Gold Catalyzed Cyclization, Cycloisomerization to Fused N-Heterocycles and Phosphine Mediated α-Halogenation: A Consequence of Ambivalent Ynamide

A Thesis
Submitted for the Degree of
DOCTOR OF PHILOSOPHY

By

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June, 2015

To

My Parents

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STATEMENT

I hereby declare that the matter embodied in this thesis **entitled** "Gold Catalyzed Cyclization, Cycloisomerization to Fused N-Heterocycles and Phosphine Mediated α-Halogenation: A Consequence of Ambivalent Ynamide" is the result of investigation carried out by me in the School of Chemistry, University of Hyderabad, Hyderabad, India, under the supervision of **Dr. Akhila Kumar Sahoo**.

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CERTIFICATE

Certified that the work contained in the thesis entitled "***Gold Catalyzed Cyclization, Cycloisomerization to Fused N-Heterocycles and Phosphine Mediated α-Halogenation: A Consequence of Ambivalent Ynamide***" has been carried out by ***Mr. Sanatan Nayak*** under my supervision. I declare that this work has not been submitted previously in part or in full to this university or other university or institution for the award of any degree.

Dr. Akhila Kumar Sahoo

(Supervisor)

Dean

School of Chemistry

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Sanatan Nayak

University of Hyderabad

June, 2014

List of Abbreviations

α	alpha
aq	aqueous
β	beta
Boc	*tert*-butyloxycarbonyl
Bn	benzyl
br	broad
^{t}Bu	*tert*-butyl
Bz	benzoyl
°C	degree celsius
^{13}C NMR	carbon-13 nuclear magnetic resonance spectroscopy
CH_3CN	acetonitrile
$CHCl_3$	chloroform
m-CPBA	*m*-chloroperbenzoic acid
d	doublet
1,2-DCE	1,2-dichloroethane
DCM	dichloromethane
DMAP	4-dimethylaminopyridine
dd	doublet of doublet
DG	directing group
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
dt	doublet of triplet
ESI	electron-spray ionization
FT-IR	fourier transform infrared spectroscopy
^{1}H NMR	proton nuclear magnetic resonance spectroscopy
HRMS	high-resolution mass spectroscopy
Hz	hertz
J	coupling constant in hertz
NBS	*N*-bromosuccinimide

NCS	*N*-chlorosuccinimide
Ns	nosyl
$PhI(OCOCF_3)_2$	phenyl iodo trifluoroacetate
^{i}Pr	*iso*-propyl
THF	tetrahydrofuran
TMS	trimethylsilyl
Ts	tosyl
Ns	nosyl
DEAD	Dietyl azodicarboxylate
DIAD	Diisopropyl azodicarboxylate

Chapter 1

Ynamide a Versatile Tool for Gold Catalyzed Organic Transformation: An Introduction

Abstract

The emergence and ambivalence nature of ynamide is briefly discussed. The preparation of ynamide under the influence metal catalyst is discussed. The synthetic utility of ynamides towards the construction of various nitrogen-containing structural motifs is briefed. In the second part, the physical features and reactivity of gold catalysis is briefly highlighted. The importance of gold-catalysis in the development novel synthetic transformations is underlined. The origin of carbophilic reactivity of gold is discussed. The synthetic potential of gold-catalyzed cycloisomerizations is highlighted. Inspiration drawn from the overview of the work on Au-catalyzed transformations of ynamides, this thesis work primarily focused on the development of novel Au-catalyzed transformations of ambivalent ynamides.

Section I: Ynamide a versatile Tool for Organic synthesis: An introduction

1.1. Introduction

Heteroatom substituted alkyne is one of the versatile building blocks in organic chemistry.[1] The alkyne having a nitrogen in the terminus is called ynamines. The inherent polarization of lone pair electron of nitrogen differentiate two sp-hybridized carbon atoms in ynamines and became highly reactive.[1] Unlike enamines, synthetic potential of ynamines remain limited because of the difficulties in synthesis, high reactivity and handling. Interestingly, induction of an electron withdrawing group on the nitrogen diminishes the electron delocalization towards the alkyne, which in turn contributes increasing stability of ynamines. The electron-deficient ynamines are called ynamides. Ynamides possess superior stability and balanced reactivity compared to traditional ynamines. The electron withdrawing group attached on nitrogen can be vinylogous amide, carbamate or sulfonamide. Some typical ynamide structures are shown in Figure 1.1.[1]

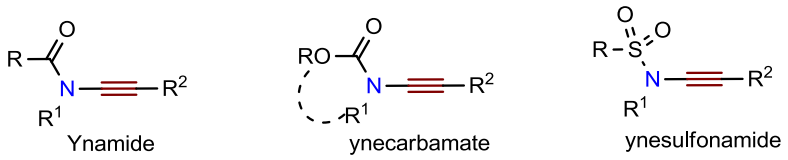
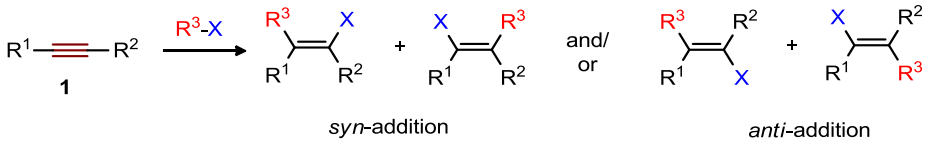


Figure 1.1. Typical structure of ynamide

Alkynes are extremely useful building blocks in organic synthesis; however, intermolecular addition on alkynes can often produce mixture of possible product isomers (Scheme 1.1).[2]



Scheme 1.1. Addition reaction on alkyne

Gratifyingly, electron withdrawing group (EWG) bearing N-protected ynamides, a surrogate of alkynes, exclusively undergoes various reactions with high regioselectivity. The inherent polarization of the nitrogen lone pair of ynamide differentiates the reactivity at both-end of the alkyne motifs (Figure 1.2). Ynamide is an ambivalent species; therefore, addition of electrophile and nucleophile occurs at the particular site of ynamide in a regioselective manner.

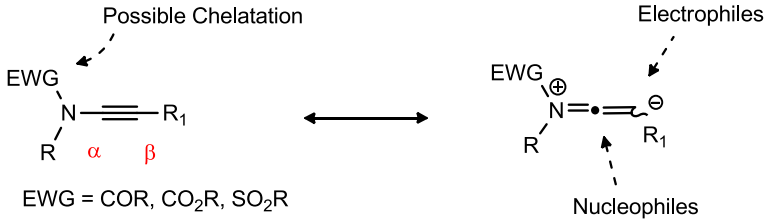


Figure 1.2. Reactivity of ynamide

Furthermore, the profound chelation ability of the electron withdrawing group in ynamide to the metal permits the occurrence of various selective transformations. The chelation also directs the regioselective addition to the ynamide triple bond.

Ynamides undergo wide variety of transformations providing opportunity for the inclusion of nitrogen moiety in a molecule (Figure 1.3). The feasible reactions on ynamides is shown in Figure 1.3.[3]

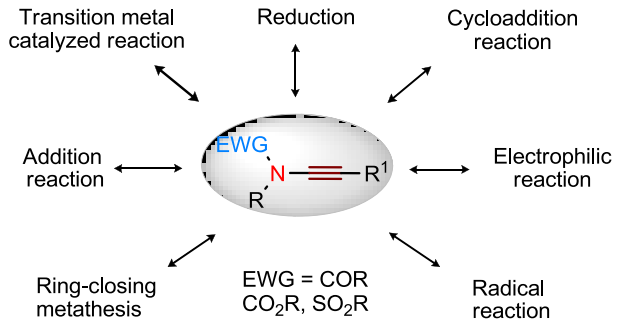
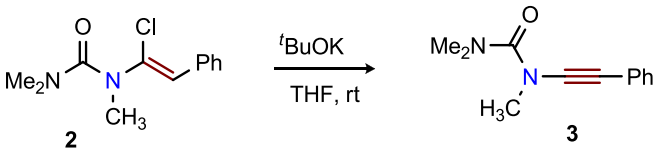


Figure 1.3. Synthetic transformation on ynamide

1.2. Synthesis of Ynamides

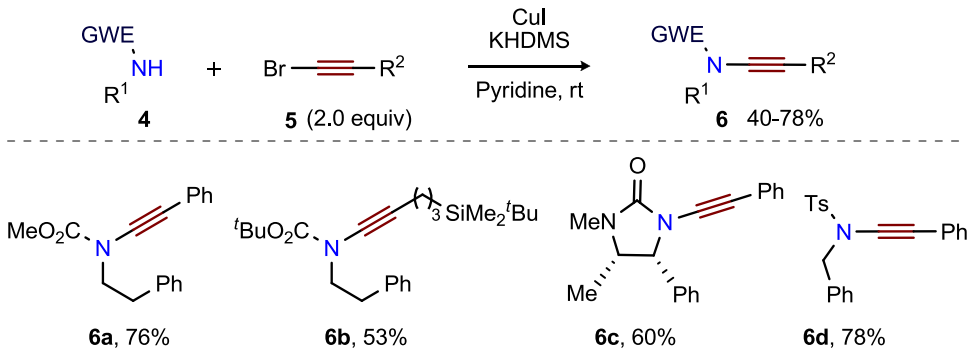
In 1972, Veihe and co-workers at first reported synthesis of ynamide from haloenamide.[4] The base promoted elimination of HCl from urea substituted chloroenamide ***2*** delivered ynamide ***3*** (Scheme 1.4). Although successful, this method suffers with restricted substrate scope.



Scheme 1.4. Synthesis of ynamide from halo-enamides

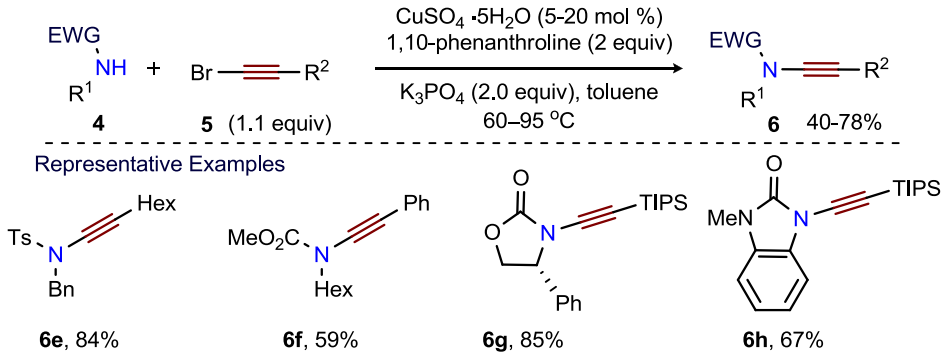
Synthetic study of ynamides has become practical in recent years; for instance, the Cu-catalyzed coupling reactions are extensively employed for the synthesis of ynamides. In 2003, Danheiser and Dunetz reported stoichiometric CuI mediated coupling of bromoalkynes with nitrogen-containing compound for the synthesis of ynamides at room temperature (Scheme 1.5).[5] This method provides access to the synthesis of few N-carbamate protected ynamides in moderate yields (**6a–d**). The requirement of moisture

sensitive base, stoichiometric amount of Cu-salt and the use of large quantity of pyridine inhibit synthetic viability.[5]



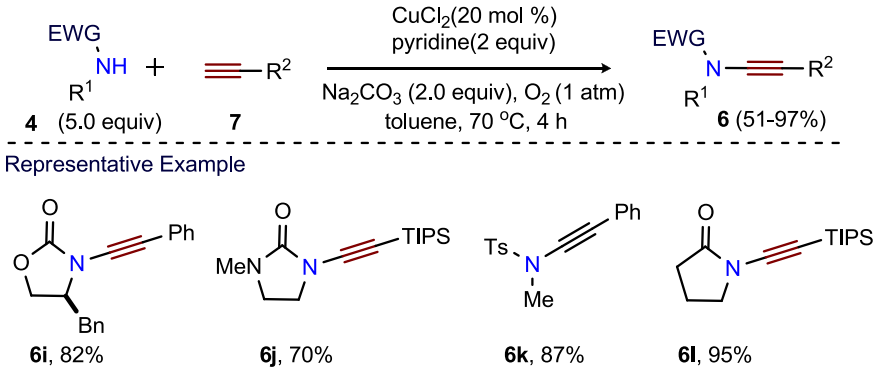
Scheme 1.5. CuI mediated C–N bond formation.

Hsung and co-workers developed an improved method for the synthesis of ynamides through the $CuSO_4$-catalyzed coupling of N-protected amide with bromo-alkynes in the presence of 1.10-phenanthroline ligand and base K_3PO_4 (Scheme 1.6).[8] The reaction showed broad substrate scope tolerating various functional groups and therefore widely useful.[6]



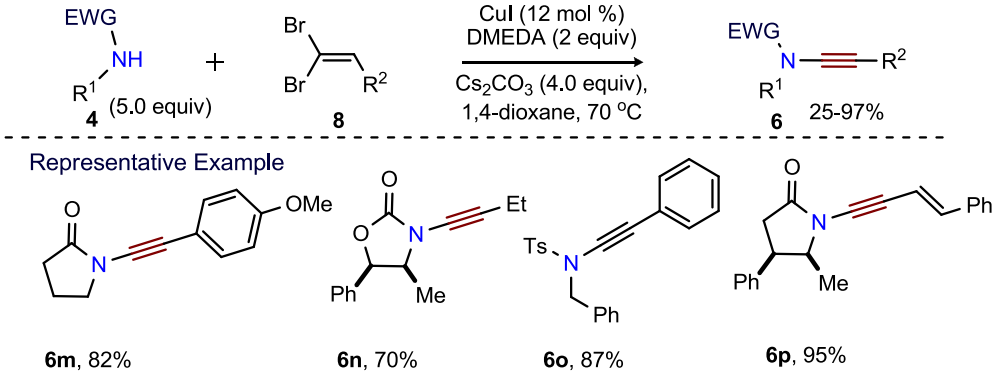
Scheme 1.6. $CuSO_4 \cdot H_2O$ mediated C–N bond formation

The Cu-catalyzed base assisted direct coupling between N-protected amide and terminal-alkynes for the synthesis of ynamides is demonstrated by Stahl and co-workers (Scheme 1.7).[7] Oxygen helps aerobic re-oxidation of copper catalyst, making the catalytic cycle alive. Wide varieties of ynamides **6i–l** are synthesized in good yields. This method is unsuccessful for the synthesis of acyclic N-carbamate bearing ynamides. The slow addition of alkyne under the source of nitrogen prevents the formation of alkyne homocoupling, a necessary condition required for the formation of major amount of ynamides.



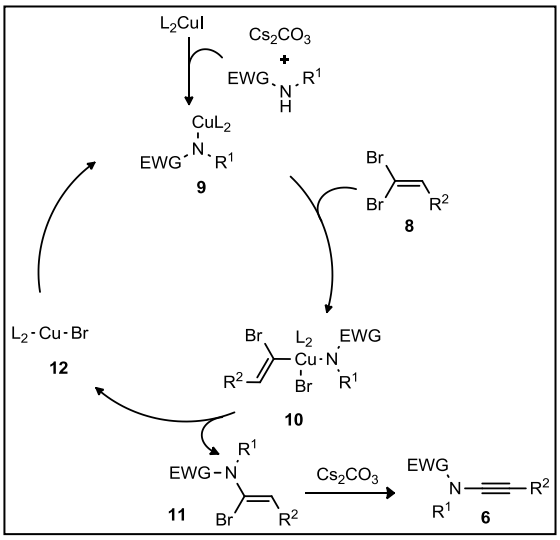
Scheme 1.7. $CuCl_2$ mediated C–N bond formation

Evano and co-workers showed an alternate method for the synthesis of ynamide involving CuI-catalyzed coupling between **4** and dibromoalkenes **8** in the presence of DMEDA-ligand (Scheme 1.8). In case of expensive or unavailable alkyne-precursors employed for ynamide preparation, the current protocol has especially been useful. Dibromoalkenes **8** are readily synthesized from an aldehyde using Seyferth-Gilbert homologation reaction. The reaction exhibited broad scope, for example, pyrrolidinone based ynamide **6p** is prepared in 95% yield.[8]



Scheme 1.8. Ynamide from dihaloalkene

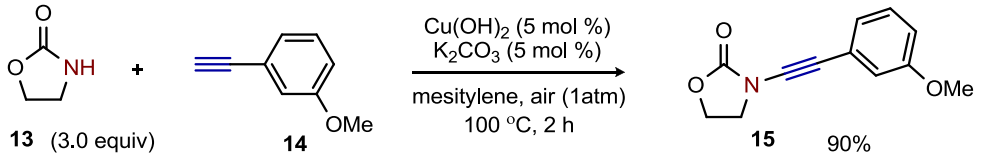
The plausible mechanistic cycle involved for the synthesis of ynamide from **4** and **8** is shown in Scheme 1.9. The reaction begins through the coordination of N-in amide with Cu-salt to give **9**. The oxidative addition of the C–Br bond *trans* to the R^2 group of dibromoalkene to produce **10**. Reductive elimination of **10** then delivers intermediate **11**, which subsequently undergoes base-promoted HBr elimination to afford ynamide **6**. The *trans* C–Br bond of the dibromoalkene is most reactive to undergo oxidative addition.



Scheme 1.9. Mechanistic Cycle

With the isolation of intermediate **11** and Cs_2CO_3 assisted elimination of HBr leading to **6** supports the mechanism drawn in scheme 1.9.[9]

Mizuno and co-workers reported an improved method of Stahl's protocol[7] for the synthesis of ynamides through the coupling of oxazolidin-2-one **13** with terminal alkynes **14** under the influence of $Cu(OH)_2$, K_2CO_3 base in air (Scheme 1.10).[10] The oxazolidinone-based ynamides **15** are readily accessed.

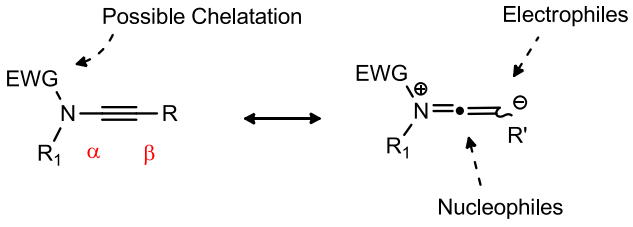


Scheme 1.10. C–N coupling reaction from terminal alkyne

The summary of Cu-mediated coupling methods for the synthesis of ynamides revealed that the reaction of appropriate N-protected amides with specific reagents is essential for the synthesis of the corresponding desired ynamides.

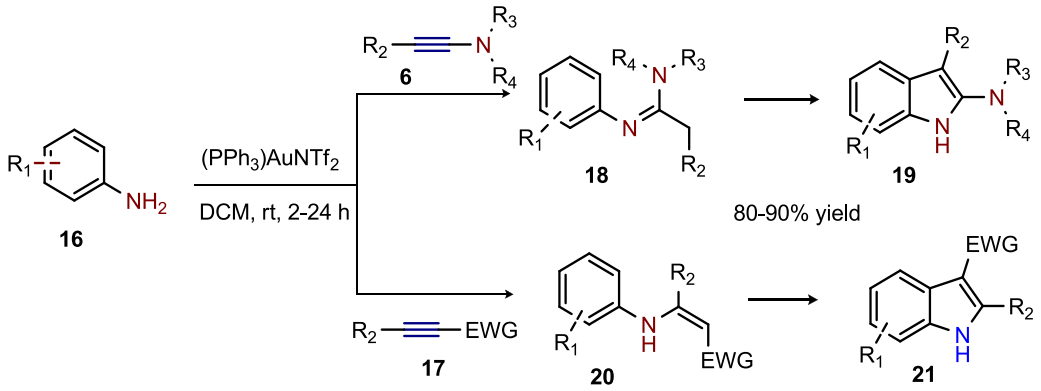
1.3. Reactivity and Synthetic Utilization of Ynamides

Ynamide readily attains a zwitterion ketiniminium species through the inherent polarization of lone pair of electrons of N-atom in ynamide (Scheme 1.11). Hence, the β-carbon of ynamide is nucleophilic, while α-carbon is electrophilic. In addition, the EWG on N-atom offers assistance for coordination. With these strong preferences of the existence of reactive-sides, ynamide has thus been used for the development of novel transformations. Inspite of the broad synthetic potential of ynamides, the attack of nucleophile at the α-carbon of ynamides is particularly important; this leads to the formation of highly functionalized enamides and complex novel molecular entities. In view of the importance of this thesis work, the known organic transformations involving α-addition to ynamides have been briefly enumerated.



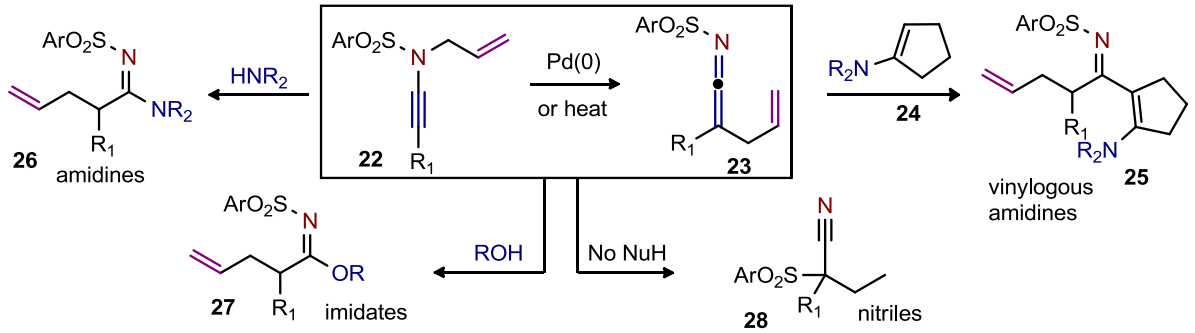
Scheme: 1.11. Ambivalence of ynamide

In 2009, Skrydstrup et al.[11] disclosed Au(I)-catalyzed highly regioselective hydroamination of anilines **16** with ynamides **6** followed by electrophilic-cyclization for the synthesis of 2-amino-indoles **19** (Scheme 1.12). This method also provides the synthesis of 2-alkyl-indoles through the hydroamination and cyclization sequence from aniline with alkynes **17**.



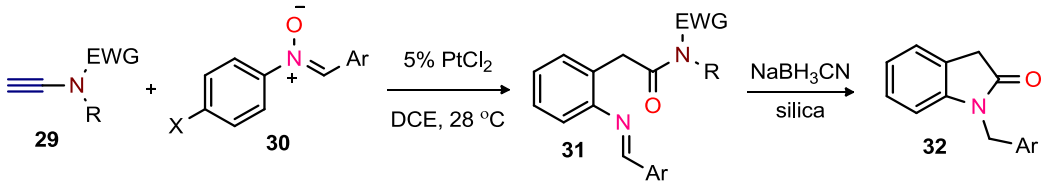
Scheme 1.12. Regioselective hydroamination and electrophilic cyclization

Hsung and Zhang group independently reported the synthesis of amidine **26** or vinylogous amidine **25** via the addition of amines and enamines to the in situ generated ketenimine **23** from **22** through allyl-transfer, respectively (Scheme 1.13).[12] The reaction proceeds via a Pd(0)-catalyzed aza-Claisen rearrangement of *N*-allyl ynamides **22** leading to ketenimine **23**. In addition, 1,3-sulfonyl migration from *N*-to-C occurs swiftly via aza-Claisen rearrangements to produce nitriles **28**. Whereas vinyl imidates **27** are accessed through the attack of alcohol to **23**.



Scheme 1.13. Allyl transfer and aza-Claisen rearrangement.

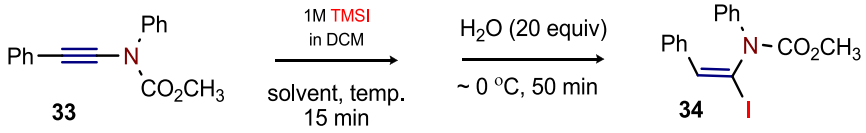
Liu group demonstrated Pt-catalyzed oxoarylation of ynamides **29** with nitrones **30** (Scheme 1.14).[13] Arylation followed by oxygen transfer from N-oxide of nitrone to the ynamide in a cascade sequence lead to oxoarylation product **31**. Reduction of amine with $NaBH_3CN$ followed by nucleophilic substitution of **31** provides indolin-2-ones **32.**



Scheme 1.14. Pt–catalyzed oxoarylaion reaction

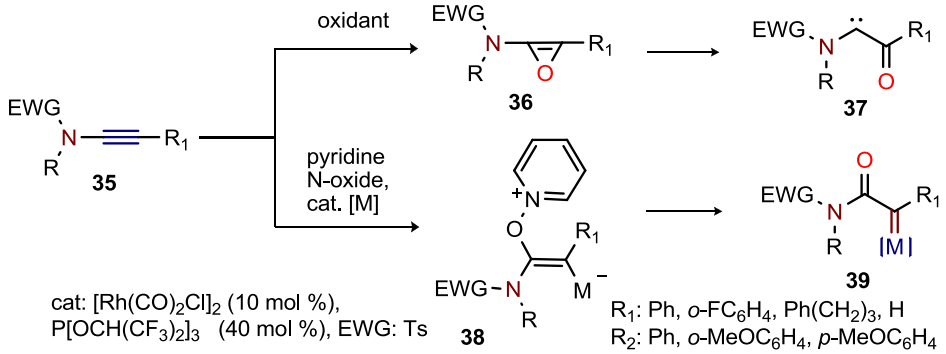
Iwasawa group described the synthesis of *(E)*-α-haloenamides **34** from ynamides **33** with bromo- or iodotrimethylsilane (Scheme 1.15).[14] The protocol enables the occurrence of

regio- and stereoselective hydrohalogenation to the triple bond of ynamides; gram-scale synthesis of novel enamide analogues is also accomplished.



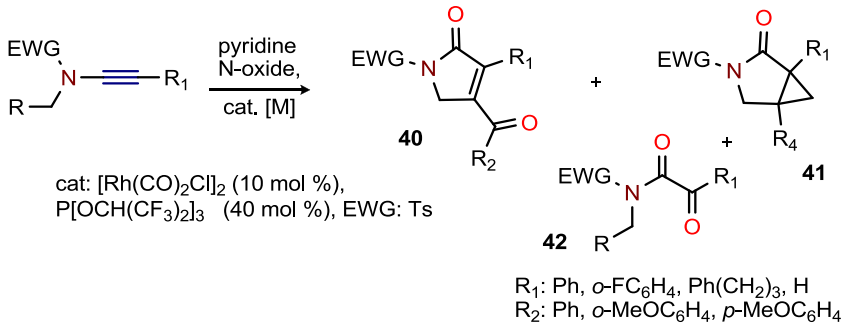
Scheme: 1.15. Stereoselective hydrohalogenation of ynamide

Oxidation of ynamides by dimethyl dioxirane (DMDO) or other oxidants led to push–pull α-oxo carbenes ***37*** (Scheme 1.16); the reaction involves the participation of oxirene intermediates ***36***.[15] The Au-catalyzed oxidation of ynamide ***35*** with external oxidants, *e.g.* pyridine *N*-oxide, affords α-oxo gold carbenes ***39*** (M = Au); the reaction initiates through the attack of pyridine *N*-oxide to the Au-activated ynamide in the formation of intermediate ***38*** in situ, which subsequently rearranges to give ***39*** (Scheme 1.16).



Scheme 1.16. α-Oxocarbene generation from ynamide

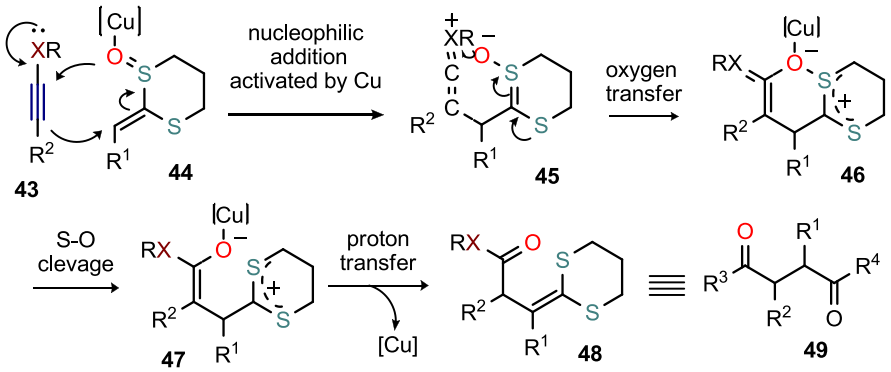
The metal catalyst and ligand plays significant impact on the reactivity of carbene ***39***. For instance, the reaction of α-oxo Rh(I) carbenes ***39*** (M = Rh) with the tethered alkyne or alkene affords heterocycles **40** and **41**, respectively (Scheme 1.17). In contrast, α-oxo Au(I) carbenes ***39*** (M = Au) generates ketoimide **42** (Scheme 1.17).[15]



Scheme 1.17. α-oxo Au(I) carbenes to heterocycles.

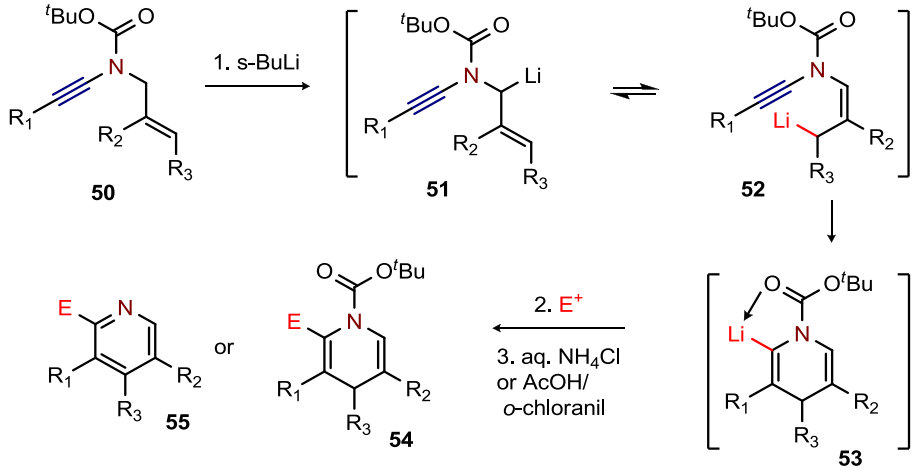
The Cu-catalyzed extended Pummerer reactions of sulfoxides **44** with ynamide **43** for the synthesis of γ,γ-disulfanyl-β,γ-unsaturated carbonyl compounds **48** has been accomplished (Scheme 1.18). The Cu-catalyzed reactions of ketene dithioacetal sulfoxide **44** with

ynamides **43** provided γ,γ-disulfanyl-β,γ-unsaturated carbonyl compounds **48** with an accompanying oxygen rearrangement (Scheme 1.18). The product **48** is easily converted into 1,4-dicarbonyl compounds **49** and substituted heteroaromatics.[16]



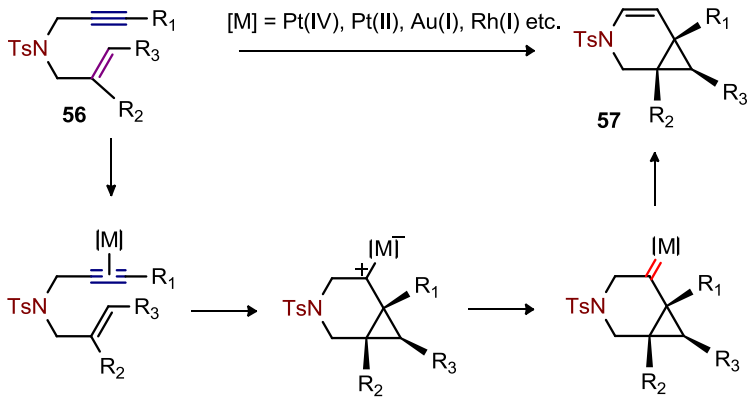
Scheme 1.18. Copper mediated Pummerer reactions on ynamide

Evano's group described a general method for the synthesis of polysubstituted 1,4-dihydropyridines and pyridines (***54*** and ***55***) from *N*-allyl-ynamides ***50*** in the presence of strong base BuLi and electrophile (Scheme 1.19). The transformation involves highly regioselective lithiation of allyl C–H bond followed by [1,3-Li] migration, intramolecular carbolithiation to the alkyne-moiety of ynamide, and finally quenching with electrophile (Scheme 1.19).[17]



Scheme 1.19. Synthesis of dihydropyridine and pyridine from N-ally-ynamide

The Rh-catalyzed asymmetric cycloisomerization of heteroatom-bridged 1,6-ene-ynamides ***56*** for the enantioselective synthesis of functionalized 3-aza-oxabicyclo[4.1.0]heptene derivatives ***57*** has successfully been demonstrated by T. Hayashi group (Scheme 1.20) The 2-oxazolidinone and 2-azetidinone moieties at the alkyne terminus played crucial for the high induction of selectivity, whereas chelation of alkyne moiety and the N-carbamate oxygen of the eneynamides is responsible for the high catalytic activity.[18]



Scheme 1.20. Metal catalyzed cycloisomerization on 1,6-eneynamide

1.4. Conclusions:

In summary, some of the general synthetic methods on ynamide are described. The ambivalent nature of ynamide is briefly reported. It is apparent from the above discussion that ynamide possesses versatile synthetic potential, which can be utilized in accessing diverse nitrogen bearing compound.

Section II. Gold Catalysis

1.5. Background of gold catalysis

Gold has extensively been used from ancient days. The utility of gold in chemical synthesis has recently been actively investigated. Considerable interest has thus been imposed in examining the utility of gold catalysis for the development of novel synthetic methods for the rapid synthesis of target oriented complex molecules. Gold catalysts are environmentally benign. Gold catalyzed transformations generally occur at ambient conditions within short time, therefore highly efficient; furthermore, gold catalysts can tolerate air and moisture environments.

1.5.1 Salient features of gold catalysis

What makes gold a special Lewis acid?

Cationic gold complexes, especially gold(I) compounds are superior Lewis acids. The unique 'alkynophilicity' of Au(I) species and reluctance to switch between different oxidation states paved in the development of novel synthetic methods. Nontoxicity and tolerance to moisture and air renders them to be much user friendly. The parameter accounts for special reactivity of Au-complex compared to other metals are narrated herewith.[19]

'π acidity' of gold:

Based on the molecular orbital studies, four different mode of interaction between metal (M) and π ligand (L) is possible (Figure 1.3); among those interactions, only two mode of bonding interaction between a metal (M) and a π ligand (L) (alkyne, alkene, allene, or carbonyl moieties) significantly contributes to the total bond energy. As exemplified, the in-plane π orbitals make σ- symmetric L→M donation as well as π symmetric M→L back donation. Computational study upon gold-acetylene [(Au(C_2H_2)] and gold-ethylene [(Au(C_2H_4)] complexes revealed that the σ interaction (L→M) accounts for 65% of the total bonding situation, while the π interaction contributes only 27%.[20]

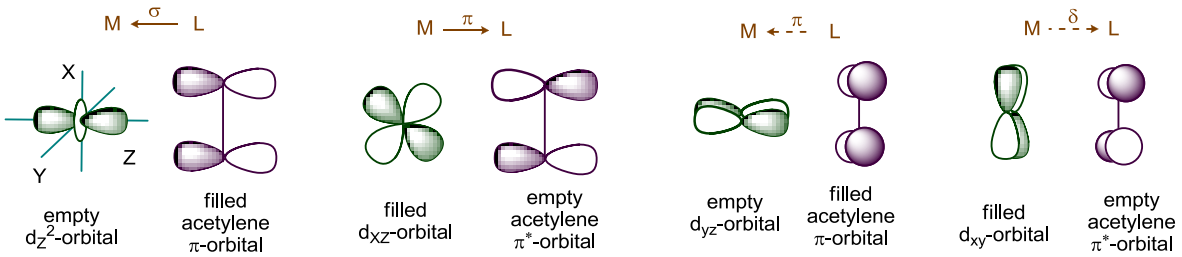


Figure 1.3. Orbital picture of metal ligand interaction

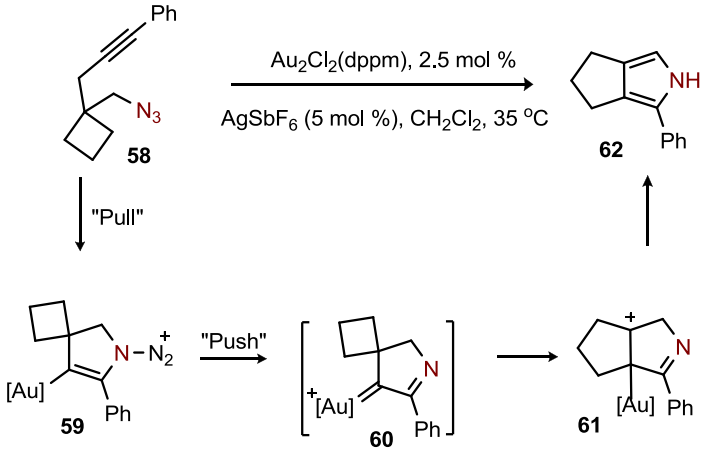
Due to the lack of back bonding effect of Au, the gold-π ligated species makes the π-moiety electron deficient, which in turn facilitates the attack of nucleophile to the unsaturated

system. As the Au-alkyne complex possesses lower LUMO compared to an Au-alkene complex, the Au-catalysts are therefore 'alkynophilic' than 'alkenophilic'.[20]

Pull-Push reactivity of gold:

Gold cations possess inherent ability to coordinate to multiple bond and deplete the electron density ('pull' effect), therefore Au-cations are good 'π acids'. As a result, attack of nucleophile to unsaturated bonds is feasible. The other late transition metal cations, such as Hg, Pt, Cu, Ag, Ir, Rh, and Ga are also able to activate the π-bond possessing significant back-bonding effect, whereas Au-catalysis lacks significant back-donation ability.[21]
Advanced computational study on Au-CH_2^+ showed that the bond energy of these species is surprisingly higher compared to other analogous late transition-metal species. These findings indicated showing the existence of considerable multiple bond character between gold and carbon atom. Alternatively, it is assumed that Au can avail electron back-donation from metal to the carbene ligand; the usage of term 'carbene' for Au-carbon complexes is debatable. As the Au–C bond lengths for the known Fischer or NHC complexes bearing "Au-carbene" complexes showed single bond character. The experimental evidence supports displaying the existence of metal-stabilized cation species rather metal-carbene intermediate. These findings are in sharp contrast to the fact showcasing the absence of back bonding of Au-alkyne/alkene/carbonyl complexes. Thus, Au-cationic species is able to drag the π-electrons of the multiple bond species and facilitates the attack of nucleophile. Simultaneously, Au- is able to stabilize the positive charge developed at the vicinal 'carbene' carbon (when the nucleophile is a double bond) by back-donation ('push' effect) of electrons.

Thus, the 'pull-push' effect of Au-catalyst simultaneously initiates and stabilizes the cationic (or 'carbene') centers produced in situ during the transformations. The acetylenic-Schmidt reaction is a true demonstration of this effect (Scheme 1.21). Thus, the activation of



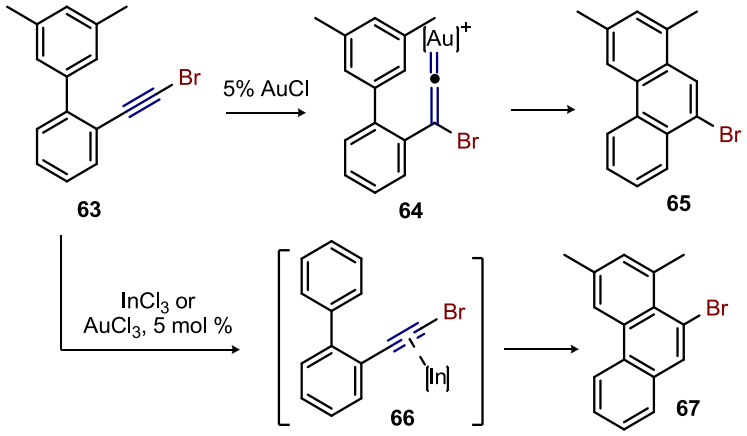
Scheme 1.21. push-pull reactivity of gold

alkyne by Au-species provokes the *5-endo-dig* attack of azide nucleophile to afford **59** followed by liberation of N_2 and stabilization of the resulting 'nitrene' by back donation of

Au to nurture **60**. Finally, stabilization of Au-carbenium species through [1,2]-bond migration and deauration lead to **62** (Scheme 1.21).[22]

Au(I)-Species: A 'carbene' friendly gold

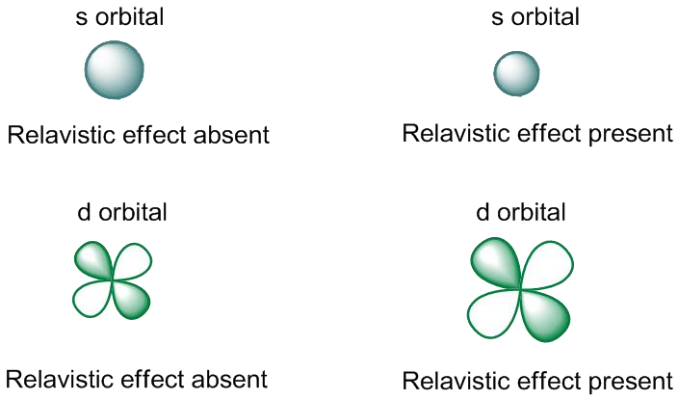
The Au(I)-species are soft over Au(III) catalysts. Thus, Au(I)-catalyzed transformations involve the participation of Au-vinylidene intermediates through the back-donation ability of Au(I)-species. In contrast, In(III), Ga(III), and Au(III) catalysts behave Lewis acidic. Synthesis of halophenanthrenes A **65** is a typical example showcasing 'method of operation' of Au(I) catalysts (Scheme 1.22). The 'halide walk' observed for the formation of **65** from **63** with AuCl involves the participation of metal-vinylidene intermediate **64**. The less electron rich $InCl_3$ or $AuCl_3$ assisted Friedel-Crafts hydroarylation of **63** provides **67** (Scheme 1.22).[23, 24]



Scheme 1.22. Synthesis of halophenanthrenes via halide walk under gold catalysis

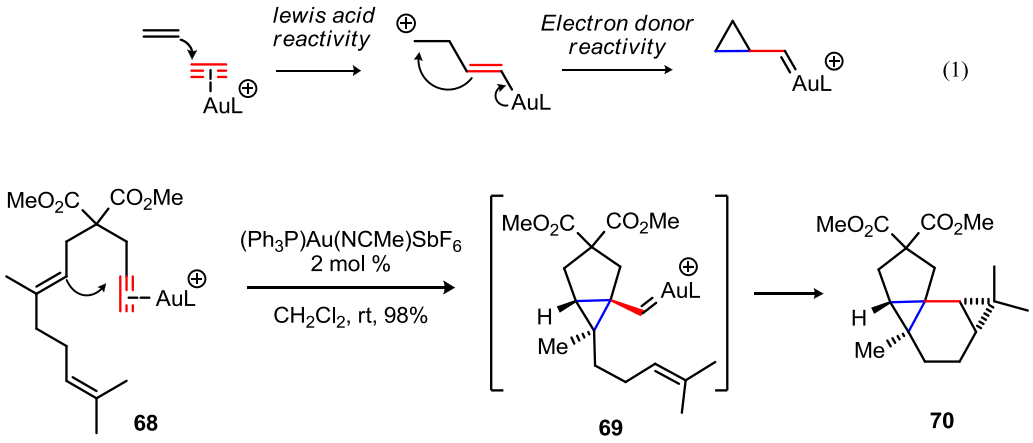
Relativistic effects in gold catalysis:

Relativistic effect plays crucial for predicting reactivity and physical phenomena of the elements.[25] The heavier transition metals with highly positive nucleus tend to attract the valence shell electrons, resulting the contraction of the "s" orbitals which is closer to the nucleus. The effect is more pronounced for Au-metal where the outer 6s orbital contracts and shields the penultimate 5d orbital from the attraction of the nucleus, causing the expansion of 5d orbital. Lewis acidity of gold is the consequence of the relativistic expansion of 5d orbitals. The bigger charged species has the better 'softness', consequence of HSAB concept, having poor nucleophilicity



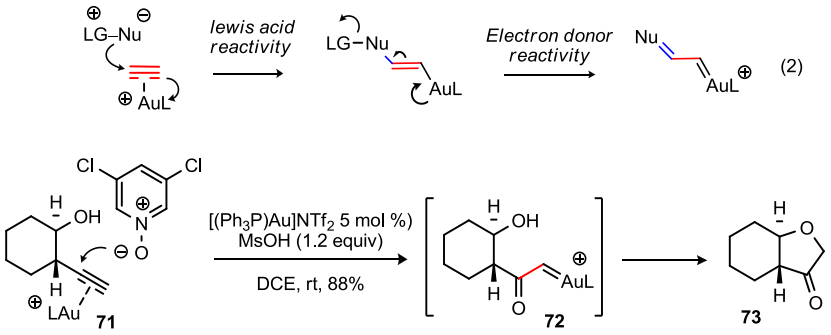
(low affinity to undergo oxidative addition). Poor nucleophilicity of organoaurate (I) species than the organocopper complexes is a true illustration of this concept. Furthermore, the relativistic contraction (of course the lanthanide contraction) reduces the size of the metal, which in turn results strong metal-ligand bonding. The higher electronegativity of Au with respect to other members of the group is also a consequence of relativistic effects.

The expansion of 5d orbital, due to the relativistic effect, permits the outer-shell electrons for delocalization. Accordingly, Au works as an electron donor species and significantly contributes to the stabilization of carbocation intermediates. The Lewis acid/electron donor dual behavior of Au-catalyst has been witnessed in various organic transformations. Precisely nucleophilic attack of an olefin to Au-alkyne complex followed by the stabilization of carbenium species through the back-donation of Au for the formation of cyclopropyl-tethered Au-carbene intermediate is a true model showing dual behavior of Au-catalyst (eq 1, Scheme 1.23). The cycloisomerization of dienyne **68** to the tetracyclic compound **70** is a logical demonstration of dual behavior of Au-catalyst, reported from Echavarren group (Scheme 1.23). The activation of the alkyne moiety in **68** by the cationic gold(I) complex produces a gold(I) carbene intermediate **69**. Subsequent trapping of the internal olefin to Au-carbene furnishes **70** (Scheme 1.23).[26]



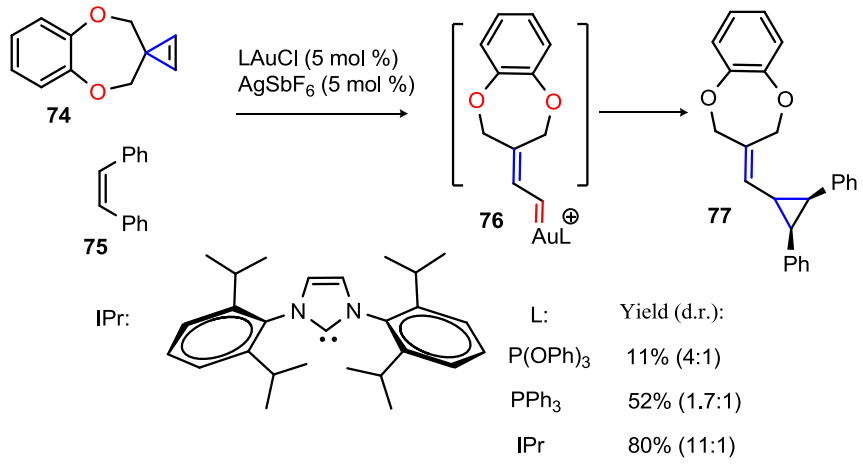
Scheme 1.23. Lewis acid and electron donor reactivity of gold

The dual-behavior of Au-catalysts is presented for the formation of α-ene-Au-carbene involving nucleophilic attack of a salt to Au-activated alkyne followed by the expulsion of leaving group (LG) through the back-donation of Au-species (eq 2, Scheme 1.24). Thus, the nucleophilic addition of 3,5-dichloropyridine *N*-oxide onto the gold(I)- activated alkyne **71** induces the formation of the α-oxo gold carbene **72** with the expulsion of 3,5-dichloropyridine (Scheme 1.24). The interception of the gold(I) carbene by the pendant hydroxyl group delivered dihydrofuranone product **73**.



Scheme 1.24. Lewis acid and electron donor reactivity of gold

The carbocation or carbenoid character of organo-gold species hinges on the nature of gold catalyst and the substitution pattern of the substrate. Toste group examined vast theoretical calculations to understand the nature of the carbon-gold bond in the important intermediate L-Au(I)-CR_2^+ involved for Au-catalyzed transformations; influence of carbene moiety and the ligand (phosphite, phosphine, halogen and N-heterocyclic carbene) on Au-species are also studied. The σ-donating and π-accepting ligand showed strong impact on the potential reactivity of L-Au(I)-CR_2^+ species. The strong π-acid phosphite ligand decreases the π-donation from gold to the substrate and consequently favors the participation of carbocation-type reactivity. Conversely, weak π-acid and strong σ-donating ligand *N*-heterocyclic carbenes, decreases σ-donation from the substrate to Au, favoring carbene-type reactivity.



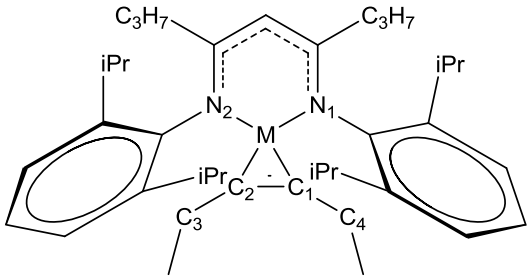
Scheme 1.25. Effect of phosphine ligand on the selectivity

The theoretical results were in agreement with the experimental observations found in the various cationic gold(I)-ligated catalyst mediated reaction between (*Z*)-stilbene and cyclopropene **74** for the synthesis of **77** (Scheme 1.25). As the reaction involves the participation of Au-carbene intermediate **76**, the strong σ-donating ligand IPr-Au-species turned out to be effective catalyst over the phosphite and phosphine ligated Au-catalyst.

1.6. Silver & Copper-catalyzed cyclizations:

Copper, silver and gold are group 11 elements. Each metal carries notable differences of reactivity and therefore unique. Silver possess to some degree larger atomic volume than gold because of lacking in lanthanide contraction and decreasing relativistic effects. However, copper acquire smaller molecular volume compared to gold, displaying harder Lewis acidity as a result of diminished relativistic effects.
Kroll and co-workers investigated examining the reactivity of monomeric Cu(I), Ag(I), and Au(I) alkyne complexes. Silver generally possesses long metal-ligand bond lengths than copper and gold. In case of Cu, the metal-ligand bond length is similar to that of Au. Au(I)-complex is linear bi-coordinate system, whereas Ag(I) and Cu(I) exists in tricoordinate or tetracoordinate systems. The low-lying LUMO of gold, makes it better Lewis acidic than Ag(I) and Cu(I) species. Interestingly, the metal-alkyne bonds are in the order: Cu(I) < Au(I) < Ag(I) (Figure 1.4). Based on X-ray studies, the bending of alkyne is more pronounced for Au(I) species than the Cu(I) species; while Ag(I) showed least impact for the bending of alkyne.

DFT calculations data indicated that Au(I) complexes form stronger metal-alkyne back donation, followed by Cu(I) and Ag(I).



	M–C$_1$ (Å)	M–C$_1$–C$_4$ (Å)
M = Au	2.069	155.0
= Ag	2.233	164.7
= Cu	1.983	156.5

Figure 1.4. Bond length and bond angle of metal alkyne complexes

1.7. Classification of the homogeneous gold catalysts

Gold catalysts exhibit +1 and +3 oxidations states. Both Au(I) and Au(III) complexes have extensively been used for various transformations. Highlighting comprehensive list of homogeneous Au-catalyzed transformations is beyond the scope of discussion in this thesis; the origin of reactivity under the assistance of Au(I) and Au(III) catalysts is briefly narrated.

1.7.1. Gold(III) catalysts:

Gold(III) is d^8 system; it is available in AuX_3, AuX_4^- or $LAuX_3$ composition. Usually Au(III) complexes prefer square planar with tetracoordinated geometry. The most common commercially available gold(III) catalyst is $AuCl_3$, which exists as a dimer Au_2Cl_6 (Figure

1.5). The cationic complexes $Au(OTf)_3$ and $AuBr_3$ have also been employed in various transformations.[27]

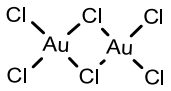


Figure 1.5. Structure of Au_2Cl_6

$H[AuCl_4]$ and $Na[AuCl_4]$ are another kind of gold(III)-catalysts (Figure 1.6). These catalysts are the cheapest source of Au(III) and recurrently used in homogeneous gold catalysis. Use of these catalysts in the reaction produces number of side-products, limiting synthetic potential of the transformations.

$H[AuCl_4]$ $Na[AuCl_4]$ $[n\text{-}Bu_4N][AuCl_4]$

Figure 1.6. Tetrachloroauric acid and its tetrachloroaurates derivatives

The pyridine coordinated Au(III) complexes are versatile, as some of these complexes are air-stable and easy to handle (Figure 1.8).[28]

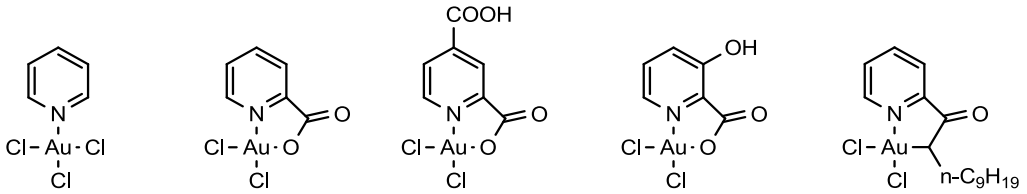


Figure 1.8. Gold(III) complexes functionalized with a pyridine ligand

1.7.2. Gold(I) catalysts:

Gold(I) has d^{10} systems; it holds LAuX or L_2Au^+ composition. Au(I) complexes prefer linear bicoordinated geometry. AuCl is the simplest available source of Au(I). It exists in a polymeric form of a chain with the bridging of μ-Cl ligands in between gold (Figure 1.9). AuCl is bench stable; however, it is readily reduced to Au(0), showing modest catalytic activity.

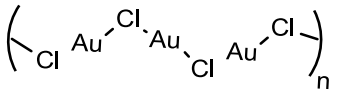


Figure 1.9. Polymeric chain of AuCl

Au(I) complexes having LAuX composition requires strong σ-donor ligand, which in turn stabilizes metal center. The commonly used ligands are phosphines or *N*-heterocyclic carbenes. The bonding of X to the metal should be weak, as it needs to be readily displaced from the substrate during the catalytic reaction. Based on the nature of Au–X bond, LAuX complexes can either be covalent (X typically being a Cl) or cationic (X = BF_4^-, PF_6^-, SbF_6^-, TfO^-, ClO_4^-, $(R_2O)P(O)O^-$ etc.). Figure 1.10 presents some of the most common gold(I) complexes having LAuX composition.[29]

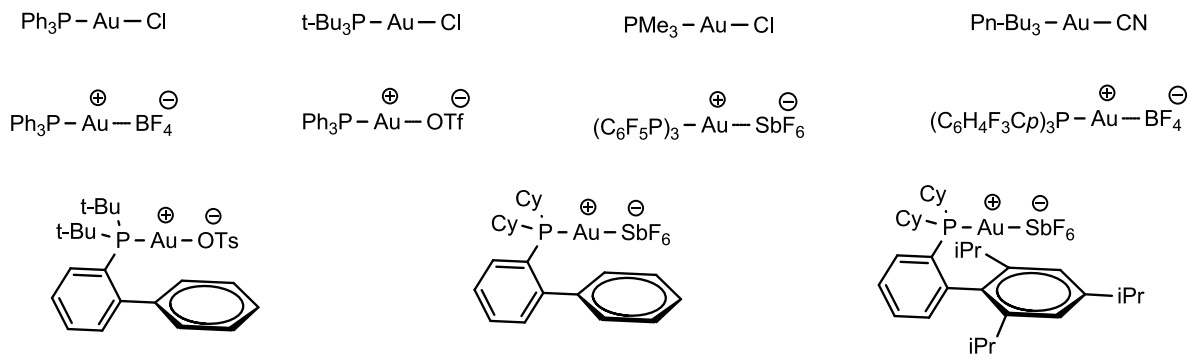


Figure 1.10. Au(I) complexes with LAuX composition

The gold(I) cationic complexes are frequently used in homogeneous Au-catalyzed transformations. Recently, numerous dinuclear Au(I) catalysts have been used in various synthetic transformations. Mostly, the diphosphine ligand have been used for the preparation dinuclear cationic gold(I)-phosphine complexes (Figure 1.11). These complexes usually formed *in situ*.[30]

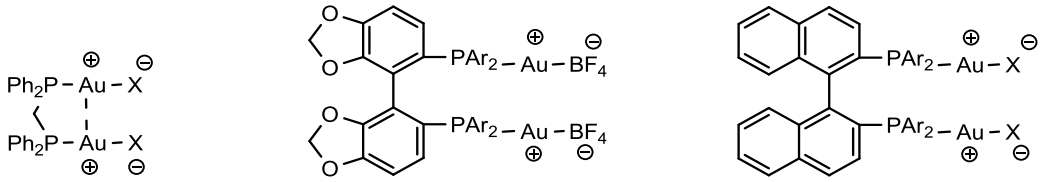


Figure 1.11. Dinuclear cationic gold(I)-phosphine catalysts

The catalysts of L_2Au^+ contain a gold(I) atom with bicoordinated neutral ligands: a strong σ-donor ligand such as a *N*-heterocyclic carbene or a phosphine and a weakly coordinating ligand like solvent such as acetonitrile, toluene, which can be easily displaced by the substrate during the catalysis reaction. These complexes are cationic having a non-coordinating counter anion (usually SbF_6^- or PF_6^-) (Figure 1.12).[30]

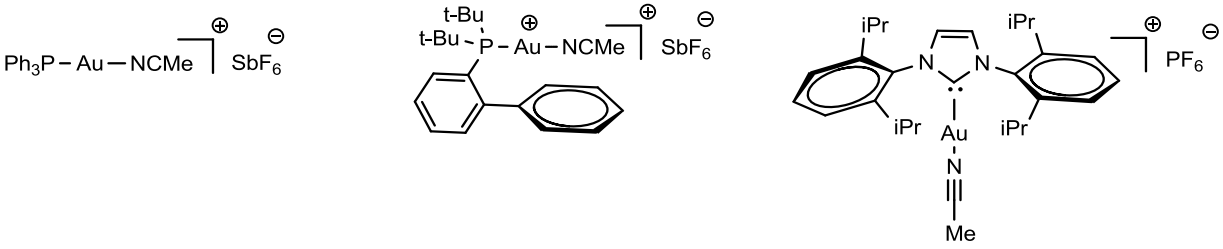


Figure 1.12. Some L_2Au^+ cationic Au(I) catalyst

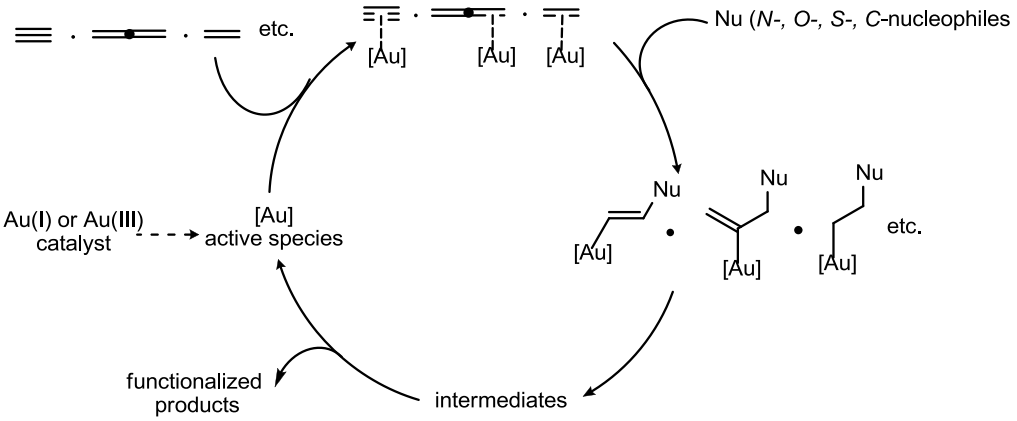
1.8. Types of reactions involving homogeneous gold catalysts:

General mechanism:

A general mechanistic path for the homogeneous Au-catalyzed organic transformations is shown in Scheme 1.26. The first step is the formation of active catalyst species. While the precatalysts (typically Au(I) or Au(III) complexes) are well defined compounds, the exact nature of the active species involved in the reaction is entirely unknown. Investigations are

always made to understand the participation of active Au-catalytic species in the reaction. Thus, the active catalyst species is denoted as [Au] in this thesis.

At first, selective coordination of [Au] on the π-system renders allowing the attack of a nucleophile to the [Au]-π-activated species.[31]



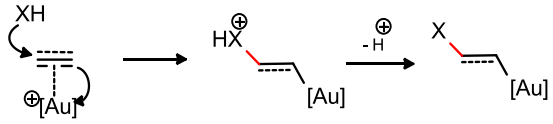
Scheme 1.26. General mechanistic path for homogeneous Au-catalyzed transformations

The nitrogen, oxygen, sulfur, and/or carbon bearing nucleophiles are generally employed for the reactions. Gold undergo η^2 to η^1 migrations, the attack of nucleophile results in the formation of two new C–Nu and C –[Au] bonds.[31]

The final step is the regeneration of active [Au]-species with the liberation of final products. Protodemetalation, substitution with electrophile, or elimination of the organo-gold intermediates led to the final products.

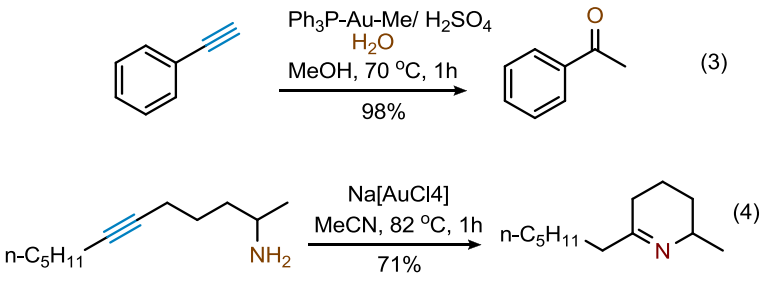
1.8.1. Heteroatom nucleophilic attack to Carbon–Carbon multiple bonds:

An *anti*-attack of hydrogen-bearing heteroatom XH to the Au-π-complex led to the formation of vinyl gold species with the loss of proton (Scheme 1.27). Finally, protodeauration provides *trans*-products.



Scheme 1.27. Nucleophilic attack of heteroatom to π-bond.

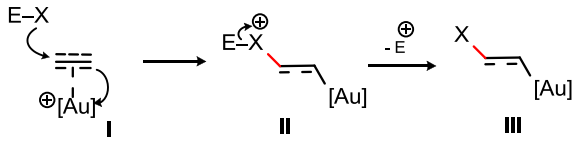
Following the path shown in Scheme 1.27, various nucleophiles as alcohols, ammonia,



Scheme 1.28. Representative reaction involving heteronucleophile

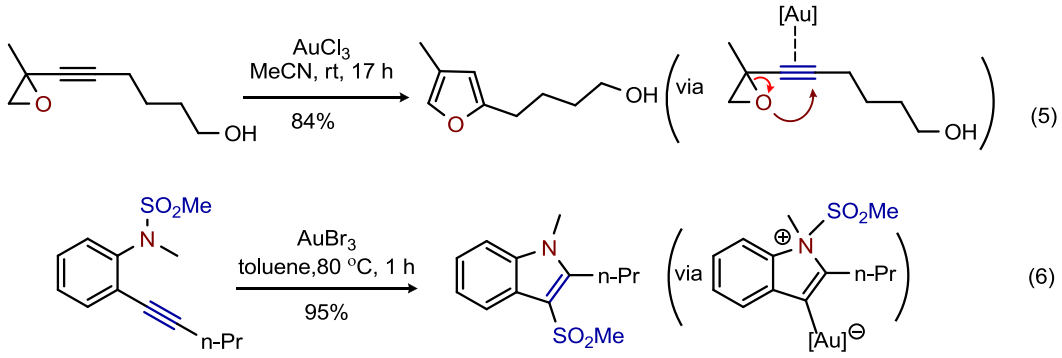
water, and carboxylic acids can attack to unactivated π-bond inter- or intramolecular fashion under the influence of Au-catalyst. For example, intermolecular attack of H_2O to alkyne in the presence of Au(I)-catalyst led to ketones (eq 3, Scheme 1.28). Similarly, intramolecular attack of amine moiety to alkyne-motif provides N-heterocycles (eq 4, Scheme 1.28).[32]

Similarly, intermolecular *anti*-attack of an electrophile-bearing nucleophile species to Au-activated π-system generates III; the fragmentation of the electrophile from III followed by replacement of C-Au bond with electrophile led to di-functionalized product. (Scheme 1.29).



Scheme 1.29. Nucleophilic attack of a sp3-hybridized heteroatom

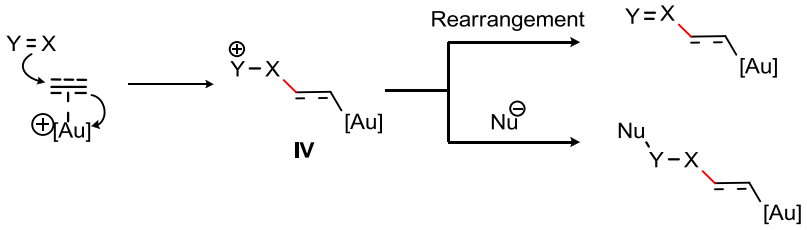
The intramolecular rearrangement of Au-intermediate (shown in eq 5, Scheme1.30) and the deauration with E^+ group (presented in eq 6, Scheme1.30) are successful demonstration of the concept highlighted in Scheme 1.29.[33]



Scheme 1.30. Examples of nucleophilic attack of a sp³-hybridized heteroatom

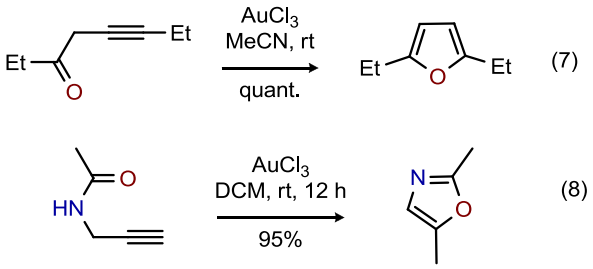
1.8.2. sp²-Hybridized heteroatom nucleophiles:

The intermolecular attack of sp²-hybridized heteroatoms, carbonyl or imino groups to the Au-activated-π-system produce densely functionalized products. The intermediate **IV** formed at first undergoes rearrangement or the attack of foreign nucleophilic to deliver different products (Scheme 1.31).



Scheme 1.31. Nucleophilic attack of a sp²-hybridized heteroatom

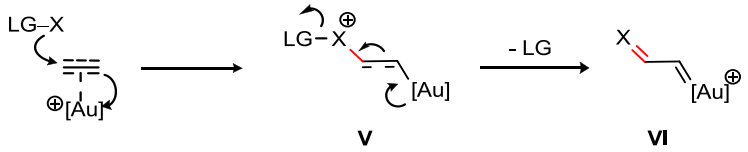
Interestingly, the intramolecular *5-endo*, *5-exo* and *6-exo* attack of carbonyl or imino group to the Au-π-system provides access to various novel heterocycles, as exemplified for the synthesis of furan and oxazole derivatives (eq 7 and 8, Scheme 1.32). This process has extensively been utilized for the construction of complex heterocycles.[34]



Scheme: 1.32 Nucleophilic attack of a sp^2-hybridized heteroatom

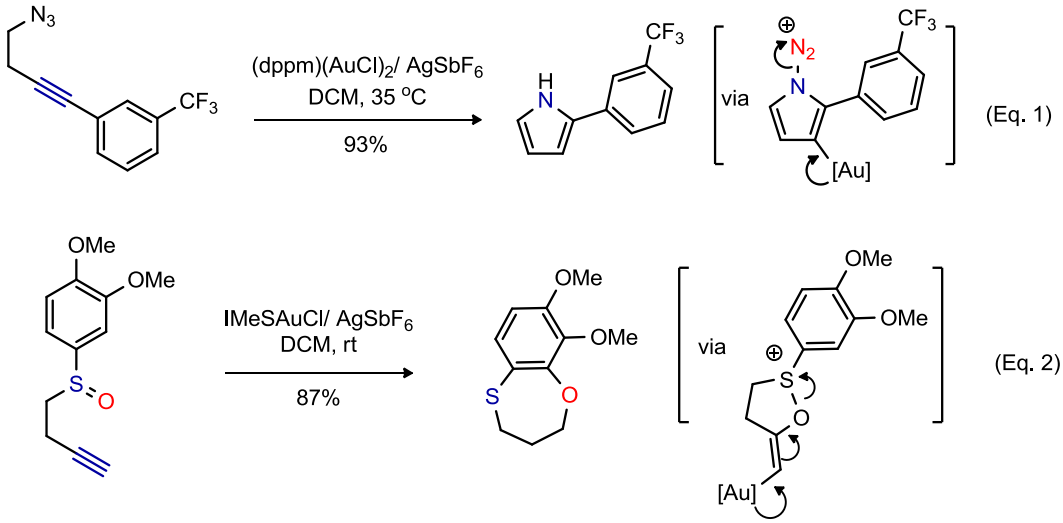
1.8.3. Heteroatom nucleophile bearing leaving group:

The *anti*-attack of leaving group bearing heteroatom nucleophiles generates a non-classical gold-carbenoid intermediate VI, this moiety has efficiently been trapped for the synthesis of useful molecular entities (Scheme 1.33).



Scheme 1.33. Nucleophilic attack of leaving group bearing heteroatom

The intramolecular attack of azide and sulfoxide, to the Au-activated alkyne followed by the elimination of N_2 or ring opening of sulfonium species supported by the back-donation of Au for the synthesis of functionalized new molecular entities are some of the true



Scheme 1.34. Nucleophilic attacks involving leaving group-bearing heteroatoms

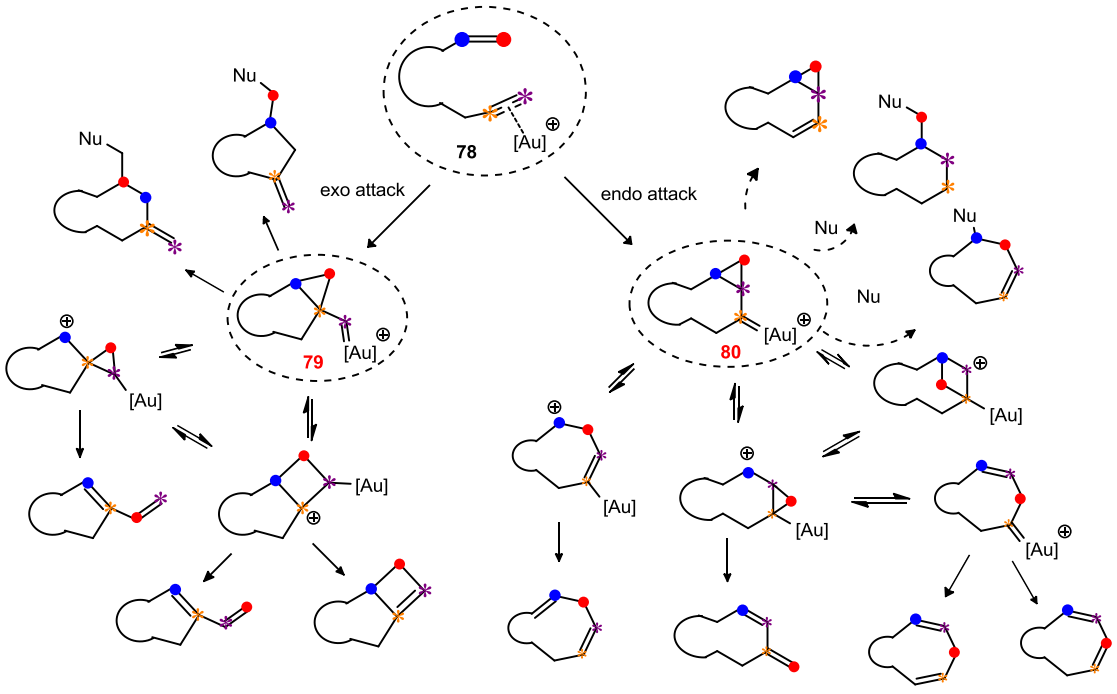
demonstration of the Au-catalyzed transformations using LG-bearing nucleophiles (Scheme 1.34).[35]

1.8.4. Carbon attacks to C–C multiple bonds:

The carbon-bearing nucleophiles can attack to C–C multiple bonds under the influence of homogeneous gold catalysts. The intramolecular attack of sp^2- and sp^3-hybridized C-bearing nucleophiles to the Au-activated-olefin entities efficiently led to complex carbocycles from linear precursors.

1.8.5. Enyne cycloisomerizations:

Enyne cycloisomerization is an important method for the development of functionalized cyclic structures. Gold and platinum are powerful catalysts used for the enyne cyclization. These catalysts are capable of forming diverse cyclic structure with excellent selectivity and high efficiency. Enyne cycloisomerizations involving gold-catalysis proceed with the activation of the pendant alkyne motif followed by the attack of nucleophilic double bond. The reaction proceeds involving *exo-dig* or an *endo-dig* attack of olefin to the alkyne moiety (Scheme 1.35). The two important non-classical carbenoid intermediate **79** and **80** are the key-motifs broadly useful in accessing diversified products (Scheme 1.33). Various types of cycloisomerization strategies and its implication for the construction of novel molecular entities are detailed in Chapter 3 in this thesis.[36]



Scheme 1.35. Gold catalyzed cycloisomerization reactions involving enynes

1.9. Conclusion:

In summary, the physical features and reactivity of gold catalysis is briefly highlighted. It is apparent from the above discussion that the development of novel Au-catalyzed transformations for the construction of complex molecular entities of biological and material applications offers abundant opportunities and cumulative challenges. Inspired from these challenges, we thus became interested in the explorations of novel and efficient Au-catalyzed transformations. This thesis work primarily focused on the development of novel Au-catalyzed transformations of ambivalent ynamides.

1.10. References:

1. For a review of ynamides see: (a) Zificsak, C. A.; Mulder, J. A.; Hsung, R. P.; Rameshkumar, C.; Wei, L.-L. *Tetrahedron.* **2001**, *57*, 7575. (b) DeKorver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. *Chem. Rev.* **2010**, *110*, 5064 (c) Evano, G.; Coste, A.; Jouvin, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 2840.

2. For relevant reviews see: (a) Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. *Angew. Chem. Int. Ed.* **2004**, *43*, 3368. (b) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079. (c) Willis, M. C. *Chem. Rev.*, **2010**, *110*, 725-748.

3. For select examples see: (a) Witulski, B; Alayrac, C; Tevzadze-Saeftel, L. *Angew. Chem., Int. Ed.* **2003**, *42*, 4257. (b) Li, H.; Hsung, R. P. *Org. Lett.* **2009**, *11*, 4462. (c) Kramer, S.; Madsen, J. L. H.; Rottlander, M.; Skrydstrup, T. *Org. Lett.* **2010**, *12*, 2758.

4. Janousek, Z.; Collard, J.; Viehe, H. G. *Angew. Chem., Int. Ed.* **1972**, *11*, 917.

5. Dunetz, J. R.; Danheiser, R. L. *Org. Lett.*, **2003**, *5*, 4011.

6. Zhang, Y.; Hsung, R. P.; Tracey, M. R.; Kurtz, K. C. M.; Vera, E. L. *Org. Lett.*, **2004**, *6*, 1151.

7. Hamada, T.; Ye, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 833-835.

8. Coste, A.; Karthikeyan, G.; Couty, F.; Evano, G. *Angew. Chem., Int. Ed.* **2009**, *48*, 4381.

9. (a) Shen, W.; Wang, L. *J. Org. Chem.* **1999**, 64, 8873. (b) Zapata, A. J.; Ruíz, J. *J. Organomet. Chem.* **1994**, *479*, c6-c8. b) Jin, X.; Yamaguchi, K.; Mizuno, N. *Chem. Commun.* **2012**, *48*, 4974.

10. Evano, G.; Coste, A.; Jouvin, K. *Angew. Chem. Int. Ed.* **2010**, *10*, 2840.

11. Kramer, S.; Dooleweerdt, K.; Lindhardt, A. T.; Rottlander, M.; Skrydstrup, T. *Org. Lett.* **2009**, *11*, 4208.

12. DeKorver, K.; Johnson, W. L.; Zhang, Y.; Hsung, R. P.; Dai, H.; Deng, J.; Lohse, A. G.; Zhang, Y.-S. *J. Org. Chem.* **2011**, *76*, 5092.

13. Bhunia, S.; Chang, C.-J.; Liu, R.-S. *Org. Lett.* **2012**, *14*, 5522.

14. Sato, A. H.; Ohashi, K.; Iwasawa, T. *Tetrahedron Lett.* **2013**, *54*, 1309.

15. Liu, R.; Winston-McPherson, G. N.; Yang, Z.-Y.; Zhou, X.; Song, W.; Guzei, I. A.; Xu, X.; Tang, W. *J. Am. Chem. Soc.* **2013**, *135*, 8201.

16. Murakami, K.; Imoto, J.; Matsubara, H.; Yoshida, S.; Yorimitsu, H.; Oshima, K. *Chem. Eur. J.* **2013**, *19*, 5625.

17. Gati, W.; Rammah, M. M.; Rammah, M. B.; Evano, G. *Beilstein J. Org. Chem.* **2012,** *8*, 2214.

18. Nishimura, T.; Takiguchi, Y.; Maeda, Y.; Hayashi, T. *Adv. Synth. Catal.* **2013**, *355*, 1374.

19. (a) Zhang G.; Peng Y.; Cui L.; Zhang L. *Angew. Chem. Int. Ed.* **2009**, *48*, 3112. (b) Kar A.; Mangu N.; Kaiser H. M.; Beller M.; Tse M. K. *Chem. Commun.* **2008**, 386. (c) Wegner H. A.; Ahles S.; Neuburger M. *Chem. Eur. J.* **2008**, *14*, 11310.

20. (a) Frenking G.; Fröhlich N. *Chem. Rev.* **2000**, *100*, 717. (b) Deieu De, *Chem. Rev.* **2000**, *100*, 543 and references therein.

21. (a) Irikura K. K.; Goddard W. A. *J. Am. Chem. Soc.* **1994**, *116*, 8733. (b) Heinemann C.; Hertwig, R. H.; Wesendrup R.; Koch, W.; Schwarz, H., *J. Am. Chem. Soc.* **1995**, *117*, 495.

22. (a) Fürstner, A.; Morency L. *Angew. Chem. Int. Ed.* **2008**, *47*, 5030 (b) Hashmi, A. S. K. *Angew. Chem. Int. Ed.* **2008**, *47*, 6754 (c) Seidel, G.; Mynott, R.; Fürstner A. *Angew. Chem. Int. Ed.* **2009**, *48*, 1. (d) Fernández, E. J.; Laguna A.; Olmos, M. E. *Adv. Organomet. Chem.* **2005**, *52*, 77. (e) Lin, I. J. B.; Vasam C. S. *Can. J. Chem.* **2005**, *83*, 812

23. (a) Fürstner, A.; Mamane, V. *J. Org. Chem.* **2002**, *67*, 6264. (b) Chatani, N.; Inoue, H.; Kotsuma, T.; Murai S. *J. Am. Chem. Soc.* **2002**, *124*, 10294. (c) Sromek A. W., Rubina M., Gevorgyan V. *J. Am. Chem. Soc.* **2005**, *127*, 10500.

24. (a) H.-C. Shen, S. Pal, J.-J. Lian, R.-S. Liu, *J. Am. Chem. Soc.* **2003**,*125*, 15762; (b) T. Miura, N. Iwasawa, *J. Am. Chem. Soc.***2002**, *124*, 518.

25. (a) McKelvey, D. R. *J. Chem. Educ.* **1983**, *60*, 112; (b) Pyykkö, P.; Desclaux, J. P., *Acc. Chem. Res.* **1979**, *12*, 276

26. For some reviews on the theoretical chemistry of gold, see: (a) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395. (b) Pyykkö, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 4412. (c) Pyykkö, P. *Inorg. Chim. Acta* **2005**, *358*, 4113.

27) Hashmi, A. S. K. *Catal. Today* **2007**, *122*, 211.

28. (a) Hashmi, A. S. K.; Weyrauch, J. P.; Rudolph, M.; Kurpejovic, E. *Angew. Chem. Int. Ed.* **2004**, *43*, 6545. (b) Hashmi, A. S. K.; Rudolph, M.; Bats, J. W.; Frey, W.; Rominger, F.; Oeser, T. *Chem. Eur. J.* **2008**, *14*, 6672.

29. (a) Mezailles, N.; Ricard, L.; Gagosz, F. *Org. Lett.* **2005**, *7*, 4133. (b) Baker, M. V.; Barnard, P. J.; Brayshaw, S. K.; Hickey, J. L.; Skelton, B. W.; White, A. H. *Dalton Transactions* **2005**, 37. (c) Gorin, D. J.; Davis, N. R.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 11260. (d) LaLonde, R. L.; Sherry, B. D.; Kang, E. J.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 2452. (e) Hamilton, G. L.; Kang, E. J.; Mba, M.; Toste, F. D. *Science* **2007**, *317*, 496.

30. (a) Nieto-Oberhuber, C.; López, S.; Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Eur. J.* **2006**, *12*, 5916. (b) Herrero-Gómez, E.; Nieto-Oberhuber, C.; López, S.; Benet-Buchholz, J.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 5455.

31. Hashmi, A. S. K.; Blanco, M. C.; Fischer, D.; Bats, J. W. *Eur. J. Org. Chem.* **2006**, *2006*, 1387.

32. (a) Mizushima, E.; Sato, K.; Hayashi, T.; Tanaka, M. *Angew. Chem. Int. Ed.* **2002**, *41*, 4563. (b) Fukuda, Y.; Utimoto, K. *Synthesis* **1991**, *1991*, 975. (c) Liu, Y.; Song, F.; Song, Z.; Liu, M.; Yan, B. *Org. Lett.* **2005**, *7*, 5409. (d) Genin, E.; Toullec, P. Y.; Antoniotti, S.; Brancour, C.; Genet, J.-P.; Michelet, V. *J. Am. Chem. Soc.* **2006**, *128*, 3112.

33. (a) Hashmi, A. S. K.; Sinha, P. *Adv. Synth. Catal.* **2004**, *346*, 432-438. (b) Nakamura, I.; Yamagishi, U.; Song, D.; Konta, S.; Yamamoto, Y. *Angew. Chem. Int. Ed.* **2007**, *46*, 2284.

34. (a) Hashmi, A. S. K.; Schwarz, L.; Choi, J.-H.; Frost, T. M. *Angew. Chem. Int. Ed.* **2000**, *39*, 2285. (b) Hashmi, A. S. K.; Weyrauch, J. P.; Frey, W.; Bats, J. W. *Org. Lett.* **2004**, *6*, 4391.

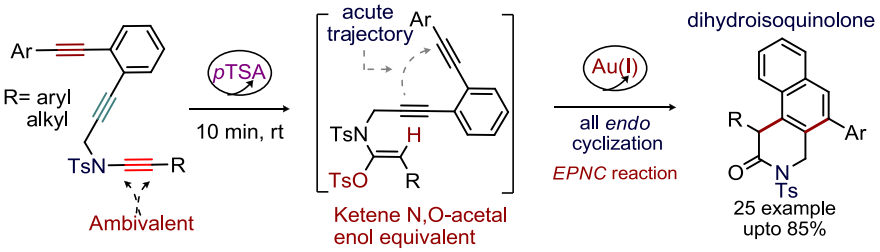
35. (a) Gorin, D. J.; Davis, N. R.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 11260-11261. (b) Shapiro, N. D.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 4160.

36. (a) Luzung, M. R.; Markham, J. P.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 10858. (b) Nieto-Oberhuber, C.; Muñoz, M. P.; Buñuel, E.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 2402. (c) Nieto-Oberhuber, C.; López, S.; Muñoz, M. P.; Cárdenas, D. J.; Buñuel, E.; Nevado, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 6146. (d) Gagosz, F. *Org. Lett.* **2005**, *7*, 4129.

Chapter 2

Brønsted Acid Promoted Au(I) Catalyzed Consecutive *endo* Cyclization of Ynamide: Access to Benzofused Dihydroisoquinolone

Abstract



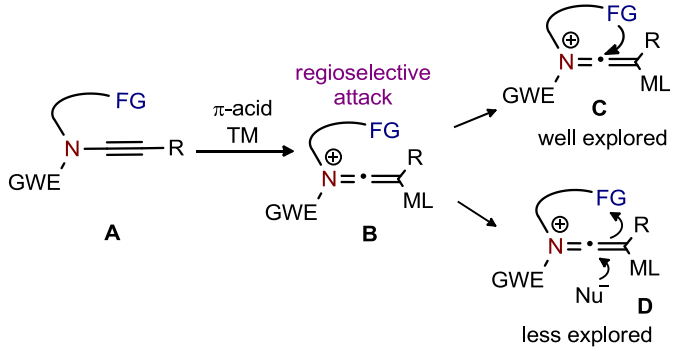
The ambivalent diyne-tethered-ynamides are synthesized from cost-effective commercially available *o*-iodoaniline involving Sonogashira coupling reactions and the Cu-mediated C–N bond formation in good to excellent yields. A novel synthetic route to dihydroisoquinolone through Brønsted acid promoted cascade cyclization of the easily accessible diyne-tethered-ynamides in the presence of Echavarren's catalyst has been shown. The reaction exhibits broad substrate scope producing wide range of new dihydroisoquinolones in overall good yields.

Reference:

Sanatan Nayak, Nayan Ghosh, B Prabagar and Akhila K. Sahoo (*communicated).*

2.1. Introduction

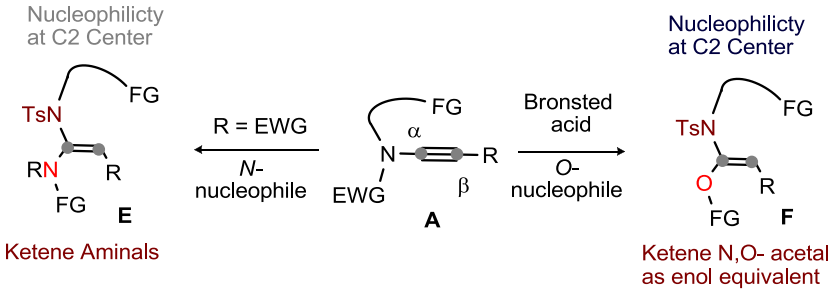
Ynamide is a versatile structural motif. The ring forming transformations on ynamides allow the fabrication of novel N-bearing molecular scaffolds of synthetic potential.[1,2] As a consequence, development of convenient ring-formation protocols on readily accessible stable ynamides for the construction of N-bearing complex heterocycles is always enviable. The alkene, allene or alkyne bearing ynamides inherently undergo ring-formations under the assistance of Brønsted/Lewis acids or transition-metal catalysis. The inherent polarization of the nitrogen lone-pair of ynamide to the triple-bond under the influence of π-acids/Brønsted acids enhances the electrophilicity at the α-carbon to the nitrogen atom, which in turn propels regioselective attack of nucleophile to the keteniminium intermediate **B** (Scheme 2.1). Thus, intramolecular cyclizations of ene-ynamides,[2a-c] allene-ynamides,[2d] enyne-ynamides,[2e] arene-ynamides,[2f] and various other π-nucleophile tethered ynamide derivatives have successfully been carried out for the synthesis of novel biologically important nitrogen-containing molecules. Accordingly, significant progresses have been made for cyclizations involving intramolecular attack of π-moiety to the *in situ* generated keteniminium species **B** (shown in **C**); in contrast, the attack of nuclephilic β-carbon of keteniminium species **B** to the pendant activated alkyne moiety is less explored (shown in **D**) (Scheme 2.1).



Scheme 2.1. Intramolecular ring forming transformation on ynamide

Thus, development of new synthetic methods on *endo*-cyclization of nuclephilic β-carbon of keteniminium species **B** to the pendant activated olefin moiety is envisaged. We anticipate that the reaction of species **A** with Brønsted acid would rapidly generate a ketene N,O-acetal **F**, a masked *frozen enol equivalent* of amide *in situ* (Scheme 2.2). The nucleophilic attack of Brønsted acid at the α-position of the transient keteniminium intermediate **B** would lead to **F**. The electron delocalization of hetero atom to the olefin unit in the ketene N,O-acetal **F** makes the C2 center highly nucleophilic, which in turn provokes undergoing 1,n-enyne cyclization with the pendant alkyne under the influence of gold(I) catalyst. Furthermore, the presence of EWG in the alkyne-terminus of ynamide unit in **B** would possibly allows the

hydroamidation with amide to provide ketene N,N-acetal **E** (Scheme 2.2). The *in situ* generation of enol equivalent of less enolizable amide and the synthesis of novel N-bearing heterocycles through the one pot C–C bond forming cyclizations are some of the merits and novelty of the current work.



Scheme 2.2. Generation of ketene N,O-acetals as an enol equivalent of amide

The preformed enol equivalent of carbonyls found broad synthetic utility. The enol-motifs of carbonyls possess sufficient stability, offering ways to examine its reactivity, to develope reliable-methods for preparation, purification, storage, and easy-handling. In contrast, the less enolizable character of amide led to the synthesis of preformed enol equivalent of amide difficult. Looking in to the structural coherence and the reactivity of ynamide, the enol-equivalent of amide can easily be realized. Hence, exploration of reactivity on the *in situ* generated ketene equivalent of the alkyne tethered ynamide towards cascade C–C bond forming enyne cyclization is the working theme of this chapter.

Cascade reactions have been the subject of intense research in recent years. These reactions have the potential to rapidly increase molecular complexity in a single operation, concomitantly utilizing the reactive intermediates that are not stable enough for isolation. Recent advances in homogeneous gold catalysis[3,4] have opened up further possibilities in the exploration of cascade reactions because it promotes several types of nucleophilic reaction through the electrophilic activation of carbon-carbon multiple bonds. Among different C–C bond forming cascade reaction involving Au(I)-catalyzed activation of alkynes, the addition of activated methylene compounds such as malonates and β-ketoesters to an unactivated alkyne has particularly been well-studied. Furthermore, variety of preformed electron-rich enol equivalents derived from ketones and aldehydes, for instance, alkyl enol ethers, silyl enol ethers, silyl ketene amides, and enamines have efficiently been employed in Au(I)-catalyzed cyclization reactions. The requirement of additional synthetic step for the preparation of enol equivalents, its stability and handling poses concerns in diminishing broad synthetic utility of the reagent. With the established use of preformed enol equivalent to the Au(I)-catalyzed transformations, a consecutive all-*endo* cyclization of *in situ* generated ketene N,O-acetal **G** from ynamide to the stereo-electronically embodied pendant alkyne is thus envisaged (Figure 2.1). The less enolizable amides lack the required nucleophilicity to

react directly with the Au(I)-complexed alkynes under C–C bond forming α-functionalization of amide. On the basis of Baldwin's rule, a consecutive endo cyclization from ketene N,O-acetal to the tethered Au-activated alkyne motif is possible.

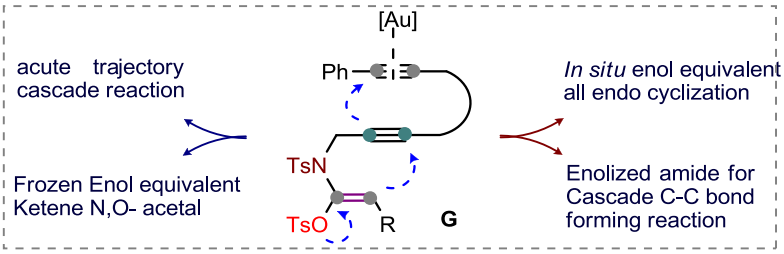
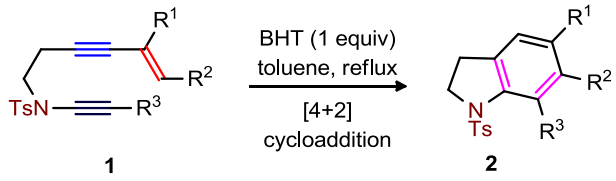


Figure 2.1. Cascade protocol of N-linker ynamide under gold(I) catalysis

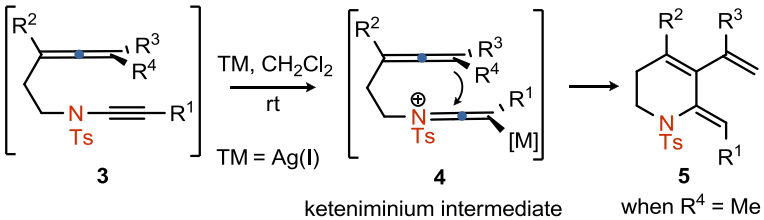
2.1.1. Precedents and strategy for the ring forming transformation on ynamide

The conjugated enyne- and dienes-ynamides readily undergo intramolecular [4+2] cycloaddition. BHT (butylated hydroxyl toluene) mediated intramolecular [4+2] cycloaddition of enyne-ynamides 1 gave indolines 2 (Scheme 2.3).[5]



Scheme 2.3. Intramolecular [4+2] cycloaddition

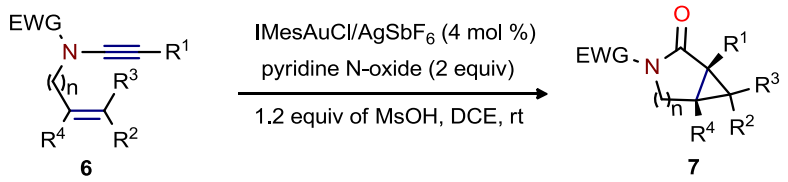
Malacria and co-workers reported the Ag(I)-catalyzed cycloisomerization of de novo allene-ynamides **3**, leading to amide-substituted cross-conjugated trienes **5** (Scheme 2.4). The reaction proceeds through the activation of triple bond by Ag-catalyst followed by 6-exo-dig cyclization of allene to the β-carbon of keteniminium intermediate **4** and the isomerization sequence (Scheme 2.4).[6]



Scheme 2.4. Cycloisomerization of allene-ynamides

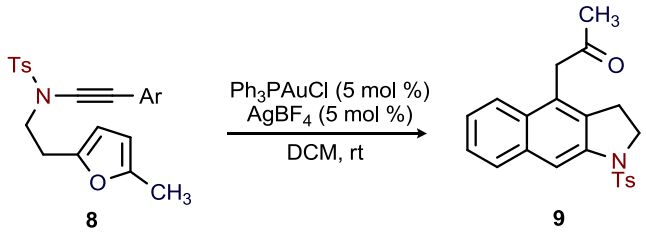
An elegant method for the synthesis of 3-azabicyclo[3.1.0]hexan-2-one derivatives **7** via Au(I)-catalyzed oxidative cyclopropanations of N-allyl-ynamides **6** in the presence of

external oxidant pyridine N-oxide has been demonstrated by Li and co-workers. The reaction involves α-addition of pyridine N-oxide to the metalated ynamide **6** (Scheme 2.5).[7]



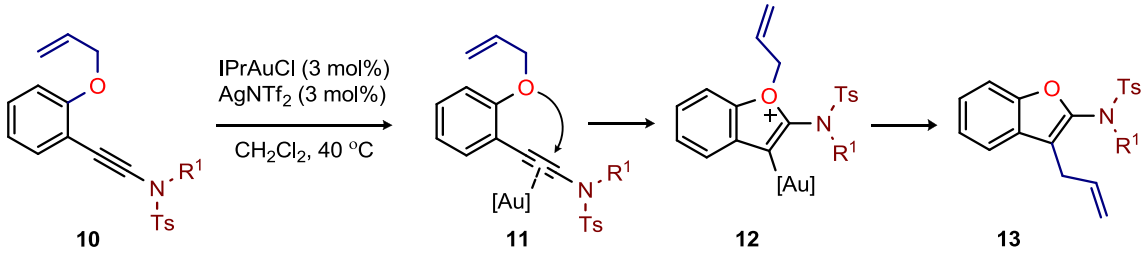
Scheme 2.5. Gold carbenoid in ring forming transformation

Hashmi group developed Au-catalyzed cyclization of furanyl-ynamides **8** to the synthesis of fused heterocycles **9** (Scheme 2.6). The transformation begins with the activation of triple bond of the ynamide by Au-catalyst followed by the attack of the pendant furan ring at C2 center; finally, ring cleavage cycloisomerization provides fused heterocycle **9** (Scheme 2.6).[8]



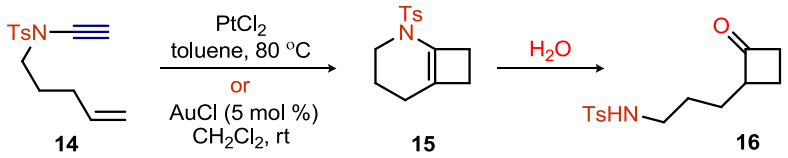
Scheme 2.6. Gold catalyzed cyclization of furanyl-ynamides

The Au-catalyzed 5-endo-dig cyclization via the attack of lone pair of O to the Au-activated-alkyne moiety of ynamide followed by allyl rearrangement in *ortho*-O-allyl aryl substituted ynamide **10** produce highly substituted benzo[b]furan skeleton **13** (Scheme 2.7). The reaction involves nucleophilic attack of oxygen to the activated triple bond of **11** to deliver **12**. Finally, 1,3-allyl migration on **12** produce **13** (Scheme 2.7).[9]



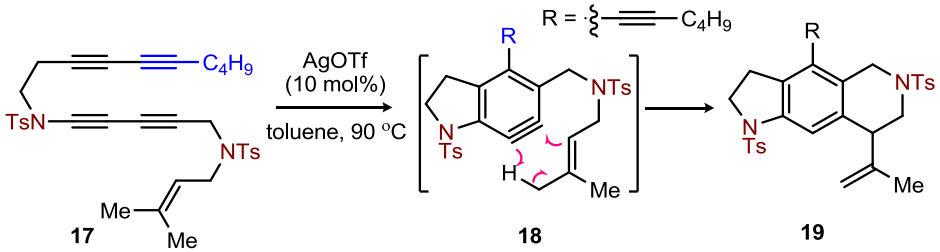
Scheme 2.7. Synthesis of benzo[b]furan

The Malacria and Cossy groups independently reported the Pt and Au-catalyzed cycloisomerization of ene-ynamides. A formal [2+2] cycloaddition of ene-ynamide **14** provides cyclobutenyl fused bicyclic derivative **15**; hydrolysis of **15** in presence of moisture forms cyclic ketone moiety **16** (Scheme 2.8).[10a-b]



Scheme 2.8. Cycloisomerization of ene-ynamide

Lee and co-workers have shown the intramolecular Alder-ene cycloaddition with the aryne intermediates **18**, readily obtained through Ag-catalyzed hexadehydro-Diels-Alder (HDDA) cycloaddition of ynamide **17**. The metal catalyst increases the reaction rate of the process providing clean conversion of **17** to **19** (Scheme 2.9).[11a-b]

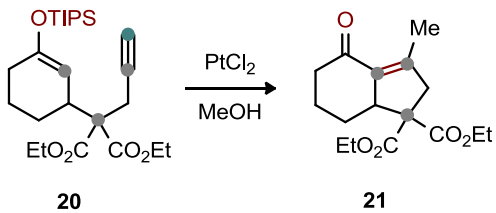


Scheme 2.9. HDDA reaction for ring forming transformation on ynamide

2.1.2. Precedents for the cyclization of the alkyne tethered enol equivalent

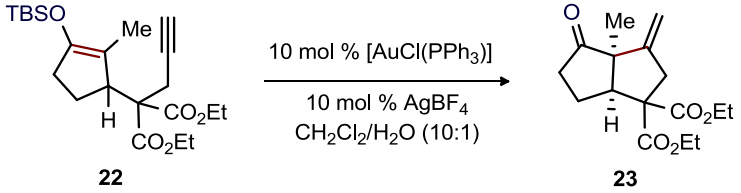
Silyl enol ethers, the "frozen enol equivalents" have successfully been employed for the C–C bond forming processes in the Au-catalyzed transformations. Due to the lack of proton source in silyl-enol ethers, the reaction essentially requires a proton source for the termination of vinyl-Au(I) intermediate, obtained upon the addition of nucleophile to the Au-alkyne complex. Accordingly, various Au-catalyzed transformations involving silyl-enol ether and alkynes in the presence of proton source have been developed.

Echavarren group shown Pt(II) or Au(III) catalyzed intramolecular 5-*exo*-dig (6-*endo*-dig) cyclization of enol ether **20** with alkynes to obtain five- or six-membered bearing carbocycles **21** (Scheme 2.10). The reaction takes place by the anti addition of enol ether to the metal-alkyne complex. The possible involvement of vinylidene complex is excluded. In addition to the participation of usual 5-exo-dig pathways, the reaction also suitably involves 6-endo-dig pathway (Scheme 2.10).[12]



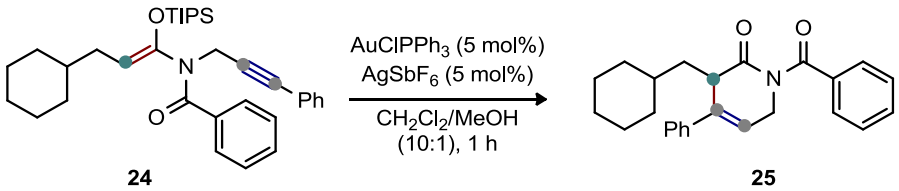
Scheme 2.10. Cyclizations of silyl enol ether with alkynes

Toste and co-workers demonstrated an intramolecular 5-exo-dig cyclization of silyl enol ether **22** in the presence of mixture of Au(I) and Ag salts in chloroform and water to produce fused carbocyle **23** with two carbon stereocenter (Scheme 2.11).[13]



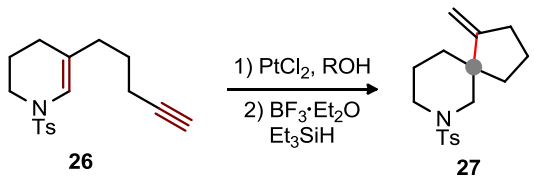
Scheme 2.11. Silyl enol ether in 5-exo-dig cyclization reaction

The Au(I)-catalyzed regioselective cyclization of silyl ketene amide or carbamate **24** with the pendant alkyne led to the formation of dehydro-*δ*–lactams **25** as shown by Shen and co-workers (Scheme 2.12); methanol served as a proton source. The 6-endo-dig cyclization products were exclusively formed from the enyne precursor **24**. Whereas the terminally unsubstituted 1,6-enyne precursor exclusively undergo 5-exo-dig cyclization. The regioselectivity in these Au-catalyzed cyclizations are solely substrate-dependent.[14]



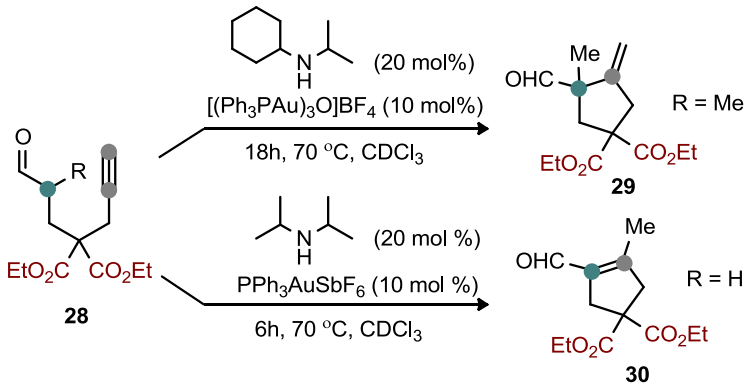
Scheme 2.12. Regioselective cyclizations of silyl ketene amides with alkynes

Cyclic enesulfonamides **26**, enecarbamates, or enamides tethered alkynes undergo intramolecular cyclization under the influence of $PtCl_2$ to generate spiro-fused heterocyclic ring systems **27** (Scheme 2.13). The reaction proceeds via nitrogen lone pair assisted cyclization to the pendant alkyne. The imine intermediate formed was trapped by alcoholic solvent to produce mixture of diastereomeric hemiacetal and desired product. Interestingly, one-pot cyclization-reduction sequence allowed the formation of desired produt (Scheme 2.13).[15]



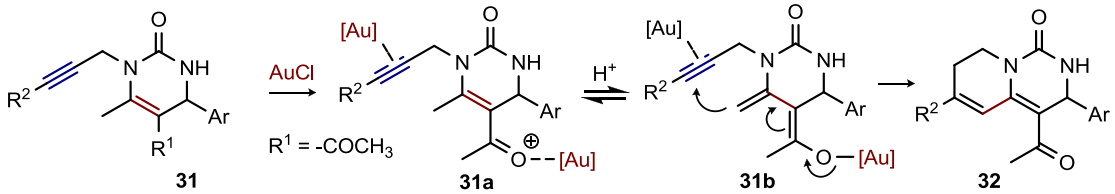
Scheme 2.13. Cyclization reaction of enamides

The Kirsch group demonstrated 5-exo-dig cyclization of formyl alkynes in the presence of a combination of Au(I) complexes and amine bases. The α-functionalization of aldehydes with the internal unactivated alkynes proceeds through the participation of enol equivalent enamine, formed *in situ* from aldehyde and amine. The cyclization of α-methyl group bearing aldehyde with the alkyne motifs produced exocyclic double bond bearing product **29** (Scheme 2.14). While the Au-catalyzed reaction of α-unsubstituted aldehyde **28** provided **30** with endocyclic double bond (Scheme 2.14).[16]



Scheme 2.14. Direct carbocyclization with comination of gold and aminocatalysis

An interesting observation from Schaus group demonstrates Au-catalyzed cyclization of alkyne-tethered dihydropyrimidones to yield pyridopyrimidones (Scheme 2.15). The reaction proceeds involving vinylogous Conia-ene reaction with dual activation, both oxophilic and alkynophilic in **31**, by Au-catalyst (**31a** and **31b**). The 6-endo-dig cyclization followed by protodemetalation and double bond isomerization gives product ***32*** (Scheme 2.15). Deuterium leveling experiment confirmed the occurrence of enolization prior to cyclization reaction.[17]



Scheme 2.15. Pyridopyrimidone formation via 6-endo-dig cyclization

2.1.3. Comparision of orbital interaction and the expected regioselectivity for nucleophilic and electrophilic cyclization of alkynes:

Radical *exo*-attack: When a nucleophile is radical, the reaction is called nucleophile promoted electrophilic cyclization. Here the nucleophile HOMO interacts with the alkyne

LUMO (Ψ_2 i.e π^*). In case of endo-attack, the nucleophile approaches attacking the alkyne motif in endo-dig manner, i.e acute angle of attack. In this process, the nucleophile crosses the nodal plane of LUMO, suffering both bonding (same sign) and antibonding (opposite sign) interaction (Figure 2.2). As a result, the net bonding interaction is zero, an unfavorable process. Whereas the exo-attack of nucleophile to the alkyne-unit does not need to cross the nodal point of LUMO, i.e obtuse angle of attack. As a consequence, bonding interaction between radical based nucleophile and the LUMO of alkyne is only possible (Figure 2.2). Hence the exo attack of nucleophile to alkyne through obtuse angle trajectory is favorable.[18a-b]

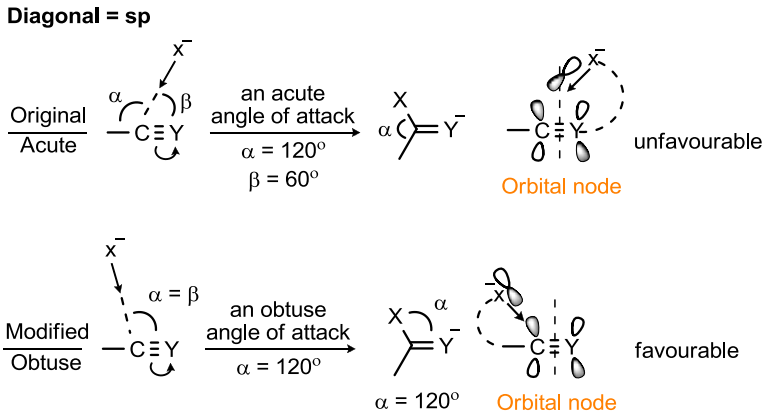


Figure 2.2. Nucleophilic radical alkyne cyclization

Metal assisted *endo*-attack: In case of Au(I)-catalyzed transformations, the reaction begins with the favorable 2e-interaction of π-bond HOMO of alkyne to the electrophile LUMO of Au(I) species. This interaction favors an acute trajectory, bringing electrophiles at the center of the π-bond and forms nonclassical cations (Figure 2.3). As a result, the HOMO of alkyne under the activation of Au-catalyst becomes LUMO (Ψ_1 i.e LUMO-umpolung), enabling the intramolecular attack of nucleophile in endo- and exo-fashion and facilitates the formation of ring-closure entity (Figure 2.3). The endo attack involves the participation of aromatic TS, while exo-attack is possible through metal assisted reaction (i.e EPNC) (Figure 2.3).[18a-b]

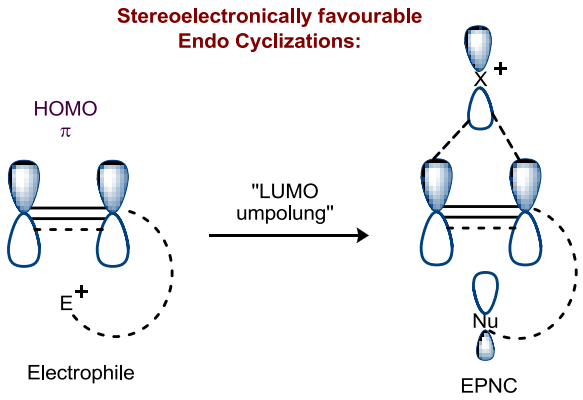
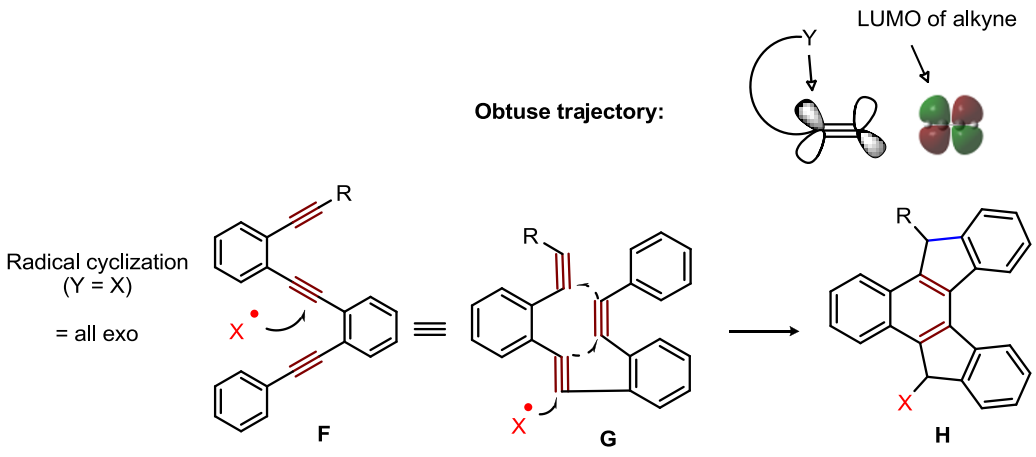


Figure 2.3. Electrophile promoted nucleophilic cyclization (EPNC)

Alabugin group significantly contributed in understaning and demonstrating novel organic transformations through the mode of cyclizations shown in Figure 2.3. In this context, the attack of a radical to the three alkynes appended conjugated polyaromatic scaffold **F** successfully undergoes three consecutive cascade exo-dig cyclizations involving obtuse trajectory (Figure 2.4). The product **H** formed exclusively with exo-selectivity relies on the revised rules of alkyne cyclizations, contrary to the Baldwin's rules. On the otherhand, when an alkyne coordinates to an external Lewis acid ("electrophile-assisted cyclizations") due to the stereoelectronic effect ("the LUMO umpolung") the cyclization proceeds via endo-dig fashion. Hence diyne scaffold **I** succesfuly undergoes electrophile promoted nucleophilic cyclization to provide polycyclic fused compound **K**. The aromaticty of the product **K** is the driving force for the 6-endo-dig cyclization (Figure 2.4).[19a-b]



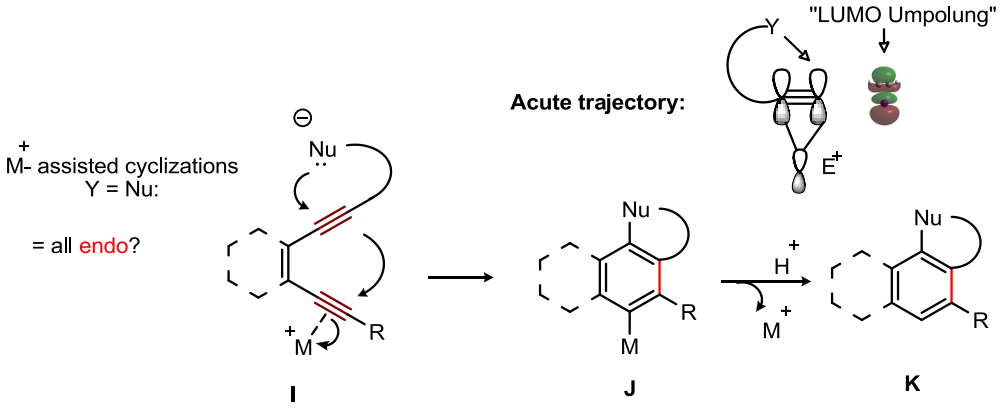
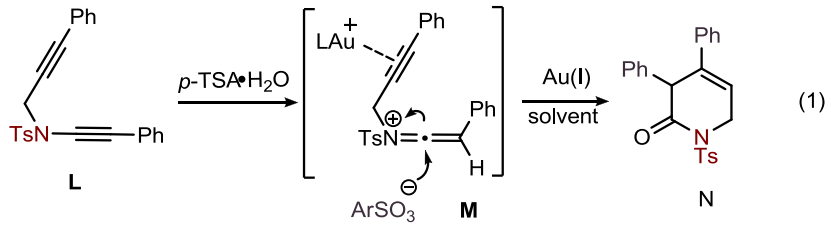


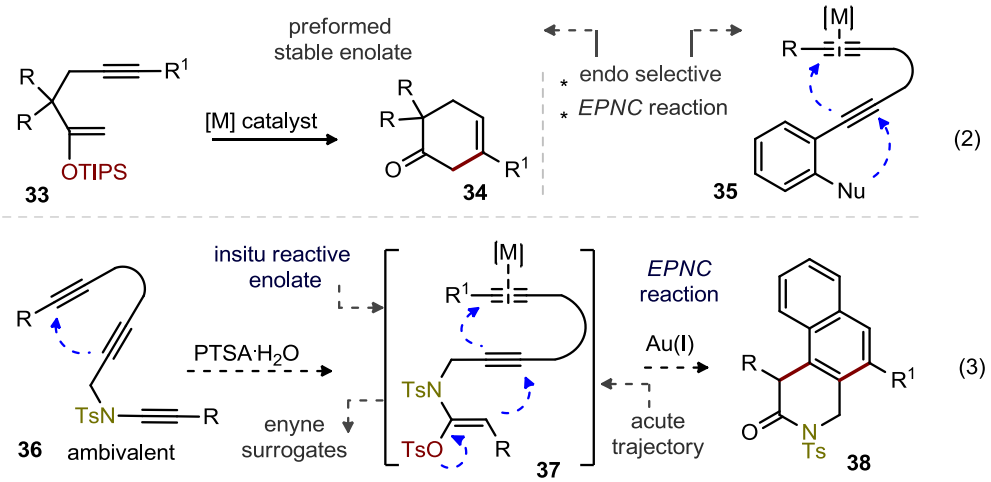
Figure 2.4. Reactions depicting the endo and exo attack mode

2.2. Motivation, Hypothesis and Design

The Au-catalyzed C–C bond forming cyclization methods significantly contributes to build complexity and construct novel cyclic molecular entities with ease.[20] A detailed survey on the strategies for cascade C–C bond formations on ynamide reveals that the use of alkyne tethered ynamide for the *in situ* generation of ketene N,O-acetals followed by cascade C–C bond forming transformation remains unprecedented (Scheme 2.16).

Recently, we have demonstrated Au–catalyzed, *p*-TSA·H_2O triggered hydrative cyclization of alkyne tethered ynamide for the synthesis of dihydropyridinone (eq 1, Scheme 2.16).[3c]The transient alkyne-tethered ketene N,O-acetal obtained via the attack of *p*-TSA on an activated ynamide, presumably participates in the cyclization to form dihydropyridone (Scheme 2.16). A critical evaluation on the metal catalyzed C–C bond forming reactions of enol equivalents ***33*** and electrophile promoted nucleophilic cyclization (EPNC) reactions of the species ***35*** (eq 2, Scheme 2.16) prompted us to explore examining the cascade all endo cyclization process for the ynamide ***36*** (eq 3, Scheme 2.16).





Scheme 2.16. Ynamide as enol equivalent for cascade cyclization/1,5-enyne cycloisomerization strategy

We at first envisioned the synthesis of suitably substituted N-linked alkyne tethered ambivalent ynamide ***36***. Based on our experience, we anticipate the formation of ketene N,O-acetal ***37***, a frozen enol equivalent of amide as 1,5-enyne precursor, through the addition of Brønsted acid at the C2-position of ***36***. Next, the electrophilic Au(I) promoted one pot consecutive endo-cyclization constructs fused dihydroisoquinolone derivative ***38*** (eq 3, Scheme 2.16).

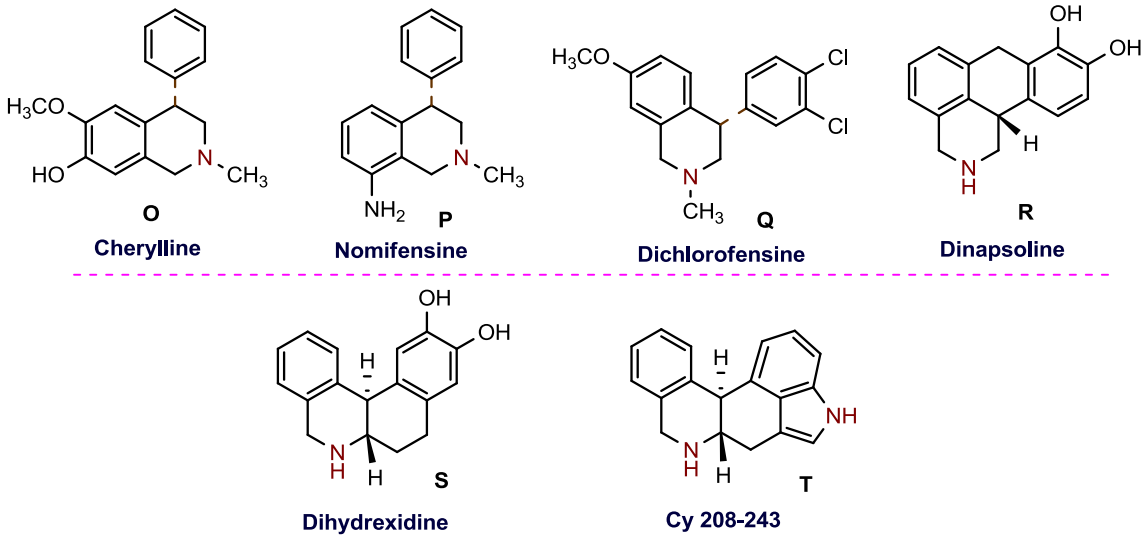


Figure 2.5. Derivatives of isoquinolone containing biologically important molecules

Dihydroisoquinoline is pervasive structural motifs found in natural products especially in amaryllidaceae alkaloids and pharmaceutically active compounds, for instance, protein kinase B (PKB) inhibitors, anti-parkinson's drugs, anti-depressants, antihistamines, selective serotonin reuptake inhibitors (SSRI) with powerful biological properties (Figure 2.5).[21, 22] As

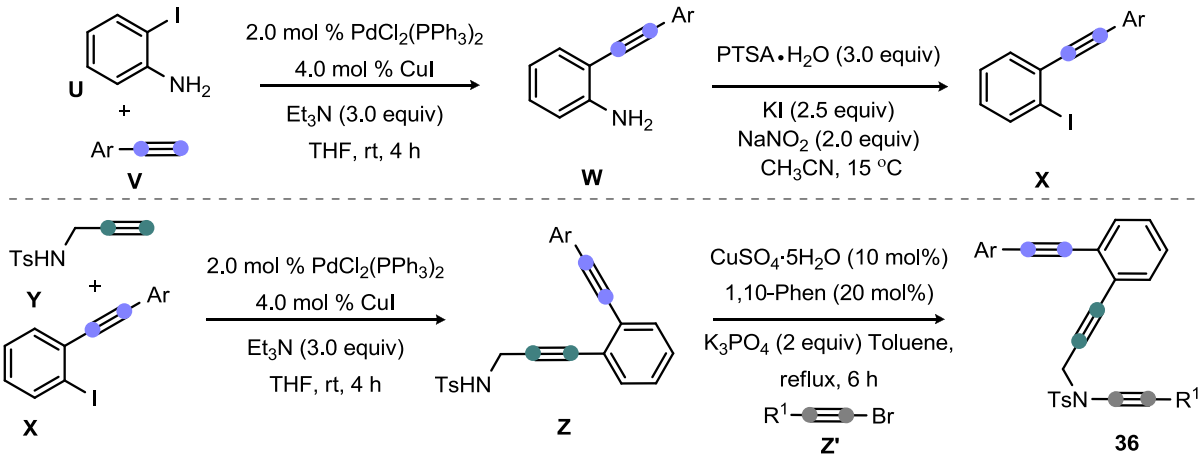
a consequence, development of straightforward method for the efficient synthesis of polycyclic dihydrisoquinolone scaffolds is always desirable.

In this context, fabrication of dihydroisoquinolone motifs through cascade endo cyclization of ynamide ***36*** is envisaged. This chapter enumerates detailed investigation for the synthesis of ynamide precursor ***36*** followed by Au-catalyzed cycloisomerization of ***36*** for the construction of dihydroisoquinolone.

2.3. Results and Discussion

2.3.1. Synthesis of Precursors

To validate workable conditions for the cascade cyclization, compound ***36*** was at first synthesized from cost-effective 2-iodoaniline **U** involving two consecutive Sonogashira coupling reactions followed by C–N bond formations in overall lucrative yields (Scheme 2.17). At first, 2-iodo aniline was subjected to Sonogashira reaction in presence of aryl acetylene **V** to give compound **W**.[23] Diazotization followed by iodination of aniline moiety of **W** readily produced compound **X** (Scheme 2.17).



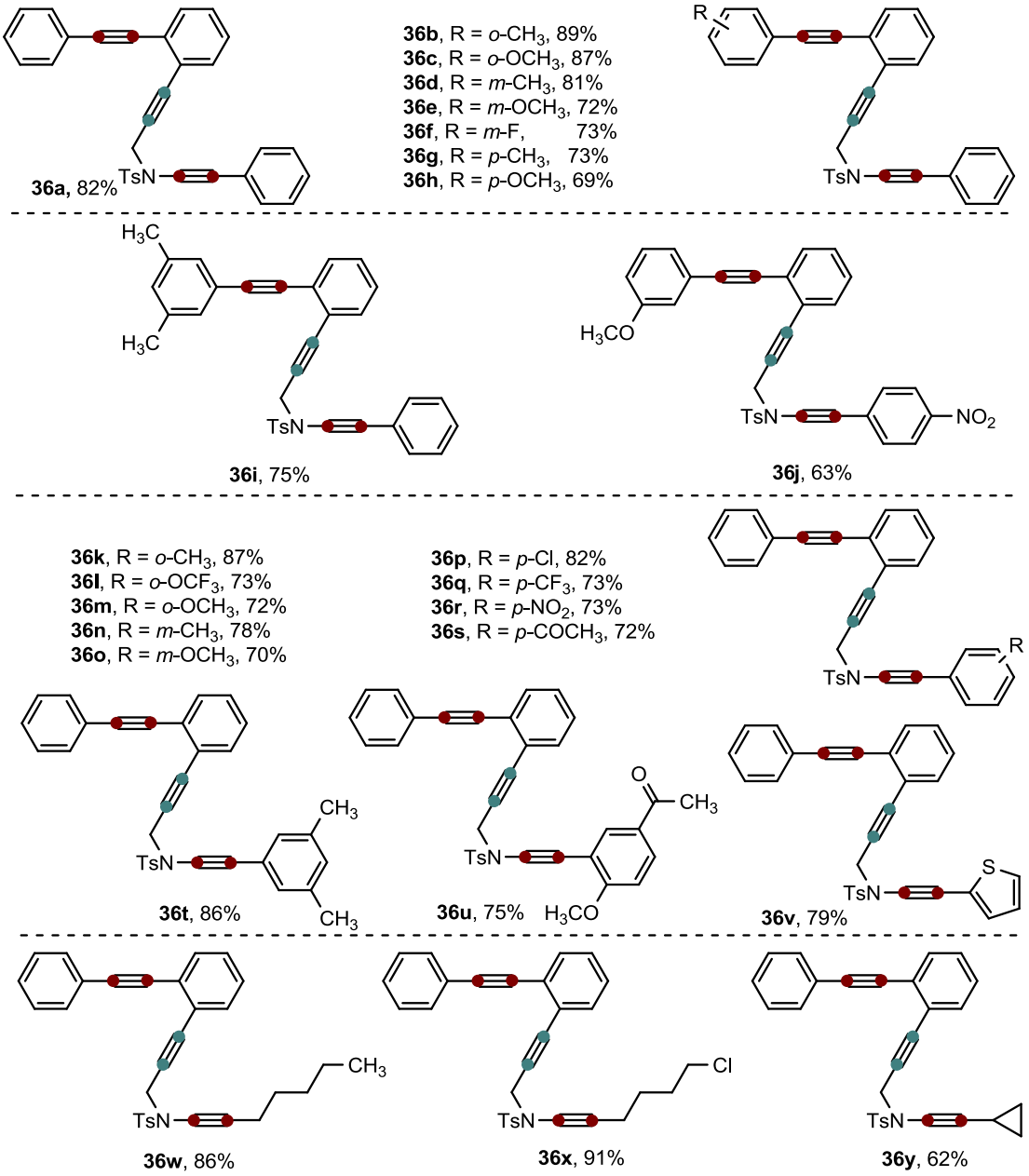
Scheme 2.17. Starting material preparation

Next, Sonogashira coupling reaction between **X** and NTs-propargyl amide **Y** delivered **Z** in good to excellent yields. Finally, Cu(II) catalyzed C–N bond formation of **Z** with bromoalkynes **Z′** readily provided precursors ***36*** in overall appreciable yields.

Following the above workable steps, variety of alkyne tethered ynamide precursors ***36*** are prepared (Table 2.1). The commercially available 2-iodoaniline has exclusively been employed connecting two alkynyl moieties. Sonogashira coupling of sterically encumbered and electron-rich (Me, OMe, and di-Me) aryl acetylenes with 2-iodoaniline has successfully been conducted at first; this process enables the formtion of corresponding 2-alkynyl substituted anilines. Diazotization, iodination of anilines followed by Sonogashira reaction with NTs-propargyl amides and finally C–N coupling with a range of aryl-bromoalkynes

led to **36a–36v** (Table 2.1); both the terminal aryl moieties are easily modulated through the incorporation of various electronically and sterically-encumbered common functional groups. Interestingly, alkyl substituted bromo alkynes undergo C–N coupling to afford precursors **36w–36y** in good overall yield (Table 2.1).

Table 2.1. Preparation of alkyne tethered ynamide 36.[a,b]

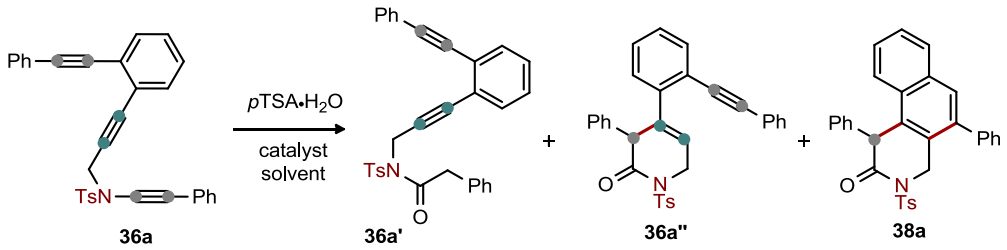


[a]Reactions were carried out using **Z**(1.0 mmol), **Z′** (1.2 mmol), $CuSO_4.H_2O$ (0.1 mmol), 1, 10- phenanthroline (0.2 mmol), K_3PO_4 (2.0 equiv) in toluene (4.0 mL) at 70 °C. [b]Isolated yields.

2.3.2. Reaction Optimization:

To directly access dihydroisoquinolone skeleton, we at first investigated examining Brønsted acid promoted consecutive *endo*-cyclizations on yne-tethered ynamide **36a**. As the ynamide-unit in **36a** is highly reactive to acid-catalysts, we therefore anticipate the possible formation of amide **36a'**, dihydropyridinone **36a''**, and the desired dihydroisoquinolone **38a** from **36a**. Recent results in the Au-catalyzed cyclization and cycloisomerization of yne-tethered ynamides inspired us to use *p*-TSA in conjunction with cationic Au-complexes for the consecutive *endo*-cyclizations of poly-yne-ynamide in **36a** (Table 2.2).

Table 2.2. Optimization of reaction parameters[a]



entry	catalyst (mol %)	solvent	yield (%)[e]		
			36a'	**36a''**	**38a**
1[b]	A (5)	CH_3CN	-	-	-
2	A (5)	Dioxane	6	35	50
3[c]	A (5)	Dioxane	80	-	-
4	B (5)	Dioxane	10	35	40
5	C (5)	Dioxane	45	20	20
6	D (5)	Dioxane	-	40	48
7	E (5)	Dioxane	79	5	-
8	F (5)	Dioxane	82	-	-
9[c]	A (5)	DCE	trace	-	10
10[d]	A (5)	Dioxane/DCE	0	5	62
11	**A (5)**	**Dioxane/DCE**	**0**	**5**	**83**
12	B (5)	Dioxane/DCE	-	30	60
13	D (5)	Dioxane/DCE	-	30	50

Catalyst A: JohnphosAu(I)(NCMe)]$^+SbF_6^-$, B: JohnphosAuCl/ $AgSbF_6$, C: JohnphosAuNTf_2, D: IPrAuCl/ $AgSbF_6$, E: $Ph_3PAuCl/AgSbF_6$, F: $Ph_3PAuCl/AgNTf_2$, [a]Reactions were carried out using **36a** (0.2 mmol), *p*-TSA.H_2O (0.3 mmol), catalyst A (5.0 mol %) in solvent Dioxane/DCE (1:2, 3.0 mL) at rt–80 °C for 24 h. [b]Starting material decomposed, [c]at 80 °C, [d]at rt. [e]Isolated yields.

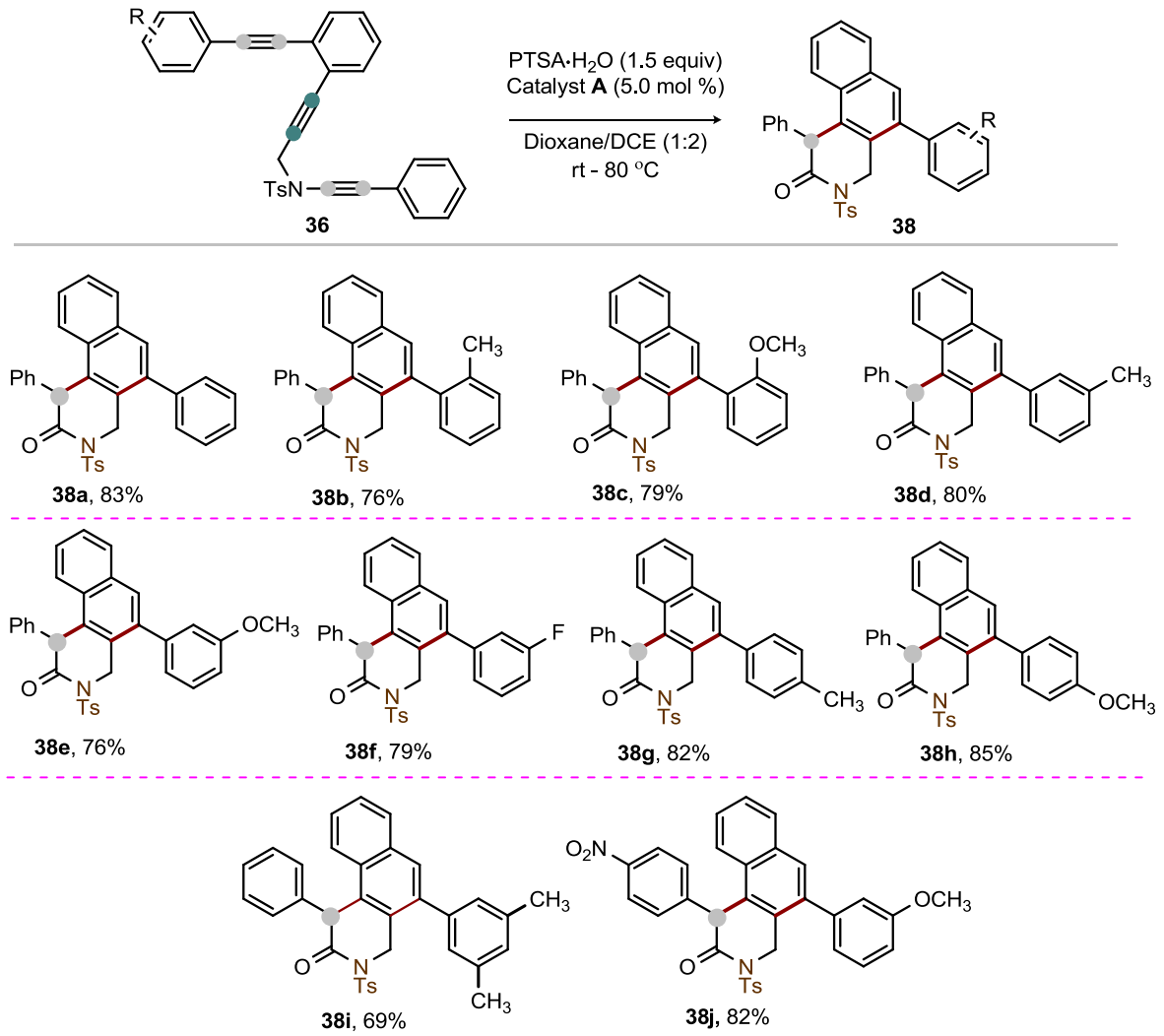
Thus, compound **36a** was exposed to *p*-TSA (1.5 equiv) in presence of Echavarren's catalyst[25] A (5.0 mol %) in CH_3CN; to our dismay, **36a** did not survive providing complex mixture (Table 2.2, entry 1). To our delight, compound **38a** was isolated 50% yield along with **36a′** (6%) and **36a″** (35%), when the reaction was carried out in dioxane (entry 2). Surprisingly, reaction at an elevated temperature exclusively led to hydration product **36a′** (entry 3). The use of combination of JohnphosAuCl and silver salts produced moderate amount of **38a** (entries 4) and catalyst C gave **38a** only 20% (entry 5). The reaction with IprAuCl & $AgSbF_6$ mixture gave 48% of **38a** (entry 6). Other silver salts, such as $AgSbF_6$ and $AgNTf_2$ in combination with Ph_3PAuCl readily delivered **36a′** (entries 7 and 8). Vast screening of Au-reagents revealed that catalyst A was best. We next explored screening solvents; the reaction with catalyst-A and *p*-TSA in $ClCH_2CH_2Cl$ (DCE) did not proceed at room temperature, in contrast trace amount of **36a′** was formed with incomplete consumption of **36a** at 80 °C (entry 9); the lack of solubility of *p*-TSA in DCE is presumably responsible for poor outcome. The results from entries 2 and 9 helped us investigating the role of mixture of solvents. Interestingly, reaction in dioxane and DCE (1:2) mixture resulted 62% of **38a** (entry 10). We then looked into examining the reaction profile by sequential addition of reagents and conducting reaction at various temperatures. Accordingly **36a** was stirred with *p*-TSA in dioxane for 10 min leading to complete consumption of **36a**; next, a solution of catalyst A in DCE was added and reaction continued for 4 h till the reactive species converted to **36a″**; finally, the reaction mixture heated at 80 °C for 20 h affording **38a** in 83% yield (entry 11). Under the identical conditions, other catalysts turned moderate (entries 12 and 13).

2.3.3. Scope of the reaction

With the optimized reaction conditions in hand, we set out to define the scope of this cascade protocol. Table 2.3 and 2.4 showcased the detailed scope of the synthesis of dihydroisoquinolone skeleton. The electron-neutral phenyl-ring bearing alkyne tethered ynamide **36a** under the optimized conditions produced **38a** in 83% yield. The electron-rich aryl moiety in propargyl alkyne terminus of diyne-tethered-ynamide smoothly participated cascade cyclization in the presence of *p*-TSA under the optimized conditions. Interestingly, the ynamides **36b** and **36c** having *o*-substitution on the aryl group in propargyl alkyne terminus smoothly undergoes hydrative cyclization to provide 1:1 mixture of two atropisomers **38b** and **38c** in good yields. The *m*-substitution of the aryl-moiety in propargyl alkyne terminus of ynamide did not affect the formation of corresponding dihydroisoquinolones **38d–f**. To our delight, the electron withdrawing flouro-group bearing

ynamide **36f** smoothly participated in the cascade cyclization process affording 79% of the desired dihydroisquinolinone **38f**. The Me/OMe substitution at the *para* position of aryl group in **38g** and **38h** were isolated in good yields. The 3,5-dimethyl substituted ynamide **36i** under the optimized condition reacted smoothly to provide the desired product **38i** in 69% yield. Variation on the substituent on the aryl ring in both the propargyl alkyne and ynamide alkyne terminus in ynamides **36j** smoothly underwent hydrative cyclization to yield **38j** in appreciable yields.

Table 2.3. Synthesis of dihydroisoquinolone skeleton, substrate scope-I [a,b]

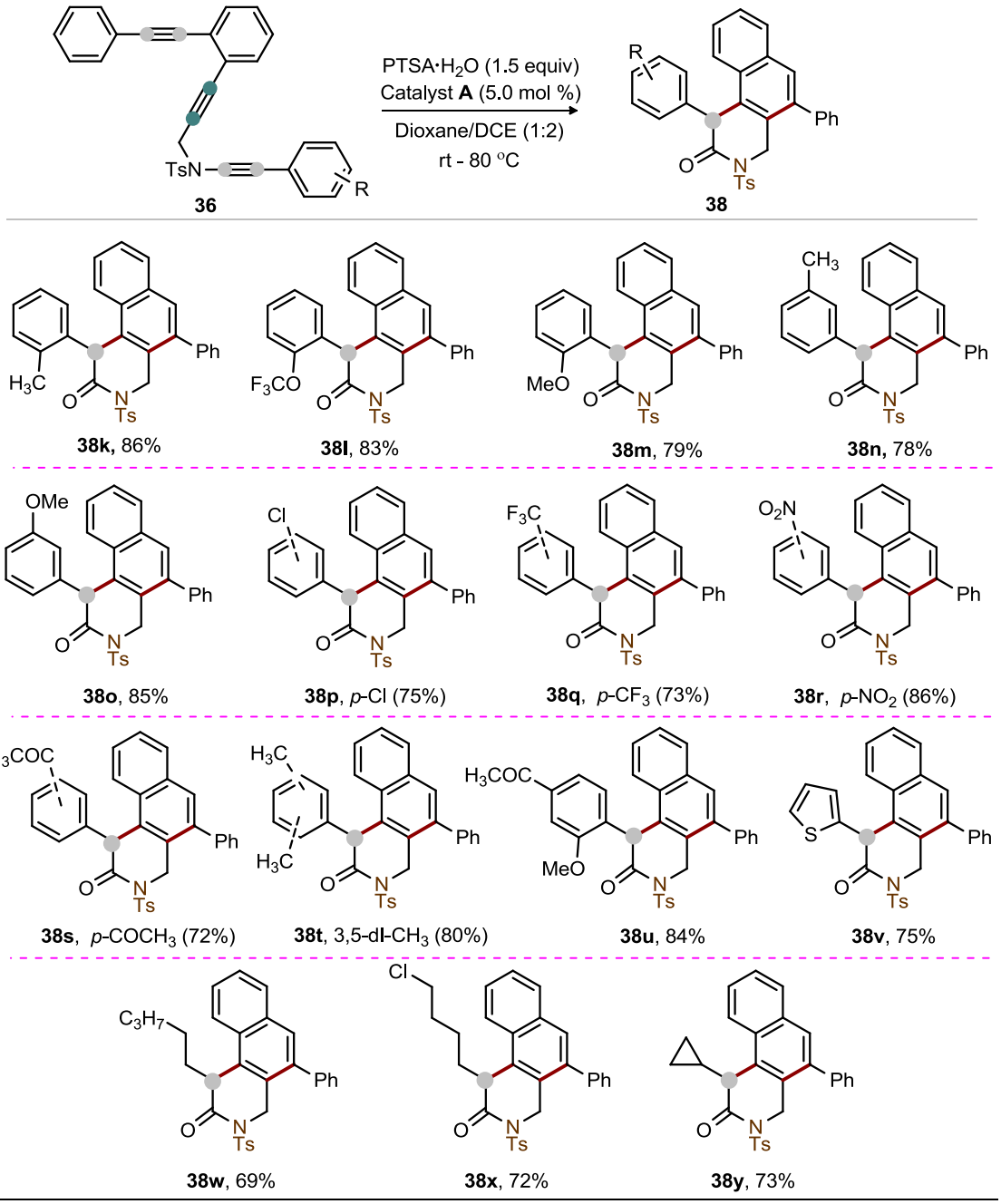


[a]Reactions were carried out using **36** (0.25 mmol), catalyst A (3.0 mol %) in Dioxane:DCE (1:2) 3 ml at rt–80 °C for 24 h. [b]Isolated yields.

Next, the ynamides **36** having variation of substitutions on aryl moiety in the ynamide-alkyne terminus was subjected to the cascade hydrative cyclization under the optimized conditions (Table 2.4). Keeping both steric and electronic properties in mind, the effect of

ortho-substituted aryl moiety at the ynamide-alkyne terminus has been examined. Electron donating methyl, triflouromethoxy and methoxy groups on the aryl-moiety of ynamides **36k–m** provided the desired dihydroisoquinolone products **38k–m** in good yields.

Table 2.4. Synthesis of dihydroisoquinolone skeleton, substrate scope-II[a,b]



[a]Reactions were carried out using **36** (0.25 mmol), catalyst A (3.0 mol %) in Dioxane: DCE [(1:2) 3 mL] at rt–80 °C for 24 h. [b]Isolated yields.

Compound **38l** was further confirmed by X-ray crystallographic analysis (Figure 2.6).The substitution on the *meta*-position did not have any impact on the hydrative cyclization to provide **38n** and **38o** in excellent yields. Chloro groups at the *para*-position of the aryl moiety smoothly underwent cyclization delivering the dihydroisoquinolone **38p** in 75% yield. The electron withdrawing group such as $-CF_3$, $-NO_2$ and $-COCH_3$ on the *para*-position in aryl-ring of the ynamides **36q–s** reacted efficiently and the corresponding products **38q–s** are isolated in appreciable yields. The two electron donating group on the aryl moiety of ynamide **36t** does provide the desired product **38t** in 80% yield. The presence of both donating (OMe) and withdrawing (COMe) substituent on the aryl ring of ynamide **36u** underwent cyclization smoothly to provide the dihydroisoquinolone core **38u** in 84% yield. Heterocyclic moiety on ynamide did not affect the reaction efficiency, producing the dihydroisoquinolone **38v** in 75% yield. The effect of aliphatic substituent on ynamide was next surveyed. Gratifyingly, the reaction of a long chain hexyl group bearing ynamide **36w** under the optimized consitions proceeded sluggishly and mixture of dicyclization (**38w**) and monocyclization (**38w′**) products (4:1) are isolated in overall 69% yield. The chloro hexyne group bearing ynamide **36x** gave mixture of **38x** and monocyclized product **38x′** in (9:1) ratios in 72% yield. Cyclopropyl group on ynamide did not affect the cascade cyclization reaction affording the desired dihydroisoquinolone **38y** in 73% yield.

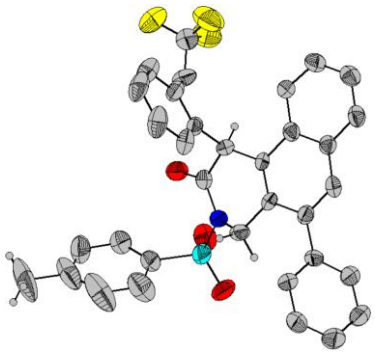
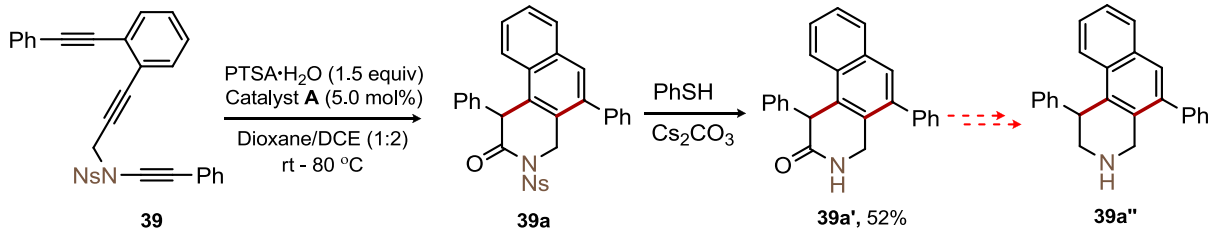


Figure 2.6. X- Ray crystal structure for compound **38l**

2.3.4. Deprotection of nosyl group:

The labile N-Ns protected diyne-tethered ynamide **39** smothly underwent hydrative cascade cyclization under the optimized conditions to afford the dihydroisoquinolone **39a** (Scheme 2.18). Reductive removal of nosyl group in the same pot without isolation of **39a** with

thiophenol in the presence of base provided **39a′** in overall 52% yield. The amide **39a′** can further undergo reduction to delivers dihydroisoquinoline core **39a″**.[27]

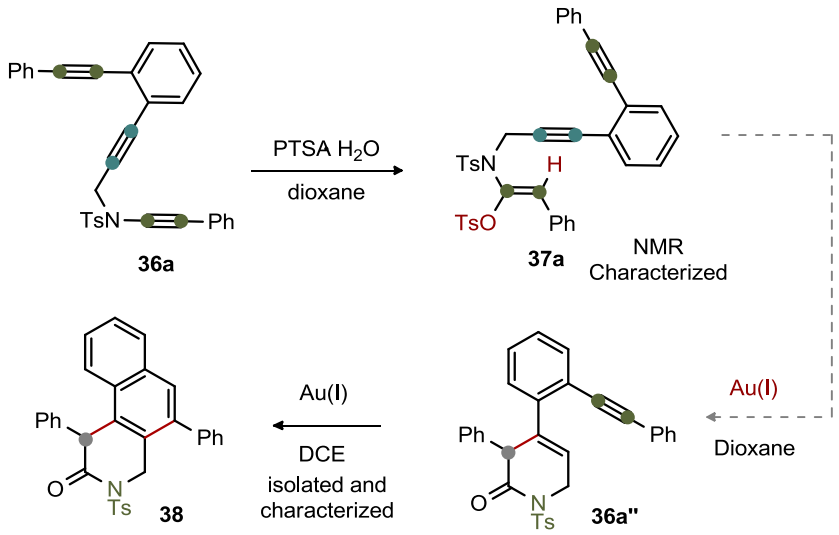


39 **39a** **39a'**, 52% **39a"**

Scheme 2.18. Nosyl group deprotection from 39a

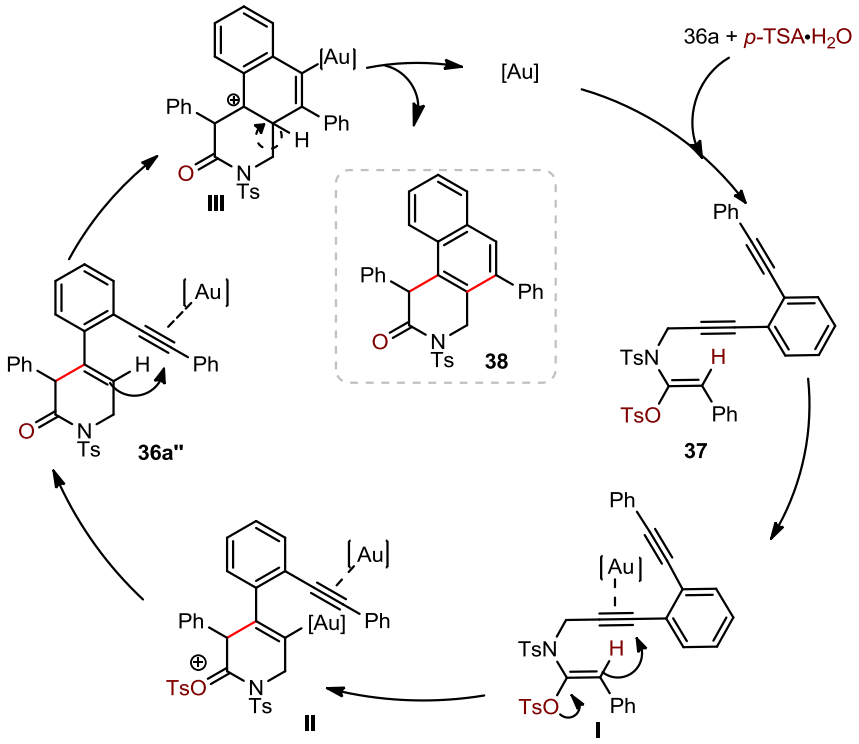
2.3.5. Mechanistic investigation

To gain insight into the mechanism of this novel cascade reaction, various controlled experiments are conducted (Scheme 2.19). Considering the facile reactivity of ynamide to acid-catalyst, the reaction profile is examined by sequential addition of reagents and conducting reaction at various temperatures. To begin with, compound **36a** was exposed to *p*-TSA·H_2O (1.5 equiv) in dioxane at room temperature for 10 minutes. To our surprise, complete consumption of **36a** was noticed with the concomitant formation of ketene N,O-acetal **37**; compound **37** was thoroughly characterized by ^{1}H NMR of the crude reaction mixture. Unfortunately, our effort to isolate intermediate **37** by column chromatography is failed. Next, a solution of JohnPhosAu(MeCN)SbF_6 catalyst in DCE was added and reaction continued for 4 h at an ambient temperature; complete conversion of ketene N,O-acetal **37** to monocyclized product **36a″** along with trace amount of **38a** has been observed. The monocyclized product **36a″** is isolated by flash column chromatography and characterized by NMR spectroscopy and HRMS analysis. Finally, heating the reaction mixture containing **36a″** and the catalyst-A for 20 h led to produce the desired dihydroisoquinolone **38a**. From these observations, it is clear that the hydrative cyclization of diyne-tethered-ynamide **36a** to the synthesis of dihydroisoquinolone **38a** is a step-wise process involving the participation of two intermediates.



Scheme 2.19. Mechanistic study

Based on the aforementioned experimental observations, the plausible mechanism for the formation of dihdroisoquinolone is sketched (Scheme 2.20).[3c] It appears that in presence of Brønsted acid *p*-TSA·H_2O, the ynamide ***36a*** is succeptible to form keteniminium intermediate via protolysis. Subsequently, the attack of nucleophile $ArSO_3^-$ to the in situ generated reactive keteniminium intermediate generates ***37,*** which was thoroughly characterized. Next, the 6-*endo* dig cyclization involving the attack of enol-moiety to the Au(I) activated alkyne-motifs of the TsN-propargyl component affords the monocyclic vinyl–Au species II, which undergoes tautomerization, hydrolysis, and protodeauration to yield the monocyclized product ***36a″***. The presence of pendant alkyne in the monocyclic compound ***36a″*** showed perfect 1,5-enyne character. In presence of Au(I) catalyst, the 1,5-enyne precursor ***36a″*** undergoes 6-endo-cyclization to form intermediate **III**. Finally, aromatization followed by protodeauration affords the desired dihdroisoquinolone ***38*** with the regeneration of the cationic Au complex for the use in the next catalytic cycle.[21]



Scheme 2.20. Mechanistic cycle

2.4. Conclusion:

In summary, we have shown a novel synthetic route to dihydroisoquinolone through Brønsted acid promoted cascade cyclization of the easily accessible diyne-tethered-ynamides in the presence of Echavarren's catalyst. The reaction exhibits broad substrate scope producing the dihydroisoquinolones in good yields; various functional groups are well-tolerated. With the reductive deprotection of N-nosyl protecting group and the reduction of amide functionality, naturally occuring dihydroisoquinoline motifs can readily be accessed. The reaction proceeds in a step-wise manner involving the particiption of *N,O*-ketene acetal, rapidly obtained through the attack of *p*-TSA to ynamide followed by Au-catalyzed monocyclization and finally the formation of dihydroisoquinolone. Investigations aimed at applying this methodology for the synthesis of complex molecular frameworks is currently underway.

2.5. General Experimental

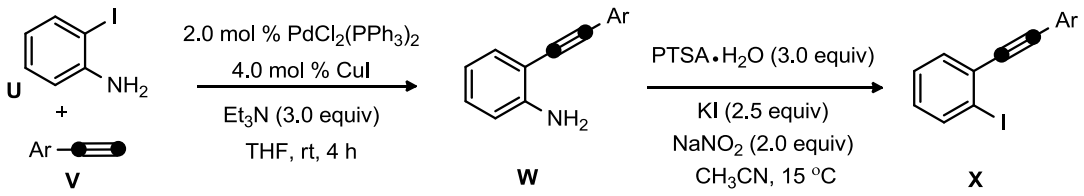
2.5.1. General experimental information for all the work

All the reactions were performed in an oven-dried Schlenk flask under an argon atmosphere. Commercial grade solvents were distilled prior to use. Column chromatography was performed using silica gel (100-200 Mesh) eluting with hexanes and ethyl acetate mixture. Flash column chromatography was performed using silica gel (230-400 Mesh) eluting with hexanes and ethyl acetate mixture. Thin layer chromatography (TLC) was performed on silica gel GF254 plates. Visualization of spots on TLC plate was accomplished with UV light (254 nm) and staining over I_2 chamber or an aqueous alkaline $KMnO_4$ solution followed by heating.

Proton and carbon nuclear magnetic resonance spectra (^{1}H NMR, ^{13}C NMR and ^{19}F NMR) were recorded on a Bruker Avance 400 (^{1}H NMR, 400 MHz; ^{13}C NMR, 101 MHz; ^{19}F NMR, 376 MHz) spectrometer, Bruker Avance 500 (^{1}H NMR, 500 MHz; ^{13}C NMR, 126 MHz; ^{19}F NMR, 470 MHz) spectrometer having solvent resonance as internal standard (^{1}H NMR, $CHCl_3$ at 7.26 ppm; ^{13}C NMR, $CDCl_3$ at 77.0 ppm). Few cases tetramethylsilane (TMS) at 0.00 ppm was used as reference standard. Data for ^{1}H NMR are reported as follows: chemical shift (ppm), multiplicity (s = singlet; br s = broad singlet; d = doublet; br d = broad doublet, t = triplet; br t = broad triplet; q = quartet; m = multiplet), coupling constants, *J*, in (Hz), and integration. Data for ^{13}C NMR, ^{19}F NMR were reported in terms of chemical shift (ppm). IR spectra were recorded on FT/IR-5300 spectrometer and reported in cm^{-1}. High resolution mass spectra were obtained in ESI mode. Melting points were determined by electro-thermal heating and are uncorrected. X-Ray data was collected at 298K on a SMART APEX CCD single crystal diffractometer using graphite monochromated Mo-Kα radiation (0.71073 Å),

2.5.2. Materials: Unless otherwise noted, all the reagents and intermediates were obtained commercially and used without purification. Dichloromethane (CH_2Cl_2), toluene, acetonitrile, ethyl acetate, dichloroethane (DCE) and 1,4-dioxane were distilled over CaH_2. THF was freshly distilled over sodium/benzophenone ketyl under dry nitrogen. Catalyst A (99.9 %), B (99.9 %), C (99.9 %), IPrAuCl (99.9 %), Ph_3PAuCl (99.9 %), $In(OTf)_2$, $Pd(OAc)_2$, $PdCl_2(PPh_3)_2$ and $Sc(OTf)_3$ were purchased from Sigma Aldrich Ltd. and used as received. Silver salts such as $AgSbF_6$, $AgNTf_2$, and $Ag(OCOCF_3)$ were purchased from Aldrich and used as received. PTSA·H_2O was purchased from Aldrich Ltd. and used as received. PPh_3, DEAD, $CuSO_4·H_2O$, 1.10-phenanthroline, K_3PO_4, Na_2CO_3 were purchased from Merck. The aryl iodides were purchased from Aldrich and used. Analytical and spectral data of all those known compounds are exactly matching with the reported values.

2.5.3. General Experimental Procedures:

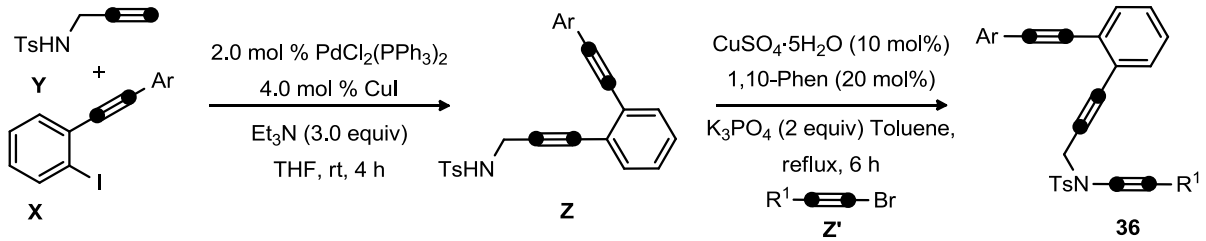


Scheme 2.21: Preparation of **X** from 2-iodoaniline

Compound **X** was prepared via two step procedure starting from simple cost effective 2-iodoaniline **U**. At first, 2-iodo aniline was subjected to Sonogashira reaction in presence of aryl acetylene to give compound **W**.[24] Diazotization followed by iodination of aniline moiety of **W** readily produced compound **X** shown scheme 2.21.

Next, compound **Y** was prepared based on two known synthetic steps staring from the commerically available tosyl amine. First step involves the –Boc protection of the tosylamine, Mitsunobu reaction between the N-Boc-protected tosylamine with the propargyl alcohol in the presence of triphenyl phosphine (Ph_3P) and diisopropyl azodicarboxylate (DIAD) in THF followed by deprotection of N-Boc moiety by trifluoroacetic acid (TFA) to obtain **Y**.

Following the reported procedure, substrate ***36*** was prepared from **Y** in two simple synthetic steps. Sonogashira reaction between **Y** and aryl iodides **X** provides **Z** in good to excellent yields. Finally, Cu–catalyzed C–N bond formations between **Z** and (1-bromo-2-arylacetylene) **Z′** afford the precursor ***36*** in overall good yields. Compounds ***36*** are thorougly characterized by physical and spectroscopic data.



Scheme 2.22: Preaparation of 36

2.5.4. General Procedure for the Synthesis of Z (GP 1):[24]

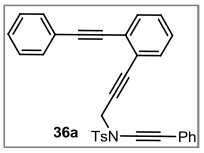
To a solution of substrate **Y** (1.0 mmol), $PdCl_2(PPh_3)_2$ (0.02 mmol) and CuI (0.04 mmol) in THF (5.0 mL) were added aryl iodide **X** (1.2 mmol) and Et_3N (3.0 mmol) successively under an argon atmosphere. The resulting mixture was stirred at room temperature for 4 h. The crude reaction mixture was filtered through a small pad of Celite and concentrated under

the reduced pressure. The crude residue was purified using column chromatography on silica gel to afford **Z**.

2.5.5. General Procedure for the Synthesis of *36* (GP 2):

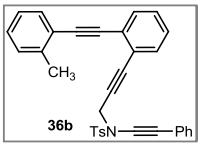
A solution of **Z** (1.0 mmol), $CuSO_4 \cdot 5H_2O$ (0.10 mmol), 1,10-phenanthroline (0.20 mmol) and K_3PO_4 (2.0 mmol) in dry toluene (5.0 mL) was stirred in a Schlenck tube. The 1-bromo-2-arylacetylene **Z′** was subsequently introduced into the Schlenck tube. The reaction mixture was heated at 70 °C under the nitrogen atmosphere. The progress of the reaction was monitored periodically by TLC. Upon completion, the reaction mixture was cooled to room temperature and diluted with dichloromethane (10 mL). The crude mixture was filtered through a small pad of Celite and concentrated under the reduced pressure. The crude residue was purified using column chromatography on silica gel to provide ***36***.

4-Methyl-N-(phenylethynyl)-N-(3-(2-(phenylethynyl)phenyl)prop-2-ynyl)benzene-

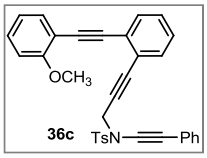


sulfonamide (*36a*): Following the general procedure of GP-1 and GP-2, compound ***36a*** (398 mg) was obtained in overall 82% yield as pale yellow gummy liquid; R_f = 0.39 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 6.8 Hz, 2H), 7.43 (d, J = 6.4 Hz, 3H), 7.28 (br t, 2H), 7.23–7.16 (m, 8H), 7.13 (d, J = 8 Hz, 3H), 4.60 (s, 2H), 2.10 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.9, 134.2, 132.4, 131.85, 131.79, 131.5, 129.6, 128.55, 128.46, 128.4, 128.3, 127.9, 127.7, 125.9, 124.4, 122.9, 122.6, 93.7, 87.7, 85.2, 85.1, 82.2, 71.2, 43.1, 21.6; IR (Neat) ν_{max} 2975, 2926, 1720, 1627, 1600, 1490, 1364, 1161 cm^{-1}; HRMS (ESI) for $C_{32}H_{23}NO_2SNa$ $(M+Na)^+$: calcd 508.1347, found 508.1347.

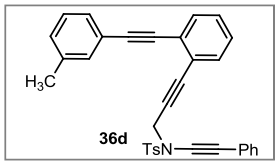
4-Methyl-N-(phenylethynyl)-N-(3-(2-(o-tolylethynyl)phenyl)prop-2-ynyl)benzenesulf-



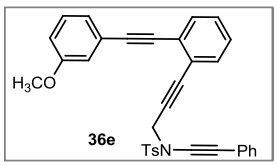
onamide (*36b*): Following the general procedure GP-1 and GP-2, compound ***36b*** (445 mg) was obtained in overall 89% yield as brown gummy liquid; R_f = 0.42 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 8.4 Hz, 2H), 7.42 (t, J = 8.0 Hz, 2H), 7.29–7.24 (m, 2H), 7.23–7.10 (m, 9H), 7.09–7.00 (m, 2H), 4.56 (s, 2H), 2.46 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.9, 140.2, 138.7, 134.3, 132.9, 132.5, 132.2, 131.9, 131.6, 131.5, 129.8, 129.6, 129.5, 128.6, 128.5, 128.3, 128.2, 128.0, 127.9, 127.6, 126.1, 125.7, 124.2, 122.8, 122.6, 92.6, 91.6, 85.5, 85.0, 82.1, 71.3, 43.1, 42.9, 21.6, 20.8; IR (Neat) ν_{max} 3068, 3024, 2920, 2207, 1703, 1599, 1495, 1358, 1166, 1117, 1084 cm^{-1}; HRMS (ESI) for $C_{33}H_{26}NO_2S$ $(M+H)^+$: calcd 500.1684, found 500.1680.

N-(3-(2-((2-methoxyphenyl)ethynyl)phenyl)prop-2-ynyl)-4-methyl-N-(phenylethynyl)-benzenesulfonamide (36c): 

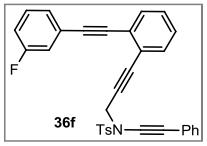
Following the general procedure GP-1 and GP-2, compound **36c** (449 mg) was obtained in overall 87% yield as brown gummy liquid; R_f = 0.4 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 8.0 Hz, 2H), 7.50 (dd, J = 7.2, 1.6 Hz, 2H), 7.40–7.39 (m, 2H), 7.38–7.28 (m, 7H), 7.15 (dd, J = 7.2, 1.6 Hz, 2H), 6.95–6.80 (m, 2H), 4.68 (s, 2H), 3.93 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.9, 144.9, 134.2, 133.9, 132.3, 131.9, 131.5, 130.1, 129.6, 128.3, 128.2, 127.8, 127.5, 126.3, 124.3, 122.7, 120.6, 112.2, 110.7, 91.7, 90.2, 85.3, 84.9, 82.1, 71.2, 55.9, 43.1, 21.5; IR (Neat) ν_{max} 3062, 2942, 2837, 2235, 1703, 1599, 1495, 1358, 1254, 1177, 1111, 1023 cm^{-1}; HRMS (ESI) for $C_{33}H_{26}NO_3S$ $(M+H)^+$: calcd 516.1633, found 516.1631.

4-Methyl-N-(phenylethynyl)-N-(3-(2-(m-tolylethynyl)phenyl)prop-2-ynyl)benzene-sulfonamide(36d): 

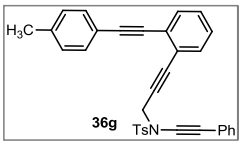
Following the general procedure GP-1 and GP-2, compound **36d** (405 mg) was obtained in overall 81% yield as pale yellow gummy liquid; R_f = 0.40 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 7.6 Hz, 2H), 7.54 (d, J = 7.6 Hz, 1H), 7.46–7.35 (m, 4H), 7.35–7.13 (m, 10H), 4.72 (s, 2H), 2.35 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.9, 138.1, 134.2, 132.40, 132.35, 131.8, 131.6, 129.6, 129.5, 128.9, 128.5, 128.31, 128.28, 128.23, 127.9, 127.7, 126.1, 124.4, 122.8, 122.6, 94.0, 87.5, 85.3, 85.1, 82.2, 71.3, 43.2, 21.6, 21.2; IR (Neat) ν_{max} 2235, 1600, 1495, 1364, 1172, 1090, 761 cm^{-1}; HRMS (ESI) for $C_{33}H_{25}NO_2SNa$ $(M+Na)^+$: calcd 522.1504, found 522.1503.

N-(3-(2-((3-methoxyphenyl)ethynyl)phenyl)prop-2-ynyl)-4-methyl-N-(phenylethynyl)-benzenesulfonamide(36e): 

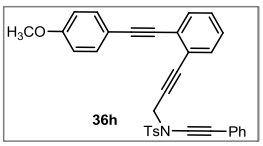
Following the general procedure GP-1 and GP-2, compound **36e** (371 mg) was obtained in overall 72% yield as pale yellow gummy liquid; R_f = 0.36 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 7.6 Hz, 2H), 7.53 (d, J = 7.6 Hz, 1H), 7.39-7.35 (m, 2H), 7.33–7.28 (m, 1H), 7.28-7.23 (m, 4H), 7.23-7.19 (m, 3H), 7.19-7.13 (m, 2H), 7.08 (br s, 1H), 6.91-6.86 (m, 1H), 4.69 (s, 2H), 3.80 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.4, 144.9, 138.7, 134.2, 132.4, 131.9, 131.6, 129.6, 129.5, 128.5, 128.3, 128.2, 127.9, 127.8, 125.9, 124.5, 123.9, 122.6, 116.3, 115.3, 93.6, 87.6, 85.2, 85.1, 82.1, 71.3, 55.3, 43.1, 21.6; IR (Neat) ν_{max} 3057, 3013, 2958, 2931, 2827, 2235, 1599, 1489, 1358, 1232, 1177, 1095, 1023 cm^{-1}; HRMS (ESI) for $C_{33}H_{26}NO_3S$ $(M+H)^+$: calcd 516.1633, found 516.1636.

N-(3-(2-((3-fluorophenyl)ethynyl)phenyl)prop-2-ynyl)-4-methyl-N-(phenylethynyl)-benzenesulfonamide (36f): 

Following the general procedure GP-1 and GP-2, compound **36f** (368 mg) was obtained in overall 73% yield as pale yellow gummy liquid; R_f = 0.50 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 8.0 Hz, 2H), 7.52 (d, J = 7.2 Hz, 1H), 7.40–7.18 (m, 13H), 7.01 (brt, J = 8.4 Hz, 1H), 4.69 (s, 2H), 2.30 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.5, 161.1, 144.9, 134.2, 132.5, 131.9, 131.5, 130.1, 130.0, 129.6, 128.5, 128.1, 128.0, 127.8, 125.4, 124.8, 124.7, 122.5, 118.5 (d, J = 88 Hz, 1C) , 118.2, 115.9, 115.7, 92.2, 88.6, 85.4, 85.1, 82.1, 71.3, 43.1, 21.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.48; IR (Neat) ν_{max} 2975, 2920, 2241, 1715, 1621, 1512, 1358, 1156 cm^{-1}; HRMS (ESI) for $C_{32}H_{22}FNO_2SNa$ $(M+Na)^+$: calcd 526.1253, found 526.1254.

4-Methyl-N-(phenylethynyl)-N-(3-(2-(p-tolylethynyl)phenyl)prop-2-ynyl)benzenesulfonamide (36g): 

Following the general procedure GP-1 and GP-2, compound **36g** (365 mg) was obtained in overall 73% yield as brown gummy liquid; R_f = 0.50 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 8.0 Hz, 2H), 7.52 (d, J = 7.6 Hz, 1H), 7.44 (d, J = 8.0 Hz, 2H), 7.40–7.36 (m, 2H), 7.34–7.26 (m, 4H), 7.26–7.19 (m, 4H), 7.09 (d, J = 8.0 Hz, 2H), 4.70 (s, 2H), 2.36 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.9, 138.7, 134.2, 132.4, 131.72, 131.67, 131.5, 129.6, 129.2, 128.4, 128.3, 128.2, 127.9, 127.5, 126.1, 124.3, 122.7, 119.9, 93.9, 87.1, 85.3, 85.0, 82.2, 71.2, 43.1, 21.6; IR (Neat) ν_{max} 2975, 2920, 2235, 1600, 1495, 1364, 1172 cm^{-1}; HRMS (ESI) for $C_{33}H_{25}NO_2SNa$ $(M+Na)^+$: calcd 522.1504, found 522.1504.

N-(3-(2-((4-methoxyphenyl)ethynyl)phenyl)prop-2-ynyl)-4-methyl-N-(phenylethynyl)-benzenesulfonamide (36h): 

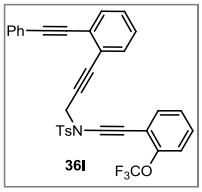
Following the general procedure GP-1 and GP-2, compound **36h** (356 mg) was obtained in overall 69% yield as yellow gummy liquid; R_f = 0.41 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 8.0 Hz, 2H), 7.53 (d, J = 7.6 Hz, 1H), 7.45 (d, J = 8.4 Hz, 2H), 7.39 (brd, J = 8.0 Hz, 3H), 7.34 (d, J = 7.6 Hz, 1H), 7.33–7.23 (m, 6H), 6.85 (d, J = 8.4 Hz, 2H), 4.82 (s, 2H), 3.73 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.2, 145.8, 133.9, 133.6, 132.7, 131.9, 131.4, 130.4, 129.6, 129.1, 128.7, 128.3, 125.7, 123.7, 122.2, 114.8, 114.4, 94.2, 86.9, 86.5, 84.8, 82.9, 71.0, 55.7, 43.1, 21.5; IR (Neat) ν_{max} 3063, 2964, 2936, 2838, 2235, 1600, 1572, 1490, 1457, 1430, 1369, 1249 cm^{-1}; HRMS (ESI) for $C_{33}H_{26}NO_3S$ $(M+H)^+$: calcd 516.1633, found 516.1637.

N-(3-(2-((3,5-dimethylphenyl)ethynyl)phenyl)prop-2-ynyl)-4-methyl-N-(phenylethynyl)benzenesulfonamide (36i): Following the general procedure GP-1 and GP-2, compound **36i** (385 mg) was obtained in overall 75% yield as pale yellow gummy liquid; R_f = 0.50 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 8.0 Hz, 2H), 7.51 (d, J = 8.0 Hz, 1H), 7.42–7.34 (m, 3H), 7.32–7.18 (m, 8H), 7.05 (d, J = 8.0 Hz, 1H), 4.71 (s, 2H), 2.30 (s, 3H), 2.27 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.9, 137.6, 136.8, 134.2, 132.8, 132.4, 131.7, 131.6, 129.8, 129.6, 129.3, 128.5, 128.3, 128.2, 127.9, 127.5, 126.6, 124.3, 122.7, 120.2, 94.2, 87.0, 85.4, 85.0, 82.2, 71.3, 43.2, 21.6, 19.8, 19.6; IR (Neat) ν_{max} 3056, 6024, 2920, 2865, 2230, 1594, 1501, 1441, 1364, 1172, 1084 cm^{-1}; HRMS (ESI) for $C_{34}H_{27}NO_2SNa$ $(M+Na)^+$: calcd 536.1660, found 516.1653.

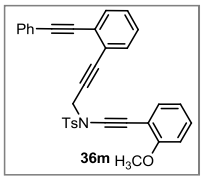
4-Methyl-N-((4-nitrophenyl)ethynyl)-N-(3-(2-(m-tolylethynyl)phenyl)prop-2-ynyl)benzenesulfonamide (36j): Following the general procedure GP-1 and GP-2, compound **36j** (343 mg) was obtained in overall 63% yield as pale yellow gummy liquid; R_f = 0.30 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 8.8 Hz, 2H), 7.92 (d, J = 8.4 Hz, 2H), 7.52 (d, J = 7.6 Hz, 1H), 7.38 (d, J = 8.8 Hz, 2H), 7.35–7.13 (m, 7H), 7.07 (d, J = 7.6 Hz, 1H), 7.01 (s, 1H), 6.85 (dd, J = 8.4, 2 Hz, 1H), 4.70 (s, 2H), 3.79 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3, 146.3, 145.4, 134.0, 133.4, 132.3, 132.0, 131.1, 129.93, 129.87, 129.5, 129.7, 127.9, 125.9, 124.3, 124.1, 123.8, 123.5, 116.6, 115.0, 93.6, 87.8, 87.5, 85.6, 84.6, 55.3, 42.9, 21.6; IR (Neat) ν_{max} 2975, 2920, 2241, 1715, 1621, 1512, 1358, 1156 cm^{-1}; HRMS (ESI) for $C_{33}H_{25}N_2O_5S$ $(M+H)^+$: calcd 561.1484, found 561.1484.

4-Methyl-N-(3-(2-(phenylethynyl)phenyl)prop-2-ynyl)-N-(o-tolylethynyl)benzene-sulfon-amide (36k): Following the general procedure GP-1 and GP-2, compound **36k** (487 mg) was obtained in overall 87% yield as pale yellow gummy liquid; R_f = 0.48 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 8.0 Hz, 2H), 7.51 (dt, J = 7.6, 1.6 Hz, 3H), 7.37–7.26 (m, 5H), 7.21 (d, J = 8.0 Hz, 3H), 7.19–7.14 (m, 3H), 7.12–7.07 (m, 1H), 4.72 (s, 2H), 2.36 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.9, 140.05, 134.3, 132.3, 131.9, 131.7, 131.6, 129.6, 129.3, 128.5, 128.5, 128.37, 128.3, 127.9, 127.7, 125.9, 125.5, 124.4, 122.9, 122.4, 93.7, 87.7, 85.9, 85.2, 70.2, 43.2, 21.6, 20.8; IR (Neat) ν_{max} 3057,

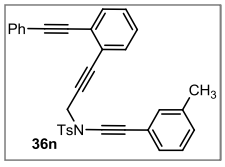
3019, 2975, 2926, 2230, 1600, 1501, 1441, 1369, 1167, 1084, 1046 cm^{-1}; HRMS (ESI) for $C_{33}H_{25}NO_2SNa$ $(M+Na)^+$: calcd 520.1504, found 522.1503.

4-Methyl-N-(3-(2-(phenylethynyl)phenyl)prop-2-ynyl)-N-((2-(trifluoromethoxy)phenyl)ethynyl)benzenesulfonamide (36l): 

Following the general procedure GP-1 and GP-2, compound **36l** (415 mg) was obtained in overall 73% yield as brown gummy liquid; R_f = 0.39 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 8.0 Hz, 2H), 7.52 (t, J = 6.8 Hz, 3H), 7.42 (bd, J = 7.6 Hz, 1H), 7.34–7.26 (m, 5H), 7.25–7.13 (m, 6H), 4.70 (s, 2H), 2.28 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.9, 145.0, 134.3, 133.5, 132.4, 131.7, 129.7, 128.9, 128.5, 128.4, 128.4, 128.2, 127.7, 126.6, 125.9, 124.4, 123.0, 121.9, 121.0, 119.3, 117.4, 93.6, 87.8, 87.1, 85.3, 84.8, 65.9, 43.1, 21.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -57.39; IR (Neat) ν_{max} 3057, 3030, 2920, 2241, 1605, 1501, 1446, 1375, 1254, 1227, 1167, 1084, cm^{-1}; HRMS (ESI) for $C_{33}H_{22}F_3NO_3SNa$ $(M+Na)^+$: calcd 592.1170, found 592.1173.

N-((2-methoxyphenyl)ethynyl)-4-methyl-N-(3-(2-(phenylethynyl)phenyl)prop-2-ynyl)benzenesulfonamide (36m): 

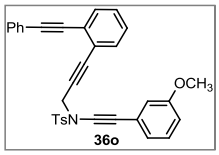
Following the general procedure GP-1 and GP-2, compound **36m** (370 mg) was obtained in overall 72% yield as brown gummy liquid; R_f = 0.41 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 8.0 Hz, 2H), 7.51 (d, J = 6.8 Hz, 3H), 7.35–7.15 (m, 10H), 6.89–6.79 (m, 2H), 4.69 (s, 2H), 3.80 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.0, 144.7, 134.4, 133.3, 132.5, 131.8, 129.5, 129.3, 128.5, 128.4, 128.35, 127.7, 125.8, 124.6, 123.0, 120.4, 112.0, 110.8, 93.6, 87.8, 85.9, 85.3, 85.2, 67.6, 55.7, 43.2, 21.6; IR (Neat) ν_{max} 3063, 2964, 2936, 2838, 2235, 1600, 1572, 1490, 1457, 1430, 1369, 1249, 1172, 1090 cm^{-1}; HRMS (ESI) for $C_{33}H_{25}NO_3SNa$ $(M+Na)^+$: calcd 538.1453, found 538.1455.

4-Methyl-N-(phenylethynyl)-N-(3-(2-(m-tolylethynyl)phenyl)prop-2-ynyl)benzenesulfonamide (36n): 

Following the general procedure GP-1 and GP-2, compound **36n** (390 mg) was obtained in overall 78% yield as pale yellow gummy liquid; R_f = 0.57 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 7.2 Hz, 2H), 7.52 (d, J = 6.0 Hz, 3H), 7.36–7.10 (m, 11H), 7.08 (br d, J = 6.8 Hz, 1H), 4.69 (s, 2H), 2.29 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.9, 137.9, 134.2, 132.4, 132.1, 131.8, 129.6, 128.8, 128.6, 128.5, 128.45, 128.38, 128.3, 128.1, 127.7, 125.9, 124.5, 123.0, 122.4, 93.7, 87.8, 85.2,

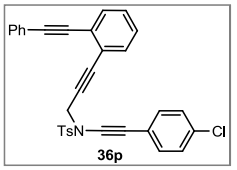
81.8, 71.4, 43.1, 21.6, 21.2; IR (Neat) ν_{max} 2235, 1600, 1495, 1364, 1172, 1090, 761 cm^{-1}; HRMS (ESI) for $C_{33}H_{25}NO_2SNa$ $(M+Na)^+$: calcd 522.1504, found 522.1504.

N-((3-methoxyphenyl)ethynyl)-4-methyl-N-(3-(2-(phenylethynyl)phenyl)prop-2-ynyl)-benzenesulfonamide (36o): Following the general procedure GP-1 and GP-2, compound **36o** (361 mg) was obtained in overall 70% yield as brown gummy liquid; R_f = 0.41 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 8.0 Hz, 2H), 7.51 (d, J = 8.0 Hz, 3H), 7.33–7.26 (m, 4H), 7.25–7.19 (m, 4H), 7.16 (t, J = 8.0 Hz, 1H), 6.96 (d, J = 7.6 Hz, 1H), 6.89 (s, 1H), 6.82 (dd, J = 8.0, 2.0 Hz, 1H) 4.69 (s, 2H), 3.74 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2, 144.9, 134.2, 132.4, 131.8, 131.8, 129.6, 129.3, 128.54, 128.5, 128.4, 128.3, 127.7, 125.9, 124.4, 124.0, 123.6, 122.9, 116.2, 114.6, 93.7, 87.7, 85.3, 85.1, 82.0, 71.3, 55.2, 43.1, 21.6; IR (Neat) ν_{max} 3052, 2920, 2241, 1594, 1572, 1495, 1369, 1287, 1167, 1079, 1041 cm^{-1}; HRMS (ESI) for $C_{33}H_{25}NO_3SNa$ $(M+Na)^+$: calcd 538.1453, found 538.1454.



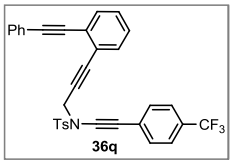
36o

N-((4-chlorophenyl)ethynyl)-4-methyl-N-(3-(2-(phenylethynyl)phenyl)prop-2-ynyl)-benzenesulfonamide (36p): Following the general procedure GP-1 and GP-2, compound **36p** (426 mg) was obtained in overall 82% yield as brown gummy liquid; R_f = 0.63 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 8.0 Hz, 2H), 7.50 (t, J = 8.0 Hz, 3H), 7.35–7.15 (m, 12H), 4.67 (s, 2H), 2.29 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.0, 134.1, 133.8, 132.7, 131.9, 131.7, 129.6, 128.5, 128.4, 128.2, 127.7, 125.9, 124.3, 122.9, 121.1, 93.6, 87.7, 85.3, 84.9, 82.9, 70.3, 43.0, 21.6; IR (Neat) ν_{max} 3063, 2920, 2849, 2230, 1600, 1495, 1441, 1364, 1172, 1090 cm^{-1}; HRMS (ESI) for $C_{32}H_{22}ClNO_2SNa$ $(M+Na)^+$: calcd 542.0957, found 542.0958.



36p

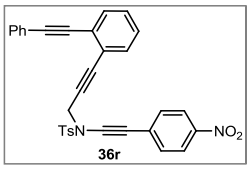
4-Methyl-N-(3-(2-(phenylethynyl)phenyl)prop-2-ynyl)-N-((4-(trifluoromethyl)phenyl)-eth-ynyl)benzenesulfonamide (36q): Following the general procedure GP-1 and GP-2, compound **36q** (404 mg) was obtained in overall 73% yield as pale yellow gummy liquid; R_f = 0.723 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 8.0 Hz, 2H), 7.52 (d, J = 7.6 Hz, 1H), 7.47 (brt, J = 6.4, Hz, 4H), 7.39 (d, J = 8.0 Hz, 2H), 7.35–7.18 (m, 8H), 4.70 (s, 2H), 2.30 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.2, 134.1, 132.3, 131.9, 131.7, 131.2, 129.7, 128.6, 128.3, 128.2, 127.8, 126.6, 125.9, 125.1, 124.3, 122.9, 93.6, 87.6, 85.4, 84.8, 84.6, 70.6, 43.0, 21.6; ^{19}F NMR (376 MHz,



36q

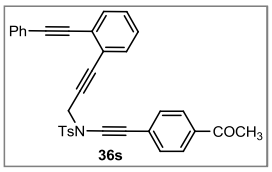
$CDCl_3$) δ -112.5; IR (Neat) ν_{max} 3057, 2926, 1616, 1600, 1501, 1375, 1320, 1167, 1123, 1068 cm^{-1}; HRMS (ESI) for $C_{33}H_{22}F_3NO_2SNa$ $(M+Na)^+$: calcd 576.1221, found 576.1224.

4-Methyl-N-((4-nitrophenyl)ethynyl)-N-(3-(2-(phenylethynyl)phenyl)prop-2-ynyl)-



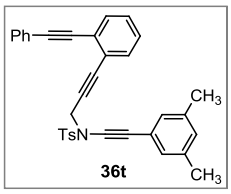
benzenesulfonamide (36r): Following the general procedure GP-1 and GP-2, compound **36r** (387 mg) was obtained in overall 73% yield as pale yellow gummy liquid; R_f = 0.30 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^1H NMR (400 MHz, $CDCl_3$) δ) δ 8.08 (dt, J = 7.2, 1.6 Hz, 2H), 7.93 (d, J = 6.8 Hz, 2H), 7.54 (d, J = 6.4 Hz, 1H), 7.49 (dd, J = 6.4, 1.2 Hz, 2H), 7.40 (dt, J = 6.8, 2.0 Hz, 2H), 7.36–7.21 (m, 8H), 4.73 (s, 2H), 2.33 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.4, 145.4, 134.2, 133.4, 132.3., 132.0, 131.7, 131.1, 130.0, 129.8, 128.7, 128.6, 128.4, 128.2, 127.8, 126.0, 124.1, 123.8, 123.5, 122.9, 93.7, 87.8, 87.7, 85.6, 84.6, 71.0, 43.0, 21.6; IR (Neat) ν_{max} 3073, 2920, 2854, 2224, 1593, 1511, 1445, 1369, 1341, 1171, 1100, 1040 cm^{-1}; HRMS (ESI) for $C_{32}H_{22}N_2O_4SNa$ $(M+Na)^+$: calcd 553.1198, found 553.1198.

N-((4-Acetylphenyl)ethynyl)-4-methyl-N-(3-(2-(phenylethynyl)phenyl)prop-2-ynyl)-



benzenesulfonamide (36s): Following the general procedure GP-1 and GP-2, compound **36s** (380 mg) was obtained in overall 72% yield as pale yellow gummy liquid; R_f = 0.39 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 8.0 Hz, 2H), 7.82 (d, J = 8.4 Hz, 2H), 7.50 (t, J = 8.4 Hz, 3H), 7.38 (d, J = 8.4 Hz, 2H), 7.35–7.19 (m, 8H), 4.71 (s, 2H), 2.57 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.3, 145.2, 135.6, 134.1, 132.7, 131.9, 131.7, 130.9, 129.7, 128.6, 128.4, 128.2, 127.8, 125.9, 124.3, 122.9, 93.7, 87.7, 85.7, 85.4, 84.8, 71.3, 43.1, 26.6, 21.6; IR (Neat) ν_{max} 3062, 2914, 2848, 2229, 1681, 1593, 1489, 1374, 1265, 1171, 1111 cm^{-1}; HRMS (ESI) for $C_{34}H_{25}NO_3SNa$ $(M+Na)^+$: calcd 550.1453, found 550.1453.

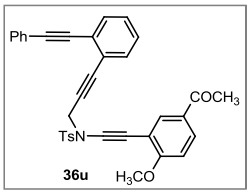
N-((3,5-dimethylphenyl)ethynyl)-4-methyl-N-(3-(2-(phenylethynyl)phenyl)prop-2-



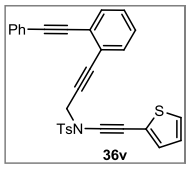
ynyl)benzenesulfonamide (36t): Following the general procedure GP-1 and GP-2, compound **36t** (442 mg) was obtained in overall 86% yield as brown gummy liquid; R_f = 0.54(9:1 hexane/EtOAc); [Silica, UV and I_2]; ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 8.4 Hz, 2H), 7.53 (dd, J = 6.4, 2.0 Hz, 3H), 7.34–7.25 (m, 5H), 7.24–7.18 (m, 4H), 7.00 (s, 2H), 6.90 (s, 1H), 4.68 (s, 2H), 2.30 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.8, 137.7, 134.3, 132.4, 131.8, 129.8, 129.6, 129.2, 128.5, 128.41, 128.37, 128.25, 127.7, 125.9, 124.5, 123.0, 122.2, 93.7, 87.8, 85.2, 81.5, 71.5, 43.1, 21.6, 21.1; IR (Neat) ν_{max} 3057, 3030, 2926, 2860, 2241,

1600, 1490, 1446, 1369, 1167, 1084, 1052 cm^{-1}; HRMS (ESI) for $C_{34}H_{27}NO_2SNa$ $(M+Na)^+$: calcd 536.1660, found 536.1653.

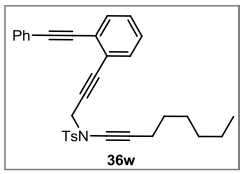
N-((5-acetyl-2-methoxyphenyl)ethynyl)-4-methyl-N-(3-(2-(phenylethynyl)phenyl)-prop-2-ynyl)benzenesulfonamide (36u): Following the general procedure GP-1 and GP-2, compound **36u** (419 mg) was obtained in overall 75% yield as brown gummy liquid; R_f = 0.47 (7:3 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 8.4 Hz, 2H), 7.92–7.85 (m, 2H), 7.52–7.46 (m, 3H), 7.32–7.19 (m, 8H), 6.84 (d, J = 8.8 Hz, 1H), 4.69 (s, 2H), 3.84 (s, 3H), 2.47 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.3, 163.5, 144.9, 134.3, 134.0, 132.4, 131.8, 131.7, 130.0, 129.9, 129.6, 128.5, 128.34, 128.31, 127.7, 125.9, 124.5, 122.9, 112.2, 110.2, 93.7, 87.7, 86.5, 85.4, 85.1, 66.9, 56.0, 43.2, 26.3, 21.6; IR (Neat) ν_{max} 3046, 2926, 2849, 2241, 1682, 1600, 1490, 1364, 1265, 1243, 1167, 1084 cm^{-1}; HRMS (ESI) for $C_{35}H_{27}NO_4SNa$ $(M+Na)^+$: calcd 580.1558, found 580.1558.



4-Methyl-N-(3-(2-(phenylethynyl)phenyl)prop-2-ynyl)-N-(thiophen-2-ylethynyl)-benzenesulfonamide (36v): Following the general procedure GP-1 and GP-2, compound **36v** (389 mg) was obtained in overall 79% yield as black gummy liquid; R_f = 0.63 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 8.0 Hz, 2H), 7.56–7.51 (m, 2H), 7.28 (s, 1H), 7.27 (dd, J = 6.8, 2.0 Hz, 1H), 7.26–7.25 (m, 4H), 7.24–7.22 (m, 4H), 7.16 (dd, J = 6.8, 2.0 Hz, 1H), 6.95 (dd, J = 6.8, 2.0 Hz, 1H), 4.69 (s, 2H), 2.32 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.9, 134.3, 133.2, 132.4, 131.8, 129.6, 128.5, 128.41, 128.36, 1238.3, 127.9, 127.7, 126.9, 125.9, 124.5, 123.0, 122.7, 93.7, 87.7, 85.7, 85.3, 85.1, 64.8, 43.2, 21.5; IR (Neat) ν_{max} 3095, 3062, 2224, 1593, 1489, 1445, 1374, 1177, 1089 cm^{-1}; HRMS (ESI) for $C_{30}H_{21}NO_2S_2Na$ $(M+Na)^+$: calcd 514.0911, found 514.0916.

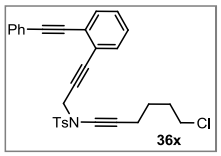


4-Methyl-N-(oct-1-ynyl)-N-(3-(2-(phenylethynyl)phenyl)prop-2-ynyl)benzenesulfon-amide (36w): Following the general procedure GP-1 and GP-2, compound **36w** (424 mg) was obtained in overall 86% yield as pale yellow gummy liquid; R_f = 0.62 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 8.4 Hz, 2H), 7.60–7.48 (m, 3H), 7.35 (br t, J = 8.4 Hz, 2H), 7.32–7.25 (m, 1H), 7.24–7.19 (m, 3H), 7.14 (d, J = 7.6 Hz, 1H), 4.56 (s, 2H), 2.30 (s, 3H), 2.20 (t, J = 6.8 Hz, 2H), 1.48–1.38 (m, 2H), 1.35–1.25 (m, 2H), 1.23–1.11 (m, 4H), 0.83 (t, J = 6.8 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.5, 134.2, 132.3, 131.8, 129.4, 128.6, 128.4, 128.3, 127.27, 127.6, 125.9, 124.6, 123.0, 93.6, 87.8,

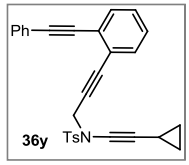


85.5, 84.8, 72.8, 71.1, 4.0, 31.4, 28.8, 28.4, 21.6, 21.5, 18.5, 14.1; IR (Neat) ν_{max} 3057, 3024, 2958, 2931, 2860, 2257, 2213, 1589, 1495, 1446, 1364, 1227, 1178, 1095 cm^{-1}; HRMS (ESI) for $C_{32}H_{32}NO_2S$ $(M+H)^+$: calcd 494.2154, found 494.2152.

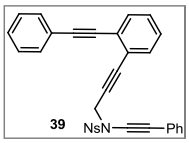
N-(8-chlorooct-1-ynyl)-4-methyl-N-(3-(2-(phenylethynyl)phenyl)prop-2-ynyl)benzenesulfonamide (36x): Following the general procedure GP-1 and GP-2, compound **36x** (455 mg) was obtained in overall 91% yield as pale yellow gummy liquid; R_f = 0.48 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 7.6 Hz, 2H), 7.53 (dd, J = 11.2, 3.2 Hz, 3H), 7.40–7.33 (m, 3H), 7.30 (t, J = 7.6 Hz, 1H), 7.22 (d, J = 9.2 Hz, 3H), 7.15 (d, J = 7.6 Hz, 3H), 4.56 (s, 2H), 3.41 (t, J = 6.4 Hz, 2H), 2.32 (s, 3H), 2.26 (t, J = 6.8 Hz, 2H), 1.78 (quintet, J = 7.2 Hz, 2H), 1.60–1.51 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.7, 134.1, 132.3, 131.8, 129.6, 128.6, 128.5, 128.2, 127.8, 125.9, 124.5, 123.0, 93.6, 87.8, 85.4, 84.9, 73.5, 70.2, 44.6, 42.9, 31.4, 25.9, 21.6, 17.8; IR (Neat) ν_{max} 3534, 3057, 2958, 2926, 2860, 2252, 2208, 1594, 1490, 1441, 1369, 1293, 1167, 1090 cm^{-1}; HRMS (ESI) for $C_{30}H_{27}ClNO_2S$ $(M+H)^+$: calcd 500.1451, found 500.1451.



N-(cyclopropylethynyl)-4-methyl-N-(3-(2-(phenylethynyl)phenyl)prop-2-ynyl)benzenesulfonamide (36y): Following the general procedure GP-1 and GP-2, compound **36y** (278 mg) was obtained in overall 62% yield as pale yellow gummy liquid; R_f = 0.68 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 8.4 Hz, 2H), 7.59-7.54 (m, 2H), 7.51 (d, J = 7.6 Hz, 1H), 7.39-7.34 (m, 3H), 7.32-7.24 (m, 2H), 7.22 (d, J = 8 Hz, 3H), 7.19-7.14 (m, 1H), 4.54 (s, 2H), 2.30 (s, 3H), 1.49 (m, 1H), 0.74-0.71 (m, 2H), 0.69-0.6 (m, 2H), ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.6, 134.3, 132.3, 131.8, 131.8, 129.4, 128.5, 128.4, 128.3, 128.2, 127.7, 125.9, 124.6, 123.0, 93.6, 87.8, 85.5, 84.8, 75.5, 68.4, 43.0, 21.5, 8.9; IR (Neat) ν_{max} 3534, 3057, 2958, 2926, 2860, 2252, 2208, 1594, 1490, 1441, 1369, 1293, 1167, 1090 cm^{-1}; HRMS (ESI) for $C_{29}H_{24}NO_2S$ $(M+H)^+$: calcd 450.1528, found 450.1530.

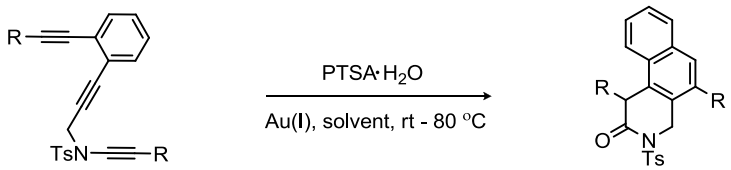


4-nitro-N-(phenylethynyl)-N-(3-(2-(phenylethynyl)phenyl)prop-2-ynyl)benzenesulfonamide (39): Following the general procedure GP-1 and GP-2, compound **39** (209 mg) was obtained in overall 66% yield as pale yellow thick liquid; R_f = 0.39(4:1 hexane/EtOAc); [Silica, UV and I_2]; ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (dd, J = 8.8 Hz, 2H), 8.13 (d, J = 8.8 Hz, 2H), 7.57–7.46 (m, 4H), 7.40 (dd, J = 7.2, 1.6 Hz, 2H), 7.36–7.17 (m, 12H), 4.78 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.4, 142.7, 132.3, 132.2, 131.71, 131.66, 129.5, 129.0, 128.7, 128.4, 128.0, 125.8, 124.0, 123.6,



122.7, 121.8, 93.7, 87.6, 86.0, 84.3, 81.1, 71.7, 43.8; IR (Neat) ν_{max} 3101, 3062, 1709, 1593, 1522, 1495, 1440, 1352, 1171, 1106 cm^{-1}; HRMS (ESI) for $C_{31}H_{21}N_2O_4S$ $(M+H)^+$: calcd 517.1222, found 517.1222.

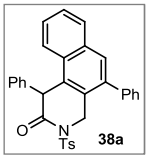
2.5.6. General procedure for the Au-catalyzed consecutive *endo*-cyclization cyclization of ynamide 36 to the preparation of 38 (GP–3):



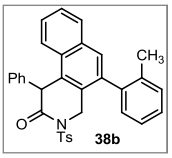
36 **38**

The compound ***36*** (0.25 mmol) and PTSA.H_2O (0.3 mmol) was placed in a Schlenk flask under an argon atmosphere. The reaction mixture was stirred for 10 min in dioxane (1.0 mL). The catalyst [(2-biphenyl)di-*t*Bu-phosphineAu(MeCN)]SbF_6 (**A**; 9.65 mg, 0.0125 mmol) in dichloroethane (2.0 mL) was introduced in to the Schlenk tube. The reaction mixture was stirred for 4 h at an ambient temperature. The progress of the reaction was periodically monitored by TLC. Next, the reaction was stirred for another 20 h at 80 °C. After satisfactory conversion of monocyclized product, the reaction mixture was cooled to room temperature, diluted with dichloromethane (10 mL), and filtered over a small pad of Celite. After evaporation of solvent under the reduced pressure, the residue was purified by column chromatography on silica gel.

1,5-Diphenyl-3-tosyl-3,4-dihydrobenzo[f]isoquinolin-2(1H)-one (38a): Following the general procedure GP-3, compound **38a** (101 mg) was obtained in overall 83% yield as pale yellow solid; mp = 136–138 °C, R_f = 0.36 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 7.6 Hz, 1H), 7.85 (br d, J = 8.8 Hz, 2H), 7.75 (d, J = 8.0 Hz, 2H), 7.60–7.47 (m, 5H), 7.43 (d, J = 6.8 Hz, 2H), 7.31–7.16 (m, 5H), 7.00 (d, J = 7.6 Hz, 2H), 5.73 (s, 1H), 5.45 (d, J = 16.0 Hz, 1H), 4.51 (d, J = 16.4 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.4, 144.8, 139.2, 137.7, 135.3, 133.7, 132.9, 131.4, 130.7, 130.1, 129.2, 129.1, 128.9, 128.8, 128.7, 128.5, 128.3, 128.0, 127.8, 127.4, 127.1, 126.8, 122.6, 51.6, 46.5, 21.6; IR (Neat) ν_{max} 3052, 2915, 1704, 1600, 1484,1446, 1358, 1265, 1172, 1123, 1090, 1013 cm^{-1}; HRMS (ESI) for $C_{32}H_{25}NO_3SNa$ $(M+Na)^+$: calcd 526.1453, found 526.1453.

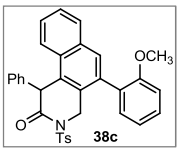


(S)-1-Phenyl-5-*o*-tolyl-3-tosyl-3,4-dihydrobenzo[f]isoquinolin-2(1H)-one (38b):

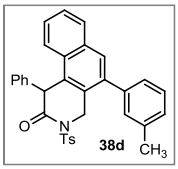


Following the general procedure GP-3, compound **38b** (99 mg) was obtained in overall 76% yield as pale yellow solid; mp = 160–161 °C, R_f = 0.38 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 7.6 Hz, 2H), 7.75 (d, J = 8.0 Hz, 2H), 7.69–7.60 (m, 6H), 7.44 (q, J = 6.8 Hz, 4H), 7.35–7.28 (m, 2H), 7.28–7.20 (m, 3H), 7.19–7.05 (m, 14H), 6.92 (d, J = 7.2 Hz, 2H), 6.85 (d, J = 7.2 Hz, 2H), 5.61 (s, 2H), 5.00 (d, J = 16.4 Hz, 1H), 5.00 (d, J = 16.4 Hz, 1H), 4.93 (d, J = 16.4 Hz, 1H), 4.22 (d, J = 16.0 Hz, 1H), 4.21 (d, J = 16.4 Hz, 1H), 2.32 (s, 3H), 2.31 (s, 3H), 2.09 (s, 3H), 1.98 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7, 144.9, 137.1, 136.3, 135.6, 135.4, 135.3, 133.91, 133.86, 133.1, 130.6, 130.5, 129.8, 129.4, 129.3, 129.1, 129.0, 128.8, 128.7, 128.6, 128.5, 128.3, 127.9, 127.8, 127.4, 127.2, 127.2, 126.9, 126.8, 126.2, 126.1, 122.7. 51.8, 51.6, 46.6, 46.1, 21.7, 20.3, 19.9; IR (Neat) ν_{max} 3062, 3024, 2914, 2854, 1692, 1593, 1495, 1445, 1347, 1177, 1133 cm^{-1}; HRMS (ESI) for $C_{33}H_{28}NO_3S$ $(M+H)^+$: calcd 518.1790, found 518.1790.

(S)-5-(2-Methoxyphenyl)-1-phenyl-3-tosyl-3,4-dihydrobenzo[f]isoquinolin-2(1H)-one (38c): Following the general procedure GP-3, compound **38c** (106 mg) was obtained in overall 79% yield as yellow solid; mp = 125–126 °C, R_f = 0.36 (7:3 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (br d, J = 7.2 Hz, 2H), 7.86–7.79 (m, 4H), 7.77 (d, J = 8.4 Hz, 2H), 7.66 (d, J = 8.4 Hz, 2H), 7.57–7.45 (m, 6H), 7.41 (dd, J = 7.6, 1.6 Hz, 1H), 7.32–7.22 (m, 7H), 7.21–7.15 (m, 5H), 7.15–7.07 (m, 6H), 7.04 (d, J = 8.0 Hz, 1H), 6.84 (d, J = 7.6 Hz, 2H), 5.70 (s, 1H), 5.69 (s, 1H), 5.34 (d, J = 15.6 Hz, 1H), 5.10 (d, J = 16.4 Hz, 1H), 4.60 (d, J = 16.4 Hz, 1H), 4.21 (d, J = 15.6 Hz, 1H), 3.89(s, 3H), 3.76 (s, 3H), 2.43 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7, 156.9, 156.2, 144.8, 144.7, 135.7, 135.6, 134.7, 133.8, 133.3, 131.5, 130.8, 130.5, 130.2, 130.0, 129.6, 129.3, 129.2, 129.0, 128.9, 128.3, 128.2, 127.9, 127.7, 127.4, 127.2, 126.6, 122.7, 122.6, 121.3, 121.0, 111.0, 110.8, 55.9, 55.5, 51.8, 51.5, 46.5, 21.6; IR (Neat) ν_{max} 3062, 3024, 2914, 2854, 1698, 1593, 1495, 1467, 1369, 1166, 1128 cm^{-1}; HRMS (ESI) for $C_{33}H_{28}NO_4S$ $(M+H)^+$: calcd 534.1739, found 534.1741.



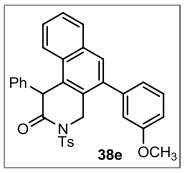
(S)-1-Phenyl-5-*m*-tolyl-3-tosyl-3,4-dihydrobenzo[f]isoquinolin-2(1H)-one(38d):



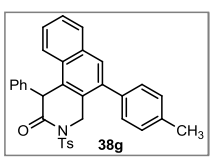
Following the general procedure GP-3, compound **38d** (104 mg) was obtained in overall 80% yield as pale yellow solid; mp = 125–126 °C; R_f = 0.39 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 8.0 Hz, 1H), 7.85 (br d, J = 4.0 Hz, 2H), 7.76 (d, J = 8.4, 2H), 7.60–7.49 (m, 2H), 7.45 (t, J = 7.6 Hz, 1H), 7.34–7.19 (m, 8H), 7.0 (d, J = 7.6 Hz, 2H), 5.73

(s, 1H), 5.47 (d, J = 16 Hz, 1H), 4.50 (d, J = 16 Hz, 1H), 2.51 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (101 MHz, CDCl3) δ 169.5, 159.8, 144.9, 140.7, 137.7, 135.4, 133.7, 133.0, 130.8, 130.2, 129.9, 129.3, 129.0, 128.9, 128.6, 128.4, 127.7, 127.5, 127.2, 126.9, 122.7, 121.6, 115.2, 113.3, 55.4, 51.7, 46.5, 21.7; IR (Neat) ν_{max} 3424, 3041, 2920, 2860, 1715, 1600, 1495, 1358, 1172, 1117 cm^{-1}; HRMS (ESI) for $C_{33}H_{28}NO_3S$ $(M+H)^+$: calcd 518.1790, found 518.1792.

(S)-5-(3-Methoxyphenyl)-1-phenyl-3-tosyl-3,4-dihydrobenzo[f]isoquinolin-2(1H)-one (38e): Following the general procedure GP-3, compound **38e** (101 mg) was obtained in overall 76% yield as yellow solid; mp = 115–116 °C; R_f = 0.34 (7:3 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 8.4 Hz, 1H), 7.85 (br d, J = 10 Hz, 2H), 7.76 (d, J = 8.0 Hz, 2H), 7.59–7.49 (m, 2H), 7.46 (t, J = 8.0 Hz, 1H), 7.28-7.17 (m, 5H), 7.05–6.99 (m, 2H), 6.97 (d, J = 7.6 Hz, 3H), 5.71 (s, 1H), 5.47 (d, J = 16.4, 1H), 4.48 (d, J = 16.4 Hz, 1H), 3.92 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.5, 159.8, 144.9, 140.7, 137.7, 135.4, 133.7, 133.0, 130.8, 130.2, 129.9, 129.3, 129.0, 128.9, 128.6, 128.4, 127.7, 127.5, 127.2, 126.9, 122.7, 121.6, 115.2, 113.3; IR (Neat) ν_{max} 3046, 3002, 2925, 1703, 1599, 1495, 1363, 1171, 1117, 1040 cm^{-1}; HRMS (ESI) for $C_{33}H_{28}NO_4S$ $(M+H)^+$: calcd 534.1739, found 534.1739.



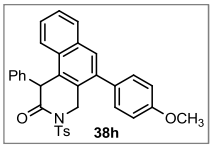
(S)-5-(3-Fluorophenyl)-1-phenyl-3-tosyl-3,4-dihydrobenzo[f]isoquinolin-2(1H)-one (38f): Following the general procedure GP-3, compound **38f** (103 mg) was obtained in overall 79% yield as white solid; mp = 130–131 °C; R_f = 0.40 (7:3 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 8.0 Hz, 1H), 7.76 (m, 1H), 7.67 (d, J = 8.4 Hz, 2H), 7.52–7.39 (m, 3H), 7.21–7.09 (m, 7H), 7.03 (d, J = 9.2 Hz, 1H), 6.88 (d, J = 7.6 Hz, 2H), 5.62 (s, 1H), 5.30 (d, J = 16.0 Hz, 1H), 4.39(d, J = 16.0 Hz, 1H) 2.32 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.5, 159.8, 144.9, 140.7, 137.7, 135.4, 133.7, 133.0, 130.8, 130.2, 129.9, 129.3, 129.0, 128.9, 128.6, 128.4, 127.7, 127.5, 127.2, 126.9, 122.7, 121.6, 118.5 (d, J = 88 Hz, 1C) , 118.2, 93.9, 87.1, 85.3, 85.0, 82.2, 71.2, 43.1, 21.6; ^{19}F NMR (376 MHz) δ -112.10; IR (Neat) ν_{max} 2975, 2920, 2241, 1715, 1621, 1512, 1358, 1156 cm^{-1}; HRMS (ESI) for $C_{32}H_{24}FNO_3SNa$ $(M+Na)^+$: calcd 544.1359, found 544.1362



(S)-1-Phenyl-5-*p*-tolyl-3-tosyl-3,4-dihydrobenzo[f]isoquinolin-2(1H)-one (38g): Following the general procedure GP-3, compound **38g** (106 mg) was obtained in overall 82% yield as colorless solid; mp = 148–149 °C; R_f = 0.46 (7:3 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 7.2 Hz, 1H), 7.89–7.85 (m, 2H), 7.76 (d, J = 8.4 Hz, 2H), 7.60–7.51 (m,

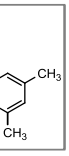
2H), 7.34 (q, J = 8.0 Hz, 4H), 7.29–7.19 (m, 5H), 7.01 (d, J = 7.2 Hz, 2H), 5.72 (s, 1H), 5.48 (d, J = 16.0 Hz, 1H), 4.52 (d, J = 16.0 Hz, 1H), 2.50 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.5, 144.9, 137.9,136.4, 135.4, 133.8, 133.1, 130.6, 130.1, 129.5, 129.3, 129.14, 129.08, 129.0, 128.8, 128.7, 128.4, 127.8, 127.3, 127.2, 126.8, 122.7 ,51.7, 46.6, 21.7, 21.3; IR (Neat) ν_{max} 3424, 3041, 2920, 2860, 1715, 1600, 1358, 1172, 1117, 904 cm^{-1}; HRMS (ESI) for $C_{33}H_{28}NO_3S$ (M+H)$^+$: calcd 518.1790, found 518.1792.

(S)-5-(4-Methoxyphenyl)-1-phenyl-3-tosyl-3,4-dihydrobenzo[f]isoquinolin-2(1H)-one

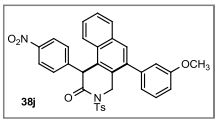


(38h): Following the general procedure GP-3, compound **38h** (109 mg) was obtained in overall 85% yield as colorless solid; mp = 106–107 °C; R_f = 0.50 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 8.0 Hz, 1H), 7.88–7.82 (m, 2H), 7.75 (d, J = 8.0 Hz, 2H), 7.59–7.48 (m, 2H), 7.35 (d, J = 8.8 Hz, 2H), 7.28–7.17 (m, 4H), 7.07 (d, J = 8.8 Hz, 2H), 6.99 (d, J = 7.6 Hz, 2H), 5.71 (s, 1H), 5.48 (d, J = 16.0 Hz, 1H), 4.51 (d, J = 16.0 Hz, 1H), 3.92 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.5, 159.5, 144.9, 137.6, 135.4, 133.8, 133.1, 131.6, 130.6, 130.4, 130.0, 129.7, 129.3, 129.2, 129.0, 128.82, 128.77, 128.4, 127.9, 127.3, 127.2, 126.9, 122.7, 114.3, 55.4, 51.7, 46.6, 21.7; IR (Neat) ν_{max} 3046, 3002, 2925, 1703, 1599, 1495, 1363, 1171 cm^{-1}; HRMS (ESI) for $C_{33}H_{28}NO_4S$ (M+H)$^+$: calcd 534.1739, found 534.1739.

(S)-5-(3,5-Dimethylphenyl)-1-phenyl-3-tosyl-3,4-dihydrobenzo[f]isoquinolin-2(1H)-one (38i): Following the general procedure GP-3, compound **36i** (89 mg) was obtained in overall 69% yield as colorless solid; mp = 120–121 °C; R_f = 0.42 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 8.0 Hz, 1H), 7.84 (br s, 2H), 7.76 (d, J = 8.0 Hz, 2H), 7.59–7.47 (m, 2H), 7.34–7.18 (m, 7H), 7.14 (d, J = 7.6 Hz, 1H), 7.01 (d, J = 7.2 Hz, 2H), 5.71 (s, 1H), 5.49 (d, J = 16.4 Hz, 1H), 4.49 (d, J = 16.4 Hz, 1H), 2.41 (s, 3H), 2.39 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.6, 144.9, 138.0, 137.1, 136.8, 136.5, 135.5, 133.9, 133.1, 130.6, 130.4, 130.1, 130.0, 129.3, 129.1, 129.0, 128.83, 128.77, 128.4, 127.58, 127.2, 126.8, 126.6, 122.7, 51.7, 46.6, 21.7, 19.9, 19.6; IR (Neat) ν_{max} 2235, 1600, 1495, 1364, 1172, 1090, 761 cm^{-1}; HRMS (ESI) for $C_{34}H_{29}NO_3SNa$ (M+Na)$^+$: calcd 554.1766, found 554.1766.



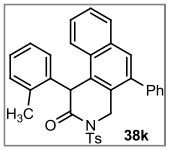
(S)-5-(3-Fluorophenyl)-1-phenyl-3-tosyl-3,4-dihydrobenzo[f]isoquinolin-2(1H)-one



(38j): Following the general procedure GP-3, compound **38j** (119 mg) was obtained in overall 82% yield as colorless solid; mp = 155–156 °C; R_f = 0.26 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 8.8 Hz, 2H), 7.97 (d, J = 8.0 Hz, 1H), 7.92 (s, 1H), 7.79 (d, J = 8.4 Hz,

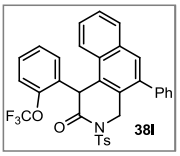
2H), 7.76 (d, *J* = 8.4 Hz, 1H), 7.64–7.53 (m, 2H), 7.48 (t, *J* = 8.0 Hz, 1H), 7.28 (d, *J* = 2.0 Hz, 1H), 7.26 (s,1H), 7.19 (d, *J* = 8.8 Hz, 2H), 7.06 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.01 (d, *J* = 8.0 Hz, 1H), 6.97 (d, *J* = 1.6 Hz, 1H), 5.77 (s, 1H), 5.41 (d, *J* = 16.4 Hz, 1H), 4.46 (d, *J* = 16.4 Hz, 1H), 3.94 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.2, 159.9, 147.6, 145.4, 141.4, 140.3, 137.8, 135.0, 133.1, 130.0, 129.9, 129.7, 129.4, 129.2, 128.5, 128.3, 127.9, 127.2, 124.1, 122.2, 121.5, 115.2, 113.5, 55.5, 51.5, 46.5, 21.7; IR (Neat) ν_{max} 2975, 2920, 2241, 1715, 1621, 1512, 1358, 1156 cm^{-1}; HRMS (ESI) for $C_{33}H_{26}N_2O_6SNa$ $(M+Na)^+$: calcd 601.1409, found 601.1409

5-Phenyl-1-*o*-tolyl-3-tosyl-3,4-dihydrobenzo[f]isoquinolin-2(1H)-one (38k):



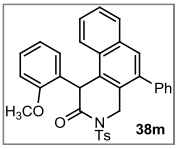
Following the general procedure GP-3, compound **38k** (111 mg) was obtained in overall 86% yield as pale yellow solid; mp = 120–121 ^{o}C; R_f = 0.39 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 24.8 Hz, 1H), 7.9 (d, *J* = 4.8 Hz, 2H), 7.76 (d, *J* = 8.4, Hz, 2H), 7.59 – 7.52 (m, 2H), 7.35 (q, *J* = 8.0 Hz, 4H), 7.29-7.20 (m, 5H), 7.01 (d, *J* = 7.2 Hz, 2H), 5.72 (s, 1H), 5.48 (d, 1H), 4.52 (d, *J* = 16 Hz, 1H); 2.50 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.5, 144.9, 137.9, 136.4, 135.4, 133.8, 133.1, 130.6, 130.1, 129.5, 129.3, 129.1, 129.1, 129.0, 128.8, 128.7,128.4, 127.8, 127.3, 127.2, 126.8, 122.7, 51.7, 46.7, 21.7, 21.3; IR (Neat) ν_{max} 2230, 1594, 14901, 1440, 1364, 1177, 1095, 1029, 909, 810, 761, 695, 597 cm^{-1}; HRMS (ESI) for $C_{33}H_{25}NO_2SNa$ $(M+H)^+$: calcd 518.1790, found 518.1792.

5-Phenyl-3-tosyl-1-(2-(trifluoromethoxy)phenyl)-3,4-dihydrobenzo[f]isoquinolin-2(1H) one (38l):



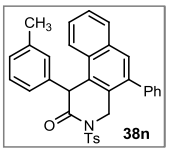
Following the general procedure GP-3, compound **38l** (122 mg) was obtained in overall 83% yield yellow solid; mp = 156–157 ^{o}C; R_f = 0.32 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.0 Hz, 1H), 7.81(s, 1H), 7.75 (d, *J* = 8.4 Hz, 3H), 7.62–7.42 (m, 6H), 7.35–7.25 (m, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.11 (t, *J* = 7.6 Hz, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 5.94 (s, 1H), 5.37 (d, *J* = 16.8 Hz, 1H), 4.96 (d, *J* = 16.8 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2, 147.9, 144.9, 139.3, 137.6, 135.2, 133.1, 129.6, 129.52, 129.5, 129.3, 129.3, 129.1, 128.9, 128.5, 128.2, 128.0, 127.9, 127.4, 126.9, 126.7, 122.5, 121.9, 119.9, 119.3, 48.0, 46.8, 21.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ -55.9; IR (Neat) ν_{max} 3058, 2926, 1710, 1600, 1490, 1370, 1260, 1178, 893 cm^{-1}; HRMS (ESI) for $C_{33}H_{25}F_3NO_4S$ $(M+H)^+$: calcd 588.1456, found 588.1456.

1-(2-Methoxyphenyl)-5-phenyl-3-tosyl-3,4-dihydrobenzo[f]isoquinolin-2(1H)-one



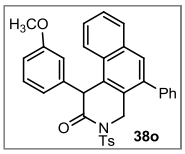
(38m): Following the general procedure GP-3, compound **38m** (105 mg) was obtained in overall 79% yield as colorless solid; mp = 133–134 °C; R_f = 0.50 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 7.6 Hz, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.79–7.73 (m, 3H), 7.60–7.54 (m, 2H), 7.53–7.41 (m, 6H), 7.19 (d, J = 8.4 Hz, 3H), 6.92 (d, J = 8.4 Hz, 1H), 6.87 (d, J = 7.6 Hz, 1H), 6.79 (t, J = 7.2 Hz, 1H), 6.01 (s, 1H), 5.34 (d, J = 16.8 Hz, 1H), 5.05 (d, J = 16.8 Hz, 1H), 3.92 (s, 3H) 2.36 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.9, 157.4, 144.7, 139.6, 137.6, 135.6, 133.0, 131.0, 129.9, 129.3, 129.2, 129.1, 129.0, 128.8, 128.6, 128.5, 128.1, 127.5, 127.1, 126.6, 125.5, 123.1, 121.0, 111.9, 56.0, 48.3, 46.1, 21.6; IR (Neat) ν_{max} 3058, 2921, 2833, 1699, 1595, 1484, 1359, 1244, 1167, 1090, 1024 cm^{-1}; HRMS (ESI) for $C_{33}H_{28}NO_4S$ $(M+H)^+$: calcd 534.1739, found 534.1737.

5-Phenyl-1-*m*-tolyl-3-tosyl-3,4-dihydrobenzo[f]isoquinolin-2(1H)-one (38n):



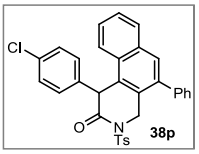
Following the general procedure GP-3, compound **38n** (101 mg) was obtained in overall 78% yield as colorless solid; mp = 134–135 °C; R_f = 0.40 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 7.6 Hz, 1H), 7.89–7.83 (m, 2H), 7.77 (d, J = 8.4 Hz, 2H), 7.60–7.55 (m, 3H), 7.54–7.47 (m, 2H), 7.44 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 8.0 Hz, 2H), 7.07 (br d, J = 5.6 Hz, 2H), 6.89 (s, 1H), 6.67 (br d, J = 5.6 Hz, 1H), 5.69 (s, 1H), 5.46 (d, J = 16.0 Hz, 1H), 4.53 (d, J = 16.0 Hz, 1H), 2.41 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.6, 144.9, 139.4, 138.8, 137.9, 135.4, 133.6, 133.1, 131.0, 130.2, 129.33, 129.26, 129.2, 128.9, 128.8, 128.7, 128.6, 128.4, 128.1, 127.9, 127.4, 126.9, 124.1, 122.8, 51.7, 46.6, 21.7, 21.5; IR (Neat) ν_{max} 3424, 3041, 2920, 2860, 1715, 1600, 1358, 1172, 1117 cm^{-1}; HRMS (ESI) for $C_{33}H_{28}NO_3S$ $(M+H)^+$: calcd 518.1790, found 518.1792.

1-(3-Methoxyphenyl)-5-phenyl-3-tosyl-3,4-dihydrobenzo[f]isoquinolin-2(1H)-one

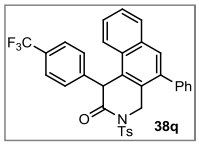


(38o): Following the general procedure GP-3, compound **38o** (113 mg) was obtained in overall 85 % yield as colorless solid; mp = 136–137 °C; R_f = 0.29 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (dd, J = 8.0, 1.2 Hz, 1H), 7.84 (d, J = 7.6 Hz, 2H), 7.74 (d, J = 8.0 Hz, 2H), 7.59–7.48 (m, 5H), 7.42 (t, J = 1.2 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 7.12 (t, J = 8.0 Hz, 1H), 6.78 (q, J = 2.4 Hz, 1H), 6.58 (s, 1H), 5.44 (d, J = 16 Hz, 1H), 4.54 (d, J = 16 Hz, 1H), 3.67 (s, 3H), 2.40 (s,3H), ^{13}CNMR(101MHz,$CDCl_3$) 169.3, 160.1, 144.9, 139.3, 137.8, 135.4, 135.2, 133.1, 130.6, 130.2, 129.9, 129.2, 128.9, 128.8, 128.6, 128.4, 128.1, 127.4, 126.9, 122.7, 119.4, 113.3, 113.1, 55.1, 51.7, 46.6, 21.7 (Neat) ν_{max} 3052, 2926, 2844, 1704, 1605, 1490, 1364, 1266,

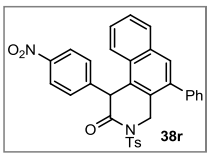
1173, 1129, 1085, 1036; HRMS (ESI) for $C_{33}H_{28}NO_4S$ $(M+Na)^+$: calcd 533.1661, found 556.1563.

1-(4-Chlorophenyl)-5-phenyl-3-tosyl-3,4-dihydrobenzo[f]isoquinolin-2(1H)-one (38p): 

Following the general procedure GP-3, compound **38p** (101 mg) was obtained in overall 75% yield as colorless solid; mp = 132–133 °C; R_f = 0.42 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 7.6 Hz, 1H), 7.87 (s, 1H), 7.78 (d, J = 7.6 Hz, 1H), 7.74 (d, J = 7.6 Hz, 2H), 7.61–7.47 (m, 5H), 7.41 (d, J = 6.0 Hz, 2H), 7.25 (d, J = 6.8 Hz, 2H), 7.16 (d, J = 7.2 Hz, 2H), 6.90 (d, J = 7.6 Hz, 2H), 5.65 (s, 1H), 5.43 (d, J = 16.0 Hz, 1H), 4.48 (d, J = 16.4 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0, 145.1, 139.2, 137.9, 135.1, 134.0, 133.1, 132.4, 130.1, 130.0, 129.5, 129.3, 129.2, 129.0, 128.9, 128.6, 128.4, 128.2, 127.6, 127.1, 122.5, 51.0, 46.6, 21.7; IR (Neat) ν_{max} 3052, 2921, 2849, 1699, 1600, 1496, 1359, 1167, 1123, 1090 cm^{-1}; HRMS (ESI) for $C_{32}H_{25}ClNO_3S$ $(M+H)^+$: calcd 538.1244, found 538.1243.

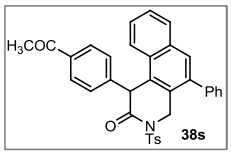
5-Phenyl-3-tosyl-1-(4-(trifluoromethyl)phenyl)-3,4-dihydrobenzo[f]isoquinolin-2(1H)-one (38q): 

Following the general procedure GP-3, compound **38r** (97 mg) was obtained in overall 73% yield as colorless solid; mp = 150–151 °C; R_f = 0.38 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 8.0 Hz, 1H), 7.89 (s, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.73 (d, J = 7.6 Hz, 2H), 7.58–7.50 (m, 5H), 7.44 (br t, J = 7.6 Hz, 4H), 7.22 (d, J = 7.6 Hz, 2H), 7.11 (d, J = 8.0 Hz, 2H), 5.73 (s, 1H), 5.44 (d, J = 16.4 Hz, 1H), 4.48 (d, J = 16.4 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.7, 145.2, 139.1, 138.0, 137.9, 135.0, 133.1, 130.7, 130.4, 130.0, 129.7, 126.0, 125.2, 122.4, 51.4, 46.67, 21.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ -112.5; IR (Neat) ν_{max} 3058, 2926, 2855, 1704, 1595, 1501, 1370, 1326, 1173, 1123, 1068, 1014 cm^{-1}; HRMS (ESI) for $C_{33}H_{25}F_3NO_3S$ $(M+H)^+$: calcd 572.1507, found 572.1507.

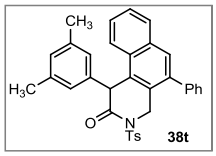
1-(4-Nitrophenyl)-5-phenyl-3-tosyl-3,4-dihydrobenzo[f]isoquinolin-2(1H)-one (38r): 

Following the general procedure GP-3, compound **38r** (117 mg) was obtained in overall 86% yield as yellow solid; mp = 156–157 °C; R_f = 0.26 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 8.8 Hz, 2H), 7.95 (d, J = 8.0 Hz, 1H), 7.90 (s, 1H), 7.75 (d, J = 8.0 Hz, 3H), 7.62–7.48 (m, 5H), 7.42 (d, J = 6.8 Hz, 2H), 7.25 (d, J = 8.0 Hz, 2H), 7.18 (d, J = 8.4 Hz, 2H), 5.76 (s, 1H), 5.45 (d, J = 16.4 Hz, 1H), 4.47 (d, J = 16.4 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.2, 147.6, 145.4, 141.4, 138.9, 138.0, 135.0, 133.2, 129.9, 129.4, 129.2, 128.9, 128.5, 128.3, 127.9, 127.3, 124.2, 122.2, 51.4, 46.6, 21.7; IR (Neat) ν_{max}

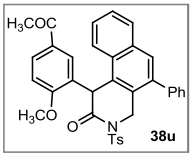
3084, 3052, 3030, 2915, 1682, 1600, 1528, 1347, 1172, 1084, 854 cm^{-1}; HRMS (ESI) for $C_{32}H_{24}N_2O_5SNa$ $(M+Na)^+$: calcd 571.1304, found 571.1304.

1-(4-Acetylphenyl)-5-phenyl-3-tosyl-3,4-dihydrobenzo[f]isoquinolin-2(1H)-one (38s): 

Following the general procedure GP-3, compound **38s** (98 mg) was obtained in overall 72% yield as pale yellow solid; mp = 121–122 °C; R_f = 0.50 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 8.4 Hz, 1H), 7.88 (s, 1H), 7.82–7.73 (m, 5H), 7.59–7.46 (m, 5H) 7.43 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 8.0 Hz, 2H), 5.74 (s, 1H), 5.45 (d, J = 16.4 Hz, 1H), 4.49 (d, J = 16.4 Hz, 1H), 2.54 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.4, 168.8, 145.2, 139.3, 139.1, 137.9, 136.6, 135.2, 133.1, 130.03, 129.96, 129.5, 129.4, 129.2, 129.0, 128.9, 128.5, 128.4, 128.2, 127.7, 127.5, 127.1, 122.5, 51.7, 46.6, 26.6, 21.7; IR (Neat) ν_{max} 3057, 2915, 1709, 1682, 1605, 1358, 1260, 1167, 1090, 904 cm^{-1}; HRMS (ESI) for $C_{34}H_{28}NO_4S$ $(M+H)^+$: calcd 546.1739, found 546.1739.

1-(3,5-Dimethylphenyl)-5-phenyl-3-tosyl-3,4-dihydrobenzo[f]isoquinolin-2(1H)-one (38t): 

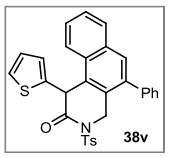
Following the general procedure GP-3, compound **38t** (106 mg) was obtained in overall 80% yield as colorless solid; mp = 110–111 °C; R_f = 0.39 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 8.0 Hz, 1H), 7.87 (br d, J = 5.6 Hz, 2H), 7.75 (d, J = 8.0 Hz, 2H) 7.60–7.48 (m, 5H), 7.43 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 4.8 Hz, 2H), 6.87 (s, 1H), 6.55 (s, 2H), 5.65 (s, 1H), 5.44 (d, J = 16.0 Hz, 1H), 4.52 (d, J = 16.0 Hz, 1H), 2.41 (s, 3H), 2.14 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.6, 144.8, 139.3, 138.5, 137.8, 135.3, 133.5, 133.0, 131.1, 130.2, 129.5, 129.2, 129.0, 128.7, 128.6, 128.4, 128.0, 127.3, 126.8, 124.8, 122.8, 51.6, 46.5, 21.6, 21.3; IR (Neat) ν_{max} 3058, 3024, 2926, 2855, 1715, 1605, 1468, 1353, 1271, 1167, 1123 cm^{-1}; HRMS (ESI) for $C_{34}H_{29}NO_3SNa$ $(M+H)^+$: calcd 532.1946, found 532.1951.

1-(5-Acetyl-2-methoxyphenyl)-5-phenyl-3-tosyl-3,4-dihydrobenzo[f]isoquinolin-2(1H)-one (38u): 

Following the general procedure GP-3, compound **38u** (121 mg) was obtained in overall 84% yield as colorless solid; mp = 123–124 °C; R_f = 0.23 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86–7.79 (m, 3H), 7.76 (d, J = 8.0 Hz, 3H), 7.59–7.55 (m, 3H), 7.53–7.46 (m, 5H), 7.19 (d, J = 8.4 Hz, 2H), 6.95 (d, J = 8.8 Hz, 1H), 6.04 (s, 1H), 5.36 (d, J = 17.2 Hz, 1H), 5.10 (d, J = 17.2 Hz, 1H), 4.0 (s, 3H), 2.43 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.1, 168.3, 161.1, 144.9, 139.4, 137.8, 135.5, 133.0, 130.6, 130.3, 130.1, 129.7, 129.3, 129.1, 128.92, 128.85, 128.5, 128.2, 127.6, 127.2, 126.7,

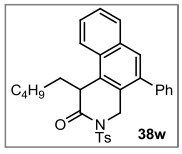
125.9, 122.7, 111.0, 56.4, 48.5, 45.8, 26.1, 21.6; IR (Neat) ν_{max} 2958, 2926, 2849, 1704, 1676, 1594, 1495, 1353, 1271, 1172, 1090, 1019 cm^{-1}; HRMS (ESI) for $C_{35}H_{30}NO_5S$ $(M+H)^+$: calcd 576.1845, found 576.1842.

5-Phenyl-1-(thiophen-2-yl)-3-tosyl-3,4-dihydrobenzo[f]isoquinolin-2(1H)-one (38v):



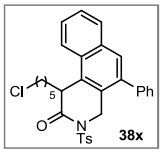
Following the general procedure GP-3, compound **38v** (96 mg) was obtained in overall 75% yield as pale brown solid; mp = 108–109 °C; R_f = 0.45 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (br t, J = 5.2 Hz, 2H), 7.85 (s, 1H), 7.79 (d, J = 8.0 Hz, 2H), 7.59–7.51 (m, 4H), 7.50 (d, J = 6.8 Hz, 1H), 7.42 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 8.8 Hz, 2H), 7.15 (d, J = 5.2 Hz, 1H), 6.85 (t, J = 4.8 Hz, 1H), 6.60 (dd, J = 2.4, 0.8 Hz, 1H), 5.83 (s, 1H), 5.46 (d, J = 16.4 Hz, 1H), 4.68 (d, J = 16.4 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.3, 145.0, 139.2, 137.8, 137.3, 135.2, 133.1, 130.8, 129.7, 129.5, 129.3, 129.2, 128.9, 128.8, 128.5, 128.1, 127.5, 127.2, 127.0, 126.0, 125.8, 122.5, 47.7, 46.6, 21.7; IR (Neat) ν_{max} 2975, 2920, 2241, 1715, 1621, 1512, 1358, 1156 cm^{-1}; HRMS (ESI) for $C_{30}H_{24}NO_3S_2$ $(M+H)^+$: calcd 510.1198, found 510.1197.

1-Pentyl-5-phenyl-3-tosyl-3,4-dihydrobenzo[f]isoquinolin-2(1H)-one (38w):



Following the general procedure GP-3, compound **38w** (86 mg) was obtained in overall 69% yield as pale yellow thick liquid; R_f = 0.46 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91–7.83 (m, 4H), 7.78 (t, J = 8.4 Hz, 0.75H), 7.72 (s, 1H), 7.60–7.46 (m, 6H), 7.41 (brd, J = 8.4 Hz, 2.5 x 1H), 7.31–7.24 (m, 3.65 x 1H), 5.42 (d, J = 16.4 Hz, 1H), 4.90 (d, J = 16.4 Hz, 1H), 4.36 (t, J = 6.4 Hz, 1H), 2.40 (s, 3H), 1.90–1.80 (m, 2H), 1.48–1.10 (m, 11H), 0.87 (t, J = 7.2 Hz, 3.97 x 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2, 144.9, 139.5, 137.8, 135.9, 135.8, 133.0, 132.5, 129.3, 129.1, 128.91, 128.86, 128.8, 128.7, 128.5, 128.1, 127.9, 127.1, 126.7, 126.4, 126.1, 122.3, 119.4, 118.5, 47.0, 46.6, 32.2, 31.5, 27.0, 26.0, 22.5, 21.6, 14.1; IR (Neat) ν_{max} 3058, 2953, 2926, 2855, 1699, 1600, 1496, 1463, 1359, 1178, 1090 1036; cm^{-1}; HRMS (ESI) for $C_{31}H_{32}NO_3S$ $(M+H)^+$: calcd 498.2103, found 498.2105

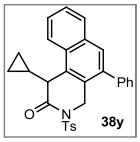
1-Pentyl-5-phenyl-3-tosyl-3,4-dihydrobenzo[f]isoquinolin-2(1H)-one (38x):



Following the general procedure GP-3, compound **38x** (93 mg) was obtained in overall 72% yield as pale yellow gummy liquid; R_f = 0.46 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (brt, J = 8.0 Hz, 4H), 7.73 (s, 1H), 7.61–7.47 (m, 6H), 7.41 (d, J = 7.6 Hz, 3H), 7.27 (d, J = 8.4 Hz, 3H), 5.42 (d, J = 16.4 Hz, 1H), 4.90 (d, J = 16.8 Hz, 1H), 4.37 (t, J = 6.4 Hz, 1H), 3.47 –

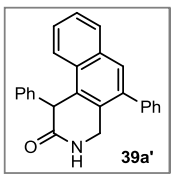
3.41 (m, 2H), 2.40 (s, 3H), 1.92–1.82 (m, 2H), 1.81–1.65 (m, 3H), 1.55–1.47 (m, 2H), 1.42 (bd, J = 13.6 Hz, 1H), 0.93–0.13 (m, 2H), 0.86 – 0.57 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.9, 145.1, 139.4, 137.8, 135.6, 133.1, 132.0, 129.4, 129.1, 129.0, 128.8, 128.7, 128.5, 128.1, 127.2, 126.8, 126.5, 122.1, 47.0, 46.3, 44.4, 32.1, 31.5, 24.5, 21.7; IR (Neat) ν_{max} 3047, 3025, 2948, 2926, 2860, 1704, 1595, 1458, 1359, 1178, 1085 cm^{-1}; HRMS (ESI) for $C_{30}H_{29}ClNO_3S$ $(M+H)^+$: calcd 518.1557, found 518.1560

1-Cyclopropyl-5-phenyl-3-tosyl-3,4-dihydrobenzo[f]isoquinolin-2(1H)-one (38y):

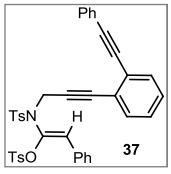


Following the general procedure GP-3, compound **38y** (85 mg) was obtained in overall 73% yield as yellow thick liquid; R_f = 0.50 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 – 7.83 (m, 3H), 7.78 (d, J = 8.8 Hz, 2H), 7.62 – 7.48 (m, 5H), 7.45 (d, J = 16.4 Hz, 2H), 7.32–7.25 (m, 5H), 5.01 (d, J = 16.4 Hz, 1H), 4.06 (d, J = 6.8 Hz, 1H), 2.41 (s, 3H), 1.24 (d, J = 7.2 Hz, 1H), 0.51–0.04 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.9, 144.9, 139.5, 137.9, 135.7, 133.0, 131.5, 129.38, 129.4, 129.3, 129.1, 128.9, 128.9, 128.8, 128.7, 128.7, 128.6, 128.5, 128.1, 127.2, 127.0, 126.7, 122.8, 48.8, 47.0, 21.7, 13.3, 4.3, 2.8; IR (Neat) ν_{max} 3058, 3025, 2921, 2866, 1748, 1693, 1600, 1496, 1463, 1359, 1173, 1085, 888, 816, 762, 690 cm^{-1}; HRMS (ESI) for $C_{29}H_{26}NO_3S$ $(M+H)^+$: calcd 468.1633, found 468.1636

1,5-Diphenyl-3,4-dihydrobenzo[f]isoquinolin-2(1H)-one (39a′): Following the general procedure GP-2, compound ***39a′*** (68 mg) was obtained in overall 52% yield as pale yellow gummy liquid; R_f = 0.36 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (t, J = 8.0 Hz, 2H), 7.76 (s, 1H), 7.56–7.30 (m, 8H), 7.28–7.18 (m, 5H), 5.56 (s, 1H), 4.60 (d, J = 8.0 Hz, 1H), 4.60 (d, J = 16.8 Hz, 1H), 4.35 (d, J = 16.8, 4.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.6, 140.0, 137.7, 137.6, 132.9, 130.6, 130.3, 130.0, 129.2, 128.9, 128.7, 128.6, 128.2, 128.0, 127.8, 127.4, 127.0, 126.4, 123.1, 49.0, 44.4; IR (Neat) ν_{max} 2975, 2920, 2241, 1715, 1621, 1512, 1358, 1156 cm^{-1}; HRMS (ESI) for $C_{25}H_{19}NONa$ $(M+Na)^+$: calcd 372.1364, found 372.1365.

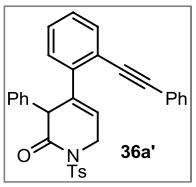


(Z)-1-(4-Methyl-N-(3-(2-(phenylethynyl)phenyl)prop-2-ynyl)phenylsulfonamido)-2-phenylvinyl 4-methylbenzenesulfonate (37): The compound ***36a*** (0.25 mmol) and PTSA.H_2O (0.3 mmol) was placed in a Schlenk flask under an argon atmosphere. The reaction mixture was stirred for 10 min in dioxane (1.0 mL). The complete consumption of compound ***36a*** was monitored by TLC. The reaction mixture was diluted with dichloromethane (10 mL), and filtered over a small



pad of Celite. After evaporation of solvent under the reduced pressure, the residue was kept under high vaccum. Finally the product ***37*** was characterized by crude NMR and HRMS data. brown solid; R_f = 0.30 (9:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8.0 Hz, 4H), 7.59 (br t, J = 7.2 Hz, 4H), 7.51 (d, J = 8.0 Hz, 1H), 7.38 (d, J = 8.0 Hz, 3H), 7.33–7.24 (m, 4H), 7.20 (d, J = 8.0 Hz, 3H), 7.15 (d, J = 8.0 Hz, 3H), 6.93 (d, J = 7.6 Hz, 1H), 6.53 (s, 1H), 4.72 (s, 2H), 2.37 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.5, 144.3, 137.8, 135.7, 132.7, 132.4, 131.8, 131.7, 131.5, 129.7, 129.4, 129.1, 128.8, 128.6, 128.5, 128.2, 127.7, 125.6, 124.7, 123.3, 123.1, 93.5, 87.9, 86.0, 84.9, 67.1, 39.8, 21.7, 21.6; IR (Neat) ν_{max} 2975, 2920, 2241, 1715, 1621, 1512, 1358, 1156 cm^{-1}; HRMS (ESI) for $C_{39}H_{32}NO_5S_2$ $(M+H)^+$: calcd 658.1722, found 658.1725.

3-Phenyl-4-(2-(phenylethynyl)phenyl)-1-tosyl-1,6-dihydropyridin-2(3H)-one (36a′):



The compound ***36a*** (0.25 mmol) and PTSA.H_2O (0.3 mmol) was placed in a Schlenk flask under an argon atmosphere. The reaction mixture was stirred for 10 min in dioxane (1.0 mL). The progress of the reaction was monitored by TLC till the complete consumption of compound ***36a*** was observed. Next, the catalyst (2-biphenyl)di-*t*Bu-phosphine(MeCN)Au)SbF_6 (**A**; 9.65 mg, 0.0125 mmol) in dioxane (1.0 mL) was introduced in to the Schlenk tube. The reaction mixture was stirred for 4 h at an ambient temperature. The progress of the reaction was periodically monitored by TLC. After satisfactory conversion to monocyclized product, the reaction mixture was diluted with dichloromethane (10 mL), and filtered over a small pad of Celite. After evaporation of solvent under the reduced pressure, the residue was purified by column chromatography on silica gel.

Following the above procedure, compound ***36a′*** (42 mg) was obtained in overall 40% yield as pale yellow solid; mp = 121–122 °C, R_f = 0.32 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 8.4 Hz, 1H), 8.04 (d, J = 8.0 Hz, 2H), 7.83 (d, J = 8.0 Hz, 2H), 7.40–7.21 (m, 14H), 6.54 (dd, J = 5.6, 2.4 Hz, 1H), 4.80 (dd, J = 18.0, 6.0 Hz, 1H), 4.68 (s, 1H), 4.55 (d, J = 18.0 Hz, 1H), 2.45 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.7, 144.8, 139.3, 138.5, 137.9, 137.4, 135.9, 135.7, 135.6, 135.4, 135.3, 133.2, 131.5, 130.0, 129.3, 129.2, 128.9, 128.7, 128.6, 128.5, 128.2, 128.0, 127.9, 127.8, 126.9, 126.2, 122.8, 121.4, 119.3, 88.0, 47.0, 21.6; IR (Neat) ν_{max} 3052, 2915, 1704, 1600, 1484,1446, 1358, 1265, 1172, 1123, 1090, 1013 cm^{-1}; HRMS (ESI) for $C_{32}H_{25}NO_3SNa$ $(M+Na)^+$: calcd 526.1453, found 526.1457.

Table 2.5. Crystal data and structure refinement for **38l**.

Identification code	38l	
Empirical formula	C H F N O S	
Formula weight	94.09	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	triclinic	
Space group	P_1^-	
Unit cell dimensions	a = 14.2696(19) Å	α= 67.374(18)°.
	b = 14.853(3) Å	β= 72.768(15)°.
	c = 14.948(3) Å	γ = 89.623(12)°.
Volume	2772.3(8) $Å^3$	
Z	31	
Density (calculated)	1.747 Mg/m^3	
Absorption coefficient	0.724 mm^{-1}	
F(000)	1457	
Theta range for data collection	2.77 to 29.14°.	
Index ranges	-18<=h<=18, -19<=k<=18, -20<=l<=20	
Reflections collected	22776	
Independent reflections	12641 [R(int) = 0.1111]	
Completeness to theta = 29.14°	84.6 %	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	12641 / 0 / 759	
Goodness-of-fit on F^2	0.887	
Final R indices [I>2sigma(I)]	R1 = 0.0811, wR2 = 0.1249	
R indices (all data)	R1 = 0.3251, wR2 = 0.2265	
Largest diff. peak and hole	0.303 and -0.287 $e.Å^{-3}$	

2.6. References:

1. Selected reviews on alkyne and ynamide chemistry, see: (a) Zoellner, R. W.; Klabunde, K. J. *Chem. Rev.* **1984**, *84*, 545. (b) DeKorver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. *Chem. Rev.* **2010**, *110*, 5064. (c) Evano, G.; Coste, A.; Jouvin, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 2840. (d) Mulder, J. A.; Kurtz, K. C. M.; Hsung, R. P. *Synlett* **2003**, 1379. (e) Zificsak, C. A.; Mulder, J. A.; Hsung, R. P.; Rameshkumar, C.; Wei, L.-L. *Tetrahedron* **2001**, *57*, 7575.

2. a) Couty, S.; Meyer, C.; Cossy J. *Angew. Chem. Int. Ed.* **2006**, *45*, 6726. b) Marion, F., Coulomb, J., Courillon, C.; Fensterbank, L.; Malacria, M. *Org. Lett.* **2004**, *6*, 1509.c) Couty S., Meyer, C.; Cossy J. *Tetrahedron.* **2009**, *65*, 1809. d) Garcia P.; Harrak Y.; Diab L.; Cordier P.; Ollivier C.; Gandon V.; Malacria M.; Fensterbank L.; Aubert C. *Org. Lett.* **2011**, *13*, 2952. e) Dunetz J. R.; Danheiser R. L. *J. Am. Chem. Soc.* **2005**, *127*, 5776. f) Zhang Y.; Hsung R. P.; Zhang X.; Huang J.; Slafer B. W.; A. Davis, *Org. Lett.* **2005**, *7*, 1047. g) Witulski B.; Lumtscher J.; Bergsträßer U. *Synlett* **2003**, 708. h) Martínez-Esperön M. F.; Rodríguez D.; Castedo L.; Saá, C. *Org. Lett.* **2005**, *7*, 2213.

3. (a) Kuram, M. R.; Bhanuchandra, M.; Sahoo, A. K. *J. Org. Chem.* **2010**, *75*, 2247. (b) Ghosh, N.; Nayak, S.; Sahoo, A. K. *J. Org. Chem.* **2011**, *76*, 500. c) Ghosh, N.; Nayak, S.; Sahoo, A. K. *Chem. –Eur. J.* **2013**, *19*, 9428

4. For recent reviews on gold catalysis, see: (a) Rudolph, M.; Hashmi, A. S. K. *Chem. Soc. Rev.* **2012**, *41*, 2448. (b) Corma, A.; Leyva-Pérez, A.; Sabater, M. J. *Chem. Rev.* **2011**, *111*, 1657. (c) López, F.; Mascareńas, J. L. *Beilstein J. Org. Chem.* **2011**, *76*, 1075. (d) Rudolph, M.; Hashmi, A. S. K. *Chem. Commun.* **2011**, *47*, 6536. (e) Hashmi, A. S. K.; Buhrle, M. *Aldrichimica Acta*, **2010**, *43*, 27. (f) Fürstner, A. *Chem. Soc. Rev.* **2009**, *38*, 3208. (g) Sohel, S. M. A.; Liu, R.-S. *Chem. Soc. Rev.* **2009**, *38*, 2269. (h) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395. (i) Michelet, V.; Toullec, P. Y.; Genét, J. P. *Angew. Chem., Int. Ed.* **2008**, *47*, 4268. (j) Li, Z.; Brower, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239. (k) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326. (l) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351. (m) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (n) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410.

5. Dunetz, J. R.; Danheiser, R. L. *J. Am. Chem. Soc.* **2005**, *127*, 5776.

6. Garcia, P.; Harrak, Y.; Diab, L.; Cordier, P.; Ollivier, C.; Gandon, V.; Malacria, M.; Fensterbank, L.; Aubert, C. *Org. Lett.* **2011**, *13*, 2952.

7. Wang, K.-B.; Ran, R.-Q.; Xiu, S.-D.; Li, C.-Y. *Org. Lett.* 2013, 15, 2374.

8. Hashmi, A. S. K.; Pankajakshan, S.; Rudolph, M.; Enns, E.; Bander, T.; Rominger, F.; Frey, W. *Adv. Synth. Catal.* **2009**, *351*, 2855.

9. Jaimes, M. C. B.; Weingand, V.; Rominger, F.; Hashmi, A. S. K. *Chem.–Eur. J.* **2013**, *16*, 9846.

10. (a) Couty, S.; Meyer, C.; Cossy, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 6726. (b) Marion, F.; Coulomb, J.; Courillon, C.; Fensterbank, L.; Malacria, M. *Org. Lett.* **2004**, *6*, 1509.

11. (a) Yun, S. Y.;Wang, K.-P.; Lee, N.-K.; Mamidipalli, P.; Lee, D. *J. Am. Chem. Soc.* **2013**, *135*, 4668. (b) Karmakar, R.; Mamidipalli, P.; Yun, S. Y.; Lee, D. Alder-Ene Reactions of Arynes. *Org. Lett.* **2013**, *15*, 1938.

12. Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Chem. –Eur. J.* **2003**, *9*, 2627.

13. Staben, S. T.; Kennedy-Smith, J. J.; Huang, D.; Corkey, B. K.; Lalonde, R. L.; Toste, F. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 5991.

14. Minnihan, E. C.; Colletti, S. L.; Toste, F. D.; Shen, H. C. *J. Org. Chem.* **2007**, *72*, 6287.

15. Harrison, T. J.; Patrick, B. O.; Dake, G. R. *Org. Lett.* **2007**, 9, 367.

16. Binder, J. T.; Crone, B.; Haug, T. T.; Menz, H.; Kirsch, S. F. *Org. Lett.* **2008**, 10, 1025-1028.

17. Brown, L. E.; Dai, P.; Porco, J. A., Jr.; Schaus, S. E. *Org. Lett.* **2011**, *13*, 4228–4231.

18. (a) Alabugin, I. V.; Gilmore, K.; Manoharan, M. *J. Am. Chem. Soc.* **2011**, *133*, 12608. (b) Alabugin, I. V.; Gilmore, K. *Chem. Commun.*, **2013**, *49*, 11246.

19. (a) Byers, P. M.; Alabugin, I. V. *J. Am. Chem. Soc.* **2012**, *134*, 9609. (b) Byers, P. M.; Rashid, J. I.; Mohamed, R. K.; Alabugin, I. V. *Org. Lett.* **2012**, *14*, 6032.

20. For biologically important heterocyclic molecules, see: (a) Amat, M.; Pérez, M.; Bosch, J. *Chem.– Eur. J.***2011**, *17*, 7724. (b) Escolano, C.; Amat, M.; Bosch, J. *Chem.–Eur. J.* **2006**, *12*, 8198. (c) Strunz, G. M.; Findlay, J. A. *Pyridine and piperidine alkaloids*, *In The Alkaloids*; Brossi, A., Ed.; Academic Press: Orlando, **1985**, vol. 26, pp 89. (d) Nowata, A.; Ibuka, I. Alkaloids from ants and others insects, in The Alkaloids, ed. A. Brose, Academic Press, New York, 1987, vol. 31, pp. 193.

21. (a) Candeias N. R.; Branco L. C.; Gois P. M. P.; Afanso C. A. M.; Trindade A. F. *Chem. Rev.* **2009**, *109*, 2703. (b) Sridharan V.; Suryavanshi P. A.; Menéndez J. C. *Chem. Rev.* **2011**, *111*, 2703. (c) Joule J. A.; Mills K. *Heterocycl. Chem., Wiley, UK, 5th edn*, 2010.

21 (a) Crecente-Campo J.; Vázquez-Tato M. P.; Seijas J. A. *Tetrahedron*, **2009**, *65*, 2655 and references cited therein;

23. (a) Ali, S.; Zhu, H.-T.; Xia, X.-F.; Ji, K.-G.; Yang, Y.-F.; Song, X.-R.; Liang, Y.-M. *Org. Lett.* **2011**, *13*, 2598. (b) Lloyd-Williams, P.; Giralt, E. *Chem. Soc. Rev.* **2001**, *30*, 145. (c) Suzuki A. *Metal-Catalyzed Cross-Coupling Reactions*, (Eds.: F. Diederich, P. J. Stang), Wiley-VCH, Weinheim, Germany, **1998**, p. 49.

24. Sonogashira, K. In *Metal-Catalyzed Cross-Coupling Reactions*, (Eds.: Diederich, F.; Stang, P. J.), Wiley-VCH, Weinheim, Germany, **1998**, Chapter 5, pp 203.

25. Nieto-Oberhuber, C.; López, S.; Echavarren, A. M. *J. Am. Chem. Soc.* **2005**, *127*, 6178.

26. Liu, R.; Winston-McPherson, G. N.; Yang, Z. Y.; Zhou, X.; Song, W.; Guzei, I. A.; Xu, X.; Tang, W. *J. Am. Chem. Soc.* **2013**, *135*, 8201.

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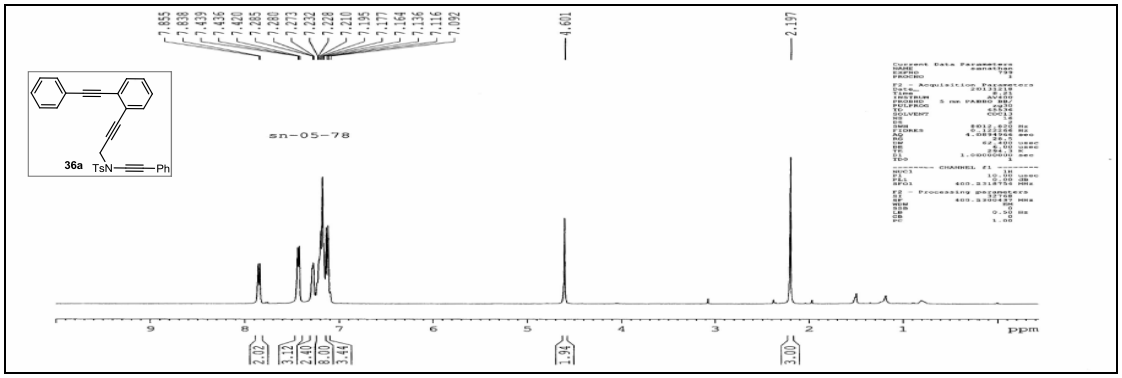
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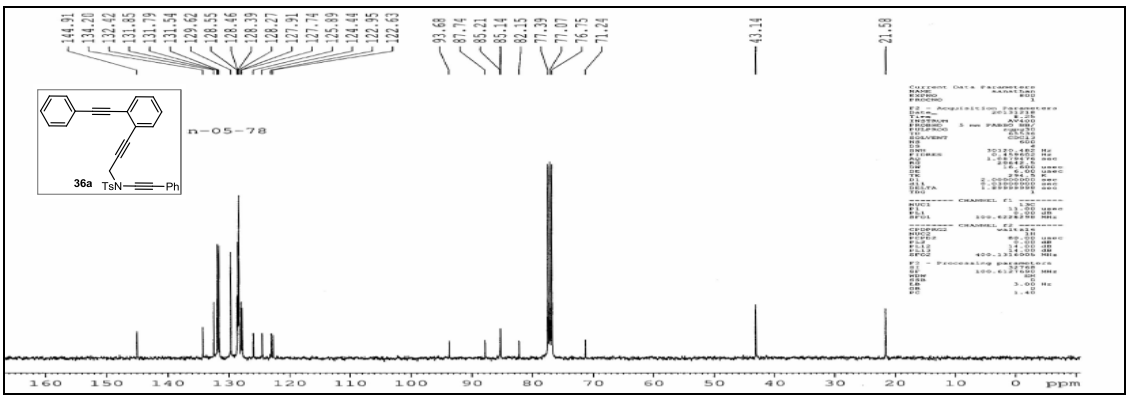
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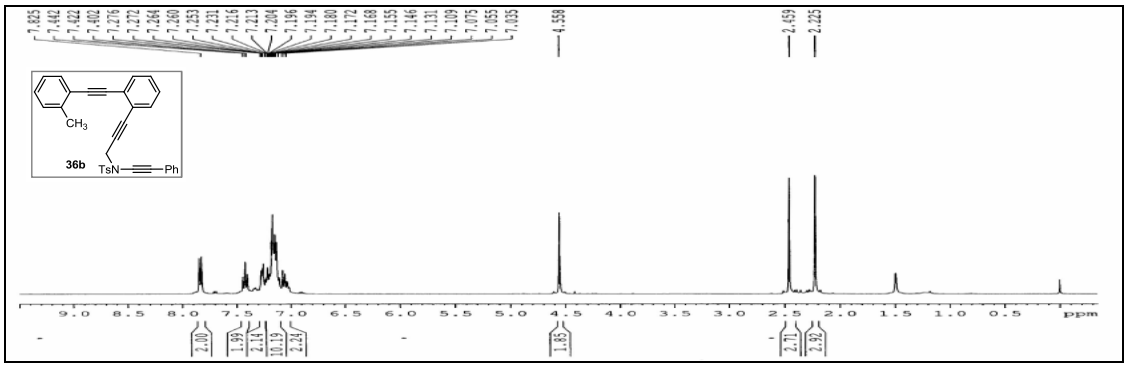
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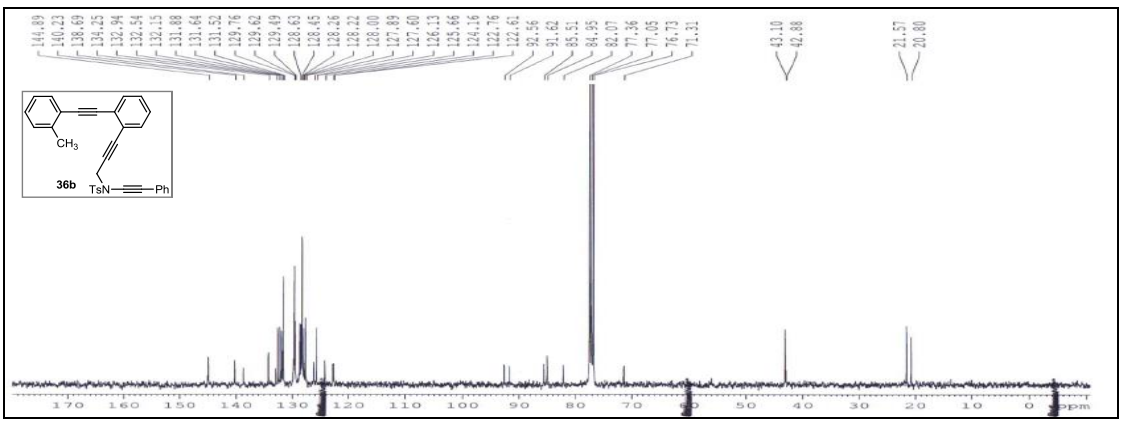
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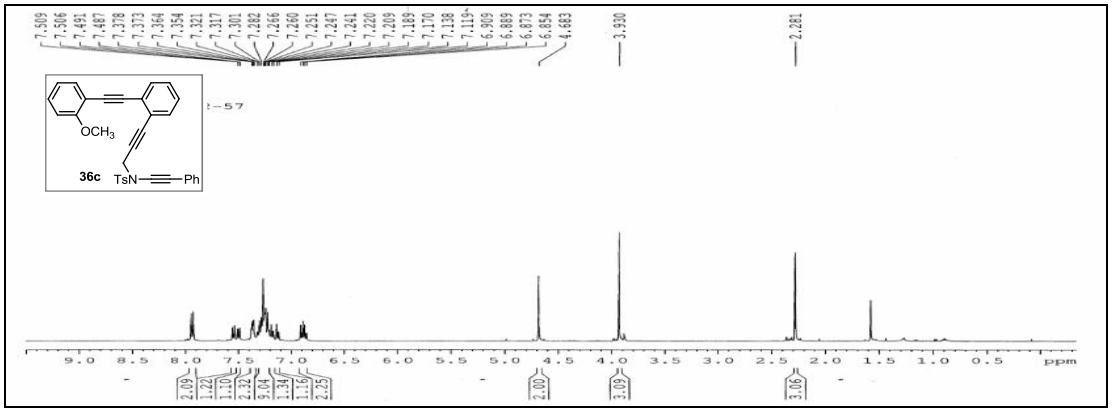
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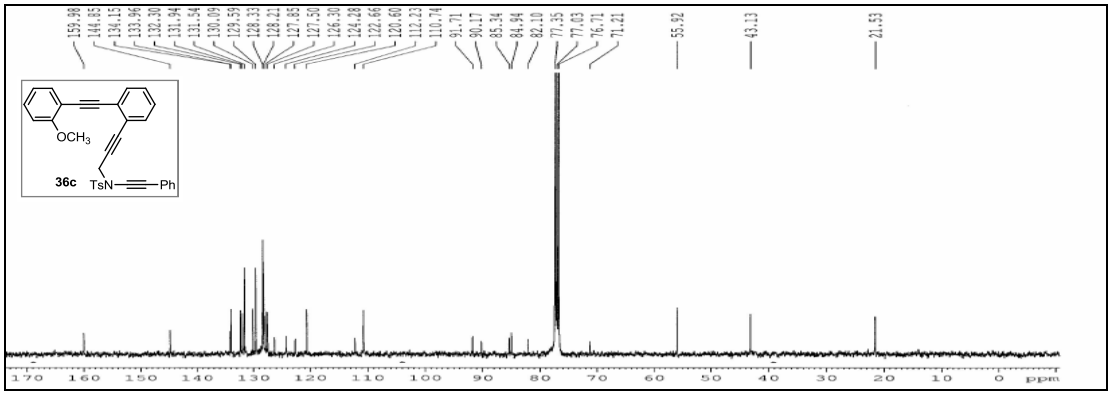
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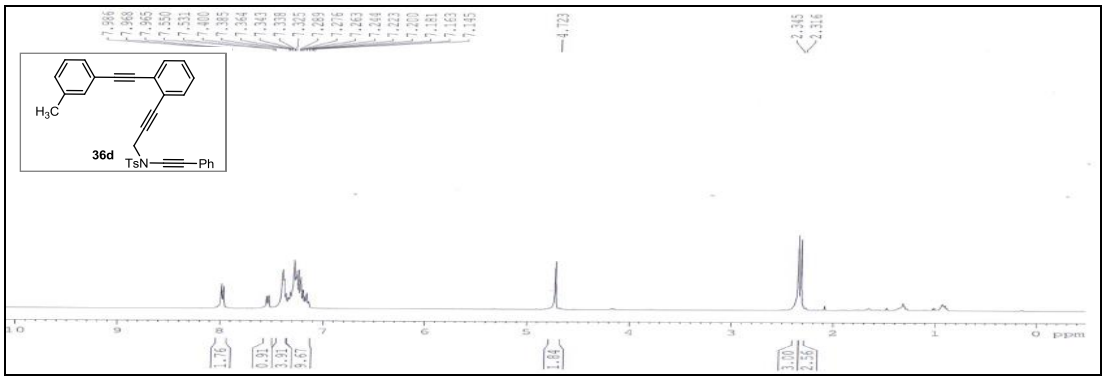
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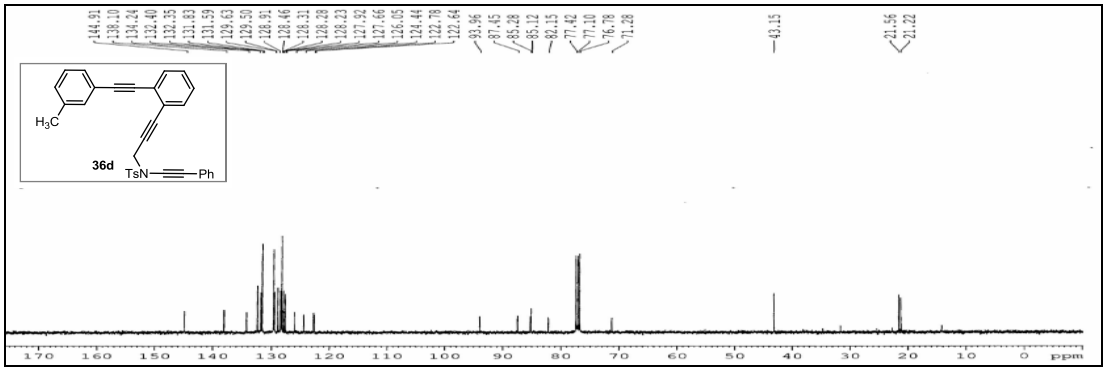
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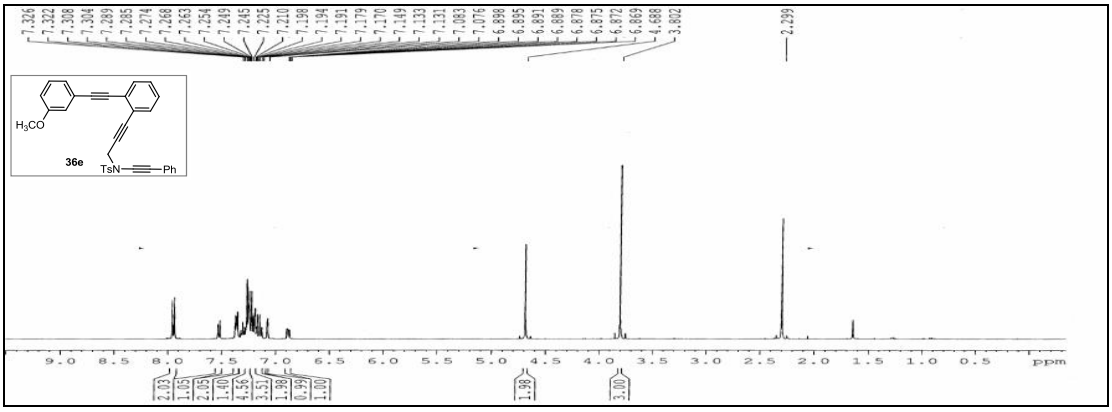
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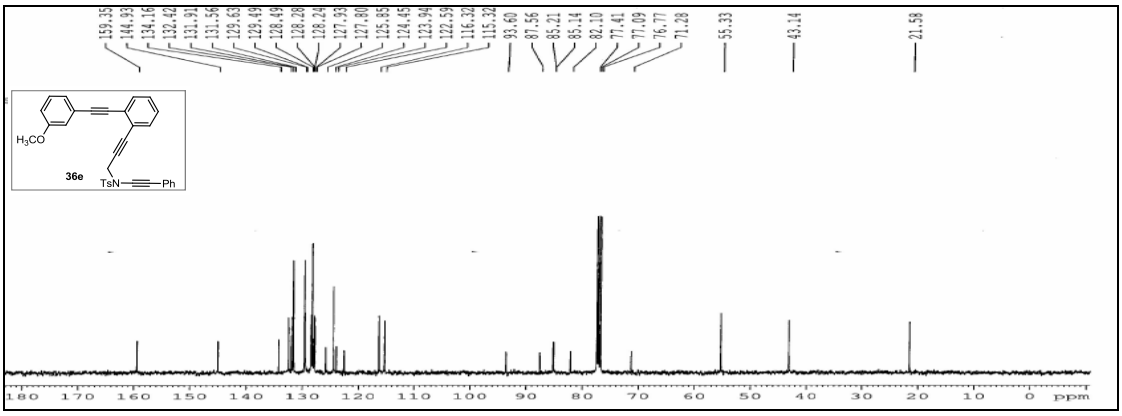
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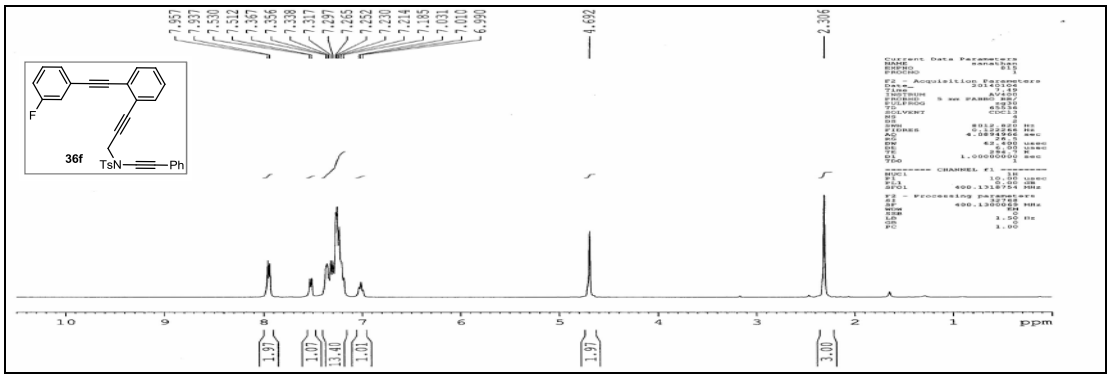
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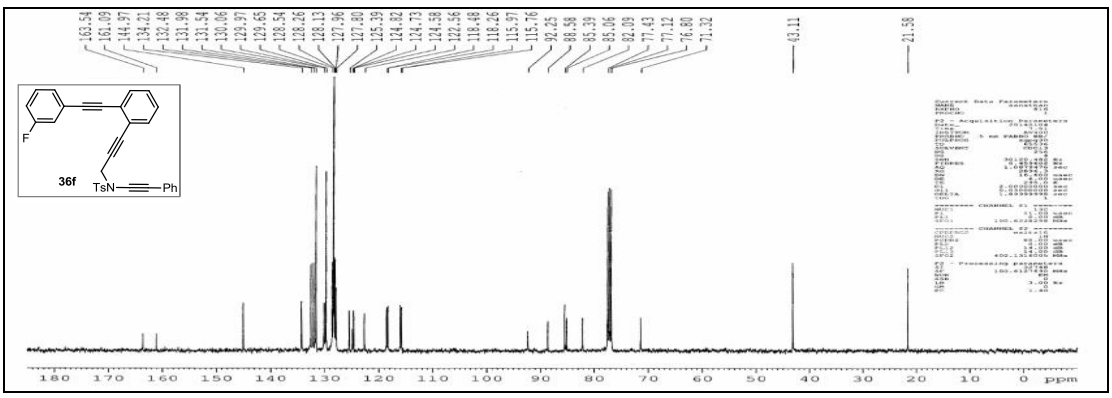
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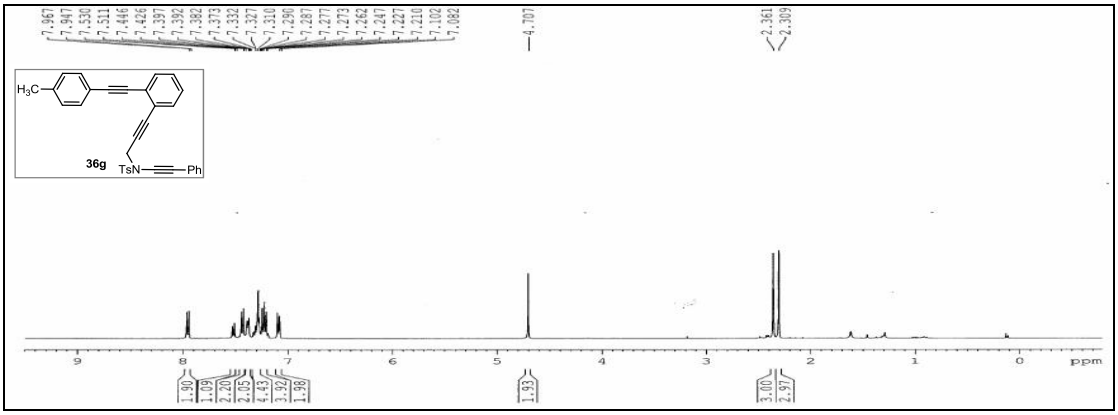
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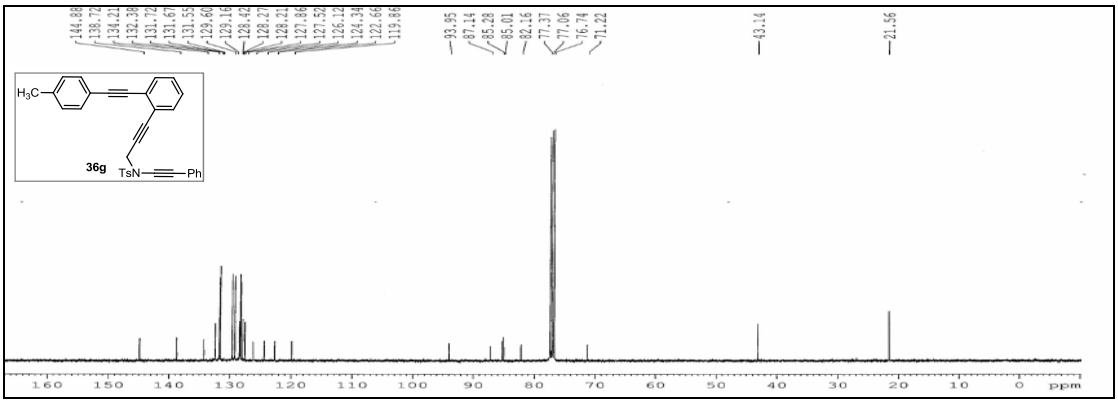
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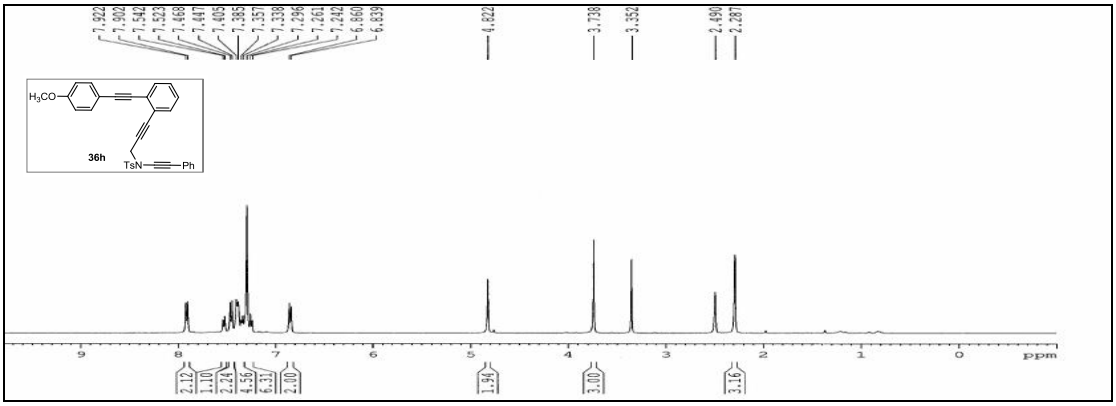
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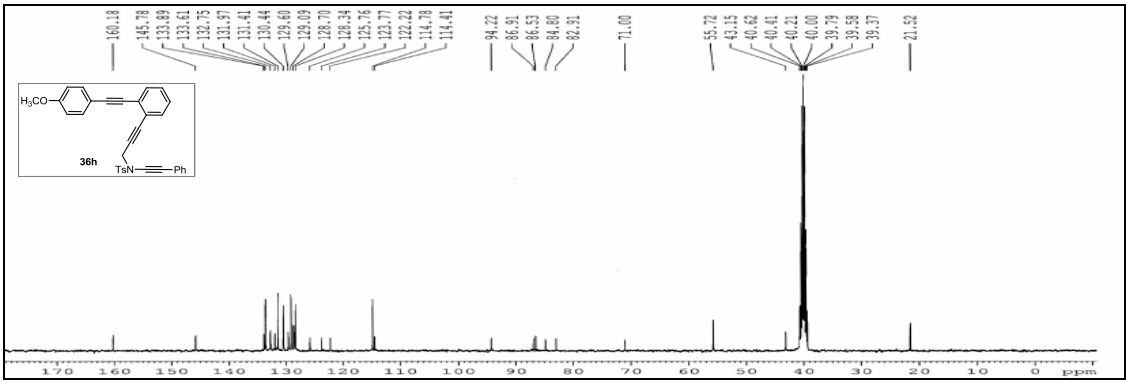
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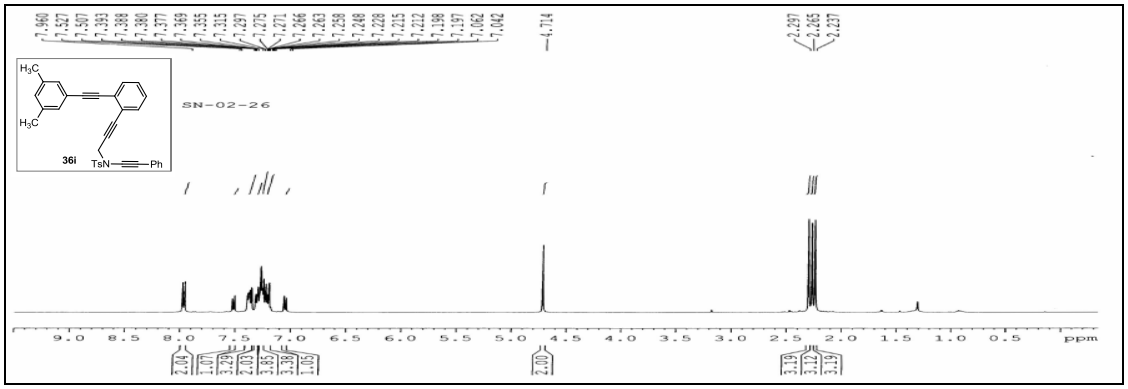
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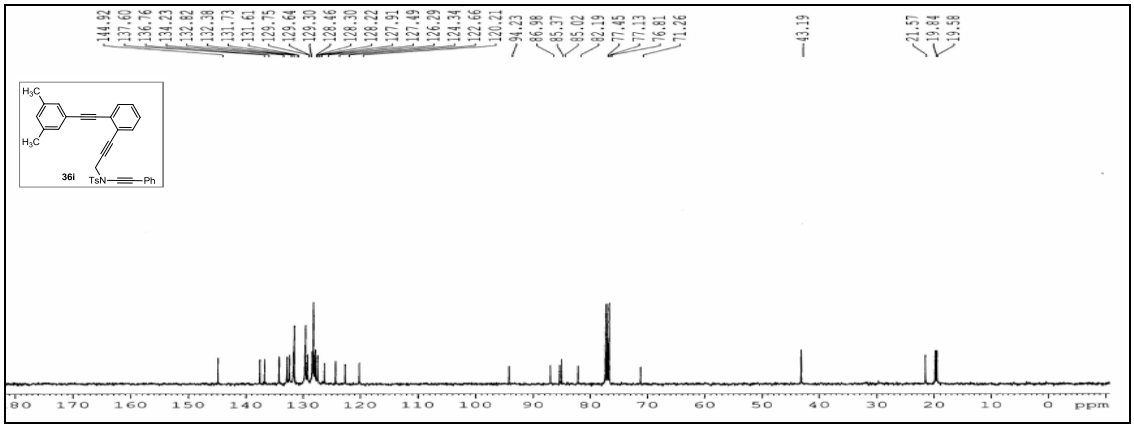
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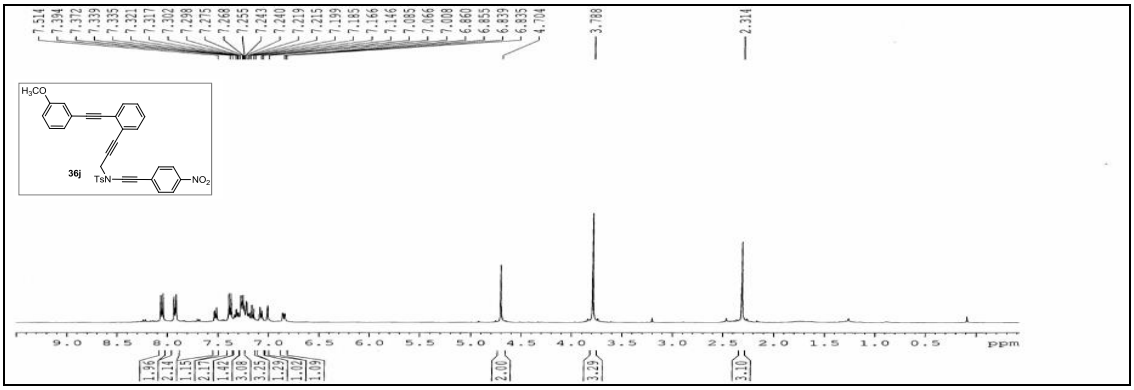
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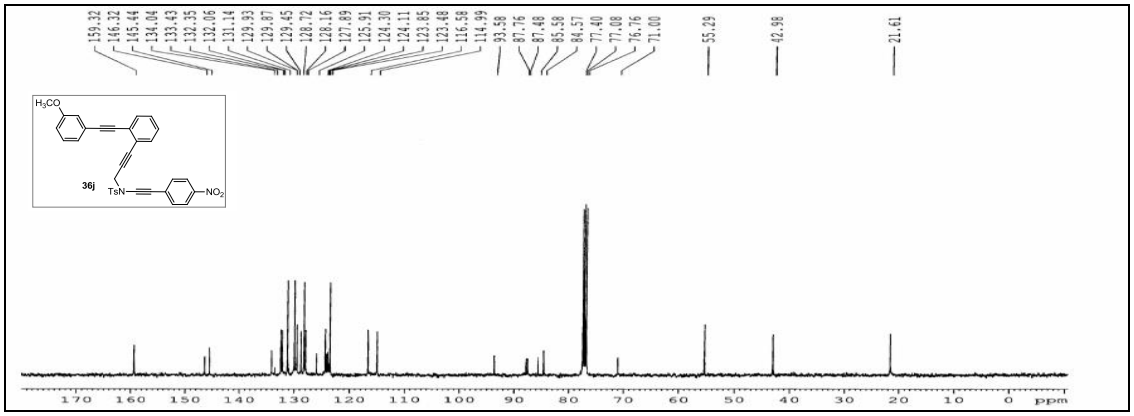
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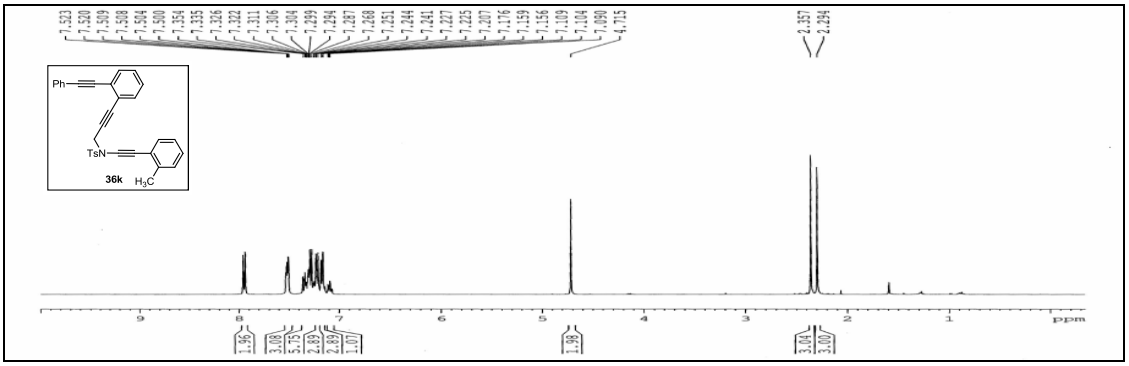
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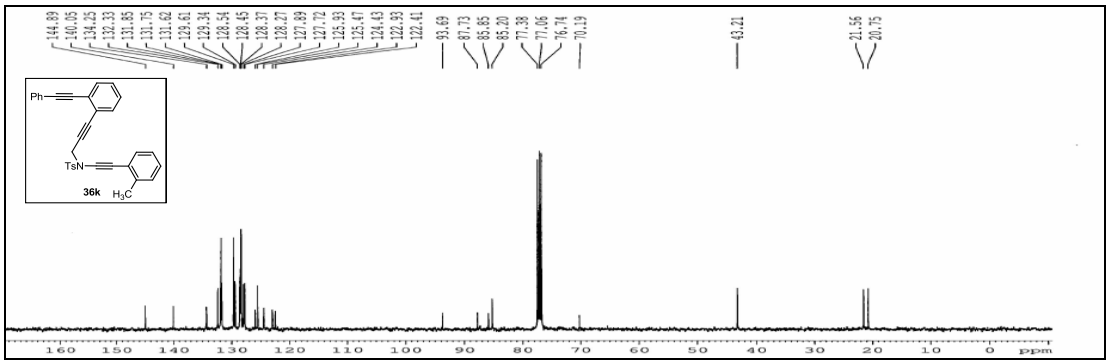
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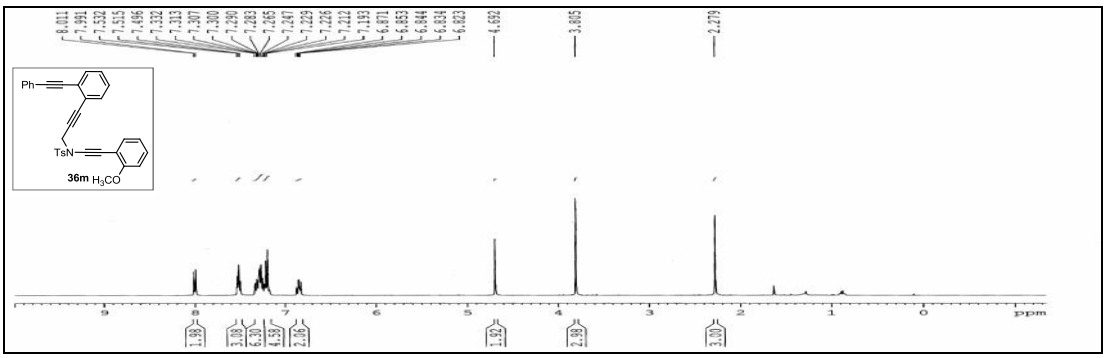
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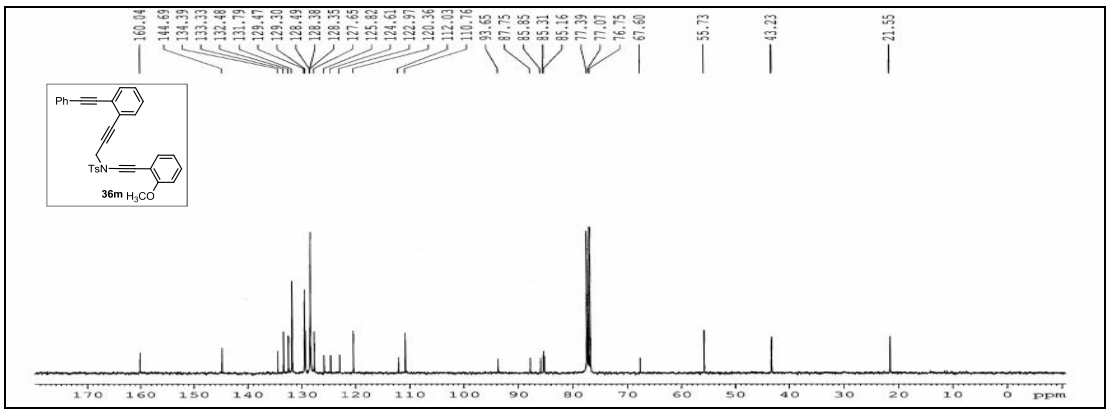
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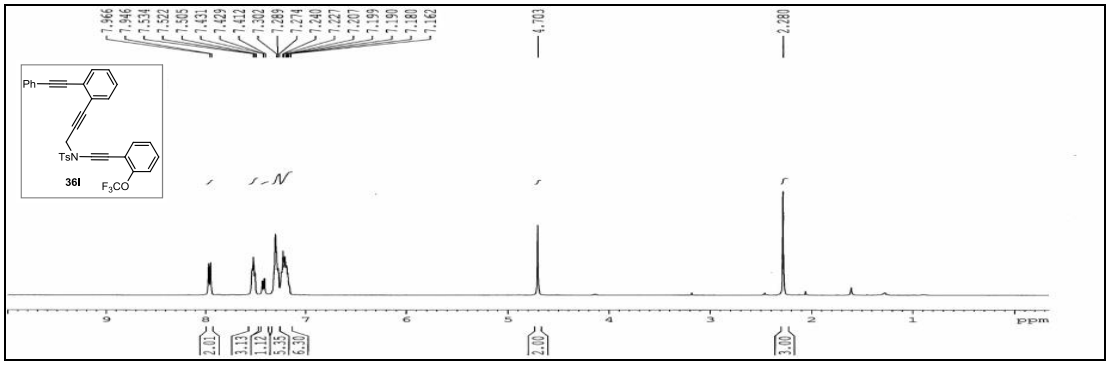
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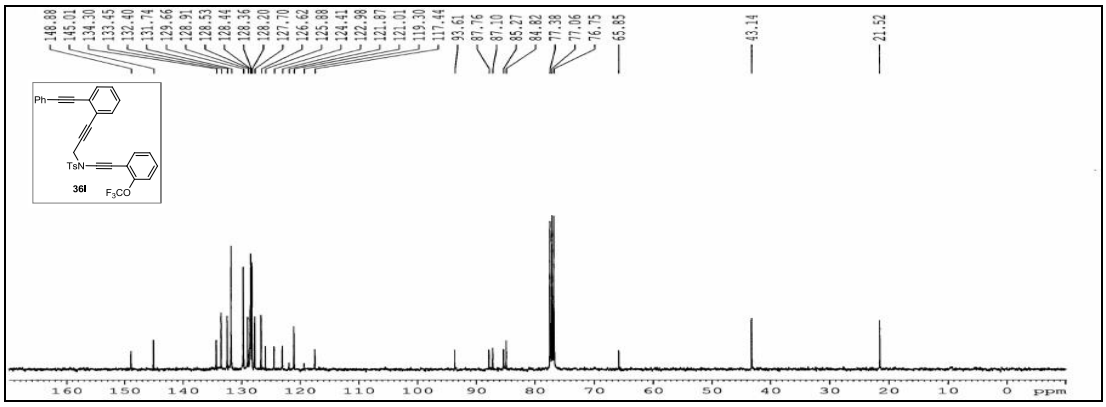
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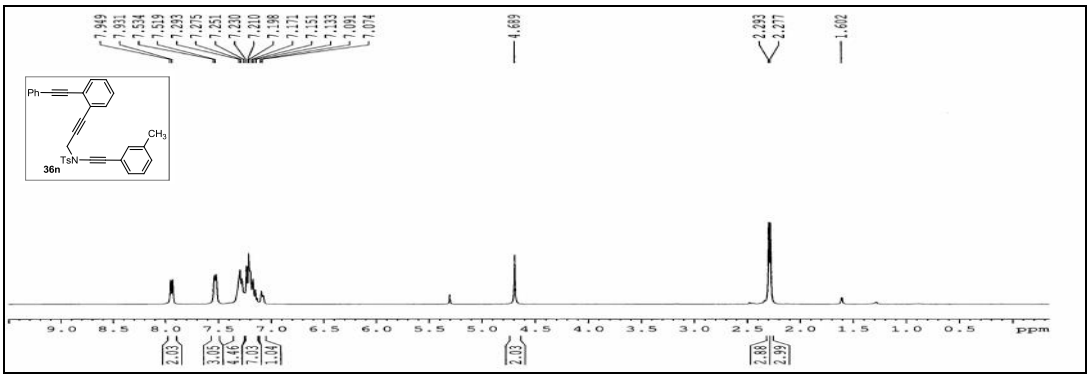
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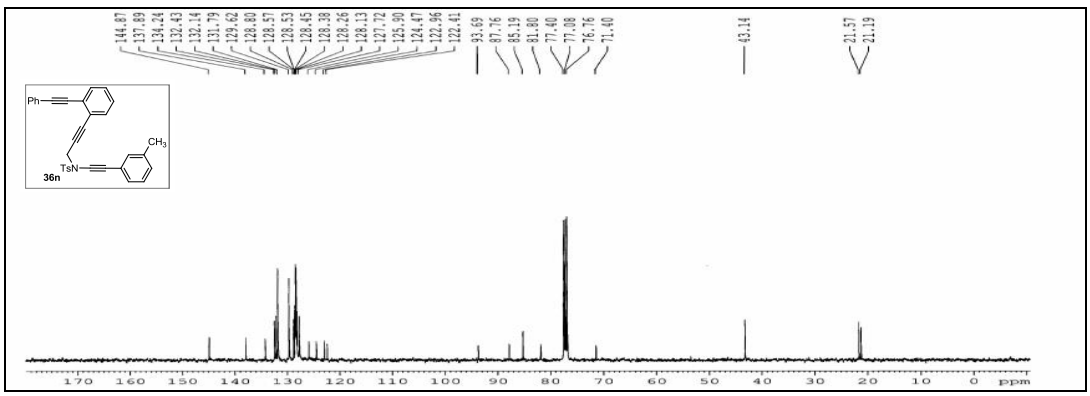
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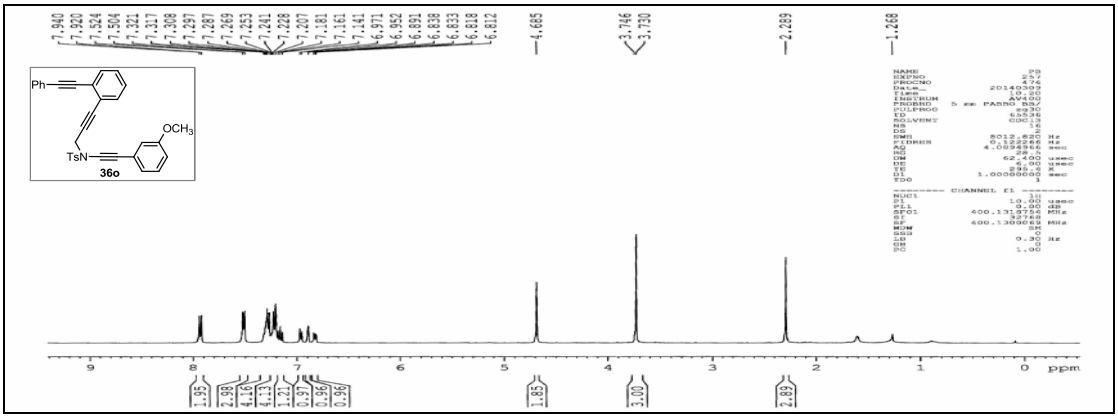
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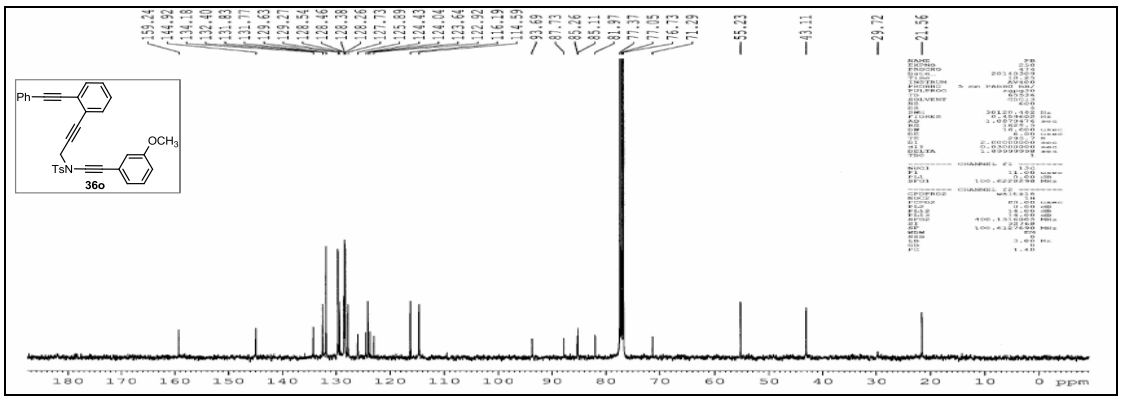
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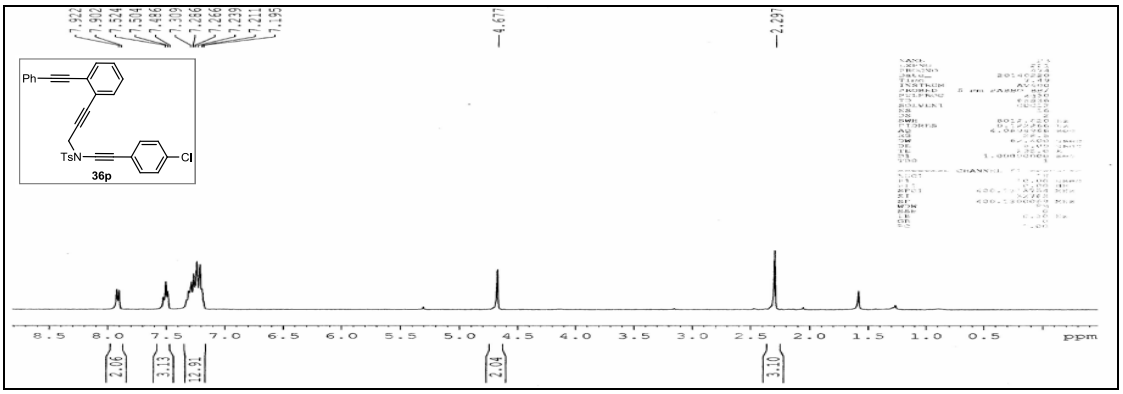
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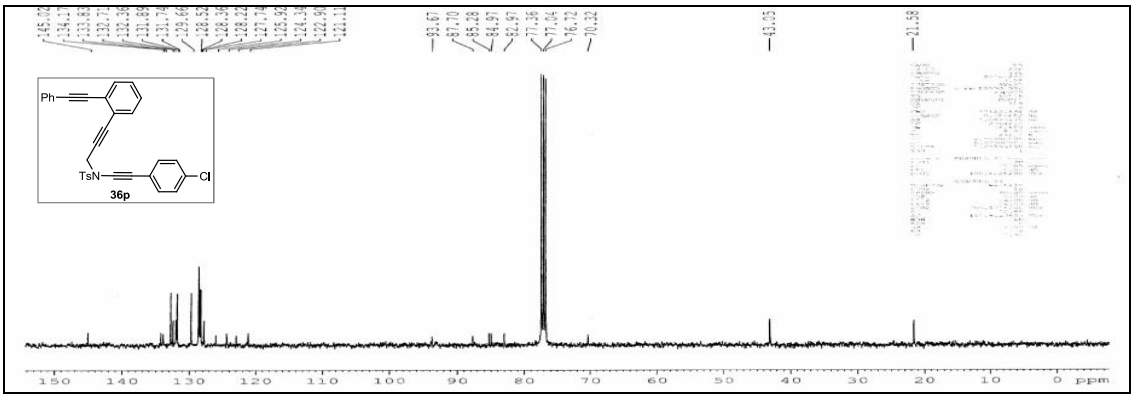
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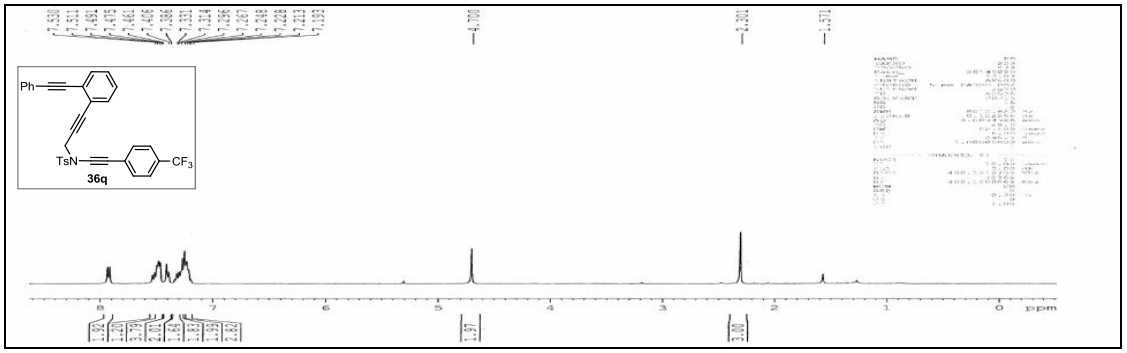
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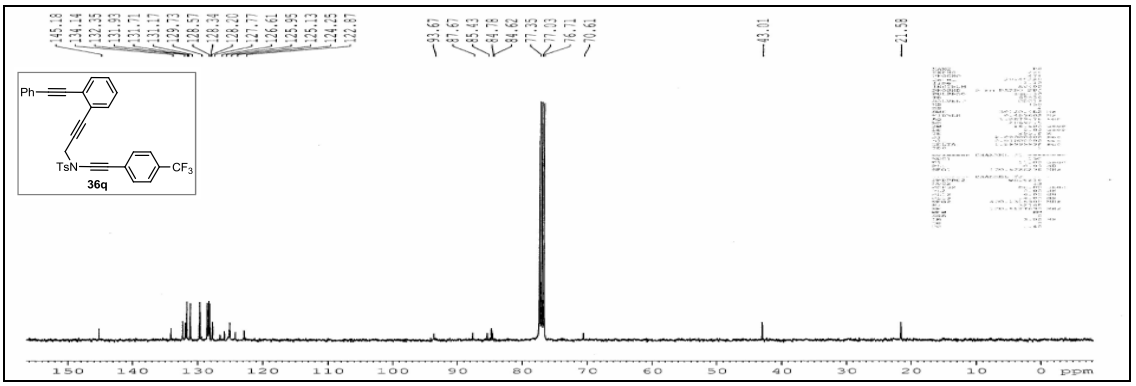
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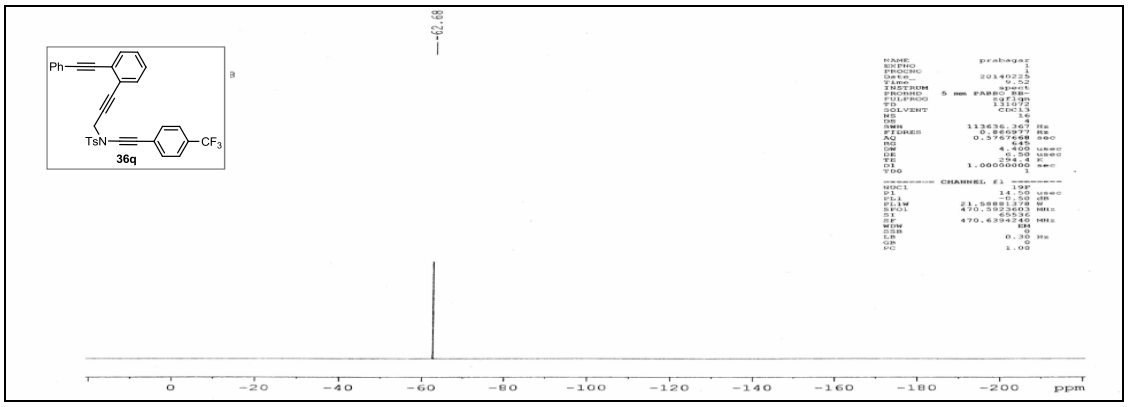
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CF3
36q
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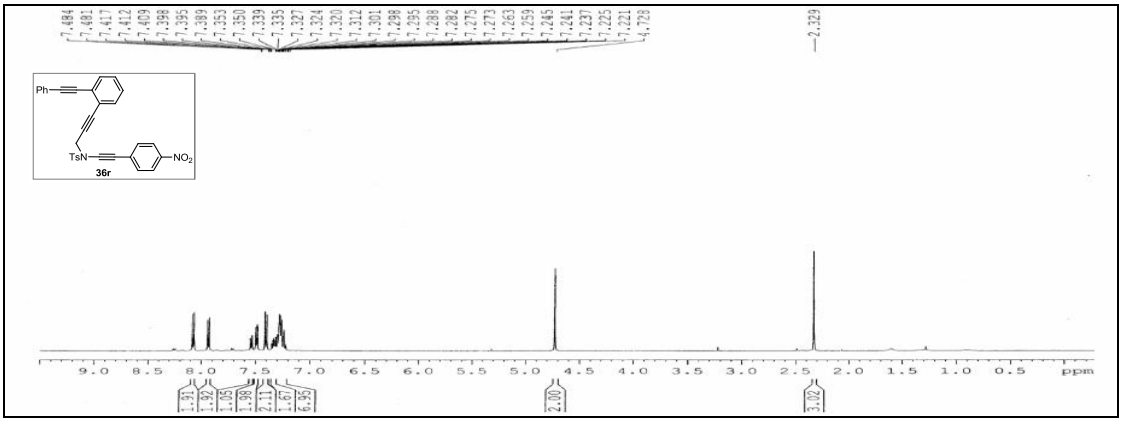
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NO2
36r
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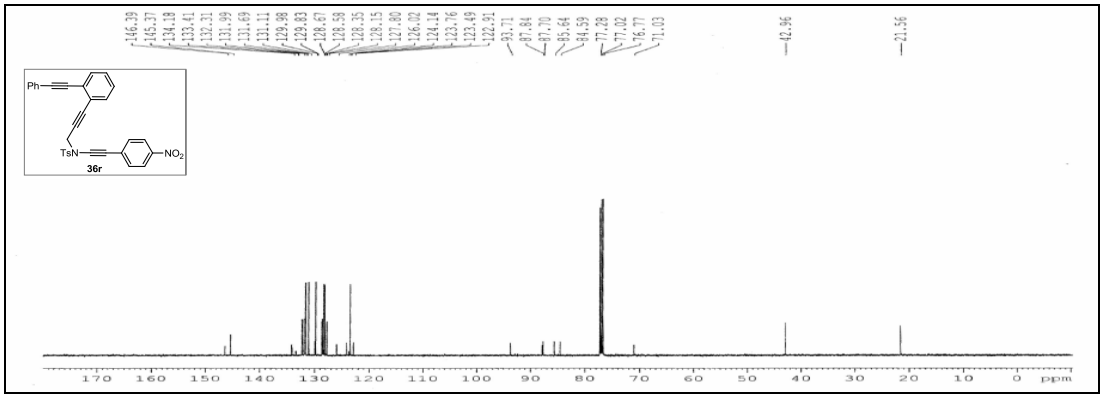
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NO2
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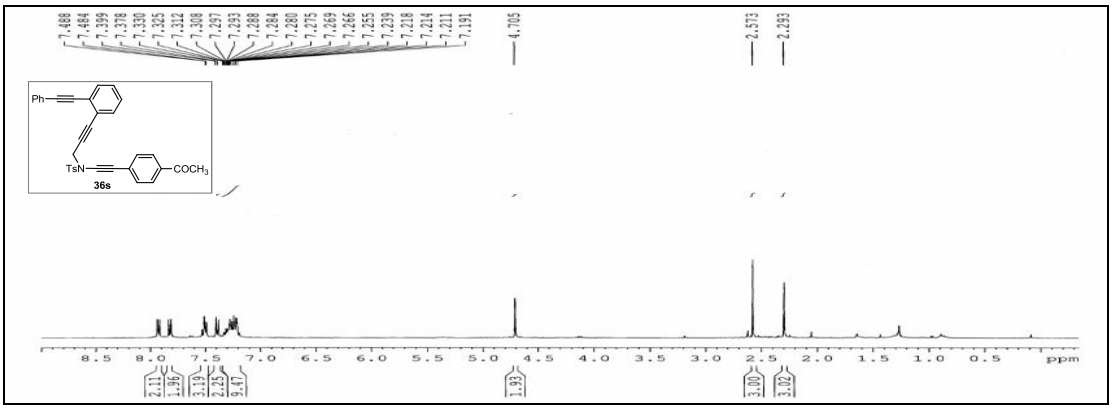
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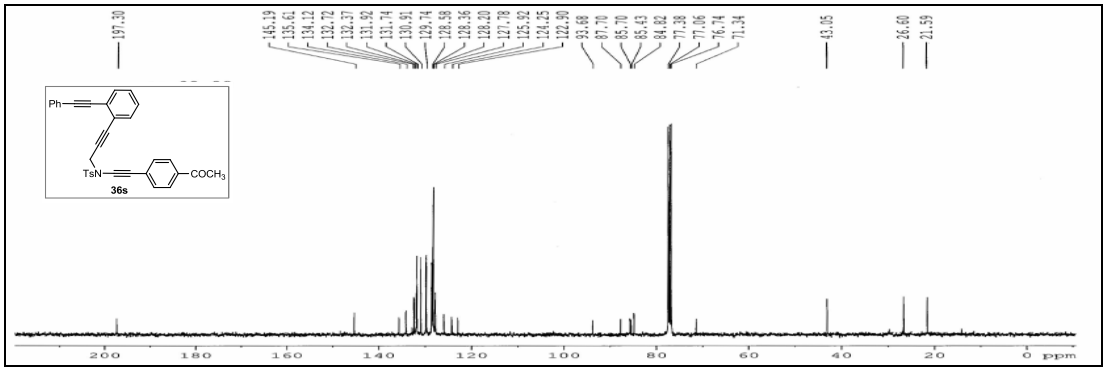
COCH3
36s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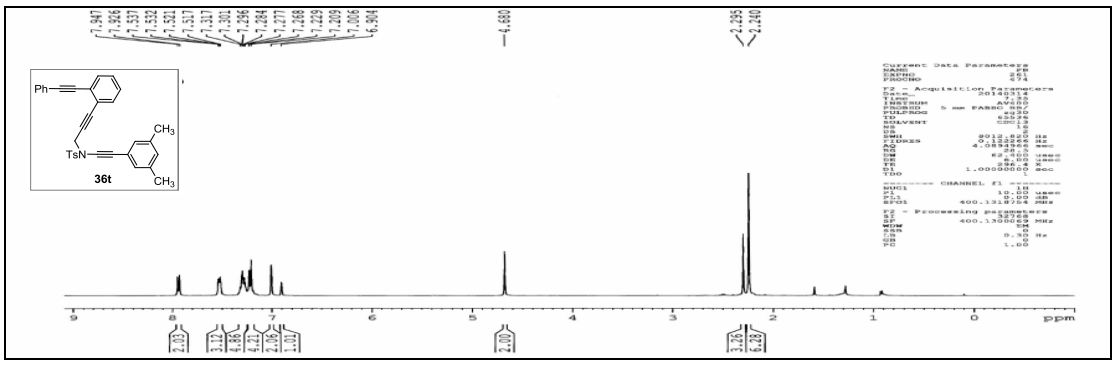
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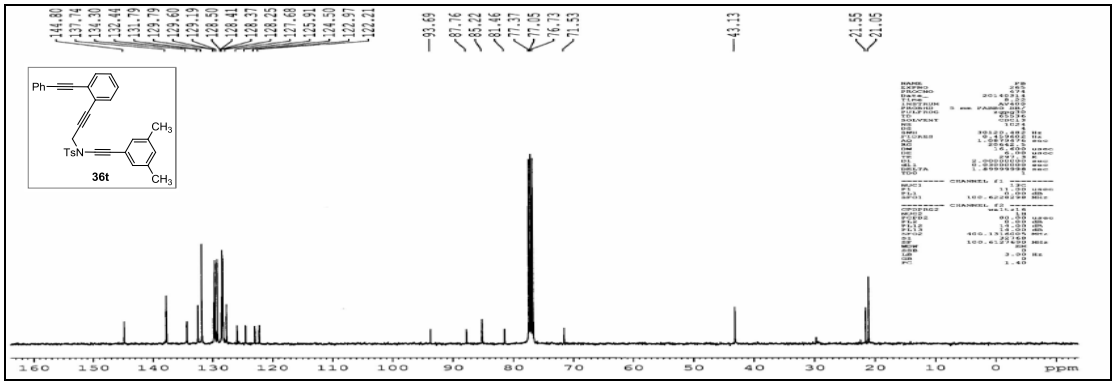
CH3
CH3
36t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CH3
CH3
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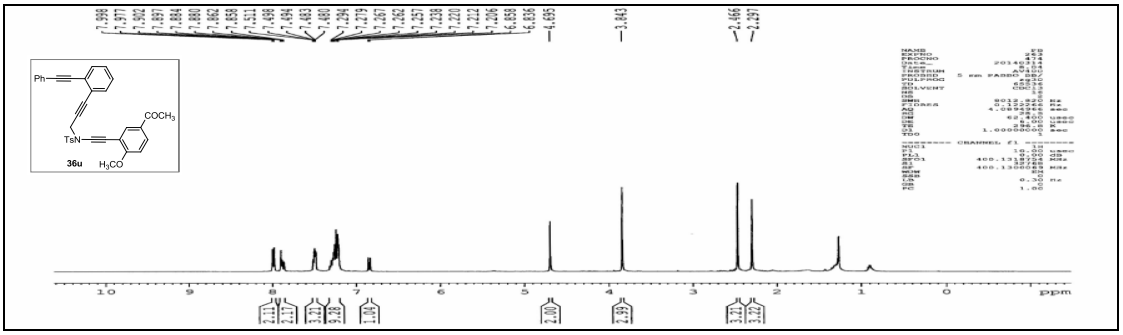
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H3CO
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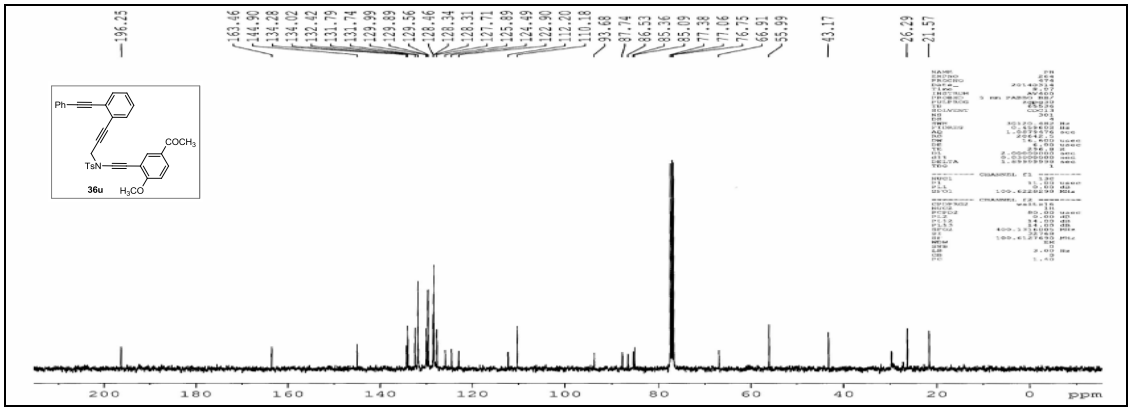
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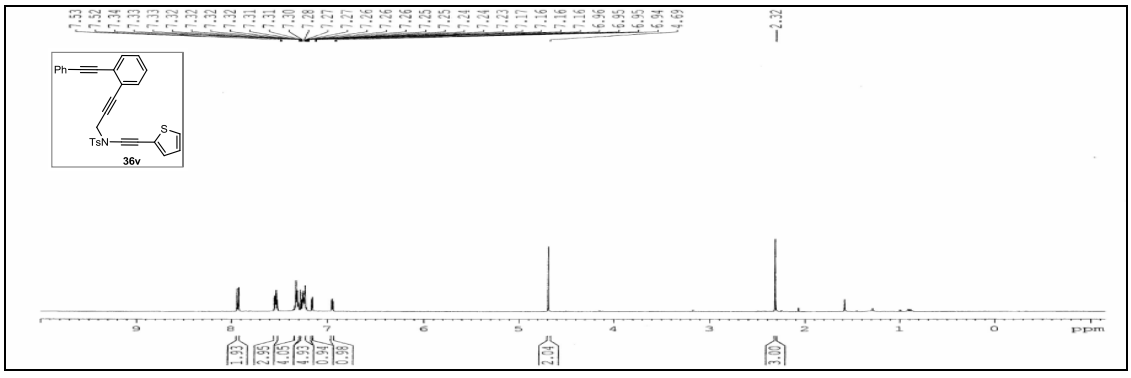
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S
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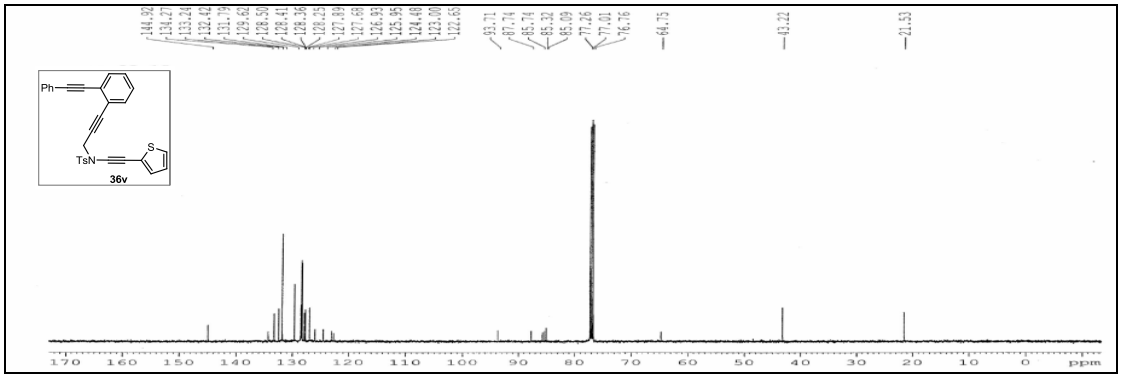
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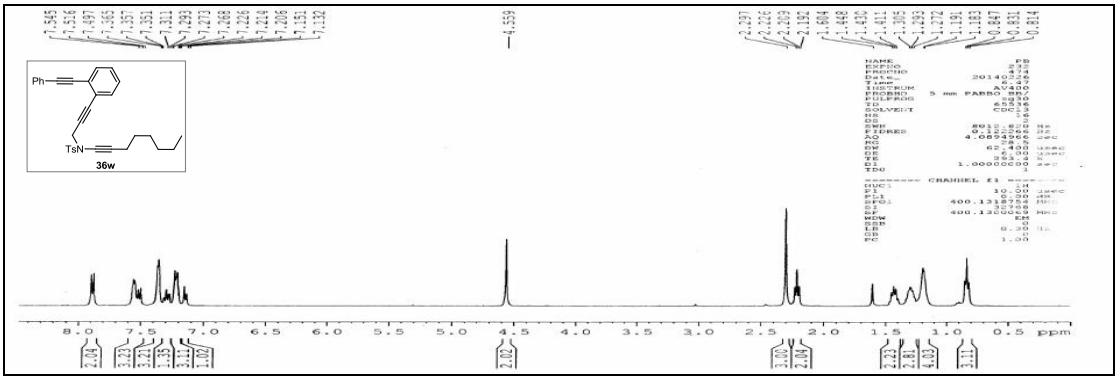
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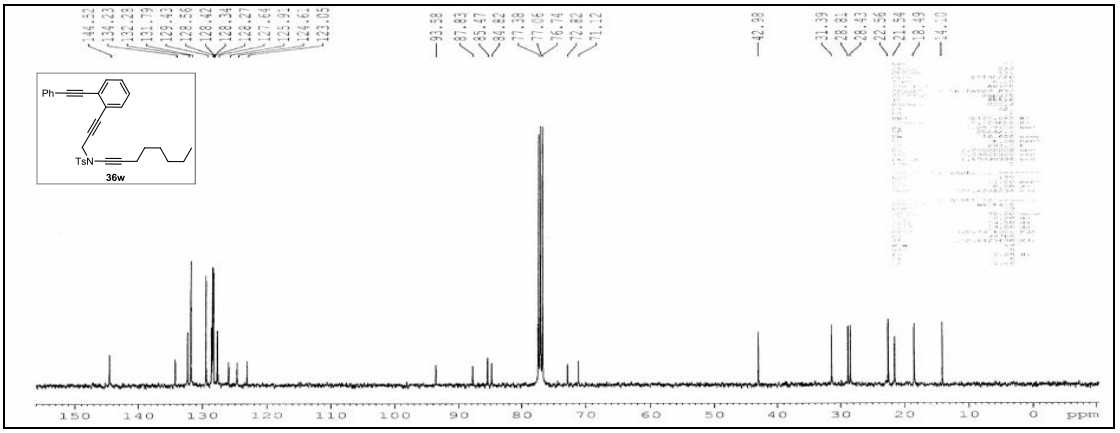
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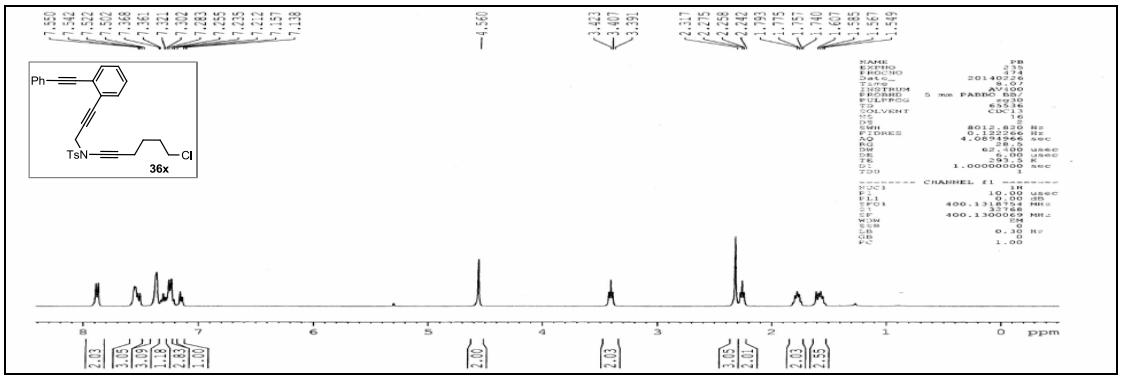
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TsN
Cl
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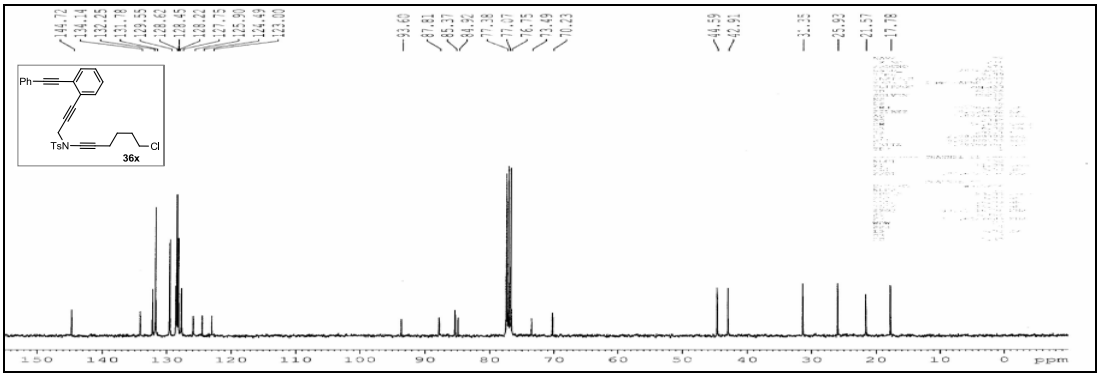
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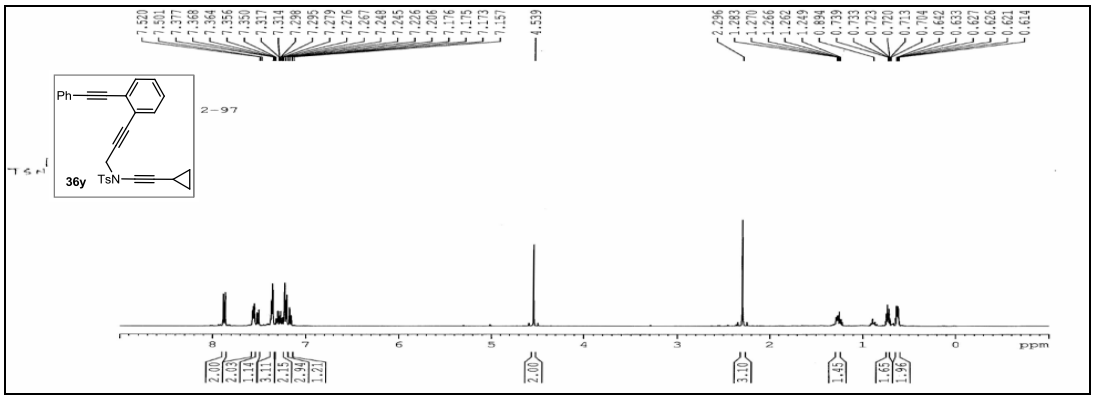
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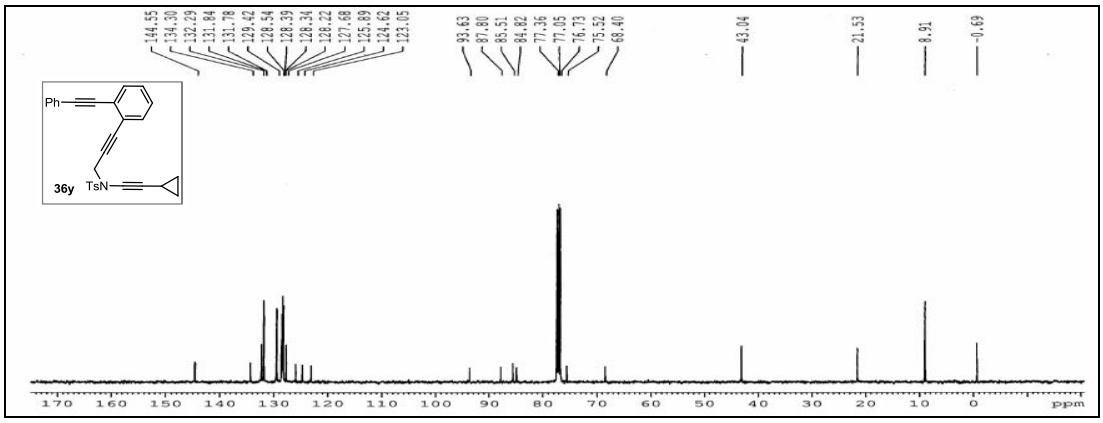
TsN
36y
2-97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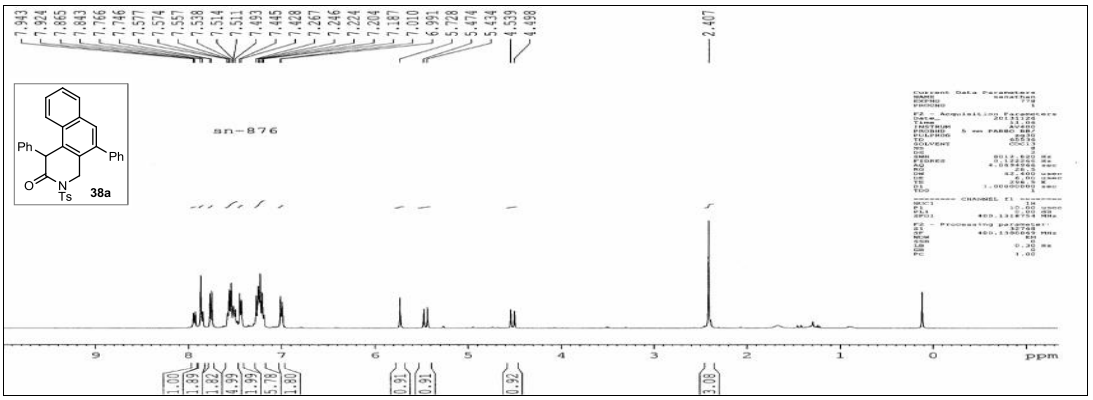
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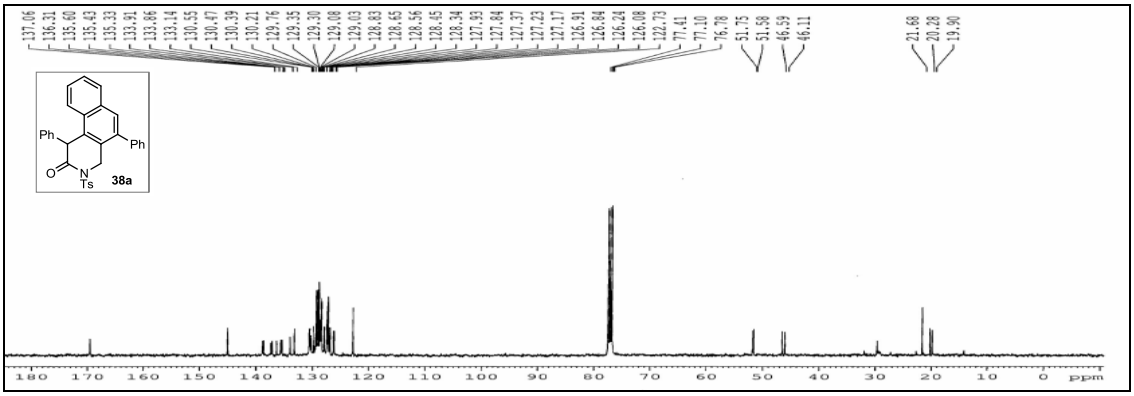
Ph
O
N
Ts
38a
sn-876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Ph
O
N
Ts
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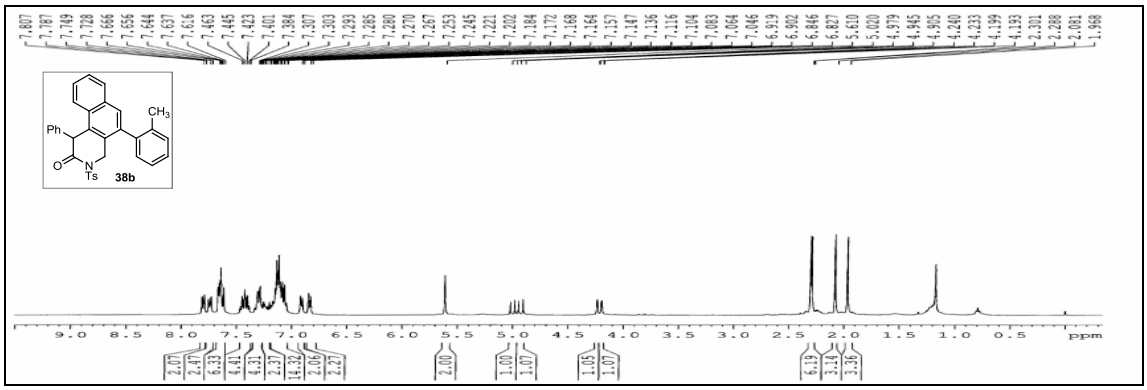
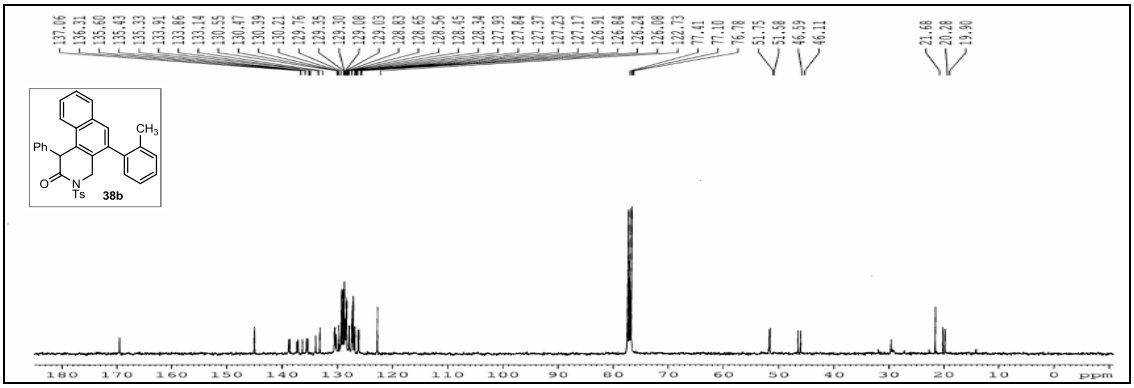

Ph
CH3
O
N
Ts
38b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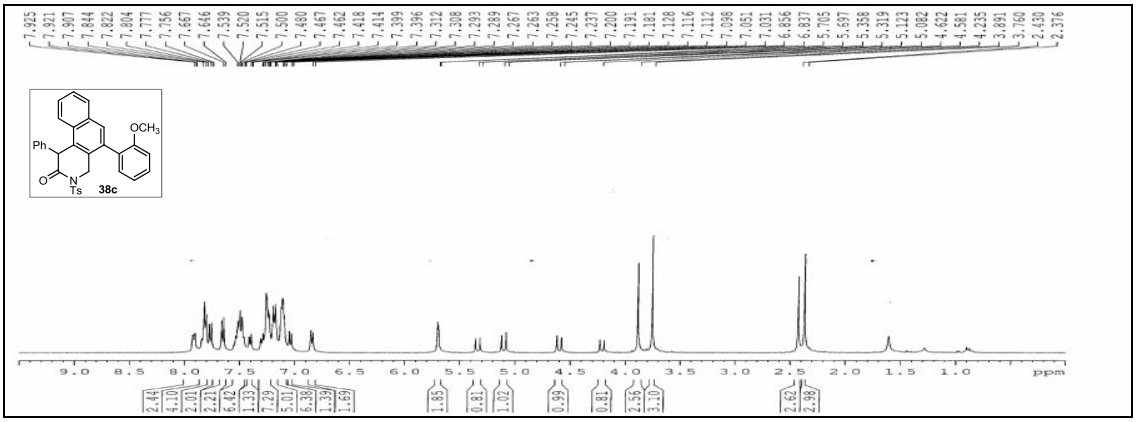
CH3
O
N
Ts
38b


Ph
OCH3
O
N
Ts
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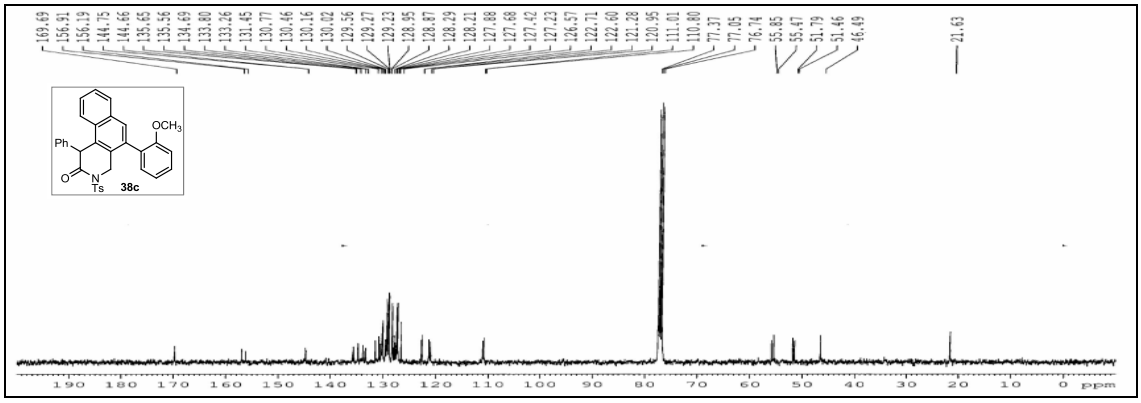
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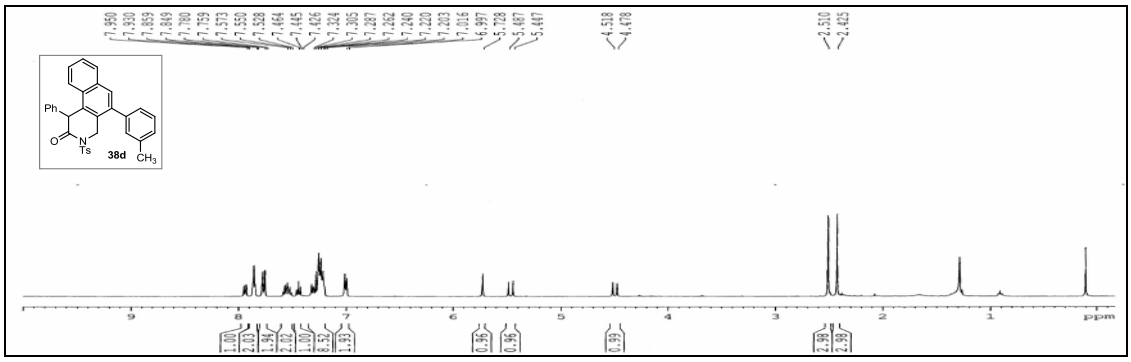
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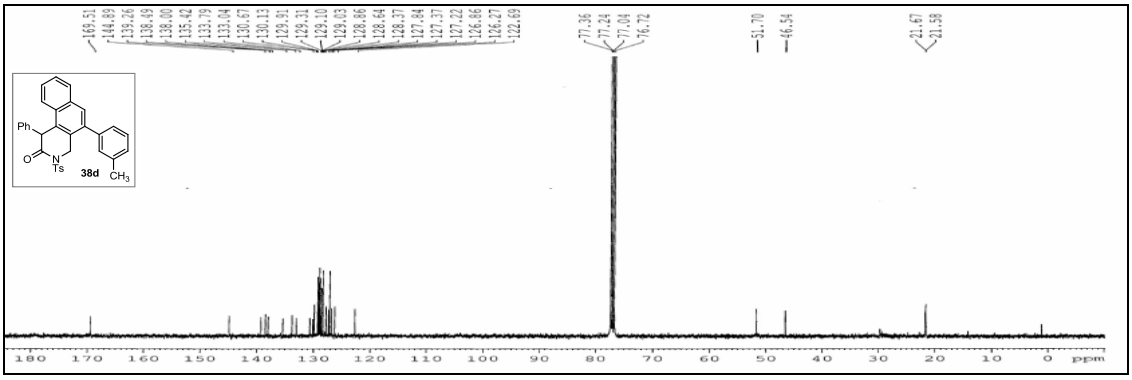
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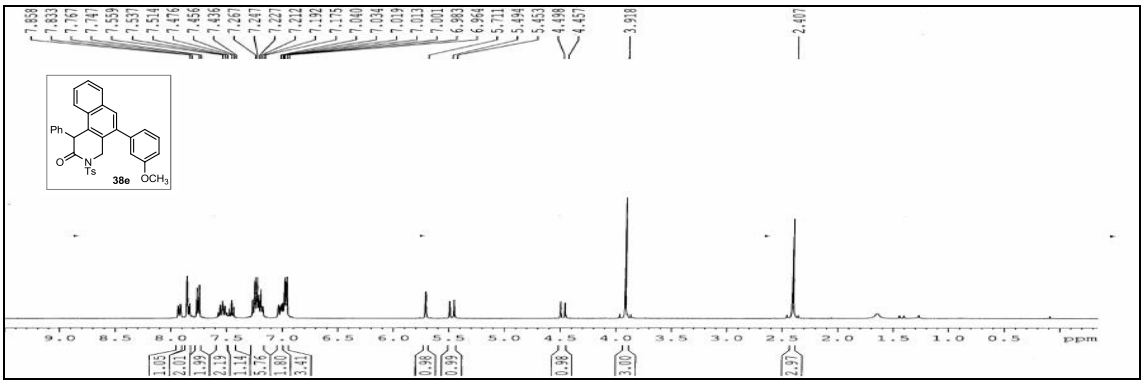
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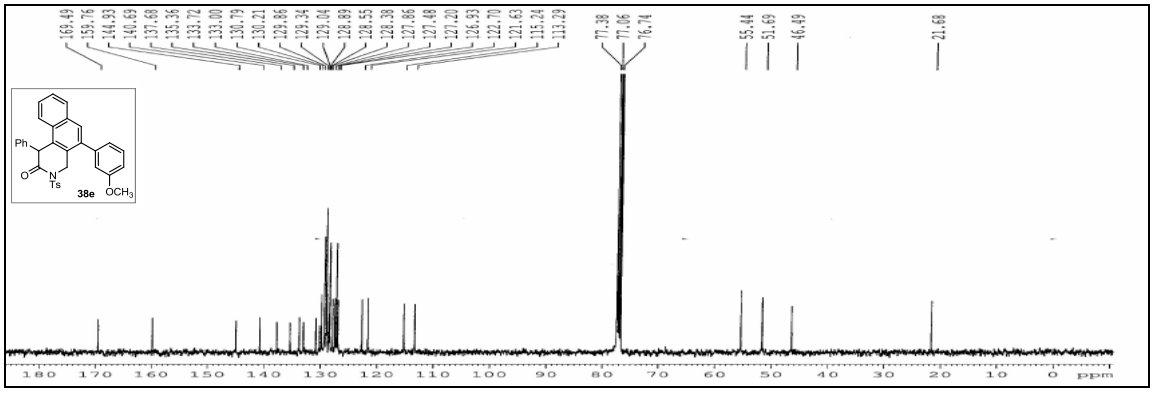
169.49
159.76
144.93
140.69
137.68
135.36
133.72
133.00
130.79
130.21
129.86
129.34
129.04
128.89
128.55
128.38
127.86
127.48
127.20
126.93
122.70
121.63
115.24
113.29
77.38
77.06
76.74
55.44
51.69
46.49
21.68
Ph
N
Ts
OCH3
38e
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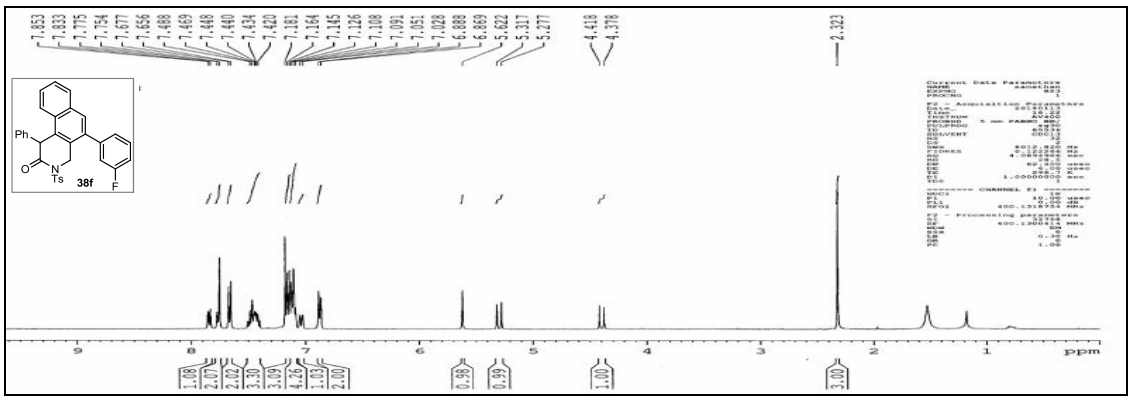
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7.775
7.754
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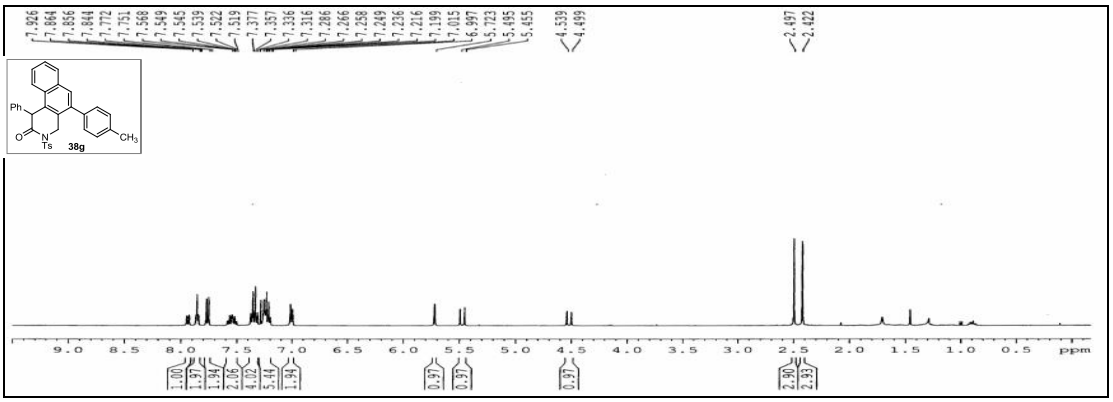
7.469
7.448
7.440
7.434
7.420
7.181
7.164
7.145
7.126
7.108
7.091
7.051
7.028
6.888
6.869
5.622
5.337
5.277
4.418
4.378
2.321
Ph
N
Ts
38f
F
9 8 7 6 5 4 3 2 1 ppm
1.08
2.07
2.02
3.30
3.09
4.26
1.03
2.00
0.98
0.99
1.00
3.00


-102.89
-102.98
-103.13
-103.23
-103.34
Ph
N
Ts
38f
F
0 -20 -40 -60 -80 -100 -120 -140 -160 -180 -200 ppm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7.856
7.844
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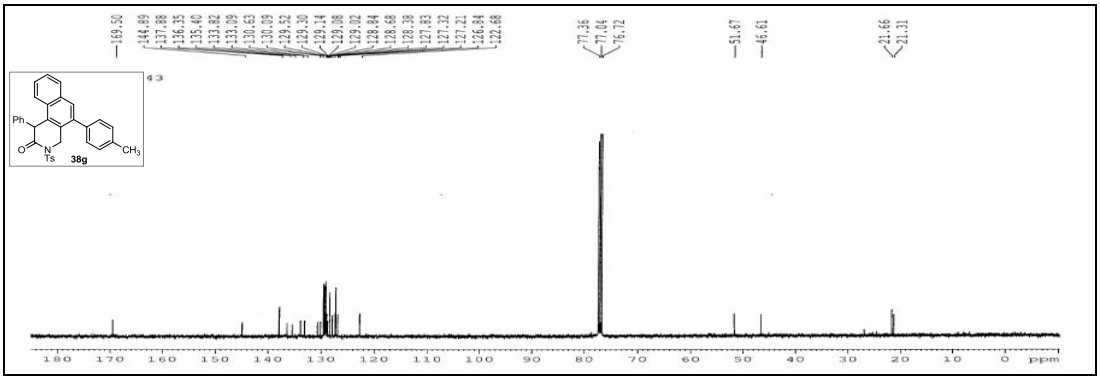
7.751
7.568
7.549
7.545
7.539
7.522
7.519
7.377
7.357
7.336
7.316
7.286
7.266
7.258
7.249
7.236
7.216
7.199
7.015
6.997
5.723
5.495
5.455
4.539
4.499
2.497
2.422
Ph
N
Ts
38g
CH3
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00
1.97
1.94
2.06
4.02
5.44
1.94
0.97
0.97
0.97
2.90
2.93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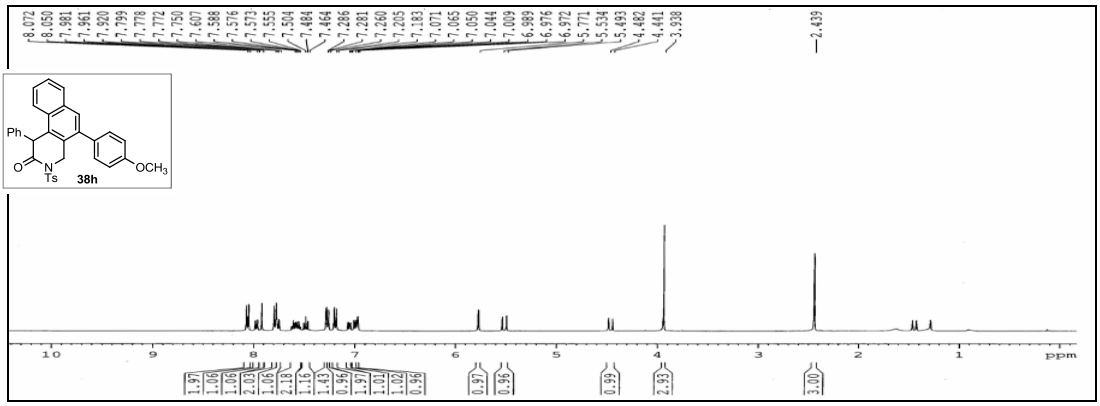
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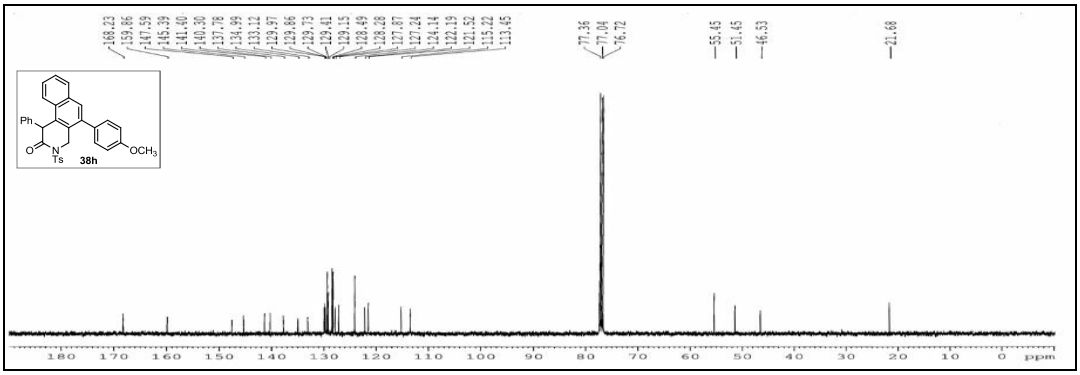
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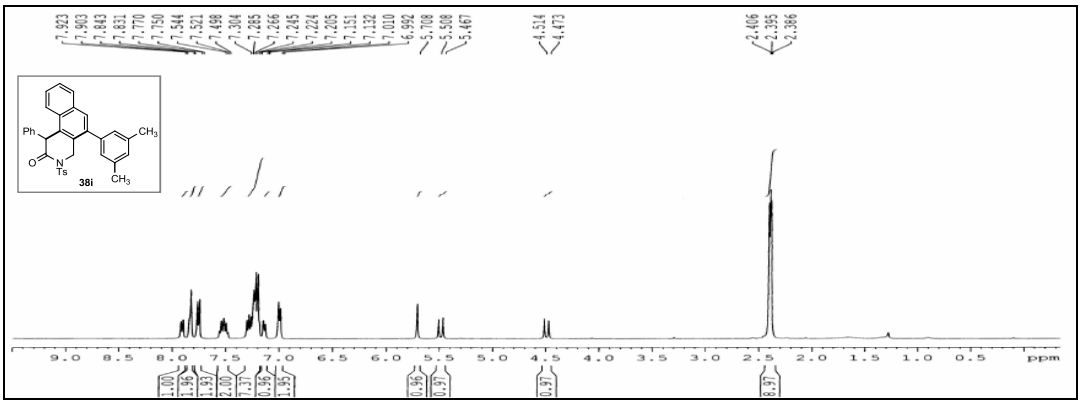
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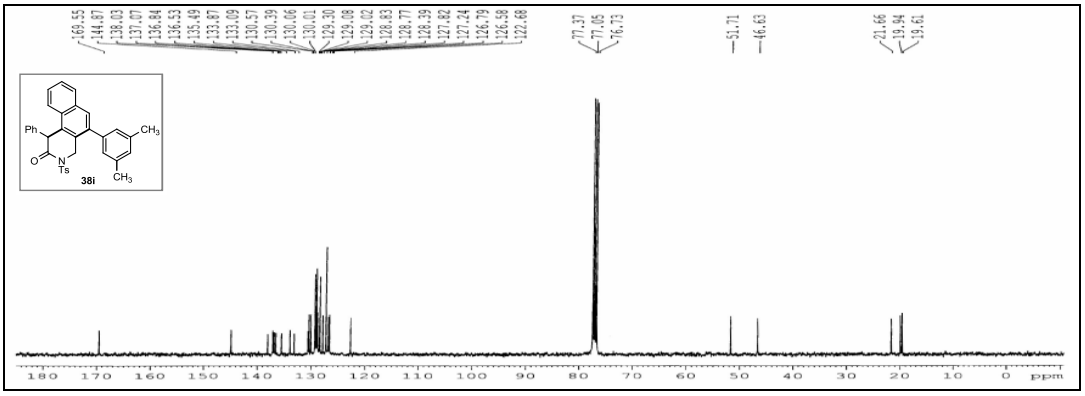
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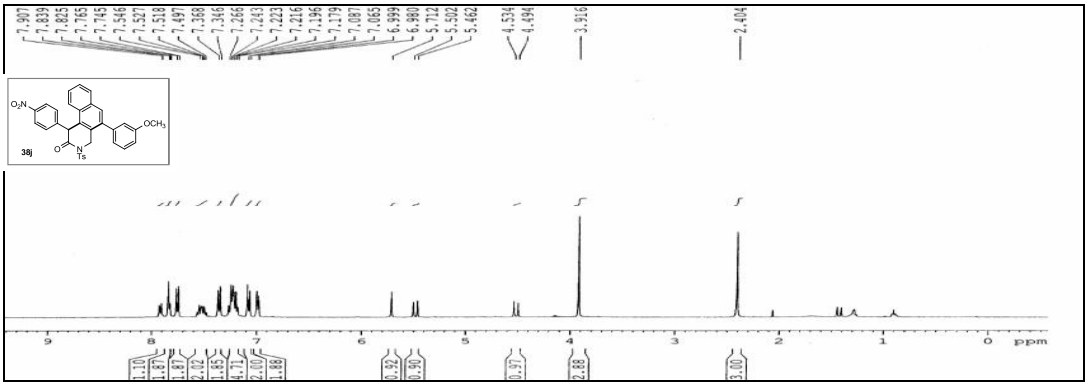
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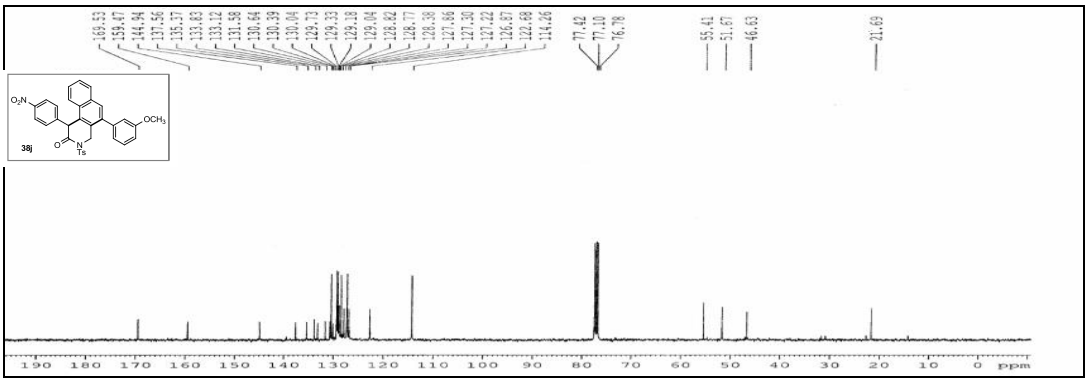
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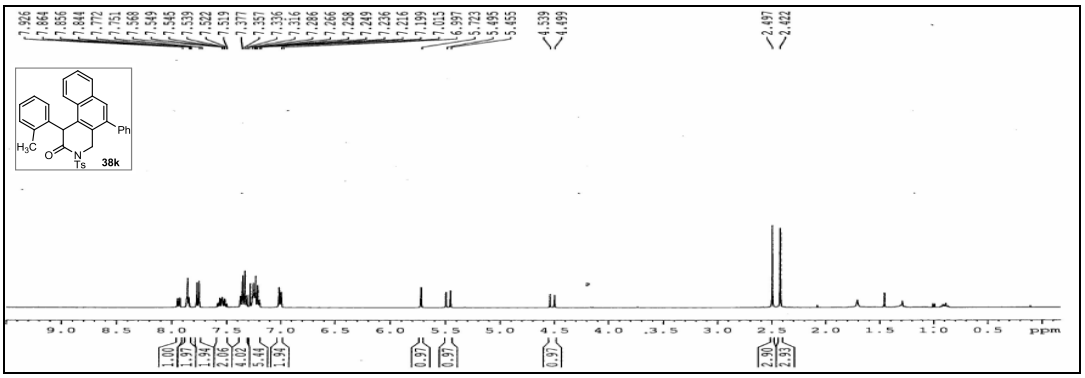
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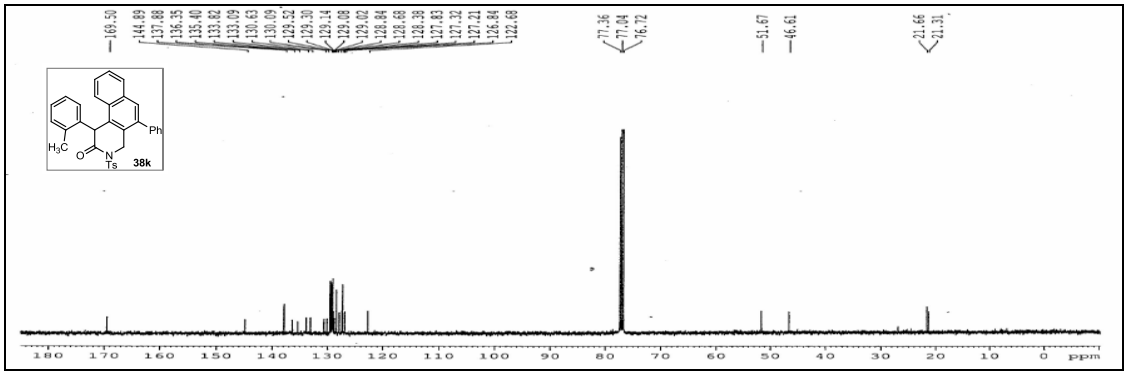
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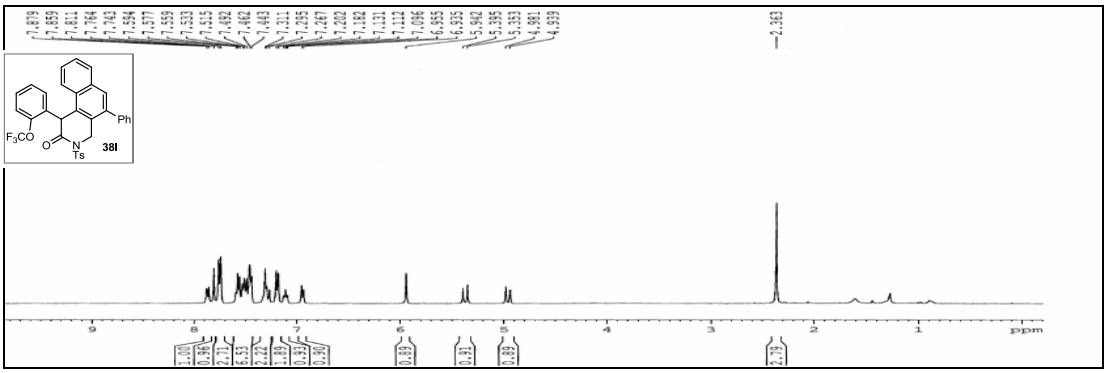
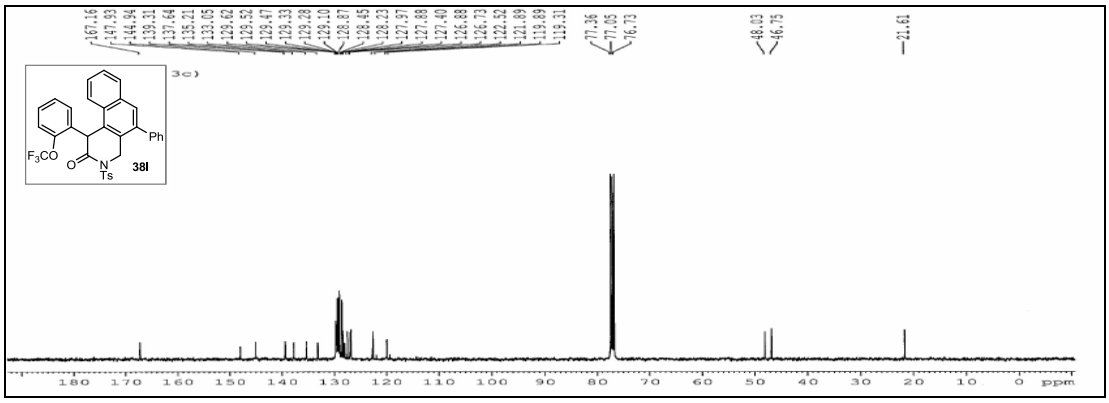

38l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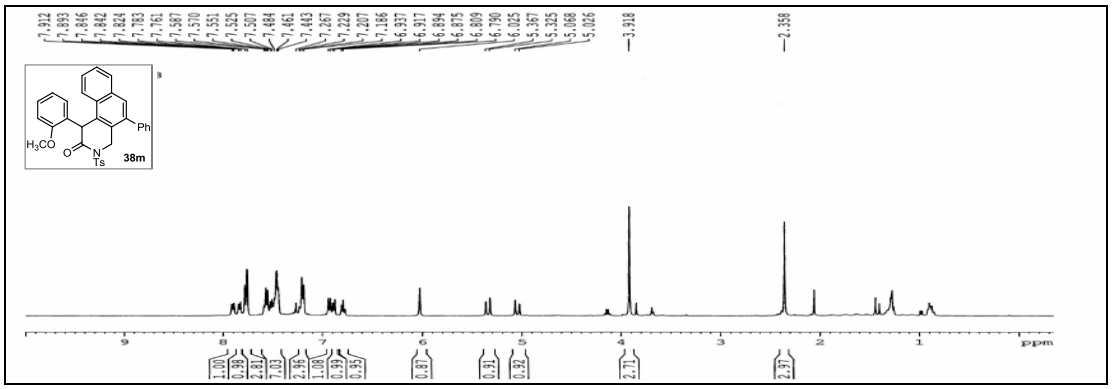
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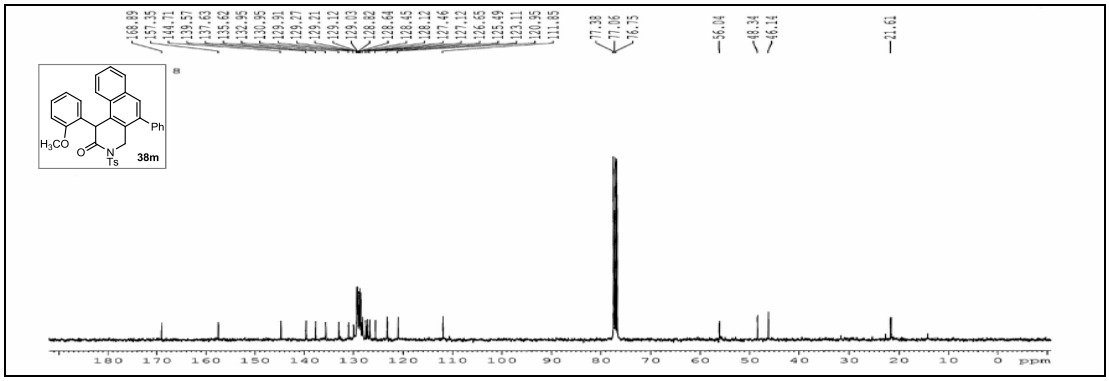
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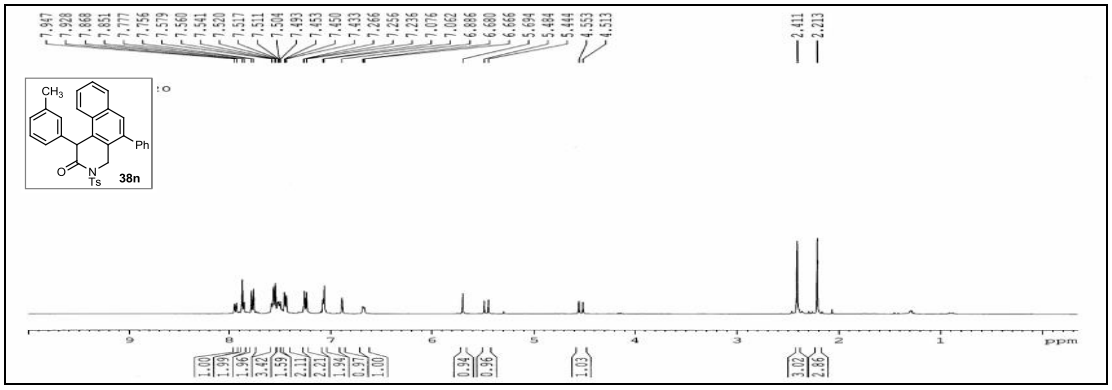
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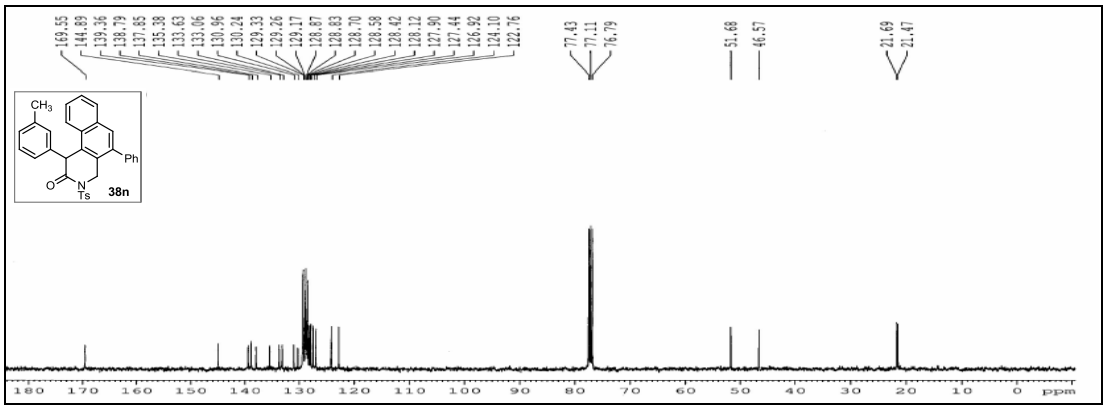
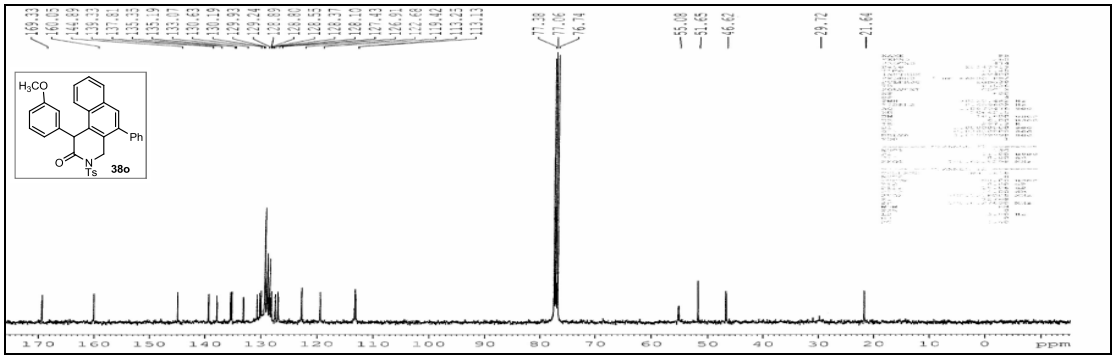
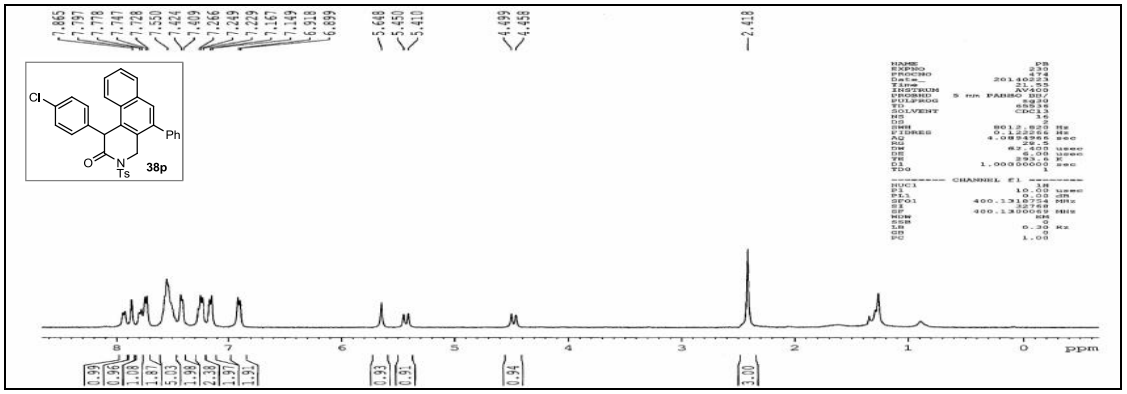
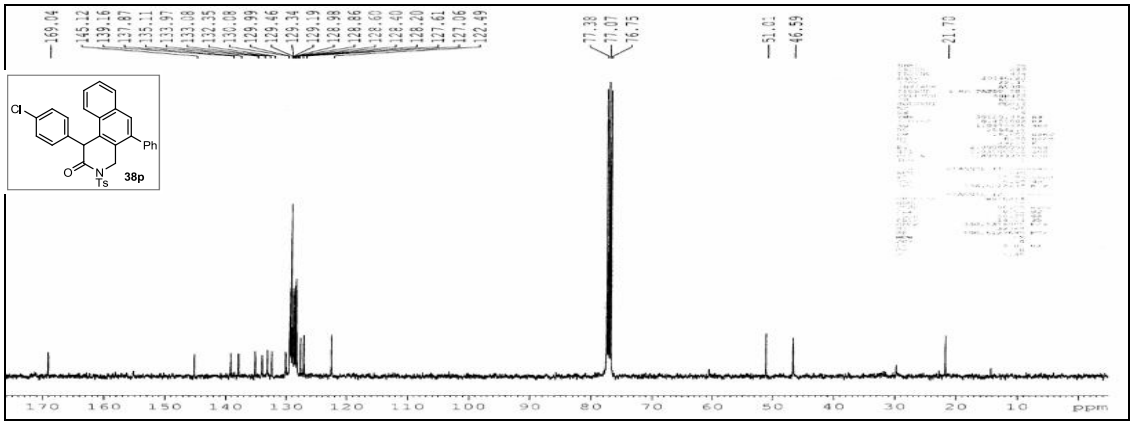

38n


38o


H3CO
Ph
O
N
Ts
38o


Cl
Ph
O
N
Ts
38p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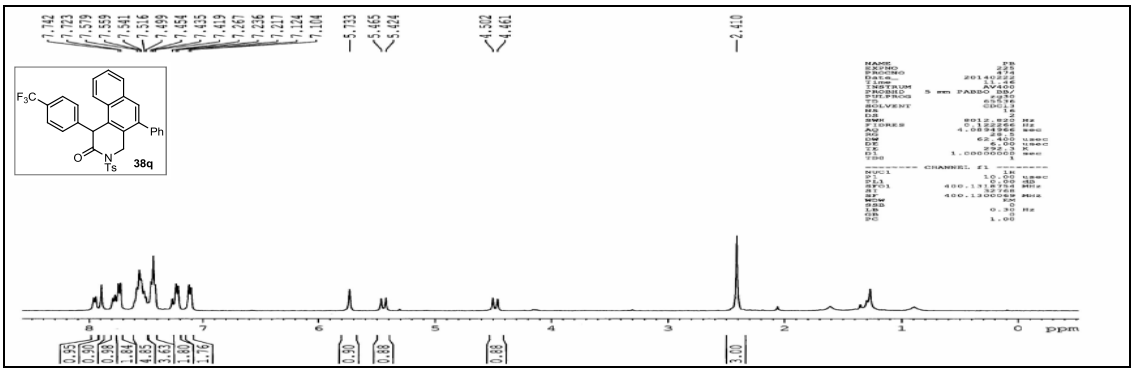
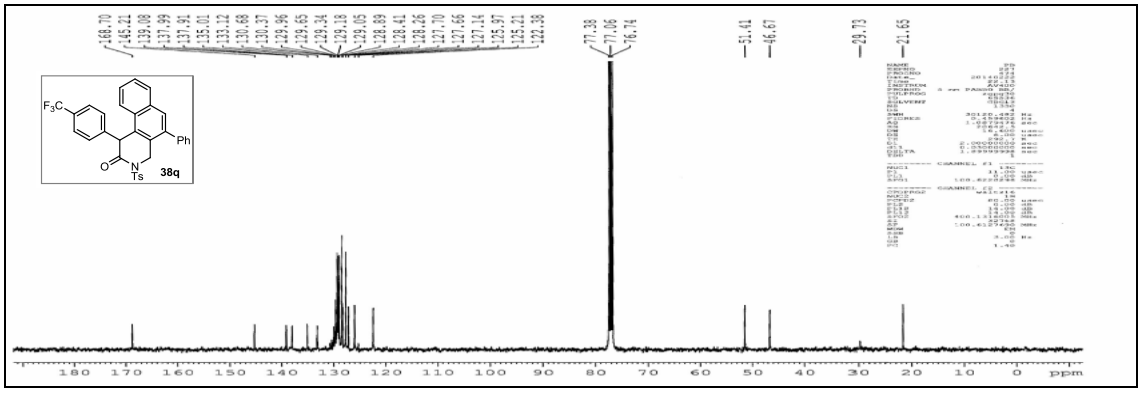
Ph
O
N
Ts
38p


F3C
Ph
O
N
Ts
38q


F3C
Ph
O
N
Ts
38q
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145.21
139.08
137.99
137.91
135.01
133.12
130.68
130.37
129.96
129.65
129.34
129.18
129.05
128.89
128.41
128.26
127.70
127.66
127.14
125.97
125.21
122.38
77.38
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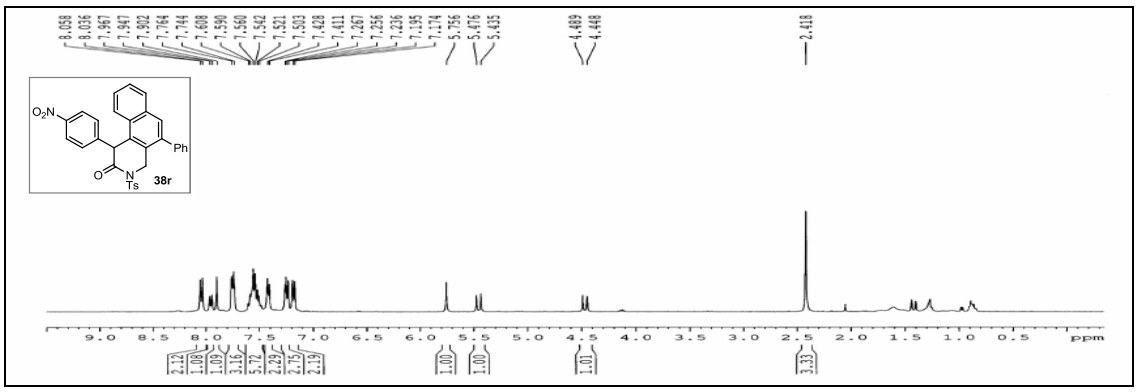
76.74
51.41
46.67
29.73
21.65
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


O2N
Ph
O
N
Ts
38r
8.058
8.056
7.967
7.947
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7.764
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7.608
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7.542
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7.411
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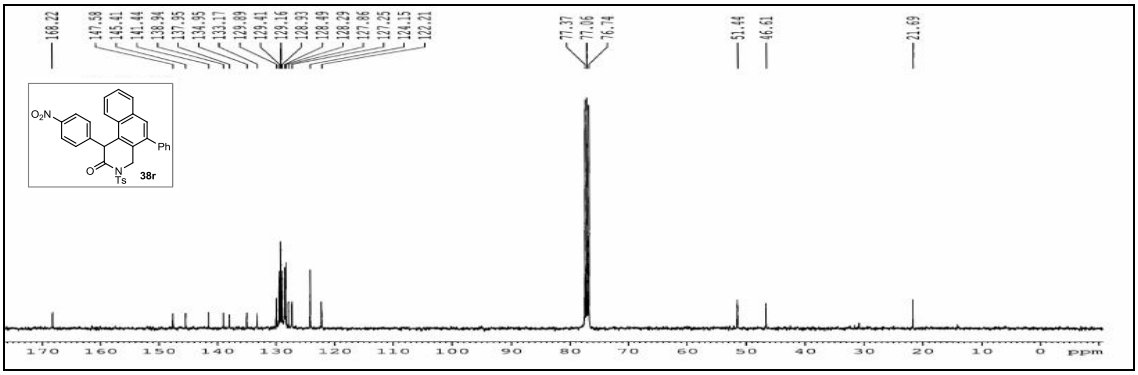
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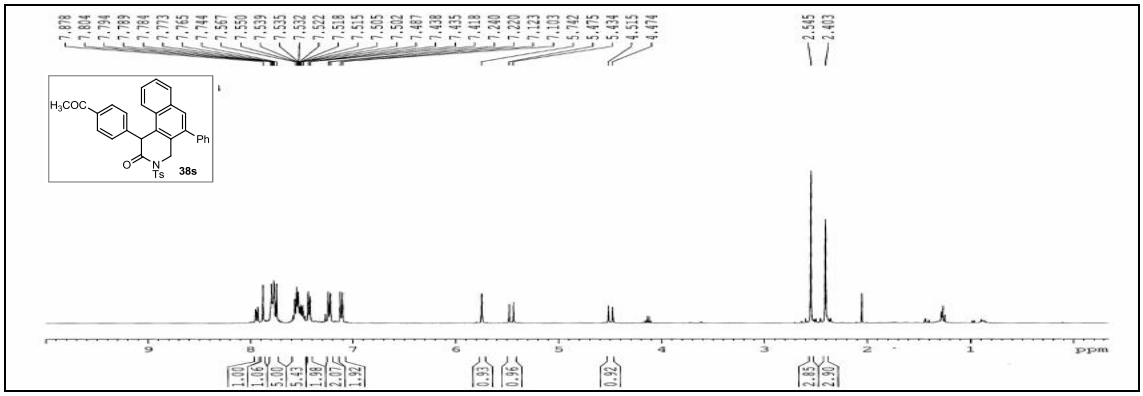
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7.435
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7.280
7.220
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5.434
4.515
4.474
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2.493
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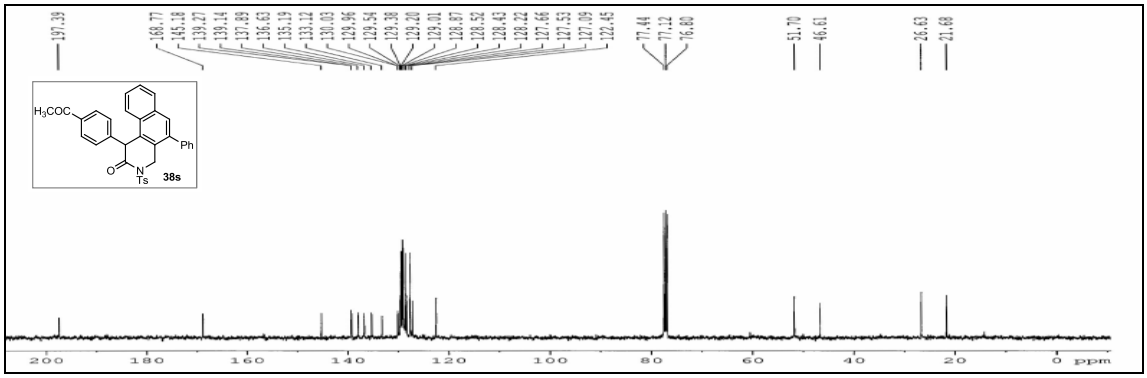
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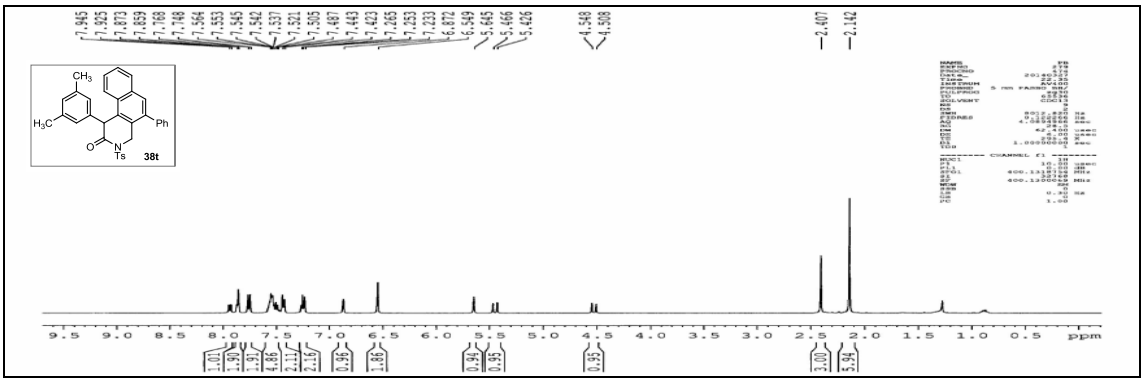
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CH3
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Ph
N
Ts
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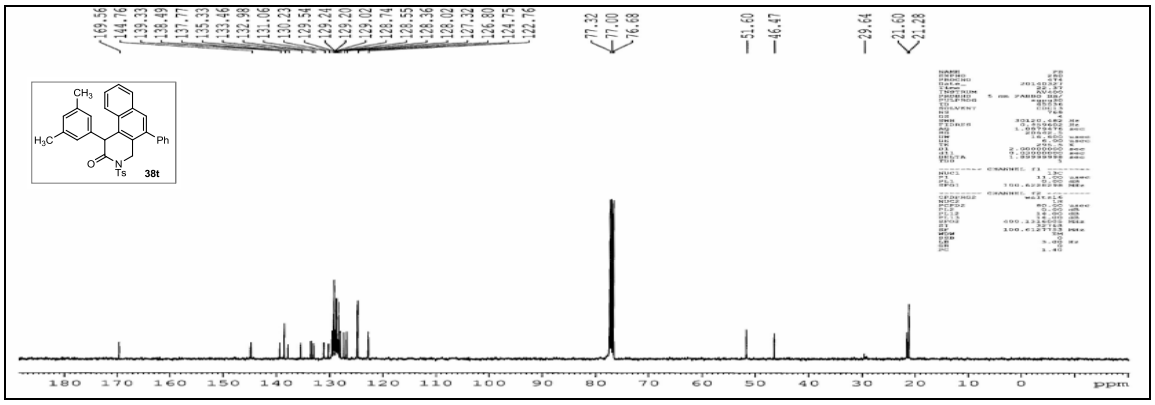
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Ts
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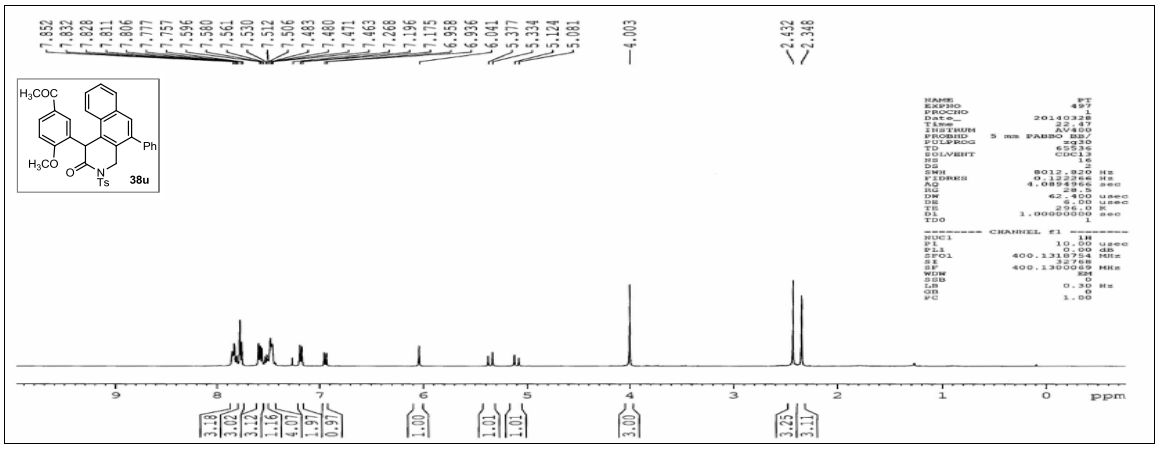
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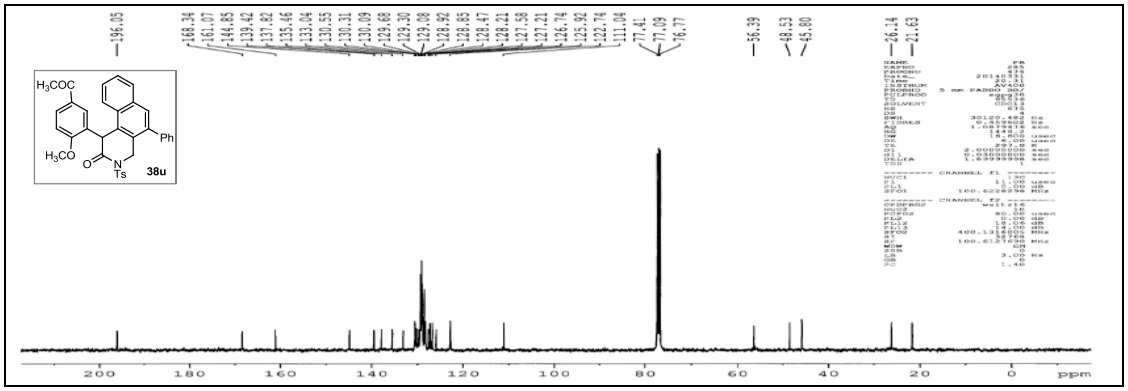
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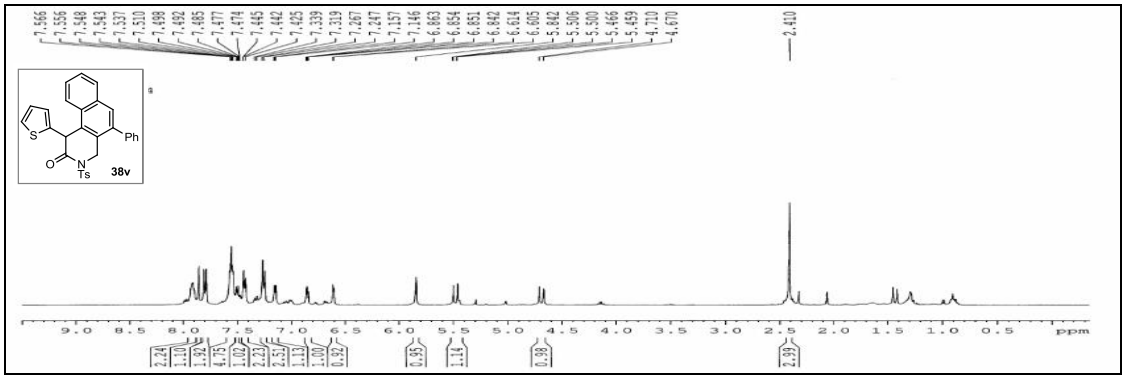
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Ph
N
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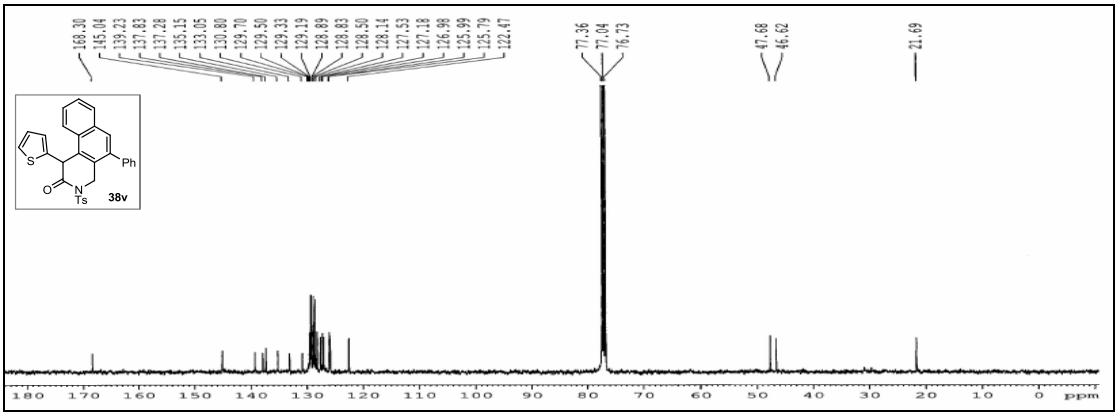
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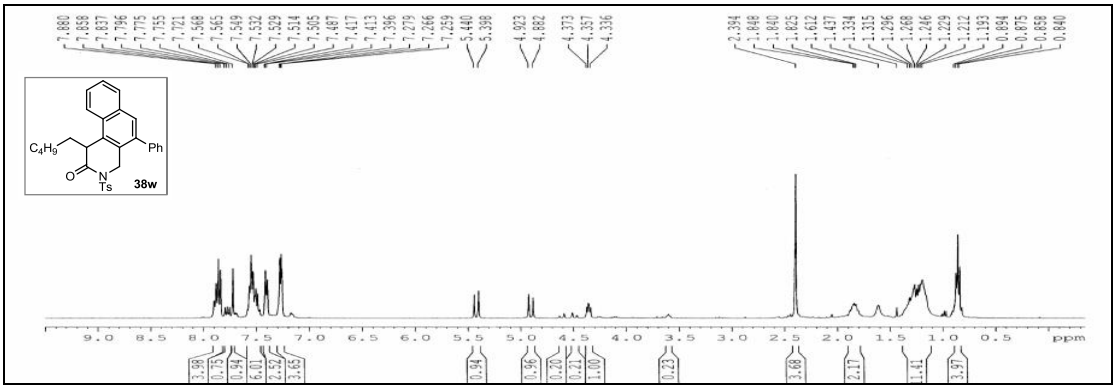
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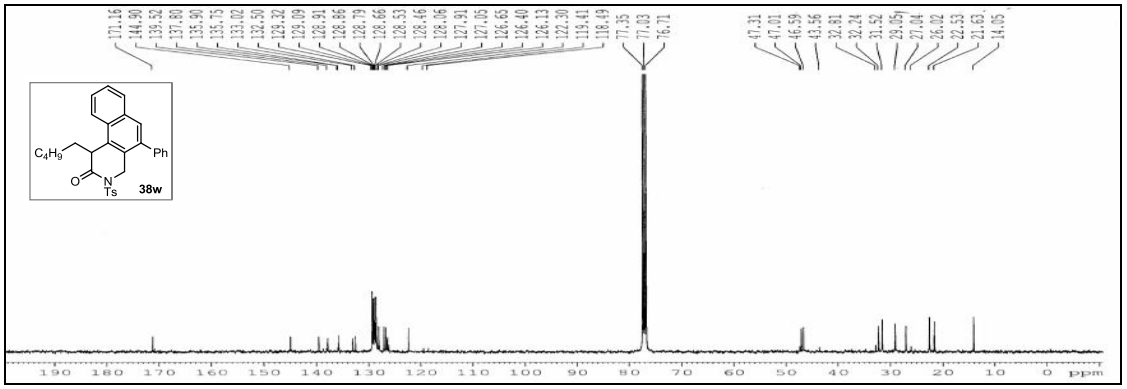
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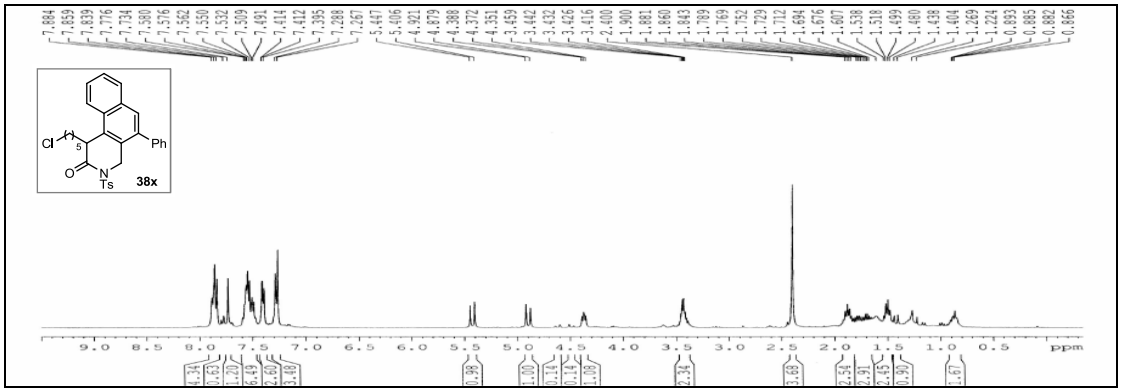
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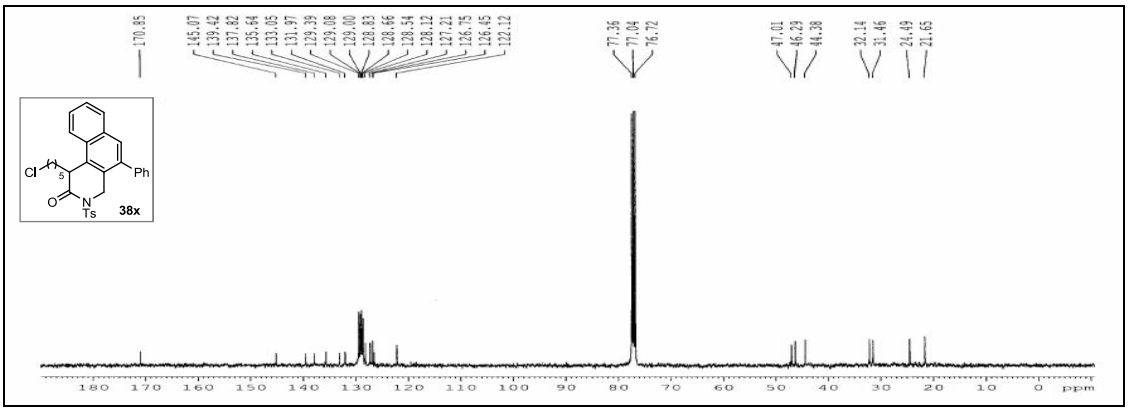
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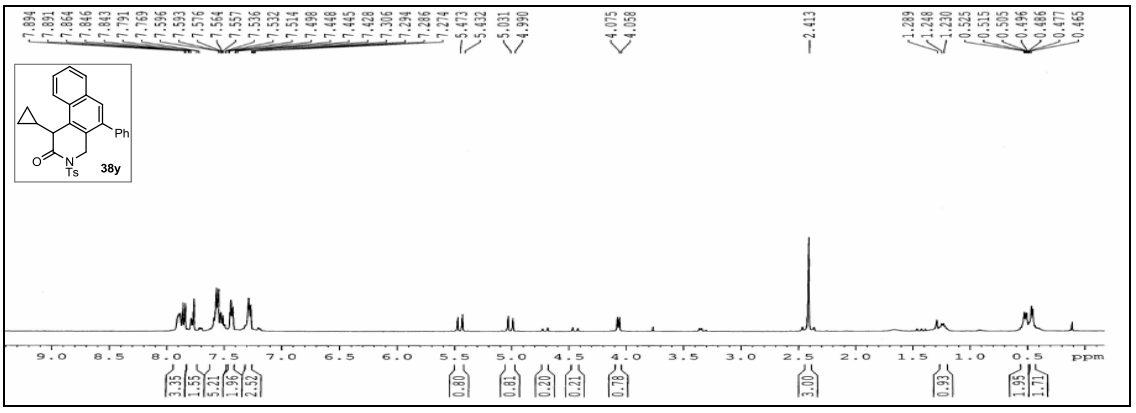
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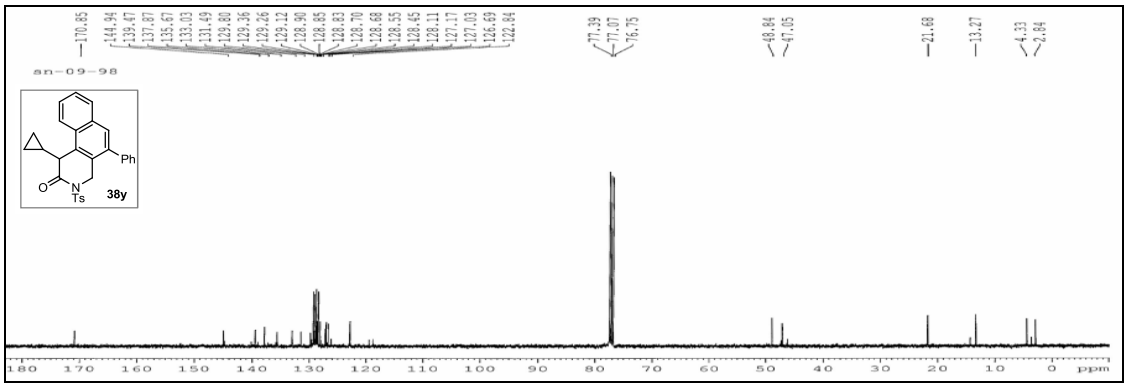
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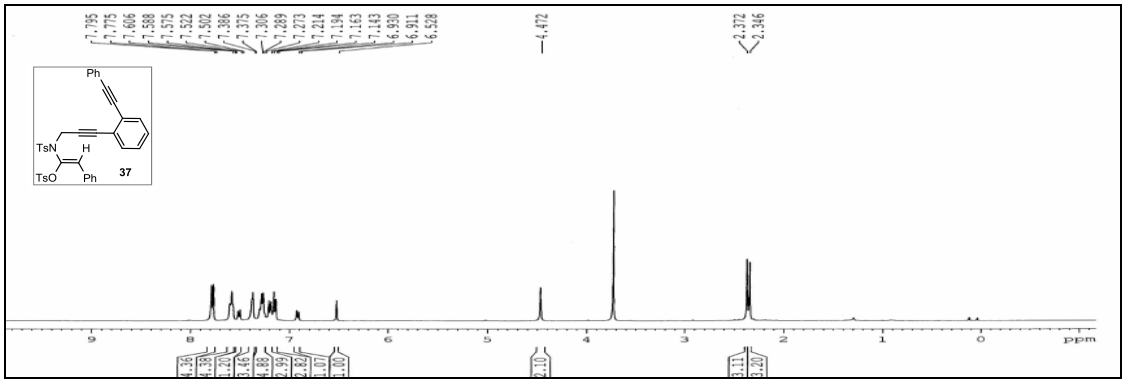
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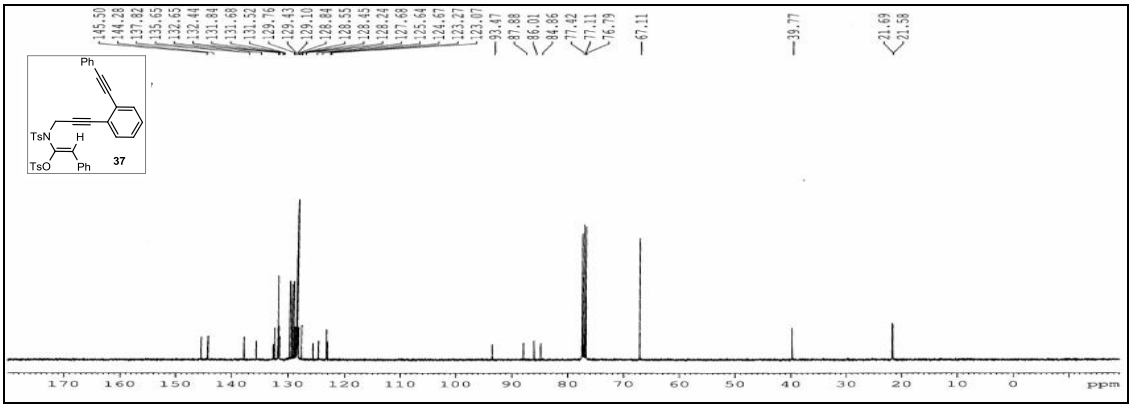
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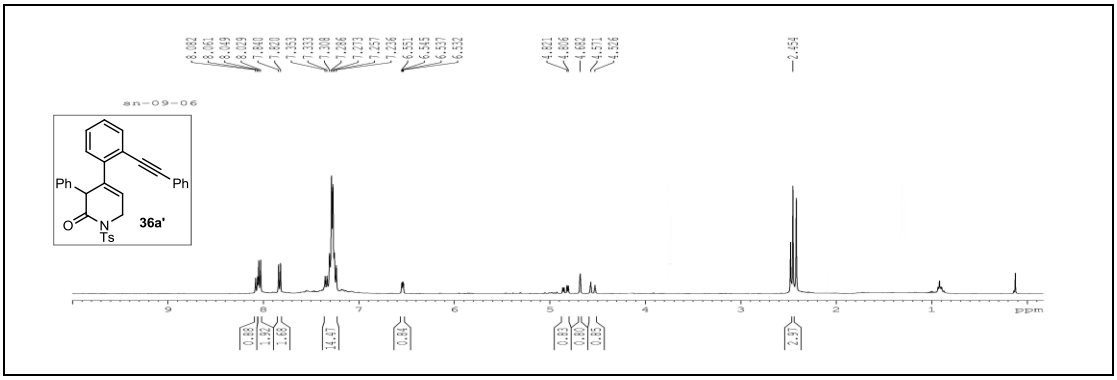
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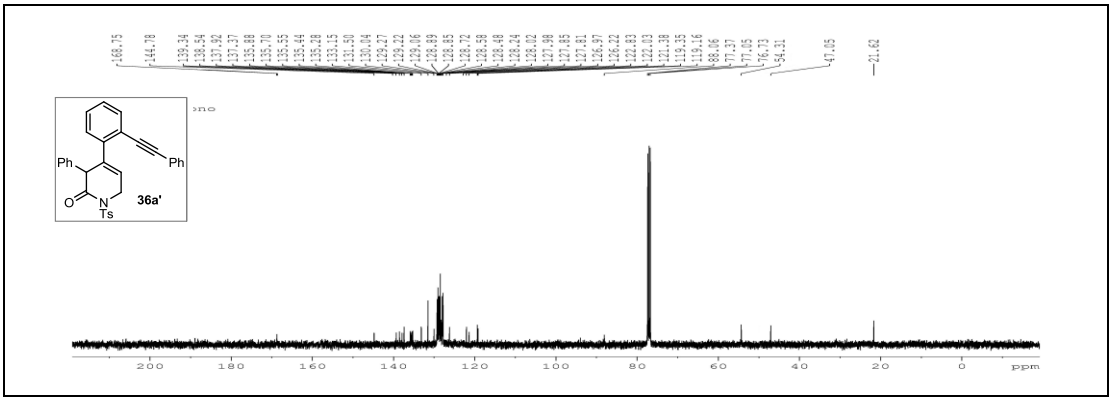
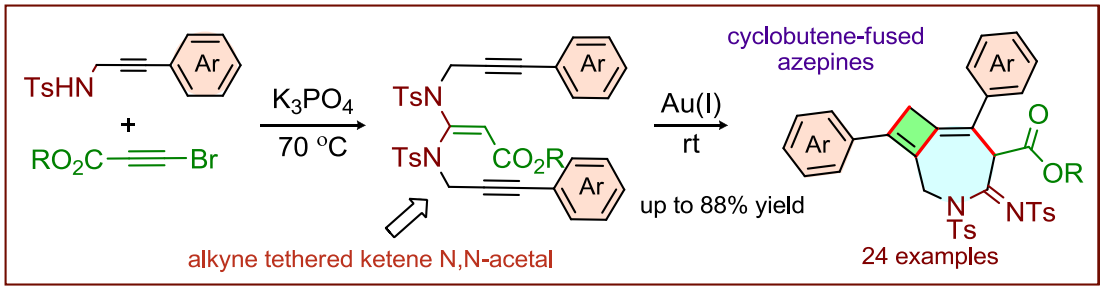

Ph
Ph
O
N
Ts
36a'
ppm

Chapter 3

Access to Cyclobutene fused Azepines via Au-Catalyzed Cycloisomerization of Stable Alkyne Tethered Ketene Aminals

Abstract



The base promoted reaction between *N*-protected propargyl amines and 3-bromopropiolate readily provides an array of novel stable alkyne-tethered ketene *N,N*-acetals in good yields. A wide range of structurally complex cyclobutene-fused azepine heterocycles are synthesized through the gold-catalyzed intramolecular cycloisomerization of ketene *N,N*-acetals for the first time. The plausible reaction pathway is deduced on the basis of the ^{1}H NMR studies.

Reference:

Sanatan Nayak, Nayan Ghosh, and Akhila K. Sahoo *Org. Lett.* **2014**, *16*, 2996.

Section I. Base Promoted Preparation of Ketene N,N-acetals

3.1. Introduction

Enamine is a versatile structural entity in organic chemistry; Stork and co-workers at first demonstrated a route for the synthesis of enamine.[1] This unit has been witnessed on enormous utility in the development of novel synthetic methods, asymmetric synthesis, and construction of complex molecular scaffolds of broad synthetic potential. Accordingly, the territory of enamine has grown up significantly; as a consequence, the subject of enamine has therefore been well perceived in the graduate-teaching curriculum with wider perspective.

The heterocyclic ketene aminals or cyclic 1,1-enediamines **1** is a useful surrogate of enamine family. Two enamine units are well integrated in ketene aminal, exhibiting significant nucleophilicity at C-2 center (Figure 3.1). The inherent delocalization of lone pair electrons of *N*-atoms with the conjugated double bond and the presence of electron withdrawing substituent at the terminal position of double bond makes the ketene aminal highly polarized; as a result, electron density at the C-2 center is relatively higher than the nitrogen (Figure 3.1). Owing to the inherent polar nature of ketene aminals, these structural entities are significantly useful for the creation of novel transformations and fabrication of unnatural complex heterocyclic compounds. Dissapointingly, the exceptional reactivity of ketene aminals leads to their synthesis and storage difficult. Hence, the use of ketene aminals for the development of new reactions is poorly explored over *O,O*-, *S,S*-, *N,O*-, or *N,S*- counterparts.[2, 3]

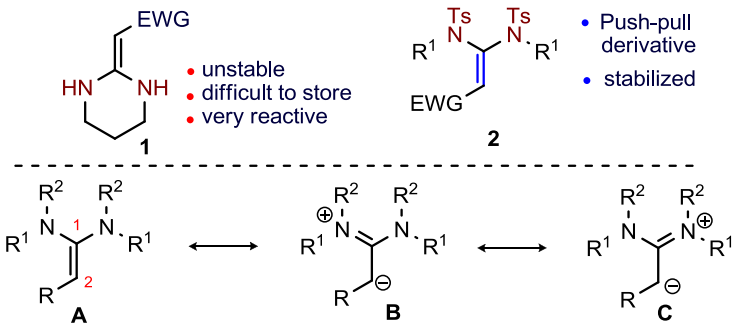


Figure 3.1. Resonance structures of ketene *N,N*-acetals

Interestingly, the incorporation of an electron-withdrawing group in the nitrogen atoms could contribute enhancing the stability of ketene *N,N*-acetals, which in turn can control the reactivity of the compound. A stable derivative of push-pull ketene aminal **2** is shown in figure 3.2.[4,5] An electron-poor group such as tosyl-moiety on *N*-atom in ketene aminal diminishes the electron-donation ability of nitrogen atoms, offering greater stability of **2**

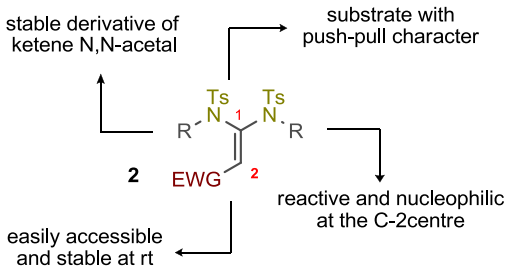
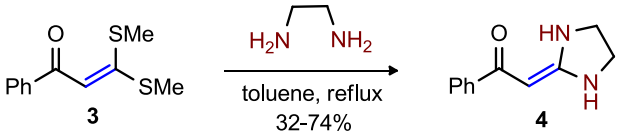


Figure 3.2 Stable ketene aminals

compared to traditional ketene aminals. Accordingly, various synthetic strategies have been developed for the fabrication of wide range of peripheral-substituted stable ketene aminals (Figure 3.2). Apart from the stability, the inherent existence of push-pull nature of ketene aminal assists the occurrence of substitution at C-2.[4,5]

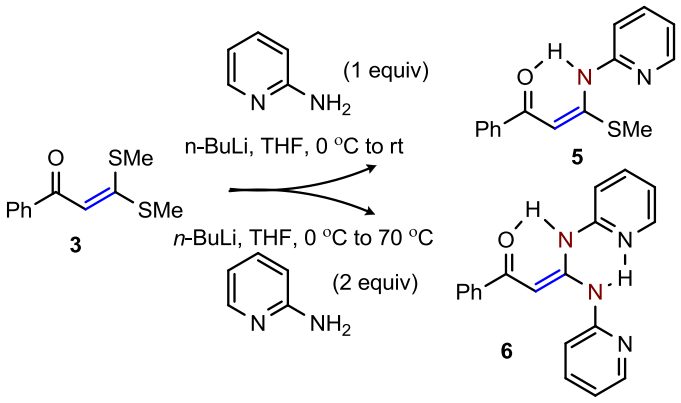
3.1.1. Synthesis of ketene *N,N*-acetals: The known strategies

The Huang group reported the synthesis of aroyl and acetyl- substituted heterocyclic ketene aminals **4** by refluxing a mixture of readily accessible ketene dithioacetals ***3*** and commercially available diamines (Scheme 3.1).[6] The reactivity of N-protected aminals has subsequently been examined under various reaction conditions.



Scheme 3.1. Synthesis of aroyl-substituted ketene aminals

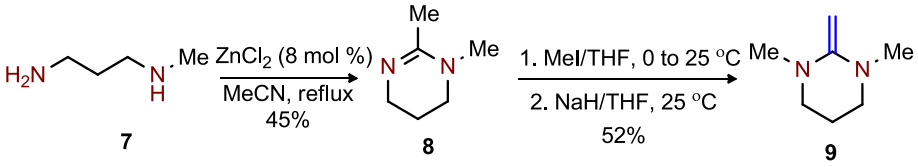
The Ila group described a reliable method to access α-oxo ketene *N,S*- and *N,N*- acetals ***5*** and **6** from α-oxoketene *S,S*-acetals ***3***; the reaction involves the displacement of SMe group of ***3*** by 2-aminopyridine in the presence of *n*-butyllithium (Scheme 3.2).[7] The compounds ***5*** and **6** were successfully used for the regioselective synthesis of substituted 2-(methylthio)pyrido



Scheme 3.2. Synthesis of α-oxo ketene *N,S*- and *N,N*- acetals

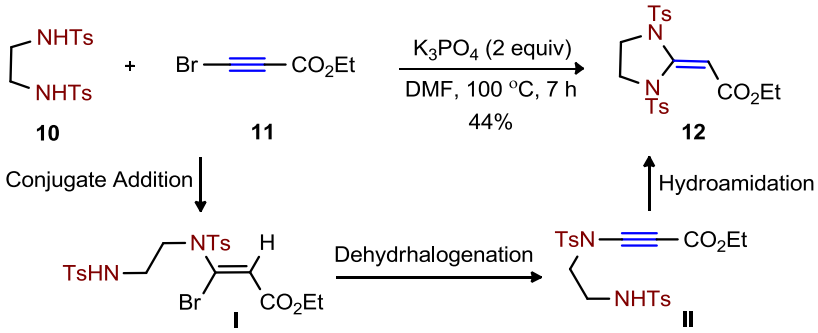
pyrimidinium fluoroborates and 2-(2-pyridylamino) pyrido[1,2-*a*]pyrimidinium tetrafluorobor-ates salts in presence of Lewis acid BF_3.OEt respectively.

A $ZnCl_2$-catalyzed condensation between N-methyl-1,3-propanediamine **7** and MeCN for the synthesis of 1,2-dialkyl-1,4,5,6-tetrahydropyrimidines **8** has been developed by the Pittman Jr group (Scheme 3.3).[3b] The reaction of **8** with MeI in presence of NaH in THF leads to cyclic 1,3-dimethyl-2-methylenehexahydropyrimidine **9** (Scheme 3.3). The compund **9** is relatively unstable, posing problems for long-time storage.



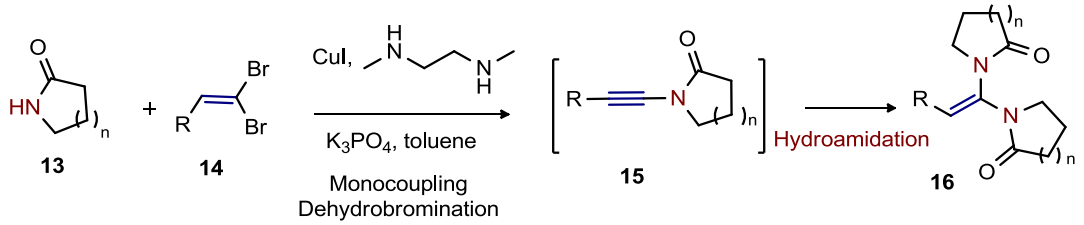
Scheme 3.3. Syntheisis of 1,3-dimethyl-2-methylenehexahydropyrimidine

Urabe group conveniently accessed 2-alkylidene-1,3-imidazolidines **12** from *N*-Ts protected 1,2-diamines **10** and ethyl 3-bromopropiolate **11** (Scheme 3.4).[5c] At first, the base promoted conjugate addition of amide **10** to **11** followed by 1,2-elimination leads to β-(sulfonylamino) propiolate **II** (Scheme 3.4). Subsequently, intramolecular addition of tethered amide to the α-position of ynamide forms an enolate *in situ*, which readily undergoes protonation to produce the sterically less biased cyclic ketene acetal **12**.



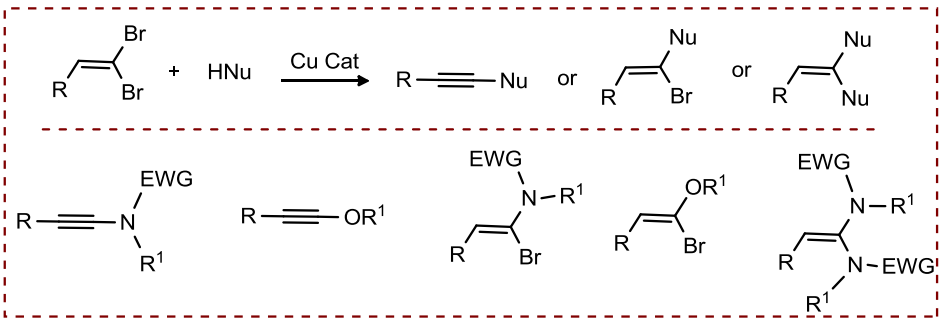
Scheme 3.4. Synthesis of cyclic ketene *N,N*- acetal

A Cu-catalyzed double amidation of 1,1-dibromo-1-alkenes for the preparation of stable ketene *N,N*-acetals has been demonstrated by the Evano group for the first time.[8a] The reaction involves K_3PO_4 base and CuI-mediated monocoupling of pyrrolidinone (**13**) with 1,1-dibromo-1-alkenes (**14**), followed by dehydrobromination to form **15** (Scheme 3.5). Next, the hydroamidation of **13** with **15** generates the desired ketene aminal **16**. Following these reaction sequences, a wide range of stable acyclic ketene aminals are synthesized in good yields (Scheme 3.5).



Scheme 3.5. Synthesis of pyrrolidinone based stable ketene aminals

The Cu-catalyzed protocol shown above proved to be efficient and general. Following these identical reaction conditions, the *N*-, *O*-, and *P*-nucleophiles were successfully inducted on 1,1-dibromoalkenes (Scheme 3.6). Furthermore, this method also allows accessing acyclic ketene *N,N*-aminals (Scheme 3.6).[8b]



Scheme 3.6. Copper catalyzed synthesis of stable ketene aminals

3.1.2. Reactivity of ketene N,N-acetals

A general structure of heterocyclic ketene aminals (HKAs, **17**) is shown in Figure 3.3; it has electron-donating amino groups, an electron-withdrawing carbonyl group, and a highly polarized double bond (C=C). The inherent delocalization of *N*-lone pair to the double bond enhances the electron density at the C3 center. Thus, C3, N1, and N5 are relatively nucleophilic; as a result, reaction of HKAs with electrophiles is highly succeptible, which in turn provides a way for the fabrication of fused heterocycles such as **18** (Figure 3.3). In addition, reaction of HKAs with 1,3-dipoles leads to triazoles or isoxazoles, for example **19** shown in figure 3.3. A one-pot condensation and cascade reaction involving N1, C3 and the

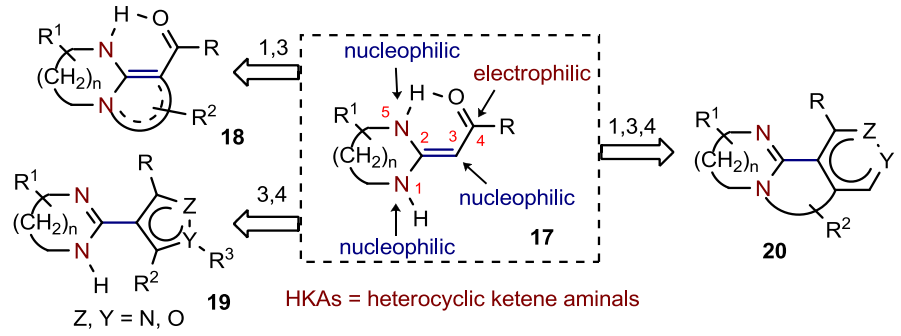
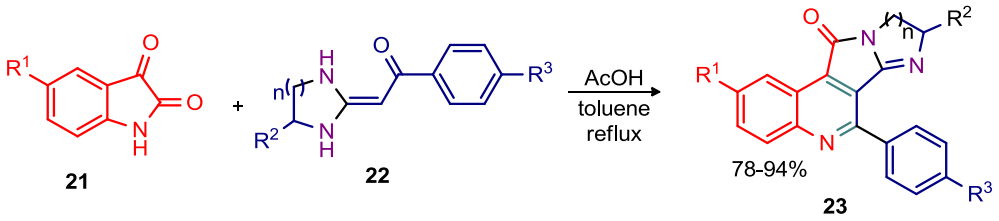


Figure 3.3. Reactivity of heterocyclic ketene aminals

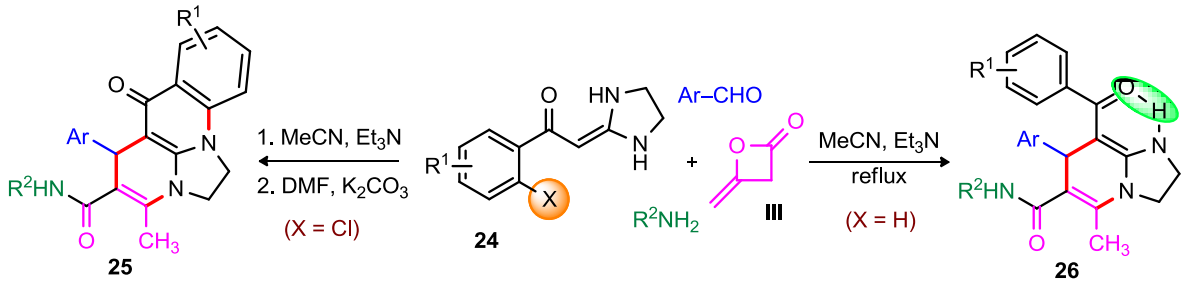
electrophilic site C4 (C=O) of HKAs **17** with a substituted electrophile/nucleophile directly generates polycyclic framework **20** (Figure 3.3).[9]

The Lin group developed a concise and efficient route for the synthesis of complex imidazopyrroloquinoline derivatives **23**. A mixture of isatins **21** and HKAs **22** was refluxed **in** acetic acid to provide **23** in good yields (Scheme 3.7).[9] This method is successfully applied for the construction of a library of imidazopyrroloquinoline derivatives.



Scheme 3.7. Synthesis of imidazopyrroloquinoline derivatives

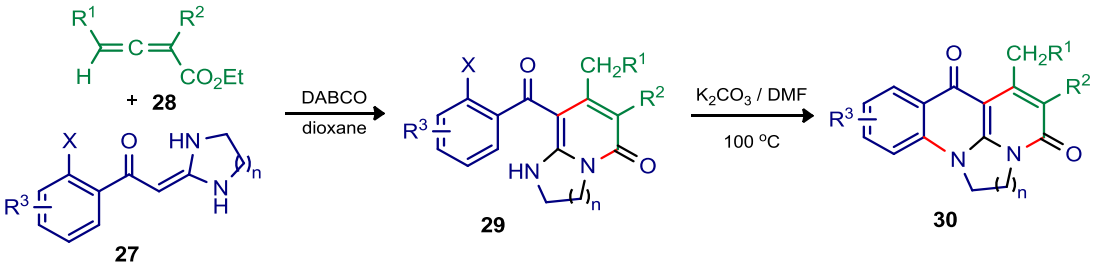
A synthetic protocol for imidazo[1,2-a]pyridines **25** and imidazo[1,2,3-ij][1,8]naphthyridine **26** derivatives is demonstrated through a four-component reaction using HKAs **24**, aldehyde, amine, and 4-methyleneoxetan-2-one **III**. This reaction involves 3 centers of the compound 2-(imidazolidin-2-ylidene)-1-phenylethanone **24**, 2 centers of diketene **III**, and the aldehyde. The attack of aryl amine to the carbonyl group of diketene III at first generates a carbanion, which then undergoes Knoevenagel condensation with the aromatic aldehyde. Next, the condensation between **24** and the intermediates formed in the Knoevenagel reaction, followed by imine–enamine tautomerization and intramolecular cyclization led to imidazo[1,2-a]pyridines **26** (Scheme 3.8). During the multicomponent transformation, the presence of *o*-Cl group in the compound **24** readily undergoes intramolecular nucleophilic substitution with the NH group and generates benzo[b]imidazo[1,2,3-ij][1,8]naphthyridine derivative **25** (Scheme 3.8). This unique reaction sequence involves nine chemically distinct reactive sites and creates a heteroatom bearing ring with the formation of four new bonds (two C–C bonds and two C–N bonds).[10]



Scheme 3.8. Four-component cascade heteroannulation of ketene aminals

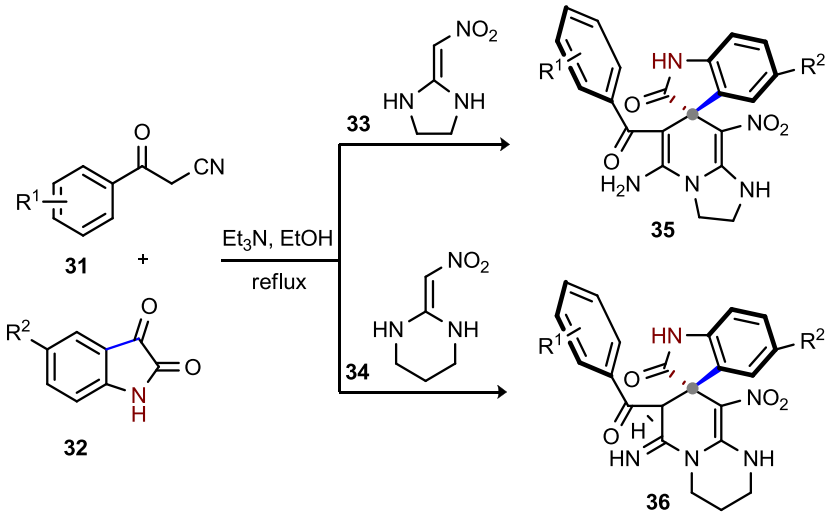
The base promoted reaction between HKAs **27** and allene **28** rapidly constructs imidazo(pyrido)[1,2-a]pyridine derivatives **29**. The Michael attack of C3 of **27** to the β-

carbon of **28** followed by condensation leads to the heterocyclic-amide **29**. Next, the intramolecular C–N bond formation provides complex novel heterocycles **30** (Scheme 3.9).[11]



Scheme 3.9. Synthesis of imidazo(pyrido)[3,2,1-ij]-[1,8]naphthyridines

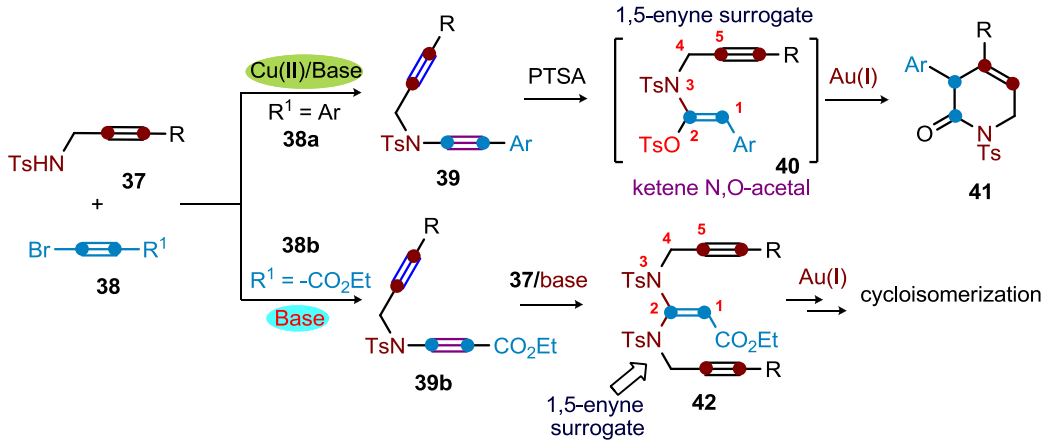
Recently, the Ranjith Kumar group disclosed a highly efficient one-pot route to imidazo[1,2-a]pyridines ***35*** and pyrido[1,2-a]pyrimidines ***36*** using a three-component reaction involving aroyl acetonitriles, nitroketene aminals, and isatins in the presence of Et_3N.[12] The reaction involves a domino Knoevenagel condensation, aza-ene addition, imine-enamine tautomerization, and chemoselective N-cyclization sequence. The base mediated Knoevenagel condensation of 3-oxo-3-propanenitrile ***31*** with isatin ***32*** followed by aza-ene addition of 2-(nitromethylene) imidazolidine ***33/34*** at first affords the imine intermediate, which subsequently undergoes an imine–enamine tautomerization to give the respective enamines (Scheme 3.10). Finally, intramolecular N-cyclization of enamines with -CN or C=O moieties forms spirooxindolo-imidazo[1,2-a]pyridines ***35*** or ***36*** (Scheme 3.10).



Scheme 3.10. Synthesis of spirooxindoloaroylimidazo [1,2-a]pyridines and spirooxindolo-aroylpyrido [1,2-a]pyrimidines

3.2. Motivation, Hypothesis, and Design

A detailed survey on the strategies known for the synthesis and reactivity of stable push-pull ketene aminals derivatives reveals that the cyclic ketene aminals are susceptible undergoing multicomponent reactions involving condensation, aromatic substitution,[8-12] etc. It has been observed that low-stability and exceptional reactivity of ketene aminals to specific reagents hinders the reaction out-come, narrowing the synthetic potential of the strategy. Therefore, development of novel transformations on acyclic stable push-pull ketene aminals involving modern tools of organic reactions is always desirable. In particular, unraveling the reactivity of ketene aminals to the transition-metal catalysts is interesting and receives attention.



Scheme 3.11. Alkyne tethered ketene aminals: a novel 1,5- enyne surrogate

Recently, our group have reported a Au(I)-catalyzed hydrative cyclization of 1,5-yne ynamide **39** to provide an array of novel 1,6-dihydropyridin-2(3H)-one derivatives **41** (Scheme 3.11).[13] The 1,5-yne ynamide **39** was prepared involving the cross-coupling between bromo aryl acetylene **38a** and *N*-tosyl protected propargyl amine **37** under the influence of Cu-catalysts. It has been proposed that the enol equivalent **40** (1,5-enyne surrogate), obtained *in situ* from **39** when reacted with *p*-TSA, undergoes 6-*endo dig* cyclization with the Au-activated alkyne moiety to deliver **41**. The experience drawn for the preparation of **39** led us to envision performing a reaction between **37** and activated bromoalkyne (1-bromo ethyl propiolate, **38b**). We hypothesized that **37** could readily couple with **38b** to provide **39b**; the presence of ester moiety at the alkyne terminus facilitates the polarization of the *N*-lone pair to alkyne unit enhancing the electrophilicity at the α-C in **39b**; this in turn provokes addition of NH-bearing nucleophile **37** to **39b** to construct **42**. Thus, the acyclic alkyne tethered push-pull derivative of ketene *N,N*-acetal **42** can be synthesized through the formation of ynamide **39b** involving monocoupling of **37** with **38b** followed by the hydroamidation of **37** with **39b**. Furthermore, we envisioned examining transition-metal catalyzed organic transformations on the peripheral decorated highly

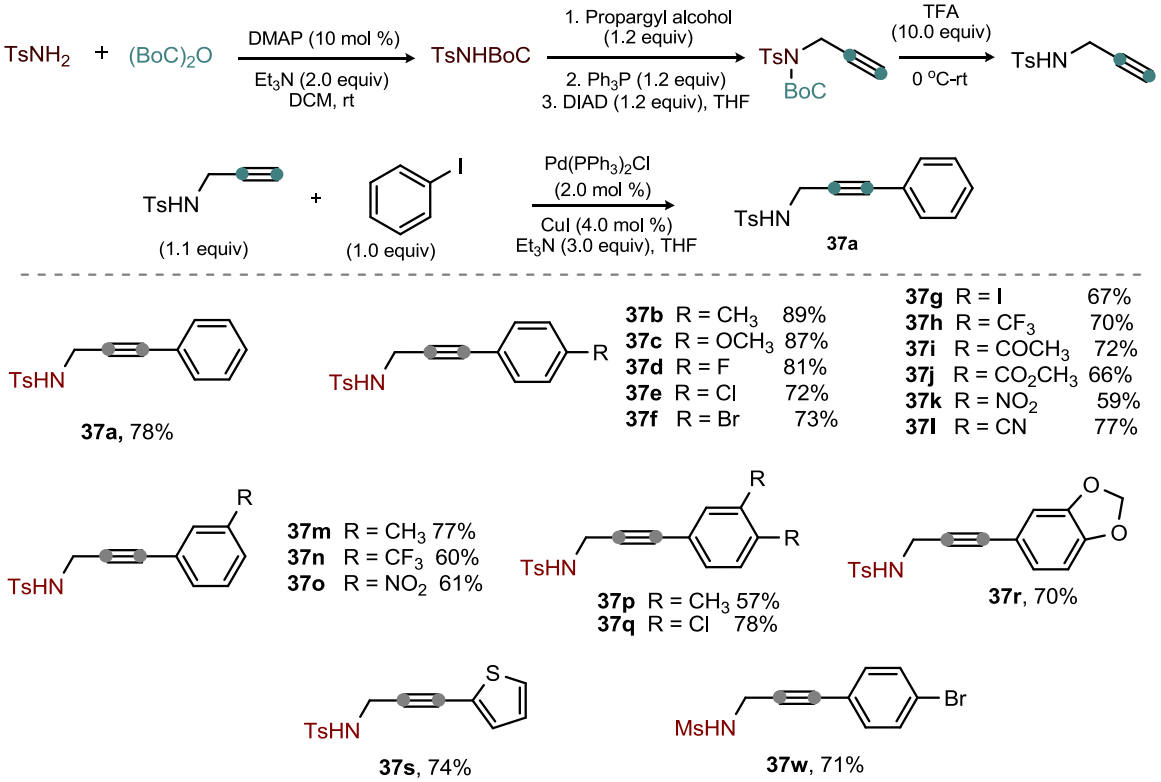
functionalized ketene *N,N*-acetals **42**, a perfect 1,5-enyne surrogate, for the construction of complex molecular entities.

3.3. Results and Discussion

To begin with, a reliable synthetic sequence for the construction of *N*-Ts-propargyl amine **37** is planned.

3.3.1. Preparation of 37

A wide range of *N*-Ts-propargyl amines **37** are readily prepared from commercially available $TsNH_2$ and propargyl alcohol (Scheme 3.12).



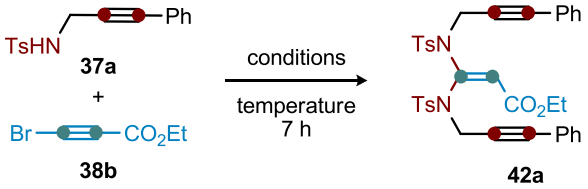
Scheme 3.12. Preparation of N-tosyl protected propargyl amines

The tosyl amine was at first protected with Boc moiety. The reaction of N-Boc protected tosyl amide with propargyl alcohol under Mistnobu conditions leads to N-propargyl bearing product. The removal of Boc-group followed by the Sonogashira reaction of terminal alkyne with iodo arenes gave the desired TsN-protected aryl propargyl amine **37**.

3.3.2. Reaction optimization

As envisioned, a reaction between 4-methyl-N-(3-phenylprop-2-ynyl)benzenesulfonamide (**37a**, 1.0 equiv) and ethyl-3-bromopropiolate (**38b**, 1.5 equiv) was planned under various conditions; the results are detailed in Table 3.1. At first, a reaction between **37a** (1.0 equiv) and **38b** (1.5 equiv) under the conditions comprising with $CuSO_4 \cdot 5H_2O$ (10 mol %), 1,10-phenanthroline (20 mol %), K_3PO_4 (2.5 equiv) in toluene at 70 °C for 7 h led to the corresponding alkyne tethered ketene N,N-acetal **42a** in 40% yield (entry 1); the poor mass-balance is due to the formation of polymeric uncharacterized species. The lack of general methods for the synthesis of **42a**, thus inspired us to develop a viable strategy for the preparation of electron deficient ketene *N,N*-acetals **42a**.

Table 3.1. Optimization for the synthesis of **42a** from **37a** and **38b**.



entry	**37a** (equiv)	**38b** (equiv)	catalyst (mol %)	additive (equiv)	solvent	yield[b] (%)
1	1	1.5	$CuSO_4 \cdot 5H_2O$ (10)	1,10-phenanthroline(0.2)/ K_3PO_4 (2.5)	toluene	40
2	1	1	$CuSO_4 \cdot 5H_2O$ (10)	1,10-phenanthroline(0.2)/ K_3PO_4 (2.5)	toluene	69
3	1	0.5	$CuSO_4 \cdot 5H_2O$ (10)	1,10-phenantrholine(0.2)/ K_3PO_4 (2.5)	toluene	60
4	1	1	CuI (10)	DMEDA (0.2)/ K_3PO_4 (2.5)	toluene	62
5	1	0.5	CuI (10)	DMEDA / K_3PO_4 (2.5)	toluene	58
6	1	1	-	K_3PO_4 (2.5)	toluene	70
7	**1**	**0.5**	-	**K_3PO_4 (2.5)**	**toluene**	**78**
8	1	0.5	-	K_3PO_4 (2.5)	dioxane	35
9	1	0.5	-	K_3PO_4 (2.5)	DMF	75

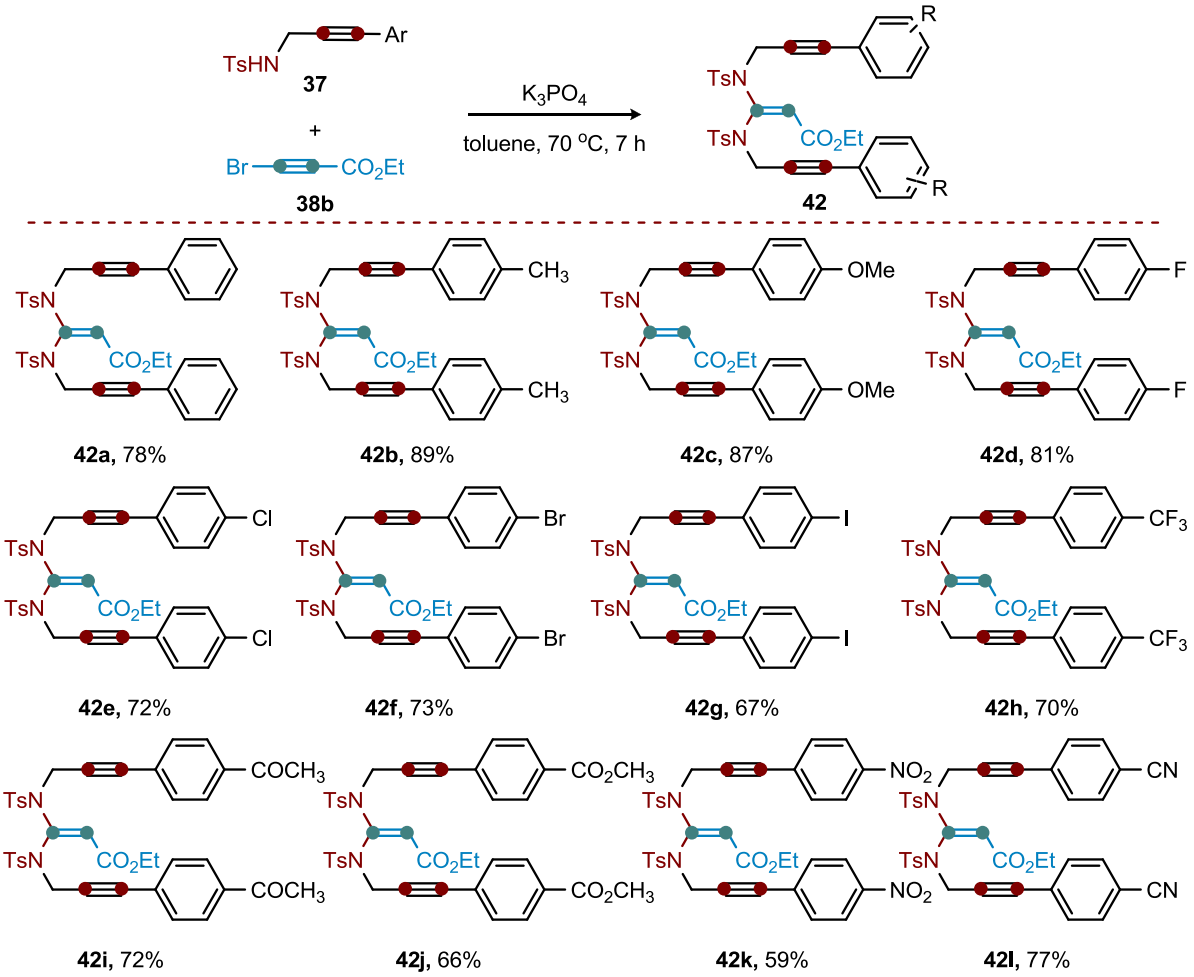
[a]Reactions were carried out using **37a** (1.0 mmol), **38b** (0.5 mmol), K_3PO_4 (2.5 equiv) in toluene (4.0 mL) at 70 °C. [b]Isolated yields; the product yield is calculated with respect to **38b**.

Pleasingly, 69% of **42a** was isolated when **37a** (1.0 equiv) and **38b** (1.0 equiv) were reacted under the previous conditions shown in (entry 2). Use of less amount of **38b** (0.5 equiv) is equally effective (entry 3), demonstrating a facile reactivity of the *in situ* formed ynamide with **37a**. The reaction with CuI and DMEDA in the presence of K_3PO_4 provides good amount of **42a** (entries 4 and 5). Notably, the reaction of **37a** (1.0 equiv) with **38b** (1.0 equiv) smoothly proceeded in the presence of only base K_3PO_4 (2.5 equiv) in toluene at 70 °C, affording **42a** in 70% isolated yield (entry 6). Gratifyingly, the yield of **42a** was increased to 78%, when reduced amount of **38b** (0.5 equiv) used in the reaction (entry 7). The reaction in dioxane drastically decreased the product yield (entry 8), whereas the use of DMF showed comparable result (entry 9). The solvent toluene is found suitable for this reaction.

3.3.3. Scope of the Reaction

To the best of our knowledge, synthesis of alkyne-tethered ketene *N,N*-acetals of type **42** is

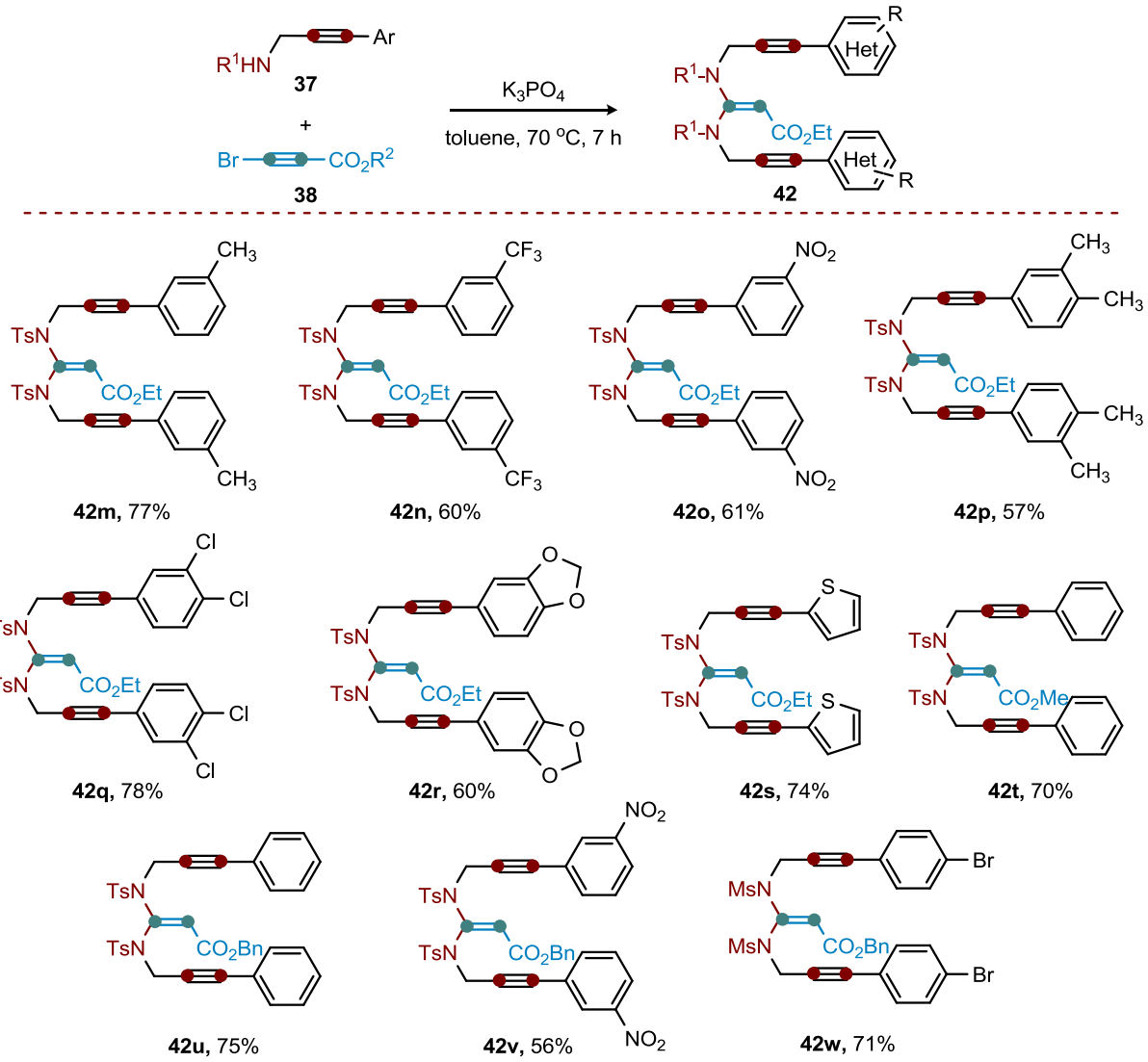
Table 3.2. Synthesis of stable alkyne tethered ketene *N,N*-acetals; substrate scope-I [a,b]



[a]Reactions were carried out using **37** (1.0 mmol), **38b** (0.5 mmol), K_3PO_4 (2.5 equiv) in toluene (4.0 mL) at 70 °C for 7 h. [b]Isolated yields of **42**, calculated based on the use of **38b**.

the first report. We therefore investigated examining a general startegy for the preparation of a wide range of compound **42** involving K_3PO_4 promoted reaction between easily accessible **37** and **38**. The outcome of the reaction is detailed in Table 3.2 and Table 3.3. The reaction between electron neutral 4-methyl-N-(3-phenylprop-2-ynyl) benzenesulfonamide **37a** and **38b** provided the desired ketene N,N-acetal **42a** in 78% yield. The electron-rich aryl moiety bearing **37** efficiently reacted with **38b** to afford the respective **42b** and **42c** in 89% and 87% yield, respectively. The halo functional group (F, Cl, Br, I) containing ketene N,N-acetals **42d–42g** were readily accessed in appreciable amounts; these halo groups are useful for various metal-catalyzed transformation.

Table 3.3. Synthesis of stable alkyne tethered ketene *N,N*-acetals; substrate scope-II[a,b]



[a]Reactions were carried out using **37** (1.0 mmol), **38** (0.5 mmol), K_3PO_4 (2.5 equiv) in toluene (4.0 mL) at 70 °C for 7 h. [b]Isolated yields of **42**, calculated based on the use of **38**.

The electron poor (CF_3) aryl substituted TsN-propargyl amine **37h** did not hinder the reaction efficiency with **38b**, affording the desired product **42h** in 70% yield**.** Pleasingly, some of the modifiable functional groups (NO_2, ester, keto, and CN) on the aryl moiety in **37** did not affect reaction outcome (Table 3.2). The X-ray crystallography analysis confirms the structure of **42l** (Figure 3.4).[35, 37]

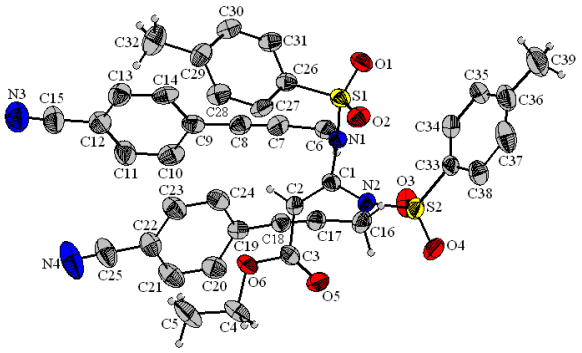
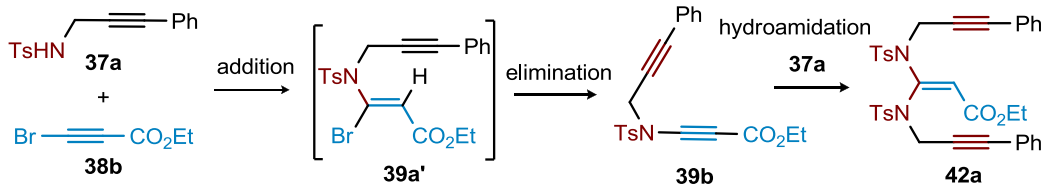


Figure 3.4. X- Ray crystal structure for compound **42l**

Next, the reaction of compound **37** having substituents at the *meta* -position on the aryl ring with **38b** is examined for the synthesis of **42**. The results are detalied in Table 3.3. The compounds **42m–o** with substituents CH_3, CF_3, or NO_2 in the *meta*-position on aryl moiety are accessed in good yields. The presence of multiple substitutents at the *p*- and *m*- position on aryl moiety in **37** reacted well with **38b** providing the corresponding products **42p** and **42q** in 57% and 78% yields, respectively. The methylene dioxy bearing TsN-propargyl amine **37r** with **38b** delivered **42r** (60%). Interestingly, the reaction was found compatible to the formation of thienyl-substituted aminal **42s** in 74% yield. The reaction of methyl or benzyl 3-bromopropiolates (**38c**/**38d)** with **37a** independently produced **42t–v** in moderate yields. The N-Ms protected propargyl amine was also no exception delivering **42w** in 71% yield.

3.3.4. Mechanism

As the reaction between **37** and **38** in presence of base cleanly delivers the unprecedented **42**, a tentative reaction pathway for this transformation is shown in scheme 3.13. At first, the base assisted conjugate addition of TsN-propargyl amine **37a** to the activated propiolate **38b** gives a transient intermediate **39a′**, which rapidly undergoes dehydrohalogenation to provide **39**. Finally, hydroamidation of **37a** with ynamide **39** generates a stable ketene aminal **42a**.[35b]

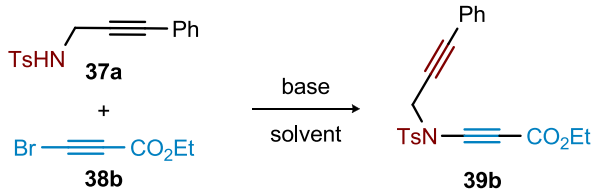


Scheme 3.13. Proposed mechanism for the preparation of **42**

3.3.5. Preparation of unsymmetrical alkyne tethered ketene N,N-acetals

The successful synthesis of a range of symmetrical ketene aminals **42a–42w** inspires in the development of a trust-worthy method for the construction of unsymmetrical ketene aminals. The synthesis of **42** is realized with the participation of 1,5-yne ynamide ***39*** *in situ*, as proposed in the mechanistic path in Scheme 3.13. Thus, a two step protocols for the construction of unsymmetrical aminals is envisaged; accordingly, synthesis of an activated 1,5-yne ynamide precursor followed by the base promoted hydroamidation of ***37*** with 1,5-yne ynamide is planned. To forsee the formation of **39b**, a reaction between 4-methyl-N-(3-phenylprop-2-ynyl) benzenesulfonamide (**37a**, 1.0 equiv) and ethyl 3-bromopropiolate (**38b**, 2.0 equiv) under various organic and inorganic bases was envisioned (Table 3.4). The reaction in the presence of KOH (1.0/2.0 equiv) in toluene at 70 °C led to 20-35% of the product **39b** (entries 1 and 2). The use of different amount of K_3PO_4 provided minor amount of **39b** along with major amount of ketene *N,N*-acetal **42a** (entries 3–10); screening of various solvents instead of toluene are inferior (entries 7–9). The other inorganic bases, such as: K_2CO_3, Ag_2CO_3, Na_2CO_3 are ineffective (entries 11–13). The use of Et_3N in the reaction provided maximum 30% of **39** (entries 14 and 15); while pyridine and DBU are ineffective (entries 16 and 17). The NaO^{t}Bu base is found poor (entry 18). Interestingly, an enhanced product yield was observed when the reaction conducted with NaOH (1.0 to 4.0 equiv) in toluene at 70–80 °C (entries 19–21); in contrast, the reaction in benzene/DCE is poor (entries 22 and 23). Pleasingly, the reaction of **37a** (1.0 equiv) with **38b** (2.0 equiv) in the presence of more amount of NaOH (4.0 equiv) in toluene at rt afforded **39** in 50% isolated yield (entry 24); while the identical reaction with less amount of base gave 40% of product (entry 25).

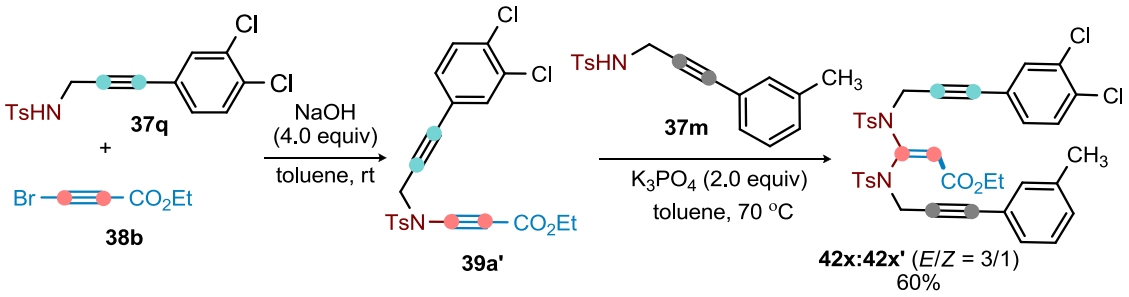
Table 3.4. Synthesis of 5-yne-ynamide **39**; Optimization studies



entry	base (equiv)	solvent	temp (°C)	time (h)	yield (%)
1	KOH (1.0)	toluene	70	12	20
2	KOH (2.0)	toluene	70	04	35
3	K_3PO_4 (1.0)	toluene	80	12	10
4	K_3PO_4 (2.0)	toluene	80	12	15
5	K_3PO_4 (3.0)	toluene	80	12	15
6	K_3PO_4 (4.0)	toluene	80	12	15
7	K_3PO_4 (4.0)	benzene	80	12	20
8	K_3PO_4 (4.0)	DCE	80	12	25
9	K_3PO_4 (4.0)	dioxane	80	12	15
10	K_3PO_4 (4.0)	toluene	rt	12	05
11	$AgCO_3$ (1.0)	toluene	70	12	NR
12	K_2CO_3 (1.0)	toluene	70	12	NR
13	Na_2CO_3 (1.0)	toluene	70	12	NR
14	Et_3N (1.0)	toluene	70	12	25
15	Et_3N (2.0)	toluene	70	24	30
16	Pyridine (2.0)	toluene	70	04	NR
17	DBU (4.0)	toluene	80	12	NR
18	NaO^{t}Bu (4.0)	toluene	80	12	25
19	NaOH (1.0)	toluene	70	12	25
20	NaOH (2.0)	toluene	70	04	40
21	NaOH (4.0)	toluene	80	12	48
22	NaOH (4.0)	benzene	80	12	30
23	NaOH (4.0)	DCE	80	12	10
24	NaOH (4.0)	toluene	rt	04	50
25	NaOH (2.0)	toluene	rt	12	40

[a]Reactions were carried out using **37a** (1.0 mmol), **38b** (**2.0** mmol), base in solvent (4.0 mL).

[b]Isolated yields.



Scheme 3.14. Preparation of unsymmetrical ketene aminals

With the isolation of decent yield of the activated ynamide **39a**, investigation for the synthesis of unsymmetrical ketene aminals is initiated. Accordingly, a reaction between **37q** and **38b** in the presence of NaOH (4.0 equiv) in toluene at rt afforded ynamide **39a′** in 50% yield (Scheme 3.14). Further, the K_3PO_4 mediated reaction of amine **37m** with **39a′** in toluene delivered the hydroamidation product ketene N,N–acetals **42x**:**42x′** (E/Z = 3:1) in 60% yield (Scheme 3.14).

3.4. Conclusion

A synthetically viable strategy for the preparation of wide array of bench-stable symmetrical alkyne-tethered ketene-*N*,*N*-acetals from easily accessible *N*-Ts/Ms protected propargyl amines and 3-bromopropiolates under the influence of K_3PO_4 base has been demonstrated for the first time. The reaction is general; various common functional groups are tolerated under the optimized conditions. Two differnet N-tosyl protected propargyl amines are successfully employed for the synthesis of unsymmetrical aminals; the reaction involves the addition of amine moiety to Br-propiolate for the synthesis of 1,5-yne-ynamide derivative followed by the hydroamidation of other amine to the ynamide. The ketene *N*,*N*-acetal is an 1,5-enyne surrogate; thus Au-catalyzed cycloisomerization of the ketene aminal is therefore envisaged.

Section II. Gold(I)-Catalyzed Cycloisomerization of 1,5-Enyne Surrogate Keten Aminals: Access to Cyclobutenefused Azepines.

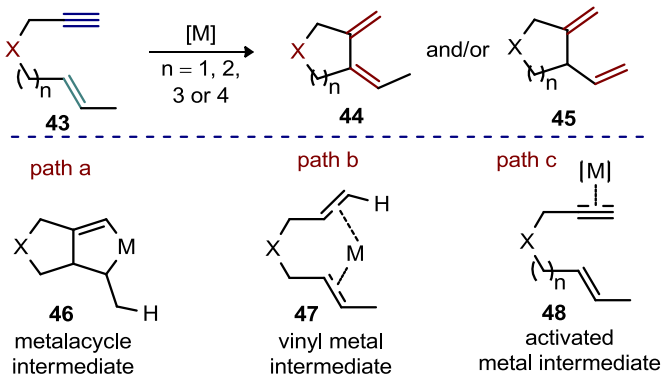
3.5. Introduction to cycloisomerization

The formation of cyclic congeners through the isomerization of the acyclic substrate is termed as cycloisomerization. The cycloisomerization is an atom-efficient process, holding all the atoms of the precursor in the product.

3.5.1. Enyne Cycloisomerization

Fabrication of carbo-/heterocycles through the isomerization of enynes under the influence of Lewis-/Brønsted-acids/transition-metal catalysts is termed as enyne-cycloisomerization.[15] The activation of the enyne-motifs by the π-coordination ability of the reagents initiates the transformations. The activation of enyne precursors occurs in three possible ways:[16, 17]

a) the simultaneous coordination of metal-reagent to the alkyne and the alkene moieties for the formation of a metalacycle intermediate **46**; in this process metal undergoes two-electron oxidation (path a, Scheme 3.15).
b) the hydrometalation of metal-species with the alkyne moiety leading to the generation of transient vinyl metal species **47** (path b, Scheme 3.15); the intramolecular carbometalation of vinyl-metal species with the olefin allows the construction of functionalized carbo-/heterocycles.
c) the selective activation of alkyne by the LA-metal species (path c, Scheme 3.15); the intramolecular cyclization of olefin to the alkyne-activated moiety provides acess to the synthesis of complex molecular entities.



Scheme: 3.15. Possible ways for the activation of enyne-presursor.

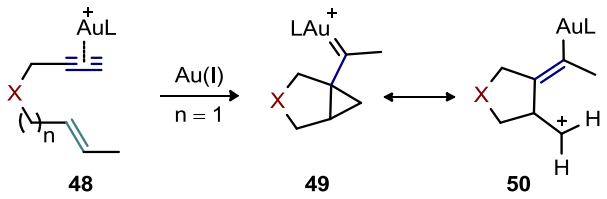
In general, the low oxidation state transition-metal complexes palladium (0), ruthenium (II), or platinum (II) used for the cycloisomerization involves path **a** and **b** in Scheme 3.15. In

contrast, path c is liable for the Au-catalyzed transformations.[14] The Au-catalyzed enyne-cycloisomerization involving oxidative cyclometalation paths **a** and **b** is difficult; as the participation of Au(I) and Au(III) intermediates in the oxidative transformations is rather non-trivial. The Au(I)-complexes are bicordinated; thus, the insertion of a substrate to the bicordination complex of Au(I)-species proceeds through the exchange of ligand, which in turn pose concerns for the simultaneous coordination of alkyne and alkene moieties.[18, 19]

3.6. 1,n-Enyne Cycloisomerization: The Known Strategies

3.6.1. Gold-catalyzed cycloisomerizations of 1,6-enynes:

The gold(I)-catalyzed cyloisomerization of 1,6-enynes is well explored. The gold(I) complexes are generally used for the 1,6-enyne cycloisomerization of enynes.[16,17] The activation of alkyne-moiety over the alkene by gold(I) reagents is well established. For instance, nucleophilic attack of C=C bond to the carbon–carbon triple bond of the Au-π-activated complex **48** produces an intermediate **49**; ring opening of the cyclopropyl-unit in **49** then forms **50.** Wide range of organic transformations has been developed through the successful trapping of the intermediate **50**.



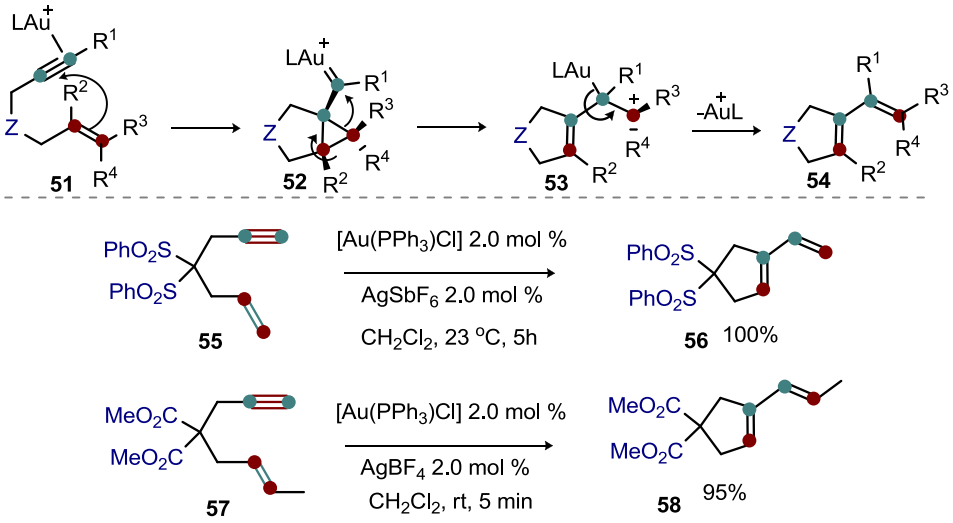
Scheme 3.16. Gold(I)-catalyzed activation of alkynes via π-complexes

The 5-*exo*-dig or 6-*endo*-dig pathways are generally involved for the Au-catalyzed transformations of 1,6-enynes. The cycloisomerization of 1,6-enynes is realized through the single/double cleavage of olefin moieties or endocyclic rearrangement of enynes.[20,21]

3.6.2. Single cleavage skeleton rearrangement of 1,6-enyne:

A single cleavage skeletal rearrangement of gold activated 1,6-enyne complex **51** involves the attack of olefin to the Au-activated alkyne moiety in a 5-*exodig* cyclization to form diene **54** (Scheme 3.17).[22] In this process, migration of terminal alkene carbon to the terminus of alkyne center occurs with the cleavage of olefin moiety. The reaction sequence involves a 5-*exodig* cyclization of olefin to the Au-activated alkyne moiety in **51** followed by the back-donation of Au to produce cyclopropyl-bearing Au-carbene intermediate **52**. The cleavage of cyclopropyl ring and 1,2-migration of cyclopropyl bond to Au-carbene leads to **53**. With the removal of –AuL species from **53** delivers **54**. The Au(I) catalyzed conversion of enyne **55** to diene **56** is a true demonstration of this method (Scheme 3.17). Interestingly, the

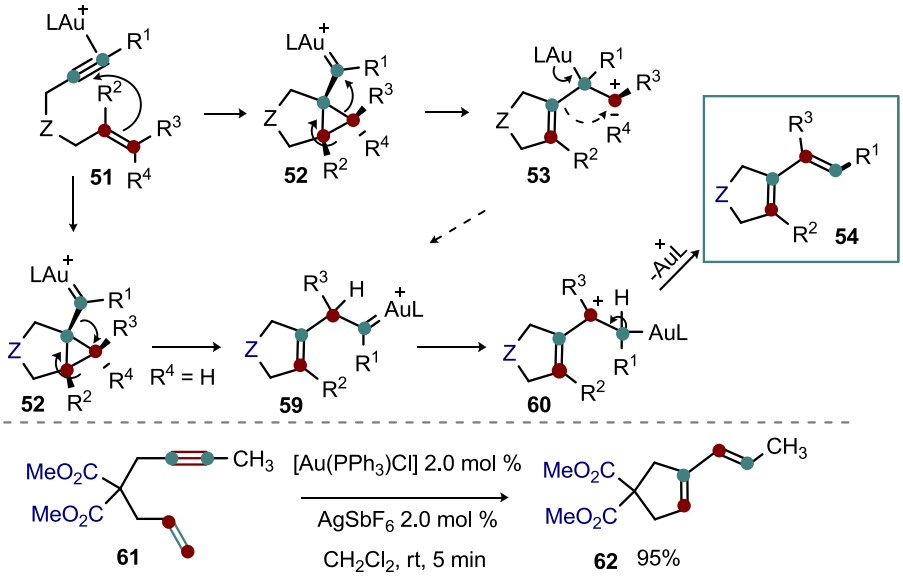
configuration of alkene in 1,6-enyne is retained in the product, as observed in the conversion of **57** to **58** (Scheme 3.17). This reaction occurs under the mild conditions and is stereospecific.[22]



Scheme 3.17. Formation of 1,3-dienes via single cleavage rearrangement of 1,6-enyne

3.6.3. Double cleavage skeleton rearrangement of 1,6-enyne:

The double cleavage rearrangements of 1,6-enyne involves the breakage of both alkene and alkyne moieties in **51** to the formation of conjugated-diene **54** (Scheme 3.18).



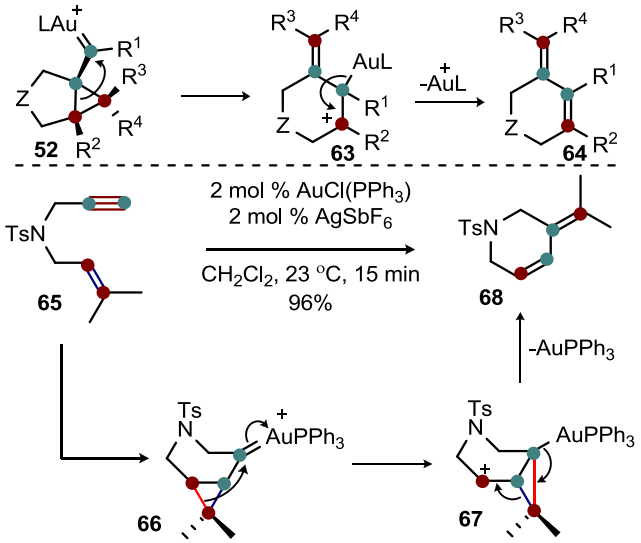
Scheme 3.18. Double cleavage skeleton rearrangement for 1,6-enyne

The cyclopropyl gold(I) carbene intermediate **52** undergoes a direct formal diatropic rearrangement **52→59**, or a 1,2-shift of the cyclopropyl moiety to carbene followed by the 1,2-migration of alkenyl group to the carbocation center **52→53→59** (Scheme 3.18).[23] Finally, [1,2-H] shift to Au-carbene followed by deauration from **60** led to **54**. The conversion of **61** having alkyl group at the alkyne terminus to **62** is a nice demonstration of

Au(I)-catalyzed double cleavage rearrangement of 1,6-enyne (Scheme 3.18). This process delivers exclusively *Z*-dienes.

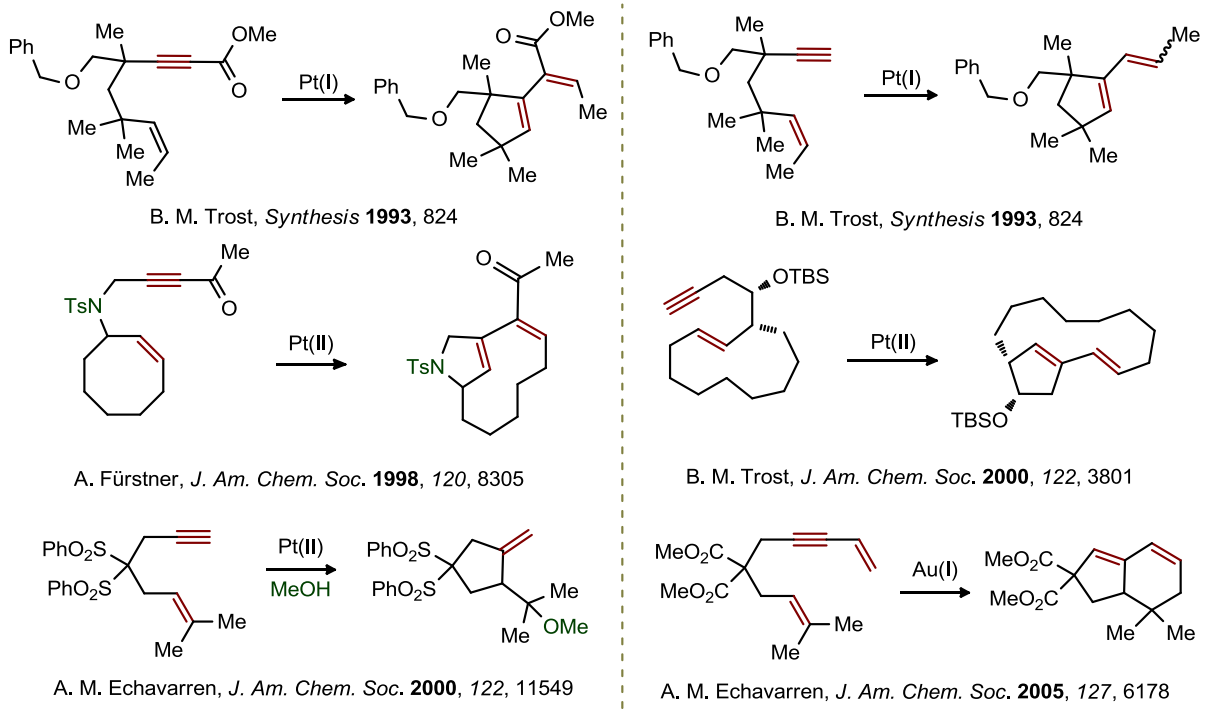
3.6.4. Endocyclic skeleton rearrangement

In the presence of cationic gold(I) complex, the 1,6-enyne **51** undergo cycloisomerization through 5-*exodig* pathway to give six-membered ring dienes **64** (Scheme 3.19).[23] On the basis of the DFT calculations, the alkyne activation by Au(I) induces 5-*exo*dig attack of olefin to produce intermediate **66** from **65**.[24] The rearrangement of **66** leads to the cationic intermediate **67**; finally, deauration concomitantly neutralizes the cabocation species to produce **68**. The terminal unsubstituted or the hetero atom bearing alkynes in 1,6-enynes in the presence of cationic Au(I) catalysts participated undergoing endocyclic rearrangement to produce cyclic dienes.



Scheme 3.19. Endocyclic skeleton rearrangement of 1,6-enyne

Following the concept of cycloisomerization of 1,6-enyne, a range of organic transformations have been developed involving single, double clevage or endocyclic rearrangement of olefine moieties; scheme 3.20 briefly outlines some of the known Au-catalyzed cycloisomerization of 1,6-enynes.



Scheme: 3.20. Known transformations of 1,6-enyne cycloisomerization

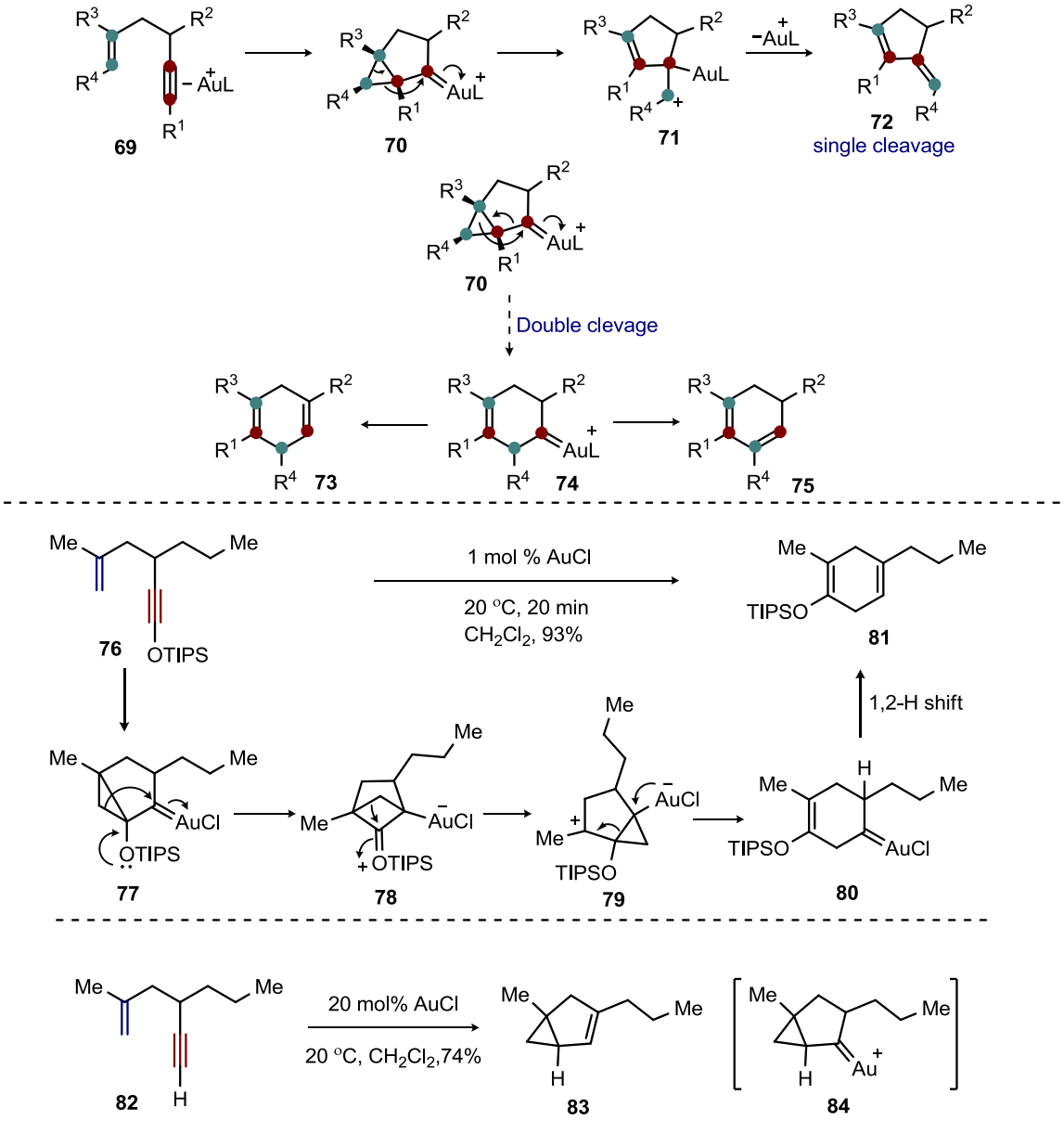
3.6.5. Gold-catalyzed cycloisomerizations of 1,5-enynes:

Despite tremendous progress witnessed on the Au-catalyzed cycloisiomerization of 1,6-enynes for the construction of a large variety of complex structural entities with broad synthetic potential, the Au(I)-catalyzed cycloisomerization of 1,5-enynes has also been contributed for the fabrication of synthetically useful products albeit in a less-extent (Scheme 3.20).[25]

The Au-catalyzed cyclization of 1,5-enynes proceeds through single/double cleavage rearrangements involving 6-*endo*dig pathways. The transformation initiates with the attack of alkene-moiety to the Au-activated-alkyne complex, subsequent back donation of Au forms cyclopropyl gold carbene **70** (Scheme 3.20). The single-cleavage rearrangement involves opening of cyclopropyl ring and 1,2-migration of cyclopropyl bond to Au-carbene followed by the removal of –AuL species from **71** to the formation of **72** (Scheme 3.20). Alternatively, the double cleavage rearrangement of 1,5-enynes involves the opening and migration of C–C bonds of cyclopropyl and cyclopentyl rings in **70** creating the six-membered-Au-carbene intermediate **74** (Scheme 3.20). Finally, deprotonation and protodemetalation of **74** leads to cyclohexadienes **73** or **75** (Scheme 3.20).[26]

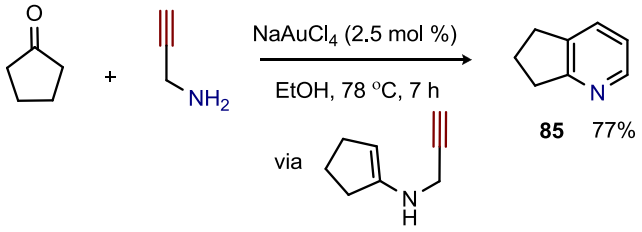
Zhang and Kozmin reported concise methods for the synthesis of 1,4-cyclohexadiene **81** from 1,5-enynes **76** involving series of C–C bond cleavage induced by lone pair of oxygen in cyclopropyl gold carbene **77**.[27] The silyl group stabilizes the oxocarbenium intermediate **78**.

Whereas the reaction of enyne **82** having no silyloxy moiety on the alkyne-terminus with AuCl in CH_2Cl_2 gave 5-methyl-3-propylbicyclo[3.1.0]hex-2-ene **83**; this transformation involves a 1,2-H shift of the metallocarbene intermediate **84** (Scheme 3.20).[27]



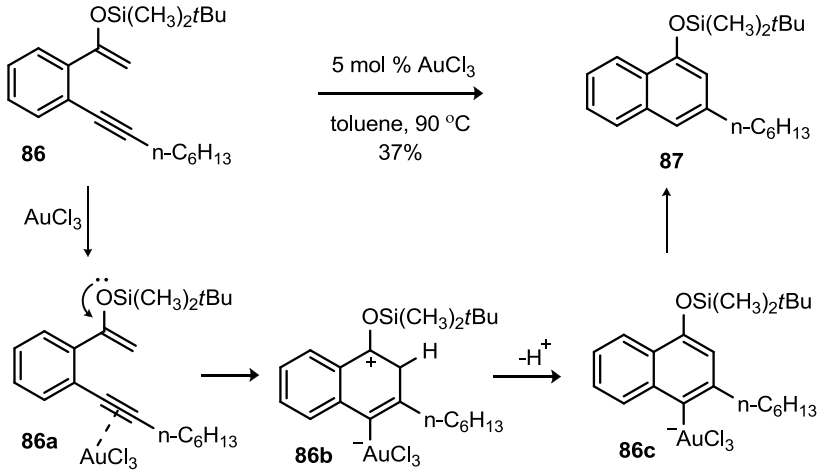
Scheme 3.20. Single and Double cleavage skeleton rearrangement for 1,5-enynes

A synthetic method for fused-pyridine skeleton is demonstrated through Au-catalyzed reaction between ketone and propargyl amine (Scheme 3.21).[28] The condensation between ketone and the propargylamine followed by imine-enamine isomerization at first produce the transient N-tethered 1,5-enyne. Next, the regioselective 6-*endodig* cyclization of 1,5-enyne followed by a dehydrogenation of the resulting dihydropyridine affords pyridine derivative **85** (Scheme 3.21).



Scheme 3.21. Synthesis of fused-pyridine derivatives

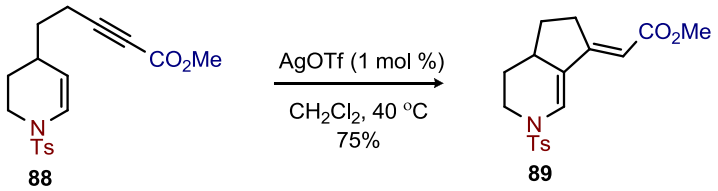
Dankwardt group described Au-mediated cyclization of *o*-alkynylphenylvinyl silyl ether **86** for the synthesis of naphthalene derivatives **87** (Scheme 3.22). The reaction involves nucleophilic addition of the silyl-enol ether to the Au-coordinated triple bond for the formation of vinylic gold intermediate **86b**; aromatization followed by deauration finally produces **87** (Scheme 3.22).[29]



Scheme 3.22. Endo cyclization of o-alkynylphenylvinyl silyl ether

3.6.6. Ag-catalyzed cycloisomerizations:

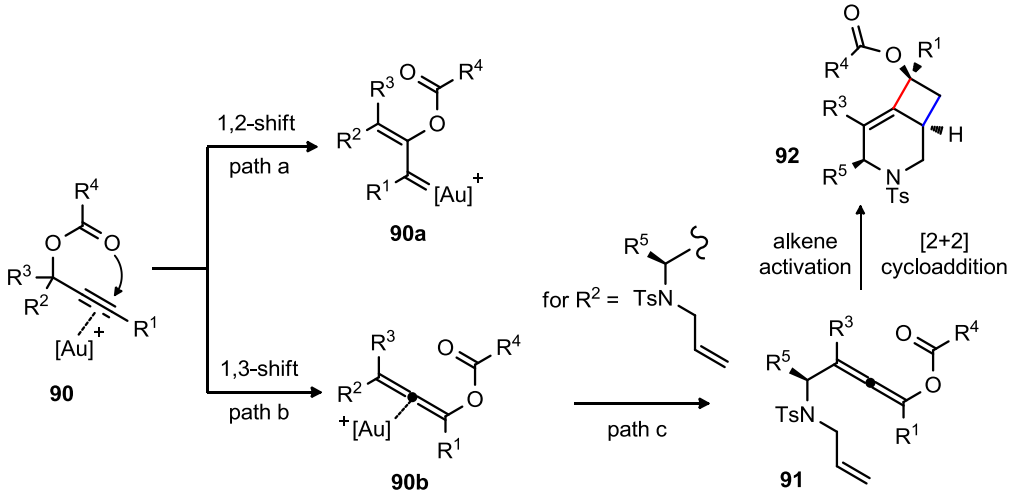
Silver salts are good halide scavengers. Accordingly, the use of Ag-salts for the metal chloride mediated cycloisomerization reactions is extremely important, as it enhances the efficiency of the reaction. Dissappointingly, the Ag-catalyzed enyne cyclizations has been poorly investigated. Interestingly, AgOTf mediated cycloisomerization of 1,6-enyne has been accomplished for the conversion of **88** to bicyclic derivative **89** (Scheme 3.23).[30] The substrates having EWG (keto, ester, amide, and nitro) at the alkyne terminus efficiently participated, while the compounds having Me/Ph substitution on alkyne terminus failed to undergo the desired cycloisomerization.



Scheme 3.23. Silver catalyzed cycloisomerization of enynes

3.6.7. Gold-catalyzed cycloisomerizations of 1,7-Enynes

In 2012, Phillip group demonstrated an elegant method for the construction of novel azabicyclo[4.2.0]oct-5-enes **92** from 1,7-enyne benzoates **90** under the influence of Au(I)-catalysts.[31a] The reaction begins with the Au-asisted 1,3-*O*-ester migration of carboxylate moiety in **90** to the formation of allenyl ester **91**; subsequently, the [2+2]-cycloaddition between the allene and the pendant olefin leads to the fused azabicyclo system. The scope of the reaction is broad; this method is successfully applied to the fabrication of complex molecular entities (Scheme 3.24).

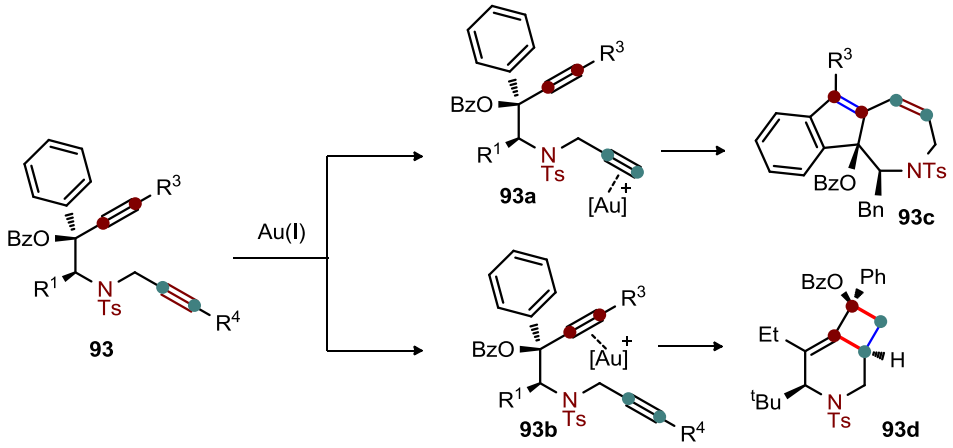


Scheme 3.24. Au-Catalyzed cycloisomerization of 1,7-enyne carboxylate.

3.6.8. Gold-catalyzed cycloisomerizations of 1,7-diynes:

The Phillip group revealed an elegant strategy for the Au(I)-catalyzed cycloisomerization of 1,7-diyne benzoate **93** for the construction of complex molecular framework indeno[1,2-c]azepines **93c** and azabicyclo[4.2.0]octa-1(8),5-dienes **93d**.[31b] This transformation proceeds via selective activation of terminal alkyne moiety followed by concerted double cyclization by the nucleophilic attack of the aryl group situated at the carbinol carbon center. Rearomatization followed by protodeauration leads to the product **93c**. In case of the substitution at the propargyl amine alkyne terminus, the gold preferentially activate the triple bond adjacent to ester moiety, resulting syn 1,3-migration of the benzoate group to

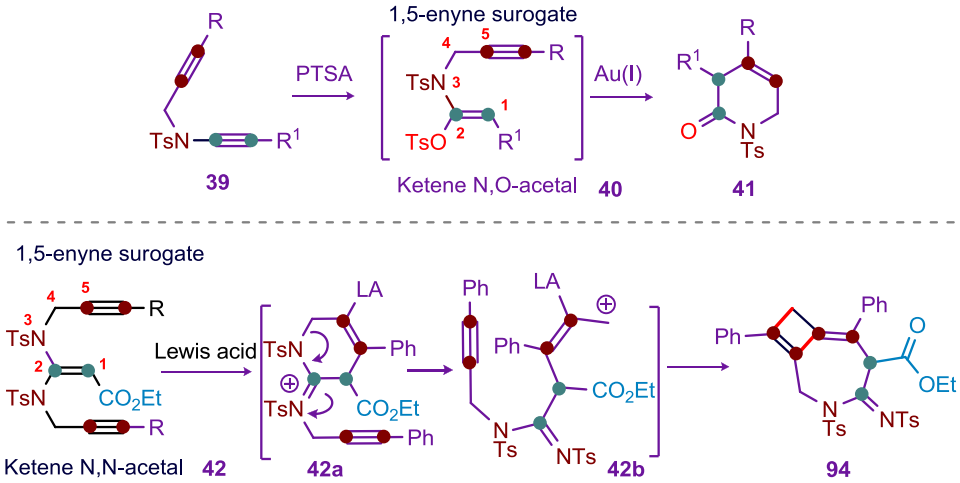
generate an allenyl intermediate. Further activation of the pendant alkyne under the influence of gold(I) catalyst affords [2+2] cycloaddition product **93d**.



Scheme 3.25. Au-catalyzed cycloisomerization of 1,7-diyne esters

3.7. Motivation, Hypothesis, and Design

Recently, we have demonstrated a Au–catalyzed, *p*-TSA·H_2O triggered hydrative cyclization of alkyne tethered ynamide **39** for the synthesis of dihydropyridinone **41** (Scheme 3.26).[13] The transient alkyne-tethered ketene N,O-acetal **40**, obtained via the attack of *p*-TSA on an activated ynamide, presumably participates in the cyclization to form **41** (Scheme 3.26).[13] To our disappointment, we could not isolate ketene N,O-acetal **40.** Gratifyingly, we are successful in the synthesis of an analogous alkyne-tethered ketene N,N-acetal **42** as a 1,5-enyne surrogate, as detailed in the previous section in this thesis.



Scheme 3.26. Lewis acid mediated cycloisomerization of ketene *N,N*-acetal

A detailed survey on the strategies for the reaction on 1,*n*-enynes reveals that the cyclization and isomerization sequence contributes significantly towards building complexity, introducing numerous functionalities and substituents, and constructing novel cyclic

molecular entities from readily accessible precursors. For instance, Au-catalyzed cycloisomerization of 1,*n*-enynes and 1,*n*-diynes enable the synthesis of various novel carbo- and heterocycles. Since we have achieved a reliable synthetic strategy for the construction of alkyne tethered ketene *N,N*-acetal **42**, an 1,5-enyne surrogate, we therefore intend to examine Au(I)/Ag–catalyzed cycloisomerization of **42** having an electron rich olefin bearing enamine integrated with an alkyne moiety (Scheme 3.26). To the best of our knowledge, reactivity and application of ketene aminals under Au/Ag-catalysis remains unexplored.

We at first envisaged the inherent delocalization of the nitrogen lone pair in ketene N,N-acetals **42** would assist the 6–*endo*–dig attack of C-2 to the LA-activated alkyne unit to form intermediate **42a** (Scheme 3.26). The single cleavage rearrangement would then produce the transient LA-allyl-cation species **42b**. Elimination of the LA- species from **42b**, followed by a [2+2] intramolecular cycloaddition between the LA-activated pendant alkyne and *in situ* generated allene-moiety would afford an unusual cyclobutene-fused azepine skeleton **94** (Scheme 3.26).[32] The construction of cyclobutene fused heterocycles has been a fascinating challenge for synthetic chemists. Of note, the synthetic methods for cyclobutene-fused azepine structural entities have remained elusive so far. Seven membered azepines and its analogues are an important class of heterocycles because of their bioactivities and pharmaceutical applications (Figure 3.5).[33] Natural products containing azepine core show protein inhibition, antimalerial and anti-bacterial properties.[34] Due to the enormous importance, we are pleased to develop an efficient synthetic method for the access of azepine derivatives.

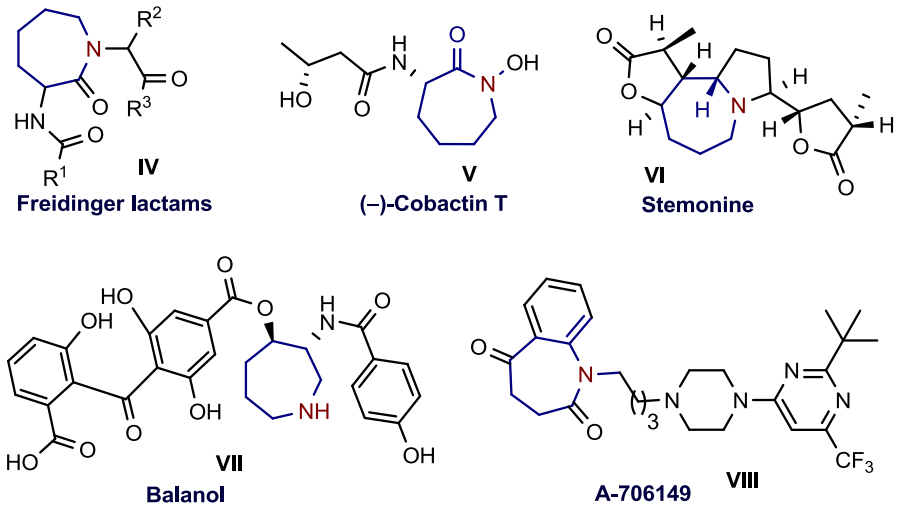


Figure 3.5. Biologically active azepine derivatives

In section-I, a cost-effective K_3PO_4 base promoted one-step method for the synthesis of stable alkyne-tethered ketene *N,N*-acetals **42** from easily accessible *N*-protected propargyl

amines and 3-bromopropiolates is detailed. In this section, the Au(I)-catalyzed cycloisomerization of alkyne-tethered ketene *N,N*-acetals **42** for the synthesis of cyclobutene-fused azepines **94** is demonstrated.

3.8. Results and Discussion

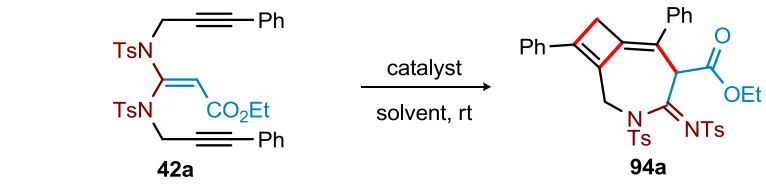
3.8.1. Reaction optimization

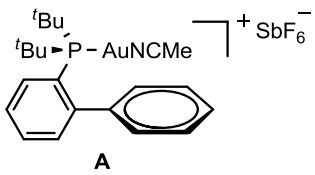
With an array of stable ketene aminals **42** in our hand, we then explored examining the possibility of cycloisomerization of **42a** under the influence of Lewis or Brønsted acid catalysts (Table 3.5). The investigation was initiated by exposing **42a** to various gold-catalysts. The reaction of **42a** with catalyst A (5.0 mol %) in the presence of *p*-TSA (2.5 equiv) in CH_3CN produces the anticipated cyclobutene-fused azepine skeleton bearing compound **94a** in 68% yield (entry 1).[13] The X-ray crystallographic analysis unambiguously confirmed the structure of **94a** (Figure 3.6).[37] The cyclobutene-fused substituted azepine structural entity makes the morphology **94a** impressive. In contrast, the strategies for the synthesis of cyclobutene-fused piperidines and indeno azepines involve the Au-catalyzed cycloisomerization of 1,7-enynes and 1,7-diynes, respectively (Scheme 3.24 and 3.25).[2e] These informations thus provoked us finding an optimized conditions for the efficient conversion of **42a** to **94a**. The reaction was found to be sluggish in the absence of *p*-TSA·H_2O, although **42a** consumed completely (entry 2). The dioxane, THF, and toluene solvents appeared moderate (entries 3–5). To our delight, the use of chlorinated solvents found effective. For instance, the reaction in CH_2Cl_2/1,2-dichloroethane (DCE) occurred rapidly, producing **94a** in 78% and 82% yield, respectively within 2 h (entries 6 and 7). Gratifyingly, cycloisomerization of **42a** with lower loading of catalyst A (3.0 mol %) in DCE did not affect the product yield, delivering 80% of **94a** in 4 h (entry 8). The other Au-catalysts were found ineffective (entries 9–13). Attempt to cycloisomerize **42a** in presence of $In(OTf)_3$, $Cu(OTf)_2$, or $Pd(OAc)_2$ turned futile (entries 14-16). Other Lewis acids such as $AgNTf_2$ and AgOTf were ineffective (entries 17 and 18).[35a-b]

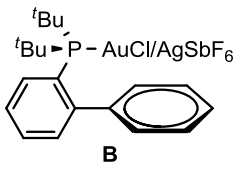
3.8.2. Subsrate scope

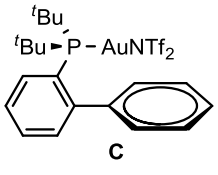
The essence of the optimized Au-catalyzed cycloisomerization conditions (entry 8, Table 3.5) is examined assessing the reactivity as well as the scope of this transformation. The results are detailed in (Table 3.6). The desired cycloisomerization product **94a** (80%) was isolated from the electron-neutral phenyl bearing ketene aminal **42a**. The compounds **42b** and **42c** having electron donating *p*-Me and *p*-OMe groups on the aryl-ring underwent cycloisomerization efficiently, furnishing **94b** and **94c** in 74%, 75% yields, respectively. The structure of **94c** was further confirmed by X-ray crystallography analysis (Figure 3.6).[35b]

Table 3.5. Optimization for the cycloisomerization of **42a**[a]









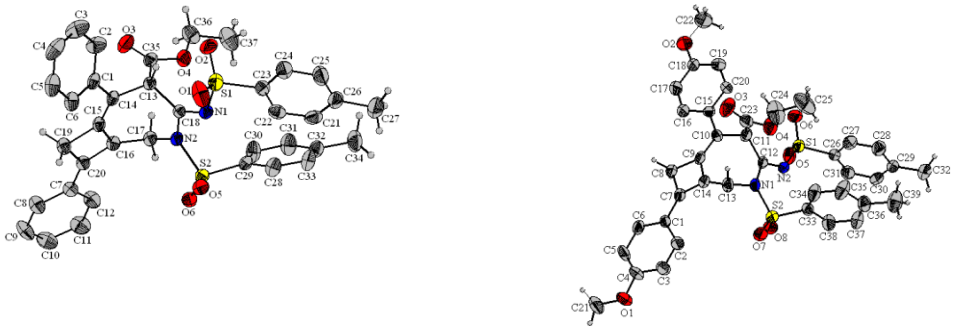
IPrAuCl/AgSbF$_6$ **D**

Ph$_3$PAuCl/AgSbF$_6$ **E**

Ph$_3$PAuCl/AgNTf$_2$ **F**

entry	catalyst (mol %)	solvent	time (h)	yield **94** (%)[b]
1[c]	**A** (5)	CH_3CN	4	68
2	**A** (5)	CH_3CN	30	52
3	**A** (5)	dioxane	30	43
4	**A** (5)	THF	30	33
5	**A** (5)	toluene	30	35
6	**A** (5)	CH_2Cl_2	2	78
7	**A** (5)	DCE	2	82
8	A (3)	DCE	4	80
9	**B** (5)	DCE	24	43
10	**C** (5)	DCE	24	22
11	**D** (5)	DCE	24	15
12	**E** (5)	DCE	24	28
13	**F** (5)	DCE	24	45
14	In(OTf)$_3$	DCE	24	trace
15	Cu(OTf)$_2$	DCE	24	trace
16	Pd(OAc)$_2$	DCE	24	trace
17	$AgNTf_2$	DCE	24	20
18	AgOTf	DCE	24	22

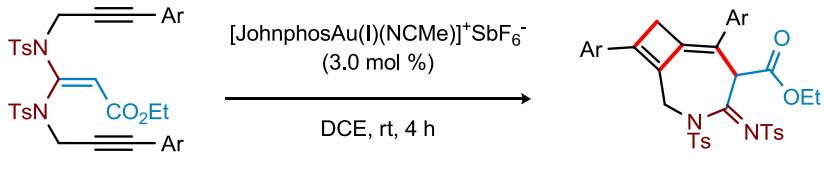
[a]Reactions were carried out using **42a** (0.2 mmol) in solvent (3.0 mL). [b]Isolated yields. [c]*p*-TSA = *p*-toluenesulfonic acid is used. IPr = 1,3-di(*iso*-propylphenyl)imidazol-2-ylidene, Tf = trifluoromethanesulfonyl, THF = tetrahydrofuran, DCE = 1,2-dichloroethane.



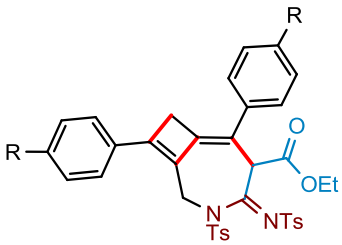
94a **94c**

Figure 3.6. X- Ray crystal structure of the compound **94a** and **94b**

Table 3.6. Synthesis of cyclobutene-fused azepines **94**; substrate scope-I[a,b]

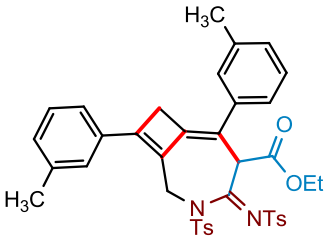


42 **94**

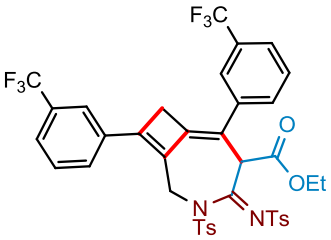


94a R = H 80%
94b R = CH_3 74%
94c R = OCH_3 75%
94d R = F 64%
94e R = Cl 82%
94f R = Br 88%

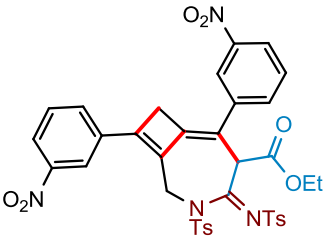
94g R = I 71%
94h R = CF_3 75%[c]
94i R = $COCH_3$ 48%[c]
94j R = CO_2CH_3 56%[c]
94k R = NO_2 66%[c]
94l R = CN 63%[c]



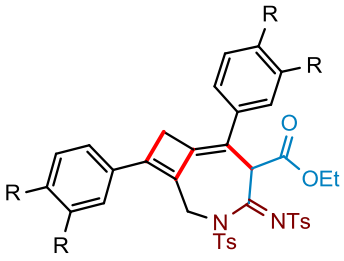
94m 80%



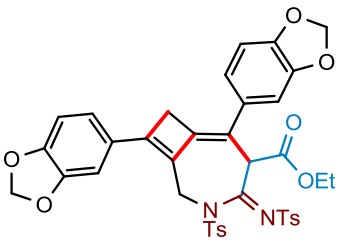
94n 68%[c]



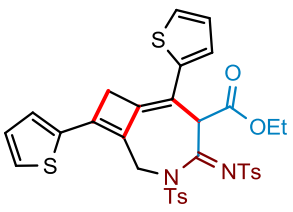
94o 51%[c]



94p R = CH_3 67%
94q R = Cl 61%[c]



94r 58%

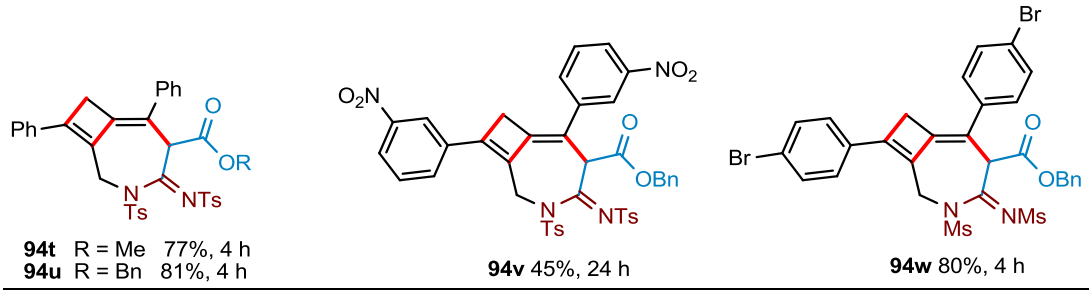


94s 82%

[a]Reactions were carried out using **42** (0.2 mmol), catalyst **A** (3.0 mol %) in DCE (3.0 mL) at room temperature for 4 h. [b]Isolated yields. [c]Reaction continued for 20 h.

The desired products **94d–g** were isolated in excellent yields from the corresponding halo group (F, Cl, Br and I) bearing precursors **42d–g**. The CF_3-bearing product **94h** was obtained in 75% yield. The keto, ester, nitro and cyano functional groups on arenes in the ketene *N,N*-acetals **42i–l** did not affect the cycloisomerization; however, the reaction proceeded sluggishly, justifying the poor activation by the Au-complex to the electron-deficient alkynes, and the products **94i–l** were obtained in moderate to good yields. The cycloisomerization of *m*-Me, *m*-CF_3, and *m*-NO_2 on aryl-ring containing ketene aminals **42m–o** led to the desired products **94m–o**. The precursors **42p** and **42q** having two methyl or chloro groups on arenes in *m*-/*p*- positions smoothly participated in the cycloisomerizations, affording **94p** and **94q** in 67% and 61% yields, respectively. Similarly, **94r** (58%) was produced from **42r**. Gratifyingly, the 2-thienyl substituted ketene aminal **42s** underwent cycloisomerization delivering **94s** in 82% yield.

Table 3.7. Synthesis of cyclobutene-fused azepines **94**; substrate scope-II[a,b]



94t R = Me 77%, 4 h
94u R = Bn 81%, 4 h

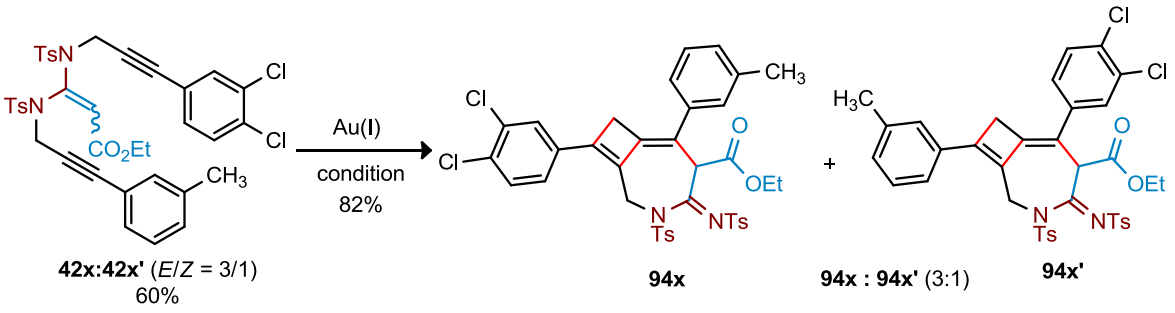
94v 45%, 24 h

94w 80%, 4 h

[a]Reactions were carried out using **42** (0.2 mmol), catalyst **A** (3.0 mol %) in DCE (3.0 mL) at room temperature for 4 h. [b]Isolated yields. [c]Reaction continued for 20 h.

We next examined the effect of various vinyl-ester and N-protecting groups in the ketene *N,N*-acetals to this cycloisomerization (Table 3.7). The methyl and benzyl ester groups did not show pronounced effect to the efficiency and reactivity; the products **94t** and **94u** were produced in 77% and 81% yields, respectively. Moderate yield of **94v** is the consequence of electron-deficient *m*-NO_2-phenyl substituted alkyne moiety on **42v**; the reaction did not proceed to completion even after 24 h, with the recovery of 26% of **42v**. Gratifyingly, the N-mesyl protected compound **42w** efficiently cycloisomerized to result **94w** in good yield in 4 h.[35]

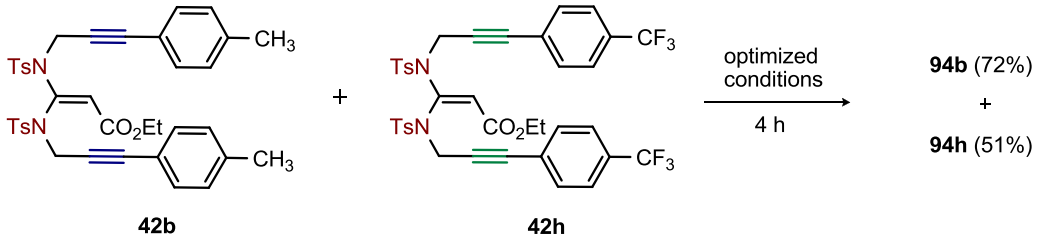
We next looked into the cycloisomerization of the unsymmetrical alkyne-tethered ketene N,N-acetals **42x**+**42x′**. The non-separable E/Z (3/1) mixture of **42x** and **42x′**was isolated in 60% yield following the addition/elimination and K_3PO_4 mediated hydroamidation sequence (page 17: Section I).



Scheme 3.27. Cycloisomerization of unsymmetrical ketene *N,N*-acetal

Gratifyingly, the cycloisomerization of **42x** and **42x′** under the optimized Au-catalyzed conditions led to non-separable mixture of cyclobutene-fused azepines **94x** and **94x′** (3:1, 82%) (Scheme 3.27). The regioselective attack of the C-2 enediamine to the elctron-rich substituted alkyne possibly allows the formation of major product **94x**.

3.8.3. Competetion experiment



Scheme 3.28. Cycloisomerization of unsymmetrical ketene *N, N*-acetal

To probe the occurrence of intramolecular attack of an enamine nucleophile to the Au-activated alkyne moiety for the conversion of **42** to **94**, reaction between electron-rich,-deficient aryl moiety bearing ketene aminals **42b** and **42h** was performed under the optimized conditions for 4 h. The compounds **94b** (72%) and **94h** (51%) were exclusively isolated.[35] We did not even observe a trace of the crossover products between **42b** and **42h**. It is thus clear that the intramolecular cyclization of **42** led exclusively to **94**.

To understand the probable path of the reaction, we performed a series of ^{1}H NMR experiment. The compound **42f** (spectrum-I) was thus subjected to the optimized catalytic conditions in $CDCl_3$ in the NMR tube (Figure 3.7). The ^{1}H NMR spectrum of the crude mixture was recorded in a regular time intervals. Surprisingly, we observed an instant shift of vinyl-H_a (5.76 ppm, s) in **42f** to (6.32 ppm, t) in 5 minutes (spectrum-II). The two propargyl –CH_2 protons in **42f** [4.50 (s) and 4.63 (s) ppm] are shifted to [4.91 (dd) and 5.29 (bt) ppm] with finer splitting, reflecting the chemically non-equivalent nature of one of the –CH_2 group; the two Me-groups of N-Ts are also moved from 2.40 and 2.37 ppm to 2.44 and 2.52 ppm along with minor relevant changes found in the aryl-ring and CO_2Et protons (spectrum-II).[35]

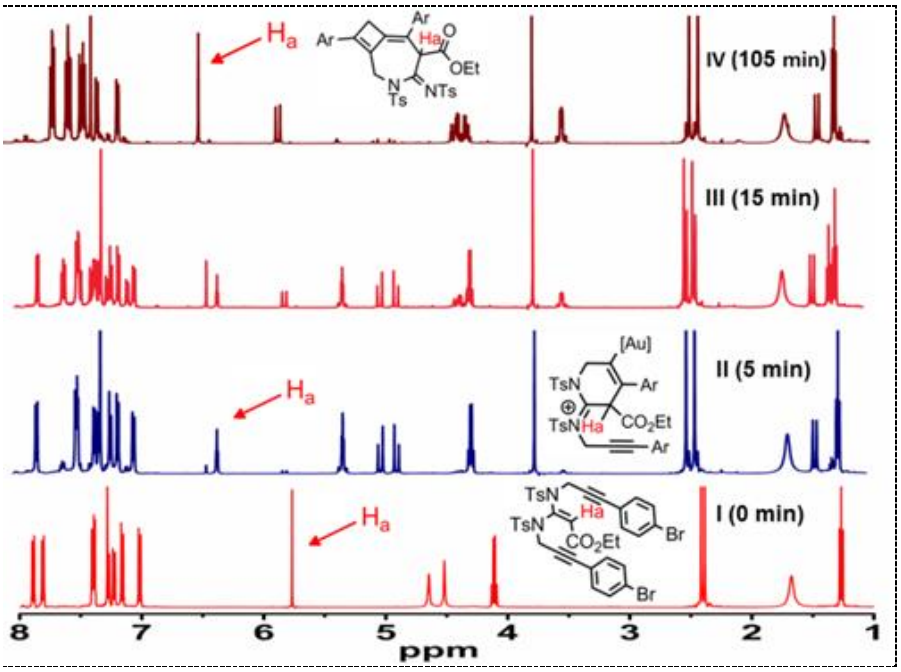
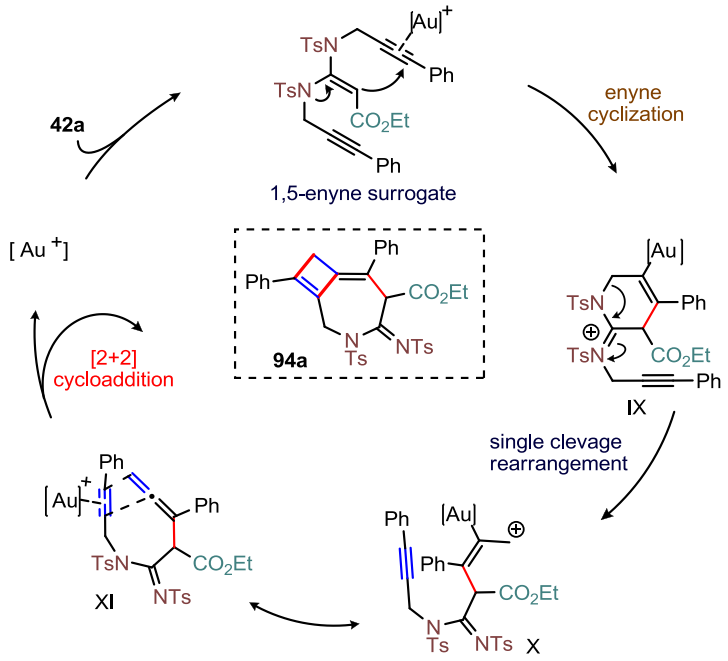


Figure 3.7. ^{1}H NMR experiment

These observations support the rapid formation of transient 6-membered N-heterocycle. As the time proceeds, the intensity of relevant peaks of the transient species (spectrum-II) slowly reduced with the appearance of the coresponding peaks related to **94f** (spectrum-III); this transition was noticed from 15 minutes. As observed from the crude ^{1}H NMR spectrum, the reaction was complete in 105 minutes (spectrum IV) with the disappearence of the peaks in spectrum II. These studies truly witness the cycloisomerization of **42** to **94**.



Scheme 3.29. Mechanism for the cycloisomerization

Although the mechanistic details are yet to be established, the plausible mechanistic cycle is sketched in (Scheme 3.29). The reaction begins with the activation of the triple bond of ketene *N,N*-acetal **42** by the Au-catalyst, triggering the regioselective 6-*endo*dig attack of the olefin C-2 of enediamine or 1,5-enyne surrogate. The inherent participation of the nitrogen lone pair assists this cyclization[13] and allows the rapid formation of a six membered iminium-gold-vinyl species I; the ^{1}H NMR experiment study supports this fact (Figure 3.7). The single cleavage rearrangement of the C–N bond in IX would then generate the vinyl-gold-allyl-cationic species X *in situ*. The removal of the Au-species from X readily forms the transient allene-species XI. Finally, [2+2]-cycloaddition between the reactive allene and Au-activated alkyne produces the azabicyclo-[5.2.0]nona-1(9),5-diene-5-carboxylate heterocycles (cyclobutene-fused azepines) with the release of the Au-complex. Although we could not detect the allene intermediate in the ^{1}H NMR experiment, the participation of an allene intermediate suitably explains the formation of an unusually strained cyclobutene-fused azabicyclic moiety.

3.9. Conclusions

In conclusion, a gold-catalyzed cycloisomerization of alkyne-tethered ketene aminals delivering the rather unusual cyclobutene-fused azepine skeletons has been shown; the reaction exhibits broad substrate scope and tolerates various functional groups. The ^{1}H NMR studies allowed deducing the plausible reaction pathway. These preliminary results would boost in the development of novel transformations on ketene aminals.

3.10. Experimental

3.10.1. General experimental information

All the reactions were performed in an oven-dried Schlenk flask. Commercial grade solvents were distilled prior to use. Column chromatography was performed using either 100-200 Mesh or 230-400 Mesh silica gel. Thin layer chromatography (TLC) was performed on silica gel GF254 plates. Visualization of spots on TLC plate was accomplished with UV light (254 nm) and staining over I_2 chamber.

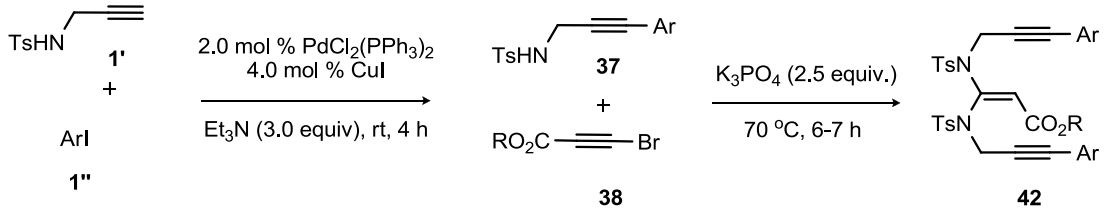
Proton, and carbon nuclear magnetic resonance spectra (^{1}H NMR, and ^{13}C NMR) were recorded based on the resonating frequencies as follows: (^{1}H NMR, 400 MHz; ^{13}C NMR, 101 MHz) and (^{1}H NMR, 500 MHz; ^{13}C NMR, 126 MHz) having the solvent resonance as internal standard (^{1}H NMR, $CHCl_3$ at 7.26 ppm; ^{13}C NMR, $CDCl_3$ at 77.0 ppm). Few cases tetramethylsilane (TMS) at 0.00 ppm was used as reference standard. Data for ^{1}H NMR are reported as follows: chemical shift (ppm), multiplicity (s = singlet; bs = broad singlet; d = doublet; bd = broad doublet, t = triplet; bt = broad triplet; q = quartet; dd = doublet of doublet; td = triplet of doublet, dt = doublet oftriplet, ddd; doublet of doublet of doublet; m = multiplet), coupling constants, *J*, in (Hz), and integration. Data for ^{13}C NMR were reported in terms of chemical shift (ppm). IR spectra were reported in cm^{-1}. LC-MS spectra were obtained with ionization voltage of 70ev; data was reported in the form of *m/z* (intensity relative to base peak = 100). Elemental (C, H, N) analysis were carried out using FLASH EA 1112 analyzer. Melting points were determined by electro-thermal heating and are uncorrected. X-ray data was collected at 298 K using graphite monochromated Mo-Kα radiation (0.71073 Å).

3.10.2. Materials

Unless otherwise noted, all the reagents and intermediates were obtained commercially and used without purification. Dichloromethane (CH_2Cl_2), toluene, acetonitrile, ethyl acetate, dichloroethane (DCE) and 1,4-dioxane were distilled over CaH_2. THF was freshly distilled over sodium/benzophenone ketyl under dry nitrogen. Catalyst **A** (99.9 %), **B** (99.9 %), **C** (99.9 %), IPrAuCl (99.9 %), Ph_3PAuCl (99.9 %), $In(OTf)_2$, $Pd(OAc)_2$, $PdCl_2(PPh_3)_2$ and $Sc(OTf)_3$ were purchased from Sigma Aldrich Ltd. and used as received. Silver salts such as $AgSbF_6$, $AgNTf_2$, and $Ag(OCOCF_3)$ were purchased from Aldrich and used as received. PTSA·H_2O was purchased from Aldrich Ltd. and used as received. PPh_3, DEAD, $CuSO_4·H_2O$, 1.10-phenanthroline, K_3PO_4, Na_2CO_3 were purchased from Merck. The aryl iodides were purchased from Aldrich and used. Analytical and spectral data of all those known compounds are exactly matching with the reported values.

3.10.3. Experimental procedures:

Scheme 1 Preparation of ketene *N,N*-acetal



Compound **1′** was prepared based on two known synthetic steps starting from the commerically available tosyl amine. First step involves the –Boc protection of the tosylamine, Mitsunobu reaction between the N-Boc-protected tosylamine with the propargyl alcohol in the presence of triphenyl phosphine (Ph_3P) and diisopropyl azodicarboxylate (DIAD) in THF followed by deprotection of N-Boc moiety by trifluoroacetic acid (TFA) to obtain **1′**.[36]

Following the reported procedure, substrate **42** was prepared from **1′** in two simple synthetic steps. Sonogashira reaction between **1′** and aryl iodides provides **37** in good to excellent yields. The base promoted mono-addition of **37** to bromopropiolates **38** followed by hydroamidation of **37** with the in-situ generated ynamides readily affords the precursors **42** in overall good yields.

3.10.4. General procedure for the synthesis of 37 (GP 1):[36]

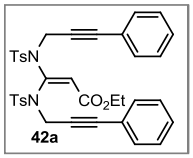
To a solution of substrate **1′** (1.0 mmol), $PdCl_2(PPh_3)_2$ (0.02 mmol) and CuI (0.04 mmol) in THF (5.0 mL) were added aryl iodide **1″** (1.2 mmol) and Et_3N (3.0 mmol) successively under an argon atmosphere. The resulting mixture was stirred at room temperature for 4 h. The crude reaction mixture was filtered through a small pad of Celite and concentrated under the reduced pressure. The crude residue was purified using column chromatography on silica gel to afford **37**.

3.10.5. General procedure for the synthesis of 42 (GP 2):[3]

A solution of **37** (1.0 mmol), K_3PO_4 (2.5 mmol) in dry toluene (3.0 mL) was stirred in a Schlenck tube. The 3-bromopropiolates **38** was subsequently introduced into the Schlenck tube. The reaction mixture was heated at 70 °C under the nitrogen atmosphere. The progress of the reaction was monitored periodically by TLC. Upon completion, the reaction mixture was cooled to room temperature and diluted with dichloromethane (10 mL). The crude mixture was filtered through a small pad of Celite and concentrated under the

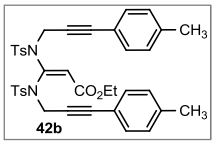
reduced pressure. The crude residue was purified using column chromatography on silica gel to provide **42**.

Ethyl-3,3-bis(4-methyl-N-(3-phenylprop-2-ynyl)phenylsulfonamido)acrylate (42a):



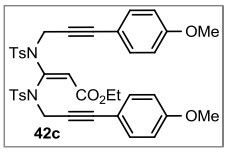
Following the general procedure of GP-2, compound **42a** (249 mg) was obtained in overall 78% yield as pale yellow gummy liquid; R_f = 0.57 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (t, J = 8.8 Hz, 4H), 7.36–7.23 (m, 10H), 7.17 (d, J = 7.6 Hz, 4H), 5.76 (s, 1H), 4.67 (br s, 2H), 4.50 (br s, 2H), 4.14 (q, J = 7.2 Hz, 2H), 2.39 (s, 3H), 2.33 (s, 3H), 1.28 (t, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.9, 144.6, 144.3, 142.7, 136.3, 135.8, 131.8, 131.6, 129.6, 129.5, 128.6, 128.5, 128.3, 128.2, 122.3, 122.1, 113.1, 86.3, 83.1, 82.9, 60.8, 41.1, 39.8, 21.63, 21.57, 14.1; IR (Neat) ν_{max} 2975, 2926, 1720, 1627, 1600, 1490, 1364, 1161 cm^{-1}; HRMS (ESI) for $C_{37}H_{34}N_2O_6S_2Na$ $(M+Na)^+$: calcd 689.1756, found 689.1757.

Ethyl-3,3-bis(4-methyl-N-(3-*p*-tolyl-prop-2-ynyl)phenylsulfonamido)acrylate (42b):



Following the general procedure GP-2, compound **42b** (309 mg) was obtained in overall 89% yield as pale yellow gummy liquid; R_f = 0.50 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (t, J = 7.6 Hz, 4H), 7.26 (d, J = 7.6 Hz, 2H), 7.18 (t, J = 7.2 Hz, 4H), 7.07 (br s, 6H), 5.74 (s, 1H), 4.66 (br s, 2H), 4.47 (br s, 2H), 4.14 (q, J = 7.2 Hz, 2H), 2.39 (s, 3H), 2.34 (s, 9H), 1.28 (q, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.0, 144.5, 144.2, 142.6, 138.7, 136.4, 135.9, 131.7, 131.5, 129.6, 129.5, 129.0, 128.9, 128.5, 128.2, 119.2, 119.0, 113.2, 86.4, 82.4, 82.2, 60.8, 41.1, 39.8, 21.60, 21.56, 21.48, 14.1; IR (Neat) ν_{max} 2975, 2920, 2241, 1715, 1621, 1512, 1358, 1156 cm^{-1}; HRMS (ESI) for $C_{39}H_{39}N_2O_6S_2$ $(M+H)^+$: calcd 695.2249, found 695.2250.

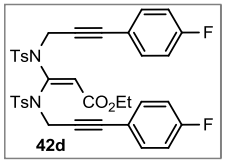
Ethyl-3,3-bis(N-(3-(4-methoxyphenyl)prop-2-ynyl)-4-methylphenyl-sulfonamido)-acryl-ate (42c):



Following the general procedure GP-2, compound **42c** (316 mg) was obtained in overall 87% yield as pale yellow gummy liquid; R_f = 0.44 (7:3 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (dd, J = 11.6, 8.0 Hz, 4H), 7.24 (d, J = 8.4 Hz, 4H), 7.20 (d, J = 7.6 Hz, 2H), 7.12 (d, J = 8.8 Hz, 2H), 6.78 (dd, J = 8.8, 2.4 Hz, 4H), 5.72 (s, 1H), 4.64 (br s, 2H), 4.46 (br s, 2H), 4.13 (q, J = 7.2 Hz, 2H), 3.80 (s, 6H), 2.39 (s, 3H), 2.35 (s, 3H), 1.27 (br t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.0, 159.7, 144.4, 144.2, 142.6, 136.4, 135.9, 133.3, 133.1, 129.6, 129.5, 128.6, 128.2, 114.4, 114.2, 113.85, 113.81, 113.1, 86.2, 81.7, 81.6, 60.8, 55.3, 41.1, 39.8, 21.6, 14.1; IR (Neat) ν_{max} 2980, 2931, 2832,

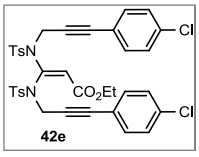
1715, 1610, 1512, 1364, 1287, 1249, 1156 cm^{-1}; HRMS (ESI) for $C_{39}H_{38}N_2O_8S_2Na$ $(M+Na)^+$: calcd 749.1967, found 749.1968.

Ethyl-3,3-bis(N-(3-(4-fluorophenyl)prop-2-ynyl)-4-methylphenylsulfonamido)-



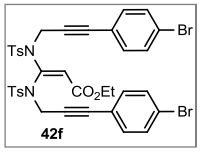
acrylate (42d): Following the general procedure GP-2, compound **42d** (284 mg) was obtained in overall 81% yield as yellow oil; R_f = 0.58 (7:3 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 8.4 Hz, 2H), 7.81 (d, J = 8.4 Hz, 2H), 7.32–7.24 (m, 4H), 7.20 (d, J = 8.0 Hz, 2H), 7.15 (dd, J = 8.8, 5.6 Hz, 2H), 6.95 (t, J = 8.4 Hz, 4H), 5.75 (s, 1H), 4.64 (br s, 2H), 4.51 (br s, 2H), 4.11 (q, J = 7.2 Hz, 2H), 2.39 (s, 3H), 2.36 (s, 3H), 1.26 (t, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.8, 162.6 (d, J = 247.4 Hz), 144.6, 144.3, 142.6, 136.2, 135.7, 133.7, 133.7, 133.6, 133.5, 129.6, 129.5, 128.6, 128.2, 118.2 (d, J = 8.4 Hz), 115.5 (d, J = 8.4 Hz), 113.0, 85.2, 82.9, 82.7, 60.8, 41.1, 39.6, 21.6, 14.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ −110.1 to −110.2 (m); IR (Neat) ν_{max} 3068, 2975, 2926, 2849, 1715, 1621, 1600, 1512, 1358, 1221, 1161 cm^{-1}; HRMS (ESI) for $C_{37}H_{33}F_2N_2O_6S_2(M+H)^+$: calcd 703.1748, found 703.1745.

Ethyl-3,3-bis(N-(3-(4-chlorophenyl)prop-2-ynyl)-4-methylphenylsulfonamido)-



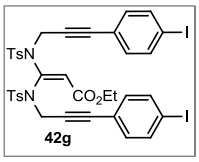
acrylate (42e): Following the general procedure GP-2, compound **42e** (360 mg) was obtained in overall 72% yield as thick brown gummy liquid; R_f = 0.62 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 8.0 Hz, 2H), 7.80 (d, J = 8.4 Hz, 2H), 7.32–7.19 (m, 10H), 7.07 (dt, J = 8.0, 2.4 Hz, 2H), 5.76 (s, 1H), 4.64 (br s, 2H), 4.52 (br s, 2H), 4.10 (q, J = 6.8 Hz, 2H), 2.39 (s, 3H), 2.36 (s, 3H), 1.25 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.8, 144.7, 144.4, 142.6, 136.2, 135.7, 134.7, 133.0, 132.8, 129.6, 129.5, 128.6, 128.5, 128.1, 120.7, 120.5, 112.9, 85.1, 84.1, 84.0, 60.8, 41.1, 39.5, 21.6, 14.1; IR (Neat) ν_{max} 3057, 2980, 2920, 1906, 1715, 1627, 1600, 1490, 1364, 1172, 1084 cm^{-1}; HRMS (ESI) for $C_{37}H_{33}Cl_2N_2O_6S_2$ $(M+H)^+$: calcd 735.1157, found 735.1161.

Ethyl-3,3-bis(N-(3-(4-bromophenyl)prop-2-ynyl)-4-methylphenylsulfonamido)-

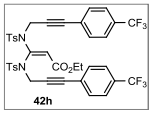


acrylate (42f): Following the general procedure GP-2, compound **42f** (301 mg) was obtained in overall 73% yield as pale yellow gummy liquid; R_f = 0.62 (7:3 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 8.4 Hz, 2H), 7.79 (d, J = 8.4 Hz, 2H), 7.38 (dd, J = 8.8, 4.0 Hz, 4H), 7.22 (t, J = 8.0 Hz, 4H), 7.14 (d, J = 8.0 Hz, 2H), 7.01 (d, J = 8.4 Hz, 2H), 5.75 (s, 1H), 4.63 (br s, 2H), 4.51 (br s, 2H), 4.09 (q, J = 7.2 Hz, 2H), 2.40 (s, 3H), 2.37 (s, 3H), 1.25 (t, J =

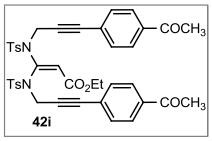
7.2 Hz, 3H); ^{13}C NMR (101MHz, $CDCl_3$) δ 163.7, 144.7, 144.4, 142.6, 136.2, 135.7, 133.2, 133.0, 131.5, 129.6, 129.5, 128.6, 128.1, 123.0, 121.2, 120.9, 112.9, 85.2, 84.3, 84.2, 60.8, 41.1, 39.5, 22.7, 21.6, 14.1; IR (Neat) ν_{max} 2975, 2920, 1715, 1627, 1594, 1490, 1358, 11671112 cm^{-1}; HRMS (ESI) for $C_{37}H_{32}Br_2N_2O_6S_2Na$ $(M+Na)^+$: calcd 844.9966, found 844.9973.

Ethyl-3,3-bis(N-(3-(4-iodophenyl)prop-2-ynyl)-4-methylphenylsulfonamido)-acrylate (42g): 

Following the general procedure GP-2, compound **42g** (307 mg) was obtained in overall 67% yield as pale yellow gummy liquid; R_f = 0.60 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 8.0 Hz, 2H), 7.79 (d, J = 8.0 Hz, 2H), 7.58 (t, J = 8.0 Hz, 4H), 7.23 (dd, J = 16.0 Hz, 8.0 Hz, 4H), 7.00 (d, J = 8.0 Hz, 2H), 6.85 (d, J = 8.0 Hz, 2H), 5.75 (s, 1H), 4.63 (br s, 2H), 4.50 (br s, 2H), 4.08 (q, J= 7.2 Hz, 2H), 2.39 (s, 3H), 2.32 (s, 3H), 1.24 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.7, 144.7, 144.4, 142.6, 137.4, 136.1, 135.6, 133.2, 133.0, 129.6, 129.5, 128.6, 128.1, 127.5, 121.7, 121.5, 112.8, 94.7, 85.35, 85.31, 84.6, 84.5, 60.8, 41.1, 39.5, 21.6, 14.1; IR (Neat) ν_{max} 2233, 1593, 1371, 1170, 1114, 1033 cm^{-1}; HRMS (ESI) for $C_{37}H_{33}I_2N_2O_6S_2$ $(M+H)^+$: calcd 918.9869, found 918.9872.

Ethyl-3,3-bis(4-methyl-N-(3-(4-(trifluoromethyl)phenyl)prop-2-ynyl)phenyl-sulfonamido)acrylate (42h): 

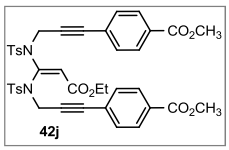
Following the general procedure GP-2, compound **42h** (350 mg) was obtained in overall 70% yield as thick pale yellow gummy liquid; R_f = 0.57 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 8.0 Hz, 2H), 7.78 (d, J = 8.4 Hz, 2H), 7.52–7.46 (m, 4H), 7.39 (d, J = 8.0 Hz, 2H), 7.29–7.19 (m, 6H), 5.81 (s, 1H), 4.68 (br s, 2H), 4.59 (br s, 2H), 4.09 (q, J = 7.2 Hz, 2H), 2.39 (s, 3H), 2.36 (s, 3H), 1.25 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.6, 144.9, 144.5, 142.6, 136.1, 135.5, 132.0, 131.8, 130.2 (q, J = 30 Hz), 129.6, 129.6, 128.1, 127.8, 125.9 (d, J = 25.2 Hz), 125.8, 125.2, 122.4, 112.8, 85.7, 85.6, 84.8, 60.8, 41.1, 39.4, 21.6, 21.5, 14.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ –63.0 (s), –62.9 (s); IR (Neat) ν_{max} 2926, 2843, 1726, 1594, 1358, 1320, 1117 cm^{-1}; HRMS (ESI) for $C_{39}H_{33}F_6N_2O_6S_2$ $(M+H)^+$: calcd 803.1684, found 803.1684.

Ethyl-3,3-bis(N-(3-(4-acetylphenyl)prop-2-ynyl)-4-methylphenyl-sulfonamido)acrylate (42i): 

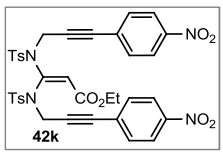
Following the general procedure GP-2, compound **42i** (270 mg) was obtained in overall 72% yield as thick brown liquid; R_f = 0.35 (2:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 8.0 Hz, 2H), 7.85–7.77 (br t, J = 7.6 Hz, 6H), 7.36 (d, J = 8.0 Hz, 2H), 7.26–7.19 (m, 6H), 5.78 (s, 1H), 4.67 (br s, 2H), 4.57 (br s, 2H), 4.16–3.98 (m, 2H), 2.57 (s, 3H), 2.55 (s, 3H), 2.39 (s, 3H), 2.35 (s, 3H), 1.24 (br t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$)

δ 197.2, 163.7, 144.8, 144.5, 142.6, 136.5, 136.1, 135.6, 131.8, 131.7, 129.6, 129.5, 128.7, 128.1, 128.0, 127.0, 126.8, 112.8, 86.5, 86.4, 85.4, 60.8, 41.1, 39.4, 26.6, 21.6, 14.1; IR (Neat) ν_{max} 2980, 2925, 1714, 1687, 1604, 1363, 1259, 1171 cm^{-1}; HRMS (ESI) for $C_{41}H_{39}N_2O_8S_2$ $(M+H)^+$: calcd 751.2148, found 751.2148.

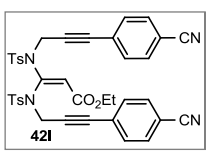
Dimethyl 4,4'-(3,3'-(3-ethoxy-3-oxoprop-1-ene-1,1-diyl)bis(tosylazanediyl)bis-(prop-1-yne-3,1-diyl))dibenzoate (42j): Following the general procedure GP-2, compound **42j** (258 mg) was obtained in overall 66% yield as thick brown liquid; R_f = 0.29 (7:3 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92–7.85 (m, 6H), 7.80 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H), 7.20 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 8.4 Hz, 2H), 5.79 (s, 1H), 4.67 (br s, 2H), 4.56 (br s, 2H), 4.08 (q, J = 7.2 Hz, 2H), 3.91 (s, 6H), 2.39 (s, 3H), 2.34 (s, 3H), 1.24 (br t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 163.7, 144.8, 144.4, 142.7, 136.1, 135.6, 131.6, 131.4, 129.9, 129.6, 129.5, 129.4, 129.3, 128.7, 128.1, 126.8, 126.6, 112.8, 86.1, 86.0, 85.5, 85.4, 60.8, 52.3, 41.2, 39.5, 21.6, 14.1; IR (Neat) ν_{max} 2953, 1720, 1604, 1440, 1363, 1276, 1111 cm^{-1}; HRMS (ESI) for $C_{41}H_{39}N_2O_{10}S_2$ $(M+H)^+$: calcd 783.2046, found 783.2047.



Ethyl-3,3-bis(4-methyl-N-(3-(4-nitrophenyl)prop-2-ynyl)phenylsulfonamido)-acrylate (42k): Following the general procedure GP-2, compound **42k** (223 mg) was obtained in overall 59% yield as pale yellow gummy liquid; R_f= 0.43 (7:3 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (dd, J = 8.4, 4.0 Hz, 4H), 7.88 (d, J = 8.0 Hz, 2H), 7.75 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 7.29–7.24 (m, 4H), 5.81 (s, 1H), 4.67 (s, 2H), 4.62 (s, 2H), 4.06 (q, J = 7.2 Hz, 2H), 2.40 (s, 3H), 2.39 (s, 3H), 1.24 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.5, 147.3, 145.1, 144.6, 142.7, 135.9, 135.3, 132.5, 132.3, 129.7, 129.6, 128.7, 128.1, 123.5, 113.0, 88.7, 88.4, 84.3, 84.1, 60.9, 41.2, 39.4, 21.6, 14.1; IR (Neat) ν_{max} 3063, 2980, 1715, 1600, 1715, 1337, 1156 cm^{-1}; HRMS (ESI) for $C_{37}H_{33}N_4O_{10}S_2$ $(M+H)^+$: calcd 757.1638, found 757.1640.

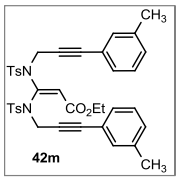


Ethyl-3,3-bis(N-(3-(4-cyanophenyl)prop-2-ynyl)-4-methylphenylsulfonamido)-acrylate (42l): Following the general procedure GP-2, compound **42l** (276 mg) was obtained in overall 77% yield as brown liquid; R_f= 0.35 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 8.0 Hz, 2H), 7.75 (d, J = 8.4 Hz, 2H), 7.60–7.51 (m, 4H), 7.38 (d, J = 8.4 Hz, 2H), 7.30–7.21 (m, 6H), 5.78 (s, 1H), 4.64 (br s, 2H), 4.58 (br s, 2H), 4.06 (q, J = 7.2 Hz, 2H), 2.42 (s, 3H), 2.38 (s, 3H), 1.24 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101MHz, $CDCl_3$) δ 163.6, 145.0,



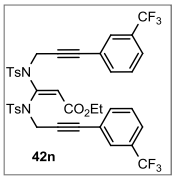
144.6, 142.7, 136.0, 135.3, 132.2, 132.1, 132.0, 129.7, 129.6, 128.7, 128.1, 127.1, 126.8, 118.2, 113.1, 112.2, 112.1, 87.8, 87.5, 84.6, 84.3, 60.9, 41.2, 39.4, 21.6, 14.1; IR (Neat) ν_{max} 3090, 2964, 2931, 2230, 1923, 1715, 1605, 1495, 1364, 1161, 1090 cm^{-1}; HRMS (ESI) for $C_{39}H_{32}N_4O_6S_2Na$ $(M+Na)^+$: calcd 739.1661, found 739.1661.

Ethyl 3,3-bis(4-methyl-N-(3-*m*-tolyl-prop-2-ynyl)phenylsulfonamido)acrylate (42m):



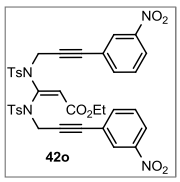
Following the general procedure GP-2, compound **42m** (268 mg) was obtained in overall 77% yield as brown gummy liquid; R_f = 0.57 (7:3 hexane/EtOAc); [Silica, UV and I_2]; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 8.4 Hz, 2H), 7.87 (d, J = 8.4 Hz, 2H), 7.29–7.26 (m, 2H), 7.19 (d, J = 8.4 Hz, 2H), 7.18–7.09 (m, 6H), 7.01–6.96 (m, 2H), 5.77 (s, 1H), 4.66 (br s, 2H), 4.49 (br s, 2H), 4.14 (q, J = 7.2 Hz, 2H), 2.39 (s, 3H), 2.36 (s, 3H), 2.29 (s, 3H), 2.28 (s, 3H), 1.27 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.9, 144.5, 144.3, 142.8, 137.9, 137.8, 136.4, 135.9, 132.3, 132.1, 129.6, 129.5, 128.9, 128.8, 128.7, 128.6, 128.2, 122.1, 121.9, 112.9, 86.5, 86.4, 82.7, 82.6, 60.7, 41.2, 39.7, 21.6, 21.5, 21.2, 14.1; IR (Neat) ν_{max} 2975, 2914, 2229, 1714, 1626, 1593, 1484, 1440, 1358, 1166 cm^{-1}; HRMS (ESI) for $C_{39}H_{39}N_2O_6S_2$ $(M+H)^+$: calcd 695.2250, found 695.2249.

Ethyl-3,3-bis(4-methyl-N-(3-(3-(trifluoromethyl)phenyl)prop-2-ynyl)phenyl-sulfonamido)acrylate (42n): Following the general procedure GP-2, compound **42n** (241 mg) was obtained in overall 60% yield as brown gummy liquid; R_f= 0.44 (7:3 hexane/EtOAc);



[Silica, UV and I_2]; ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 8.4 Hz, 2H), 7.82 (d, J = 8.4 Hz, 2H), 7.56–7.47 (m, 4H), 7.39–7.30 (m, 4H), 7.27 (d, J = 8.0 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 5.82 (s, 1H), 4.69 (br s, 2H), 4.58 (br s, 2H), 4.10 (q, J = 7.2 Hz, 2H), 2.39 (s, 3H), 2.33 (s, 3H), 1.24 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.6, 144.9, 144.5, 142.9, 136.1, 135.6, 134.8, 134.6, 130.8 (q, J = 28.2 Hz, 1C), 130.6 (q, J = 28.2 Hz, 1C), 129.6, 129.5, 128.9, 128.8, 128.6, 128.3 (d, J = 16 Hz, 1C), 128.1, 127.8, 125.2 (d, J = 12 Hz, 1C), 124.9, 123.2, 122.9, 122.2, 119.5, 112.8, 84.9, 84.7, 84.6, 60.8, 41.1, 39.5, 21.5, 21.4, 14.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ –63.0 (s); IR (Neat) ν_{max} 3063, 2980, 2926, 2865, 2224, 1715, 1621, 1600, 1495, 1353, 1156, 1084 cm^{-1}; HRMS (ESI) for $C_{39}H_{33}F_6N_2O_6S_2$ $(M+H)^+$: calcd 803.1684, found 803.1683.

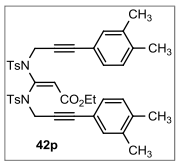
Ethyl-3,3-bis(4-methyl-N-(3-(3-nitrophenyl)prop-2-ynyl)phenylsulfonamido)-acrylate



(42o): Following the general procedure GP-2, compound **42o** (231 mg) was obtained in overall 61% yield as brown liquid; R_f = 0.35 (7:3 hexane/EtOAc); [Silica, UV and I_2]; ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (t,

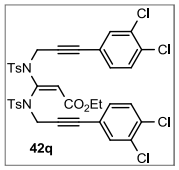
J = 8.0 Hz, 2H), 8.07 (br s, 1H), 7.90 (d, *J* = 8.0 Hz, 3H), 7.79 (d, *J* = 8.4 Hz, 2H), 7.64 (d, *J* = 7.6 Hz, 1H), 7.50 (d, *J* = 7.6 Hz, 1H), 7.44 (td, *J* = 8.0, 2.0 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 4H), 5.82 (s, 1H), 4.69 (br s, 2H), 4.61 (br s, 2H), 4.10 (q, *J* = 7.6 Hz, 2H), 2.42 (s, 3H), 2.40 (s, 3H), 1.24 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.5, 148.0, 145.2, 144.7, 142.8, 137.4, 137.2, 136.0, 135.5, 129.7, 129.6, 129.4, 128.7, 128.1, 126.4, 126.2, 124.0, 123.7, 123.4, 123.3, 112.8, 86.0, 85.8, 83.6, 60.9, 41.1, 39.2, 21.6, 14.1; IR (Neat) ν_{max} 3095, 1726, 1621, 1534, 1358, 1167 cm^{-1}; HRMS (ESI) for $C_{37}H_{33}N_4O_{10}S_2$ $(M+H)^+$: calcd 757.1638, found 757.1636.

Ethyl-3,3-bis(N-(3-(3,4-dimethylphenyl)prop-2-ynyl)-4-methylphenylsulfon-amido)-

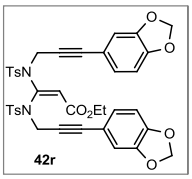


acrylate (42p): Following the general procedure GP-2, compound **42p** (206 mg) was obtained in overall 57% yield as brown liquid ; R_f = 0.62 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (t, *J* = 8.4 Hz, 4H), 7.26 (d, *J* = 7.6 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.09–6.96 (m, 4H), 6.95–6.87 (m, 2H), 5.73 (s, 1H), 4.65 (br s, 2H), 4.46 (br s, 2H), 4.14 (q, *J* = 7.2 Hz, 2H), 2.40 (s, 3H), 2.36 (s, 3H), 2.24 (s, 6H), 2.20 (s, 3H), 2.19 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.0, 144.4, 144.2, 142.7, 137.5, 136.5, 136.0, 132.8, 132.7, 129.6, 129.5, 129.4, 129.3, 129.1, 128.6, 128.2, 119.5, 119.4, 113.1, 86.5, 82.1, 82.0, 60.7, 41.1, 39.7, 21.63, 21.59, 19.8, 19.6, 14.1; IR (Neat) ν_{max} 3024, 2975, 2920, 2860, 2224, 1720, 1632, 1501, 1452, 1358, 1112 cm^{-1}; HRMS (ESI) for $C_{41}H_{42}N_2O_6S_2Na$ $(M+Na)^+$: calcd 745.2382, found 745.2380

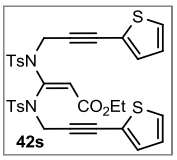
Ethyl-3,3-bis(N-(3-(3,4-dichlorophenyl)prop-2-ynyl)-4-methylphenylsulfon-amido)-



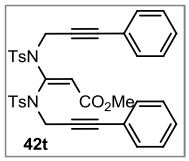
acrylate (42q): Following the general procedure GP-2, compound **42q** (314 mg) was obtained in overall 78% yield as pale yellow liquid; R_f = 0.43 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.4 Hz, 2H), 7.77 (d, *J* = 8.4 Hz, 2H), 7.34–7.23 (m, 7H), 7.16–7.09 (m, 2H), 6.98 (dd, *J* = 8.4, 2.0 Hz, 1H), 5.78 (s, 1H), 4.64 (br s, 2H), 4.54 (br s, 2H), 4.08 (q, *J* = 7.2 Hz, 2H), 2.42 (s, 3H), 2.40 (s, 3H), 1.24 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.6, 144.9, 144.5, 142.7, 136.0, 135.6, 133.3, 133.2, 133.1, 132.5, 130.8, 130.6, 130.3, 129.7, 129.6, 128.7, 128.1, 122.1, 121.8, 112.6, 85.2, 85.1, 84.0, 83.9, 60.8, 41.0, 39.3, 21.6, 14.1; IR (Neat) ν_{max} 2975, 1715, 1621, 1463, 1358, 1221 cm^{-1}; HRMS (ESI) for $C_{37}H_{31}Cl_4N_2O_6S_2$ $(M+H)^+$: calcd 803.0377, found 803.0378.

Ethyl-3,3-bis(N-(3-(benzo[d][1,3]dioxol-5-yl)prop-2-ynyl)-4-methylphenyl-sulfonamido) acrylate (42r): 

Following the general procedure GP-2, compound **42r** (264 mg) was obtained in overall 70% yield as yellow thick liquid; R_f= 0.28 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 8.0 Hz, 2H), 7.84 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 6.82 (dd, J = 8.0, 1.6 Hz, 1H), 6.75–6.67 (m, 4H), 6.56 (br s, 1H), 5.96 (s, 4H), 5.72 (s, 1H), 4.62 (br s, 2H), 4.44 (br s, 2H), 4.13 (q, J = 7.2 Hz, 2H), 2.40 (s, 3H), 2.38 (s, 3H), 1.27 (br t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.9, 148.1, 147.3, 144.6, 144.3, 142.6, 136.4, 135.9, 129.6, 129.5, 128.5, 128.2, 126.5, 126.3, 115.5, 115.3, 113.0, 111.7, 111.5, 108.4, 108.3, 101.4, 86.2, 81.4, 81.3, 60.8, 41.0, 39.6, 21.6, 14.1; IR (Neat) ν_{max} 2985, 2958, 2925, 2224, 1714, 1626, 1599, 1484, 14445, 1352, 1166 cm^{-1}; HRMS (ESI) for $C_{39}H_{35}N_2O_{10}S_2Na$ $(M+H)^+$: calcd 755.1733, found 755.1732.

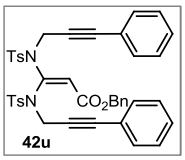
Ethyl 3,3-bis(4-methyl-N-(3-(thiophen-2-yl)prop-2-ynyl)phenylsulfonamido)-acrylate (42s): 

Following the general procedure GP-2, compound **42s** (251 mg) was obtained in overall 74% yield as thick brown liquid; R_f = 0.55 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (t, J = 8.4 Hz, 4H), 7.28 (d, J = 9.6 Hz, 3H), 7.24 (t, J = 5.2 Hz, 3H), 7.13 (br d, J = 3.2 Hz, 1H), 7.02 (br d, J = 3.2 Hz, 1H), 6.98–6.91 (m, 2H), 5.70 (s, 1H), 4.67 (br s, 2H), 4.47 (br s, 2H), 4.13 (q, J = 7.2 Hz, 2H), 2.40 (s, 3H), 2.37 (s, 3H), 1.27 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.9, 144.7, 144.4, 142.7, 136.3, 135.8, 132.7, 132.6, 129.7, 129.6, 128.4, 128.1, 127.6, 127.5, 127.0, 126.9, 122.1, 121.9, 113.3, 87.1, 86.9, 79.7, 79.5, 60.8, 41.3, 39.8, 21.6, 14.1; IR (Neat) ν_{max} 3106, 2975, 2224, 1715, 1627, 1600, 1364, 1161 cm^{-1}; HRMS (ESI) for $C_{33}H_{31}N_2O_6S_4$ $(M+H)^+$: calcd 679.1065, found 679.1063.

Methyl-3,3-bis(4-methyl-N-(3-phenylprop-2-ynyl)phenylsulfonamido)acrylate (42t): 

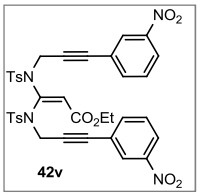
Following the general procedure GP-2, compound **42t** (229 mg) was obtained in overall 70% yield as pale brown liquid; R_f = 0.58 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (t, J = 7.2 Hz, 4H), 7.33–7.24 (m, 10H), 7.22–7.14 (m, 4H), 5.75 (s, 1H), 4.66 (s, 2H), 4.51 (s, 2H), 3.67 (s, 3H), 2.39 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.4, 144.6, 144.3, 142.9, 136.3, 135.8, 131.7, 131.6, 129.6, 129.5, 128.6, 128.5, 128.3, 128.2, 122.3, 122.1, 122.5, 86.3, 86.2, 83.0, 82.9, 51.7, 41.0, 39.7, 21.6, 21.5. IR (Neat) ν_{max} 2947, 2843, 1726, 1638, 1495, 1358, 1221, 1178, 1112, 1041 cm^{-1}; HRMS (ESI) for $C_{36}H_{33}N_2O_6S_2$ $(M+H)^+$: calcd 653.1780, found 653.1781.

Benzyl 3,3-bis(4-methyl-N-(3-phenylprop-2-ynyl)phenylsulfonamido)acrylate (42u):



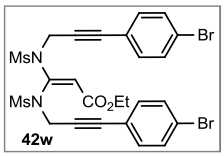
Following the general procedure GP-2, compound **42u** (273 mg) was obtained in overall 75% yield as thick yellow liquid; R_f = 0.56 (7:3 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, J = 10.8, 2.8 Hz, 4H), 7.39–7.22 (m, 15H), 7.16 (t, J = 8.4 Hz, 4H), 5.87 (s, 1H), 5.14 (s, 2H), 4.66 (br s, 2H), 4.55 (br s, 2H), 2.39 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.5, 144.5, 144.2, 143.1, 136.1, 135.6, 135.5, 131.7, 131.5, 129.44, 129.39, 128.6, 128.5, 128.4, 128.3, 128.1, 122.1, 121.9, 112.0, 86.3, 86.2, 82.9, 66.2, 41.0, 39.6, 21.5, 21.4; IR (Neat) ν_{max} 3086, 1720, 1621, 1490, 1364, 1172 cm^{-1}; HRMS (ESI) for $C_{42}H_{37}N_2O_6S_2$ $(M+H)^+$: calcd 729.2093, found 729.2090.

Benzyl-3,3-bis(4-methyl-N-(3-(3-nitrophenyl)prop-2-ynyl)phenylsulfonamido)-acrylate (42v):



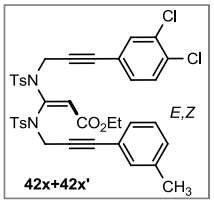
Following the general procedure GP-2, compound **42v** (229 mg) was obtained in overall 56% yield as brown gummy liquid; R_f = 0.35 (7:3 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (td, J = 9.6, 0.8 Hz, 2H), 8.02 (br s, 1H), 7.89 (d, J = 8.0 Hz, 3H), 7.76 (d, J = 8.0 Hz, 2H), 7.58 (d, J = 7.6 Hz, 1H), 7.46 (d, J = 7.6 Hz, 2H), 7.39 (td, J = 8.0, 2.0 Hz, 1H), 7.35–7.23 (m, 9H), 5.90 (s, 1H), 5.06 (s, 2H), 4.67 (s, 2H), 4.64 (s, 2H), 2.41 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.3, 147.9, 145.3, 144.8, 143.4, 137.4, 137.3, 135.9, 135.6, 135.3, 129.7, 129.6, 129.4, 128.8, 128.5, 128.4, 128.1, 126.3, 126.1, 123.9, 123.6, 123.4, 123.3, 111.7, 85.8, 83.9, 83.6, 66.4, 41.1, 39.2, 21.7, 21.6; IR (Neat) ν_{max} 3095, 1726, 1621, 1534, 1358, 1167 cm^{-1}; HRMS (ESI) for $C_{42}H_{35}N_4O_{10}S_2$ $(M+H)^+$: calcd 819.1794, found 819.1794.

Benzyl-3,3-bis(N-(3-(4-bromophenyl)prop-2-ynyl)methylsulfonamido)acrylate (42w):



Following the general procedure GP-2, compound **42w** (261 mg) was obtained in overall 71% yield as brown gummy liquid; R_f = 0.35 (7:3 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.32 (m, 9H), 7.18 (d, J = 8.4 Hz, 2H), 7.14 (d, J = 8.4 Hz, 2H), 6.19 (s, 1H), 5.20 (s, 2H), 4.68 (br s, 2H), 4.62 (br s, 2H), 3.23 (s, 3H), 3.21 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.7, 144.7, 135.3, 133.2, 133.1, 131.7, 131.6, 128.7, 128.6, 128.5, 123.4, 123.2, 120.8, 120.6, 110.6, 86.06, 85.3, 84.4, 83.4, 66.8, 41.48, 41.3, 41.0, 40.2, 30.9; IR (Neat) ν_{max} 3029, 2931, 1709, 1632, 1489, 1358, 1155, 1117, 1067 cm^{-1}; HRMS (ESI) for $C_{30}H_{27}Br_2N_2O_6S_2$ $(M+H)^+$: calcd 732.9677, found 732.9677.

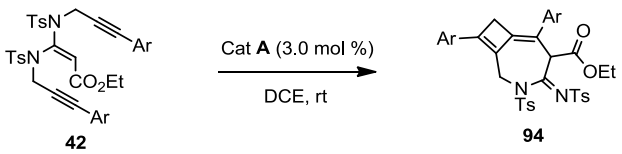
Ethyl-3-(N-(3-(3,4-dichlorophenyl)prop-2-yn-1-yl)-4-methylphenylsulfonam-ido)-3-(4-methyl-N-(3-(m-tolyl)prop-2-yn-1-yl)phenylsulfonamido)acrylate (42x+42x′): The



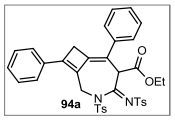
ynamide compound ethyl 3-(N-(3-(4-chloro-3-methylphenyl)-prop-2-yn-1-yl)-4-methylphenylsulfonamido)propiolate ***39a′*** (480 mg, 50%) was prepared by reacting N-(3-(4-chloro-3-methylphenyl)-prop-2-yn-1-yl)-4-methylbenzenesulfonamide (**42q**; 500 mg, 1.5 mmol), 3-bromopropiolate (**38b**; 497 mg, 3.0 mmol), $CuSO_4 \cdot 5H_2O$ (37 mg, 10 mol%), 1, 10-phenanthroline (53 mg, 20 mol%) and K_3PO_4 (636 mg, 3.0 mmol) in toluene at 70 °C for 4 h.

The compound ***39a′*** (80 mg, 0.18 mmol) was subsequently subjected to conjugate addition by reacting with 4-methyl-N-(3-(*m*-tolyl)prop-2-yn-1-yl)benzenesulfonamide (**37m**; 53 mg, 0.18 mmol) and K_3PO_4 (75 mg, 0.36 mmol) in toluene to produce inseparable (*E/Z*) mixture of compounds **42x** and **42x′** (79 mg) in 60% yield as brown gummy liquid; R_f = 0.46 (7:3 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 8.4 Hz, 4H), 7.88–7.75 (m, 5H), 7.33–7.21 (m, 14H), 7.10–7.07 (m, 4H), 7.03–6.93 (m, 3H), [5.79 (s, 1H) & 5.75 (s, 1H); (76:24)], 4.66–4.45 (m, 8H) 4.10 (br q, J = 6.8 Hz, 4H), [{2.42 (s, 3H), 2.37 (s, 3H)} & {2.40 (s, 3H), 2.39 (s, 3H)}; (24:76)], [2.29 (s, 3H) & 2.27 (s, 3H); (24:76)], 1.27 (br t, J= 6.8 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.7, 144.7, 144.3, 142.7, 137.9, 136.2, 135.6, 133.3, 133.1, 132.2, 130.7, 130.2, 129.6, 129.5, 128.9, 128.8, 128.6, 128.2, 122.0, 113.0, 112.5, 86.7, 85.3, 83.7, 82.5, 60.8, 41.2, 39.4, 21.6, 21.2, 14.1; IR (Neat) ν_{max} 2964, 2926, 2854, 1720, 1627, 1463, 13644, 1216, 1167, 1095 cm^{-1}; HRMS (ESI) for $C_{38}H_{35}Cl_2N_2O_6S_2$ $(M+H)^+$: calcd 749.1314, found 749.1316.

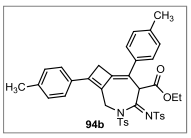
3.10.6. General Procedure for the Au-catalyzed cycloisomerization of 42 to the preparation of 94 (GP 3):



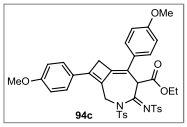
The compound **42** (0.20 mmol) was placed in a Schlenk flask under an argon atmosphere. The catalyst (2-biphenyl)di-*t*Bu-phosphine(MeCN)Au)SbF_6 (**A**; 4.6 mg, 0.006 mmol) in dichloroethane (3.0 mL) was introduced in to the Schlenk tube. The reaction mixture was stirred for the specified time shown in the respective Schemes at an ambient temperature. The progress of the reaction was periodically monitored by TLC. After satisfactory conversion of starting material, the reaction mixture was diluted with dichloromethane (10 mL), and filtered over a small pad of Celite. After evaporation of solvent under the reduced pressure, the residue was purified by column chromatography on silica gel.

Ethyl-6,9-diphenyl-3-tosyl-4-(tosylimino)-3-azabicyclo[5.2.0]nona-1(9),6-diene-5-carboxy-late (94a): 

Following the general procedure GP-3, compound **94a** (106 mg) was obtained in 80% yield as colorless solid; mp = 217–218 °C; R_f = 0.44 (7:3 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 8.4 Hz, 2H), 7.55–7.42 (m, 8H), 7.39 (br t, J = 7.6 Hz, 3H), 7.28 (d, J = 7.6 Hz, 1H), 7.20 (d, J = 8.0 Hz, 2H), 7.07 (d, J = 8.0 Hz, 2H), 6.55 (s, 1H), 5.86 (d, J = 18 Hz, 1H), 4.37 (dt, J = 18, 3.2 Hz, 1H), 4.33–4.20 (m, 2H), 3.54 (dd, J = 18, 3.2 Hz, 1H), 3.51 (dd, J = 18, 3.2 Hz, 1H), 2.44 (s, 3H), 2.38 (s, 3H), 1.30 (t, J = 7.2 Hz, 3H); ^{13}C NMR (127 MHz, $CDCl_3$) δ 168.3, 160.3, 145.0, 144.5, 143.1, 139.2, 138.1, 137.9, 135.4, 133.1, 133.0, 129.3, 129.1, 129.0, 128.9, 128.4, 128.3, 127.2, 126.9, 126.84, 126.82, 116.2, 62.7, 51.6, 41.6, 36.7, 21.6, 21.5, 14.0; IR (KBr) ν_{max} 2980, 2926, 1736, 1589, 1495, 1446, 1353, 1265, 1079 cm^{-1};HRMS (ESI) for $C_{37}H_{35}N_2O_6S_2$ $(M+H)^+$: calcd 667.1937, found 667.1933.

Ethyl-6,9-di*p*-tolyl-3-tosyl-4-(tosylimino)-3-azabicyclo[5.2.0]nona-1(9),6-diene-5-carboxylate (94b): 

Following the general procedure GP-3; compound 9**4b** (103 mg) was obtained in 74% yield as colorless solid; mp = 185–186 °C; R_f = 0.45 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 7.6 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 8.0 Hz, 2H), 7.19 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 8.0 Hz, 2H), 7.03 (d, J = 8.4 Hz, 2H), 6.47 (s, 1H), 5.79 (d, J = 18 Hz, 1H), 4.39–4.20 (m, 3H), 3.52 (dd, J = 14, 2.4 Hz, 1H), 3.45 (dd, J = 14, 3.2 Hz, 1H), 2.42 (s, 3H), 2.39 (s, 3H), 2.35 (s, 3H), 2.34 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.6, 160.5, 144.8, 144.6, 143.2, 139.7, 138.9, 138.4, 137.0, 135.7, 135.3, 132.3, 130.6, 129.8, 129.3, 129.2, 129.1, 128.4, 127.0, 126.9, 126.8, 115.8, 62.7, 51.8, 41.8, 36.9, 21.7, 21.6, 21.2, 14.1; IR (KBr) ν_{max}2920, 2849, 1737, 1589, 1156, 1079 cm^{-1}; HRMS (ESI) for $C_{39}H_{39}N_2O_6S_2$ $(M+H)^+$: calcd 695.2249, found 695.2247.

Ethyl-6,9-bis(4-methoxyphenyl)-3-tosyl-4-(tosylimino)-3-azabicyclo[5.2.0]nona-1(9),6-diene-5-carboxylate (94c): 

Following the general procedure GP-3, compound **94c** (109 mg) was obtained in 75% yield as pale yellow solid; mp = 196–197 °C; R_f = 0.35 (7:3 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 8.4 Hz, 2H), 7.44 (dd, J = 8.4, 2.0 Hz, 4H), 7.40 (d, J = 8.8 Hz, 2H), 7.20 (d, J= 8.0 Hz, 2H), 7.03 (d, J = 8.4 Hz, 2H), 6.95 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 6.46 (s, 1H), 5.76 (d, J = 18 Hz, 1H), 4.40–4.20 (m, 3H), 3.85 (s, 3H), 3.81 (s, 3H), 3.48 (dd, J = 15, 3.2 Hz, 1H), 3.44 (dd, J = 15, 3.2 Hz, 1H), 2.43 (s, 3H), 2.35 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$)δ 168.6, 160.5, 160.4,

158.7, 144.5, 144.1, 143.2, 138.3, 138.1, 135.6, 130.8, 129.1, 128.5, 128.4, 128.1, 126.9, 126.2, 114.6, 114.5, 113.9, 62.7, 55.4, 55.3, 51.8, 41.7, 36.8, 21.7, 21.6, 14.1; IR (KBr) ν_{max} 3068, 2980, 2936, 2838, 1731, 1693, 1065, 1512, 1358, 1293, 1260, 1172, 1090 cm^{-1}; HRMS (ESI) for $C_{39}H_{39}N_2O_8S_2$ $(M+H)^+$: calcd 727.2148, found 727.2149.

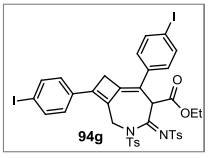
Ethyl-6,9-bis(4-fluorophenyl)-3-tosyl-4-(tosylimino)-3-azabicyclo[5.2.0]nona-1(9),6-diene-5-carboxylate (94d): Following the general procedure GP-3, compound **94d** (90 mg) was isolated in 64% yield as pale yellow solid; mp = 173–174 °C; R_f = 0.44 (7:3 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 8.0 Hz, 2H), 7.51–7.40 (m, 6H), 7.23 (d, J = 8.4 Hz, 2H), 7.13 (t, J = 8.8 Hz, 2H), 7.08–6.99 (m, 4H), 6.42 (s, 1H), 5.76 (d, J = 18 Hz, 1H), 4.36 (dt, J = 17, 2.8 Hz, 1H), 4.32–4.19 (m, 2H), 3.46 (br s, 2H), 2.44 (s, 3H), 2.37 (s, 3H), 1.28 (t, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.3, 163.1 (d, J = 252 Hz, 1C), 162.1 (d, J = 248 Hz, 1C), 160.1, 144.7, 143.8, 143.4, 138.9,138.1, 135.4, 134.2, 132.6, 129.5, 129.2, 128.85, 128.79, 128.3, 126.9, 116.3 (d, J = 22 Hz, 2C), 115.5 (d, J = 22 Hz, 2C), 115.4,62.9, 52.2, 41.5, 36.7, 29.7, 21.7, 21.6, 14.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ −109.6 (m), −114.5 (m);IR (KBr) ν_{max} 2931, 1742, 1600, 1506, 1342, 1227, 1194, 1156 cm^{-1}; HRMS (ESI) for $C_{37}H_{33}F_2N_2O_6S_2$ $(M+H)^+$: calcd 703.1748, found 703.1749.

Ethyl 6,9-bis(4-chlorophenyl)-3-tosyl-4-(tosylimino)-3-azabicyclo[5.2.0]nona-1(9),6-diene-5-carboxylate (94e): Following the general procedure GP-3, compound **94e** (121 mg) was obtained in 82% yield as pale yellow solid; mp = 196–197 °C; R_f = 0.52 (7:3 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 8.4 Hz, 2H), 7.47–7.36 (m, 8H), 7.31 (dt, J = 8.8, 2.4 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 7.05 (d, J = 8.0 Hz, 2H), 6.41 (s, 1H), 5.76 (d, J = 18 Hz, 1H), 4.39–4.19 (m, 3H), 3.53–3.42 (m, 2H), 2.44 (s, 3H), 2.37 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.2, 160.1, 144.8, 144.0, 143.5, 139.5, 138.1, 136.4, 135.4, 133.6, 133.3, 131.4, 129.4, 129.2, 128.8, 128.4, 128.3, 128.2, 126.9, 115.9, 63.0, 51.9, 41.5, 36.7, 21.7, 21.6, 14.1; IR (KBr) ν_{max} 2986, 2926, 2854, 1731, 1594, 1490, 1364, 1298, 1254, 1156, 1190 cm^{-1}; HRMS (ESI) for $C_{37}H_{33}Cl_2N_2O_6S_2$ $(M+H)^+$: calcd 735.1157, found 735.1158.

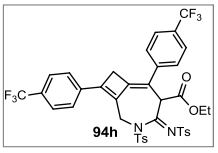
Ethyl 6,9-bis(4-bromophenyl)-3-tosyl-4-(tosylimino)-3-azabicyclo[5.2.0]nona-1(9),6-diene-5-carboxylate (94f): Following the general procedure GP-3, compound **94f** (145 mg) was obtained in 88% yield as pale yellow solid; mp = 206–207 °C; R_f = 0.60 (7:3 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR

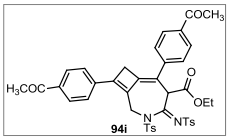
(400 MHz, $CDCl_3$) δ 7.58 (t, J = 7.2 Hz, 4H), 7.45 (t, J = 8.8 Hz, 4H), 7.38–7.29 (m, 4H), 7.22 (d, J = 8.0 Hz, 2H), 7.05 (d, J = 8.0 Hz, 2H), 6.40 (s, 1H), 5.76 (d, J = 18 Hz, 1H), 4.40–4.19 (m, 3H), 3.53–3.42 (m, 2H), 2.44 (s, 3H), 2.37 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1, 160.0, 144.8, 144.0, 143.5, 139.5, 138.1, 136.8, 135.4, 133.9, 132.3, 131.8, 131.7, 129.2, 128.6, 128.4, 128.3, 126.9, 123.7, 121.6, 116.1, 62.9, 51.8, 41.5, 36.7, 21.7, 21.6, 14.1; IR (KBr) ν_{max} 1726, 1589, 1484, 1304, 1260, 1178, 1156, 1091 cm^{-1}; HRMS (ESI) for $C_{37}H_{33}Br_2N_2O_6S_2$ $(M+H)^+$: calcd 823.0147, found 823.0147.

Ethyl 6,9-bis(4-iodophenyl)-3-tosyl-4-(tosylimino)-3-azabicyclo[5.2.0]nona-1(9),6-diene-5-carboxylate (94g): Following the general procedure GP-2, the compound **94g** (130 mg) was obtained in 71% yield as yellow solid. mp = 213–214 °C; R_f = 0.56 (7:3 hexane/EtOAc); [Silica, UV and I_2]; **^{1}H** NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 8.0 Hz, 2H), 7.65 (d, J = 8.4 Hz, 2H), 7.57 (d, J = 8.0 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 7.24–7.15 (m, 6H), 7.05 (d, J = 8.4 Hz, 2H), 6.39 (s, 1H), 5.76 (d, J = 18 Hz, 1H), 4.39–4.19 (m, 3H), 3.53–3.42 (m, 2H), 2.44 (s, 3H), 2.37 (s, 3H), 1.27 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1, 160.1, 144.8, 144.2, 143.5, 139.6, 138.3, 138.1, 137.6, 137.4, 135.4, 134.1, 132.3, 129.2, 128.7, 128.4, 126.9, 116.2, 95.7, 93.2, 63.0, 51.7, 41.5, 36.7, 21.73, 21.67, 14.1; IR (Neat) ν_{max} 2986, 2926, 2854, 2219, 1720, 1594, 1452, 1364, 1260, 1183, 1156 cm^{-1}; HRMS (ESI) for $C_{37}H_{33}I_2N_2O_6S_2$ $(M+H)^+$: calcd 918.9869, found 918.9869.

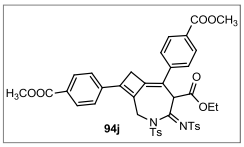


Ethyl 3-tosyl-4-(tosylimino)-6,9-bis(4-(trifluoromethyl)phenyl)-3-azabicyclo[5.2.0]-nona-1(9),6-diene-5-carboxylate (94h): Following the general procedures GP-3, compound **94h** (121 mg) was obtained in 75% yield as yellow solid; mp = 196–197 °C; R_f = 0.32 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 8.0 Hz, 2H), 7.63–7.55 (m, 8H), 7.45 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 7.06 (d, J = 8.4 Hz, 2H), 6.48 (s, 1H), 5.83 (d, J = 18 Hz, 1H), 4.40 (dt, J = 18, 3.2 Hz, 1H), 4.37–4.21 (m, 2H), 3.62–3.51 (m, 2H), 2.44 (s, 3H), 2.38 (s, 3H), 1.28 (t, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9, 159.8, 144.9, 144.2, 143.6, 141.2, 140.5, 138.0, 135.9, 135.6, 135.3, 131.0 (m, 1C), 129.24, 129.21, 128.4, 127.3, 127.2, 126.9, 126.1 (d, J = 12 Hz,1C), 125.5 (d, J = 12 Hz, 1C), 125.1, 122.8, 122.4, 116.9, 63.1, 51.8, 41.4, 36.8, 21.7, 21.6, 14.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ –62.6 (s), –62.8 (s); IR (KBr) ν_{max} 2926, 2843, 1726, 1594, 1358, 1320, 1117 cm^{-1}; HRMS (ESI) for $C_{39}H_{33}F_6N_2O_6S_2$ $(M+H)^+$: calcd 803.1684, found 803.1680.

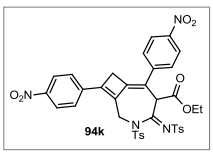


Ethyl 6,9-bis(4-acetylphenyl)-3-tosyl-4-(tosylimino)-3-azabicyclo[5.2.0]nona-1(9),6-diene-5-carboxylate (94i): 

Following the general procedures GP-3, compound **94i** (72 mg) was obtained in 48% yield as pale brown solid; mp = 179–189 °C; R_f= 0.37 (7:3 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$)δ 8.03 (d, J = 8.0 Hz, 2H), 7.96 (d, J = 8.4 Hz, 2H), 7.63–7.55 (m, 6H), 7.43 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H), 7.04 (d, J = 8.4 Hz, 2H), 6.53 (s, 1H), 5.85 (d, J = 18 Hz, 1H), 4.45–4.21 (m, 3H), 3.63 (dd, J = 14, 2.0 Hz, 1H), 3.56 (dd, J = 14, 2.0 Hz, 1H), 2.64 (s, 3H), 2.60 (s, 3H), 2.44 (s, 3H), 2.37 (s, 3H), 1.27 (br t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$)δ 197.6, 197.2, 168.0, 159.7, 144.9, 144.7, 143.6, 142.4, 141.0, 138.0, 137.9, 137.2, 136.8, 135.8, 135.7, 135.3, 129.2, 129.1, 128.7, 128.3, 127.1, 127.0, 126.9, 117.2, 63.1, 51.6, 41.5, 37.0, 26.7, 26.6, 21.7, 21.6, 14.1; IR (KBr)ν_{max} 2926, 1747, 1676, 1660, 1594, 1358, 1260 cm^{-1}; HRMS (ESI) for $C_{41}H_{39}N_2O_8S_2$ $(M+H)^+$: calcd 751.2148, found 751.2148.

Dimethyl 4,4'-(5-(ethoxycarbonyl)-3-tosyl-4-(tosylimino)-3-azabicyclo[5.2.0]nona-1(9),6-diene-6,9-diyl)dibenzoate (94j): 

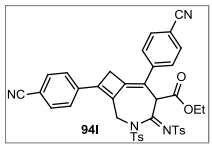
Following the general procedures GP-3, compound **94j** (88 mg) was obtained in 56% yield as colorless solid; mp = 184–185 °C; R_f = 0.24 (7:3 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$)δ 8.11 (d, J = 8.4 Hz, 2H), 8.02 (d, J = 8.4 Hz, 2H), 7.62–7.49 (m, 6H), 7.45 (d, J = 8.4 Hz, 2H), 7.20 (d, J = 8.4 Hz, 2H), 7.05 (d, J = 8.4 Hz, 2H), 6.51 (s, 1H), 5.84 (d, J = 18 Hz, 1H), 4.45–4.21 (m, 3H), 3.94 (s, 3H), 3.92 (s, 3H), 3.62 (dd, J = 14, 2.0 Hz, 1H), 3.53 (dd, J = 14, 3.2 Hz, 1H), 2.43 (s, 3H), 2.37 (s, 3H), 1.28 (br t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$)δ 168.2, 166.8, 166.4, 159.8, 144.9, 144.7, 143.5, 142.2, 140.8, 138.0, 136.7, 135.6, 135.3, 130.6, 130.3, 129.9, 129.2, 128.9, 128.4, 126.92, 126.89, 126.8, 117.1, 63.0, 52.4, 52.1, 51.5, 41.5, 36.9, 21.7, 21.6, 14.1; IR (KBr)ν_{max} 2924, 1753, 1715, 1698, 1583, 1375, 1282 cm^{-1}; HRMS (ESI) for $C_{41}H_{39}N_2O_{10}S_2$ $(M+H)^+$: calcd 783.2046, found 783.2045.

Ethyl 6,9-bis(4-nitrophenyl)-3-tosyl-4-(tosylimino)-3-azabicyclo[5.2.0]nona-1(9),5-diene-5-carboxylate (94k): 

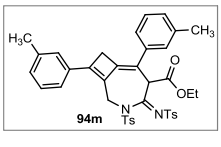
Following the general procedures GP-3, compound **94k** (100 mg) was obtained in 66% yield as pale yellow solid; mp = 165–166 °C; R_f= 0.36 (7:3 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$)δ 8.30 (d, J = 8.8 Hz, 2H), 8.21 (d, J = 8.8 Hz, 2H), 7.65 (dd, J = 8.4, 3.2 Hz, 4H), 7.61 (d, J = 8.0 Hz, 2H),7.41 (d, J = 8.4 Hz, 2H), 7.31–7.23 (m, 2H), 7.04 (d, J = 8.0 Hz, 2H) , 6.50 (s, 1H), 5.84 (d, J = 18 Hz, 1H), 4.49–4.20 (m, 3H), 3.68–3.57 (m, 2H), 2.46 (s, 3H), 2.37 (s, 3H), 1.28 (br t, J = 7.2 Hz, 3H); ^{13}CNMR(101 MHz, $CDCl_3$) δ 167.6,159.3, 147.8, 146.8, 145.1, 144.0, 143.8, 141.6, 138.3,

137.8, 137.5, 135.1, 129.3, 128.3, 127.8, 127.8, 126.9, 124.5, 124.0, 123.5, 117.7, 63.3, 51.9, 41.3, 37.0, 22.7, 21.7, 21.6, 14.0. IR (KBr) ν_{max} 3101, 3079, 2926, 2854, 1742, 1589, 1517, 1336, 1172, 1156, 1079 cm^{-1}; HRMS (ESI) for $C_{37}H_{33}N_4O_{10}S_2$ $(M+H)^+$: calcd 757.1638, found 757.1636.

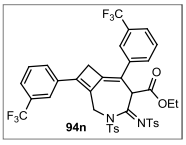
Ethyl 6,9-bis(4-cyanophenyl)-3-tosyl-4-(tosylimino)-3-azabicyclo[5.2.0]nona-1(9),6-diene-5-carboxylate (94l): Following the general procedures GP-3, compound **94l** (90 mg) was obtained in 63% yield as pale yellow solid; mp = 179–180 °C; R_f= 0.28 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 8.4 Hz, 2H), 7.66 (d, J = 8.8 Hz, 2H), 7.65–7.56 (m, 4H), 7.40 (d, J = 8.4 Hz, 2H), 7.30–7.23 (m, 4H), 7.04 (d, J = 8.0 Hz, 2H), 6.46 (s, 1H), 5.80 (d, J = 17.6 Hz, 1H), 4.43–4.19 (m, 3H), 3.57 (bs, 2H), 2.47 (s, 3H), 2.38 (s, 3H), 1.27 (br t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.7, 159.3, 145.0, 144.1, 143.8, 142.1, 141.1, 137.8, 136.8, 136.5, 135.1, 132.8, 132.5, 129.6, 129.3, 128.3, 127.6, 127.4, 126.9, 126.4, 117.5, 112.7, 111.1, 63.2, 51.8, 41.3, 36.8, 21.74, 21.68, 14.1;IR (KBr) ν_{max} 2975, 2920, 2854, 1704, 1594, 1490, 1375, 1161, 1084, 1046 cm^{-1}; HRMS (ESI) for $C_{39}H_{33}N_4O_6S_2$ $(M+H)^+$: calcd 717.1842, found 717.1840.



Ethyl 6,9-dim-tolyl-3-tosyl-4-(tosylimino)-3-azabicyclo[5.2.0]nona-1(9),6-diene-5-carboxylate (94m): Following the general procedure GP-3, the compound **94m** (111 mg) was obtained in 80% yield as colorless solid; mp = 198–199 °C; R_f= 0.50 (7:3 hexane/EtOAc); [Silica, UV and I_2]; ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 8.4 Hz, 2H), 7.48 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 4.8 Hz, 2H), 7.32–7.22 (m, 4H), 7.19 (d, J = 8.0 Hz, 3H), 7.10–7.03 (m, 3H), 6.51 (s, 1H), 5.83 (d, J = 18 Hz, 1H), 4.44–4.20 (m, 3H), 3.54 (dd, J = 14.0, 1.6 Hz, 1H), 3.48 (dd, J = 14.0, 3.2 Hz, 1H), 2.43 (s, 3H), 2.40 (s, 3H), 2.32 (s, 3H), 2.29 (s, 3H), 1.30 (t, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.5, 160.5, 145.2, 144.6, 143.2, 139.3, 138.7, 138.3, 138.0, 137.9, 135.6, 133.1, 133.0, 130.2, 129.2, 129.1, 128.9, 128.4, 128.1, 127.64, 127.57, 126.9, 124.2, 116.2, 62.7, 51.7, 41.7, 36.9, 21.66, 21.62, 21.4, 14.1. IR (KBr) ν_{max} 3052, 2980, 2920, 1742, 1583, 1490, 1446, 1358, 1156, 1084, 1019 cm^{-1}; HRMS (ESI) for $C_{39}H_{39}N_2O_6S_2$ $(M+H)^+$: calcd 695.2249, found 695.2250.

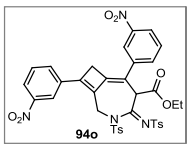


Ethyl 3-tosyl-4-(tosylimino)-6,9-bis(3-(trifluoromethyl)phenyl)-3-azabicyclo[5.2.0]-nona-1(9),6-diene-5-carboxylate (94n): Following the general procedures GP-3, the compound **94n** (109mg) was obtained in 68% yield as pale brown solid; mp = 185–186 °C; R_f= 0.35 (7:3 hexane/EtOAc); [Silica, UV and I_2]; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69–766 (m, 4H), 7.65–7.51 (m, 5H), 7.48 (d, J = 8.4 Hz,

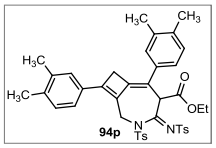


3H), 7.21 (d, J = 8.0 Hz, 2H), 7.07 (d, J = 8.4 Hz, 2H), 6.49 (s, 1H), 5.82 (d, J = 18 Hz, 1H), 4.42 (br d, J = 18 Hz, 1H), 4.37–4.21 (m, 2H), 3.62–3.49 (m, 2H), 2.43 (s, 3H), 2.38 (s, 3H), 1.27 (bt, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8, 159.5, 148.8, 148.4, 145.0, 143.7, 143.5, 140.5, 139.3, 137.9, 136.0, 135.1, 134.2, 131.8 (q, J = 32.3 Hz, 1C), 130.7(q, J = 20.2 Hz, 1C), 130.1, 129.9, 129.6, 129.2, 129.1,128.3, 128.4, 126.8, 126.3, 125.9, 124.0 (q, J = 273.7 Hz,1C), 123.9 (d, J = 11.1 Hz, 1C), 123.6(q, J = 273.7 Hz, 1C), 123.5, 116.5, 62.9, 51.7, 41.4, 36.5, 21.6, 21.5, 13.9; ^{19}F NMR (376 MHz, $CDCl_3$)δ –62.6 (s), -62.9 (s); IR (KBr)ν_{max} 3260, 3073, 2980, 2920, 1731, 1594, 1441, 1331, 1167, 1084 cm^{-1}. HRMS (ESI) for $C_{39}H_{33}F_6N_2O_6S_2$ $(M+H)^+$: calcd 803.1684, found 803.1684.

Ethyl 6,9-bis(3-nitrophenyl)-3-tosyl-4-(tosylimino)-3-azabicyclo[5.2.0]nona-1(9),6-diene-5-carboxylate (94o): Following the general procedures GP-3, the compound **94o** (77 mg) was obtained in 51% yield as colorless solid; mp = 169–170 ^{o}C; R_f = 0.28 (7:3 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$)δ 8.29 (d, J = 11.2 Hz, 2H), 8.24 (d, J = 8.0 Hz, 1H), 8.15 (dd, J = 8.0, 1.2 Hz, 1H), 7.87 (d, J = 7.6 Hz, 2H), 7.66 (t, J = 7.6 Hz, 1H), 7.63–7.54 (m, 3H), 7.45 (d, J = 8.4 Hz, 2H), 7.24 (bd, J = 8.0 Hz, 2H), 7.06 (d, J = 8.4 Hz, 2H), 6.45 (s, 1H), 5.84 (d, J = 18 Hz, 1H), 4.43 (dt, J = 18, 2.8 Hz, 1H), 4.39–4.22 (m, 2H), 3.67 (dd, J = 14, 2.0 Hz, 1H), 3.61 (dd, J = 14, 3.2 Hz, 1H), 2.44 (s, 3H), 2.38 (s, 3H), 1.27 (bt, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$)δ 167.8, 159.5, 148.8, 148.4, 145.0, 143.7, 143.5, 140.5, 139.3, 137.9, 136.0, 135.1, 134.2, 132.8, 132.4, 130.3, 129.8, 129.3, 128.4, 126.9, 124.0, 122.3, 122.1, 121.7, 116.6, 63.3, 52.0, 41.3, 36.7, 21.7, 21.6, 14.0; IR (KBr)ν_{max} 2239, 1593, 1363, 1168, 1109, 1086 cm^{-1}; HRMS (ESI) for $C_{37}H_{33}N_4O_{10}S_2$ $(M+H)^+$: calcd 757.1638, found 757.1642.



Ethyl 6,9-bis(3,4-dimethylphenyl)-3-tosyl-4-(tosylimino)-3-azabicyclo[5.2.0]nona-1(9),6-diene-5-carboxylate (94p): Following the general procedure GP-3; the compound **94p** (97 mg) was obtained in 67% yield as colourless solid. mp = 195–196 ^{o}C; R_f = 0.50 (7:3 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$)δ 7.58 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 8.4 Hz, 2H), 7.30–7.23 (m, 3H), 7.19 (d, J = 8.0 Hz, 4H), 7.09 (d, J = 8.8 Hz, 1H), 7.03 (d, J = 8.0 Hz, 2H), 6.47 (s, 1H), 5.80 (d, J = 17.6 Hz, 1H), 4.40 – 4.20 (m, 3H), 3.53 – 3.42 (m, 2H), 2.43 (s, 3H), 2.35 (s, 3H), 2.30 (s, 6H), 2.27 (s, 3H), 2.25 (s, 3H), 1.29 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101MHz, $CDCl_3$)δ 168.6, 160.6, 144.9, 144.5, 143.1, 138.4, 138.3, 137.2, 136.5, 135.7, 132.1, 131.0, 130.3, 129.8, 129.1, 129.0, 128.4, 128.2, 127.0, 124.5, 124.4, 115.6, 62.7, 51.7, 41.8, 36.9, 21.7, 20.1, 19.9, 19.5, 14.1; IR (Neat)ν_{max} 2947, 2920, 1742, 1572, 1495, 1446, 1369,



1249, 1167, 1079 cm^{-1}; HRMS (ESI) for $C_{41}H_{43}N_2O_6S_2$ $(M+H)^+$: calcd 723.2563, found 723.2562.

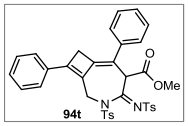
Ethyl 6,9-bis(3,4-dichlorophenyl)-3-tosyl-4-(tosylimino)-3-azabicyclo[5.2.0]nona-1(9),5-diene-5-carboxylate (94q): Following the general procedures GP-3, the compound **94q** (98 mg) was obtained in 61% yield as colorless solid; mp = 186–187 °C; R_f = 0.32 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 8.4 Hz, 2H), 7.51 (br s, 3H), 7.43 (t, J = 8.4 Hz, 3H), 7.36 (dd, J = 8.4, 1.6 Hz, 1H), 7.31 (dd, J = 8.4, 1.6 Hz, 1H), 7.23 (d, J = 8.4 Hz, 2H), 7.06 (d, J = 8.0 Hz, 2H), 6.36 (s, 1H), 5.74 (d, J = 17.6 Hz, 1H), 4. 34 (dd, J = 18.0, 7.2 Hz, 1H), 4.29–4.18 (m, 2H), 3.50 (d, J = 16.8 Hz, 1H), 3.46 (dd, J = 16.8, 1.6 Hz, 1H), 2.45 (s, 3H), 2.38 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H). ^{13}CNMR (101 MHz, $CDCl_3$) δ 167.9, 159.7, 144.9, 143.6, 143.1, 139.9, 138.0, 137.7, 135.2, 134.8, 133.6, 133.5, 132.6, 131.6, 131.2, 130.6, 129.2, 128.9, 128.6, 128.4, 126.9, 126.2, 126.0, 115.7, 63.1, 51.8, 41.3, 36.6, 21.7, 21.6, 14.0; IR (KBr) ν_{max} 2980, 2926, 1736, 1594, 1479, 1358, 1156 cm^{-1}; HRMS (ESI) for $C_{37}H_{31}Cl_4N_2O_6S_2$ $(M+H)^+$: calcd 803.0377, found 803.0375.

Ethyl 6,9-di(benzo[d][1,3]dioxol-5-yl)-3-tosyl-4-(tosylimino)-3-azabicyclo-[5.2.0]-nona-1(9),6-diene-5-carboxylate (94r): Following the general procedures GP-3, the compound **94r** (88 mg) was obtained in 58% yield as colorless solid; mp = 206–207 °C; R_f = 0.32 (7:3 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 8.0 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 7.05 (d, J = 8.4 Hz, 2H), 7.00–6.85 (m, 4H), 6.86 (d, J = 8.4 Hz, 1H), 6.78 (d, J = 8.4 Hz, 1H), 6. 37 (s, 1H), 6.02 (br d, J = 3.2 Hz, 2H), 5.96 (s, 2H), 5.72 (d, J = 17.2 Hz, 1H), 4.38–4.18 (m, 3H), 3.45 (dd, J = 14.0, 2.0 Hz, 1H), 3.39 (dd, J = 14.0, 3.2 Hz, 1H), 2.44 (s, 3H), 2.37 (s, 3H), 1.28 (br t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.4, 160.3, 148.7, 148.3, 147.8, 146.8, 144.6, 144.2, 143.3, 138.3, 135.5, 132.4, 131.2, 129.2, 129.1, 128.4, 127.5, 126.9, 121.8, 120.8, 115.2, 108.9, 108.4, 107.5, 106.6, 101.5, 101.1, 62.7, 52.1, 41.5, 36.9, 21.7, 21.6, 14.1; IR (KBr) ν_{max} 2969, 2904, 1742, 1594, 1484, 1446, 1342, 1221, 1150, 1084, 1046 cm^{-1}; HRMS (ESI) for $C_{39}H_{35}N_2O_{10}S_2$ $(M+H)^+$: calcd 755.1733, found 755.1736.

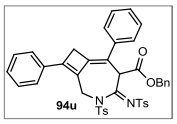
Ethyl 6,9-di(thiophen-2-yl)-3-tosyl-4-(tosylimino)-3-azabicyclo[5.2.0]nona-1(9),6-diene-5-carboxylate (94s): Following the general procedures GP-3, the compound **94s** (111 mg) was obtained in 82% yield as colorless solid; mp = 164–165 °C; R_f = 0.40 (7:3 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 8.0 Hz, 2H), 7.47 (d, J = 4.8 Hz, 1H), 7.41 (d, J = 8.0 Hz, 2H), 7.33 – 7.17 (m, 5H), 7.11 (t, J = 4.4 Hz, 1H), 7.01 (d, J = 7.6 Hz, 3H), 6.62 (s, 1H),

5.66 (d, J = 17.2 Hz, 1H), 4.42 – 4.18 (m, 3H), 3.64 (dd, J = 13.6, 2.8 Hz, 1H), 3.55 (dd, J = 13.6, 2.8 Hz, 1H), 2.45 (s, 3H), 2.34 (s, 3H), 1.27 (br t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$)δ 167.8, 159.7, 144.7, 143.4, 141.3, 138.2, 138.1, 137.2, 136.1, 135.6, 130.7, 129.2, 128.7, 128.4, 128.1, 127.6, 127.5, 127.0, 125.4, 124.9, 111.0, 62.9, 51.1, 41.4, 38.2, 21.7, 14.1; IR (KBr)ν_{max} 2241, 1579, 1485, 1437, 1361, 1165, 1091 cm^{-1}; HRMS (ESI) for $C_{33}H_{31}N_2O_6S_4$ $(M+H)^+$: calcd 679.1065, found 679.1064.

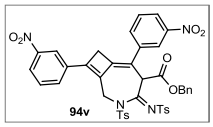
Methyl-6,9-diphenyl-3-tosyl-4-(tosylimino)-3-azabicyclo[5.2.0]nona-1(9),6-diene-5-carboxylate (94t): Following the general procedures GP-3, the compound **94t** (101 mg) was obtained in 77% yield as colorless solid; mp = 175–176 ^{o}C; R_f= 0.45 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$)δ 7.56 (d, J = 8.0 Hz, 2H), 7.53–7.41 (m, 8H), 7.39–7.31 (m, 3H), 7.27 (br d, J = 6.8 Hz, 1H), 7.19 (d, J = 8.4 Hz, 2H), 7.04 (d, J = 8.4 Hz, 2H), 6.52 (s, 1H), 5.83 (d, J = 17.6 Hz, 1H), 4.35 (br d, J = 18.0 Hz, 1H), 3.83 (s, 3H), 3.59–3.44 (m, 2H), 2.42 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$)δ 169.1, 160.1, 145.3, 144.7, 143.3, 139.4, 138.1, 137.8, 135.3, 133.1, 133.0, 131.6, 130.0, 129.5, 129.2, 129.1, 128.6, 128.4, 127.4, 126.95, 126.92, 116.1, 53.7, 51.5, 41.7, 36.8, 21.7, 21.6; IR (KBr)ν_{max} 3068, 3024, 2953, 2915, 1742, 1594, 1490, 1441, 1347, 1271, 1150, 1084 cm^{-1}; HRMS (ESI) for $C_{36}H_{33}N_2O_6S_2$ $(M+H)^+$: calcd 653.1780, found 653.1783.



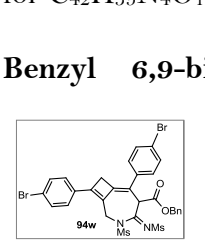
Benzyl 6,9-diphenyl-3-tosyl-4-(tosylimino)-3-azabicyclo[5.2.0]nona-1(9),6-diene-5-carboxylate (94u): Following the general procedures GP-3, the compound **94u** (118 mg) was obtained in overall 81% yield as colorless solid; mp = 145–146 ^{o}C; R_f= 0.50 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$)δ 7.55 (d, J = 8.4 Hz, 2H), 7.49–7.41 (m, 6H), 7.38–7.31 (m, 10H), 7.27 (t, J = 3.6 Hz, 1H), 7.16 (d, J = 8.0 Hz, 2H), 6.98 (d, J = 8.4 Hz, 2H), 6.60 (s, 1H), 5.56 (d, J = 17.6 Hz, 1H), 5.35 (d, J = 12.4 Hz, 1H), 5.19 (d, J = 12.0 Hz, 1H), 3.93 (d, J = 17.6 Hz, 1H), 3.54 (d, J = 14.0 Hz, 1H), 3.47 (dd, J = 14.0, 3.2 Hz, 1H), 2.42 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$)δ 168.1, 160.1, 145.1, 144.5, 143.2, 139.5, 138.1, 137.9, 135.5, 134.8, 133.2, 133.1, 129.4, 129.1, 129.0, 128.7, 128.6, 128.5, 128.4, 128.3, 127.3, 126.9, 116.1, 68.1, 51.4, 41.3, 36.8, 21.7, 21.6; IR (KBr)ν_{max} 3062, 2942, 1736, 1582, 1445, 1352, 1166 cm^{-1};HRMS (ESI) for $C_{42}H_{37}N_2O_6S_2$ $(M+H)^+$: calcd 729.2093, found 729.2090.



Benzyl 6,9-bis(3-nitrophenyl)-3-tosyl-4-(tosylimino)-3-azabicyclo[5.2.0]nona-1(9),6-diene-5-carboxylate (94v): Following the general procedures GP-3, the compound **94v** (74 mg) was obtained in 45% yield as colorless solid; mp = 168–169 °C; R_f= 0.36 (7:3 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$)δ 8.27 (d, J = 2.0 Hz, 1H), 8.22 (d, J = 8.4 Hz, 1H), 8.19 (s, 1H), 8.14 (dd, J = 8.4, 2.0 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.77 (d, J = 7.6 Hz, 1H), 7.64 (t, J = 8.0 Hz, 1H), 7.57 (t, J = 8.4 Hz, 3H), 7.43–7.29 (m, 7H), 7.21 (d, J = 8.4 Hz, 2H), 6.98 (d, J = 8.4 Hz, 2H), 6.53 (s, 1H),5.53 (d, J = 18.0 Hz, 1H), 5.44 (d, J = 12.0 Hz, 1H), 5.20 (d, J = 12.0 Hz, 1H), 3.95 (dt, J = 17.6, 2.4 Hz, 1H), 3.66 (dd, J = 14.0, 2.4 Hz, 1H), 3.56 (dd, J = 14.0, 3.2 Hz, 1H), 2.43 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$)δ 167.5, 159.2, 148.7, 148.3, 144.9, 143.7, 143.4, 140.7, 139.1, 137.8, 136.0, 135.1, 134.4, 134.1, 132.7, 132.3, 130.3, 129.9, 129.2, 129.0, 128.8, 128.7, 128.3, 126.9, 124.0, 122.3, 122.1, 121.7, 116.4, 68.7, 51.7, 40.7, 36.7, 21.7, 21.6; IR (KBr) ν_{max} 2915, 1753, 1583, 1523, 1353, 1150, 1090 cm^{-1}; HRMS (ESI) for $C_{42}H_{35}N_4O_{10}S_2$ $(M+H)^+$: calcd 819.1794, found 819.1796.

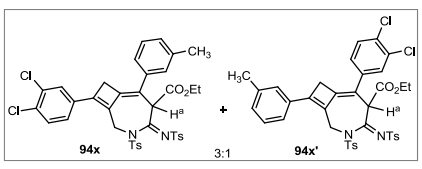


Benzyl 6,9-bis(4-bromophenyl)-3-(methylsulfonyl)-4-(methylsulfonylimino)-3-azabicyclo[5.2.0]nona-1(9),6-diene-5-carboxylate (94w): Following the general procedures GP-3, the compound **94w** (118 mg) was obtained in 80% yield as colorless solid; mp = 173–174 °C; R_f= 0.43 (7:3 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$)δ 7.54 (d, J = 8.4 Hz, 2H), 7.49 (d, J = 8.8 Hz, 2H), 7.40–7.33 (m, 7H), 7.18 (d, J = 8.4 Hz, 2H), 6.51 (s, 1H), 5.37 (d, J = 12.0 Hz, 1H), 5.20 (d, J = 12.4 Hz, 2H), 3.71 (d, J = 17.6, 1H), 3.51 (dd, J = 14.0, 2.0 Hz, 1H), 3.43 (dd, J = 14.4, 3.2 Hz, 1H), 3.34 (s, 3H), 3.09 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6, 161.6, 144.2, 139.8, 136.4, 134.5, 133.2, 132.3, 131.8, 131.6, 128.9, 128.8, 128.6, 128.5, 128.3, 123.8, 121.8, 115.6, 68.5, 51.5, 43.0, 42.9, 40.8, 36.7. IR (KBr)ν_{max} 3090, 2931, 1731, 1589, 1490, 1353, 1326, 1265, 1156, 1156 cm^{-1}; HRMS (ESI) for $C_{30}H_{27}Br_2N_2O_6S_2$ $(M+H)^+$: calcd 732.9677, found 732.9679.



<u>Cycloisomerization of unsymmetrical ketene N,N-acetal 42x and 42x′</u>

Ethyl 9-(3,4-dichlorophenyl)-6-m-tolyl-3-tosyl-4-(tosylimino)-3-azabicyclo[5.2.0]-nona-1(9),6-diene-5-carboxylate (94x) and Ethyl 6-(3,4-dichlorophenyl)-9-m-tolyl-3-tosyl-4-(tosylimino)-3-azabicyclo[5.2.0]nona-1(9),6-diene-5-carboxylate(94x′):

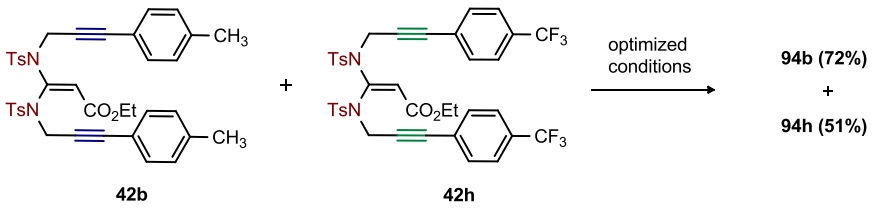


Following the general procedure GP-3, the reaction of mixture of compounds **42x** and **42x′**(50 mg, 0.07 mmol) under the optimized cycloisomerization conditions gave inseparable mixture of compounds **94x** and **94x′**(41 mg)

in 82% yield as semi solid; R_f= 0.40 (7:3 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$)δ 7.61–7.54 (m, 4H), 7.53–7.43 (m, 8H), 7.42–7.31 (m, 4H), 7.30–7.22 (m, 5H), 7.22–7.17 (m, 4H), 7.12–7.03 (m, 5H), [6.51 (s, 1H) & 6.34 (s, 1H); (77:23)], [5.84 (d, J = 18 Hz, 1H) & 5.73 (d, J = 18 Hz, 1H); (23:77)], 4.42–4.20 (m, 6H), 3.56–3.42 (m, 4H), [{2.44 (s, 3H), 2.41 (s, 3H)} & {2.43 (s, 3H), 2.38 (br s, 3H)}; (23:77)], [2.37 (br s, 6H); (23:77)], 1.30 (br t, J= 6.8 Hz,6H); ^{13}C NMR (101 MHz, $CDCl_3$)δ 168.2, 160.2, 144.8, 143.3, 142.1, 140.9, 138.8, 138.4, 138.1, 137.7, 135.4, 135.1, 133.4, 133.1, 132.8, 132.5, 131.1, 130.7, 130.5, 129.2, 129.2, 129.0, 128.5, 128.4, 127.7, 126.95, 126.89, 126.1, 125.8, 124.2, 118.0, 63.0, 62.9, 51.9, 51.6, 41.4, 36.8, 36.7, 30.9, 30.8, 21.7, 21.6, 21.5, 14.1. IR (Neat)ν_{max} 2920, 1736, 1578, 1468, 1358, 1156, 1084, 1034 cm^{-1}; HRMS (ESI) for $C_{38}H_{35}Cl_2N_2O_6S_2$ $(M+H)^+$: calcd 749.1314, found 749.1319.

The proton adjacent to ester group (H^a) in **94m** appears at 6.51 (s) ppm, whereas the proton adjacent to ester group (H^a) in **94q** resonates at 6.36 (s) ppm. The protons adjacent to ester group (H^a) in the inseparable mixture of compounds **94x** and **94x'** are appeared at 6.51 (s) and 6.34 (s) ppm. As the H^a proton of **94m** appears in deshielded region over the H^a proton of **94q**, we therefore assume that the peak at 6.51 (s) ppm corrosponds to H^a proton of **94x**,while the peak at 6.36 (s) ppm corrosponds to H^a proton of **94x'.** Based on the peak integration, the products **94x** and **94x'**are obtained in 77:23 ratio.

Crossover Experiment:



Following the general procedure GP-3, a crossover experiment was performed by reacting electron-rich, -deficient aryl moiety bearing ketene aminals **42b** (50 mg, 0.07 mmol) and **42h** (58 mg, 0.07 mmol) under the optimized conditions for 4 h. The compounds **94b** (36 mg, 72%) and 9**4h** (29 mg, 51%) were exclusively isolated.

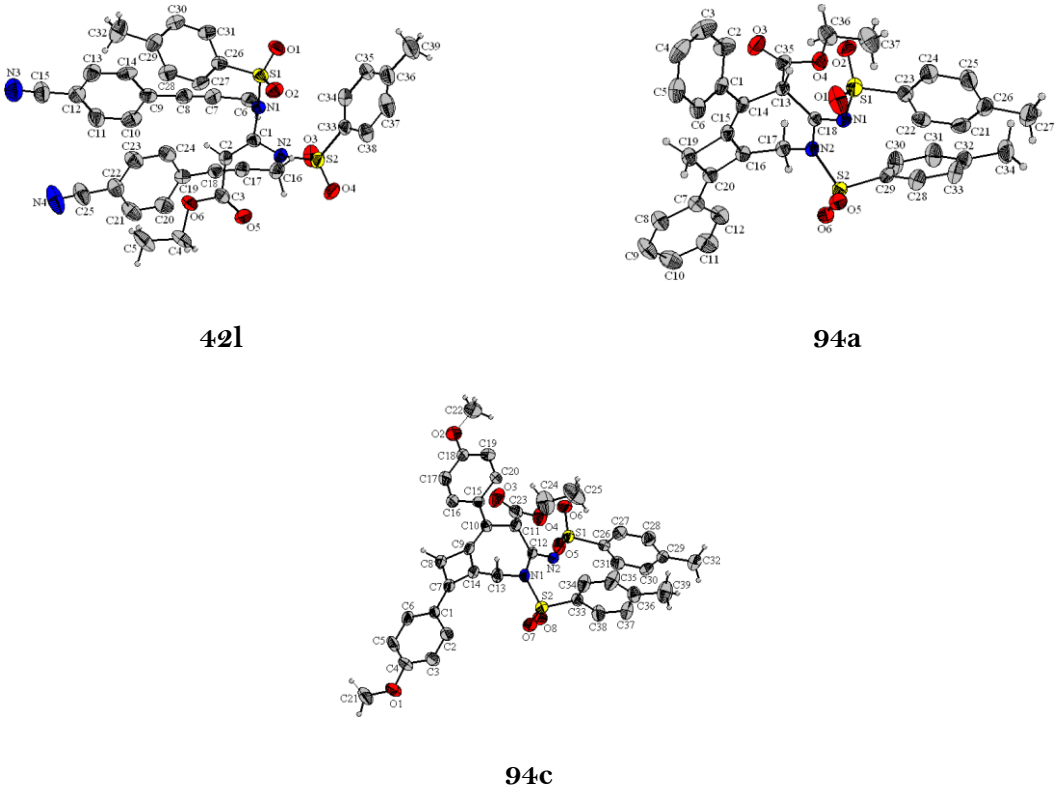
3.10.7. X-ray crystallography

X-Ray reflections for compounds **94a** was collected on a Bruker SMART APEX CCD diffractometer that was equipped with a graphite monochromator and Mo Kα fine-focus sealed tube (λ = 0.71073 Å). Data integration was done by using SAINT. The Intensities of the absorption were corrected by using SADABS. Structure solution and refinement were carried out by using Bruker SHELX-TL. X-ray reflections for compounds **42l** and **94c** were

collected on an Oxford Xcalibur Gemini Eos CCD diffractometer by using Mo-Kα radiation. Data reduction was performed using CrysAlisPro (version 1.171.33.55). The OLEX2-1.0 and SHELX-TL 97 programme were used to solve and refine the data. All non-hydrogen atoms were refined anisotropically, and C−H hydrogen atoms were placed at fixed positions.

Table 3.7. Crystallographic Data for Compounds 42l, 94a and 94c:

Compound	**42l**	**94a**	**94c**
formula	$C_{39}H_{32}N_4O_6S_2$	$C_{37}H_{34}N_2O_6S_2$	$C_{39}H_{38}N_2O_8S_2$
M_w	716.83	666.80	726.85
crystal system	orthorhombic	monoclinic	triclinic
space group	*Pbca*	$P2_1/c$	P_1^-
T [K]	298	293	298
a[Å]	15.0516(15)	17.511(3)	8.7849(11)
b [Å]	28.646(3)	10.814(2)	12.6893(16)
c [Å]	18.0316(18)	23.711(8)	16.278(2)
a[°]	90	90	85.618(10)
β [°]	90	130.536(18)	79.626(11)
γ[°]	90	90	82.116(11)
V [Å^3]	7774.7(14)	3412.3(17)	1765.6(4)
Z	8	4	2
ρ_{calcd} [g cm^{-3}]	1.225	1.298	1.367
μ [mm^{-1}]	0.186	0.205	0.208
total reflns	10464	6787	9591
unique reflns	6466	6748	8061
observed reflns	3063	4510	2180
R_1[$I>2\sigma(I)$]	0.0803	0.0552	0.0736
wR_2[all]	0.2453	0.1469	0.1458
GOF	0.967	1.023	0.841
Diffractometer	Xcalibur Gemini Eos CCD	SMART APEX CCD	Xcalibur Gemini Eos CCD



42l **94a**

94c

Figure 3.8. Molecular structures of compounds **42l, 94a** and **94c**; thermal ellipsoids are set at 30% probability**.** Oxygen (red), nitrogen (blue), and sulphur (yellow).

3.11. References:

1. (a) Stork, G.; Terrell, R.; Szmuszkovicz, J. *J. Am. Chem. Soc.* **1954**, *76*, 2029. (b) Stork, G.; Landesman, H. *J. Am. Chem. Soc.* **1956**, *78*, 5182. (c) Stork, G.; Brizzolara, A. *J. Am. Chem. Soc.* **1963**, *85*, 207.

2. For a general reference, see: Kantlehner, W. In *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*; de Meijere, A., Ed.; Thieme: Stuttgart, 2005; Vol. 24, pp 571-746.

3. For examples, see: (a) Gruseck, U.; Heuschmann, M. *Tetrahedron Lett.* **1987**, *28*, 6027. (b) Ye, G.; Henry, W. P.; Chen, C.; Zhou, A.; Pittman, C. U., Jr. *Tetrahedron Lett.* **2009**, *50*, 2135.

4. For a review, see: Huang, Z. T.; Wang, M. X. In *The Chemistry of Enamines*; Rappoport, Z., Ed.; John Wiley: New York, **1994**; 1303.

5. For selected recent examples on ketene N,N-acetal, see: (a) Shi, Y.; Zhang, J.; Grazier, N.; Stein, P. D.; Atwal, K. S.; Traeger, S. C.; Callahan, S. P.; Malley, M. F.; Galella, M. A.; Gougoutas, J. Z. *J. Org. Chem.* **2004**, *69*, 188. (b) Yu, C.-Y.; Yang, P.-H.; Zhao, M.-X.; Huang, Z.-T. *Synlett* **2006**, 1825. (c) Naito, H.; Hata, T.; Urabe, H. *Tetrahedron Lett.* **2008**, *49*, 2298. (d) Yaqub, M.; Yu, C.-Y.; Jia, Y.-M.; Huang, Z.-T. *Synlett* **2008**, 1357. (e) Coste, A.; Couty, F.; Evano, G. *Org. Lett.* **2009**, *11*, 4208.

6. Zhao, M.-X.; Wang, M.-X.; Huang, Z.-T. *Tetrahedron Lett.* **2002**, 58, 1309.

7. Sing, O. M.; Devi, L. R.; Singh, T. P.; Ila, H. *Arkivok.* **2011**, 297.

8. Coste, A.; Couty, F.; Evano, G. *Org. Lett.* **2009**, *11*, 4454. (b) Jouvin, K.; Coste, A.; Bayle, A.; Legrand, F.; Karthikeyan, G.; Tadiparthi, K.; Evano, G. *Organometallics.* **2012**, *31*, 7933.

9. Yu, F.-C.; Yan, S.-J.; Hu, L.; Wang, Y.-C.; Lin, J. *Org. Lett.* **2011**, *13*, 4782.

10. Li, M.; Shao, P.; Wang, S.-W.; Kong, W.; Wen, L.-R. *J. Org. Chem.* **2012**, *77*, 8956.

11. Li, M.; Zhou, Z.-M.; Wen, L.-R.; Qiu, Z.-X. *J. Org. Chem.* **2011**, *76*, 3054.

12. Sivakumar, S.; Kumar, R. R. *Asian J. Org. Chem.* **2014**, *3*, 974.

13. Ghosh, N.; Nayak, S.; Sahoo, A. K. *Chem.–Eur. J.* **2013**, *19*, 9428.

14. (a) For recent reviews on gold catalysis, see: (a) Rudolph, M.; Hashmi, A. S. K. *Chem. Soc. Rev.* **2012**, *41*, 2448. (b) Garayalde, D.; Nevado, C. *ACS Catal.* **2012**, *2*, 1462. (c) Corma, A.; Leyva-Pérez, A.; Sabater, M. J. *Chem. Rev.* **2011**, *111*, 1657. (d) Rudolph, M.; Hashmi, A. S. K. *Chem. Commun.* **2011**, *47*, 6536. (e) Hashmi, A. S. K.; Buhrle, M. *Aldrichimica Acta* **2010**, *43*, 27. (f) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2010**, *49*, 5232. (g) DeKorver, K. A.; Li, H. Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. *Chem. Rev.* **2010**, *110*, 5064. (h) Sohel, S. M. A.; Liu, R.-S. *Chem. Soc. Rev.* **2009**, *38*, 2269. (i) Fürstner, A. *Chem. Soc. Rev.*

2009, *38*, 3208. (j) Li, Z.; Brower, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239. (k) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326. (l) Michelet, V.; Toullec, P. Y.; Genêt, J.-P. *Angew. Chem., Int. Ed.* **2008**, *47*, 4268; reference cited there in. (m) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351. (n) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (o) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410.

15. Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813.

16. Echavarren, A. M; Jiménez-Núñez, E. *Top. Catal.* **2010**, *53*, 924.

17. Lloyd-Jones, G. C. *Org. Biomol. Chem.* **2003**, *1*, 215.

18. Trost, B. M.; Gutierrez, A. C.; Ferreira, E. M. *J. Am. Chem. Soc.* **2010**, *132*, 9206.

19. (a) Méndez, M.; Muñoz, M. P.; Echavarren, A. M. *J. Am. Chem. Soc.* **2000**, *122*, 11549. (b) Baumgarten, S.; Lesage, D.; Gandon, V.; Goddard, J.-P.; Malacria, M.; Tabet, J.-C.; Gimbert, Y.; Fensterbank, L. *Chem CatChem* **2009**, *1*, 138.

20. Escribano-Cuesta, A.; Perez-Galan, P.; Herrero-Gomez, E.; Sekine, M.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *Org. Biomol. Chem.* **2012**, *10*, 6105.

21. (a) Seidel, G.; Mynott, R.; Fürstner, A. *Angew. Chem. Int. Ed.* **2009**, *48*, 2510. (b) Benitez, D.; Shapiro, N. D.; Tkatchouk, E.; Wang, Y.; Goddard, W. A.; Toste, F. D. *Nature Chem.* **2009**, *1*, 482. (c) Casanova, J.; Kent, D. R.; Goddard, W. A.; Roberts, J. D. *Proc. Natl. Acad. Sci. U. S. A.* **2003**, *100*, 15.

22. Nieto-Oberhuber, C.; López, S.; Muñoz, M. P.; Cárdenas, D. J.; Buñuel, E.; Nevado, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 6146.

23. (a) Reetz, M. T. *Angew. Chem. Int. Ed.* **1972**, *11*, 129. (b) Reetz, M. T. *Angew. Chem. Int. Ed.* **1972**, *11*, 130.

23. Nieto-Oberhuber, C.; Muñoz, M. P.; López, S.; Jiménez-Núñez, E.; Nevado, C.; Herrero-Gómez, E.; Raducan, M.; Echavarren, A. M. *Chem. Eur. J.* **2006**, *12*, 1677.

24. Cabello, N.; Jiménez-Núñez, E.; Buñuel, E.; Cárdenas, D. J.; Echavarren, A. M. *Eur. J. Org. Chem.* **2007**, *2007*, 4217.

25. Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351.

26. Gagosz, F. *Org. Lett.* **2005**, *7*, 4129.

27. Zhang L., Kozmin S. A.; *J. Am. Chem. Soc.* **2004**, *126*, 11806.

28. Abbiati, G.; Arcadi, A.; Bianchi, G.; Di Giuseppe, S.; Marinelli, F.; Rossi, E. *J. Org. Chem.* **2003**, *68*, 6959.

29. Dankwardt, W. *Tetrahedron Lett.* **2001**, *42*, 5809.

30. Harrison, J.; Dake, G. R. *Org. Lett.* **2004**, *6*, 5023.

31. Rao, W.; Susanti, D.; Chan, P. W. H. *J. Am. Chem. Soc.* **2011**, *133*, 15248. (b) Rao, W.; Koh, M. J.; Kothandaraman, P.; Chan, P. W. H. *J. Am. Chem. Soc.* **2012**, *134*, 10811.

32. For allene [2+2] cycloaddition, see: Aubert, C., Fensterbank, L.; Garcia, P.; Malacria, M.; Simonneau, A. *Chem. Rev.* **2011**, *111*, 1954; reference cited there in.

33. (a) Torres-Marquez, E.; Sinnett-Smith, J.; Guha, S.; Kui, R.; Waldron, R. T.; Rey, O.; Rozengurt, E. *Biochem. Biophys. Res. Commun.* **2010**, *391*, 63. (b) Song, Y.-F.; Qu, Y.; Cao, X.-P.; Zhang, W. *Mar. Biotechnol.* **2011**, *13*, 868. (c) Smith III, A. B.; Cho, Y. S.; Zawacki, L. E.; Hirschmann, R.; Pettit, G. R. *Org. Lett.* **2001**, *3*, 4063. (d) Gijsen, H. J. M.; Berthelot, D.; Zaja, M.; Brone, B.; Geuens, I.; Mercken, M. *J. Med. Chem.* **2010**, *53*, 7011. (e) Tomasi, S.; Renault, J.; Martin, B.; Duhieu, S.; Cerec, V.; Roch, M. L.; Uriac, P.; Delcros, J.-G. *J. Med. Chem.* **2010**, *53*, 7647.

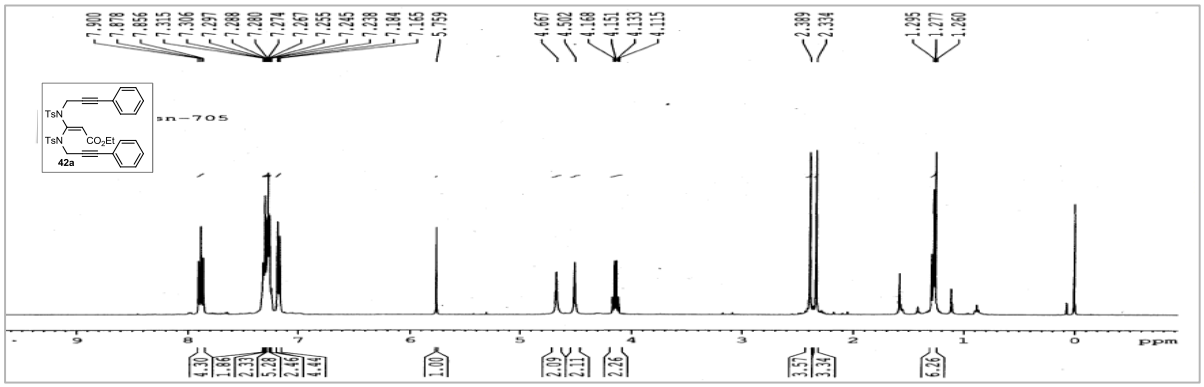
34. For synthesis of azepines via classical methods, see: (a) Stogryn, E. L.; Brois, S. J.; *J. Am. Chem. Soc.* **1967**, *89*, 605. (b) Hu, J.; Miller, M. J. *Tetrahedron Lett.* **1995**, *36*, 6379. (c) Hassner, A.; D' Costa, R.; McPhail, A. T.; Butler, W. *Tetrahedron Lett.* **1981**, *22*, 3691. (d) Masse, C. E.; Morgan, A. J.; Panek, J. S. *Org. Lett.* **2000**, *2*, 2571. (e) Bergen, T. J. V.; Kellogg, R. M. *J. Org. Chem.* **1971**, *36*, 978. (f) Kantorowski, E. J.; Kurth, M. J. *Tetrahedron* **2000**, *56*, 4317. (g) Maier, M. E. *Angew. Chem., Int. Ed.* **2000**, *39*, 2073. (h) Jakubec, P.; Hawkins, A.; Felzmann, W.; Dixon, D. J. *J. Am. Chem. Soc.* **2012**, *134*, 17482.

35. (a) Nayak, S.; Ghosh, N.; Sahoo, A. K. *Org. Lett.* **2014**, *16*, 2996. (b) See supporting information.

36. (a) Shi, Y.; Zhang, J.; Grazier, N.; Stein, P. D.; Atwal, K. S.; Traeger, S. C.; Callahan, S. P.; Malley, M. F.; Galella, M. A.; Gougoutas, J. Z. *J. Org. Chem.* **2004**, *69*, 188. (b) Yu, C.-Y.; Yang, P.-H.; Zhao, M.-X.; Huang, Z.-T. *Synlett* **2006**, 1825. (c) Naito, H.; Hata, T.; Urabe, H. Tetrahedron Lett. **2008**, *49*, 2298. (d) Yaqub, M.; Yu, C.-Y.; Jia, Y.-M.; Huang, Z.-T. *Synlett* **2008**, 1357. (e) K. Sonogashira, Y. Tohda, N. Hagihara, *Tetrahedron Lett.* **1975**, 4467.

37. (a) SAINT-Plus, *version 6.45*, Bruker AXS Inc. Madison, WI, **2003**. Sheldrick, G. M. SADABS, *Program for Empirical Absorption Correction of Area Detector Data*, University of Gottingen, Germany, **1997**. (b) SMART (*version 5.625*), SHELX-TL (*version 6.12*), Bruker AXS Inc. Madison, WI, **2000**; b) Sheldrick, G. M. SHELXS-97, SHELXL-97, University of Gottingen, Germmany, **1997**. (c). Dolomanov O. V., Blake A. J., Champness N. R., Schroder M. *J. Appl. Cryst.* **2003**, *36*, 1283.

3.12. Spectra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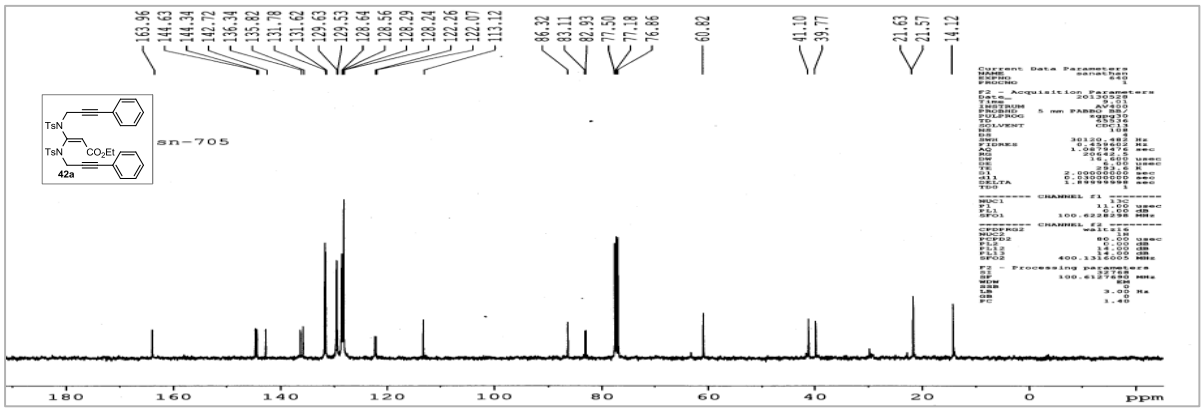
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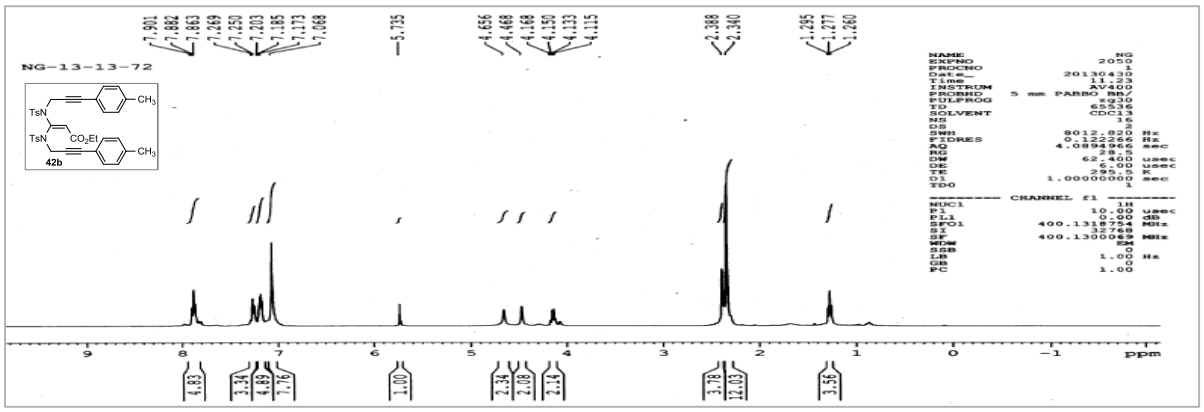
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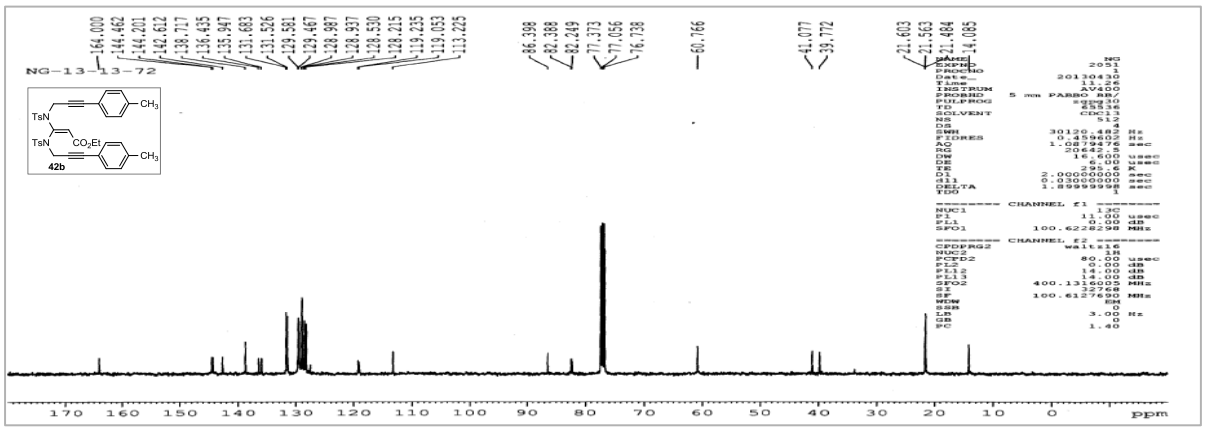
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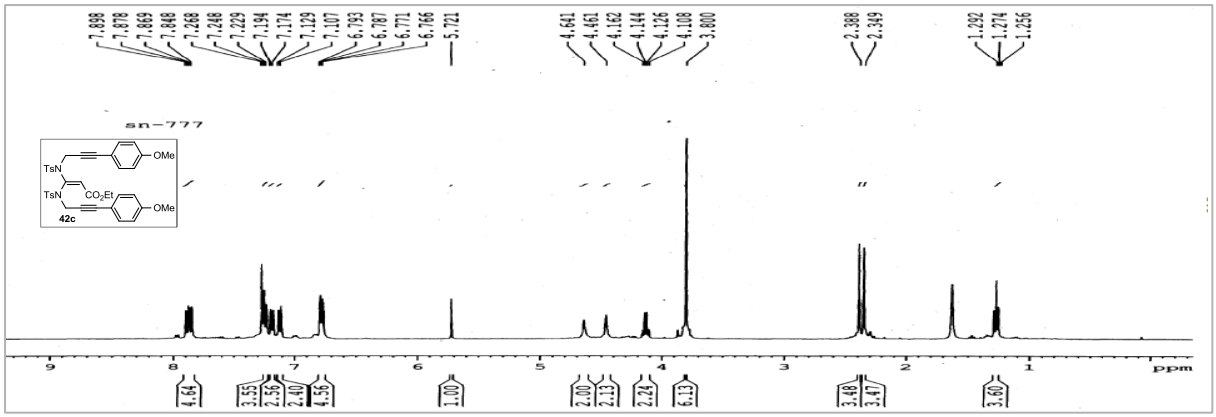
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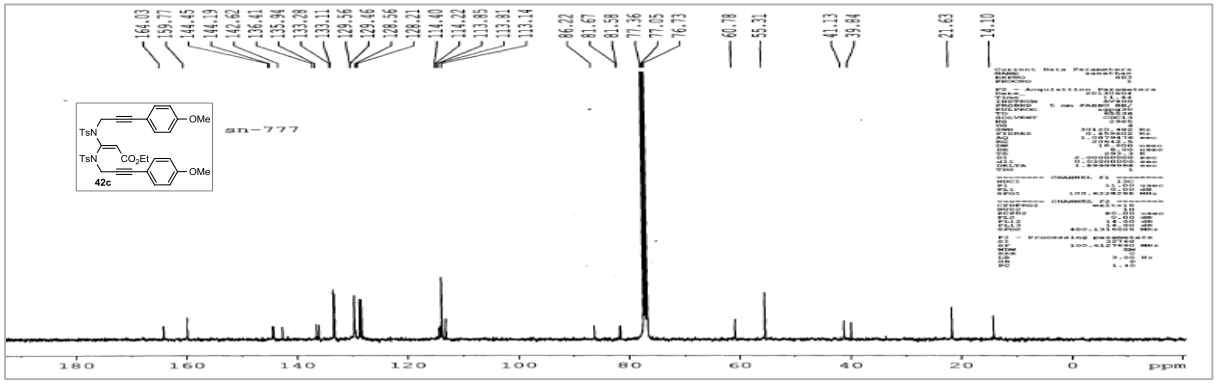
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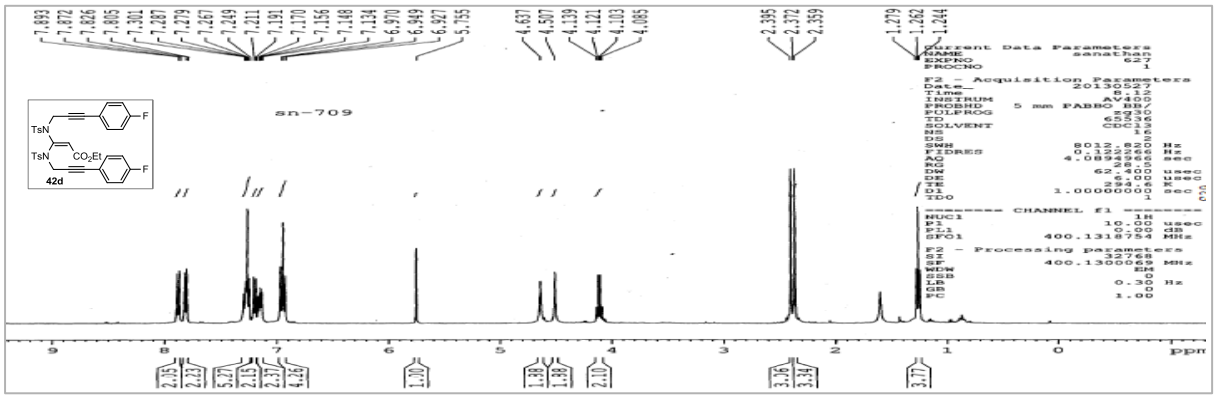
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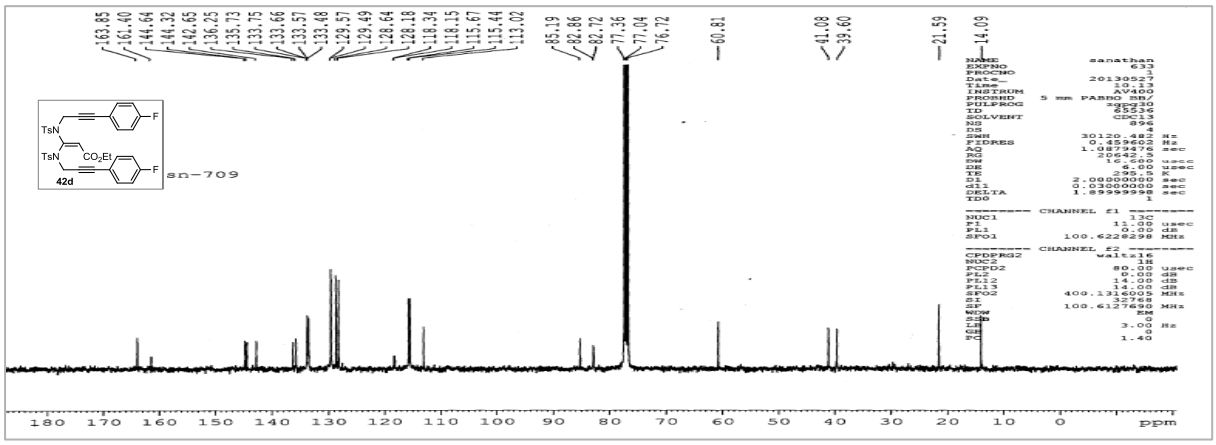
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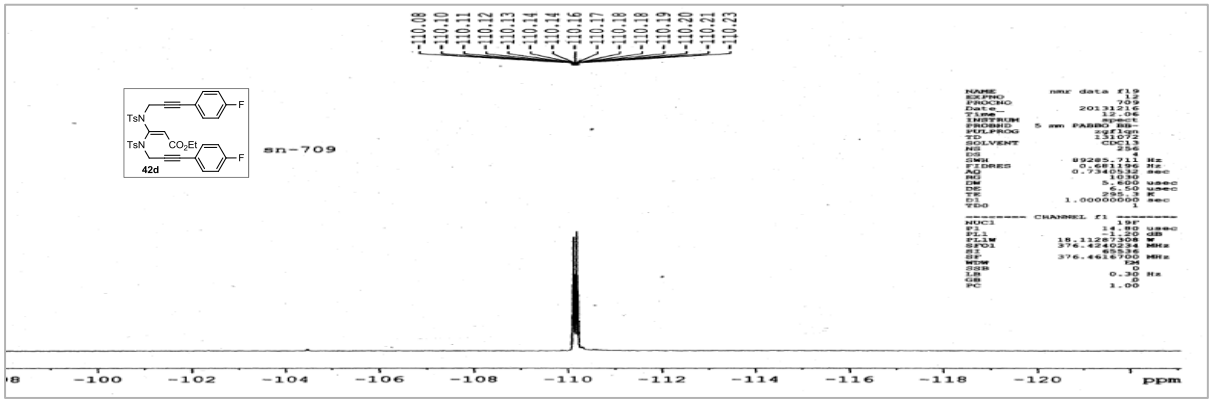
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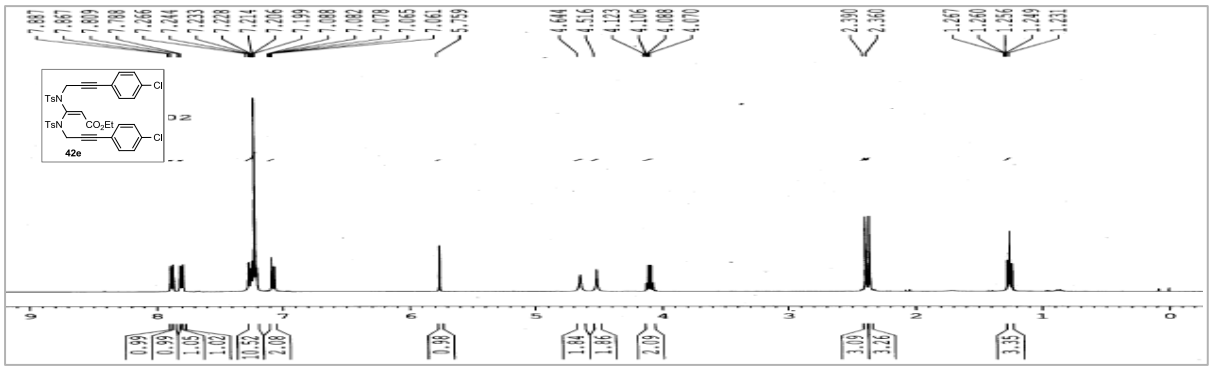
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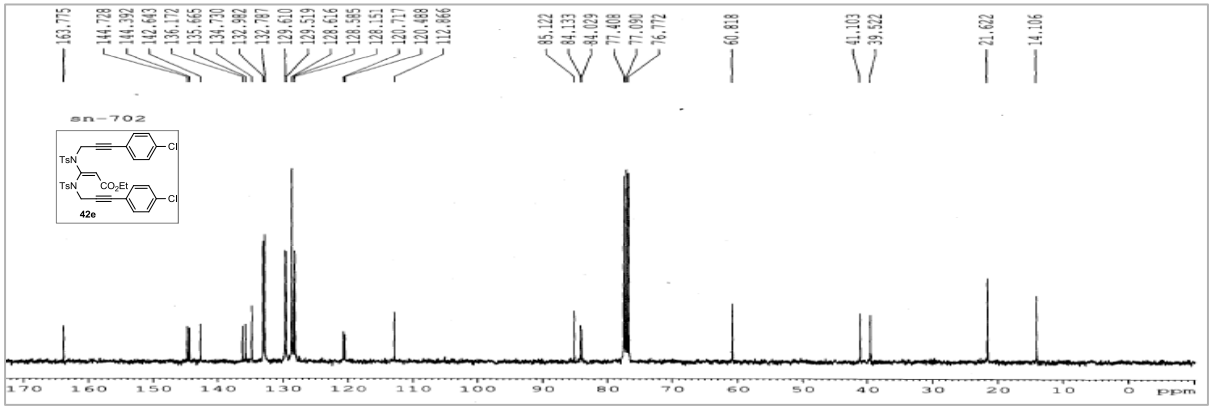
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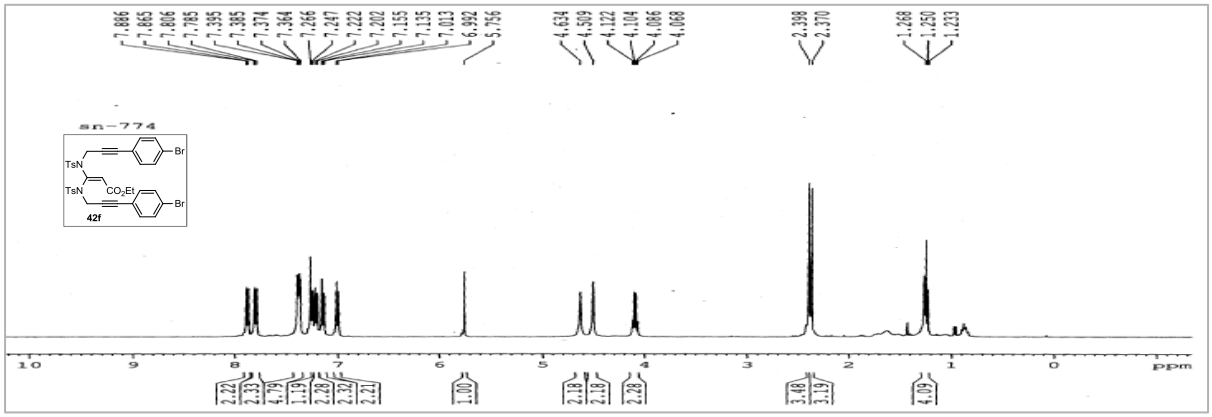
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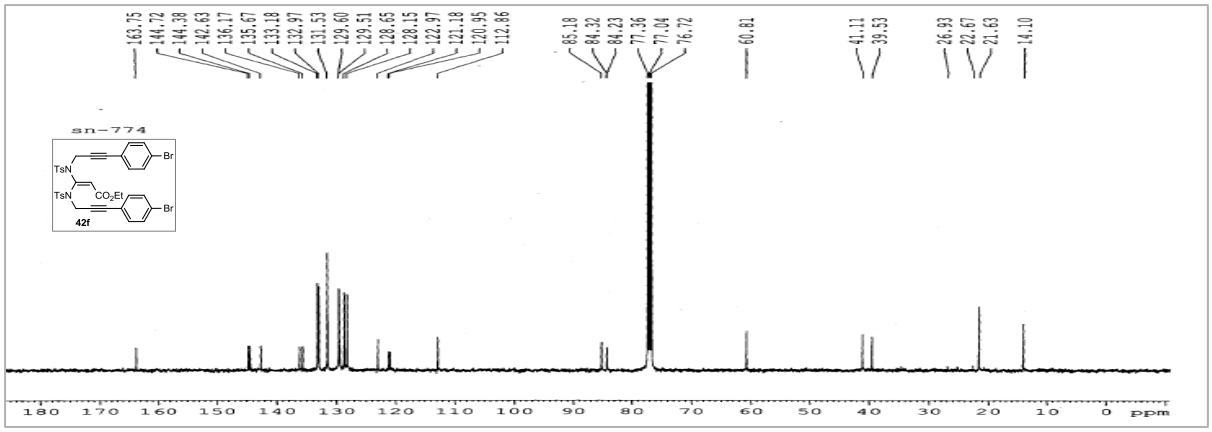
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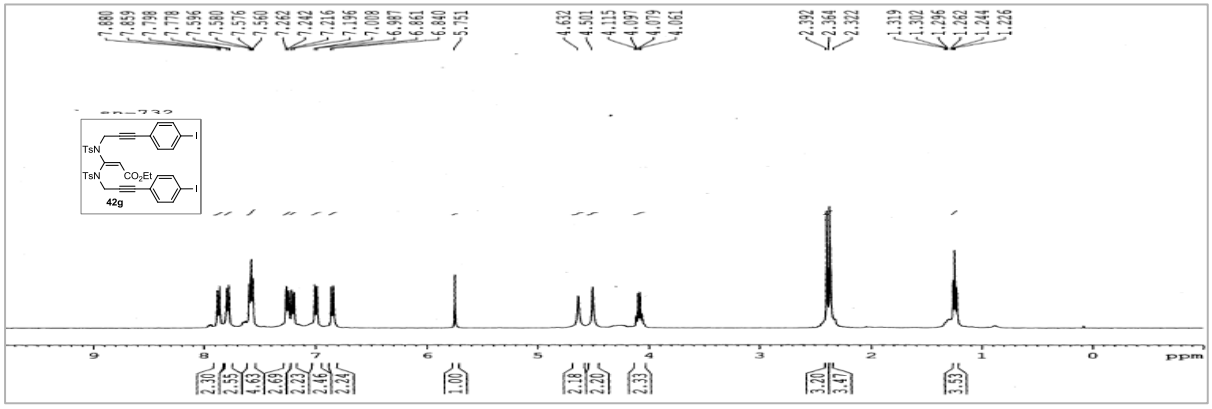
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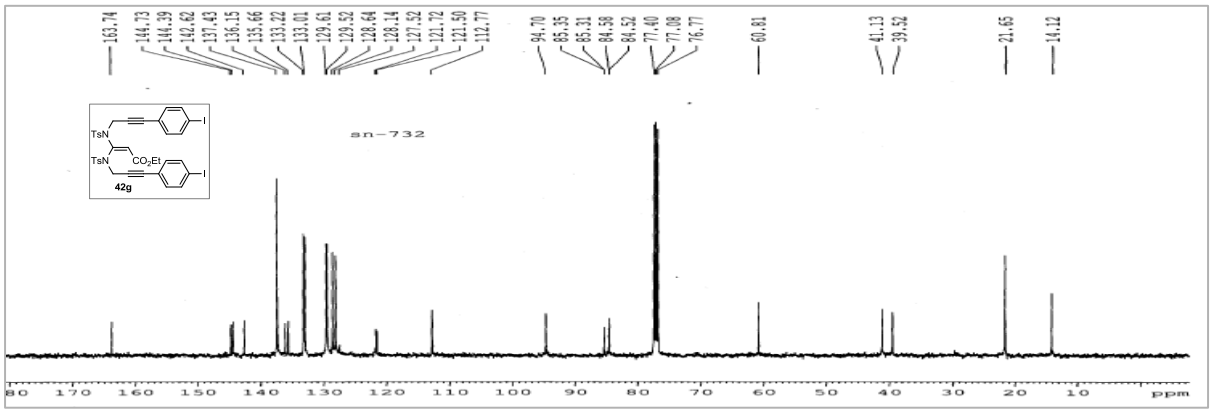
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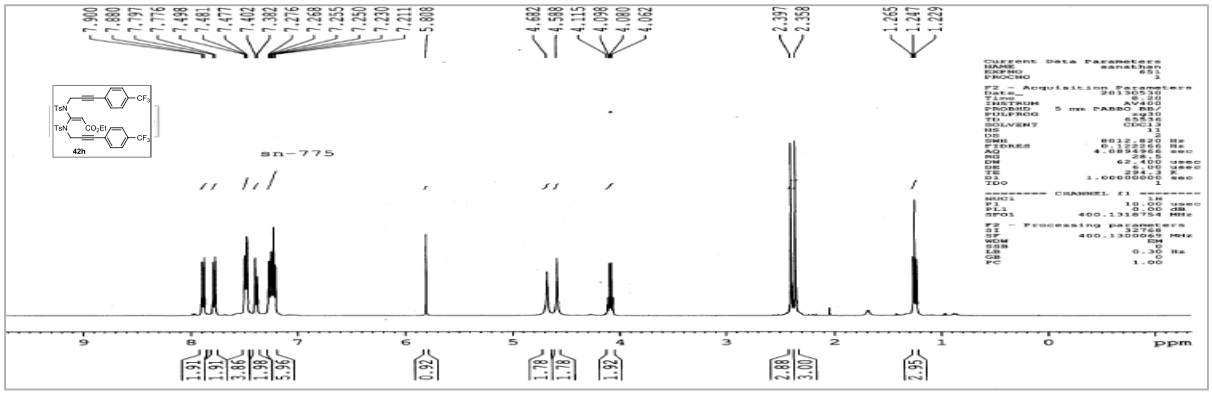
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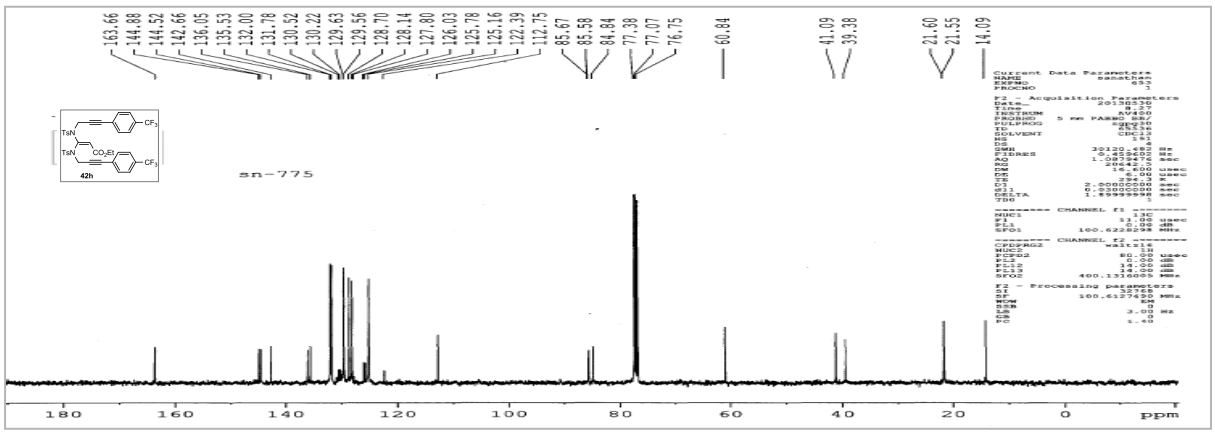
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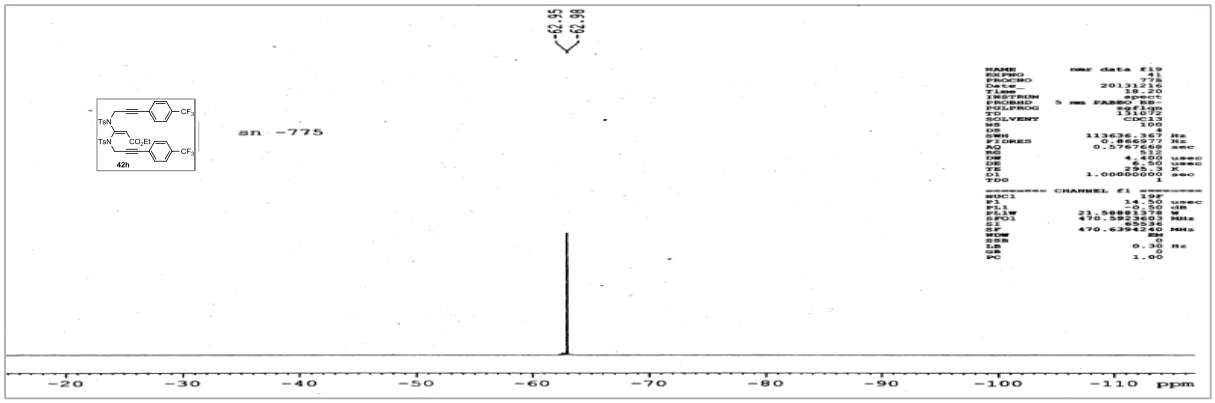
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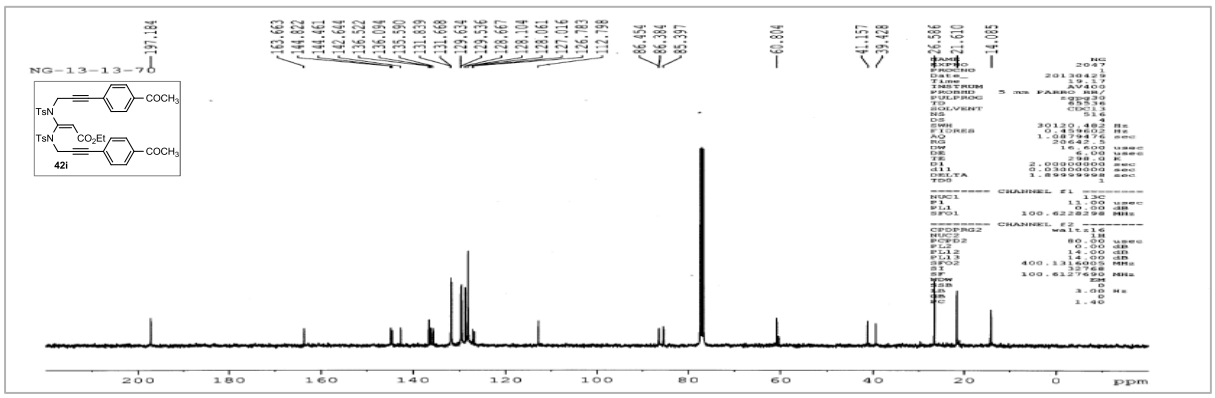
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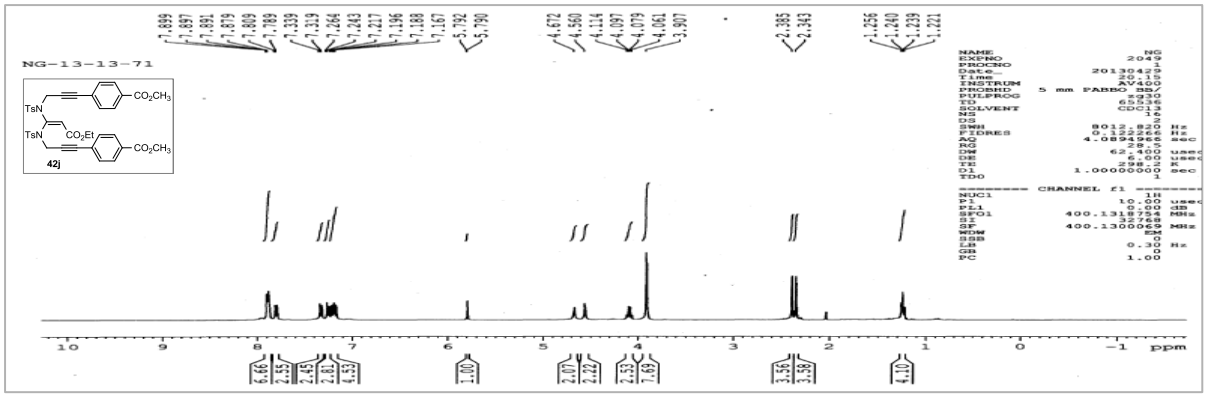
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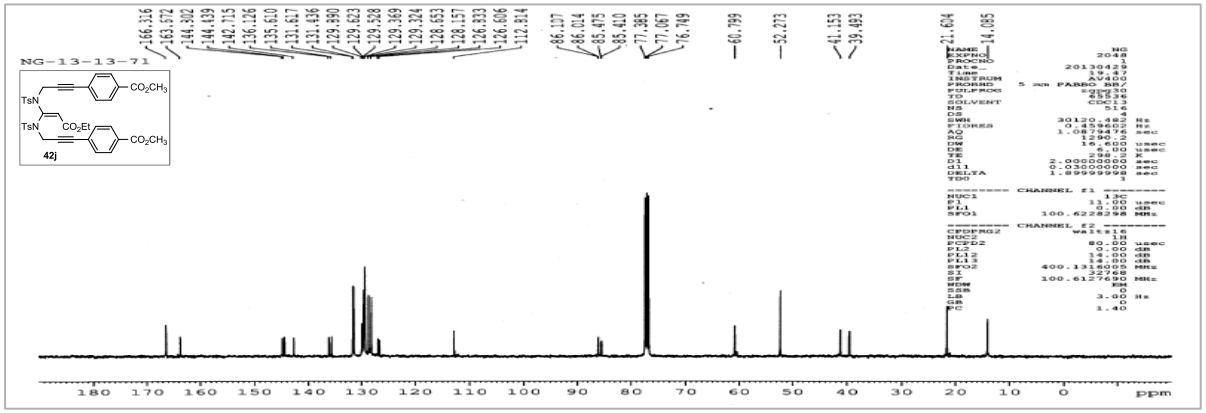
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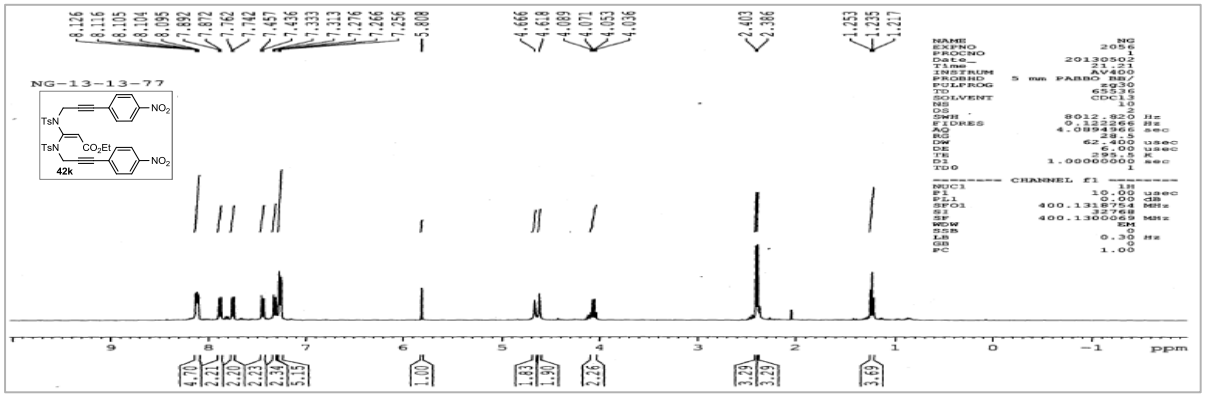
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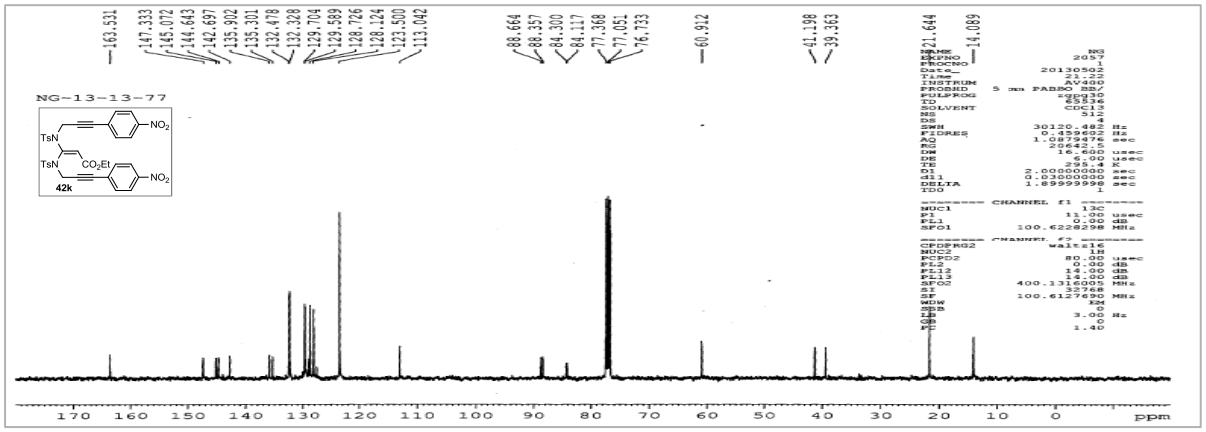
42k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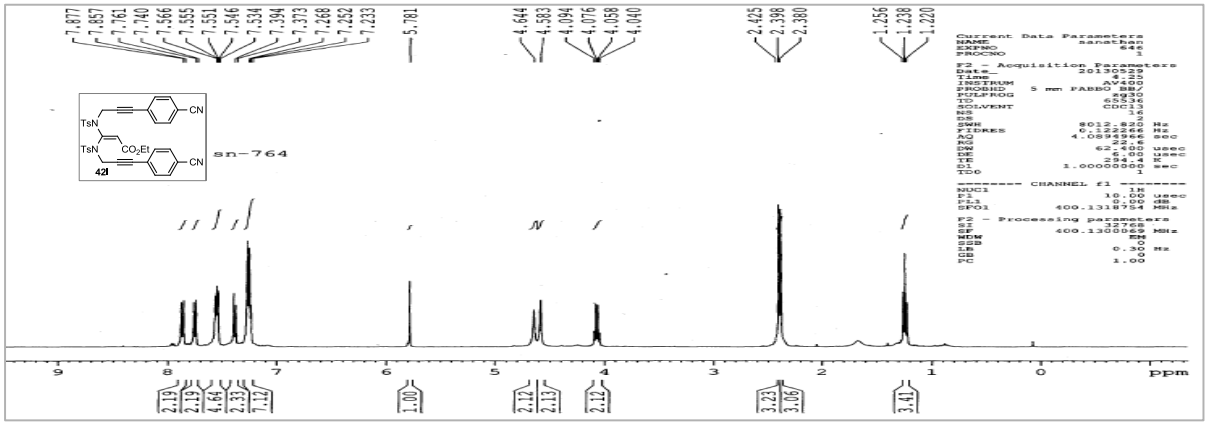
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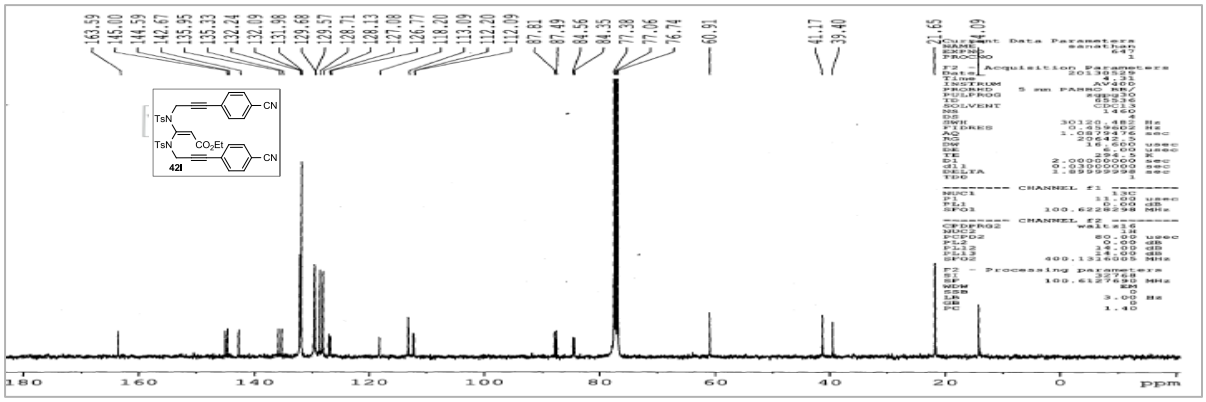
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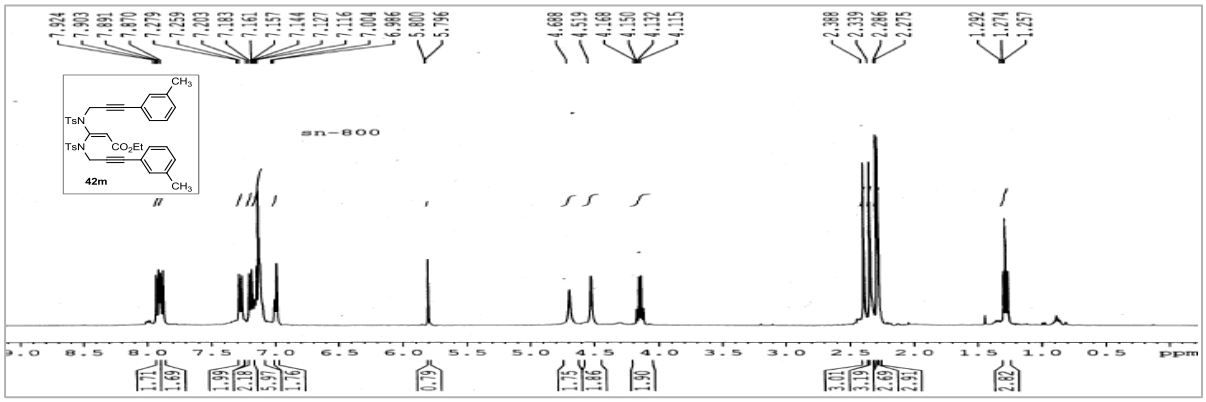
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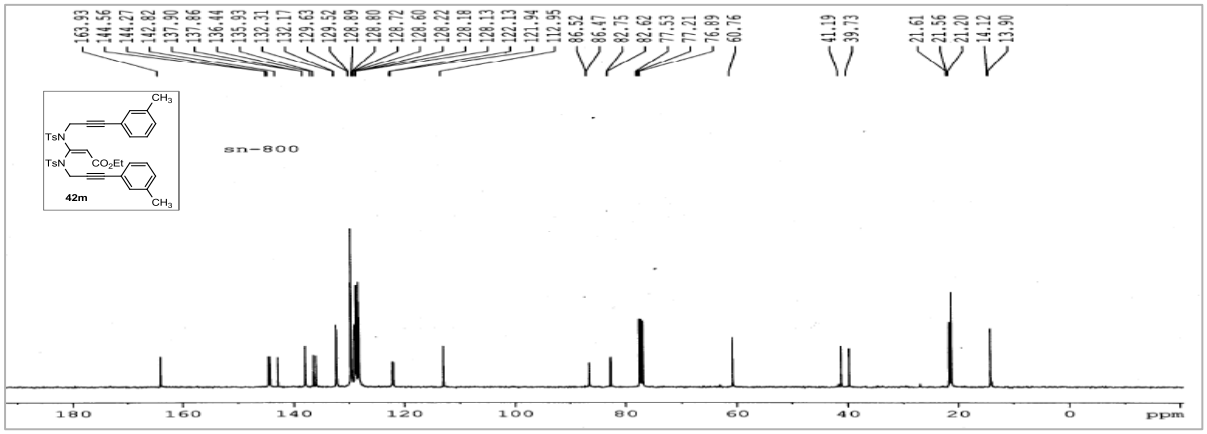
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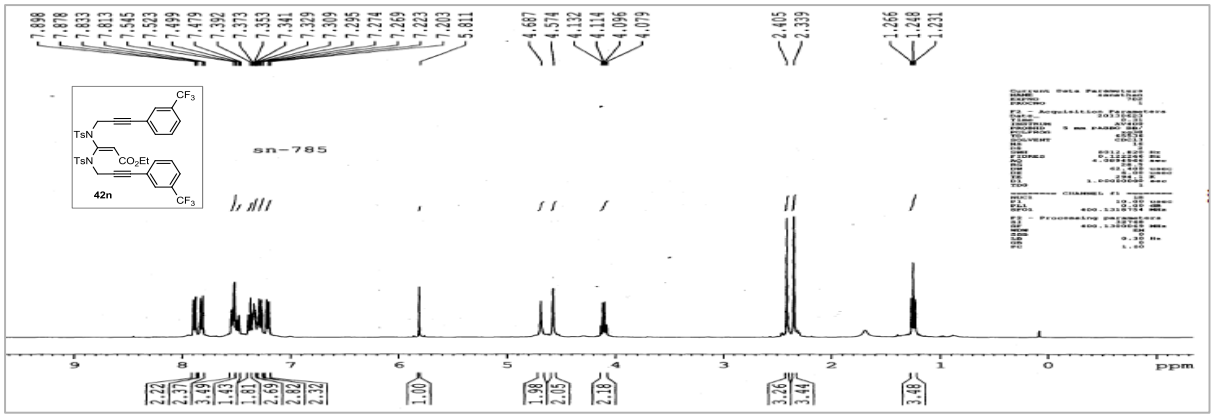
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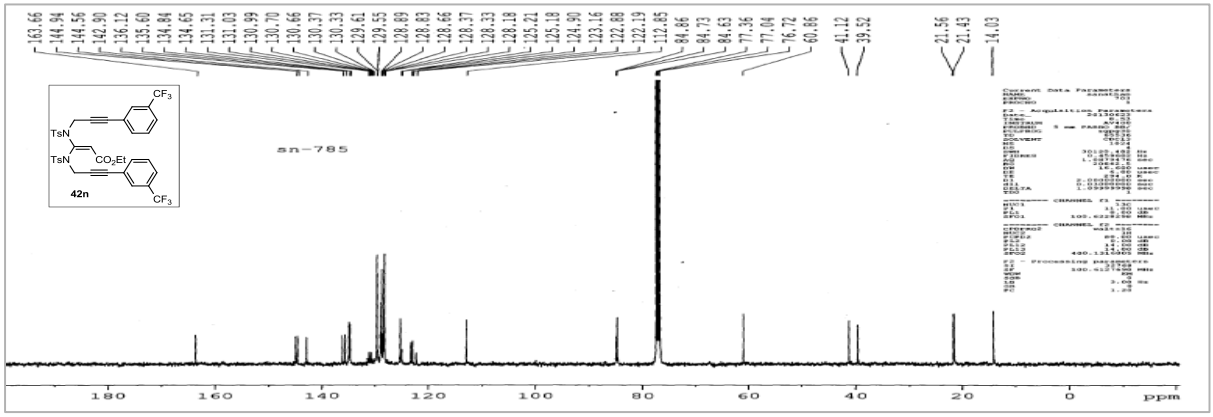
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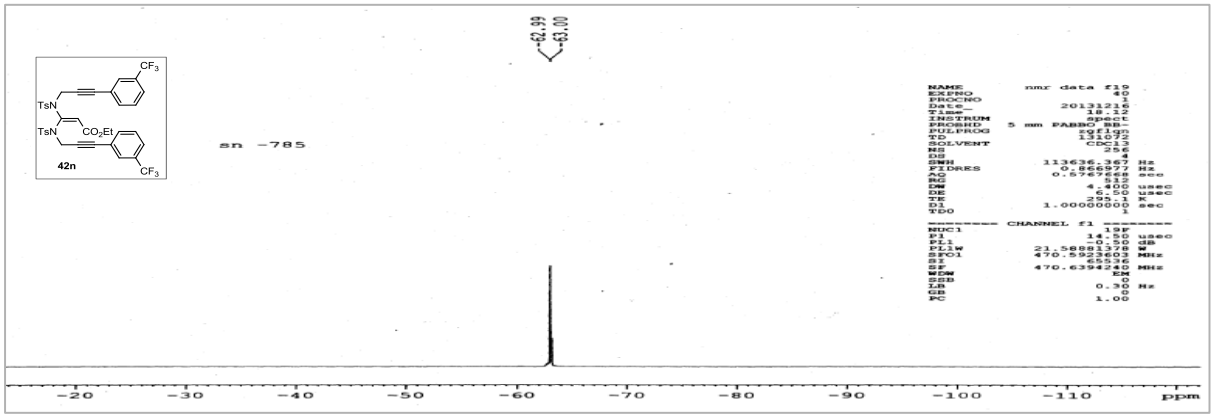
42n
ppm


sn -785
42n
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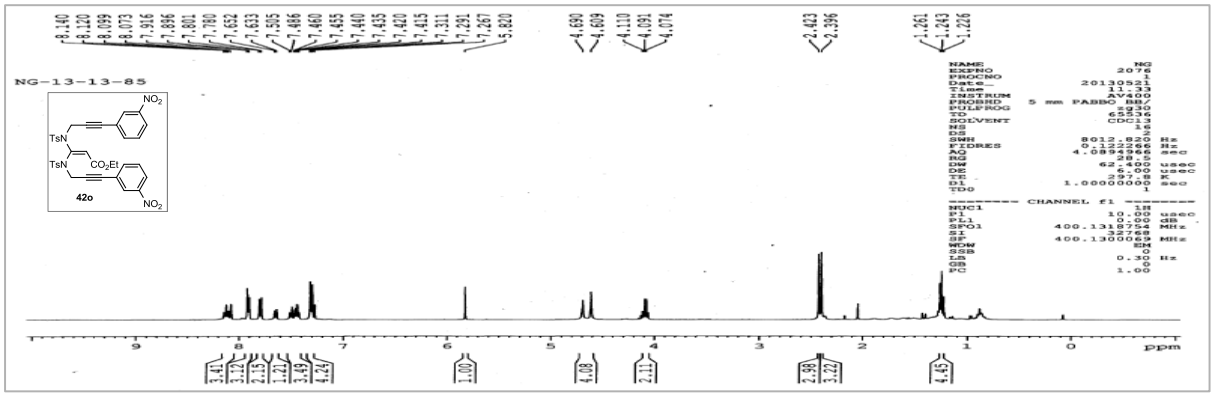
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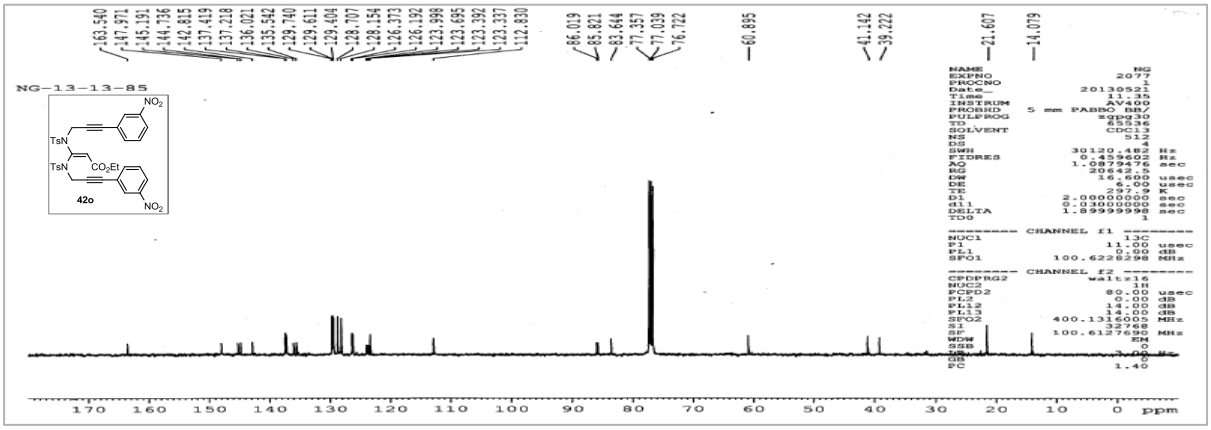
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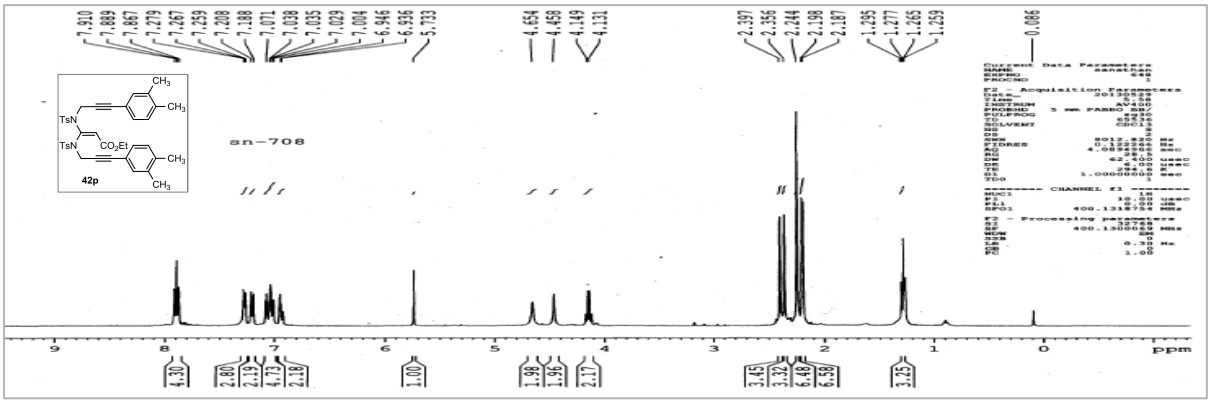
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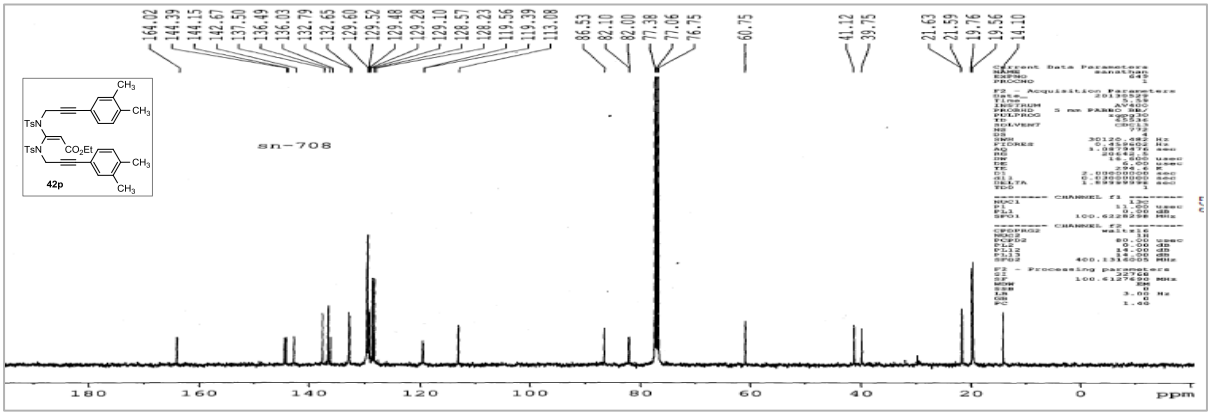
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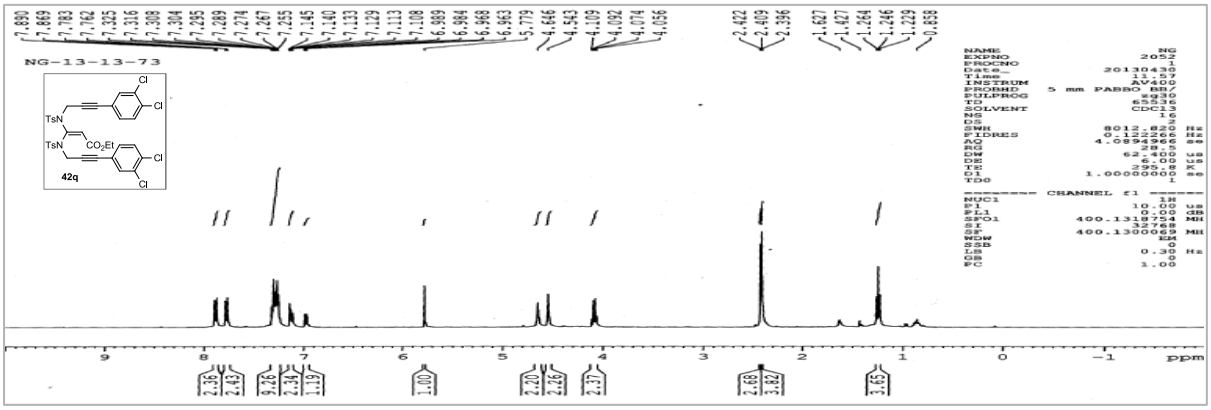
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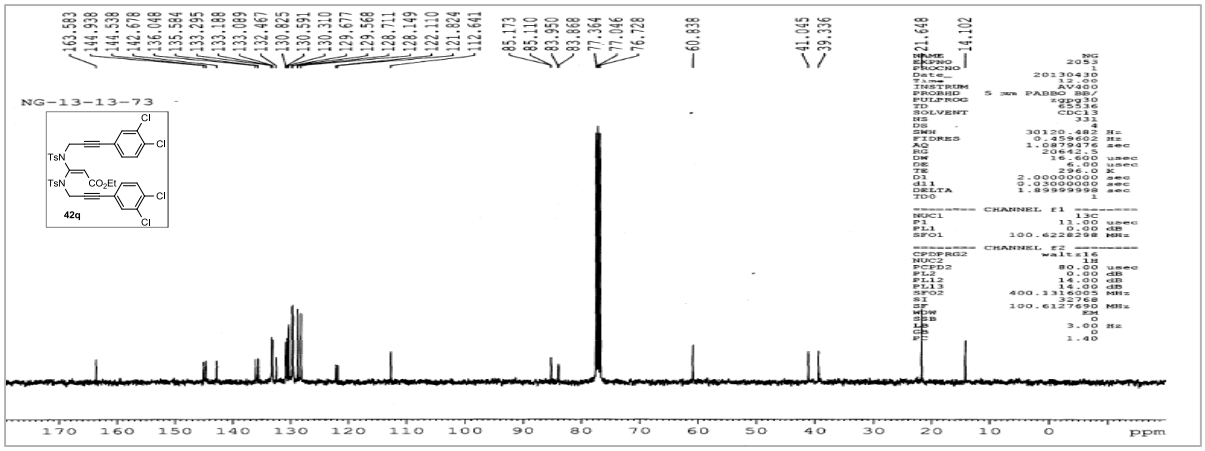
42q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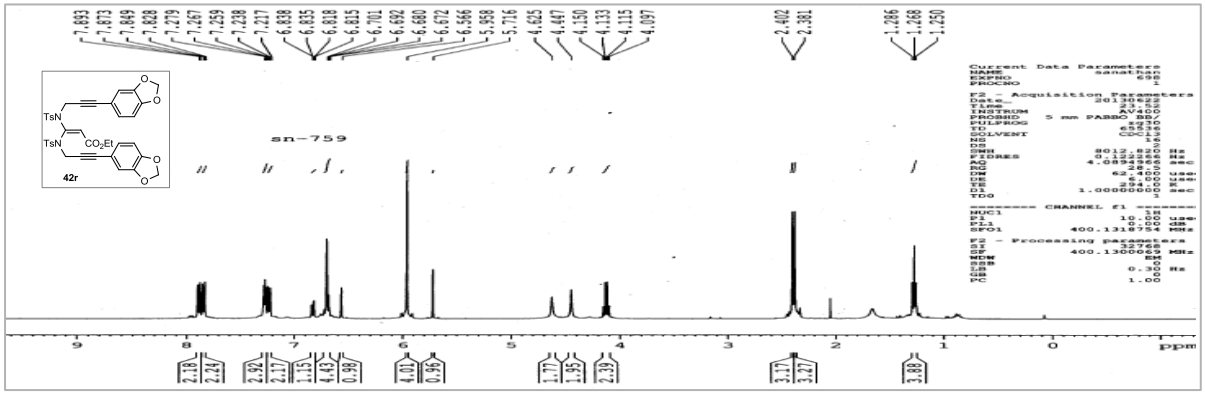
42q
ppm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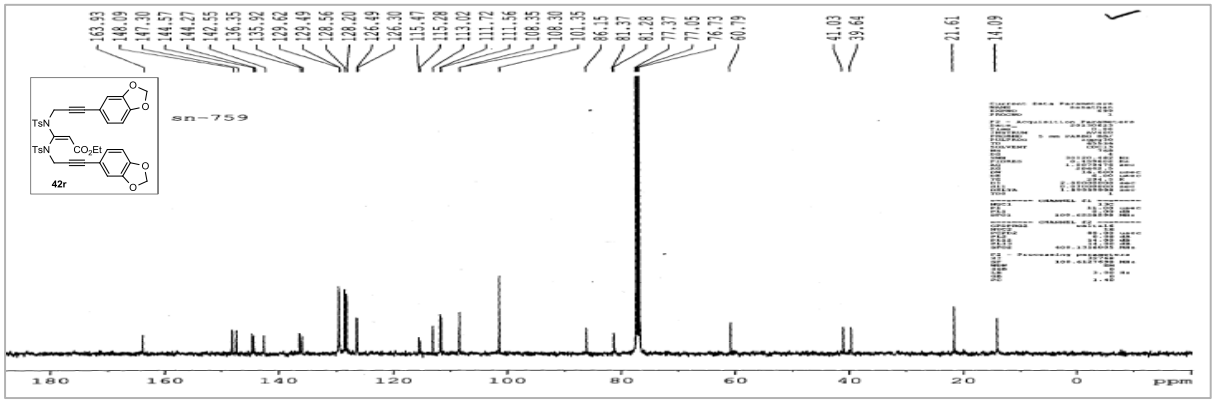
42r
ppm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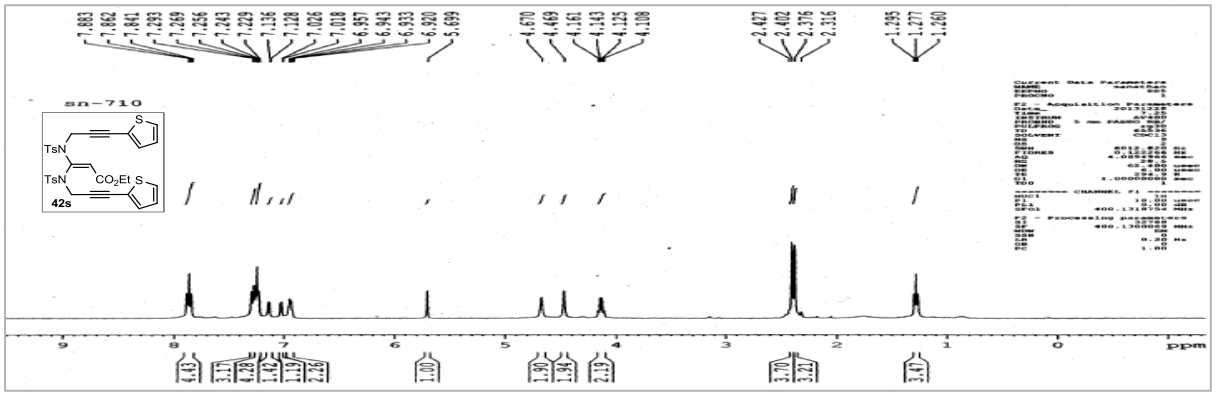
42r
ppm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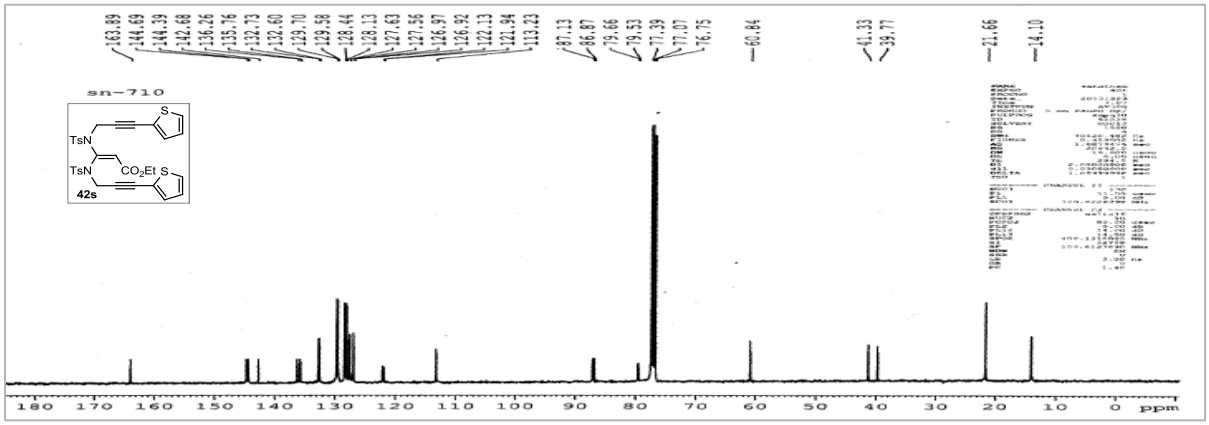
42s
ppm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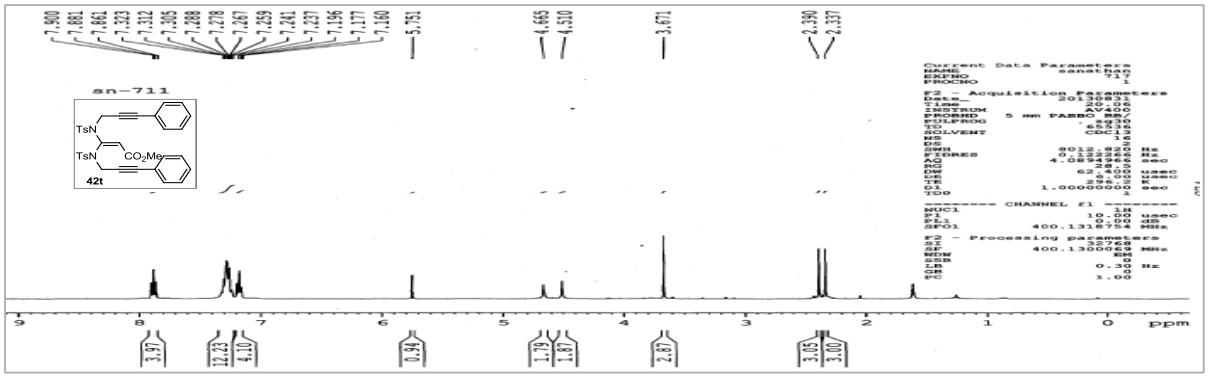
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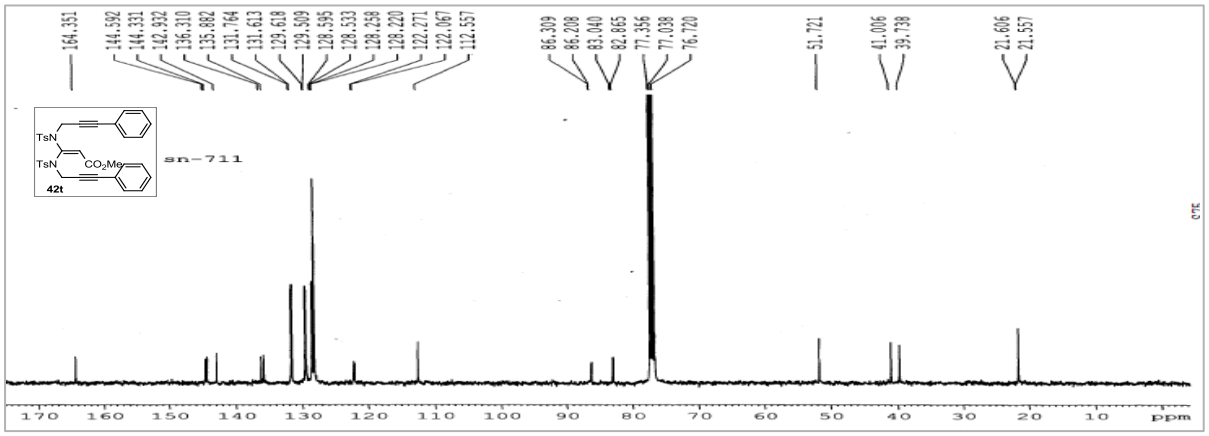
42t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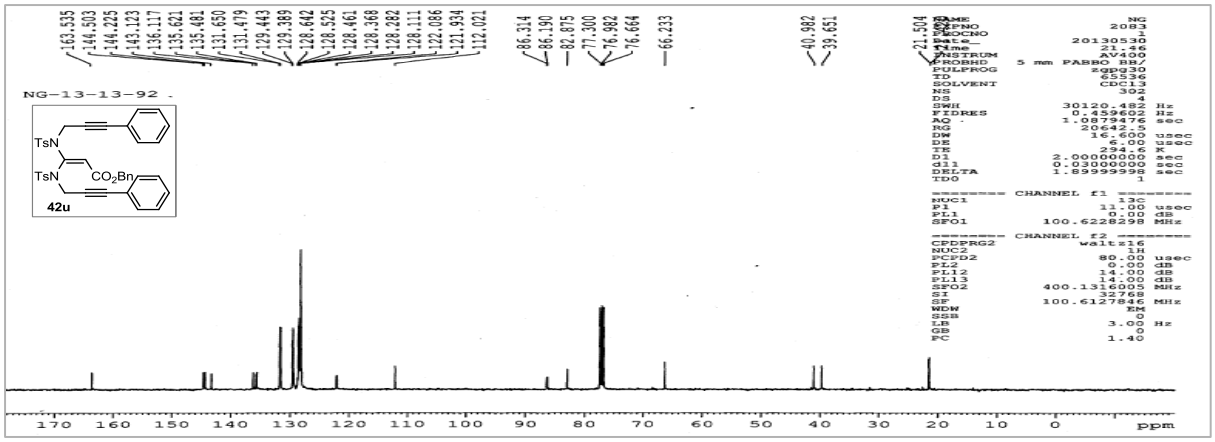
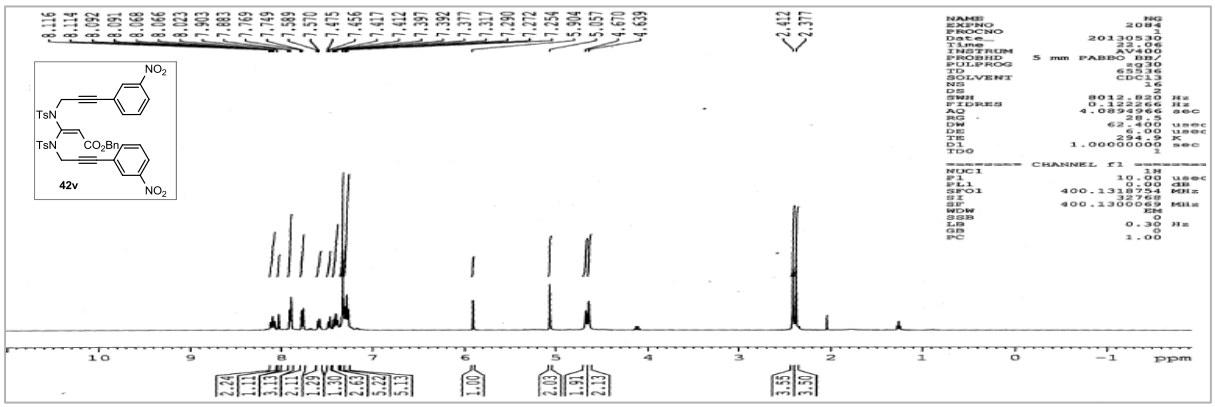
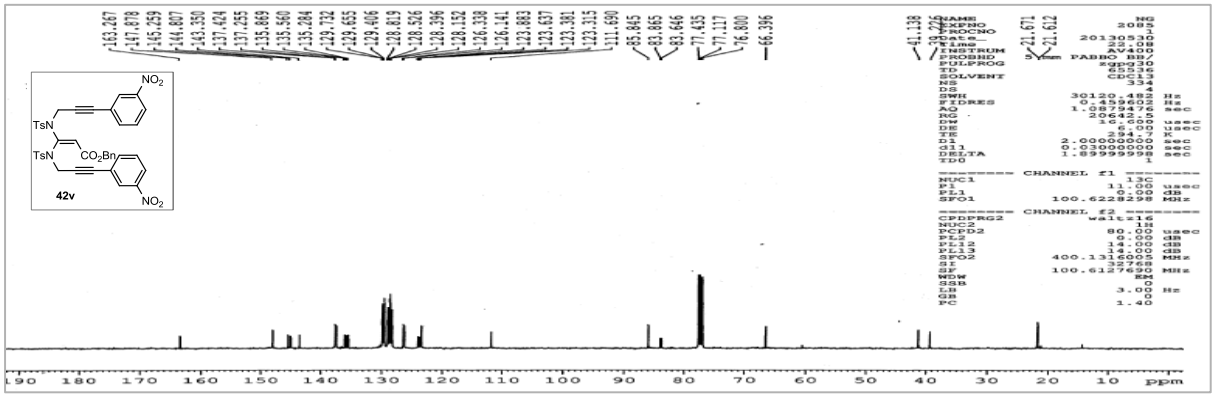
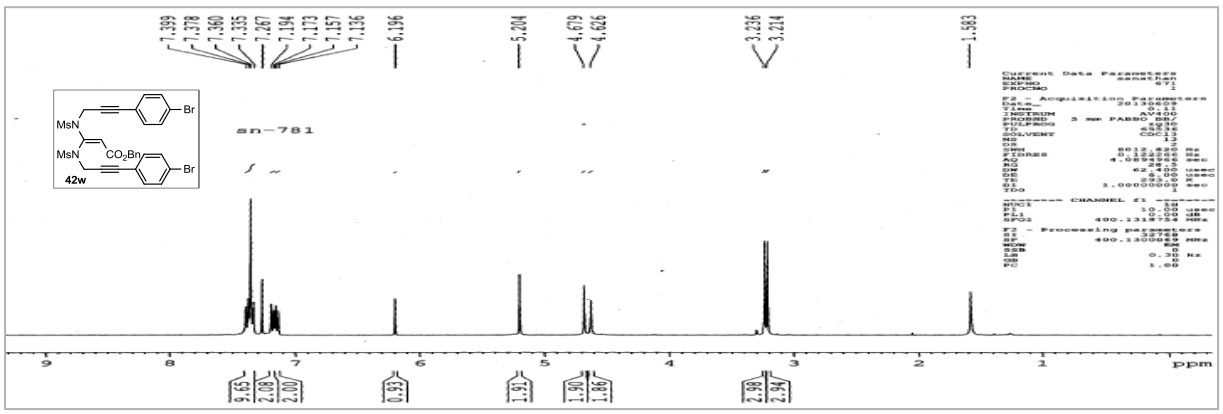
42t

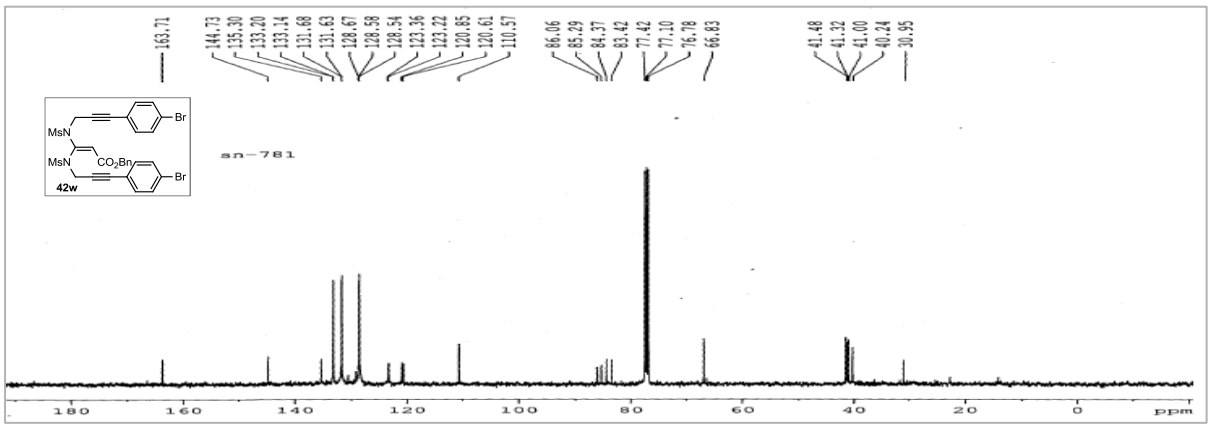

NG-13-13-92
42u


NG-13-13-92
TsN
TsN
CO2Bn
42u
ppm


NO2
TsN
TsN
CO2Bn
42v
NO2
ppm


NO2
TsN
TsN
CO2Bn
42v
NO2
ppm


sn-781
MsN
MsN
CO2Bn
Br
Br
42w
ppm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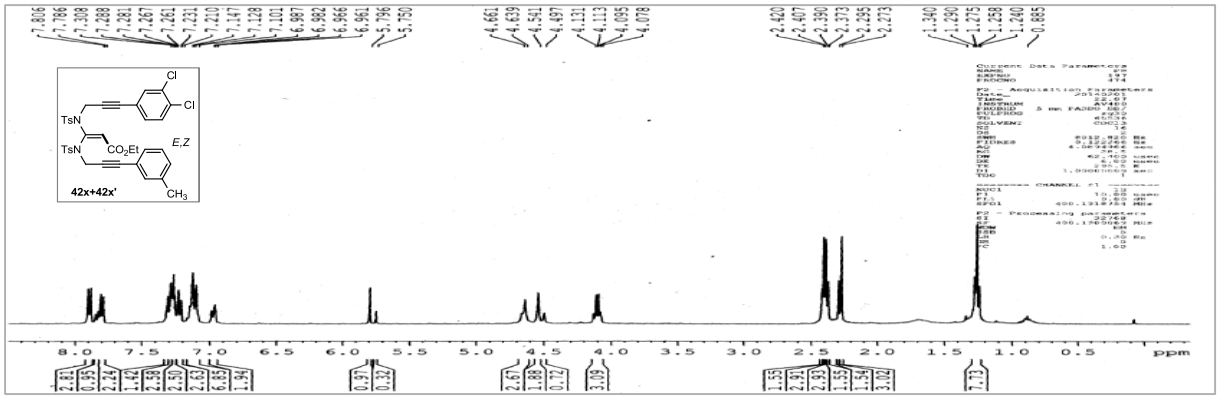
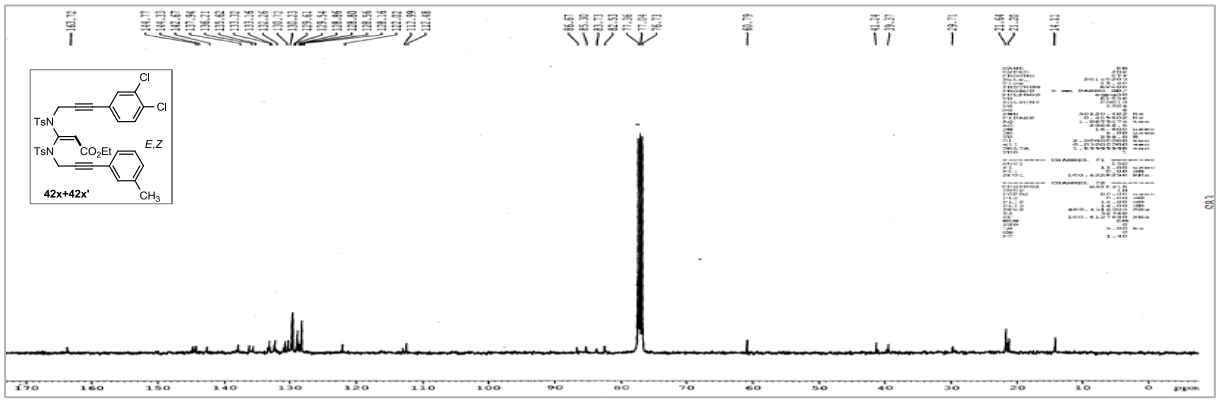
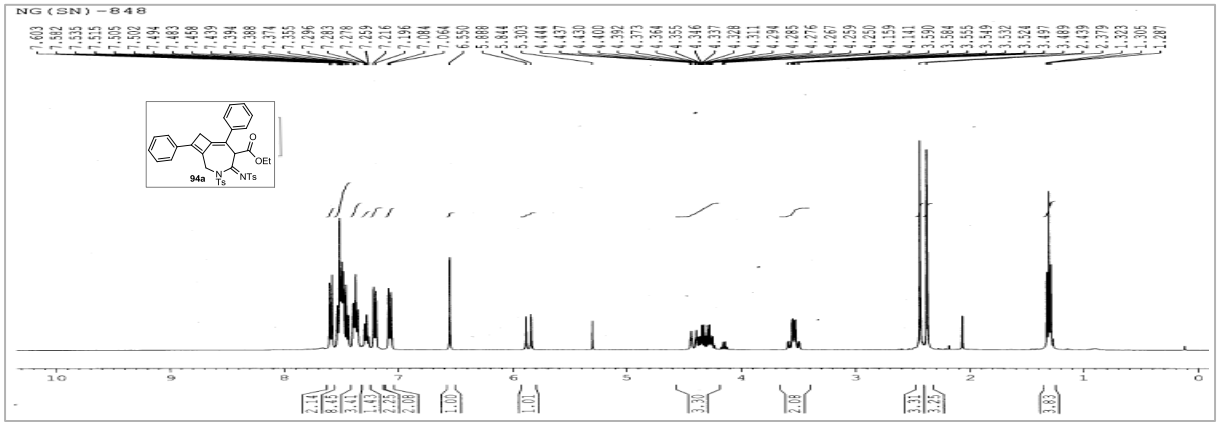

42x+42x'


42x+42x'


NG(SN)-848
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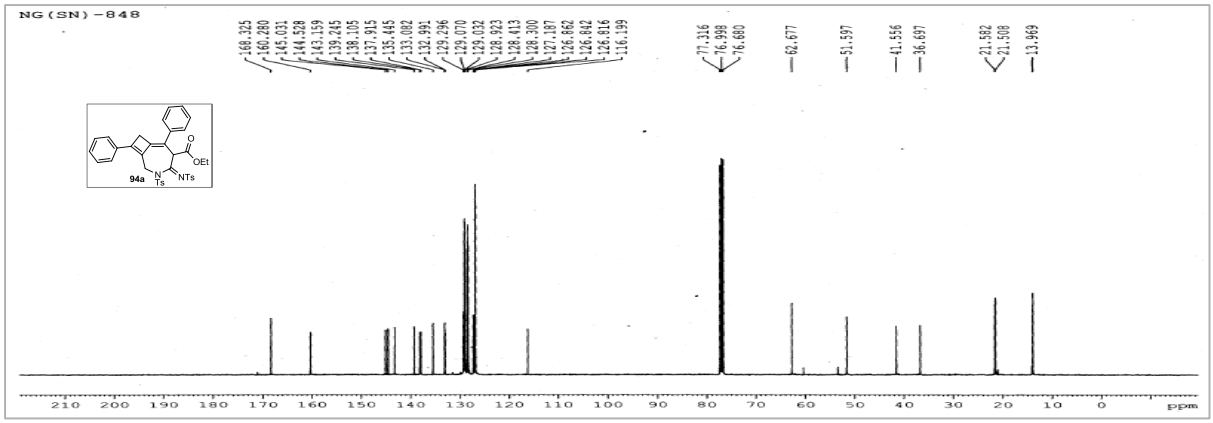
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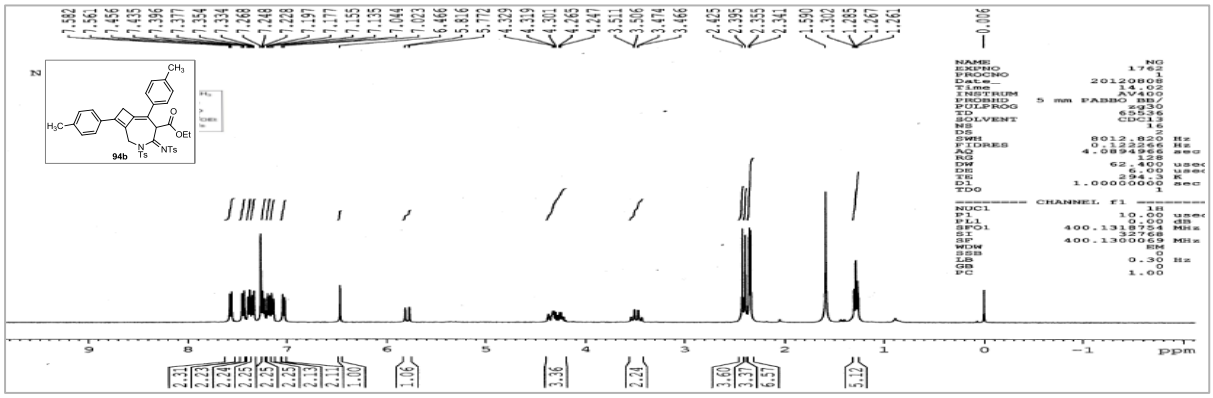
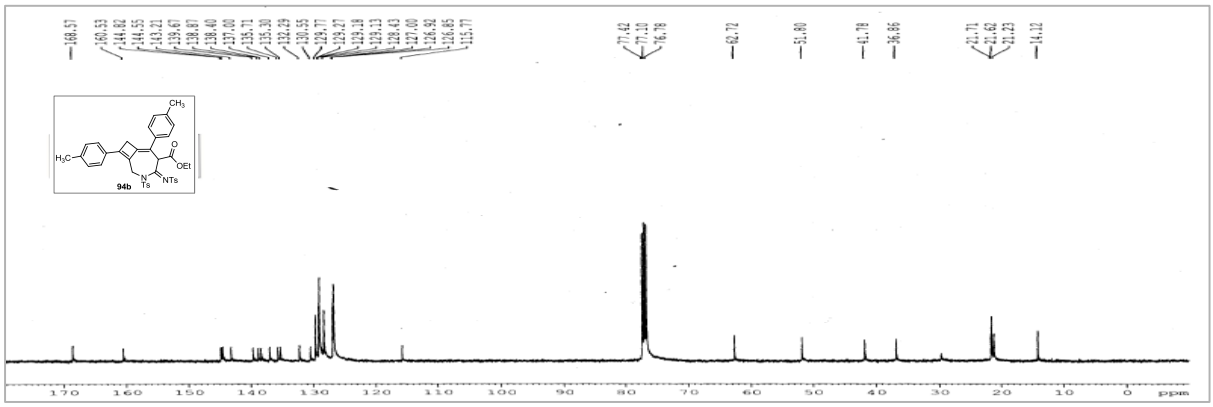
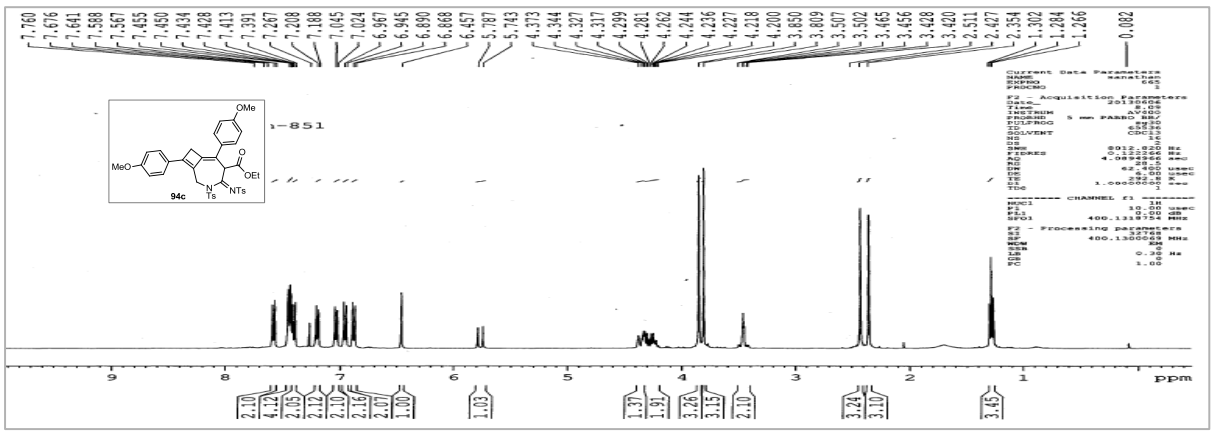
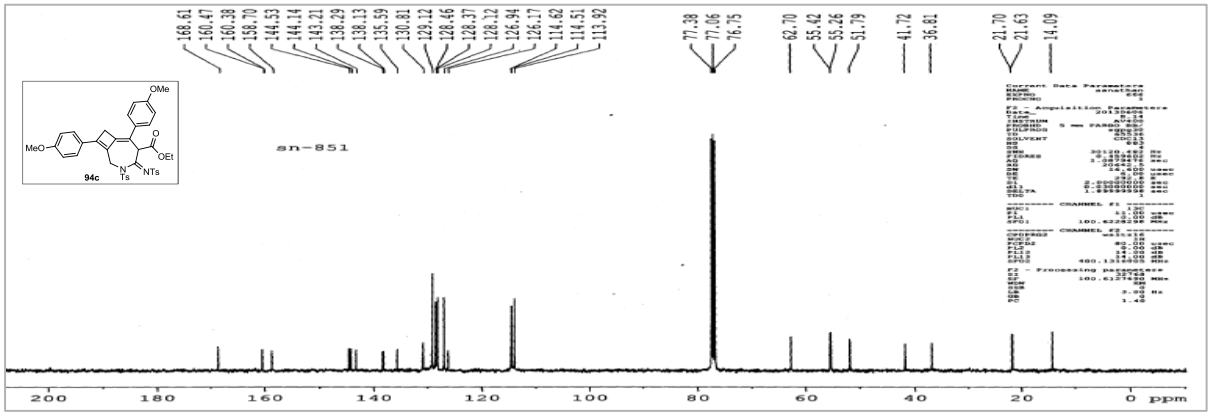

94b


94b


94c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160.38
158.70
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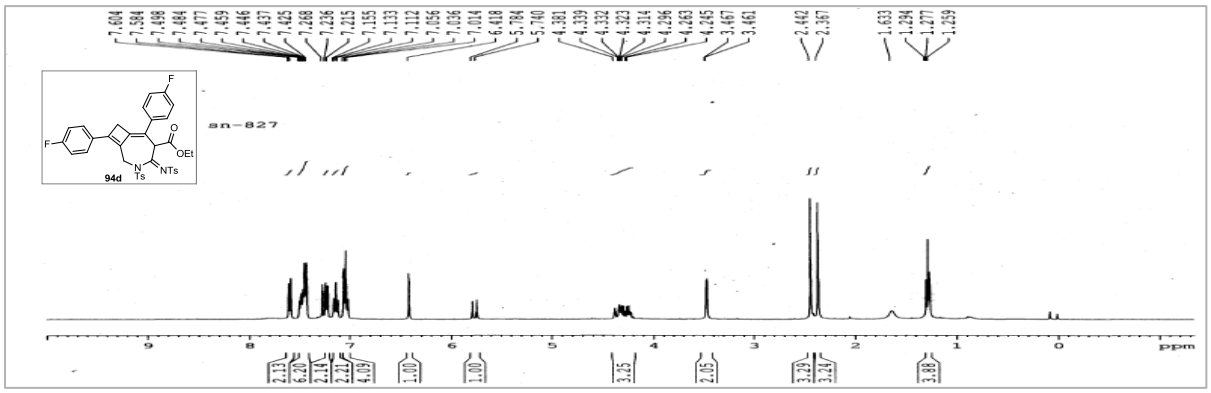
144.14
143.21
138.29
138.13
135.59
130.81
129.12
128.46
128.37
128.12
126.94
126.17
114.62
114.51
113.92
77.38
77.06
76.75
62.70
55.42
55.26
51.79
41.72
36.81
21.70
21.63
14.09
an-851
94c
200
180
160
140
120
100
80
60
40
20
0 ppm


7.604
7.594
7.498
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7.477
7.459
7.446
7.437
7.425
7.268
7.236
7.215
7.155
7.133
7.112
7.056
7.036
7.014
6.418
5.784
5.740
4.381
4.339
4.332
4.323
4.314
4.296
4.263
4.245
3.467
3.461
2.442
2.367
1.633
1.294
1.277
1.259
an-827
94d
9
8
7
6
5
4
3
2
1
0
ppm
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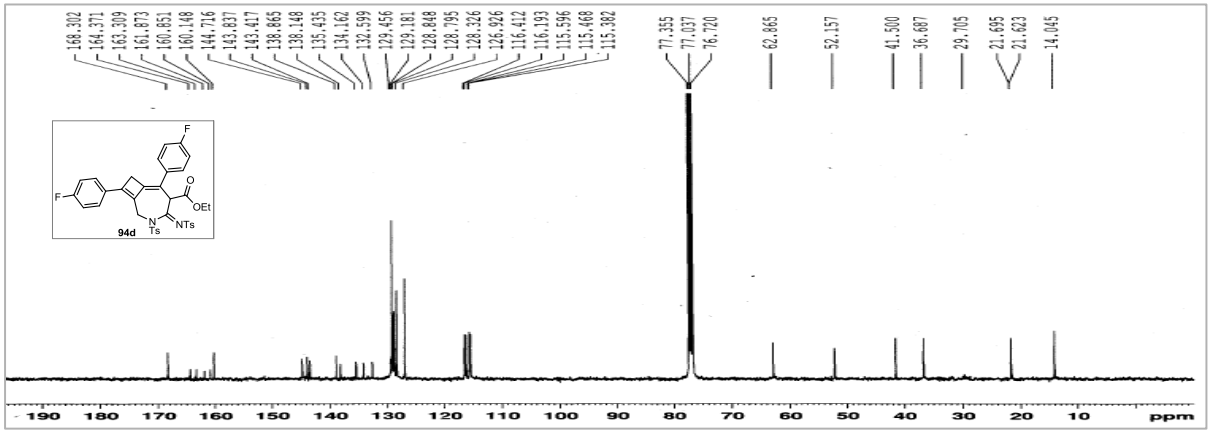
2.14
2.12
4.09
1.00
1.00
3.25
2.05
3.29
3.24
3.08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138.865
138.148
135.435
134.162
132.599
129.456
129.181
128.848
128.795
128.326
126.926
116.412
116.193
115.596
115.468
115.382
77.355
77.037
76.720
62.865
52.157
41.500
36.687
29.705
21.695
21.623
14.045
94d
190
180
170
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150
140
130
120
110
100
90
80
70
60
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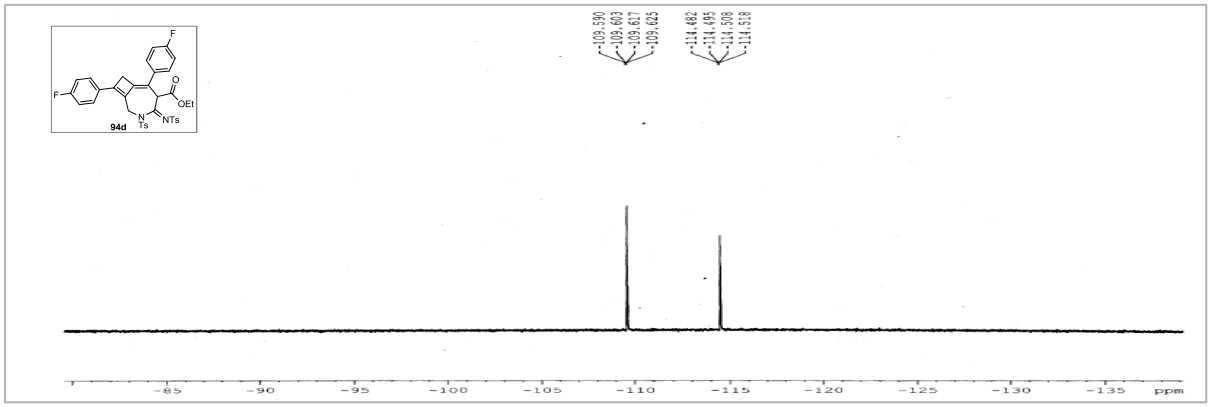
40
30
20
10
ppm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94d
-85
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-110
-115
-120
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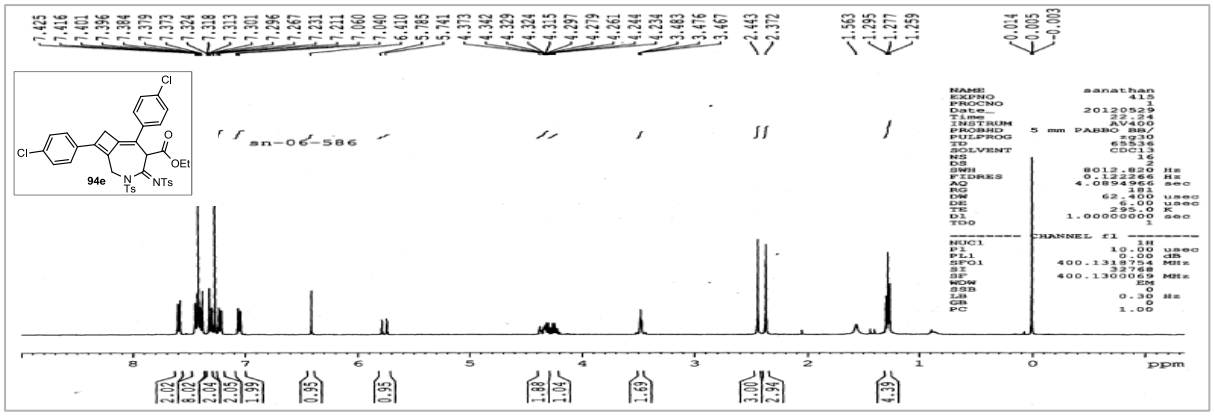
-130
-135
ppm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94e
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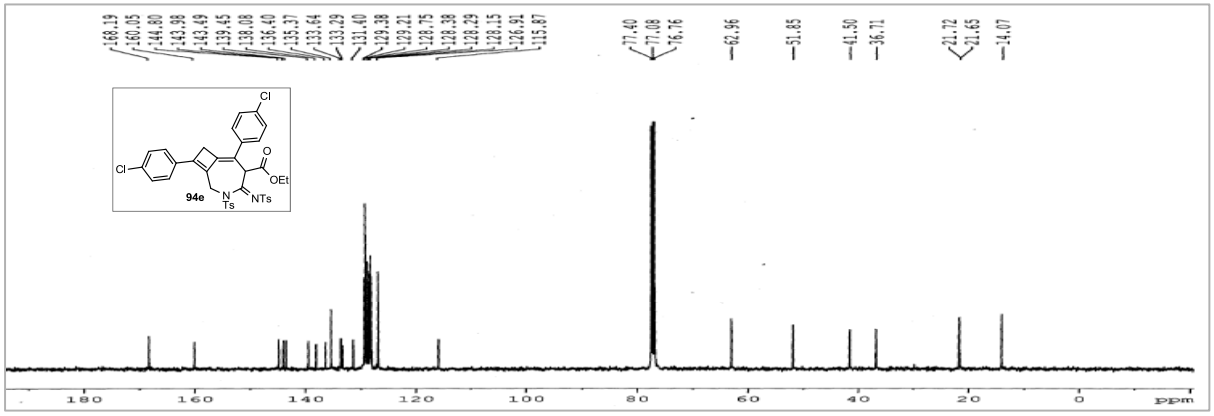
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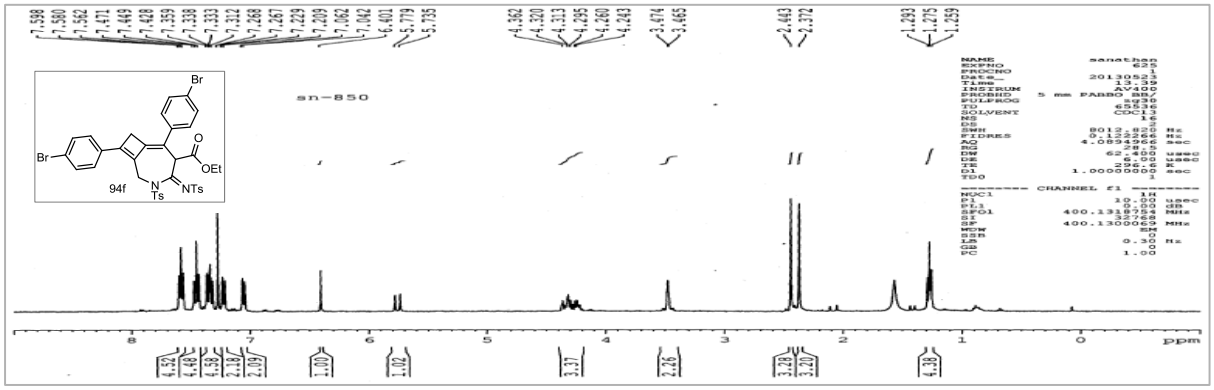
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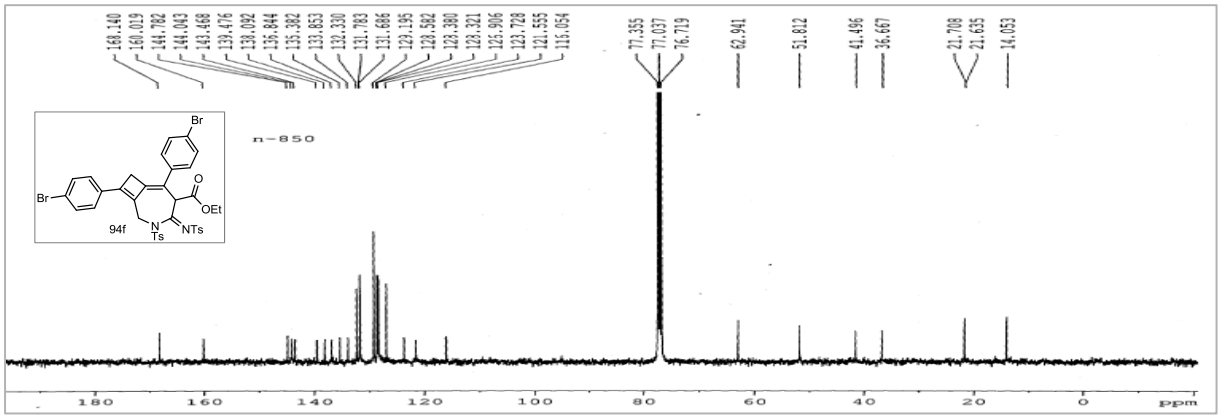
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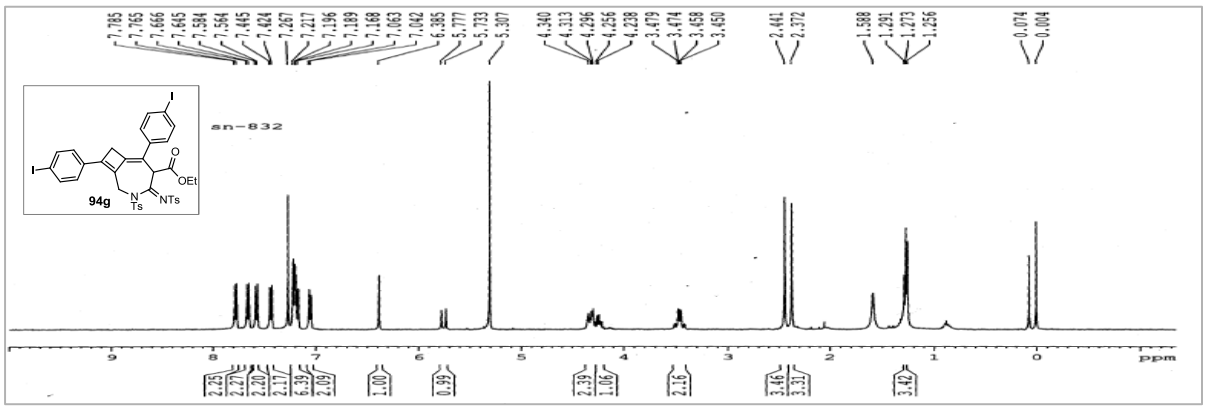
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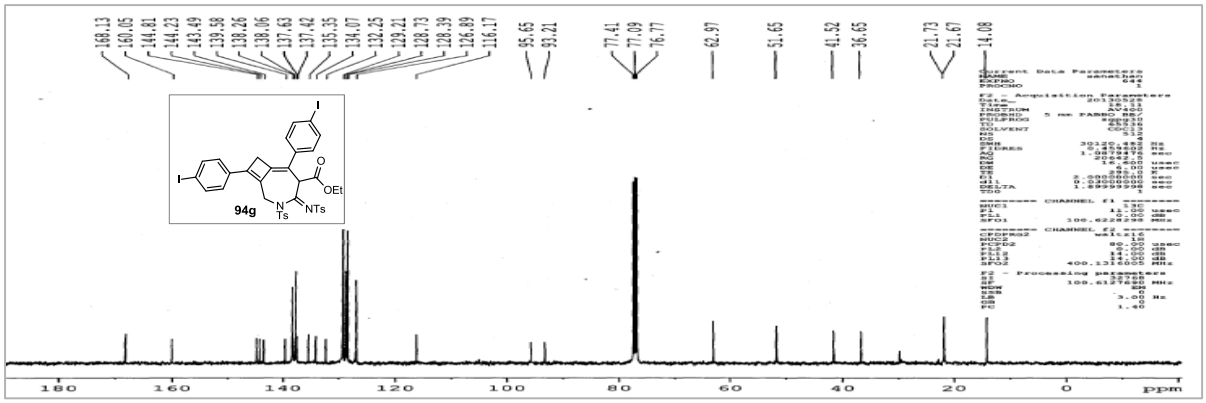
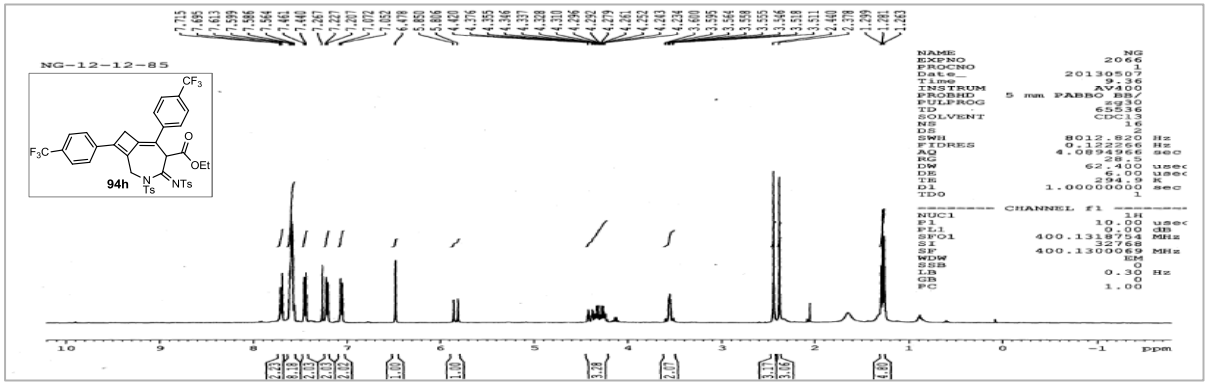
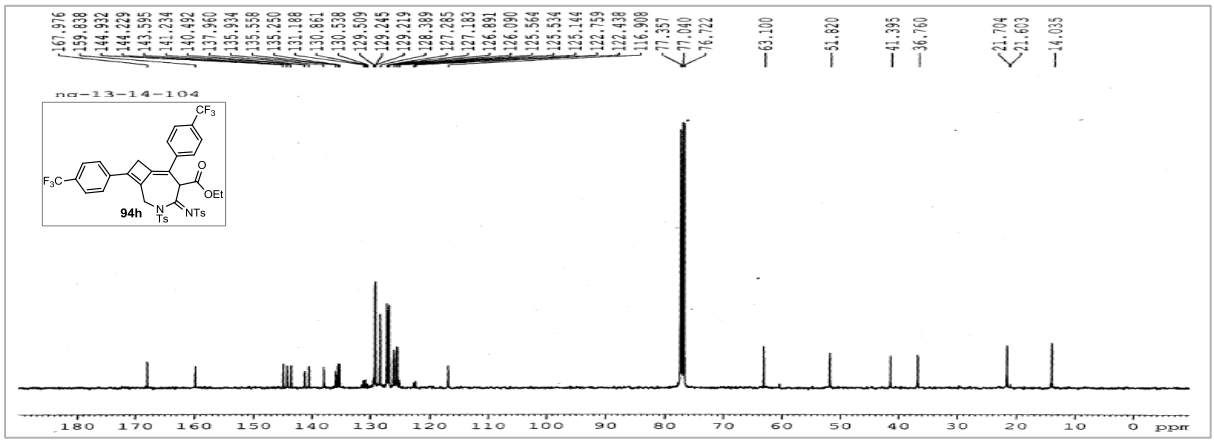
94g


94g


NG-12-12-85
94h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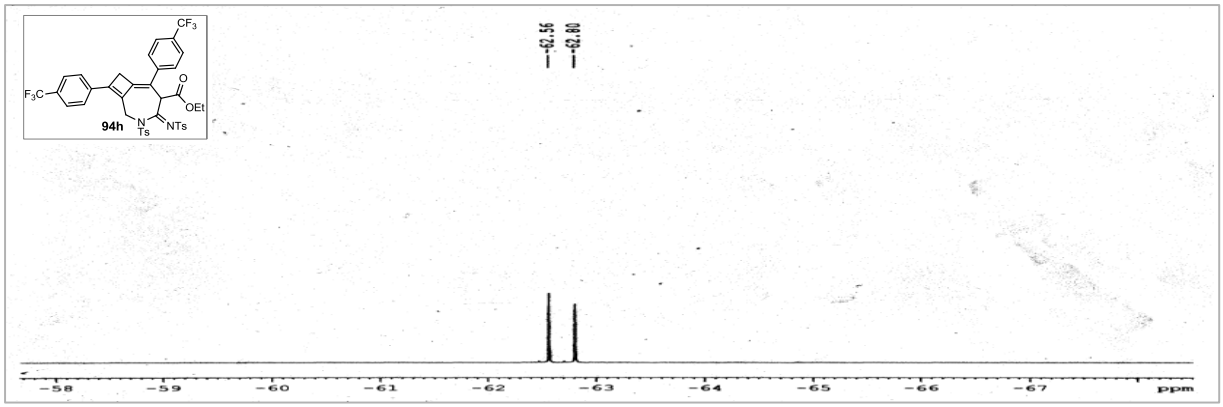
94h


94h
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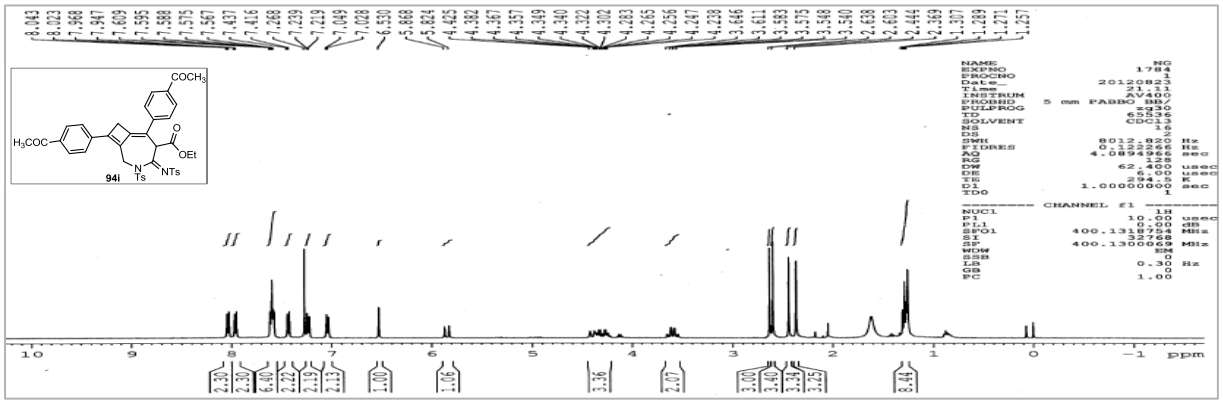
ppm


94i
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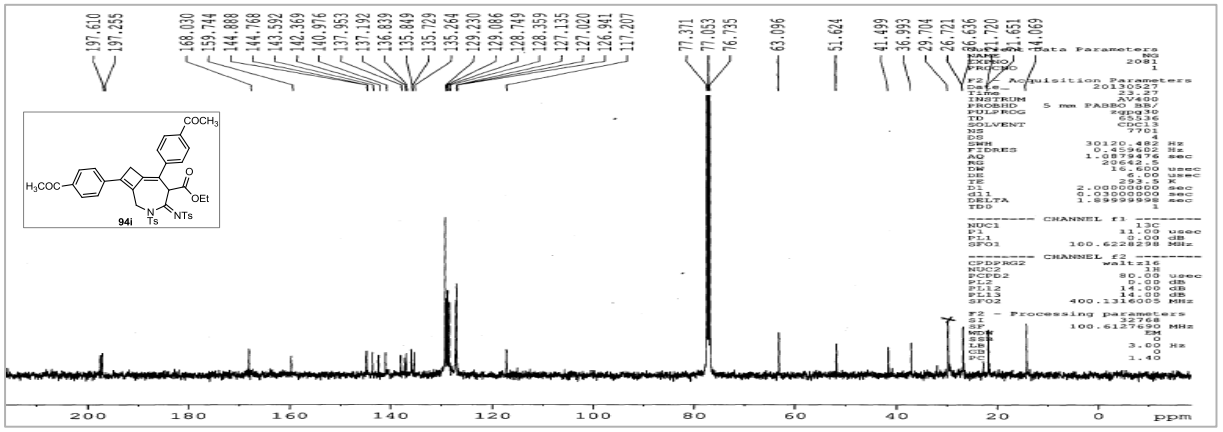
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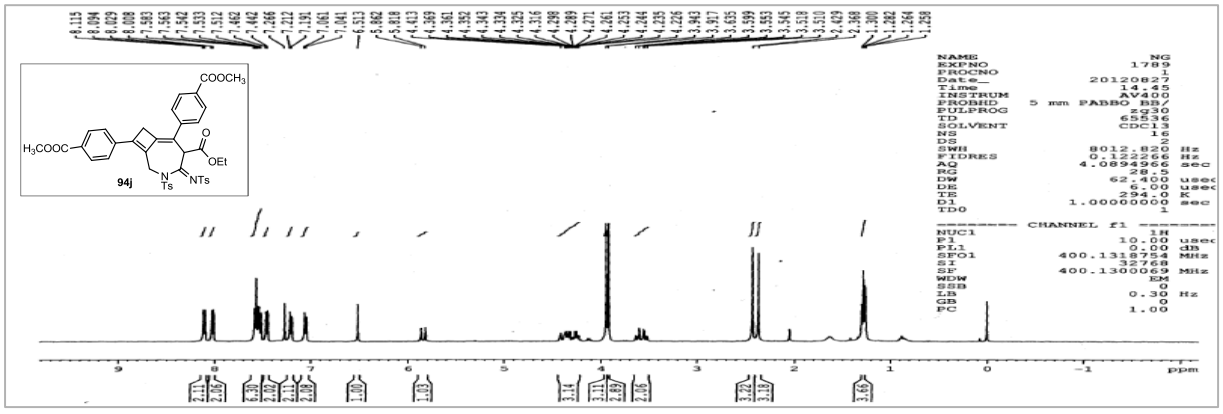
94j
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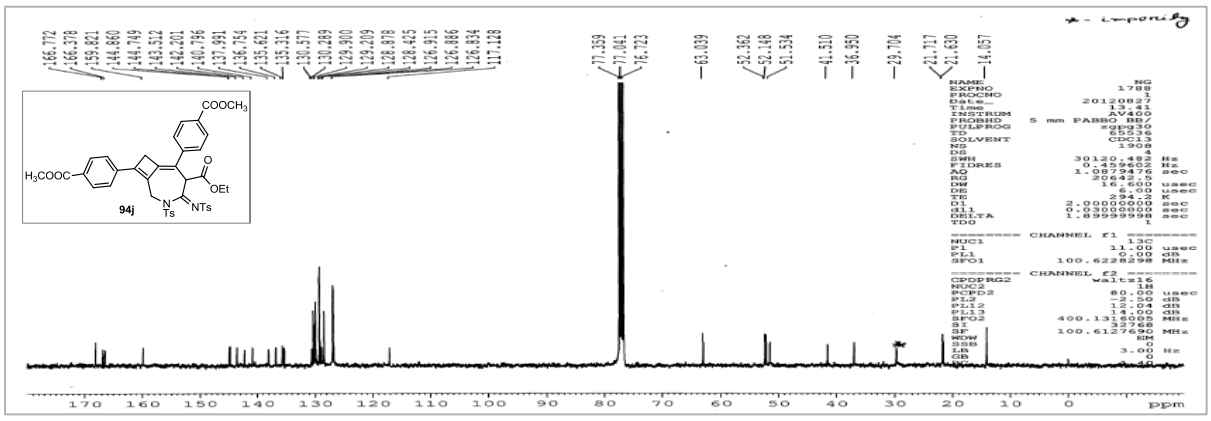
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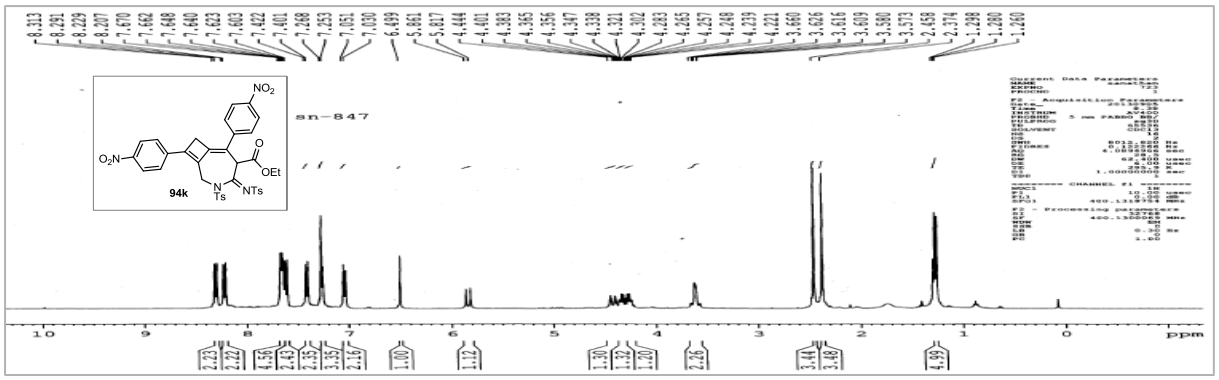
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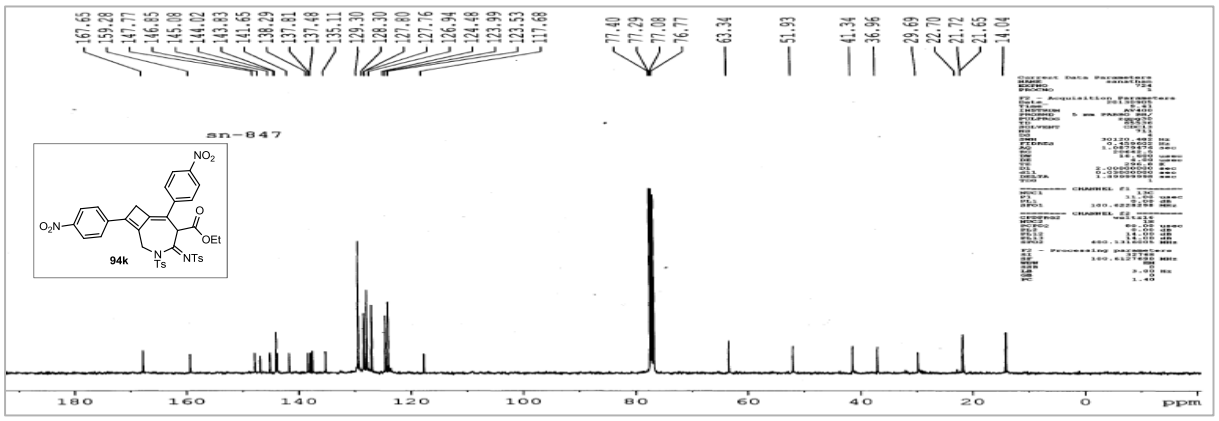
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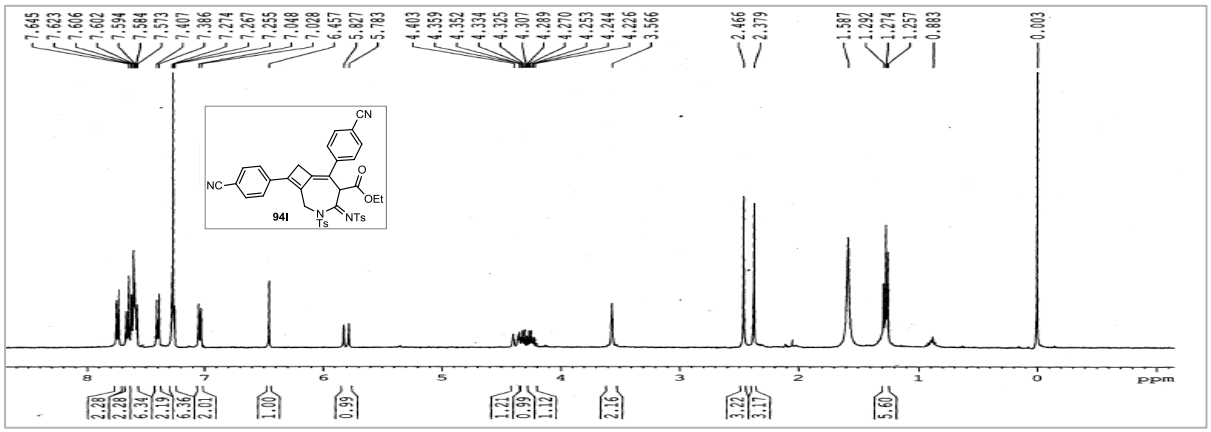
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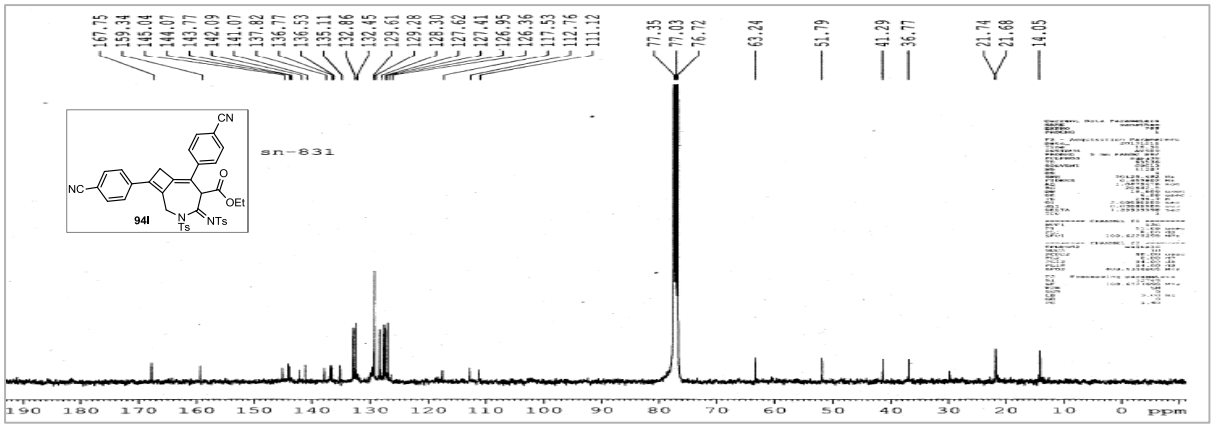
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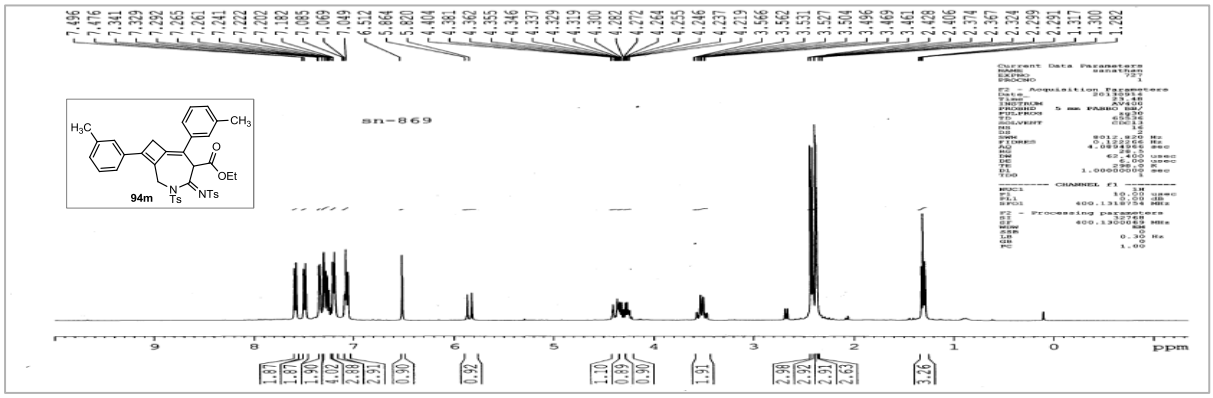
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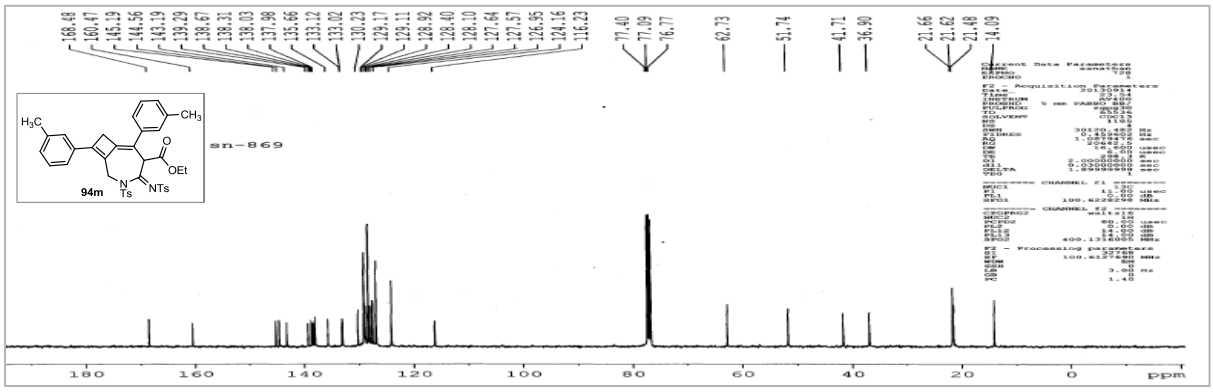
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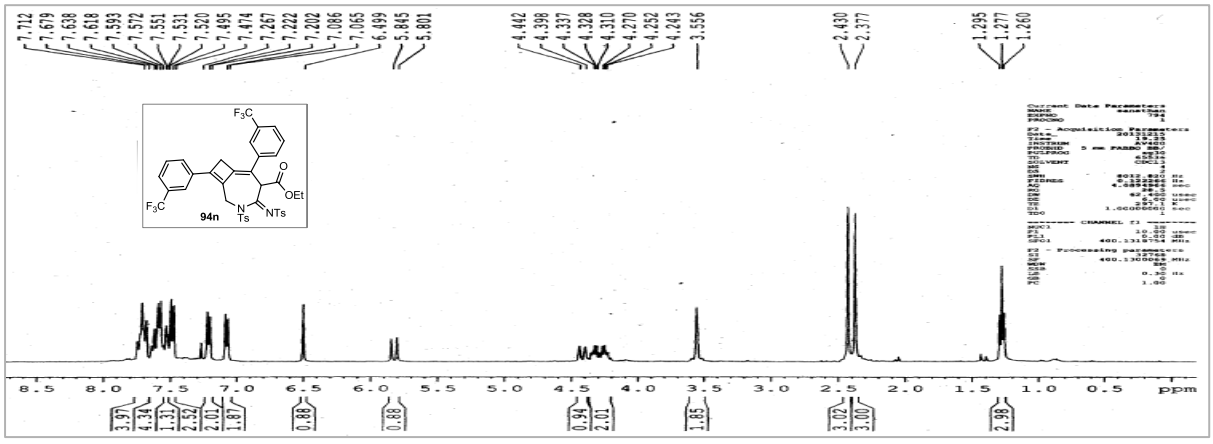
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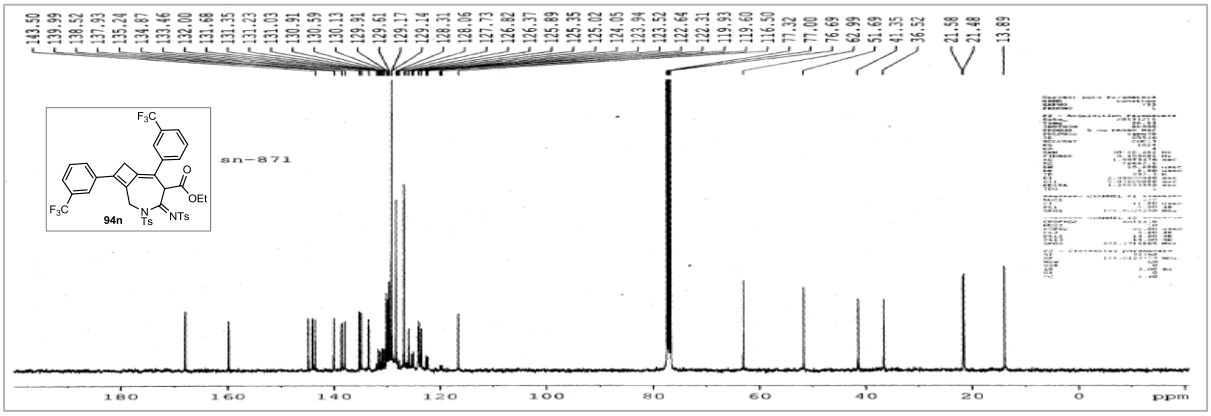
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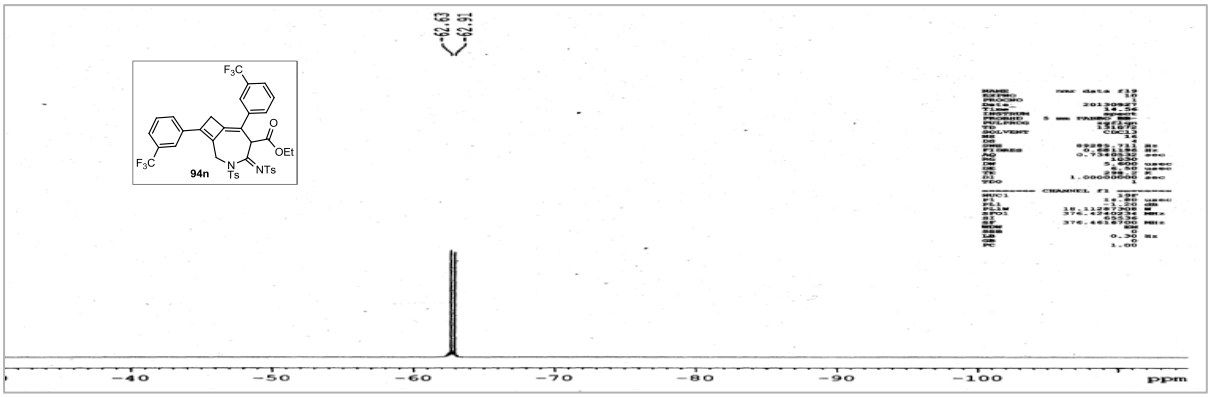
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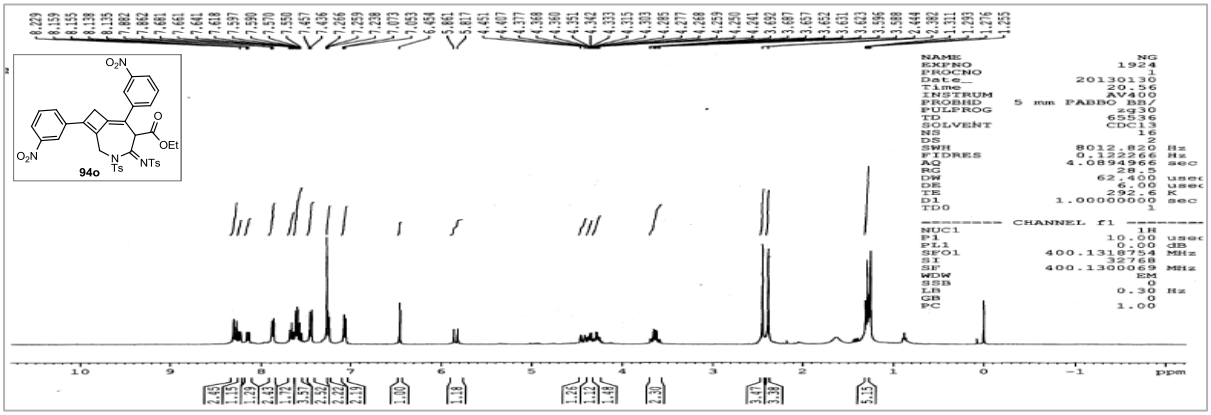
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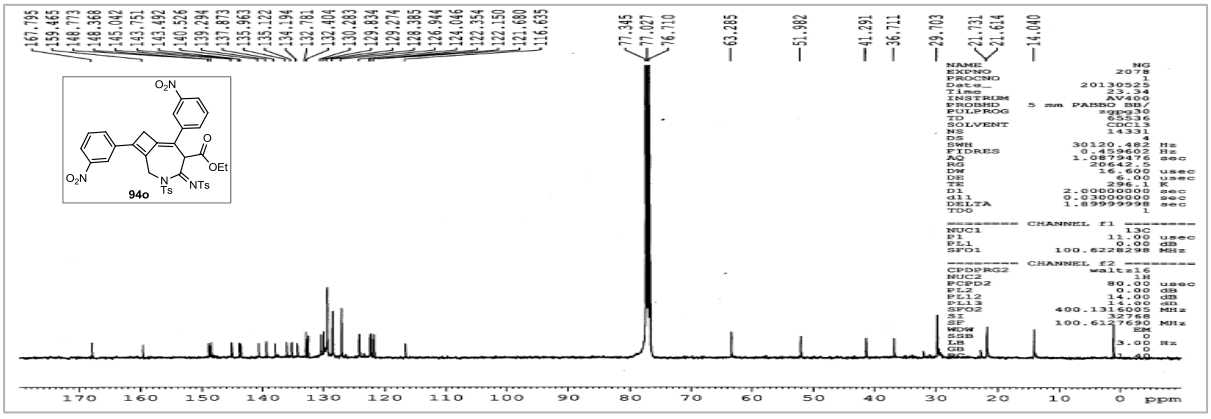
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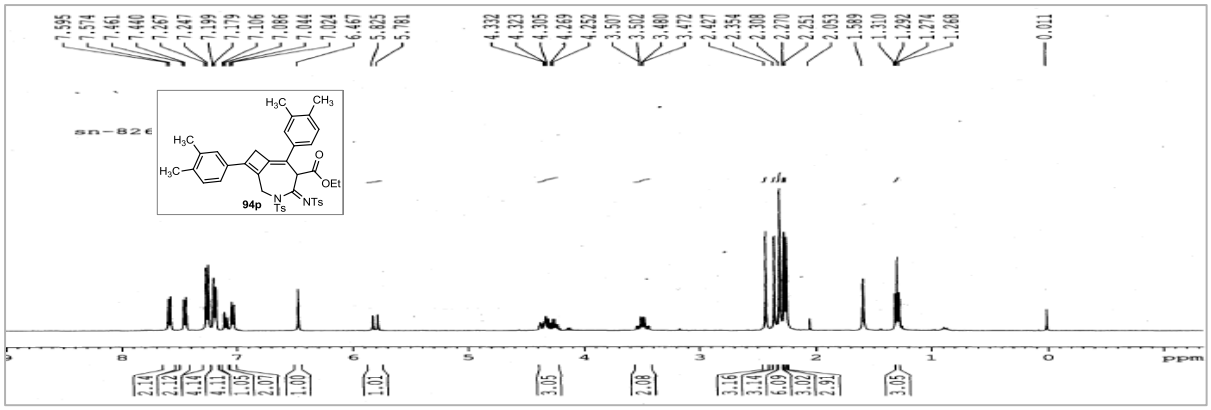
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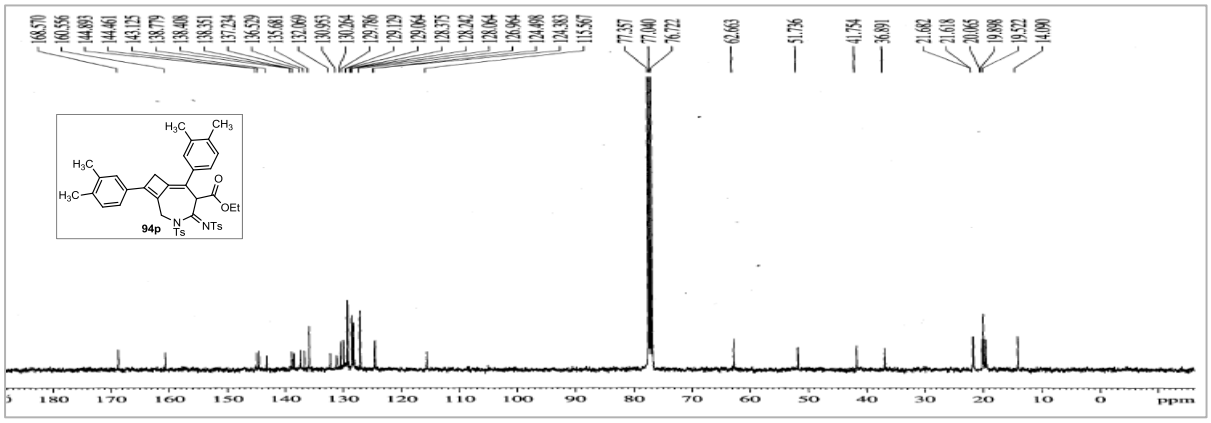
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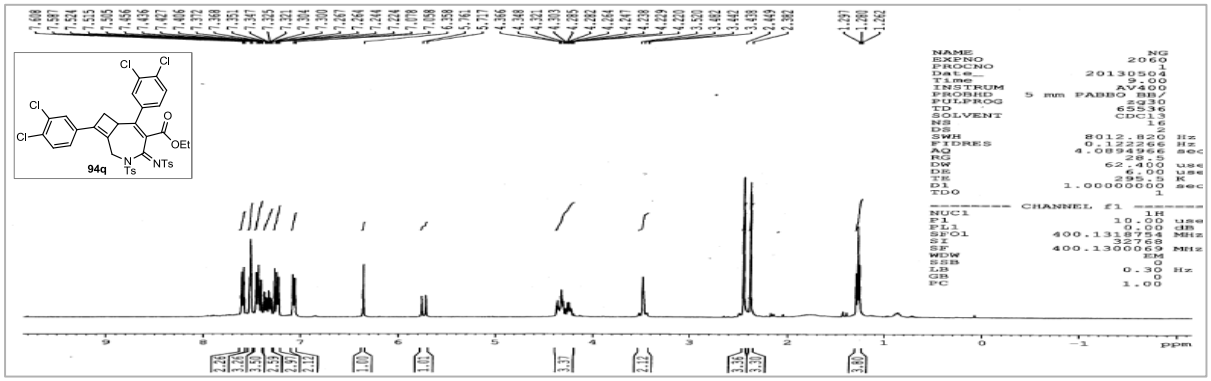
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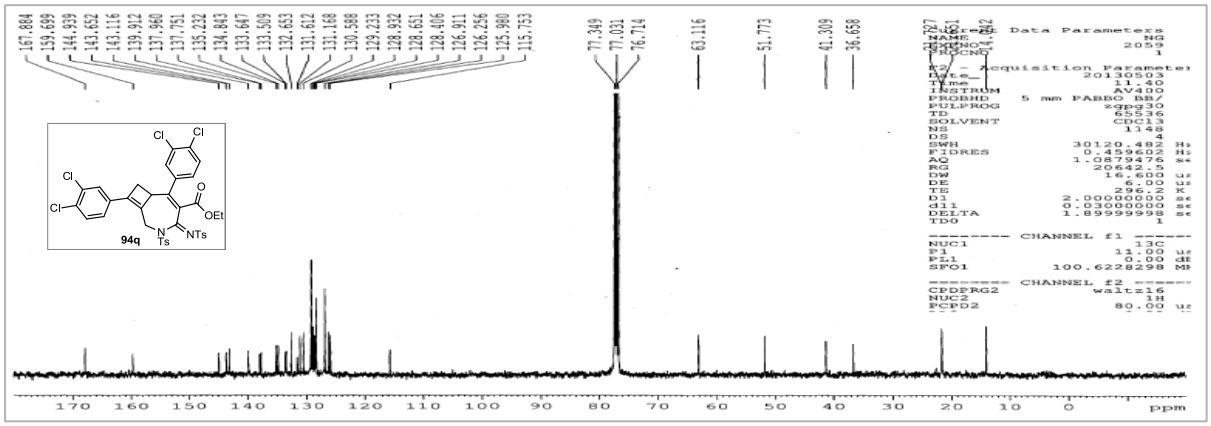
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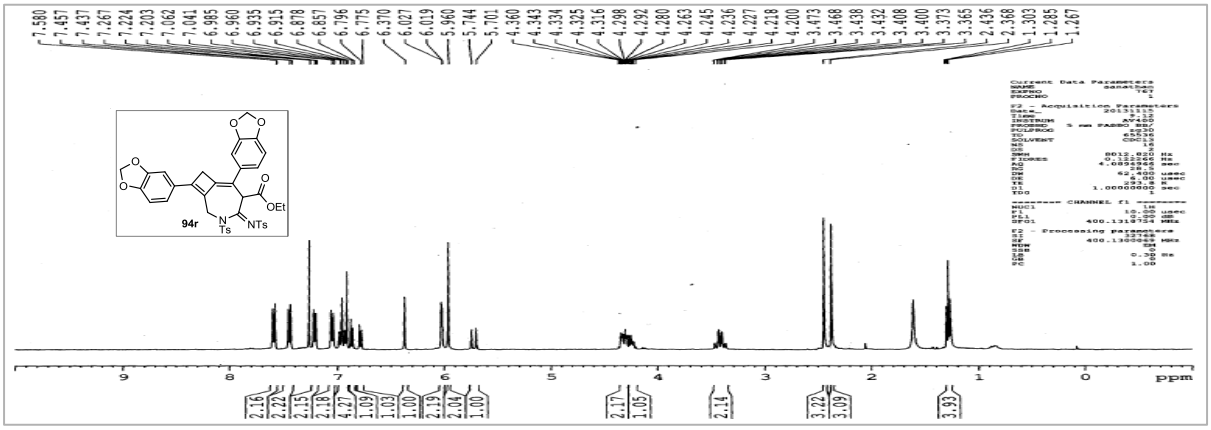
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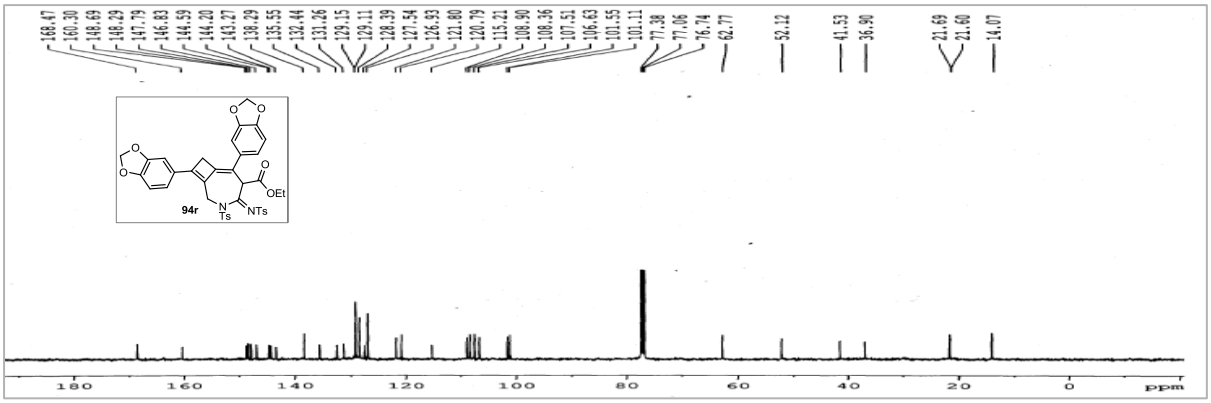
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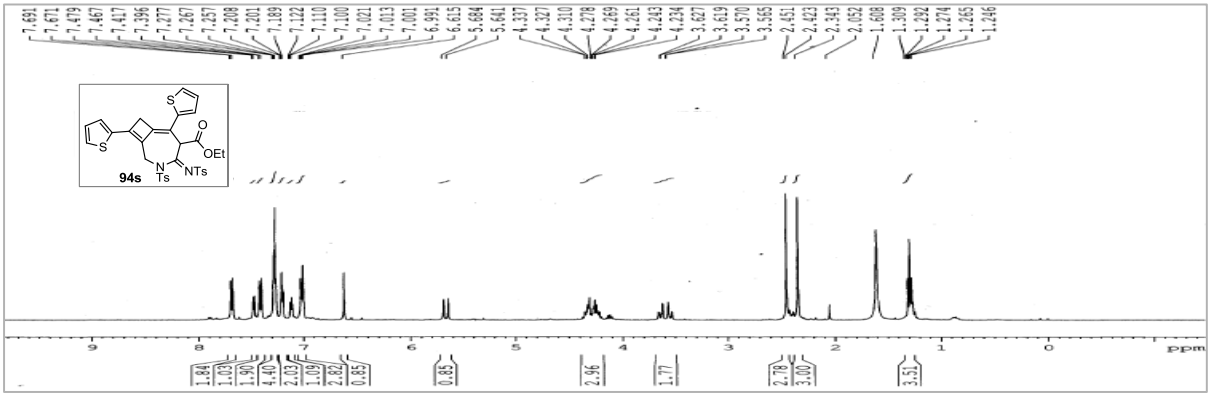
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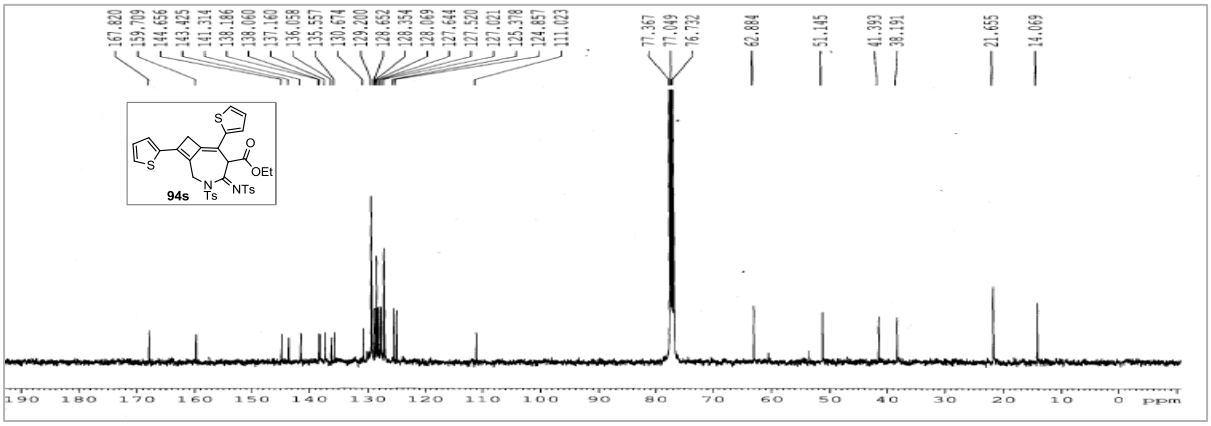
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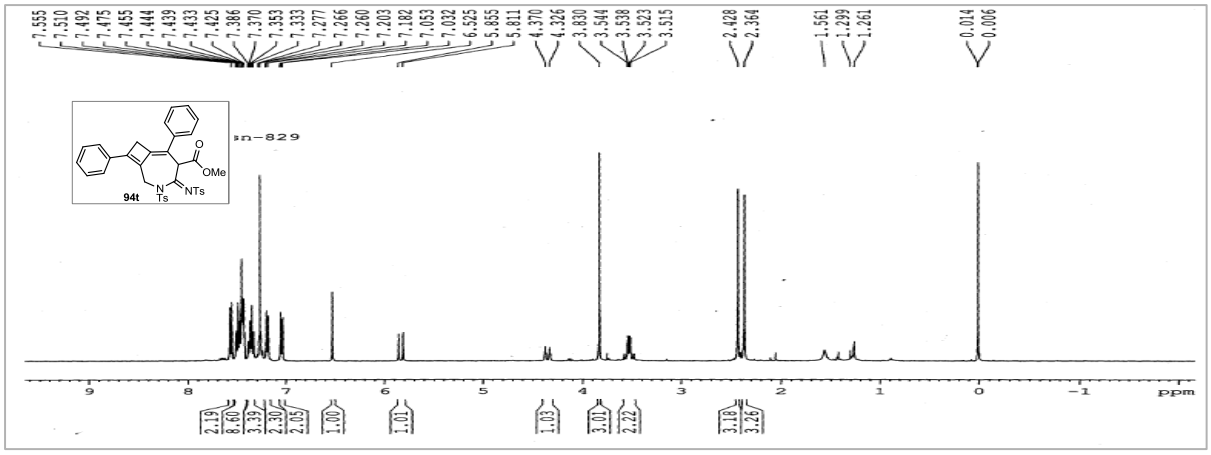
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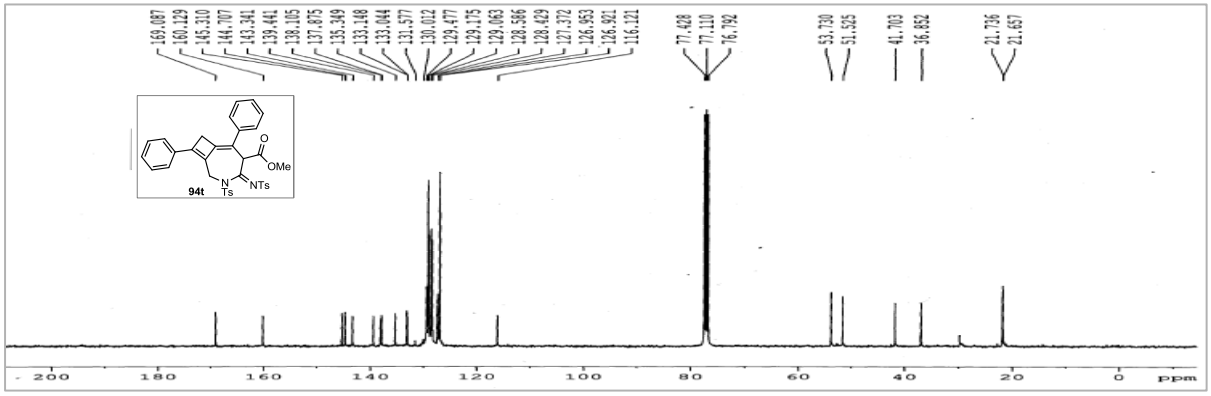
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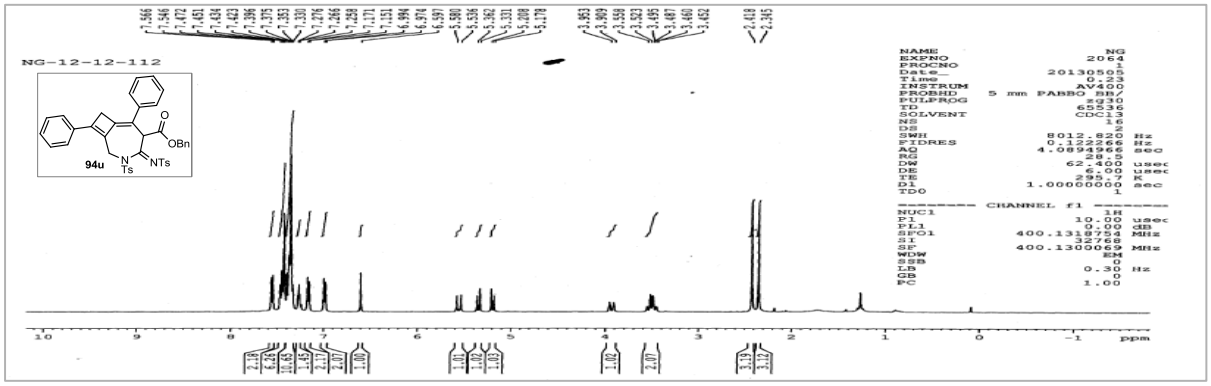
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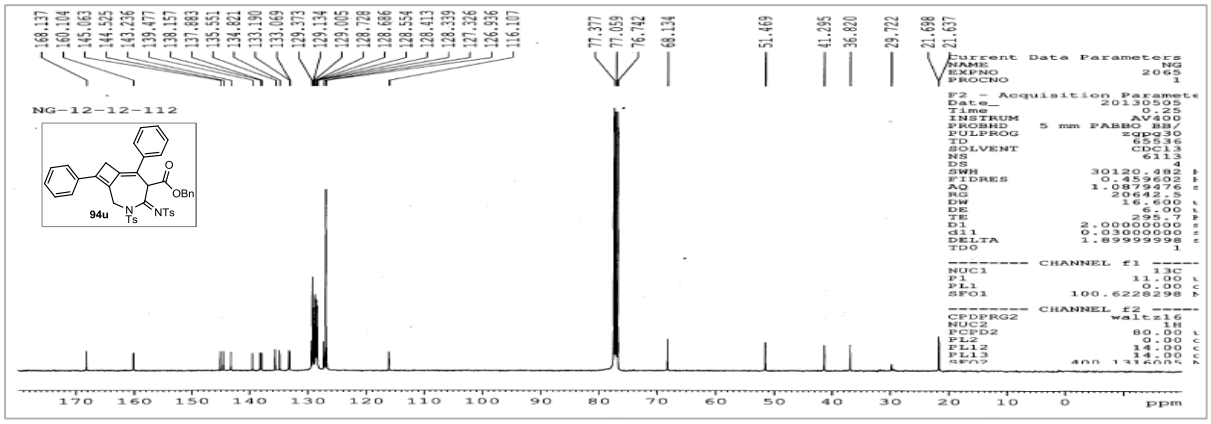
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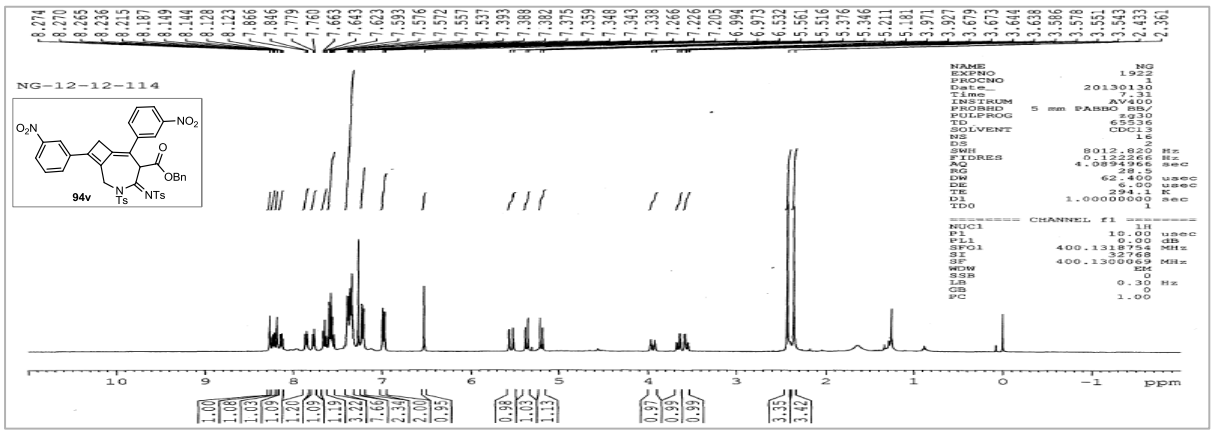
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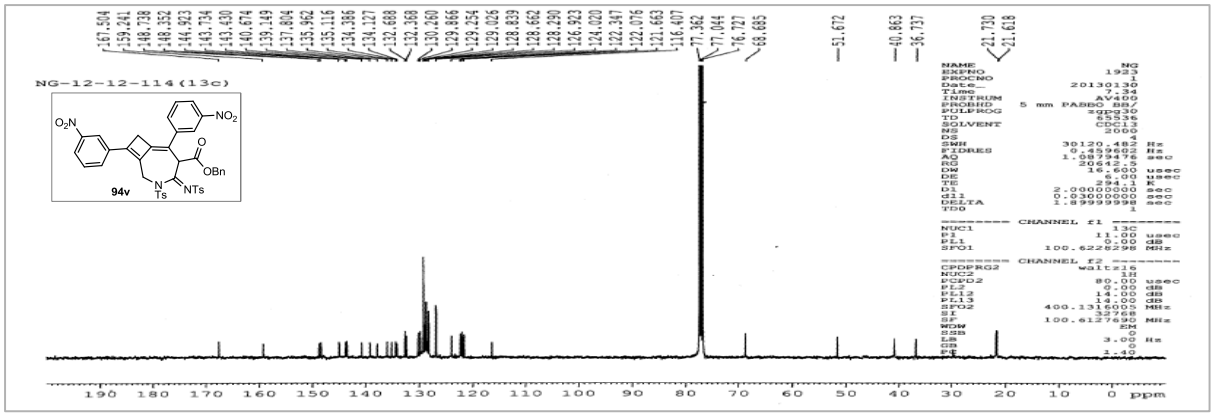
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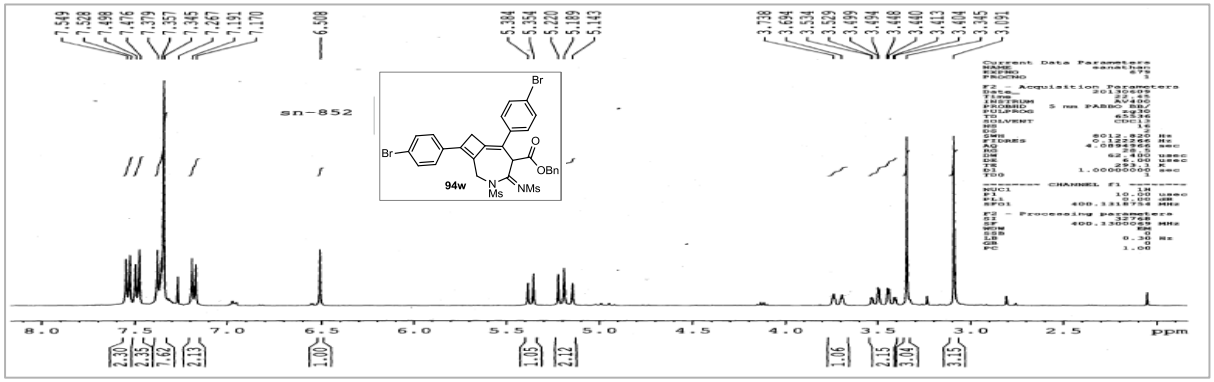
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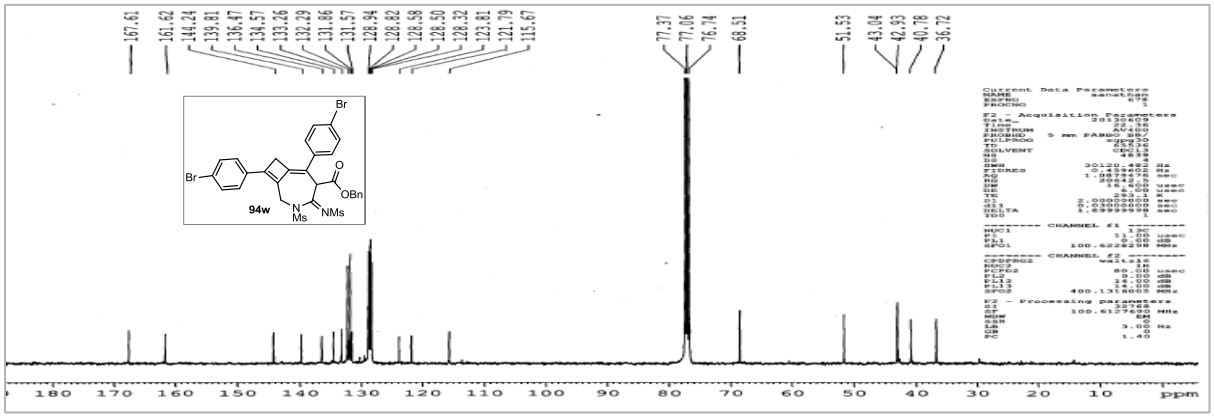
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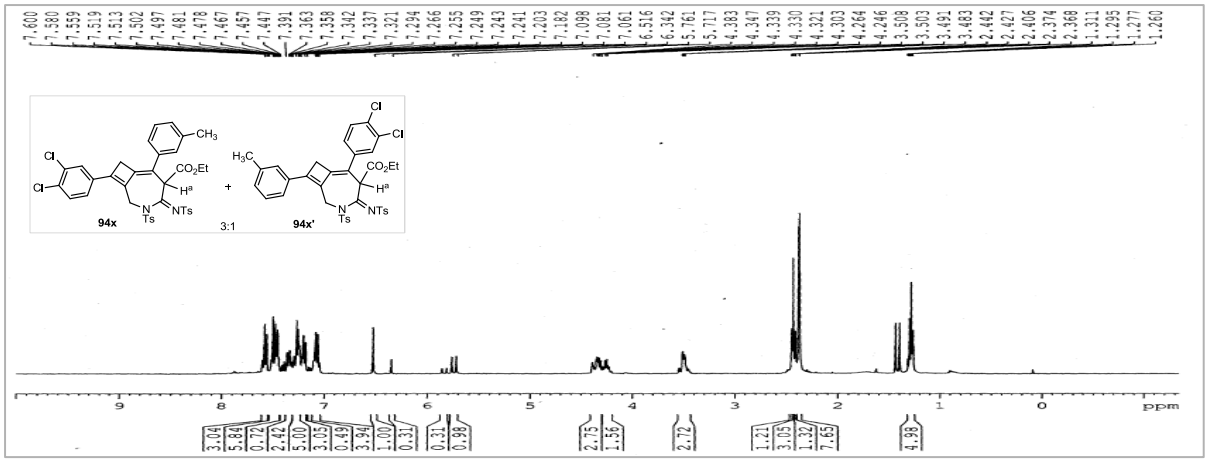
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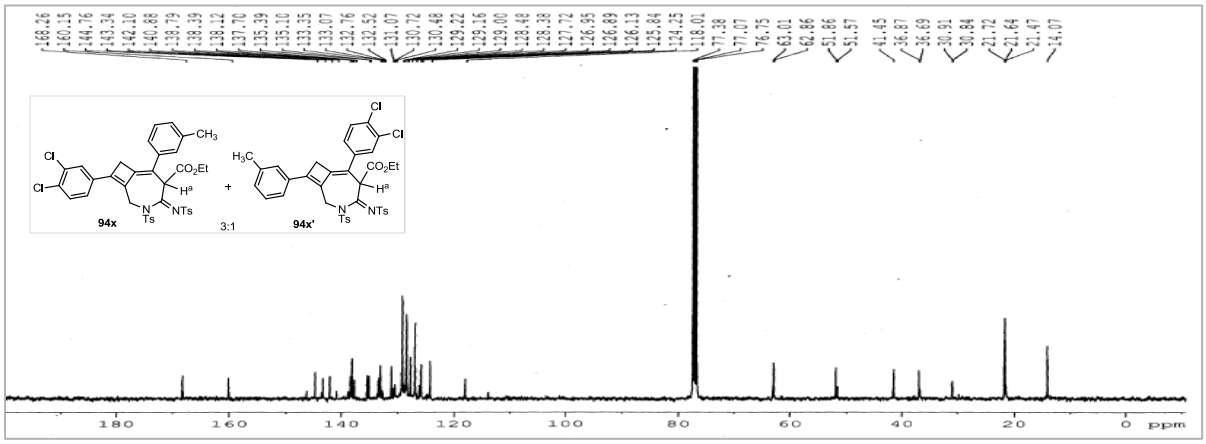
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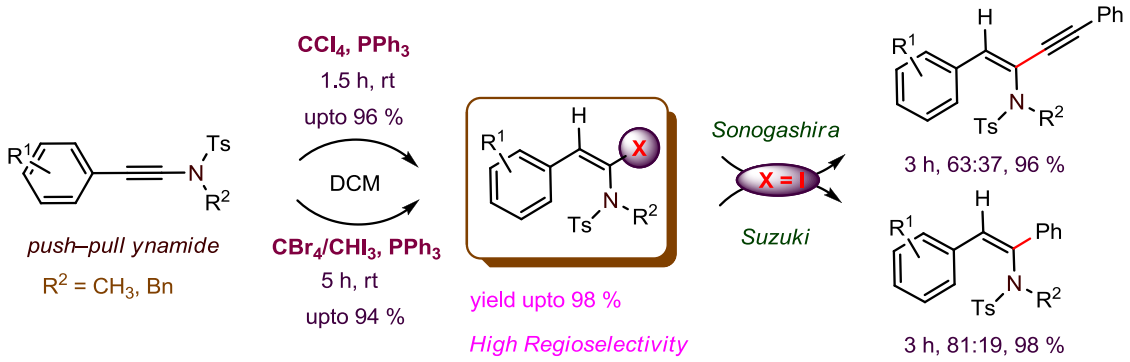
Chapter 4

Phosphine Mediated Stereoselective Synthesis of α-Haloenamides via a Mild and Efficient α-Addition of Ynamides

Abstract



Metal-free regio- and stereoselective α-hologenation of ynamides is demonstrated. Triphenylphosphine assisted halogenation of ynamide occurred in the presence of halogenating source CCl_4/CBr_4/CHI_3 to exclusively provide E-α-haloenamide. A wide variety of hitherto unknown stable α-haloenamide are readily synthesized from easily accessible ynamides in good-to-excellent yields. This protocol is reliably tested for the gram scale preparation of α-haloenamide.

Reference

B Prabagar, Sanatan Nayak, Rajendra K. Mallick, Rangu Prasad, and Akhila K. Sahoo (*communicated*)

4.1. Introduction

Enamides are important building blocks for synthetic organic chemistry. These prevalent structural motifs are widely found in various natural products and complex molecular entities.[1] Architecturally unique marine-derived alkaloids chartellines A and chartellines B (Figure 4.1) holds indoline, imidazole, and β-lactam entities along with a bridged enamide unit. The functionalized enamide component is present in complex natural products such as securine and securamine (Figure 4.1). The peptide alkaloids frangulanin also contain an enamide fragment.[1d] The α-substituted enamides are present in many natural products of potential biological importance; for example, peptidyl allyl sulfone is cysteine protease inhibitors (Figure 4.1).[1e]

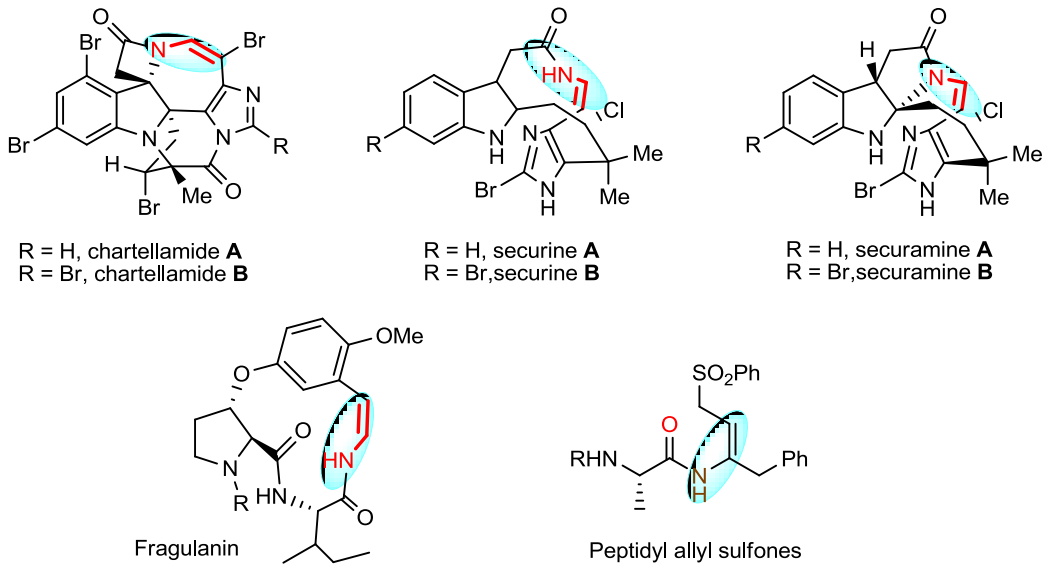


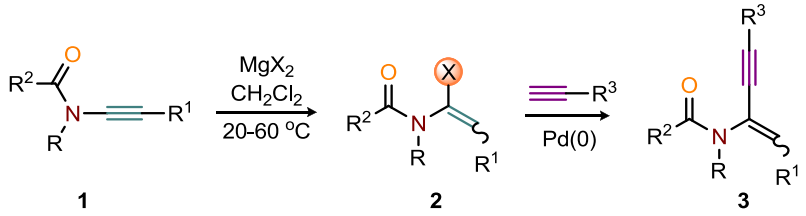
Figure 4.1. Natural products containing enamide component.

Enamide is a potential nucleophile useful for the stereoselective C–C and C–N bond forming reactions; which contributes in the diversification of enamide structural entity.[2] Among various structural diversified enamides, the halo-enamides in particular possess broad synthetic applications. The halo group in the halo-enamide can readily be functionalized through metal-halogen exchange reactions.[3-5] The transition-metal catalyzed cross-coupling of halo group in halo-enamide enable building complexity in the molecular scaffold.[6-7] The importance of α-haloenamides is significant; as both the α- and β-carbons of α-haloenamides can readily be functionalized, which contributes enlarging the structural diversity. The nucleophilic β-carbon of α-haloenamides useful for the stereoselective C–C bond formations, while the α–halo group effectively replaced by the organometallic reagents for the construction of C–C, C–O, and C–N bonds. Accordingly, various complex molecular entities can be fabricated from α-haloenamides. Despite versatile synthetic potential of

α–haloenamides, reliable methods to access these molecular entities are far more challenging. In general, hydrohalogenation of stable ynamides led to α–haloenamides; however, α-regioselective hydrohalogenation of ynamides is difficult.[8] The known reports for the synthesis of α-haloenamides from ynamides are breifly described.

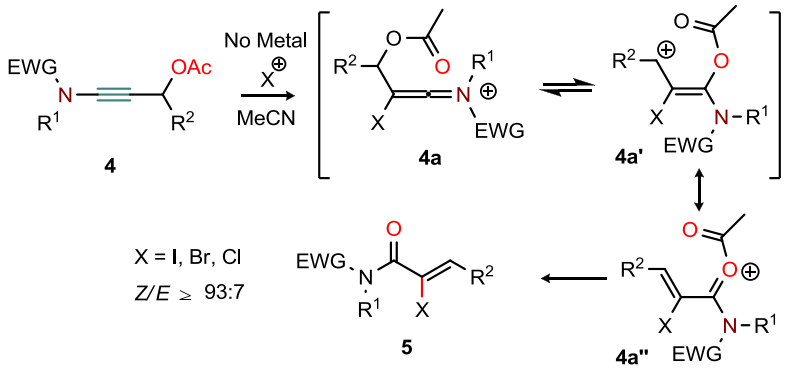
4.1.1. Precedents and strategies for the synthesis of α-haloenamide

In 2003, Hsung group reported stereoselective synthesis of α-haloenamides involving an unexpected hydrohalogenation of ynamide **1** (Scheme 4.2).[9] The reaction of ynamide with $MgBr_2$ in CH_2Cl_2 at ambient temperature led to α-bromoenamides in excellent yield; HBr used for the hydobromination of ynamide is *in situ* generated from $MgBr_2$ and trace of water present in the reaction system. The identical reaction for the chlorination of ynamide is possible with $MgCl_2.6H_2O$ in dichloroethane at an elevated temperature. Similarly, reaction of ynamide with MgI_2 in DCM readily delivered α-iodoenamides. The halo group was further functionalized; for instance, Sonogashira reaction of halo moiety of ***2*** with substituted acetylenes produced ***3*** (Scheme 4.1).



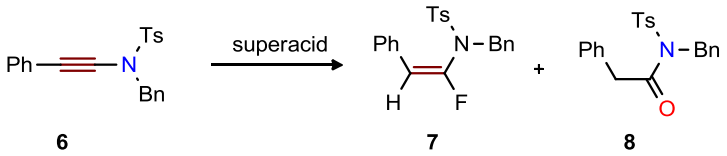
Scheme 4.1. Synthesis of α-haloenamide via hydrohalogenation of ynamides

The Skydstrup group demonstrated synthesis of α-halo acrylamides/acrylimides ***5*** from ***3***-acetoxy ynamide **4**.[10] The inherent polarization of ynamide allows attacking the halonium species and forms keteniminium intermediate **4a**. Next, the intramolecular 1,3-acetate migration to the ketiminium intermediate generates stable carbenium ion species **4a′**. Finally, isomerization and hydrolysis of acetate group leads to Z-selective α-halogenated product ***5***. The NIS/NBS mediated reaction cleanly affords the desired α-iodo/bromo acrylamide ***5*** (Scheme 4.2). In contrast, reaction with NCS displayed low conversion. The formation of single diastereomer Z-selective product is established by ^{1}H NMR and X-ray analysis.



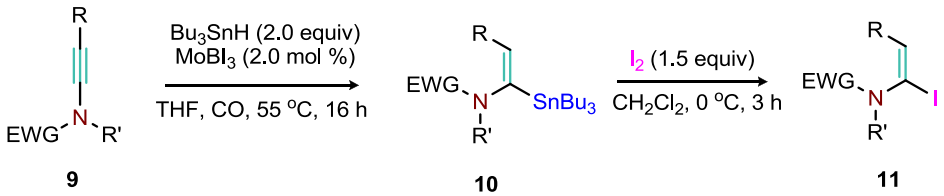
Scheme 4.2. Neighbouring acetate assisted haloenamide synthesis

A straightforward method for the synthesis of novel α-flouroenamides **7** via stereoselective hydroflourination of ynamides is reported by Evano and co-workers (Scheme 4.3).[11] As the keteniminium intermediate is highly reactive, the reaction of anhydrous HF with ynamide generates large number of undesired by-products. Interestingly, hydroflourination of ynamides is successfully demonstrated in presence of HF-containing superacid (HF-SbF_5). Quenching the reaction with HF-pyridine allows providing acceptable yield of the desired α-flouroenamide product (Scheme 4.3).



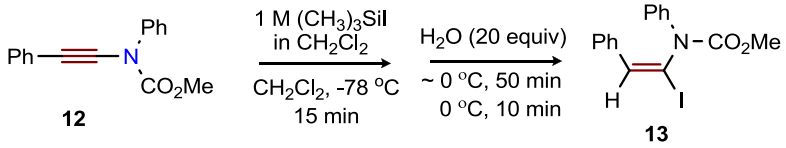
Scheme 4.3. Synthesis of α-flouroenamide via super acid mediated hydroflourination

The Kazmaier group showed molybdenum-catalyzed hydrostannylation of ynamide **9** to deliver **10** (Scheme 4.4).[12] The reaction was carried out under the CO atmosphere, as CO benefits increasing life time of the catalyst. The hydrostannylation of ynamide **9** occurred smoothly to give (*E*)-α-stannylation product **10** in good yield. The α-stannylated enamides are stable and purified easily by flash coloumn chromatography. The α-stannylated product **10** underwent Sn-iodine exchange to afford the corresponding α-iodo-enamide **11** with retention of olefin geometry (Scheme 4.4).



Scheme 4.4. Synthesis of α-iodination of enamide via α-stannylation

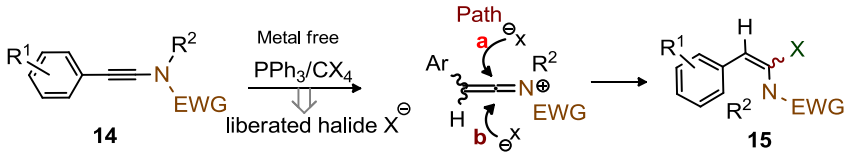
Recently, Iwasawa group reported highly regio- and stereospecific synthesis of (*E*)-α-iodoenamide **13** from ynamides **12** in the presence of iodotrimethylsilane and H_2O (Scheme 4.5).[13] The reaction involves the regioselective addition of HI, obtained *in situ* from TMSI and H_2O to ynamide producing quantitative amount of single isomer **13**. Mechanism of this reaction is uncertain; the deuterium incorporation studies using D_2O suggest that the reaction does not proceed in a stepwise manner. It is believed that the chelation of Si-group with N- in the ynamide or O- in the ester group assists stereoselective syn addition of HI to the alkyne-motif of ynamide.



Scheme 4.5. (*E*)-α-iodoenamide moieties via iodotrimethylsilane-mediated hydration

4.2. Motivation, Hypothesis and Design

A detailed survey on the strategies known for the synthesis α-haloenamide reveals that the use of expensive reagents, step-wise conversion from Sn-species to iodo,[12] issue of regioselective addition of HX to ynamide, and the requirement of harsh conditions are essential. In addition, no methods provide direct access to synthesize α-Cl/Br/I enamides under mild reaction conditions using cost-effective ragents. With our ongoing research activities on ynamides, we looked for an alternate reliable procedure for the synthesis of α-haloenamide from stable ynamides. We thus envisaged the use of Ph_3P and CX_4/CHX_3 mixture, a halogen source generated *in situ*, for the synthesis of α-haloenamide at room temperature (Scheme 4.6). The inherent polarization of lone pair electrons of N-atom in ynamide **14** helps the formation of reactive keteniminium ion species, which would readily trap the *in situ* generated halide-moiety to yield the desired α-haloenamide **15** (Scheme 4.6).



Scheme 4.6. Synthesis of (*E*)-α-haloenamide moieties via metal free halogenation

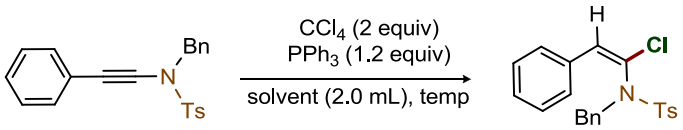
4.3. Results and Discussions:

4.3.1. Synthesis of (*E*)-α-chloroenamide; optimization I:

Investigation is initiated examining α-chlorination of ynamide. Thus, the reaction of ynamide **14** with the mixture of PPh_3 and CCl_4, a chlorinating agent, is examined (Table

4.1). The known synthetic methods for the α-chlorination of ynamide required high temperature. The reaction of **14** (0.5 mmol) with PPh_3 (1.2 equiv) and CCl_4 (2.0 equiv) was conducted at 60 °C for 16 h; the color of the reaction mixture changed to light brown, producing stereoselective (*E*)-α-chloroenamide **15** in 50% yield with the incomplete consumption of starting material (entry 1). The compound **15** was characterized by NMR, IR and HRMS data. The reaction at room temperature did not yield the product, recovering the unreacted **14** (entry 2). Gratifyingly, reaction at 80 °C, provided **14** in 68 % of yield in 12 h (entry 3); continuing the reaction for 24 h yielded 98 % of **15** (entry 4). The reaction at lower temperature is unsuitable.

Table 4.1. Optimization for α-chlorination of ynamide[a]



14a **15a**

entry	phosphine (1.2 eq)	solvent	temp (°C)	time (h)	yield (%)[b]
1	PPh_3	CCl_4	60	16	50
2	PPh_3	CCl_4	24	24	NR
3	PPh_3	CCl_4	80	12	68
4	PPh_3	CCl_4	80	24	98
5	-	CCl_4	80	24	NR
6	$(EtO)_3P$	CCl_4	80	24	45
7	Et_3P	CCl_4	80	24	50
8	Me_3P	CCl_4	80	24	25
9	$(iPrO)_3P$	CCl_4	80	24	10
10	PPh_3	DCE	100	24	NR
11	PPh_3	CH_2Cl_2	100	24	NR
12	PPh_3	$CHCl_3$	100	24	NR
13	PPh_3	CCl_4/CH_2Cl_2	24	1.5	95

[a]Reactions were carried out using **14a** (0.5 mmol), CCl_4 (2 equiv), phosphine (1.2 equiv) in solvent (2.0 mL) at rt to 80 °C. [b]Isolated yields.

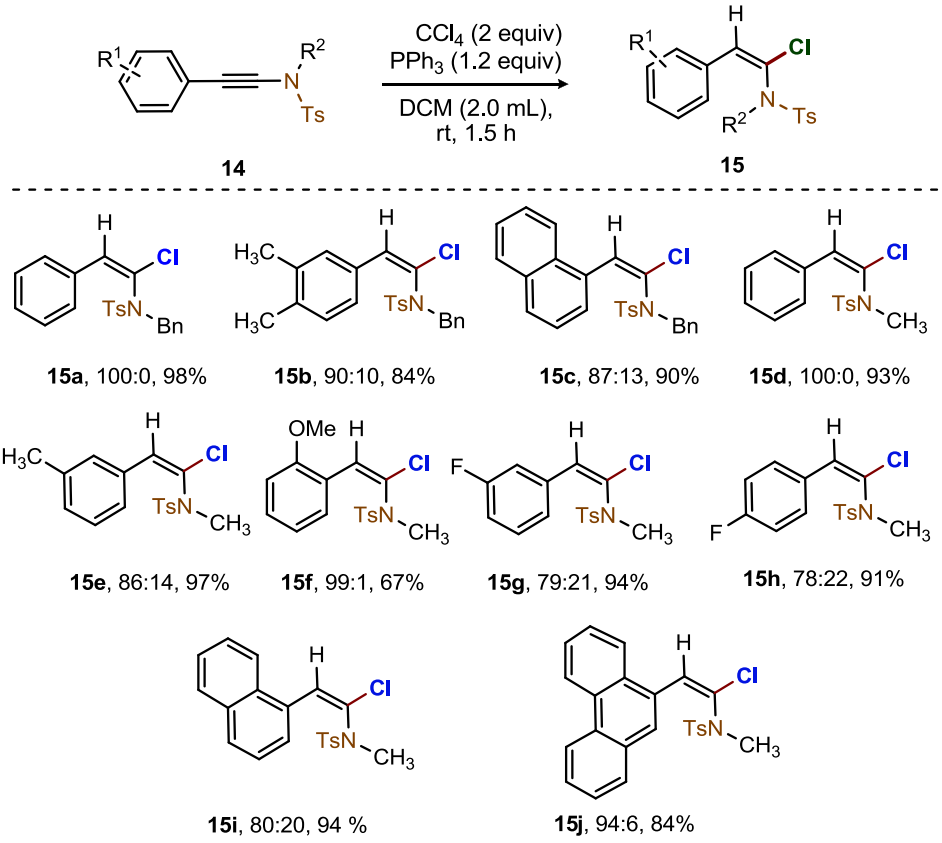
In the absence of PPh_3, reaction did not proceed (entry 5). Effect of other phosphines was further examined; $(EtO)_3P$, $(Et)_3P$, $(Me)_3P$, and $(iPrO)_3P$ were ineffective (entries 6–9). Other chlorinated solvents like DCM, DCE, and $CHCl_3$ were not helpful (entries 10–12). Surprisingly, reaction of **14** with PPh_3 and CCl_4 in DCM (2.0 mL) found to be highly efficient at room temperature, producing **15** in 95% yield in 1.5 h (entry 13). Presumably,

the better solubility of PPh_3 in DCM at RT offers faster interaction with CCl_4, which in turn enhances the formation of salt and facilitates the reaction with ynamides. As such PPh_3 in CCl_4 provides turbid mixture at an ambient temperature, the solubility enhances at higher temperature showing clear solution at 80 °C. Thus, the use of solvent mixture CCl_4 and DCM for the construction of α-chloroenamide from ynamide at RT is truly a novel observation; to the best our knowledge the regio- and stereoselective α-chlorination of ynamide at RT is the first report.

4.3.2. Scope for the Synthesis of α-Chloroenamides

With the optimized conditions in hand, the scope of α-chlorination on various functionalized ynamides is explored; the results are summarized in Table 4.2.

Table 4.2. Substrate Scope for the synthesis of α-chloroenamides[a,b]



[a]Reactions were carried out using **14** (0.5 mmol), CCl_4 (2.0 equiv), PPh_3 (0.6 mmol) in solvent (2.0 mL) at rt. [b]Isolated yields.

At first, N(Ts)benzyl/methyl-ynamides having aryl-substitution at the alkyne terminus are subjected to the optimized conditions, producing the desired (*E*)-α-chloroenesulfonamides **15a–15j** in high yield. The substrate having neutral phenyl ring bearing ynamide **14a** is easily converted to the corresponding α-chloroenamide **15a** with single *E*-isomer in 98%

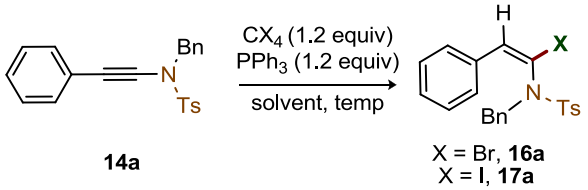
yield. Multiple electron donating substituents on aromatic ring in ynamide did not show any adverse effect on the α-chlorination reaction, affording **15b** in high yield 84% and high selectivity (*E*/*Z* = 90:10). Fused aryl such as naphthalene group on the ynesulfonamide did not affect reaction efficiency, providing the desired α-chloroenamide **15c** in 90% yield with high levels of regio and stereo-control (*E*/*Z* = 87:13).

Next, the compactibility of different substitution on nitrogen is studied. Replacing benzyl group on N- in the ynesulfonamide **15a** with methyl substituent did not show detrimental effect on the chlorination reaction. The corresponding α-chloroenamide **15d** with single (*E*) isomer is obtained in 93% yield from phenyl-bearing ynesulfonamide **14d**. The electron donating methyl group on aryl ring did not affect reaction, delivering **15e** in excellent yield with (*E*/*Z* = 86:14). To our surprise, chlorination of ynesulfonamide having electron donating OMe group at the *ortho* position on aryl ring in alkyne terminus afforded the desired α-chloroenamide **15f** in excellent selectivity (*E*/*Z* = 99:1) with moderate yield. The electron withdrawing fluoro groups at meta/para position on the aromatic moiety in ynesulfonamide did not show impact on rate or the yield of the reaction, providing desired prducts **15g-h** in 94% (*E*/*Z* = 79:21) and 91% (*E*/*Z* = 78:22) yield, respectively. Sterically bulkier naphthalene and phenanthrene group in ynesulfonamide did not inhibit the reaction efficiency to provide the corresponding product **15i** and **15j** in 94% (*E*/*Z* = 80:20) and 84% (*E*/*Z* = 94:06) yield, respectively (Table 4.2).

4.3.3. Synthesis of (*E*)-α-bromo/iodo enamide; optimization II:

After successful achievement of α-chlorination on ynamides, we next envisioned performing bromination and iodinations of ynesulfonamides for the synthesis of α-Br/I-enamides. The optimization studies for the bromination and iodinations of ynamides is shown in Table 4.3. As expected, reaction of **14a** with a mixture of PPh_3 and CBr_4 in CH_2Cl_2 at rt led to α-bromoenamide **16a** in 94% yield in 5 h (entry 1). The absence of PPh_3 did not produce **16a**, completely recovering the unreacted **14a** (entry 2). To accomplish iodination of ynamides, the reaction of **14a** with PPh_3 and iodoform (CHI_3) in CH_2Cl_2 was conducted at rt for 5 h (entry 3). Gratifyingly, the desired α-iodoenamide **17a** was isolated in 96% yield with the complete consumption of **14a** at rt (entry 3). The reaction in the absence of PPh_3 did not deliver **17a** (entry 4). The use of other solvents DCE, dioxane, and acetone were found inferior (entries 5–7). From these observations, it appears that PPh_3 plays vital role for these transformations.

Table 4.3. Optimization for α-bromination and iodination of ynamides[a]



14a

X = Br, **16a**
X = I, **17a**

entry	Additive (1.2 eq)	solvent	temp (°C)	time (h)	yield (%)[b]
1	PPh_3/CBr_4	CH_2Cl_2	24	5	94
2	- / CBr_4	CH_2Cl_2	24	5	NR
3	PPh_3/CHI_3	CH_2Cl_2	24	5	96
4	- / CHI_3	CH_2Cl_2	24	5	NR
5	PPh_3/CHI_3	DCE	24	5	80
6	PPh_3/CHI_3	Dioxane	24	5	50
7	PPh_3/CHI_3	acetone	24	5	42

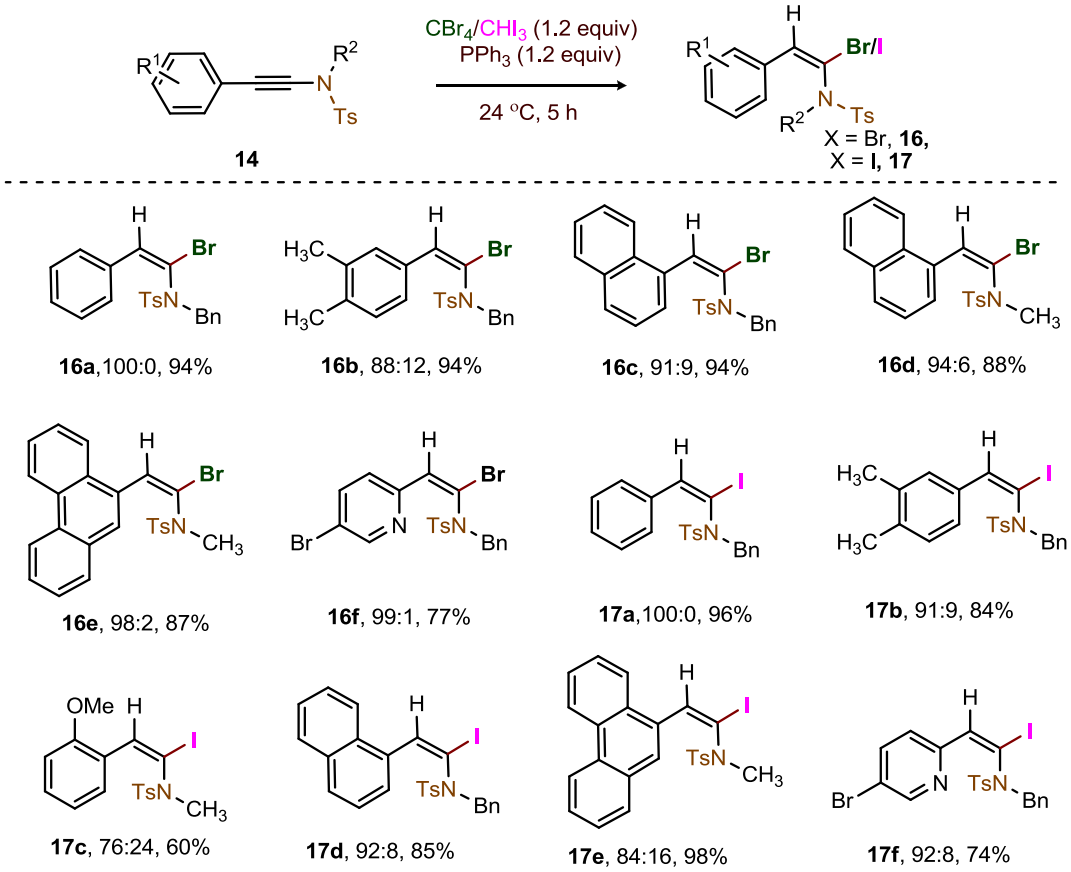
[a]Reactions were carried out using **14** (0.5 mmol), CBr_4/CHI_3(1.2 equiv), PPh_3 (1.2 equiv) in solvent (1.5 mL) at rt. [b]Isolated yields.

4.3.4. Scope for the synthesis of α-Bromo and α-Iodoenamides.

Having established the optimized condition (entries 1 and 3, Table 4.3), scope of α-bromination and α-iodination of substitued ynesulfonamides are examined. The optimal condition was proved to be broad and the results are summarized in Table 4.4. A variety of substituted α-bromoenamide and α-iodoenamide are obtained in 60-98% yield from the corresponding ynesulfonamide. Simple phenyl substituted ynesulfonamide provided the correspong α-bromoenamide **16a** in 94% yield with single (*E*) isomer; while the bromination of **14b** produced the desired α-bromoenamide **16b** (*E*/*Z* = 88:12) in 94% yield.

The N-benzyl protected ynesulfonamide having sterically demanding 1-naphthyl ring did not have adverse effect on the reaction efficiency, producing **16c** in 94% yield with high selectivity (*E*/*Z* = 91:9). Furthermore, replacing benzyl group on the nitrogen atom of ynesulfonamide with methyl group, the desired product **16d** was isolated in 88% yield with an increased selectivity (*E*/*Z* = 94:6). Similarly, the phenanthrene substituted α-bromoenamide **16e** was isolated in 87% yield with excellent stereoselectivity. Heteroaryl substrates such as 5-bromo pyridine **16f** were compatible with the optimized reaction conditions to afford the α-bromination product in good yield (77%) and excellent selectivity (*E*/*Z* = 94:6).

Table 4.4. Substrate scope for α-bromination and α-iodination[a]

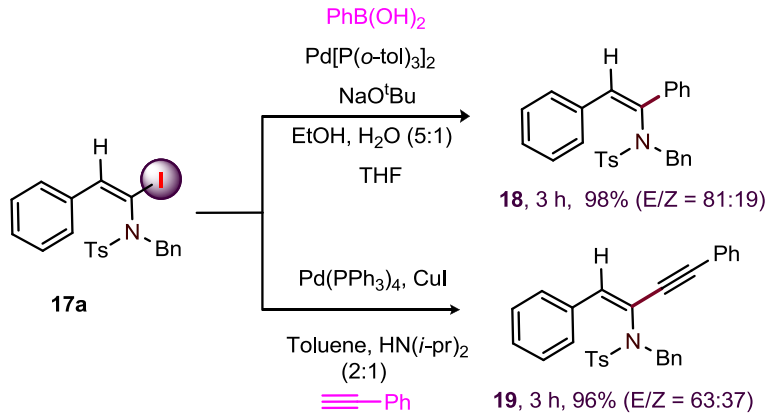


[a]Reactions were carried out using **14** (0.5 mmol), CBr_4/CHI_3 (1.2 equiv), PPh_3 (0.6 mmol) in solvent (2.0 mL) at rt.

Next, various ynesulfonamides were tested for iodination under the optimized reaction conditions shown in entry 3, Table 4.3. As shown in Table 4.4, the α-iodination of aryl substituted ynesulfonamide readily produces the desired products **17** under the optimized reaction conditions. Both electron-neutral and electron-donating groups on aryl ring in ynesulfonamides are reacted efficiently delivering the corresponding products **17a** (96% yield, with single (*E*) isomer) and **17b** (84% yield, *E*/*Z* = 91:9). The *ortho*-methoxy substituted ynesulfonamide under the optimized conditions provided the desired product α-iodoenamide **17c** in only moderte yield and moderate selectivity. The naphthalene and phenanthrene bearing substrate did not affect reaction efficiency providing the corresponding products **17d** (85% yield, *E*/*Z* = 92:8) and **17e** (98% yield, *E*/*Z* = 84:16). It is worthy to mention that the pyridyl bearing ynesulfonamide effectively participated in the iodination process, constructing **17f** (74%) in excellent selectivity (*E*/*Z* = 92:8).

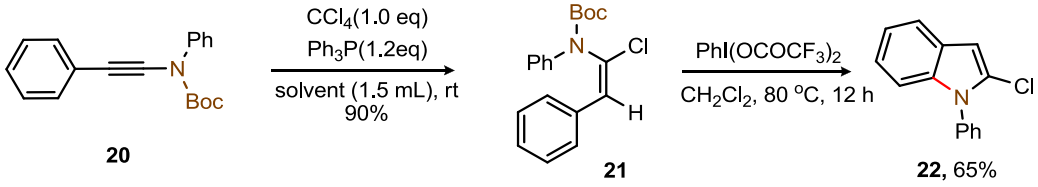
We next investigated synthetic potential of α-haloenamides. The iodo group of α-iodoenamide successfully utilized for the Sonogashira and Suzuki reactions to provide tri

substitituted enamides. Accordingly, phenyl and alkynyl moieties are installed on **17a** with the replacement of iodo group to afford **18** and **19**, respectively in appreciable yields (Scheme 4.7).



Scheme 4.7. Synthetic manipulations of α-iodoenamide

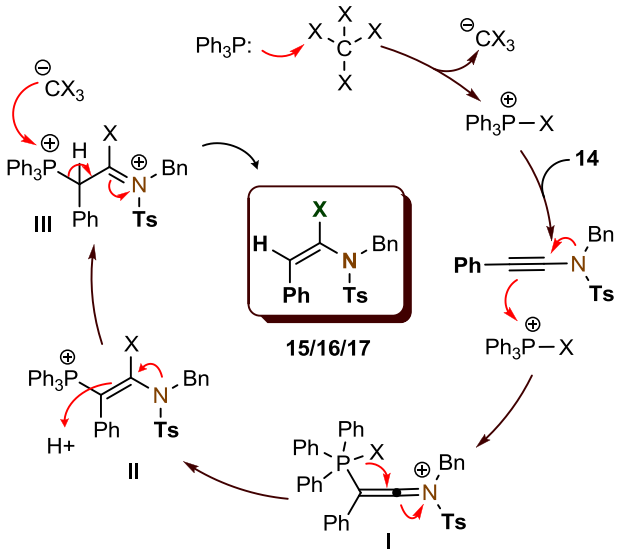
Next, the α-haloenamide obtained from ynamide **20** was utilized for the oxidative cyclization reactions. Thus, the N-Boc protected α-chloroenamide **21** in the presence of oxidant $PhI(OCOCF_3)_2$ underwent insitu deprotection of Boc-group followed by intramolecular oxidative cyclization to afford 2-chloro-N-phenyl indole **22** (Scheme 4.8).



Scheme 4.8. Intramolecular oxidative cyclization

4.3.5. Proposed mechanism:

Although the mechanism of the reaction is not clear; a plaushible mechanism is drawn in order to support the stereoselctive formation of the α-haloenamide. We presume that the attack of triphenyl phosphine on carbon tetrachloride will produce the phosphonium salt. Next, the inherent polarization of ynesulfonamide **14** allows trapping the phosphonium salt to form intermediate **I.** Intramolecular attack of halides on the α-position of keteneiminium species generates **II**. Due to the polarization of the nitrogen lone pair, protonation occurs at the β-position to generate intermediate **III**. Finally, removal of phosphonim salt and simultaneous neutralization of iminium species led to the formation of regio- and stereoselective α-halo enamides **15–17**.



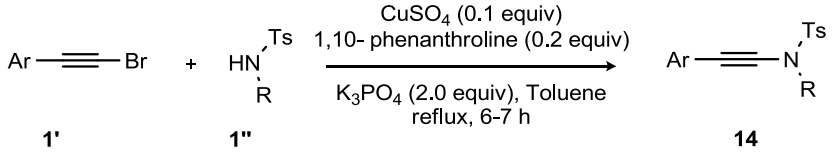
Scheme 4.9. Plausible mechanistic Path

4.4. Conclusion:

In summary, we have developed a phosphine mediated stereoselective α-halogenation of ynesulfonamide. Carbon tetrahalide or haloform in the presence of triphenyl phosphine readily converted ynesulfonamides to (*E*)-α-haloenamides in high yields with good regio- and stereochemical outcomes at room temperature. This approach showed excellent substrate compatibility, and afforded wide variety of (*E*)-α-haloenamides. The α-haloenamide was successfully implemented achieving 2-haloindole, Sonogashira and Suzuki product. Investigations are aimed at applying this methodology for the synthesis of complex molecular frameworks.

4.5. Experimental Procedure:

4.5.1. General procedure for the synthesis of 14 (GP 1):



A solution of **1″** (1.0 mmol), $CuSO_4 \cdot 5H_2O$ (0.10 mmol), 1,10-phenanthroline (0.20 mmol) and K_3PO_4 (2.0 mmol) in dry toluene (5.0 mL) was stirred in a Schlenck tube. The 1-bromo-2-aryl acetylene (**1′**) was subsequently introduced into the Schlenck tube. The reaction mixture was heated at 70 °C under the nitrogen atmosphere. The progress of the reaction was monitored periodically by TLC. Upon completion, the reaction mixture was cooled to room temperature and diluted with dichloromethane (10 mL). The crude mixture was filtered through a small pad of celite and concentrated under the reduced pressure. The crude residue was purified using column chromatography on silica gel to provide **14**.

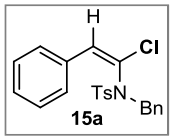
4.5.2. General procedure for the synthesis of 15 (GP 2):

The corresponding ynamide **14** (1.0 equiv), PPh_3 (1.2 equiv), and CCl_4 (2.0 equiv) were dissolved with DCM (2.0 mL) in a Schlenk tube. After stirring over 1.5 h at 24 °C, the reaction mixture was diluted with 10 mL of DCM. The crude mixture was filtered through a small pad of Celite and concentrated under the reduced pressure. The crude residue was purified using column chromatography on silica gel to provide **15**.

4.5.3. General procedure for the synthesis of 16/17 (GP 3):

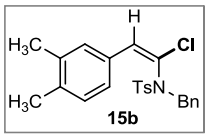
The corresponding ynamide **14** (1.0 equiv), PPh_3 (1.2 equiv), and CBr_4/CHI_3 (1.2 equiv) were dissolved with DCM (2.0 mL) in a Schlenk tube. After stirring over 5 h at 24 °C, the reaction mixture was diluted with 10 mL of DCM. The crude mixture was filtered through a small pad of Celite and concentrated under the reduced pressure. The crude residue was purified using column chromatography on silica gel to provide **16/17**.

(E)-N-Benzyl-N-(1-chloro-2-phenylvinyl)-4-methylbenzenesulfonamide(15a):



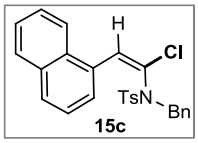
Following general procedure GP-2, compound **15a** (195 mg; *E*:*Z* = 100:0) was obtained in 98% yield as colorless solid; mp = 89–90 °C; R_f = 0.65 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, *J* = 8 Hz, 2H), 7.38 (d, *J* = 8 Hz, 3H), 7.34 (d, *J* = 6.4 Hz, 2H),7.28(d, *J* = 4.8 Hz, 2H), 7.23 (t, *J* = 7.6 Hz, 2H),7.16 (d, *J* = 9.2 Hz, 2H), 6.85 (s, 1H), 4.86 (d, *J* = 13.2 Hz, 1H), 3.97 (d, *J* = 12.8 Hz, 1H), 2.5 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.8, 139.8, 134.3, 133.6, 133.2, 130.0, 129.7, 129.6, 129.2, 129.1, 128.7, 128.64, 128.55, 128.4, 128.3, 128.2, 128.1, 119.7, 53.4, 21.7; IR (Neat)ν_{max} 1349, 1164, 1155, 1097, 1087, 1012, 925, 913 cm^{-1}; HRMS (ESI) for $C_{22}H_{24}ClN_2O_2S$ $(M+NH_4)^+$: calcd 415.1247, found 415.1249.

(E)-N-Benzyl-N-(1-chloro-2-(3,4-dimethylphenyl)vinyl)-4-methylbenzenesulfonamide



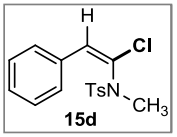
(15b): Following general procedure GP-2, compound **15b** (183 mg; *E*:*Z* = 90:10) was obtained in 84% yield as colorless solid; mp = 106–107 °C; R_f = 0.64 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.83 (d, *J* = 8 Hz, 2H), 7.33 (d, *J* = 7.2 Hz, 2H), 7.28 (d, *J* = 8.4 Hz, 3H), 7.17–7.10 (m, 4H), 7.01 (s, 1H), 6.94 (d, *J* = 7.6 Hz, 1H), 6.54 (s, 1H), 4.78 (d, *J* = 12.4 Hz, 1H), 4.07 (d, *J* = 12.8 Hz, 1H), 2.41 (s, 3H), 2.17 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 144.3, 137.1, 135.9, 135.1, 134.8, 133.6, 130.4, 129.7, 129.6, 129.5, 129.3, 129.2, 128.9, 128.7, 128.4, 128.1, 126.3, 126.2, 52.2, 21.5, 19.5; IR (Neat)ν_{max} 1596, 1453, 1359, 1161, 1106, 1087, 1020,1008, 106, 852, 814, 731, 708 cm^{-1}; HRMS (ESI) for $C_{24}H_{24}ClNO_2SNa$ $(M+Na)^+$: calcd 448.1114, found 448.1112.

(E)-N-benzyl-N-(1-chloro-2-(naphthalen-1-yl)vinyl)-4-methylbenzenesulfonamide



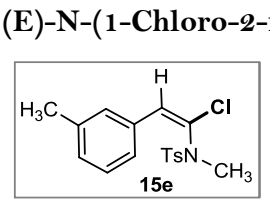
(15c): Following general procedure GP-2, compound **15c** (202 mg; *E*:*Z* = 87:13) was obtained in 90% yield as colorless solid; mp = 110-111 °C; R_f = 0.57 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (500 MHz, $CDCl_3$)*δ* 7.76 (d, *J* = 6.5 Hz, 2H), 7.73 (dd, *J* = 8.0, 3.5 Hz, 2H), 7.46 (d, *J* = 7.0 Hz, 1H), 7.41 (s, 1H), 7.40–7.38 (m, 1H), 7.33 (t, *J* = 8.0 Hz, 1H), 7.30–7.27 (m, 1H), 7.23 (s, 2H), 6.89 (m, 2H), 6.85–6.78 (m, 3H), 4.56 (br s, 1H), 4.05 (br s, 1H), 2.40 (s, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$)*δ* 144.4, 134.9, 133.1, 133.0, 133.0, 131.2, 129.7, 129.4, 129.3, 129.2, 128.8, 128.6, 128.1, 127.84, 127.81, 126.6, 125.9, 125.5, 125.2, 123.9, 52.3, 21.6; IR (Neat)ν_{max}1580, 1345, 1161, 1106, 1086, 1036, 932, 919, 873, 849, 814, 798, 776, 728, 704 cm^{-1}; HRMS (ESI) for $C_{26}H_{22}ClNO_2SNa$ $(M+Na)^+$: calcd 470.0957, found 470.0958.

(E)-N-(1-Chloro-2-phenylvinyl)-N,4-dimethylbenzenesulfonamide (**15d**):

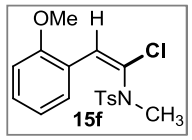


Following general procedure GP-2, compound **15d** (151 mg; *E*:*Z* = 100:0) was obtained in overall 93% yield as colorless solid; mp = 98–99 °C; R_f = 0.55 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, *J* = 7.2 Hz, 2H), 7.63 (d, *J* = 7.6 Hz, 2H), 7.41–7.32 (m, 5H), 6.68 (s, 1H), 3.06 (s, 3H), 2.47(s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$)*δ* 144.5, 134.2, 133.1, 132.4, 129.8, 129.5, 128.9, 128.8, 128.7, 128.7, 128.3, 128.2, 35.7, 21.7; IR (Neat)ν_{max} 1638, 1591, 1489, 1439, 1360, 1196, 1112, 1167, 1158, 1085, 960, 886, 839, 818, 756, 715 cm^{-1}; HRMS (ESI) for $C_{16}H_{20}ClN_2O_2S$ $(M+NH_4)^+$: calcd 339.0934, found 339.0937.

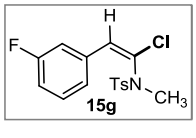
(E)-N-(1-Chloro-2-m-tolylvinyl)-N,4-dimethylbenzenesulfonamide (15e): Following general procedure GP-2, compound **15e** (164 mg; *E*:*Z* = 86:14) was obtained in 97% yield as colorless solid; mp = 105–106 °C; R_f = 0.65 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$)*δ* 7.78 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 0.32H), 7.39 (s, 1H), 7.27 (d, *J* = 6.4 Hz, 3H), 7.28–7.21 (m, 3H), 7.12 (d, *J* = 8.0 Hz, 1H), 6.9 (s, 0.15H), 7.16 (d, *J* = 9.2 Hz, 2H), 6.62 (s, 0.95H), 3.07 (s, 0.49H), 3.02 (s, 3H), 2.4 (s, 3H), 2.36 (s, 0.59), 2.34 (s, 2.98H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 144.4, 138.1, 134.4, 133.0, 132.5, 130.7, 129.63 (2 C), 129.57, 129.48 (2 C), 128.8, 128.6, 128.3, 125.7, 35.7, 21.6, 21.4; IR (Neat)ν_{max} 2356, 2338, 1631, 1593, 1451, 1356, 1287, 1207, 1163, 1087 cm^{-1}; HRMS (ESI) for $C_{17}H_{22}ClN_2O_2S$ $(M+NH_4)^+$: calcd 353.1091, found 353.1091.



(E)-N-(1-Chloro-2-(2-methoxyphenyl)vinyl)-N,4-dimethylbenzenesulfonamide(15f): Following general procedure GP-2, compound **15f** (118 mg; *E*:*Z* = 99:1) was obtained in 67% yield as colorless solid; mp = 114–115 °C; R_f = 0.59 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (dd, *J* =8.0, 1.6 Hz, 1H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 3H), 7.04 (s, 1H), 6.96 (t, *J* = 7.6 Hz, 1H), 6.85 (d, *J* = 8.4 Hz, 1H), 3.82 (s, 3H), 3.00 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 156.8, 144.2, 134.3, 129.9, 129.5, 129.4 (2 C), 128.7, 128.6 (2 C), 126.5, 122.0, 120.7, 110.6, 55.5, 35.8, 21.6; IR (Neat)ν_{max} 1593, 1492, 1457, 1435, 1349, 1292, 1250, 1159, 1108, 1084, 1019, 962, 878, 815, 763, 736, 705 cm^{-1}; HRMS (ESI) for $C_{17}H_{22}ClN_2O_3S$ $(M+NH_4)^+$: calcd 369.1040, found 369.1040



(E)-N-(1-Chloro-2-(3-fluorophenyl)vinyl)-N,4-dimethylbenzenesulfonamide (15g):

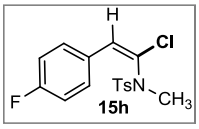


Following general procedure GP-2, compound **15g** (160 mg; E/Z = 79:21) was obtained in 94% yield as yellow semi solid; mp = 104–105 °C; R_f = 0.52

(4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, J = 8.0 Hz, 2H), 7.33–7.26 (m, 6H), 7.03–6.98 (m, 2H), 6.98 (s, 0.26H), 6.62 (s, 0.93H), 3.07 (s, 0.83 x 1H), 3.03 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.0 (d, J = 32.0 Hz) , 144.6, 135.2 (d, J = 32.0 Hz), 134.0, 131.1, 130.1(d, J = 32.0 Hz), 130.0, 129.7, 129.7, 129.6, 129.3, 128.8, 128.2, 125.6, 124.7, 124.6 (d, J = 12.0 Hz), 115.9, 115.7, 115.4, 115.2, 35.9, 35.7, 21.6; ^{19}F NMR (376 MHz, $CDCl_3$): δ -111.48; IR (Neat)ν_{max} 1720, 1581, 1448, 1352, 1273, 1247, 1162, 1088, 994, 979, 935, 884, 810, 784, 742, 723, 706 cm^{-1}; HRMS (ESI) for $C_{16}H_{19}ClFN_2O_2S$ $(M+NH_4)^+$: calcd 357.0840, found 357.0841.

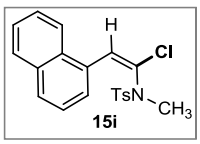
(E)-N-(1-Chloro-2-(4-fluorophenyl)vinyl)-N,4-dimethylbenzenesulfonamide (15h):

Following general procedure GP-2, compound **15h** (155 mg; E:Z = 78:22) was obtained in



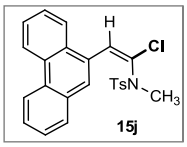
91% yield as pale yellow solid; mp = 99–100 °C; R_f = 0.53 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71 (d, J = 8.5 Hz, 2H), 7.68 (d, J = 8.5 Hz, 0.57H), 7.55–7.50 (m, 2H), 7.24 (d, J = 8 Hz, 2H), 7.19 (s, 1H), 6.98 (d, J = 7.5, 2H), 6.54 (s, 0.26H), 6.54 (s, 0.93H), 3.30 (s, 0.83H), 2.95 (s, 3H), 2.38 (s, 0.9H), 2.37 (s, 2.82H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 163.7, 161.7, 144.6, 134.1, 131.4, 131.3, 131.2, 130.7(d, J = 35.0 Hz), 129.7, 129.6, 129.4, 129.31, 129.28, 128.8, 128.3, 115.8 (d, J = 35.0 Hz), 35.7, 21.7; ^{19}F NMR (376 MHz, $CDCl_3$): δ -112.5; IR (Neat)ν_{max} 1638, 1597, 1502, 1450, 1349, 1236, 1126, 1081, 963, 882, 818, 710 cm^{-1}; HRMS (ESI) for $C_{16}H_{19}ClFN_2O_2S$ $(M+NH_4)^+$: calcd 357.0840, found 357.0840.

(E)-N-(1-Chloro-2-(naphthalen-1-yl)vinyl)-N,4-dimethylbenzenesulfonamide (15i):



Following general procedure GP-2, compound **15i** (175 mg; E:Z = 80:20) was obtained in 94% yield as colorless solid; mp = 110–111 °C; R_f = 0.65 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89–7.87 (m, 1H), 7.84–7.77 (m, 2H), 7.70 (d, J = 7.2 Hz, 1H), 7.53 (d, J = 6.7 Hz, 2H), 7.50–7.47 (m, 2H), 7.44 (t, J = 7.7 Hz, 1H), 7.27 (s, 1H), 7.06 (d, J = 8.1 Hz, 2H), 2.98 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.0, 134.3, 133.4, 131.9, 131.2, 130.2, 130.1, 129.6, 129.2, 129.0, 128.8, 128.5, 128.3, 128.2, 126.6, 126.4, 126.3, 125.9, 125.5, 123.8, 36.2, 21.5; IR (Neat)ν_{max} 1644, 1594, 1356, 1155, 1085, 958, 924, 891, 844, 824, 799, 779, 730, 705 cm^{-1}; HRMS (ESI) for $C_{20}H_{18}ClNO_2SNa$ $(M+Na)^+$: calcd 394.0644, found 394.0643.

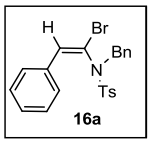
(E)-N-(1-Chloro-2-(phenanthren-9-yl)vinyl)-N,4-dimethylbenzenesulfonamide(15j):



Following general procedure GP-2, compound **15j** (177 mg; E/Z = 94:6) was obtained in 84% yield as yellow gummy liquid; R_f = 0.65 (4:1

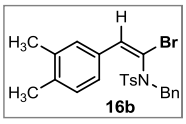
hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.67 (d, *J* = 7.6 Hz, 1H), 8.63 (d, *J* = 8.4 Hz, 1H), 7.93 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.85 (s, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.68–7.56 (m, 4H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.25 (s, 1H), 7.23 (s, 0.11H), 6.84 (d, *J* = 8 Hz, 2H), 3.17 (s, 0.19H), 3.04 (s, 3H), 2.40 (s, 0.20H), 2.17 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.8, 134.7, 132.5, 131.2, 130.3, 130.3, 130.23, 130.17, 129.1, 129.0, 128.8, 128.2, 128.0, 127.6, 127.1, 126.8, 126.74, 126.66, 124.7, 122.9, 122.5, 122.3, 36.4, 36.0, 21.4; IR (Neat)ν_{max} 2360, 2336, 1637, 1596, 1495, 1452, 1353, 1164, 1087 cm^{-1}; HRMS (ESI) for $C_{24}H_{24}ClN_2O_2S$ $(M+NH_4)^+$: calcd 439.1247, found 439.1247.

(E)-N-benzyl-N-(1-bromo-2-phenylvinyl)-4-methylbenzenesulfonamide(16a):



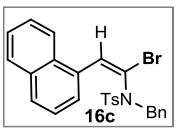
Following general procedure GP-3, compound **16a** (213 mg; E/Z= 100:0) was obtained in 94% yield as colorless solid; mp = 87–88 °C; R_f = 0.65 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, *J* = 8 Hz, 2H), 7.38 (d, *J* = 8 Hz, 3H), 7.34 (d, *J* = 6.4 Hz, 2H),7.28 (d, *J* = 5.2 Hz, 2H), 7.23 (t, *J* = 7.6 Hz, 2H), 7.17–7.13 (m, 2H), 6.85 (s, 1H), 4.86 (d, *J* = 13.2 Hz, 1H), 3.97 (d, *J* = 12.8 Hz, 1H), 2.5 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 144.8, 139.8, 134.3, 133.6, 133.2, 130.0, 129.7, 129.6, 129.2, 129.1, 128.7, 128.64, 128.6, 128.4, 128.3, 128.2, 128.1, 119.7, 53.4, 21.7; IR (Neat)ν_{max} 1349, 1164, 1155, 1097, 1087, 1012, 925, 913, 878, 866, 820, 782, 747, 706 cm^{-1}; HRMS (ESI) for $C_{22}H_{24}BrN_2O_2S$ $(M+NH_4)^+$: calcd 459.0742, found 459.0738.

(E)-N-Benzyl-N-(1-bromo-2-(3,4-dimethylphenyl)viny)-4-methylbenzenesulfonamide



(16b): Following general procedure GP-3, compound **16b** (221 mg; E/Z= 88:12) was obtained in 94% yield as colorless solid; mp = 120–121 °C; R_f= 0.65 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, *J* = 8.4 Hz, 2H), 7.64 (d, *J* = 8 Hz, 0.20H), 7.30 (d, *J* = 8 Hz, 5H), 7.24 (d, *J* = 9.6 Hz, 0.42H), 7.15 (d, *J* = 4.8 Hz, 3H), 7.07 (d, *J* = 7.6 Hz, 1H), 7.00 (s, *J* = 7.6 Hz, 1H), 6.93 (d, J = 7.6 Hz, 1H), 6.76 (s, 1H), 5.06 (s, 0.15H), 4.82 (d, *J* = 13.2 Hz, 1H), 4.00 (d, *J* = 13.2 Hz, 1H), 3.76 (s, 0.14H), 2.43 (s, 3H), 2.40 (s, 0.30H), 2.20 (s, 0.38H), 2.19 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.6, 139.7, 137.5, 136.0, 134.7, 133.6, 130.00, 129.8, 129.6, 129.4, 129.1, 128.32, 128.30, 126.3, 118.7, 53.3, 21.7, 19.7, IR (Neat)ν_{max} 1450, 1363, 1165, 1109, 1084, 1020, 1007, 906, 841, 813, 802, 767, 720 cm^{-1}; HRMS (ESI) for $C_{24}H_{24}BrNO_2SNa$ $(M+Na)^+$: calcd 492.0609, found 492.0599.

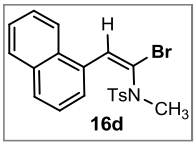
(E)-N-Benzyl-N-(1-bromo-2-(naphthalen-1-yl)vinyl)-4-methylbenzenesulfonamide



(16c): Following general procedure GP-3, compound **16c** (121 mg; E/Z = 91:9) was obtained in 94% yield as colorless solid; mp = 116–115 °C; R_f =

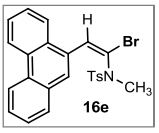
0.65 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77–7.72 (m, 4H), 7.48–7.44 (m, 1H), 7.42–7.37 (m, 3H), 7.35–7.23 (m, 5H), 6.95–6.93 (m, 1H), 6.90–6.88 (m, 1H), 6.84–6.78 (m, 3H), 4.63 (d, J = 11.6 Hz, 1H), 3.94 (d, J = 12.4 Hz, 1H), 2.4 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.5, 144.4, 138.1, 135.0, 134.5, 133.1, 133.0, 132.98, 132.91, 131.2, 130.9, 130.6, 129.8, 129.5, 129.4, 129.35, 129.3, 129.1, 128.8, 128.6, 128.1, 128.0, 127.9, 127.8, 126.6, 126.3, 125.9, 125.5, 125.24, 125.20, 123.9, 121.1, 53.1, 52.3, 21.6; IR (Neat)ν_{max} 1343, 1162, 1106, 1086, 1025, 931, 919, 886, 871, 846, 812, 797, 772, 725 cm^{-1}; HRMS (ESI) for $C_{26}H_{22}BrNO_2SNa$ $(M+Na)^+$: calcd 514.0452, found 514.0457.

(E)-N-(1-Bromo-2-(naphthalen-1-yl)vinyl)-N,4-dimethylbenzenesulfonamide (16d):



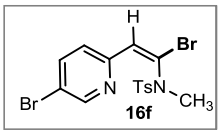
Following general procedure GP-3, compound **16d** (231 mg; E/Z = 94:6) was obtained in 88% yield as colorless solid; mp = 100–101 °C; R_f = 0.5 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (br t, J = 2.4 Hz 2H), 7.76–7.0 (m, 2H), 7.60 (d, J = 7.2 Hz 1H), 7.45 (s, 1H), 7.43–7.39 (m, 4H), 7.35 (br t, J = 7.6 Hz, 1H), 6.96 (d, J = 8 Hz, 2H), 2.87 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.1, 134.1, 132.8, 132.4, 130.0, 130.0, 128.2, 127.8, 127.5, 127.5, 125.6, 125.4, 125.2, 125.0, 124.4, 122.8, 122.3, 36.0, 20.61; IR (Neat)ν_{max} 1637, 1593, 1452, 1400, 1205, 1132, 1084, 1021, 948, 893, 927, 861, 834, 820, 775, 717, 704 cm^{-1}; HRMS (ESI) for $C_{20}H_{18}BrNO_2SNa$ $(M+Na)^+$: calcd 438.0139, found 438.0139.

(E)-N-(1-Bromo-2-(phenanthren-9-yl)vinyl)-N,4-dimethylbenzenesulfonamide(16e):



Following general procedure GP-3, compound **16e** (183 mg; E/Z = 98: 2) was obtained in 87% yield as yellow gummy liquid; R_f = 0.53 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.67 (d, J = 8.0 Hz,1H), 8.62 (d, J = 8.0 Hz, 1H), 7.92 (d, J = 7.6 Hz, 1H), 7.82 (d, J = 10.4 Hz, 2H), 7.67–7.62 (m, 3H), 7.60–7.55 (m, 2H), 7.44 (t, J = 10.4 Hz, 3H), 7.30 (d, J = 8 Hz, 0.3H), 6.83 (d, J = 8 Hz, 2H), 3.13 (s, 0.04H), 3.00 (s, 3H), 2.40 (s, 0.06H), 2.16 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ135.3, 134.5, 131.3, 130.4, 130.3, 130.0, 129.7, 129.2, 129.1, 128.5, 128.2, 127.4, 127.2, 126.9, 126.8, 126.8, 124.8, 123.8, 122.9, 122.4, 37.3, 21.5; IR (Neat)ν_{max} 2363, 2341, 1632, 1591, 1489, 1451, 1353, 1163, 1090 cm^{-1}; HRMS (ESI) for $C_{24}H_{24}BrN_2O_2S$ $(M+NH_4)^+$: calcd 483.0745, found 483.0745.

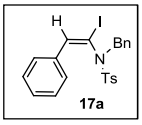
(E)-N-(1-Bromo-2-(5-bromopyridin-2-yl)vinyl)-N,4-dimethylbenzenesulfonamide



(16f): Following general procedure GP-3, compound **16f** (201 mg; E/Z = 99:01) was obtained in 77% yield as colorless liquid; mp = 84–85 °C; R_f = 0.65 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz,

$CDCl_3$): δ 8.43 (d, *J* = 1.96 Hz, 1H), 7.87 (d, *J* = 8.28 Hz, 2H), 7.63–7.56 (m, 2H), 7.36 (d, *J* = 8.12 Hz, 2H), 7.30 (d, *J* = 1.56 Hz, 1H), 7.29 (d, *J* = 2.12 Hz, 1H), 7.20–7.14 (m, 3H), 6.99 (s, 1H), 4.88 (d, *J* = 13.2 Hz,1H), 3.97 (d, *J* = 14.4 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 150.9, 149.9, 145.1, 139.3, 138.6, 134.7, 134.2, 133.2, 129.8, 129.7, 129.2, 129.0, 128.8, 128.6, 128.4, 124.2, 123.7, 119.8, 56.6, 21.8; IR (Neat)ν_{max} 1644, 1594, 1356, 1155, 1085, 958, 924, 891, 844, 824, 799, 779, 730, 705 cm^{-1}; HRMS (ESI) for $C_{15}H_{14}Br_2N_2O_2SNa$ $(M+Na)^+$: calcd 466.9040, found 466.9043.

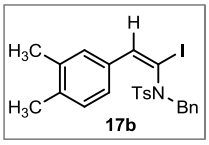
(E)-N-Benzyl-N-(1-Iodo-2-phenylvinyl)-4-methylbenzenesulfonamide(17a):



17a

Following general procedure GP-3, compound **17a** (235 mg; *E*/*Z* = 100:0) was obtained in 96 % yield as reddish-orange solid; mp = 106–107 °C; R_f= 0.65 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, *J* = 8 Hz, 2H), 7.36 (d, *J* = 8Hz, 2H), 7.29 (d, *J* = 7.6 Hz, 4H), 7.21–7.13 (m, 6H), 7.11 (s, 1H), 4.86 (d, *J* = 13.2 Hz, 1H), 3.62 (d, *J* = 13.2 Hz, 1H), 2.47 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.3, 144.9, 134.9, 133.3, 133.0, 130.0, 129.7, 129.63, 129.58, 129.4, 128.8, 128.7, 128.5, 128.4, 128.2, 128.1, 128.0, 98.0, 55.2, 21.8; IR (Neat)ν_{max}1594, 1489, 1445, 1349, 1306, 1236, 1164, 1155, 1085, 1021, 927, 910, 877, 860, 818, 778, 761, 740 cm^{-1}; HRMS (ESI) for $C_{22}H_{20}INO_2SNa$ $(M+Na)^+$: calcd 512.0157, found 512.0158.

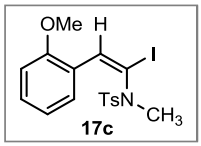
(E)-N-Benzyl-N-(1-iodo-2-(3,4-dimethylphenyl)vinyl)-4-methylbenzenesulfonamide



17b

(17b): Following general procedure GP-3, compound **17b** (164 mg; *E*:*Z* = 91:9) was obtained in 84% yield as colorless solid; mp = 83–84 °C; R_f= 0.64 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, *J* = 8.4 Hz, 2H), 7.34 (t, *J* = 7.2 Hz, 5H), 7.24 (s, 0.19H), 7.17 (dd, *J* = 5.2, 2 Hz, 3H), 7.06 (d, *J* = 7.2 Hz, 2H), 6.99 (s, 1H), 6.91 (d, *J* = 7.6 Hz, 1H), 4.85 (d, *J* = 13.2 Hz, 1H), 3.67 (d, *J* = 13.2 Hz, 1H), 2.45 (s, 3H), 2.21 (s, 0.69H), 2.16 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.2, 144.7, 137.6, 136.0, 133.8, 133.3, 132.6, 130.0, 129.9, 129.7, 129.6, 129.5, 129.4, 129.3, 128.7, 128.5, 128.3, 128.2, 126.4, 96.9, 55.1, 21.7, 19.7, 19.6; IR (Neat)ν_{max} 1598, 1494, 1456, 1401, 1356, 1164, 1087, 1022, 894, 812, 743, 715 cm^{-1}; HRMS (ESI) for $C_{24}H_{24}INO_2SNa$ $(M+Na)^+$: calcd 540.0470, found 540.0470.

(E)-N-(1-Iodo-2-(2-methoxyphenyl)vinyl)-N,4-dimethylbenzenesulfonamide(17c):

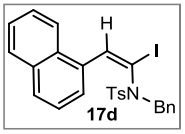


17c

Following general procedure GP-3, compound **17c** (133 mg; *E*:*Z* = 76:24) was obtained in 60% yield as colorless solid; R_f = 0.48 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.86

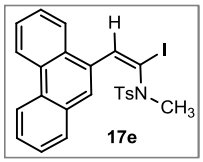
(dd, *J* = 7.6, 1.6 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 2H), 7.72 (d, *J* = 8.0 Hz, 2H), 7.51 (s, 1H), 7.26 (d, *J* = 7.6 Hz, 1H), 6.93 (t, *J* = 7.8 Hz, 1H), 6.82 (d, *J* = 8.4, 1H), 3.83 (s, 0.8H), 3.80 (s, 2.57H), 2.90 (s, .74H), 2.80 (s, 2.5H), 2.45 (s, 0.97H), 2.42 (s, 3.0H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.5, 144.4, 139.7, 132.9, 130.1, 129.5, 129.3, 129.2, 128.7, 128.6, 123.9, 120.6, 110.6, 55.5, 38.3, 21.6; IR (Neat) ν_{max} 1596, 1483, 1465, 1437, 1342, 1289, 1248, 1160, 1135, 1107, 1086, 1047, 1024, 950, 892, 860, 839, 812, 751, 740, 729, 705 cm^{-1}; HRMS (ESI) for $C_{17}H_{18}INO_3SNa$ $(M+Na)^+$: calcd 465.9950, found 465.9951.

(E)-N-Benzyl-N-(1-iodo-2-(naphthalen-1-yl)vinyl)-4-methylbenzenesulfonamide (17d):



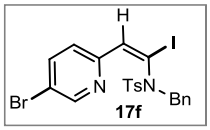
Following general procedure GP-3, compound **17d** (229 mg; *E*:*Z* = 92:8) was obtained in 85% yield as pale yellow solid; mp = 110–111 °C; R_f = 0.58 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76–7.72 (m, 5H), 7.42–7.36 (m, 3H), 7.31–7.24 (m, 8H), 6.99 (dd, *J* = 6.8, 1.6 Hz, 2H), 6.85 (br d, *J* = 6.4 Hz, 3H), 4.66 (d, *J* = 12.8 Hz, 1H), 3.65 (d, *J* = 13.6 Hz, 1H), 2.44 (s, 0.27H), 2.40 (s, 2.99H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.0, 144.6, 133.7, 132.9, 132.6, 132.0, 130.6, 129.6, 129.4, 129.3, 128.6, 128.0, 127.9, 126. 2, 125.9, 125.5, 125.2, 123.9, 99.0, 54.6, 21.6; IR (Neat)ν_{max} 1342, 1161, 1106, 1086, 1025, 931, 919, 886, 871, 846, 812, 797, 772, 725 cm^{-1}; HRMS (ESI) for $C_{26}H_{22}INO_2SNa$ $(M+Na)^+$: calcd 562.0314, found 562.0305.

(E)-N-(1-Iodo-2-(phenanthren-9-yl)vinyl)-N,4-dimethylbenzenesulfonamide(17e):



Following general procedure GP-3, compound **17e** (251 mg; *E*:*Z* = 84:16) was obtained in 98% yield as yellow semi solid; R_f = 0.53 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.75–8.71 (m, 4H), 8.68 (dd, *J* = 8.4, 1.2 Hz, 1H), 8.63 (d, *J* = 8.4 Hz, 1H), 8.17–8.13 (m, 3H), 7.93–7.89 (m, 1H), 7.82 (br t, *J* = 6 Hz, 3H), 7.75 (d, *J* = 0.8 Hz, 1H), 7.69–7.56 (m, 5H), 7.4 (d, *J* = 8 Hz, 2H), 7.33 (d, *J* = 8 Hz, 0.43H), 7.25 (s, 1H), 6.82 (d, *J* = 8 Hz, 2H), 3.0 (s, 0.58H), 2.86 (s, 3H), 2.42 (s, 0.62H), 2.16 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.1,144.0, 140.0, 134.0, 131.2, 131.0, 130.3, 130.2, 129.7, 129.7, 129.1, 129.0, 128.7, 128.3, 128.0, 127.20, 127.17, 126.8, 126.7, 126.7, 125.5, 124.7, 122.9, 122.6, 122.4, 100.3, 38.9, 21.4; IR (Neat) ν_{max} 2922, 2244, 2184, 2129, 1596, 1492, 1449, 1351, 1246, 1201, 1160, 1087, 1036, 941, 891, 812, 745, 723, 713, 704 cm^{-1}; HRMS (ESI) for $C_{24}H_{20}IN_2O_2S$ $(M+NH_4)^+$: calcd 531.0603, found 531.0603.

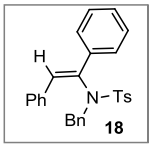
(E)-N-Benzyl-N-(1-iodo-2-(5-bromopyridin-2-yl)vinyl)-4-methylbenzenesulfonamide



17f

(17f): Following general procedure GP-3, compound **17f** (211 mg; *E*:*Z* = 92:08) was obtained in 74% yield as colorless liquid; R_f = 0.65 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.43 (s, 1H), 7.86 (d, *J* = 8.0 Hz, 2H), 7.74–7.60 (m, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.26 (d, *J* = 6.0 Hz, 2H), 7.19–7.15 (m, 3H), 6.76 (s, 1H), 4.86 (br s, 1H), 4.08 (br s, 1H), 2.47 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 150.5, 150.0, 144.9, 138.5, 134.7, 134.6, 133.3, 131.6, 129.7, 128.8, 128.5, 128.4, 124.3, 119.7, 52.6, 21.7; IR (Neat)ν_{max} 1644, 1594, 1356, 1155, 1085, 958, 924, 891, 844, 824, 799, 779, 730, 705 cm^{-1}; HRMS (ESI) for $C_{21}H_{18}BrIN_2O_2SNa$ $(M+Na)^+$: calcd 590.5915, found 590.5919.

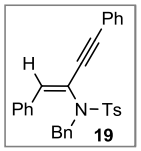
(Z)-N-Benzyl-N-(1,2-diphenylvinyl)-4-methylbenzenesulfonamide (18):



18

Following the reported procedure, compound **18** (216 mg) was obtained in overall 98% (*E*/*Z* = 81:19), yield as brown gummy liquide; R_f = 0.30 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, *J* = 8 Hz, 2H), 7.71 (d, *J* = 8.4 Hz, 0.44H), 7.48 (d, *J* = 14.4 Hz, 0.27 H), 7.35–7.28 (m, 3.6H), 7.28–7.23 (m, 3H), 7.23–7.20 (m, 1H), 7.20–7.15 (m, 3.4H), 7.14–7.08 (m, 2.4H) 7.08–7.03 (m, 3H), 6.85 (br d, *J* = 14.4 Hz, 1H), 6.84–6.79 (m, 3H), 6.80 (s, 1H), 4.62 (s, 0.5H), 4.51 (s, 2H), 2.46 (s, 3H), 2.41 (s, 0.7H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 143.6, 137.5, 137.3, 136.5, 136.3, 135.9, 135.6, 135.3, 130.6, 130.0, 129.7, 129.3, 129.0, 128.7, 128.6, 128.4, 128.4, 128.3, 128.0, 127.9, 127.7, 127.6, 127.2, 127.0, 156.9, 126.6, 126.5, 125.4, 115.3, 112.1, 52.2, 49.5, 21.7; IR (Neat)ν_{max} 1594, 1489, 1445, 1349, 1306, 1236, 1164, 1155, 1085, 1021, 927, 910, 877, 860, 818, 778, 761, 740 cm^{-1}; HRMS (ESI) for $C_{28}H_{25}NO_2SNa$ $(M+Na)^+$: calcd 462.1504, found 462.1507.

(Z)-N-Benzyl-N-(1,4-diphenylbut-1-en-3-yn-2-yl)-4-methylbenzenesulfonamide (18):

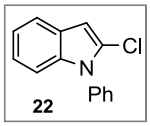


19

Following the reported procedure compound **18** (223 mg) was obtained in overall 96% (*E*/*Z* = 63:37), yield as brown gummy liquid; R_f = 0.30 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.936 (d, *J* = 8 Hz, 1H), 7.88 (d, *J* = 8Hz, 2H), 7.77 (d, *J* = 6.8 Hz, 2H), 7.70 (d, *J* = 8 Hz, 1H), 7.43 (d, *J* = 7.2 Hz, 3H), 7.41–7.27 (m, 18H), 7.19–7.08 (m, 5H), 6.99 (s, 1H), 6.84 (s, 1H), 4.69 (s, 2.38 x 1H), 2.40 (s, 3H), 2.39 (s, 1.78 x 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.9, 135.6, 135.0, 134.4, 134.1, 133.9, 131.4, 130.2, 129.7, 129.6, 129.5, 129.2, 129.2, 129.1, 129.0, 128.8, 128.6, 128.5, 128.4, 128.3, 128.17, 128.15, 128.1, 128.0, 127.8, 122.2, 122.1, 118.3, 117.0, 96.7, 91.3, 86.0, 84.0, 53.4, 52.1, 21.5; IR (Neat)ν_{max} 2924, 1594, 1489, 1445, 1349, 1306,

1236, 1164, 1155, 1085, 1021, 927, 910, 877, 860, 818, 778, 761, 740 cm^{-1}; HRMS (ESI) for $C_{30}H_{25}NO_2SNa$ $(M+Na)^+$: calcd 486.5798, found 486.5799

2-chloro-1-phenyl-1H-indole (22):



22

Following the reported procedure compound **22** (74 mg) was obtained in overall 65% yield as Brownish semi solid; R_f = 0.40 (4:1 hexane/EtOAc); [Silica, UV and I_2]; ^1H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, J = 7.6 Hz, 1H), 7.56 (br t, J = 6.8 Hz, 2H), 7.53–7.44 (m, 6H), 7.40 (bt, J = 7.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.6, 134.5, 132.0, 129.5, 129.2, 128.8, 128.7, 127.3, 126.3, 124.6, 119.9, 111.3; IR (Neat)ν_{max} 1450, 1363, 1165, 1109, 1084, 1020, 1007, 906, 841, 813, 802, 767, 720 cm^{-1}; HRMS (ESI) for $C_{14}H_{11}ClN$ $(M+H)^+$: calcd 228.0580, found 228.0576.

4.6. References.

1. (a) Yet, L. Chem. Rev. **2003**, 103, 4283. (b) Carbery, D. R. *Org. Biomol. Chem.* **2008**, 6, 3455. (c) Evano, G.; Gaumont, A.C.; Alayrac, C.; Wrona, I. E.; Giguere, J. R.; Delacroix, O.; Bayle, A.; Jouvin, K.; Theunissen, C.; Gatignol, J.; Silvanus, A. C. *Tetrahedron* **2014**, *70*, 1529. (d) Tschesche, R.; Last, H.; Fehlhaber, H.W. *Chem. Ber.* **1967**, *100*, 3937. (e) Götz, M. G.; Caffrey, C. R.; Hansell, E.; McKerrow, J. H.; Powers, J. C. *Bioorg. Med. Chem.* **2004**, 12, 5203.

2. For selected reports on the synthesis of enamides via carbometalation of ynamides, see: (a) Couty, S.; Lie´gault, B.; Meyer, C.; Cossy, J. *Org. Lett.* **2004**, *6*, 2511. (b) Chechik-Lankin, H.; Livshin, S.; Marek, I. *Synlett* **2005**, 2098. (c) Yasui, H.; Yorimitsu, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 373. (d) Gourdet, B.; Lam, H. W. *J. Am. Chem. Soc.* **2009**, *131*, 3802. (e) Greenaway, R. L.; Campbell, C. D.; Holton, O. T.; Russell, C. A.; Anderson, E. A. *Chem.-Eur. J.* **2011**, *17*, 14366. (f) Greenaway, R. L.; Campbell, C. D.; Chapman, H. A.; Anderson, E. A. *Adv. Synth. Catal.* **2012**, *354*, 3187. (g) Gati, W.; Couty, F.; Boubaker, T.; Rammah, M. M.; Rammah, M. B.; Evano, G. *Org. Lett.* **2013**, *15*, 3122. (h) Frischmuth, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2013**, *52*, 10084. For a review, see: (i) Minko, Y.; Pasco, M.; Chechik, H.; Marek, I. Beilstein *J. Org. Chem.* **2013**, *9*, 526. (j) Matsubara, R.; Kobayashi, S. *Acc. Chem. Res.* **2008**, *41*, 292. and references therein.

3. (a) Brandsma, L.; Verkruijsse, H. Preparative Polar Organometallic Chemistry 1; Springer: Berlin, **1987**. (b) Wakefield, B. J. Organolithium Methods; Academic Press: London; (c) Brandsma, L. Preparative Polar Organometallic Chemistry 2; Springer: Berlin, **1990**; (d) Schlosser, M. In Organometallics in Synthesis A Manual; Schlosser, M., Ed., 2nd ed.; Wiley: Chichester, UK, **2002**; pp 1–352.

4. (a) Neumann, H.; Seebach, D. *Chem. Ber.* **1978**, *111*, 2785. (b) Evans, D. A.; Crawford, T. C.; Thomas, R. C.; Walker, J. A. *J. Org. Chem.* **1976**, *41*, 3947.

5. Galli, C.; Rappoport, Z. Acc. *Chem. Res.* **2003**, *36*, 580.

6. (a) Funk, R. L.; Hentley, R. J. *Tetrahedron Lett.* **2011**, *52*, 6671. (b) Heffernan, S.; Carbery, D. R. *Tetrahedron Lett.* **2012**, *53*, 5180.

7. (a) Yu, Z.; Jin, Z. *J. Am. Chem. Soc.* **2000**, *122*, 9840. (b) Liu, X.; Henderson, J. A.; Sasaki, T.; Kishi, Y. *J. Am. Chem. Soc.* **2009**, *131*, 16678.

8. For an excellent review see: (a) Tracey, M. R.; Hsung, R. P.; Antoline, J.; Kurtz, K. C. M.; Shen, L.; Slafer, B. W.; Zhang, Y. *Sci. Synth.* **2005**, *5*, 387. (b) Shen, R.; Porco, J. A. *Org. Lett.* **2000**, *2*, 1333.

9. Mulder, J. A.; Kurtz, K. C. M.; Hsung, R. P.; Coverdale, H.; Frederick, M. O.; Shen, L.; Zificsak, C. A. *Org. Lett.* **2003**, *5*, 1547.

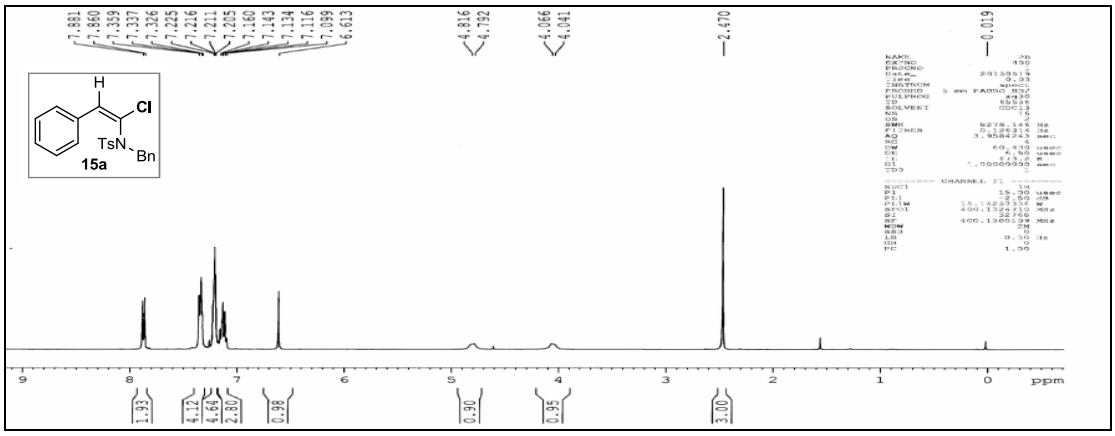
10. Kramer, S.; Friis, S. D.; Xin, Z.; Odabachian, Y.; Skrydstrup, T. *Org. Lett.* **2011**, *13*, 1750.

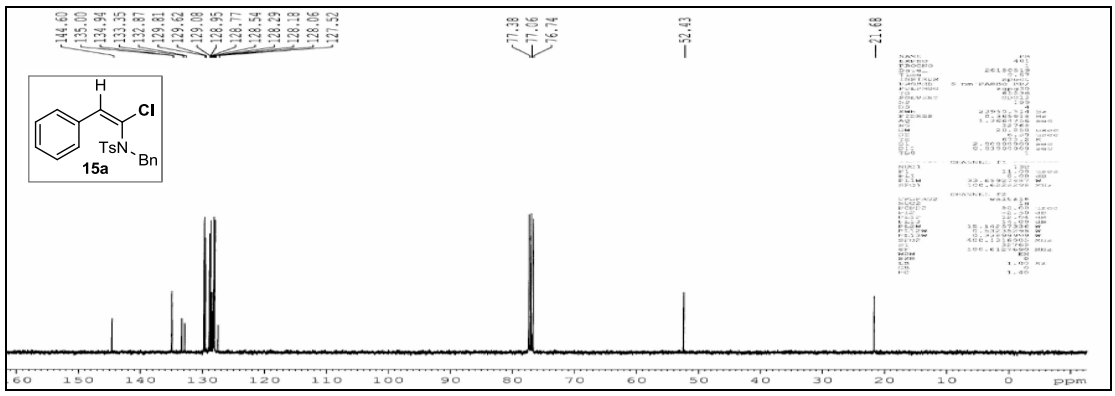
11. Compain, G.; Jouvin, K.; Martin-Mingot, A.; Evano, G.; Marrot, J.; Thibaudeau, S. *Chem. Commun.* **2012**, *48*, 5196.

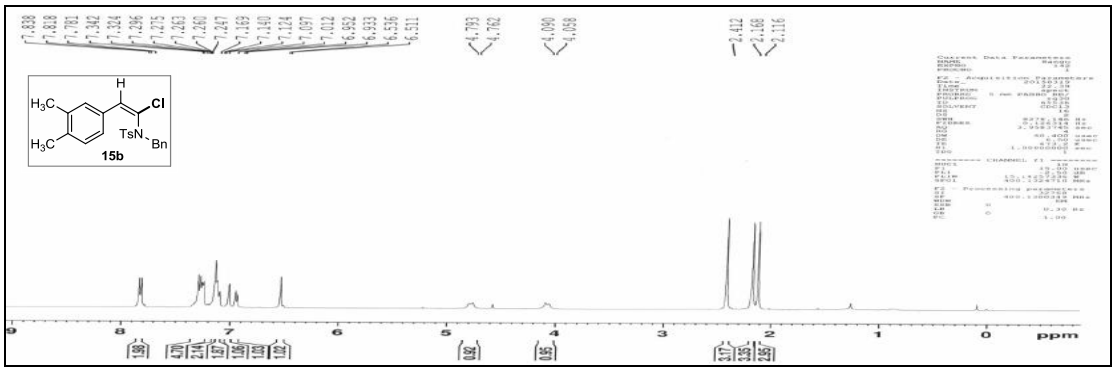
12. Maity, P.; Klos, M. R.; Kazmaier, U. *Org. Lett.* **2013**, *15*, 6246.

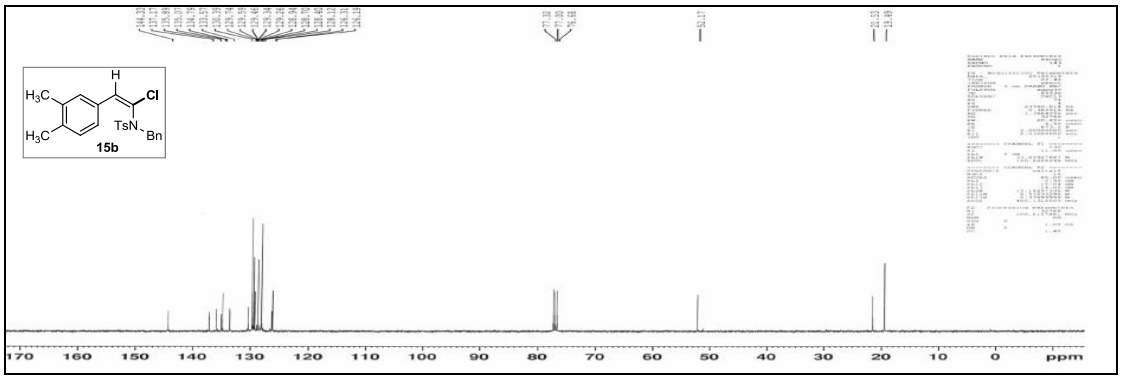
13. Akihiro, H. S.; Kazuhiro, O.; Iwasawa, T. *Tetrahedron Lett.* **2011**, *52*, 6671.

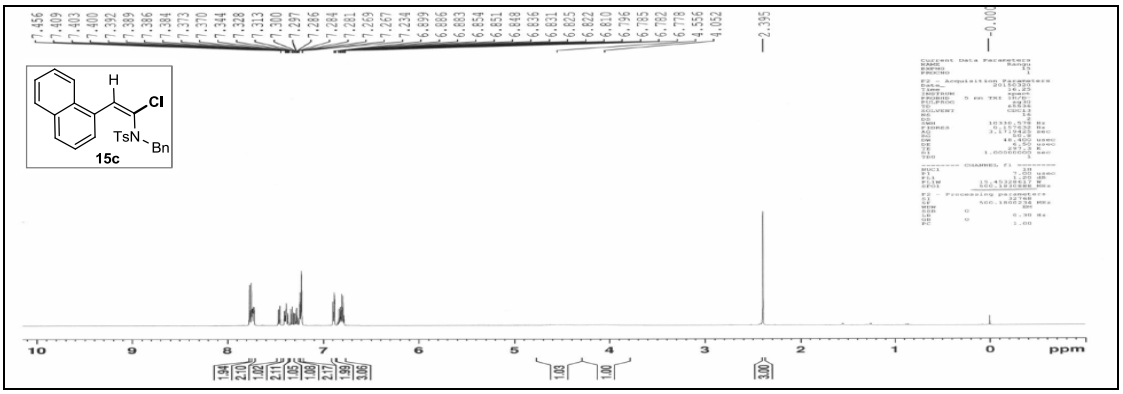
4.7. Spectra







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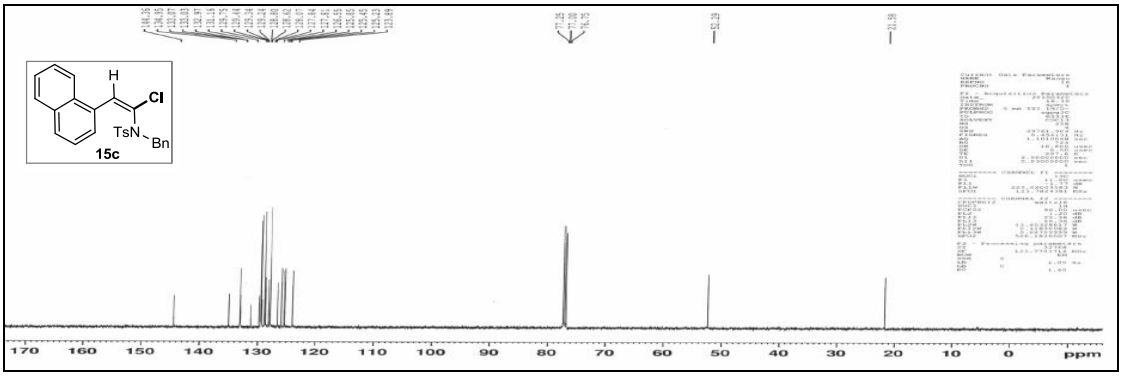
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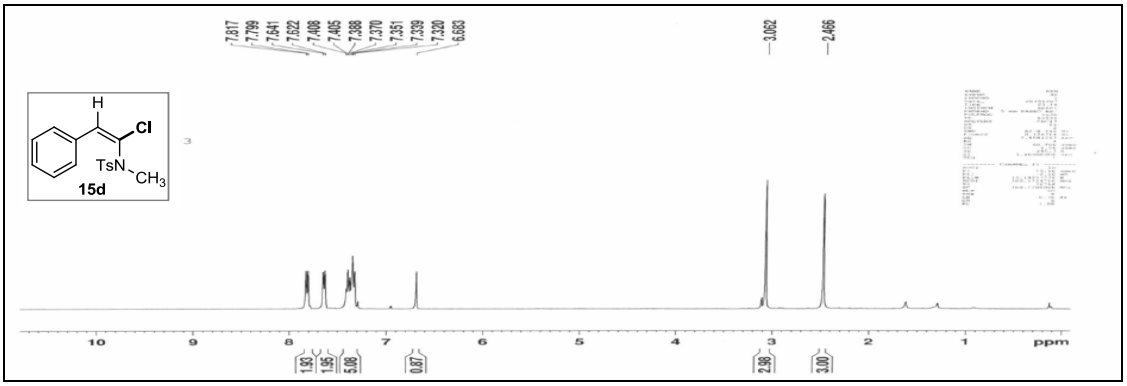
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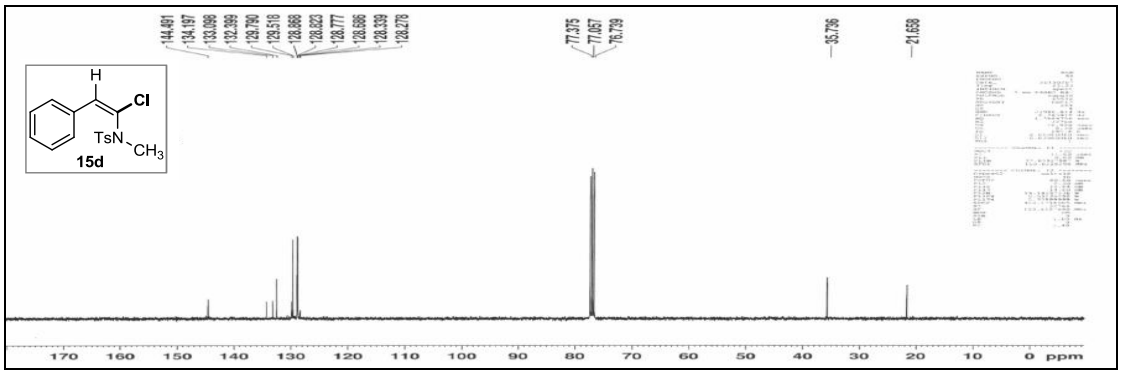
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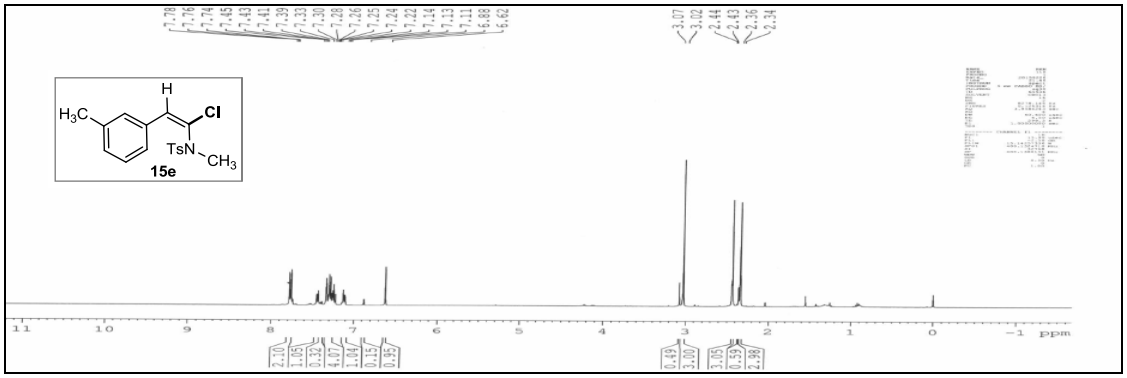
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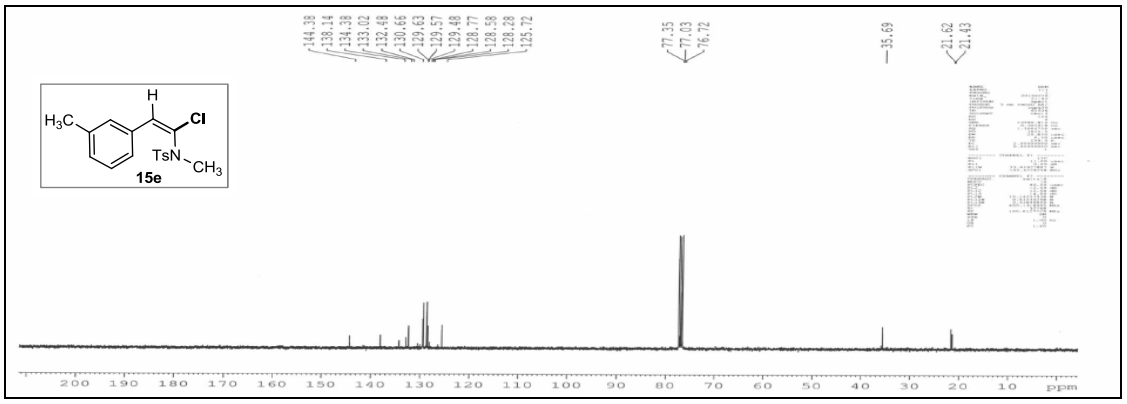
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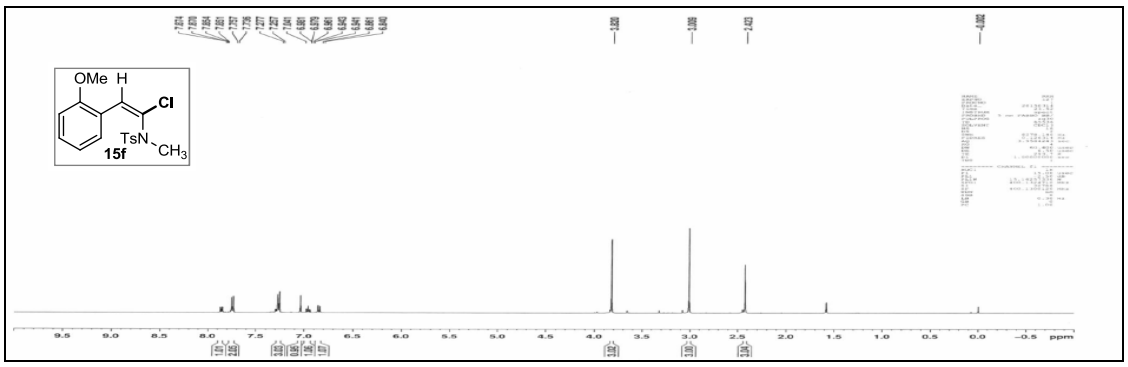
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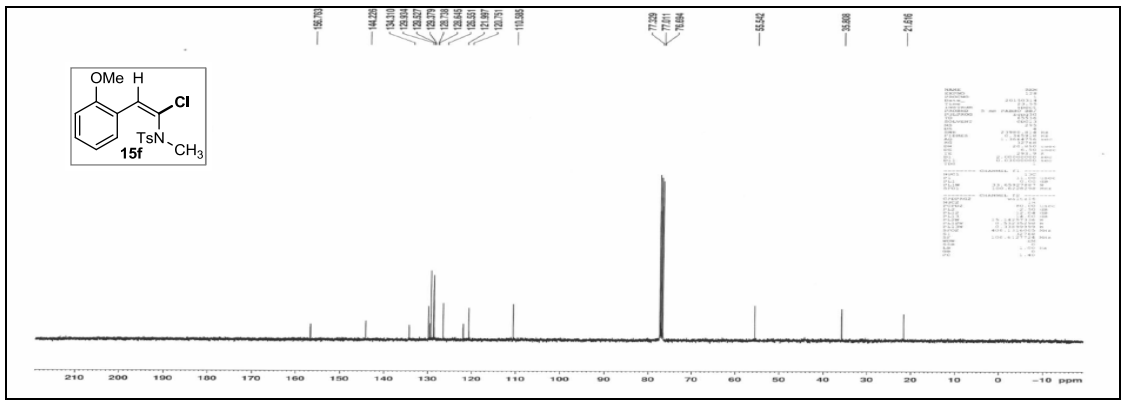
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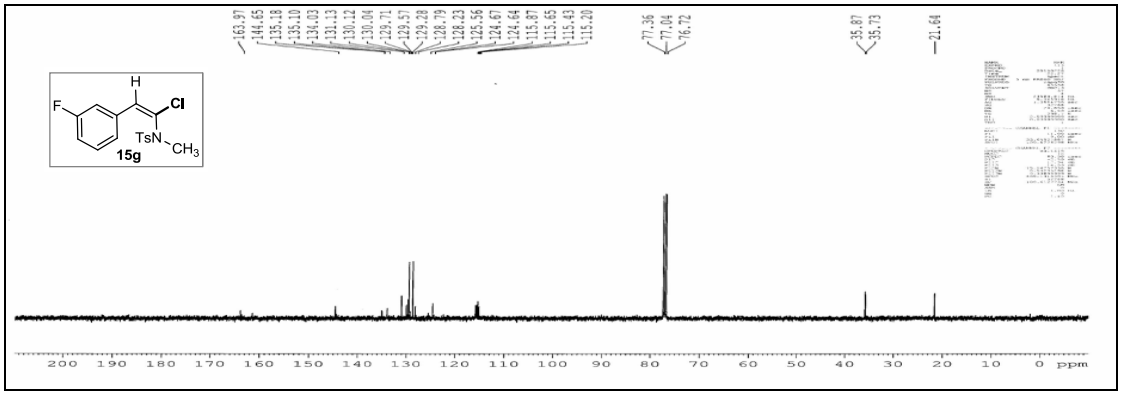
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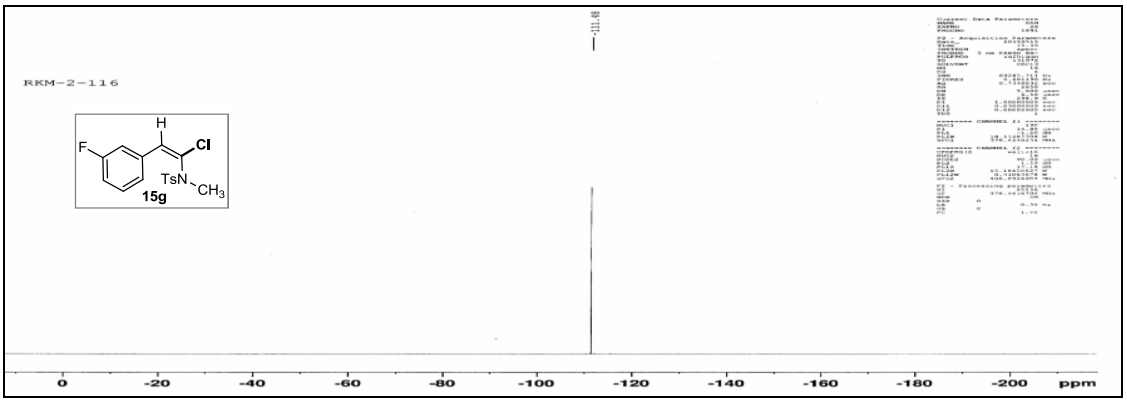
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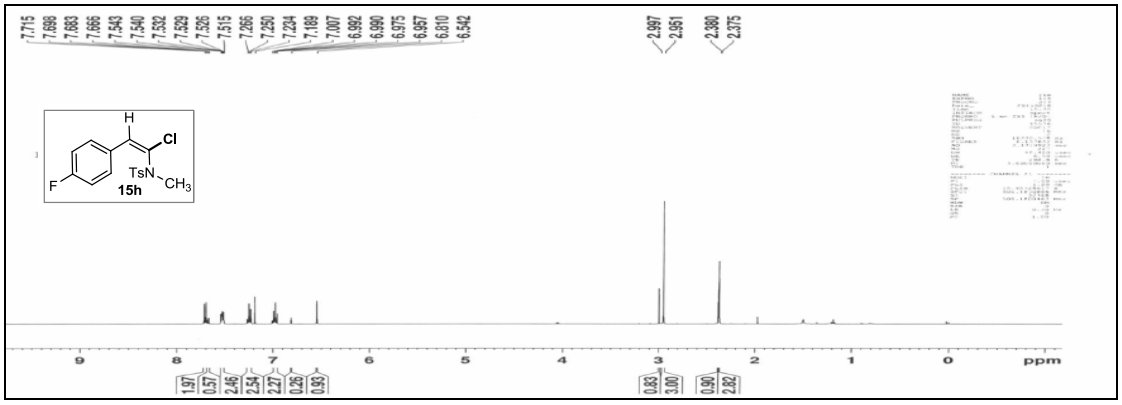
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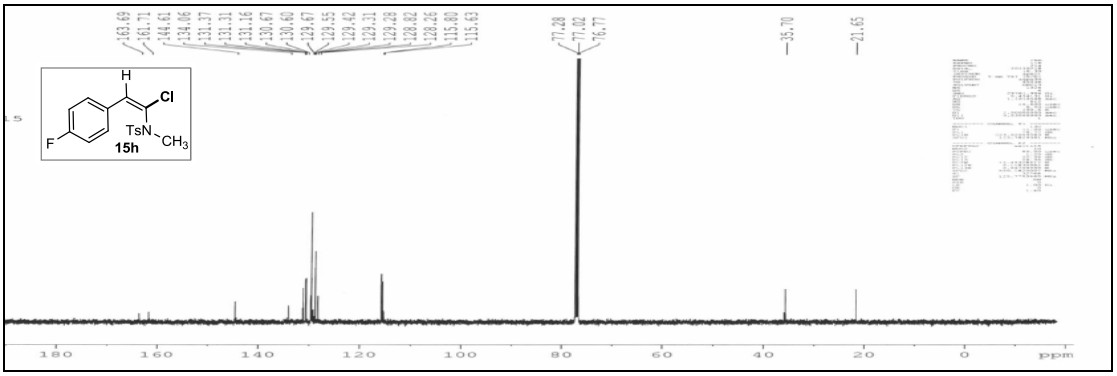
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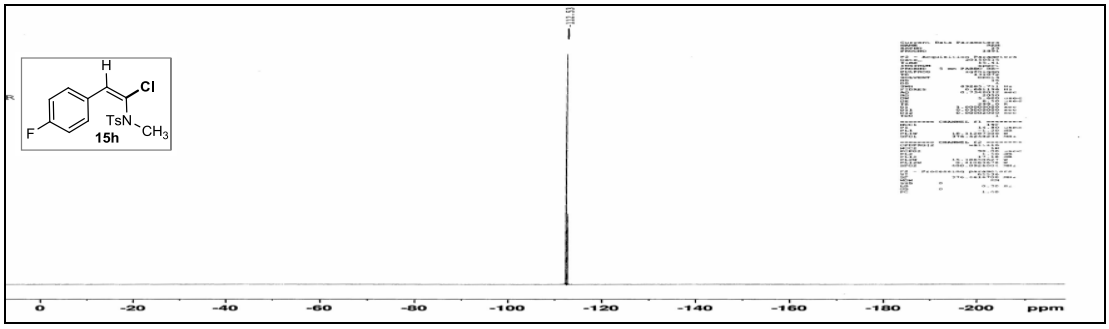
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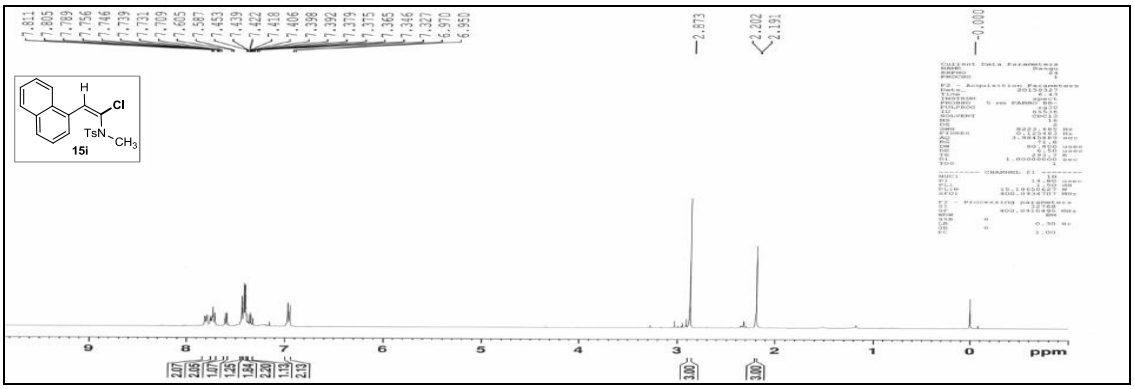
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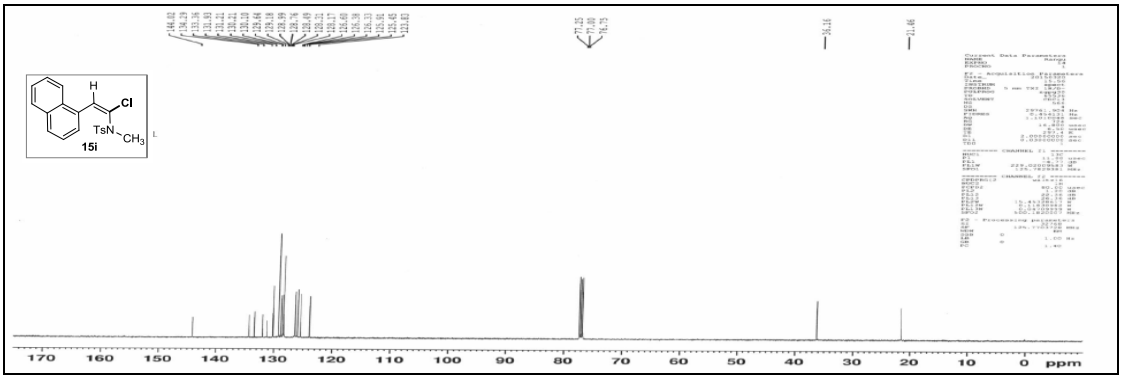
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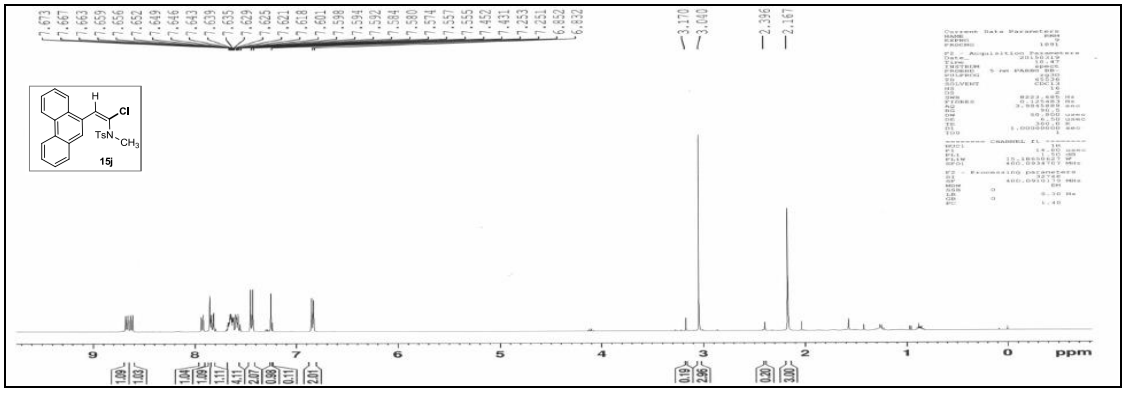
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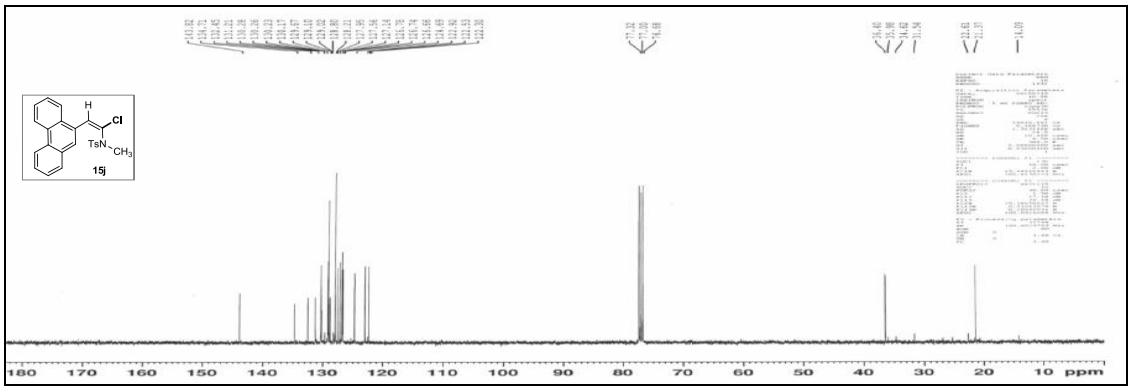
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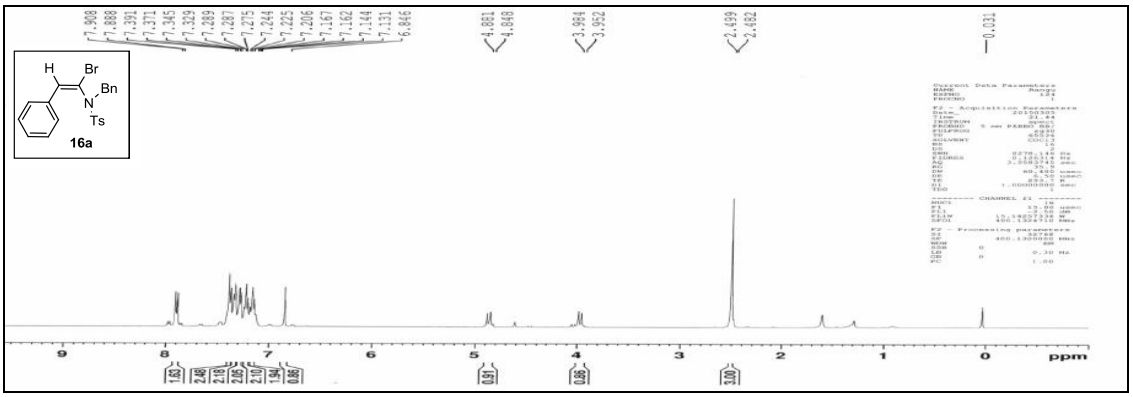
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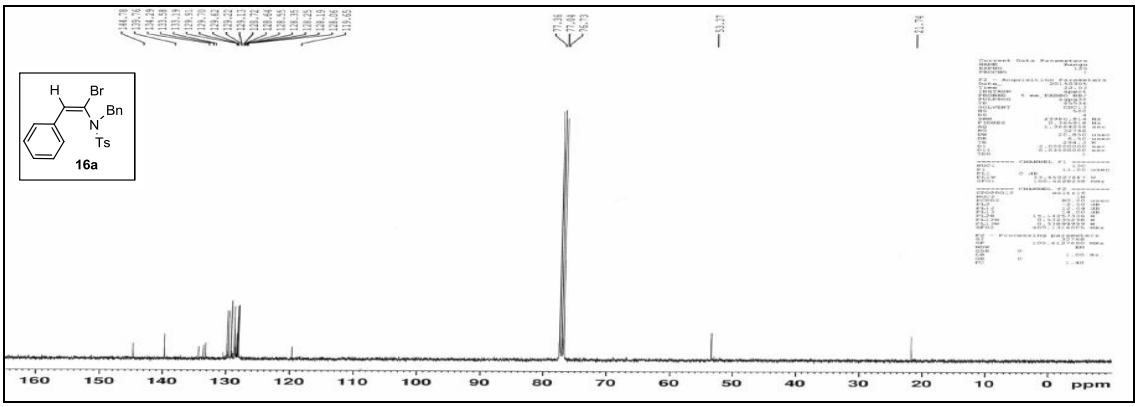
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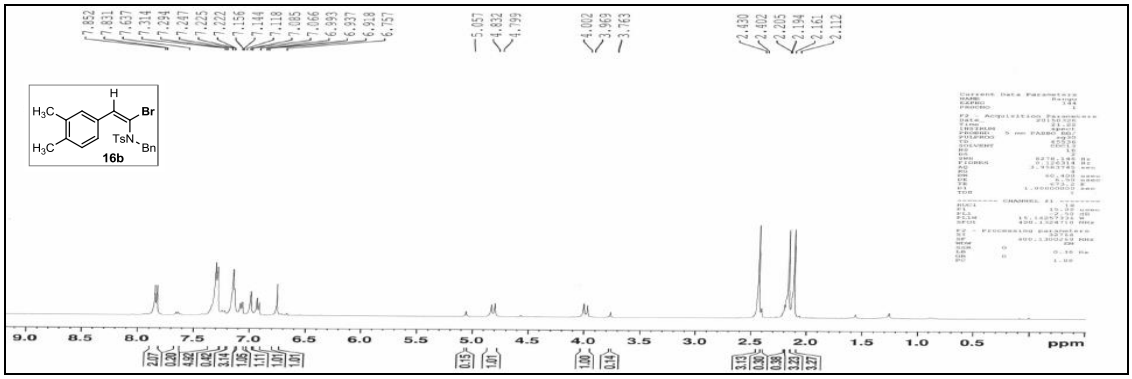
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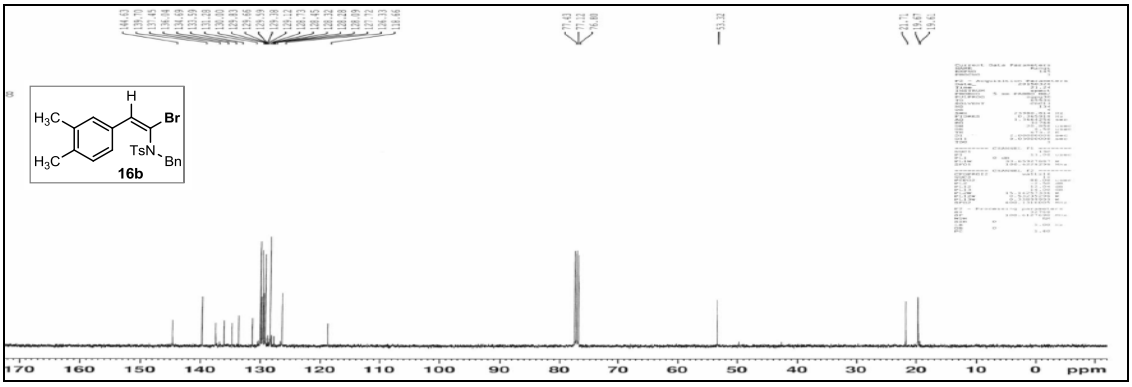
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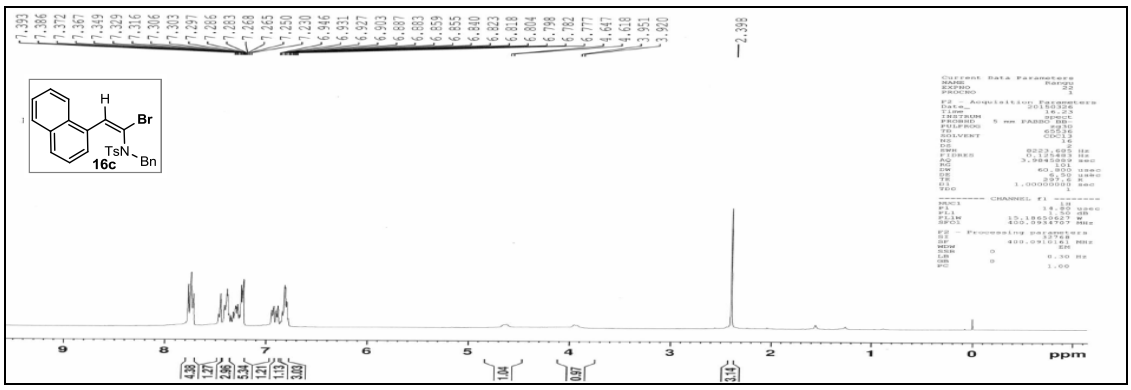
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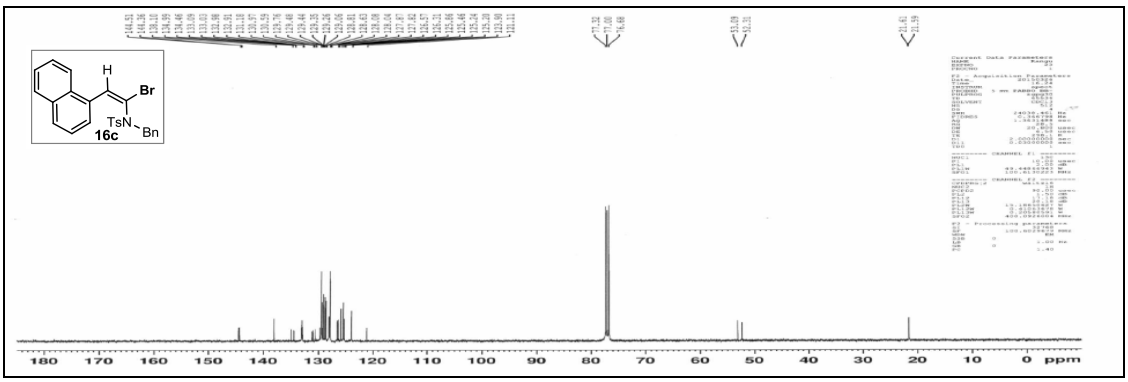
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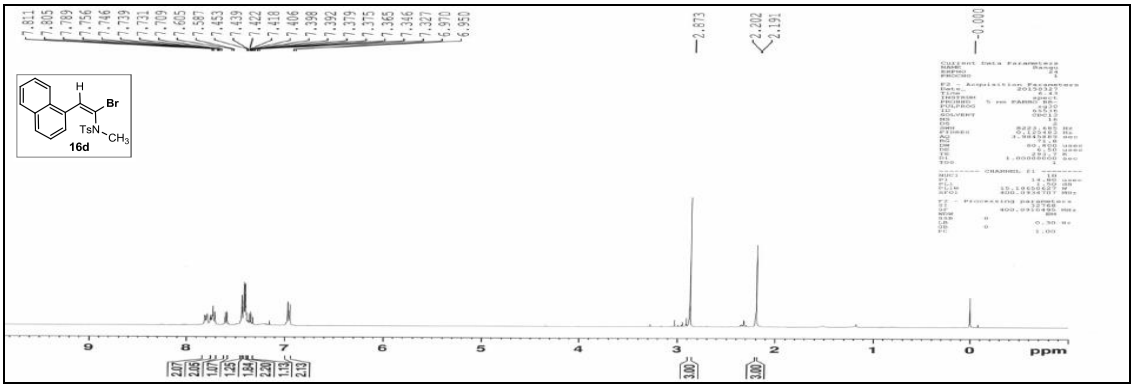
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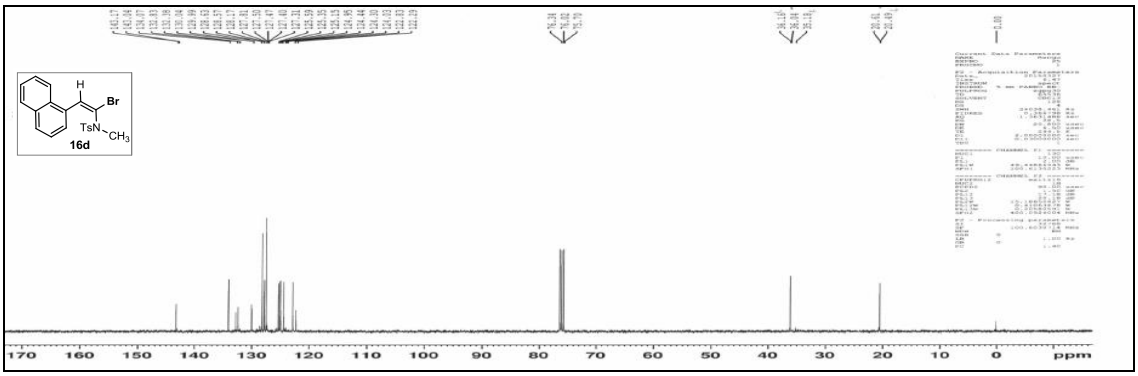
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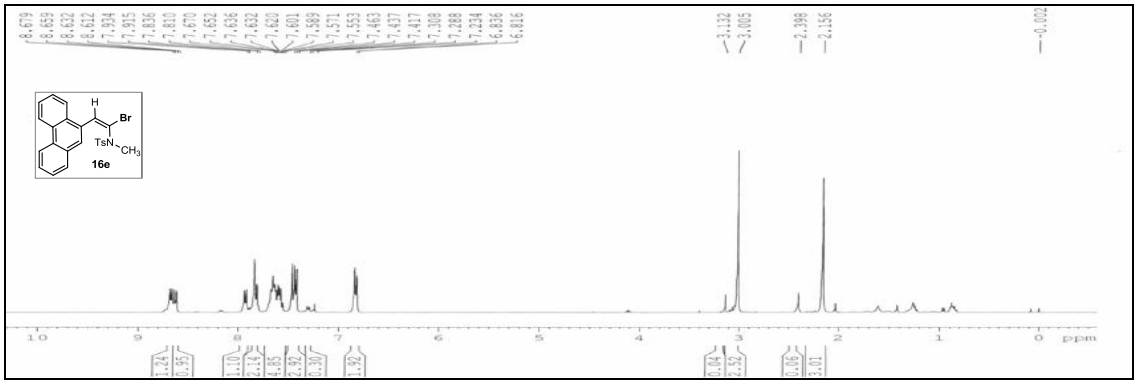
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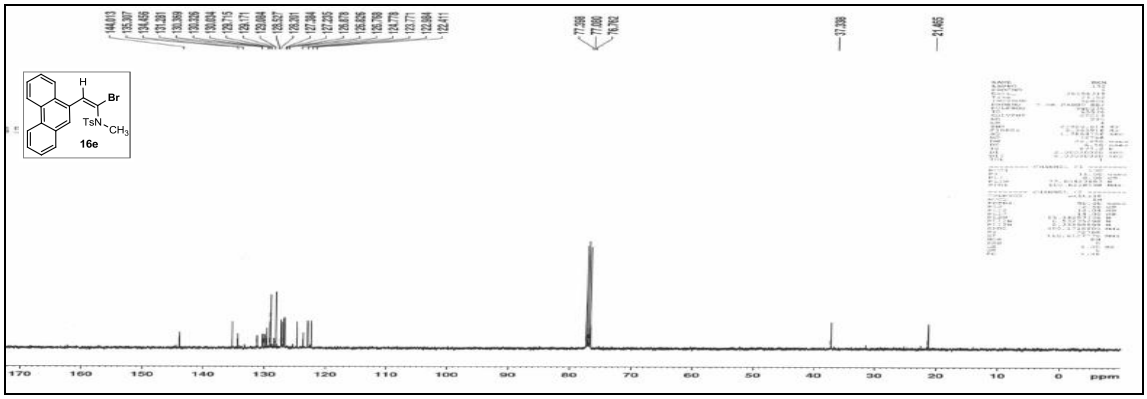
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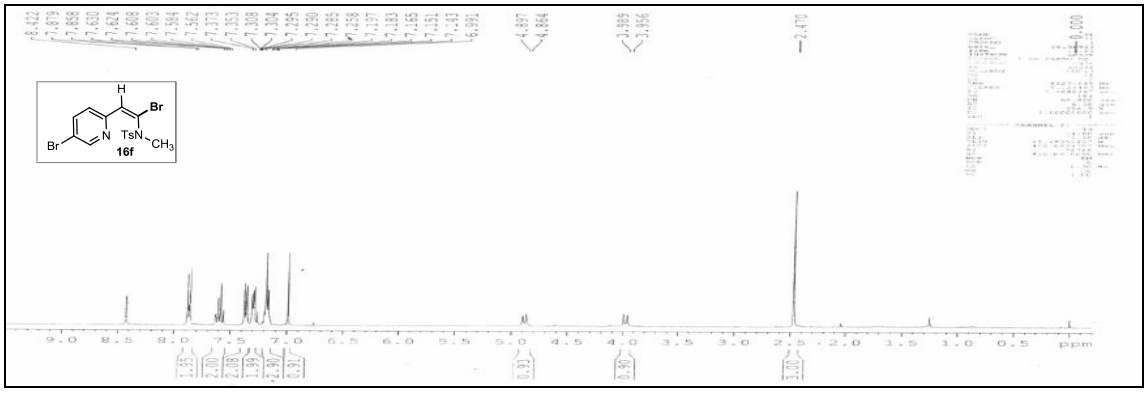
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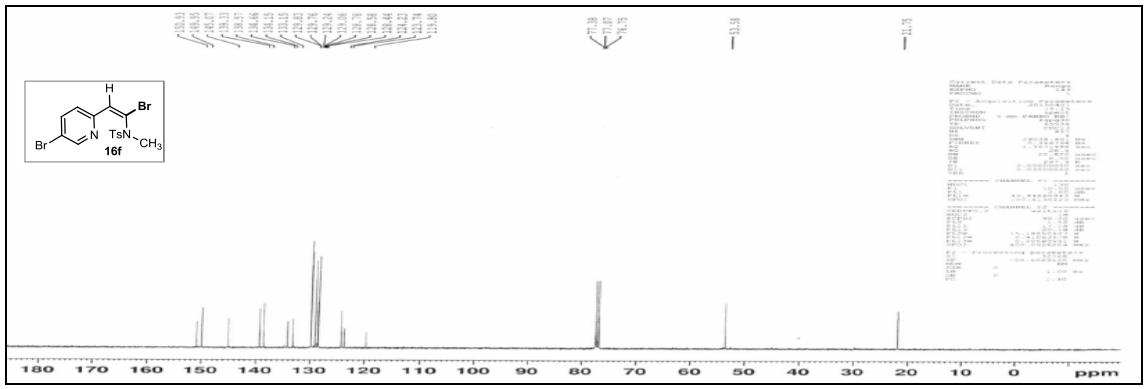
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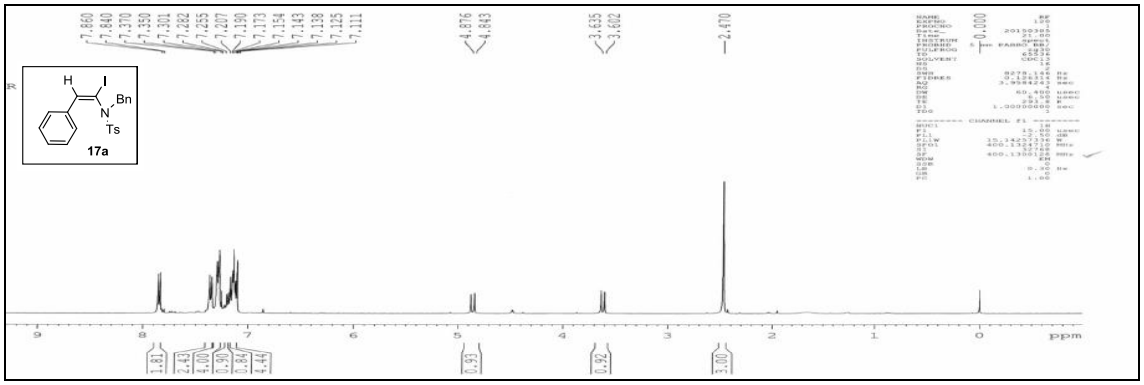
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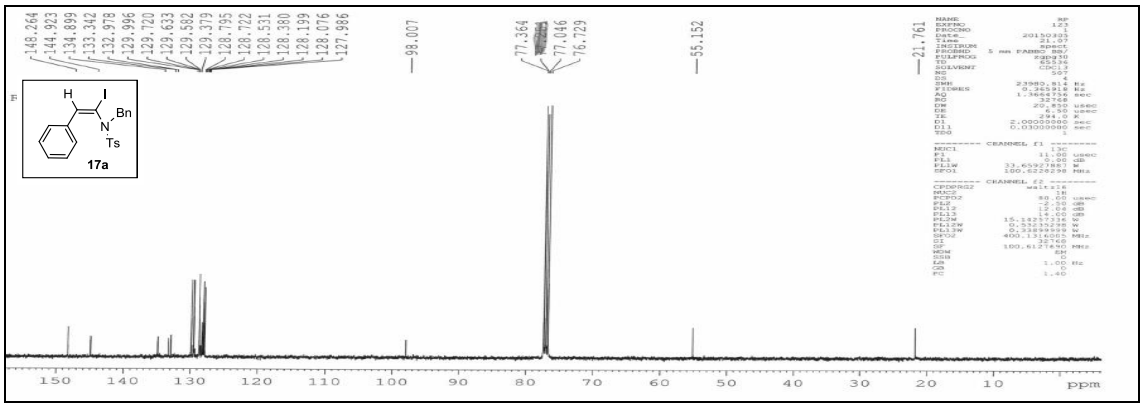
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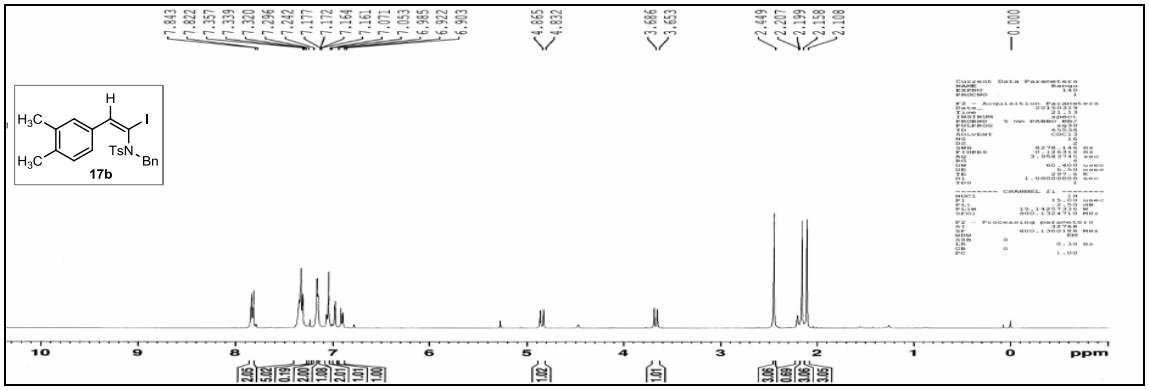
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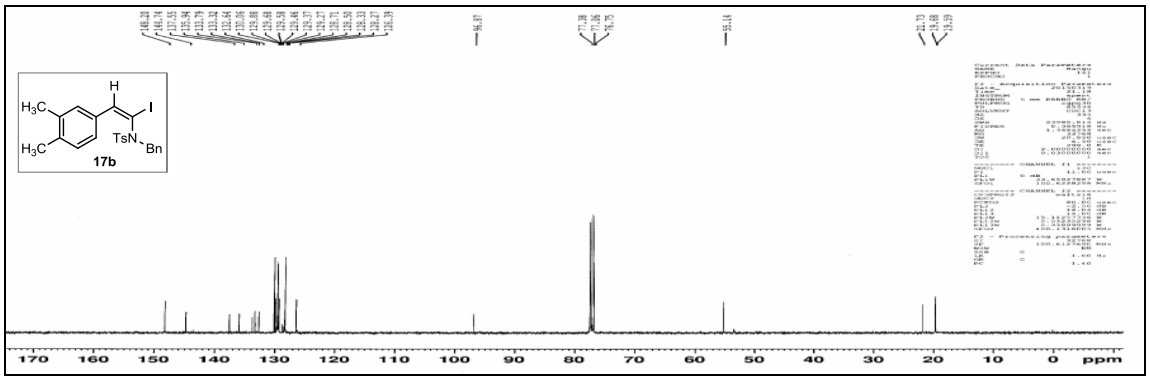
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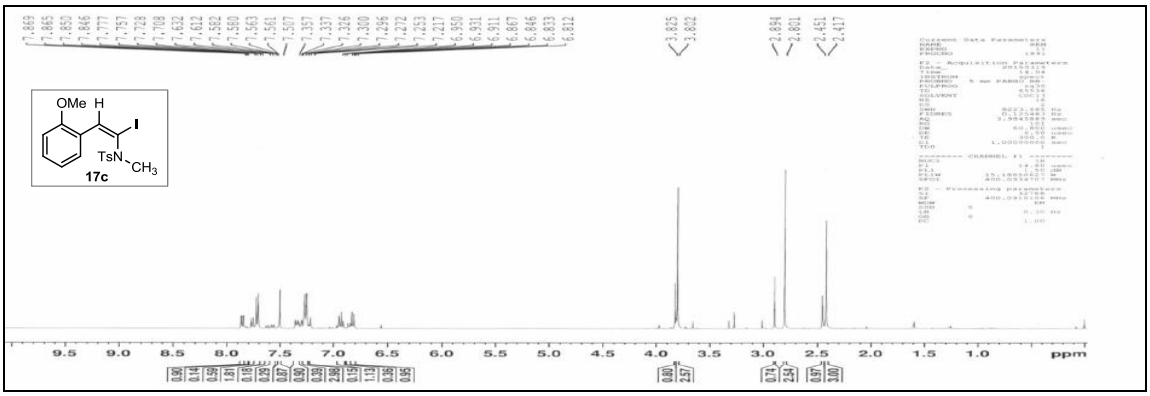
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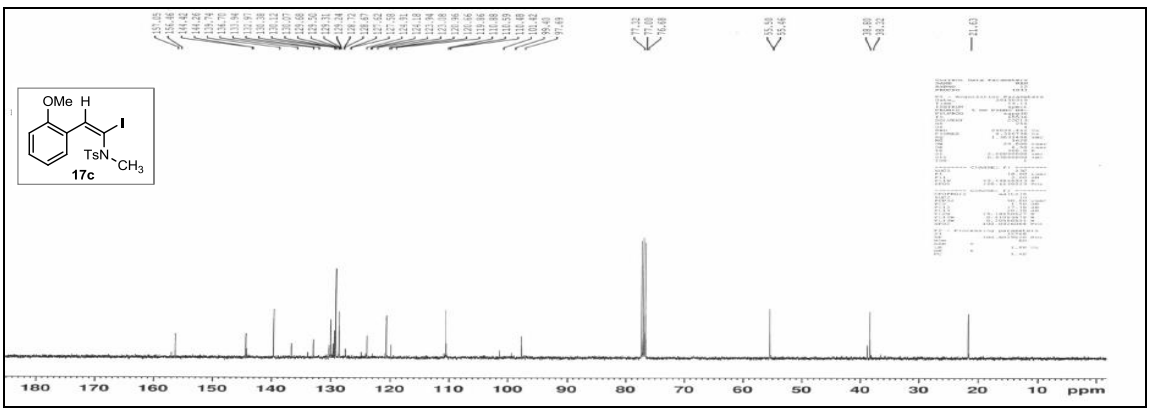
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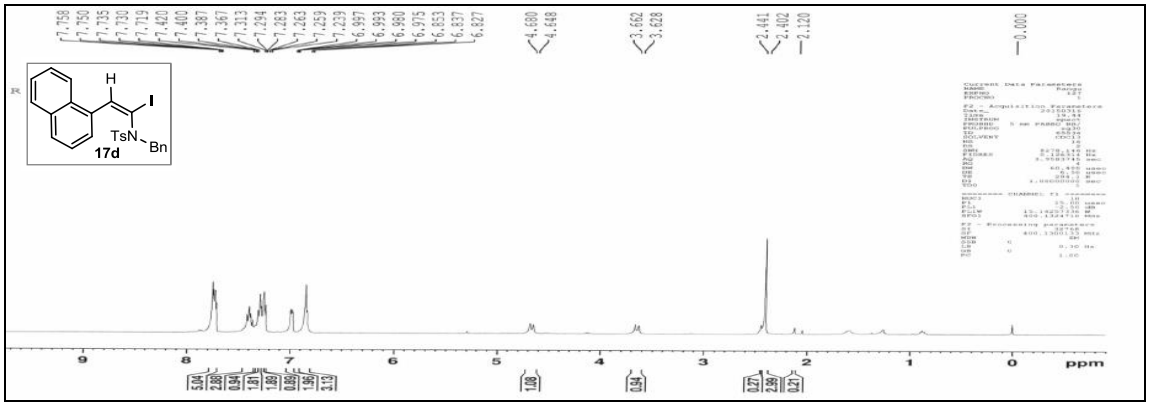
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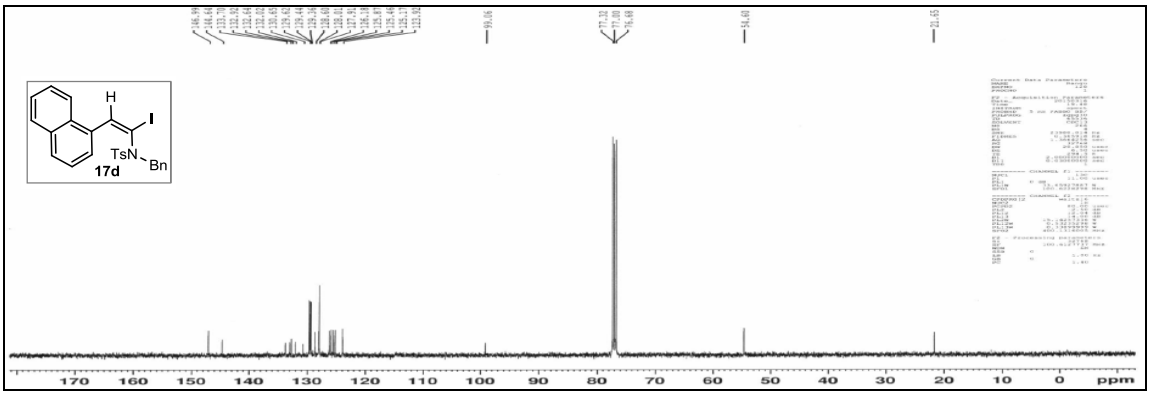
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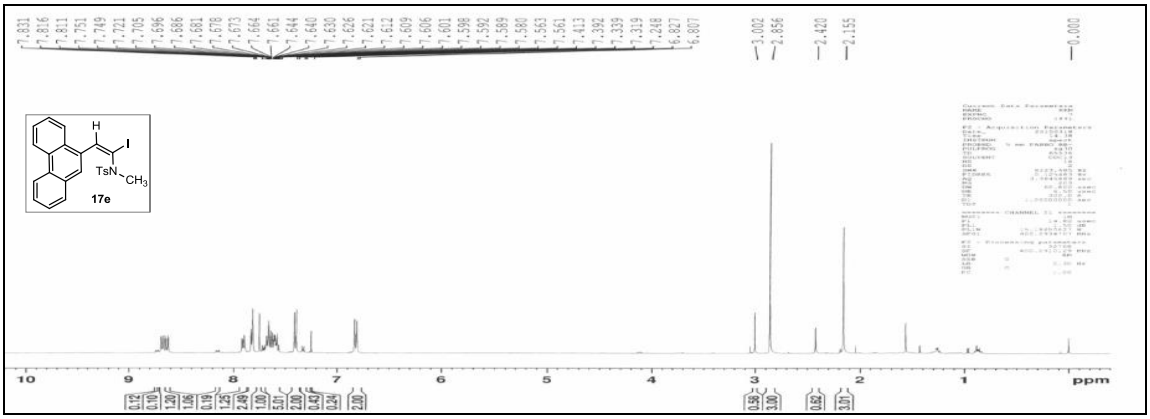
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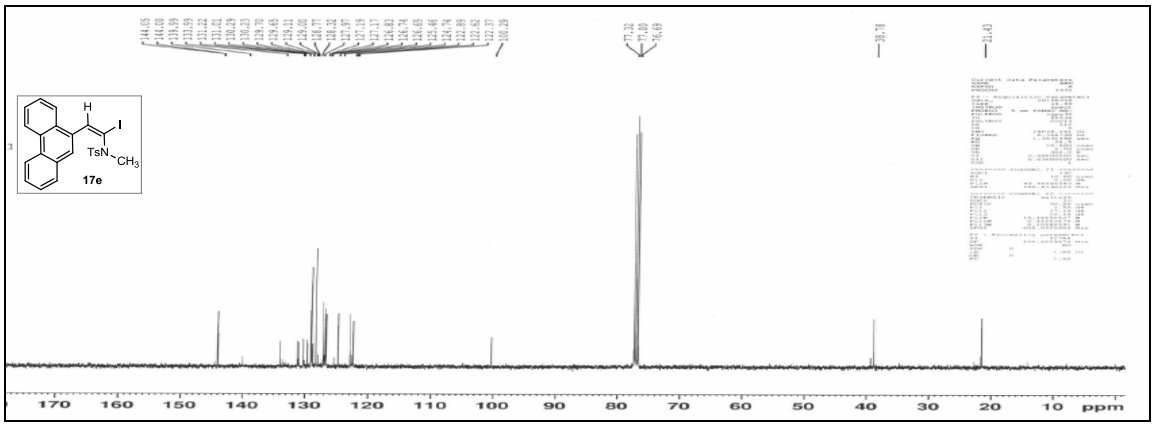
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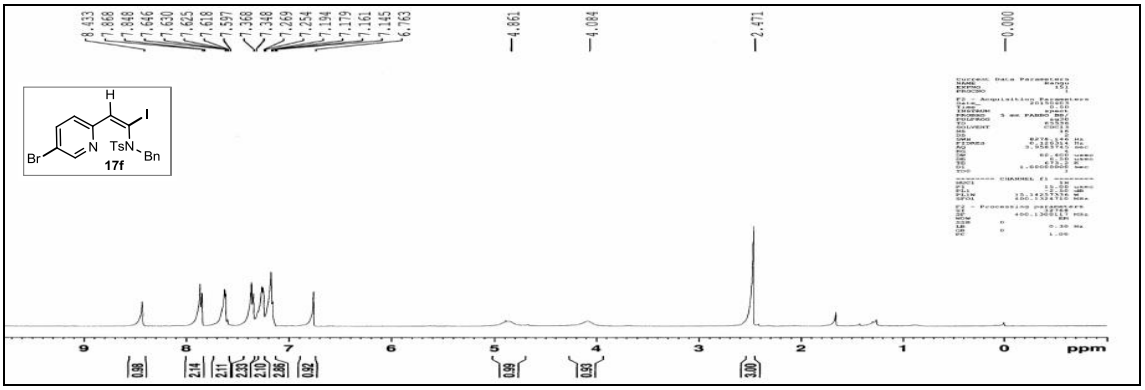
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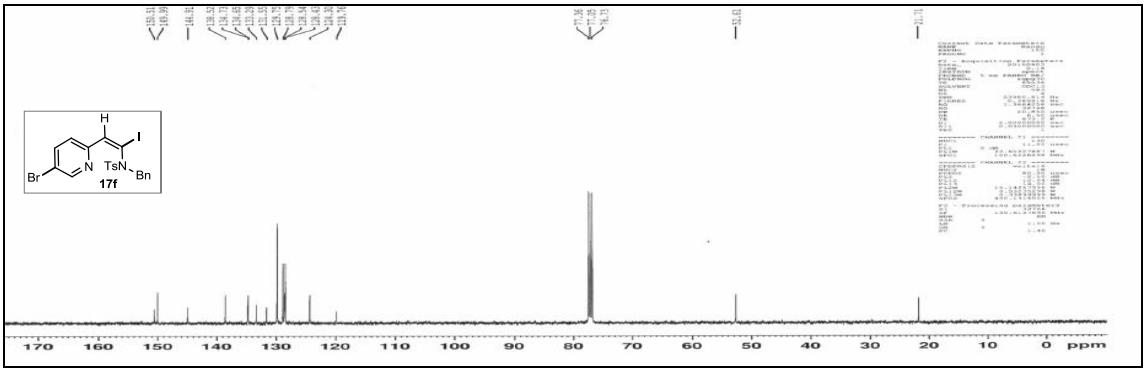
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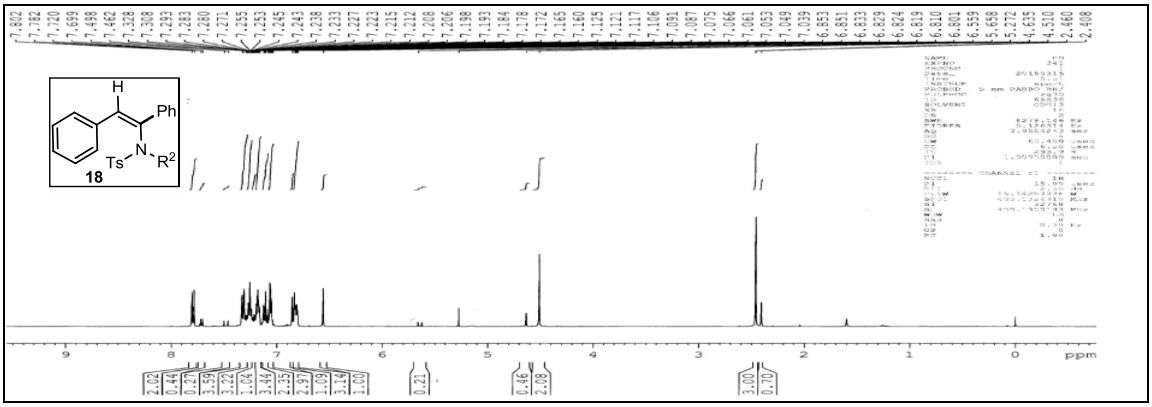
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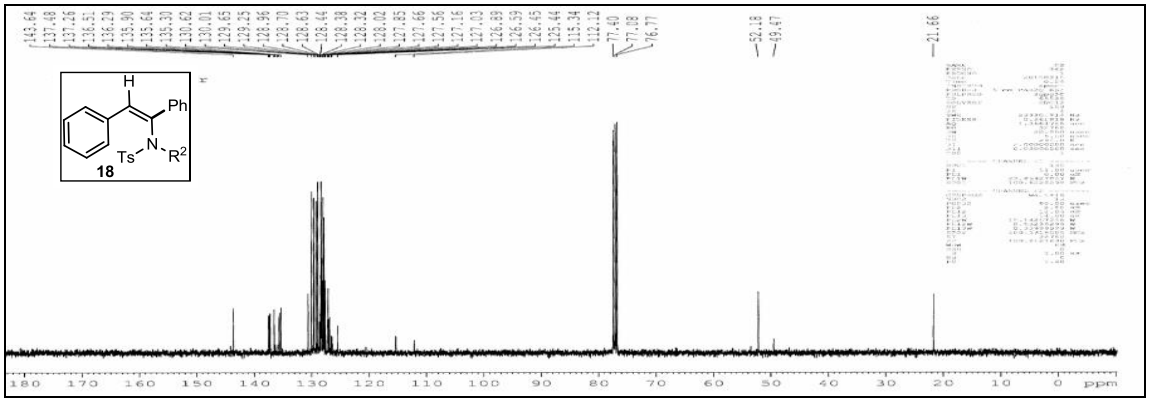
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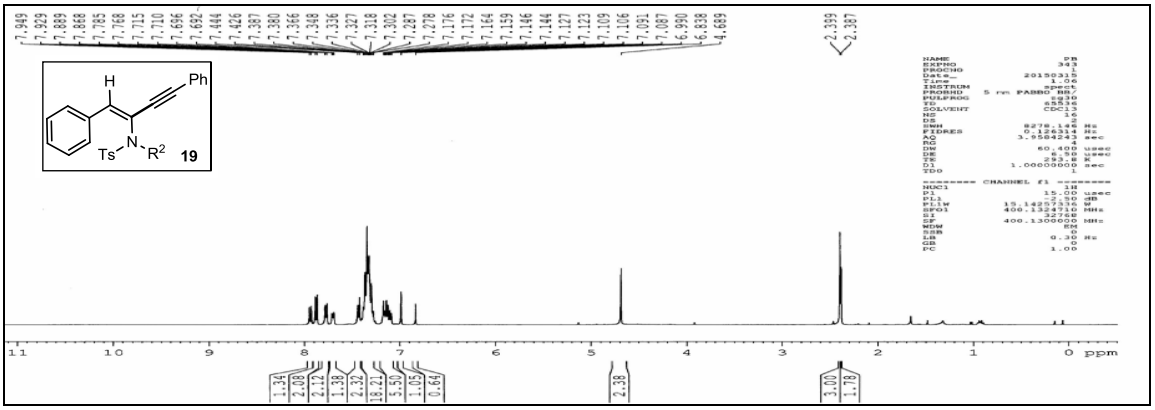
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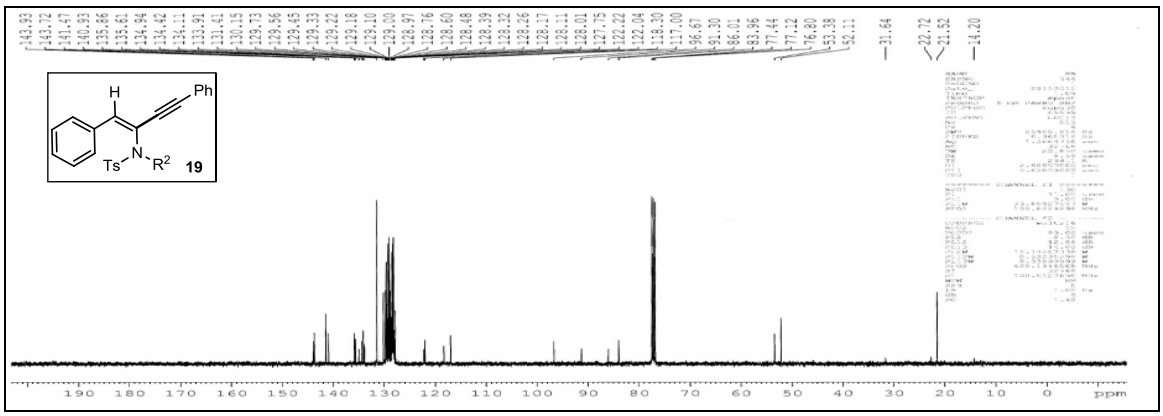
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List publications

1. Gold–Catalyzed Regioselective Hydration of Propargyl Acetates Assisted by Neighboring Carbonyl Group: Access to α–Acyloxy Methyl Ketones and Synthesis of Actinopolymorphol B. Nayan Ghosh, **Sanatan Nayak** and Akhila K. Sahoo. *J. Org. Chem.* **2011**, *76*, 500.

2. Gold (I)-Catalyzed 6-*endo*-dig Hydrative Cyclization of Alkyne-Tethered-Ynamide: Access to 1,6-Dihydropyridin-2(3*H*)-ones. Nayan Ghosh, **Sanatan Nayak** and Akhila K. Sahoo. *Chem. –Eur. J.* **2013**, *19*, 9428.

3. Synthesis of α-acyloxy-α′-halo ketones through gold-catalyzed hydration of halo-propargyl acetate" Nayan Ghosh, **Sanatan Nayak**, B Prabagar and Akhila K. Sahoo. *J. Org. Chem.* **2014**, *79*, 2453.

4. Access to Cyclobutene-fused Azepines through Au- Catalyzed Cycloisomerization of Stable Alkyne Tethered Ketene N,N-Acetals" **Sanatan Nayak**, Nayan Ghosh and Akhila K. Sahoo. *Org. Lett.* 2014, *16*, 1638.

5**.** Silver-Catalyzed Transformations of Ketene N,N-Acetals: Synthesis of Azepine and 1,2-Dihydropyridine Derivatives" **Sanatan Nayak,** Nayan Ghosh, and Akhila K. Sahoo. (Under preparation).

6. Bronsted acid promoted Au(I)-catalyzed consecutive *endo* cyclization of ynamide: Access to benzo fused dihydroisoquinolone" **Sanatan Nayak**, Nayan Ghosh, B Prabagar and Akhila K. Sahoo (submitted for Publication).

7**.** Sequential hydroarylation, and hydrative cyclization of ynamide towards fused N-heterocycles" B Prabagar, **Sanatan Nayak**, Nayan Ghosh, and Akhila K. Sahoo. (manuscript under preparation)

8. Phosphine mediated stereoselective synthesis of α-Haloenamides via a Mild and efficient α-addition of Ynamides. B Prabagar, **Sanatan Nayak**, Rajendra K. Malik, Rangu Prasad and Akhila K. Sahoo. (manuscript under preparation**).**

9. Cascade *all endo*-Cyclizataion and Cycloisomerisation to N-Heterocyles: Consequence of Ambivalent Ynamides" **Sanatan Nayak** and Akhila K. Sahoo. (Review under preparation)

Conference Attended

1. Access to Cyclobutene-fused Azepines through Au- Catalyzed Cycloisomerization of Stable Alkyne Tethered Ketene *N,N*-Acetals

   Sanatan Nayak, Nayan Ghosh and Akhila K. Sahoo

   (i) Oral presentation at "**9th J-NOST National Conference**", held at IISER Bhopal. Madhya Pradesh, India on December, 2013.

2. Brønsted Acid Promoted Au(I) Catalyzed Consecutive *endo* Cyclization of Ynamide: Access to Benzofused Dihydroisoquinolone

   Sanatan Nayak, Nayan Ghosh and Akhila K. Sahoo

   (i) Oral & poster presentation at **Recent Trends in Chemical Sciences (RTCS) Indo-Taiwan Symposium,** held at School of Chemistry, University of Hyderabad, AP, India on November, 2014.

3. Access to Cyclobutene-fused Azepines through Au- Catalyzed Cycloisomerization of Stable Alkyne Tethered Ketene *N,N*-Acetals

   Sanatan Nayak, Nayan Ghosh and Akhila K. Sahoo

   (i) Oral & poster presentation at **CHEM-FEST 2014**, held at School of Chemistry, University of Hyderabad, Hyderabad, AP, India on February, 2014.