METAL CATALYZED/MEDIATED TRANSFORMATIONS OF YNAMIDES: NEW APPROACHES TO BENZOSULTAMS AND ENAMIDES

A THESIS

SUBMITTED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

By

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UNIVERSITY OF HYDERABAD

HYDERABAD - 500 046

INDIA

JULY 2017

CONTENTS

STATEMENT

I hereby declare that the matter embodied in this thesis is the result of investigations carried out by me in the School of Chemistry, University of Hyderabad, Hyderabad, under the supervision of Prof. K. C. Kumara Swamy.

In keeping with the general practice of reporting scientific observations, due acknowledgements have been made wherever the work described is based on the findings of other investigators.

Hyderabad
July 2017

Alla Siva Reddy

DECLARATION

I, **ALLA SIVA REDDY** hereby declare that this thesis entitled "***Metal Catalyzed/Mediated Transformations of Ynamides: New Approaches to Benzosultams and Enamides***" submitted by me under the guidance and supervision of **Professor K. C. Kumara Swamy** is a bonafide research work which is also free from plagiarism. I also declare that it has not been submitted previously in part or in full to this University or any other University or Institution for the award of any degree or diploma. I hereby agree that my thesis can deposited in Shodganga/INFLIBNET.

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CERTIFICATE

This is to certify that the thesis entitled "***Metal Catalyzed/Mediated Transformations of Ynamides: New Approaches to Benzosultams and Enamides***" submitted by Mr. **Alla Siva Reddy** bearing registration number **12CHPH07** in partial fulfillment of the requirements for award of Doctor of Philosophy in the School of Chemistry is a bonafide work carried out by him under my supervision and guidance.

This thesis is free from plagiarism and has not been submitted previously in part or in full to this or any other University or Institution for award of any degree or diploma. Further the student has seven publications before the submission of his thesis.

Parts of this thesis have been published in the following five publications:

1. Siva Reddy, A.; Nagarjuna Reddy, M.; Kumara Swamy, K. C. *RSC Adv*. **2014**, *4*, 28359.
2. Siva Reddy, A.; Kumara Swamy, K. C. *Org. Lett*. **2015**, *17*, 2996.
3. Siva Reddy, A.; Leela Siva Kumari, A.; Saha, S.; Kumara Swamy, K. C. *Adv. Synth. Catal*. **2016**, *358*, 1625.
4. Siva Reddy, A.; Leela Siva Kumari, A.; Kumara Swamy, K. C. *Tetrahedron* **2017**, *73*, 2766.
5. Siva Reddy, A.; Kumara Swamy, K. C. *Angew. Chem., Int. Ed.* **2017**, *56*, 6984.

He has also made presentations in the following conferences:

1. Poster presentation in the *Recent Trends in Chemical Sciences (RTCS)-2014*, University of Hyderabad, Hyderabad, INDIA, Nov-**2014**.
2. Poster presentation in the *Chemfest-2015* (annual in-house symposium), School of Chemistry, University of Hyderabad, INDIA, Feb-**2015**.
3. Oral and Poster presentation in the *Chemfest-2016* (annual in-house symposium), School of Chemistry, University of Hyderabad, INDIA, Mar-**2016**.
4. Oral and Poster presentation in the *XIIth J-NOST Conference for Research Scholars*, CSIR-CDRI, Lucknow, INDIA, Nov-**2016**.

Further the student has passed the following courses towards fulfillment of coursework requirement for Ph. D.:

Course	Title	Credits	Pass/Fail
1. CY-801	Research Proposal	3	Pass
2. CY-805	Instrumental Methods A	3	Pass
3. CY-806	Instrumental Methods B	3	Pass
4. CY-821	Organic Reactions and Mechanisms	3	Pass

Hyderabad
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Alla Siva Reddy... 

LIST OF PUBLICATIONS

1. A simple copper-catalysed tandem cyclisation of ynamides leading to triazolo-1,2,4-benzothiadiazine-1,1-dioxides in PEG-400 medium
   Alla Siva Reddy, M. Nagarjuna Reddy and K. C. Kumara Swamy*
   RSC Adv. **2014**, *4*, 28359.

2. Use of Elemental Sulfur or Selenium in a Novel One-Pot Copper-Catalyzed Tandem-Cyclization of Functionalized Ynamides Leading to Benzosultams
   Alla Siva Reddy and K. C. Kumara Swamy*
   Org. Lett. **2015**, *17*, 2996.

3. Palladium-Catalyzed Tandem-Cyclization of Functionalized Ynamides: An Approach to Benzosultams
   Alla Siva Reddy, A. Leela Siva Kumari, Soumen Saha and K. C. Kumara Swamy*
   Adv. Synth. Catal. **2016**, *358*, 1625.

4. Palladium-catalyzed regioselective synthesis of benzosultams from functionalized ynamides and benzotriazoles/tetrazoles
   Alla Siva Reddy, A. Leela Siva Kumari and K. C. Kumara Swamy*
   Tetrahedron **2017**, *73*, 2766.

5. Ethanol as a Hydrogenating Agent: Palladium-Catalyzed Stereoselective Hydrogenation of Ynamides to Give Enamides
   Alla Siva Reddy and K. C. Kumara Swamy*
   Angew. Chem., Int. Ed. **2017**, *56*, 6984.

6. $AlCl_3$ as a regio- and stereo-specific hydrochlorinating agent for the ynamides
   Alla Siva Reddy and K. C. Kumara Swamy*
   (to be communicated).

7. Exploring the gold mine- [Au]-catalyzed transformations of enynals, enynones and enynols

A. Leela Siva Kumari, **Alla Siva Reddy** and K. C. Kumara Swamy*
Org. Biomol. Chem. **2016**, *14*, 6651.

8. Transition Metal-Free Cascade Cyclization of Epoxy-Ynamides: To Go for 1,3-Oxazines or 1,4-Oxazines?
A. Leela Siva Kumari, **Alla Siva Reddy** and K. C. Kumara Swamy*
Org. Lett. **2016**, *18*, 5752.

9. [Cu]-catalyzed cyclization of sulfonamides with isothiocyanates/ isocyanates leading to benzosultams
K. Sandeep, **Alla Siva Reddy** and K. C. Kumara Swamy
(*to be communicated*)

10. One-pot copper-catalyzed cyclization of functionalized alkynes using elemental sulfur or selenium
D. Gattaiah, **Alla Siva Reddy** and K. C. Kumara Swamy
(*to be communicated*)

Posters presented in symposia

1. A simple copper-catalysed tandem cyclisation of ynamides leading to triazolo-1,2,4-benzothiadiazine-1,1-dioxides in PEG-400 medium
   Alla Siva Reddy and K. C. Kumara Swamy*
   Recent Trends in Chemical Sciences (RTCS)-2014, University of Hyderabad, Hyderabad, INDIA, Nov-**2014** (**Poster Presentation**).

2. A simple copper-catalysed tandem cyclisation of ynamides leading to triazolo-1,2,4-benzothiadiazine-1,1-dioxides in PEG-400 medium
   Alla Siva Reddy and K. C. Kumara Swamy*
   Chemfest-2015 (annual in-house symposium), School of Chemistry, University of Hyderabad, INDIA, Feb-**2015** (**Poster Presentation**).

3. Use of Elemental Sulfur or Selenium in a Novel One-Pot Copper-Catalyzed Tandem-Cyclization of Functionalized Ynamides Leading to Benzosultams
   Alla Siva Reddy and K. C. Kumara Swamy*
   Chemfest-2016 (annual in-house symposium), School of Chemistry, University of Hyderabad, INDIA, Mar-**2016** (**Poster & Oral Presentation**).

4. Use of Elemental Sulfur or Selenium in a Novel One-Pot Copper-Catalyzed Tandem-Cyclization of Functionalized Ynamides Leading to Benzosultams
   Alla Siva Reddy and K. C. Kumara Swamy*
   XIIth J-NOST Conference for Research Scholars, CSIR-CDRI, Lucknow, INDIA, Nov-**2016** (**Oral Presentation**).

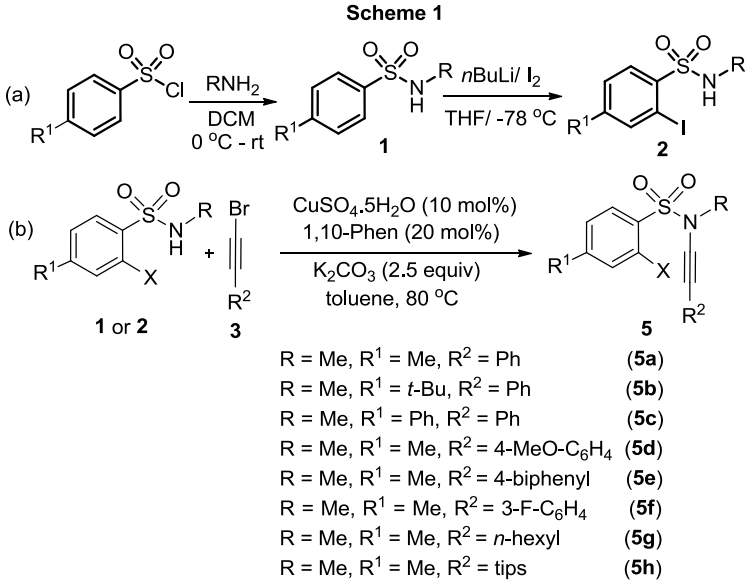
5. Probing Allene/ Alkyne Chemistry: Some New Results
   K. C. Kumara Swamy,*__Alla Siva Reddy__ and M. Nagarjuna Reddy
   National Symposium on Sustainable Chemistry Frontiers & Challenges (SCFC)-2014, North-Eastern Hill University, Shillong, INDIA, Feb-**2014** (**Invited Lecture**).

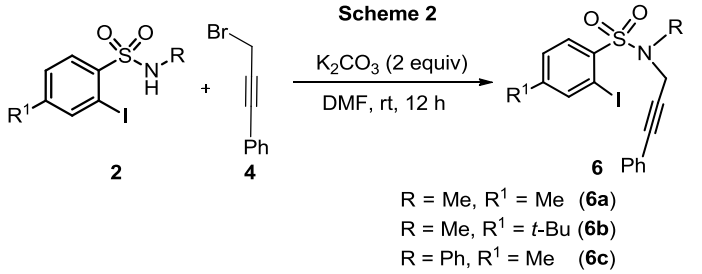
6. New Catalytic and Noncatalytic Transformations Involving Allenes/Alkynes/Ynamides and Indoles.
   K. C. Kumara Swamy,*Mandala Anitha, **Alla Siva Reddy**, A. Leela Siva Kumari and R. N. Prasad Tulichala
   6th International Collaborative and Cooperative Chemistry Symposium (ICCCS-6)-2015, Seoul National University, Seoul, Korea, Nov-**2015**.

Synopsis

This thesis deals mainly with the following topics: (i) one-pot synthesis of fused triazolo 1,2,4-benzothiadiazine-1,1-dioxides under green conditions by using functionalized ynamides and sodium azide *via* [Cu]-catalyzed intermolecular C–N bond formation and subsequent click reaction, (ii) a novel method for the regio- and stereospecific synthesis of benzo[1,4,2]dithiazine 1,1-dioxides and benzo[1,4,2]thiaselenazine 1,1-dioxides by the copper catalyzed tandem cyclization of ynamides with elemental sulfur or selenium and (iii) a new approach to hetero-substituted benzosultams by the tandem cyclization of ynamides with various nucleophiles under [Pd]-catalysis is described. In addition, two more systems that involve (i) ethanol or synergistic ethanol/ammonium formate system as a hydrogenating source for the selective hydrogenation of ynamides under [Pd]-catalysis leading to enamides, and (ii) stereo-specific hydro-chlorination of ynamides leading to α-chloro enamides using aluminium chloride, are also described. The thesis divided into three chapters: Introduction (Chapter 1; literature survey), Results and Discussion (Chapter 2) and Experimental Section (Chapter 3). The compounds synthesized in the present study are, in general, characterized by mp, IR and NMR (^{1}H, ^{13}C{^{1}H}, ^{31}P{^{1}H} and ^{77}Se as applicable) techniques in conjunction with LC-MS/ HRMS/ elemental analyses. X-ray structure determination has been undertaken wherever required. Summary as well as references are given at the end of the second and third chapters respectively.

Prominent results of the thesis are outlined here. The precursors used in the present study are shown in Schemes 1 and 2 [*Note*: The numbering of compounds given here is different from that in the main part of the thesis]. They are prepared by methodologies available (with modifications where necessary) in the literature.





Alkynes have been used extensively in numerous organic transformations to synthesize pharmaceutically useful molecules and natural products. Ynamides as an important class of alkynes with the triple bond directly attached to a nitrogen atom have also emerged as important synthons. In a significant number of cases, sulfonamide based ynamides have been chosen as the substrates of choice because of their stability and reactivity. The "predictable regio- and stereo-selective" transformations of these precursors are mainly because of the polarization of the alkyne moiety by the nitrogen atom attached to them or due to possible chelation of transition metal with the alkyne and in a few cases, to the heteroatom of the electron withdrawing group (Fig. 1).

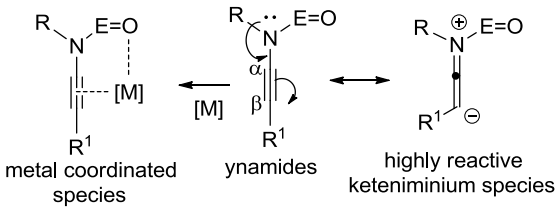


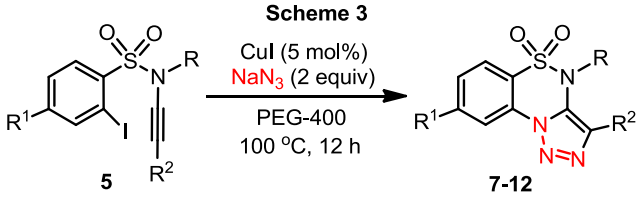
Fig.1. A drawing showing possible reactive sites in ynamides

The cyclic counterparts of sulfonamides, sultams, also exhibit significant biological activities. Hence we have developed a new strategy for the synthesis of benzosultams using ynamide precursors as described below. In addition, we have also discovered that ethanol itself can act as a hydrogenating agent for ynamides, leading to enamides stereoselectively. This aspect as well as stereospecific hydrochlorination of ynamides is also included herein.

(i) [Cu]-catalyzed synthesis of triazolo fused benzosultams from ynamides

The 1,2,3-triazole fused benzosultams **7-12** were obtained by treating functionalized ynamides **5** with sodium azide in the presence of [Cu]-catalyst under environmentally benign PEG-400 solvent (Scheme 3). This method involves the overall formation of three new bonds [two C-N; one C-C] in one-pot by the copper-catalyzed intermolecular C-N bond formation followed by [3+2] cycloaddition between the alkyne and the azide.

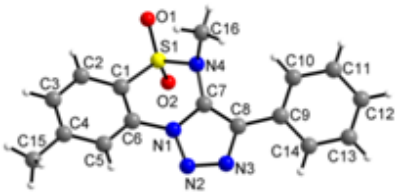
Scheme 3



5 **7-12**

R = Me, R^1 = Me, R^2 = Ph	**7** (78%, **X-ray**)
R = Me, R^1 = ^{t}Bu, R^2 =Ph	**8** (84%)
R = Me, R^1 = Ph, R^2 = Ph	**9** (78%)
R = Me, R^1 = Me, R^2 = H	**10** (80%, **X-ray**)
R = Me, R^1 = Me, R^2 = 3-F-C_6H_4	**11** (62%)
R = Me, R^1 = Me, R^2 = *n*-hexyl	**12** (72%)

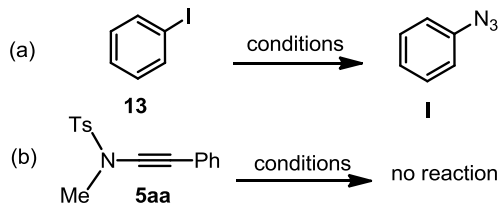
(more examples)



Compound **7**

To explain the mechanistic pathway, we have performed some control experiments. We isolated phenyl azide **I** by the reaction of phenyl iodide **13** with NaN_3. There was no reaction between ynamide **5aa** and NaN_3 (Scheme 4a-b). These control experiments and the available literature suggest that this [Cu]-catalyzed reaction proceeds *via* intermolecular C-N bond formation and subsequent cycloaddition between the alkyne and sodium azide leading to triazolo fused benzosultams.

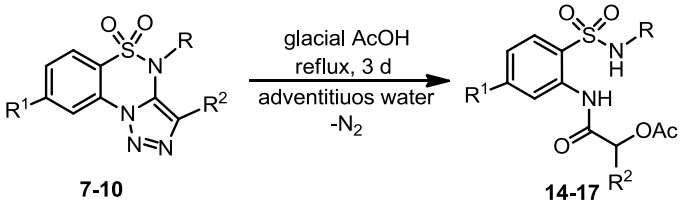
Scheme 4



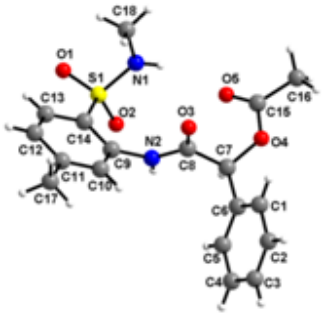
conditions: CuI (5 mol%), NaN_3 (2 equiv), PEG-400 (1 mL), 100 ^oC.

Interestingly, the triazole ring in triazolo-1,2,4-benzothiadiazine-1,1-dioxide can be readily decyclized in the presence of glacial acetic acid with the elimination of molecular nitrogen leading to the formation of products **14-17** that contain three functional groups: sulfonamide, amide and ester (Scheme 5). This type of sulfonamide N-C bond cleavage followed by acetic acid-water addition, with the nitrogen elimination from triazole moiety was not reported earlier in the literature.

Scheme 5



R = Me, R^1 = Me, R^2 = Ph **14** (80%, **X-ray**)
R = Me, R^1 = ^{t}Bu, R^2 =Ph **15** (86%)
R = Me, R^1 = Ph, R^2 = Ph **16** (78%)
R = Me, R^1 = Me, R^2 = H **17** (90%)

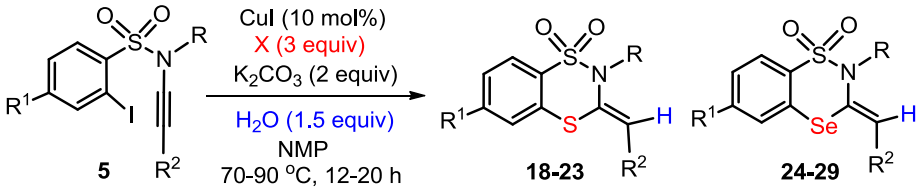


Compound **14**

(ii) [Cu]-catalyzed synthesis of benzosultams by the incorporation of elemental sulfur/ selenium onto the functionalized ynamides

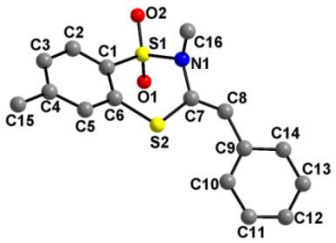
After the synthesis of triazolo fused benzosultams, we aimed for the insertion of elemental sulfur/selenium onto the functionalized ynamides. To achieve this, ynamides **5** were treated with elemental sulfur/selenium under basic conditions in the presence of a [Cu]-catalyst (Scheme 6). With this protocol, we accomplished the regio- and stereo-specific synthesis of benzosultams **18-29** with the incorporation of elemental sulfur/selenium. To our knowledge, this is a new type of reaction comprising the formation of two new C-S/C-Se bonds in a single step. The structures of compounds **18** and **24** were confirmed by X-ray crystallography. The selenium compounds were also characterized by ^{77}Se NMR.

Scheme 6

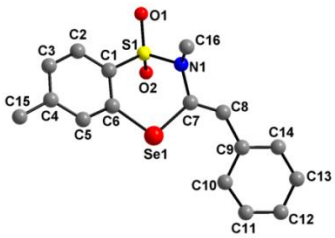


R = Me, R^1 = Me, R^2 = Ph	**18** (90%, **X-ray**)	**24** (70%, **X-ray**)
R = Me, R^1 = Ph, R^2 = Ph	**19** (84%)	**25** (68%)
R = Me, R^1 = Me, R^2 = 4-MeO-C_6H_4	**20** (86%)	**26** (60%)
R = Me, R^1 = Me, R^2 = 4-biphenyl	**21** (72%)	**27** (50%)
R = Me, R^1 = Me, R^2 = 3-F-C_6H_4	**22** (84%, **X-ray**)	**28** (62%)
R = Me, R^1 = Me, R^2 = *n*-hexyl	**23** (76%)	**29** (56%)

(more examples)



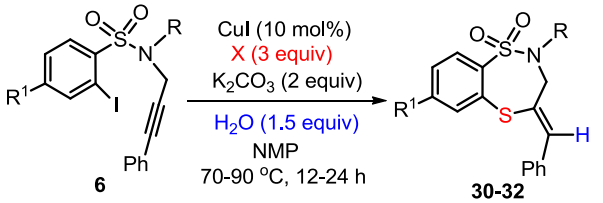
Compound **18**



Compound **24**

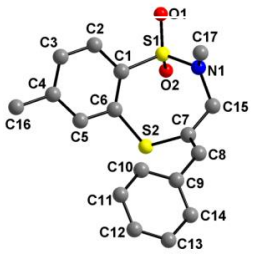
The above methodology is not restricted to activated alkynes such as ynamides and is also applicable to unactivated alkyne motifs. Pleasingly, the reaction of 2-iodo-*N*-methyl/phenyl-*N*-(3-phenylprop-2-yn-1-yl)benzenesulfonamides **6** with elemental sulfur or selenium afforded the desired seven membered ring containing benzosultams, benzodithiazepines (**30-32**) and benzothiaselenazepines (**33-35**) regio- and stereo-specifically in excellent yields (Scheme 7).

Scheme 7



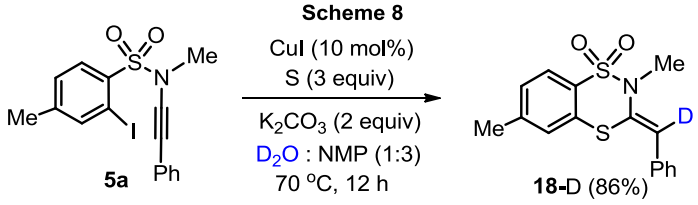
R = Me, R^1 = Me	**30** (86%, **X-ray**)	**33** (76%)
R = Me, R^1 = ^{t}Bu	**31** (84%)	**34** (82%)
R = Ph, R^1 = Me	**32** (76%)	**35** (68%)

Compound **30**



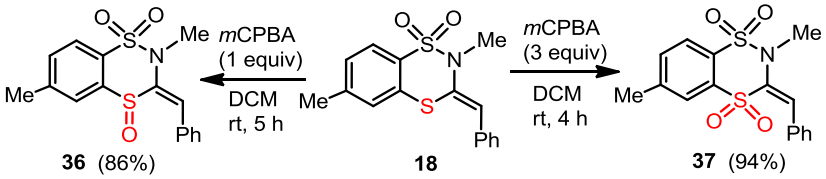
Involvement of water in the above reaction is demonstrated by the incorporation of ^{2}D at the olefinic site by using D_2O in place of water under our standard conditions. Thus the reaction of ynamide **5a** with elemental sulfur using K_2CO_3 base in D_2O and NMP (1:3) mixture provides compound **18**-D (Scheme 8).

Scheme 8



Since selective oxidation reactions are of significant interest in pharmaceutical industry, we oxidized the low-valent sulfur in the benzo[1,4,2]dithiazine 1,1-dioxide **18** by using *m*CPBA as the oxidizing agent. Fortunately, the reaction of benzo[1,4,2]dithiazine 1,1-dioxide **18** with 1 equiv (of *m*CPBA) preferentially led to mono-oxidation product **36**, whereas use of 3 equiv resulted in the formation of the di-oxidized product **37** in good yields (Scheme 9).

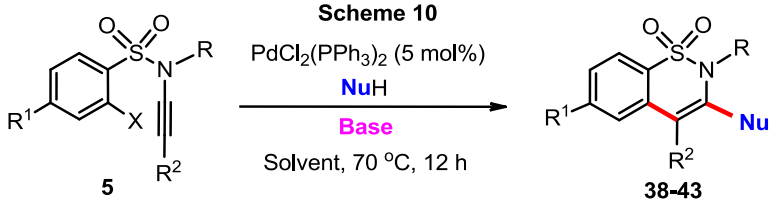
Scheme 9



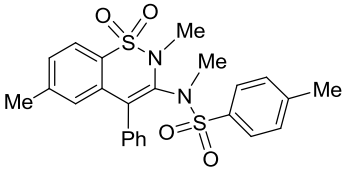
(iii) Synthesis of benzosultams by the [Pd]-catalyzed tandem cyclization of ynamides using various nucleophiles

Palladium-catalyzed tandem-cyclization of functionalized ynamides **5** to a wide range of hetero-substituted benzosultams **38-43** (1,2-benzothiazine 1,1-dioxides) has been achieved by employing different nucleophiles (Scheme 10). Medicinally useful compounds like nortriptyline and eugenol could also be used as nucleophiles. Base has a significant effect in the cyclization process, depending on the nucleophile source used.

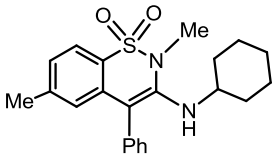
Scheme 10



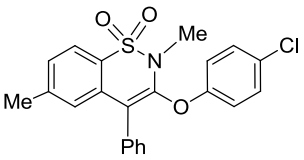
NuH = R^4R^3NH (sulfonamides, amines, benzotriazoles, tetrazoles)
NuH = ArOH (phenols)
NuH = $R^4R^3CH_2$ (active methylene compounds)



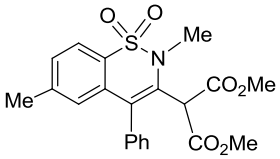
38 (92%, **X-ray**)



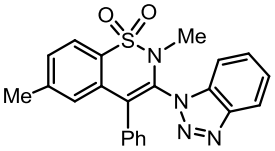
39 (86%, **X-ray**)



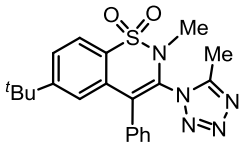
40 (82%, **X-ray**)



41 (64%, **X-ray**)

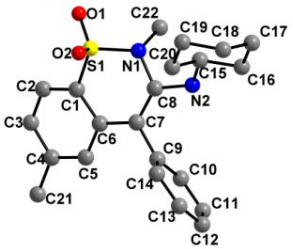


42 (82%, **X-ray**)

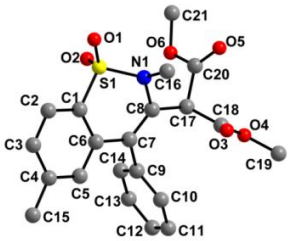


43 (56%)

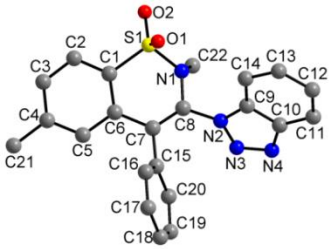
(more examples)



Compound **39**



Compound **41**

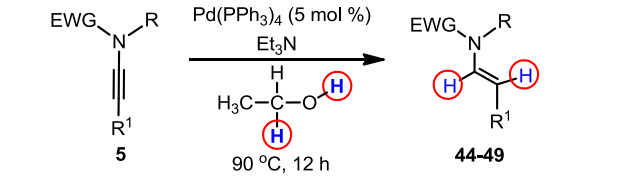


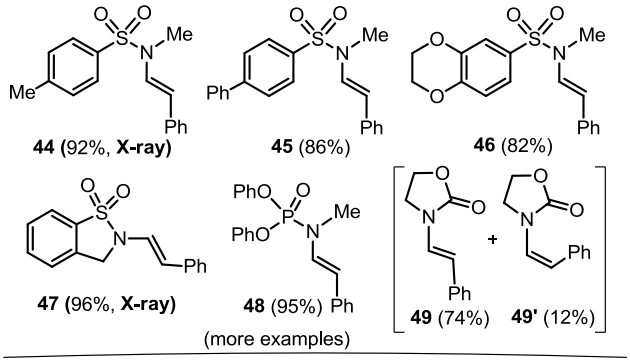
Compound **42**

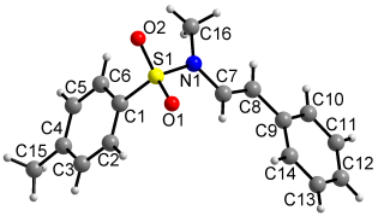
(iv) [Pd]-catalyzed reaction of ynamides with ethanol: Stereoselective formation of enamides

The reaction of ynamides **5** with ethanol in the presence of a [Pd]-catalyst produced enamides **44-49** (Scheme 11). Here ethanol acts as the ***hydrogenating agent*** for ynamides under palladium catalyzed conditions. This behavior is different from the normally expected reaction of ethanol addition to alkynes. (*E*)-Enamides are stereoselectively formed, which is in contrast to many literature reports using other hydrogenating sources. The stereochemistry and structures of compounds **44** and **47** were confirmed by X-ray crystallography.

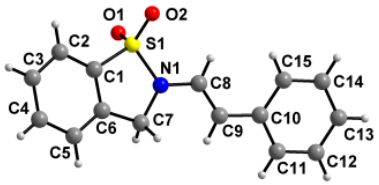
Scheme 11







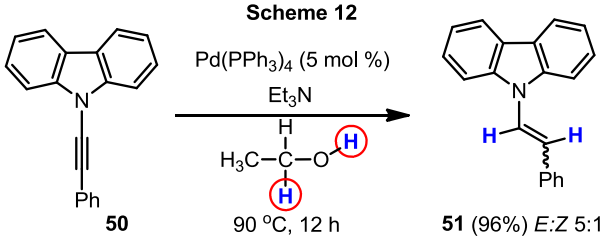
Compound **44**



Compound **47**

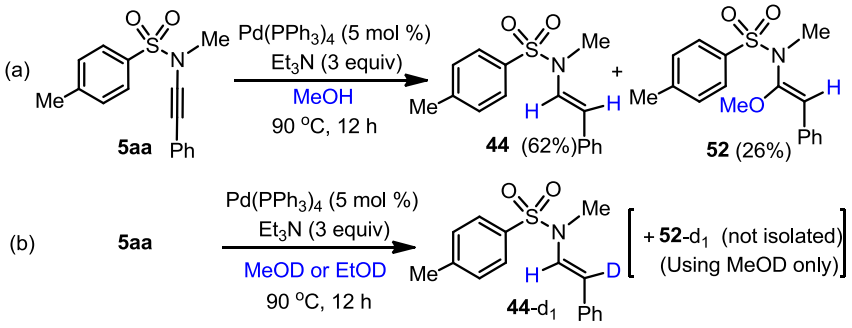
Under similar reaction conditions, the carbazole derived ynamine substrate **50** was also hydrogenated to the corresponding enamine **51** in a good overall yield with the *E*-isomer still predominating (Scheme 12).

Scheme 12



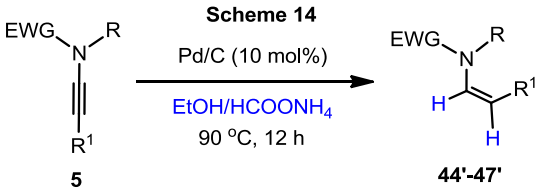
The use of methanol instead of ethanol as a hydrogenating agent also led to formation **44** along with minor amounts of the methanol addition product **52** (Scheme 13a). Use of CH_3OD or C_2H_5OD led to the isolation of **44**-d_1 (Scheme 13b). These control experiments clearly revealed that the source of hydrogen is ethanol in the present study. The coordination of the metal catalyst to the oxygen atom of the electron withdrawing group and the steric interactions caused by the nitrogen lone pair with the R^1/H group may be responsible for the *trans*-stereoselectivity.

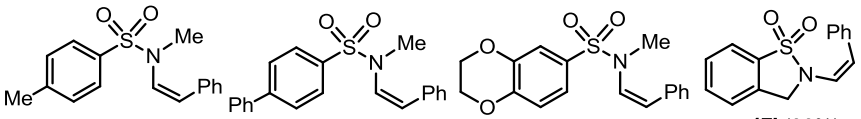
Scheme 13



In contrast to the above, the hydrogenation of ynamides **5** with synergistic EtOH/$HCOONH_4$ system as a hydrogenating source using Pd/C-catalyst afforded the (*Z*)-enamide products **44'-47'** in good yields (Scheme 14). This difference in reactivity might be due to the adsorption of hydrogen onto the catalyst, thereby favoring the *syn*-hydrogenation to afford the (*Z*)-enamide products.

Scheme 14

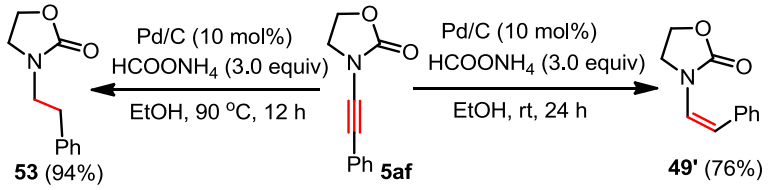




(more examples)

The more reactive ynamide **5af** offered the *Z*-selective hydrogenated product **49'** at rt (25 °C), whereas the synthesis of the fully reduced product **53** was accomplished in good yields at 90 °C (Scheme 15).

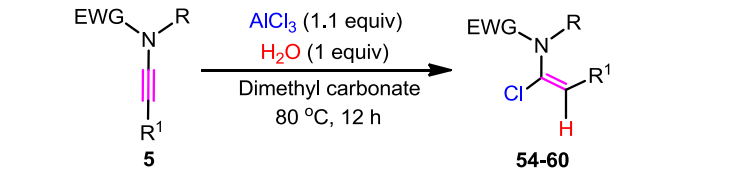
Scheme 15

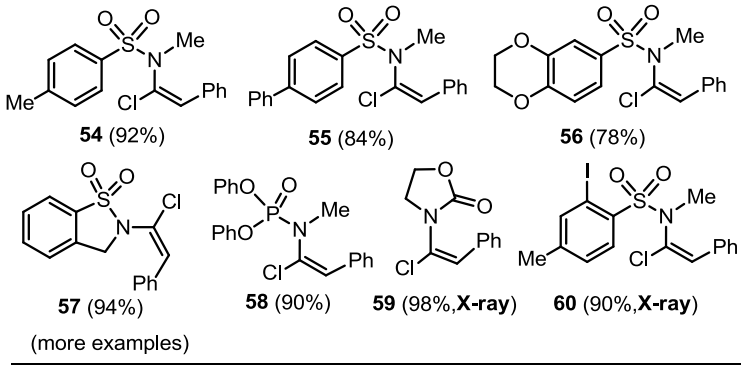


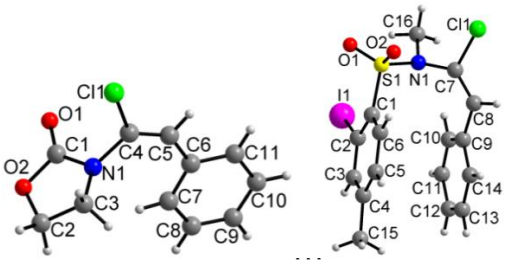
(v) Reaction of ynamides with aluminium chloride

Recently, hydrochlorination of ynamides with different sources has been described and the main problem associated with some of these methods is the lack of regio and stereo-selectivity. In our hands, the reaction of ynamides with conc. HCl led to an equimolar mixture of *Z*- and *E*- chloro-enamides. In this context, we desired to explore hydrochlorination of ynamides. Hence, an efficient access to (*E*)-α-chloroenamides **54-60** has been developed by the regio- and stereo-specific hydrochlorination of ynamides **5** using aluminium chloride as the chlorine source and water as the proton source (Scheme 16). The generality of this method was proven by the hydrochlorination of many types of ynamides. The regio- and stereo-chemistry of the products is based on X-ray crystallographic studies.

Scheme 16







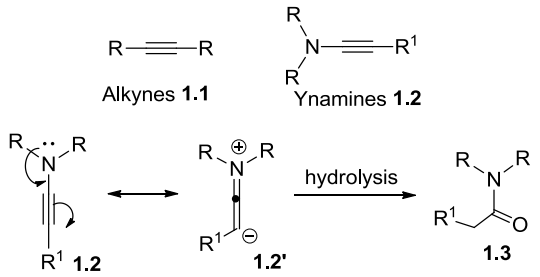
Compound **59** Compound **60**

INTRODUCTION

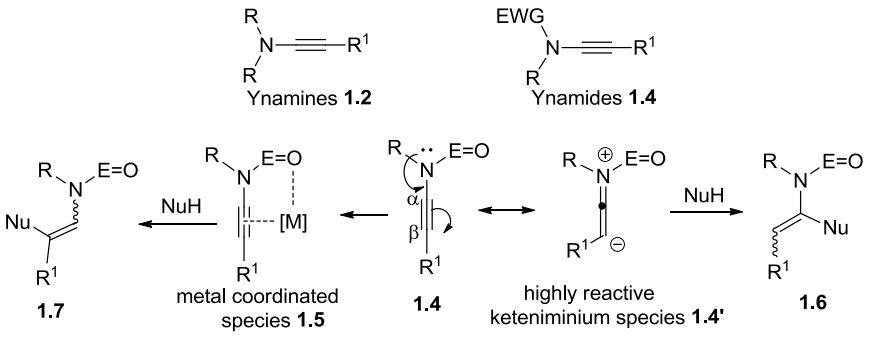
1.1 General Introduction: Ynamides

Alkynes of the type **1.1** are ubiquitous in organic transformations.[1] Heteroatom substituted alkynes, especially ynamines **1.2** (*N*-substituted alkynes), have drawn significant attention from a synthetic perspective due to their high reactivity and involvement in diverse regio-/stereo-selective transformations. Their first practical preparation was reported by Vihie in 1963.[2] These precursors act as surrogates of allenes due to the possible resonance forms (cf. **1.2'**) and are utilized in both electrophilic and nucleophilic reactions.[3] The hydrolytic instability of ynamines leading to amides of type **1.3** makes their preparation and handling difficult (Scheme 1.1). To alleviate this problem and to explore the chemistry related to ynamines, one of the alkyl/aryl groups on the nitrogen atom of ynamines can be replaced with an electron withdrawing group. Hence electron deficient ynamines or ynamides of the type **1.4** are alternative precursors to normal ynamines (Scheme 1.2).

Scheme 1.1. General representation of alkynes, ynamines and hydrolysis of ynamines



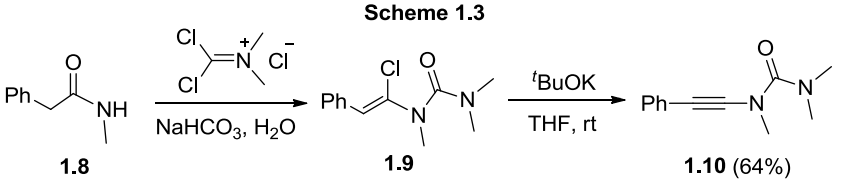
Scheme 1.2. Reactivity of ynamides



During the last two decades, ynamides have emerged as versatile synthons in organic chemistry by providing activation for carbon-carbon triple bonds.[4] The "predictable regioselectivity" involved in transformations using ynamides has been a key factor in the development of this class of compounds as valuable precursors in several organic transformations.[5] Sulfonamide based ynamides are endowed with a right balance between stability and reactivity and hence have been the substrates of choice in a large number of cases.[6] The unusual reactivity of ynamides is presumably due to the formation of a reactive keteniminium ionic species[7] or coordination of metal catalyst to the alkyne and in some cases, to the heteroatom of the electron withdrawing group.[8]

The first synthetic approach to ynamides reported by Viehe and co-workers involved the dehydrohalogenation of α-halo enamides (Scheme 1.3).[9] Thus the reaction of benzylic amides **1.8** with phosgeneimmonium chloride led to the corresponding α-chloro enamides **1.9** which, after base mediated elimination of HCl, resulted in the urea derived ynamides **1.10**.

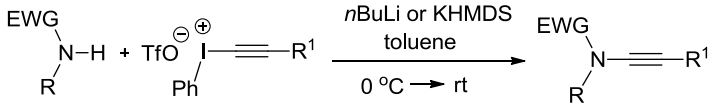
Scheme 1.3



1.8 **1.9** **1.10** (64%)

After the above report from Viehe, Witulski *et al*. developed an efficient method for the synthesis of ynamides **1.4** from amides **1.11** and alkynyliodonium salts **1.12**. This was the only popular method till the beginning of the year 2000 (Scheme 1.4).[10]

Scheme 1.4

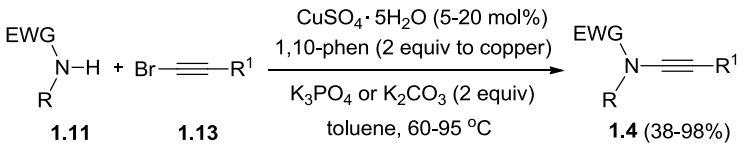


1.11 **1.12** **1.4** (28-86%)

Later, Hsung and co-workers reported the copper catalyzed *N*-alkynylation of various amides **1.11** using 1-bromoalkynes **1.13** (Scheme 1.5) that illustrates a simpler route for ynamides. This is a major breakthrough for the synthesis of a wide variety of ynamides. The best catalytic system for this transformation is $CuSO_4 \cdot 5H_2O$ in combination with

1,10-phenanthroline. Anhydrous K_3PO_4 is needed to achieve better yield of the desired products.[11]

Scheme 1.5



1.11 **1.13** **1.4** (38-98%)

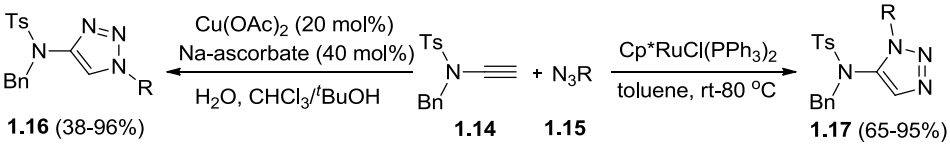
Apart from the above methods, many approaches have been explored by several research groups to prepare ynamides.[12] Stahl *et al*. developed an efficient method by the copper-catalyzed oxidative *N*-alkynylation of various amides with terminal alkynes.[12a] Evano and co-workers described a complementary approach to ynamides involving copper-catalyzed coupling of 1,1-dibromo-1-alkenes with different nitrogen nucleophiles.[12b] A later report from the same group involved the oxidative cross coupling of alkynyl copper reagents with N- and P- nucleophiles.[12c]

1.2 Cyclization/ cycloaddition reactions of ynamides

Ynamides have emerged as powerful synthons owing to their versatile ring forming transformations.[13] In particular, transition metal catalyzed cyclization of ynamides is explored for the construction of diverse and novel nitrogen containing heterocycles.[14] Over the last few years, a rapid expansion in the cycloaddition reactions of ynamides has also taken place.[15] Herein, we discuss some of the cyclization and cycloaddition reactions of ynamides that are relevant to the present work.

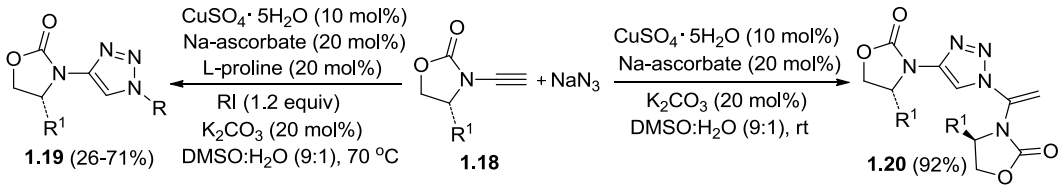
Cintrat and co-workers initially employed ynamide substrates in "click chemistry concept" to obtain 1-substituted 4-amido 1,2,3-triazoles **1.16** in good yields and high regioselectivity by copper catalyzed [3+2] cycloaddition of ynamides **1.14** with various azides **1.15** (Scheme 1.6).[16a] This transformation worked well with both $Cu(OAc)_2$-sodium ascorbate catalytic system and CuI though the former was marginally better. In contrast, the ruthenium catalyzed Huisgen [3+2] cycloaddition between ynamides **1.14** and various azides **1.15** led to the formation of 1-substituted 5-amido 1,2,3-triazoles **1.17** in a regioselective manner.[16b] This ruthenium catalyzed process is applicable to internal ynamides also.

Scheme 1.6



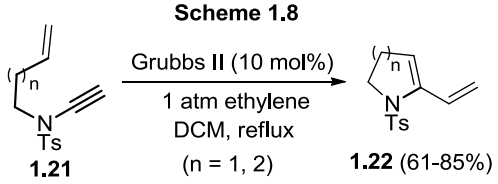
In the year 2006, Hsung's group also reported an elegant route to chiral amide substituted triazoles **1.19** in a regio- and chemo-selective manner by the tandem azidination of ynamides **1.18** with sodium azide using aryl/ alkenyl iodides in the presence of [Cu]-catalysts (Scheme 1.7).[17] The key step involved in this transformation was very slow addition (10 h) of ynamide via syringe pump. In the absence of aryl iodide, ynamide underwent hydroazidination with sodium azide and subsequent Huisgen [3+2] cycloaddition with a second molecule of ynamide leading to the formation of the triazole product **1.20**. Participation of the other molecule of ynamide has also been supported by the use of simple terminal alkyne in addition to the ynamide, wherein formation of two products was observed, as expected.

Scheme 1.7



Ene-ynamides **1.21** were first employed in ring closing metathesis by Saito *et al.* using second generation Grubbs' catalyst (Scheme 1.8).[18] Thus the ruthenium catalyzed reaction of ene-ynamide offered various nitrogen heterocycles possessing a dienamide core **1.22**. Further, the cyclic dienamide produced underwent Diels-Alder reaction to afford the indole and quinoline derivatives.

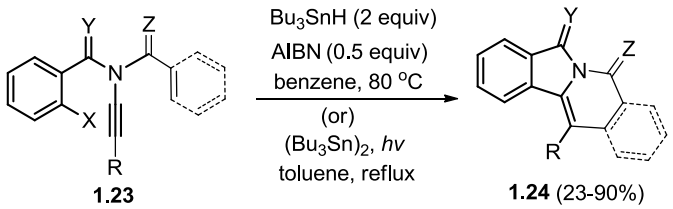
Scheme 1.8



Malacria's group discovered the first radical cyclization of ynamides **1.23** to access various nitrogen containing heterocycles **1.24** (Scheme 1.9).[19] This radical cascade

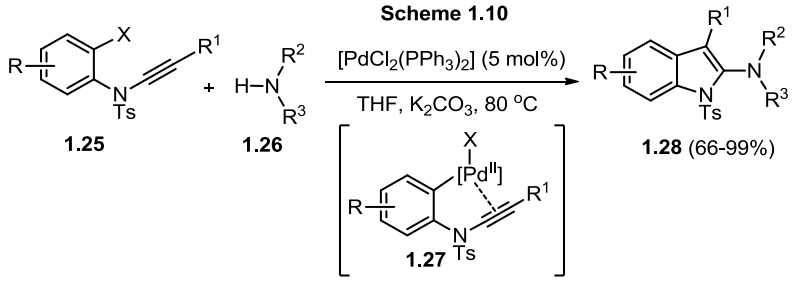
cyclization of ynamides involves 5 exo-dig cyclization, followed by 6 endo-trig trapping process leading to the formation of isoindoles, isoindolinones and pyridoisoindolones in good to excellent yields.

Scheme 1.9



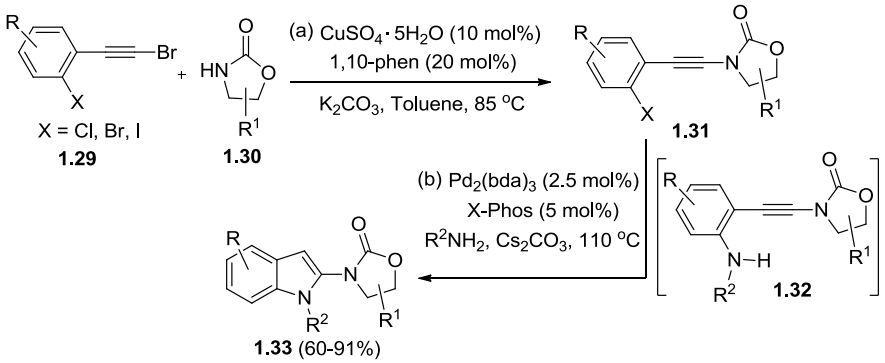
Witulski *et al*. established an efficient method to prepare 2-amino indoles **1.28** by the palladium catalyzed heteroannulation reaction of alkynyl-2-halogenanilides **1.25** with primary or secondary amines **1.26** (Scheme 1.10).[20] Even the less basic aniline offered the corresponding cyclized product in good yield. The pathway envisioned involves the initial formation of internally bound σ,π-chelated palladium species **1.27** which allows the attack of external amines onto the activated alkyne, followed by the reductive elimination of Pd^0 species furnishing the 2,3-disubstituted indoles.

Scheme 1.10



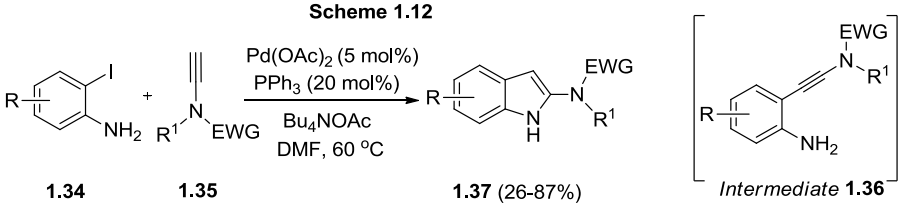
Yao *et al.* described facile synthesis of o*rtho*-haloaryl substituted ynamides **1.31** by the [Cu]-catalyzed *N*-alkynylation of carbamates **1.30** with *o*-haloaryl acetylenic bromides **1.29**.[21] This copper catalyzed amidative cross-coupling was well suited for the both cyclic and acyclic carbamates including sulfonamides. Intriguingly, these halo substituted ynamides **1.31** underwent cyclization with anilines/amines leading to 2-amido indoles **1.33** *via* a [Pd]-catalyzed 5-*endo-dig* cyclization of the *in situ* formed *o*-aminoaryl substituted ynamides **1.32** by the *N*-arylation strategy. This palladium catalyzed amination process was implemented successfully for aryl bromides and chlorides (Scheme 1.11).

Scheme 1.11



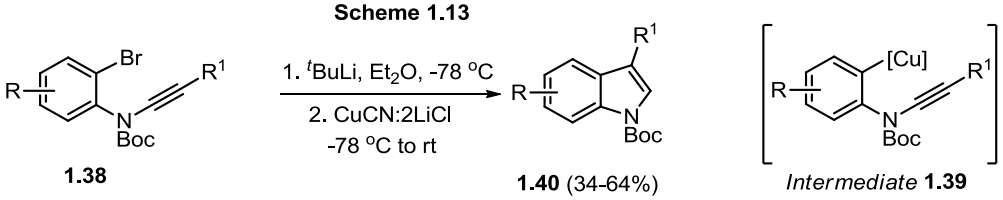
An alternative synthetic strategy towards 2-amidoindoles **1.37** was achieved by Skrydstrup and co-workers by the sequential palladium catalyzed cyclization of terminal ynamides **1.35** with *o*-iodoanilines **1.34** (Scheme 1.12).[22] Electron withdrawing substituent on the *o*-iodoaniline reduced the nucleophilicity of the -NH_2 group thereby decreasing the yield of the product, so protection was required in such cases. The reaction proceeds *via* the traditional Sonogashira cross coupling in the absence of any copper salt resulting in 2-alkynyl aniline intermediate **1.36**. Subsequent base promoted intramolecular hydroamination process leads to the formation of indole ring. This methodology was extended to *o*-iodophenols also, though the desired 2-amidobenzofurans were produced in lower yields.

Scheme 1.12



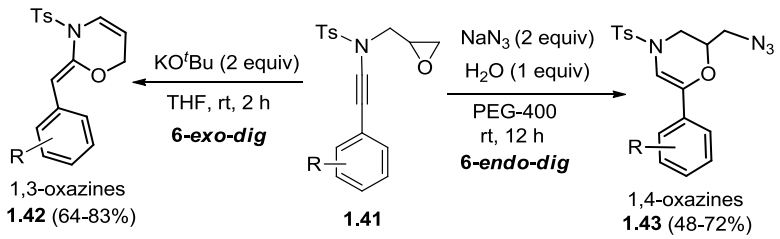
Evano and co-workers described an efficient regioselective synthetic approach to polysubstituted indoles **1.40** by intramolecular 5-*endo-dig* carbometalation of *N*-(2-bromo aryl) substituted ynamides **1.38**.[23] This strategy involved the bromine-metal exchange by using ^{t}BuLi and CuCN:2LiCl resulting in carbocuprated intermediate **1.39** which then undergoes 5-*endo-dig* cyclization with the alkyne in a regioselective manner and forms the substituted indole. Even the 1,3,5-, 1,3,6- and 1,3,7- trisubstituted indoles can be prepared easily by using this protocol (Scheme 1.13).

Scheme 1.13



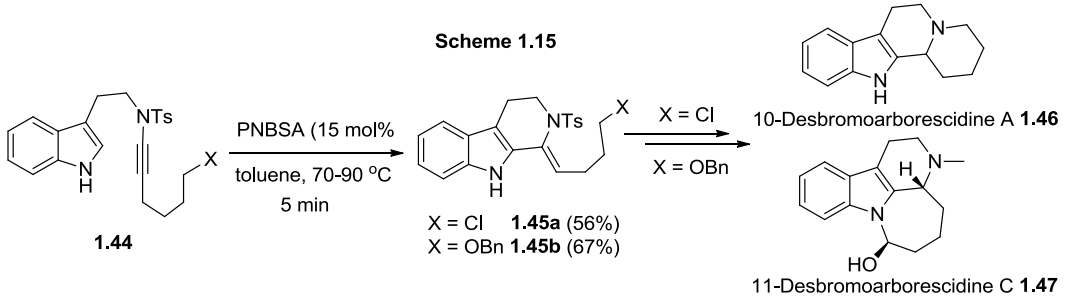
Recently our research group reported a novel transition metal-free catalyzed approach to 1,3- and 1,4-oxazines by the cyclization of epoxy tethered ynamides (Scheme 1.14).[24] This regio- and stereo-selective atom economic synthesis of 1,3-oxazines **1.42** involved the base mediated cyclization of epoxy ynamides **1.41** in a 6-*exo-dig* fashion. The highly regioselective synthesis of 1,4-oxazines **1.43** was achieved by the 6-endo-dig cyclization of epoxy ynamides **1.41** using sodium azide as the nucleophile. The role of water in the cyclization process was proven by deuterium-labelling experiment for the formation of 1,4-oxazines. Simple epoxy tethered *N*-propargylated derivatives also underwent cyclization *via* isomerization/6-*endo-dig* process illustrating the generality of the method.

Scheme 1.14



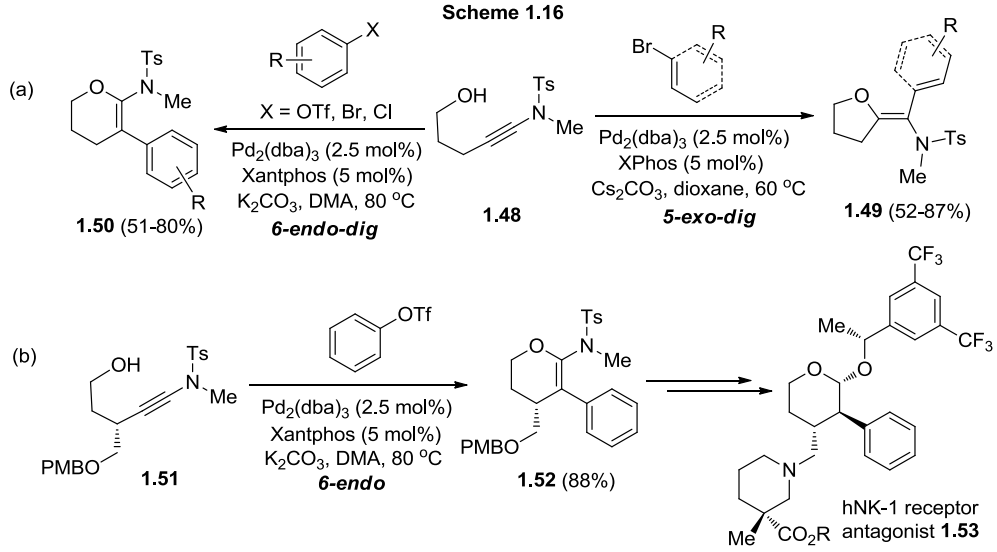
Ynamides are also the key precursors in the total synthesis of some natural products. Hsung and co-workers accomplished the first application of ynamides for the total synthesis of natural products 10-desbromoarborescidine-A (**1.46**) and 11-Desbromoarborescidine-C (**1.47**) based on sequential stereoselective keteniminium formation by using Brønsted acid and Pictet-Spengler cyclization starting from the indole tethered ynamide **1.44** (Scheme 1.15).[25]

Scheme 1.15



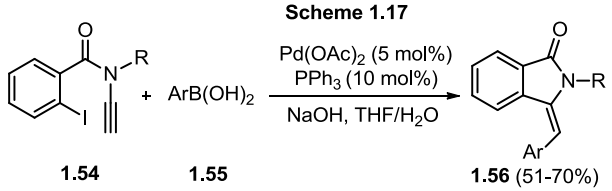
Fujino *et al*. disclosed the tunable regio-controlled arylative cyclization of alcohol bearing ynamides **1.48** under palladium catalysis that produced the five- or six-membered oxygen heterocycles **1.49-1.50**.[26] Aryl palladium intermediates play a vital role for altering the reactivity towards different modes of cyclization. Based on NMR analysis, they predicted that the hydroxyl group preferentially coordinates to the [ArPdBr(XPhos)] species thereby base mediated formation of alkoxide experiences a *5-exo-dig* cyclization. The Lewis acidic [ArPd-(Xantphos)]$^{+}$OTf^{-} species has the propensity of coordination by the alkyne part of ynamide motif and undergoes *6-endo-dig* cyclization. Further, this *6-endo-dig* mode cyclization has been applied to the formal synthesis of hNK-1 receptor antagonist **1.53** (Scheme 1.16).

Scheme 1.16



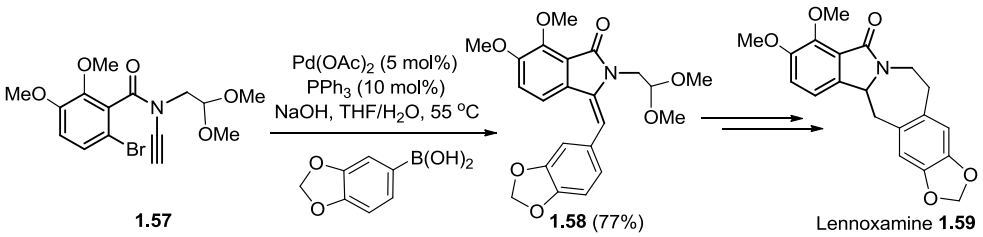
A report from Cossy and co-authors involved the stereo selective synthesis of (*E*)-3-(arylmethylene) isoindolin-1-ones **1.56** by the [Pd]-catalyzed reaction of terminal ynamides **1.54** possessing a halo-substituent with arylboronic acids **1.55**.[27a] The reaction involved palladium catalyzed Heck-Suzuki-Miyaura domino reactions. This method was also expanded to the related pyridine derived ynamides for the construction of pyrrolopyridinones (Scheme 1.17). The utility of this method was illustrated by the synthesis of natural product Lennoxamine **1.59**, an isoindolobenzazepine alkaloid, that relied on Heck-Suzuki-Miyaura reaction of the ynamide (Scheme 1.18).[27b-c]

Scheme 1.17



1.54 **1.55** **1.56** (51-70%)

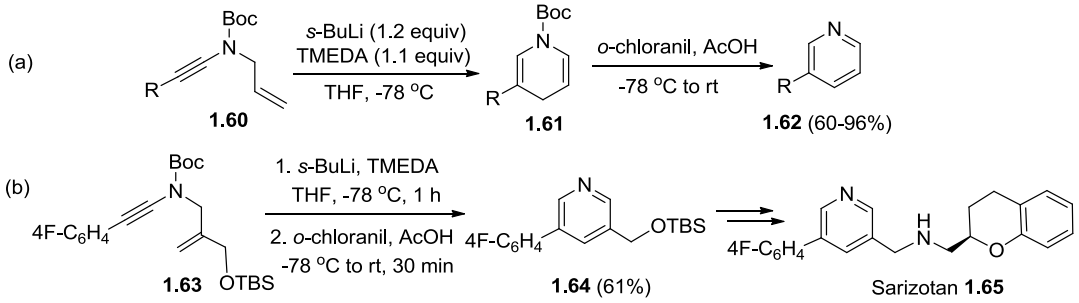
Scheme 1.18



1.57 **1.58** (77%) Lennoxamine **1.59**

Evano and co-workers developed an efficient straightforward entry to 1,4-dihydropyridines **1.61** and pyridines **1.62** by the base promoted highly regioselective cyclization of *N*-allyl substituted ynamides **1.60** (Scheme 1.19a).[28a] This transformation proceeds through the α-lithiation of Boc-protected ynamides using *s*-BuLi, followed by isomerization and subsequent intramolecular *6-endo-dig* cyclization leading to 1,4-dihydropyridines. The applicability of this method was demonstrated by the formal synthesis of the Sarizotan **1.65** (an anti-dyskinesia agent; Scheme 1.19b), 5-HT1A (receptor agonist) and dopamine-D2 (receptor ligand).[28b]

Scheme 1.19

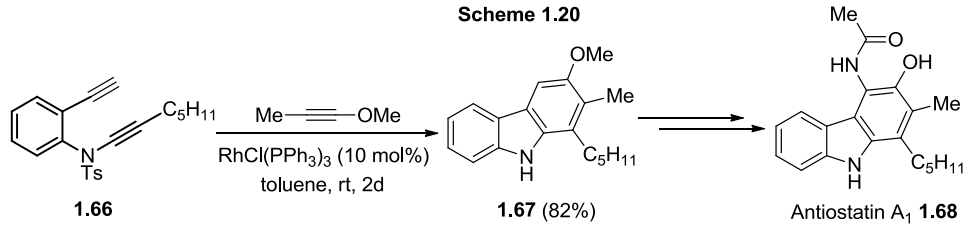


1.60 **1.61** **1.62** (60-96%)

1.63 **1.64** (61%) Sarizotan **1.65**

Witulski and co-workers have reported the first total synthesis of potent carbazole based antioxidant Antiostatin A_1 **1.68** (Scheme 1.20).[29] The key step in this total synthesis was the rhodium catalyzed chemo- and regio-selective crossed [2+2+2] alkyne cyclotrimerization of functionalized ynamide **1.66** with the alkyne.

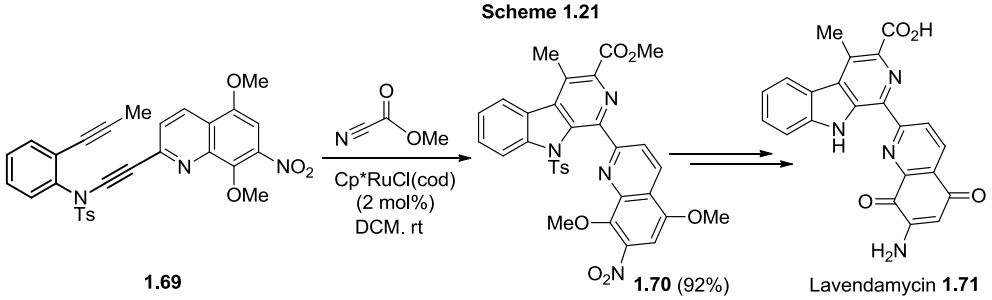
Scheme 1.20



1.66 **1.67** (82%) Antiostatin A_1 **1.68**

Nissen *et al.* achieved the total synthesis of Lavendamycin **1.71**, a pentacyclic bacterial derived antitumor antibiotic (Scheme 1.21).[30] The synthesis relies mainly on the regio- and chemo-selective ruthenium catalyzed [2+2+2] cycloaddition of the ynamide **1.69** with an electron deficient nitrile to produce the carboline core structure.

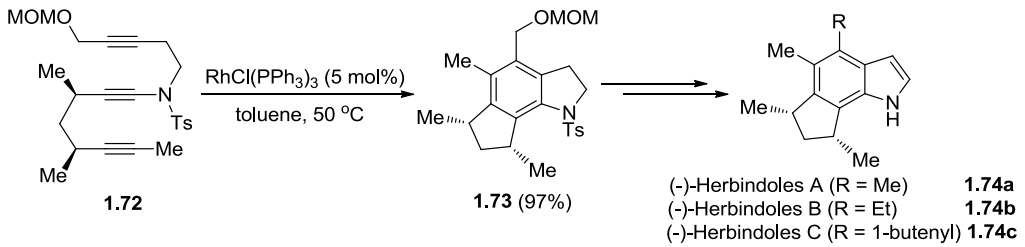
Scheme 1.21



1.69 **1.70** (92%) Lavendamycin **1.71**

Saito *et al.* succeeded in the total synthesis of polylalkylated cyclopent[g]indole alkaloids such as (-)-Herbindoles A, B, and C **1.74** in natural form from an identical indoline derivative **1.73**, which in turn was produced from the rhodium catalyzed intramolecular [2+2+2] cyclization of functionalized ynamide **1.72** (Scheme 1.22).[31]

Scheme 1.22



1.72 **1.73** (97%)

In addition to the above reports, Danheiser's group demonstrated an enantioselective approach to the antitumor agents (+)-FR900482 and (+)-FR66979 by utilizing ynamide based benzannulation strategy in combination with ring-closing metathesis.[32] Thus *N*-alkynyl sulfonamides (ynamides), in view of a highly polarized carbon-carbon triple bond

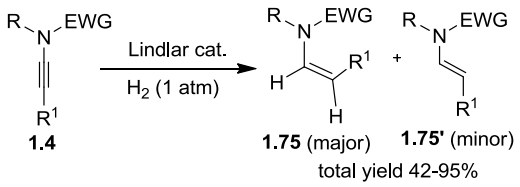
directly attached to the nitrogen atom, could be potential synthons to explore in cycloadditions and cyclizations.

1.3 Hydrogenation reactions of ynamides/ alkynes

Transition-metal catalyzed hydrogenation of alkynes leading to alkenes is a very important reaction of vast synthetic utility.[33] Either a heterogeneous catalyst (Raney Ni, Lindlar catalyst, Pd/C),[34] or a homogeneous catalyst of Rh, Ru, or Ir complex[35] by using hydrogen gas as the hydrogenating agent can be utilized to accomplish this transformation. Two problems associated with many of these methods are (a) the lack of chemo- and stereo-selectivity of the alkenes and (b) the over-reduction of the resulting alkenes to alkanes.[36] While much of the literature is devoted to diaryl/dialkyl substituted alkynes, ynamides as an important class of alkynes with the triple bond directly attached to a nitrogen atom have also emerged as important synthons.[4]

Selected examples of hydrogenation of alkynes including ynamides from the recent literature related to our present work are discussed below. We are aware of only two reports on catalytic hydrogenation of ynamides resulting in *Z*-alkenes by using hydrogen gas and either Lindlar or a [Pd]-catalyst.[37-38] Hsung and co-workers reported stereoselective access to (*Z*)-enamides **1.75** by the *syn* hydrogenation of ynamides **1.4** using the Lindlar's catalyst (Scheme 1.23).[37] This Lindlar hydrogenation process was equally applicable for the hydrogenation of macrocyclic ynamides to give the corresponding macrocyclic enamides.

Scheme 1.23

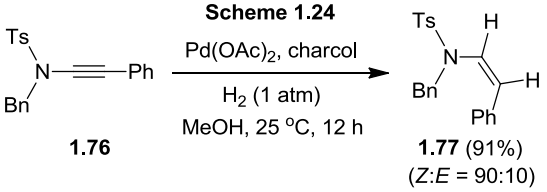


1.4 **1.75** (major) **1.75'** (minor)

total yield 42-95%

Another report from Felvin *et al.* involved the reduction of alkenes and alkynes using a palladium catalyst.[38] Thus the hydrogenation of ynamide **1.76** led to a mixture of *E*/*Z* enamides **1.77** in 1:9 ratio (Scheme 1.24). In addition to the hydrogenation of alkenes, hydrogenolysis of *O*-benzyl ethers was also observed.

Scheme 1.24

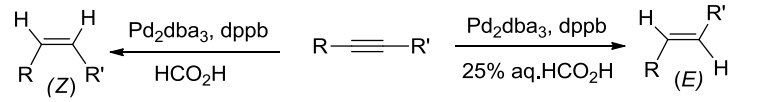


1.76 **1.77** (91%) (*Z*:*E* = 90:10)

The above two hydrogenation processes of ynamides involve the use of H_2 (1 atm) source, with predominantly *syn* addition.

With regard to general alkynes, recently, Shen *et al.* developed an unprecedented controllable palladium-catalyzed stereoselective hydrogenation of **1.78** using formic acid as the hydrogen source.[39] The use of pure formic acid afforded the *Z*-isomer **1.79** stereoselectively, whereas use of aqueous formic acid resulted in the *E*-isomer **1.79'** predominantly (Scheme 1.25). Rather surprisingly, use of the ligand PCy_3 in place of dppb produced the saturated hydrocarbons by complete hydrogenation of alkynes.

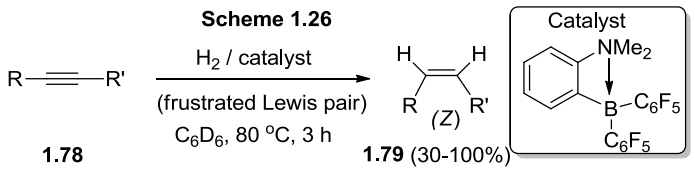
Scheme 1.25



1.79 (55-98%) **1.78** **1.79'** (85-95%)

Pápai and Repo reported the catalytic hydrogenation of alkynes **1.78** to *cis* olefins **1.79** in a highly chemo- and stereo-selective manner by using the *ansa*-aminohydroborane (a frustrated Lewis pair, FLP) as the catalyst (Scheme 1.26).[40] The mechanism proposed involves the initial activation of H_2 heterolytically by the frustrated Lewis pair resulting in the active B-H catalyst. Hydroboration of alkyne by active catalyst produces the vinylborane. This activates the hydrogen by FLP mechanism. Subsequent facile intramolecular protodeborylation affords the *cis* olefin.

Scheme 1.26

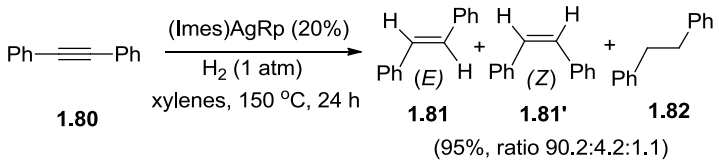


1.78 **1.79** (30-100%)

Mankad and co-workers used a heterobimetallic complex for the selective *trans*-hydrogenation of alkynes **1.80** leading to *E*-alkenes **1.81**. The unusual high *E*-selectivity was observed with the optimal Ag-Ru catalyst by using H_2 gas (Scheme 1.27).[41] The

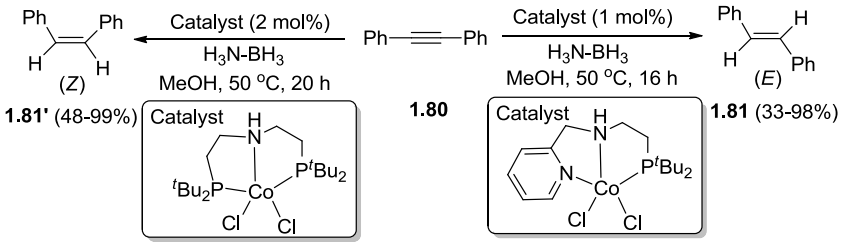
reaction is highly chemo-selective as evidenced by the selective reduction of alkynes without affecting the other reducible functional groups.

Scheme 1.27



Fu *et al.* utilized ammonia:borane as the hydrogen source for the stereodivergent transfer hydrogenation of alkynes **1.80** to either *cis*-**1.81'** or *trans*-alkenes **1.81** by using ligand controlled cobalt catalysis (Scheme 1.28).[42] It should be noted that $H_3B{:}NH_3$ adduct is utilized in methanol that acts only as a solvent. It is important to note that the less sterically crowded cobalt complex allows the isomerization of *cis* isomer to the *trans* isomer in this reaction.

Scheme 1.28

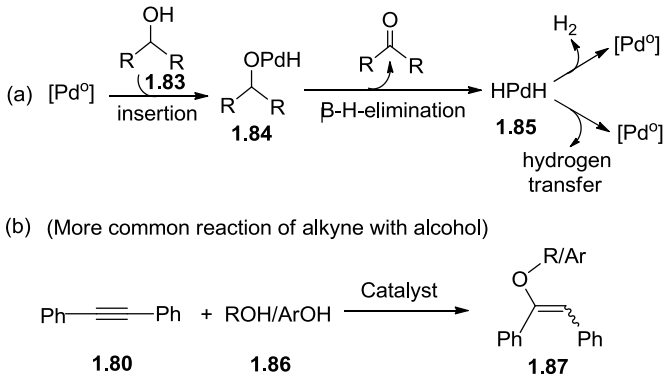


Apart from the above, several other interesting reports on semihydrogenation of alkynes have been known.[43] Szymczak and co-workers have described hydrogenation leading to *Z*-alkenes by using a borane appended-[Ru]-catalyst[43a] and Tokmic and Fout reported *E*-specific hydrogenation by using a [Co]-catalyst.[43b] Fürstner and co-workers developed a ruthenium catalyzed semihydrogenation of alkynes to *E* alkenes with a wide functional group tolerance.[43c]

Our idea was to use ***alcohol*** as the hydrogenating agent, since it can be oxidized to aldehyde with the elimination of hydrogen. This will avoid the 'more difficult to handle' hydrogen gas and is an inexpensive alternative. To the best of our knowledge, the use of ethanol as a hydrogenating agent in catalytic reduction of alkynes is rather unknown. However, [Pd]-catalyzed hydrogen-transfer reactions of alcohols to substrates containing C=C, C=N and C=O is known and an excellent review by Jacques Muzart is available

(Scheme 1.29a).[44] Even without a transition metal catalyst, it is known that alcohols can be used as reducing agents, as in the preparation of $V(O)SO_4$ from V_2O_5 in ethanol/H_2SO_4 medium.[45] Generally, though, alcohol/phenol **1.86** addition to the alkynes **1.80** (hydro-alkoxylation/aryloxyaltion) is lot more common (cf. Scheme 1.29b).[46]

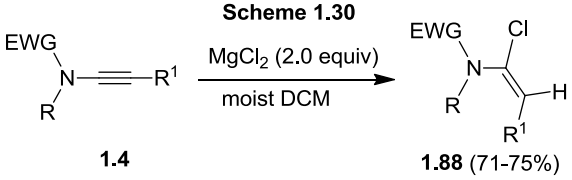
Scheme 1.29



1.4 α-Chlorination of ynamides

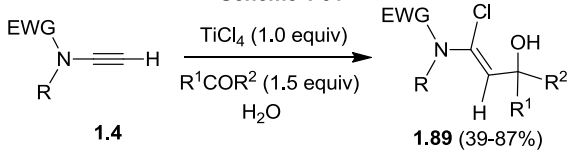
The α-chlorination of ynamides is an alternative approach to prepare enamides. In this context, Hsung and co-workers accomplished stereoselective access to enamides **1.88** by the hydrohalogenation of ynamides **1.4** using the magnesium halides in wet DCM (Scheme 1.30).[47] The α-haloenamides thus obtained were utilized in Sonogashira coupling for providing the enyne derivatives.

Scheme 1.30



A report from Matsuo *et al.* involved the titanium tetrachloride mediated addition of carbonyl compounds to terminal ynamides **1.4** resulting in α-halo-γ-hydroxyenamides **1.89** (Scheme 1.31).[48] The products were utilized in further synthetic applications involving either Suzuki coupling or intramolecular direct cyclization by using [Pd]-catalysis.

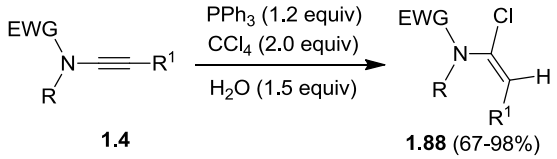
Scheme 1.31



1.4 **1.89** (39-87%)

Sahoo and co-workers developed a metal-free triphenylphosphine promoted regio- and stereo-selective hydrohalogenation of ynamides **1.4** using carbon tetrahalides as the halogen source (Scheme 1.32).[49] The synthetic potential of this method can be gauged by the implementation of products in Suzuki and Sonogashira couplings. The role of water in the reaction was elucidated by deuterium labelling experiment.

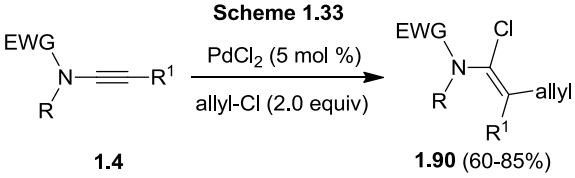
Scheme 1.32



1.4 **1.88** (67-98%)

A report from Zhu *et al*. involved an atom economic approach to stereodefined multisubstituted enamides **1.90** by the chloro-allylation of ynamides **1.4** under palladium catalysis (Scheme 1.33).[50] It is important to note that the reaction was performed at room temperature by using 5 mol % of $PdCl_2$.

Scheme 1.33



1.4 **1.90** (60-85%)

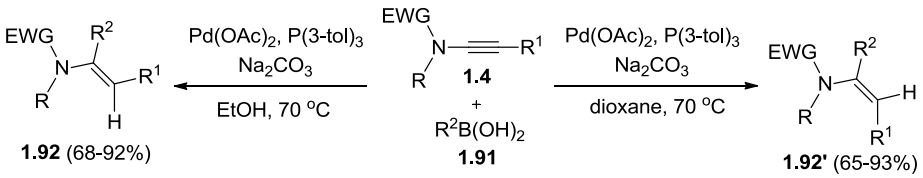
Some of the above methods often suffer from the lack of stereoselectivity. Hence there is still a need to develop an operationally simple method to prepare enamides with excellent regio- and stereo-selectivity. To our knowledge, the use of inexpensive aluminium chloride ($AlCl_3$, existing as dimer or polymer) as a chlorinating agent for the chlorination of ynamides is not explored. Because of its strong Lewis acidic character; the $AlCl_3$ may strongly activate the alkyne[51] and thereby chances of chloride-ion transfer from $AlCl_3$ are high. Even though $AlCl_3$ was utilized in some of the transformations of

ynamides either in catalytic or stoichiometric amounts, they did not involve the transfer of chlorine from $AlCl_3$.[52]

1.5 Recent approaches to enamides from ynamides

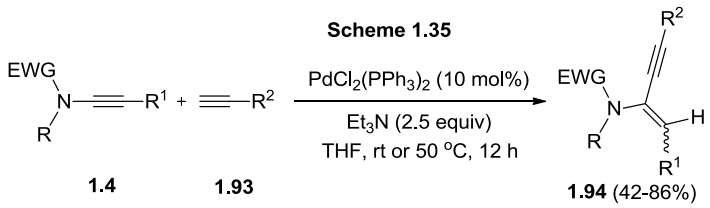
Especially during the last decade, several protocols for the synthesis of enamides from ynamide substrates have been developed,[53] revealing that these ynamides are versatile precursors. The research group of Zhu developed two independent protocols for the regio- and stereo-selective addition of boronic acids to ynamides.[54] The first report involved the palladium-catalyzed stereospecific synthesis of enamides **1.92** by the unprecedented *trans* addition of boronic acids **1.91** to ynamides **1.4** (Scheme 1.34).[54a] This unusual *trans* addition can be explained on the basis of proposed palladium carbene intermediate. A complementary approach to palladium catalyzed *cis* addition products **1.92'** of boronic acids **1.91** to ynamides **1.4** has also been achieved by the same group by varying the electron withdrawing substituent on the nitrogen atom.[54b]

Scheme 1.34



Sridhar Reddy and co-workers demonstrated a palladium catalyzed regio and stereo-selective hydroalkynylation of ynamides **1.4** by using terminal alkynes **1.93** leading to ynenamide derivatives **1.94** in good to excellent yields (Scheme 1.35).[55] The stereochemical outcome of this transformation is mainly dependent on the substituent present on the nitrogen atom or alkyne.

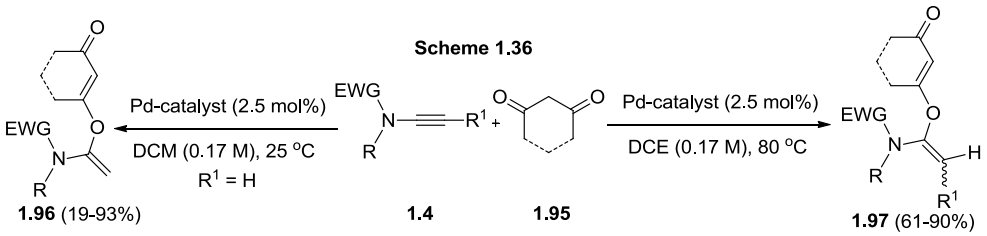
Scheme 1.35



Palladium-catalyzed access to alkoxy substituted enamides **1.96** by the addition reaction of 1,3 diones **1.95** to ynamides **1.4** was disclosed by the Graux *et al.* (Scheme

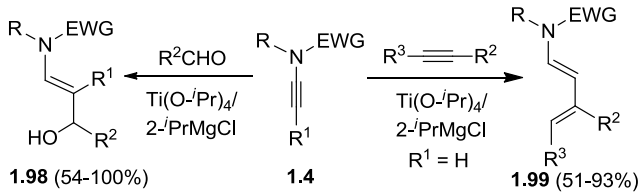
1.36).[56] This transformation proceeded at room temperature for terminal ynamides, whereas internal ynamides required a higher temperature of 80 °C. The resulting enamides **1.97** are either *E* or *Z* isomers.

Scheme 1.36



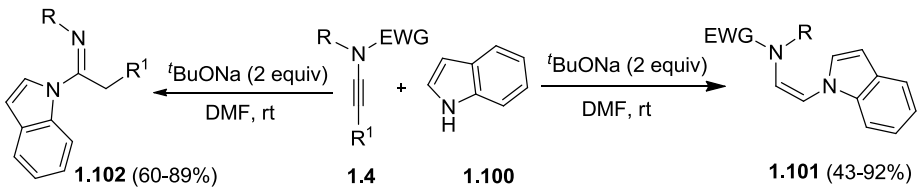
Tanaka *et al.* described a regio- and stereo-selective synthesis of enamides **1.98** by the titanium(II)-mediated coupling of ynamides **1.4** with carbonyl compounds.[57] Alternatively, the titanium mediated coupling of different alkynes with terminal ynamides **1.4** provided the stereodefined dienamides **1.99** in good yields (Scheme 1.37).

Scheme 1.37



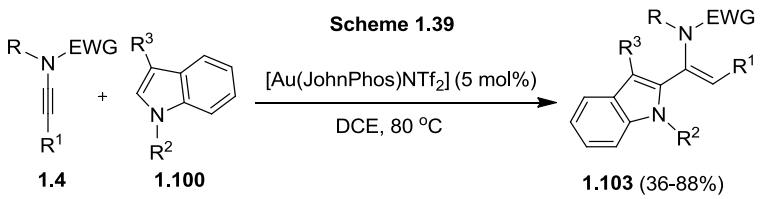
Hentz *et al.* described two unprecedented chemoselective *N*-functionalization of indoles with ynamides under transition metal-free conditions.[58] Base mediated intermolecular addition of indoles **1.100** to ynamides of type **1.4** is unprecedented and provides the *Z*-indoloetheneamides **1.101** in good yields (Scheme 1.38). In contrast, under the same reaction conditions, changing the substituents on the ynamides offered the indolo-amidines **1.102**.

Scheme 1.38



Pirovano *et al.* reported gold catalyzed regio- and stereo-selective synthesis of 2-vinylindoles **1.103** by the *cis* hydroarylation of ynamides **1.4** with indoles **1.100** (Scheme 1.39).[59] The proposed pathway involves a cyclopropyl gold-carbenoid species.

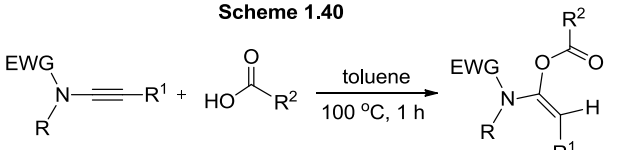
Scheme 1.39



1.4 **1.100** **1.103** (36-88%)

Xu *et al.* explored a highly efficient method for the synthesis of highly functionalized α-acyloxyenamides **1.105** by the hydroacyloxylation of ynamides **1.4** with various carboxylic acids **1.104** under metal free conditions (Scheme 1.40).[60] Furthermore, hydration of the ynamides afforded the pharmaceutically important *N*-acylsulfonamides.

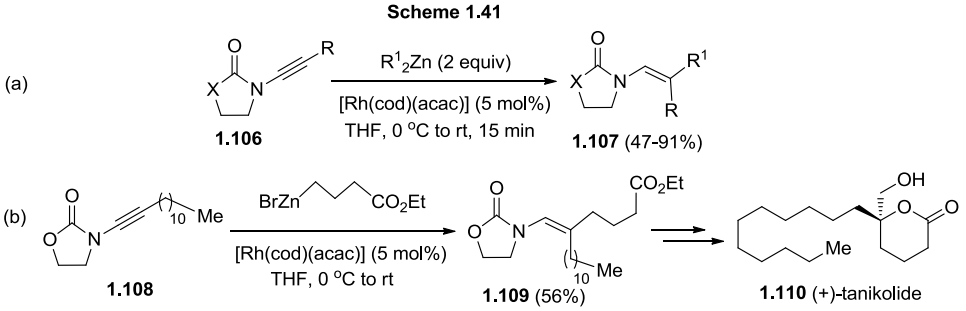
Scheme 1.40



1.4 **1.104** **1.105** (52-99%)

Lam and co-workers developed a new rhodium catalyzed highly regio- and stereo-selective synthesis of enamides **1.107** and dienamides *via* carbozin cation of ynamides **1.106** (Scheme 1.41a).[8a] This carbozincation transformation was also carried out by using *in situ* generated diorganozinc intermediates. The same group later explored the total synthesis of (+)-Tanikolide **1.110**, an antifungal natural product, involving the enamide **1.109** synthesized from rhodium catalyzed carbometallation of the ynamide **1.108** (Scheme 1.41b).[61]

Scheme 1.41



1.106 **1.107** (47-91%)

1.108 **1.109** (56%) **1.110** (+)-tanikolide

Thus numerous transformations involving ynamides have been explored in recent years for the generation of enamides.[62] Enamides are known to be versatile building blocks and their presence in the core of several natural products make them attractive synthons in organic synthesis.[63] In this context, we believed that *N*-alkynyl sulfonamides (ynamides), could be interesting substrates to explore in stereoselective transformations to produce functionalized enamides.

1.6 Benzosultams: Importance and synthetic approaches

Benzosultams play a significant role in drug discovery because of their diverse medicinal uses.[64] Recently, much interest has been directed towards 1,2-benzothiazine-1,1-dioxide and its derivatives because of the wide range of biological activities.[65] Oxicam and its derivatives are non-steroidal anti-inflammatory drugs. Sultams also exhibit inhibitory activity against enzymes such as Calpain I, COX-2, HIV integrase, carbonic anhydrase, MMP-2 and lipoxygenase. Benzosultams in particular show promising biological activity as AMPA receptors. They are probed for antimicrobial, antiviral, antileukemic, sedative and anti-inflammatory activities and for treatment of brain disorders. Examples of pharmaceutically important sultams are shown in Figure 1.

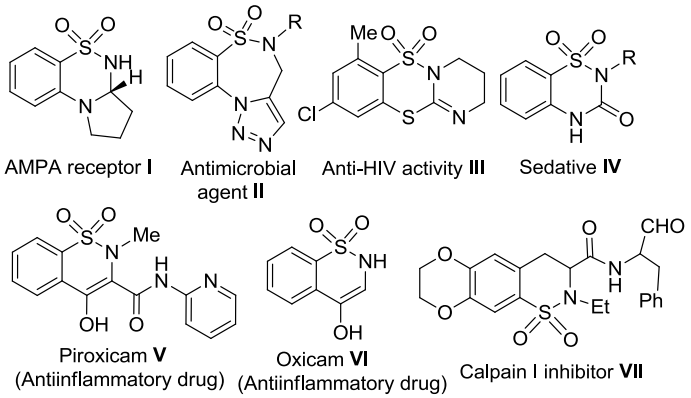
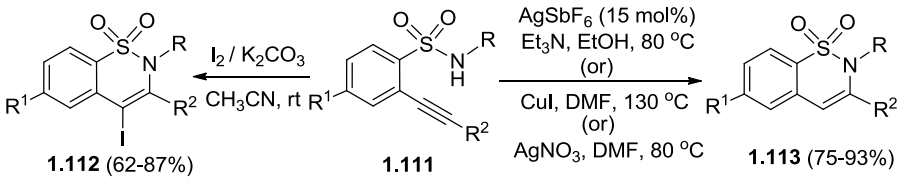


Fig. 1. Selected biologically active sultams.

Owing to the importance of benzosultams in the field of medicinal chemistry, there is still enormous scope for developing new synthetic strategies that assist in appending diverse functionalities on the skeleton. Synthetic approaches for sultam scaffolds generally involve intramolecular[66] or intermolecular[67] cyclizations. Selected recent examples that utilize mainly alkyne or halo as a key component to synthesize benzosultams are presented below.

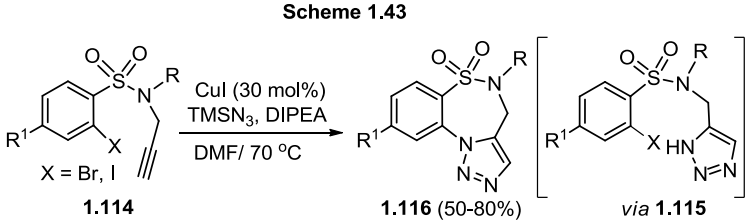
A report from Pal *et al.* involves regioselective iodine mediated cyclization of *o*-(1-alkynyl)benzenesulfonamides **1.111** for the construction of 4-iodo-2*H*-benzo[e][1,2]thiazine-1,1-dioxides **1.112**.[68a] The presence of iodo functionality on the benzosultams makes these substrates useful in further derivatizations using Sonogashira, Heck, or Suzuki cross-couplings. Subsequent report from the same group involved the $AgSbF_6$ or CuI catalyzed synthesis of 2*H*-1,2-benzothiazine 1,1-dioxides **1.113** by the intramolecular *6-endo-dig* cyclization of *o*-(1-alkynyl)benzenesulfonamides **1.111**.[68b] In another report, they utilized $AgNO_3$ as the catalyst for the intramolecular cyclization of *o*-(1-alkynyl)benzenesulfonamides **1.111** to produce the 3-substituted benzothiazines **1.113** (Scheme 1.42).[68c] Additionally, in this report, they examined the cyclooxygenase inhibiting properties of the products *in vitro* and showed that these are selective towards COX-2 inhibition based on the molecular docking studies.

Scheme 1.42



Yao *et al* reported one-pot [Cu]-catalyzed approach for the construction of triazolothiadiazepine 1,1-dioxide derivatives **1.116** from 2-iodo-*N*,4-disubstituted-*N*-(prop-2-ynyl)-benzene-sulfonamides **1.114** using $TMSN_3$ and Hunig's base (Scheme 1.43).[69] The reaction proceeds through the initial formation of 1,2,3-triazole **1.115** followed by carbon-nitrogen (C-N) bond formation *via* copper catalysis. The diversity of this method was demonstrated by synthesizing indoline- or thiophene derived triazolo-fused sultams.

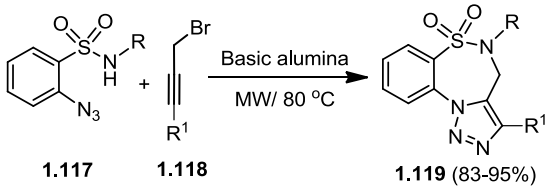
Scheme 1.43



Majumdar's group reported a one-pot strategy for the generation of triazolobenzothiadiazepine 1,1-dioxides **1.119** *via* a microwave assisted, basic alumina

supported intramolecular [3+2] azide–alkyne cycloaddition of 2-azido-*N*-substituted benzenesulfonamides **1.117** with propargyl bromides **1.118** (Scheme 1.44).[70] This protocol is attractive in view of the shorter reaction times and the low environmental impact.

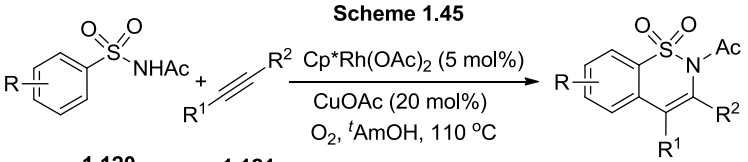
Scheme 1.44



1.117 **1.118** **1.119** (83-95%)

Cramer's group described an efficient access to benzosultams **1.122** by rhodium(III) directed oxidative C-H activation of sulfonamides **1.120** with internal alkynes **1.121** using CuOAc and molecular oxygen, which entails the use of *N*-acyl sulfonamide as the directing group (Scheme 1.45).[71] The generality of this method is highlighted by the successive C-H functionalization of the acylated COX-2 inhibitor Celecoxib. An important advantage of this method is that the acetyl directing group on the *N*-atom can be easily removed from the sultam under either basic or acidic conditions.

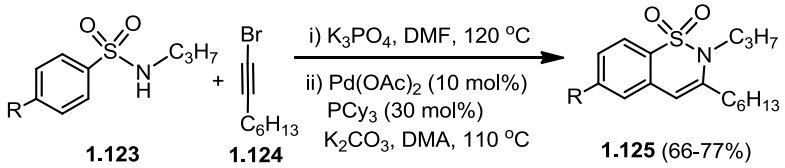
Scheme 1.45



1.120 **1.121** **1.122** (47-99%)

Urabe and co-workers described a base mediated nucleophilic addition of sulfonamides **1.123** to 1-bromoalkynes **1.124** resulting in (*Z*)-2-(*N*-alkyl-*N*-sulfonylamino)-1-bromoalkenes exclusively, followed by [Pd]-catalyzed cyclization that produced 1,2-benzothiazine 1,1-dioxides **1.125** through the activation of aromatic C-H bond. Aliphatic halo-alkynes were tolerated well in the cyclization process (Scheme 1.46).[72] Facile synthesis of indoles was also achieved by choosing *N*-aryl substituted sulfonamides as substrates.

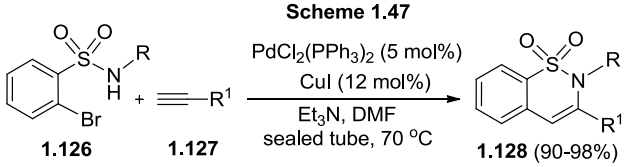
Scheme 1.46



1.123 **1.124** **1.125** (66-77%)

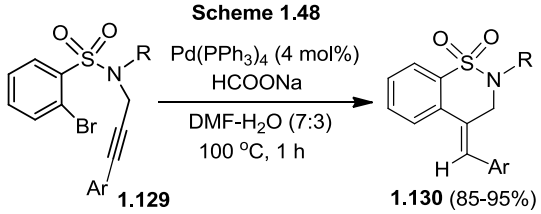
Debnath *et al*. developed a concise regioselective synthesis of benzosultams **1.128** by a one-pot sequential Sonogashira cross-coupling and cyclization of 2-bromobenzenesulfonamides **1.126** with terminal alkynes **1.127** (Scheme 1.47).[73] Density functional theory studies indicated that the cyclization proceeded through the *6-endo-dig* mode compared to the *5-exo-dig* mode of cyclization due to the lower activation energy barrier in the former. A later report from the same group involved the regio- and stereo-selective synthesis of benzo-δ-sultams **1.130** from the 2-bromo substituted *N*-propargylated benzenesulfonamides **1.129** in a *6-exo-dig* manner *via* palladium-catalyzed hydrocarbonation process (Scheme 1.48). Here, density functional theory calculations revealed that *6-exo-dig* mode cyclization proceeded with lower activation energy when compared to the *7-endo-dig* mode cyclization leading to the formation of *Z*-isomer.[74]

Scheme 1.47



1.126 **1.127** **1.128** (90-98%)

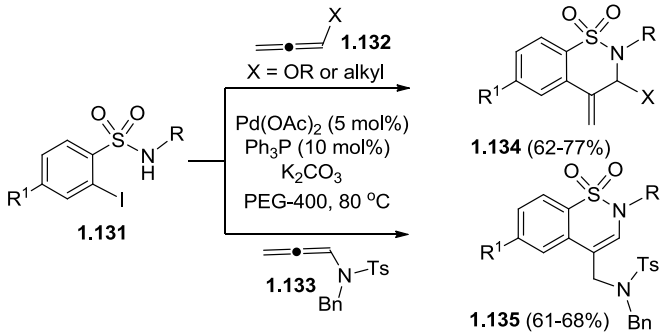
Scheme 1.48



1.129 **1.130** (85-95%)

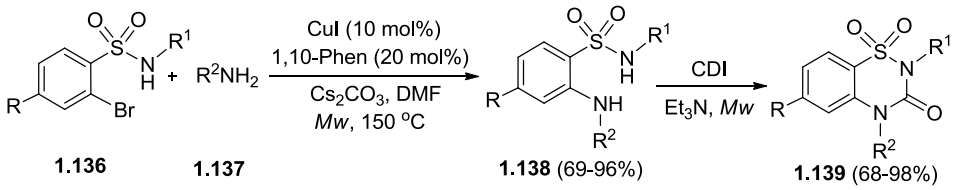
Our research group developed an expedient regiospecific approach to the benzosultams **1.134-1.135** by the palladium catalyzed annulation reaction between 2-iodobenzene sulfonamides **1.131** and allenes in PEG-400 medium (Scheme 1.49).[75] O-Substituted or alkyl allenes **1.132** preferentially led to the formation of (β,α)-cyclized sultams **1.134**, whereas the *N*-substituted allenes **1.133** gave the (β,γ)-cyclized sultams **1.135**. In the case of aryl substituted allenes, (β,γ)-cyclized sultams were formed as major isomers in addition to the minor (β,α)-cyclized isomers.

Scheme 1.49

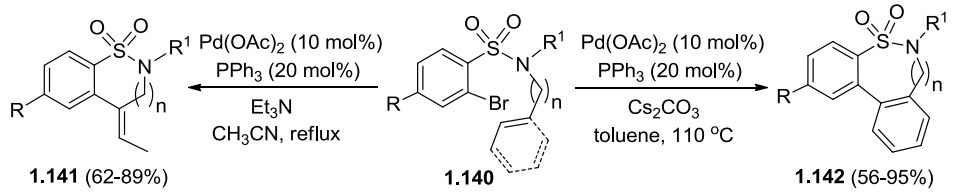


Hanson and co-workers envisioned a MW-assisted copper catalyzed *N*-arylation of 2-bromo benzene sulfonamides **1.136** with different amines **1.137** to afford the 2-amino benzene sulfonamides **1.138**.[76] These derivatives underwent cyclization in the presence of carbonyl diimidazole (CDI) reagent under MW-irradiation and produced benzothiadiazin-3-one 1,1-dioxides **1.139**. In addition, by combining both the above protocols, a sequential one-pot approach has also been developed to synthesize the benzosultams (Scheme 1.50). Later, the same group employed 2-haloaryl sulfonamide building blocks **1.140** in a cyclization process *via* intramolecular Heck cross-coupling for generating diverse bicyclic (**1.141**) and tricyclic benzosultams (**1.142**) in good yields (Scheme 1.51).[77] The Heck reaction products were utilized in additional transformations to produce skeletally diverse sultams.

Scheme 1.50



Scheme 1.51

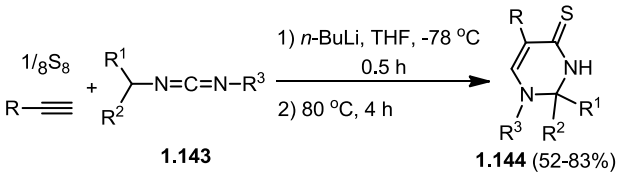


1.7 Reactivity of elemental sulfur/selenium towards alkyne or halo substrates

In the past few years, elemental sulfur as a reactant to generate sulfur based heterocycles, thioethers or thioketones is envisaged as an economically attractive concept in organic synthesis.[78] Several novel transformations that involve elemental sulfur/ selenium have been reported recently[79] and in this section we present reactions of elemental sulfur/ selenium with different alkyne and/or halo substrates that are relevant to the present work.

Elemental sulfur, terminal alkynes and carbodiimides **1.143** react in the presence of butyllithium to produce 2,3-dihydropyrimidinthiones **1.144** as reported by Zhenfeng Xi and co-workers (Scheme 1.52).[80] This is the first organolithium promoted multicomponent reaction of carbodiimide rearrangement. It involves the cleavage of C=N double bond as well as an sp^3 C-H bond functionalization.

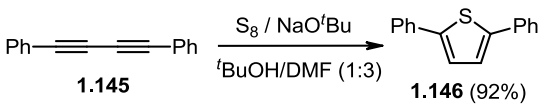
Scheme 1.52



1.143 **1.144** (52-83%)

Electron paramagnetic resonance (EPR) experiments revealed that the trisulfur radical anion ($S_3^{\bullet-}$) was involved in the formation of diarylthiophene **1.146** in the base mediated cyclization of 1,3-diynes **1.145** with elemental sulfur as reported by Zhang *et al* (Scheme 1.53).[81] In this process, the base promoted the generation of sulfur centered radical by interacting with the elemental sulfur. Addition of trisulfur radical anion ($S_3^{\bullet-}$) to the alkyne motif and subsequent intramolecular cyclization afforded the thiophene derivative.

Scheme 1.53

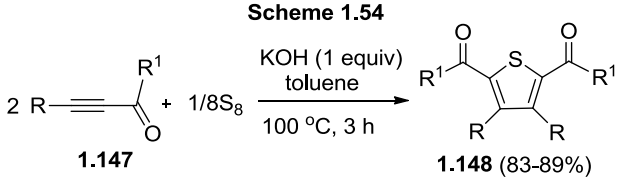


1.145 **1.146** (92%)

A convenient one-pot atom economic approach for the synthesis of polysubstituted thiophenes **1.148** was achieved by Liu's group (Scheme 1.54).[82] This method involved the base induced [2+2+1] cycloaddition of alkynes **1.147** with elemental sulfur through the formation of carbon-sulfur and carbon-carbon bonds. Based on control experiments,

they proposed a radical pathway for this cyclization process involving the initial formation of $S_3^{\bullet-}$ radical anion.

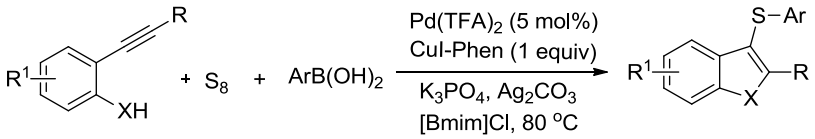
Scheme 1.54



1.147 **1.148** (83-89%)

Li *et al.* developed a novel method for the construction of 3-sulfenyl benzofurans or 3-sulfenyl indoles **1.150** with high atom- and step-economy *via* palladium and copper-catalyzed cascade annulation/arylthiolation process (Scheme 1.55).[83] In this protocol, 2-alkynyl phenols or 2-alkynyl anilines **1.149** reacted with the elemental sulfur and aryl boronic acids in an ionic liquid medium to produce the heterocycles.

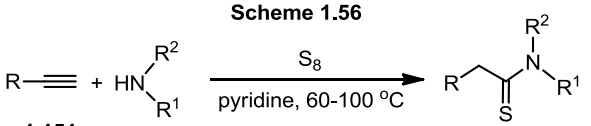
Scheme 1.55



1.149 **1.150** (63-91%)

Nguyen *et al.* developed an atom economical approach to thioamides **1.152** by the three component reaction between alkynes **1.151**, elemental sulfur and aliphatic amines (Scheme 1.56).[84a] Initial formation of $R^1R^2NS_7S^-$ via nucleophilic attack of amine on elemental sulfur is proposed by the author. This anion reacts with alkyne to form the final thioamide product in several steps.

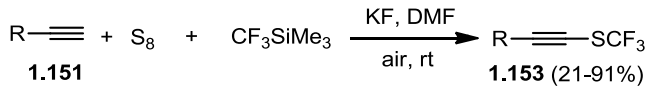
Scheme 1.56



1.151 **1.152** (51-86%)

The preparation of alkynyl trifluoromethyl sulfides **1.153** by the oxidative trifluoromethylthiolation of terminal alkynes **1.151** with elemental sulfur and CF_3SiMe_3 under metal free conditions (Scheme 1.57) was reported by Chen *et al.*[85] In this transformation, elemental sulfur, instead of air, acted as the oxidant.

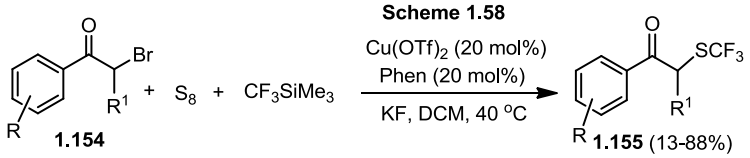
Scheme 1.57



1.151 **1.153** (21-91%)

Copper-catalyzed trifluoromethylthiolation of α-bromoketones **1.154** with elemental sulfur and CF_3SiMe_3 was reported by Huang *et al.*[86] This methodology was also applicable for the gram scale synthesis of α-trifluoromethylthio-substituted ketones **1.155**. These are valuable synthons to produce the numerous derivatives possessing an $–SCF_3$ group (Scheme 1.58).

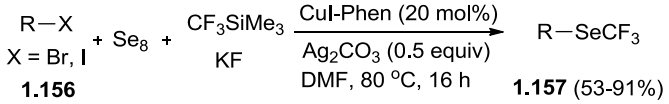
Scheme 1.58



1.154 **1.155** (13-88%)

Chen *et al.* described an efficient strategy for the trifluoromethylselenolation of alkyl and aryl halides **1.156** using elemental selenium and CF_3SiMe_3 under copper-catalysis (Scheme 1.59).[87] The reaction proceeds *via* a dinuclear copper trifluoromethylselenate intermediate $[(Phen)Cu(SeCF_3)]_2$ which has been characterized by X-ray crystallography. The efficacy of this copper-catalyzed trifluoromethylselenolation was enhanced by the addition of silver salt.

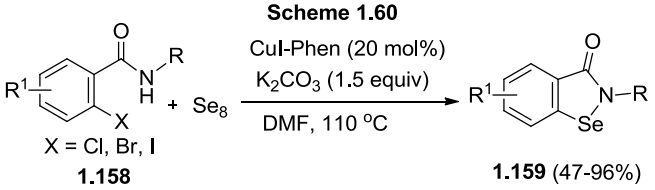
Scheme 1.59



1.156 **1.157** (53-91%)

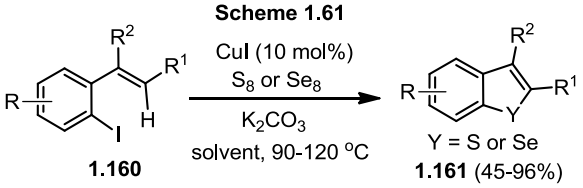
Sanjit Kumar's group synthesized the biologically important ebselen and related selenazolones **1.159** by one-pot copper catalyzed reaction between the 2-halo substituted benzamides **1.158** and elemental selenium (Scheme 1.60).[88] This is the first catalytic process concerned with selenation as well as Se-N bond formation.

Scheme 1.60



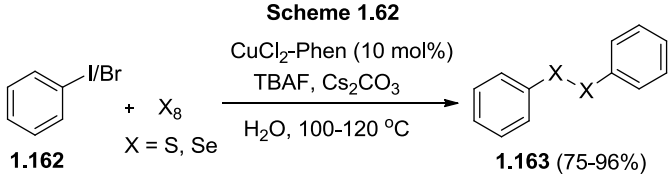
An expedient copper catalyzed chalcogenative cyclization for the synthesis of benzothiophenes or benzoselenophenes **1.161** from *ortho*-alkenylaryl iodides **1.160** and elemental sulfur/selenium was discovered by Wu *et al* (Scheme 1.61). This reaction can be construed as elimination of HX with concomitant insertion of sulfur/selenium. The corresponding benzotellurophene was synthesized *via* iodine-magnesium exchange followed by trapping with tellurium powder.[89]

Scheme 1.61



Li *et al.* have developed an efficient protocol for the synthesis of disulfides and diselenides **1.163** by the coupling reaction between aryl halides **1.162** and elemental sulfur or selenium in water medium using copper catalysis (Scheme 1.62).[90] In general, selenium is less reactive compared to sulfur and hence required higher reaction temperature to obtain better yield of the diselenides. The synthetic potential of this method allowed the preparation of cystine also.

Scheme 1.62



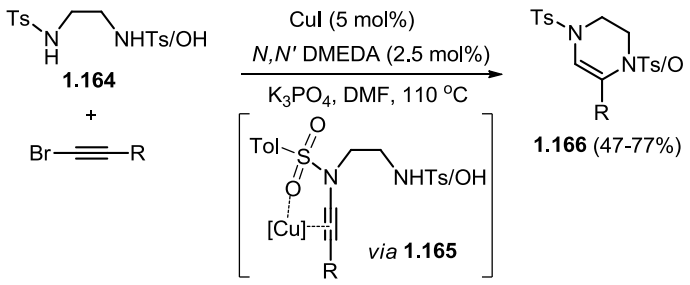
1.8 [Cu]-Catalyzed tandem/one-pot strategies for synthesis of heterocyclics

Tandem/one-pot reaction to synthesize heterocycles is an economically valuable concept that reduces the time and avoids the isolation of intermediates. Among the different catalysts used in such type of transformations, copper compounds seem to be the

cheapest and air stable. In this section, we discuss relevant literature on [Cu]-catalyzed tandem/one pot transformations to design of new heterocycles.

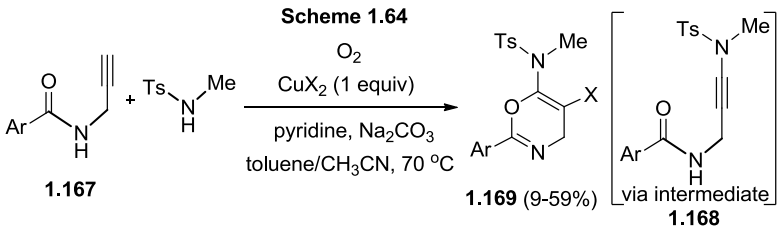
Urabe and co-workers developed a concise synthesis of *N*,*N*- or *N*,*O*- heterocycles **1.166** from diamine or ethanolamine precursors **1.164** and bromoacetylenes under [Cu]-catalysis (Scheme 1.63).[91] Initially, ynamide intermediate **1.165** could be generated *in situ* by copper catalyzed *N*-alkynylation of sulfonamides with bromoalkynes. Further, hydro-amination or hydroalkoxylation of ynamide intermediate in a 6-*endo*-*dig* fashion (but not in a 5-*exo*-*dig* fashion) due to the coordination of copper to both the alkyne and the sulfonyl groups afforded the tetrahydropyrazines or oxazines. This transformation also worked well when bromoalkynes were replaced by dibromoolefins.

Scheme 1.63



Hashmi *et al.* described the tandem cyclization of propargyl amides **1.167** with sulfonamides for providing the 5-halo-4*H*-1,3-oxazine-6-amines **1.169** by using CuX_2 under aerobic conditions (Scheme 1.64). This method initially involves the Stahl's reaction to produce the ynamide intermediate **1.168** *via* *N*-alkynylation process, followed by *6-endo-dig* halo-cyclization to furnish the 5-halo-1,3-oxazines. Both $CuCl_2$ and $CuBr_2$ worked well in this cyclization process.[92]

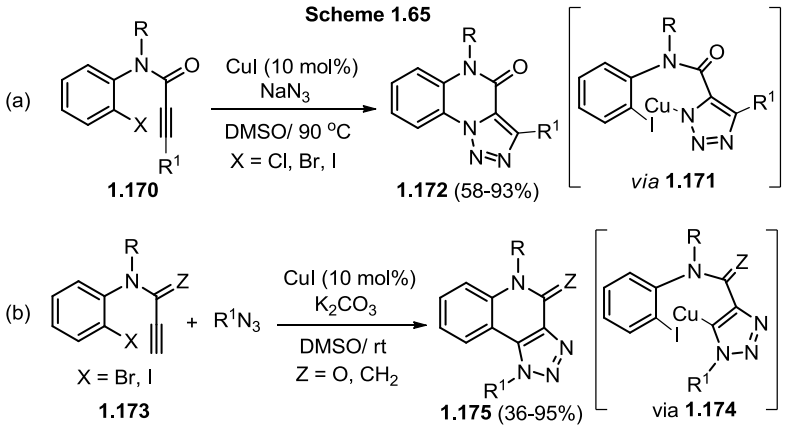
Scheme 1.64



Cai and co-workers utilized sodium azide to synthesize 1,2,3-triazolo-[1,5-a]quinoxalin-4(5H)-ones **1.172** from *N*-(2-iodoaryl)-propiolamides **1.170** with the aid of [Cu]-catalysis (Scheme 1.65a).[93a] In a later report, the same group described tandem

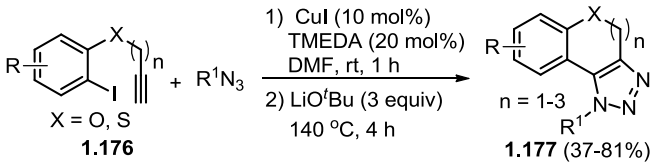
copper catalyzed azide-alkyne cycloaddition and Ullmann coupling of organic azides with *N*-(2-iodoaryl)-propiolamide **1.173** resulting in triazole fused quinolin-2-ones **1.175** (Scheme 1.65b).[93b] Aryl iodides are more compatible than the aryl bromides/chlorides and gave good yield of the desired products. Both the reactions initially involve the click reaction of activated alkyne with azide leading to triazole intermediate **1.171** or **1.174**. This is followed by the formation of either C-N bond or C-C bond *via* Ullmann type reaction.

Scheme 1.65



Our research group has reported the construction of [6,6]-, [6,7]-, [6,8]-, and [6,9] ring-fused triazoles **1.177** by the tandem copper catalyzed click and intramolecular direct arylation reaction of halo-substituted alkynes **1.176** with azides (Scheme 1.66).[94] Various alkyne tethered aryl iodides reacted smoothly with both aliphatic and aryl azides to give the fused triazoles in good to excellent yields. The resulting fused triazoles having a *o*-halo benzyl/phenyl on the *N*-substituent involved in an intramolecular cyclization/Ullmann-coupling under palladium-catalyzed reaction conditions.

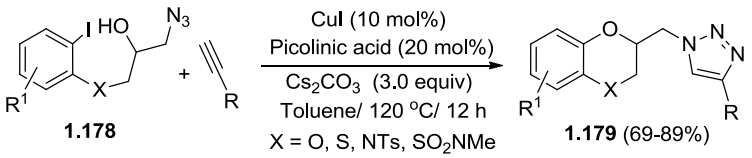
Scheme 1.66



The synthetic approach to triazole tethered dihydrobenzodioxines/ benzoxazines/ benzoxathiines/ benzodioxepines **1.179** from iodo substituted azido alcohols **1.178** and terminal alkynes using a Cu^{I} dual catalytic system has also been achieved (Scheme

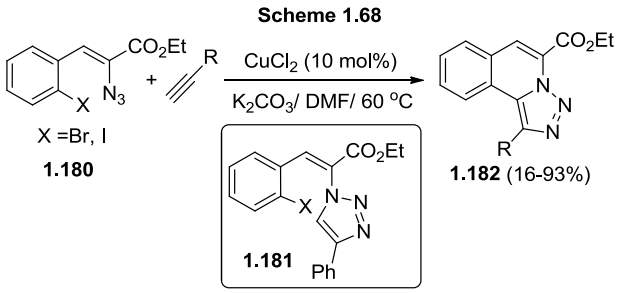
1.67).[95] This method involves two distinct sequential reactions by employing [Cu]-catalysis and proceeds in a single pot through the click reaction followed by an intramolecular C-O bond formation.

Scheme 1.67



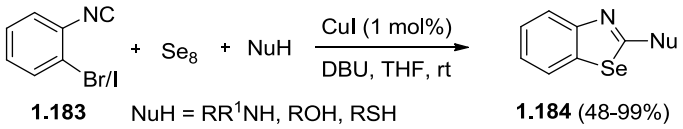
Liang and co-workers developed [Cu]-catalyzed tandem cyclization of 2-azido-3-(2-iodophenyl) acrylates **1.180** with terminal alkynes that afforded the 1,2,3-triazolo-[5,1-a]isoquinolines **1.182** without using any ligand (Scheme 1.68).[96] Control experiments performed under the optimized conditions using compound **1.181** indicated that the reaction did not proceed *via* click reaction and arylation pathway. Hence they proposed that this reaction initially proceeds *via* [Cu]-catalyzed Sonogashira cross coupling followed by an intramolecular 1,3-dipolar cycloaddition process. These triazolo fused isoquinolines were converted to 1,3-disubstituted isoquinolines in refluxing acetic acid with the expulsion of molecular nitrogen.

Scheme 1.68



Copper catalyzed reaction of 2-halo-aryl isocyanides **1.183** with elemental selenium and other hetero-nucleophiles affording the 1,3-benzoselenazoles **1.184** was developed by Fujiwara *et al* (Scheme 1.69).[97] Hetero-nucleophiles such as amines, phenols and thiophenols attack on isocyanides and selenium resulting in selenoimidoylation followed by an intramolecular [Cu]-catalyzed cyclization furnishing the benzoselenazoles. In addition to this, they also described the synthesis of 2-amino-1,3-benzotellurazoles.

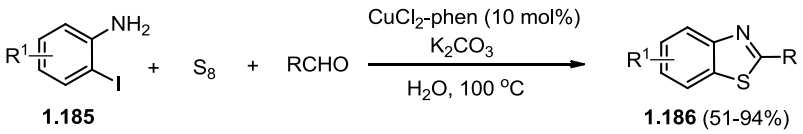
Scheme 1.69



1.183 NuH = RR^1NH, ROH, RSH **1.184** (48-99%)

An efficient one-pot procedure for the synthesis of benzothiazoles **1.186** by the three component reaction between 2-iodoanilines **1.185**, sulfur powder and aldehydes in an environmentally friendly condition has been achieved by Zhou's group (Scheme 1.70).[98] The control experiments suggested that the [Cu]-catalyst was useful to provide the diaryl disulfide from 2-iodo aniline and elemental sulfur.

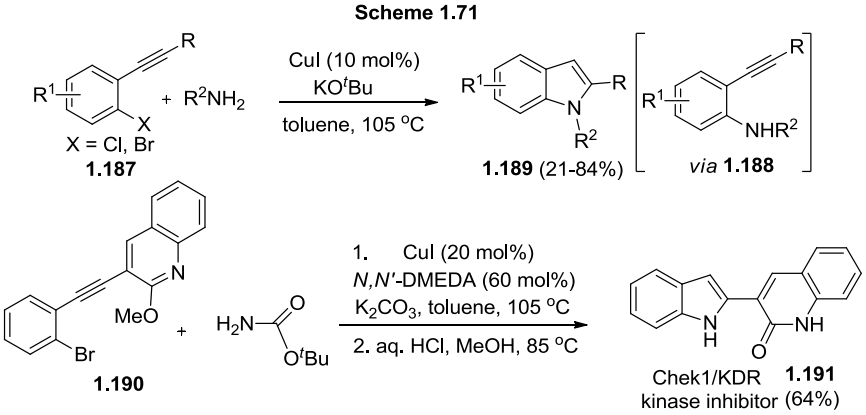
Scheme 1.70



1.185 **1.186** (51-94%)

Ackermann and co-workers described a copper catalyzed domino reaction between the *ortho*-alkynyl bromoarenes **1.187** and anilines for providing the *N*-aryl indole derivatives **1.189** *via* *N*-arylation and hydroamination process.[99a] This method also allowed an efficient synthesis of *N*-acyl or *N*-H indoles from *ortho*-alkynyl bromoarenes **1.190** and carbamates or amides. The importance of this methodology was highlighted by the preparation of Chek1/KDR **1.191** kinase inhibitor pharmacophore (Scheme 1.71).[99b]

Scheme 1.71

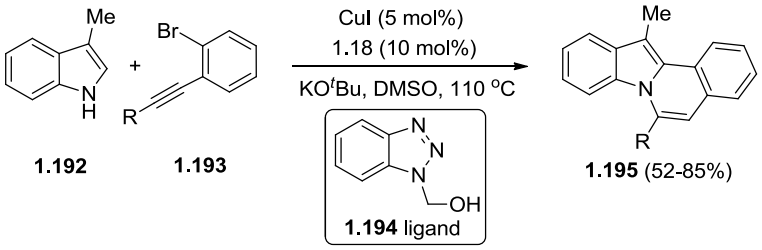


1.187 **1.189** (21-84%) **1.190** **1.191** (64%)

Verma *et al* reported a highly regioselective synthesis of diversely substituted indolo- and pyrrolo-[2,1-*a*]isoquinolines **1.195** by the [Cu]-catalyzed tandem reaction of indoles/pyrroles **1.192** with 2-bromoarylalkynes **1.193** with the use of benzotriazole-1-

ylmethanol **1.194** as a ligand (Scheme 1.72). This pathway preferentially involved the hydroamination of indoles or pyrroles onto the *o*-alkynyl halo-benzene and subsequent intramolecular cyclization *via* C2-arylation.[100]

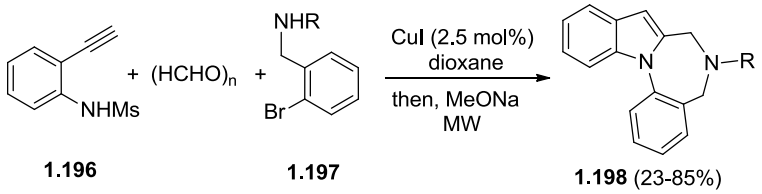
Scheme 1.72



1.192 **1.193** **1.194** ligand **1.195** (52-85%)

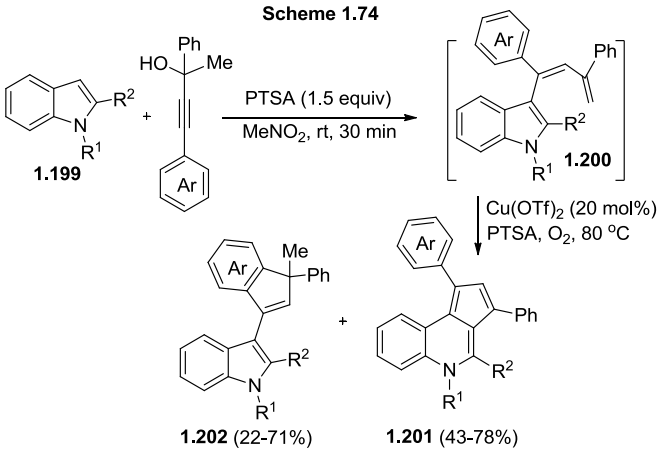
Ohno and co-workers described a three component domino reaction of *N*-mesyl-2-ethynylanilines **1.196**, paraformaldehyde and *N*-substituted-2-bromo benzylamines **1.197** that delivered the indole fused benzo-1,4-diazepines **1.198** under microwave irradiation using simple [Cu]-catalysis (Scheme 1.73).[101] This one-pot reaction involves formation of four new bonds *via* three catalytic cycles including [Cu]-catalyzed sequential amino-alkylation of terminal alkyne followed by indole formation and simultaneous *N*-arylation. This method was applicable to bromo-substituted heterocycles also providing the heterocycle-fused tetracyclic compounds.

Scheme 1.73



1.196 **1.197** **1.198** (23-85%)

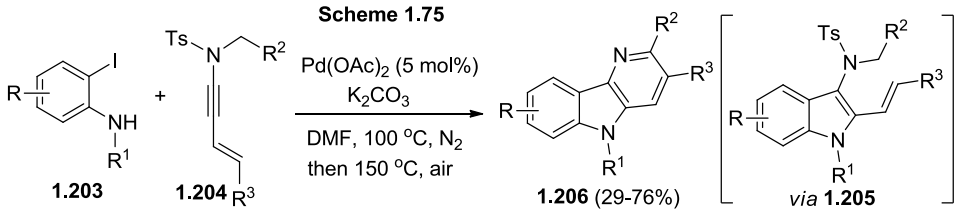
From our research group, a Brønsted acid mediated Friedel−Crafts alkenylation of indoles **1.199** with propargyl alcohols leading to the 3-dienylindoles **1.200** has been reported recently.[102] These 3-dienylindoles **1.200** undergo oxidative ring-expansion/intramolecular electrophilic substitution under [Cu]-catalysis with air as the oxidant delivering the cyclopenta[c]quinolones **1.201** and indenylindoles **1.202** in good yields (Scheme 1.74). Furthermore, one-pot strategy to synthesize the conjugated cyclopenta[c]quinolones directly from indoles and propargyl alcohols has also been developed. These products show intense fluorescence activity.



1.9 Miscellaneous [Pd]-Catalyzed tandem/one-pot reactions of ynamides/alkynes

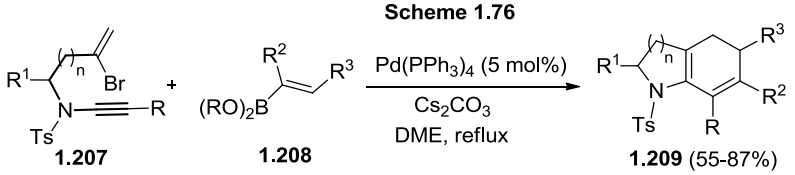
Palladium catalyzed tandem/one-pot reactions are complementary to many other transition metal catalyzed reactions after the discovery and the development of [Pd]-catalyzed cross-coupling reactions by Richard F. Heck, Ei-ichi Negishi and Akira Suzuki. Here we discuss some of the palladium catalyzed tandem/one-pot cyclization reactions of alkyne or halo-substrates.

Cao *et al.* described a facile cascade approach to the multisubstituted δ-carbolines **1.206** by palladium catalyzed sequential reaction of 2-iodoanilines **1.203** with *N*-tosyl enynamines **1.204** (Scheme 1.75).[103] Based on control experiments, they proposed that the reaction proceeds through the Larock hetero-annulation of 2-iodoaniline with ynamide resulting in indole intermediate **1.205**, followed by elimination and subsequent electrocyclization and finally oxidative aromatization by air leading to the δ-carbolines.



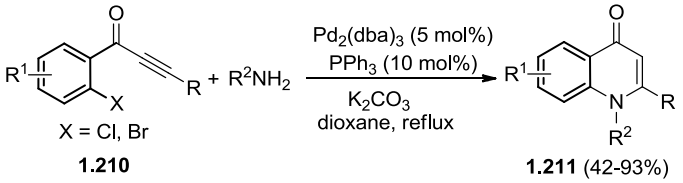
Anderson and co-workers demonstrated regiospecific cascade cyclization of bromoenynamides **1.207** with vinyl boronates **1.208** resulting in diverse bicyclic aminodienes **1.209** by using [Pd]-catalysis (Scheme 1.76).[104] It was the first synthetic approach on ynamides involving carbopalladation and subsequent Suzuki cross-coupling followed by 6π-elecrocyclization as the terminating step to provide the azabicycles.

Scheme 1.76



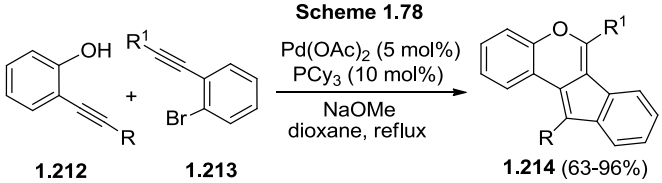
Xu and co-workers have developed an efficient one step approach to the functionalized 4-quinolones **1.211** by the tandem amination of easily accessible *o*-haloaryl acetylenic ketones **1.210** with primary amines *via* palladium-catalyzed double C-N bond formation process (Scheme 1.77).[105] Ynones reacted with amines including naphthyl and pyrimidine amines affording the corresponding quinolone derivatives in good yields.

Scheme 1.77



Wu *et al*. disclosed a facile synthesis of indeno[1,2-c]chromene scaffolds **1.214** from the reaction of 2-alkynyl phenols **1.212** with 2-alkynyl halobenzenes **1.213** under [Pd]-catalysis (Scheme 1.78).[106] Except tricyclohexyl phosphine (PCy_3), all other phosphine ligands were ineffective for this transformation. This [Pd]-catalyzed cascade reaction proceeded *via* the *syn*-insertion of R–Pd^{II}-X formed from 2-alkynyl halobenzene to the triple bond of the 2-alkynyl phenol, followed by insertion to the triple bond of 2-alkynylbromobenzene and subsequent intramolecular C–O bond formation.

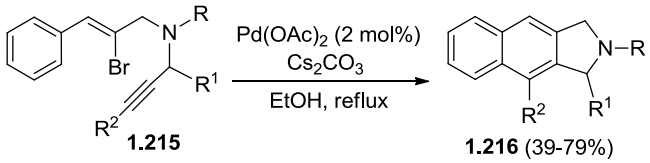
Scheme 1.78



An elegant route to tri- and tetra-cyclic heterocycles **1.216** by the palladium catalyzed tandem biscyclization of bromoenynes **1.215** has been developed by Tanaka's research group (Scheme 1.79).[107] The construction of benzoisoindole derivatives involved the formation of two new carbon-carbon bonds *via* C-H bond functionalization of the

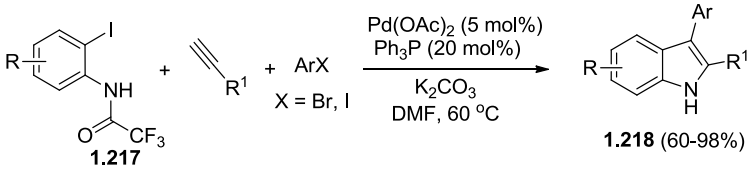
aromatic ring. Heteroaromatics such as benzofuran and indole substrates also resulted in tetracyclic heterocycles illustrating the utility of this methodology.

Scheme 1.79



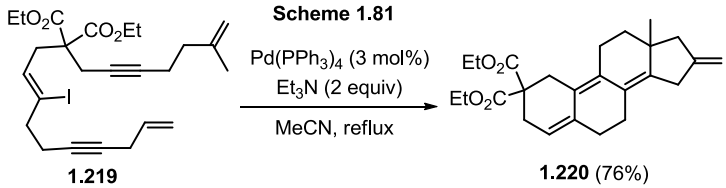
Lu *et al.* developed an economical one pot three component reaction for the regiospecific synthesis of 2,3-disubstituted indoles **1.218** *via* palladium catalyzed sequential Sonogashira cross coupling and Cacchi's protocol (Scheme 1.80).[108] However, this Sonogashira-Cacchi domino indolization process was limited to the *N*-protected 2-iodo substituted aniline substrates **1.217**, terminal arylacetylenes and aryl bromides.

Scheme 1.80



Negishi and co-workers developed an attractive strategy for the construction of two or more fused rings by the carbopalladation of the corresponding acyclic functionalized precursors (Scheme 1.81).[109] Thus the "zipper"-mode cyclization of halo-enyne substrate **1.219** involved an overall formation of four new carbon-carbon bonds in a single step under palladium catalysis and furnished the tetracyclic system **1.220** having a quaternary stereocenter.

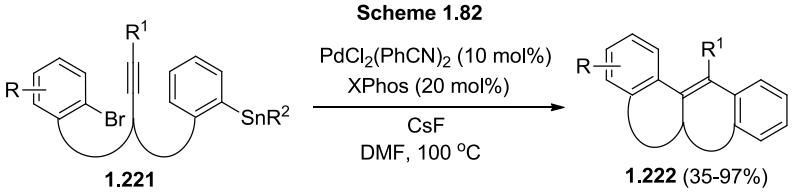
Scheme 1.81



Alkynes **1.221** having halo and stannane functionalities undergo *trans*-dicarbofunctionalization intramolecularly to form the oligocyclic ring systems **1.222**. This reaction was discovered by Werz and co-workers (Scheme 1.82).[110] The method involves

the formal *anti*-carbopalladation followed by the Stille cascade step and generates the two new carbon-carbon bonds. Double bond isomerization of the resulting oligocycles produces the heteroarenes in good yields.

Scheme 1.82



1.221 **1.222** (35-97%)

OBJECTIVES OF THE PRESENT WORK

The principal aim of the work was to research the new synthetic routes to benzosultams and enamides from ynamide substrates. Five topics chosen are given below.

(i) To examine the reactivity of functionalized ynamide substrates with sodium azide using [Cu]-catalysis in an effort to synthesize triazolo fused benzosultams,

(ii) To probe the reaction of functionalized ynamides with elemental sulfur and selenium with the aid of [Cu]-catalysis that could lead to novel sulfur and selenium containing benzosultams,

(iii) To explore the reactivity of functionalized ynamide substrates with nitrogen/ oxygen/ carbon nucleophiles in the presence of [Pd]-catalysis in order to achieve the synthesis of benzosultams,

(iv) To investigate the use of alcohols as hydrogenating agents for ynamides using [Pd]-catalysis, and

(v) To analyze the reaction of ynamides with aluminium chloride in an attempt to synthesize α-chloro-enamides.

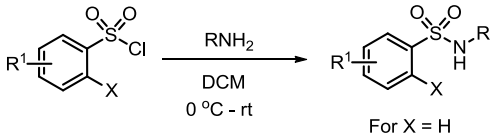
RESULTS AND DISCUSSION

This chapter deals with the results on various transformations of ynamides and related substrates leading to benzosultams and enamides. Details on the precursors that are utilized in the present study are presented in sections 2.1-2.2. After this, [Cu]-catalyzed cycloaddition of functionalized ynamides with sodium azide is discussed. Subsequently, [Cu]-catalyzed cyclization of functionalized ynamides/alkynes with elemental sulfur/selenium is described. Later sections delve on the synthesis of benzosultams by the cyclization of ynamides with various nucleophiles under [Pd]-catalysis. Hydrogenation/hydrohalogenation of ynamides leading to enamides is the topic of discussion in the ensuing sections. In this later part, the [Pd]-catalyzed stereoselective hydrogenation of ynamides using ethanol or the synergistic ethanol/ammonium formate system as hydrogenating source is discussed. This will be followed by deliberation on the regio- and stereo-specific hydrochlorination of ynamides using $AlCl_3$ as the chlorinating source and water as the proton source. All the products are well characterized by using IR, NMR, LCMS/CHN or HRMS and mp (for solids); the assigned regio- or stereo-chemistry of the products is based on X-ray crystallographic studies of illustrative compounds.

2.1 Synthesis of sulfonamides and bromo-alkyne substrates

Sulfonamides **1a-q** were prepared from the corresponding sulfonyl chlorides following a literature method (Scheme 1).[111] The 2-iodo substituted sulfonamides **2a-g** were synthesized by the iodination of sulfonamides using *n*-BuLi and I_2 (Scheme 2).[112]

Scheme 1

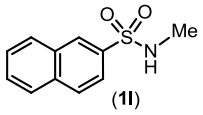


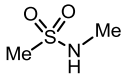
For X = H

R = Me, R^1 = 4-Me (**1a**)
R = Me, R^1 = 4-*t*-Bu (**1b**)
R = Me, R^1 = 4-OMe (**1c**)
R = Me, R^1 = 4-Ph (**1d**)
R = Me, R^1 = 4-NO_2 (**1e**)
R = Me, R^1 = 4-Br (**1f**)
R = Me, R^1 = 4-Cl, 2,5-diMe (**1g**)
R = Me, R^1 = H (**1h**)
R = allyl, R^1 = 4-Me (**1i**)
R = *i*-Pr, R^1 = 4-Me (**1j**)
R = Ph, R^1 = 4-Me (**1k**)

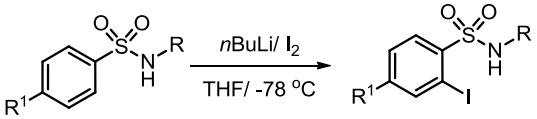
For X = Br

R = Me, R^1 = Me (**1n**)
R = Me, R^1 = CF_3 (**1o**)
R = Me, R^1 = H (**1p**)
R = *n*-butyl, R^1 = H (**1q**)


(**1l**)

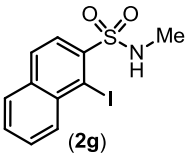

(**1m**)

Scheme 2



R = Me, R^1 = Me (**2a**)
R = Me, R^1 = *t*-Bu (**2b**)
R = Me, R^1 = OMe (**2c**)
R = Me, R^1 = Ph (**2d**)
R = *i*-Pr, R^1 = Me (**2e**)
R = Ph, R^1 = Me (**2f**)

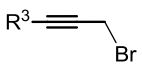
Similarly


(**2g**)

1-Bromo alkynes **3a-i**[113] and compound **4b**[114] were prepared by following a literature method; propargyl bromide **4a** is commercially available (Chart 1).

Chart 1

R^2 = Ph (**3a**)
R^2 = 4-tolyl (**3b**)
R^2 = 4-MeO-C_6H_4 (**3c**)
R^2 = 4-O_2N-C_6H_4 (**3d**)
R^2 = 4-biphenyl (**3e**)
R^2 = 3-F-C_6H_4 (**3f**)
R^2 = *n*-hexyl (**3g**)
R^2 = tips (**3h**)
R^2 = CH_2OBn (**3i**)



R^3 = H (**4a**)
R^3 = Ph (**4b**)

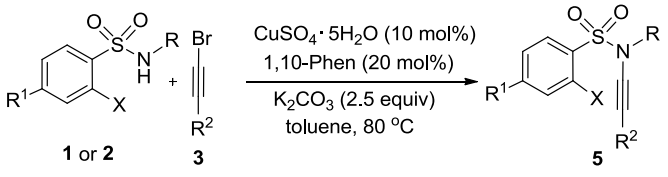
2.2 Synthesis of functionalized ynamides and alkynes

The ynamide substrates **5a-u** except **5n** were prepared following Hsung's procedure (Scheme 3).[11] For synthesizing compound **5n**, the earlier method was unsuccessful and hence it was prepared by using the iodonium salt.[10] The ynamide precursors **5a-t** are new and are characterized by using IR, NMR and HRMS/ elemental analysis. Each of these

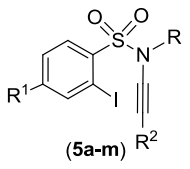
ynamide precursors showed a strong band at ~ 2200 cm^{-1} in the IR spectra due to the presence of the alkyne C≡C group. In the ^{13}C NMR spectra, two characteristic peaks at δ ~ 80 and ~ 70 because of the -C≡C- group, and a peak at δ ~ 90 owing to aromatic *C*-I carbon were observed.

Scheme 3

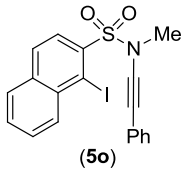
(a)



1 or **2** **3** **5**

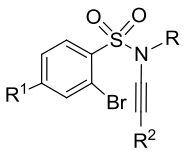


(**5a-m**)



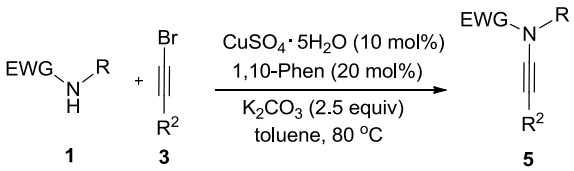
(**5o**)

R = Me, R^1 = Me, R^2 = Ph (**5a**)
R = Me, R^1 = *t*-Bu, R^2 = Ph (**5b**)
R = Me, R^1 = OMe, R^2 = Ph (**5c**)
R = Me, R^1 = Ph, R^2 = Ph (**5d**)
R = Me, R^1 = Me, R^2 = 4-tolyl (**5e**)
R = Me, R^1 = Me, R^2 = 4-MeO-C_6H_4 (**5f**)
R = Me, R^1 = Me, R^2 = 4-O_2N-C_6H_4 (**5g**)
R = Me, R^1 = Me, R^2 = 4-biphenyl (**5h**)
R = Me, R^1 = Me, R^2 = 3-F-C_6H_4 (**5i**)
R = Me, R^1 = Me, R^2 = *n*-hexyl (**5j**)
R = Me, R^1 = Me, R^2 = tips (**5k**)
R = Me, R^1 = Me, R^2 = CH_2OBn (**5l**)
R = *i*-Pr, R^1 = Me, R^2 = Ph (**5m**)
R = Ph, R^1 = Me, R^2 = Ph (**5n**)



R = Me, R^1 = Me, R^2 = Ph (**5p**)
R = Me, R^1 = CF_3, R^2 = Ph (**5q**)
R = Me, R^1 = H, R^2 = Ph (**5r**)
R = Me, R^1 = H, R^2 = *n*-hexyl (**5s**)
R = *n*-butyl, R^1 = H, R^2 = Ph (**5t**)

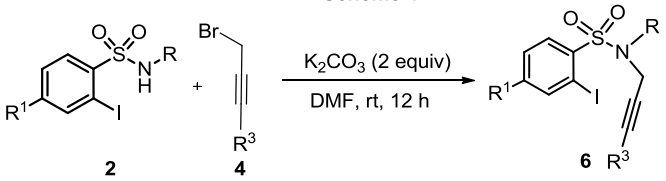
(b)



1 **3** **5**

The alkyne precursors **6a-d** were prepared by following a literature procedure with slight modification (Scheme 4).[69, 115] Iodobenzene **7**, amines **8a-e**, phenols **9a-f**, active methylene compounds **10a-c**, benzotriazoles **11a-c**, triazole **12** and tetrazoles **13a-b** are commercially available (Chart 2).

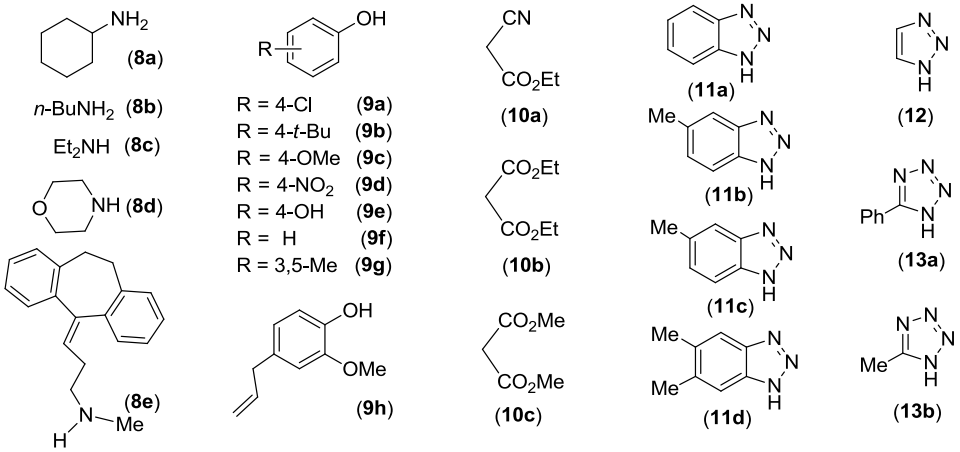
Scheme 4



2 **4** **6**

R = Me, R^1 = Me, R^3 = H (**6a**)
R = Me, R^1 = Me, R^3 = Ph (**6b**)
R = Me, R^1 = *t*-Bu, R^3 = Ph (**6c**)
R = Ph, R^1 = Me, R^3 = Ph (**6d**)

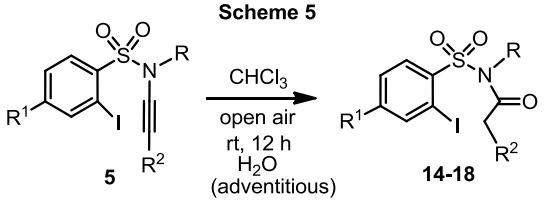
Chart 2



2.3 Conversion of ynamides into amides

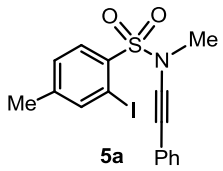
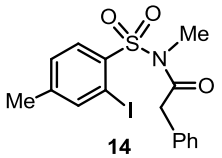
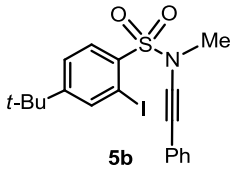
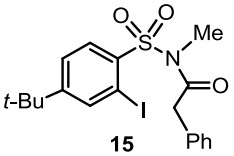
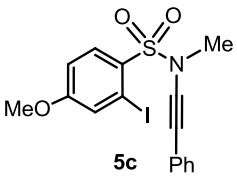
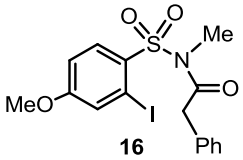
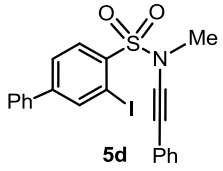
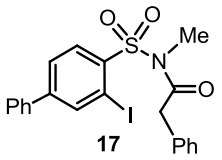
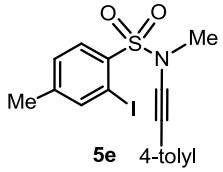
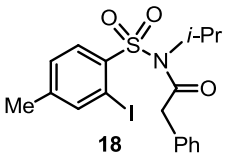
The iodo substituted ynamide substrates gradually undergo hydrolysis at room temperature (25 ^{o}C) but can be stored at low temperature (<4 ^{o}C). However, we observed that the hydrolysis of these ynamides occurs easily in halogenated solvents at rt in the presence of adventitious moisture. Thus, stirring the ynamides in $CHCl_3$ solution for 12 h in open air (adventitious moisture) afforded the corresponding *N*-sulfonylated amides **14-18** in good yields (Scheme 5). In the IR spectra, they exhibited a band δ ~ 1700 cm^{-1} ($\nu_{C=O}$) with the absence of the -*C*≡*C*- group. The ^{13}C NMR spectra showed a peak at δ ~ 170 (*C*=O) indicating that addition of water onto the alkyne functionality had taken place.

Scheme 5



5 **14-18**

Table 1: Formation of amides **14-18** from *N*-alkynyl 2-iodo-benzene sulfonamides.

Entry	Ynamide	Amide	Yield (%)[b]
1	 **5a**	 **14**	90
2	 **5b**	 **15**	90
3	 **5c**	 **16**	94
4	 **5d**	 **17**	84
5	 **5e** 4-tolyl	 **18**	86

2.4 Copper-catalyzed cycloaddition/cyclization of functionalized ynamides leading to benzosultams

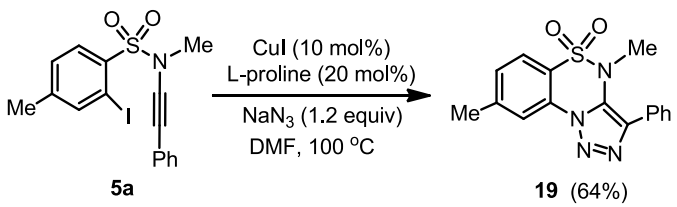
As mentioned in the Introduction, ynamides can be utilized for the synthesis of various heterocycles and benzosultams. To our knowledge, prior to our work, there were no reports on the synthesis of benzosultams from ynamide precursors. In the present work, we have developed a new synthetic strategy for benzosultams starting from ynamides.

2.4.1 [Cu]-catalyzed cycloaddition of ynamides with sodium azide to afford triazolo-fused benzosultams

Initially, we performed the reaction between *N*-alkynyl-2-iodo-benzenesulfonamide **5a** and sodium azide in the presence of CuI (10 mol%) and L-proline (20 mol%) in DMF at 100 ^{o}C for 12 h. To our delight, we obtained the desired benzosultam fused 1,2,3-

triazole product **19** in 64% isolated yield. This reaction proceeds via intermolecular C–N bond formation followed by cycloaddition between alkyne and azide. Our next step was directed towards screening various reaction parameters to improve the yield of the product and the details are given in Table 2.

Scheme 6



The absence of the ligand (L-proline) did not affect the yield (entry 1). Diethyl carbonate was ineffective and did not furnish the desired product (entry 2). Water as a solvent led to only 20% of product **19** along with 36% of the hydrolyzed product **14** (entry 3). Thus, hydrolysis was a major problem in water medium. Surprisingly, in PEG-400 as the solvent, compound **19** was isolated in 65% yield (entry 4). Although all the solvents checked had oxygen donors, PEG-400 has a combination of ether and residual hydroxyl groups which may promote the reaction better.[116] This factor might have been responsible for the improved yield of the product. Later, we found that 5 mol% of CuI furnished a similar yield (entry 5). Further decreasing catalyst loading to 2 mol%, decreased the yield of the product (entry 6). The yield was increased to 78% by using 2 equiv of NaN_3 instead of 1.2 equiv of NaN_3 (entry 7). No reaction was observed in the absence of CuI. Utilization of other copper salts did not improve yield of the desired product. Decrease in the yield was observed when the reaction was performed in open air (entry 12). Lowering the reaction temperature also decreased the yield. The reaction proceeds at room temperature (25 ^{o}C) but the yield was only 52% even after longer reaction times (48 h; entry 15). It is interesting to note that Yao's conditions[69] did give decent yields (ca. 70%) but in view of the use of simple NaN_3, the environmentally friendly solvent PEG-400, and lesser load of CuI, we have chosen conditions shown in entry 7 as the best in this work.

Table 2: Optimization of the catalytic system for the synthesis of tiazolo 1,2,4-benzothiadiazine 1,1-dioxide **19** (cf Scheme 6)[a]

Entry	CuX (mol%)	NaN_3 (equiv)	Solvent	Temp. (^oC)	Yield (%)[b]
1	CuI (10)	1.2	DMF	100	64
2	CuI (10)	1.2	$(EtO)_2CO$	100	0
3	CuI (10)	1.2	H_2O	100	20[c]
4	CuI (10)	1.2	PEG-400	100	65
5	CuI (5)	1.2	PEG-400	100	65
6	CuI (2)	1.2	PEG-400	100	58
7	**CuI (5)**	**2.0**	**PEG-400**	**100**	**78**
8	CuCl (5)	2.0	PEG-400	100	65
9	$CuSO_4 \cdot 5H_2O$(5)	2.0	PEG-400	100	62
10	$CuCl_2 \cdot 2H_2O$(5)	2.0	PEG-400	100	48
11	CuBr (5)	2.0	PEG-400	100	68
12	CuI (5)	2.0	PEG-400	100	56[d]
13	CuI (5)	2.0	PEG-400	80	72[e]
14	CuI (5)	2.0	PEG-400	60	38
15	CuI (5)	2.0	PEG-400	r.t.	52

[a]Ynamide (0.24 mmol), CuI (x mol%), NaN_3, solvent (1 mL) in the absence of L-proline for entries **1-15**. [b]Yield of the isolated product. [c]Hydrolyzed product **14** was isolated (36%). [d]Reaction was performed in an open air. [e]CuI (30 mol%), $TMSN_3$ (2.5 equiv), DIPEA (3 equiv), DMF solvent were used.

With the optimized conditions (entry 7) in hand, we examined the scope of this [Cu]-catalyzed one-pot reaction by employing various *N*-alkynyl-2-iodo-benzenesulfonamides **5** with sodium azide. Gratifyingly, the triazolo 1,2,4-benzothiadiazine 1,1-dioxide derivatives (**19-29**) were isolated in good to excellent yields (Table 3). IR, NMR and HRMS techniques were used to characterize these compounds. As expected, the band due to *C*≡*C* stretch was absent in the IR spectra of these compounds. In the ^{13}C NMR spectra, the absence of both the -*C*≡*C*- group and aromatic *C*-I carbon indicated the involvement of these functionalities in the cyclization process. The structure of compound **19** was confirmed by X-ray crystallography (Figure 1). There was no significant effect on yields of the products by altering the substituent on the benzene ring of 2-iodo-

benzenesulfonamides. While changing the substituent on the nitrogen of sulfonamide, we encountered a difficulty in the preparation of ynamide **5m**; however we did not find any problem in the course of cyclization process. Interestingly, the triisopropylsilyl substituted ynamide **5k** afforded the desired product **26** in 80% yield with the removal of triisopropylsilyl group; the structure of this product was confirmed by X-ray crystallography (Figure 1). On the other hand, the bulkier 1-bromo-2-biphenyl ethyne gave the corresponding ynamide **5h** in excellent yield, but unfortunately the cyclization was not observed. This may be due to the steric effect caused by the biphenyl moiety. Both alkyl and aryl alkynyl ynamides were amenable for this one-pot protocol to obtain benzosultam fused triazoles. Overall, the reaction involves the formation of three new C–N bonds.

Scheme 7

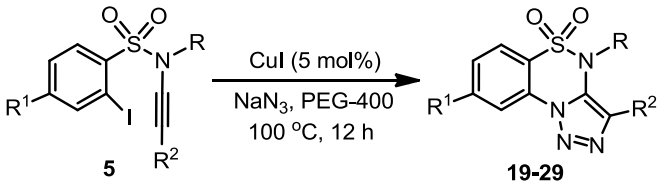
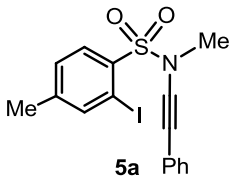
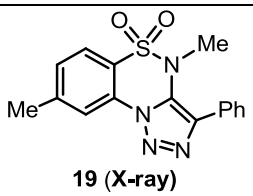
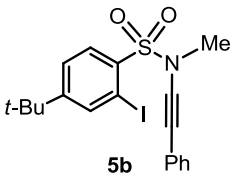
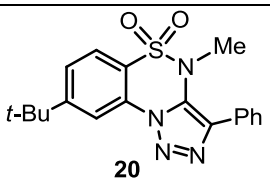
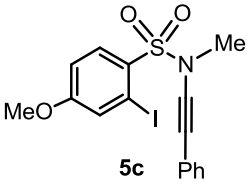
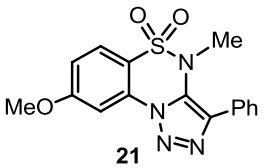
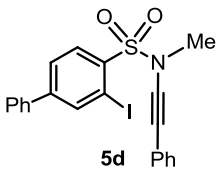
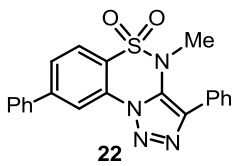
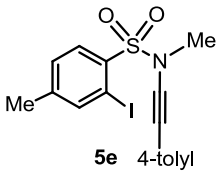
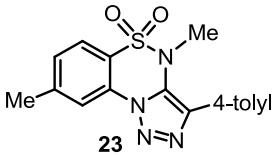
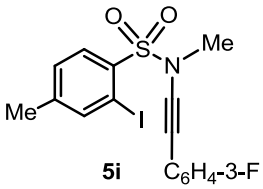
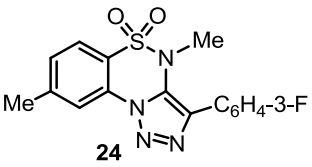
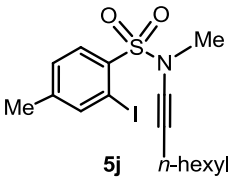
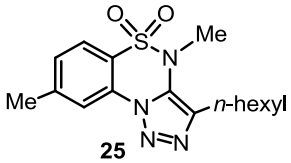
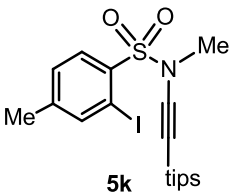
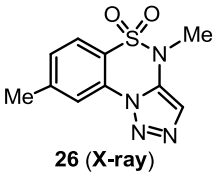
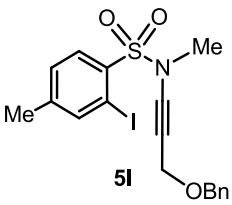
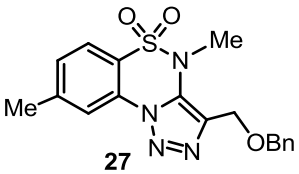
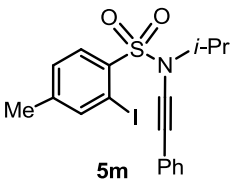
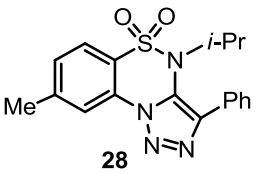
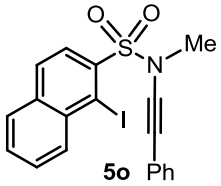
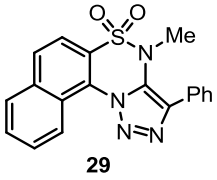


Table 3: Synthesis of triazolo 1,2,4-benzothiadiazine 1,1-dioxides from *N*-alkynyl 2-iodo-benzene sulfonamides[a]

Entry	Ynamides	Benzosultams	Yield (%)[b]
1	 **5a**	 **19 (X-ray)**	78
2	 **5b**	 **20**	84
3	 **5c**	 **21**	70

4			78
5			78
6			62
7			72
8			80
9			48
10			64

11	 5o	 29	72

[a]Ynamide (0.24 mmol), CuI (5 mol%), NaN_3 (0.48 mmol), PEG-400 (1 mL) were used. [b]Yield of the isolated product.

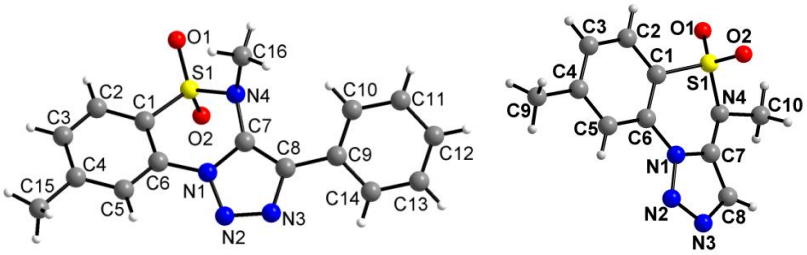


Figure 1. Molecular structures of compouds **19** and **26**. Selected bond parameters: Compoud **19** C(6)-N(1) 1.411(2), C(7)-N(1) 1.367(2), C(8)-N(3) 1.377(2), S(1)-O(1) 1.4229(13), S(1)-O(2) 1.4201(15), S(1)-N(4) 1.6487(15) [Å]. Compoud **26** C(6)-N(1) 1.403(2), C(7)-N(1) 1.348(3), C(8)-N(3) 1.357(3), S(1)-O(1) 1.4188(18), S(1)-O(2) 1.4233(19), S(1)-N(4) 1.6491(18) [Å].

In a manner similar to above, *N*-alkynyl-2-bromo-benzenesulfonamides **5** were subjected to the tandem reaction by following the optimized conditions (Scheme 8). This procedure afforded the desired cyclized products **30-32** and **19** in lower yields and required longer reaction time (Table 3). This result shows that aryl bromides are less reactive than aryl iodides, which is in accordance with the literature reports.[95]

Scheme 8

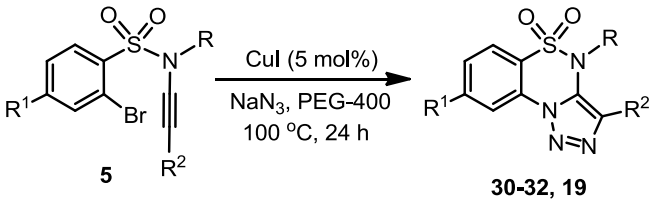
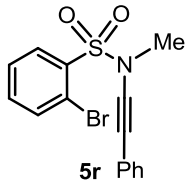
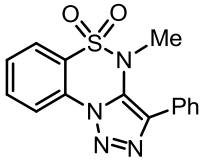
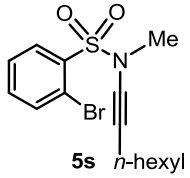
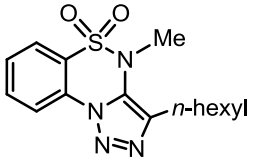
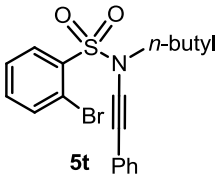
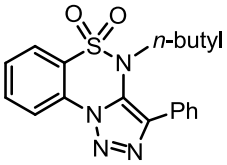
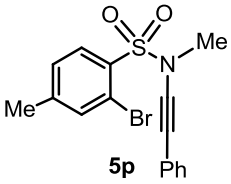
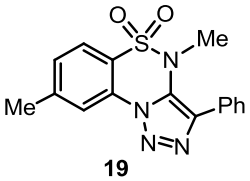


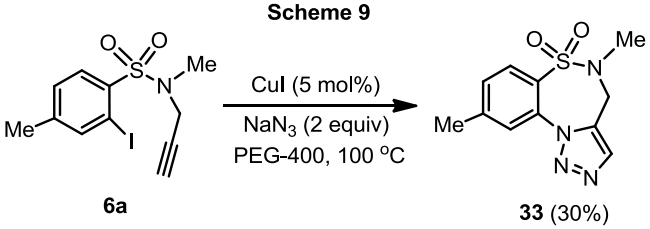
Table 3: One-pot synthesis of fused triazoles **30-32** and **19** from *N*-alkynyl 2-bromo-benzene sulfonamides[a]

Entry	Ynamides	Benzosultams	Yield (%)[b]
1	 **5r**	 **30**	56
2	 **5s** *n*-hexyl	 **31**	52
3	 **5t**	 **32**	60
4	 **5p**	 **19**	56

[a]Ynamide (0.24 mmol), CuI (5 mol%), NaN_3 (0.48 mmol) in PEG-400 (1 mL) at 100 ^oC. [b]Yield of the isolated product.

In continuation of the above, we made an attempt to synthesize a seven membered benzosultam fused triazole. Following optimized reaction conditions, we conducte the reaction between *N*-propargyl 2-iodo-benzenesulfonamide **6a** and sodium azide (Scheme 9). Here, we were able to isolate the expected triazolothiadiazepine 1,1-dioxide **33** in 30% yield. However, there were also other byproducts that were not isolated.

Scheme 9

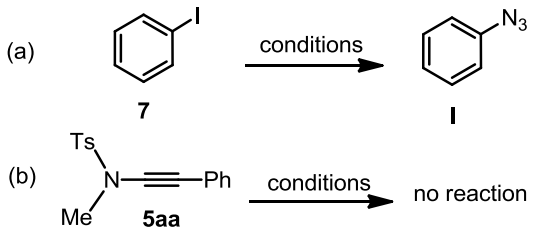


6a **33** (30%)

2.4.2 Plausible pathway for the formation of benzothiadiazines

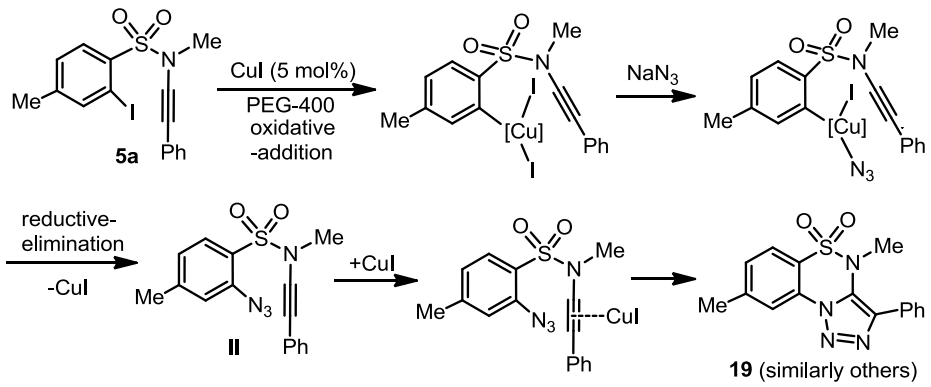
To understand the reaction pathway, we performed the reaction between phenyl iodide and ynamide with NaN_3 in the presence of [Cu]-catalyst. We observed the formation of phenyl azide **I** from phenyl iodide, but there was no reaction with ynamide **5aa** (Scheme 10a and b). Thus the azide is formed first. The other possibility involving cycloaddition between alkyne and sodium azide followed by intramolecular C–N bond formation catalyzed by [Cu][69, 93] is not observed here. A plausible catalytic cycle for the synthesis of triazolo 1,2,4-benzothiadiazine 1,1-dioxide derivative is shown in Scheme 11. The intermediate **II** is not isolated. Later, the [3 + 2] cycloaddition between alkyne and azide affords the benzosultam fused triazole.

Scheme 10



conditions: CuI (5 mol-%), NaN_3 (2 equiv), PEG-400 (1 mL), 100 ^oC.

Scheme 11



2.4.3 Utilization of the benzosultam fused triazoles

Later, we made an attempt to utilize the 1,2,3-triazoles synthesized so far. We found that in the presence of glacial acetic acid, 1,2,3-triazoles tend to undergo nitrogen elimination according to the available literature.[96, 117] We employed benzosultam fused triazoles for similar nitrogen elimination. However, we isolated only sulfonamides **34**–**37** in good yields (Scheme 12). The IR spectra of these compounds showed two peaks at ~

1750 cm^{-1} and ~ 1700 cm^{-1} due to the presence of ester and amide functionalities. These were formed by the cleavage of sulfonamide N–C bond along with nitrogen elimination from triazole moiety. The products may have considerable interest for chemists as they contain three functional groups, ester, amide and sulfonamide, in a single molecule. The structure of compound **34** was confirmed by X-ray crystallography (Fig. 5). This type of cleavage followed by acetic acid–water addition was not reported earlier in the literature.

Scheme 12

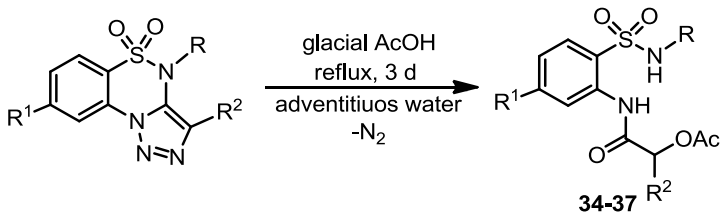
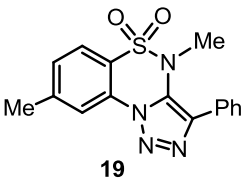
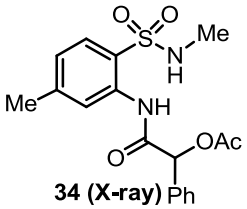
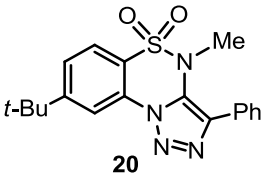
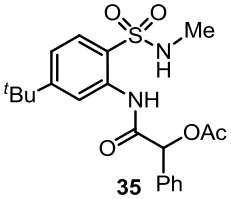
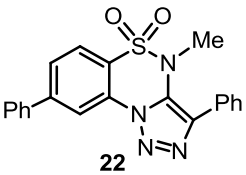
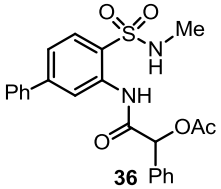
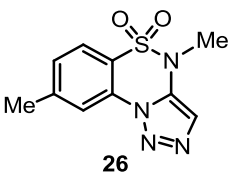
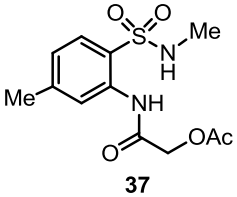


Table 4: Synthesis of functionalized sulfonamides from benzosultam fused triazoles

Entry	Benzosultams	Sulfonamides	Yield (%)
1	 **19**	 **34 (X-ray)**	80
2	 **20**	 **35**	86
3	 **22**	 **36**	78
4	 **26**	 **37**	90

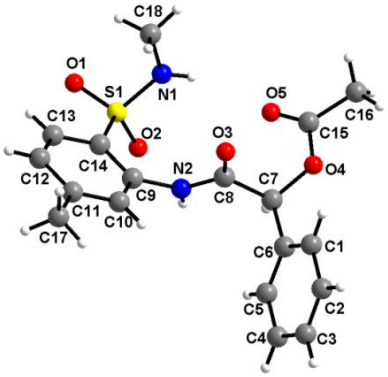


Figure 2. Molecular structure of compoud **34**. Selected bond parameters: C(8)-O(3) 1.224(5), C(7)-O(4) 1.435(5), C(7)-C(8) 1.528(6), S(1)-O(1) 1.420(4), S(1)-O(2) 1.430(4), S(1)-N(1) 1.615(5) [Å].

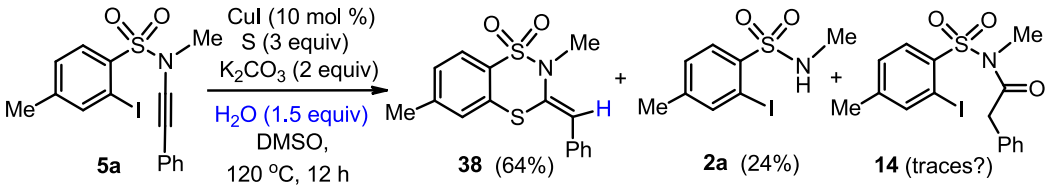
2.5 Use of elemental sulfur or selenium in a novel one-pot copper-catalyzed tandem-cyclization of functionalized ynamides leading to benzosultams

As discussed in the Introduction, among the different sources of sulfur and selenium, elemental sulfur and selenium are the cheapest, odorless and easy to handle. These properties make them attractive in organic synthesis. Air stable and inexpensive copper-catalysts are well explored in different one-pot cyclization processes. In the following sections, we describe [Cu]-catalyzed reactions of elemental sulfur or selenium with ynamides or alkyne substrates.

2.5.1 [Cu]-catalyzed reaction of ynamide 5a with elemental sulfur or selenium

We started with the reaction between *N*-alkynyl 2-iodo-benzenesulfonamide **5a** and elemental sulfur (3 equiv) in the presence of CuI as a catalyst, K_2CO_3 as a base in DMSO using water (1.5 equiv) as the proton source at 120 ^oC for 12 h. This reaction afforded benzo[1,4,2]dithiazine 1,1-dioxide **38** regio- and stereo-specifically in 64% isolated yield along with 2-iodo-*N*,4-dimethylbenzenesulfonamide **2a** in 24% yield (Scheme 13). The latter product arises from the hydrolysis of the ynamide. Hence it was required to minimize its formation in the optimization process. It should also be noted that in **38**, ***extra hydrogen*** has appeared at the olefinic site. Product **38** may be construed as the one resulting from the reaction of hydrogen sulfide with **5a**, but in this apparently straightforward reaction, only a complex mixture of products was observed.

Scheme 13



Optimization [Table 5] of the conditions was carried out to obtain the better yield of **38**. Unlike DMSO, other polar solvents like DMF and PEG-400 gave only a moderate yield. Use of water itself as a solvent led to the undesired water addition product 2-iodo-4,*N*-dimethyl-*N*-phenylacetylbenzenesulfonamide **14** in 46% in addition to the desired product **38** (32%). Solvents like toluene, diethyl carbonate and ethanol did not give **38**. Satisfyingly, NMP as a solvent led to the formation of **38** in 72% yield along with 16% of **2a** (Table 5, entry 8). To our delight, the yield of the product was enhanced to 90% by decreasing the temperature to 70 ^{o}C (Table 5, entry 10). However, further decrease in temperature to 25 ^{o}C decreased the yield of the desired product. Thus, it is revealed that temperature has great impact on the cyclization reaction. Decrease in the yield of the product (42%) was observed in the absence of water (entry 12). Thus, most probably, water is participating in the reaction. The yield of the product was reduced to 72% by using 5 mol% of CuI. Notably, in the absence of CuI catalyst, we did not observe the formation of **38**. Increasing the [Cu]-catalyst loading to 20 mol% did not enhance the yield of the product. It is noteworthy that decrease in the amount of sulfur to 2 equiv decreased the yield of the product (Table 5, entry 16). Other copper sources like CuBr, $CuSO_4.5H_2O$ etc. did not improve the yield. On the other hand, sulfur source such as $Na_2S.9H_2O$ gave undesired products **2a** and **14** with only trace amounts of product **38.** Anhydrous Na_2S and $Na_2S_2O_3.5H_2O$ were ineffective (Table 5, entry 20). H_2S gas as a sulfur source gave a complex reaction mixture with only trace amount of **38**. In the absence of K_2CO_3, we observed only **3a** and **14** (Table 5, entry 21). Thus, the best conditions are: CuI (10 mol%), sulfur (3 equiv; i.e., 3/8 S_8), water (1.5 equiv), K_2CO_3 (2 equiv) with NMP as a solvent at 70 ^{o}C for 12 h. For the corresponding selenium compounds (e.g., **50**), a higher temperature (90 ^{o}C) and longer time (20 h) was required for optimum yields [cf. Table 6].

Table 5: Optimization of the catalytic system for the synthesis of benzo[1,4,2]dithiazine 1,1-dioxide **38** (cf. Scheme 13)[a]

Entry	CuX (mol%)	Solvent	Temp (^{o} C)	Yield (%)[b]
1[c]	CuI (10)	DMSO	120	64
2	CuI (10)	DMF	120	58
3	CuI (10)	PEG-400	120	56
4[d]	CuI (10)	H_2O	120	32
5	CuI (10)	Toluene	120	n.d.
6	CuI (10)	$(EtO)_2CO$	120	n.d.
7	CuI (10)	EtOH	120	n.d.
8	CuI (10)	NMP	120	72
9	CuI (10)	NMP	100	78
10	**CuI (10)**	**NMP**	**70**	**90**
11	CuI (10)	NMP	r.t	50
12[e]	CuI (10)	NMP	70	42
13	CuI (5)	NMP	70	72
14	-	NMP	70	n.d
15	CuI (20)	NMP	70	90
16[f]	CuI (10)	NMP	70	82
17	CuBr (10)	NMP	70	76
18	$CuCl_2 \cdot 2H_2O$ (10)	NMP	70	60
19	$CuSO_4 \cdot 5H_2O$ (10)	NMP	70	52
20[g]	CuI (10)	NMP	70	trace
21[h]	CuI (10)	NMP	70	n.d

[a]Ynamide (0.24 mmol), CuI (x mol%), S (3 equiv of S or 3/8 equiv of S_8), K_2CO_3 (2 equiv), H_2O (1.5 equiv), solvent (1 mL) were used. [b]Yield of the isolated product. [c]2-iodo-*N*,4-dimethylbenzenesulfonamide **2a** was isolated (24%). [d]Water addition product **14** was isolated (46%). [e]H_2O (1.5 equiv) was not used as a reagent. [f] S (2 equiv of S or 2/8

equiv of S_8) was used. [g]Reaction was performed with $Na_2S.9H_2O$ or Na_2S or $Na_2S_2O_3.5H_2O$ as a sulfur source. [h]In the absence of K_2CO_3. n.d. = not detected.

Table 6: Optimization of the catalytic system for the synthesis of benzo[1,4,2]thiaselenazine 1,1-dioxide **50**[a]

Entry	CuX (mol%)	Solvent	Temp (^oC)	Yield (%)[b]
1	CuI (10)	NMP	70	42
2	**CuI (10)**	**NMP**	**90**	**70**
3	CuI (10)	DMSO	90	34
4	CuI (10)	DMF	90	n.d.
5	CuI (10)	PEG-400	90	68
6	CuI (5)	NMP	90	52
7	-	NMP	90	n.d.
8	CuI (10)	Toluene	90	n.d.
9	CuI (10)	$(EtO)_2CO$	90	n.d.
10	CuI (10)	EtOH	90	n.d.
11	CuBr (10)	NMP	90	46
12	$CuSO_4 \cdot 5H_2O$ (10)	NMP	90	32
13[c]	CuI (10)	NMP	90	n.d.

[a]Ynamide (0.24 mmol), CuI (x mol%), Se (3 equiv of Se or 3/8 equiv of Se_8), K_2CO_3 (2 equiv), H_2O (1.5 equiv), solvent (1 mL) were used. [b]Yield of the isolated product. [c]In the absence of K_2CO_3. n.d. = not detected.

We then explored the substrate scope of this [Cu]-catalyzed one-pot reaction by employing various *N*-alkynyl 2-iodo-benzenesulfonamides and elemental sulfur or selenium. The products, benzo[1,4,2]dithiazine 1,1-dioxides **38-49** and benzo[1,4,2]thiaselenazine 1,1-dioxides **50-57** were isolated in good to excellent yields (Scheme 14). All these compounds were characterized by using IR, NMR and HRMS techniques and the corresponding selenium compounds were characterized by ^{77}Se NMR

also. The absence of (*C*≡*C*) stretch in the IR spectra of these compounds and also the absence of both the -*C*≡*C*- group and aromatic *C*-I carbon in ^{13}C NMR spectra indicate the participation of these functionalities in the cyclization process. The structures of compounds **38** and **50** as confirmed by X-ray crystallography are shown in Figure 3. By changing the substituents on either the sulfonyl attached benzene ring or on the nitrogen atom we did not observe any significant change on yields of the products. Furthermore, there was no pronounced effect on the yields of the products by changing the substituents on the alkyne substituent R^2. Indeed, the reaction using triisopropylsilyl substituted ynamide **5k** afforded the desired product **47** in 82% yield (cf Table 7). Even the bulky 4-biphenyl substituted ynamide **5h** gave the product **43** in 72% yield. *N*-alkynyl 2-bromo-benzenesulfonamide **5r** did not react, suggesting that iodo-substituent is essential for this cyclization reaction. The method described in this report is indeed versatile for the synthesis of 1,4,2-benzodithiazines 1,1-dioxides or 1,4,2-benzothiaselenazine 1,1-dioxides.

Scheme 14

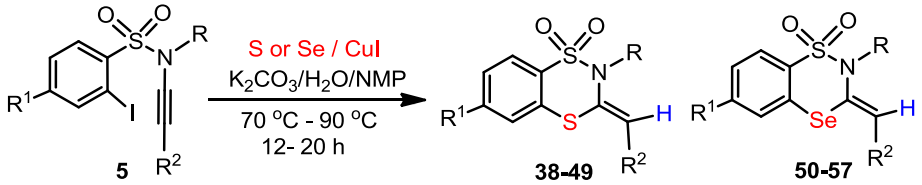
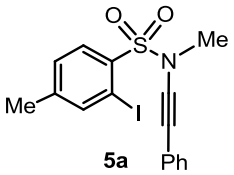
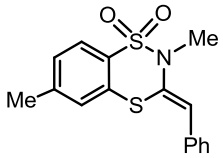
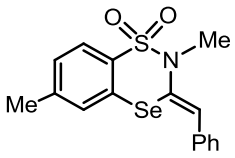
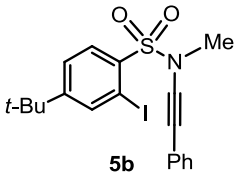
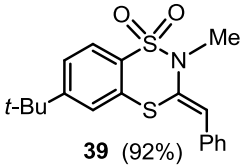
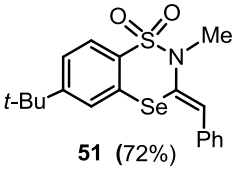
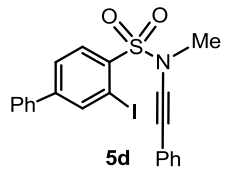
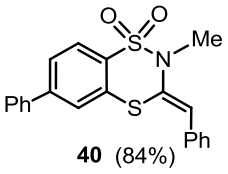
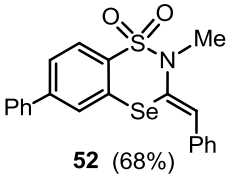
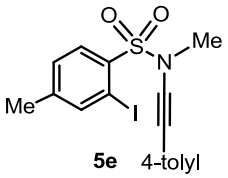
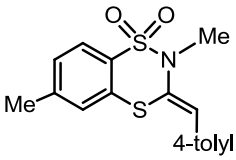
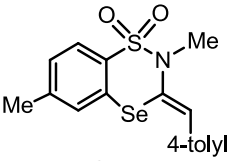
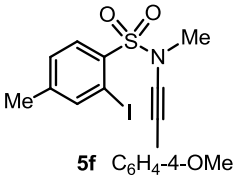
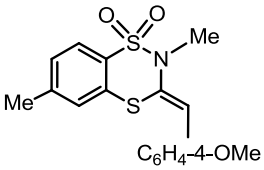
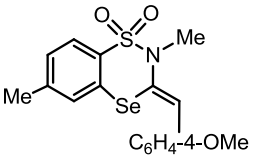
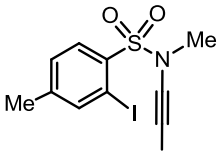
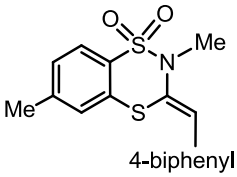
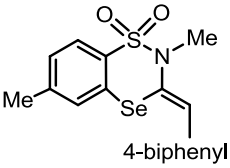
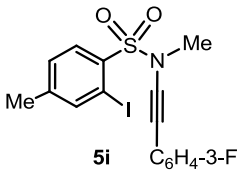
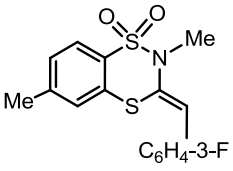
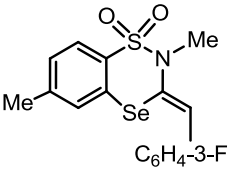
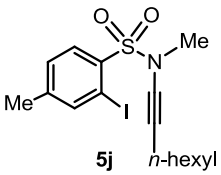
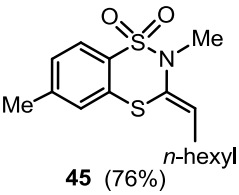
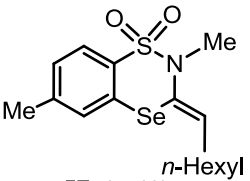
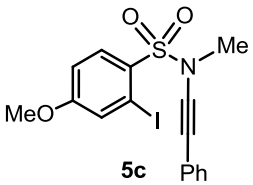
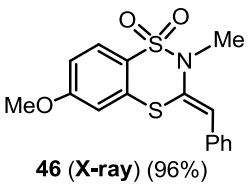
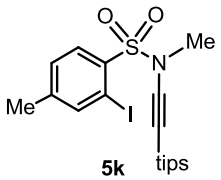
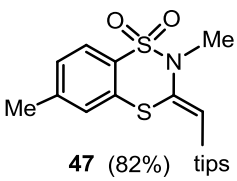
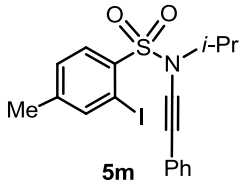
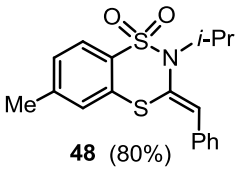
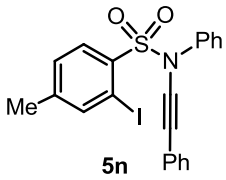
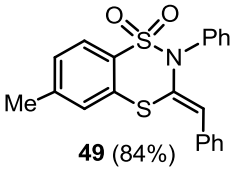


Table 7: Synthesis of benzo[1,4,2]dithiazine 1,1-dioxide derivatives **38-49** and benzo[1,4,2]thiaselenazine 1,1-dioxide derivatives **50-57**[a]

Entry	Ynamide	Benzosultam[b]	Benzosultam[b]
1	 **5a**	 **38 (X-ray)** (90%)	 **50 (X-ray)** (70%)
2	 **5b**	 **39** (92%)	 **51** (72%)

3	 **5d** Ph	 **40** (84%)	 **52** (68%)
4	 **5e** 4-tolyl	 **41** (86%)	 **53** (64%)
5	 **5f** C_6H_4-4-OMe	 **42** (86%)	 **54** (60%)
6	 **5h** 4-biphenyl	 **43** (72%)	 **55** (50%)
7	 **5i** C_6H_4-3-F	 **44** (**X-ray**) (84%)	 **56** (62%)
8	 **5j** *n*-hexyl	 **45** (76%)	 **57** (56%)
9	 **5c** Ph	 **46** (**X-ray**) (96%)	
10	 **5k** tips	 **47** (82%) tips	

11	 **5m**	 **48** (80%)
12	 **5n**	 **49** (84%)

[a]Conditions: **5** (0.24 mmol), sulfur [0.09 mmol as S_8]/ selenium [0.09 mmol as Se_8], CuI (10 mol%), K_2CO_3 (0.48 mmol) and H_2O (0.36 mmol) in NMP (1 mL) at 70 ^oC (for S)/ 90 ^oC (for Se) for 12 h (for S)/ 20 h (for Se). [b]Isolated yields after column chromatography are given in parenthesis.

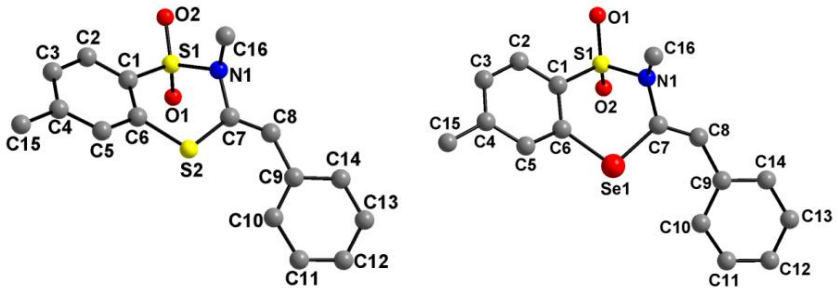


Figure 3. Molecular structures of compounds **38** (left) **50** (right). Selected bond parameters: Compound **38** S2-C6 1.756(7), S2-C7 1.786(8), C7-C8 1.315(10), C8-C9 1.452(12), C7-N1 1.425(10), C6-C1 1.418(11) (Å). Compound **50** Se1-C6 1.910(2), Se1-C7 1.915(3), C7-C8 1.328(4), C8-C9 1.471(3), C7-N1 1.432(3), C6-C1 1.400(3) (Å).

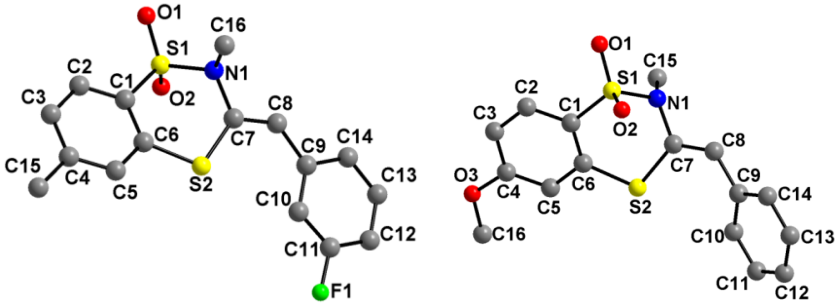


Figure 4. Molecular structures of compounds **44** (left) **46** (right). Selected bond parameters: Compound **44** S2-C6 1.770(9), S2-C7 1.762(9), C7-C8 1.333(12), C8-C9 1.444(12), C7-N1 1.444(11), C6-C1 1.379(13) (Å). Compound **46** S2-C6 1.760(3), S2-C7 1.769(3), C7-C8 1.322(4), C8-C9 1.457(3), C7-N1 1.437(3), C6-C1 1.388(3) (Å).

2.5.2 [Cu]-catalyzed reaction of alkynes with elemental sulfur or selenium

A perusal of the above reaction indicates that it need not be restricted to just sulfonamides leading to six-membered rings. Pleasingly, we realized that it can be extended to the formation of the seven-membered rings systems *via* 2-iodo-*N*-methyl/phenyl-*N*-(3-phenylprop-2-yn-1-yl)benzenesulfonamides (**6**). Thus the reaction of **6** with elemental sulfur or selenium readily afforded the desired seven membered benzosultams (Scheme 15), benzodithiazepines (**58-60**) and benzothiaselenazepines (**61-63**), regio- and stereo-specifically in excellent yields (Table 8). The structure of compound **9** was confirmed by X-ray crystallography (Figure 5).

Scheme 15

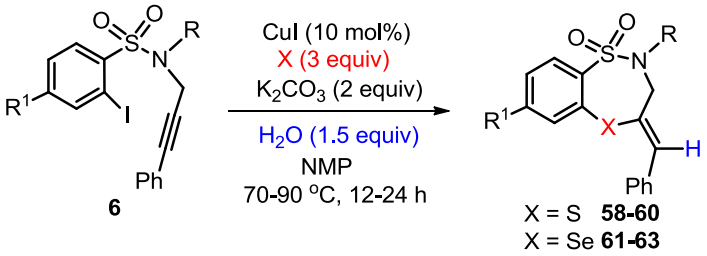
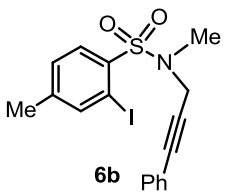
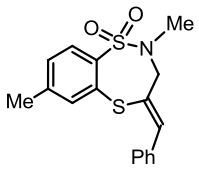
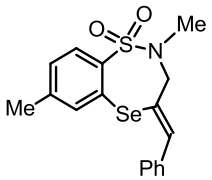
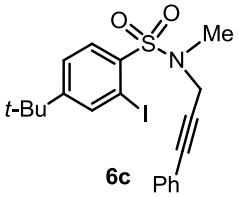
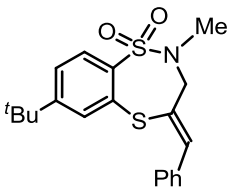
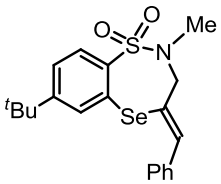
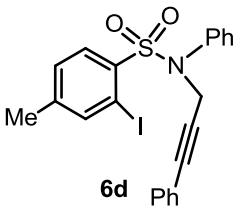
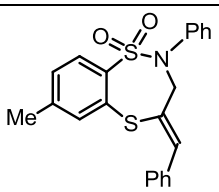
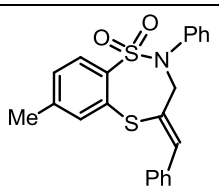


Table 8. Formation of benzodithiazepines (**58-60**) and benzothiaselenazepines (**61-63**)

Entry	Ynamides	Benzosultams	Benzosultams
1	 **6b**	 **58 (X-ray)** (86%)	 **61** (76%)
2	 **6c**	 **59** (84%)	 **62** (82%)
3	 **6d**	 **60** (76%)	 **63** (68%)

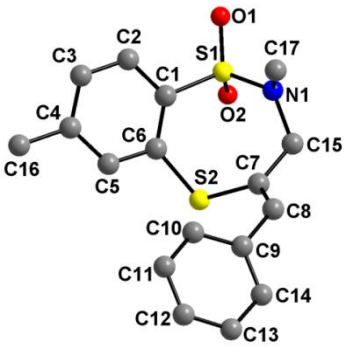
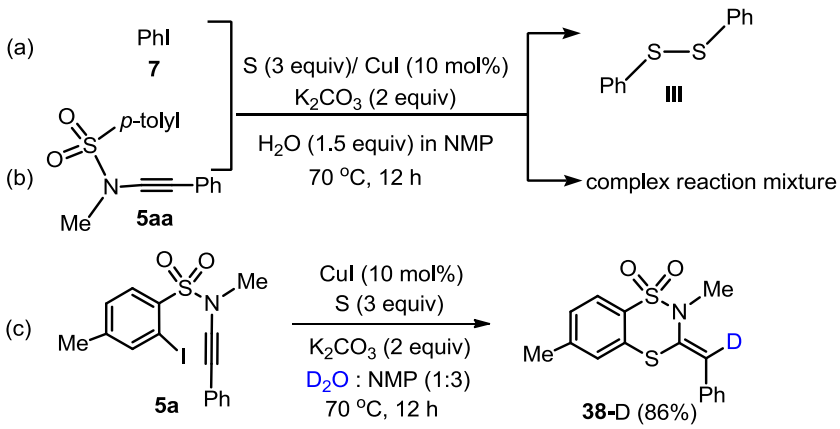


Figure 5. Molecular structure of compound **58**. Selected bond parameters: S2-C6 1.7792(17), S2-C7 1.7823(17), C7-C8 1.327(2), C8-C9 1.479(2), C7-C15 1.503(2), C6-C1 1.394(2) (Å).

2.5.3 Control experiments

In order to explain the plausible catalytic cycle, we have performed the following control experiments under our standard conditions. Thus the reaction of elemental sulfur with iodobenzene **7** afforded the product **III** (Scheme 16a). A similar observation has been made by Zhou and co-workers.[90, 98] In contrast, the reaction between sulfur and ynamide **5aa** leads to a complex reaction mixture (Scheme 16b). The reaction of ynamide **5a** with elemental sulfur in D_2O and NMP (1:3) mixture delivers compound **38**-D (Scheme 16c). Formation of this deuterated compound clearly indicates the crucial role of water during the course of the cyclization process as a proton source.

Scheme 16

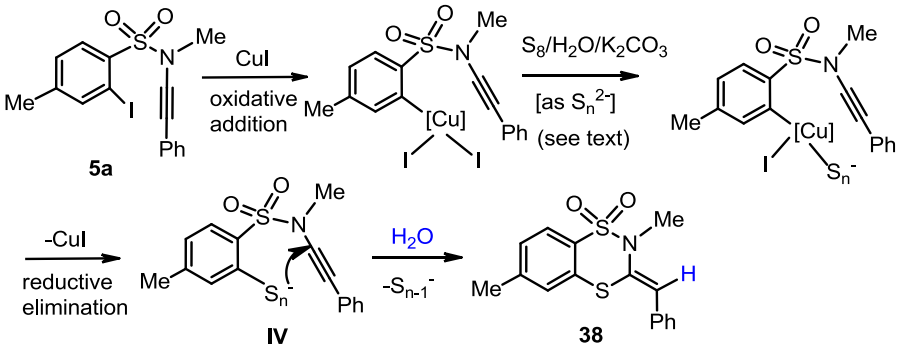


2.5.4 Proposed pathway for the formation of product 38

A plausible pathway for the formation of **38** based on the control experiments and earlier literature is shown in Scheme 17.[118] Oxidative addition of **5a** to CuI occurs

initially,[119] followed by attack of sulfur (as, possibly S_n^{2-}) /water/base and subsequent reductive elimination of CuI leading to intermediate **IV**. It is known that elemental sulfur disproportionates in the presence of a base to oligosulfide anion and sulfite.[118] Intermediate **IV** undergoes cyclization followed by abstraction of proton (source: water) to give product **38**. The fact that we could isolate the deuterated compound **38**-D (cf. Scheme 16c) is consistent with the intervention of water in this cyclization. The regiospecific attack of sulfur on the carbon N-*C*≡C carbon is consistent with that observed in hydrothiolation of ynamides.[120]

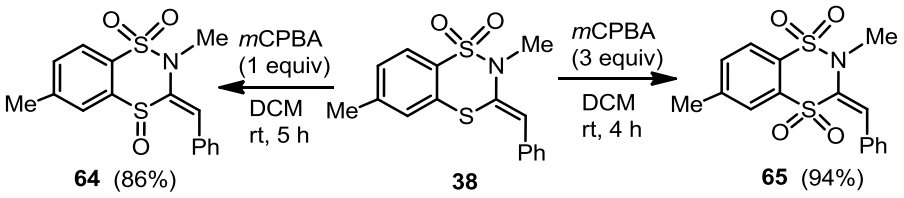
Scheme 17



2.5.5 Selective oxidation of compound 38

It may be noted that in benzo[1,4,2]dithiazine 1,1-dioxide **38**, one sulfur is in +6 oxidation state and the other in is +2 oxidation state. We felt that variability/utility of such systems will be better if we oxidize the low-valent sulfur. Selective oxidation reactions are of significant interest in the pharmaceutical industry.[121] Fortunately, oxidation of benzo[1,4,2]dithiazine 1,1-dioxide **38** with *m*CPBA (1 equiv) in dichloromethane (1 mL) preferentially gives benzo[1,4,2]dithiazine 1,1,4-trioxide **64** in 86% yield. As expected, (*S*=*O*) stretch is observed for this compound at ~ 1030 cm^{-1} in the IR spectrum. Increasing the amount of *m*CPBA (3 equiv) results in the formation of benzo[1,4,2]dithiazine 1,1,4,4-tetraoxide **65** in 94% yield (Scheme 18). The IR spectrum of this compound showed the sulfone stretching at ~ 1310 cm^{-1} and ~ 1118 cm^{-1}.

Scheme 18



2.6 Palladium-catalyzed tandem-cyclization of functionalized ynamides: An approach to benzosultams

Among the various transition metal catalysts, palladium is widely used in the tandem cyclization of various organic substrates depicted in the introduction. We present the tandem cyclization of ynamides using various nucleophiles with the aid of [Pd]-catalysis in the following section.

2.6.1 Palladium-catalyzed cyclization of ynamides with sulfonamides

When we performed the reaction between *N*-alkynyl 2-iodo-benzenesulfonamide **5a** and sulfonamide **1a** in the presence of $PdCl_2(PPh_3)_2$ catalyst in DMSO using K_2CO_3 as the base at 70 ^oC for 12 h, 1,2-benzothiazine 1,1-dioxide (**66**) was formed in 26% isolated yield. We then proceeded to optimize the conditions (Table 9 for details). Among the bases Et_3N, NaOH, KOH and KO^{t}Bu that were tested, KO^{t}Bu gave the best yield. The solvents DMSO, DMF, CH_3CN, THF, dioxane, toluene and CH_2Cl_2 were checked but DMSO was proved to be the best. Among the catalytic systems $PdCl_2/PPh_3$, $Pd(OAc)_2/PPh_3$, $Pd(dba)_2$ and Pd/C, the first two worked well but the presence of phosphine was necessary. Decreasing the catalyst loading from 5 to 3 mol% lowered the yield. Thus the best conditions that led to 92% isolated yield of **66** were: $PdCl_2(PPh_3)_2$ (5 mol%), sulfonamide (1.2 equiv), KO^{t}Bu (2 equiv) in DMSO at 70 ^oC for 12 h.

Scheme 19

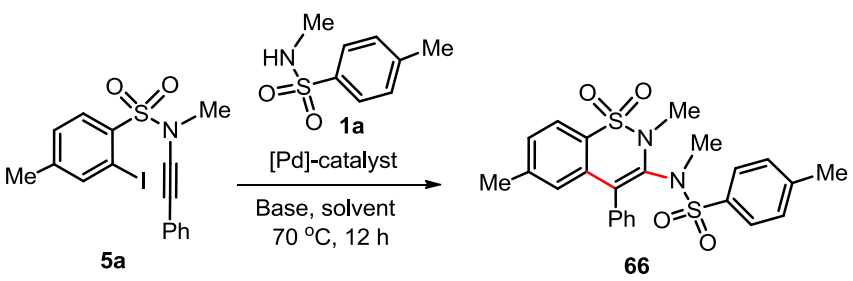


Table 9. Optimization study for the palladium-catalyzed reaction of ynamide **5a** with sulfonamide **1a** to afford compound **66**[a]

Entry	[Pd] (5 mol%)	Solvent	Base	Yield (%)[b]
1	$PdCl_2(PPh_3)_2$	THF	K_2CO_3	n.d.
2	$PdCl_2(PPh_3)_2$	Toluene	K_2CO_3	n.d.
3	$PdCl_2(PPh_3)_2$	DMSO	K_2CO_3	26
4	$PdCl_2(PPh_3)_2$	DMSO	Et_3N	n.d.
5	$PdCl_2(PPh_3)_2$	DMSO	NaOH	82
6	$PdCl_2(PPh_3)_2$	DMSO	KOH	60
7	**$PdCl_2(PPh_3)_2$**	**DMSO**	**KO^{t}Bu**	**92**
8	$PdCl_2(PPh_3)_2$	DMF	KO^{t}Bu	72
9	$PdCl_2(PPh_3)_2$	CH_3CN	KO^{t}Bu	70
10	$PdCl_2(PPh_3)_2$	THF	KO^{t}Bu	24
11	$PdCl_2(PPh_3)_2$	Dioxane	KO^{t}Bu	20
12[c]	$PdCl_2(PPh_3)_2$	DCM	KO^{t}Bu	n.d.
13	$PdCl_2$+2(PPh_3)	DMSO	KO^{t}Bu	90
14	$Pd(OAc)_2$+2(PPh_3)	DMSO	KO^{t}Bu	86
15[d]	$PdCl_2$	DMSO	KO^{t}Bu	trace
16	$Pd(PPh_3)_4$	DMSO	KO^{t}Bu	76
17	$Pd(dba)_2$	DMSO	KO^{t}Bu	trace
18	Pd/C	DMSO	KO^{t}Bu	trace

19[e]	$PdCl_2(PPh_3)_2$	DMSO	KO^{t}Bu	76

[a]Reaction conditions: Ynamide (0.24 mmol), [Pd]-catalyst (5 mol%), sulfonamide (1.2 equiv) and base (2 equiv) in the solvent (1 mL) at 70 ^oC for 12 h. [b]Yield of isolated product; n.d. = not detected. [c]Reaction was done at rt (25 ^oC). [d]Reaction was performed in the absence of PPh_3. [e] 3 mol% of catalyst was used.

After optimization, we explored the scope and versatility of this [Pd]-catalyzed one-pot reaction by employing ynamide **5a** and secondary sulfonamides **1**. The products, 1,2-benzothiazine 1,1-dioxides **66-80**, were isolated in good to excellent yields (Scheme 20). Both electron rich and electron deficient aryl groups on sulfonyl moiety were well-tolerated. Even the aliphatic sulfonamide **1m** underwent cyclization smoothly to afford compound **75** in 70% yield. Interestingly, with *N*-allyl sulfonamide **1i** as the nucleophile, ***deallylation*** occurred to give product **73**. Subsequently, we could readily extend the scope of the transformation using other *N*-alkynyl 2-iodo-benzenesulfonamides **5** and *N*,4-dimethyl benzene sulfonamide **1** (Table 10, entries 11-16). Moreover, the reaction of *N*-alkynyl 2-bromo-benzenesulfonamide **5p** also afforded the desired product **66** in 74% yield (entry 14, Table 10). This result indicates that, as expected, bromo precursors are less reactive than the corresponding iodo precursors (entries 1 and 14).

Scheme 20

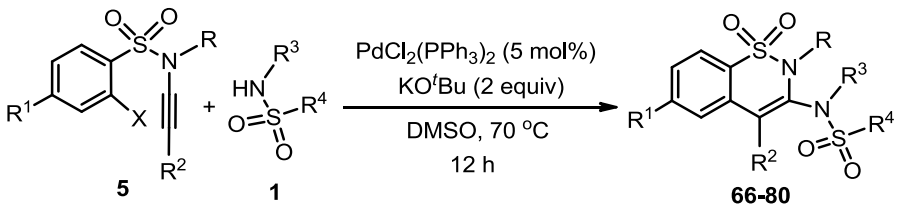
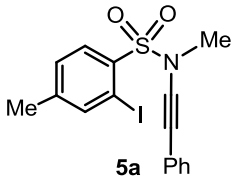
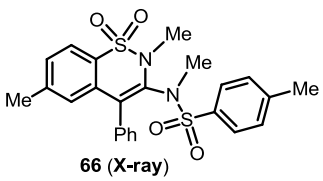
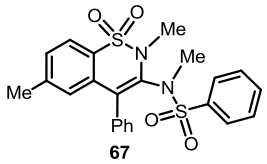
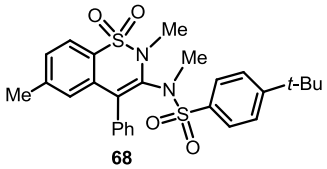
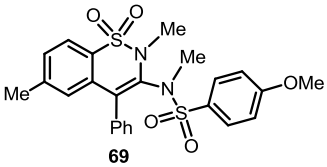
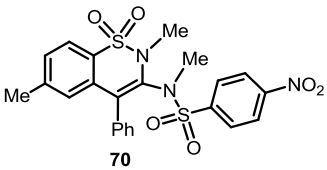
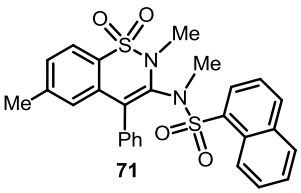
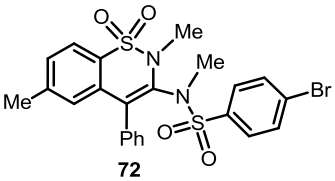
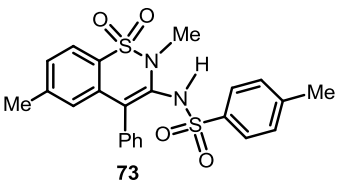
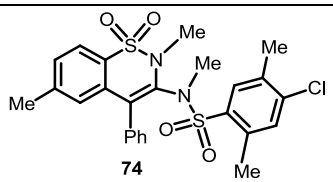
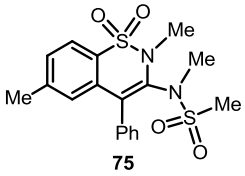
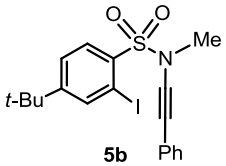
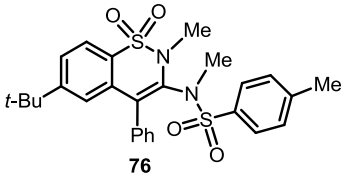
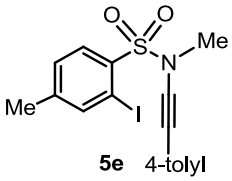
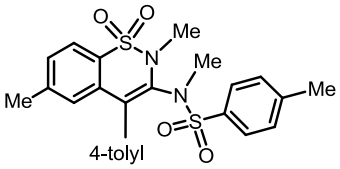
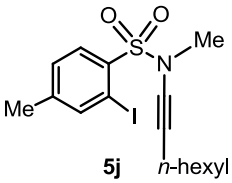
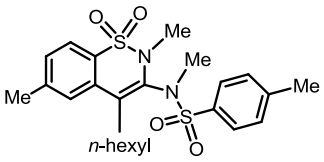
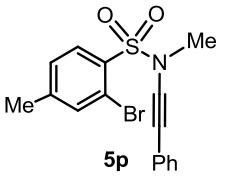
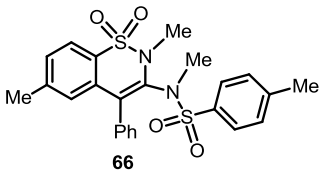
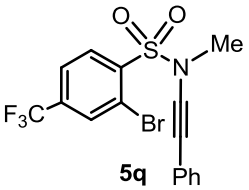
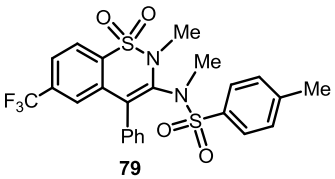
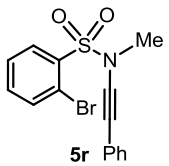
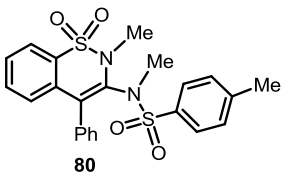


Table 10. Reaction of ynamides with sulfonamides[a]

Entry	Ynamides	Benzosultams	Yield (%)[b]
1	 **5a**	 **66** (**X-ray**)	92

2	**5a**	 **67**	90
3	**5a**	 **68**	96
4	**5a**	 **69**	88
5	**5a**	 **70**	82
6	**5a**	 **71**	80
7	**5a**	 **72**	72
8	**5a**	 **73**	80
9	**5a**	 **74**	76

10	**5a**	 **75**	70
11	 **5b**	 **76**	90
12	 **5e** 4-tolyl	 4-tolyl **77**	92
13	 **5j** *n*-hexyl	 *n*-hexyl **78**	94
14	 **5p** Ph	 **66**	74
15	 **5q** Ph	 **79**	64
16	 **5r** Ph	 **80**	76

[a]Reaction conditions: **5** (0.24 mmol), **1** (0.29 mmol), $PdCl_2(PPh_3)_2$ (5 mol%), KO^{t}Bu (0.48 mmol) in DMSO (1 mL) at 70 ^{o}C for 12 h. [b]Yield of the isolated product.

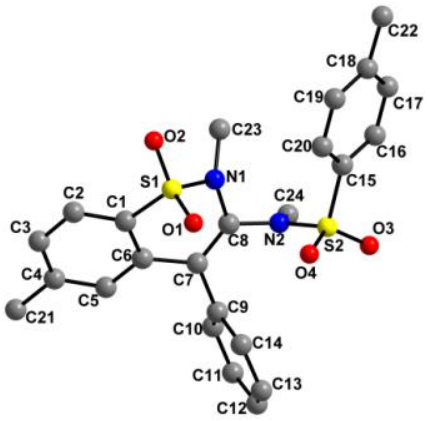


Figure 6. Molecular structure of compound **66**. Selected bond parameters: C6-C7 1.475(5), C7-C8 1.344(4), C8-N2 1.416(4), C8-N1 1.414(4), C6-C1 1.402(5), C7-C9 1.488(4) (Å). Hydrogen atoms are omitted for clarity.

2.6.2 Palladium-catalyzed cyclization of ynamides with amines

Pleasingly, the above cyclization was not restricted to sulfonamide nucleophiles and was expandable to other nitrogen nucleophiles such as amines that led to sultams **81-89** in good yields (Table 11). In these cases, even K_2CO_3 as the base worked well and hence was utilized for cyclization. The scope of the reaction includes both primary and secondary aliphatic amines, morpholine (entry 4) as well as the antidepressant drug nortriptyline (entry 5). The less basic aniline, though, was unreactive under these conditions. The structure of the product **81** was confirmed by single crystal X-ray analysis (Figure 7).

Scheme 21

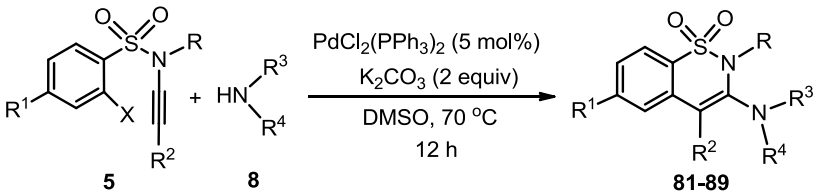
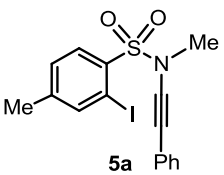
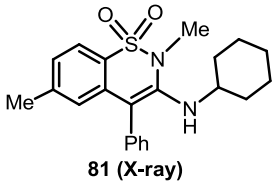
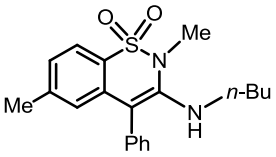
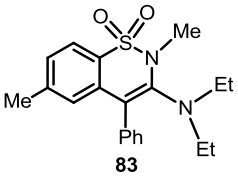
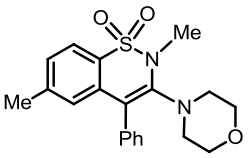
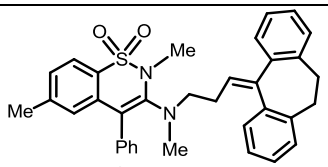
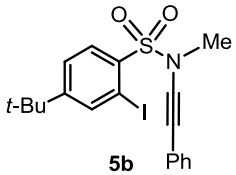
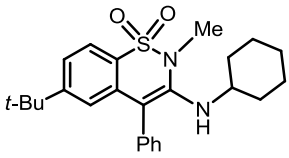
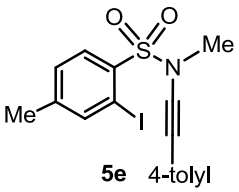
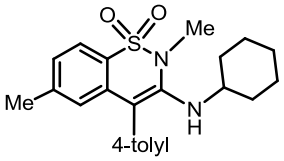
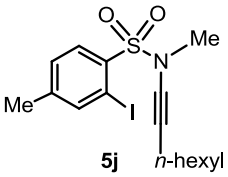
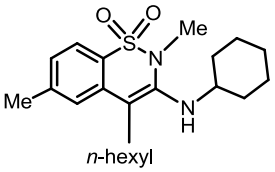
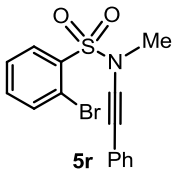
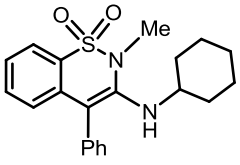


Table 11. Reaction of ynamides with amines[a]

Entry	Ynamide	Benzosultam	Yield (%)[b]
1	 **5a**	 **81 (X-ray)**	86

2[c]	**5a**	 **82**	94
3[c]	**5a**	 **83**	96
4	**5a**	 **84**	72
5	**5a**	 **85**	76
6	 **5b**	 **86**	86
7	 **5e** 4-tolyl	 4-tolyl **87**	82
8	 **5j** *n*-hexyl	 *n*-hexyl **88**	76
9	 **5r** Ph	 **89**	64

[a]Reaction conditions: **5** (0.24 mmol), **8** (0.29 mmol), $PdCl_2(PPh_3)_2$ (5 mol%), K_2CO_3 (0.48 mmol) in DMSO (1 mL) at 70 ^oC for 12 h. [b]Yield of the isolated product. [c]0.72 mmol of the amine was used due to its volatile nature.

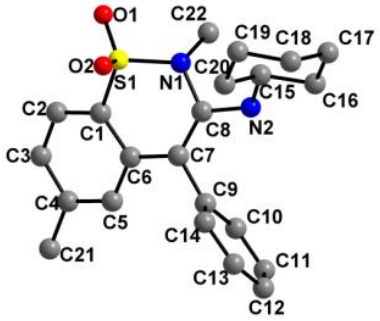


Figure 7. Molecular structure of compound **81**. Selected bond parameters: C6-C7 1.461(3), C7-C8 1.346(3), C8-N2 1.379(3), C8-N1 1.430(2), C6-C1 1.411(3), C7-C9 1.495(2) (Å). Hydrogen atoms are omitted for clarity.

2.6.3 Palladium-catalyzed cyclization of ynamides with phenols

Satisfyingly, the scope of the above methodology could be broadened further by using oxygen nucleophiles such as phenols (including eugenol). Thus, benzosultams **90-101** were obtained in good yields by reacting the ynamides **5** with phenols **9** (Scheme 22). While KO^{t}Bu as a base worked well for phenols. Phenols bearing both electron releasing and withdrawing substituents on the phenyl ring reacted smoothly with ynamide **5a** providing the corresponding cyclized products **90-97** in good yields (Table 12, entries 1-8). However, electron releasing substituents gave higher yields compared to withdrawing substituents. X-ray structure was determined for compound **90** is shown in Figure 8.

Scheme 22

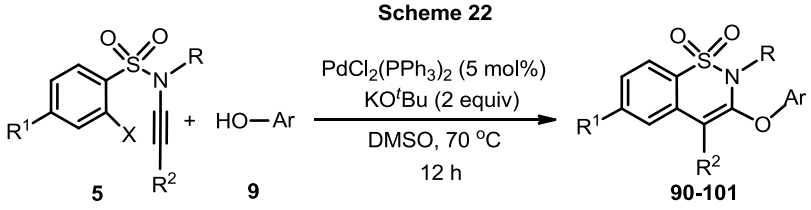
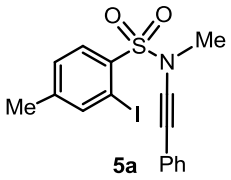
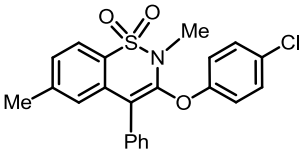
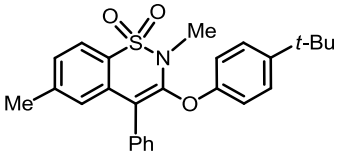
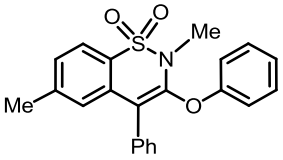
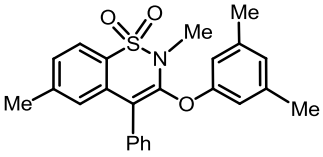
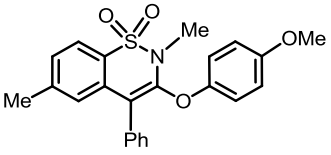
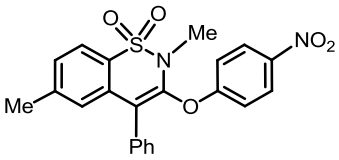
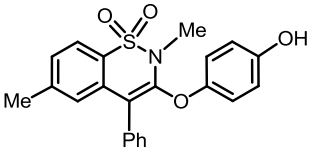
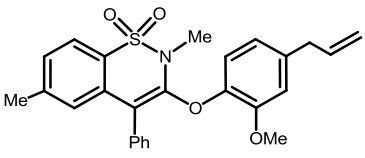
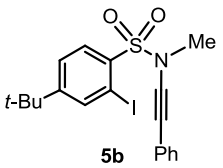
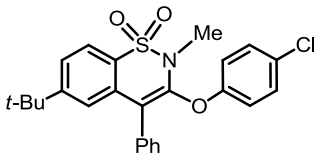
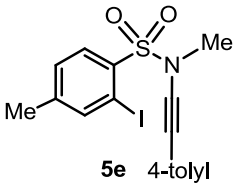
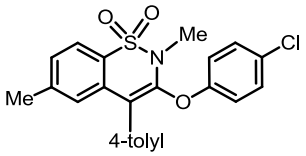
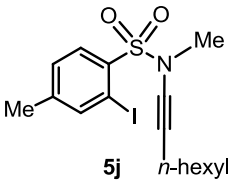
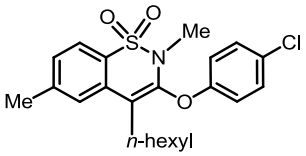
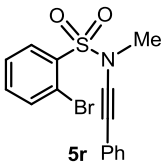
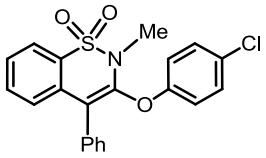


Table 12. Reaction of ynamides with phenols[a]

Entry	Ynamides	Benzosultams	Yield (%)[b]

1	 **5a**	 **90** (**X-ray**)	82
2	**5a**	 **91**	80
3	**5a**	 **92**	86
4	**5a**	 **93**	76
5	**5a**	 **94**	82
6	**5a**	 **95**	64
7	**5a**	 **96**	56
8	**5a**	 **97**	72

9	 **5b**	 **98**	86
10	 **5e** 4-tolyl	 **99**	86
11	 **5j** *n*-hexyl	 **100**	56
12	 **5r** Ph	 **101**	70

[a]Reaction conditions: **5** (0.24 mmol), **9** (0.29 mmol), $PdCl_2(PPh_3)_2$ (5 mol%), KO^{t}Bu (0.48 mmol) in DMSO (1 mL) at 70 ^{o}C for 12 h. [b]Yield of the isolated product.

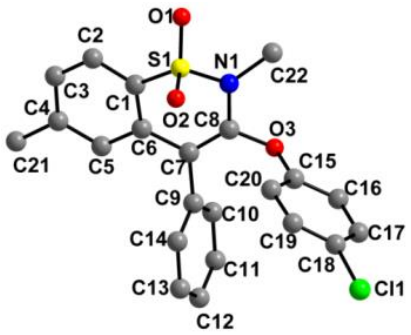


Figure 8. Molecular structure of compound **90**. Selected bond parameters: C6-C7 1.455(3), C7-C8 1.341(3), C8-O3 1.363(3), C8-N1 1.399(3), C6-C1 1.399(4), C7-C9 1.494(3) (Å). Hydrogen atoms are omitted for clarity.

Surprisingly, the use of alcohols (ethanol, *t*-butanol or benzyl alcohol) as nucleophiles resulted in a 5-exo cyclization mode, without incorporation of the nucleophile. For example, the reaction between **5a** and ethanol itself as a solvent by using either K_2CO_3 or KO^{t}Bu as the base using $PdCl_2(PPh_3)_2$ catalyst afforded isomeric mixture of products in

92% overall yield. Fortunately, the major component, sultam (**102**; Figure 9) crystallized out (80% yield) from ethyl acetate solution.

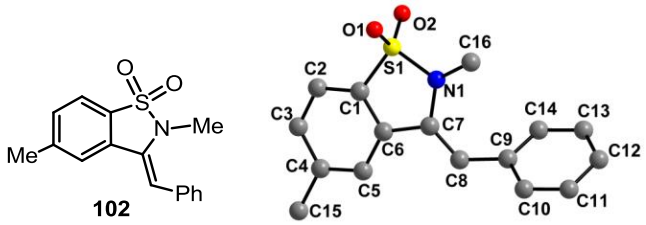


Figure 9. Compound **102**: Line drawing and molecular structure [C6-C7 1.472(3), C7-C8 1.333(3), C7-N1 1.417(3), C6-C1 1.380(3), C6-C5 1.395(3)Å].

2.6.4 Palladium-catalyzed cyclization of ynamides with active methylene compounds

Interestingly, ***carbon*** nucleophiles with an active methylene group could also be employed in this transformation (Scheme 23). Although the cyclization happened with carbon nucleophiles using KO^{t}Bu as a base, NaOH gave the best yields. Hence the carbon nucleophiles such as active methylene compounds **10** also afforded the cyclized products **103-109** in good yields (Table 13).

Scheme 23

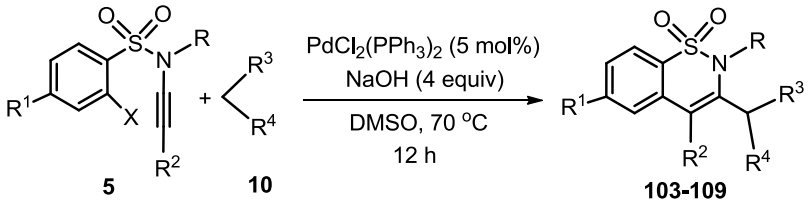
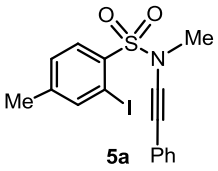
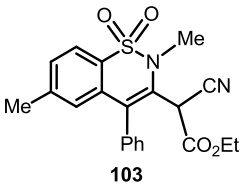
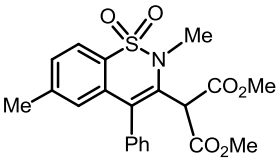
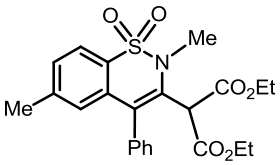
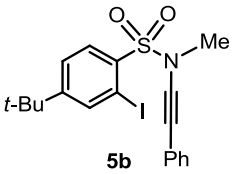
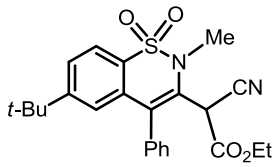
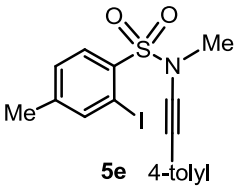
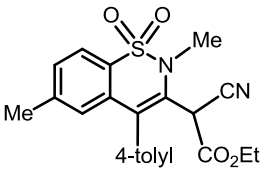
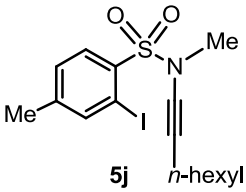
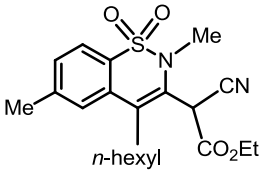
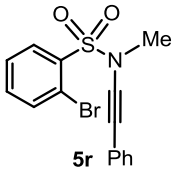
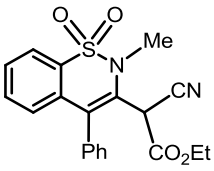


Table 13. Reaction of ynamides with active methylene compounds[a]

Entry	Ynamides	Benzosultams	Yield (%)[b]
1	 **5a**	 **103**	72

2	**5a**	 **104 (X-ray)**	64
3	**5a**	 **105**	62
4	 **5b**	 **108**	76
5	 **5e** 4-tolyl	 **106**	72
6	 **5j** *n*-hexyl	 **107**	58
7	 **5r** Ph	 **109**	52

[a]Reaction conditions: **1** (0.24 mmol), **10** (0.29 mmol), $PdCl_2(PPh_3)_2$ (5 mol%), NaOH (0.96 mmol) in DMSO (1 mL) at 70 ^oC for 12 h. [b]Yield of the isolated product.

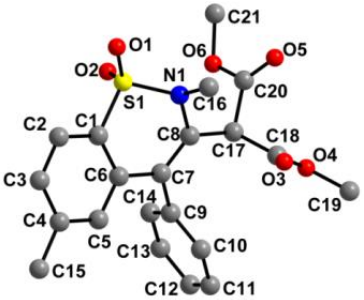


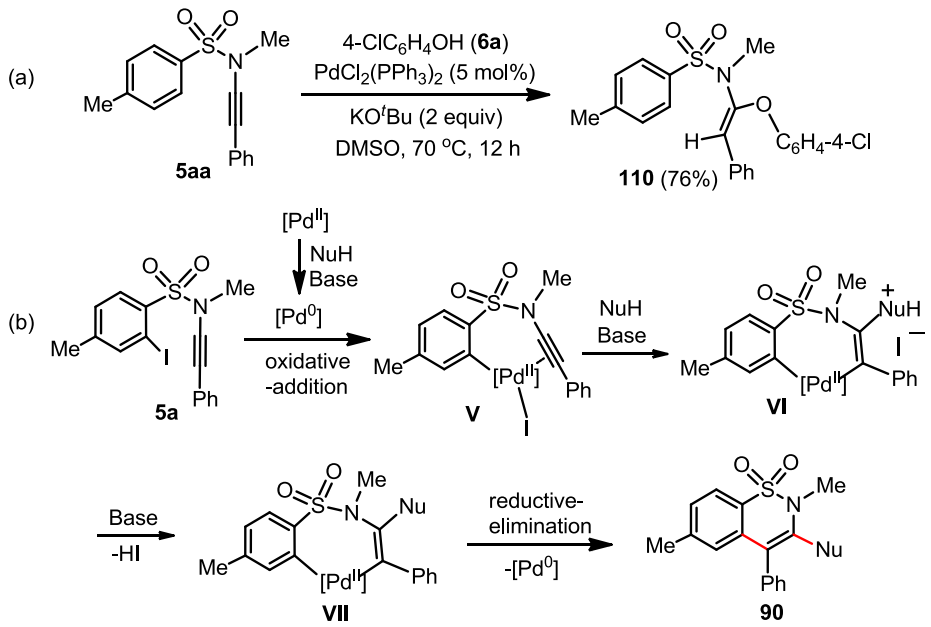
Figure 10. Molecular structure of compound **104**. Selected bond parameters: C6-C7 1.481(2), C7-C8 1.338(2), C8-C17 1.525(2), C8-N1 1.4342(19), C6-C1 1.399(2), C7-C9 1.494(2) (Å). Hydrogen atoms are omitted for clarity.

2.6.5 Control experiment and a plausible pathway for the formation of benzosultams

To explore the probable catalytic pathway, we treated ynamide **5u** with the nucleophile **9** which led to the addition product **110** (Scheme 24a). This experiment confirmed that Pd(II) species activates the triple bond of **5u** towards regioselective nucleophilic attack. For cyclization, two alternative pathways, one involving [Pd^{II}]-[Pd^{0}]-[Pd^{II}] (cf. Scheme 24b) and the other with [Pd^{II}]-[Pd^{IV}]-[Pd^{II}] (cf. Scheme 25) are possible.[20, 122]

The *in situ* formed [Pd^{0}] species could undergo oxidative addition to **5a** forming the activated [Pd^{II}] species **V** to which the nucleophile adds to give intermediate **VI** which then undergoes HI elimination to give **VII**. Reductive elimination of [Pd^{0}] from **VII** then affords the desired benzosultam (Scheme 24).

Scheme 24

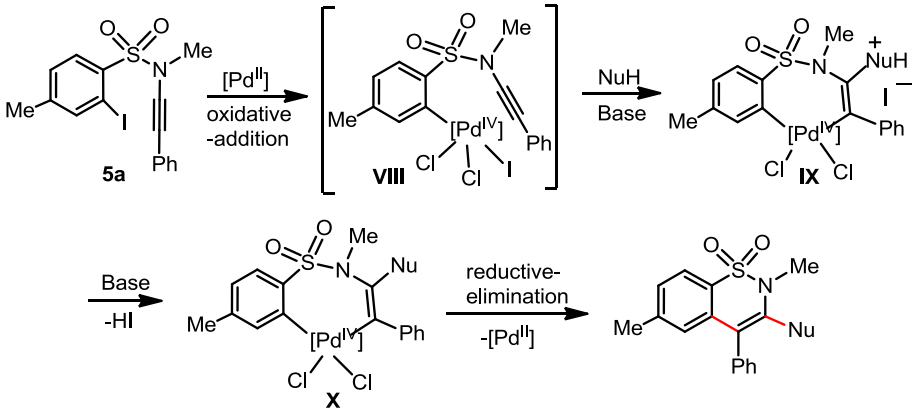


2.6.6 An alternative [Pd^{II}]-[Pd^{IV}]-[Pd^{II}] pathway for the cyclization process

Oxidative addition of **5a** to [Pd^{II}] occurs initially and results in the formation of palladium species **VIII**. This is followed by attack of external nucleophile on the triple

bond in a regioselective manner to give **IX** followed by and HI elimination that leads to **X**. Subsequent reductive elimination of [Pd^{IV}]-species as [Pd^{II}] gives the benzosultam (Scheme 25).

Scheme 25



2.6.7 Theoretical calculations

This part of the work was done in collaboration with Dr. Soumen Saha of IICT, Hyderabad. Hence we discuss herein only the main implications of the study. Thus, to gain more insight into the mechanistic details of Scheme 24b (and Scheme 25) the density functional theory (DFT) based method, B3LYP, augmented with 6-31G** basis set (DGDZVP: iodine, LANL2DZ: Pd) has been utilized.[123] While Scheme 24b was studied by considering Pd^0 and NuH as ArOH, scheme 25 was modeled by considering $Pd^{II}Cl_2$ and NuH as ArOH. Both the pathways lead to the formation of benzosultam. The DFT-calculated Gibbs free energy profile for the Scheme 24a is presented in Figure 11. Formation of benzosultam via Scheme 24b (i.e., from **5a** and Pd^0) is a thermodynamically favorable reaction, with ΔG^0 = -14.3 kcal/mol, whereas the formation of benzosultam from **5a** and $Pd^{II}Cl_2$ (as per Scheme 25, see Figure 12) is unfavorable with ΔG^0 = 14.4 kcal/mol. Moreover, the formation of Pd^{IV} from Pd^{II} is an endothermic process with ΔG^0 = 26.5 kcal/mol (cf. **VIII** in Scheme 25; Figure 12), whereas, the formation of Pd^{II} from Pd^0 (cf. **V** Scheme 24b) is an exothermic process by ΔG^0 = -29.2 kcal/mol. Thus, the formation of benzosultam benzosultam is predicted to be proceed via [Pd^0]-[Pd^{II}] pathway (cf. Scheme 24b).

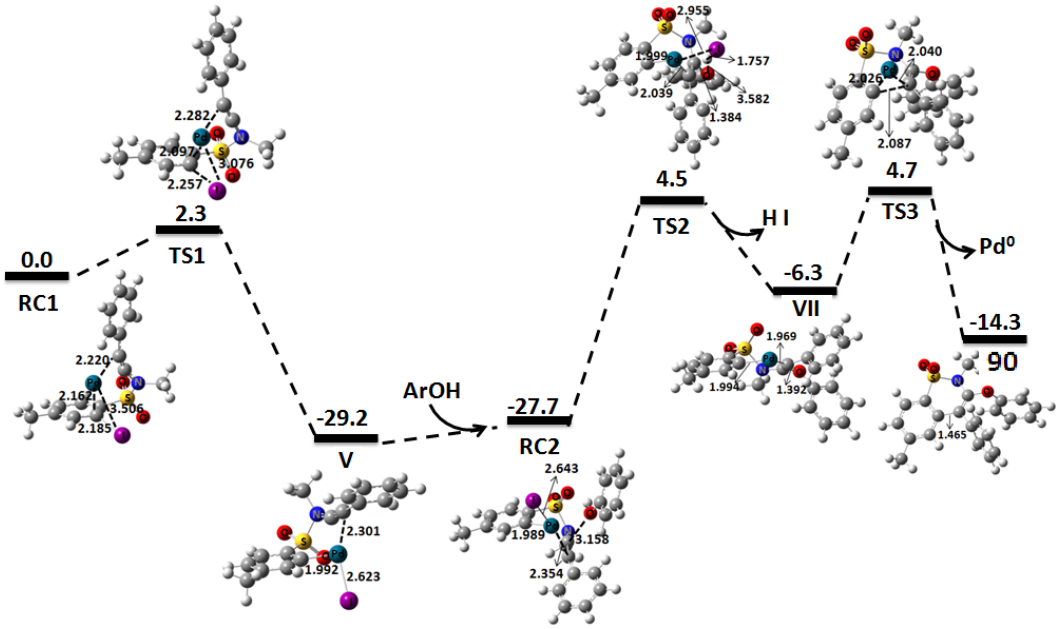


Figure 11. Schematic representation of Gibbs free energy profiles (kcal/mol) for Scheme 24b. RC1 corresponds to the reactant complex **1** between **5a** and **[**Pd^0], whereas, RC2 stands for the reactant complex 2 between **V** and ArOH. TS stands for the transition state. The energy values are with respect to RC1.

Details on Scheme 24b (and Figure 11): The **RC1** (i.e., the reactant complex 1) between **5a** and **[Pd^0]** were chosen. The approach of **[Pd^0]** toward **5a** leads to formation of three-centered transition state **TS1**. The activation barrier from **RC1** to **TS1** is only 2.3 kcal/mol. The product of oxidative addition to **5a** forming the activated **[Pd^{II}]** species, **V**, with ΔG^0 = -29.2 kcal/mol relative to **RC1**. The addition of ArOH to **V**, leads to the formation of **RC2** (i.e., the reactant complex 2) with ΔG^0 = -27.7 kcal/mol compared to **RC1**. Subsequently, a transition state **TS2** was observed with an activation barrier of 4.5 kcal/mol (with respect to **RC1**), associated with the hydrogen atom migrating from ArOH to iodine and the cleavage of Pd-I bond. After the elimination of **HI**, **VII** is formed with ΔG^0 = -6.3 kcal/mol relative to **RC1**. Next, reductive elimination of **[Pd^0]** from **VII** proceeds through a three-centered transition state **TS3**. The ΔG^0 value of TS3 is 4.5 kcal/mol higher with respect to **RC1**. Finally, the desired product, benzosultam **90**, is formed with ΔG^0 = -14.3 kcal/mol compared to **RC1**.

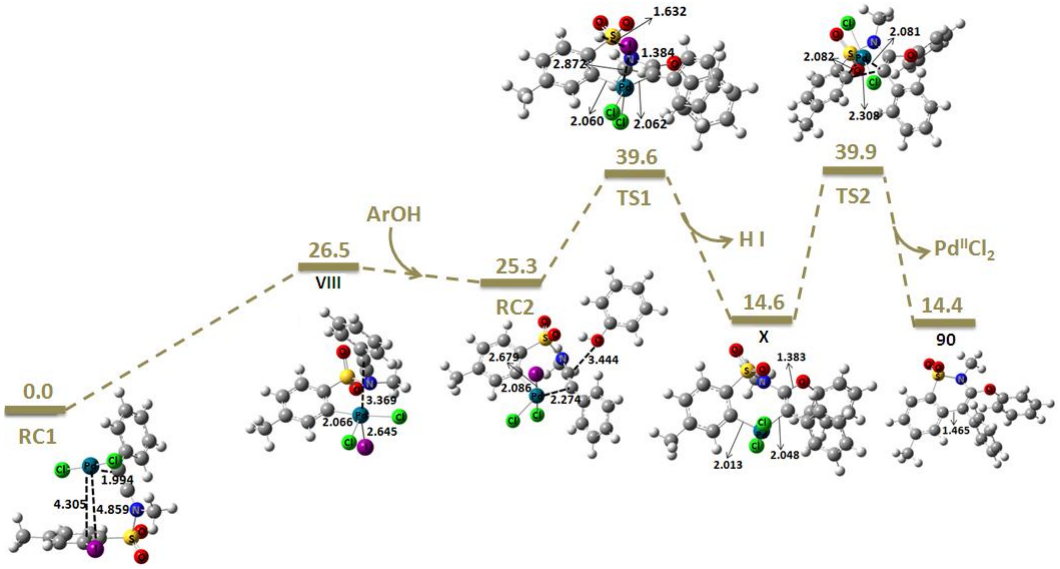


Figure 12. Schematic representation of Gibbs free energy profiles (kcal/mol) for Scheme S1. **RC1** corresponds to the reactant complex 1 between **1a** and **$Pd^{II}Cl_2$**, whereas, **RC2** stands for the reactant complex 1 between **VIII** and **ArOH**, and **TS** stands for the transition state. The energy values are with respect to **RC1**.

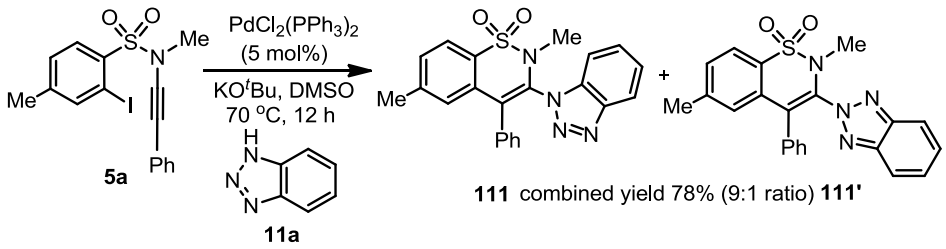
Details on Scheme 25 (and Figure 12): Figure 12 shows the free energy profiles generated for Scheme 25**.** The **RC1** (i.e., the reactant complex 1) between **5a** and **$Pd^{II}Cl_2$** were built. The product of oxidative addition, **VIII**, is formed with ΔG^0 = 26.5 kcal/mol relative to **RC1**. The calculations show that **[Pd^{II}]-[Pd^{IV}]** is a free energy unfavourable process. The approach of **ArOH** toward **VIII** leads to the formation of the reactant complex 2, **RC2** with ΔG^0 = 25.3 kcal/mol compared to **RC1**. The elimination of **HI** takes place via **TS1** which was observed with an activation barrier of 39.6 kcal/mol (with respect to RC1). The **TS1** is associated with the hydrogen atom migrating from ArOH to iodine and the cleavage of Pd-I bond. After the removal of **HI**, an intermediate, **X**, is formed with ΔG^0 = 14.6 kcal/mol relative to **RC1**. Next, reductive elimination of **[Pd^{II}]** from **X** proceeds via a three-centered transition state **TS2**. The ΔG^0 value of **TS2** is 39.9 kcal/mol higher with respect to **RC1**. The elimination of **$Pd^{II}Cl_2$** leads to the formation of benzosultam **90** with ΔG^0 = 14.4 kcal/mol compare to **RC1**.

Thus from these theoretical studies, it appears that Pd^0-Pd^{II} cycle is preferred over Pd^{II}-Pd^{IV} cycle for our reaction. However, this point needs to be ascertained more thoroughly by expereimental verifications.

2.6.8 Palladium-catalyzed regioselective synthesis of benzosultams from functionalized ynamides and benzotriazoles/tetrazoles

In an effort to generalize the above methodology to other systems, to start with, we performed the reaction between the iodo-substituted ynamide **5a** and benzotriazole **11a** using $PdCl_2(PPh_3)_2$ (5 mol%) as the catalyst and KO^{t}Bu (2 equiv) as the base in DMSO solvent at 70 ^oC for 12 h. The desired product **111** was obtained in addition to the other isomeric product **111'** in an overall yield of 78% in 9:1 ratio (Scheme 26).

Scheme 26



To improve the yield of the product **111** by lowering the yield of isomer **111'**, we then moved to optimization of the reaction conditions (Table 14). Bases such as K_2CO_3, Cs_2CO_3 and K_3PO_4 were ineffective to furnish the desired product, and the starting materials remained unreacted. Changing the solvent to DMF and acetonitrile also provided the two isomeric products. Surprisingly, by using THF as the solvent, we observed compound **111** almost as a single isomer in 82% yield with the suppression of isomer **111'**. There was no product formation in DCM as the solvent; in chloroform also, only traces of the product was observed. The product yield decreased drastically in toluene. We detected only traces of product in the absence of PPh_3 ligand with $PdCl_2$ as the catalyst. Use of Pd/C catalyst also led only traces of the product. However $Pd(PPh_3)_4$ catalyst gave moderate yield (entry no. 13) and $PdCl_2$ in combination with dppe ligand furnihed the product in yields pretty close to that using $PdCl_2(PPh_3)_2$ (entry 14). A combination of $PdCl_2$ or $Pd(OAc)_2$ with other phosphine ligands such as PCy_3 and PBu_3 was less effective for this transformation (entries 15-16). The use of SPhos ligand gave only moderate yield (entry 17). Thus the optimal conditions for this cyclization process were $PdCl_2(PPh_3)_2$ (5 mol%) as the catalyst and KO^{t}Bu (2 equiv) as the base in THF at 70 ^oC for 12 h.

Table 14: Optimization study for the synthesis of compound **111**[a]

Entry	[Pd]-catalyst (5 mol%)	Solvent	Base	Yield (%) and ratio (**111**:**111'**)[b]
1	$PdCl_2(PPh_3)_2$	DMSO	KO^tBu	78 (9:1)
2	$PdCl_2(PPh_3)_2$	DMSO	K_2CO_3	n.d.
3	$PdCl_2(PPh_3)_2$	DMSO	Cs_2CO_3	traces
4	$PdCl_2(PPh_3)_2$	DMSO	K_3PO_4	n.d.
5	$PdCl_2(PPh_3)_2$	DMF	KO^tBu	76 (~9:1)
6	$PdCl_2(PPh_3)_2$	CH_3CN	KO^tBu	80 (4:1)
7	**$PdCl_2(PPh_3)_2$**	**THF**	**KO^tBu**	**82 (>96:trace)**
8[c]	$PdCl_2(PPh_3)_2$	DCM	KO^tBu	n.d.
9	$PdCl_2(PPh_3)_2$	$CHCl_3$	KO^tBu	traces
10	$PdCl_2(PPh_3)_2$	Toluene	KO^tBu	36
11[d]	$PdCl_2$	THF	KO^tBu	traces
12	Pd/C	THF	KO^tBu	traces
13	$Pd(PPh_3)_4$	THF	KO^tBu	64
14	$PdCl_2$+dppe	THF	KO^tBu	80
15	$PdCl_2$+2PCy_3	THF	KO^tBu	traces
16	$Pd(OAc)_2$+2PBu_3	THF	KO^tBu	traces
17	$Pd(OAc)_2$+2SPhos	THF	KO^tBu	42

[a]Ynamide (0.24 mmol), [Pd]-catalyst (5 mol%), benzotriazole (1.2 equiv) and base (2 equiv) in the solvent (1 mL) at 70 ^oC for 12 h. [b]Yield of the isolated product and isomeric ratio (in parenthesis) were determined by ^1H NMR. [c]Reaction was done at rt (25 ^oC). [d]Reaction was performed in the absence of PPh_3. n.d. = not detected.

After having the optimized reaction conditions in hand, we moved to check the substrate scope for this palladium-catalyzed tandem cyclization of ynamide substrates with benzotriazoles (Scheme 27). Initially, we checked the scope of this reaction by changing the substituents on the benzotriazole skeleton. In the case of unsymmetrical 5-substituted benzotriazole as a nucleophile, we noticed the formation of two regioisomers **112** / **112'** as well as **113** / **113'** from the corresponding ynamide. Formation of

regioisomers was supported by using symmetrical 5,6-dimethyl substituted benzotriazole as a nucleophile that resulted in the formation of single isomer **114** in 80% yield. The scope of this method could be extended by varying the substituents on the ynamide functionality. Changing the substituent on the sulfonyl attached aryl moiety gave good yield of the cyclized products **115**. Electron releasing substituents such as methyl and methoxy as well as electron withdrawing substituents like nitro and fluoro groups on the alkyne attached phenyl moiety worked well and afforded the corresponding benzosultams **116-119** in excellent yields. The substrate with aliphatic substituent on the alkyne motif also underwent cyclization smoothly to furnish the cyclized compound **120** in 76% yield. The structures of compounds **111** and **119** were also confirmed by single crystal X-ray structural analysis (Figure 13). Even though bromo precursors are generally less reactive than the corresponding iodo precursors, interestingly, this methodology was applicable equally to the bromo substituted ynamides and provided the corresponding benzotriazole appended benzosultams **111** and **121-122** in good yields. These benzosultams are fairly thermally (up to 160 ^{o}C) and hydrolytically (reflux in glacial acetic acid) stable and under these conditions do not undergo elimination of molecular nitrogen.[96]

Scheme 27

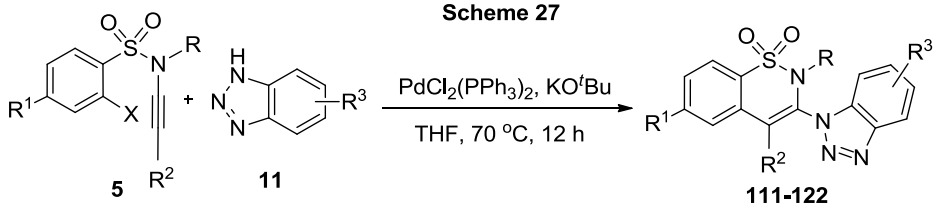
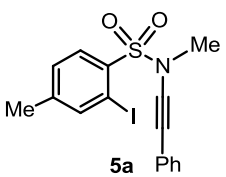
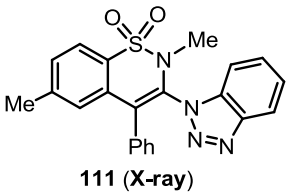
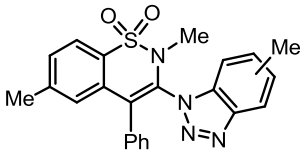
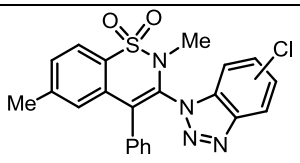
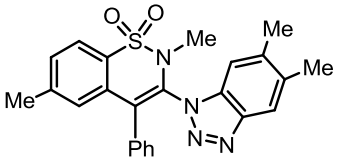
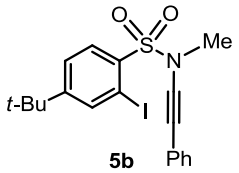
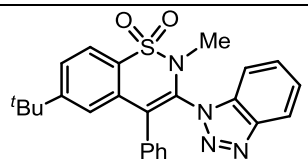
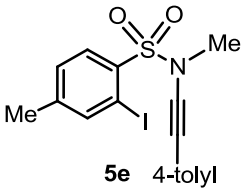
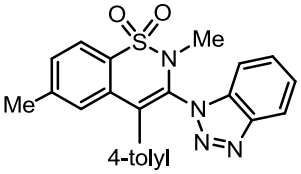
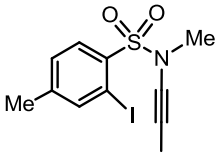
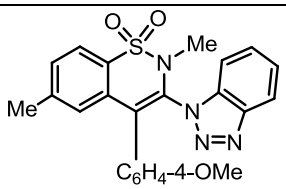
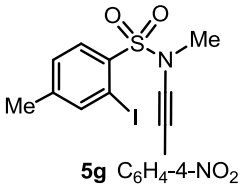
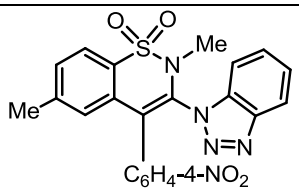
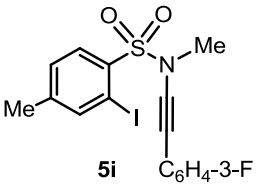
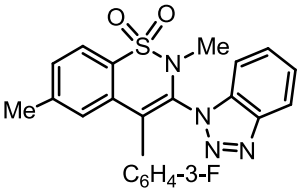
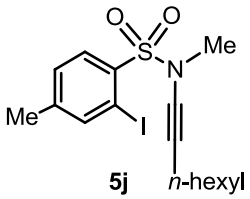
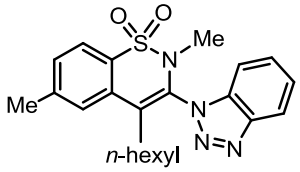
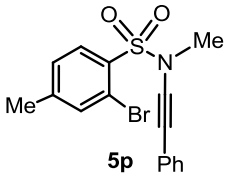
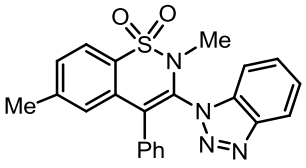
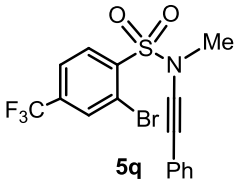
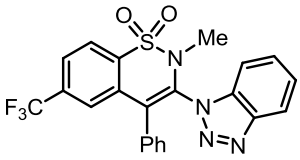
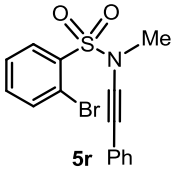
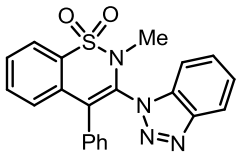


Table 15. Regioselective synthesis of benzotriazole appended benzosultams (**111-122**) from *N*-alkynyl 2-halo-benzene sulfonamides[a]

Entry	Ynamides	Benzosultams	Yield (%)[b]
1	 **5a**	 **111** (**X-ray**)	82

2	**5a**	 **112:112'**	78
3	**5a**	 **113:113'**	62
4	**5a**	 **114** (**X-ray**)	80
5	 **5b** Ph	 **115**	80
6	 **5e** 4-tolyl	 4-tolyl **116**	79
7	 **5f** C_6H_4-4-OMe	 C_6H_4-4-OMe **117**	84
8	 **5g** C_6H_4-4-NO_2	 C_6H_4-4-NO_2 **118**	76
9	 **5i** C_6H_4-3-F	 C_6H_4-3-F **119** (**X-ray**)	70

10	 **5j** *n*-hexyl	 *n*-hexyl **120**	76
11	 **5p** Ph	 Ph **111**	68
12	 **5q** Ph	 Ph **121**	46
13	 **5r** Ph	 Ph **122**	72

[a]Conditions: Ynamide **5** (0.24 mmol), benzotriazole **11** [0.29 mmol], $PdCl_2(PPh_3)_2$ (5 mol%), KO^{t}Bu (0.48 mmol) in THF (1 mL) at 70 ^oC for 12 h. [b]Isolated yields after column chromatography.

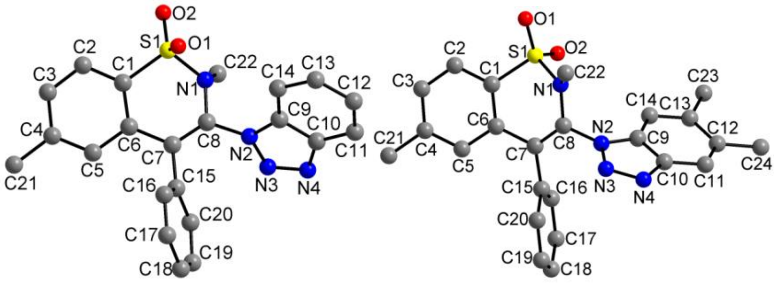
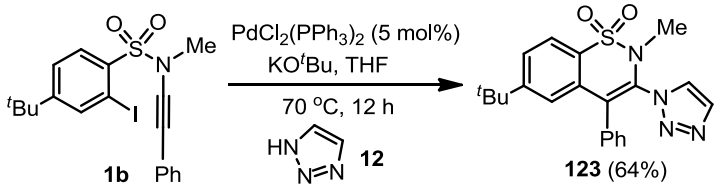


Figure 13. X-ray structures of compounds **111** (left) and **114** (right) Selected bond parameters: **111** [N1-C8 1.4231(17), N2-C8 1.4199(18), C7-C8 1.343(2), C6-C7 1.4787(18), C7-C15 1.4937(17) Å]. **114** [N1-C8 1.410(3), N2-C8 1.423(3), C7-C8 1.336(3), C6-C7 1.476(3), C7-C15 1.497(3) Å].

The above methodology also tolerated well by using simple triazole **12** instead of benzotriazole and furnished the benzosultam **123** in 64% yield (Scheme 28).

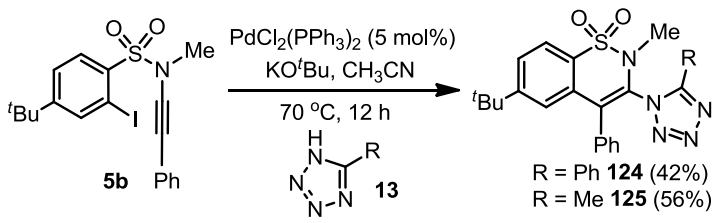
Scheme 28



2.6.9 Approach towards tetrazole appended benzosultams 124-125

As an important extension, we were also able to utilize tetrazoles as nucleophiles to afford the tetrazole appended benzosultams (Scheme 29). For this cyclization, acetonitrile was a better solvent than THF for providing the desired products. Thus the reaction of ynamide **5b** with tetrazoles **13** using $PdCl_2(PPh_3)_2$ catalyst furnished the corresponding benzosultams **124** and **125** in moderate yields.

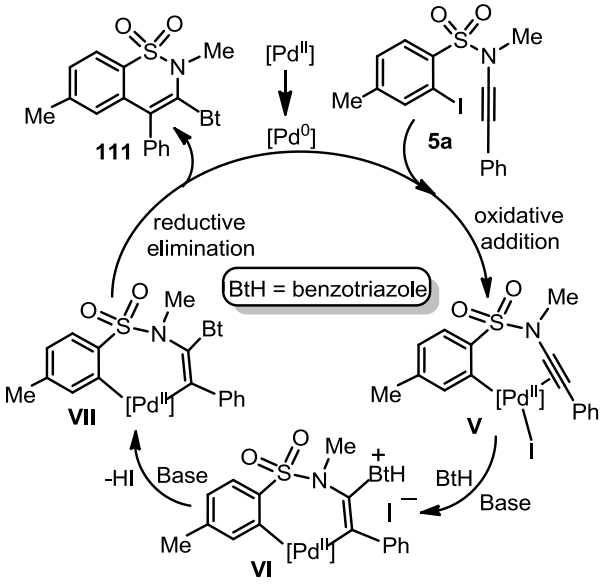
Scheme 29



2.6.10 Proposed pathway for the [Pd]-catalyzed cyclization of ynamide 5a leading to product 111

Based on the previous literature and theoretical studies,[20] we propose a plausible pathway for the formation of compound **111** from 2-iodo substituted ynamide **5a** (Scheme 30). Initially, oxidative addition of *in situ* formed [Pd^0] species to compound **5a** takes place, resulting in intermediate **V**. It is then followed by the attack of benzotriazole (BtH) nucleophile affording intermediate **VI** in the presence of the base. Further, HI-elimination leads to the formation of intermediate **VII** and subsequent reductive elimination of [Pd^0] affords the benzosultam **111**. In this reaction, donor solvents like DMSO, THF and acetonitrile appear to work better than the solvents like DCM, chloroform and toluene, suggesting a possible weak coordination to the metal in the intermediate stages.

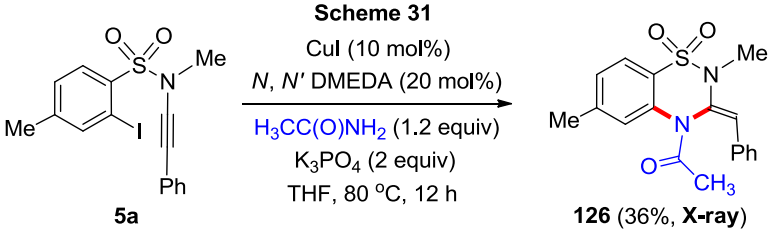
Scheme 30



2.7 Reaction of ynamide 5a with acetamide

We have also made an attempt for the cyclization of ynamides by using amide precursors. In one such case, the reaction between ynamide **5a** with acetamide afforded the benzosultam **126** in 36% yield under copper catalysis (Scheme 31). The structure of benzosultam **126** was confirmed by X-ray crystallographic analysis (Figure 14). However, it requires further optimization to improve the yield of the product. This reaction probably proceeds *via* a sequential copper-catalyzed amidation/cyclization of functionalized ynamides to benzosultams using amides.

Scheme 31



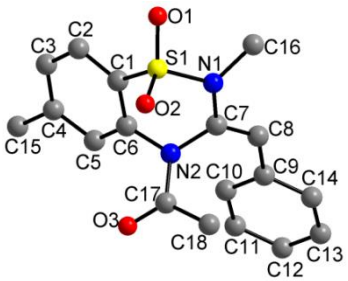


Figure 14. X-ray structure of compound **126** (H-atoms omitted). Selected bond parameters: [C6-N2 1.432(3), N2-C7 1.428(3), C7-N1 1.419(4), C7-C8 1.331(4), C8-C9 1.471(4) Å].

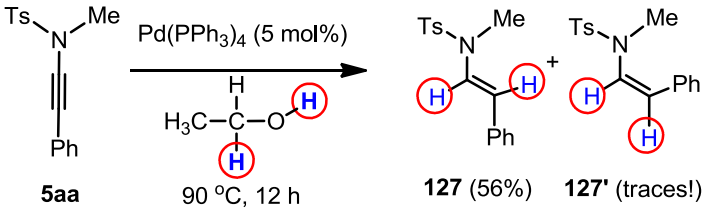
2.8 Ethanol as hydrogenating agent: Palladium-catalyzed stereoselective hydrogenation of ynamides leading to enamides

As we discussed in the Introduction, different hydrogenating sources were utilized for the hydrogenation of ynamides/ alkynes. But the use of ethanol as a hydrogenating source in catalytic reduction of alkynes is not explored. In the following section, we discuss stereoselective hydrogenation reactions of ynamides using ethanol or synergistic ethanol/ammonium formate as a hydrogenating source.

2.8.1 [Pd]-Catalyzed *trans*-hydrogenation of ynamide with ethanol

Our initial examination involved the reaction of *N*-alkynyl benzenesulfonamide **5aa** with ethanol (used as a solvent also) in the presence of $Pd(PPh_3)_4$ (5 mol%) as the catalyst at 90 ^oC for 12 h (Scheme 32). We were delighted to obtain the hydrogenated product **127** in 56% yield, in addition to the unreacted starting material, as evidenced by ^1H NMR spectrum that showed two extra protons with J = 14.5 Hz, indicating *trans*-hydrogenation. Additionally, the stereochemistry and structure of compound **127** were confirmed by X-ray crystallographic analysis (Figure 15). There was no indication of the alcohol addition product.

Scheme 32



Encouraged by the above result, we turned our attention to improve the yield of product **127** (Table 16). As expected, there was no reaction in aprotic solvents like toluene, THF and DMSO. Absence of catalyst also did not furnish the desired product. The primary alcohols ^{n}PrOH and ^{n}BuOH also worked well. The reaction rate was slower in ^{i}PrOH and no product was detected by using ^{t}BuOH as the solvent. Thus alcohols possessing at least one-hydrogen on the α-carbon atom only are suitable for the

hydrogenation process. Addition of bases such as NaOH, $CaCO_3$ and Cs_2CO_3 did not improve the yield. Intriguingly in the presence of K_2CO_3 as a base, we noticed the formation of a *cis*-hydrogenated product as the major isomer, albeit in total 36% yield (after isolation). To our delight, the reaction proceeded smoothly by the use of either Et_3N or pyridine as the base affording the desired product in 92% isolated yield with excellent stereoselectivity. Other [Pd]-catalysts such as $PdCl_2(PPh_3)_2$ or $Pd(OAc)_2$+2(PPh_3) slightly decreased the stereoselectivity. The [Pd]-catalysts which do not contain phosphine failed to produce product **127**. A complex mixture was observed in the case of $Pd(OAc)_2$. Pd/C or $Pd_2(dba)_3$ was less efficient as catalyst for this transformation. More importantly, no product formation was seen at the room temperature. This may be due to the requirement of higher dissociation energy for the hydride ion transfer. Although decreasing the catalyst loading to 3 mol% reduced the product yield by keeping the reaction time of 12 h, increasing the duration to 36-48 h afforded better yield of the product even with 2 mol% of the catalyst (i.e., substrate/catalyst ratio 50). Hence the optimal conditions for this transformation is **5aa** (0.2 mmol), $Pd(PPh_3)_4$ (5 mol%), Et_3N (0.6 mmol) in ethanol (1 mL) at 90 ^oC for 12 h (Table 16, entry 14).

Table 16: Optimization of the catalytic system for the synthesis of (*E*)-*N*,4-dimethyl-*N*-styrylbenzenesulfonamide **127** from **5aa**[a]

Entry	Catalyst	Solvent	Base	**127**/ **127'**/ **5aa**[b]	Yield of **127** after isolation (%)[c]
1	$Pd(PPh_3)_4$	EtOH	-	60/ 0/ 40	56
2	$Pd(PPh_3)_4$	Toluene	-	No reaction	No reaction
3	$Pd(PPh_3)_4$	THF	-	No reaction	No reaction
4	$Pd(PPh_3)_4$	DMSO	-	No reaction	No reaction
5	-	EtOH	-	No reaction	No reaction
6	$Pd(PPh_3)_4$	^{i}PrOH	-	36/ 0/ 64	33
7	$Pd(PPh_3)_4$	^{i}PrOH	-	54/ 0/ 46	52
8	$Pd(PPh_3)_4$	^{n}BuOH	-	56/ 0/ 44	46
9	$Pd(PPh_3)_4$	^{t}BuOH	-	No reaction	No reaction
10	$Pd(PPh_3)_4$	EtOH	NaOH	42/ 0/ 58	36
11	$Pd(PPh_3)_4$	EtOH	$CaCO_3$	4/ 0/ 96	(Traces only; not isolated)
12	$Pd(PPh_3)_4$	EtOH	Cs_2CO_3	2/ 6/ 92	(Traces only; not

					isolated)
13	$Pd(PPh_3)_4$	EtOH	K_2CO_3	18/ 82/ 0	(36)[d]
14	**$Pd(PPh_3)_4$**	**EtOH**	**Et_3N**	**100/ 0/ 0**	**92**
15	$Pd(PPh_3)_4$	EtOH	Pyridine	100/ 0/ 0 -	90
16	$PdCl_2(PPh_3)_2$	EtOH	Et_3N	96/ 4/ 0	(90)[d]
17	$Pd(OAc)_2$+ $2(PPh_3)$	EtOH	Et_3N	90/ 10/ 0	(84)[d]
18	$Pd(OAc)_2$	EtOH	Et_3N	complex	(Not isolated)
19	Pd/C	EtOH	Et_3N	0/ 6/ 94	(**127** not formed)
20	$Pd_2(dba)_3$	EtOH	Et_3N	0/ 20/ 80	(**127** not formed)
21[e]	$Pd(PPh_3)_4$	EtOH	Et_3N	No reaction	No reaction
22	$Pd(PPh_3)_4$[f]	EtOH	Et_3N	76/ 0/ 24	72

[a]Unless otherwise specified all the reactions performed by using ynamide (0.20 mmol), catalyst (5 mol%), base (0.60 mmol) and solvent (1 mL) at 90 ^oC. [b]Ratio determined by ^1H NMR analysis of the crude reaction mixture. [c]Yield of the isolated product. [d]Total (**127** + **127'**) isolated yield. [e]Reaction performed at rt. [f]3 mol% [Pd]-catalyst used.

With regard to substrate scope, we found that various types of ynamides were transformed to the corresponding (*E*)-enamides in good to excellent yields with high stereoselectivity using ethanol as the hydrogenating source (Scheme 33, Table 17). Changing the substituents on the sulfonyl attached aryl moiety worked well to give the products **127-129** in excellent yields. Even the sterically crowded ynamides furnished the products **130-132** in good yields. Halo-substituted and heterocyclic containing ynamides also reacted smoothly to provide the corresponding products **133-134**. Altering the substituents on the nitrogen atom of ynamide from aliphatic to aromatic was also tolerated well and delivered the enamides **135-137**. The functional group tolerance is shown by selective hydrogenation of ynamide functionality in the presence of non-activated alkynyl and alkenyl groups as shown by the isolation of products **138** and **139**. The ynamide having free sulfonamide functionality also worked to provide the product **140**. The reaction is compatible with cyclic sulfonamide derived ynamides to offer the enamides **141-142**. Chemoselectivity is demonstrated by the retention of the carbonyl group as in product **143 (**or **147)**. On the alkyne functionality also, this transformation proceeded well as shown by compound **144**. Interestingly, hydrogenation of two different C≡C bonds can also be accomplished readily as shown by the isolation of **145** in good yield. Replacing the sulfonyl group with the phosphoryl group does not affect the

stereoselectivity, and affords the product **146** in excellent yield. The carbamate derived ynamide slightly decreased the stereoselectivity, but with a good overall yield of **147**. Also, the enamide product does not get over-hydrogenated even after 48 h. All these products showed a band at ~ 1640 cm^{-1} in IR spectra were preferentially due to the presence of the alkene *C*=*C* group. In the ^{1}H NMR spectra, we observed two protons with a coupling constant of ~ 14.5 Hz because of the presence of –*H*C=C*H*- protons in a trans-manner to each other. The structures of compounds **131** and **141** were confirmed by X-ray crystallographic analysis (Figure 15).

Scheme 33

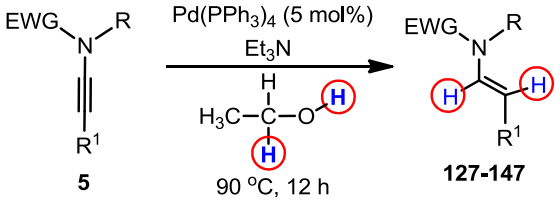
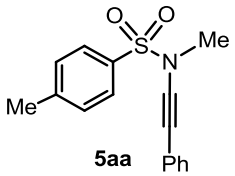
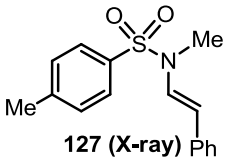
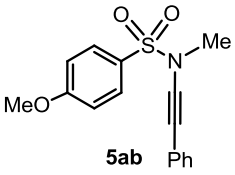
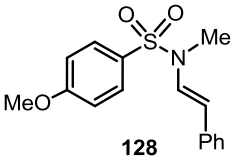
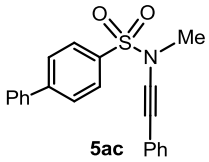
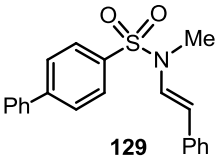
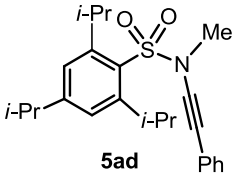
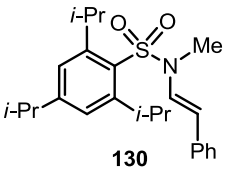
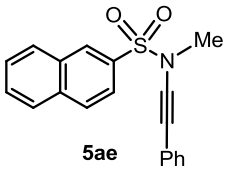
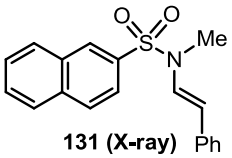
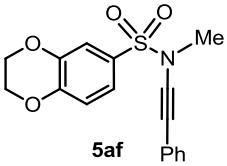
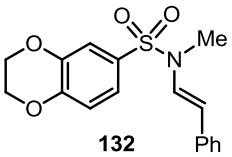
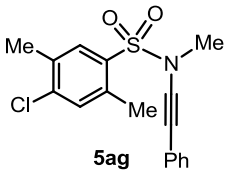
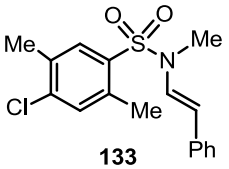
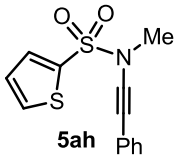
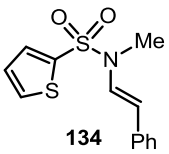
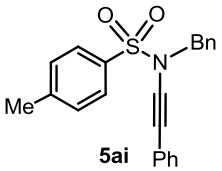
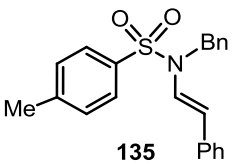
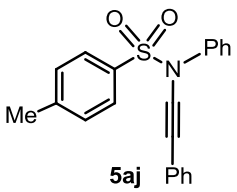
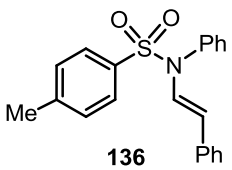
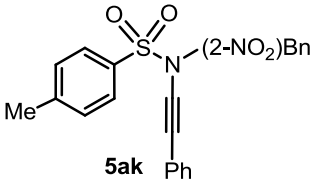
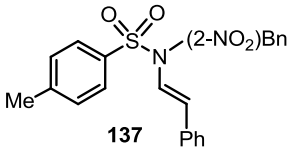
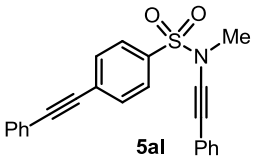
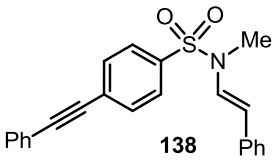
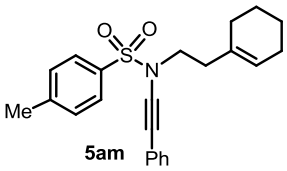
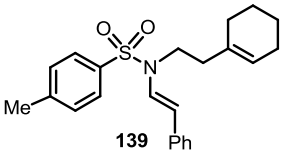
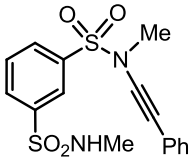
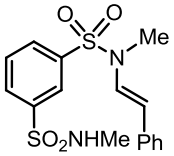
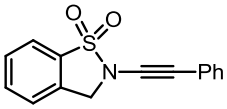
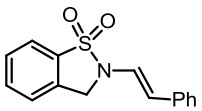
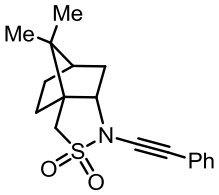
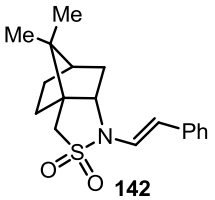
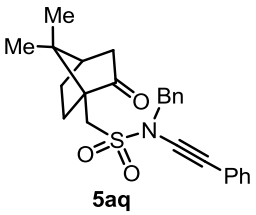
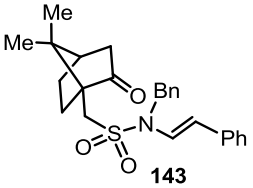
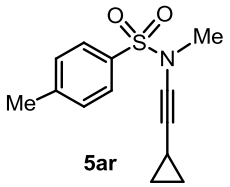
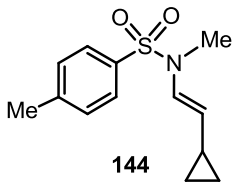
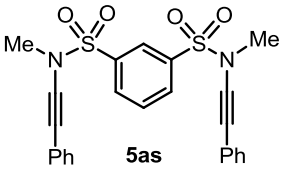
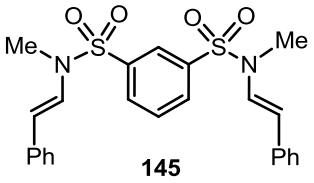
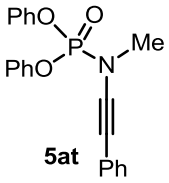
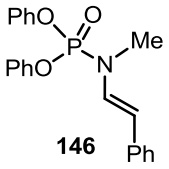
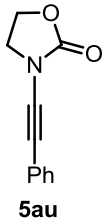
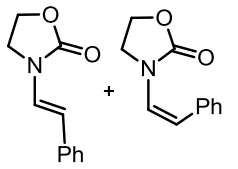


Table 17: Scope for hydrogenation of ynamides by ethanol leading to (*E*)-enamides[a]

Entry	Ynamides	Enamides	Yield (%)[b]
1	 **5aa**	 **127 (X-ray)**	92
2	 **5ab**	 **128**	94
3	 **5ac**	 **129**	86

4	 **5ad**	 **130**	82
5	 **5ae**	 **131 (X-ray)**	90
6	 **5af**	 **132**	82
7	 **5ag**	 **133**	76
8	 **5ah**	 **134**	93
9	 **5ai**	 **135**	88
10	 **5aj**	 **136**	86

11	 **5ak**	 **137**	83
12	 **5al**	 **138**	80
13	 **5am**	 **139**	87
14	 **5an**	 **140**	86
15	 **5ao**	 **141 (X-ray)**	96
16	 **5ap**	 **142**	90
17	 **5aq**	 **143**	84

18	 **5ar**	 **144**	78
19	 **5as**	 **145**	82
20	 **5at**	 **146**	95
21	 **5au**	 **147** (74%) **147'** (12%)	74

[a]Conditions: **5** (0.2 mmol), $Pd(PPh_3)_4$ (5 mol%), Et_3N (0.6 mmol) in ethanol (1 mL) at 90 [o]C for 12 h. [b]Isolated yields after column chromatography are given in parenthesis. For the preparation of compound **145** we used $Pd(PPh_3)_4$ (10 mol%), Et_3N (1.2 mmol).

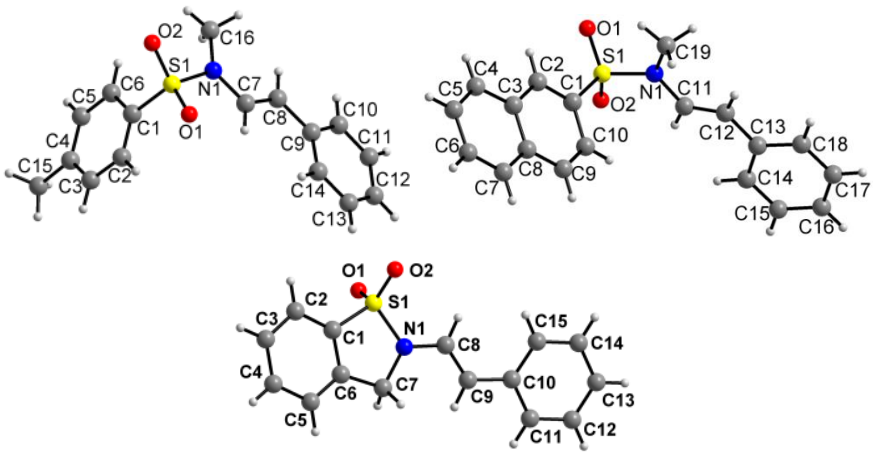


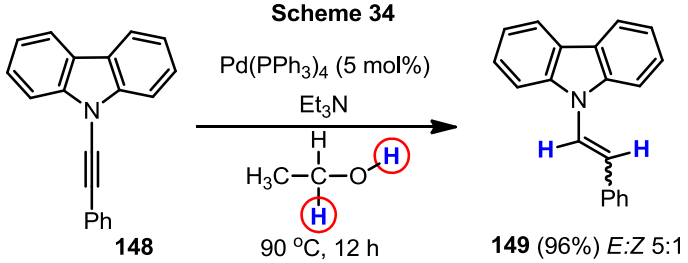
Figure 15. Molecular structures of compounds **127** (left), **131** (right) and **141** (below). Selected bond parameters: Compound **127** S1-N1 1.642(3), N1-C7 1.413(4), C7-C8

1.328(4), C8-C9 1.467(5), C9-C10 1.392(4), C9-C14 1.389(5) [Å]. Compound **131** S1-N1 1.6380(15), N1-C11 1.403(2), C11-C12 1.319(2), C12-C13 1.468(2), C13-C14 1.388(2), C13-C18 1.388(2) [Å]. Compound **141** S1-N1 1.6412(12), N1-C8 1.3992(18), C8-C9 1.3228(19), C9-C10 1.461(2), C10-C11 1.395(2), C10-C15 1.393(2) [Å].

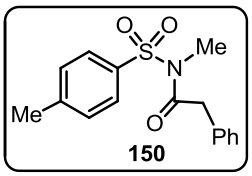
2.8.2 Hydrogenation of ynamine 148 by ethanol

In continuation of the above studies, it is important to note that the carbazole derived ynamine substrate **148** also afforded the enamine **149** in 96% overall isolated yield with the *E*-isomer still predominating (Scheme 34).

Scheme 34



Later we made an attempt for the semihydrogenation of ynamides using $Na_2S.9H_2O$ under transition-metal-free conditions.[124] In that case we isolated the water addition product **150** instead of the hydrogenated product.



2.8.3 [Pd]-Catalyzed *cis*-hydrogenation of ynamides

During optimization of the above reaction, it was noticed that use of Pd/C or $Pd_2(dba)_3$ as the catalyst preferentially led to very small quantities of the *Z*-isomer (Table 16, entries 19-20), with most of the starting ynamide unreacted. We surmised that addition of another hydrogenating source may increase the yield of this isomer. Aqueous formic acid was not useful since it led primarily to addition product with water ($^1H/^{13}C$ NMR/ HRMS). Pleasingly, EtOH/NH_4OOCH system as the hydrogenating source afforded the enamide with high stereoselectivity for the *Z*-isomer (Table 18, entry 5). This route was then utilized to obtain several *Z*-enamides (**127'**, **129'**, **130'**, **132'**, **141'**, **142'**, and **144'**) (Scheme 35, Table 19). Since the yield was lower when THF (or toluene or

acetonitrile) was used in place of EtOH, we believe that the latter plays a synergistic role in hydrogenation. In these cases also, there was no over-hydrogenation even after 48 h. In the ^{1}H NMR spectra, a coupling constant of ~ 9.0 Hz was observed for two protons suggested the cis hydrogenation of the alkyne moiety. These products also showed a band at ~ 1640 cm^{-1} in the IR spectra indicating the presence of the alkene *C*=*C* group.

Table 18: Optimization of conditions for *Z*-selective hydrogenation of **5aa** leading to (*Z*)-**127'**[a]

Entry	Catalyst	Solvent	H_2 source	**127/ 127'/ 5aa**[b]
1	$Pd_2(dba)_3$	EtOH	EtOH/ HCOOH	Not observed (only water addition product **150** was formed[c])
2	Pd/C	EtOH	EtOH/ HCOOH	Not observed (only water addition product **150** was formed[c])
3	$Pd_2(dba)_3$	EtOH	EtOH/$HCOONH_4$	38/ 62/ 0 (total yield of isolated **127**+**127'**: 74%)
4	Pd/C	EtOH	EtOH/$HCOONH_4$	2/ 64/ 34
5[d]	**Pd/C**	**EtOH**	**EtOH/$HCOONH_4$**	**4/ 96/ 0 (total yield of isolated 127+127': 82%)**
6[d]	Pd/C	THF	$HCOONH_4$	0/ 36 / 64 (yield of isolated **127'**: 31%)
7[d]	Pd/C	Toluene	$HCOONH_4$	0/ 8/ 92
8[d]	Pd/C	CH_3CN	$HCOONH_4$	0/ 23 / 77 (yield of isolated **127'**: 20%)

[a]Unless otherwise specified all the reactions performed by using ynamide (0.20 mmol), catalyst (5 mol%), H_2 source (0.60 mmol) and solvent (1 mL) at 90 ^{o}C. [b]Ratio determined by ^{1}H NMR analysis of the crude reaction mixture. [c]Primarily water addition product **150**

[purity 86% (rest was most likely formic acid addition product)] was observed by using 85% HCOOH solution. [d]Pd/C (10 mol%) was used.

Scheme 35

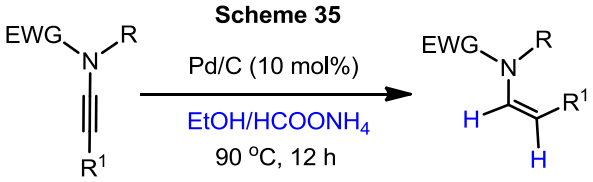
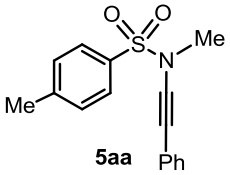
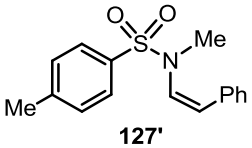
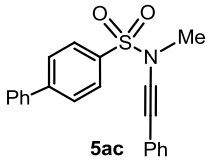
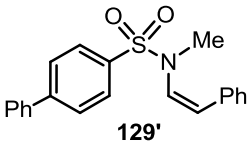
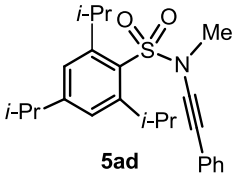
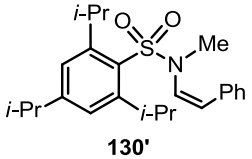
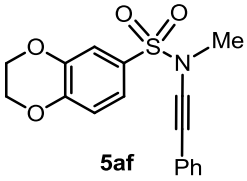
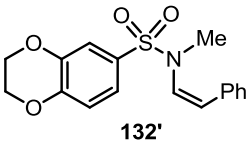
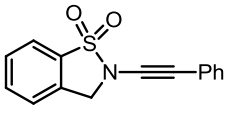
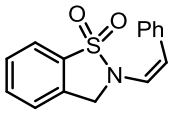
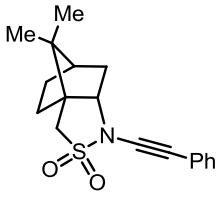
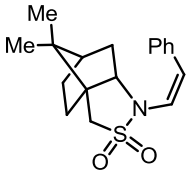
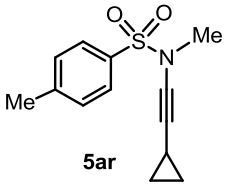
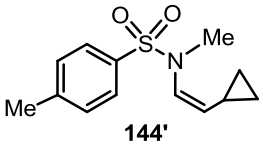


Table 19: Scope for *Z*-selective hydrogenation of ynamides[a]

Entry	Ynamides	Enamides	Yield (%)[b]
1	 **5aa**	 **127'**	82 *Z:E* 96:4
2	 **5ac**	 **129'**	74 *Z:E* 91:9
3	 **5ad**	 **130'**	76 *Z:E* 89:11
4	 **5af**	 **132'**	80 *Z:E* 93:7
5	 **5ao**	 **141'**	86 *Z:E* 93:7
6	 **5ap**	 **142'**	82 *Z:E* 86:14

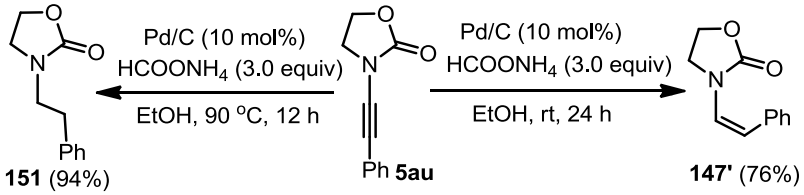
7	 5ar	 144'	72 *Z:E* 98:2

[a]Conditions: **5** (0.2 mmol), Pd/C (10 mol%), $HCOONH_4$ (0.6 mmol) in EtOH (1 mL) at 90 °C for 12 h. [b]Isolated yields after column chromatography are given in parenthesis.

2.8.4 Hydrogenation of ynamide 5au

The ynamide **5au** was lot more reactive, and afforded good yield of **147'** at rt itself; at 90 °C, fully reduced product **151** was obtained in high yields (Scheme 36).

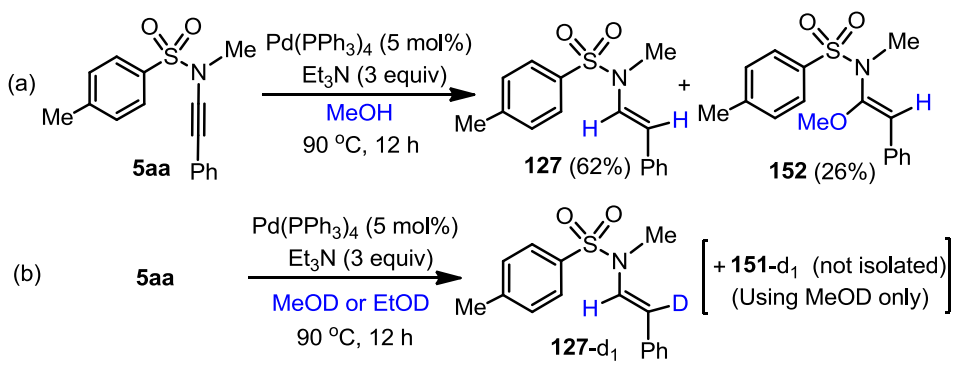
Scheme 36



2.8.5 Control experiments

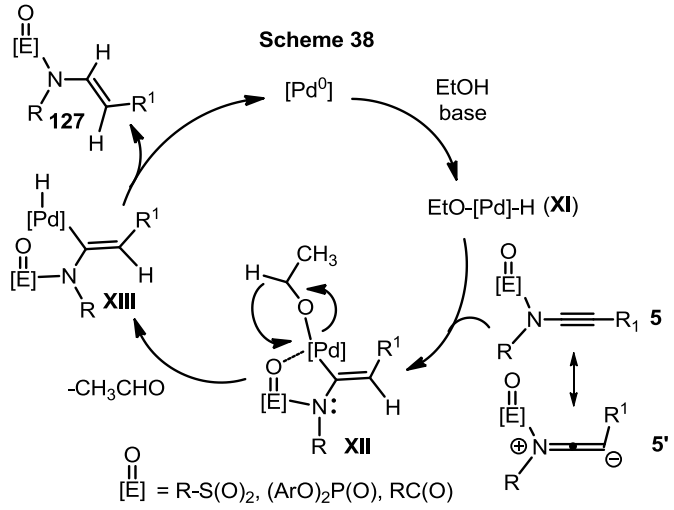
For the reaction shown in Scheme 32, replacing ethanol with methanol led to predominantly product **127** along with minor amounts of the (competitive) methanol addition product **152** (Scheme 37a). Use of CH_3OD (or C_2H_5OD) led to the isolation of **127**-d_1 (Scheme 37b). The reaction using CD_3OD did not occur probably due to kinetic reasons. Deuterium kinetic isotope effect (C-H vs C-D; primary/secondary) may be responsible for the reaction to be forbidden. Thermodynamically also, the deuterium is strongly bonded to the carbon when compared to hydrogen.

Scheme 37



2.8.6 Proposed pathway for the formation of 127

A plausible catalytic cycle for the formation of compounds **127-147** is proposed in Scheme 38 based on control experiments and earlier literature.[125] The reactant **5** is likely in resonance with the keteniminium species **5'**. The *in situ* formed [Pd]-intermediate **XI** undergoes addition to **5'** resulting in intermediate **XII**. It is likely that in **XII**, the metal is coordinated to the sulfonyl/phosphoryl oxygen atom. Steric interactions between the nitrogen lone pair and R^1/H group may be responsible for the *trans*-stereoselectivity, with the hydrogen preferring the opposite side of palladium (or R^1 preferring the opposite of nitrogen). In general, we did not observe the isomerization or over-hydrogenation. In the X-ray structures of **127**, **131** and **141**, the N-C(*H*)= hydrogen is close to one of the sulfonyl oxygen atoms (<2.87Å) which may explain the stereochemistry to some degree, but more data is required to establish this feature. Species **XII** undergoes hydride shift with subsequent elimination of acetaldehyde to lead to intermediate **XIII**. Isolation of deuterated compound **127**-d_1 is consistent with the intermediacy of **XII**. Non-reactivity of ^{t}BuOH suggests the requirement of *β*-hydride shift. Finally, **XIII** undergoes reductive elimination to afford **127** thus regenerating the active [Pd^0]-catalyst.



2.9 Aluminium chloride as a chlorinating agent for the regio- and stereo-specific hydrochlorination of ynamides

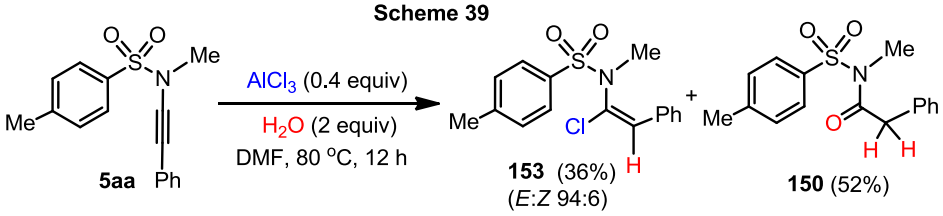
As was discussed in the Introduction, α-chlorination of ynamides is a straightforward entry to functionalized enamides. Even though aluminium chloride has been utilized in different organic transformations, it does not act as a chlorinating agent for the hydrochlorination of alkynes/ ynamides.[51, 52] In the following section, we discuss the

regio- and stereo-specific hydrochlorination of ynamides using aluminium chloride as the chlorinating agent.

2.9.1 Reaction of ynamide with aluminium chloride

Initially, we performed the reaction of *N*-alkynyl benzenesulfonamide **5aa** with aluminium chloride (0.4 equiv) using H_2O (2 equiv) as the proton source in DMF solvent at 80 ^oC for 12 h (Scheme 39). Delightfully, the α-chloroenamide **153** was isolated in 36% yield in addition to the water addition by-product **150** in 52% yield.

Scheme 39



To further improve the yield and stereoselectivity of the desired product **153**, we then moved to optimization of the reaction conditions (Table 20). The reaction using 1 equiv of water also led to the formation of both the products **153** and **150**. However, the use of nearly stoichiometric amounts of aluminium chloride (1.1 equiv) furnished the desired product **153** in good yield. It is noteworthy that, no over hydrochlorination observed even with an excess of aluminium chloride (3 equiv). Variation of solvents from DMF to THF and PEG-400 improved the stereoselectivity. The reaction was not clean in ethanol. Both the yield and stereoselectivity decreased when we performed the reaction in toluene. Interestingly, the product was obtained in good yield and stereoselectivity by using acetonitrile. Further to our surprise, the reaction proceeded cleanly by the use of dimethyl carbonate as a solvent affording the product **153** in 92% isolated yield regio- and stereo-specifically. We noticed that the reaction also proceeded at the rt (25 ^oC) but with slower reaction rate, and reducing the product yield along with unreacted starting material. $TiCl_4$ gave a mixture of products and $SnCl_4$ led mainly to the water addition product **150** with only traces of the desired product. $AlCl_3$ $6H_2O$ was also suitable as a chlorinating agent, though with decreased yield. It is important to note that the straightforward reaction with conc. HCl instead of $AlCl_3$ resulted in essentially *ca* 1:1 mixture of *E*- and *Z*- isomers. Also, the reaction with HCl in dimethyl carbonate did not proceed. Hence the optimized condition for the regio- and stereospecific hydro-chlorination of ynamides is **5aa** (0.20

mmol), aluminium chloride (0.22 mmol) in dimethyl carbonate (1 mL) and H_2O (0.20 mmol) at 80 ^oC for 12 h (Table 20, entry 10).

Table 20: Optimization study for the synthesis of (*E*)-*N*-(1-chloro-2-phenylvinyl)-*N*,4-dimethylbenzenesulfonamide **153** from ynamide **5aa**[a]

Entry	$AlCl_3$ (equiv)	Solvent	Yield (%)[b] **153** (*E:Z*)
1[c,d]	$AlCl_3$ (0.4)	DMF	36 (94:6)
2[d]	$AlCl_3$ (0.4)	DMF	42
3	$AlCl_3$ (1.1)	DMF	85
4	$AlCl_3$ (3.0)	DMF	86
5	$AlCl_3$ (1.1)	THF	90 (96:4)
6[d]	$AlCl_3$ (1.1)	PEG-400	82 (99:1)
7	$AlCl_3$ (1.1)	EtOH	traces
8	$AlCl_3$ (1.1)	toluene	76 (92:8)
9	$AlCl_3$ (1.1)	CH_3CN	92 (96:4)
10	**$AlCl_3$ (1.1)**	**$(MeO)_2CO$**	**92 (>99:traces)**
11[e]	$AlCl_3$ (1.1)	$(MeO)_2CO$	46
12	$TiCl_4$ (1.1)	$(MeO)_2CO$	traces
13[d]	$SnCl_4$ (1.1)	$(MeO)_2CO$	traces

[a]Ynamide (0.20 mmol), aluminium chloride (x equiv), solvent (1 mL) and H_2O (1 equiv) at 80 ^oC for 12 h. [b]Yield of the isolated product and stereoisomeric ratio in parenthesis was based on ^1H NMR. [c]H_2O (2 equiv) used. [d] Compound **150** was observed. [e]Performed at rt.

After having the above optimized reaction conditions in hand, we then sought to explore the substrate scope for this chloride ion transfer from aluminium chloride to ynamides. As illustrated in Scheme 40, various ynamides are transformed into the corresponding (*E*)-enamides in good to excellent yields in a regio- and stereo-specific manner (Table 21). Changing the substituents on the sulfonyl group, nitrogen atom and alkyne functionality worked well and provided the products **153-166**. Replacing the sulfonyl group with the phosphoryl group or carbonyl group does not affect the regio- and stereoselectivity (compounds **167-168**). The absence of (*C*≡*C*) stretch in the IR spectra and the presence of one extra-hydrogen in the olefinic region in ^1H NMR spectra of these products suggested the involvement of alkyne functionality in the hydrochlorination process. Further, the structures of compounds **168** and **169** were confirmed by X-ray

crystallographic analysis (Figure 16). We also made an attempt to add hydrogen azide (via Me_3SiN_3) but the starting material remained unchanged**.**

Scheme 40

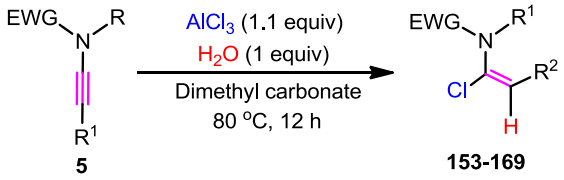
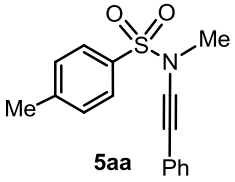
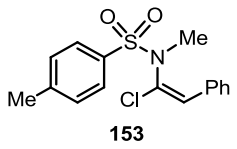
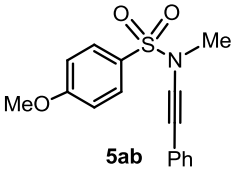
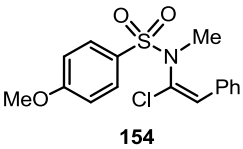
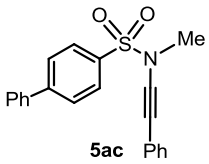
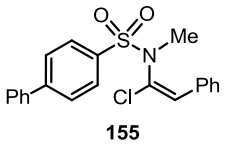
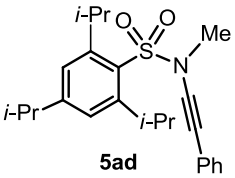
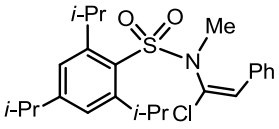
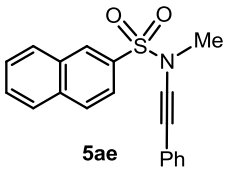
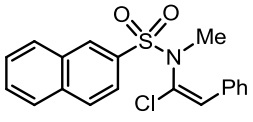
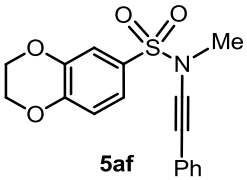
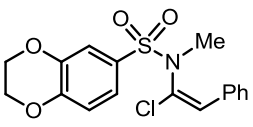
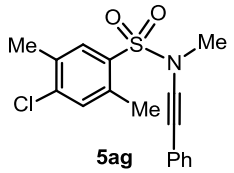
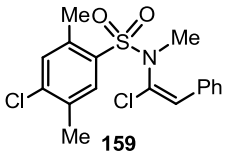
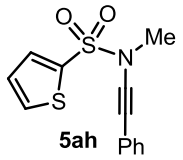
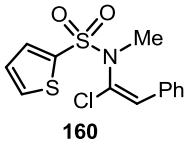
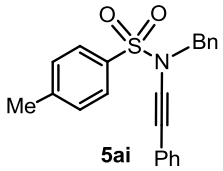
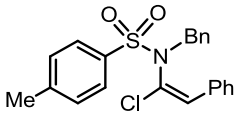
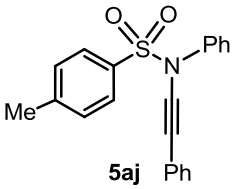
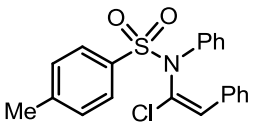
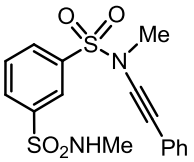
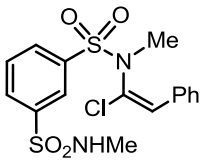
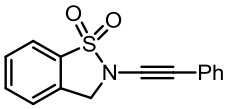
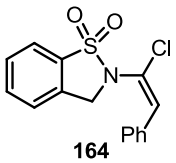
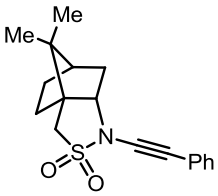
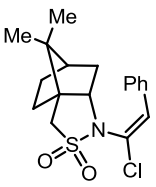
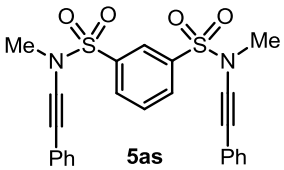
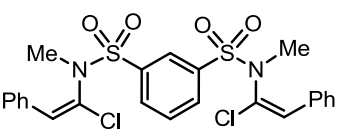
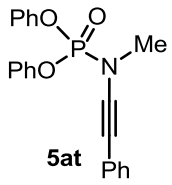
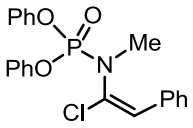
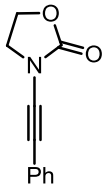
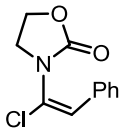
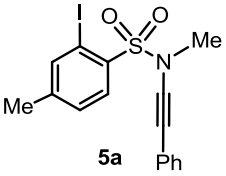
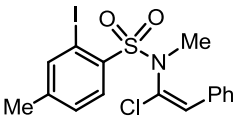


Table 21: Aluminium chloride mediated synthesis of (*E*)-α-chloroenamides from the ynamides[a]

Entry	Ynamide	Enamide	Yield (%)[b]
1	 **5aa**	 **153**	92
2	 **5ab**	 **154**	90
3	 **5ac**	 **155**	84
4	 **5ad**	 **156**	86
5	 **5ae**	 **157**	92
6	 **5af**	 **158**	78

7	 **5ag**	 **159**	82
8	 **5ah**	 **160**	86
9	 **5ai**	 **161**	85
10	 **5aj**	 **162**	82
11	 **5an**	 **163**	85
12	 **5ao**	 **164**	94
13	 **5ap**	 **165**	87
14	 **5as**	 **166**	84

15	 **5at**	 **167**	90
16	 **5au**	 **168** (**X-ray**)	98
17	 **5a**	 **169 (X-ray)**	90

[a]Conditions: **5** (0.20 mmol), aluminium chloride (0.22 mmol) in dimethyl carbonate (1 mL) and H_2O (0.20 mmol) at 80 ^oC for 12 h. [b]Isolated yields after column chromatography are given in parenthesis. For the preparation of compound **166** we used aluminium chloride (0.44 mmol), H_2O (0.40 mmol).

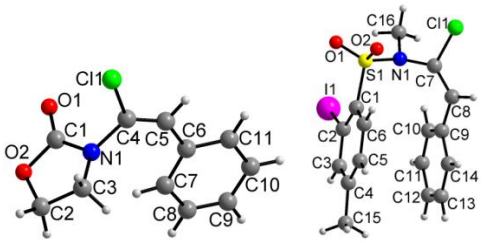


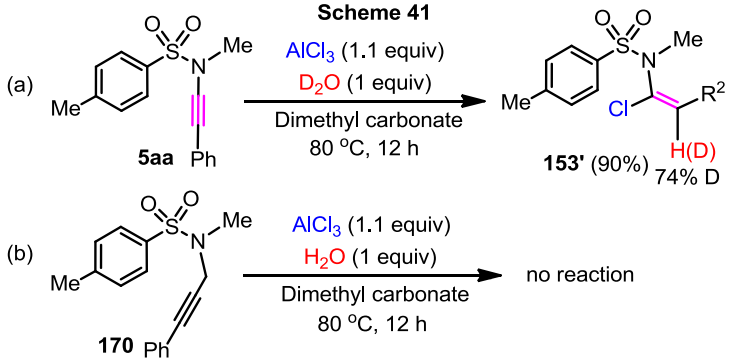
Figure 16. Molecular structures of compounds **168** (left) and **169** (right). Selected bond parameters: Compound **168** Cl1-C4 1.756(2), N1-C4 1.402(3), C4-C5 1.322(3), C5-C6 1.461(3), C6-C7 1.397(3), C6-C11 1.390(3) (Å). Compound **169** Cl1-C7 1.770(3), S1-N1 1.662(2), N1-C7 1.414(3), C7-C8 1.316(4), C8-C9 1.484(4), C9-C10 1.385(4), C9-C14 1.388(4) (Å).

2.9.2 Control experiments

To elucidate the probable catalytic pathway for this chloride ion transfer from aluminium chloride to ynamides, we have done the following control experiments. Thus the reaction of ynamide **5aa** with aluminium chloride (1.1 equiv) and D_2O (1 equiv) in dimethyl carbonate solvent delivers the compound **153'** with about 76% deuteration at

one of the olefinic positions (Scheme 41a). The isolation of monodeuterated α-chloroenamide **153'** suggested the role of water as a proton source in the reaction. No reaction occurred when we treated *N*-propargylated sulfonamide **170** under similar reaction conditions due to the nonexistence of reactive keteniminium ion (Scheme 41b).

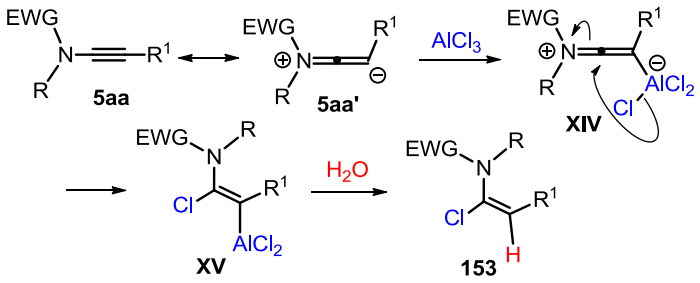
Scheme 41



2.9.3 Plausible pathway

Based on the above control experiment and the earlier literature, we propose the following plausible catalytic cycle for the formation of compound **153**.[126] Initially, the keteniminium form **5aa'** attacks on aluminium chloride, thereby producing intermediate **XIV**. Formation of intermediate **XIV** may responsible for the regio- and stereo-specificity, since if it is the *in situ* generated HCl it could have led to the formation of two stereoisomers. The intermediate **XIV** further experiences a chloride ion transfer resulting in intermediate **XV**. Subsequent reaction with water affords the enamide **153** (Scheme 42).

Scheme 42



SUMMARY

1) An efficient one-pot approach to synthesize triazolo 1,2,4-benzothiadiazine 1,1-dioxides from functionalized ynamides and sodium azide with the aid of CuI catalyst using the environmentally benign PEG-400 as the solvent has been developed. The cyclization process involves intermolecular C–N bond formation followed by cycloaddition between alkyne and azide. Thus three new C–N bonds are formed in a single step. It is also demonstrated that the triazole ring in triazolo-1,2,4-benzothiadiazine-1,1-dioxide can be readily decyclized in the presence of glacial acetic acid with the elimination of molecular nitrogen.

2) A novel and efficient one-pot protocol for the regio and stereo-specific synthesis of benzo[1,4,2]dithiazine 1,1-dioxides and benzo[1,4,2]thiaselenazine 1,1-dioxides by [Cu]-catalyzed cyclization of functionalized ynamides using elemental sulfur or selenium is developed. Involvement of water in the reaction is demonstrated by the incorporation of ^{2}D at the olefinic site by using D_2O in place of water. Selective oxidation at sulfur in benzo[1,4,2]dithiazine 1,1-dioxide by using *m*CPBA as the oxidizing agent is accomplished. This [Cu]-catalyzed cyclization is extended to benzodithiazepines/ benzothiaselenazepines illustrating its utility.

3) A simple and efficient strategy for the synthesis of a wide range of hetero-substituted benzosultams (1,2-benzothiazine 1,1-dioxides) by the nucleophilic attack of various nucleophiles on functionalized ynamides using [Pd]-catalysis has been discovered. Medicinally useful compounds like nortriptyline and eugenol could also be used as nucleophiles. DFT studies suggested that the reaction involves a $[Pd^{II}]$-$[Pd^{0}]$-$[Pd^{II}]$ cycle.

4) Ethanol can itself acts the hydrogenating agent in palladium-catalyzed reaction of ynamides, a synthetically versatile class of alkynes. The reaction is operationally simple affording (*E*)-enamides in a highly stereoselective manner. A complementary palladium catalyzed method involving $EtOH/NH_4OOCH$ is also discovered for *Z*-selective hydrogenation. This methodology is also applicable to phosphoryl and carbamate derived ynamides and ynamines. Deuterium labelling

experiment demonstrated the essential role of ***ethanol*** as the hydrogenating agent in this reaction.

5) An elegant and operationally simple approach for the regio- and stereo-specific synthesis of (*E*)-α-chloroenamides by the hydrochlorination of ynamides using aluminium chloride as the chlorinating agent is developed. In general, aluminium chloride is known to act as Lewis acid but not as hydochlorinating agent. It is noted that in these cases the use of conc. HCl leads to a mixture of *E*- and *Z*-isomers. This methodology is also applicable to phosphoramidate and carbamate derived ynamide substrates. The formation of aluminated keteniminium ionic species may account for the stereospecificity. Deuterium labelling experiment demonstrated the role of water as the proton source in the reaction.

EXPERIMENTAL SECTION

General information: Chemicals and solvents were procured from Aldrich/ Fluka or local manufacturers. Further purification was done according to standard procedures wherever required.[127] All operations, unless otherwise specified, were carried out under dry nitrogen atmosphere using standard vacuum line techniques.[128]

Melting point: Melting points were determined using a SUPERFIT hot stage apparatus and are uncorrected.

Elemental analyses: Elemental analyses were carried out on a Perkin-Elmer 240C CHN or Thermo Finnigan EA1112 CHNS analyzer.

Infrared spectroscopy: IR spectra were recorded on a JASCO FT/IR 5300 spectrophotometer.

NMR spectroscopy: From sections 3.1-3.14 ^{1}H, ^{13}C NMR spectra were recorded using 5 mm tubes on a Bruker 400 MHz NMR spectrometer (unless specified otherwise) [field strengths: 400 and 100 MHz respectively] in $CDCl_3$ solution (unless specified otherwise) with shifts referenced to $SiMe_4$ (^{1}H, ^{13}C: $\delta = 0$). From sections 3.15-3.20 ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded using 5 mm tubes on a Bruker 500 MHz NMR spectrometer (unless specified otherwise) [field strengths: 500, 125 and 202 MHz respectively] in $CDCl_3$ solution (unless specified otherwise) with shifts referenced to $SiMe_4$ (^{1}H, ^{13}C: $\delta = 0$) and ext. 85% H_3PO_4 (^{31}P: $\delta = 0$) respectively. All *J* values are in Hz.

LC-MS and HRMS: LC-MS equipment was used to record mass spectra for isolated compounds where appropriate. LC-MS data were obtained using electrospray ionization (positive mode) on a C-18 column. Mass spectra were recorded using HRMS (ESI-TOF analyzer) equipment.

The precursors, sulfonamides **1a-q**,[79] substituted 2-iodo-benzenesulfonamides **2a-g**,[80] substituted (bromoethynyl)benzene precursors **3a-i**[81] and phenyl propargyl bromide **4b**[82] were prepared following literature reports.

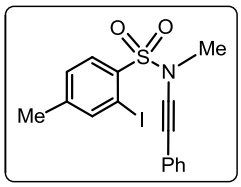
3.1 Synthesis of functionalized ynamides [5a-t]

The ynamide precursors **5a-t** except **5n** were prepared following a known procedure.[12] Compound **5n** was prepared following another procedure with slight modification.[11] All these compounds are new.

Representative procedure for 2-iodo-*N*,4-dimethyl-*N*-(phenylethynyl)benzenesulfonamide 5a

Compound **5a** was synthesized by using 2-iodo-*N*,4-dimethylbenzenesulfonamide **2a** (1.00 g, 3.21 mmol), $CuSO_4 \cdot 5H_2O$ (0.08 g, 0.32 mmol), 1,10-phenanthroline monohydrate (0.127 g, 0.64 mmol) and K_2CO_3 (1.11 g, 8.03 mmol). Later, dry toluene (5 mL) and (bromoethynyl)benzene **3a** (0.46 mL, 3.85 mmol) were added. The vessel was stoppered under nitrogen and heated on an oil-bath maintained at 80 ^oC overnight. The mixture was passed through celite and concentrated in vacuum. The crude residue was then purified by using silica gel column chromatography to obtain the pure ynamide **5a** by using hexane-ethyl acetate (9:1) as the eluent. Ynamides **5a-t** except **5n** was prepared following the representative procedure.

Compound 5a



Yield: 1.13 g (86%).

Mp: 94-96 ^oC.

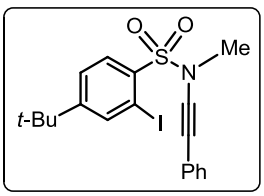
IR (KBr): 2241, 1584, 1441, 1353, 1260, 1167, 1096, 1019, 964, 756, 668 cm^{-1}.

^1H NMR: δ 8.10 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.99 (s, 1H, Ar-*H*), 7.33 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.27-7.26 (m, 5H, Ar-*H)*, 3.41 (s, 3H, NCH_3), 2.39 (s, 3H, Ar-CH_3).

^{13}C NMR: δ 145.7, 143.8, 136.9, 132.6, 131.2, 129.0, 128.3, 127.8, 122.7, 92.2 (*C*I), 83.3, 70.2, 39.7 (N*C*H_3), 20.9 (Ar*C*H_3).

HRMS (ESI): Calcd. for $C_{16}H_{15}INO_2S$ [M^++H]: m/z 411.9868. Found: 411.9866.

Compound 5b



Here, 4-*tert*-butyl-2-iodo-*N*-methylbenzenesulfonamide **2b** (1.00 g, 2.82 mmol) and (bromoethynyl)benzene **3a** (0.40 mL, 3.39 mmol) were used.

Yield: 1.12 g (88%).

Mp: 66-68 ^{o}C.

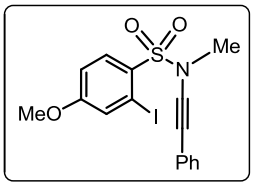
IR (KBr): 2225, 1584, 1540, 1458, 1337, 1178, 959, 751, 663 cm^{-1}.

^{1}H NMR (C_6D_6): δ 8.22 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 8.08 (s, 1H, Ar-*H*), 7.34-7.33 (m, 2H, Ar-*H*), 7.09-7.04 (m, 4H, Ar-H), 3.15 (s, 3H, NC*H*$_3$), 0.99 (s, 9H, C(C*H*$_3$)$_3$).

^{13}C NMR (C_6D_6): δ 158.1, 140.4, 137.8, 132.7, 131.4, 128.3, 127.7, 125.5, 123.2, 92.8 (*C*I), 84.3, 70.5, 39.2 (N*C*H$_3$), 34.4 (*C*(CH$_3$)$_3$), 30.3 (C(*C*H$_3$)$_3$).

HRMS (ESI): Calcd. for $C_{19}H_{21}INO_2S$ [M$^+$+H]: *m/z* 454.0337. Found: 454.0342.

Compound 5c



Here, 2-iodo-4-methoxy-*N*-methylbenzenesulfonamide **2c** (1.00 g, 3.05 mmol) and (bromoethynyl)benzene **3a** (0.43 mL, 3.66 mmol) were used.

Yield: 1.20 g (92%).

IR (neat): 2236, 1584, 1474, 1364, 1162, 1014, 959, 762 cm^{-1}.

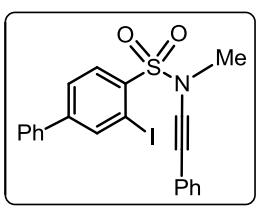
^{1}H NMR (C_6D_6): δ 8.21 (d, 1H, *J* = 8.8 Hz, Ar-*H*), 7.42-7.38 (m, 3H, Ar-*H*), 7.02 (d, *J* = 6.8 Hz, 3H, Ar-*H*), 6.35 (dd, *J* = 8.8 and 2.4 Hz, 1H, Ar-*H*), 3.16 (s, 3H, Ar-OC*H*$_3$), 2.92 (s, 3H, NC*H*$_3$).

^{13}C NMR (C_6D_6): δ 162.7, 134.3, 131.9, 131.4, 128.5, 128.4, 127.7, 123.2, 113.1, 93.6 (*C*I), 84.4, 70.4, 55.1 (Ar-O*C*H$_3$), 39.2 (N*C*H$_3$).

LC-MS: *m/z* 428 [M+1]$^+$.

Anal. Calcd. for $C_{16}H_{14}INO_3S$: C, 44.98; H, 3.30; N, 3.28. Found: C, 44.85; H, 3.36; N, 3.23.

Compound 5d



Here, 3-iodo-*N*-methylbiphenyl-4-sulfonamide **2d** (0.50 g, 1.33 mmol) and (bromoethynyl)benzene **3a** (0.19 mL, 1.60 mmol) were used.

Yield: 0.59 g (94%).

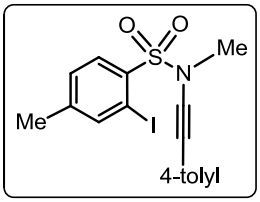
IR (neat): 2236, 1584, 1540, 1458, 1364, 1167, 964, 805, 756 cm^{-1}.

^1H NMR (C_6D_6): δ 8.29 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 8.13 (s, 1H, Ar-*H*), 7.40 (d, *J* = 6.8 Hz, 2H, Ar-*H*), 7.19-7.11 (m, 6H, Ar-*H*), 7.04-7.02 (m, 3H, Ar-*H*), 3.17 (s, 3H, NCH_3).

^{13}C NMR (C_6D_6): δ 146.8, 141.5, 138.9, 137.4, 133.0, 131.5, 129.0, 128.8, 128.6, 128.4, 127.3, 126.5, 123.1, 93.0 (*C*I), 84.1, 70.6, 39.3 (N*C*H_3).

HRMS (ESI): Calcd. for $C_{21}H_{17}INO_2S$ [M^++H]: m/z 474.0024. Found: 474.0020.

Compound 5e



Here, 2-iodo-*N*,4-dimethylbenzenesulfonamide **2a** (0.50 g, 1.60 mmol) and 1-(bromoethynyl)-4-methylbenzene **3b** (0.26 mL, 1.92 mmol) were used.

Yield: 0.56 g (82%).

Mp: 101-103 ^oC.

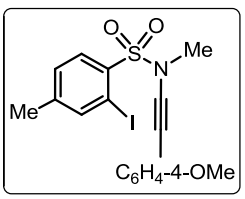
IR (KBr): 2230, 1584, 1452, 1353, 1162, 1030, 953, 816, 729, 658 cm^{-1}.

^1H NMR (C_6D_6): δ 8.15 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.53 (s, 1H, Ar-*H*), 7.33 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 6.82 (d, *J* = 7.6 Hz, 2H, Ar-*H)*, 6.53 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 3.13 (s, 3H, NCH_3), 1.99 (s, 3H, Ar-CH_3), 1.60 (s, 3H, Ar-CH_3).

^{13}C NMR (C_6D_6): δ 145.0, 143.6, 137.8, 137.7, 132.5, 131.7, 129.1, 128.7, 120.1, 92.5 (*C*I), 83.5, 70.3, 39.3 (N*C*H_3), 21.0 (Ar*C*H_3), 20.0 (Ar-*C*H_3).

HRMS (ESI): Calcd. for $C_{17}H_{17}INO_2S$ [M^++H]: *m/z* 426.0024. Found: 426.0022.

Compound 5f



Here, 2-iodo-*N*,4-dimethylbenzenesulfonamide **2a** (0.50 g, 1.60 mmol) and 1-(bromoethynyl)-4-methoxybenzene **3c** (0.407 g, 1.92 mmol) were used.

Yield: 0.63 g (90%).

Mp: 74-76 ^{o}C.

IR (KBr): 2942, 2833, 2236, 1605, 1512, 1463, 1359, 1238, 1162, 1019, 833, 734, 652 cm^{-1}.

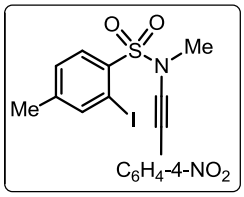
^{1}H NMR: δ 8.09 (d, *J* = 8.4 Hz, 1H), 8.01 (s, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 8.6 Hz, 2H), 6.81 (d, *J* = 8.6 Hz, 2H), 3.81 (s, 3H), 3.41 (s, 3H), 2.41 (s, 3H).

^{13}C NMR: δ 159.5, 145.7, 143.7, 137.0, 133.3, 132.4, 129.1, 114.5, 113.9, 92.1, 82.0, 69.8, 55.3, 39.8, 20.9.

LC-MS: *m/z* 442 [M+1]$^{+}$.

Anal. Calcd. for $C_{17}H_{16}INO_3S$: C, 46.27; H, 3.65; N, 3.17. Found: C, 46.37; H, 3.58; N, 3.24.

Compound 5g



Here, 2-iodo-*N*,4-dimethylbenzenesulfonamide **2a** (1.00 g, 3.20 mmol) and 1-(bromoethynyl)-4-nitrobenzene **3d** (0.87 g, 3.85 mmol) were used.

Yield: 1.20 g (82%).

Mp: 134-136 ^{o}C.

IR (KBr): 3080, 2941, 2223, 1598, 1510, 1453, 1329, 1272, 1159, 1091, 952, 849, 766, 683 cm^{-1}.

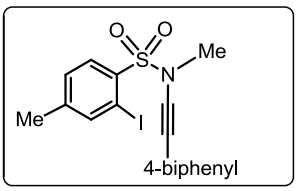
^{1}H NMR: δ 8.11-8.09 (m, 3H), 7.99 (s, 1H), 7.38-7.35 (m, 3H), 3.40 (s, 3H), 2.40 (s, 3H).

^{13}C NMR: δ 146.2$_1$, 146.1$_6$, 143.9, 136.6, 132.6, 130.8, 130.2, 129.1, 123.6, 92.2, 89.4, 70.2, 39.5, 20.9.

LC-MS: *m/z* 457 [M+1]$^{+}$.

Anal.Calcd. for $C_{16}H_{13}IN_2O_4S$: C, 42.12; H, 2.87; N, 6.14. Found: C, 42.26; H, 2.82; N, 6.23.

Compound 5h



Here, 2-iodo-*N*,4-dimethylbenzenesulfonamide **2a** (0.5 g, 1.60 mmol) and 1-(bromoethynyl)biphenyl **3e** (0.495 g, 1.92 mmol) were used.

Yield: 0.704 g (90%).

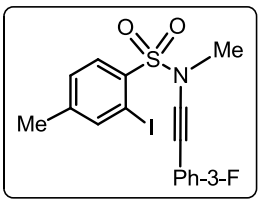
IR (neat): 2235, 1588, 1490, 1358, 1161, 1019, 964, 838, 723 cm^{-1}.

^{1}H NMR (C_6D_6): δ 8.21 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.59 (s, 1H, Ar-*H*), 7.46 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 7.41 (d, *J* = 7.6 Hz, 2H, Ar-*H*), 7.34 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 7.26-7.21 (m, 2H, Ar-*H*), 7.20 (d, *J* = 7.2 Hz, 1H, Ar-*H)*, 6.61 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 3.18 (s, 3H, NCH_3), 1.66 (s, 3H, Ar-CH_3).

^{13}C NMR (C_6D_6): δ 145.3, 143.6, 140.6, 140.4, 137.6, 132.5, 131.9, 128.9, 128.8, 127.3, 127.1, 127.0 122.0, 92.5 (*C*I), 84.8, 70.4, 39.3 (N*C*H_3), 20.1 (Ar-*C*H_3).

HRMS (ESI): Calcd. for $C_{22}H_{18}INO_2S$ [M^++Na]: *m/z* 510.0001. Found: 510.0001.

Compound 5i



Here, 2-iodo-*N*,4-dimethylbenzenesulfonamide **2a** (0.50 g, 1.60 mmol) and 1-(bromoethynyl)-3-fluorobenzene **3f** (0.23 mL, 1.92 mmol) were used.

Yield: 0.664 g (96%).

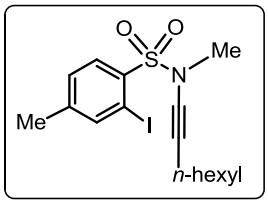
IR (neat): 2236, 1578, 1436, 1353, 1260, 1173, 1025, 888, 734, 679 cm^{-1}.

^{1}H NMR (C_6D_6): δ 8.13 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.55 (s, 1H, Ar-*H*), 7.03 (d, *J* ~ 8.0 Hz, 2H, Ar-*H*), 6.79-6.73 (m, 1H, Ar-*H*), 6.69-6.65 (m, 1H, Ar-*H*), 6.58 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 3.09 (s, 3H, NCH_3), 1.65 (s, 3H, Ar-CH_3).

^{13}C NMR (C_6D_6): δ 163.5 (d, J_{C-F} = 240 Hz), 145.6, 143.7, 137.2, 132.4, 130.0 (d, J_{C-F} = 10 Hz), 128.8, 126.9, 125.1 (d, J_{C-F} = 10 Hz), 117.7 (d, J_{C-F} = 20 Hz), 114.8 (d, J_{C-F} = 20 Hz), 92.4 (*C*I), 85.2, 69.5, 39.1 (N*C*H_3), 20.2 (Ar-*C*H_3).

HRMS (ESI): Calcd. for $C_{16}H_{15}INO_2S$ [M^++H]: *m/z* 429.9774. Found: 429.9773.

Compound 5j



Here, 2-iodo-*N*,4-dimethylbenzenesulfonamide **2a** (0.50 g, 1.60 mmol) and 1-bromooct-1-yne **3g** (0.20 mL, 1.92 mmol) were used.

Yield: 0.57 g (84%).

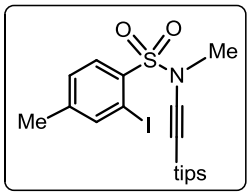
IR (neat): 2251, 1588, 1459, 1356, 1283, 1169, 1024, 828, 672 cm^{-1}.

^1H NMR (C_6D_6): δ 8.20 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.60 (s, 1H, Ar-*H*), 6.68 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 3.17 (s, 3H, NCH_3), 2.09 (t, *J* ~ 6.8 Hz, 2H, CH_2), 1.71 (s, 3H, Ar-CH_3), 1.35-1.15 (m, 8H, 4 CH_2), 0.93 (t, *J* ~ 6.8 Hz, 3H, CH_3).

^{13}C NMR (C_6D_6): δ 144.7, 143.4, 138.0, 132.4, 128.5, 92.5 (*C*I), 74.9, 69.5, 39.3 (N*C*H_3), 31.4, 28.9, 28.4, 22.7 (Ar-*C*H_3), 20.1, 18.5, 14.1.

HRMS (ESI): Calcd. for $C_{16}H_{23}INO_2S$ [M^++H]: *m/z* 420.0494. Found: 420.0496.

Compound 5k



Here, 2-iodo-*N*,4-dimethylbenzenesulfonamide **2a** (0.50 g, 1.60 mmol) and (bromoethynyl)triisopropylsilane **3h** (0.46 mL, 1.92 mmol) were used.

Yield: 0.746 g (95%).

Mp: 50-52 ^oC.

IR (KBr): 2164, 1584, 1463, 1337, 1167, 1030, 981, 888, 729, 674 cm^{-1}.

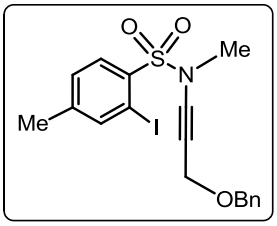
^1H NMR (C_6D_6): δ 8.20 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 7.57 (s, 1H, Ar-*H*), 6.67 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 3.13 (s, 3H, NCH_3), 1.71 (s, 3H, Ar-CH_3), 1.14-1.13 (m, 21H, Si(C*H*(CH_3)$_2$)$_3$).

^{13}C NMR (C_6D_6): δ 145.0, 143.3, 137.4, 132.9, 128.6, 98.0 (*C*I), 92.5, 68.3, 39.0 (N*C*H_3), 20.0 (Ar-*C*H_3), 18.6 (*C*H_3), 11.4 (*C*H).

LC-MS: *m/z* 490 $[M-1]^+$.

Anal. Calcd. for $C_{19}H_{30}ISNO_2Si$: C, 46.43; H, 6.15; N, 2.85. Found: C, 46.52; H, 6.20; N, 2.81.

Compound 5l



Here, 2-iodo-*N*,4-dimethylbenzenesulfonamide **2a** (0.50 g, 1.60 mmol) and ((3-bromoprop-2-ynyloxy)methyl)benzene **3i** (0.30 mL, 1.92 mmol) were used.

Yield: 0.654 g (89%).

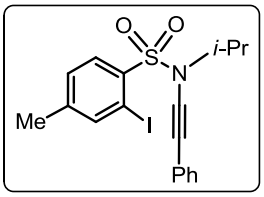
IR (neat): 2241, 1589, 1452, 1348, 1167, 1063, 1019, 701 cm^{-1}.

^{1}H NMR (C_6D_6): δ 8.14 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.55 (s, 1H, Ar-*H*), 7.33 (d, *J* = 7.6 Hz, 2H, Ar-*H*), 7.23-7.17 (m, 3H, Ar-*H)*, 6.60 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 4.42 (s, 2H, OCH_2), 4.11 (s, 2H, OCH_2), 3.07 (s, 3H, NCH_3), 1.64 (s, 3H, Ar-CH_3).

^{13}C NMR (C_6D_6): δ 145.5, 143.6, 138.1, 137.3, 132.4, 128.9, 128.3, 128.0, 127.6, 92.4 (*C*I), 81.2, 70.7 (O*C*H_2), 67.3, 57.3 (O*C*H_2), 39.2 (N*C*H_3), 20.2 (Ar-*C*H_3).

HRMS (ESI): Calcd. for $C_{18}H_{19}INO_3S$ [M^++H]: *m/z* 456.0130. Found: 456.0129.

Compound 5m



Here, 2-iodo-4-methyl-*N*-(*i*-propyl)benzenesulfonamide **2e** (0.50 g, 1.47 mmol), $CuSO_4 \cdot 5H_2O$ (0.072 g, 0.29 mmol), 1,10-phenanthroline monohydrate (0.114 g, 0.58 mmol), K_2CO_3 (0.507 g, 3.67 mmol), dry toluene (3 mL) and (bromoethynyl)benzene **3a** (0.21 mL, 1.76 mmol) were used.

Yield: 0.23 g (36%).

Mp: 80-82 ^{o}C.

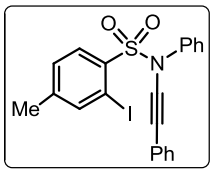
IR (KBr): 2230, 1584, 1353, 1178, 1025, 970, 756, 674 cm^{-1}.

^{1}H NMR (C_6D_6): δ 8.25 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.57 (s, 1H, Ar-*H*), 7.40 (dd, *J* ~ 8.0 and 1.6 Hz, 2H, Ar-*H*), 7.05-7.00 (m, 3H, Ar-*H*), 6.59 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 4.58-4.55 (m, 1H, NC*H*), 1.64 (s, 3H, Ar-CH_3), 1.35 (d, *J* = 6.4 Hz, 6H, CH(CH_3)$_2$).

^{13}C NMR (C_6D_6): δ 144.9, 143.5, 138.3, 132.6, 131.4, 128.6, 128.3, 123.6, 92.6 (*C*I), 80.0, 74.0, 52.6 (N*C*H), 20.9 (Ar-*C*H$_3$), 20.0 (CH(*C*H$_3$)$_2$).

HRMS (ESI): Calcd. for $C_{18}H_{18}INO_2S$ [M^++H]: *m/z* 440.0181. Found: 440.0181.

Compound 5n



To a solution of 2-iodo-4-methyl-*N*-phenyl benzenesulfonamide **2f** (0.50 g, 1.33 mmol) in dry toluene (10 mL) at -30 ^{o}C was added LiHMDS (1M solution in toluene, 1.6 mL, 1.66 mmol) drop-wise. The reaction was continued at the same temperature for 1 h followed by the portion-wise addition of phenyl (phenylethynyl)iodonium trifluoroacetate (0.78 g, 1.86 mmol). The resulting mixture was stirred at rt (25 ^{o}C) overnight under inert atmosphere. The mixture was then passed through celite and concentrated in vacuum. The crude product was purified by using silica gel column chromatography to obtain the pure ynamide **5n** by using hexane-ethyl acetate (9:1) as the eluent.

Yield: 0.20 g (32%).

Mp: 94-96 ^{o}C.

IR (KBr): 2926, 2844, 2236, 1589, 1490, 1370, 1260, 1178, 1025, 926, 690 cm^{-1}.

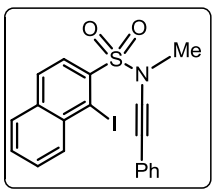
^{1}H NMR: δ 8.00-7.98 (m, 2H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.41-7.35 (m, 5H), 7.34-7.27 (m, 4H), 2.39 (s, 3H).

^{13}C NMR: δ 145.8, 143.9, 138.7, 136.8, 133.0, 131.4, 129.2, 128.8, 128.3, 128.1, 127.9, 126.1, 122.7, 92.4, 82.9, 71.7, 20.9.

LC-MS: *m/z* 474 [M+1]$^+$.

Anal. Calcd. for $C_{21}H_{16}INO_2S$: C, 53.29; H, 3.41; N, 2.96. Found: C, 53.15; H, 3.45; N, 2.89.

Compound 5o



Here, 1-iodo-*N*-methylnaphthalene-2-sulfonamide **2g** (0.50 g, 1.44 mmol) and (bromoethynyl)benzene **3a** (0.20 mL, 1.92 mmol) were used. Two isomers in the ratio 3:1 were present; the mixture was used as such.

Yield: 0.40 g (62%).

IR (neat): 2236, 1540, 1441, 1364, 1173, 970, 762, 674 cm^{-1}.

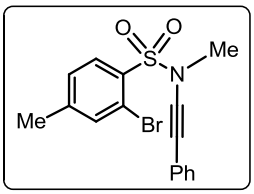
^1H NMR (C_6D_6): δ 8.41 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 8.36 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 7.34-7.32 (m, 3H, Ar-*H*), 7.22-7.15 (m, 3H, Ar-*H*), 6.99-6.98 (m, 3H, Ar-*H*), 3.15 (s, 3H, NCH_3).

^{13}C NMR (C_6D_6): δ 140.2, 135.8, 134.8, 131.4, 129.1, 128.9, 128.3, 127.7, 123.0, 84.1, 70.7, 39.3 (N*C*H_3).

LC-MS: *m/z* 448 $[M+1]^+$.

Anal. Calcd. for $C_{19}H_{14}INO_2S$: C, 51.02; H, 3.15; N, 3.13. Found: C, 51.16; H, 3.21; N, 3.18.

Compound 5p



Here, 2-bromo-*N*,4-dimethylbenzenesulfonamide **1n** (0.50 g, 1.90 mmol) and (bromoethynyl)benzene **3a** (0.28 mL, 2.28 mmol) were used.

Yield: 0.59 g (86%).

Mp: 68-70 ^oC.

IR (KBr): 2230, 1584, 1447, 1353, 1260, 1167, 1036, 948, 762 cm^{-1}.

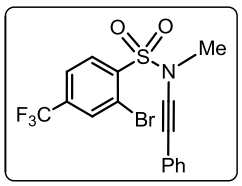
^1H NMR (C_6D_6): δ 8.15 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.39 (d, *J* = 7.6 Hz, 2H, Ar-*H*), 7.12 (s, 1H, Ar-*H*), 7.02-7.00 (m, 3H, Ar-*H*), 6.54 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 3.12 (s, 3H, NCH_3) , 1.68 (s, 3H, Ar-CH_3).

^{13}C NMR (C_6D_6): δ 145.7, 136.2, 134.4, 132.9, 131.4, 128.3, 127.7, 123.1, 120.3, 83.9, 70.2, 39.0 (N*C*H_3), 20.4 (Ar-*C*H_3).

LC-MS: *m/z* 364 and 366 $[M]^+$.

Anal. Calcd. for $C_{16}H_{14}BrNO_2S$: C, 52.76; H, 3.87; N, 3.85. Found: C, 52.65; H, 3.92; N, 3.81.

Compound 5q



Here, 2-bromo-*N*-methyl-4-(trifluoromethyl)benzenesulfonamide **1o** (1.00 g, 3.15 mmol) and (bromoethynyl)benzene **3a** (0.45 mL, 3.78 mmol) were used.

Yield: 1.08 g (82%).

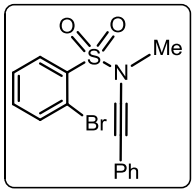
IR (KBr): 3096, 2942, 2241, 1594, 1468, 1381, 1337, 1184, 1085, 975, 756 cm^{-1}.

^{1}H NMR: δ 8.35 (d, *J* = 8.4 Hz, 1H), 8.09 (s, 1H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.29 (br, 5H), 3.48 (s, 3H).

^{13}C NMR: δ 140.4, 136.0 (d, *J* = 34 Hz), 135.8, 133.5, 132.9 (q, *J* = 4 Hz), 131.4, 128.3, 128.2, 124.5 (q, *J* = 4 Hz), 122.2 (d, *J* = 270 Hz), 122.1, 121.3, 82.1, 70.4, 39.8.

HRMS (ESI): Calcd. for $C_{16}H_{12}BrF_3NO_2S$ (M^+ + H): *m/z* = 417.9724, Found: 417.9726.

Compound 5r



Here, 2-bromo-*N*-methylbenzenesulfonamide **1p** (0.50 g, 1.99 mmol) and (bromoethynyl)benzene **3a** (0.28 mL, 1.92 mmol) were used.

Yield: 0.645 g (92%).

IR (neat): 2230, 1567, 1447, 1375, 1260, 1156, 1030, 970, 762 cm^{-1}.

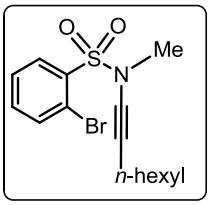
^{1}H NMR (C_6D_6): δ 8.19 (dd, *J* = 7.8 and 1.4 Hz, 1H, Ar-*H*), 7.36-7.34 (m, 2H, Ar-*H*), 7.22 (s, 1H, Ar-*H*), 7.01-7.00 (m, 3H, Ar-*H*), 6.68 (t, *J* = 7.8 Hz, 1H, Ar-*H*), 6.55 (t, *J* = 7.8 Hz, 1H, Ar-*H*), 3.06 (s, 3H, NCH_3).

^{13}C NMR (C_6D_6): δ 137.1, 135.7, 134.3, 133.0, 131.4, 128.6, 128.4, 127.4, 122.9, 120.4, 83.7, 70.3, 39.0 (N*C*H_3).

LC-MS: *m/z* 350 and 352 $[M]^+$.

Anal. Calcd. for $C_{15}H_{12}BrNO_2S$: C, 51.44; H, 3.45; N, 4.00. Found: C, 51.36; H, 3.49; N, 4.07.

Compound 5s



Here, 2-bromo-*N*-methylbenzenesulfonamide **1p** (0.36 g, 1.43 mmol) and 1-bromooct-1-yne **3g** (0.27 mL, 1.72 mmol) were used.

Yield: 0.42 g (82%).

IR (neat): 2258, 1573, 1447, 1364, 1173, 1036, 767, 652 cm^{-1}.

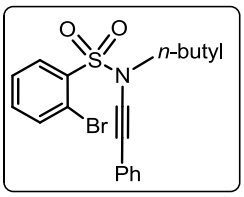
^1H NMR (C_6D_6): δ 8.24 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.28 (s, 1H, Ar-*H*), 6.78 (t, *J* ~ 7.6 Hz, 1H, Ar-*H*), 6.61 (t, *J* ~ 7.6 Hz, 1H, Ar-*H*), 3.09 (s, 3H, NCH_3), 2.06 (t, *J* = 6.8 Hz, 2H), 1.33-1.14 (m, 8H, 4CH_2), 0.93 (t, *J* = 7.2 Hz, 3H, CH_3).

^{13}C NMR (C_6D_6): δ 137.7, 135.5, 133.8, 133.0, 127.1, 120.5, 74.4, 69.5, 39.1 (N*C*H_3), 31.3, 28.9, 28.3, 22.7, 18.3, 14.0.

LC-MS: *m/z* 358 and 360 $[M]^+$.

Anal. Calcd. for $C_{15}H_{20}BrNO_2S$: C, 50.28; H, 5.63; N, 3.91. Found: C, 50.14; H, 5.68; N, 3.85.

Compound 5t



Here, 2-bromo-*N*-butylbenzenesulfonamide **1q** (0.58 g, 1.60 mmol) and (bromoethynyl)benzene **3a** (0.28 mL, 2.38 mmol) were used.

Yield: 0.63 g (82%).

IR (neat): 2230, 1573, 1452, 1364, 1184, 1030, 932, 756 cm^{-1}.

^1H NMR (C_6D_6): δ 8.26 (dd, 1H, *J* = 8.0 and 1.6 Hz , Ar-*H*), 7.35-7.34 (m, 2H, Ar-*H*), 7.28 (s, 1H, Ar-*H*), 7.01-7.00 (m, 3H, Ar-*H*), 6.73 (t, *J* ~ 7.6 Hz, 1H, Ar-*H*), 6.59 (dt, *J* = 7.6 1.2 Hz, 1H, Ar-*H*), 3.69 (t, *J* ~ 7.2 Hz, 2H, CH_2), 1.79-1.72 (m, 2H, CH_2), 1.39-1.33 (m, 2H, CH_2), 0.85 (t, *J* = 7.2 Hz, 3H, CH_3).

^{13}C NMR (C_6D_6): δ 137.8, 135.5, 133.8, 133.1, 131.4, 128.3, 127.7, 127.1, 123.2,

120.5, 82.4, 71.8, 52.0, 30.7, 19.5, 13.4.

LC-MS: *m/z* 392 and 394 $[M]^+$.

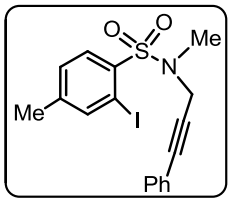
Anal. Calcd. for $C_{18}H_{18}BrNO_2S$: C, 55.11; H, 4.62; N, 3.57. Found: C, 55.21; H, 4.58; N, 3.62.

3.2 Synthesis of 2-iodo-*N*-methyl/phenyl-*N*-(3-phenylprop-2-yn-1-yl)benzenesulfonamides (6b-d)

These compounds were prepared following a known procedure with slight modification.[38, 83] The compounds **6b-d** are new.

To a mixture of sulfonamide and K_2CO_3 in DMF solvent was added propargyl bromide. The reaction mixture was stirred at rt (25 ^oC) for overnight. After completion of the reaction as monitored by TLC, the mixture was diluted with ethyl acetate (20 mL) and washed with water. The aqueous layer was extracted twice with ethyl acetate (20 mL). The combined organic layer was washed with brine solution, dried over sodium sulfate and concentrated in vacuum. The crude residue was then purified by using silica gel column chromatography using hexane-ethyl acetate (9:1) as the eluent to afford the corresponding alkyne.

Compound 6b



Here, 2-iodo-*N*,4-dimethylbenzenesulfonamide **2a** (1.00 g, 3.2 mmol), phenyl propargyl bromide **4b** (0.52 mL, 3.8 mmol) and K_2CO_3 (0.89 g, 6.4 mmol) were used.

Yield: 0.112 g (82%).

Mp: 90-94 ^oC.

IR (KBr): 3063, 2942, 2356, 1578, 1485, 1436, 1321, 1205, 1145, 986, 899, 745, 636 cm^{-1}.

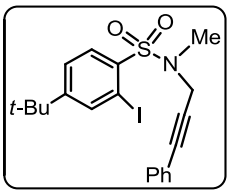
^1H NMR: δ 8.04 (d, *J* = 8.0 Hz, 1H), 7.93 (s, 1H), 7.35-7.30 (m, 5H), 7.28 (d, *J* = 7.2 Hz, 1H), 4.37 (s, 2H), 3.01 (s, 3H), 2.33 (s, 3H).

^{13}C NMR: δ 144.6, 143.6, 138.0, 131.7, 129.0, 128.6, 128.3, 122.4, 92.7, 85.6, 82.6, 40.5, 34.7, 20.7.

LC-MS: *m/z* 426 $[M+1]^+$.

Anal. Calcd. for $C_{17}H_{16}INO_2S$: C, 48.01; H, 3.79; N, 3.29. Found: C, 48.12; H, 3.72; N, 3.24.

Compound 6c



Here, 4-*tert*-butyl-2-iodo-*N*-methylbenzenesulfonamide **2a** (1.00 g, 2.8 mmol), phenyl propargyl bromide **4b** (0.46 mL, 3.4 mmol) and K_2CO_3 (0.78 g, 5.6 mmol) were used.

Yield: 0.110 g (84%).

Mp: 86-88 ^oC.

IR (KBr): 2953, 2860, 2351, 1578, 1485, 1436, 1364, 1326, 1107, 915, 641 cm^{-1}.

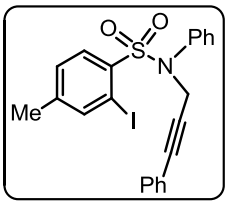
^1H NMR: δ 8.08-8.06 (m, 2H), 7.47 (dd, *J* = 8.0 Hz, *J* = 1.6 Hz, 1H), 7.34-7.26 (m, 5H), 4.39 (s, 2H), 3.03 (s, 3H), 1.27 (s, 9H).

^{13}C NMR: δ 157.5, 140.4, 138.1, 131.6_9, 131.6_8, 128.6, 128.3, 125.4, 122.3, 92.9, 85.6, 82.6, 40.6, 34.8, 30.9.

LC-MS: *m/z* 468 $[M+1]^+$.

Anal. Calcd. for $C_{20}H_{22}INO_2S$: C, 51.40; H, 4.74; N, 3.00. Found: C, 51.32; H, 4.81; N, 3.07.

Compound 6d



Here, 2-iodo-4-methyl-*N*-phenyl benzenesulfonamide **2f** (1.00 g, 2.6 mmol), phenyl propargyl bromide **4b** (0.44 mL, 3.2 mmol) and K_2CO_3 (0.89 g, 5.2 mmol) were used.

Yield: 0.98 g (76%).

IR (neat): 3052, 2926, 2241, 1589, 1490, 1441, 1321, 1216, 1156, 1079, 860, 756, 696 cm^{-1}.

^1H NMR: δ 7.93 (s, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.41-7.39 (m, 2H), 7.35-7.29 (m, 8H), 7.13 (d, *J* = 8.0 Hz, 1H), 4.88 (s, 2H), 2.32 (s, 3H).

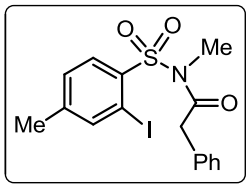
^{13}C NMR: δ 144.7, 143.3, 138.8, 138.5, 132.4, 131.6, 129.5, 129.2, 128.9, 128.5, 128.3, 122.6, 92.9, 85.7, 84.4, 43.5, 20.7.

HRMS (ESI): Calcd. for $C_{22}H_{18}INO_2SNa$ (M^+ + Na): *m/z* 510.0001. Found: 510.0004.

3.3 General procedure for the formation of acetamides 14-18

The ynamide (0.24 mmol) was dissolved in chloroform (2 mL) and stirred in open air at rt overnight. After completion of the reaction (hydrolysis due to adventitious moisture) the solvent was removed under reduced pressure. The obtained reaction mixture was purified by using silica gel column chromatography using hexane-ethyl acetate (9:1) as the eluent to afford the corresponding amide **14-18**.

Compound 14



Yield: 0.091 g (90%).

Mp: 106-108 ^oC.

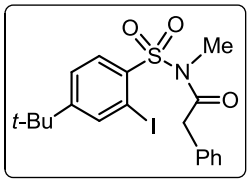
IR (KBr): 2942, 2909, 1704, 1578, 1457, 1336, 1161, 1073, 865, 766, 673 cm^{-1}.

^1H NMR: δ 8.17 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.88 (s, 1H, Ar-*H*), 7.34-7.27 (m, 4H, Ar-*H)*, 7.16 (d, *J* = 7.2 Hz, 1H, Ar-*H*), 3.96 (s, 2H, CH_2), 3.39 (s, 3H, NCH_3), 2.37 (s, 3H, Ar-CH_3).

^{13}C NMR: δ 171.3, 145.7, 143.1, 138.6, 132.8, 129.4, 129.3, 128.7, 127.3, 91.4 (*C*I), 43.3 (*C*H_2), 34.0 (N*C*H_3), 20.9 (Ar-*C*H_3).

HRMS (ESI): Calcd. for $C_{16}H_{17}INO_3S$ [M^++H]: *m/z* 429.9974. Found: 429.9969.

Compound 15



Yield: 0.100 g (90%).

Mp: 96-98 ^oC.

IR (KBr): 2959, 1709, 1572, 1451, 1336, 1177, 1073, 860, 777, 662 cm^{-1}.

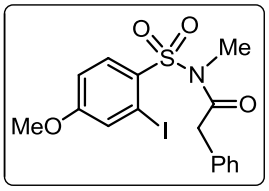
^1H NMR: δ 8.19 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 8.02 (d, *J* = 1.6 Hz, 1H, Ar-*H*), 7.53 (dd, *J* = 8.4 and 2.0 Hz, 1H, Ar-*H*), 7.32-7.27 (m, 3H, Ar-*H*), 7.16-7.15 (m, 2H, Ar-*H*), 3.99 (s, 2H, CH_2), 3.39 (s, 3H, NCH_3), 1.33 (s, 9H, C(CH_3)$_3$).

^{13}C NMR: δ 171.3, 158.6, 140.0, 138.5, 132.8, 132.7, 129.4, 128.7, 127.3, 125.8, 91.6 (*C*I), 43.4 (N*C*H$_2$), 35.1 (*C*(CH$_3$)$_3$), 34.0 (N*C*H$_3$), 30.9 (C(*C*H$_3$)$_3$).

LC-MS: *m/z* 470 [M-1]$^+$.

Anal. Calcd. for $C_{19}H_{22}INO_3S$: C, 48.42; H, 4.70; N, 2.97. Found: C, 48.56; H, 4.79; N, 2.85.

Compound 16



Yield: 0.102 g (94%).

Mp: 116-118 ^{o}C.

IR (KBr): 2953, 1698, 1583, 1468, 1353, 1172, 1073, 860, 755 cm^{-1}.

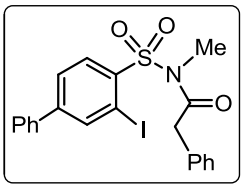
^{1}H NMR: δ 8.22 (d, *J* = 8.8 Hz, 1H, Ar-*H*), 7.54 (d, *J* = 2.4 Hz, 1H, Ar-*H*), 7.32-7.27 (m, 3H, Ar-*H)*, 7.16 (d, *J* = 6.8 Hz, 2H, Ar-*H*), 7.00 (dd, *J* = 8.8 and 2.4 Hz, 1H, Ar-*H*), 3.96 (s, 2H, C*H*$_2$), 3.86 (s, 3H, NC*H*$_3$), 3.39 (s, 3H, Ar-C*H*$_3$).

^{13}C NMR: δ 171.3, 162.9, 134.7, 133.0, 132.9, 129.4, 128.7, 128.2, 127.3, 113.4, 92.5 (*C*I), 56.0 (O*C*H$_3$), 43.4 (*C*H$_2$), 34.0 (N*C*H$_3$).

LC-MS: *m/z* 446 [M+1]$^+$.

Anal. Calcd. for $C_{16}H_{16}INO_4S$: C, 43.16; H, 3.62; N, 3.15. Found: C, 43.28; H, 3.56; N, 3.23.

Compound 17



Yield: 0.100 g (84%).

Mp: 94-96 ^{o}C.

IR (KBr): 3079, 3030, 1704, 1583, 1451, 1336, 1166, 1073, 871, 695 cm^{-1}.

^{1}H NMR: δ 8.34 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 8.25 (s, 1H, Ar-*H*), 7.73 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 7.59 (d, *J* = 7.6 Hz, 2H, Ar-*H*), 7.52-7.45 (m, 3H, Ar-*H*), 7.33-

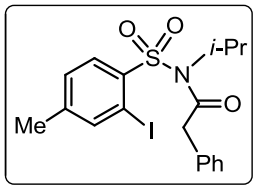
7.27 (m, 3H, Ar-*H*), 7.18 (d, *J* = 7.2 Hz, 2H, Ar-*H*), 3.99 (s, 2H, CH_2), 3.46 (s, 3H, NCH_3).

^{13}C NMR: δ 171.3, 147.3, 141.0, 140.0, 137.5, 133.3, 132.7, 129.4, 129.2, 128.8, 127.4, 127.1, 91.9 (*C*I), 43.3 (*C*H_2), 34.1 (N*C*H_3).

LC-MS: *m/z* 490 $[M-1]^+$.

Anal. Calcd. for $C_{21}H_{18}INO_3S$: C, 51.33; H, 3.69; N, 2.85. Found: C, 51.45; H, 3.62; N, 2.79.

Compound 18



Yield: 0.094 g (86%).

IR (neat): 3030, 1709, 1578, 1462, 1347, 1183, 1090, 986, 728, 662 cm^{-1}.

^{1}H NMR: δ 8.10 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.97 (s, 1H, Ar-*H*), 7.35-7.24 (m, 6H, Ar-*H*), 4.32 (s, 2H, CH_2), 3.98-3.91 (m, 1H, NC*H*), 2.41 (s, 3H, Ar-CH_3), 1.29 (d, *J* = 6.8 Hz, 6H, CH(CH_3)$_2$).

^{13}C NMR: δ 172.6, 145.8, 143.6, 137.9, 134.2, 132.0, 129.9, 129.3, 128.4, 127.0, 93.1 (*C*I), 53.9 (N*C*H), 46.2 (*C*H_2), 20.9 (Ar-*C*H_3), 19.7 (CH(*C*H_3)$_2$).

LC-MS: *m/z* 458 $[M+1]^+$.

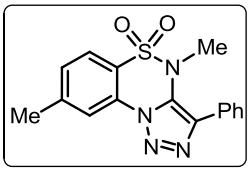
Anal. Calcd. for $C_{18}H_{20}INO_3S$: C, 47.27; H, 4.41; N, 3.06. Found: C, 47.36; H, 4.35; N, 3.12.

3.4 Synthesis of triazolo 1,2,4-benzothiadiazine 1,1-dioxide derivatives (compounds 19-32): Representative procedure for compound 19

To an oven dried Schlenk tube was added 2-iodo-4,N-dimethyl-N-phenylethynyl-benzenesulfonamide **5a** (0.24 mmol), CuI (5 mol%), NaN_3 (0.48 mmol) and PEG-400 (1 mL). The contents were sealed under nitrogen atmosphere and heated at 100 ^{o}C (oil bath temperature) overnight. After completion of the reaction as monitored by TLC, the crude reaction mixture was cooled to rt. The mixture was diluted with ethyl acetate (20 mL) and washed with water. The aqueous layer was extracted twice with ethyl acetate (20 mL). The combined organic layer was washed with brine solution, dried over sodium sulfate and concentrated in vacuum. The crude residue was then purified by using silica gel

column chromatography using hexane-ethyl acetate (9:1) as the eluent to afford triazolo-1,2,4-benzothiadiazine 1,1-dioxide **19**. Compounds **20-32** were prepared following same procedure and same molar quantities.

Compound 19



Yield: 0.062 g (78%).

Mp: 194-196 ^{o}C.

IR (KBr): 2992, 1605, 1468, 1353, 1178, 1123, 992, 849, 679 cm^{-1}.

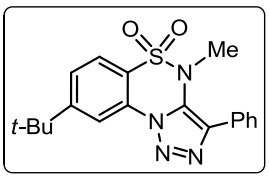
^{1}H NMR: δ 8.20 (s, 1H, Ar-*H*), 8.03 (d, *J* = 7.2 Hz, 2H, Ar-*H*), 7.88 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.53 (t, *J* ~ 7.2 Hz, 2H, Ar-*H*), 7.47-7.44 (m, 2H, Ar-*H*), 3.15 (s, 3H, NC*H*$_3$), 2.60 (s, 3H, Ar-C*H*$_3$).

^{13}C NMR: δ 146.3, 138.0, 133.1, 131.6, 129.7, 129.1, 128.6, 126.4, 124.7, 121.2, 118.9, 38.1 (N*C*H$_3$), 22.0 (Ar-*C*H$_3$).

HRMS (ESI): Calcd. for $C_{16}H_{15}N_4O_2S$ [M$^+$+H]: *m/z* 327.0915. Found: 327.0913.

This compound was crystallized from ethyl acetate–hexane (2 : 1) mixture at room temperature. X-ray structure has been determined for this compound.

Compound 20



Yield: 0.075 g (84%).

Mp: 152-154 ^{o}C.

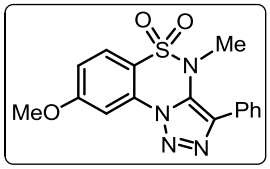
IR (KBr): 2970, 1600, 1458, 1364, 1189, 1129, 992, 833, 658, 641 cm^{-1}.

^{1}H NMR: δ 8.39 (s, 1H, Ar-*H*), 8.04 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 7.92 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 7.68 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 7.53 (t, *J* ~ 7.6 Hz, 2H, Ar-*H*), 7.44 (t, *J* = 7.6 Hz, 1H, Ar-*H*), 3.16 (s, 3H, NC*H*$_3$), 1.45 (s, 9H, C(C*H*$_3$)$_3$).

^{13}C NMR: δ 159.5, 138.0, 133.1, 131.6, 129.1, 128.6, 126.5, 126.2, 124.6, 121.1, 115.7, 38.1 (N*C*H$_3$), 36.0 (*C*(CH$_3$)$_3$), 31.0 (C(*C*H$_3$)$_3$).

HRMS (ESI): Calcd. for $C_{19}H_{20}N_4O_2SNa$ [M$^+$+Na]: *m/z* 391.1205. Found: 391.1224.

Compound 21



Yield: 0.056 g (70%).

Mp: 190-192 ^{o}C.

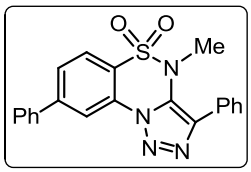
IR (KBr): 3003, 2937, 2844, 1605, 1595, 1458, 1353, 1178, 981, 844, 773 cm^{-1}.

^{1}H NMR: δ 8.03 (d, *J* = 7.2 Hz, 2H, Ar-*H*), 7.90 (d, *J* = 8.8 Hz, 1H, Ar-*H*), 7.83 (d, *J* = 2.4 Hz, 1H, Ar-*H*), 7.53 (t, *J* ~ 7.2 Hz, 2H, Ar-*H*), 7.44 (t, *J* ~ 7.2 Hz, 1H, Ar-*H*), 7.14 (dd, *J* = 8.8 and 2.4 Hz, 1H, Ar-*H*), 4.01 (s, 3H, Ar-OC*H*$_3$), 3.15 (s, 3H, NC*H*$_3$).

^{13}C NMR: δ 164.4, 138.2, 133.4, 129.1, 128.6, 126.7, 126.5, 115.9, 115.8, 102.9, 56.4 (Ar-O*C*H$_3$), 38.1 (N*C*H$_3$).

HRMS (ESI): Calcd. for $C_{16}H_{15}N_4O_3S$ [M^{+}+H]: *m/z* 343.0865. Found: 343.0864.

Compound 22



Yield: 0.073 g (78%).

Mp: 180-182 ^{o}C.

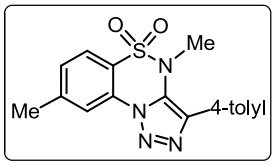
IR (KBr): 3058, 1605, 1468, 1392, 1370, 1178, 992, 827, 762 cm^{-1}.

^{1}H NMR: δ 8.59 (s, 1H, Ar-*H*), 8.07-8.04 (m, 3H, Ar-*H*), 7.86 (dd, *J* = 8.4 and 1.2 Hz, 1H, Ar-*H*), 7.72 (d, *J* = 7.2 Hz, 2H, Ar-*H*), 7.58-7.51 (m, 5H, Ar-*H*), 7.49-7.43 (m, 1H, Ar-*H*), 3.21 (s, 3H, NC*H*$_3$).

^{13}C NMR: δ 147.5, 137.5, 132.5, 131.5, 128.8, 128.5, 127.9, 126.9, 126.8, 125.9, 124.7, 121.7, 116.3, 37.5 (N*C*H$_3$).

HRMS (ESI): Calcd. for $C_{21}H_{17}N_4O_2S$ [M^{+}+H]: *m/z* 389.1072. Found: 389.1071.

Compound 23



Yield: 0.064 g (78%).

Mp: 190-192 ^{o}C.

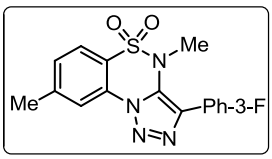
IR (KBr): 2926, 1595, 1463, 1353, 1178, 1123, 986, 849, 822, 619 cm^{-1}.

^{1}H NMR: δ 8.19 (s, 1H, Ar-*H*), 7.91 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 7.87 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.45 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.33 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 3.14 (s, 3H, NC*H*$_3$), 2.59 (s, 3H, Ar-C*H*$_3$), 2.43 (s, 3H, Ar-C*H*$_3$).

^{13}C NMR: δ 146.3, 139.1, 138.2, 132.7, 131.6, 129.8, 129.6, 126.4, 125.7, 124.7, 121.2, 118.9, 38.0 (N*C*H$_3$), 22.0 (Ar-*C*H$_3$), 21.4 (Ar-*C*H$_3$).

HRMS (ESI): Calcd. for $C_{17}H_{17}N_4O_2S$ [M$^+$+H]: *m/z* 341.1072. Found: 341.1068.

Compound 24



Yield: 0.052 g (62%).

Mp: 204-206 ^{o}C.

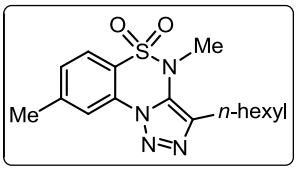
IR (KBr): 3079, 1600, 1463, 1364, 1178, 1123, 893, 789, 734, 674 cm^{-1}.

^{1}H NMR: δ 8.19 (s, 1H, Ar-*H*), 7.89 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.82 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 7.78-7.75 (m, 1H, Ar-*H*), 7.53-7.47 (m, 2H, Ar-*H*), 7.14 (dt, *J* = 8.4 and 2.4 Hz, 1H, Ar-*H*), 3.16 (s, 3H, NC*H*$_3$), 2.60 (s, 3H, Ar-C*H*$_3$).

^{13}C NMR: δ 164.3 (d, *J* = 240 Hz), 146.4, 137.0, 133.5, 131.5, 130.8, 130.7, 130.6, 129.8, 124.9, 122.0, 121.2, 118.9, 116.0 (d, *J* = 20 Hz), 113.4 (d, *J* = 20 Hz), 38.3 (N*C*H$_3$), 22.0 (Ar-*C*H$_3$).

HRMS (ESI): Calcd. for $C_{16}H_{15}N_4O_2S$ [M$^+$+H]: *m/z* 345.0821. Found: 345.0821.

Compound 25



Yield: 0.058 g (72%).

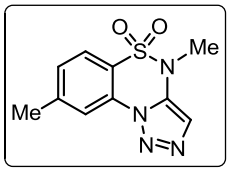
IR (neat): 2926, 2860, 1605, 1468, 1364, 1184, 1123, 838, 679 cm^{-1}.

^{1}H NMR: δ 8.12 (s, 1H, Ar-*H*), 7.83 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.41 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 3.26 (s, 3H, NC*H*$_3$), 2.80 (t, *J* ~ 8.0 Hz, 2H, C*H*$_2$), 2.56 (s, 3H, Ar-C*H*$_3$), 1.84-1.76 (m, 2H, C*H*$_2$), 1.43-1.32 (m, 6H, 3 C*H*$_2$), 0.90 (t, *J* ~ 6.8 Hz, 3H).

^{13}C NMR: δ 146.1, 139.1, 133.6, 131.7, 129.3, 124.4, 121.6, 118.7, 37.8 (N*C*H$_3$), 31.5, 28.9, 28.8, 24.7, 22.6, 22.0 (Ar-*C*H$_3$), 14.1.

HRMS (ESI): Calcd. for $C_{16}H_{23}N_4O_2S$ [M$^+$+H]: *m/z* 335.1541. Found: 335.1544.

Compound 26



Yield: 0.048 g (80%).

Mp: 172-174 ^{o}C.

IR (KBr): 3134, 1595, 1496, 1452, 1326, 1244, 1085, 975, 811, 685 cm^{-1}.

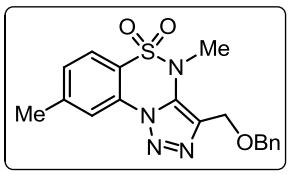
^{1}H NMR: δ 8.17 (s, 1H, Ar-*H*), 7.90 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.45-7.43 (m, 2H, Ar-*H* + triazole-C*H*), 3.47 (s, 3H, NC*H*$_3$), 2.58 (s, 3H, Ar-C*H*$_3$).

^{13}C NMR: δ 146.4, 137.9, 131.5, 129.2, 123.4, 121.3, 119.5, 118.3, 31.5 (N*C*H$_3$), 22.0 (Ar-*C*H$_3$).

HRMS (ESI): Calcd. for $C_{16}H_{15}N_4O_2S$ [M$^+$+H]: *m/z* 251.0602. Found: 251.0601.

This compound was crystallized from ethyl acetate–hexane (2 : 1) mixture at room temperature. X-ray structure has been determined for this compound.

Compound 27



Yield: 0.043 g (48%).

Mp: 106-108 ^{o}C.

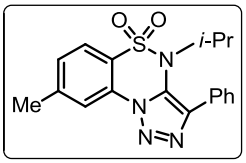
IR (KBr): 3063, 2860, 1605, 1479, 1359, 1310, 1173, 1068, 877, 745 cm^{-1}.

^{1}H NMR: δ 7.84 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.43 (s, 1H, Ar-*H*), 7.38-7.34 (m, 4H, Ar-*H*), 7.32-7.30 (m, 1H, Ar-*H*), 6.54 (s, 1H, Ar-*H*), 4.58 (s, 2H, OC*H*$_2$), 4.47 (s, 2H, OC*H*$_2$), 3.38 (s, 3H, NC*H*$_3$), 2.44 (s, 3H, Ar-C*H*$_3$).

^{13}C NMR: δ 142.8, 137.7, 133.1, 128.6, 128.2, 128.1, 127.9, 124.6, 122.1, 113.4, 71.7 (O*C*H$_2$), 68.4 (O*C*H$_2$), 34.0 (N*C*H$_3$), 21.9 (Ar-*C*H$_3$).

HRMS (ESI): Calcd. for $C_{18}H_{19}N_4O_3S$ [M$^+$+H]: *m/z* 371.1178. Found: 371.1178.

Compound 28



Yield: 0.054 g (64%).

Mp: 154-156 ^{o}C.

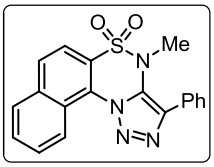
IR (KBr): 2981, 1605, 1468, 1370, 1348, 1184, 1118, 986, 778, 674 cm^{-1}.

^{1}H NMR: δ 8.16 (s, 1H, Ar-*H*), 8.02 (d, *J* = 7.2 Hz, 2H, Ar-*H*), 7.86 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.50 (t, *J* ~ 7.2 Hz, 2H, Ar-*H*), 7.44 (d, *J* = 7.2 Hz, 2H, Ar-*H*), 4.19 (m, 1H, NC*H*), 2.59 (s, 3H, Ar-CH_3), 0.98 (d, *J* = 6.8 Hz, 6H, (CH(CH_3)$_2$).

^{13}C NMR: δ 146.0, 141.2, 131.8, 130.8, 129.6, 129.2$_1$, 129.1$_9$, 128.9, 127.3, 124.3, 124.2, 119.0, 59.1 (N*C*H), 22.0 (Ar-*C*H$_3$), 20.9 (CH(*C*H$_3$)$_2$).

HRMS (ESI): Calcd. for $C_{18}H_{19}N_4O_2S$ [M$^+$+H]: *m/z* 355.1228. Found: 355.1229.

Compound 29



Yield: 0.064 g (72%).

Mp: 184-186 ^{o}C.

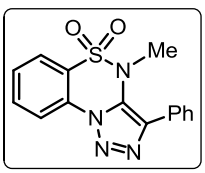
IR (KBr): 2921, 2855, 1595, 1447, 1353, 1178, 1118, 811, 690, 559 cm^{-1}.

^{1}H NMR: δ 9.66 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 8.12 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 8.05-7.99 (m, 2H, Ar-*H*), 7.86-7.77 (m, 2H, Ar-*H*), 7.56 (t, *J* ~ 7.6 Hz, 2H, Ar-*H*), 7.47 (d, *J* ~ 7.6 Hz, 1H, Ar-*H*), 3.18 (s, 3H, NCH_3).

^{13}C NMR: δ 137.9, 136.7, 133.6, 130.3, 129.7, 129.6, 129.2, 129.1, 129.0, 128.6, 128.5, 127.4, 126.5, 124.0, 122.2, 119.3, 37.9 (N*C*H$_3$).

HRMS (ESI): Calcd. for $C_{19}H_{15}N_4O_2S$ [M$^+$+H]: *m/z* 363.0915. Found: 363.0914.

Compound 30



Yield: 0.042 g (56%).

Mp: 190-192 ^{o}C.

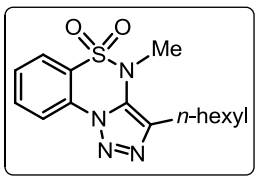
IR (KBr): 2997, 2931, 1589, 1485, 1370, 1255, 1184, 986, 822, 778, 641 cm^{-1}.

^{1}H NMR: δ 8.39 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 8.04-8.01 (m, 3H, Ar-*H*), 7.89 (t, *J* = 8.0 Hz, 1H, Ar-*H*), 7.68 (t, *J* ~ 8.0 Hz, 1H, Ar-*H*), 7.53 (t, *J* ~ 7.6 Hz, 2H, Ar-*H*), 7.45 (t, *J* ~ 7.6 Hz, 1H, Ar-*H*), 3.18 (s, 3H, NC*H*$_3$).

^{13}C NMR: δ 138.0, 134.7, 132.9, 131.7, 129.2, 129.1, 128.9, 128.5, 126.5, 124.8, 124.0, 118.7, 38.1 (N*C*H$_3$).

HRMS (ESI): Calcd. for $C_{16}H_{15}N_4O_2S$ [M^{+}+H]: *m/z* 313.0759. Found: 313.0757.

Compound 31



Yield: 0.040 g (52%).

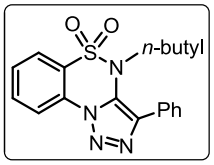
IR (neat): 2937, 2860, 1605, 1490, 1364, 1189, 1047, 849, 767 cm^{-1}.

^{1}H NMR: δ 8.31 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 7.97 (d, *J* = 7.2 Hz, 1H, Ar-*H*), 7.84 (t, *J* ~ 7.6 Hz, 1H, Ar-*H*), 7.63 (t, *J* = 7.6 Hz, 1H, Ar-*H*), 3.29 (s, 3H, NC*H*$_3$), 2.81 (t, *J* = 7.8 Hz, 2H, C*H*$_2$), 1.83-1.79 (m, 2H, C*H*$_2$), 1.43-1.33 (m, 6H, 3 C*H*$_2$), 0.90 (t, *J* ~ 6.8 Hz, 3H, C*H*$_3$).

^{13}C NMR: δ 139.0, 134.5, 133.5, 131.8, 128.5, 124.5, 124.3, 118.6, 37.8 (N*C*H$_3$), 31.5, 28.9, 28.8, 24.7, 22.6, 14.1.

HRMS (ESI): Calcd. for $C_{15}H_{21}N_4O_2S$ [M^{+}+H]: *m/z* 321.1385. Found: 321.1384.

Compound 32



Yield: 0.052 g (60%).

Mp: 90-92 ^{o}C.

IR (KBr): 2953, 2860, 1595, 1474, 1359, 1249, 1189, 1118, 981, 773, 636 cm^{-1}.

^{1}H NMR: δ 8.39 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 8.01-7.97 (m, 3H, Ar-*H*), 7.87 (t, *J* = 8.0 Hz, 1H, Ar-*H*), 7.66 (t, *J* = 7.6 Hz, 1H, Ar-*H*), 7.54-7.43 (m, 3H, Ar-*H*), 3.66 (t, *J* ~ 8.0 Hz, 2H, C*H*$_2$), 1.16-0.90 (m, 4H, 2 C*H*$_2$), 0.60 (t, *J* = 7.4 Hz, 3H, C*H*$_3$).

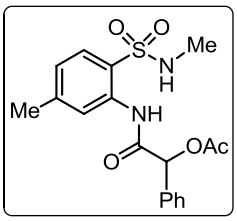
^{13}C NMR: δ 138.2, 134.5, 131.7, 131.6, 129.2, 129.0, 128.9, 128.7, 126.9, 126.1, 123.9, 118.7, 51.3, 29.1, 19.4, 13.2.

HRMS (ESI): Calcd. for $C_{16}H_{15}N_4O_2S$ [M^++H]: *m/z* 355.1228. Found: 355.1228.

3.5 General procedure for the synthesis of esters 34-37

To an oven dried Schlenk vessel was added triazolo-1,2,4-benzothiadiazine 1,1-dioxide (0.3 mmol) and glacial acetic acid (2 mL). Then the vessel was stoppered and heated under reflux for 3 d. After completion of reaction (tlc), the mixture was quenched with saturated sodium bicarbonate solution (30 mL) and extracted twice with ethyl acetate (20 mL). The combined organic layers were washed with brine solution, dried over sodium sulfate and concentrated *in vacuo.* The crude product was purified by using silica gel column chromatography using hexane-ethyl acetate (4:1) as the eluent to furnish the esters **34-37**.

Compound 34



Yield: 0.090 g (80%).

Mp: 130-132 ^{o}C.

IR (KBr): 3315, 2980, 1737, 1682, 1518, 1414, 1332, 1244, 1173, 1068, 756, 663 cm^{-1}.

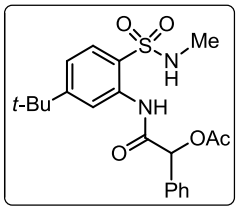
^{1}H NMR: δ 9.63 (s, 1H, CON*H*), 7.94 (s, 1H, Ar-*H*), 7.76 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.57 (d, *J* = 6.4 Hz, 2H, Ar-*H*), 7.44 (d, *J* = 6.8 Hz, 3H, Ar-*H*), 7.07 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 5.99 (s, 1H, Ar-C*H*), 4.67 (qrt, *J* = 5.2 Hz, 1H, SO_2N*H*), 2.51 (d, *J* = 5.2 Hz, 3H, NHCH_3), 2.39 (s, 3H, Ar-CH_3), 2.32 (s, 3H, COCH_3).

^{13}C NMR: δ 171.4, 167.1, 145.2, 134.4, 134.3, 129.7, 129.4, 129.0, 127.4, 125.6, 124.8, 124.6, 76.7, 29.1 (N*C*H_3), 21.7 (Ar-*C*H_3), 21.2 (CO*C*H_3).

HRMS (ESI): Calcd. for $C_{18}H_{20}N_2O_5SNa$ [M^++Na]: *m/z* 399.0991. Found: 399.1036.

This compound was crystallized from methanol at 4 ^{o}C. X-ray structure has been determined for this compound.

Compound 35



Yield: 0.106 g (86%).

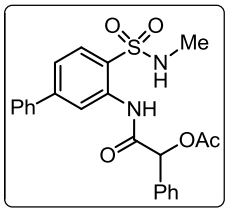
IR (neat): 3310, 2964, 1759, 1704, 1567, 1529, 1403, 1326, 1222, 1167, 1052, 838 cm^{-1}.

^{1}H NMR: δ 9.74 (s, 1H, CON*H*), 8.22 (s, 1H, Ar-*H*), 7.78 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 7.58 (d, *J* = 7.6 Hz, 2H, Ar-*H*), 7.44 (d, *J* ~ 7.6 Hz, 3H, Ar-*H*), 7.27 (s, 1H, Ar-*H*), 6.02 (s, 1H, Ar-C*H*), 4.64 (qrt, *J* = 5.6 Hz, 1H, SO_2N*H*), 2.53 (d, *J* = 5.6 Hz, 3H, NHCH_3), 2.32 (s, 3H, COCH_3), 1.32 (s, 9H, C(CH_3)$_3$).

^{13}C NMR: δ 171.3, 167.1, 158.2, 134.6, 134.4, 129.5, 129.4, 129.0, 127.4, 124.3, 121.8, 121.4, 35.4 (*C*(CH_3)$_3$), 77.1, 30.9 (C(*C*H_3)$_3$), 29.2 (N*C*H_3), 21.2 (CO*C*H_3).

HRMS (ESI): Calcd. for $C_{21}H_{26}N_2O_5SNa$ [M^++Na]: *m/z* 441.1460. Found: 441.1465.

Compound 36



Yield: 0.102 g (78%).

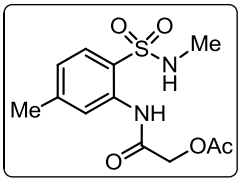
IR (neat): 3315, 2921, 1759, 1699, 1567, 1414, 1321, 1222, 1162, 1074, 701 cm^{-1}.

^{1}H NMR: δ 9.83 (s, 1H, CON*H*), 8.42 (s, 1H, Ar-*H*), 7.93 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.61-7.58 (m, 4H, Ar-*H*), 7.48-7.37 (m, 7H, Ar-*H*), 6.05 (s, 1H, Ar-C*H*), 4.88-4.87 (m, 1H, SO_2N*H*), 2.56 (d, *J* = 5.2 Hz, 3H, NHCH_3), 2.33 (s, 3H, COCH_3).

^{13}C NMR: δ 171.4, 167.3, 147.0, 138.7, 134.9, 134.4, 130.2, 129.4, 129.0_3, 128.9_8, 128.7, 127.4, 125.9, 123.1, 122.8, 76.8, 29.2 (N*C*H_3), 21.2 (CO*C*H_3).

HRMS (ESI): Calcd. for $C_{23}H_{22}N_2O_5SNa$ [M^++Na]: *m/z* 461.1147. Found: 461.1150.

Compound 37



Yield: 0.082 g (90%).

Mp: 110-112 ^{o}C.

IR (KBr): 3271, 1753, 1688, 1589, 1419, 1321, 1244, 1140, 827, 767 cm^{-1}.

^{1}H NMR: δ 9.66 (s, 1H, CON*H*), 8.13 (s, 1H, Ar-*H*), 7.75 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.07 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 4.83-4.82 (m, 1H, SO_2N*H*), 4.69 (s, 2H, $COCH_2O$), 2.56 (d, *J* = 5.2 Hz, 3H, $NHCH_3$), 2.43 (s, 3H, $COCH_3$), 2.29 (s, 3H, Ar-CH_3).

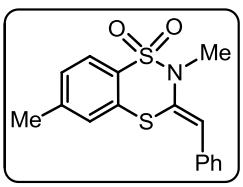
^{13}C NMR: δ 171.5, 165.9, 145.3, 134.3, 129.7, 125.4, 124.0, 123.9, 77.1, 63.4, 29.1 (NCH_3), 21.8 (Ar-CH_3), 20.9 ($COCH_3$).

HRMS (ESI): Calcd. for $C_{12}H_{16}N_2O_5SNa$ [M^++Na]: *m/z* 323.0678. Found: 323.0677.

3.6 Synthesis of benzo[1,4,2]dithiazine 1,1-dioxides 38-49: Representative procedure for synthesis of compound 38

To an oven dried Schlenk tube was added 2-iodo-4,*N*-dimethyl-*N*-phenylethynyl-benzenesulfonamide **5a** (0.24 mmol), CuI (10 mol%), sulfur [S_8, 0.09 mmol], K_2CO_3 (0.48 mmol), H_2O (0.36 mmol) and NMP (1 mL). The flask was sealed and heated at 70 ^{o}C (oil bath temperature) overnight. After completion of the reaction as monitored by TLC, the crude mixture was cooled to rt, diluted with ethyl acetate (20 mL) and washed with water. The aqueous layer was extracted twice with ethyl acetate (20 mL). The combined organic layer was washed with brine solution, dried over anh. sodium sulfate and concentrated in vacuum. The residue was then purified by using silica gel column chromatography using hexane-ethyl acetate (9:1) as the eluent to afford benzo[1,4,2]dithiazine 1,1-dioxide **38**. Compounds **39-49** were prepared following the same procedure and the same molar quantities.

Compound 38



Yield: 0.069 g (90%).

Mp: 140-146 ^{o}C.

IR (KBr): 2920, 1594, 1440, 1347, 1172, 1046, 986, 810, 673 cm^{-1}.

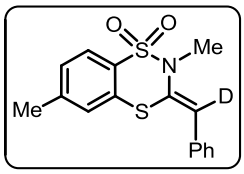
^{1}H NMR: δ 7.90 (d, *J* = 8.0 Hz, 1H), 7.54 (d, *J* = 7.6 Hz, 2H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.18 (s, 1H), 7.16 (d, *J* = 8.4 Hz, 1H), 7.02 (s, 1H), 3.00 (s, 3H), 2.41 (s, 3H).

^{13}C NMR: δ 143.6, 133.1, 132.5$_1$, 132.4$_6$, 130.8, 129.5, 128.6$_2$, 128.5$_7$, 128.5, 127.3, 127.0, 39.4, 21.6.

HRMS (ESI): Calcd. for $C_{16}H_{15}NO_2S_2Na$ (M^+ + Na): *m/z* 340.0442. Found: 340.0446.

This compound was crystallized from ethyl acetate at room temperature. X-ray structure has been determined for this compound.

Compound 38-D



Yield: 0.066 g (86%).

Mp: 142-146 ^{o}C.

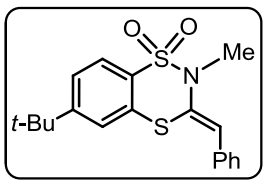
IR (KBr): 2920, 1596, 1446, 1342, 1168, 1046, 984, 810, 678 cm^{-1}.

^{1}H NMR: δ 7.90 (d, *J* = 8.0 Hz, 1H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.18 (s, 1H), 7.16 (d, *J* = 8.0 Hz, 1H), 3.00 (s, 3H), 2.41 (s, 3H).

^{13}C NMR: δ 143.6, 133.0, 132.5, 132.4, 130.5 (t, *J* = 24.0 Hz), 129.5, 128.6$_0$, 128.5$_6$, 128.5, 127.3, 127.0$_4$, 127.0$_0$, 39.4, 21.6.

HRMS (ESI): Calcd. for $C_{16}H_{14}DNO_2S_2Na$ (M^+ + Na): *m/z* 341.0505. Found: 341.0501.

Compound 39



Yield: 0.078 g (92%).

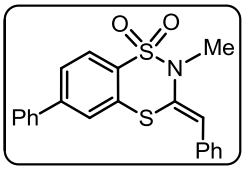
IR (neat): 2964, 2921, 1584, 1441, 1353, 1266, 1178, 882, 800 cm^{-1}.

^{1}H NMR: δ 7.94 (d, *J* = 8.4 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 2H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.39-7.33 (m, 3H), 7.02 (s, 1H), 3.03 (s, 3H), 1.35 (s, 9H).

^{13}C NMR: δ 156.6, 133.2, 132.6, 132.4, 130.6, 129.5, 128.7, 128.6, 128.4, 126.8, 123.9, 123.6, 39.4, 35.3, 30.9.

HRMS (ESI): Calcd. for $C_{19}H_{21}NO_2S_2Na$ (M^+ + Na): *m/z* 382.0912. Found: 382.0912.

Compound 40



Yield: 0.076 g (84%).

Mp: 154-156 ^{o}C.

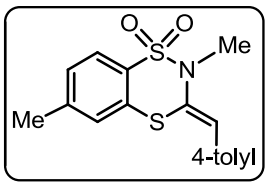
IR (KBr): 2959, 2915, 1595, 1447, 1348, 1173, 1058, 871, 696 cm^{-1}.

^{1}H NMR: δ 8.08 (d, *J* = 8.4 Hz, 1H), 7.61-7.55 (m, 6H), 7.51 (t, *J* = 8.0 Hz, 2H), 7.46 (t, *J* = 8.0 Hz, 3H), 7.37 (t, *J* = 8.0 Hz, 1H), 7.06 (s, 1H), 3.07 (s, 3H).

^{13}C NMR: δ 145.8, 138.6, 133.3, 133.1, 132.3, 131.1, 130.0, 129.5, 129.2, 128.9, 128.6$_1$, 128.5$_6$, 127.6, 127.3, 125.2, 125.1, 39.5.

HRMS (ESI): Calcd. for $C_{21}H_{17}NO_2S_2Na$ (M^+ + Na): *m/z* 402.0599. Found: 402.0599.

Compound 41



Yield: 0.068 g (86%).

Mp: 110-114 ^{o}C.

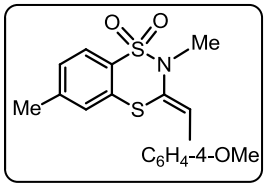
IR (KBr): 3019, 2920, 1594, 1512, 1457, 1353, 1172, 1046, 821, 679 cm^{-1}.

^{1}H NMR: δ 7.89 (d, *J* = 8.0 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.18 (s, 1H), 7.15 (d, *J* = 8.4 Hz, 1H), 6.99 (s, 1H), 3.00 (s, 3H), 2.41 (s, 3H), 2.40 (s, 3H).

^{13}C NMR: δ 143.5, 138.5, 132.7, 131.4, 131.0, 130.3, 129.4, 129.3, 128.7, 127.2, 127.0, 126.9, 39.4, 21.5, 21.4.

HRMS (ESI): Calcd. for $C_{17}H_{17}NO_2S_2Na$ (M^+ + Na): *m/z* 354.0599. Found: 354.0597.

Compound 42



Yield: 0.072 g (86%).

Mp: 140-143 ^{o}C.

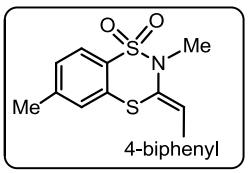
IR (KBr): 2964, 2910, 1605, 1512, 1458, 1348, 1255, 1162, 1047, 679 cm^{-1}.

^{1}H NMR: δ 7.88 (d, *J* = 8.0 Hz, 1H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.17 (s, 1H), 7.14 (d, *J* = 8.0 Hz, 1H), 6.96 (s, 2H), 6.94 (s, 1H), 3.85 (s, 3H), 2.98 (s, 3H), 2.40 (s, 3H).

^{13}C NMR: δ 159.6, 143.5, 132.7, 131.1, 130.0, 129.9, 128.6, 127.2, 127.1, 126.9, 125.6, 114.0, 55.3, 39.4, 21.5.

HRMS (ESI): Calcd. for $C_{17}H_{17}NO_3S_2Na$ (M^+ + Na): *m/z* 370.0548. Found: 370.0547.

Compound 43



Yield: 0.067 g (72%).

Mp: 168-172 ^{o}C.

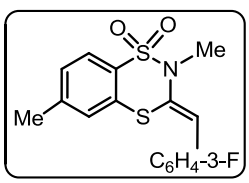
IR (KBr): 3074, 2926, 1589, 1468, 1353, 1255, 1167, 1052, 888, 723 cm^{-1}.

^{1}H NMR: δ 7.91 (d, *J* = 8.0 Hz, 1H), 7.69-7.62 (m, 6H), 7.49 (t, *J* = 7.6 Hz, 2H), 7.40 (t, *J* = 7.2 Hz, 1H), 7.21 (s, 1H), 7.18 (d, *J* = 8.0 Hz, 1H), 7.05 (s, 1H), 3.02 (s, 3H), 2.42 (s, 3H).

^{13}C NMR: δ 143.7, 141.1, 140.3, 132.5, 132.4, 132.1, 130.4, 130.0, 128.9, 128.7, 127.7, 127.4, 127.2, 127.1, 39.5, 21.6.

HRMS (ESI): Calcd. for $C_{22}H_{19}NO_2S_2Na$ (M^+ + Na): *m/z* 416.0755. Found: 416.0755.

Compound 44



Yield: 0.069 g (84%).

Mp: 180-186 ^{o}C.

IR (KBr): 3041, 2920, 1588, 1446, 1358, 1177, 1046, 816, 679 cm^{-1}.

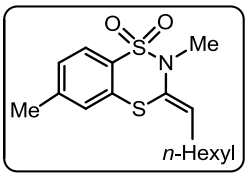
^{1}H NMR: δ 7.90 (d, *J* = 8.0 Hz, 1H), 7.42-7.37 (m, 1H), 7.30-7.28 (m, 2H), 7.20-7.17 (m, 2H), 7.07-7.02 (m, 1H), 6.94 (s, 1H), 3.00 (s, 3H), 2.42 (s, 3H).

^{13}C NMR: δ 163.7 (J_{C-F} = 240.0 Hz), 143.8, 135.2 (J_{C-F} = 8.0 Hz), 134.1, 132.0, 130.1 (J_{C-F} = 8.0 Hz), 128.9 (J_{C-F} = 2.0 Hz), 128.7, 127.5, 127.1 (J_{C-F} = 10.0 Hz), 125.3 (J_{C-F} = 3.0 Hz), 116.0 (J_{C-F} = 20.0 Hz), 115.3 (J_{C-F} = 20.0 Hz), 39.4, 21.5.

HRMS (ESI): Calcd. for $C_{16}H_{15}FNO_2S_2$ (M^+ + H): *m/z* 336.0528. Found: 336.0525.

This compound was crystallized from chloroform at room temperature. X-ray structure has been determined for this compound.

Compound 45



Yield: 0.059 g (76%).

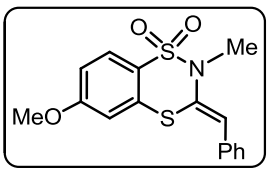
IR (neat): 2953, 2926, 1595, 1458, 1348, 1173, 1052, 805, 674 cm^{-1}.

^{1}H NMR: δ 7.86 (d, *J* = 8.0 Hz, 1H), 7.14 (s, 1H), 7.11 (d, *J* = 8.0 Hz, 1H), 6.09 (t, *J* = 8.0 Hz, 1H), 2.88 (s, 3H), 2.40 (s, 3H), 2.23 (qrt, *J* = 7.6 Hz, 2H), 1.51-1.48 (m, 2H), 1.37-1.28 (m, 6H), 0.91 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR: δ 143.3, 133.2, 132.9, 131.4, 128.3, 127.1, 126.9, 126.8, 38.9, 31.6, 28.8, 28.4, 27.3, 22.5, 21.5, 14.0.

HRMS (ESI): Calcd. for $C_{16}H_{23}NO_2S_2Na$ (M^+ + Na): *m/z* 348.1068. Found: 348.1068.

Compound 46



Yield: 0.076 g (96%).

Mp: 132-134 ^{o}C.

IR (KBr): 3025, 2926, 1584, 1479, 1348, 1238, 1173, 1047, 882, 696 cm^{-1}.

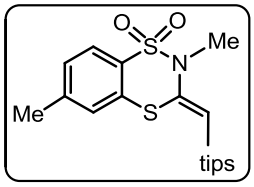
^{1}H NMR: δ 7.94 (dd, *J* = 8.0 Hz, *J* = 0.8 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 2H), 7.43 (t, *J* = 7.2 Hz, 2H), 7.35 (t, *J* = 7.2 Hz, 1H), 7.02 (s, 1H), 6.88-6.86 (m, 2H), 3.87 (s, 3H), 3.01 (s, 3H).

^{13}C NMR: δ 162.4, 134.6, 133.1, 132.5, 130.8, 129.4, 128.9, 128.6, 128.5, 123.5, 112.8, 111.1, 55.8, 39.4.

HRMS (ESI): Calcd. for $C_{16}H_{15}NO_3S_2Na$ (M^+ + Na): *m/z* 356.0391. Found: 356.0395.

This compound was crystallized from chloroform at room temperature. X-ray structure has been determined for this compound.

Compound 47



Yield: 0.078 g (82%).

Mp: 60-64 ^{o}C.

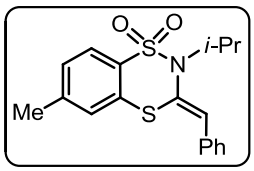
IR (KBr): 2937, 2866, 1578, 1463, 1348, 1266, 1167, 1014, 811, 679 cm^{-1}.

^{1}H NMR: δ 7.86 (d, *J* = 8.0 Hz, 1H), 7.16-7.13 (m, 2H), 5.87 (s, 1H), 2.97 (s, 3H), 2.40 (s, 3H), 1.38-1.32 (m, 3H), 1.14 (d, *J* = 7.2 Hz, 18H).

^{13}C NMR: δ 144.9, 143.4, 133.2, 129.4, 127.1, 126.9, 126.5, 122.5, 38.3, 21.5, 18.9, 12.0.

HRMS (ESI): Calcd. for $C_{19}H_{31}NO_2S_2SiNa$ (M^+ + Na): *m/z* 420.1463. Found: 420.1469.

Compound 48



Yield: 0.066 g (80%).

Mp: 152-154 ^{o}C.

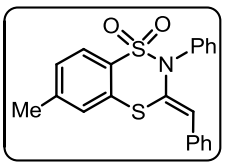
IR (KBr): 2981, 2926, 1584, 1441, 1342, 1173, 1052, 986, 899, 679 cm^{-1}.

^{1}H NMR: δ 7.90 (d, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 7.6 Hz, 2H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.15-7.12 (m, 2H), 6.84 (s, 1H), 4.20-4.16 (m, 1H), 2.40 (s, 3H), 1.23 (d, *J* = 6.8 Hz, 6H).

^{13}C NMR: δ 143.3, 133.8, 133.3, 132.1, 132.0, 129.4, 128.6, 128.3, 128.2, 127.2, 126.8, 125.8, 54.3, 21.5, 21.3.

HRMS (ESI): Calcd. for $C_{18}H_{19}NO_2S_2Na$ (M^+ + Na): *m/z* 368.0755. Found: 368.0755.

Compound 49



Yield: 0.076 g (84%).

Mp: 160-162 ^oC.

IR (KBr): 2921, 2849, 1584, 1485, 1359, 1260, 1178, 1096, 1047, 877, 690 cm^{-1}.

^1H NMR: δ 7.78 (d, *J* = 8.0 Hz, 1H), 7.54 (d, *J* = 7.6 Hz, 2H), 7.45-7.38 (m, 4H), 7.35-7.26 (m, 5H), 7.12 (d, *J* = 8.0 Hz, 1H), 6.87 (s, 1H), 2.42 (s, 3H).

^{13}C NMR: δ 144.0, 141.2, 133.4, 132.8_5, 132.8_1, 131.3, 129.3, 129.2, 128.7, 128.6, 128.2, 127.8, 127.7, 127.5, 126.4, 125.8, 21.6.

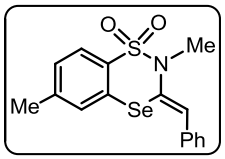
LC-MS: *m/z* 380 $[M+1]^+$.

Anal. Calcd. for $C_{21}H_{17}NO_2S_2$: C, 66.46; H, 4.52; N, 3.69. Found: C, 66.59; H, 4.48; N, 3.75.

3.7 Synthesis of benzo[1,4,2]thiaselenazine 1,1-dioxide derivatives 50-57: Representative procedure for synthesis of compound 50

To an oven dried Schlenk tube was added 2-iodo-4,*N*-dimethyl-N-phenylethynyl-benzenesulfonamide **5a** (0.24 mmol), CuI (10 mol %), Se (0.72 mmol), K_2CO_3 (0.48 mmol), H_2O (0.36 mmol) and NMP (1 mL). The contents were sealed and heated at 90 ^oC (oil bath temperature) for 20 h. After completion of the reaction as monitored by TLC, the crude reaction mixture was cooled to rt. The mixture was diluted with ethyl acetate (20 mL) and washed with water. The aqueous layer was extracted twice with ethyl acetate (20 mL). The combined organic layer was washed with brine solution, dried over anh. sodium sulfate and concentrated in vacuum. The residue was then purified by using silica gel column chromatography using hexane-ethyl acetate (9:1) as the eluent to afford benzo[1,4,2]thiaselenazine 1,1-dioxide **50**. Compounds **51-57** were prepared following the same procedure and the same molar quantities.

Compound 50



Yield: 0.060 g (70%).

Mp: 124-126 ^{o}C.

IR (KBr): 3047, 3019, 1595, 1441, 1348, 1260, 1173, 1041, 877, 674 cm^{-1}.

^{1}H NMR: δ 7.97 (d, *J* = 8.0 Hz, 1H), 7.42-7.41 (m, 4H), 7.36-7.34 (m, 1H), 7.27-7.25 (m, 2H), 7.17 (d, *J* = 8.0 Hz, 1H), 2.94 (s, 3H), 2.39 (s, 3H).

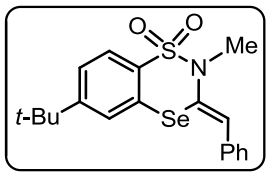
^{13}C NMR: δ 143.7, 133.8, 132.3, 131.9, 130.5, 130.4, 129.5, 128.8, 128.7, 128.5, 128.0, 127.6, 40.0, 21.5.

^{77}Se NMR: δ 219.85.

HRMS (ESI): Calcd. for $C_{16}H_{15}NO_2SSeNa$ (M^+ + Na): *m/z* 387.9887. Found: 387.9890.

This compound was crystallized from ethyl acetate at room temperature. X-ray structure has been determined for this compound.

Compound 51



Yield: 0.067 g (72%).

IR (neat): 2959, 2926, 1589, 1447, 1348, 1266, 1184, 876, 784 cm^{-1}.

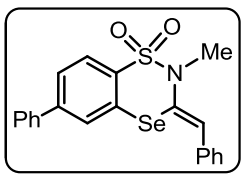
^{1}H NMR: δ 8.02 (d, *J* = 8.0 Hz, 1H), 7.46-7.43 (m, 5H), 7.40 (dd, *J* = 8.0 Hz, *J* = 2.0 Hz, 1H), 7.38-7.35 (m, 1H), 7.27 (s, 1H), 2.99 (s, 3H), 1.34 (s, 9H).

^{13}C NMR: δ 156.6, 133.8, 132.4, 131.7, 130.6, 130.2, 128.8, 128.7, 128.4, 127.4, 126.0, 124.5, 40.1, 35.2, 30.9.

^{77}Se NMR: δ 220.46.

HRMS (ESI): Calcd. for $C_{19}H_{21}NO_2SSeNa$ (M^+ + Na): *m/z* 430.0356. Found: 430.0355.

Compound 52



Yield: 0.069 g (68%).

Mp: 152-156 ^{o}C.

IR (KBr): 2915, 2844, 1595, 1441, 1348, 1167, 921, 877, 767, 674 cm^{-1}.

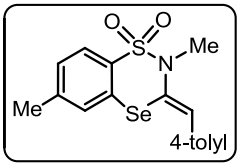
^{1}H NMR: δ 8.17 (d, *J* = 8.0 Hz, 1H), 7.67 (s, 1H), 7.59 (d, *J* = 8.0 Hz, 3H), 7.51 (t, *J* = 7.6 Hz, 2H), 7.47-7.43 (m, 5H), 7.39-7.36 (m, 1H), 7.31 (s, 1H), 3.02 (s, 3H).

^{13}C NMR: δ 145.8, 138.7, 133.7, 132.1, 131.9, 131.1, 129.1, 128.8_1, 128.7_5, 128.6, 128.1, 127.7, 127.3, 125.8, 40.1.

^{77}Se NMR: δ 225.31.

HRMS (ESI): Calcd. for $C_{21}H_{17}NO_2SSeNa$ (M^+ + Na): *m/z* 450.0043. Found: 450.0044.

Compound 53



Yield: 0.058 g (64%).

IR (neat): 2926, 2849, 1595, 1452, 1353, 1167, 1041, 882, 668 cm^{-1}.

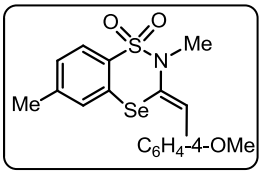
^{1}H NMR: δ 7.98 (d, *J* = 8.0 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.29-7.28 (m, 1H), 7.25-7.24 (m, 3H), 7.18 (d, *J* = 8.0 Hz, 1H), 2.95 (s, 3H), 2.41 (s, 3H), 2.40 (s, 3H).

^{13}C NMR: δ 143.6, 138.5, 132.0, 131.2, 130.9, 130.5_3, 130.5_1, 129.5, 129.4, 129.3, 128.7, 128.3, 127.9, 127.6, 40.0, 21.4_4, 21.3_6.

^{77}Se NMR: δ 217.22.

HRMS (ESI): Calcd. for $C_{17}H_{17}NO_2SSeNa$ (M^+ + Na): *m/z* 402.0043. Found: 402.0042.

Compound 54



Yield: 0.057 g (60%).

Mp: 114-116 ^{o}C.

IR (KBr): 2953, 2915, 1605, 1507, 1458, 1348, 1255, 1173, 1036, 674 cm^{-1}.

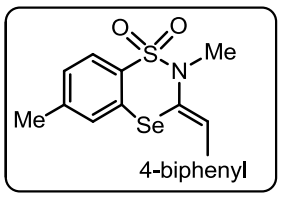
^{1}H NMR: δ 7.98 (d, *J* = 8.4 Hz, 1H), 7.37 (d, *J* = 8.8 Hz, 2H), 7.30 (s, 1H), 7.21 (s, 1H), 7.18 (d, *J* = 8.0 Hz, 1H), 6.96 (d, *J* = 8.0 Hz, 2H), 3.87 (s, 3H), 2.94 (s, 3H), 2.41 (s, 3H).

^{13}C NMR: δ 159.6, 143.6, 131.9, 130.4$_9$, 130.4$_6$, 130.3, 130.0, 129.5, 129.3, 127.9, 127.6, 126.2, 114.1, 114.0, 55.3, 40.0, 21.4.

^{77}Se NMR: δ 213.72.

HRMS (ESI): Calcd. for $C_{17}H_{17}NO_3SSeNa$ (M^+ + Na): *m/z* 417.9992. Found: 417.9992.

Compound 55



Yield: 0.052 g (50%).

Mp: 172-174 ^{o}C.

IR (KBr): 2959, 2921, 1589, 1468, 1348, 1255, 1167, 1096, 811, 729 cm^{-1}.

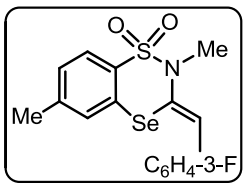
^{1}H NMR: δ 8.00 (d, *J* = 8.0 Hz, 1H), 7.67 (t, *J* = 8.4 Hz, 4H), 7.53-7.47 (m, 4H), 7.40 (t, *J* = 7.6 Hz, 1H), 7.31-7.29 (m, 2H), 7.20 (d, *J* = 8.0 Hz, 1H), 2.98 (s, 3H), 2.42 (s, 3H).

^{13}C NMR: δ 143.7, 141.2, 140.3, 132.7, 132.2, 131.5, 130.5, 130.3, 129.5, 129.3, 128.9, 128.0, 127.7, 127.6, 127.3, 127.1, 127.0, 40.1, 21.5.

^{77}Se NMR: δ 318.48.

HRMS (ESI): Calcd. for $C_{22}H_{19}NO_2SSeNa$ (M^+ + Na): *m/z* 464.0200. Found: 464.0200.

Compound 56



Yield: 0.057 g (62%).

Mp: 152-154 ^{o}C.

IR (KBr): 2915, 2849, 1578, 1452, 1353, 1173, 1041, 773, 674 cm^{-1}.

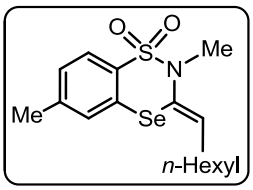
^{1}H NMR: δ 7.99 (d, *J* = 8.0 Hz, 1H), 7.43-7.38 (m, 1H), 7.30 (s, 1H), 7.22-7.20 (m, 3H), 7.16 (d, *J* = 6.8 Hz, 1H), 7.06 (t, *J* = 8.0 Hz, 1H), 2.96 (s, 3H), 2.42 (s, 3H).

^{13}C NMR: δ 162.8 (J_{C-F} = 250.0 Hz), 143.9, 135.8 (J_{C-F} = 8.0 Hz), 133.9, 130.4 (J_{C-F} = 6.0 Hz), 130.3, 130.0, 129.6, 128.2$_4$, 128.1$_6$, 127.6, 124.6 (J_{C-F} = 3.0 Hz), 115.6 (J_{C-F} = 16.0 Hz), 115.4 (J_{C-F} = 16.0 Hz), 40.0, 21.5.

^{77}Se NMR: δ 223.72.

HRMS (ESI): Calcd. for $C_{16}H_{14}FNO_2SSeNa$ (M^+ + Na): *m/z* 405.9792. Found: 405.9788.

Compound 57



Yield: 0.050 g (56%).

IR (neat): 2959, 2926, 1595, 1463, 1353, 1255, 1173, 1047, 773, 668 cm^{-1}.

^{1}H NMR: δ 7.96 (d, *J* = 8.0 Hz, 1H), 7.29 (s, 1H), 7.15 (d, *J* = 8.0 Hz, 1H), 6.25 (t, *J* = 8.0 Hz, 1H), 2.82 (s, 3H), 2.40 (s, 3H), 2.12 (qrt, *J* = 7.2 Hz, 2H), 1.52-1.48 (m, 2H), 1.39-1.32 (m, 6H), 0.91 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR: δ 143.5, 133.2, 130.4, 130.1$_4$, 130.0$_6$, 129.7, 127.7, 127.6, 39.6, 31.6, 28.8, 28.3, 28.1, 22.5, 21.4, 14.1.

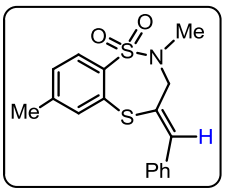
^{77}Se NMR: δ 221.71.

HRMS (ESI): Calcd. for $C_{16}H_{23}NO_2SSeNa$ (M^+ + Na): *m/z* 396.0513. Found: 396.0513.

3.8 Synthesis of benzosultams 58-63

Compounds **58-63** were prepared following the same procedure and the same molar quantities as described for compounds **38** and **50**.

Compound 58



Yield: 0.068 g (86%).

Mp: 162-164 ^{o}C.

IR (KBr): 2924, 1585, 1445, 1331, 1160, 1112, 1040, 934, 737 cm^{-1}.

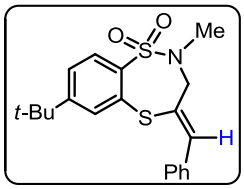
^{1}H NMR: δ 7.97 (d, *J* = 8.4 Hz, 1H), 7.65 (d, *J* = 7.2 Hz, 2H), 7.52 (s, 1H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 1H), 6.93 (s, 1H), 4.46 (s, 2H), 2.66 (s, 3H), 2.42 (s, 3H).

^{13}C NMR: δ 144.0, 141.4, 138.0, 134.9, 134.6, 131.5, 131.4, 129.9, 128.9, 128.8, 128.2, 123.7, 61.9, 34.0, 21.3.

HRMS (ESI): Calcd. for $C_{17}H_{18}NO_2S_2$ (M^+ + H): *m/z* 332.0779. Found: 332.0777.

This compound was crystallized from ethyl acetate–hexane (2 : 1) mixture at room temperature. X-ray structure has been determined for this compound.

Compound 59



Yield: 0.075 g (84%).

Mp: 140-146 ^oC.

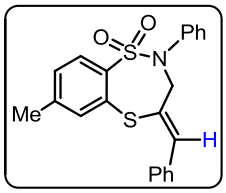
IR (KBr): 2964, 1580, 1460, 1342, 1270, 1171, 1038, 867, 735 cm^{-1}.

^1H NMR: δ 7.01 (d, *J* = 8.4 Hz, 1H), 7.74_2-7.73_7 (m, 1H), 7.60 (d, *J* = 6.4 Hz, 2H), 7.47-7.38 (m, 4H), 6.96 (s, 1H), 4.46 (s, 2H), 2.68 (s, 3H), 1.37 (s, 9H).

^{13}C NMR: δ 157.0, 141.7, 138.0, 135.1, 131.6, 131.5, 129.8, 128.7, 128.1, 125.1, 123.9, 61.8, 35.2, 34.1, 31.0.

HRMS (ESI): Calcd. for $C_{20}H_{23}NO_2S_2Na$ (M^+ + Na): *m/z* 374.1248. Found: 374.1246.

Compound 60



Yield: 0.072 g (76%).

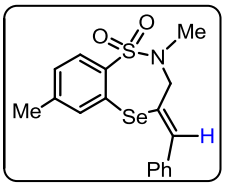
IR (neat): 3052, 2926, 1584, 1490, 1441, 1348, 1255, 1162, 882, 690, 652 cm^{-1}.

^1H NMR: δ 7.77 (d, *J* = 8.0 Hz, 1H), 7.64 (d, *J* = 7.2 Hz, 2H), 7.57 (s, 1H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.29-7.26 (m, 3H), 7.17 (d, *J* = 8.0 Hz, 1H), 7.12-7.10 (m, 2H), 6.77 (s, 1H), 4.82 (s, 2H), 2.44 (s, 3H).

^{13}C NMR: δ 143.7, 140.4, 140.3, 140.2, 135.1, 134.2, 131.5, 130.3, 129.9, 129.3, 128.7, 128.6, 128.5, 128.3, 128.2, 125.9, 63.4, 21.3.

HRMS (ESI): Calcd. for $C_{22}H_{19}NO_2S_2Na$ (M^+ + Na): *m/z* 416.0755. Found: 416.0758.

Compound 61



Yield: 0.070 g (76%).

Mp: 156-160 ^{o}C.

IR (KBr): 2925, 1585, 1441, 1328, 1281, 1168, 1106, 1078, 929, 753 cm^{-1}.

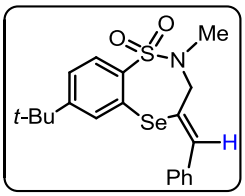
^{1}H NMR: δ 7.97 (d, *J* = 8.0 Hz, 1H), 7.62 (s, 1H), 7.53 (d, *J* = 7.2 Hz, 2H), 7.44-7.37 (m, 3H), 7.24 (d, *J* = 8.0 Hz, 1H), 6.99 (s, 1H), 4.70 (s, 2H), 2.65 (s, 3H), 2.39 (s, 3H).

^{13}C NMR: δ 143.7, 140.5, 139.5, 136.0, 135.7, 131.8, 129.7, 128.9, 128.5, 128.1, 126.3, 122.7, 63.2, 33.6, 21.2.

^{77}Se NMR: δ 291.08.

HRMS (ESI): Calcd. for $C_{17}H_{18}NO_2SSe$ (M^+ + H): *m/z* 380.0223. Found: 380.0221.

Compound 62



Yield: 0.083 g (82%).

Mp: 132-134 ^{o}C.

IR (KBr): 2965, 1580, 1445, 1331, 1269, 1169, 1031, 932, 748 cm^{-1}.

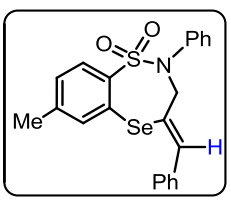
^{1}H NMR: δ 8.02 (d, *J* = 8.0 Hz, 1H), 7.82-7.81 (m, 1H), 7.51 (d, *J* = 7.2 Hz, 2H), 7.47-7.35 (m, 4H), 7.00 (s, 1H), 4.70 (s, 2H), 2.67 (s, 3H), 1.36 (s, 9H).

^{13}C NMR: δ 156.7, 140.6, 139.4, 135.9, 132.7, 131.7, 129.7, 128.5, 128.1, 126.5, 125.2, 122.9, 63.2, 35.1, 33.7, 31.0.

^{77}Se NMR: δ 296.55.

HRMS (ESI): Calcd. for $C_{20}H_{23}NO_2SSeNa$ (M^+ + Na): *m/z* 422.0693. Found: 422.0695.

Compound 63



Yield: 0.070 g (68%).

Mp: 172-174 ^{o}C.

IR (KBr): 3058, 2926, 1584, 1490, 1337, 1167, 1112, 1030, 877, 696 cm^{-1}.

^{1}H NMR: δ 7.75 (d, *J* = 8.0 Hz, 1H), 7.67 (s, 1H), 7.50 (d, *J* = 7.2 Hz, 2H), 7.43 (t, *J* = 7.2 Hz, 2H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.29-7.26 (m, 3H), 7.15 (d, *J* = 8.0 Hz, 1H), 7.10-7.08 (m, 2H), 6.78 (s, 1H), 5.04 (s, 2H), 2.40 (s, 3H).

^{13}C NMR: δ 143.5, 141.8, 139.6, 139.5, 136.0, 135.6, 130.7, 129.7, 129.3, 128.9, 128.7, 128.4$_3$, 128.3$_5$, 128.1, 126.4, 124.8, 64.9, 21.2.

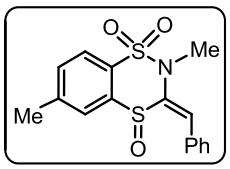
^{77}Se NMR: δ 294.21.

HRMS (ESI): Calcd. for $C_{22}H_{19}NO_2SSeNa$ (M^+ + Na): *m/z* 464.0200. Found: 464.0204.

3.9 Synthesis of benzo[1,4,2]dithiazine 1,1,4-trioxide (64)

An oven dried Schlenk tube was charged with benzo[1,4,2]dithiazine 1,1-dioxide **38** (0.15 mmol, 1 equiv), dry DCM (1 mL) and *m*CPBA (1 equiv). The contents were sealed under nitrogen atmosphere and stirred at room temperature for 5 h. After completion of the reaction as monitored by TLC, the crude reaction mixture was then purified by using silica gel column chromatography using hexane-ethyl acetate (8:2) as the eluent to afford benzo[1,4,2]dithiazine 1,1,4-trioxide **64**.

Compound 64



Yield: 0.045 g (86%).

Mp: 114-116 ^{o}C.

IR (KBr): 3019, 2920, 1715, 1578, 1447, 1342, 1173, 1030, 822, 674 cm^{-1}.

^{1}H NMR: δ 7.98 (d, *J* = 8.0 Hz, 1H), 7.81 (s, 1H), 7.75 (s, 1H), 7.71-7.70 (m, 2H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.50-7.49 (m, 3H), 3.45 (s, 3H), 2.53 (s, 3H).

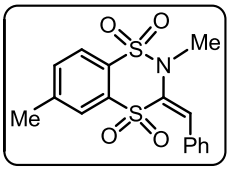
^{13}C NMR: δ 147.3, 145.0, 139.9, 139.1, 133.5, 132.0, 131.0, 130.6, 130.1, 129.8, 128.9, 126.2, 41.2, 21.6.

HRMS (ESI): Calcd. for $C_{16}H_{15}NO_3S_2Na$ (M^+ + Na): *m/z* 334.0571. Found: 334.0568.

3.10 Synthesis of benzo[1,4,2]dithiazine 1,1,4,4-tetraoxide (65)

Benzo[1,4,2]dithiazine 1,1-dioxide **38** (0.15 mmol, 1 equiv) was dissolved in dry DCM (1 mL) and to this *m*CPBA (3 equiv) was added. The contents were sealed under nitrogen atmosphere and stirred at room temperature for 4 h. After completion of the reaction as monitored by TLC, the crude reaction mixture was diluted with DCM (10 mL) and washed with saturated solution of aq. $NaHCO_3$. The aqueous layer was extracted twice with DCM (10 mL). The combined organic layer was washed with brine solution, dried over anh. sodium sulfate and concentrated in vacuum. The residue was then subjected to silica gel column chromatography using hexane-ethyl acetate (9:1) as the eluent to afford benzo[1,4,2]dithiazine 1,1,4,4-tetraoxide **65**.

Compound 65



Yield: 0.052 g (94%).

Mp: 168-172 ^{o}C.

IR (KBr): 3025, 2937, 1595, 1447, 1348, 1310, 1178, 1118, 1003, 718 cm^{-1}.

^{1}H NMR: δ 7.80 (s, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.68-7.66 (m, 3H), 7.54 (d, *J* = 8.4 Hz, 1H), 7.50-7.46 (m, 3H), 3.49 (s, 3H), 2.50 (s, 3H).

^{13}C NMR: δ 146.3, 145.4, 138.0, 136.2, 133.8, 132.9, 131.1, 130.8, 129.9, 128.1, 125.6, 125.2, 40.7, 21.8.

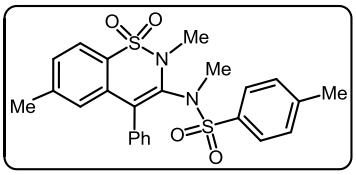
HRMS (ESI): Calcd. for $C_{16}H_{15}NO_4S_2Na$ (M^+ + Na): *m/z* 372.0340. Found: 372.0343.

3.11 Synthesis of benzosultams by the palladium-catalyzed tandem-cyclization of functionalized ynamides using various nucleophiles: Representative procedure for synthesis of compound 66

To an oven dried Schlenk tube was added 2-iodo-4,*N*-dimethyl-*N*-phenylethynyl-benzenesulfonamide **5a** (0.24 mmol), $PdCl_2(PPh_3)_2$ (5 mol %), *N*,4-dimethyl-benzenesulfonamide **1a** (0.29 mmol), KO^{t}Bu (0.48 mmol) and dry DMSO (1 mL). The contents were sealed under nitrogen atmosphere and heated at 70 ^{o}C (oil bath temperature) overnight. After completion of the reaction as monitored by TLC, the crude

reaction mixture was cooled to rt (25 ^{o}C), diluted with ethyl acetate (20 mL) and washed with water. The aqueous layer was extracted twice with ethyl acetate (20 mL). The combined organic layer was washed with brine solution, dried over anh. sodium sulfate and concentrated in vacuum. The residue was then purified by using silica gel column chromatography using hexane-ethyl acetate (4:1) as the eluent to afford 1,2-benzothiazine 1,1-dioxide **66**. Compounds **67**-**80** were prepared following the same procedure using the same molar quantities.

Compound 66



Yield: 0.104 g (92%).

Mp: 142-146 ^{o}C.

IR (KBr): 3052, 2915, 1594, 1462, 1346, 1164, 1090, 936, 854, 755 cm^{-1}.

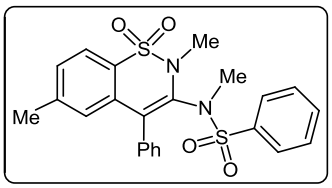
^{1}H NMR: δ 7.81 (d, *J* = 8.0 Hz, 1H), 7.44-7.43 (m, 3H), 7.36-7.32 (m, 3H), 7.12-7.11 (m, 5H), 3.15 (s, 3H), 2.89 (s, 3H), 2.39 (s, 3H), 2.34 (s, 3H).

^{13}C NMR: δ 144.0, 142.7, 135.4, 135.2, 134.6, 132.8, 130.3, 130.1, 129.6, 128.6, 128.3, 128.0, 127.8, 126.4, 122.3, 37.1, 33.5, 21.8, 21.5.

HRMS (ESI): Calcd. for $C_{24}H_{24}N_2O_4S_2Na$ (M^+ + Na): *m/z* 491.1075, Found: 491.1075.

This compound was crystallized from ethyl acetate at room temperature. The X-ray structure has been determined for this compound.

Compound 67



Yield: 0.10 g (90%).

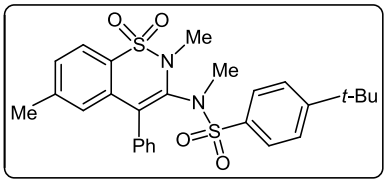
IR (neat): 3052, 2931, 1610, 1594, 1468, 1440, 1342, 1166, 1046, 931, 761 cm^{-1}.

^{1}H NMR: δ 7.81 (d, *J* = 8.0 Hz, 1H), 7.51 (t, *J* = 7.2 Hz, 1H), 7.42-7.41 (m, 3H), 7.35-7.32 (m, 5H), 7.29-7.27 (m, 2H), 7.10 (s, 1H), 3.15 (s, 3H), 2.93 (s, 3H), 2.34 (s, 3H).

^{13}C NMR: δ 142.7, 138.2, 135.2, 134.6, 133.0, 132.8, 130.3, 130.2, 129.6, 128.9, 128.6, 128.3, 128.0, 127.7, 126.6, 122.4, 37.0, 33.5, 21.8.

HRMS (ESI): Calcd. for $C_{23}H_{22}N_2O_4S_2NH_4^+$ (M^+ + NH_4): *m/z* 472.1365, Found: 472.1365.

Compound 68



Yield: 0.12 g (96%).

Mp: 150-156 ^oC.

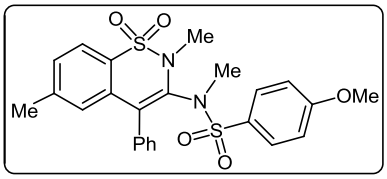
IR (KBr): 3048, 2921, 1616, 1476, 1359, 1348, 1167, 970, 866, 795 cm^{-1}.

^1H NMR: δ 7.81 (d, *J* = 8.0 Hz, 1H), 7.41-7.39 (m, 3H), 7.34-7.30 (m, 5H), 7.19 (d, *J* = 7.6 Hz, 2H), 7.08 (s, 1H), 3.18 (s, 3H), 2.93 (s, 3H), 2.34 (s, 3H), 1.33 (s, 9H).

^{13}C NMR: δ 156.8, 142.6, 135.3, 135.2, 134.6, 132.9, 130.3, 130.2, 129.9, 129.5, 128.9, 128.5, 128.3, 127.9, 127.5, 126.4, 125.9, 122.3, 36.9, 35.1, 33.5, 31.1, 21.8.

HRMS (ESI): Calcd. for $C_{27}H_{30}N_2O_4S_2Na$ (M^+ + Na): *m/z* 533.1545, Found: 533.1543.

Compound 69



Yield: 0.104 g (88%).

Mp: 134-138 ^oC.

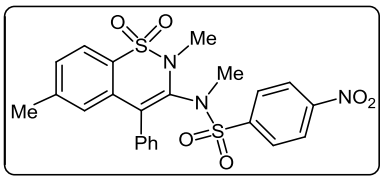
IR (KBr): 3058, 2926, 1595, 1496, 1346, 1332, 1266, 1156, 1030, 937, 668 cm^{-1}.

^1H NMR: δ 7.79 (d, *J* = 8.0 Hz, 1H), 7.45-7.44 (m, 3H), 7.35-7.31 (m, 3H), 7.16 (d, *J* = 8.8 Hz, 2H), 7.11 (s, 1H), 6.78 (d, *J* = 8.8 Hz, 2H), 3.83 (s, 3H), 3.15 (s, 3H), 2.87 (s, 3H), 2.33 (s, 3H).

^{13}C NMR: δ 163.2, 142.7, 135.3, 134.8, 132.8, 130.4, 130.1, 129.6, 128.6, 128.3, 127.9, 126.5, 122.3, 114.0, 55.7, 36.8, 33.6, 21.9.

HRMS (ESI): Calcd. for $C_{24}H_{24}N_2O_5S_2Na$ (M^+ + Na): *m/z* 507.1025, Found: 507.1029.

Compound 70



Yield: 0.10 g (82%).

Mp: 148-152 ^{o}C.

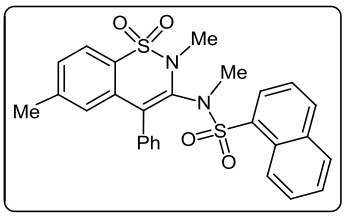
IR (KBr): 3063, 2937, 1622, 1529, 1462, 1353, 1332, 1178, 1036, 860, 745 cm^{-1}.

^{1}H NMR: δ 8.15 (d, *J* = 8.8 Hz, 2H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.46-7.37 (m, 6H), 7.32-7.29 (m, 2H), 7.06 (s, 1H), 3.20 (s, 3H), 3.05 (s, 3H), 2.36 (s, 3H).

^{13}C NMR: δ 150.0, 144.0, 142.9, 134.6, 134.4, 132.4, 130.3, 130.1, 130.0, 128.8, 128.7, 128.4, 128.3, 127.0, 124.0, 122.4, 37.4, 33.5, 21.9.

HRMS (ESI): Calcd. for $C_{23}H_{22}N_3O_6S_2$ (M^+ + H): *m/z* 500.0950, Found: 500.0952.

Compound 71



Yield: 0.096 g (80%).

Mp: 176-180 ^{o}C.

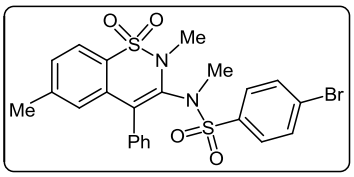
IR (KBr): 3068, 2921, 1616, 1595, 1468, 1348, 1156, 1047, 937, 866, 767, 668 cm^{-1}.

^{1}H NMR: δ 7.97 (s, 1H), 7.88-7.85 (m, 2H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 8.4 Hz, 1H), 7.67-7.58 (m, 2H), 7.39-7.33 (m, 6H), 7.17 (dd, *J* = 8.8 Hz, *J* = 1.2 Hz, 1H), 7.08 (s, 1H), 3.20 (s, 3H), 2.98 (s, 3H), 2.33 (s, 3H).

^{13}C NMR: δ 142.6, 135.2, 135.0, 134.9, 134.6, 132.9, 132.0, 130.3, 130.2, 129.6, 129.4, 129.3, 129.1, 129.0, 128.5, 128.3, 128.1, 127.8, 127.4, 126.7, 122.6, 122.4, 37.1, 33.6, 21.8.

HRMS (ESI): Calcd. for $C_{27}H_{25}N_2O_4S_2$ (M^+ + H): *m/z* 505.1255, Found: 505.1254.

Compound 72



Yield: 0.092 g (72%).

Mp: 164-168 ^{o}C.

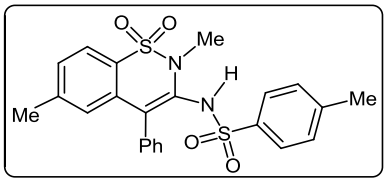
IR (KBr): 3058, 2926, 1616, 1573, 1463, 1353, 1346, 1167, 1068, 926, 756 cm^{-1}.

^{1}H NMR: δ 7.81 (d, *J* = 8.0 Hz, 1H), 7.46-7.40 (m, 5H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.31-7.29 (m, 2H), 7.10-7.07 (m, 3H), 3.17 (s, 3H), 2.94 (s, 3H), 2.33 (s, 3H).

^{13}C NMR: δ 142.7, 137.3, 135.0, 134.6, 132.7, 132.2, 130.2, 129.7, 129.2, 128.7, 128.3, 128.1, 126.7, 122.4, 37.1, 33.6, 21.8.

HRMS (ESI): Calcd. for $C_{23}H_{21}BrN_2O_4S_2Na$ (M^+ + Na): *m/z* 555.0024 and 557.0004, Found: 555.0025 and 557.0006.

Compound 73



Yield: 0.078 g (72%).

Mp: 180-184 ^{o}C.

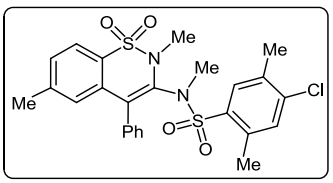
IR (KBr): 3304, 3047, 2921, 1600, 1474, 1381, 1326, 1156, 816, 751, 679 cm^{-1}.

^{1}H NMR: δ 7.76 (d, *J* = 8.0 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.36 (t, *J* = 7.2 Hz, 1H), 7.27-7.22 (m, 5H), 6.59 (d, *J* = 6.8 Hz, 2H), 6.54 (s, 1H), 6.43 (s, 1H), 3.41 (s, 3H), 2.43 (s, 3H), 2.23 (s, 3H).

^{13}C NMR: δ 144.4, 142.5, 134.6, 133.3, 133.0, 132.8, 130.7, 130.0, 129.6, 129.4, 129.0, 128.8, 128.6, 128.2, 127.3, 122.1, 115.8, 35.3, 21.6$_7$, 21.6$_5$.

HRMS (ESI): Calcd. for $C_{23}H_{23}N_2O_4S_2$ (M^+ + H): *m/z* 455.1099, Found: 455.1099.

Compound 74



Yield: 0.095 g (76%).

Mp: 144-148 ^{o}C.

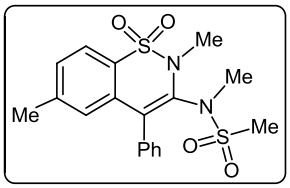
IR (KBr): 2926, 2849, 1627, 1595, 1474, 1342, 1328, 1184, 937, 871, 740, 636 cm^{-1}.

^{1}H NMR: δ 7.82 (d, *J* = 8.0 Hz, 1H), 7.35-7.26 (m, 4H), 7.20-7.19 (m, 3H), 6.84 (br, 2H), 3.25 (s, 3H), 3.17 (s, 3H), 2.46 (s, 3H), 2.31 (s, 3H), 2.18 (s, 3H).

^{13}C NMR: δ 142.6, 138.3, 136.2, 136.1, 135.1, 134.3, 133.7, 133.3, 132.7, 130.3, 130.0, 129.6, 129.5, 128.5, 128.3, 128.2, 125.9, 122.2, 38.4, 33.5, 21.8, 20.0, 19.7.

HRMS (ESI): Calcd. for $C_{25}H_{25}ClN_2O_4S_2Na$ (M^+ + Na): *m/z* 539.0842, Found: 539.0841.

Compound 75



Yield: 0.066 g (70%).

Mp: 94-98 ^{o}C.

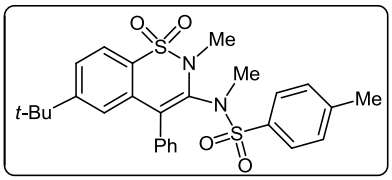
IR (KBr): 3035, 2942, 1610, 1588, 1473, 1342, 1145, 1073, 964, 777, 706 cm^{-1}.

^{1}H NMR: δ 7.81 (d, *J* = 8.0 Hz, 1H), 7.52-7.43 (m, 5H), 7.34 (d, *J* = 7.2 Hz, 1H), 7.14 (s, 1H), 3.22 (s, 3H), 3.07 (s, 3H), 2.35 (s, 3H), 2.00 (s, 3H).

^{13}C NMR: δ 142.7, 135.5, 135.2, 132.2, 130.3, 130.1, 129.5, 128.8, 128.3, 128.0, 125.0, 122.3, 37.9, 35.4, 32.9, 21.8.

HRMS (ESI): Calcd. for $C_{18}H_{20}N_2O_4S_2Na$ (M^+ + Na): *m/z* 415.0762, Found: 415.0761.

Compound 76



Yield: 0.111 g (90%).

Mp: 190-194 ^{o}C.

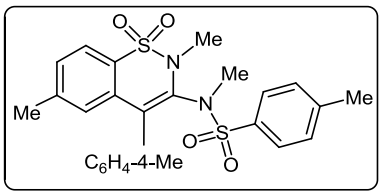
IR (KBr): 2959, 2865, 1605, 1594, 1473, 1353, 1336, 1150, 936, 854, 761 cm^{-1}.

^{1}H NMR: δ 7.86 (d, *J* = 8.0 Hz, 1H), 7.57 (dd, *J* = 8.4 Hz, *J* = 1.6 Hz, 1H), 7.46-7.44 (m, 3H), 7.38-7.37 (m, 3H), 7.14 (br, 4H), 3.19 (s, 3H), 2.92 (s, 3H), 2.41 (s, 3H), 1.24 (s, 9H).

^{13}C NMR: δ 155.6, 143.9, 135.2, 135.1, 134.8, 132.5, 130.3, 130.0, 129.5, 128.5, 127.9, 127.8, 126.9, 126.1, 124.8, 122.1, 36.7, 35.3, 33.6, 31.0, 21.5.

HRMS (ESI): Calcd. for $C_{27}H_{30}N_2O_4S_2NH_4^+$ (M^+ + NH_4): *m/z* 528.1991, Found: 528.1995.

Compound 77



Yield: 0.107 g (92%).

Mp: 186-190 ^{o}C.

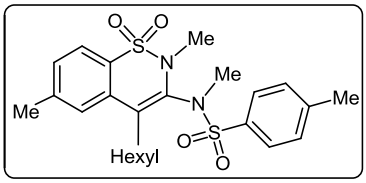
IR (KBr): 3025, 2921, 1600, 1474, 1353, 1342, 1184, 1047, 866, 734, 668 cm^{-1}.

^{1}H NMR: δ 7.81 (d, *J* = 8.0 Hz, 1H), 7.34 (d, *J* = 7.6 Hz, 1H), 7.23 (br, 4H), 7.20-7.18 (m, 2H), 7.14-7.12 (m, 3H), 3.16 (s, 3H), 2.93 (s, 3H), 2.47 (s, 3H), 2.42 (s, 3H), 2.36 (s, 3H).

^{13}C NMR: δ 143.7, 142.6, 137.7, 135.5, 135.3, 133.0, 131.6, 130.2, 129.5, 129.3, 129.2, 128.3, 127.8, 126.6, 122.3, 36.9, 33.5, 21.8, 21.5, 21.3.

HRMS (ESI): Calcd. for $C_{25}H_{26}N_2O_4S_2Na$ (M^+ + Na): *m/z* 505.1232, Found: 505.1231.

Compound 78



Yield: 0.108 g (94%).

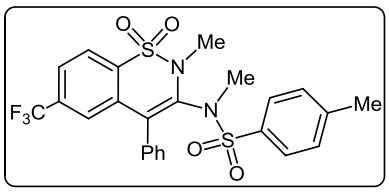
IR (neat): 2931, 2854, 1594, 1462, 1347, 1166, 1084, 876, 816, 668 cm^{-1}.

^{1}H NMR: δ 7.86 (d, *J* = 8.0 Hz, 2H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.42 (s, 1H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 1H), 3.18 (s, 3H), 2.85 (s, 3H), 2.68-2.63 (m, 2H), 2.50 (s, 3H), 2.48 (s, 3H), 1.30-1.23 (m, 2H), 1.19 (t, *J* = 6.4 Hz, 2H), 1.17-1.13 (m, 4H), 0.83 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR: δ 144.3, 142.4, 135.9, 133.7, 132.7, 131.6, 129.8, 129.3, 127.8, 127.0, 124.8, 122.6, 36.2, 33.3, 31.3, 28.8, 28.2, 28.1, 22.5, 21.9, 21.6, 14.0.

HRMS (ESI): Calcd. for $C_{24}H_{32}N_2O_4S_2Na$ (M^+ + Na): *m/z* 499.1701, Found: 499.1701.

Compound 79



Yield: 0.080 g (64%).

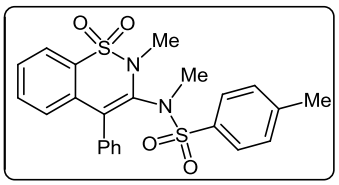
IR (KBr): 3074, 2916, 1605, 1567, 1468, 1342, 1304, 1178, 1090, 937, 833, 756, 663 cm^{-1}.

^1H NMR: δ 8.07 (d, *J* = 8.0 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.63 (s, 1H), 7.49-7.43 (m, 3H), 7.32 (dd, *J* = 7.6 Hz, *J* = 1.6 Hz, 2H), 7.16 (br, 4H), 3.24 (s, 3H), 2.93 (s, 3H), 2.42 (s, 3H).

^{13}C NMR: δ 144.2, 136.5, 135.1, 134.8, 133.9 (d, *J* = 30 Hz), 133.8, 133.6, 130.2, 129.6, 128.9, 128.4, 127.8, 125.3, 124.9 (d, *J* = 4 Hz), 123.2, 123.1 (d, *J* = 270 Hz), 36.9, 33.7, 21.5.

HRMS (ESI): Calcd. for $C_{24}H_{21}F_3N_2O_4S_2Na$ (M^+ + Na): *m/z* = 545.0793, Found: 545.0797.

Compound 80



Yield: 0.083 g (76%).

Mp: 210-214 ^oC.

IR (KBr): 3063, 2921, 1622, 1589, 1468, 1353, 1342, 1162, 1041, 948, 668 cm^{-1}.

^1H NMR: δ 7.95-7.93 (m, 1H), 7.55-7.52 (m, 2H), 7.45-7.44 (m, 3H), 7.37-7.35 (m, 3H), 7.15 (br, 4H), 3.20 (s, 3H), 2.93 (s, 3H), 2.41 (s, 3H).

^{13}C NMR: δ 144.0, 135.2, 135.1, 134.6, 132.8, 132.7, 131.9, 130.4, 129.5, 128.7, 128.6, 128.0_2, 127.9_8, 127.8, 126.5, 122.3, 36.8, 33.6, 21.5.

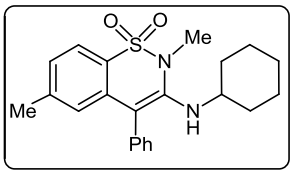
HRMS (ESI): Calcd. for $C_{23}H_{22}N_2O_4S_2NH_4^+$ (M^+ + NH_4): *m/z* 472.1365, Found: 472.1369.

3.12 Representative procedure for synthesis of compound 81

To an oven dried Schlenk tube was added 2-iodo-4,*N*-dimethyl-*N*-phenylethynyl-benzenesulfonamide **5a** (0.24 mmol), $PdCl_2(PPh_3)_2$ (5 mol %), cyclohexylamine **8a** (0.29 mmol), K_2CO_3 (0.48 mmol) and dry DMSO (1 mL). The contents were sealed under nitrogen atmosphere and heated at 70 ^oC (oil bath temperature) overnight. After completion of the reaction as monitored by TLC, the crude reaction mixture was cooled to room temperature, diluted with ethyl acetate (20 mL) and washed with water. The aqueous layer was extracted twice with ethyl acetate (20 mL). The combined organic

layer was washed with brine solution, dried over anh. sodium sulfate and concentrated in vacuum. The residue was then purified by using silica gel column chromatography using hexane-ethyl acetate (9:1) as the eluent to afford 1,2-benzothiazine 1,1-dioxide **81**. Compounds **82-89** were prepared following same procedure with same molar quantities. ***Note***: Due to high volatility of diethyl amine or *n*-butyl amine we performed the reaction by using 3 equiv (0.72 mmol) of amine in these cases.

Compound 81



Yield: 0.080 g (86%).

Mp: 130-134 ^{o}C.

IR (KBr): 3370, 2926, 2855, 1589, 1463, 1332, 1200, 1167, 1096, 751 cm^{-1}.

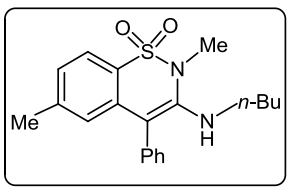
^{1}H NMR: δ 7.72 (d, *J* = 8.0 Hz, 1H), 7.53 (t, *J* = 7.2 Hz, 2H), 7.45 (t, *J* = 7.2 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.09 (d, *J* = 8.0 Hz, 1H), 6.60 (s, 1H), 3.56-3.54 (m, 1H), 3.26-3.22 (m, 1H), 3.17 (s, 3H); 2.27 (s, 3H); 1.96-1.93 (m, 2H), 1.59-1.51 (m, 3H), 1.34-1.26 (m, 2H), 1.05-1.02 (m, 1H), 0.94-0.89 (m, 2H).

^{13}C NMR: δ 144.8, 142.4, 136.0, 135.8, 131.4, 129.4, 128.0, 126.7, 126.0, 125.7, 122.6, 105.2, 54.5, 35.7, 34.1, 25.5, 24.9, 21.8.

HRMS (ESI): Calcd. for $C_{22}H_{27}N_2O_2S$ (M^+ + H): *m/z* 383.1793, Found: 383.1794.

This compound was crystallized from ethyl acetate/hexane (2:1) mixture at room temperature. X-ray structure has been determined for this compound.

Compound 82



Yield: 0.081 g (94%).

Mp: 92-96 ^{o}C.

IR (KBr): 3392, 2959, 2866, 1589, 1463, 1337, 1200, 1167, 1068, 921, 751 cm^{-1}.

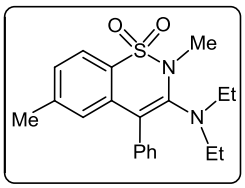
^{1}H NMR: δ 7.71 (d, *J* = 7.6 Hz, 1H), 7.56 (t, *J* = 7.2 Hz, 2H), 7.45 (t, *J* = 7.2 Hz, 1H), 7.32 (d, *J* = 7.2 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 1H), 6.60 (s, 1H), 3.77

(t, *J* = 6.4 Hz, 1H), 3.15 (s, 3H); 3.07 (qrt, *J* = 6.8 Hz, 2H), 2.26 (s, 3H); 1.45-1.37 (m, 2H), 1.20-1.11 (m, 2H), 0.84 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR: δ 145.5, 142.5, 136.1, 135.7, 131.4, 129.5, 128.0, 126.7, 125.9, 125.6, 122.8, 104.3, 45.4, 35.7, 32.8, 21.8, 19.8, 13.7.

HRMS (ESI): Calcd. for $C_{20}H_{25}N_2O_2S$ (M^+ + H): *m/z* 357.1636, Found: 357.1639.

Compound 83



Yield: 0.083 g (96%).

Mp: 120-124 ^{o}C.

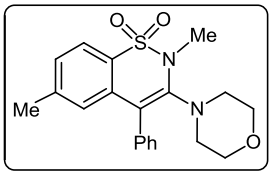
IR (KBr): 2964, 2926, 1584, 1458, 1337, 1293, 1178, 1096, 937, 811, 773 cm^{-1}.

^{1}H NMR: δ 7.73 (d, *J* = 8.0 Hz, 1H), 7.46 (t, *J* = 7.2 Hz, 2H), 7.39-7.37 (m, 3H), 7.24 (s, 1H), 7.14 (d, *J* = 8.0 Hz, 1H), 3.06 (s, 3H), 2.91 (qrt, *J* = 6.8 Hz, 4H), 2.34 (s, 3H); 0.95 (t, *J* = 7.2 Hz, 6H).

^{13}C NMR: δ 146.2, 142.1, 137.1, 135.4, 131.5, 128.5, 128.2, 127.0, 126.2, 125.7, 122.6, 109.6, 45.2, 34.7, 22.0, 13.6.

HRMS (ESI): Calcd. for $C_{20}H_{25}N_2O_2S$ (M^+ + H): *m/z* 357.1636, Found: 357.1637.

Compound 84



Yield: 0.064 g (72%).

Mp: 146-150 ^{o}C.

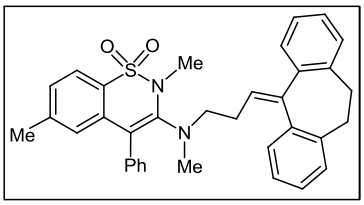
IR (KBr): 2915, 2849, 1589, 1463, 1342, 1271, 1162, 1068, 937, 877 cm^{-1}.

^{1}H NMR: δ 7.74 (d, *J* = 8.0 Hz, 1H), 7.48 (t, *J* = 7.2 Hz, 2H), 7.41 (d, *J* = 7.2 Hz, 1H), 7.37-7.35 (m, 2H), 7.27 (s, 1H), 7.18 (d, *J* = 8.0 Hz, 1H), 3.47 (t, *J* = 4.8 Hz, 4H), 3.15 (s, 3H), 2.89 (t, *J* = 4.8 Hz, 4H), 2.34 (s, 3H).

^{13}C NMR: δ 146.0, 142.4, 136.2, 134.8, 131.5, 128.6, 128.5, 127.5, 126.9, 125.9, 122.5, 110.2, 66.8, 50.1, 34.7, 21.9.

HRMS (ESI): Calcd. for $C_{20}H_{22}N_2O_3SNa$ (M^+ + Na): *m/z* 393.1249, Found: 393.1249.

Compound 85



Yield: 0.10 g (76%).

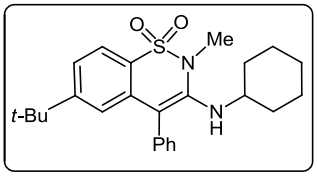
IR (neat): 3058, 2915, 1595, 1545, 1447, 1337, 1184, 1145, 1090, 948, 751 cm^{-1}.

^1H NMR: δ 7.73 (d, *J* = 8.0 Hz, 1H), 7.38 (t, *J* = 7.2 Hz, 2H), 7.32 (d, *J* = 7.6 Hz, 1H), 7.27-7.25 (m, 2H), 7.23-7.22 (m, 3H), 7.20-7.15 (m, 4H), 7.11 (t, *J* = 8.0 Hz, 2H), 7.07-7.05 (m, 1H), 5.73 (t, *J* = 7.2 Hz, 1H), 3.33 (br, 2H), 3.00 (br, 6H), 2.82-2.79 (m, 1H); 2.41 (s, 3H); 2.34 (s, 3H); 2.25-2.20 (m, 2H).

^{13}C NMR: δ 147.1, 144.4, 142.2, 141.0, 139.8, 139.3, 137.1, 136.9, 135.4, 131.7, 130.0_2, 129.5_7, 128.6, 128.4, 128.3, 128.2, 128.1, 127.5, 127.2, 127.1, 126.3, 126.1, 125.8, 125.7, 122.6, 109.0, 53.3, 39.5, 34.7, 33.8, 32.1, 28.2, 22.0.

HRMS (ESI): Calcd. for $C_{35}H_{34}N_2O_2S$ (M^+ + H): *m/z* 547.2419, Found: 547.2418.

Compound 86



Yield: 0.088 g (86%).

Mp: 138-142 ^oC.

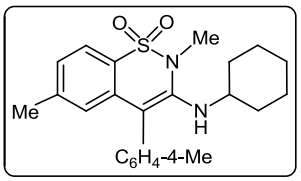
IR (KBr): 3359, 2921, 2849, 1589, 1474, 1342, 1189, 1030, 932, 745 cm^{-1}.

^1H NMR: δ 7.75 (d, *J* = 8.0 Hz, 1H), 7.52 (d, *J* = 7.6 Hz, 2H), 7.46-7.42 (m, 1H), 7.33-7.31 (m, 3H), 6.82-6.81 (m, 1H), 3.58-3.56 (m, 1H), 3.26-3.23 (m, 1H), 3.18 (s, 3H); 1.97-1.94 (m, 2H), 1.59-1.52 (m, 3H), 1.39-1.25 (m, 2H), 1.18 (s, 9H); 1.05-1.02 (m, 1H), 0.99-0.89 (m, 2H).

^{13}C NMR: δ 155.3, 144.5, 135.8, 135.7, 131.4, 129.3, 128.0, 126.7, 122.5, 122.3_0, 122.2_6, 105.7, 54.5, 35.6, 35.1, 34.1, 31.0, 25.5, 24.9.

HRMS (ESI): Calcd. for $C_{25}H_{33}N_2O_2S$ (M^+ + H): *m/z* 425.2262, Found: 425.2264.

Compound 87



Yield: 0.078 g (82%).

Mp: 146-152 ^{o}C.

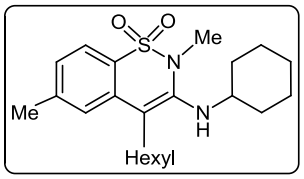
IR (KBr): 3375, 2926, 2849, 1589, 1463, 1337, 1156, 937, 805 cm^{-1}.

^{1}H NMR: δ 7.70 (d, *J* = 8.0 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 1H), 6.61 (s, 1H), 3.57-3.55 (m, 1H), 3.25-3.22 (m, 1H), 3.16 (s, 3H); 2.47 (s, 3H); 2.27 (s, 3H); 1.97-1.93 (m, 2H), 1.61-1.53 (m, 3H), 1.35-1.28 (m, 2H), 1.06-1.02 (m, 1H), 0.92-0.88 (m, 2H).

^{13}C NMR: δ 144.8, 142.3, 137.6, 136.1, 132.5, 131.2, 130.1, 126.7, 126.0, 125.6, 122.6, 105.1, 54.5, 35.7, 34.1, 25.5, 25.0, 21.8, 21.4.

HRMS (ESI): Calcd. for $C_{23}H_{29}N_2O_2S$ (M^+ + H): *m/z* 397.1949, Found: 397.1946.

Compound 88



Yield: 0.072 g (76%).

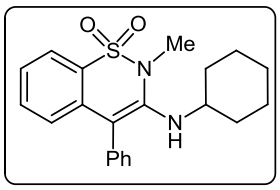
IR (neat): 3403, 2932, 2849, 1600, 1518, 1447, 1315, 1260, 1162, 1074, 970, 816, 685 cm^{-1}.

^{1}H NMR: δ 7.68 (d, *J* = 8.0 Hz, 1H), 7.15 (s, 1H), 7.11 (d, *J* = 8.0 Hz, 1H), 3.49-3.47 (m, 1H), 3.33-3.29 (m, 1H), 3.00 (s, 3H), 2.50-2.46 (m, 2H), 2.44 (s, 3H), 2.12-2.09 (m, 2H), 1.79-1.76 (m, 2H), 1.71-1.64 (m, 2H), 1.57-1.51 (m, 2H), 1.45-1.21 (m, 10H), 0.94 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR: δ 143.6, 142.3, 135.9, 127.6, 125.6, 124.3, 123.1, 102.3, 54.4, 35.5, 34.7, 31.6, 29.7, 29.4, 29.0, 27.4, 25.7, 25.2, 22.6, 22.0, 14.0.

HRMS (ESI): Calcd. for $C_{22}H_{35}N_2O_2S$ (M^+ + H): *m/z* 391.2419, Found: 391.2417.

Compound 89



Yield: 0.057 g (64%).

IR (neat): 3370, 2932, 2849, 1611, 1584, 1463, 1348, 1216, 1173, 932, 745 cm^{-1}.

^{1}H NMR: δ 7.83 (d, *J* = 8.0 Hz, 1H), 7.52 (t, *J* = 7.2 Hz, 2H), 7.45 (t, *J* = 7.2 Hz, 1H), 7.39-7.26 (m, 4H), 6.82 (d, *J* = 8.0 Hz, 1H), 3.60-3.57 (m, 1H), 3.28-3.24 (m, 1H), 3.19 (s, 3H); 1.97-1.94 (m, 2H), 1.63-1.52 (m, 3H), 1.35-1.26 (m, 2H), 1.05-1.03 (m, 1H), 0.95-0.87 (m, 2H).

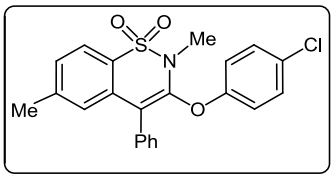
^{13}C NMR: δ 144.7, 136.0, 135.6, 131.8, 131.4, 129.4, 129.2, 128.0, 125.7, 124.7, 122.6, 105.3, 54.6, 35.7, 34.1, 25.5, 24.9.

HRMS (ESI): Calcd. for $C_{21}H_{25}N_2O_2S$ (M^+ + H): *m/z* 369.1636, Found: 369.1638.

3.13 Representative procedure for synthesis of compound 90

The procedure was the same as that for compound **66**, but by using phenols in place of sulfonamide. Eluent purify 1,2-benzothiazine 1,1-dioxide **90** was hexane-ethyl acetate (9:1). Compounds **91-102** were prepared following same procedure with same molar quantities.

Compound 90



Yield: 0.081 g (82%).

Mp: 156-160 ^{o}C.

IR (KBr): 3058, 2948, 1627, 1589, 1485, 1337, 1211, 1140, 1085, 1014, 937, 811 cm^{-1}.

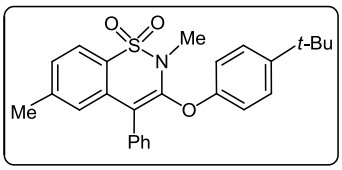
^{1}H NMR: δ 7.85 (d, *J* = 8.0 Hz, 1H), 7.42-7.35 (m, 5H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 8.8 Hz, 2H), 7.03 (d, *J* = 8.8 Hz, 2H), 6.95 (s, 1H), 3.13 (s, 3H), 2.35 (s, 3H).

^{13}C NMR: δ 154.1, 143.5, 142.9, 133.8, 133.0, 130.8, 129.7, 129.3, 128.7, 128.4_4, 128.3_8, 128.0, 127.6, 122.1, 118.0, 112.9, 32.2, 21.8.

HRMS (ESI): Calcd. for $C_{22}H_{18}ClNO_3SNa$ (M^+ + Na): *m/z* 434.0594, Found: 434.0595.

This compound was crystallized from ethyl acetate/ hexane (2:1) mixture at room temperature. The X-ray structure has been determined for this compound.

Compound 91



Yield: 0.084 g (80%).

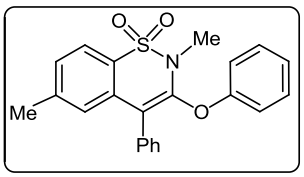
IR (neat): 2953, 2866, 1627, 1589, 1468, 1342, 1216, 1173, 1107, 1008, 932, 860, 740 cm^{-1}.

^{1}H NMR: δ 7.84 (d, *J* = 8.0 Hz, 1H), 7.46-7.39 (m, 4H), 7.37-7.33 (m, 1H), 7.31-7.29 (m, 3H), 7.01 (d, *J* = 8.8 Hz, 2H), 6.95 (s, 1H), 3.12 (s, 3H), 2.35 (s, 3H), 1.30 (s, 9H).

^{13}C NMR: δ 153.2, 146.3, 144.1, 142.6, 134.2, 133.5, 131.0, 129.2, 128.4, 128.0, 127.7, 127.5, 126.5, 122.0, 116.2, 112.0, 34.3, 32.2, 31.5, 21.8.

HRMS (ESI): Calcd. for $C_{26}H_{27}NO_3SNa$ (M^+ + Na): *m/z* 456.1610, Found: 456.1612.

Compound 92



Yield: 0.079 g (86%).

Mp: 172-176 ^{o}C.

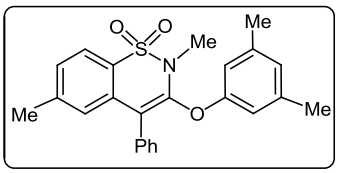
IR (KBr): 3052, 2932, 1633, 1589, 1490, 1468, 1326, 1282, 1134, 1068, 932, 822, 745, 679 cm^{-1}.

^{1}H NMR: δ 7.85 (d, *J* = 8.0 Hz, 1H), 7.45-7.39 (m, 4H), 7.36 (d, *J* = 6.8 Hz, 2H), 7.33-7.29 (m, 2H), 7.11-7.07 (m, 3H), 6.96 (s, 1H), 3.14 (s, 3H), 2.36 (s, 3H).

^{13}C NMR: δ 155.5, 143.9, 142.7, 134.0, 133.3, 130.9, 129.7, 129.2, 128.4, 128.1, 127.8, 127.5, 123.5, 122.0, 116.7, 112.3, 32.0, 21.8.

HRMS (ESI): Calcd. for $C_{22}H_{19}NO_3SNa$ (M^+ + Na): *m/z* 400.0984, Found: 400.0989.

Compound 93



Yield: 0.074 g (76%).

Mp: 140-146 ^{o}C.

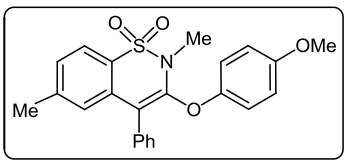
IR (KBr): 3047, 2921, 1611, 1589, 1468, 1337, 1288, 1189, 1030, 942, 816, 740, 685 cm^{-1}.

^{1}H NMR: δ 7.85 (d, *J* = 8.0 Hz, 1H), 7.44-7.36 (m, 4H), 7.38-7.36 (m, 1H), 7.30 (d, *J* = 8.4 Hz, 1H), 6.96 (s, 1H), 6.72 (br, 3H), 3.14 (s, 3H), 2.36 (s, 3H), 2.29 (s, 6H).

^{13}C NMR: δ 155.5, 143.9, 142.6, 139.5, 134.1, 133.5, 131.0, 129.2, 128.4, 128.0, 127.7, 127.4, 125.3, 121.9, 114.4, 111.9, 32.0, 21.8, 21.4.

HRMS (ESI): Calcd. for $C_{24}H_{23}NO_3SNa$ (M^+ + Na): *m/z* 428.1297, Found: 428.1289.

Compound 94



Yield: 0.081 g (82%).

Mp: 120-124 ^{o}C.

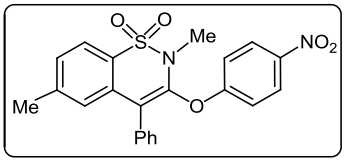
IR (KBr): 3052, 2921, 1622, 1595, 1468, 1337, 1200, 1107, 1030, 937, 855, 745, 701 cm^{-1}.

^{1}H NMR: δ 7.83 (d, *J* = 8.0 Hz, 1H), 7.43-7.40 (m, 4H), 7.38-7.36 (m, 1H), 7.30 (d, *J* = 7.2 Hz, 1H), 7.01 (d, *J* = 7.6 Hz, 2H), 6.95 (s, 1H), 6.83 (d, *J* = 8.8 Hz, 2H), 3.76 (s, 3H), 3.12 (s, 3H), 2.35 (s, 3H).

^{13}C NMR: δ 155.7, 149.3, 144.3, 142.7, 134.1, 133.4, 131.0, 129.3, 128.4, 128.0, 127.8, 127.5, 122.0, 117.7, 114.7, 111.9, 55.6, 32.1, 21.8.

HRMS (ESI): Calcd. for $C_{23}H_{22}NO_4S$ (M^+ + H): *m/z* 408.1269, Found: 408.1268.

Compound 95



Yield: 0.066 g (64%).

Mp: 172-176 ^{o}C.

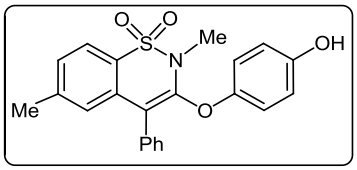
IR (KBr): 3047, 2937, 1633, 1584, 1485, 1342, 1222, 1112, 937, 860, 751, 685 cm^{-1}.

^{1}H NMR: δ 8.18 (d, *J* = 8.0 Hz, 2H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.41-7.35 (m, 6H), 7.21 (d, *J* = 8.8 Hz, 2H), 6.95 (s, 1H), 3.16 (s, 3H), 2.37 (s, 3H).

^{13}C NMR: δ 160.3, 143.6, 143.2, 142.8, 133.3, 132.4, 130.6, 129.3, 128.9, 128.6, 128.3, 127.9, 125.9, 122.2, 116.8, 114.3, 32.4, 21.8.

HRMS (ESI): Calcd. for $C_{22}H_{18}N_2O_5SNH_4^+$ (M^+ + NH_4): *m/z* 440.1280, Found: 440.1281.

Compound 96



Yield: 0.054 g (56%).

Mp: 182-186 ^{o}C.

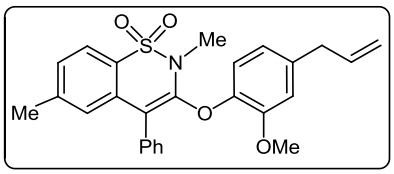
IR (KBr): 3457, 2926, 2849, 1627, 1594, 1501, 1462, 1336, 1194, 1101, 936, 816, 744 cm^{-1}.

^{1}H NMR: δ 7.82 (d, *J* = 8.0 Hz, 1H), 7.42-7.41 (m, 4H), 7.39-7.35 (m, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 6.93-6.90 (m, 3H), 6.76-6.72 (m, 2H), 5.09 (s, 1H), 3.12 (s, 3H), 2.34 (s, 3H).

^{13}C NMR: δ 152.1, 149.0, 144.2, 142.9, 134.1, 133.3, 131.0, 128.9, 128.4, 128.1, 127.8, 127.6, 122.0, 117.9, 116.1, 112.0, 32.3, 21.8.

HRMS (ESI): Calcd. for $C_{22}H_{19}NO_4SNa$ (M^+ + Na): *m/z* 416.0933, Found: 416.0936.

Compound 97



Yield: 0.076 g (72%).

Mp: 142-146 ^{o}C.

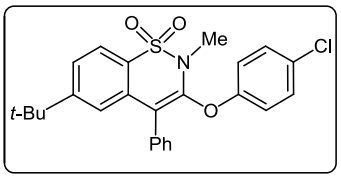
IR (KBr): 3063, 2926, 1633, 1595, 1507, 1468, 1342, 1195, 1123, 1036, 811, 740 cm^{-1}.

^{1}H NMR: δ 7.81 (d, *J* = 6.4 Hz, 1H), 7.46-7.44 (m, 2H), 7.41-7.38 (m, 2H), 7.36-7.33 (m, 1H), 7.28-7.26 (m, 1H), 6.97 (d, *J* = 6.4 Hz, 1H), 6.92 (s, 1H), 6.71-6.69 (m, 2H), 5.96-5.90 (m, 1H), 5.11-5.08 (m, 1H), 5.07-5.06 (m, 1H), 3.82 (s, 3H), 3.32 (d, *J* = 5.2 Hz, 2H), 3.12 (s, 3H), 2.34 (s, 3H).

^{13}C NMR: δ 149.0, 144.8, 142.7, 142.6, 137.2, 136.4, 134.2, 133.5, 131.1, 129.7, 129.2, 128.3, 127.9, 127.6, 127.4, 122.0, 117.9, 116.0, 112.9, 111.7, 56.0, 39.9, 32.0, 21.8.

HRMS (ESI): Calcd. for $C_{26}H_{25}NO_4SNa$ (M^+ + Na): *m/z* 470.1402, Found: 470.1405.

Compound 98



Yield: 0.091 g (86%).

Mp: 204-208 ^{o}C.

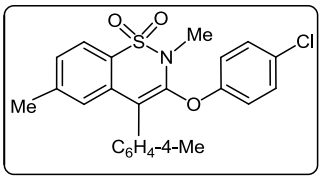
IR (KBr): 3068, 2964, 1616, 1589, 1479, 1397, 1342, 1211, 1085, 1008, 937, 822, 745 cm^{-1}.

^{1}H NMR: δ 7.89 (d, *J* = 8.4 Hz, 1H), 7.55 (dd, *J* = 8.4 Hz, *J* = 1.6 Hz, 1H), 7.42-7.41 (m, 4H), 7.39-7.36 (m, 1H), 7.26 (d, *J* = 8.8 Hz, 2H), 7.18 (s, 1H), 7.04 (d, *J* = 8.8 Hz, 2H), 3.14 (s, 3H), 1.24 (s, 9H).

^{13}C NMR: δ 155.8, 154.1, 143.3, 133.5, 133.0, 130.8, 129.7, 129.3, 128.7, 128.4, 128.0, 124.9, 124.3, 121.9, 118.0, 113.2, 35.3, 32.2, 31.0.

HRMS (ESI): Calcd. for $C_{25}H_{24}ClNO_3SNH_4^+$ (M^+ + NH_4): *m/z* 471.1505, Found: 471.1507.

Compound 99



Yield: 0.088 g (86%).

Mp: 176-182 ^{o}C.

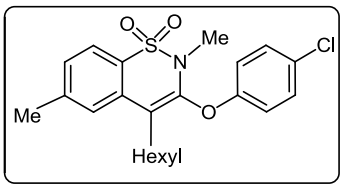
IR (KBr): 3052, 2921, 1633, 1584, 1479, 1348, 1205, 1134, 1085, 1008, 937, 816, 668 cm^{-1}.

^{1}H NMR: δ 7.83 (d, *J* = 8.0 Hz, 1H), 7.32-7.21 (m, 7H), 7.03 (d, *J* = 9.2 Hz, 2H), 6.98 (s, 1H), 3.12 (s, 3H), 2.39 (s, 3H), 2.36 (s, 3H).

^{13}C NMR: δ 154.1, 143.4, 142.8, 137.7, 134.0, 130.6, 129.9, 129.7, 129.3, 129.2, 128.7, 128.3, 127.7, 122.1, 118.0, 112.9, 32.2, 21.8, 21.3.

HRMS (ESI): Calcd. for $C_{23}H_{20}ClNO_3SNa$ (M^+ + Na): *m/z* 448.0750, Found: 448.0743.

Compound 100



Yield: 0.057 g (56%).

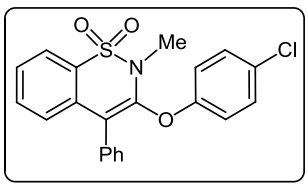
IR (neat): 2926, 2849, 1633, 1595, 1479, 1348, 1195, 1085, 1008, 685 cm^{-1}.

^{1}H NMR: δ 7.79 (d, *J* = 8.0 Hz, 1H), 7.41 (s, 1H), 7.38-7.35 (m, 2H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.16 (d, *J* = 8.8 Hz, 2H), 2.97 (s, 3H), 2.67 (t, *J* = 8.0 Hz, 2H), 2.52 (s, 3H); 1.60-1.52 (m, 2H), 1.37-1.27 (m, 2H), 1.26-1.25 (m, 4H), 0.86 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR: δ 154.5, 143.6, 142.9, 133.0, 129.8, 129.6, 128.7, 128.1, 125.4, 122.6, 118.0, 111.1, 32.5, 31.5, 29.1, 29.0, 25.4, 22.6, 22.0, 14.0.

HRMS (ESI): Calcd. for $C_{22}H_{27}ClNO_3S$ (M^+ + H): *m/z* 420.1400, Found: 420.1398.

Compound 101



Yield: 0.067 g (70%).

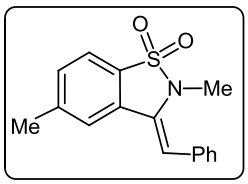
IR (neat): 3058, 2921, 1633, 1584, 1479, 1348, 1216, 1090, 1008, 932, 745 cm^{-1}.

^{1}H NMR: δ 7.97-7.95 (m, 1H), 7.53-7.51 (m, 2H), 7.42-7.40 (m, 4H), 7.38-7.36 (m, 1H), 7.26 (d, *J* = 8.8 Hz, 2H), 7.19-7.17 (m, 1H), 7.04-7.02 (m, 2H), 3.15 (s, 3H).

^{13}C NMR: δ 154.0, 143.4, 133.8, 132.9, 132.1, 131.8, 130.8, 129.7, 128.8, 128.5, 128.0, 127.4$_8$, 127.4$_6$, 122.1, 118.0, 112.9, 32.2.

HRMS (ESI): Calcd. for $C_{21}H_{17}ClNO_3S$ (M^+ + H): *m/z* 398.0617, Found: 398.0614.

Compound 102



Yield: 0.055 g (80%).

Mp: 160-164 ^{o}C.

IR (KBr): 3052, 2948, 1644, 1595, 1441, 1348, 1293, 1195, 1058, 910, 751 cm^{-1}.

^{1}H NMR: δ 7.73 (d, *J* = 8.0 Hz, 1H), 7.61 (s, 1H), 7.46-7.38 (m, 5H), 7.38-7.29 (m, 1H), 6.62 (s, 1H), 2.97 (s, 3H), 2.52 (s, 3H).

^{13}C NMR: δ 144.1, 134.2, 134.1, 132.9, 131.1, 129.7, 129.0, 128.3, 127.5, 121.0, 105.6, 32.1, 22.0.

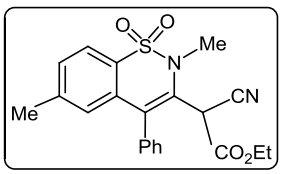
HRMS (ESI): Calcd. for $C_{16}H_{16}NO_2S$ (M^+ + H): *m/z* 286.0901, Found: 286.0901.

This compound was crystallized from ethyl acetate at room temperature. The X-ray structure has been determined for this compound.

3.14 Representative procedure for synthesis of compound 103

To an oven dried Schlenk tube was added 2-iodo-4,*N*-dimethyl-*N*-phenylethynyl-benzenesulfonamide **5a** (0.24 mmol), $PdCl_2(PPh_3)_2$ (5 mol %), cyanoethyl acetate **10a** (0.29 mmol), NaOH (0.96 mmol) and dry DMSO (1 mL). The contents were sealed under nitrogen atmosphere and heated at 70 ^{o}C (oil bath temperature) overnight. After completion of the reaction as monitored by TLC, the crude reaction mixture was cooled to rt, diluted with ethyl acetate (20 mL) and washed with water. The aqueous layer was extracted twice with ethyl acetate (20 mL). The combined organic layer was washed with brine solution, dried over anh. sodium sulfate and concentrated in vacuum. The residue was then purified by using silica gel column chromatography using hexane-ethyl acetate (4:1) as the eluent to afford 1,2-benzothiazine 1,1-dioxide **103**. Compounds **104-109** were prepared following same procedure with same molar quantities.

Compound 103



Yield: 0.07 g (72%).

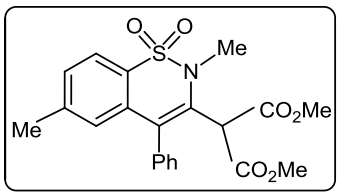
IR (neat): 3058, 2992, 2926, 2252, 1742, 1589, 1474, 1348, 1260, 1189, 937, 734 cm^{-1}.

^{1}H NMR: δ 7.83 (d, *J* = 8.0 Hz, 1H), 7.58-7.53 (m, 3H), 7.41 (t, *J* = 8.0 Hz, 2H), 7.35-7.33 (m, 1H), 6.72 (s, 1H), 4.63 (s, 1H), 4.35-4.30 (m, 2H), 3.32 (s, 3H), 2.33 (s, 3H), 1.35 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR: δ 163.5, 142.9, 134.7, 133.1, 131.8, 130.5, 130.4, 130.1, 129.9, 129.8, 129.4_3, 129.3_7, 129.0, 122.5, 114.2, 64.0, 41.4, 35.0, 21.8, 13.9.

HRMS (ESI): Calcd. for $C_{21}H_{20}N_2O_4SNa$ (M^+ + Na): *m/z* 419.1042, Found: 419.1046.

Compound 104



Yield: 0.065 g (64%).

Mp: 120-122 ^{o}C.

IR (KBr): 2953, 2926, 1758, 1736, 1594, 1446, 1336, 1293, 1183, 1029, 936, 734 cm^{-1}.

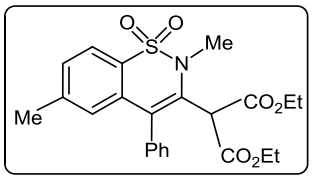
^{1}H NMR: δ 7.81 (d, *J* = 8.0 Hz, 1H), 7.49-7.48 (m, 3H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.27-7.25 (m, 2H), 6.67 (s, 1H), 4.48 (s, 1H), 3.80 (s, 6H), 3.21 (s, 3H), 2.31 (s, 3H).

^{13}C NMR: δ 167.6, 142.5, 135.7, 133.8, 132.5, 131.6, 130.2, 129.8, 129.1, 128.8, 128.7, 122.5, 55.9, 53.1, 35.4, 21.8.

HRMS (ESI): Calcd. for $C_{21}H_{21}NO_6SNa$ (M^+ + Na): *m/z* 438.0988, Found: 438.0989.

This compound was crystallized from ethyl acetate/hexane (2:1) mixture at room temperature. The X-ray structure has been determined for this compound.

Compound 105



Yield: 0.067 g (62%).

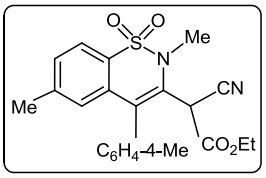
IR (neat): 2981, 2926, 1737, 1595, 1468, 1348, 1178, 1025, 937, 745 cm^{-1}.

^{1}H NMR: δ 7.81 (d, *J* = 7.6 Hz, 1H), 7.49-7.47 (m, 3H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.27-7.25 (m, 2H), 6.67 (s, 1H), 4.44 (s, 1H), 4.34-4.20 (m, 4H), 3.23 (s, 3H), 2.31 (s, 3H), 1.31 (t, *J* = 7.2 Hz, 6H).

^{13}C NMR: δ 167.2, 142.4, 135.8, 133.8, 132.9, 131.1, 130.1, 129.9, 129.7, 129.0, 128.7, 128.6, 122.4, 62.3, 56.2, 35.4, 21.7, 14.0.

HRMS (ESI): Calcd. for $C_{23}H_{25}NO_6SNa$ (M^+ + Na): *m/z* 466.1301, Found: 466.1305.

Compound 106



Yield: 0.073 g (72%).

Mp: 150-152 ^{o}C.

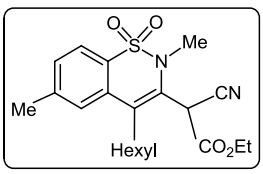
IR (KBr): 3003, 2926, 2252, 1753, 1595, 1468, 1342, 1184, 1041, 751 cm^{-1}.

^{1}H NMR: δ 7.82 (d, *J* = 8.0 Hz, 1H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.34-7.29 (m, 2H), 7.21 (d, *J* = 7.6 Hz, 1H), 6.76 (s, 1H), 4.67 (s, 1H), 4.35-4.30 (m, 2H), 3.30 (s, 3H), 2.48 (s, 3H), 2.33 (s, 3H), 1.34 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR: δ 163.6, 142.9, 139.4, 133.3, 131.9, 131.6, 130.4, 130.1_2, 130.0_6, 129.9, 129.7_3, 129.6_8, 129.1, 122.5, 114.3, 63.9, 41.5, 35.1, 21.7, 21.4, 13.9.

HRMS (ESI): Calcd. for $C_{22}H_{22}N_2O_4SNa$ (M^+ + Na): *m/z* 433.1198, Found: 433.1201.

Compound 107



Yield: 0.056 g (58%).

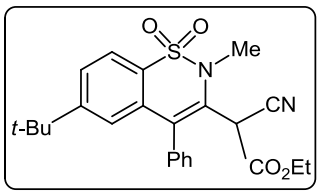
IR (neat): 2932, 2849, 1748, 1595, 1463, 1348, 1178, 1019, 822, 679 cm^{-1}.

^{1}H NMR: δ 7.77 (d, *J* = 8.4 Hz, 1H), 7.42-7.40 (m, 2H), 4.91 (s, 1H), 4.39-4.33 (m, 2H), 3.04 (s, 3H), 2.80-2.63 (m, 2H), 2.51 (s, 3H), 1.63-1.48 (m, 2H), 1.43-1.41 (m, 2H), 1.36 (t, *J* = 7.2 Hz, 3H), 1.31-1.27 (m, 4H), 0.89 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR: δ 163.5, 143.1, 132.2, 131.4, 131.0, 130.4, 129.0, 126.5, 123.6, 114.2, 64.0, 40.4, 35.8, 31.5, 29.1, 28.9, 28.6, 22.5, 22.0, 14.0, 13.9.

HRMS (ESI): Calcd. for $C_{21}H_{28}N_2O_4SNa$ (M^+ + Na): *m/z* 427.1668, Found: 427.1669.

Compound 108



Yield: 0.08 g (76%).

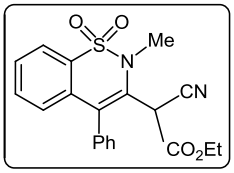
IR (neat): 3063, 2964, 2932, 2099, 1748, 1589, 1458, 1342, 1266, 1195, 937, 740 cm^{-1}.

^{1}H NMR: δ 7.87 (d, *J* = 8.4 Hz, 1H), 7.63-7.53 (m, 4H), 7.43 (d, *J* = 7.6 Hz, 1H), 7.36-7.34 (m, 1H), 6.93-6.92 (m, 1H), 4.67 (s, 1H), 4.37-4.30 (m, 2H), 3.34 (s, 3H), 1.35 (t, *J* = 7.2 Hz, 3H), 1.20 (s, 9H).

^{13}C NMR: δ 163.5, 155.9, 134.7, 132.9, 132.1, 130.3, 130.0, 129.9, 129.5, 129.3_7, 129.3_6, 127.0, 125.7, 122.2, 114.3, 63.9, 41.5, 35.2, 35.1, 30.9, 13.9.

HRMS (ESI): Calcd. for $C_{24}H_{26}N_2O_4SNa$ (M^+ + Na): *m/z* 461.1511, Found: 461.1515.

Compound 109



Yield: 0.050 g (52%).

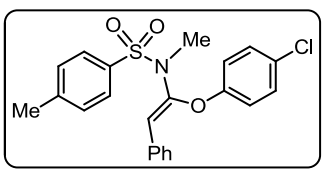
IR (neat): 3063, 2980, 2920, 2361, 1747, 1588, 1462, 1353, 1260, 1188, 931, 734 cm^{-1}.

^{1}H NMR: δ 7.95 (d, *J* = 7.6 Hz, 1H), 7.62-7.51 (m, 5H), 7.42 (d, *J* = 7.2 Hz, 1H), 7.35-7.34 (m, 1H), 6.97 (d, *J* = 7.6 Hz, 1H),, 4.67 (s, 1H), 4.36-4.31 (m, 2H), 3.34 (s, 3H), 1.35 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR: δ 163.4, 134.6, 133.1, 132.9, 132.1, 131.7, 130.5, 130.1, 129.9, 129.7, 129.5, 129.4, 129.0, 128.8, 122.4, 114.1, 64.0, 41.4, 35.0, 21.8, 13.9.

HRMS (ESI): Calcd. for $C_{20}H_{18}N_2O_4SNa$ (M^+ + Na): *m/z* 405.0885, Found: 405.0879.

Compound 110



Yield: 0.076 g (76%).

IR (neat): 3063, 2959, 1655, 1595, 1490, 1452, 1342, 1211, 1151, 1079, 964, 827, 756, 663 cm^{-1}.

^1H NMR: δ 7.69 (d, *J* = 8.4 Hz, 2H), 7.39-7.37 (m, 2H), 7.32-7.28 (m, 5H), 7.09-7.06 (m, 2H), 6.93 (s, 1H), 6.73-6.71 (m, 2H), 3.16 (s, 3H), 2.47 (s, 3H).

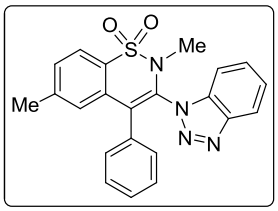
^{13}C NMR: δ 155.6, 144.0, 138.9, 135.2, 134.0, 129.8, 129.5, 128.7, 128.2, 127.0_5, 126.9_7, 125.0, 117.0, 116.2, 35.4, 21.6.

HRMS (ESI): Calcd. for $C_{22}H_{20}ClNO_3SNa$ (M^+ + Na): *m/z* 436.0750, Found: 436.0748.

3.15. Synthesis of benzotriazole/triazole appended benzosultams: Representative procedure for synthesis of compound 111

To an oven dried Schlenk tube was added ynamide **5** (0.24 mmol), $PdCl_2(PPh_3)_2$ (5 mol%), benzotriazole/triazole **11/12** (0.29 mmol), KO^{t}Bu (0.48 mmol) and dry THF (1 mL). The contents were sealed under nitrogen atmosphere and stirred at 70 ^oC (oil bath temperature) overnight. After completion of the reaction as monitored by TLC, the crude reaction mixture was passed through a pad of celite and washed with ethyl acetate (20 mL) and concentrated in vacuum. The residue was then purified by using silica gel column chromatography using hexane-ethyl acetate (9:1) as the eluent to afford benzosultams **111-123**.

Compound 111



Yield: 0.080 g (82%).

Mp: 140-142 ^oC.

IR (KBr): 3057, 2920, 1594, 1468, 1342, 1276, 1183, 1051, 947, 876, 734 cm^{-1}.

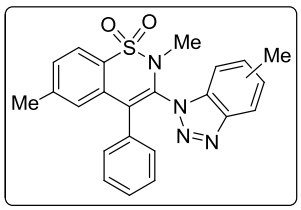
^1H NMR: δ 7.95 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.93 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.82 (d, *J* = 8.5 Hz, 1H, Ar-*H*), 7.50 (t, *J* = 8.0 Hz, 1H, Ar-*H*), 7.46 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.36-7.33 (m, 3H, Ar-*H*), 7.21-7.18 (m, 3H, Ar-*H*), 7.04 (s, 1H, Ar-*H*), 2.90 (s, 3H, NCH_3), 2.36 (s, 3H, Ar-CH_3).

^{13}C NMR: δ 145.1, 143.3, 133.9, 132.9, 132.3, 130.7, 130.2, 129.2, 129.1, 128.5, 128.2, 127.4, 122.4, 119.9, 110.5, 32.8 (N*C*H_3), 21.8 (Ar-*C*H_3).

HRMS (ESI): Calcd. for $C_{22}H_{18}N_4O_2SNa$ (M^+ + Na): *m/z* 425.1048, Found: 425.1048.

The yield using the bromo precursor **5p** was 0.066 g (68%). This compound was crystallized from chloroform at room temperature. X-ray structure has been determined for this compound.

Compound 112



Yield: 0.078 g (78%).

Mp: 184-186 ^{o}C.

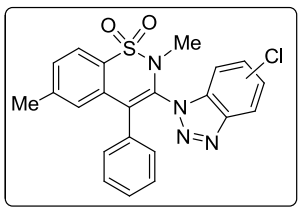
IR (KBr): 3046, 2920, 1629, 1474, 1350, 1288, 1180, 1040, 958, 880, 798 cm^{-1}.

^{1}H NMR: δ 7.93 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 7.83 (d, *J* = 8.5 Hz, 1H, Ar-*H*), 7.72 - 7.68 (m, 2H, Ar-*H*), 7.57 (s, 1H, Ar-*H*), 7.47 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 7.35-7.33 (m, 5H, Ar-*H*), 7.21-7.17 (m, 7H, Ar-*H*), 7.05 (br s, 2H, Ar-*H*), 2.90 (s, 6H, 2 NC*H*$_3$), 2.51 (s, 3H, Ar-C*H*$_3$), 2.47 (s, 3H, Ar-C*H*$_3$), 2.38 (s, 6H, 2 Ar-C*H*$_3$).

^{13}C NMR: δ 145.7, 143.7, 143.2, 140.1, 134.9, 134.4, 133.0, 132.9, 132.4$_3$, 132.3$_9$, 131.2, 130.9, 130.8, 130.6, 130.5, 130.3, 130.2, 129.1$_4$, 129.1$_1$, 128.5, 128.1, 127.1, 127.0, 122.3, 119.3, 118.9, 110.0, 109.6, 32.8 (N*C*H$_3$), 32.7 (N*C*H$_3$), 22.0 (Ar-*C*H$_3$), 21.8 (2 Ar-*C*H$_3$), 21.4 (Ar-*C*H$_3$).

HRMS (ESI): Calcd. for $C_{23}H_{21}N_4O_2S$ (M^+ + H): *m/z* 417.1385, Found: 417.1387.

Compound 113



Yield: 0.065 g (62%).

Mp: 178-180 ^{o}C.

IR (KBr): 3055, 2915, 1624, 1469, 1345, 1283, 1180, 1056, 937, 813, 746 cm^{-1}.

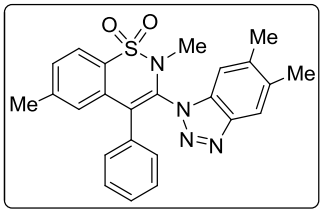
^{1}H NMR: δ 7.96-7.95 (m, 2H, Ar-*H*), 7.93$_4$-7.93$_1$ (m, 1H, Ar-*H*), 7.89 (d, *J* = 8.5 Hz, 1H, Ar-*H*), 7.81$_0$-7.80$_7$ (m, 1H, Ar-*H*), 7.76 (d, *J* = 9.0 Hz, 1H, Ar-*H*), 7.50 (s, 1H, Ar-*H*), 7.49-7.47 (m, 2H, Ar-*H*), 7.34-7.30 (m, 5H, Ar-*H*), 7.24-

7.22 (m, 6H, Ar-*H*), 7.04 (br s, 2H, Ar-*H*), 2.94 (s, 3H, NCH_3), 2.93 (s, 3H, NCH_3), 2.40 (s, 6H, 2 Ar-CH_3).

^{13}C NMR: δ 145.7, 143.7, 143.4$_0$, 143.3$_6$, 135.7, 134.5, 132.7, 132.6, 132.1, 132.0, 130.9, 130.8, 130.7$_3$, 130.7$_0$, 130.6$_7$, 130.3, 130.1, 130.0$_5$, 129.9$_8$, 129.3$_4$, 129.2$_9$, 128.7$_2$, 128.6$_7$, 128.2, 128.1, 126.1, 122.5$_0$, 122.4$_8$, 120.8, 119.3, 111.5, 110.3, 33.1 (N*C*H$_3$), 33.0 (N*C*H$_3$), 21.8 (2 Ar-*C*H$_3$).

HRMS (ESI): Calcd. for $C_{22}H_{17}ClN_4O_2SNa$ (M^+ + Na): *m/z* 459.0659, Found: 459.0657.

Compound 114



Yield: 0.083 g (80%).

Mp: 222-224 ^{o}C.

IR (KBr): 3055, 2946, 1596, 1474, 1345, 1263, 1180, 1056, 901, 849, 736 cm^{-1}.

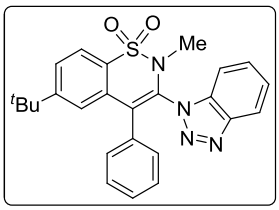
^{1}H NMR: δ 7.92 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.69 (s, 1H, Ar-*H*), 7.56 (s, 1H, Ar-*H*), 7.45 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.36-7.35 (m, 2H, Ar-*H*), 7.21-7.20 (m, 3H, Ar-*H*), 7.05 (s, 1H, Ar-*H*), 2.88 (s, 3H, NCH_3), 2.40 (s, 3H, Ar-CH_3), 2.38 (s, 3H, Ar-CH_3), 2.35 (s, 3H, Ar-CH_3).

^{13}C NMR: δ 144.3, 143.2, 139.7, 134.6, 133.0, 132.9, 132.5, 131.0, 130.5, 130.4, 130.3, 129.1, 128.4, 128.1, 126.7, 122.3, 119.0, 109.8, 32.7 (N*C*H$_3$), 21.8 (Ar-*C*H$_3$), 21.0 (Ar-*C*H$_3$), 20.4 (Ar-*C*H$_3$).

HRMS (ESI): Calcd. for $C_{24}H_{23}N_4O_2S$ (M^+ + H): *m/z* 431.1541, Found: 431.1541.

This compound was crystallized from dichloromethane at room temperature. X-ray structure has been determined for this compound.

Compound 115



Yield: 0.085 g (80%).

Mp: 178-180 ^{o}C.

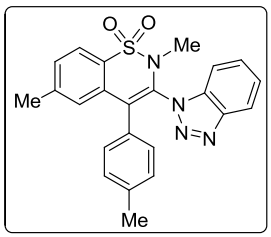
IR (KBr): 3065, 2972, 1588, 1479, 1350, 1263, 1180, 1040, 947, 884, 741, 632 cm^{-1}.

^{1}H NMR: δ 7.98 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.83 (d, *J* = 8.5 Hz, 1H, Ar-*H*), 7.71 (dd, *J* = 8.5 Hz, *J* = 2.0 Hz, 1H, Ar-*H*), 7.53 (t, *J* = 8.0 Hz, 1H, Ar-*H*), 7.39-7.33 (m, 3H, Ar-*H*), 7.27_2-7.26_9 (m, 1H, Ar-*H*), 7.26-7.20 (m, 3H, Ar-*H*), 2.92 (s, 3H, NCH_3), 1.25 (s, 9H, C(CH_3)$_3$).

^{13}C NMR: δ 156.2, 145.1, 133.9, 132.7, 132.4, 130.1, 129.1, 128.5, 128.1, 127.8, 127.2, 125.8, 124.7, 122.1, 119.9, 110.5, 35.3 (*C*(CH$_3$)$_3$), 32.8 (N*C*H$_3$), 31.0 (C(*C*H$_3$)$_3$).

HRMS (ESI): Calcd. for $C_{25}H_{25}N_4O_2S$ (M^+ + H): *m/z* 445.1698, Found: 445.1697.

Compound 116



Yield: 0.078 g (79%).

Mp: 196-198 ^{o}C.

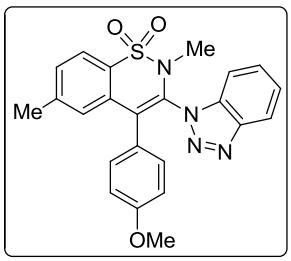
IR (KBr): 3055, 2921, 1598, 1448, 1350, 1257, 1185, 1046, 953, 891, 746 cm^{-1}.

^{1}H NMR: δ 7.98 (d, *J* = 8.5 Hz, 1H, Ar-*H*), 7.93 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.83-7.81 (m, 1H, Ar-*H*), 7.54-7.51 (m, 1H, Ar-*H*), 7.48-7.46 (m, 1H, Ar-*H*), 7.37 (t, *J* = 7.5 Hz, 1H, Ar-*H*), 7.22 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 7.06 (s, 1H, Ar-*H*), 7.01 (d, *J* = 7.5 Hz, 2H, Ar-*H*), 2.90 (s, 3H, NCH_3), 2.39 (s, 3H, Ar-CH_3), 2.23 (s, 3H, Ar-CH_3).

^{13}C NMR: δ 145.1, 143.2, 138.3, 134.0, 133.1, 130.7, 130.6, 130.1, 129.3, 129.0, 128.9, 127.7, 124.7, 122.3, 119.8, 110.6, 32.9 (N*C*H$_3$), 21.8 (Ar-*C*H$_3$), 21.2 (Ar-*C*H$_3$).

HRMS (ESI): Calcd. for $C_{23}H_{21}N_4O_2S$ (M^+ + H): *m/z* 417.1385, Found: 417.1384.

Compound 117



Yield: 0.087 g (84%).

Mp: 168-170 ^{o}C.

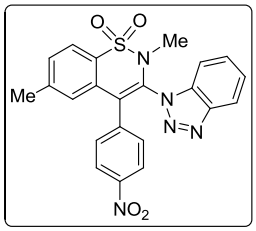
IR (KBr): 2952, 2921, 1598, 1464, 1350, 1247, 1180, 1061, 953, 818, 746 cm^{-1}.

^{1}H NMR: δ 7.99 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.92 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.80 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.51 (t, *J* = 8.0 Hz, 1H, Ar-*H*), 7.47 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.37 (t, *J* = 7.5 Hz, 1H, Ar-*H*), 7.26 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 7.05 (s, 1H, Ar-*H*), 6.73 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 3.71 (s, 3H, Ar-OC*H*$_3$), 2.90 (s, 3H, NC*H*$_3$), 2.39 (s, 3H, Ar-C*H*$_3$).

^{13}C NMR: δ 159.5, 145.1, 143.2, 133.9, 133.3, 131.5, 130.7, 130.6, 130.5, 129.4, 129.1, 127.5, 124.8, 124.3, 122.3, 119.8, 113.6, 110.6, 55.1 (Ar-O*C*H$_3$), 32.9 (N*C*H$_3$), 21.8 (Ar-*C*H$_3$).

HRMS (ESI): Calcd. for $C_{23}H_{21}N_4O_3S$ (M^+ + H): *m/z* 433.1334, Found: 433.1332.

Compound 118



Yield: 0.081 g (76%).

Mp: 236-238 ^{o}C.

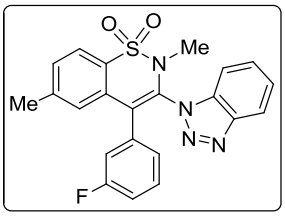
IR (KBr): 3070, 2957, 1598, 1448, 1340, 1273, 1190, 1066, 958, 849, 746 cm^{-1}.

^{1}H NMR: δ 8.09 (d, *J* = 9.0 Hz, 2H, Ar-*H*), 7.99 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.95 (d, *J* = 8.5 Hz, 1H, Ar-*H*), 7.84 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.59-7.56 (m, 3H, Ar-*H*), 7.52 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.41 (t, *J* = 8.0 Hz, 1H, Ar-*H*), 6.95 (s, 1H, Ar-*H*), 2.90 (s, 3H, NC*H*$_3$), 2.41 (s, 3H, Ar-C*H*$_3$).

^{13}C NMR: δ 147.9, 145.2, 143.7, 139.3, 133.7, 131.8, 131.6$_4$, 131.5$_6$, 131.0, 130.5, 129.7, 128.5, 125.2, 124.3, 123.4, 122.6, 120.2, 110.2, 32.7 (N*C*H$_3$), 21.8 (Ar-*C*H$_3$).

HRMS (ESI): Calcd. for $C_{22}H_{18}N_5O_4S$ (M^+ + H): *m/z* 448.1079, Found: 448.1079.

Compound 119



Yield: 0.071 g (70%).

Mp: 162-164 ^{o}C.

IR (KBr): 3070, 2931, 1578, 1490, 1345, 1283, 1175, 1056, 978, 844, 746 cm^{-1}.

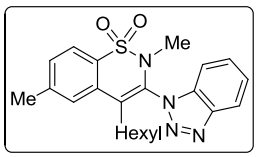
^{1}H NMR: δ 7.99 (d, *J* = 8.5 Hz, 1H, Ar-*H*), 7.94 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.83 (d, *J* = 8.5 Hz, 1H, Ar-*H*), 7.55 (t, *J* = 7.5 Hz, 1H, Ar-*H*), 7.49 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.39 (t, *J* = 7.5 Hz, 1H, Ar-*H*), 7.20-7.17 (m, 1H, Ar-*H*), 7.15-7.13 (m, 1H, Ar-*H*), 7.08 (d, *J* = 9.5 Hz, 1H, Ar-*H*), 7.03 (s, 1H, Ar-*H*), 6.91 (t, *J* = 7.5 Hz, 1H, Ar-*H*), 2.89 (s, 3H, NC*H*$_3$), 2.41 (s, 3H, Ar-C*H*$_3$).

^{13}C NMR: δ 162.1 (d, *J* = 246.0 Hz), 145.2, 143.4, 134.4 (d, *J* = 9.0 Hz), 133.8, 132.4, 131.1, 130.8, 130.6, 129.8 (d, *J* = 9.0 Hz), 129.3, 128.9, 126.2, 125.7, 124.9, 122.4, 120.0, 117.5 (d, *J* = 22.0 Hz), 115.7 (d, *J* = 20.0 Hz), 110.4, 32.7 (N*C*H$_3$), 21.8 (Ar-*C*H$_3$).

HRMS (ESI): Calcd. for $C_{22}H_{18}FN_4O_2S$ (M^+ + H): *m/z* 421.1134, Found: 421.1134.

This compound was crystallized from dichloromethane at room temperature. X-ray structure has been determined for this compound.

Compound 120



Yield: 0.074 g (76%).

Mp: 96-98 ^{o}C.

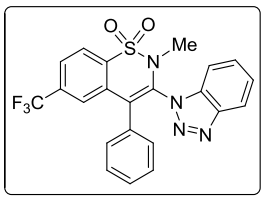
IR (KBr): 2926, 2849, 1627, 1452, 1342, 1264, 1189, 1058, 822, 756 cm^{-1}.

^{1}H NMR: δ 8.16 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.97 (d, *J* = 8.5 Hz, 1H, Ar-*H*), 7.89 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.63 (t, *J* = 8.0 Hz, 1H, Ar-*H*), 7.59 (s, 1H, Ar-*H*), 7.52-7.48 (m, 2H, Ar-*H*), 2.72 (s, 3H, NC*H*$_3$), 2.60-2.58 (m, 2H, C*H*$_2$), 2.56 (s, 3H, Ar-C*H*$_3$), 1.41 (t, *J* = 7.0 Hz, 2H, C*H*$_2$), 1.04-1.01 (m, 4H, 2 C*H*$_2$), 0.94-0.92 (m, 2H, C*H*$_2$), 0.66 (t, *J* = 7.0 Hz, 3H, C*H*$_3$).

^{13}C NMR: δ 145.7, 143.3, 134.2, 131.9, 131.4, 130.7, 130.4, 129.3, 127.1, 125.6, 125.1, 123.1, 120.0, 111.2, 33.3 (N*C*H$_3$), 31.1, 28.5, 28.3, 27.0, 22.3, 22.0 (Ar-*C*H$_3$).

HRMS (ESI): Calcd. for $C_{22}H_{27}N_4O_2S$ (M^+ + H): *m/z* 411.1854, Found: 411.1855.

Compound 121



Yield: 0.05 g (46%).

Mp: 144-146 ^{o}C.

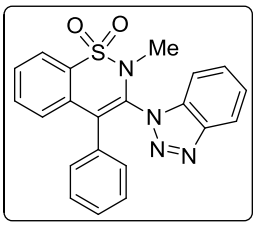
IR (KBr): 3060, 2957, 1619, 1412, 1345, 1263, 1139, 1087, 942, 808 cm^{-1}.

^{1}H NMR: δ 8.19 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 8.00 (d, *J* = 8.5 Hz, 1H, Ar-*H*), 7.94 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.79 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.57-7.55 (m, 2H, Ar-*H*), 7.40 (t, *J* = 8.0 Hz, 1H, Ar-*H*), 7.35 -7.34 (m, 2H, Ar-*H*), 7.25-7.24 (m, 3H, Ar-*H*), 2.96 (s, 3H, NC*H*$_3$).

^{13}C NMR: δ 145.2, 135.6, 134.4 (*J* = 34.0 Hz), 133.8 (*J* = 16.0 Hz), 131.8, 131.3, 130.1, 129.4, 129.1, 128.5, 126.4, 125.9$_2$, 125.8$_9$, 125.0, 123.3, 123.0 (d, *J* = 272.0 Hz), 120.1, 110.2, 32.9 (N*C*H$_3$).

HRMS (ESI): Calcd. for $C_{23}H_{16}F_3N_4O_2S$ (M^+ + H): *m/z* 457.0946, Found: 457.0947.

Compound 122



Yield: 0.067 g (72%).

Mp: 172-174 ^{o}C.

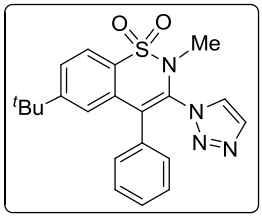
IR (KBr): 2921, 2855, 1622, 1468, 1342, 1282, 1167, 1063, 932, 751 cm^{-1}.

^{1}H NMR: δ 8.05 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.97 (d, *J* = 8.5 Hz, 1H, Ar-*H*), 7.82 (d, *J* = 8.5 Hz, 1H, Ar-*H*), 7.67 (t, *J* = 8.0 Hz, 1H, Ar-*H*), 7.61 (t, *J* = 8.0 Hz, 1H, Ar-*H*), 7.52 (t, *J* = 8.0 Hz, 1H, Ar-*H*), 7.38 -7.33 (m, 3H, Ar-*H*), 7.29-7.27 (m, 1H, Ar-*H*), 7.21-7.19 (m, 3H, Ar-*H*), 2.93 (s, 3H, NC*H*$_3$).

^{13}C NMR: δ 145.1, 133.9, 133.1, 132.9, 132.4, 132.2, 130.6, 129.8, 129.2, 129.0, 128.6, 128.2, 127.4, 124.8, 122.3, 119.9, 110.5, 32.9 (N*C*H$_3$).

HRMS (ESI): Calcd. for $C_{21}H_{16}N_4O_2SNa$ (M^+ + Na): *m/z* 411.0892, Found: 411.0895.

Compound 123



Yield: 0.061 g (64%).

Mp: 220-222 ^{o}C.

IR (KBr): 3115, 2967, 1629, 1445, 1345, 1261, 1187, 1086, 1000, 805 cm^{-1}.

^{1}H NMR: δ 7.94 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.68 (dd, *J* = 8.5 Hz, *J* = 2.0 Hz, 1H, Ar-*H*), 7.65_4-7.65_2 (m, 1H, Ar-*H*), 7.61_8-7.61_6 (m, 1H, Ar-*H*), 7.33-7.28 (m, 5H, Ar-*H*), 7.23_9-7.23_6 (m, 1H, Ar-*H*), 3.02 (s, 3H, NCH_3), 1.24 (s, 9H, C(CH_3)$_3$).

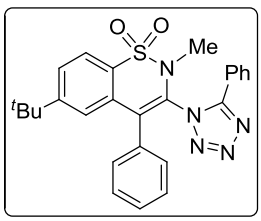
^{13}C NMR: δ 156.3, 133.7, 132.3_3, 132.3_1, 130.4, 130.1, 128.7, 128.3, 127.2, 126.4, 125.8, 125.7, 122.2, 35.3 (*C*(CH$_3$)$_3$), 33.2 (N*C*H$_3$), 30.9 (C(*C*H$_3$)$_3$).

HRMS (ESI): Calcd. for $C_{21}H_{23}N_4O_2S$ (M^+ + H): *m/z* 395.1541, found: 395.1539.

3.16 Representative procedure for the synthesis of tetrazole appended benzosultams 124-125

To an oven dried Schlenk tube was added ynamide **5b** (0.24 mmol), $PdCl_2(PPh_3)_2$ (5 mol%), tetrazole **13a-b** (0.29 mmol), KO^{t}Bu (0.48 mmol) and dry acetonitrile (1 mL). The contents were sealed under nitrogen atmosphere and stirred at 70 ^{o}C (oil bath temperature) overnight. After completion of the reaction as monitored by TLC, the crude reaction mixture was passed through a pad of celite and washed with ethyl acetate (20 mL) and concentrated in vacuum. The residue was then purified by using silica gel column chromatography using hexane-ethyl acetate (9:1) as the eluent to afford benzosultams **124-125**.

Compound 124



Yield: 0.047 g (42%).

Mp: 104-106 ^{o}C.

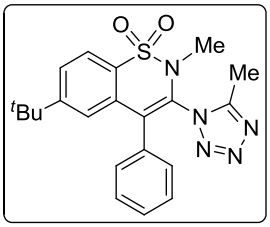
IR (KBr): 3055, 2957, 1614, 1464, 1345, 1278, 1190, 1113, 1077, 947, 694 cm^{-1}.

^{1}H NMR: δ 7.98 (d, *J* = 8.5 Hz, 1H, Ar-*H*), 7.77-7.75 (m, 2H, Ar-*H*), 7.70 (dd, *J* = 8.5 Hz, *J* = 2.0 Hz, 1H, Ar-*H*), 7.52-7.49 (m, 1H, Ar-*H*), 7.44-7.41 (m, 2H, Ar-*H*), 7.26-7.23 (m, 1H, Ar-*H*), 7.14 (t, *J* = 7.5 Hz, 2H, Ar-*H*), 7.05 -7.04 (m, 1H, Ar-*H*), 6.79 (br s, 2H, Ar-*H*), 3.28 (s, 3H, NCH_3), 1.18 (s, 9H, C(CH_3)$_3$).

^{13}C NMR: δ 156.5, 155.7, 132.0, 131.9, 131.5, 129.9, 129.4, 128.8$_8$, 128.8$_6$, 128.7, 128.5, 127.7, 127.3, 125.7, 122.2, 122.1, 35.3 (*C*(CH$_3$)$_3$), 33.6 (N*C*H$_3$), 30.9 (C(*C*H$_3$)$_3$).

HRMS (ESI): Calcd. for $C_{26}H_{26}N_5O_2S$ (M^+ + H): *m/z* 472.1807, Found: 472.1812.

Compound 125



Yield: 0.055 g (56%).

Mp: 146-148 ^{o}C.

IR (KBr): 3060, 2962, 1619, 1392, 1345, 1273, 1185, 1071, 953, 736 cm^{-1}.

^{1}H NMR: δ 7.95 (d, *J* = 8.5 Hz, 1H, Ar-*H*), 7.72 (dd, *J* = 8.5 Hz, *J* = 2.0 Hz, 1H, Ar-*H*), 7.34-7.29 (m, 3H, Ar-*H*), 7.20-7.18 (m, 2H, Ar-*H*), 7.13$_3$-7.12$_9$ (m, 1H, Ar-*H*), 3.07 (s, 3H, NCH_3), 2.40 (s, 3H, Ar-CH_3), 1.22 (s, 9H, C(CH_3)$_3$).

^{13}C NMR: δ 156.6, 153.9, 131.8, 131.5, 130.8, 130.5, 129.6, 129.4, 128.8, 128.0, 127.4, 126.3, 122.5, 35.4 (*C*(CH$_3$)$_3$), 33.7 (N*C*H$_3$), 30.9 (C(*C*H$_3$)$_3$), 8.4 (Ar-*C*H$_3$).

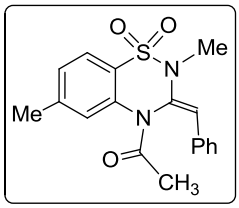
HRMS (ESI): Calcd. for $C_{21}H_{24}N_5O_2S$ (M^+ + H): *m/z* 410.1650, Found: 410.1649.

3.17 Procedure for the synthesis of benzosultam 126

To an oven dried Schlenk tube was added ynamide **5b** (0.24 mmol), CuI (10 mol%), *N, N'* DMEDA (20 mol%), acetamide (0.29 mmol), K_3PO_4 (0.48 mmol) and dry THF (1 mL). The contents were sealed under nitrogen atmosphere and stirred at 80 ^{o}C (oil bath temperature) overnight. After consumption of the starting material as monitored by TLC, the crude reaction mixture was passed through a pad of celite and washed with ethyl

acetate (20 mL) and concentrated in vacuum. The residue was then purified by using silica gel column chromatography using hexane-ethyl acetate (9:1) as the eluent to afford benzosultam **126**.

Compound 126



Yield: 0.030 g (36%).

Mp: 168-170 ^{o}C.

^{1}H NMR (400 MHz): δ 7.73 (d, *J* = 8.0 Hz, 1H), 7.69 (s, 1H), 7.43-7.38 (m, 4H), 7.30-7.27 (m, 2H), 5.89 (s, 1H), 3.26 (s, 3H), 2.55 (s, 3H), 2.10 (s, 3H).

^{13}C NMR (400 MHz): δ 169.8, 144.3, 136.8, 136.0, 134.3, 132.3, 129.2, 127.9, 127.8, 127.6_1, 127.5_6, 122.8, 108.8, 33.6, 22.0, 21.9.

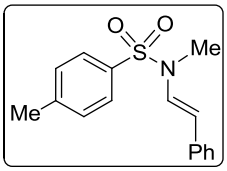
HRMS (ESI): Calcd. for $C_{18}H_{18}N_2O_3SNa$ (M^+ + Na): *m/z* 365.0936, Found: 365.0937.

This compound was crystallized from ethyl acetate–hexane (2:1) mixture at room temperature. X-ray structure has been determined for this compound.

3.18 Synthesis of (*E*)-enamides (127-147) and enamine (149): Representative procedure for synthesis of compound 127

To an oven dried Schlenk tube was added 4,*N*-dimethyl-*N*-phenylethynyl-benzenesulfonamide **5aa** (0.20 mmol), $Pd(PPh_3)_4$ (5 mol%), ethanol (1 mL) and Et_3N (0.60 mmol). The tube was sealed under nitrogen atmosphere and heated at 90 ^{o}C (oil bath temperature) overnight. After completion of the reaction as monitored by TLC, the crude mixture was cooled to room temperature. The mixture was then passed through celite, washed with ethyl acetate (20 mL) and concentrated in vacuum. The residue was then purified by using silica gel column chromatography using hexane-ethyl acetate (9:1) as the eluent to afford (*E*)-*N*,4-dimethyl-*N*-styrylbenzenesulfonamide **127**. Compounds **128-147** and **149** were prepared following the same procedure and the same molar quantities.

Compound 127



Yield: 0.053 g (92%).

Mp: 104-106 ^{o}C.

IR (KBr): 3065, 2921, 1645, 1593, 1454, 1319, 1159, 1087, 968, 818, 762, 669 cm^{-1}.

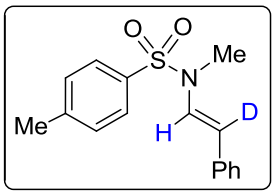
^{1}H NMR: δ 7.70 (d, *J* = 8.5 Hz, 2H), 7.55 (d, *J* = 14.5 Hz, 1H), 7.33-7.32 (m, 6H), 7.23-7.19 (m, 1H), 5.71 (d, *J* = 14.5 Hz, 1H), 3.03 (s, 3H), 2.43 (s, 3H).

^{13}C NMR: δ 144.0, 136.4, 134.6, 129.9, 128.7, 128.2, 127.0, 126.5, 125.5, 110.9, 32.2, 21.6.

HRMS (ESI): Calcd. for $C_{16}H_{17}NO_2SNa$ (M^+ + Na): *m/z* 310.0878. Found: 310.0879.

This compound was crystallized from ethyl acetate–hexane (2 : 1) mixture at room temperature. X-ray structure has been determined for this compound.

Compound 127-d$_1$



This compound was prepared by following the general procedure mentioned for compound **127**. MeOD was used as the solvent instead of EtOH to furnish the compound **127**-d$_1$ in 56% isolated yield (The MeOD addition onto ynamide was also observed, but the product was not isolated). We also performed the reaction using EtOD (ca 60% deuterated sample prepared by hydrolysis of $Si(OEt)_4$ with D_2O) and isolated **127** + **127**-d$_1$ in 90% isolated yield (0.052 g) with ≥50% deuteration.

Yield: 0.052 g (90%).

Mp: 102-104 ^{o}C.

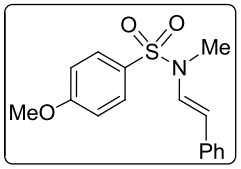
IR (KBr): 3075, 2920, 2257, 1623, 1597, 1449, 1355, 1269, 1159, 1089, 964, 816, 756, 661 cm^{-1}.

^{1}H NMR: δ 7.69 (d, *J* = 8.0 Hz, 2H), 7.54 (s, 1H), 7.33-7.32 (m, 6H), 7.22-7.19 (m, 1H), 3.02 (s, 3H), 2.43 (s, 3H).

^{13}C NMR: δ 144.0, 136.3, 134.7, 129.9, 128.7, 128.1, 127.0, 126.5, 125.5, 110.6 (t, *J* = 24.0 Hz), 32.2, 21.5.

HRMS (ESI): Calcd. for $C_{16}H_{16}DNO_2SNa$ (M^+ + Na): *m/z* 311.0941. Found: 311.0940.

Compound 128



Yield: 0.057 g (94%).

Mp: 68-70 ^{o}C.

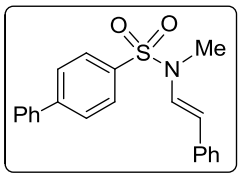
IR (KBr): 3019, 2936, 1640, 1598, 1495, 1356, 1263, 1154, 1092, 978, 808, 756, 689 cm^{-1}.

^{1}H NMR: δ 7.76-7.74 (m, 2H), 7.56 (d, *J* = 14.5 Hz, 1H), 7.33-7.32 (m, 4H), 7.22-7.20 (m, 1H), 7.00-6.98 (m, 2H), 5.71 (d, *J* = 14.5 Hz, 1H), 3.86 (s, 3H), 3.02 (s, 3H).

^{13}C NMR: δ 163.2, 136.4, 129.2, 129.1, 128.8, 128.3, 126.5, 125.5, 114.5, 110.8, 55.7, 32.2.

HRMS (ESI): Calcd. for $C_{16}H_{18}NO_3S$ (M^+ + H): *m/z* 304.1007. Found: 304.1008.

Compound 129



Yield: 0.060 g (86%).

Mp: 130-132 ^{o}C.

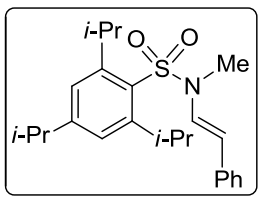
IR (KBr): 3024, 2936, 1640, 1598, 1474, 1361, 1252, 1154, 1087, 968, 674 cm^{-1}.

^{1}H NMR: δ 7.89 (d, *J* = 8.5 Hz, 2H), 7.74 (d, *J* = 8.5 Hz, 2H), 7.64-7.61 (m, 3H), 7.51 (t, *J* = 7.5 Hz, 2H), 7.47-7.44 (m, 1H), 7.36-7.35 (m, 4H), 7.25-7.22 (m, 1H), 5.77 (d, *J* = 14.5 Hz, 1H), 3.10 (s, 3H).

^{13}C NMR: δ 146.0, 139.1, 136.3, 136.1, 129.1, 128.8, 128.7, 128.1, 127.9, 127.6, 127.4, 126.6, 125.6, 111.2, 32.4.

HRMS (ESI): Calcd. for $C_{21}H_{20}NO_2S$ (M^+ + H): *m/z* 350.1214. Found: 350.1216.

Compound 130



Yield: 0.065 g (82%).

Mp: 136-138 ^{o}C.

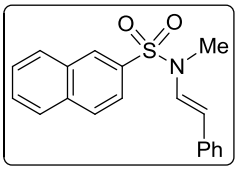
IR (KBr): 2957, 2926, 1640, 1598, 1454, 1314, 1263, 1144, 1035, 762 cm^{-1}.

^{1}H NMR: δ 7.58 (d, *J* = 14.0 Hz, 1H), 7.35-7.31 (m, 4H), 7.25 (br s, 2H), 7.22-7.18 (m, 1H), 5.79 (d, *J* = 14.0 Hz, 1H), 4.20-4.15 (m, 2H), 3.05 (s, 3H); 2.99-2.94 (m, 1H), 1.31 (d, *J* = 6.5 Hz, 6H), 1.29 (d, *J* = 6.5 Hz, 12H).

^{13}C NMR: δ 153.7, 151.4, 136.8, 130.4, 128.7, 127.2, 126.1, 125.4, 124.2, 108.4, 34.2, 31.5, 29.4, 24.9, 23.6.

HRMS (ESI): Calcd. for $C_{24}H_{34}NO_2S$ (M^+ + H): *m/z* 400.2310. Found: 400.2309.

Compound 131



Yield: 0.058 g (90%).

Mp: 74-76 ^{o}C.

IR (KBr): 3050, 2962, 1634, 1588, 1443, 1350, 1257, 1159, 1071, 762 cm^{-1}.

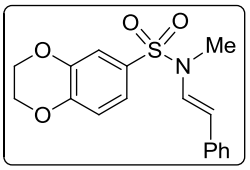
^{1}H NMR: δ 8.45_0-8.44_7 (m, 1H), 8.00 (d, *J* = 8.0 Hz, 1H), 7.97 (d, *J* = 8.5 Hz, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.78 (dd, *J* = 8.5 Hz, 2.0 Hz, 1H), 7.70-7.63 (many lines, 3H), 7.36-7.33 (m, 4H), 7.25-7.21 (m, 1H), 5.75 (d, *J* = 14.5 Hz, 1H), 3.10 (s, 3H).

^{13}C NMR: δ 136.3, 135.0, 134.5, 132.2, 129.7, 129.4, 129.1, 128.8, 128.6, 128.1, 128.0, 127.8, 126.6, 125.6, 122.0, 111.1, 32.4.

HRMS (ESI): Calcd. for $C_{19}H_{17}NO_2SNa$ (M^+ + Na): *m/z* 346.0878. Found: 346.0877.

This compound was crystallized from ethyl acetate–hexane (2 : 1) mixture at room temperature. X-ray structure has been determined for this compound.

Compound 132



Yield: 0.054 g (82%).

Mp: 154-156 ^{o}C.

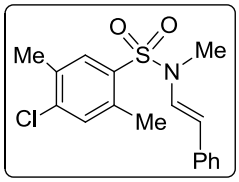
IR (KBr): 3075, 2933, 1640, 1582, 1495, 1355, 1287, 1154, 1064, 970, 758 cm^{-1}.

^{1}H NMR: δ 7.51 (d, *J* = 14.5 Hz, 1H), 7.33-7.28 (m, 6H), 7.21-7.18 (m, 1H), 6.96 (d, *J* = 8.5 Hz, 1H), 5.71 (d, *J* = 14.5 Hz, 1H), 4.31-4.27 (m, 4H), 3.03 (s, 3H).

^{13}C NMR: δ 147.8, 143.7, 136.4, 130.1, 128.7, 128.2, 126.4, 125.5, 120.7, 118.0, 116.6, 110.7, 64.5, 64.2, 32.2.

HRMS (ESI): Calcd. for $C_{17}H_{17}NO_4SNa$ (M^+ + Na): *m/z* 354.0776. Found: 354.0777.

Compound 133



Yield: 0.051 g (76%).

Mp: 82-84 ^{o}C.

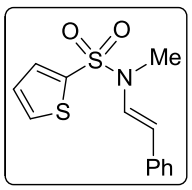
IR (KBr): 3024, 2915, 1645, 1598, 1448, 1335, 1263, 1154, 1082, 751 cm^{-1}.

^{1}H NMR: δ 7.81 (s, 1H), 7.59 (d, *J* = 14.5 Hz, 1H), 7.33-7.31 (m, 5H), 7.23-7.19 (m, 1H), 5.78 (d, *J* = 14.5 Hz, 1H), 3.06 (s, 3H), 2.55 (s, 3H), 2.42 (s, 3H).

^{13}C NMR: δ 139.4, 136.5, 136.3, 134.9, 134.5, 133.2, 131.9, 128.8, 128.0, 126.5, 125.5, 109.3, 32.1, 20.1, 19.6.

HRMS (ESI): Calcd. for $C_{17}H_{18}ClNO_2SNa$ (M^+ + Na): *m/z* 358.0645. Found: 358.0650.

Compound 134



Yield: 0.052 g (93%).

Mp: 120-122 ^{o}C.

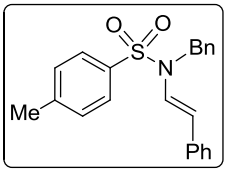
IR (KBr): 3091, 3019, 1645, 1593, 1448, 1356, 1263, 1149, 1092, 963, 756 cm^{-1}.

^{1}H NMR: δ 7.62-7.60 (m, 2H), 7.49 (d, *J* = 14.5 Hz, 1H), 7.34-7.33 (m, 4H), 7.24-7.21 (m, 1H), 7.13-7.11 (m, 1H), 5.80 (d, *J* = 14.5 Hz, 1H), 3.10 (s, 3H).

^{13}C NMR: δ 137.6, 136.1, 132.6, 132.4, 128.8, 127.7, 127.6, 126.8, 125.7, 112.4, 32.5.

HRMS (ESI): Calcd. for $C_{13}H_{13}NO_2S_2Na$ (M^+ + Na): *m/z* 302.0286. Found: 302.0285.

Compound 135



Yield: 0.064 g (88%).

Mp: 110-112 ^{o}C.

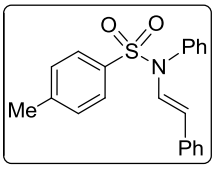
IR (KBr): 3034, 2926, 1645, 1598, 1459, 1361, 1226, 1170, 1092, 942, 777 cm^{-1}.

^{1}H NMR: δ 7.77 (d, *J* = 8.5 Hz, 2H), 7.55 (d, *J* = 14.5 Hz, 1H), 7.40-7.34 (m, 6H), 7.31-7.29 (m, 3H), 7.24-7.23 (m, 2H), 7.19-7.16 (m, 1H), 5.71 (d, *J* = 14.5 Hz, 1H), 4.70 (s, 2H), 2.46 (s, 3H).

^{13}C NMR: δ 144.1, 136.3, 135.9, 135.4, 130.0, 128.7$_2$, 128.6$_6$, 127.6, 127.0, 126.9, 126.6, 126.5, 125.5, 112.2, 49.5, 21.6.

HRMS (ESI): Calcd. for $C_{22}H_{21}NO_2SNa$ (M^+ + Na): *m/z* 386.1191. Found: 386.1191.

Compound 136



Yield: 0.060 g (86%).

Mp: 148-150 ^{o}C.

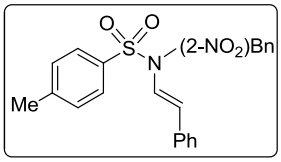
IR (KBr): 3065, 2915, 1634, 1593, 1490, 1366, 1268, 1170, 1087, 973, 818, 746, 663 cm^{-1}.

^{1}H NMR: δ 7.80 (d, *J* = 14.5 Hz, 1H), 7.63 (d, *J* = 8.0 Hz, 2H), 7.46-7.42 (m, 3H), 7.31-7.26 (m, 4H), 7.23-7.20 (m, 2H), 7.18-7.15 (m, 1H), 7.08-7.06 (m, 2H), 5.33 (d, *J* = 14.5 Hz, 1H), 2.46 (s, 3H).

^{13}C NMR: δ 144.1, 136.3, 135.8, 130.3, 129.7, 129.6, 129.5, 129.3, 128.6, 128.3, 127.6, 126.4, 125.4, 111.8, 21.6.

HRMS (ESI): Calcd. for $C_{21}H_{19}NO_2SNa$ (M^+ + Na): *m/z* 372.1034. Found: 372.1035.

Compound 137



Yield: 0.068 g (83%).

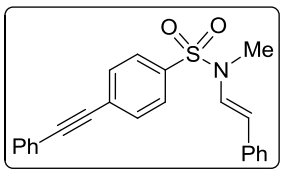
IR (neat): 3079, 2915, 1643, 1598, 1448, 1355, 1165, 1091, 939, 859, 664 cm^{-1}.

^1H NMR: δ 8.17 (dd, *J* = 8.0 Hz, 1.0 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 2H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.67-7.64 (m, 1H), 7.58 (d, *J* = 14.5 Hz, 1H), 7.50-7.46 (m, 1H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.29-7.26 (m, 2H), 7.22-7.21 (m, 2H), 7.19-7.16 (m, 1H), 5.51 (d, *J* = 14.5 Hz, 1H), 5.09 (s, 2H), 2.47 (s, 3H).

^{13}C NMR: δ 147.6, 144.6, 135.8, 135.5, 134.3, 131.6, 130.2, 128.8, 128.7, 128.4, 127.0, 126.7, 126.4, 125.5, 125.3, 111.8, 47.2, 21.6.

HRMS (ESI): Calcd. for $C_{22}H_{20}N_2O_4SNa$ (M^+ + Na): *m/z* 431.1042. Found: 431.1040.

Compound 138



Yield: 0.060 g (80%).

Mp: 122-124 ^oC.

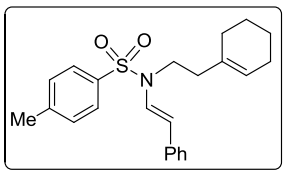
IR (KBr): 3075, 2926, 2218, 1640, 1594, 1447, 1360, 1262, 1160, 1084, 969, 839, 762, 691 cm^{-1}.

^1H NMR: δ 7.79 (d, *J* = 8.5 Hz, 2H), 7.67 (d, *J* = 8.0 Hz, 2H), 7.58-7.53 (m, 3H), 7.41-7.39 (m, 3H), 7.34-7.32 (m, 4H), 7.25-7.21 (m, 1H), 5.75 (d, *J* = 14.5 Hz, 1H), 3.06 (s, 3H).

^{13}C NMR: δ 136.6, 136.2, 132.2, 131.8, 129.1, 128.8, 128.5, 127.9, 127.0, 126.7, 125.6, 122.3, 111.6, 93.4, 87.7, 32.3.

HRMS (ESI): Calcd. for $C_{23}H_{19}NO_2SNa$ (M^+ + Na): *m/z* 396.1034. Found: 396.1037.

Compound 139



Yield: 0.066 g (87%).

IR (neat): 3027, 2928, 1641, 1598, 1445, 1358, 1261, 1161, 1093, 971, 809, 751, 664 cm^{-1}.

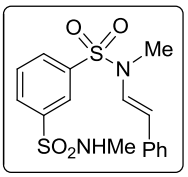
^1H NMR: δ 7.72 (d, *J* = 8.5 Hz, 2H), 7.44 (d, *J* = 14.5 Hz, 1H), 7.34-7.31 (m, 6H), 7.22-7.19 (m, 1H), 5.80 (d, *J* = 14.5 Hz, 1H), 5.50 (br s, 1H), 3.54-3.51 (m, 2H), 2.44 (s, 3H), 2.29 (t, *J* = 8.0 Hz, 2H), 2.03-2.01 (m, 4H), 1.69-1.64

(m, 2H), 1.60-1.56 (m, 2H).

^{13}C NMR: δ 143.8, 136.6, 136.3, 134.3, 129.9, 128.7, 126.9, 126.6, 126.4, 125.4, 123.7, 110.5, 44.7, 35.3, 28.5, 25.3, 22.9, 22.3, 21.5.

HRMS (ESI): Calcd. for $C_{23}H_{28}NO_2S$ (M^+ + H): *m/z* 382.1840. Found: 382.1844.

Compound 140



Yield: 0.063 g (86%).

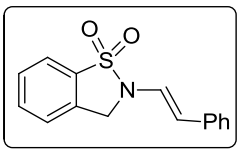
IR (neat): 3079, 2927, 1641, 1599, 1413, 1335, 1260, 1155, 1082, 971, 844, 752, 684 cm^{-1}.

^{1}H NMR: δ 8.31-8.30 (m, 1H), 8.11-8.08 (m, 1H), 7.99-7.97 (m, 1H), 7.72 (t, *J* = 8.0 Hz, 1H), 7.47 (d, *J* = 14.5 Hz, 1H), 7.32-7.30 (m, 4H), 7.23-7.20 (m, 1H), 5.77 (d, *J* = 14.5 Hz, 1H), 4.89-4.86 (m, 1H), 3.07 (s, 3H), 2.61 (d, *J* = 5.5 Hz, 3H).

^{13}C NMR: δ 140.8, 138.9, 135.7, 131.4, 130.6, 130.5, 128.8, 127.2, 127.0, 125.8, 125.7, 112.7, 32.6, 29.3.

HRMS (ESI): Calcd. for $C_{16}H_{18}N_2O_4S_2Na$ (M^+ + Na): *m/z* 389.0606. Found: 389.0608.

Compound 141



Yield: 0.052 g (96%).

Mp: 106-108 ^{o}C.

IR (KBr): 3049, 1647, 1456, 1303, 1167, 1050, 934, 752, 693 cm^{-1}.

^{1}H NMR: δ 7.84 (d, *J* = 8.0 Hz, 1H), 7.65 (dd→t, *J* = 7.5 Hz, 1H), 7.55 (dd→t, *J* = 7.5 Hz, 1H), 7.47 (d, *J* = 7.5 Hz, 1H), 7.35-7.30 (m, 5H), 7.22-7.19 (m, 1H), 5.98 (d, *J* = 14.0 Hz, 1H), 4.66 (s, 2H).

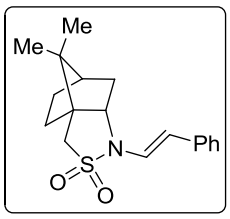
^{13}C NMR: δ 135.9, 134.2, 133.4, 132.1, 129.5, 128.8, 126.7, 125.4, 124.8, 121.4, 111.5, 47.7.

HRMS (ESI): Calcd. for $C_{15}H_{13}NO_2SNa$ (M^+ + Na): *m/z* 294.0565. Found: 294.0567.

This compound was crystallized from ethyl acetate at room temperature. X-ray structure

has been determined for this compound.

Compound 142



Yield: 0.057 g (90%).

Mp: 146-148 ^{o}C.

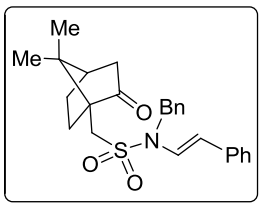
IR (KBr): 2959, 2882, 1642, 1599, 1452, 1319, 1271, 1136, 1054, 935, 749 cm^{-1}.

^{1}H NMR: δ 7.31-7.29 (m, 4H), 7.21-7.18 (m, 1H), 6.87 (d, *J* = 14.5 Hz, 1H), 5.91 (d, *J* = 14.5 Hz, 1H), 3.56-3.53 (dd, *J* ~ 7.5 Hz, 4.5 Hz, 1H), 3.33-3.26 (AB pattern, 2H), 2.20-2.16 (m, 1H), 1.94-1.89 (m, 4H), 1.54-1.50 (m, 1H), 1.40-1.36 (m, 1H), 1.12 (s, 3H), 0.96 (s, 3H).

^{13}C NMR: δ 136.1, 128.7, 126.7, 125.5, 121.0, 115.1, 63.9, 50.3, 49.8, 48.0, 44.5, 36.2, 32.1, 27.0, 20.3, 20.0.

HRMS (ESI): Calcd. for $C_{18}H_{24}NO_2S$ (M^+ + H): *m/z* 318.1527. Found: 318.1528.

Compound 143



Yield: 0.071 g (84%).

Mp: 138-140 ^{o}C.

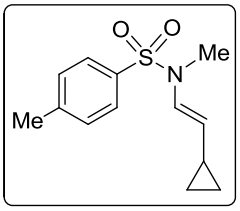
IR (KBr): 3027, 2960, 1745, 1642, 1599, 1453, 1356, 1267, 1152, 1049, 943, 794 cm^{-1}.

^{1}H NMR: δ 7.46 (d, *J* = 8.0 Hz, 2H), 7.41-7.37 (m, 3H), 7.32-7.26 (m, 5H), 7.19-7.16 (m, 1H), 5.85 (d, *J* = 14.5 Hz, 1H), 4.97-4.87 (AB pattern, 2H), 3.54 (d, *J* = 14.5 Hz, 1H), 2.95 (d, *J* = 14.5 Hz, 1H), 2.58-2.52 (m, 1H), 2.43-2.38 (m, 1H), 2.14-2.13 (m, 1H), 2.11-2.06 (m, 1H), 1.97 (d, *J* = 18.5 Hz, 1H), 1.79-1.73 (m, 1H), 1.50-1.45 (m, 1H), 1.16 (s, 3H), 0.88 (s, 3H).

^{13}C NMR: δ 214.6, 136.3, 135.7, 128.8, 128.7, 127.7, 127.2, 126.5, 126.4, 125.5, 111.6, 58.5, 49.6$_3$, 49.5$_7$, 48.0, 42.9, 42.5, 27.0, 25.4, 19.9, 19.8.

HRMS (ESI): Calcd. for $C_{25}H_{30}NO_3S$ (M^+ + H): *m/z* 424.1946. Found: 424.1947.

Compound 144



Yield: 0.040 g (78%).

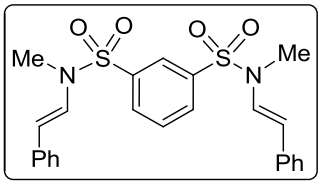
IR (neat): 3005, 2925, 1654, 1597, 1453, 1353, 1232, 1163, 1091, 976, 812, 751, 660 cm^{-1}.

^{1}H NMR: δ 7.63 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 6.77 (d, *J* = 14.0 Hz, 1H), 4.39 (dd, *J* = 14.0 Hz, *J* = 8.0 Hz, 1H), 2.79 (s, 3H), 2.42 (s, 3H), 1.37-1.33 (m, 1H), 0.69-0.66 (m, 2H), 0.29-0.26 (m, 2H).

^{13}C NMR: δ 143.6, 134.5, 129.7, 127.1, 126.3, 115.5, 32.3, 21.5, 11.5, 6.6.

HRMS (ESI): Calcd. for $C_{13}H_{17}NO_2SNa$ (M^+ + Na): *m/z* 274.0878. Found: 274.0881.

Compound 145



Yield: 0.077 g (82%).

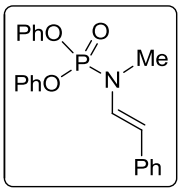
IR (neat): 3079, 2929, 1641, 1590, 1449, 1363, 1260, 1189, 969, 808, 753, 694 cm^{-1}.

^{1}H NMR: δ 8.25-8.24 (m, 1H), 7.98 (dd, *J* = 8.8 Hz, 2.0 Hz, 2H), 7.70 (t, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 14.5 Hz, 2H), 7.35-7.29 (m, 8H), 7.25-7.22 (m, 2H), 5.72 (d, *J* = 14.5 Hz, 2H), 2.99 (s, 6H).

^{13}C NMR: δ 139.1, 135.7, 130.9, 130.7, 128.8, 127.2, 127.0, 125.6, 112.7, 32.5.

HRMS (ESI): Calcd. for $C_{24}H_{24}N_2O_4S_2Na$ (M^+ + Na): *m/z* 491.1075. Found: 491.1078.

Compound 146



Yield: 0.070 g (95%).

Mp: 70-72 ^{o}C.

IR (KBr): 3065, 2915, 1646, 1593, 1489, 1283, 1188, 1011, 945, 752, 690 cm^{-1}.

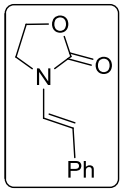
^{1}H NMR: δ 7.48 (dd, *J* = 14.5 Hz, 6.5 Hz, 1H), 7.40 (t, *J* = 8.0 Hz, 4H), 7.36-7.34 (m, 3H), 7.33-7.30 (m, 5H), 7.25-7.22 (m, 2H), 7.21-7.18 (m, 1H), 5.81 (d, *J* = 14.5 Hz, 1H), 3.13 (d, *J* = 9.0 Hz, 3H).

^{13}C NMR: δ 150.3 (d, *J* = 6.3 Hz), 137.0, 130.4 (d, *J* = 6.3 Hz), 130.0, 128.7, 126.0, 125.5, 125.3, 120.1 (d, *J* = 5.0 Hz), 108.2 (d, *J* = 11.3 Hz), 32.0 (d, *J* = 3.8 Hz).

^{31}P NMR: δ -3.46.

HRMS (ESI): Calcd. for $C_{21}H_{21}NO_3P$ (M^+ + H): *m/z* 366.1259. Found: 366.1258.

Compound 147



Yield: 0.028 g (74%).

Mp: 106-108 ^{o}C.

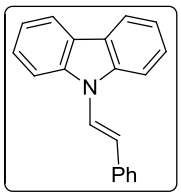
IR (KBr): 2922, 1753, 1653, 1578, 1412, 1338, 1223, 1084, 939, 753, 695 cm^{-1}.

^{1}H NMR: δ 7.39 (d, *J* = 14.5 Hz, 1H), 7.33-7.31 (m, 4H), 7.20 (br s, 1H), 5.77 (d, *J* = 14.5 Hz, 1H), 4.48 (t, *J* = 7.5 Hz, 2H), 3.82 (t, *J* = 7.5 Hz, 2H).

^{13}C NMR: δ 155.5, 135.9, 128.8, 126.7, 125.5, 124.0, 111.1, 62.3, 42.5.

HRMS (ESI): Calcd. for $C_{11}H_{11}NO_2Na$ (M^+ + Na): *m/z* 212.0688. Found: 212.0691.

Compound 149



Yield: 0.051 g (96% with *Z:E* in 5:1).

Mp: 112-114 ^{o}C.

IR (KBr): 3059, 3019, 1649, 1598, 1451, 1336, 1222, 1154, 1074, 942, 693 cm^{-1}.

^{1}H NMR: δ 8.22 (d, *J* = 7.5 Hz, 2H), 7.83 (d, *J* = 8.0 Hz, 2H), 7.78 (d, *J* = 14.5 Hz, 1H), 7.64-7.61 (m, 3H), 7.55 (t, *J* = 6.5 Hz, 2H), 7.50-7.45 (m, 3H), 7.25-7.23 (m, 1H), 7.16 (d, *J* = 14.5 Hz, 1H).

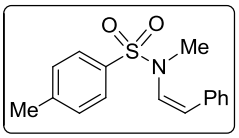
^{13}C NMR: δ 139.7, 136.5, 129.0, 127.4, 126.5, 126.0, 124.3, 123.5, 120.9, 120.5, 119.8, 110.8.

HRMS (ESI): Calcd. for $C_{20}H_{15}N$ (M^+): *m/z* 269.1204. Found: 269.1205.

3.19 Synthesis of (*Z*)-enamides: General procedure

To an oven dried Schlenk tube was added ynamide **5** (0.20 mmol), Pd/C (10 mol%), $HCOONH_4$ (0.60 mmol) and ethanol (1 mL). The tube was sealed under nitrogen atmosphere and heated at 90 ^oC (oil bath temperature) overnight. After completion of the reaction as monitored by TLC, the crude mixture was cooled to room temperature. The mixture was then passed through celite, washed with ethyl acetate (20 mL) and concentrated in vacuum. The residue was then purified by using silica gel column chromatography using hexane-ethyl acetate as the eluent to afford the corresponding (*Z*)-enamide.

Compound 127'



Yield: 0.047 g (82% with *Z:E* in 96:4).

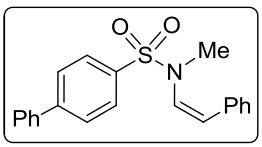
IR (neat): 3057, 2924, 1640, 1597, 1449, 1350, 1162, 1090, 953, 816, 730, 679 cm^{-1}.

^1H NMR: δ 7.77 (d, *J* = 8.5 Hz, 2H), 7.38 (d, *J* = 8.5 Hz, 2H), 7.28-7.22 (m, 5H), 6.28 (d, *J* = 9.0 Hz, 1H), 6.03 (d, *J* = 9.0 Hz, 1H), 2.78 (s, 3H), 2.47 (s, 3H).

^{13}C NMR: δ 143.9, 134.9, 129.8, 129.0, 128.2, 127.6, 127.5, 127.3, 110.9, 36.6, 21.6.

HRMS (ESI): Calcd. for $C_{16}H_{17}NO_2SNa$ (M^+ + Na): *m/z* 310.0878. Found: 310.0879.

Compound 129'



Yield: 0.052 g (74% with *Z:E* in 91:9).

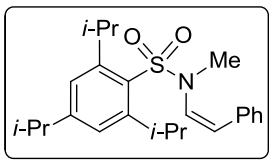
IR (neat): 3028, 2964, 1640, 1594, 1448, 1351, 1262, 1163, 1092, 952, 649 cm^{-1}.

^1H NMR: δ 7.96 (d, *J* = 8.5 Hz, 2H), 7.81-7.79 (m, 2H), 7.66-7.65 (m, 2H), 7.54-7.51 (m, 2H), 7.48-7.45 (m, 1H), 7.28-7.24 (m, 5H), 6.33 (d, *J* = 8.5 Hz, 1H), 6.09 (d, *J* = 8.5 Hz, 1H), 2.84 (s, 3H).

^{13}C NMR: δ 146.0, 139.2, 134.8, 129.1, 129.0, 128.6, 128.2, 128.0, 127.8, 127.7, 127.4, 127.2, 121.4, 36.7.

HRMS (ESI): Calcd. for $C_{21}H_{19}NO_2SNa$ (M^+ + Na): *m/z* 372.1034. Found: 372.1038.

Compound 130'



Yield: 0.060 g (76% with *Z:E* in 89:11).

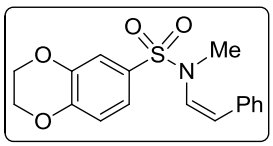
IR (neat): 2961, 2931, 1640, 1599, 1463, 1330, 1162, 1072, 925, 763, 679 cm^{-1}.

^1H NMR: δ 7.29-7.27 (m, 4H), 7.24-7.22 (m, 3H), 6.58 (d, *J* = 9.5 Hz, 1H), 6.00 (d, *J* = 9.5 Hz, 1H), 4.20-4.16 (m, 2H), 2.98-2.92 (m, 1H), 2.85 (s, 3H); 1.32-1.29 (m, 18H).

^{13}C NMR: δ 153.5, 151.5, 135.3, 129.0, 128.1, 127.3, 126.8, 125.4, 124.1, 117.9, 35.3, 34.2, 29.8, 25.0, 23.6.

HRMS (ESI): Calcd. for $C_{24}H_{33}NO_2S$ (M^+ + Na): *m/z* 422.2130. Found: 422.2132.

Compound 132'



Yield: 0.053 g (80% with *Z:E* in 93:7).

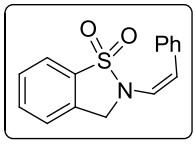
IR (neat): 3062, 2934, 1640, 1581, 1496, 1350, 1286, 1157, 1065, 952, 878, 701, 664 cm^{-1}.

^1H NMR: δ 7.41-7.40 (m, 1H), 7.37 (dd, *J* = 8.5 Hz, 2.0 Hz, 1H), 7.31-7.28 (m, 4H), 7.25-7.24 (m, 1H), 7.02 (d, *J* = 8.5 Hz, 1H), 6.25 (d, *J* = 9.0 Hz, 1H), 6.03 (d, *J* = 9.0 Hz, 1H), 4.36-4.30 (m, 4H), 2.78 (s, 3H).

^{13}C NMR: δ 147.8, 143.7, 134.9, 129.0, 128.2, 127.6, 127.4, 121.2, 121.0, 117.9, 117.1, 64.6, 64.2, 36.6.

HRMS (ESI): Calcd. for $C_{17}H_{17}NO_4SNa$ (M^+ + Na): *m/z* 354.0776. Found: 354.0775.

Compound 141'



Yield: 0.047 g (86% with *Z:E* in 93:7).

Mp: 90-92 ^oC.

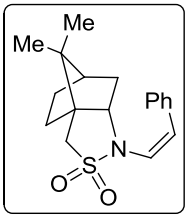
IR (KBr): 3049, 2925, 1644, 1601, 1450, 1310, 1175, 1035, 929, 758, 656 cm^{-1}.

^1H NMR: δ 7.85 (d, *J* = 7.5 Hz, 1H), 7.61 (td, *J* = 7.5 Hz, *J* = 1.0 Hz, 1H), 7.55 (td, *J* = 7.5 Hz, *J* = 1.0 Hz, 1H), 7.47 (d, *J* = 7.5 Hz, 2H), 7.39-7.36 (m, 2H), 7.32-7.27 (m, 1H), 7.28-7.27 (m, 1H), 6.70 (d, *J* = 9.0 Hz, 1H), 6.21 (d, *J* = 9.0 Hz, 1H), 4.37 (s, 2H).

^{13}C NMR: δ 136.0, 133.8, 133.5, 133.1, 129.2, 129.1, 128.4, 127.5, 124.5, 122.2, 121.4, 118.8, 51.4.

HRMS (ESI): Calcd. for $C_{15}H_{13}NO_2SNa$ (M^+ + Na): *m/z* 294.0565. Found: 294.0566.

Compound 142'



Yield: 0.052 g (82% with *Z:E* in 86:14).

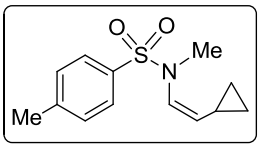
IR (KBr): 2958, 2882, 1638, 1596, 1452, 1319, 1259, 1132, 1052, 935, 700 cm^{-1}.

^1H NMR: δ 7.45-7.44 (m, 2H), 7.33-7.30 (m, 2H), 7.28-7.25 (m, 1H), 6.38 (d, *J* = 8.5 Hz, 1H), 5.93 (d, *J* = 8.5 Hz, 1H), 3.34-3.31 (dd, *J* ~ 7.5 Hz, 4.5 Hz, 1H), 3.25 (s, 2H), 1.87-1.80 (m, 2H), 1.71-1.68 (m, 2H), 1.44-1.39 (m, 1H), 1.13-1.06 (m, 1H), 0.97 (s, 3H), 0.88 (s, 3H), 0.80-0.78 (m, 1H).

^{13}C NMR: δ 135.0, 129.2, 128.0, 127.6, 125.7, 119.6, 66.7, 51.3, 49.8, 48.0, 44.2, 34.4, 31.9, 26.9, 20.2, 20.0.

HRMS (ESI): Calcd. for $C_{18}H_{23}NO_2SNa$ (M^+ + Na): *m/z* 340.1347. Found: 340.1351.

Compound 144'



Yield: 0.036 g (72% with *Z:E* in 98:2).

IR (neat): 3005, 2925, 1655, 1598, 1454, 1348, 1162, 1090, 962, 816, 717, 660 cm^{-1}.

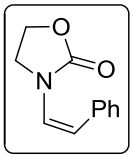
^1H NMR: δ 7.69 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 5.51 (d, *J* = 8.0 Hz, 1H), 4.74 (dd, *J* = 10.0 Hz, *J* = 8.0 Hz, 1H), 2.92 (s, 3H), 2.42 (s, 3H),

1.81-1.75 (m, 1H), 0.79-0.76 (m, 2H), 0.40-0.38 (m, 2H).

^{13}C NMR: δ 143.5, 135.0, 134.1, 129.6, 127.6, 125.6, 37.8, 21.5, 9.6, 7.4.

HRMS (ESI): Calcd. for $C_{13}H_{17}NO_2SNa$ (M^+ + Na): *m/z* 274.0878. Found: 274.0879.

Compound 147'



The reaction was carried out at rt for the preparation of this compound by following the general procedure specified for (*Z*)-enamides.

Yield: 0.029 g (76%).

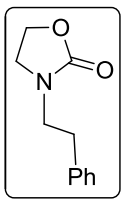
IR (neat): 2918, 1758, 1654, 1415, 1337, 1238, 1073, 928, 759, 700 cm^{-1}.

^{1}H NMR: δ 7.33-7.30 (m, 2H), 7.26-7.23 (m, 1H), 7.21-7.20 (m, 2H), 6.64 (d, *J* = 9.5 Hz, 1H), 5.97 (d, *J* = 9.5 Hz, 1H), 4.24 (t, *J* = 8.0 Hz, 2H), 3.35 (t, *J* = 8.0 Hz, 2H).

^{13}C NMR: δ 157.3, 135.5, 129.3, 128.0, 127.1, 124.2, 112.8, 62.7, 45.0.

HRMS (ESI): Calcd. for $C_{11}H_{11}NO_2Na$ (M^+ + Na): *m/z* 212.0688. Found: 212.0687.

Compound 151



This compound was prepared by following the general procedure given for (*Z*)-enamides.

Yield: 0.036 g (94%).

Mp: 63-65 ^{o}C.

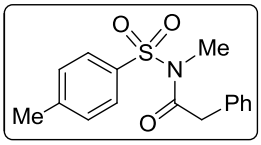
IR (KBr): 3028, 2922, 1731, 1604, 1427, 1368, 1268, 1170, 1034, 968, 703 cm^{-1}.

^{1}H NMR: δ 7.32-7.29 (m, 2H), 7.24-7.22 (m, 3H), 4.24-4.21 (m, 2H), 3.52 (t, *J* = 7.5 Hz, 2H), 3.42-3.39 (m, 2H), 2.88 (t, *J* = 7.5 Hz, 2H).

^{13}C NMR: δ 158.4, 138.4, 128.7, 126.6, 61.7, 45.6, 45.0, 34.0.

HRMS (ESI): Calcd. for $C_{11}H_{13}NO_2Na$ (M^+ + Na): *m/z* 214.0844. Found: 214.0845.

Compound 150



Mp: 78-80 ^{o}C.

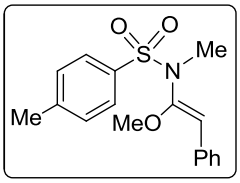
IR (KBr): 3029, 2926, 1696, 1597, 1455, 1356, 1165, 1075, 903, 862, 724, 672 cm^{-1}.

^{1}H NMR: δ 7.73-7.71 (m, 2H), 7.34-7.28 (m, 5H), 7.17-7.15 (m, 2H), 4.07 (s, 2H), 3.30 (s, 3H), 2.46 (s, 3H).

^{13}C NMR: δ 171.3, 145.0, 136.1, 133.5, 129.9, 129.4, 128.6, 127.5, 127.2, 43.1, 33.3, 21.6.

HRMS (ESI): Calcd. for $C_{16}H_{18}NO_3S$ (M^+ + H): *m/z* 304.1007. Found: 304.1002.

Compound 152



Yield: 0.016 g (26%).

Mp: 124-126 ^{o}C.

IR (KBr): 3059, 2929, 1656, 1597, 1444, 1349, 1237, 1156, 1089, 912, 815, 755, 672 cm^{-1}.

^{1}H NMR: δ 7.78-7.76 (m, 2H), 7.53-7.51 (m, 2H), 7.35-7.28 (m, 4H), 7.22-7.19 (m, 1H), 5.56 (s, 1H), 3.69 (s, 3H), 2.94 (s, 3H), 2.45 (s, 3H).

^{13}C NMR: δ 150.7, 143.5, 136.3, 134.2, 129.2, 128.5, 128.2, 127.9, 126.3, 100.8, 56.0, 35.8, 21.6.

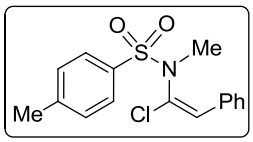
HRMS (ESI): Calcd. for $C_{17}H_{20}NO_3S$ (M^+ + H): *m/z* 318.1164. Found: 318.1167.

3.20 Synthesis of (*E*)-α-chloroenamide derivatives: Representative procedure for synthesis of compound 153

To a Schlenk tube was added 4,*N*-dimethyl-*N*-phenylethynyl-benzenesulfonamide **5aa** (0.20 mmol), anh. aluminium chloride (0.22 mmol), dimethyl carbonate (1 mL) and H_2O (0.20 mmol). The tube was sealed and heated at 80 ^{o}C (oil bath temperature) overnight. After completion of the reaction as monitored by TLC, the crude mixture was cooled to room temperature. The mixture was then passed through celite, washed with ethyl acetate

(20 mL) and concentrated in vacuum. The residue was then purified by using silica gel column chromatography using hexane-ethyl acetate (9:1) as the eluent to afford (*E*)-*N*,4-dimethyl-*N*-styrylbenzenesulfonamide **153**. Compounds **154-169** were prepared following the same procedure and the same molar quantities.

Compound 153



Yield: 0.059 g (92%).

Mp: 104-106 ^{o}C.

IR (KBr): 3060, 2926, 1634, 1593, 1443, 1361, 1164, 1092, 963, 808, 756, 689 cm^{-1}.

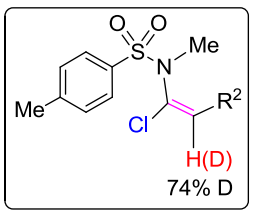
^{1}H NMR: δ 7.80 (d, *J* = 8.5 Hz, 2H), 7.63-7.61 (m, 2H), 7.40-7.36 (m, 2H), 7.35-7.32 (m, 3H), 6.68 (s, 1H), 3.06 (s, 3H), 2.46 (s, 3H).

^{13}C NMR: δ 144.5, 134.2, 133.1, 132.4, 129.8, 129.5, 128.9, 128.8$_1$, 128.7$_8$, 128.7, 35.7, 21.6.

HRMS (ESI): Calcd. for $C_{16}H_{16}ClNO_2SNH_4$ (M^+ + NH_4): *m/z* 339.0934. Found: 339.0935.

This compound has been previously reported.[49]

Compound 153'



Yield: 0.058 g (90%).

Mp: 104-106 ^{o}C.

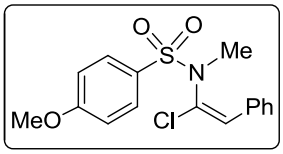
IR (KBr): 3055, 2926, 2254, 1629, 1593, 1448, 1356, 1170, 1087, 968, 818, 787, 674 cm^{-1}.

^{1}H NMR: δ 7.81 (d, *J* = 8.0 Hz, 2H), 7.65-7.63 (m, 2H), 7.40-7.36 (m, 2H), 7.35-7.31 (m, 3H), 6.68 (s, 0.26H), 3.06 (s, 3H), 2.45 (s, 3H).

^{13}C NMR: δ 144.5, 134.3, 133.1, 132.0 (t, *J* = 24.0 Hz), 129.8, 129.5, 128.9, 128.8$_1$, 128.7$_8$, 128.7, 35.7, 21.6.

HRMS (ESI): Calcd. for $C_{16}H_{16}DClNO_2S$ (M^+ + H): *m/z* 323.0731. Found: 323.0730.

Compound 154



Yield: 0.060 g (90%).

Mp: 106-108 ^{o}C.

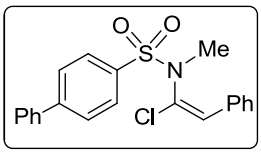
IR (KBr): 3055, 2921, 1640, 1593, 1495, 1356, 1263, 1164, 1092, 968, 803, 767, 689 cm^{-1}.

^{1}H NMR: δ 7.86-7.83 (m, 2H), 7.64-7.62 (m, 2H), 7.39-7.36 (m, 2H), 7.34-7.31 (m, 1H), 6.99-6.96 (m, 2H), 6.67 (s, 1H), 3.87 (s, 3H), 3.04 (s, 3H).

^{13}C NMR: δ 163.7, 133.1, 132.3, 131.0, 130.0, 128.9, 128.8, 128.7, 128.6, 114.1, 55.7, 35.7.

HRMS (ESI): Calcd. for $C_{16}H_{16}ClNO_3SNH_4$ (M^+ + NH_4): *m/z* 355.0883. Found: 355.0883.

Compound 155



Yield: 0.064 g (84%).

Mp: 164-166 ^{o}C.

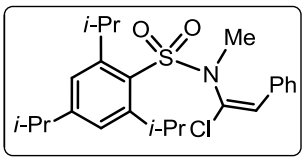
IR (KBr): 3025, 2928, 1640, 1588, 1448, 1356, 1252, 1164, 1092, 958, 855, 762, 689 cm^{-1}.

^{1}H NMR: δ 7.99 (d, *J* = 8.0 Hz, 2H), 7.73 (d, *J* = 8.5 Hz, 2H), 7.66-7.64 (m, 4H), 7.54-7.35 (m, 6H), 6.72 (s, 1H), 3.13 (s, 3H).

^{13}C NMR: δ 146.4, 139.2, 135.8, 133.1, 132.5, 129.7, 129.3, 129.1, 128.9, 128.8, 128.7_3, 128.6_6, 127.5, 127.4, 35.8.

HRMS (ESI): Calcd. for $C_{21}H_{18}ClNO_2SNH_4$ (M^+ + NH_4): *m/z* 401.1091. Found: 401.1095.

Compound 156



Yield: 0.074 g (86%).

Mp: 72-74 ^{o}C.

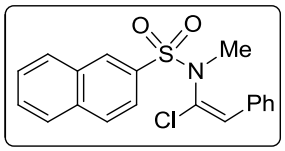
IR (KBr): 2957, 2869, 1640, 1603, 1464, 1371, 1257, 1170, 1071, 963, 684 cm^{-1}.

^{1}H NMR: δ 7.57-7.55 (m, 2H), 7.36-7.28 (m, 3H), 7.20 (br s, 2H), 6.70 (s, 1H), 4.11-4.06 (m, 2H), 3.28 (s, 3H); 2.96-2.90 (m, 1H), 1.30-1.28 (m, 18H).

^{13}C NMR: δ 153.4, 151.6, 133.2, 132.4, 132.0, 130.3, 128.7$_9$, 128.7$_6$, 128.6, 124.2, 36.1, 34.1, 30.7, 25.2, 23.6.

HRMS (ESI): Calcd. for $C_{24}H_{32}ClNO_2SNH_4$ (M^+ + NH_4): *m/z* 451.2186. Found: 451.2190.

Compound 157



Yield: 0.065 g (92%).

Mp: 174-176 ^{o}C.

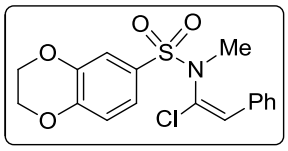
IR (KBr): 3052, 2964, 1636, 1598, 1438, 1361, 1201, 1159, 1071, 958, 674 cm^{-1}.

^{1}H NMR: δ 8.49 (s, 1H), 7.99-7.90 (m, 4H), 7.69-7.63 (m, 4H), 7.39-7.31 (m, 3H), 6.73 (s, 1H), 3.13 (s, 3H).

^{13}C NMR: δ 135.2, 134.2, 133.1, 132.6, 132.0, 130.5, 129.7, 129.5, 129.2, 129.1, 128.9, 128.8, 128.7, 128.0, 127.6, 123.7, 35.9.

HRMS (ESI): Calcd. for $C_{19}H_{16}ClNO_2SNH_4$ (M^+ + NH_4): *m/z* 375.0934. Found: 375.0936.

Compound 158



Yield: 0.057 g (78%).

Mp: 154-156 ^{o}C.

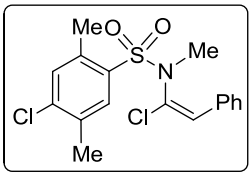
IR (KBr): 3075, 2928, 1642, 1580, 1496, 1356, 1288, 1160, 1062, 963, 753 cm^{-1}.

^{1}H NMR: δ 7.60 (d, *J* = 7.5 Hz, 2H), 7.44-7.43 (m, 1H), 7.41-7.36 (m, 3H), 7.33-7.30 (m, 1H), 6.96 (d, *J* = 8.5 Hz, 1H), 6.67 (s, 1H), 4.35-4.33 (m, 2H), 4.31-4.29 (m, 2H), 3.06 (s, 3H).

^{13}C NMR: δ 148.2, 143.4, 133.1, 132.3, 129.9, 129.5, 128.8$_3$, 128.7$_5$, 128.7, 122.6, 118.4, 117.5, 64.6, 64.1, 35.8.

HRMS (ESI): Calcd. for $C_{17}H_{16}ClNO_4SNa$ (M^+ + Na): *m/z* 388.0387. Found: 388.0389.

Compound 159



Yield: 0.061 g (82%).

Mp: 98-100 ^{o}C.

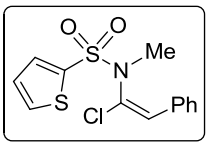
IR (KBr): 3024, 2926, 1634, 1598, 1443, 1366, 1159, 1087, 963, 803, 751 cm^{-1}.

^{1}H NMR: δ 7.73 (s, 1H), 7.39-7.37 (m, 2H), 7.31-7.28 (m, 3H), 7.14 (s, 1H), 6.65 (s, 1H), 3.19 (s, 3H), 2.53 (s, 3H), 2.35 (s, 3H).

^{13}C NMR: δ 139.6, 137.4, 134.1, 133.0$_1$, 132.9$_6$, 132.9, 132.3, 130.0, 128.7, 128.5, 128.4, 36.1, 20.9, 19.5.

HRMS (ESI): Calcd. for $C_{17}H_{17}Cl_2NO_2SNH_4$ (M^+ + NH_4): *m/z* 387.0701. Found: 387.0702.

Compound 160



Yield: 0.053 g (86%).

Mp: 130-132 ^{o}C.

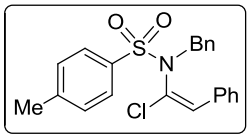
IR (KBr): 3086, 2962, 1634, 1593, 1443, 1361, 1257, 1159, 1087, 963, 860, 798, 689 cm^{-1}.

^{1}H NMR: δ 7.73-7.72 (m, 1H), 7.69-7.68 (m, 1H), 7.64 (d, *J* = 7.5 Hz, 2H), 7.41-7.33 (m, 3H), 7.15-7.14 (m, 1H), 6.71 (s, 1H), 3.14 (s, 3H).

^{13}C NMR: δ 137.2, 134.4, 133.6, 133.0, 132.7, 129.3, 129.1, 128.8$_1$, 128.7$_8$, 127.7, 36.0.

HRMS (ESI): Calcd. for $C_{13}H_{12}ClNO_2S_2NH_4$ (M^+ + NH_4): *m/z* 331.0342. Found: 331.0345.

Compound 161



Yield: 0.067 g (85%).

Mp: 138-140 ^{o}C.

IR (KBr): 3029, 2921, 1634, 1593, 1448, 1361, 1211, 1175, 1092, 932, 751 cm^{-1}.

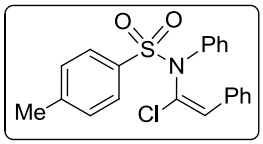
^{1}H NMR: δ 7.90-7.88 (m, 2H), 7.38-7.35 (m, 4H), 7.24-7.22 (m, 5H), 7.18-7.12 (m, 3H), 6.63 (s, 1H), 4.83 (d, *J* = 12.5 Hz, 1H), 4.06 (d, *J* = 12.5 Hz, 1H), 2.49 (s, 3H).

^{13}C NMR: δ 144.6, 135.0, 133.4, 132.9, 129.8, 129.6, 128.9, 128.8, 128.5, 128.3, 128.2, 128.1, 127.5, 52.4, 21.7.

HRMS (ESI): Calcd. for $C_{22}H_{20}ClNO_2SNH_4$ (M^+ + NH_4): *m/z* 415.1247. Found: 415.1248.

This compound has been previously reported.[49]

Compound 162



Yield: 0.062 g (82%).

Mp: 118-120 ^{o}C.

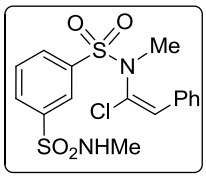
IR (KBr): 3060, 2921, 1629, 1598, 1490, 1356, 1221, 1170, 1087, 937, 808, 756, 684 cm^{-1}.

^{1}H NMR: δ 7.73-7.70 (m, 4H), 7.42-7.35 (m, 5H), 7.26-7.23 (m, 5H), 6.85 (s, 1H), 2.41 (s, 3H).

^{13}C NMR: δ 144.6, 139.1, 135.2, 133.6, 132.9, 129.3, 129.2, 129.0, 128.9, 128.6, 128.1, 126.4, 21.7.

HRMS (ESI): Calcd. for $C_{21}H_{18}ClNO_2SNH_4$ (M^+ + NH_4): *m/z* 401.1091. Found: 401.1090.

Compound 163



Yield: 0.068 g (85%).

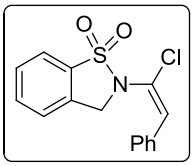
IR (neat): 3072, 2927, 1639, 1415, 1336, 1160, 1085, 968, 849, 754, 693 cm^{-1}.

^{1}H NMR: δ 8.42-8.41 (m, 1H), 8.14-8.11 (m, 1H), 8.10-8.08 (m, 1H), 7.69 (t, *J* = 8.0 Hz, 1H), 7.59-7.57 (m, 2H), 7.40-7.32 (m, 3H), 6.70 (s, 1H), 4.98 (br s, 1H), 3.11 (s, 3H), 2.66 (d, *J* = 5.0 Hz, 3H).

^{13}C NMR: δ 140.5, 138.7, 133.1, 132.7, 132.4, 131.9, 130.1, 129.2, 128.8, 128.7, 127.4, 36.0, 29.3.

HRMS (ESI): Calcd. for $C_{16}H_{17}ClN_2O_4S_2NH_4$ (M^+ + NH_4): *m/z* 418.0662. Found: 418.0664.

Compound 164



Yield: 0.058 g (94%).

Mp: 134-136 ^{o}C.

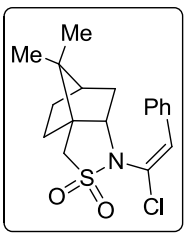
IR (KBr): 3062, 2925, 1637, 1451, 1322, 1179, 1042, 927, 755, 695 cm^{-1}.

^{1}H NMR: δ 7.81 (d, *J* = 7.5 Hz, 1H), 7.67-7.66 (m, 3H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.46 (d, *J* = 7.5 Hz, 1H), 7.34-7.29 (m, 3H), 6.93 (s, 1H), 4.77 (s, 2H).

^{13}C NMR: δ 134.8, 134.3, 133.6, 133.1, 132.7, 129.5, 129.2, 128.8, 128.7, 125.4, 124.9, 121.6, 50.0.

HRMS (ESI): Calcd. for $C_{15}H_{12}ClNO_2SNa$ (M^+ + Na): *m/z* 328.0175. Found: 328.0177.

Compound 165



Yield: 0.061 g (87%).

Mp: 112-114 ^{o}C.

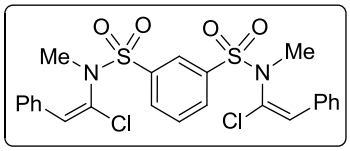
IR (KBr): 2959, 2884, 1634, 1451, 1331, 1258, 1149, 1051, 999, 879, 793, 696 cm^{-1}.

^{1}H NMR: δ 7.62-7.61 (m, 2H), 7.31-7.27 (m, 3H), 7.00 (s, 1H), 3.78 (br s, 1H), 3.30-3.24 (m, 2H), 1.93-1.87 (m, 2H), 1.80 (br s, 1H), 1.70-1.54 (m, 3H), 1.32-1.27 (m, 1H), 0.89 (s, 3H), 0.82 (s, 3H).

^{13}C NMR: δ 135.3, 132.6, 129.0, 128.7, 128.2, 125.4, 66.3, 50.4, 49.3, 47.8, 44.4, 34.4, 32.7, 26.8, 20.4, 20.1.

HRMS (ESI): Calcd. for $C_{18}H_{22}ClNO_2SNa$ (M^+ + Na): *m/z* 374.0958. Found: 374.0957.

Compound 166



Yield: 0.090 g (84%).

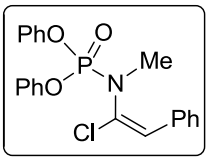
IR (neat): 3064, 2963, 1639, 1597, 1449, 1367, 1261, 1163, 970, 854, 799, 690 cm^{-1}.

^{1}H NMR: δ 8.45-8.44 (m, 1H), 8.13 (dd, *J* = 8.0 Hz, *J* = 1.5 Hz, 2H), 7.67 (t, *J* = 8.0 Hz, 1H), 7.59 (d, *J* = 7.5 Hz, 4H), 7.41-7.33 (m, 6H), 6.71 (s, 2H), 3.13 (s, 6H).

^{13}C NMR: δ 138.8, 133.2, 133.0, 132.7, 129.8, 129.2, 128.8, 128.7, 36.0.

HRMS (ESI): Calcd. for $C_{24}H_{22}Cl_2N_2O_4S_2Na$ (M^+ + Na): *m/z* 559.0296. Found: 559.0297.

Compound 167



Yield: 0.072 g (90%).

Mp: 76-78 ^{o}C.

IR (KBr): 3055, 2941, 1645, 1592, 1489, 1290, 1189, 1005, 946, 770, 690 cm^{-1}.

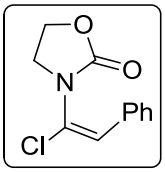
^{1}H NMR: δ 7.42-7.40 (m, 2H), 7.33-7.30 (m, 4H), 7.24-7.17 (m, 9H), 6.64-6.63 (m, 1H), 3.21 (d, *J* = 9.5 Hz, 3H).

^{13}C NMR: δ 150.6 (d, *J* = 7.5 Hz), 133.4, 132.6, 129.7, 128.9 (d, *J* = 7.5 Hz), 128.5, 128.4, 128.2, 125.2, 120.3 (d, *J* = 5.0 Hz), 35.9 (d, *J* = 4.0 Hz).

^{31}P NMR: δ -6.61.

HRMS (ESI): Calcd. for $C_{21}H_{19}ClNO_3PNa$ (M^+ + Na): *m/z* 422.0689. Found: 422.0693.

Compound 168



Yield: 0.043 g (98%).

Mp: 142-144 ^{o}C.

IR (KBr): 2921, 1758, 1655, 1495, 1402, 1242, 1087, 937, 891, 756, 689 cm^{-1}.

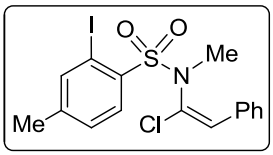
^{1}H NMR: δ 7.37-7.29 (m, 5H), 6.75 (s, 1H), 4.44 (t, *J* = 8.0 Hz, 2H), 3.78 (t, *J* = 8.0 Hz, 2H).

^{13}C NMR: δ 155.4, 133.0, 130.5, 128.8, 128.7, 128.0, 125.9, 62.9, 44.6.

HRMS (ESI): Calcd. for $C_{11}H_{10}ClNO_2Na$ (M^+ + Na): *m/z* 246.0298. Found: 246.0302.

This compound was crystallized from ethyl acetate at room temperature. X-ray structure has been determined for this compound.

Compound 169



Yield: 0.080 g (90%).

Mp: 106-108 ^{o}C.

IR (KBr): 3055, 2921, 1634, 1588, 1443, 1350, 1263, 1164, 1097, 958, 855, 751, 684 cm^{-1}.

^{1}H NMR: δ 7.90 (d, *J* = 8.0 Hz, 1H), 7.74 (s, 1H), 7.35 (d, *J* = 7.5 Hz, 2H), 7.28-7.23 (m, 3H), 7.15 (d, *J* = 8.0 Hz, 1H), 6.62 (s, 1H), 3.38 (s, 3H), 2.28 (s, 3H).

^{13}C NMR: δ 144.9, 143.7, 138.0, 132.8, 132.2$_0$, 132.1$_8$, 130.1, 128.9, 128.5, 128.4, 92.8, 37.6, 20.7.

HRMS (ESI): Calcd. for $C_{16}H_{16}ClNO_2S$ (M^+ + H): *m/z* 447.9635. Found: 447.9633.

This compound was crystallized from ethyl acetate–hexane (2:1) mixture at 25 ^{o}C. X-ray structure has been determined for this compound.

3.21 X-ray crystallography

A suitable crystal was mounted on a glass fiber (for **19**, **26**, **34**, **38**, **44**, **46**, **50**, **58**, **66**, **81**, **90**, **102**, **104**, **111**, **114**, **119**, **126**, **127**, **131**, **141**, **168** and **169**) and X-ray data were collected at 298 K on a Bruker AXS-SMART or on an OXFORD diffractometer using Mo-K_α radiation (λ = 0.71073 Å) or Cu- K_α (λ = 1.54184 Å). Structures were solved and refined using standard methods.[129] Absorption corrections were done using SADABS program, where applicable. All non-hydrogen atoms were refined anisotropically; hydrogen atoms were fixed by geometry or located by a Difference Fourier and refined isotropically. Crystal data are summarized in Tables 22-28.

Table 22: Crystal data for compounds **19**, **26**, and **34**

Compound	**19**	**26**	**34**
Emp. formula	$C_{16}H_{14}N_4O_2S$	$C_{10}H_{10}N_4O_2S$	$C_{18}H_{20}N_2O_5S$
Formula weight	326.37	250.28	374.40
Crystal system	Triclinic	Monoclinic	Monoclinic
Space group	*P*-1	$P2_1/c$	$P2_1/c$
a /Å	7.1492(7)	8.0936(11)	10.3978(17)
b /Å	7.7691(8)	21.469(3)	19.453(4)
c /Å	14.105(2)	6.2322(8)	9.6211(19)
α/deg	97.012(10)	90	90
β/deg	102.997(10)	95.001(11)	97.179(16)
γ/deg	98.628(8)	90	90
V /Å^3	744.79(15)	1078.8(2)	1930.7(6)
Z	2	4	4
*D*calc /g cm^{-3}]	1.455	1.541	1.288
μ /mm^{-1}	0.233	0.295	1.754
F(000)	340.0	520.0	784.0
Data/ restraints/ parameters	3024/0/210	2203/0/156	3614/0/238
S	1.050	1.092	1.026
R1 [I>2σ(I)]	0.0405	0.0442	0.0622
wR2 [all data]	0.1171	0.1167	0.2664
Max./min. residual electron dens. [eÅ^{-3}]	0.179/-0.505	0.381/-0.365	0.352/-0.525

[a]R1 = $\Sigma||Fo| - |Fc||/\Sigma|Fo|$ and wR2 = $[\Sigma w(Fo^2-Fc^2)^2/\Sigma wFo^4]^{0.5}$

Table 23: Crystal data for compounds **38**, **44**, **46, 50** and **58**[a]

Compound	**38**	**44**	**46**	**50**	**58**
Emp. formula	$C_{16}H_{15}NO_2S_2$	$C_{16}H_{14}FNO_2S_2$	$C_{16}H_{15}NO_3S_2$	$C_{16}H_{15}NO_2SSe$	$C_{17}H_{17}NO_2S_2$
Formula weight	317.41	335.40	333.41	364.31	331.44
Crystal system	Orthorhombic	Monoclinic	Triclinic	Orthorhombic	Monoclinic
Space group	*P*ca2$_1$	*P*12$_1$/c1	*P*-1	*P*bca	*P*12$_1$/n1
a /Å	18.773(2)	15.7817(19)	9.7686(8)	7.38023(19)	6.63588(15)
b /Å	7.8448(5)	13.0488(12)	10.4236(10)	12.8750(3)	12.9255(3)
c /Å	20.3148(19)	7.2719(7)	16.0412(15)	31.8273(8)	19.0476(4)
α/deg	90	90	90.974(8)	90	90
β/deg	90	92.391(9)	91.846(7)	90	93.665(2)
γ/deg	90	90	107.681(8)	90	90
V /Å^3	2991.7(5)	1496.2(3)	1554.8(2)	3024.25(14)	1630.41(7)
Z	8	4	4	8	4
*D*calc /g cm^{-3}]	1.409	1.489	1.424	1.600	1.350
μ /mm^{-1}	0.359	0.372	0.354	4.682	3.008
F(000)	1328.0	696.0	696.0	1472.0	696.0
Data/ restraints/ parameters	3485/0/383	2638/0/201	5478/0/401	2900/0/192	3093/0/201
S	1.086	1.172	1.031	1.092	1.046
R1 [I>2σ(I)]	0.0928	0.1243	0.0465	0.0404	0.0391
wR2 [all data]	0.2402	0.3357	0.1040	0.1125	0.1076
Max./min. residual electron dens. [eÅ^{-3}]	1.525/-0.333	1.464/-0.507	0.298/-0.358	0.387/-0.747	0.318/-0.404

[a]R1 = Σ||Fo| - |Fc||/Σ|Fo| and wR2 = [Σw(Fo^2-Fc^2)^2/ΣwFo^4]$^{0.5}$

Table 24: Crystal data for compounds **66**, **81**, **90**, **102** and **104**[a]

Compound	**66**	**81**	**90**	**102**	**104**
Emp. formula	$C_{24}H_{24}N_2O_4S_2$	$C_{22}H_{26}N_2O_2S$	$C_{22}H_{18}ClNO_3S$	$C_{16}H_{15}NO_2S$	$C_{21}H_{21}NO_6S$
Formula weight	468.57	382.51	411.88	285.35	415.45
Crystal system	Monoclinic	Triclinic	Orthorhombic	Monoclinic	Triclinic
Space group	$P2_1/c$	P-1	$Pna2_1$	$P12_1/c1$	P-1
a /Å	12.280(4)	8.712(4)	18.8552(12)	17.224(3)	10.3831(5)
b /Å	20.224(6)	10.771(5)	10.6794(7)	5.7571(7)	10.4298(3)
c /Å	18.904(5)	12.176(6)	9.8361(6)	15.546(2)	19.7239(9)
α/deg	90	107.880(7)	90	90	79.072(3)
β/deg	92.682(6)	93.495(8)	90	115.89(2)	83.544(4)
γ/deg	90	108.722(7)	90	90	86.437(3)
V /Å^3	1696.2(6)	1013.6(8)	1980.6(2)	1386.9(4)	2082.12(14)
Z	8	2	4	4	4
Dcalc /g cm^{-3}]	1.327	1.253	1.381	1.367	1.325
μ /mm^{-1}	0.260	0.179	0.321	0.234	1.704
F(000)	1968.0	408.0	856.0	600.0	872.0
Data/ restraints/ parameters	9615/0/585	4067/0/250	4040/0/255	2433/0/183	7949/0/531
S	0.996	1.020	1.102	1.073	1.022
R1 [I>2σ(I)]	0.0655	0.0509	0.0481	0.0455	0.0436
wR2 [all data]	0.1682	0.1582	0.1144	0.1227	0.1269
Max./min. residual electron dens. [eÅ^{-3}]	0.239/-0.204	0.193/-0.351	0.290/-0.147	0.220/-0.283	0.271/-0.328

[a]$R1 = \Sigma||Fo| - |Fc||/\Sigma|Fo|$ and $wR2 = [\Sigma w(Fo^2-Fc^2)^2/\Sigma wFo^4]^{0.5}$

Table 25: Crystal data for compounds **111**, **114**, **119** and **126**

Compound	**111**	**114**	**119**	**126**
Emp. formula	$C_{22}H_{18}N_4O_2S$	$C_{24}H_{22}N_4O_2S$	$C_{22}H_{17}FN_4O_2S$	$C_{18}H_{18}N_2O_3S$
Formula weight	402.46	430.52	420.46	342.40
Crystal system	Triclinic	Orthorhombic	Triclinic	Monoclinic
Space group	*P*-1	*F*dd2	*P*-1	$P2_1/c$
a /Å	9.7018(12)	18.604(5)	9.5983(12)	16.3897(8)
b /Å	10.5931(13)	45.424(12)	10.5346(13)	12.1282(6)
c /Å	11.0467(13)	10.665(3)	11.0226(13)	17.0046(8)
α/deg	85.642(2)	90	88.483(2)	90
β/deg	64.146(2)	90	66.991(2)	97.629(2)
γ/deg	73.144(2)	90	74.787(2)	90
V /Å^3	976.1(2)	9013(4)	986.3(2)	3350.2(3)
Z	2	16	2	8
*D*calc /g cm^{-3}]	1.369	1.269	1.416	1.358
μ /mm^{-1}	0.193	0.171	0.201	0.212
F(000)	420.0	3616.0	436.0	1440.0
Data/ restraints/ parameters	4520/0/264	3977/0/284	4556/0/273	6891/0/439
S	1.073	1.057	1.082	1.048
R1 [I>2σ(I)]	0.0499	0.0417	0.0764	0.0688
wR2 [all data]	0.1532	0.1071	0.2434	0.2089
Max./min. residual electron dens. [eÅ^{-3}]	0.247/-0.463	0.241/-0.288	1.891/-0.605	0.886/-0.593

[a]R1 = Σ||Fo| - |Fc||/Σ|Fo| and wR2 = [Σw(Fo^2-Fc^2)^2/ΣwFo^4]$^{0.5}$

Table 26: Crystal data for compounds **127**, **131**, and **141**

Compound	**127**	**131**	**141**
Emp. formula	$C_{16}H_{17}NO_2S$	$C_{19}H_{17}NO_2S$	$C_{15}H_{13}NO_2S$
Formula weight	287.36	323.39	271.32
Crystal system	Orthorhombic	Monoclinic	Monoclinic
Space group	$P2_12_12_1$	$C2/c$	$C2/c$
a /Å	6.3891(7)	13.6570(9)	17.3782(16)
b /Å	7.8519(7)	15.3921(10)	9.9994(9)
c /Å	29.659(3)	15.997(1)	16.2762(15)
α/deg	90	90	90
β/deg	90	102.023(2)	112.602(3)
γ/deg	90	90	90
V /Å^3	1487.9(3)	3289.0(4)	2611.1(4)
Z	4	8	8
Dcalc /g cm^{-3}]	1.283	1.306	1.380
μ /mm^{-1}	0.218	0.206	0.244
F(000)	608.0	1360.0	1136.0
Data/ restraints/ parameters	3248/0/183	3945/0/210	7824/0/172
S	1.043	1.050	1.005
R1 [I>2σ(I)]	0.0435	0.0461	0.0658
wR2 [all data]	0.1076	0.1309	0.1733
Max./min. residual electron dens. [eÅ^{-3}]	0.166/-0.326	0.249/-0.253	0.302/-0.352

[a]R1 = $\Sigma||Fo| - |Fc||/\Sigma|Fo|$ and wR2 = $[\Sigma w(Fo^2-Fc^2)^2/\Sigma wFo^4]^{0.5}$

Table 27: Crystal data for compounds **168** and **169**

Compound	**168**	**169**
Emp. formula	$C_{11}H_{10}ClNO_2$	$C_{16}H_{15}IClNO_2S$
Formula weight	223.65	447.70
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/n$	$P2_1/n$
a /Å	8.731(2)	11.342(2)
b /Å	11.599(2)	9.554(2)
c /Å	10.560(3)	16.257(3)
α/deg	90	90
β/deg	103.321(13)	104.399(3)
γ/deg	90	90
V /Å^3	1040.6(5)	1706.2(6)
Z	4	4
Dcalc /g cm^{-3}]	1.428	1.743
μ /mm^{-1}	0.344	2.161
F(000)	464.0	880.0
Data/ restraints/ parameters	2388/0/137	4097/0/201
S	1.054	1.065
R1 [I>2σ(I)]	0.0499	0.0447
wR2 [all data]	0.1236	0.1254
Max./min. residual electron dens. [eÅ^{-3}]	0.185/-0.167	0.689/-1.288

[a]$R1 = \Sigma||Fo| - |Fc||/\Sigma|Fo|$ and $wR2 = [\Sigma w(Fo^2-Fc^2)^2/\Sigma wFo^4]^{0.5}$

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A) Copies of $^{1}H/^{13}C$ NMR spectra for representative compounds Compounds 5a, 14, 20, 37, 38-D, 52, 60, 77, 84, 92, 103, 114, 127, 127-d_1, 146, 141' and 164

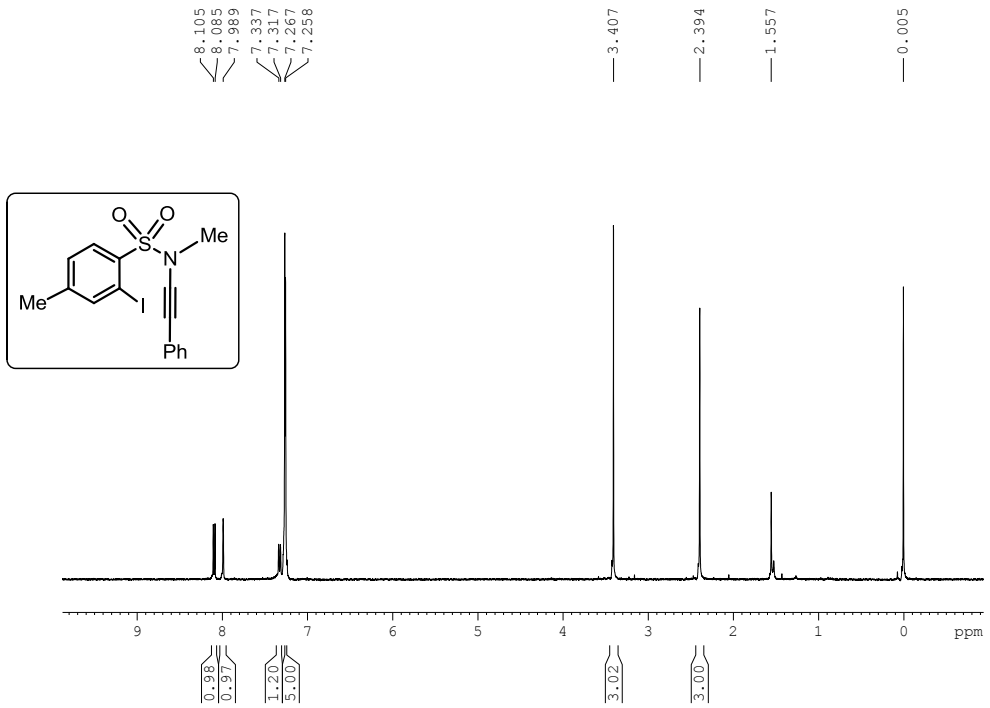

Figure A1. ^{1}H NMR spectrum of compound **5a**

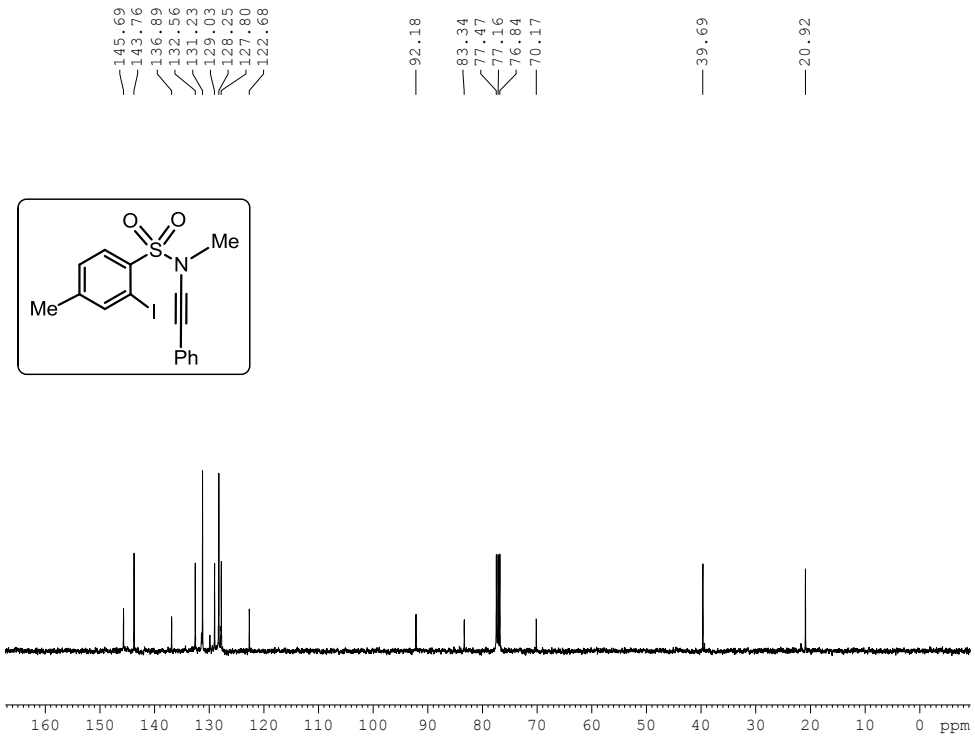

Figure A2. ^{13}C NMR spectrum of compound **5a**

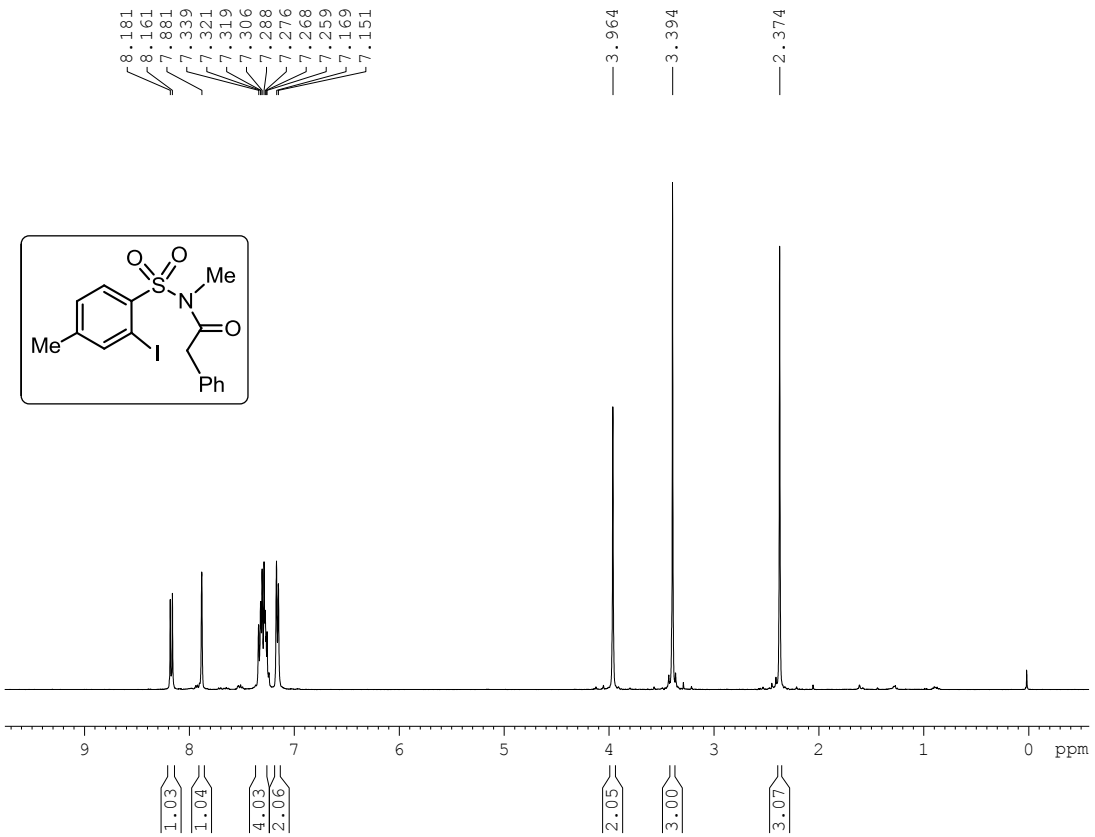

Figure A3. ^{1}H NMR spectrum of compound **14**

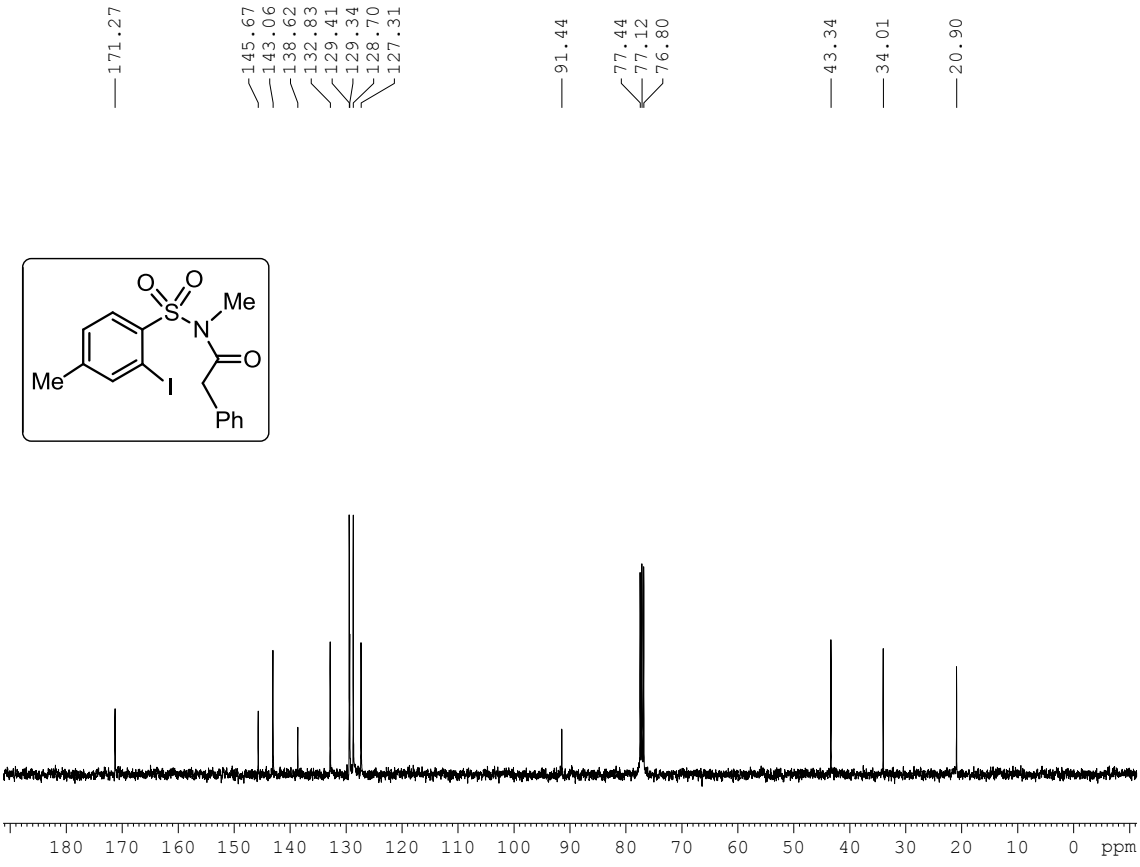

Figure A4. ^{13}C NMR spectrum of compound **14**

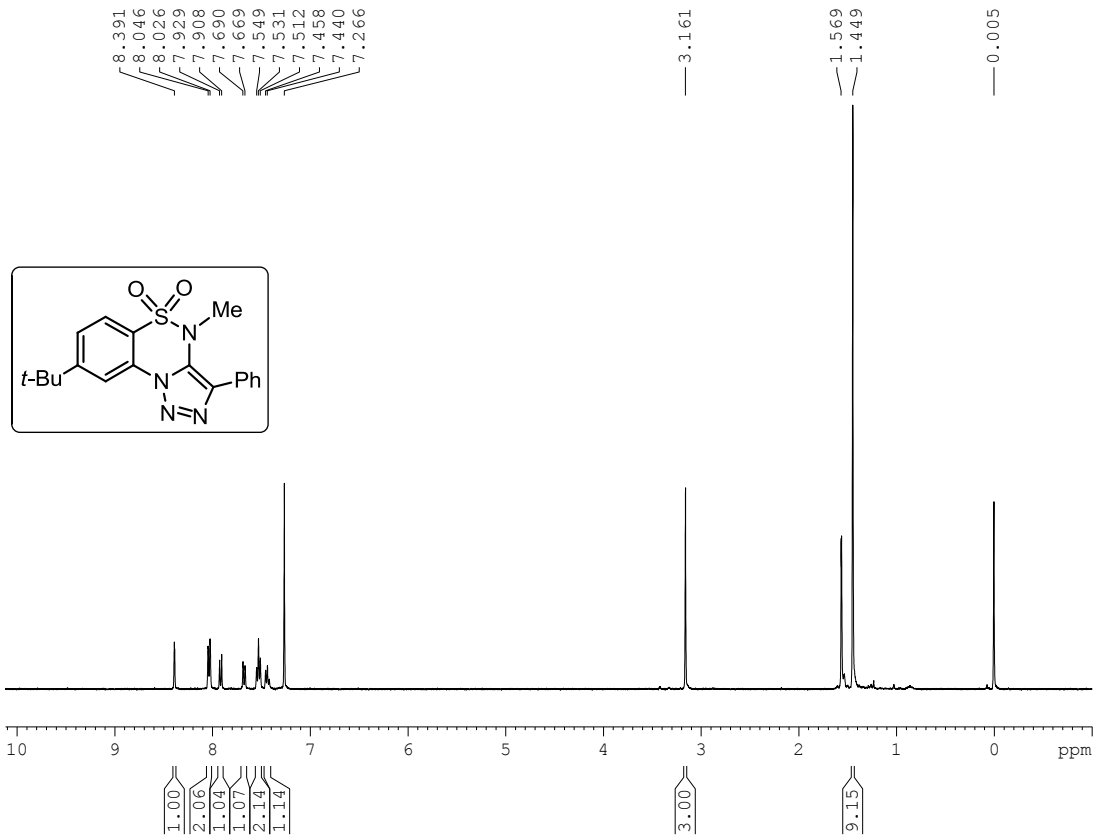

Figure A5. ^{1}H NMR spectrum of compound **20**

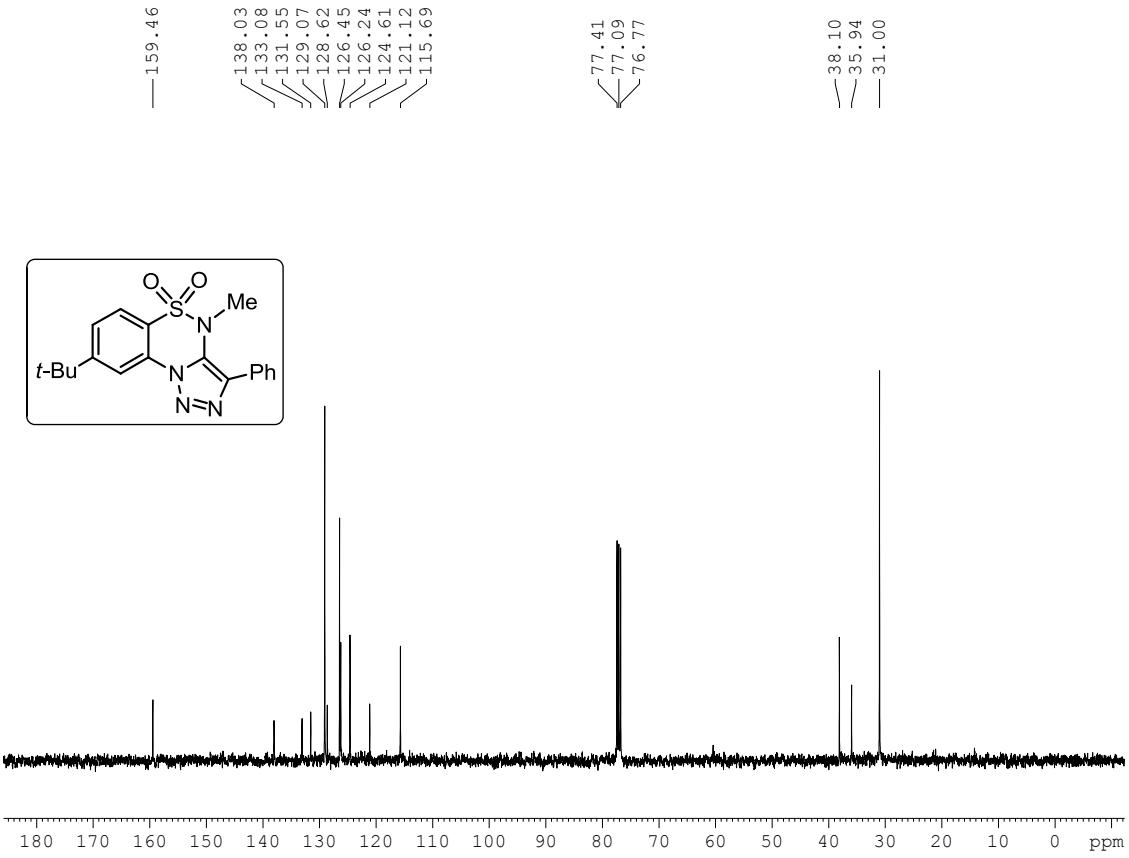

Figure A6. ^{13}C NMR spectrum of compound **20**

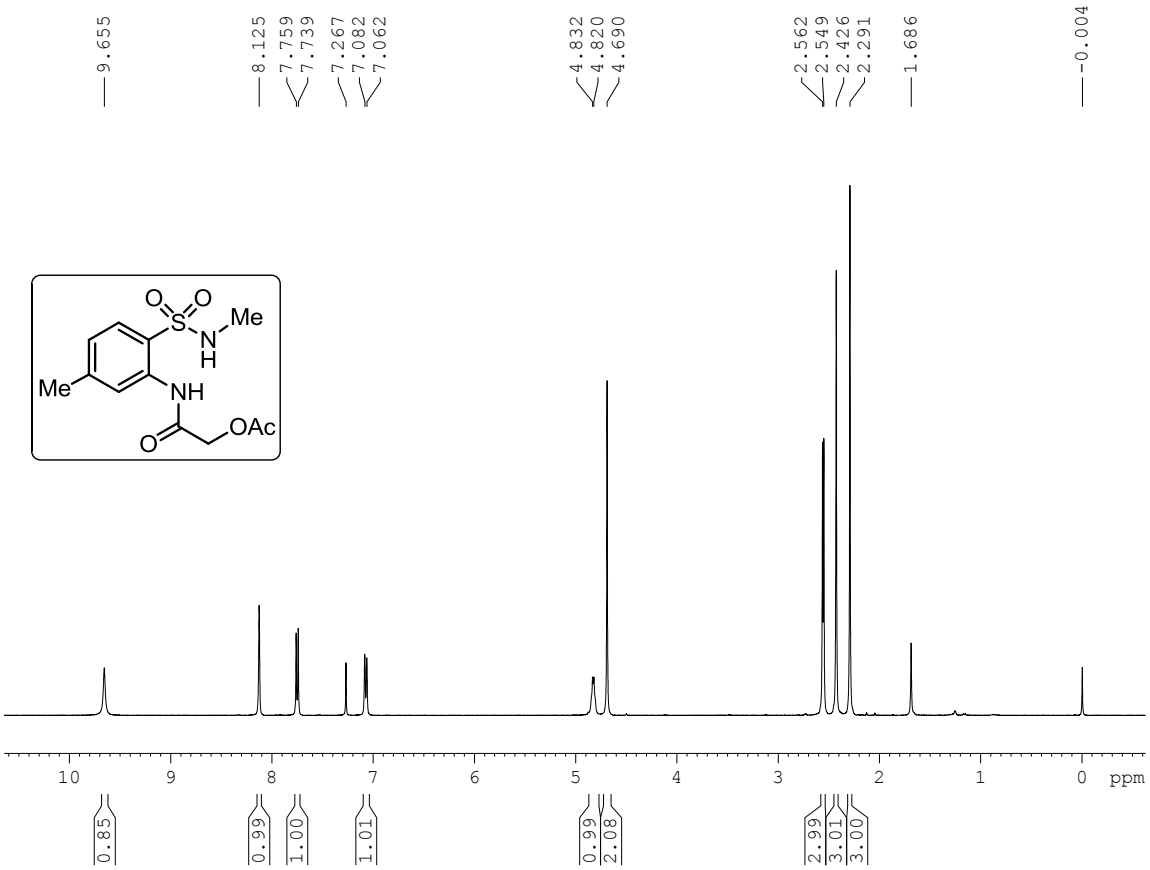

Figure A7. ^{1}H NMR spectrum of compound **37**

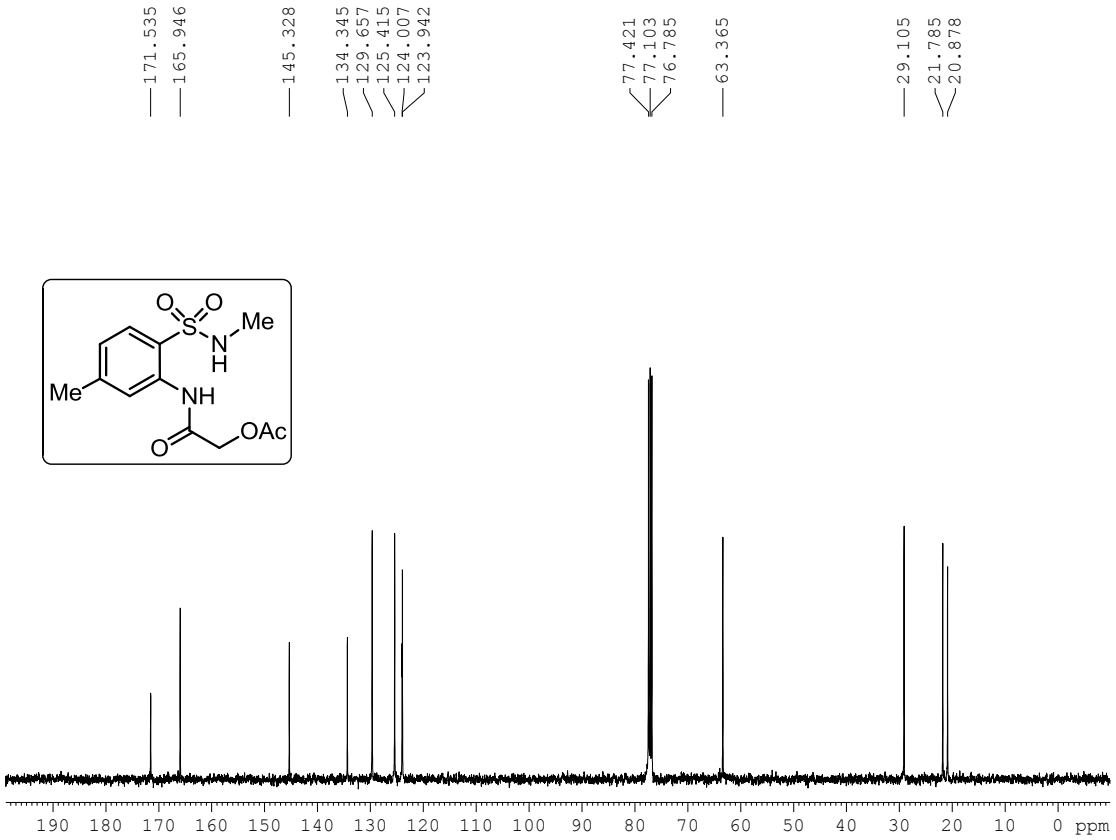

Figure A8. ^{13}C NMR spectrum of compound **37**

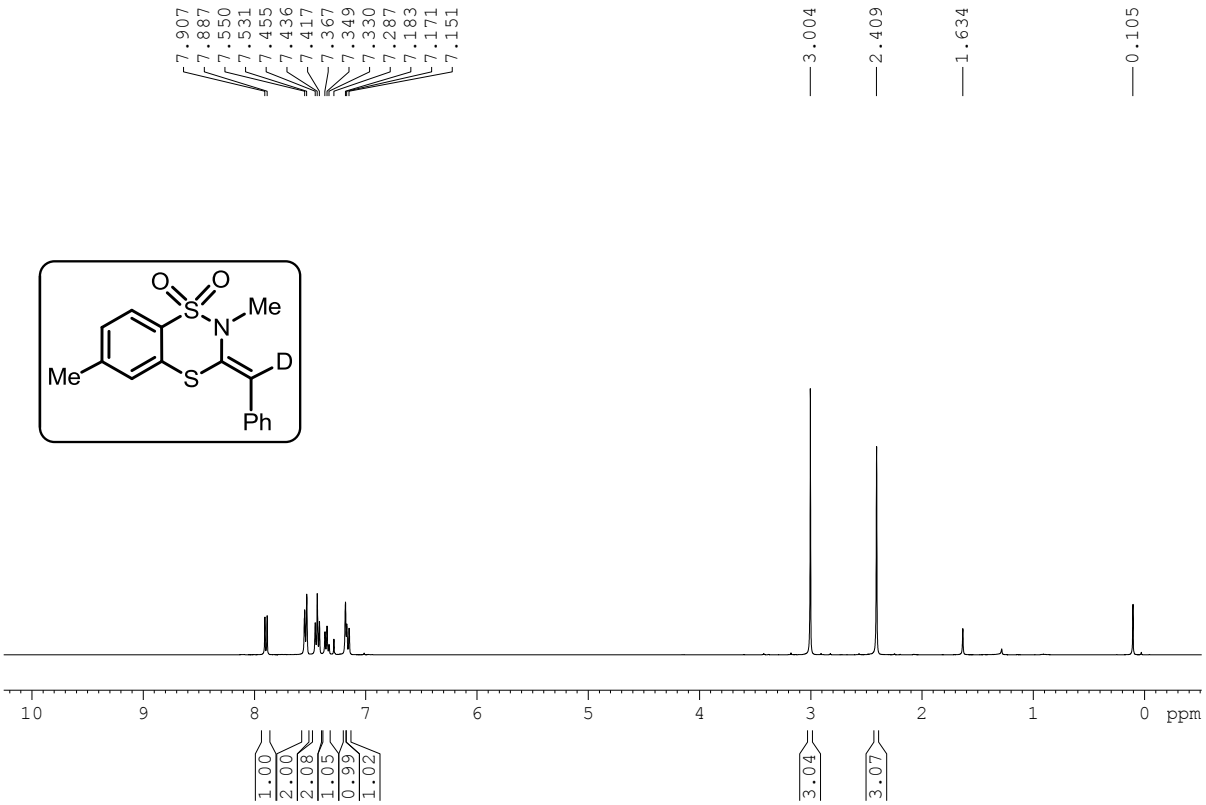

Figure A9. ^{1}H NMR spectrum of compound **38-D**

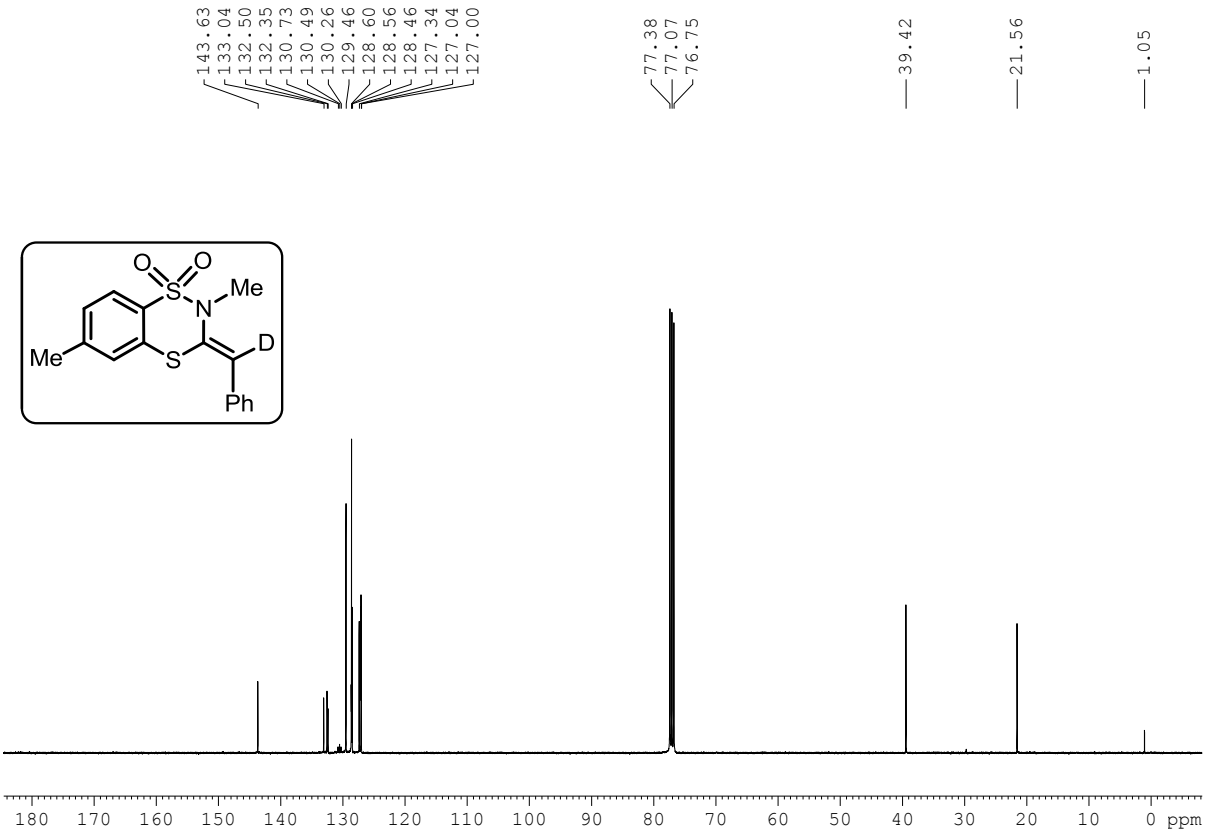

Figure A10. ^{13}C NMR spectrum of compound **38-D**

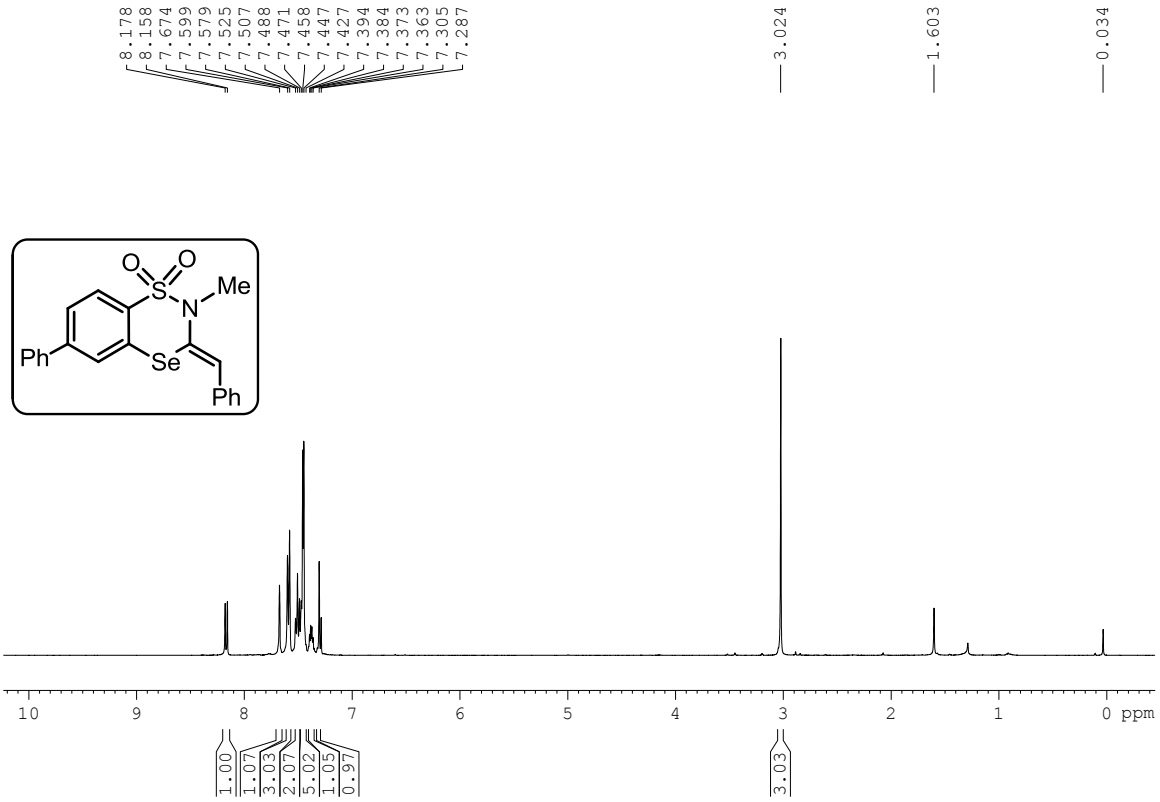

Figure A11. ^{1}H NMR spectrum of compound **52**

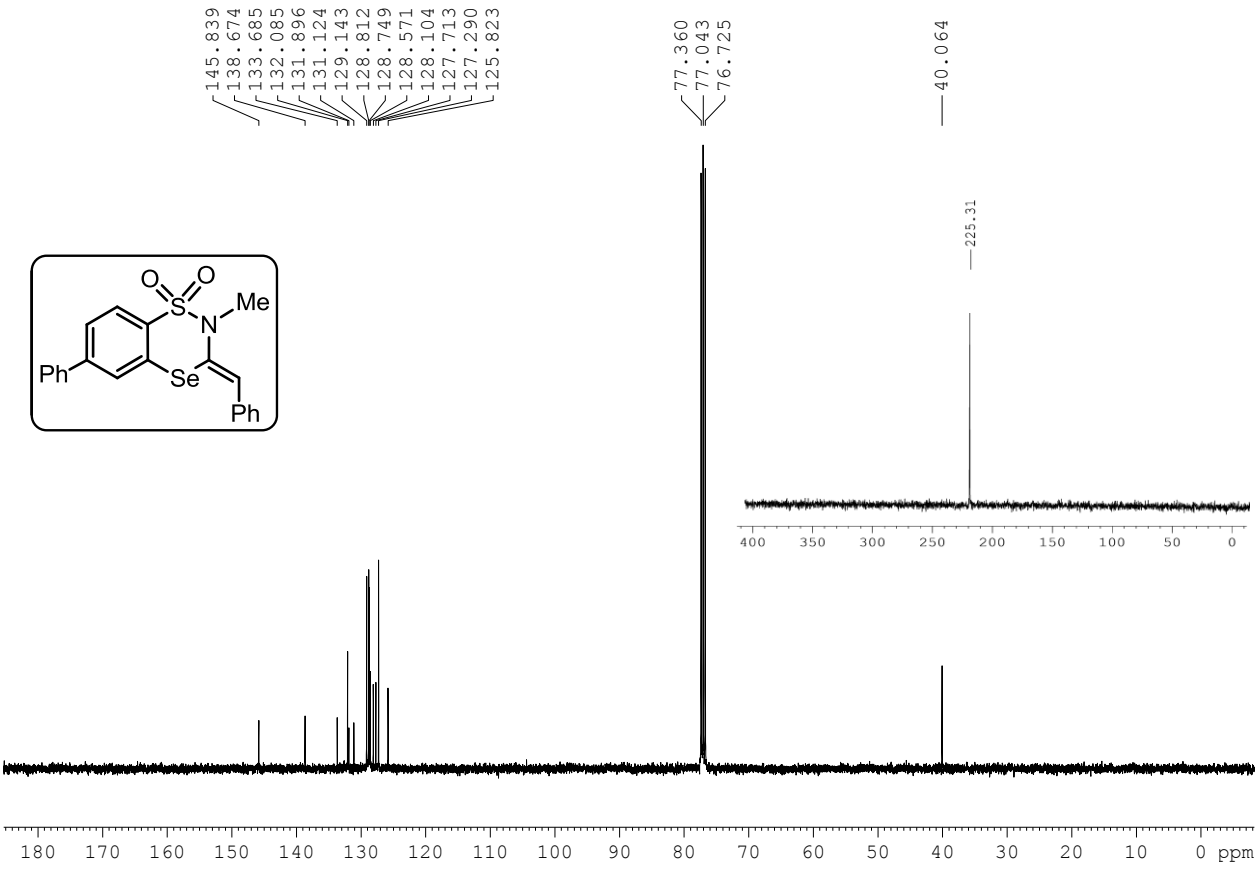

Figure A12. ^{13}C and ^{77}Se NMR spectra of compound **52**

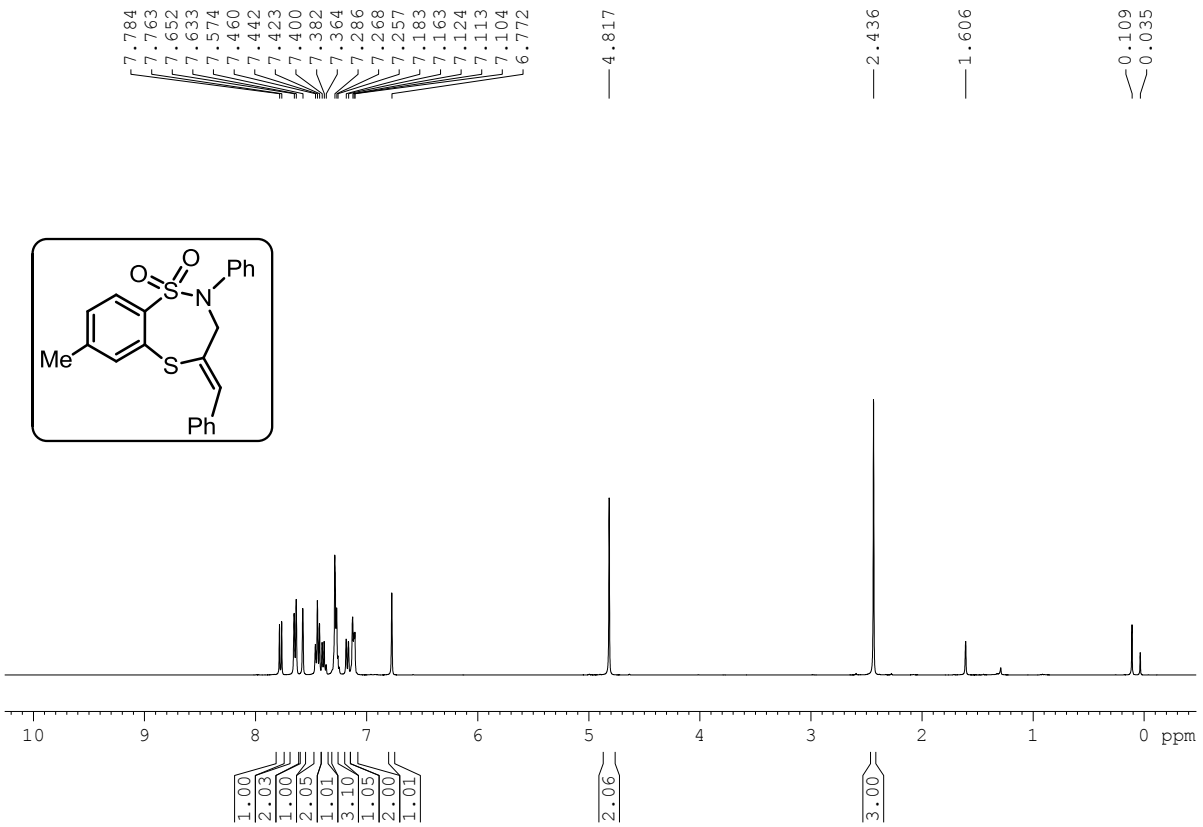

Figure A13. ^{1}H NMR spectrum of compound **60**

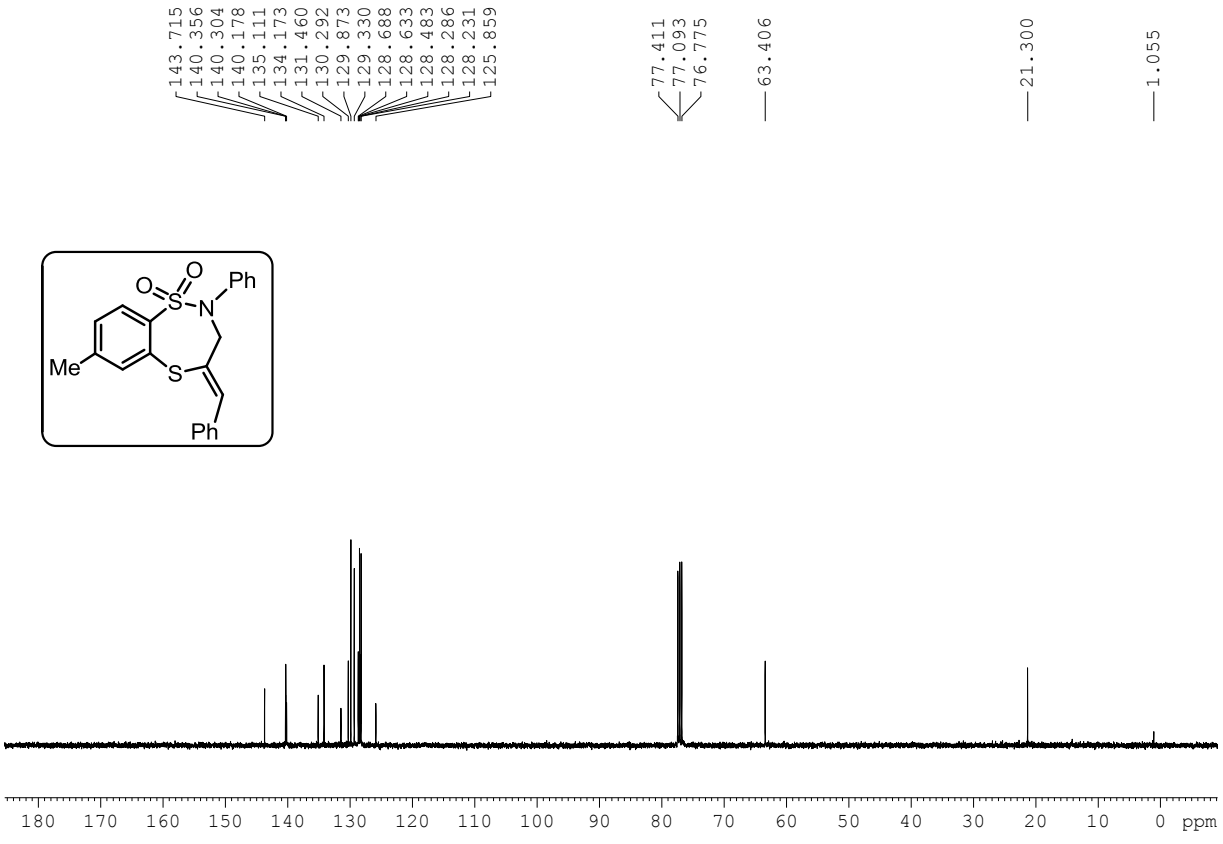

Figure A14. ^{13}C NMR spectrum of compound **60**

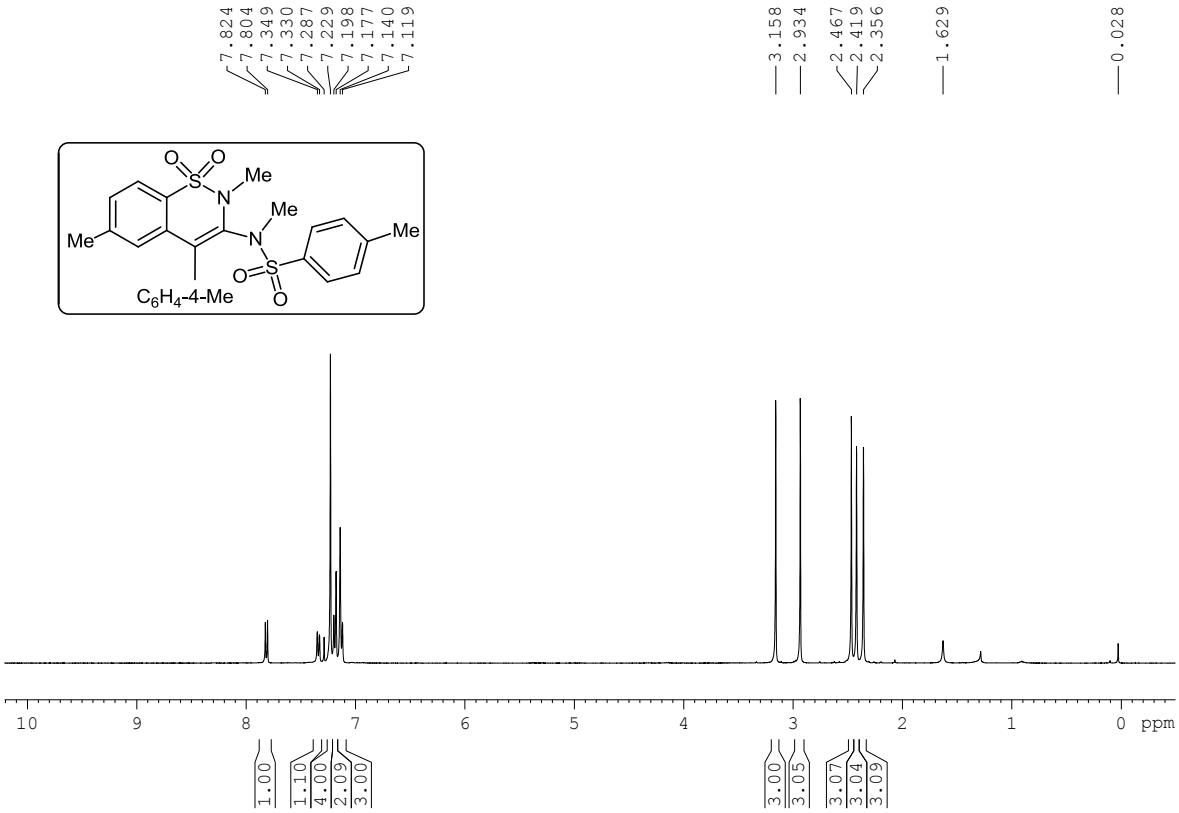

Figure A15. ^{1}H NMR spectrum of compound **77**

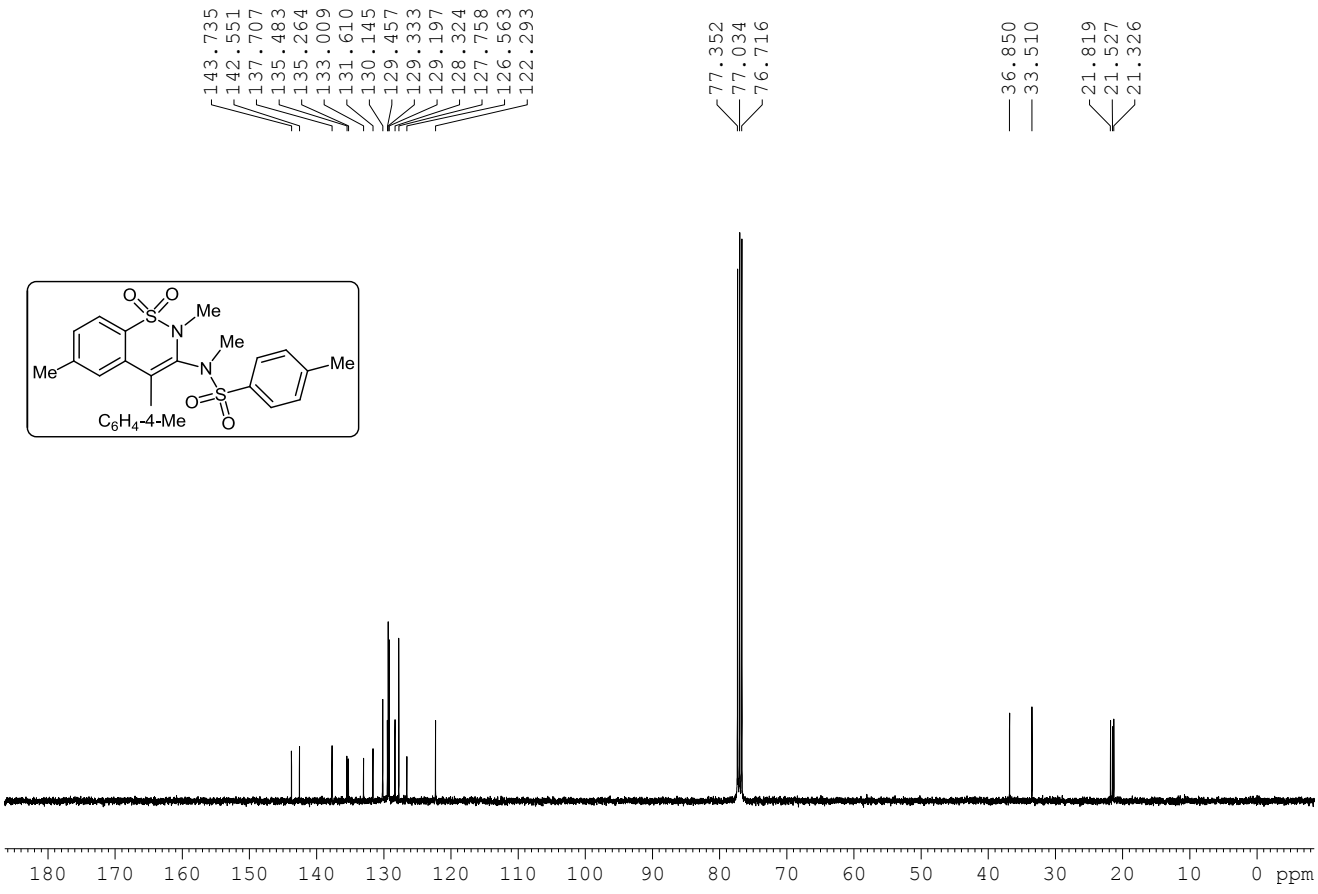

Figure A16. ^{13}C NMR spectrum of compound **77**

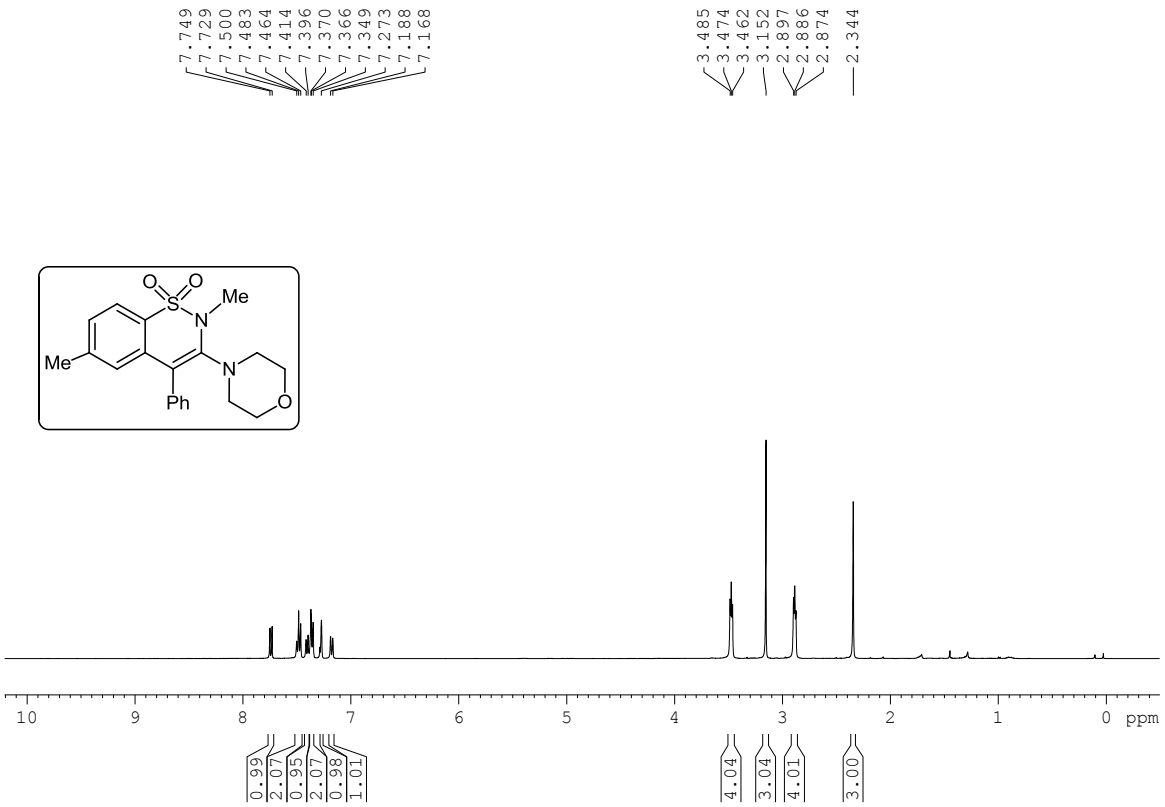

Figure A17. ^{1}H NMR spectrum of compound **84**

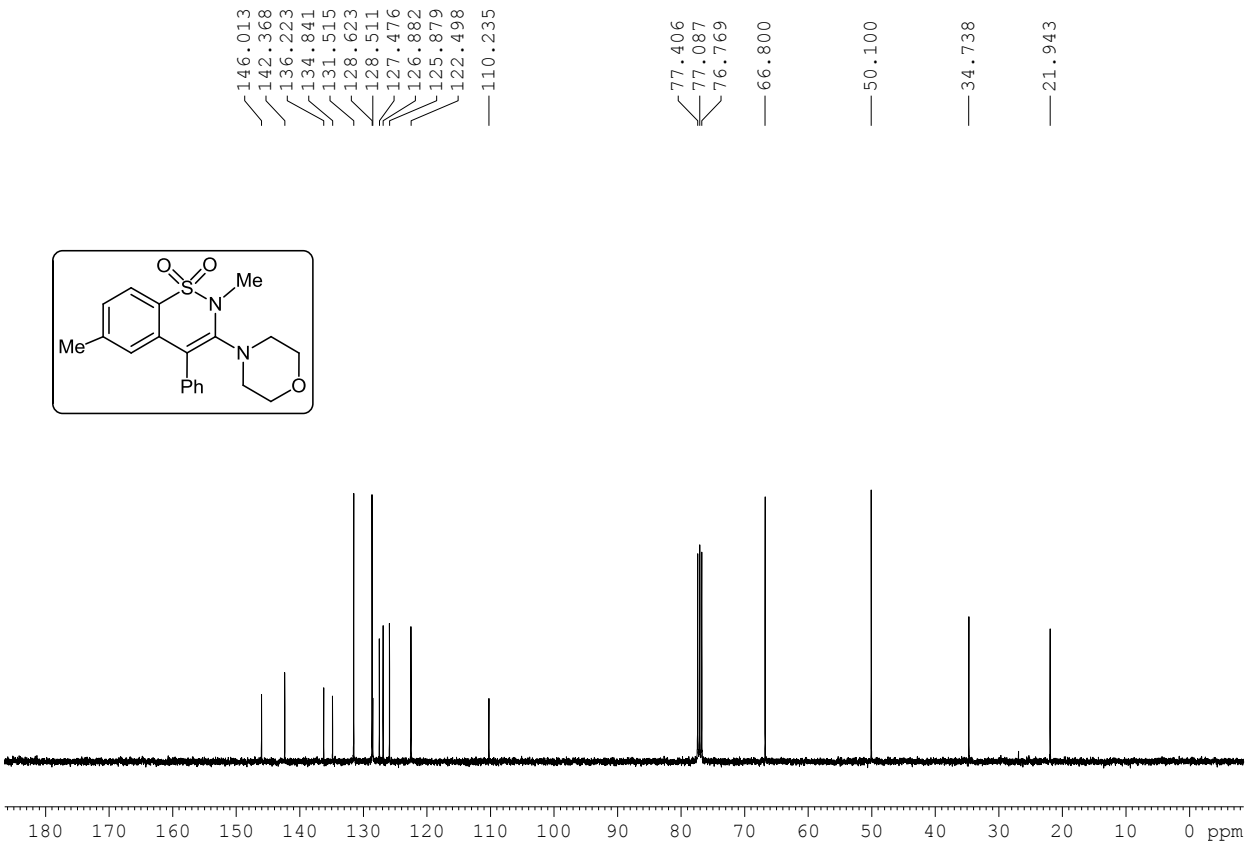

Figure A18. ^{13}C NMR spectrum of compound **84**

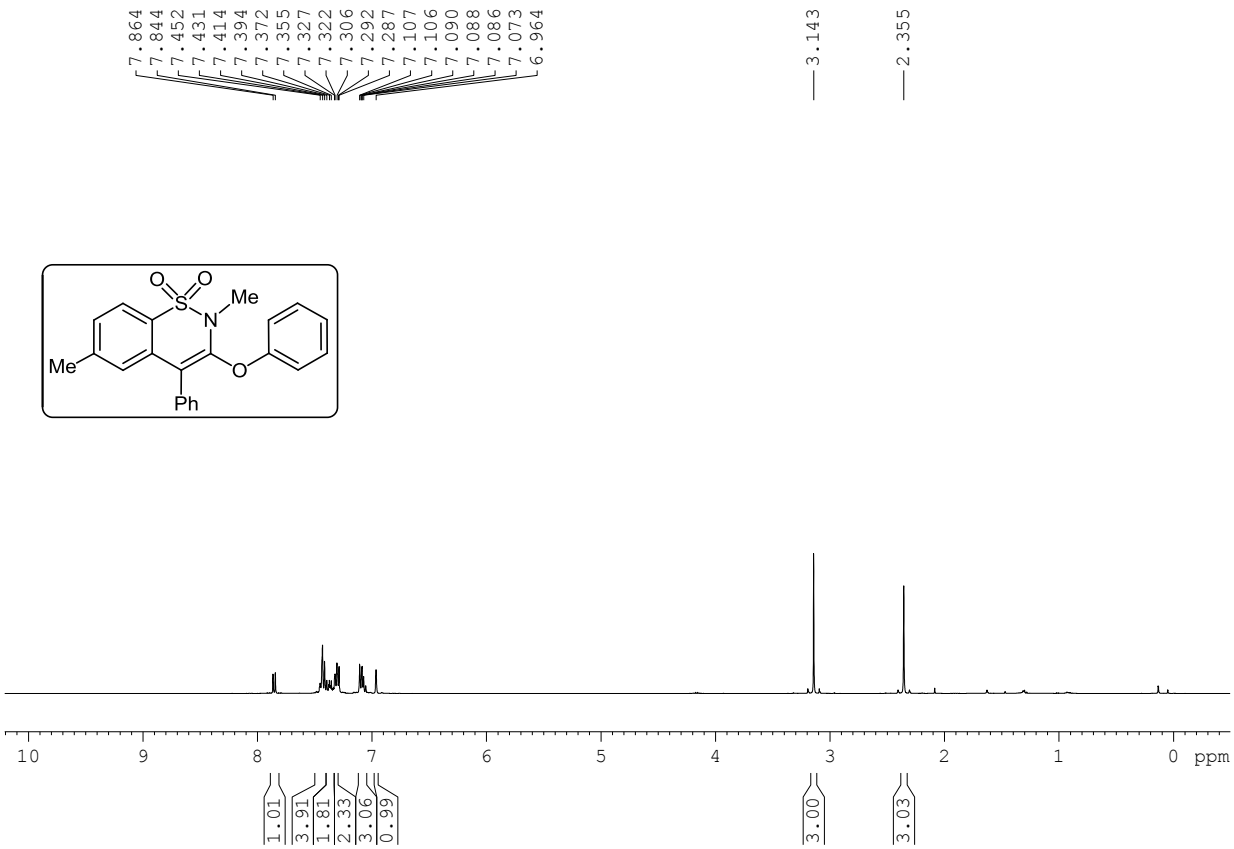

Figure A19. ^{1}H NMR spectrum of compound **92**

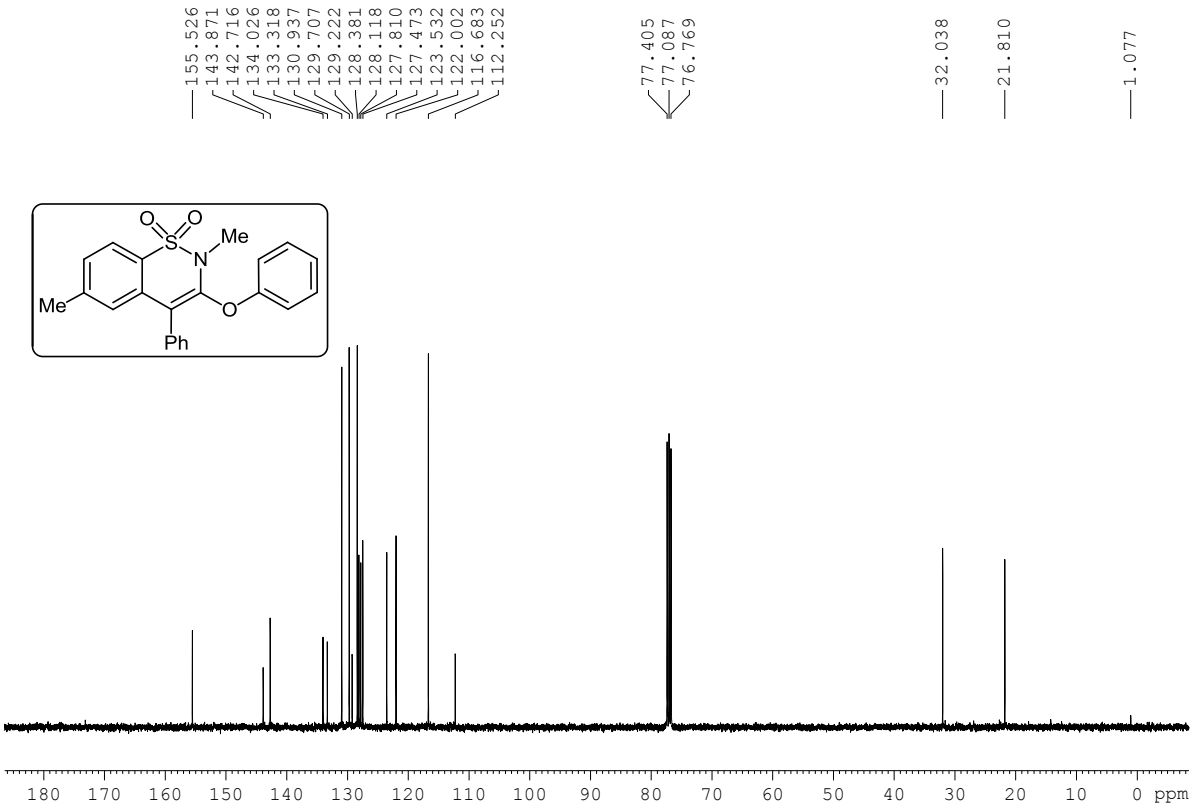

Figure A20. ^{13}C NMR spectrum of compound **92**

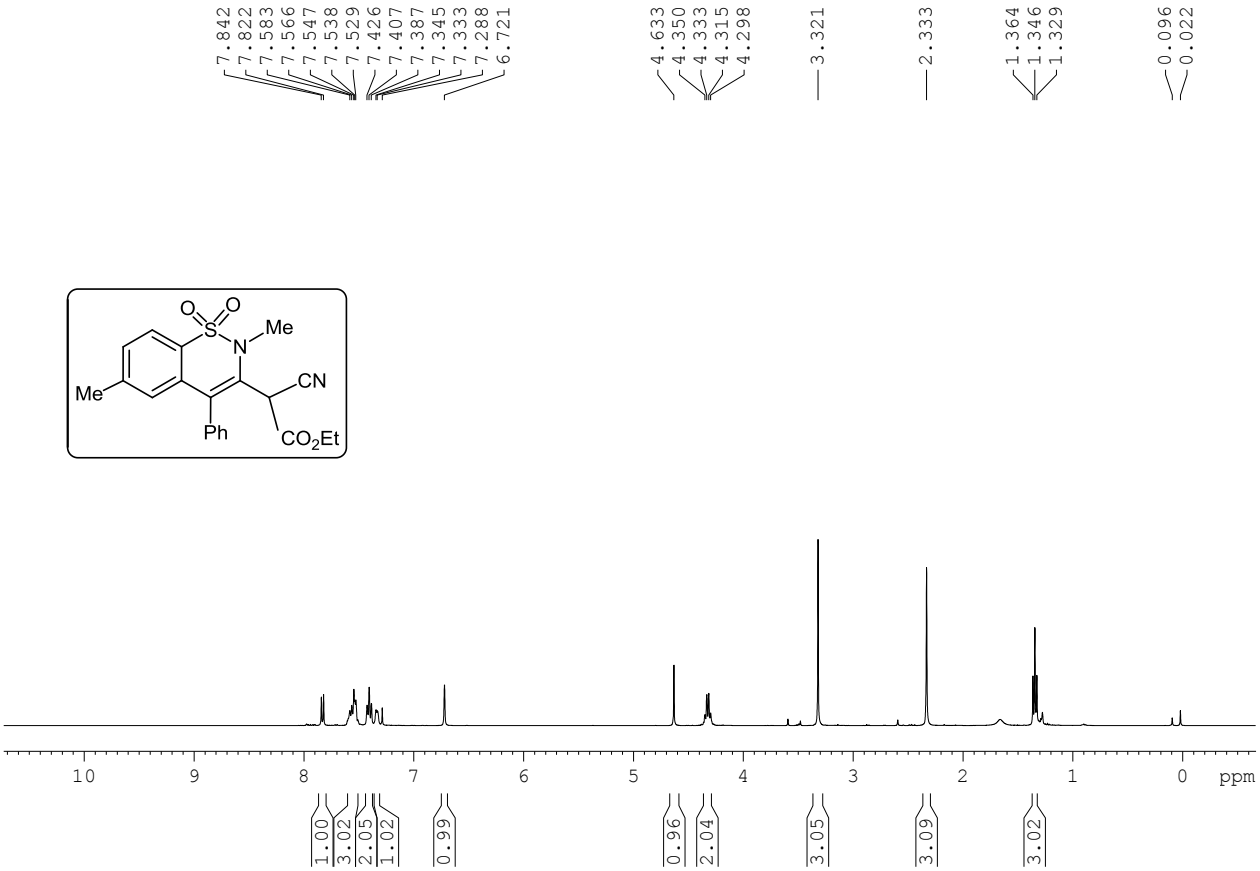

Figure A21. ^{1}H NMR spectrum of compound **103**

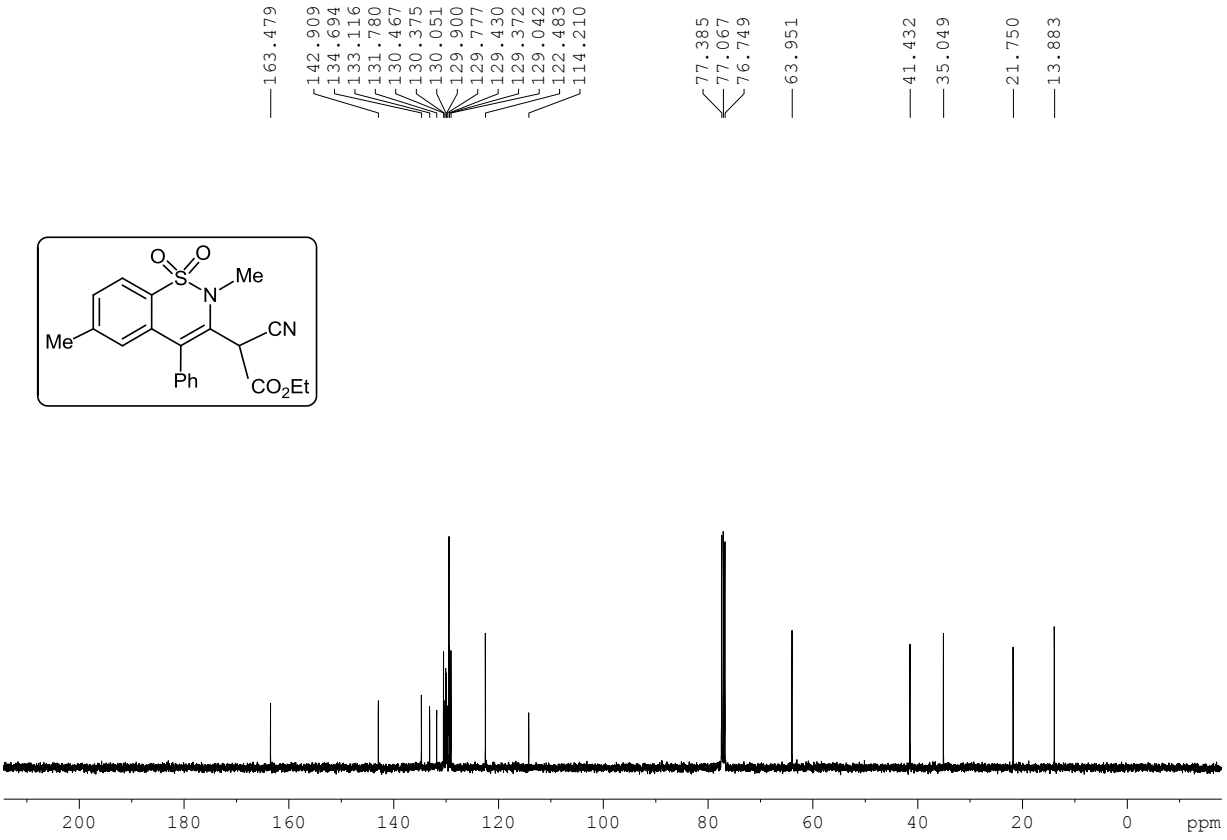

Figure A22. ^{13}C NMR spectrum of compound **103**

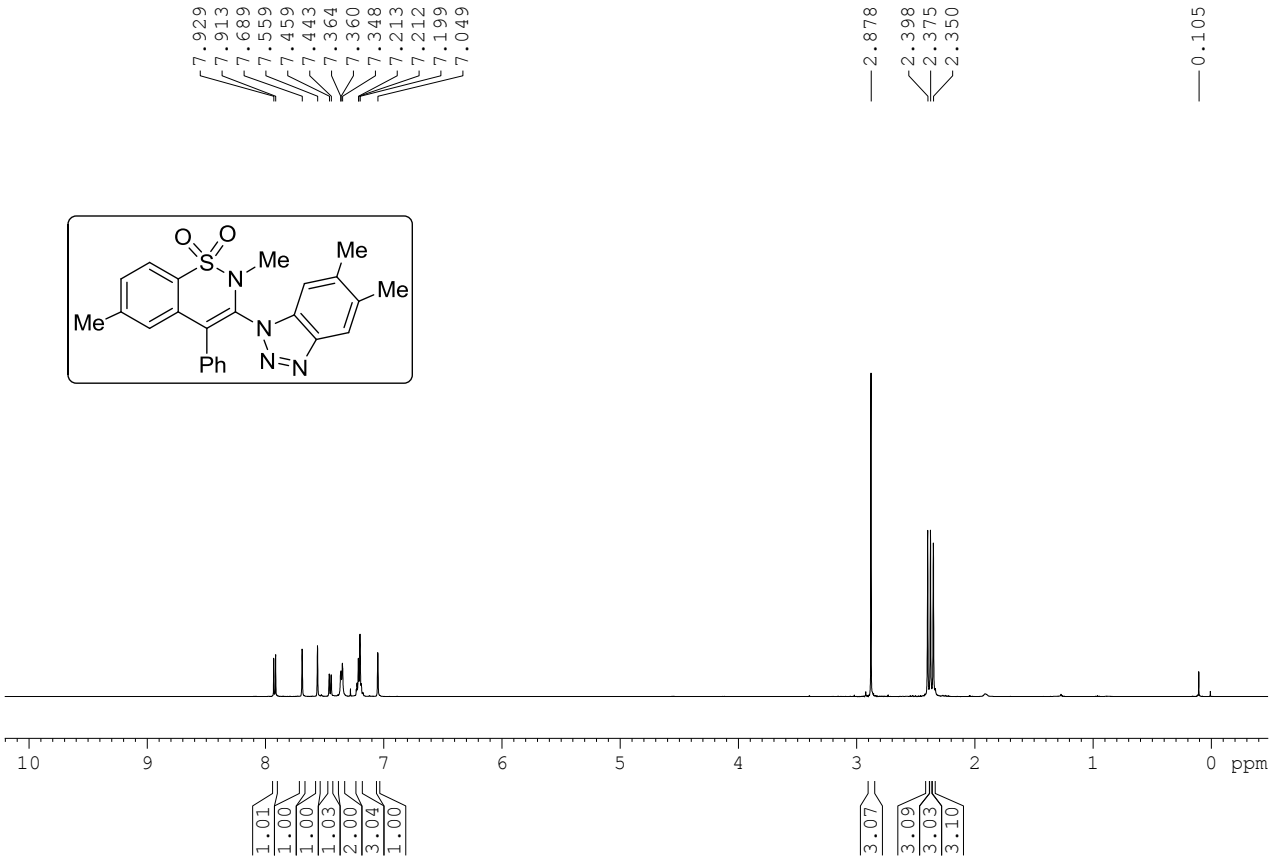

Figure A21. ^{1}H NMR spectrum of compound **114**

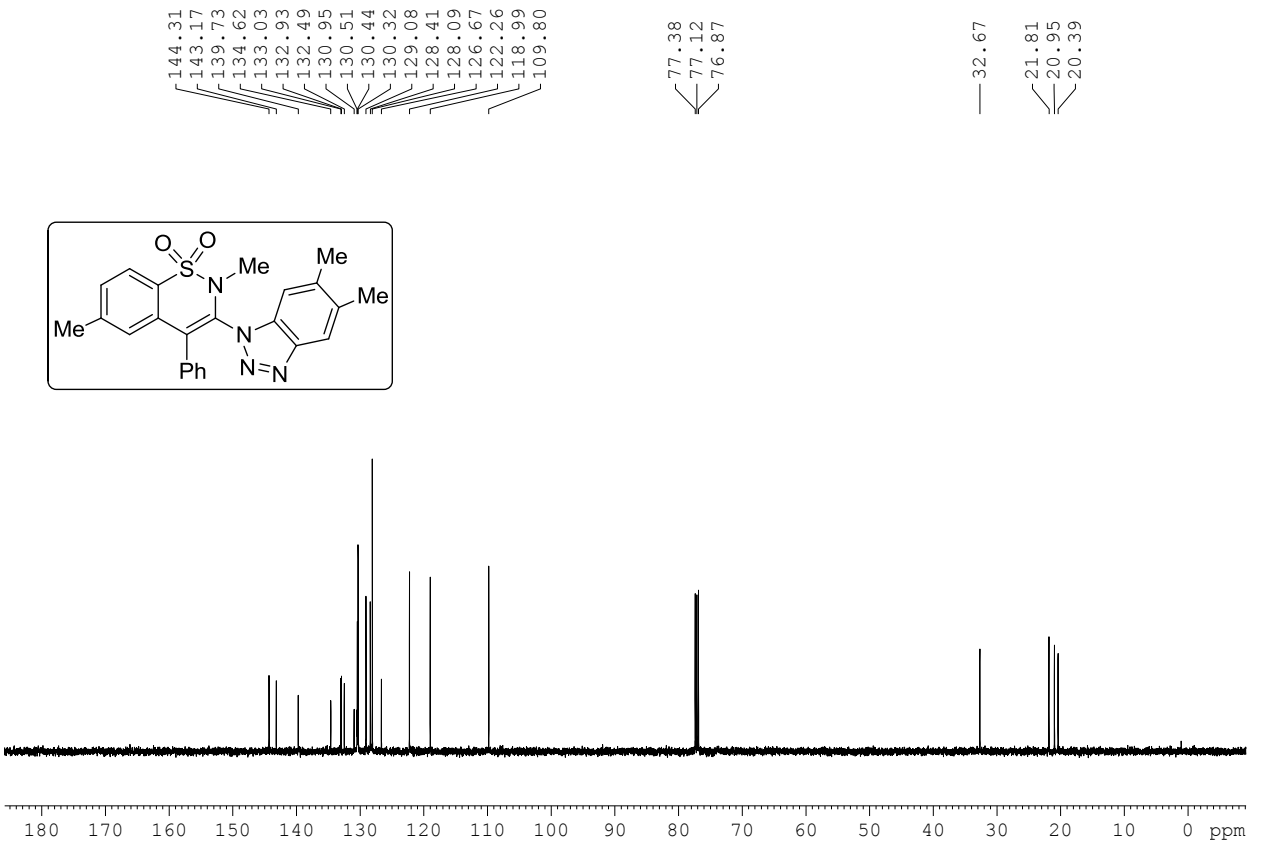

Figure A22. ^{13}C NMR spectrum of compound **114**

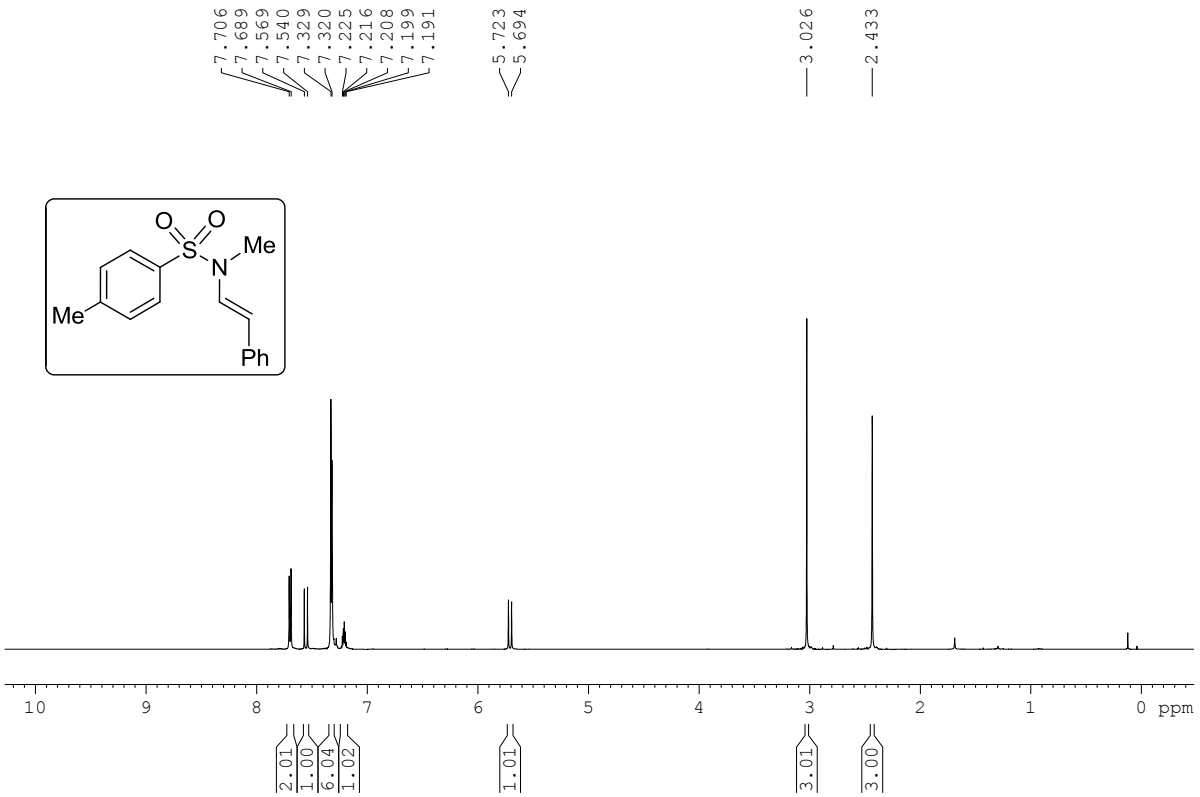

Figure S4. ^{1}H NMR spectrum of compound **127**

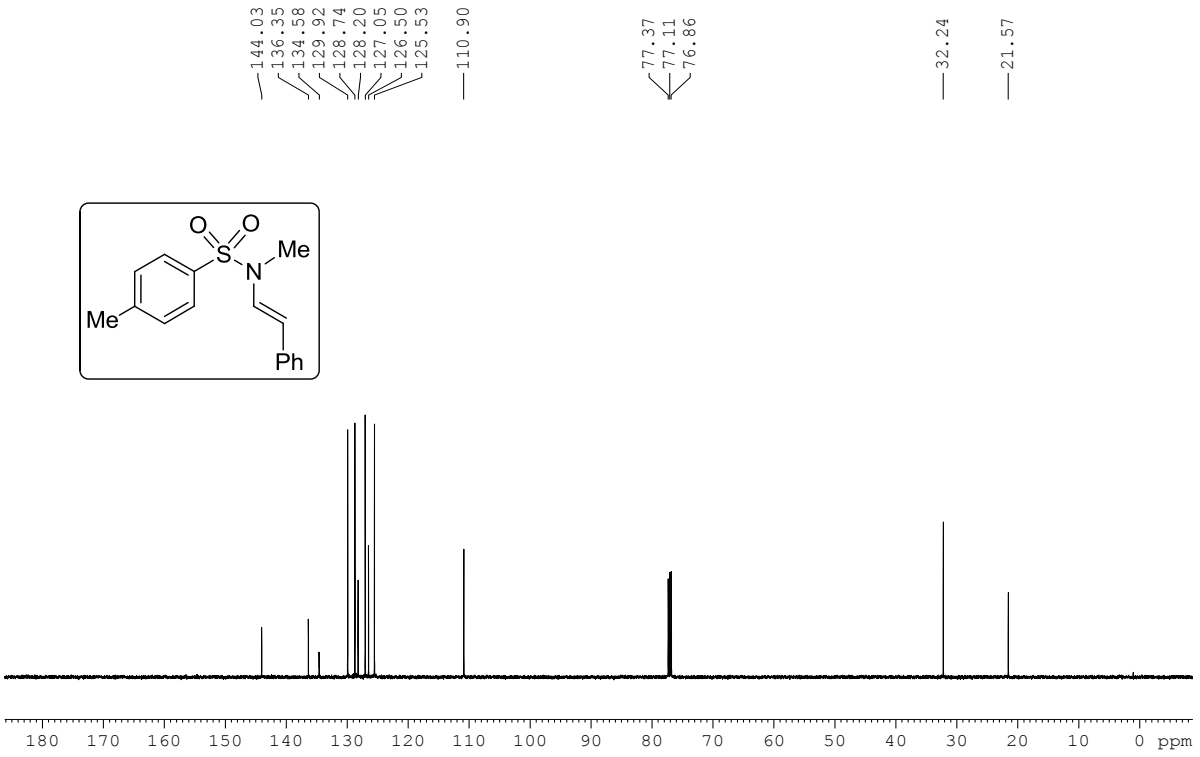

Figure S5. ^{13}C NMR spectrum of compound **127**

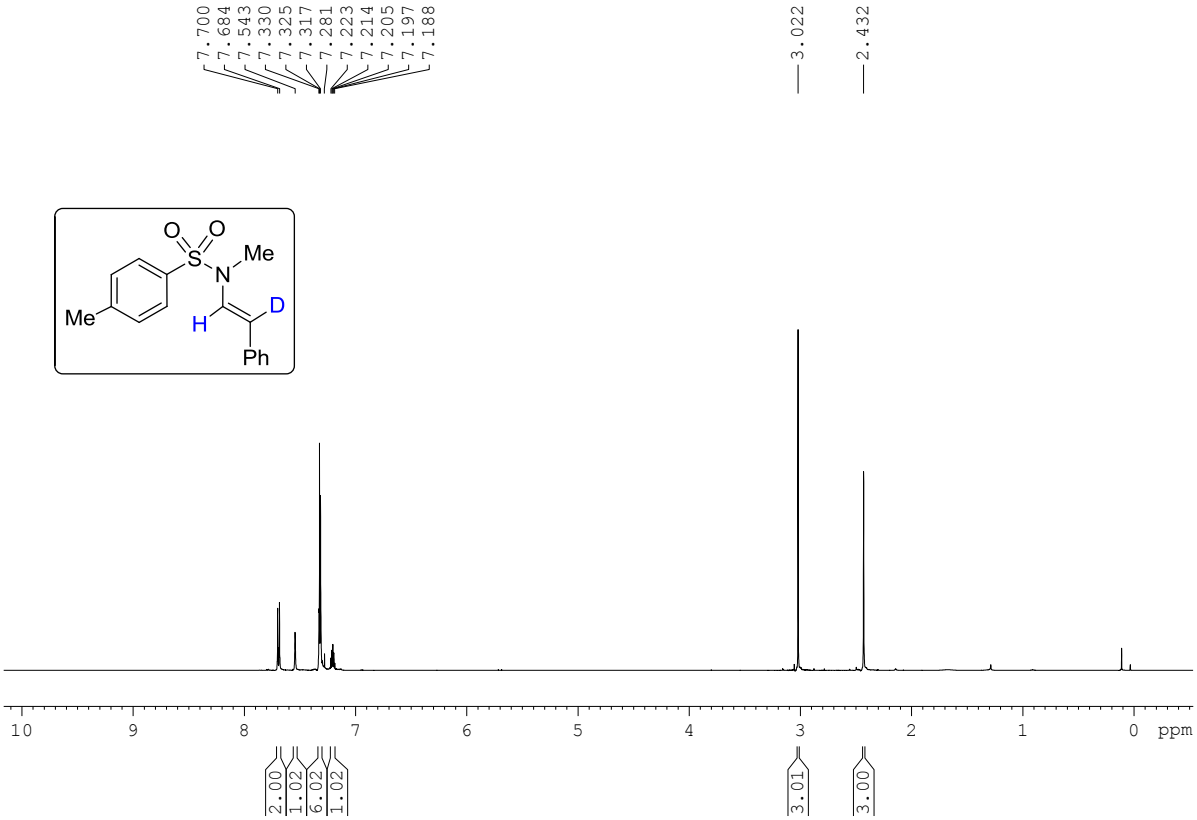

Figure S6. ^{1}H NMR spectrum of compound **127**-d_1

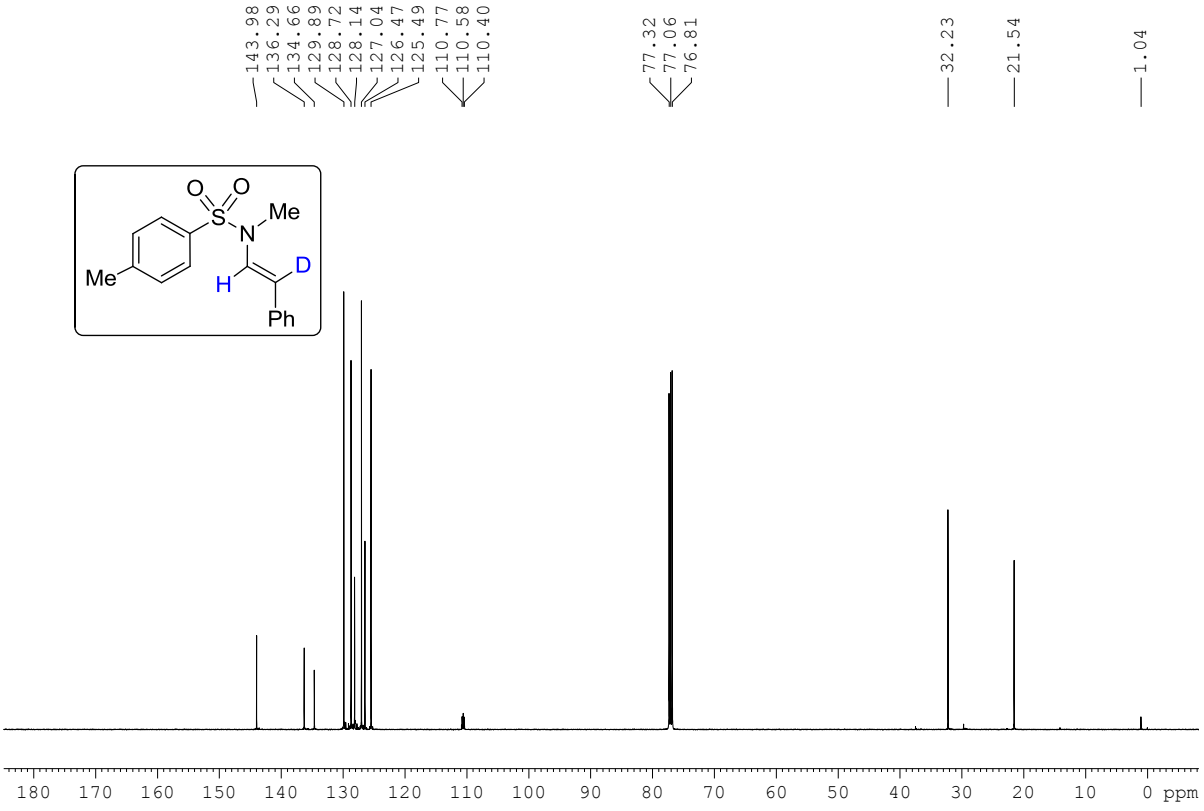

Figure S7. ^{13}C NMR spectrum of compound **127**-d_1

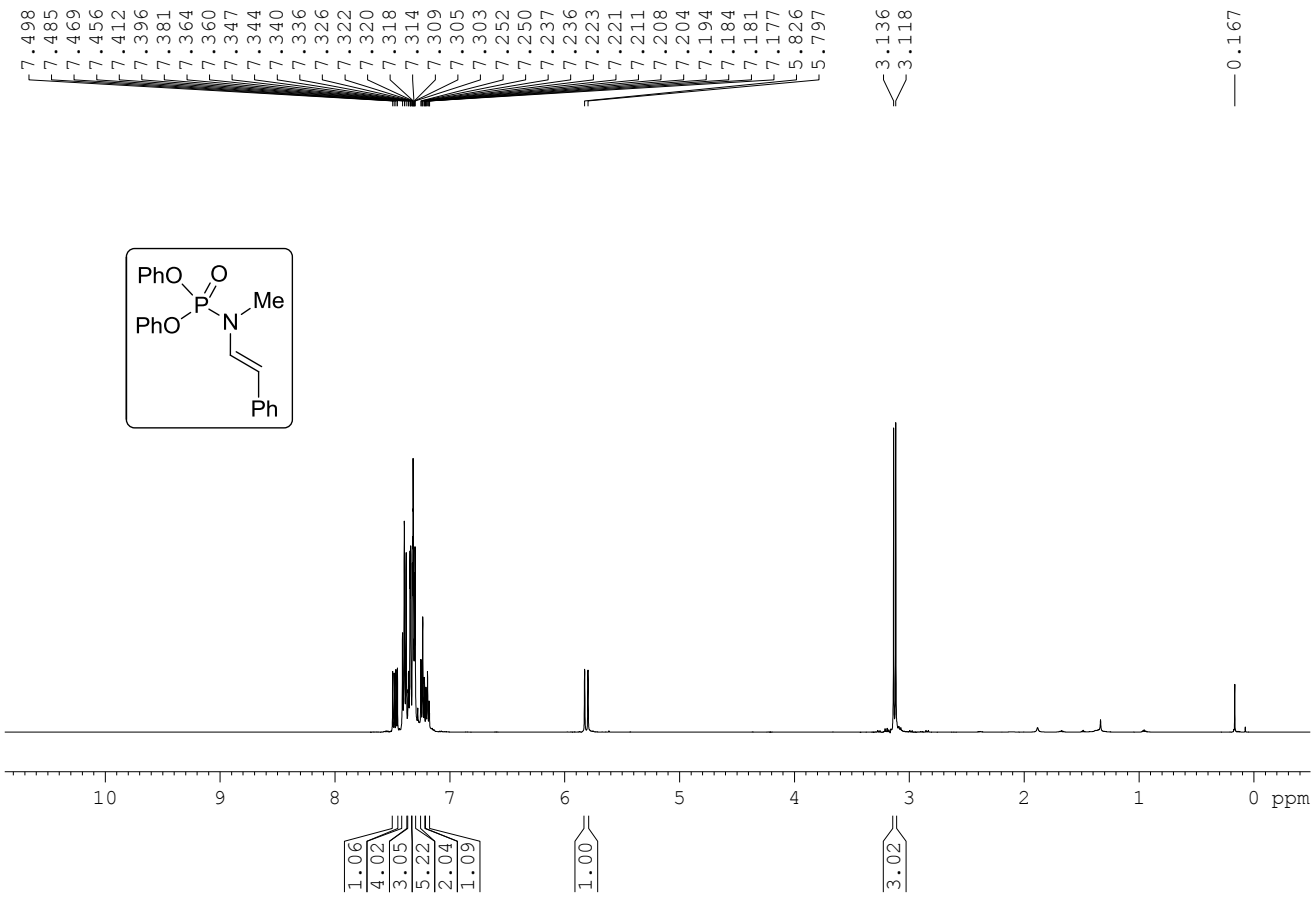

Figure S40. ^{1}H NMR spectrum of compound **146**

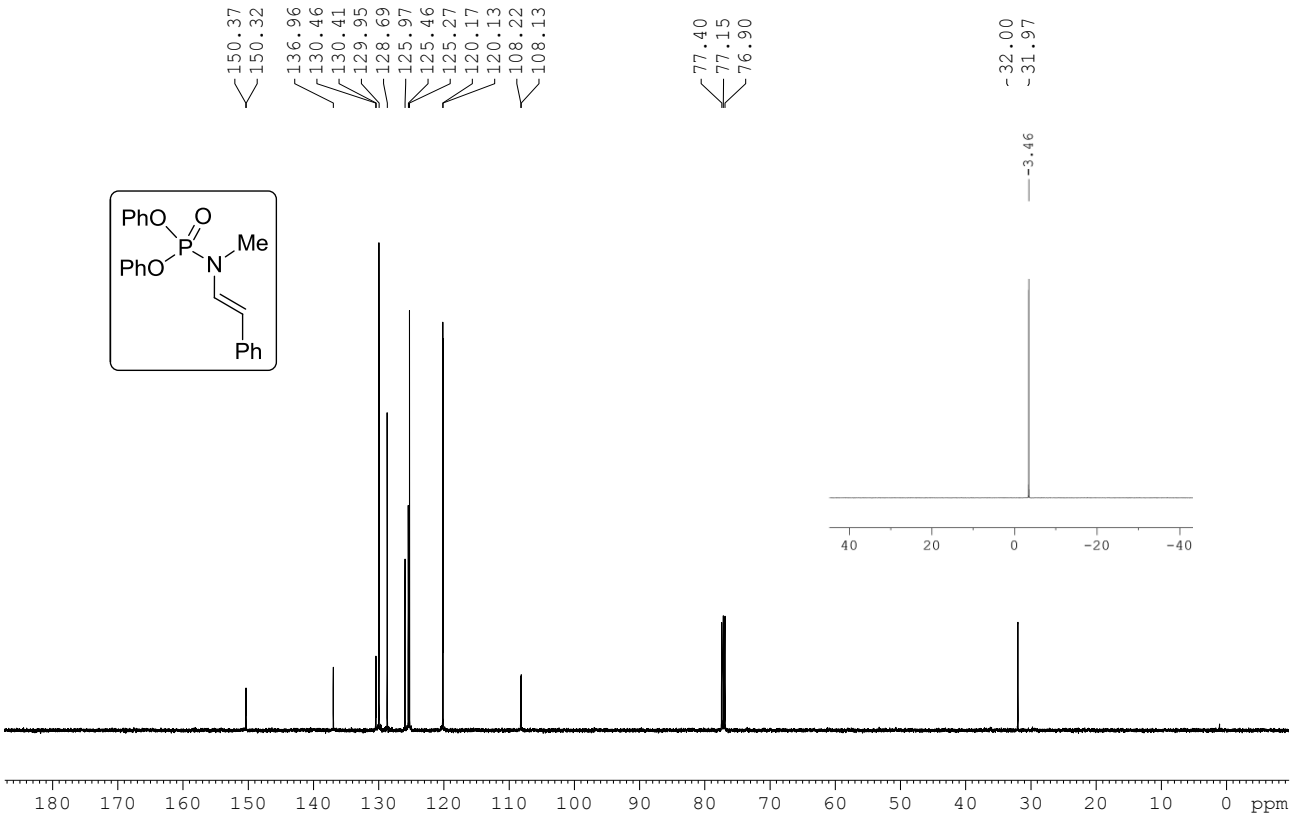

Figure S41. ^{13}C NMR spectrum of compound **146**

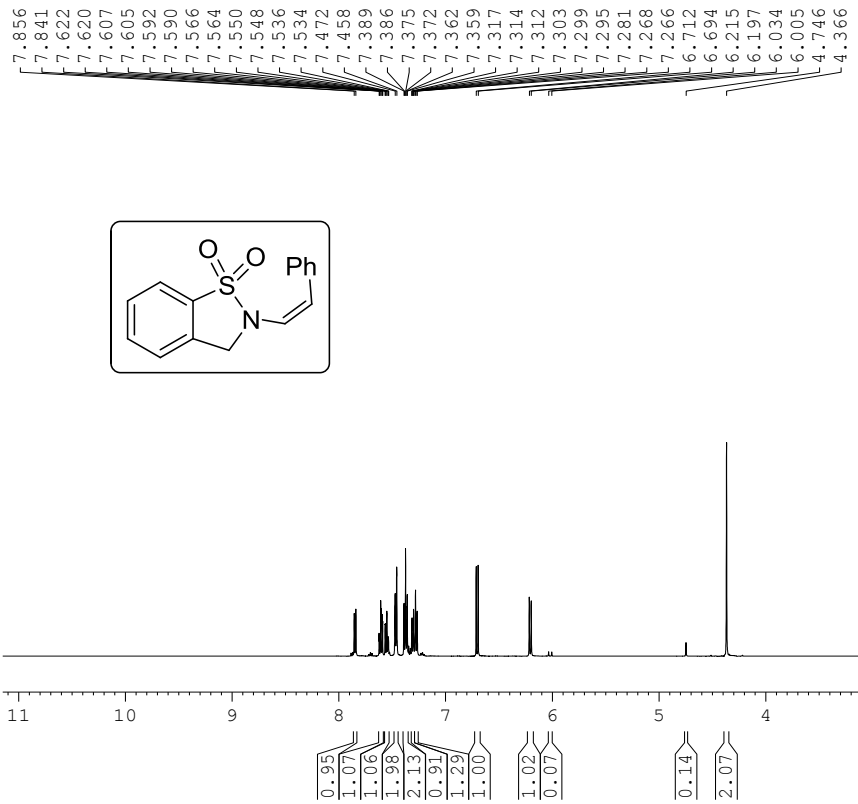

Figure S61. ^{1}H NMR spectrum of compound **141'**

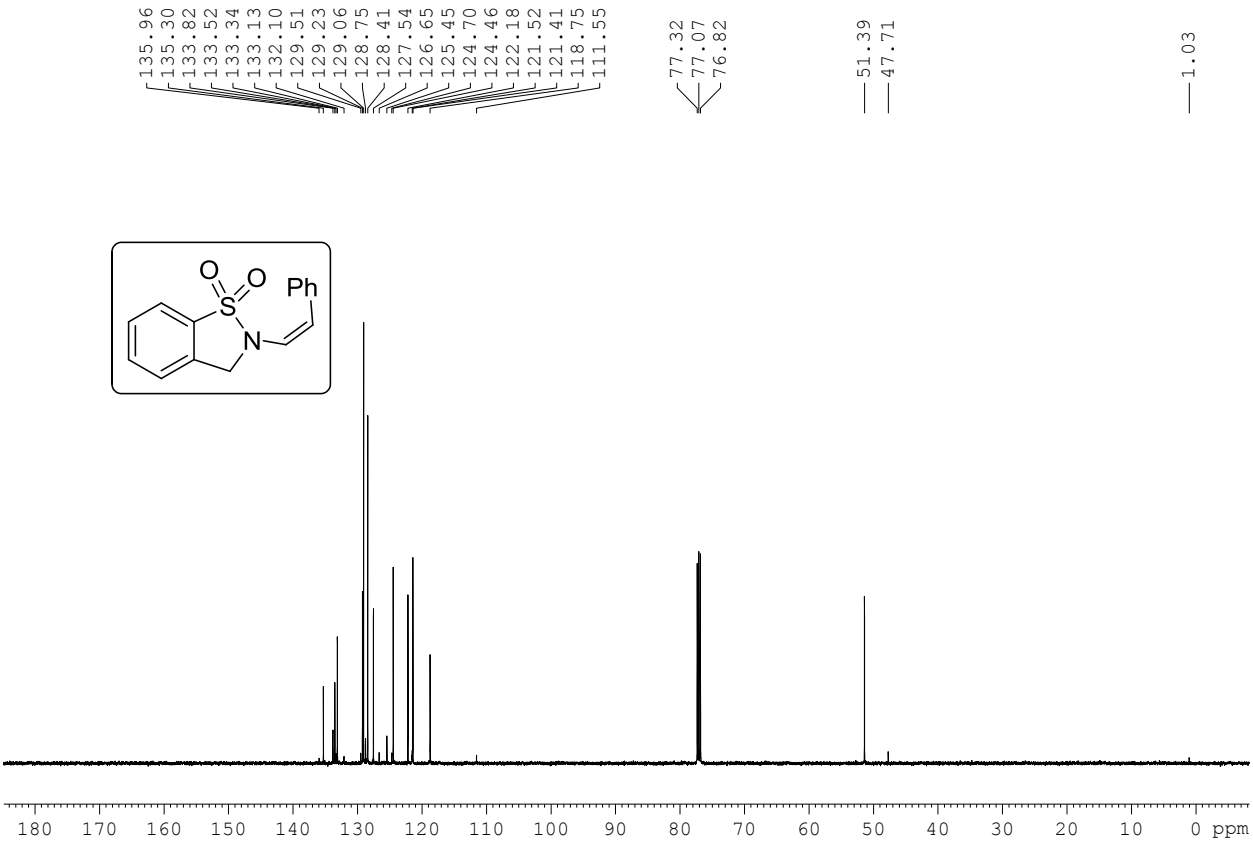

Figure S62. ^{13}C NMR spectrum of compound **141'**

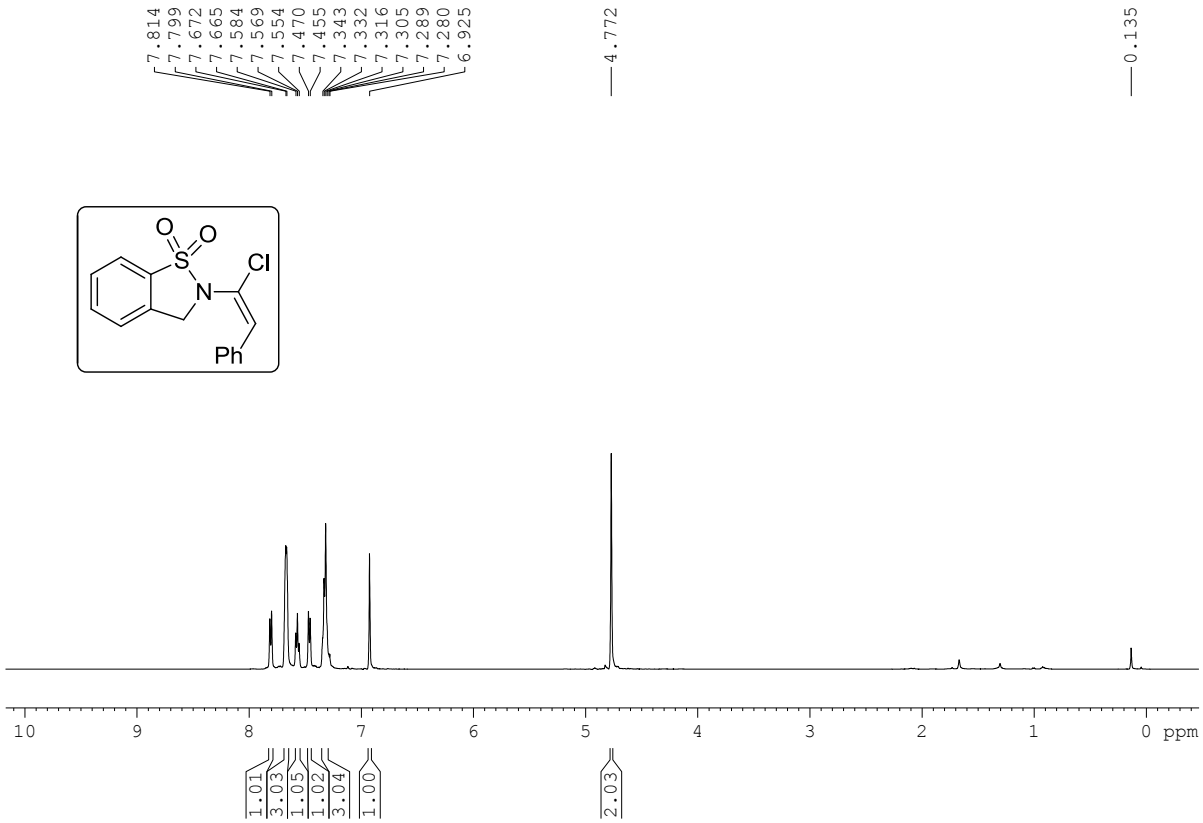

Figure S30. ^{1}H NMR spectrum of compound **164**

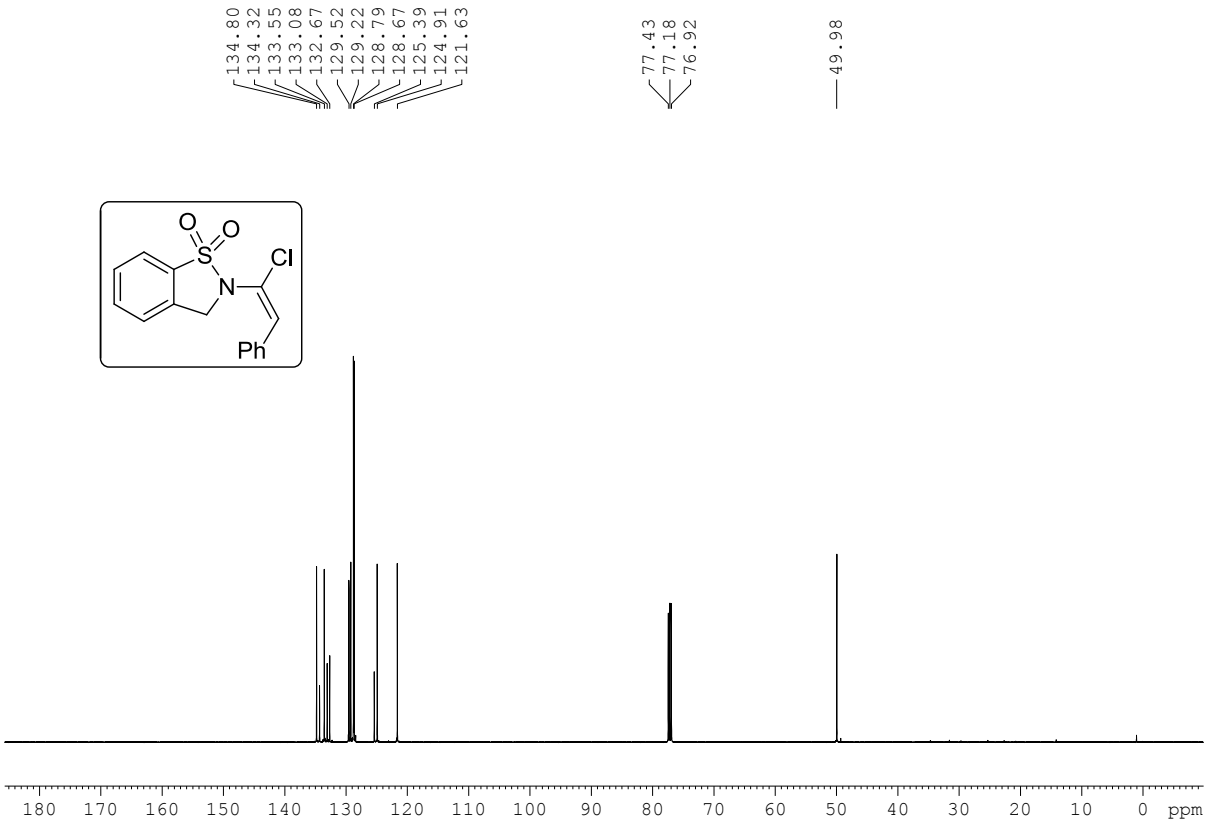

Figure S31. ^{13}C NMR spectrum of compound **164**

B) Publication numbers and atomic coordinates for X-ray structures reported in this thesis

I. Publication numbers for the published compounds
Compounds 19, 26 and 34 Publication no. 1
Compounds 38, 44, 46, 50 and 58 Publication no. 2
Compounds 66, 81, 90, 102 and 104 Publication no. 3
Compounds 111, 114 and 119 Publication no. 4
Compounds 127, 131 and 141 Publication no. 5
(Contents, p. xiii)

II. Selected atomic coordinates for compounds 126, 168 and 169.

Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for 4. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Compound 126

Atom	x	y	z	U(eq)
S(1)	-243(1)	3550(1)	2501(1)	52(0)
N(2)	1070(1)	3006(2)	3647(1)	39(1)
O(2)	351(2)	3587(2)	1965(1)	70(1)
N(1)	-194(1)	2344(2)	2950(2)	49(1)
O(1)	-1084(1)	3751(2)	2197(2)	73(1)
O(3)	2363(1)	3588(2)	3623(2)	83(1)
C(7)	466(2)	2150(2)	3563(2)	40(1)
C(6)	774(2)	4088(2)	3792(2)	40(1)
C(5)	1116(2)	4772(2)	4393(2)	46(1)
C(1)	79(2)	4424(2)	3293(2)	46(1)
C(17)	1871(2)	2863(3)	3478(2)	51(1)
C(8)	513(2)	1265(2)	4030(2)	47(1)
C(9)	1119(2)	1031(2)	4728(2)	44(1)
C(18)	2070(2)	1799(3)	3100(2)	63(1)
C(16)	-935(2)	1660(3)	2900(2)	62(1)
C(10)	1486(2)	1836(3)	5249(2)	53(1)
C(14)	1318(2)	-63(3)	4894(2)	56(1)
C(11)	2028(2)	1548(3)	5901(2)	62(1)
C(2)	-303(2)	5421(3)	3407(2)	61(1)
C(12)	2227(2)	460(3)	6056(2)	65(1)
C(4)	759(2)	5797(2)	4491(2)	53(1)
C(13)	1872(2)	-344(3)	5551(2)	64(1)
C(3)	57(2)	6101(3)	4009(2)	60(1)
C(15)	1146(3)	6556(3)	5142(2)	74(1)

Compound 168

Atom	x	y	z	U(eq)
Cl(1)	2625(2)	-778(2)	5236(1)	69(1)
N(1)	2516(5)	623(3)	7216(5)	37(1)
O(1)	3586(5)	-856(3)	8671(5)	61(1)
O(2)	1458(5)	186(4)	8856(4)	57(1)
C(6)	5515(6)	1888(5)	6757(5)	38(1)
C(1)	2640(7)	-90(5)	8236(5)	44(1)
C(5)	4605(7)	950(5)	6081(6)	46(1)
C(7)	5121(6)	2439(5)	7812(6)	43(1)
C(9)	7303(9)	3705(6)	8059(8)	66(2)
C(4)	3446(6)	351(4)	6260(5)	37(1)
C(11)	6786(6)	2277(5)	6323(6)	44(1)
C(8)	6100(8)	3323(6)	8446(6)	56(2)
C(10)	7707(7)	3211(6)	7001(8)	68(2)
C(3)	1119(7)	1244(5)	6953(6)	52(2)
C(2)	559(7)	1135(5)	8162(7)	58(2)

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Compound 169

Atom	x	y	z	U(eq)
I(1)	10063(0)	6830(0)	1524(0)	87(0)
S(1)	8121(1)	9821(1)	1260(0)	52(0)
Cl(1)	5051(1)	9823(1)	1415(1)	72(0)
N(1)	7226(2)	8618(2)	1529(1)	47(0)
C(9)	6094(3)	6666(3)	45(2)	50(1)
C(7)	6001(2)	8629(3)	1050(2)	49(1)
C(4)	8906(3)	7936(3)	-1128(2)	58(1)
C(2)	9229(3)	7875(3)	401(2)	53(1)
C(8)	5511(2)	7846(3)	387(2)	53(1)
C(1)	8513(2)	9072(3)	371(2)	47(1)
C(6)	8041(3)	9715(3)	-406(2)	54(1)
C(5)	8241(3)	9154(3)	-1140(2)	59(1)
C(10)	6807(3)	5683(3)	569(2)	61(1)
C(3)	9416(3)	7320(3)	-345(2)	61(1)
O(2)	7429(2)	11063(2)	965(1)	66(1)
C(14)	5837(3)	6454(3)	-826(2)	67(1)
C(12)	6997(3)	4349(4)	-630(2)	74(1)
C(11)	7255(3)	4530(3)	233(2)	71(1)
C(13)	6309(4)	5306(4)	-1159(2)	78(1)
C(15)	9075(4)	7274(4)	-1931(2)	80(1)
O(1)	9161(2)	9934(3)	1960(1)	75(1)
C(16)	7435(4)	8213(4)	2433(2)	70(1)