Spring 6-13-2014

Redox-Neutral Catalytic Spirocyclization of para-Methoxy Aryl Alkynoate Esters

Mark Docto Aparece
DePaul University, mark.aparece@gmail.com

Redox-Neutral Catalytic Spirocyclization of *para*-Methoxy Aryl Alkynoate Esters

A Thesis Presented in Partial Fulfillment
of the Requirements for the Degree of
Master of Science

By
Mark Docto Aparece
June 2014

Department of Chemistry
College of Science and Health
DePaul University
Chicago, Illinois

ABSTRACT

Redox-Neutral Catalytic Spirocyclization of *para*-Methoxy Aryl Alkynoate Esters

Mark Docto Aparece

Spirocycles are a class of molecules consisting of a quaternary atom at the junction of two fused rings. This structural motif is found in a number of biologically active natural products and pharmaceuticals. Current strategies to synthesize these structures include classical methods such as alkylation and rearrangement, as well as more modern methods reported in the past decade which utilize electrophilic halogen reagents. As part of our research interests in electrophilic transition metal catalysts to effect powerful transformations, we developed the first redox-neutral spirocyclization of *para*-methoxy aryl alkynoate esters using homogeneous gold catalysis. The reaction proceeds at ambient temperature in dichloromethane with 5 mol % loading each of $Au(PPh_3)Cl$ catalyst and AgOTf activator. The addition of 1 equivalent of water was found to be essential for the success of the reaction, playing a crucial role as a nucleophile in the proposed reaction mechanism. During our investigation of the substrate scope of the reaction, we found that substrates bearing various groups on the alkyne underwent spirocyclization in good to excellent yields in short reaction times. In addition, both electron-rich and electron-deficient aromatic rings were well tolerated under these reaction conditions. However, substrates bearing strongly deactivating groups on the alkyne failed to react. Using our conditions, we were also able to directly access the tricyclic core of the antifungal compound perenniporide A, a spirocyclic secondary metabolite of *Perenniporia* sp., a fungus found in the Chinese medicinal plant *Fallopia japonica*.

Thesis adviser: Dr. Paul A. Vadola

Acknowledgements

First and foremost, I would like to thank my research adviser, Professor Paul A. Vadola, for his guidance, patience, and encouragement. Under his mentorship, Paul helped me hone my skills as a chemist, learn how to think critically and troubleshoot, appreciate the value of hard work and perseverance, and—most importantly—love what I do. His continual support bolstered my confidence as a scientist to continue my graduate studies in organic chemistry.

Thank you also to the faculty of the chemistry department, from whom I learned so much during my time at DePaul. I would especially like to thank Professor Caitlin E. Karver and Professor Quinetta D. Shelby for serving on my thesis committee.

I would also like to thank Mr. Matthew Zuziak and Mr. Zachary Wahrenburg for their assistance in making sure our research runs smoothly, whether it is by ordering chemicals and supplies, attending to the maintenance of the NMR spectrometer, or submitting work orders to fix a beeping hood.

Finally, I would like to thank my friends and family for all their love and support. I would especially like to thank my parents, from whom I inherited my work ethic, my attentiveness to others, and my sense of integrity.

Table of Contents

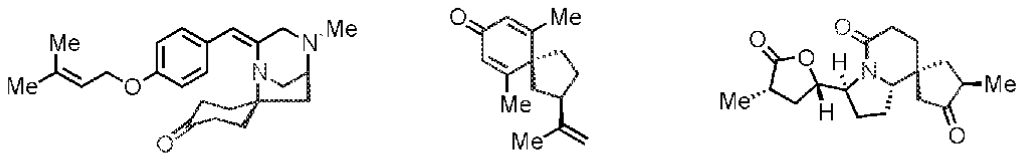
List of Figures

List of Schemes

List of Tables

I. Introduction

Spirocycles and the History of Spirocyclization Reactions. Spirocycles are a class of molecules consisting of a quaternary atom at the junction of two fused rings. The synthesis of quaternary centers is one of the most challenging tasks in synthetic chemistry, making spirocycles an attractive target for organic chemists. In addition to their unique structure and reactivity patterns, spirocycles are present in a variety of organic molecules, such as biologically active natural products and pharmaceuticals (Figure 1),[1] and have even found applications in materials science.[2]



TAN1251A
antispasmodic, antiulcer

anhydro-β-rotunol
antifungal

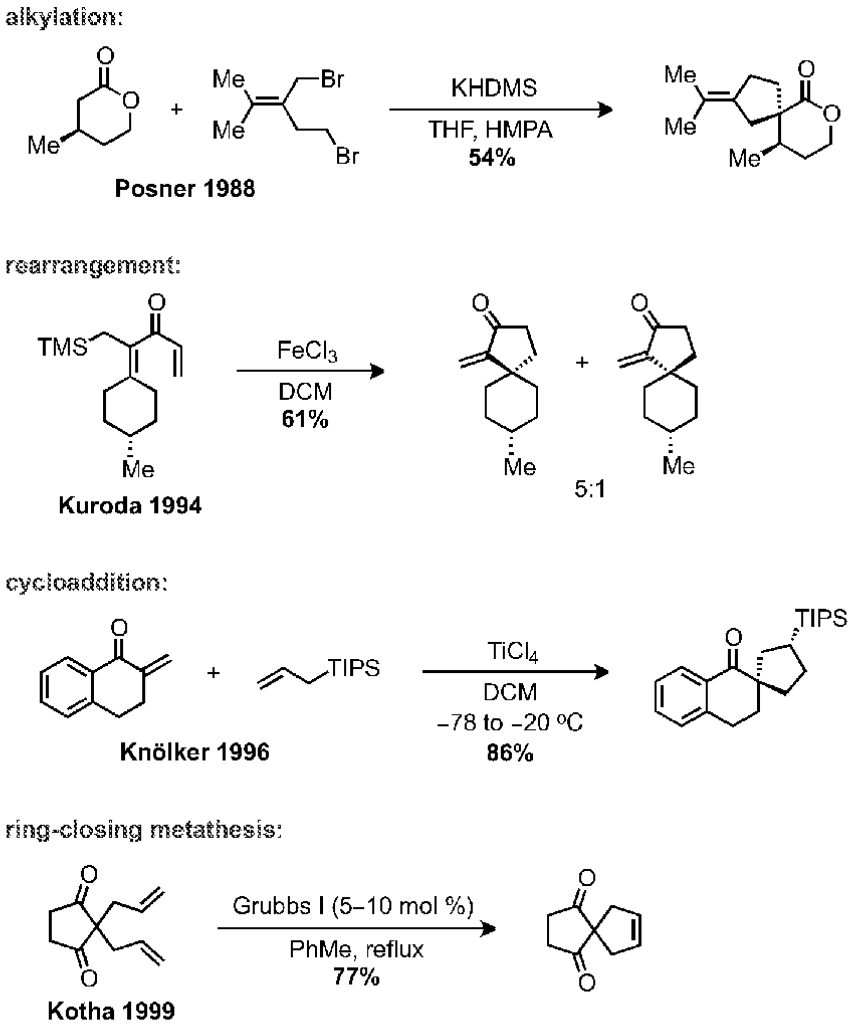
sessilifoliamide
antitussive, antibacterial

Figure 1. Selected spirocyclic natural products

Spirocycle formation has been shown to be challenging when employing classical synthetic approaches,[3] a few examples of which are given in Scheme 1. Alkylation methods, such as those employing enolate chemistry,[4] and rearrangement reactions, such as the Lewis acid-promoted Nazarov cyclization of dienones,[5] have proven difficult due to the steric congestion associated with quaternary centers. Moreover, many of these methods are plagued with functional group compatibility issues as stoichiometric amounts of highly reactive reagents are often required to effect the desired transformation. For instance, the [3+2] cycloaddition reaction between the α,β-unsaturated ketone shown in Scheme 1 and triisopropyl allylsilane proceeds at cold temperatures using stoichiometric amounts of $TiCl_4$.[6]

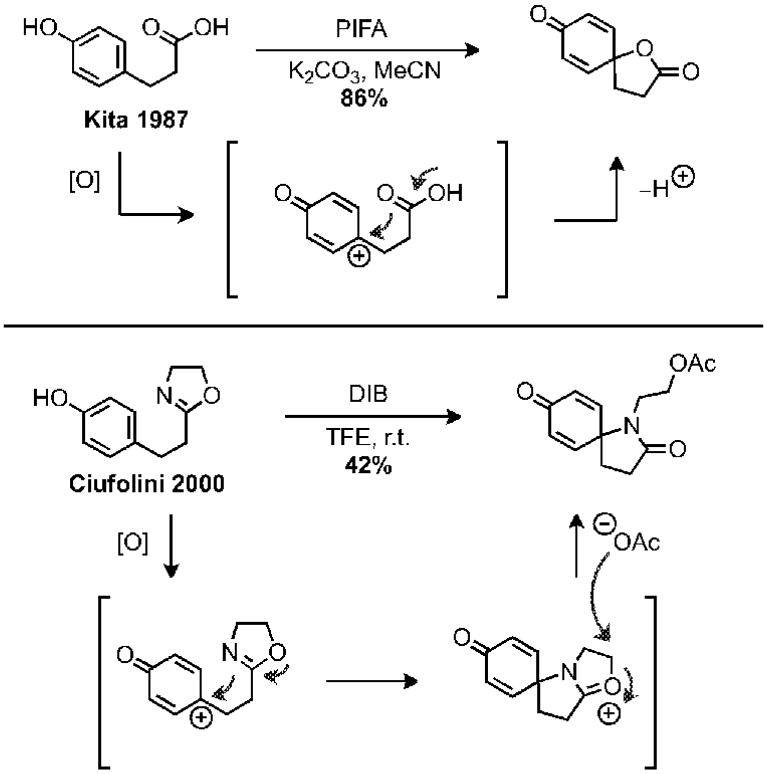
The most modern of these cyclization reactions is the ring-closing metathesis. One example is the formation of a spirocyclopentene from a *gem*-diallyl dicarbonyl compound using the first generation Grubbs catalyst (Scheme 1).[7] However, ring-closing metathesis reactions often require dilute conditions to avoid competing intermolecular reactions. In light of the many limitations involved in synthesizing spirocycles using classical techniques, novel methodologies that access these structures directly and under mild conditions are particularly desirable.

Scheme 1. Selected classical cyclization methods



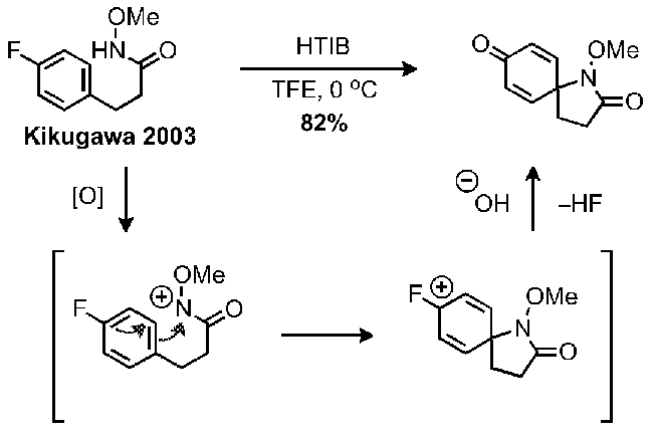
In 1987, Kita and coworkers reported the intramolecular *ipso*-cyclization of 3-(*para*-hydroxyphenyl) propionic acids to spirolactones mediated by phenyliodosyl bis(trifluoroacetate) (PIFA), a hypervalent iodine reagent (Scheme 2).[8] In this reaction, the aromatic ring undergoes oxidative dearomatization forming a highly reactive carbocation which, following nucleophilic interception by the carboxylic acid, furnishes the spirolactone. Just over a decade later, Ciufolini and coworkers disclosed the formation of spirolactams from phenolic oxazolines using iodobenzene diacetate (DIB) as a way to complement Kita's spirolactonization method (Scheme 2).[9] In subsequent years, other spirocyclization methods proceeding via oxidative dearomatization by hypervalent iodine reagents have been reported.[10]

Scheme 2. Spirocyclization via oxidative dearomatization



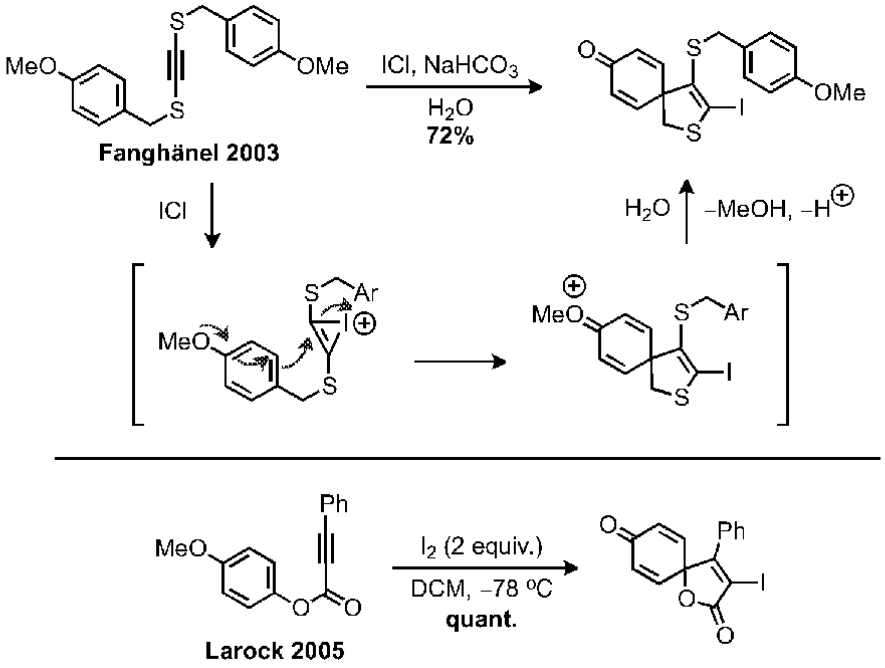
A report by Kikugawa and coworkers in 2003 makes use of the hypervalent iodine reagent [hydroxy(tosyloxy)iodo]benzene (HTIB) in the *ipso*-cyclization of *N*-methoxy-(*para*-halophenyl)amides (Scheme 3).[11] However, this methodology is unique among those which utilize hypervalent iodine reagents: the mechanism proceeds not through the oxidative dearomatization of the aromatic ring, but rather through the oxidation of the *N*-methoxyamide to a nitrenium cation. This highly reactive intermediate undergoes attack by the aromatic ring and subsequent hydrolysis to furnish the spirocycle. This simple reversal in reactivity pattern gives rise to the possibility of milder conditions to activate tethered functional groups for nucleophilic attack by the aromatic ring as an alternative to the harsh conditions associated with oxidative dearomatization.

Scheme 3. Spirocyclization via nitrenium cation intermediate



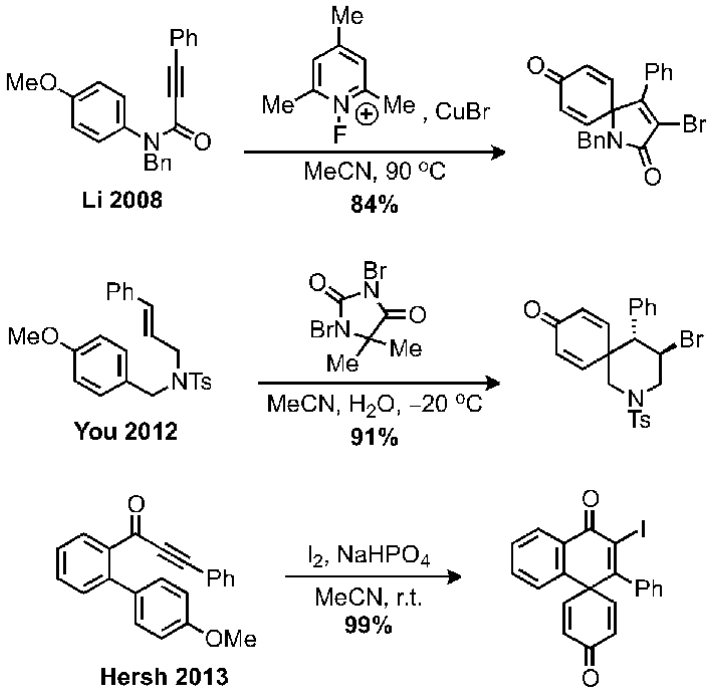
The key paper in the field which follows this principle was published in 2005 in which Zhang and Larock disclosed a highly efficient route in the synthesis of spirolactones via the intramolecular *ipso*-halocyclization of 4-(*para*-methoxyaryl)-1-alkynes using electrophilic diatomic halogens, such as I_2, Br_2, or ICl (Scheme 4).[12] This method is based on a reaction previously reported by Fanghänel and coworkers, the substrate scope of which was not thoroughly investigated by Fanghänel but exploited solely for mechanistic studies.[13]

Scheme 4. Intramolecular *ipso*-cyclization of 4-(*para*-methoxyaryl)-1-alkynes



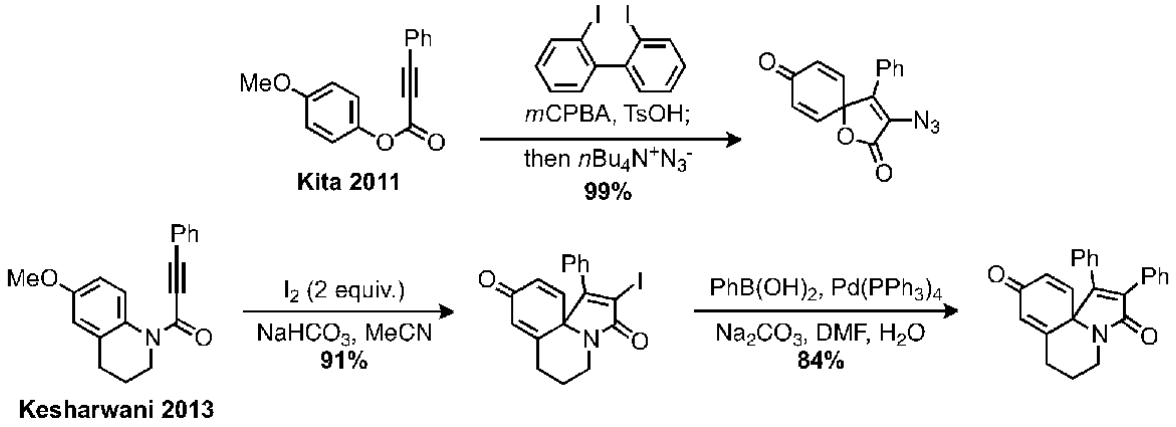
In this reaction, the halogen source reacts with the alkynyl moiety to form a highly reactive halonium intermediate, which is attacked by the *ipso*-carbon of the aromatic ring in a Friedel–Crafts-type fashion; demethylation as the final step yields the spirolactone. Since Larock's report, the last decade has seen a number of *ipso*-cyclization reactions utilizing a variety of electrophilic halogen sources, such as CuBr and 1,3-dibromo-5,5-dimethylhydantoin, to activate pendant alkynes[14] and alkenes[15] into nucleophilic *ipso*-attack by the aromatic ring, resulting in a diverse array of spirocyclic structures (Scheme 5).

Scheme 5. Selected halospirocycles formed from electrophilic halogen sources



Based on the mechanism of the Larock methodology, the use of these electrophilic halogenating reagents results in the incorporation of a halogen atom—most commonly iodine—into the structure of the newly forged ring. This is an attractive feature of this method as the halogen atom serves as a synthetic handle for further manipulation such as substitution with azide, nitro, and thiocyanate[14d] and Suzuki–Miyaura cross-coupling reactions[14i] (Scheme 6). Functionality is often absent in spirocycles formed using more classical techniques.[3b]

Scheme 6. Derivatization of halospirocycles

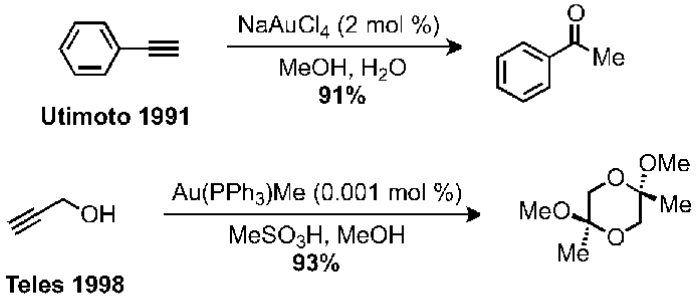


However, if the halogen atom is not desired in the final molecule, it must be removed in an additional step. Therefore, methods which forge spirocycles without halogen incorporation are particularly desirable. Another major limitation of the Larock methodology and its variations is that these reactions require stoichiometric amounts of halogen-based reagents, which can be caustic and hazardous. Furthermore, halogenating reagents are known to be incompatible with a variety of functional groups due to their high reactivity, which may lead to increased production of byproducts or waste formed from undesired side reactions.

As part of our research program aimed at using electrophilic transition metal catalysts to effect powerful transformations, the Vadola group decided to investigate their potential as substitutes for halogen-based reagents in spirocyclization reactions. Transition metal catalysts pose several advantages to electrophilic halogenating reagents as only sub-stoichiometric amounts of metal with respect to the substrate(s) are required to effect the desired transformation, making these metal catalysts safer to use and more environmentally benign. In addition, they are easier to handle and pose much higher functional group tolerance compared to halogen-based reagents. We were particularly interested in the possibility of gold to effect this transformation due to its known carbophilicity as a soft π-Lewis acid.

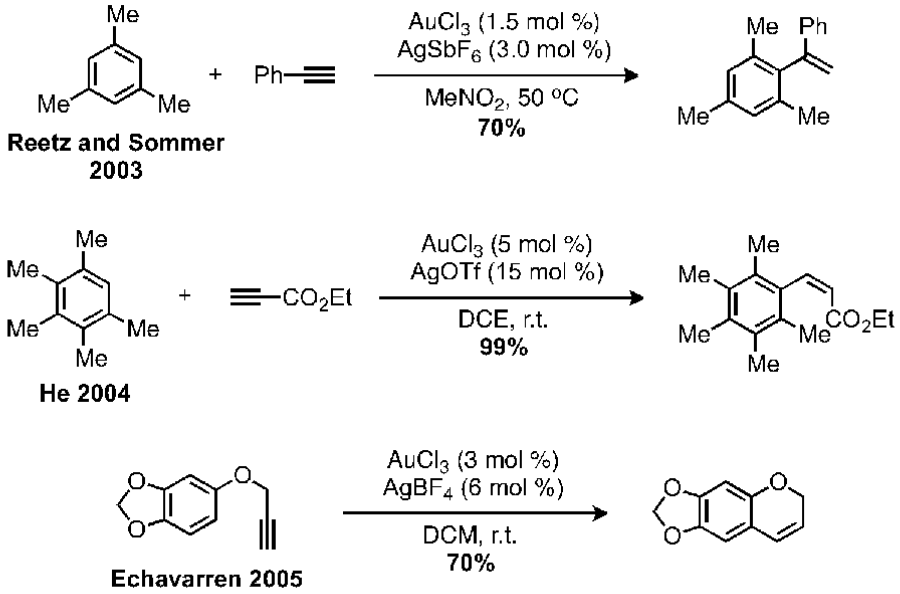
Homogeneous Gold Catalysis. The electrophilic activation of π-systems by gold cations has been known since at least 1991 when Utimoto reported the Au(III)-catalyzed addition of nucleophiles such as alcohols and water across alkynes to form acetals and ketones, respectively.[16] Six years later, this method was improved and further developed by Teles whose method utilizes a Au(I) salt.[17a] These same transformations have long been known to occur with Hg(II) salts, but the development of a cationic gold catalyst as an alternative to stoichiometric amounts of toxic mercury substances has made these reactions particularly valuable in industrial settings due to the nontoxicity of gold compared to other transition metals, as well as the possibility of extremely low catalyst loadings[17b] (Scheme 7).

Scheme 7. Au-catalyzed addition of nucleophiles across alkynes



Prior to these publications, there have been few examples in the literature which employ gold-based compounds in homogeneous catalysis, which is due in no small part to the prevailing attitude at the time of gold being expensive and inert;[18] some have ventured to call it the "least useful of the noble metals as catalysts"[19] and even "catalytically dead."[20] Subsequent years following these reports by Utimoto and Teles have seen exponential growth in the number of publications on gold catalysis.[21] A key advance in the field was reported in a 2003 publication by Reetz and Sommer in which they disclosed the Au-catalyzed hydroarylation of aryl alkynes (Scheme 8).[22] This was followed shortly afterwards with a report by He on the hydroarylation of ethyl propiolates[23] as well as an intramolecular variant and computational mechanistic study by Nevado and Echavarren.[24] These reactions all proceed through the activation of the alkyne via Au-π complexation which induces a Friedel–Crafts-type C–C bond forming event.

Scheme 8. Au-catalyzed hydroarylation of aryl alkynes



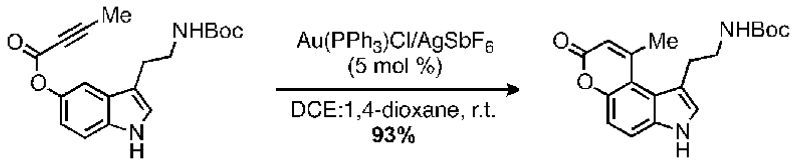
The effectiveness of gold in promoting these addition reactions across alkynes is due to its carbophilicity. Gold and other transition metals such as platinum and palladium are excellent π-Lewis acids due to the high degree of overlap between the alkenyl or alkynyl π-orbitals and the empty *d*-orbitals of the metal center; back-donation from the filled *d*-orbitals of the metal into the antibonding π*-orbitals of the ligand also contributes to the carbophilicity of these transition metals.[25]

Gold is an exceptionally soft carbophilic Lewis acid due to relativistic effects. In atoms with high nuclear charge (*Z*), such as the late transition metals, the electrons in the *s*-orbitals have a higher affinity for the nucleus. In order to avoid spiraling into the nucleus, these electrons must increase their average velocity close to the speed of light. Consequently, their relativistic mass increases. Since the Bohr radius is inversely proportional to mass, this increase in mass induces a contraction of the *s*-orbitals, which propagates to all *s*-orbitals, resulting in higher shielding (decreased effective nuclear charge *Z**) between the nucleus and the outer *d*- and *f*-electrons. This in turn causes the *d*- and *f*-orbitals to become larger and therefore more receptive to binding by π-systems.[25, 26]

One of the many papers that were published during the aforementioned "gold rush" of the last two decades was a 2012 report by the Sames group on the synthesis of coumarins via the intramolecular hydroarylation of aryl and indolyl alkynoates using $Au(PPh_3)Cl$ as the catalyst

and $AgSbF_6$ as the activator (Scheme 9).[27] Silver salts are known to increase the electrophilicity of gold centers by triggering a metathesis, which leads to the precipitation of silver halide salts with concomitant generation of "naked" Au(I) cations.[28] This highly electrophilic Au cation undergoes complexation with the alkynyl moiety, which is attacked by the aromatic ring from the position *ortho* to the alkynoate tether. Subsequent rearomatization and protodemetalation furnishes the coumarin.

Scheme 9. Au-catalyzed intramolecular *ortho*-cyclization of indolyl alkynoates



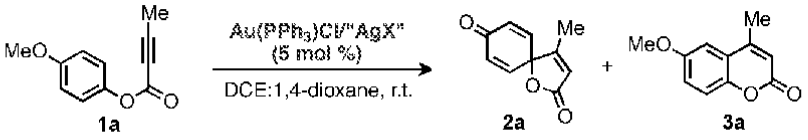
Sames 2012

From the transition metal chemistry described by Sames et al., we were inspired to investigate the possibility of *ipso*- rather than *ortho*-cyclization of aryl alkynoates to form spirocycles in a Larock-type transformation. Herein, we report the first redox-neutral spirocyclization of *para*-methoxy aryl alkynoate esters using homogeneous gold catalysis under ambient conditions.

II. Results and Discussion

Optimizing the Reaction Conditions. We began our investigation of *ipso*-cyclization conditions using aryl alkynoate **1a** as the lead substrate (Table 1), which is readily prepared from the esterification of *para*-methoxyphenol and 2-butynoic acid promoted by diisopropyl-carbodiimide (DIC).[23] As a starting point, we used the Sames conditions of 5 mol % each of $Au(PPh_3)Cl$ catalyst and $AgSbF_6$ activator in a 1:1 solution of dichloroethane (DCE) and 1,4-dioxane as the solvent (Table 1). Promisingly, we observed both spirocycle **2a** and coumarin **3a**, the product mixture slightly favoring the coumarin.

Table 1. Initial discovery of the *ipso*-cyclization of substrate **1a**[a]



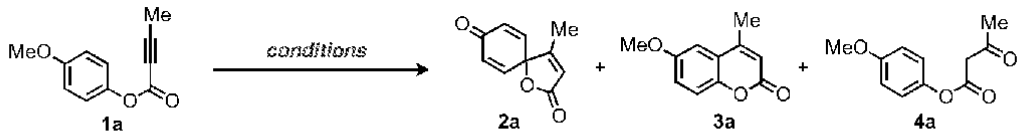
"AgX"	Yield[b] **2a** (%)	Yield[b] **3a** (%)
$AgSbF_6$	39	48
$AgBF_4$	53	19
AgOTf	93	0

[a]Reactions performed at room temperature with 5 mol % $Au(PPh_3)Cl/AgOTf$. [b]Determined by ^1H NMR of the crude reaction mixture with *para*-nitrobenzaldehyde as an external standard.

Since it is known that counterions can modulate the reactivity of Au(I) cations (due to degree of coordination, electrostatic effects, etc.), we decided to experiment with other silver salt additives. When $AgBF_4$ was used, we were able to favor formation of **2a** over **3a** in a 2.79:1 ratio. When AgOTf was used, we were able to exclusively form **2a**. However, this result proved irreproducible and inconsistent in later trials, giving a mixture of **2a** and **3a** in variable ratios. Disappointingly, coumarin was observed to be the major product in these cases.

We then systematically tested variables that could contribute to the irreproducibility of our initial AgOTf result, including the quality of the $Au(PPh_3)Cl$ catalyst and/or the AgOTf activator and the type of reaction vial used. None of these factors altered the outcome of the reaction. Since the methyl group from the methoxy arene is ultimately lost during spirocyclization, we speculated that the removal of this methyl group would be mediated by the presence of a nucleophile such as water in the reaction medium.

Table 2. Optimization of the *ipso*-cyclization of substrate **1a**[a]



1a **2a** **3a** **4a**

Entry	Solvent	Conc. (*M*)	H_2O (equiv.)	Time	Yield[b] **2a** (%)	Yield[b] **3a** (%)	Yield[b] **4a** (%)	Unreacted[b] **1a** (%)
1	DCE:1,4-dioxane	0.05	0	8.5 h	26	74	0	0
2	DCE:1,4-dioxane	0.05	0.5	5 h	60	10	trace	0
3	DCE:1,4-dioxane	0.05	1	5 h	93	0	0	0
4	DCE	0.05	0	6 h	6	85	0	0
5	DCE	0.05	1	30 min	91	0	3	0
6	DCE, anhydrous	0.05	1	20 min	91	0	4	0
7	1,4-dioxane	0.05	1	5 h	97	0	0	0
8	EtOAc	0.05	1	22h	91	0	trace	0
9	MeCN	0.05	1	30 h	10	70	0	0
10	THF	0.05	1	30 h	32	45	0	0
11	$MeNO_2$	0.05	1	1 h	59	26	3	0
12	benzene	0.05	1	30 h	67	5	6	0
13	MeOH	0.05	1	30 h	31	trace	31	0
14	*i*PrOH	0.05	1	30 h	9	54	0	trace
15	**DCM**	**0.05**	**1**	**30 min**	**98**	**0**	**2**	**0**
16	DCM, anhydrous	0.05	1	20 min	95	0	2	0
17	DCM	0.05	0	6 h	15	61	0	0
18	DCM	0.1	1	1h	94	0	2	0
19	DCM	0.2	1	7.5 h	82	0	4	0

[a]Reactions performed at room temperature with 5 mol % $Au(PPh_3)Cl/AgOTf$. [b]Determined by ^1H NMR of the crude reaction mixture with *para*-nitrobenzaldehyde as an external standard.

To our delight, the addition of 1 equivalent of water was effective to once again bias the reaction in favor of the desired spirocycle with no observed coumarin, forming **2a** in 93% yield by ^1H NMR (Table 2, entry 3). When 0.5 equivalents of water were added, the yield of **2a** dropped to 60% and **3a** was formed in 10% yield (Table 2, entry 2). Given the known toxicity of 1,4-dioxane, we tested our modified reaction conditions using only DCE as the solvent and found that **2a** was formed in 91% yield by ^1H NMR in only 30 minutes with no observed coumarin (Table 2, entry 5). Using only 1,4-dioxane as the solvent gave a better yield of 97% yield **2a**

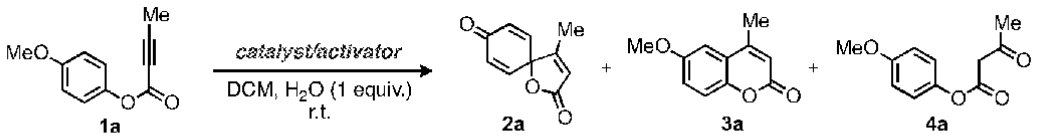
(Table 2, entry 7), but since 1,4-dioxane is toxic and DCE is relatively uncommon, we were prompted to explore other solvent options.

A rigorous solvent screen revealed dichloromethane (DCM) as the superior solvent for this reaction at 0.05 *M* concentration of **1a**, furnishing **2a** in 98% yield by ^{1}H NMR in 30 minutes (Table 2, entry 15). A small amount of *β*-keto ester **4a** also forms under these conditions, resulting from conjugate addition of water into the Au-activated alkyne. No significant difference in either reaction time or percent yield was observed when anhydrous DCM (Table 2, entry 16) was used with exogenous water as opposed to "wet" DCM from a bench top bottle. Presumably, fortuitous water that was present in either the solvents or a previous batch of **1a** was sufficient to favor the formation of **2a** in our initial discovery of the reaction.

Identifying the Ideal Catalyst System. With these new reaction conditions in hand, we then screened a variety of gold catalysts and silver activators against **1a** (Table 3). We also chose to screen other electrophilic transition metal complexes. Platinum and palladium, for example, are also known to activate alkynes into Friedel–Crafts-type attack by aromatic rings.[29] Copper is another carbophilic metal known to activate alkynes into nucleophilic attack.

We were pleased to find our original catalyst/activator combination of $Au(PPh_3)Cl$/AgOTf was still the best system (Table 3, entry 7). The platinum and copper catalysts did not react at all, and the palladium catalysts gave poor yields, even after prolonged reaction time (24 hours). All other gold and silver combinations were not as selective or high-yielding. Interestingly, $(p\text{-}CF_3Ph)_3PAuCl$/AgOTf and $(dppm)(AuCl)_2$/AgOTf both proved to be competent systems as well, exclusively giving **2a** in excellent ^{1}H NMR yields (Table 3, entries 11 and 13) with no observed **3a** or **4a**. While these conditions proceeded with complete conversion and no side products, we ultimately decided on $Au(PPh_3)Cl$/AgOTf as the ideal catalyst/activator system, as $Au(PPh_3)Cl$ is much cheaper than the other gold catalysts. As a control, we tested to see if the reaction would work with only $Au(PPh_3)Cl$ or AgOTf. As expected, the reaction fails without a silver salt to activate the $Au(PPh_3)Cl$ catalyst (Table 3, entry 16). Interestingly, **2a** forms in 6% yield when AgOTf alone is used (Table 3, entry 17). This is most likely formed from the Brønsted acid-promoted spirocyclization of the substrate by the small amount of triflic acid generated in solution. This hypothesis is consistent with findings by Hartwig and coworkers in which they observed that triflic acid is the true catalyst in many reactions utilizing metal triflate complexes.[30]

Table 3. Catalyst screen of the *ipso*-cyclization of substrate **1a**[a]



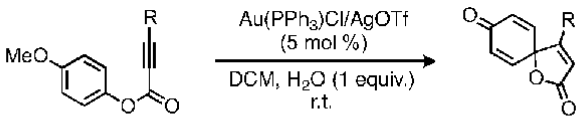
Entry	Catalyst (5 mol %)	Activator (5 mol %)	Time	Yield[b] **2a** (%)	Yield[b] **3a** (%)	Yield[b] **4a** (%)	Unreacted[b] **1a** (%)
1	$PtCl_4$	–	24 h	0	0	0	100
2	PtI_4	–	24 h	0	0	0	100
3	(dppp)Pd(OTf)$_2$	–	24 h	52	0	0	25
4	[(*R*)-BINAP]Pd(OTf)$_2$·H_2O	–	24 h	45	0	0	17
5	$Cu(OTf)_2$	–	24 h	0	0	0	100
6	$(MeCN)_4CuPF_6$	–	24 h	0	0	0	100
7	**Au(PPh$_3$)Cl**	**AgOTf**	**30 min**	**98**	**0**	**2**	**0**
8	Au(PPh$_3$)Cl	$AgSbF_6$	1 h	58	19	10	0
9	Au(PPh$_3$)Cl	$AgBF_4$	22 h	87	trace	7	0
10	Au(P*t*Bu$_3$)Cl	AgOTf	40 min	77	0	16	0
11	(*p*CF_3Ph)$_3$PAuCl	AgOTf	1.5 h	93	0	0	0
12	(IPr)AuCl	AgOTf	15 min	66	0	31	0
13	(dppm)(AuCl)$_2$	AgOTf	40 min	89	0	0	0
14	Au(IPr)BF_4(MeCN)	–	1 h	26	10	55	0
15	$(Ph_3PAu)_3OBF_4$	–	22 h	80	trace	8	0
16	Au(PPh$_3$)Cl	–	24 h	0	0	0	100
17	–	AgOTf	24 h	6	0	0	94

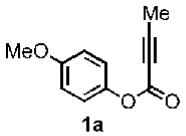
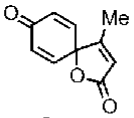
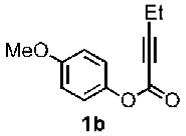
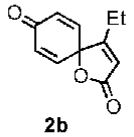
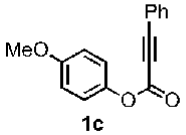
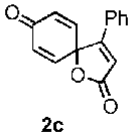
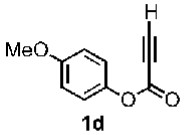
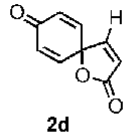
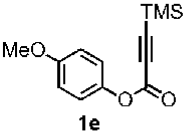
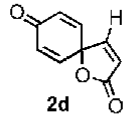
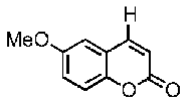
[a]Reactions performed at 0.05 *M* **1a**. [b]Determined by ^{1}H NMR of the crude reaction mixture with *para*-nitrobenzaldehyde as an external standard.

Substrate Scope of the *ipso*-Cyclization of Aryl Alkynoate Esters. Treatment of **1a** with 5 mol % of Au(PPh$_3$)Cl/AgOTf and 1 equivalent of water in DCM afforded the desired product **2a** in 98% ^{1}H NMR yield (90% isolated yield after column chromatography) with complete consumption of the starting material in only 30 minutes at ambient temperature. We then decided to investigate the substrate scope of this reaction with different aryl alkynoate esters derived from *para*-methoxyphenol and various alkynoic acids.

As expected, the substrate bearing the ethyl group **1b** behaved similarly to the lead substrate in both reaction time and isolated yield of **2b** (Table 4, entry 2). We found that phenyl-bearing **1c** and unsubstituted **1d** also exclusively gave the desired spirocycles **2c** and **2d** in good

Table 4. Substrate scope of the *ipso*-cyclization of *para*-methoxyphenyl alkynoates[a]



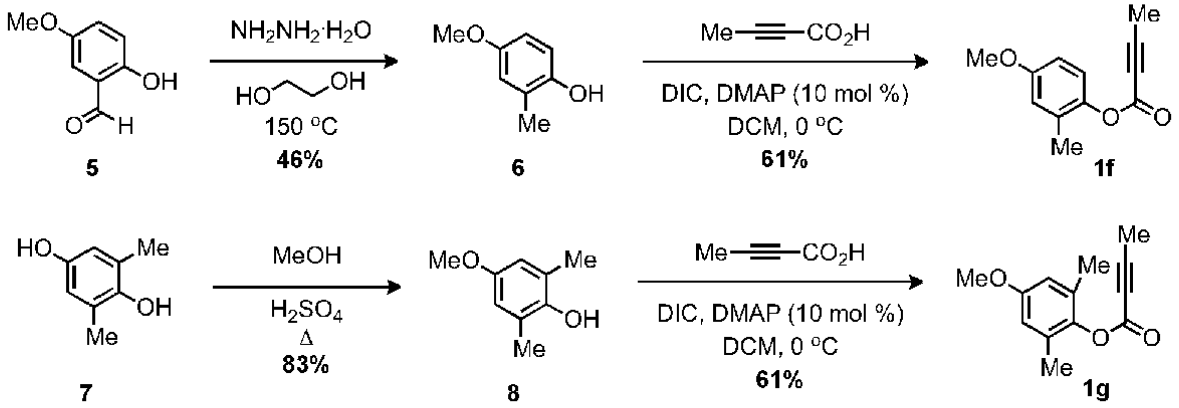
Entry	Substrate	Product	Time	Yield[b] (%)
1	 **1a**	 **2a**	30 min	90
2	 **1b**	 **2b**	40 min	86
3	 **1c**	 **2c**	1 h	85
4	 **1d**	 **2d**	3 h	74
5	 **1e**	 **2d** +  **3d**	20 h	25 (**2d**) 18 (**3d**)

[a]Reactions performed at 0.05 *M* substrate. [b]Isolated yields averaged over three trials.

yields (Table 4, entries 3 and 4), showing that large groups and reactive terminal alkynes are well tolerated under our reaction conditions. However, the substrate with the terminal trimethylsilyl (TMS) group **1e** did not furnish the desired TMS-bearing spirocycle, leading to a complex mixture consisting primarily of desilylated spirocycle **2d** and coumarin **3d** in 25% and 18% isolated yields, respectively (Table 4, entry 5). The acidic medium of the reaction is most likely responsible for the loss of the TMS moiety.

We then decided to investigate the scope of our reaction on aryl alkynoates derived from various methoxy phenols and 2-butynoic acid. The Wolff–Kishner reduction of 2-hydroxy-5-methoxy benzaldehyde **5** furnished phenol **6**, the precursor to **1f**, following a literature procedure.[31] Likewise, the regioselective acid-catalyzed methylation of 2,6-dimethyl hydroquinone **7** to give phenol **8**, the precursor to **1g**, is also known (Scheme 10).[32]

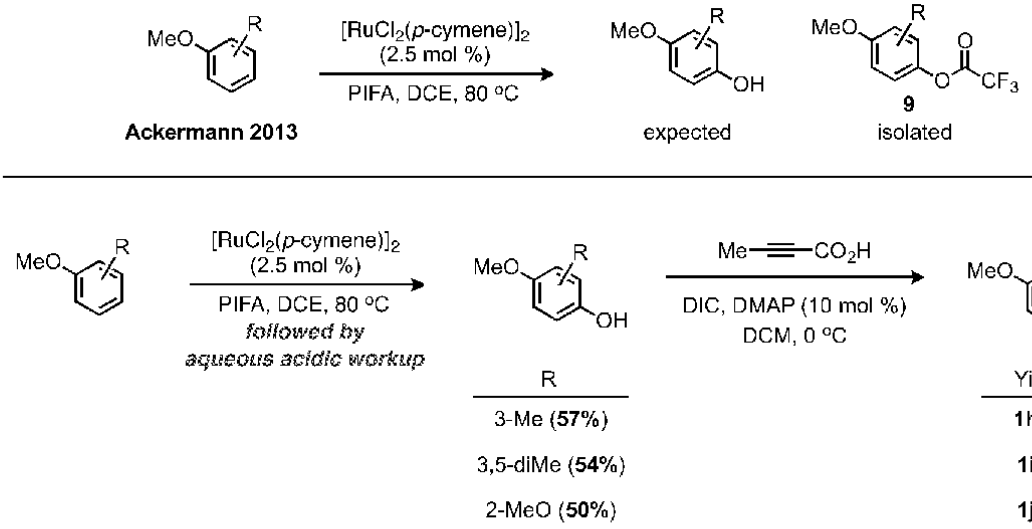
Scheme 10. Synthesis of substrates **1f** and **1g**



Synthesizing the phenol precursors of alkynoate esters **1h**, **1i**, and **1j** proceeded to be more challenging. The synthesis of these phenols was attempted following a recent report by the Ackermann group in which they describe the Ru-catalyzed *para*-hydroxylation of anisoles in the presence of PIFA.[33] However, when we tried to replicate their procedure to synthesize **1h** and **1j**, we found that our ^{1}H NMR spectra did not match theirs; most notably, the phenol peaks were absent. Furthermore, when we subjected the products of these reactions to our standard DIC-promoted esterification conditions, no reaction was observed. After much deliberation, the products of the Ru-catalyzed reactions were determined *not* to be the desired phenols, but rather their trifluoroacetate esters **9** (Scheme 11). This suspicion was confirmed by GC-MS: indeed, the M^+ peak of the isolated product matched the predicted *m/z* value of the aryl trifluoroacetate.

Fortunately, esters are readily cleaved in aqueous acidic solution, and a modified workup procedure with this in mind was formulated. Upon completion of each reaction, rather than diluting the reaction mixture in water as per the authors' protocol, the solvent was removed *in vacuo* and the remaining residue was dissolved in a 1:1 solution of 10% HCl and THF. Stirring this solution at room temperature for 30 minutes to an hour followed by standard extractive

Scheme 11. Synthesis of substrates **1h**, **1i**, and **1j**



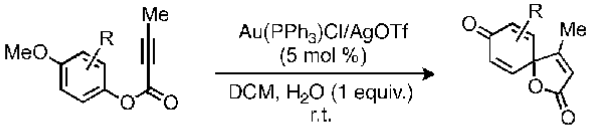
workup and chromatography afforded the desired free phenols in modest yields. Esterification of these phenols with 2-butynoic acid then proceeded as normal (Scheme 11).

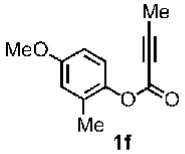
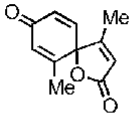
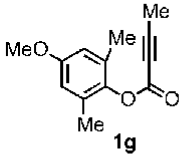
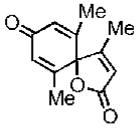
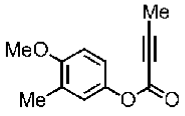
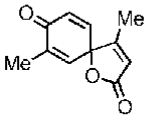
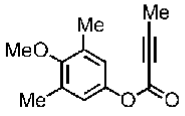
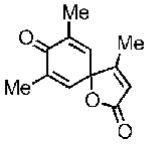
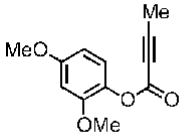
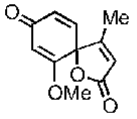
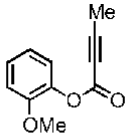
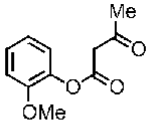
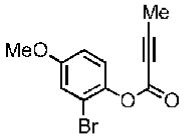
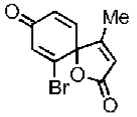
When subjected to our reaction conditions, these substrates all gave the corresponding spirocycles. Notably, **1f** and **1g** gave products in 97% and quantitative yields, respectively (Table 5, entries 1 and 2). This excellent result for **1g** is most likely due to the two methyl groups flanking the *ipso* carbon, which would preclude coumarin formation. We had predicted that **1f** would lead to a mixture of products, as steric hindrance from the methyl group *ortho* to the ester would promote a 1,2-migration of the newly-formed bond from the *ipso* carbon to the *ortho* position, forming the competing coumarin product (see Scheme 18). We were pleased to discover that this was not the case.

1h underwent cyclization in good yield as well (Table 5, entry 3), but **1i** gave **2i** in only 65% yield (Table 5, entry 4). The TLC of the reaction showed more product spots compared to the other substrates, accounting for the lower yield. This may be due to the electronic structure of this substrate: by having both methyl groups *meta* to the ester moiety, the electron density is increased at the *ortho* positions, which potentially lowers the activation barrier for side reactions such as coumarin formation.

The substrate bearing two methoxy groups **1j** performed well, giving **2j** in 92% yield (Table 5, entry 5). In order to confirm that the methoxy group *para* rather than *ortho* to the ester group becomes demethylated, the reaction was tested on the *ortho*-methoxy aryl alkynoate **1k**.

Table 5. Substrate scope of the *ipso*-cyclization of various *para*-methoxyaryl 2-butynoates[a]



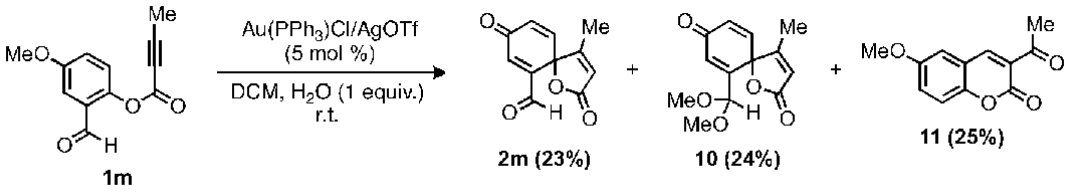
Entry	Substrate	Product	Time	Yield[b] (%)
1	 **1f**	 **2f**	50 min	97
2	 **1g**	 **2g**	30 min	quant.[c]
3	 **1h**	 **2h**	30 min	90
4	 **1i**	 **2i**	30 min	65
5	 **1j**	 **2j**	1 h	92[c]
6	 **1k**	 **4k**	3 h	22[c]
7	 **1l**	 **2l**	1 h	86[c]

[a]Reactions performed at 0.05 *M* substrate. [b]Isolated yields averaged over three trials unless otherwise noted. [c]Isolated yield averaged over two trials.

Having the methoxy group *para* to the ester tether increases the electron density of the *ipso* carbon, thus enhancing its nucleophilicity. When the methoxy group is in the *ortho* position, this effect is less pronounced, making the *ipso* carbon less nucleophilic. Indeed, **1k** failed to undergo *ipso*-cyclization; the substrate gave a complex mixture of products out of which the *β*-keto ester **4k** was isolated as the major product in 22% yield (Table 5, entry 6).

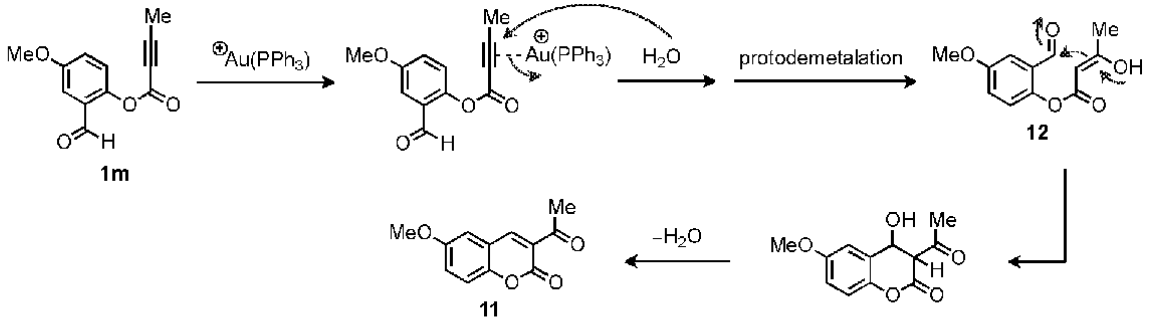
All aryl alkynoates described so far contain electron donating groups on the aromatic rings, which enhance their nucleophilicity. We then decided to test our reaction on less activated substrates, which bear electron withdrawing groups in addition to the methoxy group. We found the bromo compound **1l**, prepared from the esterification of 2-bromo-4-methoxyphenol and 2-butynoic acid, performed well, giving **2l** in 86% yield in 1 hour (Table 5, entry 7). As an added bonus, the bromine atom could serve as a synthetic handle for further transformations such as cross coupling reactions.

Scheme 12. Reaction of substrate **1m** under cyclization conditions



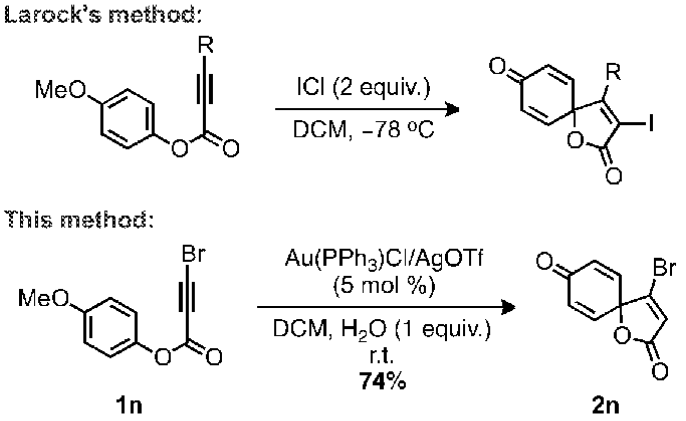
The substrate bearing the aldehyde **1m** was synthesized from the esterification of 2-hydroxy-5-methoxy benzaldehyde and 2-butynoic acid. When subjected to our reaction conditions, **1m** gave a mixture of products: the desired spirocycle **2m** in 23% yield and the dimethoxyacetal **10** in 24% yield (Scheme 12). The formation of **10** comes as no surprise given the continual liberation of MeOH molecules from the substrate molecules and the acidic reaction medium. Interestingly, coumarin **11** was also formed in 25% yield but not through the *ortho*-cyclization of the aromatic ring as described before. Instead, we proposed that water undergoes conjugate addition into the Au-activated alkyne of **1m** followed by protodemetalation to give enol intermediate **12**. This species then undergoes an aldol condensation onto the aldehyde to give **11** (Scheme 13).

Scheme 13. Proposed mechanism for the formation of **11** from **1m**



We then decided to investigate substrates bearing electron withdrawing groups on the alkyne, which may reduce its proclivity for π-coordination with the Au(I) cation. We found the alkynyl bromide **1n**, which is formed from the bromination of **1d**, gives **2n** in 74% yield (Scheme 14). This product is particularly interesting as the newly formed ring contains a bromine atom at the *β*-position. This makes our methodology complementary to that of Larock which incorporates halogens at the *α*-position, opening several potential avenues for further derivatization.

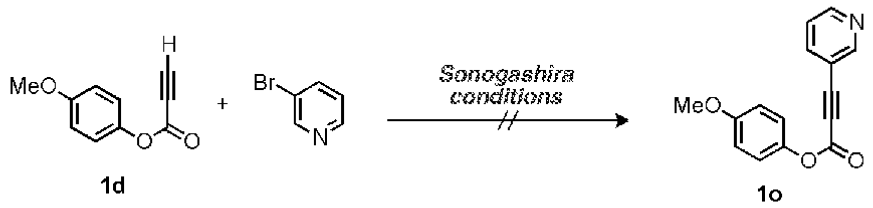
Scheme 14. Complementary methods in the synthesis of halospirocycles



We were then interested in testing our reaction on a substrate bearing a pyridine ring attached to the alkyne **1o**, as the pyridyl group is not only electron withdrawing but is also Lewis basic. This substrate would therefore test the limits of the cationic Au(I) catalyst when an sp^2-hybridized basic nitrogen atom is present in the reaction. We envisioned that **1o** could be derived from the Sonogashira cross-coupling of **1d** with 3-bromopyridine (Scheme 15).[34] Unfortunately, all attempts to synthesize **1o** failed. This is likely due to **1d** undergoing conjugate addition by

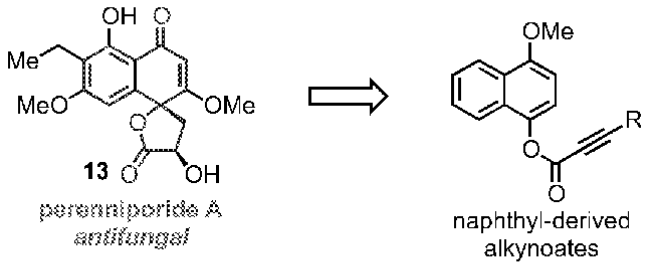
either an alkynyl copper species in solution or an amine base, preventing the transmetalation step with the palladated pyridine species required to complete the catalytic cycle.

Scheme 15. Attempts to synthesize **1o** via Sonogashira cross-coupling reactions



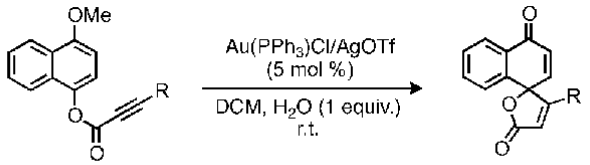
We recognized the antifungal natural product perenniporide A **13** could potentially be synthesized using our *ipso*-cyclization method (Scheme 16). Perenniporide A is a recently isolated secondary metabolite of *Perenniporia* sp., a fungus found in the Chinese medicinal plant *Fallopia japonica* and the weevil *Euops chinesis*, which feeds on the plant.[35] To demonstrate our proposed idea, as well as access more elaborate spirocyclic structures, substrates derived from 4-methoxy-1-naphthol were subjected to our reaction conditions. Methyl-bearing substrate **1p** gave **2p** in excellent yield after 10 hours (Table 6, entry 1). We were especially delighted to find that unsubstituted **1q** gave **2q** in good yield (Table 6, entry 2), since this spirocycle forms the tricyclic core of perenniporide A.

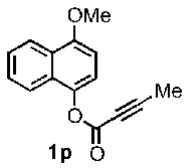
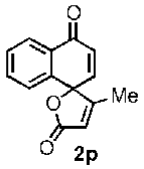
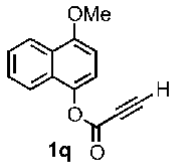
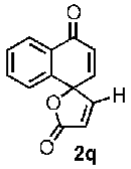
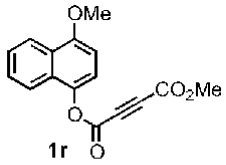
Scheme 16. Natural product-inspired investigation of naphthyl-derived alkynoate ester substrates



As a final test of the efficacy of our reaction on substrates with electron withdrawing groups appended to the alkyne, methyl ester **1r** was synthesized from the deprotonation of **1q** with *t*-butyllithium and subsequent reaction with methylchloroformate (Scheme 17).

Table 6. Substrate scope of the *ipso*-cyclization of 4-methoxynaphthyl alkynoates[a]

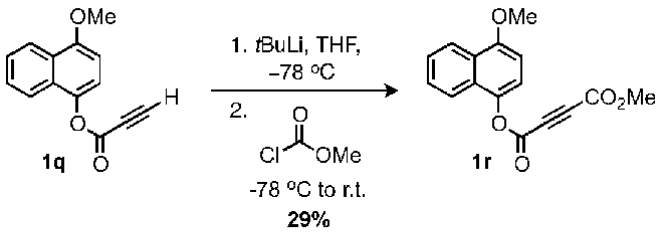


Entry	Substrate	Product	Time	Yield[b] (%)
1	 **1p**	 **2p**	10 h	89
2	 **1q**	 **2q**	4 h	77
3	 **1r**	--	24 h	N.R.
4[c]	**1r**	--	18 h	N.R.
5[d]	**1r**	--	5.5 h	N.R.

[a]Reactions performed at 0.05 *M* substrate. [b]Isolated yields averaged over three trials. [c]Reaction ran in DCE at 50 °C. [d]Reaction ran in DCE at 80 °C

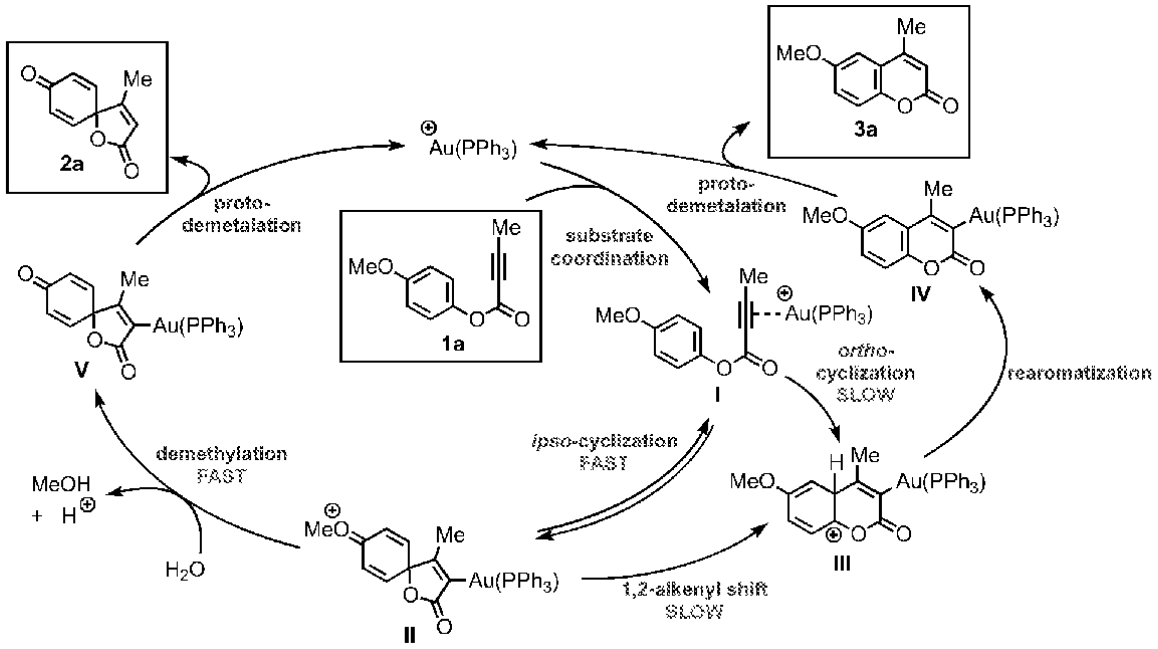
However, when we subjected **1r** to our reaction conditions, no reaction was observed (Table 6, entry 3). Changing the solvent to DCE and heating to 50 °C and 80 °C at prolonged reaction times also failed to produce the spirocycle (Table 6, entries 4 and 5). Presumably, the second ester significantly depolarizes the Au-coordinated alkyne and weakens binding to the Au(I) cation, making the π system inactive to Friedel–Crafts attack by the aromatic ring.

Scheme 17. Synthesis of substrate **1r**



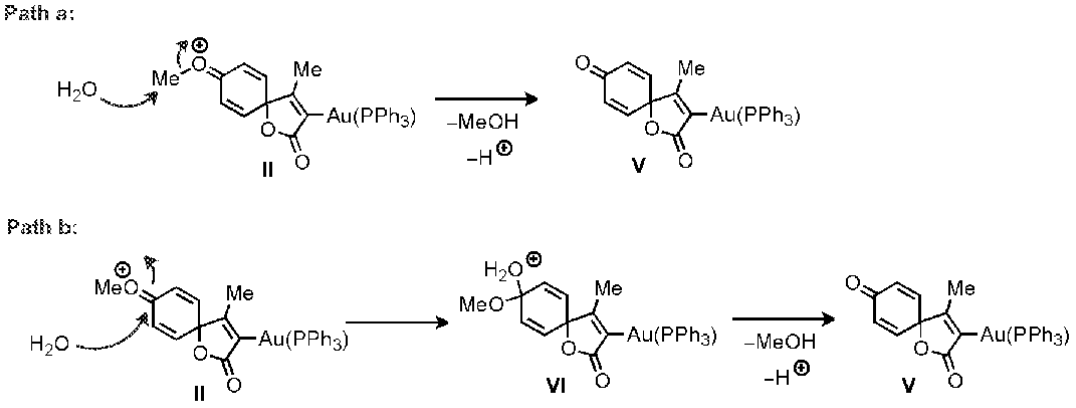
Proposed Mechanism. A proposed reaction mechanism is given in Scheme 18. Coordination of the alkynyl group on **1a** to the Au(I) cation gives complex **I**. The carbon *ipso* to the ester moiety then attacks the activated alkyne in a Friedel–Crafts-type fashion at the position *beta* to the carbonyl, forming the cationic spirocycle **II** as a key reactive intermediate. Under anhydrous conditions, **II** can undergo a slow 1,2-alkenyl shift to give **III**; accessing **III** directly from **I** is unlikely as the carbon with the highest electron density is the *ipso* carbon on the aromatic ring. Furthermore, this 1,2-shift was proposed by Fanghänel and coworkers in their mechanistic studies of iodocyclizations: by substituting various alcohols as the nucleophile in the reaction medium, they observed that the methoxy group on the arene was replaced by the corresponding alkoxy substituent in the coumarin product.[13] This product could only be observed if **II** is formed during the course of the mechanism. Rearomatization of **III** to form **IV** followed by protodemetalation gives the coumarin **3a** and regenerates the gold catalyst.

Scheme 18. Proposed reaction mechanism of the *ipso*- vs. *ortho*-cyclization of **1a**



In the presence of water, however, **II** can readily undergo nucleophilic attack by water to give demethylated intermediate **V** with concomitant liberation of methanol and proton by one of two possible mechanisms: either water can directly attack the methyl group of the oxocarbenium in an S_N2 fashion (Scheme 19, path a), or it can attack the carbonyl carbon to form hemiacetal

Scheme 19. Two possible mechanisms for the formation of **V** from **II**



VI, which then undergoes proton transfer and elimination to reform a carbon-oxygen double bond (Scheme 19, path b); the latter mechanism was proposed by Fanghänel as the most likely pathway.[13]

Protodemetalation of **V** forms the spirocycle **2a** and completes the catalytic cycle. The spirocyclic product is always observed by TLC at the onset of the reaction, implying that its formation is quite fast. The undesired coumarin product is observed to form much later over the course of the reaction. Thus, nucleophilic attack by water on **II** to give **V** must occur much faster than the competing 1,2-alkenyl shift to give **III**. This is also compelling evidence for the facile *ipso*-cyclization of **I** as a key step to form **II** rather than the less favorable *ortho*-cyclization to form **III**.

III. Summary and Future Directions

A new method to synthesize spirocycles via the redox-neutral *ipso*-cyclization of *para*-methoxy aryl alkynoate esters was developed and its scope investigated. This transformation utilizes a gold catalyst as a benign alternative to spirocyclization methods reported in the past decade which employ stoichiometric amounts of halogen-based reagents. Furthermore, this reaction proceeds under ambient conditions and with 1 equivalent of water, precluding the need to use moisture-free techniques required of most other methods. Both electron-rich and electron-deficient aromatic rings were well-tolerated under these reaction conditions.

Future projects could explore the spirocyclization of substrates such as aryl alkynamides **14** and alkynyl benzyl ketones **15**, or even homologized species such as **16** (Figure 2). It would also be interesting to test substrates that lack the carbonyl group such as propargyl ethers **17**, propargyl amines **18**, and homopropargyl substrates **19**; we anticipate that these substrates would require more forcing conditions as the removal of the electron-withdrawing carbonyl moiety significantly decreases the polarizability of the alkyne, which may be crucial for the reactivity and/or regiospecificity of our reaction. Nevertheless, these substrates would diversify the types of spirocyclic products that could be accessed using transition metal catalysis.

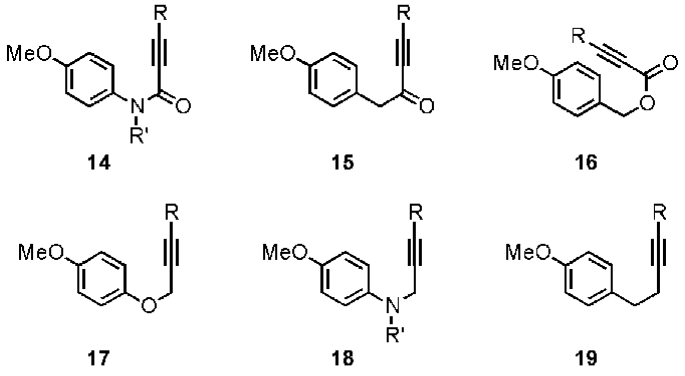


Figure 2. Potential substrates for spirocyclization

Another future project could explore conditions that render this transformation stereoselective, which has hitherto been unreported. During our catalyst screen, we observed that the chiral catalyst [(*R*)-BINAP]Pd(OTf)$_2$·H$_2$O was capable of forming the spirocyclic product of our lead substrate (Table 3, entry 4), a promising find in spite of the low yield. Reactions with a

high level of stereochemical induction are highly desirable, and this potential modification to our methodology would add to the ever-growing toolbox of stereoselective reactions.

Perhaps even more exciting would be the application of our method to the synthesis of a natural product, especially if an enantioselective variant of our reaction were developed. The spirocyclic core of the perenniporide A **13** was easily accessed during the course of this reaction's development, so even if the total synthesis of this molecule using our gold-catalyzed spirocyclization reaction does not come to fruition in the near future, this preliminary result suggests that it is possible.

IV. Experimental Procedures and Characterization Data

General Remarks

All chemicals were obtained from commercial courses and were used without further purification. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker 300 instrument. ^{1}H NMR spectra recorded in $CDCl_3$ solutions were referenced to TMS (0.00 ppm). ^{1}H NMR spectra recorded in DMSO-d_6 solutions were referenced to the residual solvent peak at 2.50 ppm. ^{13}C NMR spectra recorded in $CDCl_3$ and DMSO-d_6 were referenced to the residual solvent peaks at 77.16 ppm and 39.52 ppm, respectively. High-resolution mass spectra (HRMS) were acquired by electrospray ionization (ES+). Reactions were monitored by TLC analysis using EtOAc/hexanes and/or Et_2O/hexanes mixtures as the eluent and visualized using UV light followed by potassium permanganate stain and/or ceric ammonium molybdate stain. Flash column chromatography was conducted on silica gel (230-400 mesh).

General Procedure for the DIC-promoted Esterification of 4-Methoxyphenols and Alkynoic Acids. A procedure described previously was followed with minor modifications.[27] To a solution of alkynoic acid (1.2 equiv.) in dichloromethane (DCM, 0.25 *M*) cooled to 0 °C in an ice-water bath was added diisopropylcarbodiimide (DIC, 1.5 equiv.) and the solution was stirred for 5 minutes. 4-methoxyphenol (1 equiv.) was added followed by a solution of 4-(dimethylamino)pyridine (DMAP) in DCM (10 mol %, 0.5 *M*), and the reaction mixture was stirred at 0 °C. Upon consumption of the starting material as determined by TLC, the reaction mixture was passed through a pad of Celite which was washed with a minimal amount of DCM. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography to afford pure product.

4-methoxyphenyl 2-butynoate (1a). The general procedure was followed using 2-butynoic acid and 4-methoxyphenol. The reaction mixture was stirred at 0 °C for 30 minutes. Isolation by flash column chromatography (10% Et_2O/hexanes) afforded **1a** (85%) as an amorphous white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.05 (d, J = 9.3 Hz, 2H), 6.89 (d, J = 9.0 Hz, 2H), 3.80 (s, 3H), 2.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.6, 152.4, 143.5, 122.2, 114.5, 87.9, 72.1, 55.6, 4.0; HRMS (ES+) *m/z* calcd. for $C_{11}H_{11}O_3$ $[M+H]^+$ 191.0708, found 191.0706.

4-methoxyphenyl 2-pentynoate (1b). The general procedure was followed using 2-pentynoic acid and 4-methoxyphenol. The reaction mixture was stirred at 0 °C for 1 hour. Isolation by flash column chromatography (10% Et_2O/hexanes) afforded **1b** (82%) as a viscous yellow oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.05 (d, J = 9.3 Hz, 2H), 6.89 (d, J = 9.3 Hz, 2H), 3.80 (s, 3H), 2.41 (q, J = 7.5 Hz, 2H), 1.25 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.7, 152.7, 143.7, 122.3, 114.6, 93.2, 72.3, 55.7, 12.7, 12.6; HRMS (ES+) *m/z* calcd. for $C_{12}H_{13}O_3$ $[M+H]^+$ 205.0865, found 205.0859.

4-methoxyphenyl 3-phenylpropiolate (1c). The general procedure was followed using phenylpropiolic acid and 4-methoxyphenol. The reaction mixture was stirred at 0 °C for 90 minutes. Isolation by flash column chromatography (10% Et_2O/hexanes) afforded **1c** (75%) as an amorphous white solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.63 (d, J = 6.9 Hz, 2H), 7.49 (m, 1H), 7.41 (m, 2H), 7.11 (d, J = 9.3 Hz, 2H), 6.92 (d, J = 9.0 Hz, 2H), 3.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.7, 152.8, 143.6, 133.2, 131.0, 128.7, 122.2, 119.3, 114.6, 88.6, 80.3, 55.7; HRMS (ES+) *m/z* calcd. for $C_{16}H_{13}O_3$ $[M+H]^+$ 253.0865, found 253.0859.

4-methoxyphenyl propiolate (1d). The general procedure was followed using propiolic acid and 4-methoxyphenol. The reaction mixture was stirred at 0 °C for 1 hour. Isolation by flash column chromatography (10% Et_2O/hexanes) afforded **1d** (59%) as an amorphous white solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.07 (d, J = 9.3 Hz, 2H), 6.90 (d, J = 9.3 Hz, 2H), 3.80 (s, 3H), 3.06 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 157.5, 151.2, 142.8, 122.4, 114.6, 81.4, 74.3, 55.5; HRMS (ES+) *m/z* calcd. for $C_{10}H_9O_3$ $[M+H]^+$ 177.0552, found 177.0548.

4-methoxyphenyl 3-(trimethylsilyl)propiolate (1e). The general procedure was followed using 3-(trimethylsilyl)propiolic acid and 4-methoxyphenol. The reaction mixture was stirred at 0 °C for 40 minutes. Isolation by flash column chromatography (5% Et_2O/hexanes) afforded **1e** (37%) as a viscous yellow oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.05 (d, J = 9.3 Hz, 2H), 6.89 (d, J = 9.0 Hz, 2H), 3.79 (s, 3H), 0.28 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.8, 151.8, 143.6, 122.3, 114.7, 96.7, 94.2, 55.7, –0.8; HRMS (ES+) *m/z* calcd. for $C_{13}H_{17}O_3Si$ $[M+H]^+$ 249.0947, found 249.0943.

4-methoxy-2-methylphenyl 2-butynoate (1f). The general procedure was followed using 2-butynoic acid and 4-methoxy-2-methylphenol. The reaction mixture was stirred at 0 °C for 20 minutes. Isolation by flash column chromatography (5% Et_2O/hexanes) afforded **1f** (61%) as an amorphous white solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 6.95 (d, J = 8.4 Hz, 1H), 6.77–6.70

(m, 2H), 3.78 (s, 3H), 2.18 (s, 3H), 2.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.7, 152.4, 142.4, 131.3, 122.5, 116.4, 112.1, 88.0, 72.2, 55.7, 16.6, 4.1; HRMS (ES+) *m/z* calcd. for $C_{12}H_{13}O_3$ $[M+H]^+$ 205.0865, found 205.0858.

4-methoxy-2,6-dimethylphenyl 2-butynoate (1g). The general procedure was followed using 2-butynoic acid and 4-methoxy-2,6-dimethylphenol. The reaction mixture was stirred at 0 °C for 3 hours. Isolation by flash column chromatography (10% Et_2O/hexanes) afforded **1g** (48%) as an amorphous white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.60 (s, 2H), 3.76 (s, 3H), 2.15 (s, 6H), 2.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.4, 152.1, 141.3, 131.2, 113.8, 87.8, 72.1, 55.6, 16.7, 4.1; HRMS (ES+) *m/z* calcd. for $C_{13}H_{15}O_3$ $[M+H]^+$ 219.1021, found 219.1017.

4-methoxy-3-methylphenyl 2-butynoate (1h). The general procedure was followed using 2-butynoic acid and 4-methoxy-3-methylphenol. The reaction mixture was stirred at 0 °C for 90 minutes. Isolation by flash column chromatography (20% Et_2O/hexanes) afforded **1h** (81%) as an amorphous white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.93–6.90 (m, 2H), 6.79 (m, 1H), 3.81 (s, 3H), 2.20 (s, 3H), 2.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 115.9, 152.7, 143.2, 128.2, 123.5, 119.1, 110.4, 87.9, 72.3, 55.8, 16.4, 4.1; HRMS (ES+) *m/z* calcd. for $C_{12}H_{13}O_3$ $[M+H]^+$ 205.0865, found 205.0860.

4-methoxy-3,5-dimethylphenyl 2-butynoate (1i). The general procedure was followed using 2-butynoic acid and 4-methoxy-3,5-dimethylphenol. The reaction mixture was stirred at 0 °C for 25 minutes. Isolation by flash column chromatography (20% Et_2O/hexanes) afforded **1i** (80%) as an amorphous white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.76 (s, 2H), 3.70 (s, 3H), 2.27 (s, 6H), 2.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.1, 152.5, 145.5, 132.3, 121.3, 87.9, 72.3, 59.9, 16.3, 4.1; HRMS (ES+) *m/z* calcd. for $C_{13}H_{15}O_3$ $[M+H]^+$ 219.1021, found 219.1015.

2,4-dimethoxyphenyl 2-butynoate (1j). The general procedure was followed using 2-butynoic acid and 2,4-dimethoxyphenol. The reaction mixture was stirred at 0 °C for 90 minutes. Isolation by flash column chromatography (5% Et_2O/hexanes) afforded **1j** (60%) as a viscous yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.98 (d, J = 8.7 Hz, 1H), 6.54 (d, J = 2.7 Hz, 1H), 6.44 (dd, J = 8.7 Hz, J = 2.7 Hz, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 2.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.9, 152.1, 151.8, 132.9, 122.8, 104.0, 100.4, 88.0, 72.1, 56.0, 55.8, 4.1; HRMS (ES+) *m/z* calcd. for $C_{12}H_{13}O_4$ $[M+H]^+$ 221.0814, found 221.0811.

2-methoxyphenyl 2-butynoate (1k). The general procedure was followed using 2-butynoic acid and 2-methoxyphenol. The reaction mixture was stirred at 0 °C. Isolation by flash

column chromatography (10% Et_2O/toluene) afforded **1k** (74%) as an amorphous white solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.25–7.19 (m, 1H), 7.09–7.06 (m, 1H), 6.99–6.92 (m, 2H), 3.85 (s, 3H), 2.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 151.6, 151.1, 139.1, 127.5, 122.8, 120.9, 112.6, 88.0, 72.1, 56.0, 4.2; HRMS (ES+) *m/z* calcd. for $C_{11}H_{11}O_3$ $[M+H]^+$ 191.0708, found 191.0706.

2-bromo-4-methoxyphenyl 2-butynoate (1l). The general procedure was followed using 2-butynoic acid and 2-bromo-4-methoxyphenol. The reaction mixture was stirred at 0 °C for 50 minutes. Isolation by flash column chromatography (20% Et_2O/hexanes) afforded **1l** (46%) as an amorphous white solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.14 (d, J = 3.0 Hz, 1H), 7.06 (d, J = 9.0 Hz, 1H), 6.86 (dd, J = 9.0 Hz, J = 3.0 Hz, 1H), 3.79 (s, 3H), 2.08 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.3, 151.6, 141.2, 123.9, 118.4, 116.3, 114.4, 88.9, 71.9, 56.0, 4.2; HRMS (ES+) *m/z* calcd. for $C_{11}H_{10}BrO_3$ $[M+H]^+$ 268.9813, found 268.9809.

2-carbaldehyde-4-methoxyphenyl 2-butynoate (1m). The general procedure was followed using 2-butynoic acid and 2-hydroxy-5-methoxybenzaldehyde. The reaction mixture was stirred at 0 °C for 2 hours. Isolation by flash column chromatography (20% Et_2O/hexanes) and recrystallization from Et_2O/hexanes afforded **2m** (70%) as white needles. ^1H NMR ($CDCl_3$, 300 MHz) δ 10.14 (s, 1H), 7.37 (dd, J = 2.4 Hz, J = 0.9 Hz, 1H), 7.17–7.15 (m, 2H), 3.86 (s, 3H), 2.10 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 188.1, 158.1, 152.0, 145.2, 128.5, 124.4, 122.4, 112.5, 89.5, 71.7, 56.0, 4.2; HRMS (ES+) *m/z* calcd. for $C_{12}H_{11}O_4$ $[M+H]^+$ 219.0657, found 219.0653.

4-methoxynaphthyl 2-butynoate (1p). The general procedure was followed using 2-butynoic acid and 4-methoxy-1-naphthol. The reaction mixture was stirred at 0 °C for 30 minutes. Isolation by flash column chromatography (10% Et_2O/hexanes) afforded **1p** (56%) as an amorphous beige solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.27 (d, J = 7.5 Hz, 1H), 7.84 (d, J = 7.8 Hz, 1H), 7.53 (m, 2H), 7.19 (d, J = 8.4 Hz, 1H), 6.76 (d, J = 8.4 Hz, 1H), 4.00 (s, 3H), 2.10 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.0, 152.7, 139.5, 127.3, 127.3, 126.4, 126.0, 122.6, 121.0, 118.0, 102.9, 88.4, 72.3, 55.9, 4.2; HRMS (ES+) *m/z* calcd. for $C_{15}H_{13}O_3$ $[M+H]^+$ 241.0865, found 241.0863.

4-methoxynaphthyl propiolate (1q). The general procedure was followed using propiolic acid and 4-methoxy-1-naphthol. The reaction mixture was stirred at 0 °C for 1 hour. Isolation by flash column chromatography (10% Et_2O/hexanes) afforded **1q** (57%) as an amorphous beige solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.28 (d, J = 7.8 Hz, 1H), 7.84 (d, J = 7.8

Hz, 1H), 7.55 (m, 2H), 7.22 (d, J = 8.4 Hz, 1H), 6.77 (d, J = 8.4 Hz, 1H), 4.01 (s, 3H), 3.12 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 153.4, 151.4, 138.4, 127.7, 126.4, 126.2, 125.3, 122.1, 120.4, 118.6, 103.6, 82.0, 74.1, 55.9; HRMS (ES+) *m/z* calcd. for $C_{14}H_{11}O_3$ $[M+H]^+$ 227.0708, found 227.0703.

Synthesis of 4-methoxyphenyl 3-bromopropiolate (1n). Following a literature procedure for the bromination of terminal alkynes,[36] $AgNO_3$ (25.5 mg, 0.15 mmol, 0.1 equiv) was added to a solution of 4-methoxyphenyl propiolate (264.0 mg, 1.5 mmol, 1 equiv.) in acetone (0.5 *M*) followed by NBS (294.0 mg, 1.65 mmol, 1.1 equiv.). The reaction mixture was stirred at room temperature for 5 minutes. Upon consumption of the starting material as determined by TLC, the reaction mixture was filtered through a pad of Celite which was washed several times with acetone. The filtrate was concentrated under reduced pressure and the residue was purified by flash column chromatography (20% Et_2O/hexanes) to afford **1n** (52%) as an amorphous yellow solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.05 (d, J = 9.0 Hz, 2H), 6.89 (d, J = 9.0 Hz, 2H), 3.79 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.9, 151.3, 143.5, 122.1, 114.7, 72.6, 55.7, 55.3; HRMS (ES+) *m/z* calcd. for $C_{10}H_8BrO_3$ $[M+H]^+$ 254.9657, found 254.9659.

Synthesis of 4-methoxy-3,5-dimethylphenol. Following a modified literature procedure,[33] $[RuCl_2(p\text{-cymene})]_2$ (38.3 mg, 0.0625 mmol), [bis(trifluoroacetoxy)iodo]benzene (PIFA, 1.18 g, 2.75 mmol), DCE (10 mL), and 2,6-dimethylanisole (354 µL, 2.5 mmol) were added to an oven-dried 50 mL round bottom flask. The reaction mixture was stirred at 80 °C for 3 hours under N_2 atmosphere. The reaction mixture was allowed to cool to room temperature, and the solvent was removed *in vacuo*. The remaining residue was dissolved in a 1:1 solution of 10% HCl and THF (40 mL), and the solution was stirred at room temperature for 30 minutes to an hour. The solution was extracted with EtOAc (40 mL × 3), and the combined organic phases were washed with water (80 mL) and brine (40 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Isolation by flash column chromatography (20% Et_2O/hexanes) afforded **4-methoxy-3,5-dimethylphenol** (197 mg, 57%) as an amorphous white solid, whose ^{1}H and ^{13}C NMR spectra are consistent with the literature data.[37]

General Procedure for the *ipso*-Cyclization of Aryl Alkynoates. All reactions were conducted at 0.05 *M* concentration of substrate in DCM with 5 mol % of catalyst and additive. AgOTf (2.6 mg, 0.01 mmol) and $Au(PPh_3)Cl$ (4.9 mg, 0.01 mmol) were weighed into a 4-mL glass vial equipped with a magnetic stir bar. DCM (4 mL) was added to the vial and the solution was stirred for 2 minutes. Water (3.6 μL, 0.2 mmol, 1 equiv.) was added and the solution was stirred for an additional 2 minutes prior to addition of the substrate (0.2 mmol, 1 equiv.). The vial was sealed under air with a solid Teflon lined screw-cap and the reaction mixture was stirred at room temperature. Upon consumption of the starting material as determined by TLC, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography to afford pure product.

2a. The general procedure was followed using **1a** (38.0 mg, 0.2 mmol). The reaction mixture was stirred at room temperature for 30 minutes. Isolation by flash column chromatography (50% Et_2O/hexanes) afforded **2a** (31.6 mg, 90%) as an amorphous white solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 6.53 (d, J = 10.5 Hz, 2H), 6.46 (d, J = 10.5 Hz, 2H), 6.10 (q, J = 1.5 Hz, 1H), 1.93 (d, J = 1.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 184.0, 171.3, 166.4, 143.2, 131.9, 119.3, 83.9, 12.6; HRMS (ES+) *m/z* calcd. for $C_{10}H_9O_3$ $[M+H]^+$ 177.0552, found 177.0549.

2b. The general procedure was followed using **1b** (40.8 mg, 0.2 mmol). The reaction mixture was stirred at room temperature for 40 minutes. Isolation by flash column chromatography (50% Et_2O/hexanes) afforded **2b** (32.6 mg, 86%) as an amorphous white solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 6.54 (d, J = 10.2 Hz, 2H), 6.44 (d, J = 10.2 Hz, 2H), 6.09 (t, J = 1.8 Hz, 1H), 2.15 (qd, J = 7.2 Hz, J = 1.8 Hz, 2H), 1.21 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 184.1, 172.6, 171.4, 143.5, 131.7, 117.4, 83.6, 20.1, 11.5; HRMS (ES+) *m/z* calcd. for $C_{11}H_{11}O_3$ $[M+H]^+$ 191.0708, found 191.0706.

2c. The general procedure was followed using **1c** (50.4 mg, 0.2 mmol). The reaction mixture was stirred at room temperature for 1 hour. Isolation by flash column chromatography (40% Et_2O/hexanes) afforded **2c** (40.2 mg, 85%) as an amorphous white solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.52–7.46 (m, 3H), 7.42–7.37 (m, 2H), 6.72 (d, J = 10.2 Hz, 2H), 6.57 (s, 1H), 6.51 (d, J = 9.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 184.2, 170.6, 165.4, 143.5, 132.2, 131.9, 129.5, 129.0, 127.3, 117.0, 81.5; HRMS (ES+) *m/z* calcd. for $C_{15}H_{11}O_3$ $[M+H]^+$ 239.0708, found 239.0706.

2d. The general procedure was followed using **1d** (35.2 mg, 0.2 mmol). The reaction mixture was stirred at room temperature for 3 hours. Isolation by flash column chromatography (50% Et_2O/hexanes) afforded **2d** (24.0 mg, 74%) as an amorphous white solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.17 (d, J = 5.7 Hz, 1H), 6.55 (d, J = 10.2 Hz, 2H), 6.41 (d, J = 10.2 Hz, 2H), 6.36 (d, J = 5.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 183.7, 171.5, 154.5, 142.4, 131.4,123.8, 82.0; HRMS (ES+) *m/z* calcd. for $C_9H_6O_3$ $[M+Na]^+$ 185.0215, found 185.0219.

2f. The general procedure was followed using **1f** (40.8 mg, 0.2 mmol). The reaction mixture was stirred at room temperature for 50 minutes. Isolation by flash column chromatography (50% Et_2O/hexanes) afforded **2f** (36.7 mg, 97%) as an amorphous white solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 6.48 (d, J = 9.9 Hz, 1H), 6.42 (dd, J = 9.9 Hz, J = 1.5 Hz, 1H), 6.33 (q, J = 1.5 Hz, 1H), 6.14 (q, J = 1.5 Hz, 1H), 1.85 (d, J = 1.5 Hz, 3H), 1.82 (d, J = 1.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 184.7, 171.8, 166.9, 152.5, 143.4, 131.6, 130.0, 119.5, 86.0, 16.8, 12.3; HRMS (ES+) *m/z* calcd. for $C_{11}H_{11}O_3$ $[M+H]^+$ 191.0708, found 191.0703.

2g. The general procedure was followed using **1g** (43.6 mg, 0.2 mmol). The reaction mixture was stirred at room temperature for 30 minutes. Isolation by flash column chromatography (50% Et_2O/hexanes) afforded **2g** (42.0 mg, quantitative yield) as an amorphous white solid. ^1H NMR (DMSO-d_6, 300 MHz) δ 6.48 (q, J = 1.5 Hz, 1H), 6.35 (s, 2H), 1.77 (d, J = 1.5 Hz, 3H), 1.75 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 184.5, 172.3, 167.5, 152.6, 129.9, 119.6, 88.4, 16.7, 12.1; HRMS (ES+) *m/z* calcd. for $C_{12}H_{13}O_3$ $[M+H]^+$ 205.0865, found 205.0865.

2h. The general procedure was followed using **1h** (40.8 mg, 0.2 mmol). The reaction mixture was stirred at room temperature for 30 minutes. Isolation by flash column chromatography (40% Et_2O/hexanes) afforded **2h** (32.7 mg, 90%) as an amorphous white solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 6.50 (dd, J = 10.2 Hz, J = 3.0 Hz, 1H), 6.44 (d, J = 9.9 Hz, 1H), 6.29 (q, J = 1.5 Hz, 1H), 6.05 (d, J = 1.2 Hz, 1H), 1.97 (d, J = 1.2 Hz, 3H), 1.90 (d, J = 1.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 184.9, 171.5, 167.0, 143.0, 139.3, 138.1, 131.8, 118.9, 84.5, 15.9, 12.7; HRMS (ES+) *m/z* calcd. for $C_{11}H_{11}O_3$ $[M+H]^+$ 191.0708, found 191.0706.

2i. The general procedure was followed using **1i** (43.6 mg, 0.2 mmol). The reaction mixture was stirred at room temperature for 30 minutes. Isolation by flash column chromatography (40% Et_2O/hexanes) afforded **2i** (26.7 mg, 65%) as an amorphous white solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 6.26 (s, 2H), 6.01 (d, J = 1.2 Hz, 1H), 1.97 (s, 6H), 1.88 (d, J =

1.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 185.7, 171.8, 167.6, 139.0, 137.9, 118.5, 84.5, 16.1, 12.7; HRMS (ES+) *m/z* calcd. for $C_{12}H_{13}O_3$ $[M+H]^+$ 205.0865, found 205.0861.

2j. The general procedure was followed using **1j** (44.0 mg, 0.2 mmol). The reaction mixture was stirred at room temperature for 1 hour. Isolation by flash column chromatography (75% Et_2O/hexanes) afforded **2j** (37.7 mg, 92%) as an amorphous white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.39 (dd, J = 9.9 Hz, J = 1.5 Hz, 1H), 6.30 (d, J = 9.9 Hz, 1H), 6.08 (q, J = 1.5 Hz, 1H), 5.74 (d, J = 1.5 Hz, 1H), 3.75 (s, 3H), 1.89 (d, J = 1.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 186.0, 171.7, 167.4, 165.6, 139.0, 131.6, 119.3, 104.3, 83.8, 56.6, 12.5; HRMS (ES+) *m/z* calcd. for $C_{11}H_{11}O_4$ $[M+H]^+$ 207.0657, found 207.0653.

2l. The general procedure was followed using **1l** (53.8 mg, 0.2 mmol). The reaction mixture was stirred at room temperature for 1 hour. Isolation by flash column chromatography (50% Et_2O/hexanes) afforded **2l** (43.7 mg, 86%) as an amorphous white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.94 (d, J = 1.5 Hz, 1H), 6.65 (d, J = 9.9 Hz, 1H), 6.51 (dd, J = 9.9 Hz, J = 1.5 Hz, 1H), 6.21 (q, J = 1.5 Hz, 1H), 1.91 (d, J = 1.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 184.0, 171.3, 166.4, 143.2, 131.9, 119.3, 83.9, 12.6; HRMS (ES+) *m/z* calcd. for $C_{10}H_8BrO_3$ $[M+H]^+$ 254.9657, found 254.9662.

2m. The general procedure was followed using **1m** (43.6 mg, 0.2 mmol). The reaction mixture was stirred at room temperature for 2 hours. Isolation by flash column chromatography (50% Et_2O/hexanes) afforded **2m** (9.5 mg, 23%) as an amorphous yellow solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.68 (d, J = 0.3 Hz, 1H), 7.00 (d, J = 1.5 Hz, 1H), 6.56 (dd, J = 9.9 Hz, J = 1.5 Hz, 1H), 6.49 (dd, J = 9.9 Hz, J = 0.3 Hz, 1H), 6.20 (q, J = 1.5 Hz, 1H), 1.85 (d, J = 1.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 189.6, 184.4, 171.2, 164.2, 145.3, 144.9, 140.9, 131.2, 120.3, 82.5, 12.5; HRMS (ES+) *m/z* calcd. for $C_{11}H_9O_4$ $[M+H]^+$ 205.0501, found 205.0502.

2n. The general procedure was followed using **1n** (51.0 mg, 0.2 mmol). The reaction mixture was stirred at room temperature for 22 hours. Isolation by flash column chromatography (20% Et_2O/hexanes) afforded **2n** (35.2 mg, 73%) as an amorphous beige solid. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.154 (s, 1H), 6.93 (d, J = 9.9 Hz, 2H), 6.54 (d, J = 9.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 183.5, 168.7, 150.4, 141.0, 133.1, 124.1, 84.4; HRMS (ES+) *m/z* calcd. for $C_9H_6BrO_3$ $[M+H]^+$ 240.9500, found 240.9502.

2p. The general procedure was followed using **1p** (48.0 mg, 0.2 mmol). The reaction mixture was stirred at room temperature for 10 hours. Isolation by flash column chromatography

(50% Et_2O/hexanes) afforded **2p** (40.3 mg, 89%) as an amorphous white solid. ^1H NMR (DMSO-d_6, 300 MHz) δ 8.07 (dd, J = 7.8 Hz, J = 1.2 Hz, 1H), 7.75 (dt, J = 7.5 Hz, J = 1.5 Hz, 1H), 7.65 (dt, J = 7.5 Hz, J = 1.2 Hz, 1H), 7.28 (dd, J = 7.8 Hz, J = 0.9 Hz, 1H), 7.00 (d, J = 10.2 Hz, 1H), 6.68 (d, J = 9.9 Hz, 1H), 6.43 (q, J = 1.5 Hz, 1H), 1.65 (d, J = 1.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 183.3, 172.3, 169.4, 143.6, 136.7, 133.8, 132.0, 130.9, 129.9, 127.4, 125.4, 117.7, 84.9, 12.7; HRMS (ES+) *m/z* calcd. for $C_{14}H_{11}O_3$ $[M+H]^+$ 227.0708, found 227.0701.

2q. The general procedure was followed using **1q** (45.2 mg, 0.2 mmol). The reaction mixture was stirred at room temperature for 4 hours. Isolation by flash column chromatography (25% → 50% Et_2O/hexanes) afforded **2q** (32.7 mg, 77%) as an amorphous white solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.19 (dd, J = 7.8 Hz, J = 1.2 Hz, 1H), 7.63 (dt, J = 7.5 Hz, J = 1.8 Hz, 1H), 7.56 (dt, J = 7.5 Hz, J = 1.2 Hz, 1H), 7.25–7.23 (m, 2H), 6.67 (d, J = 10.2 Hz, 1H), 6.59 (d, J = 10.2 Hz, 1H), 6.37 (d, J = 5.4 Hz, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 182.8, 172.8, 158.4, 144.1, 136.5, 133.7, 130.4, 130.0, 129.8, 126.5, 126.2, 121.2, 82.7; HRMS (ES+) *m/z* calcd. for $C_{13}H_9O_3$ $[M+H]^+$ 213.0552, found 213.0545.

VI. References

1. (a) Shirafuji, H.; Tsubotani, S.; Ishimaru, T.; Harada, S. (Takeda Chem. Ind. Ltd., Japan), *PCT Int. Appl.* WO 9113887 A1 19910919, **1991**. (b) Snider, B. B.; Lin, H. *Org. Lett.* **2000**, *2*, 643–646. (c) Coxon, D. T.; Price, K. R.; Howard, B.; Osman, S. F.; Kalan, E. B.; Zacharius, R. M. *Tetrahedron Lett.* **1974**, *15*, 2921–2924. (d) Blay, G.; Cardona, L.; Collado, A. M.; García, B.; Morcillo, V.; Pedro, J. R. *J. Org. Chem.* **2004**, *69*, 7294–7302. (e) Liu, X.-K.; Ye, J.-L.; Ruan, Y.-P.; Li, Y.-X.; Huang, P.-Q. *J. Org. Chem.* **2013**, *78*, 35–41.

2. Feuerbacher, N.; Vögtle, F.; Windscheidt, J.; Poetsch, E.; Nieger, M. *Synthesis* **1999**, 117–120.

3. (a) Sannigrahi, M. *Tetrahedron* **1999**, *55*, 9007–9071. (b) Kotha, S.; Deb, A. C.; Lahiri, K.; Manivannan, E. *Synthesis* **2009**, 165–193.

4. Posner, G. H.; Hamill, T. G. *J. Org. Chem.* **1988**, *53*, 6031–6035.

5. Kuroda, C.; Hirono, Y. *Tetrahedron Lett.* **1994**, *35*, 6895–6896.

6. Knölker, H.-J.; Jones, P. G.; Graf, R. *Synlett* **1996**, 1155–1158.

7. Kotha, S.; Manivannan, E.; Ganesh, T.; Sreenivasachary, N.; Deb, A. *Synlett* **1999**, 1618–1620.

8. Tamura, Y.; Yakura, T.; Haruta, J.-I.; Kita, Y. *J. Org. Chem.* **1987**, *52*, 3927–3930.

9. Braun, N. A.; Ousmer, M.; Bray, J. D.; Bouchu, D.; Peters, K.; Peters, E.-M.; Ciufolini, M. A. *J. Org. Chem.* **2000**, *65*, 4397–4408.

10. (a) Dohi, T.; Maruyama, A.; Yoshimura, M.; Morimoto, K.; Tohma, H.; Kita, Y. *Angew. Chem. Int. End.* **2005**, *44*, 6193–6196. (b) Dohi, T.; Maruyama, A.; Minamitsuji, Y.; Takenaga, N.; Kita, Y. *Chem. Commun.* **2007**, 1224–1226. (c) Zheng, C.; Wang, L.; Li, J.; Wang, L.; Wang, D. Z. *Org. Lett.* **2013**, *15*, 4046–4049.

11. Miyazawa, E.; Sakamoto, T.; Kikugawa, Y. *J. Org. Chem.* **2003**, *68*, 5429–5432.

12. Zhang, X.; Larock, R. C. *J. Am. Chem. Soc.* **2005**, *127*, 12230–12231.

13. Appel, T. R.; Yehia, N. A. M.; Baumeister, U.; Hartung, H.; Kluge, R.; Ströhl, D.; Fanghänel, E. *Eur. J. Org. Chem.* **2003**, 47–53.

14. (a) Tang, B.-X.; Tang, D.-J.; Tang, S.; Yu, Q.-F.; Zhang, Y.-H.; Liang, Y.; Zhong, P.; Li, J.-H. *Org. Lett.* **2008**, *10*, 1063–1066. (b) Tang, B.-X.; Yin, Q.; Tang, R.-Y.; Li, J.-H. *J. Org. Chem.* **2008**, *73*, 9008–9011. (c) Leon, R.; Jawalekar, A.; Redert, T.; Gaunt, M. J. *Chem. Sci.* **2011**, *2*, 1487–1490. (d) Dohi, T.; Nakae, T.; Ishikado, Y.; Kato, D.; Kita, Y. *Org. Biomol. Chem.* **2011**, *9*, 6899–6902. (e) Jia, M.-Q.; You, S.-L. *Chem. Commun.* **2012**, *48*, 6363–6365. (f) Jia, M.-Q.; Liu, C.; You, S.-L. *J. Org. Chem.* **2012**, *77*, 10996–11001. (g) Tang, B.-X.; Zhang, Y.-H.; Song, R.-J.; Tang, D.-J.; Deng, G.-B.; Wang, Z.-Q.; Xie, Y.-X.; Xia, Y.-Z.; Li, J.-H. *J. Org. Chem.* **2012**, *77*, 2837–2849. (h) Chen, Y.; Liu, X.; Lee, M.; Huang, C.; Inoyatov, I.; Chen, Z.; Perl, A. C.; Hersh, W. H. *Chem. Eur. J.* **2013**, *19*, 9795–9799. (i) Low-Beinart, L.; Sun, X.; Sidman, E.; Kesharwani, T. *Tetrahedron Lett.* **2013**, *54*, 1344–1347.

15. Yin, Q.; You, S.-L. *Org. Lett.* **2012**, *14*, 3526–3529.

16. Fukada, Y.; Utimoto, K. *J. Org. Chem.* **1991**, *56*, 3729–3731.

17. (a) Schultz, M.; Teles, J. H. (BASF AG), *PCT Int. Appl.* WO 9721648 A1 19970619, **1997**. (b) Teles, J. H.; Brode, S.; Chabanas, M. *Angew. Chem. Int. Ed.* **1998**, *37*, 1415–1418.

18. Dyker, G. *Angew. Chem. Int. Ed.* **2000**, *39*, 4237–4239.

19. Xu, Q.; Imamura, Y.; Fujiwara, M.; Souma, Y. *J. Org. Chem.* **1997**, *62*, 1594–1598.

20. Schmidbaur, H. *Naturwiss. Rundsch.* **1995**, *48*, 443–451.

21. Hashmi, A. S. K. *Gold Bull.* **2004**, *37*, 51–65.

22. Reetz, M. T.; Sommer, K. *Eur. J. Org. Chem.* **2003**, 3485–3496.

23. Shi, Z.; He, C. *J. Org. Chem.* **2004**, *69*, 3669–3671.

24. Nevado, C.; Echavarren, A. M.; *Chem. Eur. J.* **2005**, *11*, 3155–3164.

25. Fürstner, A.; Davies, P. W.; *Angew. Chem. Int. Ed.* **2007**, *46*, 3410–3449.

26. (a) Bartlett, N. *Gold Bull.* **1998**, *31*, 22–25. (b) Gorin, D. J.; Toste, D. F. *Nature* **2007**, *446*, 395–403.

27. Vadola, P. A.; Sames, D. *J. Org. Chem.* **2012**, *77*, 7804–7814.

28. (a) Crook, R.; Deering, J.; Fussell, S. J.; Happe, A. M.; Mulvihill, S. *Tetrahedron Lett.* **2010**, *51*, 5181–5184. (b) Tarselli, M. A.; Liu, A.; Gagné, M. R. *Tetrahedron* **2009**, *65*, 1785–1789.

29. (a) Jia, C.; Piao, D.; Oyamada, J.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Science* **2000**, *287*, 1992–1995. (b) Jia, C.; Lu, W.; Oyamada, J.; Kitamura, T.; Matsuda, K.; Irie, M.; Fujiwara, Y. *J. Am. Chem. Soc.* **2000**, *122*, 7252–7263. (c) Nevado, C.; Echavarren, A. M. *Synthesis* **2005**, 167–182. (d) Kitamura, T. *Eur. J. Org. Chem.* **2009**, 1111–1125.

30. Rosenfeld, D. C.; Shekhar, S.; Takemiya, A.; Utsunomiya, M.; Hartwig, J. F. *Org. Lett.* **2006**, *8*, 4179–4182.

31. Edson, J. B.; Wang, Z.; Kramer, E. J.; Coates, G. W. *J. Am. Chem. Soc.* **2008**, *130*, 4968–4977.

32. Correale, M.; Panseri, P.; Romano, U.; Minisci, F. (EniChem Synthesis S.p.A.), *PCT Int. Appl.* EP 0317898 A2 19890531, **1989**.

33. Liu, W.; Ackermann, L. *Org. Lett.* **2013**, *15*, 3484–3486.

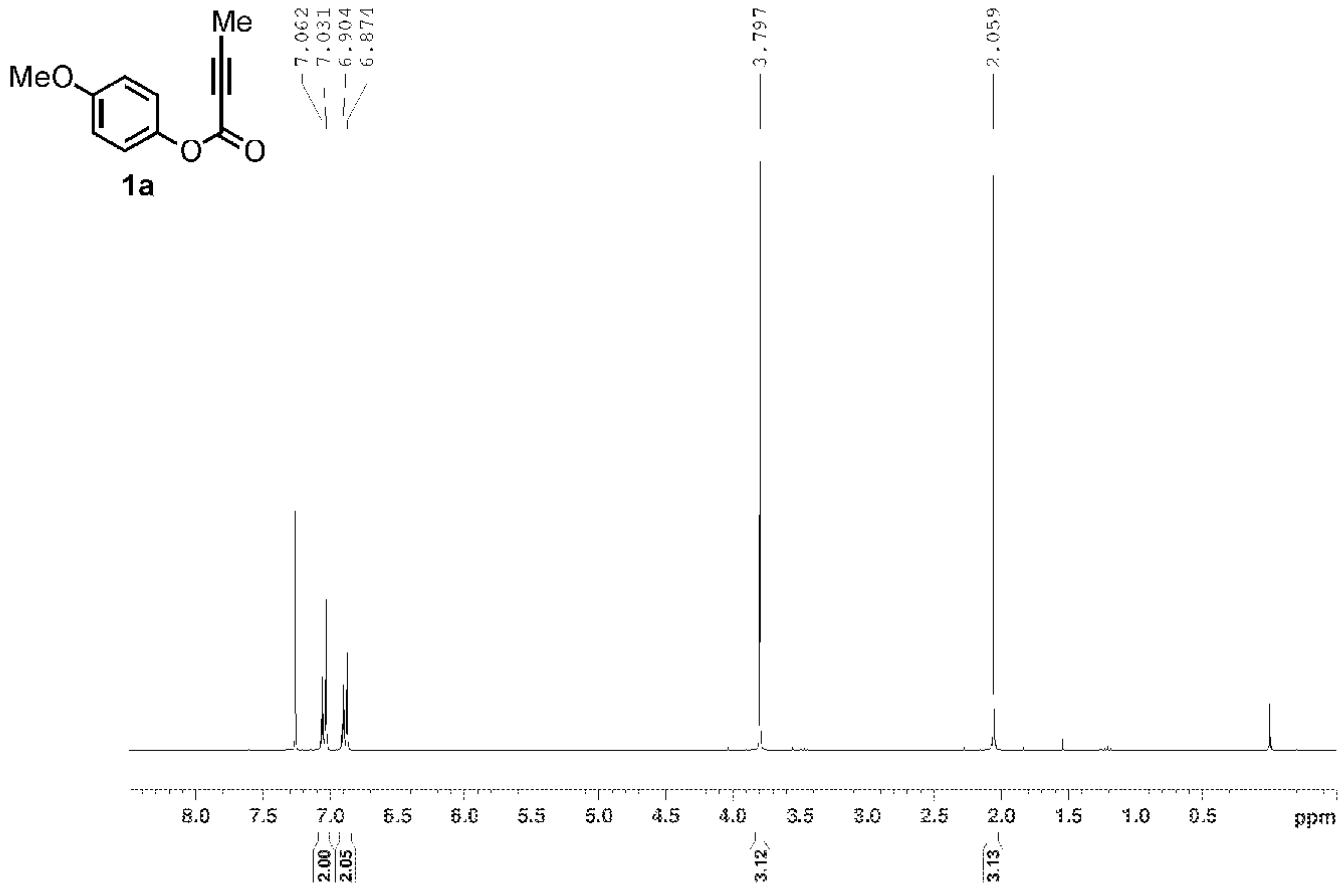
34. (a) Sakai, N.; Komatsu, R.; Uchida, N.; Ikeda, R.; Konakahara, T. *Org. Lett.* **2010**, *12*, 1300–1303. (b) Eckert, T.; Ipaktschi, J. *Synth. Commun.* **1998**, *28*, 327–335. (c) García, D.; Cuadro, A. M.; Alvarez-Builla, J.; Vaquero, J. J. *Org. Lett.* **2004**, *6*, 4175–4178.

35. Feng, Y.; Wang, L.; Niu, S.; Li, L.; Si, Y.; Liu, X.; Che, Y. *J. Nat. Prod.* **2012**, *75*, 1339–1345.

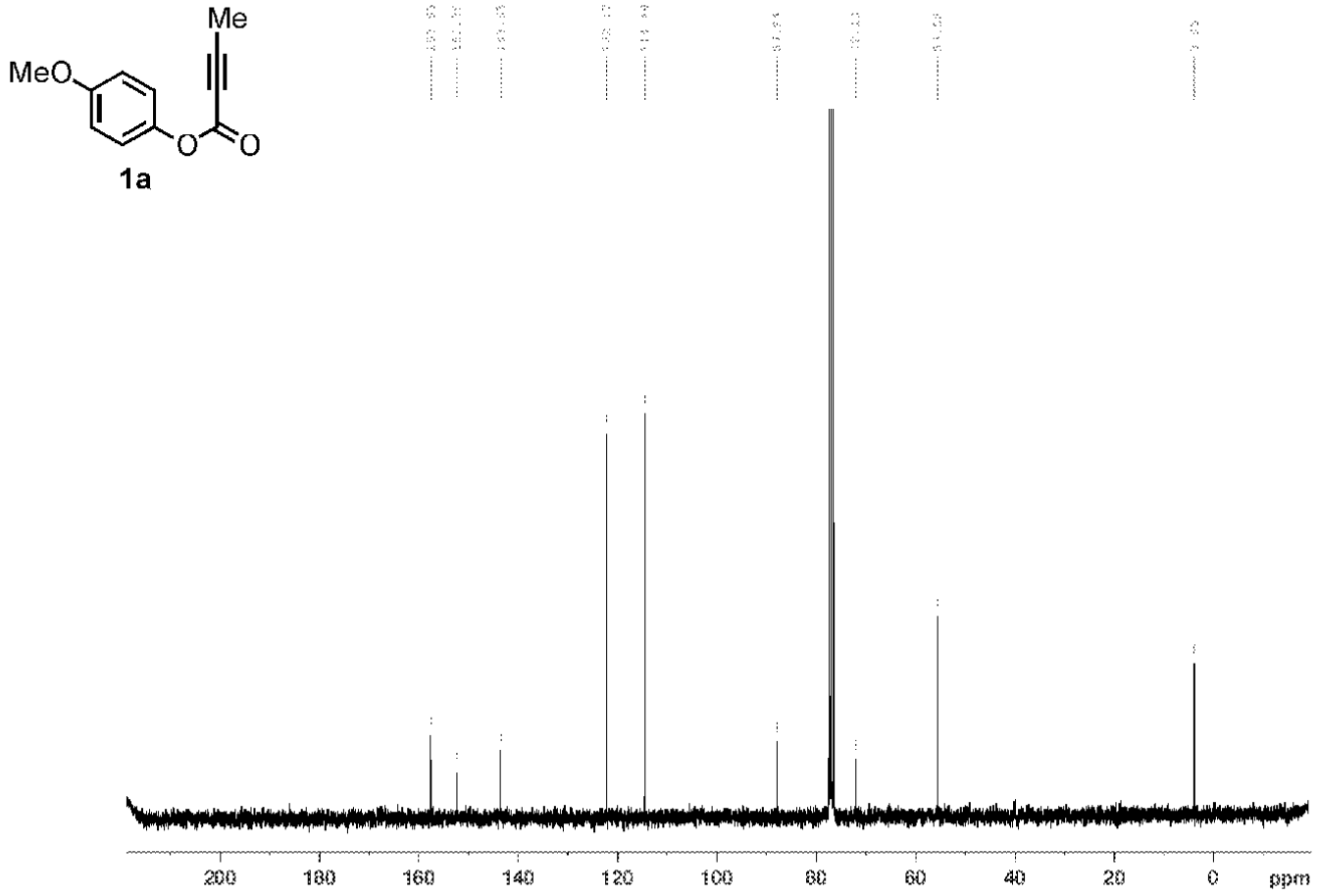
36. Leroy, J. *Org. Synth.* **1997**, *74*, 212.

37. Nakamura, R.; Obora, Y.; Ishii, Y. *Chem. Commun.* **2008**, 3417–3419.

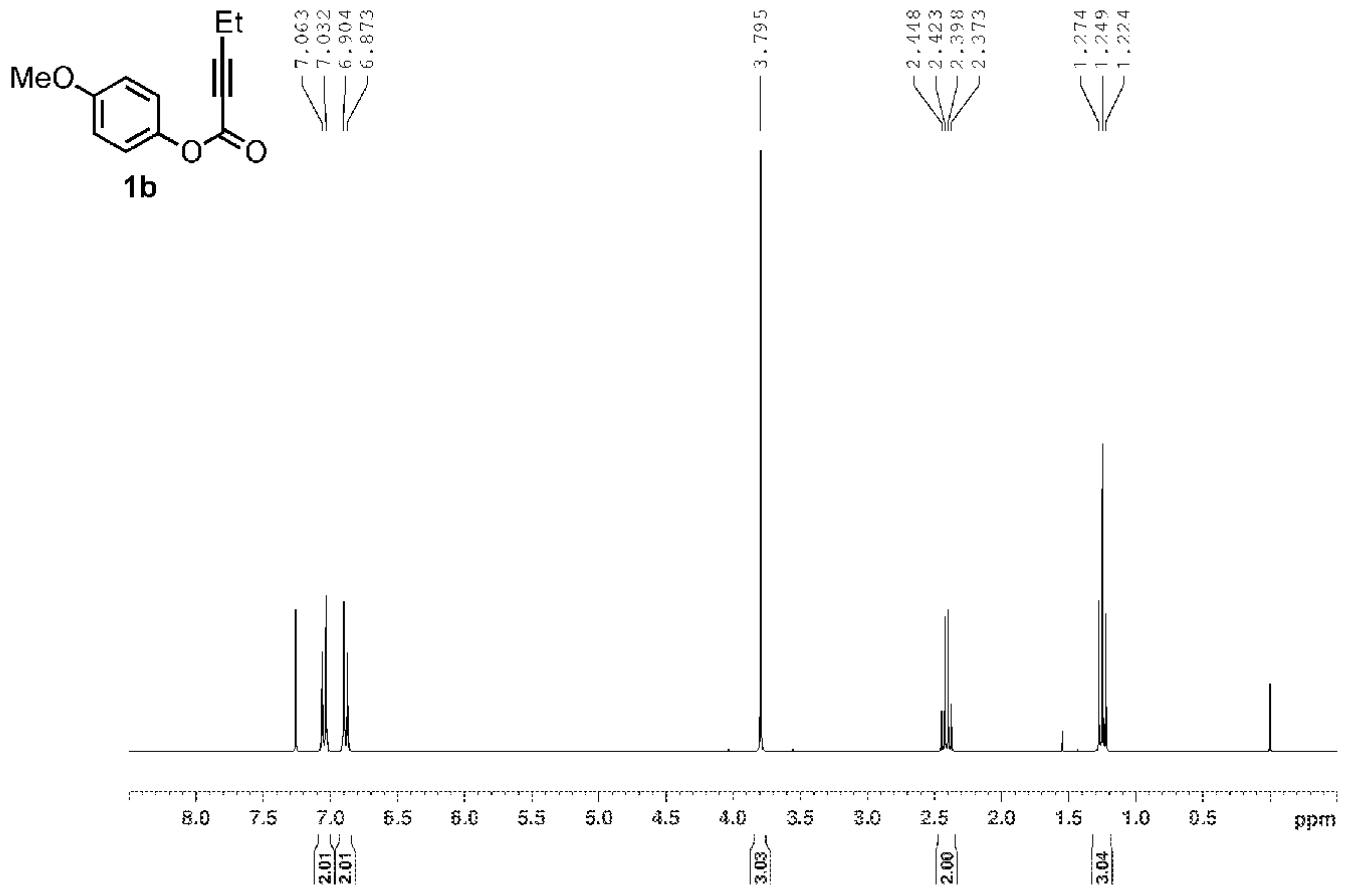
^{1}H NMR spectrum of **1a** recorded in $CDCl_3$



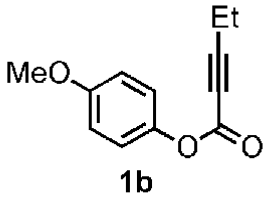
^{13}C NMR spectrum of **1a** recorded in $CDCl_3$



^{1}H NMR spectrum of **1b** recorded in $CDCl_3$

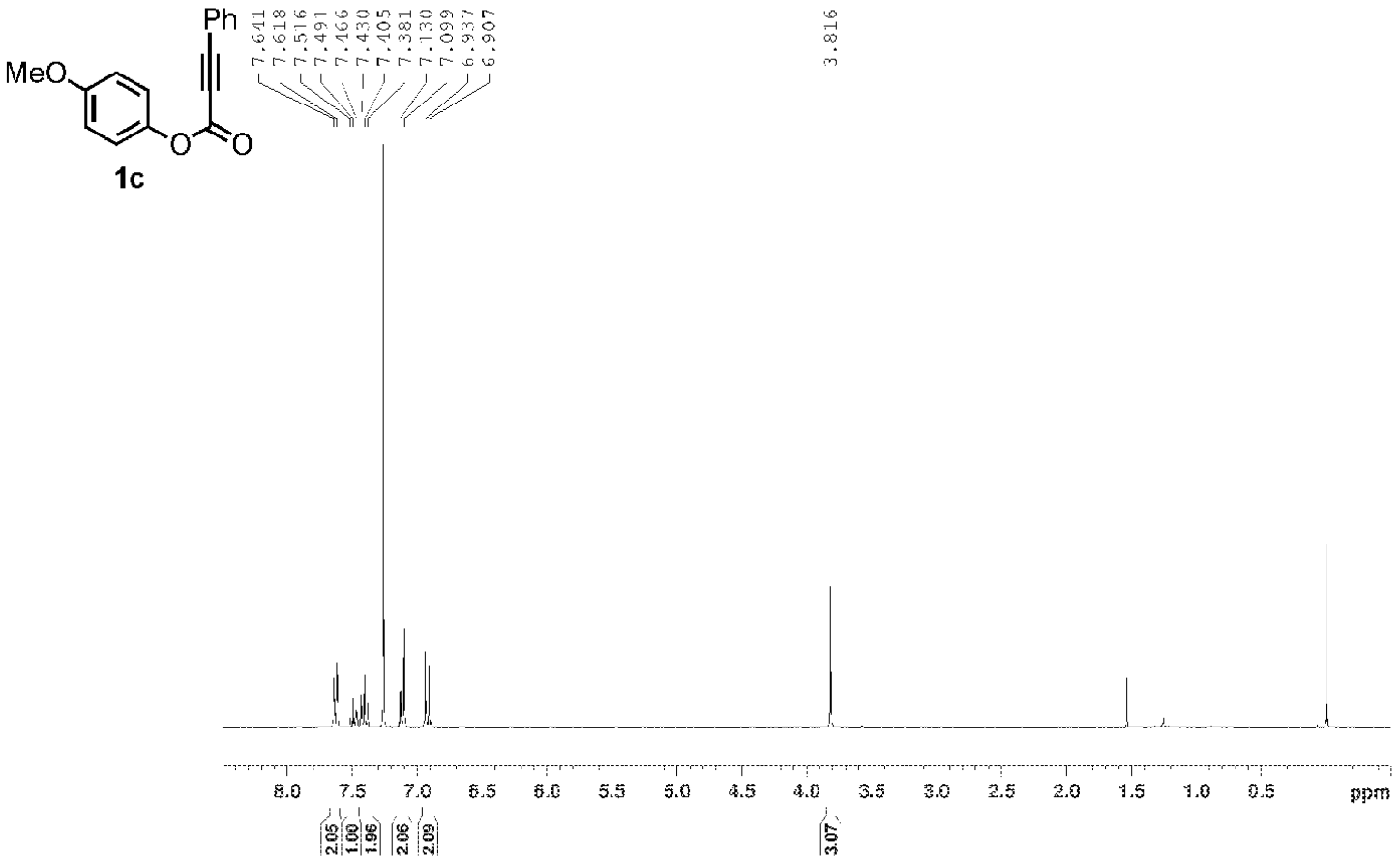


^{13}C NMR spectrum of **1b** recorded in $CDCl_3$

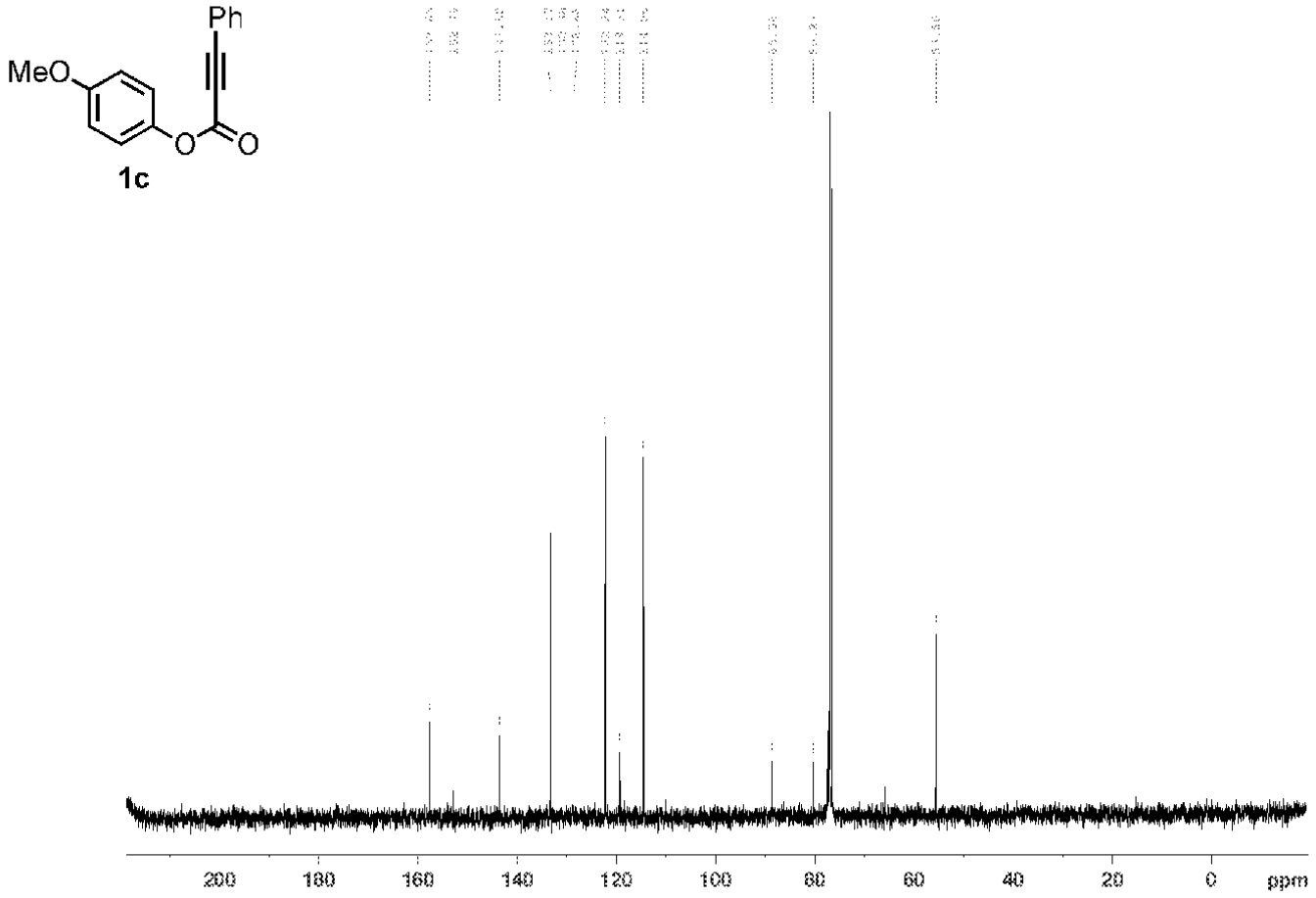


1b

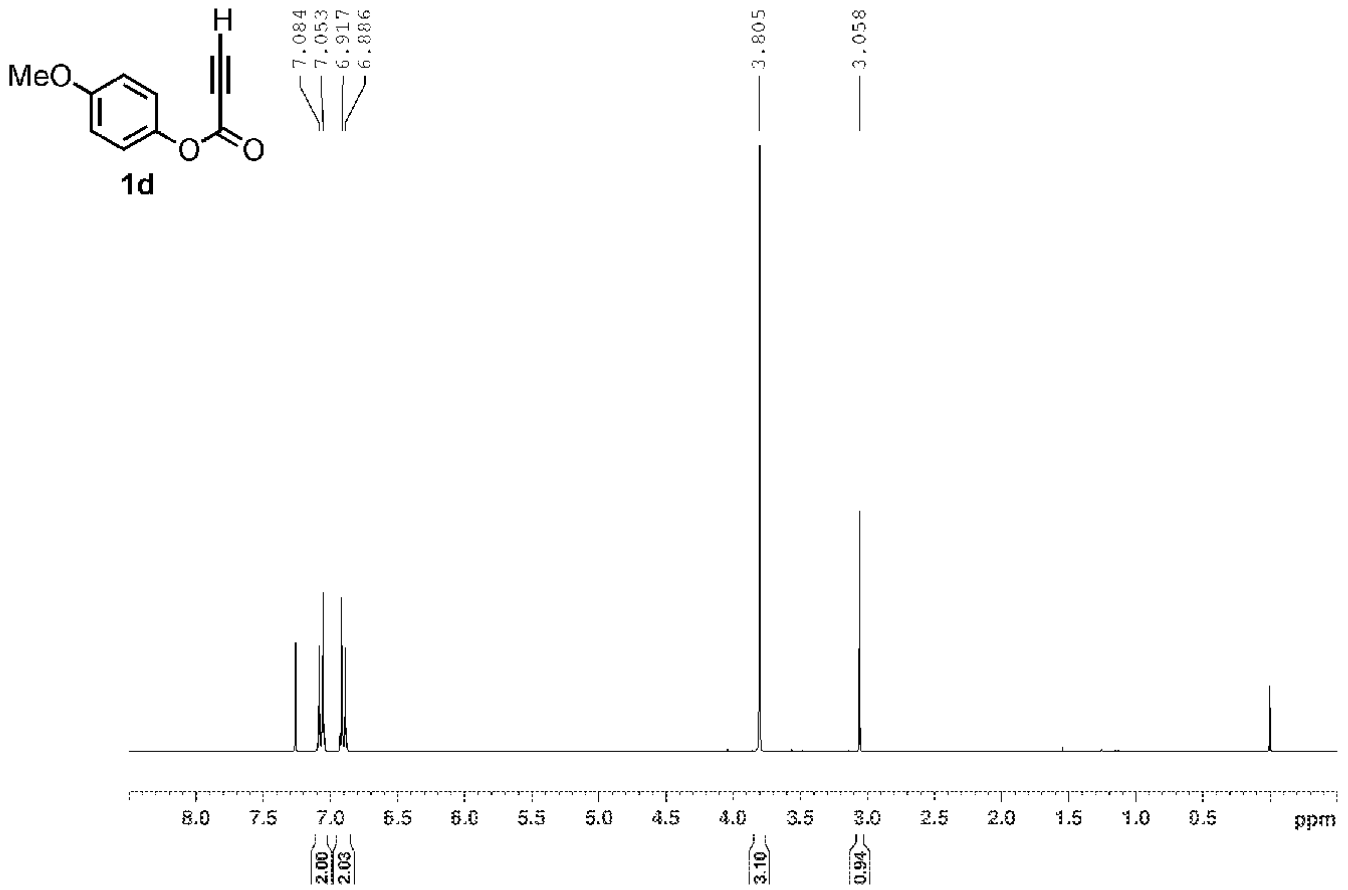
^{1}H NMR spectrum of **1c** recorded in $CDCl_3$



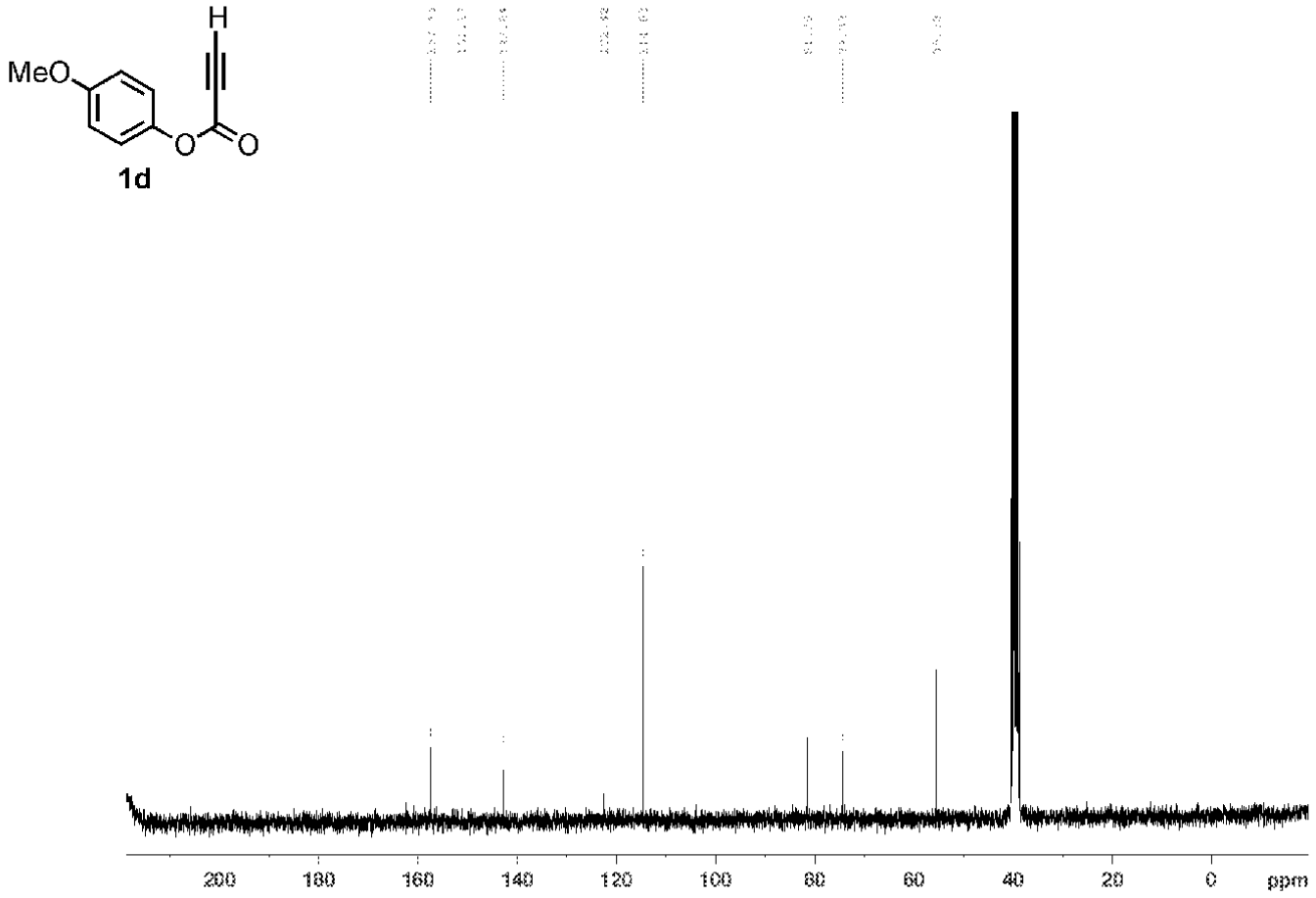
^{13}C NMR spectrum of **1c** recorded in $CDCl_3$



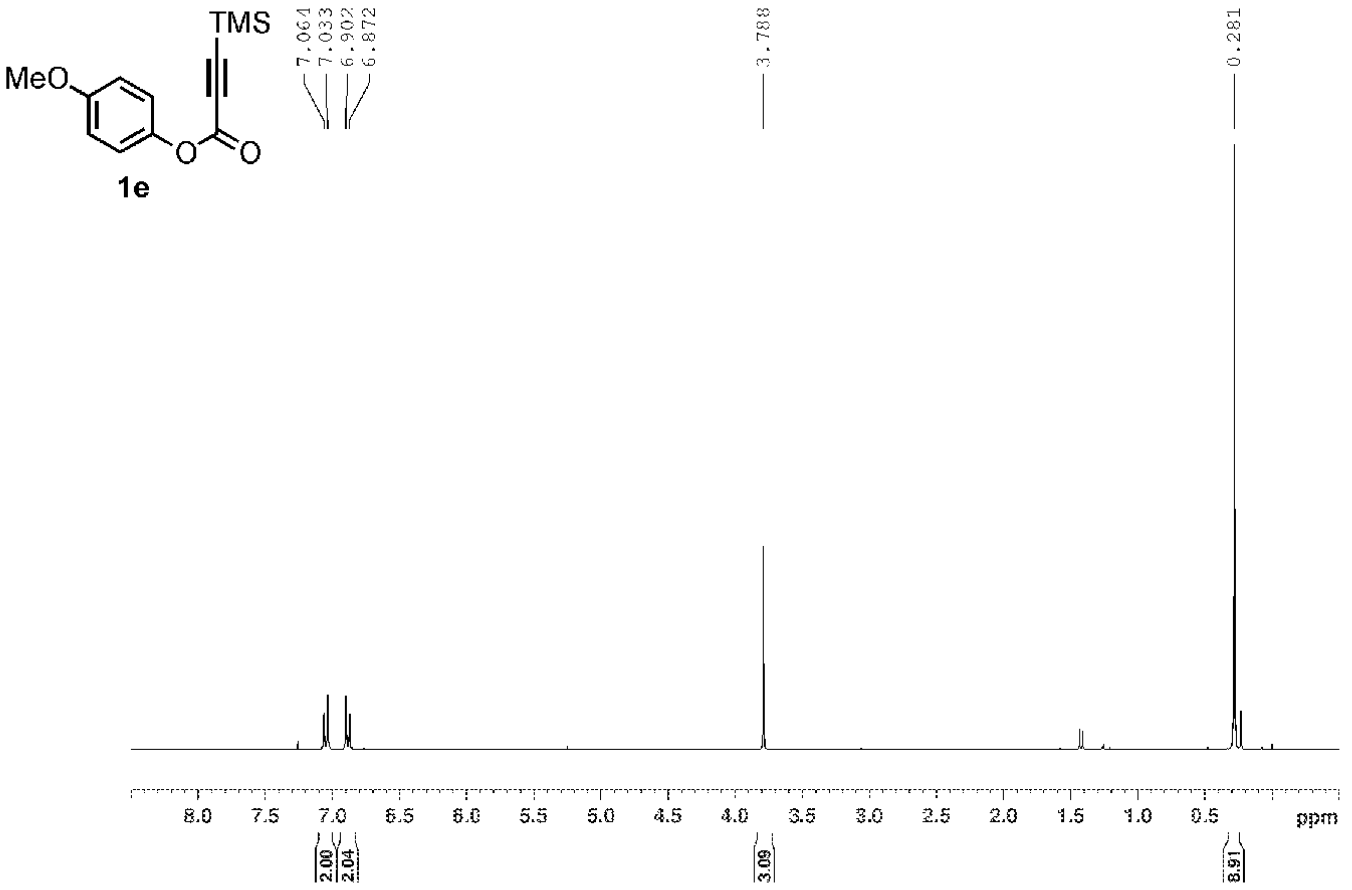
^{1}H NMR spectrum of **1d** recorded in $CDCl_3$



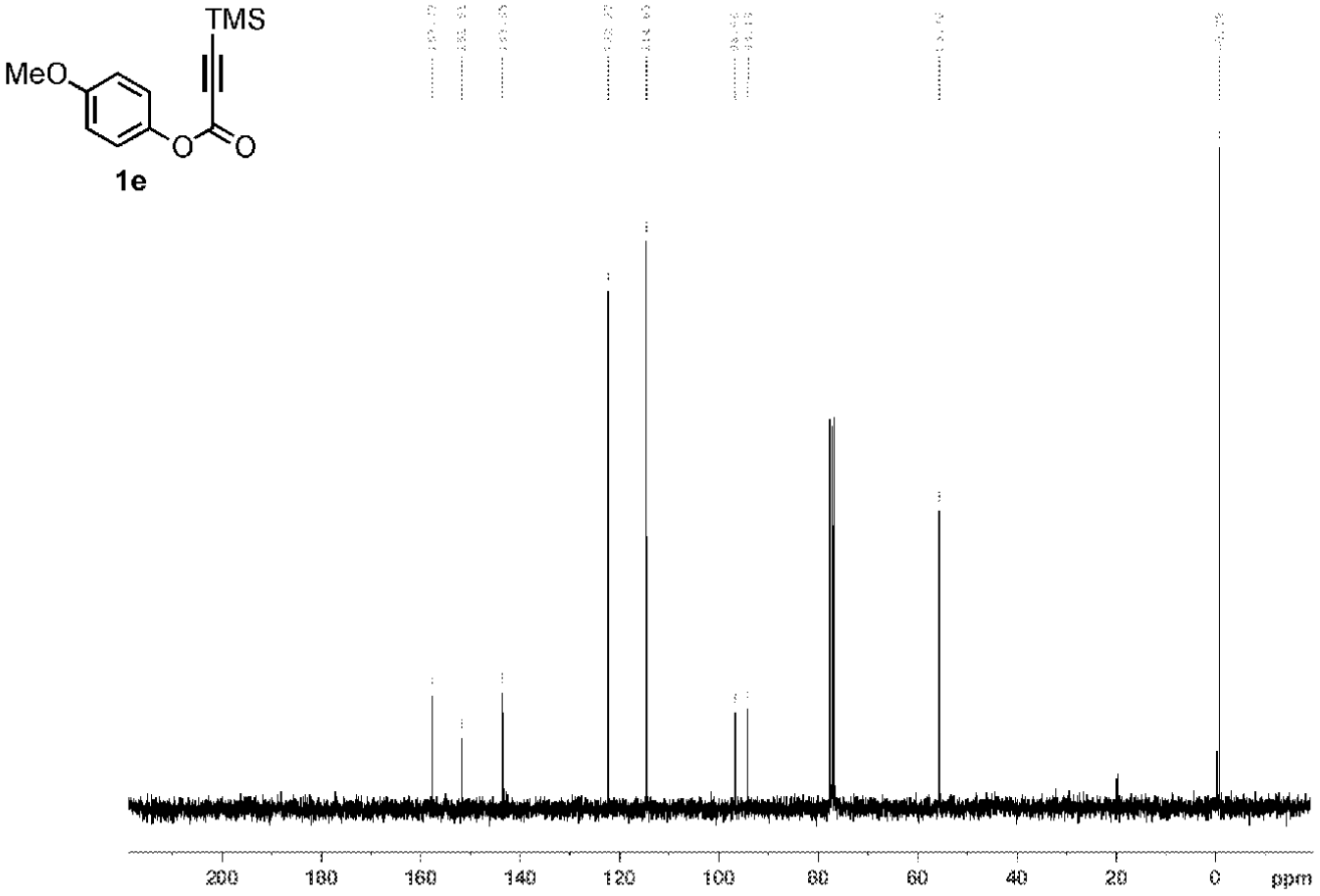
^{13}C NMR spectrum of **1d** recorded in DMSO-d_6



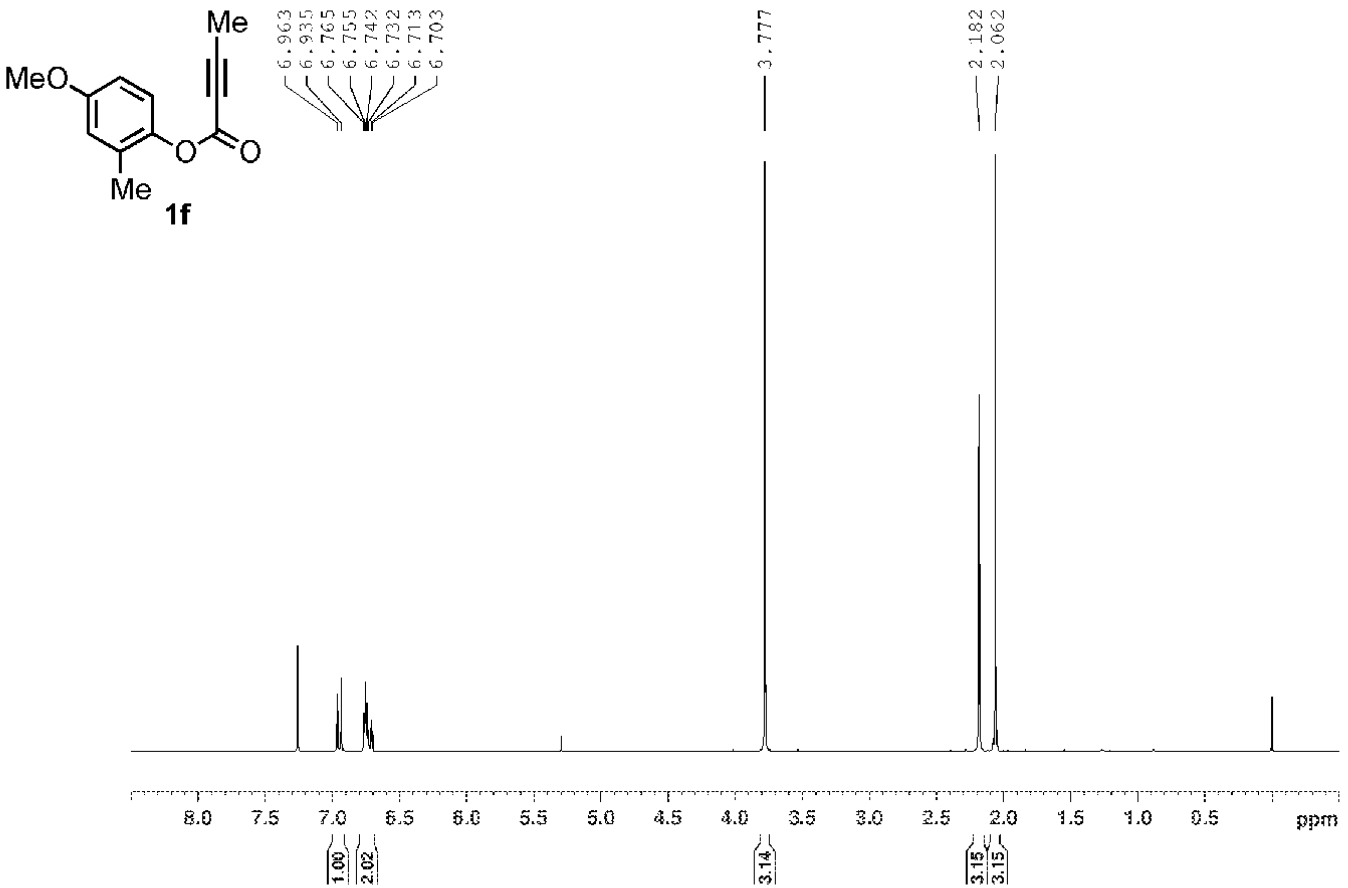
^{1}H NMR spectrum of **1e** recorded in $CDCl_3$



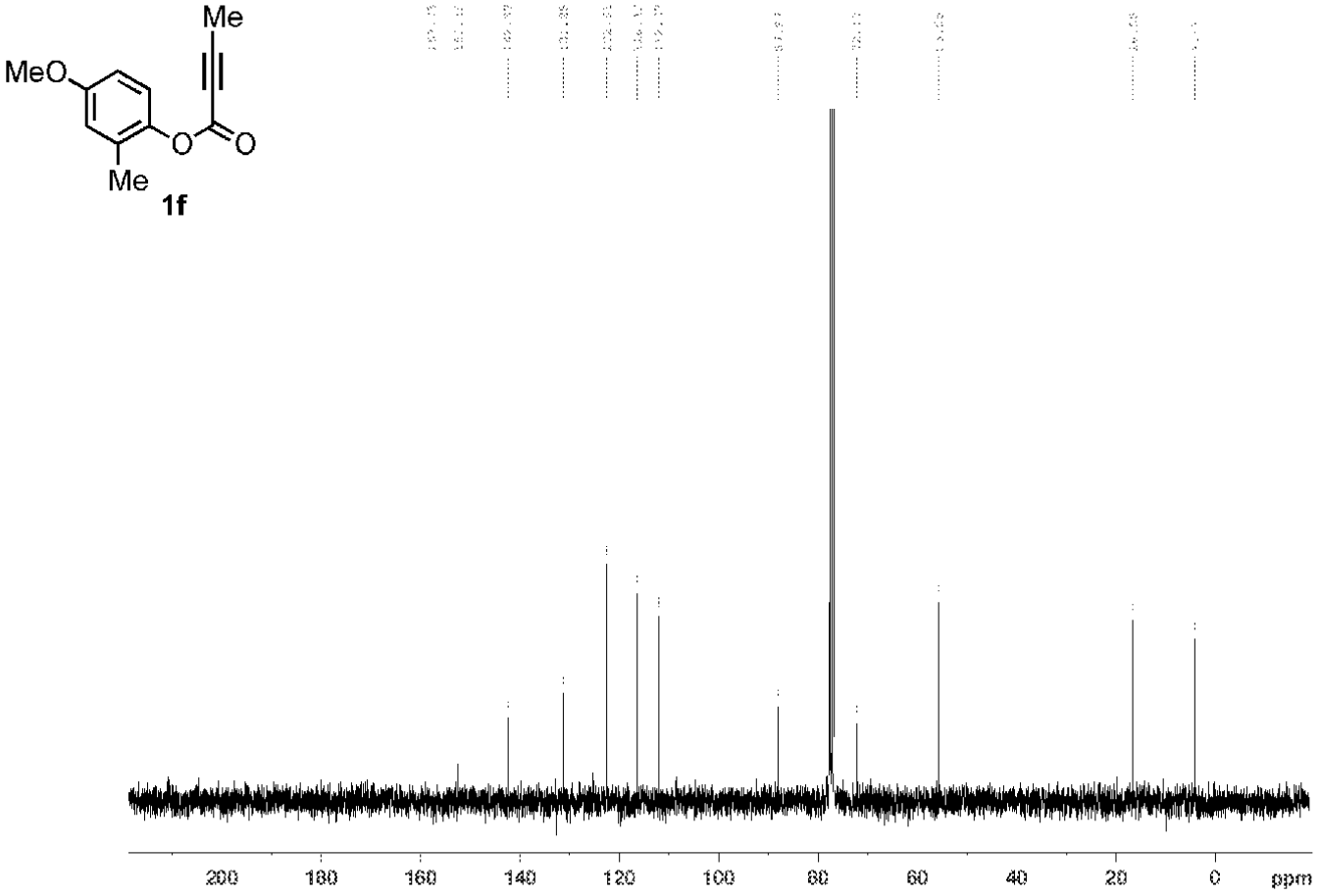
^{13}C NMR spectrum of **1e** recorded in $CDCl_3$



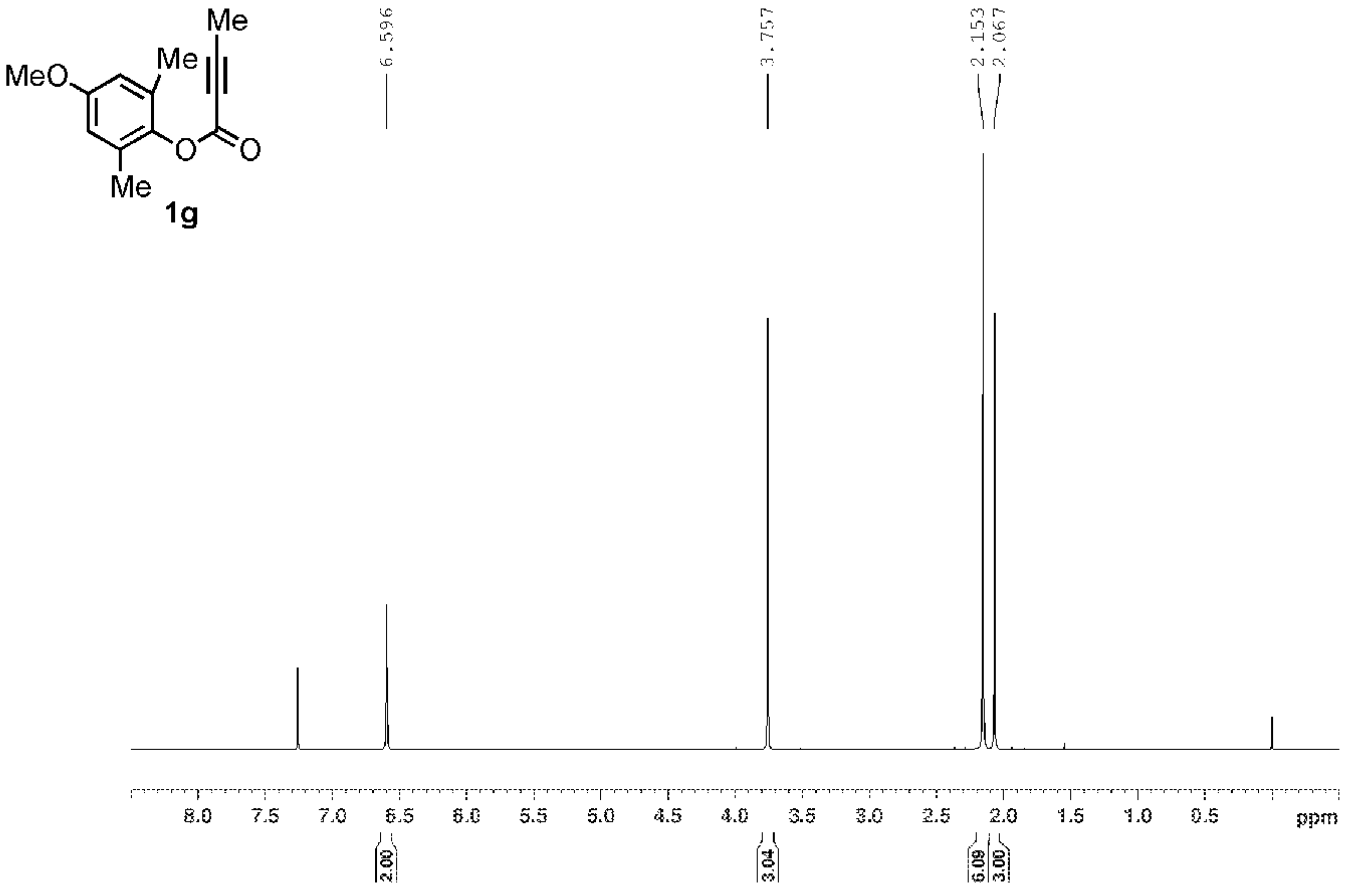
^{1}H NMR spectrum of **1f** recorded in $CDCl_3$



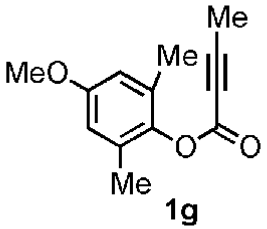
^{13}C NMR spectrum of **1f** recorded in $CDCl_3$



^{1}H NMR spectrum of **1g** recorded in $CDCl_3$

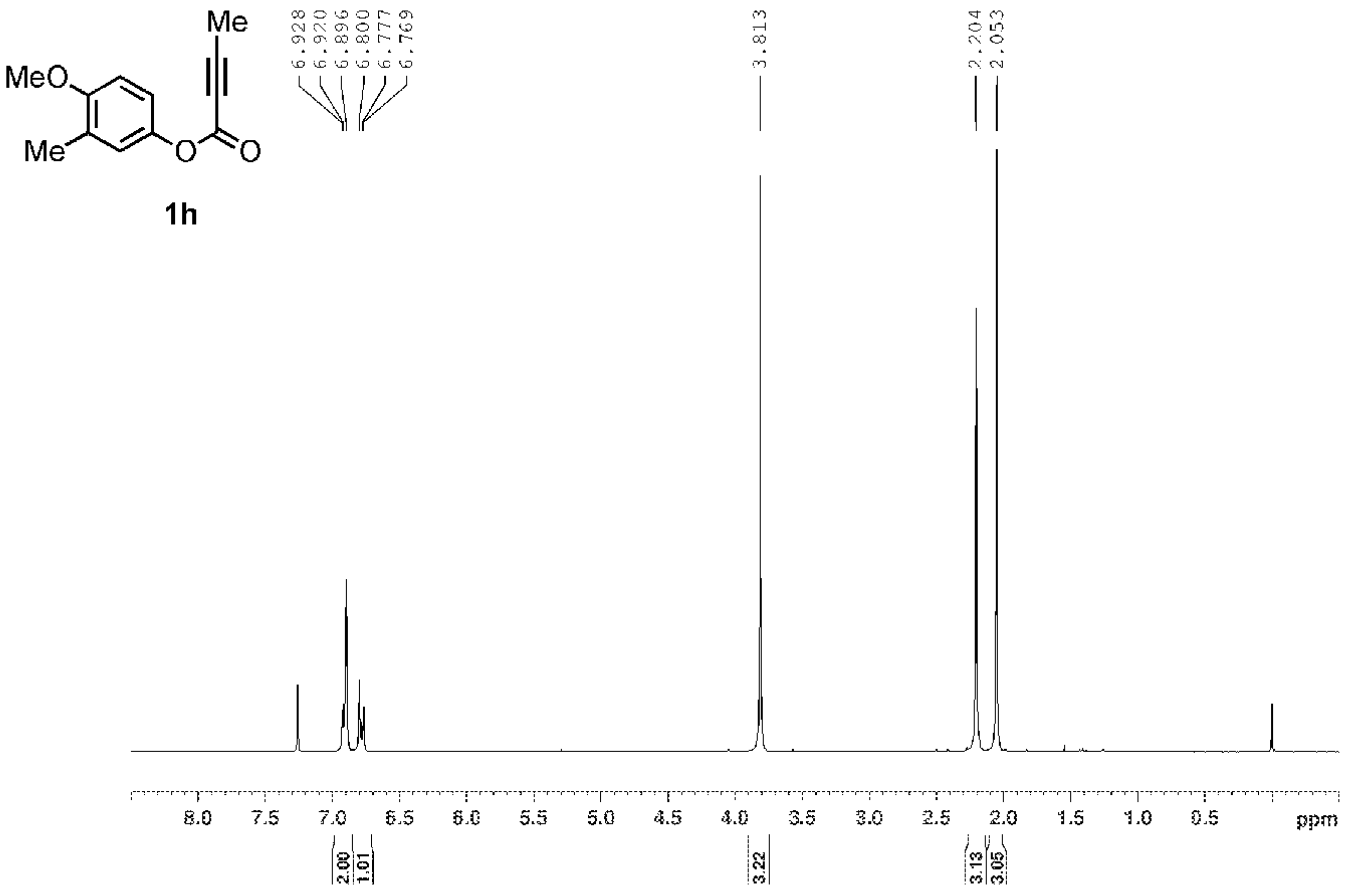


^{13}C NMR spectrum of **1g** recorded in $CDCl_3$

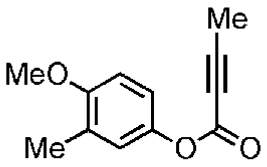


1g

^{1}H NMR spectrum of **1h** recorded in $CDCl_3$

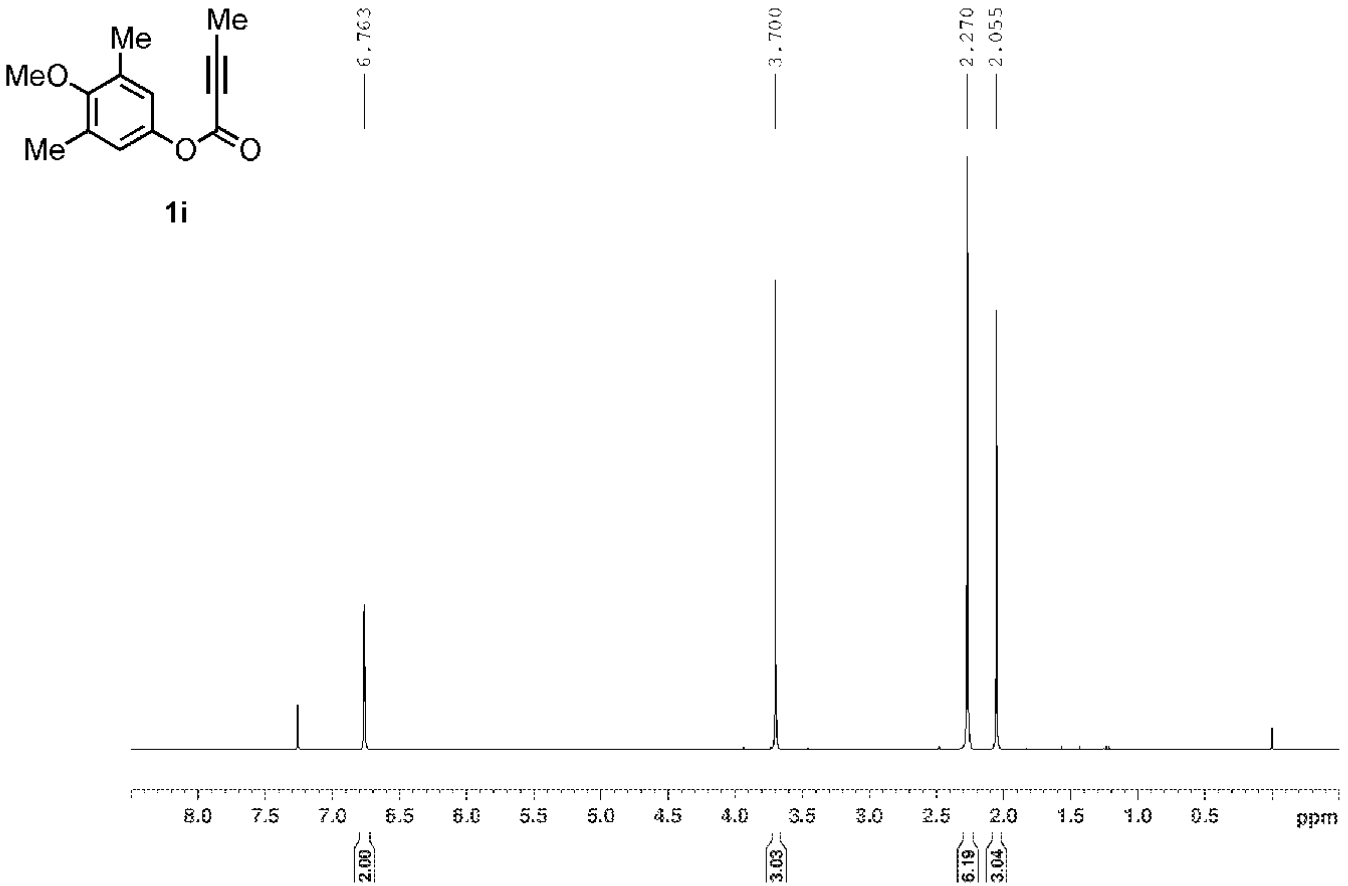


^{13}C NMR spectrum of **1h** recorded in $CDCl_3$

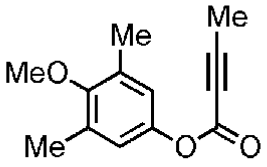


1h

^{1}H NMR spectrum of **1i** recorded in $CDCl_3$

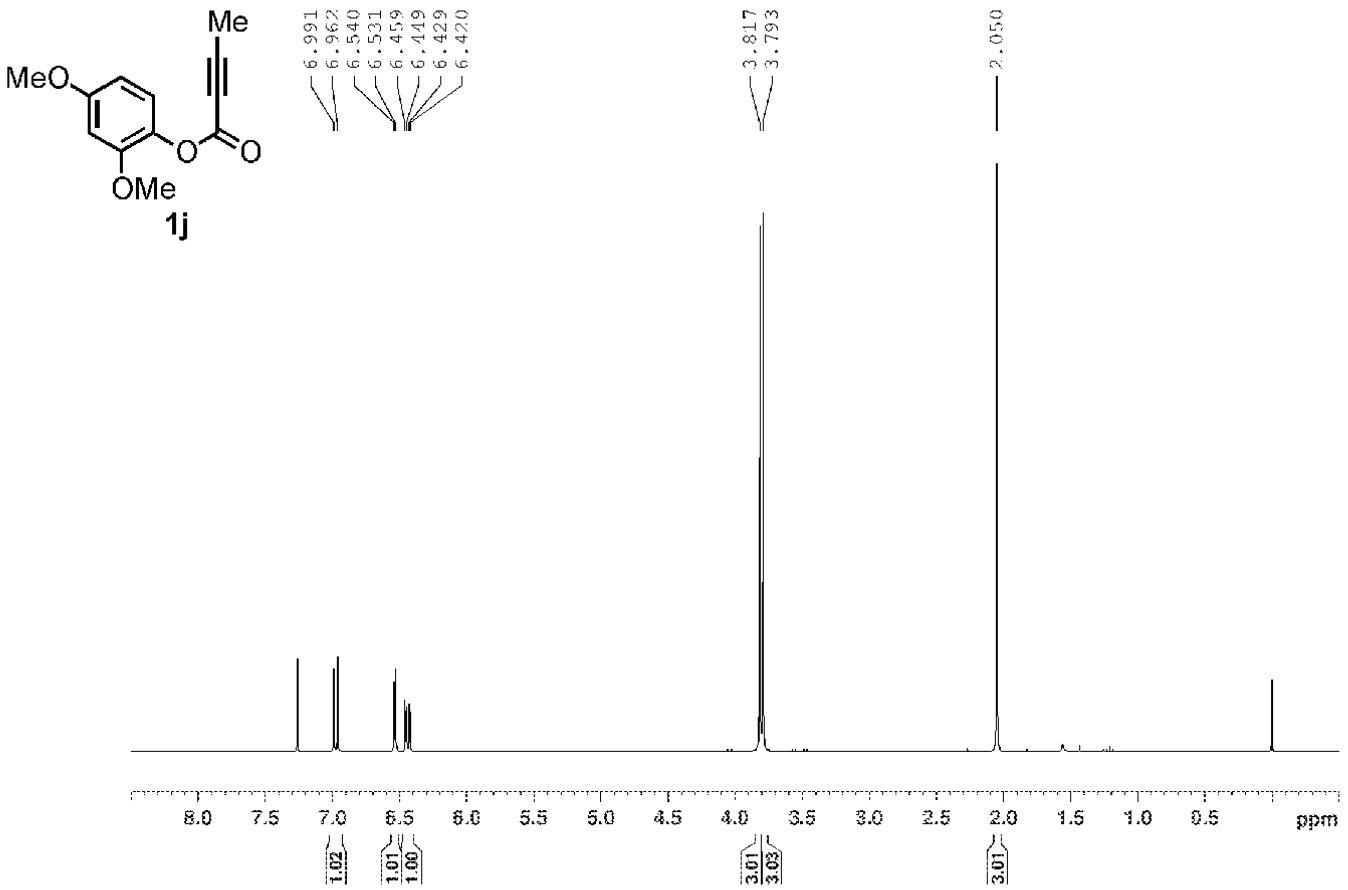


^{13}C NMR spectrum of **1i** recorded in $CDCl_3$

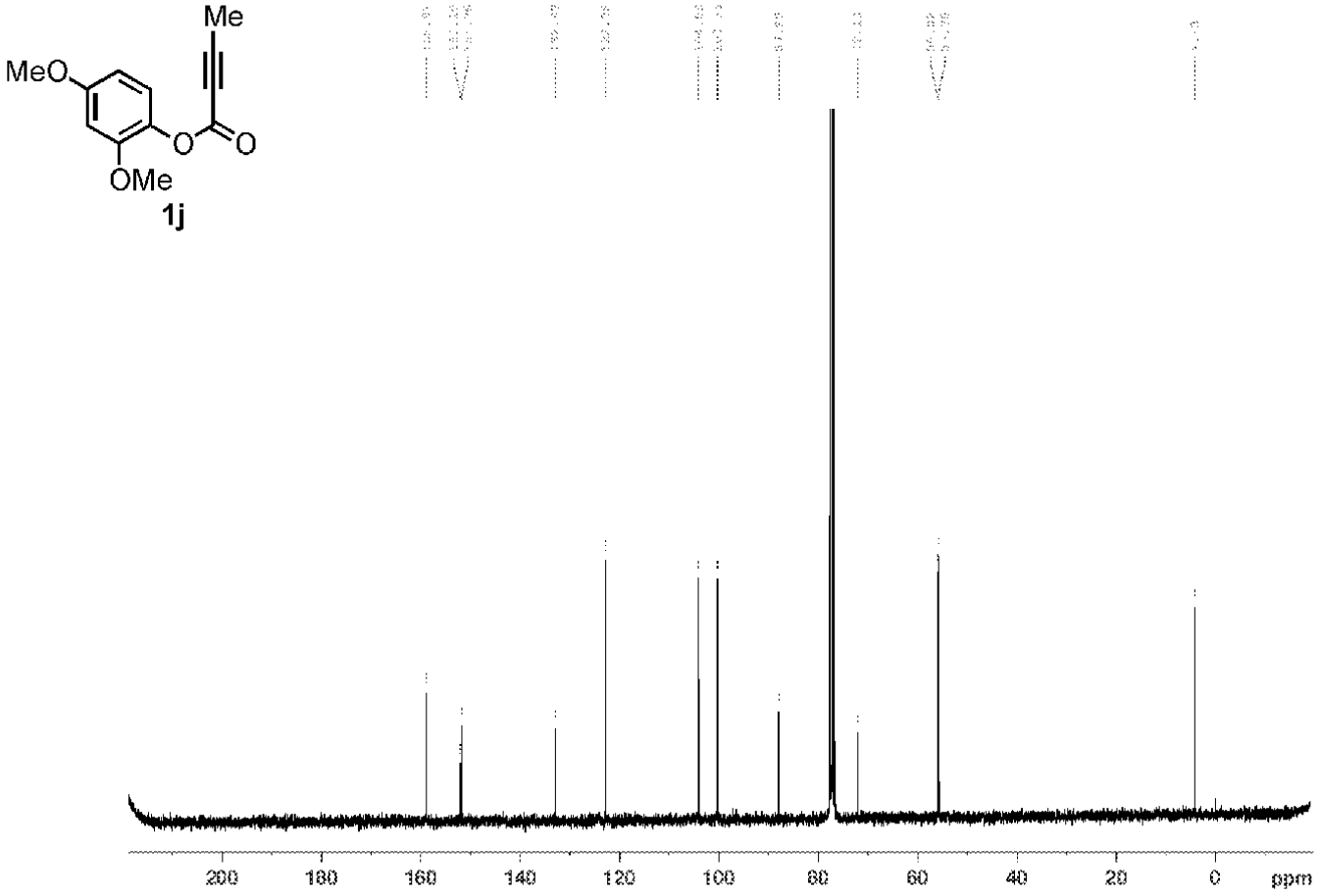


1i

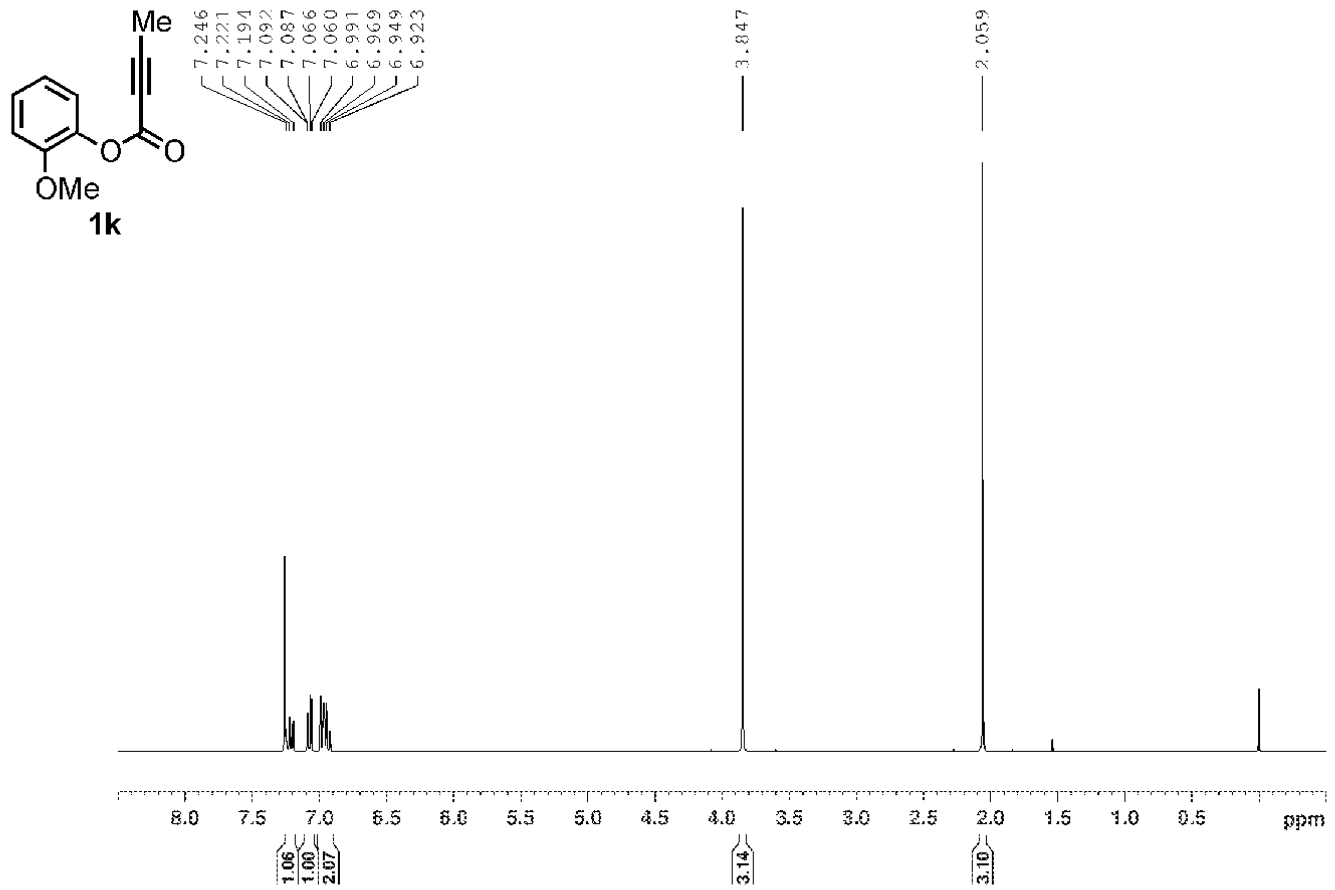
^{1}H NMR spectrum of **1j** recorded in $CDCl_3$



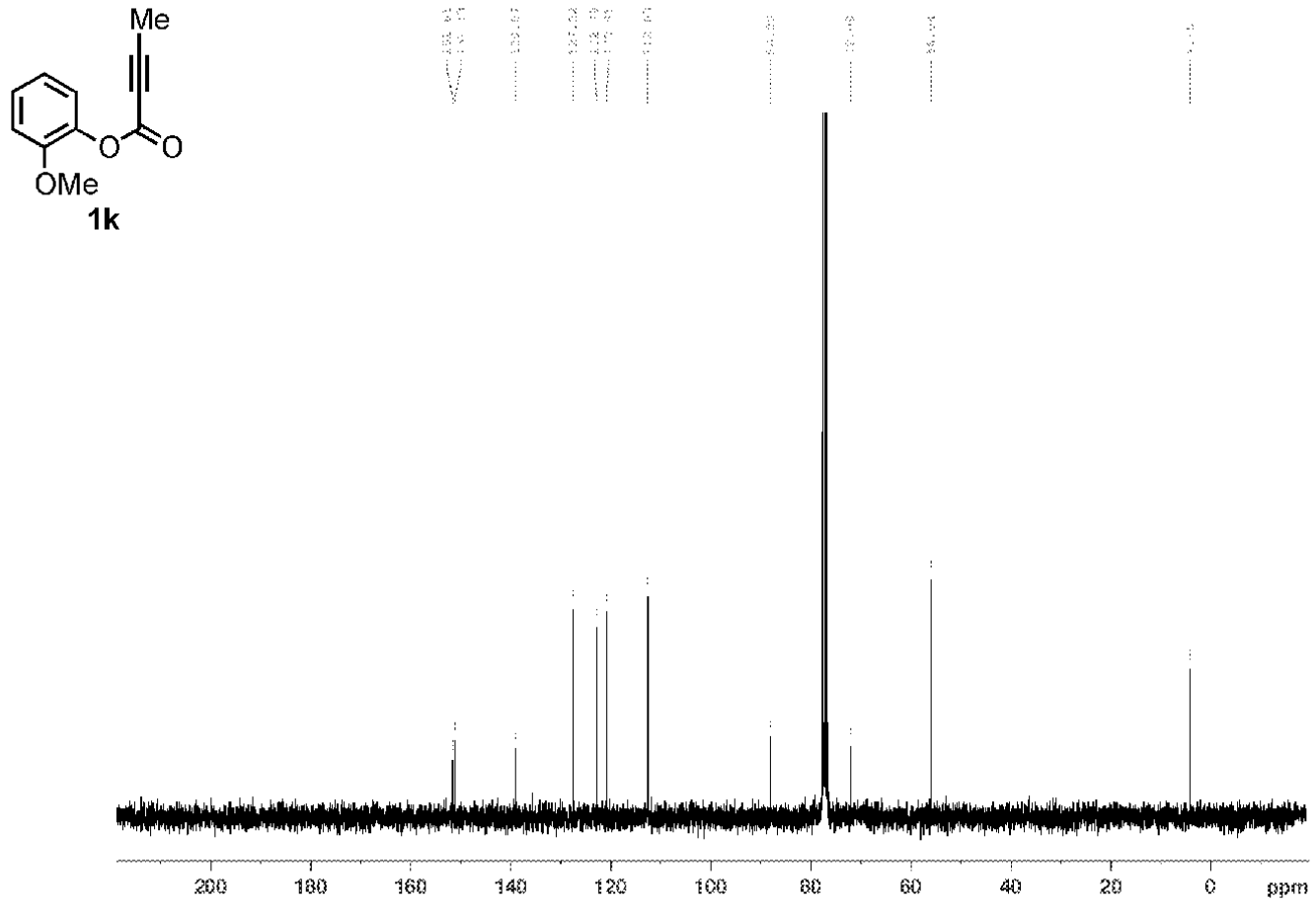
^{13}C NMR spectrum of **1j** recorded in $CDCl_3$



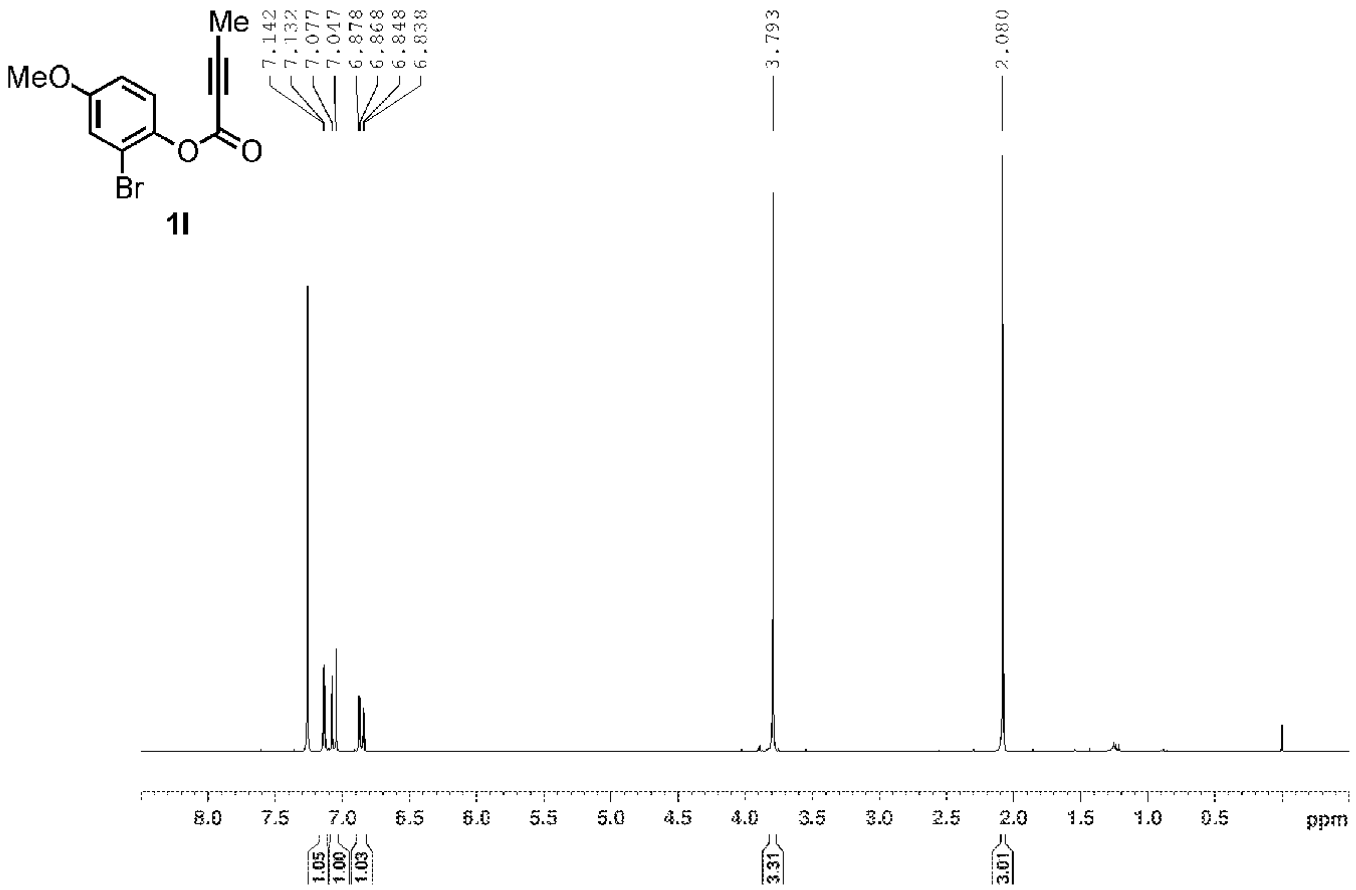
^{1}H NMR spectrum of **1k** recorded in $CDCl_3$



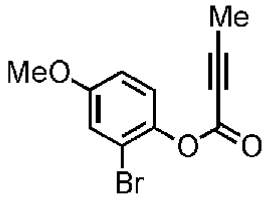
^{13}C NMR spectrum of **1k** recorded in $CDCl_3$



^{1}H NMR spectrum of **1l** recorded in $CDCl_3$

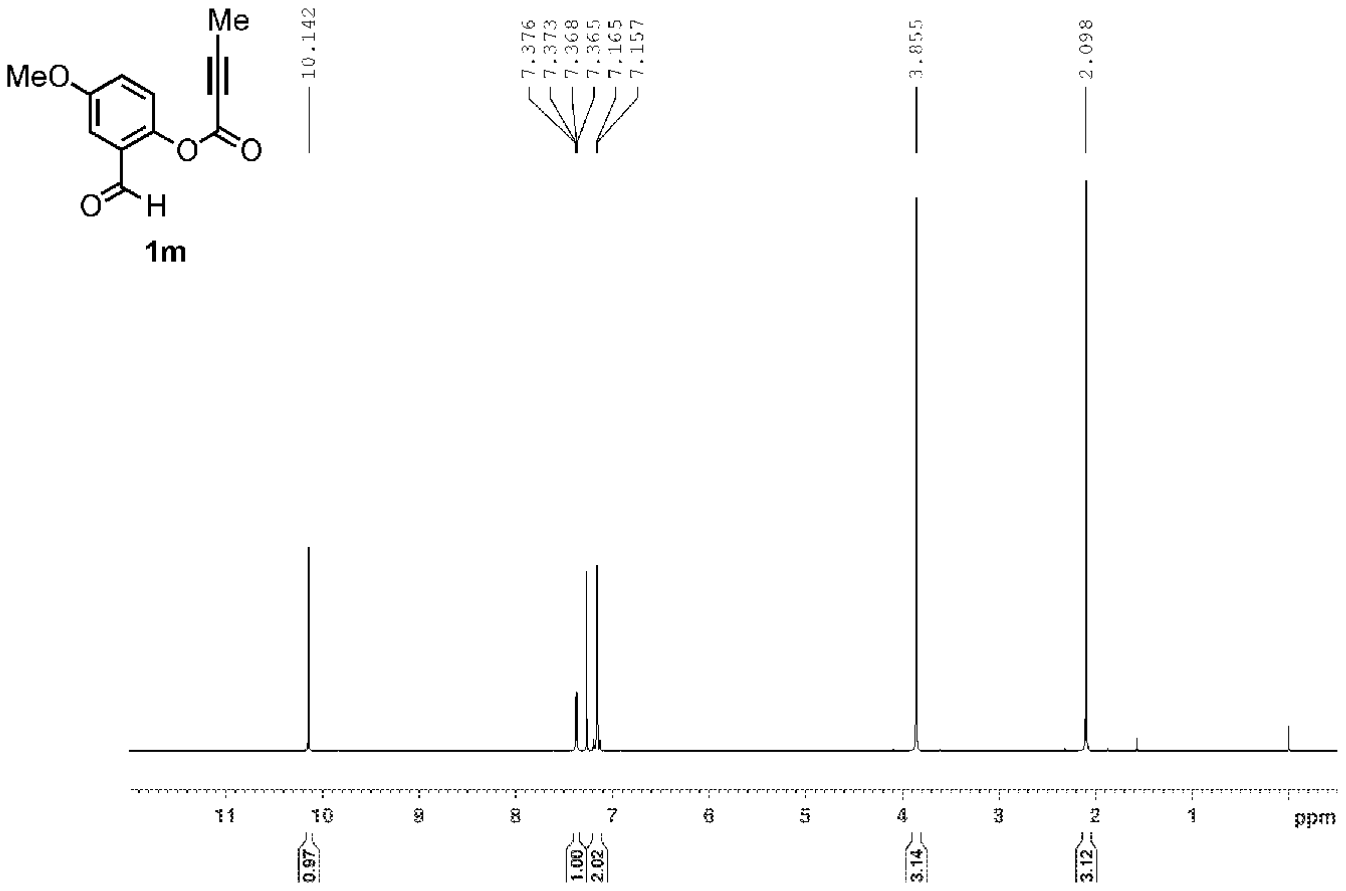


^{13}C NMR spectrum of **1l** recorded in $CDCl_3$

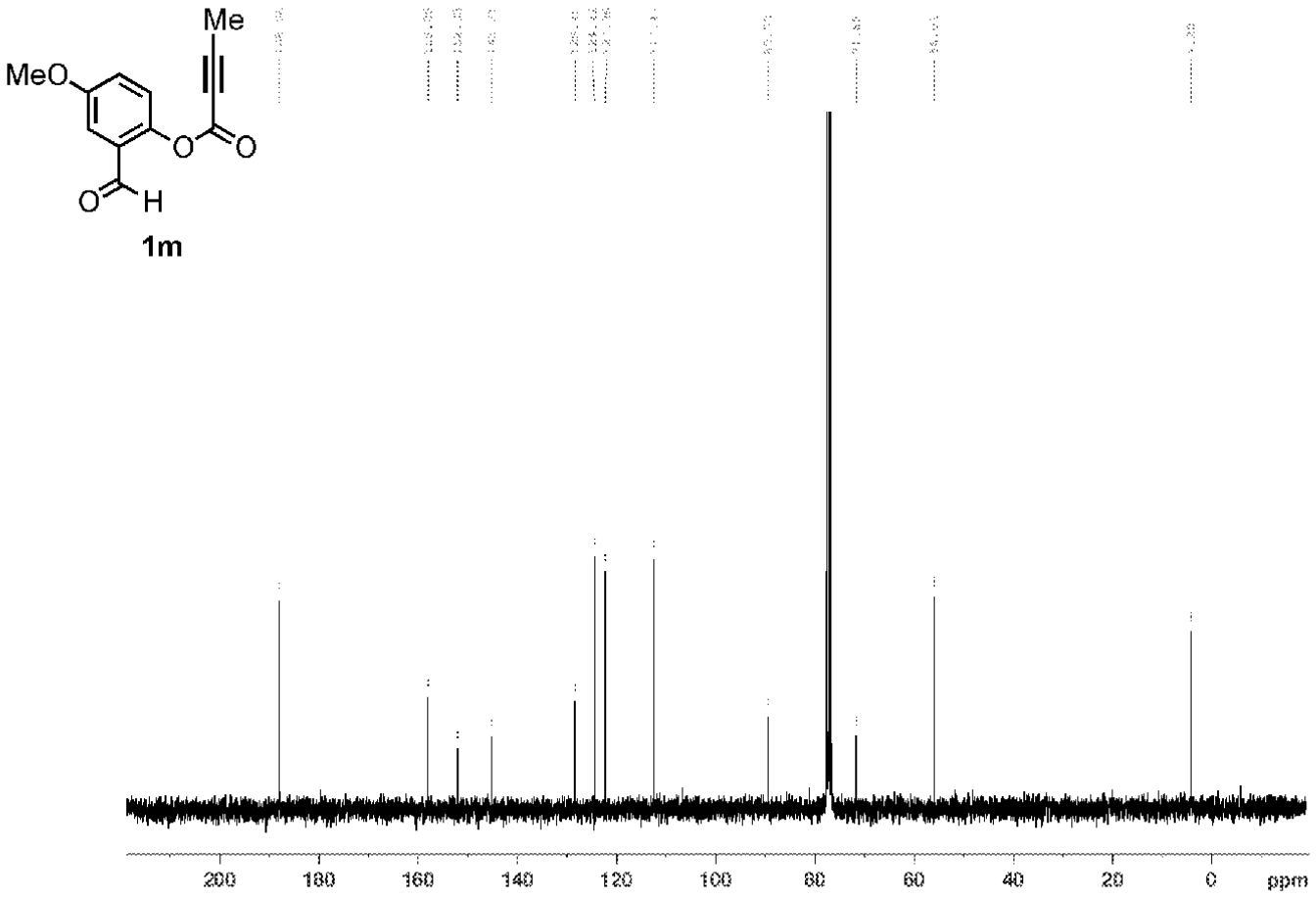


1l

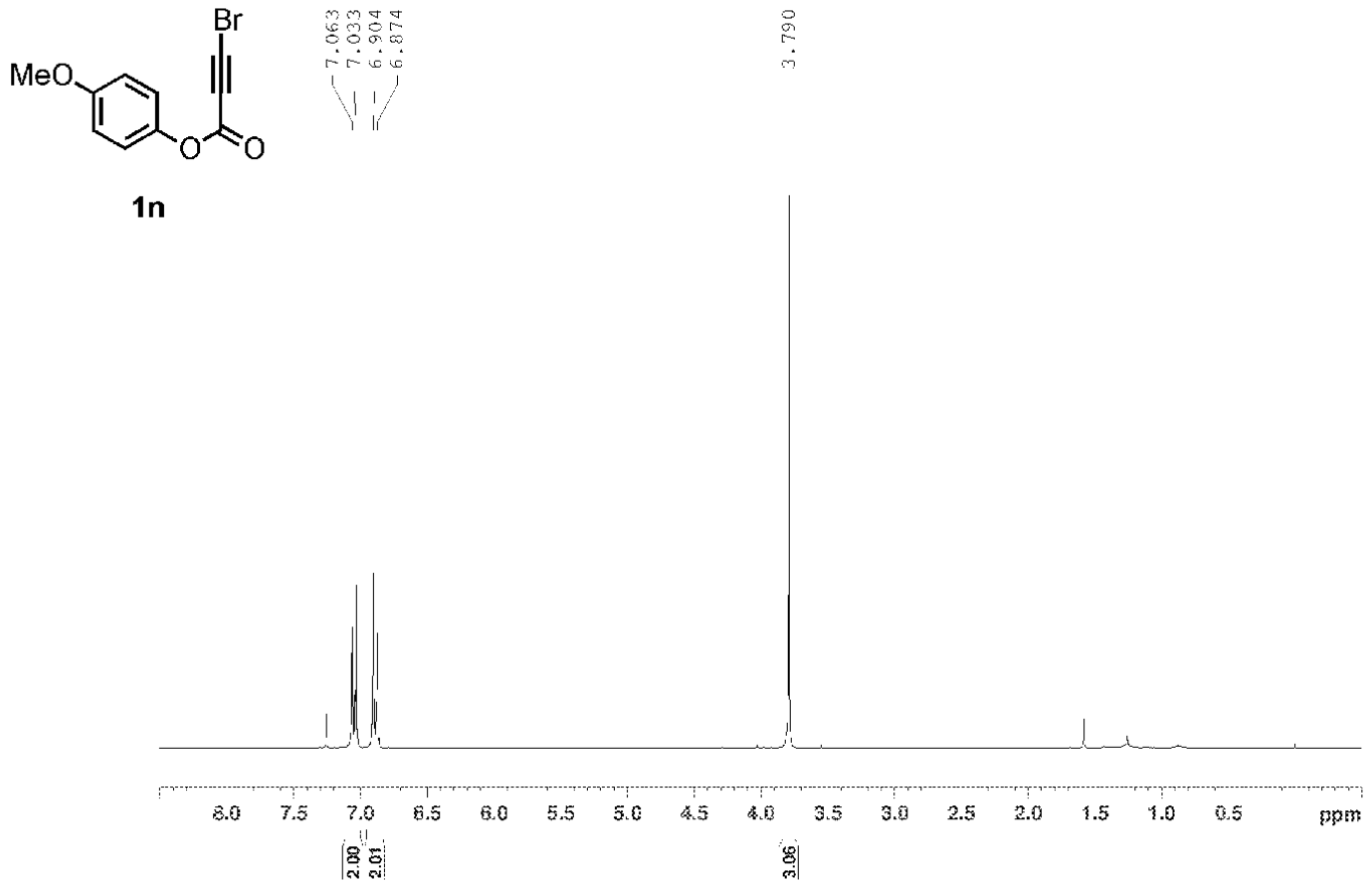
^{1}H NMR spectrum of **1m** recorded in $CDCl_3$



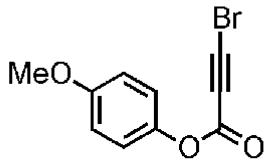
^{13}C NMR spectrum of **1m** recorded in $CDCl_3$



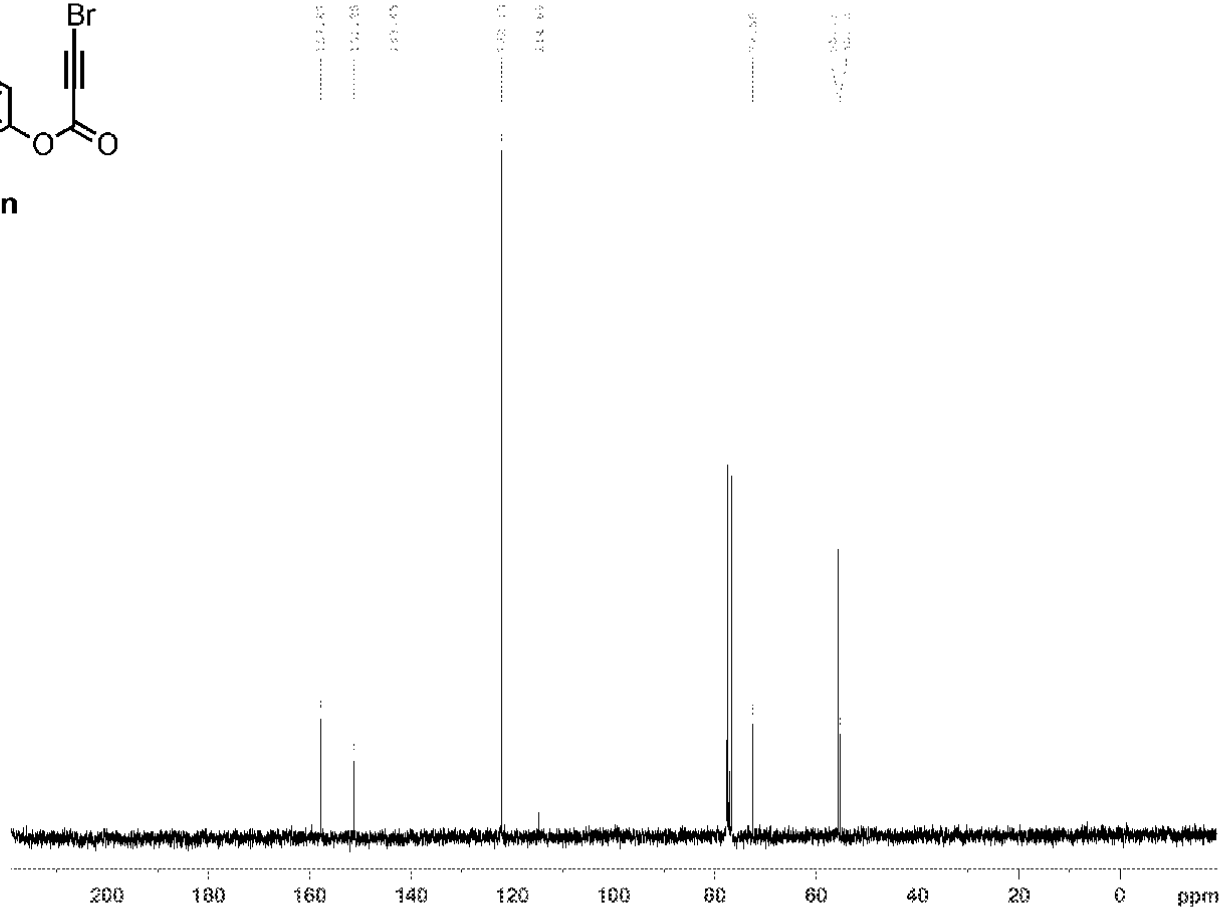
^{1}H NMR spectrum of **1n** recorded in $CDCl_3$



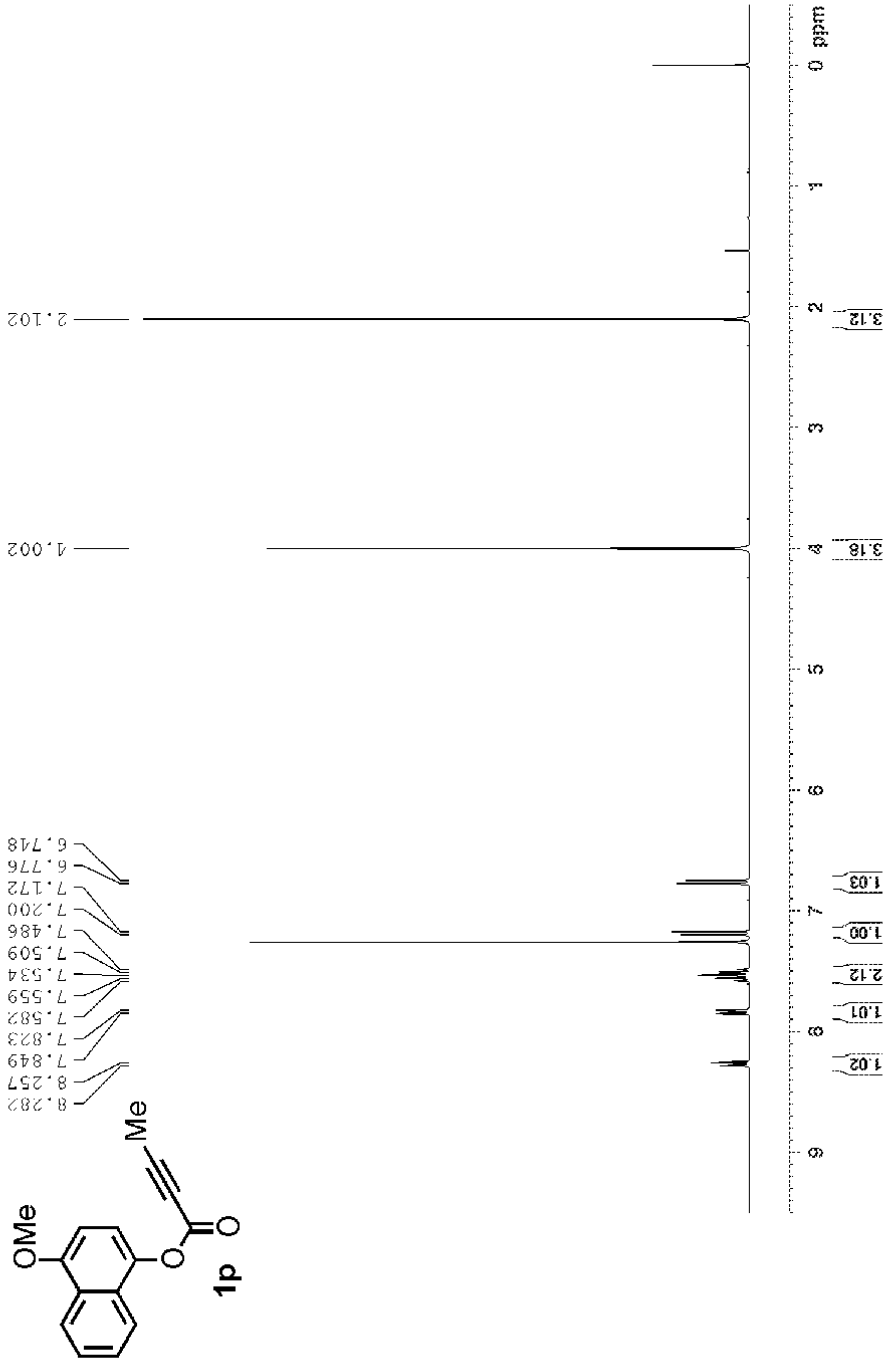
^{13}C NMR spectrum of **1n** recorded in $CDCl_3$



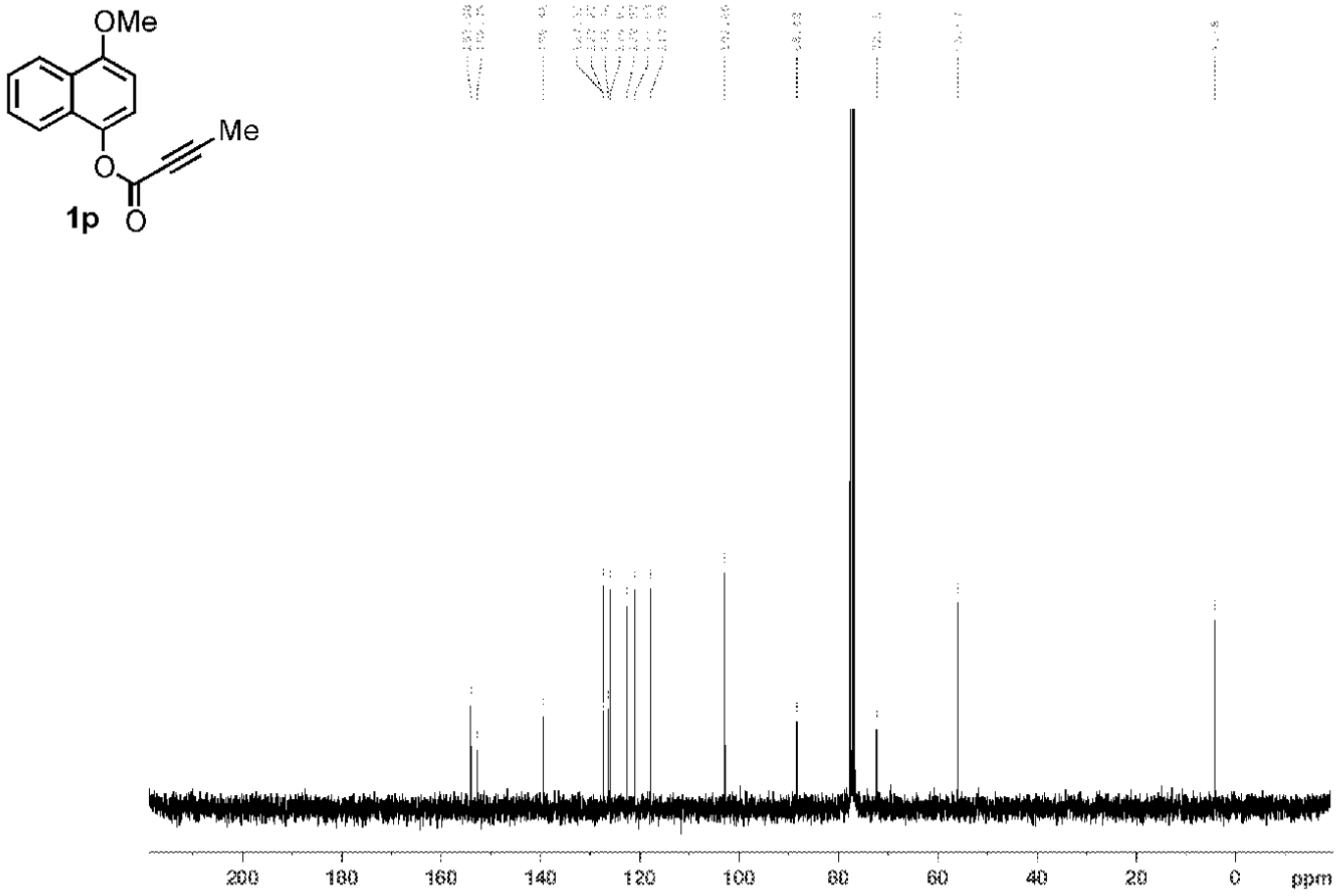
1n



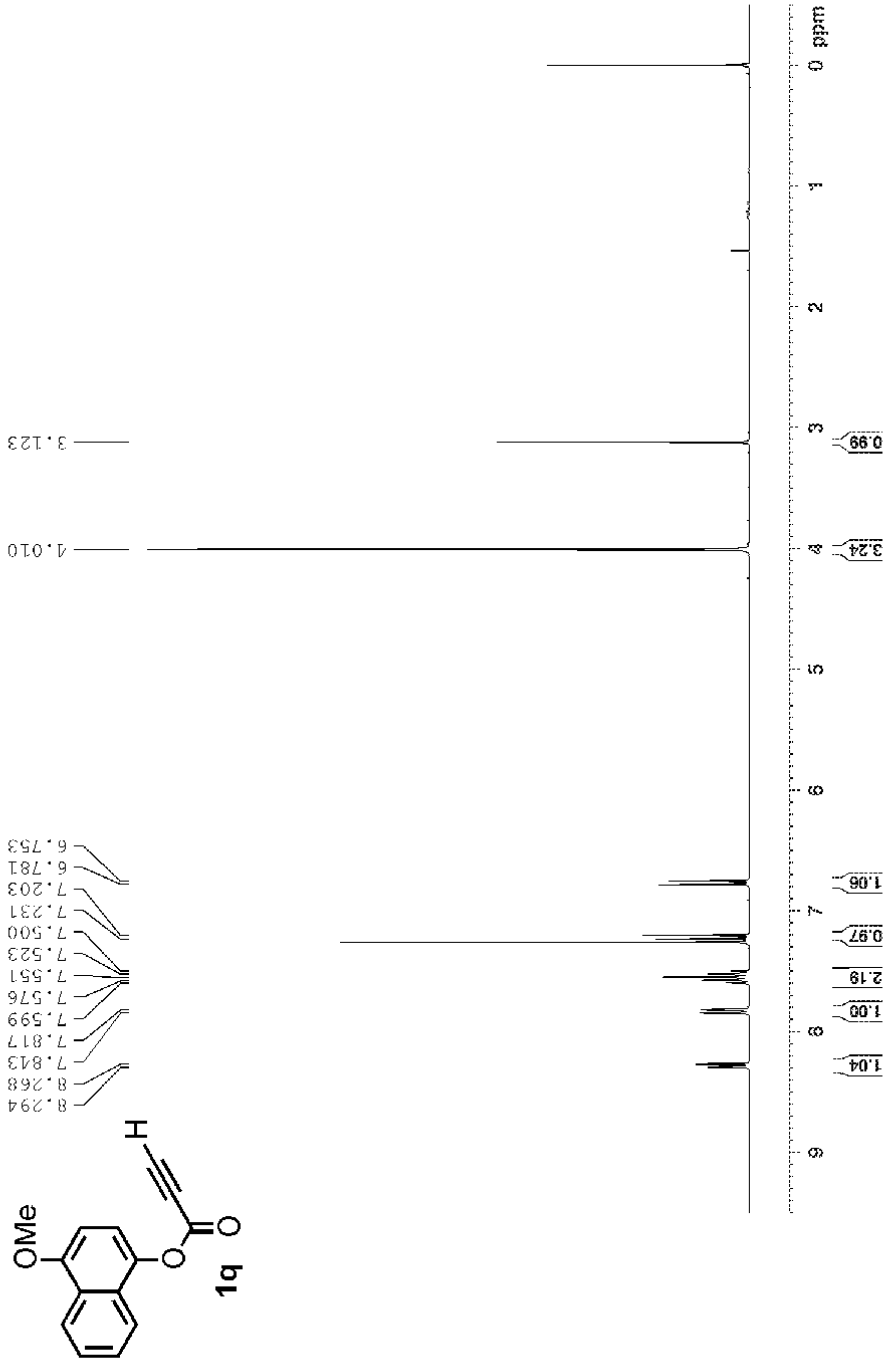
^{1}H NMR spectrum of **1p** recorded in $CDCl_3$



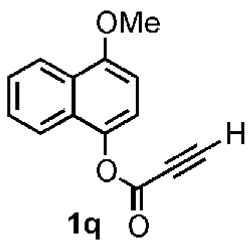
^{13}C NMR spectrum of **1p** recorded in $CDCl_3$

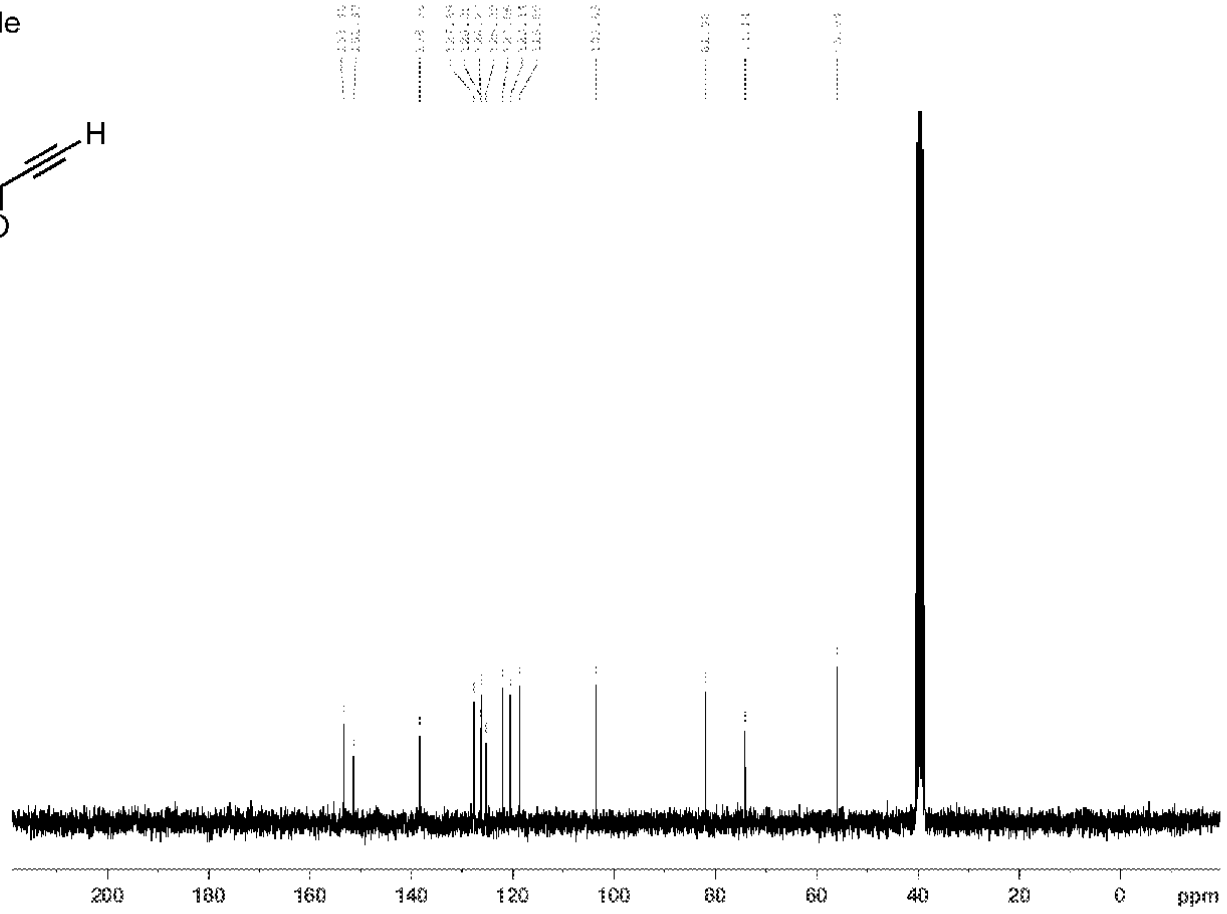


^{1}H NMR spectrum of **1q** recorded in $CDCl_3$

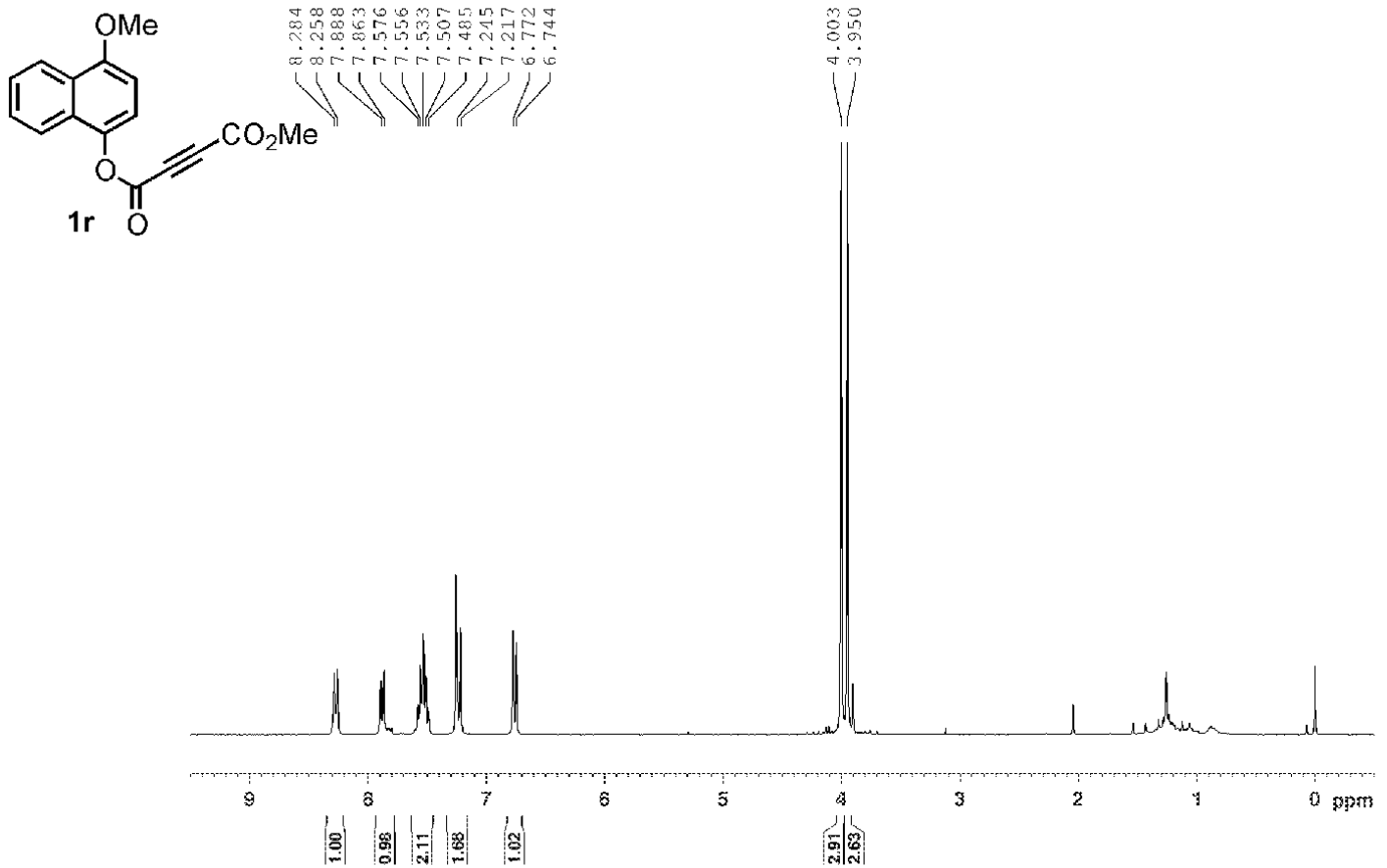


^{13}C NMR spectrum of **1q** recorded in DMSO-d_6

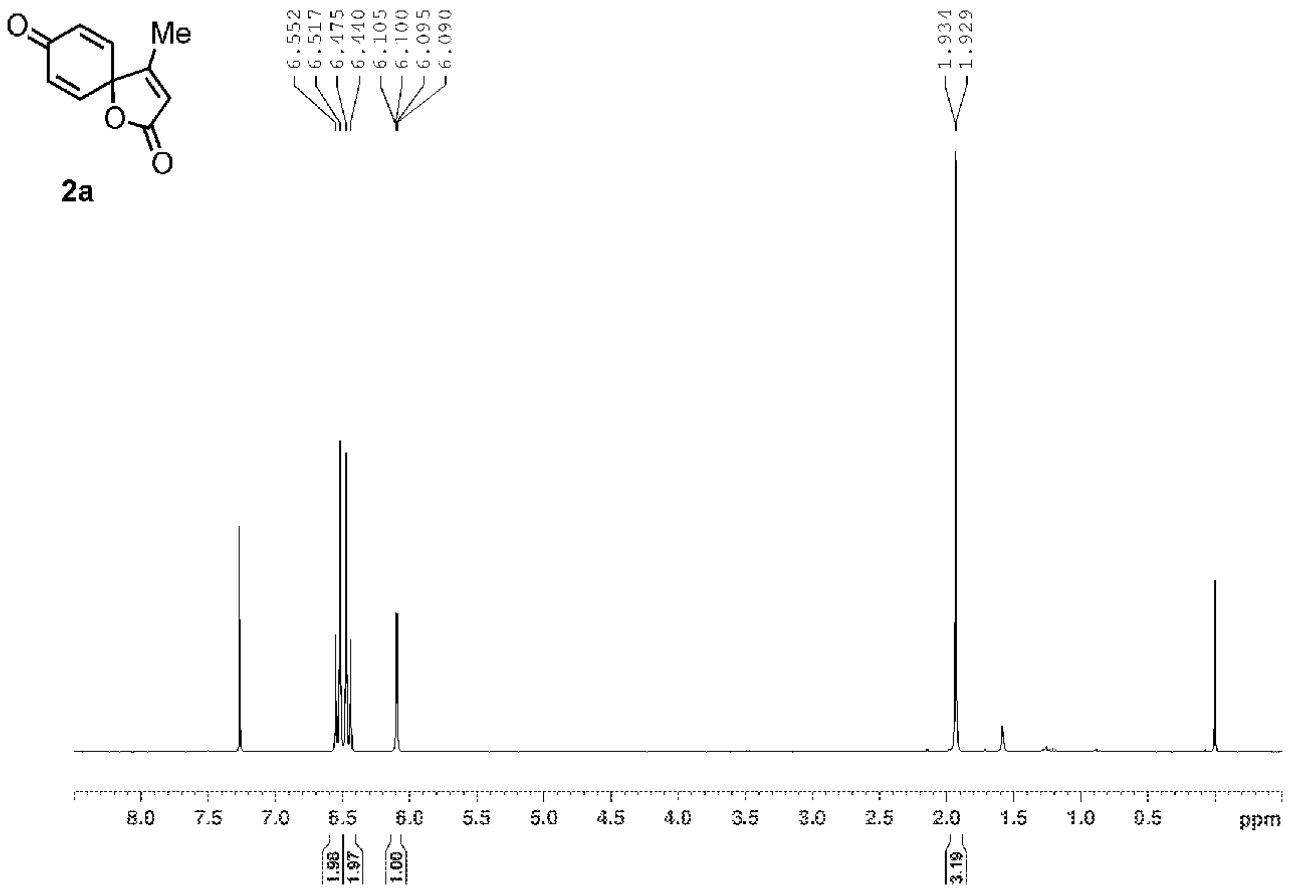




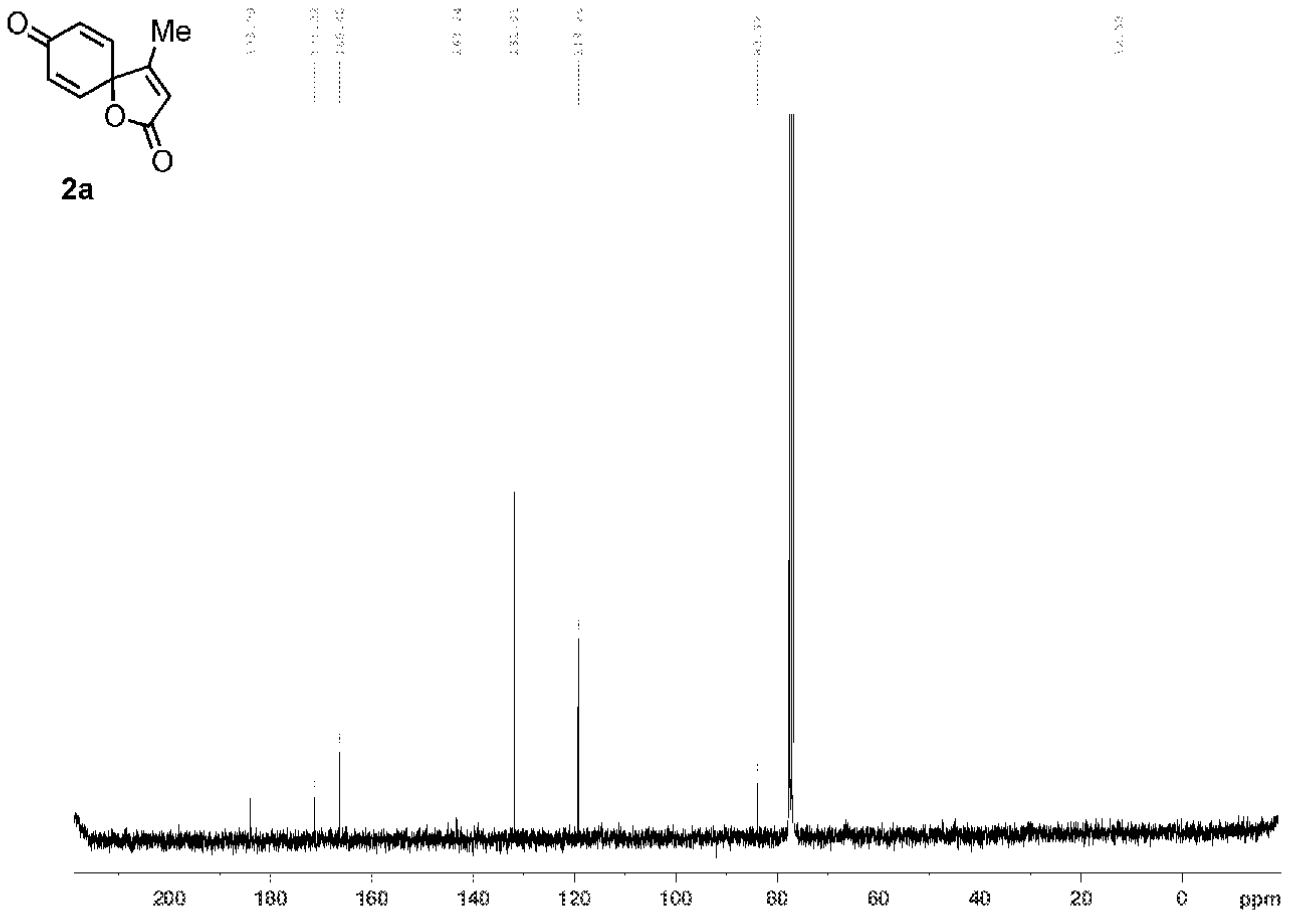
^{1}H NMR spectrum of **1r** recorded in $CDCl_3$



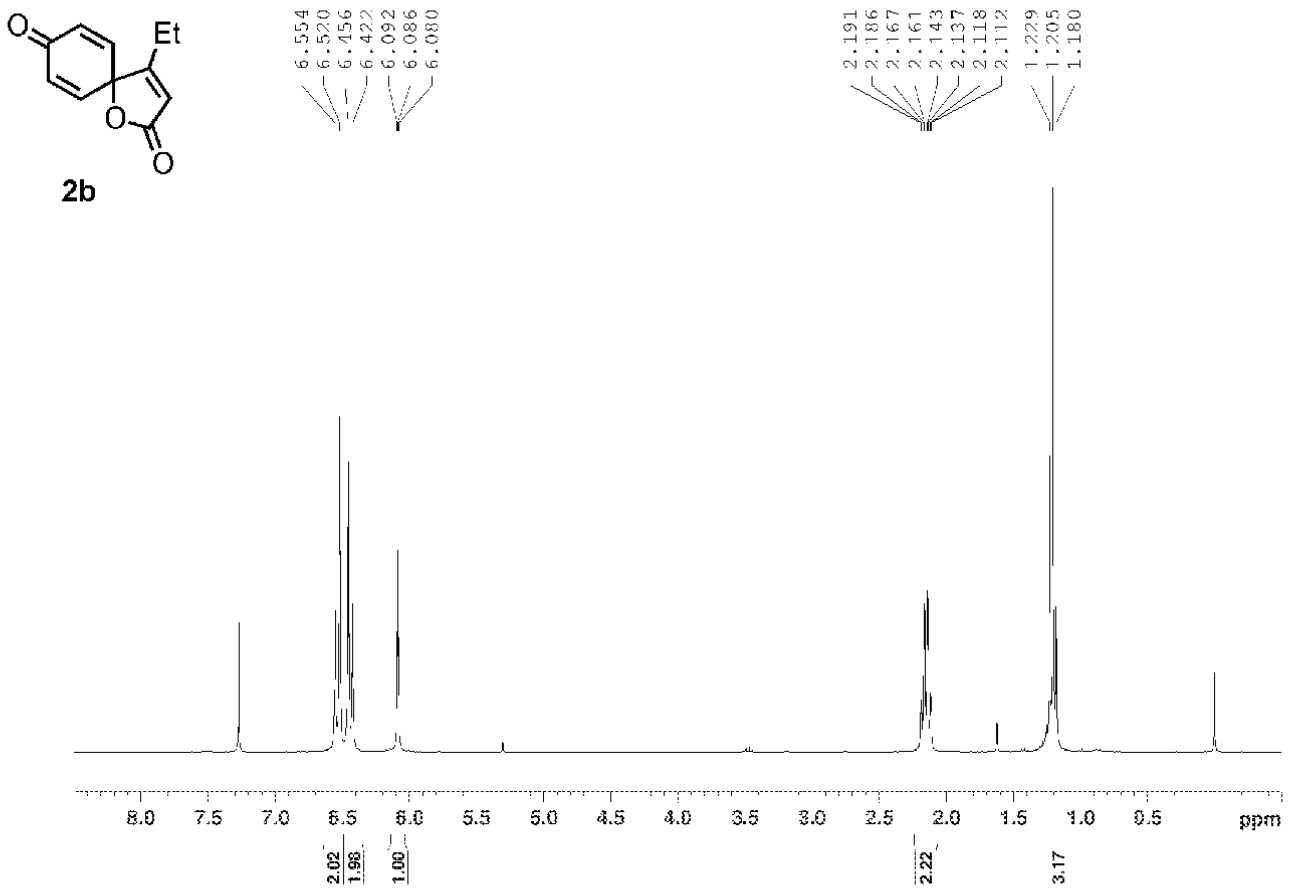
^{1}H NMR spectrum of **2a** recorded in $CDCl_3$



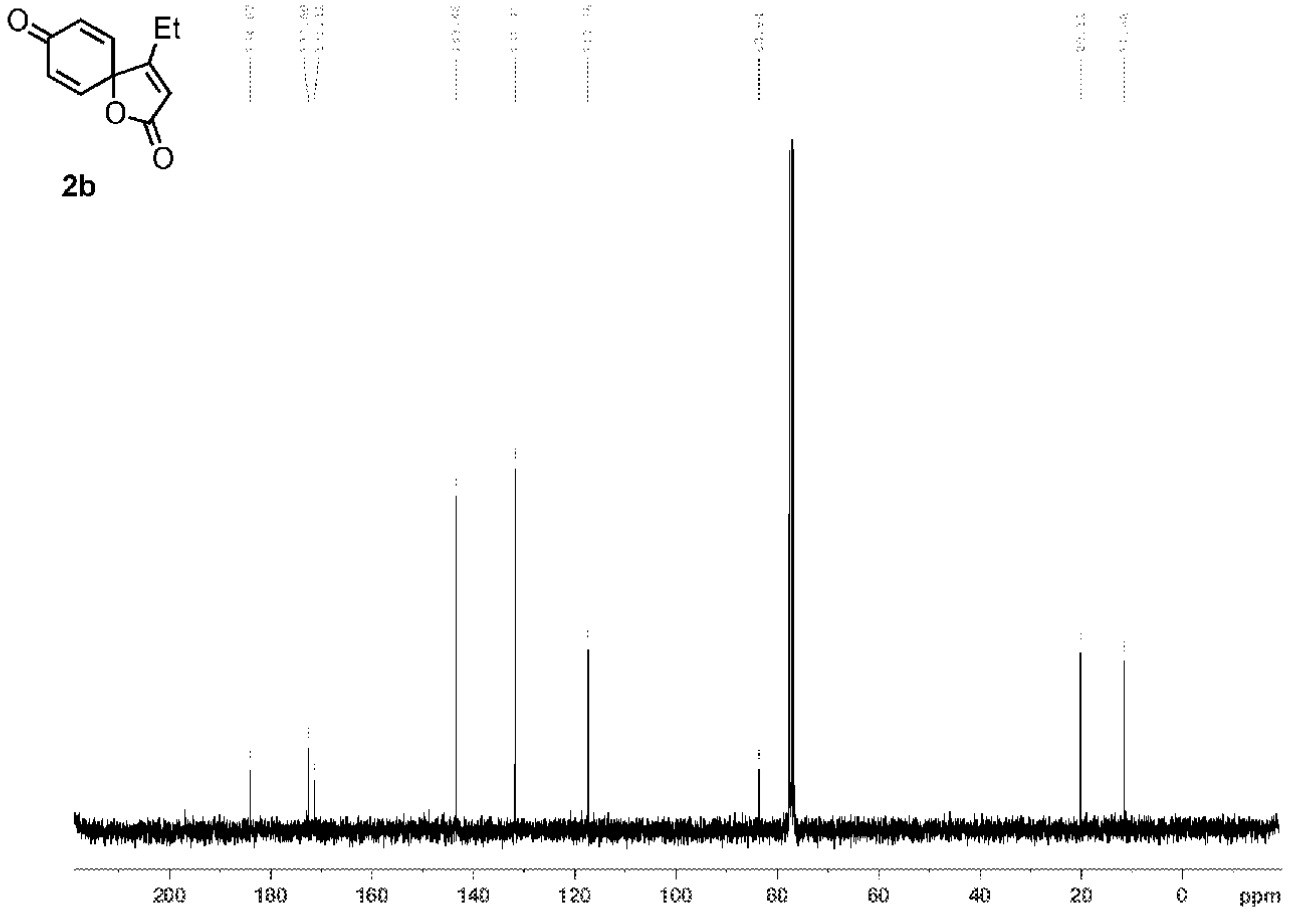
^{13}C NMR spectrum of **2a** recorded in $CDCl_3$



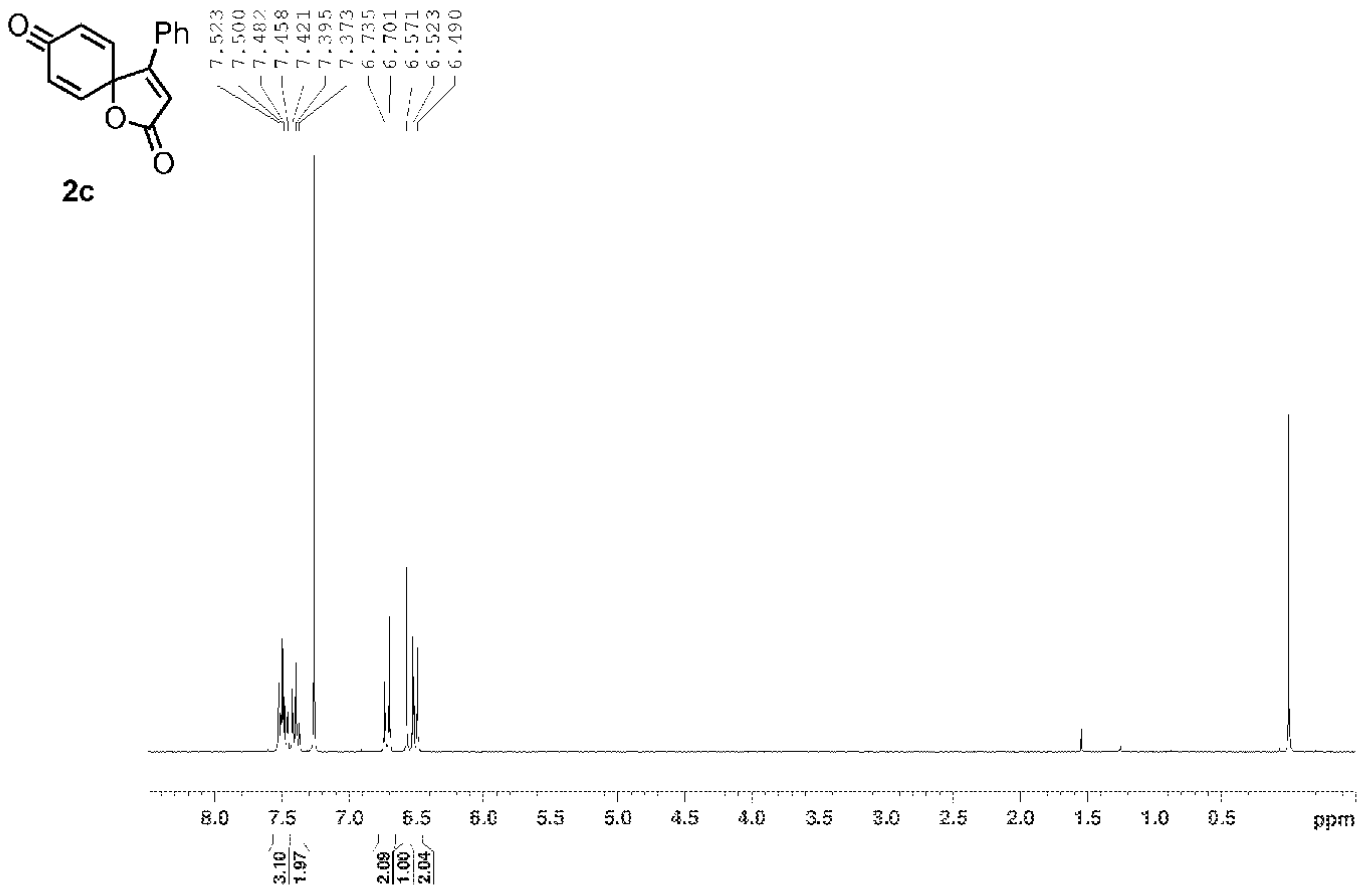
^{1}H NMR spectrum of **2b** recorded in $CDCl_3$



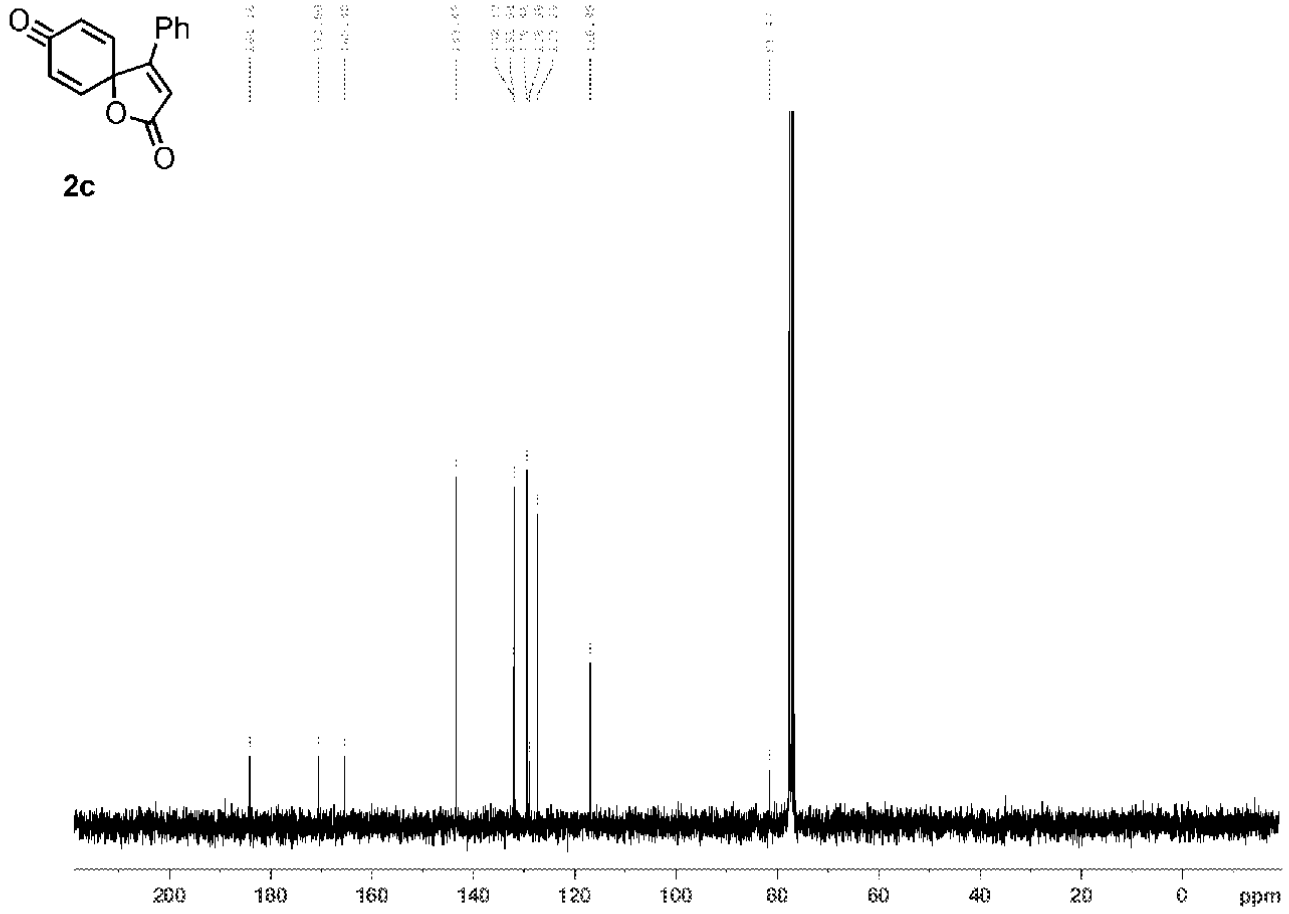
^{13}C NMR spectrum of **2b** recorded in $CDCl_3$



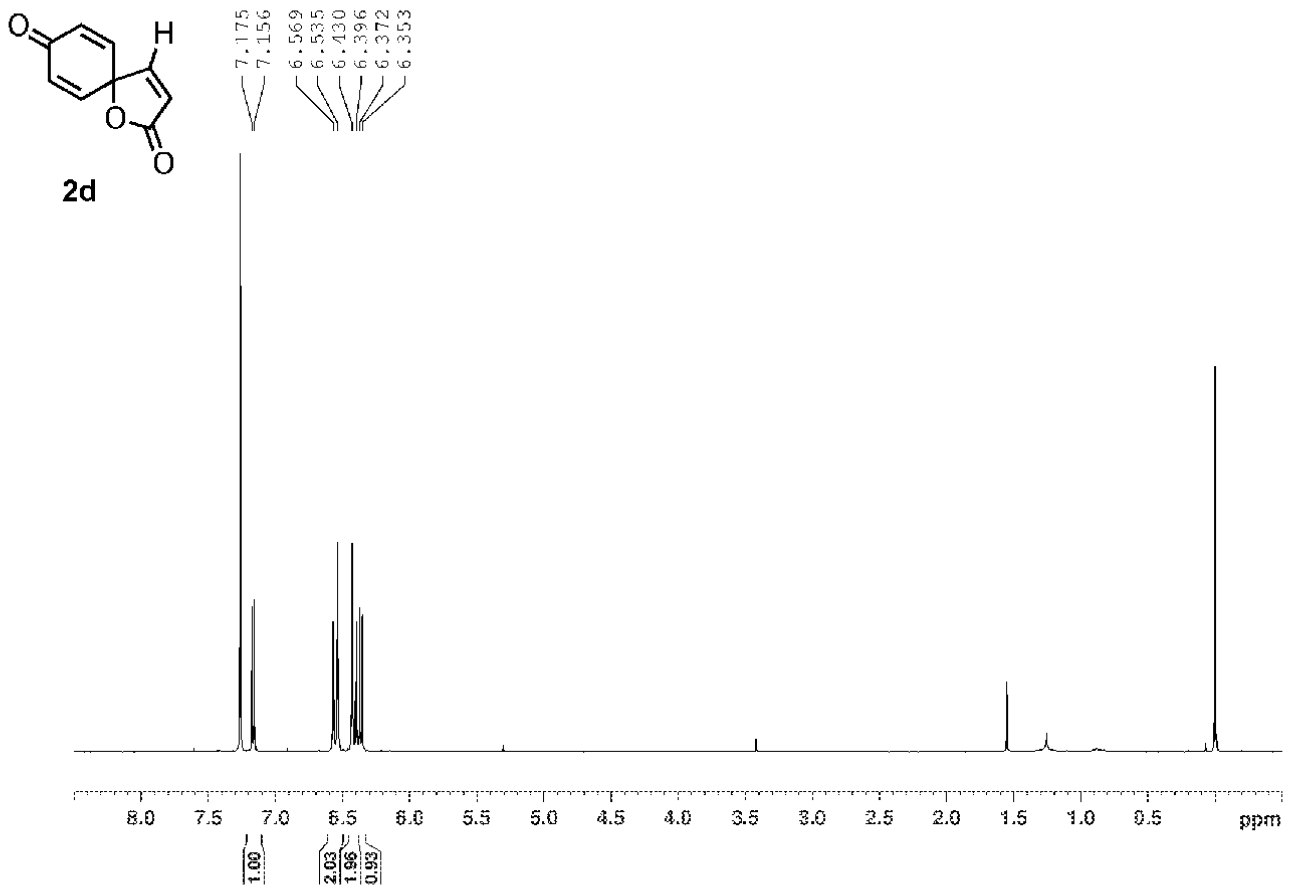
^{1}H NMR spectrum of **2c** recorded in $CDCl_3$



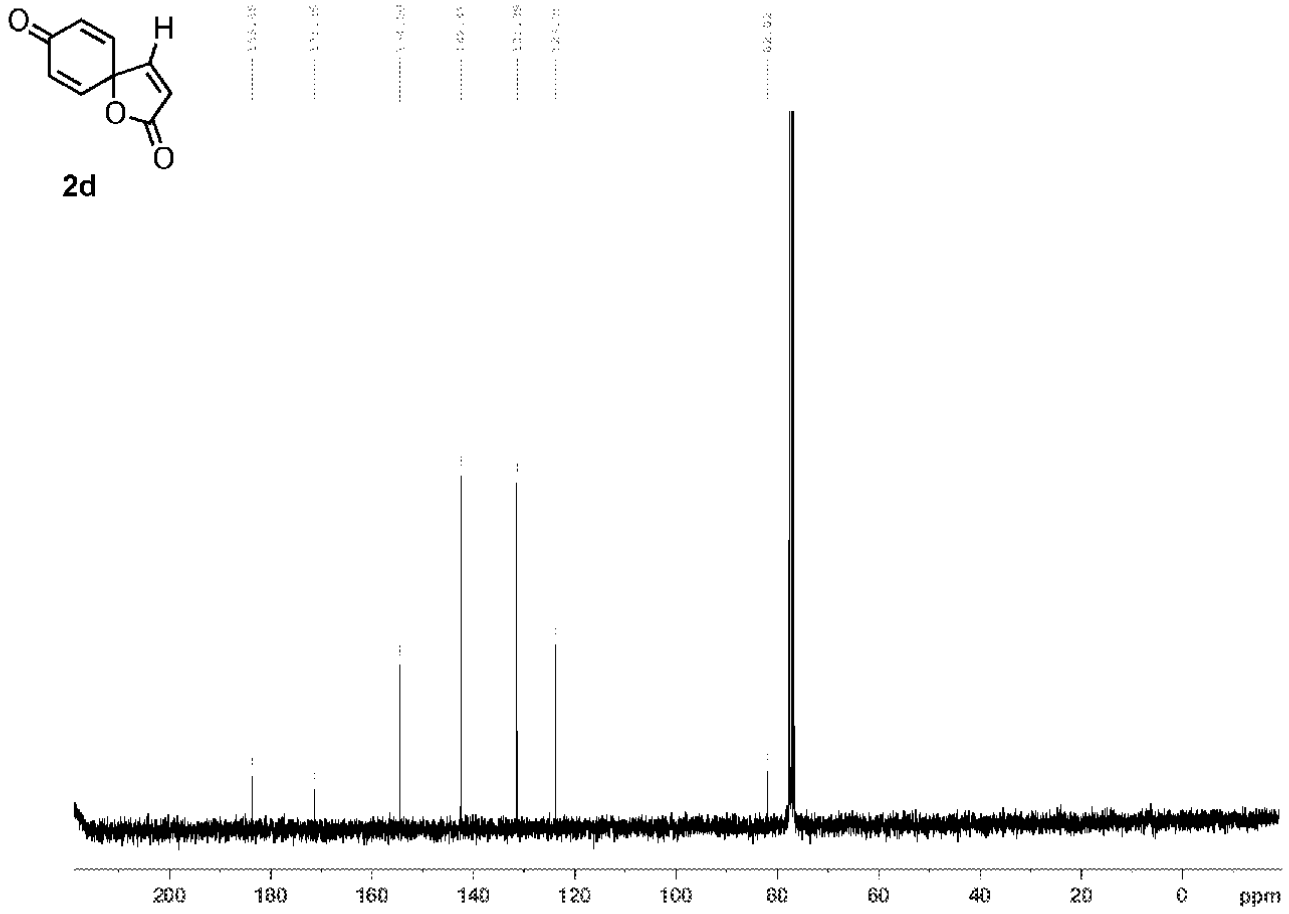
^{13}C NMR spectrum of **2c** recorded in $CDCl_3$



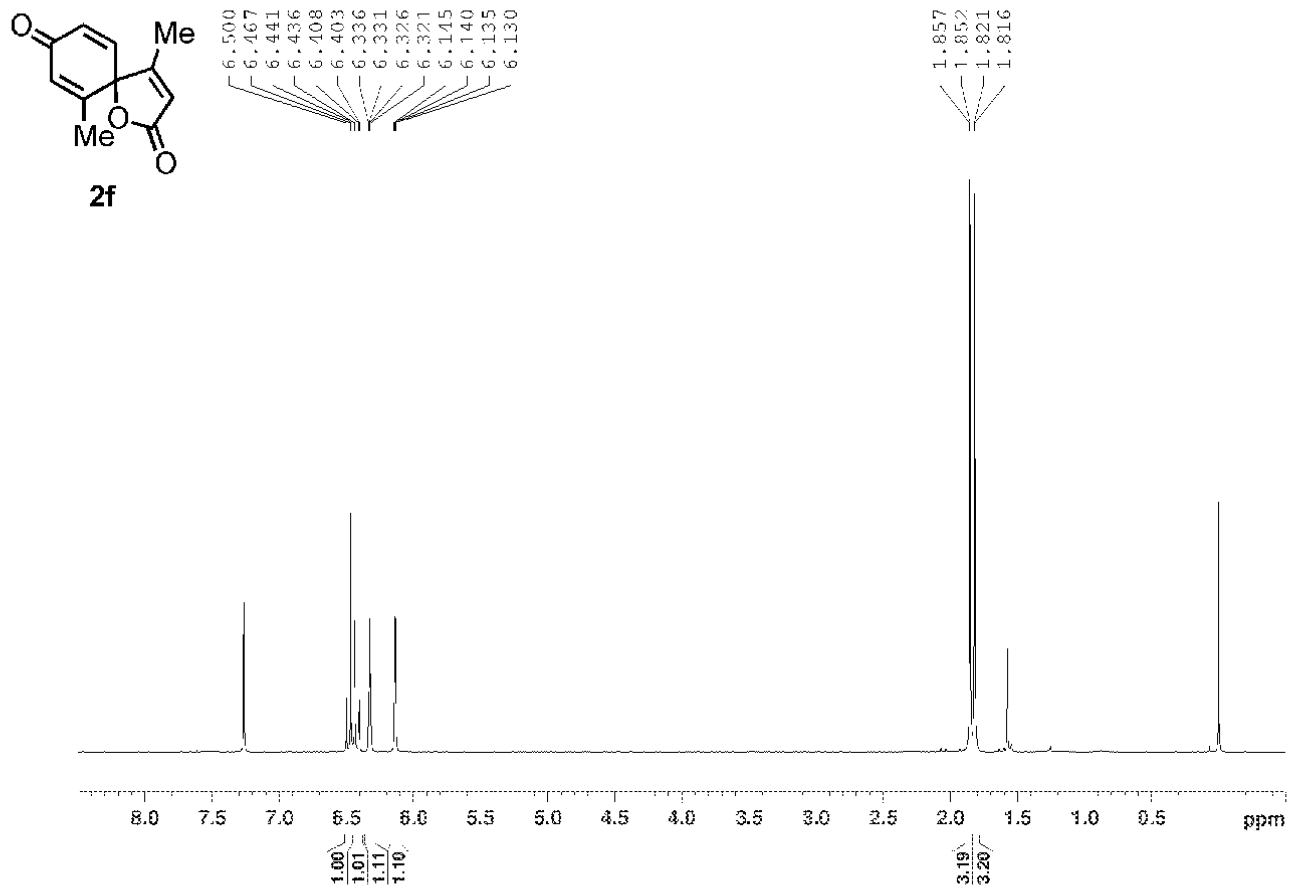
^{1}H NMR spectrum of **2d** recorded in $CDCl_3$



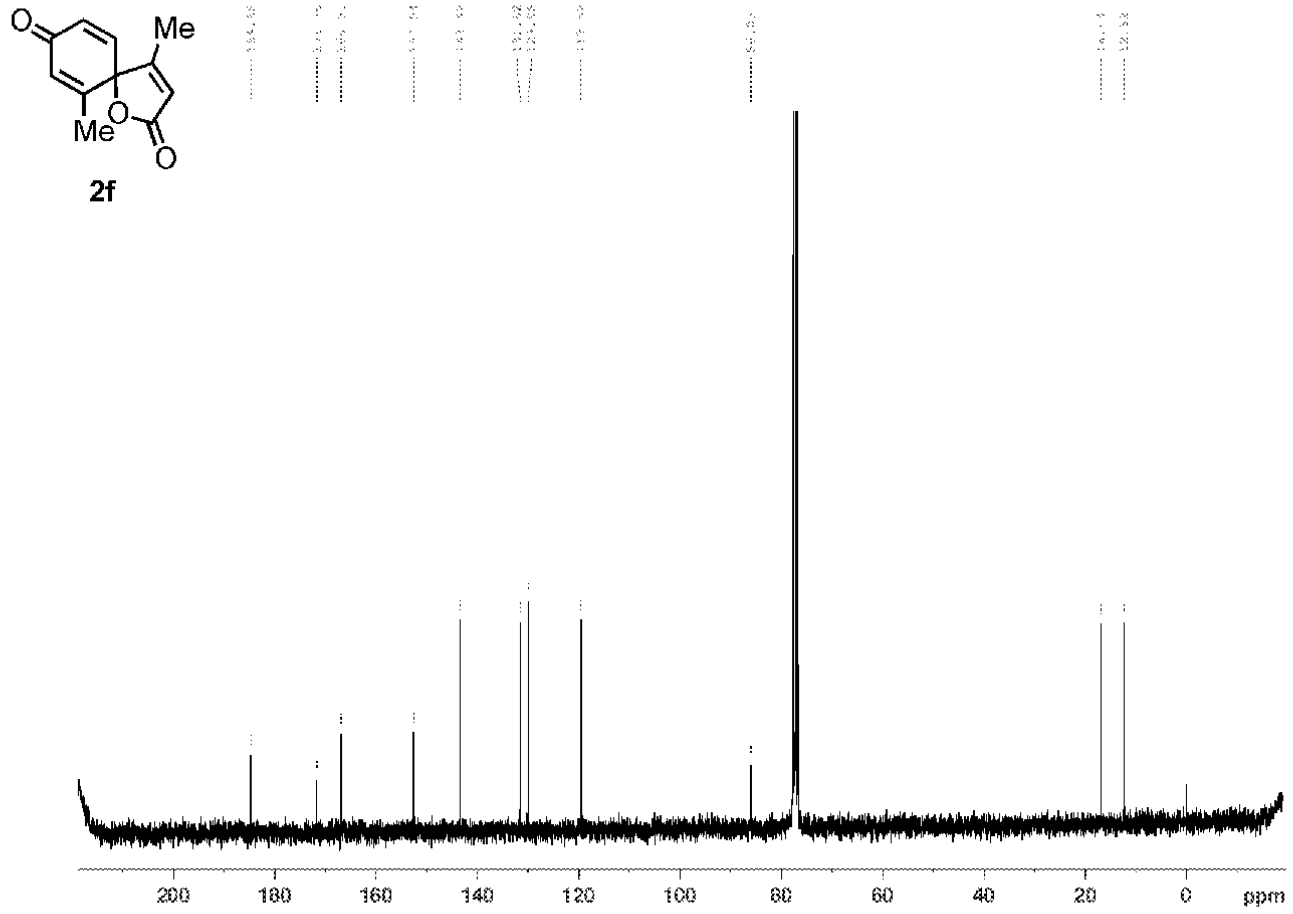
^{13}C NMR spectrum of **2d** recorded in $CDCl_3$



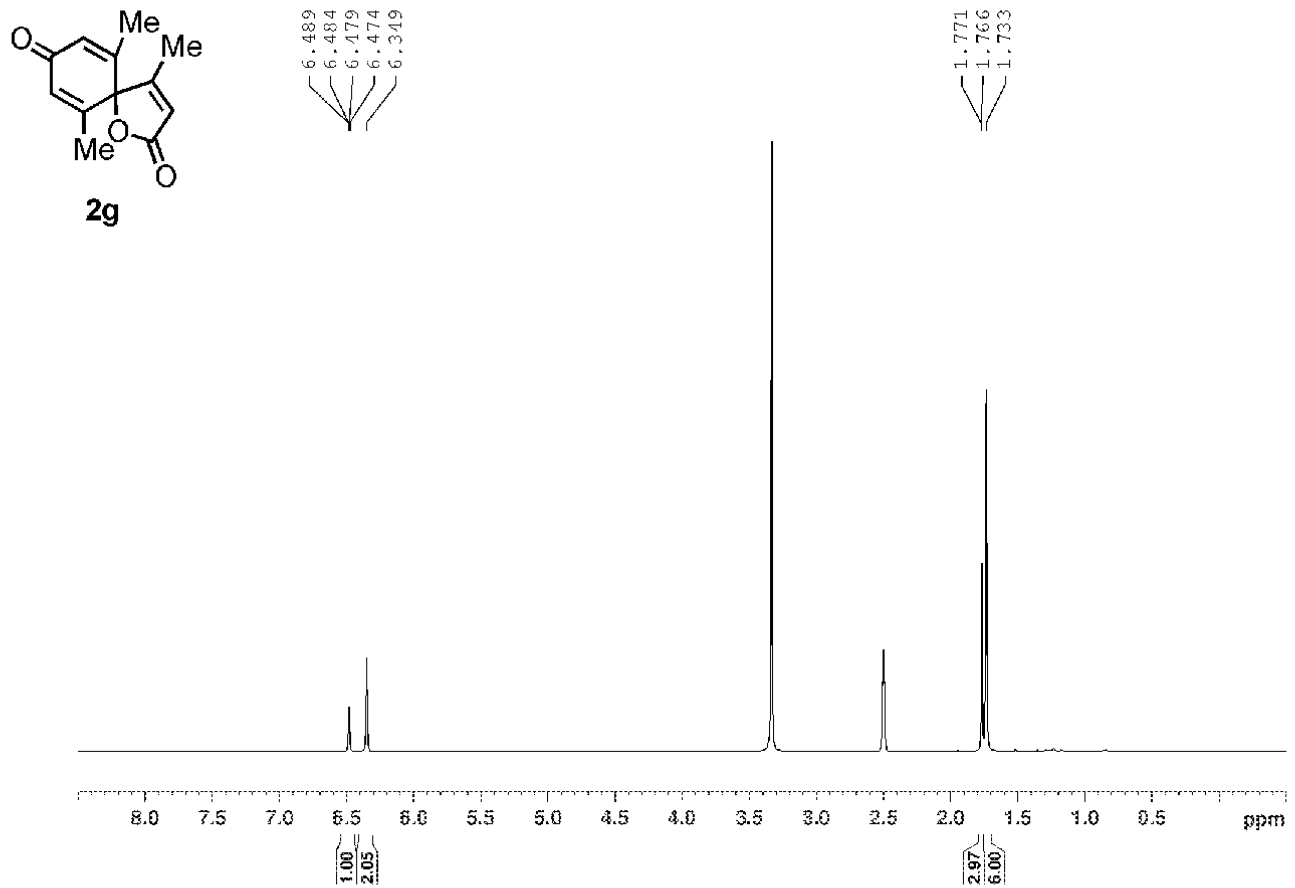
^{1}H NMR spectrum of **2f** recorded in $CDCl_3$



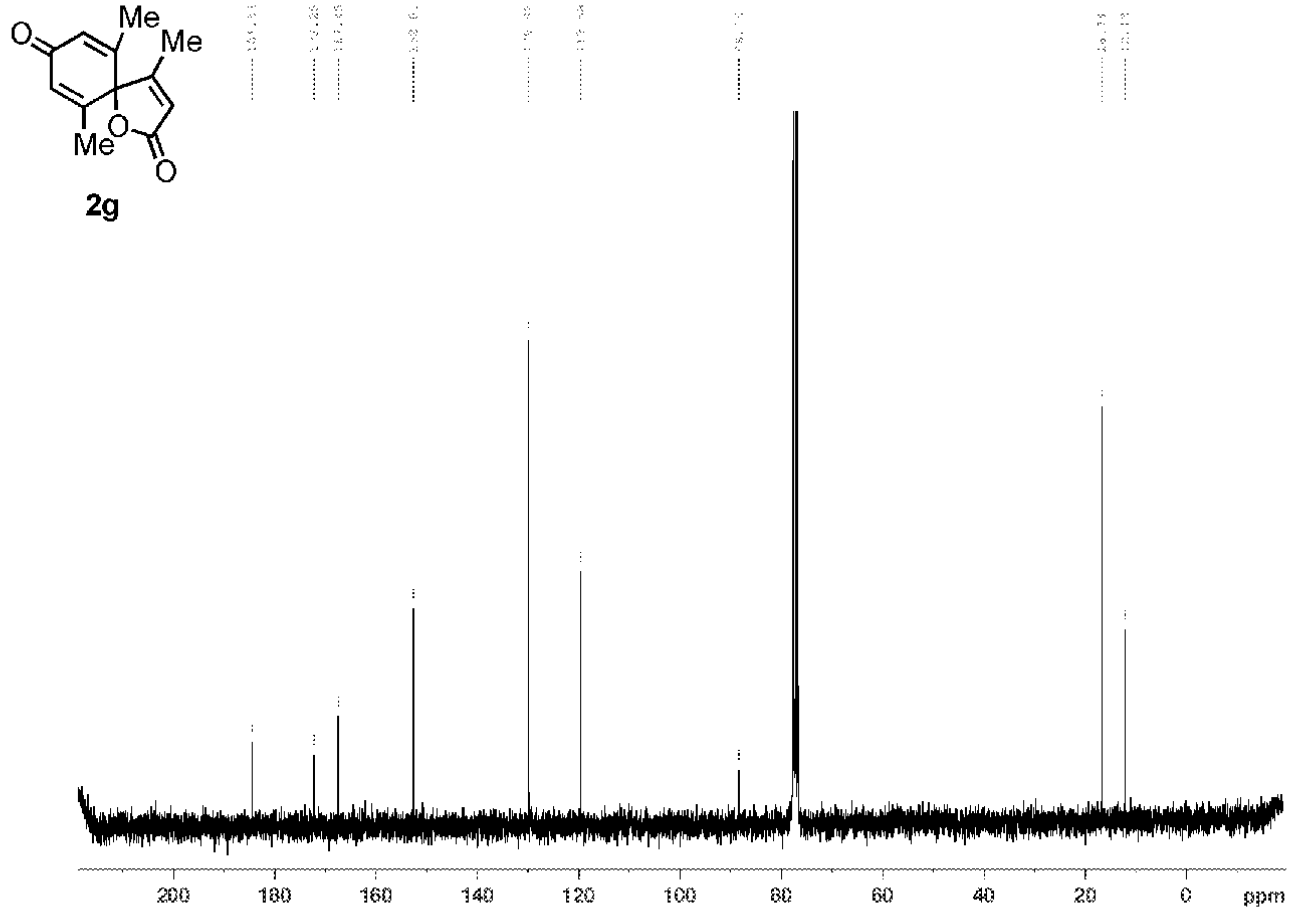
^{13}C NMR spectrum of **2f** recorded in $CDCl_3$



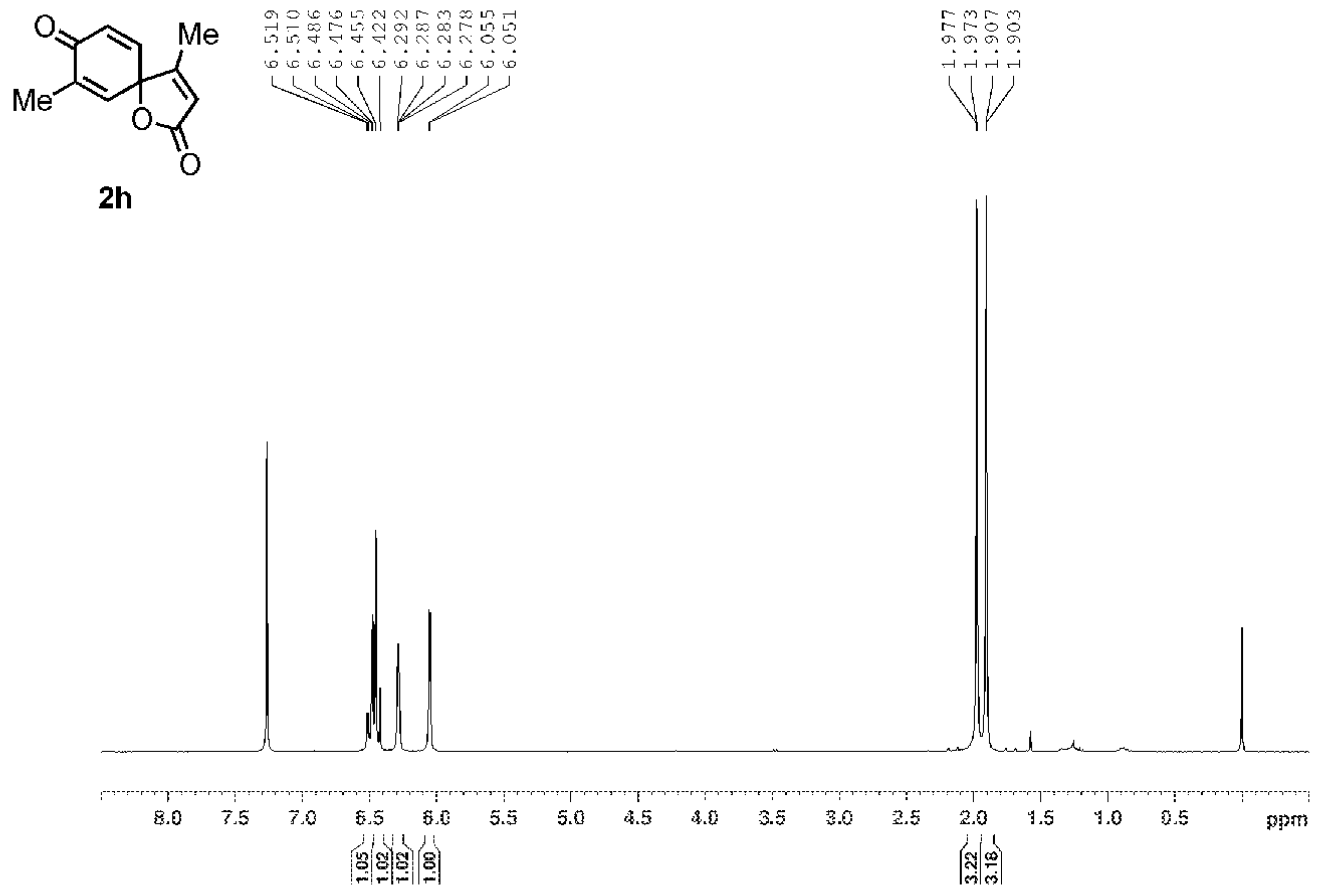
^{1}H NMR spectrum of **2g** recorded in DMSO-d_6



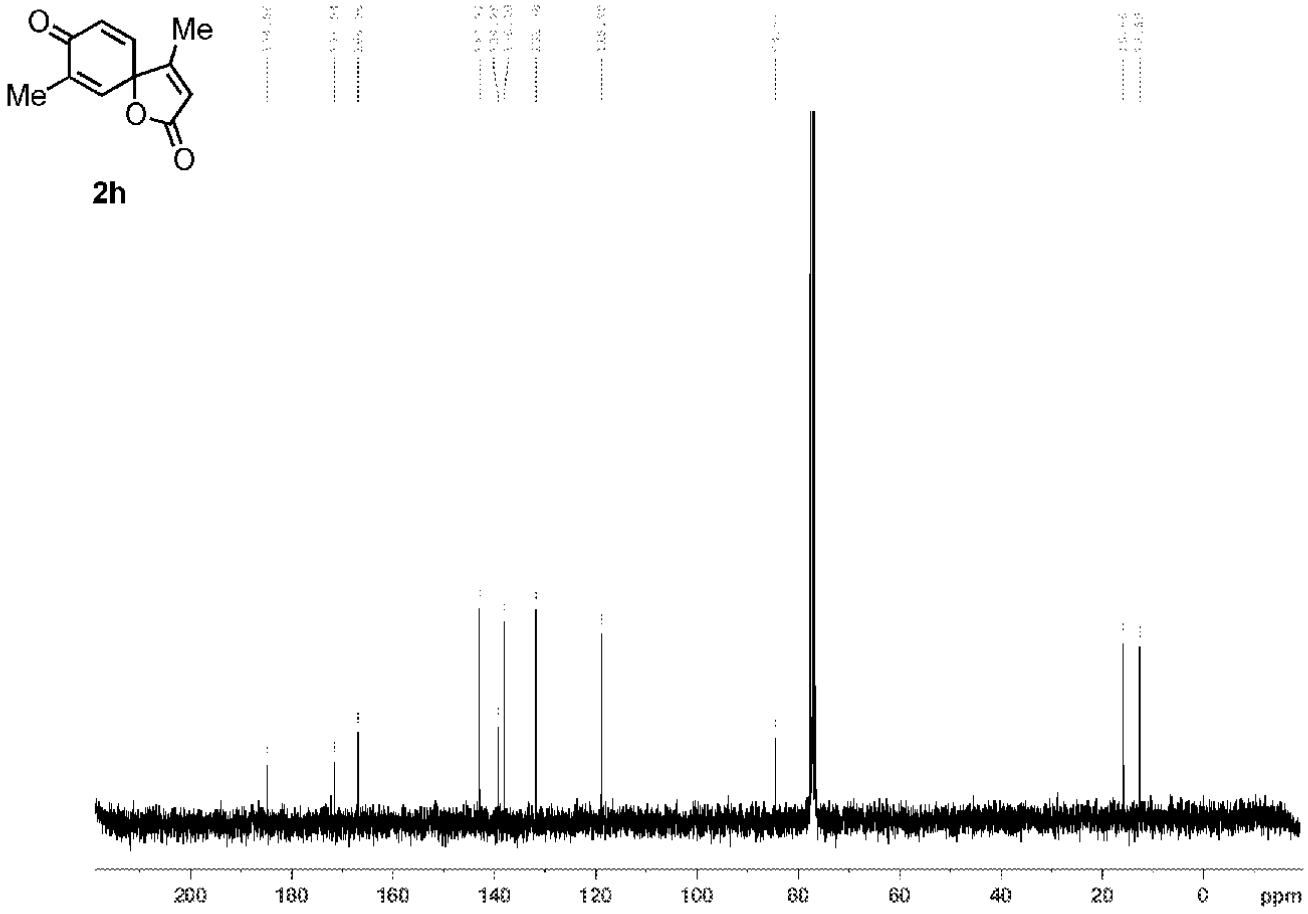
^{13}C NMR spectrum of **2g** recorded in $CDCl_3$



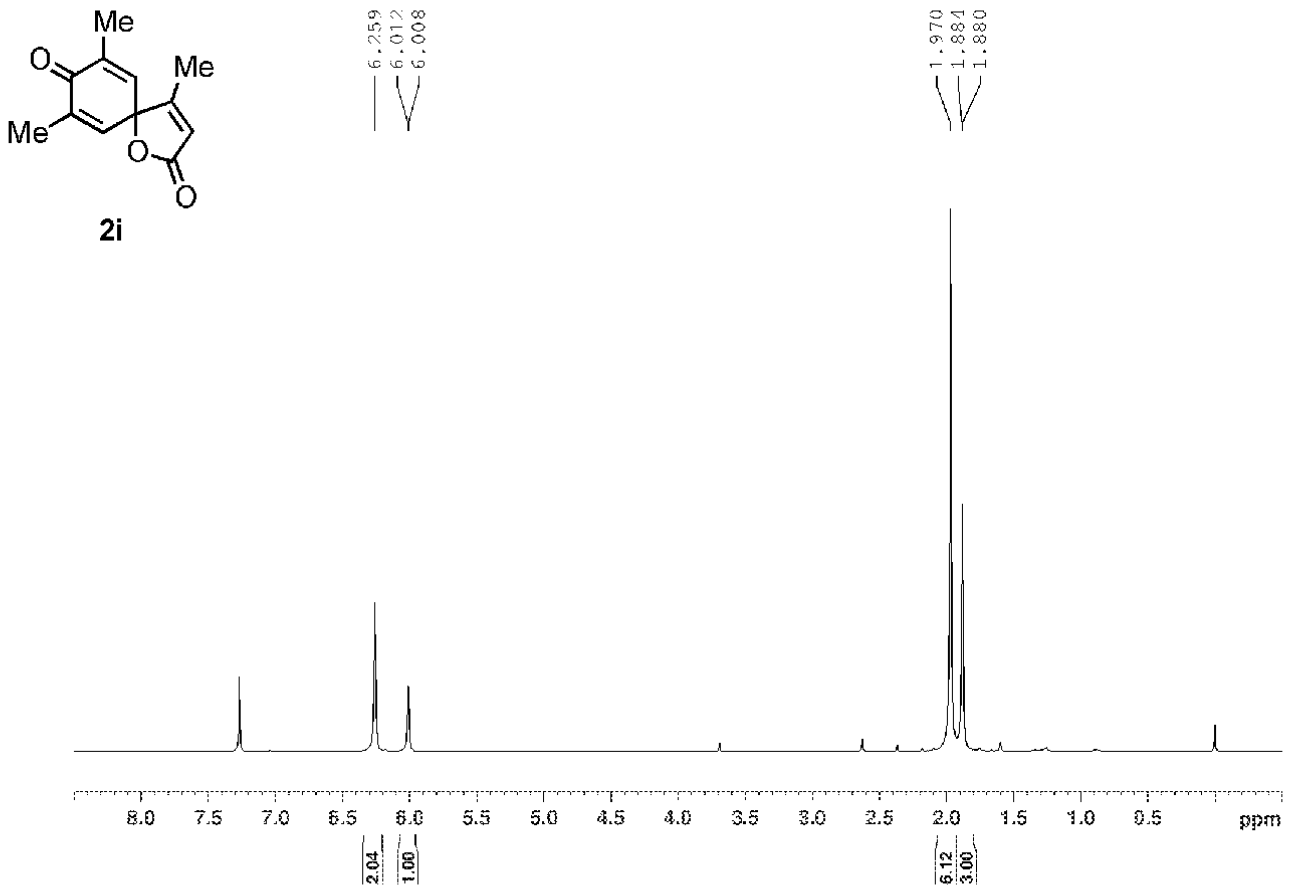
^{1}H NMR spectrum of **2h** recorded in $CDCl_3$



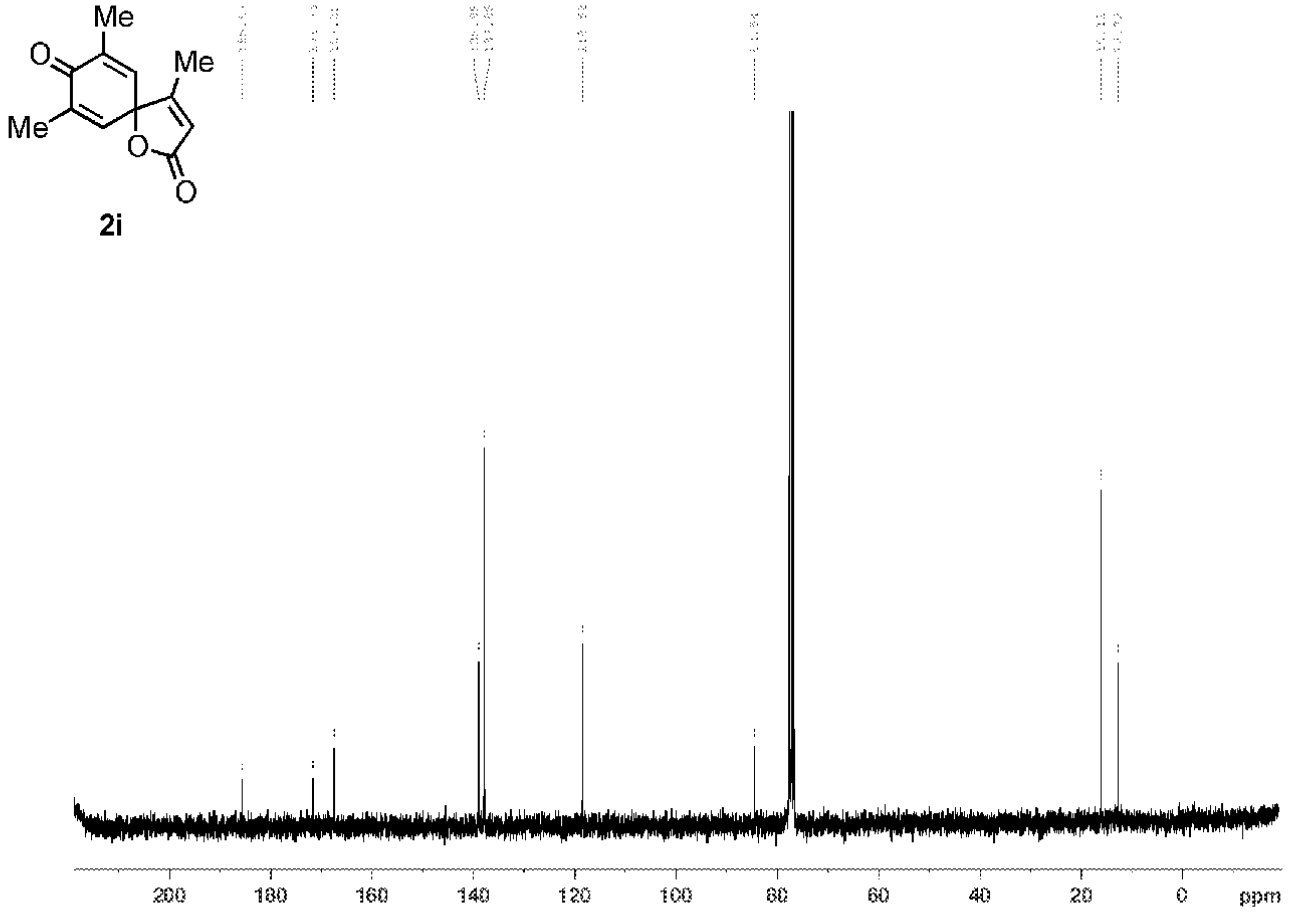
^{13}C NMR spectrum of **2h** recorded in $CDCl_3$



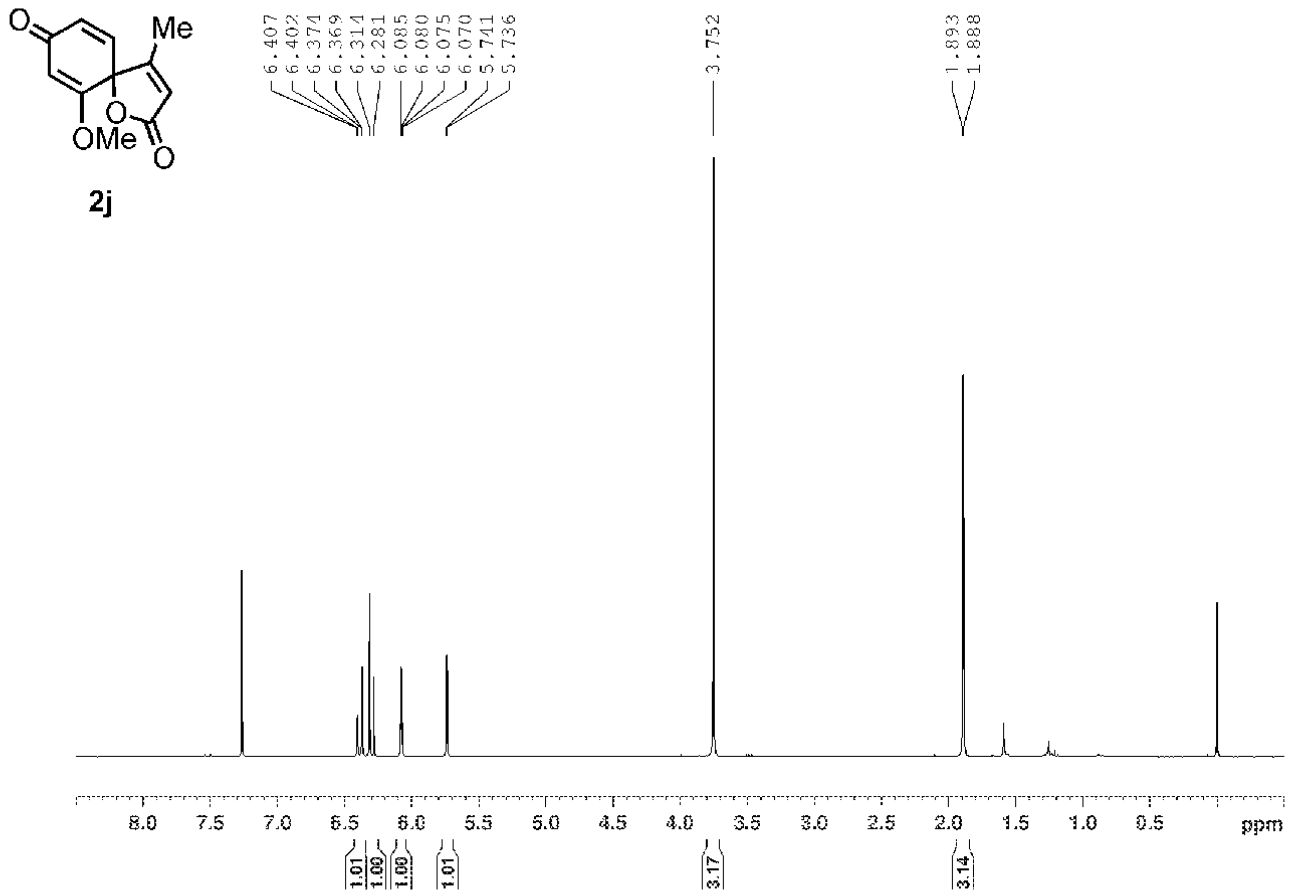
^{1}H NMR spectrum of **2i** recorded in $CDCl_3$



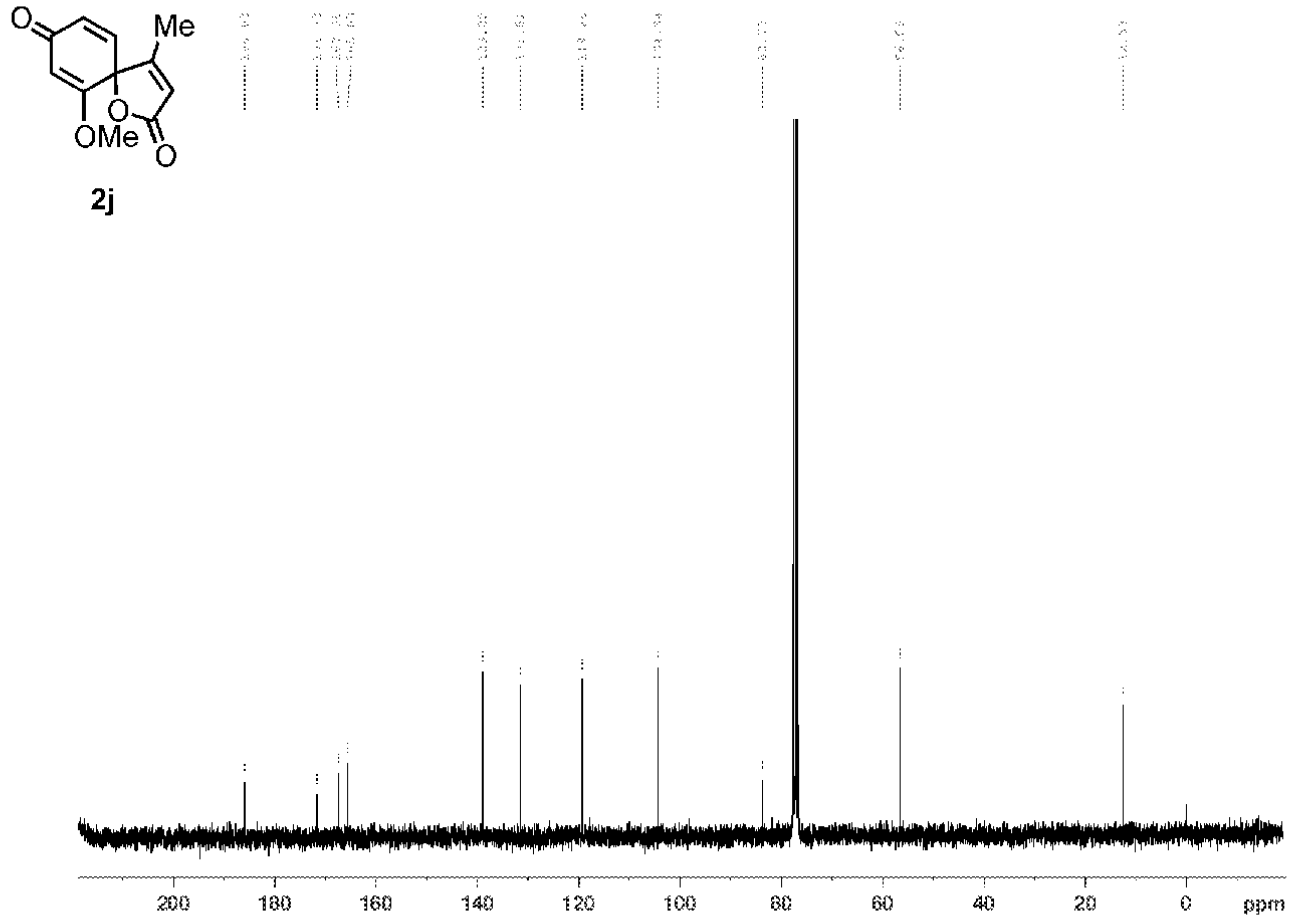
^{13}C NMR spectrum of **2i** recorded in $CDCl_3$



^{1}H NMR spectrum of **2j** recorded in $CDCl_3$

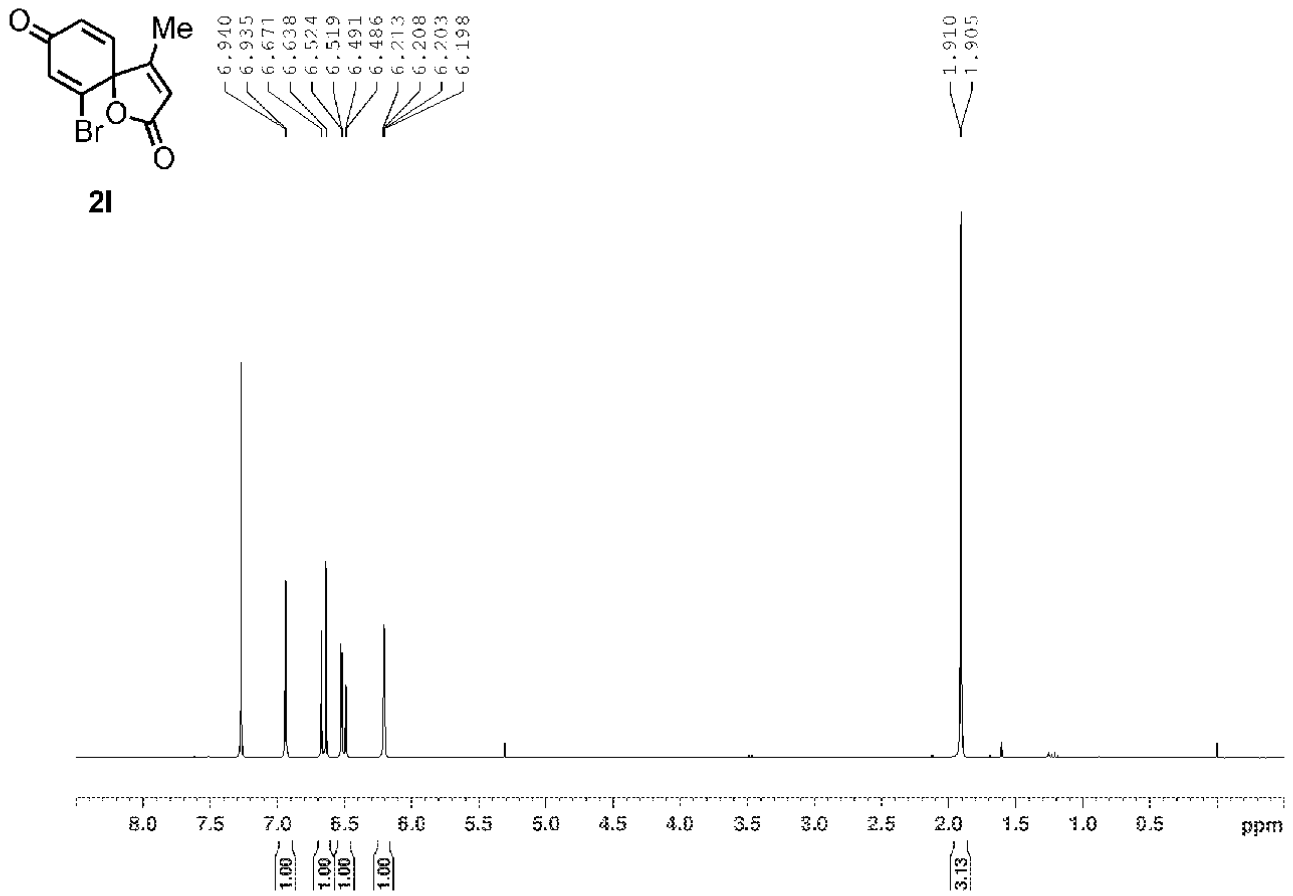


^{13}C NMR spectrum of **2j** recorded in $CDCl_3$

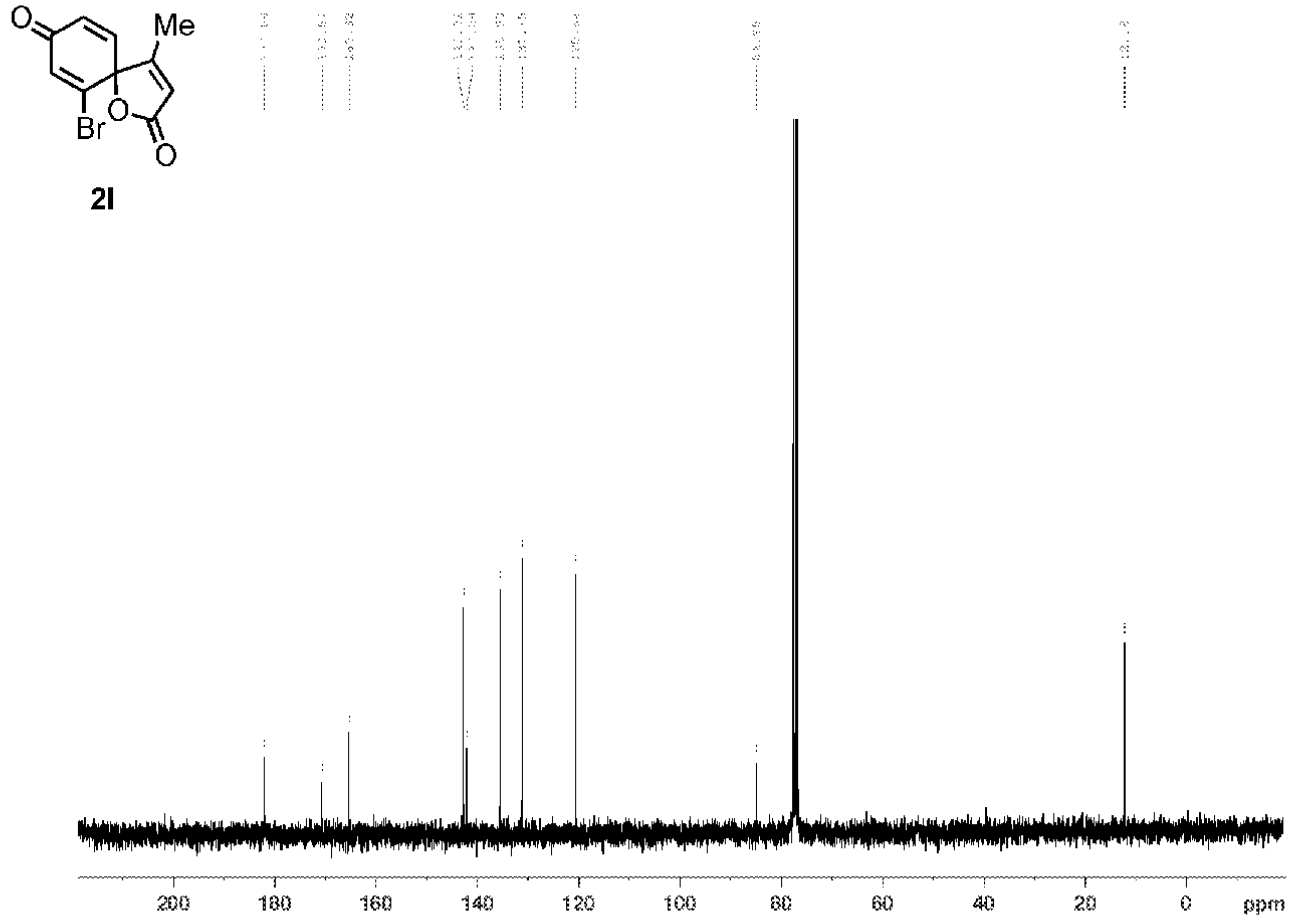


2j

^{1}H NMR spectrum of **2l** recorded in $CDCl_3$

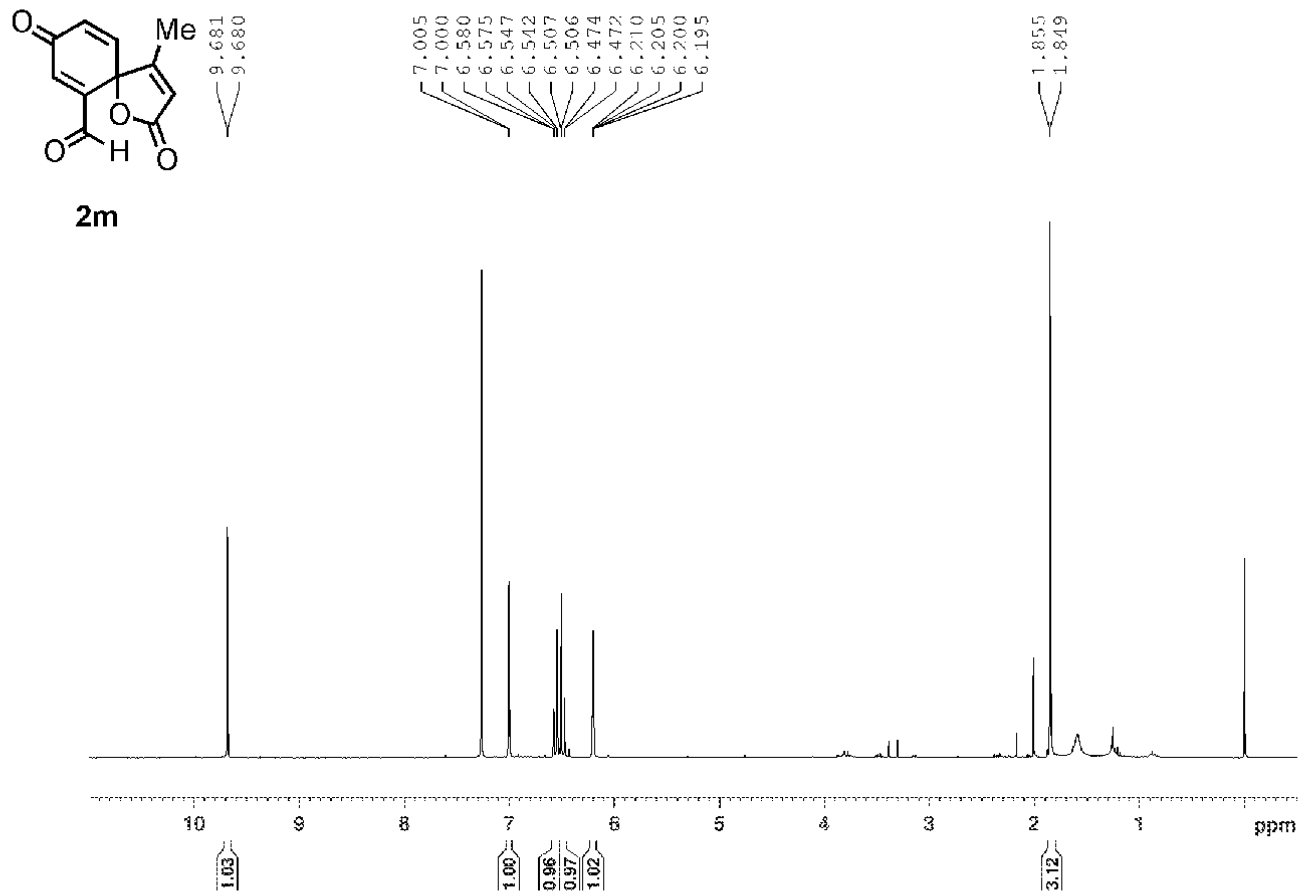


^{13}C NMR spectrum of **2l** recorded in $CDCl_3$

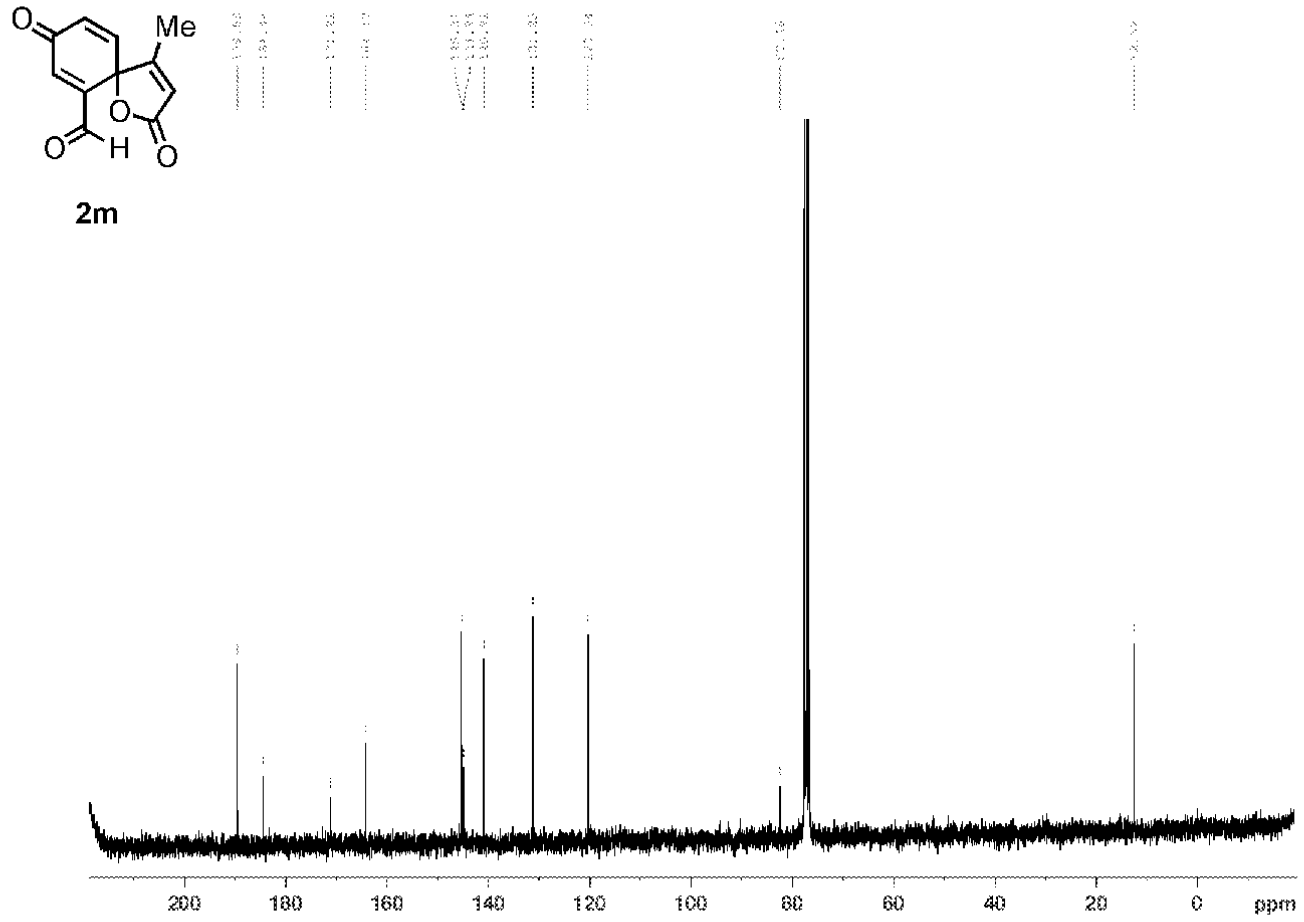


2l

^{1}H NMR spectrum of **2m** recorded in $CDCl_3$

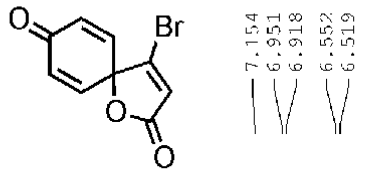


^{13}C NMR spectrum of **2m** recorded in $CDCl_3$

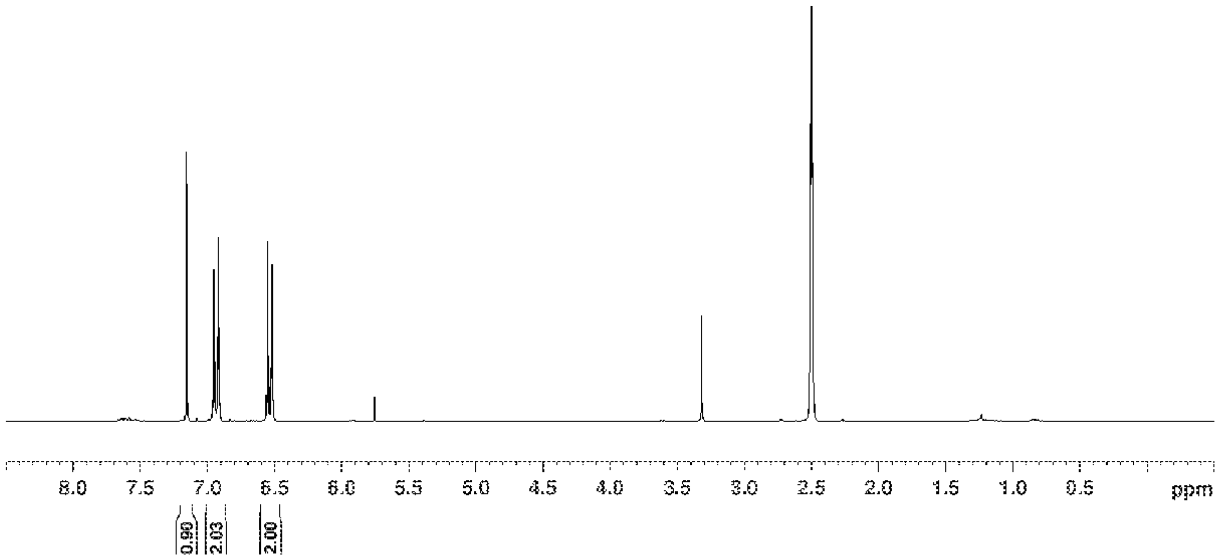


2m

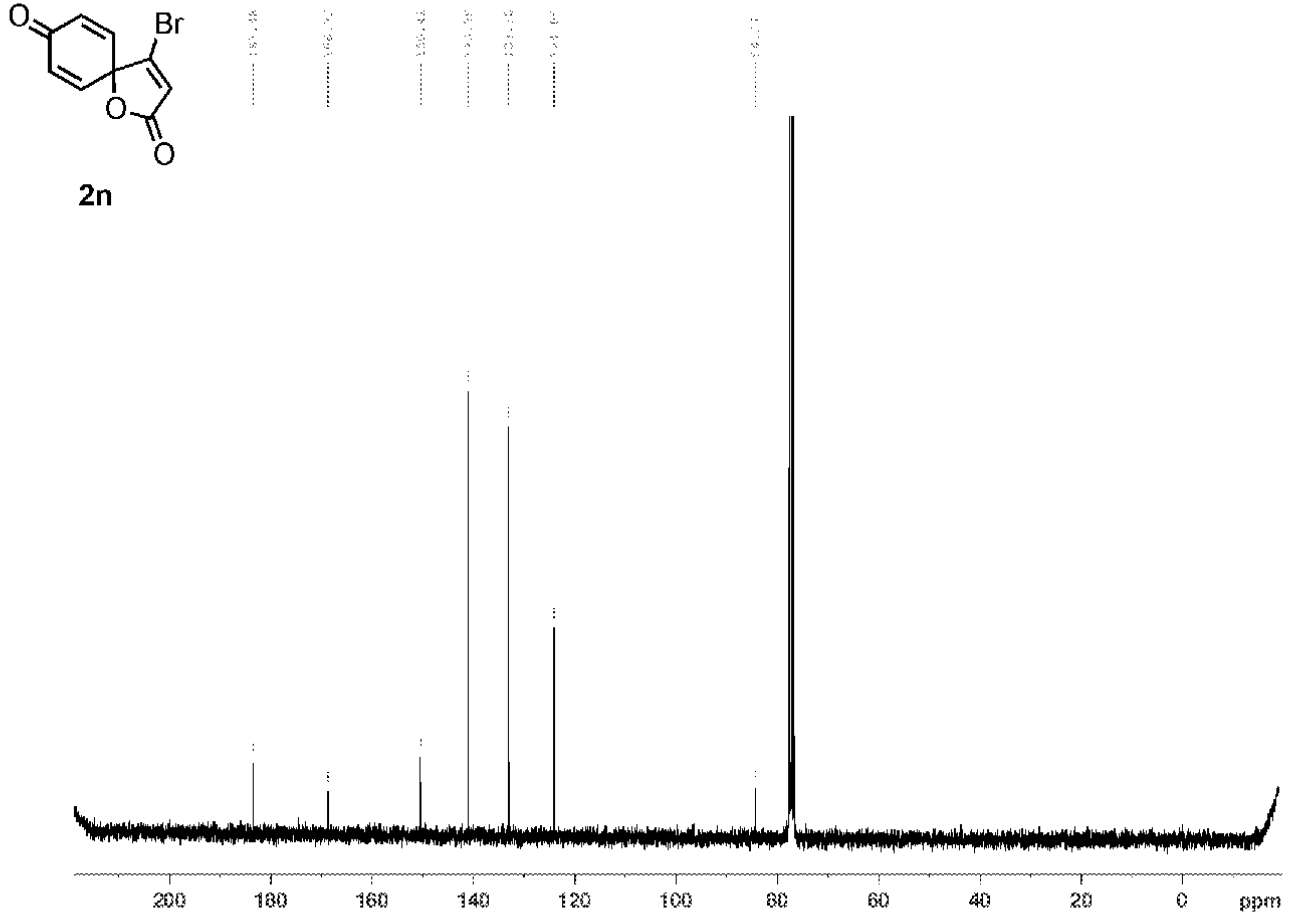
^{1}H NMR spectrum of **2n** recorded in DMSO-d_6



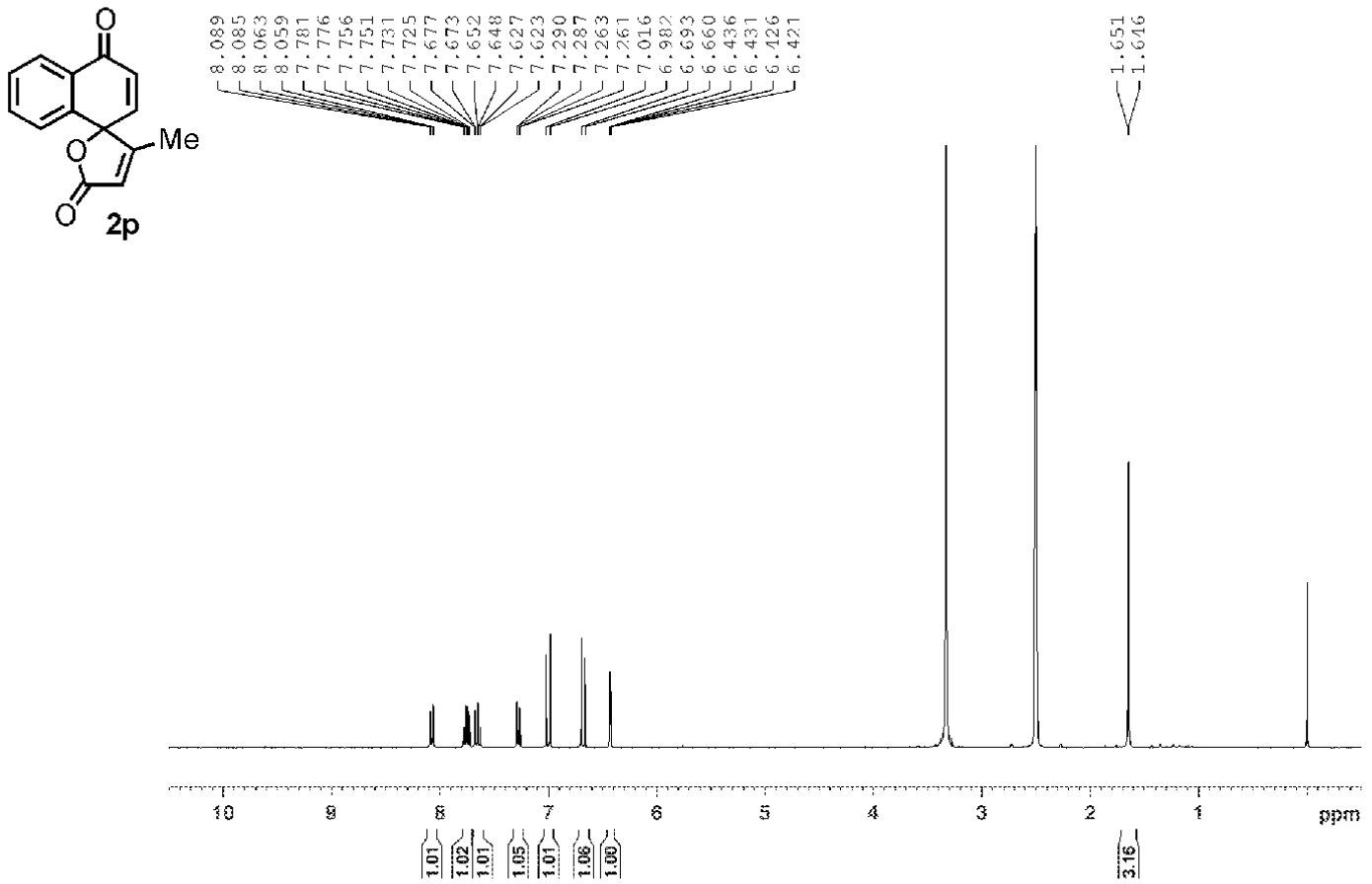
2n



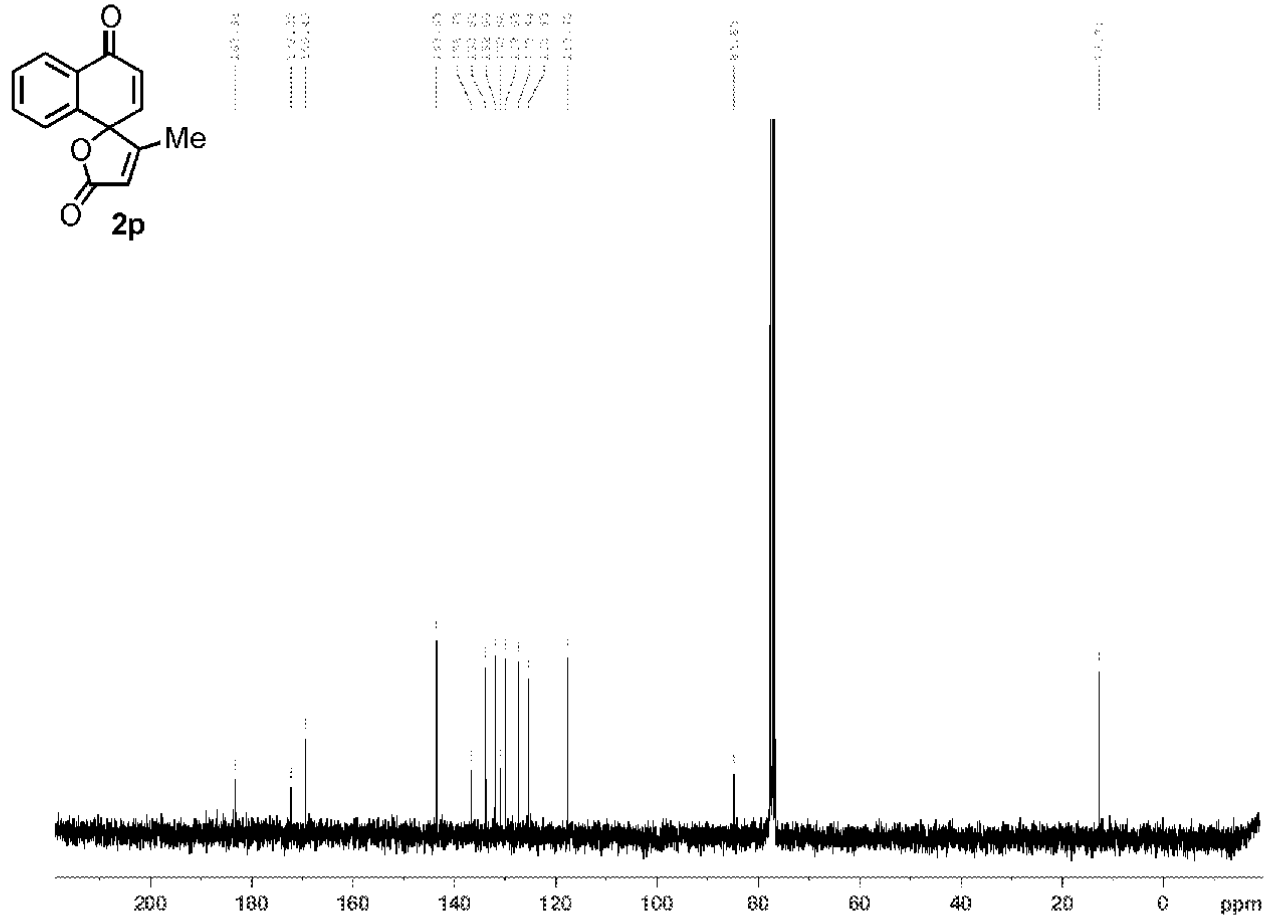
^{13}C NMR spectrum of **2n** recorded in $CDCl_3$



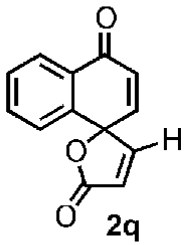
^{1}H NMR spectrum of **2p** recorded in DMSO-d_6

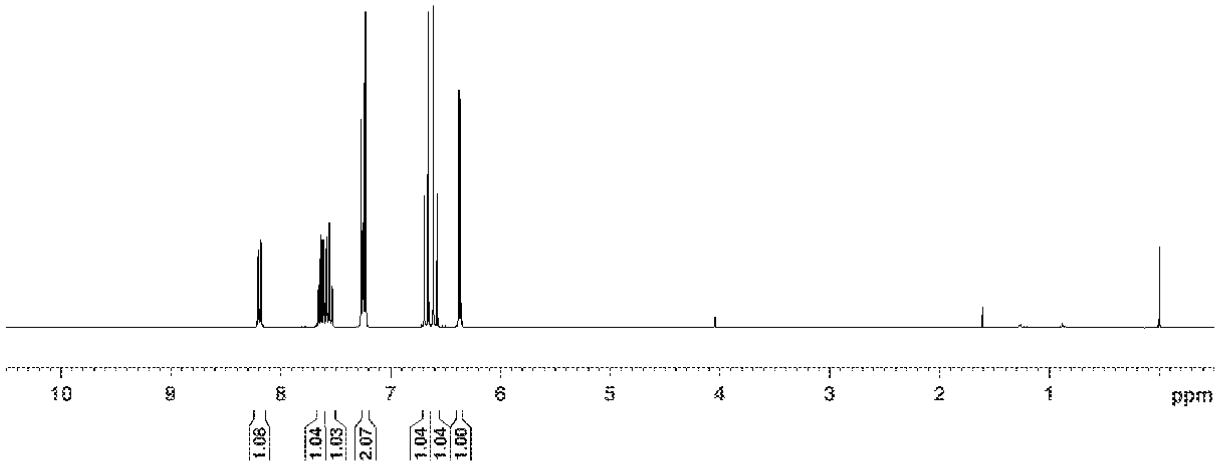


^{13}C NMR spectrum of **2p** recorded in $CDCl_3$

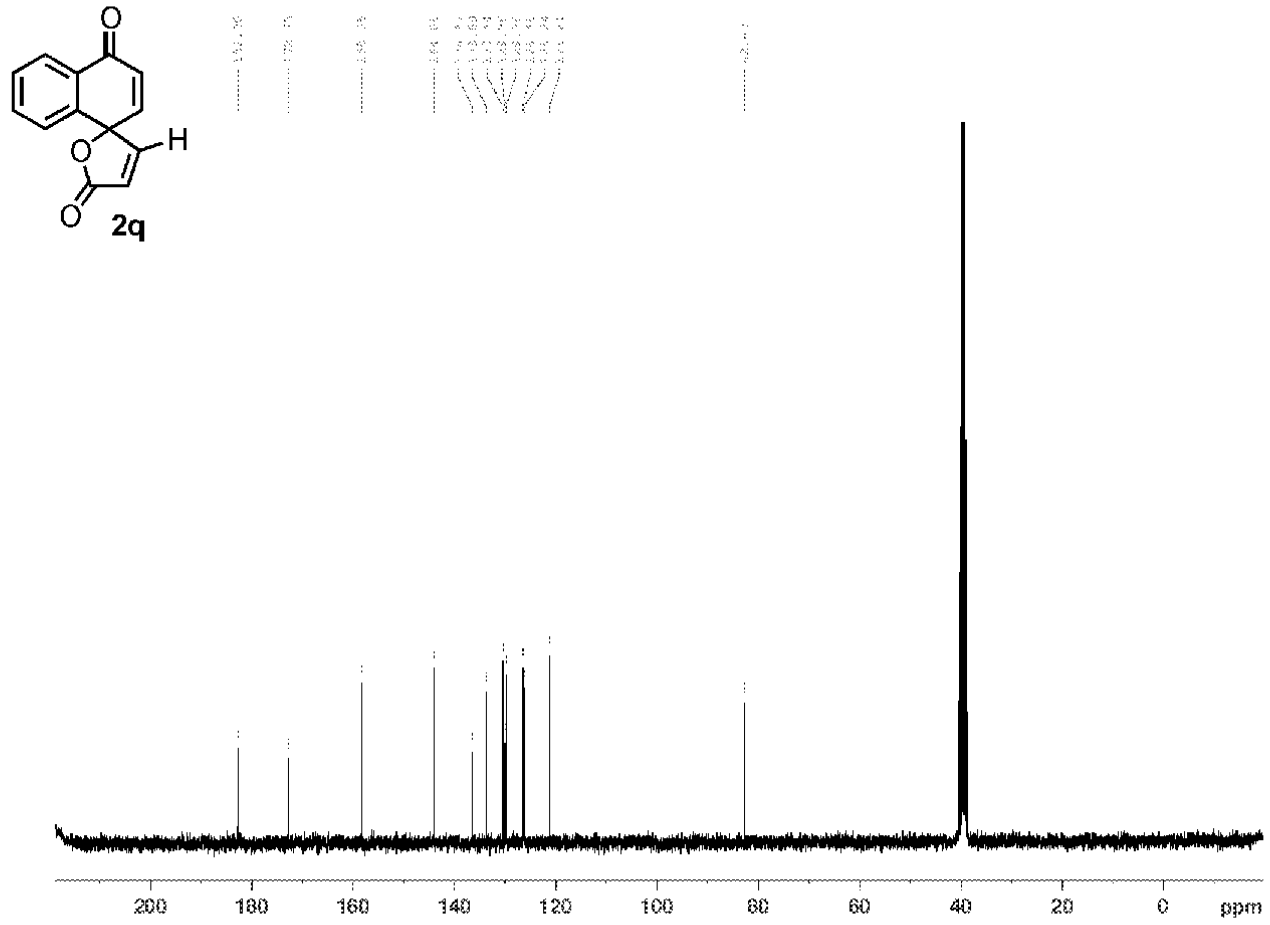


^{1}H NMR spectrum of **2q** recorded in $CDCl_3$





^{13}C NMR spectrum of **2q** recorded in DMSO-d_6



ABSTRACT

Redox-Neutral Catalytic Spirocyclization of *para*-Methoxy Aryl Alkynoate Esters

Mark Docto Aparece

Spirocycles are a class of molecules consisting of a quaternary atom at the junction of two fused rings. This structural motif is found in a number of biologically active natural products and pharmaceuticals. Current strategies to synthesize these structures include classical methods such as alkylation and rearrangement, as well as more modern methods reported in the past decade which utilize electrophilic halogen reagents. As part of our research interests in electrophilic transition metal catalysts to effect powerful transformations, we developed the first redox-neutral spirocyclization of *para*-methoxy aryl alkynoate esters using homogeneous gold catalysis. The reaction proceeds at ambient temperature in dichloromethane with 5 mol % loading each of $Au(PPh_3)Cl$ catalyst and AgOTf activator. The addition of 1 equivalent of water was found to be essential for the success of the reaction, playing a crucial role as a nucleophile in the proposed reaction mechanism. During our investigation of the substrate scope of the reaction, we found that substrates bearing various groups on the alkyne underwent spirocyclization in good to excellent yields in short reaction times. In addition, both electron-rich and electron-deficient aromatic rings were well tolerated under these reaction conditions. However, substrates bearing strongly deactivating groups on the alkyne failed to react. Using our conditions, we were also able to directly access the tricyclic core of the antifungal compound perenniporide A, a spirocyclic secondary metabolite of *Perenniporia* sp., a fungus found in the Chinese medicinal plant *Fallopia japonica*.