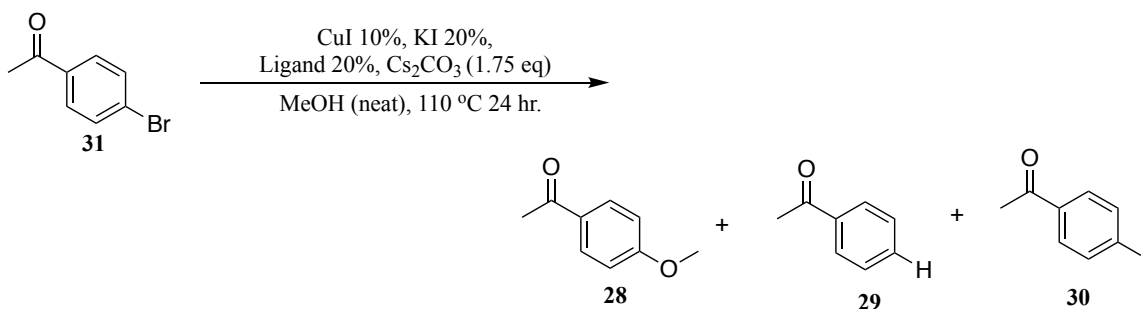
**Scheme 8.**



The ligand *N*<sup>1</sup>, *N*<sup>2</sup>-dibenzylethane-1,2-diamine (compound **23**) was diversified by adding different electron donating and electron withdrawing groups to the para position of the aromatic ring on either side of the ethylenediamine substructure. This was done to test the electronic effects of the ligand in the domino process. It has been reported in the literature that when the ligands in these types of reactions are electron rich, the reaction will progress further than if the ligand is electron poor.<sup>17</sup> The hypothesis was that if electron rich aromatic rings were added to the ethylenediamine ligand, there would be improved reactivity, whereas adding electron poor aromatic rings to the ligand frame would hinder the reaction. The full structure of each ligand used is shown in Table 7. The reaction conditions that used ligand **23** proceeded 79.0 % in 24 hours. The reactions using

ligands **24** and **25** went 75.2 and 79.6 % to completion respectively. The reactions using ligands **26** and **27** showed similar results with the reactions going 81.0 and 82.4% to completion respectively. All of the Table 7 ligands fell short compared to the reaction that used ethylenediamine as the ligand, which proceeded 97.8 % to completion.

**Scheme 12.**



**Table 8.** A comparison of the 5 ligands that were synthesized in Table 7 with the purpose of studying the electronic and steric effects that the ligands have on the system.

Entry	Ligand	<b>31</b>	<b>28</b>	<b>29</b>	<b>30</b>
1	<b>23</b>	21.0	79.0	0	0
2	<b>24</b>	24.8	75.2	0	0
3	<b>25</b>	20.4	79.6	0	0
4	<b>26</b>	19.0	81.0	0	0
5	<b>27</b>	17.6	82.4	0	0
6	<b>En<sup>a</sup></b>	1.5	97.8	0.7	0

a) ethylenediamine.

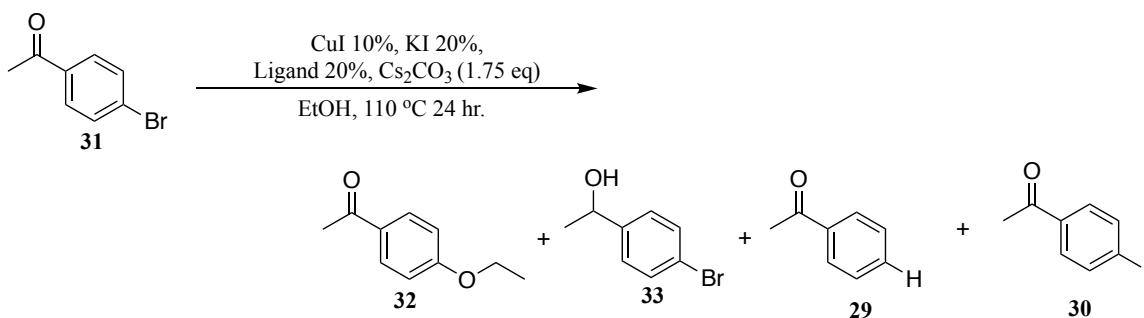
The results from Table 8 show very little variance between the ligands displayed in Table 7 despite having different electronic environments in the aromatic groups. Since all of the synthesized ligands report conversions between 15 and 25% lower than that of ethylenediamine, this suggests that the sterics of the aromatic rings is hindering the reaction process as the bulky ligands chelate to the copper. This is likely independent of whether the ligands have electron donating or electron withdrawing substituents on the

benzene rings. This is due to the fact that the five synthesized ligand systems show very similar results, all within 8 % of each other.

The ligands shown in Table 7 were also tested in the domino reaction using ethanol as the solvent and nucleophile instead of methanol. The reaction conditions that used ligand **23** produced 8% of the ether product (**32**) and 18% of compound **29** with a similar amount of compound **33** in 24 hours. The reactions using ligands **24** and **25** produced 5% and 9% of the aryl ether (**32**) respectively, again with the majority of the product distribution being towards side products **29** and **33**. The reactions using ligands **26** and **27** resulted in 14% and 7.5% of the total analytes being the compound **32** with most of the products being reduced forms of 4-bromoacetophenone (compounds **29** and **33**). The reaction that used ethylenediamine showed similar product distribution to that of ligand **26**, having produced 14% of the desired product with 31% of compound **33**



## Scheme 13.



**Table 9<sup>a</sup>.** A comparison of the 5 ligands that were synthesized in Table 7 using ethanol as a solvent, with the purpose of studying the electronic and steric effects that the ligands have on the system in a larger solvent.

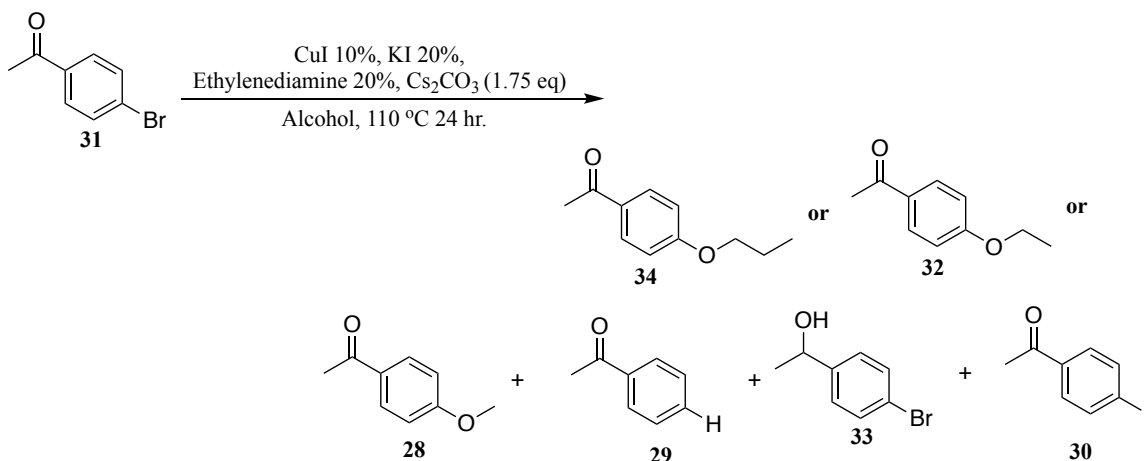
Entry	Ligand <sup>b</sup>	<b>31</b>	<b>32</b>	<b>29</b>	<b>30</b>	<b>33</b>
1	<b>23</b>	60.8	7.9	18.0	0	13.3
2	<b>24</b>	67.3	5.3	19.5	0	7.9
3	<b>25</b>	75.5	9.1	5.0	0	10.4
4	<b>26</b>	54.5	14.4	0.8	0	30.3
5	<b>27</b>	68.2	7.5	22.6	0	2.5
6	<b>En<sup>c</sup></b>	53.6	14.9	0	0	31.5

- a) Percentages in Table 9 are derived from raw area GC values and do not account for R<sub>f</sub> values of individual species. b) see Table 7 for ligand identities. c) ethylenediamine.

The results from Table 9 show much greater variance in the product distribution. All ligands including ethylenediamine and those shown in Table 7 show preference to the compounds **29** and **33** with very little of the ether product (**32**) being produced. It is unknown why the larger alcohols like ethanol show a preference for compounds **29** and **33**, which are both achieved through either, reduction of the carbonyl, or an exchange from halide to hydrogen. These reports are not uncommon however. Production of both **29** and **33** have been reported in conditions that use Cs<sub>2</sub>CO<sub>3</sub> as a base, isopropyl alcohol and using either Iridium or Palladium based catalysts.<sup>18</sup> These conditions are not unlike the ones shown in Scheme 13. Additionally, when compound **27** was used as a ligand, that catalyst complex showed the most preference for the production of compound **29**, with 22.6 % production. If it were the goal to produce this reduced aryl halides like **29**, it is

possible that using compound **27** as a ligand, combined with the conditions from Table 5, entry 7 (which produced 55.9 % of **29**), could have an even higher degree of preference for the production of **29**.

Since ethylenediamine consistently gave the best results as far as producing the ether product and overall reaction progress, the copper ligand complex was tested in three, increasingly large alcohols, starting with methanol, then ethanol and finally n-propanol. This was done to test the reactions versatility among larger alcohols. Entry 1, which used MeOH as a solvent produced 97.9 % of compound **28**. Entry 2, which used ethanol as a solvent, produced mostly compound **33**, but did produce some of the ether product (**32**). Entry **3**, which used n-propanol as the solvent, ran almost to completion with only 4.7 % of 4-bromoacetophenone (**31**) remaining, but had a preference to producing the reduced forms of the starting material **29**, and **33** with 14.3 % and 62.0 % produced respectively.

**Scheme 14.**

**Table 10<sup>a</sup>.** A comparison of the domino reaction using three increasingly larger alcohols as solvents.

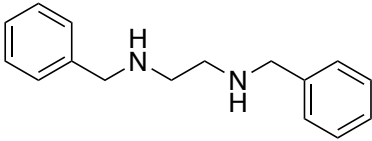
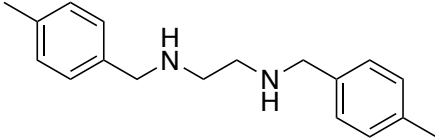
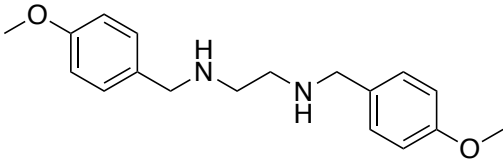
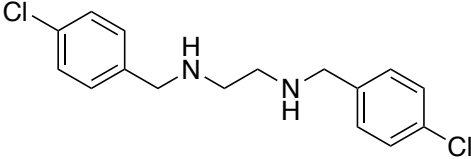
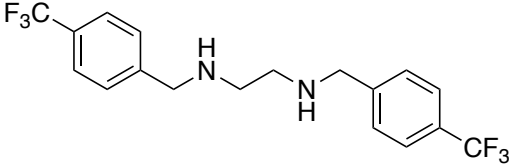
Entry	Alcohol	31	34	32	28	29	33	30
1	MeOH	1.7	0	0	97.9	0.4	0	0
2	EtOH	56.3	0	14.8	0	0.6	28.3	0
3	n-Propanol	4.7	19.0	0	0	14.3	62.0	0

a) Percentages in Table 9 are derived from raw area GC values and do not account for R<sub>f</sub> values of individual species

The results from Table 10 show that methanol produces the most corresponding ether (**28**). The ethers produced by ethanol and n-propanol (**32** and **34** respectively) are much less abundant. This could be due to the decreasing solubility of KI and Cs<sub>2</sub>CO<sub>3</sub> in the less polar solvents. The larger alcohols as solvents also seems to promote reaction pathways that result in compound **33**, which is the reduction of the carbonyl to an alcohol.

## 4. Conclusion

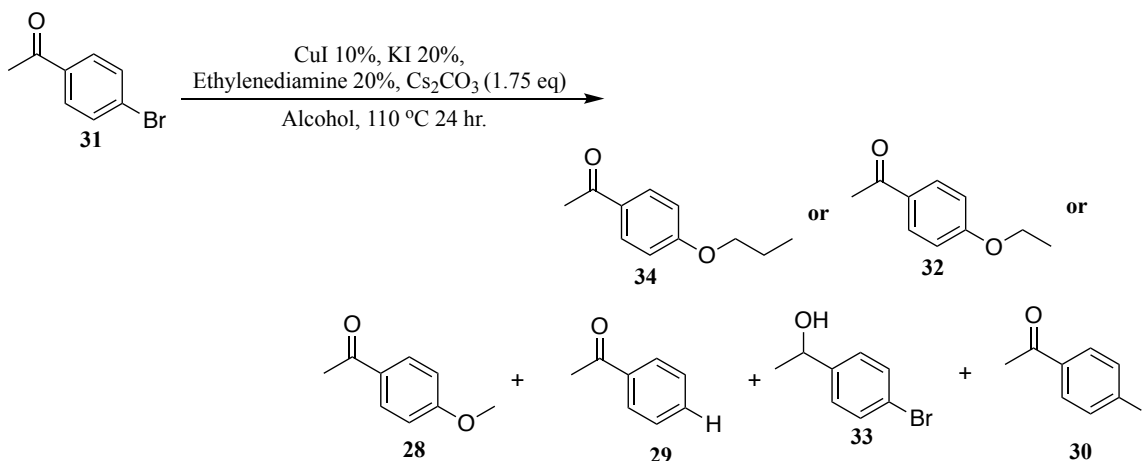
This process attempts to provide a simple pathway to produce an aryl ether from an aryl bromide which is noted to be difficult to do given the less reactive nature of aryl bromides compared to aryl iodides. Ethylenediamine as a ligand was determined to give the best results based on GC data when it comes to producing aryl ethers from aryl bromides in the conditions shown in Scheme 12 and 13. The literature surrounding this topic however, has shown 1,10-phenanthroline<sup>2</sup> and N<sup>1</sup>, N<sup>2</sup>-cyclohexane-1,2-diamine<sup>13</sup> to work best for the Ullman reaction and halogen exchange reaction respectively, with neither reaction having shown much progress from ethylenediamine catalyst systems. These data paired with the results from using compounds **23-27** as ligands suggests that the large N-substituted groups reduce the tendency for aryl ether formation to occur. This is consistent with reports that say larger N-substituents can retard the reaction.<sup>6</sup>

Entry	Ligand
23	
24	
25	
26	
27	

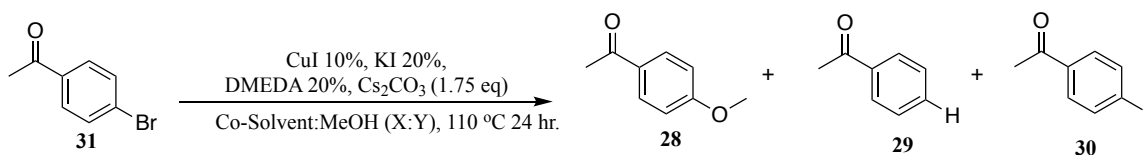
The NMP:MeOH (1:4) solvent system gave the best results in terms of producing the aryl ether from 4-bromoacetophenone when compared to other solvent systems, aside from neat methanol as a solvent. The NMP:MeOH (1:4) solvent system showed reaction progress approximately 15% further than the next best solvent system which can be seen in Table 5. The general trend seems to be that the greater part of the solution that methanol represents, the more aryl ether is formed (Table 4 and 5). This is likely due to the fact that the alcohol is one of the reactants, and a higher concentration of reactants results in a higher likelihood of substitution. This also likely explains why neat methanol worked better than any combination of solvents. This however poses a problem when moving to less polar alcohols like ethanol and n-propanol because both  $\text{Cs}_2\text{CO}_3$  and KI

are salts are not going to be as soluble in larger alcohols.<sup>16</sup> This can be seen in Table 10 as methanol shows significantly more ether (**28**) production than ethanol (**32**) or n-propanol (**34**), with 97.9 %, 14.8 %, and 19.0 % respectively. These obstacles need to be overcome in order to be able to use this reaction in the synthesis of larger organic molecules.

When the domino reaction was run in larger alcohols such as ethanol and n-propanol, the amount of ether produced dropped significantly. Instead, the conditions show favorability for the reduction of the aryl bromide to either compound **29** or compound **33**, shown in Scheme 14. This shows that the current conditions might not be suitable for the coupling of larger aliphatic alcohols to aryl bromides, which is one of the goals of the project. An interesting continuation of the work would be to try the conditions shown in Scheme 14, but use the solvent system from Table 5, entry 8, which uses NMP as a co-solvent to the alcohol. Since the NMP:MeOH (1:4) solvent system worked the best out of the conditions studied in table 5, it could be worth investigating if the success of this NMP:ROH (1:4) solvent system, where R is an alkyl substituent, could translate to larger alcohols, which would give the reaction a wider range of application. This could be a possible solution to the problem of the lack of production of the ether in larger alcohols, observed in Table 10, which currently limits the reaction to methanol as the alcohol.

**Scheme 14.**

It would also be interesting to try the Scheme 14 conditions using sodium iodide with the larger alcohols instead of potassium iodide, given that sodium iodide has been shown to be more soluble than potassium iodide in the larger alcohols.<sup>16</sup> It seems likely that the greater solubility of the salt could allow the halogen exchange step to happen faster, increasing the production of ether product over that of compounds **29** and **33**.

**Scheme 10.**

One more interesting direction that this project could go in the future is the production of compound **29** using the conditions from Table 5, entry 7, which uses a NMP:MeOH (4:1) solvent system. This solvent system, combined with the conditions in Scheme 10, caused 55.9 % of the product distribution to be due to compound **29**. This would be an interesting method of reducing the halogen on aryl halide to hydrogen using

a copper catalyst. It could be worth attempting to make the conditions of Scheme 10 even more favorable to a halogen reduction just to see if it is possible to get even higher conversion of **29** than 55.9 %.



## 5. References

1. Fritz Ullmann, Paul Sponagel (1905). "Ueber die Phenylirung von Phenolen". *Berichte der deutschen chemischen Gesellschaft*. **38** (2): 2211–2212.
2. Wolter, M.; Nordmann, G.; Job, G. E.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, **6**, 973-976.
3. Fagan, P. J.; Hauptman, E.; Shapiro, R.; Casalnuovo, A. *J. Am. Chem. Soc.* **2000**, *122*, **21**, 5043–5051.
4. Torraca, K. E.; Huang, X.; Parrish, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 10770–10771.
5. Han, R.; Hillhouse, G. L. *J. Am. Chem. Soc.* **1997**, *119*, 8135–8136.
6. Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2010**, *1*, 13-31.
7. Giri, R.; Brusoe, A.; Troshin, K.; Wang, J. Y.; Font, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2018**, *140*, 793-806.
8. Cristau, H. J.; Cellier, P. P.; Hamada, S.; Spindler, J. F.; Taillefer, M. *Org. Lett.* **2004**, *6*, 913-916.
9. Strieter, E.R.; Bhayana, B.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 78-88.
10. Zanon, J.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 2890-2891.
11. Corbett J. W.; Rauckhorst M. R.; Qian F.; Hoffman R. L.; Knauer C. S.; Fitzgerald L. W. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6250–6256.
12. Toumi, M.; Couty, F.; Evano, G. *Angewandte Chemie Int. Ed.* **2007**, *46*, 572-575.
13. Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 14844-14845.
14. Liu, Y.; Bai Y.; Zhang, J.; Li, Y.; Jiao, J.; Qi, X. *Eur. J. Org. Chem.* **2007**, 6084-6088.

15. Khan, M. S. Y.; Chawla, G. *Indian Journal of Chemistry*. **2002**, *41B*, 653-663.
16. Larson, R. G.; Hunt, H. *J. Phys. Chem.* **1939**, *43*, **4**, 417-423.
17. Ouali, A.; Spindler, J-F.; Jutand, A.; Taillefer, M. *Adv. Synth. Catal.* **2007**, *349*, 1906-1916.
18. Zanardi, A.; Mata, J. A.; Peris, E. *J. Am. Chem. Soc.* **2009**, *131*, 14531-14537.