

SYNTHESIS OF ARYL YNOL ETHERS AND THEIR SYNTHETIC APPLICATIONS

APPROVED BY SUPERVISORY COMMITTEE

To my family

SYNTHESIS OF ARYL ENOL ETHERS AND THEIR SYNTHETIC APPLICATIONS

By

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SYNTHESIS OF ARYL YNOL ETHERS AND THEIR SYNTHETIC APPLICATIONS

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Joseph Martin Ready, Ph.D.

Ynol ethers are known as very important synthetic intermediates that are widely used in the syntheses of natural products and pharmaceuticals. The ynol ethers have also been used as ideal precursors of ketenes and surrogates of alkynes with a higher oxidation state in many reactions.

However, few studies focused on the applications of aryl ynol ethers, because their synthetic methods are limited. To make aryl ynol ethers practical synthetic intermediates, we developed a direct and efficient method to synthesize aryl ynol ethers using coupling reactions between aryl iodides and alkoxyacetylides. The aryl ynol ethers participate in a [1,5]-hydride shift, which extrude alkenes to generate aryl ketenes. The aryl ketene intermediates were

trapped with multiple nucleophiles to provide different aryl acetic acid derivatives and benzyl ketones.

Additionally, we employed the aryl ketenes in a 6π electrocyclic ring closure reaction to yield hydroxynaphthalenes and quinolones. Moreover, we discovered a hetero-[2+2]-cycloaddition reaction between aryl ketenes and aryl ynol ethers, and the forming cyclobutenones could undergo a retro- $4\pi/6\pi$ electrocyclization reaction to afford naphthalenes. Finally, we utilized this novel electrocyclization in the synthesis of dictyodendrins F, H, and I. In particular, we used the hetero-[2+2]-cycloaddition reaction between aryl ynol ethers to form cyclobutenone rings followed by the rearrangement to produce a highly substituted carbazole. Subsequently, the *N*-acylation and the oxidative cyclization furnished the final skeletons of dictyodendrins.

Our synthetic methodology of aryl ynol ethers largely broadens the application of ynol ethers and facilitates the syntheses of natural products and pharmaceuticals.

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PRIOR PUBLICATIONS

1. Wenhan Zhang, Joseph M. Ready. “The Ketene-Surrogate Coupling: Catalytic Conversion of Aryl Iodides into Aryl Ketenes through Ynol Ethers” *Angew. Chem. Int. Ed.* **2014**, 53, 8980-8984.
2. Wenhan Zhang, Joseph M. Ready. “A Concise Total Synthesis of Dictyodendrins F, H, and I Using Aryl Ynol Ethers as Key Building Blocks” *J. Am. Chem. Soc.* **2016**, 138, 10684-10692.

LIST OF DEFINITIONS

Å – Ångström

Ac – acetyl, acetate

acac – acetylacetonate

aq. – aqueous

Bn – benzyl

Boc – tert-butyloxycarbonyl

BOM – benzyloxymethyl

br – broad

Bu – butyl

°C – degrees Celsius

calcd – calculated

cat. – catalytic

CBS – Corey-Bakshi-Shibata oxazaborolidine

Cbz – carboxybenzyl

CD – circular dichroism

CSA – camphorsulfonic acid

d – doublet

DCC – N,N'-Dicyclohexylcarbodiimide

DCM – dichloromethane

DEAD – diethyl azodicarboxylate

decomp. – decomposition

DFT – density functional theory

DIBAL – diisobutylaluminium hydride

DIPEA – N,N-diisopropylethylamine

DMAP – 4-dimethylaminopyridine

DMAS – dimethylaminosulfonyl

DMB – dimethoxybenzyl

DMDO – dimethyldioxirane

DMF – N,N-dimethylformamide

DMP – Dess-Martin periodinane

DMSO – dimethyl sulfoxide

EC₅₀ – half maximal effective concentration

equiv – equivalent

ESI – electrospray ionization

Et – ethyl

g – gram(s)

gCOSY – gradient-selected Correlation Spectroscopy

GGTase I – geranylgeranyltransferase type I

h – hour(s)

HMBC – heteronuclear multiple-bond correlation spectroscopy

HMDS – bis(trimethylsilyl)amide

HMQC – heteronuclear multiple-quantum correlation spectroscopy

HPLC – high performance liquid chromatography

Hz – hertz

IBX – 2-Iodoxybenzoic acid

IC₅₀ – half-maximal inhibitory concentration

J – coupling constant

λ – wavelength

L – liter

m – multiplet or milli

m/z – mass to charge ratio

μ – micro

MALDI – matrix-assisted laser desorption/ionization

mCPBA – m-chloroperoxybenzoic acid

Me – methyl

MHz – megahertz

min – minute(s)

mmpp – magnesium monoperoxyphthalate

mol – mole(s)

Ms – methanesulfonyl (mesyl)

M.S. – molecular sieves

NBS – N-bromosuccinimide

NCS – N-chlorosuccinimide

N.D. – not detected

NIS – N-iodosuccinimide

NMO – N-Methylmorpholine N-oxide

NMR – nuclear magnetic resonance

nOe – nuclear Overhauser effect

NOESY – nuclear Overhauser enhancement spectroscopy

[O] – oxidation

Ph – phenyl

pH – hydrogen ion concentration in aqueous solution

PIA – pyrrole-imidazole alkaloids

PP2A – protein phosphatase 2A

ppm – parts per million

ⁱPr – isopropyl

Pn – Pentyl

q – quartet

Red-Al – sodium bis(2-methoxyethoxy)aluminumhydride

ROESY – rotating-frame nuclear Overhauser effect correlation spectroscopy

r.t. – room temperature

R_f – retention factor

s – singlet

SEM – [2-(trimethylsilyl)ethoxy]methyl

SET – single –electron transfer

t – triplet

TBAF – tetrabutylammonium fluoride

TBAOxone – tetrabutylammonium Oxone

TBD – 1,5,7-triazabicyclo-[4.4.0]dec-5-ene

TBDPS – tert-butyldiphenylsilyl

TBS – tert-butyldimethylsilyl

Temp. – temperature

Teoc – trimethylsilylethyl carbamate

Tf – trifluoromethanesulfonyl

TFA – trifluoroacetic acid

TFE – trifluoroethanol

THF – tetrahydrofuran

TIPS – triisopropylsilyl

TLC – thin layer chromatography

TMS – trimethylsilyl

Ts – p-toluenesulfonyl (tosyl)

Tse – 2-(trimethylsilyl)ethyl

UV – ultraviolet

CHAPTER ONE

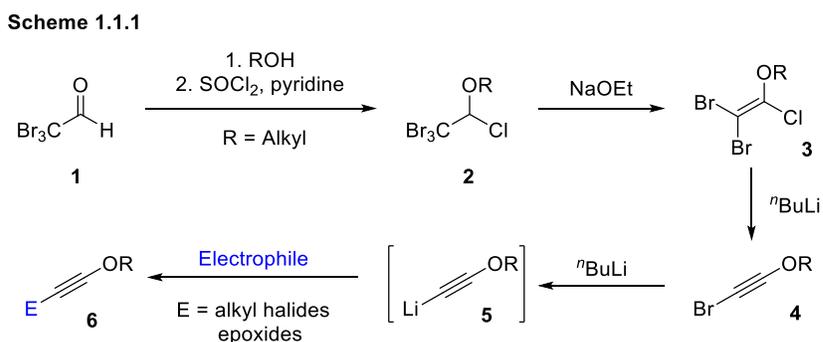
INTRODUCTION

1.1 Synthesis of Ynol Ethers

Since 1950s, ynol ethers have been synthesized and used in syntheses of many important natural products. From then on, ynol ethers were more and more commonly used in synthetic and theoretical studies. The developing synthetic methods extend the applications of ynol ethers. In turn, the demands of ynol ether motifs in the specific structural surroundings also encouraged the developments of new synthetic methods of ynol ethers. In recent years, transition-metal catalysts allowed many new ways to introduce the ynol ether motifs onto synthetic intermediates. Here, we are going to review the synthesis of ynol ethers briefly.

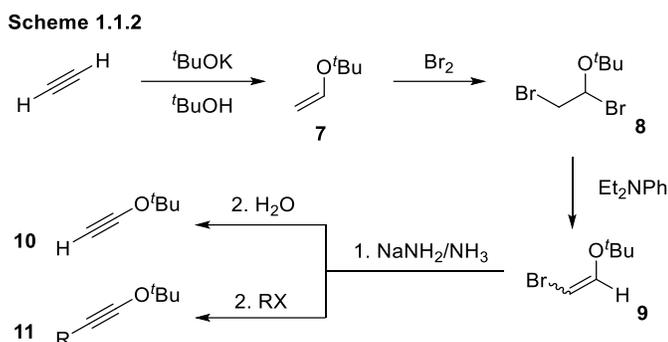
1.1.1 Synthesis of Alkyl Ynol Ethers

The synthetic study of ynol ethers started in the middle 1900s, but the systemic descriptions and studies of ynol ether syntheses did not appear until the late 1980s. In this section, we listed some representative historic examples for the synthesis of alkyl ynol ethers.



A classic way of ynol ether synthesis derived from the synthesis of chlorohemiacetals **2** (**Scheme 1.1.1**).¹ The elimination of HBr from the chlorohemiacetals **2** produced α -chloro- β -

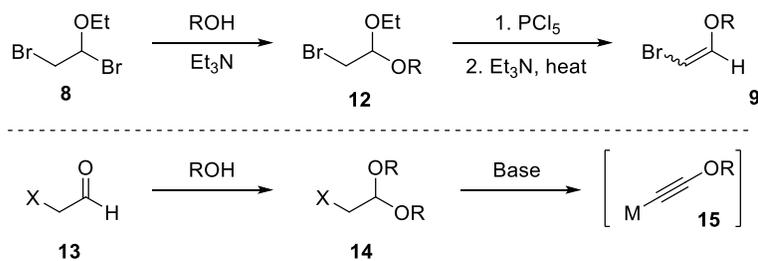
dibromovinyl ethers **3**, and the following halogen exchange triggered an elimination giving the corresponding bromoacetylene **4** and lithium alkoxyacetylides **5**. The generated lithium species reacted with various electrophiles, like epoxides² and alkyl halides, to form different alkyl ynol ethers **6**.³ This method had been widely used in synthesis of alkyl ynol ethers before 1980s.



However, this synthetic route had a limitation of the R- groups of the ynol ethers **6**. Some sterically hindered R-groups, such as *tert*-butyl or adamantyl, would suffer the low yields during the formation of chlorohemiacetals. To generate the tertiary alkyl ynol ethers, other methods were developed (**Scheme 1.1.2**). The addition reaction of *tert*-butanol to acetylene generated *tert*-butyl ethynyl ether **7**, and the dibromination of vinyl ether **7** was followed by the alkaline elimination to give bromovinyl ether **9**. The further extrusion of HBr required a harsh base, sodium amide, and to quench this elimination reaction with water or alkyl halides provided the terminal ynol ether **10** and alkyl ynol ether **11**.⁴ Moreover, a practical isolation procedure of ynol ethers was first described in this reference. Interestingly, people also found the mixed acetal **12** could react with PCl₅ and triethylamine to give the bromovinyl ether **9**, which was the precursor of alkoxyacetylides (**Scheme 1.1.3**).⁴ Similarly, some reports demonstrated the synthesis of α -haloacetals **14** from α -haloacetaldehyde **13**,⁵ and strong bases

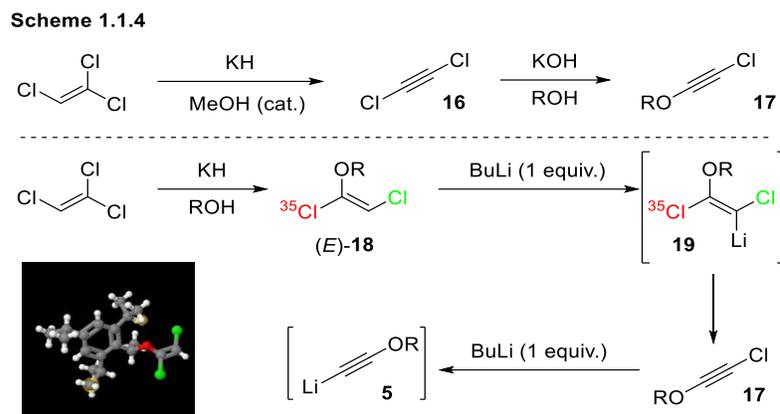
could convert the acetals **14** into various metal alkoxyacetylides **15**. But these early studies all described the use of strange bases. In the 1980s, more simple and practical methods were invented using lithium amide base, such as LDA or LiHMDS. However, the low yields and the by-products of this reaction narrowed down the further applications of the metallic alkoxyacetylides generated in this pathway.

Scheme 1.1.3



In the late 1980s and early 1990s, several groups independently reported an easier synthesis of terminal ynol ethers and metallic alkoxyacetylides using trichloroethene as the starting materials.⁶ In details, trichloroethene was found to undergo an elimination to yield dichloroacetylene **16**, which would further react with various alcohols or phenols to give alkoxyacetylenylchlorides **17** (Scheme 1.1.4).⁷ Similar to bromoacetylides **4** (Scheme 1.1.1), intermediates **17** could serve as the precursor in the preparation of any metallic alkoxyacetylides. Later, the Greene group reported a simple preparation of terminal ynol ethers originating from the trichloroethene,⁸ and this method was widely used until today.⁹ Preformed potassium alkoxide would substitute a chloride on trichloroethene to generate dichlorovinyl ethers **18**, and the subsequent elimination and the halogen exchange rapidly afforded the lithium alkoxyacetylides **5** in one-pot. After 20 year debates on the reaction mechanism, Poisson, Greene, and their co-workers finally elucidated the reaction pathway of this

transaction in 2011.¹⁰ The crystal of dichlorovinyl ether **18** indicated the *E*-configuration of the olefin, and the ³⁵Cl isotope experiment demonstrated that a *syn* β-elimination other than a Fristach-Buttenberg-Wiechell rearrangement led to the formation of intermediate **17**.¹¹

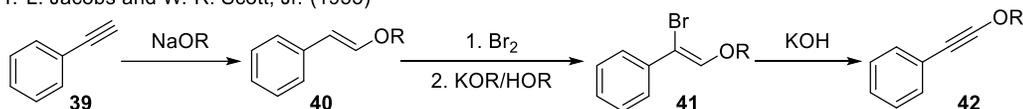


Alternatively, people developed some other approaches to alkyl ynoles (**Scheme 1.1.5**). In 1978, the Nakai group disclosed a synthesis of ynoles and thioethers **23**, and, in this report, they employed the trifluoroethyl ether or thioether **20** to react with different lithium reagents. They proposed the transaction occurred via the intermediate **21** and **22** producing the products.¹² A year later, P. Vermeer and co-workers reported a synthesis of methyl ynoles **25** using an organocopper reagent which induced a 1,3-substitution reaction of the disubstituted allene **24**.¹³ Both syntheses of ynoles provide various types of products, but the limited source of their starting material precluded their further synthetic applications. In 1994, an interesting paper from the Oehlschlager group discussed a synthesis of terminal ynoles **28** from acetates **26**, where an enol phosphate intermediate **27** was formed as the precursor of ynoles ethers.¹⁴ However, this method was not widely accepted by other chemists due to the difficult reaction conditions and the low yields.

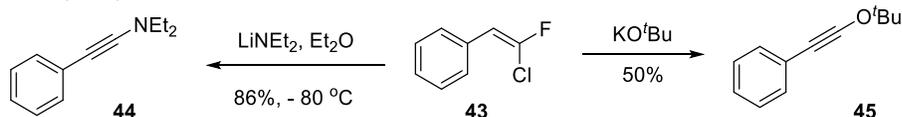
developed before 1990s. In 1992, several groups started to use coupling reactions to make the desired $sp-sp^2$ carbon bond between aryl halides **37** and metallic acetylides **38**. Alternatively, the early syntheses of aryl ynol ethers focused on the formation of the carbon-heteroatom bond (**bold red** in **30**). This strategy also allowed the synthesis of ynol thioethers **31**, ynamides, and silyl ynol ethers **32**.

Scheme 1.1.6

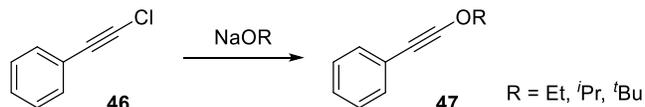
T. L. Jacobs and W. R. Scott, Jr. (1953)



H. G. Viche (1963)



S. I. Miller (1971)

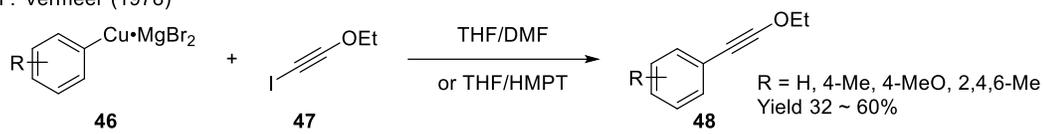


The first synthesis of aryl ynol ether, which has solid evidences, was reported in 1953 by Jacobs and Scott (**Scheme 1.1.6**).¹⁵ They claimed to obtain the aryl ynol ether **42** from β -bromostyrenyl ether **41**. In their back-to-back papers, they disclosed the synthesis of β -bromostyrenyl ether deriving from phenylacetylene **39**.¹⁶ After a decade, Viche accidentally found KO^tBu could serve as the nucleophile and the base in the synthesis of *tert*-butyl phenyl ynol ether **45** derived from dihalostyrene **43**.¹⁷ Meanwhile, this reaction gave rise to ynamines **44**. In 1971, Miller and co-workers developed a more general method. By simply using the phenylacetylene chloride **46** and sodium alkoxide, they obtained the primary, secondary, and tertiary alkoxy aryl ynol ethers **47**.¹⁸ These precedential works preliminarily revealed the chemical and physical properties of aryl ynol ethers, which encouraged the explorations of aryl

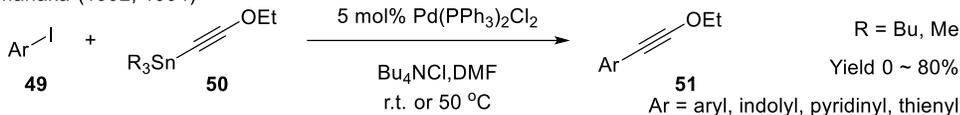
ynol ethers. For instance, people realized another major difficulty to handle aryl ynol ethers was their instability, and they were found more prone to nucleophilic attacks comparing to alkyl ynol ethers.¹⁹ On the other hand, to use the harsh conditions (strong base, high temperature, protic solvents) in their synthesis would affect the efficiency (low yields, isolation methods) to acquire the aryl ynol ethers.

Scheme 1.1.7

P. Vermeer (1978)



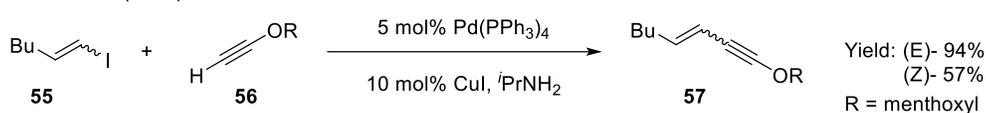
H. Yamanaka (1992, 1994)



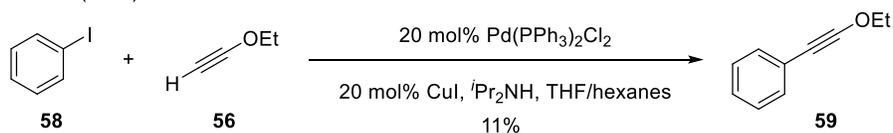
G. Himbert (1992)



P. H. Dussault (1998)



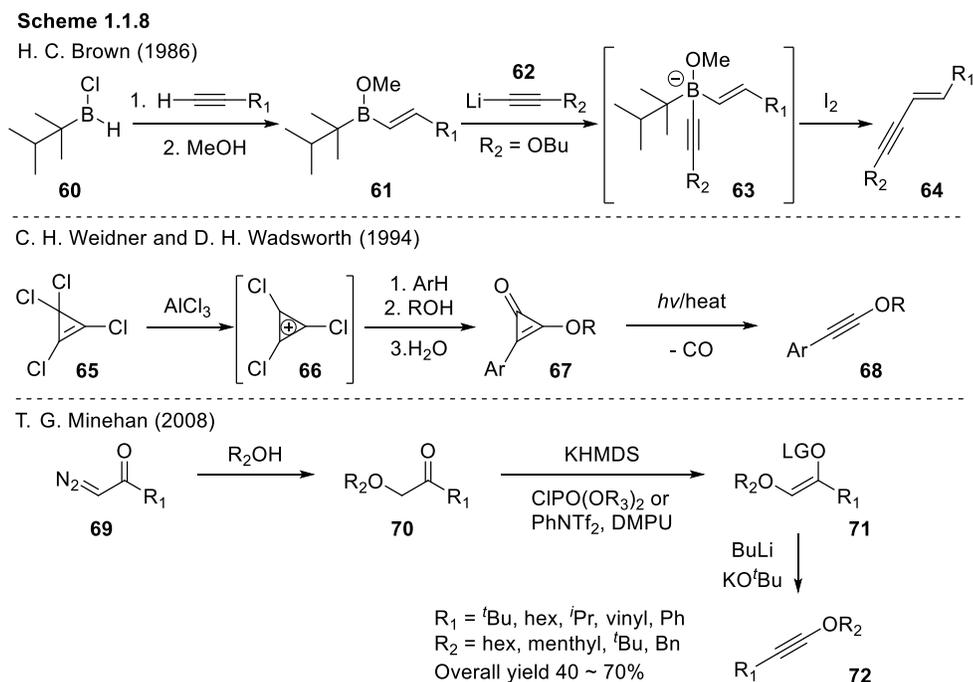
P. W. Davies (2011)



As the transition-metal involved cross coupling reactions developed, the transition-metal participated $sp-sp^2$ bond formation predominated the syntheses of aryl ynol ethers (**Scheme 1.1.7**). The first report was in 1978 by the Vermeer group, where the aryl cuprates **46** underwent a cross coupling reaction with ethoxyacetylene iodide **47**.²⁰ This coupling showed the tolerance with a steric hindered coupling partner, and it gave a moderate yield. However,

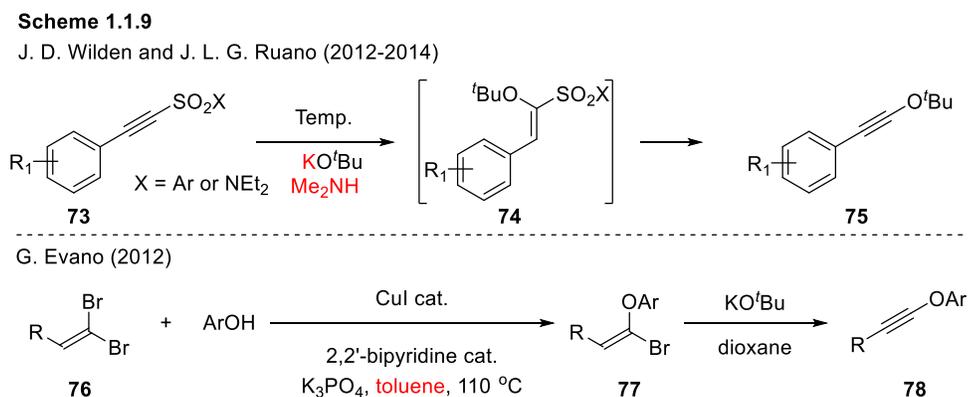
the first transition-metal catalyzed synthesis of aryl ynol ethers became available in the early 1990s. H. Yamanaka and co-workers discovered a Stille coupling reaction between aryl iodides **49** and trialkyltin ethoxyacetylide **50**. In contrast to Vermeer's pioneering work, the Yamanaka group switched the polarity of two coupling partners, which simplified the preparation of the coupling partners. Especially, the aryl iodides **49** were readily available, and the trialkyltin ethoxyacetylide **50** could be synthesized directly from lithium ethoxyacetylide.²¹ Moreover, this coupling reaction tolerated a wide range of substitutions on the aromatic rings, such as nitro-, esters, and amides, as well as the heteroaryls, such as pyridinyl, indolyl, and thienyl iodides. In their following article, an optimization of the reaction conditions promoted the yield up to 80% using the trimethyltin instead of the tributyltin.²² While they achieved the success in this Stille coupling reaction, there were still several problems. First, the yields of this reaction were still not satisfying, and most substrates only gave yields below 60%. Another concern of this reaction was the toxicity of organotin reagents. Meanwhile, the Himbert group demonstrated a Negishi coupling to generate ynol ethers **54**.²³ At the outset of their study, they discussed the formation of zinc alkoxyacetylides **53** via a transmetallation from the lithium species. This method avoided to use the toxic organotin reagent, but the improvement of the reaction yields was not significant. In 1998, P. H. Dussault and co-workers reported a Sonogashira coupling to synthesize the chiral 1,3-dienol ethers.²⁴ As the precursor of 1,3-dienol ethers, the enynol ethers **57** was obtained by coupling terminal menthoxyacetylenes **56** with vinyl iodides **55**. This sp-sp² carbon bond formation inspired the following works using Sonogashira coupling between aryl iodides and terminal alkoxyacetylenes. Of note, they observed a steric effect among the *trans*- and the *cis*-vinyl iodides, wherein the less hindered

trans- starting materials offered better yields. Nevertheless, there was an interlude over a decade before a practical method was discovered to couple the terminal alkoxyacetylenes with aryl halides. In 2011, the Davies group reported a synthesis of the phenyl ynol ether **59**, which was a substrate for their gold-catalyzed [3+2] cycloaddition in the synthesis of trisubstituted oxazoles.²⁵ Unfortunately, only 11% of the desired phenyl ynol ether **59** was obtained via a Sonogashira coupling reaction, and they only used iodobenzene **58** in this reaction. Although the terminal alkoxyacetylenes have a long shelf life and a low toxicity, a practical Sonogashira coupling between aryl iodides and terminal alkoxyacetylenes remains unknown.



In addition to the cross coupling reactions, some other groups contributed to the syntheses of aryl ynol ethers in other ways. For example, Nakai's approach was suitable for both alkyl and aryl ynol ethers (**Scheme 1.1.5**).¹² A fabulous and ingenious work from the Brown group demonstrated the addition of the lithium acetylides **62** to a boronic ester **61**, and the subsequent

halogenation-induced 1,2-alkynyl migration formed the desired $sp-sp^2$ carbon-carbon bond. In this manner, they synthesized vinyl ynol ethers **64** (Scheme 1.1.8),²⁶ and they further applied this synthetic strategy for the synthesis of pheromone. In 1994, C. H. Weidner, D. H. Wadsworth, and co-workers employed the fragmentations of cyclopropenones **67** to get aryl ynol ethers **68** under the thermal or photo conditions.²⁷ This method worked well with various types of substituted aromatic rings and alkoxy groups in a large scale, and the only side product was carbon monoxide gas. Recently, the Minehan group developed a novel and general synthetic method of ynol ethers from α -alkoxyketones **70**, which allowed the synthesis of both aryl and alkyl ynol ethers **72** via the enol phosphates or triflates intermediates **71**.²⁸

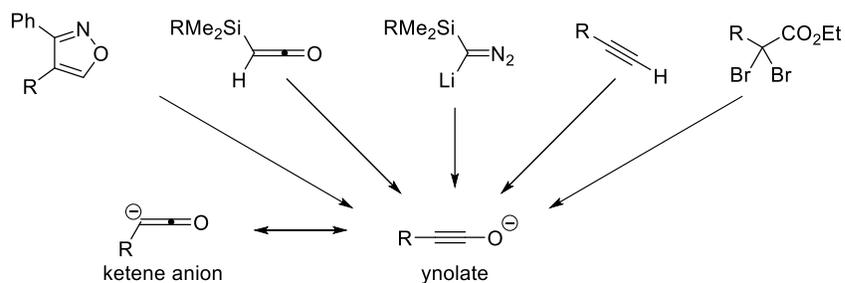


Recently, several groups showed novel synthetic approaches to aryl ynol ethers via the formation of the carbon-oxygen bond (Scheme 1.1.9). In 2012, the Wilden group and the Ruano group independently discovered potassium alkoxide would undergo an unusual *anti*-Michael addition to arylsulfonylacetylenes or arylsulfonamideacetylenes **73**. The adducts **74** eliminated the sulfonyl moiety to form aryl ynol ethers **75**.²⁹ The potassium served as an important role in this reaction to give the excellent regioselectivity (Michael or *anti*-Michael addition).^{29a} In their preliminary work, only *tert*-butoxide were able to afford reasonable yields,

because of the selectivity during the reaction as well as the stability of products. In Wilden's following research, they broadened the substrate scope and achieved higher yields using dimethylamine as the additive in the reaction.³⁰ However, the difficult synthesis of the starting material would still be an obstacle for people to use this method. On the other hand, inspired by their ynamide syntheses, G. Evano and co-worker used phenols and dibromostyrenes **76** as the starting materials in their copper-catalyzed carbon-heteroatom coupling reactions. Under the coupling conditions, they generated the bromoketeneacetals **77**, which underwent an elimination reaction to afford aryl ynol ethers **78** in decent yields.³¹ When this coupling took place in dioxane, it would generate keteneacetals instead (not shown). In contrast to Viche's precedential work (**Scheme 1.1.5**), this novel method avoided to use a strong base in the formation of aryl or alkyl ynol ethers **78**. However, the high temperature of the reaction limited the applications of this synthetic method. Although these works had their own flaws, they are still suitable for some scenarios, and they provided a great contribution to the synthesis of ynol ethers.

1.1.3 Synthesis of Silyl Ynols Ethers and Ynolates

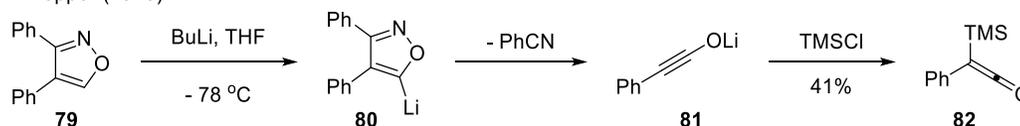
Figure 1.1.2



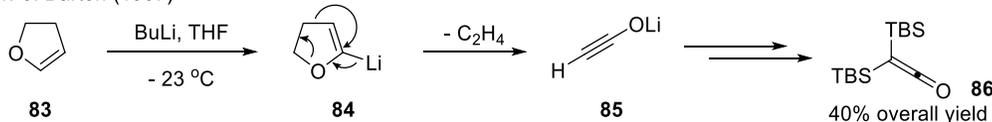
Silyl ynol ethers and ynolates are also important synthetic intermediates. In most case, silyl ynol ethers are prepared via a silylation of ynolates, whose syntheses are easier than alkoxyacetylenes. Despite their simple synthesis, they showed the excellent stability as well. Therefore, they have been extensively employed and studied in many cycloaddition reactions. In this section, we are going to introduce some representative synthetic pathways to obtain the silyl ynol ethers and ynolates.³²

Scheme 1.1.10

I. Hopper (1975)



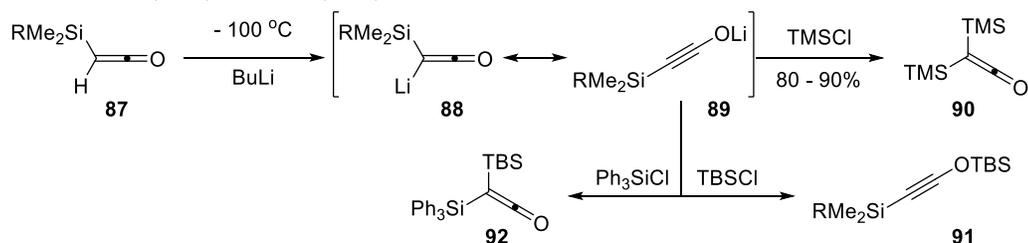
T. J. Barton (1987)



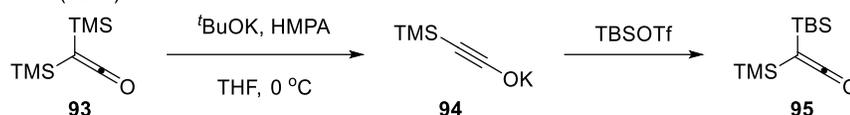
The early syntheses of ynolates relied on the base-induced fragmentations of the heterocycles. I. Hopper and co-workers claimed the first observation of ynolate intermediates.³³ A deprotonation of isoxazole **79** generated a lithioisoxazole **80**, which quickly underwent a fragmentation giving benzonitrile and phenylethynolate **81**. A carbon silylation of the intermediate provided α -silylketene **82** as the major product. Similar to this work, the Barton group accidentally found an unexpected fragmentation of 2,3-dihydrofuran **83** to form ynolate **85** during the preparation of α -lithiodihydrofuran **84**.³⁴ However, synthetic utility of these reactions has not sufficiently explored.

Scheme 1.1.11

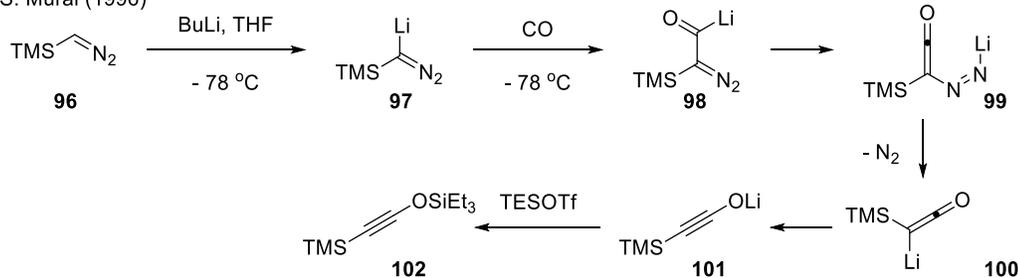
M. W. Rathke (1978); Y. K. Kita (1996)



M. Ito (2002)



S. Murai (1996)

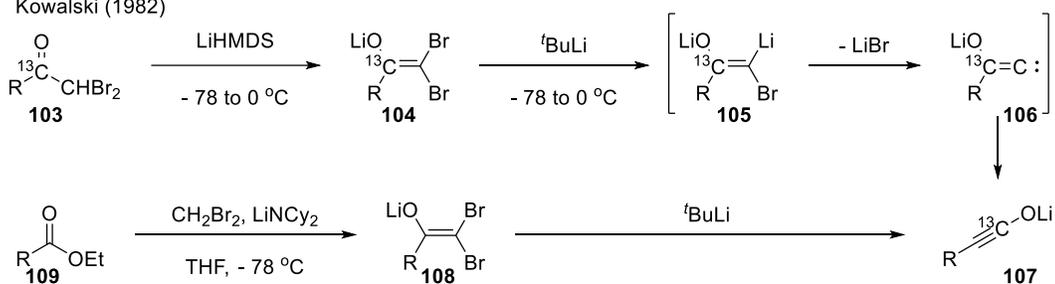


In addition to fragmentation, people used the metallated α -silylketenes as the surrogates of ynoates (**Scheme 1.1.11**). In contrast to monoalkyl ketenes, the silyl groups helped to stabilize the ketenes, which also enable the deprotonation of the ketene's α -proton. M. W. Rathke and co-workers made the first attempt in 1978.³⁵ At -100 °C, BuLi was added to α -silylketene **87**, and it deprotonated the α -proton of the ketene. The lithioketene **88**, then, tautomerized into lithium ynoate **89**, and quenching this reaction with silylchlorides generated disilylketene **90**. In Kita's following research, they found to quench lithium ynoate **89** with TBSCl would yield silyl ynole ether **91**, while the Ph₃SiCl gave the disilylketene **92** instead.³⁶ Furthermore, the Ito group also noticed the ynoate **94** could be generated through a transmetallation using potassium *tert*-butoxide and HMPA to treat disilylketene **93**. The formed ynoate could further react with TBSOTf to give the hetero-disilylketene **91**.³⁷ Additionally, S. Murai and co-

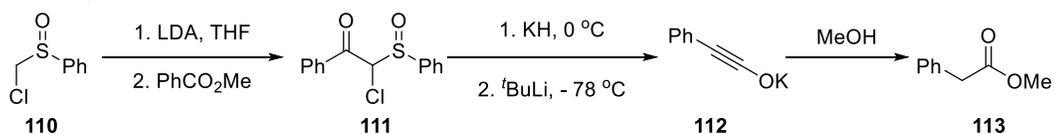
workers discovered an interesting synthetic method of the silyl ynol ethers using trimethylsilyldiazomethane **96** as the starting material.³⁸ After the deprotonation by BuLi, the lithioazomethane **97** reacted with carbon monoxide to form the α -diazoacyllithium **98**, and the subsequent rearrangement and tautomerization generated lithium ynolate **101**. Finally, the reaction was quenched with TESOTf to give the silyl ynol ether **102**.

These pioneering syntheses of silyl ynol ethers or ynolates enabled people to study their chemical and physical properties. However, there were many drawbacks of these methods including the limited substrate scopes, the harsh conditions, and the low yields. To address those problems, people developed newer and more efficient methods to obtain silyl ynol ethers.

Scheme 1.1.12
Kowalski (1982)



T. Satoh (1995, 2001)

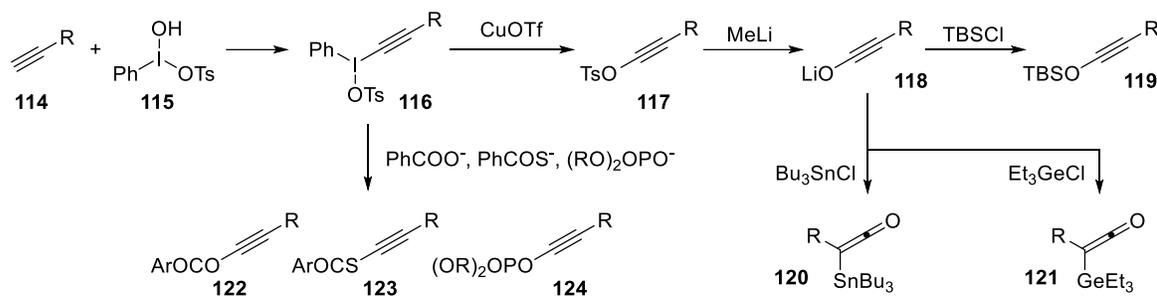


In 1982, Kowalski developed the first real practical synthesis of ynolates **107**, which was based on a modification of Hofmann rearrangement (**Scheme 1.1.12**).³⁹ They clarified the mechanistic insight of this reaction using a ^{13}C labeling experiment. The migration of alkyl group from ^{13}C to ^{12}C indicated the reaction passed through a carbene intermediate **106**. In the same paper, they also described a one-pot procedure to synthesize ynolates **107** from ethyl

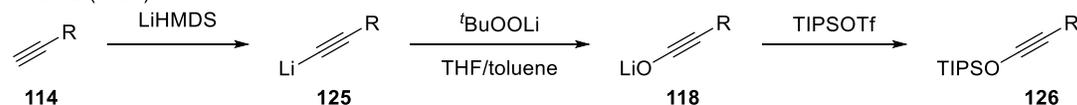
esters **109**, and this method provided reasonable yields among the different types of substrates. Similarly, the Satoh group discovered another route to synthesize ynolates **112**.⁴⁰ The precursor **111** was prepared from the benzoate ester and chloromethyl phenyl sulfoxide **110**, and the following lithium exchange and the leaving of PhSO^- gave the rise to ynolate **112**.⁴¹

Scheme 1.1.13

P. J. Stang (1985-1992)



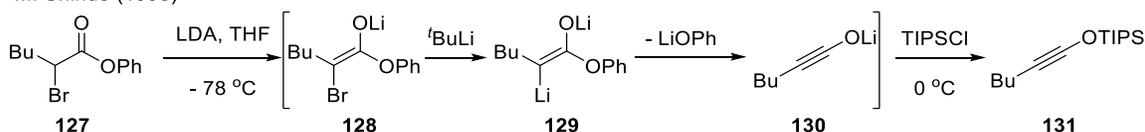
M. Julia (1993)



Moreover, another synthetic approach to silyl ynol ethers or ynolates were through an oxidation reaction of the terminal acetylenes (**Scheme 1.1.13**). The easy access to terminal acetylenes **114** made these protocols the most commonly used methods nowadays. Peter Stang set the example in this area.⁴² They discover iodosobenzene could oxidize terminal acetylenes **114**, in the presence of TsOH , into iodonium tosylates **116**, which were treated with CuOTf to afford the ynol tosylates **117**. Finally, the addition of MeLi to ynol tosylates **117** gave lithium ynolate **118**, and the reaction could be quenched with different electrophiles to generate silyl ynol ethers **119** and metallated ketenes **120** and **121**. In addition, when they treated the iodonium tosylates **116** with nucleophiles, such benzoyl acid, benzoyl thioacid, and phosphates, it offered the corresponding alkynyl carboxylates **122**, alkynyl thiocarboxylates **123**, and

alkynyl phosphates **124**. However, they mentioned this method could not afford any aryl ynolates, because of the instability of the phenylacetylenyl iodonium tosylates **116**.⁴³ In 1993, M. Julia and co-workers invented a direct oxidation of lithium acetylides **125** using TBHP as the oxidant, and the generating ynolates **118** were trapped with TIPSOTf to produce the silyl ynol ethers **126**.⁴⁴ In contrast to Stang's method, this novel oxidation protocol could provide the access to the aryl ynolates. Our group modified Julia's method and developed a one-pot protocol to synthesize aryl ynolates.⁴⁵

Scheme 1.1.14
M. Shindo (1998)

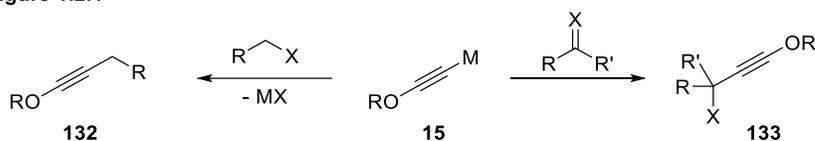


In 1994, the Shindo group converted α -bromoester **127** into ynolate **130** utilizing an alkaline elimination followed by the lithium exchange. They hypothesized that this reaction went through a dianion intermediate **129**, which would further extrude lithium phenoxide.⁴⁶

1.2 Synthetic Application of Ynol Ethers

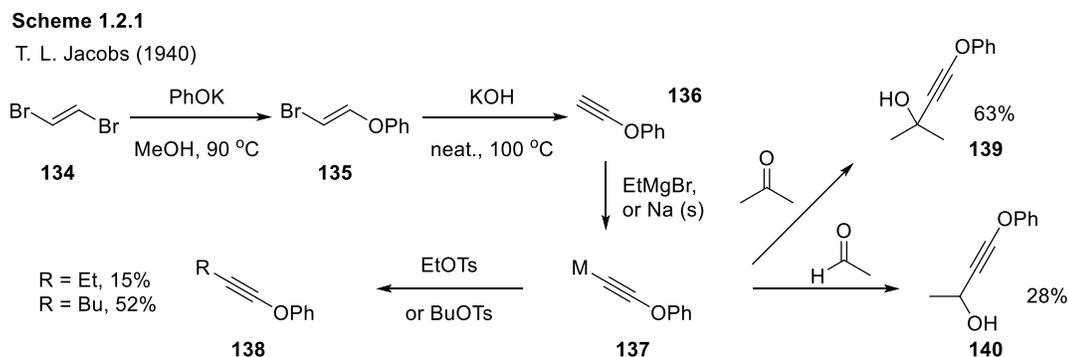
1.2.1 Addition and Substitution Reaction of Metallated Alkoxyacetylides

Figure 1.2.1



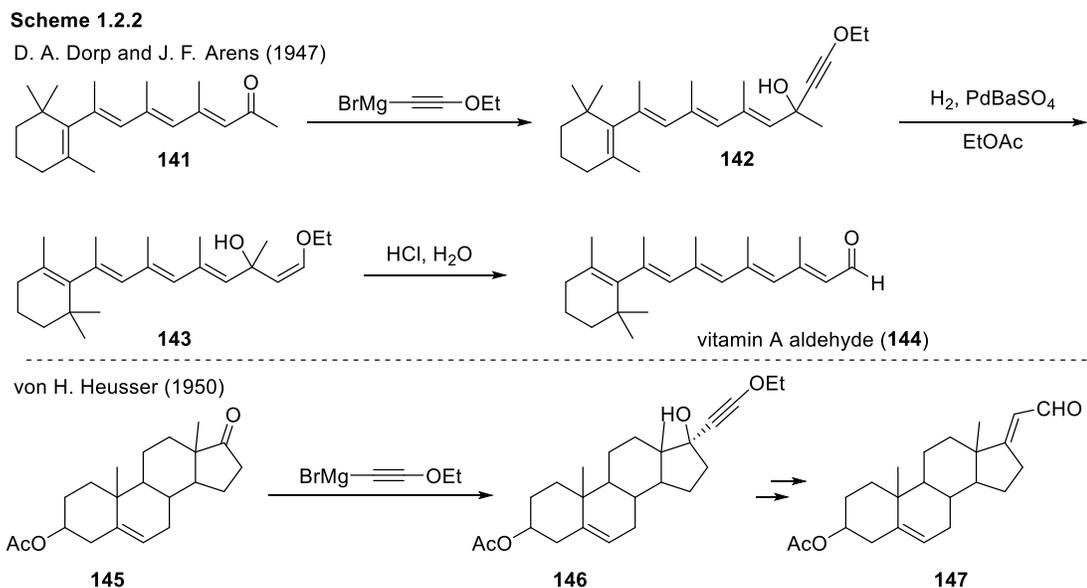
Since the synthesis of metal alkoxyacetylides **15** was developed, people have been using them in the nucleophilic additions and substitution reactions to introduce the ynol ether motifs onto synthetic molecules. In addition, these two reactions are also the most common and direct

methods to obtain alkyl ynol ethers nowadays. In this section, we are going to introduce some representative works using these two reactions. The earliest synthetic examples of alkyl ynol ethers via nucleophilic substitutions were reported during WWII in 1940 and 1942 (**Scheme 1.2.1**). T. L. Jacobs and co-workers reported the synthesis of the phenoxyacetylides **137** via the deprotonation of phenoxyethyne **136**.⁴⁷ *Trans*-dibromoethene **134** reacted with potassium phenolate to form *trans*-phenoxybromoethene **135**, and the treatment of **135** with potassium hydroxide gave the key intermediate **136**. Once the metal phenoxyacetylides **137** were prepared by the deprotonations, several electrophiles served to trap the intermediates. For instance, the phenoxyacetylide **137** substituted the OTs group to generate ethyl and butyl ynol ethers **138**. Moreover, it (**137**) could also undergo nucleophilic addition to acetone and acetaldehyde providing the tertiary alcohol **139** and the secondary alcohol **140**.



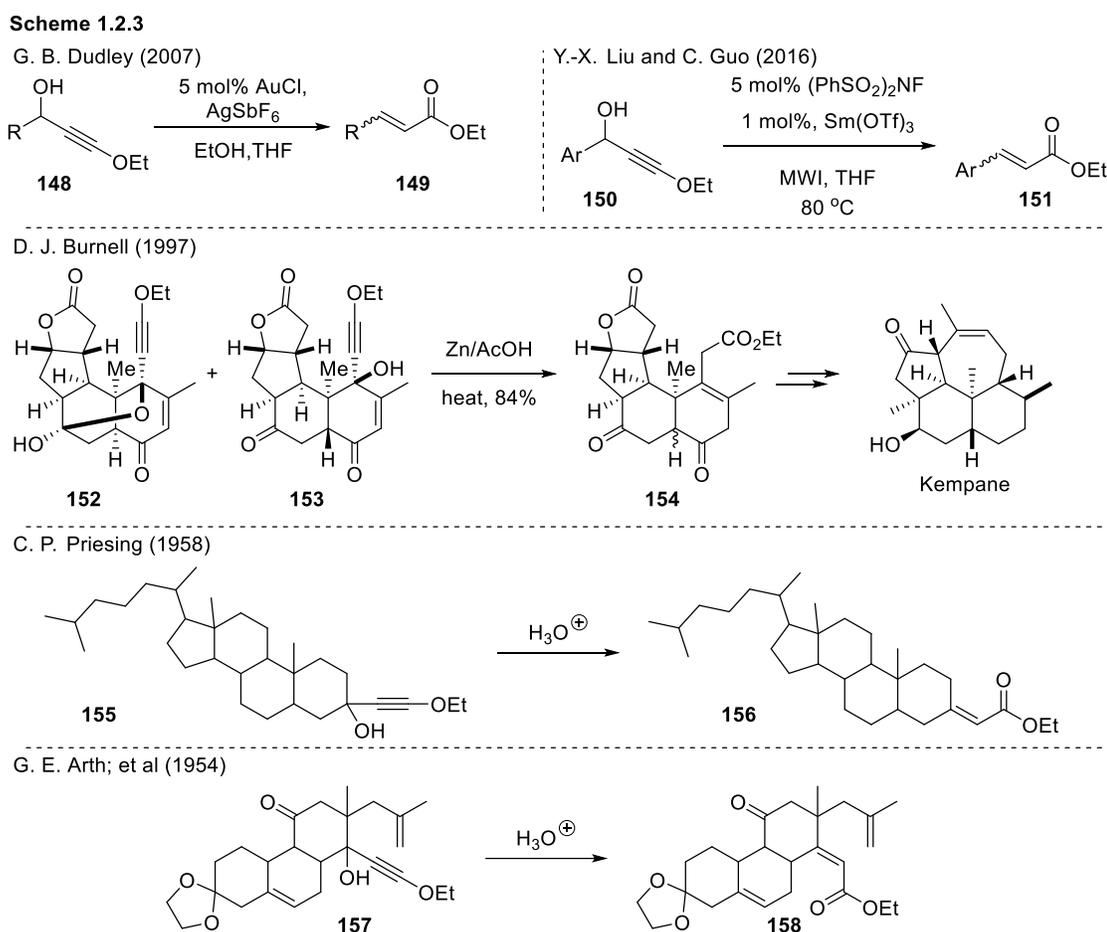
After the War, D. A. van Dorp and J. F. Arens applied this addition reaction in the synthesis of vitamin A aldehyde (**Scheme 1.2.2**).⁴⁸ The magnesium ethoxyacetylide was prepared according to Jacobs' reports, and the starting material **141** originated from β -ionone. The addition reaction took place between the ketone **141** and the magnesium ethoxyacetylide to generate the ynol ether **142**, which was reduced to vinyl ether **143** using a hydrogenation reaction. They finished synthesis of vitamin A aldehyde **144** by treating the vinyl ether **143**

with the mineral acid in water. In the next few years, the same strategy was employed in the syntheses of vitamin A's analogs and sexual hormones.⁴⁹ In 1950s, a number of syntheses used this addition reaction and the subsequent transformation to construct the unsaturated aldehydes in the synthesis of natural products.⁵⁰



The addition reaction of ynol ethers to carbonyls was closely related to Meyer-Schuster rearrangement.⁵¹ Under the acidic conditions, the protonation of the propargyl hydroxyl groups would extrude water and generate the allenyl cations, which might be trapped with nucleophiles to form α,β -unsaturated esters or acids. This reaction was widely used in many syntheses of important natural products (**Scheme 1.2.3**), and, recently, people used Lewis acids to trigger this rearrangement under much milder conditions. The Dudley group⁵² and the Liu and Guo group showed two representative examples,⁵³ where the gold or the samarium catalysts initiated the rearrangement and gave the high yields and the good stereoselectivities. Moreover, this synthetic method also facilitated several syntheses, where the ynol ether motifs were rapidly converted into the unsaturated esters. For instance, under the acidic and reductive

conditions, the intermediates **152** and **153** afforded the desired ester **154** in a decent yield during the synthesis of kempene.⁵⁴ The less steric effect of lithium alkoxyacetylides allowed the easier addition reactions to some complexed molecules, which showed such advances over the corresponding addition reactions using ester enolates. The Meyer-Schuster reactions of ynol ethers could derivate back to 1950s. A lot cases were reported in synthesis of complicated steroids and hormones.⁵⁵ Under the Brønsted acidic conditions, people realized the stereoselective of the forming double bonds was controlled by the substrates.⁵⁶

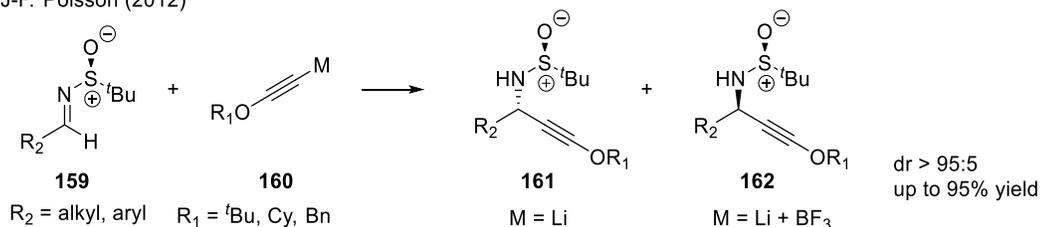


Similarly, imines are also able to react with metal acetylides. Recently, a lot of studies emerged in this field (**Scheme 1.2.4**).⁵⁷ The Poisson group developed the diastereoselective addition

reactions of lithiated ynoal ethers **160** to Ellman's chiral sulfinylimines **159**. This addition reaction worked excellently with alkyl and aryl imines, and several alkoxyacetylides were tested as nucleophiles in this reaction. More interestingly, the presence of boron trifluoride reversed the diastereoselectivity of this addition reaction. In Poisson's following study, they simplify the reaction conditions using dimethylaluminum alkoxyacetylides to avoid the addition of boron trifluoride.⁵⁸ As their expectation, the adducts **161** and **162** allowed the rapid access to β -amino esters via the hydrolysis of the ynoal ethers (not shown).

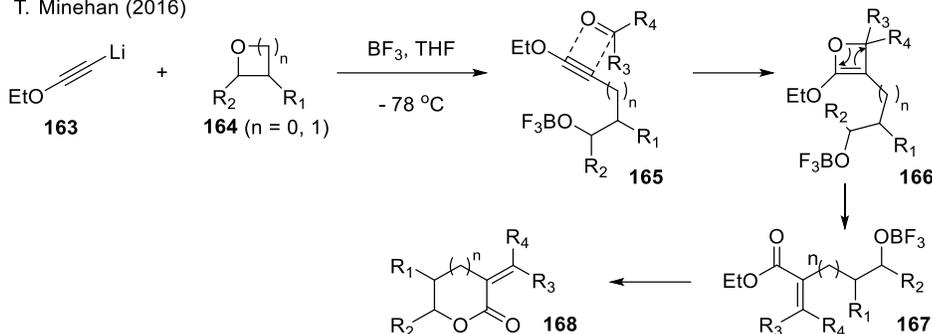
Scheme 1.2.4

J-F. Poisson (2012)



Additionally, alkyl ynoal ethers could be synthesized via the epoxide or oxetane opening reactions. T. Minehan reported a brilliant cascade reaction using the epoxide opening reaction (**Scheme 1.2.5**).⁵⁹ The lithium ethoxyacetylide **163** opened the epoxides (n = 0) or oxetanes (n = 1) **164**, followed by an ynoal ether-carbonyl metathesis reaction,⁶⁰ to generate intermediates **166**. The opening of 4-member rings and the subsequent lactonization gave the desired lactones **168**.

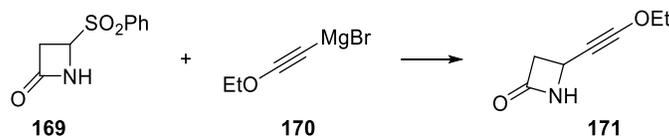
Scheme 1.2.5
T. Minehan (2016)



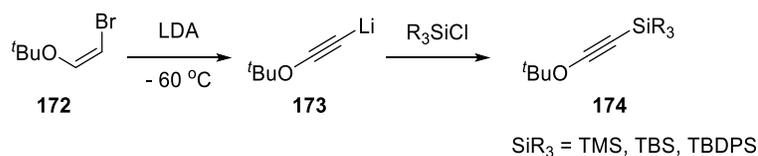
The Hiraoka group discussed a special substitution reaction using the metal alkoxyacetylides in 1980 (**Scheme 1.2.6**).⁶¹ Magnesium alkoxyacetylide **170** conducted the substitution reaction on the four-membered lactam **169** to replace the sulfonyl group. Moreover, lithium *tert*-butoxyacetylide **173** was found to form carbon-silicon bonds with the silylchlorides. The resultants, 1-*tert*-butoxy-2-silylethyne **174**, were the precursors to silylketenes.⁶²

Scheme 1.2.6

T Hiraoka (1980)



M. A. Pericàs (1990)

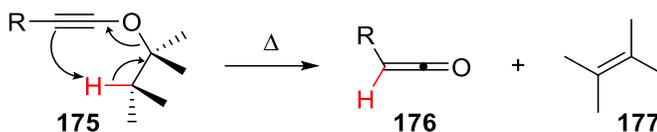


1.2.2 Ketene Generation from Ynol Ethers and the Corresponding [2+2] Cycloaddition

Another important chemical property of ynol ethers **175** is the ability to generate the ketene intermediates **176** under the thermal conditions (**Scheme 1.2.7**), and this thermolysis of ynol

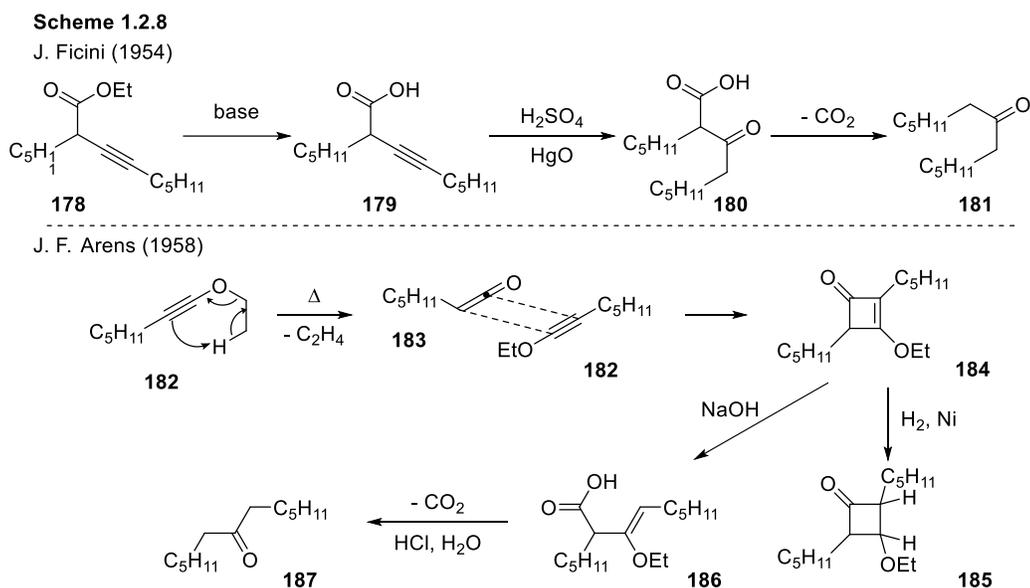
ethers will extrude the corresponding olefins **177**. This transformation, also known as [1,5]-hydride shift or retro-ene reaction, has been widely used in synthesis.

Scheme 1.2.7



In fact, J. Ficini accidentally discovered this thermolysis of ynoethers in 1958. She observed that ethyl heptynyl ether **182** evolved ethylene smoothly when it was heated at 120 °C. After the reaction, she isolated a substrate from the slightly colored reaction mixture. According to its composition, the compound combined two molecules of the ynoethers minus one molecule of ethylene.⁶³ She proposed the structure of the product **178** based on the following clues: 1. under a basic hydrolysis condition, a monobasic acid **179** was formed; 2. When this generated acid **179** was treated with concentrated sulfuric acid and mercuric oxide, she obtained dihexyl ketone **181** (**Scheme 1.2.8**).⁶⁴ However, four years later, J. F. Arens disagreed the conclusion that Ficini made. He analyzed the IR spectrum of the product, which suggested the product should contain an α,β -unsaturated carbonyl functional group. Therefore, the Arens group did a series work to reveal the real structure of the product. They proposed the extrusion of ethylene from ynoether **182** via a retro-ene reaction generated the ketene **183**, which would undergo a [2+2]-cycloaddition reaction with another molecule of ynoether **182**. They hypothesized cyclobutenone **184** was the correct structure of the compound that Ficini actually obtained. To verify their suggestion, they did a hydrogenation on the cyclobutenone **184** using Raney nickel catalyst, and they found its absorbed one molecule of hydrogen gas. On the other hand, they corrected the mechanism of the formation of dihexyl ketone **181**. In contrast to the mechanism

claimed by Ficini, they proposed a ring opening reaction of the cyclobutenone ring under the basic conditions, and the hydrolysis of esters and the following decarboxylation reactions would offer the dihexyl ketone **187** under the acidic conditions. With the development of analytic methods, Arens' hypothesis was proven right. Due to the discovery of this retro-ene reaction by Ficini and the elucidation of the reaction mechanism by Arens, people were able to use ynol ethers as ketene surrogates in many scenarios, which made ynol ethers useful tools in organic syntheses.

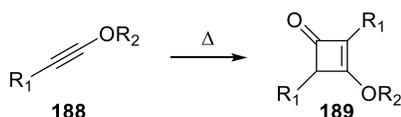


The elucidation of the real mechanism of this retro-ene reaction made it more synthetically useful. J. F. Arens and co-workers also demonstrated an early work in this area. After they synthesized the *tert*-butyl alkyl ynol ethers **11** (Scheme 1.1.2), they were able to compare the reactivities between ethoxyl, *iso*-propoxyl, and *tert*-butoxyl ynol ethers **188** in the formation of homodimer **189** (Figure 1.2.2).⁶⁵ They found *O*-alkyl group with less α -branches would have a better thermal stability. On the other hand, the *O-tert*-butyl ynol ethers underwent the [1,5]-hydride shift at a lower temperature than the *O-iso*-propyl and the *O-ethyl* ynol ethers

did. Additionally, they measured the rate constants of the cycloaddition reactions at multiple temperatures. They found the reactivity of ynol ethers was roughly proportional to the number of β -hydrogen atoms in R_2 of **188**, and the acceleration of the thermolysis was due in part to the statistical factors and in part to the electronic factors in R_1 of **188**.

Figure 1.2.2

J. F. Arens (1961)



Rate Constants:

$$R_1 = \text{Pent}, R_2 = \text{Et} \quad 105^\circ\text{C}: k = 1.12 \times 10^{-3} \text{ min}^{-1}$$

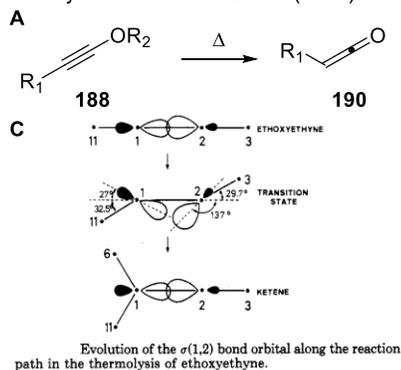
$$120^\circ\text{C}: k = 4.36 \times 10^{-3} \text{ min}^{-1}$$

$$R_1 = \text{Pent}, R_2 = \textit{i}\text{Pr} \quad 105^\circ\text{C}: k = 9.30 \times 10^{-3} \text{ min}^{-1}$$

Thermal Stability:

$$R_2 = \text{Et} > R_2 = \textit{i}\text{Pr} > R_2 = \textit{t}\text{Bu}$$

A. Moyano and M. A. Pericàs (1987)

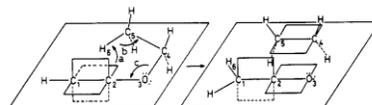


B

Compound ^{a,b}	E_a	ΔS^\ddagger
Et—C≡C—O ^t Bu	23	-15
Et—C≡C—O ⁱ Pr	26	-10
Et—C≡C—OEt	29	-6
C ₅ H ₁₁ —C≡C—OEt	29	-12

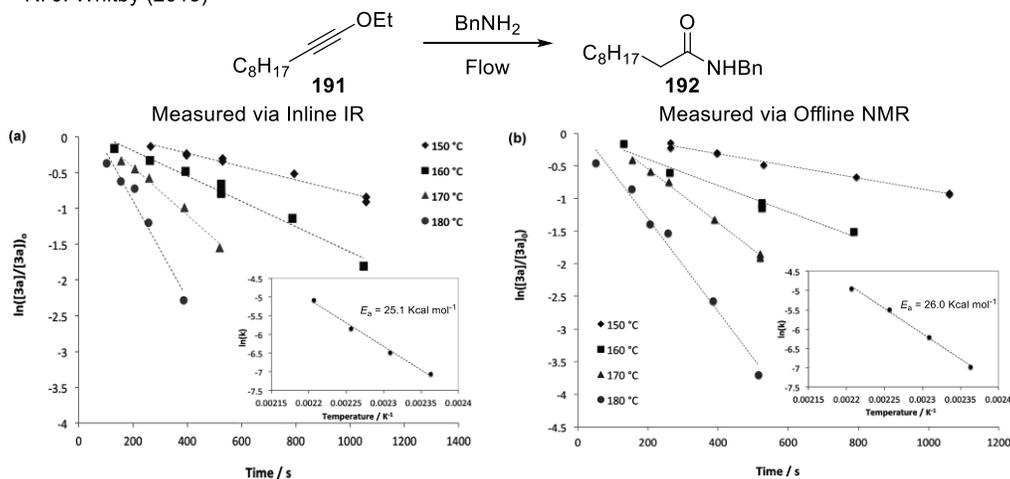
^a Values measured in decalin solution at 358–388 K. ^b E_a in kcal mol⁻¹ and ΔS^\ddagger in cal mol⁻¹ deg⁻¹.

D



Schematic representation of the electronic reorganization along the reaction path in the thermolysis of ethoxyethyne: (a) $\pi_y(1,2) \rightarrow \sigma(1,6)$; (b) $\sigma(5,6) \rightarrow \pi_x(5,4)$; (c) $\sigma(3,4) \rightarrow \pi_x(2,3)$.

R. J. Whitby (2015)



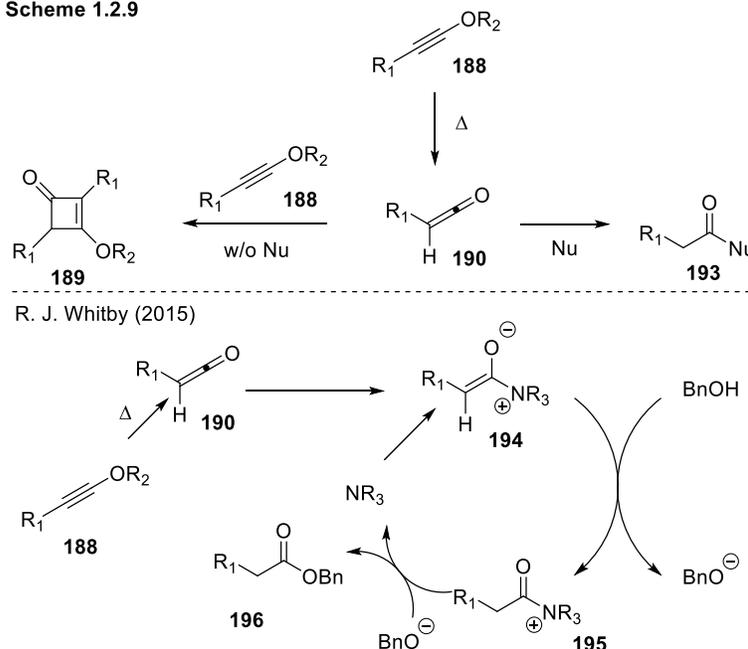
Actually, the understanding of thermodynamic and kinetic properties of this reaction was not clear. No theoretical study devoting to the thermolysis of ynol ethers was available until 1987,

when A. Moyano and M. A. Pericàs combined the experiment data and the calculation data of this reaction.⁶⁶ They measured the activation parameters for the thermolysis of some ynol ethers (**Part B**). According to their theoretical model, they described “the reaction as a nucleophilic attack of a π -component of the C₁-C₂ triple bond to the β -hydrogen atom; the electronic deficiency created in C₂ is simultaneously compensated by formation of a π -bond between the C₂ and O₃, which is accompanied by the formation of the C₅-C₄ π -bond. (**Part D**)” They also interpreted the percentage of the p character in C₁'s hybrid orbital during the transition state was greater than in the reactant or the product (**Part C**). Their studies among this reaction provided theoretic evidences of a concerted [1,5]-hydride shift mechanism for this reaction. In addition to the study from Moyano and Pericàs, new methods of mechanistic studies allowed more accurate measurements of the reaction parameters. For example, utilizing the flow chemistry equipment, R. J. Whitby and co-workers tested the kinetic thermolysis parameters for the thermolysis of ynol ether **191**. With the inline IR, they measured the activation energy of the reaction at 25.1 kcal mol⁻¹, while the offline NMR showed a slightly difference at 26.0 kcal mol⁻¹.⁶⁷

Due to the formation of ketenes from ynol ethers, people developed numerous methodologies to construct structures more than the cyclobutenones **189** (**Scheme 1.2.9**). With the presence of nucleophiles *in situ*, the ketenes **190** were trapped to form acetic acid derivatives **193**. In some cases, weak nucleophiles resulted in the formation of the cyclobutenones **189**. Especially, some ynol ethers need a higher reaction temperature to generate the ketene **190**, which would also accelerate the undesired [2+2]-cycloaddition reactions. To address this problem, people

employed a tertiary amine as the additive in the reaction to form the ketene enolates **194**, which would favor the reaction with nucleophiles rather than the cycloaddition reactions.⁶⁷

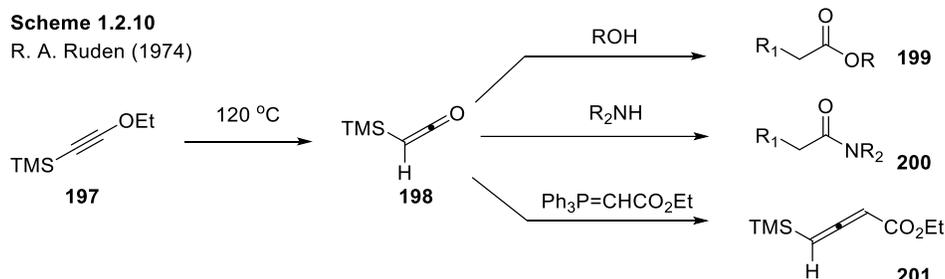
Scheme 1.2.9



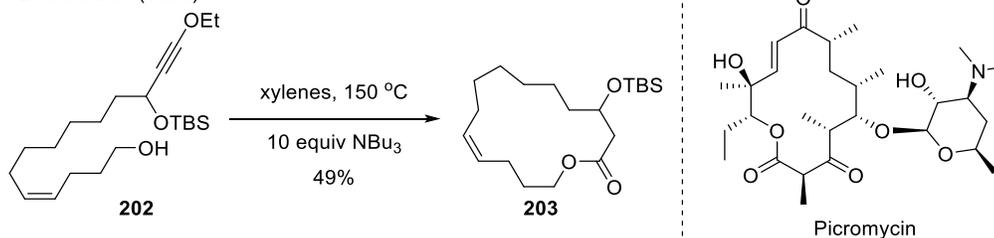
There are several representative examples using ynol ethers to generate the ketene intermediates (**Scheme 1.2.10**). As is shown, the silyl ketene **198** could not only be trapped intermolecularly to form the corresponding esters **199** and amides **200**, but it was also noticed to react with a phosphonium salt to generate allene **201**.⁶⁸ Moreover, due to its high reactivity, ynol ethers appeared to be a powerful tool in the macro size ring closure reactions via the ketene intermediates. The MaGee group disclosed an early study in this field.⁶⁹ In 1993, they developed a model study targeting to picromycin, which was a macro size lactone. In the model study, they successfully generated the ketene from ynol ether **202**, and the subsequent intramolecular ketene trapping reaction afforded the desired lactone in a reasonable yield.⁷⁰ In 2006, T. F. Jamison proved ynol ethers could be easily introduced onto a complex molecule

and serve as the ketene surrogates. The intramolecular ketene trapping reaction formed the macro size lactone **205** at the late stage of the synthesis of acutiphycin.⁷¹

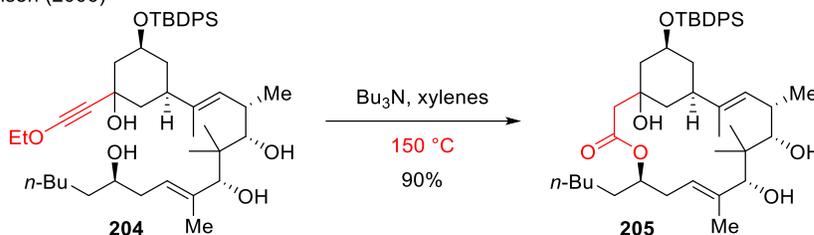
Scheme 1.2.10
R. A. Ruden (1974)



D. I. MaGee (1993)



T. F. Jamison (2006)

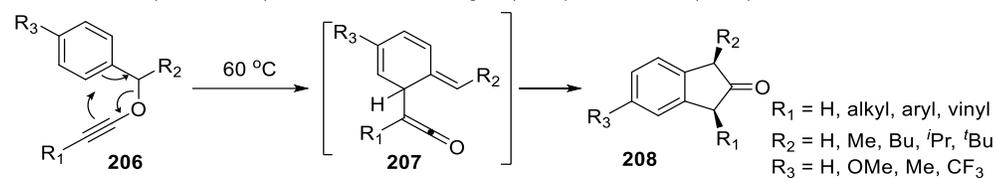


Analogously, J. F. Arens and co-worker found the sigmatropic rearrangement using *O*-benzyl ynol ethers **206** (Scheme 1.2.11).⁷² After the ketene intermediate **207** was formed by the sigmatropic rearrangement, Arens discovered *O*-benzyl ynol ethers **206** underwent a cyclization to generate 2-indanone **208**. The following research by the Katzenellenbogen group indicated the R₁ as alkyl groups could be introduced onto the indanone as well as a proton.⁷³ However, this chemistry left untouched for over 30 years, before T. G. Minehan broadened its substrate scope in 2008.⁷⁴ They found multiple functional groups were allowed on the aromatic ring (R₃) as well as benzyl position (R₂) during this reaction. Interestingly, the Minehan group

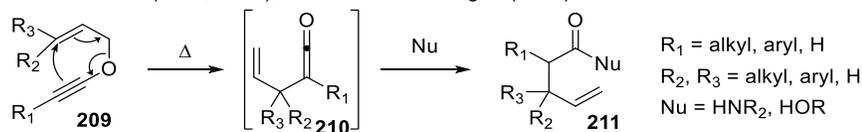
also mentioned a better diastereoselectivity of the cyclization was found with the steric hindered substrates. Inspired by sigmatropic rearrangements of the *O*-benzyl ynoal ethers, the Katzenellenbogen group pioneered to use *O*-allyl ynoal ethers **209** in a similar protocol. They originally planned to obtain a cyclopentanone, but they got the α -allyl acetamide **211** instead. In this manner, the Minehan group introduced the substituted groups on the olefins.⁷⁵ Additionally, they used different nucleophiles to trap the ketene intermediates **210** to generate various α -allyl acetic acid derivatives. Unfortunately, Minehan failed to see any noticeable diastereoselectivity of this reaction.⁷⁶

Scheme 1.2.11

T. G. Minehan (2008, 2011); J. A. Katzenellenbogen (1975); J. F. Arens (1964)



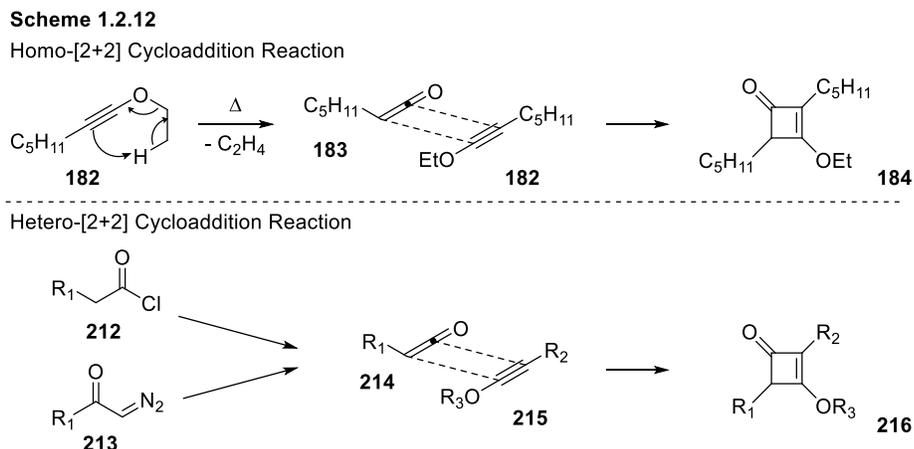
T. G. Minehan (2006, 2008); J. A. Katzenellenbogen (1975)



1.2.3 Ring Opening Reaction of Cyclobutenone and Danheiser benzannulation.

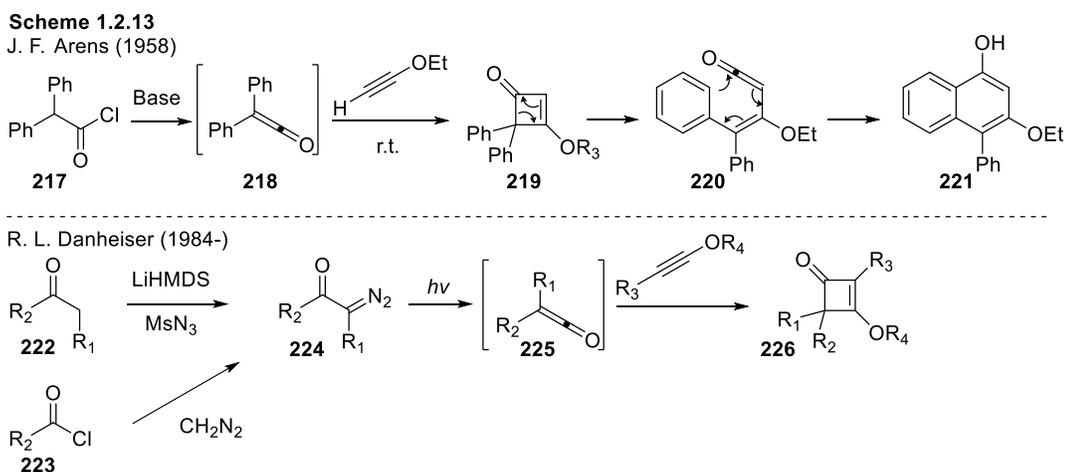
Cyclobutenone rings were the major products from the [2+2]-cycloaddition reactions between ketenes and ynoal ethers. As the Ficini's report (**Scheme 1.2.12**), cyclobutenone **184** formed as the homo-[2+2] cycloadduct from ynoal ether **182** under the thermal conditions. From then on, people showed interests in the syntheses and applications of the cyclobutenones. In addition to the homo-[2+2] cycloaddition reactions, the corresponding hetero-[2+2] cycloaddition

reactions normally took place at a lower temperature between the ynol ethers **215** and the ketenes **214** that were generated from other sources than ynol ether.



For instance, J. F. Arens employed diphenyl acetic acid chloride **217** to generate diphenyl ketene **218**, which underwent the hetero-[2+2]-cycloaddition reaction with the terminal ynol ether at room temperature (**Scheme 1.2.13**). They also observed the cyclobutenone ring of the cycloaddition product **219** was opened to give a conjugated ketene intermediate **220** under the thermal conditions, and the subsequent 6π electrocyclization generated the multisubstituted naphthol **221**.⁷⁷ However, R. B. Woodward proposed a different reaction mechanism using some chemical and analytic methods (**Scheme 1.2.16**).⁷⁸ Since 1984, the Danheiser group has been dedicating to making this cyclobutenone formation and re-opening reaction synthetically useful (**Scheme 1.2.13**). Nowadays, this cascade reaction is named after him as Danheiser benzannulation, and we will discuss more details and synthetic applications of this chemistry later in this section.⁷⁹ The Danheiser group first developed a simple one-pot ketene generation procedure as an alternative approach to the cyclobutenones **226**.⁸⁰ In particularly, they chose the photochemistry-initiated ketene generation from the precursors, α -diazo ketones **224**,

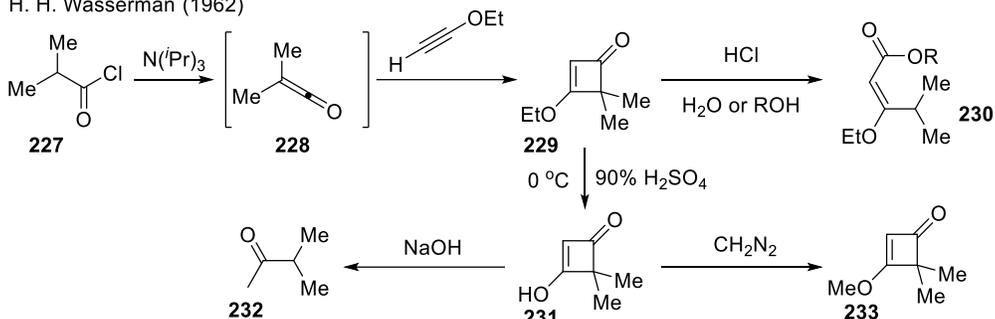
which were excited under the photo conditions. The diazo ketones **224** occurred a photo Wolff rearrangement to give the ketene intermediates **225**, and the ketenes underwent the cycloadditions with the different ynol ethers, ynol thioethers, and ynamides to form the corresponding cyclobutenone **226**. Since a wide variety of the functionalized α -diazo ketones **224** could be obtained in short steps, the scope of this cycloaddition reaction was significantly expanded.



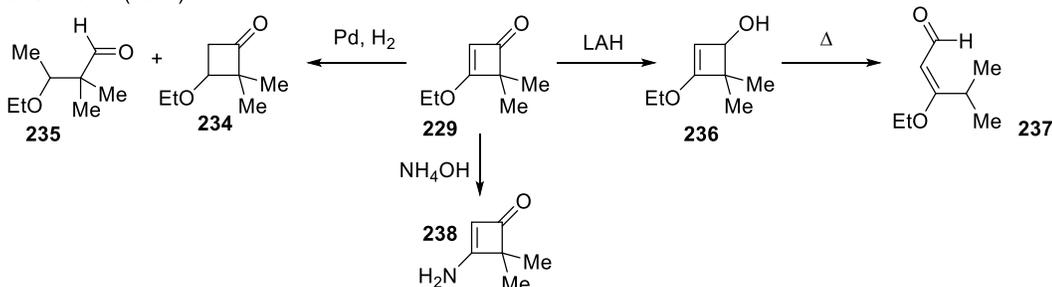
The early attempts to utilize the cycloaddition product, cyclobutenone **229**, were shown Wasserman (**Scheme 1.2.14**).⁸¹ He focused on the hydrolysis of the cyclobutenone **229**. He demonstrated the ring opening reaction gave an α,β -unsaturated ester or acid **230** under the thermal and acidic conditions.⁸² Meanwhile, he also observed the cleavage of the ethyl ether on the cyclobutenone **229**, and this diketone **231** was formed when the cyclobutenone **229** was stored with concentrated sulfuric acid in the refrigerator. This diketone **231** was found to react with diazomethane and regenerate a methyl ether **233**. Moreover, they described a strong base opened the four-member ring of the diketone **231** followed by a decarboxylation, which gave the ketone product **232**.

Scheme 1.2.14

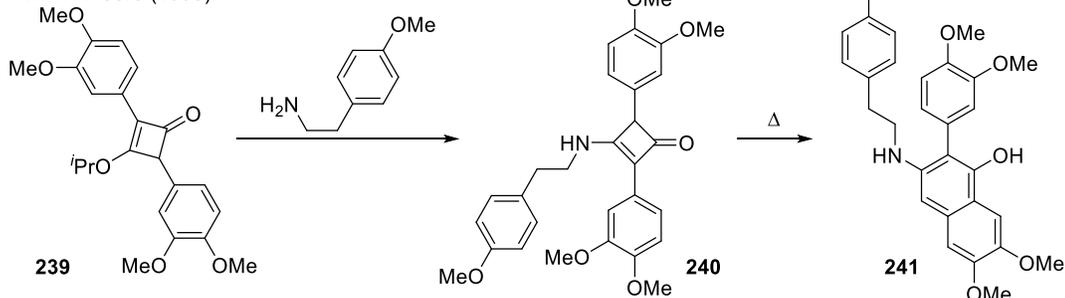
H. H. Wasserman (1962)



J. C. Martin (1964)



H. W. Moore (1995)

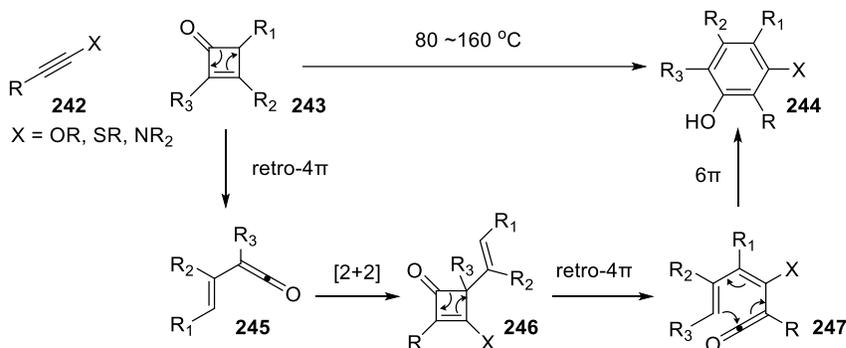


Two years later, the Martin group reported some transformations of the cyclobutenone **229**, which was also generated from the hetero-[2+2] cycloaddition reaction between the ketene **228** and the ynoether (Scheme 1.2.14).⁸³ Alternatively, they reduced the α,β -unsaturated cycloketone using LAH or hydrogenation conditions. They reduced the ketone into an allylic alcohol **236** using LAH, and this intermediate **236** would still be able to undergo a retro- 4π ring opening reaction to generate the α,β -unsaturated aldehyde **237**. On the other hand, under the hydrogenation conditions, the double bond of the cyclobutenone **229** was reduced into a

single bond. Nevertheless, Martin also noted the existence of the ring-open product **235** due to the carbon-carbon bond insertion by palladium. The Martin group also disclosed that a substitution reaction allowed to replace the ethoxyl group with amine, which generated the enamine **238**. Twenty years later, H. W. Moore and co-workers further applied this substitution reaction in the synthesis of the biologically active targets. With the diaryl cyclobutenone **239** in hand, they substituted the *iso*-propyl group of the cyclobutenone with a tyramine side chain. Under the thermal conditions, the retro-4 π /6 π -electrocyclization of the enamine **240** gave the desired aniline product **241**.⁸⁴

Scheme 1.2.15

Danheiser Benzannulation (1984-)



Since 1984, The Danheiser group published a series of papers discussing the constructions and applications of the cyclobutenones. According to the pioneering works (**Scheme 1.2.16**), the Danheiser group designed a delicate annulation reaction to form the highly substituted benzenes, and this transaction was latterly named after R. L. Danheiser as the Danheiser benzannulation reaction (**Scheme 1.2.15**). During that time, obtaining a highly substituted (> 4 substituted groups) aromatic ring was very challenging. Because the regioselectivity of the substitution reaction was difficult to control when several functional groups had been already attached to the aromatic rings. Different orientation effects from the existing substitution

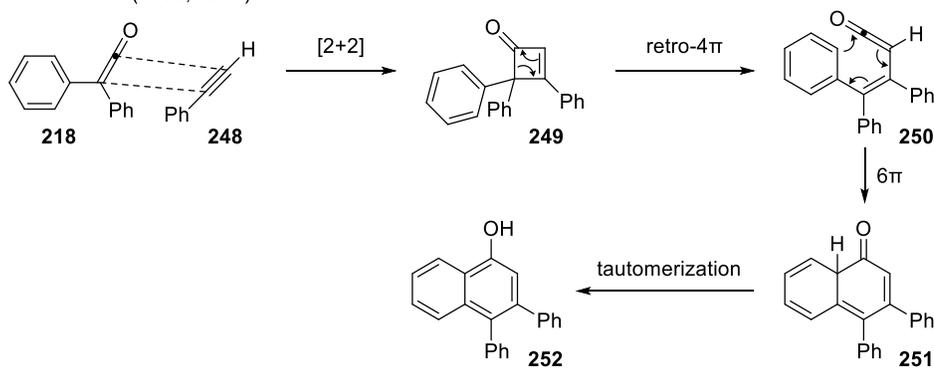
groups sometimes led to a poor selectivity for the new substitutions. Meanwhile, the existing group on the aromatic rings could be sterically hindered to prevent from attaching more substituted groups on the aromatic rings. Addressing these problems, the Danheiser group used this benzannulation reaction as a very powerful tool in synthesis of many natural products containing a highly substituted central aromatic ring. Mechanistically, Danheiser utilized the property of the cyclobutenones **243**, which could undergo a retro- 4π ring opening reaction to form the conjugated ketenes **245**. These ketene intermediates would participate a [2+2]-cycloaddition reaction with the electron rich alkyne *in situ*, such as ynol ethers, ynamides, ynol thioethers. Then, the newly formed cyclobutenones **246** would further undergo the ring opening reaction, and the generated ketene intermediates **247** would produce an aromatic ring **244** via the 6π electrocyclization and the following tautomerization. According to the substitutions on the cyclobutenones **242** and the alkynes, the Danheiser benzannulation provided a good flexibility on the choice of positions and types of substitutions group in the product.

In fact, as early as the late 1930s, people had already discovered such benzannulation reactions. H. H. Hoehn reported a [2+2]-cycloaddition reaction between diphenyl ketene **218** and phenylacetylene **248** at room temperature (Scheme 1.2.16).⁸⁵ Subsequently, the formed cyclobutenone **249** rearranged into the diphenyl substituted naphthol **252**. For the first time, they described this reaction went through a retro- 4π ring opening reaction generating the ketene intermediate **250**, followed by a 6π cyclization yielding the intermediate **251**. Two year later, they further disclosed the experimental details and elucidations of all intermediates, and some functional group transformations were also reported. Inspired by Hoehn's work, the Arens

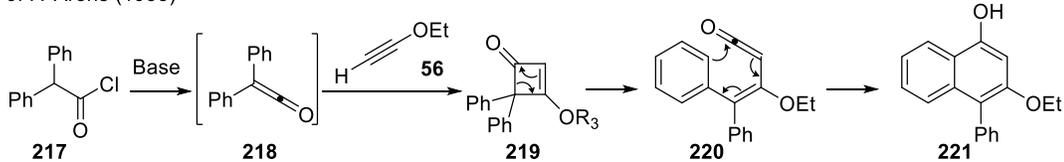
group used ynol ethers as the cycloaddition partner with diphenyl ketene **218**.⁸⁶ In contrast to phenylacetylene **248**, ynol ether **56** showed a different regioselectivity during the cycloaddition reaction. With the oxygen attached to the acetylene, the polarity of the triple bond reversed. The cyclobutenone **219** was generated with the ethyl ether connected to 3-position, and it gave the 1,3-dihydroxyl naphthol **221** in the same sequence.

Scheme 1.2.16

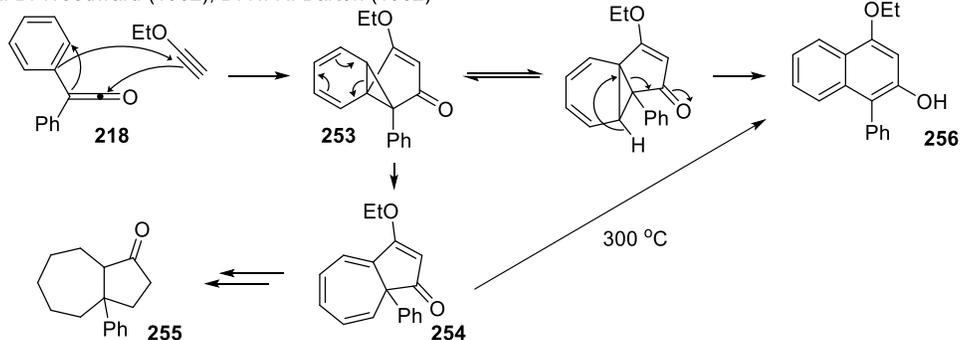
H. H. Hoehn (1939, 1941)



J. F. Arens (1958)



R. B. Woodward (1962); D. H. R. Barton (1962)



However, R. B. Woodward and D. H. R. Barton believed this reaction actually went through a different mechanism.⁸⁷ They claimed ynol ether **56** and diphenyl ketene **218** participated a stepwise [3+2]-cycloaddition reaction to form the fused ring system **253**. The following 6π

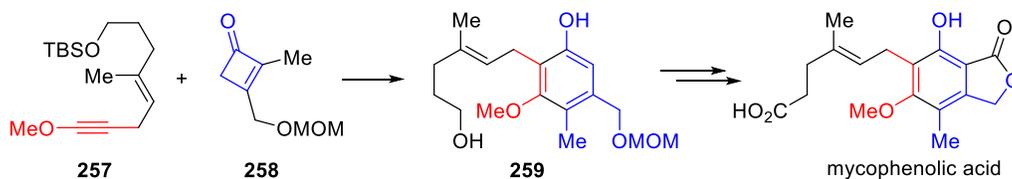
ring opening reaction converted the intermediate **253** into a 5,7-fused ring intermediates **254**. To verify this reaction mechanism and the intermediate **254**, the Woodward and Barton groups tried to transform the intermediate **254** into other intermediates in order to identify the structures via the IR and UV. One evidence was the formation of the reduced product **255**, which had the 5,7-fused ring system. Moreover, they also noted the intermediate **254** rearranged into the 1,3-dihydroxyl naphthol product **256** at 300 °C. However, from a modern view of the reaction mechanism, the mechanism proposed by Arens and Hoehn is more reasonable due to the polarity and the molecular orbital matching during the cycloaddition reactions. On the other hand, the Woodward and Barton's hypothesis was supported by the analysis of intermediate **254**, which looked suspicious nowadays due to the accuracy of the analytic methods they used at that time. Even though, their preliminary work supported Danheiser's discovery of benzannulation.

After the Danheiser group reported their benzannulation, a number of groups, including themselves, demonstrated the utilizations of this reaction in syntheses of significant intermediates and natural products (**Scheme 1.2.17**). In 1986, Danheiser and co-workers reported a total synthesis of mycophenolic acid using their benzannulation reaction to construct the fully substituted central benzene ring.⁸⁸ They utilized the retro-4 π of the cyclobutenone **258** to form the ketene intermediate, which participated the [2+2]-cycloaddition with the ynol ether **257**. Through the following 6 π -electronic cyclization reaction, the key intermediate **259** was obtained. Alternatively, H. W. Moore converted the cyclobuten-di-one **260** into the chlorinated cyclobutenone **261**. Under the thermal conditions, the Danheiser benzannulation occurred to generate the chlorinated naphthol **263** via the ketene intermediate **262**.⁸⁹ In the

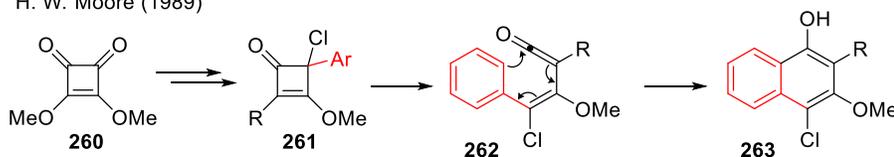
accordance with the protocols of the photo Wolff rearrangement (**Scheme 1.2.13**),⁸⁰ the Danheiser benzannulation became more practical in the complexed systems proportional to its flexibility.

Scheme 1.2.17

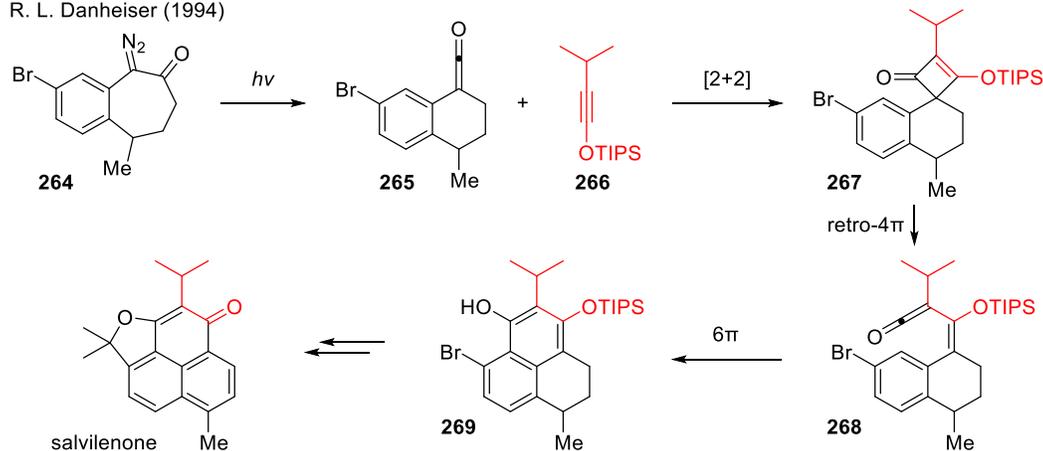
R. L. Danheiser (1986)



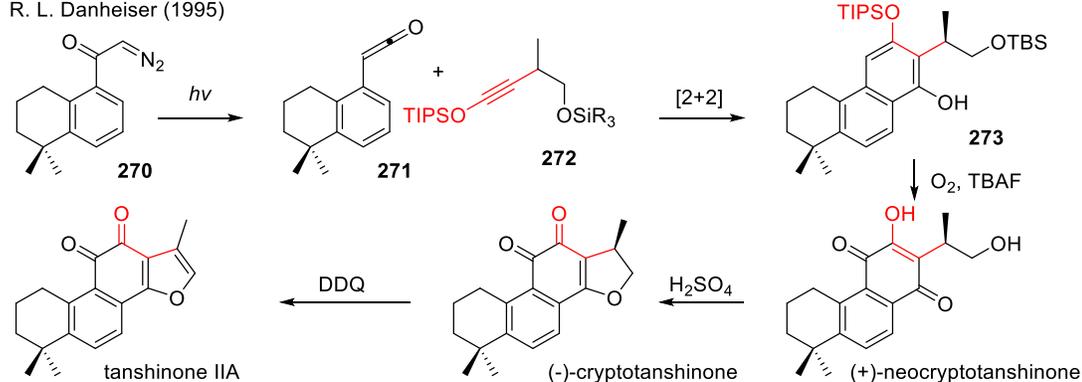
H. W. Moore (1989)



R. L. Danheiser (1994)



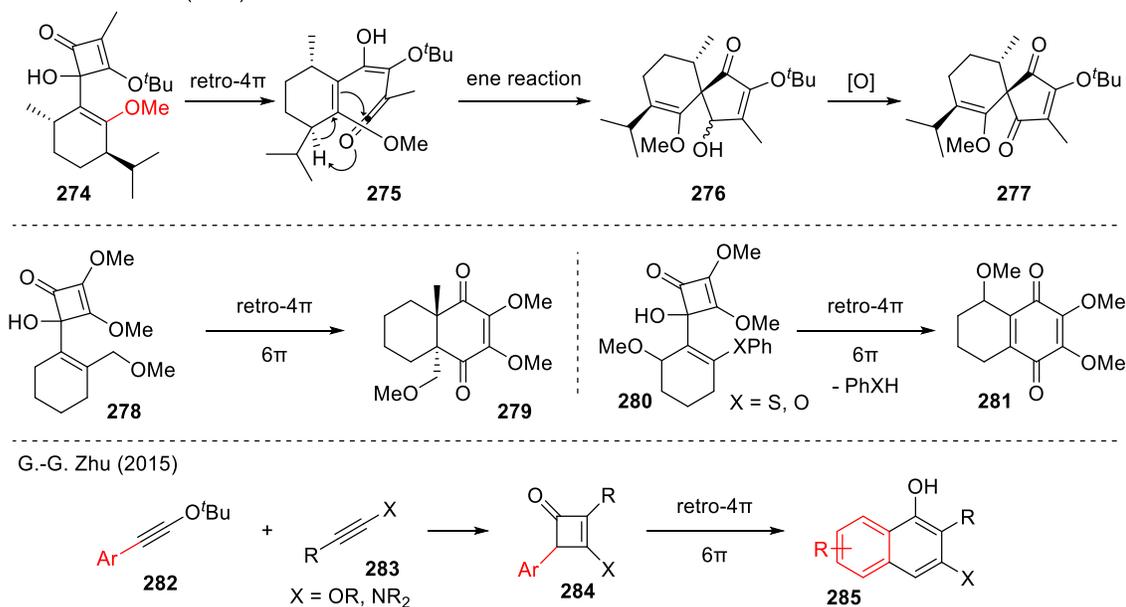
R. L. Danheiser (1995)



In 1994 and 1995, Danheiser and co-workers reported the syntheses of salvilenone and the cryptotanshinone-type natural products. They used the Danheiser benzannulation to introduce the central aromatic rings, and this reaction allowed concise and convergent synthetic strategies. In detail, under the photo conditions, the α -diazo ketone **264** rearranged into the aryl ketene **265**, which would react with the silyl ynol ether **266** to form the spiro-cyclic intermediate **267**. The following Danheiser benzannulation converted the cyclobutenone motif into the conjugated ketene substructure in **268** and, then, into the fully substituted benzene intermediate **269**. Through the introduction of the side chain, the formation of ether ring, and oxidation steps, salvilenone was synthesized.⁹⁰ Analogously, they utilized the same synthetic strategy to construct the highly substituted aromatic ring in the intermediates **273** from the diazo aryl ketone **270**. Interestingly, the aerobic oxidation yielded neocryptotanshinone, which was further treated with sulfuric acid to give another natural product, cryptotanshinone. The DDQ oxidation of cryptotanshinone provided tanshinone IIA.⁹¹

Scheme 1.2.18

D. C. Harrowven (2007)



In 2007, D. C. Harrowven and co-workers demonstrated the thermal rearrangements of the cyclobutenones and the domino reactions in the synthesis of quinones **281** (Scheme 1.2.18).⁹² In contrast to the previous research of hydroquinone syntheses using vinylcyclobutenones, the Harrowven group used the vinyl methyl ethers (in **274** red) instead of the bare vinyl groups (not shown). They planned to eliminate the alkoxy groups after the cyclization reaction to give the quinones. However, they found the spiro[4,5]deca-2,6-dien-1,4-dione **277** as the major product after the oxidation of the crude product mixtures **276** using the Dess-Martin reagent. They ascertained the mode of the collapse of the ketene intermediates was determined by electronic factors. To switch the vinyl ether into the alkyl vinyl groups in the starting material **278** led to the formation of the hydroquinones **279** indicated the electrocyclization pathway outpaced the carbonyl-ene reaction in those cases. Thus, they modified their original plan by the simply expedient of attenuating the electron density in the vinyl ether using phenoxy yl ethers in the starting material **280**. This change promoted the Danheiser annulation and the following elimination sequence over the spirocyclization pathway, and it resulted in the formation of the quinone **281**. Recently, another modification of Danheiser benzannulations was disclosed by G.-G. Zhu and co-workers. They demonstrated a practical hetero-[2+2]-cycloaddition reaction between the aryl ynol ethers **282** and the electron rich alkynes **283** (ynol ethers or ynamides). In this manner, the aryl substituted cyclobutenone rings **284** were formed. The following retro- $4\pi/6\pi$ electrocyclization could provide naphthol and naphthyl aniline **285**.⁹³

1.2.4 Other Cycloaddition Reactions and Cyclization Reactions of Ynol Ethers.

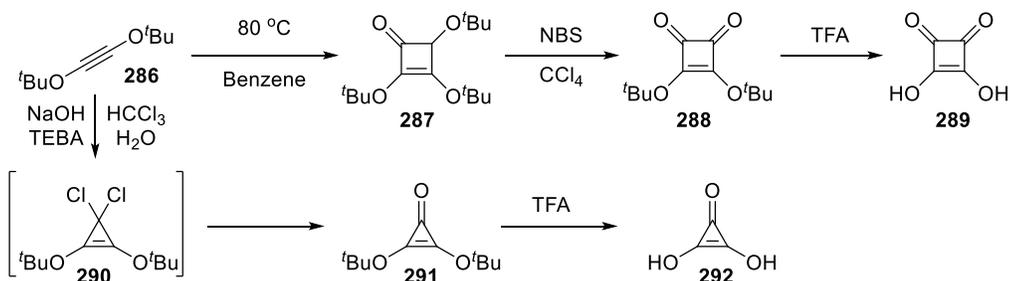
In addition to the [2+2]-cycloaddition reactions and the Danheiser benzannulations of ynol ethers, other cyclizations of the ynol ethers were also developed. In 1977, when M. A. Pericàs worked under the supervision of F. Serratosa, they together developed the synthesis of deltic acid **292** and squaric acid **289** using di-*tert*-butoxyethyne **286** (Scheme 1.2.19).⁹⁴ In detail, under the thermal conditions, the di-*tert*-butoxyethyne **286** dimerized to form tri-*tert*-butoxyl cyclobutenone **287**. Via the oxidation using NBS and the hydrolysis using TFA, they synthesized squaric acid **289**. Moreover, the di-*tert*-butoxyl ynol ether reacted with dichloromethane to generate dichlorocyclopropene **290**, and the aqueous workup of this reaction gave the deltic ester **291**. The deltic acid **292** was obtained when they treated the precursor **291** with TFA. Later, J. A. Hyatt and co-workers used the carbonyl ynol ethers **293** as the surrogate of dioxinone **295**, which would provide the acetylketene intermediate **294** under the thermal conditions.⁹⁵ Meanwhile, they observed the formation of the acetylketene **294** using the acetyl ynol ether **293** as well. The acetylketene **294** was utilized in the cycloadditions with phenyl isocyanate, cyclohexanone, the imine, and tetramethoxyethylene. As the result, the corresponding oxazine-dione **299**, dioxaspiro[5,5]undecenone **300**, hydroxazinone **298**, and hydropyranone **301** was obtained.

Additionally, the [4+2] dimerization of the acetyl ketene **294** generated the dehydroacetic acid **296**, whereas the alcoholysis of the ketene intermediate gave the β -ketoester **297**. Furthermore, a French group reported a titanium tetrachloride promoted metathesis between the ketones **302** and the ethoxyl ynol ether **303**,⁶⁰ and they thought the four-membered cycloether **304** served as the key intermediates in the conversion to the α,β -unsaturated ester **305**. According to D. Zakarya and A. Rayadh's work, T. G. Minehan reported an intramolecular version of the cross

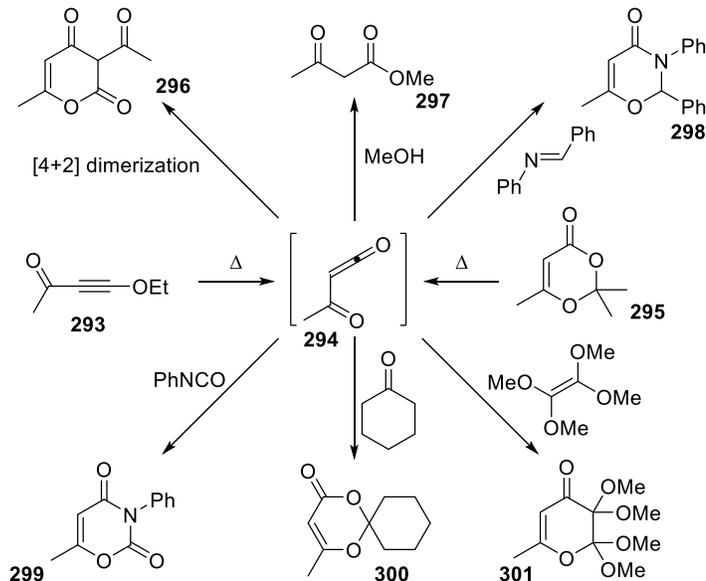
metathesis between ynoal ethers and ketones.⁹⁶ In contrast to use stoichiometric amount of titanium tetrachloride, Minehan used only a catalytic amount of scandium triflate to initiate the reaction. The conjugated ester **308** was formed via the methylated oxonium intermediate **307**.

Scheme 1.2.19

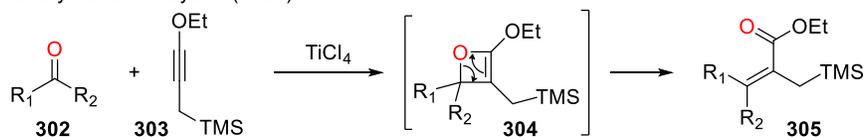
M. A. Pericàs and F. Serratosà (1977)



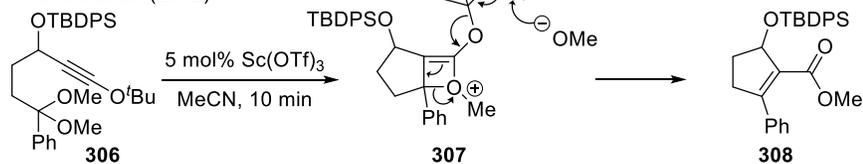
J. H. Hyatt (1984)



D. Zakarya and A. Rayadh (1994)

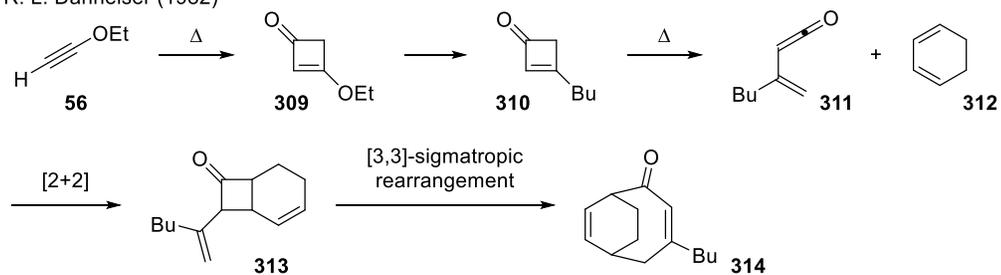


T. G. Minehan (2012)

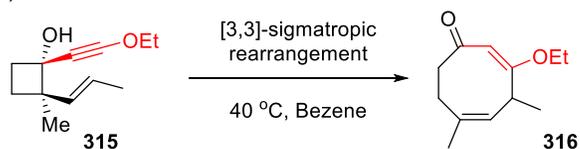


Scheme 1.2.20

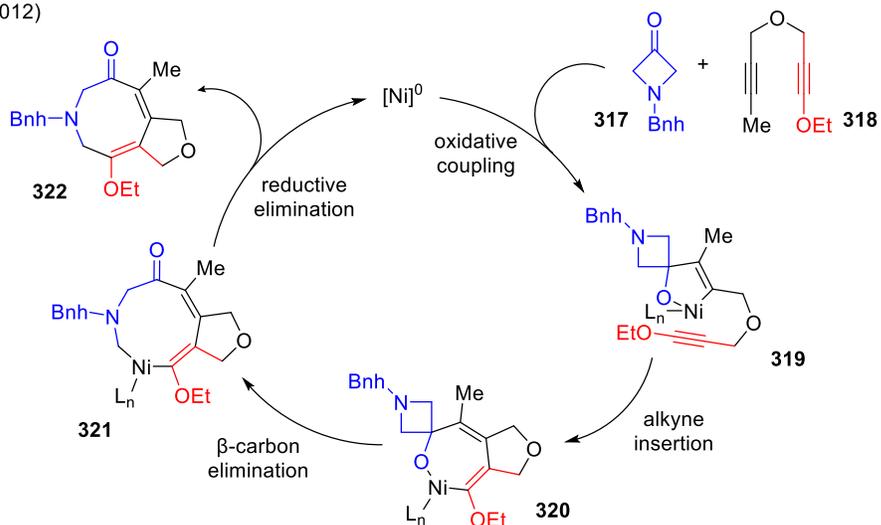
R. L. Danheiser (1982)



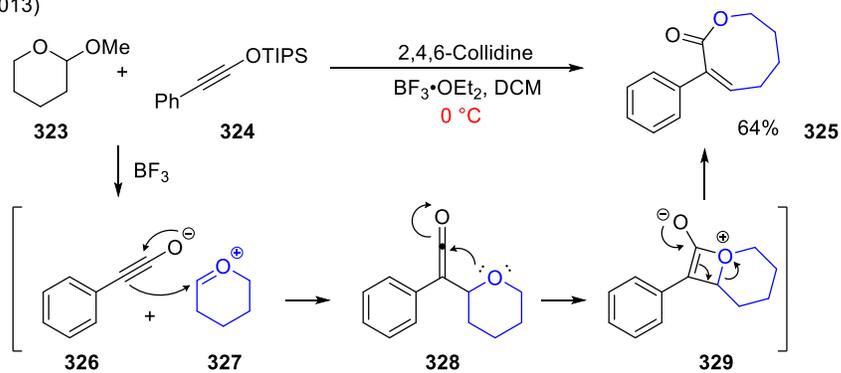
S. A. Miller (1988)



J. Louie (2012)



J.-W. Sun (2013)



Additionally, ynol ethers were found useful substructures in the construction of medium size rings (**Scheme 1.2.20**). In 1982, R. L. Danheiser and co-workers utilized the cyclobutenones in the synthesis of the cage structure of **314**.⁹⁷ The dimerization of ynol ethers provided a convenient method to synthesize the cyclobutenone **310**, just by switching the ethoxyl group of **309** into the alkyl groups. Under the thermal conditions, the cyclobutenone **310** was opened to afford the ketene **311**, which underwent a [2+2] cycloaddition with the cyclohexylidene **312** *in situ*. The adduct **313** underwent a subsequent sigmatropic rearrangement to generate the caged product **314**. Inspired by this work, the Miller group disclosed a ring expansion reaction from the ynol ether and vinyl substituted cyclobutane **315**.⁹⁸ They claimed the ring strain of cyclobutane and the tautomerization of enol drove the sigmatropic rearrangement towards the cyclooctenone **316**. Alternatively, J. Louie reported a nickel-catalyzed cycloaddition reaction to synthesize the eight-membered heterocycles.⁹⁹ This reaction was previously reported as a nickel-catalyzed coupling reaction between the azetidinones and the alkynes to afford the 3-piperodinones (not shown).¹⁰⁰ According to the previous research, they proposed if two tethered alkynes **318** were employed instead of one alkyne, both of the alkynes would insert into the sp^2 - sp^3 carbon bond of the azetidinone **317**. As they expected, the spirocyclic intermediate **319**, arising from the tethered alkynes **318** and the azetidinones **317**, would undergo an intramolecular insertion of the pendant alkyne, and it generated a seven-member ring **320**, which could then undergo the β -carbon elimination. The final reductive elimination transformed the spirocyclic system into the dihydroazocine product **322**. A year later, J.-W. Sun demonstrated that a [2+2]-cycloaddition reaction between silyl ynolate **324** and the cycloacetal **323** gave the rise to the medium and large ring size lactones, which were the

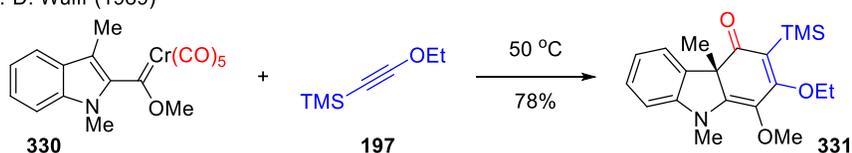
widespread subunits in natural products and therapeutic agents.¹⁰¹ Under the strong but diluted Lewis acidic conditions, the ynolate intermediates **326** and the cyclooxonium intermediates **327** would form the disubstituted ketene **328**. The arising cycloketene enolate **329** rearranged into the eight-membered lactone **325**.

Around 1990, the Wulff and the Greene group reported two types of annulations involving the carbon monoxide and ynol ether insertions (**Scheme 1.2.21**). The Wulff group utilized an aryl carbene complexes of chromium. They found indolyl chromium carbene **330** would undergo alkyne insertion to form the cyclochromium intermediate. Carbon monoxide inserted into the intermediates to give a six-member ring subunit in **331**.¹⁰² A related work from Wulff's group was disclosed a year later. They demonstrated an annulation using the aryl iminyl chromium carbene complex **332** and the ynol ether **333**.¹⁰³ In contrast to the previous report, once the imine attached to cyclochromium intermediate **334**, the expected carbon monoxide insertion did not happen. Instead, a direct reductive elimination of the chromium resulted in the formation of the substituted pyrrole **335**. On the other hand, A.E. Greene employed the ynol ethers in the Pauson-Khand reactions. Their first report demonstrated the cyclization of the ynol ether **336** using stoichiometric amount of $\text{Co}_2(\text{CO})_8$, and the carbon monoxide coordinated on the cobalt served as the CO source for the carbonyl formation in the adduct **337**. However, the 24% to 38% reaction yields were displeasing.¹⁰⁴ A menthyl group served as the chiral auxiliary in this reaction, but the low diastereoselectivity was observed after the reaction. A decade later in 2000, the Livinghouse group expanded upon Greene's previous work, wherein they mentioned a $\text{Co}_2(\text{CO})_8$ catalyzed Pauson-Khand reaction using ynol ether **338** as the starting material. In this way, they synthesized the cyclopentanone product **339**.¹⁰⁵ The yields

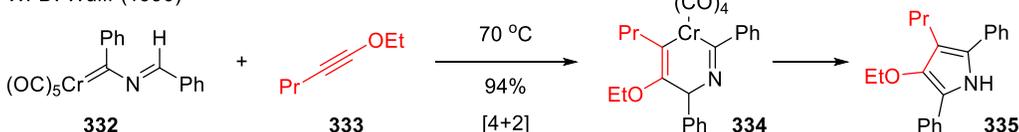
of this reaction were improved in comparison to their previous work, which might result from the introduction of the two methyl groups and the steric hindered silyl ether on the tethered bridge. On the other hand, they used a less hindered ethoxyl ynoyl ether instead of the adamantoxyl or menthoxy ynoyl ethers during the reaction. A 86% yield of **339** was claimed from the substrate **338**, and a slight diastereoselectivity was found in the product.

Scheme 1.2.21

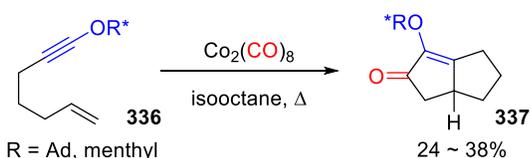
W. D. Wulff (1989)



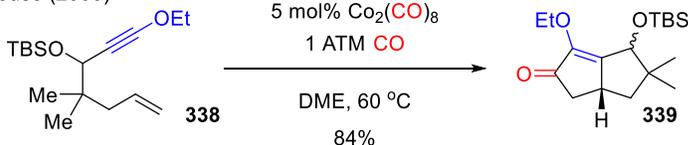
W. D. Wulff (1990)



A. E. Greene (1990)



T. Livinghouse (2000)



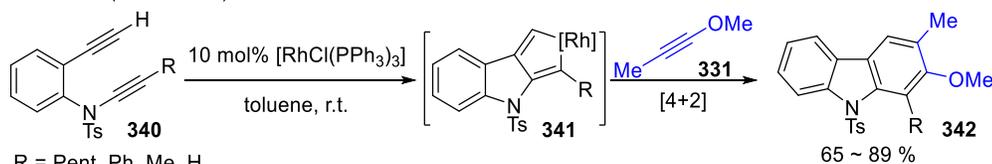
Moreover, ynoyl ethers could also participate in some transition-metal catalyzed ring formations.

B. Witulski and co-workers found rhodium could catalyze an alkyne trimerization (**Scheme 1.2.22**).¹⁰⁶ They found the tethered di-alkyne starting material would interact with the rhodium catalyst to form a metallic heterocycle **341**. In the presence of an electron rich alkyne (as ynoyl ether **331**) *in situ*, an alkyne insertion followed by the reductive elimination would generate the carbazole product **342**. For this reaction, Witulski reported decent yields of the products

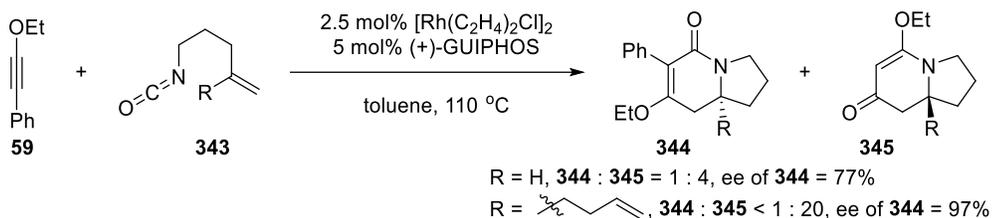
ranging from 65% to 89%. An intriguing asymmetric cyclization reaction between the ynol ether **59** and the alkenyl isocyanate **343** was mentioned by T. Rovis.¹⁰⁷ In his paper, many internal alkynes were employed in the rhodium-catalyzed cycloadditions with the alkenyl isocyanates, and they documented the impact of the steric and electronic effects of the alkynes during this reaction in order to systemically predict the stereochemistry outcome of this reaction. In particular, when the linear alkenes (R = H) were used, a great yield of the unsaturated lactam **344** and the vinylogous lactam **345** was observed. The vinylogous lactam **345** was noticed as the major product with no observation of *ee*, whereas the unsaturated lactam **344** was the minor product with a 77% *ee*. Branched alkenes gave enlarged selectivity between **344** and **345** from 1:4 (R = H) to 1:20 (R = homo allyl) compared to terminal alkenes. In addition, a greater *ee* value of **344** was noticed.

Scheme 1.2.22

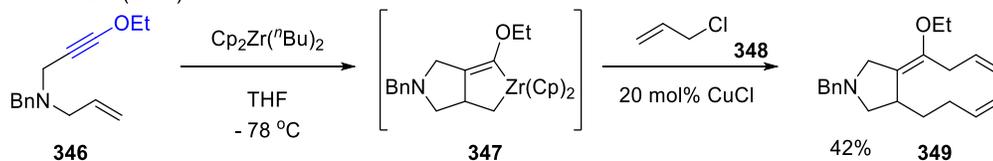
B. Witulski (2002, 2009)



T. Rovis (2009)



M. Kotora (2016)



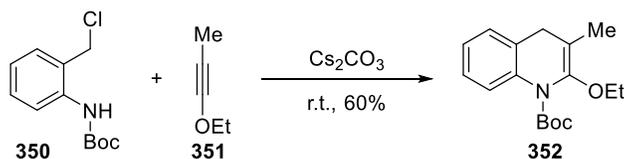
In 2016, M. Kotora stated the stoichiometric amount of di-butyl zirconocene could trigger the cyclization of the 1,6- and 1,7- enynes **346**.¹⁰⁸ According to the references, the zirconocene reagent was prepared from the Negishi reagent.¹⁰⁹ During the reaction, the enynes **346** would react with the di-butyl zirconocene to proceed the corresponding zirconacyclopentenes **347**. The ring strain of the zirconacyclopentenes and the possible four-member ring product stopped this intermediate from the reductive elimination. To quench the zirconacyclic intermediates, allyl chloride **348** was added as the electrophile to form two new carbon-carbon bonds. The two terminal alkenes in the product **349** were further used in the ring close metathesis in order to form a large size ring. Unfortunately, the product carrying the enol ether motif failed to give any desired ring close metathesis product.

Meanwhile, ynol ethers could participate other cycloaddition reactions, such as [4+2] cycloadditions and 1,3-dipolarcycloaddition reactions. With the alkoxy groups attached to acetylene, the triple bond became electron rich due to the donation from oxygen lone pair electrons to the π orbital of the triple bond, and the polarity of the triple bond also reversed because of the σ -withdraw effect by the oxygen. For those reasons, the other cycloaddition partners with ynol ethers always need to be electron deficient. Therefore, ynol ethers could be suitable for the polarity reversed [4+2]-cycloadditions as well as the 1,3-dipolar cycloadditions (**Scheme 1.2.23**). E. J. Corey found a simple method for the *o*-azaxylylenes production, where the elimination of hydrogen chloride from the amide or sulfonamide derivatives of the *o*-chloromethylaniline **350** would generate the *o*-azaxylylenes.¹¹⁰ As they discovered, the *o*-azaxylylene intermediates were trapped by the electron rich olefins to form the hydroquinoline derivatives (not shown). In addition to the cycloaddition with the olefins, the *o*-

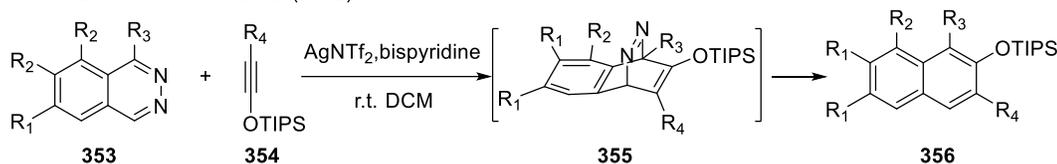
chloromethylanilines **350** were employed to produce *o*-azaxylylenes *in situ*, which reacted with the ynol ether **351** furnishing the dihydroquinoline derivatives **352**.

Scheme 1.2.23

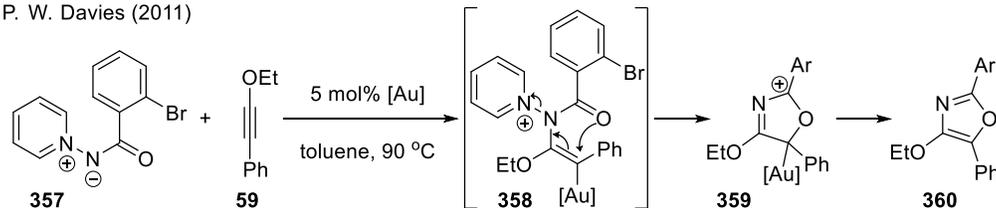
E. J. Corey (1999)



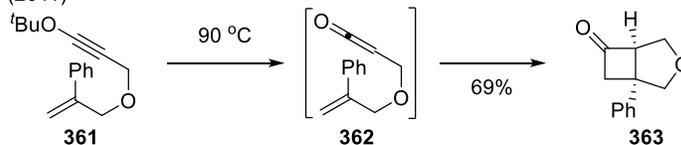
S. A. Kozmin and V. H. Rawal (2012)



P. W. Davies (2011)



T. G. Minehan (2011)



Analogously, Kozmin and Rawal demonstrated a silver-catalyzed Diels-Alder reaction of the 1,2-diazines **353** and the silyl ynolate **354**.¹¹¹ They proposed a stepwise reaction mechanism, wherein the silver helped the diazines **353** dearomatize and increased their electrophilic ability. In other words, the silver cut down the activation energy of the cycloaddition reaction. The bridged intermediates **355** were considered as the key intermediates, and the silver catalyst promoted the extrusion of the nitrogen gas and reformation of the naphthalene structure in the product **356**.

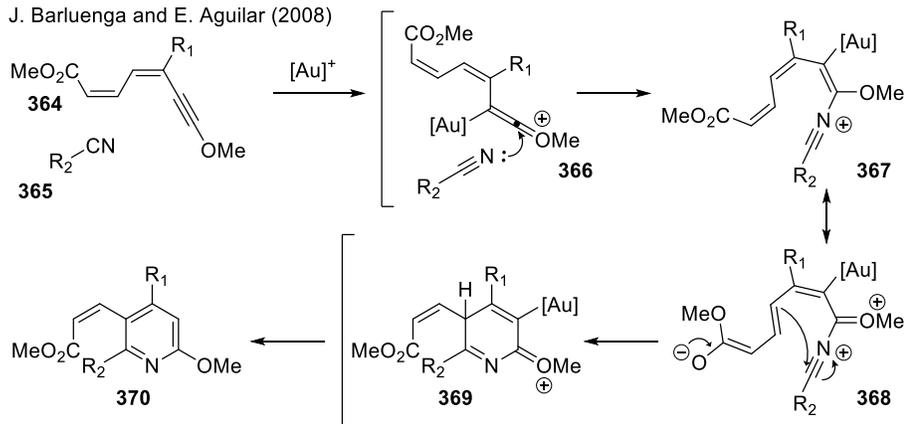
Additionally, ynoles were the excellent substrates in the dipolar cycloaddition reactions. In 2011, P. W. Davies reported the synthesis of 2,4,5-trisubstituted oxazoles using a gold-catalyzed formal [3+2] cycloaddition reaction (**Scheme 1.2.23**).²⁵ As the strong π -bonding Lewis acid, the gold catalyst helped the polarization of ynole ether **59**, and it also made the α -carbon more electrophilic. By these means, the anion on the robust pyridine-N-aminides **357** would attack the α -carbon of the ynole ether to produce the intermediate **358**, which would cyclize from the carbonyl oxygen and extrude the pyridine. The following electronic quenching and the gold elimination from **359** furnished the synthesis of the trisubstituted oxazole products **360**. In addition to the 1,3-dipolar cycloadditions and the [4+2]-cycloaddition reactions, ynole ether motifs were found to undergo an intramolecular [2+2]-cycloaddition reaction with an electronically neutral olefin.¹¹² In Minehan's report, the ynole ether **361** provided the ketene intermediate **362** under the thermal conditions. The ketene and the alkenyl motif would participate in an intramolecular cycloaddition yielding the corresponding cyclobutane product **363**. An excellent diastereoselectivity in the products was observed when a steric hindered functional group was linked to the substrates.

Furthermore, people realized some π -bonding Lewis acids, such as ionic gold or copper, could catalyze the intramolecular cyclization reactions using the ynoles (**Scheme 1.2.24**). A representative work in this area was documented by J. Barluenga and E. Aguilar from Spain.¹¹³ They discovered the ynoles **364** interacted with the gold species to form a very reactive intermediate, methylated gold ketene cation **366**. When there were alkyl, vinyl, or aryl nitriles **365** in the reaction system, the lone pair electrons on the nitrile nitrogen would attack the gold ketene cation **366**. The resonance structure **368** of the adduct **367** underwent the intramolecular

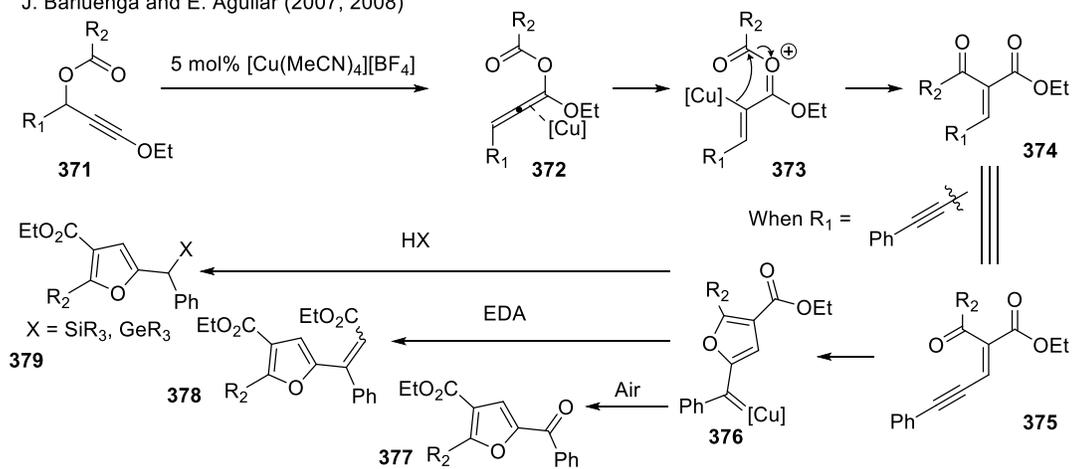
nucleophilic addition to the carbon-nitrogen triple bond. Subsequent deprotonation of the methylated oxonium intermediate **369** generated the aromatic six-member ring and gave the desired pyridine product **370**. Another interesting work from J. Barluenga and E. Aguilar was the synthesis of the substituted furans using ionic copper catalyst. In detail, they found the propargyl acetate ynoyl ether **371** would tautomerized into an allenyl ketene acetal **372**, whose metallated isomer structure **373** could engage in an acyl migration to form the Knoevenagel derivatives.¹¹⁴ Moreover, the stereoselectivity of the olefins was controlled by the metal catalyst used in the reaction. The copper catalyst would give (*E*)-olefins, whereas the platinum afforded the (*Z*)-olefins. In their following paper, they proposed a special substrate **375** ($R_1 =$ phenylacetylenyl) underwent a cascade reaction with the copper catalyst. Consequentially, the furans would be cyclized under the same reaction conditions, and the furanyl copper carbenes **376** were formed after the reaction. To further utilize the copper carbene **376**, they tried the oxidation, the olefination and the hydrosilylation of the carbene to give the products **379**, **378**, and **377**, respectively.¹¹⁵

Scheme 1.2.24

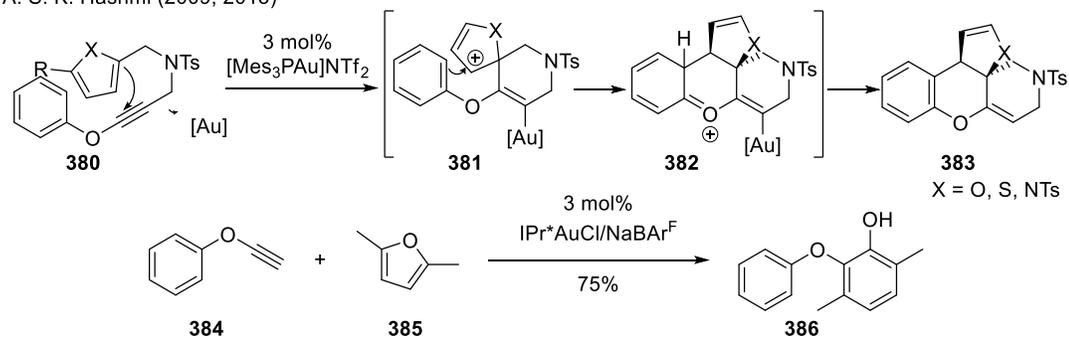
J. Barluenga and E. Aguilar (2008)



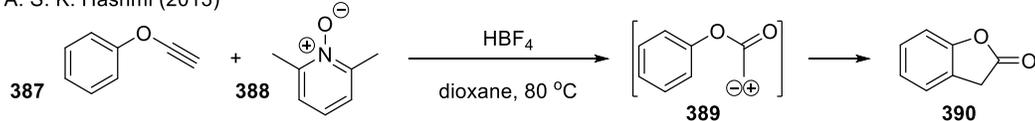
J. Barluenga and E. Aguilar (2007, 2008)



A. S. K. Hashmi (2009, 2015)



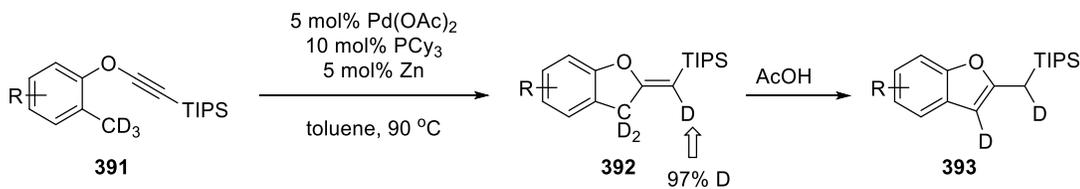
A. S. K. Hashmi (2013)



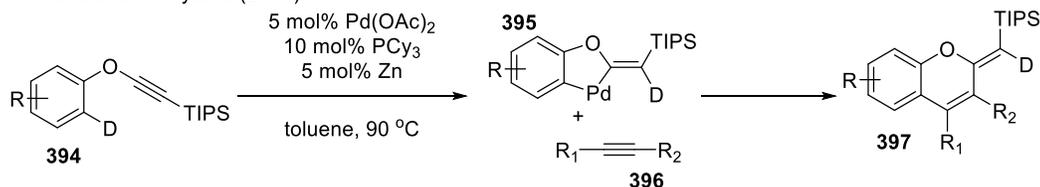
Stephen Hashimi is famous for the activation of triple bonds using gold catalysts. He and his co-workers also researched the activations and the applications of ynol ethers using gold catalysts. In 2009, they reported the gold-catalyzed cyclization of phenoxy ynol ethers **380**, which tethered to a furan, pyrrole, or thiophene (**Scheme 1.2.24**).¹¹⁶ The gold catalyst would force the ynol ether into a Friedel-Crafts type domino reaction, which firstly generated the [4,5]-spirocyclic ring system **381**. Another Friedel-Crafts reaction would generate the intermediate **382**, which was followed by a tautomerization to afford the product **383**. As a complementary work, the Hashimi group developed an intermolecular version of this reaction utilizing phenoxy ynol ether **384** and dimethylfuran **385**. However, a diaryl ether **386** would result from this reaction instead.¹¹⁷ Moreover, Hashimi and co-workers also developed the synthetic approach to benzofuranones through a metal-free oxidative cyclization of phenoxy ynol ethers **387**. Dimethyl pyridine *N*-oxide **388** acted as the oxidant during the reaction, which was proposed to give the expected product via an acetic carbene intermediate **389**.¹¹⁸

Scheme 1.2.25

Y. Minami and T. Hiyama (2013)



Y. Minami and T. Hiyama (2015)



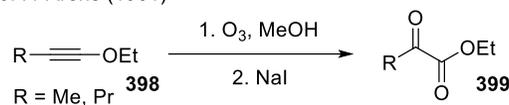
More recently, Y. Minami and T. Hiyama brought a novel concept in the exploration of the ynol ethers (**Scheme 1.2.25**). For the first, they used the ynol ether partially as the directing

group in a palladium catalyzed C-H functionalization reactions. Their first attempts focused on the activation of the benzyl protons in **391**.¹¹⁹ A deuterated experiment of this hydrobenzylation showed the migration of the benzyl proton to the ynol ether motif in **392**, and the benzofurans **393** was obtained via a proton transfer. A plausible mechanism indicated the strong binding between the electron rich triple bond of the ynol ethers and the palladium catalyst. A hydride abstraction was followed by the carbometalation setting up the right bond connection between the benzylic carbon and the α -carbon of the ynol ether motif. The reductive elimination step donated the hydride to the β -carbon of the ynol ether, and this pathway produced the desired products in excellent yields. The substrates or the directing group in the substrates was designed prudently. The ynol ether motif ensured the strong binding between the π -bond of the alkyne and the metal catalyst, and the silyl group attached to the alkyne helped to stabilize the product of carbometalation more than just to reduce the activation energy of the carbometalation. Finally, the ynol ether skeleton was perfectly used in the newly formed molecule, so it is not only served as the directing group but the construction component during the reaction. The silyl group could be easily converted into some other functional groups, which made this reaction more practical. Two years later, they employed the same strategy using the ynol ethers as the directing group in the functionalization of the *ortho*-phenyl position in **394**.¹²⁰ The deuterated experiment implied the formation of the five-member ring **395** containing palladium via the C-H bond insertion. The external alkyne **396** was added to undergo an alkyne insertion with the palladium intermediates. The final reductive elimination produced product **397**.

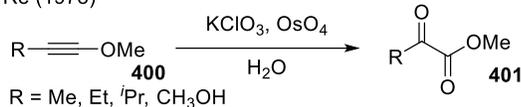
1.2.5 Redox Reactions and Lewis Acid Promoted Activations of Ynol Ethers.

Scheme 1.2.26

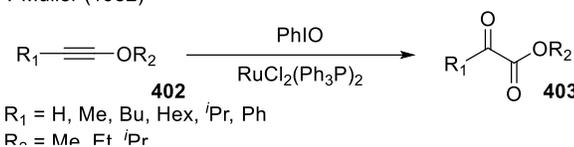
J. F. Arens (1961)



L. Re (1978)



P. Müller (1982)



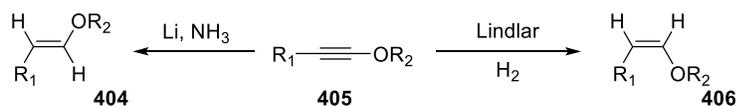
Ynol ethers are also considered as special alkynes. Therefore, the oxidation, reduction, and activation methods for the normal alkynes could be applied on the ynol ethers to achieve many special structures. In this section, we are going to review the history of the ynol ethers activation reaction and any other related reactions.

Early in 1960, the Arens group published a series of papers discussing the synthesis of the ynol ethers as well as the functionalizations of ynol ethers (**Scheme 1.2.6**). They discovered the ynol ether **398** could be oxidized by ozone, and to quench the oxidation reaction with sodium iodide gave the rise to the α -ketoester **399**.¹²¹ According to the dihydroxylation of the olefins using osmium tetroxide, L. Re and co-workers used a catalytic amount of osmium tetroxide and the stoichiometric amount of potassium chlorate in the oxidation of ynol ether **400**, and this oxidation also gave the α -ketoester **401**.¹²² Alternative, another transition-metal catalyzed oxidation was demonstrated by P. Müller. In their report, $\text{RuCl}_2(\text{PP}_3)_2$ served as the catalyst, whereas iodosobenzene was the oxidant. Under their conditions, the ynol ethers **402** was

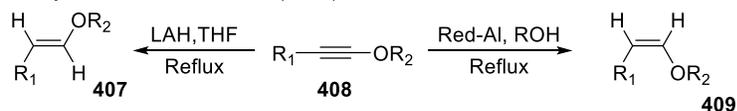
oxidized into the α -ketoester **403**.¹²³ These oxidation conditions were milder, easier to handle, and less toxic than those previous reports.

Scheme 1.2.27

A. E. Greene (1987)

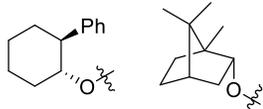


A. Moyano and M. A. Pericàs (1992)

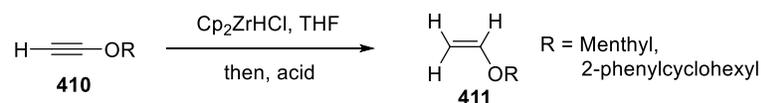


$\text{R}_1 = \text{CH}_3, \text{C}_5\text{H}_{11}, (\text{CH}_3)_3\text{CCH}_2, \text{HCC}(\text{CH}_2)_3, \text{CH}_3\text{CC}(\text{CH}_2)_3$

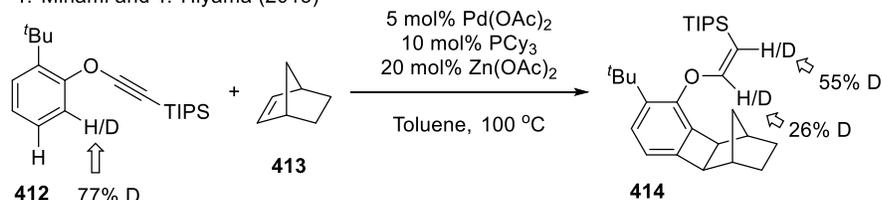
$\text{R}_2 =$



P. H. Dussault (1999)



Y. Minami and T. Hiyama (2015)

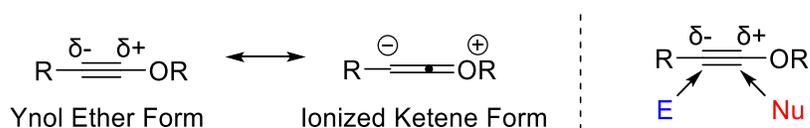


However, the controlled reduction of ynol ethers did not appear until the late 1980s (**Scheme 1.2.27**). The Greene group reported the *syn*- and *anti*- reductions using the different reagents. For instance, the catalytic hydrogenation of the ynol ethers **405** give the *cis*-olefins **406**, but, under the Birch reduction conditions, the ynol ethers would afford the *trans*-olefins **404**.¹²⁴ Four years later, A. Moyano and M. A. Pericàs documented a more practical reductive conditions for the ynol ethers. They aimed at increasing the steric effect of the alkoxy group on the ynol ether **408** to increase the stereoselectivity of the reduction. To treat the ynol ether

408 with LAH in THF would give the *trans*-olefins **407**, while the more hindered Red-Al reductant in alcohol solvent would generate the *cis*-olefins **409**.¹²⁵ The hydrozirconocene chloride could promote the hydrozirconation reaction with the terminal ynol ethers **410**. To workup the vinyl zirconocene intermediates under the acidic conditions, the vinyl ether **411** was generated.¹²⁶ According to the findings of the ynol ethers as the directing group, Minami and Hiyama found the aromatic hydrogen could transfer to the ynol ether and reduce it into the vinyl ether. Mechanistically, norbornene **413** served as the bridge for the palladium to reach the *meta*-hydride. Product **414** was obtained.¹²⁷

Ynol ethers are very reactive alkynes largely due to the conjugation between the π -bond and the oxygen lone pairs (**Figure 1.2.3**). This conjugation allows the ynol ethers to have the ionized ketene form as the resonance structure. Under the ynol ether form, the α -carbon of the ynol ethers is partially positive charged, and the β -carbon of the ynol ethers carries partially negative charge. But Under the ionized ketene form, the oxygen of the ynol ethers carries the positive charge, while the β -carbon of the ynol ether has negative charge. This electronic property of the ynol ethers made the α -carbon prone to nucleophilic attacks and the β -carbon prone to electrophilic attacks.

Figure 1.2.3



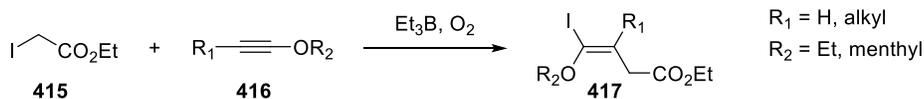
Utilizing this property, people developed a series of alkyne activations of the ynol ethers (**Scheme 1.2.28**). The synthesis of the tri- and tetra-substituted olefins are always difficult, and to control the stereoselectivity of the generated olefins was tricky. One widely used method

for the highly substituted olefin is the carbonation of the alkynes. F. Longprè found the carbon-iodide bond of the iodoethyl acetate **415** homolyzed with the radical generators ($\text{Et}_3\text{B}/\text{O}_2$).¹²⁸ The generated carbon radical attacked the ynol ether **416**, and the resultant vinyl radical was quenched by iodine radical giving the tetra-substituted olefin **417**. From 2011, the Zhu group published a lot of beautiful works on the activation of the ynol ether triple bonds.¹²⁹ Their first success in this area used a palladium catalyst to activate the triple bond of the aryl ynol ethers **418**, and the chloride anion attacked the α -carbon. This chloropalladation of the ynol ether gave the intermediate **419**, and the following olefin insertion and β -chloroelimination offered the chlorovinyl ether **421**. Two years later, he published a hydroarylation of the ynol ethers **422**.¹³⁰ Under the basic conditions, the arylpalladation afforded the vinyl palladium species, and the protonation of this intermediate produced the *cis*-hydroarylation product **425**. In contrast to the *cis*-addition, the Zhu group also created a method allowing the *trans*-addition product from the ynol ethers.¹³¹ They employed the benzoic acids **426** to add to the aryl ynol ethers **59**, and the adduct could generate the benzoic acid radical with the silver oxide under the thermal condition. The *trans*-addition products **427** were further converted into the *trans*-hydroarylation products by the cleavage of the carbon-oxygen bond in **427** via a nickel-catalyzed reaction. Alternatively, the Zhu and Suzuki group reported the hydroboration of the ynol ethers **416**.¹³² The hydride was successfully delivered to the α -carbon of the ynol ether, and the related vinyl pinacol boron (by Zhu) and catechol boron (by Suzuki) **429** was obtained. In one-pot, a subsequent Suzuki coupling reaction using the boron intermediate **429** constructed a new carbon-carbon bond. The β -disubstituted vinyl ynol ether **430** was obtained. Furthermore, M. S. Reddy developed a useful synthetic methodology of the 1,4-enyn-3-ones

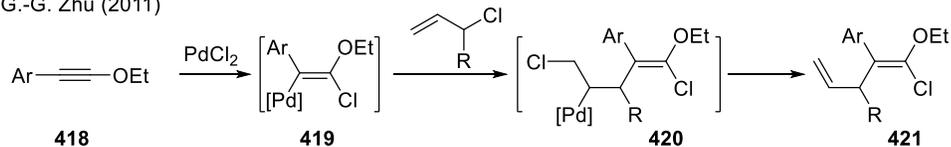
433 utilizing a hydroalkynylation of the phenoxy ynol ethers **431**.¹³³ The palladium catalyzed the carbometalation of the ynol ethers, while the TEA acted as the proton scavenger to complete the catalytic cycle. After the acidic workup, the corresponding hydroalkynylation products provided the desired enynone products **433**. In recent years, the fluoride atoms were found to increase the biological activities in many pharmaceuticals. In contrast to its important property, the synthesis of fluorinated compound is currently limited. Under this background, the Zhu group invented a difluorination reaction of the ynol ethers **434** via a radical pathway.¹³⁴ The selectfluor was employed as the fluorine radical source, which initiated the fluorination reaction. In the presence of other halides, the selectfluor and lithium halides gave the mixed fluorohalogenated product **436**. Last year, N. Saito and Y. Sato developed a hydrocarboxylation of the ynol ethers **422** using the nickel catalysts and carbon dioxide gas.¹³⁵ The nickel lactone intermediated could be quenched to afford the corresponding β -aryloxypropionic acid derivatives and furnish the catalytic cycle.

Scheme 1.2.28

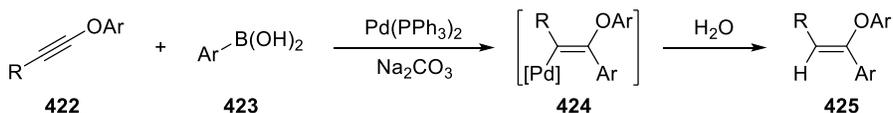
F. Longpré (2008)



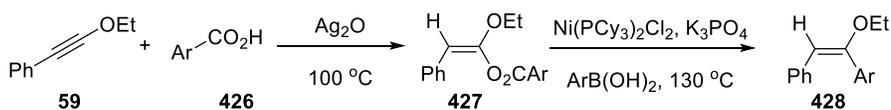
G.-G. Zhu (2011)



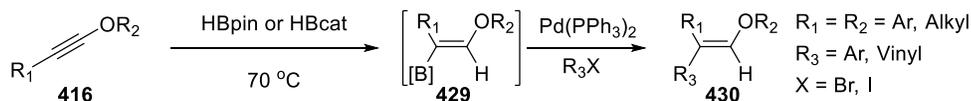
G.-G. Zhu (2013)



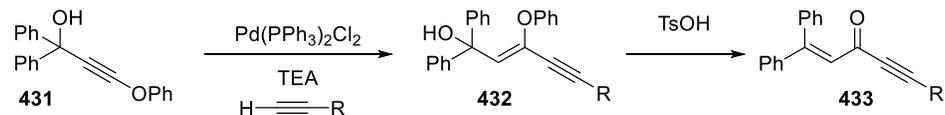
G.-G. Zhu (2014)



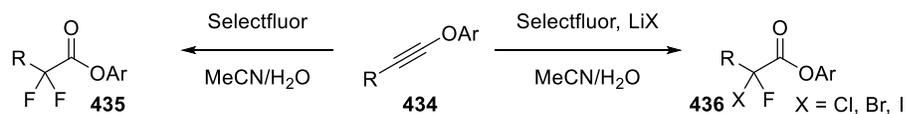
A. Suzuki (1987); G.-G. Zhu (2013)



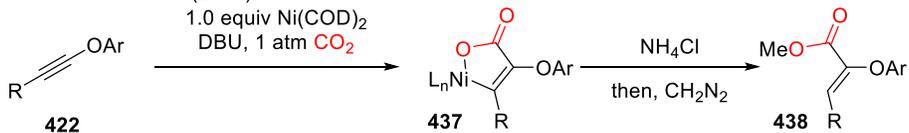
M. S. Reddy (2015)



G.-G. Zhu (2014)

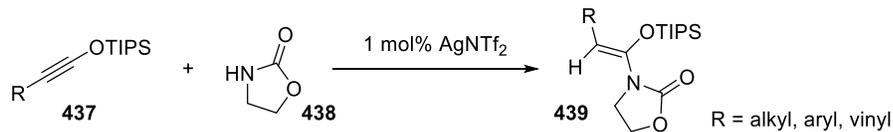


N. Saito and Y. Sato (2015)

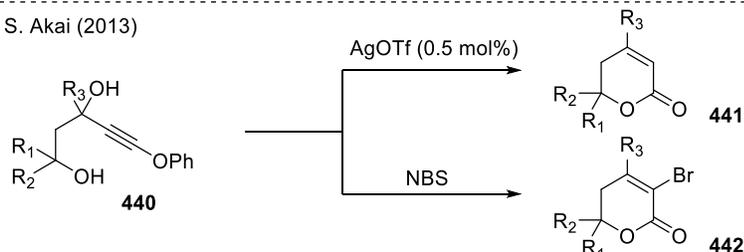


Scheme 1.2.29

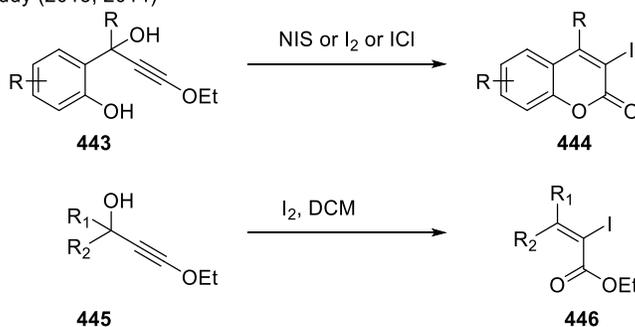
S. A. Kozmin (2006)



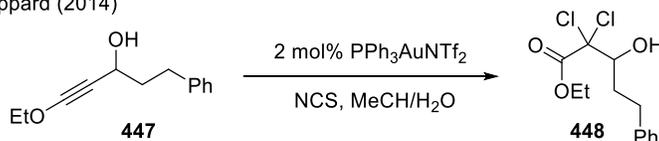
S. Akai (2013)



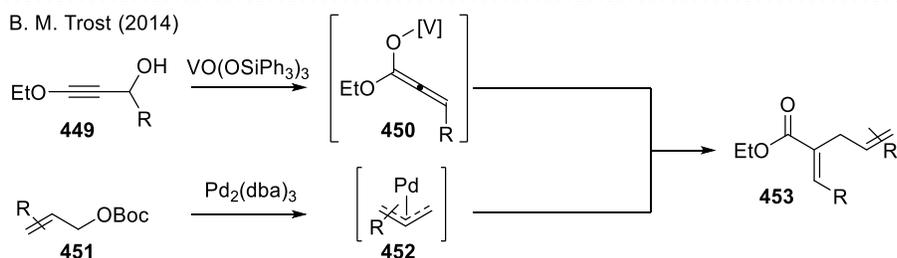
M. S. Reddy (2013, 2014)



T. D. Sheppard (2014)



B. M. Trost (2014)



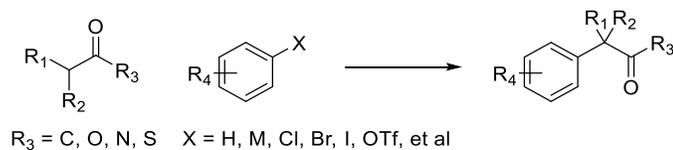
Several other groups reported the addition reactions to ynoles using the heteroatom nucleophiles (**Scheme 1.2.29**). J.-W. Sun developed a silver-catalyzed hydroamination of the silyl ynoles under the supervision of S. A. Kozmin.¹³⁶ They found the amide nitrogen would attack the α -carbon of the silyl ynole **437** to form the silyl enols **438**. Meanwhile,

there were more reports about using the intramolecular nucleophiles to attack the ynol ethers.¹³⁷ M. S. Reddy modified the Schuster-Meyer rearrangement using the ynol ether **442**. The halogenated unsaturated lactones **443** was synthesized following their procedure.¹³⁸ Additionally, they found the iodine could trigger the Schuster-Meyer reaction and generate the halogenated unsaturated ester **445**.¹³⁹ Interestingly, Sheppard reported a gold-catalyzed dichlorination reaction of the ynol ethers **446**.¹⁴⁰ In contrast to the previous report, the Lewis acidic condition did not offer the Schuster-Meyer rearrangement products, unsaturated ester, but it gave the rise to the α -dichlorinated β -hydroxide esters **447**. In 2014, B. M. Trost demonstrated a modification of the Schuster-Meyer rearrangement, and their dual-catalyst system was employed in this methodology.¹⁴¹ The vanadium catalyst would push the ynol ether **448** to rearrange into the allenyl ketene acetal **449**, but the vanadium would hold the rearrangement at this stage from the formation of the unsaturated ester (SM rearrangement product). On the other hand, the allylic Boc ester **450** would react with the palladium catalyst to give the allyl palladium **451**, which served as the nucleophile trapping the allenyl ketene acetal **449**. The α -allyl substituted α,β -unsaturated ester **452** was formed.

1.3 Synthesis of Aryl Acetic Acid Derivatives and Dictyodendrins

1.3.1 Synthesis of Aryl Acetic Acid Derivatives

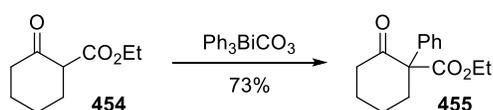
Figure 1.3.1



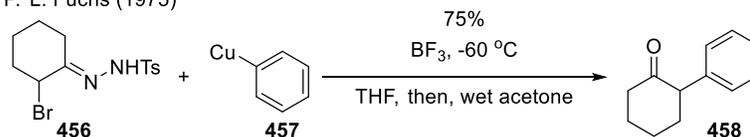
Aryl acetic acid derivatives are common subunits in the biologically active natural products and pharmaceuticals. Therefore, people have never stopped in the exploration of the synthetic methods targeting the α -arylated carbonyl compound. Among the different periods, people invented many distinguished methods to synthesize them, which diversified the approaches to the α -arylated acetic acid derivatives.

Scheme 1.3.1

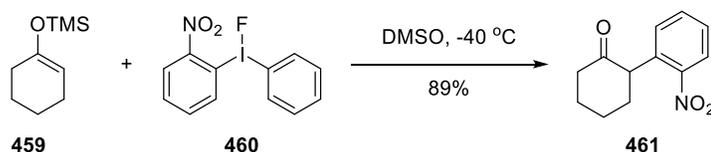
D. H. R. Barton (1988)



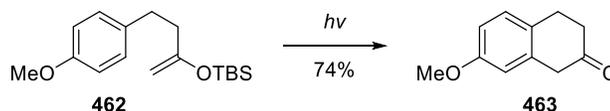
P. L. Fuchs (1975)



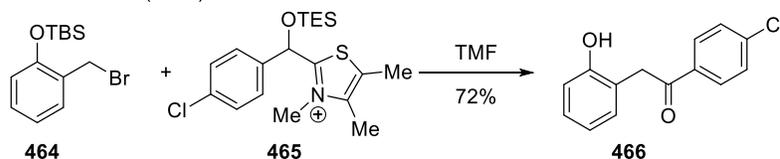
V. H. Rawal (1999)



G. Pandey (1993)



K. A. Scheidt (2007)



The early studies of the α -arylation were summarized in Barton's review in 1988. Their group had developed a series of the α -arylation of the carbonyl compounds using the aryl bismuth reagents (**Scheme 1.3.1**). One representative example was shown as the arylation of 2-

(ethoxycarbonyl)-cyclohexanone **454**, and, in this work, they obtained the phenylated product **455** with a quaternary carbon center.¹⁴² Alternatively, the aryl coppers **457** were employed in the coupling of the β -bromohydrazone **456**, and the α -arylated cyclohexanone **458** was generated after the hydrolysis of the tosylated hydrazone.¹⁴³ As the electronic deficient reagents, iodonium salts were found to be extraordinarily reactive in many types of electrophilic reactions, such as Friedel-Crafts reactions. According to Koser's earlier report,¹⁴⁴ the Rawal group utilized the α -nitroaryl iodonium salt **460** to arylate the silyl enol ether **459**.¹⁴⁵ The nitro-reduction of the arylation product **461** would furnish the synthesis of the indoles. In addition, people found the intramolecular arylation under the photo conditions. In a protic solvent, which was also a proton scavenger, the photo-induced electron transfer would cyclize the silyl enol ether **462** giving the fused ring system **463**.¹⁴⁶ In recent years, people found a number of utilizations of the NHCs including the umpolung of the aldehyde, which could generate an acyl anion **465**. The acyl anion underwent the addition to *o*-quinone methide **464** to synthesize the benzyl aryl ketone **466**.¹⁴⁷

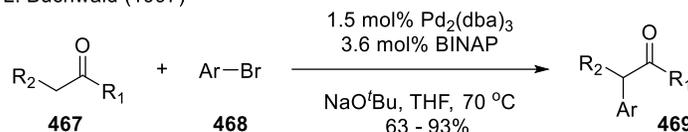
In fact, the discovery of the palladium-catalyzed α -arylation were totally incidental. Hartwig used to mention," The observation of phenylacetone as a side product of an aryl hydride amination in acetone solvent inspired the development of a practical synthetic method for the α -arylation of a variety of ketones and carboxylic acid derivatives."¹⁴⁸ S. L. Buchwald and J. F. Hartwig were two leading people contributing to this area the most by elucidating the mechanism of this reaction, the trends of the conditions changes, and the practical aspects of this reaction. The first publication in the palladium-catalyzed arylation of the ketones were finished by Buchwald in 1997.¹⁴⁹ Simultaneously, the Hartwig group independently disclosed similar

research on the arylation of the aryl alkyl ketones (**Scheme 1.3.2**).¹⁵⁰ These two initial reports on the α -arylation of the carbonyl compounds had similarities. Both of their reports mentioned the use of aryl bromide, the strong base as sodium *tert*-butoxide, the palladium (0) catalyst as Pd₂(dba)₃, and the reaction temperature at 70 °C. However, there were still some slight differences between these two reports, such as the catalysts and the ligands loading as well as the substrate scope. In particular, Buchwald demonstrated the availability of this reaction on the dialkyl ketones **467**, but the Hartwig group only discussed the arylation of the acetophenones **470** due to the regioselective reasons. Moreover, the BINAP type ligands for palladium catalysts were employed by Buchwald in this reaction, whereas Hartwig used dppe type bidentate ligands. Meanwhile, the Miura group also noticed the arylation of the dibenzyl ketone **472** during the arylation of phenols, and they also published this work in 1997. The Miura group did not utilize any ligands with the palladium, and they found the tetraphenylated acetone **474** as the major product.¹⁵¹ For improvement of the efficiency of this reaction, some other catalyst systems were invented. For example, S. P. Nolan applied NHC ligands on palladium, which was incredibly efficient for a broad aryl chloride scopes, including the electron deficient, rich, and neutral starting material.¹⁵² In the initial and the following research by Buchwald and Hartwig, they rationalized some trends, rules, and clues for the reaction mechanism. Buchwald's first paper observed that the arylation tended to occur at the least hindered site, and he explained this outcome as involving the deprotonation prior to the Pd coordination. Both of the groups noted the lack of the competing β -hydride elimination, which was explained as the chelating bis(phosphine) ligands rendered the Pd square with no open coordination site. However, Hartwig prove this idea wrong by the ¹H and ³¹P NMR of the

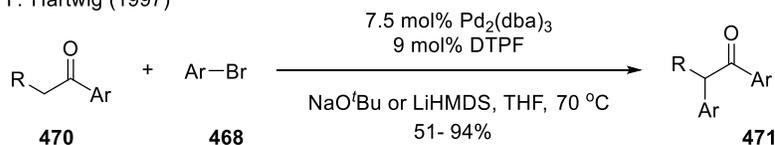
coupling intermediates, and he found the dppf ligand was bound to metal by only one phosphorous. Through the NMR experiments, he also discovered a metal-bound methylene indicating the reductive elimination probably occurred via this coordination state. Furthermore, Hartwig also discovered a trend of the mono vs. bis arylation among the substrates with the different electronic properties and the base employed in the reactions. He demonstrated the electron rich and neutral substrates would only hold the mono- over the bis- selectivity using LiHMDS, while the electron deficient substrates needed the sodium *tert*-butoxide as the base to maintain the selectivity. In their following independent elaboration studies, they both achieved the success using the monodentate bulky ligands at a low catalyst loading.¹⁵³

Scheme 1.3.2

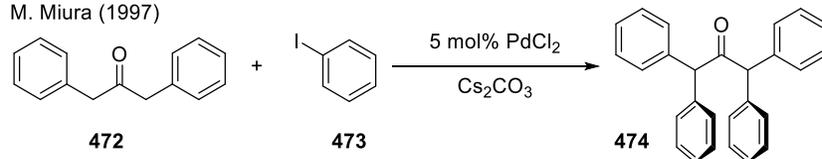
S. L. Buchwald (1997)



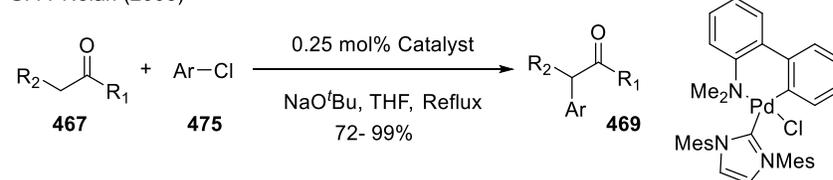
J. F. Hartwig (1997)



M. Miura (1997)



S. P. Nolan (2006)



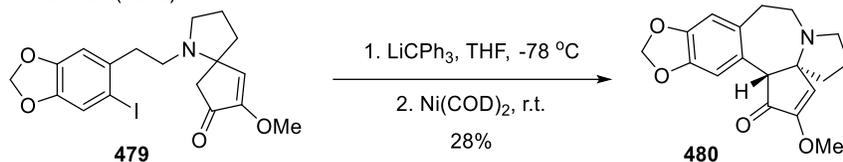
At the outset, the Buchwald group started the attempts in the asymmetric α -arylation in 1998.

With some progress made, they gradually built up the practical reaction conditions for the

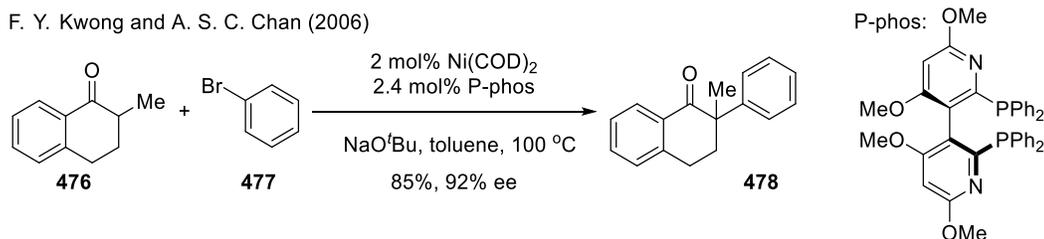
cyclization reaction at the α -position of the carbonyl in **479**. This reaction began with a deprotonation of the α -proton of the carbonyl, followed by the intramolecular coupling reaction.

Scheme 1.3.4

M. F. Semmelhack (1975)



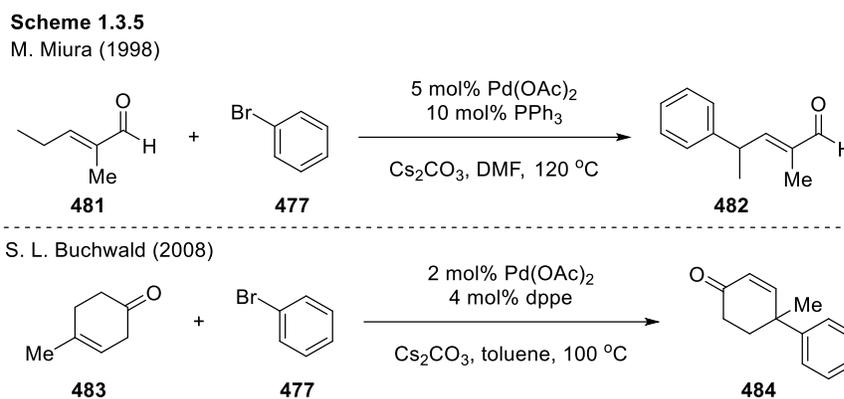
F. Y. Kwong and A. S. C. Chan (2006)



This reaction successfully constructed the fused ring system diastereoselectively, despite the low yield of the product **480**.¹⁵⁶ The nickel-catalyzed asymmetric α -arylations are currently available. Two scientist from Hong Kong, F. Y. Kwong and A. S. C. Chan, described an established reaction conditions using Ni(COD)₂ and P-phos, and they used the β -methyl tetralone **476** and bromobenzene **477** as their reaction model, which has been used by Buchwald and Hartwig. The encouraging yields and *ee* values of this reaction condition indicated nickel was an alternative powerful catalyst for the asymmetric α -arylation of the carbonyl compounds.¹⁵⁷

Interestingly, with the careful design of the reaction substrates, the γ -arylation would take place over the α -arylation of the carbonyl (**Scheme 1.3.5**). M. Miura and co-workers employed the α,β -unsaturated aldehyde **481** in the coupling reaction with bromobenzene **477**. Consequently, the γ -arylated product **482** was obtained from this reaction in a 95% yield.¹⁵⁸ Nevertheless, this reaction only afforded the second and tertiary carbon centers but not the quaternary carbon

centers. To address this problem, Buchwald designed a modification of the Heck reaction in the arylation of the β,γ -unsaturated ketones **483**. During the optimization of the reaction conditions, the α -arylated and the α,γ -bisarylated products were also noted as the side products, but they obtained the desired γ -monoarylation products **484** exclusively using the dppe ligands.¹⁵⁹

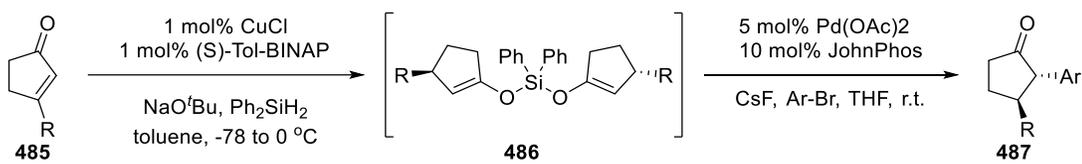


After a decade of the fast development, the Buchwald-Hartwig enolate couplings became more and more practical with a broad substrate scope and good regio- and stereoselectivities in the α -arylation. However, there were still some drawbacks of this method using enolate as the coupling reaction partners. First, many functional groups couldn't tolerate the strongly basic conditions of the coupling reactions, and the strong base could also racemize some acidic tertiary centers in the starting materials or in the products. Second, the arylations would favor the less hindered site of the ketone. To overcome those limitations, Buchwald pioneered the use of the silyl enol ethers in the coupling reaction, and some mild basic fluoride salts were employed to promote the coupling reactions (**Scheme 1.3.6**). He developed a stepwise enantioselective hydroarylation of the α,β -cycloenones **485**,¹⁶⁰ and the forming intermediates, silyl enol ethers **486**, were found to react with the aryl bromide to generate the product in *one-*

pot, respectively. Inspired by this work, the Hartwig group also provided the contribution to this area. They utilized the silyl enol ether **488** to couple with the aryl bromides **468** under the promotion of zinc fluoride and cesium fluoride, and they successfully arylated the ketone on the internal site rather than the terminal site to give the desired product **489**.¹⁶¹

Scheme 1.3.6

S. L. Buchwald (2004)



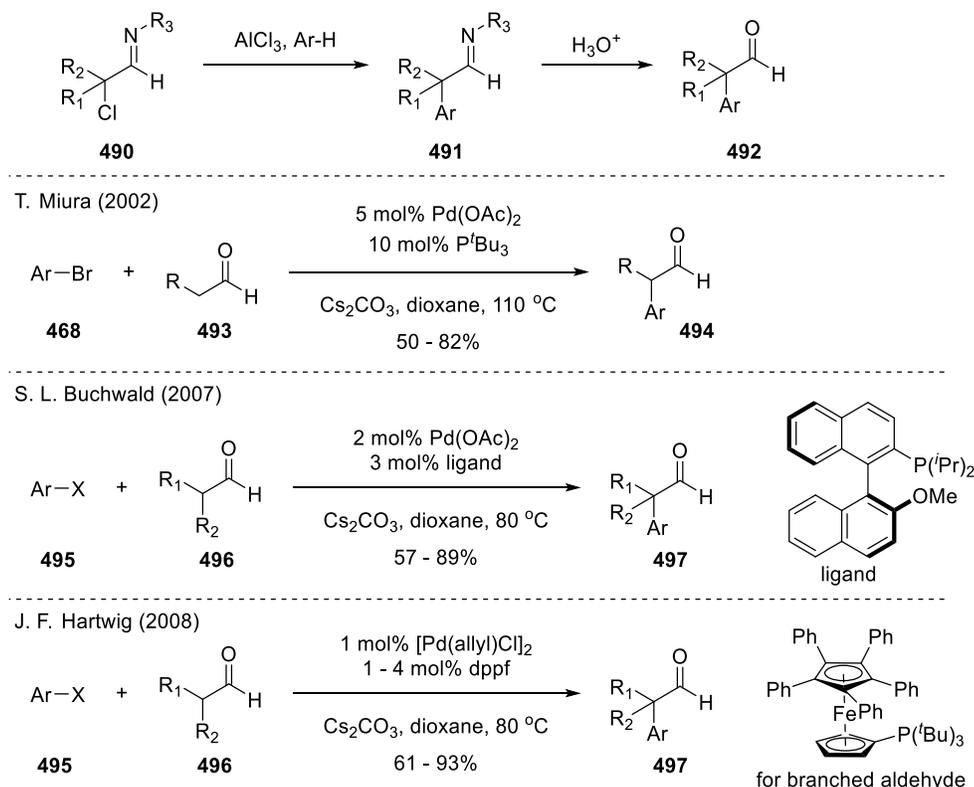
J. F. Hartwig (2006)



The development of catalytic α -arylation of carbonyl compounds also allowed the arylations in somewhat difficult substrates, such as aldehydes. Previously, the α -arylation of the aldehyde were only allowed in the acidic conditions to avoid any possible side reactions, such as the aldol condensation. The early methods focused on the Friedel-Crafts type reactions (**Scheme 1.3.7**). N. De Kimpe reported α -chloroaldehyde **490** would undergo the Friedel-Crafts reaction with the arenes under the promotion of aluminum chloride.¹⁶² The formed α -arylated aldehydes **491** hydrolyzed into the related α -arylaldehyde **492**. This situation changed when T. Miura and co-workers found the palladium-catalyzed arylation using the aldehyde **493** and the aryl bromide **468** as the starting material. Nevertheless, this preliminary coupling conditions required an undesirably high temperature, and it also had a limited substrate scope with the linear aldehydes. Ten examples of the products **494** were displayed in their report from 50% to 82% yields.¹⁶³ Five years later, Buchwald modified the coupling reaction conditions, and

they decreased the reaction temperature from 110 °C (Miura's report) to 80 °C. By switching the ligand to MOP, they largely extended the substrate scopes for this aldehyde's arylation, like branched aldehydes **496**. Although, the reported examples were mostly electron deficient aryl bromides or aryl chlorides **495**.¹⁶⁴ Now, the most successful catalytic system for the arylation of aldehydes was reported by Hartwig. In detail, an easily reducible pre-catalyst entered into the catalytic cycle faster to outcompete with the aldol reactions, and they emphasized the dppf advanced the Buchwald's BINAP-derived ligands in a comprehensive scope with the respect to arene **495** electronics. However, the branched aldehydes **496** needed a special pentaphenyl substituted dppf ligand to achieve the ideal yields of coupling products **497**.¹⁶⁵

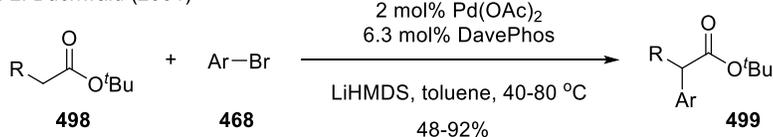
Scheme 1.3.7
N. De Kimpe (1982)



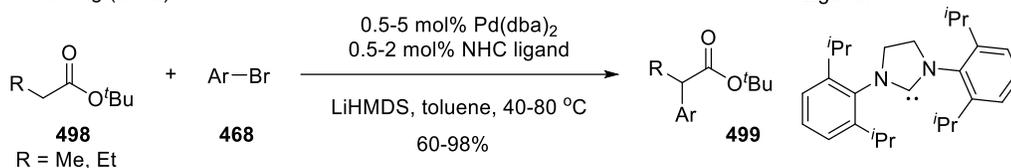
In addition to the arylation of ketones and aldehydes, the Buchwald and Hartwig group also developed the coupling reaction using carboxylates **498** (Scheme 1.3.8). In these reactions, the Buchwald group utilized the DavePhos,¹⁶⁶ but Hartwig relied on the NHC ligands. Among their studies, the use of LiHMDS was essentially important for completing the conversion, and the *tert*-butyl ester, which is hindered, was also necessary to minimize the undesired Claisen condensations.¹⁶⁷

Scheme 1.3.8

S. L. Buchwald (2001)



J. F. Hartwig (2002)

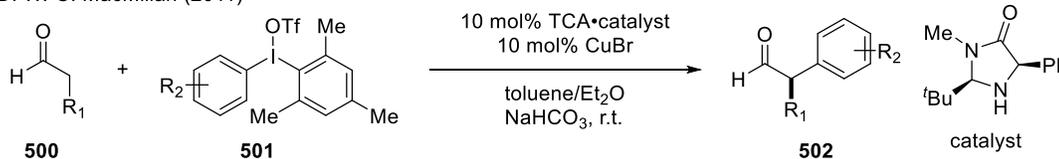


Even the Buchwald-Hartwig enolate coupling reaction became a very practical synthetic method after many years' extensive research. There were still some flaws of this coupling reaction needed to address, such as the strong bases, the limited substrate scopes, the unreachable ligands or catalysts. In recent years, some new methods emerged as the complementary solution in order to extend the scopes of the arylation of the carbonyl compounds. For example, the diaryl iodonium salt were used in the arylation for long time (Scheme 1.3.1), but, recently, D. W. C. MacMillan and M. J. Guant discovered an asymmetric arylation of the carbonyl compounds using the iodonium salt **501** as the electrophilic aryl source. The first paper was published by D. W. C. MacMillan, where they utilized their own diagnostic organocatalyst to induce the enantioselectivity.¹⁶⁸ Presumably, the catalyst would

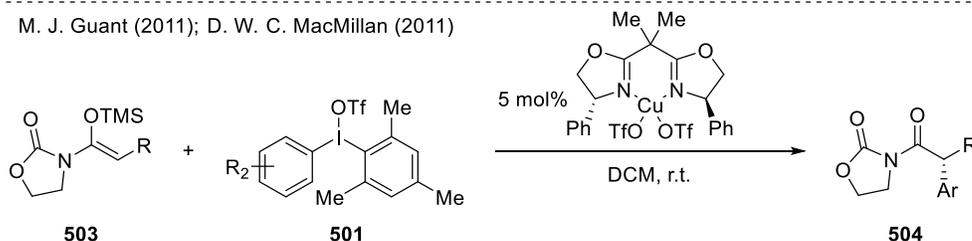
form an enamine intermediate with the aldehyde **500**, and the chiral amine catalyst would create an asymmetric environment for the electrophilic attacks to the enamine species. The catalytic amount of copper chloride accelerated the aryl cation generation from the iodonium salt **501**, which reacted with the enamine intermediates. After the hydrolysis and the cleavage of the organocatalyst, the catalytic cycle enantioselectively donated the α -arylated aldehyde **502**. This method gave better yields and *ee* values of a comprehensive substrate scope comparing to the palladium-catalyzed enolate couplings of the aldehydes, and the conditions of this reaction were much milder than the palladium or nickel-catalyzed couplings. In the same year, the Guant and MacMillan groups published two back-to-back papers on JACS, where they discussed the enantioselective arylation of silyl ketenimides **503** using the iodonium salts **501**.¹⁶⁹ However, in this report, the chiral Py-Box binded copper catalysts offered the excellent yields and *ee* values of the α -arylated amides **504**. Moreover, this method of arylation was proven viable in many other cases, such as lactones, heterocycles, and with many fragile functional groups. The allowance of the broad substrate scope was largely due to the thermally mild and pH neutral conditions of this reactions.

Scheme 1.3.9

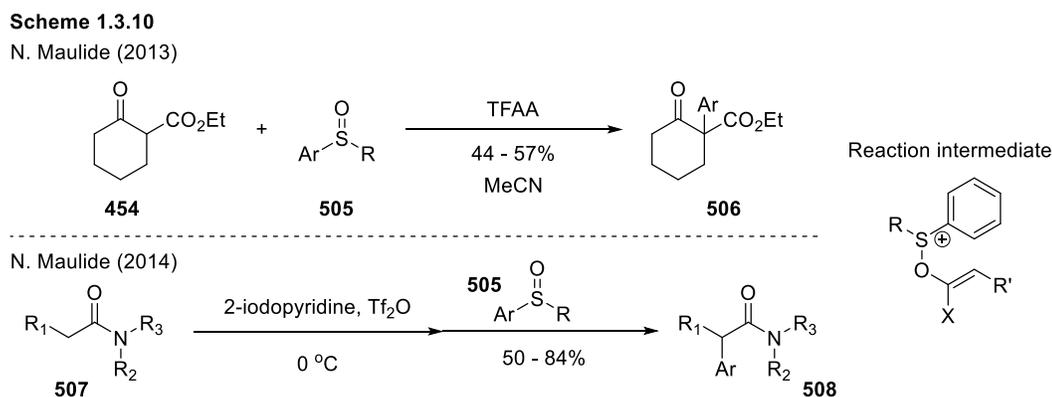
D. W. C. MacMillan (2011)



M. J. Guant (2011); D. W. C. MacMillan (2011)



The Maulide group in Germany demonstrated an intriguing rearrangement reaction, where they used the β -ketoesters **454** and the secondary amides **507** to react with the aryl sulfoxides **505** under the acidic conditions (**Scheme 1.3.10**).¹⁷⁰ They surprisingly noted the α -arylation of the carbonyl in **506** after the reaction. Via some theoretical and mechanistic studies, they thought this reaction actually went through a sigmatropic rearrangement affording the arylated product. However, a limitation narrowed down the scope of this reaction, where the product always ended up with a sulfide group attached on the arenes.

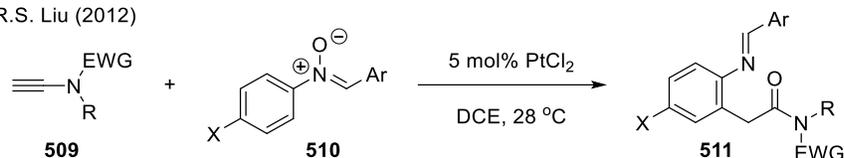


Moreover, some other interesting α -arylations of the carboxylic acid derivatives were shown in recent years. The Liu group upgraded the reaction between the aryl ynamides and the nitrones, and they found the terminal ynamide **509** would be attacked by the charged oxygen atom in the aryl nitrones **510** (**Scheme 1.3.11**). Mechanistically, this reaction went through a pathway similarly to Maulide's reactions, where a charged sigmatropic rearrangement precursor was proposed during the reactions.¹⁷¹ In this manner, *o*-iminyl aryl acetamides **511** were formed. Different from Maulide and Liu's arylations, the Lee group used an oxidation strategy to form the α -arylation products, but this reaction wasn't actually an arylation reaction. Because there was no carbon-carbon bond formation during the reaction, but this reaction

enabled the synthesis of various aryl acetic acid derivatives simply from the aryl acetylenes **513**.¹⁷² In details, the terminal alkynes **513** were oxidized into the aryl ketenes using 4-methylpyridine N-oxide and the rhodium catalyst, and the aryl ketene intermediates were trapped *in situ* by the existing nucleophiles **512** in the reaction system, which afforded the corresponding aryl acetic acid derivatives, such as amides, esters, acids. This synthetic method provided a general approach to all kinds of aryl acetic acid derivatives.

Scheme 1.3.11

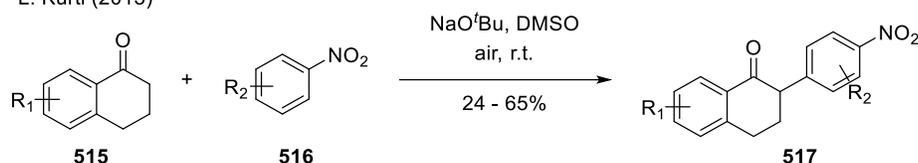
R.S. Liu (2012)



C. Lee (2013)



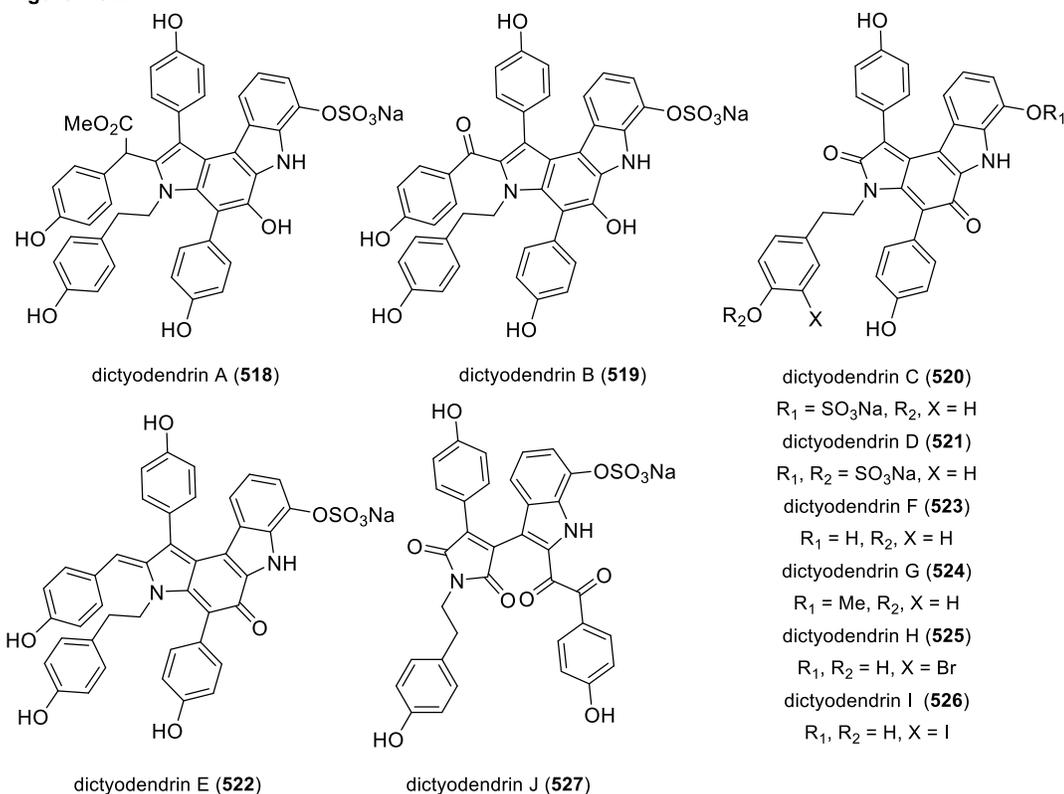
L. Kürti (2013)



In 2013, the Kürti group found an oxidative enolate coupling reaction between the ketones **515** and the nitrobenzenes **516**. In the open vial, the reaction system was exposed to the aerobic conditions, and the strong base, sodium *tert*-butoxide, deprotonated the α -proton of the ketone and allowed it to participate in a conjugate addition reaction with nitrobenzene. Air served as the oxidant to regenerate the aromatic system and furnish the reaction ending up with the α -arylated ketones **517**.¹⁷³

1.3.2 Synthesis of Dictyodendrins

Figure 1.3.2



Synthetic Steps (L.L.S)

Dictyodendrins	A	B	C	D	E	F	H	I
Furstner		13	10		13	9		
Ishibashi		18						
Tokuyama	21	21	21	21	22			
Jia		9	13		11			
Davies		12					10	
Guant		13						

Biological activity

dictyodendrin A-E:
telomerase inhibitor

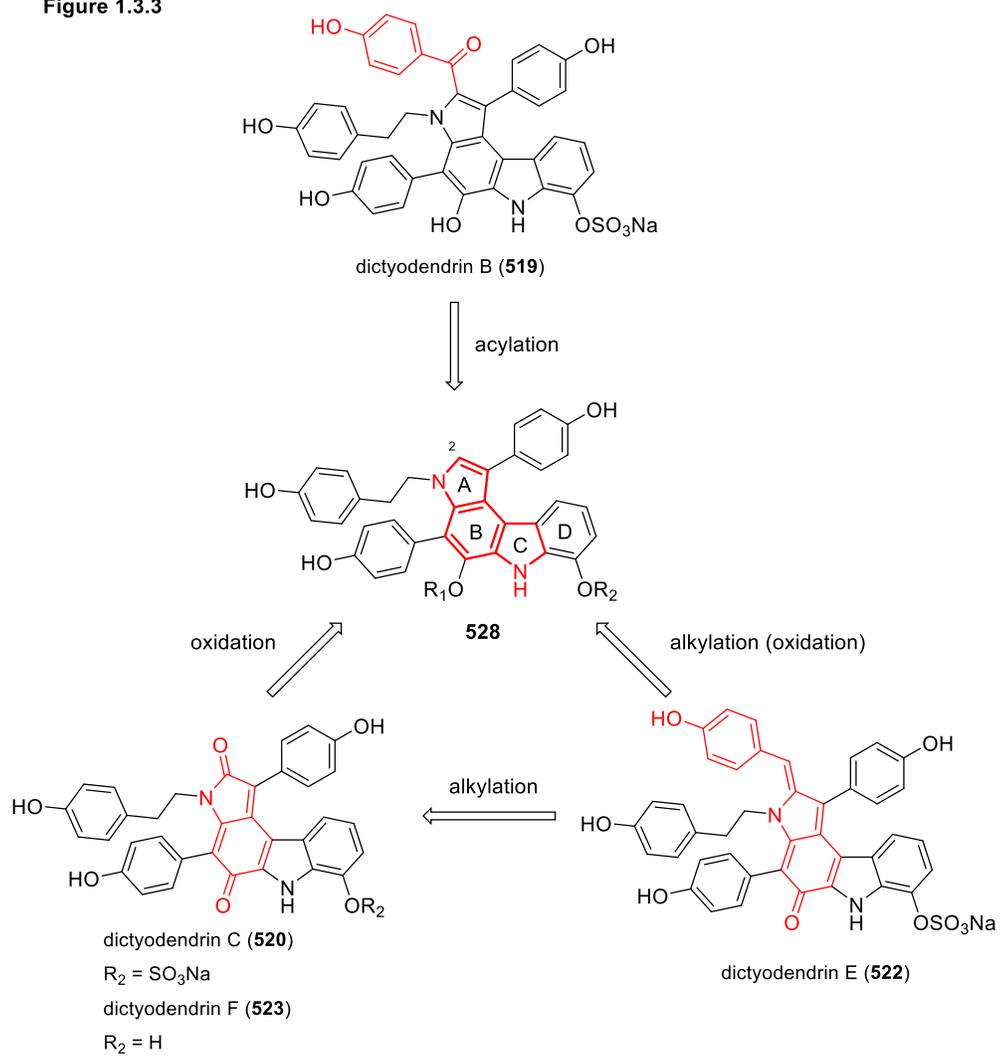
dictyodendrin F-J:
BACE1 inhibitor

In 2003, Fusetani and co-workers isolated dictyodendrins A-E (**518-522**) from the marine sponge *dictyodendrilla verongiformis* (Figure 1.3.2) in the search for inhibitors of telomerase.¹⁷⁴ Later in 2012, another Australian isolation group, the Capon group, successfully extracted five other family members of dictyodendrins F-J (**523-527**) from the *Ianthella* sponge, and they showed these natural products had the moderately potent inhibition of the β -site

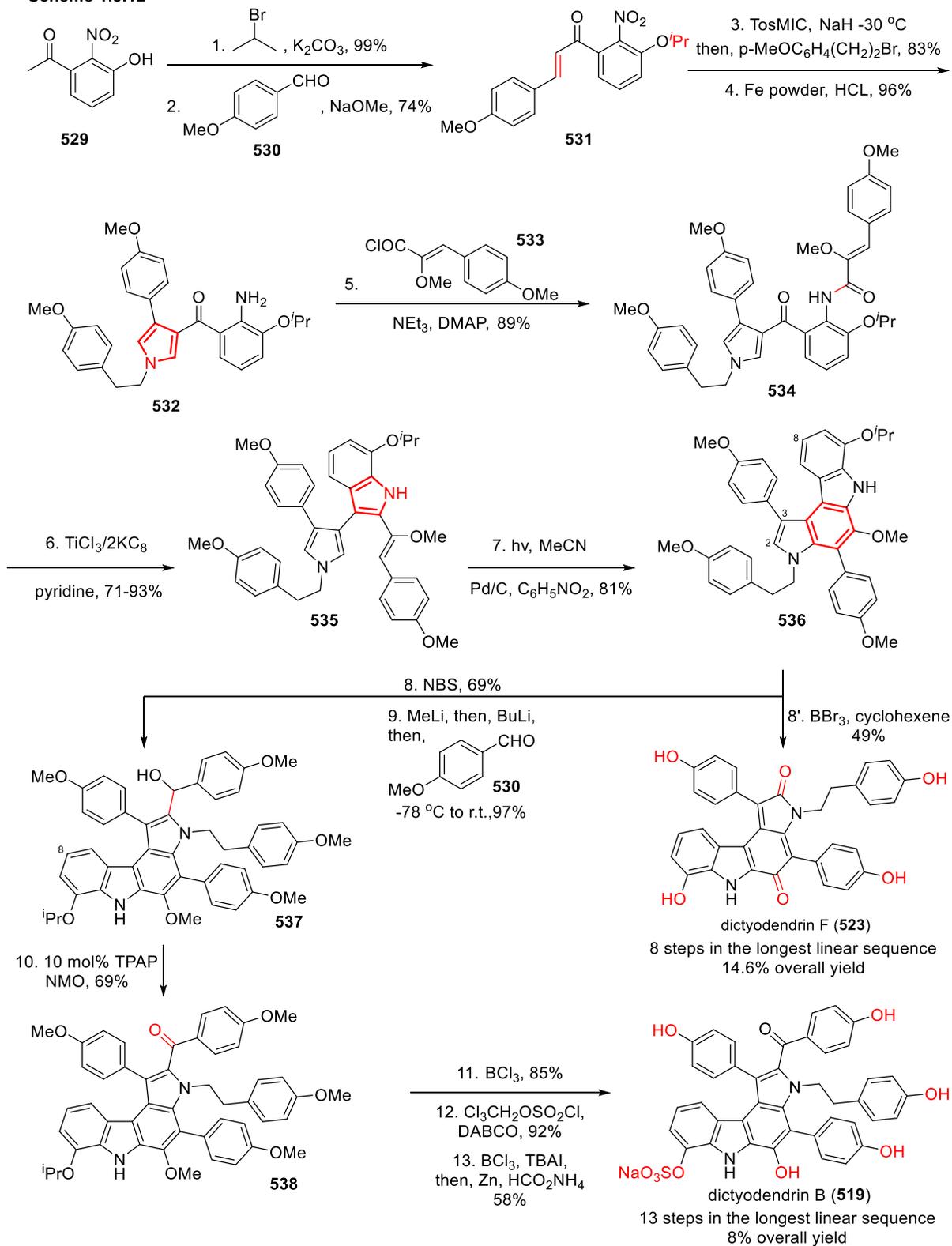
amyloid-cleaving enzyme 1 (BACE1),¹⁷⁵ a potential target for treating Alzheimer's disease.¹⁷⁶ Because of their unique structures and the intriguing biological activities, the dictyodendrins became popular synthetic targets. Structurally, dictyodendrins contain a highly substituted pyrrolo[2,3-c]carbazole core at the phenol or quinone oxidation states. The highly conjugated ring system attracted a number of synthetic groups, and they brought a perfect arena for chemists trying their creative synthetic strategies and skills. In this section, we are going to review the previous syntheses targeting to this natural product family. A small table is shown in the **Figure 1.3.2**, wherein we listed all the total and formal syntheses of dictyodendrins with their longest linear sequence.

The first total syntheses of dictyodendrins B, C, E, and F were finished by the Füstner group.¹⁷⁷ One interesting thing was the synthesis of dictyodendrin F, which has not ever been isolated from any natural sources yet at that time. But Füstner and co-workers obtained this natural product as a side product along their synthetic route to dictyodendrin B. Füstner's synthesis is a relatively general synthesis to get to all the family members of dictyodendrins. They focused on the construction of the most substituted A, B, and C ring in dictyodendrins, which saved a lot steps and efforts so that they could finish the convergent synthesis with the prepared building blocks (**Figure 1.3.3**). They hypothesized that the core intermediate **528** could easily transform into dictyodendrin B by the acylation, dictyodendrin C and F by the oxidation, and dictyodendrin E by the alkylation. All the late stage modifications surrounded the most electron rich and reactive site, C2 position of **528**. In addition, they also had a backup plan of the synthesis of dictyodendrin E accessing from the alkylation of dictyodendrin F or C.

Figure 1.3.3



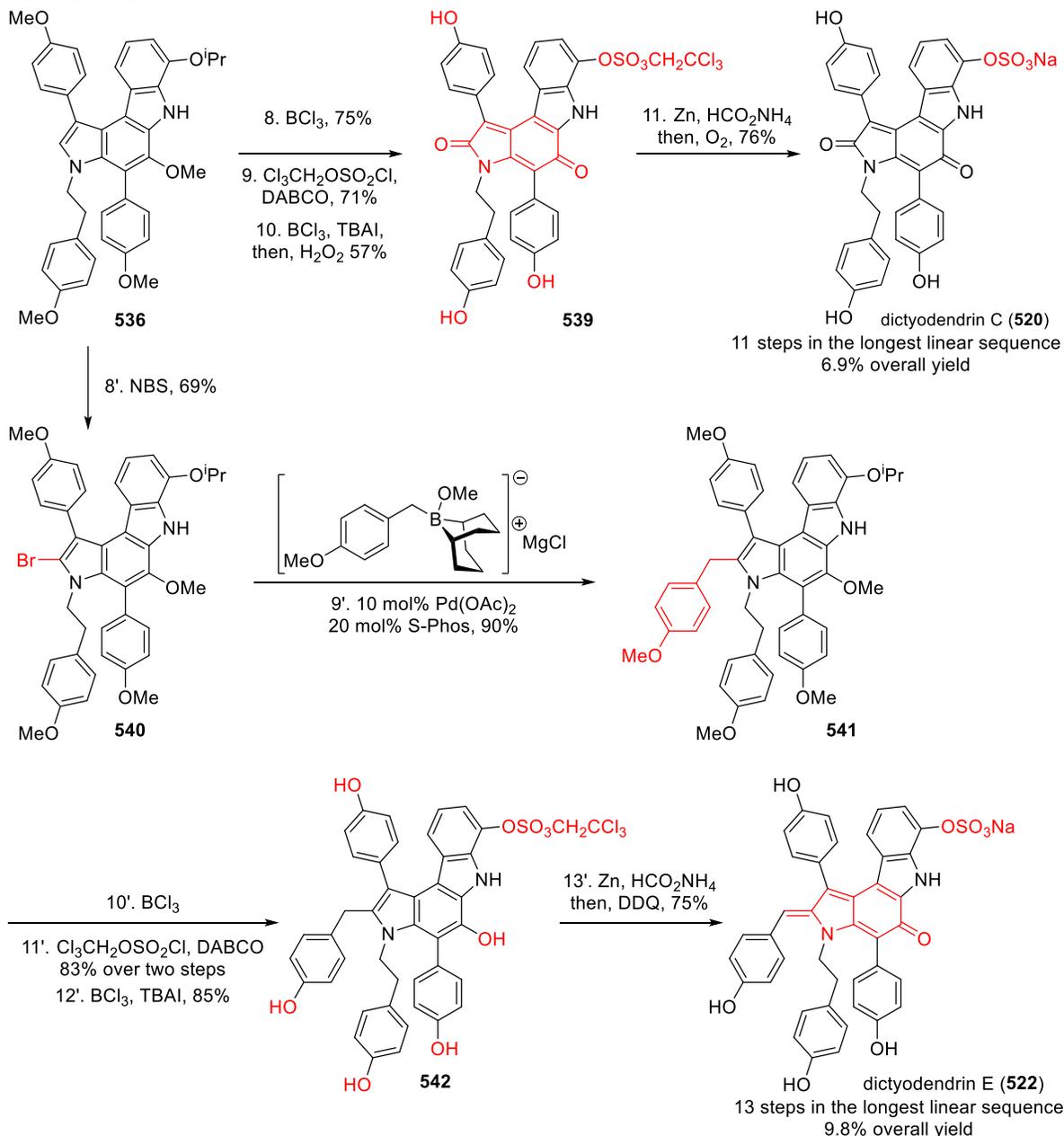
Scheme 1.3.12



The Füstner group started their synthesis from the readily available acetophenone **529**, which was protected as the isopropyl ether form prior to the condensation with *para*-MeOC₆H₄CHO (**Scheme 1.3.12**).¹⁷⁷ The resulted chalcone **531** was exposed to TosMIC and NaH at low temperature to cyclize the A ring of dictyodendrins, and the following reduction of the nitro-group afforded the pyrrole intermediate **532**. With this intermediate in hand, they used a condensation between the aniline group in **532** and the acid chloride **533** to introduce the last fragment of the core **528**. The following indolization of intermediate **534** was conducted via an intramolecular reductive coupling conditions using TiCl₃ and KC₈ as the reductants, and this reaction successfully connected the two carbonyl groups, the ketone and the amide in **534**, to yield C ring of the core **528**. The exposure of the indolization product **535** under the light conditions led to a 6 π -electronic cyclization reaction, and the cyclized product would further be oxidized *in-situ* using the Pd/C and nitrobenzene oxidation system. The core **528**, which contained the fully substituted fused A, B, and C ring system, was synthesized, and the following deprotection test accidentally provided an aerobic oxidation product, dictyodendrin F (**523**). However, the C2 acylation of the indole remained very unsuccessful. The initial attempts of the Friedel-Crafts type acylation migrated the C3 aryl group to the C2 position of the A ring (not shown). Moreover, when the C2 brominated product was stored in chloroform over a day, the bromine would migrate to C8 position on the D ring. Fortunately, after the bromination of **536** using NBS, they found the N-deprotonated intermediate would further undergo a halogen exchange with BuLi. To quench this reaction with anisaldehyde **530** generated the benzyl alcohol **537**, respectively. They converted the alcohol functional group

into the ketone oxidation state and obtained the intermediate **538** using the TPAP oxidation, and the product **538** contained all the carbon skeletons for dictyodendrin B. The last three steps were focused on the global deprotection of the phenyl methoxyl ethers as well as the selective introduction of the sulfate.

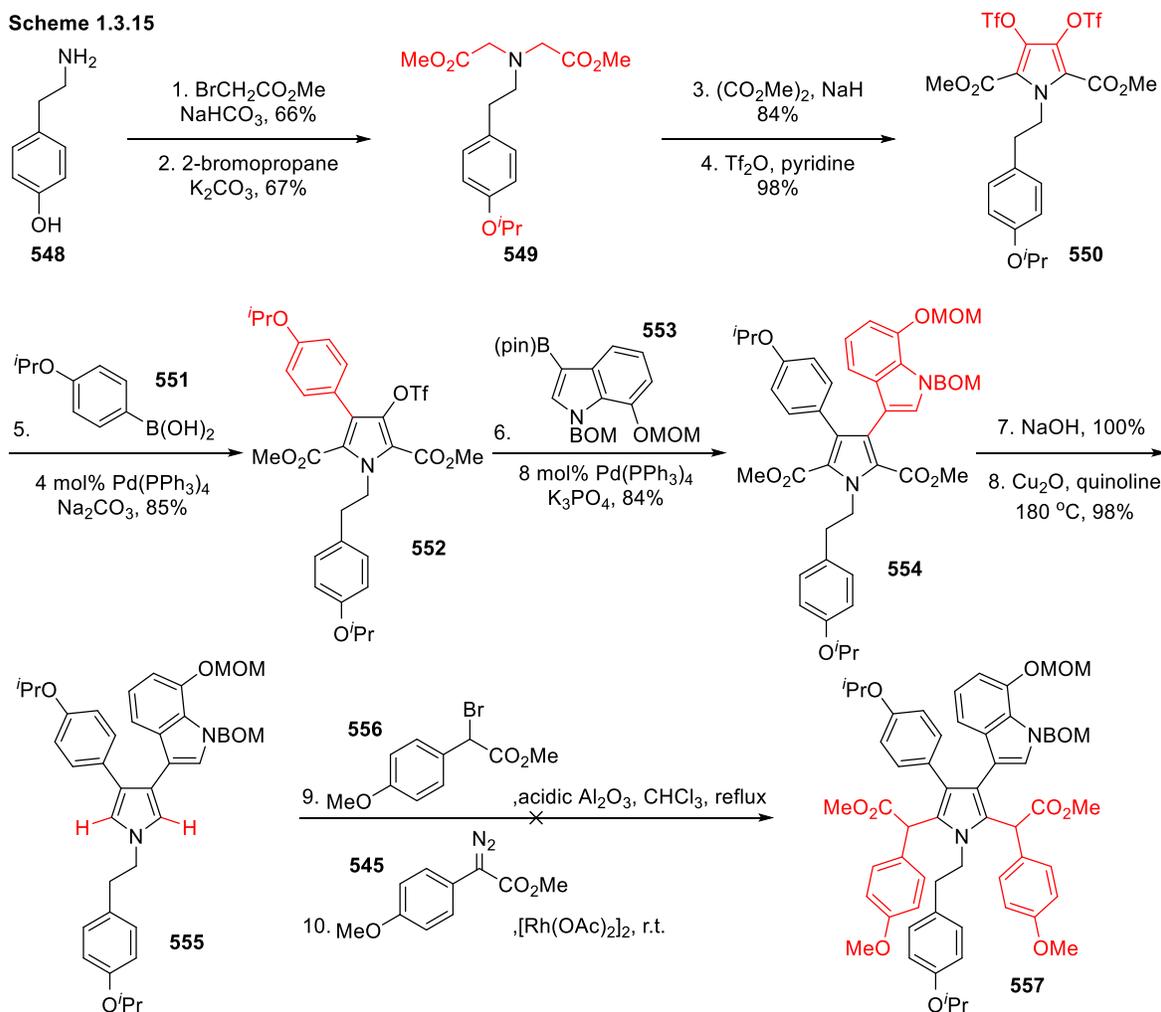
Scheme 1.3.13



They cleaved the isopropyl group selectively followed by the introduction of the sulfate trichloroethyl ester, and all methyl groups were removed under the acidic conditions (**Scheme 1.3.12**). Finally, the trichloroethyl sulfate was cleaved under the reductive condition to afford the dictyodendrin B in 13 steps. In summary, the Füstner group developed a very efficient synthesis of dictyodendrin B. The introduction of the carbon fragments and the following oxidation state changes made the synthesis convergent and concise. Actually, the introduction of the sulfate cost a lot of efforts in the synthesis of the dictyodendrin B, but no newer methods was developed in the latter syntheses. A year later, the Füstner group published a full article regarding the details of their synthesis of dictyodendrin B and the further synthesis of dictyodendrins C and E (**Scheme 1.3.13**).¹⁷⁸ According to their discoveries, a spontaneous oxidation would take place on the intermediate **536** to give the quinone oxidation state. To synthesize dictyodendrin C, they firstly replaced the isopropyl group with the trichloroethyl sulfate, followed by a global demethylation. The resulting intermediate was spontaneously oxidized into the quinone oxidation state shown as intermediate **539**, where the reductive conditions were employed to afford the dictyodendrin C. In contrast to dictyodendrin C, the synthesis of dictyodendrin E proved more difficult. Due to the failure to convert the alcohol **537** (**Scheme 1.3.12**) into the quinone methide structure in dictyodendrin E (**Scheme 1.3.13**), Füstner and co-workers turned to use a sp^2 - sp^3 Suzuki coupling reaction to introduce the benzyl side chain on the well-established brominated intermediate **540**. After the extensive screens of the coupling partners, they found the steric hindered boronate offered the benzylation product **542** quantitatively in the combination with the $Pd(OAc)_2$ and Buchwald's sterically encumbered S-Phos ligand. The same method and reactions was employed in the deprotection

settled on the pyrrole core **543**, they hypothesized a 6π electronic cyclization would furnish the fully substituted C ring in dictyodendrin.

Scheme 1.3.15



Nevertheless, the Ishibashi group failed to get the desired natural product, dictyodendrin A (**518**), under the planned route (Scheme 1.3.15).¹⁷⁹ They began the synthesis with the construction of the core pyrrole structure in four steps according to their previous synthesis of lamellarins D, N, and L.¹⁸⁰ They successfully obtained the 3,4-bistriflatedpyrrole **550** in 31% overall yield. With two positions activated with triflates, they directly introduced the anisyl group **551** using a Suzuki cross coupling reaction, and they selectively obtained the

monoarylated pyrrole intermediate **552**. The following Suzuki coupling connected the indolyl motif **553** to the pyrrole ring. With 3,4-bisfunctionalized pyrrole **554** in hand, Ishibashi further hydrolyzed the two ester groups, promoting a decarboxylation reaction to generate the bare pyrrole structure **555**. Their synthesis succeeded to this point, but their fortune terminated here. By any means, they failed to use the Friedel-Crafts type of the C-H functionalization and the rhodium carbene conducted C-H functionalization reactions to obtain the desired key intermediate **557**.

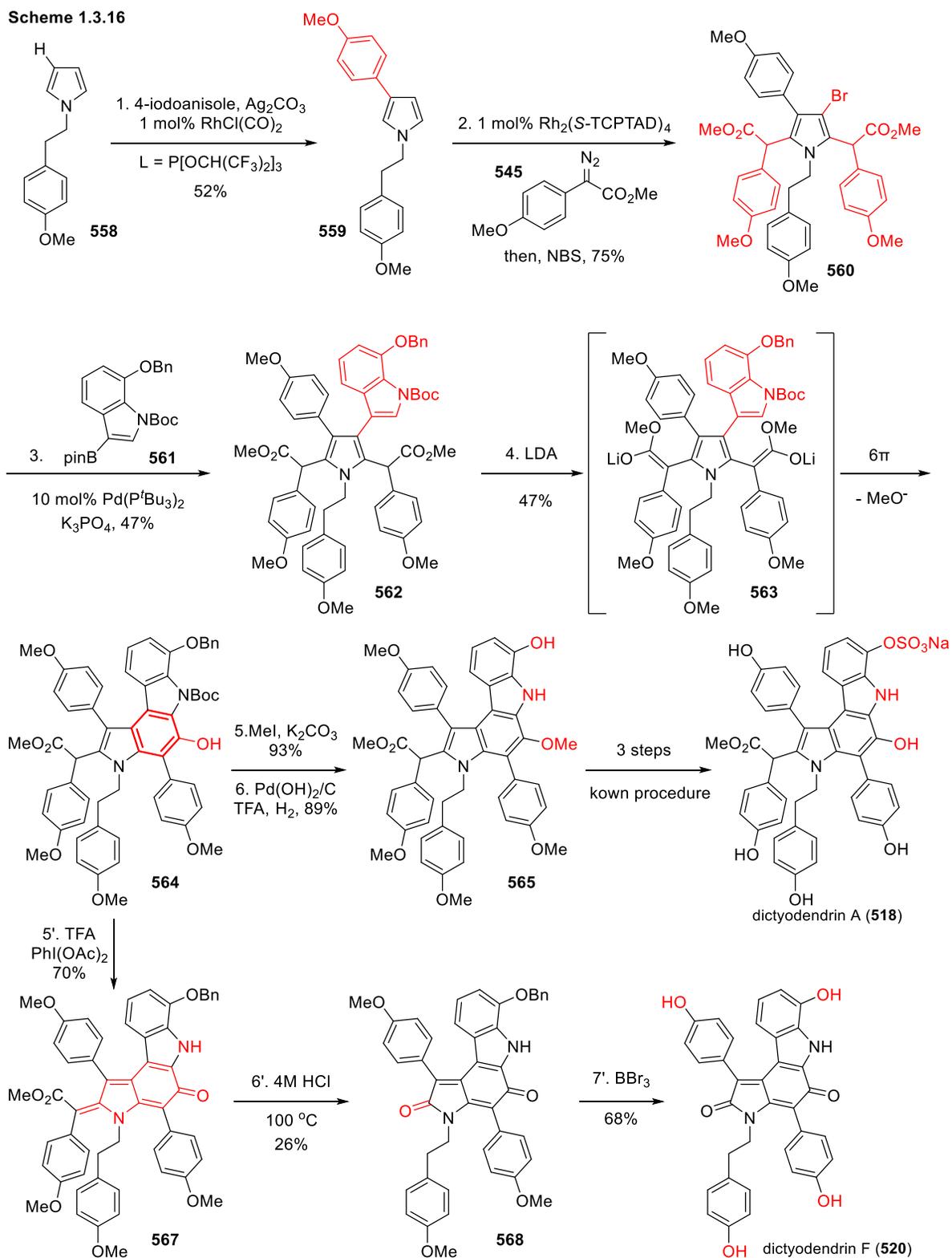
Inspired by Ishibashi's synthetic strategy, the Davies' synthesis of dictyodendrin A and F started from a similar pyrrole core **558** (Scheme 1.3.16).¹⁸¹ However, they utilized a more efficient arylation method, which allowed the direct arylation of the non-functionalized pyrrole ring. In fact, the installation order of the fragments deviated from their original plan, which planned to conduct the double carbenoid C-H insertion of the pyrrole **558** prior to the C-H arylation at C3 position. However, they noted the subsequent arylation was unsuccessful. Then, they reversed the order of the fragment installation. They introduced the C3 aryl group using a rhodium-catalyzed C-H arylation on the bare pyrrole core **558** at the outset of their synthesis. Next, they found the best conditions for the double carbenoid C-H insertion reaction, which gave the 2,5-disubstituted pyrrole exclusively over the mono-insertion and the C4 substitution products (not shown). In one-pot, NBS was added into the reaction system to yield the C4 brominated pyrrole **560**, which was a precursor for the following Suzuki coupling reaction with the indolyl boronate **561**. The final piece of dictyodendrins was introduced through the Suzuki coupling reaction, and it gave the key intermediate **562**. Comparing to Ishibashi's failure in the construction of this key intermediate, the Davies addressed the problem by switching the order

of the bond formation and trimming the coupling conditions. Regarding to his and Ishibashi's proposal, the pyrrole **562** would undergo a 6π -electronic cyclization reaction and the extrusion of the methoxyl group under the basic conditions, which provided the product **564** with the final aromatic ring cyclized. After a methylation and a deprotection of the *N*-Boc and *O*-benzyl groups, they obtained the intermediate **565** previously reported by the Füstner group. Finally, they synthesized dictyodendrin A using Füstner's procedures. Additionally, Davies and co-workers synthesized dictyodendrin F via a fragmentation reaction. At the outset of their synthesis, all the attempts failed to generate the C5 momo-insertion product using the rhodium catalyst. Instead, they would be able to finish the synthesis using a less elegant fragmentation of the quinone methide intermediate **567**, which was previously considered as the precursor of dictyodendrin E via a decarboxylation. Ironically, the decarboxylation cleaved the whole side chain, and they finished the synthesis of dictyodendrin F using the accidentally formed intermediate **568** after the global deprotection reaction.

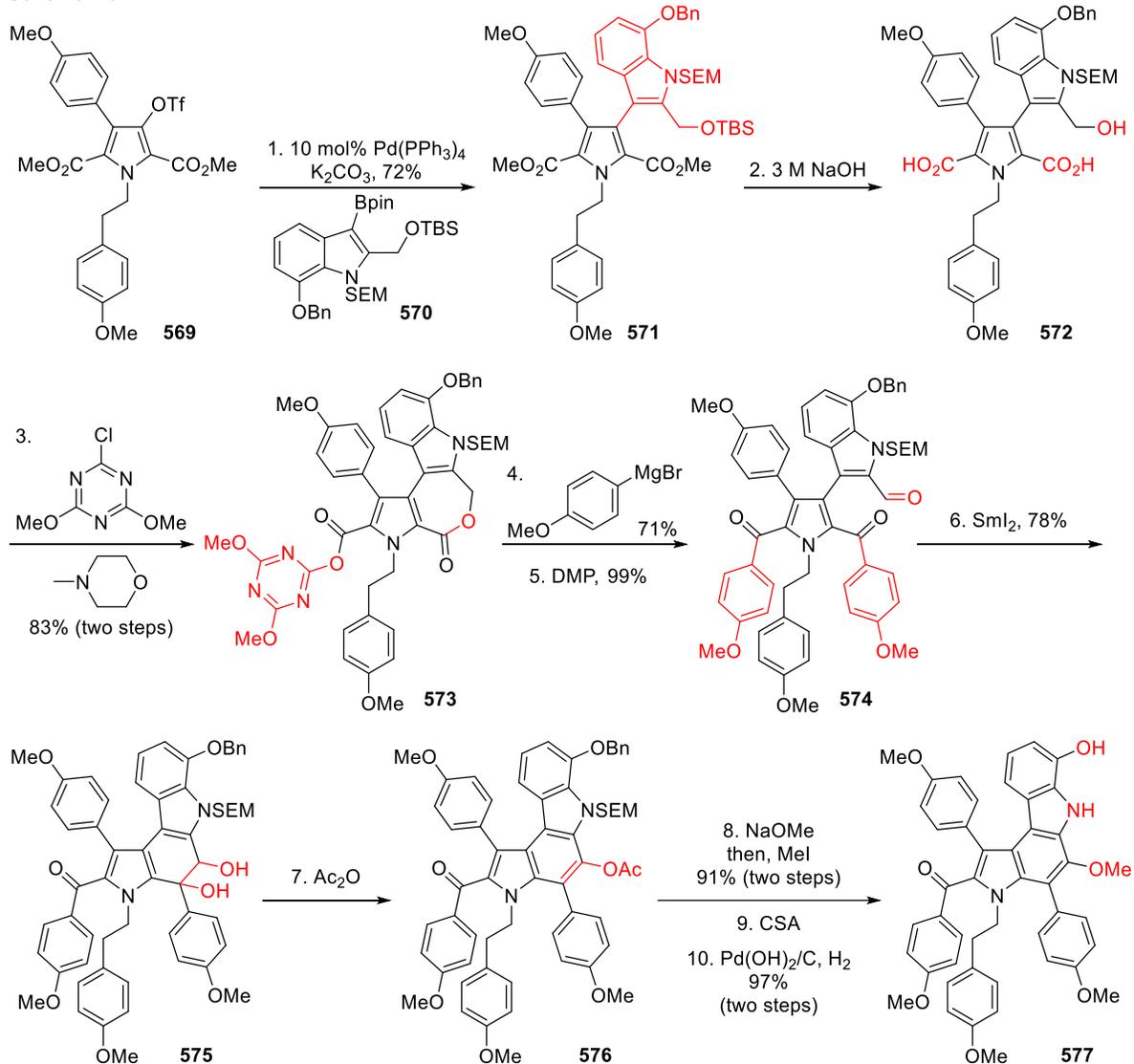
To avoid the hard introduction of the two carbon side chains at the late stage, Ishibashi and co-workers came up with their second generation of total synthesis of dictyodendrins (**Scheme 1.3.17**).¹⁸² They pre-installed a protected hydroxymethylene on the C2 position of the indole motif **570**, and the following Suzuki coupling reaction set the connection between the pyrrole **569** and the indolyl boronate **570**. The alkaline hydrolysis of the diester **517** proceeded with concomitant removal of the TBS group to give the diacid **572**. They used 2-chloro-4,6-dimethoxy-1,3,5-triazine to activate the carboxylic acid in the presence of *N*-methyl morpholine to form the lactone **573**. The anisyl side chain was installed via a Grignard addition reaction to the lactone and the triazinoxyl ester, and this reaction yielded the diketone product

in a quantitative yield. The subsequent Dess-Martin oxidation converted the alcohol into the aldehyde **574**. Treating the aldehyde diketone **574** with SmI_2 generated the corresponding six-membered ring through a reductive coupling reaction, and the acetic anhydride helped the extrusion of the tertiary hydroxide group of **575** to aromatize the B ring of **576**. The last steps of their synthesis focused on the alternation of the protecting groups to get the intermediate **577** previously reported by the Füstner group. A brief comparison between Ishibashi and Davies's synthesis proves the efficiency and the power of the C-H activations in total synthesis. The Davies group could shorten their synthesis of dictyodendrin A, because they avoided the pre-functionalization steps of the coupling substrates. On the other hand, the C-H functionalizations also indirectly allowed the synthetic group to try different orders of the coupling reactions, which made a flexible synthetic route possible and guaranteed any possible backup plans that were always available.

Scheme 1.3.16

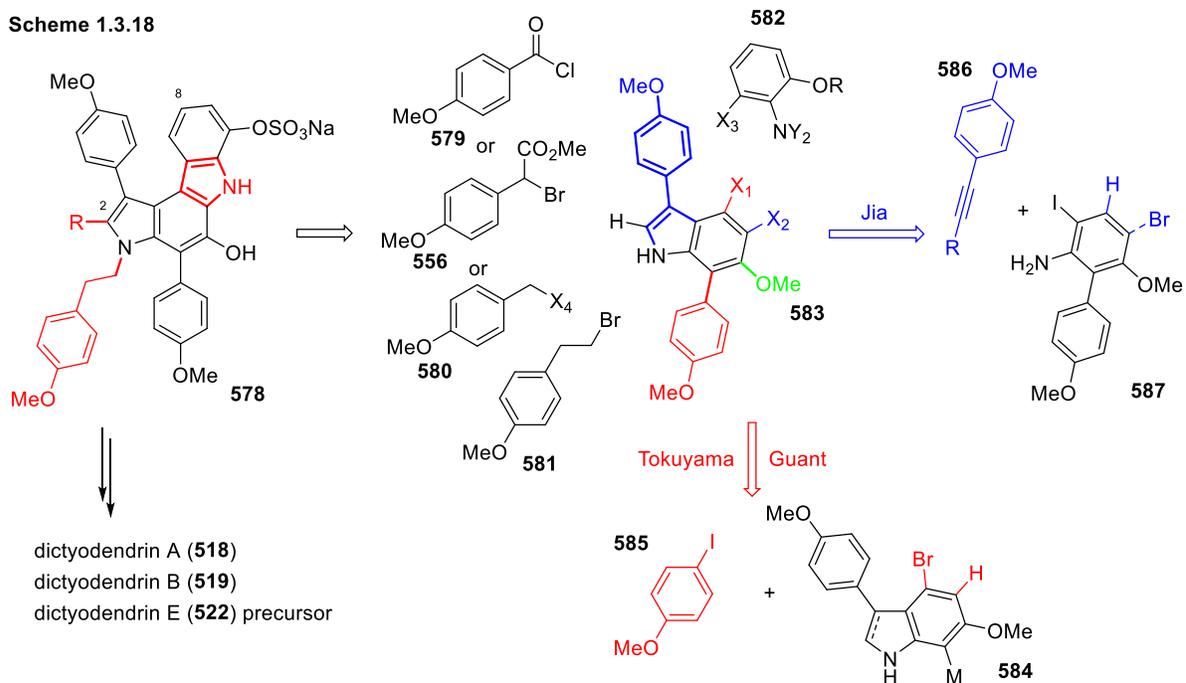


Scheme 1.3.17



Inspired by Füstner's preliminary data using the Friedel-Crafts reaction to install the side chain at the C2 position, the Tukuyama, Jia and Guant group hypothesized that a late stage formation of the carbazole core would help the Friedel-Crafts reaction at the C2 position (**Scheme 1.3.18**). The Friedel-Crafts reaction would provide a general access to multiple dictyodendrins by the change of the related reactants during the reaction. Compared to Füstner's failure, these successors rationalized the late stage formation of the carbazole would improve the Friedel-

Crafts reactions in two ways. First, according to Füstner's reports, the C8 position of the carbazole core is relatively electron rich and is prone to electrophilic attack, and it also competed with the C2 position during the bromination and the Friedel-Crafts reactions. Therefore, if the side chain installation was prior to the formation of the carbazole core, the C2 position would be the most electron rich position to accept any electrophilic attacks. Second, Füstner noted an aryl migration from C3 to C2 position, which could be driven by the repulsion between the C3-aryl group and the carbazole core. Therefore, the construction of the carbazole in the end would release this possible driving force for the migration under the acidic conditions.



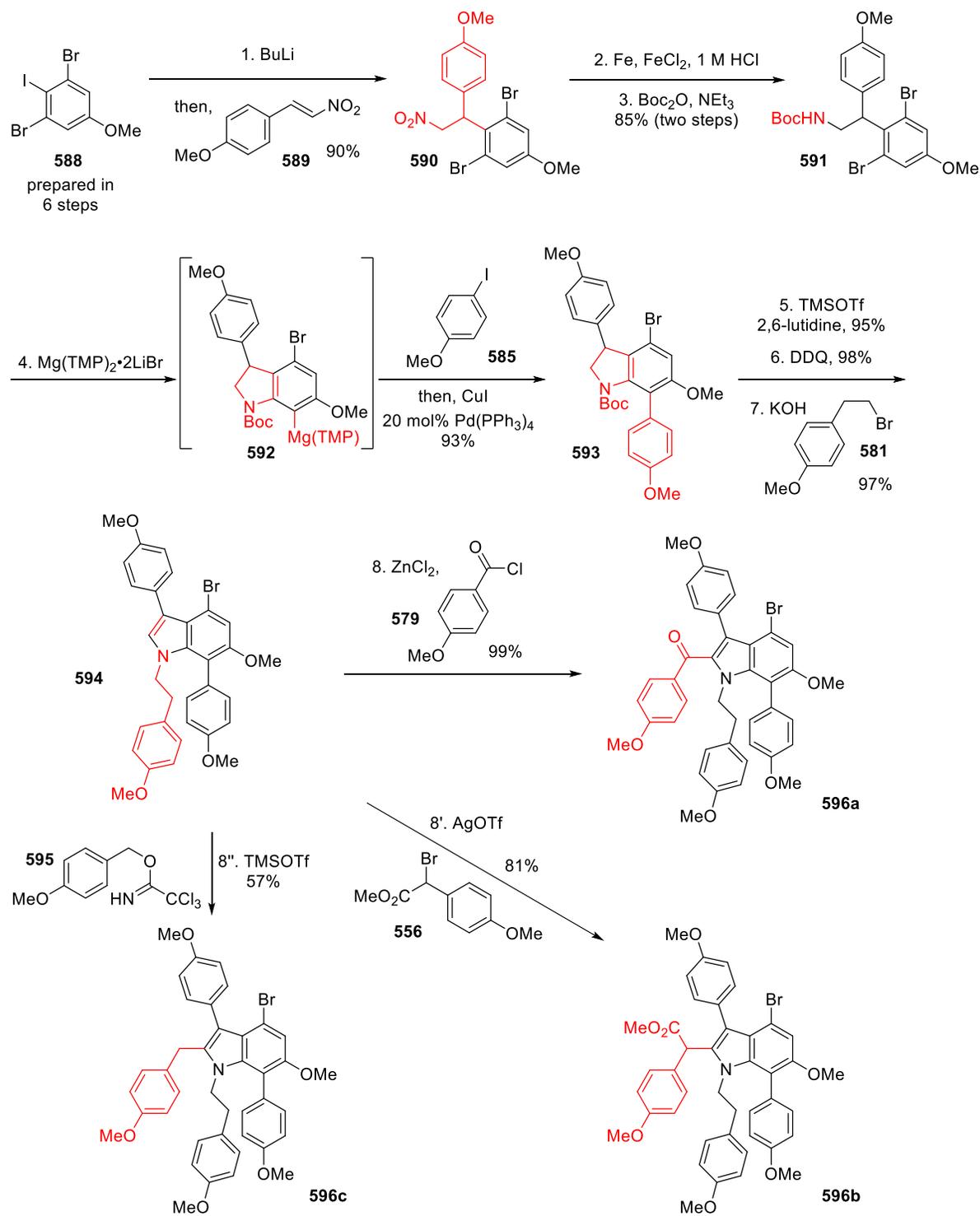
As shown in Scheme **1.3.18**, all three synthetic groups (Tokuyama, Jia, and Guant) shared the similar synthetic strategies involving the late stage formation of the carbazole core between the indole core **583** and the coupling partner **582**, the *N*-alkylation using the alkyl bromide **581**,

and the Friedel-Crafts reactions to introduce the C2 side chains using the alkylation and the acylation reagents **580**, **556**, and **579**. There was a small difference in the formation of the carbazole core between Jia and Tukuyama. Jia group used a cascade reaction to form the carbazole utilizing a Buchwald-Hartwig aryl amination followed by an *ortho*- C-H arylation. But the Tukuyama and Guant group planned the Suzuki coupling reaction to form the carbon-carbon bond first, followed by the cyclization of the carbazole via a C-H nitrene insertion. Apparently, Jia's method was more concise, because it did not need to convert the aniline group into the azide for the cyclization. Moreover, the electronic property of the indole core allowed the bromination at the X₂ position on the **583**, but Guant and Tukuyama had to pre-install the bromide at the X₁ position on the **583**. To synthesis the key intermediate **583**, the precursor for the Friedel-Crafts reactions, Jia applied the Larock indole synthesis, whose starting materials, the silyl or acyl anisylacetylene **586** and the biaryl compound **587**, were readily available. On the other hand, both the syntheses of Tukuyama and Guant involved the C7 arylation and the C4 pre-bromination of the indole **584**.

At the outset of synthesis, Tukuyama and co-workers commenced with a tetrasubstituted iodoanisole **588** (Scheme 1.3.19).¹⁸³ The starting material was treated with BuLi to generate the related aryl lithium, which could add to the nitroolefin **589** to afford the Michael adduct **590**. The nitro-group was reduced, and the resultant primary amine was protected as Boc-carbamate to yield the desired product **591**. With the key intermediate **591** in hand, they cyclized the dihydroindole ring using a benzyne-mediated cyclization/arylation sequence. To treat the substrate **591** with Mg(TMP)₂ formed the dianion (not shown), which would further extrude the HBr from the aromatic ring to yield a benzyne intermediates. The nitrogen anion

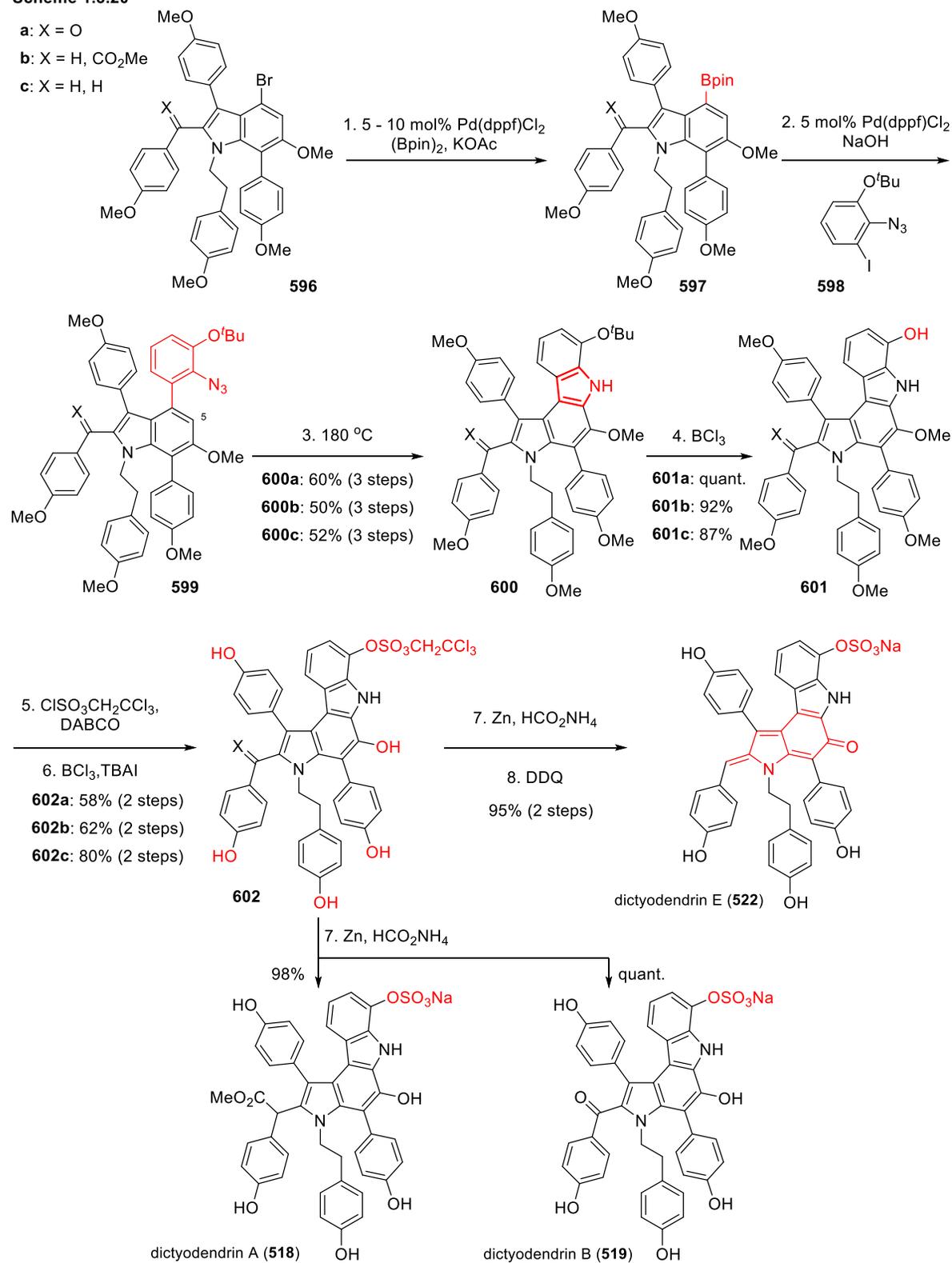
attacked the benzyne to cyclize the dihydroindole ring and provide the 7-metallated indole **592**, which served as a suitable substrate for the subsequent C7 arylation reaction. The product **593** was obtained via the cross coupling reaction between the metallated indole **592** and the iodoanisole **585**. The removal of Boc protecting group and the DDQ oxidation aromatized the indole ring, and the following S_N2 reaction with 4-methylphenylethyl bromide **581** provided the precursor **594** for the Friedel-Crafts reactions. For the Friedel-Crafts reaction, Tukuyama developed the specific conditions of each alkylation reagent. Specifically, they found zinc chloride promoted the acylation best with the acid chloride **579** to generate **596a**, while the alkylation was only available with silver triflates using the α -bromoacetate **556** to form **596b**. However, the benzylation cost the extra efforts. When 4-methoxybenzylchloride was used, neither zinc chloride nor silver triflate produced any noticeable amount of the desired product. Luckily, they succeeded in the benzylation reaction using the trichloroacetimidate **595** and TMSOTf. Under these conditions, they obtained the desired product **596c**. Jia's syntheses also benefited from these reaction conditions, where they exactly followed Tukuyama's procedures. After the Friedel-Crafts reaction, Tukuyama and co-workers moved on to construct the carbazole systems and the alternation of the protecting groups on dictyodendrins (Scheme 1.3.20). All three intermediates **596** shared the similar construction procedures towards the natural products. First, they converted the bromide of **596** into the pinacol boronate **597**, which underwent the Suzuki coupling reaction with the aryl iodide **598** offering the azide precursor **599**. Under the thermal conditions, the azide extruded nitrogen gas and formed the nitrene intermediate that inserted into the C5 C-H bond, and it gave the expected carbazole structure **600** in the reasonable yields for all three analogs.

Scheme 1.3.19

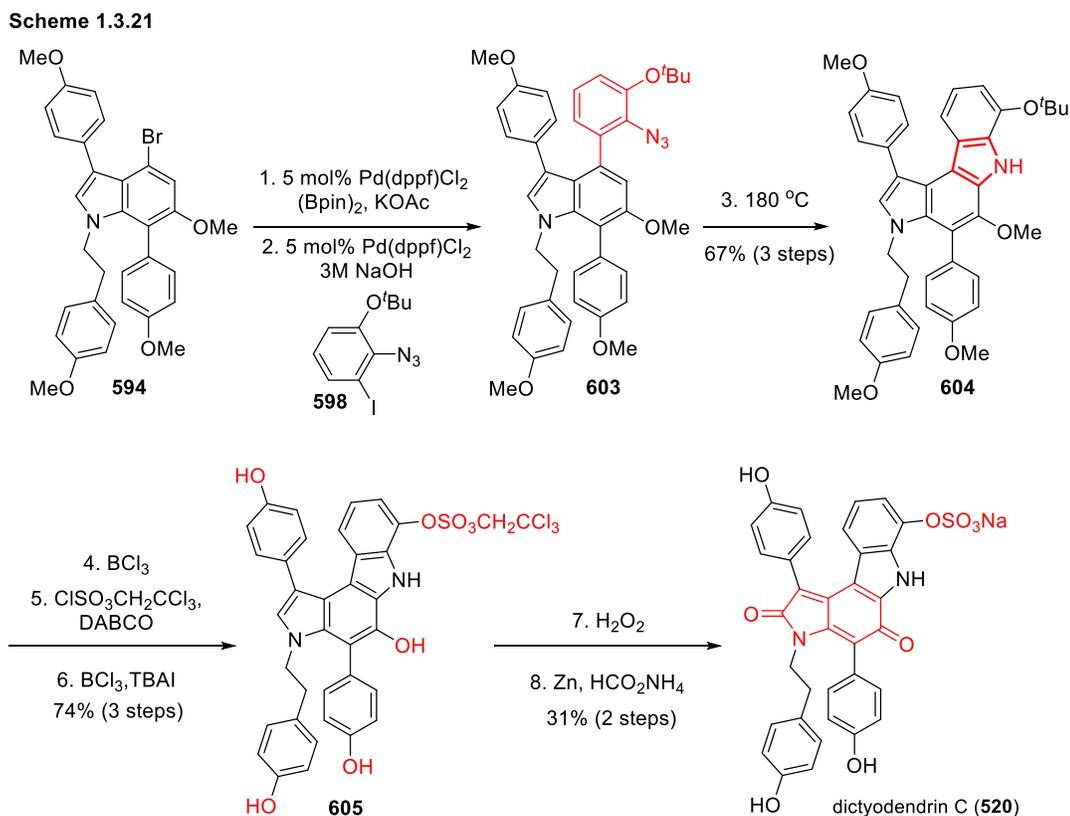


Scheme 1.3.20

- a: X = O
 b: X = H, CO₂Me
 c: X = H, H



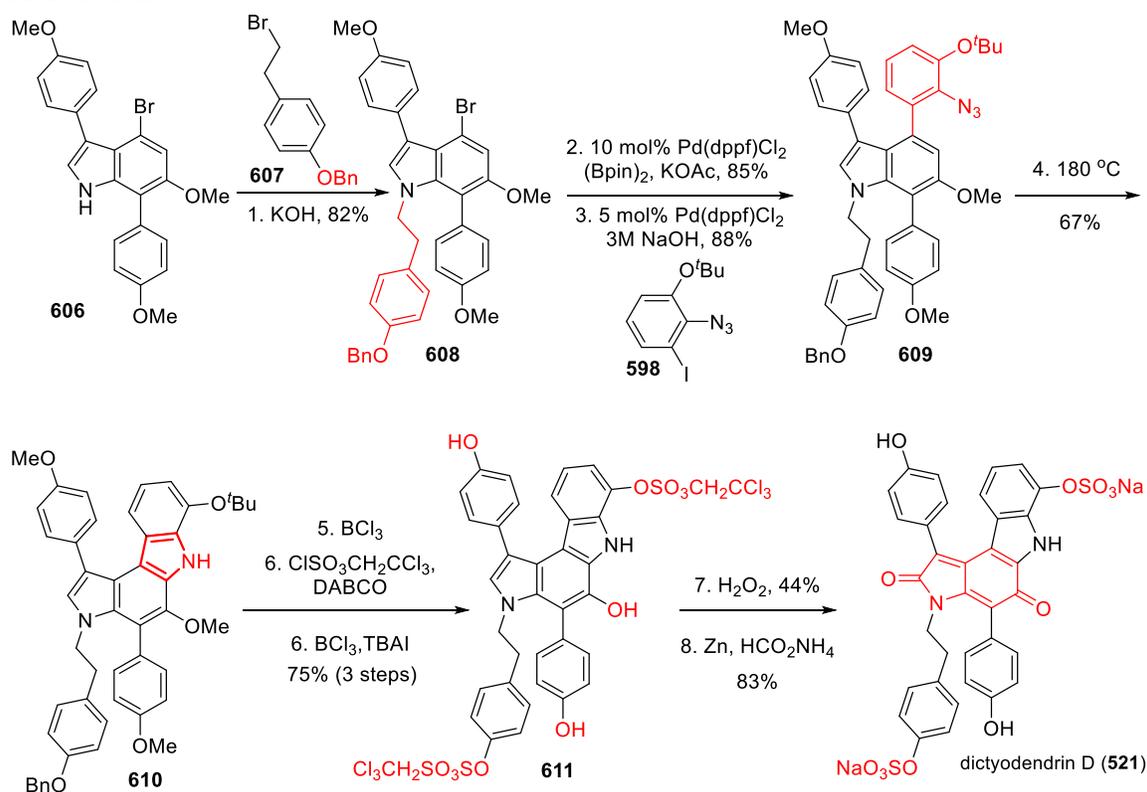
Finally, Tukuyama finished the synthesis using the methods reported by Füstner, where the *tert*-butyl protecting group was removed under the acidic conditions followed by the sulfonate formation and the global demethylation. According to Füstner's reports, dictyodendrins A (**518**) and B (**519**) were obtained via the cleavage of the trichloroethyl group using the zinc reduction, but dictyodendrins C (**522**) required an extra oxidation using DDQ after the zinc reduction. Later, they also published the details of the syntheses of dictyodendrins A and B in a full article as well as their syntheses of dictyodendrins C (Scheme 1.3.21), D (Scheme 1.3.22), and E using the same synthetic approach.¹⁸⁴

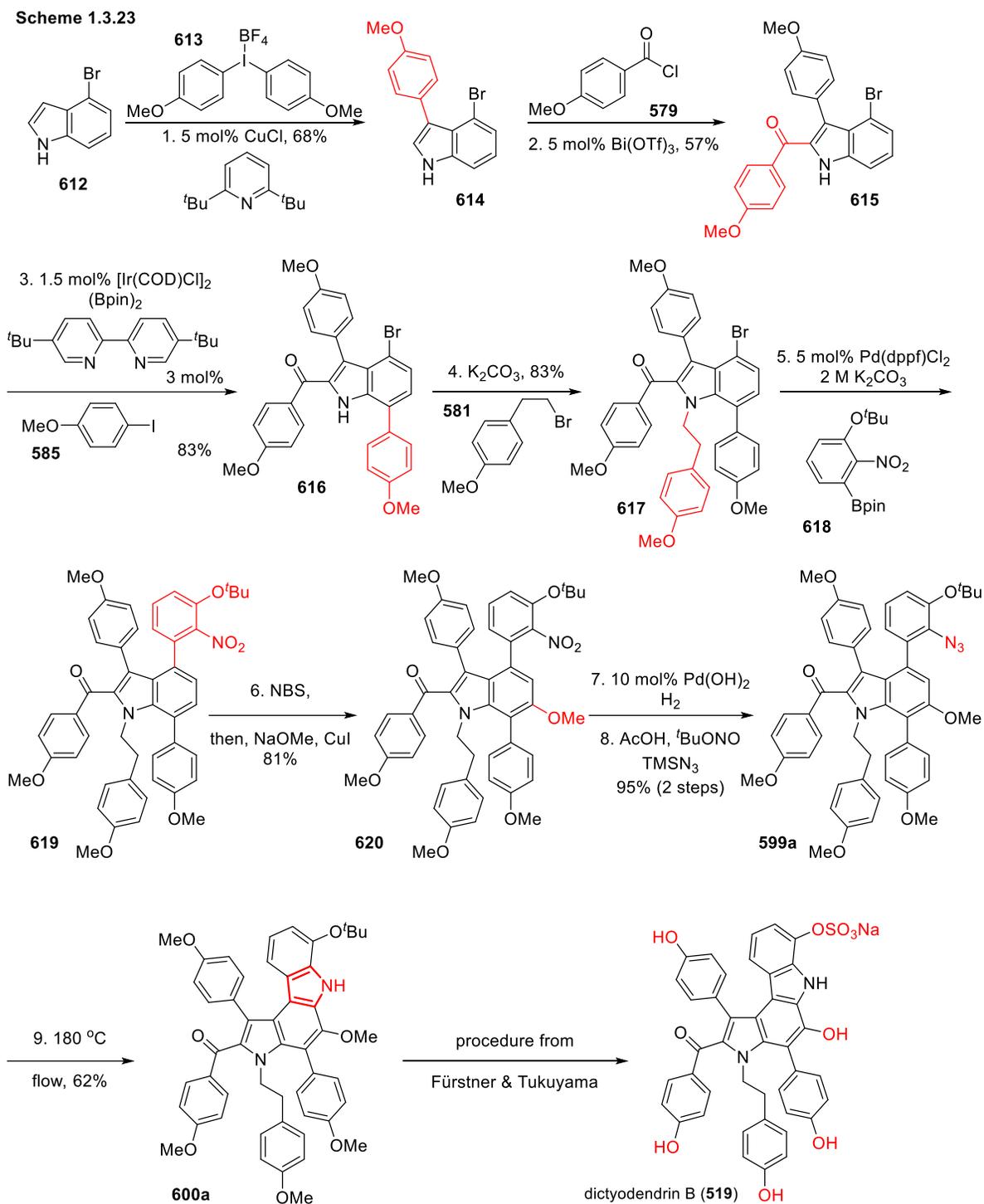


Unlike dictyodendrins A and B, dictyodendrins C, D, and E have the quinone oxidation states, and dictyodendrins C and D have an extra side chain over dictyodendrins A and B. Without the need

for introducing the side chains, the synthesis of dictyodendrins C and D directly used the precursor for the Friedel-Crafts reaction. However, because dictyodendrins D has another sulfate attached to the phenol, it required the N-alkylation of the indole **606** using *para*-benzoyloxyphenylethyl bromide **607** instead (Scheme 1.3.22). In accordance with the synthesis of dictyodendrins A, B, and E, they completed the synthesis of dictyodendrins C involving the bromide-pinacol boronate switch and the Suzuki coupling reaction to get the cyclization precursors **603** and **609**, the nitrene insertion under the thermal conditions to get the carbazole **604** and **610**, and the alternation of protecting groups. According to the Füstner's procedure, they obtained dictyodendrins C, and D in the same manner.

Scheme 1.3.22

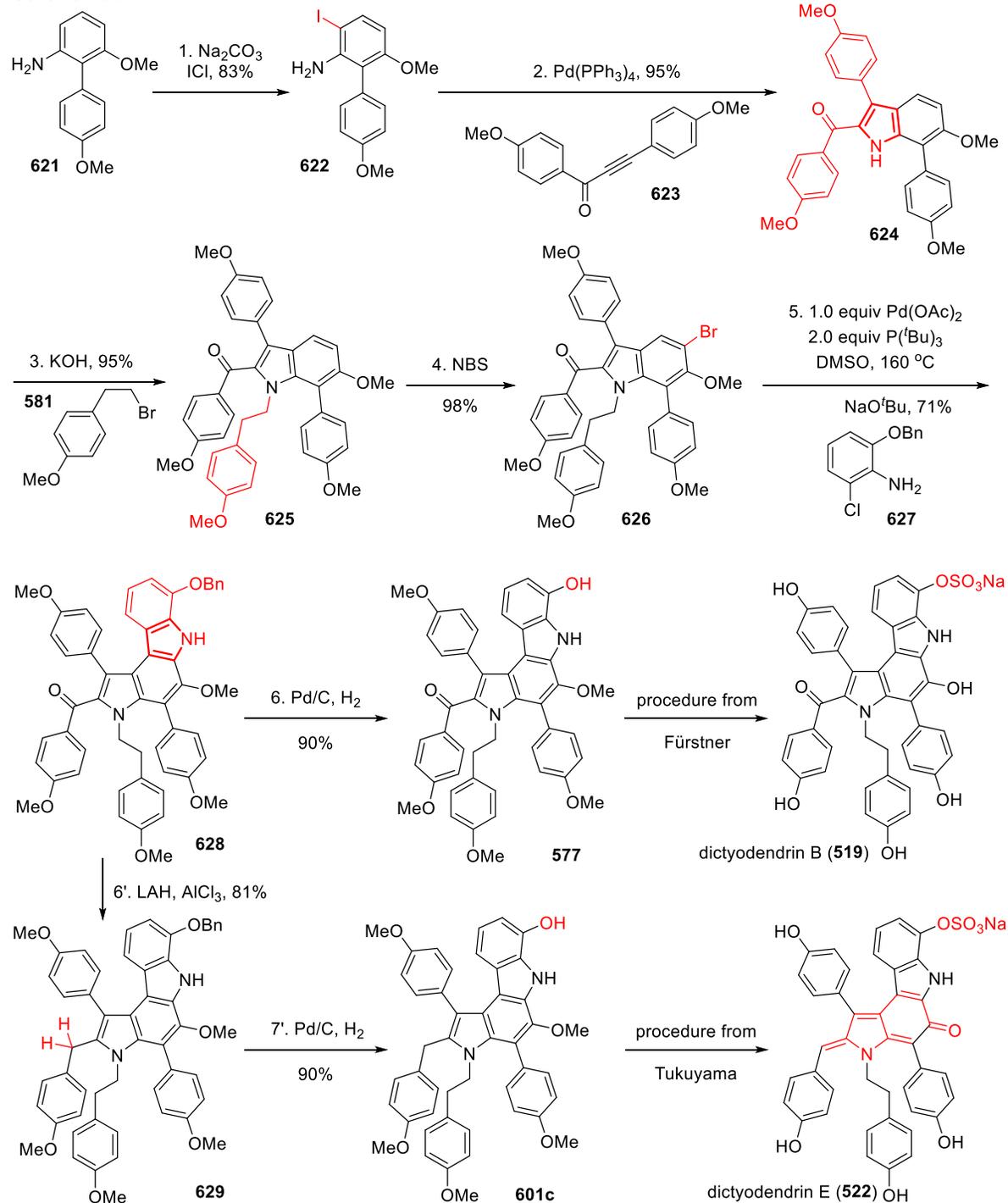




Resembling Tukyama's synthetic strategy, Guant rearrange the assembling orders for the fragments.¹⁸⁵ He began his synthesis with a commercially available 4-bromoindole **612**, and

he synthesized the 3-arylated indole **614** via his own C-H functionalization methodology using the diaryl iodonium salt **613** and the copper catalysts. Different from Tukuyama's synthetic strategy, they did the Friedel-Crafts acylation using bismuth triflate and obtained the 2-acylated indole **615** prior to the N-alkylation and the C7 arylation. The utilization of the iridium-catalyzed C-H functionalization allowed the following C7 arylation, wherein the indole nitrogen served as the directing group. The corresponding arylated product **616** underwent a S_N2 addition to the alkyl bromide **581** to afford the N-alkylation product **617**. Subsequently, the Suzuki coupling between the C4 bromide of **617** and the pinacol boronate **618** provided the C4-arylated product **619**. Here, a highly selective C6 bromination successfully activated the C6 carbon of **619**, and it allowed the formation of the phenol methyl ether **620**. Then, Guant and co-workers turned to the synthesis of carbazole cyclization precursor **599a**. They reduced the nitro-group into the aniline, which would react with *tert*-butyl nitrite to form the diazonium intermediate. The replacement of the diazonium group by the azide offered the desired precursor **599a**, respectively. With the known intermediate **599a** in hand, the Guant group optimized the nitrene cyclization using a novel flow chemistry to increase the yield of the carbazole **600a** to 62% in gram scale. He completed his synthesis of dictyodendrin B according to Tukuyama and Füstner's previous report.

Scheme 1.3.24



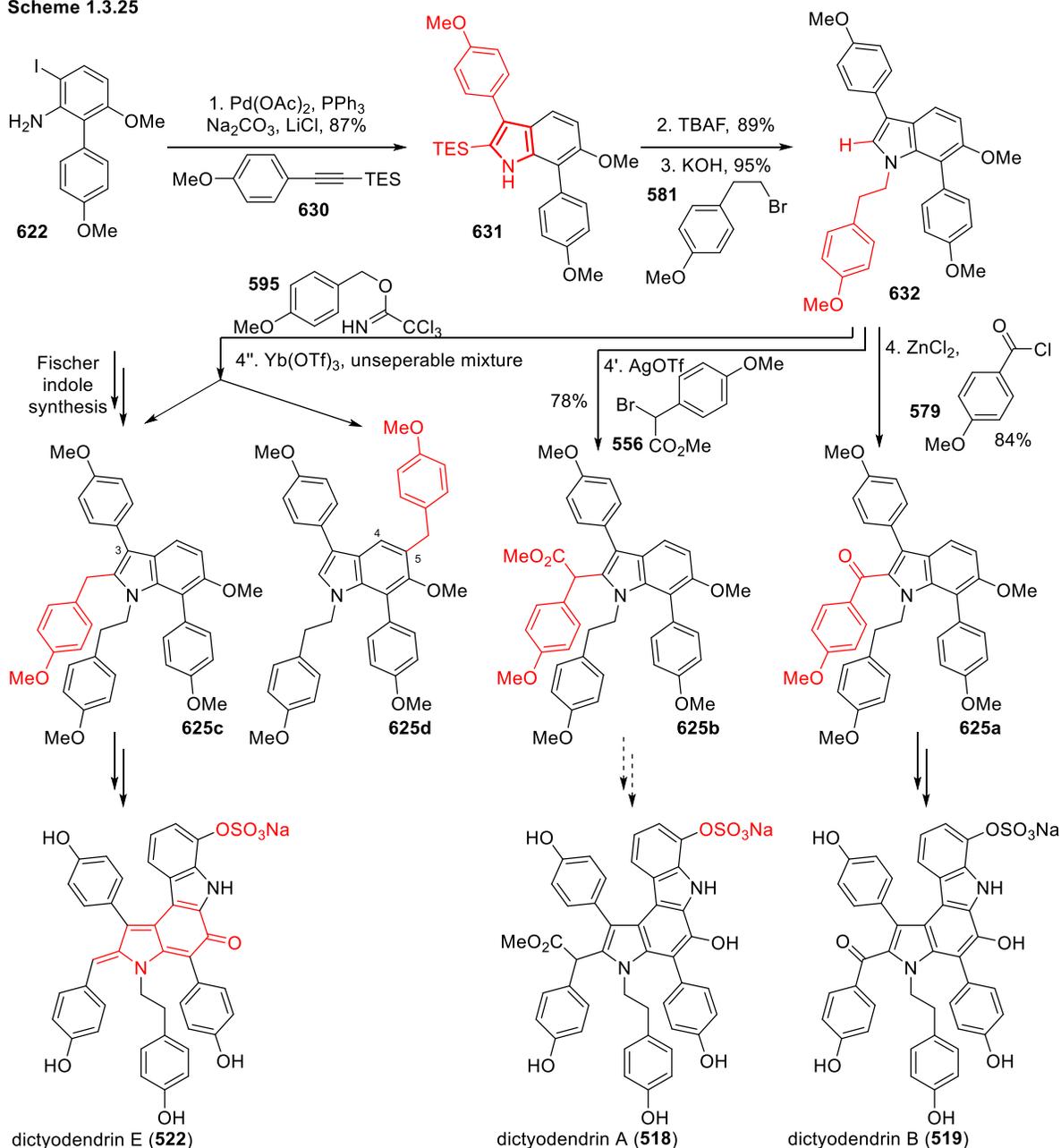
Another smart modification of Tukuyama's approach was reported by Y.-X. Jia and co-workers. In their first generation synthesis of dictyodendrin B (Scheme 1.3.24),¹⁸⁶ they utilized

a pre-functionalized anisylacetylene **623** and a readily available iodobiarylaniline **622** in the palladium-catalyzed Larock indole synthesis. In this manner, it significantly saved the steps to obtain the highly functionalized indole core **624**. Referring to Tukuyama's procedure, they obtained the N-alkylated product through a S_N2 reaction to alkyl bromide **581**, and the following bromination offered the starting material **626** for the Buchwald-Hartwig arylation/cyclization cascade reaction. After the extensive screening of the reaction conditions, the Jia group finally established a highly efficient cyclization of the pyrrole structure in the carbazole **628**. Via the palladium-catalyzed hydrogenation de-benzylation, a known intermediate **577** was obtained; it was further converted into dictyodendrin B in accordance with Füstner's procedure. On the other hand, the Jia group solved a straggling problem for Füstner, which hampered their synthesis of dictyodendrin E from an intermediate for the synthesis of dictyodendrin B. Füstner and co-workers gave up the conversion of the benzyl alcohol **537** into the desired quinone methide structure (**Scheme 1.3.12** and **Scheme 1.3.13**) under the acidic conditions. However, the Jia group just simply employed the LAH reduction of the ketone **628** to give the intermediate **629**, and the following palladium-catalyzed hydrogenation de-benzylation provided an intermediate **601c** disclosed by Tukuyama. By this path, they completed the synthesis of dictyodendrin E.

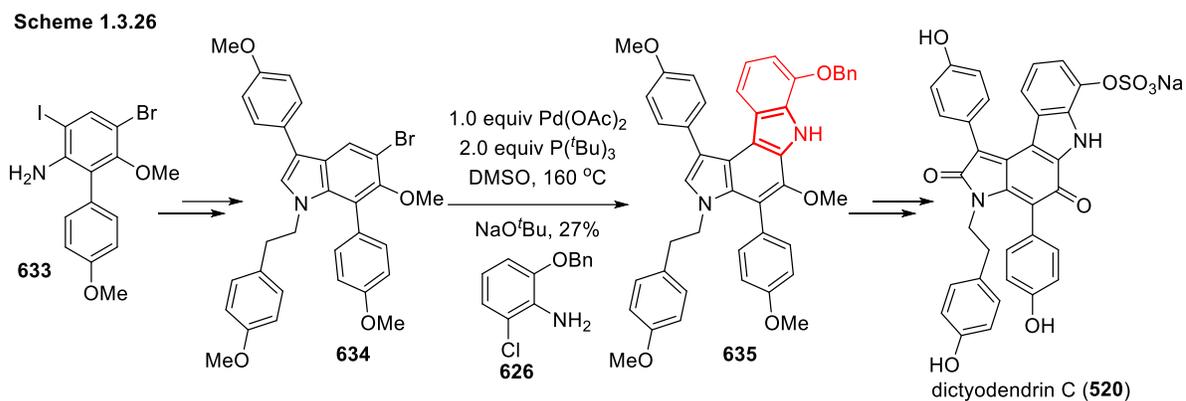
To develop a more general synthesis of dictyodendrins, Jia referred his second generation synthesis to Tukuyama's idea. They also utilized the Friedel-Crafts reactions to install the side chains for the different natural products (**Scheme 1.3.25**). Their second generation synthesis avoids using the pre-functionalized anisylacetylenes in the Larock indole synthesis. Instead, a silyl acetylene **630** served as the coupling partner with the iodobiarylaniline **622** to form the

indole skeleton **631**. The removal of TES group and the N-alkylation gave the indole **632**, which would undergo the Friedel-Crafts reactions with the different electrophiles. Referring to Tukuyama's condition, the Jia group succeeded in the acylation reaction, and they acquired the product **625a** using the acid chloride **579** and zinc chloride. Meanwhile, silver triflate promoted the alkylation using the α -bromoester **556** to afford the corresponding product **625b**. But they struggled with the benzylation under Tukuyama's condition, which resulted in two inseparable isomer mixtures, **625c** and **625d**. This side reaction was largely due to the lack of the hindered bromide on the C4 position of **632** blocking the acylation on the C5 position. They circumvented this problem via a Fischer indole synthesis to obtain the intermediate **625c**. In their last part of the synthesis, they used the same synthetic methods they developed in their first generation of syntheses of dictyodendrins. After the bromination, the aryl amination, the subsequent cyclization of the carbazole, they were able to complete the syntheses of dictyodendrins A, B, E following the Füstner and Tukuyama's procedures.

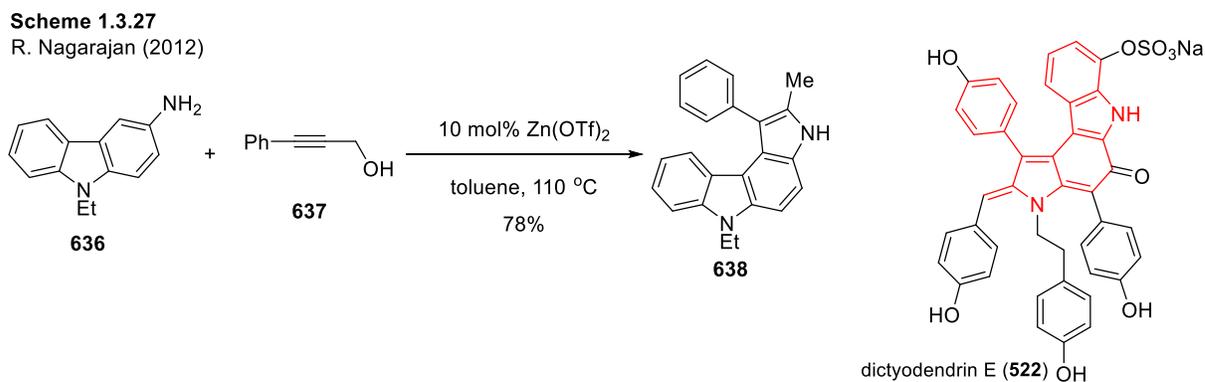
Scheme 1.3.25



In the synthesis of dictyodendrin C, they pre-brominate the starting material **633** to avoid the C2 or C5 selectivity issue. Under this sequence, the Jia group utilized their Larock indole synthesis to construct the indole **634** and their amination/cyclization cascade reaction to build the carbazole **635** in the synthesis of dictyodendrin C (Scheme 1.3.26).



In addition, some other groups also developed some synthetic methodologies targeting to dictyodendrins. For example, R. Nagarajan and co-workers disclosed a Lewis acid, zinc triflates, catalyzed indolization between the carbazole aniline **636** and the phenyl propargyl alcohol **637** (Scheme 1.3.27).¹⁸⁷ The resultant **638** shared similar carbon skeletons with dictyodendrin E.



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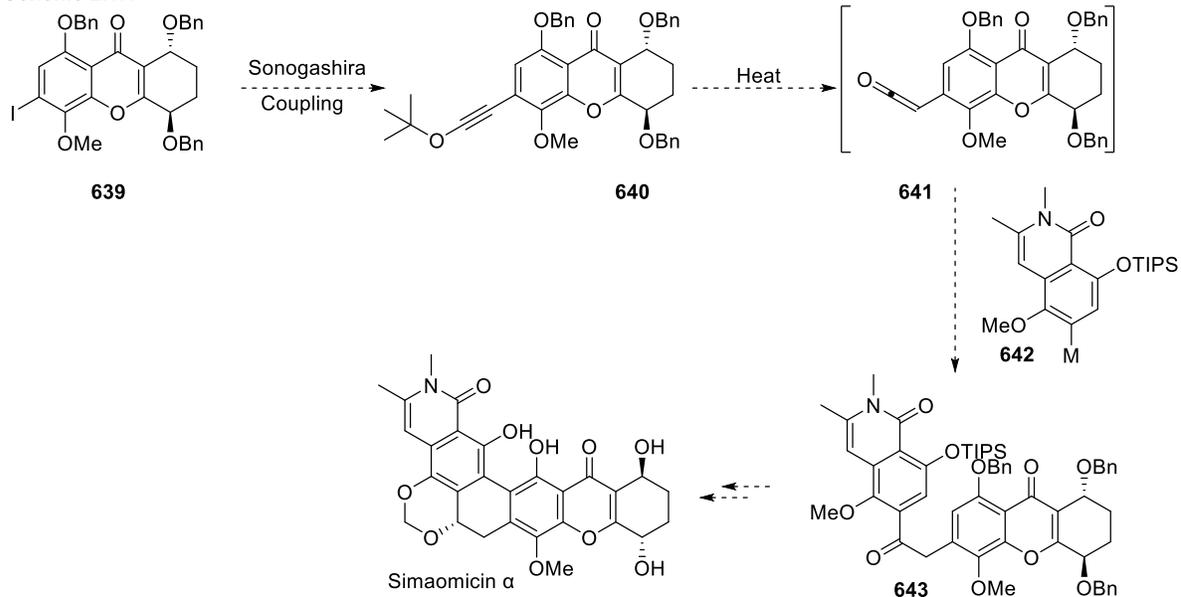
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CHAPTER TWO

SYNTHESIS OF ARYL YNOL ETHER AND THEIR APPLICATIONS

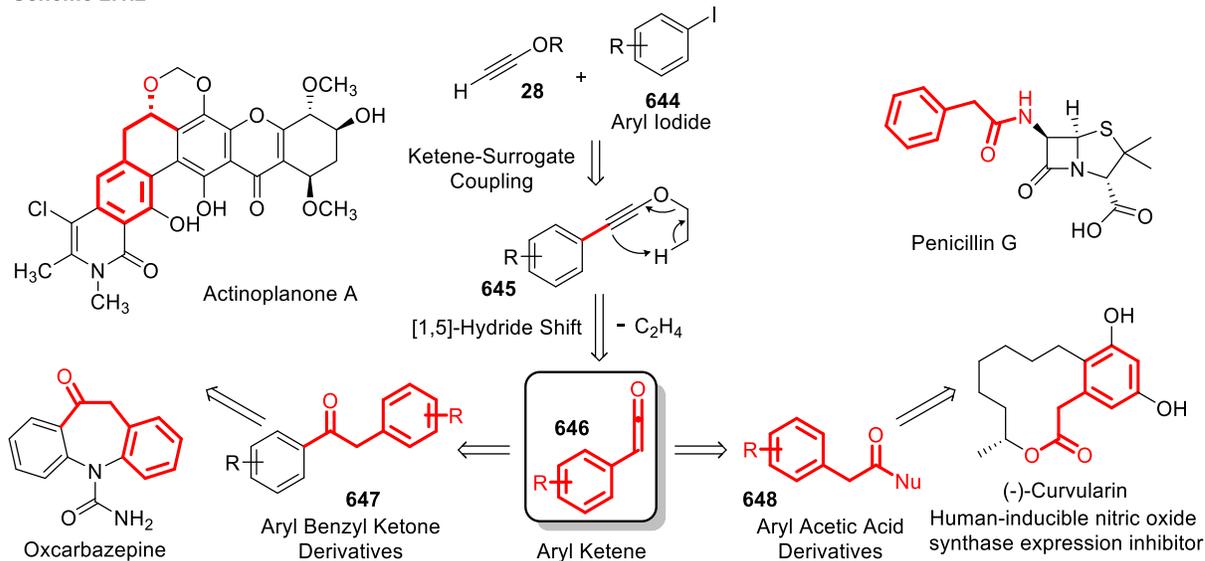
2.1 Synthesis of Aryl Ynol Ethers

Scheme 2.1.1



A total synthesis of Simaomicin α in our group drove our initial interests in developing a synthesis of aryl ynol ethers (**Scheme 2.1.1**). Together with its natural product analogs, simaomicin α was found to display remarkable anticancer properties. Our group had long-term interests in developing an asymmetric synthesis of it. The addition of aryl-metal species **642** to the aryl ketene **641** might construct the central framework. To implement this strategy, an efficient synthesis of aryl ketenes is needed. We planned a new strategy utilizing the Sonogashira coupling to introduce *tert*-butyl ynol ether motifs onto the aromatic rings, followed by the ketene generation under the thermal conditions.

Scheme 2.1.2



Moreover, aryl acetic acid derivatives **648** and aryl benzyl ketones **647** are found in a large number of biologically active natural products and drug candidates (**Scheme 2.1.2**). For example, aryl benzyl ketones **647** or their derivatives are substructures within the polycyclic natural product actinoplanone A and the epilepsy drug oxcarbazepine. Likewise, aryl acetic acid derivatives **648** appear in many natural products and drug candidates, such as (-)-curvularin and penicillin G. However, no general catalytic method has been developed to access either of these intermediates from aryl iodides **644**, despite the ready availability of diversely substituted aryl halides. We hypothesized that aryl ketenes **646** represented promising precursors to aryl benzyl ketones **647** and a wide range of aryl acetic acid derivatives **648**. In particular, the efficient access to aryl ketenes would provide a route to esters, amides, carboxylic acids, ketones and thioesters from the same intermediate.

Previous catalytic approaches to aryl acetic acid derivatives relied on the α -arylation of enolates, which we discussed in the **Chapter One**. The most widely used α -arylations are the nickel- (**Scheme 1.3.4**) and palladium-catalyzed couplings of ketones (**Scheme 1.3.2**),

aldehydes (**Scheme 1.3.7**), esters (**Scheme 1.3.8**), and amides with aryl halides. These precedent methods have proven relatively general, and, sometimes, enantioselective (**Scheme 1.3.3**). Nonetheless, enolate couplings require the strongly basic conditions, elevated temperatures, and/or independent pre-functionalizations of the enolates. They frequently involve specialized ligands, and achieving selective monoarylation over bisarylation can be challenging due to the formation of more stabilized enolates (**Scheme 1.3.6**). Alternative catalytic approaches to the α -arylation of carbonyl compounds include α -arylation with iodonium salts (**Scheme 1.3.9**) or activated sulfoxides (**Scheme 1.3.10**), addition of aldehydes to *in-situ* generated quinone derivatives, and a recent oxidative coupling of ketones with nitroarenes (**Scheme 1.3.11**).

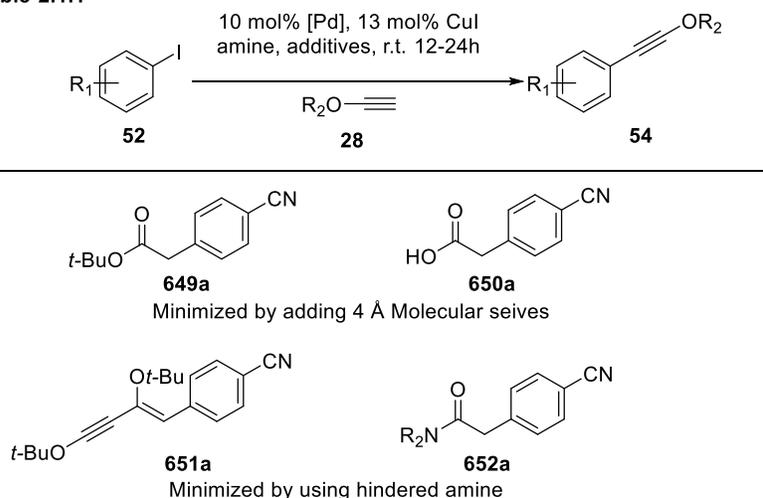
To date, no direct methods have been reported to couple ketene with an aromatic ring, and such a reaction appeared implausible. An alternative presented itself, however, in the [1,5]-hydride shift of ynol ethers **645**. This process is accompanied by the sigmatropic extrusion of an olefin, and occurs under thermal conditions. Finally, we reasoned that the requisite aryl-substituted ynol ethers could arise from couplings of alkoxyacetylene **28** with aryl halides **644**. Taken together, the sequence of acetylide coupling followed by sigmatropic extrusion of an olefin would yield aryl ketenes, and constitute a formal ketene arylation. In this way, an alkoxyacetylene **645** could serve as a ketene surrogate, so we refer to the process as a ketene surrogate coupling.

2.1.1 The Optimization of the Sonogashira (Ketene Surrogate) Coupling Reaction

We chose the Sonogashira coupling as our starting point, because it could directly connect the aryl iodides and ynol ethers without necessitating a pre-functionalization of the acetylene motif.

While a limited success has been achieved in the Sonogashira coupling between menthol-derived ynol ethers and terminal vinyl iodides,¹ related couplings with aryl halides are not efficient. Indeed, the only reported Sonogashira coupling between an ynol ether and phenyl iodide proceeded in only 11% yield (**Scheme 1.1.7**).^{2,3}

Table 2.1.1



Entry ^a	R ₁	R ₂	Catalyst	Amine	Additive	Yield (NMR) ^b
1	4-CN (52a)	Et	Pd(PPh ₃) ₄	Et ₃ N	-	<5%
2	4-CN	^t Bu	Pd(PPh ₃) ₄	Et ₃ N	-	54%
3	4-CN	^t Bu	Pd(PPh ₃) ₄	ⁱ Pr ₂ NEt	4 Å M.S.	85%
4	4-CN	^t Bu	Pd ₂ (dba) ₃ / PPh ₃ ^c	ⁱ Pr ₂ NEt	4 Å M.S.	95%
5	4-Me (52b)	^t Bu	Pd ₂ (dba) ₃ / PPh ₃ ^c	ⁱ Pr ₂ NEt	4 Å M.S.	66%
6	4-Me	^t Bu	Pd ₂ (dba) ₃ / PPh ₃ ^c	ⁱ Pr ₂ NH	4 Å M.S.	89%
7	2-Me (52c)	^t Bu	Pd ₂ (dba) ₃ / PPh ₃ ^c	ⁱ Pr ₂ NH	4 Å M.S.	55%
8	2-Me	^t Bu	Pd ₂ (dba) ₃ / TFP ^c	ⁱ Pr ₂ NH	4 Å M.S.	79%

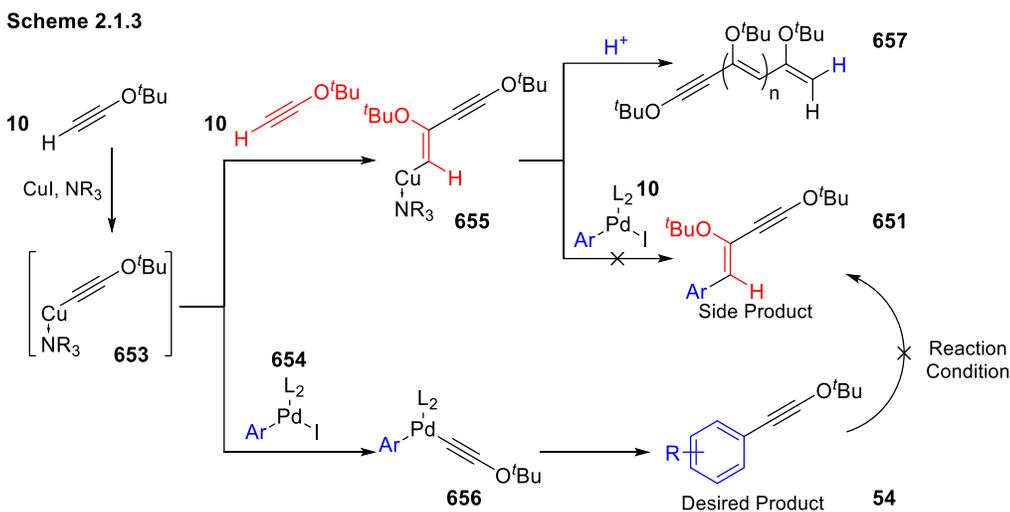
^aReactions were conducted on a 0.1 mmol scale; 0.25m in 1:1 (v/v) amine/ynol ether.

^bYields determined by NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. ^cUsed 20 mol% phosphine. dba=dibenzylideneacetone, M.S.=molecular sieves, TFP=tri(2-furyl)phosphine.

To develop the ketene surrogate coupling, we first investigated the Pd-catalyzed coupling of terminal ynol ethers **28** with aryl iodides **52** and optimized its reaction conditions (**Table 2.1.1**). 4-cyanoiodobenzene (**52a**) was combined with ethoxy acetylene, Pd(Ph₃)₄ and CuI in triethyl amine (entry 1). We were unable to isolate any appreciable amount of the desired product, and ¹H NMR analysis suggested that the ynol ether motifs had polymerized under the reaction conditions. Reasoning that a more sterically hindered alkyne might be less prone to such polymerization, we repeated the experiment using *tert*-butoxy acetylene instead of ethoxy acetylene.⁴ To our delight, the bulky *tert*-butyl group stabilized the ynol ether from nucleophilic and electrophilic additions. Moreover, *tert*-butoxy acetylenes rearrange to ketenes at around 70 °C compared to the 120 °C that is required for conversion of ethoxyacetylenes to ketenes.⁵ In this circumstance, we were gratified when alkyne **54a** was formed in 54% yield using *tert*-butoxyacetylene (entry 2). In addition to the desired ynol ether, we also identified the side products arising from hydration and hydrolysis of the desired product **54a** (**649a** and **650a**, respectively). We also observed the formation of enyne **651a**, a 2:1 adduct of *tert*-butoxy acetylene and the aryl iodide, and the amide **652a**, an aminolysis product, was confirmed as well.

To minimize the formation of ester and carboxylic acid side-products, we included molecular sieves as the additives in the reaction. Additionally, we found that a bulkier base, ⁱPr₂NEt, suppressed the generation of enynol ether **651a** (entry 3). Under these conditions, an encouraging 85% yield of the aryl-substituted ynol ether **54** encouraged us for the further optimizations. Mechanistically, the copper would promote the amine-conducted deprotonation of terminal ynol ether **10** (**Scheme 2.1.3**) and form the copper complex **653**. If the reaction

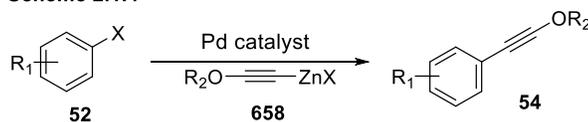
went under the right path, the acetylide motif would be transmetallated to the aryl palladium iodide **654**, and the resultant **656** would further undergo a reductive elimination to give the desired product **54**. We envisioned enynol **651** could arise from the dimerization of *tert*-butoxyacetylene and the subsequent coupling with the aryl iodide. We favored this hypothesis because *tert*-butoxyacetylene did not add to the isolated ynoyl ether **54** under the coupling conditions. We speculate that a bulky amine prevents $[(R_3N)_nCu(enynol)_nacetylide]$ complex **655** from delivering the polymerized motifs to the aryl palladium halides **10**. The generation of carbometalated oligomers **657** supports this mechanistic hypothesis. Ultimately, the reproducibility of the reaction could be improved by forming $Pd(PPh_3)_4$ in situ from $Pd_2(dba)_3$ and PPh_3 (entry 4).⁶



Unfortunately, when applying these conditions to an electron neutral substrate (**52b**), we observed incomplete conversion (entry 5). Changing to a secondary amine (iPr_2NH) accelerated the coupling (entry 6) without introducing impurities. Under these conditions, aryl iodide **52b** was completely consumed, and the aryl-substituted ynoyl ether (**54b**) ether was formed in

89% yield (entry 6). Reactions with $i\text{Pr}_2\text{NH}$ are generally faster than those containing $i\text{Pr}_2\text{NEt}$, but electron-poor arenes formed small quantities of the corresponding tertiary amide (e.g. **652a**) during the reaction. Accordingly, we generally recommend $i\text{Pr}_2\text{NEt}$ for electron poor substrates, which have the relatively fast reaction rates, and $i\text{Pr}_2\text{NH}$ for electron rich and neutral substrates. Finally, sterically hindered substrates such as **52c** benefited from an even more active catalyst. In particular, tri(2-furyl)phosphine (TFP), smaller but more electron-deficient than PPh_3 , formed a competent catalyst in conjunction with $\text{Pd}_2(\text{dba})_3$, thus promoting the coupling of a hindered aryl iodide in good yield (entry 8). To summarize, three closely related reaction conditions accommodate a wide variety of substrate classes: the couplings are usually more efficient with $i\text{Pr}_2\text{NH}$ than with $i\text{Pr}_2\text{NEt}$, although with electron deficient substrates, we observed minor amounts of the amide **652** when $i\text{Pr}_2\text{NH}$ was used. While these substrates perform admirably with inexpensive PPh_3 , challenging aryl iodides often necessitate the electron deficient phosphine TFP.

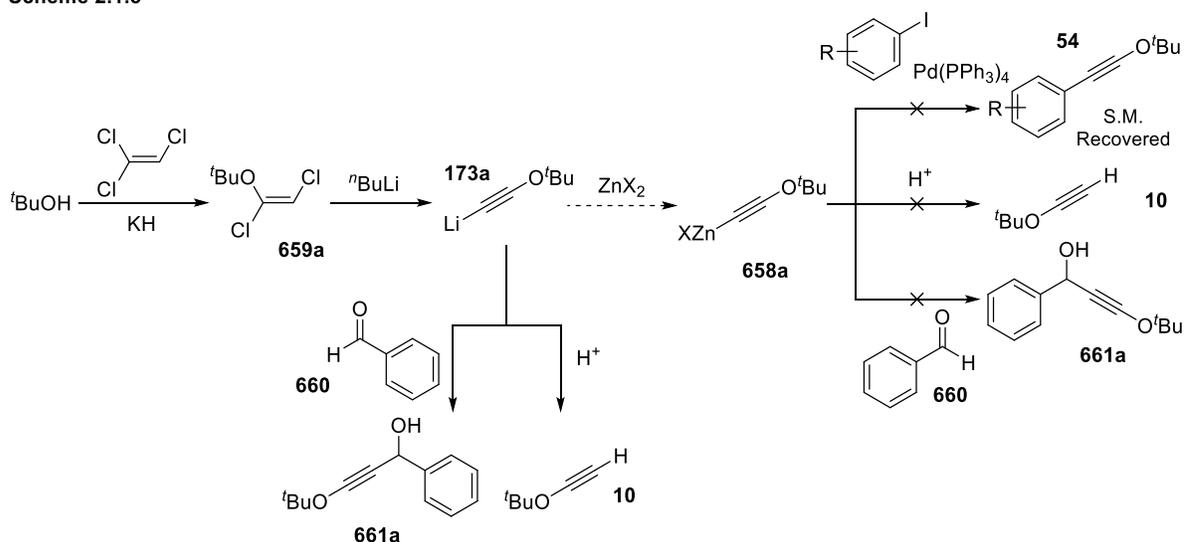
Scheme 2.1.4



However, aryl *tert*-butoxyl ynol ethers **54** still suffer from several problems during the exploration of potential applications of ynol ethers. The major issues of the Sonogashira coupling conditions include the acidic instability of *tert*-butoxyl group, low conversions of the sterically hindered substrates, and the thermolysis during the reaction with aryl bromide at an elevated temperature, the long reaction time, the complicated catalytic systems, and the hard purification of terminal *tert*-butoxyl ynol ether **10**. To address the problems, we envisioned that the Negishi coupling between the zinc alkoxyacetylides and aryl halide **52** would have a

faster reaction rate, simplified reaction conditions, and provide access to the less reactive substrates. On the other hand, we would attempt to acquire the zinc alkoxyacetylides **658** via a one-pot procedure, which would avoid the hard purification of terminal ynol ethers **10**.

Scheme 2.1.5

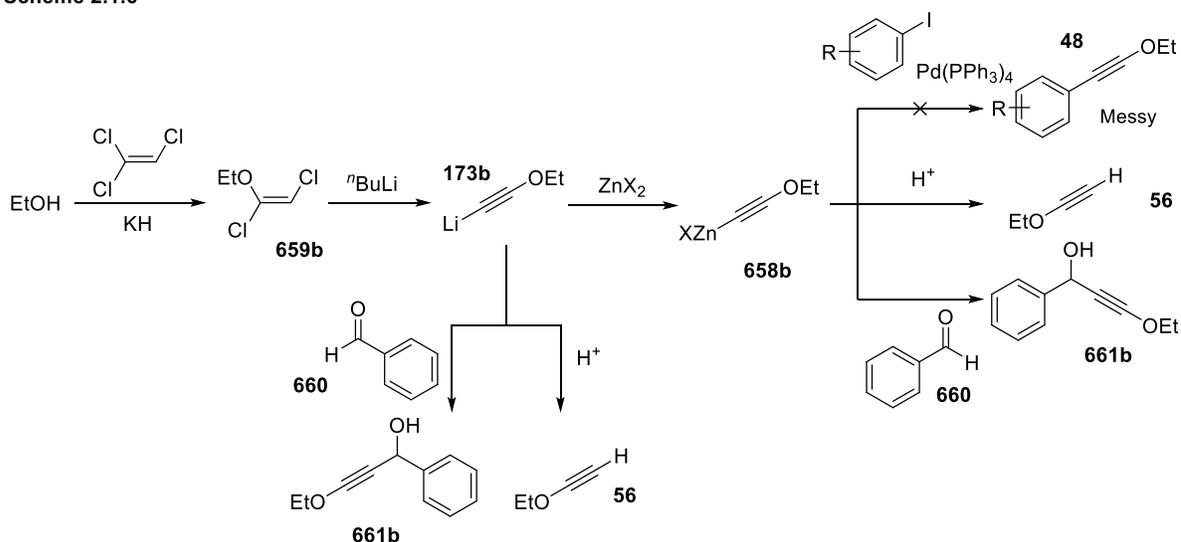


According to Himbert's report, we synthesized lithium *tert*-butoxyacetylide **173a**, which could be trapped with benzaldehyde **660** and water (Scheme 2.1.5). The formation of benzyl alcohol **661a** and terminal ynol ether **10** confirmed the formation of lithium *tert*-butoxyacetylide **173a**. Nevertheless, we speculated the transmetallation from lithium to zinc failed. Because we were neither able to trap the zinc species **658a** with benzaldehyde **660** and water nor to use it in the Negishi coupling reaction. We assumed the failure was due to the instability of *tert*-butyl groups under the Lewis acidic conditions.

Likewise, lithium ethoxyacetylide **173b** could be acquired in the same protocol (Scheme 2.1.6). After the transmetallation, we found it generated the corresponding benzyl alcohol **661b** and ethoxyl ynol ether **56** via the trapping of zinc acetylides **658b**, which implied the formation of the transmetallated products. Unfortunately, the Negishi coupling was a messy reaction,

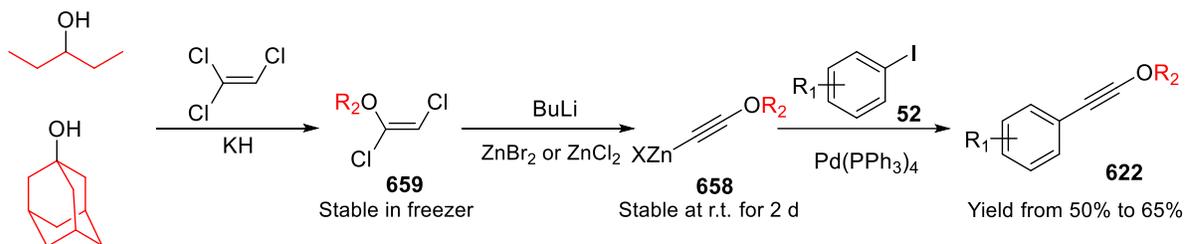
wherein the aryl iodide was consumed. We proposed that the failure of the coupling shared the same underlying mechanism with the Sonogashira reaction, and a more sterically hindered alkoxy group might minimize the carbometallation affording the aryl ynol ether exclusively.

Scheme 2.1.6



In order to test our hypothesis, we utilized 3-pentanol and 1-adamantol to form the related lithium and zinc acetylides ($R_2 = 3\text{-pent}$ **658c**, $R_2 = \text{Ad}$ **658d**). To our delight, we found the Negishi coupling produced the desired aryl ynol ether **662** in moderated yields (Scheme 2.1.7), and the Pd(PPh₃)₄ loading did not affect the yield of the coupling obviously. Additionally, we tested the stability of dichlorovinyl ethers **659** and zinc alkoxyacetylides **658**. We noticed the dichlorovinyl ethers could stay in a toluene solution over a year in a -20 °C freezer, which provided the convenience for us in the preparation of zinc acetylides **658**. However, zinc alkoxyacetylides **658** decomposed at room temperature overnight, indicating the zinc alkoxyacetylides should be prepared freshly before the coupling reactions.

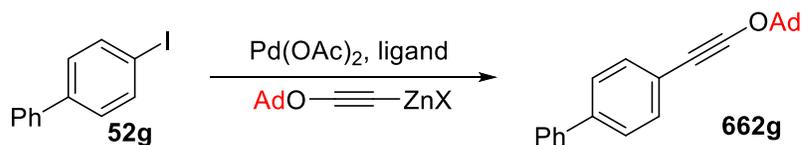
Scheme 2.1.7



Pd(PPh ₃) ₄ loading (mol%)	Yield (¹ H NMR)
10	61%
5	63%
3	60%
1	66%

The further optimization of the Negishi coupling focused on the ligand of the palladium (**Table 2.1.2**). Himbert and Löffler's original protocol of the related couplings used PPh₃ as the ligand.⁷ In our hands, these conditions resulted in the carbometallation of the ynoles. Similarly, in 2014 the Stoltz group disclosed a Negishi coupling between methoxyacetylide zinc chloride and a vinyl iodide. They noted that a xantphos ligand minimized the polymerization of the alkyne due to its large bite angle.^{8,9} Following their lead, we evaluated chelating diphosphines in the series Ph₂P-(CH₂)_n-PPh₂ and found that the yield in the Negishi coupling correlated with the bite angle (from entry 2 to entry 7). Clearly, the yield increased with the increasing length of the tethered carbon link between two phosphines. Under the optimized conditions, 1,6-bis(diphenylphosphine)hexane (dpph) ligand afforded adamantyl anisoyl ynoles **622g** in an 84% NMR yield and an 80% isolated yield (entry 8).¹⁰

Table 2.1.2



entry ^a	ligand	yield ^b
1	TFP	67%
2	dppm	<10%
3	dppe	<10%
4	dppp	35%
5	dppb	79%
6	dppf	71%
7	dpph	84%
8 ^c	dpph	83%

^a10 mol% catalyst loading. ^bYields determined by NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. ^c5 mol% catalyst loading.

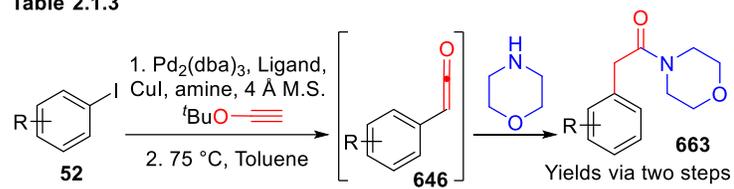
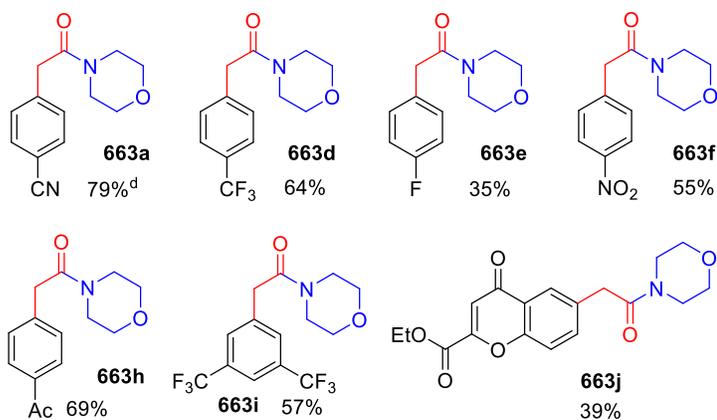
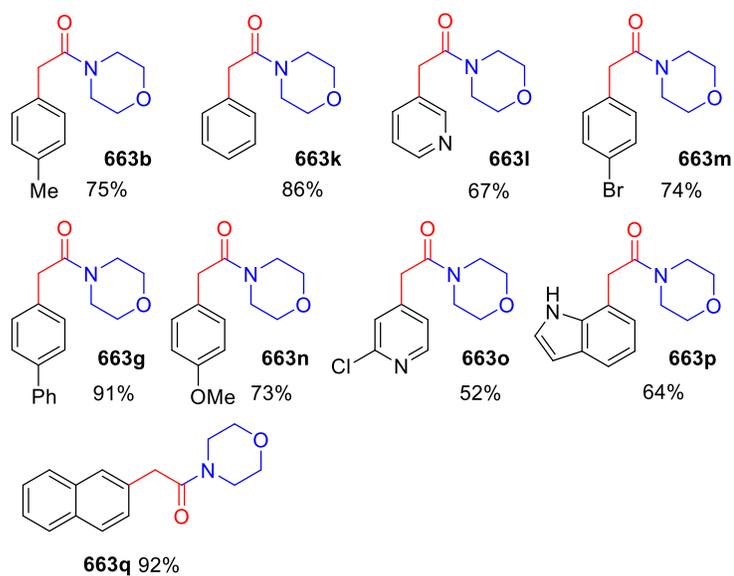
2.1.2 The Substrate Scope of the Sonogashira (Ketene Surrogate) Coupling Reaction

We tested substrate scope of this novel ketene surrogate coupling reaction and found that the coupling tolerates a wide range of electronic properties and functional groups, like ester, ketone, and heterocyclic (Table 2.1.3 and Table 2.1.4). For all the electron deficient substrates, the Sonogashira coupling reactions occurred quickly and cleanly affording the great NMR yields, but the coupling products hydrolyzed very quickly during work up. In general, we found that the electron deficient *tert*-butoxyl ynol ethers are not stable under acidic conditions, and the ammonium salt, a side product of the coupling reaction, accelerated the hydrolysis of the coupling products. However, the electron neutral and electron rich Sonogashira products hydrolyzed in a much slower rate than electron deficient substrates did. Therefore, the electron

rich and neutral *tert*-butoxyl aryl ynol ethers could be isolated in high purity with minimal hydrolysis products. In these experiments, Cu, Pd, and amines were removed by a rapid chromatography over neutral Al₂O₃ following the complete conversion of the aryl iodide. For example, the ynol derived from 4-methoxy-iodobenzene **52n** was stored for >1 year at 4 °C with no signs of decomposition. In contrast, the *p*-CN-substituted ynol (**54a**) underwent hydrolysis to the extent of 5-10% upon attempted purification. To get a unified evaluation of the all types of substrates in this ketene surrogate coupling, following filtration over Al₂O₃, the crude aryl-substituted ynol ethers **54** were heated in the presence of morpholine to generate, consecutively, the aryl ketenes **646** and then the morpholine amides **663** (Table 2.1.3 and Table 2.1.4).¹¹ These morpholine amides **663** were targeted because of their utility in the synthesis of ketones (see below). They are comparable to Weinreb amides in terms of synthetic utility, but are generally more stable and less expensive.¹²

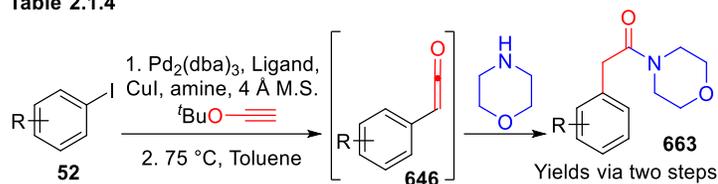
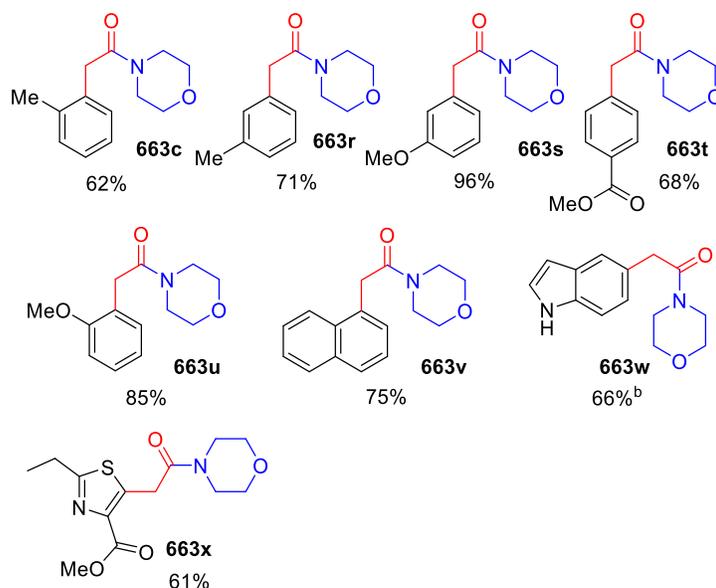
For the electron deficient substrates, we still found the small amount of diisopropyl amide **652** in crude NMR, so DIPEA was used in order to minimize the undesired amide formation. We found that ketones, esters, and nitro-, cyano- and trifluoromethyl groups were all compatible with the reaction conditions. However, 4-fluoro-iodobenzene provided **663e** in poor yield due to a combination of volatility of the ynol ether and instability of the amide, and the relatively low yield for the chromone morpholine amide **633j** was due to the decomposition of the heterocycle during the morpholine trapping step.

Table 2.1.3

Condition A: DIPEA+ PPh_3 ^aCondition B: DIPA+ PPh_3 ^b

^aReactions conducted at neat. amine and tert-butyl vinyl ether (0.25M 1:1 vol. ratio) with 5 mol% $\text{Pd}_2(\text{dba})_3$, 20 mol% PPh_3 and 13 mol% of CuI for 12-24h at r.t.. ^bDiisopropylamine was used instead of diisopropylethylamine.

Table 2.1.4

Condition C: DIPA+TFP^a

^aReactions conducted at neat. amine and tert-butyl ynol ether (0.25M 1:1 vol. ratio) with 5 mol% $\text{Pd}_2(\text{dba})_3$, 20 mol% Tri-(2-furyl)phosphorine and 13 mol% of CuI for 12-24h at r.t.. ^b48h reaction time

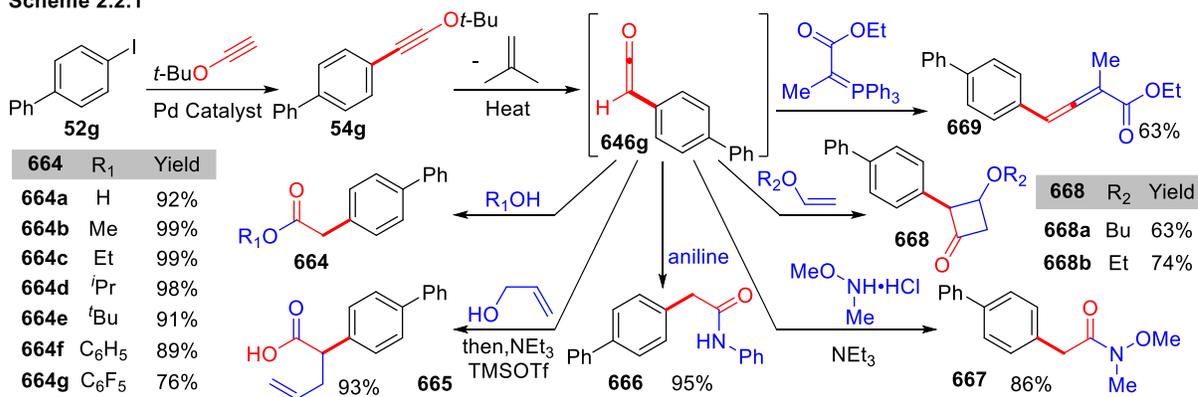
Furthermore, the electron rich substrates were tested with our method, and DIPA was used to increase conversion. Actually, the electron rich and neutral substrates provided higher yields because of their better stabilities comparing to electron deficient substrates. For instance, electron donating groups including 2-, 3- and 4-methyl (**663c**, **663r**, **663b**) and 2-, 3- and 4-methoxy (**663u**, **663s**, **663n**) substitution provided the corresponding morpholine amides in good yield. Both 1- and 2-iodonaphthlene were excellent substrates (**663v**, **663q**). Moreover, several heterocycles participated in the reaction yielding 3- and 4-substituted pyridines (**663l**, **663o**) and 5- and 7-substitued indoles (**663w**, **663p**). In the latter cases, the indole NH did not require protection. A current limitation of the method is that aryl bromides do not couple

efficiently, but this characteristic does allow for the selective coupling of 4-bromo-iodobenzene to form the 4-bromophenyl acetamide **663m** in 74% yield. Of note, 4-phenyl-benzyl morpholine amide **663g** was obtained in 2.9 gram scale and 91% yield.

2.2 Synthesis of Aryl Acetic Acid Derivatives and Benzyl Ketones

2.2.1 Synthesis of Aryl Acetic Acid Derivatives

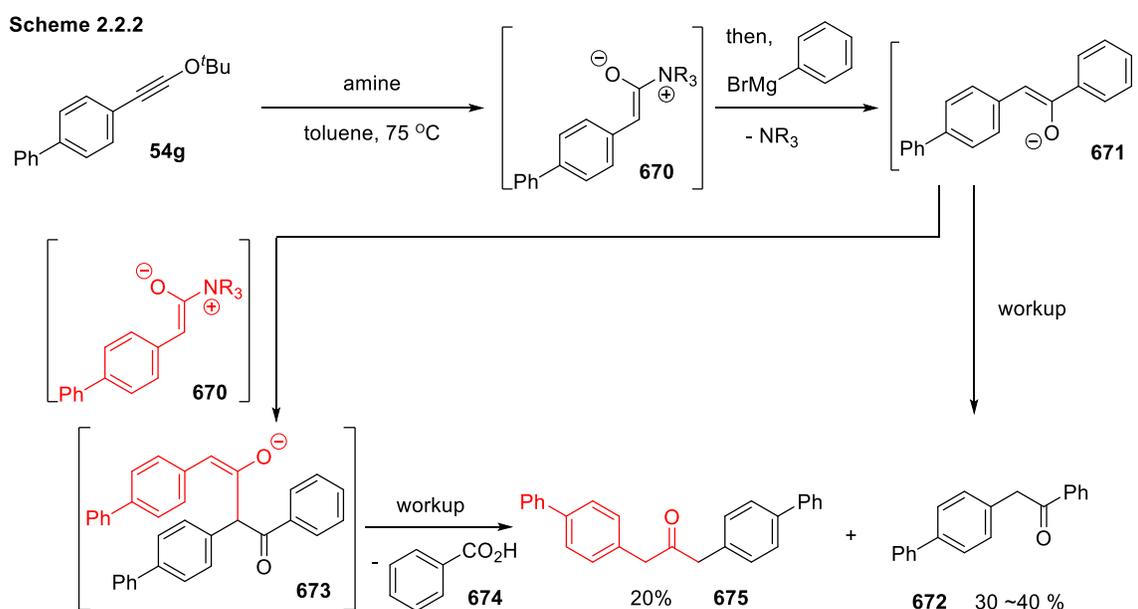
Scheme 2.2.1



The reactivity of aryl ketenes **646** was broadly tested, and we demonstrated the synthesis of multiple aryl acetic acid derivatives by trapping the aryl ketene with a variety of nucleophiles (**Scheme 2.2.1**). Oxygen-based nucleophiles reacted cleanly and efficiently. For example, water, phenol, pentafluorophenol, methanol, primary, and secondary alcohols yielded the carboxylic acid or esters (**664a** to **664g**) in high yield. The tertiary alcohol, *tert*-butanol, needs a specific drying procedure to offer a 91% yield of the corresponding ester **664e**. In the special case of using allyl alcohol, the intermediate allyl ester was exposed to soft enolization conditions to promote a Claisen rearrangement in a two-step, one-pot procedure to provide an α -allyl aryl acetic acid **665**. In related transformations, amines other than morpholine react with equal facility. Thus, Weinreb amides **667** emerge from trapping with (MeO)MeNH, most conveniently free-based *in situ* from the hydrochloride salt, and aniline reacted to form anilide

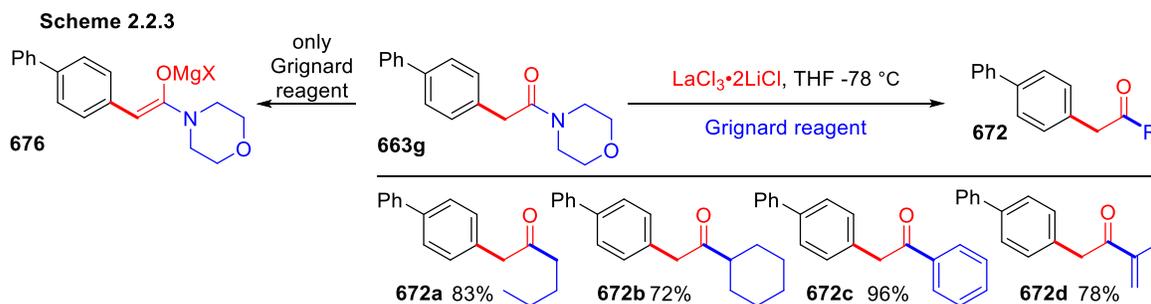
666 in nearly quantitative yield. As a carbon-based nucleophile, a phosphonium ylide trapped the ketene **646g** to generate the allene **669**. In addition, we explored other carbon-carbon bond formations using the ketene intermediate **646g**. The [2+2] cycloaddition with alkyl vinyl ethers affording cyclobutones **668** further substantiated the formation of arylketene **646g** under the thermal conditions.

2.2.2 Synthesis of Benzyl Ketones



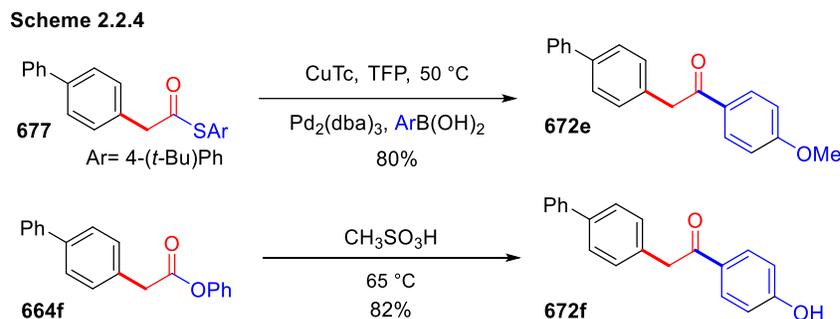
At the outset of benzyl ketone synthesis, we employed the phenyl Grignard reagent to trap the ketene intermediates directly, but we observed a messy reaction with polymerized products (**Scheme 2.2.2**). We envisioned the polymerization was between the adduct enolate and the ketene intermediates during the reaction. To avoid such polymerizations, we assumed that the formation of the sterically hindered ketene enolates **670** would minimize the polymerization, which derived by trapping ketenes with the tertiary amines. In this manner, we found triethylamine and diisopropylethyl amine served the stabilizer of the ketene and converted the

ketenes into the less reactive ketene enolates **670**. Then, the reaction system was cooled to room temperature before the addition of Grignard reagents. Consequently, it generated the desired phenyl benzyl ketone **672** in 30 ~ 40% yield according to the amine employed in the reaction, but we also isolated 20% dibenzyl ketone **675** as the major side product. We speculated the generation of the dibenzyl ketone was from the condensation between the ketene enolate **670** and the enolate intermediate **671**, and, during the aqueous workup, the adduct **673** underwent a fragmentation of benzoic acid **674** offering the diketone **675**. We were unsatisfied with the yield of this direct ketene trapping reaction utilizing Grignard reagents.



As an alternative to direct addition to the ketene, we exploited the ability of morpholine amides **663** to react with hard nucleophiles to provide ketones (**Scheme 2.2.3**).¹⁷ In the event, Grignard reagents proved too basic for these transformations, and enolate **676** formation dominated the reaction. However, we found that $\text{LaCl}_3 \cdot 2\text{LiCl}$ promoted these additions effectively. This additive, introduced by Knochel and colleagues,¹³ has previously been shown to assist nucleophilic addition to acidic aldehydes,¹⁴ but this is the first report of its use to facilitate addition to morpholine amides. It is generally more convenient and effective than CeCl_3 owing to its increased solubility.¹⁵ Thus, a primary and a secondary Grignard reagent performed well to give adducts **672a** and **672b**, as did a vinyl and phenyl reagent offering adducts **672d** and

672c. No tertiary alcohols were observed from double addition when the reactions were carried out at $-78\text{ }^{\circ}\text{C}$. Taken together, these examples demonstrate that the ketene surrogate coupling provides efficient access to aryl, vinyl and alkyl ketones.



The facile synthesis of a variety of arylacetic acid derivatives provided an entry into several other types of ketones **672** (Scheme 2.2.4). For example, the phenol ester **664f** underwent Brønsted acid-catalyzed Fries rearrangement to yield the aryl benzyl ketone **672f** as a single regioisomer.¹⁶ The thiol ester **677** was formed in good yield, and then converted into the ketone **672e** under reaction conditions introduced by Liebeskind and co-workers.¹⁷

In summary, we have found that *tert*-butoxyacetylene serves the role of metallated ketene in cross-coupling reactions. It can undergo Sonogashira coupling with aryl iodides, and then transform into a ketene under thermal conditions. This ketene surrogate coupling leads to aryl acetic acid derivatives, ketones, allenes and cyclobutanone products in good yield. An advantageous characteristic of the ketone surrogate coupling is the ability to access a wide range of carbonyl compounds from a single intermediate.

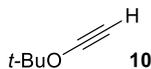
2.3 Experimental Details.

2.3.1 General Information

General. Unless otherwise stated, reactions were performed under argon using freshly purified solvents, which were purified using solvent purification columns purchased from Glass Contour, Laguna Beach, CA. All Reactions were monitored by thin-layer chromatography with E. Merck silica gel 60 F₂₅₄ pre-coated plates (0.25 mm). All work-up and purification procedures were carried out with reagent-grade solvents in air. Flash chromatography was performed with indicated solvents using silica gel (particle size 40-63 μm) purchased from Sorbent Technologies. ¹H and ¹³C NMR spectra were recorded on Varian Inova-400 MHz, 500 MHz, or MR-400 spectrometer. Chemical shift are reported relative to internal chloroform (CDCl₃: ¹H, δ = 7.26 ppm, ¹³C, δ = 77.36 ppm), benzene (C₆D₆: ¹H, δ = 7.15 ppm, ¹³C, δ = 128.62 ppm), toluene (C₇D₈: ¹H, δ = 2.09 ppm, ¹³C, δ = 20.4 ppm), methanol (CD₃OD: ¹H, δ = 3.31 ppm, ¹³C, δ = 49.15 ppm), and pyridine (C₅D₅N: ¹H, δ = 7.22 ppm, ¹³C, δ = 123.87 ppm) . Coupling constants are in Hz and are reported as d (doublet), t (triplet), q (quartet), b (broad peak), and m (multiplet). Mass spectra were acquired on an Agilent Technologies 1200 series LC/MS using indicated ionization methods.

Materials. Chemicals were purchased from Aldrich, Fisher or Alfa Aesar, TCI, and Chemical Strem and used without purification.

***tert*-Butyl acetylenyl ether. CAUTION: 1. terminal ynol ethers have been reported to explode upon heating in neat form. 2. Avoid heating *t*-butoxy acetylene. We have never experienced an explosion with the aryl-substituted ynol ethers, even after heating to >100 °C, but caution is still recommended.**



Potassium hydride in mineral oil was washed by anhydrous hexane four times and dried under

high vacuum pump for 30 minutes. To a 1000 ml flask charged with potassium hydride (53.5 g, 400 mmol) and equipped with a gas outlet, was added ether (100 ml) then *tert*-butanol (19.13 ml, 200 mmol) in 200 ml ether under argon at room temperature. After bubbling ceased, trichloroethene (17.4 ml, 196 mmol) in 150 ml ether was added dropwise at -40 °C. The cooling bath was removed, and the reaction was stirred for 1-2 h until the mixture turned brown. The suspension was cooled to -78 °C, and a 2.5 M butyllithium solution (200 ml, 500 mmol) in hexanes was added. The reaction mixture was allowed to warm to -50 °C over about 30 min and then was stirred at that temperature for 1 hour. Water was added to quench the reaction at -50 °C, and the crude product was extracted by ether 3 times, dried with anhydrous sodium sulfate and filtered. Following the procedure described by Pericàs et al.³ the crude reaction mixture was fractionally distilled on a rotary evaporator. We had 650 ~ 700 ml solution after reaction. To dissolve all the solids in the reaction mixtures, we added about 200 ml water. The extraction introduced about 400 ~ 500 ml diethyl ether. Then, we used another 200 ml diethyl ether to wash sodium sulfate drierite during filtration. Therefore, we had 1300 ~ 1500 ml diethyl ether solution on the rotavap in total. During the distillation, we first controlled the pressure maintaining between 500 mbar, and, later slowly reduced the pressure to 250 mbar. At this range of pressure, 900 ~ 1000 ml diethyl ether was removed, and we saw the evaporation became much slower (by the dropping speed on the condenser). We used a vacuum gauge (the picture showing below) to control the pressure.



The upper condenser and lower solvent collector were displayed in the picture below. In the condenser, we used a dry ice-acetone bath, which maintain the temperature at $-78\text{ }^{\circ}\text{C}$, whereas we kept the collector in ice bath at $0\text{ }^{\circ}\text{C}$ to minimize the evaporation of solvent from the collector. We kept maintained crude product in a water bath at room temperature so that the solvent vapor would keep generating from the crude mixture. We dumped the first fraction of the distillation (900 ~ 1000 ml), whose major component was the diethyl ether. At this time, there are only about 200 ~ 350 ml crude mixture left in the flask, and the slow reducing of the

pressure from 250 to 50 mbar will give us 150 ml ~200 ml solution in the collector.



The further purification of product was via redistillation from calcium hydride. For the redistillation, we preferred to use the micro-distillation equipment, which gave us a higher yield. After several hours stirring with calcium hydride, the flask with the desired fraction from the first distillation was connected to the other distillation equipment (showing in the picture below).



We placed the left flask stirring in a water bath at room temperature. The left top head was connected to the manifold to purge system with argon. We employed a chiller to circulate at -20 °C. The collecting flask was in a dry ice-acetone bath to collect product. Normally, we collect the last fraction (60 ~ 80 ml) below 120 torr to 10 torr from the distillation. We utilized the pressure was control by a similar vacuum gauge from Welch pump company. The collected fraction was allowed warm up under the argon to keep away from moisture in air. The ynol ether **10** appeared like a 30 wt% solution in hexanes and diethyl ether. We executed a freeze-pump

degas procedure on the solution, which allow the anhydrous solution to store in a Schlenk flask at -20 °C over a year.

2.3.2 Ketene Surrogate Coupling Reaction and Morpholine Trapping

General Method for the Coupling Reaction:

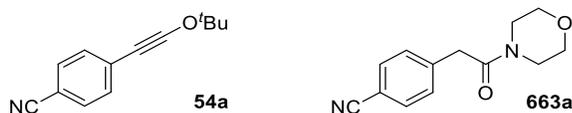
Method A. All solid reagents, aryl iodides (0.3 mmol), Pd₂(dba)₃ (15.6 mg, 0.015 mmol), PPh₃ (15.9 mg, 0.06 mmol), CuI (7.5 mg, 0.039 mmol), and 150 mg 4 Å molecular sieves were combined in vials and purged with argon. To the reaction, 0.6 ml diisopropylethyl amine and 0.6 ml *tert*-butyl acetylenyl ether were added at room temperature. If the aryl iodides were liquid, they were added after amine was added. The reaction was monitored via TLC for the completion (12-24 h), and the reaction mixtures were directly loaded to the aluminum plug and washed off with ethyl acetate and hexane (1:10) yielding the products and dibenzylideneacetone. The mixture can be used directly in next step. For electron deficient substrates, they have higher reactivity and shorter reaction time, and extending the reaction time may lead to hydrolysis of desired product.

Method B. Same as Method A except diisopropyl amine was used instead of diisopropylethyl amine. The reaction was monitored via TLC for the completion, and the reaction mixtures were directly loading to the aluminum column and washed off with ethyl acetate and hexane (1:10), yielding the pure products *tert*-butyl arylacetylenyl ether.

Method C. Same as Method B except tri(2-furyl)phosphine was used. The reaction was monitored via TLC for the completion, and the reaction mixtures were directly loading to the aluminum column and washed off with ethyl acetate and hexane (1:10), yielding the pure products *tert*-butyl arylacetylenyl ether.

Ketene Formation and Morpholine Trapping (Table 2.1.3 and Table 2.1.4):

The *tert*-butyl arylacetylenyl ethers (products from coupling reaction) were dissolved in 2.0 ml toluene and 0.2 ml morpholine was added at room temperature under argon. The reaction was heated to 75 °C for 3 hours. The reaction mixture was concentrated under reduced pressure, and the pure morpholine amides were obtained following flash chromatography on silica gel with ethyl acetate and hexane (3:2).



***tert*-Butyl 4-nitrile-phenylacetylenyl ether (54a).** Method A. ^1H NMR (400 MHz, CDCl_3) δ : 7.52 (d, $J = 8.4$ Hz, 2H), 7.37 (d, $J = 8.4$ Hz, 2H), 1.49 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ : 132.2, 131.9, 130.7, 119.35, 109.5, 100.6, 88.8, 43.1, 27.6. TLC (ethyl acetate:hexane = 1:10) r.f. = 0.7.

4-Nitrile-phenylacetate morpholine amide (663a). ^1H NMR (400 MHz, CDCl_3) δ : 7.62 (d, $J = 8.4$ Hz, 2H), 7.35 (d, $J = 8.4$ Hz, 2H), 3.76 (s, 2H), 3.62-3.68 (m, 4H), 3.58 (t, $J = 9.6$ Hz, 2H), 3.45 (t, $J = 9.6$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ : 176.2, 169.1, 140.35, 132.6, 129.9, 118.8, 66.8, 66.5, 46.6, 42.5, 40.3. ESI MS m/z : 231.1, $[\text{M}+\text{H}]^+$. TLC (ethyl acetate:hexane = 3:2) r.f. = 0.3.



***tert*-Butyl 4-methyl-phenylacetylenyl ether (54b).** Method B. ^1H NMR (400 MHz, CDCl_3) δ : 7.24 (d, $J = 6.4$ Hz, 2H), 7.06 (d, $J = 6.0$ Hz, 2H), 2.32 (s, 3H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ : 136.4, 131.6, 129.2, 121.8, 95.2, 86.9, 42.9, 27.5, 21.6. TLC (ethyl

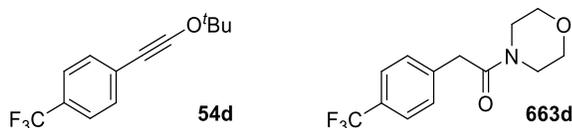
acetate:hexane = 1:10) r.f. = 0.8.

4-Methyl-phenylacetate morpholine amide (663b). ^1H NMR (400 MHz, C_6D_6) δ : 7.09 (d, J = 8.0 Hz, 2H), 6.95 (d, J = 7.6 Hz, 2H), 3.42 (t, J = 4.4 Hz, 2H), 3.37 (s, 2H), 3.19 (t, J = 4.4 Hz, 2H), 2.98 (t, J = 4.8 Hz, 2H), 2.75 (t, J = 4.8 Hz, 2H), 2.08 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ : 169.6, 136.9, 133.3, 130.2, 129.4, 67.3, 66.9, 47.0, 42.8, 41.1, 21.6. ESI MS m/z : 220.1, $[\text{M}+\text{H}]^+$. TLC (ethyl acetate:hexane = 3:2) r.f. = 0.5.



tert-Butyl 2-methyl-phenylacetylenyl ether (54c). Method C. ^1H NMR (400 MHz, CDCl_3) δ : 7.32-7.34 (m, 1H), 7.16-7.18 (m, 1H), 7.06-7.13 (m, 2H), 2.41 (s, 3H), 1.50 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ : 139.6, 131.9, 129.5, 126.5, 125.8, 124.8, 99.8, 87.0, 42.1, 27.5, 21.4. TLC (ethyl acetate:hexane = 1:10) r.f. = 0.8.

2-Methyl-phenylacetate morpholine amide (663c). ^1H NMR (400 MHz, CDCl_3) δ : 7.11-7.19 (m, 5H), 3.68 (s, 4H), 3.67 (s, 2H) 3.55 (t, J = 4.8 Hz, 2H), 3.40 (t, J = 4.8 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ : 170.0, 136.5, 133.7, 130.7, 128.9, 127.4, 126.6, 67.2, 66.8, 46.7, 42.4, 38.6, 20.0. ESI MS m/z : 220.1, $[\text{M}+\text{H}]^+$. TLC (ethyl acetate:hexane = 3:2) r.f. = 0.4.



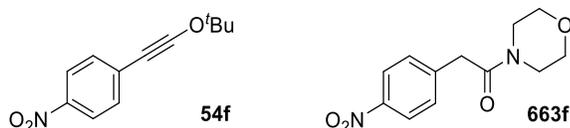
tert-Butyl 4-(trifluoromethyl)phenylacetylenyl ether (54d). Method A. ^1H NMR (400 MHz, CDCl_3) δ : 7.49 (d, J = 8.0 Hz, 2H), 7.41 (d, J = 8.0 Hz, 2H), 1.49 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ : 131.6, 129.7, 128.2 (q, J = 32.3), 125.4 (q, J = 3.8), 124.6 (q, J = 270.3) 98.4, 88.2, 42.7, 27.6. TLC (ethyl acetate:hexane = 1:10) r.f. = 0.6.

4-Trifluoromethyl-phenylacetate morpholine amide (663d). ^1H NMR (400 MHz, CDCl_3) δ : 7.58 (d, $J = 8.0$ Hz, 2H), 7.35 (d, $J = 8.0$, 2H), 3.76 (s, 2H), 3.65 (s, 4H), 3.55 (t, $J = 4.8$ Hz, 2H), 3.45 (t, $J = 4.8$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ : 169.0, 139.2, 129.6 (q, $J = 32.3$ Hz), 129.5, 126.0 (q, $J = 3.8$ Hz), 124.4 (q, $J = 270.5$ Hz), 67.1, 66.7, 46.7, 42.5, 40.5. ESI MS m/z : 274.1, $[\text{M}+\text{H}]^+$. TLC (ethyl acetate:hexane = 3:2) r.f. = 0.3.



tert-Butyl 4-fluoro-phenylacetylenyl ether (54e). Method A. ^1H NMR (400 MHz, CDCl_3) δ : 7.27-7.33 (m, 2H), 6.94 (tt, $J_1 = 8.8$ Hz, $J_2 = 2.8$ Hz, 2H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ : 161.6 (d, $J = 245$ Hz), 133.2 (d, $J = 7.9$ Hz), 120.9 (d, $J = 3.3$ Hz), 115.5 (d, $J = 21.8$ Hz), 95.2, 87.2, 42.0, 27.4. TLC (ethyl acetate:hexane = 1:10) r.f. = 0.4.

4-fluoro-phenylacetate morpholine amide (663e). ^1H NMR (500 MHz, CDCl_3) δ : 7.20-7.23 (m, 2H), 7.03 (tt, $J_1 = 8.0$ Hz, $J_2 = 2.5$ Hz, 2H), 3.70 (s, 2H), 3.66 (s, 4H), 3.53 (t, $J = 5.0$ Hz, 2H), 3.45 (t, $J = 5.0$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ : 169.4, 161.8 (d, $J = 245$ Hz), 130.4 (d, $J = 3.3$ Hz), 130.1 (d, $J = 7.9$ Hz), 115.6 (d, $J = 22.4$ Hz), 66.8, 66.4, 46.4, 42.1, 39.7. ESI MS m/z : 224.1, $[\text{M}+\text{H}]^+$. TLC (ethyl acetate:hexane = 3:2) r.f. = 0.5.



tert-Butyl 4-nitro-phenylacetylenyl ether (54f). Method A. ^1H NMR (400 MHz, CDCl_3) δ : 8.11 (d, $J = 9.2$ Hz, 2H), 7.41 (d, $J = 9.2$ Hz, 2H), 1.51 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ : 145.9, 133.0, 131.8, 123.9, 101.8, 89.2, 43.4, 27.6. TLC (ethyl acetate:hexane = 1:10) r.f. = 0.6.

4-Nitro-phenylacetate morpholine amide (663f). ^1H NMR (400 MHz, CDCl_3) δ : 8.18 (d, J = 8.8 Hz, 2H), 7.41 (d, J = 8.8 Hz, 2H), 3.81 (s, 2H), 3.63-3.69 (m, 4H), 3.60 (t, J = 5.2 Hz, 2H), 3.47 (t, J = 4.8 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ : 168.4, 147.3, 142.7, 130.3, 124.1, 67.1, 66.7, 46.7, 42.6, 40.3. ESI MS m/z : 250.1, $[\text{M}+\text{H}]^+$. TLC (ethyl acetate:hexane = 3:2) r.f. = 0.3.



tert-Butyl 4-biphenylacetylenyl ether (54g). Method B. ^1H NMR (400 MHz, CDCl_3) δ : 7.59 (dt, J_1 = 7.2 Hz, J_2 = 1.2 Hz, 2H), 7.52 (dt, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 2H), 7.42-7.47 (m, 4H), 7.35 (tt, J_1 = 7.2 Hz, J_2 = 2.0 Hz, 1H) 1.51 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ : 141.1, 139.3, 132.1, 129.1, 127.6, 127.23, 127.17, 124.1, 96.6, 87.3, 43.0, 27.6. TLC (ethyl acetate:hexane = 1:10) r.f. = 0.7.

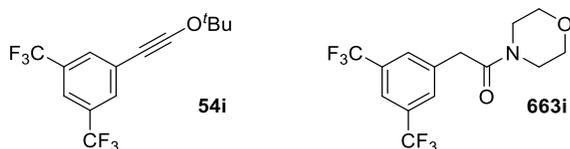
4-biphenylacetate morpholine amide (663g). ^1H NMR (400 MHz, C_6D_6) δ : 7.42-7.47 (m, 4H), 7.18-7.23 (m, 4H), 7.12 (tt, J_1 = 7.2 Hz, J_2 = 2.0 Hz, 1H), 3.44 (t, J = 4.8 Hz, 2H), 3.40 (s, 2H), 3.22 (t, J = 4.8 Hz, 2H), 3.02 (t, J = 2.0 Hz, 2H), 2.76 (t, J = 2.0 Hz, 2H); ^{13}C NMR (100 MHz, C_6D_6) δ : 169.3, 141.8, 140.8, 135.4, 130.1, 129.7, 128.3, 128.1, 127.9, 67.3, 66.9, 47.0, 42.8, 41.0. ESI MS m/z : 282.1, $[\text{M}+\text{H}]^+$. TLC (ethyl acetate:hexane = 3:2) r.f. = 0.3.



tert-Butyl 4-aceto-phenylacetylenyl ether (54h). Method A. ^1H NMR (400 MHz, CDCl_3) δ : 7.28 (d, J = 8.8 Hz, 2H), 6.79 (d, J = 8.8 Hz, 2H), 3.79 (s, 2H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ : 158.5, 133.1, 130.7, 117.1, 114.1, 94.4, 86.7, 55.6, 42.5, 27.5. TLC (ethyl

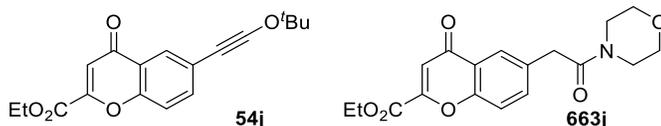
acetate:hexane = 1:10) r.f. = 0.7.

4-Aceto-phenonylacetate morpholine amide (663h). ^1H NMR (400 MHz, CDCl_3) δ : 7.91 (d, $J = 8.0$ Hz, 2H), 7.33 (d, $J = 8.0$ Hz, 2H), 3.76 (s, 2H), 3.63 (s, 4H), 3.51 (t, $J = 4.8$ Hz, 2H), 3.42 (t, $J = 4.8$ Hz, 2H), 2.58 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ : 197.9, 169.1, 140.6, 136.2, 129.3, 129.1, 67.1, 66.7, 46.8, 42.5, 40.9, 26.9. ESI MS m/z : 248.1, $[\text{M}+\text{H}]^+$. TLC (ethyl acetate:hexane = 3:2) r.f. = 0.3.



tert-Butyl 3,5-bis-(trifluoromethyl)-phenylacetylenyl ether (54i). Method A. ^1H NMR (400 MHz, CDCl_3) δ : 7.72 (s, 2H), 7.66 (s, 1H), 1.51 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ : 131.9 (q, $J = 33.1$ Hz), 131.4, 127.7, 123.5 (q, $J = 271.2$ Hz), 119.8, 99.0, 89.0, 41.6, 27.6. ESI MS m/z : 252.0, $[\text{M}-\text{Bu}-\text{H}]^-$. TLC (ethyl acetate:hexane = 1:10) r.f. = 0.7.

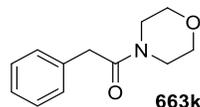
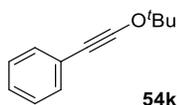
3,5-bis-(trifluoromethyl)-phenylacetate morpholine amide (663i). ^1H NMR (400 MHz, CDCl_3) δ : 7.78 (s, 1H), 7.69 (s, 2H), 3.81 (s, 2H), 3.66 (m, 4H), 3.65 (t, $J = 5.2$ Hz, 2H), 3.51 (t, $J = 5.2$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ : 167.8, 137.2, 131.7 (q, $J = 33.1$ Hz), 129.5, 123.2 (q, $J = 271.3$ Hz), 121.0, 66.7, 66.4, 46.2, 42.3, 39.4. ESI MS m/z : 342.1, $[\text{M}+\text{H}]^+$. TLC (ethyl acetate:hexane = 3:2) r.f. = 0.3.



tert-Butyl 4-oxo-4H-chromene-2-(ethyl)-carboxyl-6-acetylenyl ether (54j). ^1H NMR (400 MHz, CDCl_3) δ : 8.11 (d, $J = 2.0$ Hz, 1H), 7.65 (dd, $J_1 = 8.8$ Hz, $J_2 = 2.4$ Hz, 1H), 7.49 (d, $J =$

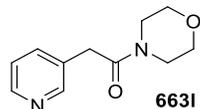
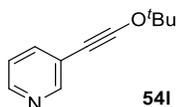
8.8 Hz, 1H), 7.09 (s, 1H), 4.45 (q, $J = 6.8$ Hz, 2H), 1.49 (s, 9H), 1.43 (t, $J = 6.4$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ : 178.3, 160.9, 154.6, 152.4, 137.9, 128.0, 124.6, 123.7, 119.1, 114.9, 97.5, 88.3, 63.4, 42.0, 27.6, 14.4. TLC (ethyl acetate:hexane = 1:10) r.f. = 0.3.

4-Oxo-4H-chromene-2-(ethyl)-carboxyl-6-acetate morpholine amide (663j). ^1H NMR (400 MHz, CDCl_3) δ : 7.98 (d, $J = 2.0$ Hz, 1H), 7.69 (dd, $J_1 = 8.8$ Hz, $J_2 = 2.0$ Hz, 1H), 7.58 (d, $J = 8.8$ Hz, 1H), 7.09 (s, 1H), 4.44 (q, $J = 7.2$ Hz, 2H), 3.80 (s, 2H), 3.62-3.68 (m, 4H), 3.58 (t, $J = 4.8$ Hz, 2H), 3.49 (t, $J = 4.8$ Hz, 2H), 1.42 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ : 178.4, 169.0, 160.7, 155.3, 152.6, 136.1, 133.4, 125.8, 124.6, 119.6, 115.0, 67.1, 66.8, 63.3, 46.7, 42.6, 39.8, 14.4. ESI MS m/z : 345.1, $[\text{M}+\text{H}]^+$. TLC (ethyl acetate:hexane = 3:2) r.f. = 0.3.



tert-Butyl phenylacetylenyl ether (54k). Method B. ^1H NMR (400 MHz, CDCl_3) δ : 7.34-7.36 (m, 2H), 7.18-7.28 (m, 3H), 1.49 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ : 131.7, 128.5, 126.6, 125.1, 95.9, 87.1, 43.1, 27.5. TLC (ethyl acetate:hexane = 1:10) r.f. = 0.7.

Phenylacetate morpholine amide (663k). ^1H NMR (400 MHz, CDCl_3) δ : 7.29-7.33 (m, 2H), 7.21-7.25 (m, 3H), 3.72 (s, 2H), 3.63 (s, 4H), 3.43 (dt, $J_1 = 19.2$ Hz, $J_2 = 4.8$ Hz, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ : 169.9, 135.1, 129.1, 128.8, 127.2, 67.1, 66.7, 46.8, 42.4, 41.1. ESI MS m/z : 206.1, $[\text{M}+\text{H}]^+$. TLC (ethyl acetate:hexane = 3:2) r.f. = 0.5.



tert-Butyl pyridinyl-3-acetylenyl ether (54l). Method B. ^1H NMR (400 MHz, CDCl_3) δ : 8.56 (s, 1H), 8.40 (d, $J = 4.0$ Hz, 1H), 7.60 (dt, $J_1 = 6.4$ Hz, $J_2 = 1.6$ Hz, 1H), 7.17 (dd, $J_1 = 6.4$ Hz,

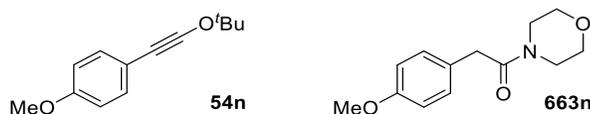
$J_2 = 4.0$ Hz, 1H), 1.49 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ : 152.4, 147.0, 138.5, 123.2, 122.3, 98.6, 88.2, 40.1, 27.6. TLC (ethyl acetate:hexane = 1:10) r.f. = 0.4.

Pyridinyl-3-acetate morpholine amide (663l). ^1H NMR (400 MHz, C_6D_6) δ : 8.47 (d, $J = 1.2$ Hz, 1H), 8.45 (dd, $J_1 = 4.0$ Hz, $J_2 = 1.2$ Hz, 1H), 7.37 (d, $J = 6.0$ Hz, 1H), 6.73 (dd, $J_1 = 6.0$ Hz, $J_2 = 4.0$ Hz, 1H), 3.33 (t, $J = 4.0$ Hz, 2H), 3.15 (t, $J = 4.0$ Hz, 2H), 3.05 (s, 2H), 2.99 (t, $J = 4.0$ Hz, 2H), 2.59 (t, $J = 4.0$ Hz, 2H); ^{13}C NMR (100 MHz, C_6D_6) δ : 168.5, 151.2, 149.3, 136.9, 131.8, 124.0, 67.2, 66.9, 46.6, 42.7, 37.7. ESI MS m/z : 207.1, $[\text{M}+\text{H}]^+$. TLC (ethyl acetate:hexane = 3:2) r.f. = 0.3.



***tert*-Butyl 4-bromo-phenylacetylenyl ether (54m).** Method B. ^1H NMR (400 MHz, CDCl_3) δ : 7.36 (d, $J = 8.4$ Hz, 2H), 7.19 (d, $J = 8.4$ Hz, 2H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ : 133.2, 131.6, 124.1, 120.3, 96.9, 87.6, 42.4, 27.5. TLC (ethyl acetate:hexane = 1:10) r.f. = 0.7.

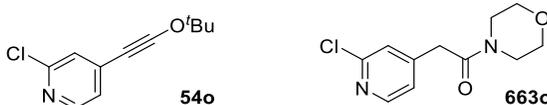
4-Bromo-phenylacetate morpholine amide (663m). ^1H NMR (400 MHz, CDCl_3) δ : 7.44 (d, $J = 8.4$ Hz, 2H), 7.11 (d, $J = 8.4$ Hz, 2H), 3.65 (s, 2H), 3.63 (s, 4H), 3.52 (t, $J = 4.8$ Hz, 2H), 3.41 (t, $J = 4.8$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ : 169.3, 134.1, 132.1, 130.7, 121.2, 67.1, 66.7, 46.7, 42.5, 40.3. ESI MS m/z : 284.0, 286.0, $[\text{M}+\text{H}]^+$. TLC (ethyl acetate:hexane = 3:2) r.f. = 0.4.



***tert*-Butyl 4-methoxy-phenylacetylenyl ether (54n).** Method B. ^1H NMR (400 MHz, CDCl_3)

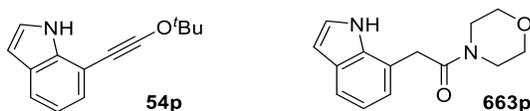
δ : 7.28 (d, $J = 8.4$ Hz, 2H), 6.79 (d, $J = 8.4$ Hz, 2H), 3.79 (s, 3H) 1.46 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ : 158.6, 133.1, 117.1, 114.1, 94.4, 86.7, 55.6, 42.5, 27.5. TLC (ethyl acetate:hexane = 1:10) r.f. = 0.6.

4-methoxy-phenylacetate morpholine amide (663n). ^1H NMR (400 MHz, CDCl_3) δ : 7.15 (d, $J = 8.4$ Hz, 2H), 6.86 (d, $J = 8.4$ Hz, 2H), 3.79 (s, 3H), 3.66 (s, 2H), 3.63 (s, 4H), 3.46 (dt, $J_1 = 22.0$ Hz, $J_2 = 4.8$ Hz, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ : 170.3, 158.8, 129.9, 127.1, 114.5, 67.1, 66.8, 55.6, 46.8, 42.5, 40.3. ESI MS m/z : 236.0, $[\text{M}+\text{H}]^+$. TLC (ethyl acetate:hexane = 3:2) r.f. = 0.3.



tert-Butyl 2-chloro-4-pyridinylacetylenyl ether (54o). Method B. ^1H NMR (400 MHz, CDCl_3) δ : 8.21 (d, $J = 5.2$ Hz, 1H), 7.21 (s, 1H), 7.08 (d, $J = 5.2$ Hz, 1H), 1.50 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ : 150.5, 149.4, 137.0, 125.9, 124.5, 102.3, 89.7, 41.6, 27.6. TLC (ethyl acetate:hexane = 1:10) r.f. = 0.4.

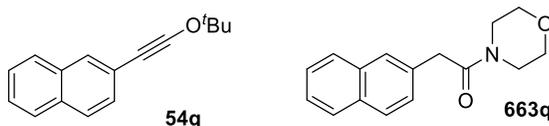
2-Chloro-4-pyridinylacetate morpholine amide (663o). ^1H NMR (400 MHz, CDCl_3) δ : 8.32 (d, $J = 5.2$ Hz, 1H), 7.24 (s, 1H), 7.11 (d, $J = 4.8$ Hz, 1H) 3.68 (s, 2H), 3.60-3.67 (m, 6H), 3.45 (t, $J = 4.8$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ : 181.6, 152.3, 150.2, 147.3, 125.1, 123.4, 67.1, 66.8, 46.8, 42.7, 39.6. ESI MS m/z : 241.0, $[\text{M}+\text{H}]^+$. TLC (ethyl acetate:hexane = 3:2) r.f. = 0.2. These products are not stable to prolonged storage.



tert-Butyl 7-indolylacetylenyl ether (54p). Method B. ^1H NMR (400 MHz, CDCl_3) δ : 8.37

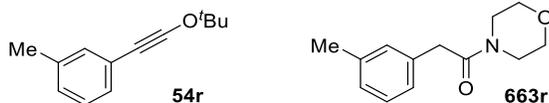
(bs, 1H), 7.54 (d, $J = 8.0$ Hz, 1H), 7.23 (dd, $J_1 = 6.0$ Hz, $J_2 = 1.2$ Hz, 1H), 7.22 (t, $J = 3.2$ Hz, 1H), 7.04 (dd, $J_1 = 8.0$ Hz, $J_2 = 7.6$ Hz, 1H), 6.55 (dd, $J_1 = 3.2$ Hz, $J_2 = 2.0$ Hz, 1H), 1.53 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ : 137.0, 127.0, 125.1, 123.8, 119.8, 119.5, 107.4, 103.1, 98.8, 87.1, 38.5, 27.2. TLC (ethyl acetate:hexane = 1:10) r.f. = 0.4.

7-Indolylacetate morpholine amide (663p). ^1H NMR (400 MHz, CDCl_3) δ : 9.68 (bs, 1H), 7.58 (d, $J = 8.0$ Hz, 1H), 7.25 (t, $J = 2.8$ Hz, 1H), 7.05 (t, $J = 7.6$ Hz, 1H), 6.94 (d, $J = 7.2$ Hz, 1H), 6.55 (dd, $J_1 = 3.2$ Hz, $J_2 = 2.0$ Hz, 1H), 3.98 (s, 2H), 3.53-3.61 (m, 6H), 3.42 (t, $J = 4.8$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ : 170.0, 135.8, 128.7, 125.2, 122.4, 120.3, 119.9, 117.1, 102.5, 66.9, 66.6, 47.2, 42.6, 39.6. ESI MS m/z : 245.1, $[\text{M}+\text{H}]^+$. TLC (ethyl acetate:hexane = 3:2) r.f. = 0.3.



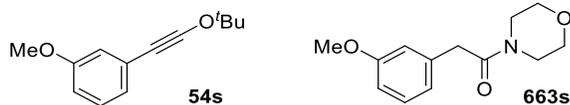
***tert*-Butyl 2-naphthalenylacetylenyl ether (54q).** Method B. ^1H NMR (400 MHz, CDCl_3) δ : 7.82 (s, 1H), 7.77 (d, $J = 6.4$ Hz, 1H), 7.71-7.74 (m, 2H), 7.40-7.46 (m, 3H), 1.52 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ : 133.6, 132.2, 130.4, 129.5, 128.0, 127.6, 126.5, 125.9, 122.4, 96.3, 87.4, 43.6, 27.6. TLC (ethyl acetate:hexane = 1:10) r.f. = 0.7.

2-Naphthalenylacetate morpholine amide (663q). ^1H NMR (400 MHz, C_6D_6) δ : 7.58-7.61 (m, 3H), 7.52 (s, 1H), 7.36 (d, $J = 6.4$ Hz, 1H), 7.21-7.27 (m, 2H), 3.50 (s, 2H), 3.44 (t, $J = 3.6$ Hz, 2H), 3.19 (t, $J = 3.6$ Hz, 2H), 2.93 (t, $J = 3.6$ Hz, 2H), 2.74 (t, $J = 3.6$ Hz, 2H); ^{13}C NMR (100 MHz, C_6D_6) δ : 179.1, 169.3, 134.7, 133.9, 133.5, 129.3, 128.1, 127.9, 127.0, 126.5, 67.3, 66.9, 46.9, 42.8, 41.7. ESI MS m/z : 256.1, $[\text{M}+\text{H}]^+$. TLC (ethyl acetate:hexane = 3:2) r.f. = 0.4.



***tert*-Butyl 3-methyl-phenylacetylenyl ether (54r)**. Method C. ¹H NMR (400 MHz, CDCl₃) δ: 7.12-7.18 (m, 3H), 7.00-7.03 (m, 1H), 2.31 (s, 3H), 1.48 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ: 138.1, 132.3, 128.8, 128.4, 127.5, 124.8, 95.6, 87.0, 43.2, 27.5, 21.6. TLC (ethyl acetate:hexane = 1:10) r.f. = 0.8.

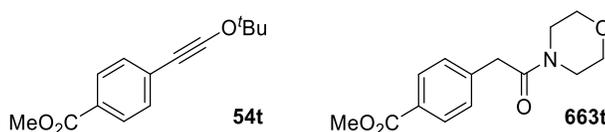
3-Methyl-phenylacetate morpholine amide (663r). ¹H NMR (400 MHz, CDCl₃) δ: 7.20 (t, J = 8.0 Hz, 1H), 7.06 (s, 1H), 7.02 (t, J = 8.0 Hz, 2H) 3.69 (s, 2H), 3.63 (s, 4H), 3.45 (dt, J₁ = 23.6 Hz, J₂ = 3.6 Hz, 4H); ¹³C NMR (100 MHz, CDCl₃) δ: 170.0, 138.8, 134.9, 129.5, 128.9, 127.9, 125.8, 67.1, 66.8, 46.8, 42.4, 41.1, 21.7. ESI MS m/z: 220.1, [M+H]⁺. TLC (ethyl acetate:hexane = 3:2) r.f. = 0.4.



***tert*-Butyl 3-methoxy-phenylacetylenyl ether (54s)**. Method C. ¹H NMR (400 MHz, CDCl₃) δ: 7.16 (t, J = 8.0 Hz, 1H), 6.94 (dt, J₁ = 7.6 Hz, J₂ = 1.2 Hz, 1H), 6.88 (dd, J₁ = 2.4 Hz, J₂ = 1.2 Hz, 1H), 6.76 (ddd, J₁ = 8.4 Hz, J₂ = 6.4 Hz, J₃ = 0.8 Hz, 1H), 3.79 (s, 3H), 1.48 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ: 159.6, 129.4, 126.2, 124.3, 116.7, 113.0, 95.8, 87.3, 55.5, 43.1, 27.5. TLC (ethyl acetate:hexane = 1:10) r.f. = 0.7.

3-Methoxy-phenylacetate morpholine amide (663s). ¹H NMR (400 MHz, CDCl₃) δ: 7.18-7.22 (m, 1H), 6.75-6.79 (m, 3H), 3.76 (s, 3H), 3.67 (s, 2H), 3.60 (s, 4H), 3.45 (dt, J₁ = 24.0 Hz, J₂ = 4.0 Hz, 4H); ¹³C NMR (100 MHz, CDCl₃) δ: 169.7, 160.1, 136.5, 130.0, 121.0, 114.4, 112.5, 67.0, 66.7, 55.4, 46.7, 42.3, 41.1. ESI MS m/z: 236.1, [M+H]⁺. TLC (ethyl

acetate:hexane = 3:2) r.f. = 0.4.



tert-Butyl 4-methyl-carboxyl-phenylacetylenyl ether (54t). Method C. ^1H NMR (400 MHz, CDCl_3) δ : 7.91 (d, $J = 8.4$ Hz, 2H), 7.36 (d, $J = 8.4$ Hz, 2H), 3.89 (s, 3H), 1.49 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ : 167.1, 131.2, 130.3, 129.6, 127.7, 99.1, 88.0, 52.3, 43.3, 27.5. TLC (ethyl acetate:hexane = 1:10) r.f. = 0.4.

4-Methyl-carboxyl-phenylacetate morpholine amide (663t). ^1H NMR (400 MHz, CDCl_3) δ : 7.98 (d, $J = 8.0$ Hz, 2H), 7.30 (d, $J = 8.0$ Hz, 2H), 3.88 (s, 3H), 3.75 (s, 2H), 3.62 (s, 4H), 3.44 (dt, $J_1 = 31.2$ Hz, $J_2 = 4.4$ Hz, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ : 169.1, 167.0, 140.3, 130.3, 129.2, 129.0, 67.0, 66.7, 52.4, 46.7, 42.5, 40.9. ESI MS m/z : 264.1, $[\text{M}+\text{H}]^+$. TLC (ethyl acetate:hexane = 3:2) r.f. = 0.2.



tert-Butyl 2-methoxyl-phenylacetylenyl ether (54u). Method C. ^1H NMR (400 MHz, CDCl_3) δ : 7.32 (d, $J = 7.6$ Hz, 1H), 7.17 (t, $J = 8.4$ Hz, 1H), 6.83-6.89 (m, 2H), 3.86 (s, 3H), 1.50 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ : 160.0, 133.1, 127.6, 120.7, 114.3, 110.8, 100.0, 87.2, 56.1, 39.2, 27.5. TLC (ethyl acetate:hexane = 1:10) r.f. = 0.7.

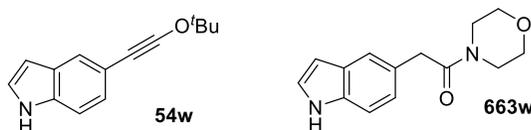
2-Methoxyl-phenylacetate morpholine amide (663u). ^1H NMR (400 MHz, CDCl_3) δ : 7.21-7.25 (m, 2H), 6.92 (t, $J = 7.6$ Hz, 1H), 6.86 (d, $J = 8.4$ Hz, 1H), 3.81 (s, 3H), 3.68 (s, 2H), 3.64 (s, 4H), 3.47 (dt, $J_1 = 26.4$ Hz, $J_2 = 5.6$ Hz, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ : 170.5, 156.8, 130.2, 128.5, 123.7, 121.1, 110.7, 67.1, 66.9, 55.7, 46.7, 42.5, 34.4. ESI MS m/z : 236.1,

$[M+H]^+$. TLC (ethyl acetate:hexane = 3:2) r.f. = 0.4.



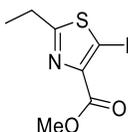
***tert*-Butyl 1-naphthalenylacetylenyl ether (54v)**. Method C. ^1H NMR (400 MHz, CDCl_3) δ : 8.34 (d, $J = 8.4$ Hz, 1H), 7.83 (d, $J = 8.4$ Hz, 1H), 7.72 (d, $J = 8.4$ Hz, 1H), 7.47-7.58 (m, 3H), 7.39 (dd, $J_1 = 8.4$ Hz, $J_2 = 7.2$ Hz, 1H), 1.58 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ : 134.0, 133.7, 129.9, 128.5, 126.9, 126.8, 126.5, 126.3, 125.7, 122.9, 100.5, 87.5, 41.3, 27.7. TLC (ethyl acetate:hexane = 1:10) r.f. = 0.7.

1-Naphthalenylacetate morpholine amide (663v). ^1H NMR (400 MHz, C_6D_6) δ : 7.96 (d, $J = 8.4$ Hz, 1H), 7.64 (d, $J = 8.0$ Hz, 1H), 7.55 (d, $J = 8.0$ Hz, 1H), 7.18-7.35 (m, 4H), 3.80 (s, 2H), 3.45 (t, $J = 4.4$ Hz, 2H), 3.21 (t, $J = 4.4$ Hz, 2H), 2.95 (t, $J = 3.6$ Hz, 2H), 2.71 (t, $J = 4.4$ Hz, 2H); ^{13}C NMR (100 MHz, C_6D_6) δ : 169.5, 135.0, 133.2, 132.7, 129.7, 128.5, 127.2, 127.0, 126.7, 126.3, 124.7, 67.4, 67.0, 46.9, 42.8, 39.1. ESI MS m/z : 256.1, $[M+H]^+$. TLC (ethyl acetate:hexane = 3:2) r.f. = 0.4.

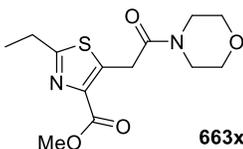


***tert*-Butyl 5-indolylacetylenyl ether (54w)**. Method C. ^1H NMR (400 MHz, CDCl_3) δ : 8.14 (bs, 1H), 7.68 (s, 1H), 7.28 (d, $J = 8.4$ Hz, 1H), 7.21 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.6$ Hz, 1H), 7.18 (t, $J = 2.4$ Hz, 1H), 6.48-6.50 (m, 1H), 1.49 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ : 134.9, 128.2, 126.3, 125.0, 124.3, 115.9, 111.2, 102.8, 93.4, 86.4, 43.8, 27.5. TLC (ethyl acetate:hexane = 1:10) r.f. = 0.4.

5-Indolylacetate morpholine amide (663w). ^1H NMR (400 MHz, CDCl_3) δ : 8.34 (bs, 1H), 7.48 (s, 1H), 7.33 (d, $J = 8.4$ Hz, 1H), 7.19 (t, $J = 2.8$ Hz, 1H), 7.07 (d, $J = 8.4$ Hz, 1H), 6.49 (t, $J = 2.0$ Hz, 1H), 3.84 (s, 2H), 3.62-3.67 (m, 4H), 3.43-3.47 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ : 170.9, 135.2, 128.6, 126.3, 125.1, 122.8, 120.6, 111.8, 102.7, 67.1, 66.8, 46.9, 42.5, 41.5. ESI MS m/z : 245.1, $[\text{M}+\text{H}]^+$. TLC (ethyl acetate:hexane = 3:2) r.f. = 0.3.



Methyl 2-ethyl-5-iodothiazole-4-carboxylate. To a solution of thiazole (0.1 M in THF), the fresh made LDA (1.0 M in THF, 1.2 equiv.) was added rapidly at -78 °C; after stirring for 3 min at -78 °C, the I_2 solution (1.0 M in THF, 2.5 equiv.) was added. The reaction was stirring for another 5 min at -78 °C before adding sat. $\text{Na}_2\text{S}_2\text{O}_3$ (aq.) to quench the reaction at -78 °C. The aqueous phase was extracted with EtOAc for 3 times, and the organic layer was combined, dried through the Na_2SO_4 and concentrated to give the crude product. The pure product was obtained with a flash chromatograph. ^1H NMR (400 MHz, CDCl_3) δ : 4.44 (q, $J = 7.1$ Hz, 1H), 2.75 (s, 1H), 1.43 (t, $J = 7.1$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ : 171.8, 161.7, 147.6, 78.8, 62.2, 19.9, 14.7. ESI MS m/z : 297.9, $[\text{M}+\text{H}]^+$. TLC (ethyl acetate:hexane = 1:1) r.f. = 0.7.

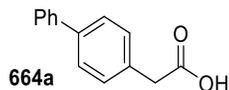


2-(2-ethyl-4-(methoxycarbonyl)thiazol-5-yl)acetate morpholine amide (663x). The coupling reaction was stopped after 50 min. Under the high vacuum pump the diisopropyl

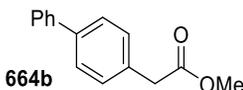
amine was removed from the crude product before morpholine was added and the mixture was heated. (0.1 mmol scale) ^1H NMR (500 MHz, C_6D_6) δ : 4.16 (q, $J = 7.1$ Hz, 2H), 4.10 (s, 2H), 3.36 (t, $J = 4.8$ Hz, 2H), 3.18 (t, $J = 4.9$ Hz, 2H), 3.18 (t, $J = 5.0$ Hz, 2H), 2.90 (t, $J = 5.0$ Hz, 2H), 2.20 (s, 3H), 1.08 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ : 167.2, 164.2, 163.5, 142.0, 141.9, 66.6, 66.4, 60.9, 45.9, 42.5, 31.9, 18.6, 14.4. ESI MS m/z : 299.1, $[\text{M}+\text{H}]^+$. TLC (ethyl acetate:hexane = 1:1) r.f. = 0.3.

2.3.3 Synthesis of Aryl Acetic Acid Derivatives and Benzyl Ketones

Ketene Trapping With Reagents Other Than Morpholine:

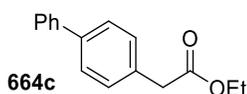


4-Biphenylacetic acid (664a). Toluene (2.0 ml) with 0.2 ml water and then 0.2 ml TEA were added to *tert*-butyl 4-biphenylacetylenyl ether **54g** (18.7 mg, 0.074 mmol). The reaction was heated at 75 °C for 12h and then concentrated under reduced pressure. The residue was partitioned between 1.0 N HCl and EtOAc, and the organic layer was washed with brine, dried with anhydrous sodium sulfate, and concentrated under reduced pressure. Flash chromatography on silica gel provided 14.7 mg pure acid as light yellow solid in 92% yield. ^1H NMR (400 MHz, CDCl_3) δ : 7.58 (t, $J = 5.2$ Hz, 4H), 7.44 (t, $J = 6.0$ Hz, 2H), 7.33-7.38 (m, 3H), 3.71 (s, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ : 177.9, 141.0, 140.7, 132.6, 130.1, 129.1, 127.8, 127.7, 127.4, 41.0. ESI MS m/z : 213.1, $[\text{M}+\text{H}]^+$. TLC (ethyl acetate:hexane = 3:2) r.f. = 0.6.

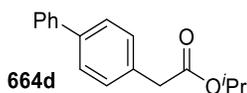


Methyl 4-phenylbenzoate (664b). Anhydrous MeOH (2.5 ml) was added to 4-

biphenylacetylenyl ether **54g** (14.6 mg, 0.058 mmol), and the solution was heated at 75 °C for 12h. Concentration under reduced pressure provided 13.1 mg pure ester in 99% yield. ¹H NMR (400 MHz, CDCl₃) δ: 7.58 (t, J = 8.4 Hz, 4H), 7.44 (t, J = 8.0 Hz, 2H), 7.33-7.38 (m, 3H), 3.73 (s, 3H), 3.68 (s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ: 172.4, 141.1, 140.4, 133.3, 130.0, 129.1, 127.7, 127.6, 127.4, 52.5, 41.2. ESI MS m/z: 227.1, [M+H]⁺. TLC (ethyl acetate:hexane = 1:5) r.f. = 0.5.

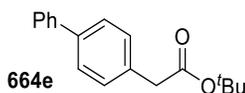


Ethyl 4-phenylbenzoate (664c). Anhydrous EtOH (1.1 ml) was added to 4-biphenylacetylenyl ether **54g** (14.6 mg, 0.058 mmol), and the solution was heated at 75 °C for 12h. Concentration under reduced pressure provided pure ester in 99% yield. ¹H NMR (400 MHz, CDCl₃) δ: 7.56-7.60 (m, 4H), 7.44 (t, J = 7.6 Hz, 2H), 7.33-7.38 (m, 3H), 4.18 (q, J = 7.2 Hz, 2H), 3.67 (s, 2H), 1.28 (t, J = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ: 171.9, 141.1, 140.3, 133.5, 130.0, 129.1, 127.63, 127.58, 127.4, 61.3, 41.4, 14.5. ESI MS m/z: 241.1, [M+H]⁺. TLC (ethyl acetate:hexane = 1:5) r.f. = 0.5.

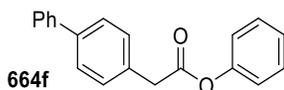


iso-propyl 4-phenylbenzoate (664d). Anhydrous *i*-PrOH (2.5 ml) was added to 4-biphenylacetylenyl ether **54g** (26.4 mg, 0.105 mmol) and the solution was heated at 75 °C for 12h. Concentration under reduced pressure provided 26.2 mg pure ester in 98% yield. ¹H NMR (400 MHz, CDCl₃) δ: 7.55-7.61 (m, 4H), 7.44 (t, J = 8.0 Hz, 2H), 7.32-7.38 (m, 3H), 5.05 (dq, J₁ = 6.4 Hz, J₂ = 6.0 Hz, 1H), 3.63 (s, 2H), 1.26 (d, J = 6.4 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ: 171.5, 141.2, 140.2, 133.7, 130.0, 129.1, 127.59, 127.56, 127.4, 68.6, 41.7, 22.1.

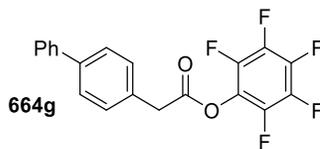
ESI MS m/z : 254.1, $[M+H]^+$. TLC (ethyl acetate:hexane = 1:5) r.f. = 0.5.



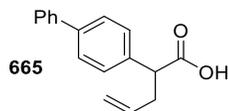
tert-butyl 4-phenylbenzoate (644e). Anhydrous *t*-BuOH (1.0 ml) was added to 4-biphenylacetylenyl ether **54g** (9.1 mg, 0.036 mmol), and the solution was heated at 75 °C for 6h. Concentration under reduced pressure provided 8.9 mg pure ester in 91% yield. ^1H NMR (400 MHz, CDCl_3) δ : 7.55-7.60 (m, 4H), 7.44 (t, $J = 8.0$ Hz, 2H), 7.32-7.38 (m, 3H), 3.58 (s, 2H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ : 170.9, 140.9, 139.7, 133.7, 129.6, 128.7, 127.18, 127.15, 127.0, 80.9, 42.2, 28.0. ESI MS m/z : 269.2, $[M+H]^+$. TLC (ethyl acetate:hexane = 1:5) r.f. = 0.6.



Phenyl 4-phenylbenzoate (664f). To 4 ml vial with 4-biphenylacetylenyl ether **54g** (20.3 mg, 0.081 mmol), 1.6 ml pre-mixed phenol (0.25M, 0.405 mmol) and TEA (0.5M, 0.81 mmol) toluene solution was added, followed by heating reaction at 75 °C for 5h. The crude product mixture was washed by saturated aqueous sodium hydrocarbonate and brine, and dried with anhydrous sodium sulfate. 20.8 mg pure product was obtained by flash chromatography (89% yield). ^1H NMR (400 MHz, CDCl_3) δ : 7.62 (d, $J = 8.0$ Hz, 4H), 7.44-7.50 (m, 4H), 7.35-7.40 (m, 3H), 7.24 (t, $J = 7.2$ Hz, 1H), 7.10 (d, $J = 7.6$ Hz, 2H), 3.92 (s, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ : 170.3, 151.1, 141.0, 140.7, 132.8, 130.0, 129.8, 129.1, 127.8, 127.7, 127.4, 126.2, 121.8, 41.4. ESI MS m/z : 287.0, $[M-H]^-$. TLC (ethyl acetate:hexane = 1:5) r.f. = 0.4.

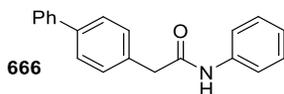


Pentafluorophenyl 4-phenylbenzoate (664g). To 4 ml vial with 4-biphenylacetylenyl ether **54g** (25.3 mg, 0.103 mmol), 2.0 ml toluene was added, followed by TEA (0.16 ml, 1.13 mmol) and 0.66 ml pentafluorophenol solution (0.63M in toluene, 1.03 mmol, freshly treated with 4 Å Molecular sieves). The reaction was heated to 75 °C for 5h. The crude product was washed by brine, dried with sodium sulfate anhydrous. 29.0 mg pure product was obtained following flash chromatography in 76% yield. ¹H NMR (400 MHz, CDCl₃) δ: 7.60-7.63 (m, 4H), 7.43-7.48 (m, 4H), 7.37 (t, J = 7.2 Hz, 1H), 4.02 (s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ: 167.8, 142.7, 141.1, 140.8, 140.2, 139.5, 136.9, 131.3, 130.0, 129.2, 128.0, 127.8, 127.4, 40.1. ESI MS m/z: 378.7, [M-H]⁻. TLC (ethyl acetate:hexane = 1:10) r.f. = 0.4.

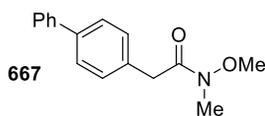


4-Biphenyl-2'-allylacetic acid (665). To 4 ml vial with *tert*-butyl 4-biphenylacetylenyl ether **54g** (11.0 mg, 0.046 mmol), 0.5 ml toluene was added, followed by TEA (52 μl, 0.23 mmol) and allylic alcohol (9.3 μl, 0.14 mmol). The reaction was heated at 75 °C for 5h, and then cooled to room temperature. TMSOTf (42 μl, 0.23 mmol) was added dropwise at room temperature, and the reaction was stirred for another 2h. The crude products were obtained by washing with 1.0 N HCl and brine, drying with anhydrous sodium sulfate, and concentrating via rotavap. After a flash chromatography, 10.3 mg pure product was afforded as white solid in 93% yield. ¹H NMR (400 MHz, CDCl₃) δ: 7.54-7.58 (m, 4H), 7.38-7.45 (m, 4H), 7.34 (tt, J₁ = 7.2 Hz, J₂ = 1.2 Hz, 1H), 5.71-5.81 (m, 1H), 5.12 (dd, J₁ = 17.2 Hz, J₂ = 1.2 Hz, 1H), 5.04

(dd, $J_1 = 10.4$ Hz, $J_2 = 1.6$ Hz, 1H), 3.70 (t, $J = 7.6$ Hz, 1H), 2.87 (m, 1H), 2.58 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ : 179.4, 141.0, 140.9, 137.2, 135.2, 129.1, 128.8, 127.8, 127.7, 127.4, 117.7, 51.4, 37.4. ESI MS m/z : 253.1, $[\text{M}+\text{H}]^+$. TLC (ethyl acetate:hexane = 3:2) r.f. = 0.7.

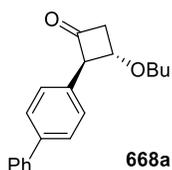


4-Biphenylacetanilide (666). To 4 ml vial with 4-biphenylacetylenyl ether **54g** (28.4 mg, 0.113 mmol), 2.0 ml toluene was added, followed by aniline (0.2 ml, 2.25 mmol). The reaction was heated to 75 °C for 12h. The crude product was washed by 1 N HCl twice and brine, extracted with ethyl acetate, and dried by sodium sulfate. 31.0 mg pure product was isolated as light yellow solid after a flash chromatography in 95% yield. ^1H NMR (400 MHz, CDCl_3) δ : 7.60-7.64 (m, 4H), 7.36-7.48 (m, 7H), 7.29 (t, $J = 6.4$ Hz, 2H), 7.23 (bs, 1H), 7.10 (t, $J = 6.0$ Hz, 1H), 3.78 (s, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ : 169.4, 140.9, 140.8, 137.9, 133.7, 130.3, 129.3, 129.2, 128.2, 127.8, 127.4, 124.8, 120.2, 44.8. ESI MS m/z : 288.1, $[\text{M}+\text{H}]^+$. TLC (ethyl acetate:hexane = 1:1) r.f. = 0.7.

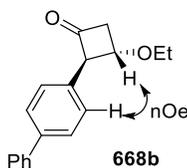


N-Methoxy-N-methyl-4-biphenylacetamide (667). To 4 ml vial with *tert*-butyl 4-biphenylacetylenyl ether **54g** (21.1 mg, 0.088 mmol), 1.2 ml toluene was added, followed by 0.88 ml pre-mixed Weinreb amide hydrochloride salt (1.0 M) and TEA (1.5 M) toluene solution. Then, the reaction was heated at 75 °C for 3h, and then 50 °C 10 hours. The crude products were obtained by washing with water and brine, drying with anhydrous sodium sulfate, and

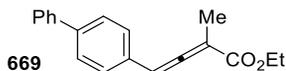
concentration under reduced pressure. After flash chromatography, 19.0 mg pure product was isolated in 86% yield. ^1H NMR (400 MHz, CDCl_3) δ : 7.54-7.59 (m, 4H), 7.43 (t, $J = 7.6$ Hz, 2H), 7.37 (d, $J = 8.0$ Hz, 2H), 7.34 (t, $J = 7.2$ Hz, 1H) 3.82 (s, 2H), 3.66 (s, 3H), 3.22 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ : 172.7, 141.2, 140.1, 134.3, 130.1, 129.1, 127.6, 127.5, 127.4, 61.7, 39.3, 32.6. ESI MS m/z : 256.1, $[\text{M}+\text{H}]^+$. TLC (ethyl acetate:hexane = 3:2) r_f = 0.5.



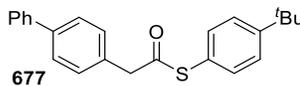
3-Butoxy-2-(4-biphenyl)-cyclobutanone (668a). To 4 ml vial with 4-biphenylacetylenyl ether **54g** (22.9 mg, 0.091 mmol), 1.0 ml vinyl butyl ether was added, and then the reaction was heated to 75 °C for 12h. The crude product was obtained following concentration under reduced pressure. 17.0 mg of product were obtained following flash chromatography in 63% yield. ^1H NMR (400 MHz, CDCl_3) δ : 7.53-7.57 (m, 4H), 7.42 (t, $J = 8.0$ Hz, 2H), 7.29-7.35 (m, 3H), 4.46-4.49 (m, 1H), 4.39 (q, $J = 6.4$ Hz, 1H), 3.49-3.59 (m, 2H), 3.21-3.25 (m, 2H), 1.57-1.64 (m, 2H), 1.36-1.46 (m, 2H), 0.93 (t, $J = 7.6$ Hz) ; ^{13}C NMR (100 MHz, CDCl_3) δ : 204.2, 140.7, 140.2, 134.0, 128.8, 127.6, 127.5, 127.3, 127.0, 71.3, 70.9, 70.0, 51.6, 31.7, 19.3, 13.9. ESI MS m/z : 295.1, $[\text{M}+\text{H}]^+$. TLC (ethyl acetate:hexane = 1:5) r_f = 0.6. Relative stereochemistry was assigned by analogy to **668b**.



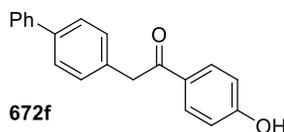
3-Ethoxyl-2-(4-biphenyl)-cyclobutanone (668b). Synthesized analogously to **668a**. 21.1 mg of product were isolated following flash chromatography in 74% yield. ^1H NMR (400 MHz, CDCl_3) δ : 7.55-7.59 (m, 4H), 7.44 (t, $J = 8.0$ Hz, 2H), 7.30-7.37 (m, 3H), 4.50-4.52 (m, 1H), 4.43 (q, $J = 6.4$ Hz, 1H), 3.56-3.69 (m, 2H), 3.25-3.28 (m, 2H), 1.29 (t, $J = 7.2$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 204.4, 140.9, 140.5, 134.2, 129.0, 127.9, 127.8, 127.6, 127.3, 71.6, 71.0, 65.9, 51.9, 15.5. ESI MS m/z : 267.1, $[\text{M}+\text{H}]^+$. TLC (ethyl acetate:hexane = 1:5) r.f. = 0.6. Relative stereochemistry was assigned based on an NOE between the oxygenated methine and the 2-position of the aryl ring.



Ethyl 4-(4-biphenyl)-2-methyl-2,3-butadienoate (669). To 4 ml vial with 4-biphenylacetylenyl ether **54g** (18.6 mg, 0.074 mmol) and (carbethoxyethylidene)-triphenylphosphorane (40.44 mg, 0.11 mmol), 1.5 ml toluene was added. The reaction mixture was heated to 75 °C for 12h. The crude products were obtained after washing with water and brine, drying with anhydrous sodium sulfate, and concentrating under reduced pressure. 12.9 mg pure product was afforded via flash chromatography as white solid in 63% yield. ^1H NMR (400 MHz, CDCl_3) δ : 7.56-7.61 (m, 4H), 7.45 (t, $J = 8.0$ Hz, 2H), 7.33-7.37 (m, 3H), 6.52 (q, $J = 2.8$ Hz, 1H), 4.23 (qd, $J_1 = 7.2$ Hz, $J_2 = 2.0$ Hz, 2H), 2.02 (d, $J = 2.8$ Hz, 3H), 1.28 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ : 212.9, 167.4, 140.94, 140.87, 131.9, 129.2, 128.1, 127.8, 127.7, 127.3, 99.9, 97.2, 61.5, 15.5, 14.6. ESI MS m/z : 279.1, $[\text{M}+\text{H}]^+$. TLC (ethyl acetate:hexane = 3:2) r.f. = 0.8.

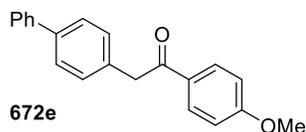


4'-tert-butyl-phenyl 4-phenylthiobenzoate (677). To 4 ml vial with 4-biphenylacetylenyl ether **54g** (28.0mg, 0.112 mmol), TEA (0.12 ml, 0.67 mmol) was added, followed by 4-tert-butylthiophenol (0.1 ml, 0.56 mmol). The reaction mixture was heated to 75 °C for 12 h, and the reaction was quenched with 1.0 ml 1 N HCl. Stirring was continued for 2h to hydrolyze thioketene acetal (ca. 50% of the reaction mixture) to the thioester. The crude product was obtained following extraction with ethyl acetate, washing with brine, and drying with anhydrous sodium sulfate. 30.4 mg pure product was isolated after flash chromatography (78% yield). ¹H NMR (400 MHz, CDCl₃) δ: 7.57-7.62 (m, 4H), 7.40-7.47 (m, 6H), 7.31-7.38 (m, 3H), 3.96 (s, 2H), 1.32 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ: 196.1, 153.0, 141.0, 140.7, 134.4, 132.7, 130.4, 129.1, 127.74, 127.68, 127.4, 126.6, 124.6, 50.0, 35.1, 31.5. ESI MS m/z: 361.2, [M+H]⁺. TLC (ethyl acetate:hexane = 1:10) r.f. = 0.5.



1-(4-hydroxyphenyl)-2-(4-biphenyl)ethanone (627f). Methansulfonic acid (MSA) anhydride was added to commercially available MSA, and the mixture was heated at 90 °C for 1h. The water content was essential to this reaction, and it was monitored as 666.7 ppm using a Karl-Fischer apparatus. To 4 ml vial with phenyl 4-phenylbenzoate **664f** (17.1 mg, 0.113 mmol), 0.2 ml MSA (KF% = 666.7 ppm) was added, and the reaction was heated to 65 °C for 30h. Methanol was added to quench the reaction at room temperature, and the reaction system was neutralized by sodium carbonate solution. The crude product was extracted by warm DCM 6 times, and washed by brine. Flash chromatography provided the pure product (14.1mg, 82%) as white solid. ¹H NMR (400 MHz, CD₃OD + CDCl₃) δ: 7.98 (d, J = 8.8 Hz, 2H), 7.57 (t, J =

8.4 Hz, 4H), 7.41 (t, $J = 8.0$ Hz, 2H), 7.29-7.35 (m, 3H), 6.87 (d, $J = 8.8$ Hz, 2H), 4.30 (s, 2H); ^{13}C NMR (100 MHz, $(\text{CD}_3)_2\text{SO}$) δ : 195.7, 162.3, 140.0, 138.3, 134.9, 131.1, 130.1, 128.9, 127.8, 127.3, 126.59, 126.56, 115.3, 43.9. ESI MS m/z : 289.1, $[\text{M}+\text{H}]^+$. TLC (MeOH:DCM = 1:10) r.f. = 0.4.

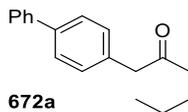


1-(4-methoxyphenyl)-2-(4-biphenyl)ethanone (672e). To 4 ml vial, 1'-*tert*-butyl-phenyl 4-phenylthiobenzoate **677** (20.9 mg, 0.058 mmol), 4-methoxyphenylboronic acid (9.7 mg, 0.064 mmol) copper thiophene-2-carboxylate (16.6 mg, 0.087 mmol), $\text{Pd}_2(\text{dba})_3$ (0.6 mg, 1 mol%), and TFP (0.4 mg, 3 mol%) were combined. THF (0.6 ml) was added to the solid mixture, and the reaction was heated to 50 °C for 12h. The crude product was washed by water and brine, and then dried with anhydrous sodium sulfate. After a flash chromatography, 13.9 mg pure product was isolated as a white solid in 80% yield. ^1H NMR (400 MHz, CDCl_3) δ : 8.03 (d, $J = 8.8$ Hz, 2H), 7.56 (m, 4H), 7.43 (t, $J = 8.0$ Hz, 2H), 7.31-7.36 (m, 3H), 6.95 (d, $J = 8.8$ Hz, 2H), 4.28 (s, 2H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $(\text{CD}_3)_2\text{SO}$) δ : 196.5, 163.9, 141.2, 140.1, 134.3, 131.3, 130.2, 130.0, 129.1, 127.7, 127.6, 127.4, 114.1, 55.8, 45.2. ESI MS m/z : 303.1, $[\text{M}+\text{H}]^+$. TLC (ethyl acetate:hexane = 1:5) r.f. = 0.4.

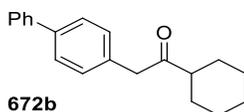
General Method for lanthanum promoted morpholine amide addition:

To $\text{LaCl}_3 \cdot 2\text{LiCl}$ 0.6 M THF solution, 1.0 equivalent of Grignard reagent was added via syringe pump over 30 minutes at -20 °C, and the mixture was stirred at -20 °C for 1h. The pre-mixed LaCl_3 and Grignard solution was added to 4-biphenylacetate morpholine amide **633g** dissolved in THF (0.1 M) via syringe pump over 30 minutes at -78 °C. The reaction was stirred at -78 °C

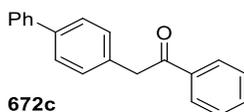
for 2h, and it was quenched by saturated aqueous ammonium chloride. The crude product was extracted with ethyl acetate and washed by brine. Ketones **672a** – **672d** were purified using preparative TLC.



1-butyl-2-(4-biphenyl)ethanone (672a). ^1H NMR (400 MHz, CDCl_3) δ : 7.55-7.61 (m, 4H), 7.44 (t, $J = 7.6$ Hz, 2H), 7.35 (tt, $J_1 = 7.2$ Hz, $J_2 = 1.6$ Hz, 1H), 7.28 (d, $J = 8.0$ Hz, 2H), 3.73 (s, 2H), 2.45 (t, $J = 7.6$ Hz, 2H), 1.57 (tt, $J_1 = 7.6$ Hz, $J_2 = 7.2$ Hz, 2H), 1.29 (m, 2H), 0.89 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ : 208.9, 141.1, 140.2, 133.7, 130.2, 129.1, 127.7, 127.6, 127.4, 50.0, 42.2, 26.2, 22.6, 14.2. ESI MS m/z : 253.1, $[\text{M}+\text{H}]^+$. TLC (ethyl acetate:hexane = 1:10) r.f. = 0.4.

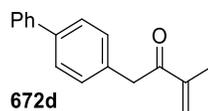


1-cyclohexyl-2-(4-biphenyl)ethanone (672b). ^1H NMR (400 MHz, CDCl_3) δ : 7.55-7.61 (m, 4H), 7.44 (t, $J = 7.6$ Hz, 2H), 7.34 (t, $J = 7.2$ Hz, 1H), 7.27 (d, $J = 7.6$ Hz, 2H), 3.78 (s, 2H), 2.50 (tt, $J_1 = 7.2$ Hz, $J_2 = 3.2$ Hz, 1H), 1.78-1.88 (m, 4H), 1.65-1.69 (m, 1H), 1.15-1.43 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3) δ : 211.5, 141.1, 140.1, 133.8, 130.2, 129.1, 127.6, 127.5, 127.4, 50.6, 47.7, 28.9, 26.2, 26.0. ESI MS m/z : 279.1, $[\text{M}+\text{H}]^+$. TLC (ethyl acetate:hexane = 1:10) r.f. = 0.5.



1-iso-propenyl-2-(4-biphenyl)ethanone (672c). ^1H NMR (400 MHz, CDCl_3) δ : 7.54-7.60 (m,

4H), 7.43 (t, $J = 7.6$ Hz, 2H), 7.34 (t, $J_1 = 7.2$ Hz, $J_2 = 2.0$ Hz, 1H), 7.27 (d, $J = 7.6$ Hz, 2H), 6.12 (s, 1H), 5.87 (d, $J = 1.6$ Hz, 1H), 4.06 (s, 2H), 1.91 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ : 199.6, 144.6, 141.2, 140.1, 134.3, 130.1, 129.1, 127.7, 127.5, 127.4, 126.1, 44.4, 18.2. ESI MS m/z : 237.1, $[\text{M}+\text{H}]^+$. TLC (ethyl acetate:hexane = 1:10) r.f. = 0.5.



1-phenyl-2-(4-biphenyl)ethanone (672d). ^1H NMR (400 MHz, CDCl_3) δ : 8.05 (d, $J = 7.2$ Hz, 2H), 7.55-7.59 (m, 5H), 7.48 (t, $J = 7.6$ Hz, 2H), 7.43 (t, $J = 8.0$ Hz, 2H), 7.31-7.36 (m, 3H), 4.34 (s, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ : 197.9, 141.1, 140.2, 136.9, 133.9, 133.6, 130.2, 129.1, 129.0, 128.9, 127.7, 127.5, 127.3, 45.4. ESI MS m/z : 273.2, $[\text{M}+\text{H}]^+$. TLC (ethyl acetate:hexane = 1:10) r.f. = 0.4.

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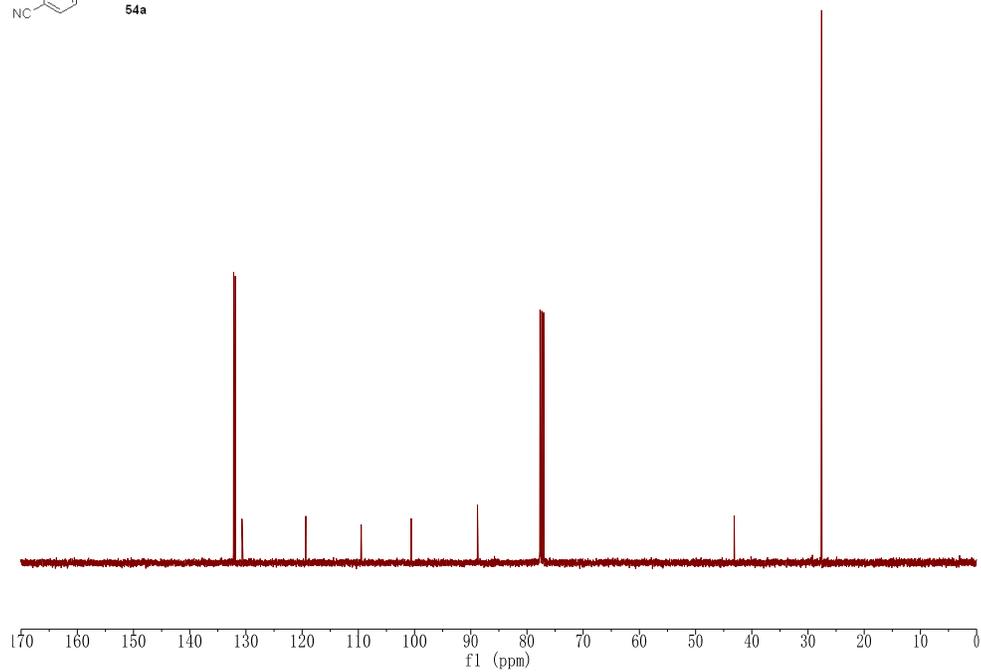
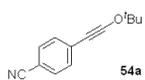
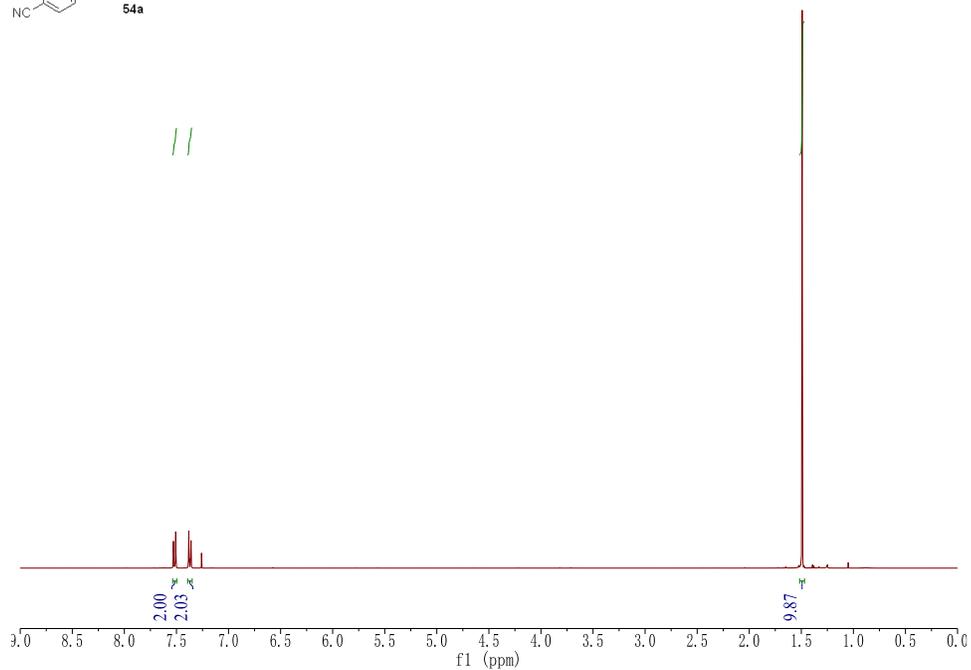
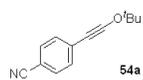
(10) (a) dpp-hexane is a poor ligand for palladium-catalyzed CO/C₂H₄ copolymerization. See: Leeuwen, P. W. N. M. v.; Freixa, Z. In *Modern Carbonylation Methods*; Wiley-VCH Verlag GmbH & Co. KGaA: 2008, p 10. (b) For bite angle of Pd[PH₂(CH₂)₆PH₂], see: van Zeist, W.-J.; Visser, R.; Bickelhaupt, F. M. *Chem. Eur. J.* **2009**, *15*, 6112-6115.

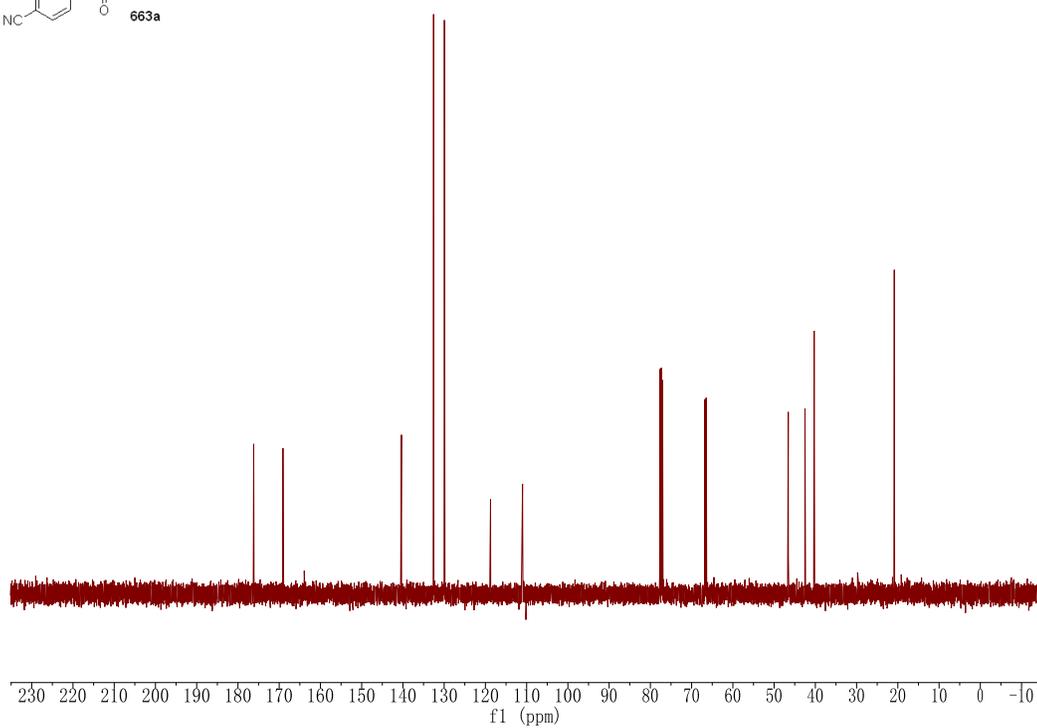
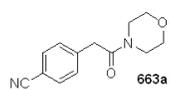
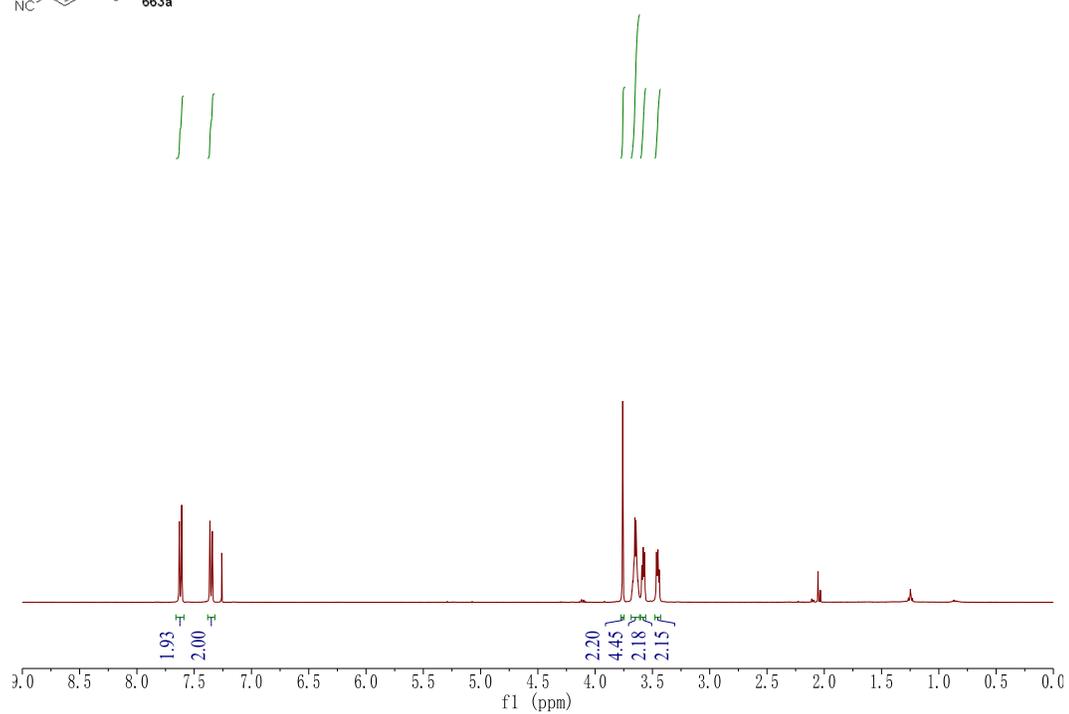
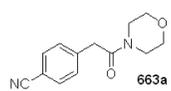
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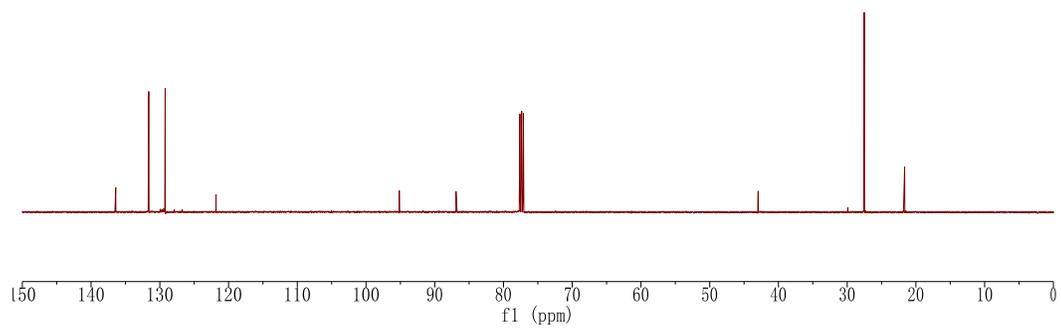
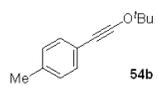
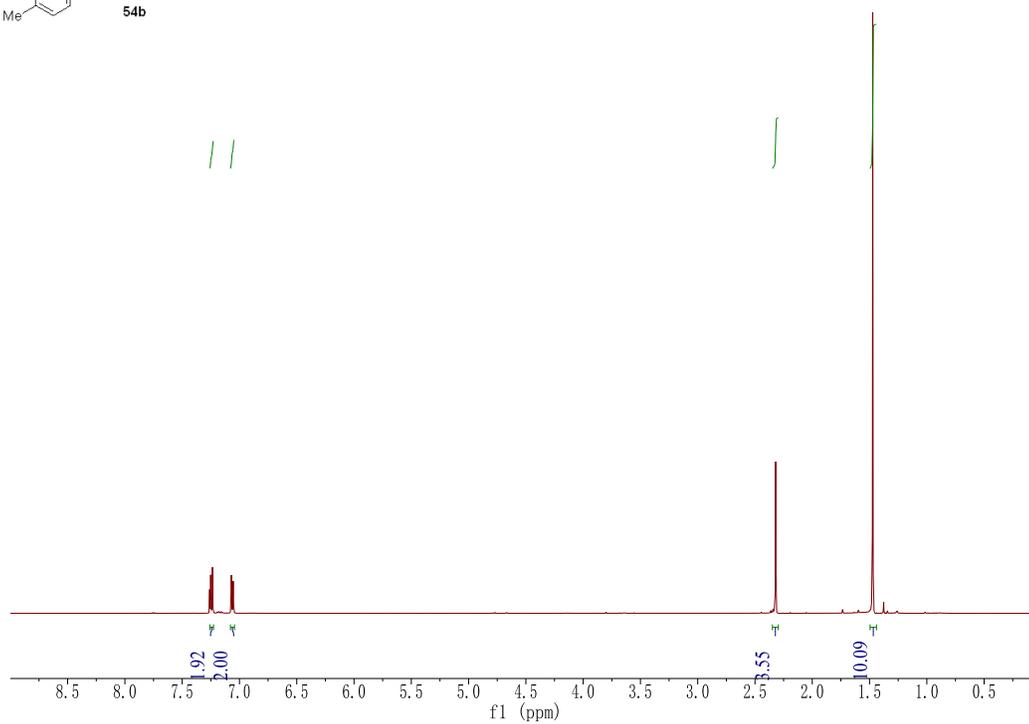
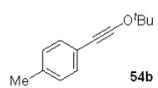
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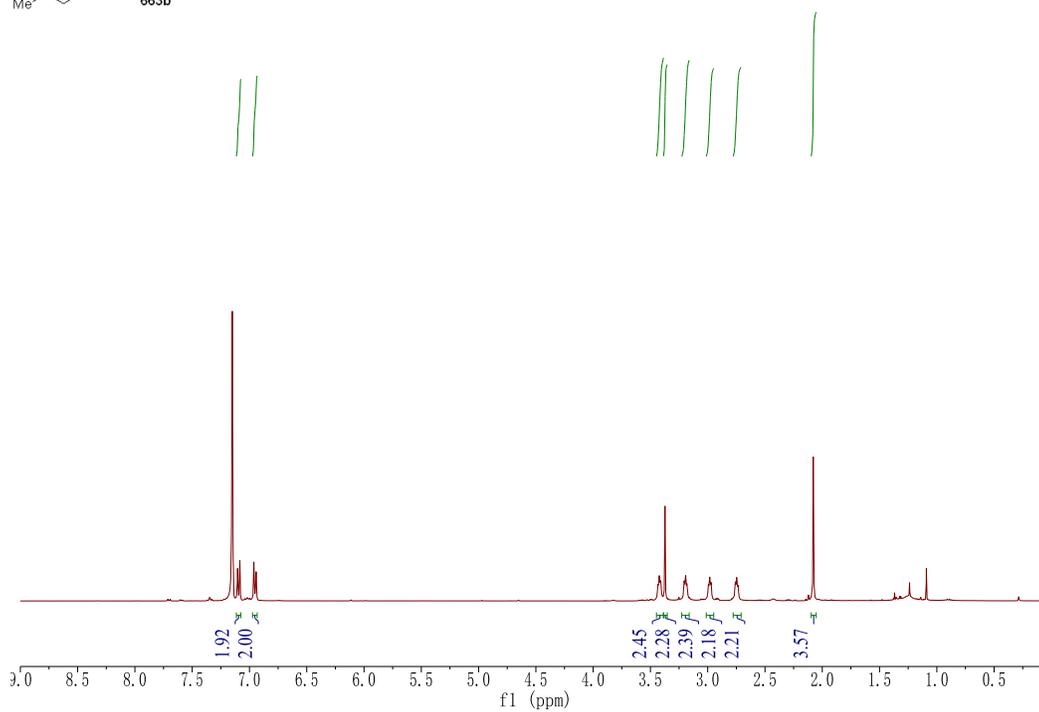
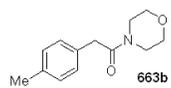
APPENDIX A

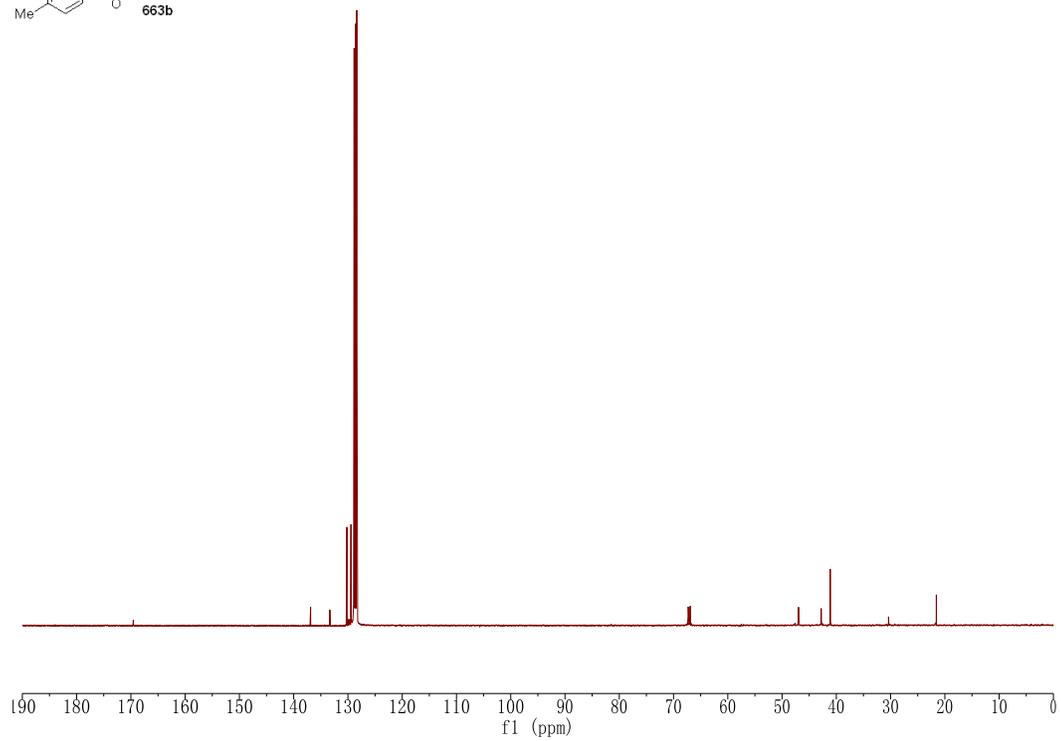
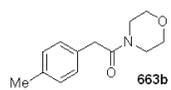
^1H , ^{13}C and 2D NMR SPECTRA

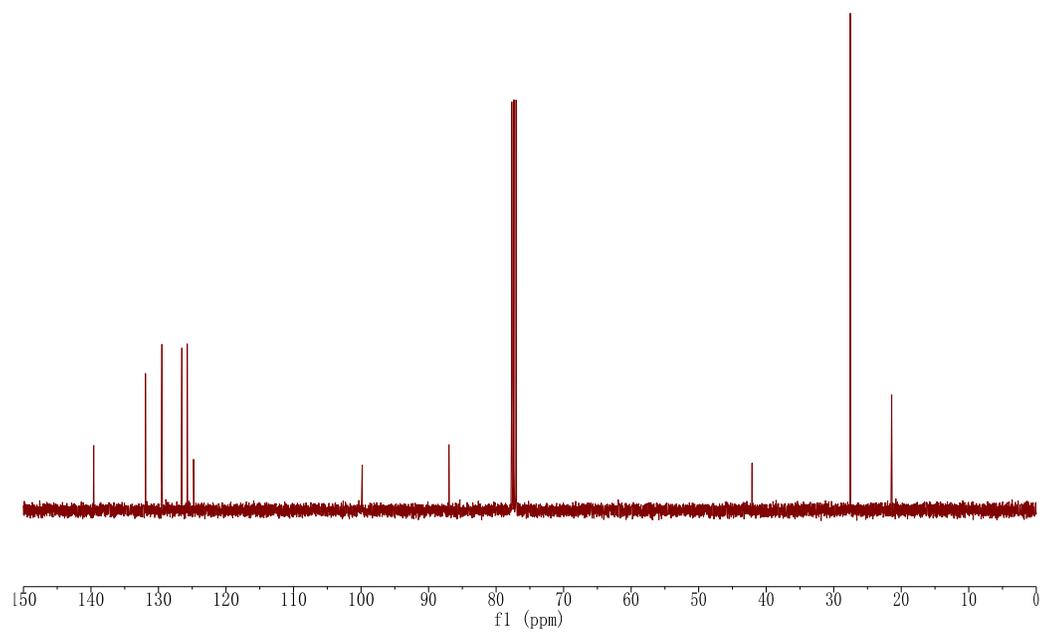
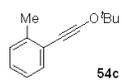
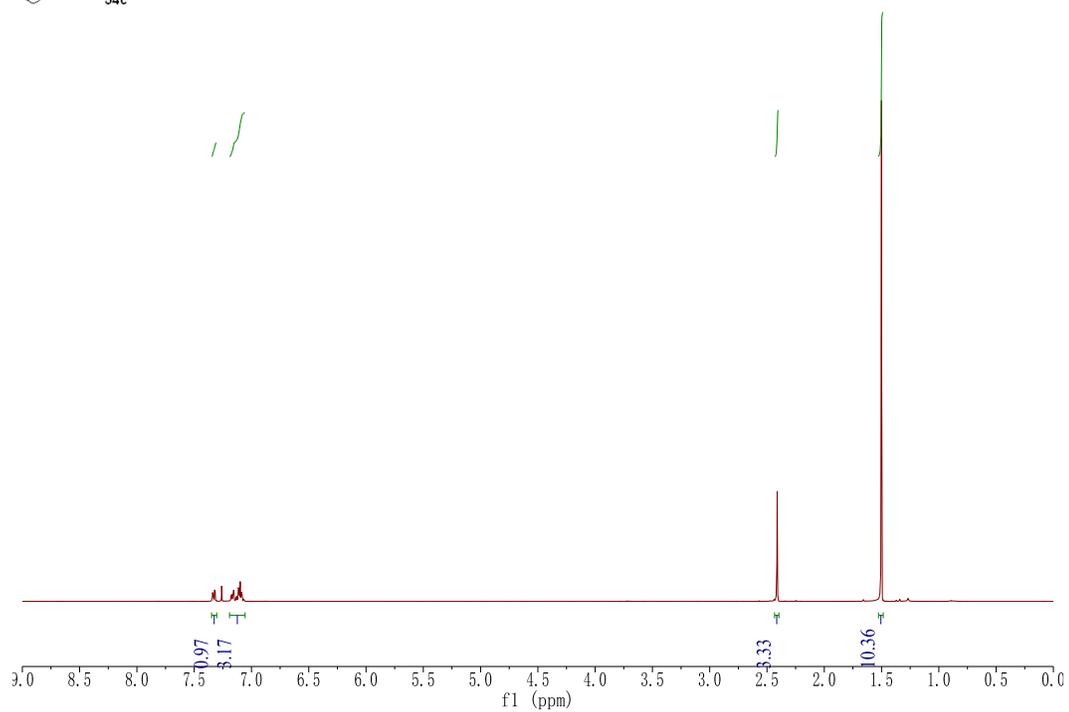
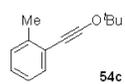


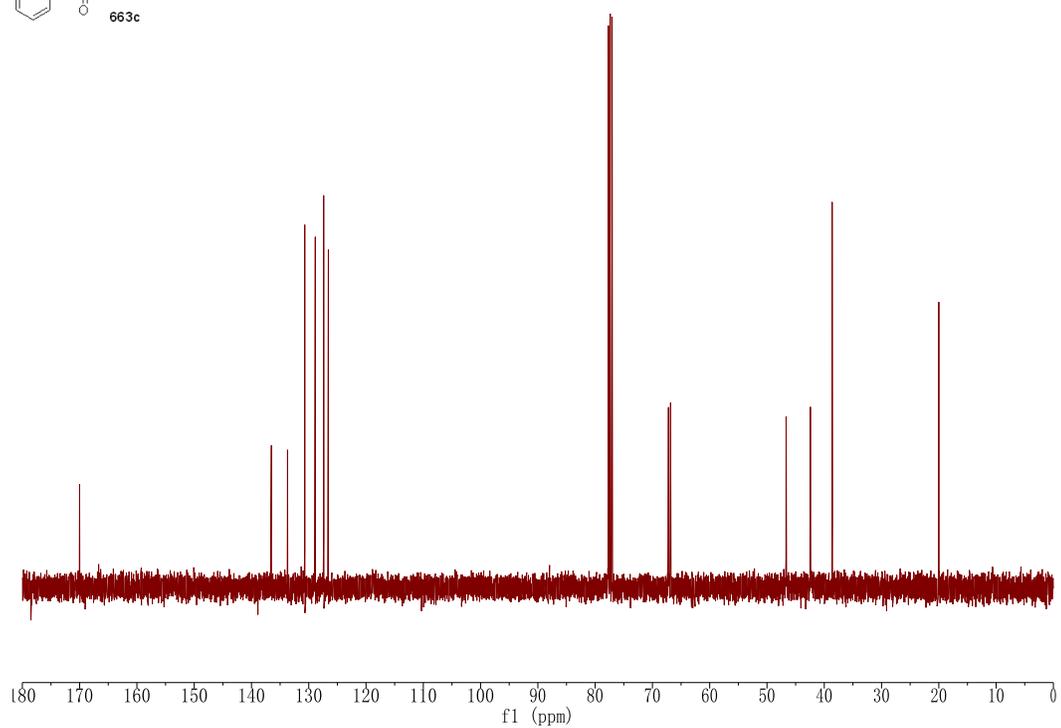
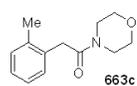
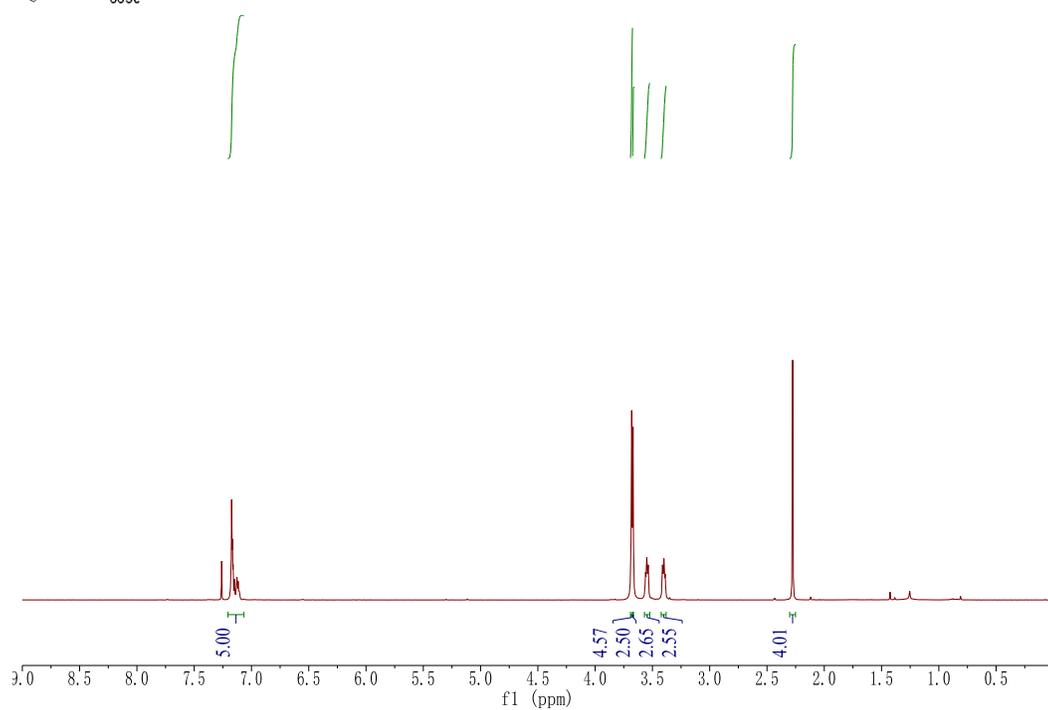
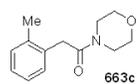


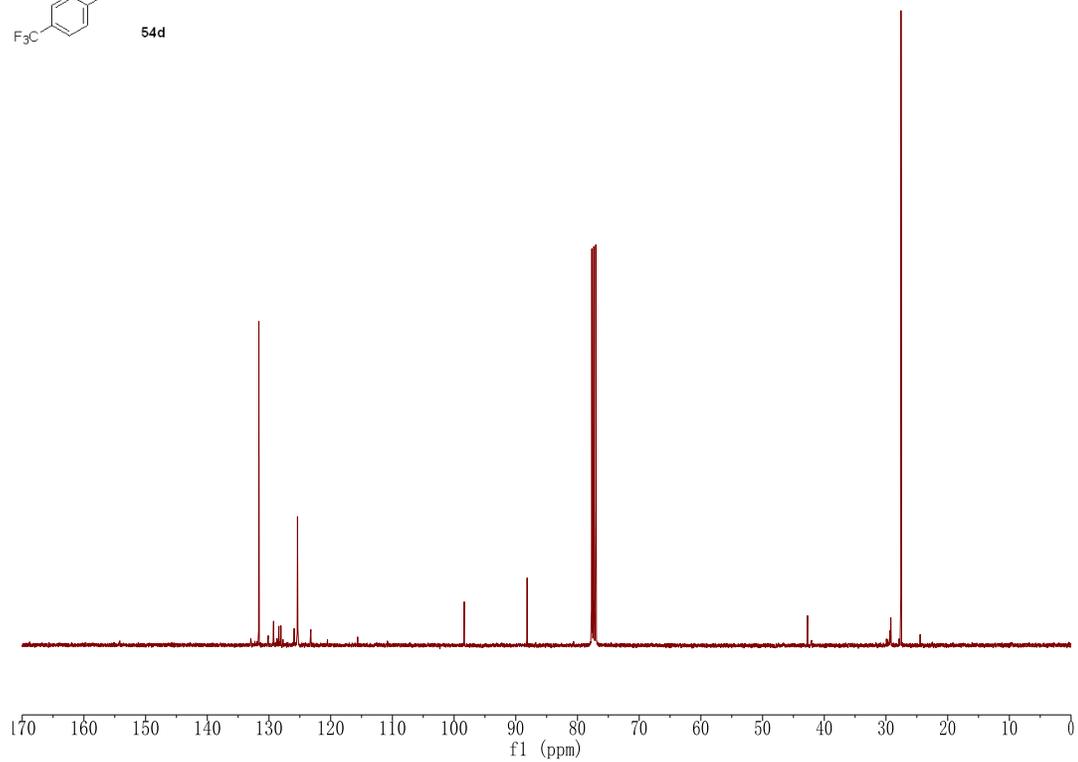
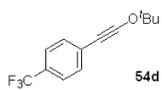
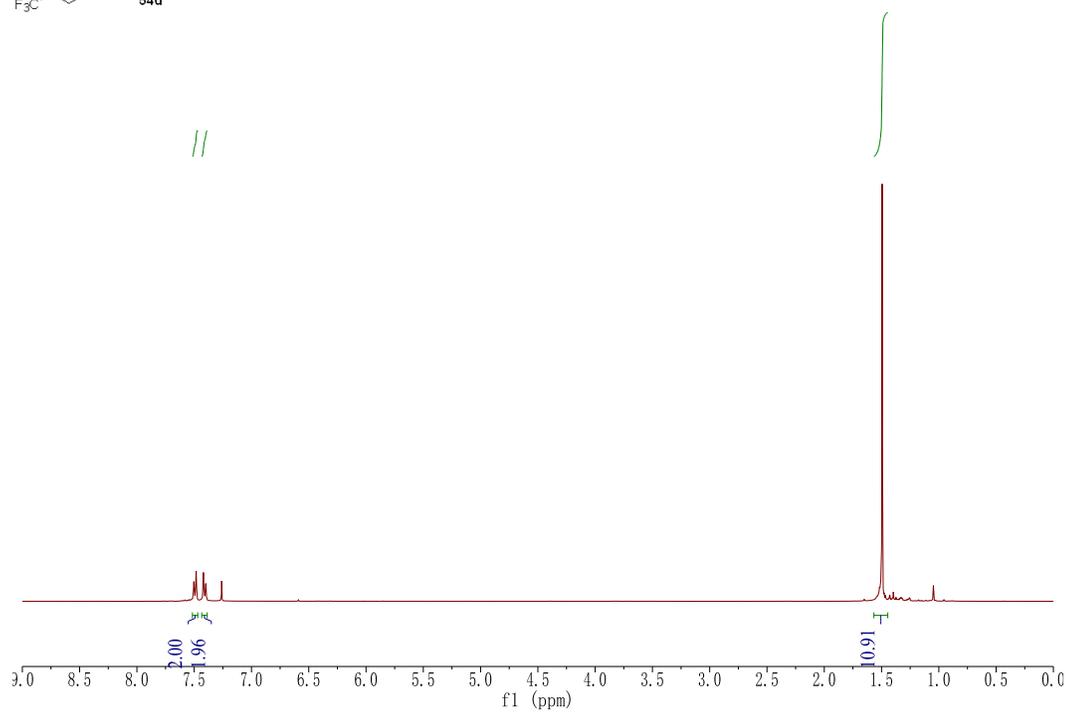
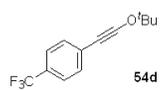


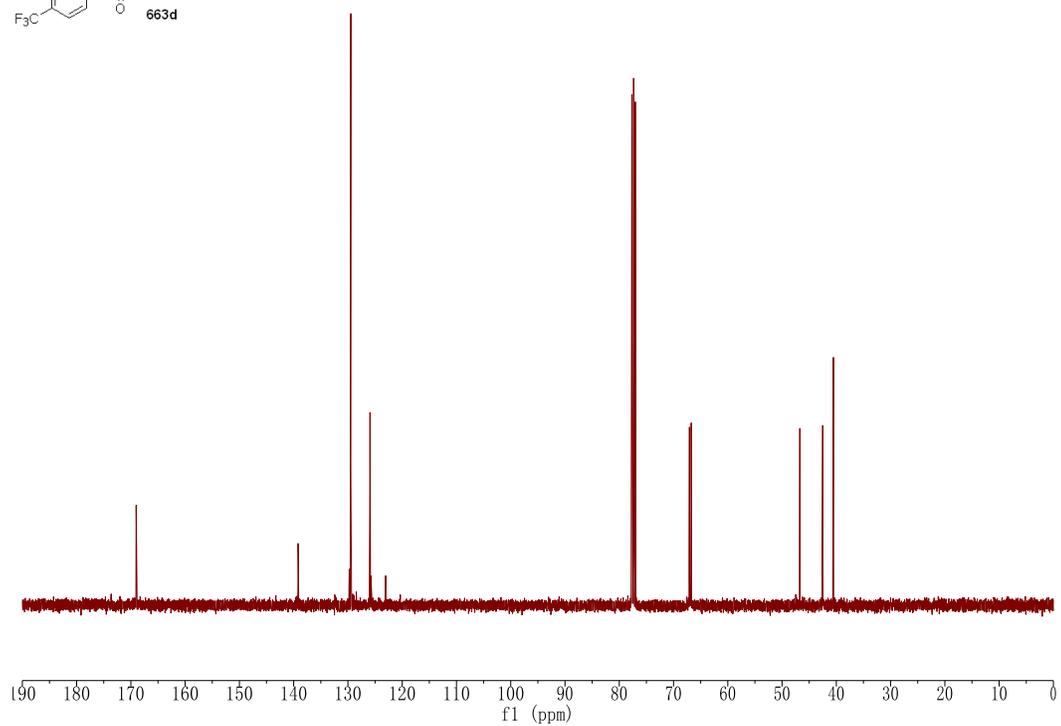
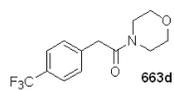
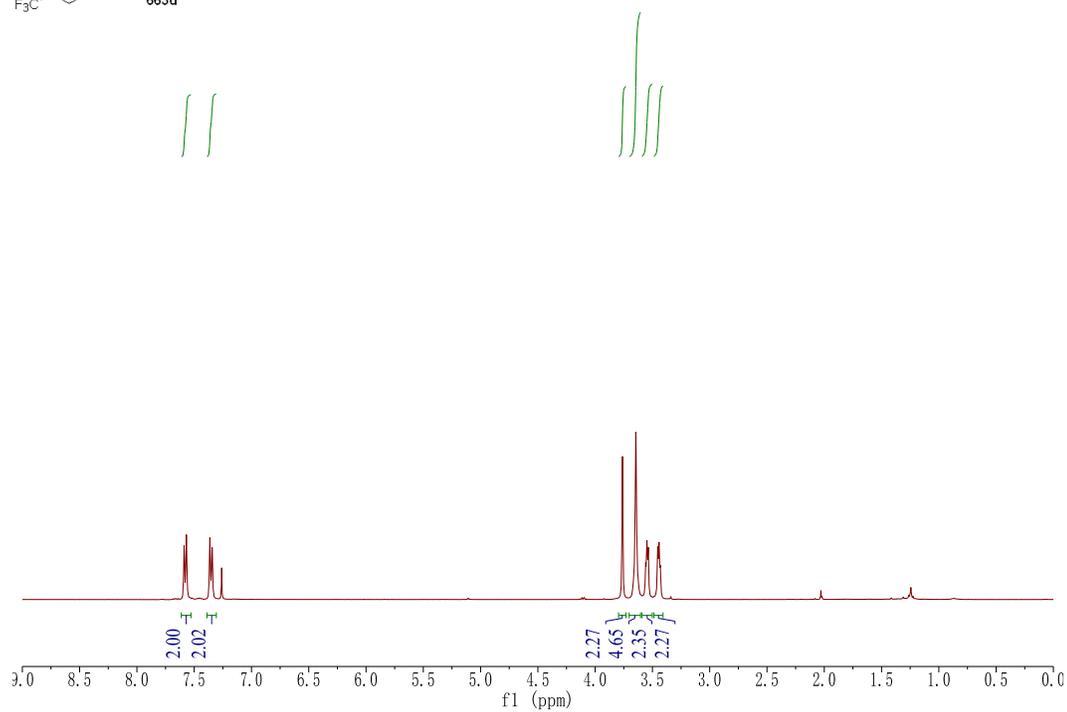
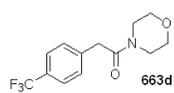


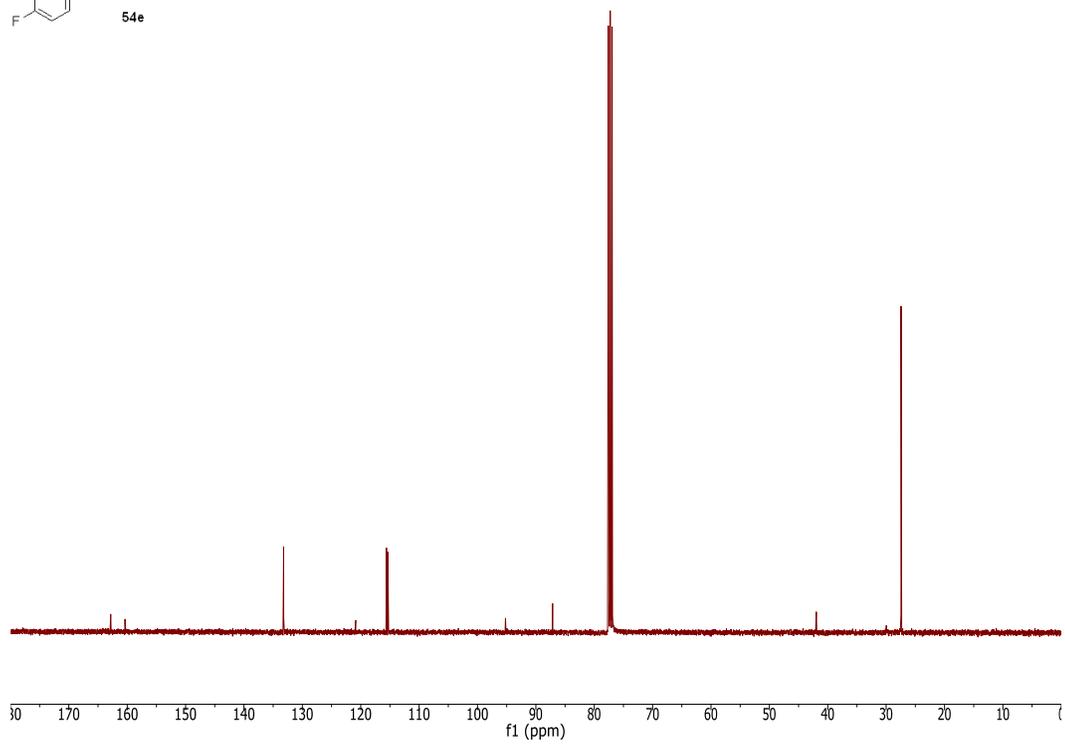
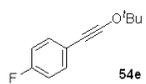
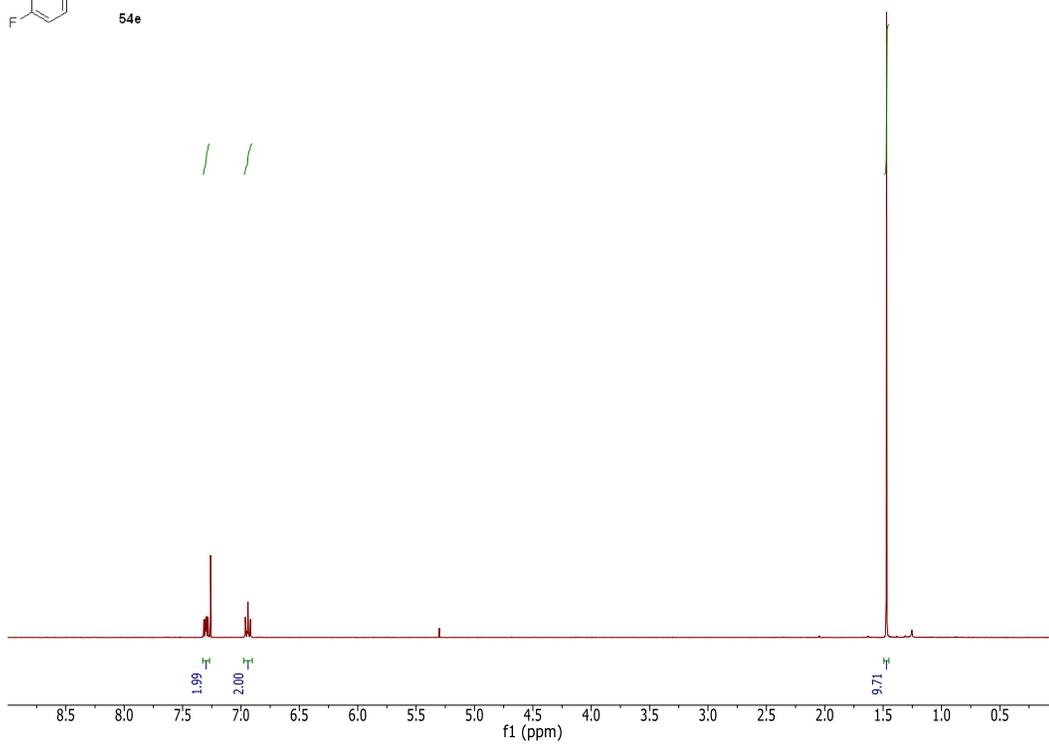
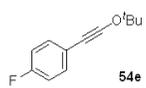


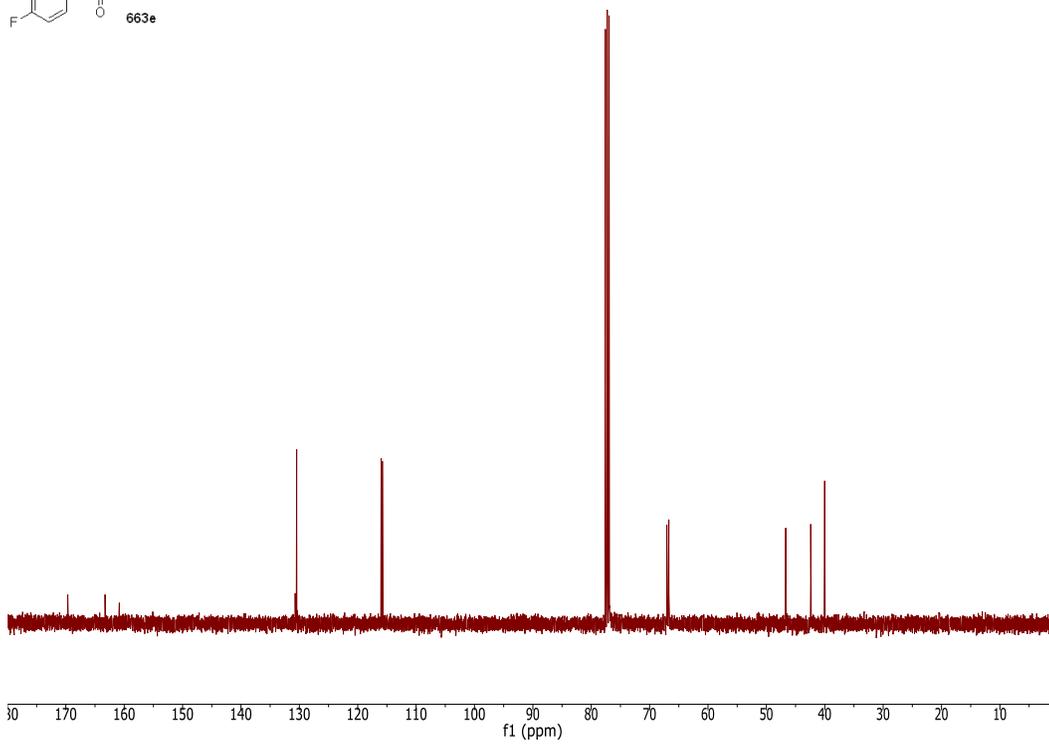
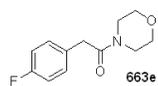
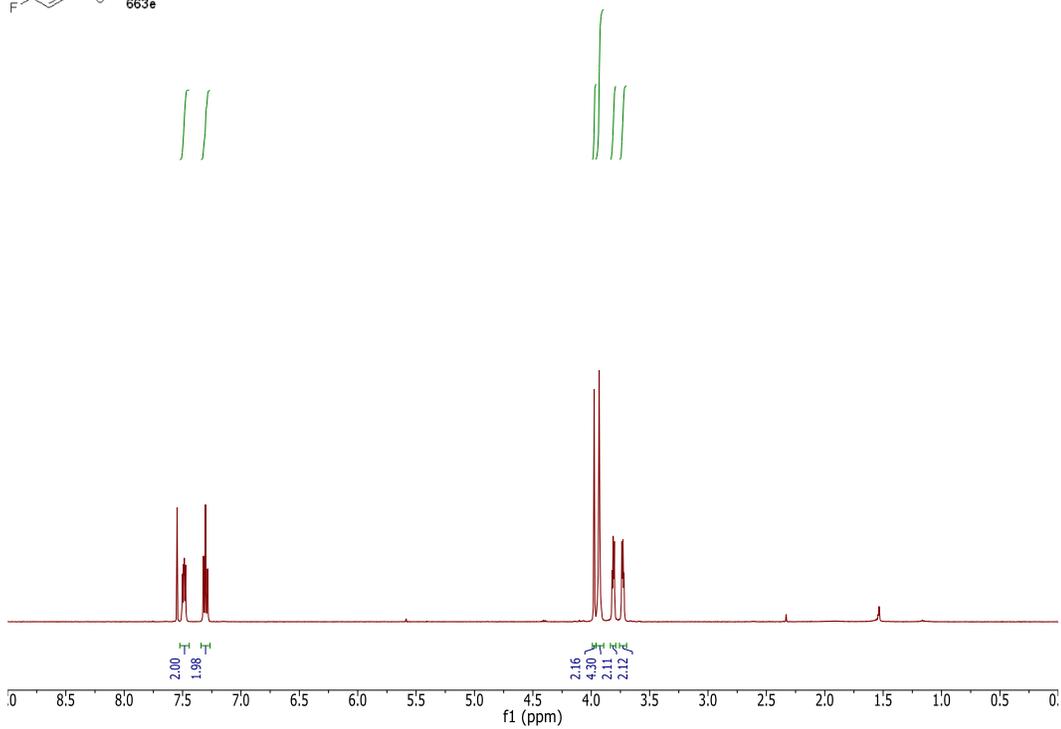
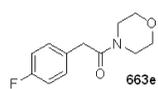


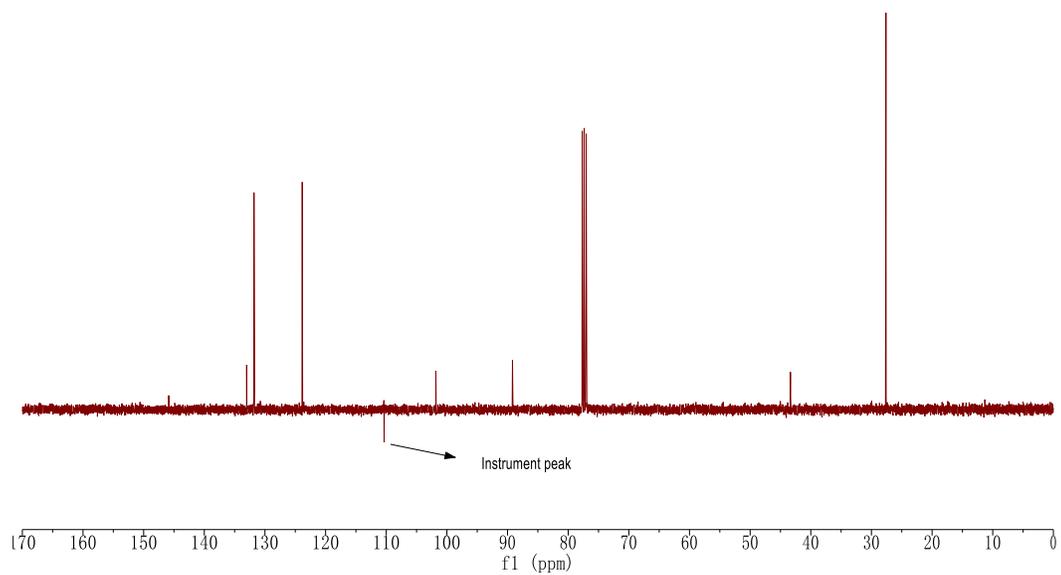
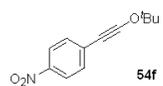
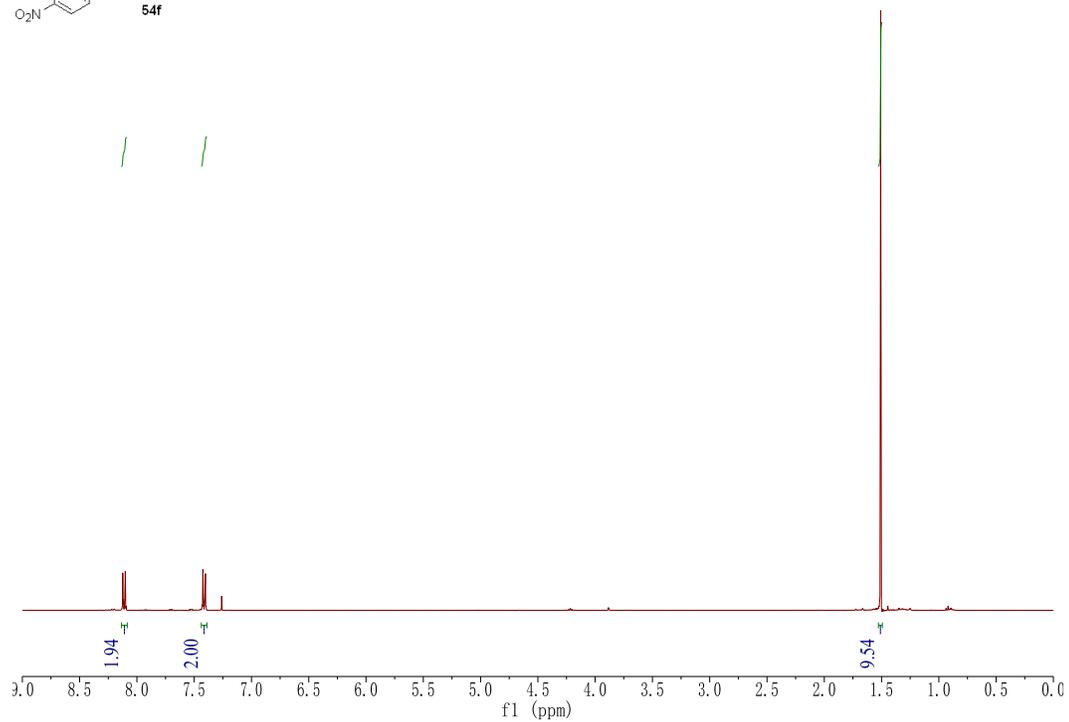
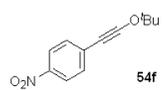


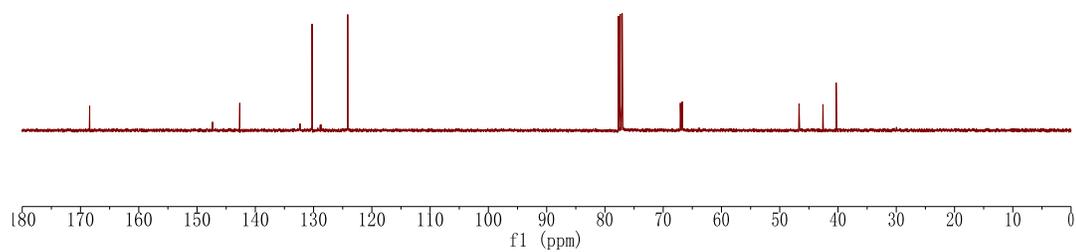
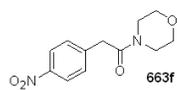
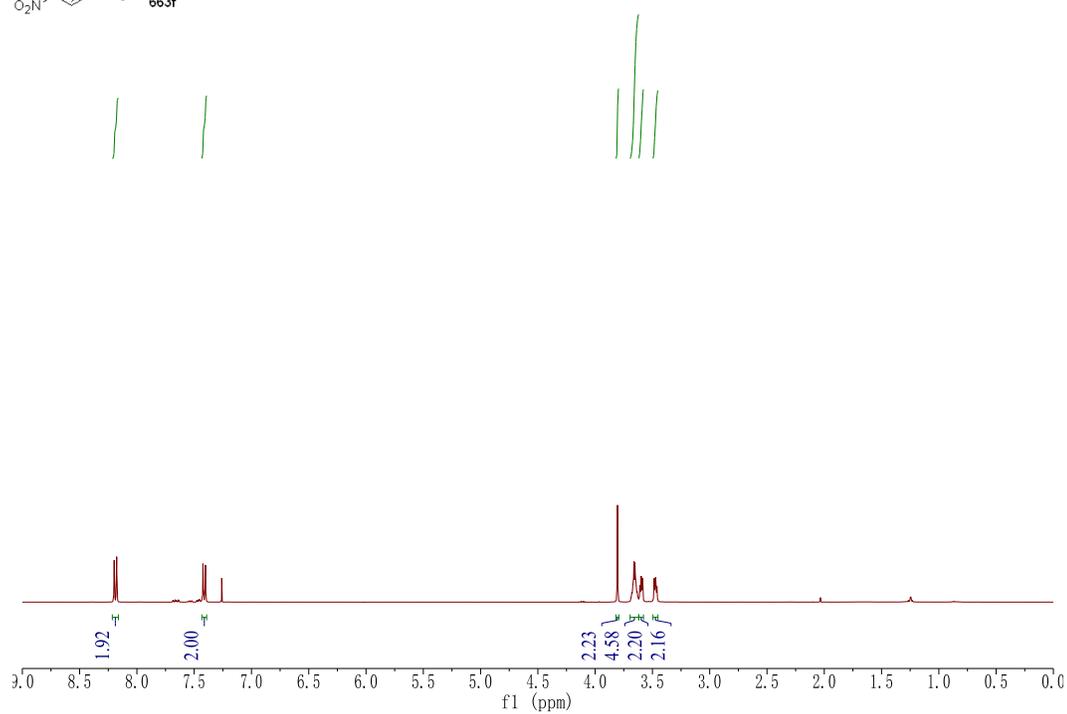
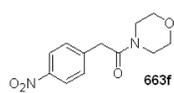


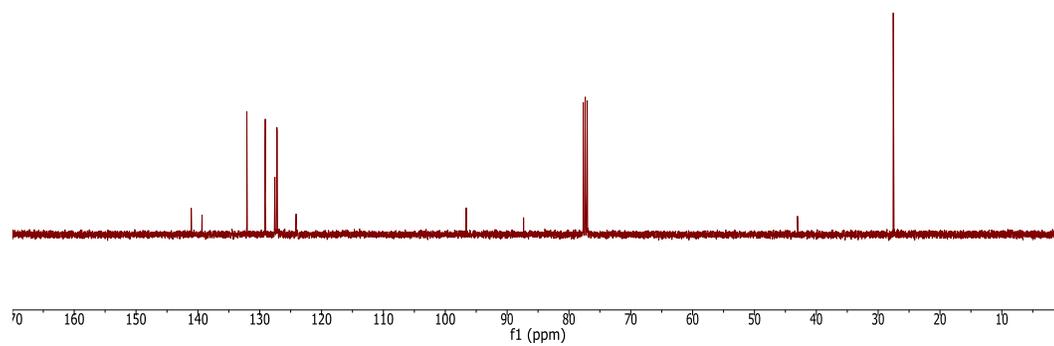
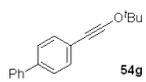
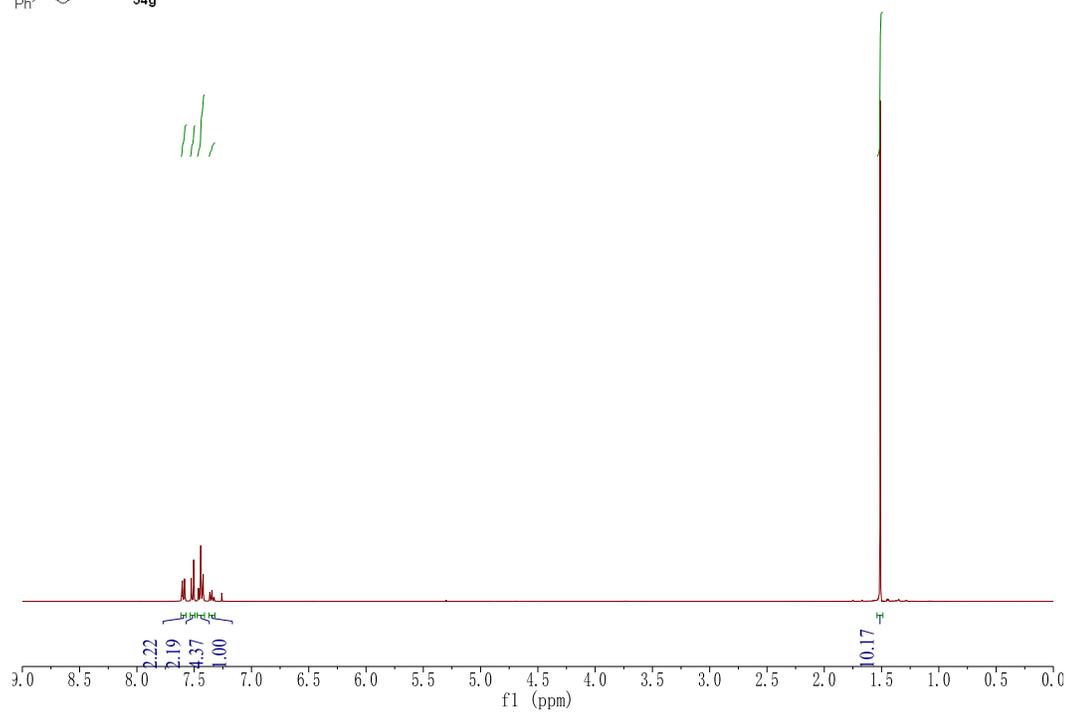
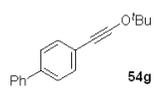


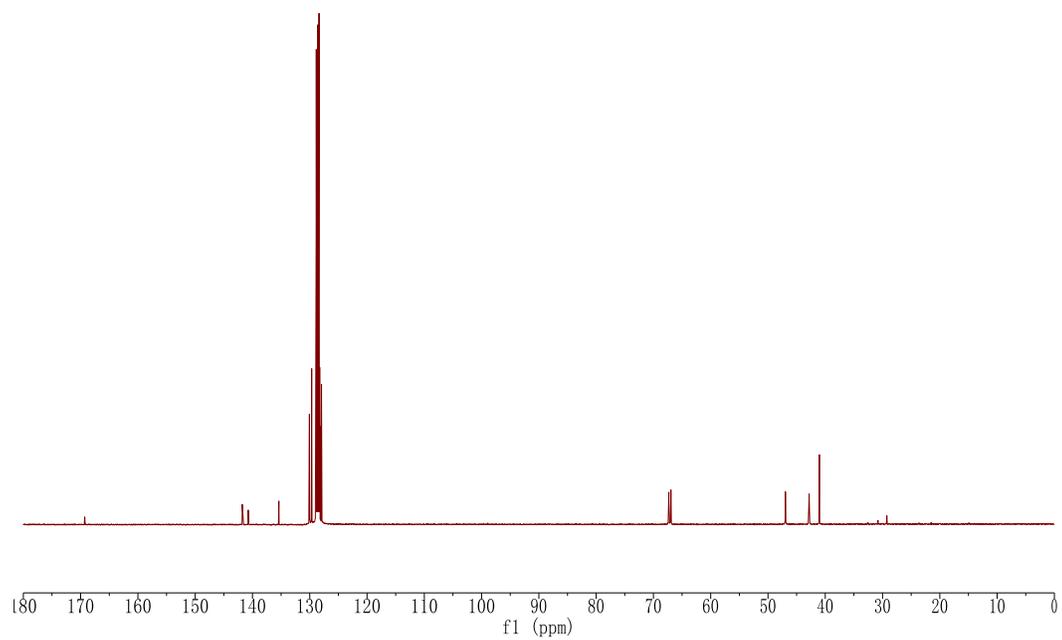
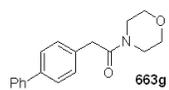
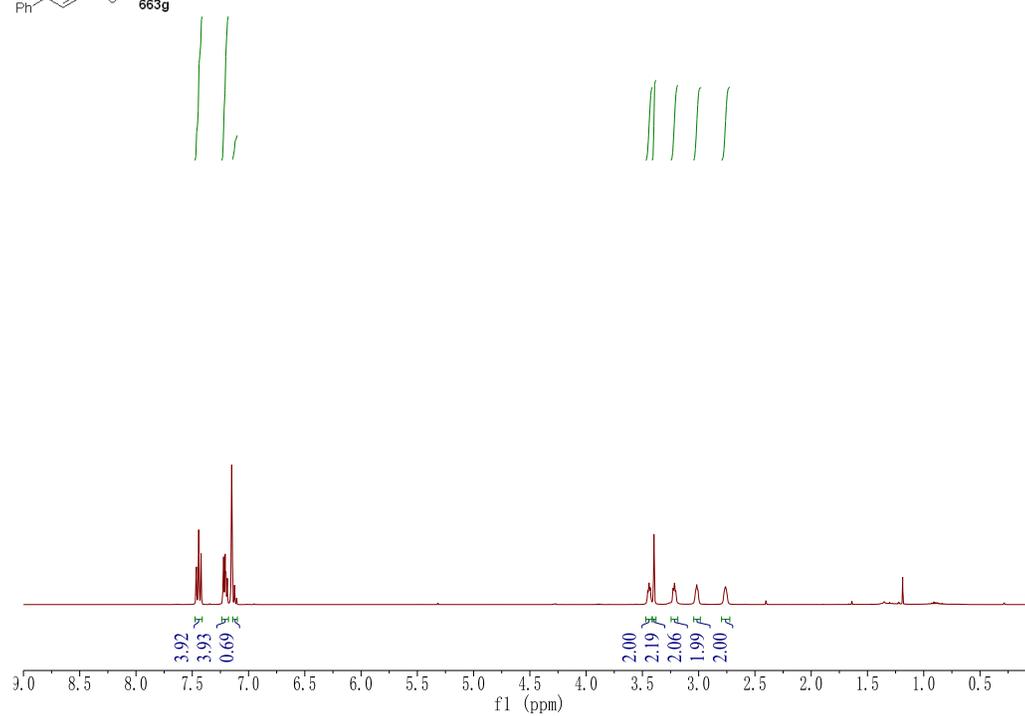
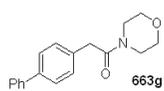


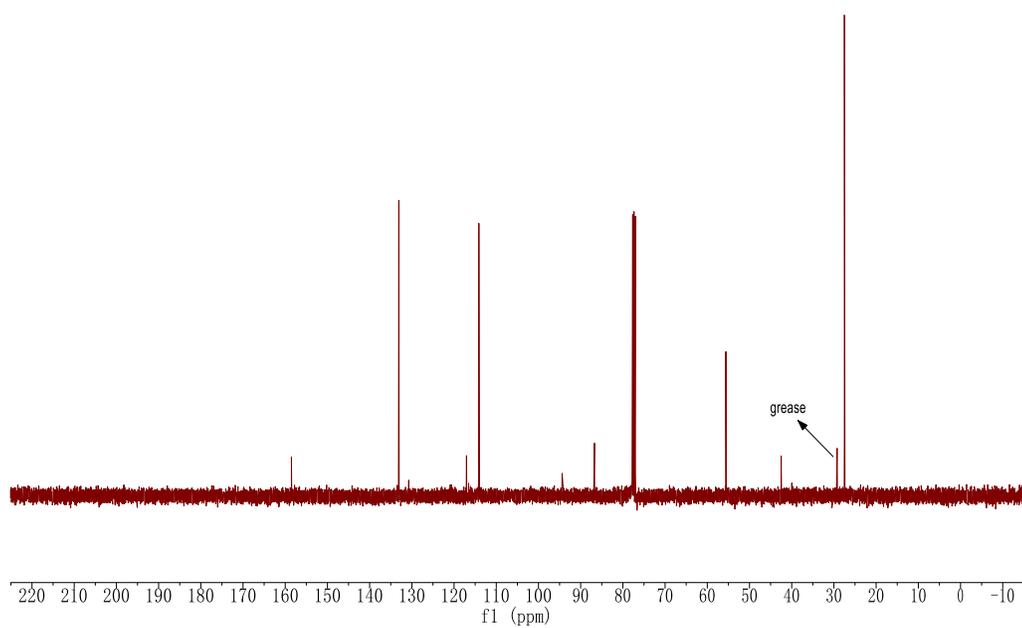
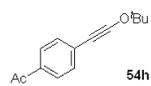
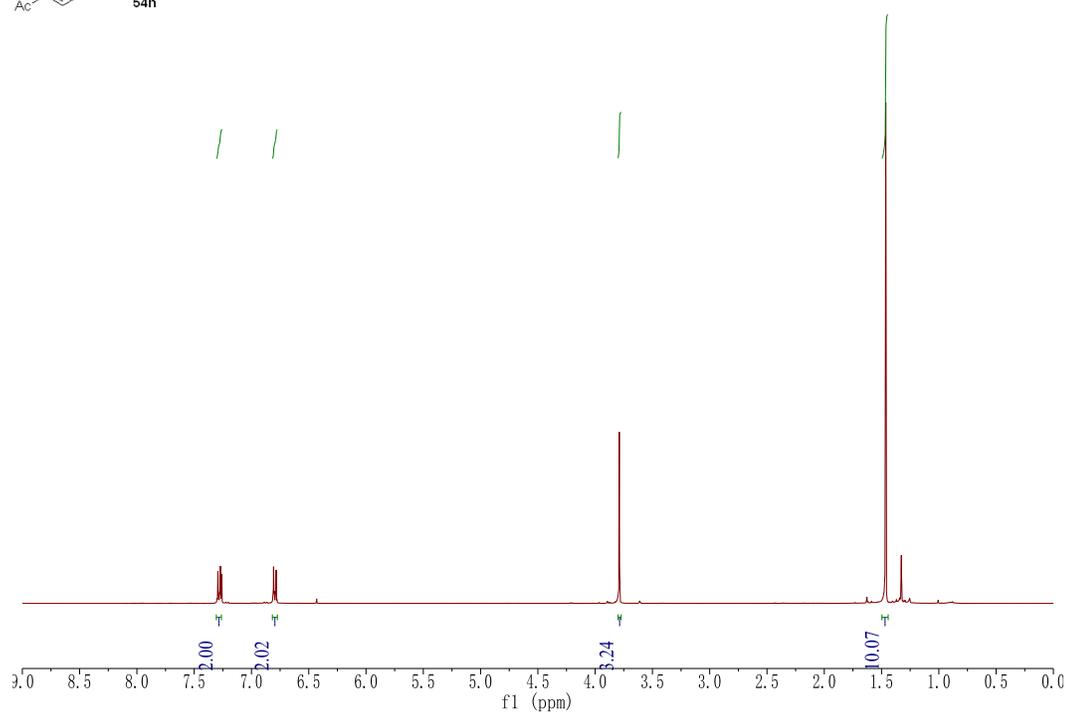
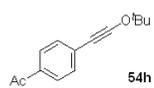


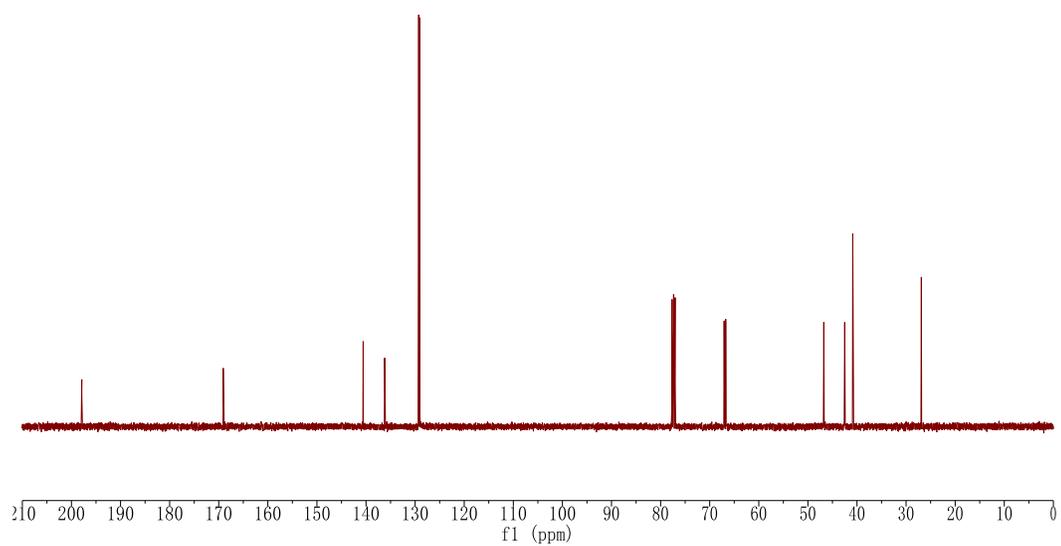
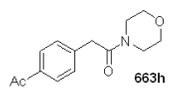
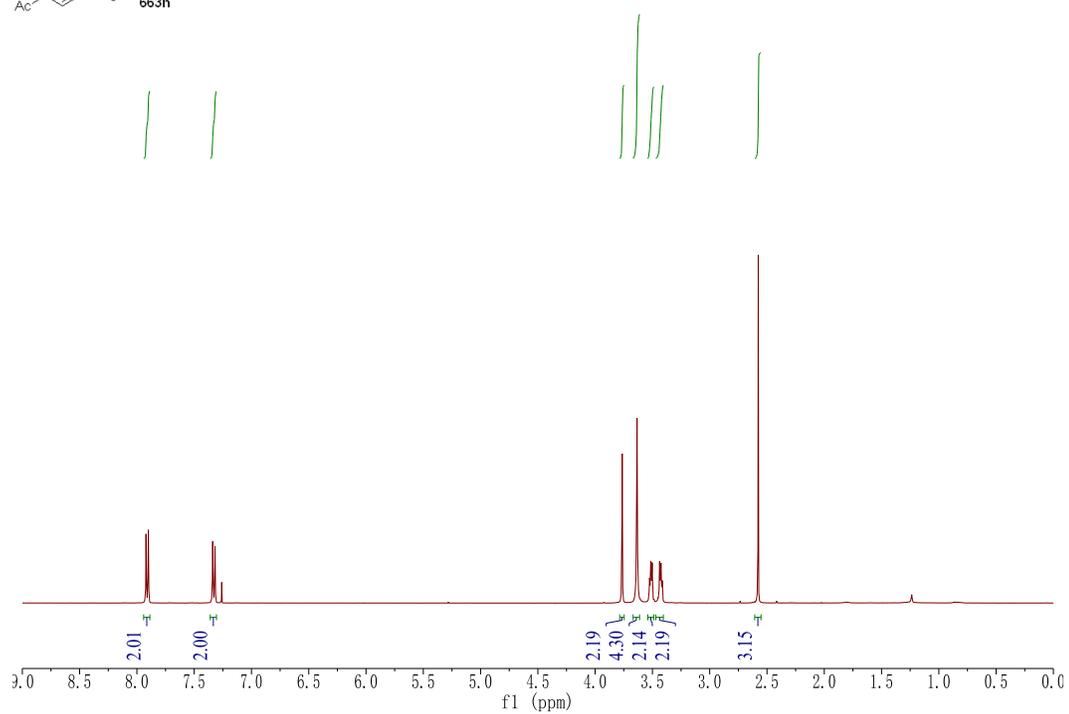
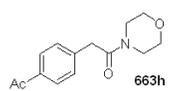


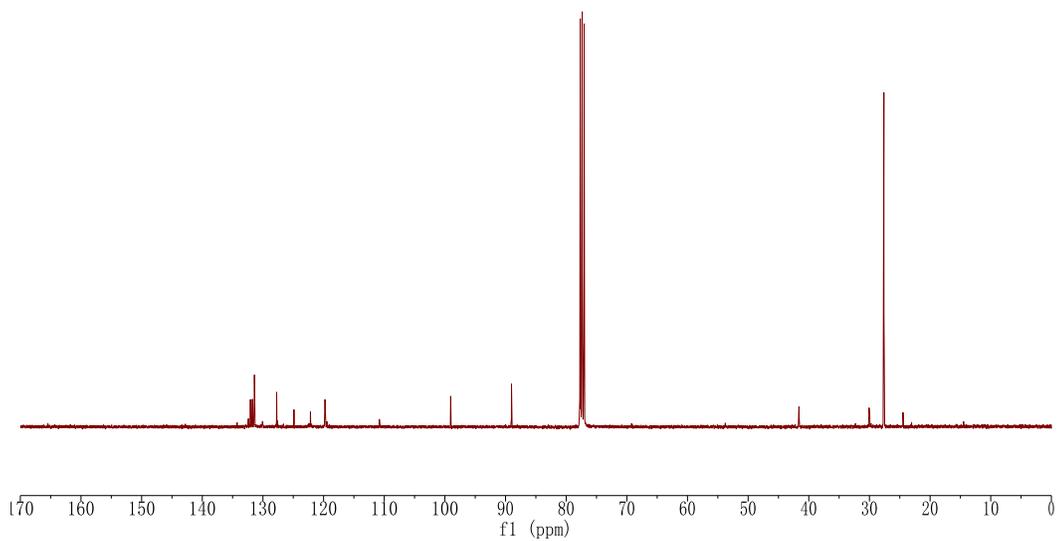
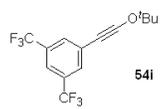
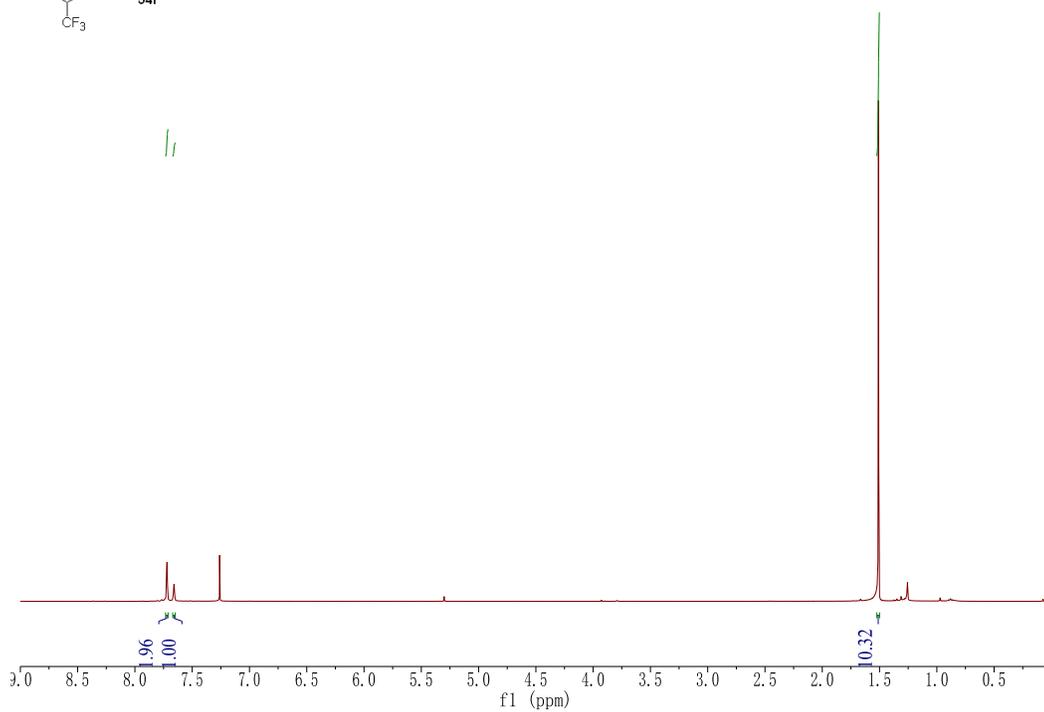
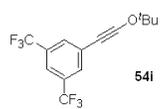


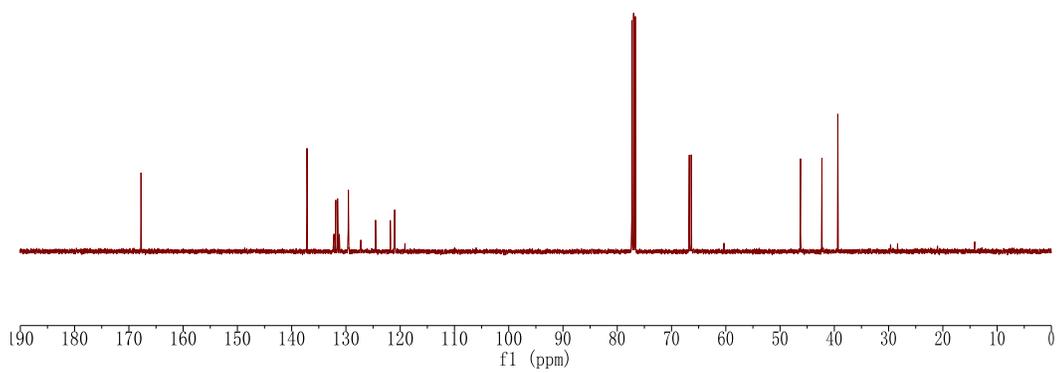
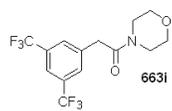
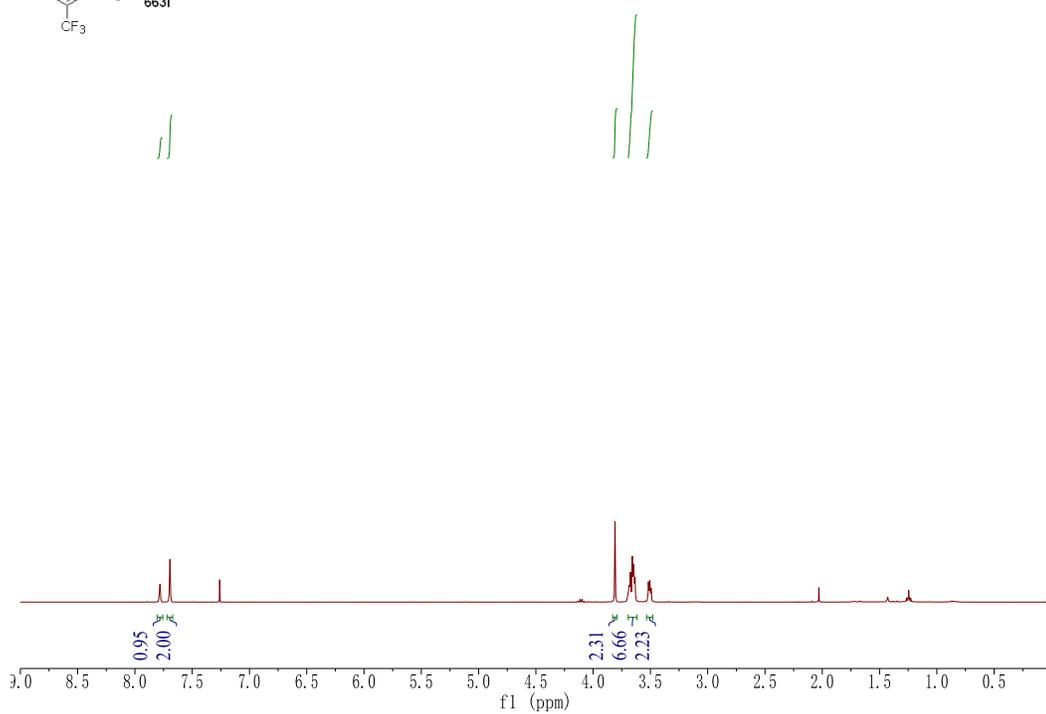
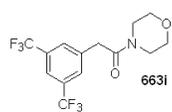


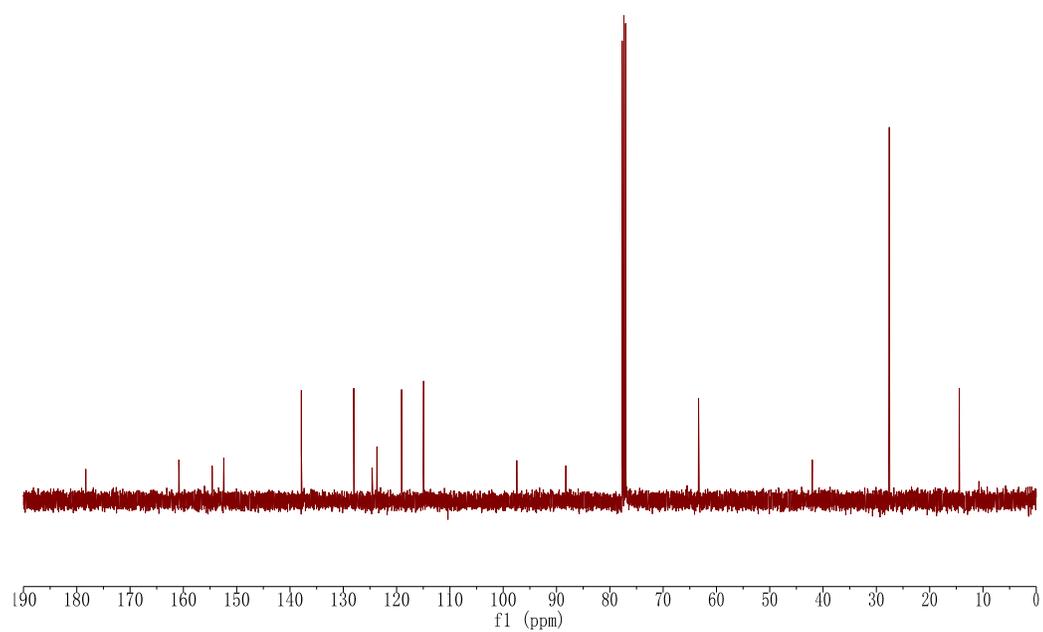
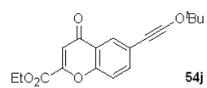
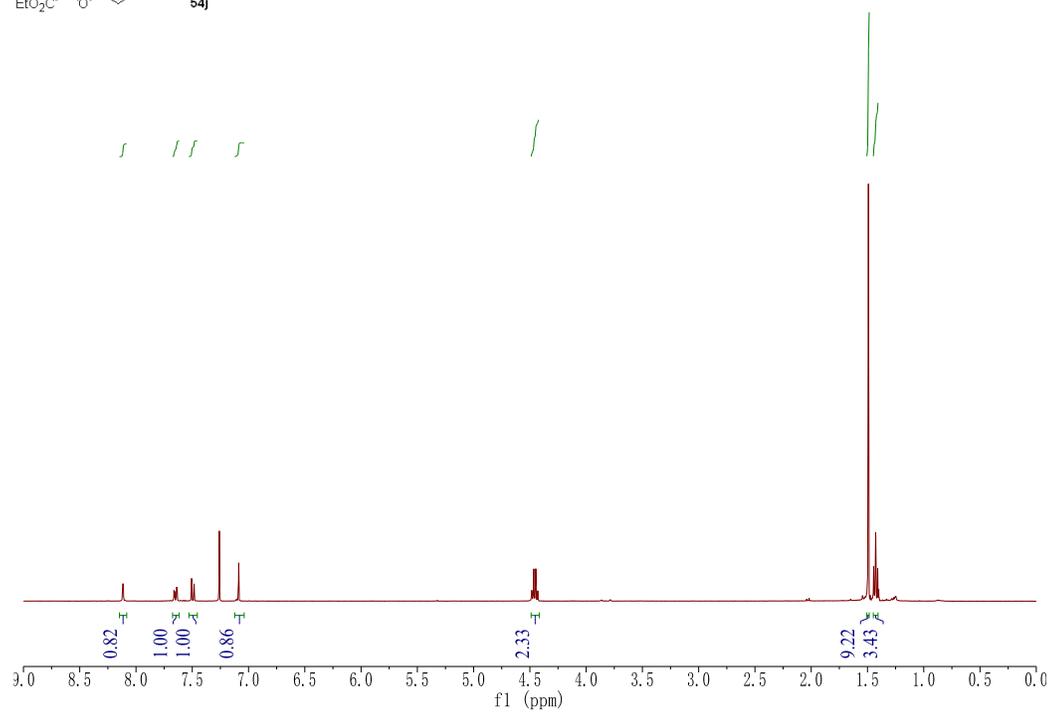
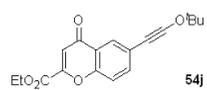


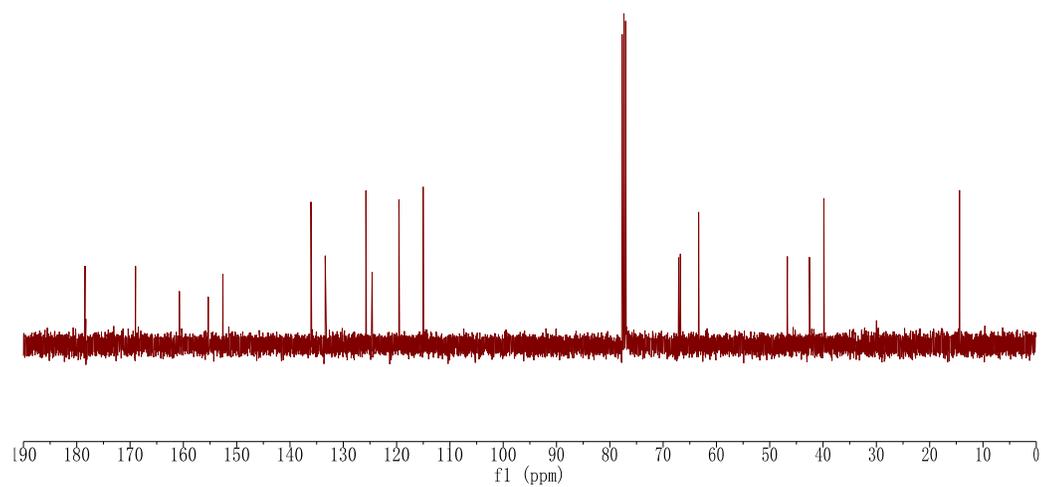
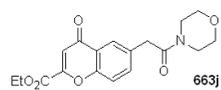
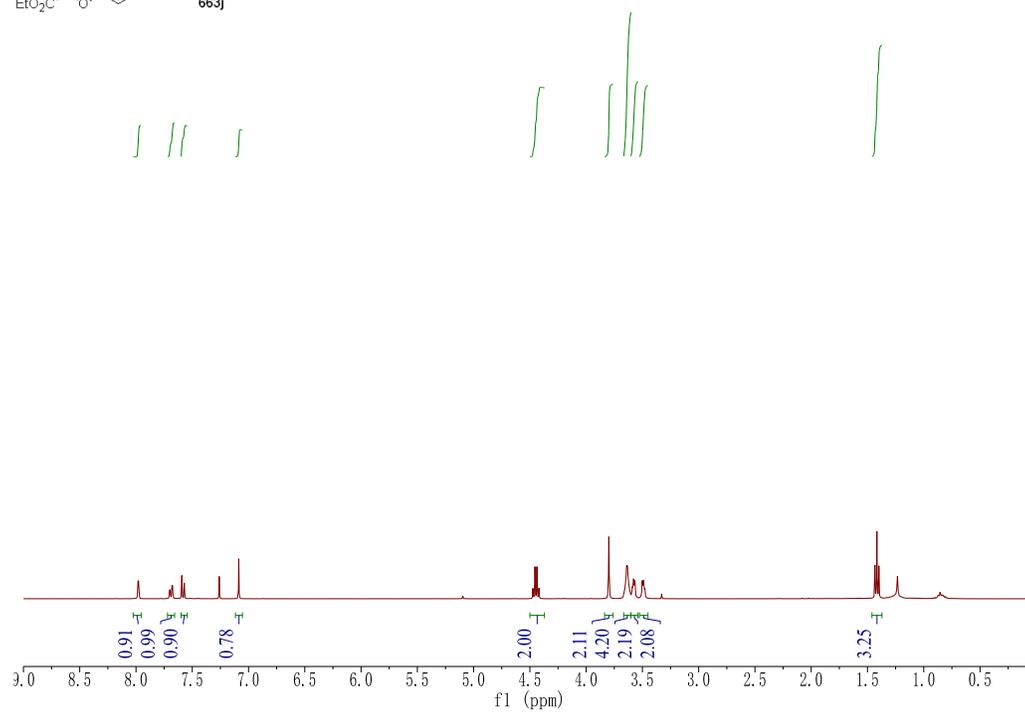
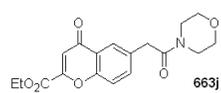


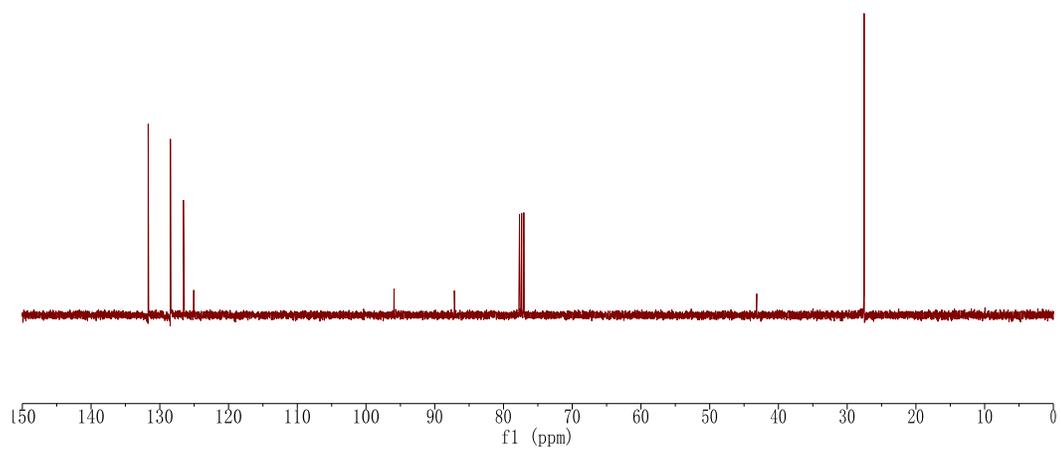
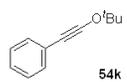
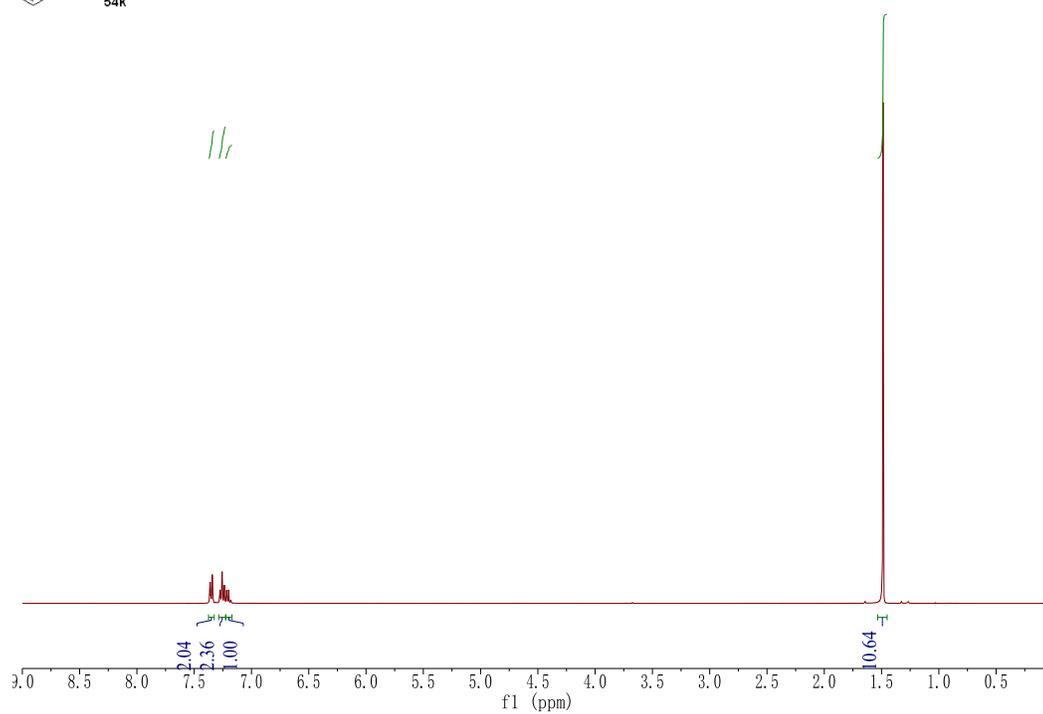
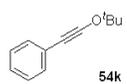


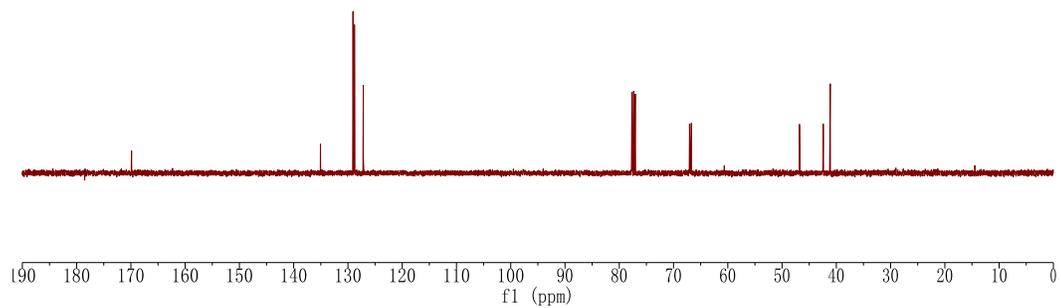
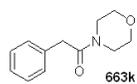
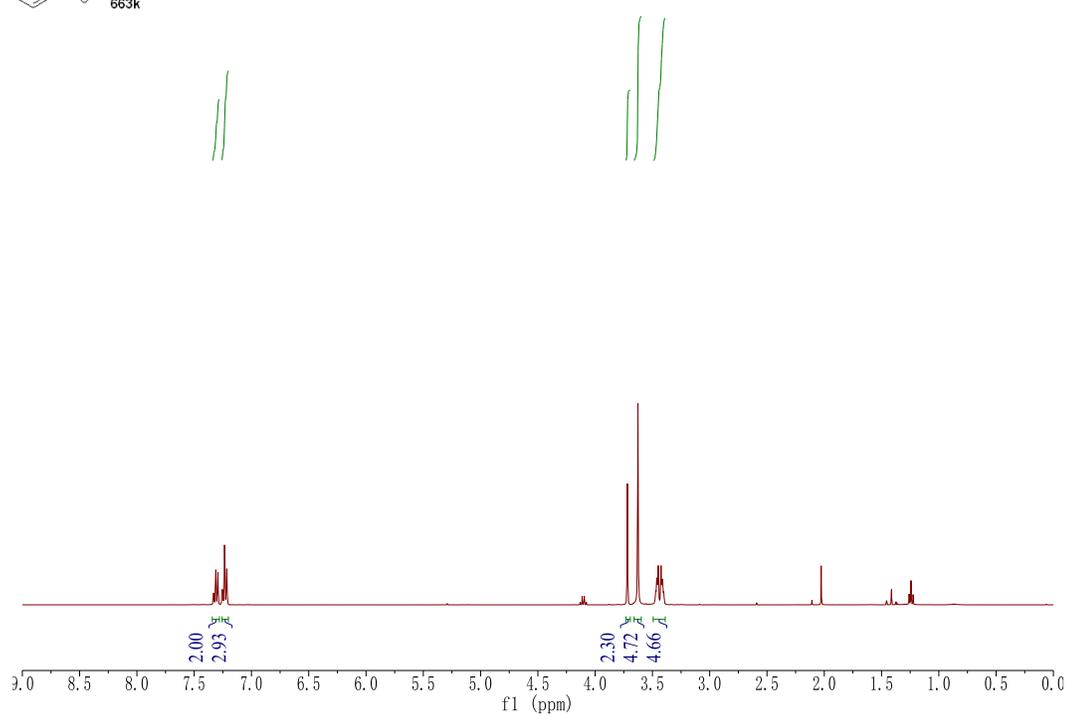
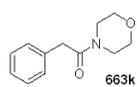


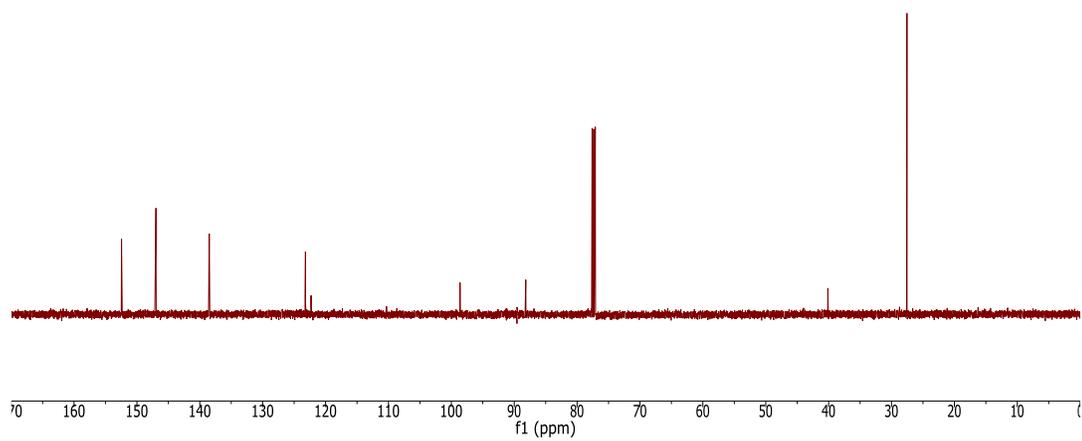
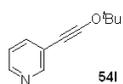
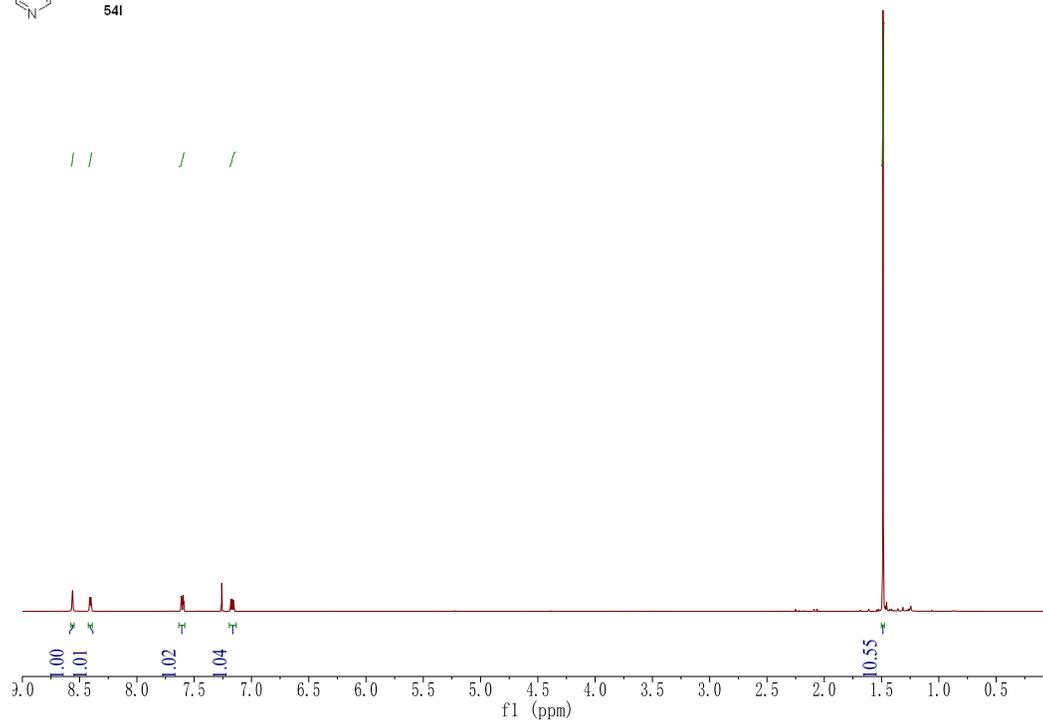
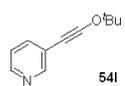


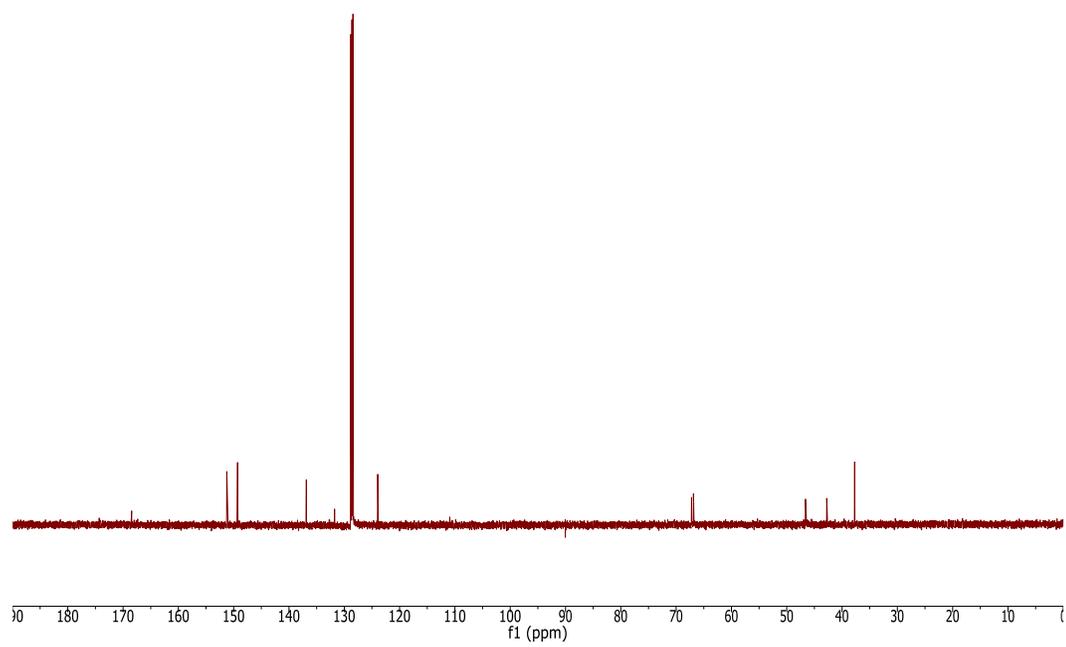
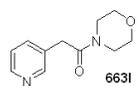
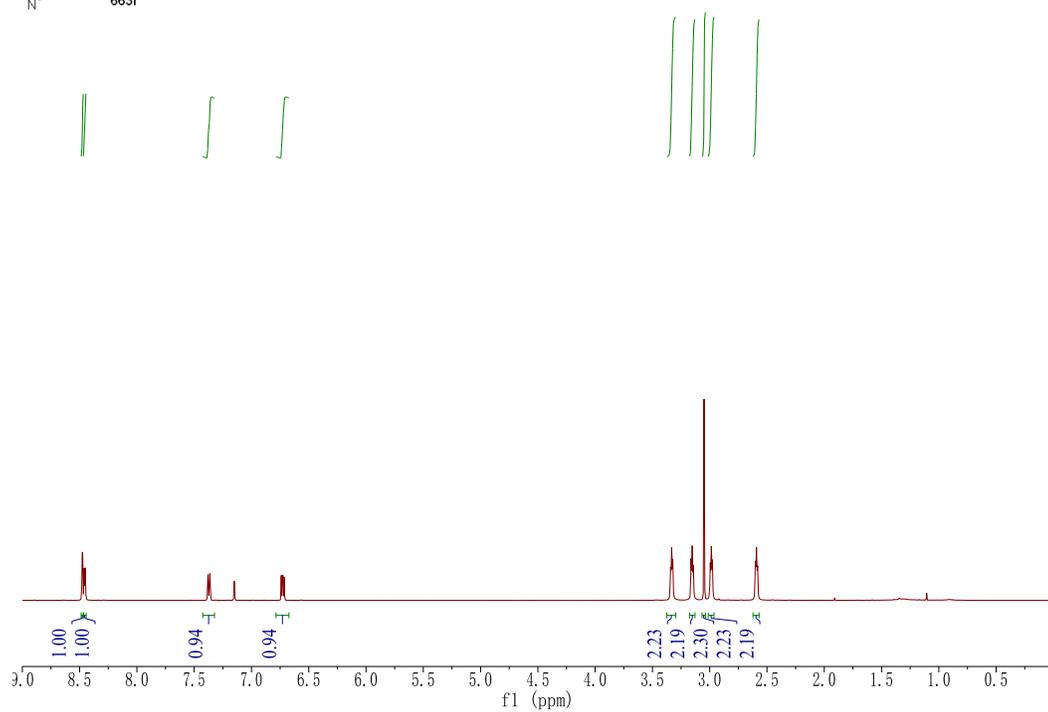
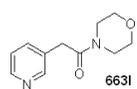


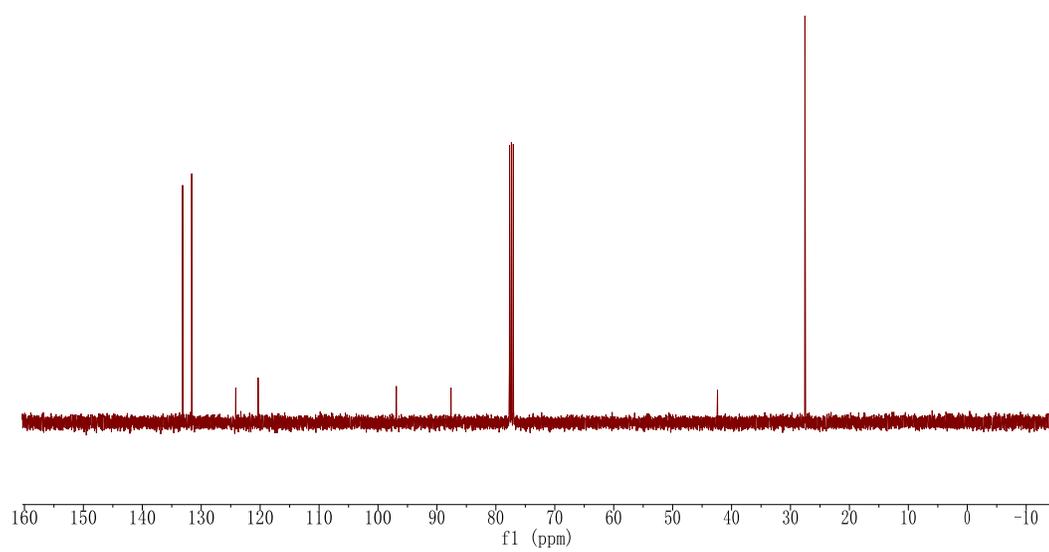
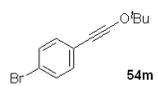
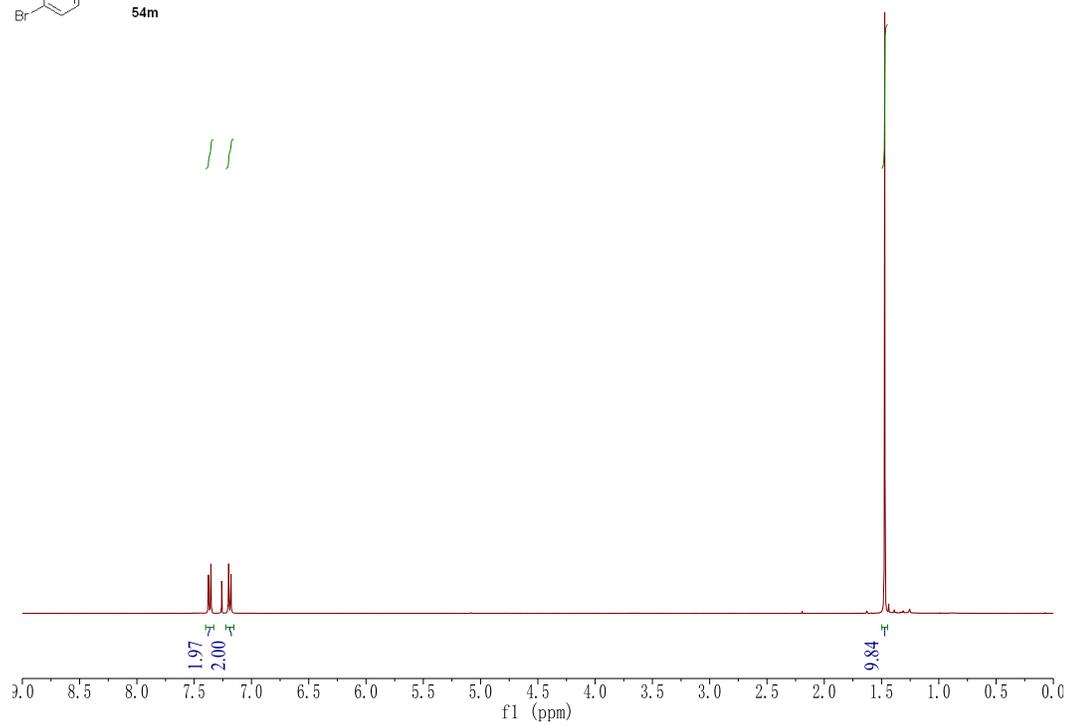
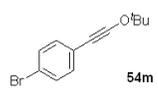


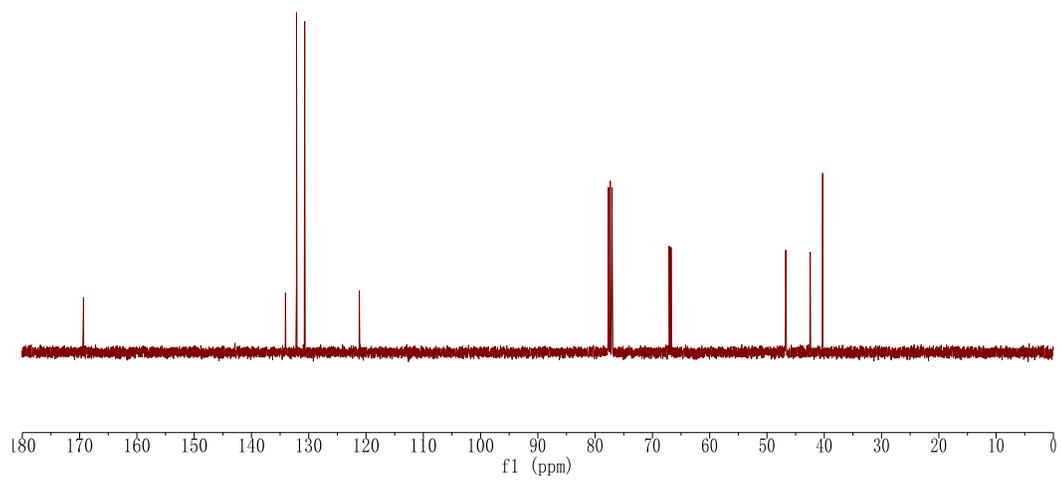
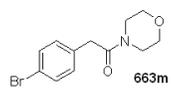
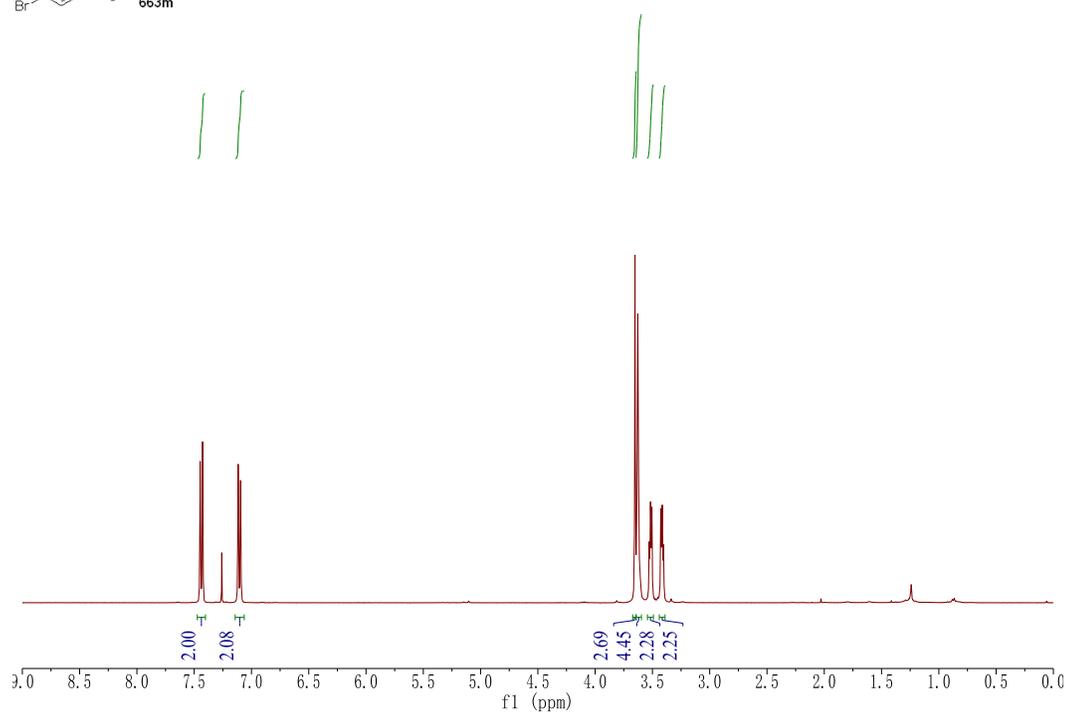
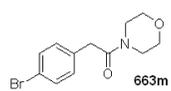


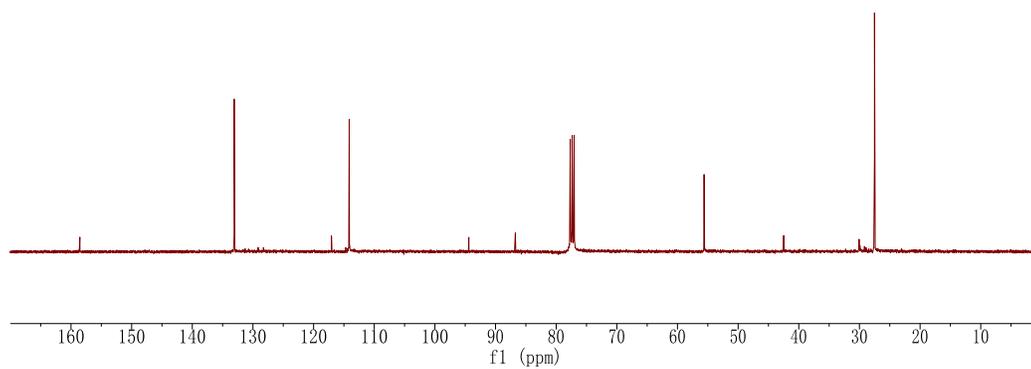
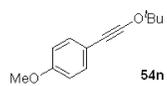
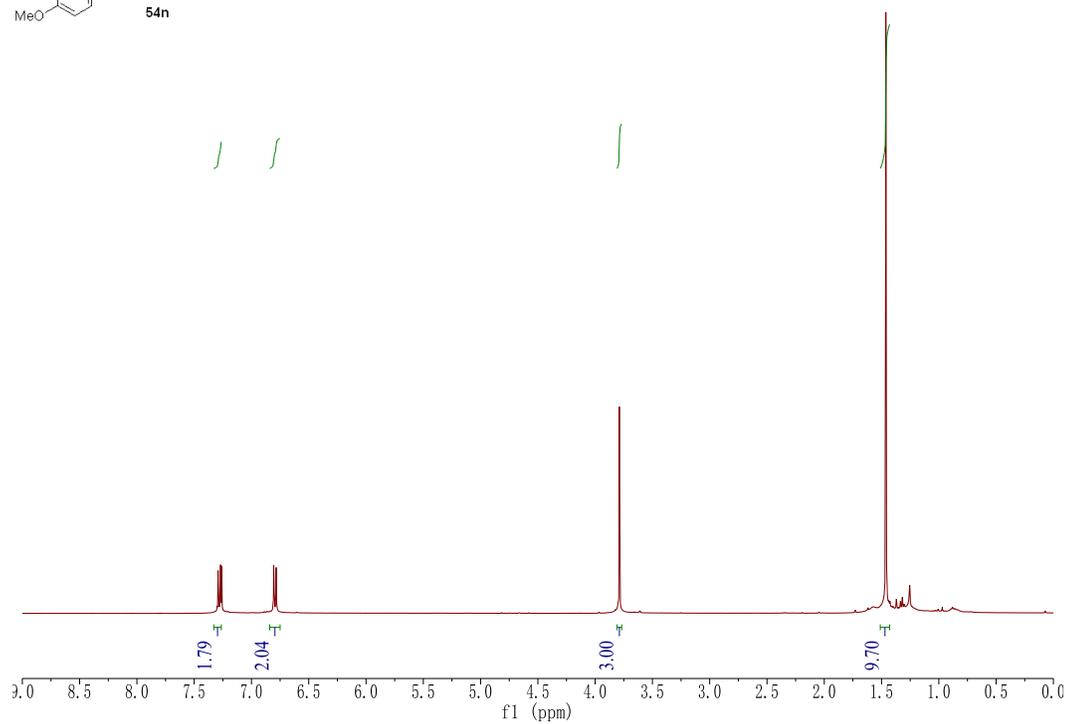
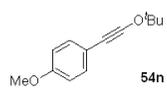


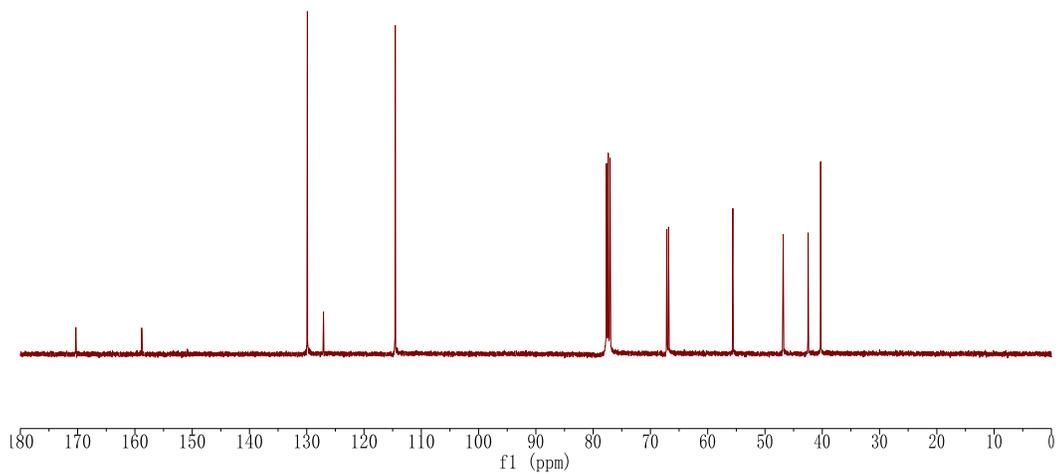
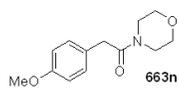
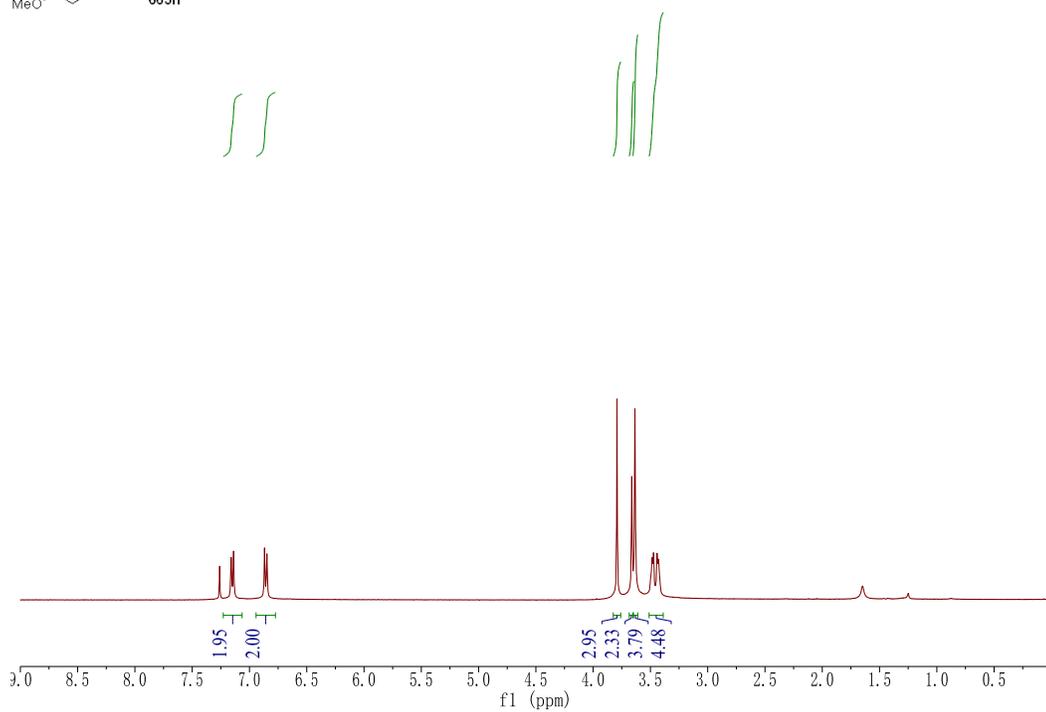
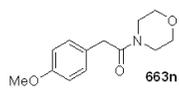


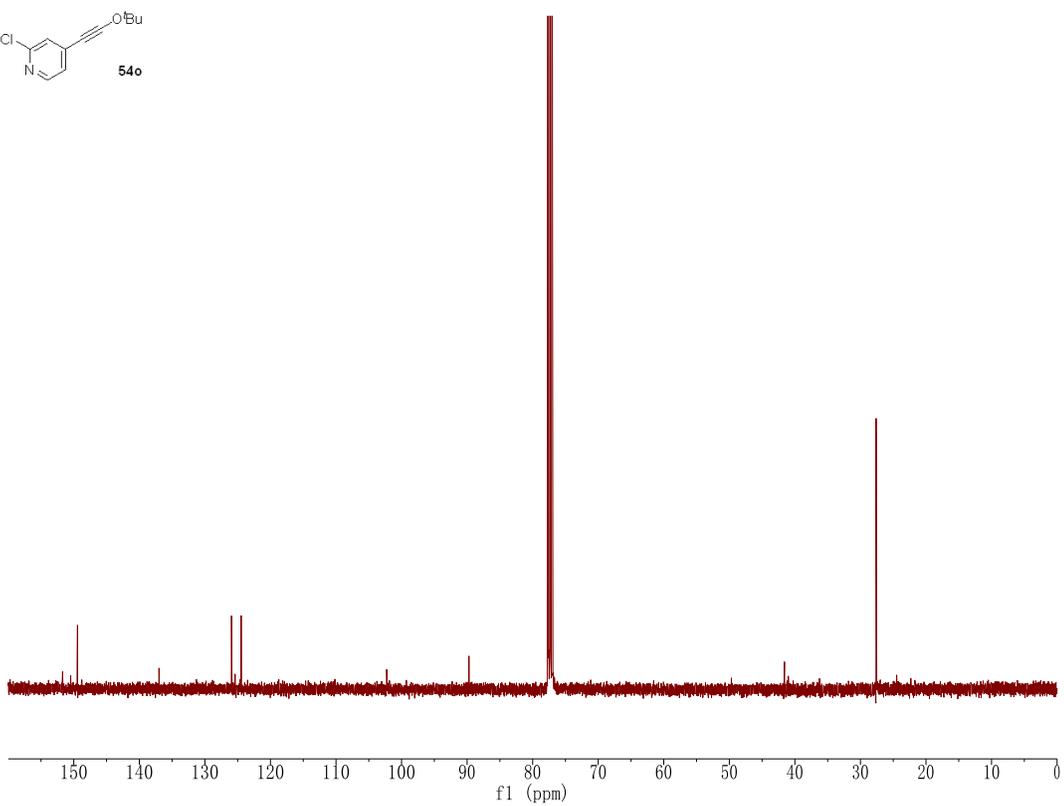
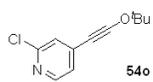
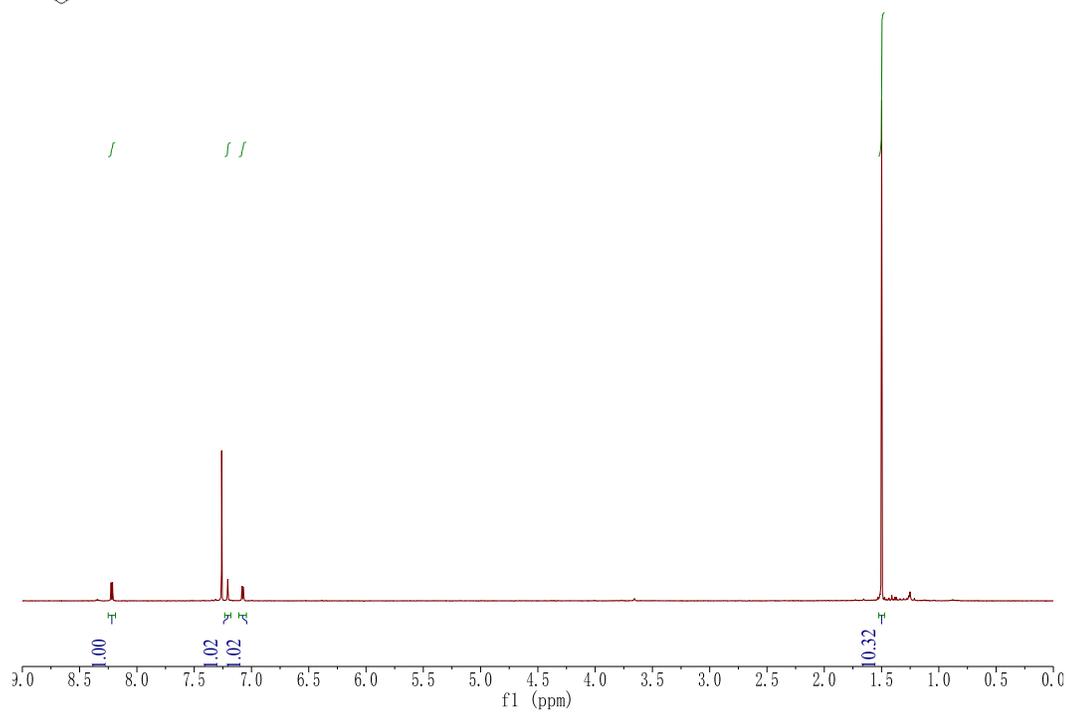
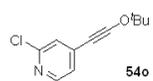


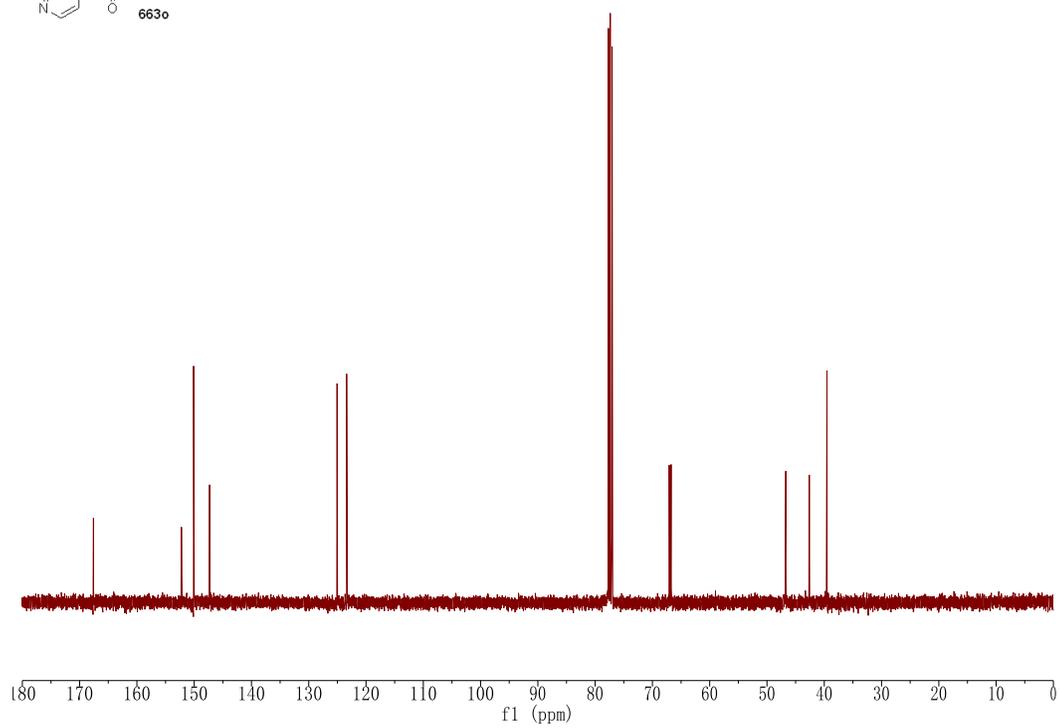
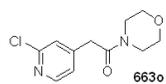
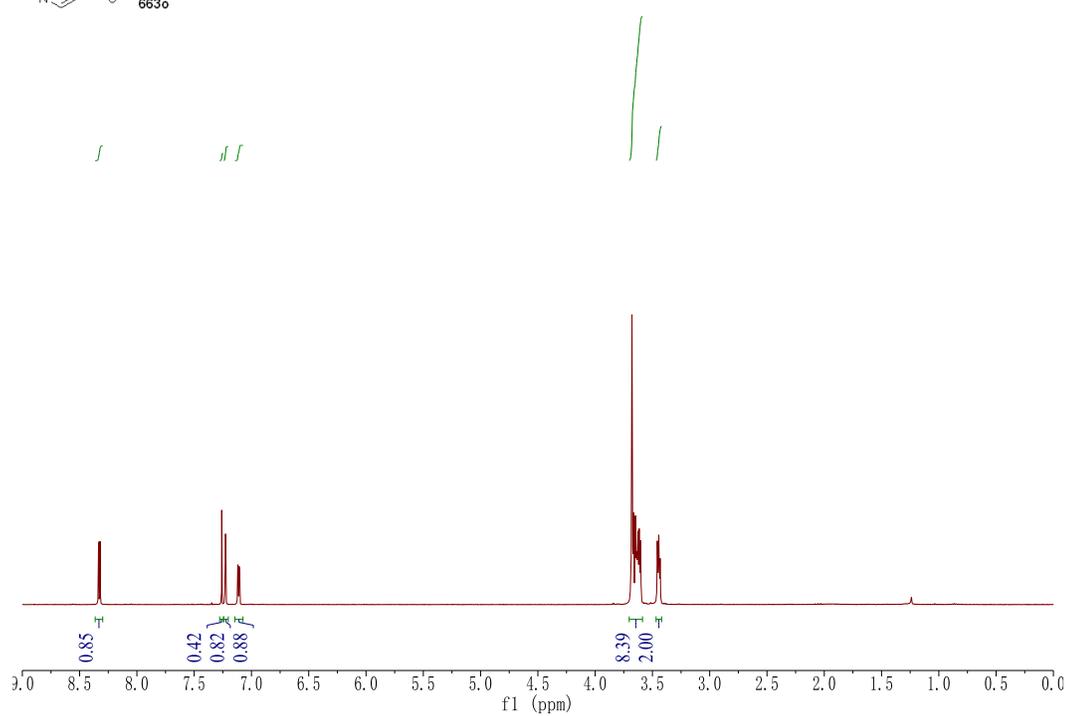
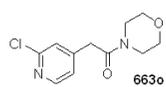


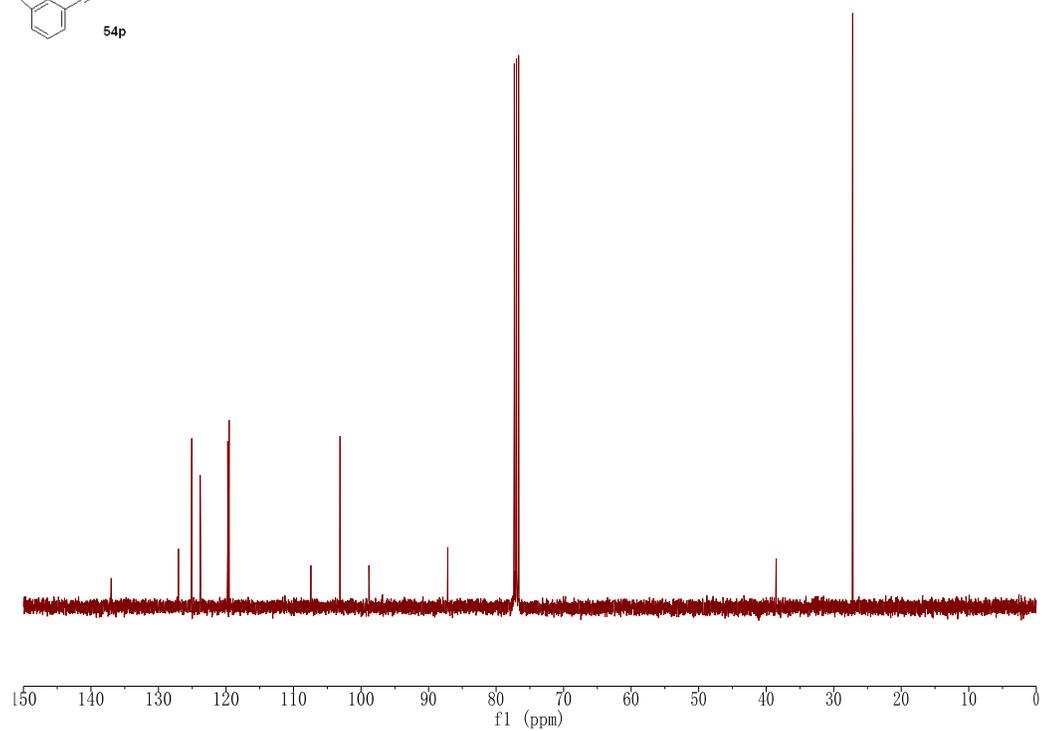
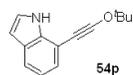
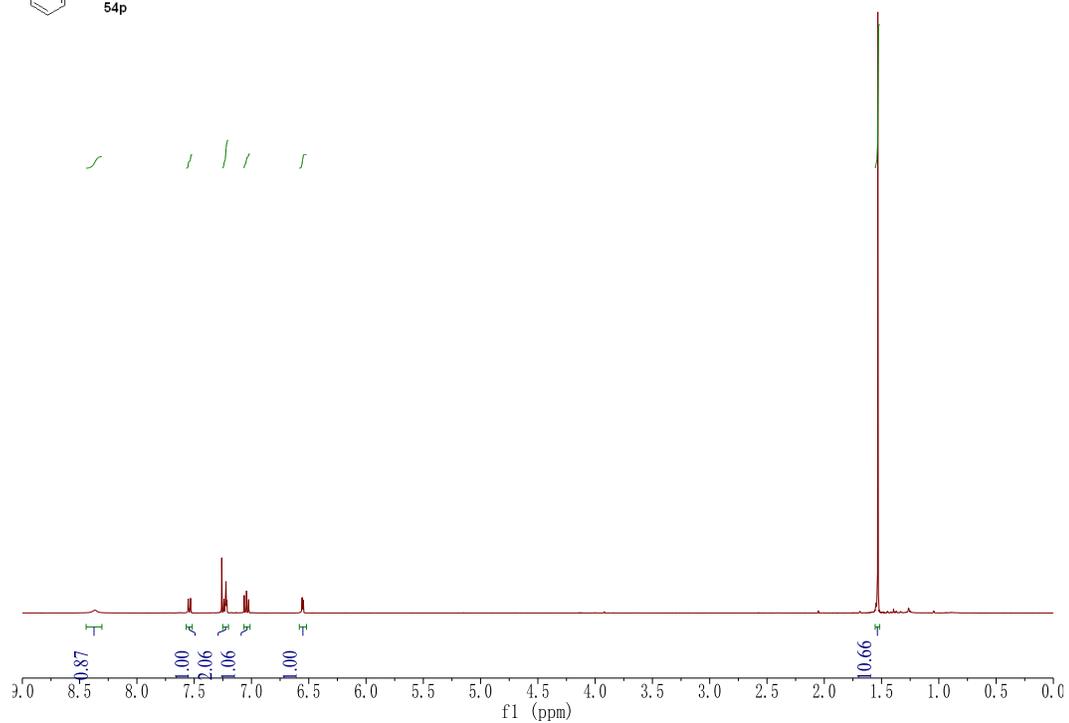
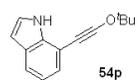


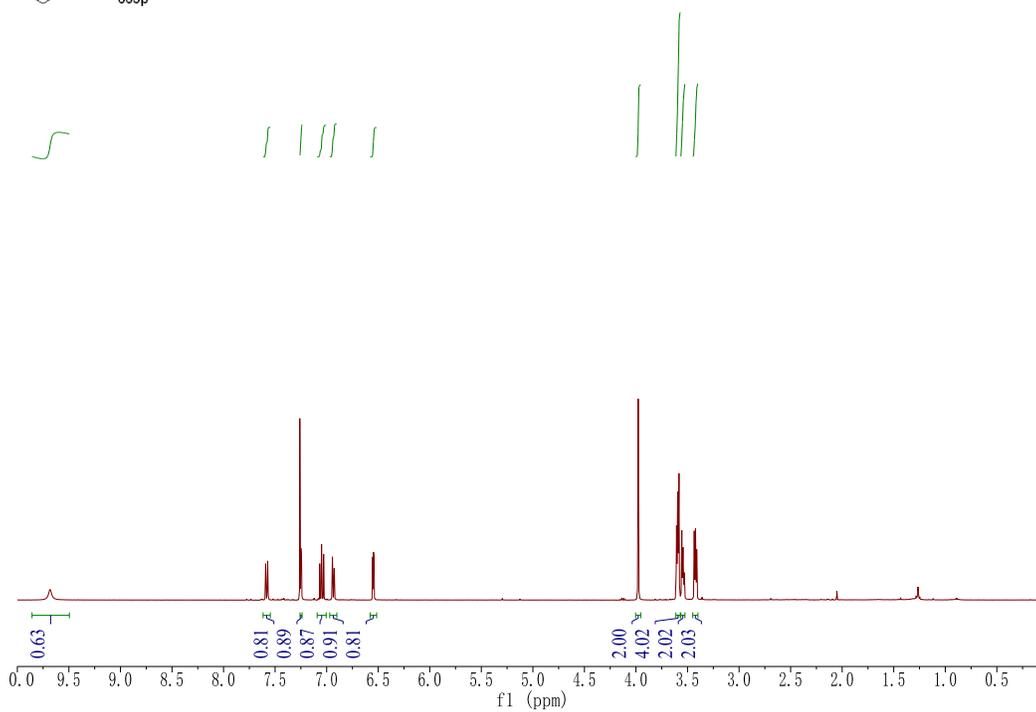
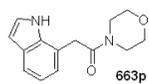


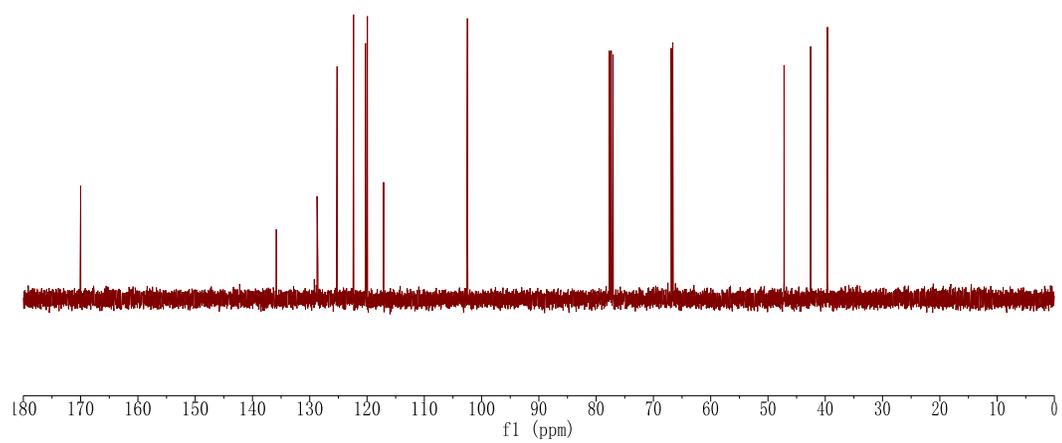
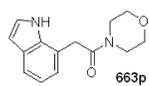


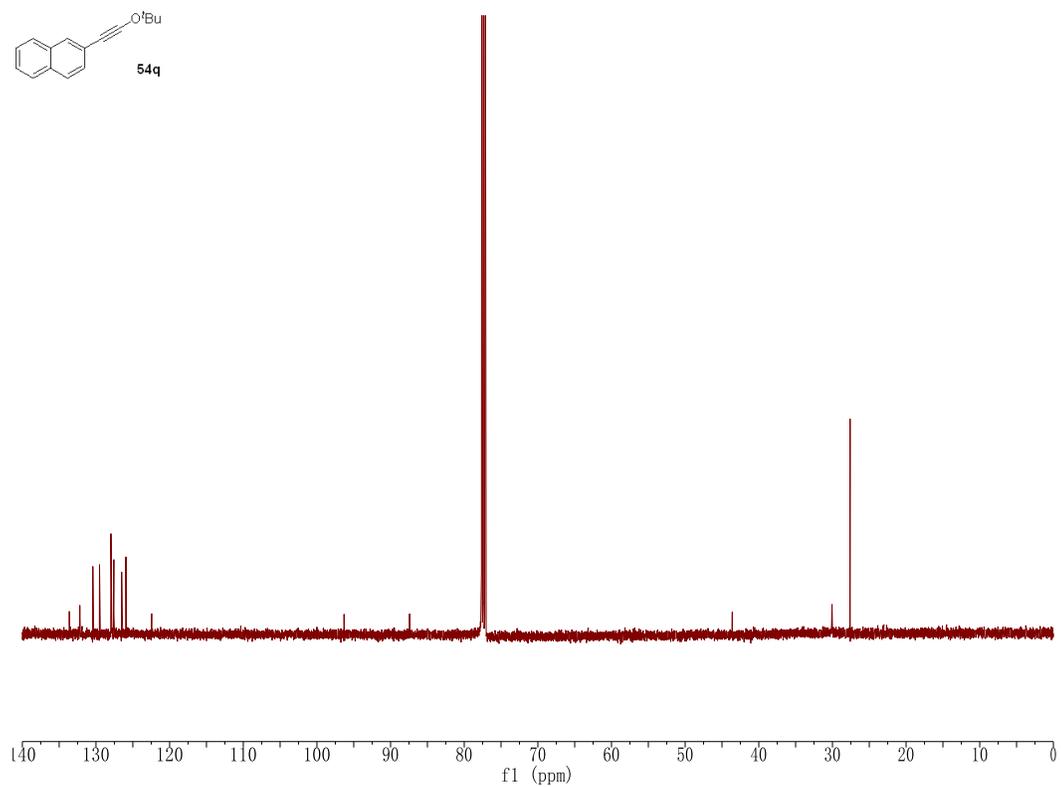
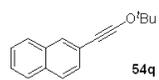
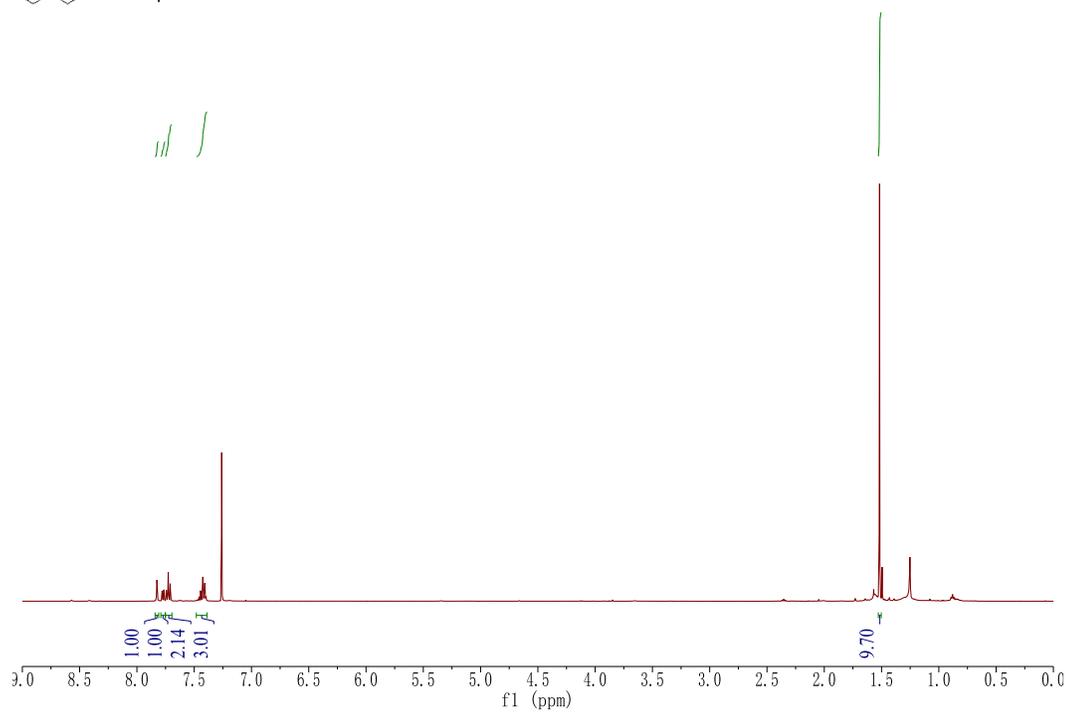
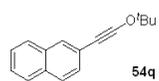


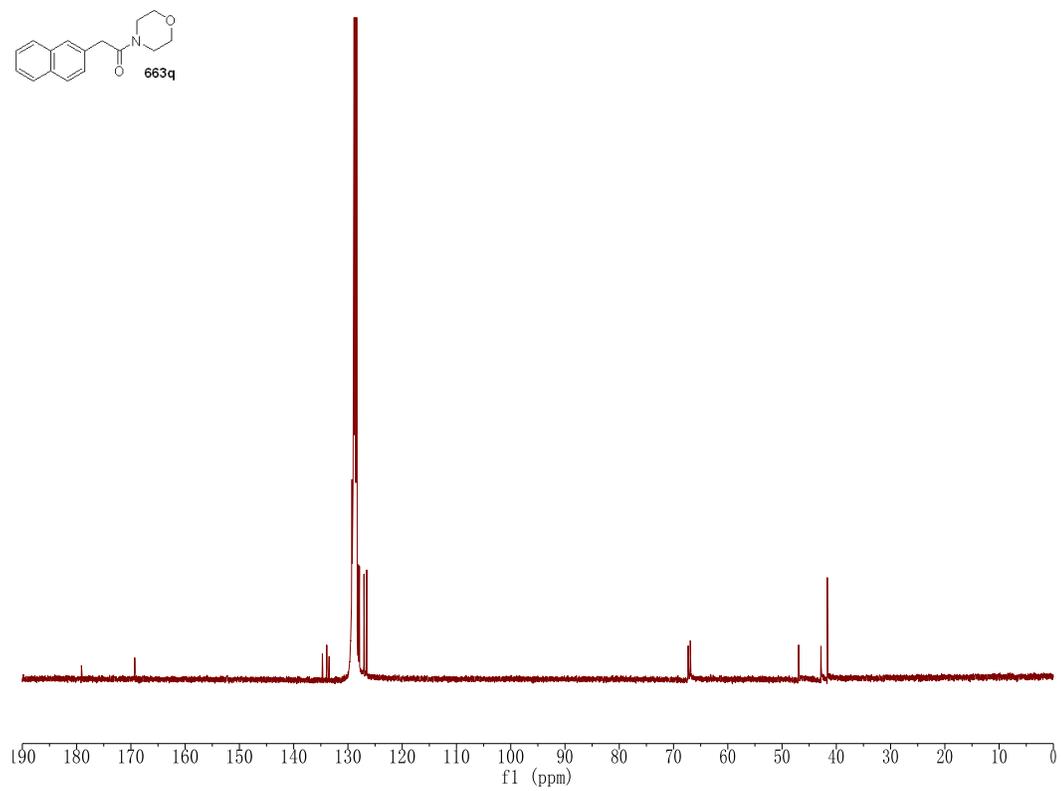
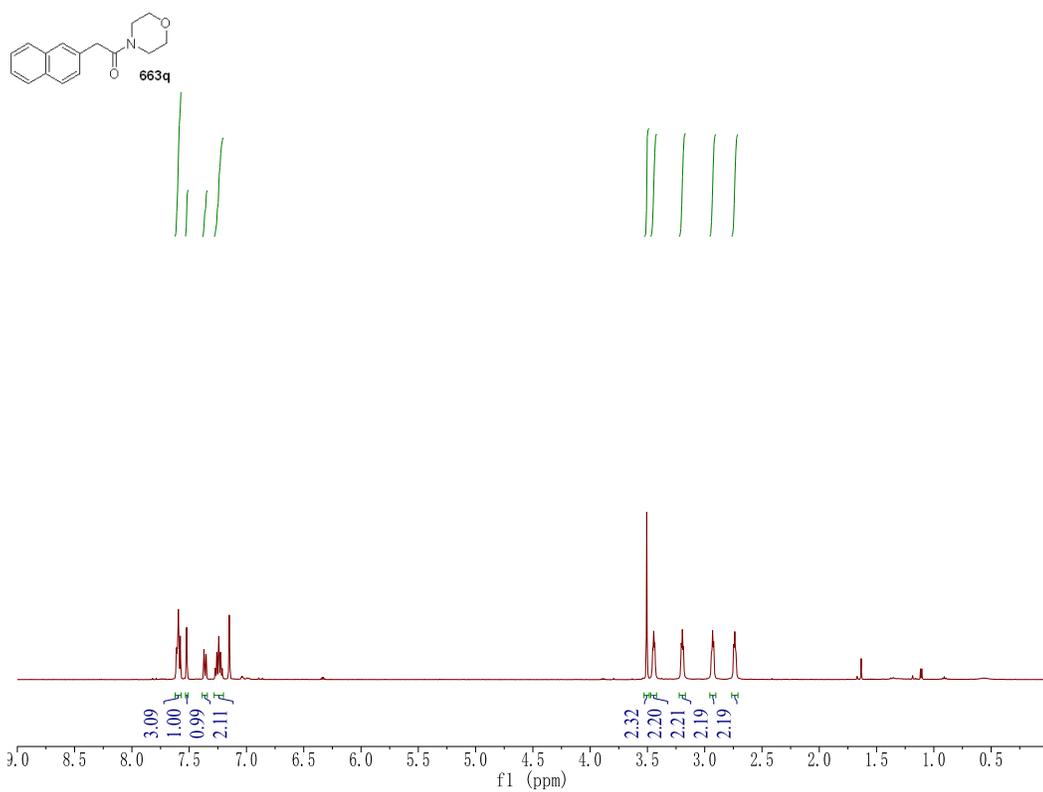


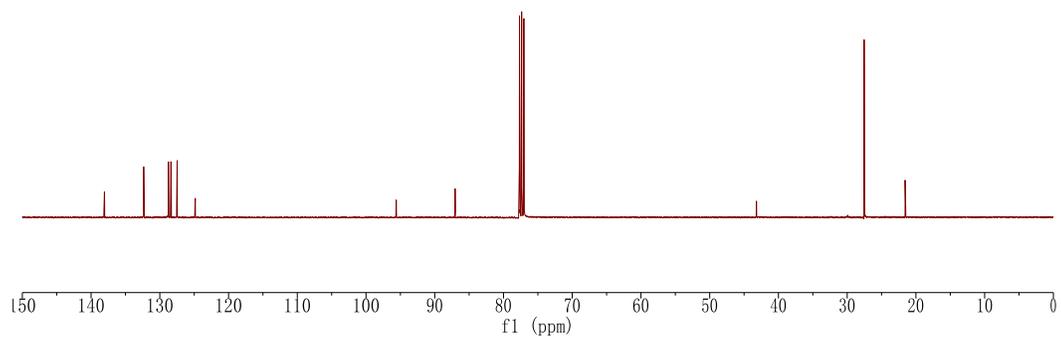
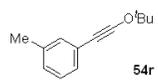
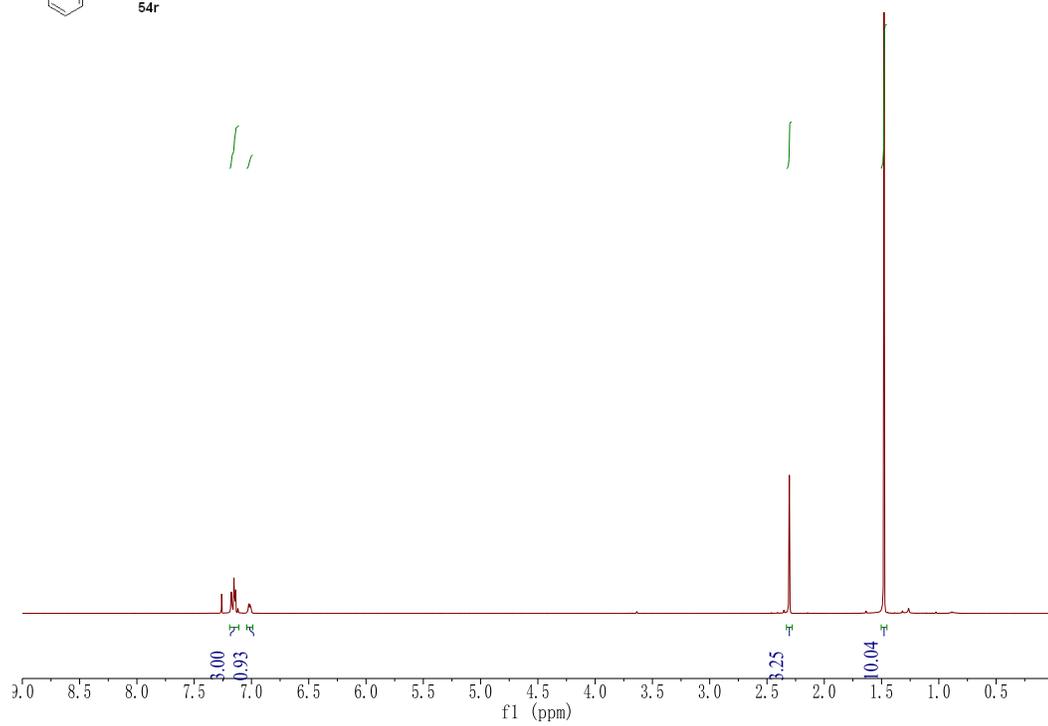
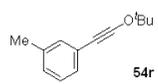


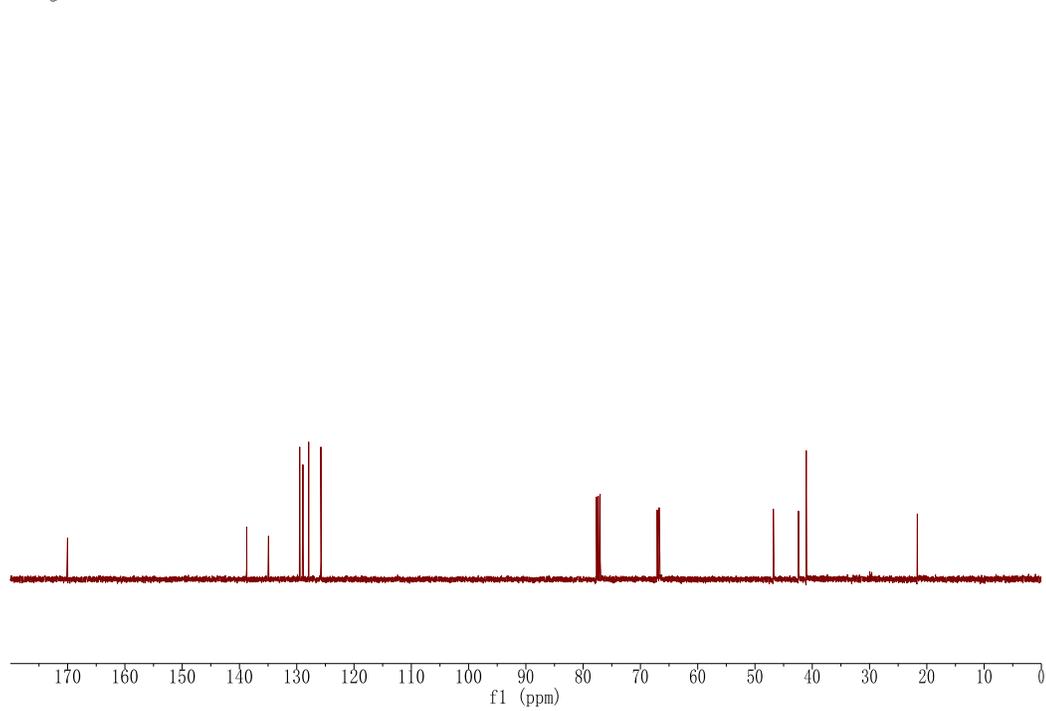
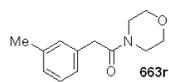
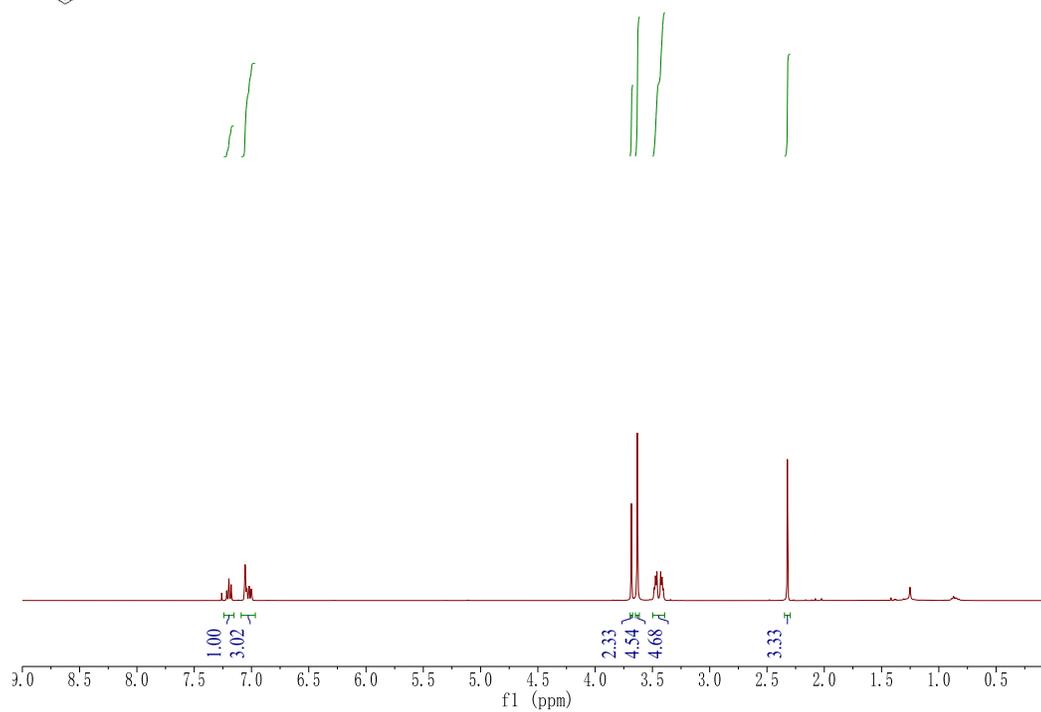
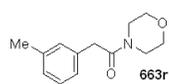


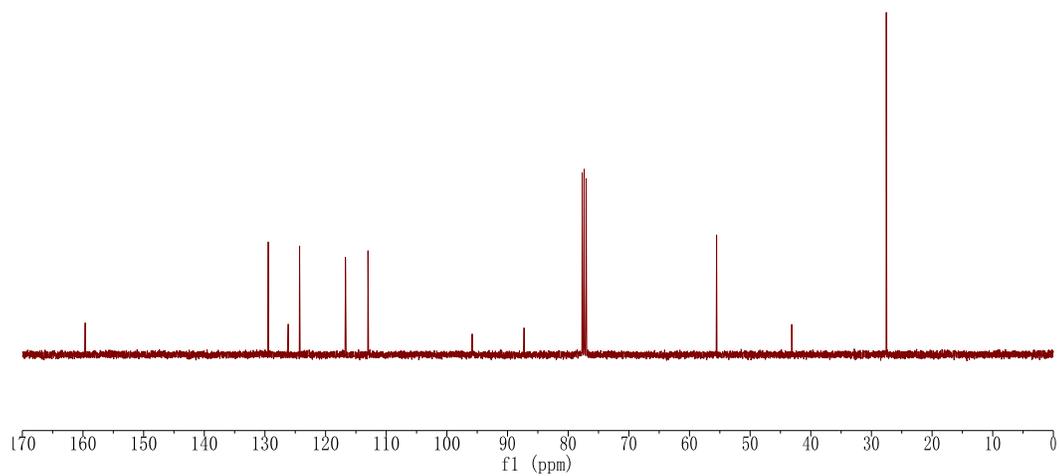
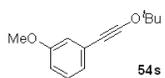
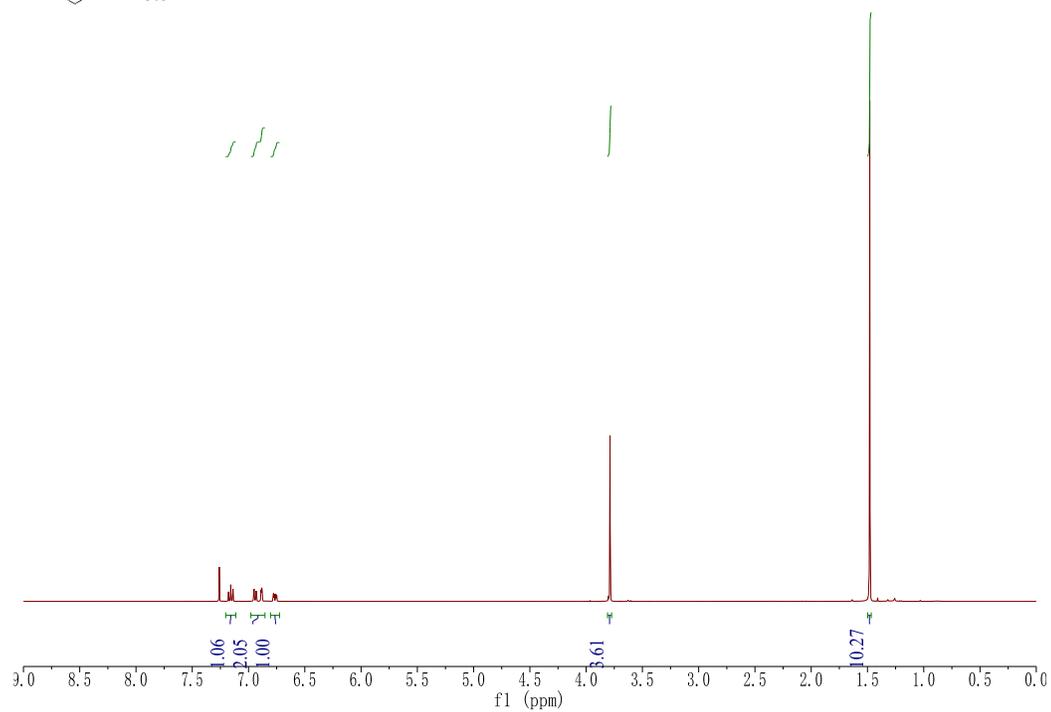
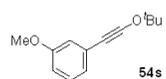


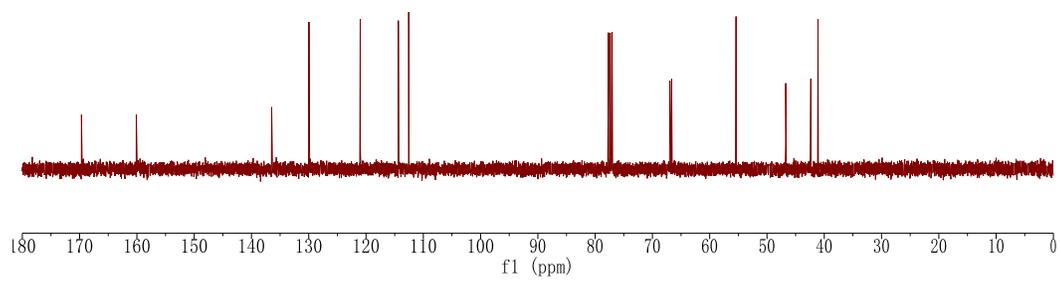
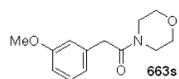
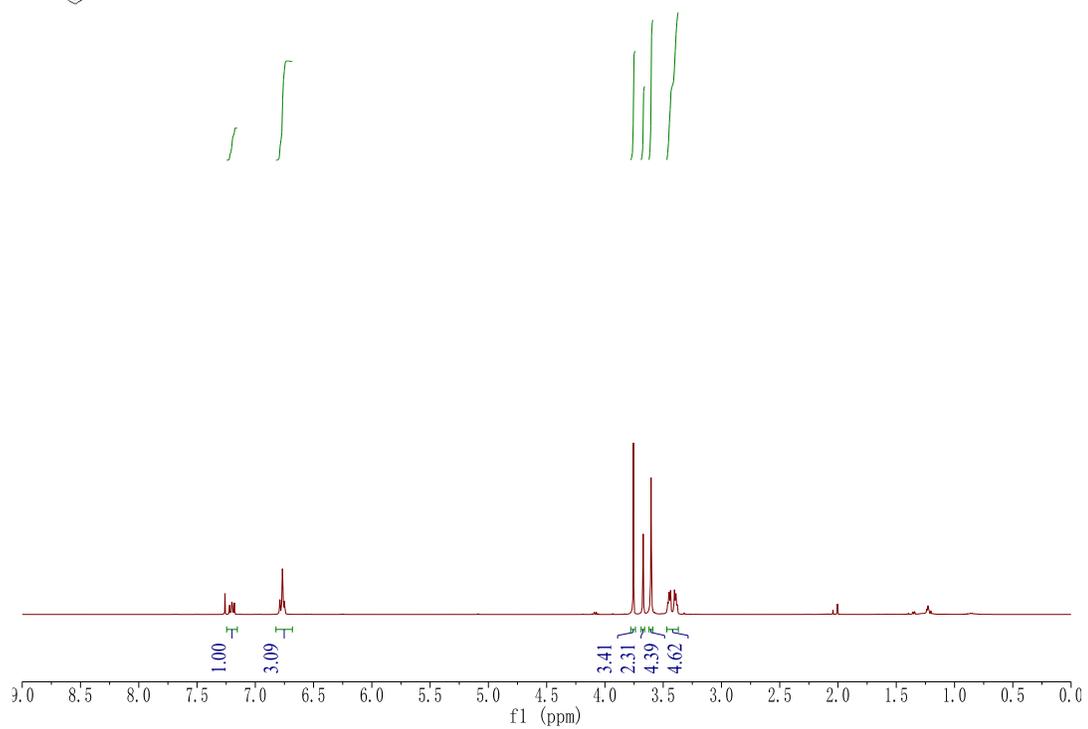
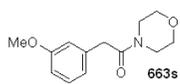


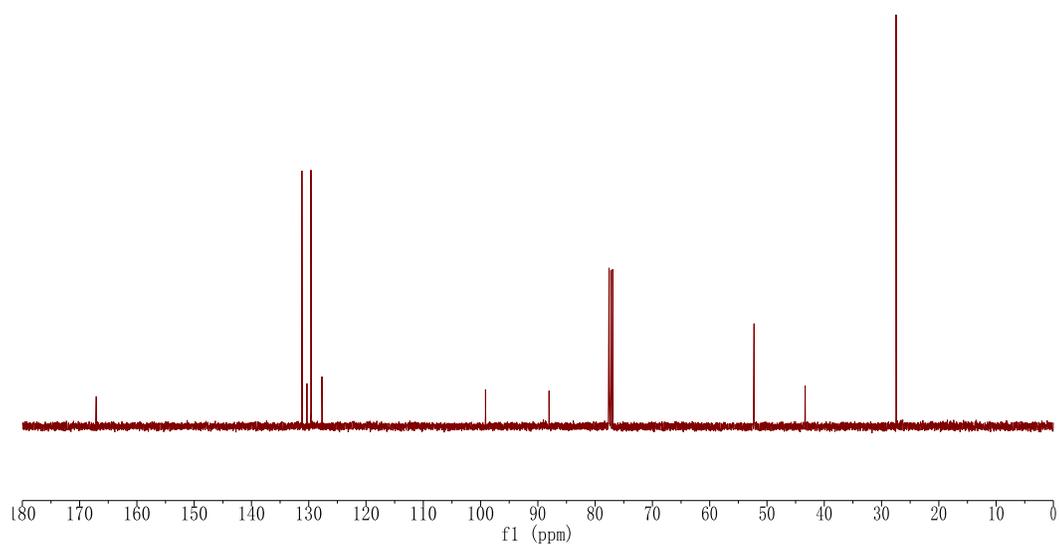
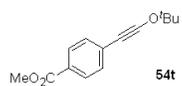
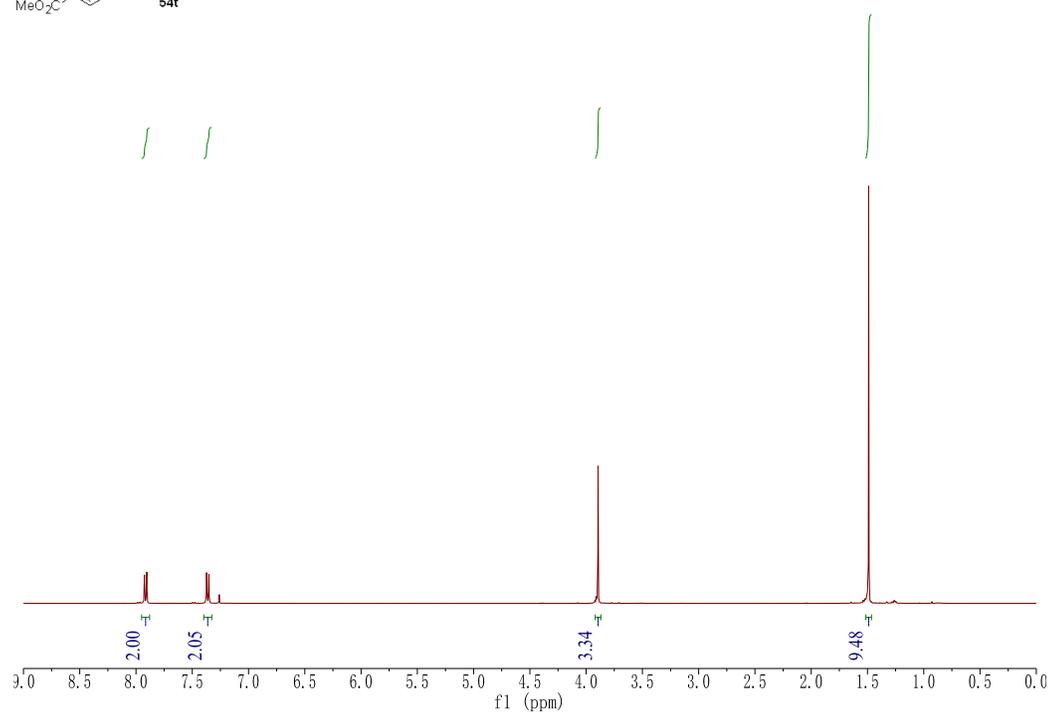
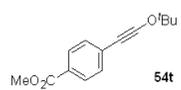


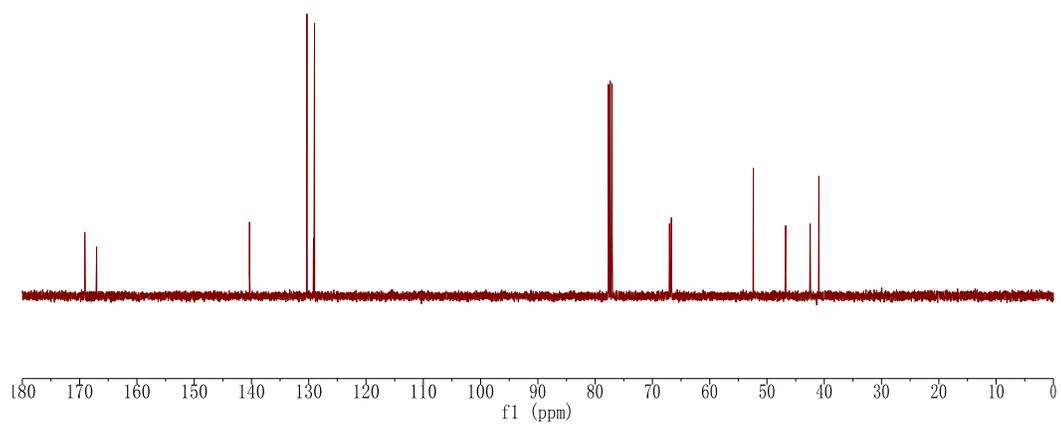
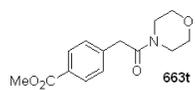
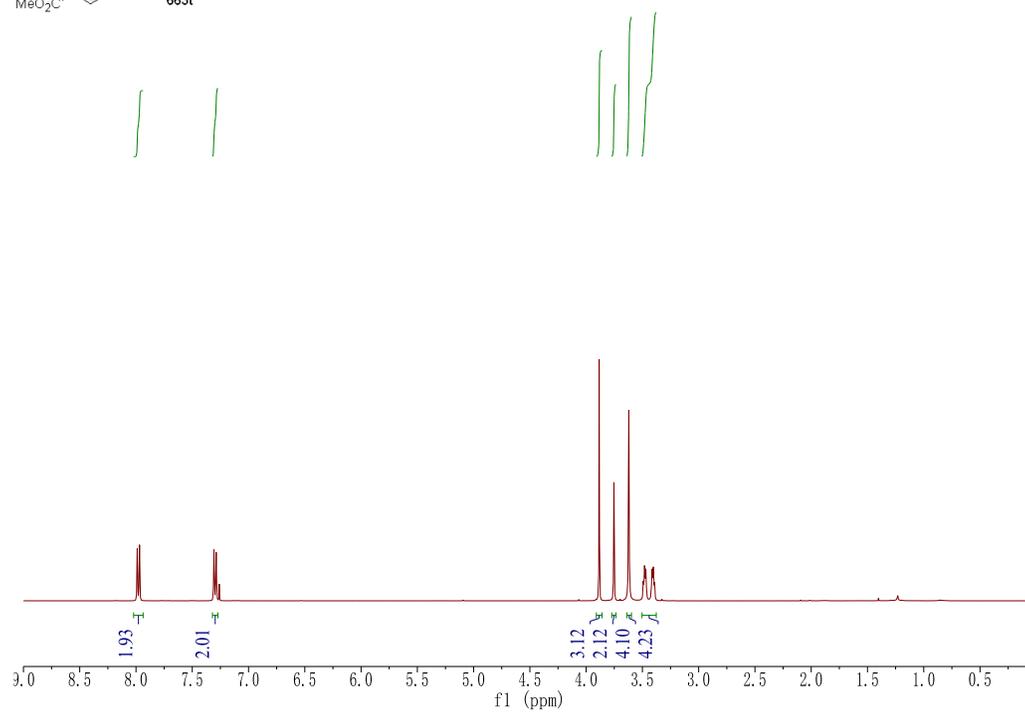
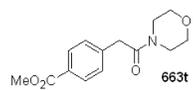


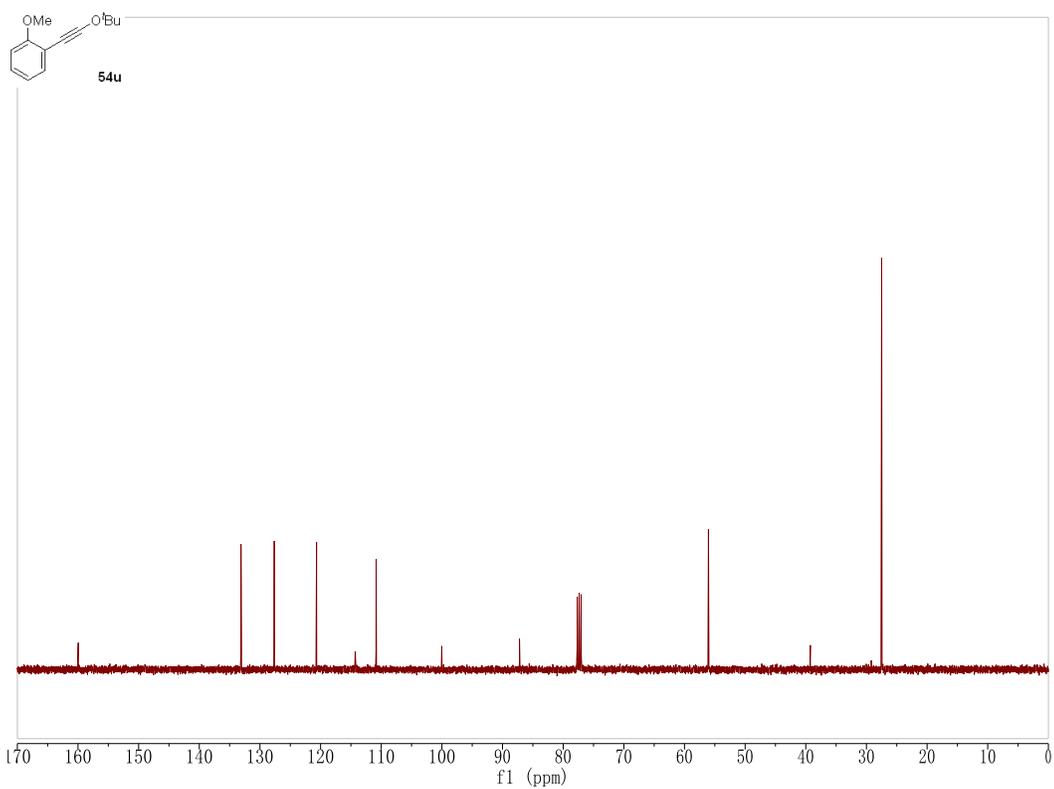
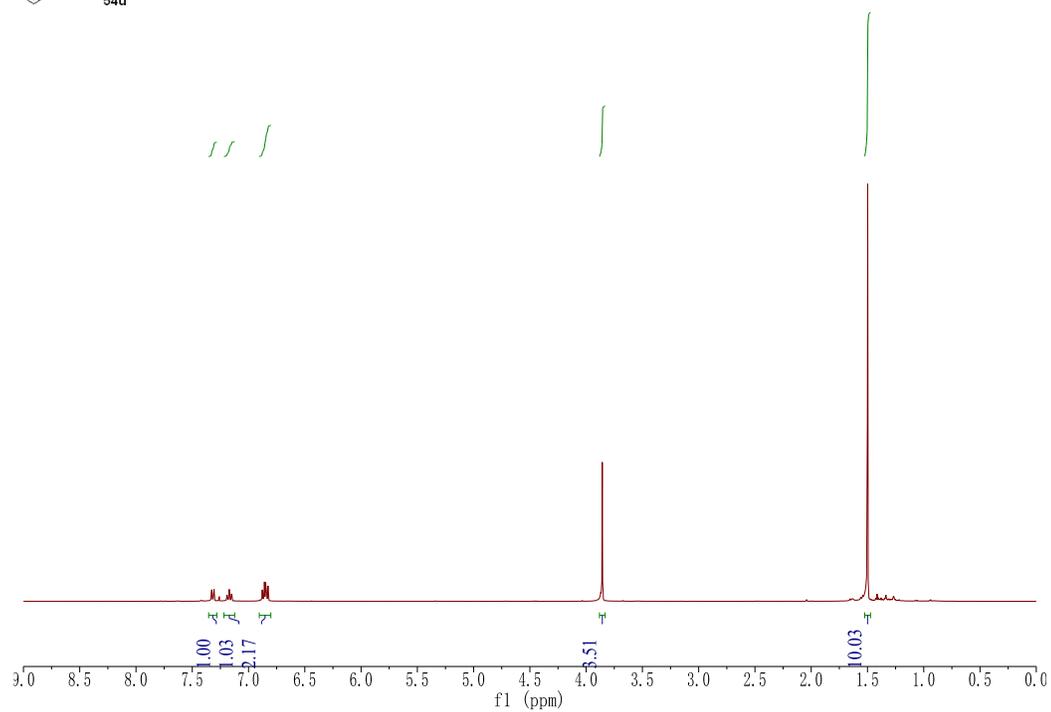
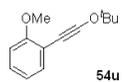


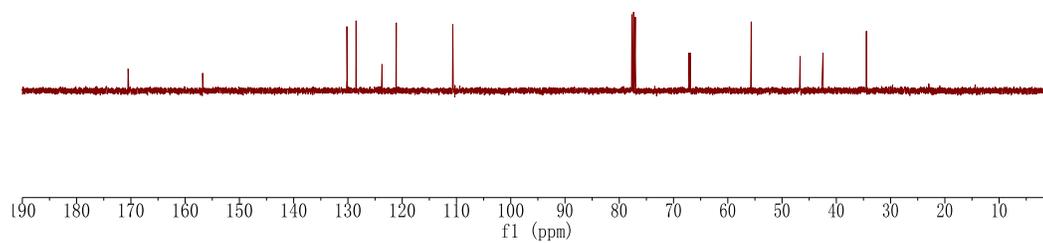
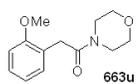
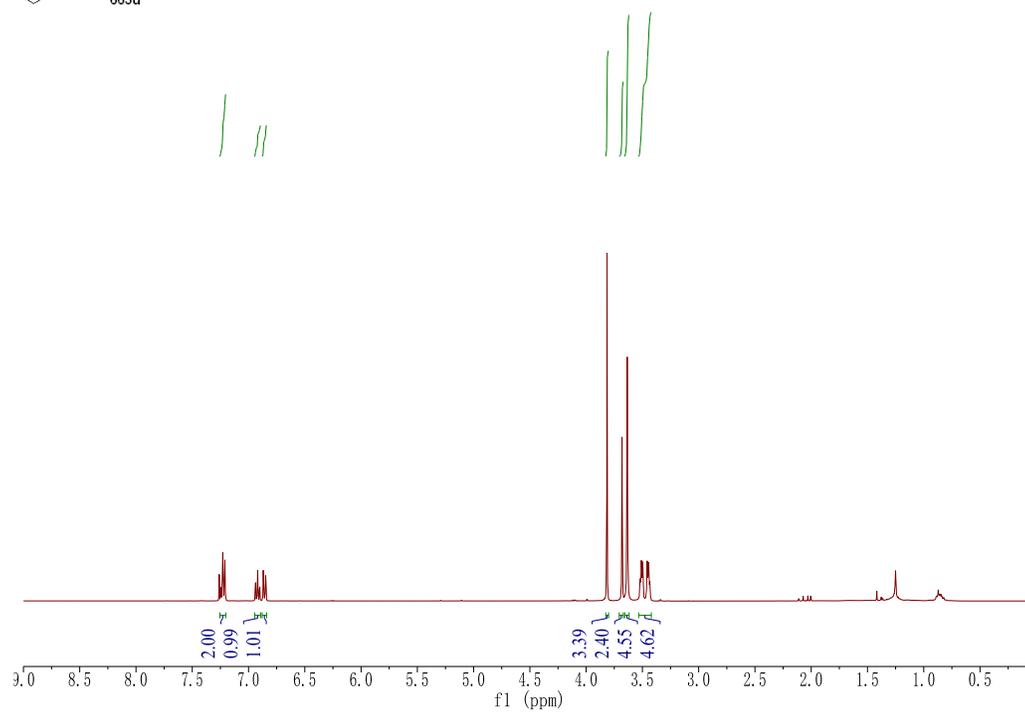
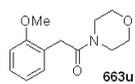


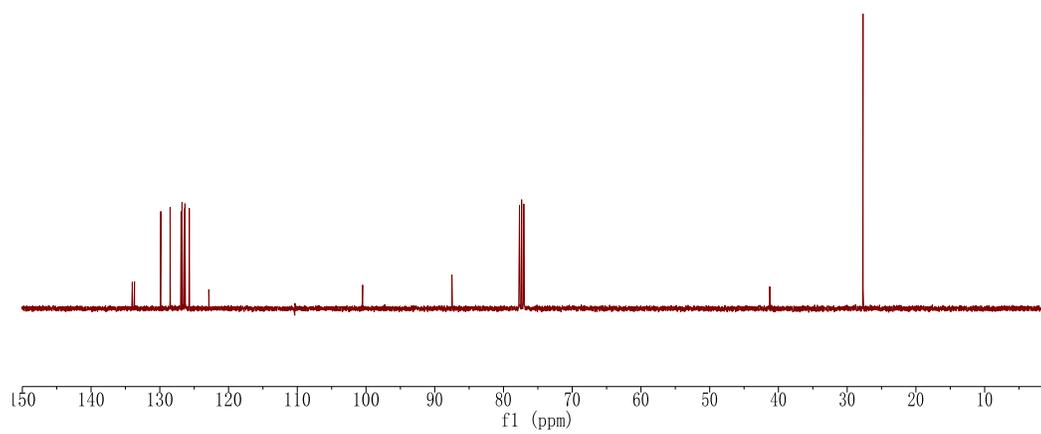
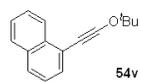
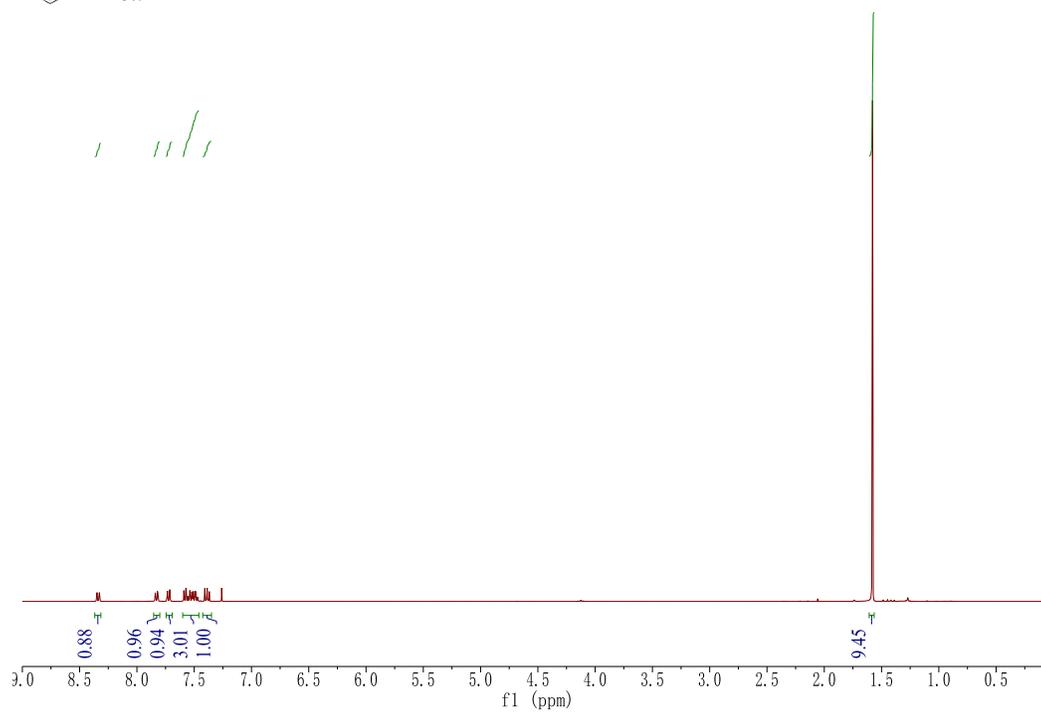
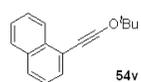


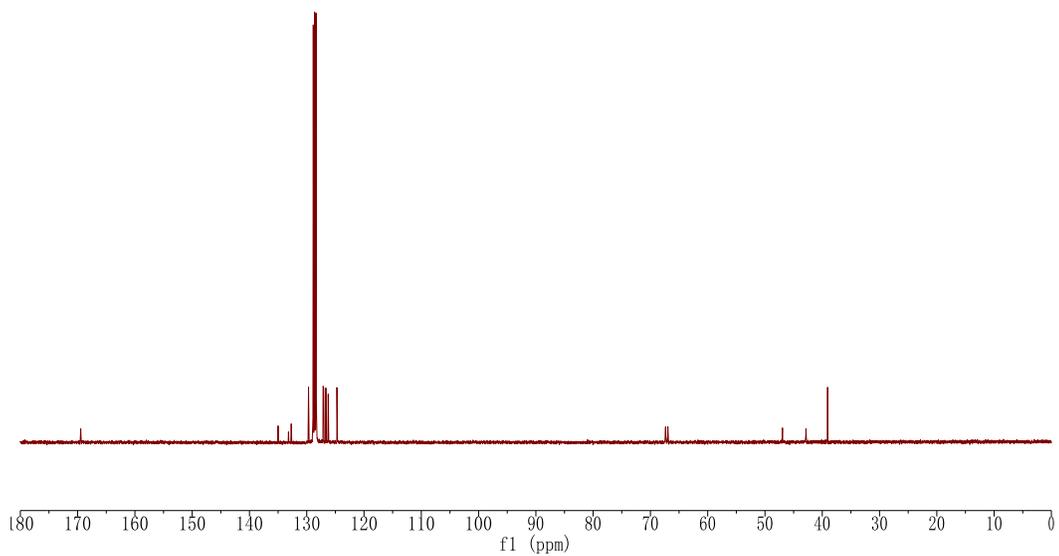
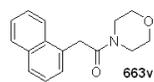
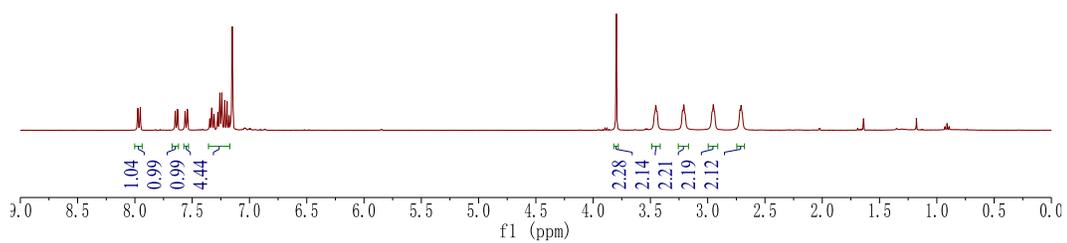
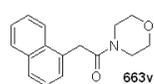


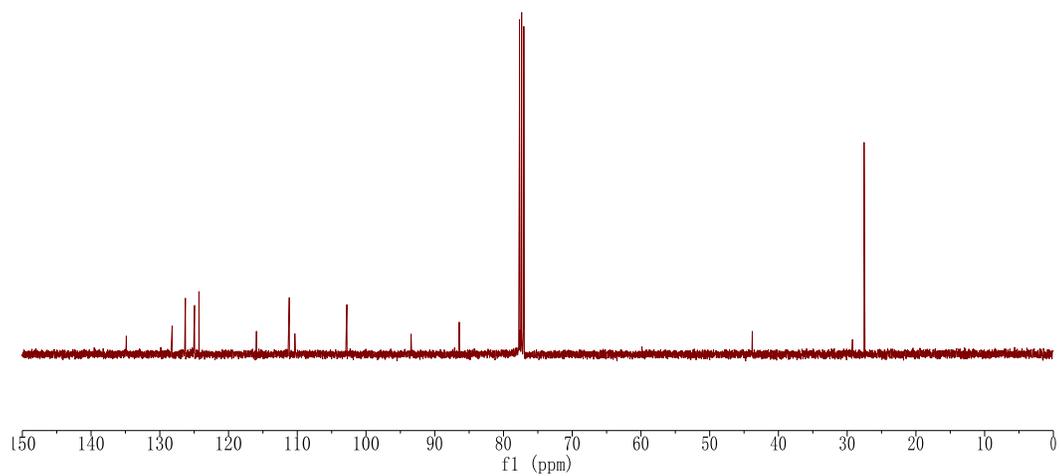
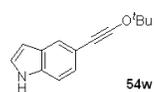
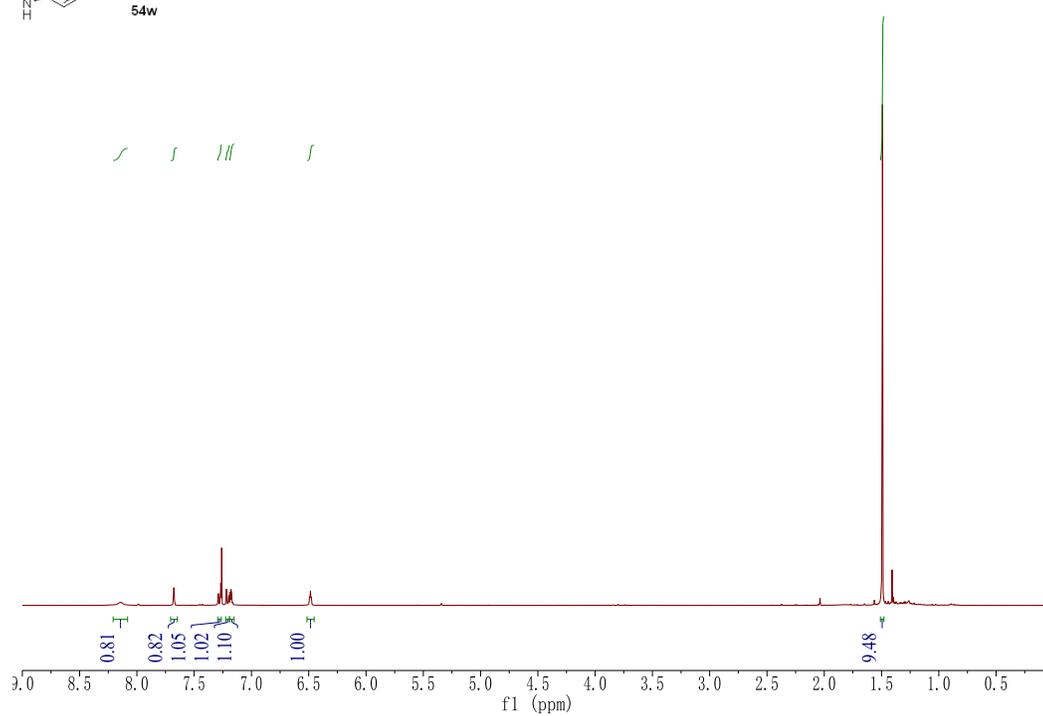
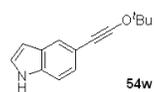


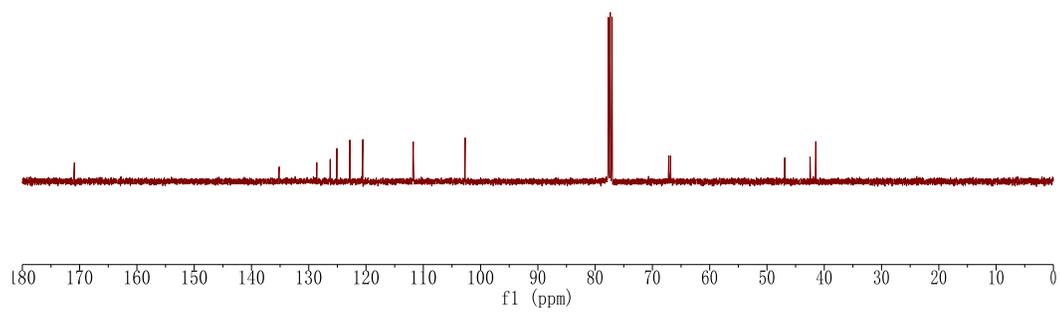
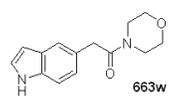
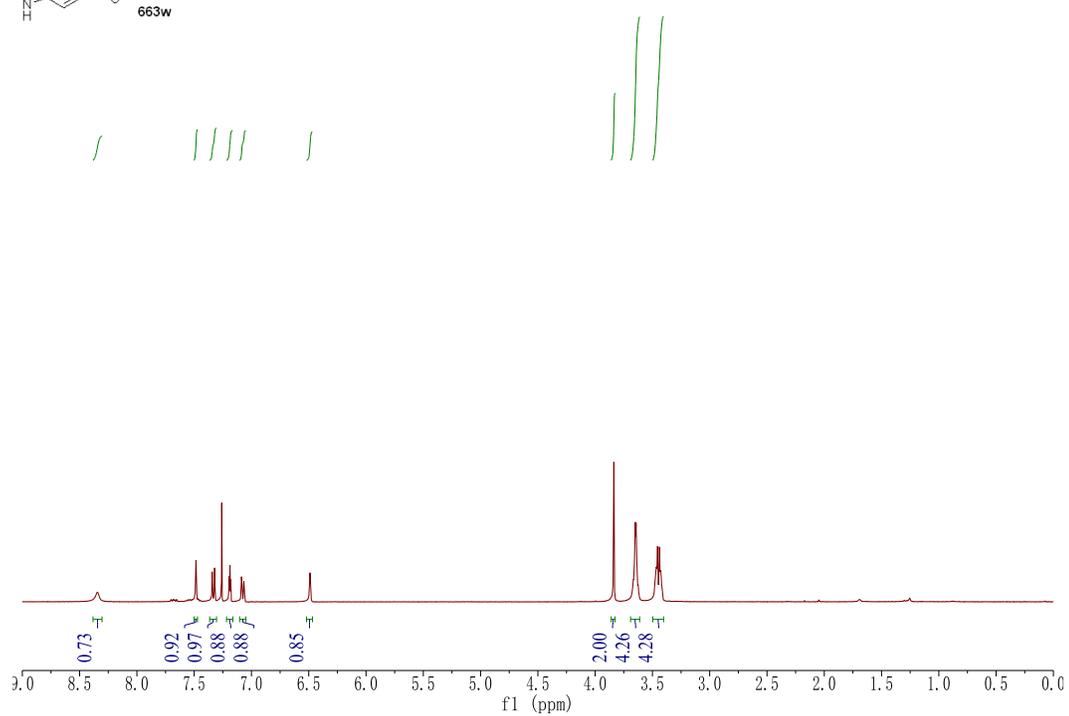
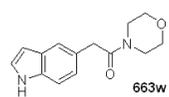


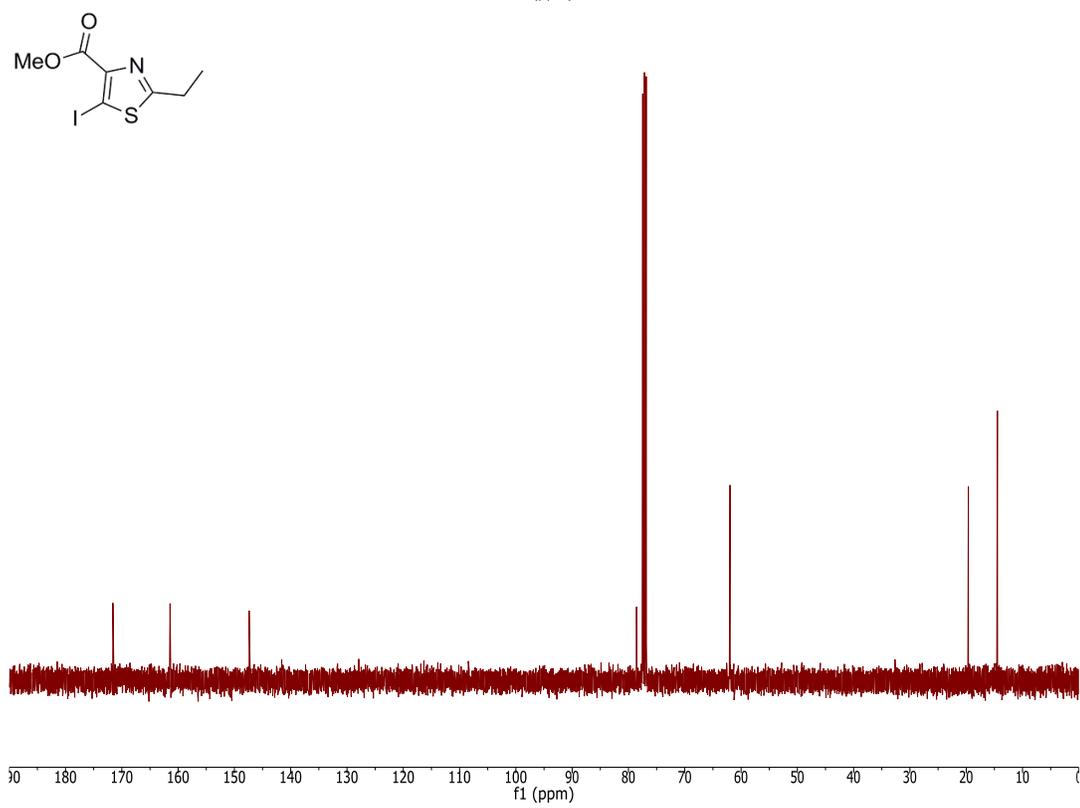
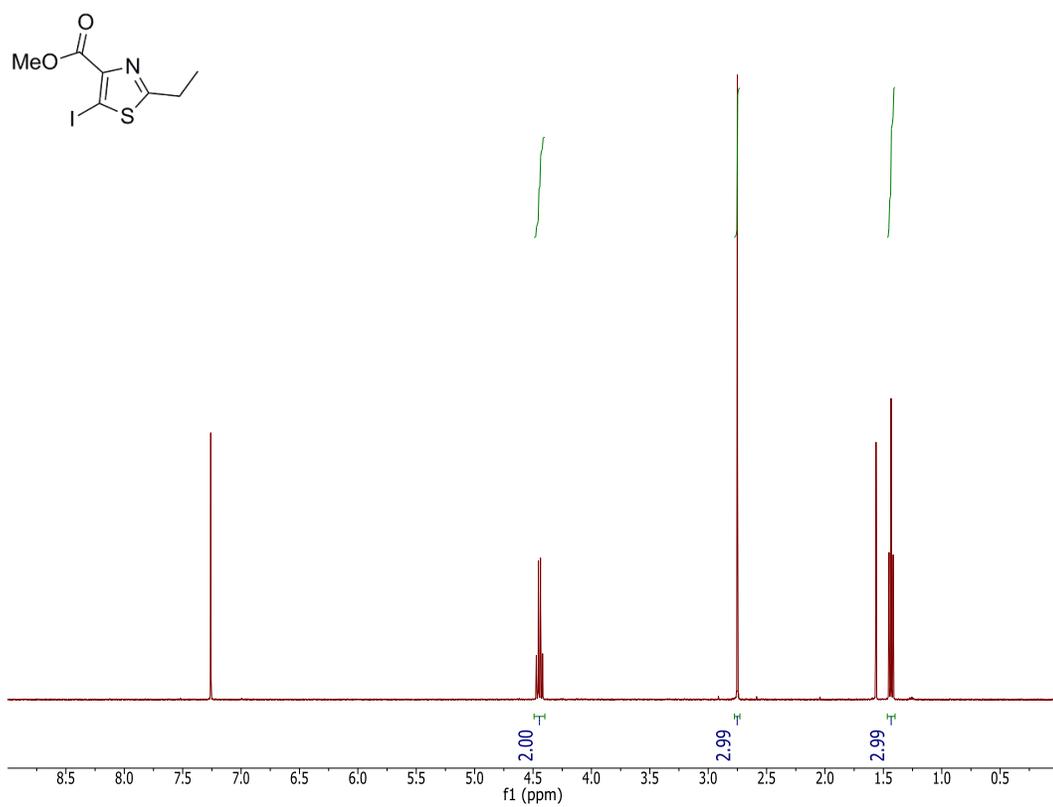


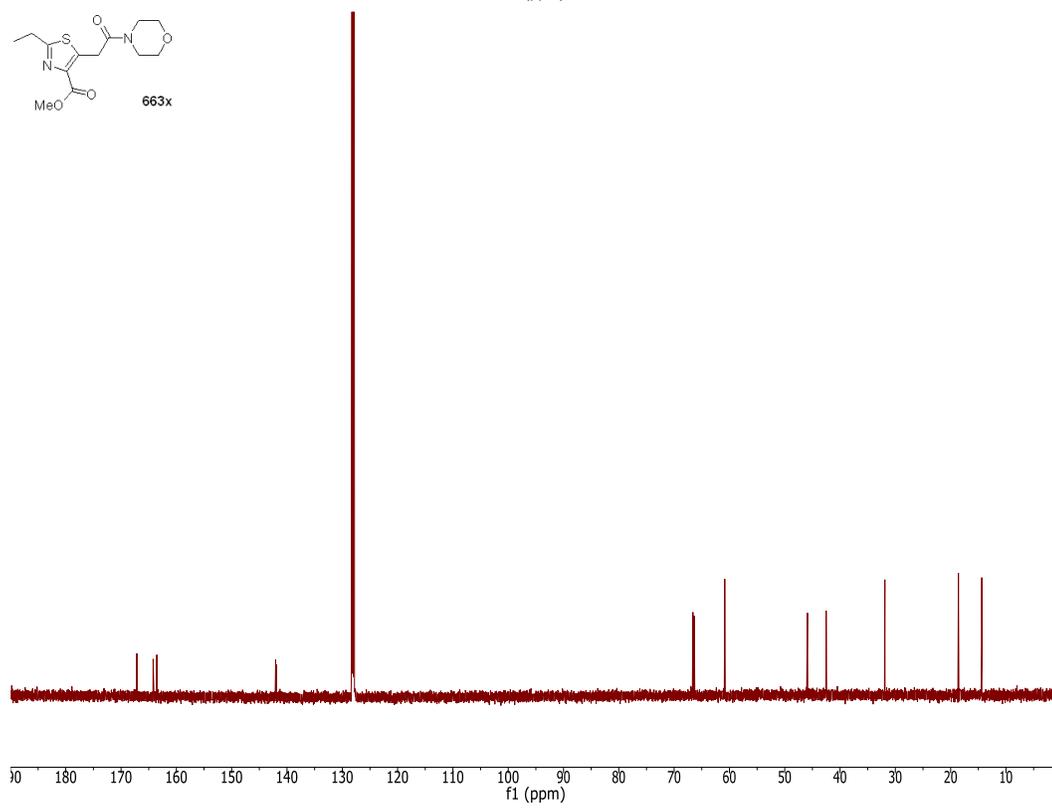
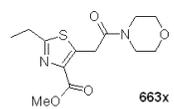
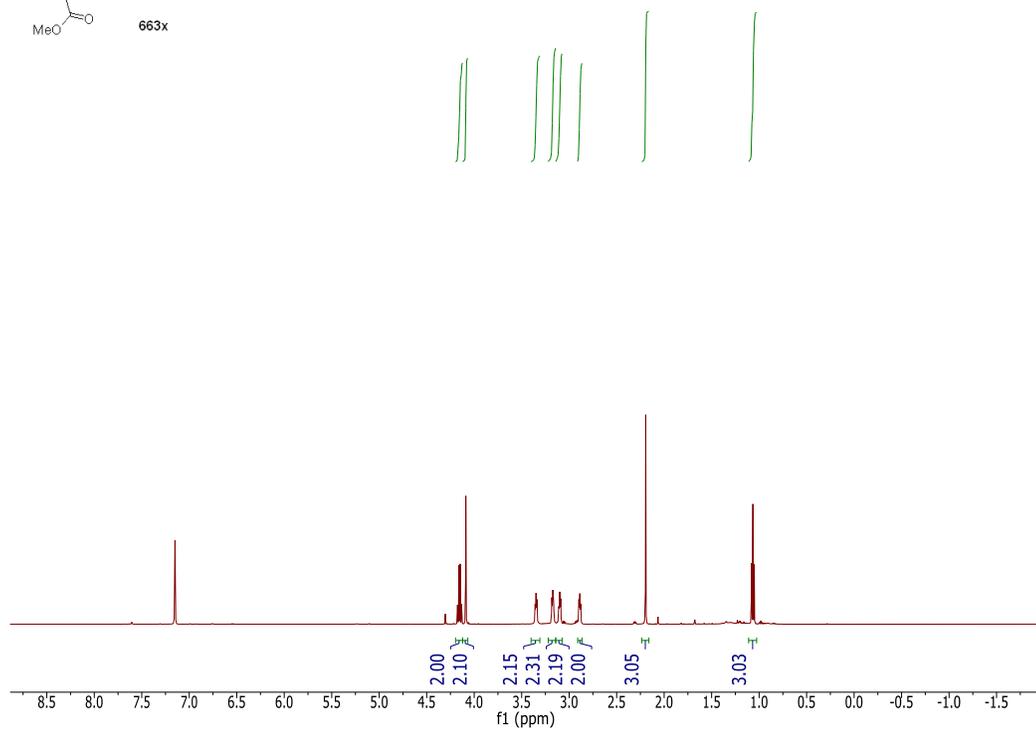
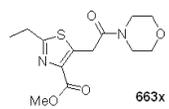


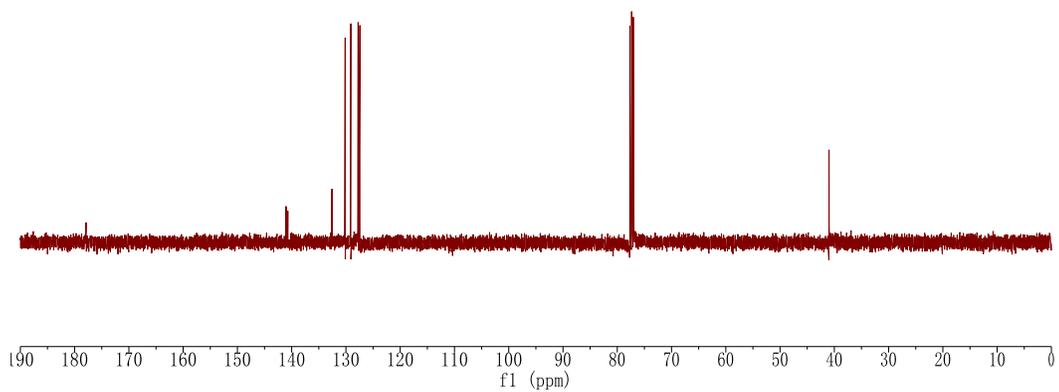
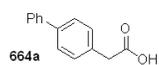
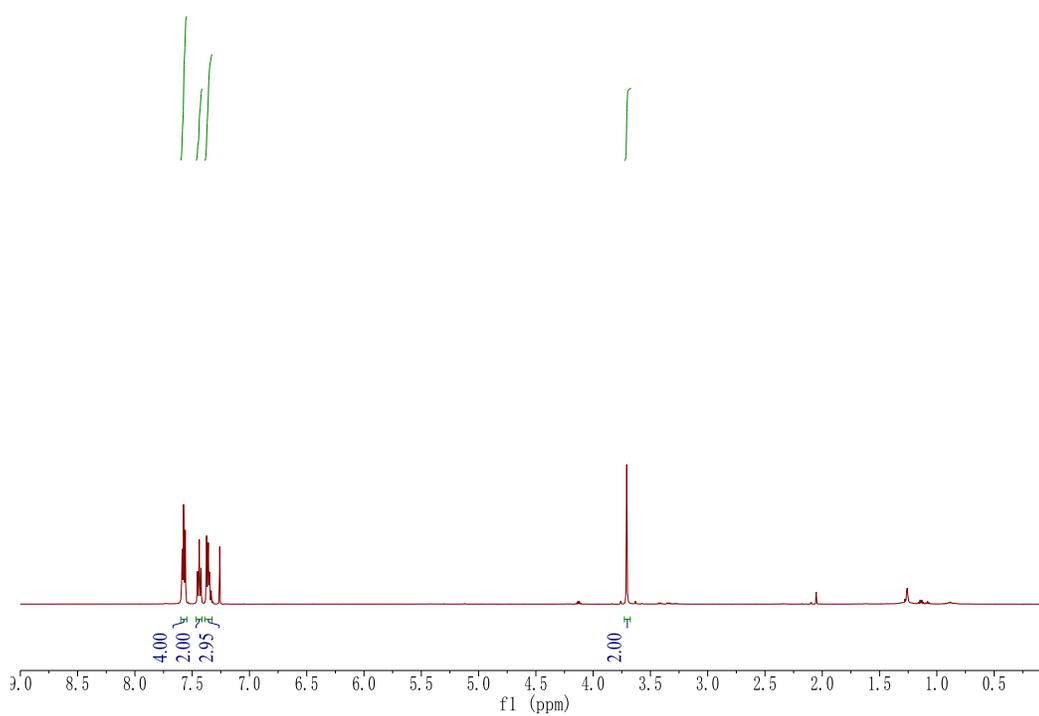
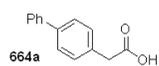


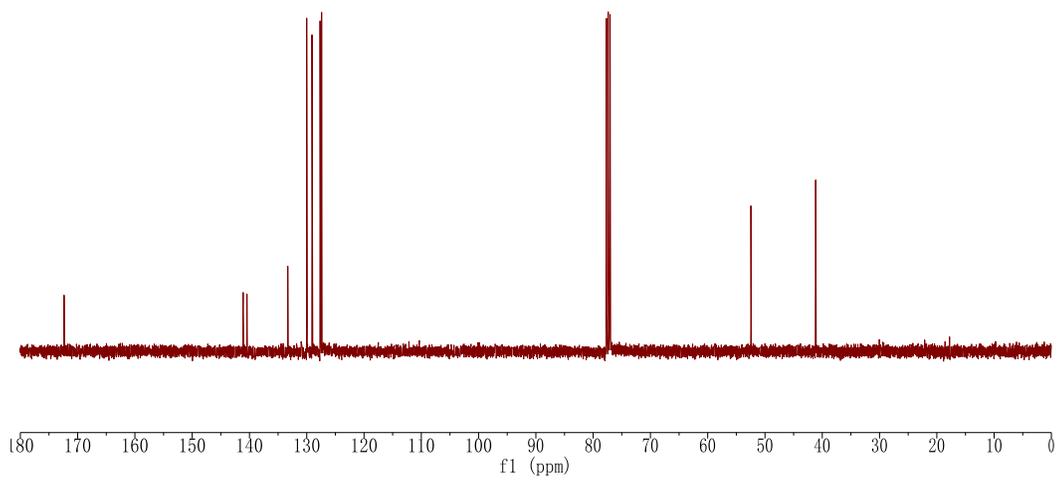
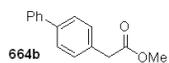
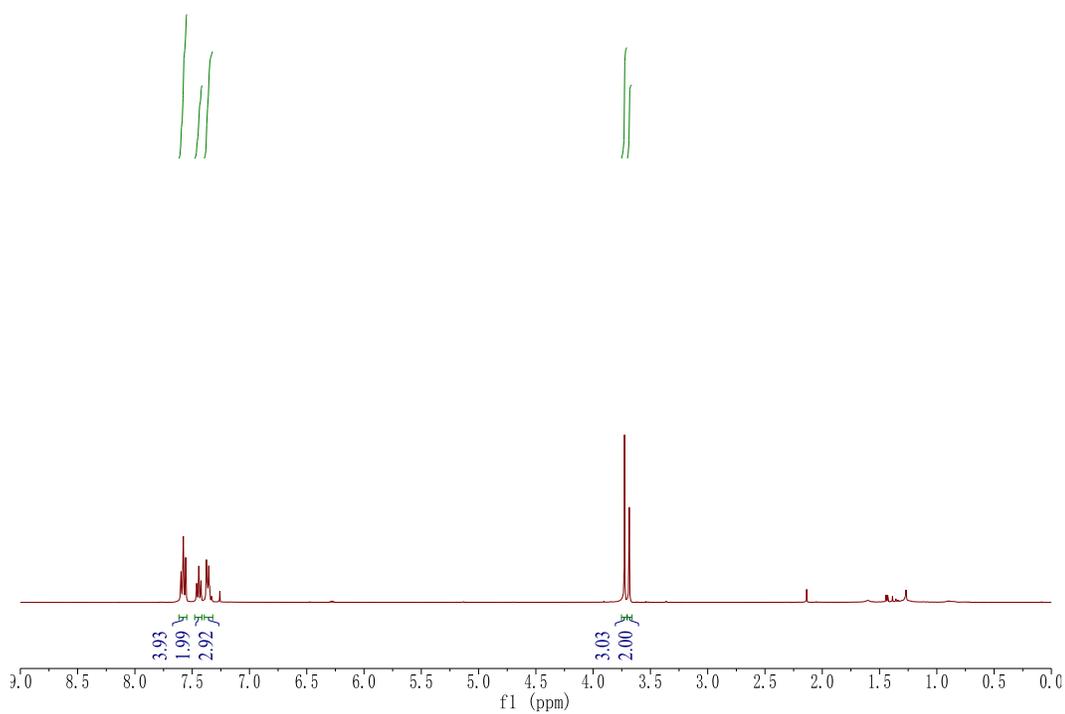
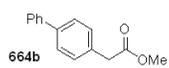


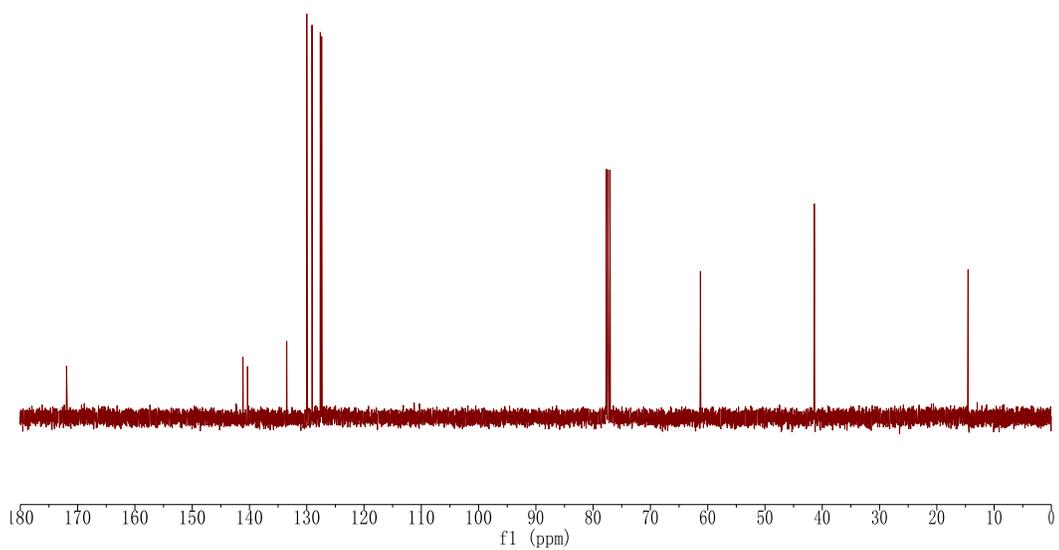
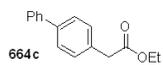
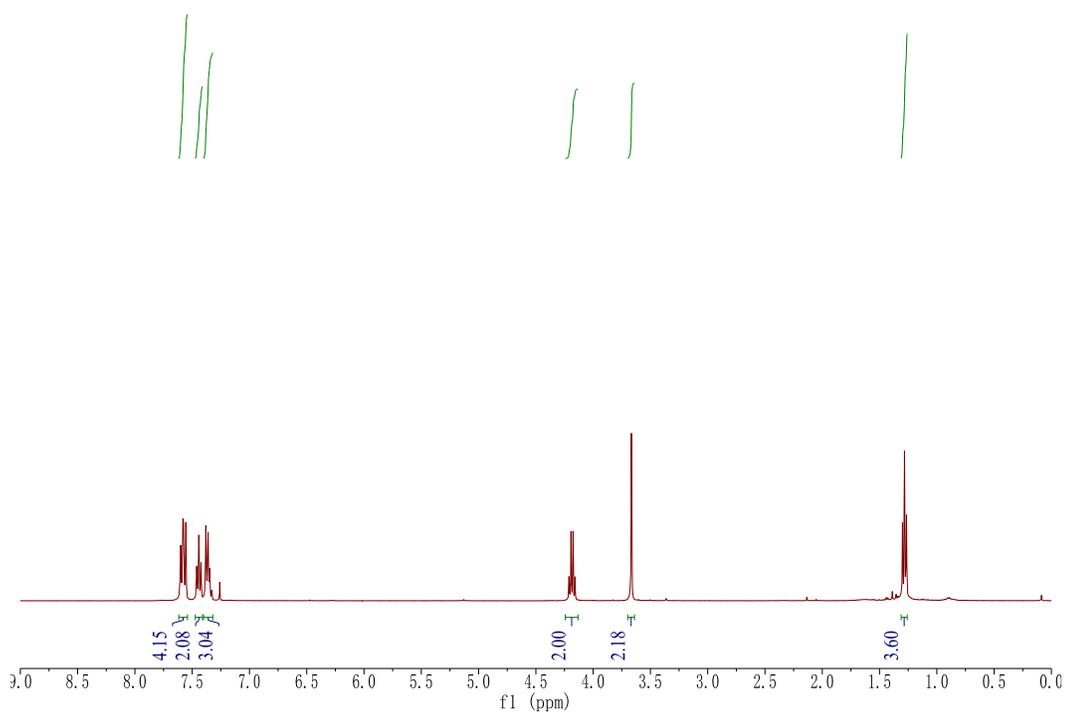
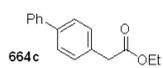


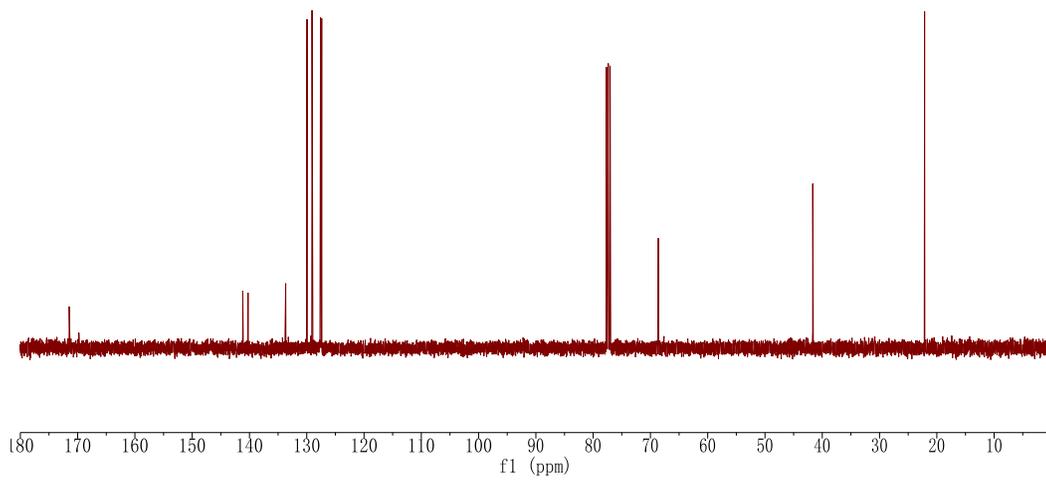
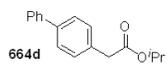
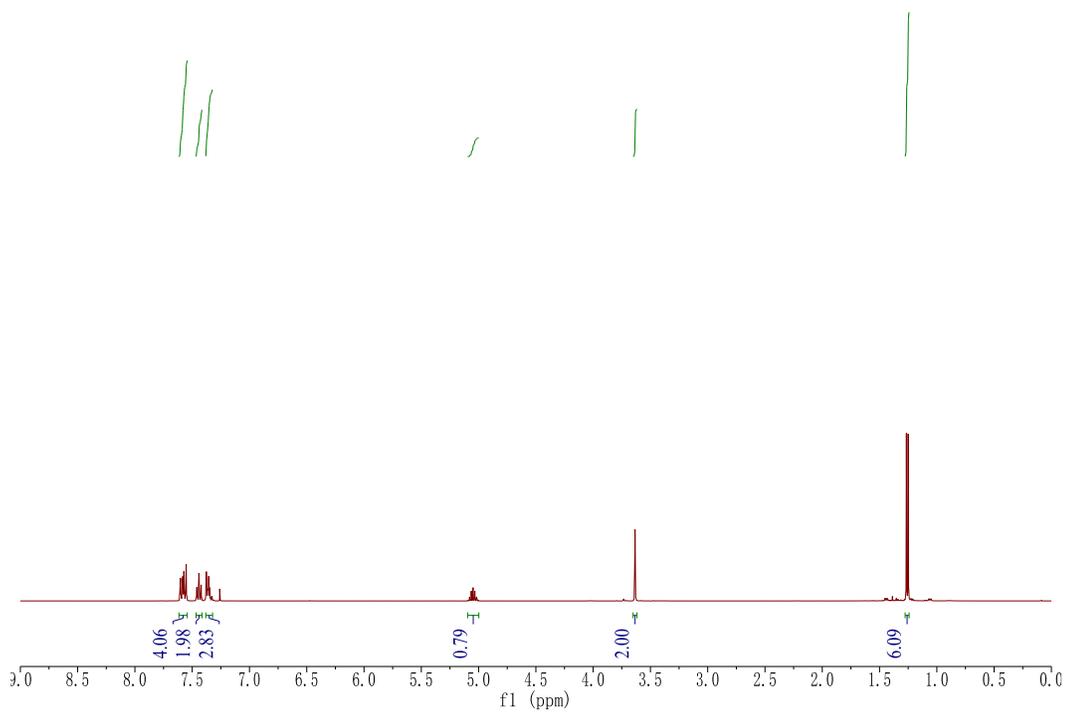
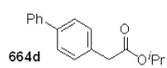


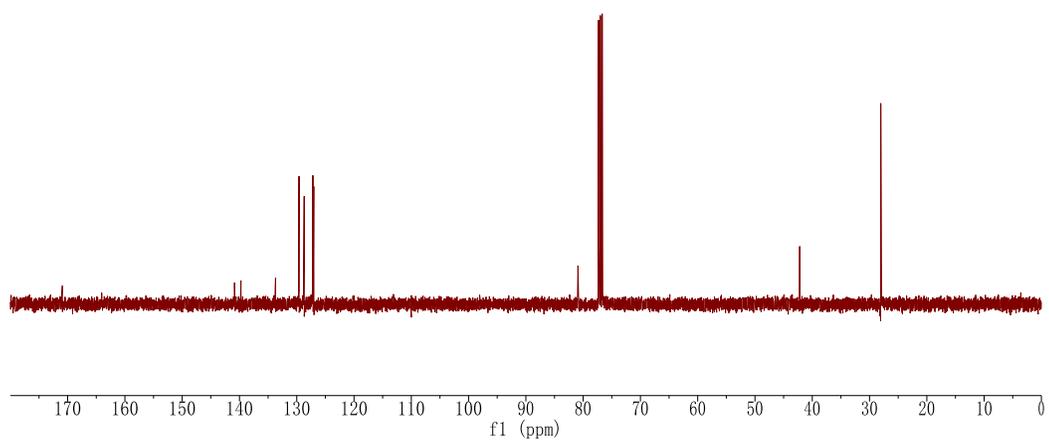
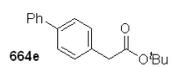
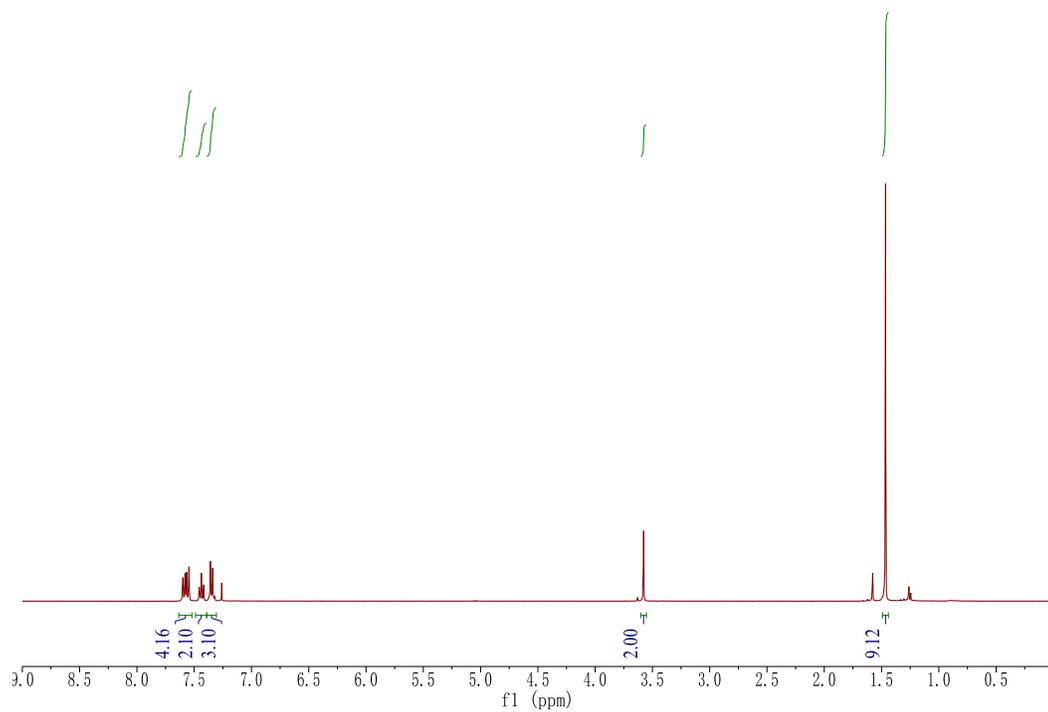
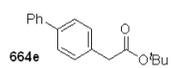


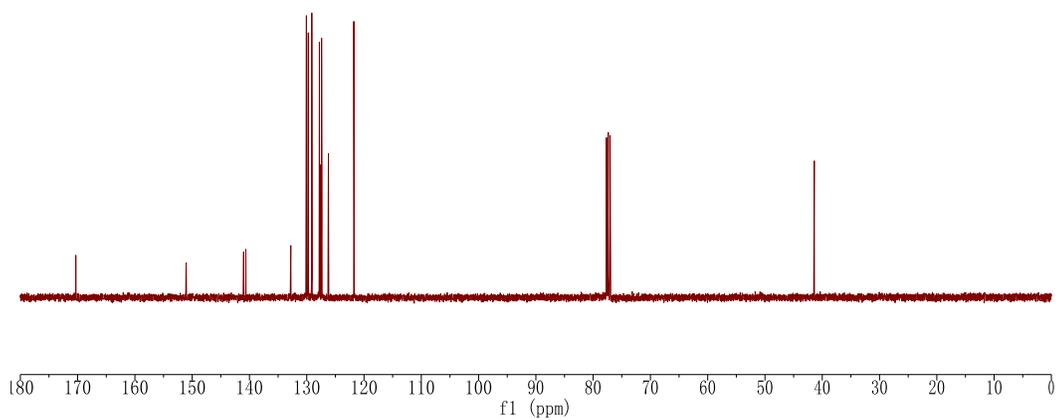
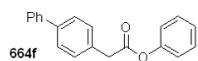
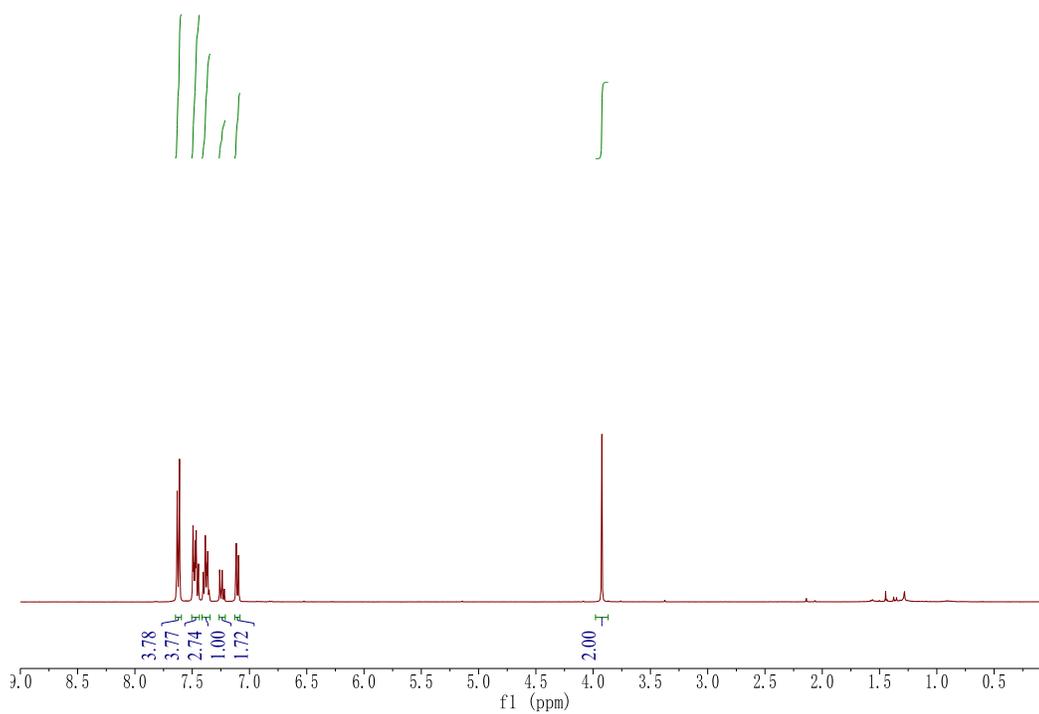
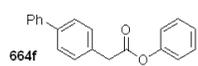


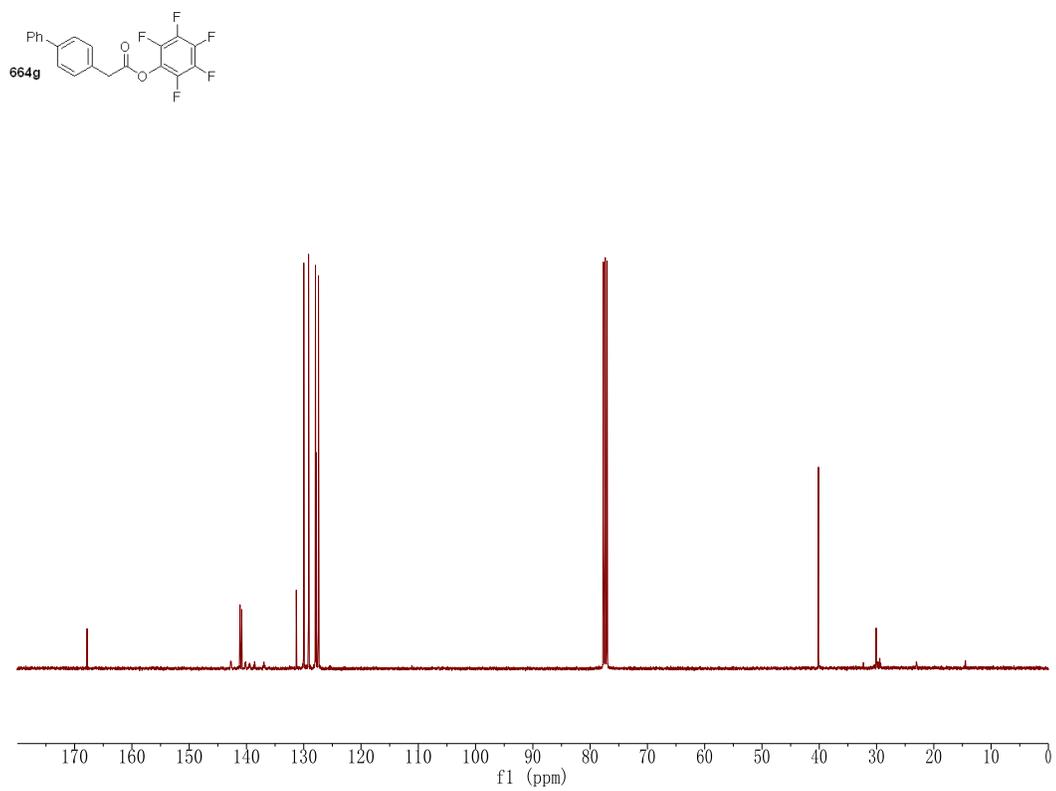
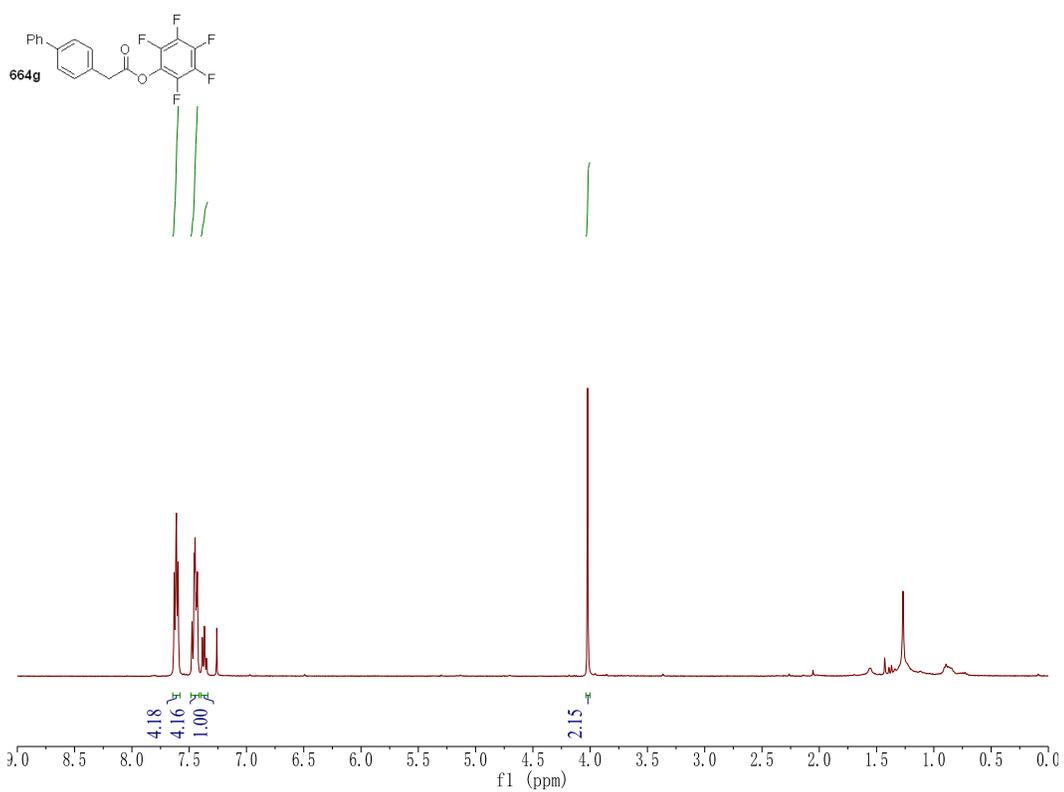


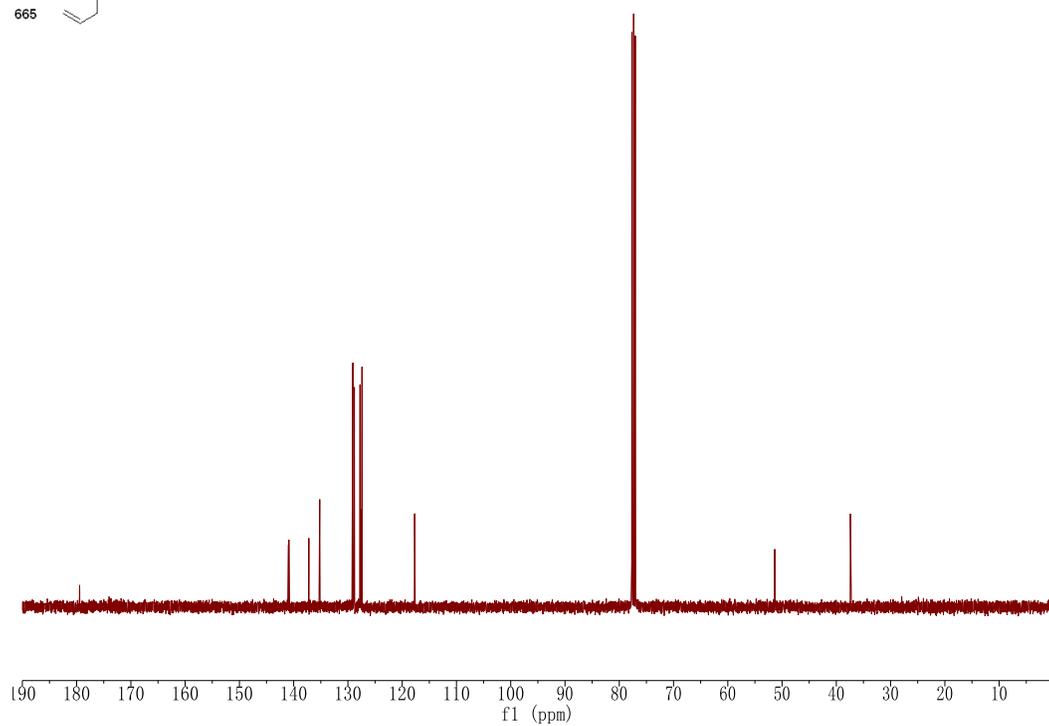
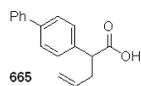
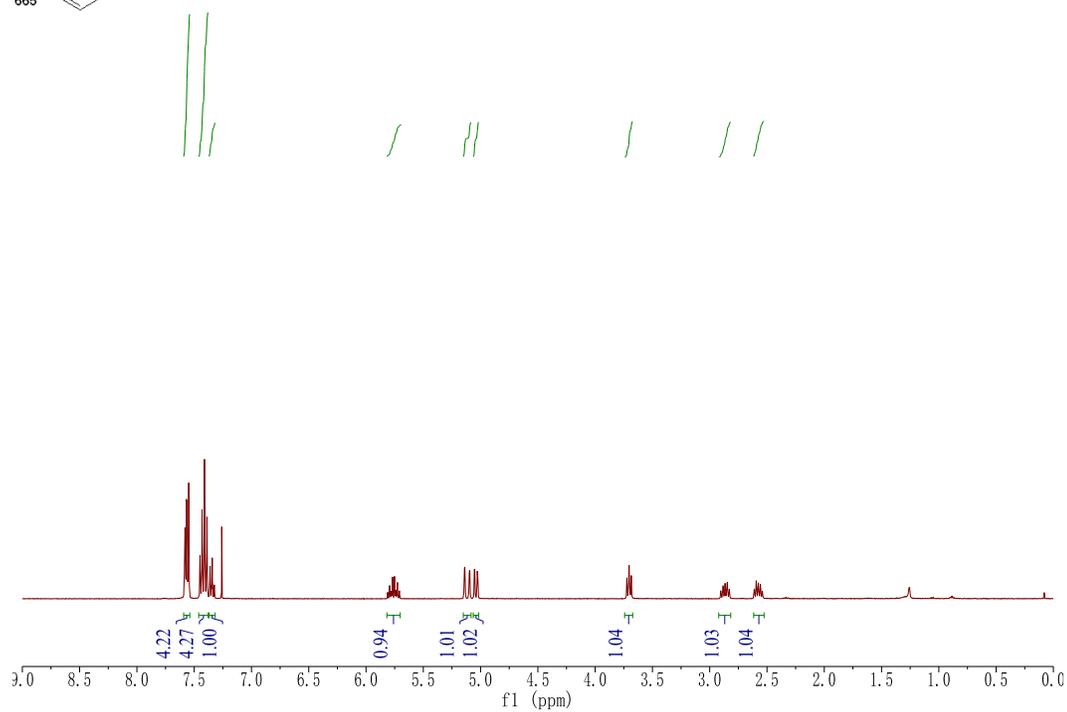
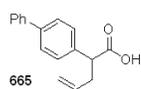


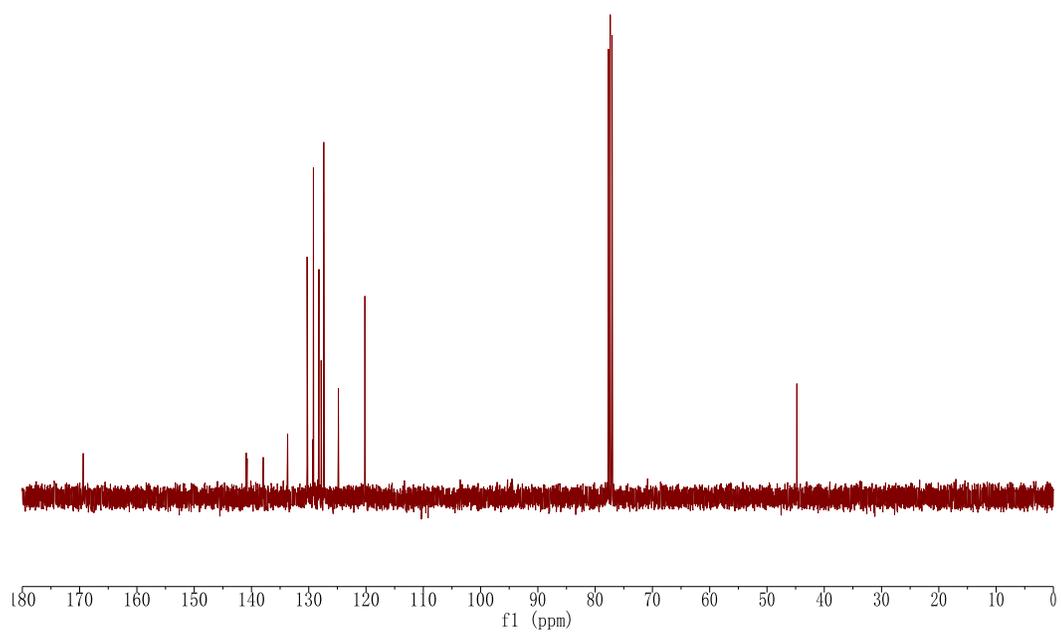
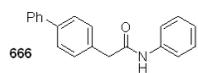
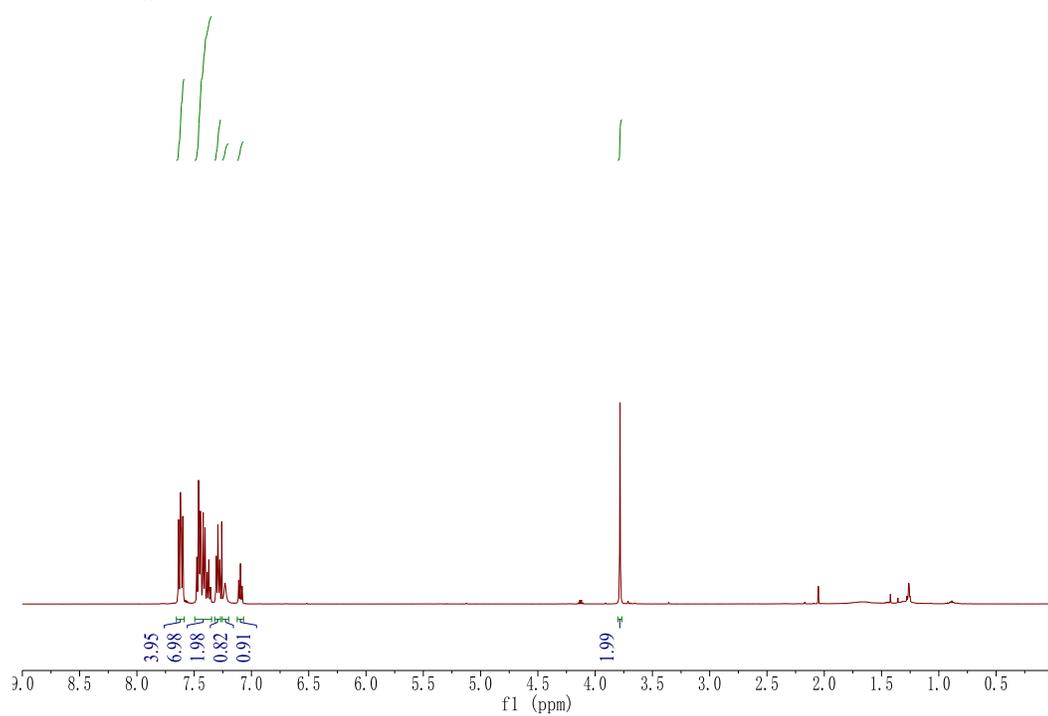
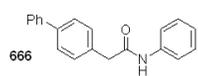


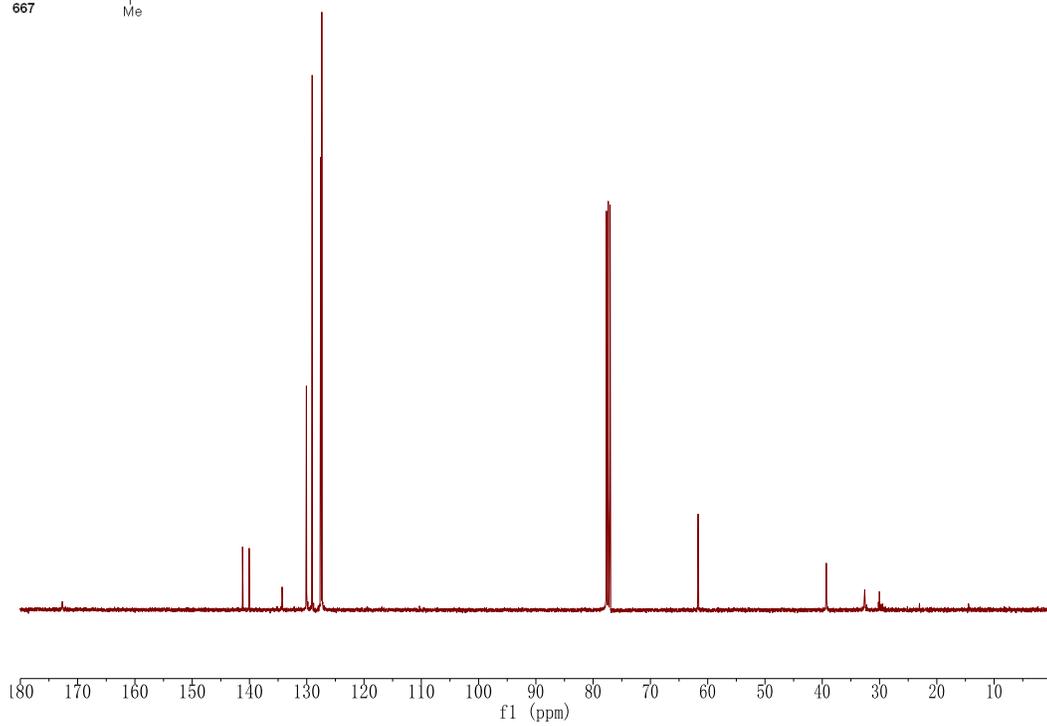
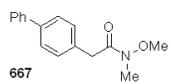
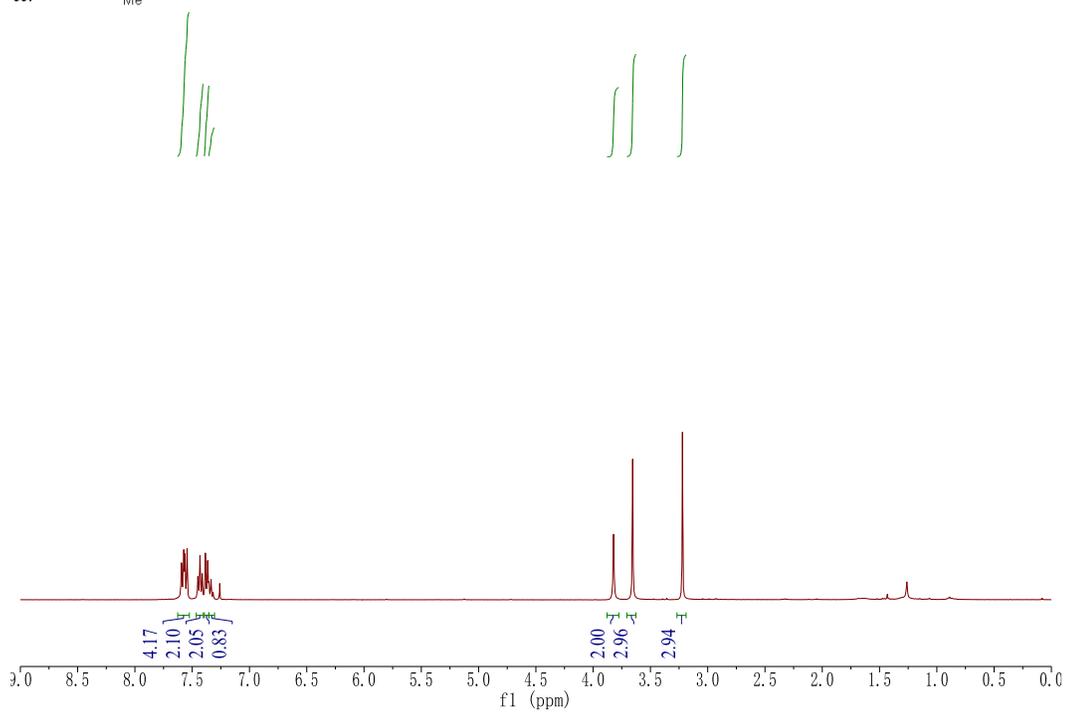
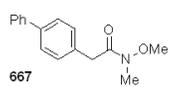


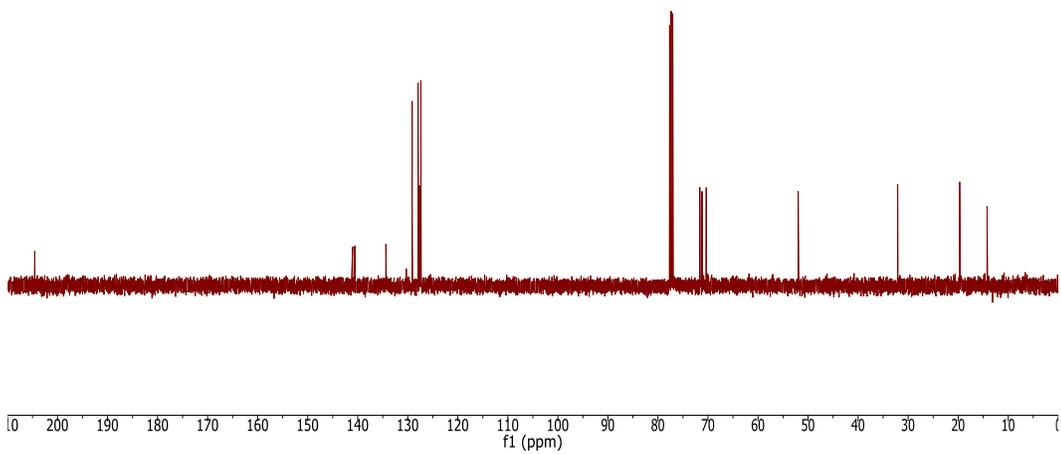
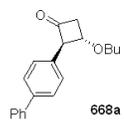
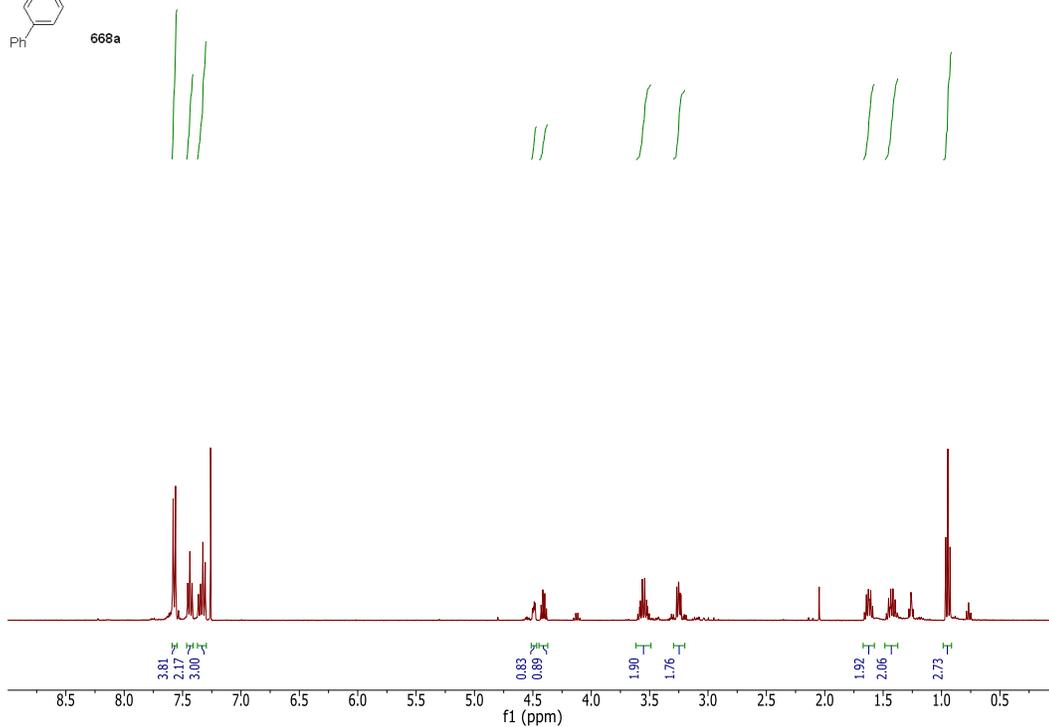
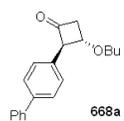


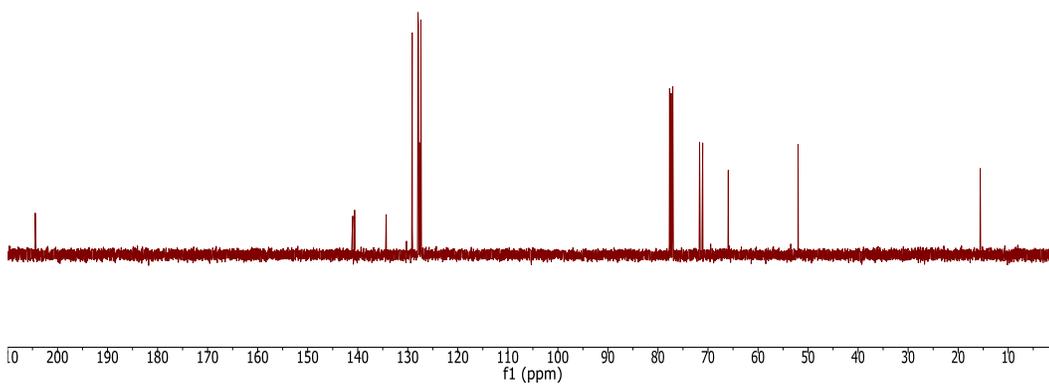
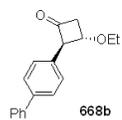
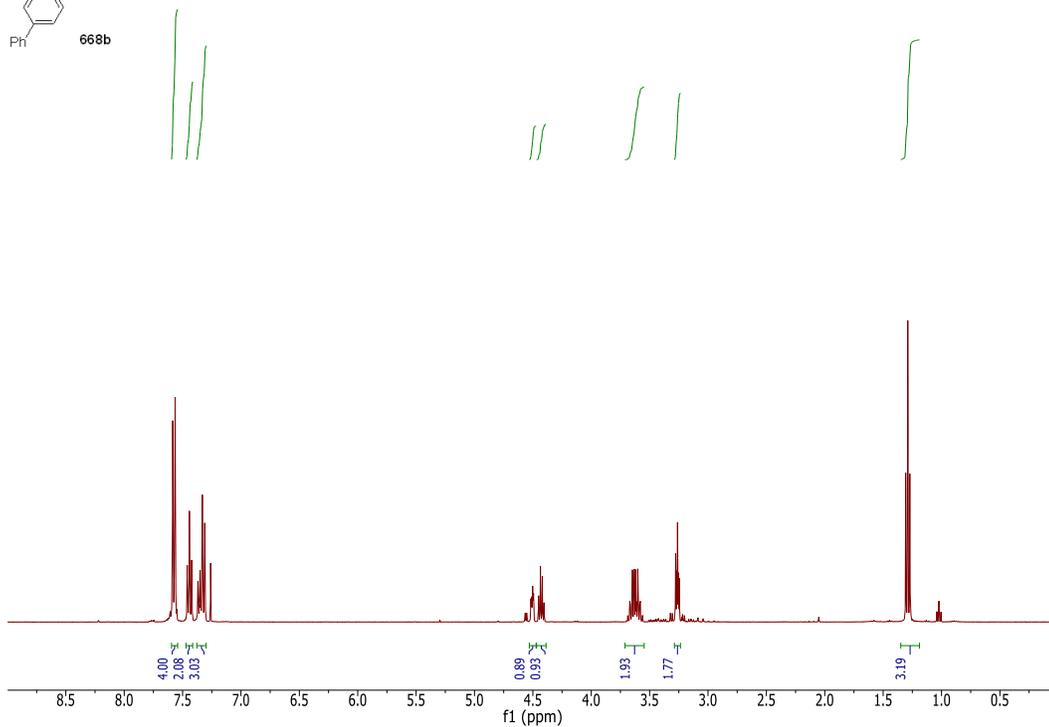
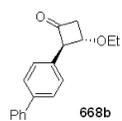


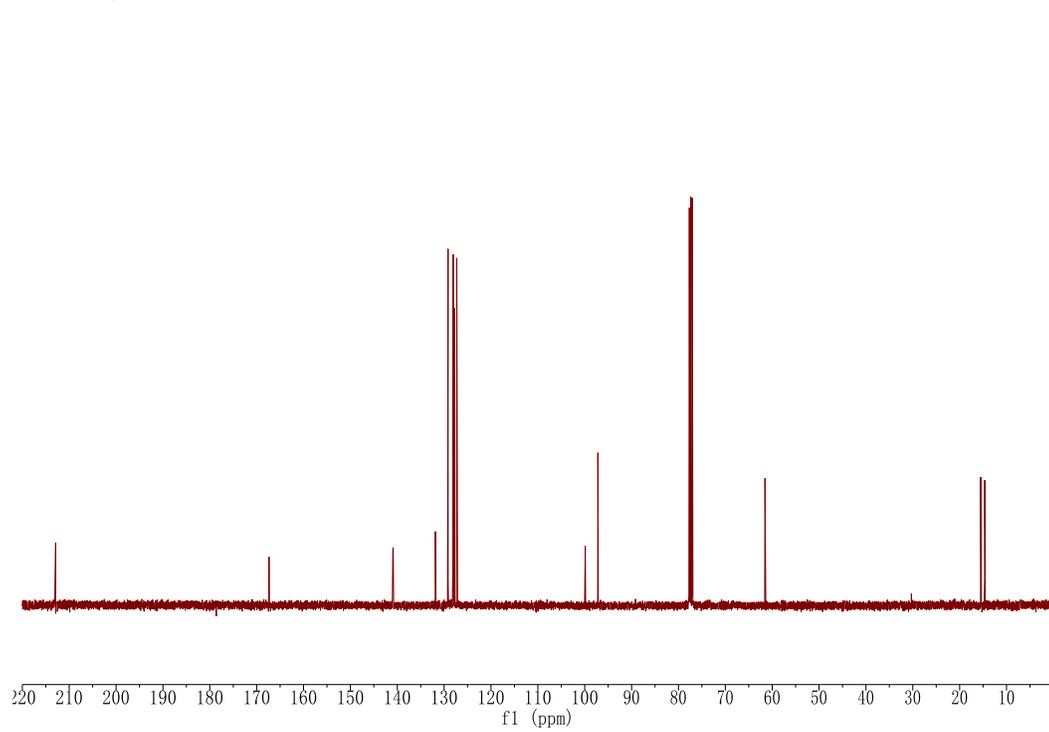
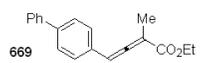
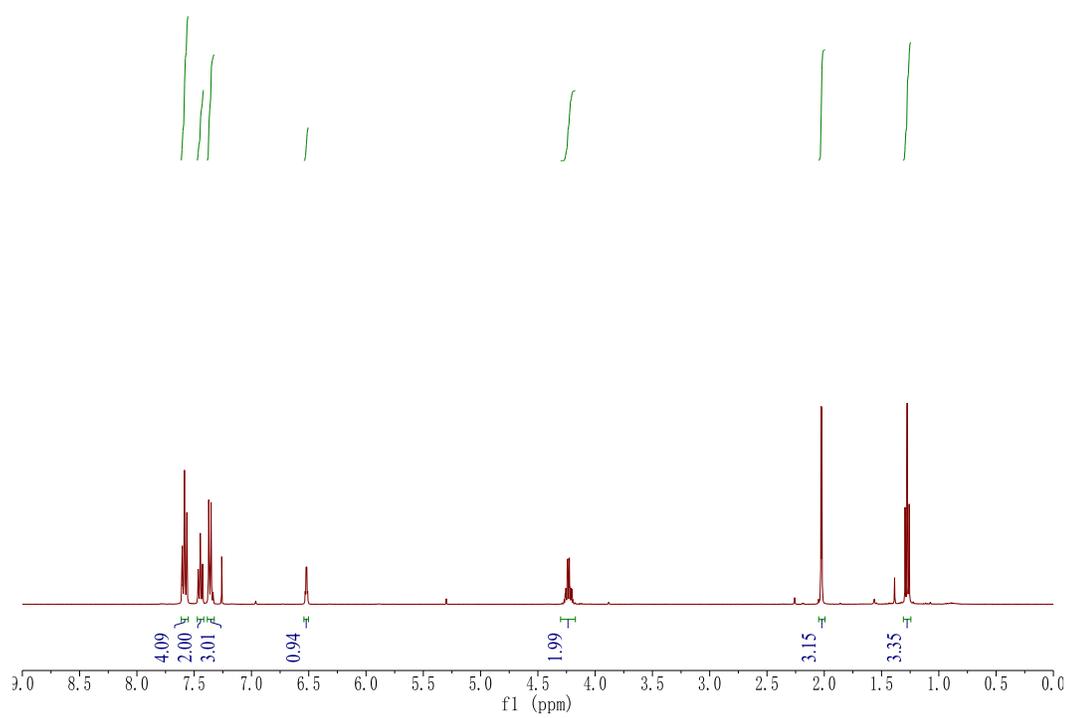
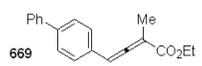


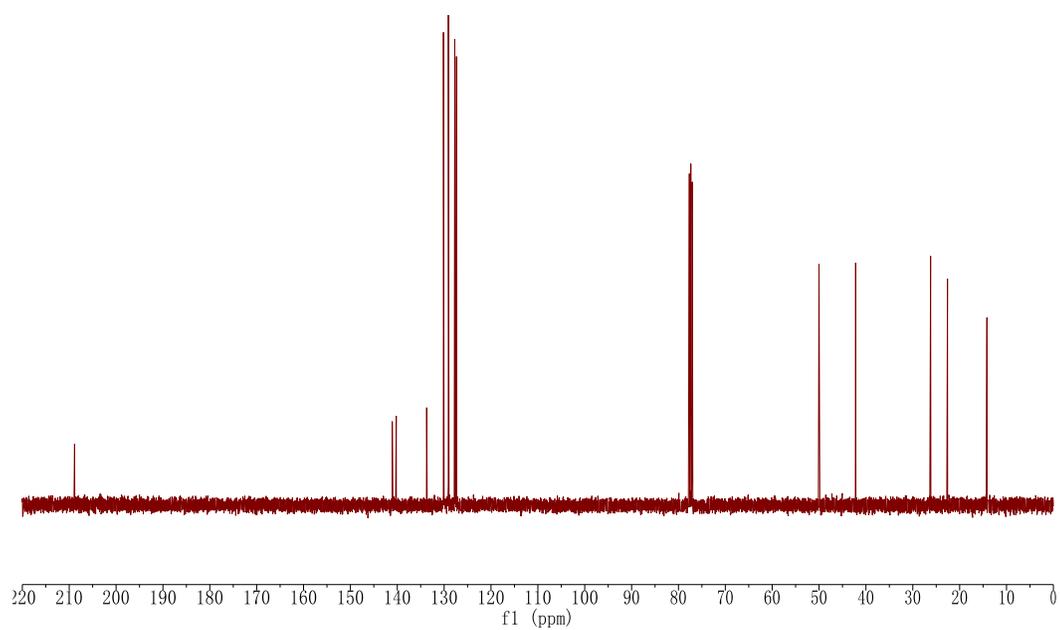
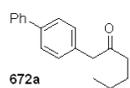
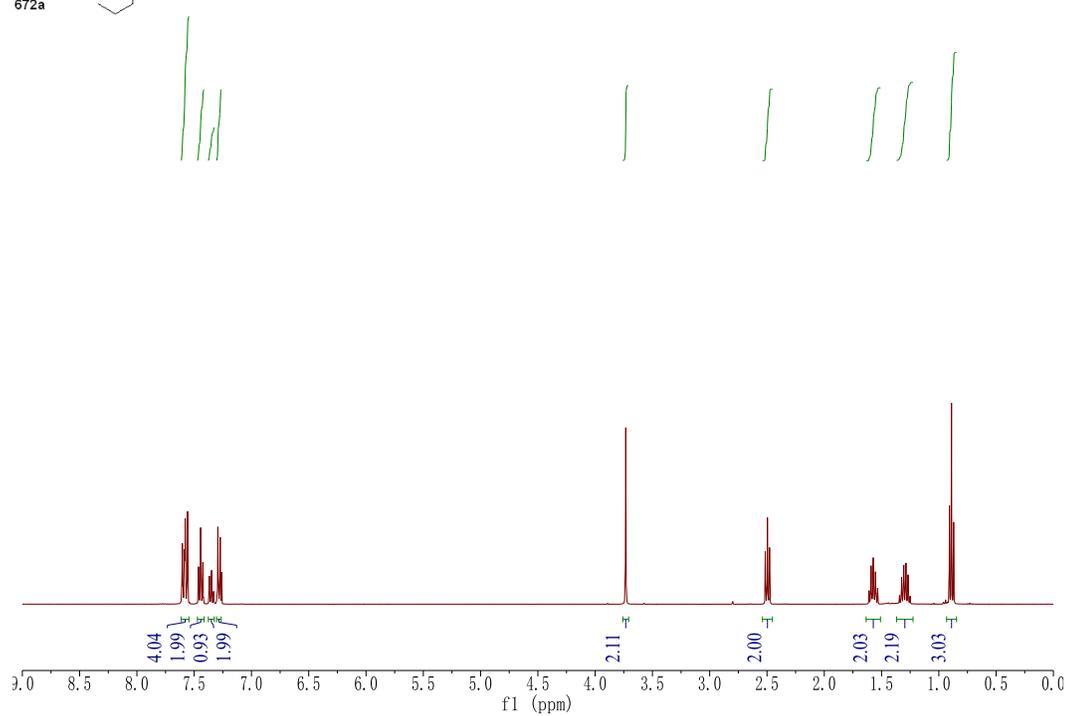
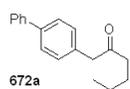


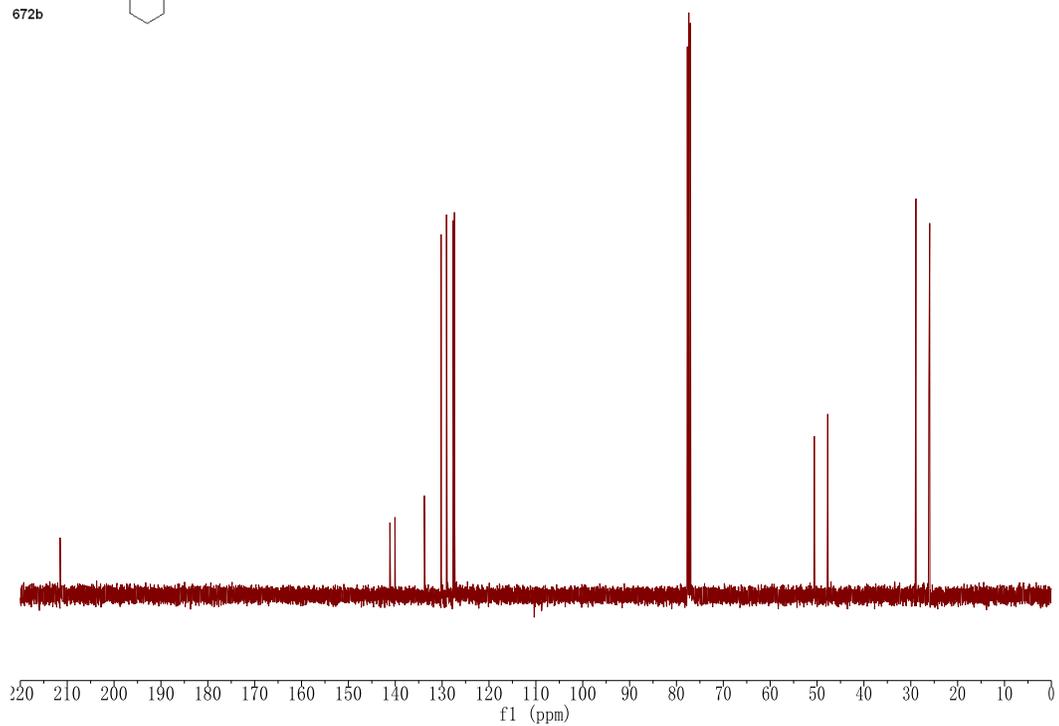
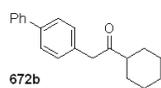
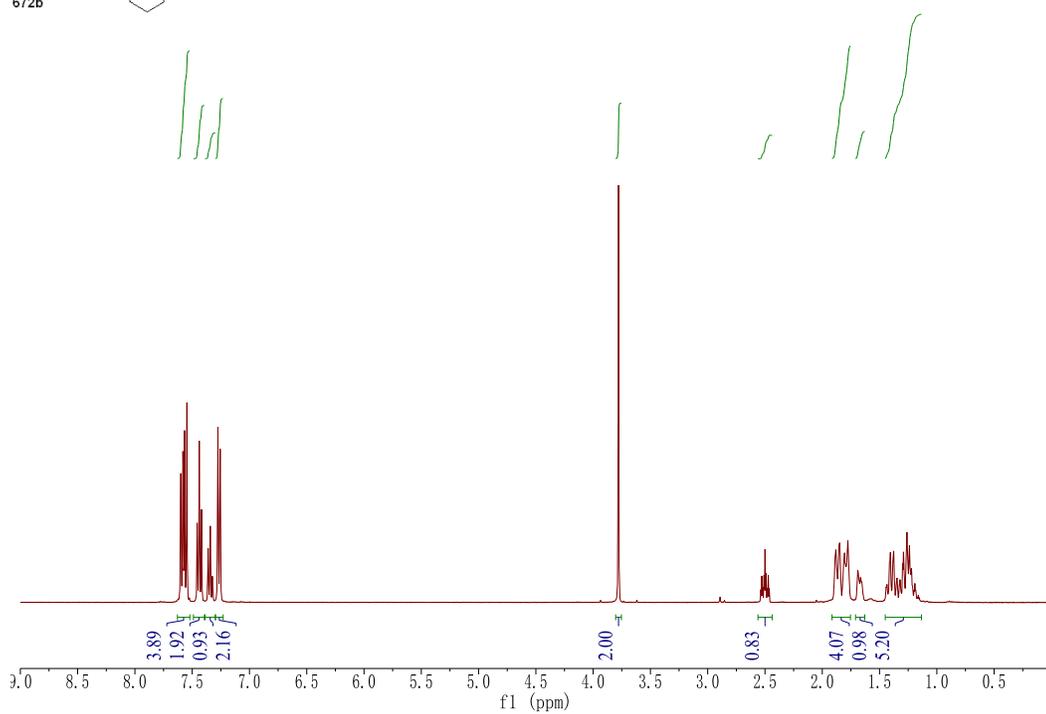
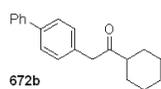


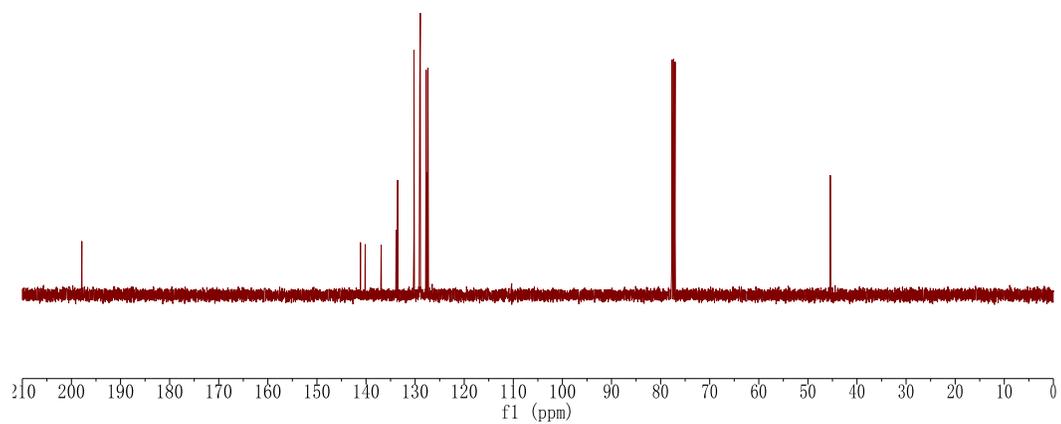
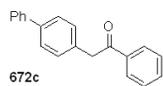
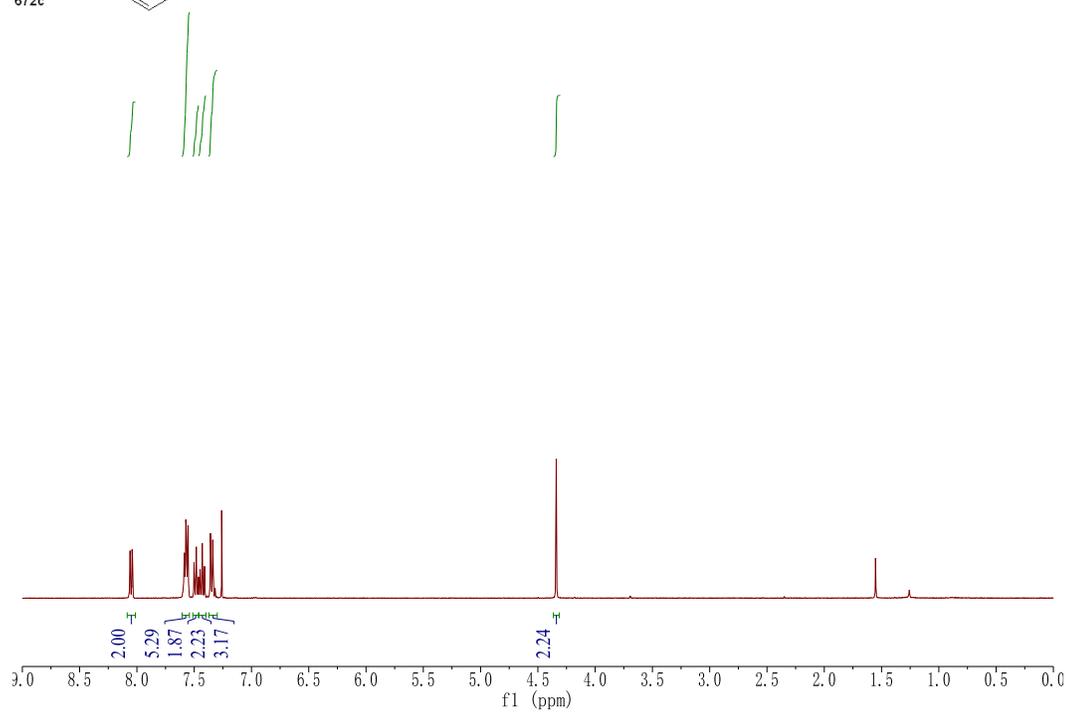
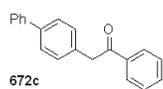


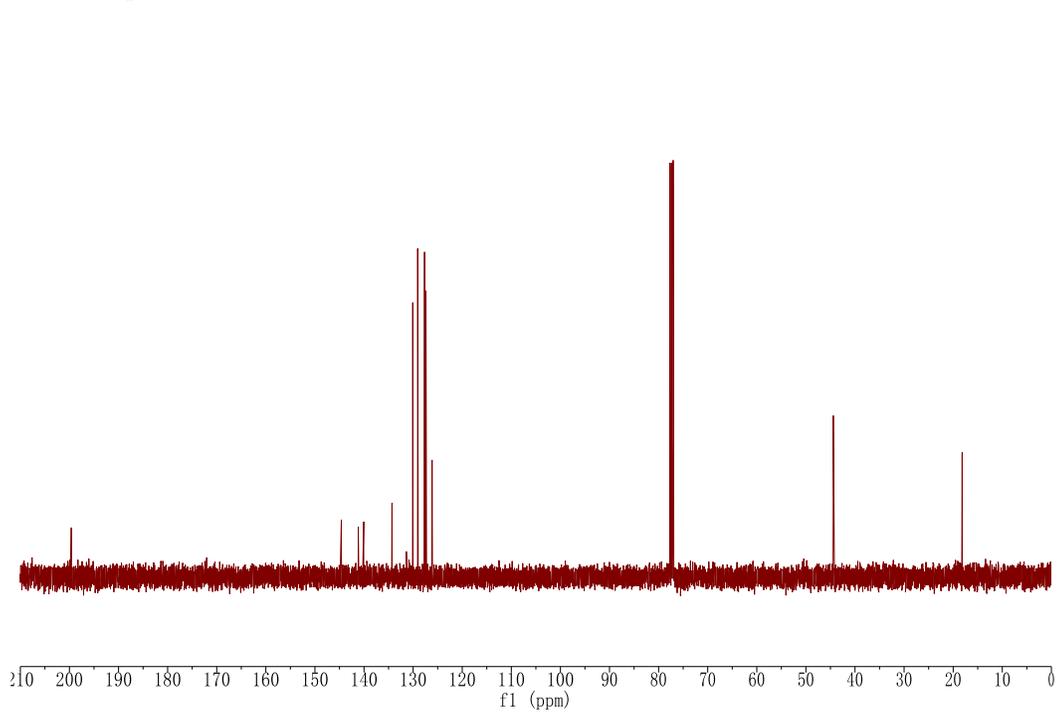
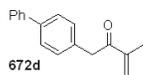
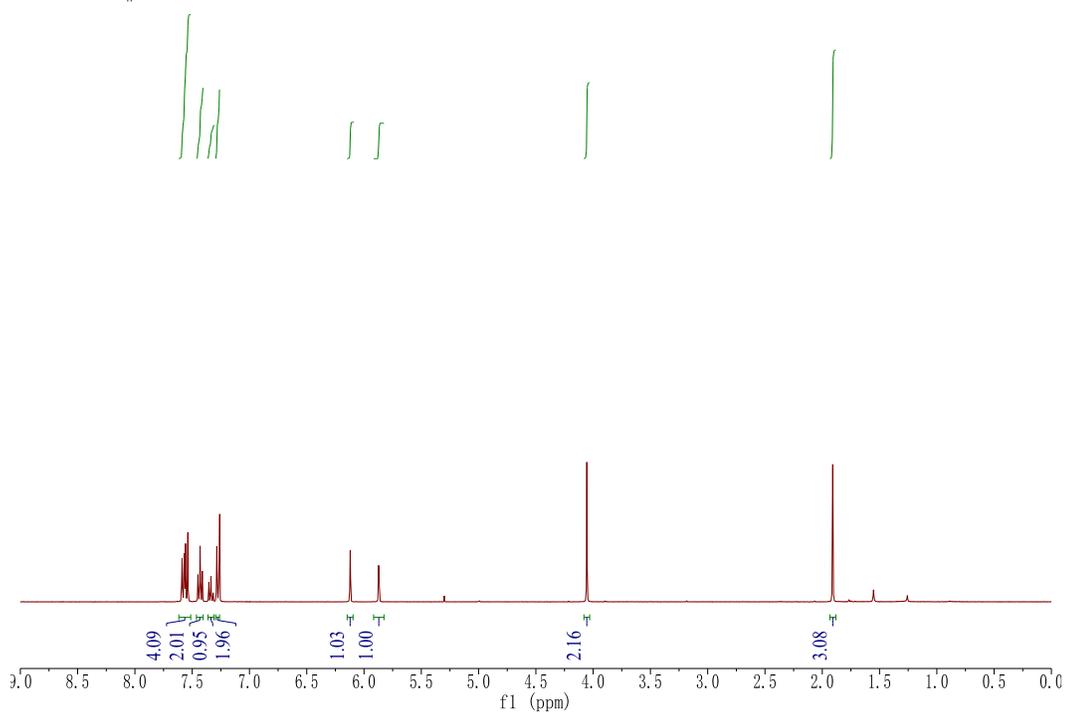
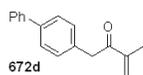


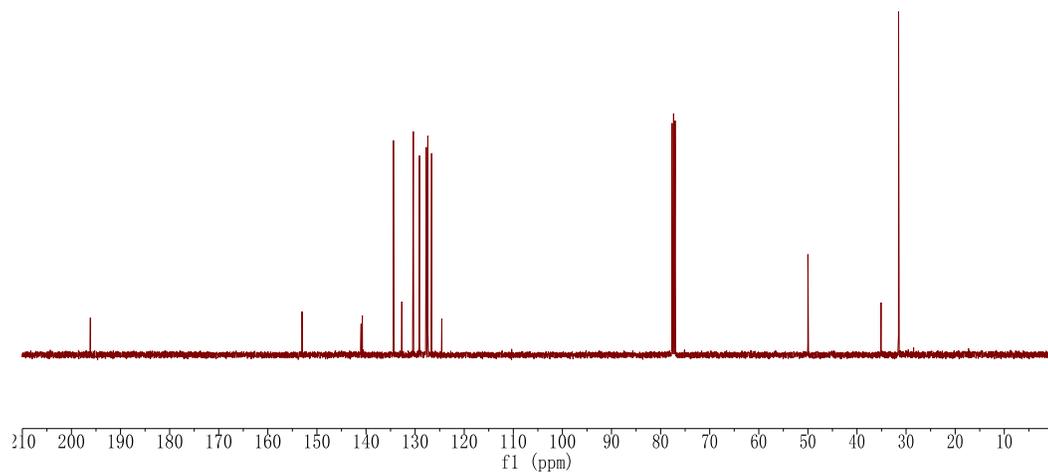
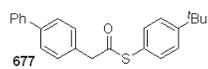
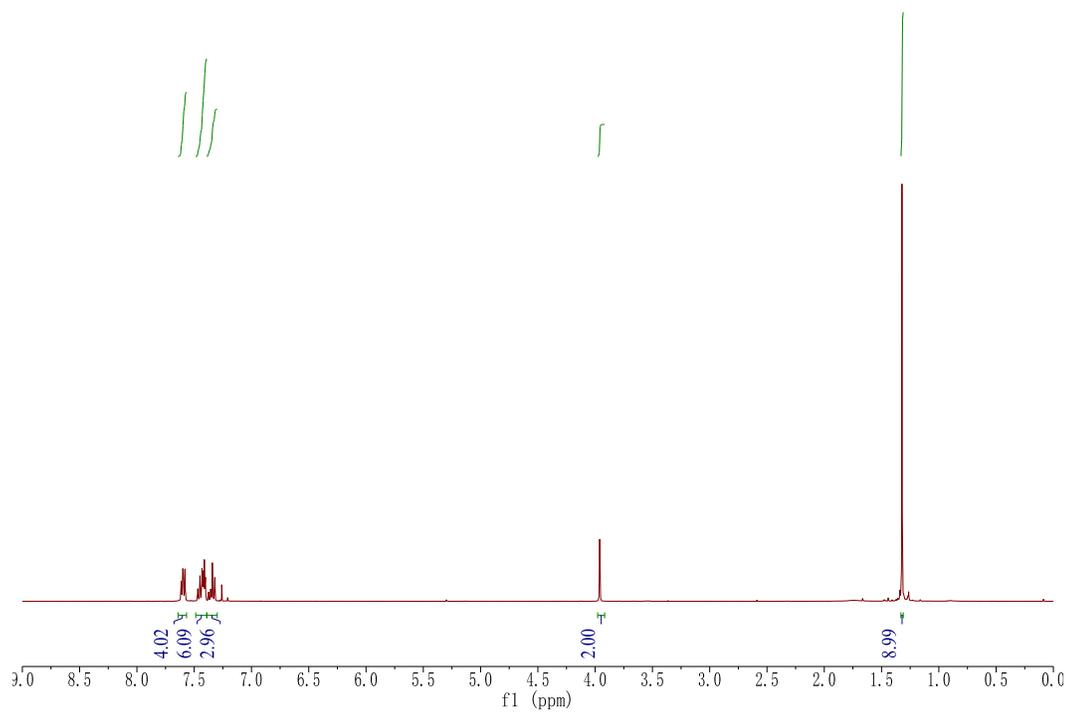
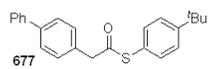


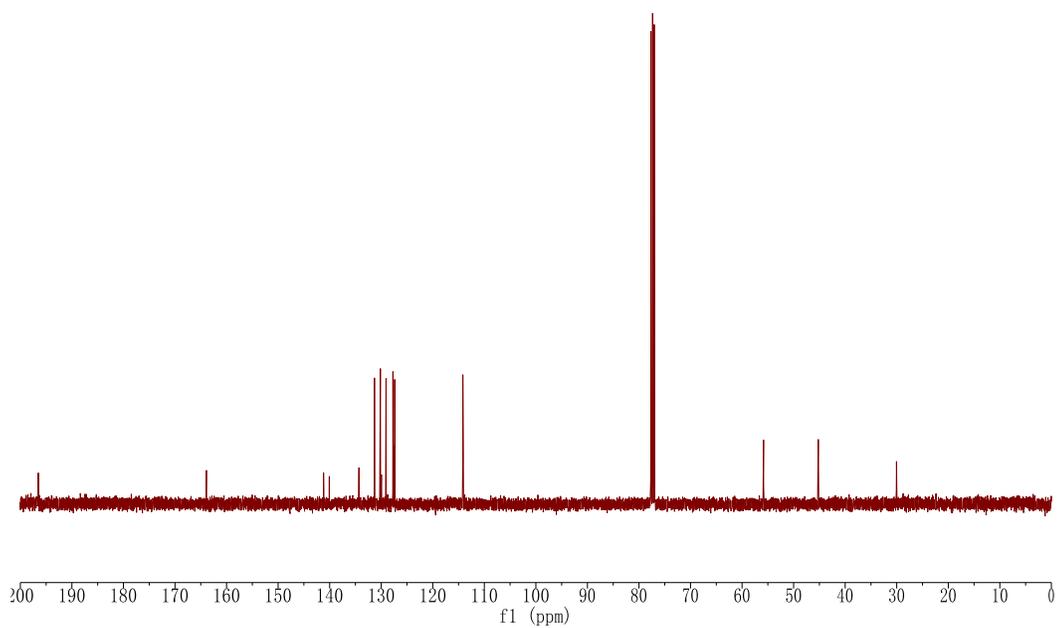
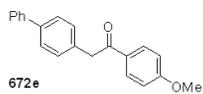
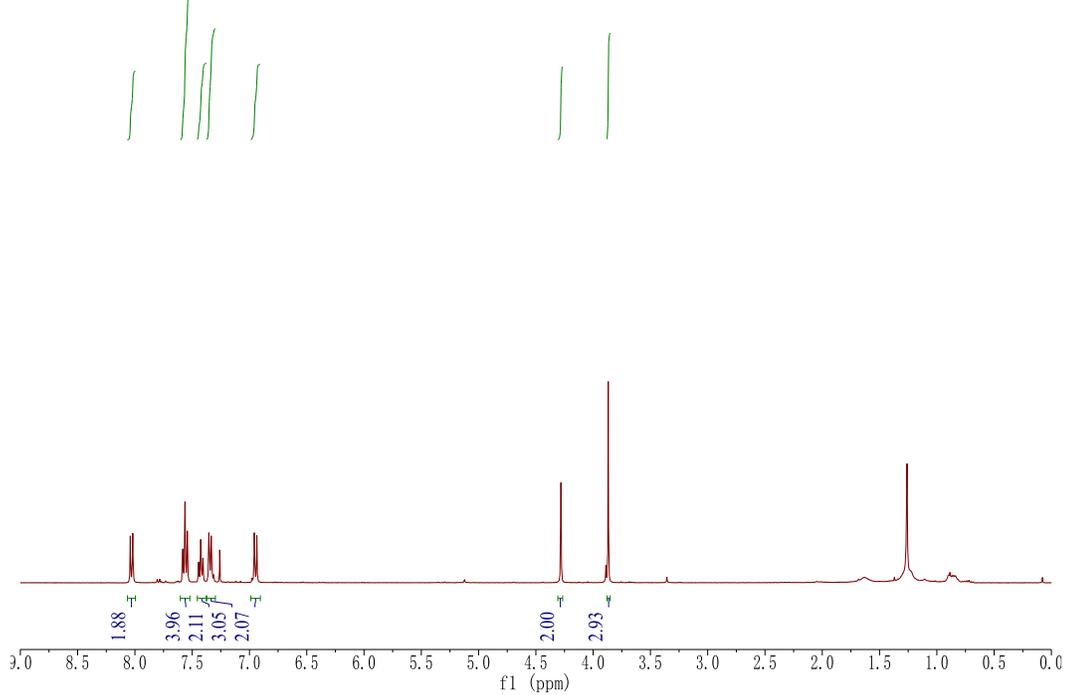
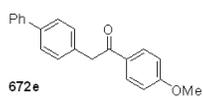


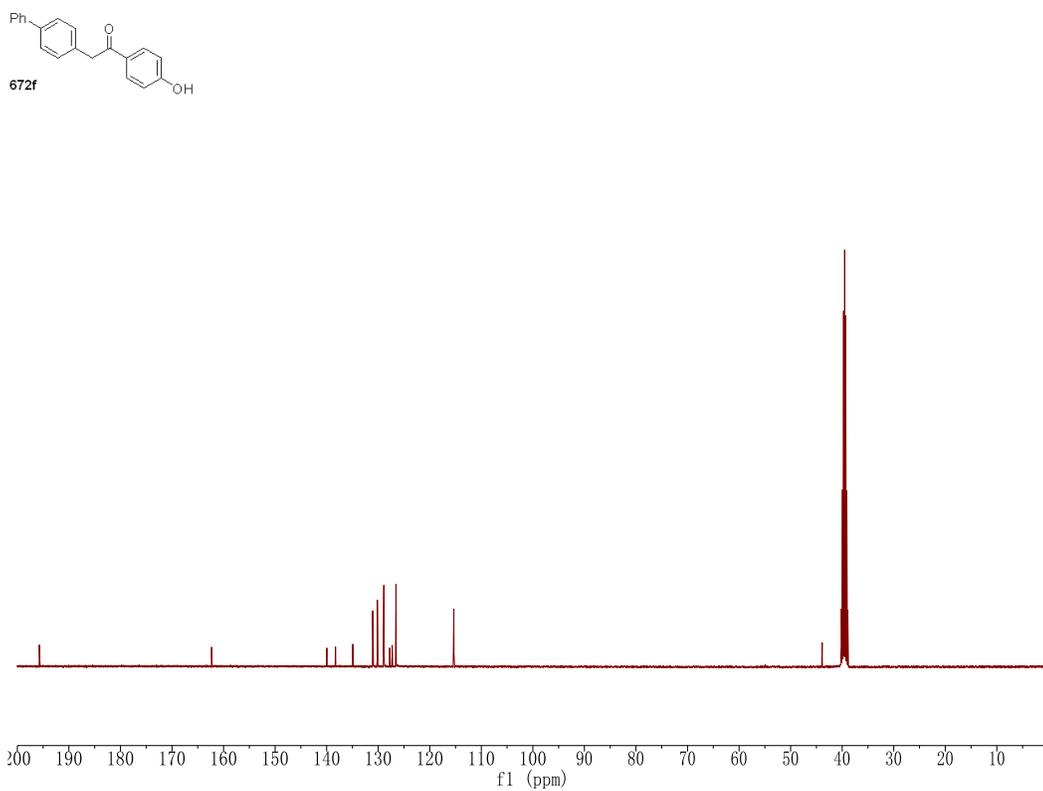
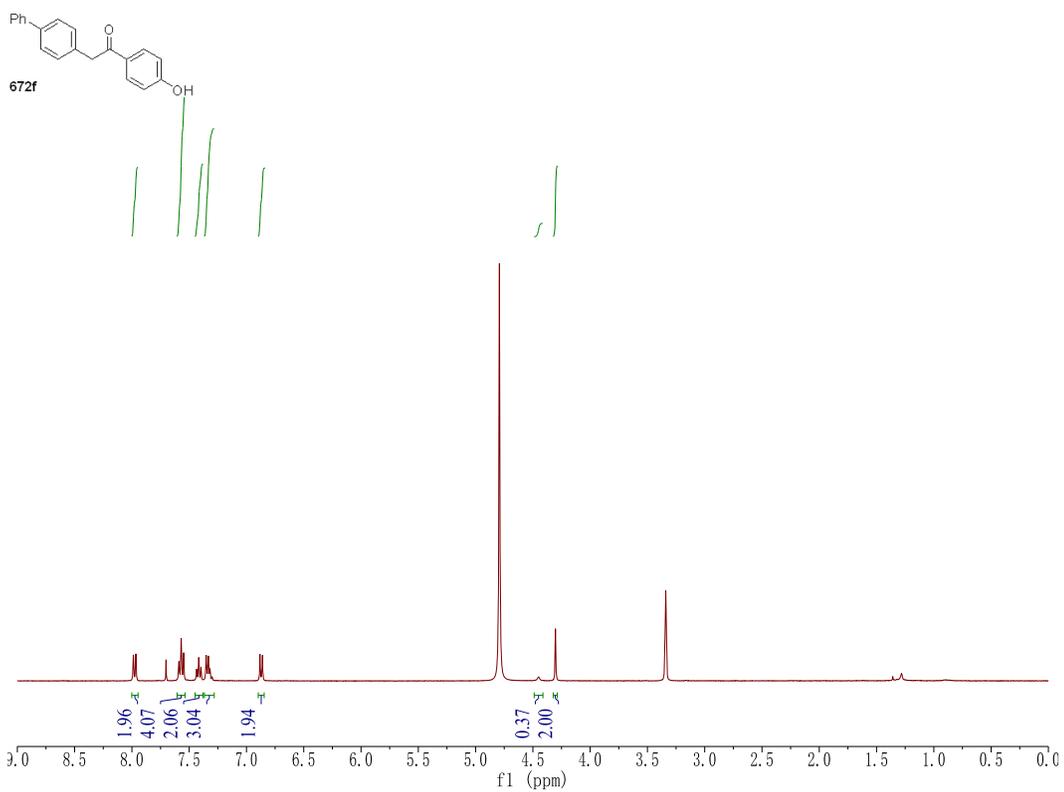












CHAPTER THREE

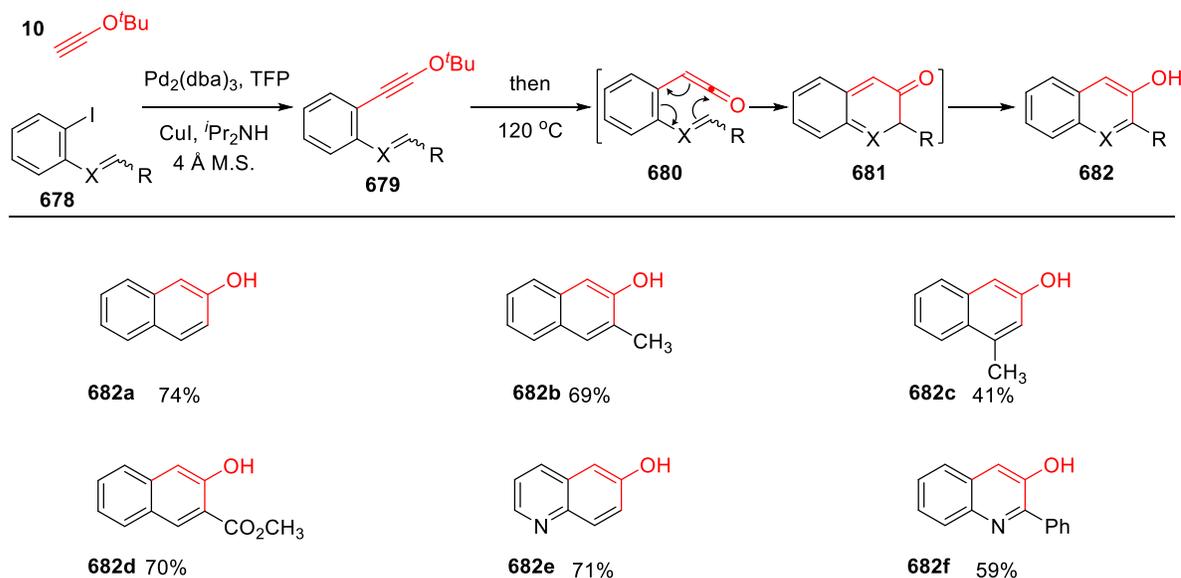
TOTAL SYNTHESIS OF DICTYODENDRINS F, H, AND I

3.1 The Discovery of Ketene Cyclization Reactions

After we developed a novel and practical synthesis of aryl ynol ethers, we found that aryl ynol ethers were ideal synthetic precursors of many useful intermediates and natural products. In this section, we mainly focus on the electrocyclization and cycloaddition reactions, and we will discuss the total synthesis of dictyodendrins. For example, we discovered a novel 6π electrocyclization to form naphthols or quinolinols. Moreover, we developed a hetero-[2+2]-cycloaddition reaction between two aryl ynol ethers, which allowed a rapid synthesis of the highly substituted fused aromatic rings. We further employed this new cyclization reaction in the synthesis of dictyodendrins F, H, and I.

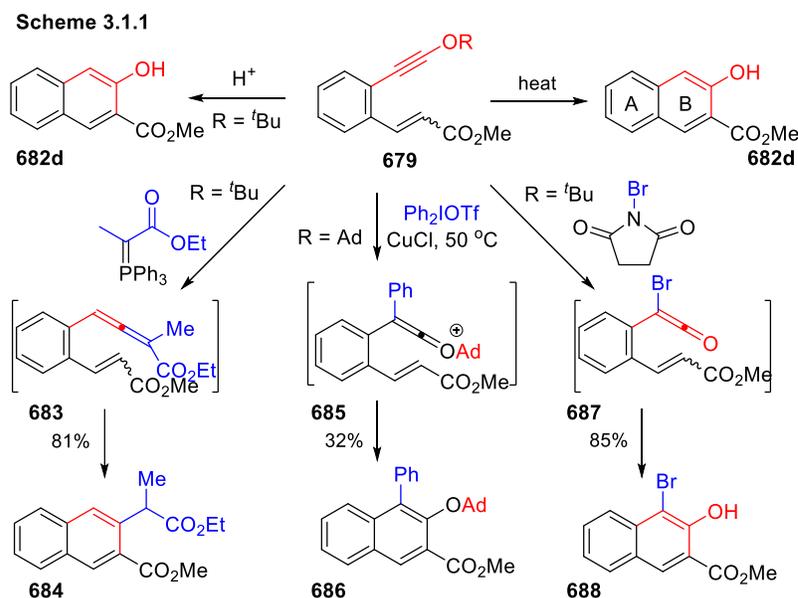
3.1.1 The Discovery of Ketene 6π Electronic Cyclization Reactions

Table 3.1.1



Taking inspiration from the Danheiser benzannulation, we developed a new benzannulation protocol as outlined in **Table 3.1.1**. 2-Iodostyrenes **678** (X = CH, CCH₃) were found to couple

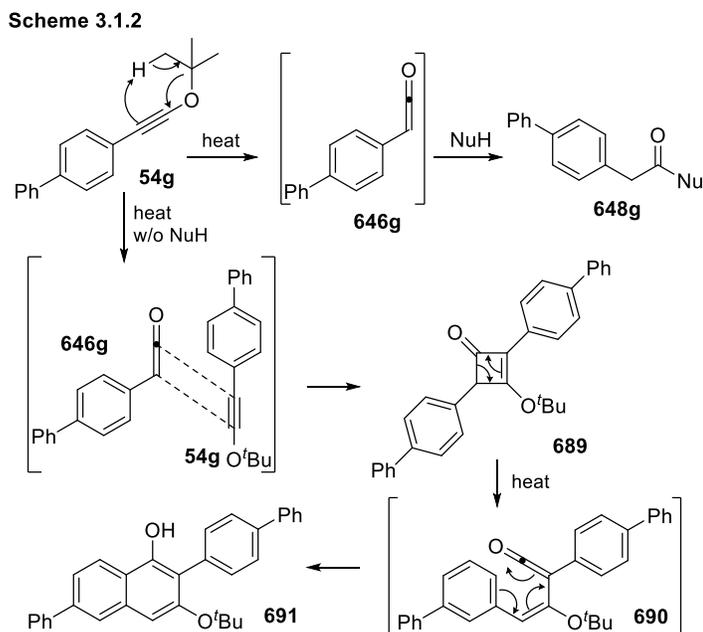
with *tert*-butoxy acetylene **10** and generate *o*-vinylaryl ynol ethers **679**. The following rearrangement proceeded the aryl ketene **680** under the thermal conditions, and the ketene intermediate **680** underwent a 6π electrocyclic ring closure to provide, after tautomerization, the naphthols **682a** - **682d** in good yield. The β -substituted iodostyrenes leading to **682b** and **682d** were used as mixture of *E* and *Z* isomers, and both isomers appeared to participate in the 6π electrocyclizations. The annulation was successful with 2-vinyl-3-iodopyridine to generate quinoline **682e** showing its availability with heteroaryl iodides. Moreover, this cyclization reaction even showed a modest success with the imine derived from 2-iodoaniline to afford the corresponding quinolinol **682f**.



Inspired by the allene **669** formation using the phosphorous ylide to trap the ketene intermediate (**Scheme 2.2.1**), we conducted such allene formation to intercept into the 6π electrocyclization reaction (**Scheme 3.1.1**). As we expected, the allene **683** would give the rise to naphthalene **684**. Accidentally, we found the cyclization would take place under the Lewis

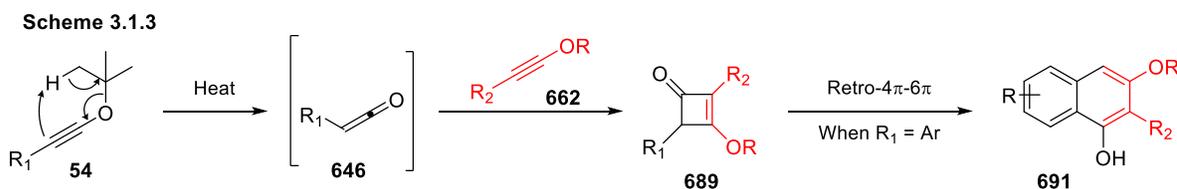
or Brønsted acidic conditions instead of the thermal conditions. In particular, we noted ammonium chloride promoted the cyclization and gave the naphthol product **682d** without heating the substrate **679**. In this manner, we proposed electrophiles other than a proton would initiate the 6π cyclization reactions by triggering the ketene formation from yno-ether **679**. NBS is an ideal electrophile that releases the bromonium cation slowly. Treating the yno-ether **679** with NBS and triethylamine yielded the bromonaphthol **688**. We proposed a bromoketene intermediate **687** was formed before the cyclization. Likewise, we used copper chloride and iodonium salt to generate a phenyl cation, which proceeded the formation of the disubstituted ketene cation and the following 6π electronic cyclization. The cyclized product **686** was formed in a moderate yield.

3.1.2 The Discovery of Hetero-[2+2]-Cycloaddition Reactions Between Yno-ethers



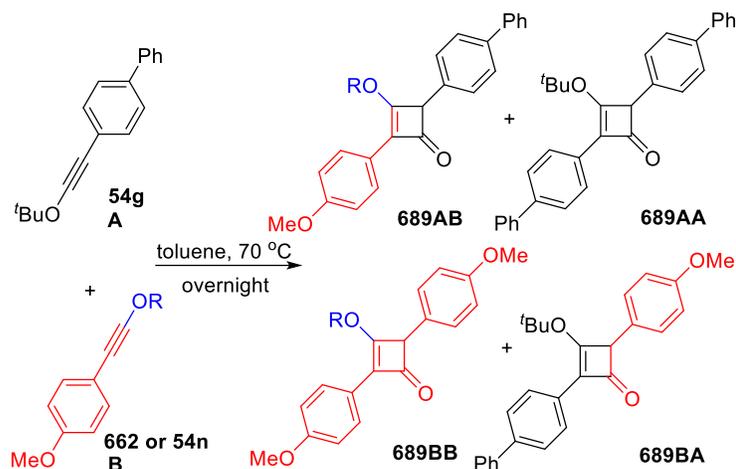
As we discussed in **Chapter Two**, upon heating, the yno-ether **54g** converted to aryl ketene **646g**, which could react with diverse nucleophiles to form the corresponding aryl acetic acid

derivatives **648g** (Scheme 2.2.1).¹ This method allowed for the rapid introduction of a two-carbon motif on the aromatic ring. However, we also noticed the propensity of aryl ketene **646g** to undergo a [2+2]-cycloaddition reaction with the aryl ynol ether starting material **54g** when nucleophilic trapping was slow. This homo-[2+2]-cycloaddition gave di-arylated cyclobutenone **689**.² Upon further heating, cyclobutenone **689** underwent a tandem retro-4 π /6 π electrocyclicization to generate 1,3-dihydroxyl naphthalene **691** in high yield. This transformation is reminiscent of the Danheiser benzannulation, in which vinylated cyclobutenones undergo a retro-4 π affording the corresponding ketene **690** and subsequent 6 π electrocyclicization to generate highly substituted aromatic rings.³ However, the homo-[2+2]-cyclization of the ynol ether limited the diversity of the product, and it highly restricted the type of functional groups attached to the cyclobutenone ring **689**. Consequently, the homo-[2+2]-cyclization and the subsequent rearrangement would only be able to provide minimal functionality onto the final aromatic ring **691**.



We hypothesized a hetero-version of the [2+2]-cycloaddition reaction between ynol ethers would introduce various functional groups and substitution patterns on the cyclobutenone **689** and the subsequent naphthol **691** (Scheme 3.1.3). This modification could make the [2+2]-cyclization more synthetically useful and practical.

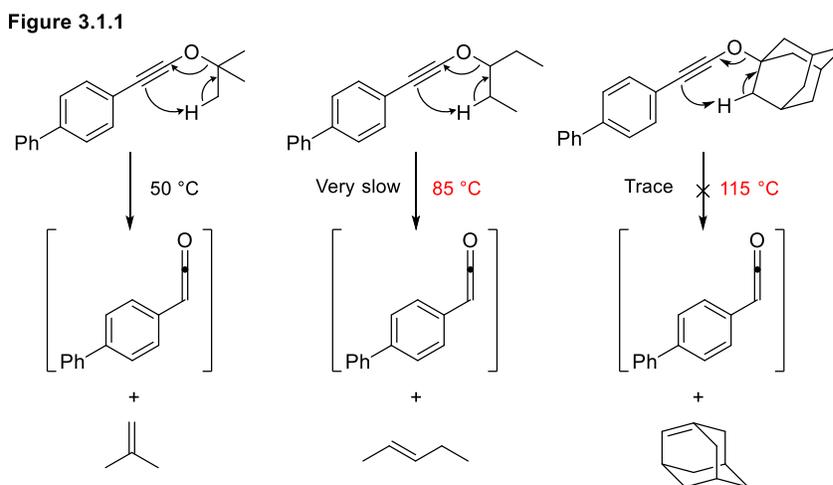
Table 3.1.1



entry	R	equiv B	AB : AA : BB : BA ^a
1	^t Bu (54n)	0.5	1 : 1 : 0.25 : 0.25
2	^t Bu	1.0	4 : 1 : 2.5 : 1
3	^t Bu	2.5	5 : 1 : 10 : 1.5
4	Ad (662)	0.5	3 : 1 : NA : NA
5	Ad	1.0	8 : 1 : NA : NA
6 ^b	Ad	2.5	19 : 1 : NA : NA

^acrude ratio by ¹H NMR. ^b69% isolated yield of **AB**

We first explored the hetero-[2+2]-cycloaddition reaction via a model study between two *tert*-butyl ynol ethers (**54g** and **54n**) (Table 3.1.1). Unfortunately, we observed all four possible cycloaddition products **689**. Changing the equivalents of ynol ether **54g** induced a slight improvement of the selectivity towards the desired hetero-dimer **AB** (entries 1-3). However, increasing **54g** also introduced more undesired hetero-dimer **BA** and homo-dimer **BB**. Since the selectivity was not improved by changing the ratio of the starting materials, we next explored the use of different ynol ethers.

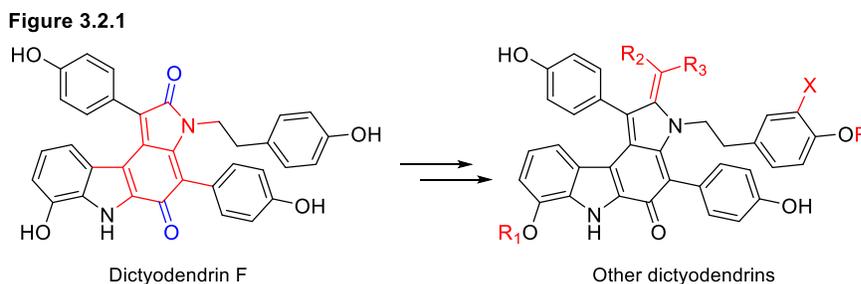


In particular, we reasoned that the use of a thermally stable aryl ynoxy ether would suppress its ketene formation, which should eliminate two undesired products, **BA** and **BB**. As displayed in **Figure 3.1.1**, different alkoxy groups of the ynoxy ethers varied with regard to the temperature required to generate the ketene intermediates. Tert-butyl group gave a relatively fast ketene generation rate, because of the statistical reason related to the number of the β -protons. Respectively, 3-pentyl group formed the ketene at a high temperature and a low rate. With this in mind, we synthesized adamantyl ynoxy ether **662** (**Chapter Two**), and we suggested its cage structure forbade the 1,5-hydride shift to prevent the generation of a bridge-head double bond. As expected, no aryl ketene was generated when adamantyl ynoxy ether **662** was heated at reflux in toluene for several days, and a quantitative recovery of **662** was possible. Therefore, we tested adamantyl ynoxy ether **622** in the [2+2]-cycloaddition reaction with *tert*-butyl ynoxy ether **54g** (**Table 3.1.1**, entries 3-6). To our delight, a vast improvement for the desired homodimer **AB** was observed with no appreciable amount of products **BB** and **BA**. Further improvement in this reaction was achieved by increasing the amount of ynoxy ether **662** (entries 3-6). A 19:1 selectivity of the hetero- versus homo-cyclization product was obtained

when 2.5 equivalents of **662** were used. In this context, the methyl ynoyl ether would also not undergo the retro-ene reaction to form ketene. However, methyl ynoyl ethers are much more hydrolytically labile than their bulkier counterparts. Thus, the adamantyl ynoyl ether appeared to combine stability with the reactivity profile we needed.

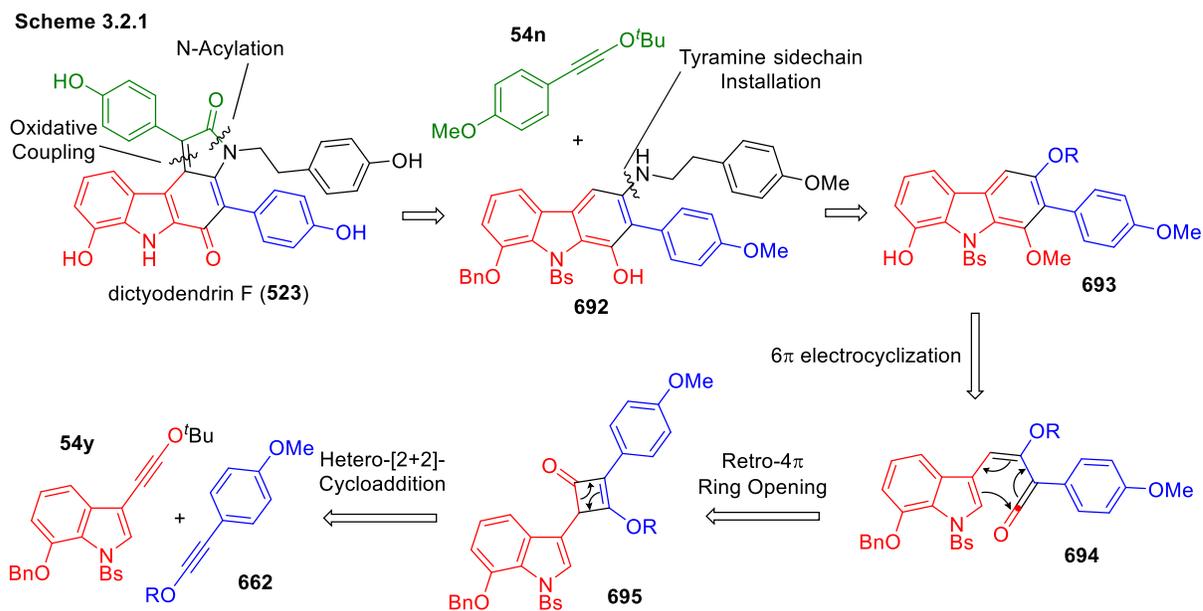
3.2 Total Synthesis of Dictyodendrins F, H, and I

As we discussed in **Chapter One**, dictyodendrins were isolated from marine sponges, and they show many interesting biological activities, like telomerase inhibition,^{4,5} β -site amyloid-cleaving enzyme 1 (BACE1) inhibition,⁶ and cytotoxicity to several cancer cell lines. Additionally, dictyodendrins contain a highly substituted pyrrolo[2,3-c]carbazole core⁷ at the phenol or quinone oxidation state, whose intriguing structures attracted a number of top synthesis group worldwide.



In contrast to all the previous report, we thought the synthesis of dictyodendrin F as the mother member of this natural products family (**Figure 3.2.1**). In particular, we envisioned some small modification of dictyodendrin F, like halogenation, selective sulfate formation, and alkylations, could provide the concise access to other dictyodendrins. Therefore, we proposed a total synthesis of dictyodendrin F

3.2.1 *Retro-Synthetic Analysis of Dictyodendrins*

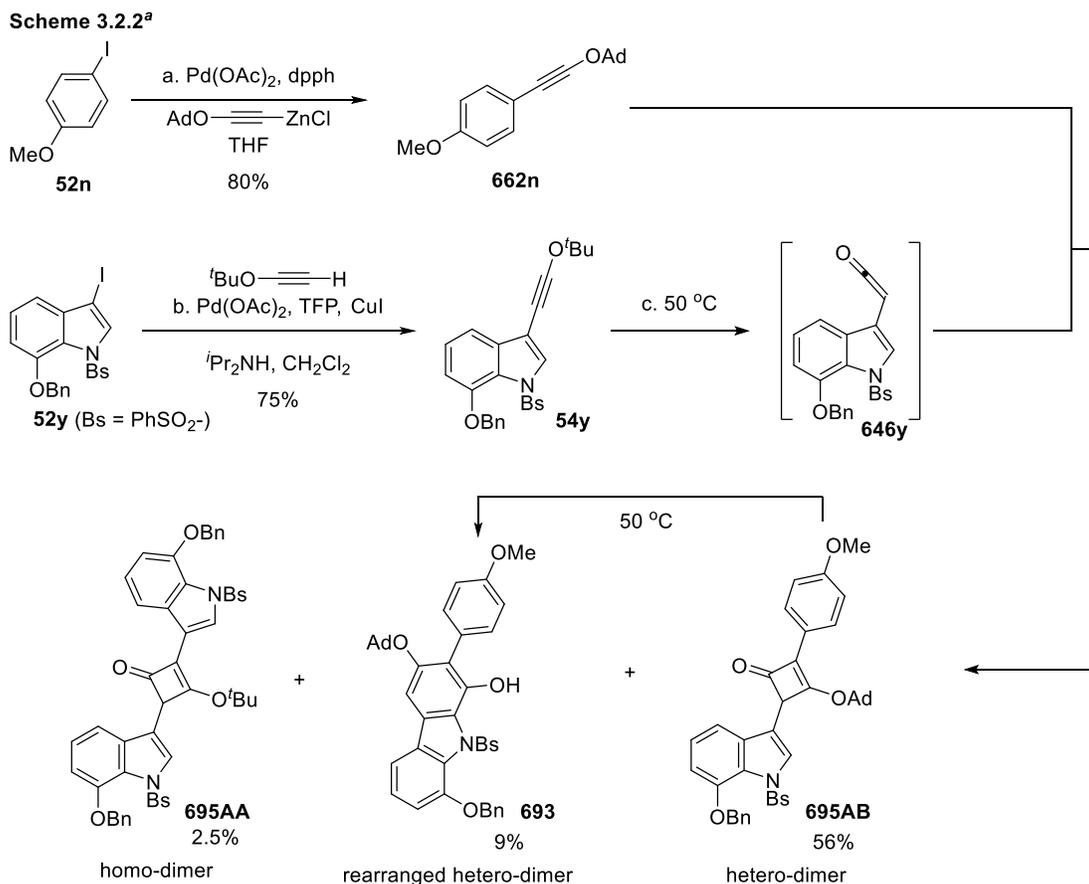


In the accordance with the cycloaddition/rearrangement sequence, we hypothesized that a hetero-[2+2]-cycloaddition between indole ynoles **54y** and 4-anisoyl ynoles **662** would allow for a rapid synthesis of the dictyodendrin carbazole core **693** via the cyclobutenone **695** and ketene **694** (Scheme 3.2.1). To advance carbazole **693** towards the dictyodendrin F (**523**) we envisioned replacing the phenol ether with the tyramine side chain to give aminocarbazole **692**. A late stage construction of the oxypyrrrole ring could involve *N*-acylation followed by an intramolecular oxidative coupling to obtain the desired natural product. This new synthetic route is short but flexible as it also provides access to dictyodendrins H and I with an installation of a halogenated tyramine side chain.

3.2.2 Total Synthesis of Dictyodendrin F

Following the preliminary optimization of the hetero-[2+2]-cycloaddition reaction, we next attempted to use this reaction with *tert*-butyl indolyl ynoles **52y** and **662n** to synthesize

dictyodendrins. The adamantyl anisoyl ynol ether **662n** was synthesized via a Negishi coupling of adamantoxyethynyl zinc chloride and 4-iodoanisole **52n** (Scheme 3.2.2). We optimized this reaction according to Himbert and Löffler's original protocol for related couplings used PPh₃ as the ligand.⁸ As a complementary work to our ketene surrogate coupling reaction, the details of optimization have been discussed in **Chapter Two**.



^aReagents and conditions: (a) 1,6-bis(diphenylphosphine)hexane (10 mol%), Pd(OAc)₂ (5 mol%), adamantoxyethynyl zinc chloride (1.5 equiv), THF, 23 °C, 4h, 80%; (b) Pd(OAc)₂ (10 mol%), tri(2-furyl)phosphine (20 mol%), CuI (15 mol%), *t*-butoxyacetylene (10 equiv), diisopropylamine/DCM (1:1), 23 °C, 12 h, 75%; (c) toluene, 50 °C, 9 h, 56% **695AB** (68% b.r.s.m.).

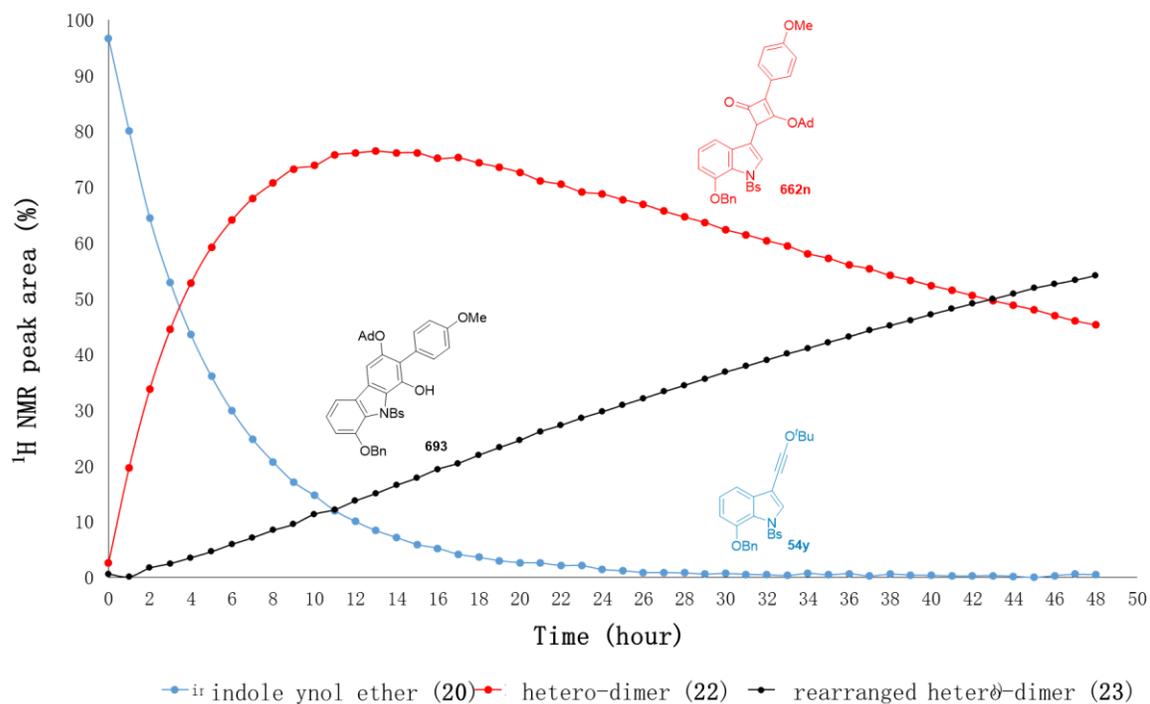
Under optimized conditions, 1,6-bis(diphenylphosphine)hexane (dppe) ligand afforded adamantyl anisoyl ynol ether **662n** in 80% yield (Scheme 3.2.2).⁹ In parallel, *tert*-butyl indolyl

ynol ether **54y** was synthesized according to the Sonogashira coupling condition that we discussed previously.¹ Dichloromethane was added as co-solvent to improve the solubility of the starting material **52y**, and a 75% yield of the benzene sulfonamide (Bs) protected indole **54y** was obtained.

With the desired ynol ethers **54y** and **662n** in hand, we turned our attention to the key [2+2]-cycloaddition reaction. As we established in the model study, heating indolyl *tert*-butyl ynol ether **54y** to 50 °C afforded indolyl ketene **646y**, which reacted with adamantyl ynol **662n**. The cycloaddition formed the desired product **695AB** as an 11:1 mixture with homo-dimer **695AA**. As expected there was no ketene generated from adamantyl ynol ether **662n**. Interestingly, the protecting group of the indole nitrogen affected the hetero/homo dimer selectivity (**695AB:695AA**; N-Bs: 11:1; N-Cbz: 7:1; N-Ns: unstable; N-Ts: poor solubility). Moreover, the Bs-protected indole could be synthesized most efficiently among the substrates that we examined.¹⁰

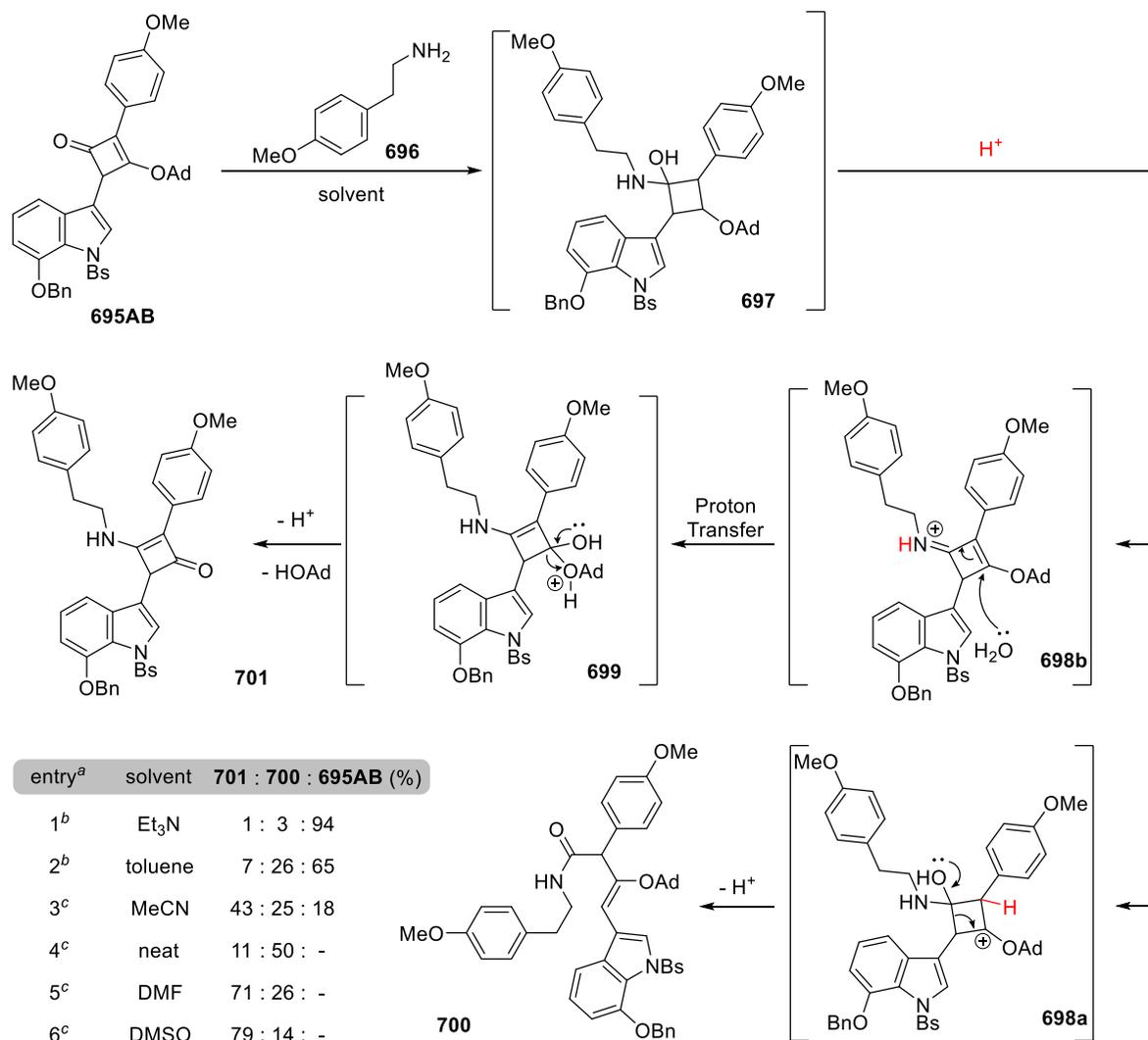
To our surprise, the desired cyclobutenone **695AB** spontaneously underwent the retro- $4\pi/6\pi$ electrocyclization to yield the *O*-adamantyl carbazole **693** in 50-60% yield after 48 h at 50 °C. In the model study (**Table 3.1.1**), the electrocyclization product was not formed until the reaction was heated over 90 °C for extended times. To take advantage of the unexpected formation of carbazole **693**, we next attempted to introduce the tyramine side chain. Unfortunately, we were unable to displace or remove the adamantyl group successfully. We therefore decided to introduce the tyramine moiety onto the cyclobutenone **695AB** instead of at the carbazole stage. This idea was inspired by literature precedent from Turnbull and Moore, wherein they replaced a methoxyl group on a cyclobutenone with an aliphatic amine.^{3d}

Figure 3.2.2



For cyclobutanone **695AB** to serve as a viable synthetic intermediate, we needed to stop the reaction of ynl ethers **622n** and **54y** after [2+2]-cycloaddition, but before rearrangement to carbazole **693**. *In situ* ^1H NMR was utilized to study the product distribution from this reaction as a function of time (Figure 3.2.2).¹¹ Analysis of this experiment showed a quick consumption of *tert*-butyl ynl ether **54y** as well as accumulation of the desired cyclobutenone **695AB** within the first 12 hours. Meanwhile, the formation of the undesired carbazole **693** was comparatively slow. Therefore, terminating the cycloaddition after 9 hours at 50 °C allowed us to isolate 56% cyclobutenone **695AB**, 9% carbazole **693**, 2.5% homo-dimer **695AA**, and 20% unreacted indolyl ynl ether **54y** (Figure 3.2.2). Re-subjection of the unreacted indolyl ynl ether **54y** to the reaction conditions afforded a 68% total yield of the desired cyclobutenone **695AB** and 14% of undesired carbazole **693** (Scheme 3.2.2).¹²

Scheme 3.2.3



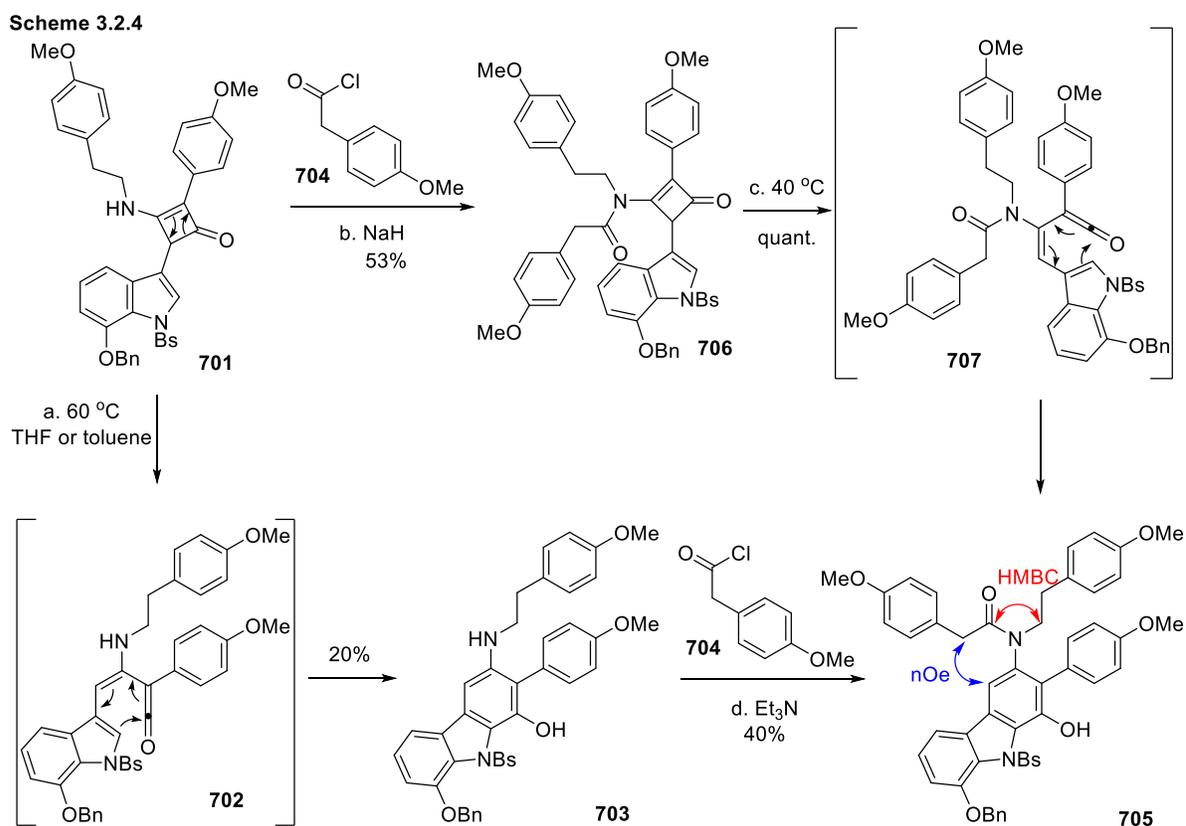
^aReagents and conditions: *O*-methyltyramine (5 equiv), solvent, 36 h, 23 °C. ^bNMR Integration ratio. ^cIsolated yields.

With access to gram quantities of cyclobutenone **695AB**, the substitution reaction was then studied. Besides Turnbull and Moore's work,^{3d} similar substitution reactions have been extensively studied, wherein different nucleophiles were investigated to replace alkoxy moieties on cyclobutenediones.¹³ Inspired by previous studies, we assumed that *O*-methyltyramine **696** would react with the carbonyl on cyclobutenone **695AB** to form hemiaminal **697** (Scheme 3.2.3). Loss of water would yield the iminium **698b**. Substitution

with water and loss of adamantanol from enamine **699** should furnish the desired cyclobutenone **701**. Alternatively, loss of adamantyl cation from **698b** could also form ketone **701** directly. Performing the reaction in acetonitrile unfortunately led to a substantial amount of undesired ring-open product **700** (Scheme 3.2.3, entry 3). The ring-open product **700** presumably also arose from hemiaminal intermediate **698a** via protonation and fragmentation. The product distribution was inert to changes in temperature, pH, or concentration, but it displayed a noticeable solvent effect. In non-polar solvents (such as toluene, entry 2) or amine solvent (such as Et₃N, entry 1), the reaction was slow and favored the ring-open product **700**. Even if cyclobutenone **695AB** was treated with neat tyramine **696**, we failed to obtain a reasonable yield of the desired product **701**, although starting material was consumed (entry 4). In contrast, highly polar solvents accelerated the reaction and preferentially led to the formation of vinylogous amide **701**. For example, when DMF was the reaction solvent, full conversion of starting material **695AB** indicated a faster reaction rate, and the desired tyramine-substituted product **701** was isolated in 71% yield (entry 5). Finally, DMSO gave the desired product in the highest yield, 79% (entry 6). Cyclobutenone **701** proved to be light-sensitive, but it could be handled in amber vials and dark fume hoods.

The next step in the synthesis was the retro-4 π /6 π rearrangement. We first tested this rearrangement by heating cyclobutenone **701** at 60 °C (Scheme 3.2.4). A 4 π electrocyclic ring-opening could generate the conjugated ketene intermediate **702**; subsequent 6 π electrocyclization and tautomerization would afford carbazole **703**. However, this substrate generated only a 20% yield of desired product **703** along with numerous unidentified decomposition products. Further study revealed carbazole **703** was prone to aerobic oxidation

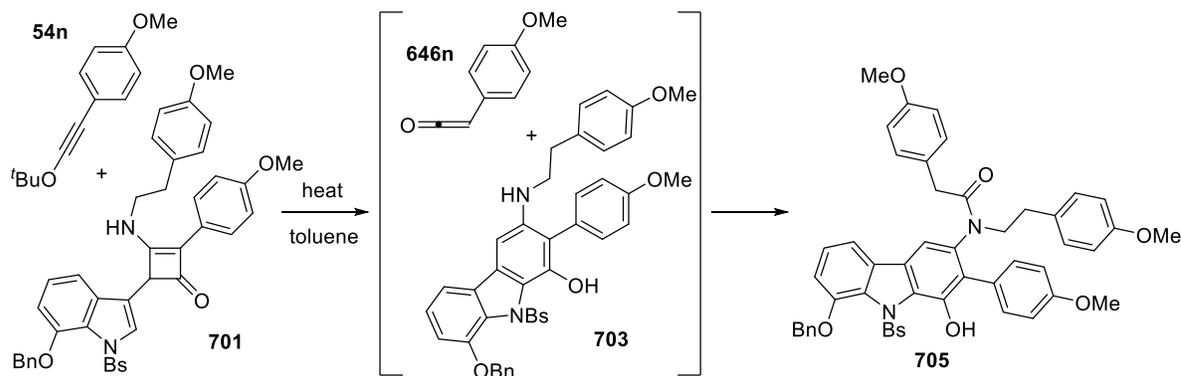
and was thermally unstable. We hypothesized that the instability of carbazole **703** arose from electron-rich heteroaromatic ring system. We therefore reasoned that N-acylation might reduce the electron density of carbazole **703**, thereby generating a more stable intermediate. To test this hypothesis, we acylated carbazole **703** using the acid chloride **704** to generate carbazole **705** in 40% yield. The regioselectivity of this acylation was confirmed using HMBC and nOe experiments. As expected, the N-acylated carbazole **705** was much more stable under aerobic and thermal conditions than its N-H counterpart **703** was. Given the increased stability of the acylated product, we attempted to avoid isolating the unstable intermediate **703** in order to improve the total yield of the sequence.



^aReagents and conditions: (a) THF or toluene, 60 °C, overnight, 20%; (b) NaH (1.1 equiv), 4-anisoyl acetic acid chloride (**704**, 1.1 equiv), THF, -78 °C to r.t., 3-4 h, 53%; (c) toluene, 40 °C, overnight, quantitative yield; (d) Et₃N (2.0 equiv), 4-anisoyl acetic acid chloride (2.0 equiv), THF, -78 °C to r.t., overnight, 40%.

Thus, cyclobutenone **701** was N-acylated to provide vinylogous imide **706**. Unlike the N-acylation of carbazole **703**, the acylation of cyclobutenone **701** required a strong base, NaH. Moreover, this acylation was messy, only yielding 53% of the desired intermediate **706**. Even though the subsequent electrocyclization gave the carbazole **705** in quantitative yield, the total yield for these two steps was disappointing due to the difficult N-acylation.

Table 3.2.1



Entry ^a	Temp.	Product	Conv.
1	50 °C	27%	40%
2	60 °C	38%	60%
3	70 °C	47%	100%

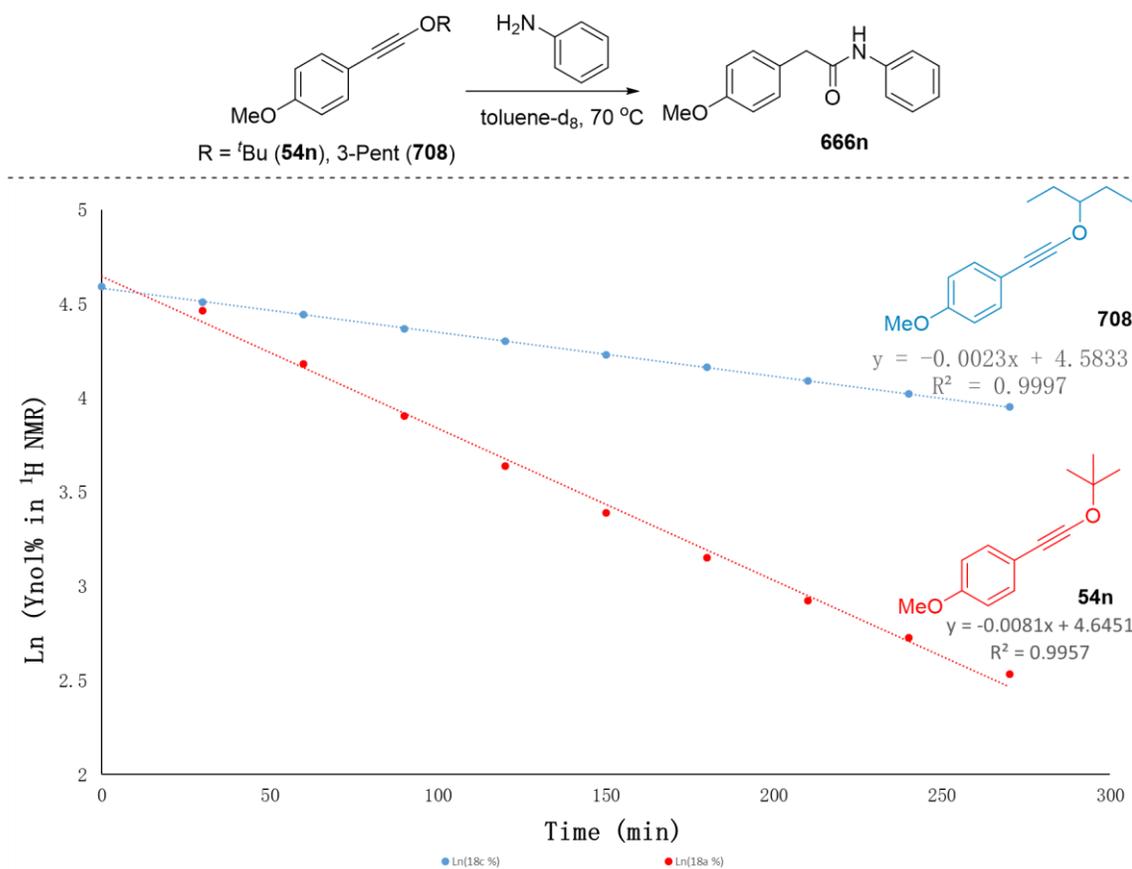
^aReaction conditions: **18a** (5.0 equiv), 12 h, toluene.

An alternative solution to address the instability of unacylated carbazole **703** would be to trap it *in situ* in a one-pot electrocyclization/acylation sequence. All efforts to effect this one-pot procedure were in vain using a traditional acid chloride/base conditions. The starting material **701** quickly decomposed under thermal conditions in the presence of any base. We therefore turned to chemistry previously developed in our lab using *tert*-butyl ynoyl ethers as acylating reagents. Heating ynoyl ethers generates aryl ketenes under neutral conditions. Hence, we carried out a one-pot electrocyclization-acylation reaction with cyclobutenone **701** and 4-anisoyl *tert*-butyl ynoyl ether **54n** as the acylating reagent (Table 3.2.1). We were pleased to

see a 27% yield of the acylated carbazole **705** was obtained with 60% starting material **701** recovered at 50 °C (40% conversion, entry 1). The mass recovery of this reaction was encouraging, but the low conversion left room for improvement.

Initial efforts to optimize this retro-4 π /6 π -cyclization-acylation cascade reaction focused on increasing the reaction temperature to achieve a high conversion. A slight increase in temperature to 60 °C led to a small improvement in yield (38%, **Table 3.2.1**, entry 2). Unfortunately, the unacylated carbazole **703** was also observed, as well as its decomposition products at this temperature. Increasing the reaction temperature further to 70 °C only gave a 47% yield at 100% conversion (entry 3). Again, we used *in situ* ¹H NMR to study this reaction. Unacylated carbazole **703** was present throughout the reaction time course, indicating that the acylation actually occurred on carbazole **703**, not on the cyclobutenone **701**. Moreover we found that the *tert*-butyl ynol ether **54n** was consumed in the first 4 hours at 60 °C. These observations indicated that there was insufficient ketene **646n** being formed in the later stages of the reaction to trap newly formed carbazole **703**. Accordingly, we next tried a batchwise addition of ynol ether **54n** to introduce aryl ketene **646n** slowly, but this attempt to increase the yield had a limited success.¹⁴ Batchwise addition of ynol **54n** likely sustained low levels of ketene **646n** for a longer time relative to our original reaction conditions, as intended. However, this protocol also increased the chance of introducing oxygen and diluted the reaction medium, both of which were detrimental. We therefore considered alternative approaches to generate aryl ketene **646n** more slowly.

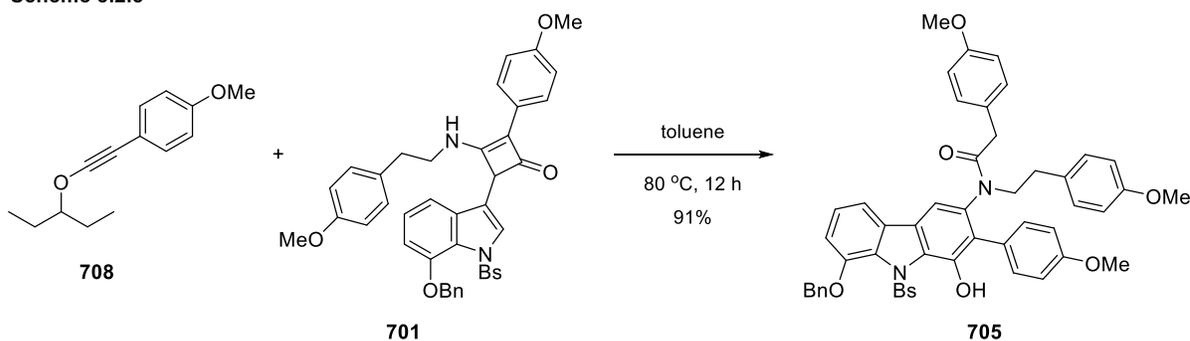
Figure 3.2.2



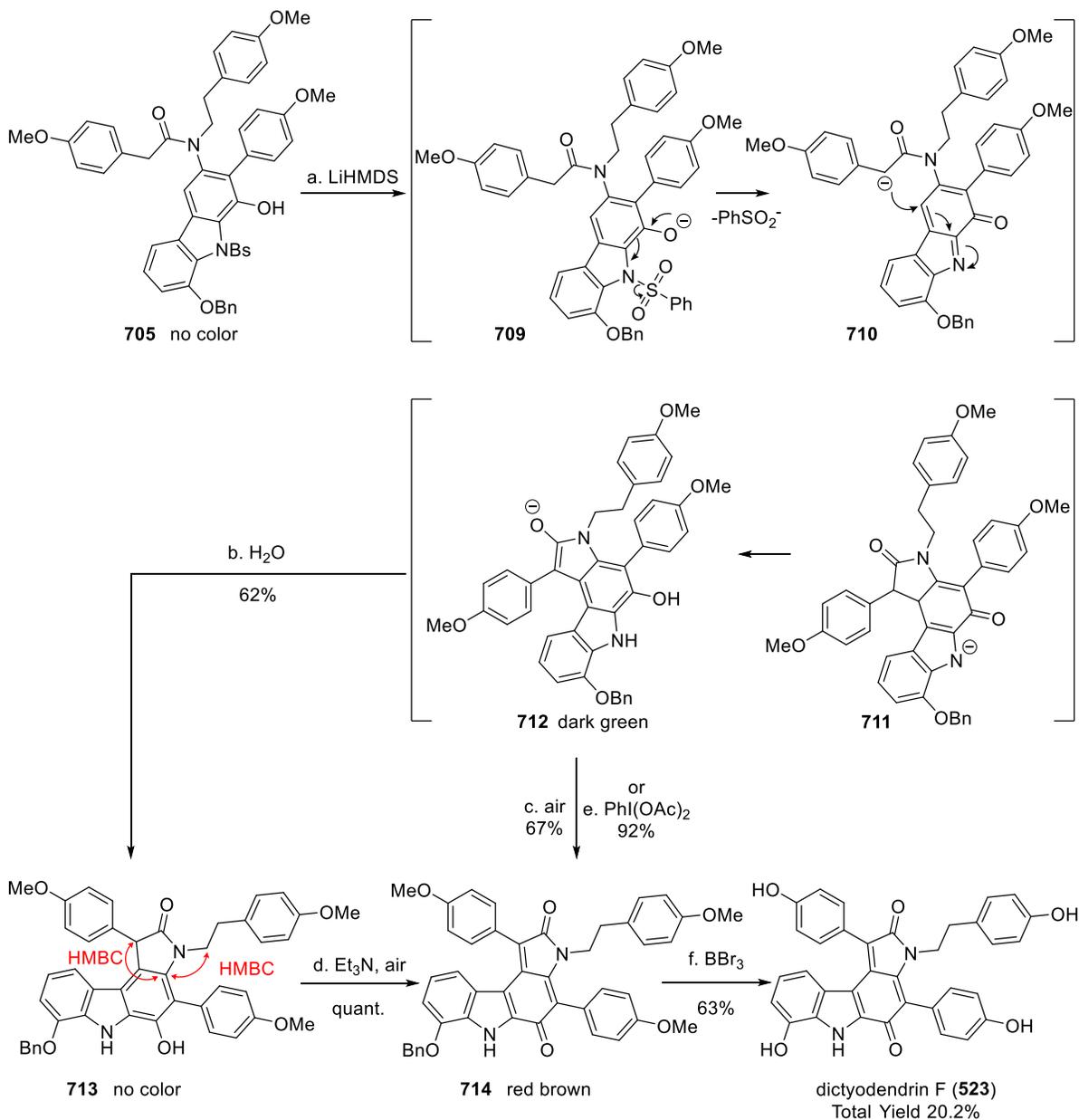
We reasoned that the kinetics of ketene generation could be modulated by changing the *tert*-butyl group of the yno1 ether, which could allow for extending the release time of aryl ketene **646n** during the reaction. Thus, with slower generation, aryl ketene **646n** could be available to acylate carbazole **703** throughout the entire 12 hours reaction without the need for a slow addition protocol. To identify an appropriate ketene precursor and to quantify the rate of ketene generation, we studied the acylation of aniline (**Figure 3.2.2**). Tracking these reactions by *in situ* ¹H NMR, we could obtain the rate of ketene generation from various anisoyl ynol ethers at 70 °C.¹¹ The kinetic traces shown in **Figure 3.2.2** indicated that ketene generation was 1st order in ynol ether **54n** and **708**, as expected. The 3-pentyl anisoyl ynol ether **708** emerged as

an ideal aryl ketene precursor. Specifically, 3-pentyl yno l ether **708** generated ketene **646n** approximately one-third as quickly as *tert*-butyl yno l ether **54n**, leading to ketene generation over a longer time period. Ultimately, utilizing 3-pentyl anisolyl yno l ether **708** as the acylating reagent in the retro- $4\pi/6\pi$ -cyclization-acylation cascade sequence, we obtained the desired N-acylated carbazole product **705** in 91% isolated yield (**Scheme 3.2.5**).

Scheme 3.2.5



With the acylated carbazole intermediate **705** in hand, we turned our attention to the oxidative coupling reaction to form the desired oxypyrrole ring. Although not totally unprecedented, there are limited reports of analogous intramolecular oxidative couplings between benzyl and aryl carbons. The Baran group demonstrated a series of iron- and copper-mediated intermolecular oxidative couplings between enolates and indoles or pyrroles,¹⁵ but this was limited to electron rich heterocycles as the oxidative coupling partner. More recently, the Ma group used a di-radical intermediate to couple the C3 of an indole and the α -position of an aryl acetamide in their synthesis of communisin F.¹⁶ However, an electron withdrawing group on the aryl acetamide was required to achieve a good yield for this reaction. Subjecting substrate **705** to Ma's conditions, I₂ and LiHMDS, only resulted in *para*-iodination of the phenol.¹⁷

Scheme 3.2.6^a

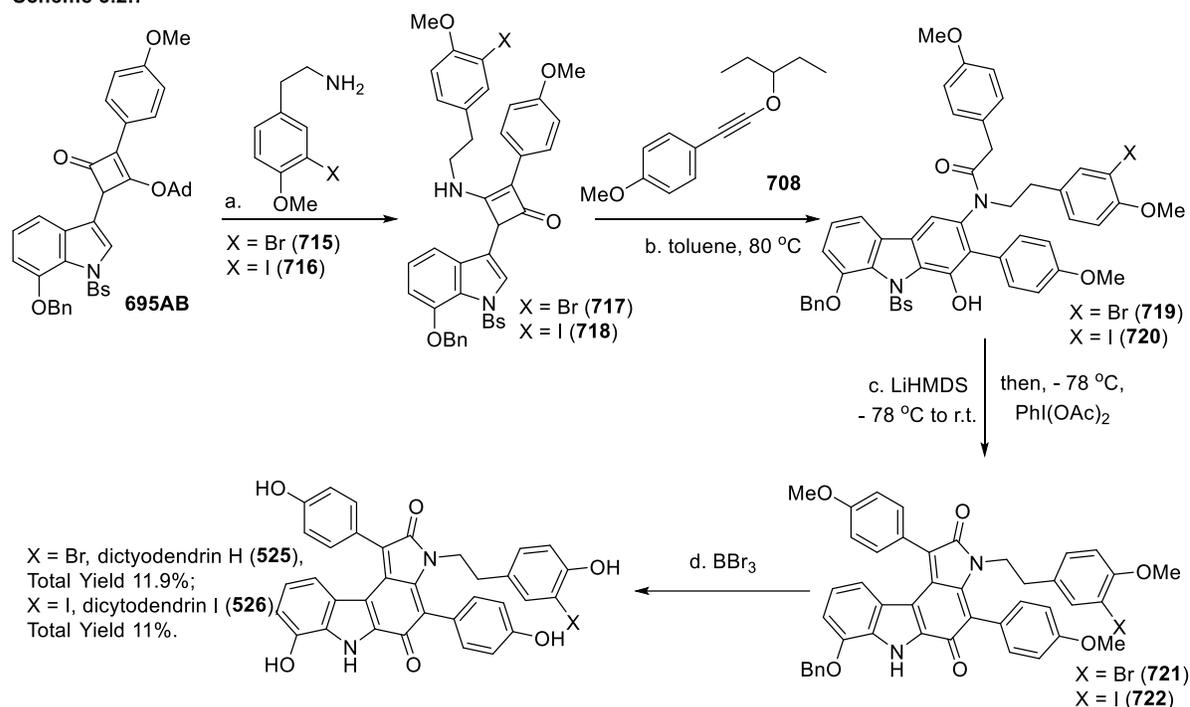
^aReagents and conditions: (a) LiHMDS (2.1 equiv), THF, $-78\text{ }^\circ\text{C}$ to r.t., 15 min; (b) H_2O (degas), r.t., 3 min, 62%; (c) air, r.t., 10 min, 67%; (d) Et_3N (5.0 equiv), CH_2Cl_2 , r.t., 1.5 h, quantitative yield; (e) $-78\text{ }^\circ\text{C}$, $\text{PhI}(\text{OAc})_2$ (1.0 equiv), 20 min, THF 92%; (f) BBr_3 (100 equiv) CH_2Cl_2 , $-78\text{ }^\circ\text{C}$ to r.t., overnight, 63%.

Fortuitously, we found that the benzenesulfonate protecting group could act as the oxidant in the oxidative cyclization of amide **705** (Scheme 3.4.6). In detail, when LiHMDS was added to substrate **705** at $-78\text{ }^\circ\text{C}$ and warmed to room temperature, the reaction solution changed from

colorless to dark green. The reaction mixture subsequently evolved to a red-brown solution from which we isolated the desired oxidative coupling product **714**. To our surprise, the benzenesulfonate group was lost during the reaction. We first excluded air as the oxidant in the reaction by executing a strict degassing protocol. The dramatic color change still occurred, indicating the formation of the large conjugated system in the dictyodendrins' scaffold. Quenching the dark green intermediate **712** with a degassed aqueous solution of NaHCO_3 afforded a colorless cyclized product **713** at a phenolic oxidation state in 62% yield. The structure of cyclized product **713** was confirmed through 1- and 2-dimensional NMR. Intermediate **713** slowly converted into the red-brown quinone **714** in the presence of Et_3N under aerobic conditions. However, injecting a trace amount of air to the dark green anionic intermediate **712** immediately gave the red-brown quinone product **714** in 67% yield.

The rapid aerobic oxidation of intermediate **712** excludes trace oxygen as the oxidant for the first C-C bond-forming step in this sequence (**705** \rightarrow **712**). In particular, oxidation of **712** is faster than the oxidative cyclization of **705**. For this reason, had trace levels of oxygen been present in the reaction mixture, 4-electron oxidation to **705** to quinone **714** would have been observed. In practice, we were able to isolate phenol **713**, the product of a 2 electron oxidative cyclization. The oxidative cyclization could use the S-O bond of the benzenesulfonate as the oxidizing equivalent as illustrated in Scheme 4. Following deprotonation, loss of sulfinate ion PhSO_2^- from carbazole **705** could generate an azaquinone-type intermediate **710**. 5-Exo cyclization of the enolate could form the final C-C bond of the natural product, and tautomerization and protonation could yield the lactam **713**.^{18,19} Our final optimized conditions for the oxidative coupling reaction used $\text{PhI}(\text{OAc})_2$ as a co-oxidant instead of air to oxidize

diphenolic intermediate **712** into the desired quinone **714**, and it gave a 92% yield of the desired product **714**. This protected form of dictyodendrin F was previously prepared by the Davies group.²⁰ Following their prescription, global deprotection gave dictyodendrin F in 63% yield. In summary, we synthesized dictyodendrin F with the longest linear sequence of 6 operations from indole **52y** and a 20.2% total yield.

Scheme 3.2.7^a

^aReagents and conditions: (a) **715** or **716** (5.0 equiv), DMSO, r.t., 24-36 h, 73% for **717** or 66% for **718**; (b) **708** (5-10 equiv), toluene, 80 °C, 12 h, 75% for **719** or 88% for **720**; (c) LiHMDS (2.1 equiv), THF, -78 °C to r.t., 15 min, then, -78 °C, PhI(OAc)₂ (1.0 equiv), 20 min, 79% for **721** or 62% for **722**; (d) BBr₃ (100 equiv), CH₂Cl₂, -78 °C to r.t., overnight, 54% for dictyodendrin H (**525**) or 60% for dictyodendrin I (**526**)

With this highly efficient synthetic strategy developed, we were also able to synthesize dictyodendrins H and I using the same synthetic sequence and only changing tyramine to a halogenated tyramine (Scheme 3.2.7). Unlike dictyodendrin F, dictyodendrins H and I contain a halogen atom on the tyramine side chain, making transition-metal catalyzed cross-couplings or C-H activation strategies challenging. In addition, a late stage halogenation could also be

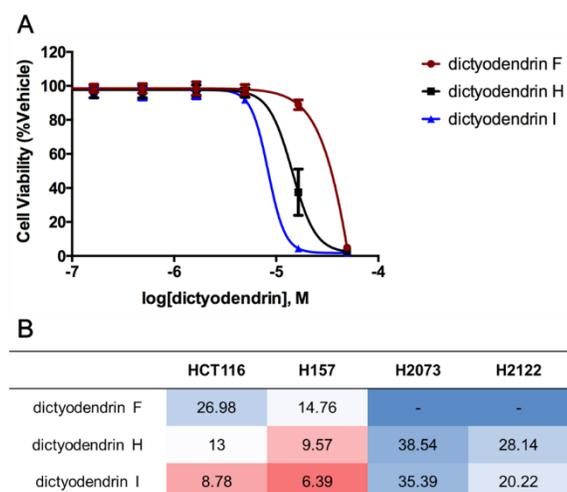
difficult given the large number of electron-rich aromatic rings. By contrast, our approach avoids these problems by using the desired halogenated tyramines to replace the adamantoxyl group on the cyclobutenone. In detail, halogenated *O*-methyl tyramines **715** (X = Br) and **716** (X = I)²¹ were used to replace the adamantoxyl group on cyclobutenone **695AB** to obtain the tyramine substituted cyclobutenones **717** and **718**. The subsequent retro-4 π /6 π -cyclization-acylation cascade reaction afforded the carbazole intermediates **719** and **720** using 3-pentyl anisoyl ynol ether **708** as the acylating reagent. Finally, oxidative coupling and global deprotection gave dictyodendrins H and I. The ¹H NMR spectra for the synthetic materials matched the reported data for the natural products. The isolation group was unable to obtain complete ¹³C NMR data sets, but our synthetic material generated spectra that were consistent with the limited data that is available.²² During the synthesis, we found that the halide on the side chain caused some instability during the cascade reaction (more light-sensitive) as well as during the oxidative coupling reaction. In conclusion, we report the first total synthesis of dictyodendrins H (**525**) and I (**526**) in six steps with an 11.9% and 11% total yield, respectively.

3.2.3 Cytotoxicity Test Against Cell Lines

The cytotoxicity of dictyodendrins F, H, and I was evaluated against three non-small cell lung cancer cell lines (H157, H2073, H2122) and a colorectal cancer cell line (HCT116).²³ Interestingly, with the increasing size of the tyramine side chain from dictyodendrin F to I, we observed increasing, albeit modest cytotoxicity of the natural products against cancer cells. For example, the IC₅₀ values against HCT116 decreased from dictyodendrin F (26.9 μ M) to dictyodendrin H (13 μ M) and dictyodendrin I (8 μ M) (**Figure 3.2.3**). The concise syntheses described here should provide a route to access multiple

derivatives of the dictyodendrins to optimize their activity and identify relevant biological targets.

Figure 3.2.3



(A) Cytotoxicity of dictyodendrins against colon cancer cell line HCT 116. (B) The IC_{50} values of dictyodendrins (μM) against cancer cell lines.

3.3 Experimental Details

3.3.1 General Information

General. Unless otherwise stated, reactions were performed under argon using freshly purified solvents, which were purified using solvent purification columns purchased from Glass Contour, Laguna Beach, CA. All Reactions were monitored by thin-layer chromatography with E. Merck silica gel 60 F₂₅₄ pre-coated plates (0.25 mm). All work-up and purification procedures were carried out with reagent-grade solvents in air. Flash chromatography was performed with indicated solvents using silica gel (particle size 40–63 μm) purchased from Sorbent Technologies. 1H and ^{13}C NMR spectra were recorded on Varian Inova-400 MHz, 500 MHz, or MR-400 spectrometer. Chemical shift are reported relative to internal chloroform ($CDCl_3$: 1H , $\delta = 7.26$ ppm, ^{13}C , $\delta = 77.36$ ppm), benzene (C_6D_6 : 1H , $\delta = 7.15$ ppm, ^{13}C , $\delta =$

128.62 ppm), toluene (C_7D_8 : 1H , $\delta = 2.09$ ppm, ^{13}C , $\delta = 20.4$ ppm), methanol (CD_3OD : 1H , $\delta = 3.31$ ppm, ^{13}C , $\delta = 49.15$ ppm), and pyridine (C_5D_5N : 1H , $\delta = 7.22$ ppm, ^{13}C , $\delta = 123.87$ ppm). Coupling constants are in Hz and are reported as d (doublet), t (triplet), q (quartet), b (broad peak), and m (multiplet). Mass spectra were acquired on an Agilent Technologies 1200 series LC/MS using indicated ionization methods.

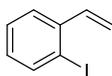
Materials. Chemicals were purchased from Aldrich, Fisher or Alfa Aesar, TCI, and Chemical Strem and used without purification.

The synthesis and characterization of **54g** and **54n** was shown in Chapter Two and Appendix A.

3.3.2 Electronic Cyclizations

General Method for Wittig Reaction:

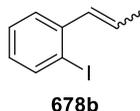
To a vigorously stirred slurry of phosphonium salt (1.15 equiv.) in THF was added n-butyllithium solution (2.5 M in hexane, 1.12 equiv.) at 0 °C. The reaction is allowed to stir for 15 min and then 2-iodoaryl-1-aldehyde solution in THF (1.0 equiv.) was added dropwise at 0 °C. After 15 min, the ice bath was removed and the reaction was allowed to stir for 2 h. The reaction was quenched with sat. ammonium chloride aq., and extracted with EtOAc. The combined organics was dried through the Na_2SO_4 and concentrated to get the crude product. The pure product was able to obtain via a flash chromatograph.



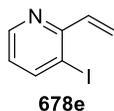
678a

1-iodo-2-vinylbenzene (678a). 1H NMR (400 MHz, $CDCl_3$) δ : 7.84 (dd, $J_1 = 7.9$ Hz, $J_2 = 1.3$ Hz, 1H), 7.51 (dd, $J_1 = 7.8$ Hz, $J_2 = 1.7$ Hz, 1H), 7.32 (t, $J = 7.2$ Hz, 1H), 7.00 - 6.84 (m, 2H),

5.63 (dd, $J_1 = 17.3$ Hz, $J_2 = 1.0$ Hz, 1H), 5.32 (dd, $J_1 = 10.9$ Hz, $J_2 = 1.0$ Hz, 1H). ^1H NMR and ^{13}C NMR was described.²⁴ ^1H NMR data was consistent.



2-iodopropenylbenzene (678b). (as a 1:2 mixture of *Z/E* isomers) ^1H NMR (400 MHz, CDCl_3) δ : 7.87 (dd, $J_1 = 8.0$ Hz, $J_2 = 1.2$ Hz, 1H), 7.81 (dd, $J_1 = 7.9$ Hz, $J_2 = 1.3$ Hz, 1H), 7.43 (dd, $J_1 = 7.8$ Hz, $J_2 = 1.7$ Hz, 1H), 7.35 – 7.26 (m, 1+2H), 6.91 (m, 1+1H), 6.58 (dq, $J_1 = 15.5$ Hz, $J_2 = 1.7$ Hz, 1H), 6.37 (dq, $J_1 = 11.3$ Hz, $J_2 = 1.8$ Hz, 1H), 6.11 (dq, $J_1 = 15.5$ Hz, $J_2 = 6.7$ Hz, 1H), 5.85 (dq, $J_1 = 11.4$ Hz, $J_2 = 7.1$ Hz, 1H), 1.93 (dd, $J_1 = 6.7$ Hz, $J_2 = 1.7$ Hz, 3H), 1.76 (dd, $J_1 = 7.1$ Hz, $J_2 = 1.8$ Hz, 3H). ^1H NMR and ^{13}C NMR was described.⁴ ^1H NMR data was consistent.



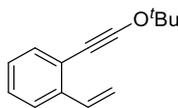
3-iodo-2-vinylpyridine (678e). ^1H NMR (400 MHz, CDCl_3) δ : 8.52 (dd, $J_1 = 4.5$ Hz, $J_2 = 1.5$ Hz, 1H), 8.09 (dd, $J_1 = 8.0$ Hz, $J_2 = 1.6$ Hz, 1H), 7.17 (dd, $J_1 = 16.8$ Hz, $J_2 = 10.6$ Hz, 1H), 6.88 (dd, $J_1 = 8.0$ Hz, $J_2 = 4.5$ Hz, 1H), 6.38 (dd, $J_1 = 16.8$ Hz, $J_2 = 1.9$ Hz, 1H), 5.51 (dd, $J_1 = 10.6$ Hz, $J_2 = 1.9$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ : 155.6, 148.9, 147.3, 137.5, 123.9, 122.0, 96.1. ESI MS m/z : 231.9, $[\text{M}+\text{H}]^+$. TLC (ethyl acetate:hexane = 1:5) r.f. = 0.5.

Compound **678c**,²⁵ **678e**²⁶ were prepared as described previously.

General Method for 6- π electrocyclization from 2-iodo-1-enylbenzene:

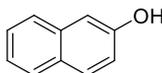
Same as Method C of coupling reaction except 16 mol% CuI was loaded in the reaction. The reaction was monitored via TLC for the completion, and the reaction mixtures were directly loading to the aluminum plug and washed off with ethyl acetate and hexane eluent. The

yielding products were dissolved in toluene (0.03M) and heated to 120 °C over night. The mixture after the reaction was concentrated and further purified with flash chromatograph to yield the pure product.



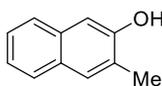
679a

1-(tert-butoxyethynyl)-2-vinylbenzene (679a). ^1H NMR (400 MHz, CDCl_3) δ : 7.58 – 7.50 (m, 1H), 7.40 – 7.32 (m, 1H), 7.26 – 7.11 (m, 3H), 5.76 (d, $J = 17.7$ Hz, 1H), 5.30 (d, $J = 11.0$ Hz, 1H), 1.51 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ : 138.8, 136.0, 132.7, 127.7, 126.8, 124.8, 124.0, 114.9, 100.4, 87.4, 41.6, 27.6. TLC (ethyl acetate:hexane = 1:10) r.f. = 0.8.



682a

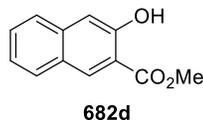
naphthalen-2-ol (682a). ^1H NMR (400 MHz, CDCl_3) δ : 7.77 (t, $J = 8.2$ Hz, 2H), 7.69 (d, $J = 8.2$ Hz, 1H), 7.44 (ddd, $J_1 = 8.2$ Hz, $J_2 = 6.9$ Hz, $J_3 = 1.3$ Hz, 1H), 7.34 (ddd, $J_1 = 8.1$ Hz, $J_2 = 6.8$ Hz, $J_3 = 1.3$ Hz, 1H), 7.16 (d, $J = 2.5$ Hz, 1H), 7.11 (dd, $J_1 = 8.8$ Hz, $J_2 = 2.6$ Hz, 1H), 5.22 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ : 153.4, 134.7, 130.0, 129.0, 127.9, 126.7, 126.5, 123.8, 117.9, 109.6. ESI MS m/z : 145.0, $[\text{M}+\text{H}]^+$. TLC (ethyl acetate:hexane = 1:10) r.f. = 0.4.



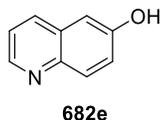
682b

3-methylnaphthalen-2-ol (682b). ^1H NMR (400 MHz, CDCl_3) δ : 7.71 (d, $J = 8.1$ Hz, 1H), 7.65 (d, $J = 8.2$ Hz, 1H), 7.60 (s, 1H), 7.38 (dd, $J_1 = 8.3$ Hz, $J_2 = 6.8$ Hz, 1H), 7.31 (dd, $J_1 = 8.2$ Hz, $J_2 = 6.8$ Hz, 1H), 7.09 (s, 1H), 4.94 (s, 1H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ :

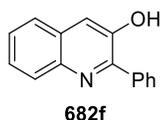
152.9, 133.5, 129.5, 129.3, 127.1, 126.5, 126.0, 125.7, 123.6, 109.1, 16.7. ESI MS m/z : 159.0, $[M+H]^+$. TLC (ethyl acetate:hexane = 1:5) r.f. = 0.4.



methyl 3-hydroxy-2-naphthoate (682d). ^1H NMR (400 MHz, CDCl_3) δ : 10.44 (s, 1H), 8.48 (s, 1H), 7.79 (d, $J = 8.3$ Hz, 1H), 7.68 (d, $J = 8.3$ Hz, 1H), 7.50 (dd, $J_1 = 8.3$ Hz, $J_2 = 6.8$ Hz, 1H), 7.37 – 7.28 (m, 2H), 4.02 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ : 170.4, 156.4, 138.0, 132.6, 129.3, 129.3, 127.1, 126.4, 124.1, 114.3, 111.8, 52.7. ESI MS m/z : 203.0, $[M+H]^+$. TLC (ethyl acetate:hexane = 1:5) r.f. = 0.4.



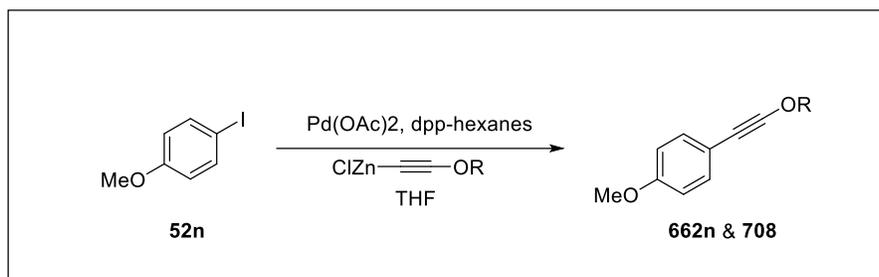
quinolin-6-ol (682e). ^1H NMR (400 MHz, CD_3OD) δ : 8.60 (dd, $J_1 = 4.3$ Hz, $J_2 = 1.7$ Hz, 1H), 8.13 (d, $J = 8.0$ Hz, 1H), 7.87 (d, $J = 9.1$ Hz, 1H), 7.41 (dd, $J_1 = 8.0$ Hz, $J_2 = 4.3$ Hz, 1H), 7.35 (dd, $J_1 = 9.1$ Hz, $J_2 = 2.8$ Hz, 1H), 7.14 (d, $J = 2.8$ Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ : 157.4, 147.9, 144.0, 136.6, 131.4, 130.4, 123.5, 122.5, 109.6. ESI MS m/z : 146.1, $[M+H]^+$. TLC (ethyl acetate:hexane = 1:3) r.f. = 0.4.



2-phenylquinolin-3-ol (682f). ^1H NMR (400 MHz, CD_3OD) δ : 9.67 (s, 1H), 8.23 (s, 1H), 8.04 (d, $J = 7.1$ Hz, 2H), 8.01 (d, $J = 7.7$ Hz, 1H), 7.88 – 7.77 (m, 3H), 7.58 (t, $J = 7.7$ Hz, 1H), 7.31 (d, $J = 7.8$ Hz, 1H), 7.23 (t, $J = 7.7$ Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ : 170.9, 142.1,

137.9, 135.2, 130.3, 130.0, 129.7, 129.0, 128.0, 123.4, 122.2, 122.0, 110.7. ESIMS m/z : 222.1, $[M+H]^+$. TLC (ethyl acetate:hexane = 1:3) r.f. = 0.4.

General method for 4'-methoxyl alkyl ynol ether (662n & 708)

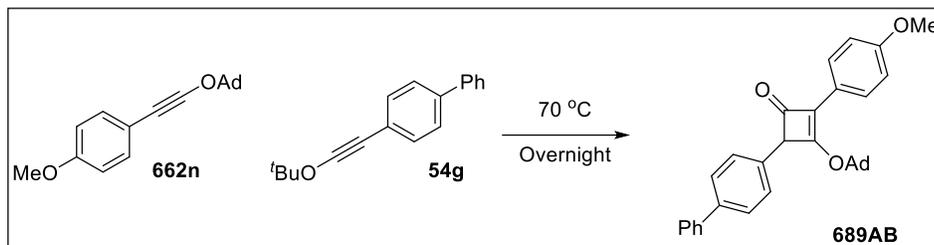


According to Himbert's report,⁸ the alkoxy acetylene-zinc chloride was synthesized and used directly. The 4-iodoanisole (1.0 equiv), Pd(OAc)₂ (5 mol%), and dpp-hexane (10 mol%) were combined in a round-bottom flask. The flask was charged with argon. The freshly made alkoxy acetylenyl zinc chloride solution in THF (0.28 M, 1.5 equiv) was added at room temperature. The reaction was stirred at room temperature and monitored with TLC for completion (1-2 hours). The reaction was quenched with NaHCO₃ (sat. aq.), and ethyl acetate was added to dilute the reaction. The bi-phasic mixture was filtered through a celite plug. The organic phase was separated, and the aqueous phase was extracted with EA X 2. The organic phase was combined and washed with brine and dried over anhydrous Na₂SO₄. The crude product was purified with silica gel chromatography (eluent: DCM:hexanes = 1:2 ~ 1:5).

4'-methoxyl adamantyl ynol ether (662n) The pure product was obtained according to the general method. (903 mg, 75%) ¹H NMR (400 MHz, CDCl₃) δ 7.29 (d, *J* = 8.3 Hz, 2H), 6.80 (d, *J* = 8.2 Hz, 2H), 3.79 (s, 3H), 2.26 (s, 3H), 2.00 (s, 6H), 1.66 (s, 6H). ¹³C NMR (101 MHz, CDCl₃) δ 158.29, 132.91, 116.87, 113.89, 93.55, 85.07, 55.38, 42.20, 41.14, 35.93, 31.28. Mass spectrum was not acquired due to poor ionization.

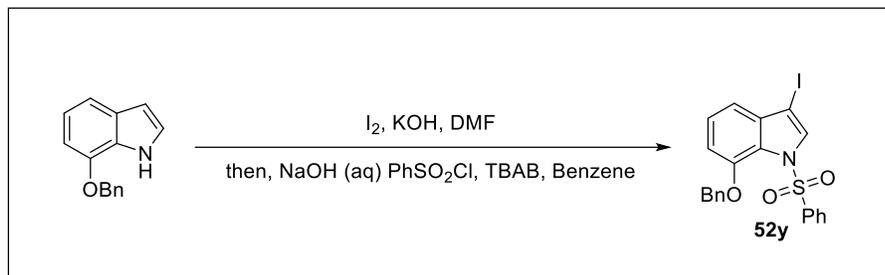
4'-methoxyl 3-pentyl ynol ether (708) The pure product was obtained according to the general method. (1.18 g, 81%) ^1H NMR (400 MHz, CDCl_3) δ 7.28 (d, $J = 8.9$ Hz, 2H), 6.80 (d, $J = 8.9$ Hz, 2H), 3.96 (tt, $J = 7.1, 5.1$ Hz, 1H), 3.79 (s, 3H), 1.81 (dq, $J = 14.8, 7.4$ Hz, 2H), 1.70 (dtd, $J = 14.7, 7.4, 5.2$ Hz, 2H), 1.02 (t, $J = 7.4$ Hz, 6H). ^{13}C NMR (101 MHz, CDCl_3) δ 158.36, 132.88, 116.59, 113.90, 96.39, 92.15, 55.36, 40.10, 25.95, 9.63. Mass spectrum was not acquired due to poor ionization.

4-([1,1'-biphenyl]-4-yl)-3-(adamantan-1-oxy)-2-(4'-methoxyphenyl)cyclobut-2-en-1-one (689AB)



The adamantyl ynol ether **662n** (36 mg, 2.5 equiv) was combined with the *tert*-butyl ynol ether **54g** (12.8 mg, 1.0 equiv). The flask with the ynol ethers was charged with argon, and toluene (1.5 ml) was added. The reaction was heated at 70 °C for 12 hour. The crude mixture was concentrated and the product was purified by flash chromatography to provide cyclobutenone **689AB** (19 mg, 78%). ^1H NMR (400 MHz, CDCl_3) δ 7.83 (d, $J = 8.7$ Hz, 2H), 7.61 – 7.56 (m, 4H), 7.47 – 7.41 (m, 3H), 7.38 (d, $J = 8.2$ Hz, 2H), 7.35 (t, $J = 7.2$ Hz, 1H), 6.92 (d, $J = 8.7$ Hz, 2H), 4.85 (s, 1H), 3.83 (s, 3H), 2.19 – 2.11 (bs, 3H), 2.00 – 1.87 (m, 6H), 1.64 – 1.48 (m, 6H). ^{13}C NMR (101 MHz, cdcl_3) δ 184.74, 172.72, 158.85, 140.77, 140.68, 135.55, 128.90, 128.24, 128.13, 127.67, 127.46, 127.15, 125.80, 122.62, 113.98, 85.62, 69.16, 55.42, 43.04, 35.64, 31.10. ESI MS m/z : 477.2, $[\text{M}+\text{H}]^+$.

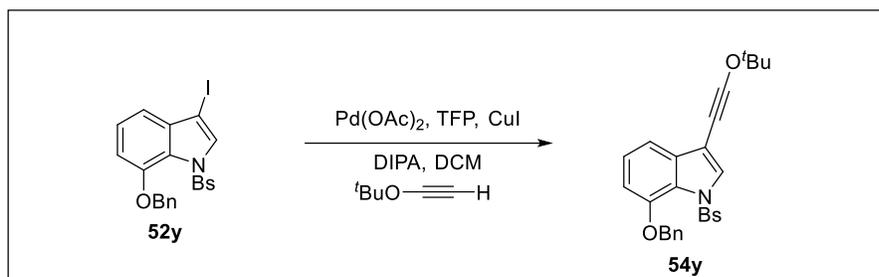
3.3.3 Total Synthesis of Dictyodendrins F, H, and I.

N-benzenesulfonate-7-benzoxyl-3-iodoindole (52y)

To a 100 ml round bottomed flask, containing a magnetic stirring bar was added 7-benzoxylindole (2.65 g, 1.0 equiv), KOH (2.55 g, 3.8 equiv), and DMF (10 ml). To the slurry mixture, iodine (3.05 g, 1.015 equiv) solution in 10 ml DMF was added at 0 °C. The reaction was allowed to warm to room temperature over 30 min then stirred for another 30 min at room temperature. Next, NaOH (aq., 5 g in 20 ml water), TBAB (0.32 g, 0.1 equiv), and 30 ml benzene were added at 0 °C. To the vigorously stirring reaction, PhSO₂Cl (3.0 ml, 2.0 equiv) was injected. The reaction was then stirred at room temperature for 2 hours. When the reaction completed as judged by TLC analysis, 200 ml ethyl acetate was added. The organic phase was washed with water (40 ml X 3). The aqueous phase was collected and extracted with 40 ml ethyl acetate. All organic phases were combined, washed with 40 ml brine, and dried with anhydrous Na₂SO₄. Evaporating the solvent gave the crude product. Crystallization (Hot EA:hexanes = 1:5) was employed to give pure product as white crystals (3.4 g, 71%). ¹H NMR (400 MHz, CDCl₃) δ 8.00 (s, 1H), 7.58 (dd, *J* = 8.8, 1.6 Hz, 2H), 7.47 (tt, *J* = 7.6, 1.2 Hz, 1H), 7.40 – 7.34 (m, 3H), 7.32 – 7.25 (m, 4H), 7.16 (t, *J* = 7.9 Hz, 1H), 7.03 (dd, *J* = 7.6, 1.2 Hz, 1H), 6.75 (d, *J* = 8.0 Hz, 1H), 5.01 (s, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 146.00, 139.61,

136.10, 135.31, 133.14, 132.10, 128.79, 128.52, 128.16, 127.90, 127.24, 124.54, 124.11, 114.65, 108.75, 70.82, 64.62.

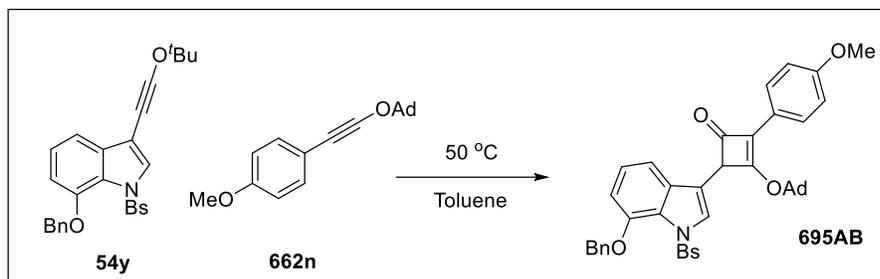
N-benzenesulfonate-7'-benzoxyl-3'-indolyl tert-butyl ynol ether (54y)



All solid reagents, N-benzenesulfonate-7-benzoxyl-3-iodoindole (**52y**, 1.47 g, 1.0 equiv), Pd(OAc)₂ (135 mg, 20 mol%), tri(2-furyl)phosphine (279 mg, 40 mol%), and CuI (150 mg, 26 mol%) were combined in a dried flask and purged with argon. To the flask, diisopropylethyl amine (7.5 ml), DCM (15 ml) and *tert*-butyl acetylenyl ether (7.5 ml, 60 wt% in hexanes and diethyl ether) were added at room temperature. The reaction was stirred at room temperature and monitored via TLC for completion (12 h), and the reaction mixture was directly loaded onto silica gel that had been pretreated with 5% TEA in hexanes overnight. The crude material was eluted with DCM:hexanes = 5:1. The partially purified material was concentrated and reloaded onto a second column (silica gel pretreated with 5% TEA in hexanes overnight) with a minimum DCM. Pure product was eluted with DCM:hexanes = 1:1 (1.1 g, 80%). The pure product was combined with ynol ether **662n** and used directly in the [2+2] cycloaddition reaction. The ¹³C NMR was not acquired due to instability of pure product at room temperature, and mass spectrum was not acquired due to poor ionization. ¹H NMR (400 MHz, CDCl₃) δ 7.88 (s, 1H), 7.57 (dd, *J* = 7.6, 1.2 Hz, 2H), 7.44 (t, *J* = 7.6, 1H), 7.40 – 7.32 (m, 3H), 7.32 –

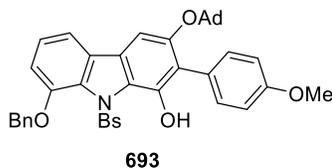
7.26 (m, 3H), 7.24 (d, $J = 7.6$ Hz, 2H), 7.10 (t, $J = 8.0$ Hz, 1H), 6.69 (d, $J = 7.6$ Hz, 1H), 5.00 (s, 2H), 1.53 (s, 9H).

2-(4'-anisoyl)-3-adamantoxyl-4-(N-benzensulfonyl-7'-benzoxyl-3'-indolyl)-cyclobut-2-en-1-one (695AB)



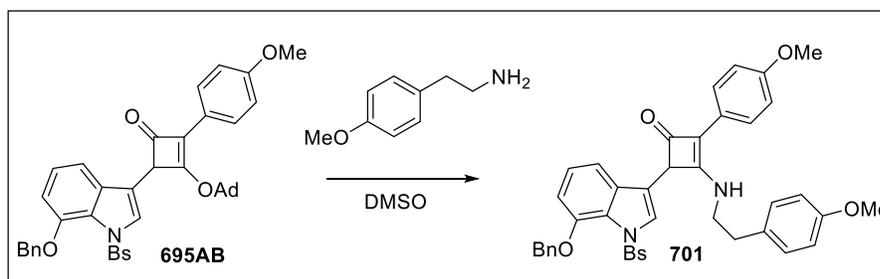
The adamantyl ynol ether **662n** (920 mg, 2.5 equiv) was combined with the indolyl *tert*-butyl ynol ether **54y** (700mg, 1.0 equiv). The mixture was dried under high vacuum for 12 hours. The flask with the ynol ethers was charged with argon, and toluene (15 ml) was added. The reaction was heated at 50 °C for 9 hour. The crude mixture was concentrated and the product was purified by flash chromatography to provide cyclobutenone **695AB** (590 mg, 56%) and the starting material **54y** (140 mg, 20%). This procedural was repeated to give another batch of the pure product (114 mg). Total yield was 704 mg (68%). ^1H NMR (400 MHz, CDCl_3) δ 7.85 (s, 1H), 7.87 – 7.81 (m, 2H), 7.57 – 7.51 (m, 2H), 7.44 (tt, $J = 7.5, 1.2$ Hz, 1H), 7.39 – 7.33 (m, 3H), 7.28 – 7.17 (m, 5H), 7.01 (t, $J = 8.0$ Hz, 1H), 6.93 (m, 2H), 6.66 (dd, $J = 8.0, 0.9$ Hz, 1H), 5.06 (s, 1H), 4.98 (d, $J = 12.0$, 1H), 4.95 (d, $J = 12.0$, 1H), 3.84 (s, 3H), 2.16 (s, 3H), 1.98 (q, $J = 11.2$ Hz, 6H), 1.58 (dd, $J = 19.0$ Hz, 6H). ^{13}C NMR (101 MHz, CDCl_3) δ 185.02, 173.72, 158.89, 146.48, 140.06, 136.37, 133.05, 132.79, 128.85, 128.56, 128.17, 128.14, 128.00, 127.31, 127.15, 125.14, 125.09, 124.48, 122.58, 115.59, 114.02, 112.83, 108.43, 85.89, 70.71, 61.06, 55.40, 42.91, 35.59, 31.08. ESI MS m/z : 708.2, $[\text{M}+\text{Na}]^+$.

3-(adamantan-1-oxo)-8-(benzyloxy)-9-(phenylsulfonyl)-2-(4-methoxyphenyl)-9H-carbazol-1-ol (693)



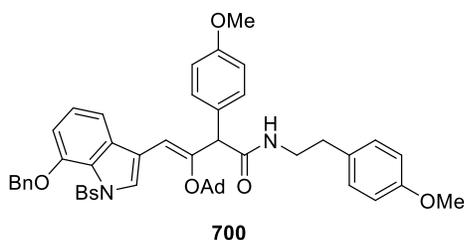
^1H NMR (400 MHz, CDCl_3) δ 8.11 (s, 1H), 7.54 – 7.46 (m, 4H), 7.43 – 7.34 (m, 5H), 7.34 – 7.30 (m, 1H), 7.25 (d, $J = 8.0$ Hz, 2H), 7.22 – 7.15 (m, 2H), 7.03 – 6.95 (m, 3H), 6.94 (s, 1H), 5.24 (s, 2H), 3.88 (s, 3H), 2.01 (s, 3H), 1.56 – 1.49 (m, 6H), 1.45 – 1.39 (m, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 158.64, 152.12, 150.80, 145.31, 136.93, 135.30, 133.54, 133.50, 133.05, 131.02, 130.27, 128.72, 128.25, 128.00, 127.62, 127.50, 127.46, 127.38, 126.50, 126.44, 113.61, 113.16, 112.85, 108.65, 79.79, 71.28, 55.42, 42.78, 36.14, 30.99. ESI MS m/z : 686.0, $[\text{M}+\text{H}]^+$.

2-(4'-anisoyl)-3-(4'-methoxyphenethylamino)-4-(N-benzensulfonyl-7'-benzoxyl-3'-indolyl)-cyclobuten-1-one (701)



An aluminum foil-wrapped flask (or an amber vial) was charged with compound **695AB** (600 mg, 1.0 equiv) and charged with argon. To the flask, DMSO (4.0 ml) was added, followed by O-methyltyramine (0.7 ml, 5.0 equiv) at room temperature. The reaction was stirred for 24-48 hours and checked for completion via TLC. The reaction was quenched with ammonium

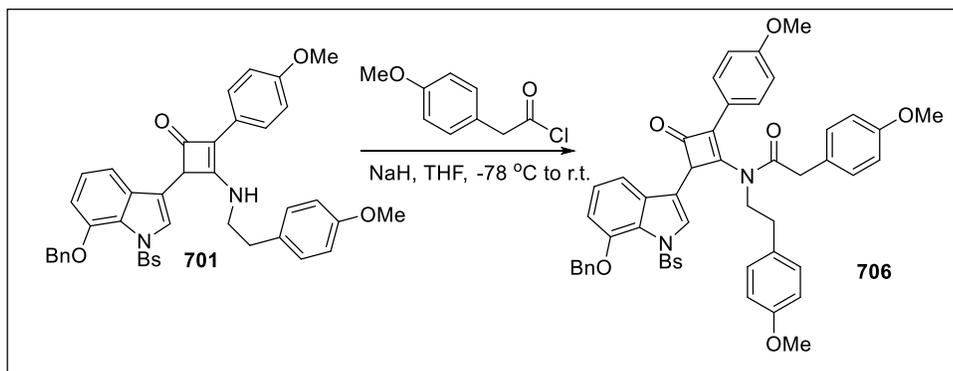
chloride (15 ml, sat. aq.), and 20 ml EA was added. All the workup steps were carried out in a room with the lights turned off to minimize exposure to light. The organic phase was washed with another 15 ml ammonium chloride (sat. aq.) and 10 ml water X 2. The combined aqueous phase was extracted with 20 ml EA. All organic phases was combined and washed with brine. The solution was dried with anhydrous sodium sulfate and concentrated to afford the crude product. The crude product was purified twice via flash chromatography. The eluent for the first purification was EA:hexanes = 1:1. The eluent for the second purification was acetone:hexanes = 3:200 to give the pure product **701** (479 mg, 80%). ^1H NMR (400 MHz, CDCl_3) δ 7.81 (s, 1H), 7.58 (d, $J = 7.8$ Hz, 2H), 7.48 – 7.41 (m, 3H), 7.37 – 7.31 (m, 3H), 7.26 – 7.18 (m, 5H), 7.00 (t, $J = 8.0$ Hz, 1H), 6.90 (d, $J = 7.6$ Hz, 4H), 6.82 (d, $J = 8.2$ Hz, 2H), 6.65 (d, $J = 8.0$ Hz, 1H), 5.91 (s, 1H), 4.99 (d, $J = 12.3$ Hz, 1H), 4.94 (d, $J = 12.3$ Hz, 1H), 4.67 (s, 1H), 3.81 (s, 3H), 3.78 (s, 3H), 3.46 (b, 2H), 2.62 (t, $J = 6.8$ Hz, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 180.72, 163.79, 158.74, 157.88, 146.47, 140.07, 136.49, 136.45, 133.09, 132.93, 129.92, 129.30, 128.87, 128.60, 128.58, 128.15, 127.89, 127.26, 126.97, 126.61, 125.15, 124.47, 124.04, 114.45, 114.38, 112.76, 108.44, 70.61, 56.27, 55.47, 55.43, 47.62, 36.63. ESI MS m/z : 685.2, $[\text{M}+\text{H}]^+$.



3-(adamantan-1-oxo)-4-(7'-benzyloxy-1'-phenylsulfonyl-1H-indol-3'-yl)-N-(4'-methoxyphenethyl)-2-(4'-methoxyphenyl)-but-3-enamide (27)

^1H NMR (400 MHz, CDCl_3) δ 8.51 (s, 1H), 7.57 (d, $J = 8.4$ Hz, 2H), 7.44 (t, $J = 7.6$ Hz, 1H), 7.38 – 7.33 (m, 3H), 7.32 – 7.28 (m, 2H), 7.24 (d, $J = 8.4$ Hz, 2H), 7.17 (d, $J = 8.8$ Hz, 2H), 7.11 (d, $J = 8.8$ Hz, 2H), 7.00 (t, $J = 8.0$ Hz, 1H), 6.89 (d, $J = 8.7$ Hz, 2H), 6.85 (d, $J = 8.0$ Hz, 1H), 6.80 (d, $J = 8.6$ Hz, 2H), 6.65 (d, $J = 8.1$ Hz, 1H), 6.16 (t, $J = 5.8$ Hz, 1H), 5.68 (s, 1H), 4.99 (s, 2H), 4.69 (s, 1H), 3.84 (s, 3H), 3.67 (s, 3H), 3.67 – 3.48 (m, 2H), 2.81 (t, $J = 6.7$ Hz, 2H), 2.16 (s, 3H), 2.05 (s, 6H), 1.61 (s, 6H). ^{13}C NMR (101 MHz, CDCl_3) δ 171.04, 159.00, 158.43, 153.39, 146.45, 140.32, 136.54, 133.49, 132.96, 130.85, 130.28, 129.93, 129.77, 128.82, 128.60, 128.19, 128.05, 127.82, 127.24, 123.94, 123.86, 115.02, 114.38, 114.22, 111.92, 108.67, 108.15, 81.17, 70.84, 60.73, 55.45, 55.31, 43.86, 41.18, 36.21, 34.90, 31.27. ESI MS m/z : 837.3, $[\text{M}+\text{H}]^+$.

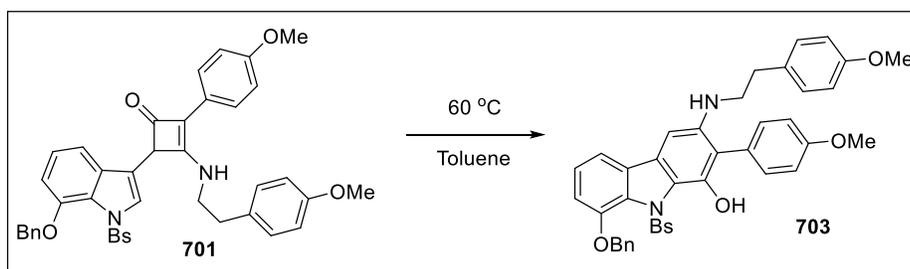
2-(4'-anisoyl)-3-(4'-methoxyphenethylamino)-3-(4'-methoxyphenylacetyl)-4-(N-benzensulfonyl-7'-benzoxyl-3'-indolyl)-cyclobuten-1-one (706)



In the glove box, the NaH (7 mg, 60 wt%, 10 equiv) was added into a 4 ml reaction vial. The vial was removed from the glovebox. To the reaction vial, a solution of compound **701** (12 mg, 1.0 equiv) in THF (200 μl) was added slowly at -78 °C. After 5 min stirring at -78 °C, the acid chloride (7 μl , 2.5 equiv) was added dropwise by micro syringe. The reaction was allowed to warm to room temperature. The reaction was stirred (30-60 min) and checked by TLC for

completion. The reaction was quenched with ammonium chloride (sat. aq.) at 0 °C. The aqueous layer was extracted with EA X 3, washed with brine, and dried with anhydrous sodium sulfate. The solution was concentrated to give crude product **706**, which was purified using PTLC (7.7 mg, 53%). ^1H NMR (400 MHz, CDCl_3) δ 7.77 (s, 1H), 7.54 (d, $J = 7.8$ Hz, 2H), 7.49 (d, $J = 8.4$ Hz, 2H), 7.45 (t, $J = 7.6$ Hz, 1H), 7.37 – 7.32 (m, 3H), 7.25 – 7.19 (m, 3H), 7.07 – 6.94 (m, 4H), 6.85 (d, $J = 8.4$ Hz, 2H), 6.75 (d, $J = 8.4$ Hz, 2H), 6.70 (s, 4H), 6.67 (d, $J = 7.8$ Hz, 2H), 5.14 (s, 1H), 4.98 (s, 2H), 4.00 – 3.93 (m, 1H), 3.90 – 3.57 (m, 3H), 3.86 (s, 3H), 3.74 (s, 3H), 3.72 (s, 3H), 2.72 (m, 1H), 2.56 (m, 1H). ^{13}C NMR (101 MHz, CDCl_3) δ 186.42, 171.36, 160.22, 159.50, 158.89, 158.67, 146.57, 140.07, 136.44, 133.11, 132.84, 132.19, 130.09, 130.08, 129.90, 129.37, 128.89, 128.63, 128.20, 127.89, 127.49, 127.37, 127.26, 125.37, 125.10, 124.54, 121.76, 114.39, 114.34, 114.20, 112.67, 108.53, 70.73, 59.51, 55.57, 55.40, 55.37, 49.60, 41.47, 34.86. ESI MS m/z : 833.2, $[\text{M}+\text{H}]^+$.

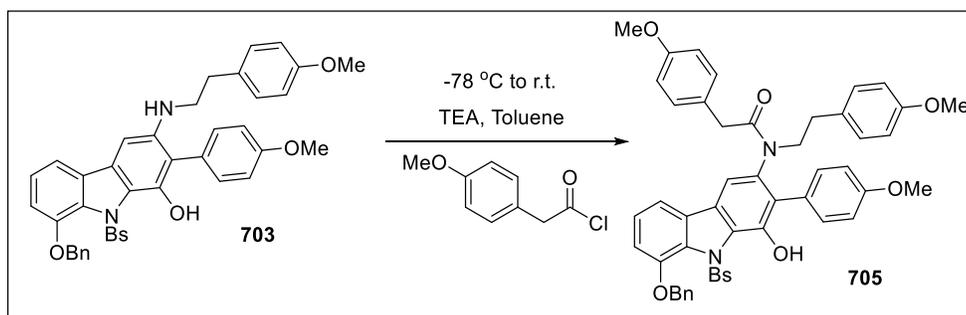
8-(benzyloxy)-N-(benzenesulfonyl)-3-(4'-methoxyphenethylamino)-2-(4'-anisoly)-9H-carbazol-1-ol (703)



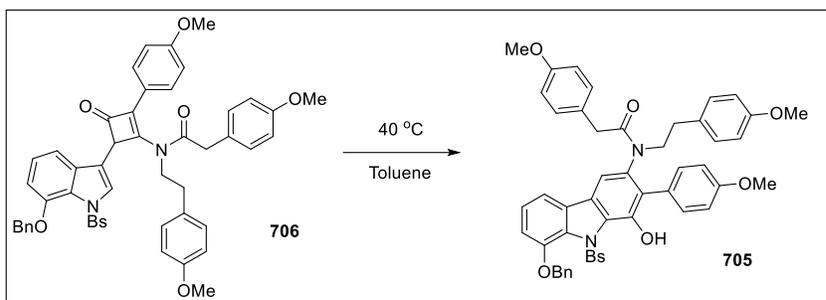
A solution of the starting material **701** (30 mg) 1.5 ml toluene was prepared in the glove box and heated to 60 °C overnight. The crude product was obtained through concentration under vacuum and purified through PTLC to give the pure product **703** (6.1 mg, 20%). The product was not stable during acquisition of the ^{13}C NMR. ^1H NMR (400 MHz, CDCl_3) δ 8.12 (s, 1H),

7.51 (d, $J = 7.5$ Hz, 2H), 7.46 (dd, $J = 8.4, 1.2$ Hz 2H), 7.41 (m, 1H), 7.36 (d, $J = 8.0$ Hz, 2H), 7.33 – 7.30 (m, 1H), 7.23 – 7.17 (m, 4H), 7.15 (d, $J = 8.7$ Hz, 2H), 6.98 – 6.90 (m, 5H), 6.78 (d, $J = 8.6$ Hz, 2H), 6.48 (s, 1H), 5.26 (s, 2H), 3.88 (s, 3H), 3.80 (s, 3H), 3.28 (t, $J = 6.8$ Hz, 2H), 2.74 (t, $J = 6.8$ Hz, 2H). ESI MS m/z : 685.2, $[M+H]^+$.

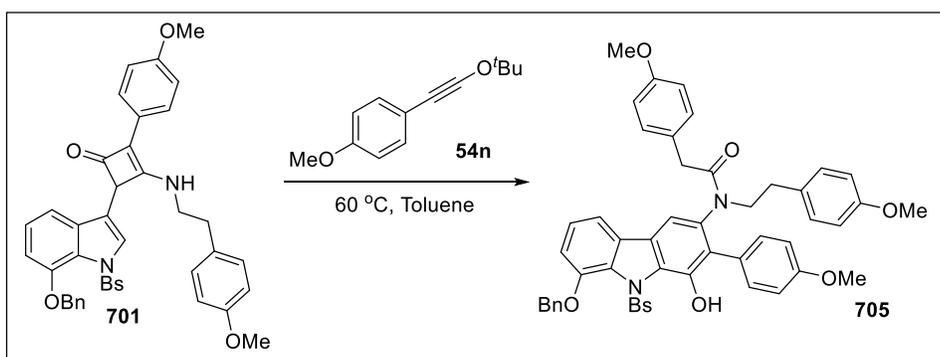
N-(8-(benzyloxy)-9-(benzenesulfonyl)-1-hydroxy-2-(4'-anisoly)-9H-carbazol-3-yl)-N-(4-methoxyphenethyl)-2-(4'-anisoly)acetamide (705)



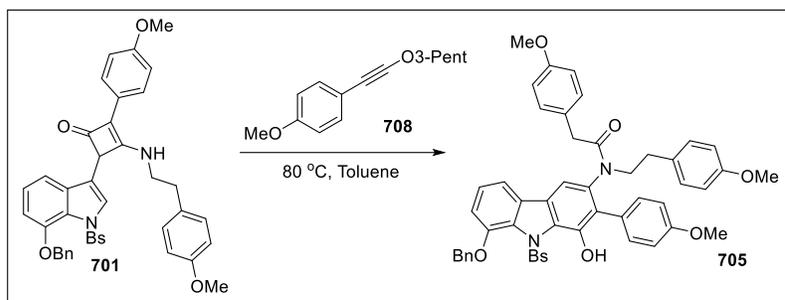
A 4 ml reaction vial was charged with the carbazole **703** (1.0 mg, 1.0 equiv), 0.2 ml toluene (degassed) and TEA (0.4 μ l, 2.0 equiv) at room temperature under argon. The mixture was cooled to -78 $^{\circ}$ C, and the acid chloride (0.32 μ l, 1.3 equiv) was added. The reaction was allowed to warm to room temperature over 15 min, and it was stirred at room temperature overnight. The reaction was checked by TLC for completion, and it was quenched by ammonium chloride (sat. aq.). The crude product was obtained via extraction, drying, and concentration. Purification by preparative TLC gave the product (0.5 mg, 40%). Analytical data provided below.



The intermediate **706** is not very stable at room temperature. Immediately after being synthesized, it was dried under high vacuum and then protected with argon. To the reaction vial with intermediate **706** (4.3 mg), toluene (1.5 ml, freshly collected from solvent system) was added. The solution was heated to 40 °C overnight. Concentration of the reaction solution yielded the product **705** (4.2 mg, quantitative yield). Analytical data provided below.

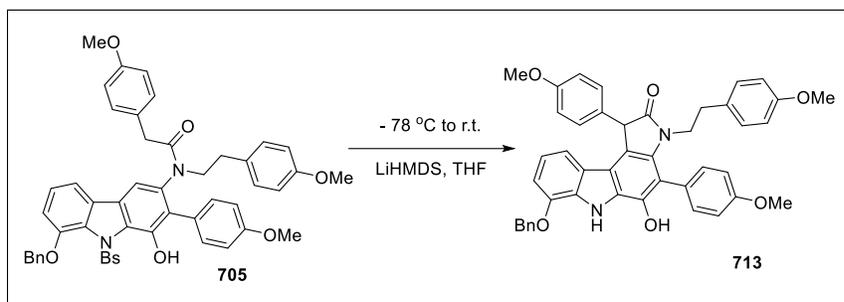


To a 4 ml reaction vial containing cyclobutenone **701** (24 mg, 1.0 equiv) was added a solution of anisoyl ynone ether **54n** (35 mg, 5.0 equiv) in toluene (2.0 ml) under argon. The reaction was degassed before it was heated to 60 °C for 12 hour. Concentration of the reaction solution gave the crude product. The pure product was obtained via a PTLC (13.7 mg, 47%). Analytical data provided below.



To a 4 ml amber reaction vial containing cyclobutenone **701** (12 mg, 1.0 equiv) was added a solution of anisoyl ynol ether **708** (19 mg, 5.0 equiv) in toluene (1.0 ml) under argon. The reaction was degassed before it was heated to 80 °C for 12 hour. Concentration of the reaction solution gave the crude product. The pure product was obtained via PTLC (13.2 mg, 91%). ¹H NMR (400 MHz, CDCl₃) δ 8.26 (s, 1H), 7.64 (d, *J* = 7.6 Hz, 2H), 7.49 – 7.25 (m, 9H), 7.19 (d, *J* = 8.4 Hz, 2H), 7.01 (d, *J* = 7.9 Hz, 2H), 6.98 (d, *J* = 8.9 Hz, 2H), 6.88 (d, *J* = 7.9 Hz, 4H), 6.75 (d, *J* = 8.6 Hz, 2H), 6.66 (d, *J* = 8.5 Hz, 2H), 6.17 (s, 1H), 5.21 (s, 2H), 3.96 (ddd, *J* = 12.9, 8.0, 4.3 Hz, 1H), 3.85 (s, 3H), 3.79 (s, 3H), 3.72 (s, 3H), 3.33 (d, *J* = 14.3 Hz, 1H), 3.21 (d, *J* = 14.3 Hz, 1H), 2.79 (dt, *J* = 12.5, 8.0 Hz, 1H), 2.69 (dt, *J* = 12.9, 8.0 Hz, 1H), 2.58 (ddd, *J* = 12.4, 8.0, 4.3 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 171.13, 159.32, 158.51, 158.12, 150.41, 145.59, 140.59, 136.65, 136.21, 133.88, 132.19, 131.27, 131.03, 130.87, 130.59, 130.43, 130.27, 129.37, 128.78, 128.49, 128.46, 128.13, 127.70, 127.54, 127.48, 127.27, 126.12, 114.24, 114.15, 113.84, 113.77, 113.68, 112.92, 71.20, 55.45, 55.38, 55.22, 51.58, 40.83, 32.63. ESI MS *m/z*: 833.2, [M+H]⁺.

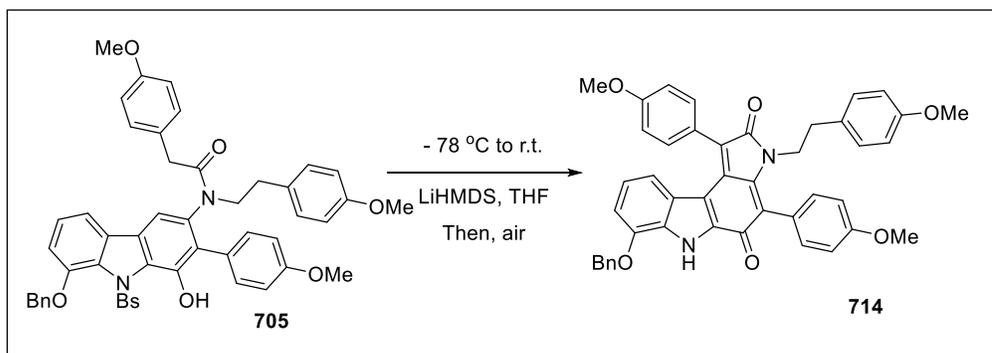
7-(benzyloxy)-6-(benzenesulfonyl)-5-hydroxy-3-(4'-methoxyphenethyl)-1,4-bis(4'-anisoyl)-3,6-dihydropyrrolo[2,3-c]carbazol-2(1H)-one (713)



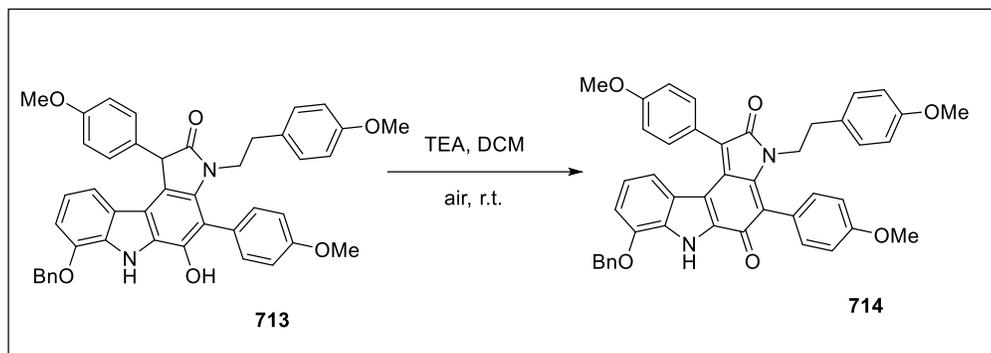
A 4 ml reaction vial containing acylated carbazole **705** (4.2 mg, 1.0 equiv) was charged with argon and 0.6 ml THF. The reaction solution was degassed, and LiHMDS solution in THF (0.1 M, 126 μ l, 2.5 equiv) was added at -78 °C. The reaction was allowed to warm to room temperature over 15 min. There was a dramatic color change during the warm-up from light yellow to dark green. After 15 min stirring at room temperature, the reaction was quenched with degassed NaHCO₃ (sat. aq.). The reaction mixture was quickly extracted with ethyl acetate, dried with anhydrous sodium sulfate, and concentrated to give the crude product. A PTLC was employed to obtain the pure product (2.2 mg, 62 %) as light yellow oil. Some oxidized product **714** was also obtained during workup. Moreover, the pure product **713** generated variable amounts of the oxidized product **714** in the course of obtaining a proton NMR spectrum. To obtain the ¹³C NMR, we loaded the sample in glove box, but we still observed trace oxidized product **713**. ¹H NMR (400 MHz, CDCl₃) δ 8.39 (s, 1H), 7.58 – 7.32 (m, 7H), 7.23 (d, *J* = 8.5 Hz, 2H), 7.13 (d, *J* = 8.7 Hz, 2H), 6.93 – 6.80 (m, 5H), 6.67 (s, 4H), 5.22 (s, 2H), 5.10 (s, 1H), 4.89 (s, 1H), 3.92 (s, 3H), 3.76 (s, 3H), 3.73 (s, 3H), 3.51 (ddd, *J* = 13.9, 11.0, 5.5 Hz, 1H), 3.38 (ddd, *J* = 13.8, 10.9, 5.3 Hz, 1H), 2.53 (ddd, *J* = 12.8, 10.9, 5.5 Hz, 1H), 2.42 (td, *J* = 12.8, 12.0, 5.5 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 177.94, 160.62, 159.06, 158.11, 145.02, 139.30, 136.97, 134.75, 133.12, 133.05, 131.34, 130.40, 129.78,

129.39, 128.82, 128.61, 128.40, 128.05, 124.66, 124.04, 123.29, 121.70, 119.67, 115.99, 115.39, 115.31, 114.50, 113.65, 112.59, 109.80, 107.57, 70.55, 55.68, 55.36, 55.32, 50.53, 43.30, 33.53. ESI MS m/z : 691.2, $[M+H]^+$.

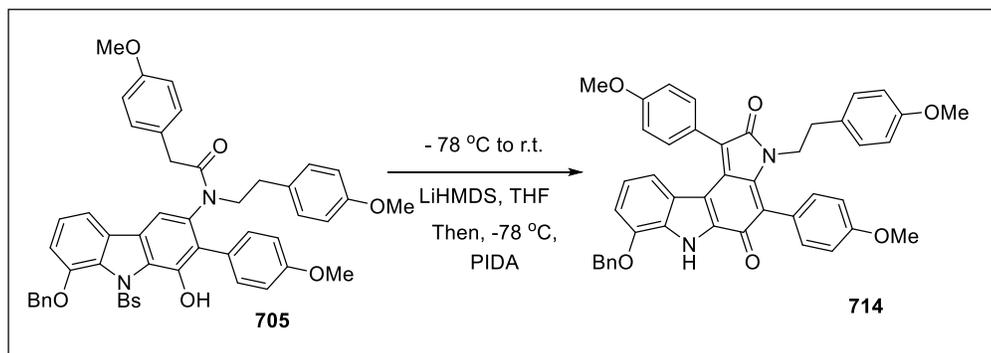
7-(benzyloxy)-6-(benzenesulfonyl)-3-(4'-methoxyphenethyl)-1,4-bis(4'-anisoyl)pyrrolo[2,3-c]carbazole-2,5(3H,6H)-dione (714)



A 4 ml reaction vial with acylated carbazole **705** (1.6 mg, 1.0 equiv) was charged with argon, and 0.2 ml THF. The reaction system was degassed, and LiHMDS solution in THF (0.1 M, 50 μ l, 2.5 equiv) was added at -78 °C. The reaction was allowed to warm to room temperature over 15 min. There was a dramatic color change during the warm-up from light yellow to dark green. After 15 min stirring at room temperature, 0.2 ml air was injected into the reaction system. The color of the reaction turned to red brown after the air injection. TLC was used to check the completion of this reaction, and the reaction was quenched with NaHCO_3 (sat. aq.). The crude product was obtained through an extraction (EA X 3), drying (sodium sulfate anhydrous), and a concentration. PTLC was used to afford the pure product **714** (0.9 mg, 67%). Analytical data provided below.



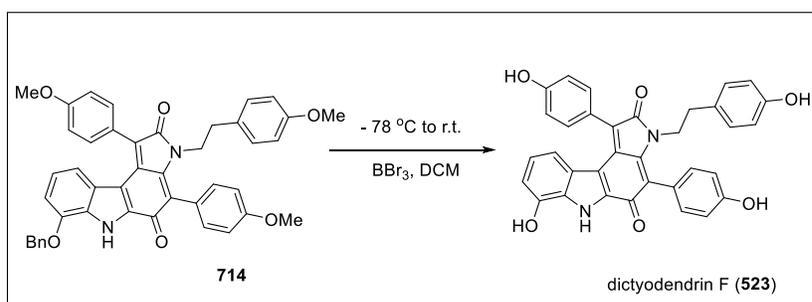
A reaction vial was charged with intermediate **713** (2.2 mg), 2.0 ml DCM and 0.5 ml TEA at room temperature. The reaction vial was capped under air. The solution was stirred overnight. TLC was used to check the completion of this reaction. The crude product was obtained through concentration under vacuum followed by purification with PTLC (2.0 mg). Analytical data provided below.



A 4 ml reaction vial with acylated carbazole **705** (2.1 mg, 1.0 equiv) was charged with argon, and 0.2 ml THF was added. The reaction system was degassed, and LiHMDS solution in THF (0.1 M, 63 μ l, 5.0 equiv) was added at -78 °C. The reaction was allowed to warm to room temperature over 15 min. There was a dramatic color change during the warm-up from light yellow to dark green. After 15 min stirring at room temperature, the reaction was cooled to -78 °C again. Then, PIDA in THF solution (100 μ l, 10 mg/ml, 1.2 equiv, degassed) was injected

into the reaction system. The color of the reaction turned to red brown. TLC was used to check the completion of this reaction after 30-60 min, and the reaction was quenched with NaHCO_3 (sat. aq.). The crude product was obtained through following extraction (EA X 3), drying (sodium sulfate anhydrous), and concentration under vacuum. PTLC was used to afford the pure product (1.6 mg, 91%). ^1H NMR (400 MHz, CDCl_3) δ 9.32 (s, 1H), 7.52 (d, $J = 8.8$ Hz, 2H), 7.48 – 7.32 (m, 7H), 7.07 – 6.98 (m, 4H), 6.80 – 6.72 (m, 2H), 6.69 (s, 4H), 6.03 (d, $J = 7.7$ Hz, 1H), 5.20 (s, 2H), 3.91 (s, 3H), 3.89 (s, 3H), 3.73 (s, 3H), 3.46 (t, $J = 8.0$ Hz, 2H), 2.46 (t, $J = 8.0$ Hz, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 179.08, 171.48, 160.93, 160.03, 158.26, 149.46, 146.12, 136.42, 133.80, 132.58, 132.50, 131.78, 130.07, 129.89, 129.29, 129.14, 128.88, 128.55, 127.95, 124.89, 124.11, 123.68, 122.22, 117.30, 117.06, 114.09, 113.98, 113.77, 113.28, 106.29, 70.59, 55.61, 55.54, 55.36, 43.14, 34.11.²⁰ ESI MS m/z : 689.2, $[\text{M}+\text{H}]^+$.

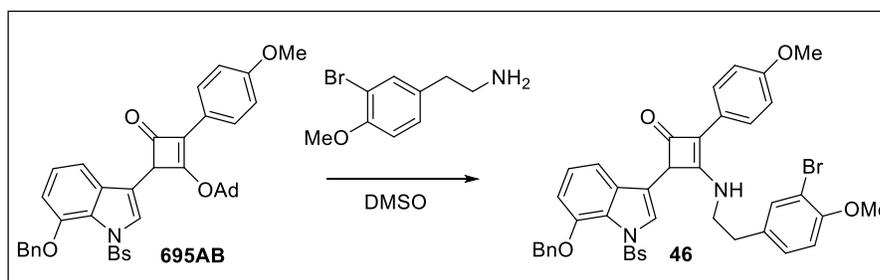
Dictyodendrin F²⁰



A reaction vial with intermediate **714** (2.7 mg, 1.0 equiv) was charged with argon, and the starting material was dissolved in 1.5 ml DCM . A solution of BBr_3 (0.3 ml, 1.0 M in DCM , 100 equiv) was added slowly at $-78\text{ }^\circ\text{C}$. The BBr_3 was a newly opened bottle sold by Aldrich, whereas an older BBr_3 solution gave a messy reaction. The reaction was allowed to warm up slowly and stir overnight. The reaction was quenched with water at $0\text{ }^\circ\text{C}$. The crude product

was obtained following extraction (EA X 3), drying (anhydrous sodium sulfate), and concentration. To the crude product, DCM was added, this suspension was sonicated for 2 min and filter through cotton. The solid on the cotton was redissolved in methanol and loaded on reverse phase PTLC for purification (eluent: acetonitrile:water = 2:1). The pure product was obtained through a quick C18-silica pipet column (1.4 mg, 63%). ^1H NMR (400 MHz, Methanol- d_4) δ 7.31 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 7.6 Hz, 2H), 6.93 (d, J = 7.6 Hz, 2H), 6.89 (d, J = 8.0 Hz, 2H), 6.66 (d, J = 8.0 Hz, 2H), 6.62 – 6.52 (m, 4H), 5.82 (d, J = 7.5 Hz, 1H), 3.42 (t, J = 7.8 Hz, 2H), 2.40 (t, J = 7.8 Hz, 2H). ^{13}C NMR (101 MHz, cd_3od) δ 180.90, 173.45, 160.35, 159.24, 156.90, 150.49, 146.34, 135.53, 133.84, 133.52, 133.08, 130.89, 130.85, 130.04, 129.97, 126.34, 124.14, 123.74, 123.16, 119.29, 116.31, 116.24, 116.08, 115.99, 114.05, 110.06, 44.15, 34.92. ESI MS m/z : 557.2, $[\text{M}+\text{H}]^+$. See below for a tabular comparison of these data with those reported by the isolation group.

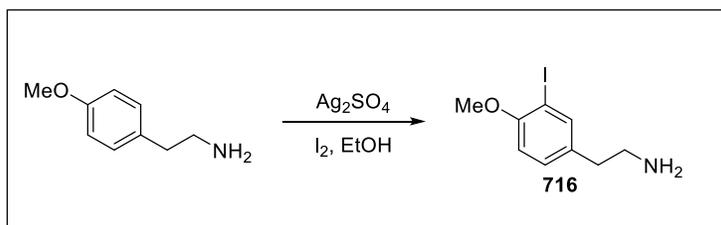
2-(4'-anisoyl)-3-(4'-methoxy-3'-bromo-phenethylamino)-4-(N-benz磺onyl-7'-benzoxyl-3'-indolyl)-cyclobuten-1-one (717)



A 4 ml amber vial was charged with compound **695AB** (135 mg) under argon. DMSO (2.0 ml) and *O*-methylbromotyramine (0.2 ml) were added to the vial at room temperature. The reaction was stirred at room temperature (24-48 h) and checked for completion via TLC. The reaction was quenched with ammonium chloride (10 ml, sat. aq.), and 10 ml EA was added. All the

workup steps were carried out in room with the lights turned off to minimize exposure to light. The organic phase was washed with another 10 ml ammonium chloride (sat. aq.), 10 ml water X 2. The combined aqueous phase was extracted with 10 ml EA. All organic phase was combined and washed with brine. The solution was dried with anhydrous sodium sulfate and concentrated to afford the crude product. The crude product was purified twice via flash chromatography. The eluent for the first purification was EA:hexanes = 1:1. The eluent for the second purification was acetone:hexanes = 3:200. The pure product was obtained (108 mg, 73%). ¹H NMR (400 MHz, CDCl₃) δ 7.80 (s, 1H), 7.55 (d, *J* = 7.6 Hz, 2H), 7.50 (d, *J* = 7.9 Hz, 2H), 7.43 (t, *J* = 7.5 Hz, 1H), 7.32 – 7.35 (m, 3H), 7.26 – 7.10 (m, 6H), 6.99 (t, *J* = 7.9 Hz, 1H), 6.86 (d, *J* = 8.1 Hz, 2H), 6.72 (bs, 2H), 6.66 (d, *J* = 7.9 Hz, 1H), 6.45 – 6.37 (bs, 1H), 4.98 (d, *J* = 12.4 Hz, 1H), 4.94 (d, *J* = 12.4 Hz, 1H), 4.62 (s, 1H), 3.82 (s, 3H), 3.75 (s, 3H), 3.40 – 3.32 (m, 2H), 2.50 (m, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 180.62, 163.72, 157.73, 154.76, 146.34, 139.82, 136.27, 133.35, 133.02, 132.76, 130.92, 128.82, 128.75, 128.47, 128.04, 127.78, 127.09, 126.80, 126.56, 124.95, 124.46, 123.83, 115.19, 114.63, 114.23, 112.55, 112.22, 111.70, 108.40, 70.48, 56.24, 55.86, 55.29, 47.37, 36.04. ESI MS *m/z*: 763.2, [M+H]⁺.

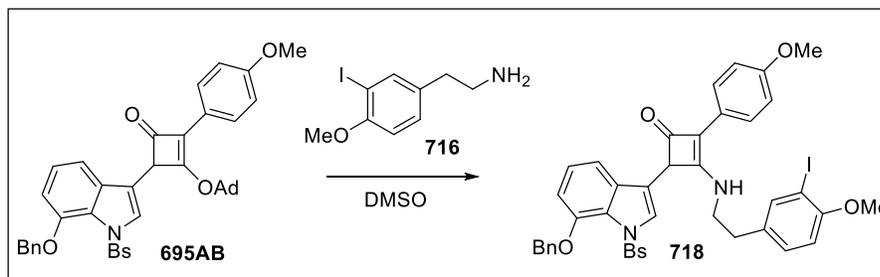
4-methoxy-3-iodo-phenethylamine (716)



To a 500 ml flask containing Ag₂SO₄ (6.2 g, 2.0 equiv) and I₂ (5.0 g, 2.0 equiv), 200 ml ethanol was added at room temperature,²⁷ followed by *O*-methyl tyramine (1.5 g, 1.0 equiv). The

reaction was stirred overnight. TLC showed incompleteness of this reaction. Another 6.0 gram silver sulfate and 5.0 gram iodine were added. The reaction was finished after another 36 hours. The yellow solid was removed by filtration, and the filtrate was concentrated and redissolved in chloroform. The solution was washed with 5 wt% NaOH aqueous solution, water, brine. After separation, the organic phase was dried through anhydrous sodium sulfate and concentrated to give crude product. Flash chromatography (eluent: MeOH:DCM = 1:10) was employed to give the pure product as light yellow oil (2.3 g, 83%). ^1H NMR (400 MHz, CDCl_3) δ 7.61 (dd, $J = 2.2, 0.6$ Hz, 1H), 7.13 (dd, $J = 8.4, 2.0$ Hz, 1H), 6.75 (d, $J = 8.4$ Hz, 1H), 3.85 (s, 3H), 2.92 (t, $J = 6.8$ Hz, 2H), 2.65 (t, $J = 6.8$ Hz, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 156.73, 139.70, 134.22, 129.95, 110.99, 86.16, 56.53, 43.68, 38.74. ESI MS m/z : 278.0, $[\text{M}+\text{H}]^+$.

2-(4'-anisoyl)-3-(4'-methoxy-3'-bromo-phenethylamino)-4-(N-benzensulfonyl-7'-benzoxyl-3'-indolyl)-cyclobuten-1-one (718)

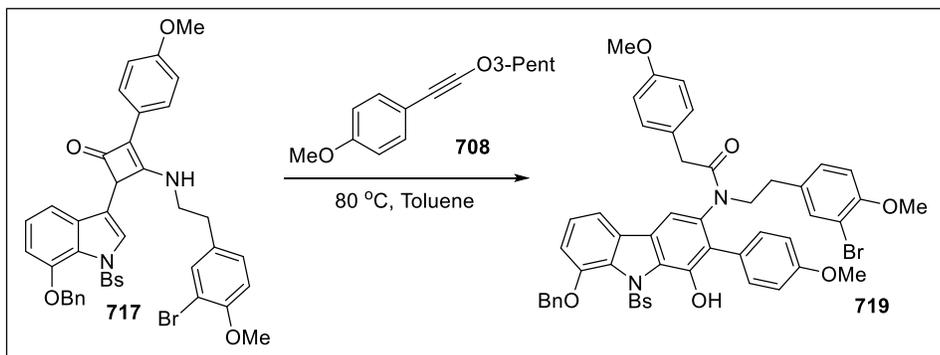


A 4 ml amber vial with compound **695AB** (129 mg) was purged with argon. DMSO (2.0 ml) and *O*-methyliodotyramine **716** (0.4 ml) were added to the vial at room temperature. The reaction was stirred at room temperature (24-48 h) and checked for completion via TLC. The reaction was quenched with ammonium chloride (10 ml, sat. aq.), and 10 ml EA was added. All the workup steps were carried out in a room with the lights turned off to minimize exposure to light. The organic phase was washed with another 10 ml ammonium chloride (sat. aq.), 10

ml water X 2. The combined aqueous phase was extracted with 10 ml EA. The combined organic phases were washed with brine. The solution was dried with anhydrous sodium sulfate and concentrated to afford the crude product. The crude product was purified twice via flash chromatography. The eluent for the first purification is EA:hexanes = 1:1. The eluent for the second purification is acetone:hexanes = 3:200. The pure product was obtained (102 mg, 66%).

^1H NMR (400 MHz, CDCl_3) δ 7.82 (s, 1H), 7.57 (d, $J = 7.6$ Hz, 2H), 7.42 – 7.46 (m, 4H), 7.31 – 7.36 (m, 3H), 7.19 – 7.26 (m, 5H), 7.02 (t, $J = 8.0$ Hz, 1H), 6.91 (d, $J = 8.3$ Hz, 2H), 6.86 (d, $J = 8.4$ Hz, 1H), 6.69 (d, $J = 8.4$ Hz, 1H), 6.66 (d, $J = 7.6$ Hz, 1H), 5.96 (s, 1H), 4.99 (d, $J = 12.3$ Hz, 1H), 4.94 (d, $J = 12.3$ Hz, 1H), 4.68 (s, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.42 (b, 2H), 2.55 (b, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 180.50, 163.57, 157.80, 157.18, 146.33, 139.87, 139.49, 136.28, 132.98, 132.76, 131.39, 129.89, 128.74, 128.46, 128.02, 127.75, 127.12, 126.83, 126.55, 124.97, 124.44, 123.77, 115.10, 114.82, 114.30, 112.54, 111.19, 108.36, 86.26, 70.46, 56.40, 56.04, 55.32, 47.29, 35.91. ESI MS m/z : 811.0, $[\text{M}+\text{H}]^+$.

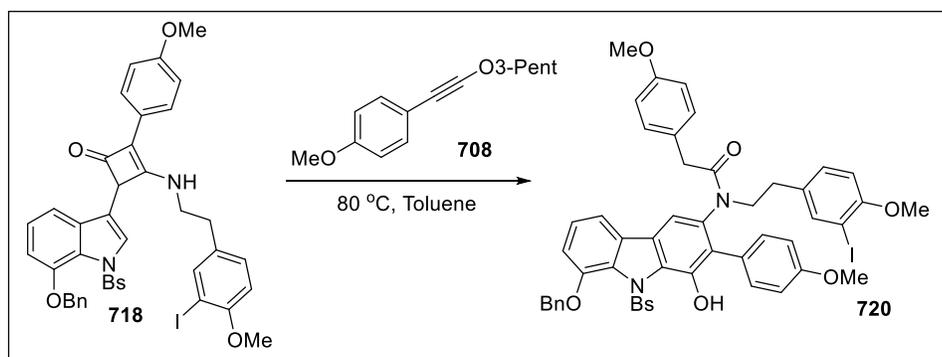
N-(8-(benzyloxy)-9-(benzenesulfonyl)-1-hydroxy-2-(4'-anisoyl)-9H-carbazol-3-yl)-N-(3-bromo-4-methoxyphenethyl)-2-(4-methoxyphenyl)acetamide (719)



A solution of anisoyl ynol ether **708** (30 mg, 10.0 equiv) in toluene (1.5 ml) was added under argon to a 4 ml amber reaction vial with cyclobutenone **717** (17.5 mg, 1.0 equiv). The reaction

was degassed before it was heated to 80 °C for 12 hour. Concentration of the reaction solution gave the crude product. The pure product was obtained via PTLC (15.7 mg, 75%). ¹H NMR (400 MHz, CDCl₃) δ 8.29 (s, 1H), 7.64 (d, *J* = 8.4, 1.2 Hz, 2H), 7.46 – 7.42 (m, 3H), 7.41 – 7.25 (m, 6H), 7.19 (d, *J* = 8.3 Hz, 2H), 7.16 (d, *J* = 2.1 Hz, 1H), 7.06 – 6.95 (m, 4H), 6.91 – 6.88 (m, 1H), 6.87 (d, *J* = 8.6 Hz, 2H), 6.75 (d, *J* = 8.6 Hz, 2H), 6.62 (d, *J* = 8.4 Hz, 1H), 6.29 (s, 1H), 5.21 (s, 2H), 4.02 – 3.91 (m, 1H), 3.85 (s, 3H), 3.79 (s, 3H), 3.76 (s, 3H), 3.36 (d, *J* = 14.3 Hz, 1H), 3.24 (d, *J* = 14.3 Hz, 1H), 2.78 – 2.62 (m, 2H), 2.61 – 2.50 (m, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 171.25, 159.35, 158.53, 154.39, 150.38, 145.68, 140.18, 136.62, 136.23, 134.00, 133.91, 132.79, 132.03, 131.03, 130.86, 130.60, 130.27, 129.43, 129.07, 128.77, 128.50, 128.35, 128.13, 127.79, 127.49, 127.42, 127.26, 126.03, 114.27, 114.09, 113.94, 113.74, 112.90, 111.89, 111.26, 71.20, 56.23, 55.42, 55.39, 50.83, 40.83, 32.39. ESI MS *m/z*: 911.0, [M+H]⁺.

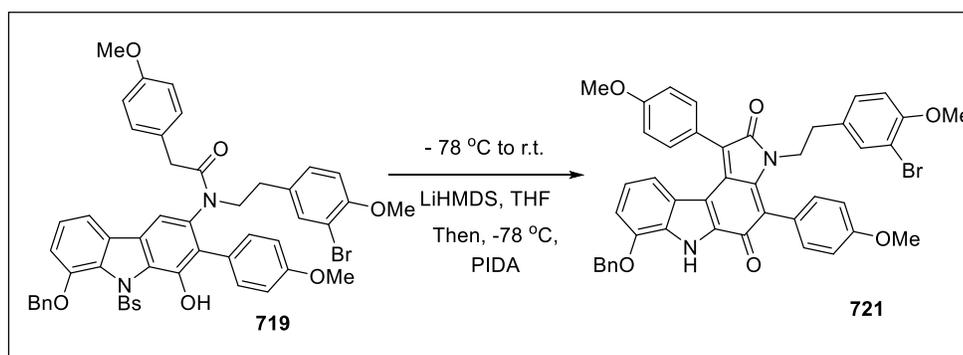
N-(8-(benzyloxy)-9-(benzenesulfonyl)-1-hydroxy-2-(4'-anisoyl)-9H-carbazol-3-yl)-N-(3-iodo-4-methoxyphenethyl)-2-(4-methoxyphenyl)acetamide (720)



A solution of anisoyl ynone ether **708** (30 mg, 12.5 equiv) in toluene (1.5 ml) was added under argon to a 4 ml amber reaction vial with cyclobutenone **718** (15 mg, 1.0 equiv), The reaction was degassed before it was heated to 80 °C for 12 hour. Concentration of the reaction solution

gave the crude product. The pure product was obtained via PTLC (15.7 mg, 88%). ^1H NMR (400 MHz, CDCl_3) δ 8.29 (s, 1H), 7.64 (dd, $J = 8.5, 1.3$ Hz, 2H), 7.47 – 7.41 (m, 3H), 7.41 – 7.25 (m, 7H), 7.19 (d, $J = 8.4$ Hz, 2H), 7.10 – 6.96 (m, 4H), 6.92 (dd, $J = 8.4, 2.1$ Hz, 1H), 6.87 (d, $J = 8.7$ Hz, 2H), 6.75 (d, $J = 8.7$ Hz, 2H), 6.54 (d, $J = 8.4$ Hz, 1H), 6.29 (s, 1H), 5.21 (s, 2H), 4.02 – 3.91 (m, 1H), 3.85 (s, 3H), 3.79 (s, 3H), 3.74 (s, 3H), 3.36 (d, $J = 14.3$ Hz, 1H), 3.24 (d, $J = 14.3$ Hz, 1H), 2.77 – 2.61 (m, 2H), 2.53 (m, 1H). ^{13}C NMR (101 MHz, CDCl_3) δ 171.23, 159.35, 158.51, 156.68, 150.37, 145.68, 140.18, 140.04, 136.63, 136.22, 133.91, 133.39, 132.04, 131.04, 130.86, 130.62, 130.27, 130.13, 129.42, 128.77, 128.49, 128.34, 128.12, 127.78, 127.49, 127.44, 127.26, 126.04, 114.27, 114.10, 113.97, 113.75, 113.04, 110.84, 85.66, 71.20, 56.35, 55.43, 55.39, 50.80, 40.82, 32.21. ESI MS m/z : 959.0, $[\text{M}+\text{H}]^+$.

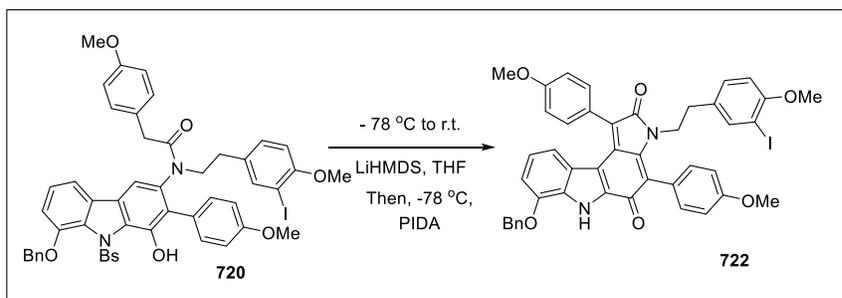
7-(benzyloxy)-6-(benzenesulfonyl)-3-(4'-methoxy-3'-bromo-phenethyl)-1,4-bis(4'-anisoyl)pyrrolo[2,3-c]carbazole-2,5(3H,6H)-dione (721)



A 4 ml reaction vial containing acylated carbazole **719** (9.8 mg, 1.0 equiv) was purged with argon, and 1.6 ml THF was added. The reaction system was degassed, and LiHMDS solution in THF (0.2 M, 268 μl , 5.0 equiv) was added at -78 $^\circ\text{C}$. The reaction was allowed to warm to room temperature over 15 min. There was a dramatic color change during the warm-up from light yellow to dark green. After 15 min stirring at room temperature, the reaction was cooled

to $-78\text{ }^{\circ}\text{C}$ again. Then, PIDA in THF solution (420 μl , 20 mg/ml, 1.2 equiv, degassed) was injected into the reaction system. The color of the reaction turned to red brown. TLC was used to check the completion of this reaction after 30-60 min, and the reaction was quenched with NaHCO_3 (sat. aq.). The crude product was obtained following extraction (EA X 3), drying (sodium sulfate anhydrous), and concentration. PTLC was used to afford the pure product (6.6 mg, 79%). ^1H NMR (400 MHz, Benzene- d_6) δ 9.29 (s, 1H), 7.53 (d, $J = 8.7$ Hz, 2H), 7.49 – 7.36 (m, 5H), 7.34 (d, $J = 8.6$ Hz, 2H), 7.06 (d, $J = 8.7$ Hz, 2H), 7.03 (d, $J = 8.7$ Hz, 2H), 6.84 – 6.71 (m, 4H), 6.69 (d, $J = 8.4$ Hz, 1H), 6.09 – 6.00 (d, $J = 7.6$ Hz, 1H), 5.19 (s, 2H), 3.92 (s, 3H), 3.91 (s, 3H), 3.81 (s, 3H), 3.45 (t, $J = 8.4$ Hz, 2H), 2.45 (t, $J = 8.4$ Hz, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 179.01, 171.43, 160.96, 160.11, 154.56, 149.22, 146.11, 136.40, 133.83, 133.57, 132.57, 132.51, 131.76, 131.63, 129.22, 129.15, 128.95, 128.88, 128.55, 127.95, 124.88, 123.88, 123.60, 122.24, 117.34, 117.08, 114.11, 113.97, 113.27, 111.88, 111.41, 106.31, 70.59, 56.36, 55.61, 55.55, 42.92, 33.77. ESI MS m/z : 767.0, $[\text{M}+\text{H}]^+$.

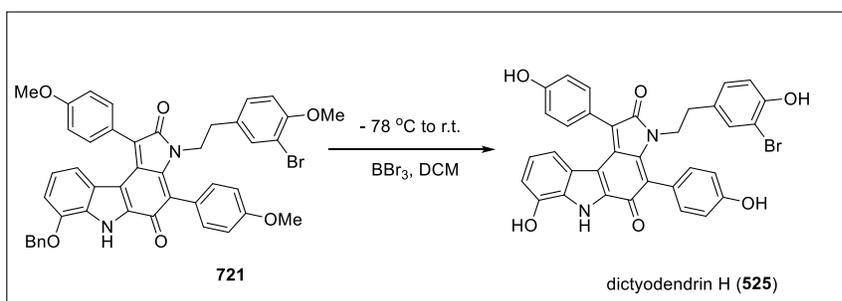
7-(benzyloxy)-6-(benzenesulfonyl)-3-(4'-methoxy-3'-iodo-phenethyl)-1,4-bis(4'-anisoyl)pyrrolo[2,3-c]carbazole-2,5(3H,6H)-dione (722)



A 4 ml reaction vial containing acylated carbazole **720** (4.8 mg, 1.0 equiv) was purged with argon, and 0.8 ml THF was added. The reaction system was degassed, and LiHMDS solution in THF (0.2 M, 130 μl , 5.0 equiv) was added at $-78\text{ }^{\circ}\text{C}$. The reaction was allowed to warm to

room temperature over 15 min. There was a dramatic color change during the warm-up from light yellow to dark green. After 15 min stirring at room temperature, the reaction was cooled to -78 °C again. Then, PIDA in THF solution (200 μ l, 20 mg/ml, 1.0 equiv, degassed) was injected into the reaction system. The color of the reaction turned to red brown. TLC was used to check the completion of this reaction after 30-60 min, and the reaction was quenched with NaHCO_3 (sat. aq.). The crude product was obtained following extraction (EA X 3), drying (sodium sulfate anhydrous), and concentration. PTLC was used to afford the pure product (2.6 mg, 63%). ^1H NMR (400 MHz, CDCl_3) δ 9.28 (s, 1H), 7.53 (d, $J = 8.6$ Hz, 2H), 7.48 – 7.36 (m, 5H), 7.33 (d, $J = 8.6$ Hz, 2H), 7.11 – 7.00 (m, 5H), 6.85 – 6.69 (m, 3H), 6.62 (dd, $J = 8.3$ Hz, 1H), 6.04 (d, $J = 7.8$ Hz, 1H), 5.19 (s, 2H), 3.92 (s, 3H), 3.91 (s, 3H), 3.79 (s, 3H), 3.48 – 3.41 (t, $J = 8.1$ Hz, 2H), 2.43 (t, $J = 8.1$ Hz, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 179.00, 171.46, 160.96, 160.09, 156.86, 149.27, 146.11, 139.67, 136.40, 133.85, 132.56, 132.53, 132.25, 131.77, 130.02, 129.22, 129.14, 128.88, 128.55, 127.96, 124.90, 123.87, 123.61, 122.23, 117.35, 117.11, 114.10, 113.96, 113.28, 110.82, 106.30, 85.83, 70.59, 56.49, 55.63, 55.61, 42.95, 33.59. ESI MS m/z : 815.0, $[\text{M}+\text{H}]^+$.

Dictyodendrin H

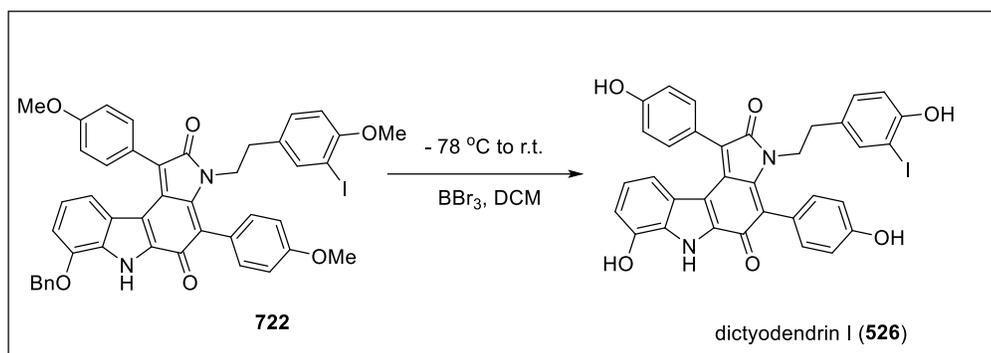


A reaction vial containing intermediate **721** (6.0 mg, 1.0 equiv) was charged with argon, and the starting material was dissolved in 2.5 ml DCM. The BBr_3 (0.8 ml, 1.0 M in DCM, 100

equiv) solution was added slowly at $-78\text{ }^{\circ}\text{C}$. The BBr_3 was a newly opened bottle sold by Aldrich, because older BBr_3 gave messy reaction. The reaction was allowed to warm up slowly, and it was stirred overnight. The reaction was quenched with water at $0\text{ }^{\circ}\text{C}$. The crude product was obtained following extraction (EA X 3), drying (sodium sulfate anhydrous), and concentration. To the crude product, DCM was added, and this suspension was sonicated for 2 min and filtered through cotton. The solid on the cotton was redissolved in methanol and loaded on reverse phase PTLC for purification (eluent: acetonitrile:water = 2:1). The pure product was obtained through a quick C18-silica pipet column (2.7 mg, 54%). ^1H NMR (400 MHz, Methanol- d_4) δ 7.32 (d, $J = 8.5$ Hz, 2H), 7.24 (d, $J = 8.5$ Hz, 2H), 6.99 – 6.92 (m, 3H), 6.90 (d, $J = 8.6$ Hz, 2H), 6.71 – 6.63 (m, 2H), 6.63 – 6.53 (m, 2H), 5.84 (dd, $J = 7.1, 2.1$ Hz, 1H), 3.43 (t, $J = 7.6$ Hz, 2H), 2.41 (t, $J = 7.6$ Hz, 2H). ^{13}C NMR (101 MHz, cd_3od) δ 180.83, 173.44, 160.12, 159.23, 153.85, 150.36, 145.96, 135.67, 134.42, 133.86, 133.53, 133.16, 131.85, 130.70, 130.08, 129.92, 126.36, 124.03, 123.82, 123.11, 119.32, 116.96, 116.48, 116.24, 116.07, 114.04, 110.50, 109.94, 43.91, 34.45.

^1H NMR (400 MHz, Pyridine- d_5) δ 7.95 (d, $J = 8.2$ Hz, 2H), 7.66 (d, $J = 8.0$ Hz, 2H), 7.42 – 7.36 (m, 5H), 7.08 – 7.05 (m, 2H), 7.01 – 6.91 (m, 2H), 6.68 (d, $J = 8.2$ Hz, 1H), 3.84 (t, $J = 8.0$ Hz, 2H), 2.75 – 2.68 (t, $J = 8.0$ Hz, 2H). ^{13}C NMR (101 MHz, pyridine) δ 180.34, 172.27, 160.76, 159.82, 154.58, 149.40, 147.07, 134.92, 134.31, 134.17, 133.90, 133.85, 131.66, 131.38, 129.95, 128.82, 126.66, 122.93, 118.51, 117.40, 116.59, 116.43, 116.31, 113.95, 111.36, 109.93, 43.69, 34.54. ESI MS m/z : 635.1, $[\text{M}+\text{H}]^+$. See below for a tabular comparison of these data with those reported by the isolation group.

Dictyodendrin I



A reaction vial containing intermediate **722** (2.0 mg, 1.0 equiv) was charged with argon, and the starting material was dissolved in 1.5 ml DCM. The BBr_3 (0.3 ml, 1.0 M in DCM, 120 equiv) solution was added slowly at $-78\text{ }^{\circ}\text{C}$. The BBr_3 was a newly opened bottle sold by Aldrich, because older BBr_3 gave messy reaction. The reaction was allowed to warm up slowly, and it was stirred overnight. The reaction was quenched with water at $0\text{ }^{\circ}\text{C}$. The crude product was obtained following extraction (EA X 3), drying (sodium sulfate anhydrous), and concentration. To the crude product, DCM was added, and this suspension was sonicated for 2 min and filtered through cotton. The solid on the cotton was redissolved in methanol and loaded on reverse phase PTLC for purification (eluent: acetonitrile:water = 2:1). The pure product was obtained through a quick C18-silica pipet column (1.0 mg, 54%). ^1H NMR (400 MHz, Methanol- d_4) δ 7.31 (dd, $J = 6.8, 1.2$ Hz, 2H), 7.23 (dd, $J = 6.8, 1.2$ Hz, 2H), 7.19 (s, 1H), 6.94 (dd, $J = 6.8, 1.6$ Hz, 2H), 6.89 (dd, $J = 6.8, 1.2$ Hz, 2H), 6.68 (d, $J = 8.4$, 1H), 6.62 (dd, $J = 8.0, 1.2$ Hz, 1H), 6.58 – 6.56 (m, 2H), 5.84 (d, $J = 7.1$ Hz, 1H), 3.42 (t, $J = 7.5$ Hz, 2H), 2.39 (t, $J = 7.5$ Hz, 2H). ^{13}C NMR (101 MHz, cd_3od) δ 180.82, 173.50, 160.11, 159.19, 156.57, 150.45, 145.94, 140.67, 135.70, 133.85, 133.57, 133.17, 132.17, 131.09, 130.70,

129.92, 126.39, 124.01, 123.83, 123.08, 119.34, 116.55, 116.22, 116.06, 115.46, 114.08, 109.94, 84.36, 43.92, 34.26.

^1H NMR (599 MHz, Pyridine- d_5) δ 7.94 (d, J = 8.2 Hz, 2H), 7.68 (s, 1H), 7.65 (d, J = 8.1 Hz, 2H), 7.40 – 7.38 (m, 4H), 7.05 (d, J = 7.5 Hz, 1H), 7.01 (d, J = 8.1 Hz, 1H), 6.99 – 6.95 (m, 2H), 6.68 (d, J = 8.2 Hz, 1H), 3.84 (t, J = 8.4 Hz, 2H), 2.71 (t, J = 8.4 Hz, 2H). ^{13}C NMR (151 MHz, Pyridine- d_5) δ 180.33, 172.32, 160.77, 159.80, 157.22, 149.46, 147.06, 140.36, 134.95, 134.18, 133.88, 133.87, 131.88, 131.67, 130.89, 128.84, 126.68, 122.92, 118.54, 116.60, 116.47, 116.32, 115.85, 113.96, 109.97, 86.40, 43.73, 34.38. ESI MS m/z : 683.1, $[\text{M}+\text{H}]^+$. See below for a tabular comparison of these data with those reported by the isolation group.

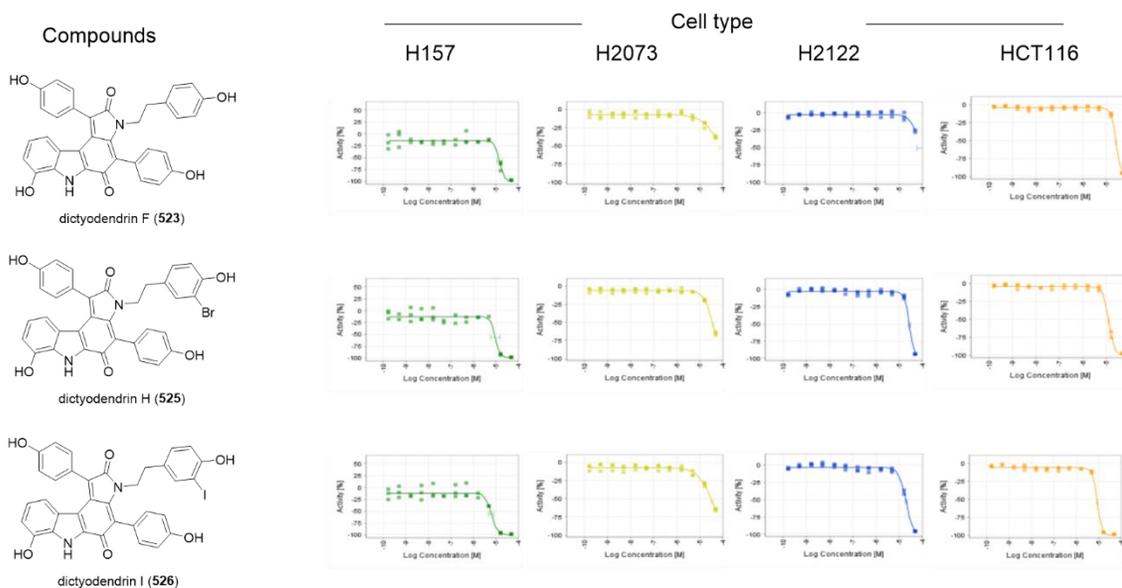
3.3.4 Cytotoxicity Assays and Results

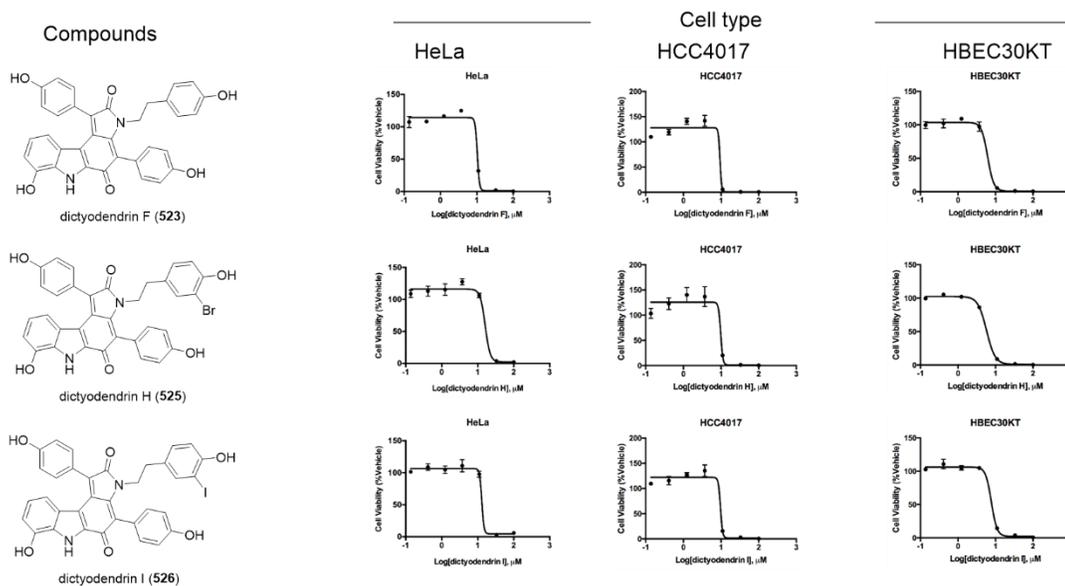
Cytotoxicity assays:

H2122, H2073, H157 and were plated in 384-well plates (900, 900, 420 cells, respectively) in 5% RPMI + 2 mM L-glutamine media 1000 U/ml penicillin (Invitrogen, Inc.), 1 mg/ml streptomycin (Invitrogen, Inc.), and 5% fetal bovine serum (Atlanta Biologicals, Inc.), 60 mL. DMSO or compound was added, at 50 μM to 0.85 nM in 3-fold dilutions, in triplicate. After 4 days at 37 $^\circ\text{C}$, cell viability was measured using CellTiter-Glo. HCT116 cells were plated in 96-well plates (1500 cells) in 5% RPMI + L-glutamine + PenStrep, in triplicate. They were cultured for 3 days at 37 $^\circ\text{C}$. Cell viability was measured using CellTiter-Glo. IC_{50} data was calculated using Prism 6.

HeLa, HCC4017 and HBEC30KT cells were plated in 96-well plates (3,000, 3,000 and 5,000 cells, respectively). HeLa cells were grown in DMEM media supplemented with 10% fetal bovine serum (FBS, Atlanta Biologicals) and 1% penicillin and streptomycin (GIBCO), while

HCC4017 and HBEC30KT were grown in ACL4 media (RPMI 1640 with 25 mM HEPES and 2.0 g/L NaHCO₃ supplemented with 0.02 mg/ml insulin, 0.01 mg/ml transferrin, 25 nM sodium selenite, 50 nM hydrocortisone, 10 mM HEPES, 1 ng/ml EGF, 0.01 mM ethanolamine, 0.01 mM O-phosphorylethanolamine, 0.1 nM triiodothyronine, 2 mg/ml BSA, 0.5 mM sodium pyruvate) with 2% FBS and 1% antibiotics . DMSO or compounds were added the next day from 100 μ M to 137 nM with 3-fold dilutions in triplicate. Cells were incubated with compounds for another 3 days at 37 °C with 5% CO₂. Cell viability was measured using CellTiter-Glo. IC₅₀ data was calculated using Prism 6.





3.3.5 The in-situ NMR Experiment Parameters.

Figure 3.2.2:

Two ynol ether (**54y** and **662n**, all solids) was combined in reaction vial, which was purged with argon. The degassed d_8 -toluene was added to the mixture, and all solid was dissolve. A NMR tube with septum was purged argon, and the reaction mixture was injected into the NMR tube by a syringe. Once the NMR tube was settled. An array of “pad” experiment was chose. Select proton NMR. A ^1H NMR was taken every 1 hour.

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Parameter	Value
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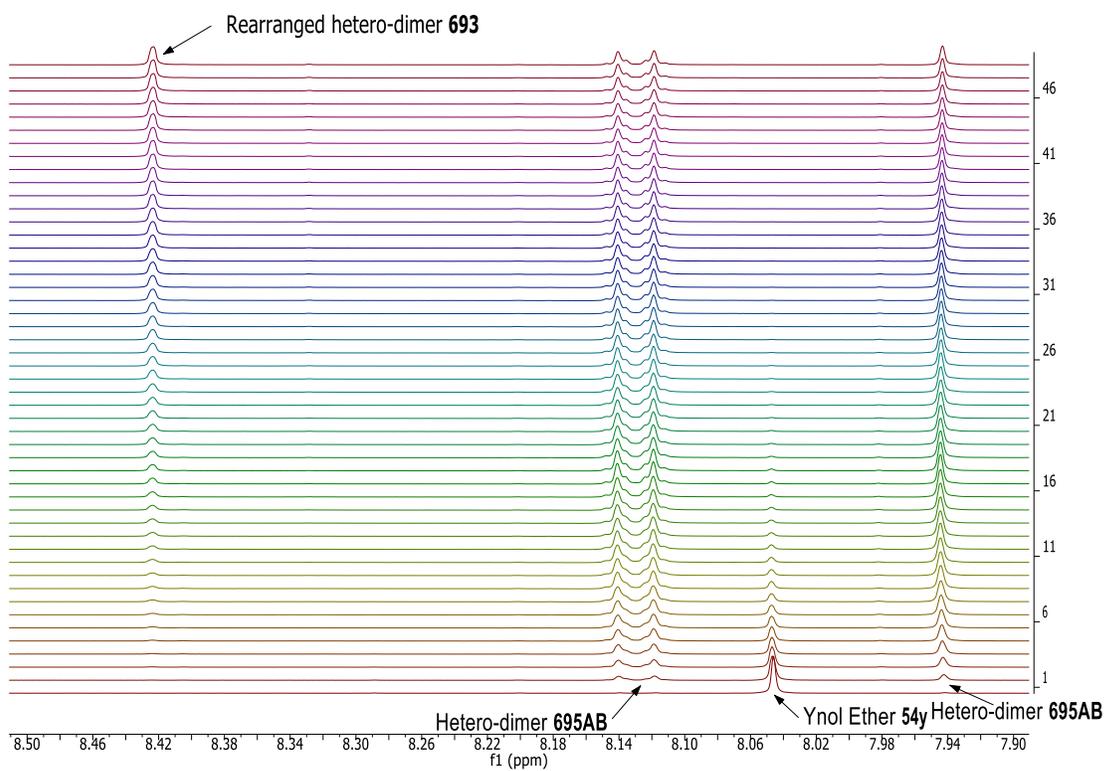
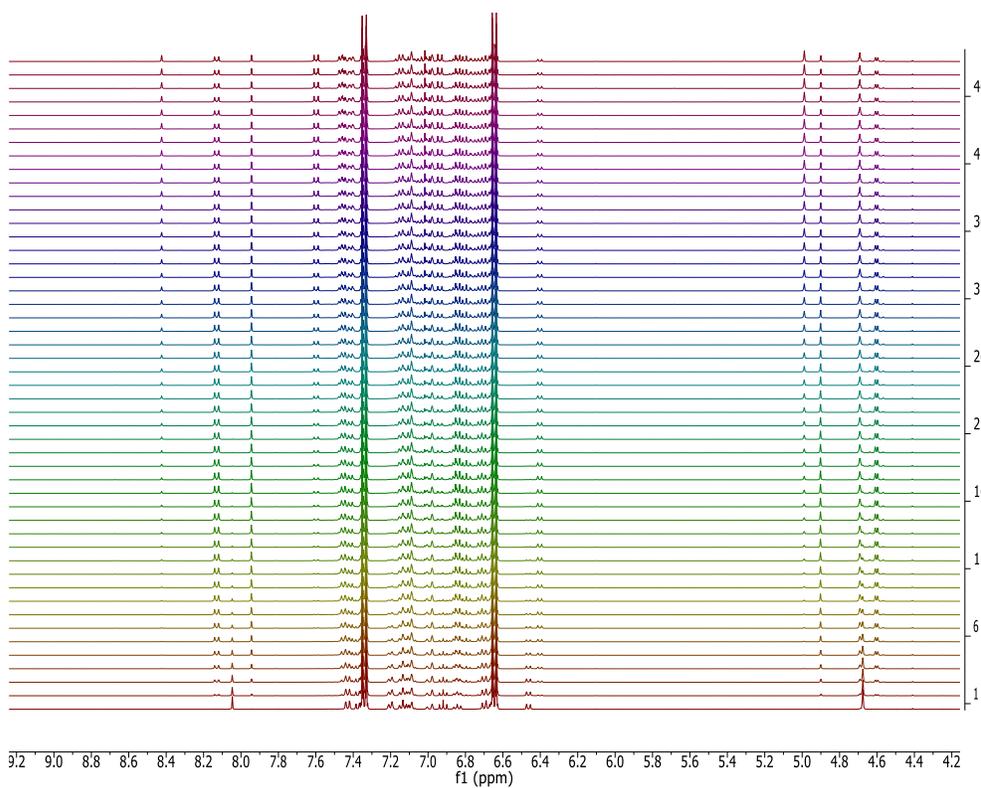


Table 3.2.1:

The ynol ether **54n** was dissolved in molecular sieves pretreated d6-benzene, and the solution was added to the cyclobutenone **701** in a vial under argon. The mixture was injected to a NMR tube with septum and charged with argon. A degas procedure was executed in the NMR tube, before heat in NMR. Once the NMR tube was settled. An array of “pad” experiment was chose. Select proton NMR. A ^1H NMR was taken every half hour.

Typing Code:

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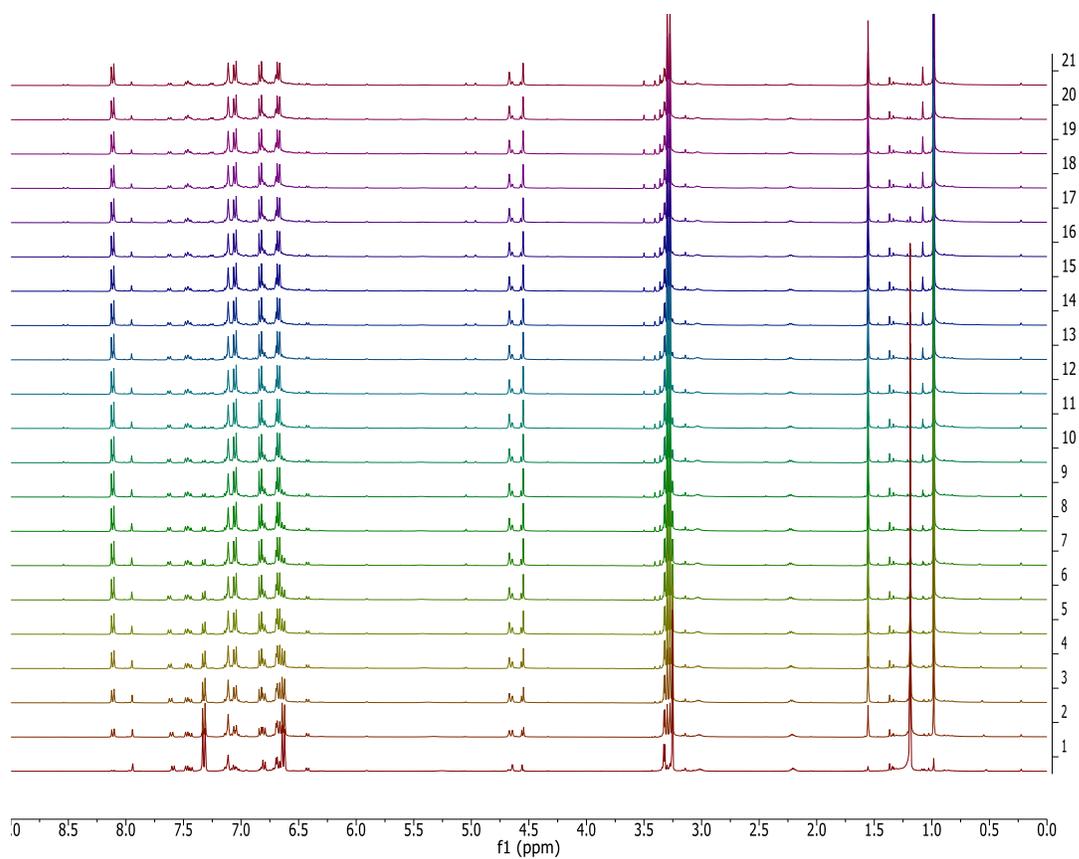
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4	Temperature	60.0
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6	Experiment	1D
7	Number of Scans	32
8	Receiver Gain	30
9	Relaxation Delay	4.0000

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11	Spectrometer Frequency	399.78
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14	Nucleus	^1H
15	Acquired Size	16384
16	Spectral Size	65536



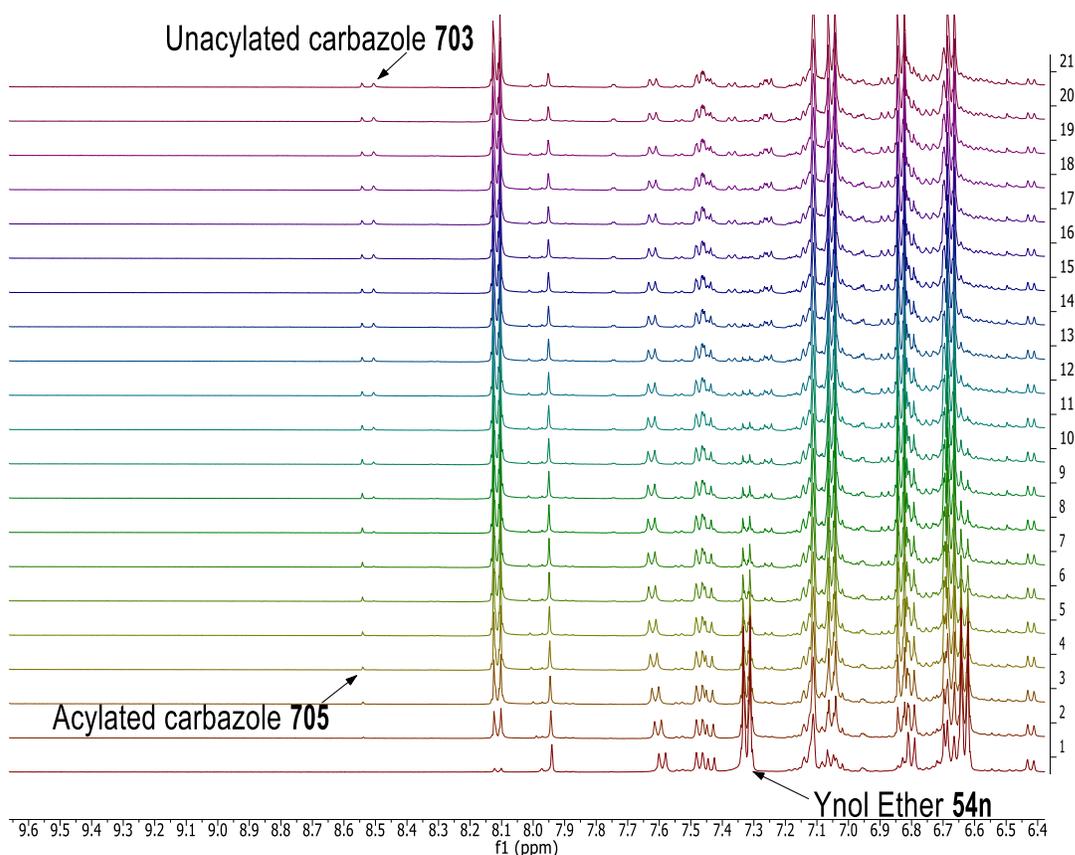
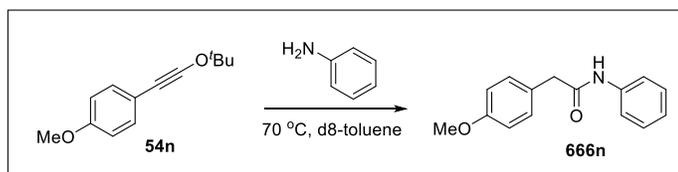


Figure 3.2.2:



The ynol ether **54n** (1.0 equiv) and aniline (1.5 equiv) were dissolved in molecular sieves pretreated d₈-toluene. The mixture was injected to a NMR tube with septum and charged with argon. Once the NMR tube was settled. An array of “pad” experiment was chose. Select proton NMR. A ¹H NMR was taken every half hour.

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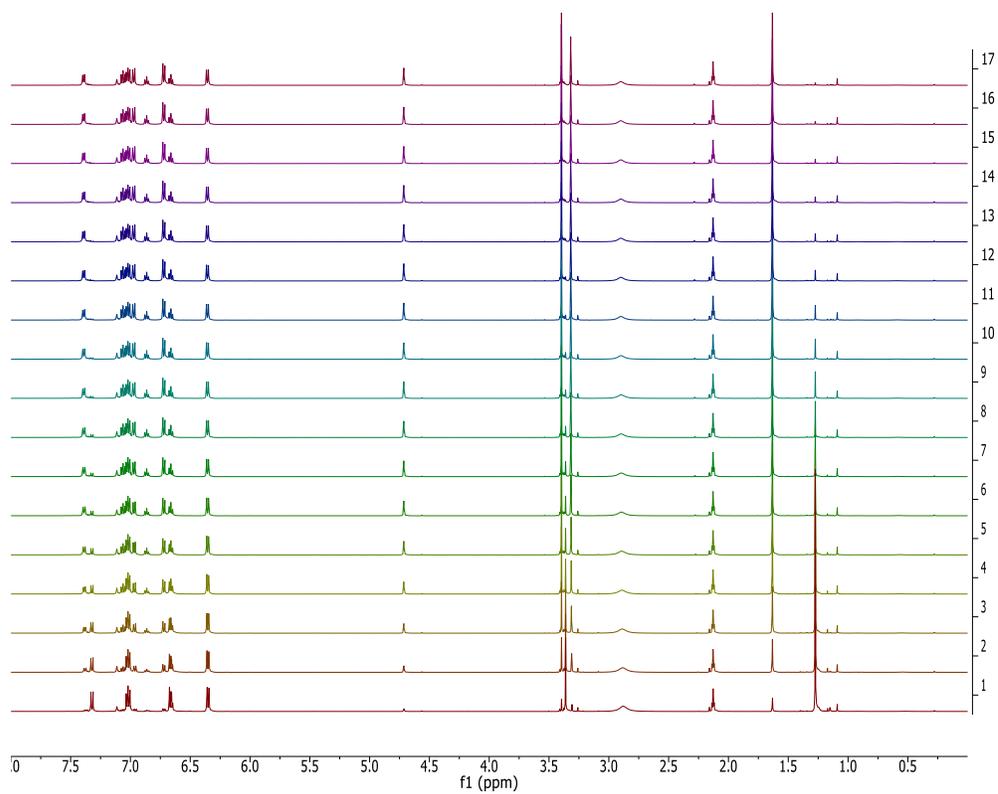
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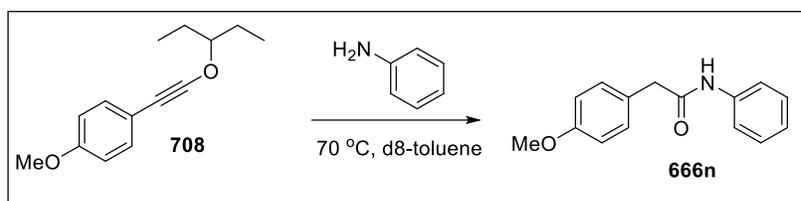
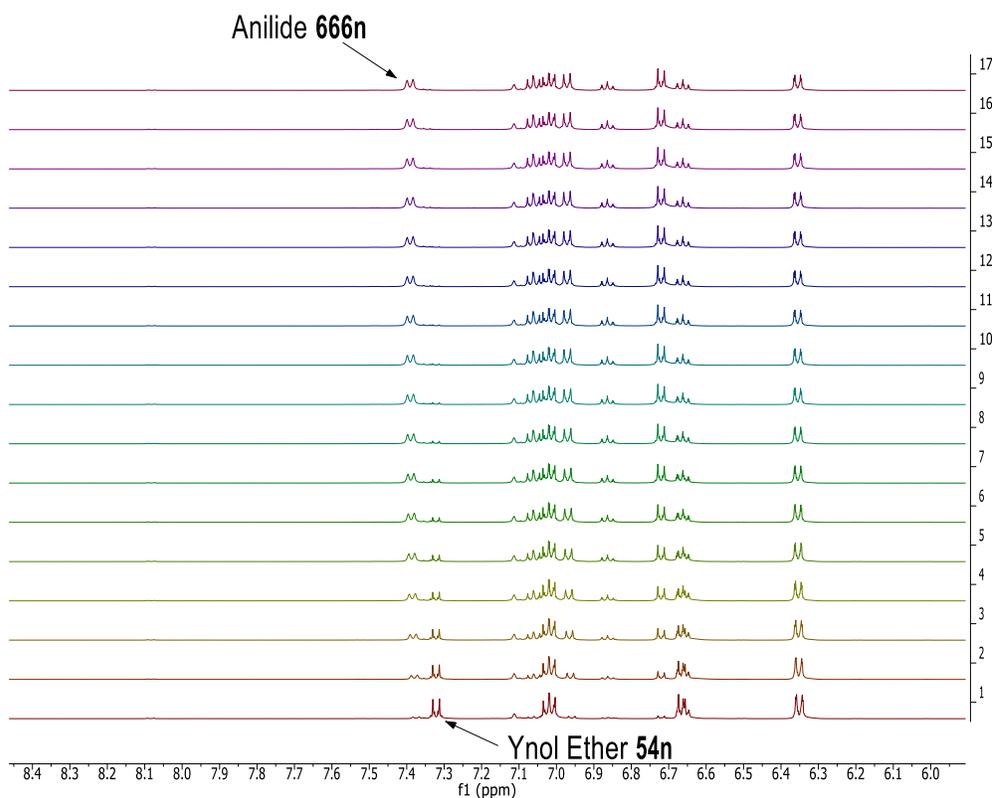
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2	Spectrometer	inova
3	Solvent	toluene
4	Temperature	70.0
5	Pulse Sequence	s2pul
6	Experiment	1D
7	Number of Scans	32
8	Receiver Gain	30
9	Relaxation Delay	1.0000
10	Acquisition Time	2.0488
11	Spectrometer Frequency	499.78
12	Spectral Width	7996.8
13	Lowest Frequency	-999.7
14	Nucleus	1H
15	Acquired Size	16384
16	Spectral Size	65536





The ynol ether **708** (1.0 equiv) and aniline (1.5 equiv) were dissolved in molecular sieves pretreated d₈-toluene. The mixture was injected to a NMR tube with septum and charged with argon. Once the NMR tube was settled. An array of “pad” experiment was chose. Select proton NMR. A ¹H NMR was taken every half hour.

Typing Code:

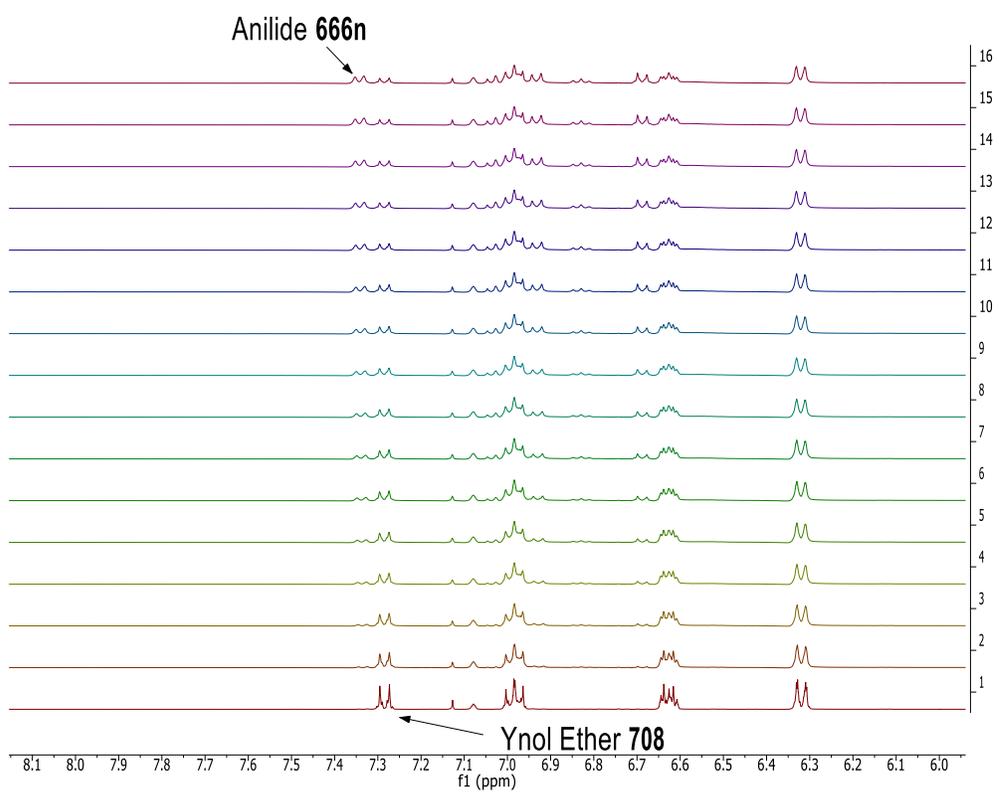
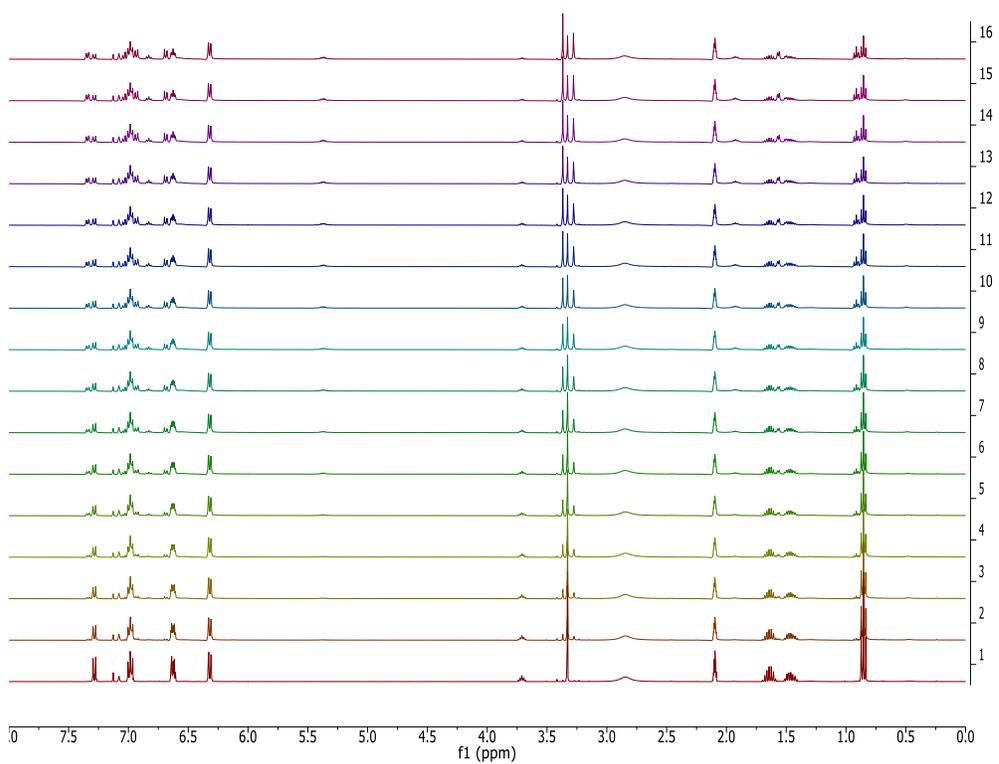
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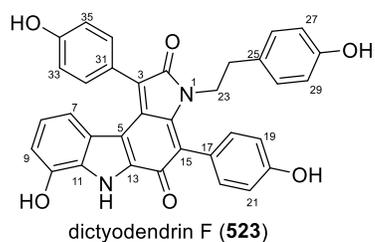
pad[1]=1a

ga

Parameter	Value
1 Origin	Varian
2 Spectrometer	inova
3 Solvent	toluene
4 Temperature	70.0
5 Pulse Sequence	s2pul
6 Experiment	1D
7 Number of Scans	32
8 Receiver Gain	30
9 Relaxation Delay	1.0000
10 Acquisition Time	2.0488
11 Spectrometer Frequency	499.78
12 Spectral Width	7996.8
13 Lowest Frequency	-999.7
14 Nucleus	1H
15 Acquired Size	16384
16 Spectral Size	65536

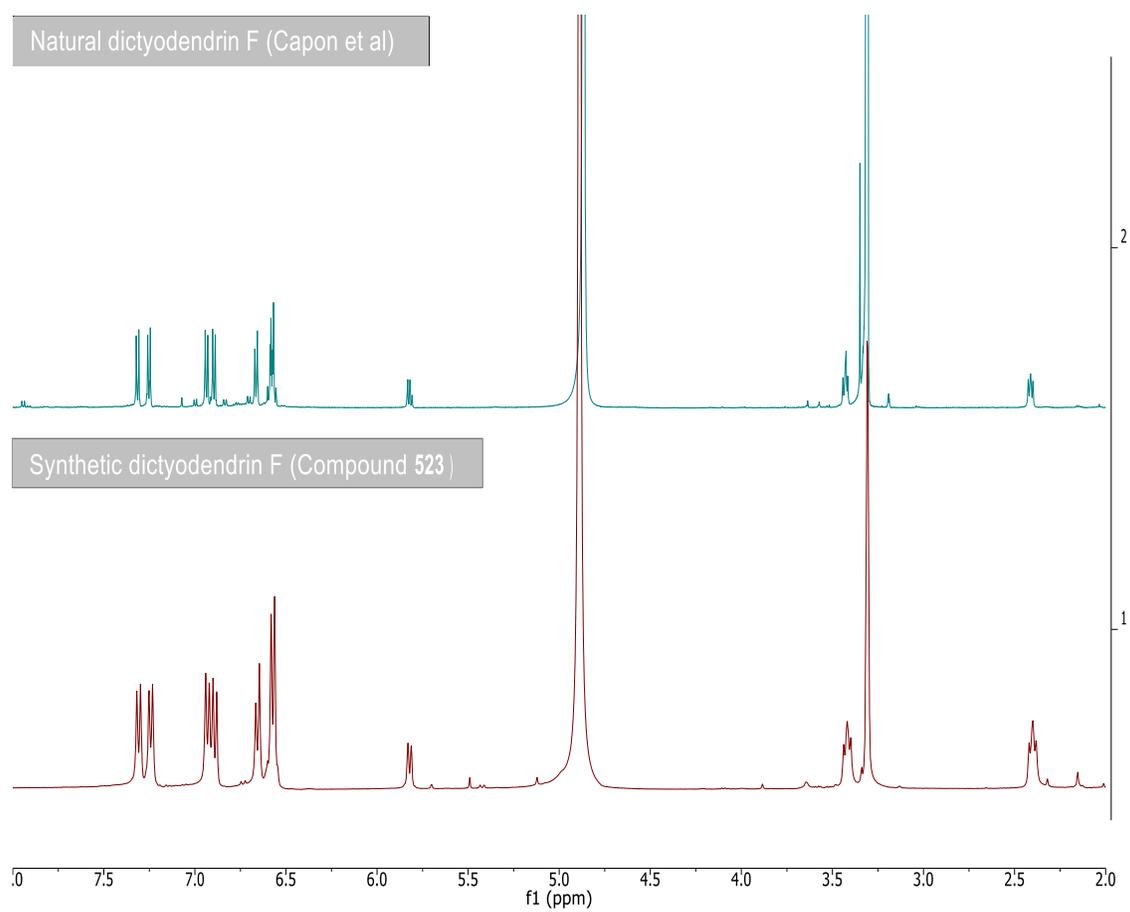


3.3.6 Spectra comparison Between Natural Product and Synthetic Compounds

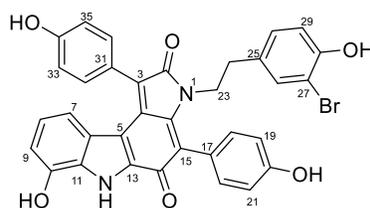
¹H and ¹³C NMR (Methanol-*d*₄) data comparison for dictyodendrin F

No.	δ_C (Davies)	δ_C (Ready)	$\Delta\delta_C$ (Davies-Ready)	δ_H (natural) (m, J (Hz))	δ_H (synthetic) (m, J (Hz))	$\Delta\delta_H$ (natural-synthetic)
2	173.4	173.4	-	-	-	-
3	130.1	130.0	-0.1	-	-	-
4	135.6	135.5	-0.1	-	-	-
5	114.0	114.0	-	-	-	-
6	126.4	126.3	-0.1	-	-	-
7	116.3	116.2	-0.1	5.83 (dd, 7.8, 1.2)	5.82 (d, 7.8)	-0.01
8	123.1	123.2	+0.1	6.55-6.60	6.52-6.62	-
9	110.0	110.0	-	6.55-6.60	6.52-6.62	-
10	146.0	146.3	+0.3	-	-	-
11	130.7	130.8	+0.1	-	-	-
13	133.2	133.1	-0.1	-	-	-
14	180.4	180.9	+0.5	-	-	-
15	119.3	119.3	-	-	-	-
16	150.5	150.5	-	-	-	-
17	124.2	124.1	-0.1	-	-	-
18/22 ^a	133.8	133.8	-	7.25 (d, 8.6)	7.24 (d, 7.6)	-0.01
19/21	116.4	116.3	-0.1	6.94 (d, 8.6)	6.93 (d, 7.6)	-0.01
20	159.2	159.2	-	-	-	-
23	44.2	44.2	-	3.43 (t like, 7.8)	3.42 (t, 7.8)	-0.01
24	34.9	34.9	-	2.41 (t like, 7.8)	2.40 (t, 7.8)	-0.01
25	130.0	130.0	-	-	-	-
26/30	130.9	130.9	-	6.55-6.60	6.52-6.62	-
27/29	116.0	116.0	-	6.66 (d, 8.5)	6.66 (d, 8.0)	-
28	156.9	156.9	-	-	-	-
31	123.9	123.7	-0.2	-	-	-
32/36 ^a	133.5	133.5	-	7.32 (d, 8.6)	7.31 (d, 8.0)	-0.01
33/35	116.1	116.1	-	6.90 (d, 8.6)	6.89 (d, 8.0)	-0.01
34	160.2	160.3	+0.1	-	-	-

^aAssignment of C18/C22 vs. C32/C36 is ambiguous.



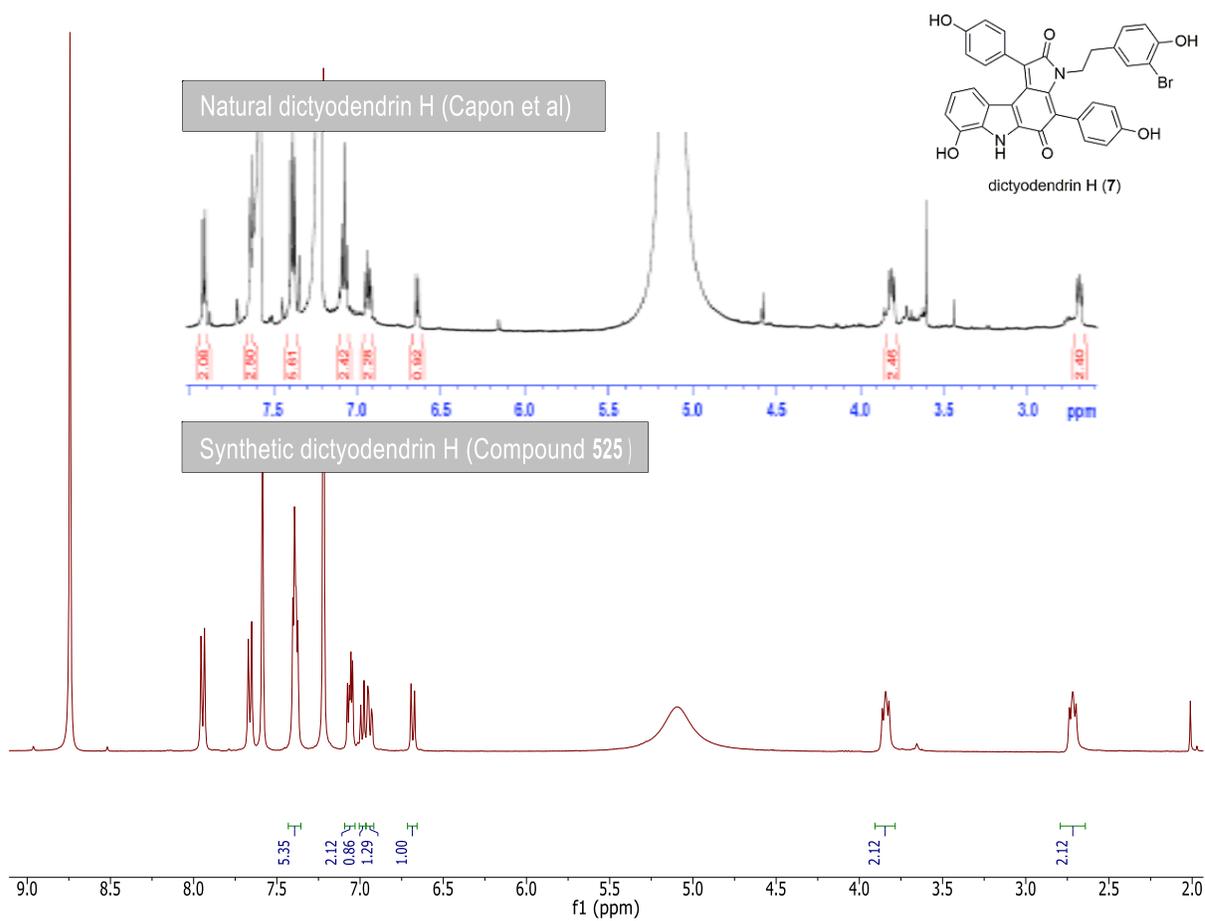
Spectrum of natural Dictyodendrin F courtesy of Robert Capon.

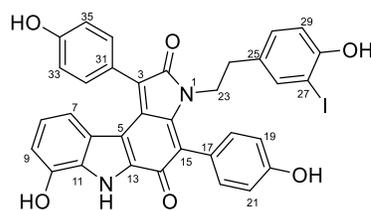


dictyodendrin H (525)

No.	δ_C (natural) ^a	δ_C (synthetic)	$\Delta\delta_C$ (natural-synthetic)	δ_H (natural) (m, J (Hz))	δ_H (synthetic) (m, J (Hz))	$\Delta\delta_H$ (natural-synthetic)
2	172.1	172.3	+0.2	-	-	-
3	128.8	128.8	-	-	-	-
4	- ^b	134.9	-	-	-	-
5	113.8	113.9	+0.1	-	-	-
6	126.6	126.7	+0.1	-	-	-
7	116.3	116.4	+0.1	6.64 (d, 8.2)	6.68 (d, 8.2)	+0.04
8	122.9	122.9	-	6.94 (dd, 8.2, 7.6)	6.98 (d, 8.0)	+0.04
9	109.9	109.9	-	7.06 (d, 7.6)	7.05 (d, 8.0)	-0.01
10	146.9	147.1	+0.2	-	-	-
11	131.5	131.7	+0.2	-	-	-
13	- ^b	134.2	-	-	-	-
14	- ^b	180.3	-	-	-	-
15	118.4	118.5	+0.1	-	-	-
16	149.2	149.4	+0.2	-	-	-
17	124.0	- ^c	-	-	-	-
18/22	133.8	133.8	-	7.63 (d, 8.5)	7.66 (d, 8.0)	+0.03
19/21	116.3	116.3	-	7.38 (d, 8.5)	7.38 (d, 8.0)	-
20	159.7	159.8	+0.1	-	-	-
23	43.6	43.7	+0.1	3.81 (t, 8.2)	3.84 (t, 8.0)	+0.03
24	34.5	34.5	-	2.69 (t, 8.2)	2.72 (t, 8.0)	+0.03
25	131.1	131.4	+0.3	-	-	-
26	134.1	134.3	+0.2	7.37 (d, 2.1)	7.38	+0.01
27	111.3	111.4	+0.1	-	-	-
28	154.4	154.6	+0.2	-	-	-
29	117.0	117.4	+0.4	7.08 (d, 8.2)	7.06 (d, 8.0)	-0.02
30	129.8	129.9	+0.1	6.92 (dd, 8.2, 2.1)	6.92 (dd, 8.8, 1.2)	-
31	123.6	- ^c	-	-	-	-
32/36	133.8	133.9	+0.1	7.91 (d, 8.6)	7.94 (d, 8.4)	+0.03
33/35	116.6	116.6	-	7.39 (d, 8.6)	7.39 (d, 8.0)	-
34	160.7	160.8	+0.1	-	-	-

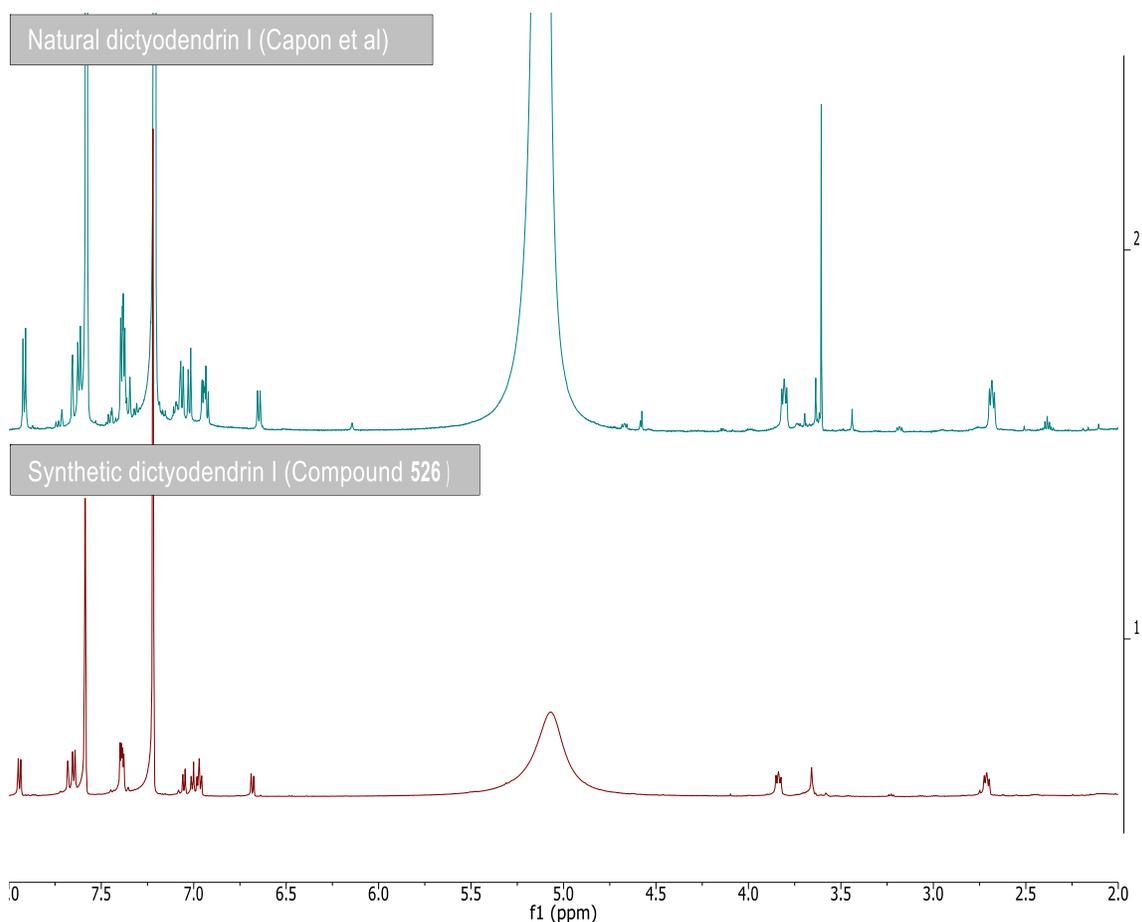
^a¹³C NMR assignments were supported by HSQC and HMBC experiment. ^bSignals not detected. ^cUnder pyridir *d*₅ peaks.



dictyodendrin I (**526**)¹H and ¹³C NMR (pyridine-*d*₅) data comparison for dictyodendrin I

No.	δ_C (natural) ^a	δ_C (synthetic)	$\Delta\delta_C$ (natural-synthetic)	δ_H (natural) (m, J (Hz))	δ_H (synthetic) (m, J (Hz))	$\Delta\delta_H$ (natural-synthetic)
2	172.3	172.3	-	-	-	-
3	128.8	128.8	-	-	-	-
4	134.9	134.9	-	-	-	-
5	113.9	114.0	+0.1	-	-	-
6	126.6	126.7	+0.1	-	-	-
7	116.4	116.5	+0.1	6.65 (d, 8.2)	6.68 (d, 7.8)	+0.03
8	123.0	122.9	-0.1	6.93 (dd, 8.2, 7.6)	6.96 (d, 7.8)	+0.03
9	109.9	110.0	+0.1	7.06 (d, 7.6)	7.05 (d, 7.8)	-0.01
10	147.0	147.0	-	-	-	-
11	131.6	131.7	+0.1	-	-	-
13	134.1	134.2	+0.1	-	-	-
14	180.3	180.3	-	-	-	-
15	118.5	118.5	-	-	-	-
16	149.4	149.5	+0.1	-	-	-
17	124.0	- ^b	-	-	-	-
18/22	133.8	133.8	-	7.62 (d, 8.5)	7.65 (d, 7.8)	+0.03
19/21	116.3	116.3	-	7.38 (d, 8.5)	7.38 (d, 7.8)	-
20	159.8	159.8	-	-	-	-
23	43.7	43.7	-	3.81 (t, 8.2)	3.84 (t, 8.4)	+0.03
24	34.3	34.4	+0.1	2.68 (t, 8.2)	2.71 (t, 8.4)	+0.03
25	131.8	131.9	+0.1	-	-	-
26	140.3	140.4	+0.1	7.66 (d, 2.1)	7.68	+0.02
27	86.3	86.4	+0.1	-	-	-
28	157.2	157.2	-	-	-	-
29	115.8	115.8	-	7.02 (d, 8.2)	7.01 (d, 8.4)	-0.01
30	130.8	130.9	+0.1	6.95 (dd, 8.2, 2.1)	6.98 ^c	-
31	123.6	- ^b	-	-	-	-
32/36	133.8	133.9	+0.1	7.92 (d, 8.6)	7.94 (d, 8.4)	+0.02
33/35	116.5	116.6	+0.1	7.39 (d, 8.6)	7.39 (d, 8.4)	-
34	160.7	160.8	+0.1	-	-	-

^a¹³C NMR assignments were supported by HSQC and HMBC experiment. ^bUnder pyridine-*d*₅ peaks. ^cSignals overlapped.



Spectrum of natural Dictyodendrin I courtesy of Robert Capon

References:

- ¹ Zhang, W.; Ready, J. M. *Angew. Chem. Int. Ed.* **2014**, *53*, 8980-8984.
- ² Kohnen, A. L.; Mak, X. Y.; Lam, T. Y.; Dunetz, J. R.; Danheiser, R. L. *Tetrahedron* **2006**, *62*, 3815-3822.
- ³ For selected Danheiser benzannulation reactions, see: (a) Danheiser, R. L.; Gee, S. K. *J. Org. Chem.* **1984**, *49*, 1672-1674. (b) Xu, S. L.; Moore, H. W. *J. Org. Chem.* **1989**, *54*, 4024-4026. (c) Danheiser, R. L.; Brisbois, R. G.; Kowalczyk, J. J.; Miller, R. F. *J. Chem. Am. Soc.* **1990**,

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⁵ Parkinson, E. K. *Ann. Med.* **2003**, *35*, 466-475.

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⁷ Ayats, C.; Soley, R.; Albericio, F.; Alvarez, M. *Org. Biomol. Chem.* **2009**, *7*, 860-862.

⁸ Löffler, A.; Himbert, G. *Synthesis* **1992**, *1992*, 495-498.

⁹ (a) dpp-hexane is a poor ligand for palladium-catalyzed CO/C₂H₄ copolymerization. See: Leeuwen, P. W. N. M. v.; Freixa, Z. In *Modern Carbonylation Methods*; Wiley-VCH Verlag GmbH & Co. KGaA: 2008, p 10. (b) For bite angle of Pd[PH₂(CH₂)₆PH₂], see: van Zeist, W.-J.; Visser, R.; Bickelhaupt, F. M. *Chem. Eur. J.* **2009**, *15*, 6112-6115.

¹⁰ N-Cbz gave 84% yield of impure material in the coupling reaction; N-Ns decomposed during coupling reaction; N-Ts had poor solubility for coupling reaction and gave 21% yield.

¹¹ ¹H NMR key parameters: nt = 32, d1= 4. The graph in Scheme 1B was generating by assuming [20]% + [22]% + [23]% = 100%. No other products were observed in the ¹H NMR spectra. The hetero/homo-dimer selectivity did not change over the course of the reaction.

¹² The starting material was reused once.

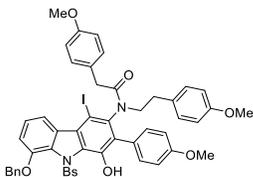
¹³ (a) Schmidt, A. H.; Debo, M.; Wehner, B. *Synthesis* **1990**, 1990, 237-242. (b) Sejwal, P.; Han, Y.; Shah, A.; Luk, Y.-Y. *Org. Lett.* **2007**, 9, 4897-4900. (c) Li, J.; Han, Y.; Freedman, T. B.; Zhu, S.; Kerwood, D. J.; Luk, Y.-Y. *Tetrahedron Lett.* **2008**, 49, 2128-2131.

¹⁴ We added 2.5 equivalents of the ynol ether every 4 hours. Batchwise addition gave 42% of **37** at 60 °C compared to 38% yield when all reagents were combined at the beginning of the reaction.

¹⁵ (a) Richter, J. M.; Whitefield, B. W.; Maimone, T. J.; Lin, D. W.; Castroviejo, M. P.; Baran, P. S. *J. Chem. Am. Soc.* **2007**, 129, 12857-12869. (b) DeMartino, M. P.; Chen, K.; Baran, P. S. *J. Chem. Am. Soc.* **2008**, 130, 11546-11560.

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¹⁷ The iodinated product was the only product we isolated after the reaction.



¹⁸ For benzenesulfonate acting as an oxidant in the Shapiro reaction, see: Adlington, R. M.; Barrett, A. G. M. *Acc. Chem. Res.* **1983**, 16, 55-59.

¹⁹ An alternative mechanism involves migration of the benzenesulfonate from the indole nitrogen to the phenolate anion to form an ArOSO₂Ph intermediate. Enolate addition to the aromatic ring with loss of PhSO₂⁻ and tautomerization would form carbazole **41**.

²⁰ Yamaguchi, A. D.; Chepiga, K. M.; Yamaguchi, J.; Itami, K.; Davies, H. M. L. *J. Am. Chem. Soc.* **2015**, *137*, 644–647.

²¹ Wing-Wah, S. *Tetrahedron Lett.* **1993**, *34*, 6223-6224.

²² HSQC and HMBC were employed to assign carbons of dictyodendrins H and I by the isolation group. The quantity of natural products was not enough for direct a ¹³C NMR experiment. See Ref 3.

²³ The cytotoxicity test against cell lines was conducted by HTS Core at UTSW, and Chensu Wang at UTSW

²⁴ Barbasiewicz, M.; Michalak, M.; Grela, K. *Chem. Eur. J.* **2012**, *18*, 14237.

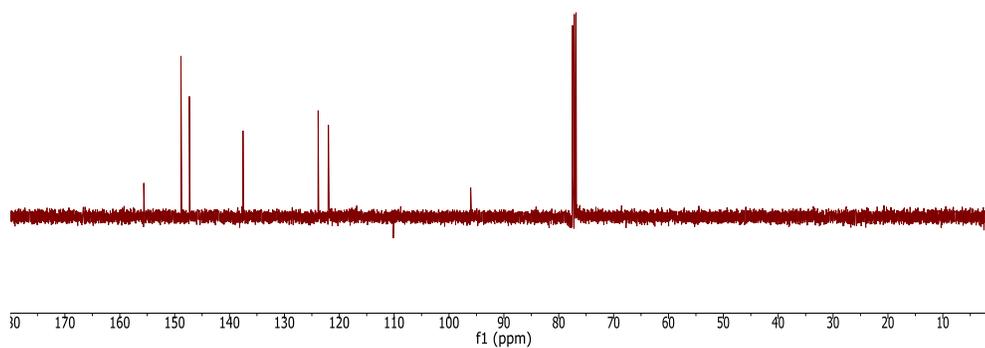
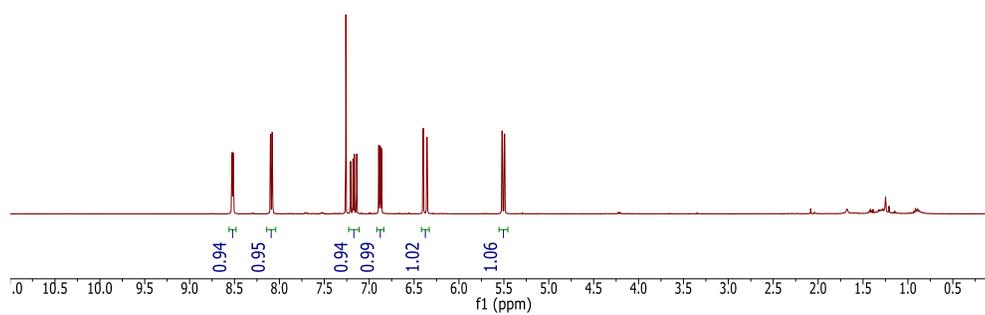
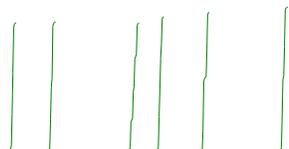
²⁵ Grigg, R.; Inman, M.; Kilner, C.; Köppen, I.; Marchbank, J.; Selby, P.; Sridharan, V. *Tetrahedron* **2007**, *63* 6152.

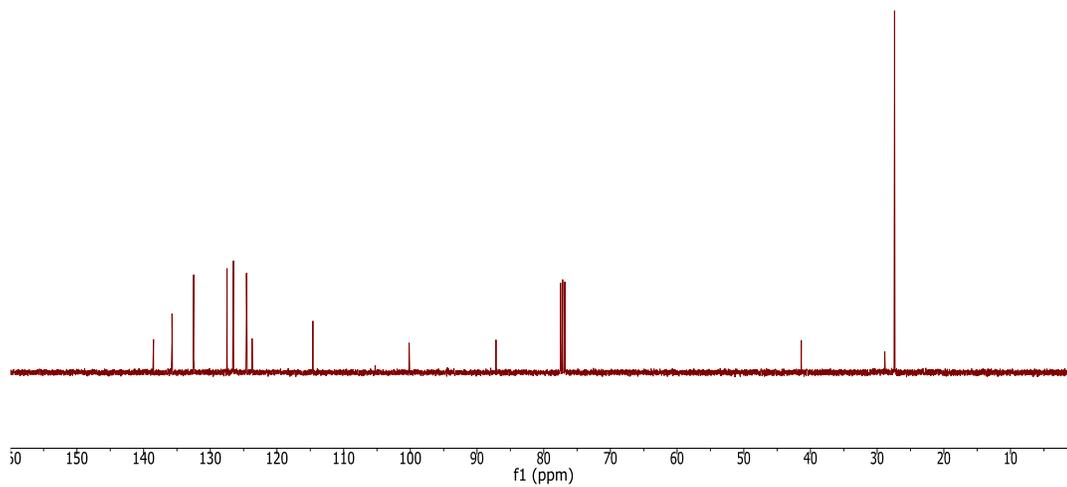
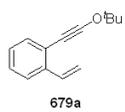
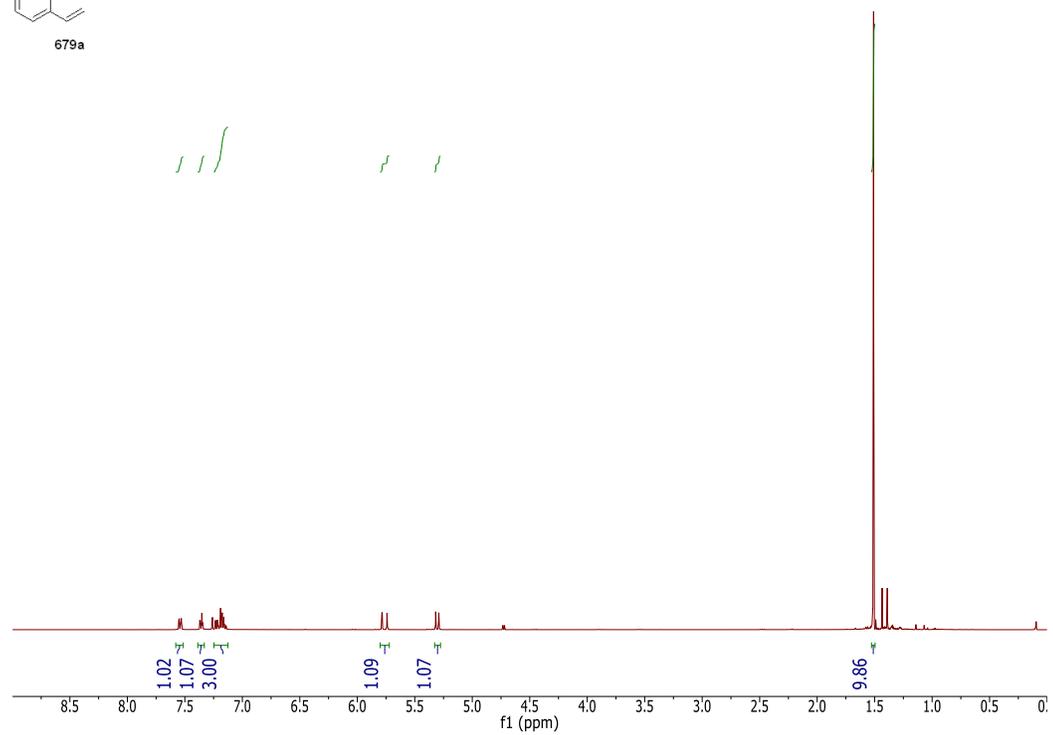
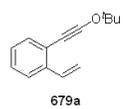
²⁶ Lautens, M.; Tayama, E.; Herse, C. *J. Am. Chem. Soc.* **2004**, *127*, 72-73

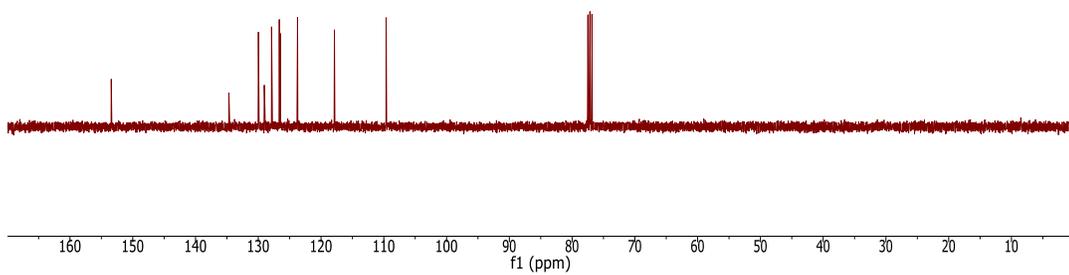
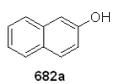
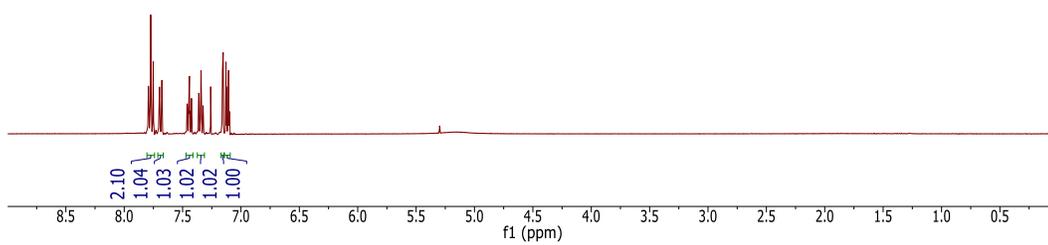
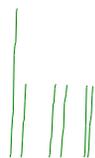
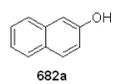
²⁷ Wing-Wah, S. *Tetrahedron Lett.* **1993**, *34*, 6223-6224.

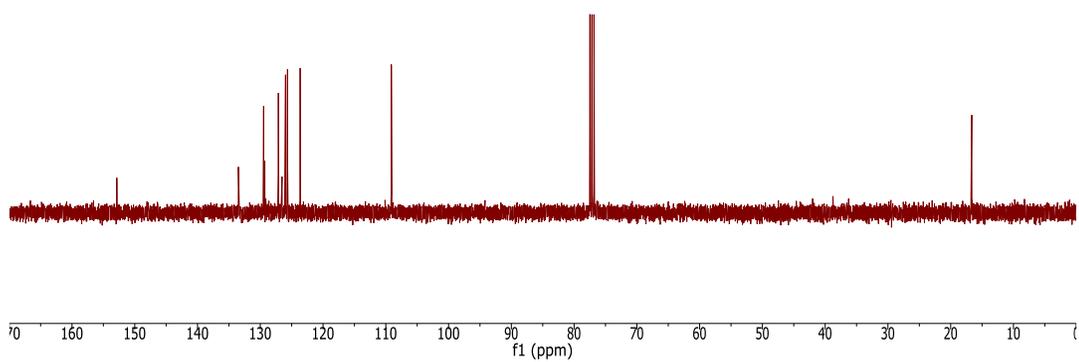
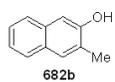
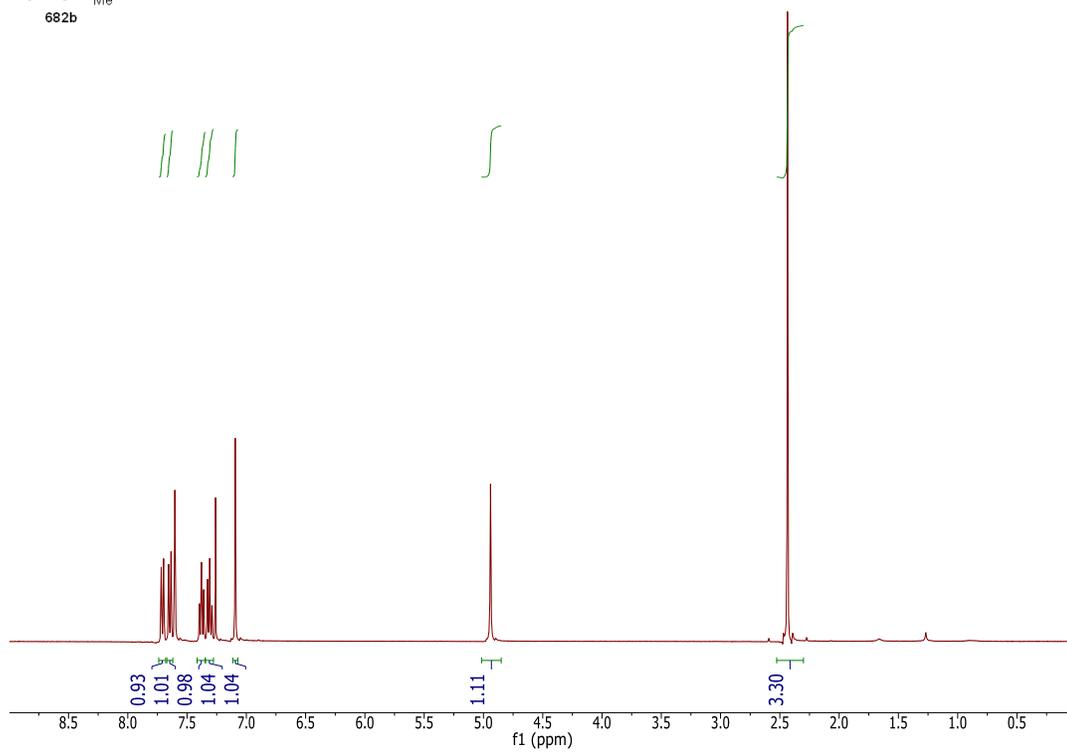
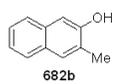
APPENDIX B

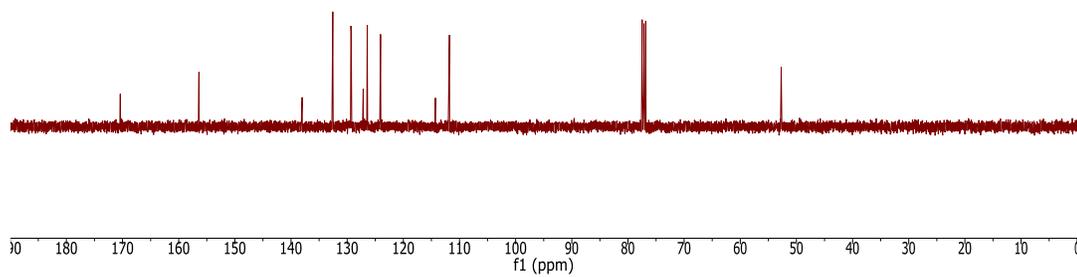
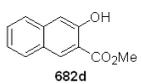
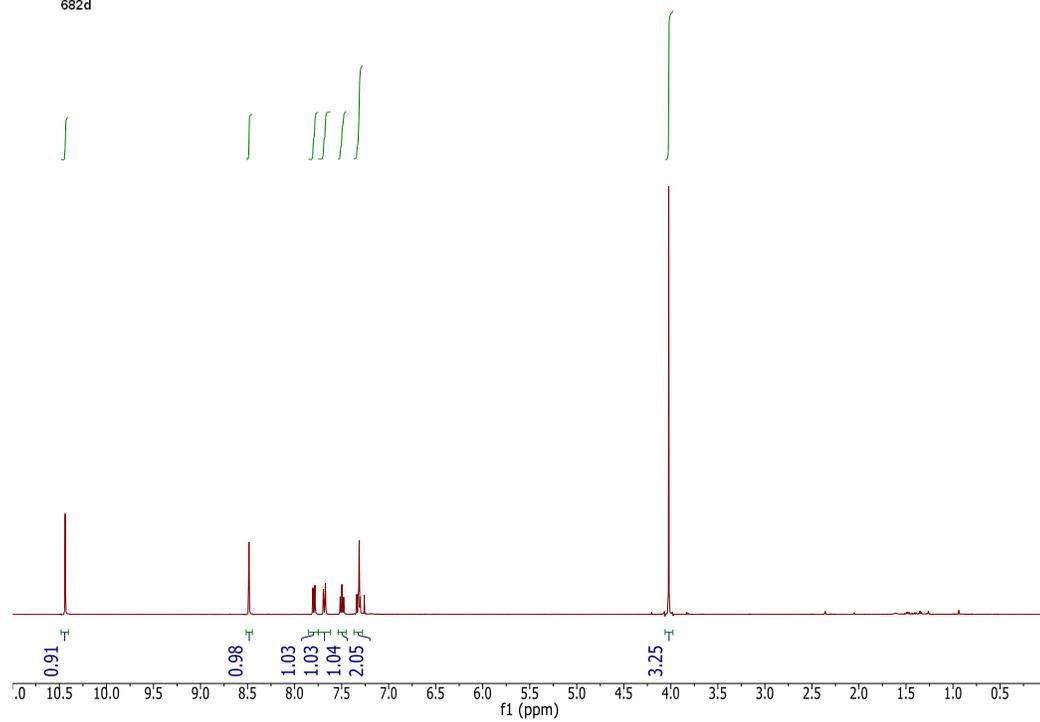
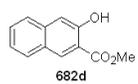
^1H , ^{13}C and 2D NMR SPECTRA

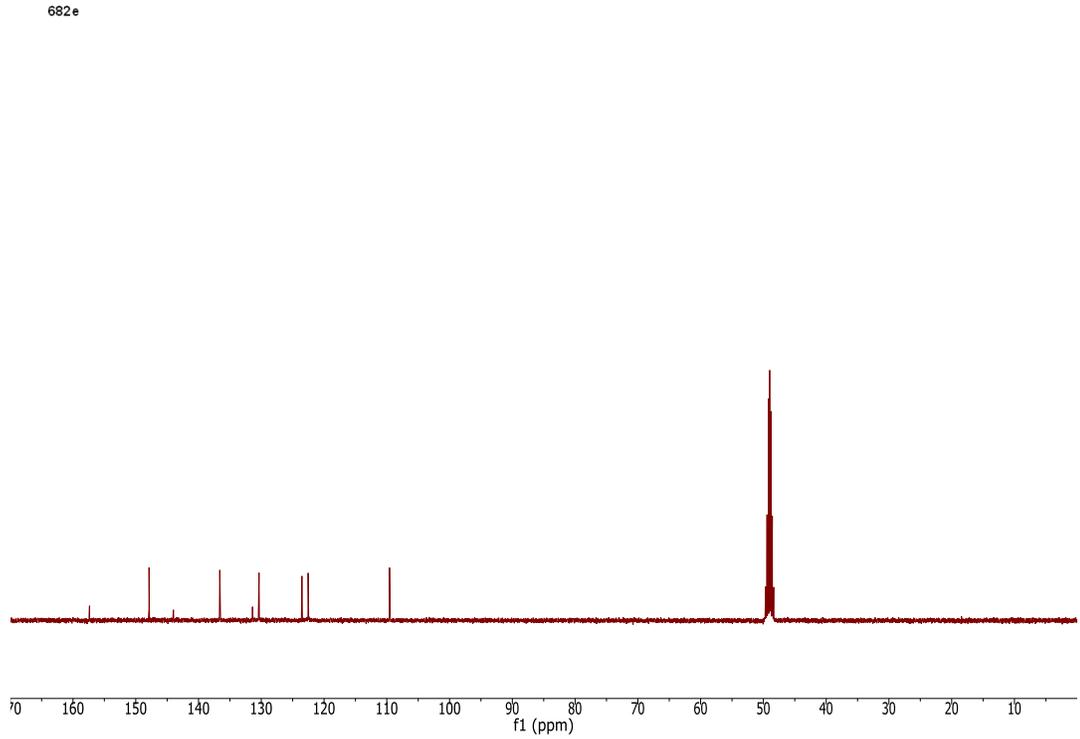
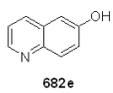
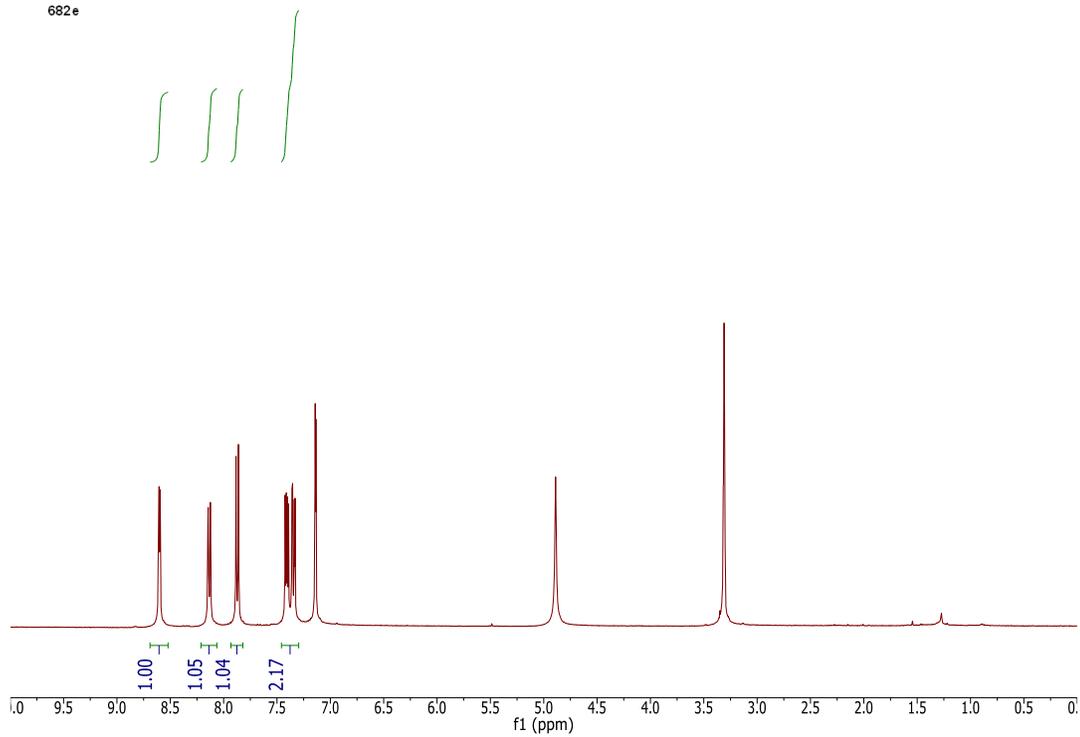
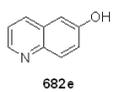


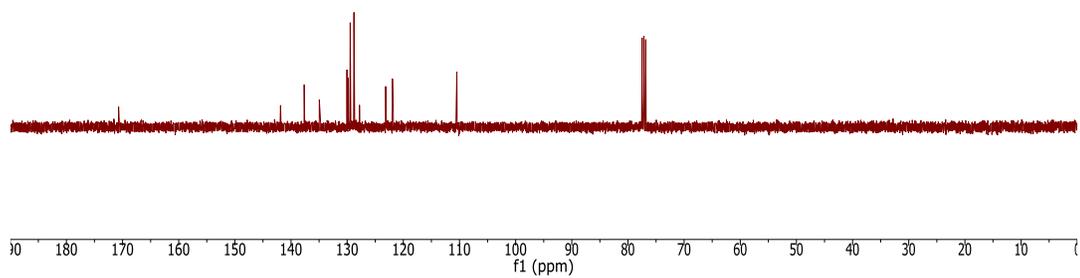
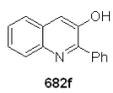
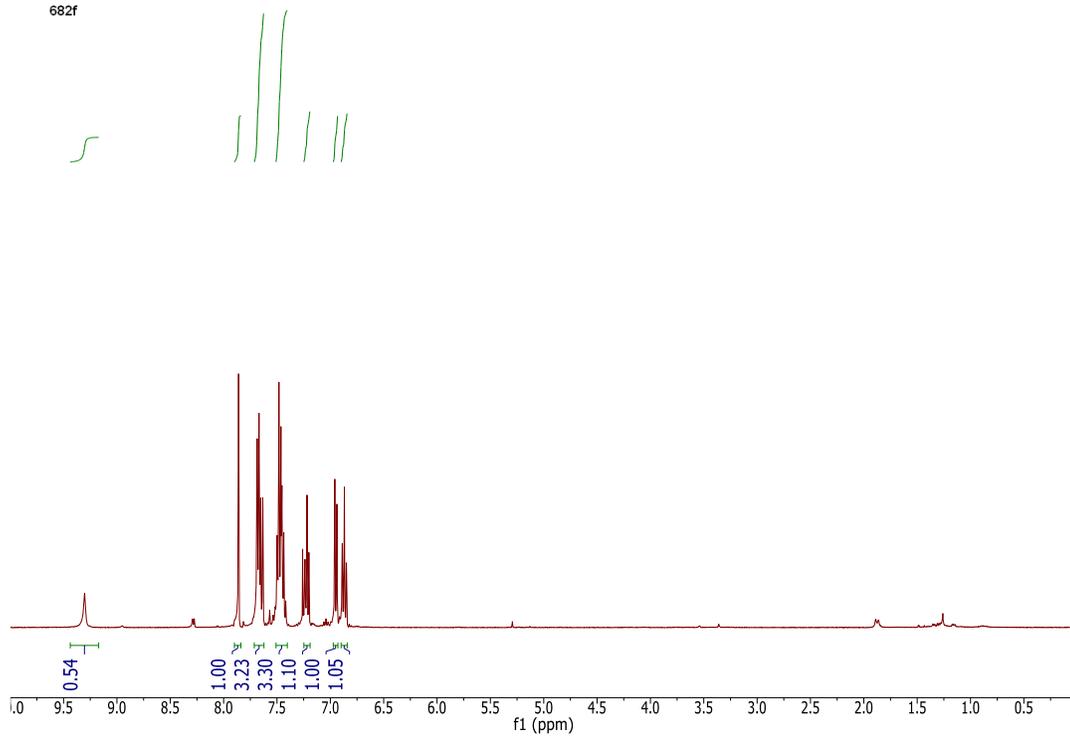
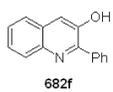


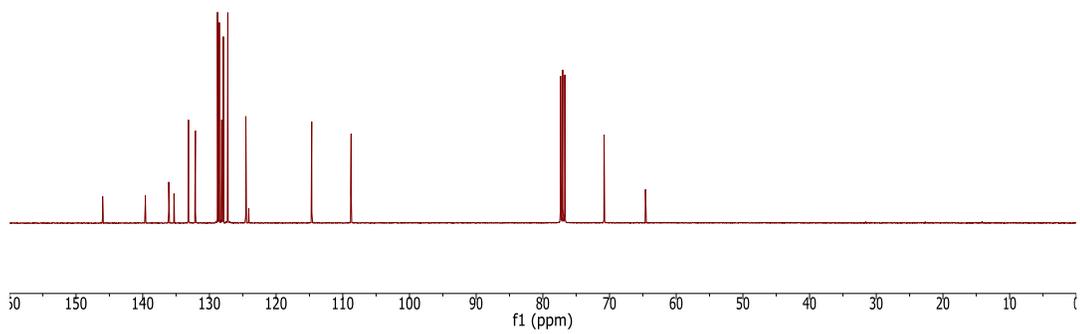
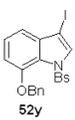
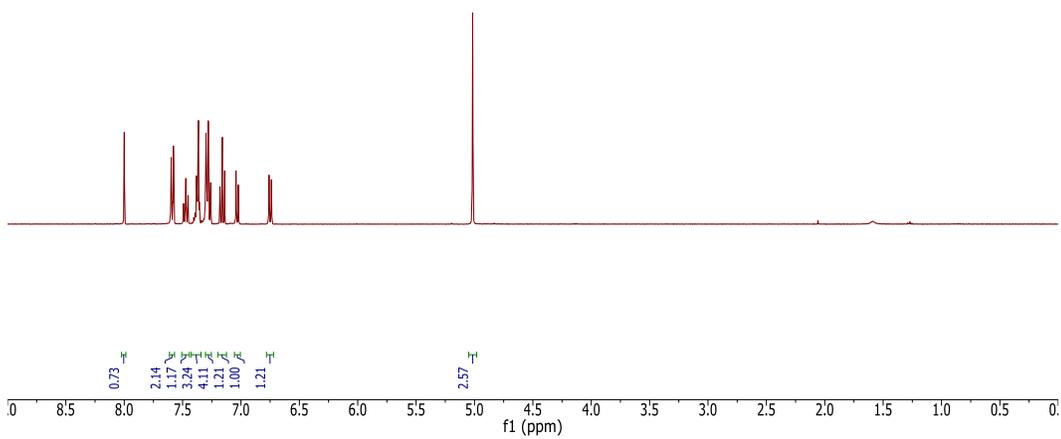
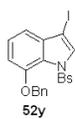


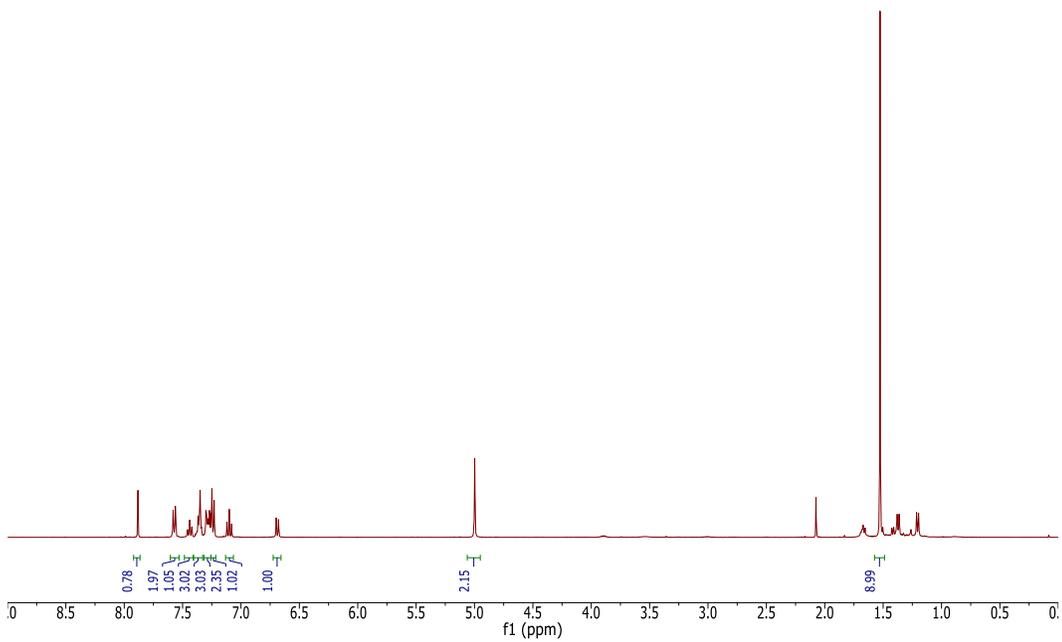
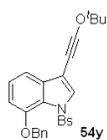


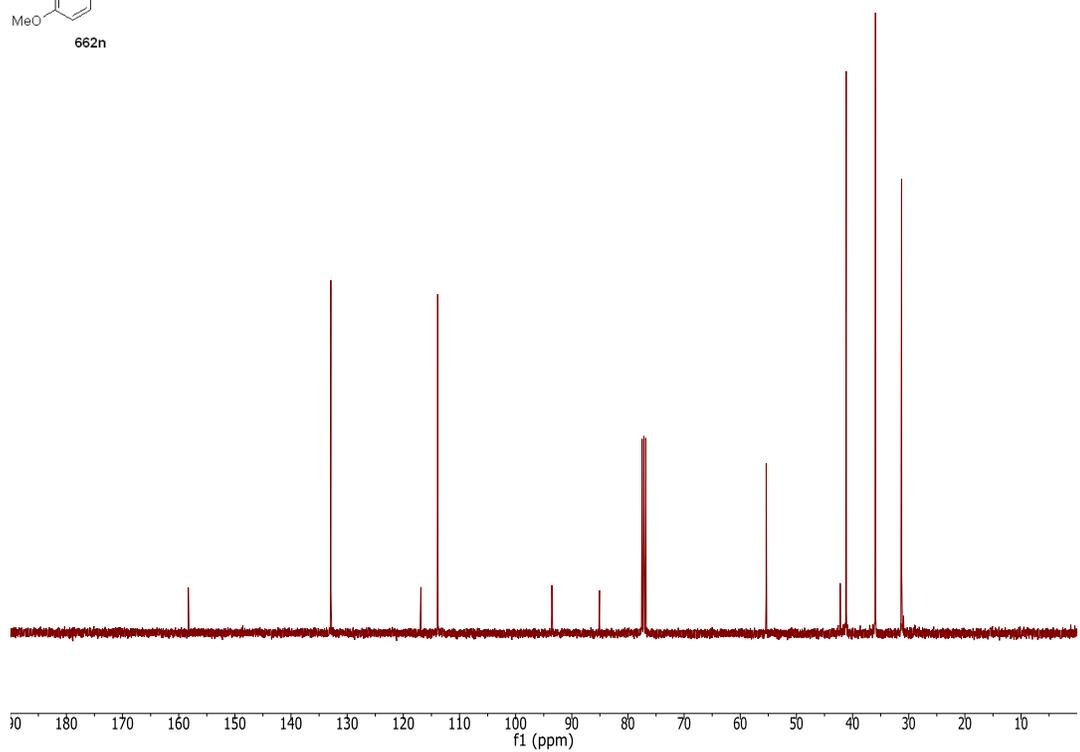
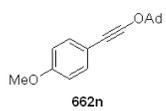
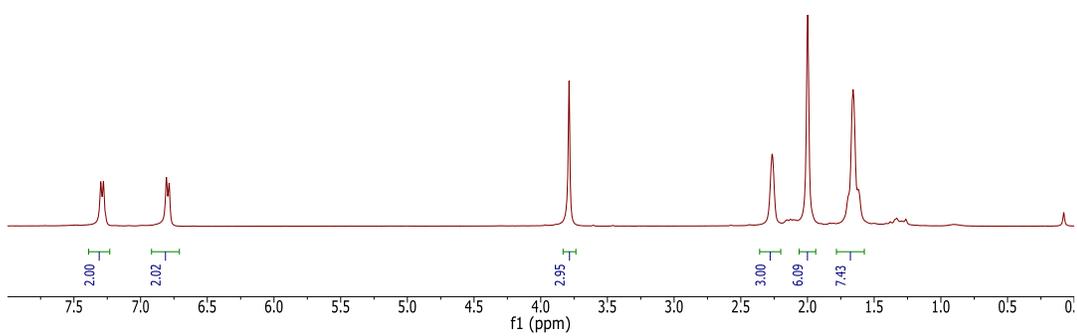
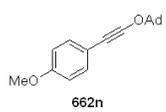


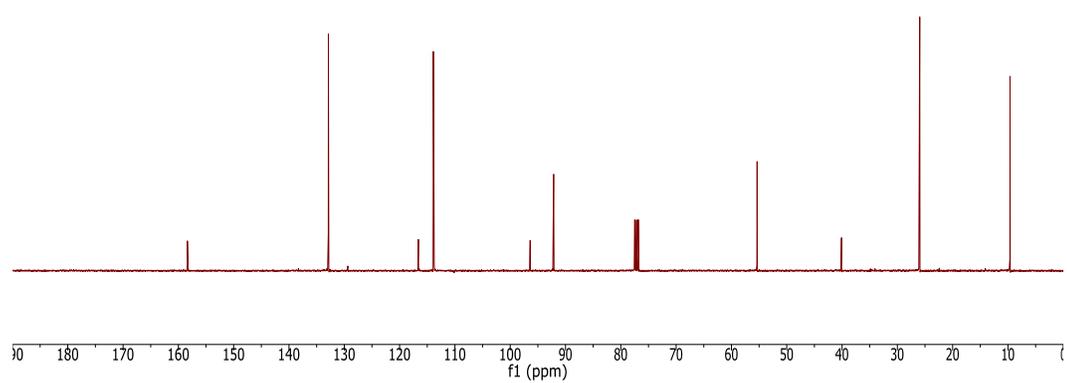
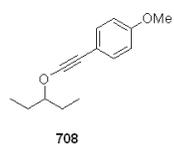
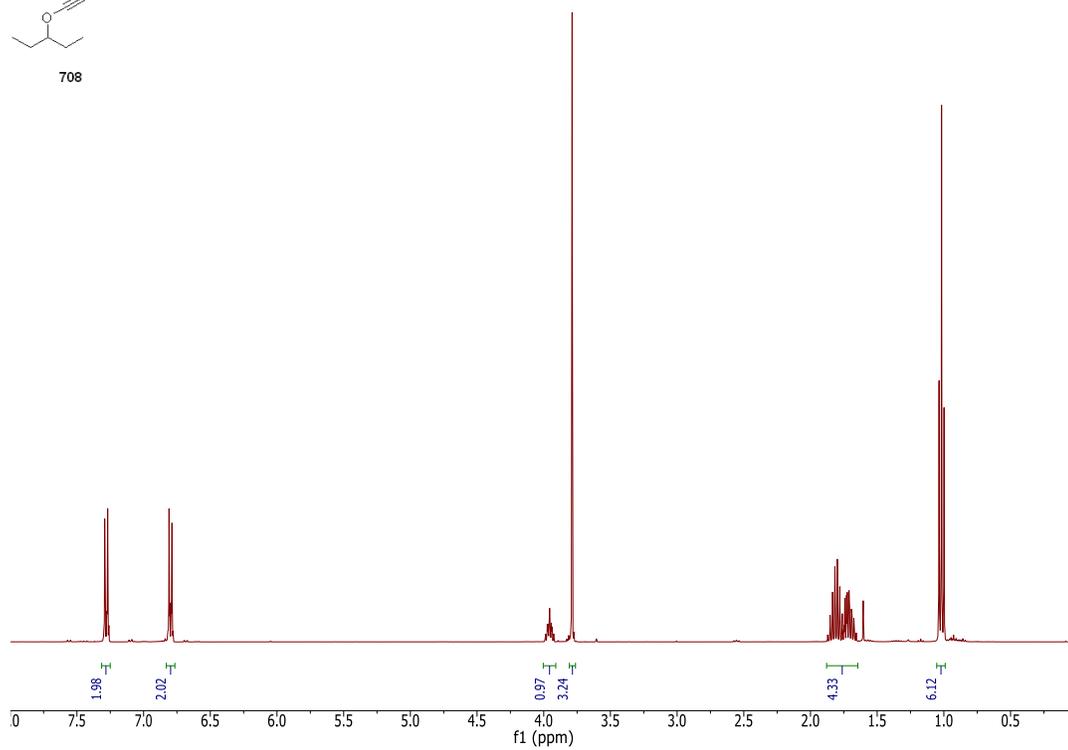
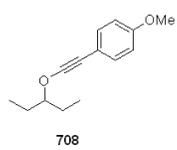


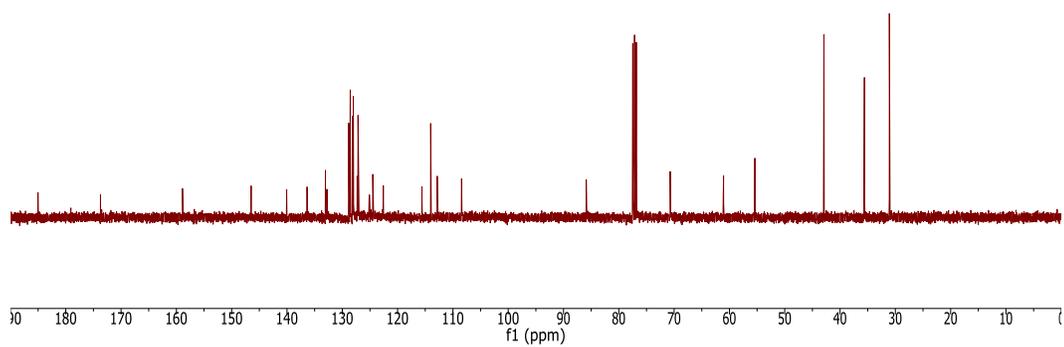
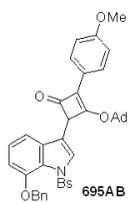
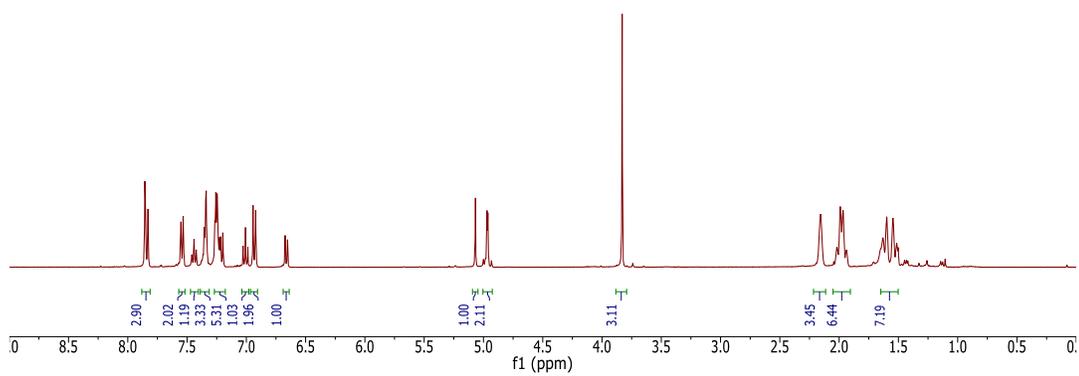
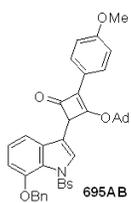


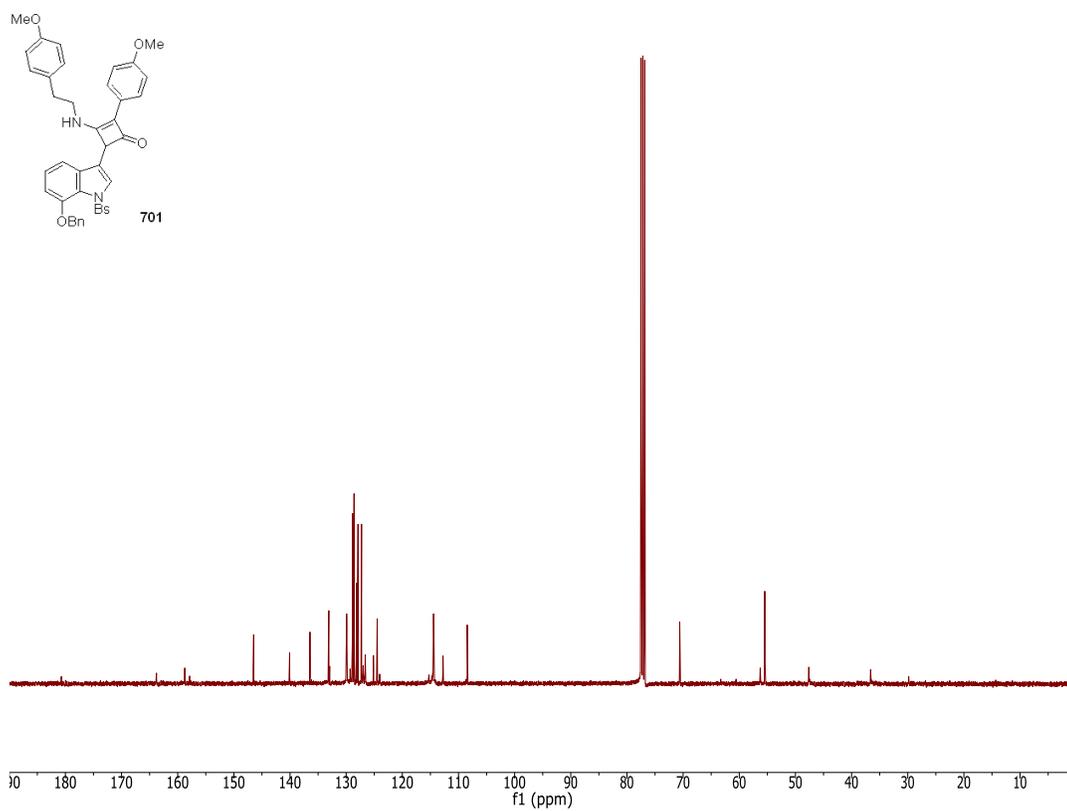
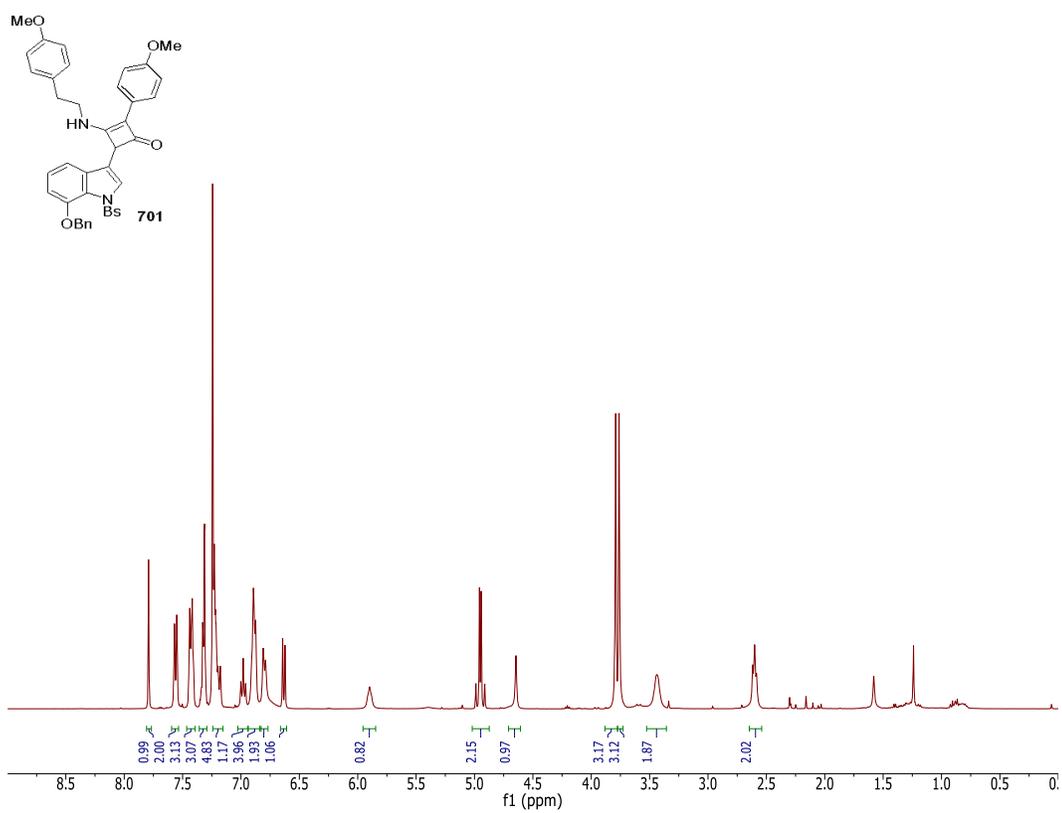


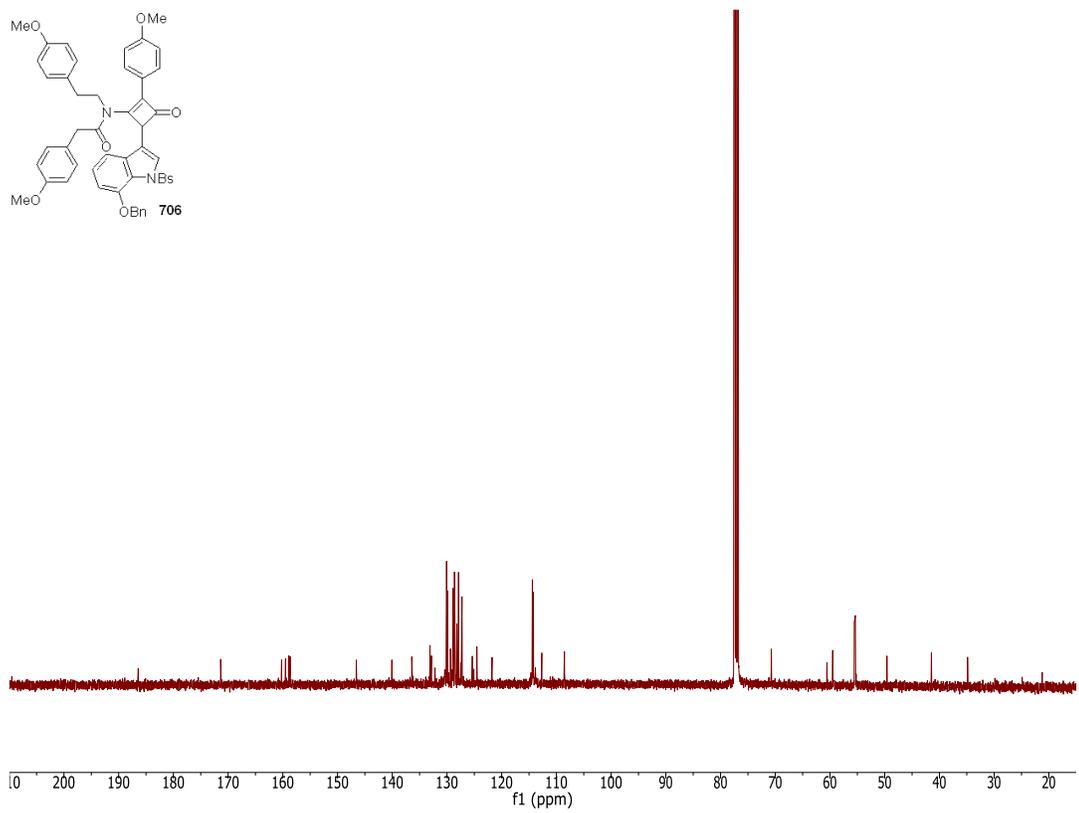
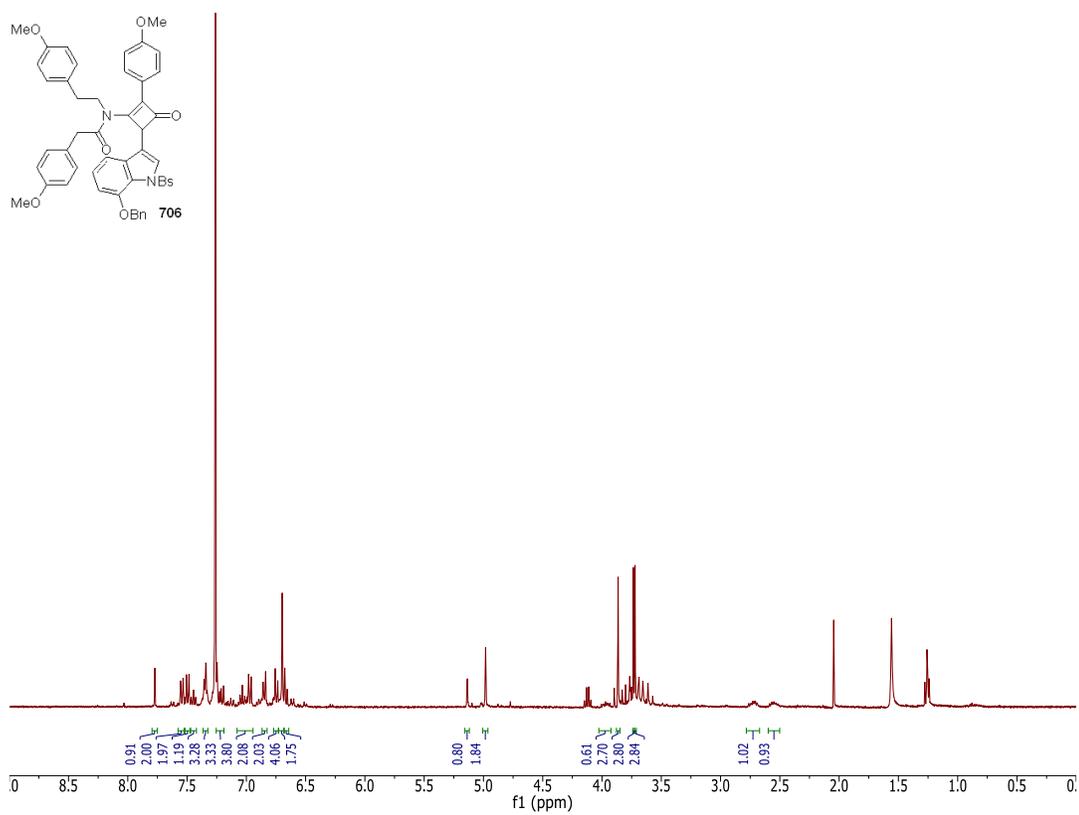


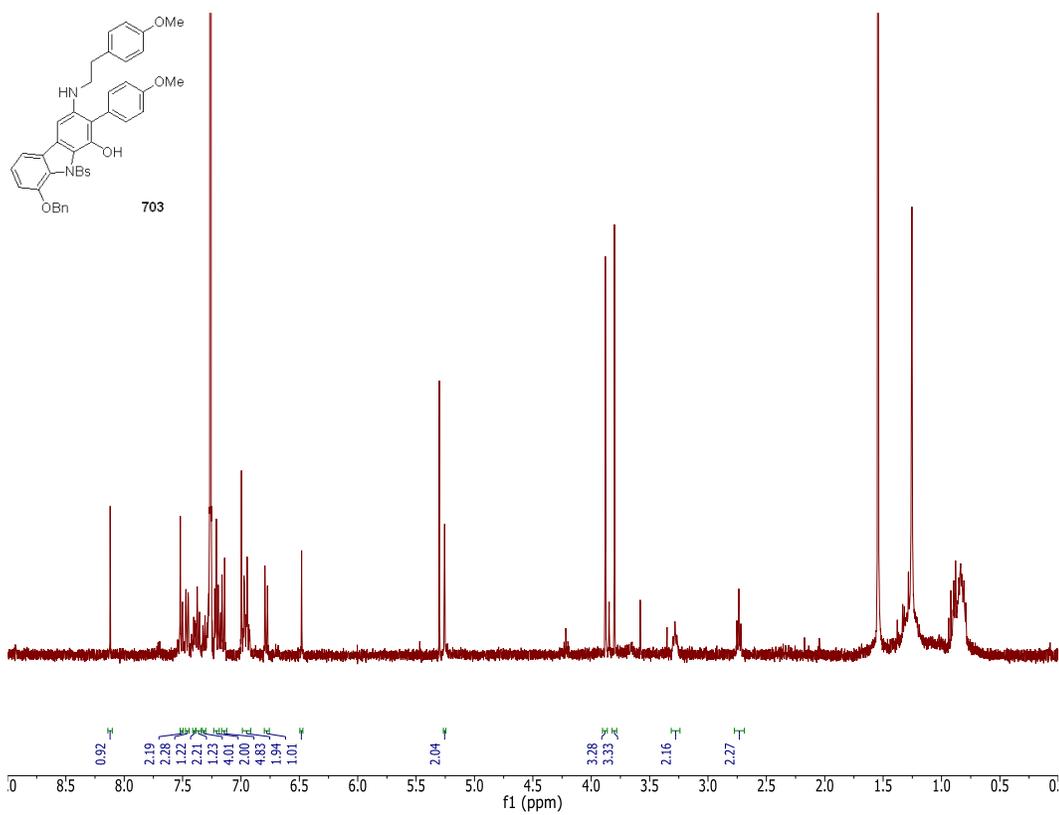


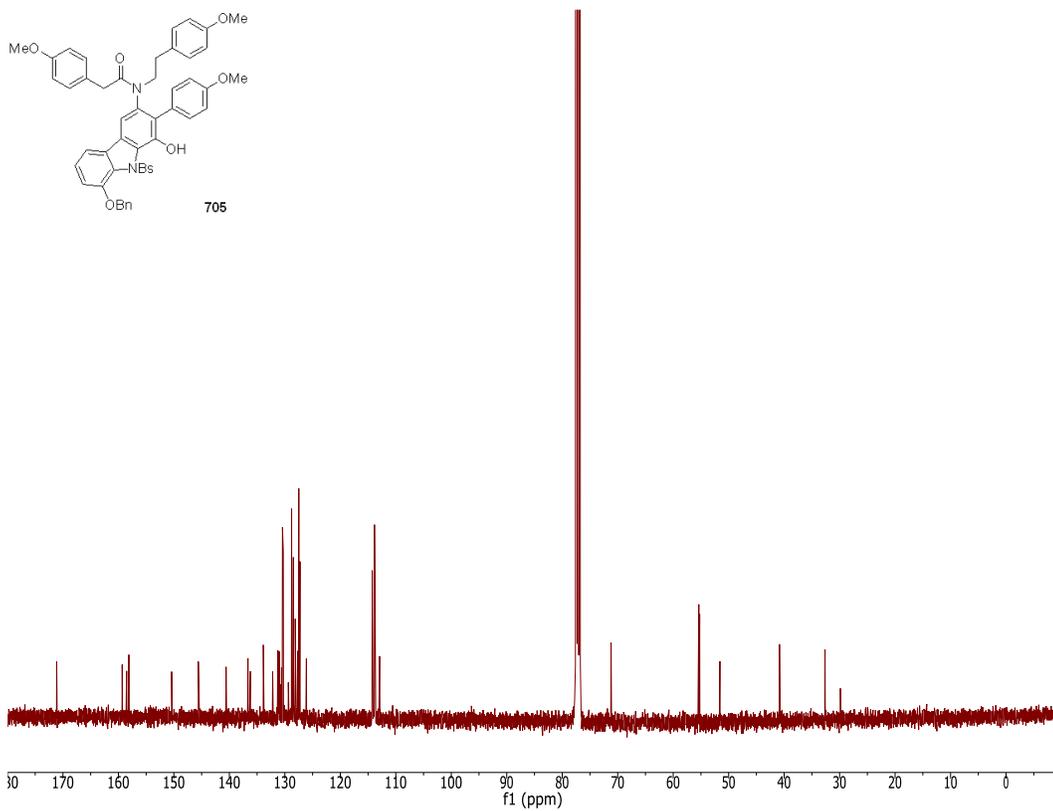
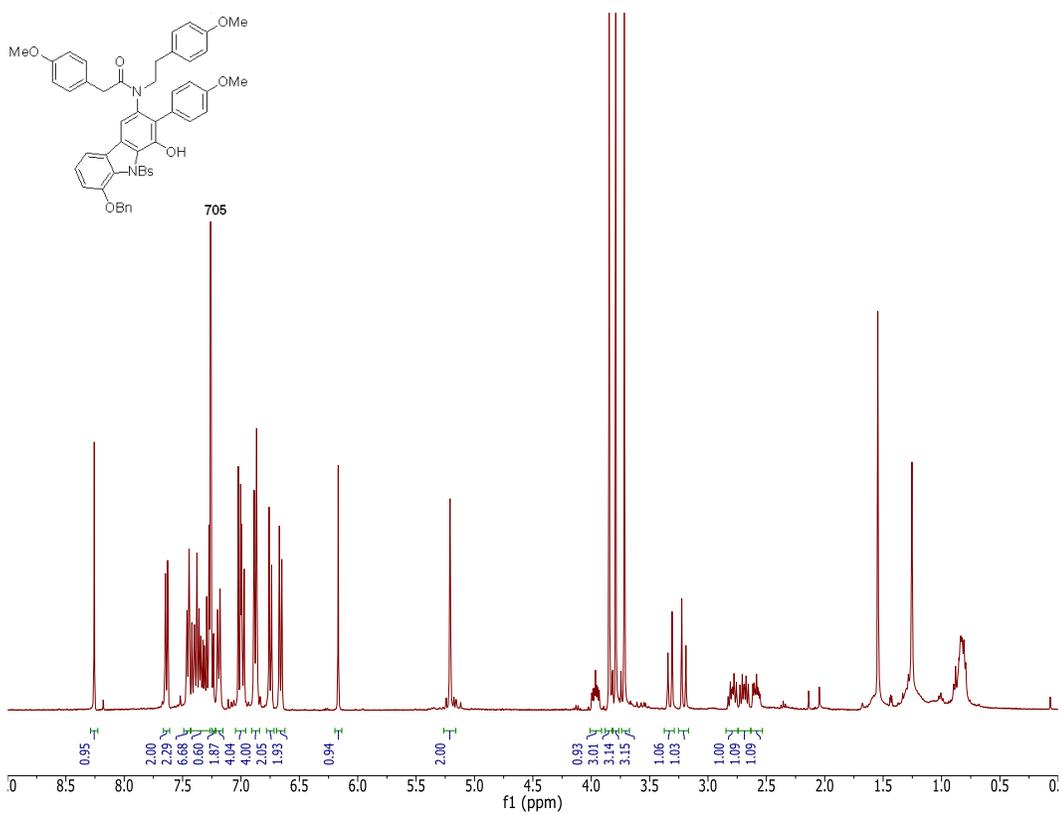


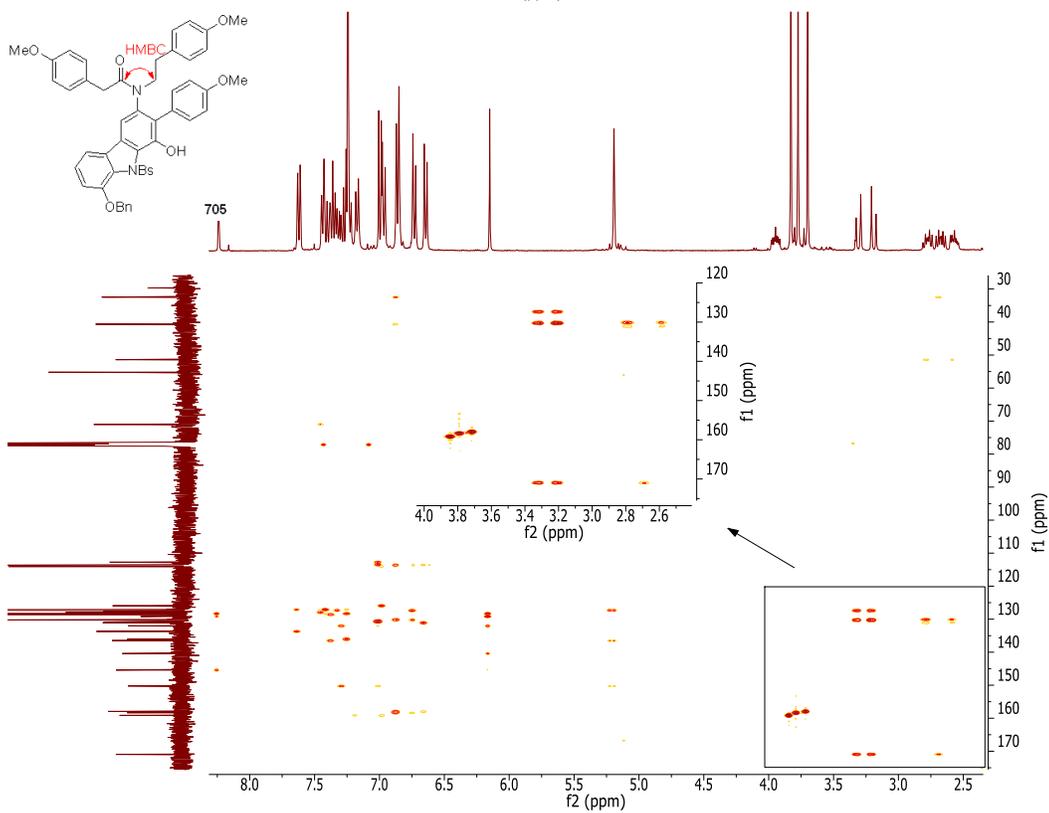
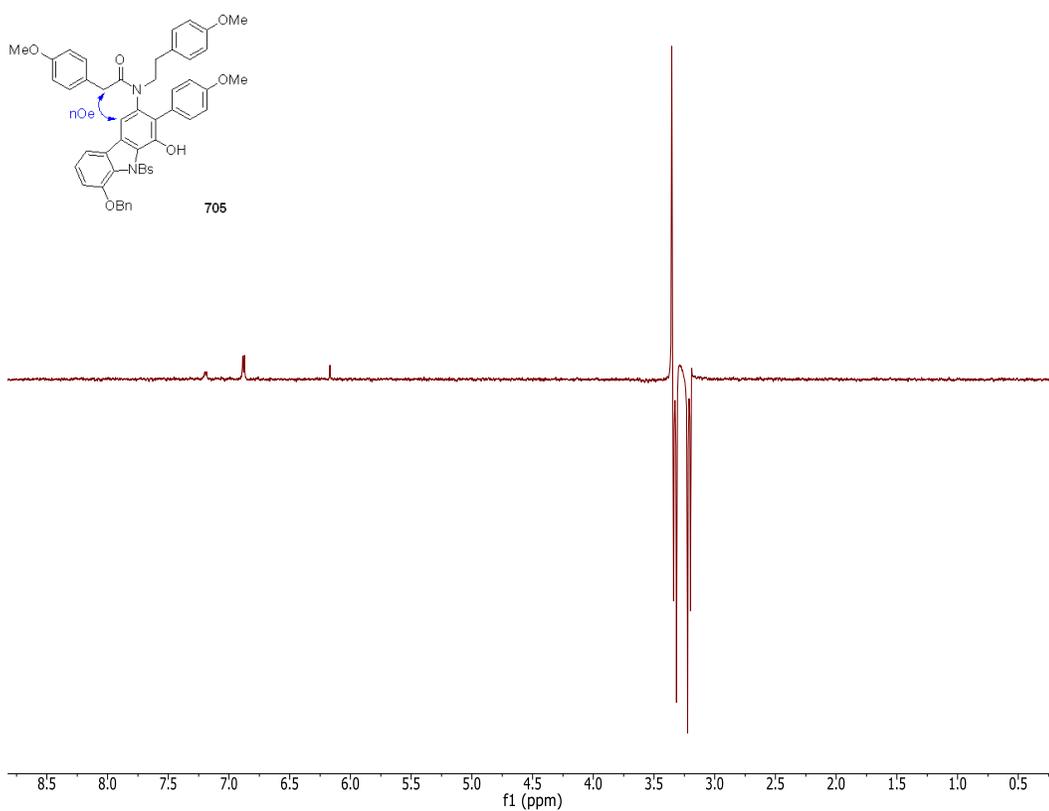


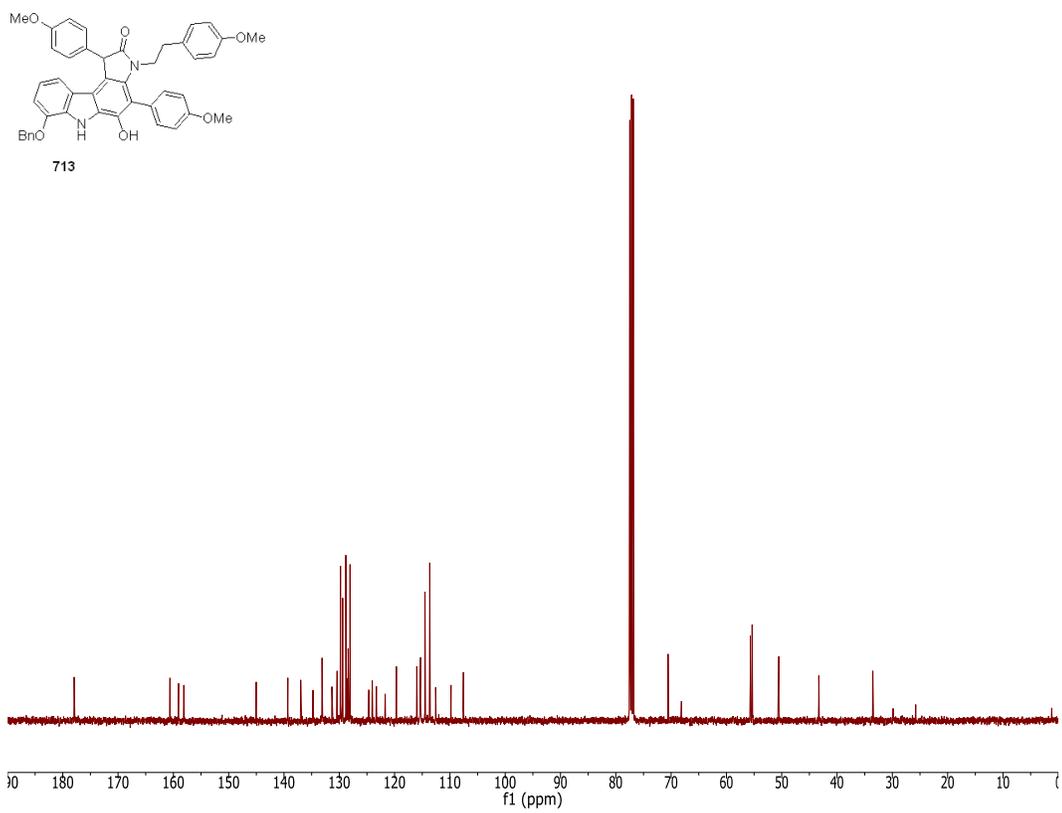
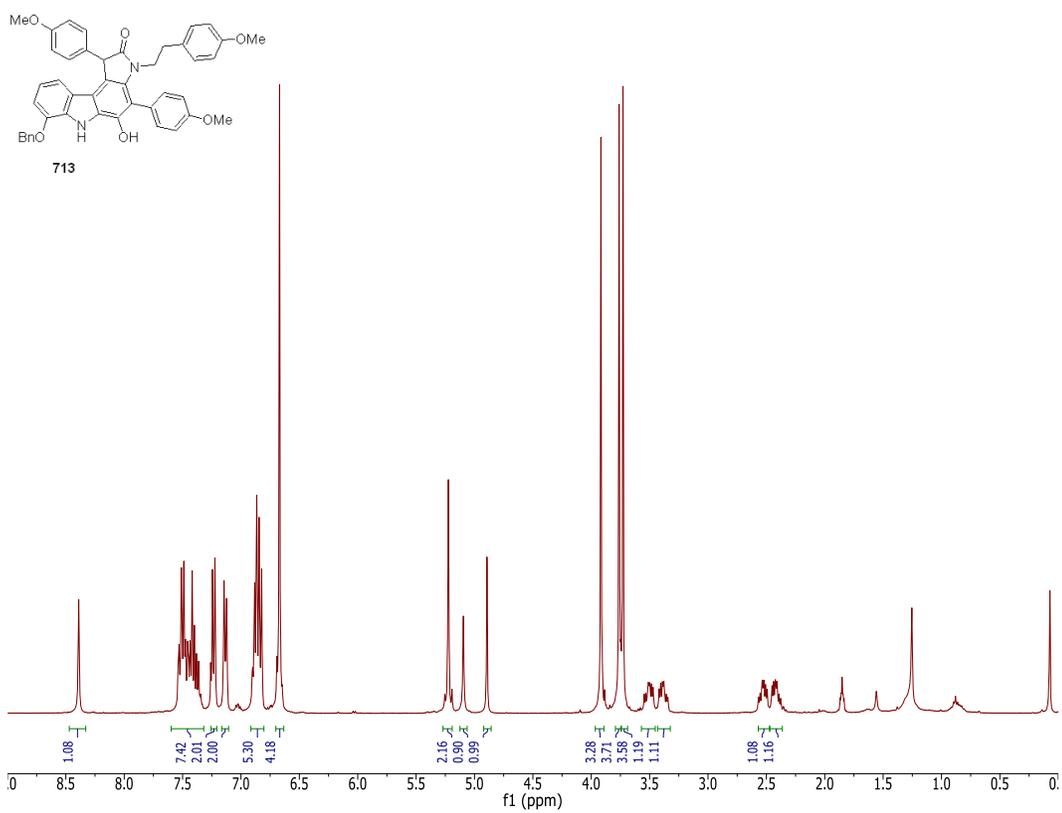


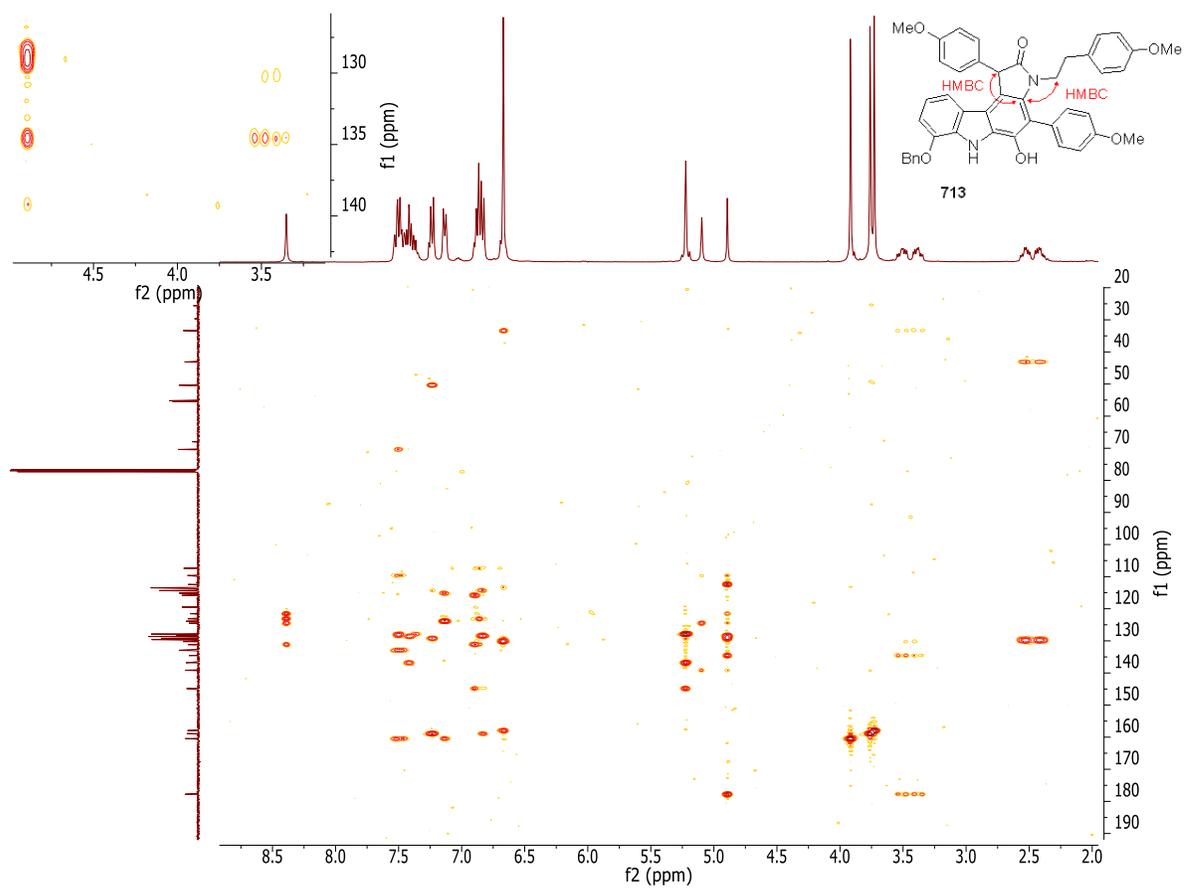


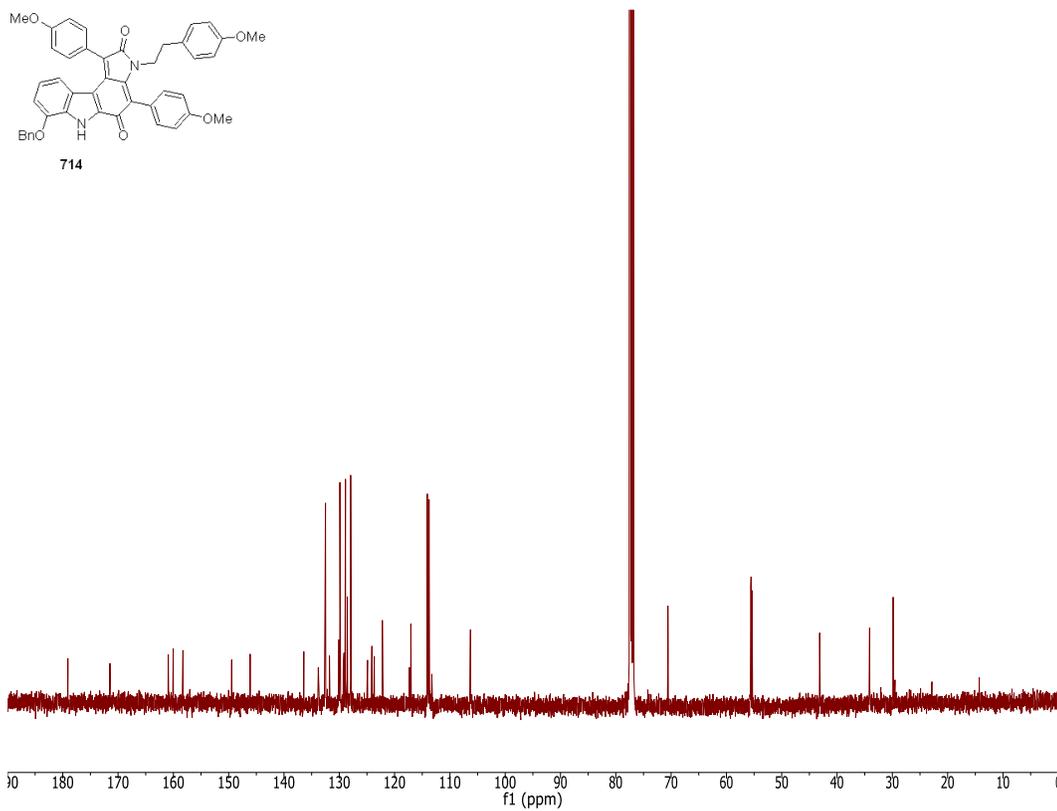
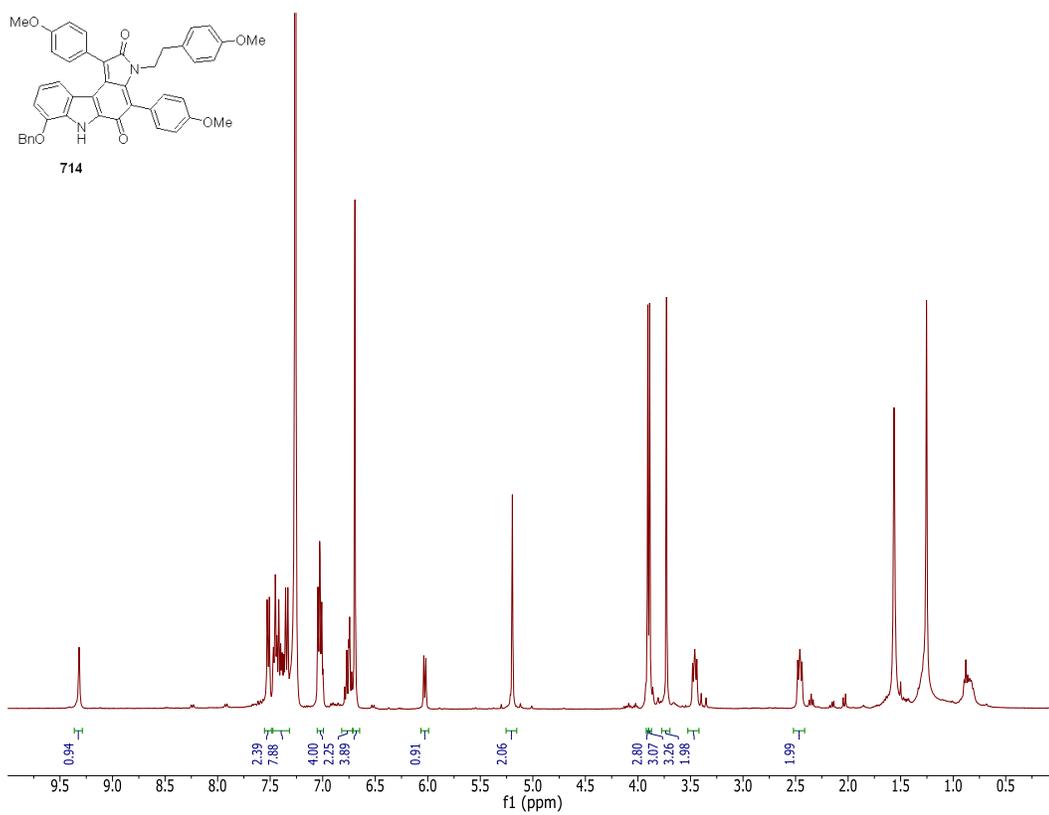


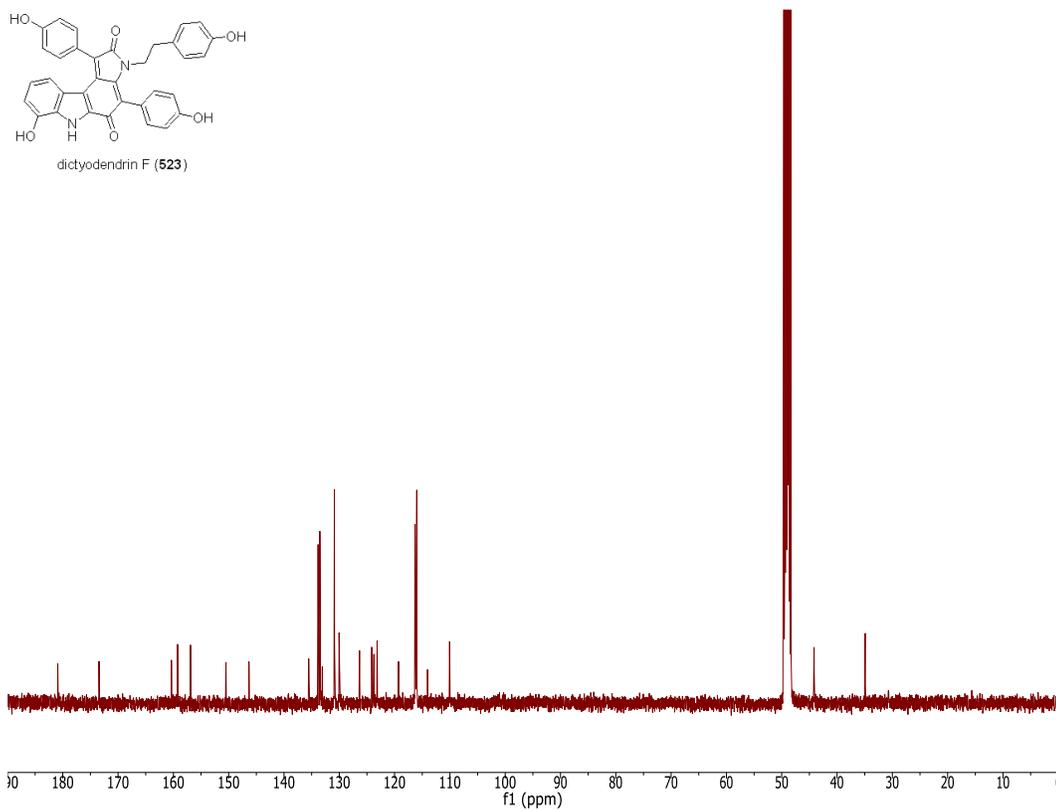
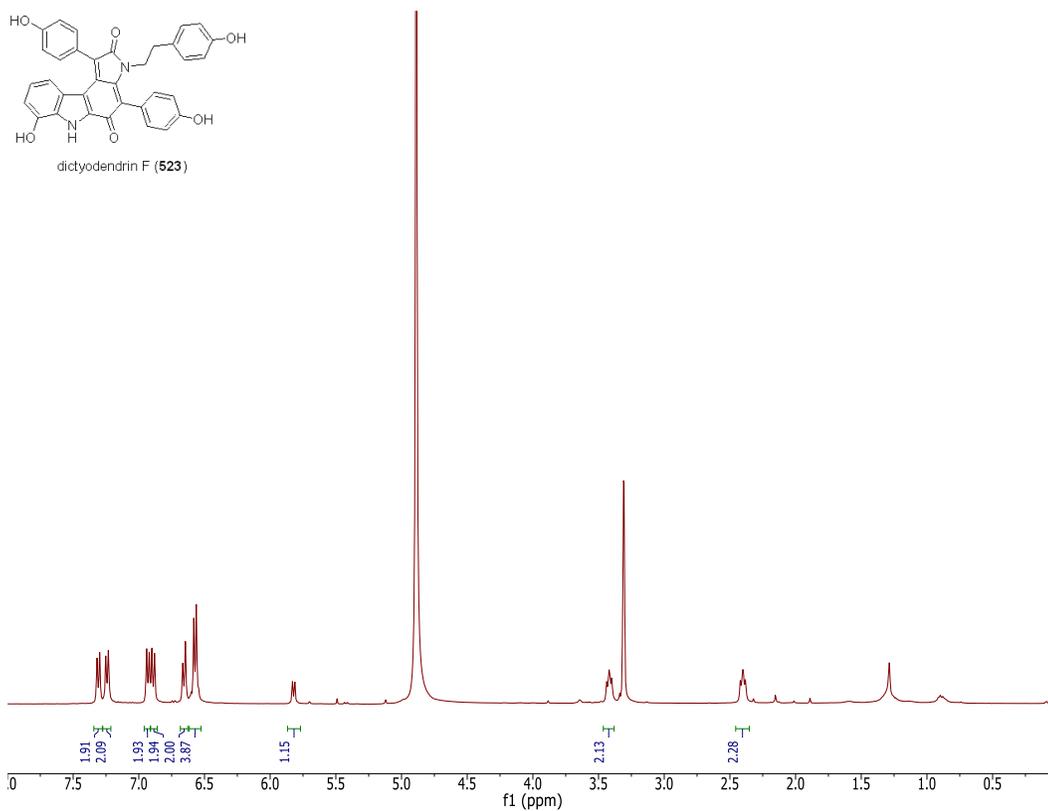


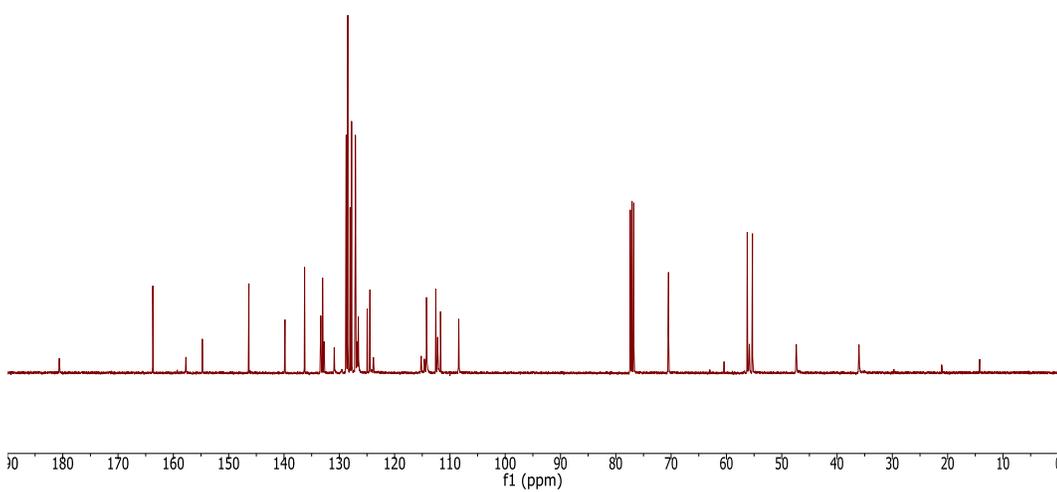
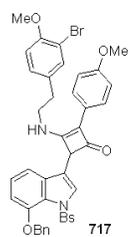
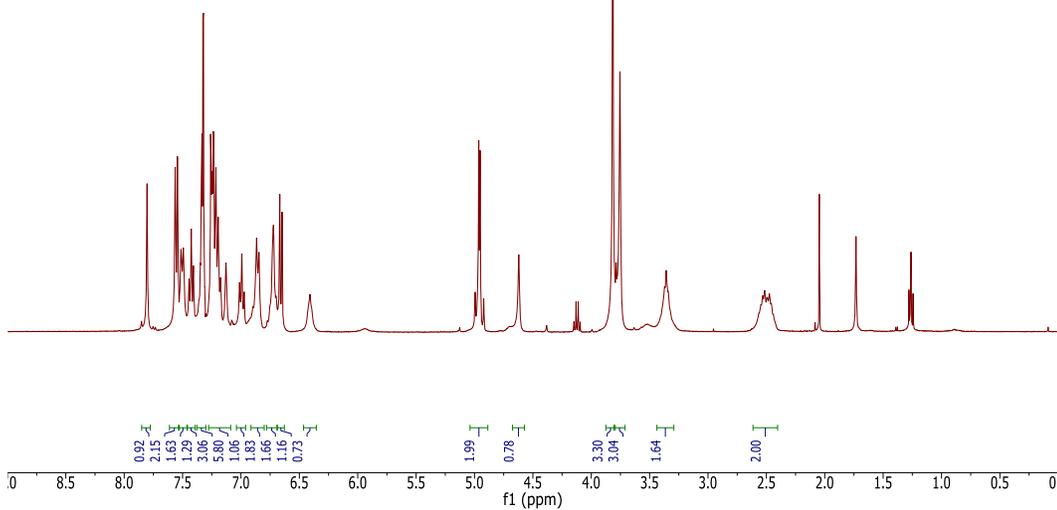
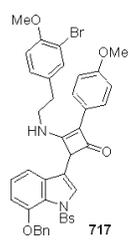


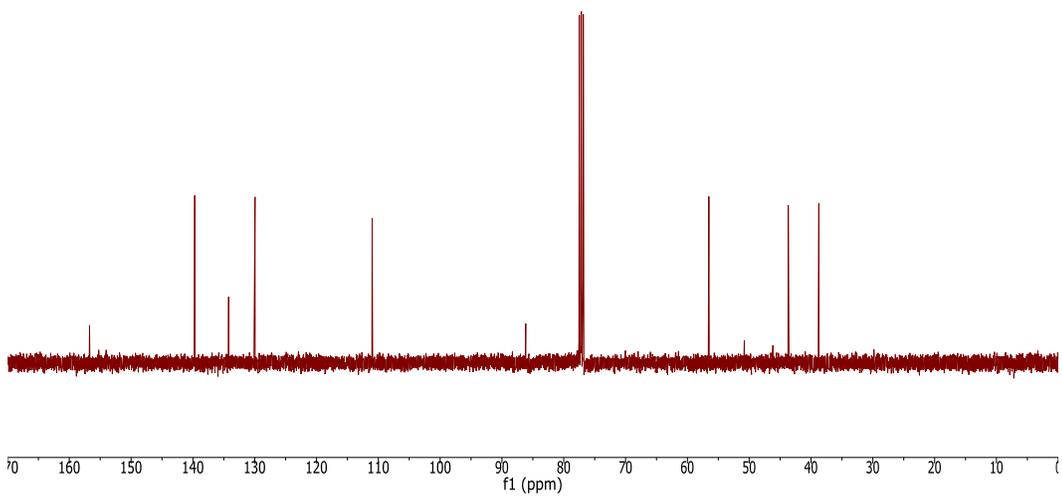
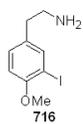
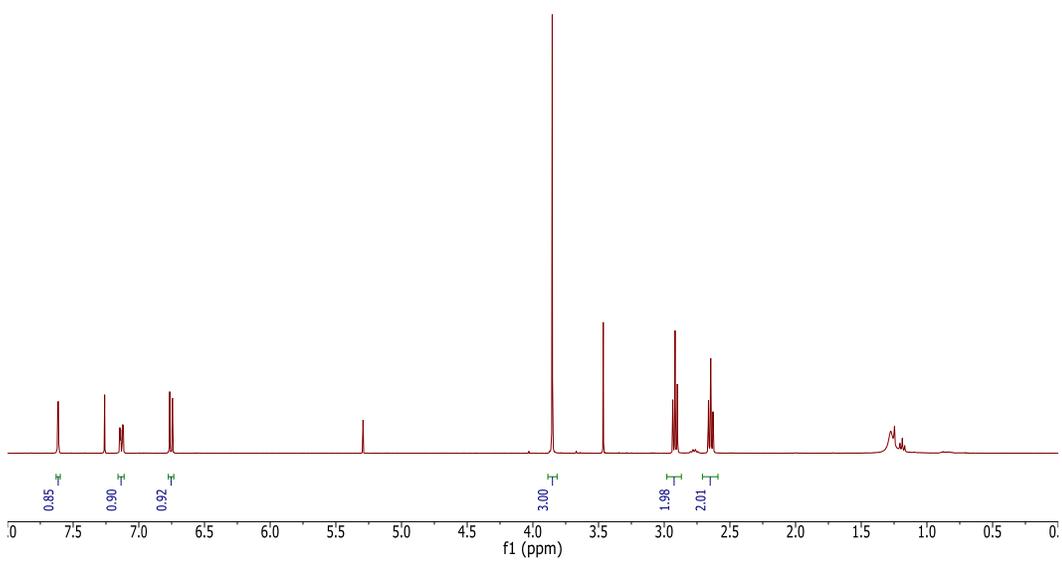
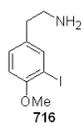


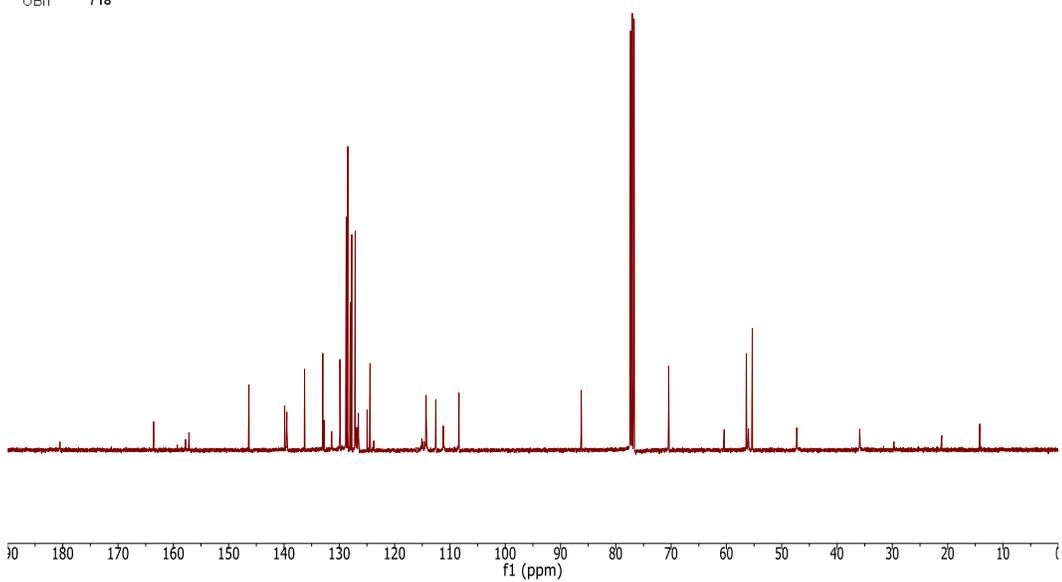
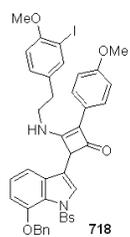
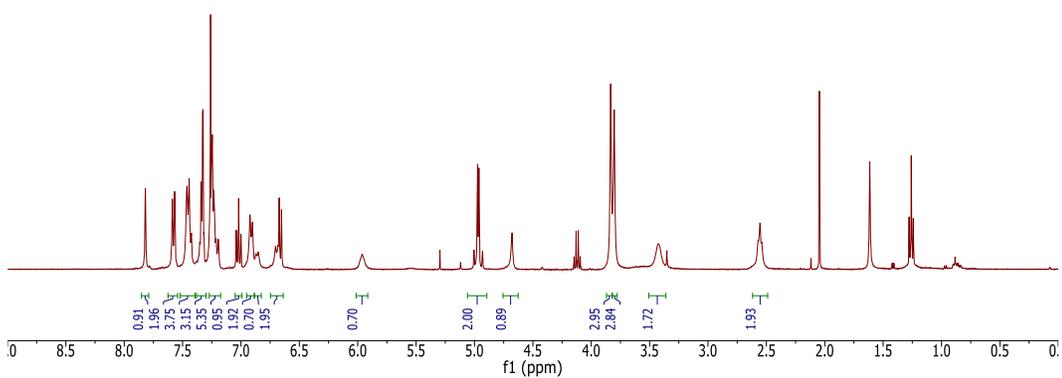
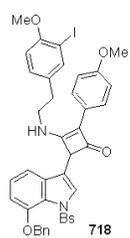


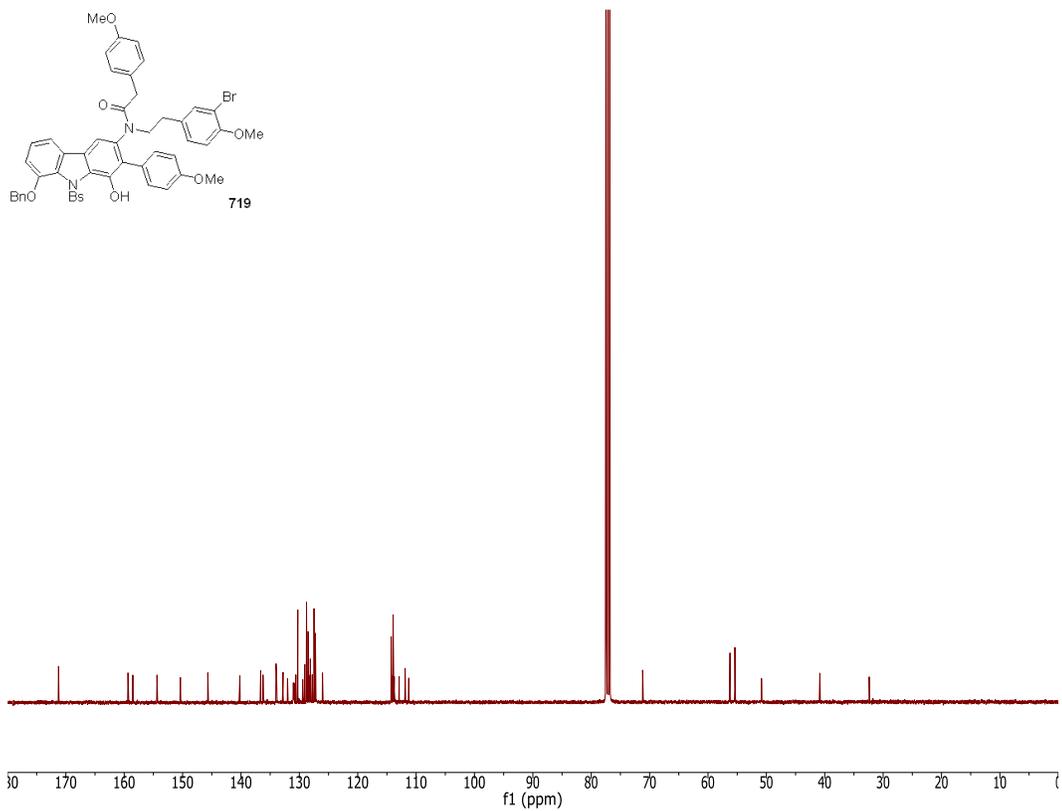
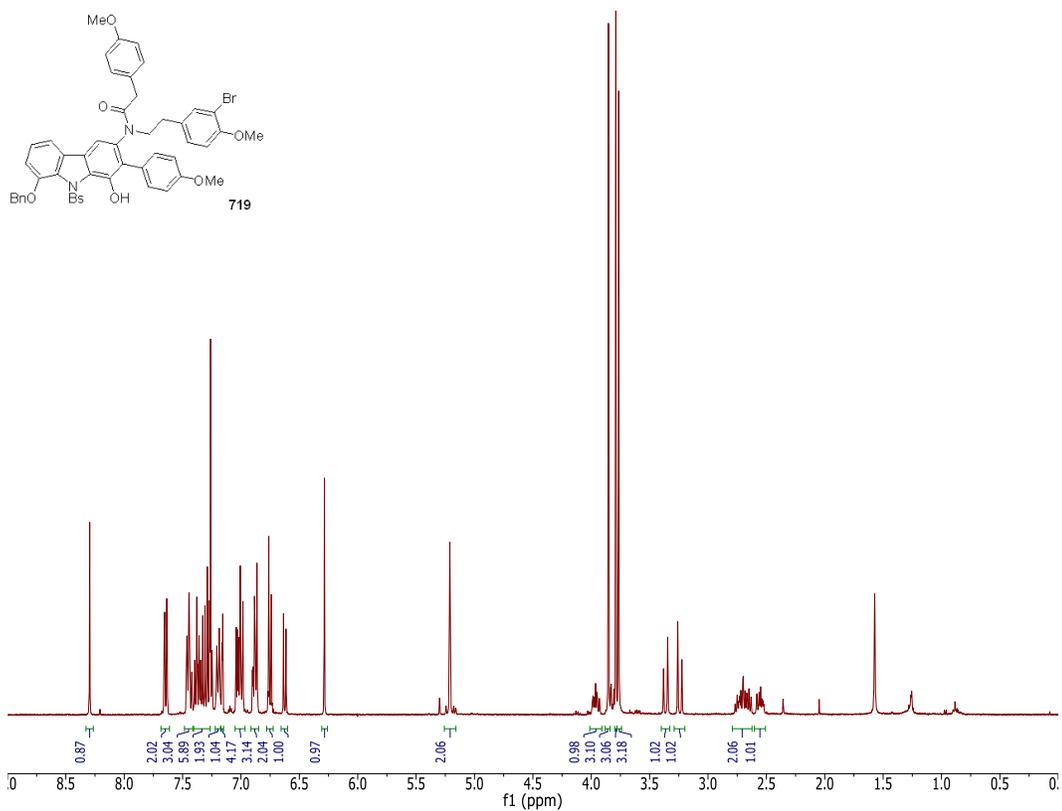


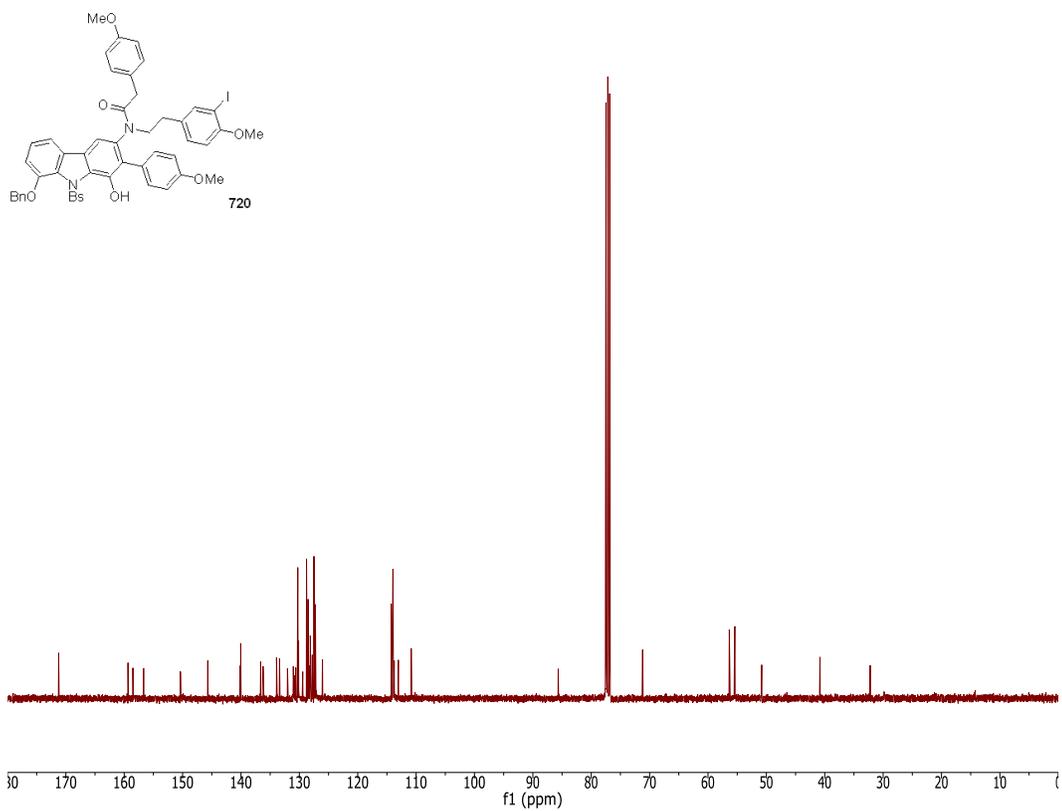
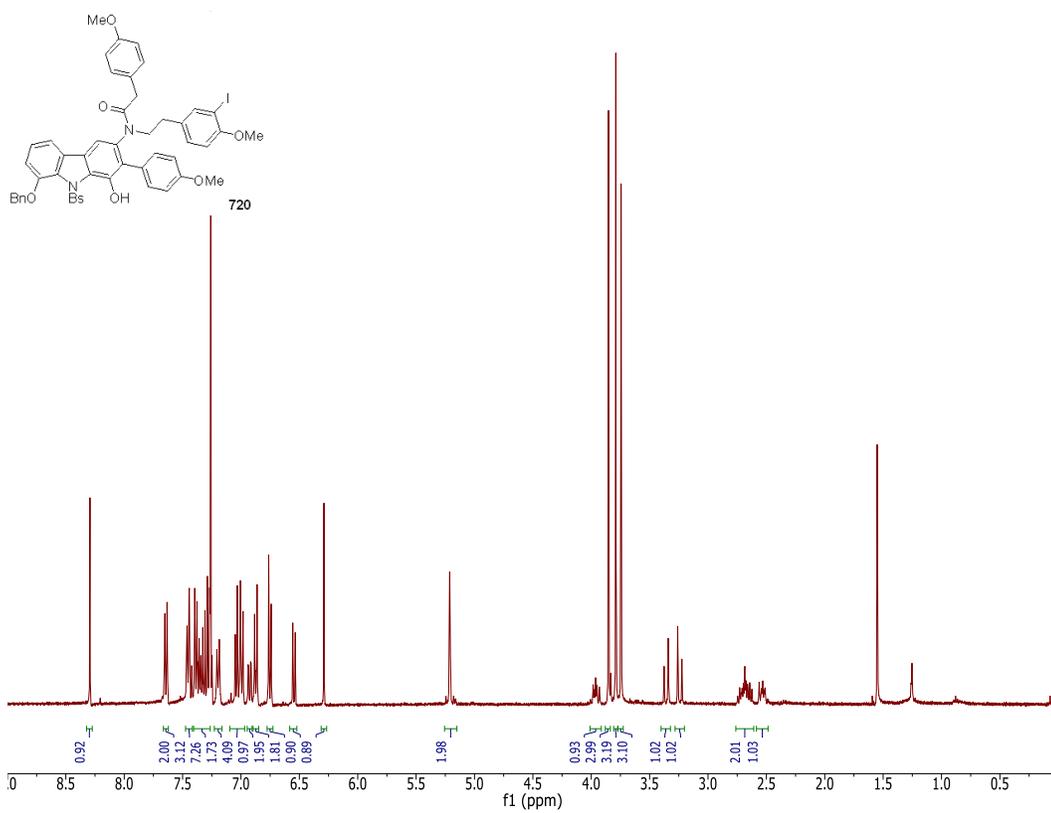


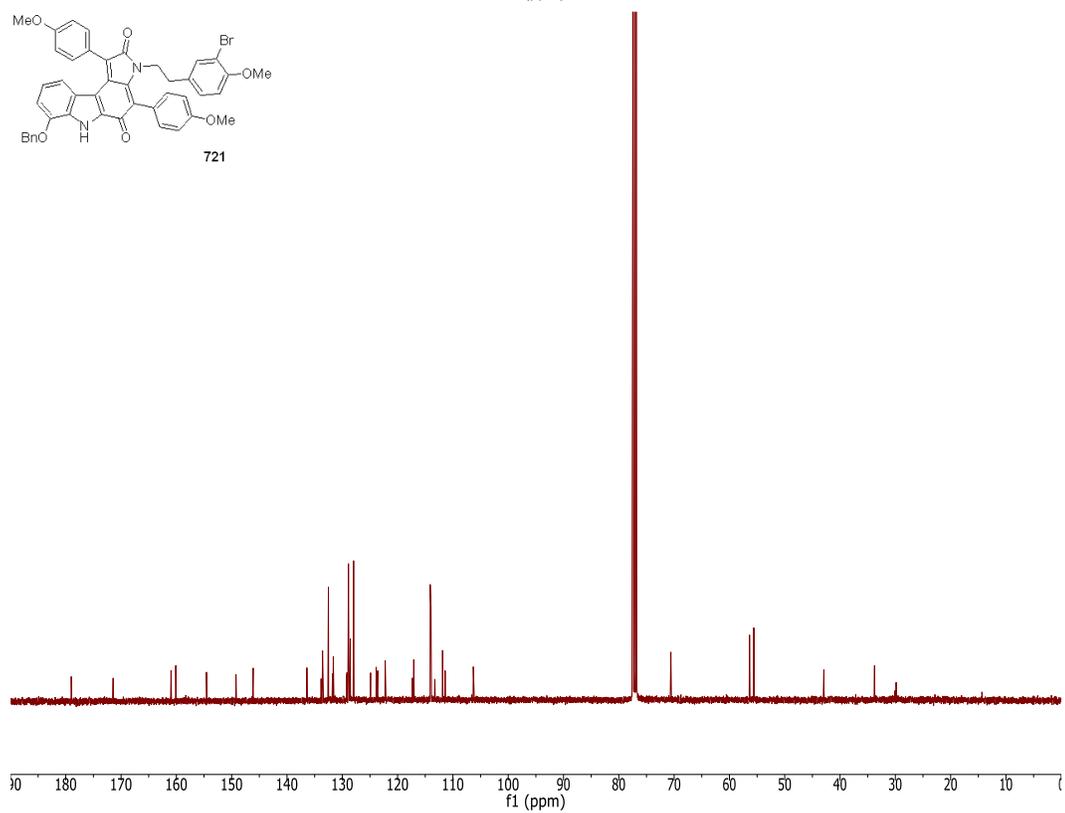
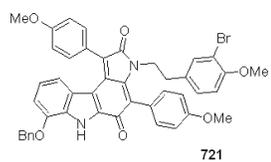
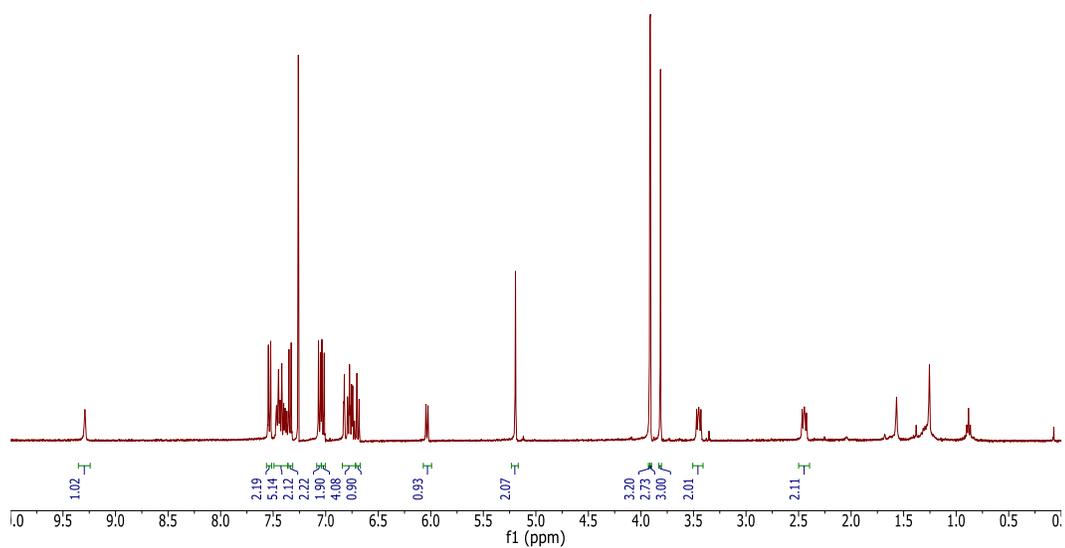
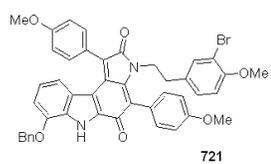


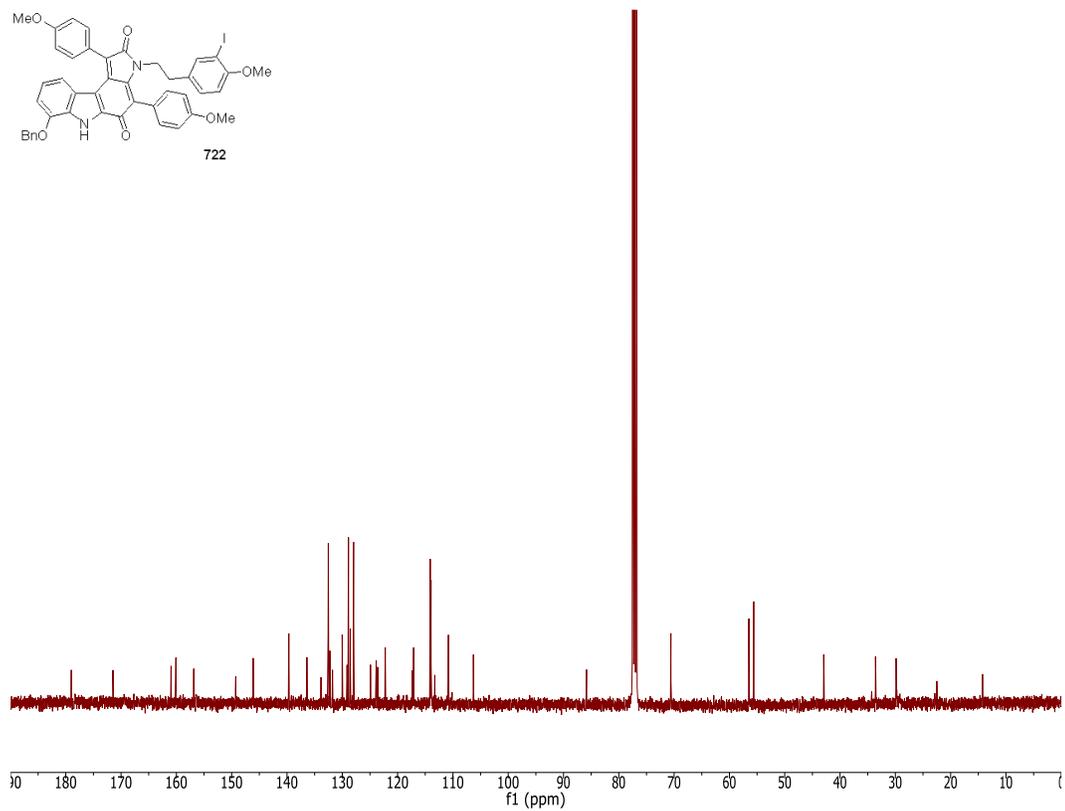
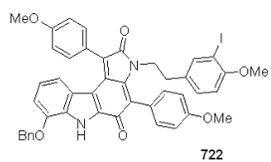
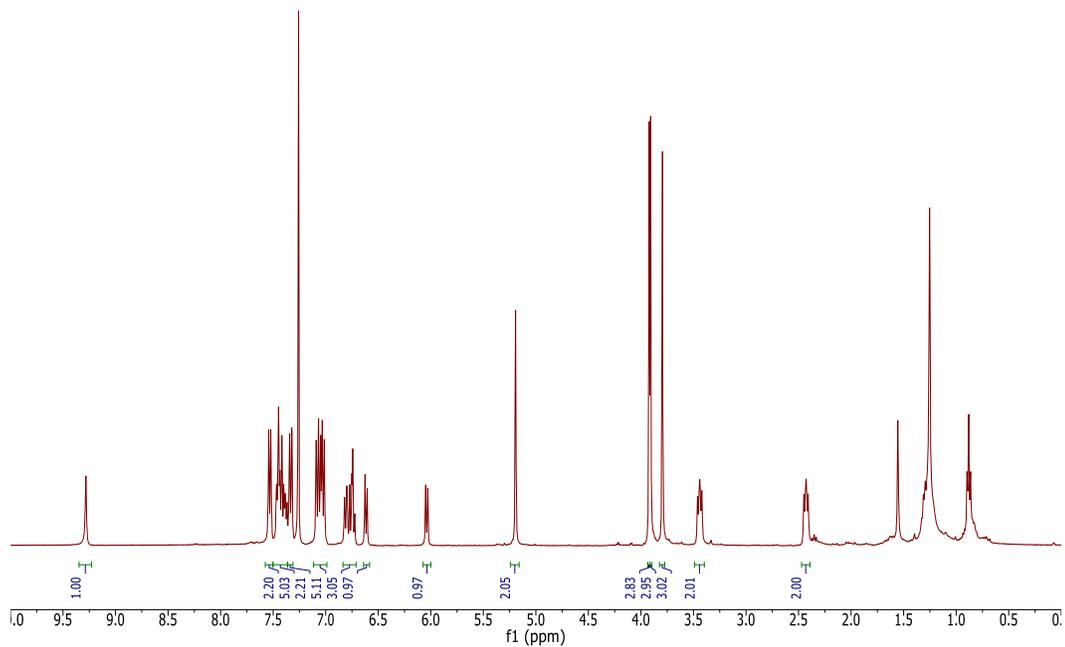
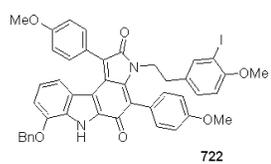


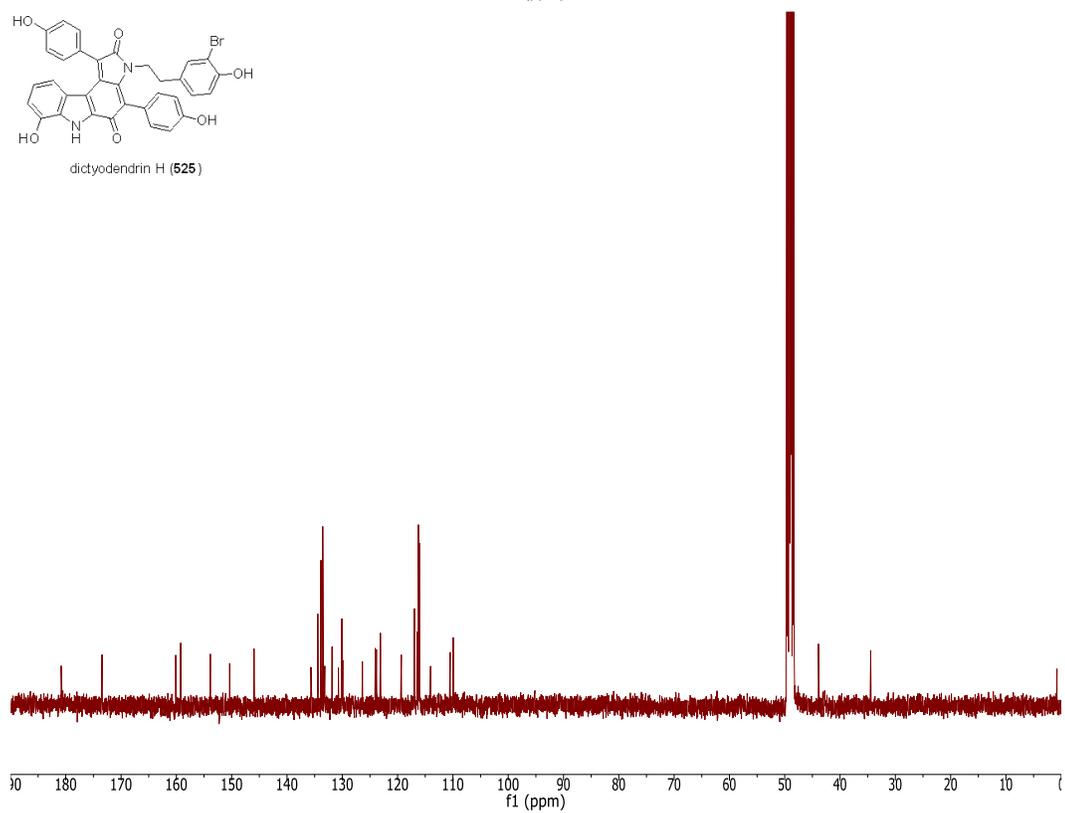
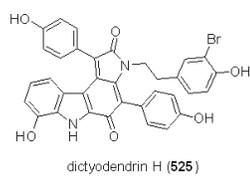
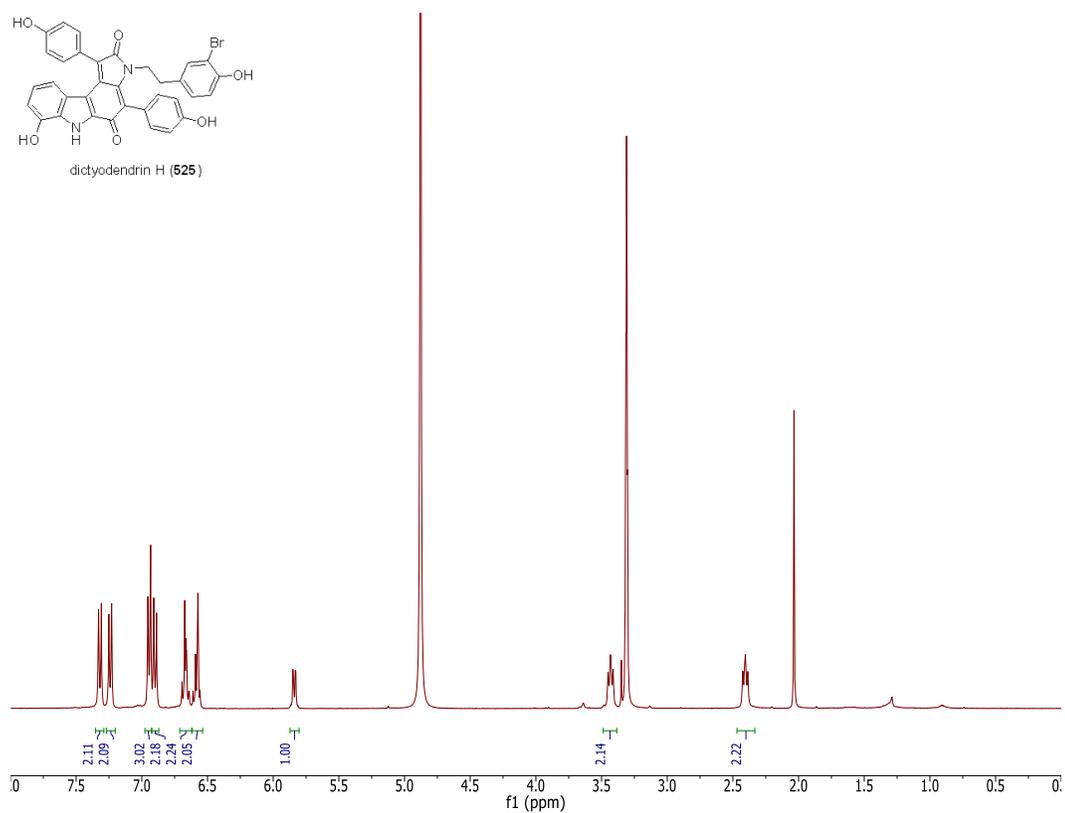
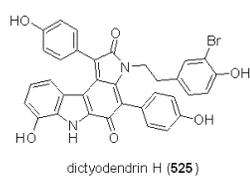


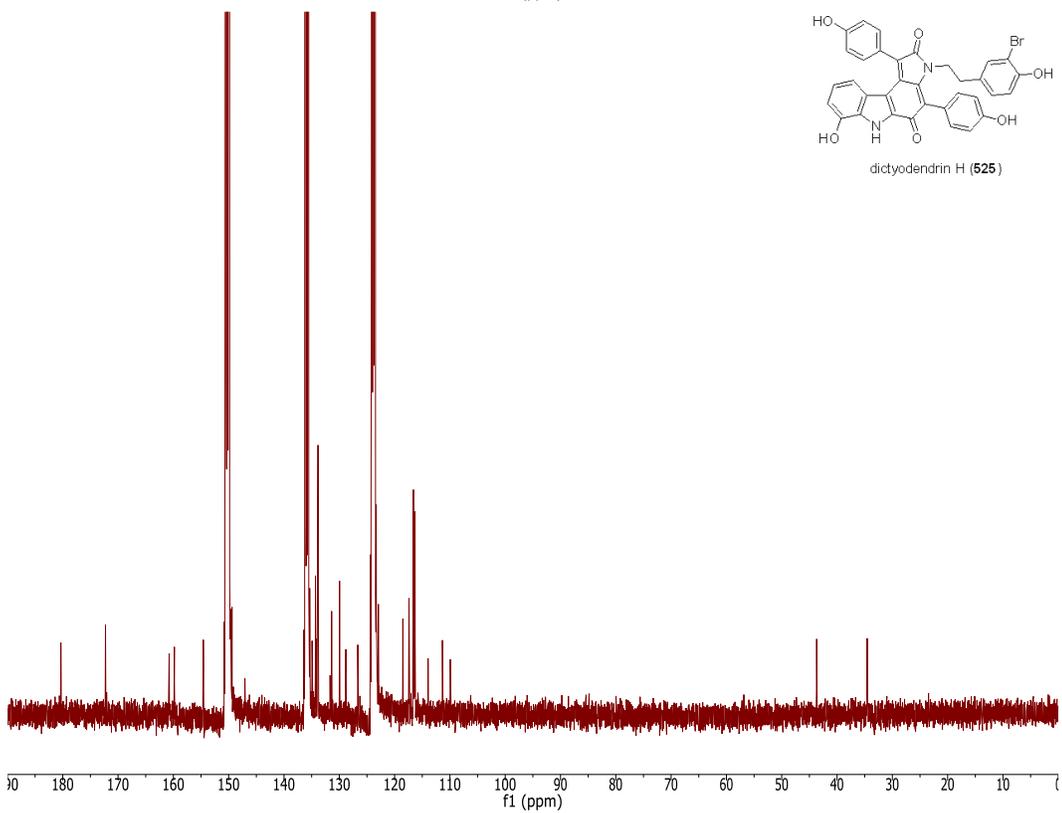
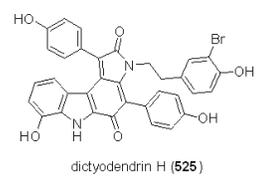
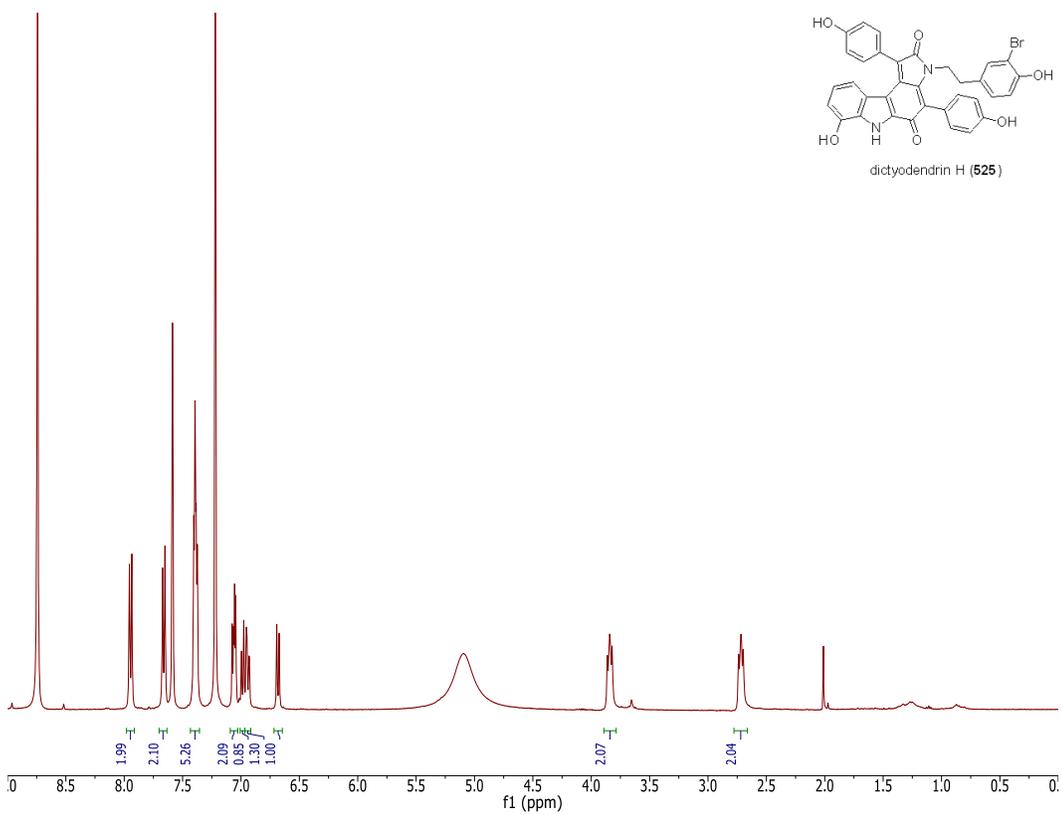
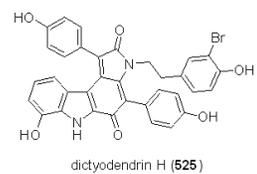


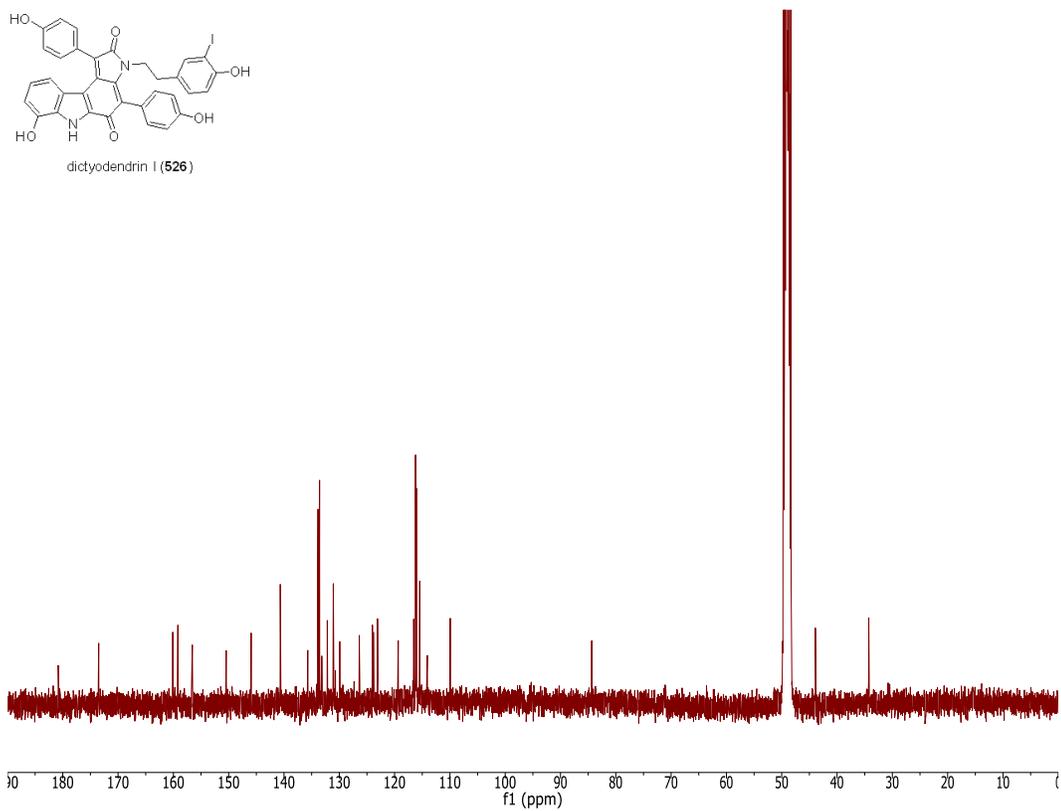
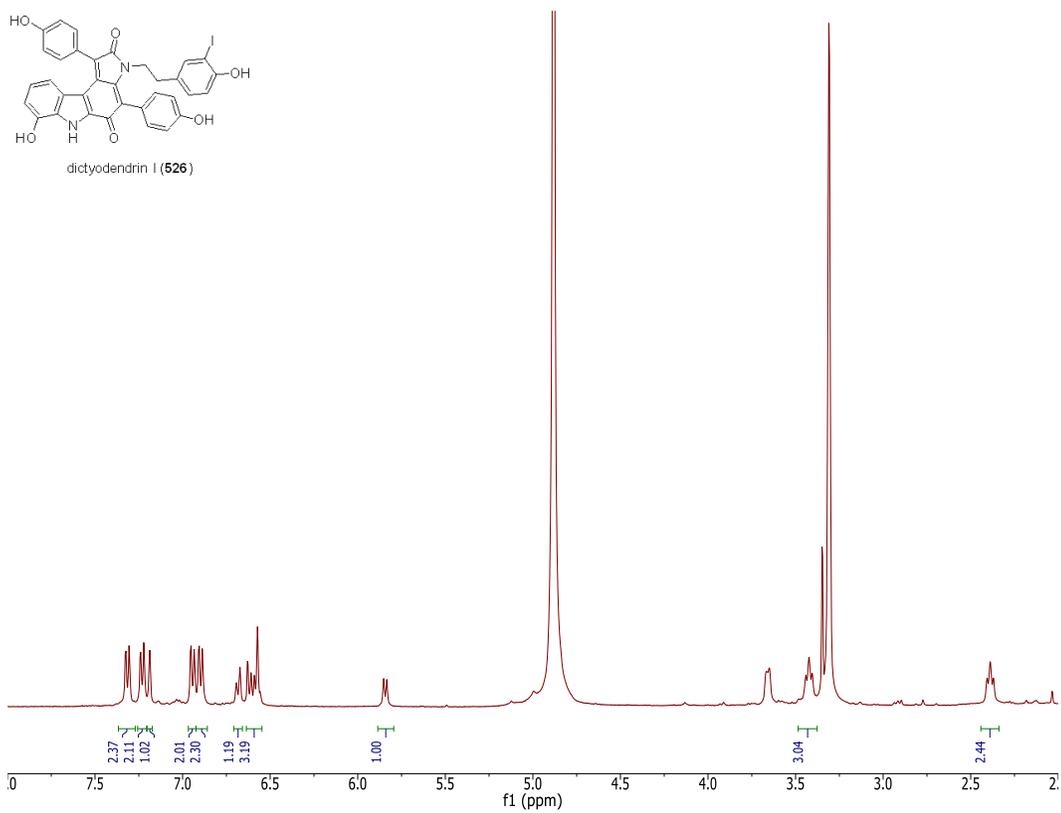


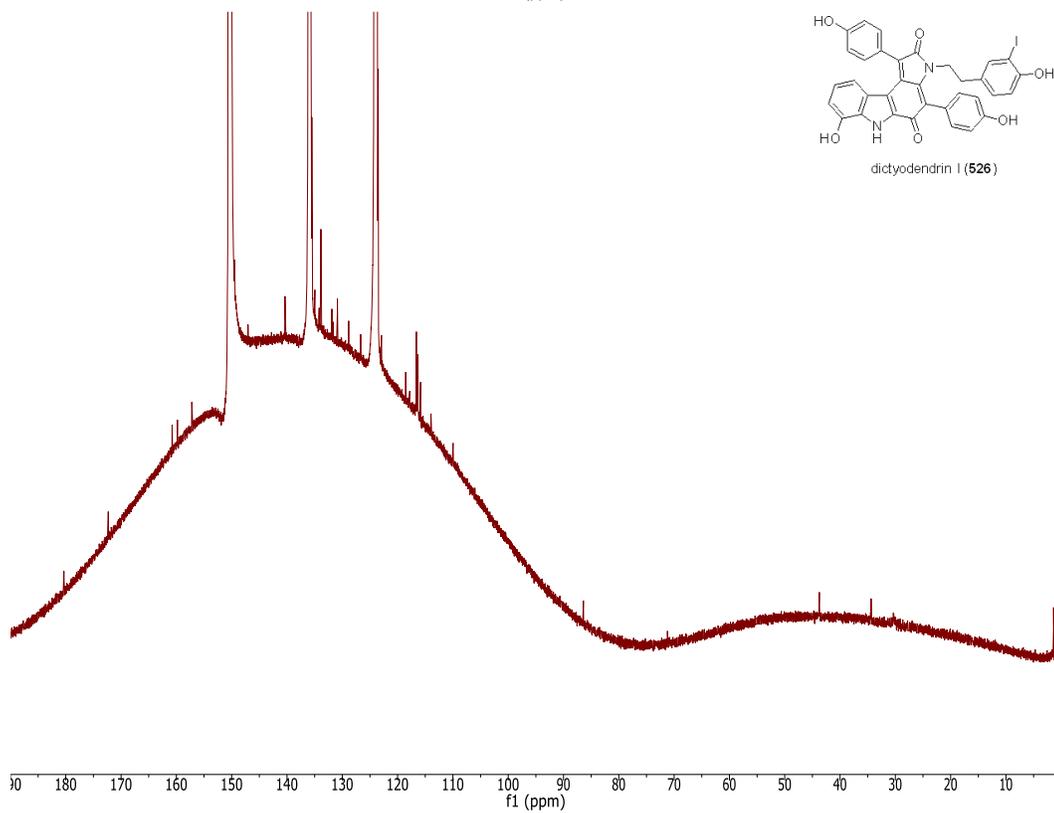
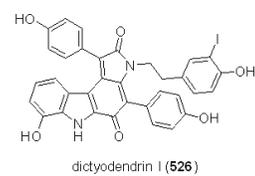
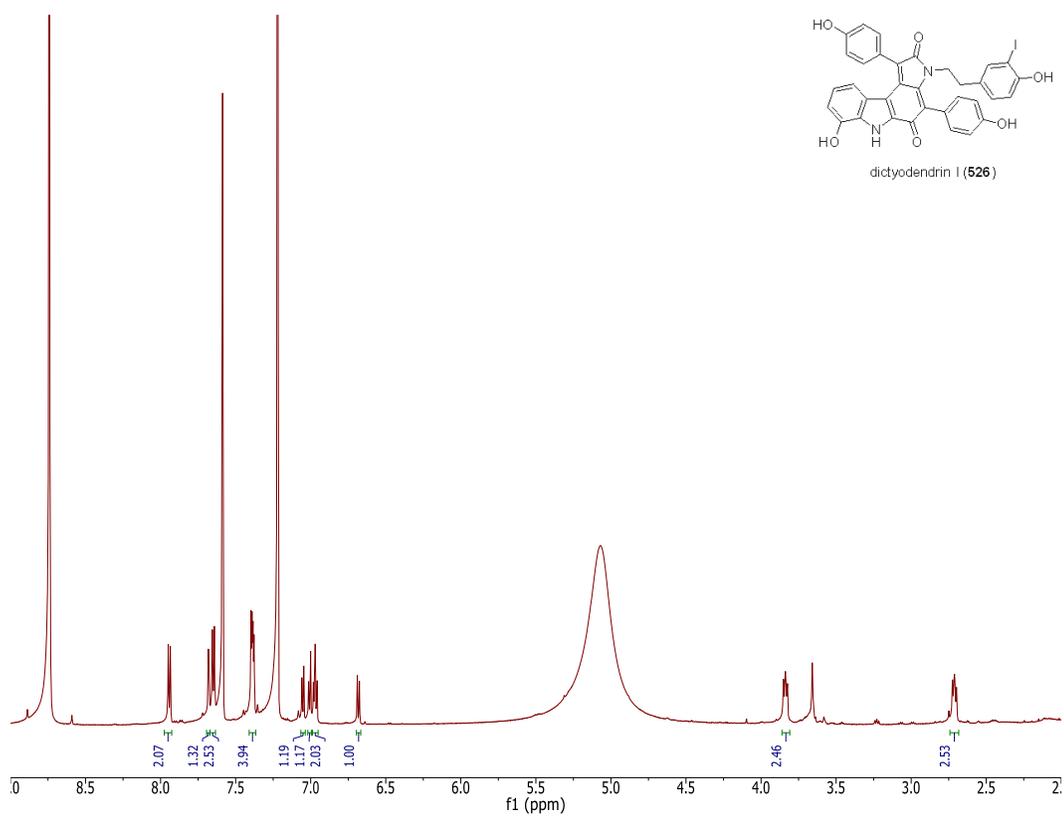
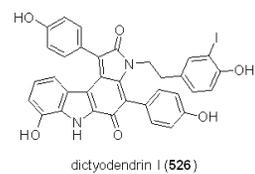


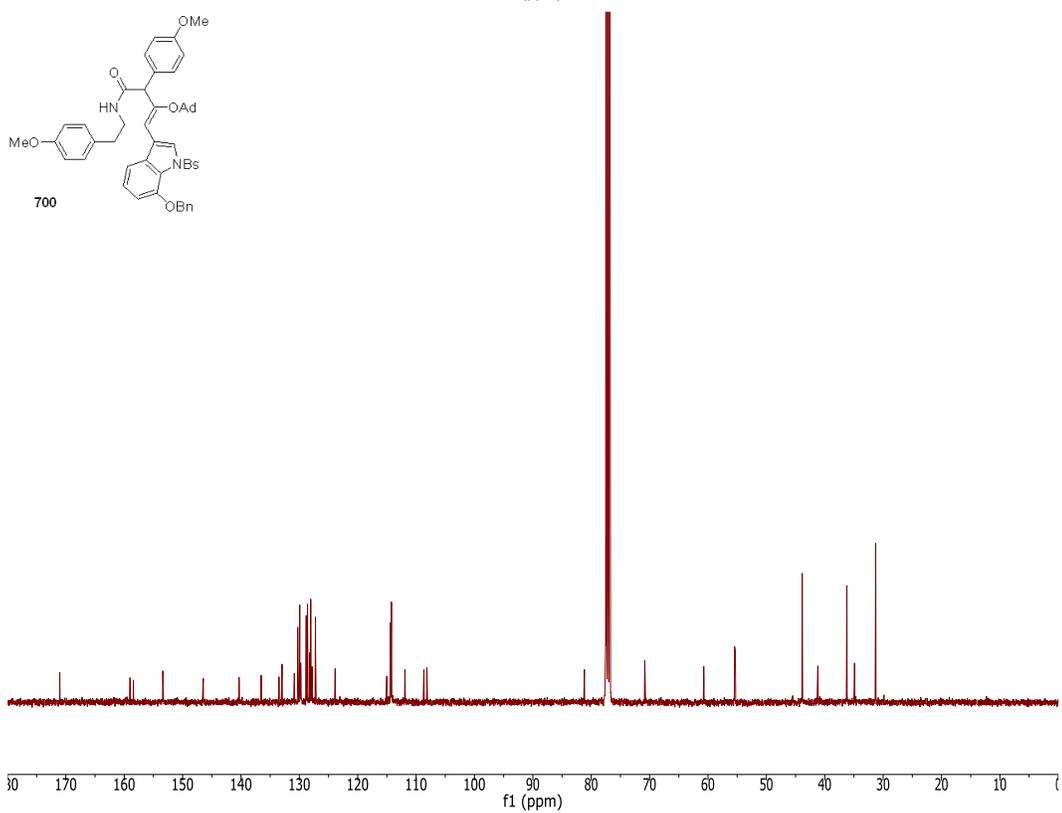
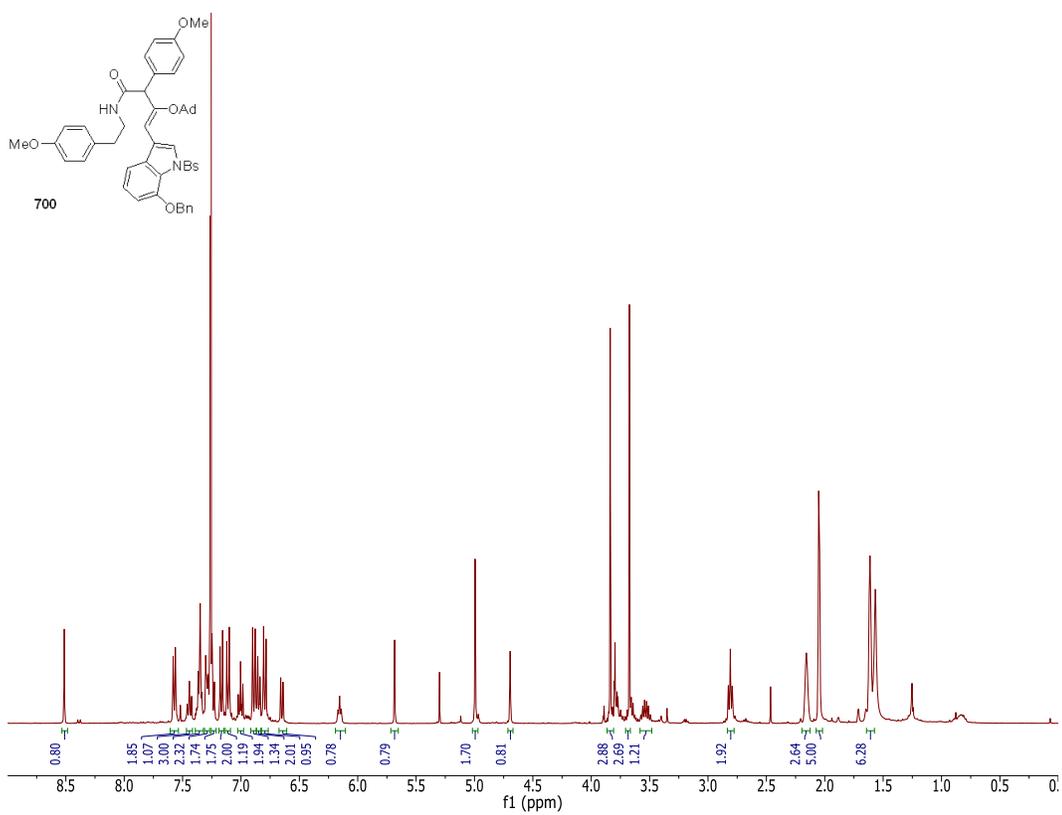


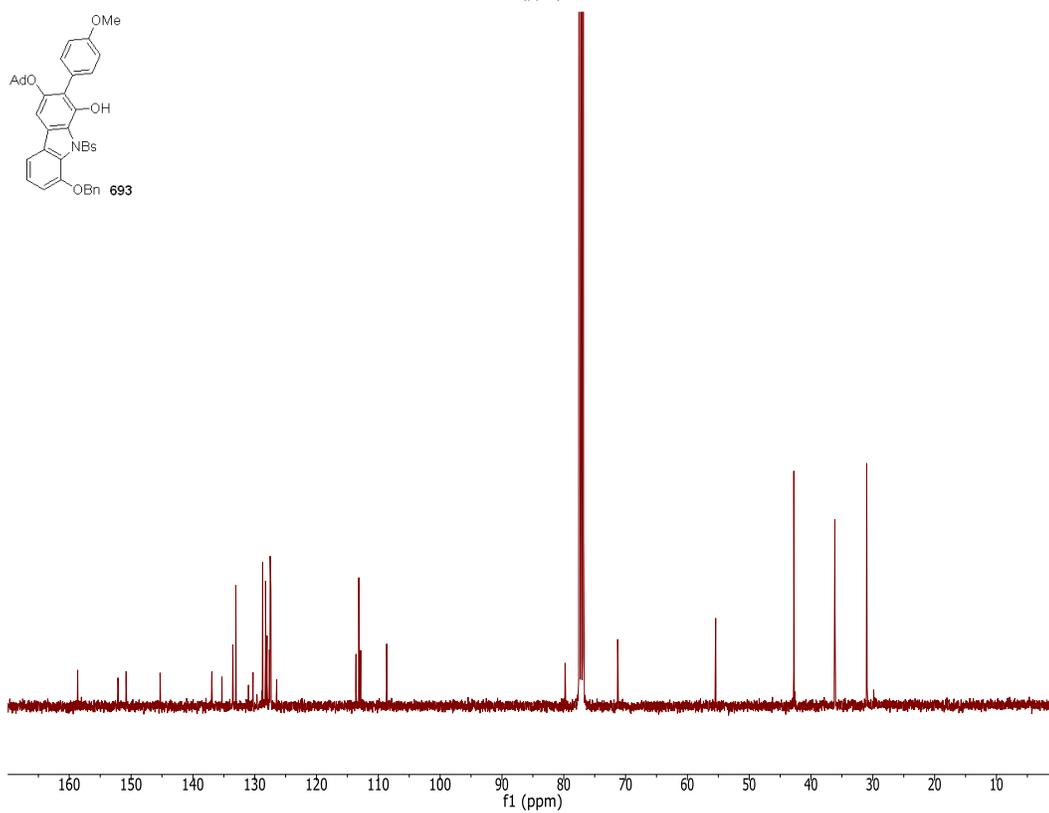
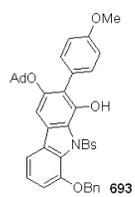
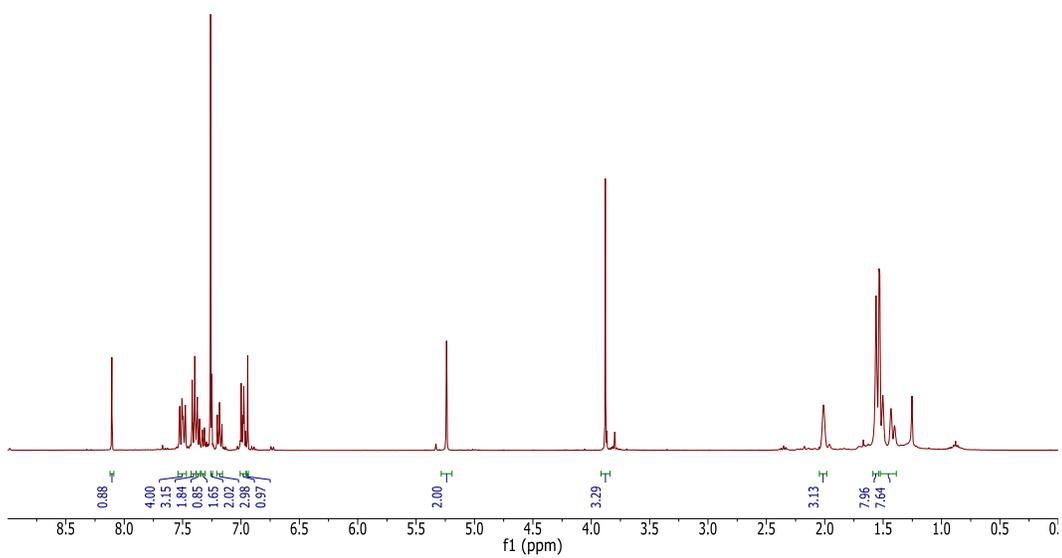
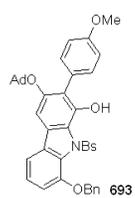


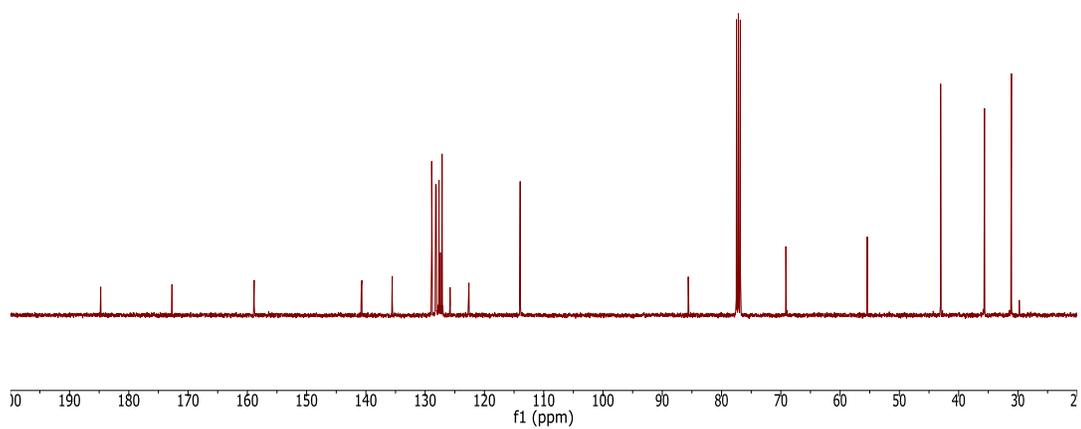
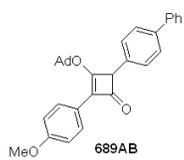
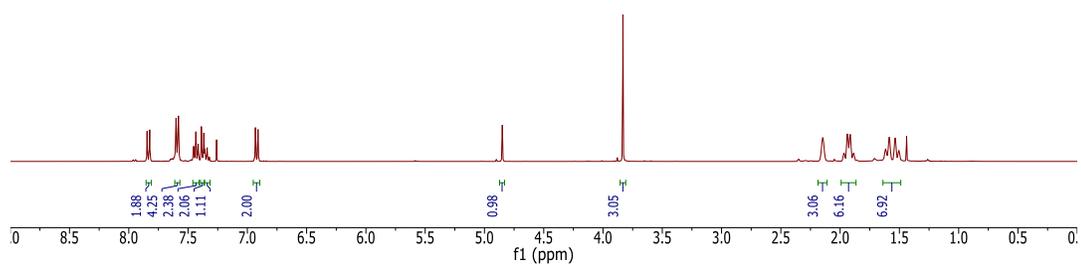
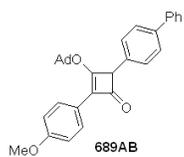








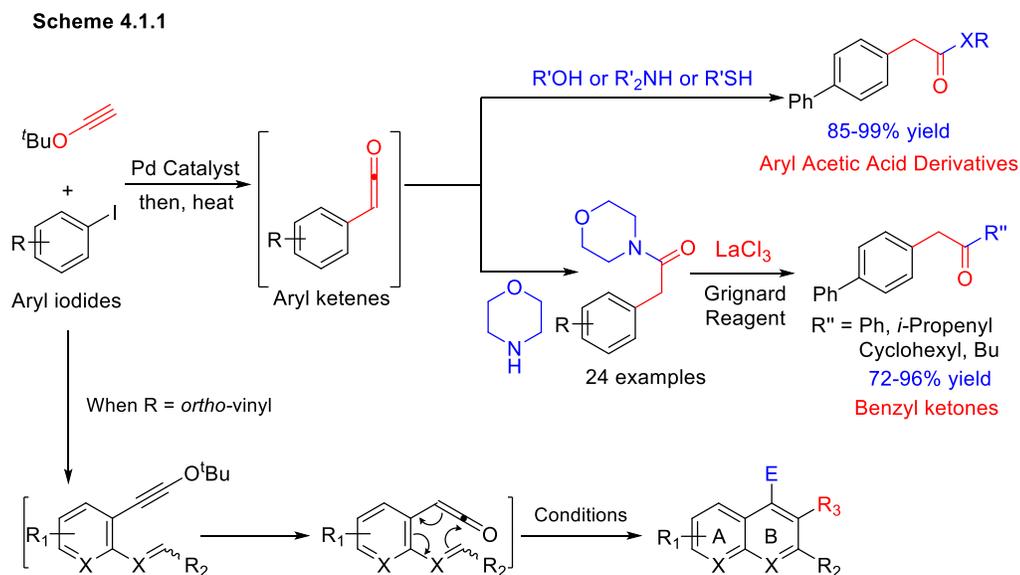




CHAPTER FOUR

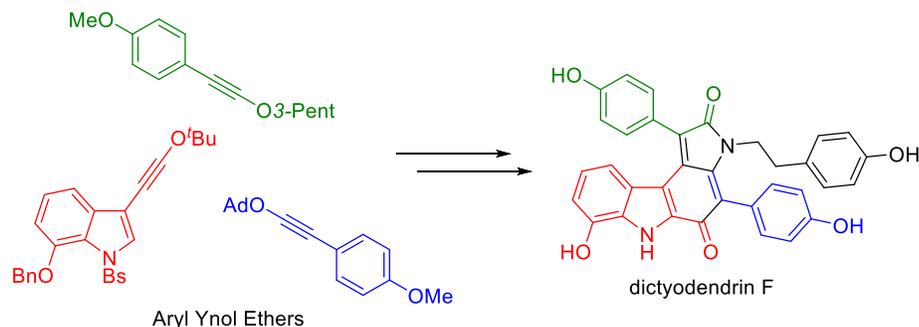
Conclusions and Recommendations

4.1 Conclusion



In summary, we discovered a novel Sonogashira coupling between *tert*-butoxyacetylene and aryl iodide to synthesize aryl ynol ethers, which serves as the surrogates of aryl ketenes under a mild thermal condition. We further utilized different nucleophiles to trap the ketene leading to aryl acetic acid derivatives, ketones, allenes, and cyclobutanones in good yield. An advantageous property of the ketene surrogate coupling is the ability to access a wide range of carbonyl compounds from a single intermediate. Moreover, we invented an efficient benzannulation reaction to give the rise to multisubstituted naphthols and quinolinols.

Scheme 4.1.2

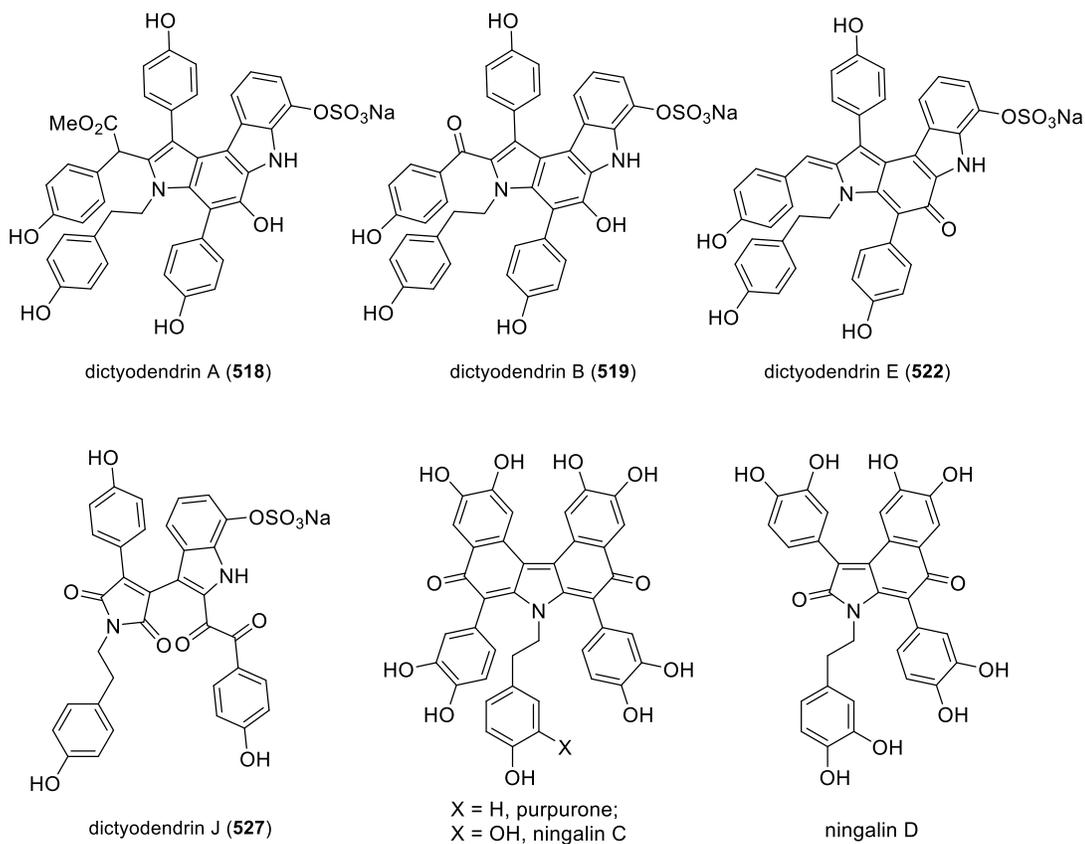


According to the synthesis of aryl ynol ethers, we used ynol ethers as the key building blocks in the synthesis of dictyodendrins F, H, and I in six steps. We developed a hetero-[2+2]-cycloaddition reaction between ynol ethers to yield a cyclobutenone ring, which was subsequently converted into a highly substituted carbazole via a retro- $4\pi/6\pi$ -electrocyclization-*N*-acylation cascade reaction. Consecutive intramolecular oxidative coupling finally gave dictyodendrins F, H, and I.

4.2 Future Direction

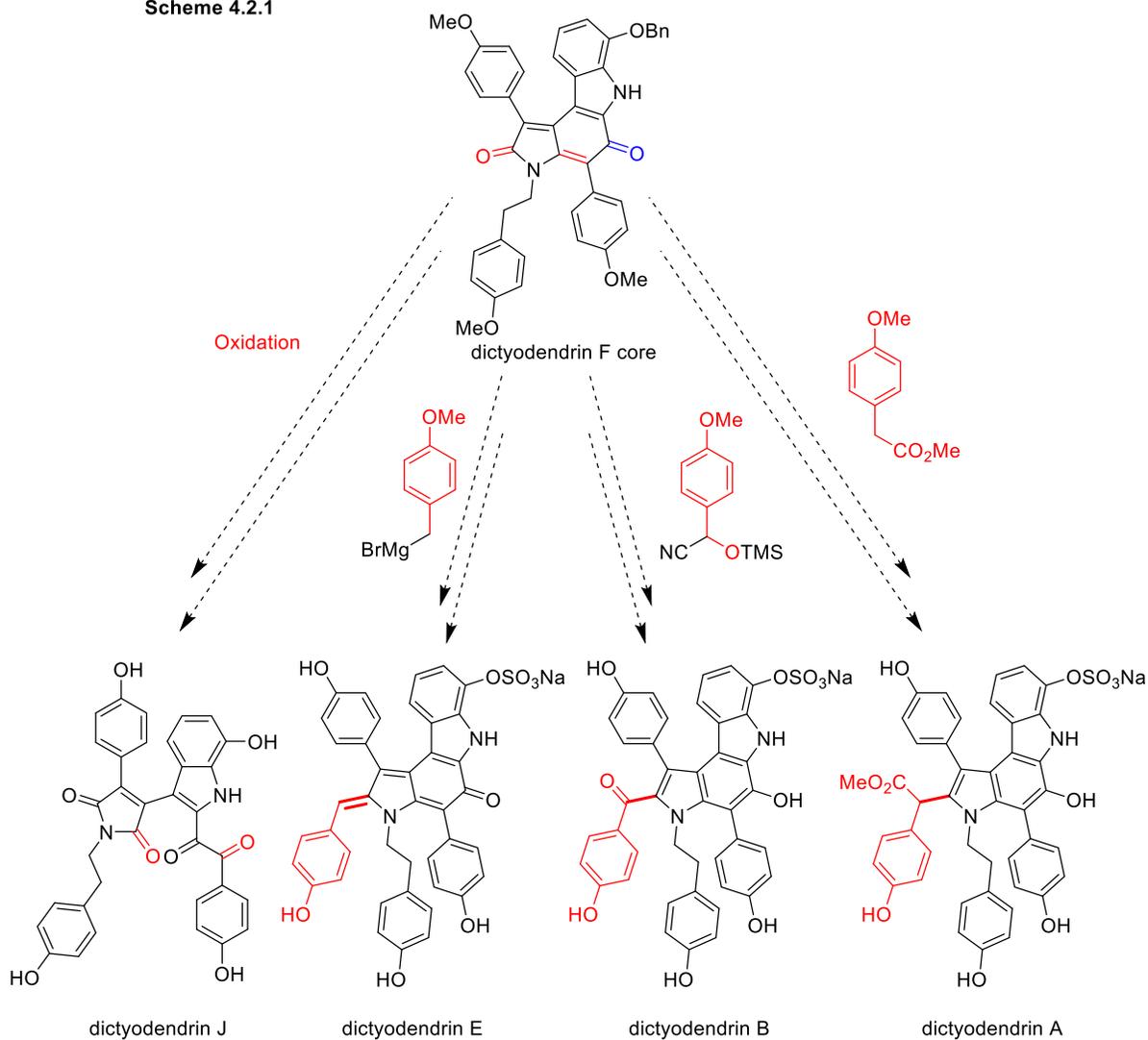
In the future, we are interested in the syntheses of dictyodendrins A, B, and E, which contain the different carbon side chains. Additionally, we will apply this synthetic strategy in the syntheses of other natural products, such as purpurone, nivalins C, and D, which have the intriguing biologic activities as well (**Figure 4.2.1**). This synthetic method allows the rapid installation of highly substituted aromatic ring systems, so we believe it will provide a practical route with fewer steps in the syntheses of complex natural products and pharmaceuticals.

Figure 4.2.1



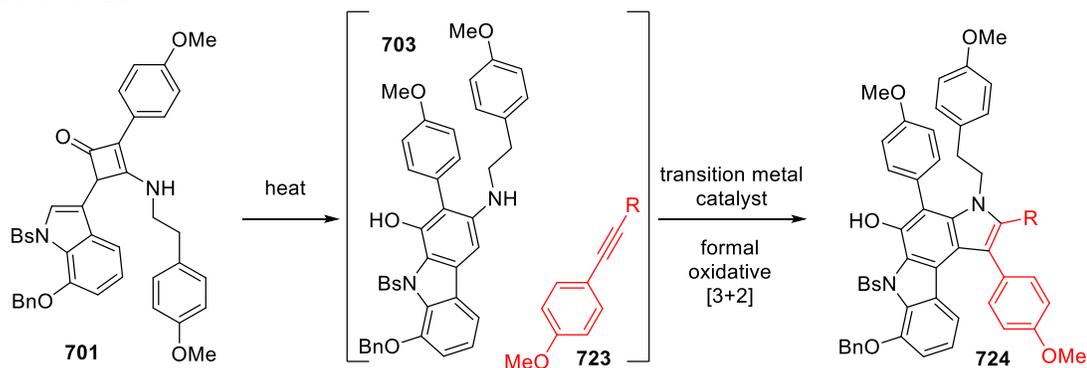
To approach the natural products listed in **Figure 4.2.1**, I recommend two possible strategies (**Scheme 4.2.1** and **Scheme 4.2.2**). According to our current first generation of the synthesis, we could use the carbon-based nucleophiles to regioselectively attack the carbonyl (red) in the dictyodendrin F core. In this way, we assume to add the side chains on the dictyodendrin F core in order to obtain dictyodendrins A, B, and E, and we propose an oxidation cleavage of the double bond (red) in the dictyodendrin F will give the rise to the carbon skeleton of dictyodendrin J. However, there will be some selectivity issues using this synthetic approach to other dictyodendrins. We assume the most electrophilic carbonyl is the blue one. To address this selectivity, we considerate to use some Lewis acids to selectively induce the carbon nucleophiles to add to the desired position.

Scheme 4.2.1



The other method accords to our observation of the retro- $4\pi/6\pi$ electronic cyclization reaction, where we found this reaction was robust under the acidic conditions. Therefore, we hypothesize that the unstable intermediate **703** can occur a nitrometallation to the alkynes **723**, which carry various side chains. The following oxidative cyclization will furnish the formal (stepwise) [3+2] cycloaddition reaction to generate the desired indole rings **724** containing various side chains.

Scheme 4.2.2



For the further research, I suggest to developed an asymmetric [2+2]-cycloaddition reaction between ynol ethers (**Scheme 4.2.3**). We have found that the zinc chloride could promote the ketene generation from ynol ethers and the consequentially cycloaddition reaction at a low temperature. Therefore, I assume that a certain chiral Lewis should enantioselectively catalyze the [2+2]-cycloaddition between ynol ethers to afford a chiral cyclobutenone, which would facilitate the total synthesis of important natural product showing below.

Scheme 4.2.3

