COPPER-CATALYZED CROSS-COUPLING REACTIONS: THE FORMATION OF CARBON-CARBON AND CARBON-SULFUR BONDS

A Dissertation Presented

by

CRAIG G. BATES

Submitted to the Graduate School of the
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of the requirements for the degree of

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DEDICATION

For Mom and Dad

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ABSTRACT

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We have developed copper-catalyzed cross-coupling reactions for the formation of carbon-carbon and carbon-sulfur bonds. These newly developed methods demonstrate that the conditions of the traditional Ullmann reaction can be improved. We describe the synthesis of diarylacetylenes through the cross-coupling of aryl iodides and phenylacetylene using [Cu(phen)PPh_3Br] as the catalyst. This method is then utilized for the synthesis of 2-aryl-benzo[*b*]furans via a copper-catalyzed cross-coupling reaction between aryl acetylenes and 2-iodophenols and a subsequent 5-endo-dig cyclization. The formation of carbon-acetylene bonds is also extended to include vinyl iodides for the purpose of synthesizing 1,3-enynes. Due the lack of a general metal-mediated synthesis of aryl sulfides, we developed a copper-catalyzed cross-coupling reaction between aryl iodides and thiols using a catalytic amount of CuI and 2,9-dimethyl-1,10-phenanthroline as an additive. This method was also extended to include vinyl iodides for the synthesis of vinyl sulfides using [Cu(phen)$(PPh_3)_2$]NO_3 as the catalyst. All of these methods afford the desired product in good to excellent yields without the use of palladium or expensive / air sensitive additives.

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LIST OF ABBREVIATIONS

acac	- 2,4-pentanedione
bipy	- 2,2'-bipyridine
dba	- dibenzylideneacetone
DBU	- 1,8-diazabicyclo[5.4.0]undec-7-ene
DIBAL-H	- diisobutyl aluminium hydride
DMPU	- 1,3-dimethyl hexahydro-2-pyrimidinone
DMSO	- dimethyl sulfoxide
DPEPhos	- (Oxydi-2,1-phenylene)bis(diphenylphosphine)
GC	- Gas Chromatography
HMPA	- hexamethyl phosphoramide
neocup	- 2,9-dimethyl-1,10-phenanthroline
P_2–Et	-1-Ethyl-2,2,4,4,4-pentakis(dimethylamino)-2λ^5,4λ^5-catenadi(phosphazene)
phen	- 1,10-phenanthroline
PPh_3	- triphenylphosphine
R-(+)-Tol-BINAP	- (R)-(+)-2,2'-bis(di-p-tolylphosphino)-1,1'-binaphthyl
TLC	- thin layer chromatography

CHAPTER 1

PROLOGUE

1.1 Introduction:

Carbon-carbon and carbon-heteroatom bonds are found in many compounds that exhibit important biological, pharmaceutical and materials properties.[1-4] Due to the importance of these bonds, there has been a need to develop mild and general methods for their synthesis.[5-7] Classically, the synthesis of these bonds involved nucleophilic aromatic substitution reactions, which required the use of electron-deficient aryl halides or N_2 as a leaving group. The discovery of transition-metal mediated reactions for the synthesis of carbon-carbon and carbon-heteroatom bonds was an important discovery for synthetic chemists. Most prevalent among these methods are the palladium(0)-catalyzed cross-coupling reactions such as the Heck reaction, Sonogashira-Miyaura reaction, the Suzuki reaction and the Hartwig-Buchwald coupling (Figure 1.1).[8] These palladium(0)-based methods are mild, tolerate a variety of functional groups and provide reproducible yields.

Although these palladium(0)-based reactions are routinely used in organic synthesis, it is not uncommon to find substrates that are incompatible with the published procedures. Examples of substrates that do not cross-couple well with palladium(0)-catalysts include aryl halides that are substituted in the *ortho*-position or contain electron-donating groups, secondary alcohols, active methylene compounds, heterocycles and aryl selenols. Furthermore, there is a lack of tolerance for certain functional groups such as amides, amines, alcohols and carboxylic acids.[9-11]

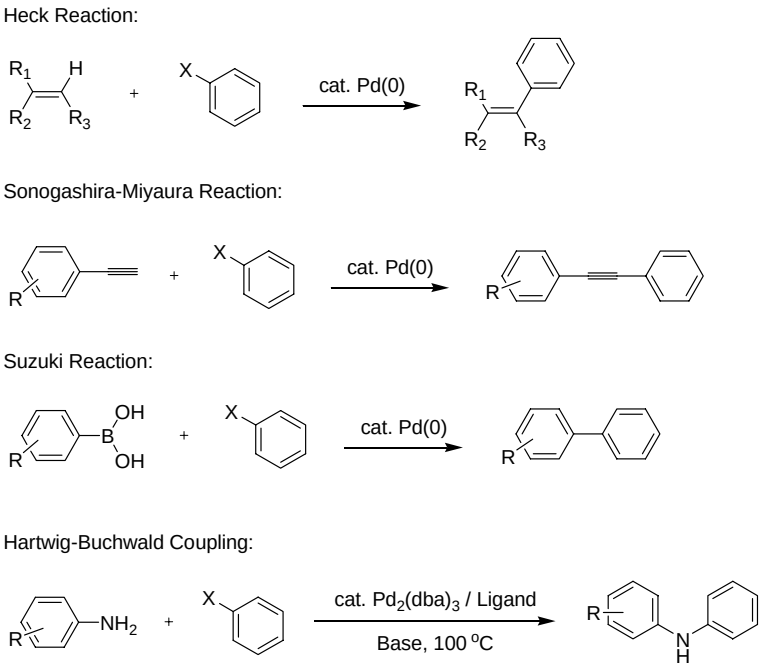


Figure 1.1: Various Palladium(0)-catalyzed cross-coupling reactions.

Prior to the discovery of these palladium(0)-based reactions, copper-mediated reactions such as the Ullmann reaction and the Castro-Stevens coupling were used for the formation of these carbon-carbon and carbon-heteroatom bonds (Figure 1.2).[12-15] These reactions are known to suffer from some drawbacks, which include poor solubility of the copper salts, high reaction temperatures (>180 ^{o}C), the need for stoichiometric or in certain instances greater than stoichiometric amounts of copper, low functional group tolerance and irreproducible results.[16, 17] Despite these drawbacks the copper-based cross-coupling reactions remain the method of choice in large industrial-scale reactions and have been successfully used where the palladium methods have failed.[16, 18, 19] If the limitations of the copper-based methods can be addressed, then it may be feasible to provide complementary or alternative methods to the current palladium(0) chemistry.

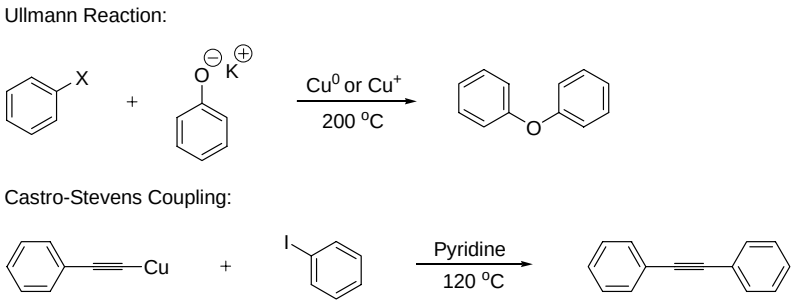


Figure 1.2: Examples of the Ullmann reactions and the Castro-Stevens coupling reaction.

In the literature, observations have been made which indicate that the traditional copper protocols can be improved if the solubility of the copper salts can be increased. In 1964, Harold Weingarten noted that an impurity in his solvent led to increased reaction rates in the coupling of potassium phenoxide and bromobenzene.[20] A thorough examination of this impurity revealed that it was a diester and Weingarten hypothesized that this ester was increasing the solubility of the catalyst. In 1975, Cohen reported on the homocoupling of *o*-bromonitrobenzene at room temperature with a copper(I) salt (copper(I) trifluoromethanesulfonate) that was soluble in the reaction solvent of acetone and ammonia.[21] Moreover, in 1987 Paine reported that the catalytically active species in the Ullmann reaction is a soluble cuprous ion.[22] In 1993, Capdevielle reported on the copper-catalyzed methanolysis of aryl bromides.[23] Similar to Weingarten, he observed that the use of various esters increases the reaction rate. These examples demonstrate that it is feasible in improve the conditions of the traditional Ullmann reaction.

More recently in 1997, Buchwald demonstrated the cross-coupling of phenols with aryl bromides in toluene at 110 ^{o}C using the soluble copper complex copper(I) trifluoromethanesulfonate–benzene with 1-napthoic acid and ethyl acetate as additives and Cs_2CO_3 as a base.[24] This report on the synthesis of diaryl ethers is exemplified by the

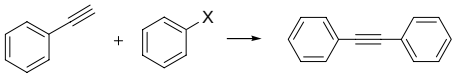
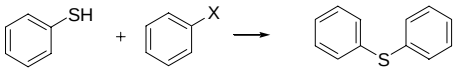
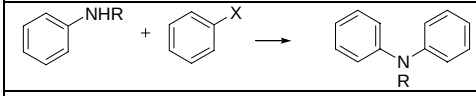
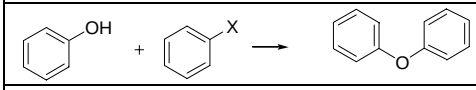
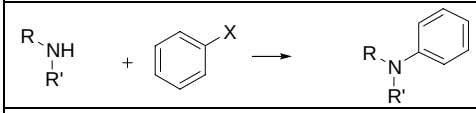
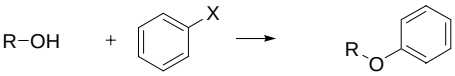
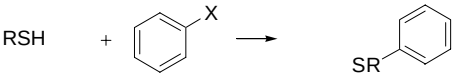
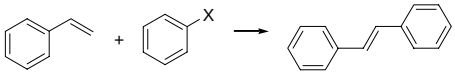
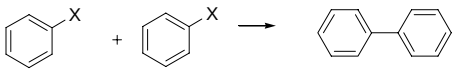
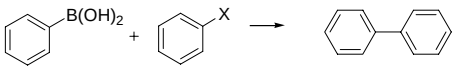
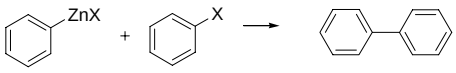
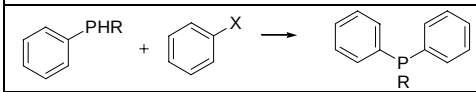
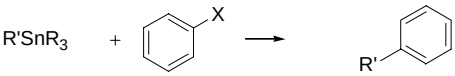
following aspects: (a) the use of a catalytic amount of copper rather than the stoichiometric (or greater) amounts required for the traditional copper-based methods and (b) it avoided the use of air-sensitive and expensive ligands that are required with the established palladium methodology. Shortly thereafter in 1999, Goodbrand had demonstrated the rate accelerating effects of 1,10-phenanthroline as an additive in the copper-catalyzed synthesis of triarylamines.[25]

Based on these prior examples, our group began a study of using copper(I) complexes as catalysts for cross-coupling reactions. These complexes are soluble in a variety of organic solvents and bear ligands that have been shown to be effective as additives in the modern copper-catalyzed cross-coupling reactions. Promising results were first obtained in the synthesis of both diaryl ethers and triarylamines using $Cu(PPh_3)_3Br$ as the catalyst (Figure 1.3).[19, 26] Thus providing examples that these copper(I) complexes can be used catalytically in Ullmann-type reactions under mild reaction conditions.

This dissertation will describe the expansion of our copper-based methodologies through the use of soluble copper(I) complexes as catalysts in a variety of cross-coupling reactions. It will also demonstrate that the reaction conditions of the traditional copper-mediated reactions can be greatly improved. These newly discovered reactions are general, tolerate a variety of functional groups and substrates, avoids the use of expensive and/or air-sensitive additives and overcomes some of the limitations of the palladium(0)-catalyzed analogues. Table 1.1 lists the reactions that are known to occur with Ullmann conditions, modified Ullmann conditions and palladium catalysis as of 2000. We decided

to initially focus on areas where there is a deficiency of literature precedences for Ullmann type reactions.

Table 1.1: Cross-coupling reactions known to be mediated by palladium, traditional Ullmann conditions, and modified Ullmann reaction conditions. Selected examples are given.

Cross-Coupling Reaction	Palladium	Ullmann	Modified Ullmann
	✓ 27	✓ 14, 15	✓ 28
	✓ 29-33	✓ 16	✓ 34
	✓ 31, 35	✓ 16	✓ 19, 25, 36, 37
	✓ 32	✓ 16, 38	✓ 24, 26
	✓ 31	✓ 16	✓ 16
	✓ 39	✓ 16, 38	✗
	✓ 30	✓ 16	✗
	✓ 40	✗	✗
	✓ 41	✓ 42	✓ 42
	✓ 40	✗	✗
	✓ 40	✗	✗
	✓ 43	✗	✗
	✓ 44	✗	✓ 45

Key: Green check – reaction known to exist with good reaction conditions
Yellow check – reaction known to exist but reactions are limited
Red "X" – reaction is not known to exist

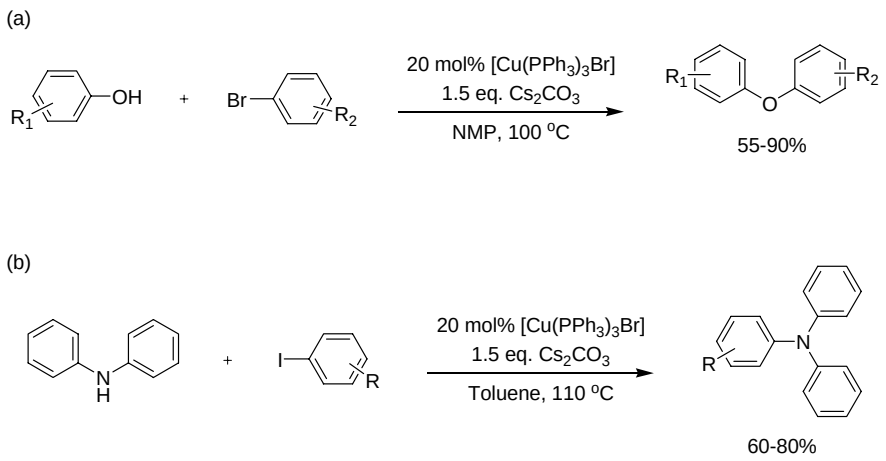


Figure 1.3: Copper-catalyzed cross-coupling reactions for the synthesis of (a) diaryl ethers and (b) triarylamines developed by the DV group.

Chapter 2 concentrates on the development of a copper-catalyzed synthesis of diarylacetylenes through the cross-coupling of aryl iodides and phenylacetylene. Previous copper-based methods for this transformation either required the use of a stoichiometric amount of copper or failed to establish the scope and functional group tolerance of the method. Our method addresses these two issues by demonstrating that a copper(I) complex can be used catalytically while tolerating a variety of functional groups on the aryl iodide.

In Chapter 3, we apply the method developed for the synthesis of diarylacetylenes and apply it towards a biological and pharmaceutically important class of compounds, 2-arylbenzo[*b*]furans. This approach involves a domino cross-coupling reaction and 5-endo-dig cyclization. We demonstrate that a wide-range of 2-aryl-benzo[*b*]furans can be synthesized in one-step in good yields. There is a high tolerance of functional groups and unlike other metal-mediated approaches avoids the use of palladium.

In Chapter 4 we extend our aryl acetylene methodology to include vinyl iodides. The 1,3-enyne moiety is important class of compounds and we developed a mild, and

general method for their synthesis. Through a copper-catalyzed cross-coupling reaction between acetylenes and vinyl iodides, we synthesized a wide-range of 1,3-enynes in very good yields. This method tolerated an extensive amount of functional groups and substrates with full retention of the vinyl iodide's geometry.

Chapter 5 describes the formation of carbon-sulfur bonds via a copper-catalyzed cross-coupling reaction between thiols and aryl iodides. This methodology is an improvement of the previously reported methods for the formation of these bonds. Our methodology includes a wide-range of aryl iodides and both aryl and alkyl thiols can be used. The protocol tolerates a variety of functional groups and substrates. This method also avoids the use of expensive additives and bases which are required for similar transition-metal catalyzed reactions.

Finally in Chapter 6, we apply our aryl sulfide methodology towards the synthesis of vinyl sulfides. This is achieved through a cross-coupling reaction between a wide range of thiols and vinyl iodides. The desired vinyl sulfides are obtained in excellent yields with short reaction times and a low catalytic amount of copper. The geometry of the starting vinyl iodide is retained and the scope of the method is described through the functional group and substrate tolerance. This method is also mild, and avoids the use of palladium and air sensitive and/or expensive additives.

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CHAPTER 2

COPPER-CATALYZED SYNTHESIS OF DIARYLACETYLENES

2.1 Introduction:

Acetylene-based compounds are of known importance throughout synthetic chemistry. The [2+2+2] cyclotrimerization of alkynes is important reaction that can afford hexasubstitiuted benzenes in one step.[1-5] They have been shown to be useful intermediates in the synthesis of naturally occurring and biologically active compounds such as dehydrotremetone,[6] lunularic acid[7] and cicerfuran[8] (Figure 2.1). The acetylene moiety has also been used in compounds that have shown to exhibit interesting electronic, optical and other materials-based properties.[9-15] Many acetylenic-based compounds have been examined for use as molecular wires and nonlinear optics.[16, 17]

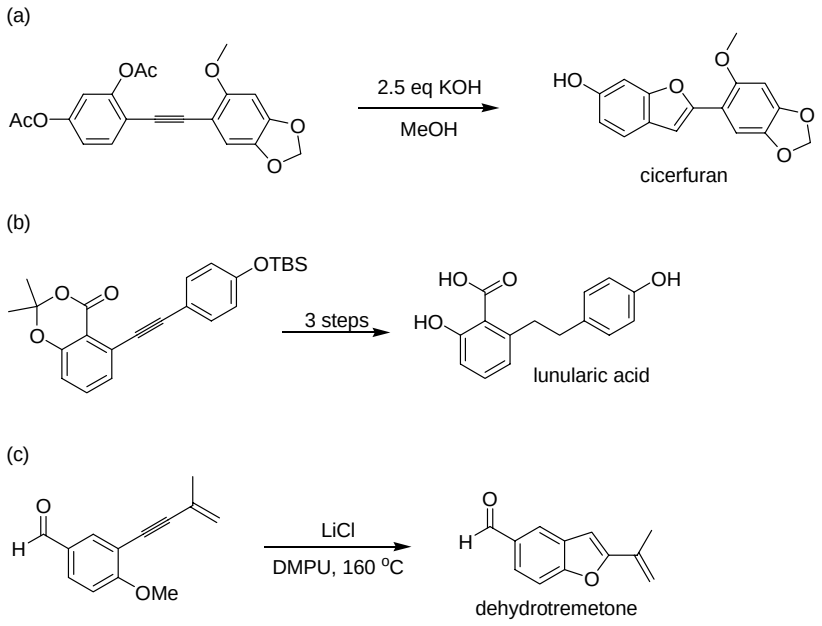


Figure 2.1: The use of acetylenes as intermediates in the synthesis of the naturally occurring compounds (a) cicerfuran, a compound found to protect wild chick peas from *Fugarium* wilt (b) lunularic acid, an inhibitor of angiogenesis and (c) dehydrotremetone, a natural compound found in white snake root.

2.2 Background:

One of the first metal-mediated synthesis of diarylacetylenes was reported by Castro and Stevens in 1963 (Figure 2.2).[18, 19] This involved the cross-coupling of aryl iodides with a preformed cuprous phenylacetylide in refluxing pyridine. Shortly thereafter in 1975, Sonogashira developed a palladium-catalyzed coupling reaction between aryl halides and aryl acetylenes using copper(I) iodide as a co-catalyst.[20] This method was an improvement over Castro and Stevens method since the role of the transition metal was now catalytic. The advent of this palladium/copper catalyzed method has greatly improved the reaction conditions and functional group tolerance and is currently the method of choice for the synthesis of a variety of diarylacetylenes.[21] However, homocoupling of the acetylene is an observed side product in certain Sonogashira reactions.[22] In 1992, Miura and coworkers demonstrated the first copper-catalyzed coupling of a limited range of aryl and vinyl iodides with acetylenes using copper iodide and triphenylphosphine as an additive in DMF to produce aryl and vinyl acetylene derivatives.[23, 24] Miura's work demonstrated that copper alone can catalyze the cross-coupling of acetylenes and aryl iodides.

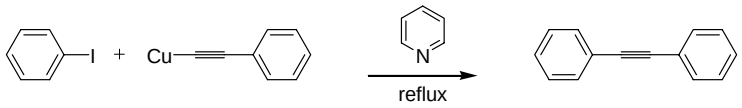


Figure 2.2: An example of the Castro-Stevens coupling reaction.

2.3 [$Cu(PPh_3)_3Br$] as a catalyst for diarylacetylene synthesis:

Due to the early success of our group's ability to develop protocols for the formation of C-O and C-N bonds,[25, 26] we decided to see if this chemistry can be extended to acetylenes. Starting with [$Cu(PPh_3)_3Br$] as the catalyst, its ability to catalyze the

coupling of iodobenzene and phenylacetylene with various bases in toluene at 110 ^{o}C for 24 hours was examined (Figure 2.3). By screening a variety of bases and checking the reaction by TLC, the desired product, diphenylacetylene, was observed. However, large amounts of starting material remained and the yield was estimated to be less than 50%. It was observed that the best base for the coupling reaction using [Cu(PPh$_3$)$_3$Br] as the catalyst was K_2CO_3. Other bases such as Cs_2CO_3 and K_3PO_4 appeared less effective. Other bases that were tried but were found to be ineffective were KO*t*Bu and Et_3N. The effect of the solvent was also examined with this catalyst using K_2CO_3 as the base. After this initial screening process it was shown that [Cu(PPh$_3$)$_3$Br] was not as effective as a catalyst as we had hoped.

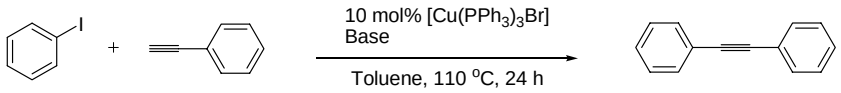


Figure 2.3: Early attempts at developing a copper-catalyzed cross-coupling reaction of iodobenzene and phenylacetylene using [Cu(PPh$_3$)$_3$Br] as the catalyst.

2.4 Improved success with [Cu(phen)PPh$_3$Br] as the catalyst:

In 1999, Goodbrand had noted the rate accelerating effects of using 1,10-phenanthroline as an additive in the copper-catalyzed synthesis of triarylamines.[27] 1,10-phenanthroline (phen) and 2,9-dimethyl-1,10-phenanthroline (neocup) are known chealtors of copper and could be used as ligands in copper(I) complexes.[28, 29] Therefore, we synthesized both [Cu(phen)PPh$_3$Br] and [Cu(neocup)PPh$_3$Br] from [Cu(PPh$_3$)Br] (Figure 2.4). These complexes are soluble in a variety of organic solvents and are stable under ambient conditions. I then examined the efficacy of both [Cu(phen)PPh$_3$Br] and [Cu(neocup)PPh$_3$Br] to catalyze the coupling reaction seen in Figure 2.3 using K_2CO_3 as the base. A dramatic improvement over [Cu(PPh$_3$)$_3$Br] was made when

[Cu(phen)PPh_3Br] was used as the catalyst. GC analysis of the reaction showed that almost all of the starting acetylene was consumed within 24 hours. Surprisingly, a similar complex, [Cu(neocup)PPh_3Br], was very ineffective at catalyzing the reaction. Therefore, using [Cu(phen)PPh_3Br] a variety of bases and solvents were screened to develop an optimized procedure (Table 2.1).

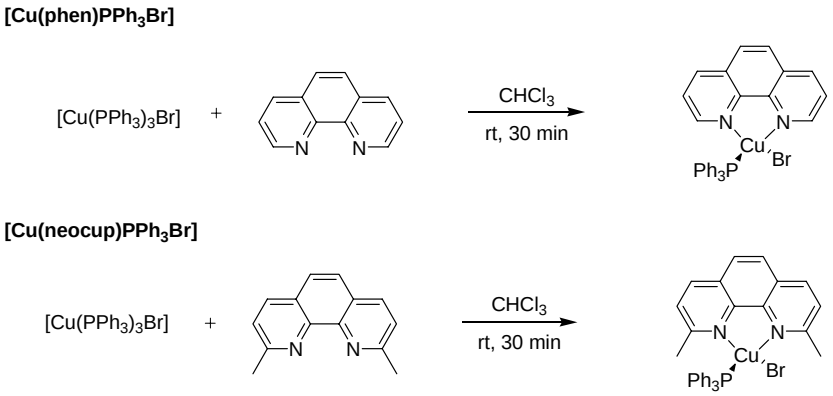
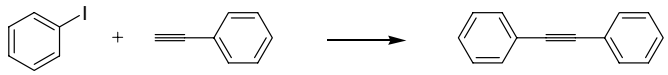


Figure 2.4: The synthesis of both [Cu(phen)PPh_3Br] and [Cu(neocup)PPh_3Br] using [Cu$(PPh_3)_3Br$] as the precursor complex.

From Table 2.1 it can be seen that for the cross-coupling of iodobenzene and phenylacetylene the optimal conditions are as follows: 10 mol% [Cu(phen)PPh_3Br], 2.0 equivalents of K_2CO_3 as the base in Toluene at 110 ^oC for 24 hours. Running the reaction at a lower temperature of 70 ^oC and decreasing the equivalents of base to 1.0 had negative effects on the yield. A series of control reactions were also performed and it was found that the reaction fails in the absence of either base or catalyst. Furthermore, with the use of the copper(I) salt CuI or CuI and 1,10-phenanthroline as an additive the reaction fails. This demonstrates the necessity of using well-defined complexes for this coupling reaction.

Table 2.1: Optimization of both base and solvent using [Cu(phen)PPh_3Br] as the catalyst for the synthesis of diphenylacetylene.



Catalyst (mol%)	Base (eq.)	Solvent (°C)	Result[a]
[Cu(phen)PPh_3Br] (5)	K_2CO_3 (1.0)	DMF (70)	N.R.
[Cu(phen)PPh_3Br] (5)	K_2CO_3 (1.0)	THF (70)	<5%
[Cu(phen)PPh_3Br] (5)	KO*t*Bu (1.0)	Toluene (70)	N.R.
[Cu(phen)PPh_3Br] (10)	K_2CO_3 (2.0)	Toluene (70)	10-15%
[Cu(phen)PPh_3Br] (10)	K_3PO_4 (2.0)	Toluene (110)	50%
[Cu(phen)PPh_3Br] (10)	CsF (2.0)	Toluene (110)	60-70%
None	K_2CO_3 (2.0)	Toluene (110)	N.R.
[Cu(phen)PPh_3Br] (10)	None	Toluene (110)	N.R.
[Cu(phen)PPh_3Br] (10)	K_2CO_3 (2.0)	Toluene (110)	80-90%
CuI / 1,10-phenanthroline	K_2CO_3 (2.0)	Toluene (110)	<5%
CuI	K_2CO_3 (2.0)	Toluene (110)	N.R.

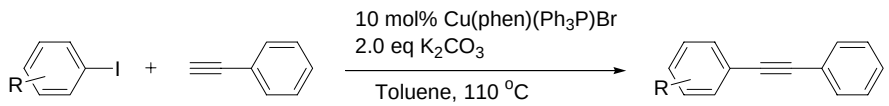
[a]GC estimates based on optimal reaction

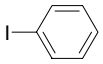
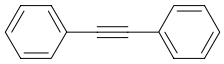
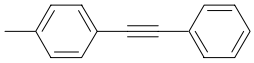
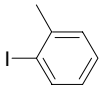
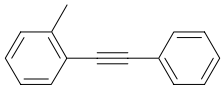
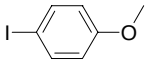
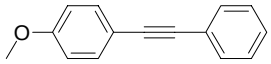
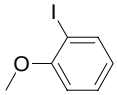
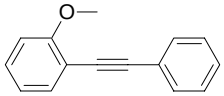
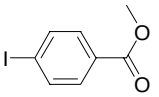
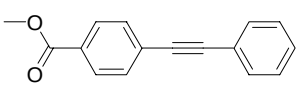
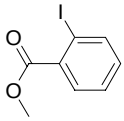
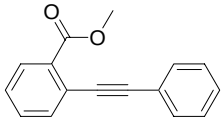
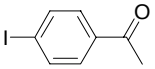
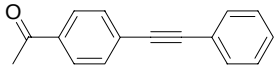
2.5 Results using optimal conditions:

Using the abovementioned optimal conditions, we investigated the effect of having both electron-donating and electron-withdrawing groups on the aryl halide (Table 2.2). As seen in Table 2.2 the protocol tolerated a wide variety of aryl iodides. Electron-donating groups (Table 2.2 entries 2-5) and electron-withdrawing groups (Table 2.2 entries 6-8) were successfully coupled to phenylacetylene in good to excellent yields. Furthermore, aryl iodides that were substituted in the *ortho* position (Table 2.2 entries 3,5 and 7) showed only a slight decrease in yield when compared with the *para* substituted

analogue. Also, base sensitive functional groups such a methyl ketone (Table 2.2 entry 8) and an ester (Table 2.2 entries 6 and 7) were well tolerated.

Table 2.2: The cross-coupling reaction of a variety of aryl iodides and phenylacetylene using the optimized protocol.



Entry	Aryl Iodide	Product	Isolated Yield (%)
1			80
2			74
3			71
4			97
5			70
6			89
7			76
8			85

2.6 Discovering a more active catalyst [Cu(phen)(PPh_3)$_2$]NO_3:

After the development of the method for the cross-coupling of aryl iodides and phenylacetylene described above, our group had synthesized additional copper(I)

complexes bearing bidentate nitrogen-based ligands. To determine if a more active complex was available I monitored the formation of diphenylacetylene over time (Figure 2.5). We discovered that the most active catalyst was $[Cu(phen)(PPh_3)_2]NO_3$ (▽ in Figure 2.5). $[Cu(phen)(PPh_3)Br]$ (○) was slightly less effective and the use of $[Cu(PPh_3)_3Br]$ (□) resulted in only 40% conversion to the desired product in 24 hours. Surprisingly, complexes such as $[Cu(neocup)(PPh_3)Br]$ (◇) and $[Cu(bipy)(PPh_3)Br]$ (△) (bipy = 2,2'-bipyridine) were found to be much less effective at catalyzing this reaction. Based on the screening of these newer complexes we now suggest the use of $[Cu(phen)PPh_3)_2]NO_3$ as the catalyst of choice for the cross-coupling of aryl iodides and phenylacetylene. The synthesis of this new complex from $[Cu(PPh_3)_2NO_3]$ can be seen in Figure 2.6 and the single crystal X-ray structure can be seen in Figure 2.7.

2.7 Conclusions:

In summary, we have developed a protocol for the cross-coupling of aryl iodides and phenylacetylene using 10 mol% $[Cu(phen)PPh_3Br]$ as the catalyst, 2.0 equivalents of K_2CO_3 as the base in toluene.[30] This method tolerates a wide-variety of functional groups including electron-withdrawing, electron-donating and base sensitive groups. After this protocol was published, we discovered that $[Cu(phen)(PPh_3)_2]NO_3$ is a more active catalyst for the same cross-coupling reaction. Furthermore, this method does not require the use of palladium and/or air-sensitive and expensive phosphine ligands.

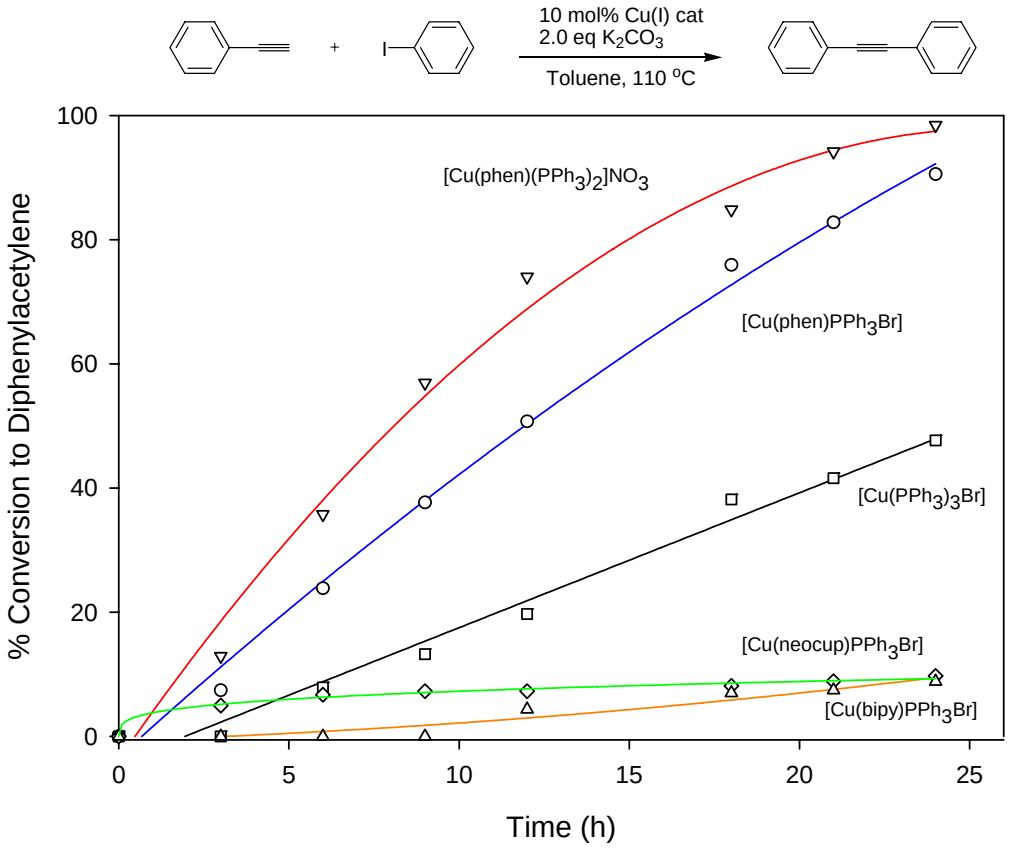


Figure 2.5: The activity of a variety of copper(I) complexes as catalysts for the cross-coupling of iodobenzene and phenylacetylene. (Note: the lines are drawn for visual reference only.)

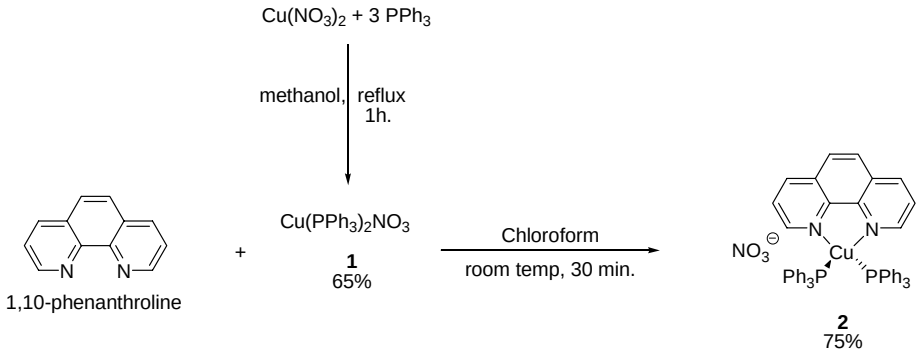


Figure 2.6: The synthesis of $[Cu(phen)(PPh_3)_2]NO_3$ from $[Cu(PPh_3)_2NO_3]$.

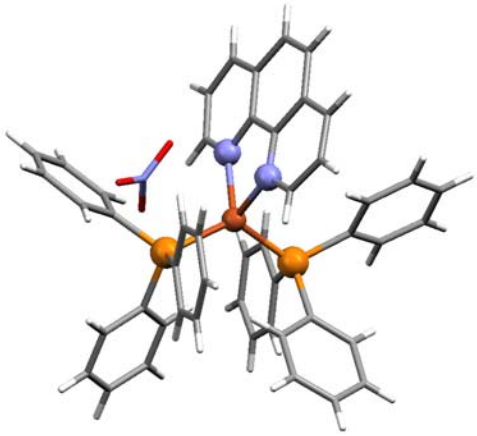


Figure 2.7: Single crystal X-ray structure of $[Cu(phen)(PPh_3)_2]NO_3$ (**2**).

2.8 References:

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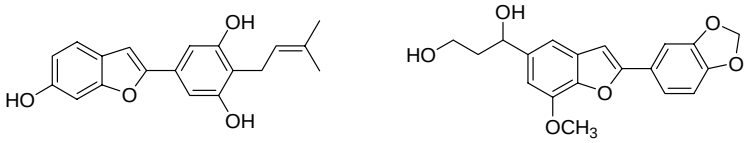
CHAPTER 3

SYNTHESIS OF 2-ARYL-BENZO[*b*]FURANS: VIA A COPPER-CATALYZED DOMINO CROSS-COUPLING REACTION AND 5-ENDO-DIG CYCLIZATION

3.1 Introduction:

Benzo[*b*]furans are prevalent in many compounds and natural products that have important biological properties[1] (Figure 3.1). These include: anti-tumor properties,[2] inhibition of protein phosphatase 1B,[3] 5-HT_2 and 5-HT_3 antagonist activity,[4] inhibition of 5-Lipoxygenase (5-LO),[5] and anti-fungal properties.[6] Pharmaceutically, these properties are relevant in the treatment for cancer, cardiovascular disease, type 2 diabetes, migraines, dementia, and anxiety.[2, 5]



(a) Moracin C (b) (±)-Machicendiol

Figure 3.1: 2-aryl-benzo[*b*]furans found to exist in nature: (a) Moracin C an antifungal produced by the mulberry *Morus alba* (b) (±)-Machicendiol, a naturally occurring compound found in the Extracts of *Machilus glaucescens*.

3.2 Background:

The current methods for the synthesis of benzo[*b*]furans include the dehydrative cyclization of α-(phenoxy)-alkyl ketones, cyclofragmentation of oxiranes, acidic dehydration of *o*-hydroxybenzyl ketones, and base-mediated decarboxylation of *o*-acylphenoxyacetic acids and esters (Figure 3.2).[7] These traditional methods are often multi-step reactions, limited to a particular substrate and do not tolerate a variety of functional groups. More recently, palladium-based cross-coupling reactions with copper

iodide as a co-catalyst have been developed for the synthesis of benzofurans.[8-18] This is accomplished through a tandem Sonagashira coupling/5-*endo-dig* cyclization starting from either *o*-iodophenols or *o*-ethynylphenols. In comparison to the traditional methods, these palladium-based protocols offer increased functional group tolerance and improved yields of the desired benzo[*b*]furan.

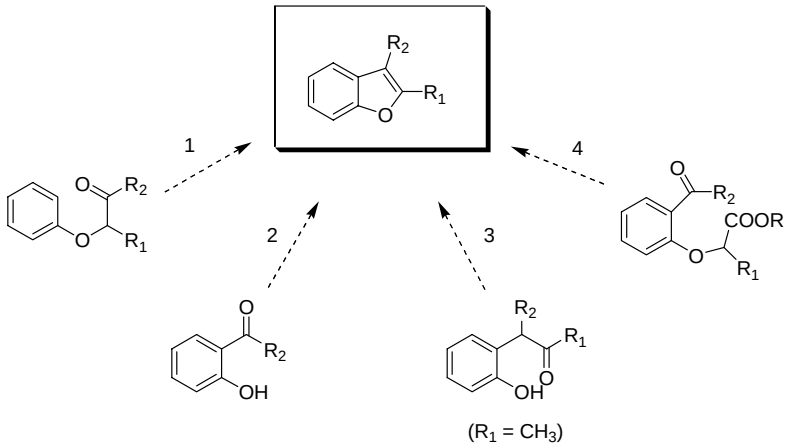


Figure 3.2: The traditional methods of benzo[*b*]furan synthesis: (1) dehydrative cyclization of α-(phenoxy)alkyl ketones, (2) cyclofragmentation of oxiranes (four steps), (3) acidic dehydration of *o*-hydroxybenzyl ketones and (4) base-mediated decarboxylation of *o*-acylphenoxyacetic acids and esters.

The use of copper has previously been shown to mediate the synthesis of benzo[*b*]furans. Castro and co-workers synthesized 2-phenyl-benzo[*b*]furan through the coupling reaction of cuprous phenylacetylene and *o*-iodophenol.[19] This procedure, however, requires the use of a stoichiometric amount of the preformed cuprous acetylide and refluxing pyridine. Owen and coworkers modified Castro's procedure using cuprous oxide (63 mol %) and various acetylenes, but this procedure still requires the use of refluxing pyridine and the amount of copper required is still high.[20] The scope and potential of these reactions have not been fully explored.

In recent years, our group,[21-24] the Buchwald group[25-31] and others[32-35] have been interested in developing copper-catalyzed cross-coupling reactions. In contrast to the traditional Ullmann coupling, these methods are mild and tolerate a wide range of functional groups. When compared to noble-metal catalysts, copper-based methods have an economic attractiveness and hence remain the reactions of choice in large and industrial scale reactions.

In chapter 2 we had shown that [Cu(phen)(PPh_3)Br] can be used as a catalyst for the coupling of phenylacetylene and iodobenzene using K_2CO_3 as the base in toluene.[22] In an ongoing search for more active copper(I)-catalysts, we had prepared a variety of copper(I) complexes bearing bidentate nitrogen-based ligands and monitored the formation of diphenylacetylene over time (Figure 2.5). We discovered that the most active catalyst was [Cu(phen)(PPh_3)$_2$]NO_3. Based on these findings we chose to use [Cu(phen)(PPh_3)$_2$]NO_3 as the catalyst for the coupling of o-iodophenols and aryl acetylenes to synthesize 2-aryl-benzo[b]furans.

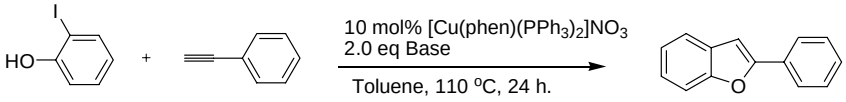
3.3 Optimization of the Base:

We then screened various bases using *o*-iodophenol and phenylacetylene as the reactants, [Cu(phen)(PPh_3)$_2$]NO_3 as the catalyst in toluene (Table 3.1). We found that Cs_2CO_3 was the most effective base. Other bases such as K_3PO_4, K_2CO_3, NaO*t*Bu and KO*t*Bu were less effective and Et_3N was ineffective.

3.4 Additional control experiments:

Through control experiments we found that CuI, CuBr or CuCl could not effectively catalyze the reaction and the conversion to 2-phenylbenzo[*b*]furan was 10%, 10%, and 20% respectively. Finally, 2-phenylbenzo[*b*]furan was not observed by GC when the reaction was run in either the absence of Cs_2CO_3 or $[Cu(phen)(PPh_3)_2]NO_3$. Based on these control experiments, we decided to use $[Cu(phen)(PPh_3)_2]NO_3$ as the catalyst, Cs_2CO_3 as the base in toluene as the standard protocol to synthesize 2-aryl-benzo[*b*]furans from *o*-iodophenols and aryl acetylenes.

Table 3.1: Base effects on the copper(I) catalyzed synthesis of 2-aryl-benzo[*b*]furans.



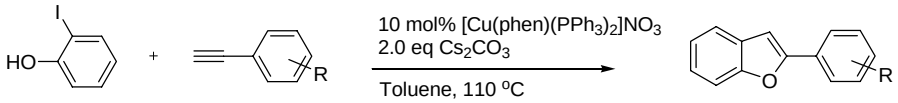
Base	% conversion (by GC)
Cs_2CO_3	>95
K_3PO_4	67
K_2CO_3	53
KO*t*-Bu	40
NaO*t*-Bu	29
Et_3N	0

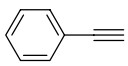
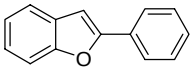
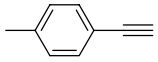
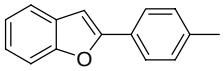
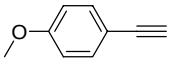
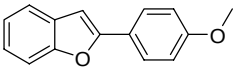
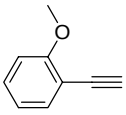
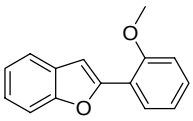
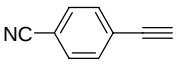
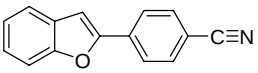
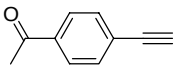
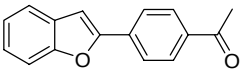
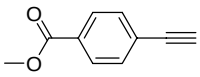
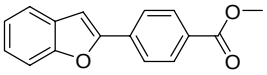
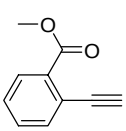
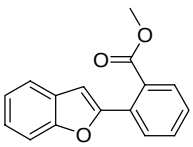
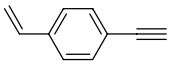
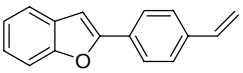
3.5 Coupling *o*-iodophenol with various aryl acetylenes:

To examine the efficacy of our new protocol we first examined the coupling of a variety of aryl acetylenes with o-iodophenol (Table 3.2). Using our protocol, we were able to couple *o*-iodophenol with electron-rich and electron-poor aryl acetylenes in good to excellent yields (Table 3.2). Base-sensitive functional groups such as methyl ketones (entry 6, Table 3.2) and methyl esters (entry 7, Table 3.2) were tolerated by this protocol.

Ortho-substituted aryl acetylenes could also be coupled to *o*-iodophenol in good yields (entry 4 and 8, Table 3.2). Aryl acetylenes bearing an alkene as a substitutent could also be successfully coupled in good yields with no observed Heck-like coupling; the Heck reaction may be observed if a palladium-based system is used (entry 9, Table 3.2).

Table 3.2: Synthesis of 2-aryl-benzo[*b*]furans via copper(I) catalyzed coupling of *o*-iodophenol and various aryl acetylenes.

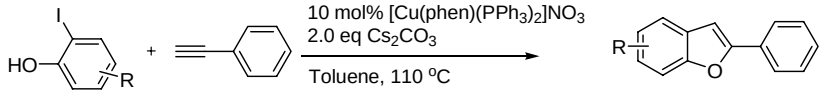


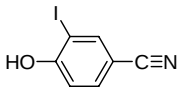
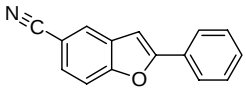
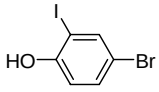
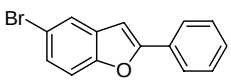
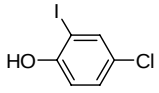
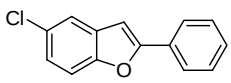
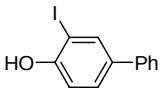
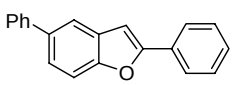
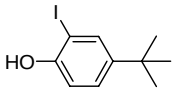
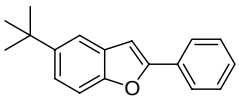
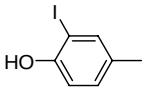
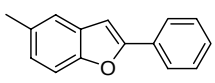
entry	aryl acetylene	product	time	isolated yield
1			24	92
2			24	64
3			24	62
4			48	77
5			24	77
6			24	69
7			24	67
8			48	91
9			24	68

3.6 Coupling of phenylacetylene with various *o*-iodophenols:

We had also successfully coupled a variety of 4-substituted-*o*-iodophenols with phenylacetylene in good to excellent yields (Table 3.3). The potential for further functionalization of the benzo[*b*]furan skeleton is made possible by the incorporation of a terminal alkene, bromine, and chlorine groups (entry 9, Table 3.2 and entries 4 and 5, Table 3.3 respectively). Our observed yields are comparable to, and in some cases better than, the yields reported using palladium-catalyzed reactions.

Table 3.3: Synthesis of 2-aryl-benzo[*b*]furans *via* copper(I) catalyzed coupling of phenylacetylene and various 4-substituted-*o*-iodophenols.



entry	iodophenol	product	time	isolated yield
1			24	96
2			24	86
3			24	90
4			24	79
5			24	80
6			24	85

3.7 Conclusions:

Using our protocol, we were able to couple *o*-iodophenol with electron-rich and electron-poor aryl acetylenes in good to excellent yields (Table 3.2). Base-sensitive functional groups such as methyl ketones (entry 6, Table 3.2) and methyl esters (entry 7, Table 3.2) were tolerated by this protocol. *Ortho*-substituted aryl acetylenes could also be coupled to *o*-iodophenol in good yields (entry 4 and 8, Table 3.2). Aryl acetylenes bearing an alkene as a substitutent could also be successfully coupled in good yields with no observed Heck-like coupling; the Heck reaction may be observed if a palladium-based system is used (entry 9, Table 3.2). Furthermore, we successfully coupled a variety of 4-substituted-*o*-iodophenols with phenylacetylene in good to excellent yields (Table 3.3). The potential for further functionalization of the benzo[*b*]furan skeleton is made possible by the incorporation of a terminal alkene, bromine, and chlorine groups (entry 9, Table 3.2 and entries 4 and 5, Table 3.3 respectively). Our observed yields are comparable to and in some cases better than the yields reported using palladium-catalyzed reactions.

3.8 References:

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CHAPTER 4

COPPER-CATALYZED SYNTHESIS OF 1,3-ENYNES

4.1 Introduction:

1,3-Enynes can be found in many naturally occurring and biologically active compounds.[1-4] Terbinafine, which is commonly known as Lamisil®, contains the 1,3-enyne moiety and is a pharmaceutically important compound used in the treatment of superficial fungal infections.[5] Another pharmaceutically important compound is Calicheamicin γ_1^I which has been shown to be an effective antitumor antibiotic.[6] 1,3-Enynes are also important precursors to polysubstituted benzenes[7] and conjugated dienes via hydroboration-protonolysis.[8]

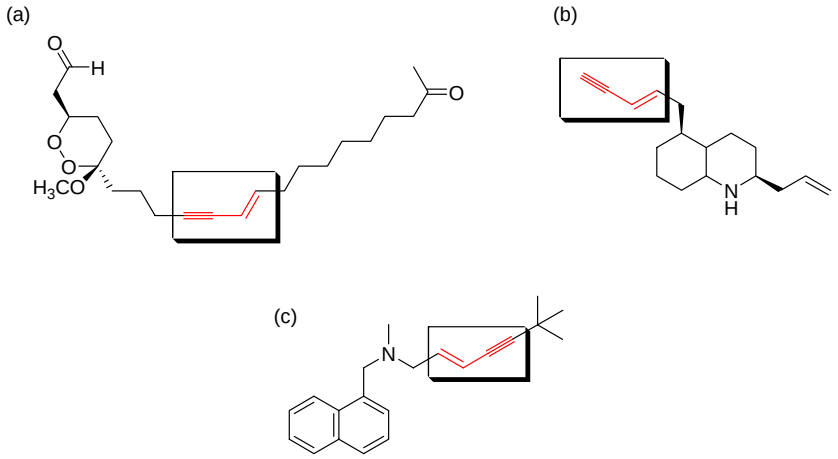


Figure 4.1: Examples of naturally occurring and biologically active compounds containing the 1,3-enyne moiety: (a) natural product isolated from the Indian sponge *Acarnus bicladotylota* (b) isolated from skin extracts of dendrobatid frogs, (c) terbinafine, commonly known as Lamisil®, used to treat fungal infections.

4.2 Background:

Among the methods developed to synthesize 1,3-enynes, the Pd-Cu catalyzed Sonogashira coupling reaction between an alkyne and a vinyl halide is most prevalent (Figure 4.2).[9-13] Other methods include the Pd-catalyzed coupling between a terminal organometallic alkyne (Cu, Mg, Si, Zn, Sn)[9, 14-22] and an alkene or the alkynylation of alkenyl metals (Al, B, Cu Mg, Zr).[9, 23-26] The latter methods do suffer from some drawbacks such as toxic reagents, the need to prepare an organometallic alkyne or alkene, poor functional group tolerance, and undesired side-products resulting in low yields.

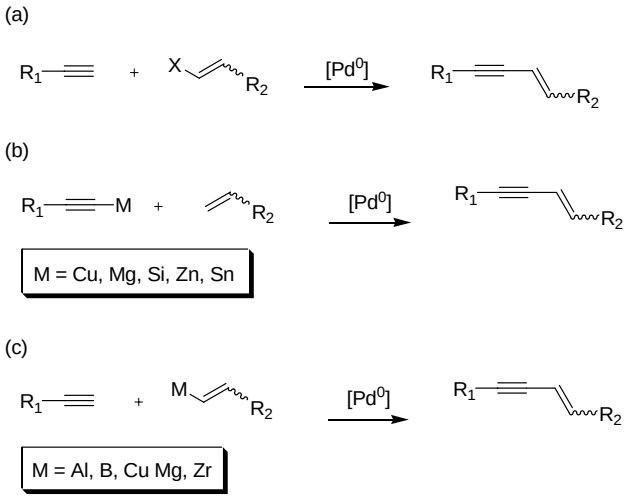


Figure 4.2: Traditional methods for the synthesis of 1,3-enynes: (a) Sonogashira coupling, (b) Pd-catalyzed coupling of a terminal organometallic alkyne and an alkene and (c) Alkynylation of alkenyl metals.

The use of copper has also been shown to mediate the synthesis of conjugated enynes. Marshall and co-workers synthesized 1,3-enynes by coupling trimethylsilyl alkynes with vinyl iodides.[27] However, this procedure requires the use of a greater than stoichiometric amount of CuCl and is limited to propargylic alcohol derivatives. Hoshi synthesized conjugated enynes through the coupling of alkenyldialkylboranes and

(trimethylsilyl)ethynyl bromide using strong bases such as NaOMe and LiOH and a catalytic amount of $Cu(acac)_2$.[28]

In recent years, there has been a resurgence in the development of copper-based protocols for a variety of cross-coupling reactions.[29-51] These newly developed protocols have been shown to be mild and tolerate a wide variety of functional groups and substrates. Based on these precedences, we now report a Cu(I)-catalyzed cross-coupling reaction of vinyl iodides and acetylenes for the synthesis of 1,3-enynes.

4.3 Optimization of the catalyst:

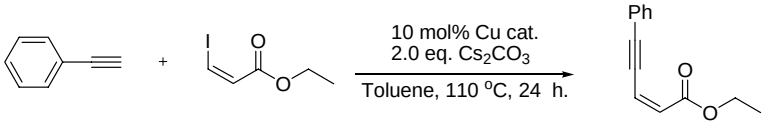
To optimize the reaction protocol we chose the cross-coupling of phenylacetylene and (*Z*)-ethyl-3-iodoacrylate as the test reaction. We examined a variety of copper(I) complexes, copper(I) salts, and copper(I) salts with certain additives in toluene at 110 ^oC with 2.0 equivalents of Cs_2CO_3 as the base (Table 4.1). It was found that both $[Cu(phen)(PPh_3)_2]NO_3$ and $[Cu(bipy)PPh_3Br]$ were effective at catalyzing the reaction.

4.4 Optimization of the base:

Using these two complexes as potential catalysts, we then screened a variety of bases for the cross-coupling of phenylacetylene and (*Z*)-ethyl-3-iodoacrylate in toluene at 110 ^oC for 24 hours. It was found that the optimal base for $[Cu(phen)(PPh_3)_2]NO_3$ remained Cs_2CO_3 (Table 4.2). This afforded the desired product with a yield of 76% by GC. Pranorm Saejueng in our group performed the base optimization for $[Cu(bipy)PPh_3Br]$ (Figure 4.3). She discovered when $[Cu(bipy)PPh_3Br]$ was the catalyst and K_2CO_3 as the base, the yield was improved to 99% (Table 4.3). Lowering the amount

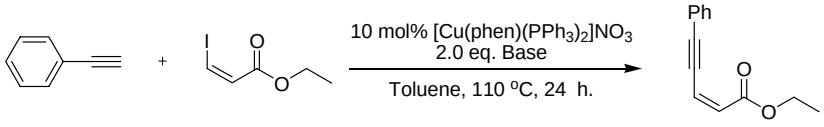
of base to 1.5 equivalents resulted in lower yields. Other bases such as K_3PO_4, Na_2CO_3, KO*t*Bu, NaO*t*Bu, Et_3N and DBU were ineffective with this reaction. When this reaction was monitored over a period of time it was discovered that the reaction was complete within 8 hours. Lowering the catalytic loading of [Cu(bipy)PPh_3Br] to 2.5 mol% for the cross-coupling of phenylacetylene and (*Z*)-ethyl-3-iodoacrylate using 2.0 eq. of K_2CO_3 as the base, decreased the yield to 51% in 24 hours. When the reaction was run either in the absence of catalyst or in the absence of base the product was not observed by GC.

Table 4.1: A comparison of w*ell-defined* copper(I) complexes, copper(I) Salts and additives as catalysts for the cross-coupling of phenylacetylene and (*Z*)-ethyl-3-iodoacrylate.



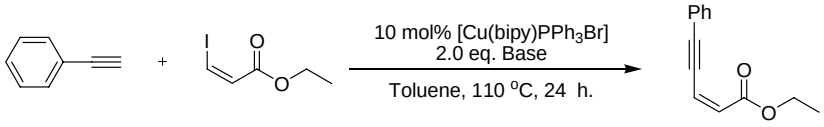
Catalyst	GC yield
Well-defined complexes:	
[Cu(phen)(PPh_3)$_2$]NO_3	76%
[Cu(bipy)PPh_3Br]	74%
[Cu(phen)PPh_3Br]	69%
[Cu(PPh_3)$_3$Br]	51%
[Cu(neocup)PPh_3Br]	34%
[Cu(acac)(PPh_3)$_2$]	21%
[Cu(neocup)$_2$Br]H_2O	7%
[Cu(CH_3CN)$_4$]PF_6	4%
Copper(I) salts:	
CuCl	2%
CuI or CuBr or Cu_2O	0%
Copper(I) salts / additives:	
CuI / phen / PPh_3 (1:1:2)	53%
CuI / phen (1:1)	36%
CuI / bipy (1:1)	16%

Table 4.2: Optimization of the base using $[Cu(phen)(PPh_3)_2]NO_3$ as the catalyst.



Base	GC yield
Cs_2CO_3	76%
K_2CO_3	52%
K_3PO_4	37%
Na_2CO_3	0%
KO*t*Bu	0%
NaO*t*Bu	0%
NaOAc	0%
DBU	0%
Et_3N	0%

Table 4.3: Optimization of the base using $[Cu(bipy)PPh_3Br]$ as the catalyst.



Base	GC yield
K_2CO_3	99%
K_3PO_4	47%
Cs_2CO_3	44%
Na_2CO_3	5%
KO*t*Bu	0%
NaO*t*Bu	0%
NaOAc	0%
DBU	0%
Et_3N	0%

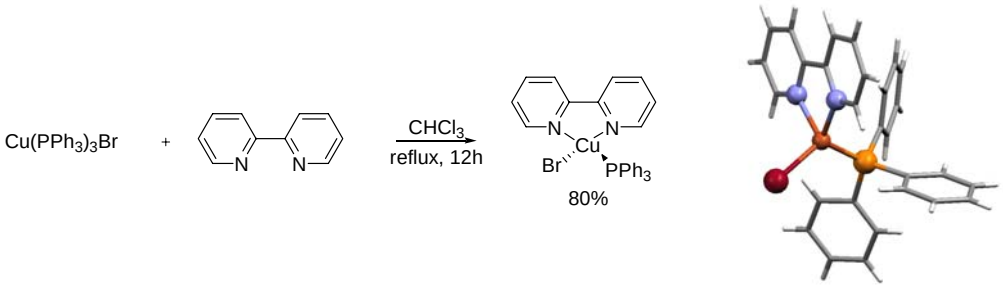


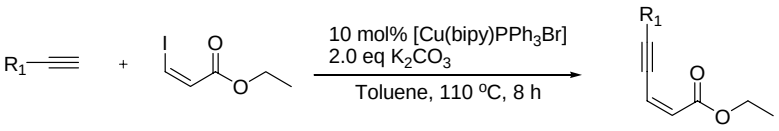
Figure 4.3: Synthesis of [Cu(bipy)PPh_3Br] and its single crystal X-ray structure.

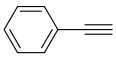
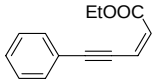
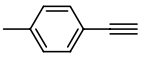
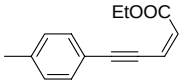
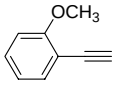
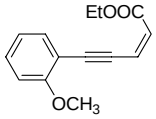
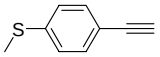
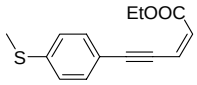
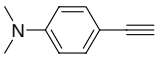
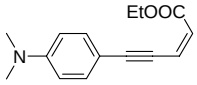
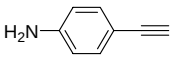
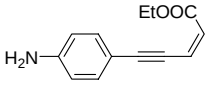
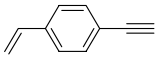
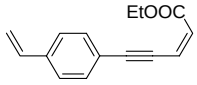
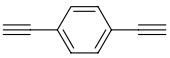
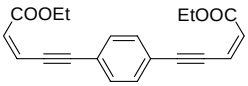
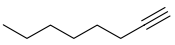
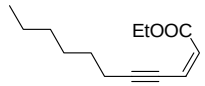
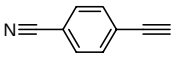
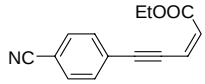
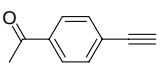
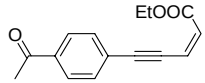
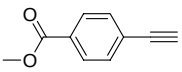
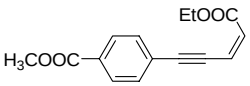
4.5 Results:

Based on the results of the optimization and control experiments we decided to use 10 mol% of [Cu(bipy)PPh_3Br] as the catalyst, 2.0 equivalents of K_2CO_3 as the base in toluene, at 110 ^oC for the standard protocol for synthesizing 1,3-enynes. We first chose to examine the efficacy of coupling a variety of acetylenes to (*Z*)-ethyl-3-iodoacrylate (Table 4.4). Pranorm Saejueng had found that a wide-range of aryl acetylenes could be coupled in good to excellent yields with complete retention of stereochemistry. This method tolerated both electron-rich and electron-poor aryl acetylenes. Sterically hindered aryl acetylenes (Table 4.4 entires 3 and 13) are also successfully coupled in good to excellent yields. Notably, base-sensitive functional groups such as methyl ketones (Table 4.4 entry 11) and methyl esters (Table 4.4 entires 12 and 13) are also tolerated by this method. A free aniline group (Table 4.4 entry 6), terminal alkene (Table 4.4 entry 7) and a bromine (Table 4.4 entry 16) all proved to be compatible functional groups. Heterocyclic acetylenes such as a pyridine moiety and a thiophene (Table 4.4 entries 15 and 16 respectively) were also compatible substrates with this protocol. However for 3-ethynylpyridine, the use of [Cu(phen)$(PPh_3)_2$]NO_3 as the catalyst and Cs_2CO_3 base was needed to obtain the cross-coupled product in a moderate yield. The cross-coupling of *n*-

octyne and (*Z*)-ethyl-3-iodoacrylate demonstrated that this procedure was not specific to aryl acetylenes (Table 4.4 entry 9).

Table 4.4: Copper-catalyzed cross-coupling of various acetylenes with (*Z*)-ethyl-3-iodoacrylate using the standard protocol.



entry	acetylene	product	Isolated yield
1			99
2			85
3			98
4			91
5			88
6			90
7			95
8			87[a]
9			96
10			85
11			92
12			88

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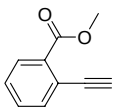
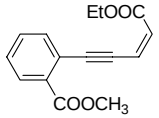
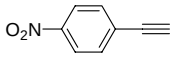
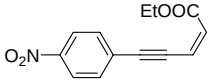
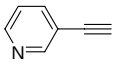
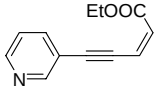
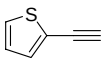
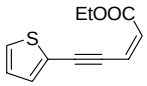
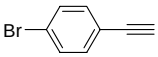
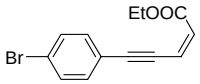
13			77
14			89
15			51[a,b]
16			62
17			65[c]

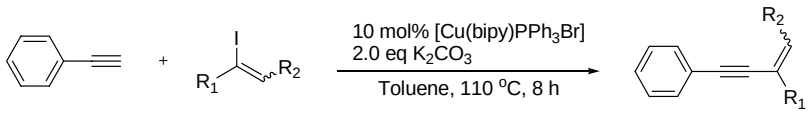
[a]reaction run for 12 hours, [b]10 mol% [Cu(phen)(PPh_3)$_2$$NO_3$] as catalyst and 2.0 eq of Cs_2CO_3 used as base, [c] reaction run for 20 hours.

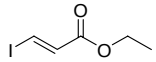
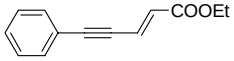
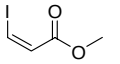
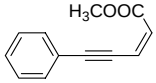
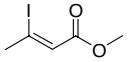
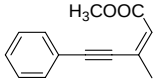
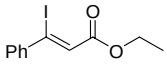
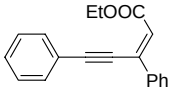
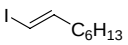
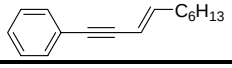
We then chose to examine cross-coupling of phenyl acetylene to a variety of vinyl iodides (Table 4.5). The standard protocol worked well for a variety of β-(*Z*)-iodo-α,β-unsaturated esters (Table 4.5). When (*E*)-ethyl-3-iodoacrylate was used as the vinyl iodide the reaction yield after 8 hours was only 55% when [Cu(bipy)PPh_3Br] was used as the catalyst and K_2CO_3 was used as the base. However, allowing the reaction to continue for 24 hours improved the yield to 81%. A similar observation was made when (*E*)-1-iodo-octene was used as the vinyl iodide (Table 4.5 entry 5). This reaction also required 24 hours to afford the desired product in excellent yield.

For reactions that were difficult using our standard protocol, we found that when the catalyst was changed to [Cu(phen)(PPh_3)$_2$]NO_3 and the base changed to Cs_2CO_3 the yields were greatly improved (Table 4.6). We were now able to successfully couple electron-rich vinyl iodides in excellent yields. (*E*)-ethyl-3-iodoacrylate can now be coupled to phenyl acetylene with a near quantitative yield in 8 hours (Table 4.6, entry 1). The cross-coupling of both (*E*)-1-iodo-octene and (*Z*)-1-iodo-octene to phenyl acetylene (Table 4.6, entries 2 and 3 respectively) were complete in 8 hours with retention of

stereochemistry. We did find the use of a cyclic vinyl iodide resulted in slightly lower yields and longer reaction times (Table 4.6 entry 4).

Table 4.5: Copper-catalyzed cross-coupling of phenylacetylene with various vinyl iodides using the standard protocol.



entry	vinyl iodide	product	isolated yield
1			81[a]
2			90
3			97
4			97
5			99[a]

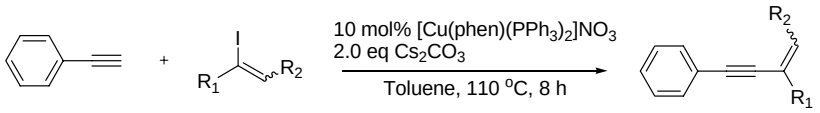
[a]reaction run for 24 hours.

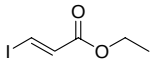
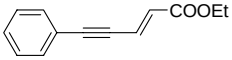
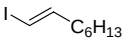
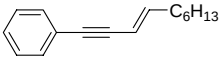
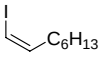
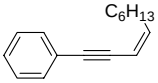
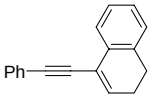
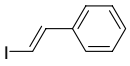
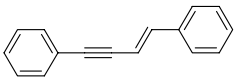
4.6 Conclusions:

In conclusion, we have developed a mild protocol for the synthesis of 1,3-enynes via a copper(I)-catalyzed cross-coupling reaction between an acetylene and a vinyl iodide. For most substrates, we recommend the use of [Cu(bipy)PPh_3Br] as the catalyst and K_2CO_3 as the base. In cases where the vinyl halide is an (*E*)-alkene, we recommend the use of [Cu(phen)$(PPh_3)_2$]NO_3 as the catalyst and Cs_2CO_3 as the base. Our protocol tolerates a wide-range of substrates and functional groups affording the desired enynes in high yields. The cross-coupled products retain the stereochemistry of the starting vinyl

iodides. Furthermore, this protocol is palladium-free, does not rely on the use of expensive/air-sensitive additives and eliminates the need for an organometallic alkene or alkyne species.

Table 4.6. Copper-catalyzed cross-coupling of phenylacetylene with various vinyl iodides using 10 mol% $[Cu(phen)(PPh_3)_2]NO_3$ as the catalyst and Cs_2CO_3 as the base.



entry	vinyl iodide	product	isolated yield
1			99[a]
2			98
3			98
4			78[b]
5			98

[a]GC yield. [b]reaction run for 24 hours.

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CHAPTER 5

A GENERAL METHOD FOR THE FORMATION OF ARYL-SULFUR BONDS USING COPPER(I) CATALYSTS

5.1 Introduction:

Methods for the formation of aryl-sulfur bonds are indispensable tools in synthetic chemistry. Their importance stems from the prevalence of aryl-sulfur bonds in many molecules that are of biological, pharmaceutical and materials interest (Figure 5.1).[1-7]

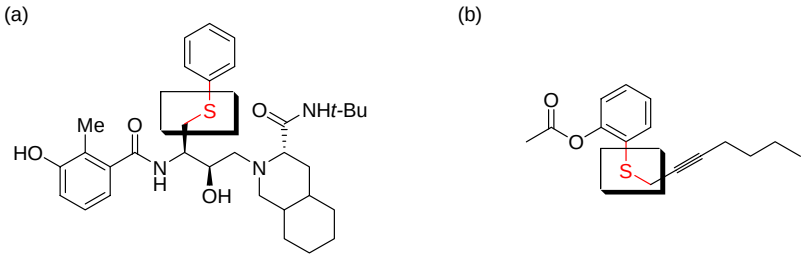


Figure 5.1: Biologically important compound containing an aryl-sulfur bond. (a) Nelfinavir, an inhibitor of HIV protease and (b) *o*-(acetoxyphenyl)hept-2-ynyl sulfide a non-steroidal anti-inflammatory molecule that can also inhibit HIV.

5.2 Background:

Traditional methods for the synthesis of aryl-sulfur bonds often require harsh reactions conditions. For example, coupling of copper thiolates with aryl halides requires polar solvents such as HMPA and temperatures around 200 °C. Reduction of aryl sulfones or aryl sulfoxides requires strong reducing agents such as DIBAL-H or $LiAlH_4$.[8-11] In 1980, Migita and co-workers first reported the cross-coupling reaction of aryl halides and thiols with $Pd(PPh_3)_4$ as the catalyst, NaO*t*Bu as the base, in polar solvents such as refluxing ethanol or DMSO at 90 °C.[12, 13] However, only few reports have

appeared in the literature for the formation of aryl-sulfur bonds using transition metal catalysts (Pd(0) or Ni(0)) since Migita's report (Figure 5.2).[14-22] This is in sharp contrast to the volume of literature that exists for the formation of aryl-nitrogen and aryl-oxygen bonds. Following Hartwig's mechanistic studies[17-19, 21] on the reductive elimination of palladium(II) arylthiolate complexes with chelating phosphines, in 1996, Zheng and co-workers reported the first general palladium-based protocol for the synthesis of aryl sulfides from aryl triflates.[16] More recently, in 2001, Schopfer and Schlapbach reported a general palladium catalyzed method for the synthesis of aryl sulfide from aryl iodides, in toluene, using DPEPhos as the ligand.[23]

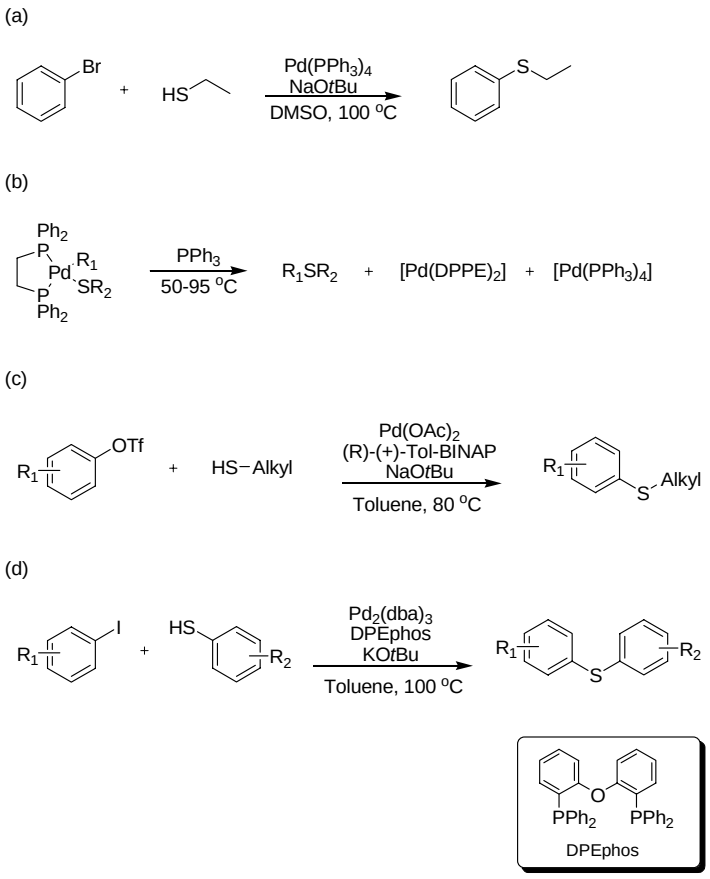


Figure 5.2: The limited number of metal-mediated methods for the synthesis of C-S bonds. (a) Migita's 1980 protocol, (b) Hartwig's palladium(II) arylthiolate complexes with chelating phosphines, (c) Zheng's 1996 protocol and (d) method developed by Schopfer and Schlapbach.

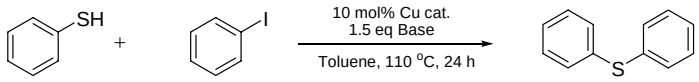
Traditional copper-mediated reactions suffer from drawbacks such as high reaction temperatures, the use of copper salts in greater than stoichiometric amounts, sensitivity to functional groups on the aryl halide and irreproducibility.[11] Yet, they remain as the reactions of choice in large and industrial scale syntheses. In the past seven years, there has been a resurgence of interest in developing mild synthetic methods based on copper-based catalysts as an alternative to palladium(0)-catalysts for the formation of aryl-carbon and aryl-heteroatom bonds. In addition to being simple and mild, these copper-based protocols also accommodate substrates that do not undergo coupling by palladium catalysis.[24-27] Moreover, in comparison to palladium, copper-based catalysts are quite attractive from an economic standpoint. We now extend the utility of copper-based catalysts for the formation of aryl-sulfur bonds through the cross-coupling reaction between aryl iodides and thiols

5.3 Reaction optimization:

We first chose to study the efficacy of copper(I)–based catalysts in the cross-coupling reaction between iodobenzene and thiophenol, in toluene, using the copper complexes [Cu(phen)(PPh_3)Br], [Cu(phen)(PPh_3)$_2$]NO_3 and [Cu(neocup)(PPh_3)Br] (Table 5.1). We had previously shown the utility of these complexes in the formation of aryl-acetylene, aryl-nitrogen and aryl-oxygen bonds. Our initial choice of the base was Cs_2CO_3. We based this choice on the observations by Buchwald, Snieckus and by our group that Cs_2CO_3 was essential in copper-based protocols for the formation of aryl-oxygen bonds. In 24 h, although we observed the formation of diphenyl sulfide by GC, the overall conversion was 80%. When we replaced Cs_2CO_3 with NaO*t*Bu, we observed

complete consumption of the starting materials when [Cu(neocup)(PPh_3)Br] was the catalyst. However, if [Cu(phen)(PPh_3)Br] was used as the catalyst, GC traces showed the presence of starting materials in trace amounts in the same time period. Trace amounts of starting materials were also observed if KO*t*Bu was used as the base. Diphenyl sulfide was formed only in trace amounts if bromobenzene was used indicating that the reaction was selective to iodides.

Table 5.1: Optimization of the catalyst and base for the copper-catalyzed cross-coupling of aryl iodides and thiols.



Catalyst	Base	GC Yield (%)
[Cu(neocup)PPh_3Br]	NaO*t*Bu	>99
[Cu(phen)PPh_3Br]	NaO*t*Bu	88
[Cu(phen)PPh_3Br]	Cs_2CO_3	80
[Cu(phen)(PPh_3)$_2$]NO_3	Cs_2CO_3	75
[Cu(phen)(PPh_3)$_2$]NO_3	KO*t*Bu	60
[Cu(phen)(PPh_3)$_2$]NO_3	NaO*t*Bu	40
[Cu(phen)PPh_3Br]	KO*t*Bu	30
[Cu(PPh_3)$_3$Br]	KO*t*Bu	5

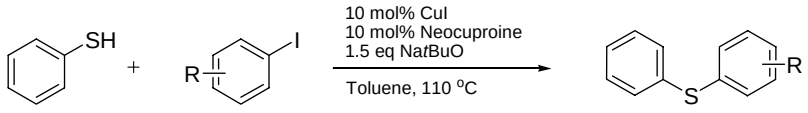
As a part of our control experiments, we replaced [Cu(neocup)(PPh_3)Br] with 10 mol% of CuI, CuI/neocuproine or CuCl/neocuproine as the catalyst. We found that CuI/neocuproine was as effective as [Cu(neocup)(PPh_3)Br]. However, only a trace amount of diphenyl sulfide was observed if CuI alone was used as the catalyst. This indicated that neocuproine was essential to accelerate the reaction. Also, GC traces indicated the presence of starting materials if CuCl/neocuproine was the catalyst. While we found that K_3PO_4 was as effective as KO*t*Bu, other bases such as triethylamine and

K_2CO_3 were ineffective in the coupling of iodobenzene with thiophenol. Based on these aforementioned observations, we decided to use CuI (10 mol%) / neocuproine (10 mol%) as the catalyst, NaO*t*Bu as the base and toluene as the solvent as a standard protocol for the formation of aryl-sulfur bonds.

5.4 Results:

Using our protocol, we were able to couple thiophenol with electron-rich and electron-poor aryl iodides in excellent yields (Table 5.2). Furthermore, we successfully coupled a variety of readily available thiophenols with iodobenzene in excellent yields (Table 5.3). A wide-range of aryl iodides containing both electron-withdrawing and electron-donating groups we easily tolerated. We were pleased to note that our protocol can also be used to couple, sterically hindered thiophenols such as 2,6-dimethylthiophenol with iodobenzene in 95% yield (entry 7, Table 5.3). Moreover, Rattan Gujadhur in our group used this protocol and demonstrated that it can be extended to couple aryl halides with *n*-butanethiol in excellent yields. A selection of his results can be seen in Table 5.4. The only other report that we are aware of that deals with the coupling of unactivated aryl iodides and thiols in the presence of catalytic amount of copper(I), in refluxing toluene was reported by Palomo and co-workers in 2000.[15] This protocol, however, calls for the use of expensive Schwesinger's Phosphazene bases such as P_2-Et which costs $250 for 5 mL from Aldrich. Moreover, this procedure was not shown to couple aryl iodides with alkyl thiols.

Table 5.2: Copper-catalyzed cross-coupling of a variety of aryl iodides and thiophenol using the standard protocol.



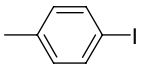
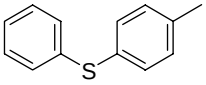
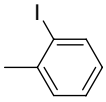
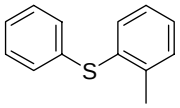
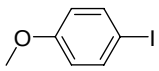
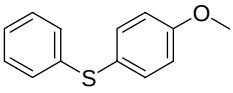
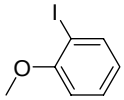
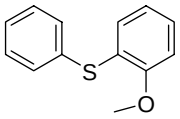
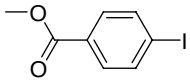
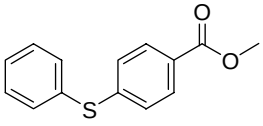
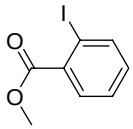
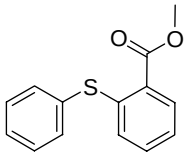
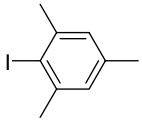
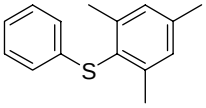
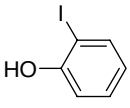
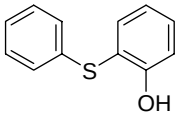
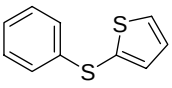
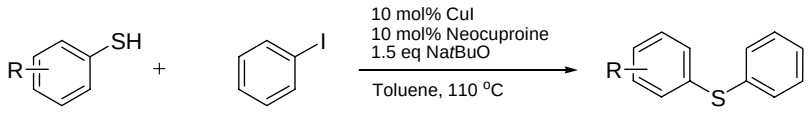
entry	aryl iodide	product	isolated yield (%)
1			94
2			96
3			96
4			95
5			84
6			81
7			97
8			81
9			91

Table 5.3: Copper-catalyzed cross-coupling of a variety of aryl thiols with iodobenzene using the standard protocol.



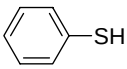
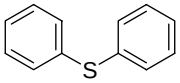
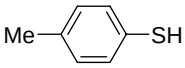
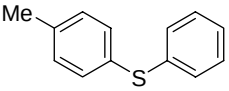
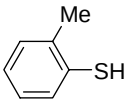
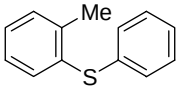
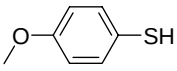
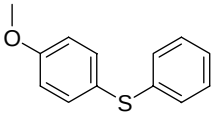
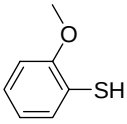
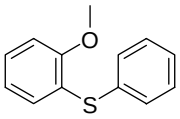
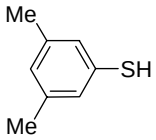
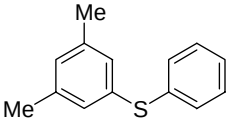
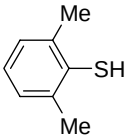
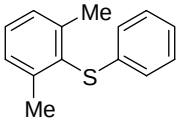
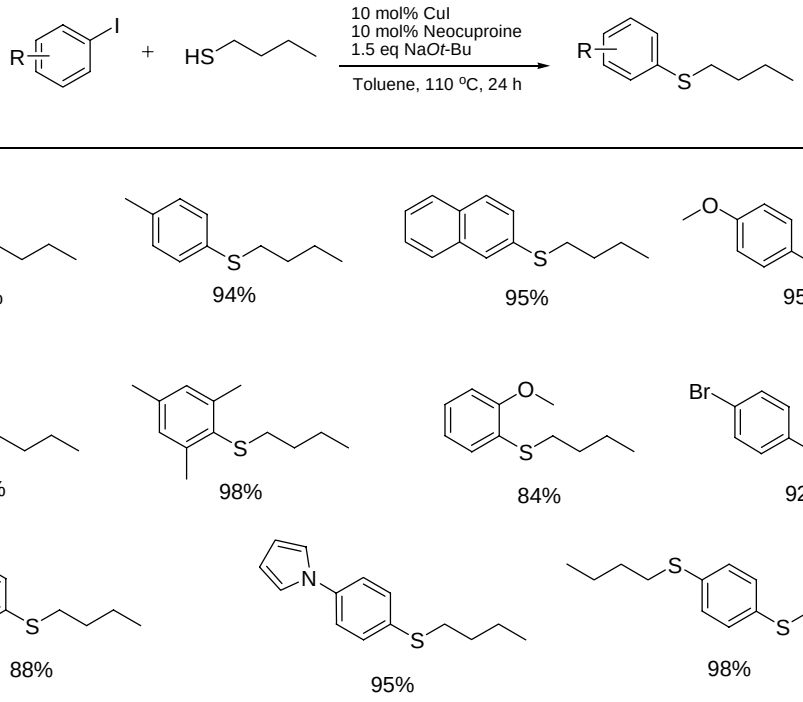
entry	thiol	product	time (h)	yield (%)
1			24	99
2			24	97
3			24	96
4			24	94
5			24	94
6			24	97
7			24	95

Table 5.4: Copper-catalyzed cross-coupling of *n*-butanethiol with a variety of aryl iodides using the standard protocol.



5.5 Conclusions:

In summary, we have reported a general synthetic protocol for the formation of aryl-sulfur bonds, using copper(I)-catalysts. The optimized protocol tolerates a variety of electron-donating and electron-withdrawing groups on the aryl halide. There is no observed loss in yield when sterically hindered thiols and aryl iodides are used. Furthermore, we have compared the cross-coupling of 2,4,6-trimethyl-iodobenzene with 4-methoxy-thiophenol using our protocol and the published protocol by Schopfer and Schlapbach and it can be seen in Figure 5.3 that in this case our method is superior.

In this protocol, we recommend the use of 10 mol% CuI, 10 mol% neocuproine, NaO*t*Bu as the base and toluene as the solvent. In cases where NaO*t*Bu cannot be used,

we recommend the use of K_3PO_4. Our protocol is palladium-free and avoids the use of expensive and/or air-sensitive ligands.

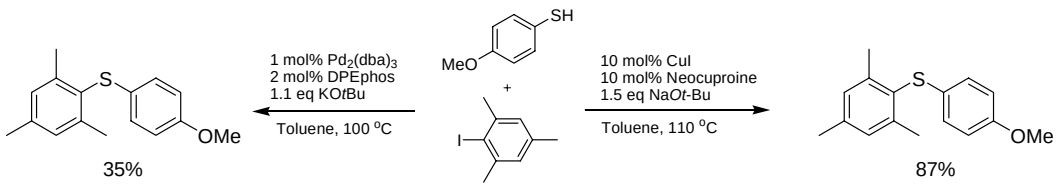


Figure 5.3: A comparison of our standard protocol with the published method by Schopfer and Schlapbach.

Shortly after this method was published, Buchwald published a similar for the synthesis of diaryl sulfides and aryl alkyl sulfides (Figure 5.4). His protocol requires the use of 5 mol% CuI and 2.0 equivalents of ethylene glycol and K_2CO_3 as the base in isopropyl alcohol.

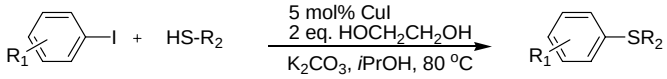


Figure 5.4: Method for the cross-coupling of aryl iodides to thiols developed by the Buchwald group.

5.6 References:

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CHAPTER 6

COPPER-CATALYZED SYNTHESIS OF VINYL SULFIDES

6.1 Introduction:

Vinyl sulfides play an important role as synthetic intermediates in organic chemistry (Figure 6.1). They are used as equivalents of enolate ions[1] and Michael acceptors.[2] They are important intermediates in the synthesis of oxetanes,[3] cyclopentanones[4] and cyclopentanes.[5, 6] Many natural products and compounds exhibiting interesting biological properties contain the vinyl sulfide moiety (Figure 6.2).[7-12]

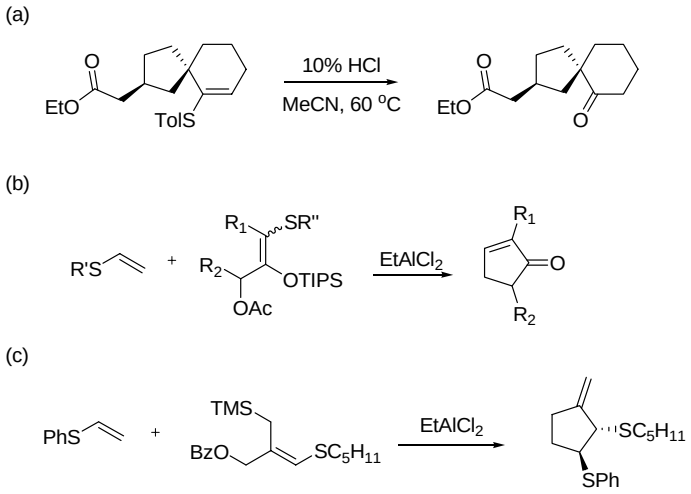


Figure 6.1: The use of vinyl sulfides as synthetic intermediates in organic synthesis: (a) enolate equivalent, (b) cyclopentanones and (c) cyclopentanes.

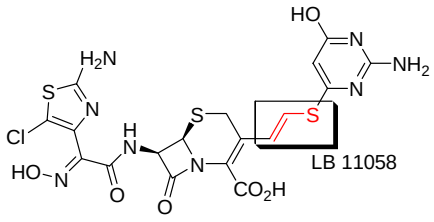


Figure 6.2: LB 11058 an antimicrobial agent active towards multidrug-resistant bacteria which contains a vinyl sulfide.

6.2 Background:

Due to the importance of these compounds, there have been a number of reported methods for synthesizing vinyl sulfides.[13, 14] Most noteworthy among them involves the addition of a thiol to an alkyne. This can either occur under radical conditions[15-18] affording the anti-Markovnikov product containing a mixture of E and Z isomers, or through the employment of transition-metal catalysts (Mo, Pd, Pt, Rh, Ru).[19-24] The Wittig reaction has also been utilized in the synthesis of vinyl sulfides.[25-29] This approach requires the use of strong bases and the synthesis of the appropriate Wittig reagents can be problematic.[13] Vinyl sulfides have also been prepared from the cross-coupling of vinyl halides and sodium or lithium benzenethiolates or their tin analogues.[30-32] However, the scope and functional group tolerance of these cross-coupling reactions have not been fully explored.

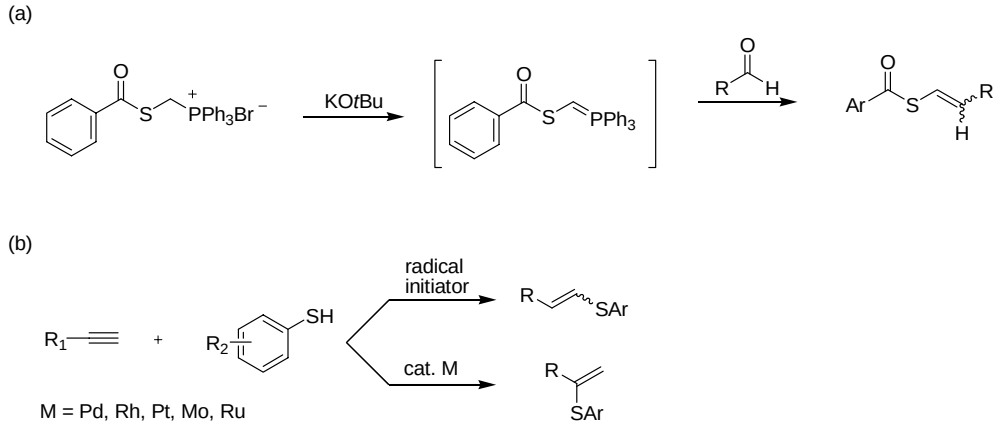


Figure 6.3: Various methods for the synthesis of vinyl sulfides: (a) vinyl sulfides via the Wittig reaction and (b) either the radical initiated addition of a thiol to an alkyne or the transition-metal mediated addition of a thiol to an alkyne.

Recently there has been a resurgence in interest in developing copper-catalyzed cross-coupling reactions.[33-39] These methods are mild and tolerate a variety of functional groups or substrates. These copper-based methods work extremely well with soft nucleophiles such as sulfur, selenium and phosphorus.[40-44] Due to the importance of vinyl sulfides and the lack of a general protocol for their synthesis, we felt that the copper-based protocols may be readily extended to the synthesis of vinyl sulfides. However, the extension was not trivial and required a thorough reoptimization of the reactions conditions with respect to catalyst, base and solvent.

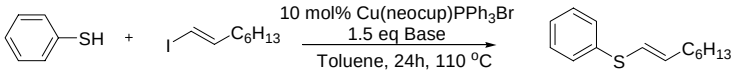
6.3 Reaction optimization:

The optimization process was performed using the cross-coupling of thiophenol and (*E*)-1-iodooctene. We first screened a variety of bases using 10 mol% [Cu(neocup)PPh_3Br] as the catalyst. It was observed that bases such as K_3PO_4, K_2CO_3, Cs_2CO_3 and CsOAc were very effective. However, the ratio of E to Z isomers of the product was best when K_3PO_4 was used as the base. Other bases such as Na_2CO_3, NaO*t*Bu, KO*t*Bu and DBU (1,8-Diazabicyclo[5.4.0]undec-7-ene) were less effective (Table 6.1).

We then examined a variety of copper(I) complexes, copper(I) salts, and copper(I) salts with certain additives in toluene at 110 ^oC with 1.5 equivalents of K_3PO_4 as the base (Table 6.2). The copper(I) complexes [Cu(phen)$(PPh_3)_2$]NO_3, [Cu(phen)PPh_3Br] and [Cu(neocup)PPh_3Br] demonstrated an excellent ability of catalyzing the reaction. The use of copper(I) iodide and 1,10-phenanthroline as an additive also exhibited similar results. However, when we compared the rate of product formation with

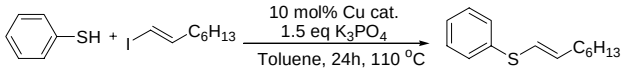
[Cu(phen)(PPh_3)$_2$]NO_3 and CuI/phen as the catalyst it was seen that the well-defined complex [Cu(phen)(PPh_3)$_2$]NO_3 was more active. After only two hours the yield of the product was 99% using [Cu(phen)(PPh_3)$_2$]NO_3. This is compared to an 80% yield using CuI/phen. Lowering the catalytic loading of [Cu(phen)(PPh_3)$_2$]NO_3 to 5 mol% using 1.5 eq. of K_3PO_4 as the base had no observed effect on the yield after 4 hours. When the reaction was run either in the absence of catalyst or in the absence of base the desired product was not observed by GC. We also observed that the toluene could be used "as is" without further purification. When toluene was replaced with isopropanol the reaction did proceed but after four hours the yield of the desired product was only 60%. It took 24 hours for the reaction to afford similar yields to toluene (Figure 6.4). Based on these optimization experiments we decided to use 5 mol% [Cu(phen)(PPh_3)$_2$]NO_3 (**1**) as the catalyst, 1.5 equivalents of K_3PO_4 as the base in toluene as our protocol for the copper-catalyzed synthesis of vinyl sulfides.

Table 6.1: A comparison of various bases for the cross-coupling of thiophenol and (*E*)-1-iodooctene using 10 mol% [Cu(neocup)PPh_3Br] as the catalyst in toluene for 24 hours.



Base (1.5 eq)	GC Yield	E/Z
K_3PO_4	99%	15:1
K_2CO_3	99%	10:1
Cs_2CO_3	96%	4:1
CsOAc	94%	5:1
DBU	86%	15:1
Na_2CO_3	84%	3:1
NaO*t*Bu	83%	19:1
KO*t*Bu	47%	>25:1

Table 6.2: A comparison of *well-defined* copper(I) complexes, copper(I) salts and additives as catalysts for the cross-coupling of thiophenol and (*E*)-1-iodooctene.



catalyst	GC yield
Well-defined complexes:	
$[Cu(phen)(PPh_3)_2]NO_3$	>99%
$[Cu(phen)PPh_3Br]$	97%
$[Cu(neocup)PPh_3Br]$	93%
$[Cu(CH_3CN)_4]PF_6$	16%
$[Cu(bipy)PPh_3Br]$	16%
$[Cu(PPh_3)_3Br]$	14%
Copper(I) salts / additives:	
CuI / phen / PPh_3 (1:1:2)	97%
CuI / phen (1:1)	96%
CuI	0%

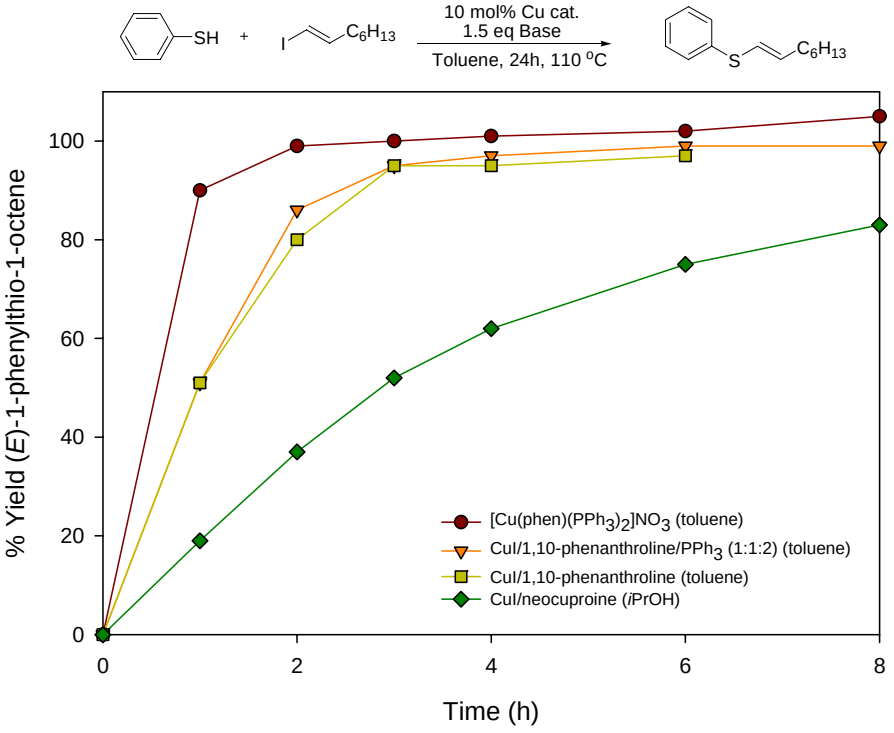


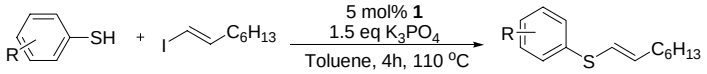
Figure 6.4: A comparison of w*ell-defined* copper(I) complexes, copper(I) salts and additives as catalysts for the cross-coupling of thiophenol and (*E*)-1-iodooctene. (Note: The lines drawn are for visual reference only.)

6.4 Results:

To determine the scope of the reaction, we first examined the cross-coupling of a variety of aryl thiols to (*E*)-1-iodooctene using the developed procedure (Table 6.3). It was discovered that a wide-range of aryl thiols could be coupled in high yields. Electron-rich and electron-poor thiols were easily tolerated using this procedure. Sterically hindered thiols such as 2,6-dimethylthiophenol and 2-isopropylthiophenol (Table 6.3, entries 4 and 5 respectively) could be coupled to (*E*)-1-iodooctene in high yields. Base-sensitive thiols such as a methyl ester (Table 6.3, entry 9) and an amide (Table 6.3, entry 12) also coupled very nicely. Thiols bearing bromine, chlorine and fluorine (Table 6.3, entries 7, 8 and 11 respectively) were also tolerated in this protocol. Furthermore, the stereochemistry of the vinyl iodide was retained in the product. We then explored the coupling of various vinyl iodides to thiophenol using the standard protocol. It was seen that the corresponding vinyl sulfides were obtained in very good yields (Table 6.4). It was observed that both *E* and *Z* isomers were well tolerated. The standard protocol also worked well for a variety of β-iodo-α,β-unsaturated esters (Table 6.4, entries 3-5).

We then investigated the ability to couple alkyl thiols to *trans*-β-iodostyrene (Table 6.5). We successfully coupled a variety of primary, secondary and tertiary thiols in excellent yields. The presence of an ester and an alkyl thiol attached to a furan were also tolerated (Table 6.5, entries 5 and 7 respectively). We also discovered that this method shows excellent selectivity in the presence of a hydroxyl group without the need of protection; there was no observed cross-coupling between the vinyl iodide and the alcohol. These coupling reactions were typically complete within four hours, but 4-mercapto-1-butanol required eight hours for completion (Table 6.5, entry 6).

Table 6.3: Copper-catalyzed cross-coupling of various aryl thiols with (*E*)-1-iodooctene using the standard protocol.



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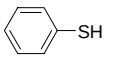
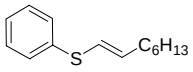
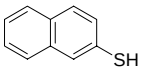
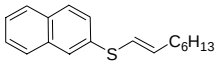
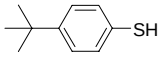
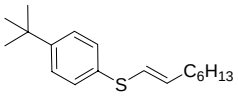
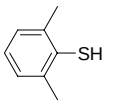
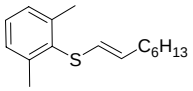
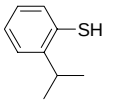
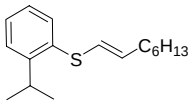
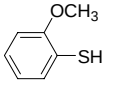
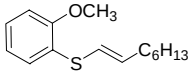
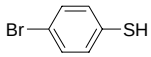
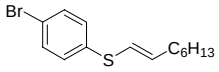
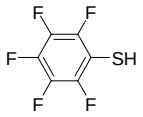
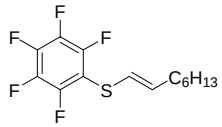
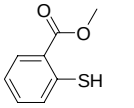
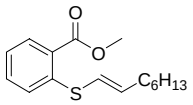
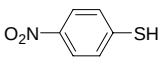
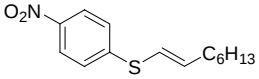
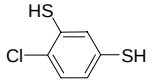
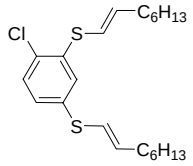
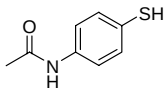
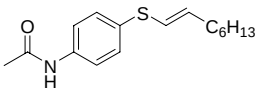
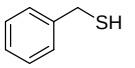
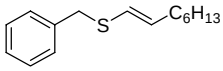
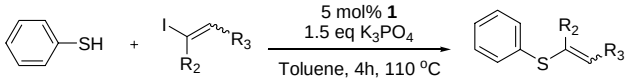
1			93
2			97
3			92
4			99
5			97
6			94
7			96
8			98
9			94
10			93
11			91
12			97
13			99

[a]isolated yields. [b]The starting vinyl iodide (*E*)-1-iodooctene contained ~10% of the *Z*-isomer; this led to ~10% of the *cis*-isomer in the product.

Table 6.4: Copper-catalyzed cross-coupling of thiophenol with an assortment of vinyl iodides using the standard protocol.



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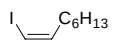
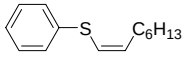
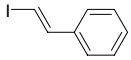
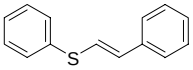
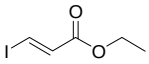
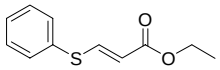
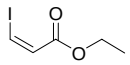
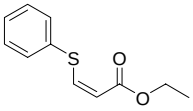
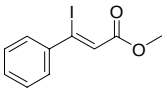
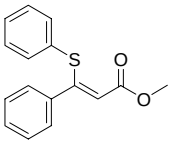
1			93
2			97
3			98
4			98
5			96

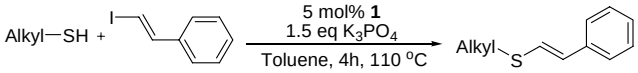
[a]isolated yields.

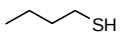
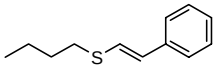
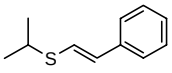
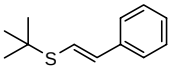
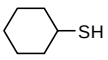
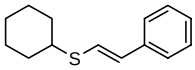
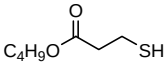
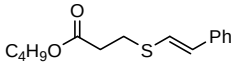
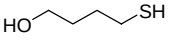
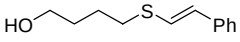
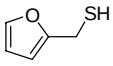
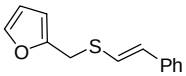
We then investigated the ability to couple alkyl thiols to *trans*-β-iodostyrene (Table 6.5). We successfully coupled a variety of primary, secondary and tertiary thiols in excellent yields. The presence of an ester and an alkyl thiol attached to a furan were also tolerated (Table 6.5, entries 5 and 7 respectively). We also discovered that this method shows excellent selectivity in the presence of a hydroxyl group without the need of protection; there was no observed cross-coupling between the vinyl iodide and the alcohol. These coupling reactions were typically complete within four hours, but 4-mercapto-1-butanol required eight hours for completion (Table 6.5, entry 6).

Due to the occurrence of heterocycles in many compounds that are of biological and materials interest, Pranorm Saejueng of our group used this protocol and examined

the ability of this method to tolerate a variety of heterocyclic thiols (Table 6.6). She found that a wide-range of heterocyclic thiols could be coupled to (*E*)-1-iodooctene in excellent yields. However, in contrast to the coupling of aryl and alkyl thiols the coupling reactions were slower. It was also observed that the coupling of thiadiazole-based thiols to (*E*)-1-iodooctene was unsuccessful.

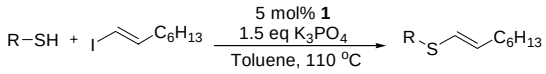
Table 6.5: Copper-catalyzed cross-coupling of various alkyl thiols with *trans*-β-iodostyrene using the standard protocol.



entry	thiol	product	yield[a]
1			99
2			90
3			80
4			95
5			98
6			97[b]
7			97

[a]isolated yields. [b]reaction run for 8 hours.

Table 6.6: Copper-catalyzed cross-coupling of various heterocyclic thiols with (*E*)-1-iodooctene using the standard protocol.



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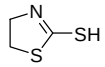
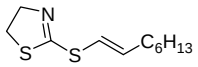
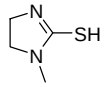
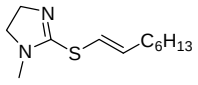
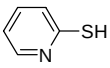
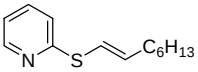
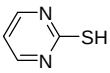
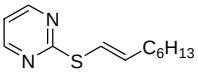
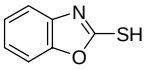
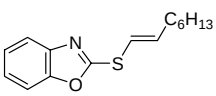
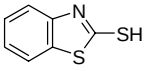
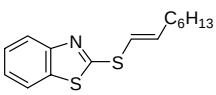
1			88[b]
2			99[c]
3			99[c]
4			97[c]
5			99[d]
6			98[d]

[a]isolated yields. [b]reaction run for 12 hours. [c]reaction run for 24 hours [d]reaction run for 8 hours.

6.5 Conclusions:

In conclusion, we have developed a copper-catalyzed method for the stereospecific synthesis of vinyl sulfides in excellent yields using a combination of 5 mol% $[Cu(phen)(PPh_3)_2]NO_3$ (**1**) and 1.5 equivalents K_3PO_4 in toluene.[45] This method tolerates a wide-range of functional groups and substrates. We have also demonstrated the ability to couple both alkyl thiols and heterocyclic thiols to vinyl iodides. The latter may be especially useful for the potential synthesis of biologically important compounds. Additionally, the reaction avoids the use of palladium and/or expensive additives.

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CHAPTER 7

CONCLUSIONS

7.1 Summary:

Transition-metal mediated cross-coupling reactions have become an invaluable tool for the synthetic chemist. These methods, in particular Pd(0)-based ones, have been used for the synthesis of a variety of compounds which have been used for their biological, pharmaceutical and materials properties. These modern protocols tolerate a variety of functional groups and substrates and are reproducible. Recently there has been a renewal of interest in developing copper-based methods for a variety of cross-coupling reactions. There have been observations in the literature that suggest that the problems that once plagued the traditional copper-mediated reactions can be greatly improved. Furthermore, there are also observations that these newly developed copper-based protocols can be successfully used where the Pd(0)-based methods have failed.

My research began an expansion of the group's early copper-based methodologies using soluble copper(I)-complexes as catalysts for cross-coupling reactions. The group had shown that these newly developed copper-based protocols can tolerate a variety of functional groups and provide reproducible results under mild conditions. These initial results were promising and we wanted to explore the possibility of exploring other substrates.

I had first shown that the soluble copper(I)-complex [Cu(phen)PPh_3Br] with K_2CO_3 as the base in toluene can be used to couple a variety of aryl iodides and phenylacetylene in good yields. This method tolerated a variety of aryl iodides with

electron-donating, electron-withdrawing and base-sensitive groups. Shortly thereafter our group had synthesized $[Cu(phen)(PPh_3)_2]NO_3$ and I discovered that this complex was more effective at coupling iodobenzene to phenylacetylene than $[Cu(phen)PPh_3Br]$.

This method of coupling aryl iodides to phenylacetylene was then applied towards the synthesis of 2-aryl-benzo[*b*]furans. This was achieved by coupling a variety of aryl acetylenes to *o*-iodophenol using $[Cu(phen)(PPh_3)_2]NO_3$ as the catalyst and Cs_2CO_3 as the base which then underwent a 5-*endo*-*dig* cyclization. Using this method, I was able to synthesize a wide-range of 2-aryl-benzo[*b*]furans in good yields. The protocol tolerated aryl acetylenes that bore both electron-donating and electron-withdrawing groups. An aryl acetylene with a terminal alkene was also tolerated. Furthermore, a range of *o*-iodophenols were successfully coupled to phenylacetylene. Phenols with bromine and chlorine were well tolerated with no observed coupling to the acetylene.

Expansion of our existing protocols to include vinyl halides was also achieved. Through the use either $[Cu(phen)(PPh_3)_2]NO_3$ and $[Cu(bipy)PPh_3Br]$ as the copper(I)-catalysts we were able to successfully couple terminal acetylenes to vinyl iodides for the synthesis of 1,3-enynes in excellent yields. This method tolerated a wide-range of acetylenes and vinyl iodides. The coupling reaction was generally complete within 8 hours and the geometry of the starting vinyl iodide was retained in the product.

The formation of carbon-sulfur bonds via transition-metal catalysts had received little attention. I successfully showed the use of a catalytic amount of CuI and neocuproine to be an effective method for the formation of carbon-sulfur bonds. This newly developed method tolerated a wide-range of thiols and aryl iodides. Sterically hindered thiols and aryl iodides were tolerated very nicely. Furthermore, Rattan Gujadhur

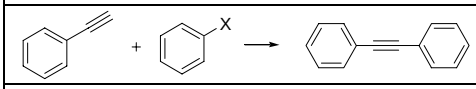
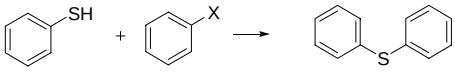
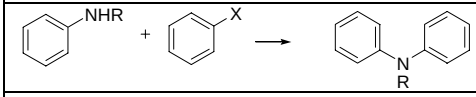
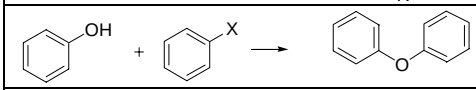
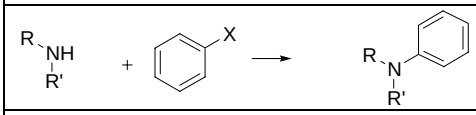
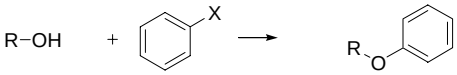
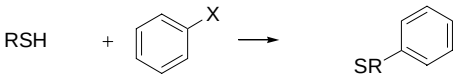
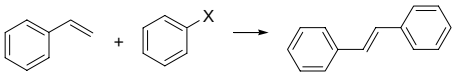
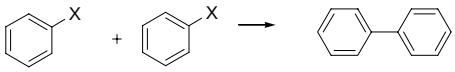
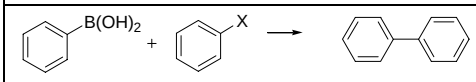
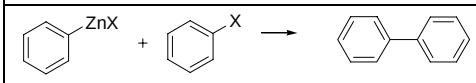
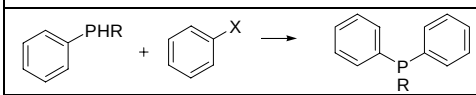
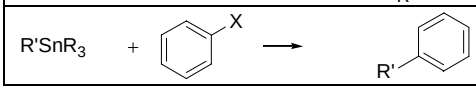
of our group had demonstrated that this method can be utilized to couple *n*-butane thiol to a variety of aryl iodides. The incorporation of alkyl thiols further demonstrated the versatility of this method.

The synthesis of vinyl sulfides was also achieved through copper(I)-catalysis. A wide-range of vinyl sulfides was synthesized using $[Cu(phen)(PPh_3)_2]NO_3$ as the catalyst. The general protocol afforded the desired vinyl sulfide in 4 hours with 5 mol% of the catalyst. A large variety of thiols bearing electron-donating, electron-withdrawing and base sensitive groups were well tolerated. A good selection of vinyl halides were also coupled in high yield to thiophenol. This method also tolerated a variety of primary, secondary and tertiary thiols. An alkyl thiol bearing a primary alcohol group was selectively coupled; there were no observed side-products from a possible C-O coupling. Pranorm Saejueng of our group demonstrated that a wide-range of heterocyclic thiols could be coupled to (*E*)-iodooctene in good yields. As was seen with the 1,3-enynes the geometry of the double bond was retained in the product.

All of these newly developed methods further demonstrate that the Ullmann reaction can be improved. Our methods tolerate a wide-range of function groups, the obtained yields are highly reproducible, a catalytic amount of copper has been employed and the reaction conditions are much milder than the traditional methods. Furthermore, we have been able to tolerate functional groups that have been shown to be problematic with the established palladium(0) chemistry. This is an important development which may help the copper-catalyzed cross-coupling reactions be seen as a viable alternative. Finally, our methods do not rely on the use of expensive and / or air-sensitive phosphine

ligands (Figure 7.1). Table 7.1 illustrates the improvements we and others have made with copper-catalyzed cross-coupling reactions since I began my research in 2000.

Table 7.1: Improvements made to various modified Ullmann reactions as of 2004. (For a comparison of the Modified Ullmann reaction prior to 2000 see Table 1.1).

Cross-Coupling Reaction	Modified Ullmann (2005)
	✓ 1-6
	✓ 7-15
	✓ 12, 13, 16
	✓ 12, 13, 16
	✓ 12, 13, 16
	✓ 12, 13, 16
	✓ 8, 9
	✗
	✓ 17
	✓ 18
	✗
	✓ 19, 20
	✓ 21

Key:
- ✓ - reaction known to exist with good reaction conditions
- ✓ - reaction known to exist but conditions need improvement
- ✗ - reaction is not known to exist

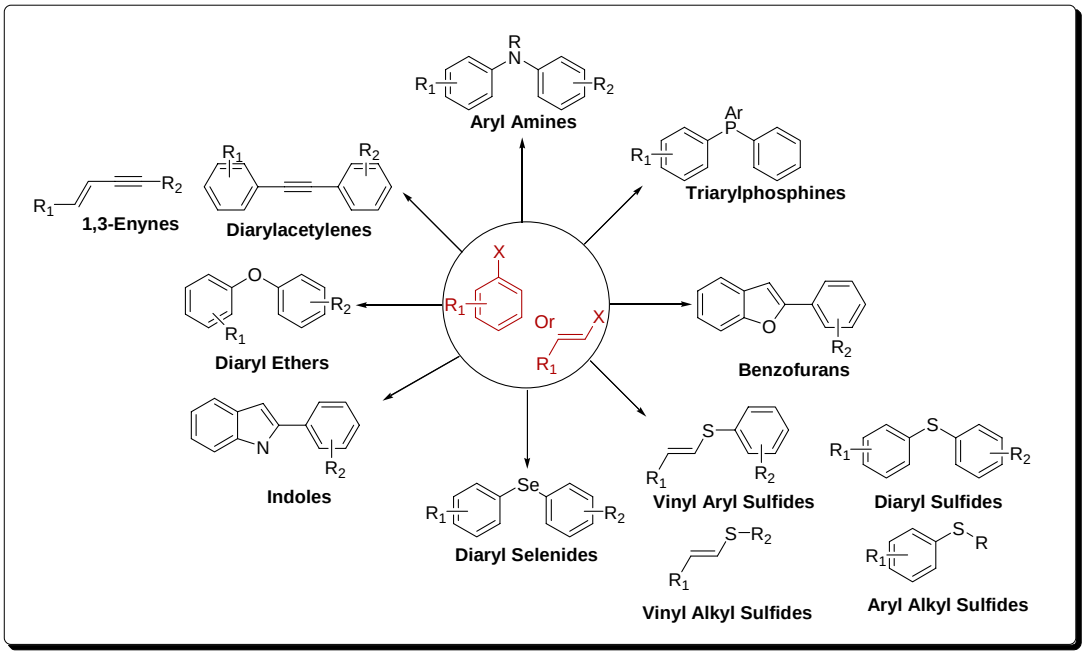


Figure 7.1: Copper-catalyzed cross-coupling reactions developed by the D.V. Group.

7.2 Future outlook:

I feel that the future is bright for the development of new and more active copper-based cross-coupling reactions. This recent renewal of interest has generated some very promising and sometimes surprising results. The development of copper-based methods for the cross-coupling of aryl boronic acids and aryl halides would have an immediate impact on the pharmaceutical industry. Also, the coupling of terminal alkenes and aryl halides is another cross-coupling reaction that could be investigated.

Currently the state-of-the-art copper-based methods primarily tolerate aryl and vinyl iodides. This may continue to be a limitation until the exact mechanistic details of these reactions are discovered; this is an area that is currently being pursued by our group. The limitation to aryl iodides may also be overcome through the use of microwave synthesis. The use of microwaves has become increasingly popular tool for synthetic

chemists and there are some initial results that demonstrate the use of copper catalysts under such conditions.[10, 22-26]

The ability to provide complementary methods to the well-established palladium(0)-based methods is off to a good start. Both our group and others have observed copper's ability to succeed when palladium has failed. One has to remember that these copper-based methods are still in their infancy. As further improvements are made and more substrates are tolerated; I feel more synthetic chemists will be turning to copper as their catalyst of choice.

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APPENDIX

EXPERIMENTAL

General Information:

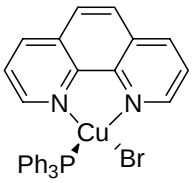
All of the reactions reported herein were conducted under an inert atmosphere of argon in oven-dried glassware. All reagents and solvents were obtained from Acros, Alfa Aesar or from Aldrich and were used without further purification. Potassium Carbonate (Alfa Aesar, 99%) was stored in an argon filled glove box. All vinyl iodides used in this paper have been synthesized using procedures previously reported in the literature.[1-4] Purification was performed by flash chromatography using ICN Flash Silica Gel, 230-400 mesh. The yields given refer to isolated yields of the characterized compounds, deemed pure by elemental analyses, ^{1}H NMR and ^{13}C NMR. In certain cases GC yields were reported. All GC yields were calculated using dodecane as an internal standard; the correction factors used to calculate the product yields were determined using an analytically pure sample. NMR spectra were recorded on a on a Bruker AVANCE 300 MHz spectrometer or a Bruker AVANCE 400 MHz spectrometer. Chemical shifts were reported in parts per million (δ). The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; dd, doublet of doublets; dt, doublet of triplets; m, multiplet; and q, quartet. The coupling constants, *J*, are reported in Hertz (Hz). TMS was used as the internal reference. Elemental analyses were performed at the Microanalysis Laboratory, University of Massachusetts - Amherst by Dr. Greg Dabkowski. The reported melting points were uncorrected. X-ray data were collected using a Nonius kappa-CCD diffractometer with MoKα (λ=0.71073 Å) as the incident radiation. Diffraction data were

collected at ambient temperature. The raw data were integrated, refined, scaled and corrected for Lorentz polarization and absorption effects, if necessary, using the programs DENZO and SCALEPAK, supplied by Nonius. Structures solutions and refinements were done (on F_o^2) using SIR92 and SHELXL 97 within the Nonius' MAXUS module. All structures were checked for any missing symmetry using MISSYM of PLATON. The Gas Chromatograph was a Hewlett Packard 6850 GC series with a 30-meter HP-1 100% dimethylpolysiloxane capillary column

Synthesis of Copper(I) Complexes

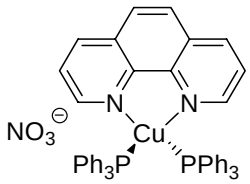
Nitratobis(triphenylphosphine)copper(I) [$Cu(PPh_3)_2NO_3$]): In an Erlenmeyer flask equipped with a Teflon-coated stir bar, methanol (100 mL) was heated to boiling and triphenylphosphine (Alfa Aesar, 24.22 g, 92.34 mmol) was slowly added to the stirring methanol. After the complete dissolution of triphenylphosphine, $Cu(NO_3)_2 \cdot 2.5\ H_2O$ (Fisher Scientific, 7.16 g, 30.78 mmol) was added in small portions. No special precautions were taken for the exclusion of air. Upon addition of the copper(II) nitrate, a white precipitate formed. After the completion of the addition, the contents were stirred for 30 minutes and the flask was allowed to cool to ambient temperature. The reaction mixture was then filtered through a Buchner funnel and the white residue was washed repeatedly with ethanol and then with diethyl ether. The resultant white solid was dried under dynamic vacuum to give $Cu(PPh_3)_2NO_3$ (12.378 g, 62% yield). m.p. – 238-240 ^oC. The cell constants, contents and the space group are identical to that of the already reported structure of $Cu(PPh_3)_2NO_3$ (Cambridge Structural Database Refcode-NITPPC01).

Tris(triphenylphosphine)copper(I) bromide ([$Cu(PPh_3)_3Br$]): In an Erlenmeyer flask equipped with a Teflon-coated stir bar, methanol (100 mL) was heated to boiling and triphenylphosphine (Alfa Aesar, 24.22 g, 92.34 mmol) was slowly added to the stirring methanol. After the complete dissolution of triphenylphosphine, $CuBr_2$ (Acros, 5.15 g, 23.09 mmol) was added in small portions. No special precautions were taken for the exclusion of air. Upon addition of the copper(II) bromide, a white precipitate formed. After the completion of the addition, the contents were stirred for 30 minutes and the flask was allowed to cool to ambient temperature. The reaction mixture was then filtered through a Buchner funnel and the white residue was washed repeatedly with ethanol and then with diethyl ether. The resultant white solid was dried under dynamic vacuum to give $Cu(PPh_3)_3Br$ (20.03 g, 93% yield). m.p. – 164-166 ^oC. The cell constants, contents and the space group are identical to that of the already reported structure of $Cu(PPh_3)_3Br$ (Cambridge Structural Database Refcode-FEYVAG).

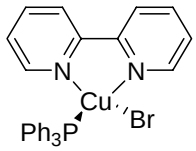


[Cu(phen)(PPh_3)Br]: In an Erlenmeyer flask equipped with a Teflon-coated magnetic stir bar, tris(triphenylphosphine)copper(I) bromide (1.40 g, 1.50 mmol) was added to chloroform (50 mL). After complete dissolution, 1,10-phenanthroline (856 mg, 1.50 mmol) was then added. The colorless solution immediately turned orange. The contents of the flask were allowed to stir for 30 minutes at room temperature. Afterwards the solvent was removed *in vacuo* to afford an orange solid. Recrystallization was achieved by layering 40 mL of diethyl ether onto a solution of the solid dissolved in 20 mL of dichloromethane (931 mg, 75% yield). m.p. –

252-253 ^{o}C. The cell constants, contents and the space group are identical to that of the already reported structure of [Cu(phen)(PPh_3)Br] (Cambridge Structural Database Refcode-BEQLAK).

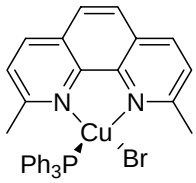


[Cu(phen)(PPh_3)$_2$]NO_3: In an Erlenmeyer flask equipped with a Teflon-coated magnetic stir bar, Nitratobis(triphenylphosphine)copper(I) (977 mg, 1.50 mmol) was added to chloroform (20 mL). After complete dissolution, triphenylphosphine (393 mg, 1.50 mmol), followed by 1,10-phenanthroline (270 mg, 1.50 mmol) was then added. The colorless solution immediately turned yellow. The contents of the flask were allowed to stir for 30 minutes at room temperature. Afterwards the solvent was removed *in vacuo* to afford a yellow solid. Recrystallization was achieved by vapor diffusion of diethyl ether into a solution of the solid dissolved in 30 mL of dichloromethane (931 mg, 75% yield). m.p. – 202-204 ^{o}C. The cell constants, contents and the space group are identical to that of the already reported structure of [Cu(phen)(PPh_3)$_2$]NO_3 (Cambridge Structural Database Refcode- MUQXAX).



[Cu(bipy)(PPh_3)Br]: In a round bottom flask equipped with a Teflon-coated magnetic stir bar and reflux condenser, tris(triphenylphosphine)copper(I) bromide (7.663 g, 8.23 mmol) was added to chloroform (50 mL). After complete dissolution, 2,2'-bipyridine (1.93 g, 12.37 mmol) was then added. The colorless solution immediately turned orange. The contents of the flask were allowed to reflux for 12 hours at 75 ^{o}C. Afterwards the solvent was removed *in vacuo* to

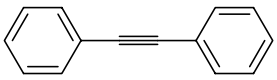
afford an orange solid. Recrystallization was achieved by layering 80 mL of diethyl ether onto a solution of the solid dissolved in 30 mL of dichloromethane (3.594 g, 78% yield). m.p. – 198-200 ^{o}C. The cell constants, contents and the space group are identical to that of the already reported structure of [Cu(bipy)(PPh_3)Br] (Cambridge Structural Database Refcode-COYNOT).



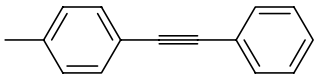
[Cu(neocup)(PPh_3)Br]: In an Erlenmeyer flask equipped with a Teflon-coated magnetic stirrer, neocuproine hydrochloride 0.244 g, 1 mmol) and Na_2CO_3 (0.116g, 1 mmol) were added to dichloromethane (50 mL). After 2 h, the mixture was filtered to remove the inorganic salts and the solvent removed under dynamic vacuum yield neocuproine as a white solid (0.149 g, 72% yield). In a 250 mL RB flask, Cu(PPh_3)$_3$Br (0.66 g, 0.71 mmol) was dissolved in 50 mL of chloroform. To this stirring chloroform solution, neocuproine (0.149, 0.71 mmol) was added. The solution instantly turned orange red and was allowed to stir for 25 minutes. Afterwards, the solvent was removed under dynamic vacuum to afford an orange-yellow solid. The crude solid was dissolved in 60 mL of dichloromethane and layered with 20 mL of diethylether to obtain [Cu(neocup)(PPh_3)Br] as yellow needles (0.33g, 78% yield). The cell constants, contents and the space group are identical to that of the already reported structure of [Cu(neocup)(PPh_3)Br] (Cambridge Structural Database Refcode-CADNIF).

COPPER-CATALYZED SYNTHESIS OF DIARYLACETYLENES:

General Procedure: In an argon-filled glove box, a Pyrex glass tube (2.5 cm in diameter) equipped with a Teflon stir bar, was charged with potassium carbonate (Acros, 2.0 mmol) and [Cu(phen)PPh_3Br] (10 mol% with respect to the phenylacetylene) and was sealed with a rubber septa. The sealed tube was taken out of the glove box and the phenylacetylene (2.50 mmol), the aryl halide (2.00 mmol) and toluene (15.0 mL) were injected into the tube through the septum. The contents were then stirred at 110 °C for the time indicated in Table 2.2. The reaction was mixture was then cooled to room temperature and filtered to remove any insoluble residues. The filtrate was reduced in vacuo and the residue was purified by flash column chromatography on silica gel to obtain the analytically pure product.

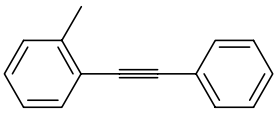


Diphenylacetylene (entry 1, Table 2.2): The general procedure was used to convert phenylacetylene and iodobenzene to the title product; except using a one mmol scale. Purification by flash chromatography (hexane as the eluent) gave the analytically pure product as a white solid (143 mg, 80% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (m, 4H), 7.35 (m, 6H). 13C NMR (75 MHz, $CDCl_3$) δ 131.6, 128.3, 128.2, 123.3, 89.3. Anal. Calcd. for $C_{14}H_{10}$: C, 94.34; H, 5.66. Found: C, 94.20; H, 5.67. mp 59 °C.

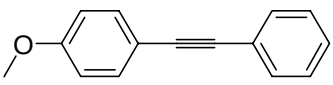


Phenyl-*p*-tolyl-acetylene (entry 2, Table 2.2): The general procedure was used to convert phenylacetylene and 4-

iodotoluene to the title product. Purification by flash chromatography (hexanes as the eluent) gave the analytically pure product as a white solid (285 mg, 74% yield).). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (m, 2H), 7.46 (d, *J*=8.1, 2H), 7.35 (m, 3H), 7.19 (d, *J*=7.9, 2H) 2.38 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.3, 131.5, 131.4, 129.1, 128.3, 128.0, 123.4, 120.1, 89.5, 88.7, 21.5. Anal. Calcd. for $C_{15}H_{12}$: C, 93.71; H, 6.29. Found C, 93.51; H, 6.44. mp 71 °C.

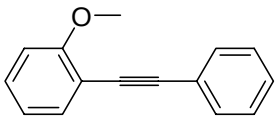


Phenyl-*o*-tolyl-acetylene (entry 3, Table 2.2): The general procedure was used to convert phenylacetylene and 2-iodotoluene to the title product. Purification by flash chromatography (hexanes as the eluent) gave the analytically pure product as an off-white oil (273 mg, 71% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42(m, 3H), 7.22 (m, 3H), 7.08, (m, 3H), 2.40 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.1, 131.8, 131.5, 129.4, 128.3, 128.2, 128.1, 125.5, 123.5, 122.9, 93.3, 88.3, 20.7. Anal. Calcd. for $C_{15}H_{12}$: C, 93.71; H, 6.29. Found C, 93.48; H, 6.38.

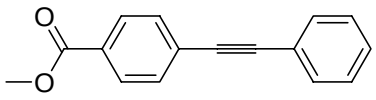


4-Methoxydiphenylacetylene (entry 4, Table 2.2): The general procedure was used to convert phenylacetylene and 4-iodoanisole to the title product. Purification by flash chromatography (4:1 hexanes / dichloromethane as the eluent) gave the analytically pure product as a white solid (396 mg, 97% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (m, 2H), 7.49 (dt, *J*=9.04, 2H), 7.35 (m, 3H), 6.88 (dt, *J*=9.04, 2H), 3.83, (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.6, 133.0,

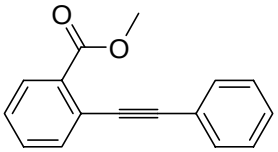
131.4, 128.3, 127.9, 123.6, 115.3, 113.9, 89.3, 88.0, 55.3. Anal. Calcd. for $C_{15}H_{12}O$: C, 86.51; H, 5.81. Found C, 86.39; H, 5.84. mp 56-57 °C.



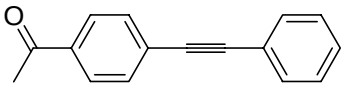
2-methoxydiphenylacetylene (entry 5, Table 2.2): The general procedure was used to convert phenylacetylene and 2-iodoanisole to the title product. Purification by flash chromatography (hexanes as the eluent) gave the analytically pure product as amber colored oil (289 mg, 70% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (m, 2H), 7.54 (dd, *J*=5.8, 1H), 7.4-7.30 (m, 4H), 6.96 (dd, *J*=6.4, 1H), 6.90 (d, *J*=8.5, 1H), 3.92 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.8, 133.5, 131.6, 129.7, 128.2, 128.0, 123.5, 120.4 112.4, 110.6, 93.4, 85.7, 55.7. Anal. Calcd. for $C_{15}H_{12}O$: C, 86.51; H, 5.81. Found C, 86.61; H, 5.87.



Methyl 4-(Phenylenthynyl)benzoate (entry 6, Table 2.2): The general procedure was used to convert phenylacetylene and methyl 4-iodobenzoate to the title product. Purification by flash chromatography (hexanes as the eluent) gave the analytically pure product as a white solid (421 mg, 89% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (dt, *J*=8.29, 2H), 7.59 (dt, *J*=8.29, 2H), 7.55 (m, 2H), 7.4-7.3 (m, 3H), 3.91 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 131.6, 131.4, 129.4, 129.3, 128.6, 128.3, 127.9, 122.6, 92.3, 88.6, 52.1. Anal. Calcd. for $C_{16}H_{12}O_2$: C, 81.34; H, 5.12. Found C, 81.34; H, 5.07. mp 119-120 °C.



Methyl 2-(Phenylenthynyl)benzoate (entry 7, Table 2.2): The general procedure was used to convert phenylacetylene and methyl 2-iodobenzoate to the title product. Purification by flash chromatography (hexanes as the eluent) gave the analytically pure product as amber oil (358 mg, 76% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (dd, *J*=7.5, 1H, 7.65 (dd, *J*=6.2, 1H), 7.60m (d, 2H), 7.50 (td, *J*=7.5,1H), 7.40-7.33 (m, 4H), 3.97 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 133.9, 131.8, 131.7, 131.6, 130.4, 128.4, 128.3, 127.8, 123.6, 123.2, 94.3, 88.2, 52.1. Anal. Calcd. for $C_{16}H_{12}O_2$: C, 81.34; H, 5.12. Found C, 81.21; H, 5.18.

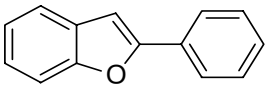


4-(Phenylethynyl)acetophenone (entry 8, Table 2.2): The general procedure was used to convert phenylacetylene and 4-iodoacetophenone to the title product. Purification by flash chromatography (3:1 dichloromethane / hexanes as the eluent) gave the analytically pure product as a white solid (373 mg, 85% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (dt, *J*=8.7, 2H), 7.61 (dt, *J*=8.7, 2H), 7.58 (m,2H), 7.38 (m, 3H), 2.61 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.3, 136.1, 131.7, 131.6, 128.8, 128.4, 128.2, 128.1, 122.6, 92.7, 88.6, 26.6. Anal. Calcd. for $C_{16}H_{12}O$: C, 87.25; H, 5.49. Found C,87.06; H, 5.49. mp 98-99 °C.

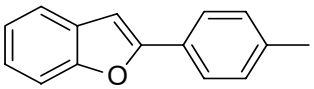
SYNTHESIS OF 2-ARYL-BENZO[*b*]FURANS: VIA A COPPER-CATALYZED DOMINO CROSS-COUPLING REACTION AND 5-ENDO-DIG CYCLIZATION:

General Procedure: In an argon-filled glove box, a Pyrex glass tube (2.5 cm in diameter) equipped with a Teflon-coated stir bar, was charged with cesium carbonate

(Aldrich, 1.31g, 4.0 mmol), $[Cu(phen)(PPh_3)_2]NO_3$ (10 mol% with respect to the iodophenol), and 2.0 mmol of the appropriate 2-iodophenol. The tube was then sealed with a rubber septum, taken out of the glove box and toluene (5.0 mL) and 2.00 mmol of the appropriate phenylacetylene were injected into the tube through the septum. The contents were then stirred at 110 °C for the time indicated in Table 2 and 3. The reaction mixture was then cooled to room temperature and filtered to remove any insoluble residues. The filtrate was concentrated *in vacuo*; the residue was purified by flash column chromatography on silica gel to obtain the analytically pure product.

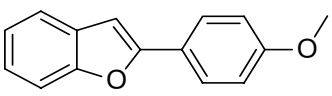


2-phenyl-benzo[*b*]furan (entry 1, Table 3.2): The general procedure was used to convert phenylacetylene and 2-iodophenol to the title product. Purification by flash chromatography (hexanes as the eluent) gave the analytically pure product as a white solid (358 mg, 93% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86-7.83 (dd, *J*= 7.0, 2H) 7.56-7.49 (m, 2H), 7.41-7.39 (m, 2H), 7.34-7.18 (m, 3H), 6.97 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9, 154.9, 130.44, 129.2, 128.8, 128.5, 124.9, 124.2, 122.9, 120.9, 111.2, 101.3. Anal. Calcd. for $C_{14}H_{10}O$: C, 86.57; H, 5.19; Found C, 86.41; H, 5.34. m.p. – 120 ^{o}C.

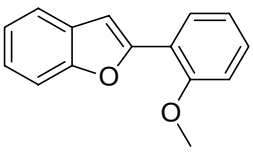


2-*p*-Tolyl-benzo[*b*]furan (entry 2, Table 3.2): The general procedure was used to convert 4-ethynyl-toluene and 2-iodophenol to the title product. Purification by flash chromatography (10% CH_2Cl_2 in hexanes as the eluent) gave the analytically pure product as a white solid (268 mg, 64%

yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, *J*= 8.3, 2H), 7.56-7.48 (m, 2H), 7.28-7.17 (m, 4H), 6.93 (s, 1H), 2.37 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.2, 154.7, 138.6, 132.9, 129.5, 127.7, 124.9, 124.0, 122.8, 120.7, 111.1, 100.5, 21.4. Anal. Calcd. for $C_{15}H_{12}O$: C, 86.51; H, 5.81; Found C, 86.34; H, 5.98. m.p. – 124-125 ^{o}C.

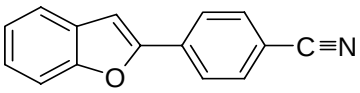


2-(4-Methoxy-phenyl)-benzo[*b*]furan (entry 3, Table 3.2): The general procedure was used to convert 4-ethynyl-anisole and 2-iodophenol to the title product. Purification by flash chromatography (20% ethyl acetate in hexanes as the eluent) gave the analytically pure product as a white solid (277 mg, 62% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, *J*= 8.5, 2H), 7.54-7.47 (m, 2H), 7.34-7.20 (m, 2H), 6.95 (d, 2H), 6.85 (s, 1H), 3.82 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.0, 156.0, 154.7, 129.5, 126.4, 123.7, 123.3, 122.8, 120.6, 114.2, 111.0, 99.7, 55.3. Anal. Calcd. for $C_{15}H_{12}O_2$: C, 80.34; H, 5.39; Found C, 80.34; H, 5.40. m.p. – 149-150 ^{o}C.

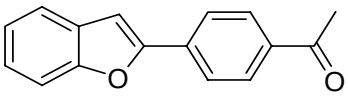


2-(2-Methoxy-phenyl)-benzo[*b*]furan (entry 4, Table 3.2): The general procedure was used to convert 2-ethynyl-anisole and 2-iodophenol to the title product. Purification by flash chromatography (10% ethyl acetate in hexanes as the eluent) gave the analytically pure product as a white solid (348 mg, 77% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, *J*= 7.7, 1H), 7.58 (d, *J*= 6.4, 1H), 7.48 (d, *J*= 8.1, 1H), 7.34 (s, 1H), 7.26-7.18 (m, 3H), 7.03 (t, 1H), 6.89 (d, *J*= 8.3, 1H), 3.86 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.4, 153.8,

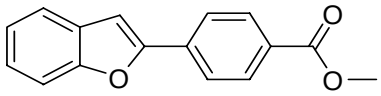
152.2, 129.8, 129.2, 126.9, 124.1, 122.6, 121.0, 120.7, 119.3, 110.9, 110.8, 106.3, 55.9. Anal. Calcd. for $C_{15}H_{12}O_2$: C, 80.34; H, 5.39; Found C, 80.60; H, 5.65. m.p. – 76 ^oC.



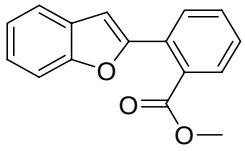
4-Benzo[*b*]furan-2-yl-benzonitrile (entry 5, Table 3.2): The general procedure was used to convert 4-ethynyl-benzonitrile and 2-iodophenol to the title product. Purification by flash chromatography (20% ethyl acetate in hexanes as the eluent) gave the analytically pure product as a white solid (337 mg, 77% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, *J*= 8.9, 2H), 7.71 (d, *J*= 8.7, 2H), 7.62 (d, *J*= 7.5, 1H), 7.53 (d, *J*=8.1, 1H), 7.38-7.24 (m, 2H), 7.16 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.1, 153.4, 134.3, 132.5, 128.5, 125.5, 124.9, 123.3, 121.4, 118.7, 111.3, 111.3, 104.2. Anal. Calcd. for $C_{15}H_9NO$: C, 82.18; H, 4.14; N, 6.39; Found C, 81.98; H, 4.09; N, 6.15. m.p. – 149 ^oC.



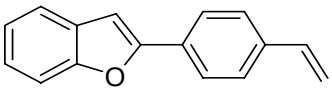
2-(4-Acetylphenyl)benzo[*b*]furan (entry 6, Table 3.2): The general procedure was used to convert 1-(4-ethynyl-phenyl)-ethanone and 2-iodophenol to the title product. Purification by flash chromatography (10% ethyl acetate in hexanes as the eluent) gave the analytically pure product as a white solid (326 mg, 69% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, *J*= 8.67, 2H), 7.92 (d, *J*= 8.7, 2H), 7.60 (d, *J*= 7.7, 1H), 7.52 (d, *J*= 7.4, 1H), 7.35-7.22 (m, 2H), 7.14 (s, 1H), 2.62 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.3, 155.2, 154.5, 136.5, 134.6, 128.9, 128.9, 125.1, 124.8, 123.2, 121.3, 111.4, 103.7, 26.6. HRMS EI calcd for $C_{16}H_{12}O_2$ – 236.0837, Found – 236.0835. mp. – 168-170 ^oC.



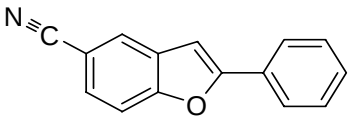
2-(4-(Methoxycarbonyl)phenyl)benzo[*b*]furan (entry 7, Table 3.2): The general procedure was used to convert 4-ethynyl-benzoic acid methyl ester and 2-iodophenol to the title product. Purification by flash chromatography (10% ethyl acetate in hexanes) gave the analytically pure product as a white solid (300 mg, 67% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (dd, *J*= 8.7, 2H), 7.90 (d, *J*= 8.7, 2H), 7.52-7.62 (dd, *J*= 8.1, 2H), 7.24-7.33 (m, 2H), 7.13 (s, 1H), 3.93 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ. 167.0, 155.5, 155.0, 134.0, 130.5, 130.0, 129.3, 125.4, 125.0, 123.6, 121.6, 111.7, 103.8, 52.6. Anal. Calcd. for $C_{16}H_{12}O_3$: C, 76.18; H, 4.79. Found C, 75.97; H, 4.75. m.p. 176-178 ^{o}C.



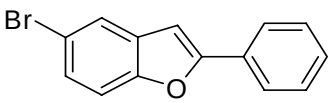
2-(2-(Methoxycarbonyl)phenyl)benzo[*b*]furan (entry 8, Table 3.2): The general procedure was used to convert 2-ethynyl-benzoic acid methyl ester and 2-iodophenol to the title product. Purification by flash chromatography (10% ethyl acetate in hexanes) gave the analytically pure product as an oil (458 mg, 67% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75-7.70 (m, 2H), 7.61-7.40 (m, 4H), 7.31-7.22 (m, 2H), 6.92 (s, 1H), 3.81 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ. 169.4, 155.1, 154.7, 131.1, 130.9, 129.6, 129.4, 129.0, 128.9, 128.6, 124.5, 122.9, 121.2, 111.1, 104.4, 52.5. Anal. Calcd. for $C_{16}H_{12}O_3$: C, 76.18; H, 4.79. Found C, 75.95; H,4.75.



2-(4-Vinyl-phenyl)-benzo[*b*]furan (entry 9, Table 2): The general procedure was used to convert 1-ethynyl-4-vinyl-benzene and 2-iodophenol to the title product. Purification by flash chromatography (hexanes as the eluent) gave the analytically pure product as a white solid (300 mg, 68% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, *J*= 8.5, 2H), 7.56-7.44 (m, 4H), 7.29-7.19 (m, 2H), 6.98 (s, 1H), 6.74 (dd, *J*=10.9 and *J*=6.6, 1H), 5.78 (d, *J*= 17.7, 1H), 5.28 (d, *J*= 10.9, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.7, 154.9, 137.7, 136.3, 129.8, 129.2, 126.6, 125.0, 124.3, 122.9, 120.9, 114.4, 111.1, 101.4. Anal. Calcd. for $C_{16}H_{12}O$: C, 87.25; H, 5.49; Found C, 87.54; H, 5.62. m.p. - 164-165 ^{o}C.

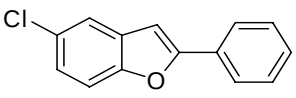


5-Cyano-2-phenyl-benzo[*b*]furan (entry 1, Table 3.3): The general procedure was used to convert phenylacetylene and 4-cyano-2-iodophenol to the title product. Purification by flash chromatography (15% ethyl acetate in hexanes as the eluent) gave the analytically pure product as a white solid (421 mg, 96% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88-7.82 (m, 3H), 7.58-7.40 (m, 5H), 7.01 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 156.4, 129.9, 129.6, 129.2, 129.0, 127.8, 125.7, 125.2, 119.6, 112.3, 106.9, 100.7. Anal. Calcd. for $C_{15}H_9NO$: C, 82.18; H, 4.14; N, 6.39; Found C, 82.04; H, 4.21; N, 6.21. m.p. – 143-145 ^{o}C

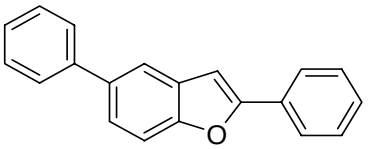


5-Bromo-2-phenyl-benzo[*b*]furan (entry 2, Table 3.3): The general procedure was used to convert phenylacetylene and 4-bromo-2-iodophenol to the title product. Purification by flash chromatography (20%

CH_2Cl_2 in hexanes as the eluent) gave the analytically pure product as a white solid (468 mg, 86% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, *J*= 7.0, 2H), 7.69-7.67 (m, 1H), 7.46-7.35 (m, 5H), 6.91 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.2, 153.6, 131.2, 129.0, 129.0, 128.8, 127.0, 125.0, 123.4, 116.0, 112.6, 100.6. Anal. Calcd. for $C_{14}H_9BrO$: C, 61.57; H, 3.32; Br, 29.26; Found C, 61.46; H, 3.26; Br, 29.50. m.p. – 157 ^{o}C.

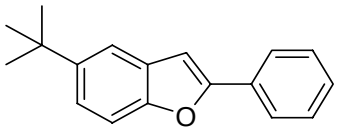


5-Chloro-2-phenyl-benzo[*b*]furan (entry 3, Table 3.3): The general procedure was used to convert phenylacetylene and 4-chloro-2-iodophenol to the title product. Purification by flash chromatography (10% CH_2Cl_2 in hexanes as the eluent) gave the analytically pure product as a white solid (411 mg, 90% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, *J*= 7.0, 2H), 7.52 (d, *J*= 2.3, 1H), 7.46-7.35 (m, 4H), 7.21 (dd, *J*= 6.6, 1H), 6.93 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.4, 153.2, 130.6, 129.9, 129.0, 128.8, 128.5, 125.0, 124.4, 120.4, 112.1, 100.8. Anal. Calcd. for $C_{14}H_9ClO$: C, 73.53; H, 3.97; Cl, 15.50; Found C, 73.31; H, 3.99; Cl, 15.68. m.p. – 155.5-157 ^{o}C.

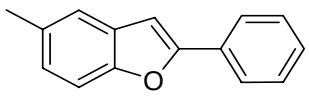


2,5-Diphenyl-benzo[*b*]furan (entry 4, Table 3.3): The general procedure was used to convert phenylacetylene and 4-phenyl-2-iodophenol to the title product. Purification by flash chromatography (10% CH_2Cl_2 in hexanes as the eluent) gave the analytically pure product as a white solid (427 mg, 79% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, *J*= 7.53, 2H), 7.78-7.75 (m, 1H), 7.67-7.33 (m, 10H), 7.07 (s, 1H). ^{13}C

NMR (75 MHz, $CDCl_3$) δ 156.6, 154.5, 141.6, 136.6, 130.4, 129.7, 128.8, 128.7, 128.6, 127.4, 126.9, 124.9, 124.0, 119.4, 111.3, 101.5. Anal. Calcd. For $C_{20}H_{14}O$: C, 88.86; H, 5.22; Found C, 88.99; H, 5.28. m.p. – 166-167 ^oC.



5-*tert*-Butyl-2-phenyl-benzo[*b*]furan (entry 5, Table 3.3): The general procedure was used to convert phenylacetylene and 4-*tert*-butyl-2-iodophenol to the title product. Purification by flash chromatography (10% ethyl acetate in hexanes as the eluent) gave the analytically pure product as a white solid (398 mg, 80% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 7.83 (dd, *J*=7.2, 2H), 7.57-7.56 (m, 1H), 7.44-7.38 (m, 3H), 7.34-7.30 (m, 2H), 6.96 (s, 1H), 1.38 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.0, 153.1, 145.9, 130.7, 128.9, 128.7, 128.3, 124.8, 122.2, 117.1, 110.4, 101.5, 34.7, 31.8. Anal. Calcd. for $C_{18}H_{18}O$: C, 86.36; H, 7.25; Found C, 86.34; H, 7.13. m.p. – 103-104 ^oC.



5-Methyl-2-phenyl-benzo[*b*]furan (entry 6, Table 3.3): The general procedure was used to convert phenylacetylene and 4-methyl-2-iodophenol to the title product. Purification by flash chromatography (hexanes as the eluent) gave the analytically pure product as a white solid (353 mg, 85% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, *J*=7.2, 2H), 7.41-7.30 (m, 5H), 7.06 (d, *J*= 7.4, 1H), 6.88 (s, 1H), 2.41 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9, 153.3, 132.2, 130.6,

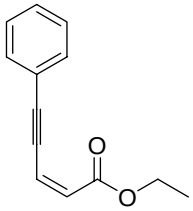
129.3, 128.7, 128.4, 125.5, 124.8, 120.7, 110.6, 101.1, 21.3. Anal. Calcd. for $C_{15}H_{12}O$: C, 86.51; H, 5.81; Found C, 86.28; H, 5.90. m.p. – 131 ^{o}C.

COPPER-CATALYZED SYNTHESIS OF 1,3-ENYNES:

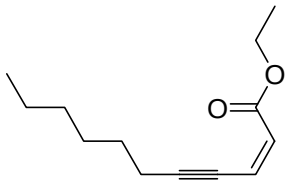
General Procedure: In an argon-filled glove box, a Pyrex glass tube (2.5 cm in diameter) equipped with a Teflon-coated stir bar, was charged with potassium carbonate (Alfa Aesar, 0.553 g, 4.0 mmol) and [Cu(bipy)(PPh_3)Br] (10 mol% with respect to the acetylene). The tube was then sealed with a rubber septum, taken out of the glove box and toluene (4.0 mL) and 2.00 mmol of the appropriate acetylene and 2.20 mmol of the appropriate vinyl iodide were injected into the tube through the septum. The contents were then stirred at 110 °C for 8 hours unless specified otherwise. The reaction mixture was then cooled to room temperature and filtered through a pad of celite to remove any insoluble residues. The filtrate was concentrated *in vacuo*; the residue was purified by flash column chromatography on silica gel to obtain the analytically pure product.

Modified Procedure: In an argon-filled glove box, a Pyrex glass tube (2.5 cm in diameter) equipped with a Teflon-coated stir bar, was charged with cesium carbonate (Aldrich, 1.303 g, 4.0 mmol) and [Cu(phen)(PPh_3)$_2NO_3$] (10 mol% with respect to the acetylene). The tube was then sealed with a rubber septum, taken out of the glove box and toluene (4.0 mL) and 2.00 mmol of the appropriate acetylene and 2.20 mmol of the

appropriate vinyl iodide were injected into the tube through the septum. The contents were then stirred at 110 °C for 8 hours unless specified otherwise. The reaction mixture was then cooled to room temperature and filtered through a pad of celite to remove any insoluble residues. The filtrate was concentrated *in vacuo*; the residue was purified by flash column chromatography on silica gel to obtain the analytically pure product.

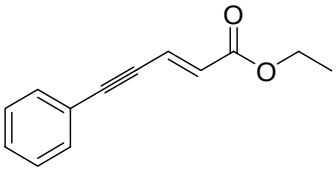


Ethyl (*Z*)-5-phenyl-2-buten-4-ynoate (Table 4.4, entry 1): The general procedure was used to convert phenylacetylene and (*Z*)-ethyl-3-iodoacrylate to the title product. Purification by flash chromatography (15% ethyl acetate in hexanes as the eluent) gave the analytically pure product as a light yellow oil (396 mg, 99% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54-7.52 (m, 2H), 7.34 (m, 3H), 6.36 (d, *J*=11.4, 1H), 6.12 (d, *J*=11.4, 1H), 4.26 (q, 2H), 1.33 (t, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 132.0, 129.1, 128.3, 128.2, 122.8, 122.6, 101.1, 86.3, 60.4, 14.2. Anal. Calc'd. for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04; Found C, 77.78; H, 6.06.

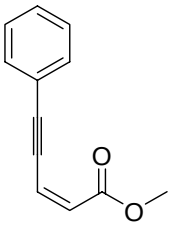


(*Z*)-ethyl undec-2-en-4-ynoate (Table 4.4, entry 9): The general procedure was used to convert *n*-octyne and (*Z*)-ethyl-3-iodoacrylate to the title product. Purification by flash chromatography (5% ethyl acetate in hexane as the eluent) gave the analytically pure product as a light yellow oil (401 mg, 96% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.13 (dt, *J*= 10.8, 1H), 6.02 (d, *J*=11.0, 1H), 4.21 (q, 2H), 2.44 (m, 2H), 1.58 (p, 2H), 1.42 (m, 2H), 1.30-1.28 (m, 7H), 0.89 (t, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 127.3, 123.9,

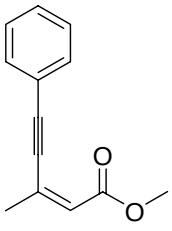
104.2, 77.7, 60.2, 31.3, 28.6, 28.4, 22.5, 20.1, 14.2, 14.0. Anal. Calcd. for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68; Found C, 74.96; H, 9.56.



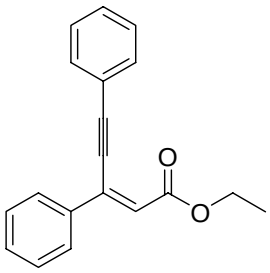
Ethyl (*E*)-5-phenyl-2-buten-4-ynoate (Table 4.5, entry 1): The general procedure was used to convert phenylacetylene and (*E*)-ethyl-3-iodoacrylate to the title product in 24 hours. Purification by flash chromatography (10% ethyl acetate in hexanes as the eluent) gave the analytically pure product as a light yellow oil (325 mg, 81% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (m, 2H), 7.35 (m, 3H), 6.98 (d, *J*=15.8, 1H), 6.30 (d, *J*=15.8, 2H), 4.24 (q, 2H), 1.31 (t, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 131.9, 130.0, 129.2, 128.4, 125.0, 122.2, 98.2, 86.3, 60.7, 14.2. Anal. Calc'd. for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04; Found C, 78.06; H, 6.13.



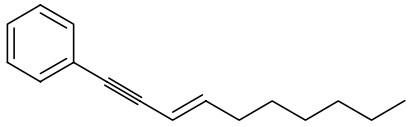
Methyl (*Z*)-5-phenyl-2-penten-4-ynoate (Table 4.5, entry 2): The general procedure was used to convert phenylacetylene and (*Z*)-methyl-3-iodoacrylate to the title product. Purification by flash chromatography (15% ethyl acetate in hexanes as the eluent) gave the analytically pure product as a light yellow oil (336 mg, 90% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (m, 2H), 7.35 (m, 3H), 6.36 (d, *J*= 11.4, 1H), 6.14 (d, *J*=11.4, 1H), 3.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 132.2, 129.3, 128.4, 127.8, 123.2, 122.6, 101.5, 86.4, 51.6. Anal. Calc'd. for $C_{12}H_{10}O_2$: C, 77.40; H, 5.41; Found C, 77.41; H, 5.35.



***cis*-3-methyl-5-phenyl-pent-2-en-4-ynoic acid methyl ester (Table 4.5, entry 3)**: The general procedure was used to convert phenylacetylene and (*Z*)-β-Iodo-β-methyl methyl acrylate to the title product. Purification by flash chromatography (15% ethyl acetate in hexanes as the eluent) gave the analytically pure product as a light yellow oil (388 mg, 97% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (m, 2H), 7.33 (m, 3H), 6.03 (q, 1H), 3.76 (s, 3H), 2.13 (d, *J*= 1.5, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 135.0, 132.0, 129.0, 128.3, 123.9, 122.7, 100.3, 88.3, 51.2, 25.1. Anal. Calc'd. for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04; Found C, 77.83; H, 6.04.

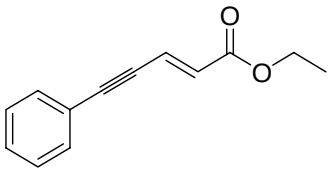


(*Z*)-ethyl 3,5-diphenylpent-2-en-4-ynoate (Table 4.5, entry 4): The general procedure was used to convert phenylacetylene and (*Z*)-ethyl 3-iodo-3-phenylacrylate to the title product. Purification by flash chromatography (5% ethyl acetate in hexanes as the eluent) gave the analytically pure product as a light yellow oil (530 mg, 96% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (m, 2H), 7.63 (m, 2H), 7.38 (m, 6H), 6.59 (s, 1H), 2.06 (q, 2H), 1.35 (t, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 136.9, 136.1, 131.9, 129.7, 129.0, 128.4, 128.2, 127.0, 122.5, 122.5, 101.9, 86.7, 60.2, 14.2. Anal. Calc'd. for $C_{19}H_{16}O_2$: C, 82.58; H, 5.84; Found C, 82.71; H, 5.93.

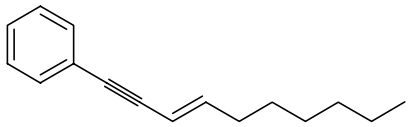


(*E*)-1-Phenyldec-3-en-1-yne (Table 4.5, entry 5): The general procedure was used to convert phenylacetylene

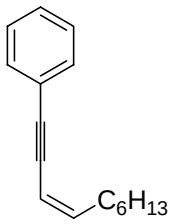
and (*E*)-1-iodooctene to the title product in 24 hours. Purification by flash chromatography (light petroleum ether as eluent) gave the analytically pure product as a clear oil (423 mg, 99% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (m, 2H), 7.28 (m, 3H), 6.24 (m, 1H), 5.68 (d, *J*=15.8, 1H), 2.15 (q, 2H), 1.41-1.28 (m, 8H), 0.89 (t, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.1, 131.2, 128.1, 127.7, 123.5, 109.3, 88.2, 87.7, 33.1, 31.5, 28.7, 28.6, 22.5, 13.9. Anal. Calc'd. for $C_{16}H_{20}$: C, 90.51; H, 9.49; Found C, 90.65; H, 9.58.



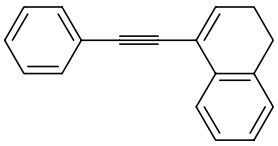
Ethyl (*E*)-5-phenyl-2-buten-4-ynoate (Table 4.6, entry 1): The modified procedure was used to convert phenylacetylene and (*E*)-ethyl-3-iodoacrylate to the title product. GC yield was found to be 74% and 99% after 8 and 24 hours respectively.



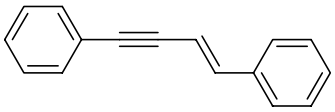
(E)-1-Phenyldec-3-en-1-yne (Table 4.6, entry 2): The modified procedure was used to convert phenylacetylene and (E)-1-iodooctene to the title product. Purification by flash chromatography (light petroleum ether as eluent) afforded a clear oil (418 mg, 98% yield). The proton spectra obtained matches that of the analytically pure compound previously isolated (see Table 4.5, entry 5). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (m, 2H), 7.28 (m, 3H), 6.24 (m, 1H), 5.66 (d, *J*=15.9, 1H), 2.15 (q, 2H), 1.42-1.29 (m, 8H), 0.89 (t, 3H).



Dec-3-en-1-ynyl-benzene (Table 4.6, entry 3): The modified procedure was used to convert (*Z*)-1-Iodo-oct-1-ene and phenyl acetylene to the title product. Purification by flash chromatography (hexane as the eluent) gave the analytically pure product as a colorless oil (420 mg, 98% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.41 (m, 2H), 7.29-7.27 (m, 3H), 5.99-5.92 (m, 1H), 5.67-5.65 (d, *J*= 10.7, 1H), 2.42-2.36 (m, 2H), 1.46-1.43 (m, 2H), 1.37-1.29 (m, 6H), 0.89-0.86 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.4, 131.4, 128.3, 128.0, 123.8, 109.1, 93.5, 86.6, 31.8, 30.5, 29.0, 28.9, 22.7, 14.2. Anal. Calcd. for $C_{16}H_{20}$: C, 90.51; H, 9.49; Found C, 90.24; H, 9.47.



1,2-dihydro-4-(2-phenylethynyl)naphthalene (Table 4.6, entry 4): The modified procedure was used to convert phenylacetylene and 1,2-dihydro-4-iodonaphthalene to the title product in 24 hours. Purification by flash chromatography (20 % CH_2Cl_2 in hexanes) gave the analytically pure product as a light yellow oil (360 mg, 78% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.6, 1H), 7.52 (m, 2H), 7.31 (m, 3H), 7.25 (m, 1H), 7.18 (t, 1H), 7.13 (d, *J* = 7.3, 1H), 6.54 (t, 1H), 2.80 (t, 2H), 2.42, (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.5, 135.1, 132.6, 131.5, 128.3, 128.1, 127.7, 127.4, 126.6, 125.1, 123.4, 121.7, 90.3, 87.3, 27.1, 23.7. Anal. Calc'd. for $C_{18}H_{14}$: C, 93.87; H, 6.13; Found C, 93.79; H, 6.36.



(*E*)-1,4-diphenylbutenyne (Table 4.6, entry 5): The modified procedure was used to convert phenyl acetylene and β-iodostyrene to the title product. Purification by flash chromatography (20 % CH_2Cl_2 in hexanes) gave the analytically pure product as a light yellow solid (399 mg, 98% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (m, 2H), 7.43 (d, *J*= 7.2, 2H), 7.4-7.27 (m, 6H), 7.03 (d, *J*= 16.2, 1H), 6.37 (d, *J*= 16.2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.2, 136.3, 131.5, 128.7, 128.6, 128.3, 128.2, 126.3, 123.4, 108.1, 91.8, 88.9. Anal. Calcd. for $C_{16}H_{12}$: C, 94.08; H, 5.92; Found C, 93.96; H, 6.10. m.p. : 97-98 ^{o}C.

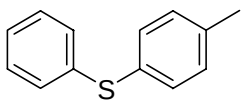
A GENERAL METHOD FOR THE FORMATION OF ARYL-SULFUR BONDS USING COPPER(I) CATALYSTS

General. All of the reactions reported herein were conducted under an inert atmosphere of argon in oven-dried glassware. All reagents and solvents were obtained from Acros or from Aldrich and were used without further purification. Sodium *tert*-Butoxide (Acros, 99%) was stored in an argon filled glove box. Purification was performed by flash chromatography using ICN Flash Silica Gel, 230-400 mesh. The yields given refer to isolated yields of the characterized compounds, deemed pure by elemental analyses, ^{1}H NMR and ^{13}C NMR. NMR spectra were recorded on a Bruker AVANCE 300 MHz spectrometer. Chemical shifts were reported in parts per million (δ). The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; dd, doublet of doublets; dt,

doublet of triplets; and m, multiplet. The coupling constants, *J*, are reported in Hertz (Hz). The residual solvent peak was used as the internal reference. All proton and ^{13}C NMR assignments for the diphenylsulfides were made using the work done by Perumal et. al. (*Magn. Reson. Chem.* 1987, *25*, 1001-1006; *Magn. Reson. Chem.* 1995, *33*, 779-790.) as a reference. Elemental analyses were performed at the Microanalysis Laboratory, University of Massachusetts at Amherst by Dr. Greg Dabkowski. The reported melting points were uncorrected.

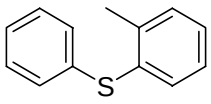
Cu-Catalyzed Coupling of thiophenols with aryl iodides

General Procedure: In an argon-filled glove box, a Pyrex glass tube (2.5 cm in diameter) equipped with a Teflon stir bar, was charged with sodium *tert*-butoxide (Acros, 3.0 mmol), CuI (10 mol% with respect to the aryl iodide), and neocuproine (10 mol% with respect to the aryl iodide). The tube was then sealed with a rubber septum, taken out of the glove box and thiophenol (2.2 mmol), the aryl iodide (2.00 mmol) and toluene (6.0 mL) were injected into the tube through the septum. The contents were then stirred at 110 °C for 24 hours. The reaction mixture was then cooled to room temperature and filtered to remove any insoluble residues. The filtrate was concentrated in vacuo; the residue was purified by flash column chromatography on silica gel to obtain the analytically pure product. Due to the stench of the thiols, all glassware and syringes used were washed with bleach to reduce the odor of the thiols.

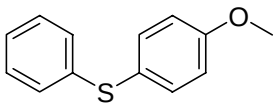


***p*-Tolylthiophenol (Table 5.2, entry 1):** The general procedure was used to convert 4-iodotoluene and thiophenol to the title product.

Purification by flash chromatography (hexane as the eluent) gave the analytically pure product as a clear oil (379 mg, 94% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22-7.08 (m, 7H) 7.04-7.00 (d, *J*= 7.9, 2H), 2.25 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.5, 137.1, 132.2, 131.2, 130.0, 129.7, 129.0, 126.4, 21.1. Anal. Calcd. for $C_{13}H_{12}S$: C, 77.95; H, 6.04; S, 16.01; Found C, 78.00; H, 6.06; S, 15.88.

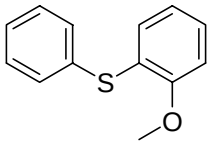


***o*-Tolylthiophenol (Table 5.2, entry 2):** The general procedure was used to convert 2-iodotoluene and thiophenol to the title product. Purification by flash chromatography (hexane as the eluent) gave the analytically pure product as a clear oil (386 mg, 96% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20-7.00 (m, 9H), 2.26 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.9, 136.1, 133.7, 132.9, 130.5, 129.6, 129.1, 127.8, 126.7, 126.3, 20.6. Anal. Calcd. for $C_{13}H_{12}S$: C, 77.95; H, 6.04; S, 16.01; Found C, 77.87; H, 6.06; S, 15.81.

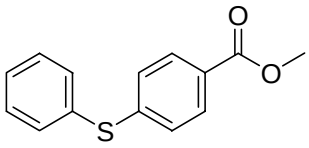


1-Methoxy-4-(phenylthio)benzene (Table 5.2, entry 3): The general procedure was used to convert 4-iodoanisole and thiophenol to the title product. Purification by flash chromatography (hexane / CH_2Cl_2 [3:1] as the eluent) gave the analytically pure product as a clear oil (416 mg, 96% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (dt, *J*= 7.7, 2H), 7.13-6.97 (m, 5H), 6.77 (d, *J*=7.5, 2H), 3.67 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.7, 138.5, 135.3, 128.9, 128.1, 125.7,

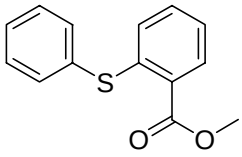
124.2, 114.9, 55.2. Anal. Calcd. for $C_{13}H_{12}OS$: C, 72.19; H, 5.59; S, 14.82; Found C, 72.34; H, 5.70; S, 14.81.



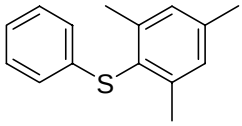
1-Methoxy-2-(phenylthio)benzene (Table 5.2, entry 4): The general procedure was used to convert 2-iodoanisole and thiophenol to the title product. Purification by flash chromatography (hexane / CH_2Cl_2 [3:1] as the eluent) gave the analytically pure product as a clear oil (412 mg, 95% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.25 (m, 6H), 7.12 (dd, *J*=6.0, 1H), 6.96-6.89 (m, 2H), 3.90 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.2, 134.4, 131.5, 131.4, 129.1, 128.3, 127.0, 124.0, 121.2, 110.8, 55.8. Anal. Calcd. for $C_{13}H_{12}OS$: C, 72.19; H, 5.59; S, 14.82; Found C, 72.23; H, 5.70; S, 14.67.



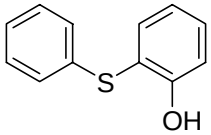
4-Phenylsulfanyl-benzoic acid methyl ester (Table 5.2, entry 5): The general procedure was used to convert Methyl-4-iodobenzoate and thiophenol to the title product. Purification by flash chromatography (hexane / ethyl acetate [6:1] as the eluent) gave the analytically pure product as a white solid (411 mg, 84% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (dt, *J*=8.7, 2H), 7.51-7.47 (m, 2H), 7.39-7.37 (m, 3H), 7.21 (dt, *J*=8.7, 2H), 3.89 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 144.3, 133.6, 132.3, 130.0, 129.6, 128.6, 127.5, 127.4, 52.0. Anal. Calcd. for $C_{14}H_{12}O_2S$: C, 68.83; H, 4.95; S, 13.13; Found C, 68.87; H, 4.95; S, 12.96. mp found: 70-71 ^{o}C.



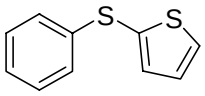
2-Phenylsulfanyl-benzoic acid methyl ester (Table 5.2, entry 6): The general procedure was used to convert Methyl-2-iodobenzoate and thiophenol to the title product. Purification by flash chromatography (hexane / ethyl acetate [6:1] as the eluent) gave the analytically pure product as a clear oil (397 mg, 81% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (dd, *J*=6.2, 1H), 7.47 (m, 2H), 7.33 (m, 3H), 7.14 (td, *J*=5.4, 1H), 7.04 (td, *J*=6.0, 1H), 6.73 (dd, *J*=6.8, 1H), 3.85 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 143.2, 135.5, 132.4, 132.2, 130.9, 129.7, 129.0, 127.3, 126.6, 124.2, 52.1. Anal. Calcd. for $C_{14}H_{12}O_2S$: C, 68.83; H, 4.95; S, 13.13; Found C, 68.94; H, 5.10; S, 12.90.



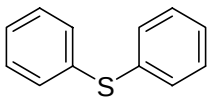
(2,4,6-trimethyl-phenyl)-phenyl sulfide (Table 5.2, entry 7): The general procedure was used to convert 2,4,6-trimethyliodobenzene and thiophenol to the title product. Purification by flash chromatography (hexane as the eluent) gave the analytically pure product as a clear oil (444 mg, 97% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (m, 2H), 7.09 (m, 3H), 6.96 (m, 2H) 2.44 (s, 6H), 2.37 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.7, 139.2, 138.4, 129.3, 128.8, 127.2, 125.4, 124.4, 21.7, 21.1. Anal. Calcd. for $C_{15}H_{16}S$: C, 78.90; H, 7.06; S, 14.04; Found C, 78.76; H, 7.23; S, 14.10.



2-Phenylsulfanyl-phenol (Table 5.2, entry 8): The general procedure was used to convert 2-iodothiophene and thiophenol to the title product. Purification by flash chromatography (hexane / ethyl acetate (6:1) as the eluent) gave the analytically pure product as a light brown oil (328 mg, 81% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (dd, *J*=5.7, 1H), 7.28 (m, 1H), 7.14 (m, 2H), 7.07-6.97 (m, 4H), 6.86 (td, *J*=6.02, 1H,), 6.44 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.2, 136.9, 135.8, 132.3, 129.2, 126.8, 126.1, 121.3, 116.2, 115.5. Anal. Calcd. for $C_{12}H_{10}S$: C, 71.25; H, 4.98; S, 15.85; Found C, 71.25; H, 5.01; S, 15.82.

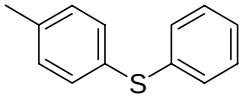


2-Phenylsulfanyl-thiophene (Table 5.2, entry 9): The general procedure was used to convert 2-iodophenol and thiophenol to the title product. Purification by flash chromatography (hexane as the eluent) gave the analytically pure product as a clear oil (349 mg, 91% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (dd, *J*=4.1, 2H), 7.36-7.21 (m, 6H), 7.12 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.6, 136.0, 131.2, 131.0, 128.9, 127.9, 127.0, 126.0. Anal. Calcd. for $C_{10}H_8S_2$: C, 62.46; H, 4.19; S, 33.35; Found C, 62.56; H, 4.21; S, 33.13.

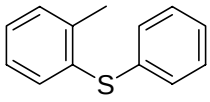


Phenylsulfide (Table 5.3, entry 1): The general procedure was used to convert iodobenzene and thiophenol to the title product. Purification by flash chromatography (hexane as the eluent) gave the analytically pure product as a clear oil (360 mg, 98% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48-7.44 (m, 4H), 7.42-

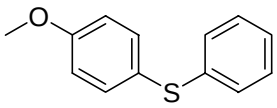
7.39 (m, 4H), 7.37-7.31 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.7, 130.9, 129.1, 126.9. Anal. Calcd. for $C_{12}H_{10}S$: C, 77.37; H, 5.41; S, 17.21; Found C, 77.50; H, 5.45; S, 17.00.



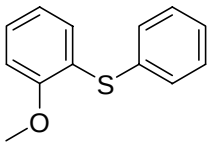
***p*-Tolylthiophenol (Table 5.3, entry 2):** The general procedure was used to convert iodobenzene and *p*-toluenethiol to the title product. Purification by flash chromatography (hexane as the eluent) gave the analytically pure product as a clear oil (388 mg, 97.0% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (dt, *J*= 8.1, 2H), 7.15-7.12 (m, 4H), 7.08 (m, 1H), 7.04-7.00 (d, *J*= 7.34, 2H), 2.22 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.1, 137.6, 132.8, 131.8, 130.6, 130.2, 129.5, 126.9, 21.6. Anal. Calcd. for $C_{13}H_{12}S$: C, 77.95; H, 6.04; S, 16.01; Found C, 77.78; H, 6.01; S, 16.19.



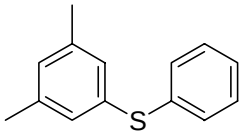
***o*-Tolylthiophenol (Table 5.3, entry 3):** The general procedure was used to convert iodobenzene and *o*-toluenethiol to the title product. Purification by flash chromatography (hexane as the eluent) gave the analytically pure product as a clear oil (383 mg, 95% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20-6.98 (m, 9H), 2.27 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.9, 136.1, 133.7, 132.9, 130.5, 129.6, 129.1, 127.9, 126.7, 126.3, 20.5. Anal. Calcd. for $C_{13}H_{12}S$: C, 77.95; H, 6.04; S, 16.01; Found C, 78.02; H, 6.01; S, 16.01.



1-Methoxy-4-(phenylthio)benzene (Table 5.3, entry 4): The general procedure was used to convert iodobenzene and 4-methoxybenzenethiol to the title product. Purification by flash chromatography (hexane / CH_2Cl_2 [3:1] as the eluent) gave the analytically pure product as a clear oil (410 mg, 95% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (dt, *J*= 8.9, 2H), 7.12-6.96 (m, 5H), 6.75 (dt, 2H), 3.67 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.8, 138.6, 135.3, 128.9, 128.1, 125.7, 124.2, 114.9, 55.3. Anal. Calcd. for $C_{13}H_{12}OS$: C, 72.19; H, 5.59; S, 14.82; Found C, 72.26; H, 5.59; S, 14.65.

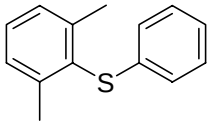


1-Methoxy-2-(phenylthio)benzene (Table 5.3, entry 5): The general procedure was used to convert iodobenzene and 2-methoxybenzenethiol to the title product. Purification by flash chromatography (hexane / CH_2Cl_2 [3:1] as the eluent) gave the analytically pure product as a clear oil (406 mg, 94% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.25 (m, 6H), 7.14 (dd, 1H), 6.96-6.89 (m, 2H), 3.90 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.2, 134.4, 131.9, 131.4, 129.2, 128.3, 127.4, 123.9, 121.1, 110.8, 55.8. Anal. Calcd. for $C_{13}H_{12}OS$: C, 72.19; H, 5.59; S, 14.82; Found C, 72.22; H, 5.70; S, 14.63.



(3,5-dimethyl-phenyl)-phenyl sulfide (Table 5.3, entry 6): The general procedure was used to convert iodobenzene and 3,5-dimethylthiophenol to the title product. Purification by flash chromatography (hexane as

the eluent) gave the analytically pure product as a clear oil (417 mg, 97% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17-7.01 (m, 5H), 6.84 (s, 2H), 6.72 (s, 1H), 2.10 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.8, 136.4, 134.7, 130.4, 129.1, 129.0, 128.7, 126.6, 21.1. Anal. Calcd. for $C_{14}H_{14}S$: C, 78.45; H, 6.58; S, 14.96; Found C, 78.53; H, 6.62; S, 14.89.

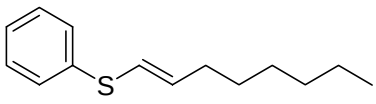


(2,6-dimethyl-phenyl)-phenyl sulfide (Table 5.3, entry 7): The general procedure was used to convert iodobenzene and 2,6-dimethylthiophenol to the title product. Purification by flash chromatography (hexane as the eluent) gave the analytically pure product as a clear oil (409 mg, 95% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.1-6.98 (m, 5H), 6.93-6.86 (m, 1H), 6.77 (d, *J*= 7.16, 2H) 2.34 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.9, 138.0, 130.4, 129.2, 128.9, 128.4, 125.6, 124.6, 21.8. Anal. Calcd. for $C_{14}H_{14}S$: C, 78.45; H, 6.58; S, 14.96; Found C, 78.58; H, 6.71; S, 14.98.

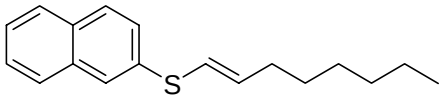
COPPER-CATALYZED SYNTHESIS OF VINYL SULFIDES:

General Procedure: In an argon-filled glove box, a Pyrex glass tube (2.5 cm in diameter) equipped with a Teflon-coated stir bar, was charged with potassium phosphate (Alfa Aesar, 0.6368 g, 3.00 mmol) and $[Cu(phen)(PPh_3)_2]NO_3$ (.0831g, 5.0 mol%). The tube was then sealed with a rubber septum, taken out of the glove box and toluene (4.0 mL) and 2.00 mmol of the appropriate thiol and 2.00 mmol of the appropriate vinyl iodide were injected into the tube through the septum. The contents were then stirred at

110 °C for 4 hours unless specified otherwise. The reaction mixture was then cooled to room temperature and filtered through a pad of celite to remove any insoluble residues and the pad of celite was washed with 50 mL of ethyl acetate. The filtrate was concentrated *in vacuo*; the residue was purified by flash column chromatography on silica gel or neutral aluminum oxide to obtain the analytically pure product.

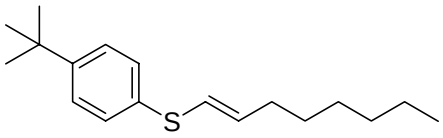


(*E*)-1-phenylthio-1-octene (Table 6.3, entry 1): The general procedure was used to convert thiophenol and (*E*)-1-iodooctene to the title product. Purification by flash chromatography (silica gel) (3% triethylamine in hexanes as the eluent) gave the analytically pure product as a colorless liquid (407 mg, 93% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.27 (m, 4H), 7.16 (m, 1H), 6.14 (td, *J*=14.9, 2.4; 1H), 5.98 (td, *J*= 15.0, 6.8 Hz; 1H), 2.16 (m, *J*= 8.1, 7.0, 1.2 Hz; 2H), 1.42-1.29 (m, 8H), 0.89 (t, *J*= 6.8 Hz; 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8, 136.7, 128.9, 128.3, 125.9, 122.5, 33.1, 31.6, 28.9, 28.8, 22.6, 14.1. Anal. Calc'd. for $C_{14}H_{20}S$: C - 76.30; H - 9.15; S - 14.58 Found, C - 76.31; H - 9.16; S - 14.58.

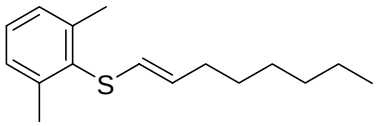


(*E*)-naphthalen-2-yl(oct-1-enyl)sulfane (Table 6.3, entry 2): The general procedure was used to convert 2-naphthalenethiol and (*E*)-1-iodooctene to the title product. Purification by flash chromatography (silica gel) (3% triethylamine in hexanes as the eluent) gave the analytically pure product as a colorless liquid (526 mg, 97% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78-7.71 (m, 4H), 7.47-7.37 (m, 3H), 6.21 (td, *J*=14.9, 1.2 Hz; 1H), 6.05 (td,

J= 14.9, 6.8 Hz; 1H), 2.18 (m, *J*= 7.7, 6.8, 1.1 Hz; 2H), 1.44-1.30 (m, 8H), 0.90 (t, *J*= 6.6 Hz; 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 134.2, 133.8, 131.7, 128.4, 127.7, 127.0, 126.6, 126.5, 126.1, 125.6, 120.4, 33.1, 31.6, 29.0, 28.8, 22.6, 14.1. Anal. Calc'd. for $C_{18}H_{22}S$: C - 79.94; H - 8.20; S - 11.86; Found, C - 79.93; H - 8.05; S - 11.86.

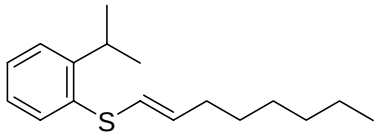


(*E*)-(4-tert-butylphenyl)(oct-1-enyl)sulfane (Table 6.3, entry 3): The general procedure was used to convert 4-*tert*-butylthiophenol and (*E*)-1-iodooctene to the title product. Purification by flash chromatography (silica gel) (3% triethylamine in hexanes as the eluent) gave the analytically pure product as a colorless liquid (509 mg, 92% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.24 (m, 4H), 6.11 (td, *J*= 15.0, 1.2 Hz; 1H), 5.94 (td, *J*= 14.9, 6.8 Hz; 1H), 2.14 (m, *J*= 7.8, 6.9. 1.0 Hz; 2H), 1.45-1.29 (m, 17H), 0.89 (t, *J*= 6.6 Hz; 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.4, 136.8, 133.0, 128.7, 126.0, 121.4, 34.5, 33.1, 31.7, 31.3, 29.1, 28.8, 22.7, 14.2. Anal. Calc'd. for $C_{18}H_{28}S$: C - 78.04; H - 10.11; S - 11.60 Found, C - 78.19; H - 10.21; S - 11.60.

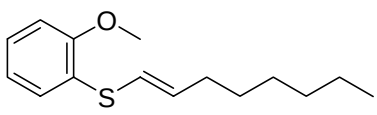


(E)-(2,6-dimethylphenyl)(oct-1-enyl)sulfane (Table 6.3, entry 4): The general procedure was used to convert 2,6-dimethylthiophenol and (*E*)-1-iodooctene to the title product. Purification by flash chromatography (silica gel) (3% triethylamine in hexanes as the eluent) gave the analytically pure product as a colorless liquid (493 mg, 99% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (m, 3H), 5.79 (td, *J*=14.9, 1.3; 1H), 5.23 (td, *J*= 14.8, 7.0 Hz; 1H), 2.47 (s,

6H), 2.14 (m, *J*= 7.7, 7.0, 1.2 Hz; 2H), 1.45-1.29 (m, 17H), 0.89 (t, *J*= 6.6 Hz; 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.4, 136.8, 133.0, 128.7, 126.0, 121.4, 34.5, 33.1, 31.7, 31.3, 29.1, 28.8, 22.7, 14.2. Anal. Calc'd. for $C_{18}H_{28}S$: C - 78.04; H - 10.11; S - 11.60 Found, C - 78.19; H - 10.21; S - 11.60.

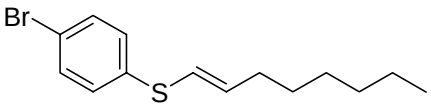


(*E*)-(2-isopropylphenyl)(oct-1-enyl)sulfane (Table 6.3, entry 5): The general procedure was used to convert 2-isopropylthiophenol and (*E*)-1-iodooctene to the title product. Purification by flash chromatography (silica gel) (3% triethylamine in hexanes as the eluent) gave the analytically pure product as a colorless liquid (511 mg, 97% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.12 (m, 4H), 6.06 (td, *J*=14.9, 1.3; 1H), 5.90 (m, 1H), 3.40 (sept., 1H), 2.15 (m, 2H) 1.42-1.22 (m, 14 H), 0.88 (t, *J*= 6.8 Hz; 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 147.7, 136.8, 134.3, 129.5, 126.7, 126.3, 125.4, 121.3, 33.1, 31.6, 30.2, 29.0, 28.8, 23.2, 22.6, 14.1. Anal. Calc'd. for $C_{17}H_{26}S$: C - 77.80; H - 9.99; S - 12.22 Found, C - 77.62; H - 9.92; S - 12.17.

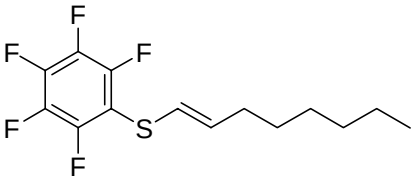


(*E*)-(2-methoxyphenyl)(oct-1-enyl)sulfane (Table 6.3, entry 6): The general procedure was used to convert 2-methoxythiophenol and (*E*)-1-iodooctene to the title product. Purification by flash chromatography (silica gel) (5% ethyl acetate in a 3% triethylamine in hexanes solution as the eluent) gave the analytically pure product as a colorless liquid (471 mg, 94% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (dd, *J*= 7.8, 1.5 Hz; 1H), 7.16 (m, 1H), 6.90

(m, 2H), 6.09 (d, *J*= 15.2 Hz; 1H), 6.03 (td, *J*= 14.9, 6.2 Hz; 1H), 3.87 (s, 3H), 2.16 (m, 2H), 1.43-1.29 (m, 8H), 0.89 (t, *J*= 6.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 138.6, 128.2, 126.8, 125.2, 121.1, 119.3, 110.4, 55.7, 33.1, 31.6, 28.9, 28.7, 22.6, 14.0. Anal. Calc'd. for $C_{15}H_{22}OS$: C - 71.95; H - 8.86; S - 12.81 Found, C - 72.20; H - 8.92; S - 12.73.

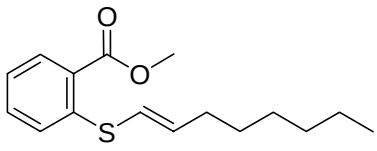


(*E*)-(4-bromophenyl)(oct-1-enyl)sulfane (Table 6.3, entry 7): The general procedure was used to convert 4-bromothiophenol and (*E*)-1-iodooctene to the title product. Purification by flash chromatography (silica gel) (3% triethylamine in hexanes as the eluent) gave the analytically pure product as a colorless liquid (575 mg, 96% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (td, *J*= 8.5, 2.0 Hz; 2H), 7.14 (td, *J*= 8.5, 1.9 Hz; 2H), 6.06 (d, *J*= 14.9 Hz; 1H), 6.0 (m, 1H), 2.16 (m, 2H), 1.44-1.29 (m, 8H), 0.89 (t, *J*= 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1, 136.1, 131.9, 129.6, 119.8, 119.6, 33.1, 31.6, 28.9, 28.8, 22.6, 14.1. Anal. Calc'd. for $C_{14}H_{19}BrS$: C - 56.19; H - 6.40; Br - 26.70; S - 10.71 Found, C - 56.41; H - 6.45; Br - 26.90; S - 10.56.

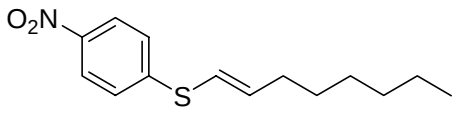


(*E*)-oct-1-enyl(perfluorophenyl)sulfane (Table 6.3, entry 8): The general procedure was used to convert pentafluorothiophenol and (*E*)-1-iodooctene to the title product. Purification by flash chromatography (silica gel) (2% triethylamine in hexanes as the eluent) gave the analytically pure product as a colorless liquid (608 mg, 98%

yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.96 (m, 2H), 2.08 (m, 2H), 1.32 (m, 8H), 0.88 (t, *J*= 6.4 Hz; 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 118.0, 32.8, 31.6, 28.7, 28.6, 22.6, 14.0. Anal. Calc'd. for $C_{14}H_{15}F_5S$: C - 54.18; H - 4.87; S - 10.33 Found, C - 54.12; H - 4.80; S - 10.50.

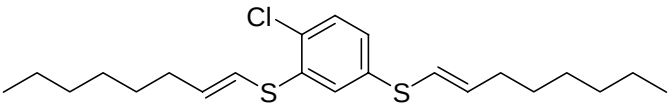


(*E*)-methyl 2-(oct-1-enylthio)benzoate (Table 6.3, entry 9): The general procedure was used to convert methyl thiosalicylate and (*E*)-1-iodooctene to the title product. Purification by flash chromatography (neutral alumina) (5% ethyl acetate in hexanes as the eluent) gave the analytically pure product as a colorless liquid (524 mg, 94% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, *J*= 7.8, 1.5 Hz; 1H), 7.44-7.34 (m, 2H), 7.16 (m, 1H), 6.33 (td, *J*= 14.9, 6.6 Hz; 1H), 6.13 (d, *J*= 15.0 Hz; 1H), 3.91 (s, 3H), 2.23 (q, *J*= 6.7 Hz; 2H), 1.48-1.30 (m, 8H); 0.90 (t, *J*= 6.8 Hz; 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.65, 142.20, 132.20, 131.13, 126.72, 126.57, 124.16, 119.65, 52.01, 33.21, 31.57, 28.77, 28.73, 22.57, 14.01. Anal. Calc'd. for $C_{16}H_{22}O_2S$: C - 69.02; H - 7.96; S - 11.52 Found, C - 68.97; H - 7.95; S - 11.75.

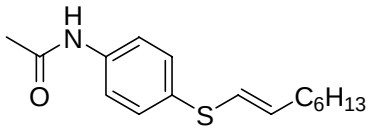


(*E*)-(4-nitrophenyl)(oct-1-enyl)sulfane (Table 6.3, entry 10): The general procedure was used to convert 4-nitrothiophenol and (*E*)-1-iodooctene to the title product. Purification by flash chromatography (silica gel) (5% ethyl acetate in a 3% triethylamine in hexanes solution as the eluent) gave the analytically pure product as a yellow liquid (494 mg, 93% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (td, *J*= 8.9, 2.0 Hz; 2H), 7.32 (td, *J*= 9.0, 2.5 Hz; 2H), 6.25 (m, 1H), 6.13 (d, *J*= 14.9 Hz; 1H), 2.25 (m, 2H), 1.50-1.31 (m, 8H), 0.91 (t, *J*= 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.7, 145.2, 143.8, 125.9, 123.9, 116.7, 33.2, 31.5, 28.7, 28.6, 22.5, 14.0. Anal. Calc'd. for $C_{14}H_{19}NO_2S$: C - 63.36; H - 7.22; N - 5.28; S - 12.08 Found, C - 63.24; H - 7.15; N - 5.42; S - 11.93.

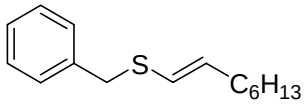


1-chloro-2,4-bis((E)-oct-1-enylthio)benzene (Table 6.3, entry 11): The general procedure was used to convert 3-chloro-1,3-benzenedithiol and (*E*)-1-iodooctene to the title product. Purification by flash chromatography (silica gel) (3% triethylamine in hexanes as the eluent) gave the analytically pure product as a colorless liquid (722 mg, 91% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (m, 2H), 7.00 (m, 1H), 6.10 (m, 4H), 2.18 (m, 4H), 1.43-1.30 (m, 16H), 0.89 (m, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 142.5, 139.4, 137.5, 136.2, 129.7, 129.3, 126.7, 126.0, 119.8, 117.9, 33.0, 33.2, 31.7, 29.0, 28.9, 22.7, 14.1. Anal. Calc'd. for $C_{22}H_{33}ClS_2$: C - 66.54; H - 8.38; Cl - 8.93; S - 16.15 Found, C - 66.62; H - 8.41; Cl - 8.95; S - 16.03.

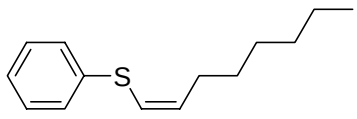


(*E*)-*N*-(4-(oct-1-enylthio)phenyl)acetamide (Table 6.3, entry 12): The general procedure was used to convert *N*-(4-mercaptophenyl)acetamide and (*E*)-1-iodooctene to the title product in 6 hours. Purification by flash chromatography (silica gel) (5% ethyl acetate, 10% methanol and

3% triethylamine in hexane as the eluent) gave the analytically pure product as a slightly yellow solid (541 mg, 97% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.46-7.43 (d, *J*= 8.6 Hz; 2H), 7.25-7.22 (d, *J*= 8.6 Hz; 2H), 6.08-6.05 (d, *J*= 14.9 Hz; 1H), 5.96-5.89 (td, *J*= 14.9, 6.8 Hz; 1H), 2.18-2.11 (m, 5H), 1.42-1.25 (m, 8H), 0.90-0.87 (t, *J*= 7.0 Hz; 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ168.8, 136.9, 136.4, 131.4, 129.5, 121.0, 120.6, 33.0, 31.5, 28.9, 28.7, 24.3, 22.5, 14.0. Anal. Calc'd. for $C_{16}H_{23}NOS$: C - 69.27; H - 8.36; N - 5.05; S - 11.56; Found, C - 69.44; H - 8.24; N - 4.92; S - 11.35. m.p. 61-62 ^{o}C.

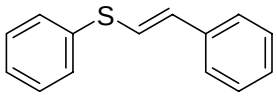


(*E*)-benzyl(oct-1-enyl)sulfane (Table 6.3, entry 13): The general procedure was used to convert benzyl mercaptan and (*E*)-1-iodooctene to the title product in 4 hours. Purification by flash chromatography (silica gel) (3% triethylamine in hexane as the eluent) gave the analytically pure product as a colorless oil (464 mg, 99% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.30 (m, 4H), 7.25-7.23 (m, 1H), 5.91-5.87 (td, *J*= 15.0, 1.2 Hz; 1H), 5.70-5.63 (td, *J*= 14.9, 6.9 Hz; 1H), 3.83 (s, 2H), 2.05-2.00 (dt, *J*= 7.8, 6.8 Hz; 2H), 1.34-1.20 (m, 8H), 0.89-0.85 (t, *J*= 7.0 Hz; 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8, 132.6, 128.8, 128.4, 127.0, 121.8, 37.6, 33.1, 31.6, 29.1, 28.6, 22.6, 14.1. Anal. Calc'd. for $C_{15}H_{22}S$: C - 76.86; H - 9.46; S - 13.86; Found, C - 76.93; H - 9.41; S - 13.96.

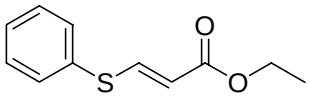


(*Z*)-1-phenylthio-1-octene (Table 6.4, entry 1): The general procedure was used to convert thiophenol and (*Z*)-1-iodooctene to the title product. Purification by flash chromatography (silica gel) (3%

triethylamine in hexanes as the eluent) gave the analytically pure product as a colorless liquid (425 mg, 96% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.27 (m, 4H), 7.18 (m, 1H), 6.17 (td, *J*=9.20, 1.36; 1H), 5.82 (m, 1H), 2.25 (m, *J*= 8.1, 7.1, 1.3 Hz; 2H), 1.44-1.30 (m, 8H), 0.89 (t, *J*= 6.8 Hz; 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.5, 133.7, 128.9, 128.7, 126.0, 122.5, 31.7, 29.1, 29.0, 28.9, 22.6, 14.1. Anal. Calc'd. for $C_{14}H_{20}S$: C - 76.30; H - 9.15; S - 14.58 Found, C - 76.03; H - 8.85; S - 14.32.

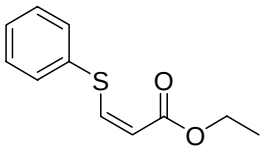


(E)-phenyl(styryl)sulfane (Table 6.4, entry 2): The general procedure was used to convert thiophenol and *trans*-β-iodostyrene to the title product. Purification by flash chromatography (neutral alumina) (pentane as the eluent) gave the analytically pure product as a colorless liquid (416 mg, 98% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (m, 2H), 7.33-7.19 (m, 8H), 6.86 (d, *J*= 15.5 Hz; 1H), 6.71 (d, *J*= 15.5 Hz; 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.5, 135.2, 131.8, 129.8, 129.1, 128.6, 127.5, 12689, 126.0, 123.4. . Anal. Calc'd. for $C_{14}H_{12}S$: C - 79.20; H - 5.70; S - 15.10 Found, C - 79.32; H - 5.70; S - 15.04.

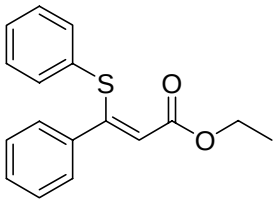


(*E*)-ethyl 3-(phenylthio)acrylate (Table 6.4, entry 3): Pranorm Saejueng used the general procedure was used to convert thiophenol and (*E*)-3-iodopropenoate to the title product. Purification by flash chromatography (silica gel) (3% triethylamine in hexane as the eluent) gave the analytically pure product as a light yellow oil (409 mg, 98% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80-7.76 (d, *J*= 15.0 Hz; 1H), 7.48-7.46 (m, 4H), 7.42-7.38 (m, 1H), 5.67-5.64

(d, *J*= 15.1 Hz; 1H), 4.18-4.13 (q, *J*= 7.1 Hz; 2H), 1.27-1.23 (t, *J*= 7.1 Hz; 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 146.7, 132.9, 130.4, 129.6, 129.0, 115.5, 60.2, 14.2. Anal. Calc'd. for $C_{11}H_{12}O_2S$: C - 63.43; H - 5.81 - S 15.40; Found, C - 63.50; H - 5.81; S - 15.28.

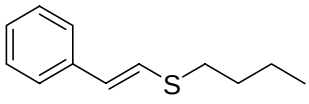


(*Z*)-ethyl 3-(phenylthio)acrylate (Table 6.4, entry 4): The general procedure was used to convert thiophenol and (*Z*)-3-iodopropenoate to the title product. Purification by flash chromatography (silica gel) (5% ethyl acetate in mixture of 3% triethylamine in hexane as the eluent) gave the analytically pure product as a slightly yellow oil (412 mg, 98% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49-7.46 (m, 4H), 7.37-7.31 (m, 1H), 7.27-7.24 (d, *J*= 10.0 Hz; 1H), 5.92-5.89 (d, *J*= 10.0 Hz; 1H), 4.26-4.21 (q, *J*= 7.1 Hz; 2H), 1.33-1.29 (t, *J*= 7.1 Hz; 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 149.5, 136.0, 130.9, 129.2, 128.0, 113.2, 60.1, 14.2. Anal. Calc'd. for $C_{11}H_{12}O_2S$: C - 63.43; H - 5.81; S - 15.40; Found, C - 63.66; H - 5.82; S - 15.24.

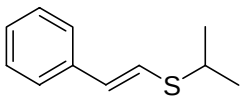


(*Z*)-methyl 3-phenyl-3-(phenylthio)acrylate (Table 6.4, entry 5): Pranorm Saejueng used the general procedure was used to convert thiophenol and (*Z*)-methyl-3-iodo-3-phenylacrylate to the title product. Purification by flash chromatography (silica gel) (5% ethyl acetate in mixture of 3% triethylamine in hexane as the eluent) gave the analytically pure product as a white solid (523 mg, 96% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17-7.02 (m, 10H),

6.09 (s, 1H), 3.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 159.5, 138.1, 133.9, 132.2, 128.7, 128.4, 128.3, 127.7, 127.7, 115.6, 51.4. Anal. Calc'd. for $C_{16}H_{14}O_2S$: C - 71.08; H - 5.22; S - 11.86; Found, C - 70.93; H - 5.21; S - 11.88. m.p. 72-73 ^oC.

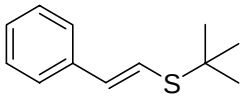


(*E*)-butyl(styryl)sulfane (Table 6.5, entry 1): Pranorm Saejueng used the general procedure was used to convert *n*-butanethiol and *trans*-β-iodostyrene to the title product in 4 hours. Purification by flash chromatography (silica gel) (3% triethylamine in hexane as the eluent) gave the analytically pure product as a colorless oil (379 mg, 98% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.27 (m, 4H), 7.20-7.15 (m, 1H), 6.74-6.70 (d, *J*= 15.6 Hz; 1H), 6.47-6.43 (d, *J*= 15.6 Hz; 1H), 2.81-2.77 (t, *J*= 7.3 Hz; 2H), 1.71-1.63 (m, 2H), 1.50-1.41 (m, 2H), 0.96-0.92 (t, *J*= 7.3 Hz; 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.1, 128.6, 126.7, 126.5, 125.4, 125.3, 32.3, 31.5, 21.9, 13.6. Anal. Calc'd. for $C_{12}H_{16}S$: C - 74.94; H - 8.39; S - 16.67; Found, C - 75.08; H - 8.37; S - 16.88.

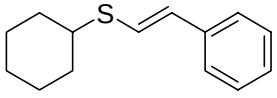


(*E*)-isopropyl(styryl)sulfane (Table 6.5, entry 2): Pranorm Saejueng used the general procedure was used to convert propane-2-thiol and *trans*-β-iodostyrene to the title product in 4 hours. Purification by flash chromatography (silica gel) (5% ethyl acetate in mixture of 3% triethylamine in hexane as the eluent) gave the analytically pure product as a colorless oil (320 mg, 89% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.26 (m, 4H), 7.21-7.15 (m, 1H), 6.77-6.73 (d, *J*= 15.6 Hz; 1H), 6.58-6.54 (d, *J*= 15.6 Hz; 1H), 3.27-3.17 (septet, *J*= 6.7 Hz; 1H), 1.36-1.34

(d, *J*= 6.7 Hz; 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.0, 128.8, 128.6, 126.9, 125.5, 124.0, 36.8, 23.4. Anal. Calc'd. for $C_{11}H_{14}S$: C - 74.10; H - 7.91; S - 17.98; Found, C - 73.82; H - 7.91; S - 18.03.

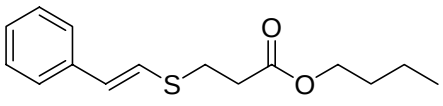


(*E*)-*tert*-butyl(styryl)sulfane (Table 6.5, entry 3): Pranorm Saejueng used the general procedure was used to convert 2-methylpropane-2-thiol and *trans*-β-iodostyrene to the title product in 4 hours. Purification by flash chromatography (silica gel) (3% triethylamine in hexane as the eluent) gave the analytically pure product as a colorless oil (309 mg, 80% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.27 (m, 4H), 7.22-7.18 (m, 1H), 6.89-6.85 (d, *J*= 15.4 Hz; 1H), 6.73-6.69 (d, *J*= 15.4 Hz; 1H), 1.40 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.0, 131.9, 128.6, 127.2, 125.8, 122.0, 44.3, 31.0. Anal. Calc'd. for $C_{12}H_{16}S$: C - 74.94; H - 8.39; S - 16.67; Found, C - 74.73; H - 8.29; S - 16.51.

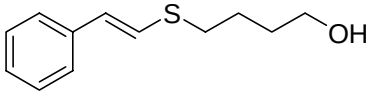


(E)-cyclohexyl(styryl)sulfane (Table 6.5, entry 4): The general procedure was used to convert cyclohexanethiol and β-iodostyrene to the title product. Purification by flash chromatography (silica gel) (3% triethylamine in hexanes as the eluent) gave the analytically pure product as a light yellow liquid (417 mg, 95% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 4H), 7.18 (m, 1H), 6.76 (d, *J*= 15.6 Hz, 1H), 6.56 (d, *J*= 15.6 Hz; 1H), 2.98 (m, 1H), 2.05 (m, 2H), 1.79 (m, 2H), 1.63 (m, 1H), 1.45-1.28 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.1, 128.6,

126.8, 125.5, 124.0, 45.3, 35.6, 26.0, 25.6. Anal. Calc'd. for $C_{14}H_{18}S$: C - 77.01; H - 8.31; S - 14.68 Found, C - 76.88; H - 8.32; S - 14.75.

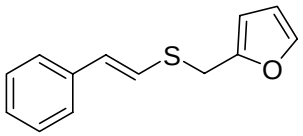


(*E*)-butyl 3-(styrylthio)propanoate (Table 6.5, entry 5): The general procedure was used to convert butyl 3-mercaptopropanoate and (*E*)-1-(2-iodovinyl)benzene to the title product in 4 hours. Purification by flash chromatography (silica gel) (3% triethylamine in hexane as the eluent) gave the analytically pure product as a colorless oil (521 mg, 98% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.28(m, 4H), 7.22-7.17 (m, 1H), 6.70-6.66 (d, *J*= 15.5 Hz; 1H), 6.53-6.50 (d, *J*= 15.5 Hz; 1H), 4.12-4.08 (t, *J*= 6.7 Hz; 2H), 3.07-3.04 (t, *J*= 7.3 Hz; 2H), 2.72-2.68 (t, *J*= 7.3 Hz; 2H), 1.64-1.57 (m, 2H), 1.42-1.32 (m, 2H), 0.94-0.90 (t, *J*= 7.3 Hz; 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 136.7, 128.6, 128.3, 127.0, 125.5, 123.8, 64.7, 34.6, 30.5, 27.6, 19.0, 13.6. Anal. Calc'd. for $C_{15}H_{20}O_2S$: C - 68.14; H - 7.62; S - 12.13; Found, C - 67.98; H - 7.60; S - 12.26.



(*E*)-4-(styrylthio)butan-1-ol (Table 6.5 entry 6): The general procedure was used to convert 4-mercapto-1-butanol and β-iodostyrene to the title product. Purification by flash chromatography (silica gel) (3% triethylamine in ethyl acetate as the eluent) gave the analytically pure product as a colorless liquid (403 mg, 97% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J*= 4.4 Hz; 4H), 7.17 (m, 1H), 6.70 (d, *J*= 15.6 Hz; 1H), 6.46 (d, *J*= 15.6 Hz; 1H), 3.67 (t, *J*= 6.3 Hz; 2H), 2.83 (t, *J*= 7.0 Hz; 2H), 1.80-1.63 (m, 4H), 1.53 (broad s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.97, 128.57, 127.02, 126.80, 125.42, 124.90, 62.27, 32.37,

31.62, 25.76. IR (KBr): 3355 (s,br); 3074 (m); 3020 (m); 2936 (s); 2871 (s); 1944 (w); 1594 (s); 1568 (s); 1446 (s); 1056 (s); 937 (s); 736 (s); 691 (s). Anal. Calc'd. for $C_{12}H_{16}OS$: C - 69.19; H - 7.74; S - 15.39 Found, C - 69.18, H - 7.66; 15.51.



(*E*)-2-(styrylthiomethyl)furan (Table 6.5 entry 7): The general procedure was used to convert furfuryl mercaptan and β-iodostyrene to the title product. Purification by flash chromatography (silica gel) (5% ethyl acetate in a 3% triethylamine in hexanes solution as the eluent) gave the analytically pure product as a colorless liquid (419 mg, 97% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (dd, *J*= 1.8, 0.8 Hz; 1H), 7.27 (m, 4H), 7.18 (m, 1H), 6.72 (d, *J*= 15.9 Hz; 1H), 6.55 (d, *J*= 15.9 Hz; 1H), 6.31 (dd, *J*= 3.3, 1.9 Hz; 1H), 6.24 (dd, *J*= 3.5, 0.7 Hz; 1H), 3.98 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.79, 142.32, 136.74, 128.64, 128.57, 127.08, 125.63, 123.72, 110.51, 107.84, 29.63. Anal. Calc'd. for $C_{13}H_{12}OS$: C - 72.19; H - 5.59; S - 14.82 Found, C - 72.01; H - 5.51; S - 14.98.

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