Copper-mediated C-S Bond Formation and C(sp^2)-H Functionalization via Cascade Cyclization

by

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Author's Declaration

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

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Abstract

Organosulfur compounds have a wide variety of applications in pharmaceutical compounds and synthetic materials. Carbon-sulfur bonds are often found in natural and important bioactive compounds, thus the formation of C-S bonds is of high research interest. A novel method has been discovered to generate C-S bonds in tandem with C-C bond formation. This new reaction starts with aryl diynes and a sulfinate salt under copper-mediated conditions to form a new C-S bond and two new C-C bonds, which involves the functionalization of an aromatic C-H bond and a formal [3+2] cycloaddition. This thesis will discuss the reaction optimization, reaction scope and preliminary mechanistic investigations.

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Table of Contents

List of Figures

List of Schemes

List of Tables

List of Abbreviations

Ac	acetyl
AcOH	acetic acid
Ar	Aromatic
9-BBN	9-borabicyclo[3.3.1]nonane
BHT	butylated hydroxytoluene
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Boc	*tert*-butyloxycarbonyl
Bpin	bis(pinacolato)diboron
BQ	benzoquinone
cat.	catalyst
cod	1,5-cyclooctadiene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
DG	directing group
DMAc	*N*,*N*-dimethylacetamide
DMF	*N*,*N*-dimethylformamide
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
eq	equation
eq.	equivalent
Et	ethyl
Et_3N	triethylamine
EtOAc	ethyl acetate
FG	functional group
h	hour
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectrometry
KIE	kinetic isotope effect
Me	methyl
MeCN	acetonitrile
MW	microwave
*n*Bu	normal butyl
n-Dec	normal decyl
n-Hex	normal hexyl
NMR	nuclear magnetic resonance
o-	*ortho*
OTf	triflate
p-	*para*
PCy_3	tricyclohexylphosphine
Ph	phenyl

Piv	pivalogyl
PDTITN	poly(1,3-dithienylisothianaphthene)
Pr	propyl
RDS	rate-determining step
rt	room temperature
*t*Bu	*tert*-butyl
SM	starting material
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl ether
TLC	thin-layer chromatography
tol	toluene
TsNa	sodium *p*-toluenesulfinate
TsOH	*p*-toluenesulfonic acid
TsSK	potassium *p*-toluenethiosulfonate

Chapter 1 Introduction

1.1 Organosulfur compounds

1.1.1 Introduction

Organosulfur compounds are essential in pharmaceuticals and organic materials as well as many other industrial fields. Some typical examples are given in **Figure 1**. Methionine and cysteine are two of the sulfur-containing amino acids, both of which have biological functions such as promoting body development and antioxidant activity and involvement in biosynthesis of proteins (**Figure 1**).[1] Garlic is not only a food flavoring but a kind of traditional medicine; it contains various biologically active compounds that have been shown to decrease rates of cancer.[2] Allicin and ajoene are biologically active compounds (**Figure 1**), which were isolated from garlic in 1944 and 1983, respectively, and it was reported that both compounds have antibacterial activities.[3] In the pharmaceutical field, organic sulfur compounds are also employed widely. For example, sulfamethoxazole and its derivatives are used to produce antibiotic or antiprotozoal drugs such as Bactrim.[4] Organic sulfur compounds are also very popular in material science; one such important example is the thiophene-based conjugated polymers, such as poly(1,3-dithienylisothianaphthene) (PDTITN), that have promising application in organics electronics and photonics;[5] moreover, organosulfur compounds with S-S bonds were proposed as a novel class of cathode material for batteries.[6]

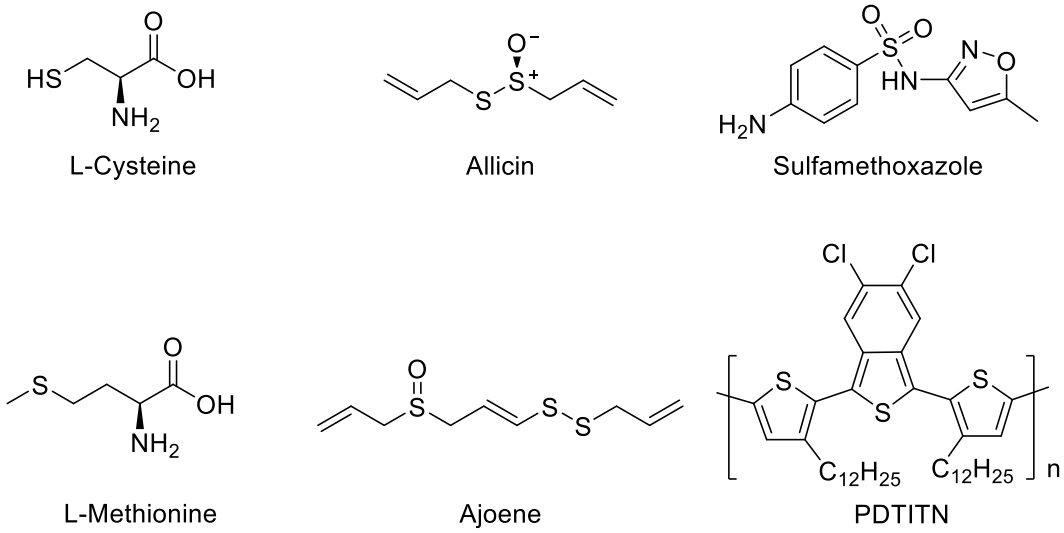


Figure 1 Organosulfur compounds

Sulfur and oxygen belong to the same oxygen group, so sulfur has many properties similar to oxygen; however, due to sulfur's larger orbital size, sulfur is more polarizable and it has more available valence states than oxygen. Organosulfur compounds can be classified by the oxidation state of the sulfur atom of the sulfur-containing functional groups, from the low valence state to high valence state, such as thiol, sulfide, sulfoxide, sulfone and so on **(Figure 2)**. Most of these organic sulfur compounds involve at least one C-S bond; therefore, synthetic methods to form C-S bonds are very important for the preparation of the organosulfur substrates.

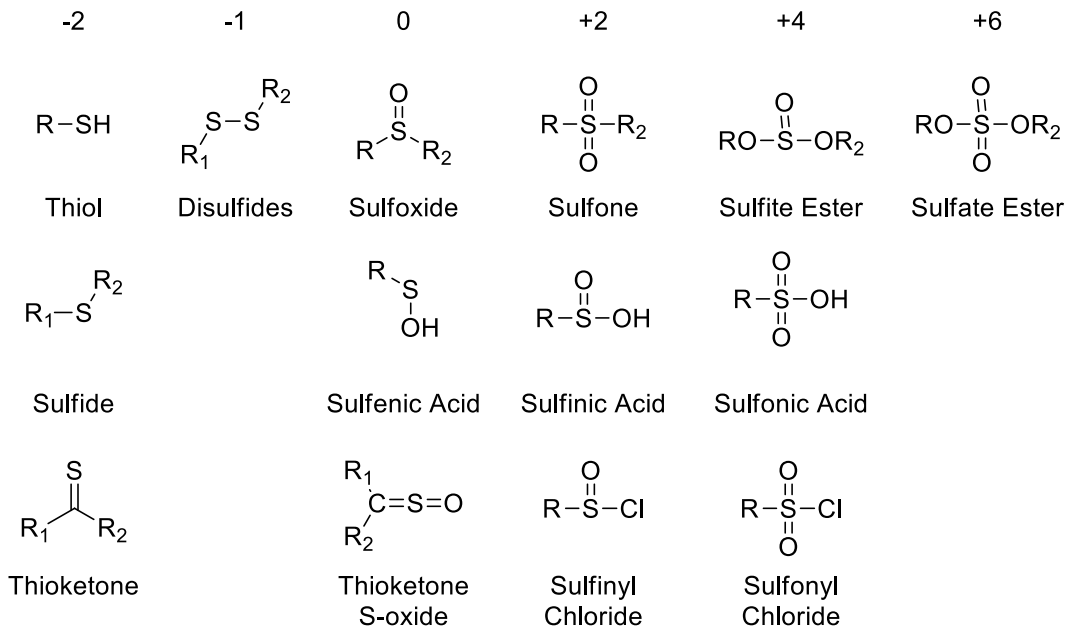


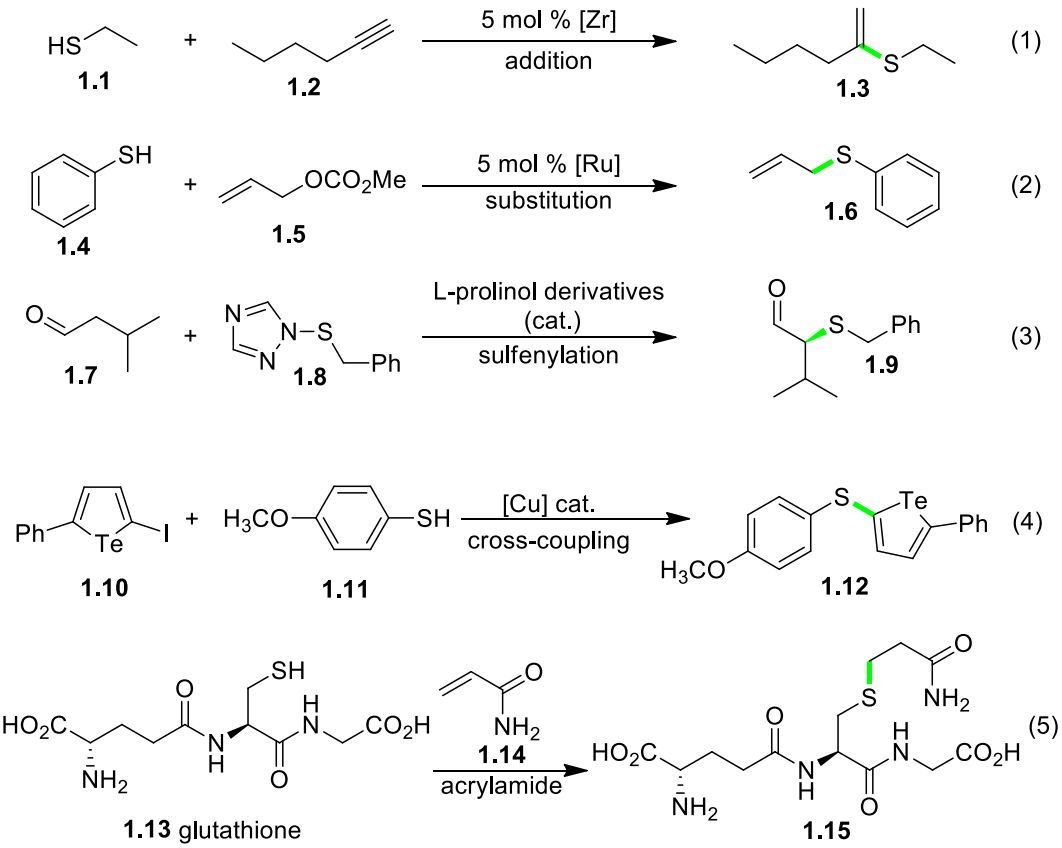
Figure 2 General structures of major sulfur-containing functional groups

1.1.2 Formation of C-S bonds

The generation of a carbon-sulfur bond can be achieved in multiple ways, including addition reaction, substitution reaction, and cross-coupling reaction, as well as biological strategies (**Scheme 1**).[7] Generally, the addition reactions involve a nucleophilic sulfur reagent and an electrophile with carbon-carbon double bonds, triple bonds or epoxides. Weiss and Marks reported an organozirconium-catalyzed hydrothiolation of terminal alkynes, which follows the Markovnikov selective rule to offer vinyl sulfides with a new C-S bond generated between the thiol **1.1** and the terminal alkyne **1.2** (**Scheme 1**, eq 1).[8]

Another strategy for the synthesis of C-S bonds is the substitution reaction, which involves either nucleophilic or electrophilic sulfur sources.[9] Mitsodo and colleagues firstly investigated the ruthenium-catalyzed allylation of thiols to construct allylic sulfides **1.6** in 1999.[10] In the presence of ruthenium-catalyst, thiol acts as a nucleophile, reacting

with allyl methyl carbonate **1.5** to provide the desired product **1.6** with high yield via allylic substitution (**Scheme 1**, eq 2).



Scheme 1 Examples of synthetic strategies for the generation of C-S bonds

An electrophilic sulfur reagent with a good leaving group attached to the sulfur atom reacting with a nucleophile to give the corresponding sulfide is called sulfenylation. Marigo and co-workers devised an organocatalytic enantioselective α-sulfenylation of aldehydes **1.7**. In the presence of catalytic L-prolinol derivatives, this reaction offered α-sulfenylated aldehydes **1.9** in excellent yields and high enantioselectivities (**Scheme 1**, eq 3).[11]

Metal-catalyzed cross-coupling reaction is a significant synthetic strategy that can

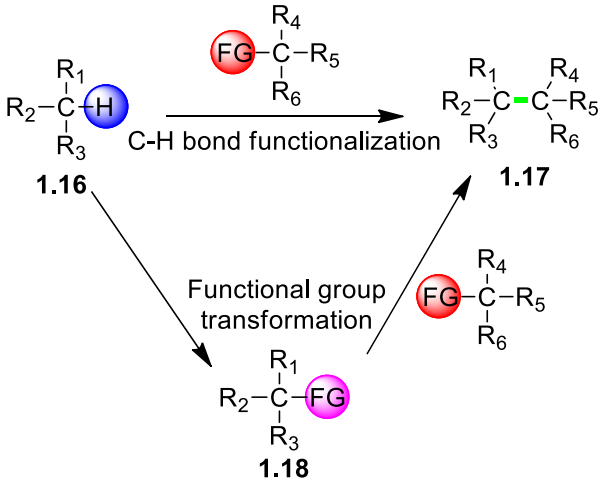
also be applied in forming C-S bonds. For example, Zeni presented a copper-catalyzed thiol cross-coupling reaction (**Scheme 1**, eq 4),[12] in which 2-iodo-5-phenyltellurophene **1.10** reacted with 4-methoxybenzenethiol **1.11** effectively in the presence of copper catalyst without any ligand or co-catalyst to give (2-sulfides)-chalcogenophenes **1.12** in excellent yield.

In biological processes, the formation of C-S bonds is also important. For example, acrylamide (**1.14**) is a carcinogen that forms in intensely heated food, for example in frying.[13] The metabolism of acrylamide occurs via sulfa-Michael addition from glutathione (**1.13**) to form a C-S bond in adduct **1.15**. (**Scheme 1**, eq 5).[14]

1.2 C(sp^2)-H bond functionalization

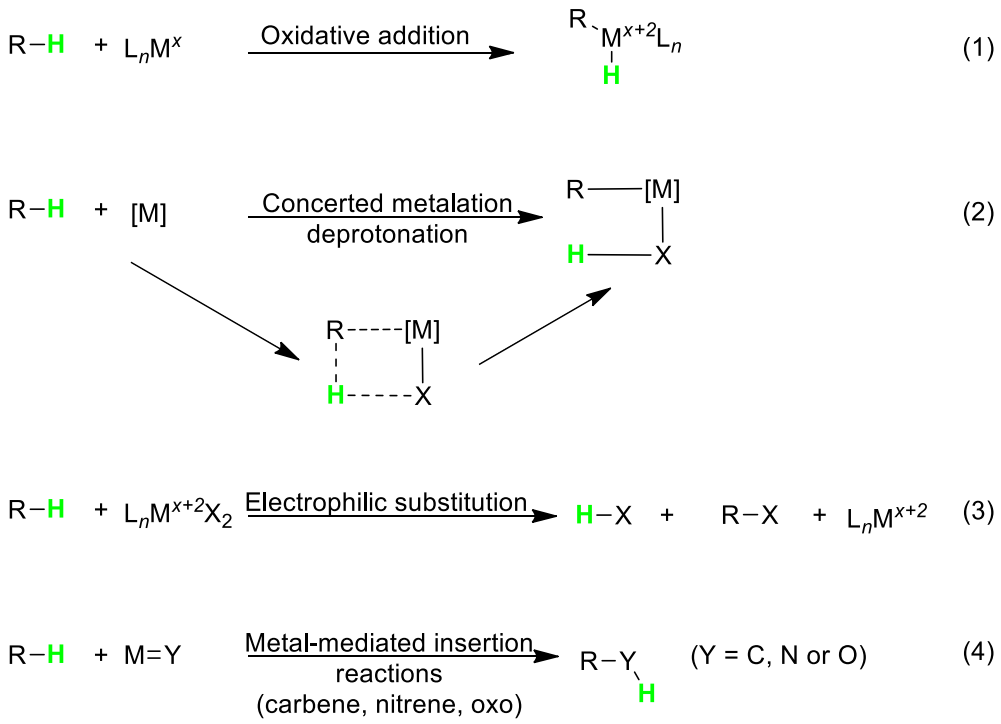
The carbon-hydrogen bond is ubiquitous in organic compounds. Traditionally the C-H bond has been considered as an unreactive bond, the cleavage of which often requires forcing reaction conditions such as high temperature or high pressure. Therefore, the investigation of C-H bond functionalization has received much attention recently.[15] The transformation of C-H bonds to carbon-carbon or carbon-heteroatom bonds (such as C-S, C-O, C-N or C-X bond) provides a significant strategy for organic synthesis. The activation of the C-H bond can provide a concise and streamlined pathway to build carbon-carbon or carbon-heteroatom bonds, which gives access to more effective and atom-economical synthesis. As shown in **Scheme 2**, traditionally the transformation from **1.16** to **1.17** is achieved through the conversion of **1.16** to a compound **1.18**, in which the H atom is replaced with a functional group, such as a halogen or an unsaturated group.

Afterwards, intermediate **1.18** reacts with another compound that is modified with another functional group to provide final structure **1.17**. The traditional approach involves extra but unavoidable reaction steps that may change the structures and properties of the starting material significantly and consequently causes potential complications in many cases, while the direct transformation of the C-H bond offers a much more straightforward way to achieve the new and desired bond formation in a single step.[16]



Scheme 2 Traditional functional group (FG) transformation vs. C-H bond functionalization

The activation of the C-H bond is significant for organic synthesis, and the C-H bond undergoes cleavage through four possible pathways in C-H bond activation, which includes oxidative addition, concerted metalation deprotonation, electrophilic substitution and metal-mediated insertion reaction (**Scheme 3**).[17]

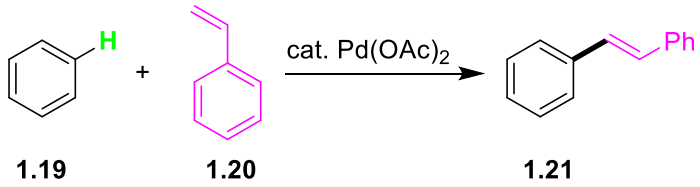


Scheme 3 Classification of C-H bond functionalization

Oxidative addition reactions involve electron-rich complexes with low-valent transition-metals such as Fe, Ru, Rh, Pt and so on, in which reaction the C-H bond is broken by the species L_nM^x generated *in situ* (**Scheme 3**, eq 1). Concerted metalation deprotonation involves the formation of carbon-metal bond along with the cleavage of C-H bond (**Scheme 3**, eq 2). Transition-metal complexes in high valent are applied in electrophilic attack, which is followed by deprotonation to achieve the functionalization of the C-H bond (**Scheme 3**, eq 3). The fourth approach is metal-mediated insertion that involves carbene, nitrene or oxo insertion products to build new C-C (including $C(sp^3)$-$C(sp^3)$, $C(sp^2)$-$C(sp^2)$ and $C(sp^2)$-$C(sp^3)$ bonds), C-N or C-O bonds respectively (**Scheme 3**, eq 4).

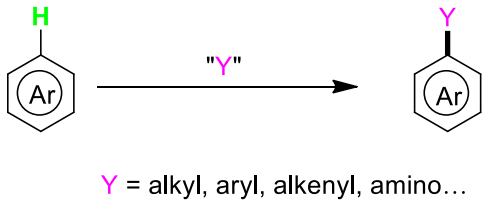
Compared with the relatively unreactive $C(sp^3)$-H bond, it is easier to activate the

C(sp^2)-H bond, and there are many more reports about the functionalization of C(sp^2)-H bonds than that of C(sp^3)-bonds. For example, an early report about Pd-catalyzed C(sp^2)–H activation on the benzene ring was developed by Fujiwara in 1967 (**Scheme 4**).[18] Afterwards, more related works were reported. There are several ways to build new bonds between the C(sp^2) and carbon or heteroatoms.



Scheme 4 Pd(II)/Pd(0) catalyzed olefination of benzene ring

Specifically, aromatic substrates containing C(sp^2)-H bonds can be treated by alkylation, olefination, arylation, amination, borylation and so on to construct new C-carbon or C-heteroatom bonds (**Scheme 5**). In the following section, C(sp^2)-H activation and functionalization will be discussed in these different aspects.

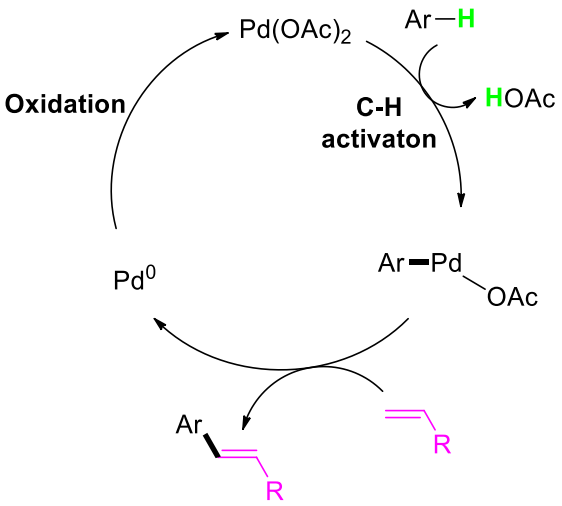


Scheme 5 C(sp^2)-H activation and functionalization

1.2.1.1 Olefination of C(sp^2)-H bonds

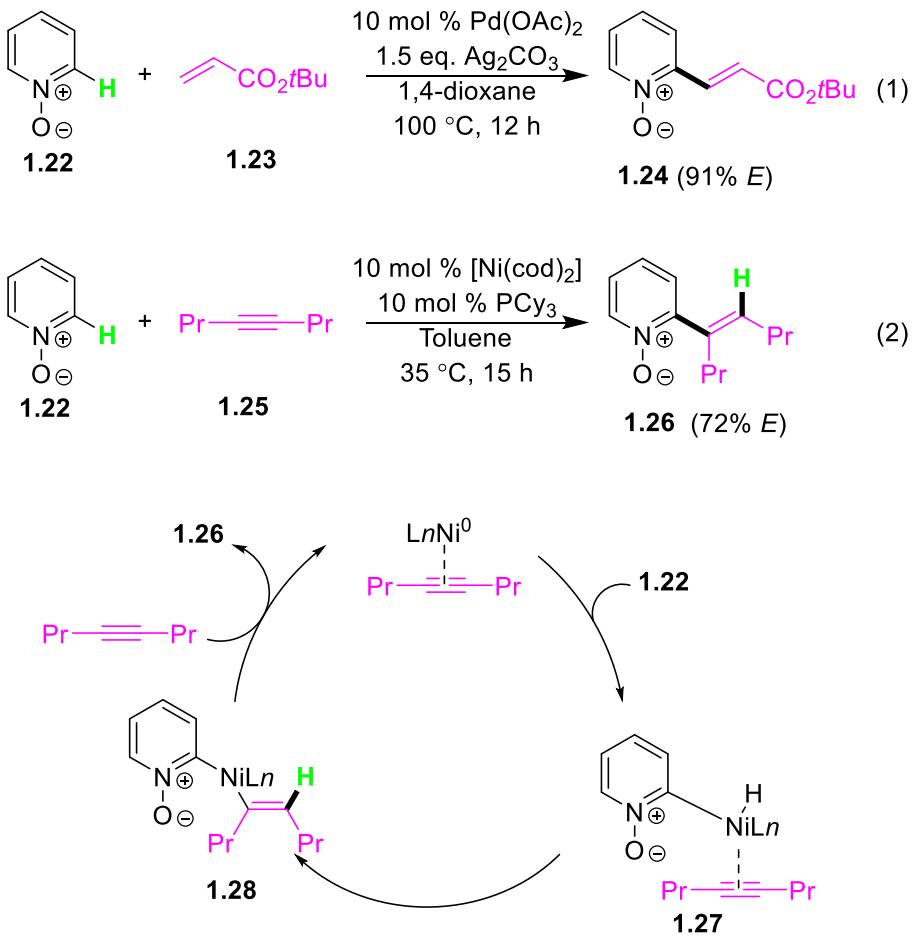
An early report about the olefination of C(sp^2)-H bonds was mentioned earlier,

which was also reported by Fujiwara in 1967.[18] The possible mechanism started from C-H bond activation, with subsequent steps perhaps following the Heck-type mechanism to give the *E*-product (**Scheme 6**).



Scheme 6 Possible mechanism of olefination of C(sp^2)-H bond activation

Interestingly, an important olefination of pyridine *N*-oxides was reported by Chang and colleagues (**Scheme 7**).[19] This reaction involves a highly regioselective C-H bond activation at the *ortho* position, and no di-alkenylation product was observed. Furthermore the main product **1.24** is the *E*-olefin with a yield of up to 91%, so this reaction is stereoselective (**Scheme 7,** eq 1). Therefore, this strategy can be applied in synthesizing highly regioselective and stereoselective pyridine derivatives.

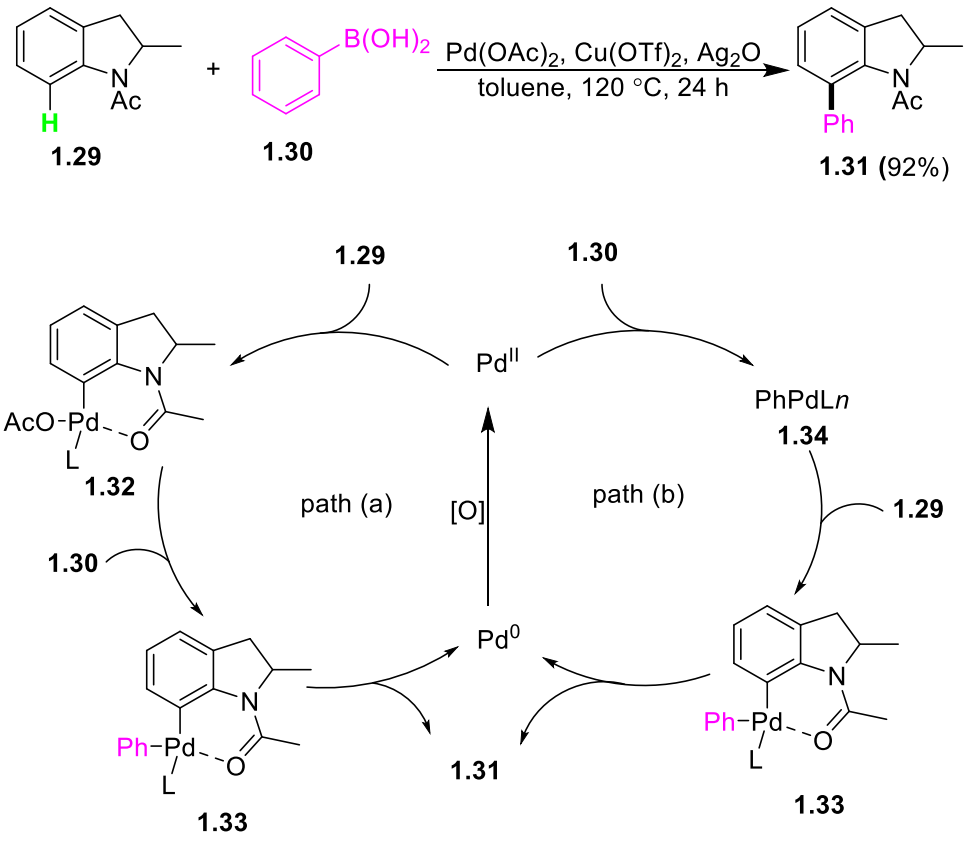


Scheme 7 Alkenylation of pyridine *N*-oxides

Hiyama and co-workers described a similar reaction, which is the nickel-catalyzed alkenylation of pyridine *N*-oxides through addition with alkynes (**Scheme 7,** eq 2).[20] It is also a highly stereoselective alkenylation with 72% *E*-product **1.26**. A possible mechanism for this alkenylation reaction is given in **Scheme 7**. Firstly, the alkyne coordinates catalytic Ni(0), which is followed by C(sp^2)-H activation to give the intermediate **1.27**. Along with the *syn*-addition, it provides another intermediate **1.28** with a new C-H bond formation. The last step involves reductive elimination and regeneration of the Ni(0) species. The mechanism for the second reaction is distinct from the first one, which perhaps follows the mechanism shown in **Scheme 6**.

1.2.1.2 Arylation of C(sp^2)-H bonds

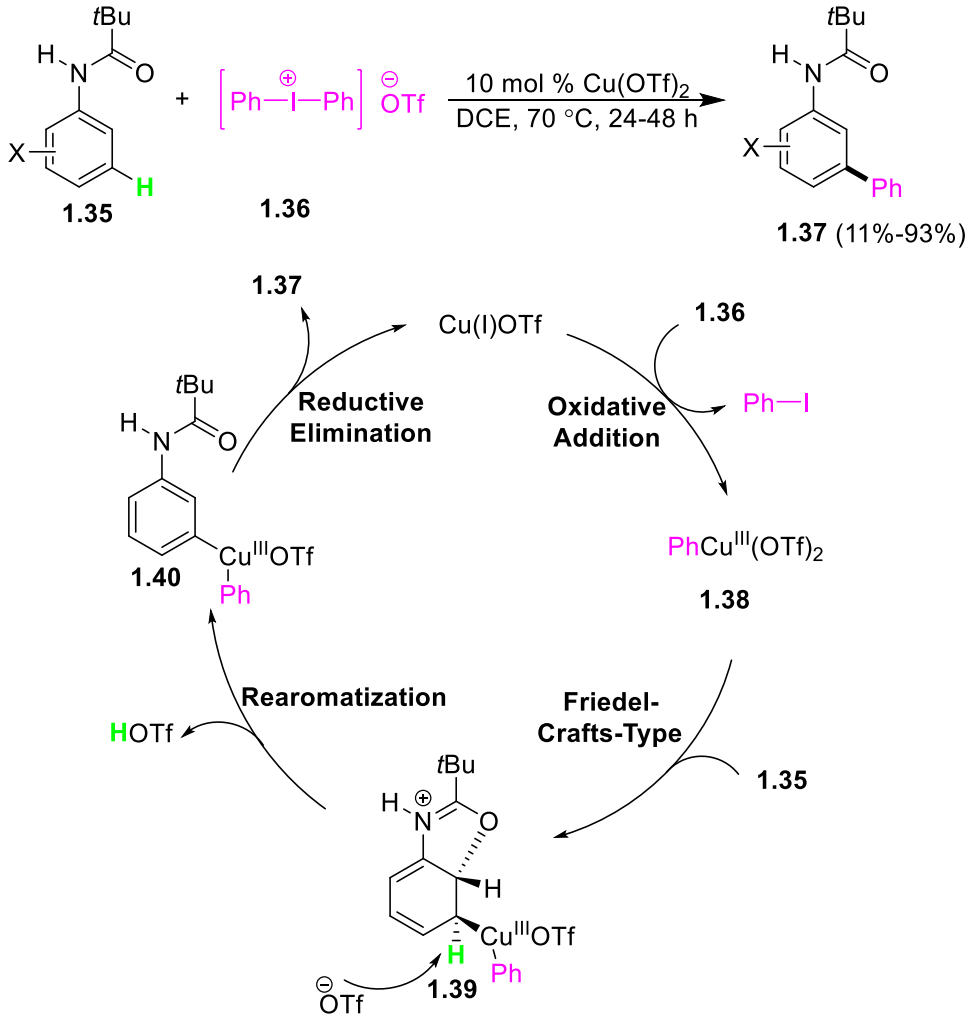
There are abundant reports about the direct arylation of C(sp^2)-H bonds.[21] Most of them involve metal-catalysts such as Pd, Ru or Cu. For instance, Shi and co-workers developed a direct arylation of C(sp^2)-H bonds in combination with a Suzuki-Miyaura coupling.[22] This reaction avoided the presence of halogen, and the boronic acid reacted with C(sp^2)-H bonds directly. They utilized the amide group as a directing group to help the C-H functionalization. Shi and colleagues proposed two plausible mechanisms (**Scheme 8**). Path (a) is initiated by electrophilic aromatic substitution to activated C-H bond, which is followed by transmetalation to give the important intermediate **1.33**. Path (b) is initiated by transmetalation, which is followed by C-H bond activation to provide **1.33**. Both of these proposed mechanisms proceed by reductive elimination to produce the final product.



Scheme 8 Suzuki–Miyaura Coupling Reaction involved in aromatic C-H bond activation

Most Pd-catalyzed arylation with directing groups would provide *ortho*-position C(sp^2)-H activated products.[23] Gaunt and Phipps in 2009 published a paper that discussed a *meta*-position selective C(sp^2)-H arylation in the presence of copper catalyst (**Scheme 9**).[24] They studied differently substituted benzene rings, and the yields of **1.37** ranged from 11% to 93%. They also investigated and proposed a plausible mechanism (**Scheme 9**) that started from the reduction of $Cu(OTf)_2$ to Cu(I)OTf by amide[31] then was followed by the oxidation of diaryl-iodine(III) compound **1.36** to generate Cu(III) species **1.38** that was demonstrated to be highly electrophilic due to a +3 charge and a d^8 configuration. Then it provided a new bond between *meta*-C(sp^2) and Cu(III) in the intermediate **1.40** via a Friedel-Crafts-type reaction and aromatization. The final product

1.37 was generated through reductive elimination, and at the same time the Cu(I) species was regenerated. This protocol prompted others to investigate C-H bond activation by utilizing copper reagent to get regioselective product, which is more economical than Pd or Ru catalysts.



Scheme 9 *meta*-position selective C(sp^2)-H arylation in the presence of copper catalyst

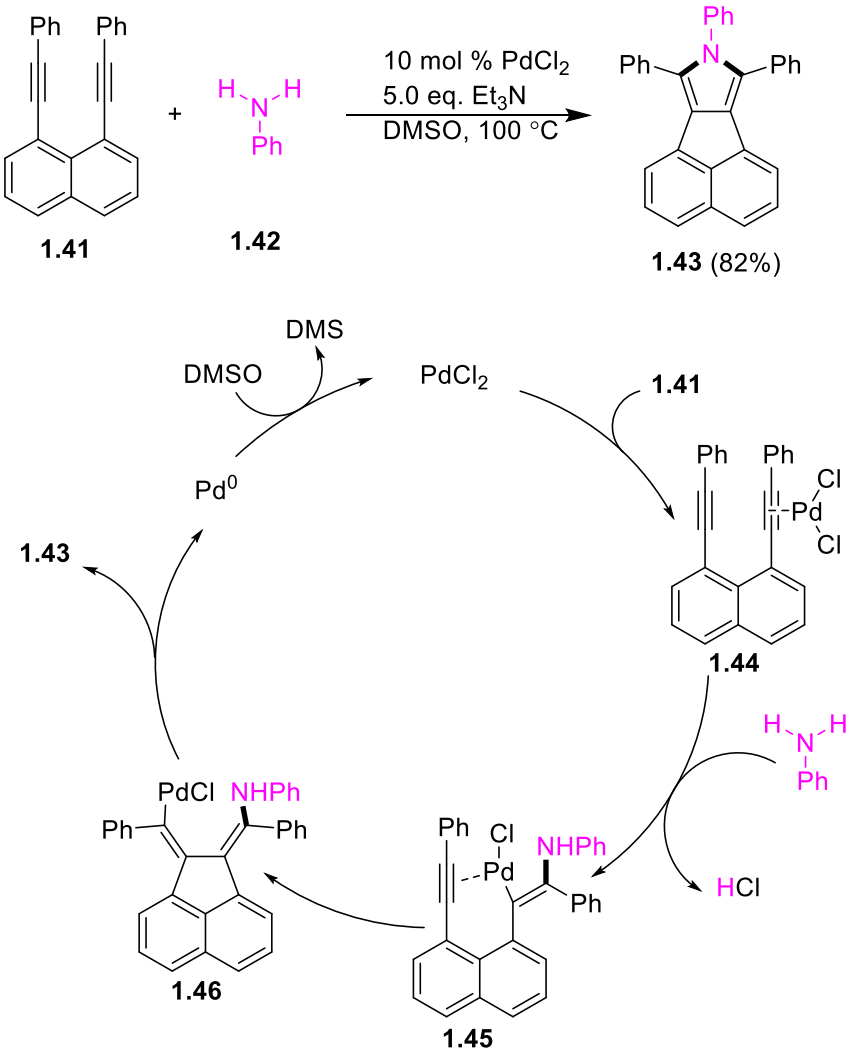
1.3 Cyclization reaction of alkynes

The cyclization reaction is one of the most important strategies for the construction of organic ring-structures. One of the most popular cyclization reactions for diynes is the

Diels-Alder reaction, which is a [4+2] cycloaddition.[25] Most recent examples related on alkyne cycloaddition were catalyzed by transition metal such as Pd, Ru, Ag, Au, Cu and so on. The following section will discuss the intermolecular and intramolecular cyclization of alkynes in detail.

1.3.1 Intermolecular cyclization of diynes

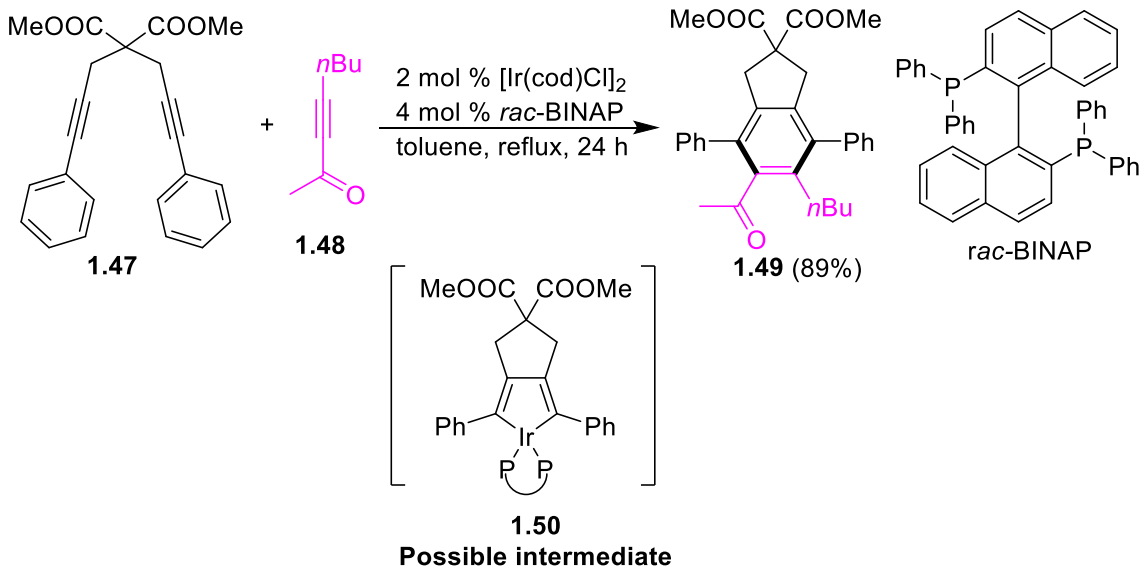
Pyrrole and its derivatives are very important compounds, as they are frequently used in producing some medicines.[26] Chen and co-workers investigated a Pd-catalyzed cyclization from diyne 1,8-diphenylacetylenyl naphthalene **1.41** and amine **1.42** to prepare pyrrole derivatives.[27] In the presence of Pd-catalysts, they screened solvent systems, temperature, bases, as well as different diynes and amines. Under their optimal conditions, they examined a possible mechanism with the $PdCl_2$ catalyst (**Scheme 10**). It started from the coordination between catalyst and one of the triple bonds, which made the electron transfer from the alkyne to the metal catalyst. Then the electron-deficient triple bond was attacked by the amine as a nucleophile to provide a new bond between N and one of the carbons from the activated triple bond, and at the same time one mole of HCl was generated, which was consumed by the base Et_3N. The *syn* addition of the other triple bond was proposed to occur in the following step and to gave a new C-C bond between the two former triple bond carbon atoms. After that, the coupling step formed the C-N bond that provided the final heterocyclic compound. The $PdCl_2$ could be regenerated by oxidation by DMSO from Pd(0) (**Scheme 10**).



Scheme 10 Intermolecular cyclization of 1, 8-diphenylacetylenyl naphthalene

The formation of a benzene ring can be achieved by a [2+2+2] cycloaddition. Hashimoto et al. proposed iridium-catalyzed [2+2+2] cycloaddition of diynes and alkynyl ketones or alkynyl esters.[28] Distinct from the previous example (**Scheme 10**), this reaction involves the reaction between diynes and another C-C triple bond to give a substituted benzene ring (**Scheme 11**). Based on the mechanistic study, a plausible intermediate **1.50** iridacyclopentadiene, shown in **Scheme 11**, was proposed. This protocol provides a convenient and atom-economical manner to synthesize substituted

benzene moieties, and it acts as an alternative method to the Friedel-Crafts type reaction. Besides this example of [2+2+2] cycloaddition, there is another similar reaction that replaces monoyne to alkene under Ru-catalyst.[29]

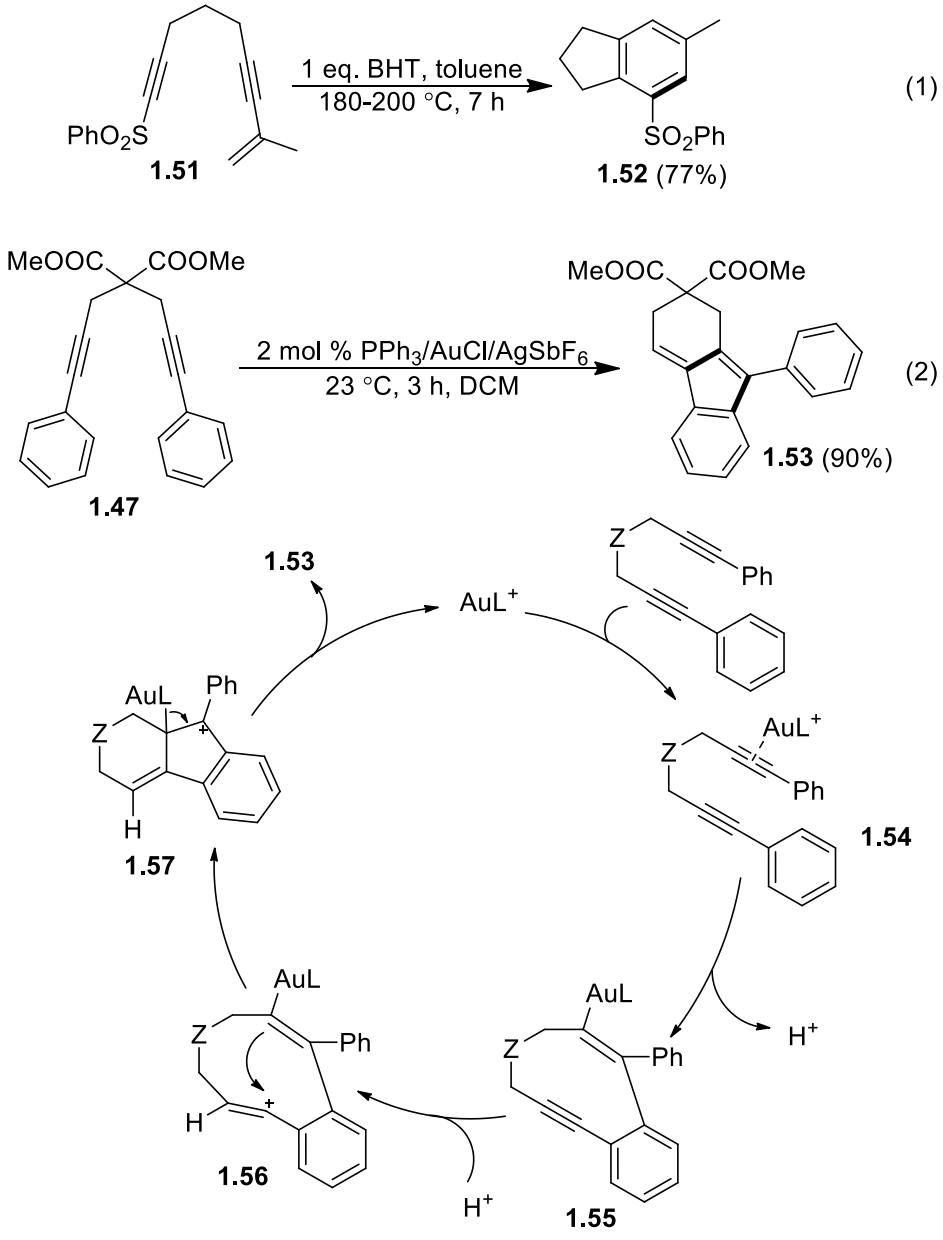


Scheme 11 Iridium-catalyzed [2+2+2] cycloaddition

1.3.2 Intramolecular cyclization of diynes

There is an early report about intramolecular [4+2] cycloaddition reactions under metal-free thermal conditions (**Scheme 12**, eq 1),[30] while most of the later works were utilizing metal catalysts that could lower the reaction temperatures. For example, Lian et al. described a gold-catalyzed intramolecular [3+2] cycloaddition;[31] under metal-catalyzed conditions, it occurred at ambient (23℃) temperature. The related mechanism was investigated by isotope labeling, and it was demonstrated that the reaction was initiated by coordination between the Au-catalyst and one of the triple bonds, which undergoes a nucleophilic attack by the other benzene ring, which afforded an

intermediate **1.55** along with the loss of a proton, which can be also considered a C-H bond activation. The following protonation at the other C-C triple bond gives complex **1.56** that underwent a ring-closing process to generate the intermediate **1.57**. Ultimately, the major product was formed (**Scheme 12**, eq 2). Later, Nieto-Oberhuber and colleagues also reported gold-catalyzed intramolecular [4+2] cycloadditions of arylalkynes. They performed molecular modeling to further explain the mechanism.[32]



Scheme 12 Intramolecular cyclization via thermal and catalytic conditions

1.4 Cascade reactions

Cascade reactions, which are also referred to as tendem reactions or domino reactions,[33] are defined as reactions in which several intermediates are generated in one sequence (**Figure 3**). Cascade reactions are very useful for organic synthesis, because they simplify the synthetic process. There is no need to isolate the intermediates, change reaction conditions, or add reagents during the reaction. One-pot reactions are similar to cascade reactions, but there is a key difference from the cascade reaction: a one-pot reaction might involve changing reaction conditions or adding new reagents into the reactor; thus, a cascade reaction can also be considered a one-pot reaction, but not vice versa. Nicolaou and co-workers classified the cascade reactions depending on the different mechanisms involved, such as nucleophilic cascades, electrophilic cascades, radical cascades, pericyclic cascades and transition-metal-catalyzed cascades.[34]

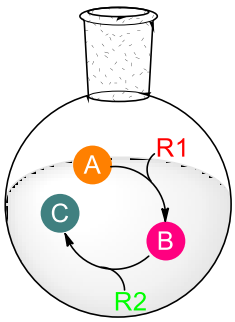
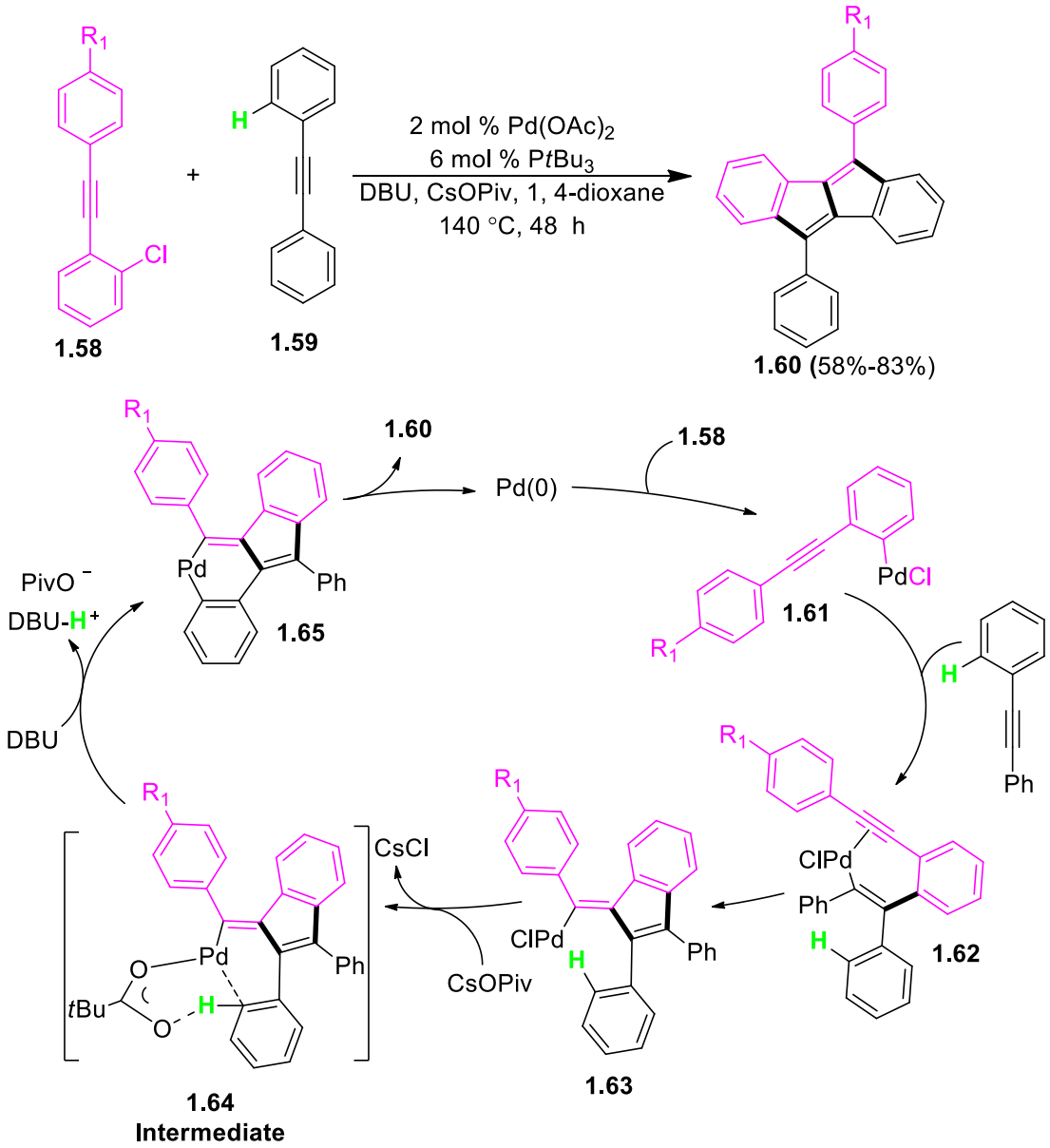


Figure 3 Cascade reaction

Cascade reactions are gaining popularity in organic synthesis. Parsons and co-workers published a review on tandem reactions in organic synthesis in 1996,[35] and after that, more related works were published; for example, Nicolaou and co-workers

investigated tandem reactions in total synthesis,[34][36] and in 2007 Padwa and Bur developed the formation of heterocycles via tandem reactions.[37] In consideration of the convenience of tandem reactions, this thesis project would exert this approach to synthesizing our target structures.

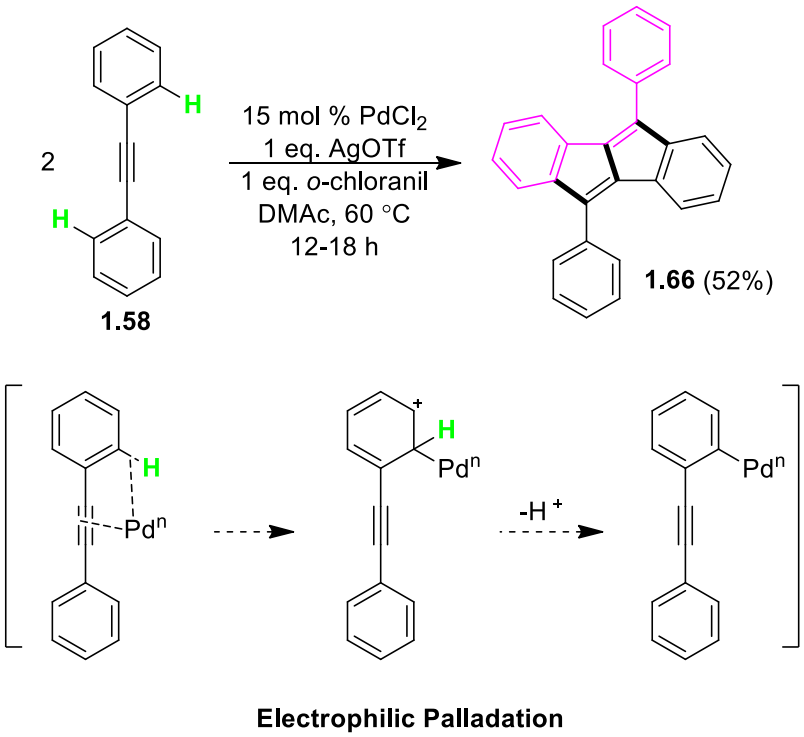
For example, Zhao and co-workers performed a novel Pd-catalyzed cascade annulation of *o*-alkynylarylhalides and diarylacetylenes, since it combined a cyclization and a C-H bond activation.[38] As seen in **Scheme 13**, they optimized the reaction conditions, such as ligands, bases, and so on. The R_1 groups were also scoped by this lab, and it was found that electron-donating groups are more reactive, while the electron-withdrawing groups need longer reaction times and greater quantities of catalyst. Zhao also carried out the mechanistic study to give a plausible mechanism (**Scheme 13**). The first step is oxidative addition, as is very common for metal-catalyzed cycles, which is followed by carbopalladation to provide intermediates **1.62** and **1.63** in turn. In the next step, the base CsOPiv helped the activation of the C-H bond to afford intermediate **1.64**. The presence of DBU as base completed the deprotonation. After that, a six-membered palladacycle **1.65** was generated, which underwent the reductive elimination to produce the final dibenzo[*a*,*e*]pentalenes **1.60**. Dibenzo[*a*,*e*]pentalene moieties could have potential electronic properties, and this method provides an efficient approach to these conjugated structures.



Scheme 13 Intermolecular annulation of *o*-alkynylarylhalides and diarylacetylenes via C(sp^2)-H bond activation

Maekawa and colleagues reported work that was also related to the cascade annulation of dibenzo[a,e]pentalenes **1.66**.[39] Relative to the previous example with only one C-H bond activation (**Scheme 13**), this reaction involved two C-H bonds activations. The mechanism for this reaction is distinct from the previous one in the first step, which

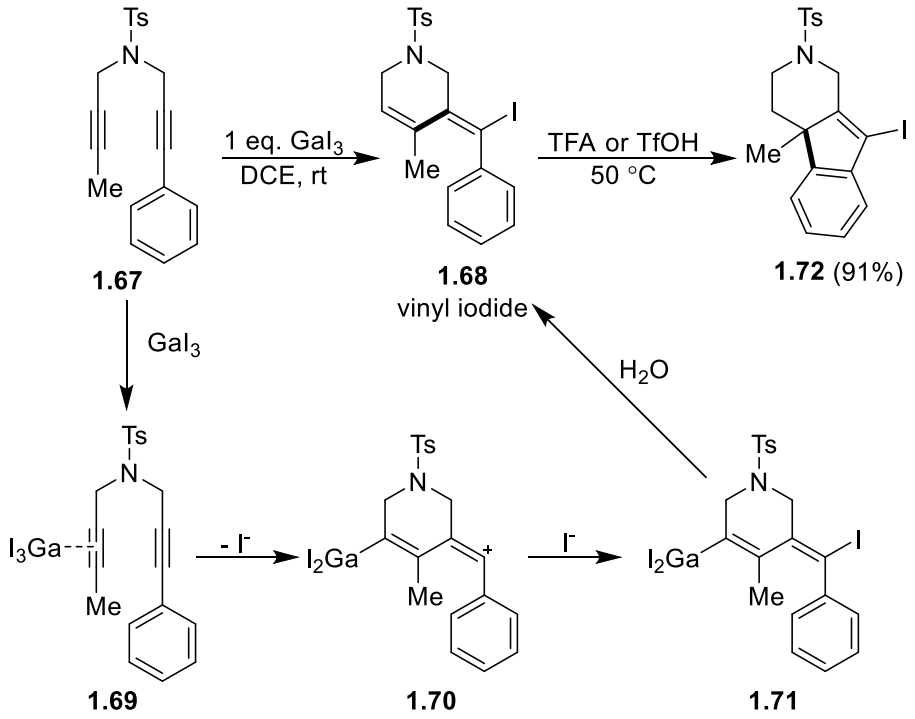
started from aromatic C-H electrophilic palladation (**Scheme 14**). The following mechanistic step was essentially the same as the previous reaction.



Scheme 14 C–H/C-H annulation to dibenzo[*a*,*e*]pentalenes

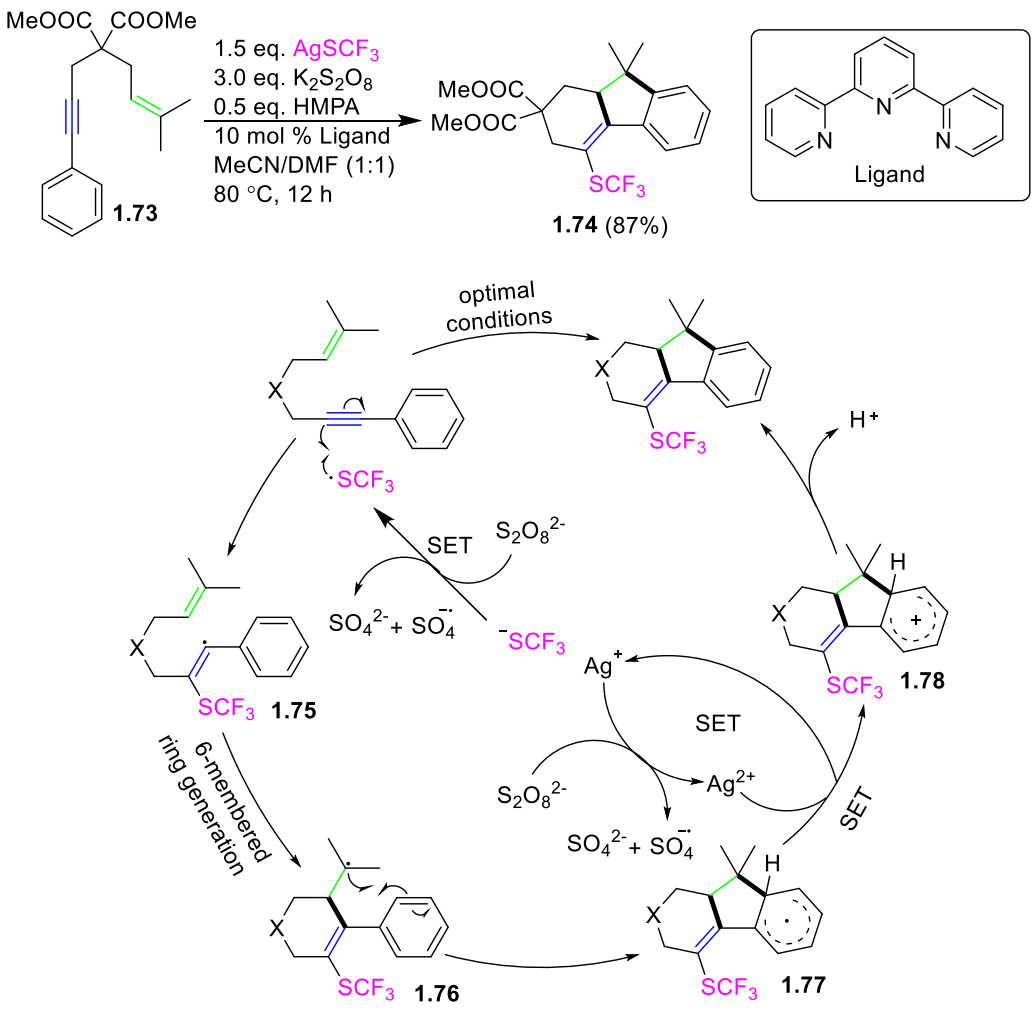
Strom and co-workers developed tandem Ga(III)-associated cyclization of 1,6-diynes, and the structure of the final product is similar to that from Lian's work (**Scheme 12**, eq 2), but the proposed mechanism is totally different.[40] This reaction is a two-step and cascade reaction as shown in **Scheme 15**. The first step is an iodocyclization and the second one is an intramolecular Friedel−Crafts reaction. Strom et al. conducted a mechanistic study of the formation of vinyl iodide **1.72**, in which the first step is the activation of one C-C triple bond, and then the intramolecular cyclization provided a vinyl carbenium complex **1.70** and a positive charge on one C-C double bond. Vinyl

carbenium ion was trapped by iodide, which was followed by aqueous workup to give the vinyl iodide. In this reaction, the metal reagent is used in stoichiometric amount instead of catalytic amount, so it suffers from a high cost of catalyst. Even so, this protocol provides a feasible approach to fused rings.



Scheme 15 Cascade Ga(III)-associated cyclization

Another interesting metal-mediated cascade cyclization is reported by Liang's group, which was demonstrated to follow a radical mechanism.[41] This reaction is a multi-task strategy; it not only afford two new cycles with two C-C bonds generated, but a new C-S bond on the alkene (**Scheme 16**).



Scheme 16 Ag-mediated cascade radical cyclization

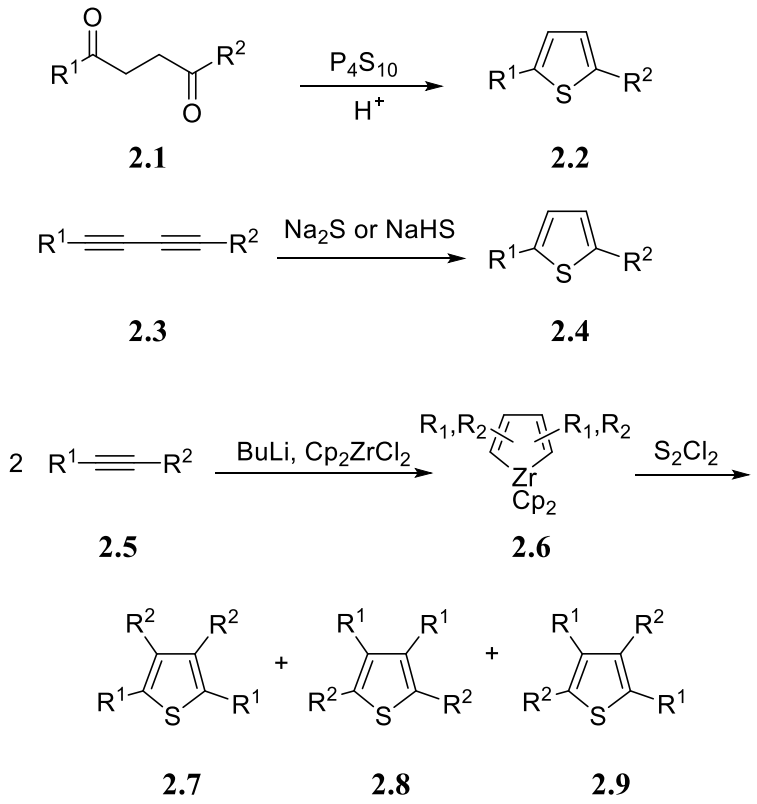
The Liang group optimized reaction conditions and they also scoped different substitutions on the benzene ring, and there was no significant difference between electron-donating groups and electron-withdrawing groups, which suggests the electron density of the benzene ring does not affect the reaction much. In order to obtain more information about the mechanism, the Liang lab conducted radical trapping experiments as well as a kinetic isotope effect study (**Scheme 16**). Firstly, $AgSCF_3$ was oxidized by $K_2S_2O_8$ to form the SCF_3• radical, which initiated the reaction with the construction of a new C-S bond (**1.75**). Subsequently, a six-membered ring intermediate **1.76** was

generated, which was followed by the formation of aryl radical structure **1.77**. The oxidant $K_2S_2O_8$ converts Ag(I) to Ag(II), and then Ag(II) completes the transition of **1.78** from radical **1.77**, at the same time as Ag(I) was regenerated. That process also activates the aromatic C-H bond. By losing a proton, the target structure is formed. It can be seen from the mechanistic cycle that the whole process did not involve coordination between the metal reagents and substrates, which is very different from the previous examples (such as **Scheme13** and **14**). This strategy provides some inspiration to this thesis project, which will be discussed in depth in Chapter 2.

Chapter 2 Copper-mediated C-S Bond Formation and C-H Functionalization via Cascade Cyclization

2.1 Research proposal

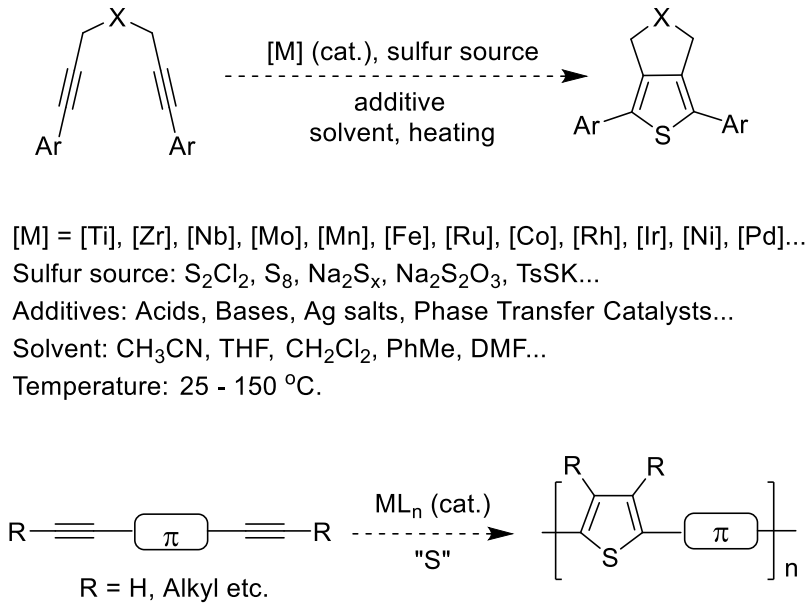
At the beginning of this thesis project, the Schipper lab sought methods to synthesize small molecules of thiophene, since thiophene and its corresponding polymers are an important class of organic electronic materials, which have enabled significant breakthroughs and important applications in fields such as photovoltaics and field-effect transistors.[42] There are several ways to generate thiophene rings. The first method is the Paal-Knorr synthesis (**Scheme 17**).[43] A 1,4-dicarbonyl compound **2.1** reacts with a sulfur source such as phosphorus pentasulfide to generate a 1,4-disubstituted thiophene **2.2**. Another method is the reaction of a diyne **2.3** with sodium sulfide or sodium hydrosulfide to form the thiophene ring (**Scheme 17**).[44] The two approaches are useful for the formation of 1,4-substituted thiophenes, but they are only intramolecular reactions and there is no new intermolecular C-C bond formation. There is a third reaction that involves two equivalents of alkyne **2.5** with zirconocene dichloride, followed by quenching with disulfur dichloride to form the thiophenes (**2.7**–**2.9**) (**Scheme 17**).[45] This reaction is an intermolecular reaction that involves the formation of a new C-C σ-bond. However, this reaction has some disadvantages. For example, when unsymmetrical alkynes are employed, the transformation suffers from regioselectivity problems.



Scheme 17 Three synthetic approaches to thiophene rings

To solve the current issues in thiophene synthesis, an alternative synthetic method for the formation of thiophenes was proposed by the Schipper group. An extensive screening of conditions, including different transition metal catalysts, sulfur donating reagents, reaction additives, solvents and temperatures, is required (**Scheme 18**). Selection of transition metals is based on their ability to form metallacycles upon reacting with alkynes and to form the necessary C-S bonds upon reaction with a sulfur source. Multiple transition metals are capable of reacting with alkynes to form the corresponding metallacycles.[46] Therefore, a wide range of transition metals need to be screened, especially those catalysts that have been previously utilized successfully in [2+2+2] cycloaddition reactions, such as [Ti], [Zr], [Co] and other metal catalysts. The sulfur

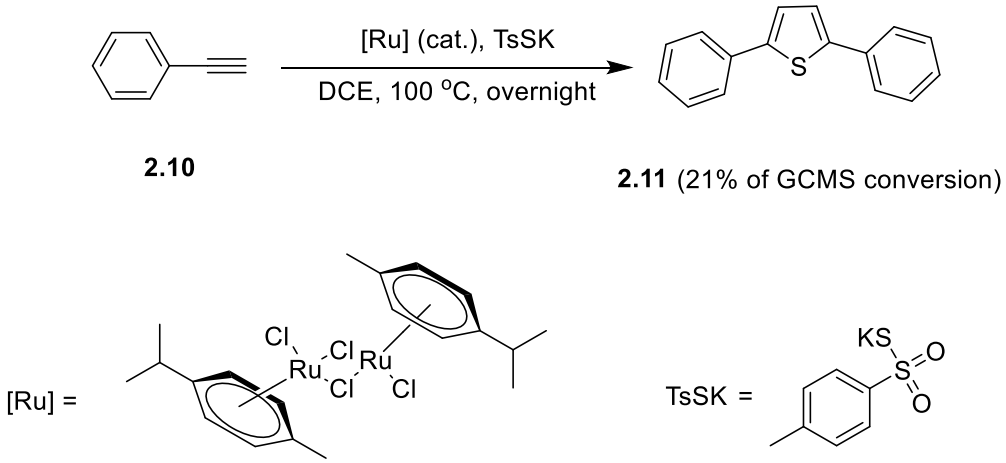
reagents can be any commercially available ones that have been reported to be capable of generating a C-S bond from a C-metal bond. Additionally, various solvents can be tested, including, but not limited to DCM, DMF, THF and DCE. Different temperatures would also be examined. Initial screening will examine both the intermolecular and a more controlled intramolecular reaction to form the thiophene. Once this proposed method could successfully generate thiophene molecules, the route might also be applied to synthesize polythiophenes and other conjugated polymer materials (**Scheme 18**).



Scheme 18 Proposed synthesis of thiophene ring

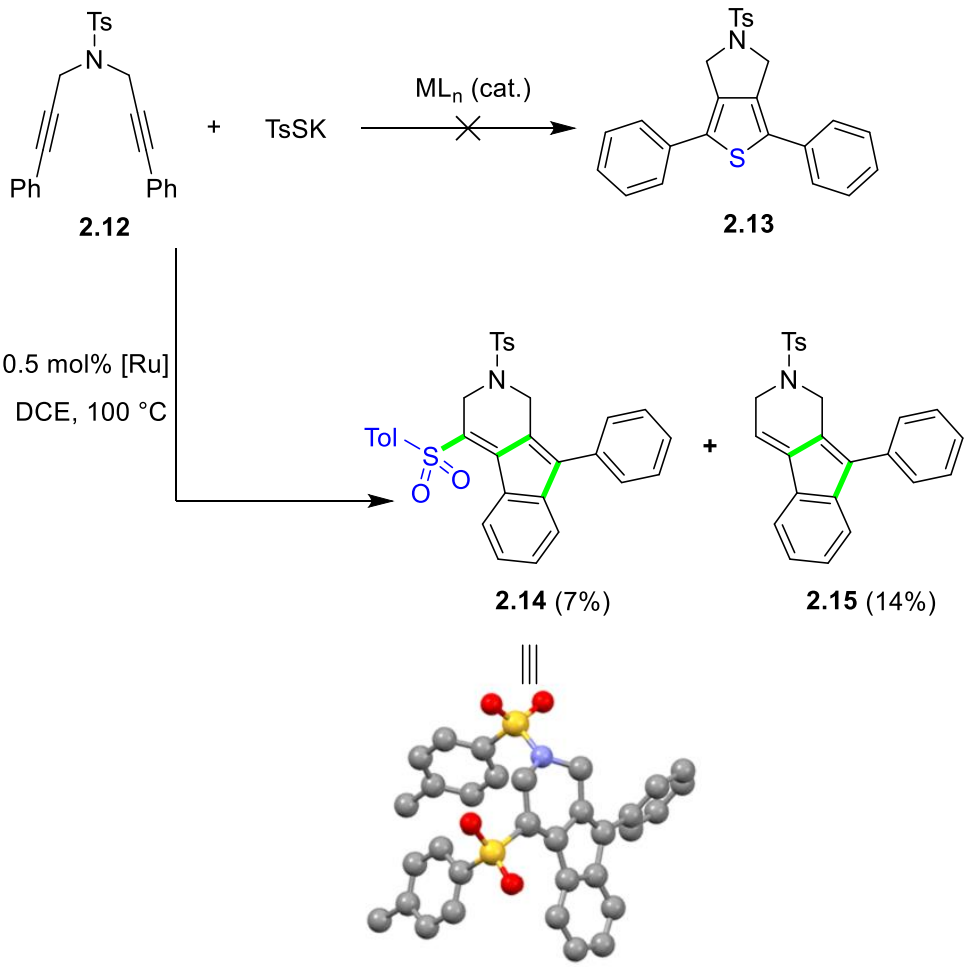
According to the proposal, previous work in the Schipper group (by Christopher Baigent and Sushant Bhasin) studied the intermolecular reaction of phenylacetylene **2.10** to form 2,5-diphenylthiophene **2.11** with sulfur sources to generate thiophene materials. Numerous catalysts, solvents, as well as sulfur sources were screened while all reactions were carried out at 100 ℃ overnight (Scheme **19**). Finally dichloro-(*p*-cymene)

ruthenium(II), *p*-toluenethiosulfonate (TsSK) and DCE gave 21% gas chromatography -mass spectrometry (GCMS) conversion of the starting material, which was better than other conditions. So [Ru], TsSK and DCE were chosen to investigate the following studies.



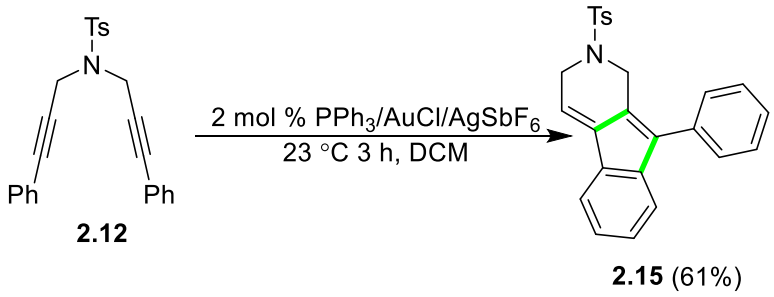
Scheme 19 The generation of thiophene materials by intermolecular reaction

The diyne **2.12** with NTs linker was used to study the intramolecular reaction to generate the thiophene ring. **2.12** acted as the starting material and potassium TsSK as the sulfur source, and in the presence of a transition metal catalyst (such as [Ru], [Rh], [Pd] and so on) this reaction did not offer the target thiophene structure but complex mixtures. Interestingly when the catalyst Ru(II) (dichloro(*p*-cymene)ruthenium(II)) was used in this reaction, two new structures were generated, which were isolated and purified by column chromatography and characterized by NMR and HRMS as well as single crystal X-ray. These two new structures are tricyclic products **2.14** and **2.15** as shown in **Scheme 20**.



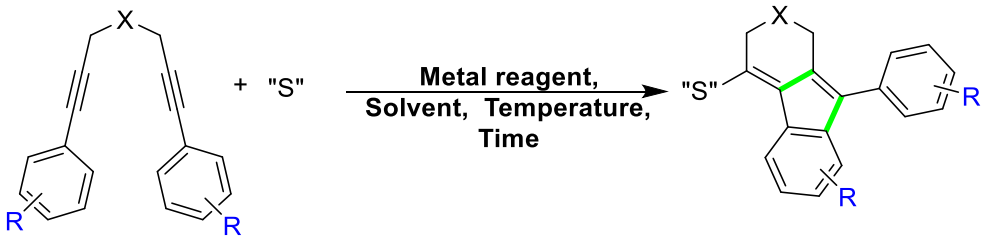
Scheme 20 The original project and the discovery of new structures

Compound **2.15** was previously reported by Lian et al. (**Scheme 21**).[31] A Au-catalyst was used to achieve the construction of compound **2.15** at room temperature and the corresponding mechanism was shown in **Scheme 21**.



Scheme 21 Gold-catalyzed intramolecular cycloaddition of **2.15** by Lian[31]

Compound **2.14** is a completely new compound and its single crystal structure is shown in **Scheme 20**. Because of the formation of a new bond between the C and S and the aromatic C-H bond functionalization, **2.14** has redirected our attention to investigate a novel method to synthesize organosulfur compounds. Based on the new discovery of the new sulfone tricyclic product **2.14**, the Schipper lab proposed a metal-mediated C-S bond formation and C(sp^2)-H bond functionalization via cascade cyclization (**Scheme 22**).



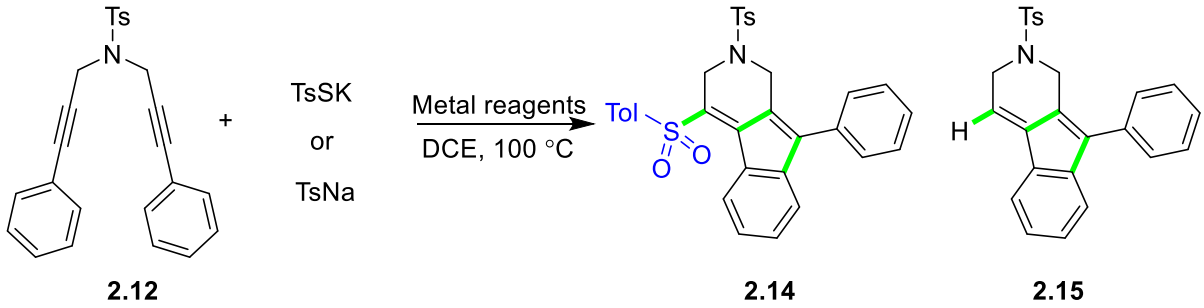
Scheme 22 New project starting from diynes to form tricyclic substrates

2.2 Optimization of reaction conditions

As shown in **Scheme 20**, the catalyst Ru(II) only provides a 7% yield of the desired structure, which is lower than that of product **2.15** (14%). In order to obtain a higher yield of organosulfur product **2.14**, reaction conditions were optimized by using a different

salt—sodium *p*-toluenesulfinate (TsNa) instead of TsSK—and a series of metal reagents, including Cu and Ag reagents (**Table 1**). On one hand, the sulfur atom from TsSK was absent from the final product, and we cannot trace it, so TsNa was tested in the reaction; on the other hand, Ru-catalysts are relatively expensive, so we would like to try some other metal reagents to set up the reaction; moreover, copper and silver reagents are utilized in activating C-H bond reactions as mentioned in Chapter 1.

Table 1 The screening of reaction conditions[a]

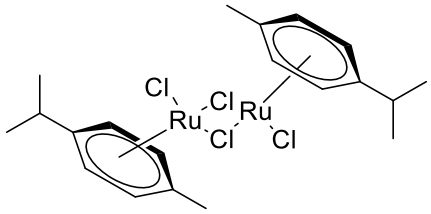


2.12 **2.14** **2.15**

Entry	Salts (2.0 eq.)	Metal reagents (eq.)	Yield of **2.14** (%)[b]	Yield of **2.15** (%)[b]
1	TsSK	[Ru] (0.05)	7[c]	14[c]
2	TsSK	$Cu(OAc)_2 \cdot 2H_2O$ (1.0)	22	0
3	TsNa	[Ru] (0.05)	0	0
4	TsNa	[Ru] (0.05) $Cu(OAc)_2 \cdot 2H_2O$ (1.0)	11	8
5	TsNa	$Cu(OAc)_2 \cdot 2H_2O$ (1.0)	33	0
6	TsNa	$CuSO_4 \cdot 5H_2O$ (1.0)	37	0

7	TsNa	$(CuOTf)_2 \cdot C_6H_5CH_3$ (1.0)	26	0
8	**TsNa**	**$Cu(OTf)_2$ (1.0)**	**42**	**0**
9	TsNa	$Cu(OTf)_2$ (0.2)	12	0
10	TsNa	AgOAc (1.0)	22	10
11	TsNa	$AgSbF_6$ (1.0)	37	12

[a]All of the listed reactions were carried out in DCE at 100 ℃ under argon, the concentration of **2.12** is 0.025mmol/ml, in this table TsNa is hydrous with $2H_2O$. [b]NMR yield; [c]Isolated yield.

[Ru] = 

Entry 1 is the original reaction conditions with the Ru-catalyst, and when 1 eq. of copper acetate replaced the Ru-catalyst, the yield of product **2.14** increased to 22% along with the absence of generation of **2.15**. When 1 eq. of $Cu(OAc)_2$ was added to the conditions of reaction 3 (entry 4), it was found that 11% of **2.14** and 8% of **2.15** were generated, which indicated that copper acetate works well in the presence of TsNa. When copper reagent was used without the presence of Ru-catalyst, that reaction provided 33% of product **2.14** (**Table 1**, entry 5). By comparing the results entries 1, 4 and 5, it is known that Ru-catalyst is beneficial for the formation of compound **2.15**. In entry 3, TsNa was used instead of TsSK to react with **2.12**, but there was no product **2.14** or **2.15** observed, which suggested that only in the presence of TsSK does the Ru-catalyst work for this

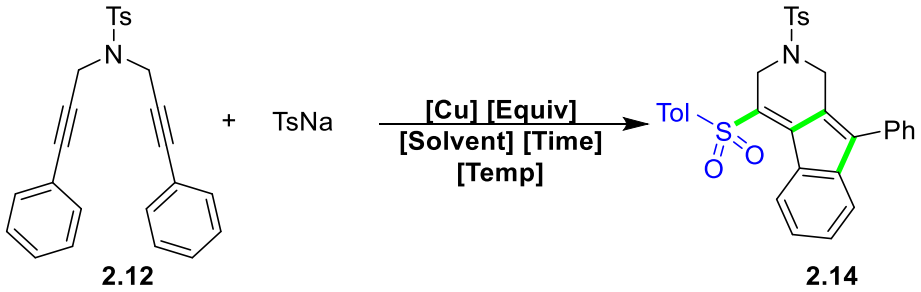
reaction. Based on the utilizing of TsNa, this thesis work sequentially tested several copper reagents such as copper triflate, copper (II) sulfate and copper (I) triflate (**Table 1**, entries 5 to 8). Among the copper reagents examined, 1.0 eq. of $Cu(OTf)_2$ gave 42% yield of desired product **2.14**, whereas using less than1.0 eq. of $Cu(OTf)_2$ led to a much lower yield (entry 9). Moreover, silver salts such as sliver acetate were also applied to screen the reaction conditions, and it was found that copper reagents offered more product **2.15** but less **2.14** (**Table 1**, entries 10 and 11). Upon the testing results, it was found that stoichiometric copper reagents, such as copper (II) triflate or copper acetate, worked better than other metal candidates. Additionally, when replacing TsSK with TsNa, the yield of compound **2.14** was getting higher than that of compound **2.15** (entry 2 vs. 5). Finally, copper reagents and sulfinate salts were chosen for the following optimization.

Based on the preliminary screening of reaction conditions, our group proposed a new project that is to apply aryl diynes with different linkers (such as NTs, malonate, methylene and oxygen linkers) as the starting materials to react with sulfinate salts in the presence of a copper reagent to prepare organosulfur products through cascade reaction. First of all, this thesis work optimized reaction conditions, including solvents, temperature, time, copper reagents and sulfinate salts, and then different linkers and substitutions on the benzene rings were examined as well.

The first part is the optimization of reaction conditions (**Table 2**). The first seven trials show the screening of different solvents, including non-polar and polar solvents at room temperature. In toluene, 1,4-dioxane and THF, there was no desired product **2.14** generated; however, in chloroform, chlorobenzene, DCM and DCE, the organosulfur

compound **2.14** was observed (**Table 2**, entries 1, 2, 6 and 7), among which DCE gave the highest yield (20%). Therefore, in the following optimizing reactions, DCE was used as the chosen solvent. In order to increase the reaction yield of **2.14**, reaction temperature and reaction time were examined. The two other reactions were conducted, one of which was heated and stirred on a hot plate inside a sealed tube at 100 ℃ for five hours and the other was reacted under microwave (MW) conditions inside a sealed tube. As shown in entries 8 and 9, there was no significant difference between the two yields (34% and 37%, respectively). It is indicated that heating by hot plate and MW machine are both acceptable for this reaction. Extending reaction time is another way to improve reaction yields. At 100 ℃, the reaction was conducted for 16 hours instead of 5 hours, and it was found that the yield increased from 37% to 42% (entry 10), which suggested that longer time is beneficial to the reaction; however, when even longer time was tested for this reaction, the yield showed no improvement. In terms of the copper reagents, this thesis work involved trials with copper (II) acetate hydrate, copper (II) sulfate pentahydrate and copper (II) tetrafluoroborate hydrate to set up reactions (**Table 2**, entries 10, 11, 12 and 13), and these experimental results indicated that $Cu(OTf)_2$ is the most efficient reagent among the tested copper catalysts (**Table 2**, entry 10).

Table 2 Optimization of conditions[a]



2.12 **2.14**

Entry	Solvent	Time	Temp.	Cu Reagent (eq.)	Yield of **2.14** (%)[b]
1	chloroform	16 h	r.t.	$Cu(OTf)_2$(1.0)	15
2	chlorobenzene	16 h	r.t.	$Cu(OTf)_2$(1.0)	11
3	toluene	16 h	r.t.	$Cu(OTf)_2$(1.0)	0
4	THF	16 h	r.t.	$Cu(OTf)_2$(1.0)	0
5	1,4-dioxane	16 h	r.t.	$Cu(OTf)_2$(1.0)	0
6	DCM	16 h	r.t.	$Cu(OTf)_2$(1.0)	16
7	DCE	16 h	r.t.	$Cu(OTf)_2$(1.0)	20
8	DCE	5 h	100	$Cu(OTf)_2$(1.0)	34
9	DCE	5 h	MW/100	$Cu(OTf)_2$(1.0)	37
10	DCE	16 h	100	$Cu(OTf)_2$(1.0)	42
11	DCE	16 h	100	$Cu(OAc)_2$ $2H_2O$ (1.0)	33
12	DCE	16 h	100	$CuSO_4$ $5H_2O$ (1.0)	36

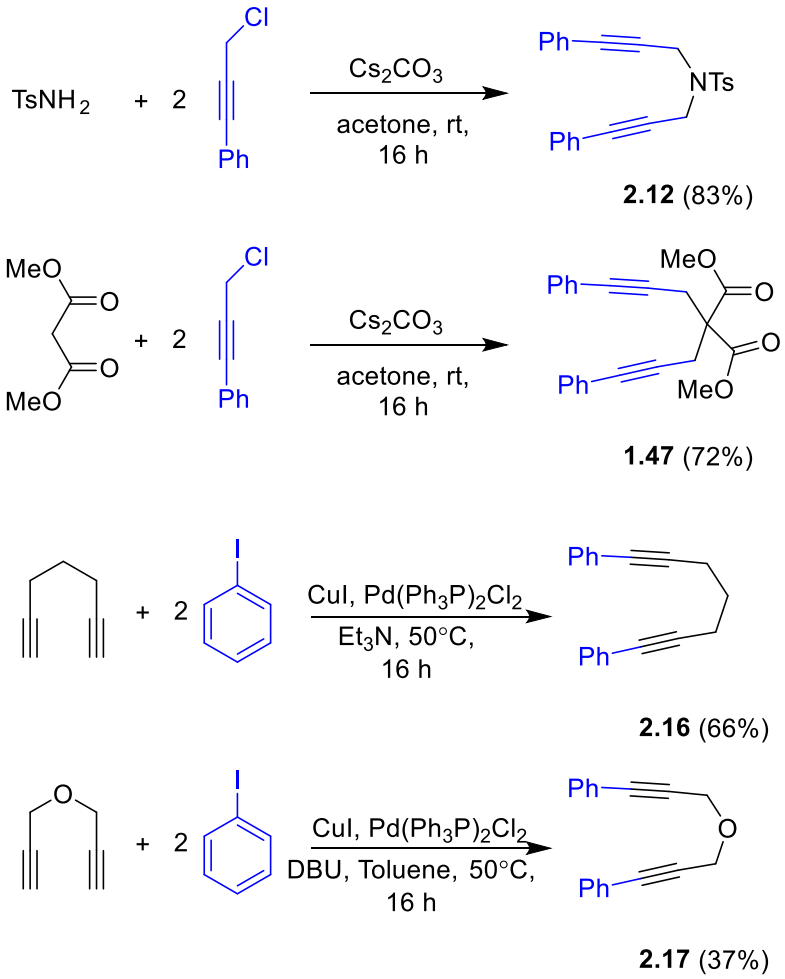
13	DCE	16 h	100	$Cu(BF_4)_2$ $5H_2O$ (1.0)	28
14[c,d]	**DCE**	**16 h**	**100**	**$Cu(OTf)_2$(2.0)**	**83**[d]
15[c,d]	DCE	16 h	80	$Cu(OTf)_2$(2.0)	72[d]

[a]Most of listed reactions applying sodium *p*-toluenesulfinate hydrate (2.0 equiv), and the concentration of **2.12** is 0.025 mmol/mL. [b]NMR yield for product **2.14**, the yields of product **2.15** is less than 5%. [c]Anhydrous sodium *p*-toluenesulfinate (2.0 equiv) is applied. [d]Isolated yields.

Subsequently, when the equivalent of copper (II) triflate was doubled (**Table 2**, entry 14), it presented a much higher yield (83% vs. 42% when only 1.0 eq. of $Cu(OTf)_2$ was used, entry 10) When more copper reagent was tested for the reaction, such as 3.0 and 4.0 eq. of $Cu(OTf)_2$, there was no improvement in the yield of **2.14**. In fact, there was a slight difference between using hydrate sodium salt and anhydrous one; the anhydrous salt can increase the yield slightly (around 3%). Later, this thesis work also assessed the influence of different temperatures, such as 60 ℃, 80 ℃, 100℃, 120 ℃. As shown in entry 15, reaction at 80 ℃ provides a 72% yield that is lower than that at 100 ℃, but higher than at room temperature and 60 ℃. When the reaction was carried out at 120 ℃, the corresponding yields decreased significantly, which may be due to the likely decomposition of the desired product at high temperature. The optimal conditions were screened out as shown in entry 14.

2.3 The scope of different linkers

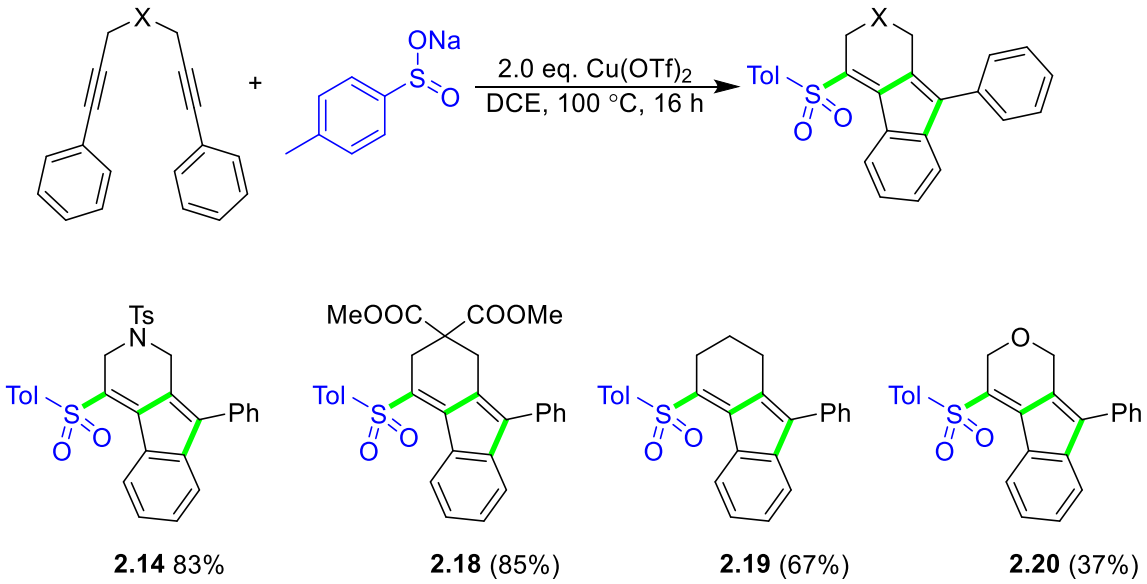
In order to extend the application of this reaction, different linkers were going to be scoped after optimizing reaction conditions. Besides the NTs linker, other linkers such as dimethyl malonate linker, methylene linker, and oxygen linker were considered. Firstly, the corresponding diyne starting materials need to be synthesized since none of them are commercially available (**Scheme 23**). Compound **2.12** with NTs linker was synthesized from *p*-toluenesulfonamide and 3-phenylpropargyl chloride in the presence of a base (Cs_2CO_3) in acetone for 16 hours via an S_N2 reaction. Under the same condition compound **1.47** was generated from dimethyl malonate and 3-phenylpropargyl chloride. The yields for both of these two diynes were around 80%. The preparation of diyne **2.16** involved the Sonogashira coupling reaction, which used Cu(I)-catalyst and Pd-catalyst in the presence of base Et_3N that also acted as solvent at 50 ℃ for 16 hours to afford the diyne product **2.16** in 66% yield. Later, Wayne Wang, an undergraduate student in the Schipper lad, synthesized compound **2.17** also under Sonogashira conditions. In his reaction he applied 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the base and toluene as the solvent to get 37% of product **2.**17.



Scheme 23 Synthesis of the diyne starting materials with different linkers

After obtaining the desired diynes, the next step is to perform the cascade reaction on these diynes possessing different linkers under the previously optimized conditions. As shown in **Scheme 24**, diyne with the dimethyl malonate linker gave the corresponding tricyclic product in 85% yield, which is slightly higher than that of the diyne possessing the NTs linker (83%), while the starting material with the methylene linker provided a lower 67% yield of **2.19**. Wayne Wang of the Schipper group conducted the reaction on the diyne with the oxygen linker, which afforded only a 37% yield of compound **2.20**. The reason for the observed low yields for the methylene linker and oxygen linker may be

because the two carbon-carbon triple bonds are slightly far away from each other, whereas the NTs and malonate groups are bulky groups that can push the two C-C triple bond closer to each other; moreover, the result that the oxygen linker only gave 37% of desired product **2.20** may be because of the electronegativity of oxygen, which lowers the reactivity of the diyne **2.17**. Upon these testing results, the malonate linker provided the highest yield among the candidates, and it was applied in the following work to scope various substitutions on the terminal benzene rings.

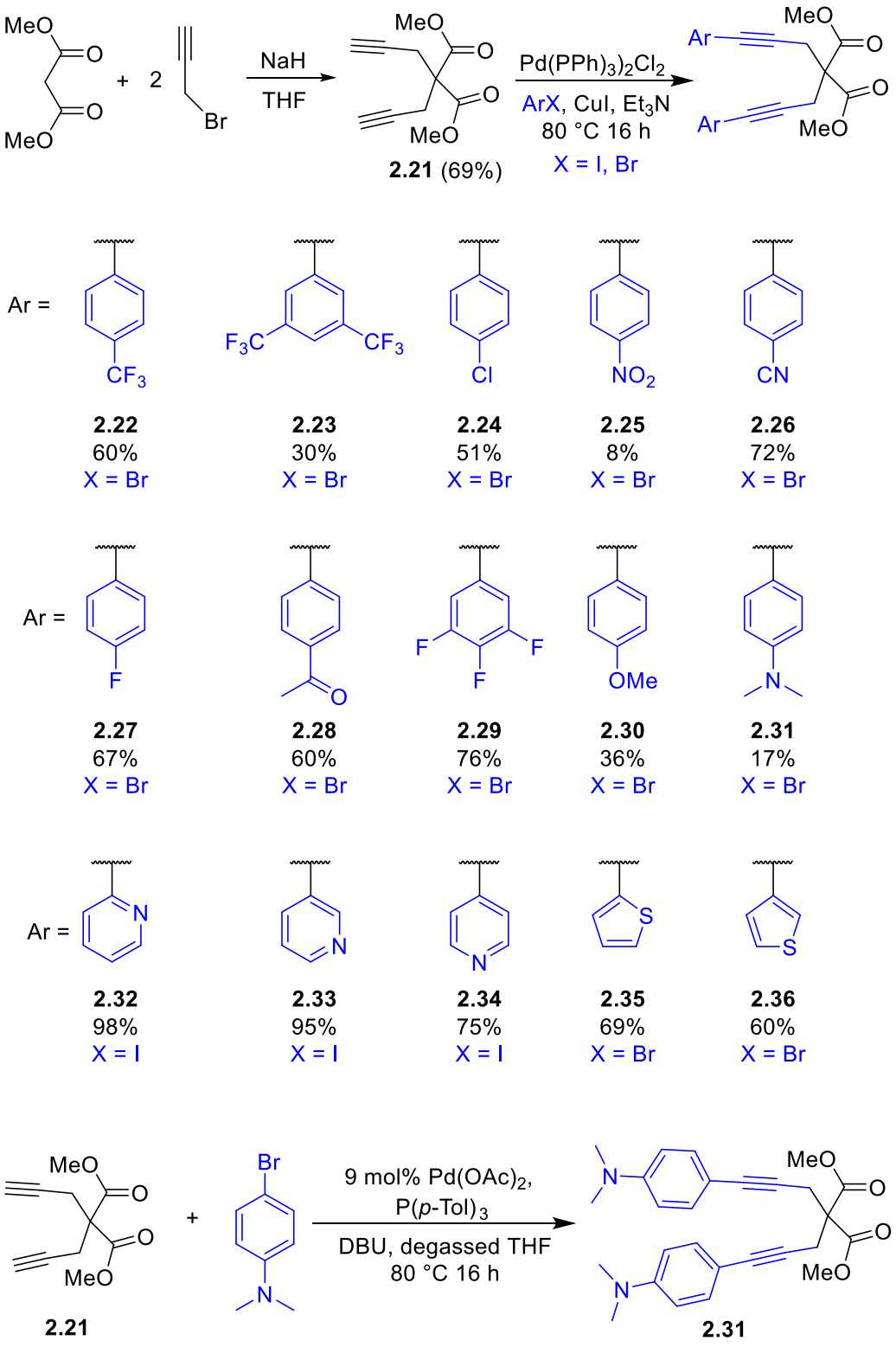


Scheme 24 Scope of different linkers under optimal conditions

2.4 The scope of aromatic groups

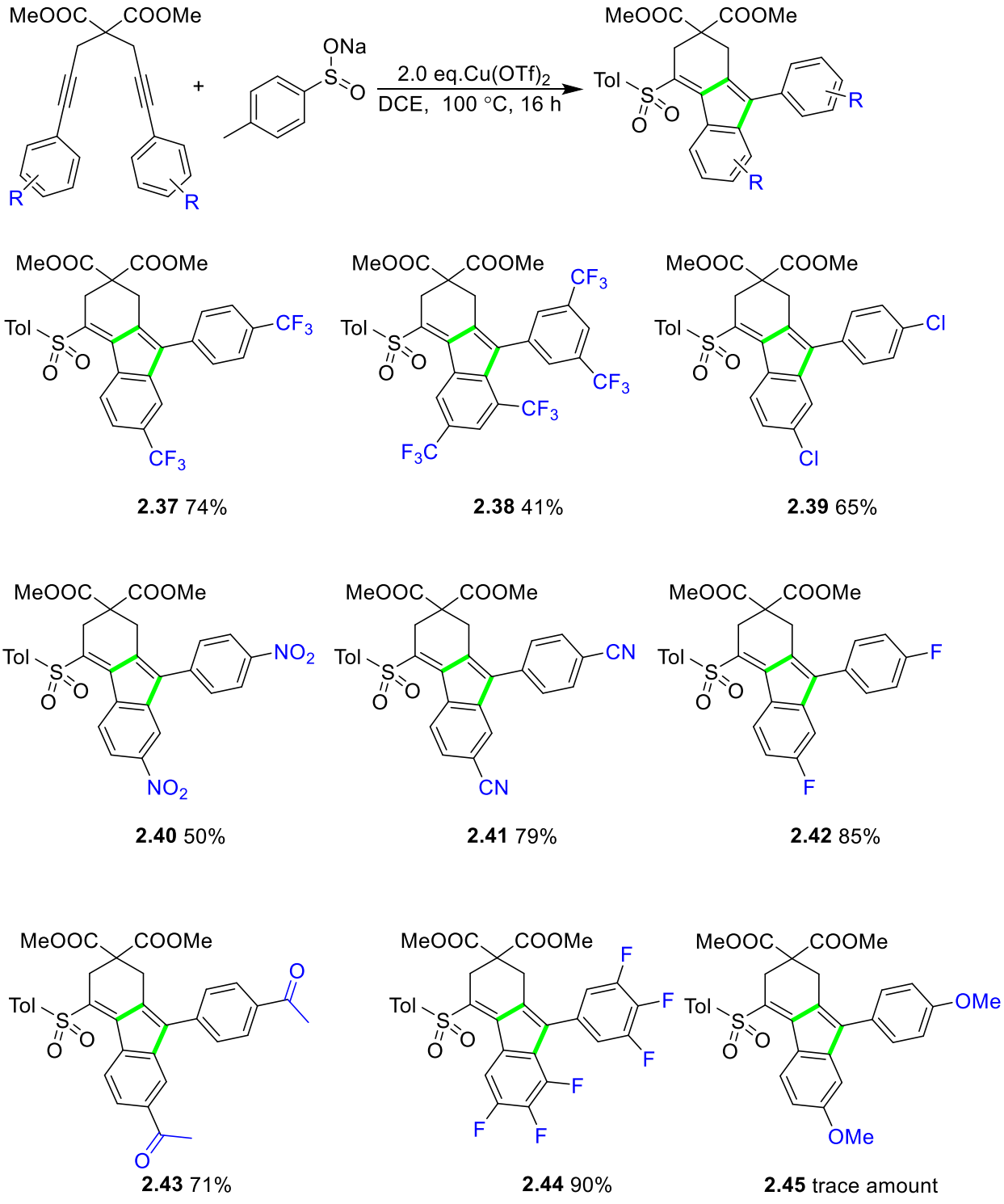
Under the optimal conditions, a series of diynes with different substituted benzene rings were synthesized in this thesis work. First, dimethyl dipropargylmalonate **2.21** was prepared in 69% yield using sodium hydride (NaH) as the base in THF (**Scheme 25**). Then, the intermediate **2.21** was used as the precursor to prepare the diynes (**2.22**–**2.36**)

under the Sonogashira coupling conditions, which involved a Cu(I)-catalyst, a Pd-catalyst, and Et_3N as both the base and solvent. Both electron-withdrawing groups (such as trifluoromethyl, chloro, fluoro, nitro) and electron-donating groups (like methoxy and dimethylamine groups) were included in the prepared compounds. Most of these compounds were obtained under the conditions shown in **Scheme 25**, but the product **2.31** could not be obtained under the typical Sonogashira conditions. After several attempts, a suitable condition was developed, which involves $Pd(OAc)_2$ as the catalyst, DBU as the base and P(*p*-Tol)$_3$ as the ligand (**Scheme 25**) to afford **2.31** in 17% yield. The low yield of **2.31** is because the electronic density was increased between C-Br due to the electron-donating group (dimethylamino), which makes it difficult to break the bond between the carbon of the benzene ring and the Br atom.[47] Moreover, diynes with thiophene and pyridine were also synthesized and most yields were satisfying (60% to 90%). The pyridine species were obtained from aryl iodide and the yields were 70–90%. Aryl bromides were initially tested for the preparation of compounds **2.32**–**2.34**, but they gave no desired product, which is because the aryl iodide is more reactive than the aryl bromide due to the weaker C-I bond.



Scheme 25 Synthesis of the diyne starting materials with different aromatic substrate group

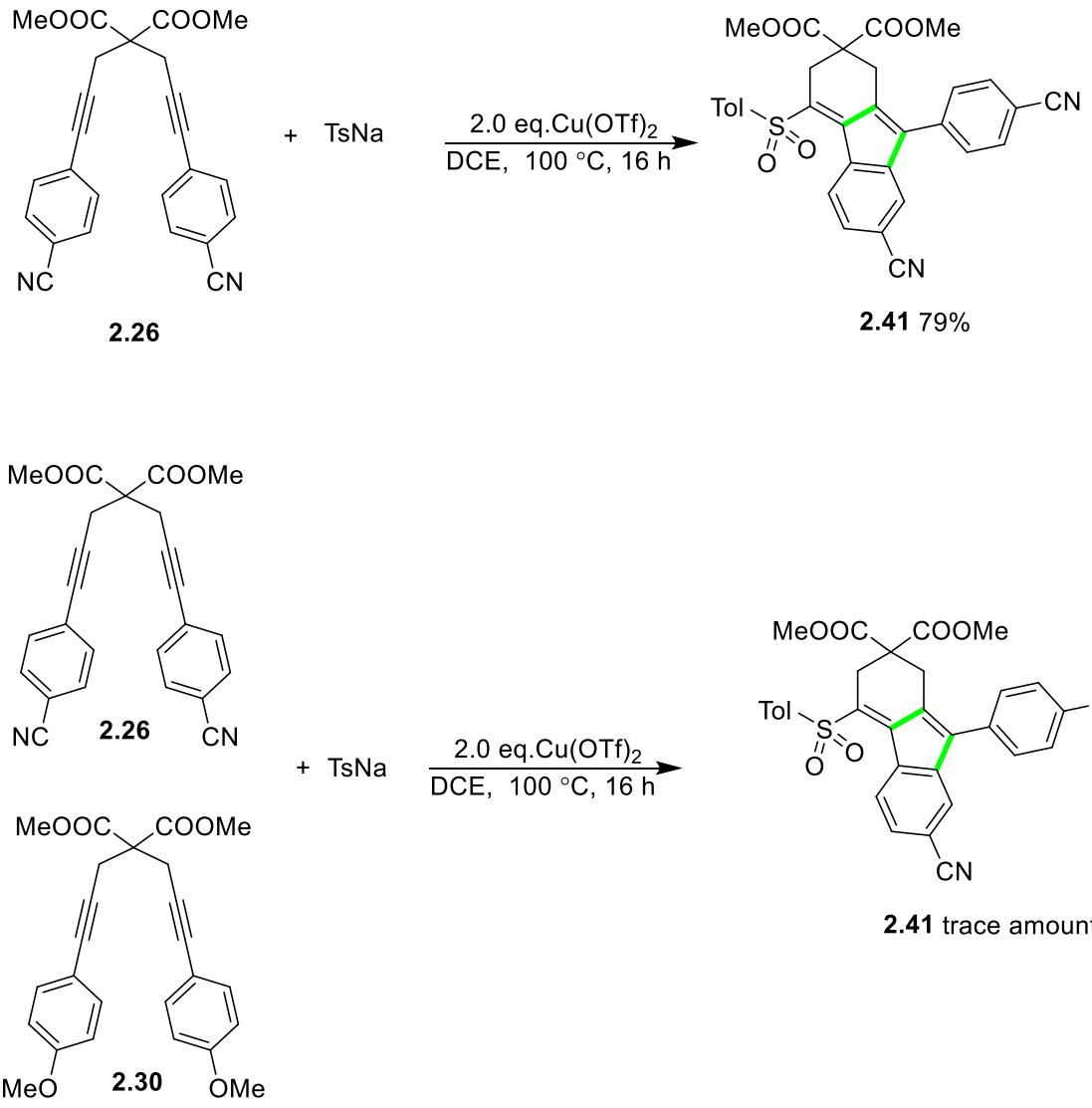
After obtaining the above diynes with different aromatic substitutions, the scope experiments were performed under the optimal conditions (**Scheme 26**). This thesis work involved the synthesis of compounds **2.37**-**2.44,** which were generated from starting materials **2.22**–**2.29**, respectively. The yields of these products ranged from 41% to 90% and the highest yield was provided by compound **2.44**. Other aryl aromatic groups with heteroatoms were also involved in the investigation, such as thiophene ring and pyridine ring (compounds **2.32**–**2.36**). Unfortunately, there was no desired product observed but some uncharacterized highly polar products. Hetero atoms may block the reactants or they may lead to some undesirable polymerizations.



Scheme 26 Scope of different aromatic substituents

Obviously, the diynes bearing aromatic substituents containing electron-withdrawing

groups gave good yields. When electron-donating groups were involved in scoping, such as the methoxy group and the dimethylamine group, the results were different. Specifically, the reaction of **2.30** only offered a trace amount of **2.45** (**Scheme 27**) and there was no product observed when dimethylamino-substituted compound **2.31** was used. The reason why the yields for electron rich groups were low is still not clear, but it was speculated that the electron-donating group may lower the reactivity of this reaction or the electron rich group may quench the copper reagent. This thesis work conducted two comparative experiments (**Scheme 27**), both of which involved starting material **2.26**. The first reaction is the regular reaction under the optimal conditions. When 1.0 equivalent of **2.30** was added into the regular reaction, it was found that the yield of **2.41** was decreased significantly to trace amount; therefore, it was speculated that the methoxy group possibly interacted the copper reagent or some intermediates. Based on a previous literature report,[48] it was speculated that the methoxy group may be oxidized by copper (II) to generate a radical cation and copper (I) species.

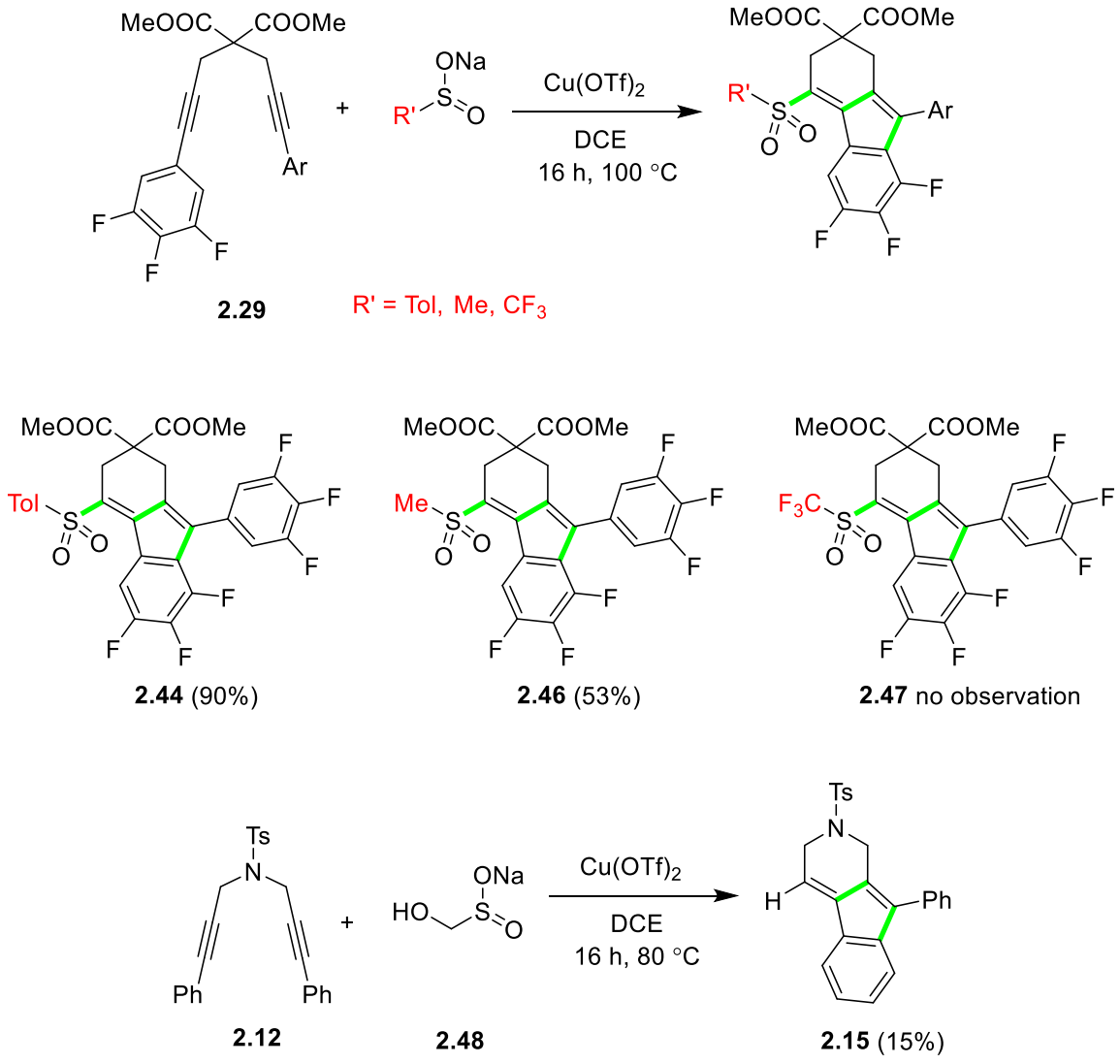


Scheme 27 Comparative experiments between diynes with **2.30** and without **2.30**

2.5 The scope of sodium sulfinate salts

Based on the results of the scope of different aromatic substitutions, the trifluoro-substituted substrate **2.29** provided the highest isolated yield (90%) of the desired structure. The following work was conducted under the optimal conditions, **2.29** reacted with three different sodium sulfinate salts to offer the corresponding products **2.44**, **2.46** and **2.47**. As shown in **Scheme 28**, the sulfinate salt with the tolyl group afforded 90% yield of **2.44**, and methyl group provided 53% yield of **2.46,** while when Wayne Wang of

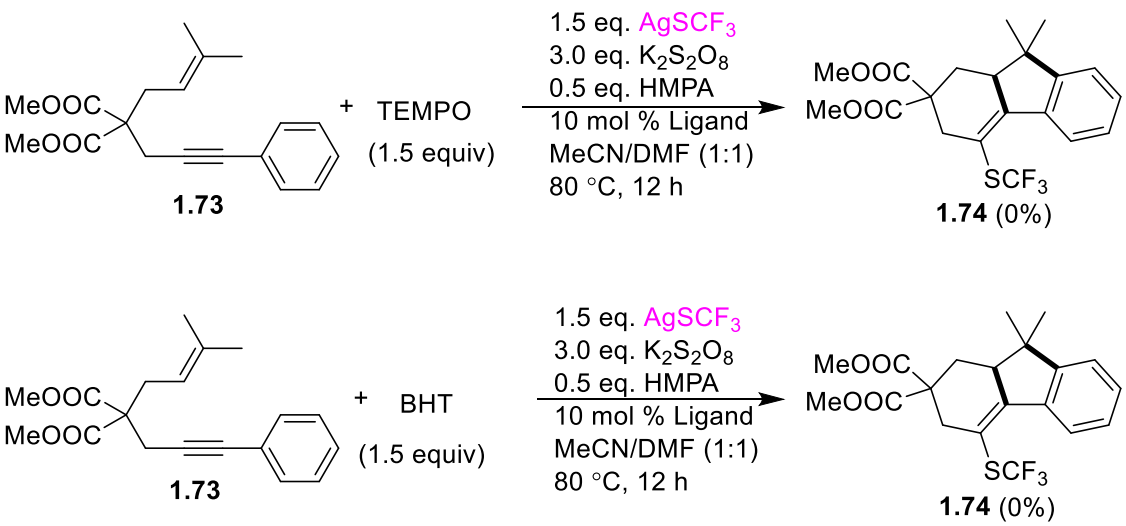
the Schipper group tested the trifluoromethyl group, there was no observation of the desired product **2.47**. Moreover, this thesis work also conducted another reaction that involved hydroxymethanesulfinic acid monosodium salt dihydrate **2.48**, in which compound **2.12** was used instead of the malonate-linker diyne (**Scheme 28**). The desired compound with the formation of C-S bond was not observed but compound **2.15** was isolated in 15% yield, which suggested that **2.48** is not a good nucleophile in this reaction when compared to TsNa. Upon these results, it is indicated that sodium *p*-toluenesulfinate salt is more active than than the other sodium sulfinate salts.



Scheme 28 The scope of sodium sulfinate salts

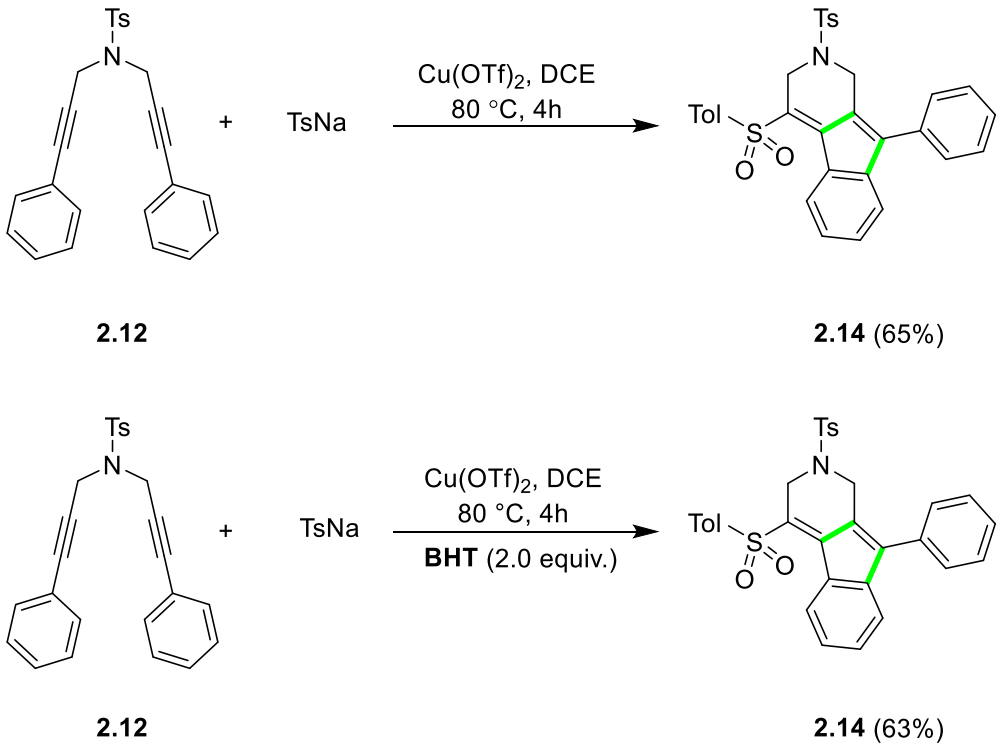
2.6 The study of mechanism

So far, this thesis work had investigated the optimal conditions of proposed reactions, the scope of different linkers, aromatic substitutions as well as sodium sulfinate salts. The next important aspect is the mechanistic study. To gain more information about the mechanism of the proposed reaction, more reactions were set up. Based on the mechanistic study by the Liang group,[41] a stable radical, (2,2,6,6-tetramethylpiperidin -1-yl) oxidanyl (TEMPO), and a common radical inhibitor, butylated hydroxytoluene (BHT), were applied in the reaction system (**Scheme 29**). Liang and co-workers conducted two radical trapping reactions. To one was added 1.5 eq. TEMPO and to the other was added 1.5 eq. BHT, and it can be seen that both of these reactions resulted in recovery of 97% and 93% starting material (SM), respectively, which indicated that this reaction involved some radical intermediates and hence both the radical reagent and radical inhibitor could quench the reaction dramatically. The corresponding mechanism is shown in **Scheme 16**.



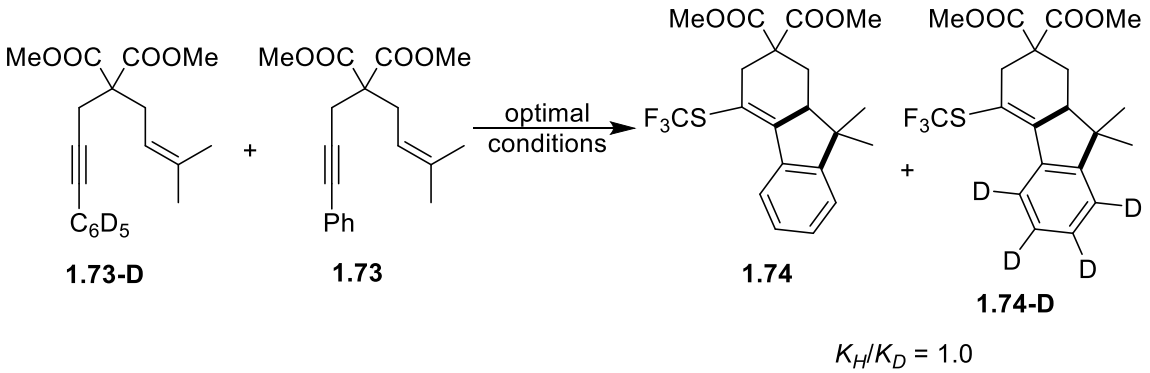
Scheme 29 Radical trapping experiments by Liang's group[41]

In terms of our own mechanistic study, BHT was also used to investigate the mechanism. We conducted two parallel experiments with NTs-starting material (**Scheme 30**), one of which is NTs starting material reacting with other two optimal reagents at 80 ℃ for 4 hours, resulting in an isolated yield for **2.14** of 65%; The other one was with 2.0 equivalents of BHT added into the comparative experiment and the isolated yield of the product **2.14** was 63%, which indicated that there was no radical intermediate generated in the reaction, and it does not follow Liang's radical mechanism (**Scheme 30**).



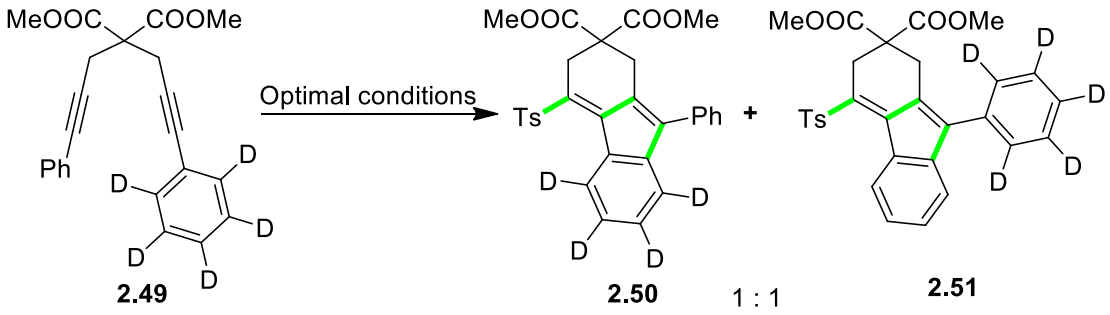
Scheme 30 Radical trapping experiments by our group

Besides the investigation of radical trapping experiments, the Schipper lab also investigated a kinetic experiment that was also inspired by Liang.[41] Liang conducted a kinetic isotope experiment under their optimal conditions, which started from a mixture of **1.73** and **1.73-D** (with fully deuterated benzene ring) to afford product **1.74** and **1.74-D**, and the relative rates of products formation K_H/K_D = 1.0 (**Scheme 31**), which indicated that the C(sp^2)-H bond activated step was not a rate determining step (RDS).



Scheme 31 Kinetic isotope effect (KIE) study[41]

The kinetic study was conducted by Geoffrey Sinclair, one of the graduate students in the Schipper lab. Firstly, Geoffrey synthesized the corresponding deuterated diynes under Sonogashira coupling conditions. By applying compound **2.49**, Geoffrey developed the internal competition experiment as shown in **Scheme 32**. This reaction gave two possible products **2.50** and **2.51** under optimal conditions and the ratio of yields between these two products was around 1:1, which can verify some results about the mechanism of this reaction. One possibility is if the aromatic C-H bond cleavage is the rate-determining step (RDS), then the previous steps are non-reversible due to the probability of attacking either C-C triple bond being the same; the other possibility is if the aromatic C-H bond cleavage is not the RDS, that steps before aromatic C-H bond activation can be reversible or non-reversible. So only setting up the internal competition experiment is not enough to determine if it is a reversible reaction or not. Our group also needed to conduct relative rate experiments to establish whether the C-H bond activation is the rate-determining step.



Scheme 32 Internal competition experiment by Geoffrey Sinclair

In the following work, Geoffrey compared the relative rates of product formation of **2.14** and **2.52** (K_H/K_D), which can provide some information about C-H bond functionalization (**Figure 4**). Based on the experiment results, it was found that K_H/K_D = 1.0, it indicates that C-H bond activation step is not the RDS. The relative experiment about the mechanism of the cleavage of C-H bond is still under investigation by Geoffrey.

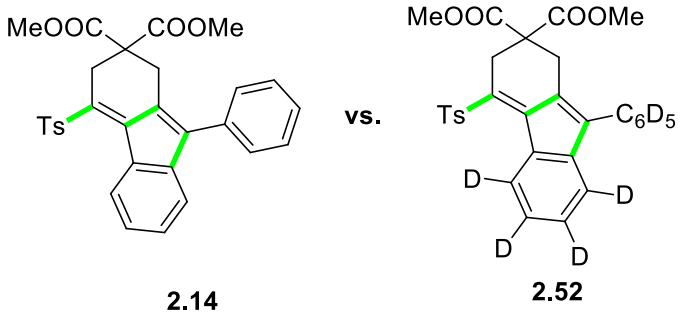
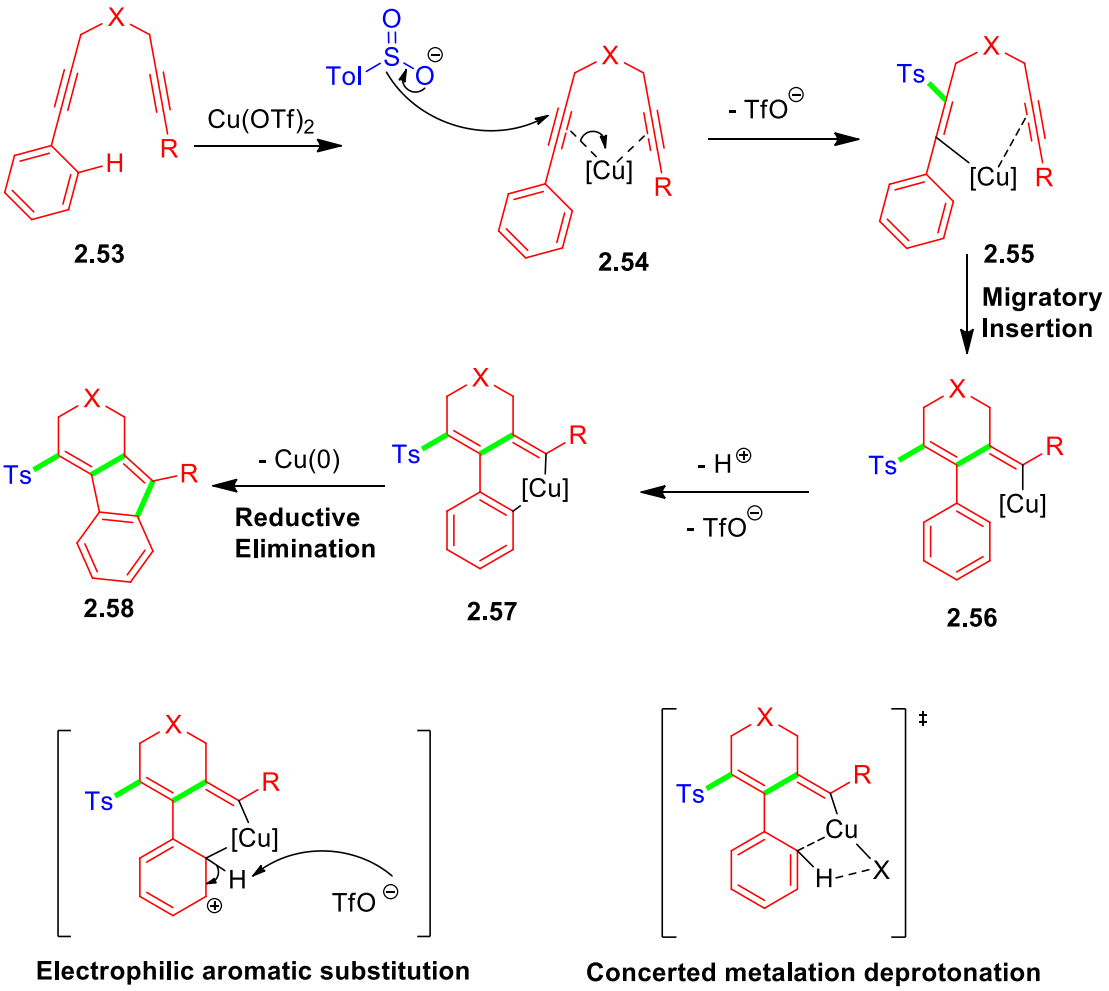


Figure 4 Relative rate experiments

According to the experimental outcome from the many and recent mechanistic studies, a five-step copper-mediated mechanism is proposed in **Scheme 33**. The diyne compound **2.53** reacted with copper (II) triflate to afford a coordinated intermediate **2.54**, which is followed by the attack of *p*-toluenesulfinate at one of the carbon-carbon triple

bonds to give the desired C-S bond. At the same time, a bond between copper and the other carbon atom from the same C-C triple bond is formed (intermediate **2.55**). The migratory insertion step provides a new carbon-carbon bond between the two carbon triple bonds in intermediate **2.56**. Along with C-H bond activation, the second copper-involved six-membered ring was obtained (**2.57**). In the C-H bond activation step, there are two possible pathways. One may follow the electrophilic aromatic substitution as shown in **Scheme 33**, which involves the attack by triflate to achieve the deprotonation; the other path is a concerted metalation deprotonation and the corresponding transition state is shown in **Scheme 33** as well. Following an elimination reaction, the final product is formed.

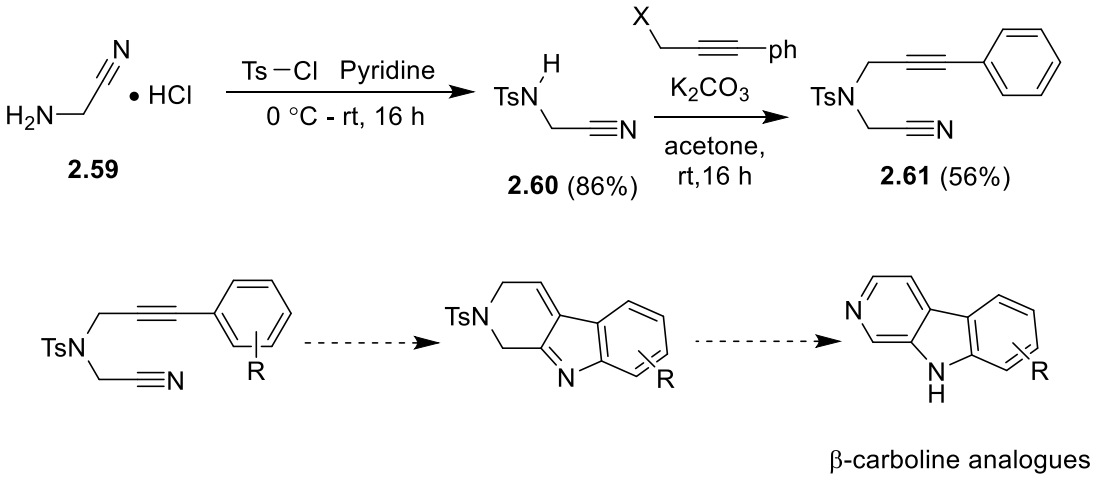


Scheme 33 Proposed mechanism for copper-mediated C-S bond formation and C(sp^2)-H functionalization via cascade cyclization

2.7 Summary and future work

In conclusion, our group has developed a convenient methodology to synthesize organosulfur compounds through the application of copper reagents via aromatic C-H activation and cascade reaction. As shown above, this thesis work optimized the reaction conditions, including solvent systems, temperatures, copper reagents and reaction time. Additionally, this thesis work also explored the scope of different linkers, aromatic substitutions, as well as sodium sulfinate salts. Based upon the experimental results, it has

been determined that electron-withdrawing groups are more effective than electron-donating groups under the optimal conditions, because electron-rich group may quench the copper reagent. By developing radical trapping experiments and kinetic experiments, a plausible copper-mediated mechanism is proposed as shown in **Scheme 33**.



Scheme 34 The synthesis of product **2.61** and future work

As mentioned above, the mechanistic study is still ongoing. After the determination of the mechanism of this proposed reaction, our group can try to use other nucleophiles besides sulfinate salts. Moreover, similar starting materials also can be employed under optimal conditions. Recently in the course of this thesis work, new starting material **2.61** was synthesized in 56% yield, in which a C-N triple bond replaces one C-C triple bond (**Scheme 34**). **2.59** reacted with TsCl to afford the intermediate **2.60** in 86% yield, from which **2.61** was generated in the presence of potassium carbonate. In future work, **2.61** may be applied to synthesize β-carboline analogues, which have biochemical and pharmacological significance (**Scheme 34**).[49]

Chapter 3 Experimental Procedures

3.1 General synthetic experimental procedures

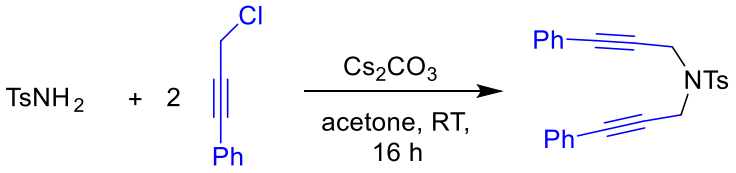
All reactions were carried out in flame or oven-dried glassware under an argon or nitrogen atmosphere. Solvents were either reagent grade or HPLC grade. Dry DCE was prepared using dry molecular sieves which were dehydrated by heating metal (200–300℃) under argon. Most chemical reagents were purchased from Sigma-Aldrich. Reactions were monitored using commercial thin-layer chromatography (TLC) plates. Developed TLC plates were examined under a UV lamp (254 nm) or exposed to iodine stain. Flash chromatography was performed using 230–400 mesh silica gel and Teledyne Isco CombiFlash.

^{1}H-NMR spectra were recorded on either a Brüker AVANCE300 (300 MHz) or Brüker AC300 (300 MHz) NMR spectrometer. ^{13}C-NMR spectra were broad band decoupled and recorded on a Brüker AVANCE300 (75.5 MHz) or Brüker AC300 (75.5 MHz) NMR spectrometer, using the carbon signal of the deuterated solvent as the internal standard. The following abbreviations are used for NMR peak multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; dt, doublet of triplets; m, multiplet; br, broad. Chemical shifts are reported in parts per million (ppm) relative to either TMS (δ 0.0), chloroform (δ 7.26) or acetone (δ 2.05) for ^{1}H-NMR, and either chloroform (δ 77.16) or acetone (δ 29.84) for ^{13}C NMR. High resolution mass spectra (HRMS) and low resolution mass spectra (LRMS), obtained via electrospray ionization (ESI) and direct analysis in real time (DART), were measured on a Thermo Scientific Q Exactive™ Plus

Hybrid Quadrupole-Orbitrap™ Mass Spectrometer in the Mass Spectrometry Facility in the Department of Chemistry, University of Waterloo. X-ray crystal structures were determined by Dr. Jalil Assoud and figures of X-ray crystal structures were generated using Mercury.

3.2 Synthetic procedures

4-Methyl-*N*,*N*-bis(3-phenylprop-2-yn-1-yl)benzenesulfonamide (2.12)

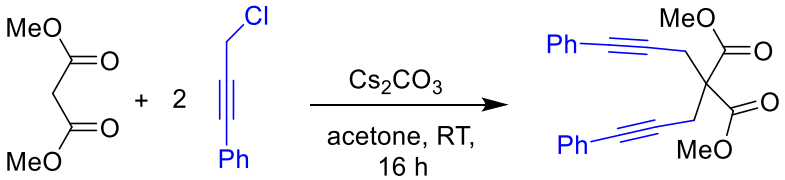


2.12

4-Methyl-*N*,*N*-bis(3-phenylprop-2-yn-1-yl)benzenesulfonamide was synthesized according to general substitution reaction conditions and exhibited spectroscopic data identical to that previously reported.[50] 4-Methylbenzenesulfonamide (49.91 mg, 0.29 mmol) was dissolved in 10 mL acetone, then $CsCO_3$ and 3-chloro-1-phenyl-1-propyne (0.12 mL, 0.87 mmol) were added into the solution. The mixture was stirred at room temperature for 16 hours. After that, the solvent was removed in vacuo. The residual solid was dissolved in water and DCM was added. The layers were separated and the aqueous layer was extracted with DCM. The combined organic layers were dried over $MgSO_4$ and filtered. Concentration in vacuo gave the diyne **2.12** as a pale yellow oil, which was purified by column chromatography (silica gel 230–400 mesh, hexanes) to give a white solid compound 94.4 mg. Yield = 82%; R*f* = 0.3 (EtOAc : Hexane = 1 : 4); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.79 (d, *J* = 8.3 Hz, 2H), 7.18–7.32 (m, 12H), 4.44 (s, 4H), 2.30 (s,

3H).

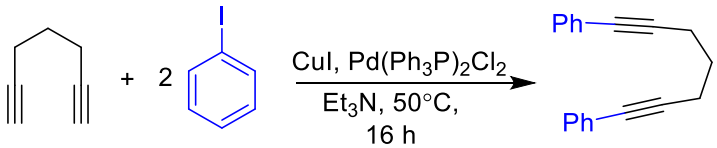
Dimethyl 2,2-bis(3-phenylprop-2-yn-1-yl)malonate (1.47)



1.47

Dimethyl 2,2-bis(3-phenylprop-2-yn-1-yl)malonate was synthesized according to standard substitution reaction conditions and exhibited characterization data identical to those previously reported.[31] The procedure follows that for the synthesis of 4-methyl-*N*,*N*-bis(3-phenylprop-2-yn-1-yl)benzenesulfonamide. Yield = 72%; R_f = 0.36 (EtOAc : hexanes = 1 : 4); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38–7.35 (m, 4H), 7.28–7.24 (m, 6H), 3.79 (s, 6H), 3.25 (s, 4H).

1,7-Diphenylhepta-1,6-diyne (2.16)

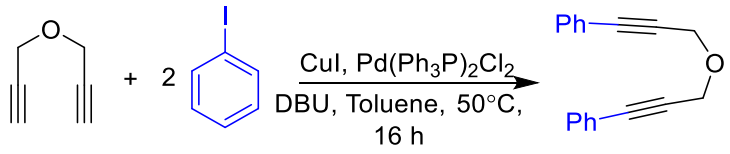


2.16

1,7-Diphenylhepta-1,6-diyne was synthesized according to standard Sonogashira coupling reaction conditions and exhibited spectroscopic data identical to those previously reported.[51] A MW tube was charged with $Pd(Ph_3P)_2Cl_2$ (90.48 mg, 0.125 mmol) and CuI (49.60 mg, 0.25 mmol), then purged with Argon for 15 minutes. To this was added 25 mL of N_2-purged Et_3N, followed by hepta-1,6-diyne (0.3 mL, 2.5 mmol) and iodobenzene (0.7 mL, 6.25 mmol). The MW tube was sealed with a cap. The mixture was stirred at 50 ℃ for 16 hours. After the reaction, the reaction mixture was filtered

through celite, and rinsed with diethyl ether. The filtrate was concentrated and then purified by column chromatography (silica gel 230–400 mesh, hexanes) to give an oily transparent compound (400 mg). Yield = 66%; R*f* = 0.25 (hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.44–7.47 (m, 4H), 7.30–7.34 (m, 6H), 2.64 (t, *J* = 7.2 Hz, 4H), 1.95 (q, *J* = 7.2 Hz, 2H).

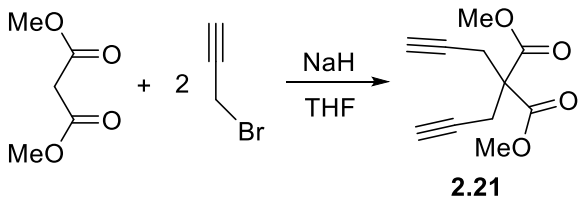
(Oxybis(prop-1-yne-3,1-diyl))dibenzene (2.17)



2.17

(Oxybis(prop-1-yne-3,1-diyl))dibenzene was synthesized according to standard Sonogashira coupling reaction conditions and exhibited characterization data identical to those previously reported.[51] A MW tube was charged with $Pd(Ph_3P)_2Cl_2$ (90.48 mg, 0.125 mmol), CuI (49.60 mg, 0.25 mmol) and DBU (1.9 ml, 12.5 mmol), then purged with Argon for 15 minutes. Toluene (25 mL) was added, followed by propargyl ether (0.26 mL, 2.5 mmol) and iodobenzene (0.7 mL, 6.25 mmol). The MW tube was sealed with a cap. The mixture was stirred at 50 ℃ for 16 hours. After the reaction, the reaction mixture was filtered through celite and rinsed with diethyl ether. The filtrate was concentrated and then purified by column chromatography (silica gel 230–400 mesh, hexanes) to give an oily transparent compound. Yield = 37%; R*f* = 0.63 (EtOAc : Hexane = 1 : 9); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45–7.48 (m, 4H), 7.31–7.33 (m, 6H), 4.55 (s, 4H).

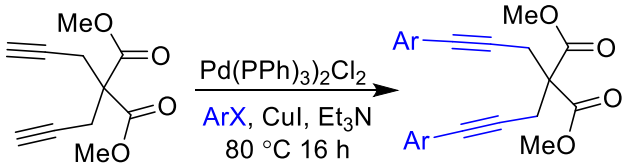
Dimethyl 2,2-di(prop-2-yn-1-yl)malonate (2.21)



2.21

Dimethyl 2,2-di(prop-2-yn-1-yl)malonate was synthesized by standard substitution reaction conditions and exhibited identical data to those previously reported.[52] Dimethyl malonate (3.5 mL, 30.0 mmol) was added dropwise to a solution of sodium hydride (60% in mineral oil, 3 g, 75.0 mmol) in dry THF (90 mL) at 0 ℃. Stirring was continued for 30 minutes while the reaction mixture was allowed to warm up to room temperature. After cooling down to 0 ℃, the propagyl bromide was added. The solution was stirred overnight while warming up to room temperature. The reaction was quenched with water and the aqueous layer was extract with EtOAc. The combined organic layers were dried over $MgSO_4$ and filtered. Concentration in vacuo gave the diyne **2.21** as a pale yellow powder, which was purified by column chromatography (silica gel 230–400 mesh, 9:1 hexane-ethyl acetate and then 7:3 hexane-ethyl acetate) to give a white solid compound (4.2 g). Yield = 69%; R*f* = 0.45 (EtOAc : hexane = 1 : 4); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.77 (s, 6H), 2.97 (d, *J* = 2.4 Hz, 4H), 2.02 (t, *J* = 2.4 Hz, 2H).

General procedure A for the synthesis of starting material diynes (2.22–2.36)



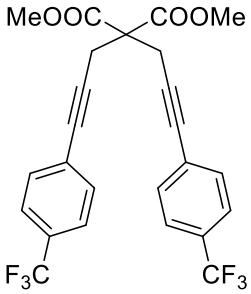
2.21 **2.22-2.36**

X = Br or I

The strating material diynes was synthesized according to the general Sonogashira

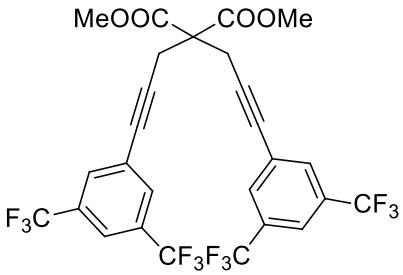
coupling reaction.[53] A 5 mL MW tube was charged with $Pd(Ph_3P)_2Cl_2$ (0.125 mmol) and CuI (0.25 mmol), then purged with argon for 15 minutes. To this was added 2.5 mL N_2-purged Et_3N, which was followed by the addition of diyne **2.21** (2.5 mmol) and aryl halides (6.25 mmol). The MW tube was sealed with a cap. The mixture was stirred at 80 ℃ for 16 hours. After the reaction, the reaction mixture was filtered through celite, and rinsed with diethyl ether. The filtrate was concentrated and then purified by column chromatography (silica gel 230–400 mesh, hexanes/EtOAc) to give the starting materials.

Dimethyl 2,2-bis(3-(4-(trifluoromethyl)phenyl)prop-2-yn-1-yl)malonate (2.22)



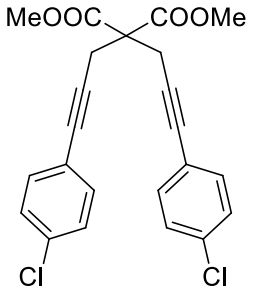
Dimethyl 2,2-bis(3-(4-(trifluoromethyl)phenyl)prop-2-yn-1-yl)malonate was synthesized according to the general procedure A. White solid. Yield = 60%; R_f = 0.2 (EtOAc : hexane = 1 : 4); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.54–7.46 (m, 8H), 3.81 (s, 6H), 3.31 (s, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.4, 132.3, 130.3 (q, *J* = 32.5 Hz), 127.1, 126.0, 125.5 (q, *J* = 3.75 Hz), 122.4, 86.8, 83.1, 57.3, 53.5, 24.2; HRMS calculated for $C_{25}H_{19}F_6O_4$ (M+H) 497.1181; found: 497.1182.

Dimethyl 2,2-bis(3-(3,5-bis(trifluoromethyl)phenyl)prop-2-yn-1-yl)malonate (2.23)



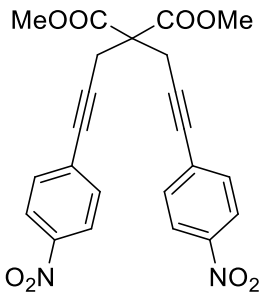
Dimethyl 2,2-bis(3-(3,5-bis(trifluoromethyl)phenyl)prop-2-yn-1-yl)malonate was synthesized according to the general procedure A. White crystals. Yield = 30%; R_f = 0.6 (EtOAc : hexane = 1 : 4); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.79 (s, 6H), 3.84 (s, 6H), 3.30 (s,4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.9, 131.9 (q, *J* = 33 Hz), 128.3, 125.1, 124.7, 121.6-121.7 (m), 121.1, 117.4, 87.5, 81.4, 56.5, 53.4, 23.9; HRMS calculated for $C_{27}H_{17}F_{12}O_4$ (M+H) 633.0927; found: 633.0930.

Dimethyl 2,2-bis(3-(4-chlorophenyl)prop-2-yn-1-yl)malonate (2.24)



Dimethyl 2,2-bis(3-(4-chlorophenyl)prop-2-yn-1-yl)malonate was synthesized according to the general procedure A. White solid. Yield = 51%; R_f = 0.5 (EtOAc : hexane = 1 : 3); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.20-7.29 (m, 8H), 3.77 (s, 6H), 3.22 (s, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.1, 134.0, 132.8, 128.4, 121.3, 84.8 82.7, 57.0, 53.0, 23.8; HRMS calculated for $C_{23}H_{19}Cl_2O_4$ (M+H) 429.0657; found: 429.0655.

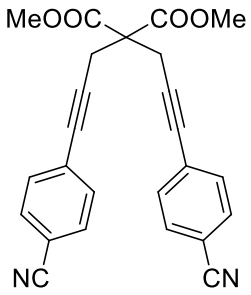
Dimethyl 2,2-bis(3-(4-nitrophenyl)prop-2-yn-1-yl)malonate (2.25)



Dimethyl 2,2-bis(3-(4-nitrophenyl)prop-2-yn-1-yl)malonate was synthesized according to the general procedure A. Pale yellow oil. Yield = 8%; R_f = 0.4 (EtOAc :

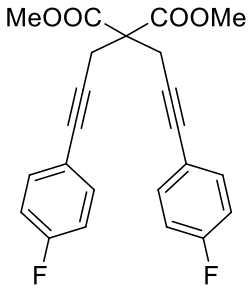
hexane = 1 : 3); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.15 (d, *J* = 8.7 Hz, 4H), 7.52 (d, *J* = 8.7 Hz, 4H), 3.82 (s, 6H), 3.30 (s, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.8, 147.0, 132.4, 129.6, 123.4, 89.3, 82.4, 56.7, 53.3, 24.0; HRMS calculated for $C_{23}H_{19}N_2O_8$ (M+H) 468.1401; found: 468.1401.

Dimethyl 2,2-bis(3-(4-cyanophenyl)prop-2-yn-1-yl)malonate (2.26)



Dimethyl 2,2-bis(3-(4-cyanophenyl)prop-2-yn-1-yl)malonate was synthesized according to the general procedure A. White solid. Yield = 72%; R_f = 0.2 (EtOAc : hexane = 1 : 3); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.55 (d, *J* = 8.1 Hz, 4H), 7.43 (d, *J* = 8.1 Hz, 4H), 3.79 (s, 6H), 3.25 (s, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.8, 132.1, 131.9, 127.6, 118.3, 111.5, 88.4, 82.5, 56.7, 53.2, 23.8; HRMS calculated for $C_{25}H_{19}N_2O_4$ (M+H) 411.1336; found: 411.1339.

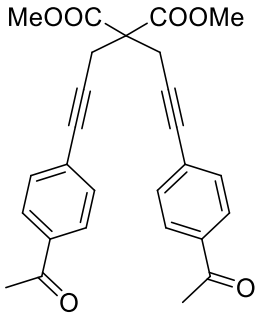
Dimethyl 2,2-bis(3-(4-fluorophenyl)prop-2-yn-1-yl)malonate (2.27)



Dimethyl 2,2-bis(3-(4-fluorophenyl)prop-2-yn-1-yl)malonate was synthesized according to the general procedure A. White solid. Yield = 67%; R_f = 0.6 (EtOAc : hexane = 1 : 2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35 (m, 4H), 6.96 (m, 4H), 3.80 (s, 6H),

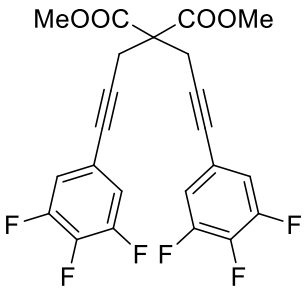
3.24 (s, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.2, 163.9, 160.6, 133.4 (d, *J* = 8.25 Hz), 118.9, 115.4 (d, *J* = 22.5 Hz), 83.1 (d, *J* = 58.5 Hz), 57.1, 53.0, 23.7; HRMS calculated for $C_{23}H_{19}F_2O_4$ (M+H) 397.1227; found: 397.1246.

Dimethyl 2,2-bis(3-(4-acetylphenyl)prop-2-yn-1-yl)malonate (2.28)



Dimethyl 2,2-bis(3-(4-acetylphenyl)prop-2-yn-1-yl)malonate was synthesized according to the general procedure A. White solid. Yield = 60%; R_f = 0.2 (EtOAc : hexane = 1 : 3); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.84 (d, *J* = 8.1 Hz, 4H), 7.43 (d, *J* = 8.1 Hz, 4H), 3.79 (s, 6H), 3.27 (s, 4H), 2.55 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 197.1, 169.0, 136.1, 131.7, 128.0, 127.7, 87.3, 83.2, 56.9, 53.1, 26.5, 23.9; HRMS calculated for $C_{27}H_{25}O_6$ (M+H) 445.1645; Found: 445.1646.

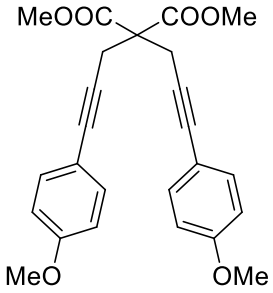
Dimethyl 2,2-bis(3-(3,4,5-trifluorophenyl)prop-2-yn-1-yl)malonate (2.29)



Dimethyl 2,2-bis(3-(3,4,5-trifluorophenyl)prop-2-yn-1-yl)malonate was synthesized according to the general procedure A. White solid. Yield = 76%; R_f = 0.6 (EtOAc : hexane = 1 : 3); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.98 (m, 4H), 3.80 (s, 6H), 3.20 (s, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.8, 152.4 (dd, *J* = 10.2, 4.5 Hz), 149.1 (dd, *J* = 10.2,

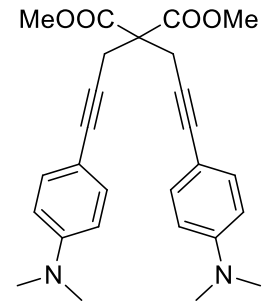
4.5), 141.9 (t, J = 15.2 Hz), 138.5 (t, J = 15.2 Hz), 118.8–118.5 (m), 116.1–115.8 (m), 85.5, 81.1, 56.6, 53.1, 23.6; HRMS calculated for $C_{23}H_{15}F_6O_4$ (M+H) 469.0869; found: 469.0869.

Dimethyl 2,2-bis(3-(4-methoxyphenyl)prop-2-yn-1-yl)malonate (2.30)



Dimethyl 2,2-bis(3-(4-methoxyphenyl)prop-2-yn-1-yl)malonate was synthesized according to the general procedure A. White solid. Yield = 36%; R_f = 0.3 (EtOAc : hexane = 1 : 3); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31 (d, J = 8.7 Hz, 4H), 6.80 (d, J = 8.7 Hz, 4H), 3.79 (s, 6H), 3.78 (s, 6H), 3.24 (s, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.4, 159.3, 133.0, 115.1, 113.7, 83.5, 82.3, 57.3, 55.1, 52.9, 23.7; HRMS calculated for $C_{25}H_{25}O_4$ (M+H) 421.1641; found: 421.1641.

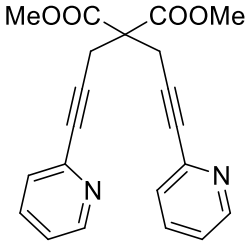
Dimethyl 2,2-bis(3-(4-(dimethylamino)phenyl)prop-2-yn-1-yl)malonate (2.31)



Dimethyl 2,2-bis(3-(4-(dimethylamino)phenyl)prop-2-yn-1-yl)malonate was synthesized according to standard Sonogashira coupling reaction conditions and exhibited spectroscopic data identical to those previously reported.[52] A 5 mL MW tube equipped with a magnetic stirring bar and a rubber septum was charged with $Pd(OAc)_2$ (10 mg,

0.045 mmol) and P(*p*-tol)$_3$ (27.4 mg, 0.09 mmol). After purging with argon, degassed THF (3mL), DBU (0.3 mL, 2 mmol), diyne **2.21** (104 mg, 0.5 mmol) and 4-bromo-*N*,*N*-dimethylaniline (250 mg, 1.25 mmol) were added via a syringe (solid compound was dissolved in degassed THF). The reaction mixture was stirred at 80 ℃ for 16 hours. After cooling to room temperature, water was added to the reaction mixture, which was then extracted with EtOAc (60 mL). The combined organic layers were dried over $MgSO_4$ and filtered. Concentration in vacuo gave the diyne **2.31** as a pale yellow powder, which was purified by column chromatography (silica gel 230–400 mes–, 9:1 hexane-ethyl acetate and then 7:3 hexane-ethyl acetate) to give a white solid compound (37 mg). Yield = 17%; R*f* = 0.25 (EtOAc : hexane = 1 : 3); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.23 (d, *J* = 8.4 Hz, 4H), 6.57 (d, *J* = 8.4 Hz, 4H), 3.77 (s, 6H), 3.23 (s, 4H), 2.93 (s, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.6, 149.9, 132.6, 111.7, 110.1, 84.2, 81.3, 57.6, 52.8, 40.2, 23.8; HRMS calculated for $C_{27}H_{31}N_2O_4$ (M+H) 447.2276; found: 447.2278.

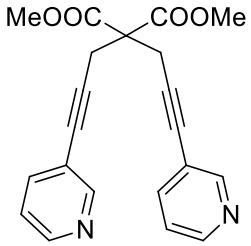
Dimethyl 2,2-bis(3-(pyridin-2-yl)prop-2-yn-1-yl)malonate (2.32)



Dimethyl 2,2-bis(3-(pyridin-2-yl)prop-2-yn-1-yl)malonate was synthesized according to the general procedure A. White solid. Yield = 98%; R_f = 0.1 (EtOAc : hexane = 1 : 2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.47 (d, *J* = 4.5 Hz, 2H), 7.55 (t, *J* = 7.5 Hz, 2H), 7.24 (d, *J* = 7.5 Hz, 2H), 7.12–7.7.14 (m, 2H), 3.75 (s, 6H), 3.28 (s, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.9, 149.7, 142.9, 135.9, 127.2, 122.7, 83.9, 83.4, 56.7, 53.1,

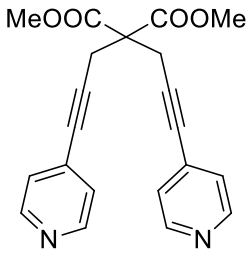
23.7; HRMS calculated for $C_{21}H_{19}N_2O_4$ (M+H) 363.1319; found: 363.1339.

Dimethyl 2,2-bis(3-(pyridin-3-yl)prop-2-yn-1-yl)malonate (2.33)



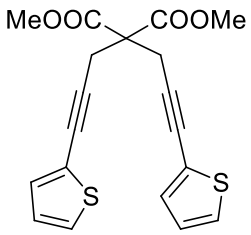
Dimethyl 2,2-bis(3-(pyridin-3-yl)prop-2-yn-1-yl)malonate was synthesized according to the general procedure A. White solid. Yield = 95%; R_f = 0.15 (EtOAc : hexane = 1 : 2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.58 (d, *J* = 1.5 Hz, 2H), 8.48 (dd, *J* = 1.5 Hz, *J* = 4.8 Hz, 2H), 7.63 (dt, *J* = 7.8 Hz, *J* = 1.8 Hz, 2H), 7.19 (dd, *J* = 4.8 Hz, *J* = 7.8 Hz, 2H), 3.79 (s, 6H), 3.26 (s, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.1, 152.4, 148.6, 138.6, 122.9, 120.0, 87.3, 80.7, 56.9, 53.3, 23.9; HRMS calculated for $C_{21}H_{19}N_2O_4$ (M+H) 363.1319; found: 363.1339.

Dimethyl 2,2-bis(3-(pyridin-4-yl)prop-2-yn-1-yl)malonate (2.34)



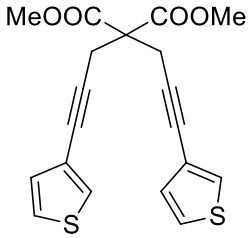
Dimethyl 2,2-bis(3-(pyridin-4-yl)prop-2-yn-1-yl)malonate was synthesized according to the general procedure A. White solid. Yield = 75%; R_f = 0.1 (EtOAc : hexane = 1 : 2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.53 (d, *J* = 6 Hz, 4H), 7.22 (d, *J* = 6 Hz, 4H), 3.80 (s, 6H), 3.26 (s, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.9, 149.7, 131.0, 125.8, 88.8, 81.7, 56.8, 53.3, 23.9; HRMS calculated for $C_{21}H_{19}N_2O_4$ (M+H) 363.1319; found: 363.1339.

Dimethyl 2,2-bis(3-(thiophen-2-yl)prop-2-yn-1-yl)malonate (2.35)



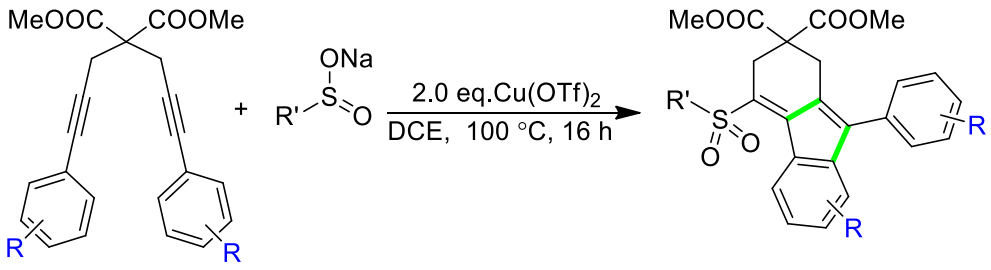
Dimethyl 2,2-bis(3-(thiophen-2-yl)prop-2-yn-1-yl)malonate was synthesized according to the general procedure A. White solid. Yield = 69%; R_f = 0.3 (EtOAc : hexane = 1 : 4); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.17–7.19 (m, 2H), 7.12–7.14 (m, 2H), 6.92 (dd, *J* = 3.6 Hz, *J* = 5.1 Hz, 2H), 3.79 (s, 6H), 3.27 (s, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.0, 131.8, 126.8, 126.7, 122.8, 87.8, 57.0, 53.1, 30.7, 24.6; HRMS calculated for $C_{19}H_{17}O_4S_2$ (M+H) 373.0559; found: 373.0563.

Dimethyl 2,2-bis(3-(thiophen-3-yl)prop-2-yn-1-yl)malonate (2.36)



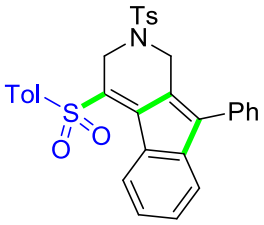
Dimethyl 2,2-bis(3-(thiophen-3-yl)prop-2-yn-1-yl)malonate was synthesized according to the general procedure A. White solid. Yield = 60%; R_f = 0.5 (EtOAc : hexane = 1 : 3); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34 (d, *J* = 2.1 Hz, 2H), 7.19–7.24 (m, 2H), 7.02 (d, *J* = 4.8 Hz, 2H), 3.76 (s, 6H), 3.23 (s, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.2, 131.6, 129.9, 128.5, 125.1, 121.9, 87.4, 78.8, 57.1, 53.0, 23.8; HRMS calculated for $C_{19}H_{17}O_4S_2$ (M+H) 373.0559; found: 373.0563.

General procedure B for the synthesis of final structure



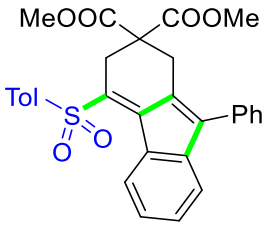
A 5 mL MW tube equipped with a magnetic stirring bar and a rubber septum was charged with sodium sulfinate salt (0.1 mmol), $Cu(OTf)_2$ (0.1 mmol), and starting material (0.05 mmol). After purging with argon, dry DCE (2mL) was added into the MW tube, which was then sealed. The reaction mixture was stirred at 100 ℃ for 16 hours. After the reaction, the product was purified directly via column chromatography (silica gel 230–400 mesh, hexanes/EtOAc).

9-Phenyl-2,4-ditosyl-2,3-dihydro-1*H*-indeno[2,1-*c*]pyridine (2.14)



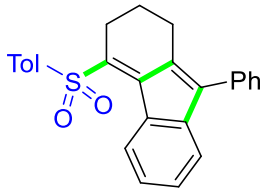
9-Phenyl-2,4-ditosyl-2,3-dihydro-1*H*-indeno[2,1-*c*]pyridine was synthesized according to general procedure B. Yellow crystal. Yield = 83%; R_f = 0.2 (EtOAc : hexane = 1 : 4); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.57–8.58 (m, 1H), 7.92 (d, *J* = 8.1 Hz, 2H), 7.07–7.54 (m, 14H), 4.38 (s, 2H), 4.29 (s, 2H), 2.48 (s,3H), 2.25 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 145.5, 143.9, 143.8, 143.3, 143.1, 134.1, 133.8, 132.3, 130.8, 130.3, 130.1, 129.5, 128.3, 128.2, 127.9, 127.5, 126.9, 120.4, 46.9. 43.5, 29.7, 21.7, 21.3; HRMS calculated for $C_{32}H_{28}NO_4S_2$ (M+H) 554.1453; found: 554.1454.

Dimethyl 9-phenyl-4-tosyl-1*H*-fluorene-2,2(3*H*)-dicarboxylate (2.18)



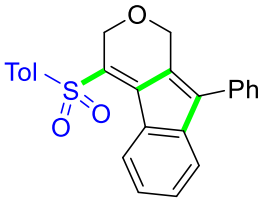
Dimethyl 9-phenyl-4-tosyl-1*H*-fluorene-2,2(3*H*)-dicarboxylate was synthesized according to general procedure B. Yellow crystal. Yield = 85%; R_f = 0.43 (EtOAc : hexane = 2 : 3); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.65–8.68 (m, 1H), 7.95 (d, *J* = 8.4 Hz, 2H), 7.33–7.51 (m, 7H), 7.17–7.22 (m, 2H), 7.06–7.09 (m, 1H), 3.59 (s, 6H), 3.39 (s, 2H), 3.13 (s, 2H), 2.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 170.0, 145.0, 144.7, 144.2, 137.5, 135.9, 133.1, 131.2, 131.1, 129.9, 129.8, 128.8, 128.5, 128.4, 127.4, 126.6, 120.1, 55.6, 53.0, 34.6, 29.2, 21.7; HRMS calculated for $C_{30}H_{26}O_6S$ (M+NH_4) 532.1791; found: 532.1788.

9-Phenyl-4-tosyl-2,3-dihydro-1*H*-fluorene (2.19)



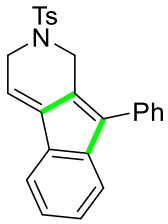
9-Phenyl-4-tosyl-2,3-dihydro-1*H*-fluorene was synthesized according to general procedure B. Yellow crystal. Yield = 67%; R_f = 0.4 (EtOAc : hexane = 1 : 4); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.72–8.74 (m, 1H), 7.88 (d, *J* = 8.4 Hz, 2H), 7.11–7.49 (m, 10H), 2.71 (t, *J* = 6 Hz, 2H), 2.58 (t, *J* = 6 Hz, 2H), 2.43 (s, 3H), 1.81 (quintet, *J* = 6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.6, 144.4, 144.3, 141.3, 140.0, 137.6, 135.0, 133.7, 131.3, 129.7, 129.4, 128.6, 128.4, 128.2, 127.9, 127.3, 125.9, 119.4, 29.7, 24.0, 23.6, 21.5; HRMS calculated for $C_{26}H_{23}O_2S$ (M+H) 399.1412; found: 399.1413.

9-Phenyl-4-tosyl-1,3-dihydroindeno[2,1-*c*]pyran (2.20)



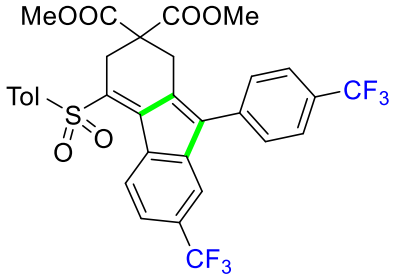
9-Phenyl-4-tosyl-1,3-dihydroindeno[2,1-*c*]pyran was synthesized according to general procedure B. Yellow crystal. Yield = 37%; R_f = 0.3 (EtOAc : hexane = 1 : 6); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.76–8.78 (m, 1H), 7.88 (d, J = 8.4 Hz, 2H), 7.90 (d, *J* = 8.1 Hz,2H), 7.23–7.50 (m, 10H), 4.63 (s, 2H), 4.60 (s, 2H), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) –145.2, 144.2, 142.4, 140.8, 137.5, 136.8, 132.7, 131.1, 130.1, 130.0, 128.8, 128.7, 128.5, 128.3, 127.7, 127.2, 126.9, 120.5, 65.9, 64.1, 21.7; HRMS calculated for $C_{25}H_{21}O_3S$ (M+H) 401.1211; found: 401.1206.

9-Phenyl-2-tosyl-2,3-dihydro-1H-indeno[2,1-*c*]pyridine (2.15)



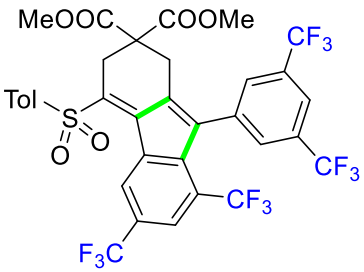
9-Phenyl-2-tosyl-2,3-dihydro-1H-indeno[2,1-*c*]pyridine was a side product from the reaction of synthesizing compound **2.15** and exhibited characterization data identical to those previously reported.[68] Pale yellow crystal. Yield < 15%; R_f = 0.3 (EtOAc : hexane = 1 : 4); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.18–7.64 (m, 13H), 6.63 (t, *J* = 3.9 Hz, 1H), 4.47 (s, 2H), 4.19 (d, *J* = 3.9 Hz, 2H), 2.32 (s,3H).

Dimethyl 4-tosyl-7-(trifluoromethyl)-9-(4-(trifluoromethyl)phenyl)-1H-fluorene- 2,2 (3H)-dicarboxylate (2.37)



Dimethyl 4-tosyl-7-(trifluoromethyl)-9-(4-(trifluoromethyl)phenyl)-1H-fluorene-2,2 (3H)-dicarboxylate was synthesized according to general procedure B. Yellow crystal. Yield = 74%; R_f = 0.15 (EtOAc : hexane = 1 : 3); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.88 (d, *J* = 8.1 Hz, 1H), 7.94 (d, *J* = 8.1 Hz, 2H), 7.79 (d, *J* = 8.1 Hz, 2H), 7.56 (d, *J* = 8.1 Hz, 2H), 7.49 (d, *J* = 8.1 Hz, 1H), 7.38 (d, *J* = 8.1 Hz, 2H), 7.23 (s, 1H), 3.59 (s, 6H), 3.40 (s, 2H), 3.12 (s, 2H), 2.45 (s,3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.5, 145.2, 144.9, 141.8, 139.9, 136.6, 136.1, 134.0, 131.0 (q, *J* = 32.2 Hz), 130.0, 128.8, 127.5, 125.9–126.0 (m), 123.8, 116.0, 115.9, 55.3, 53.1, 34.6, 29.0, 21.6; HRMS calculated for $C_{32}H_{25}F_6O_6S$ (M+H) 651.1272; found: 651.1271.

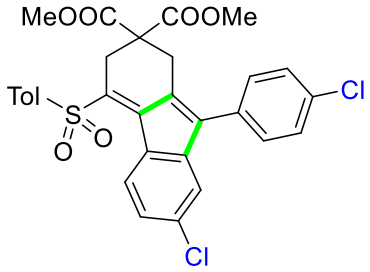
Dimethyl 9-(3,5-bis(trifluoromethyl)phenyl)-4–tosyl-6,8-bis(trifluoromethyl)-1*H*-fluorene-2,2(3*H*)-dicarboxylate (2.38)



Dimethyl 9-(3,5-bis(trifluoromethyl)phenyl)-4-tosyl-6,8-bis(trifluoromethyl)-1*H*-fluorene-2,2(3*H*)–dicarboxylate was synthesized according to general procedure B.

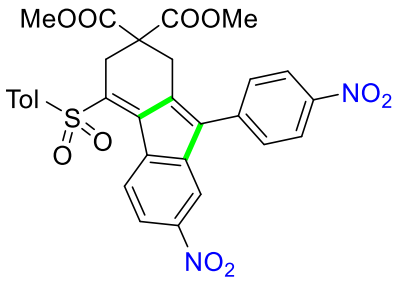
Yellow crystal. Yield = 41%; R_f = 0.25 (EtOAc : hexane = 1 : 3); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.19 (s, 1H), 7.94–7.97 (m, 3H), 7.79 (s, 1H), 7.65 (s, 2H), 7.40 (d, *J* = 8.1 Hz, 2H), 3.67 (s, 6H), 3.48 (s, 2H), 2.83, (s, 2H), 2.45 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.1, 145.8, 144.1, 141.0, 139.5, 138.8, 136.0, 135.8, 133.1, 131.7 (q, *J* = 33.6 Hz), 130.1, 129.3, 128.3, 127.7 (m), 127.6, 124.8, 122.3, 121.2, 55.3, 53.3, 35.1, 29.1, 21.6; HRMS calculated for $C_{34}H_{23}F_{12}O_6S$ (M+H) 787.1014; found: 787.1018.

Dimethyl 7-chloro-9-(4-chlorophenyl)-4-tosyl-1H-fluorene-2, 2(3H)-dicarboxylate (2.39)



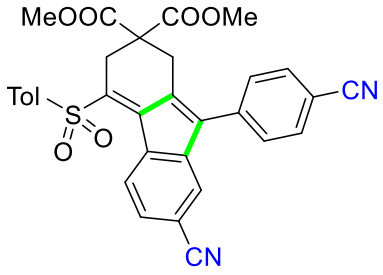
Dimethyl 7-chloro-9-(4-chlorophenyl)-4-tosyl-1H-fluorene-2,2(3H)-dicarboxylate was synthesized according to general procedure B. Yellow crystal. Yield = 65%; R_f = 0.3 (EtOAc : hexane = 1 : 3); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.64 (d, *J* = 8.4 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 2H), 7.46–7.49 (m, 2H), 7.33–7.37 (m, 4H), 7.16 (dd, *J* = 8.4 Hz, *J* = 2.1 Hz, 1H), 6.99 (d, *J* = 2.1 Hz, 1H), 3.58 (s, 6H), 3.35 (s, 2H), 3.08 (s, 2H), 2.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.6, 146.4, 144.9, 142.3, 141.8, 137.3, 136.9, 136.1, 134.6, 133.2, 130.8, 129.9, 129.7, 129.3, 129.2, 127.4, 126.1, 120.1, 55.35, 53.0, 34.4, 29.2, 29.1, 21.6; HRMS calculated for $C_{30}H_{25}Cl_2O_6S$ (M+H) 583.0743; found: 583.0743.

Dimethyl 7-nitro-9-(4-nitrophenyl)-4-tosyl-1H-fluorene-2,2(3H)-dicarboxylate (2.40)



Dimethyl 7-nitro-9-(4-nitrophenyl)-4-tosyl-1H-fluorene-2,2(3H)-dicarboxylate was synthesized according to general procedure B. Yellow crystal. Yield = 50%; R_f = 0.3 (EtOAc : hexane = 1 : 3); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.98 (d, *J* = 8.4 Hz, 1H), 8.42 (d, *J* = 8.4 Hz, 2H), 8.13 (dd, *J* = 8.4 Hz, J = 2.1 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 2H), 7.81 (d, *J* = 2.1 Hz, 1H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 3.60 (s, 6H), 3.38 (s, 2H), 3.13 (s, 2H), 2.47 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169. 4, 148.7, 148.0, 145.8, 145.3, 142.7, 140.5, 140.2, 138.7, 136.3, 136.1,130.3, 129.5, 129.0, 127.8, 124.6, 122.3, 114.0, 55.3, 53.4, 34.9, 29.3, 21.8; HRMS calculated for $C_{30}H_{25}N_2O_{10}S$ ($M+NH_4$) 622.1488; found: 622.1490.

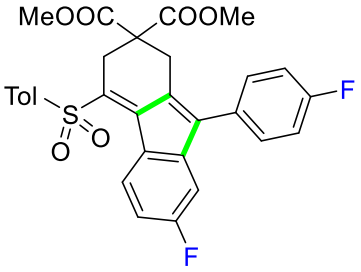
Dimethyl 7-cyano-9-(4-cyanophenyl) -4-tosyl-1*H*-fluorene -2,2 (3*H*)-dicarboxylate (2.41)



Dimethyl 7-cyano-9-(4-cyanophenyl)-4-tosyl-1H-fluorene-2,2(3H)-dicarboxylate was synthesized according to general procedure B. Yellow crystal. Yield = 79%; R_f = 0.1 (EtOAc : hexane = 1 : 3); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.90 (d, *J* = 8.1 Hz, 1H), 7.90 (d,

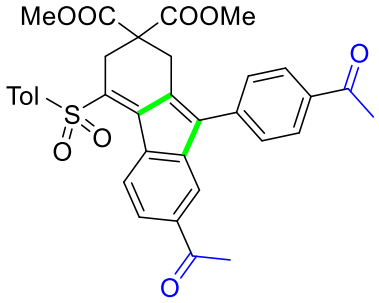
J = 8.1 Hz, 2H), 7.82 (d, *J* = 8.1 Hz, 2H), 7.54 (d, *J* = 8.1 Hz, 3H), 7.39 (d, *J* = 8.1 Hz, 2H), 3.59 (s, 6H), 3.36 (s, 2H), 3.09 (s, 2H), 2.46 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.3, 145.6, 144.5, 141.6, 141.0, 140.4, 136.8, 136.1, 134.9, 134.6, 132.8, 131.0, 130.1, 129.2, 129.1, 128.8, 127.6, 122.1, 118.4, 118.2, 113.1, 112.7, 55.2, 53.2, 34.7, 29.1, 21.6; HRMS calculated for $C_{32}H_{25}N_2O_6S$ (M+H) 565.1430; found: 565.1428.

Dimethyl 7-fluoro-9-(4-fluorophenyl)-4-tosyl- 1*H*-fluorene-2,2 (3*H*) - dicarboxylate (2.42)



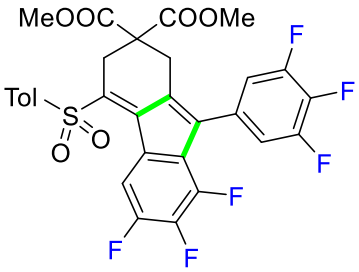
Dimethyl 7-fluoro-9-(4-fluorophenyl)-4-tosyl-1*H*-fluorene-2,2(3*H*)-dicarboxylate was synthesized according to general procedure B. Yellow crystal. Yield = 85%; R_f = 0.6 (EtOAc : hexane = 1 : 2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.66–8.71 (m, 1H), 7.92 (d, *J* = 8.4 Hz, 2H), 7.35–7.42 (m, 4H), 7.19 (t, *J* = 8.4 Hz, 2H), 6.84 (td, *J* = 8.4 Hz, *J* = 2.4, 1H), 6.73 (dd, *J* = 8.4 Hz, *J* = 2.4 Hz, 1H), 3.58 (s, 6H), 3.36 (s, 2H), 3.09 (s, 2H), 2.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.7, 165.0 (d, *J* = 105.0 Hz), 161.7 (d, *J* = 105.0 Hz), 147.6 (d, *J* = 8.9 Hz), 144.8, 142.4, 141.7 (d, *J* = 2.1 Hz), 137.1, 136.2 (d, *J* = 2.1 Hz), 133.3, 129.5-130.2 (m), 128.4 (d, *J* = 3.3 Hz), 127.3, 126.7 (d, *J* = 3.3 Hz), 115.9 (d, *J* = 22.5 Hz), 112.3 (d, *J* = 22.5 Hz), 108.0, 107.6, 55.4, 53.0, 34.3, 29.1, 21.6; HRMS calculated for $C_{30}H_{25}F_2O_6S$ (M+H) 551.1333; found: 551.1334.

Dimethyl 7-acetyl-9-(4-acetylphenyl)-4-tosyl- 1*H*- fluorene-2,2 (3*H*) - dicarboxylate (2.43)



Dimethyl 7-acetyl-9-(4-acetylphenyl)-4-tosyl-1H-fluorene-2,2(3*H*)-dicarboxylate was synthesized according to general procedure B. Yellow crystal. Yield = 71%; R_f = 0.15 (EtOAc : hexane = 1 : 3); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.83 (d, *J* = 8.1 Hz, 1H), 8.10 (d, *J* = 8.1 Hz, 2H), 7.93 (d, *J* = 8.1 Hz, 2H), 7.81 (d, *J* = 8.1 Hz, H), 7.61 (s, 1H), 7.53 (d, *J* = 8.1 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 3.59 (s, 6H), 3.38 (s, 2H), 3.12 (s, 2H), 2.67 (s, 3H), 2.57 (s, 3H), 2.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 197.6, 197.5, 169.7, 145.2, 144.9, 142.5, 142.4, 139.4, 137.9, 137.5, 137.1, 136.8, 135.2, 133.5, 130.0, 129.0, 128.8, 128.4, 127.7, 127.6, 118.7, 55.4, 53.2, 34.8, 29.2, 26.8, 21.7; HRMS calculated for $C_{34}H_{31}O_8S$ (M+H) 599.1742; found: 599.1734.

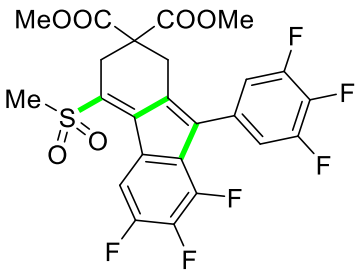
Dimethyl 6, 7, 8-trifluoro-4-tosyl–9-(3,4,5-trifluorophenyl) -1*H* –fluorene-2,2(3*H*) -dicarboxylate (2.44)



Dimethyl 6,7,8-trifluoro-4-tosyl-9- (3,4,5-trifluorophenyl) -1*H*- fluorene -2,2 (3*H*)-dicarboxylate was synthesized according to general procedure B. Yellow crystal. Yield =

90%; R_f = 0.35 (EtOAc : hexane = 1 : 3); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.57–8.62 (m, 1H), 7.87 (d, *J* = 8.1 Hz, 2H), 7.38 (d, *J* = 8.1 Hz, 2H), 7.00–7.05 (m, 2H), 3.60 (s, 6H), 3.31 (s, 2H), 2.95 (s, 2H), 2.46 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.2, 145.6, 140.8, 136.0, 128.9 (d, *J* = 187.5 Hz), 114.5 (d, *J* = 3.0 Hz), 114.2 (d, *J* = 3.0 Hz), 113.2–112.9 (m), 55.2, 53.1, 34.6, 28.9, 21.6; HRMS calculated for $C_{30}H_{21}F_6O_6S$ (M+H) 623.0964; found: 623.0958.

Dimethyl 6,7,8-trifluoro-4-(methylsulfonyl) -9- (3,4,5-trifluorophenyl) -1*H*- fluorene -2,2(3*H*)-dicarboxylate (2.46)



Dimethyl 6,7,8-trifluoro-4-(methylsulfonyl)-9-(3,4,5-trifluorophenyl)-1H-fluorene -2,2 (3H)-dicarboxylate was synthesized according to general procedure B. Yellow crystal. Yield = 53%; R_f = 0.07 (EtOAc: hexane = 15 : 85); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.34 (dd, *J* = 6.6 Hz, *J* = 6.6 Hz, 1H), 6.95–7.04 (m, 2H), 3.74 (s, 6H), 3.38 (s, 2H), 3.19 (s. 3H), 3.06 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.5, 152.7–152.9 (m), 149.4–149.6 (m), 143.1, 141.7, 141.1, 140.8, 137.8, 134.3 (d, *J* = 3.0 Hz), 128.3–128.7 (m), 127.0–127.2 (m), 126.1–126.4 (m), 113.9 (d, *J* = 2.8 Hz), 113.6 (d, *J* = 3.0 Hz) ,113.0–113.2 (m), 55.8, 53.5, 41.5, 34.2, 28.9; HRMS calculated for $C_{24}H_{17}F_6O_6S$ (M+H) 547.0649; found: 547.0645.

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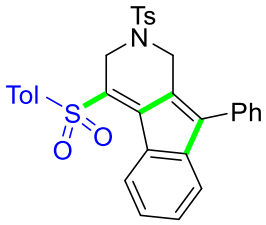
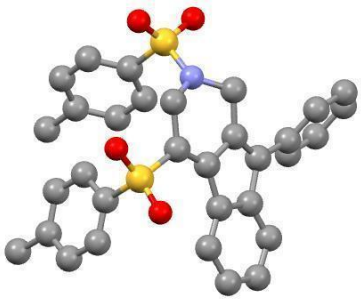
Appendix

Crystallographic data for 9-phenyl-2,4-ditosyl-2,3-dihydro-1*H*-indeno[2,1-*c*]pyridine



2.14



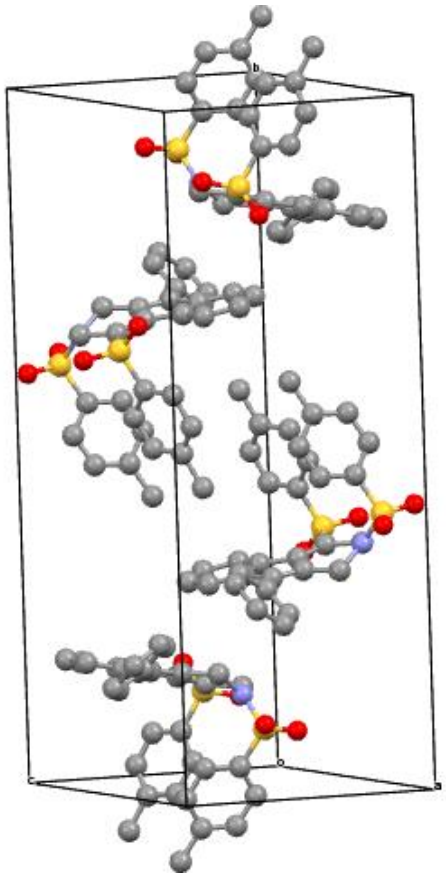


Table 3 Crystal data and structure refinement for $C_{32}H_{27}NO_4S_2$

Empirical formula	$C_{32}H_{27}NO_4S_2$
Formula weight	553.66 g/mol
Temperature	296(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$\boldsymbol{P}2_1/c$
Unit cell dimensions	a = 10.9530(2) Å, b = 26.2844(6) Å, c = 9.7874(2) Å β= 105.7060(14) °
Volume	2712.52(10) $Å^3$
Z	4
Density (calculated)	1.356 g/cm^3
Absorption coefficient	0.236 mm^{-1}
F(000)	1160
Crystal size	0.400 x 0.040 x 0.010 mm^3
Theta range for data collection	1.549 to 25.998 °.
Index ranges	-13<=h<=12, -32<=k<=32, -12<=l<=12
Reflections collected	23247
Independent reflections	5318 [$R_{(int)}$ = 0.0738]
Completeness to theta = 25.242 °	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.745986 and 0.695736
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5318 / 0 / 352
Goodness-of-fit on F^2	1.038
Final R indices [I>2σ (I)]	R1 = 0.0576, wR2 = 0.0898
R indices (all data)	R1 = 0.1456, wR2 = 0.1205
Largest diff. peak and hole	0.258 and -0.260 $e.Å^{-3}$

Table 4 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^3$x 10^3) for $C_{32}H_{27}NO_4S_2$

	x	y	z	U(eq)
S(1)	4633(1)	3614(1)	808(1)	52(1)
S(2)	9298(1)	3990(1)	1327(1)	59(1)
O(1)	3768(2)	3242(1)	1044(3)	63(1)
O(2)	4657(2)	3724(1)	-627(2)	71(1)
O(3)	10569(2)	3876(1)	2102(3)	79(1)
O(4)	8990(3)	4070(1)	-170(3)	81(1)
N(1)	8439(3)	3526(1)	1626(3)	50(1)
C(1)	11783(4)	2846(2)	8046(4)	62(1)
C(2)	11443(4)	2586(2)	6787(4)	57(1)
C(3)	10957(4)	3187(2)	8376(4)	58(1)
C(4)	9780(4)	3271(1)	7447(4)	50(1)
C(5)	10271(3)	2672(1)	5841(4)	49(1)
C(6)	9418(3)	3013(1)	6150(3)	42(1)
C(7)	8178(3)	3106(1)	5135(4)	39(1)
C(8)	7957(3)	3186(1)	3731(4)	40(1)
C(9)	8880(3)	3186(1)	2848(3)	47(1)
C(10)	7133(3)	3478(2)	809(4)	57(1)
C(11)	6211(3)	3444(1)	1727(4)	42(1)
C(12)	6606(3)	3290(1)	3083(4)	42(1)
C(13)	5980(3)	3217(1)	4242(4)	42(1)
C(14)	4725(3)	3207(1)	4286(4)	52(1)
C(15)	4458(4)	3094(2)	5563(4)	60(1)
C(16)	5404(4)	2999(1)	6762(4)	59(1)
C(17)	6661(4)	3004(1)	6739(4)	51(1)
C(18)	6944(3)	3112(1)	5484(4)	42(1)
C(19)	4342(3)	4192(1)	1577(4)	48(1)
C(20)	3291(4)	4241(2)	2063(4)	67(1)
C(21)	5109(4)	4606(2)	1606(5)	80(1)
C(22)	4843(4)	5062(2)	2154(5)	87(2)
C(23)	3032(4)	4700(2)	2596(5)	76(1)
C(24)	3809(4)	5113(2)	2678(5)	70(1)
C(25)	3538(5)	5613(2)	3288(6)	112(2)
C(26)	8828(3)	4540(1)	2074(4)	51(1)
C(27)	8730(5)	4538(2)	3431(4)	87(2)
C(28)	8578(5)	4980(2)	1323(5)	83(1)
C(29)	8271(5)	5413(2)	1949(5)	92(2)
C(30)	8425(5)	4974(2)	4029(5)	91(2)
C(31)	8184(4)	5421(2)	3296(5)	68(1)

C(32)	7844(5)	5895(2)	3960(5)	96(2)
H(1B)	12575	2791	8679	75
H(2B)	11999	2352	6568	68
H(3B)	11193	3362	9232	69
H(4B)	9224	3500	7685	60
H(5A)	10051	2498	4981	59
H(9A)	9704	3298	3419	57
H(9B)	8968	2843	2519	57
H(10A)	7044	3175	223	68
H(10B)	6909	3769	182	68
H(14A)	4074	3274	3474	62
H(15A)	3618	3084	5599	72
H(16A)	5202	2930	7607	71
H(17A)	7304	2935	7557	61
H(20A)	2754	3965	2034	80
H(21A)	5814	4579	1252	96
H(22A)	5374	5340	2170	104
H(23A)	2306	4731	2909	91
H(25A)	4188	5854	3253	169
H(25B)	2730	5739	2743	169
H(25C)	3522	5564	4255	169
H(27A)	8872	4239	3956	104
H(28A)	8615	4989	385	100
H(29A)	8117	5711	1420	110
H(30A)	8380	4965	4964	109
H(32A)	7831	5824	4918	144
H(32B)	8461	6155	3962	144
H(32C)	7021	6011	3426	144

U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

Table 5 Bond lengths [Å] and angles [°] for $C_{32}H_{27}NO_4S_2$

S(1)-O(1)	1.424(3)
S(1)-O(2)	1.440(2)
S(1)-C(19)	1.761(4)
S(1)-C(11)	1.776(3)
S(2)-O(3)	1.425(3)
S(2)-O(4)	1.427(3)
S(2)-N(1)	1.616(3)
S(2)-C(26)	1.758(4)
N(1)-C(10)	1.443(4)
N(1)-C(9)	1.465(4)
C(1)-C(2)	1.370(5)
C(1)-C(3)	1.373(5)
C(1)-H(1B)	0.9300
C(2)-C(5)	1.383(5)
C(2)-H(2B)	0.9300
C(3)-C(4)	1.379(5)
C(3)-H(3B)	0.9300
C(4)-C(6)	1.398(4)
C(4)-H(4B)	0.9300
C(5)-C(6)	1.386(4)
C(5)-H(5A)	0.9300
C(6)-C(7)	1.471(4)
C(7)-C(8)	1.345(4)
C(7)-C(18)	1.481(4)
C(8)-C(12)	1.470(4)
C(8)-C(9)	1.497(4)
C(9)-H(9A)	0.9700
C(9)-H(9B)	0.9700
C(10)-C(11)	1.524(4)
C(10)-H(10A)	0.9700
C(10)-H(10B)	0.9700
C(11)-C(12)	1.343(4)
C(12)-C(13)	1.489(4)
C(13)-C(14)	1.387(4)
C(13)-C(18)	1.404(4)
C(14)-C(15)	1.390(5)
C(14)-H(14A)	0.9300
C(15)-C(16)	1.362(5)
C(15)-H(15A)	0.9300
C(16)-C(17)	1.383(5)
C(16)-H(16A)	0.9300
C(17)-C(18)	1.375(4)

C(17)-H(17A)	0.9300
C(19)-C(20)	1.366(5)
C(19)-C(21)	1.371(5)
C(20)-C(23)	1.375(5)
C(20)-H(20A)	0.9300
C(21)-C(22)	1.376(6)
C(21)-H(21A)	0.9300
C(22)-C(24)	1.371(5)
C(22)-H(22A)	0.9300
C(23)-C(24)	1.369(5)
C(23)-H(23A)	0.9300
C(24)-C(25)	1.504(6)
C(25)-H(25A)	0.9600
C(25)-H(25B)	0.9600
C(25)-H(25C)	0.9600
C(26)-C(28)	1.359(5)
C(26)-C(27)	1.362(5)
C(27)-C(30)	1.368(6)
C(27)-H(27A)	0.9300
C(28)-C(29)	1.376(6)
C(28)-H(28A)	0.9300
C(29)-C(31)	1.348(5)
C(29)-H(29A)	0.9300
C(30)-C(31)	1.365(6)
C(30)-H(30A)	0.9300
C(31)-C(32)	1.498(6)
C(32)-H(32A)	0.9600
C(32)-H(32B)	0.9600
C(32)-H(32C)	0.9600

O(1)-S(1)-O(2)	118.98(16)
O(1)-S(1)-C(19)	108.55(17)
O(2)-S(1)-C(19)	107.28(18)
O(1)-S(1)-C(11)	110.07(16)
O(2)-S(1)-C(11)	105.78(16)
C(19)-S(1)-C(11)	105.34(16)
O(3)-S(2)-O(4)	120.14(18)
O(3)-S(2)-N(1)	106.12(17)
O(4)-S(2)-N(1)	108.11(17)
O(3)-S(2)-C(26)	107.77(18)
O(4)-S(2)-C(26)	106.90(18)
N(1)-S(2)-C(26)	107.18(16)
C(10)-N(1)-C(9)	117.2(3)
C(10)-N(1)-S(2)	120.3(3)

C(9)-N(1)-S(2)	121.9(2)
C(2)-C(1)-C(3)	120.1(4)
C(2)-C(1)-H(1B)	120.0
C(3)-C(1)-H(1B)	120.0
C(1)-C(2)-C(5)	119.9(4)
C(1)-C(2)-H(2B)	120.1
C(5)-C(2)-H(2B)	120.1
C(1)-C(3)-C(4)	120.5(4)
C(1)-C(3)-H(3B)	119.8
C(4)-C(3)-H(3B)	119.8
C(3)-C(4)-C(6)	120.4(3)
C(3)-C(4)-H(4B)	119.8
C(6)-C(4)-H(4B)	119.8
C(2)-C(5)-C(6)	121.2(3)
C(2)-C(5)-H(5A)	119.4
C(6)-C(5)-H(5A)	119.4
C(5)-C(6)-C(4)	118.0(3)
C(5)-C(6)-C(7)	120.9(3)
C(4)-C(6)-C(7)	121.0(3)
C(8)-C(7)-C(6)	126.4(3)
C(8)-C(7)-C(18)	108.1(3)
C(6)-C(7)-C(18)	125.4(3)
C(7)-C(8)-C(12)	110.6(3)
C(7)-C(8)-C(9)	128.8(3)
C(12)-C(8)-C(9)	120.6(3)
N(1)-C(9)-C(8)	110.2(3)
N(1)-C(9)-H(9A)	109.6
C(8)-C(9)-H(9A)	109.6
N(1)-C(9)-H(9B)	109.6
C(8)-C(9)-H(9B)	109.6
H(9A)-C(9)-H(9B)	108.1
N(1)-C(10)-C(11)	113.2(3)
N(1)-C(10)-H(10A)	108.9
C(11)-C(10)-H(10A)	108.9
N(1)-C(10)-H(10B)	108.9
C(11)-C(10)-H(10B)	108.9
H(10A)-C(10)-H(10B)	107.8
C(12)-C(11)-C(10)	120.8(3)
C(12)-C(11)-S(1)	125.8(3)
C(10)-C(11)-S(1)	113.3(2)
C(11)-C(12)-C(8)	120.0(3)
C(11)-C(12)-C(13)	134.6(3)
C(8)-C(12)-C(13)	105.3(3)
C(14)-C(13)-C(18)	119.3(3)

C(14)-C(13)-C(12)	133.7(3)
C(18)-C(13)-C(12)	107.0(3)
C(13)-C(14)-C(15)	118.9(3)
C(13)-C(14)-H(14A)	120.5
C(15)-C(14)-H(14A)	120.5
C(16)-C(15)-C(14)	121.1(3)
C(16)-C(15)-H(15A)	119.4
C(14)-C(15)-H(15A)	119.4
C(15)-C(16)-C(17)	120.9(3)
C(15)-C(16)-H(16A)	119.6
C(17)-C(16)-H(16A)	119.6
C(18)-C(17)-C(16)	118.8(4)
C(18)-C(17)-H(17A)	120.6
C(16)-C(17)-H(17A)	120.6
C(17)-C(18)-C(13)	121.0(3)
C(17)-C(18)-C(7)	130.1(3)
C(13)-C(18)-C(7)	108.8(3)
C(20)-C(19)-C(21)	119.2(4)
C(20)-C(19)-S(1)	119.8(3)
C(21)-C(19)-S(1)	120.9(3)
C(19)-C(20)-C(23)	119.7(4)
C(19)-C(20)-H(20A)	120.2
C(23)-C(20)-H(20A)	120.2
C(19)-C(21)-C(22)	120.4(4)
C(19)-C(21)-H(21A)	119.8
C(22)-C(21)-H(21A)	119.8
C(24)-C(22)-C(21)	121.0(4)
C(24)-C(22)-H(22A)	119.5
C(21)-C(22)-H(22A)	119.5
C(24)-C(23)-C(20)	122.0(4)
C(24)-C(23)-H(23A)	119.0
C(20)-C(23)-H(23A)	119.0
C(23)-C(24)-C(22)	117.6(4)
C(23)-C(24)-C(25)	122.0(4)
C(22)-C(24)-C(25)	120.4(4)
C(24)-C(25)-H(25A)	109.5
C(24)-C(25)-H(25B)	109.5
H(25A)-C(25)-H(25B)	109.5
C(24)-C(25)-H(25C)	109.5
H(25A)-C(25)-H(25C)	109.5
H(25B)-C(25)-H(25C)	109.5
C(28)-C(26)-C(27)	118.2(4)
C(28)-C(26)-S(2)	120.9(3)
C(27)-C(26)-S(2)	120.9(3)

C(26)-C(27)-C(30)	120.6(4)
C(26)-C(27)-H(27A)	119.7
C(30)-C(27)-H(27A)	119.7
C(26)-C(28)-C(29)	120.1(4)
C(26)-C(28)-H(28A)	120.0
C(29)-C(28)-H(28A)	120.0
C(31)-C(29)-C(28)	122.7(4)
C(31)-C(29)-H(29A)	118.7
C(28)-C(29)-H(29A)	118.7
C(31)-C(30)-C(27)	122.1(4)
C(31)-C(30)-H(30A)	119.0
C(27)-C(30)-H(30A)	119.0
C(29)-C(31)-C(30)	116.4(4)
C(29)-C(31)-C(32)	122.0(4)
C(30)-C(31)-C(32)	121.6(4)
C(31)-C(32)-H(32A)	109.5
C(31)-C(32)-H(32B)	109.5
H(32A)-C(32)-H(32B)	109.5
C(31)-C(32)-H(32C)	109.5
H(32A)-C(32)-H(32C)	109.5
H(32B)-C(32)-H(32C)	109.5

Table 6 Anisotropic displacement parameters ($Å^3 x\ 10^3$) for $C_{32}H_{27}NO_4S_2$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	41(1)	60(1)	52(1)	-8(1)	7(1)	-2(1)
S(2)	58(1)	64(1)	66(1)	-2(1)	37(1)	-6(1)
O(1)	49(2)	58(2)	78(2)	-12(1)	8(1)	-16(1)
O(2)	66(2)	101(2)	45(2)	-2(2)	12(1)	6(2)
O(3)	45(2)	83(2)	118(2)	-1(2)	37(2)	-5(2)
O(4)	117(3)	85(2)	61(2)	0(2)	58(2)	-7(2)
N(1)	41(2)	60(2)	53(2)	3(2)	20(2)	-3(2)
C(1)	50(3)	70(3)	59(3)	11(2)	2(2)	2(2)
C(2)	46(2)	59(3)	65(3)	4(2)	16(2)	15(2)
C(3)	62(3)	60(3)	46(2)	-2(2)	6(2)	-9(2)
C(4)	59(3)	46(2)	49(2)	-4(2)	20(2)	2(2)
C(5)	47(2)	52(3)	49(2)	-4(2)	15(2)	6(2)
C(6)	45(2)	35(2)	47(2)	0(2)	15(2)	-1(2)
C(7)	40(2)	31(2)	48(2)	-4(2)	15(2)	2(2)
C(8)	34(2)	39(2)	49(2)	-8(2)	15(2)	1(2)
C(9)	41(2)	50(2)	54(2)	-4(2)	18(2)	4(2)
C(10)	50(2)	75(3)	47(2)	-2(2)	17(2)	-1(2)
C(11)	38(2)	43(2)	47(2)	-10(2)	13(2)	-4(2)
C(12)	45(2)	39(2)	48(2)	-9(2)	19(2)	-4(2)
C(13)	41(2)	38(2)	51(2)	-7(2)	21(2)	-3(2)
C(14)	46(2)	54(3)	59(2)	-2(2)	21(2)	-4(2)
C(15)	47(3)	63(3)	81(3)	-6(2)	34(2)	-8(2)
C(16)	70(3)	53(3)	68(3)	0(2)	45(3)	0(2)
C(17)	61(3)	46(2)	53(2)	2(2)	26(2)	7(2)
C(18)	45(2)	36(2)	50(2)	-5(2)	22(2)	2(2)
C(19)	39(2)	47(2)	58(2)	2(2)	12(2)	-4(2)
C(20)	62(3)	53(3)	94(3)	-6(2)	36(3)	-10(2)
C(21)	56(3)	62(3)	133(4)	-7(3)	42(3)	-8(2)
C(22)	69(3)	53(3)	142(5)	-11(3)	36(3)	-14(3)
C(23)	79(3)	65(3)	98(3)	-4(3)	51(3)	-1(3)
C(24)	73(3)	52(3)	90(3)	-5(2)	29(3)	0(3)
C(25)	142(5)	57(3)	150(5)	-18(3)	59(4)	7(3)
C(26)	57(3)	52(3)	50(2)	-1(2)	22(2)	-8(2)
C(27)	149(5)	56(3)	68(3)	8(3)	52(3)	9(3)
C(28)	129(4)	64(3)	62(3)	6(3)	37(3)	-4(3)
C(29)	143(5)	54(3)	80(3)	9(3)	33(3)	10(3)
C(30)	157(5)	62(3)	66(3)	-8(3)	52(3)	0(3)
C(31)	80(3)	55(3)	68(3)	-11(3)	20(2)	-5(2)
C(32)	126(4)	66(3)	98(4)	-15(3)	35(3)	4(3)

The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U_{11} + ... + 2 h k a^* b^* U_{12}]$