CYCLIZATION/CYCLOADDITION REACTIONS OF ENYNONES, ENYNALS AND EPOXY YNAMIDES LEADING TO NEW HETEROCYCLIC SYSTEMS

A THESIS

SUBMITTED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

By

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HYDERABAD - 500 046

INDIA

JULY 2016

I dedicate this thesis to

My Parents,

Teachers,

And

Family members

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PART B

TRANSITION METAL FREE CYCLIZATIONS OF EPOXY YNAMIDES

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 2016

Anagani Leela Siva Kumari

DECLARATION

I, **ANAGANI LEELA SIVA KUMARI** hereby declare that this thesis entitled "***Cyclization/Cycloaddition Reactions of Enynones, Enynals and Epoxy Ynamides Leading to New Heterocyclic Systems***" 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 work described in this thesis entitled "***Cyclization/Cycloaddition Reactions of Enynones, Enynals and Epoxy Ynamides Leading to New Heterocyclic Systems***" has been carried out by Mrs. Anagani Leela Siva Kumari, under my supervision and the same has not been submitted elsewhere for any degree.

Hyderabad

July 2016

Prof. K. C. Kumara Swamy

(Thesis supervisor)

Dean

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A.Leela.....

LIST OF PUBLICATIONS

1. Reactivity of allenylphosphonates and allenylphosphine oxides toward 9-chloroacridines and acridone– A facile route to new *N*-substituted acridones.
   A Leela Siva Kumari, Venu Srinivas and K C Kumara Swamy*
   J. Chem. Sci. **2013**, *125*, 1405.

2. NHC–gold(I) catalyzed [4+2] cycloaddition–acyclic addition of dialkyl substituted propargylic esters with 1,3-diphenylisobenzofuran: synthesis of novel benzo[c]fluorenols and substituted dienes.
   Ramesh Kotikalapudi, **A. Leela Siva Kumari** and K. C. Kumara Swamy*
   RSC Adv. **2014**, *4*, 17717.

3. Divergence in the reactivity between amine- and phosphine-catalyzed cycloaddition reactions of allenoates with enynals: One-pot gold-catalyzed synthesis of trisubstituted benzofurans from the [3+2] cycloadduct via 1,2-alkyl migration and dehydrogenation.
   A. Leela Siva Kumari and K. C. Kumara Swamy*
   J. Org. Chem. **2015**, *80*, 4084.

4. Gold-catalyzed concomitant [3+3] cycloaddition/cascade heterocyclization of enynones/enynals with azides leading to furanotriazines.
   A. Leela Siva Kumari and K. C. Kumara Swamy*
   J. Org. Chem. **2016**, *81*, 1425.

5. 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*, 6651-6671.

6. 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.

7. Transition metal-free, base mediated, atom-economic cyclization of epoxy-ynamides leading to oxazines.

A. Leela Siva Kumari, Alla Siva Reddy and K. C. Kumara Swamy*

(*to be communicated*)

8. Regio specific synthesis of 1,4-oxazine derivatives by the tandem-cyclization of epoxy ynamides with sodium azide.

A. Leela Siva Kumari and K. C. Kumara Swamy*

(*to be communicated*)

Posters presented in symposia

1. Divergence in the reactivity between amine and phosphine catalyzed cycloaddition of allenoates with enynals: One-pot gold catalyzed synthesis of trisubstituted benzofurans.
   A.Leela Siva Kumari and K. C. Kumara Swamy*
   Chemfest-2015 (Annual in-house symposium), School of Chemistry, University of Hyderabad, Feb-**2015** (**Poster Presentation**)

2. Divergence in the reactivity between amine and phosphine catalyzed cycloaddition of allenoates with enynals: One-pot gold catalyzed synthesis of trisubstituted benzofurans.
   A.Leela Siva Kumari and K. C. Kumara Swamy*
   DRILS (Dr. Reddy's Institute of Life Sciences) Young Scholars' Science Cafe Meet-2015, University of Hyderabad, Hyderabad, Aug-**2015** (**Poster Presentation**)

3. Gold-catalyzed concomitant [3+3] cycloaddition/ cascade heterocyclization of enynones/enynals with ezides leading to furanotriazines.
   A.Leela Siva Kumari and K. C. Kumara Swamy*
   CRSI-18th National Symposium in Chemistry, Panjab University, Chandigarh, INDIA, Feb-**2016** (**Poster Presentation**)

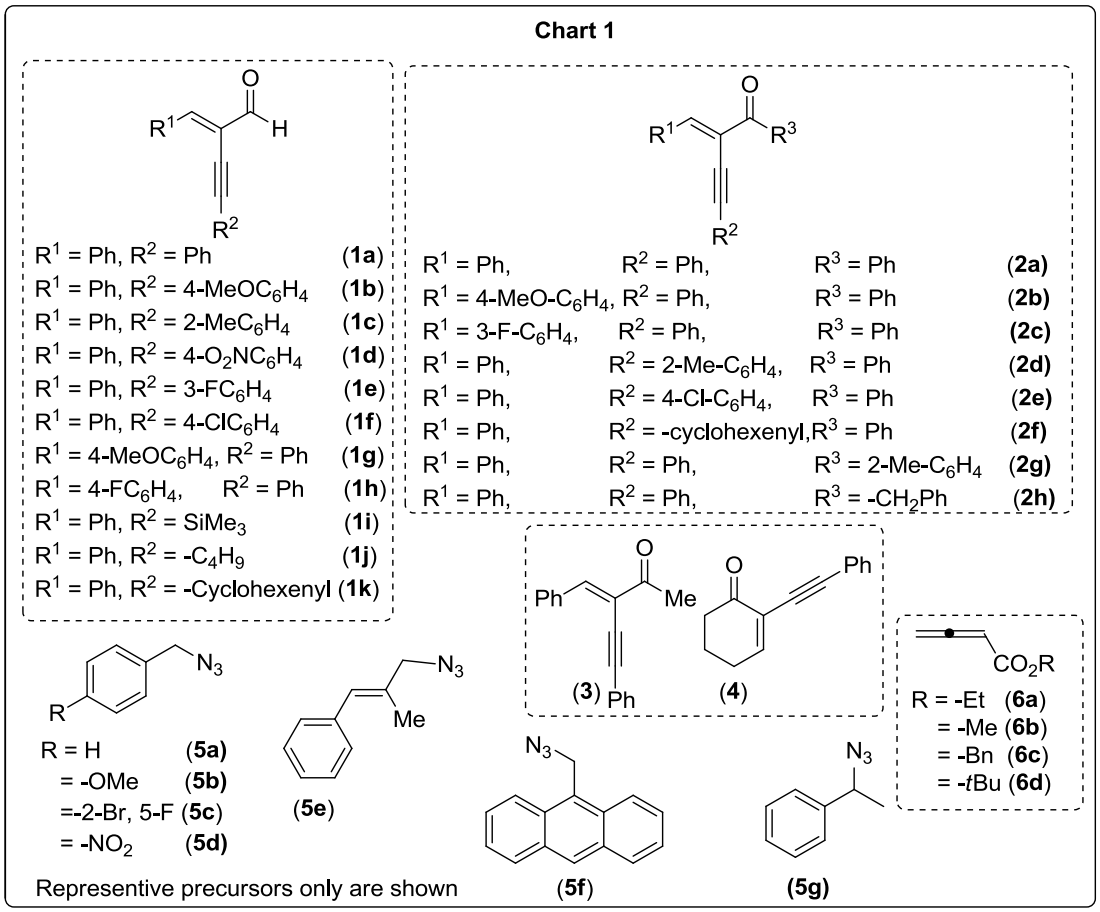
4. Gold-catalyzed concomitant [3+3] cycloaddition/ cascade heterocyclization of enynones/enynals with azides leading to furanotriazines.
   A.Leela Siva Kumari and K. C. Kumara Swamy*
   Chemfest-2016 (Annual in-house symposium), School of Chemistry, University of Hyderabad, March-**2016** (**Poster & Oral Presentation**)

Synopsis

This thesis is divided into two parts: Part-A and Part-B. **Part-A** deals with (i) [Au]-catalyzed cycloisomerization and [3+3] annulation of enynones/enynals with azides, (ii) DABCO catalyzed [2+4] cycloaddition of allenoates with enynals/enynones, and (iii) [3+2] cycloaddition of allenoates with enynals using PPh_3 catalysis. **Part-B** delves on (i) base mediated cyclization of epoxy ynamides leading to dihydro-1,3-oxazines, and (ii) tandem cyclization of epoxy ynamides with sodium azide as a nucleophile resulting in 1,4-oxazines. Each part is subdivided into three chapters: (a) Introduction (literature survey), (b) Results and Discussion and (c) Experimental Section. Compounds synthesized in the present study are, in general, characterized by mp, IR and NMR (^{1}H & ^{13}C) techniques followed by HRMS or elemental analyses in conjunction with LC-MS. X-ray structure determination is undertaken wherever is required. Summary as well as references are given at the end of each part.

PART-A

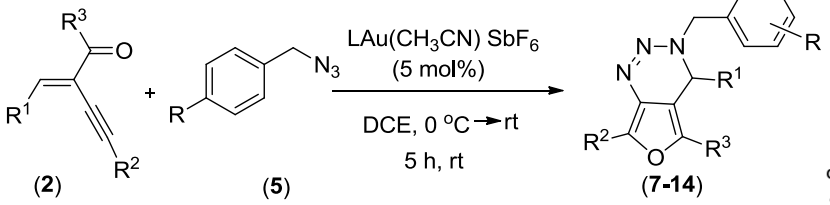
Chapter 1 deals with the survey of literature related to this part. In Chapter 2, the results obtained on these aspects are discussed while in Chapter 3, the experimental details are presented. Prominent results of this part are outlined here. The precursors used in the present study shown in Chart 1 [*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.



(i) [Au]-catalyzed synthesis of furan fused 1,2,3-triazines

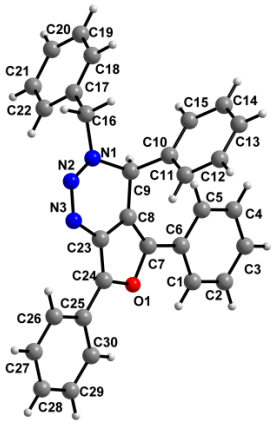
Construction of polysubstituted furans *via* gold catalysis has attracted considerable attention due to the occurrence of furan skeleton in numerous natural products and pharmaceutical ingredients in addition to their importance as building blocks in organic synthesis. Enynones/ enynals, with their multifunctional nature are versatile synthons for transition metal (including gold) catalyzed transformations. Thus the reaction of enynones **2** with azides **5** in the presence of $LAu(CH_3CN)SbF_6$ [L = (2-biphenyl)di-*tert*-butylphosphine] in DCE solvent afforded the furan fused 1,2,3-triazines (**7-14**) in excellent yields in a highly regioselective manner. The reaction proceeded through cycloisomerization of enynones resulting in furanyl gold carbocation, followed by [3+3] cycloaddition with azides leading to furanotriazines.

Scheme 1



(**2**) (**5**) (**7-14**)

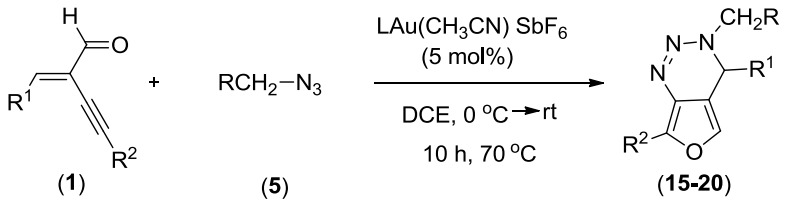
R^1 = Ph, R^2 = Ph, R^3 = Ph, (**5a**)	**7** (84%, **X-ray**)
R^1 = 3-F-C_6H_4, R^2 = Ph R^3 = Ph, (**5a**)	**8** (75%)
R^1 = Ph, R^2 = -cyclohexenyl, R^3 = Ph, (**5a**)	**9** (56%)
R^1 = Ph, R^2 = Ph, R^3 = 2-Me-C_6H_4, (**5a**)	**10** (76%)
R^1 = Ph, R^2 = Ph, R^3 = Ph, (**5c**)	**11** (65%)
R^1 = Ph, R^2 = Ph, R^3 = Ph, (**5e**)	**12** (72%)
R^1 = Ph, R^2 = Ph, R^3 = Ph, (**5f**)	**13** (80%)
R^1 = Ph, R^2 = Ph, R^3 = Ph, (**5g**)	**14** (76%)
(more examples)	



Compound **7**

The above methodology was elaborated to enynals to provide [3+3] cycloadducts in good yields. Thus we treated the (*E*)-2-benzylidene-4-phenylbut-3-ynal **1a** with benzyl azide **5a** to obtain the [3+3] cycloadduct **15** in 32% yield; upon raising the reaction temperature to 70 °C and maintaining at this temperature for 10 h, the yield could be increased to 73% (Scheme 2). At rt (25 °C), the reactions required 48 h for completion.

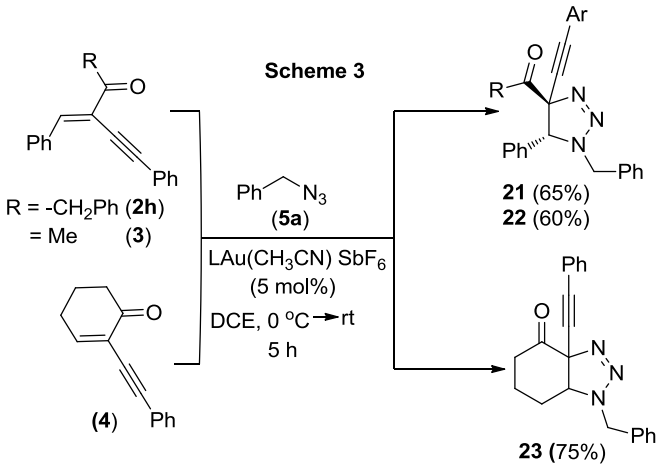
Scheme 2



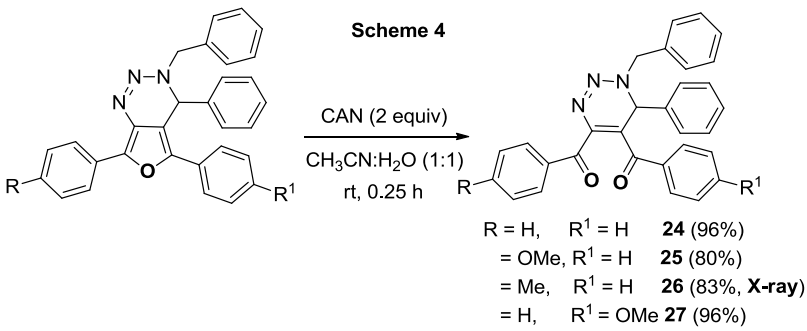
(**1**) (**5**) (**15-20**)

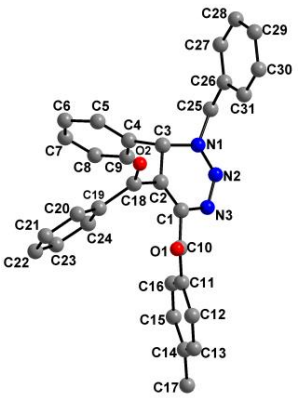
R^1 = Ph, R^2 = Ph, R = Ph	**15** (73%)
R^1 = Ph, R^2 = Ph, R = 4-MeO-C_6H_4	**16** (75%)
R^1 = Ph, R^2 = 4-MeO-C_6H_4	**17** (68%)
R^1 = Ph, R^2 = 4-Cl-C_6H_4	**18** (66%)
R^1 = Ph, R^2 = 2-Me-C_6H_4	**19** (70%)
R^1 = Ph, R^2 = 3-F-C_6H_4	**20** (72%)

In contrast to the above, enynones (**2h**, **3** and **4**) underwent [3+2] cycloaddition with benzyl azide **5a**. In these substrates, only ***alkene*** part of the enynones reacts with benzyl azide resulting in the formal [3+2] cycloadducts (**21-23**), rather than the [3+3] cycloadducts (Scheme 3).



Among the three possible triazines systems, 1,2,3-triazines are pharmaceutically useful because of their potent efficacy and minimal side effects. Hence, we performed the furan ring cleavage reaction of furanotriazine **7** with cerium(IV) ammonium nitrate (CAN) at rt/15 min that afforded the tetrasubstituted 1,2,3-triazine **24** in 96% yield. The generality of this reaction was explored using furo[3,4-d][1,2,3]triazines to obtain highly functionalized 1,2,3-triazines (**25-27**) in excellent yields (Scheme 4). The structure of compound **26** was confirmed by single crystal X-ray analysis.





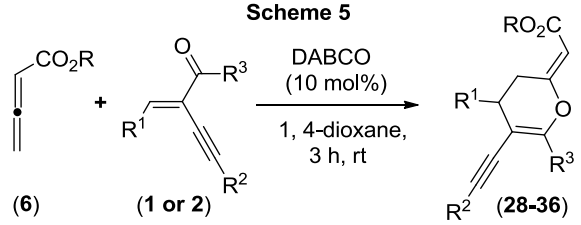
Compound **26**

(ii) DABCO-catalyzed synthesis of dihydropyrans from allenoates with enynals/enynones

In this section, we intended to check the reactivity of allenoates with enynals/enynones. Hence we performed the [2+4] cycloaddition reaction of allenoates (**6**) with enynals/enynones (**1**/**2**) by using DABCO as a Lewis base. This reaction afforded highly functionalized dihydropyrans (**28-36**) in excellent yields in a regioselective fashion (Scheme 5). We have also developed the asymmetric [2+4] cycloaddition reaction of

allenoate **6a** with enynal **1a** by using $(DHQD)_2PHAL$ as the chiral amine. The dihydropyran was obtained in 35% yield and 93% *ee*.

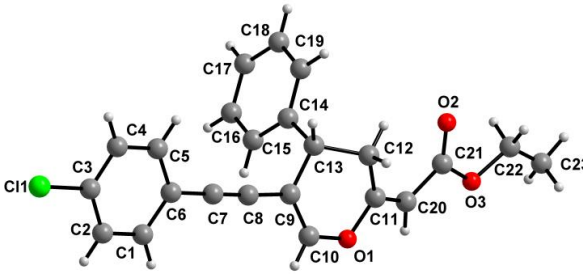
Scheme 5



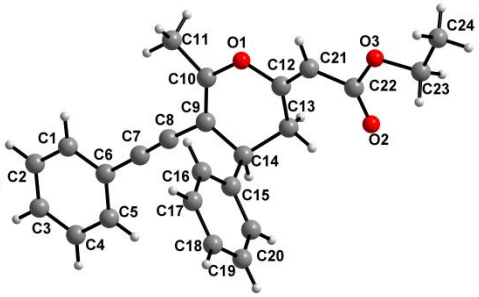
(**6**) (**1 or 2**) (**28-36**)

R^1 = Ph, R^2 = Ph, R^3 = H, R = Et	**28** (82%)
R^1 = 4-MeO-C_6H_4, R^2 = Ph, R^3 = H, R = Et	**29** (60%)
R^1 = Ph, R^2 = 2-Me-C_6H_4, R^3 = H, R = Et	**30** (71%)
R^1 = Ph, R^2 = 4-NO_2-C_6H_4, R^3 = H, R = Et	**31** (62%)
R^1 = Ph, R^2 = 4-Cl-C_6H_4, R^3 = H, R = Et	**32** (78%, **X-ray**)
R^1 = Ph, R^2 = 3-F-C_6H_4, R^3 = H, R = Et	**33** (86%)
R^1 = Ph, R^2 = $SiMe_3$, R^3 = H, R = Et	**34** (62%)
R^1 = Ph, R^2 = -Cyclohexenyl, R^3 = H, R = Et	**35** (67%)
R^1 = Ph, R^2 = Ph, R^3 = 4-Me-C_6H_4, R = Et	**36** (85%, **X-ray**)

(more examples)



Compound **32**

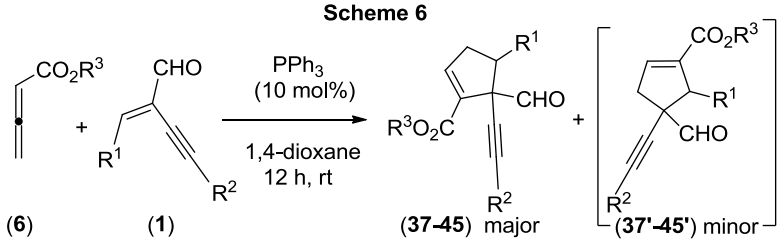


Compound **36**

(iii) Synthesis of highly functionalized cyclopentenes *via* [3+2] cycloaddition reaction of allenoates with enynals by using PPh_3 as a Lewis base

In contrast to the above, in the presence of triphenylphosphine as a base, allenoates undergo [3+2] cycloaddition with enynals providing functionalized cyclopentene derivatives (**37-45** and **37'-45'**) in good yields. This [3+2] cycloaddition reaction was well tolerated by various substrates on enynals **1** and allenoates **6** (Scheme 6). In three cases, we could isolate the minor isomer also; the structure of one of these **37'** was confirmed by the X-ray crystallographic analysis.

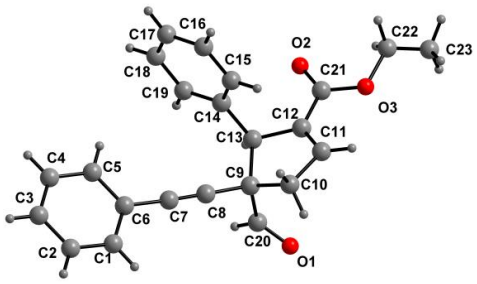
Scheme 6



(**6**) (**1**) (**37-45**) major (**37'-45'**) minor

ratio ~ 85:15

R^1 = Ph, R^2 = Ph, R^3 = Et	**37+37'** (80%, (5:1.0))
R^1 = 4-$MeOC_6H_4$, R^2 = Ph, R^3 = Et	**38+38'** (80%, (5:0.9))
R^1 = 4-FC_6H_4, R^2 = Ph, R^3 = Et	**39+39'** (77%, (5:1.3))
R^1 = Ph, R^2 = 2-MeC_6H_4, R^3 = Et	**40+40'** (83%, (5:0.9))
R^1 = Ph, R^2 = 2-$O_2NC_6H_4$, R^3 = Et	**41+41'** (62%, (5:1.5))
R^1 = Ph, R^2 = 3-FC_6H_4, R^3 = Et	**42+42'** (72%, (5:0.9))
R^1 = Ph, R^2 = 4-ClC_6H_4, R^3 = Et	**43+43'** (65%, (5:0.8))
R^1 = Ph, R^2 = $SiMe_3$, R^3 = Et	**44+44'** (77%, (5:0.9))
R^1 = Ph, R^2 = Ph, R^3 = ^{t}Bu	**45+45'** (58%, (5:1.0))
(more examples)	

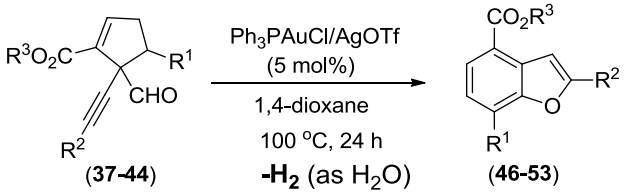


Compound **37'**

(iv) Synthesis of trisubstituted benzofurans from cyclopentene derivatives *via* [1,2]-alkyl migration by using [Au]/[Ag] catalysis

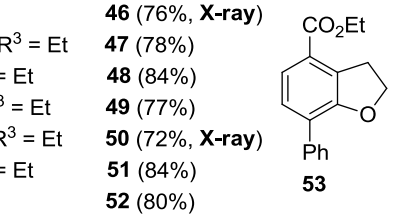
The above synthesized cyclopentenes have a reactive –*CHO* and an *alkyne* group connected to the same carbon and are consequently interesting substrates in gold catalysis. To check this, we performed the reaction of cyclopentenes (**37**-**45**) in the presence of PPh_3AuCl/AgOTf resulting in trisubstituted benzofurans (**46**-**54**) in good yields (Scheme 7). A point worth-noting here is that the substrate **44** undergoes elimination of trimethylsilyl group resulting in compound **53** in excellent yield. The structures of compounds **46** and **50** were confirmed by the X-ray crystallography.

Scheme 7

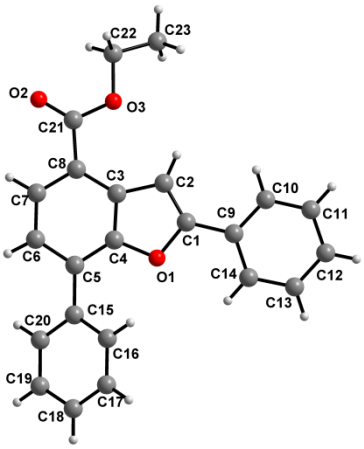


(**37-44**) (**46-53**)

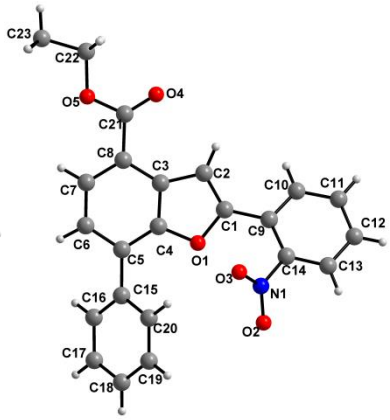
R^1 = Ph, R^2 = Ph, R^3 = Et	**46** (76%, **X-ray**)
R^1 = 4-$MeOC_6H_4$, R^2 = Ph, R^3 = Et	**47** (78%)
R^1 = 4-FC_6H_4, R^2 = Ph, R^3 = Et	**48** (84%)
R^1 = Ph, R^2 = 2-MeC_6H_4, R^3 = Et	**49** (77%)
R^1 = Ph, R^2 = 2-$O_2NC_6H_4$, R^3 = Et	**50** (72%, **X-ray**)
R^1 = Ph, R^2 = 3-FC_6H_4, R^3 = Et	**51** (84%)
R^1 = Ph, R^2 = Ph, R^3 = Bn	**52** (80%)
R^1 = Ph, R^2 = $SiMe_3$, R^3 = Et	**53** (89%)
(more examples)	



53



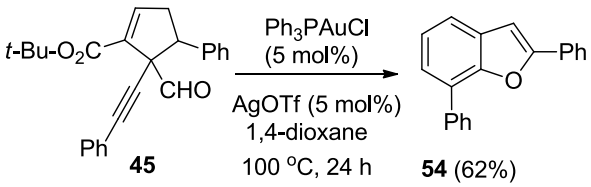
Compound **46**



Compound **50**

Cyclopentene **45** that leads to the product **54** under gold catalysis has undergone decarboxylation (Scheme 8). This feature may perhaps be used in cases when one does not require the carboxylate group in the aromatic ring.

Scheme 8

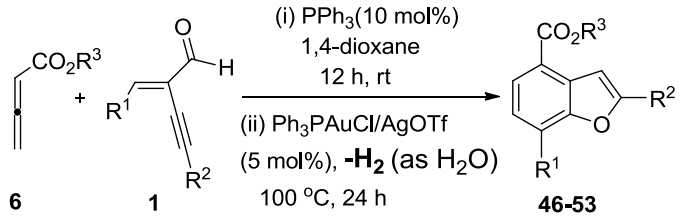


45 **54** (62%)

Synthetically, it is best if we can devise a one pot strategy since this would alleviate the problem of isolating intermediates. The yields therefore, will at least be marginally higher. Indeed in the above case, we could accomplish this and the results are shown in Scheme 9. The overall yield of substituted benzofurans (**46-53**) was 5-6% higher than that

from the two step method involving isolation of intermediate cyclopentenes of type **37-44**.

Scheme 9



6 **1** **46-53**

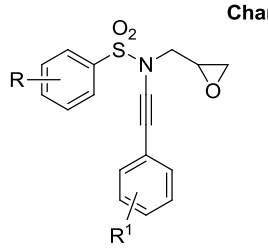
R^1 = Ph, R^2 = Ph, R^3 = Et	**46** (65%)
R^1 = 4-MeOC_6H_4, R^2 = Ph, R^3 = Et	**47** (71%)
R^1 = 4-FC_6H_4, R^2 = Ph, R^3 = Et	**48** (74%)
R^1 = Ph, R^2 = 2-MeC_6H_4, R^3 = Et	**49** (66%)
R^1 = Ph, R^2 = 2-O_2NC_6H_4, R^3 = Et	**50** (58%)
R^1 = Ph, R^2 = 3-FC_6H_4, R^3 = Et	**51** (62%)
R^1 = Ph, R^2 = $SiMe_3$, R^3 = Et	**52** (74%)
R^1 = Ph, R^2 = Ph, R^3 = Bn	**53** (73%)

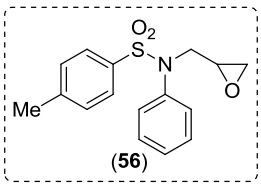
(more examples)

PART-B

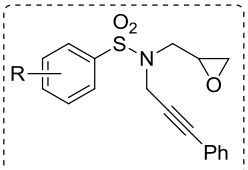
Chapter 4 deals with a review of literature on the reactivity of ynamides. Chapter 5 describes the results obtained in the present study on these aspects. Chapter 6 is the experimental section for this part. The main precursors used in the present work are shown in Chart 2. Important results of this part are outlined below.

Chart 2





(**56**)



R = 4-Me,	R^1 = H	(**55a**, 85%)
R = 4-Br,	R^1 = H	(**55b**, 78%)
R = 4-*t*Bu,	R^1 = H	(**55c**, 80%)
R = 2,4,6-triisopropyl,	R^1 = H	(**55d**, 76%)
R = -(C_4H_4)-	R^1 = H	(**55e**, 77%)
R = 4-Me, R^1 = 4-OMe		(**55f**, 86%)
R = 4-Me, R^1 = 4-Me		(**55g**, 84%)
R = 4-Me, R^1 = 3-F		(**55h**, 79%)

R = -Me,	(**57a**)
= -H,	(**57b**)
= -Br,	(**57c**)
= -$(CH_2)_4$-	(**57d**)

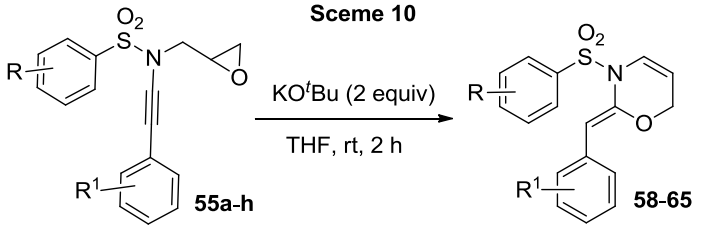
Representive precursors only are shown

(i) Atom economic synthesis of 1,3-oxazines from epoxy ynamides

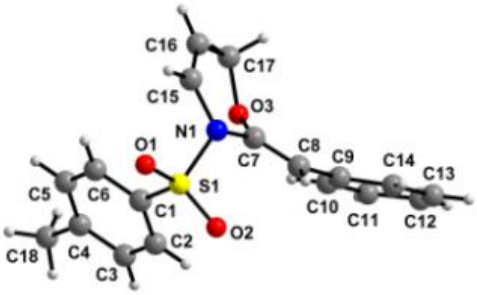
Cyclization reactions using ynamides generally lead to the formation of products with very high regio- and stereo-selectivity. Epoxide tagged ynamide substrates (**55a-h**) (Scheme 10) can generate multitudes of nitrogen and oxygen containing heterocycles.

Hence we explored the regio- and stereo-selective intramolecular **6-*exo-dig*** cyclization of epoxy ynamides (**55a-h**) by using KO^t-Bu as a base that produced 1,3-oxazines (**58-65**) (Scheme 10) in an atom economic approach. The pathway involves base mediated epoxide ring opening and subsequent cyclization with alkyne under transition metal-free conditions. Further, the structures of cyclized products **58** and **62** were conformed by X-ray crystallographic analysis.

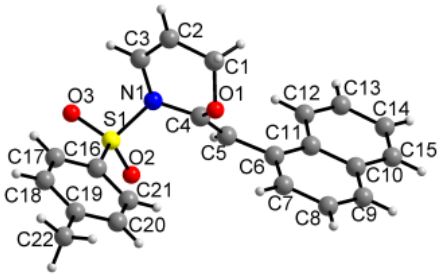
Sceme 10



R = 4-Me, R^1 = H **58** (82%, **X-ray**)
R = 4-Br, R^1 = H **59** (65%)
R = 4-*t*Bu, R^1 = H **60** (78%)
R = 2,4,6-triisopropyl, R^1 = H **61** (66%)
R = -(C_4H_4)- R^1 = H **62** (75%, **X-ray**)
R = 4-Me, R^1 = 4-OMe **63** (80%)
R = 4-Me, R^1 = 4-Me **64** (71%)
R = 4-Me, R^1 = 3-F **65** (66%)
(more examples)



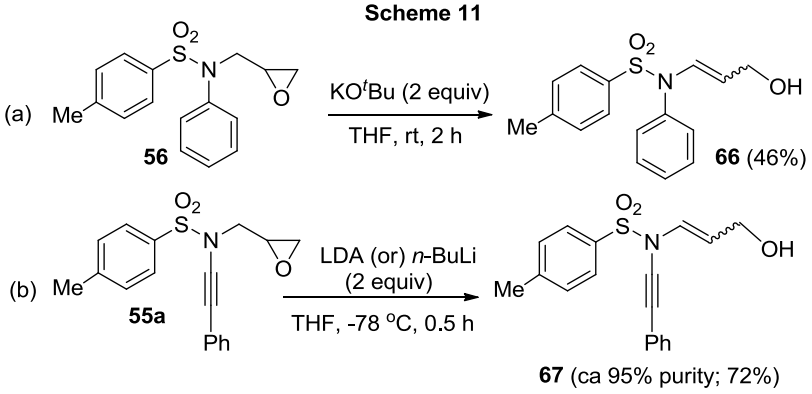
Compound **58**



Compound **62**

Control experiments were performed in order to know the plausible catalytic cycle. The reaction of alkyne unsubstituted epoxy sulfonamide **56** with KO^{t}Bu (2 equiv) as a base in THF solvent (2 mL) led to the formation of product **66** in 46% yield (Scheme 11a). This is consistent with that reported in literature with LDA as a base. The reaction of epoxy ynamide **55a** with LDA or *n*-BuLi at -78 ^{o}C for 0.5 h resulted in isomeric allyl alcohols (*E*+*Z*)-**67** (ca 95% purity; Scheme 11b); at 0 ^{o}C and above, the reaction gave rise to a complex mixture.

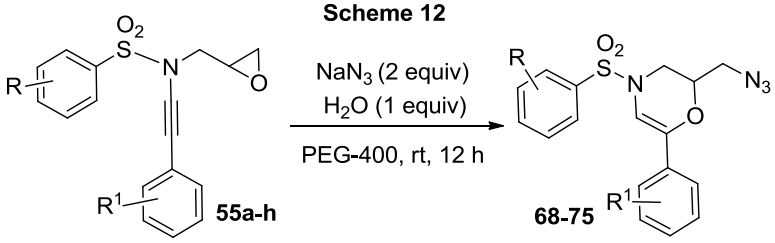
Scheme 11



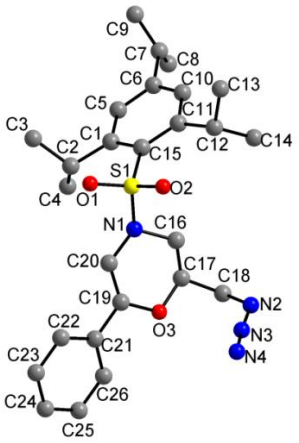
(ii) Regio-selective, transition metal free synthesis of 1,4-oxazine derivatives by tandem-cyclization of epoxy ynamides with NaN_3

Encouraged by the above results, we performed intermolecular cyclization of epoxy ynamides (**55a-h**) with sodium azide as the nucleophile resulting in 1,4-oxazines (**68-75**) under transition metal-free conditions with excellent regio-selectivity using PEG-400 as the reaction medium (Scheme 12). Initially, intermolecular nucleophilic attack of azide onto the less hindered side of epoxide group of the ynamide takes place. Subsequent **6-*endo-dig*** attack of oxide ion at the β-position of the ynamide followed by the protonation delivers the cyclized products. The attractive features are the use of environmentally benign solvent (PEG-400) and inexpensive sodium azide as the nucleophilic source, under the transition metal free conditions. The structure of one such cyclized product **71** was further confirmed by single crystal X-ray analysis.

Scheme 12



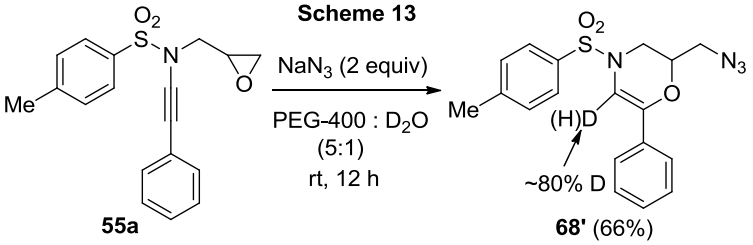
R = 4-Me, R^1 = H **68** (72%)
R = 4-Br, R^1 = H **69** (48%)
R = 4-*t*Bu, R^1 = H **70** (65%)
R = 2,4,6-triisopropyl, R^1 = H **71** (70%, X-ray)
R = -(C_4H_4)- R^1 = H **72** (64%)
R = 4-Me, R^1 = 4-OMe **73** (66%)
R = 4-Me, R^1 = 4-Me **74** (70%)
R = 4-Me, R^1 = 3-F **75** (55%)



Compound **71**

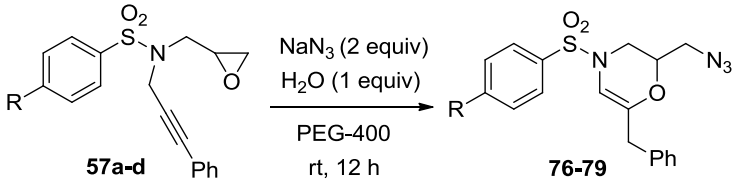
To know the plausible catalytic cycle, we have performed deuterium-labelling experiment also. Thus the reaction of epoxy ynamide **55a** (1.0 equiv) with NaN_3 (2.0 equiv) in PEG-400 - D_2O mixture (5:1) furnished compound **68'** (Scheme 13) in which ~80% deuterium incorporation was observed at the alkenyl C-*H* position of **68'**. This result clearly suggests the key role of water as a proton source in the cyclization process.

Scheme 13



In addition to the above results, epoxy tethered alkyne substrates (**57a-d**) underwent **6-*endo-dig*** cyclization with sodium azide as the nucleophile affording the 1,4-oxazine derivatives (**76-79**) in good yields (Scheme 14).

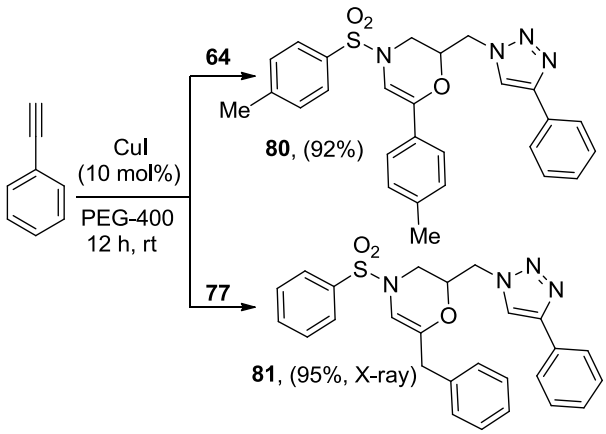
Scheme 14

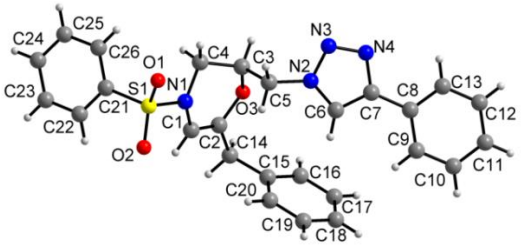


R = -Me, **76** (75%)
= -H, **77** (73%)
= -Br, **78** (66%)
= -$(CH_2)_4$- **79** (72%)

We have also utilized the above formed azide possessing 1,4-oxazine derivatives **64** and **77** in the familiar click reaction. Thus, the reaction of 1,4-oxazines **64** and **77** with phenyl acetylene using CuI as a catalyst in PEG-400 solvent at rt for 12 h resulted in the corresponding triazole appended 1,4-oxazines **80-81** in excellent yields (Scheme 16). Structure of compound **81** was further conformed by single crystal X-ray analysis. The formation of the product **81** indirectly proved the identity of compounds **76-79**.

Scheme 16





Compound **81**

PART-A

CYCLIZATIONS/CYCLOADDITIONS OF ENYNONES AND ENYNALS

INTRODUCTION

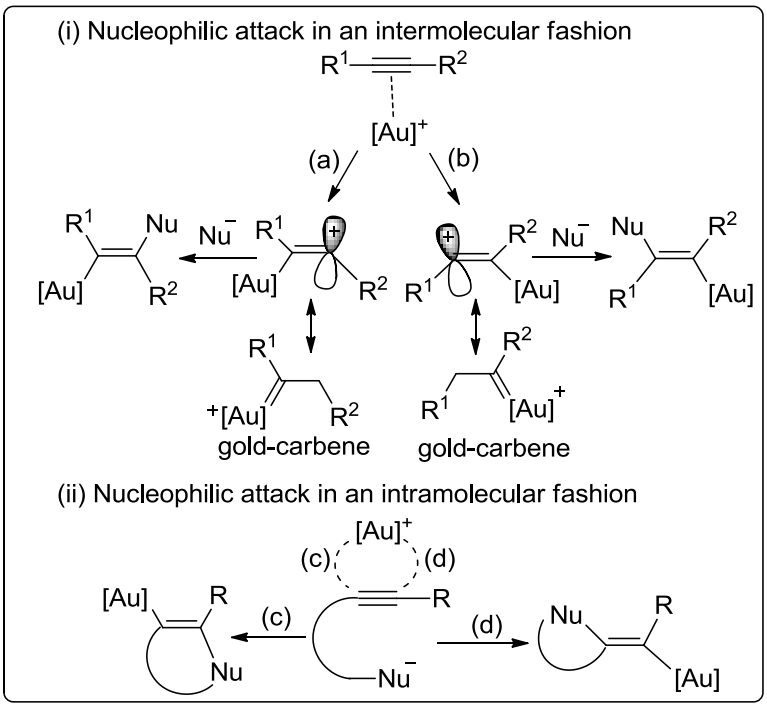
This chapter is devoted to the literature that is relevant to the topics discussed in Chapter 2. Here, the importance, reactivity modes and utility of gold catalysis are presented first in section 1.1. The available data on cycloaddition and cyclization reactions of enynones with nucleophiles will be discussed in section 1.2. Selected DABCO and phosphine catalyzed cycloaddition reactions of allenes that are relevant to the present work are narrated in the section 1.3 while 1,2-alkyl migration reactions of allenic/alkynic substrates by using transition metal catalysts are presented in section 1.4.

1.1 General Introduction-[Au] catalysis

The past two decades have witnessed a tremendous growth in the utilization of gold complexes for diverse catalytic transformations, notwithstanding the previously observed notion that the element is a 'precious' 'least reactive' metal. The rather high Pauling electronegativity (2.54, for Ag it is 1.93) and electron affinity exhibited by this transition metal, with a major contribution from relativistic effects,[1] have been known to the synthetic chemists. In a complex ion like $[Ph_3PAuL]^+$, the low-lying relativistically contracted s-orbital on the large and diffuse Au^+ ion possibly will covalently contribute to bonding. The propensity of gold(I) or gold(III) to act as a soft carbophilic Lewis acid to activate the carbon-carbon π-bonds, thus initiating nucleophilic attack on these sites inter- or intra-molecularly, has been the driving force that enables the construction of new C-C and C-heteroatom bonds.[2] A major benefit of using these gold catalysts is that they are not as oxophilic as most Lewis acids with the result that water, alcohols or air are well-tolerated; this feature permits gold catalyst a better platform to achieve its function than other transition metal species/ Lewis acids in varied catalytic transformations. The intermediates involved in gold-catalyzed transformations have a nonclassical carbocation or carbenoid feature often leading to well-controlled product selectivity.[3] It is expected that an [Au]-alkyne complex has a lower LUMO than an [Au]-alkene complex which probably is the reason for alkynophilicity

observed in Au(I) catalyzed reactions.[1d] Thomas and coworkers reported the addition of nucleophiles to alkenes/alkynes as early as the year 1976[4] and Ito and Hayashi used Au(I) complexes in the reactions of aldehydes with isocyanate in 1986,[5] but the major breakthrough came in the year 1998 when Teles[6a] and Tanaka[6b] reported activation of a π-system by Au(I) catalyst marking the beginning of an explosive growth in this area.

The important aspects of gold catalysis are low catalyst loading, less reaction time, compatibility with greener solvents, mild reaction conditions, minimal use of additives and environmentally benign byproducts. Due to high oxidation potential of Au(I) to Au(III), there is only a limited scope for redox reactions. Hence, Au(I)-catalyzed reactions can also be carried out in the presence of air. In general, alkyne coordinates to gold to form an electron deficient metal-alkyne complex which is then attacked by a nucleophile (Markovnikov) by either intra- or inter-molecular fashion (Scheme 1.1).



Scheme 1.1. Reactivity of alkyne towards gold catalyst.

In the above transformations, very often an Ag(I) salt with a non-coordinating anion such SbF_6^-, PF_6^-, or BF_4^- is also employed. This salt is supposed to produce the catalytically more active species $[LAu]^+$ from [LAuCl] after eliminating the

chloride ion. The role of 'L' is also important since it can be used to tune the electrophilicity of the reactive [Au] species.[7]

1.2 Gold catalyzed cycloaddition reactions of enynones with nucleophiles

Gold salts/ complexes have emerged as powerful catalysts for the direct functionalization of alkenes, alkynes, and allenes.[8] Enynones are attractive precursors possessing three functional groups (alkyne, alkene, and carbonyl groups) and provide highly substituted carbo-/hetero-cycles in the presence of transition metal catalysts.[9] The alkyne part of enynone can be activated by the metal catalyst. Nucleophilic attack of carbonyl oxygen can then generate the furanyl metal carbocation **1.1** (Figure 1), which undergoes cycloaddition with various nucleophiles leading to furan-fused heterocycles.[9] In this section, gold catalyzed cyclizations and cycloadditions of enynones from the literature which are relevant to this work are discussed.

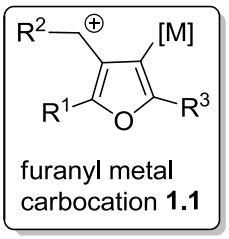
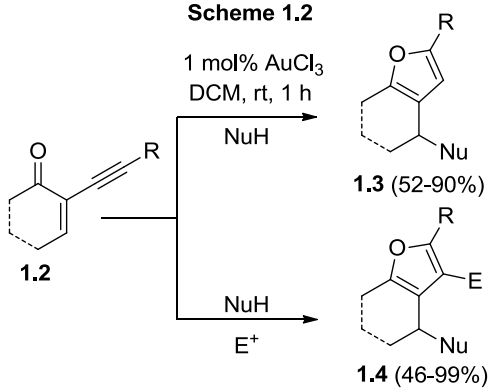


Figure 1. Structure of furanyl metal carbocation **1.1**

Larock *et al.* developed a method for the cyclization of enynones **1.2** with various nucleophiles that led to highly substituted furans **1.3** by using transition metal catalysts.[10a] $AuCl_3$ was the best catalyst due to less reaction time and high yield of products (Scheme 1.2, top). This cyclization reaction was well tolerated with different nucleophiles such as 3-phenyl-2-propyn-1-ol, protected D-pyranose, 1,3-cyclohexanedione, *N*,*N*-dimethylaniline and indole. Later, the same group expanded the scope of this [Au]-catalyzed process by the use of iodine as an electrophile resulting in iodo substituted furan derivatives **1.4** (Scheme 1.2, bottom).[10b] Using an analogous reaction, Liu *et al.* established an efficient method for the synthesis of highly substituted furans **1.6** by using recyclable and inexpensive gold catalyst in ionic liquids. Thus 2-(1-alkynyl)-2-alken-1-ones **1.5**

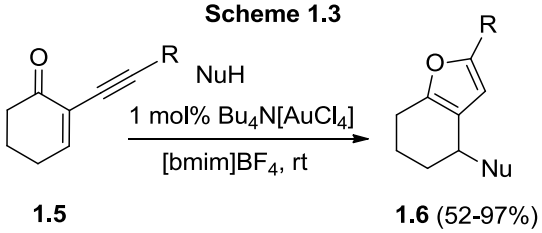
underwent cyclization with various nucleophiles under mild reaction conditions (Scheme 1.3).[11]

Scheme 1.2



E = H (cat. $AuCl_3$); NuH = ROH, enol, ArH
E = I; NuH = ROH, RCO_2H, H_2O
E = PhSe; NuH = ROH

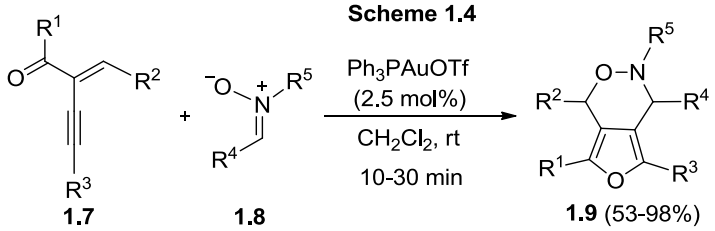
Scheme 1.3



Pioneering studies by Zhang and coworkers revealed a series of gold catalyzed [3+n] {[3+3], [4+3] and [3+2]} cycloadditions of enynones with various nucleophilic components affording highly fused substituted furans under mild reaction conditions. Thus [3+3] cycloaddition of 2-(1-alkynyl)-2-alken-1-ones **1.7** with nitrones **1.8** by using the [Au]-catalyst afforded highly substituted heterobicyclic furo[3,4-d]-[1,2]-oxazines **1.9** in good yields (Scheme 1.4).[12a] This protocol was efficient, highly regiospecific and diastereoselective. They achieved moderate *ee* values for [3+3] cycloadducts by employing (*R*)-MeO-biphep as the chiral ligand. The synthetic utility of thus formed furo[3,4-d]-[1,2]-oxazines by means of reductive cleavage of N-O bond by SmI_2 and oxidative cleavage of furan ring by CAN (cerium ammonium nitrate) was also described. The intermediate furanyl gold carbocation **1.1** played a vital role in this cycloaddition reactions.[9] The asymmetric version of gold catalyzed [3+3] cycloaddition reaction of 2-(1-alkynyl)-2-alken-1-ones with nitrones was also described by the same group.[12b] Later, they reported the synthesis of a polymer-supported gold catalyst, which also

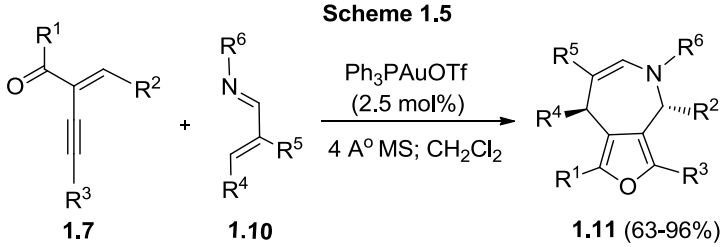
displayed the same catalytic activity as homogeneous catalysts and exhibited excellent diastereo- and enantioselectivity. This polymer-bound gold catalyst underwent eight catalytic cycles without the loss of its enantioselectivity and was applicable to large-scale synthesis also.[12c]

Scheme 1.4



The same research group of Zhang also reported the [4+3] cycloaddition reaction of enynones **1.7** with unsaturated alkenes **1.10** that provided highly substituted furo[3,4-c]azepines **1.11** under mild conditions (Scheme 1.5).[13] In the reaction shown in Scheme 1.5, cyclization of enynone most likely gives the furanyl gold carbocation intermediate.[9] Addition of imine to the carbocation then provides the allylic iminium ion, which undergoes intramolecular 2,7-cyclization leading to the spirobicyclic oxonium ion. Subsequent regioselective C-C bond cleavage followed by cyclization leads to the [4+3] cycloadduct **1.11** by the regeneration of the gold catalyst.

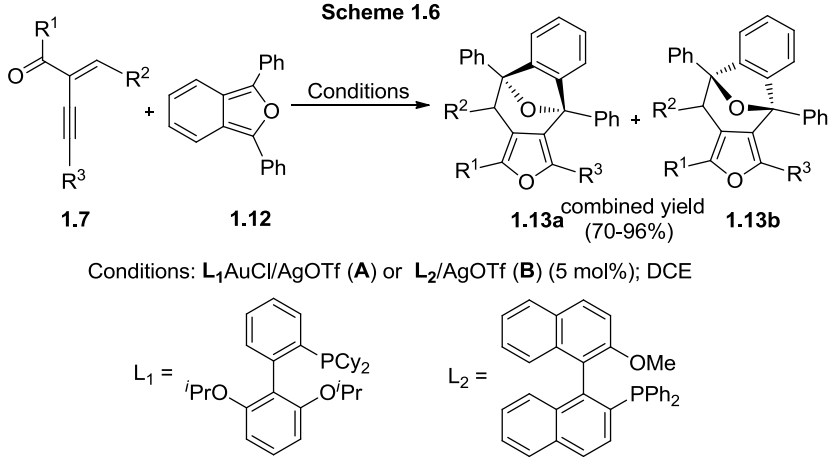
Scheme 1.5



In an another extension, when 1,3-diphenylisobenzofurans **1.12** was used instead of α,β-unsaturated imines **1.10**, double cyclization of **1.7** was observed resulting in highly fused polycyclic heterocycles *via* cycloisomerization/[4+3] cycloaddition (Scheme 1.6).[14] The authors also noted that phosphine ligands present in the metal catalyst played an important role in switching the diastereoselectivity of the products. Conditions using catalyst **A** favored the *exo*-product **1.13a**, while catalyst **B** gave the *endo*-product **1.13b** predominantly.

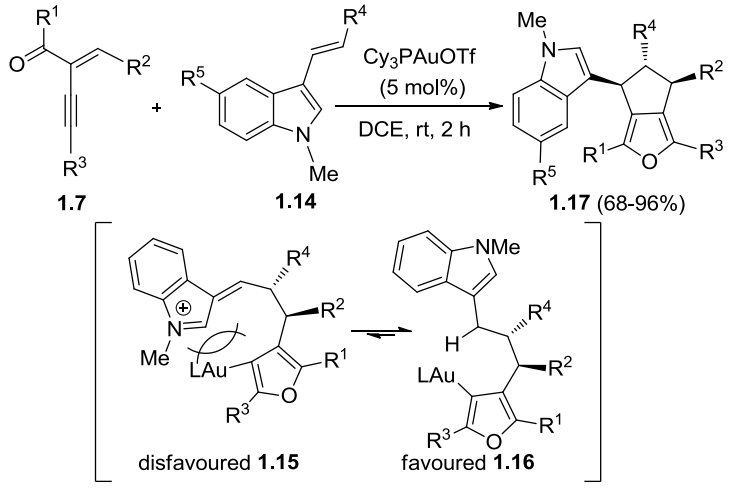
Preliminary studies suggested that moderate enantioselectivity could be achieved by the use of commercially available (*R*)-MOP as the ligand.

Scheme 1.6



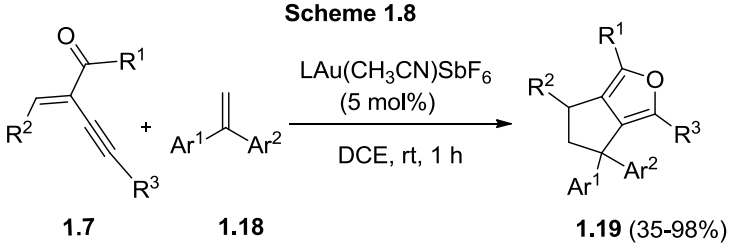
A novel approach for the synthesis of highly substituted cyclopenta[*c*]-furans **1.17** was achieved by [3+2] cycloaddition of enynones **1.7** with 3-styrylindoles **1.14** *via* gold(I)-catalysis (Scheme 1.7).[15] In this protocol, 5,5-fused cyclopenta[*c*]furan, rather than the expected 5,7-fused cyclohepta[*c*]furan, was selectively formed. In the reaction leading to compound **1.17**, furanyl metal intermediate interacts with alkene nucleophile **1.14** resulting in two intermediates **1.15** and **1.16**. Depending on the stability of aromatic indole and steric interactions, the favored intermediate **1.16** undergoes diastereoselective intramolecular 1,5-cyclization leading to the final formal [3+2] cycloadduct **1.17**.

Scheme 1.7



Recently, Liang *et al.* developed an efficient route for the synthesis cyclopenta[*c*]furans **1.19** by the [3+2] cycloaddition reaction of enynones **1.7** with diarylethenes **1.18** in the presence of gold catalyst. Here, diarylethenes reacted as 2C component nucleophiles under mild conditions (Scheme 1.8).[16]

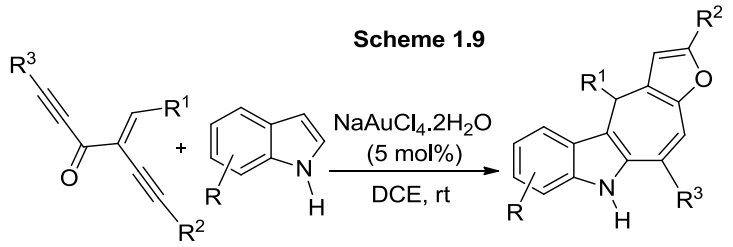
Scheme 1.8



1.7 **1.18** **1.19** (35-98%)

Double cyclization of bis(alkynyl)-2-en-1-ones **1.20** with indoles **1.21** using gold catalysis for the synthesis of indole-fused polycyclic systems **1.22** was reported by Xie *et al.* (Scheme 1.9).[17]

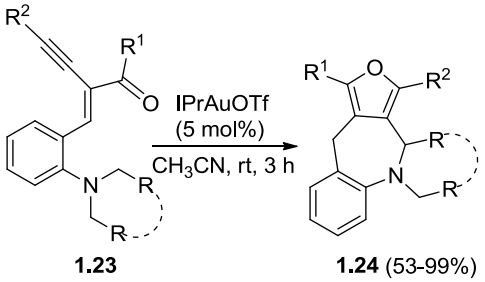
Scheme 1.9



1.20 **1.21** **1.22** (47-92%)

Zhou *et al.* developed the selective synthesis of ring-fused tetrahydroazepines **1.24** from enynones **1.23** by using carbophilic Lewis acid such as the gold catalyst (Scheme 1.10).[18] Here, the product selectivity was effectively tuned by the nature of the Lewis acid used. In the presence of gold(I) catalyst, the reaction took place by domino cycloisomerization/1,5-hydride shift to afford ring-fused tetrahydroazepines **1.24**. In contrast, substituted multifunctionalized ring-fused tetrahydroquinolines were obtained by 1,5-hydride shift/cyclization in moderate to excellent yields using scandium triflate as the catalyst.

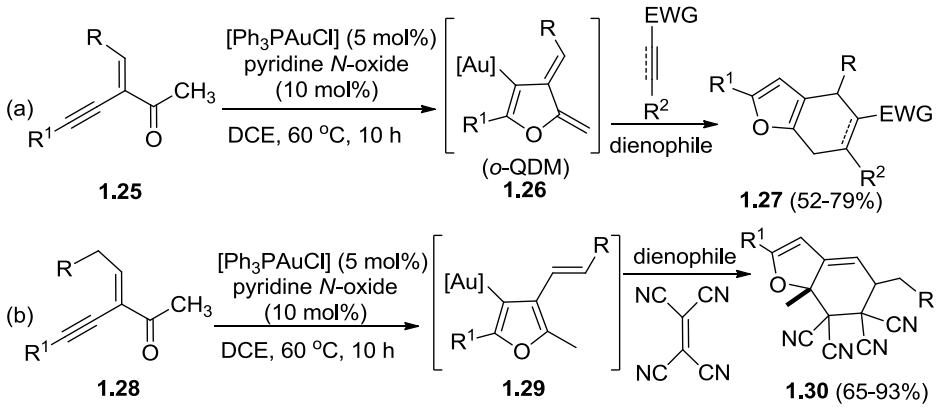
Scheme 1.10



1.23 **1.24** (53-99%)

Gold(I)-mediated dehydrogenative annulation of 2-(1-alkynyl)-2-alken-1-ones **1.25** in the presence of pyridine *N*-oxide afforded 2,3-furan-fused carbocycles **1.27** with high diastereo- and regio-selectivity (Scheme 1.11).[19] The *in situ* generated furan-based *ortho*-quinodimethanes **1.26** (*o*-QDMs) reacted with dienophiles and provided 2,3-furan-fused carbocycles **1.27**. In addition, a novel de-aromative Diels–Alder reaction was observed when aliphatic-substituted 2-(1-alkynyl)-2-alken-1-ones **1.28** were used.

Scheme 1.11

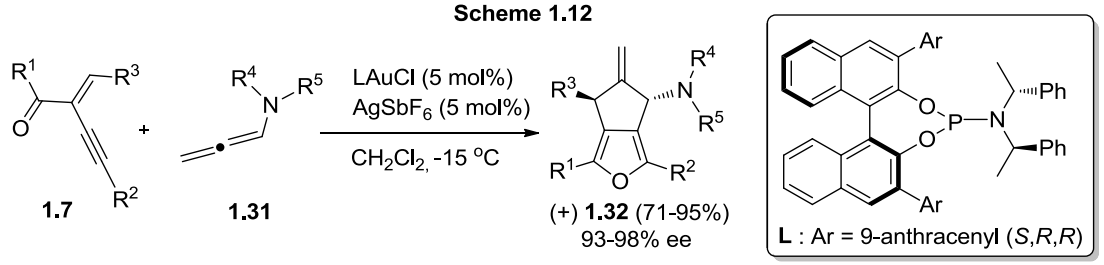


1.25 (*o*-QDM) **1.26** **1.27** (52-79%)

1.28 **1.29** **1.30** (65-93%)

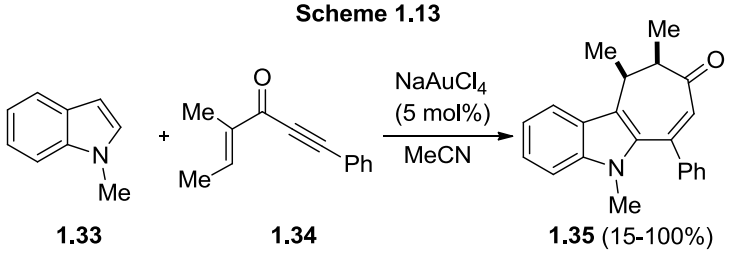
Asymmetric [3+2] annulation reaction of enynones **1.7** with the proximal C=C bond of *N*-allenamides **1.31** using gold-catalysis was described by J. Zhang's group (Scheme 1.12).[20] This is the first annulation report by using the proximal C=C bond of *N*-allenamides. They also succeeded in the gram scale synthesis of [3+2] cycloadduct. A pair of diastereomers of the ligand in the gold catalyst afforded enantiomers of the enantio-enriched furan-fused heterocycles **1.32** in good yields with up to 98% *ee*.

Scheme 1.12



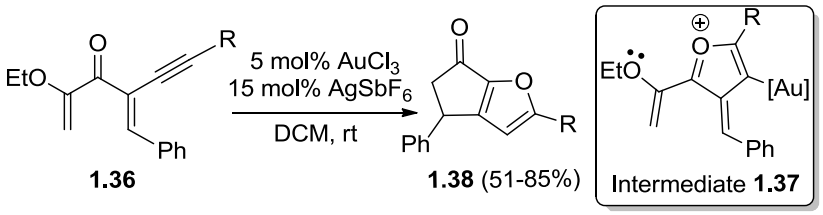
Carbery *et al.* have reported a gold-catalyzed double functionalization of indole **1.33** by enynone **1.34**. Other substituents on enynone and as well as indole were tolerated well and gave good yield of [6,5,7]-tricyclic indole **1.35** (Scheme 1.13).[21] This annulation process initially involves C-H activation of the indole moiety followed by activation of alkyne part of the enynone by using sodium tetrachloroaurate. This methodology also offers an approach to medicinally useful [6,5,7]-tricyclic indoles. Terminal alkynes appeared to be incompatible for this reaction due to possible formation of the inactive gold-acetylide.

Scheme 1.13



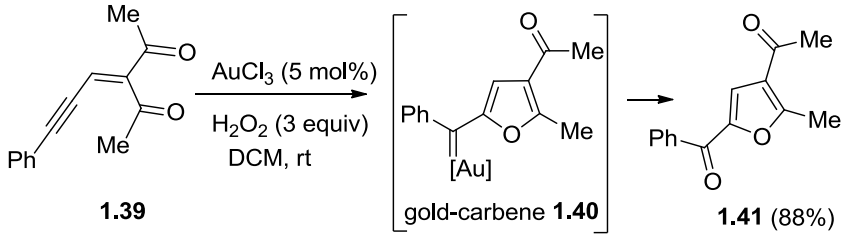
Krafft's group described tandem Au(III)-catalyzed heterocyclization/Nazarov cyclization of enynones **1.36** leading to substituted carbocycle-fused furans **1.38** (Scheme 1.14).[22] The reaction proceeds in different pathways depending upon the solvent used, as evidenced by the isolation and trapping of the reaction intermediates (*e. g.*, **1.37**). Computational studies also supported the experimental findings. Both steric and conformational effects were used to influence the mechanistic manifold.

Scheme 1.14



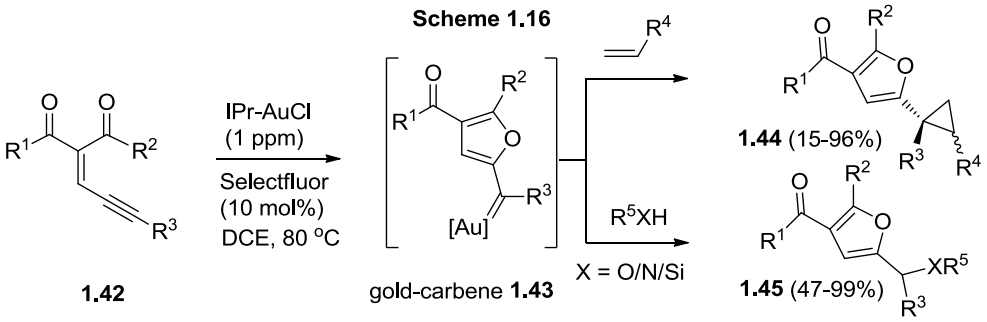
An interesting $AuCl_3$ catalyzed oxidative cyclization of 3-(1-alkynyl)-2-alken-1-ones **1.39** for the synthesis of trisubstituted 2-acylfurans **1.41** was developed by employing H_2O_2 as an efficient and green oxidizing agent (Scheme 1.15).[23] This H_2O_2-$AuCl_3$ system was also applicable to the phenylsulfonyl-substituted substrates. The proposed mechanism involves gold–carbene intermediate **1.40**, which was confirmed by cyclopropanation with styrene.

Scheme 1.15



Jun Ma *et al.* used a combination of NHC−gold complex along with selectfluor as an efficient catalytic system for the carbene-transfer reactions (TON up to 990000 and TOF up to 82500 h^{-1}).[40] The reaction probably involves the oxidation of NHC−AuCl with selectfluor to generate a cationic Au(III) species, which forms gold-carbene intermediate **1.43** with the enynone **1.42**. This gold-carbene could be trapped with alkenes to furnish the cyclopropane derivatives **1.44**. Due to the versatile reactivity of carbenes, X-H insertion reactions were also observed as shown by the isolation of the compound **1.45** (Scheme 1.16).[24]

Scheme 1.16



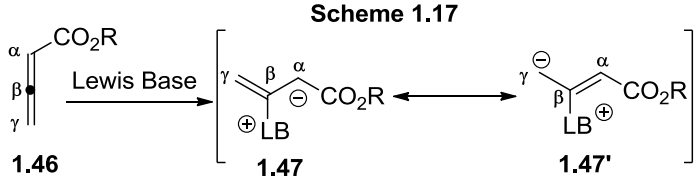
1.42 gold-carbene **1.43**

Allenes are highly useful precursors for the synthesis of biologically active compounds *via* cyclization or cycloaddition reactions.[25] In continuation of our interest in developing allene chemistry,[26] we wanted to check the reactivity of allenes with enynals/enynones under Lewis base mediation. Some of the reports related to our work shown below.

1.3 Lewis base catalyzed cycloaddition reactions of allenes

Allenes are versatile reactive synthons than normal alkenes and alkynes due to the presence of cumulative double bonds. Even so, they are also found in many natural products,[27a-b] pharmaceuticals[27c] and molecular materials.[27d] In the presence of a Lewis base, an allene/allenoate **1.46** can generate zwitterionic species **1.47**, which is in resonance with **1.47'** (Scheme 1.17). Species **1.47**/**1.47'** can undergo cycloaddition with various substrates offering spiro/fused heterocycles. The reaction pathway is regulated by the structure of the catalyst, additives and additional reaction conditions. Electron-poor nucleophile like PPh_3 stabilizes the carbanion of **1.47**, and promotes the thermodynamically favored α-addition onto an electrophile, whereas the relatively electron-rich nucleophile DABCO leads to the kinetically favored γ-addition (less sterically hindered).[28] In the following sections, a brief literature survey on the reactivity of allenes with various substrates catalyzed by bases such as DABCO and PPh_3/phosphine will be presented. Wherever possible, comparison between DABCO and the phosphine bases will be made on their reactivity difference.

Scheme 1.17



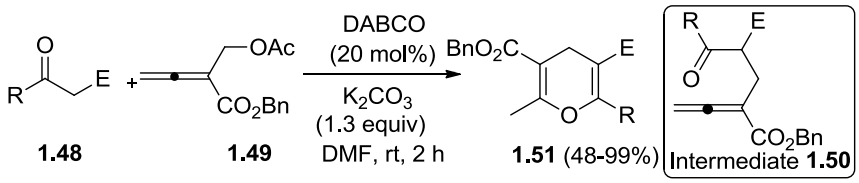
1.46 **1.47** **1.47'**

R = Et, Me, Bn Lewis Base = Phosphine, DABCO

1.3.1 DABCO catalyzed cycloaddition reactions of allenes

Xiaofeng Tong and coworkers developed a facile method for the formal (3+n) annulation of 2-(acetoxymethyl)buta-2,3-dienoate with 1,n-binucleophiles by using DABCO as the Lewis base that provided heterocyclic compounds.[29] Thus DABCO catalyzed (3+3) cycloaddition reaction of allene **1.49** with 1,3-*C,O*-binucleophiles **1.48** produced 4*H*-pyran derivatives **1.51** in good to excellent yields (Scheme 1.18). This methodology was further extended to diamine derivatives (1,n-*N,N*-binucleophiles) and produced the corresponding cycloadducts 1,4-diazepine and 1,5-diazocine *via* (3+4) and (3+5) cycloadditions, respectively. Incorporation of various functional groups on 4*H*-pyrans and fused multi-cycle 4*H*-pyrans was accomplished successfully. The mechanism involves the addition of DABCO to the *β*-carbon of allenoate followed by the Michael-type addition of binucleophile to the *β*'-position by using base and subsequent 1,2-elimination of DABCO delivered intermediate **1.50**. 6-*Endo-trig* type oxo-Michael addition of intermediate **1.50** followed by isomerization gave 4*H*-pyran derivatives.

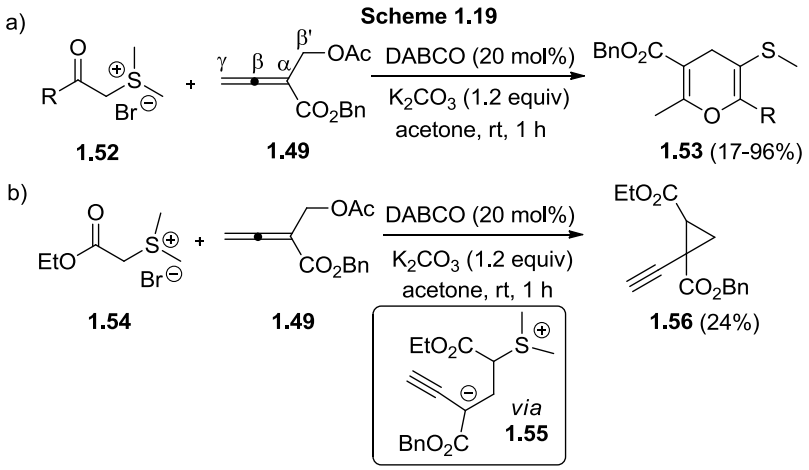
Scheme 1.18



E = -CN, -SO_2Ph, -COPh, -NHTs, *etc*.

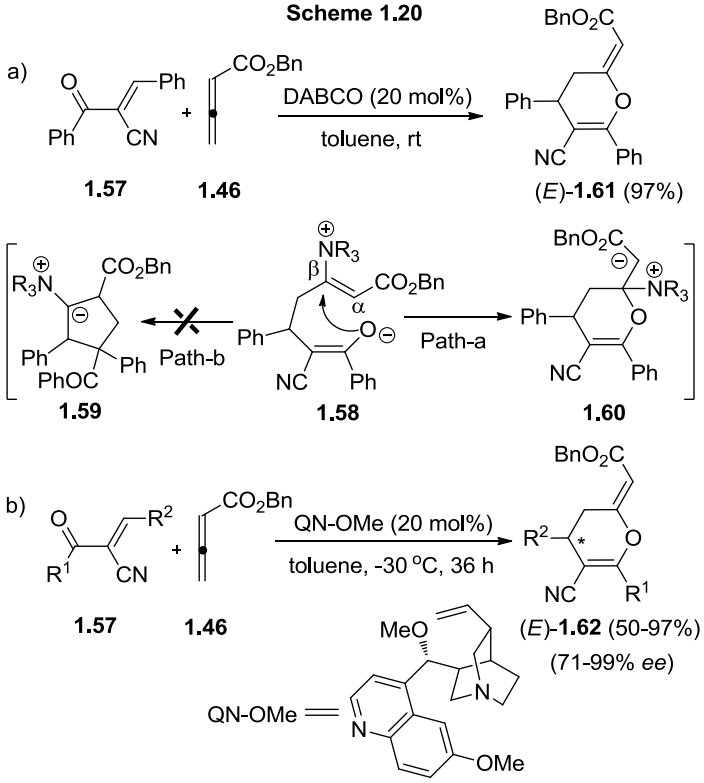
Later, the same group reported DABCO-catalyzed (3+3) cycloaddition between 2-(acetoxymethyl) buta-2,3-dienoate **1.49** and sulfur ylides **1.52** that led to diverse 4*H*-pyrans **1.53** possessing a vinyl sulfide group (Scheme 1.19a).[30] Reaction between allene and methyl ketone-stabilized sulfonium salt was very sluggish and resulted in the corresponding 4*H*-pyran only in 17% isolated yield. Lower yield of 4*H*-pyrans was observed by using *β'*-substituted allene due to steric hindrance caused by the phenyl group. The tetrahydrothiophene sulfonium salt gave the ring cleaved product instead of 4*H*-pyran. Under similar reaction conditions, ester-stabilized sulfur ylides **1.54** delivered cyclopropane derivatives **1.56** *via* intermediate **1.55** (Scheme 1.19b).

Scheme 1.19



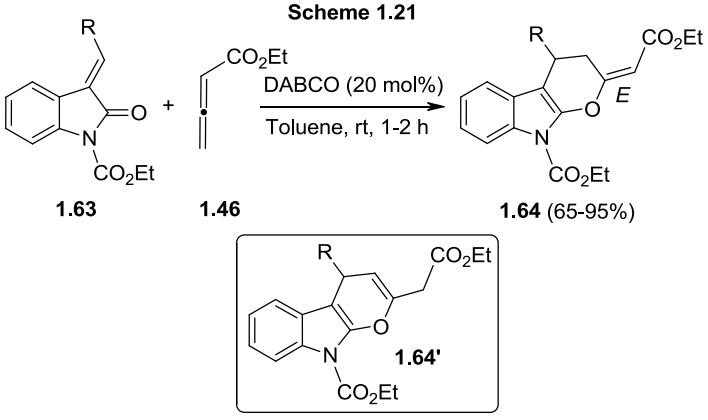
Xiaofeng Tong and coworkers demonstrated DABCO catalyzed [4+2] annulation of oxodiene **1.57** and allenoate **1.46** leading to 3,4-dihydro-2*H*-pyran **1.61** in 97% yield (Scheme 1.20a).[31] Asymmetric synthesis of 3,4-dihydro-2*H*-pyran **1.62** was also achieved successfully by using simple cinchona alkaloids. Chiral catalyst QN-OMe afforded the [4+2] cycloadduct **1.62** in 70% yield with 90% *ee*. In all the cases, *E*-isomer was exclusively formed (Scheme 1.20b). In the presence of DABCO, **1.57** specifically interacts with **1.47'** (Scheme 1.17) providing intermediate **1.58**. However path-b is not possible due to the poor capability of the ammonium ion for the stabilization of the corresponding ylide **1.59**. Thus path-a is only feasible and provided the [4+2] cycloadduct *via* intermediate **1.60**. Some pyran derivatives were obtained with excellent optical purity by simple crystallization. The reaction by using the quinidine (QD) as a catalyst in chlorobenzene afforded the opposite enantiomeric [4+2] cycloadducts with low *ee* values. Raising the temperature to 80 ^{o}C produced both the (*E*) and (*Z*) isomers due to the large separation between the nitrogen center and the chiral environment. At the same temperature, quinolone generated the (*Z*) isomer exclusively. DMAP and pyridine produced both the isomers but the *Z*-isomer was the major product at rt. All these results reveal that steric interactions around the catalytic nitrogen center may play a crucial role in the *E*/*Z* selectivity. Tertiary amines exclusively gave *E* selectivity whereas the amine incorporated into the pyridyl aromatic system favored *Z* selectivity.

Scheme 1.20



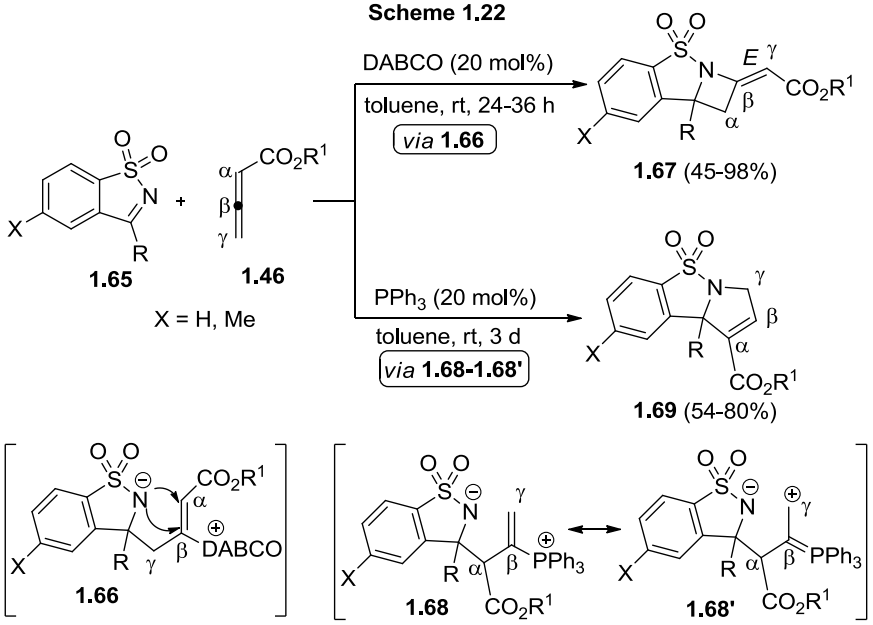
Song Ye and coworkers developed a novel DABCO catalyzed [4+2] cycloaddition of arylidenoxindole **1.63** with allenoates **1.46** that afforded dihydropyran-fused indoles **1.64** in good yields with excellent regio- and diastereo-selectivities (Scheme 1.21).[32] This is the first example in which allenoate acts as two carbon synthon in base catalyzed [4+2] cycloaddition reaction. This [4+2] cycloaddition was rationalized by DFT calculations. For arylidenoxindole having strong electron-withdrawing groups (3-NO_2, 2-NO_2), authors observed the formation of the double bond migrated isomer **1.64'** along with the normal dihydropyran-fused indole **1.64**.

Scheme 1.21



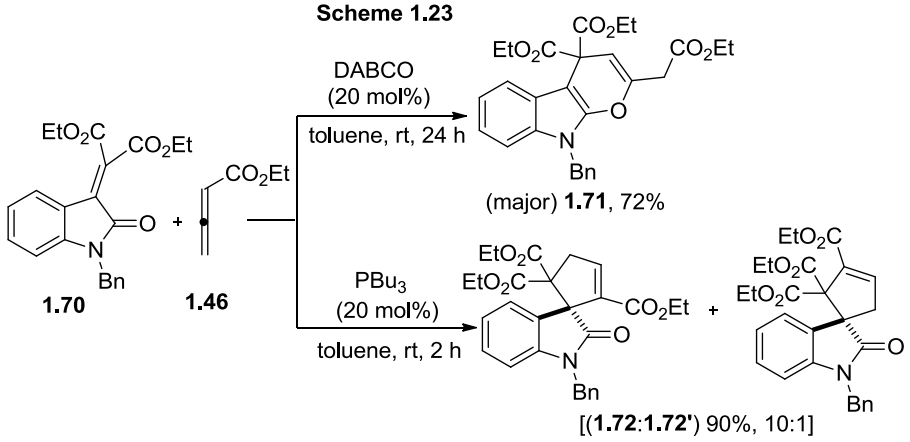
Song Ye's group investigated the cycloaddition reaction of cyclic ketimines **1.65** with allenoates **1.46**. While DABCO catalyzed reaction provided the sultam-fused azetidines **1.67** by [2+2] cycloaddition, PPh_3 as a catalyst led to dihydropyrroles **1.69** by [3+2] cycloaddition in a highly regioselective manner (Scheme 1.22).[33] The reaction pathway is influenced mainly by the different orbitals in *N*-, *P*- nucleophiles. In the intermediate **1.68**, C=C (β, γ) is in conjugation with the vacant d-orbital of phosphonium ion resulting in P(V) resonance structure **1.68'**, which has a carbonium ion at the γ-position and favors the 5-*endo* cyclization to provide the [3+2] cycloadduct **1.69**. But the DABCO-derived intermediate **1.66** favors the 4-*exo* cyclization due to the lack of vacant d-orbitals and generates the [2+2] cycloadduct **1.67**. Alkyl allenoates having (R^1 = *tert*-butyl, cyclohexyl, benzyl) also worked well during the cycloaddition process.

Scheme 1.22



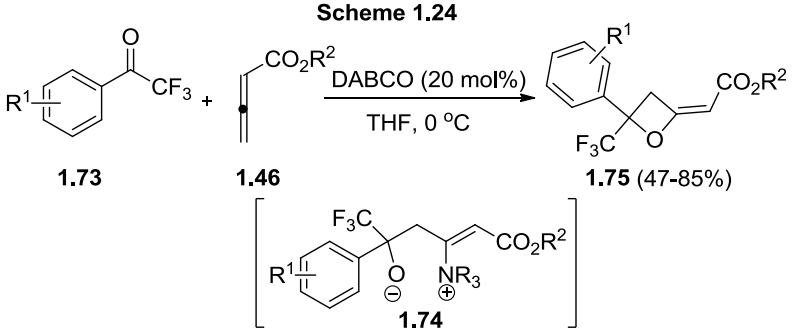
Min Shi and coworkers developed an interesting DABCO catalyzed [4+2] reaction of isatin derived α,β-unsaturated diesters **1.70** with allenic ester **1.46** resulting in the double bond migrated product **1.71** in 72% yield, along with other minor cycloadducts. On the other hand, the phosphine PBu_3 generated highly functionalized spirocyclic adducts **1.72-1.72'** in good to excellent yields (Scheme 1.23).[34]

Scheme 1.23

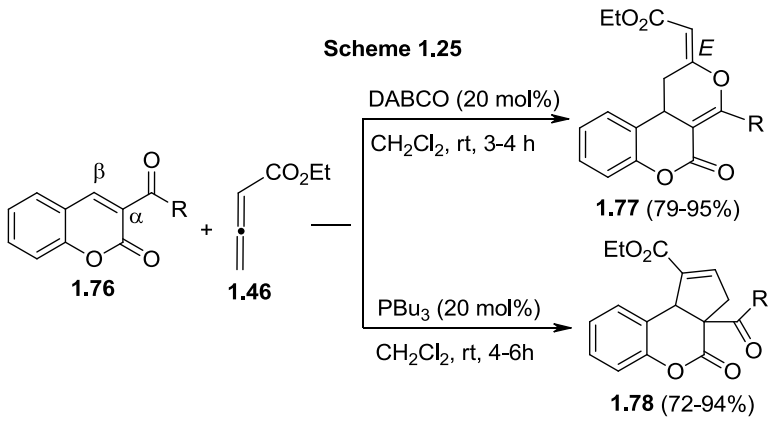


Wang *et al.* reported DABCO catalyzed [2+2] cycloaddition of trifluoromethylketones **1.73** with allenoates **1.46** providing 2-alkyleneoxetanes **1.75** in good yields as well as good diastereoselectivity (Scheme 1.24).[35] Addition of DABCO to allenoate **1.46** generates the enolate intermediate **1.47** (Scheme 1.17), which coexists with allylic carbanion **1.47'**. Subsequent γ-addition of **1.47'** to trifluoromethyl ketone **1.73** provides the α,β-unsaturated ester intermediate **1.74**, that undergoes intramolecular Michael addition and elimination of the catalyst to afford the [2+2] cycloadduct **1.75**.

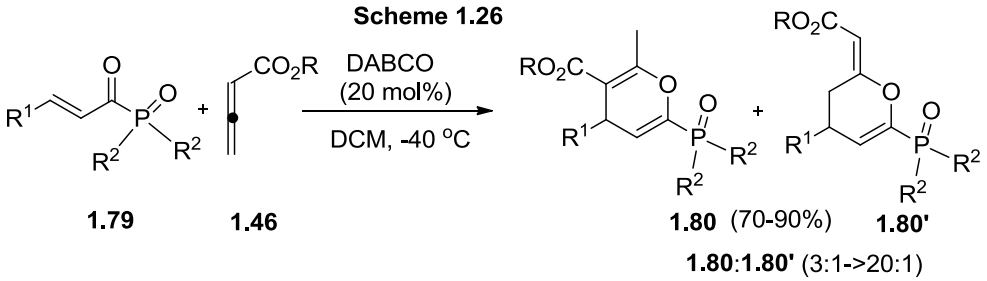
Scheme 1.24



De-Qing Shi's group reported the [4+2] and [3+2] cycloaddition reactions of 3-acyl-2*H*-chromen-ones **1.76** with ethyl 2,3-butadienoate **1.46** catalyzed by DABCO and PBu_3 to access potentially biologically active dihydropyran-fused- and cyclopenten-fused-chromen-2-ones **1.77**-**1.78**, respectively, in moderate to excellent yields (Scheme 1.25).[36] In the presence of DABCO, intermediate **1.47'** reacts with **1.76** to afford the [4+2] cycloadduct **1.77**. In the case of PBu_3, intermediate **1.47** (cf. Scheme 1.17) is stabilized by the phosphonium ion and ester group, hence acts as a 1,3-dipole to react with **1.76** to provide the [3+2] cycloadduct **1.78**.



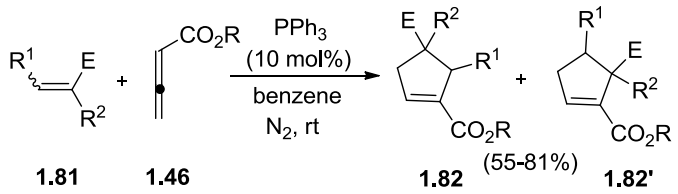
Min Shi's group described a highly efficient DABCO catalyzed [4+2] cycloaddition of β,γ-unsaturated α-ketophosphonates **1.79** with allenic esters **1.46** resulting in highly functionalized tetrahydropyrans **1.80** and dihydropyrans **1.80'** under mild conditions (Scheme 1.26).[37] They obtained all the products in good to excellent yields with moderate to good regioselectivities. Generality of this reaction was extended to (*E*)-ethyl 2-oxo-4-phenylbut-3-enoates affording the corresponding [4+2] cycloadducts in good yields.



1.3.2 Phosphine catalyzed annulation reactions of allenes

Several years ago, Xiyan Lu's group developed an efficient method for the synthesis of functionalized cyclopentenes **1.82**-**1.82'** by the [3+2] cycloaddition reaction of 2,3-butadienoates **1.46** with electron-deficient olefins **1.81** by using triphenylphosphine as a catalyst (Scheme 1.27).[38] The generality of this method was expanded to 2-butynoates to give the corresponding cyclopentenes with the use of PBu_3 catalyst. No cycloaddition occurred when triethylamine was used as the base. Methyl vinyl ketone failed to give the normal cycloadduct. The mechanism involves the reaction of PPh_3 with allene generating allylic carbanion **1.47** which then undergoes [3+2] cycloaddition with electron-deficient olefin providing cyclopentenes by regeneration of the PPh_3 catalyst.

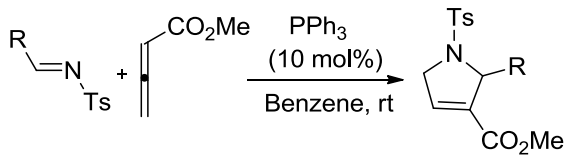
Scheme 1.27



1.81 **1.46** **1.82** **1.82'**

Later, the same group reported the [3+2] cycloaddition reaction of methyl 2,3-butadienoate **1.46** with aromatic or heteroaromatic *N*-tosylimines **1.83** at room temperature by using catalytic amount of triphenylphosphine resulting in nitrogen heterocycles **1.84** in excellent yields with high chemoselectivity (Scheme 1.28).[39a] Nitrogen nucleophiles like DABCO and DMAP failed to catalyze this reaction. Dehydrogenation and subsequent removal of tosyl group from [3+2] cycloadduct was carried out by using DDQ and NaOMe. The same group has also reported more examples on similar PPh_3 catalyzed reactions.[39b-c]

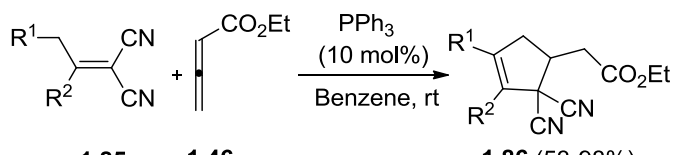
Scheme 1.28



1.83 **1.46** **1.84** (53-98%)

The above research group also developed a highly efficient method for the triphenylphosphine catalyzed [3+2] cycloaddition reaction of substituted alkylidenemalononitriles **1.85** with allenoate **1.46** providing the highly functionalized cyclopentenes **1.86** (Scheme 1.29).[40] In this protocol, allene serves as two carbon unit whereas alkylidenemalononitriles act as three carbon synthon.

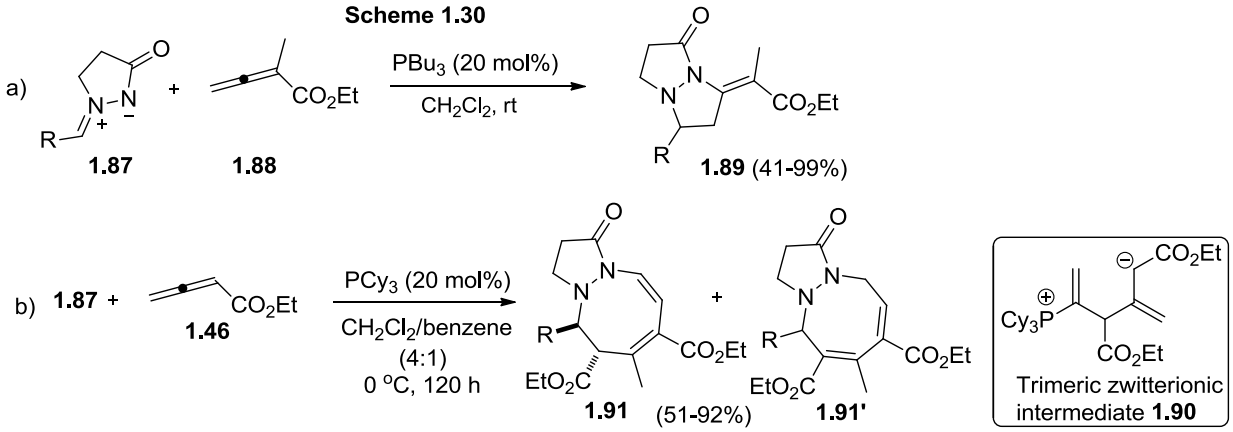
Scheme 1.29



1.85 **1.46** **1.86** (53-98%)

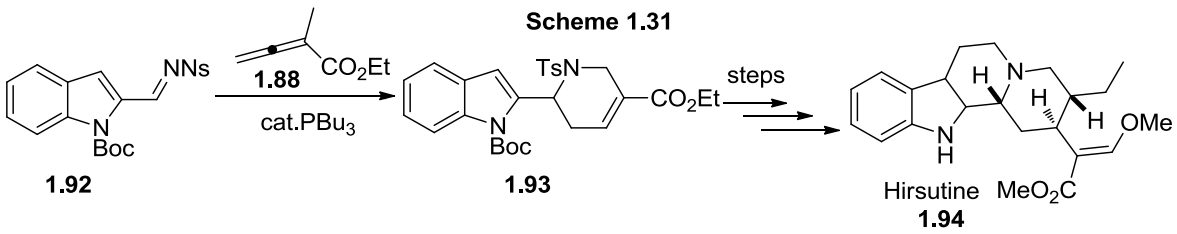
Phosphine-catalyzed [3+2] annulation reaction of azomethine amine **1.87** with allenoate **1.88** was described by the groups of Hongchao Guo and Ohyun Kwon (Scheme 1.30a).[41] In the same report, they also demonstrated the [3+3], [4+3], and [3+2+3] cycloaddition reactions of azomethine amine with various allenoates. These annulation reactions proceed under mild reaction conditions, affording a broad range of fused pyrazolidinone heterocycles in moderate to excellent yields. The reaction of PCy_3 with two molecules of ethyl 2,3-butadienoate **1.46** results in trimeric zwitterionic intermediate **1.90**, which acts as a 1,5-dipole in the cycloaddition reaction with azomethine amine **1.87** leading to [3+2+3] adducts **1.91-1.91'** (Scheme 1.30b). Under phosphine catalysis, incorporation of two molecules of allenoates in the cycloaddition reaction is a new application.

Scheme 1.30



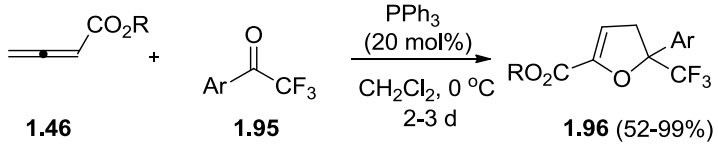
Ohyun Kwon's group developed an application of phosphine-catalyzed [4+2] annulation of the imine **1.92** with ethyl α-methyl allenoate **1.88**. This application was a key step in the total synthesis of indole alkaloid hirsutine **1.94** (6.7% overall yield; Scheme 1.31).[42]

Scheme 1.31



Song Ye's group illustrated the formal PPh_3 catalyzed [3+2] cycloaddition reaction between allenoates **1.46** and trifluoromethylketones **1.95** to furnish the corresponding dihydrofurans **1.96** in good yields with excellent regioselectivities (Scheme 1.32).[43]

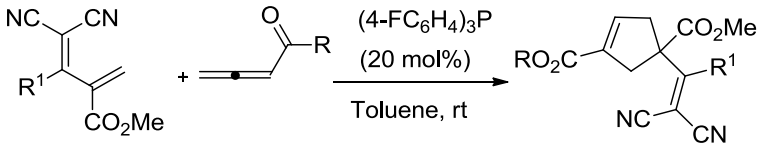
Scheme 1.32



1.46 **1.95** **1.96** (52-99%)

4,4-Dicyano-2-methylenebut-3-enoates **1.97** were first employed in the phosphine catalyzed annulations providing [3+2] cycloadduct **1.98** as demonstrated by Min Shi's group (Scheme 1.33).[44] Chiral version of this [3+2] cycloaddition was also successfully reported by using chiral thiourea-phosphines having an axially chiral binaphthyl scaffold.

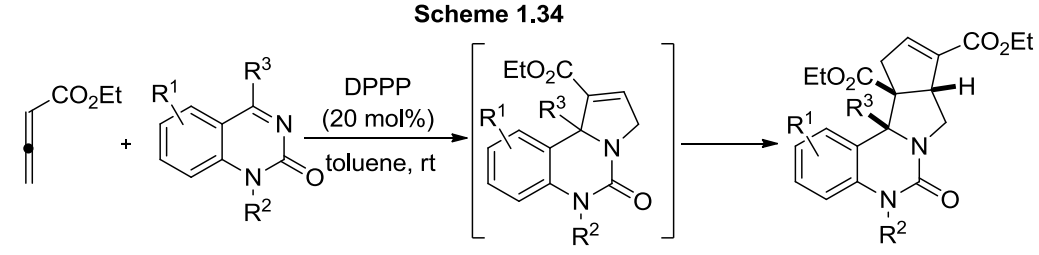
Scheme 1.33



1.97 **1.46** **1.98** (42-87%)

One-pot sequential [3+2]/[3+2] annulation of allenoates **1.46** with cyclic ketimines **1.99** was developed by Jun-An Ma's group.[45] This annulation reaction is highly regio- and diastereo-selective and four new bonds are constructed in one pot to generate the *N*-fused polycyclic compound **1.101** (Scheme 1.34). Here, R^3 must be either trifluoromethyl or difluoromethyl group; if R^3 is methyl or phenyl group, the reaction does not proceed to give the desired product.

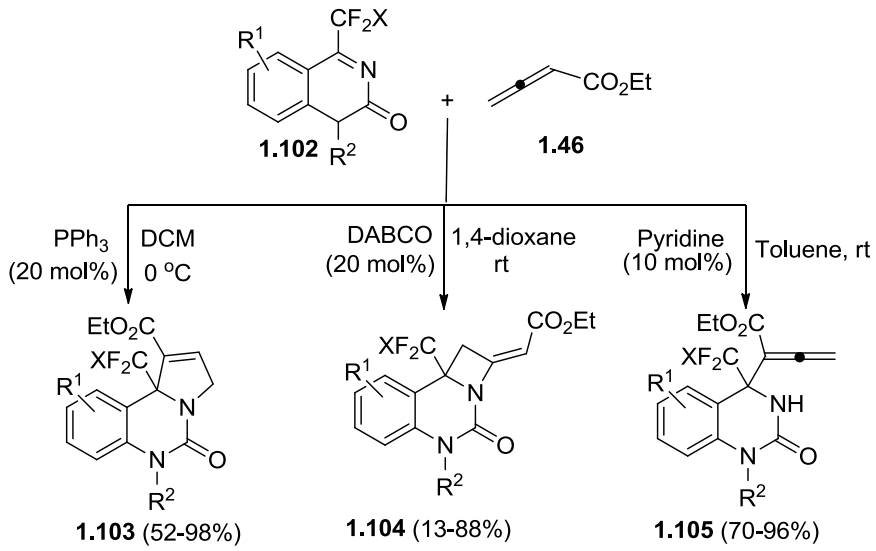
Scheme 1.34



1.46 **1.99** **1.100** **1.101** (64-97%)

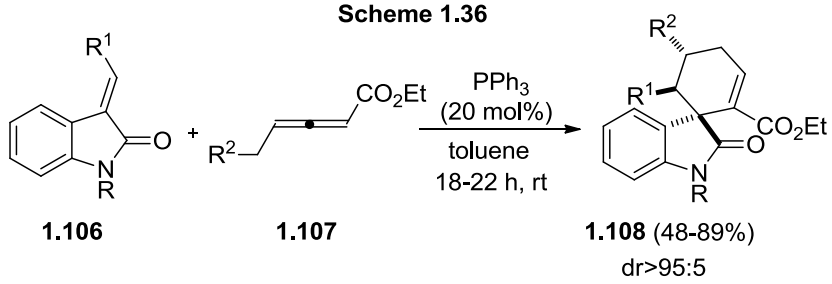
Jun-An Ma's group investigated the different reactivity of cyclic ketimines **1.102** with allenoates **1.46** by using phosphorus- and nitrogen-containing Lewis bases as catalysts.[46] Thus dihydropyrrole derivatives **1.103** were obtained in excellent yield by the [3+2] annulation reaction in the presence of catalytic triphenylphosphine, whereas use of DABCO as the catalyst led to [2+2] annulation, producing azetidine derivatives **1.104**. However, α,α′-disubstituted allenoates **1.105** were obtained in very high yields *via* aza-Morita−Baylis−Hillman (aza-MBH) reaction by choosing pyridine as the catalyst (Scheme 1.35).

Scheme 1.35



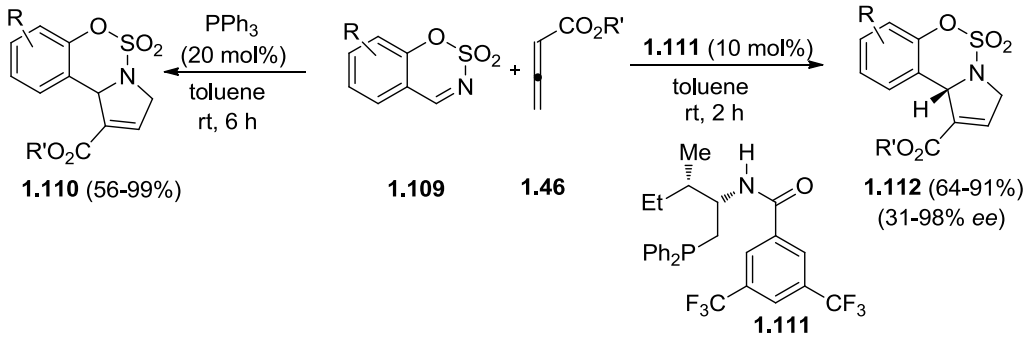
Synthesis of highly functionalized spirocyclic oxindoles **1.108** was reported by Angela Marinetti's group by using catalytic amount of PPh_3.[47] In this annulation reaction, allene **1.107** serves as a 4-carbon unit undergoing [4+2] annulation with arylideneoxindoles **1.106** and providing functionalized spiro-cyclohexene oxindoles **1.108** in good yields (Scheme 1.36). A preliminary experiment for the enantioselective [4+2] cycloaddition reaction was also studied by using chiral phosphorus catalysts.

Scheme 1.36



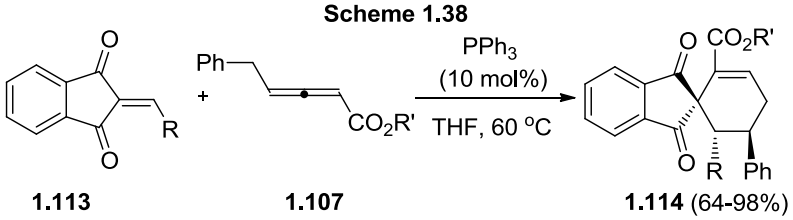
Synthesis of sulfamate-fused dihydropyrroles **1.110** from sulfamate-derived cyclic imines **1.109** and allenoate **1.46** by using triphenylphosphine catalysis was achieved by the Hongchao Guo's group (Scheme 1.37).[48] Here, the allenoate undergoes [3+2] cycloaddition reaction with sulfamate-derived cyclic imines to afford sufamate-fused dihydropyrroles in excellent yields. Asymmetric variant of the [3+2] cycloaddition has also been developed by using amino acid-based bifunctional phosphine **1.111** as a chiral catalyst, leading to chiral sulfamate-fused dihydropyrroles **1.112** in good yields with moderate to excellent enantiomeric excess.

Scheme 1.37



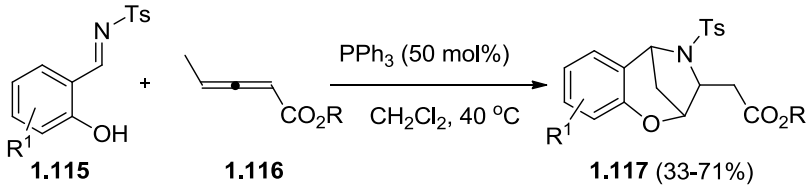
You Huang's group first utilized γ-substituted allenoates **1.107** in [4+2] annulation reaction with 2-arylidene-1*H*-indene-1,3(2*H*)-diones **1.113** under triphenylphosphine catalysis.[49] Allenoates **1.107** act as 4-carbon units in this annulation process. Highly substituted and functionalized spirocyclic skeletons **1.114** are generated in excellent yields with complete regioselectivity and high diastereoselectivily (Scheme 1.38). 2-Arylidene-1*H*-indene-1,3(2*H*)-diones with either strong electron-withdrawing or -donating substituents on the phenyl group needed slightly higher catalyst loading (20 mol% PPh_3).

Scheme 1.38



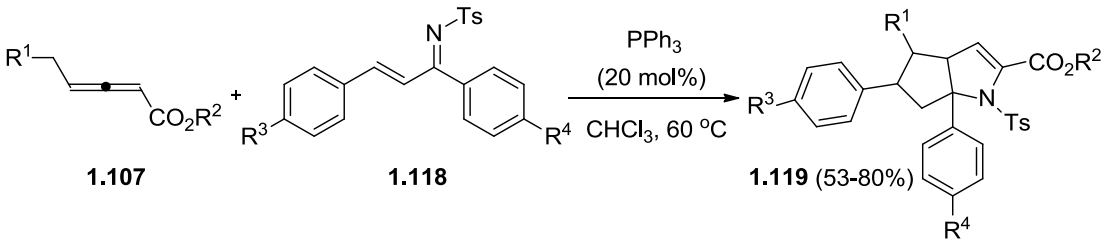
One step synthesis of benzoxazepine derivatives **1.117** *via* PPh_3-catalyzed aza-MBH domino reaction of salicyl-*N*-tosylimines **1.115** with γ-CH_3 substituted allenoates **1.116** was reported by You Huang's group (Scheme 1.39).[50] However, under standard reaction conditions 5-methoxy substituted salicyl-*N*-tosylimine failed to give the desired product. Yield of the benzoxazepine derivatives was significantly influenced by the steric effect in the allenoates. When R was changed to *t*Bu group, no desired product was observed.

Scheme 1.39



A novel annulation reaction of (*E*)-(1,3-diarylallylidene)-4-methyl-benzenesulfonamide **1.118** with γ-benzyl-substituted allenoates **1.107** resulting in bicyclo compounds **1.119** *via* [2+3] and [3+2] sequence by using triphenylphosphine as a catalyst was developed by You Huang and coworkers (Scheme 1.40).[51] A series of aza-bicyclo[3,3,0]-octanes were thus obtained in moderate to good yields with excellent diastereoselectivity (only one isomer obtained).

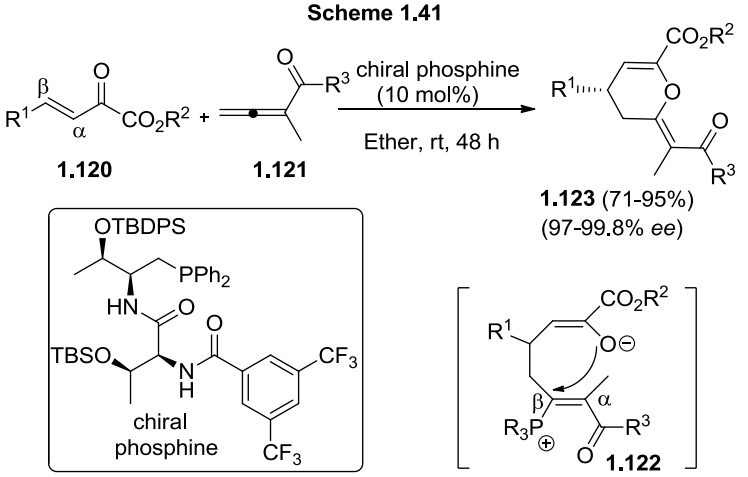
Scheme 1.40



Phosphine-catalyzed [4+2] cycloaddition between β,γ-unsaturated α-keto esters **1.120** and allenic ketones **1.121** was reported by Yixin Lu's group.[52] This is the first asymmetric synthesis of chiral pyran derivatives **1.123** *via* a phosphine-catalyzed annulation reaction (Scheme 1.41). In this annulation, they utilized dipeptide-based bifunctional phosphines which provided highly optically enriched 3,4-dihydropyrans (≥99% ee in most cases) in excellent yields. In this protocol, allenic ketones act as C_2 synthons whereas β,γ-unsaturated α-keto-esters act as C_4 synthons. Usually enolate carbon attacks at the α-position of an allene but the presence of methyl group on allene **1.121** (cf. **1.122**)

suppresses the [3+2] cycloaddition. Moreover, β-position of the allene is more electrophilic due to the presence of ketone functional group. Hence an enolate oxygen attack takes place at the β-position of allene affording the dihydropyrans **1.123**.

Scheme 1.41

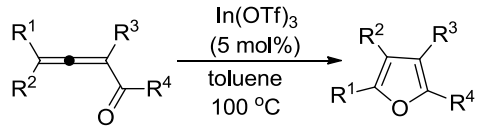


1.4 1,2-Alkyl migration of allenic/alkynic substrates in the presence of transition metal catalysts

Cascade reactions offer a novel approach for the construction of synthetically complex molecules from relatively simple starting materials by mixing two or more diverse reactions into a single transformation. The diverse reactivity of platinum and gold complexes has drawn much interest due to π-bond activation followed by the 1,2-alkyl migration for the development of cascade reactions. In most but not all cascade reactions, 1,2-alkyl migration can be usually divided into two categories: a) 1,2-alkyl migration to an adjacent metal carbenoid center, and b) pinacol-type rearrangement leading to ring expanded heterocycles.[53] In this section, a brief literature survey on cascade reactions which involve the 1,2-alkyl migration that are related to the present work will be presented.

Cycloisomerization of allenyl ketones **1.124** in the presence of $In(OTf)_3$ afforded the fully substituted furans **1.125** (Scheme 1.42).[54] This cycloisomerization proceeds *via* the vinyl cation formed from oxophilic Lewis acid activation of the enone moiety, followed by 1,2-alkyl shift generating highly substituted furans. Selective migration of the phenyl group over the methyl group occurred in allenyl ketone. Alkynyl ketones also generate trisubstituted furans in one-pot; however the yield was somewhat lower than that for cycloisomerization of allene.

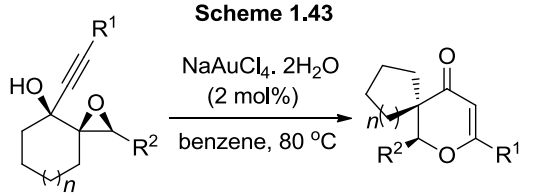
Scheme 1.42



1.124 **1.125** (10-94%)

An efficient gold catalyzed domino cyclization/[1,2]-alkyl migration reaction of epoxy alkynes **1.126** leading to spiropyranones **1.127** was reported by Xing-Zhong Shu *et al* (Scheme 1.43).[55] These epoxy alkynes are readily prepared from the corresponding enones in two steps. Furthermore, the gold-catalyzed tandem process is highly stereospecific with respect to the migrating carbon atom. Under similar reaction conditions, acyclic epoxy alkynes generated the unusual C-C bond cleaved products. The mechanism involves *via* activation of alkyne moiety by gold catalyst and subsequent nucleophilic attack of epoxide oxygen, followed by the 1,2-migration and protodeauration leading to 4(*2H*) pyranone **1.127**.

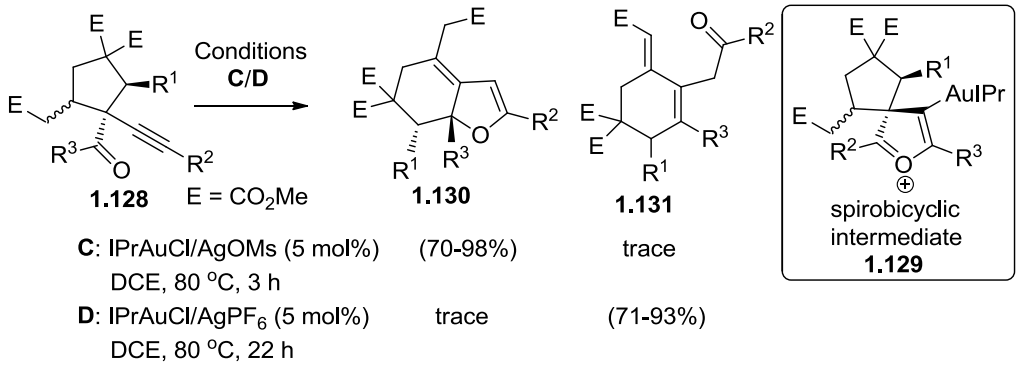
Scheme 1.43



1.126 **1.127** (44-97%)

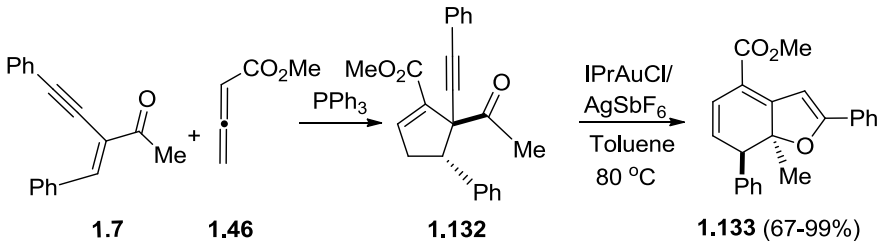
Junliang Zhang and coworkers described a highly regioselective and stereospecific 1,2-alkyl migration and heterocyclization or oxygen transfer of multifunctionalized cyclopentanes **1.128** by using cationic gold(I)-catalysts that led to the formation of highly substituted bicyclic and monocyclic products **1.130** and **1.131**, respectively (Scheme 1.44).[56a] The precursor cyclopentanes were easily prepared from the tandem cyclization of 2-(1-alkynyl)-2-alken-1-ones and crotonate-derived malonate.[56b] The migratory reaction proceeds through activation of triple bond by gold catalyst resulting in the spirobicyclic intermediate **1.129**, which then undergoes 1,2-alkyl migration followed by heterocyclization affording the bicyclic compound **1.130**. Interestingly, in the presence of [Au]-catalyst or PTSA, furan fused compound would undergo further rearrangement by protonation and C-O bond cleavage followed by the loss of the acidic proton at α-position to the ester group, affording the monocyclic compound **1.131**.

Scheme 1.44



Li *et al.* described a methodology for the synthesis of fused dihydrobenzofurans **1.133** from highly substituted cyclopentenes **1.132** in excellent regioselectivity and stereospecificity by using a cationic gold(I) catalyst (Scheme 1.45).[57] These highly substituted cyclopentenes **1.132** were prepared from triphenylphosphine catalyzed [3+2] cycloaddition between enynones **1.7** and allenes **1.46**. They also reported that 4-styrylcyclopent-1-enecarboxylates afforded the highly functionalized dihydrobenzofurans and dihydroisobenzofurans depending on the anion of the silver salt used. The reaction proceeds through the initial activation of alkyne part of enynone by the gold catalyst and subsequent intramolecular attack of carbonyl oxygen leading to spiro-bicyclic intermediate (similar to **1.129**) which undergoes 1,2-alkyl migration followed by protodeauration generating compound **1.133**.

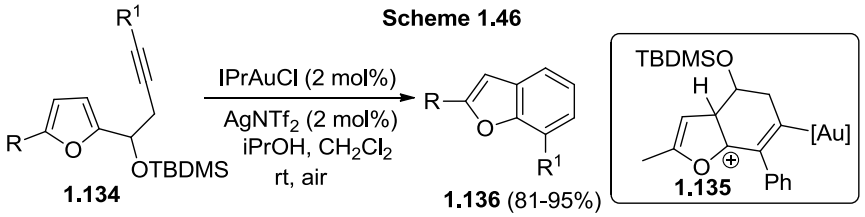
Scheme 1.45



Hashmi *et al*. developed a novel route for the synthesis of benzo[*b*]furans **1.136** from 3-silyloxy-1,5-enynes **1.134** by using gold catalysis (Scheme 1.46).[58] Silver catalyst itself was ineffective for this reaction. The reaction pathway involved the coordination of alkyne to gold inducing 5-*endo-dig* cyclization. This is followed by Wagner–Meerwein shift delivering the carboxonium ion intermediate **1.135**. This intermediate undergoes

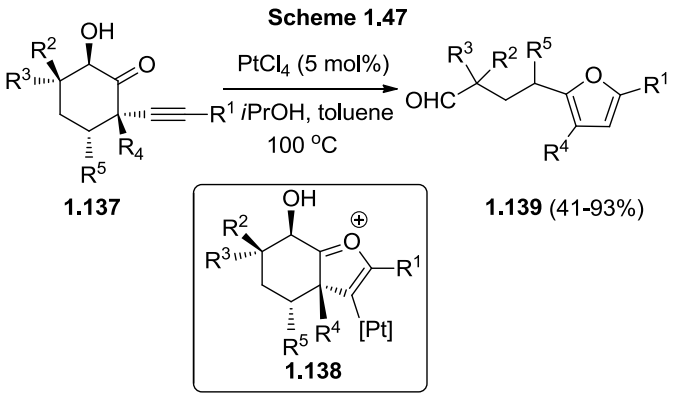
deprotonation and protodeauration followed by aromatization with the elimination of silanol to afford the benzo[*b*]furans **1.136**.

Scheme 1.46



Domino reaction of 6-hydroxy-2-alkyl-2-alkynylcyclohexanones **1.137** that affords substituted furans **1.139** by using $PtCl_4$ was reported by Stefan Kirsch's group (Scheme 1.47).[59] This reaction proceeds through activation of alkyne by the coordination of [Pt]-catalyst, followed by the nucleophilic attack of carbonyl oxygen resulting in the cyclic oxonium ion 1.**138**. A ring-contracting 1,2-shift of cyclic oxonium ion leads to spirocyclic intermediate; subsequent Grob-type fragmentation provides the substituted furan **1.139**.

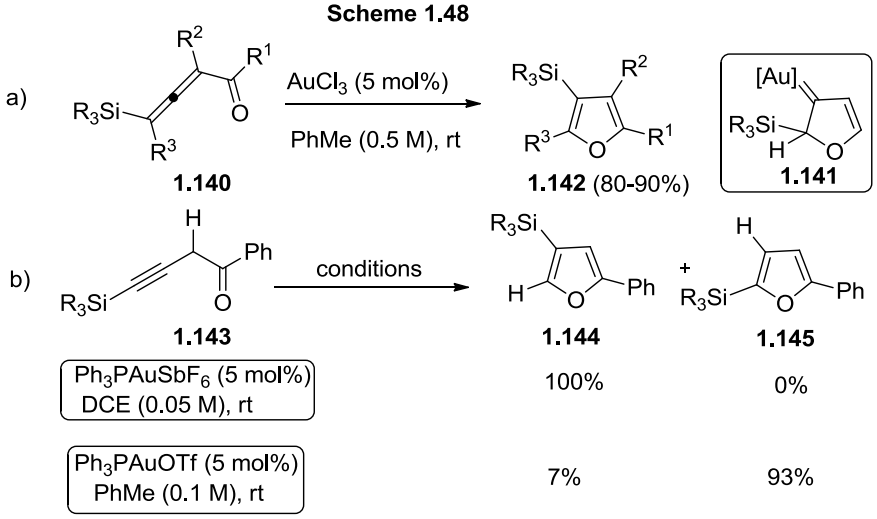
Scheme 1.47



Regiodivergent synthesis of silylfurans using gold catalysis has been reported by Gevorgyan's group.[60] Thus cycloisomerization of allenyl ketones **1.140** and homopropargylic ketones **1.143** generates highly useful 2- and 3-silylfurans **1.142**, **1.144**-**1.145** *via* the [Au]-carbene intermediate **1.141** and 1,2-Si or 1,2-H migrations (Scheme 1.48). Both experimental and computational calculations showed that the 1,2-Si migration is kinetically more favored than the 1,2-shifts of H, alkyl, and aryl groups in the *β*-Si-substituted Au-carbenes. However, counterion and solvent effects may reverse this migratory preference in the case of cycloisomerization of homopropargylic ketones. DFT-simulated reaction affords 1,2-Si migration products exclusively by using Au(I) catalyst

having non-nucleophilic SbF_6^- counterion *via* the initial propargyl-allenyl isomerization followed by cyclization into the [Au]-carbene intermediate regardless of the solvent employed in the reaction. However, in the case of the TfO^- counterion in nonpolar solvents, formation 1,2-H migration products *via* the initial 5-*endo*-*dig* cyclization of propargylic ketones to give a cyclic furyl-[Au]-intermediate followed by a subsequent *ipso*-protodeauration is observed. Polar media facilitate the formation of the 1,2-Si shift products. In all the above results, DFT calculations were validated by the experimental data.

Scheme 1.48



Thus the above literature survey clearly reveals the potential utility of enynones/enynals as substrates in cyclization/ cycloaddition reactions. Our objective was to exploit the enynone/enynal substrates for the synthesis of carbo-/hetero-cycles.

OBJECTIVES OF THE PRESENT WORK - PART A

The main objective of this part of the present work was to probe the reactivity of allenes and functionalized alkynes like enynals/enynones in cycloaddition reactions under base catalysis as well as [Au]-catalysis. Specifically, it was intended

(i) To investigate the reactivity of enynones/enynals with benzyl azides using [Au]-catalysis in an attempt to synthesize furan fused triazines,

(ii) To explore the reaction of allenes with enynones/enynals using DABCO as the catalyst that could lead to highly functionalized dihydropyrans,

(iii) To synthesize diverse alkyne tethered cyclopentenes (as substrates) possessing high functionality starting from allenes and enynals in the presence of PPh_3 as the base, and

(iv) To explore the reactivity of alkyne tethered cyclopentenes as obtained above under gold/silver catalysis that could lead to highly substituted benzofurans *via* 1,2-alkyl migration.

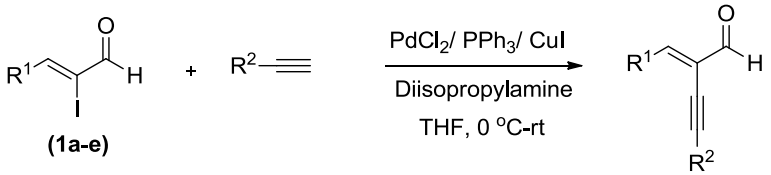
RESULTS AND DISCUSSION

In this chapter, we discuss the results on cycloaddition reactions of enynones and enynals. Details on the precursors used in the present work are presented in sections 2.1-2.4. After this, cycloaddition reaction of enynones/ enynals with azides by using gold catalyst is discussed. In a later section, DABCO catalyzed [2+4] annulation reaction of allenes with enynals/enynones, followed by phosphine catalyzed [3+2] cycloaddition reaction of allenes with enynals, and subsequent 1,2–alkyl migration under gold/silver catalytic system providing the highly substituted benzofurans are described. 2-Iodo-cinnamaldehydes **1a-e** and 2-iodo-cyclohexenone **2** have been synthesized by using standard procedures.[61] Characterization of the products is generally done by using mp (for solids), IR, NMR, LCMS, and HRMS/CHN with single crystal X-ray structure determination for illustrative compounds.

2.1 Synthesis of functionalized enynals 3a-q

Highly functionalized enynal precursors **3a-q** have been prepared from the reaction of corresponding 2-iodo-cinnamaldehydes **1a-e** with various phenyl acetylenes following an established procedure (Scheme 1).[62a-b]

Scheme 1

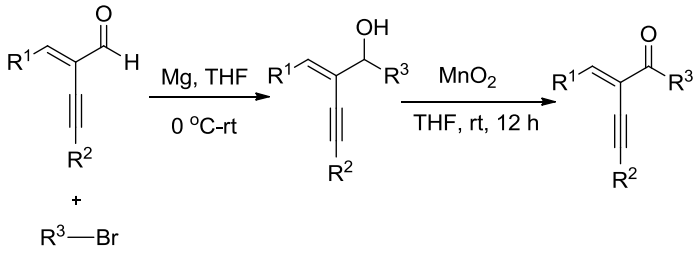


R^1 = Ph, R^2 = Ph	(**3a**)	R^1 = Ph, R^2 = 4-BrC_6H_4	(**3j**)
R^1 = Ph, R^2 = 4-$MeOC_6H_4$	(**3b**)	R^1 = 4-$MeOC_6H_4$, R^2 = Ph	(**3k**)
R^1 = Ph, R^2 = 4-MeC_6H_4	(**3c**)	R^1 = 4-$O_2NC_6H_4$, R^2 = Ph	(**3l**)
R^1 = Ph, R^2 = 2-MeC_6H_4	(**3d**)	R^1 = 4-FC_6H_4, R^2 = Ph	(**3m**)
R^1 = Ph, R^2 = 4-$O_2NC_6H_4$	(**3e**)	R^1 = 3-FC_6H_4, R^2 = Ph	(**3n**)
R^1 = Ph, R^2 = 2-$O_2NC_6H_4$	(**3f**)	R^1 = Ph, R^2 = $SiMe_3$	(**3o**)
R^1 = Ph, R^2 = 4-FC_6H_4	(**3g**)	R^1 = Ph, R^2 = -C_4H_9	(**3p**)
R^1 = Ph, R^2 = 3-FC_6H_4	(**3h**)	R^1 = Ph, R^2 = -cyclohexenyl	(**3q**)
R^1 = Ph, R^2 = 4-ClC_6H_4	(**3i**)		

2.2 Synthesis of functionalized enynones 4a-n, 5, and 6

The functionalized enynone substrates **4a-n, 5,** and **6** were synthesized from the Grignard reaction of corresponding enynals with aryl/alkyl halides, followed by oxidation with MnO_2 (Scheme 2).[62c] Of these, **4c** and **4d** are new. The presence of three functional groups (alkyne, alkene, and ketone) makes these precursors highly attractive for the construction of a variety of heterocycles by simple organic transformations like cyclization and cycloaddition. These compounds generally are stable pale yellow solids and can be handled in air without much difficulty. The IR spectra of these compounds show a weak band at ~ 2190 cm^{-1} indicating the existence of alkyne moiety. A peak at δ ~193.0 is observed in the ^{13}C NMR spectra of these compounds due to the presence of the *C=O* group.

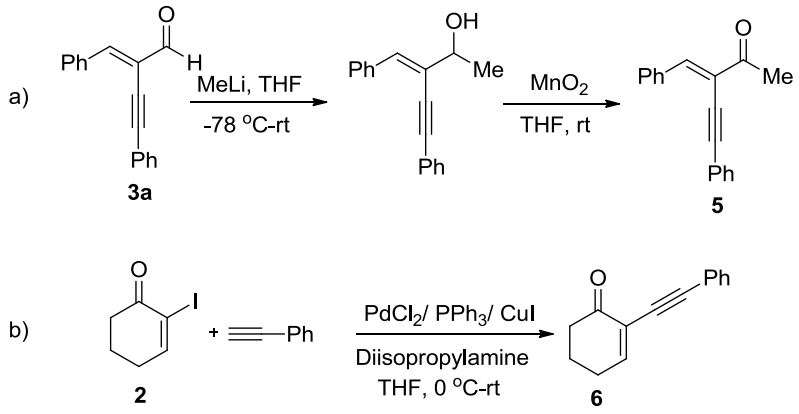
Scheme 2



R^1 = Ph,	R^2 = Ph,	R^3 = Ph	**(4a)**
R^1 = 4-MeO-C_6H_4,	R^2 = Ph,	R^3 = Ph	**(4b)**
R^1 = 4-F-C_6H_4,	R^2 = Ph,	R^3 = Ph	**(4c)**
R^1 = 3-F-C_6H_4,	R^2 = Ph,	R^3 = Ph	**(4d)**
R^1 = Ph,	R^2 = 4-MeO-C_6H_4,	R^3 = Ph	**(4e)**
R^1 = Ph,	R^2 = 4-Me-C_6H_4,	R^3 = Ph	**(4f)**
R^1 = Ph,	R^2 = 2-Me-C_6H_4,	R^3 = Ph	**(4g)**
R^1 = Ph,	R^2 = 4-F-C_6H_4,	R^3 = Ph	**(4h)**
R^1 = Ph,	R^2 = 4-Cl-C_6H_4,	R^3 = Ph	**(4i)**
R^1 = Ph,	R^2 = -cyclohexenyl,	R^3 = Ph	**(4j)**
R^1 = Ph,	R^2 = Ph,	R^3 = 4-MeO-C_6H_4	**(4k)**
R^1 = Ph,	R^2 = Ph,	R^3 = 4-Me-C_6H_4	**(4l)**
R^1 = Ph,	R^2 = Ph,	R^3 = 2-Me-C_6H_4	**(4m)**
R^1 = Ph,	R^2 = Ph,	R^3 = -CH_2Ph	**(4n)**

Enynone **5** was prepared by the reaction of corresponding enynal **3a** with methyllithium at -78 ^oC followed by the MnO_2 oxidation (Scheme 3a). However, compound **6** was synthesized from the corresponding iodo compound **2** by following a literature method (Scheme 3b).[62a]

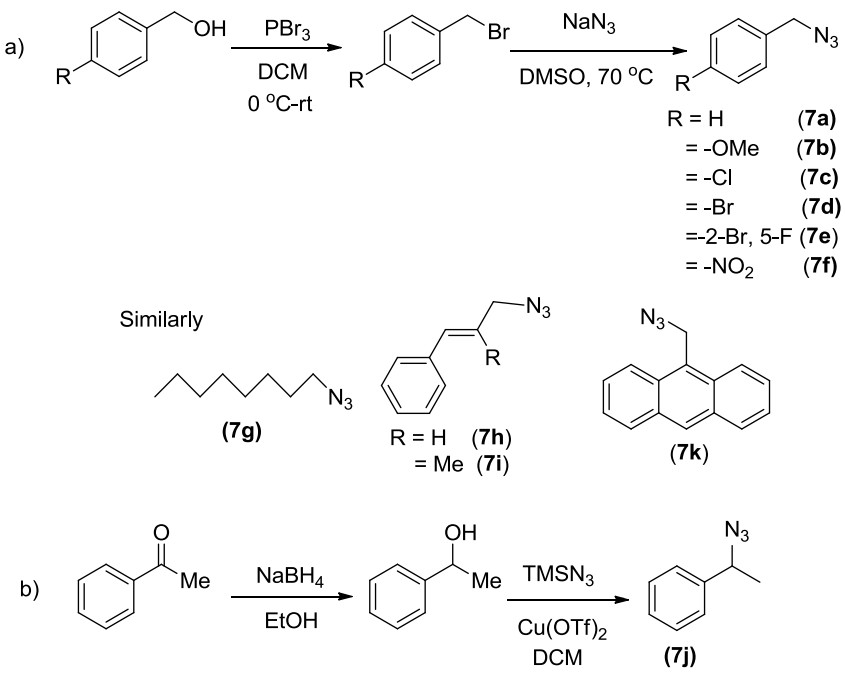
Scheme 3



2.3 Synthesis of azides 7a-k

All these azides were synthesized following known literature procedures.[63a] Thus benzyl and aliphatic bromides were subjected to S_N2 displacement with NaN_3 to afford azides **7a-i** and **7k** (Scheme 4a). Azide **7j** was prepared directly from the alcohol using trimethylsilyl azide as the azide source (Scheme 4b).[63b] IR spectra of all these compounds exhibit a characteristic band at ~2100 cm^{-1} for the azide group.

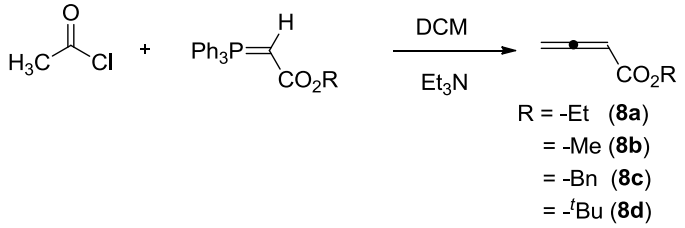
Scheme 4



2.4 Synthesis of allenes 8a-d

Allenes **8a-d** were prepared by following an established method of using drop-wise addition of acetyl chloride in DCM to a solution of the phosphorus ylide in DCM and Et_3N (Scheme 5).[64]

Scheme 5



2.5 Gold catalyzed cycloaddition reaction of enynones with azides

Enynones undergo numerous cycloaddition reactions with various nucleophiles under gold catalysis as presented in Chapter 1. Till recently, there had been hardly any report on the use of azide as a nucleophilic source for enynones to afford furan-fused 1,2,3-triazines in gold-catalyzed cycloaddition reactions. Among the three possible triazine systems, 1,2,3-triazines are pharmaceutically useful because of their potent efficacy and minimal side effects.[65] Hence there are a reasonable number of reports on the synthesis and utility of 1,2,3-triazines.[66] To our knowledge, furan-fused triazine (furanotriazine) ring system has never been reported till now and the corresponding results are discussed below.

2.5.1 Synthesis of furan fused triazines by the [3+3] cycloaddition reaction of enynones with azides

Initially, the reaction of (*E*)-2-benzylidene-1,4-diphenylbut-3-yn-1-one **4a** with benzyl azide **7a** in the presence of $Ph_3PAuCl/AgOTf$ (5 mol%) in dichloromethane (DCM) for 5 h led to the [3+3] cycloadduct **9** in 35% yield (Table 1, entry 1). The product yield improved marginally by changing the solvent from DCM to DCE (entry 2). Varying the counter-ion or the use of $IPrAuCl/AgSbF_6$ did not enhance the yield of **9** (entries 3-6). IPrAuCl itself was not effective (entry 7). Other gold catalysts like $NaAuCl_4.2H_2O$, AuCl, $HAuCl_4.3H_2O$ and $AuCl_3$ gave very poor yields (entries 8-11). Surprisingly, the reaction proceeded very smoothly with 5 mol% $LAu(CH_3CN)SbF_6$ (L = [(2-biphenyl)di-*tert*-butylphosphine]) as the catalyst in DCE solvent affording the product **9** in 84% yield (entry 12). It is important to note that enynones **4** in DCE solvent should be added

dropwise at 0 ^{o}C to the solution of gold complex and azide. At rt (25 ^{o}C), the reaction was vigorous and yield of the product was reduced (entry 13). Addition of $AgSbF_6$ to the above gold catalyst slightly decreased the yield of the desired product (entry 14). Solvents such as DCM, 1,4-dioxane, toluene and $CHCl_3$ were less effective (entries 15-18). In methanol or DMF, enynone did not react with benzyl azide, but other byproducts were formed.[62a] Other variations did not improve the yield (entries 19-22). Thus the optimal reaction conditions were: **4a** (1.0 equiv.), **7a** (1.2 equiv) and $LAu(CH_3CN)SbF_6$ (5 mol%) in DCE (2 mL) as a solvent from 0 ^{o}C to rt for 5 h.

Scheme 6

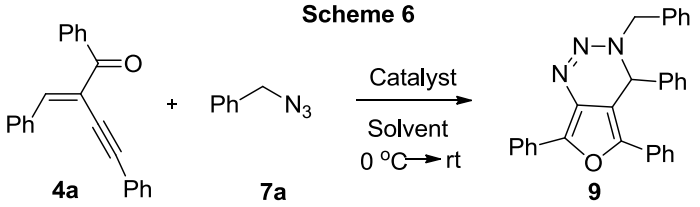


Table 1. Survey of reaction conditions for the [3+3] cycloaddition of (*E*)-2-benzylidene-1,4-diphenylbut-3-yn-1-one **4a** with benzyl azide **7a**[a]

Entry	Catalyst (5 mol%)	Solvent	Yield(%)[b]
1	$Ph_3PAuCl/AgOTf$	DCM	35%
2	$Ph_3PAuCl/AgOTf$	DCE	45%
3	$Ph_3PAuCl/AgSbF_6$	DCE	43%
4	$Ph_3PAuCl/AgBF_4$	DCE	40%
5	$Ph_3PAuCl/AgNTf_2$	DCE	33%
6.	$IPrAuCl/AgSbF_6$	DCM	20%
7.	IPrAuCl	DCM	N.R.
8.	$NaAuCl_4.2H_2O/AgOTf$	DCE	Trace
9	AuCl/AgOTf	DCE	Trace
10	$HAuCl_4.3H_2O/AgOTf$	DCE	10%
11	$AuCl_3$/AgOTf	DCE	12%
12	**$LAu(CH_3CN)SbF_6$**	**DCE**	**84%**
13	$LAu(CH_3CN)SbF_6$	DCE	65%[c]
14	$LAu(CH_3CN)SbF_6/AgSbF_6$	DCE	76%[d]

15	$LAu(CH_3CN)SbF_6$	DCM	56%
16	$LAu(CH_3CN)SbF_6$	1,4-dioxane	45%
17	$LAu(CH_3CN)SbF_6$	toluene	55%
18	$LAu(CH_3CN)SbF_6$	$CHCl_3$	47%
19	$AgSbF_6$	DCE	30%[d,e]
20	$Cu(OTf)_2$	DCE	N.R.
21	$LAu(CH_3CN)SbF_6$	DCE	40%[f]
22	-	DCE	N. R.[g]

[a]Standard conditions: Enynone **4a** (0.3 mmol), benzyl azide **7a** (0.36 mmol), catalyst (5 mol%), and solvent (2 mL), rt for 5 h unless otherwise noted. DCM = dichloromethane; DCE = 1,2-dichloroethane, [b]Isolated yields. [c]Addition of **4a** at room temperature. [d]Isolated after 12 h. [e]20 mol% $AgSbF_6$ was used. [f]2.5 mol% catalyst was used. [g] Reaction at 80 ^oC for 2 d. L = [(2-biphenyl)di-*tert*-butylphosphine]); IPr = 1,3-Bis(2,6-diisopropyl phenyl-imidazol-2-ylidene). N.R. = No reaction.

We then explored the substrate scope for the above gold catalyzed [3+3] cycloaddition between various 2-(1-alkynyl)-2-alken-1-ones and benzyl azides (Scheme 7). Both electron–donating and electron-withdrawing groups on the benzyl group of azide gave decent yields, but electron withdrawing groups $–NO_2$ and -Br marginally reduced the yield. Dihalo substituted azide **7e** also produced the desired product **13** in good yield. The generality of this method could be extended to octyl as well as cinnamyl azides like **7g**, **7h** and **7i** affording **15**, **16**, and **17** in 86%, 72%, and 72% yields, respectively. Secondary azide [(1-azidoethyl)benzene] **7j** and 9-anthracenylmethyl azide **7k** also worked well offering the corresponding cycloadducts **18** and **19** in good yields. The reaction was very clean and the corresponding furanotriazines **20**-**28** and **30**-**32** were obtained in 53-86% yield with high regioselectivity. This methodology also tolerates the presence of cyclohexenyl moiety (R^2) at the triple bond position resulting in the corresponding [3+3] annulation product **29**. A limitation though is the case of phenyl azide where multiple products were obtained. This may be due to the delocalization of electron density on azide nitrogen to the benzene ring. Absence of carbonyl (*C=O*) peak at ~ δ 193, and alkyne (*C≡C*) peaks at ~ δ 100 and ~ δ 90 in the ^{13}C NMR spectra indicated the participation of carbonyl and alkyne moieties of enynone in the reaction.

The presence of AM pattern in ^{1}H NMR spectra revealed the presence of geminal protons, which suggested the involvement of azide in the reaction. The structure of annulation product **9** was then confirmed by single crystal X-ray diffraction (Figure 1).

Scheme 7

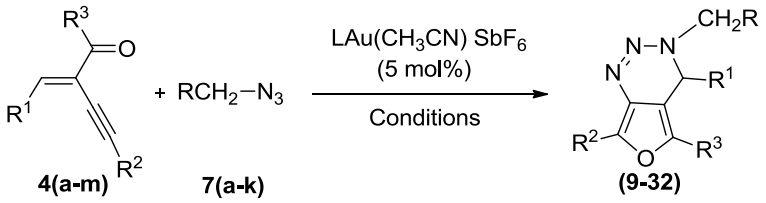
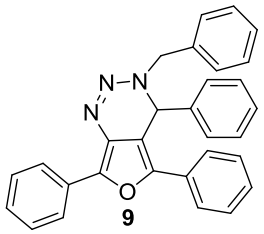
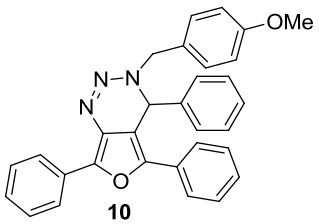
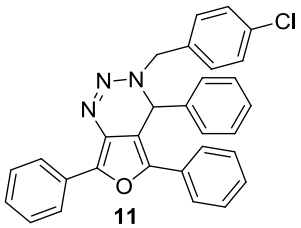
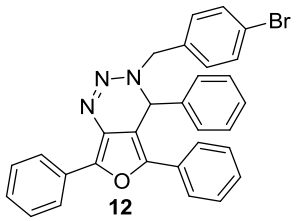
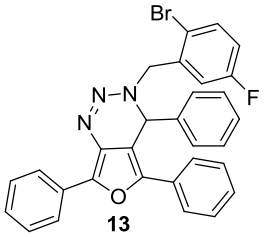
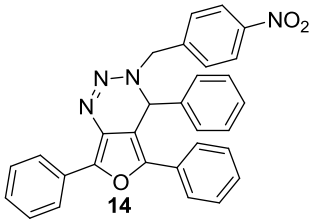
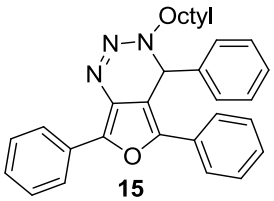
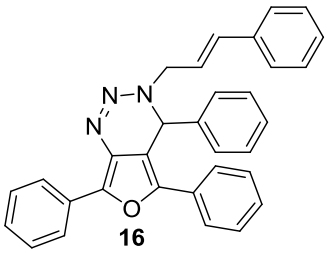
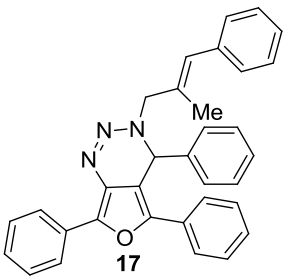
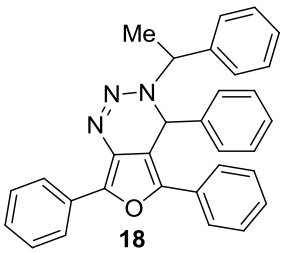
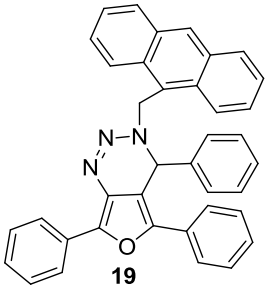
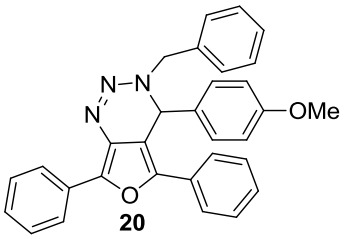
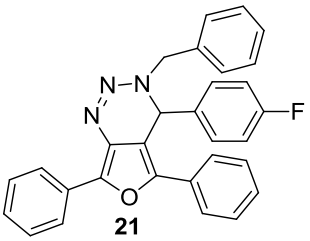
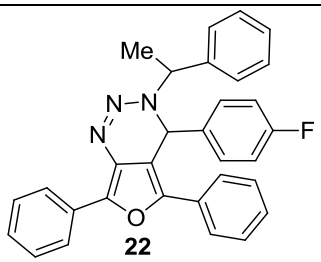
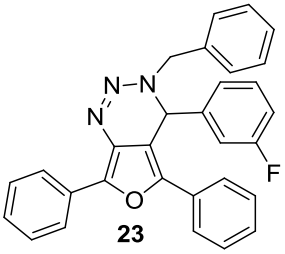
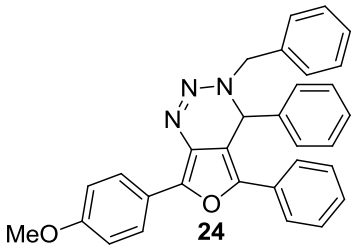
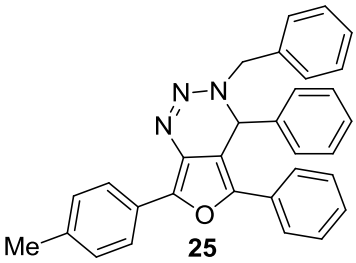
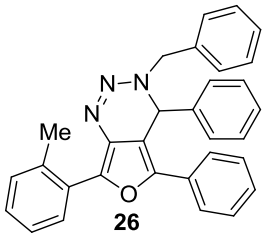
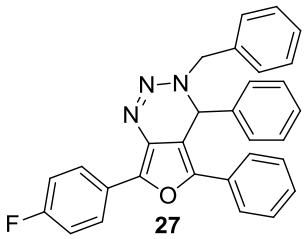
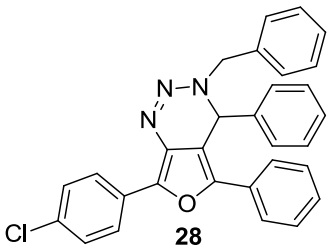


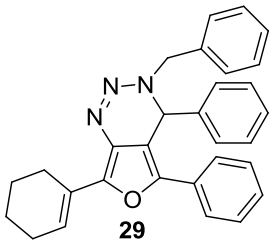
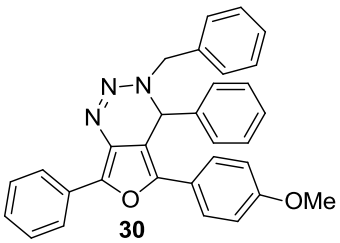
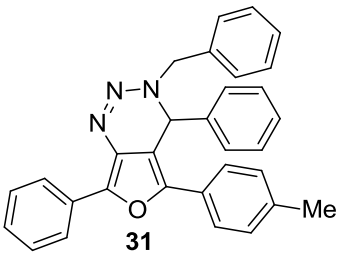
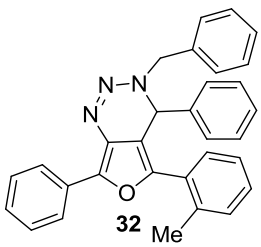
Table 2. Scope of the gold catalyzed [3+3] annulation reaction of 2-(1-alkynyl)-2-alken-1-ones **4a-m** with azides **7a-k** (cf. Scheme 7)[a]

Entry	Enynones	Azides	Furan fused 1,2,3-triazines	Yield (%)[b]
1	**4a**	**7a**	 **9** (X-ray)	84
2	**4a**	**7b**	 **10**	78
3	**4a**	**7c**	 **11**	74

4	**4a**	**7d**	 **12**	55
5	**4a**	**7e**	 **13**	65
6	**4a**	**7f**	 **14**	53
7	**4a**	**7g**	 **15**	86
8	**4a**	**7h**	 **16**	72
9	**4a**	**7i**	 **17**	72

10	**4a**	**7j**	 **18**	76
11	**4a**	**7k**	 **19**	80
12	**4b**	**7a**	 **20**	70
13	**4c**	**7a**	 **21**	78
14	**4c**	**7j**	 **22**	78
15	**4d**	**7a**	 **23**	75

16	**4e**	**7a**	 **24**	64
17	**4f**	**7a**	 **25**	66
18	**4g**	**7a**	 **26**	75
19	**4h**	**7a**	 **27**	80
20	**4i**	**7a**	 **28**	82

21	**4j**	**7a**	 **29**	56
22	**4k**	**7a**	 **30**	80
23	**4l**	**7a**	 **31**	68
24	**4m**	**7a**	 **32**	76

[a]Conditions: Enynone **4** (0.3 mmol), azide **7** (0.36 mmol), $LAu(CH_3CN)SbF_6$ (5 mol%), DCE (2 mL), rt for 5 h. [b]Isolated yield.

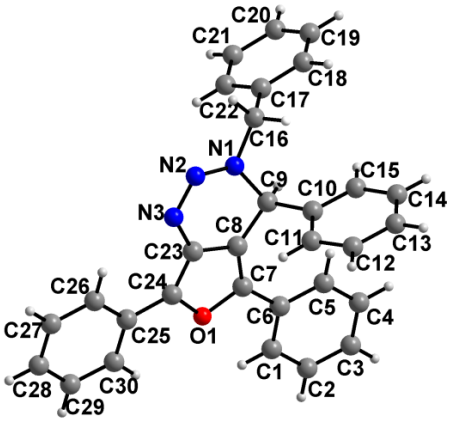


Figure 1. Molecular structure of compound **9** Selected bond lengths [Å] with esds in parentheses: O(1)-C(7) 1.3847(18), C(7)-C(8) 1.359(2), C(8)-C(9) 1.491(2), C(9)-N(1) 1.488(2), N(3)-C(23) 1.397(2), C(23)-C(24) 1.368(2), C(24)-O(1) 1.3714(18).

2.5.2 Absorbance and fluorescence emission spectra of furanotriazines

Preliminary studies of absorption and emission spectra of furanotriazines have also been performed. We compared the absorption and fluorescence emission spectra of compounds **15** and **16** with that of compound **19**. Though compound **19** has similar and slightly lower absorbance than compounds **15** and **16**, it shows higher fluorescence emission intensity as expected for an anthracenyl compound (Figure 2-3). Compounds **9**, **10**, **15**, **16**, **19** and **21** are also fluorescence active (cf. Figure 2-4). Thus these products could be of use as good fluorescence active materials.

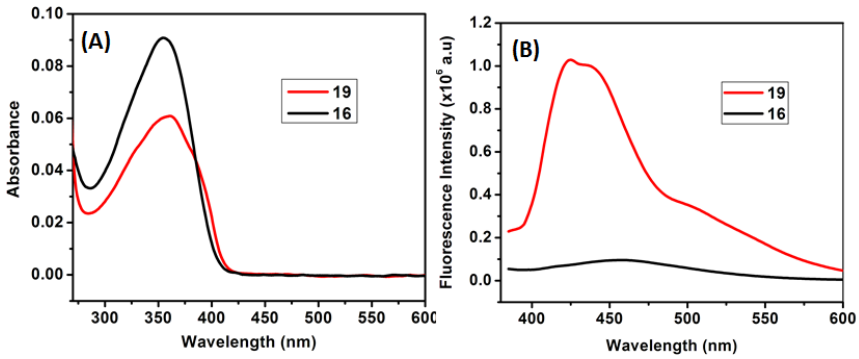


Figure 2. Absorbance (A) and fluorescence emission spectra (B) of compounds **16** and **19** with c = 1.71x10^{-2} mol/L in THF (upon excitation at 357 nm and 370 nm respectively). Quantum yields for **16** and **19** are 0.0011 and 0.014, respectively.

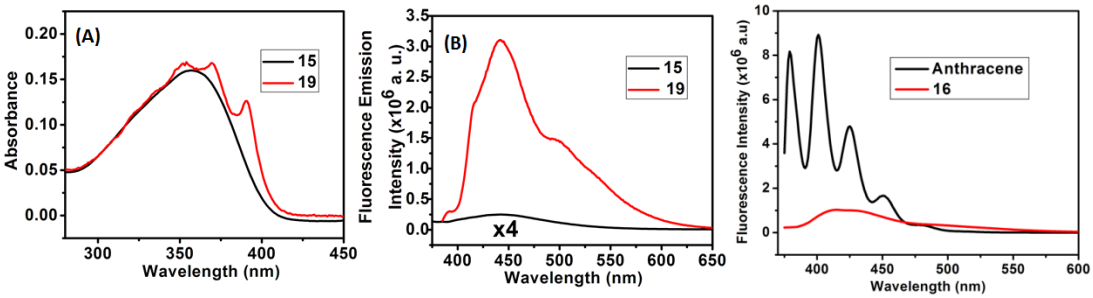


Figure 3. **Left and center**: Absorbance (A) and fluorescence emission spectra (B) of compounds **15** and **19** in THF solution (upon excitation at ~367 nm). **Right:** Fluorescence

emission spectra of compounds **19** and anthracene at c = 1.71x10^{-2} mol/L in THF (upon excitation at 370 nm 358 nm and respectively).

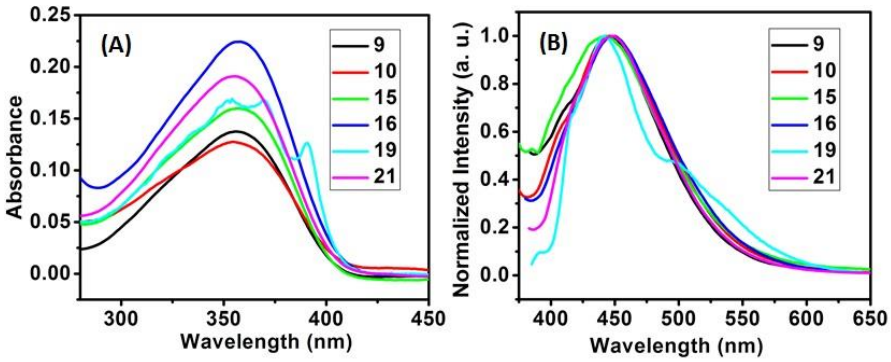


Figure 4. Absorbance (A) and normalized fluorescence emission spectra (B) of compounds **9**, **10**, **15**, **16**, **19** and **21** in THF solution (upon excitation at ~367 nm).

2.5.3 Gold catalyzed [3+3] cycloaddition of enynals with benzyl azides

We expanded the utility of the above reaction to include enynals (possessing aldehyde functionality). Thus, the reaction between (*E*)-2-benzylidene-4-phenylbut-3-ynal **3a** and benzyl azide **7a** resulted in the desired [3+3] cycloadduct **33** in 32% yield with some starting material remaining even after longer reaction time. Pleasingly, though, upon increasing the reaction temperature to 70 ^{o}C, compound **33** was obtained in 73% yield after 10 h. At room temperature it took 48 h for completion of the reaction. In an analogous manner, reactions using compounds **3b**, **3d**, and **3h-i** also proceeded smoothly and resulted in the corresponding [3+3] cycloadducts **35-38** in good yields (Scheme 8). Absence of a singlet at δ ~ 9.6 in the ^{1}H NMR spectra, of carbonyl peak at δ ~ 192.0 and alkyne peaks at δ ~ 100.0 and ~ 90.0 in the ^{13}C NMR spectra indicated the involvement of aldehyde and alkyne functionalities of enynal in the reaction. ^{1}H NMR spectra exhibited an AM pattern corresponding to geminal protons and a singlet at ~ δ 6.2 for the furanyl –C-*H* of the products.

Scheme 8

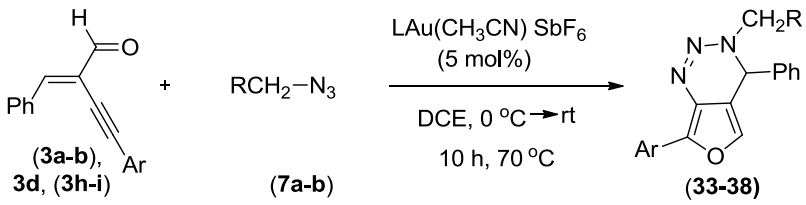
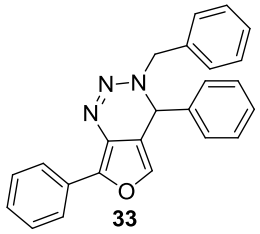
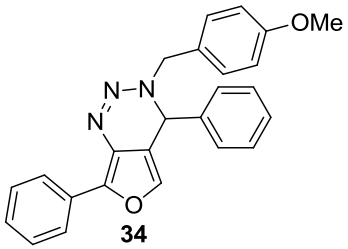
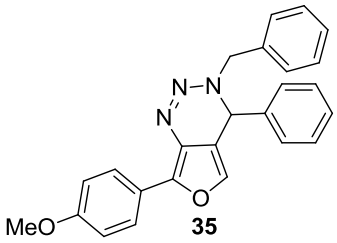
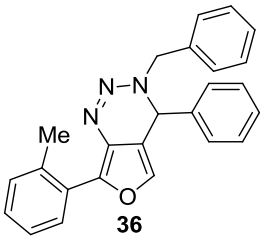
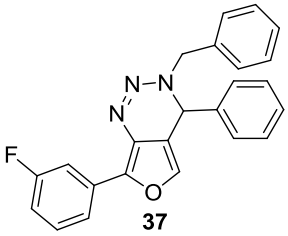
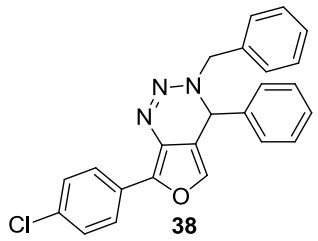


Table 3. Gold catalyzed [3+3] cycloaddition of enynals **3a-b**, **3d**, and **3h-i** with benzyl azide **7a-b** (cf. Scheme 8) [a]

Entry	Enynals	Azides	Furan fused 1,2,3-triazines	Yield (%)[b]
1	**3a**	**7a**	 **33**	73
2	**3a**	**7b**	 **34**	75
3	**3b**	**7a**	 **35**	68
4	**3d**	**7a**	 **36**	70
5	**3h**	**7a**	 **37**	72

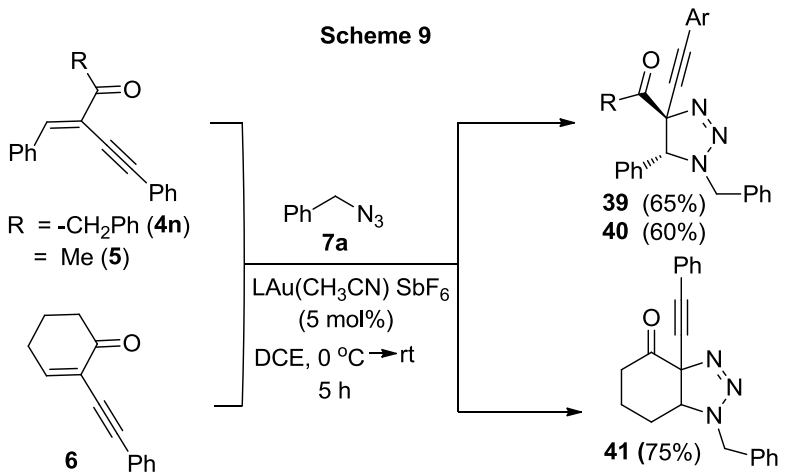
6	**3i**	**7a**	 **38**	66

[a]Conditions: Enynal **3** (0.3 mmol), azide **7** (0.36 mmol), $LAu(CH_3CN)SbF_6$ (5 mol%), DCE (2 mL), 70 ^oC for 10 h. [b]Isolated yield.

2.5.4 Gold catalyzed [3+2] cycloaddition reaction of enynones 4n, 5 and 6 with benzyl azide 7a leading to functionalized triazoles

In contrast to the above, interestingly, in the presence of above gold catalyst, enynones **4n**, **5**, and **6** underwent [3+2] cycloaddition with benzyl azide **7a**. Here, only ***alkene*** part of the enynones reacts with benzyl azide resulting in the formal [3+2] cycloadducts **39-41**, rather than the [3+3] cycloadducts, in 65%, 60% and 75% yields, respectively (Scheme 9).[67] The difference between this reaction and the one shown in Scheme 7 may be rationalized by realizing that the R^3 group is aryl in the case of **4a-m** (cf. Scheme 7) for [3+3] cycloaddition and alkyl in the case of precursors **4n**, **5**, and **6** for the [3+2] cycloaddition involving the alkene moiety. Presence of carbonyl peak at δ ~ 200, and alkyne peaks at δ ~ 90 and ~ 80 in the ^{13}C NMR spectra suggested that carbonyl and alkyne groups of enynones ***did not*** participate in the reaction. Thus only ene part of enynones reacted with the azide leading to functionalized triazoles.

Scheme 9

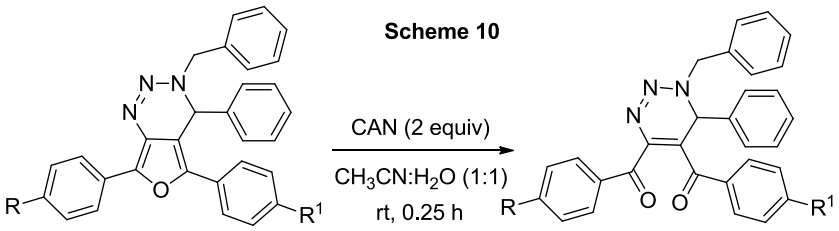


Reaction conditions: Enynone **4n or 5 or 6** (0.3 mmol), azide **7a** (0.36 mmol), $LAu(CH_3CN)SbF_6$ (5 mol%), DCE (2 mL), rt for 5 h.

2.5.5 Synthetic utility of furanotriazines- Selective opening of furan ring leading to 1,2,3-triazines

1,2,3-Triazines constitute an attractive class of compounds to develop new drugs, but synthetic routes to them are rarely reported.[65, 66] Keeping this in mind, we performed the furan ring cleavage reaction of furanotriazine **9** with cerium(IV) ammonium nitrate (CAN) at rt/15 min that afforded the tetrasubstituted 1,2,3-triazine **42** in 96% yield. The generality of this reaction was explored using furo[3,4-d][1,2,3]triazines **24**, **25** and **30**. Thus we obtained the highly functionalized 1,2,3-triazines **43-45** in excellent yields (Scheme 10). These compounds exhibited a strong carbonyl band at ~1600 cm^{-1} in the IR spectra. They also showed peaks in ^{13}C NMR spectra at δ 190-195. Compound **44** was further characterized by single crystal X-ray analysis (Figure 5). The C1-C2 distance of 1.320(6) Å proves the existence of a double bond between these two atoms. Also, the C18-O2 distance of 1.192(8) Å and C10-O1 distance of 1.224(5) Å are in the double bond range as expected. Compounds **42** and **44** are also fluorescence active (Figure 6).

Scheme 10



R = H, R^1 = H **9**
= OMe, R^1 = H **24**
= Me, R^1 = H **25**
= H, R^1 = OMe **30**

42 (96%)
43 (80%)
44 (83%, **X-ray**)
45 (96%)

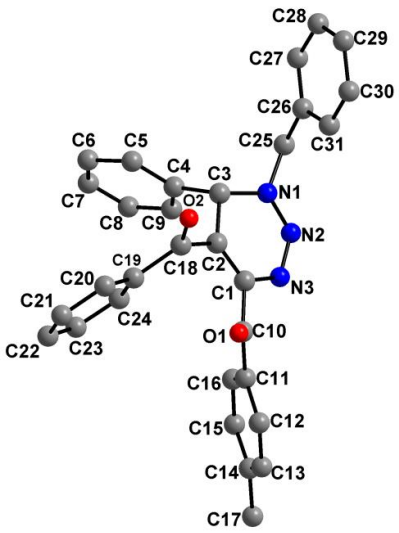


Figure 5. Molecular structure of compound **44** (H atoms omitted for clarity) Selected bond lengths [Å] with esds in parentheses: C(1)-C(2) 1.320(6), O(1)-C(10) 1.224(5), O(2)-C(18) 1.192(8), C(2)-C(18) 1.505(6), C(1)-C(10) 1.503(6).

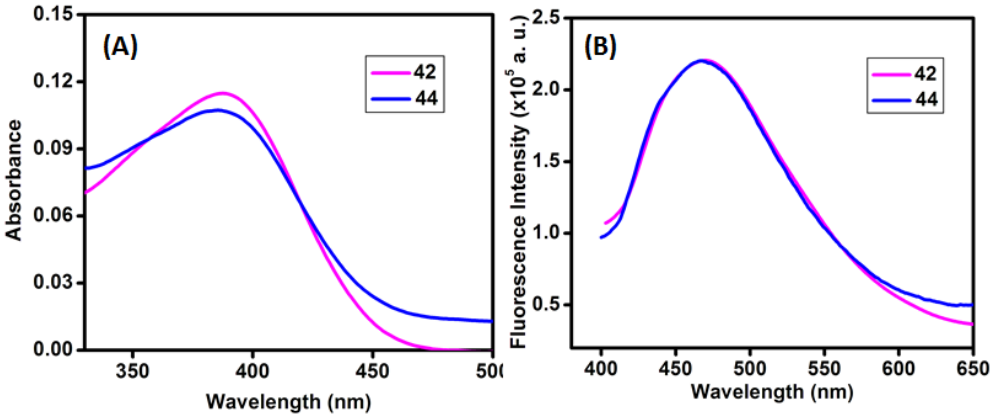
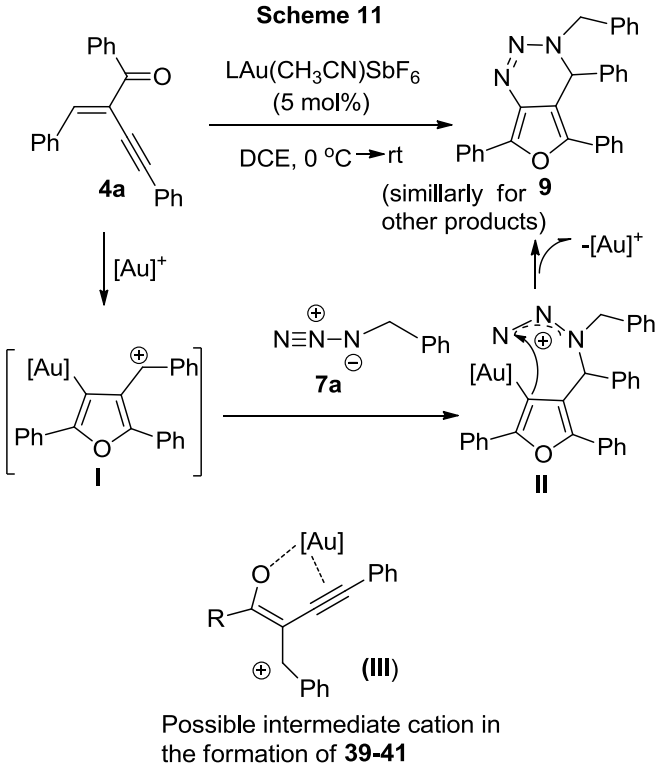


Figure 6. The absorption (A) and fluorescence emission spectra (B) of compounds **42** and **44** in THF solution upon excitation at ~388 nm.

2.5.6 Plausible pathway for the gold catalyzed cycloaddition of enynones/enynals with benzyl azide

A plausible pathway for the above [3+3] cycloaddition involves the initial activation of the alkyne end of enynone **4a** with gold catalyst followed by the intramolecular attack of carbonyl oxygen leading to furanyl gold intermediate **I**, [12a, 13a, 16, 68] which acts as a carbon electrophile (Scheme 11). Intermediate **II** is formed by nucleophilic attack of azide nitrogen on the highly activated species **I**. Intermediate **II** undergoes intramolecular C-N bond formation to furnish the desired [3+3] cycloadduct **9** with regeneration of the gold catalyst. In the formation of the [3+2] cycloaddition products **39-41**, it is likely that [Au^I] is coordinated to both the triple bond and the carbonyl oxygen with an electrophilic carbon center in the intermediate stage such as that shown in **III**.[69] It is possible that the alkyl group R in **4n** and **5- 6** and may facilitate oxygen coordination better than an aryl group at this position leading to a different type of product.



2.6 DABCO catalyzed [2+4] cycloaddition reaction of allenes with enynals/enynones

In this section, we shall discuss [2+4] cycloaddition of allenes with enynals/enynones by using DABCO as a catalyst. Previous literature related to this work is highlighted in Chapter 1.

2.6.1 DABCO catalyzed reactions of allenoates 8 with enynals 3 and enynones 4

For the amine catalyzed [2+4] cycloaddition, we chose DABCO as the catalyst with ethyl 2,3-butadienoate **8a** and (*E*)-2-benzylidene-4-phenylbut-3-ynal **3a** as substrates to afford dihydropyran **46** (Scheme 12). Although toluene has been effectively used as a solvent in such reactions,[32-34] in our case, 1,4-dioxane worked better (Table 4, entry 4). The reaction mixture showed a single product. The yields given are after isolation by column chromatography. Other solvents like diethyl carbonate and dichloromethane gave lower yields (entries 1-3). In the case of toluene, reaction was incomplete even after 6 h. The reaction was not clean when bases such as DBU (1,8-diazabicyclo-[5.4.0]undec-7-ene) and DMAP (4-dimethylaminopyridine) were used; only traces of [2+4] cycloadduct were observed (entries 6, 7). Triethylamine was ineffective for this reaction (entry 9), even after two days. In the absence of catalyst, the desired product was not observed even

at 100 ^{o}C (entry 10). Hence we chose DABCO (10 mol%) as the organocatalyst and 1,4-dioxane (2 mL) as the solvent (entry 4) for this [2+4] cycloaddition reaction.

Scheme 12

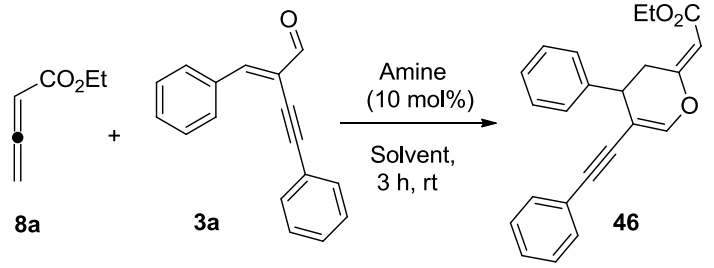


Table 4. DABCO catalyzed [2+4] cycloaddition leading to functionalized dihydropyrans[a]

Entry	Catalyst	Solvent	Yield of **46** (%)[b]
1	DABCO	$(EtO)_2CO$	73
2	DABCO	Toluene	55
3	DABCO	DCM	61
4	**DABCO**	**1,4-Dioxane**	**82**
5	DABCO	THF	68
6	DBU	1,4-Dioxane	Trace[c]
7	DMAP	1,4-Dioxane	Trace[c]
8	DMAP	Toluene	10
9	Et_3N	1,4-Dioxane	N.R. [d]
10	none	1,4-Dioxane	N.R.[e]

[a]Reaction conditions: Enynal **3a** (0.4 mmol), allenoate **8a** (0.48 mmol), catalyst (10 mol%), solvent (2 mL), rt for 3 h unless otherwise noted. [b]Isolated yields. [c]Complex mixture of products with only a trace of **46**. [d]Reaction was carried out at 70 ^{o}C for 2 days. [e]At 100 ^{o}C also, there was no reaction.

In the next step, we investigated the substrate scope for the above [2+4] cycloaddition reaction of allenoates with enynals as well as enynones (Scheme 13, Table 5). The

reaction was smooth and the corresponding dihydropyrans were obtained in 57-87% yield with high regioselectivity. Electron-releasing or –withdrawing groups on the phenyl rings gave satisfactory results **47-49** and **54-55** (entries 2-4 and entries 9-10). Halogen substituted enynals also showed good reactivity and resulted in 64-86% yield of compounds **50-53** and **56** (entries 5-8, 11). With R^2 = alkyl also, we observed the [2+4] cycloadduct **58** in good yield (entry 13). This methodology when applied to ethyl 2,3-butadienoate **8a** and enynones **4a** and **4e-4f**, afforded desired [2+4] annulation products **60-62** in excellent yields and with high regioselectivity within one hour (entries 15-17). In the ^{1}H NMR spectrum, compound **46** shows two singlets at δ 7.07 and 5.64 due to two different alkenic-protons. Two signals at δ 91.5 and 85.5 in the ^{13}C NMR spectrum indicated the presence of internal alkyne, whereas a peak at δ 164.2 showed the ester –C=O group. The structure and stereochemistry of the annulation products **52** and **62** were further confirmed by X-ray crystallography (Figure 7). In both the cases, the *E*-stereochemistry at the exocyclic double bond was observed. The highlighting feature of this work is that essentially one product is formed regioselectively. Also, the residual alkyne functionality in the products can later be used for further transformations.

Scheme 13

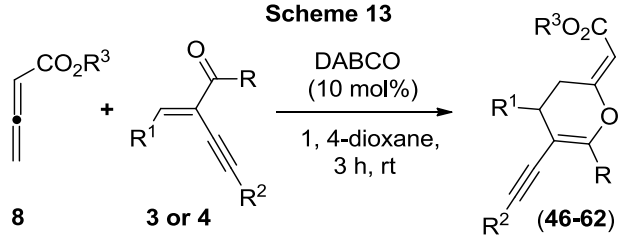
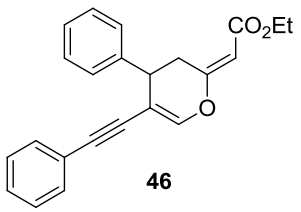
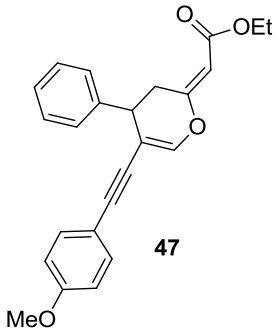
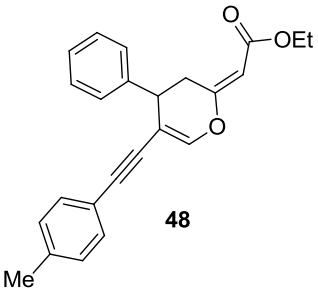
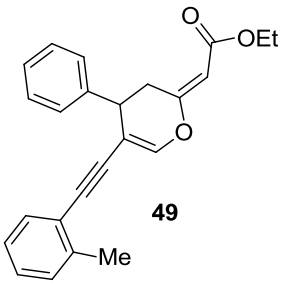
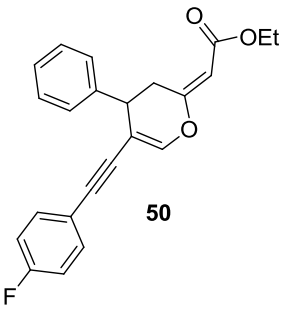
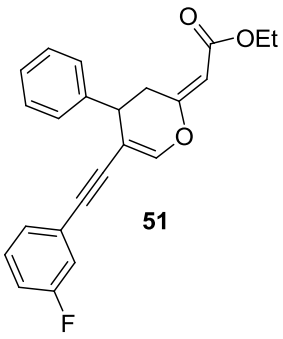
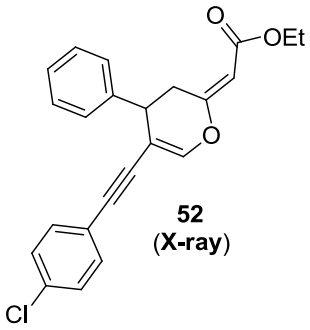
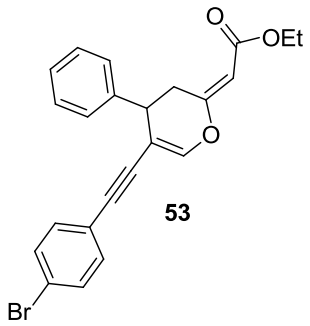
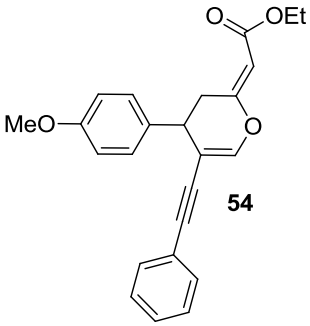
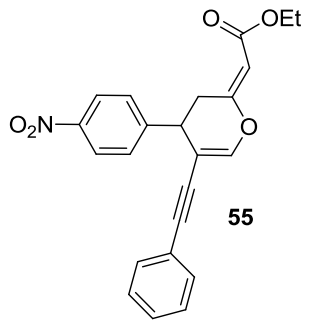
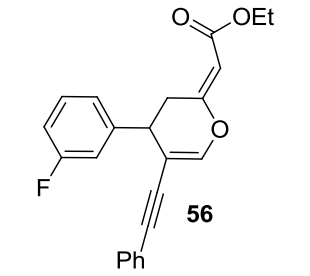
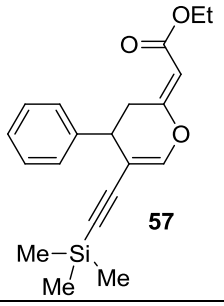
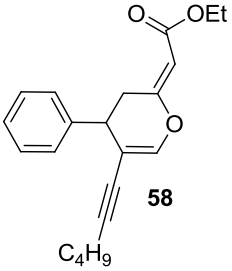
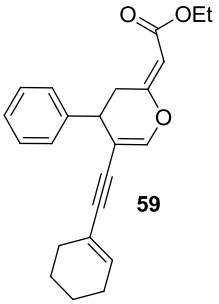
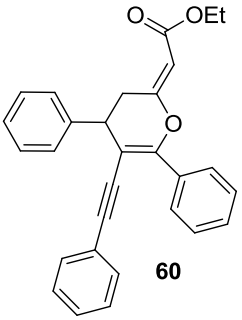
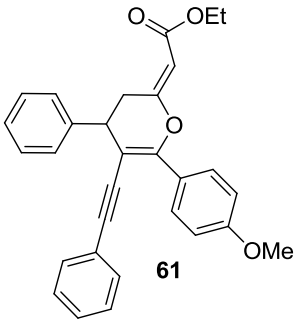


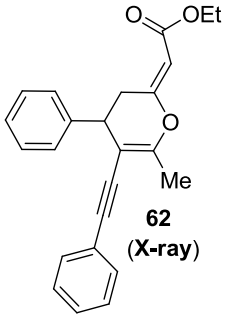
Table 5. Substrate scope for the DABCO catalyzed [2+4] cycloaddition of allenoates **8** with enynals **3** or enynones **4**[a]

Entry	Enynals/ Enynones	Allenoate	Dihydropyran	Yield (%)[b]
1	**3a**	**8a**	 **46**	82

2	**3b**	**8a**	 **47**	70
3	**3c**	**8a**	 **48**	72
4	**3d**	**8a**	 **49**	71
5	**3g**	**8a**	 **50**	80
6	**3h**	**8a**	 **51**	73

7	**3i**	**8a**	 **52** (**X-ray**)	78
8	**3j**	**8a**	 **53**	64
9	**3k**	**8a**	 **54**	60
10	**3l**	**8a**	 **55**	62
11	**3n**	**8a**	 **56**	86

12	**3o**	**8a**	 **57**	62
13	**3p**	**8a**	 **58**	57
14	**3q**	**8a**	 **59**	67
15	**4a**	**8a**	 **60**	84
16	**4e**	**8a**	 **61**	87

17	**4f**	**8a**	 **62** (**X-ray**)	85

[a]Conditions: enynal/enynone **3**/**4** (0.4 mmol), allenoate **8** (0.48 mmol), DABCO (10 mol%), 1,4-dioxane (2 mL) at rt for 3 h (for compounds **46**-**59**) or 1 h (for compounds **60**-**62**). [b]Isolated yields.

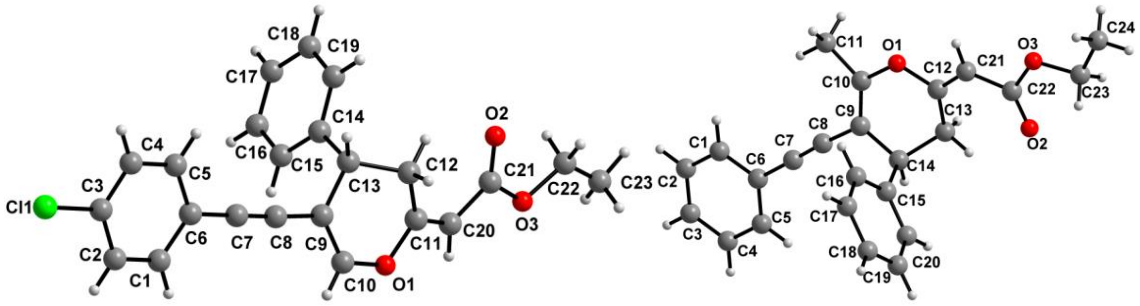


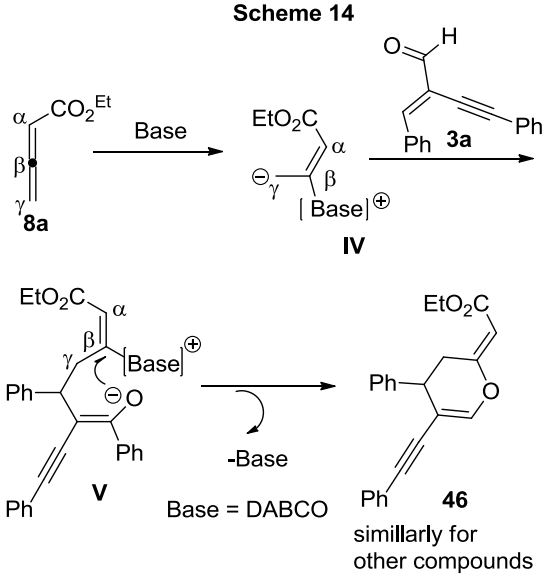
Figure 7. Molecular structure of compounds **52** (left) and **62** (right). Selected bond lengths [Å] with esd's in parentheses: Compound **52** C(9)-C(10) 1.332(4), C(10)-O(1) 1.365(3), O(1)-C(11) 1.375(3), C(11)-C(12) 1.491(4), C(12)-C(13) 1.536(4), C(13)-C(9) 1.509(3), C(11)-C(20) 1.319(4), C(20)-C(21) 1.464(4). Compound **62** C(9)-C(10) 1.321(3), C(10)-C(11) 1.472(3), C(10)-O(1) 1.376(3), O(1)-C(12) 1.365(3), C(12)-C(13) 1.474(3), C(13)-C(14) 1.523(3), C(14)-C(9) 1.489(3), C(12)-C(21) 1.310(3), C(21)-C(22) 1.445(3).

2.6.2 Plausible pathway for the DABCO catalyzed [2+4] cycloaddition of allenoates with enynals/enynones

Based on literature reports,[28] a plausible pathway for the formation of substituted dihydropyrans is shown in Scheme 14. Initially, allenoate **8a** provides zwitterionic intermediate **IV** upon addition of the Lewis base. In the presence of DABCO, enynal **3a** interacts with intermediate **IV** resulting in **V**, which undergoes intramolecular attack of oxygen nucleophile at the β-position of the allenoate and concomitant elimination of the base affording the substituted dihydropyran **46** as well as regeneration of the DABCO

catalyst. This concomitant elimination of the base (DABCO) allows the stereochemistry at the olefinic double bond intact.

Scheme 14



2.6.3 Development of asymmetric [2+4] cycloaddition of allenoate 8a with enynal 3a using chiral amines

Based on the above mechanism, it is possible to induce chirality in compounds **46**-**62** by using suitable chiral amine catalysts.[70] Initially, we tried the reaction of allenoate **8a** and enynal **3a** by using the chiral amine (+)-cinchonine (20 mol%) in 1,4-dioxane (Scheme 15). Compound **46** was obtained in 30% yield with 85% *ee* after 48 h, at rt. Increasing the temperature to 80 ^{o}C resulted decrease on both the yield and *ee* (Table 6, entry 2). Use of $(DHQD)_2PHAL$ as the catalyst led to enhancement in *ee* of compound **46** (entry 4)**.**

Scheme 15

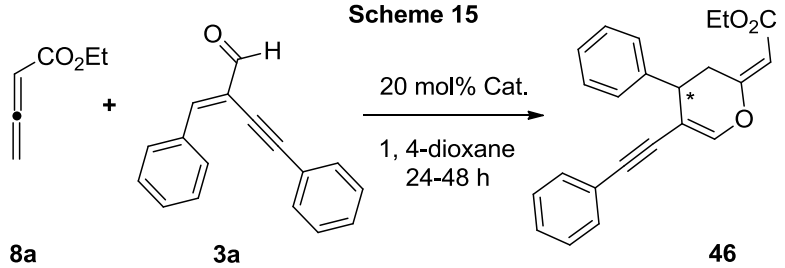


Table 6. Asymmetric [2+4] cycloaddition of allenoate **8a** with enynal **3a** using chiral amines [a]

Entry	Catalyst	T (^{0}C)/	Yield (%)[b]	*ee* (%)[c]

		time		
1	(+)-Cinchonine	rt (48 h)	30	85
2	(+)-Cinchonine	80 (24 h)	23	79
3	(+)-Cinchonine	15 (48 h)	42	86
4	$(DHQD)_2PHAL$	rt (48 h)	35	93

[a]Conditions: Enynal **3a** (0.3 mmol), allenoate **8a** (0.36 mmol), chiral amine (20 mol%), 1,4-dioxane (1 mL). [b]Isolated yields. [c]Determined by HPLC on a chiral stationary phase using a Chiralcel AD-H column.

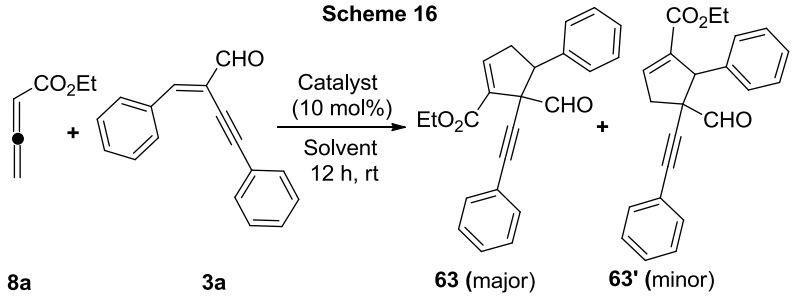
2.7 PPh_3 catalyzed [3+2] annulation reaction of allenes with enynals

In the previous section, we reported DABCO catalyzed regioselective synthesis of functionalized dihydropyrans by the [2+4] cycloaddition of allenoates with enynals or enynones. In contrast, triphenylphosphine catalyzed reaction of the same substrates (allenoates and enynals) takes place *via* [3+2] cycloaddition to afford cyclopentenes. These results are discussed below.

2.7.1 Triphenylphosphine catalyzed reaction of allenoates with enynals

In contrast to the result obtained by DABCO catalyst, in the presence of PPh_3 as a catalyst, allenoates underwent [3+2] cycloaddition with enynals to afford cyclopentenes (Scheme 16). Thus by using 10 mol% of PPh_3 as a catalyst, reaction of ethyl-2,3-butadienoate **8a** with (*E*)-2-benzylidene-4-phenylbut-3-ynal **3a** provided **63** and **63'** in 5:1 ratio with a combined yield of 76% (Table 7, entry 1). We screened several solvents like CH_3CN, DMF, THF, $(EtO)_2CO$, DCM, EtOH and 1,4-dioxane (entries 2-9) and to our satisfaction, the [3+2] cycloaddition product was obtained in 80% combined yield by using 1,4-dioxane as the solvent. Phosphine catalysts like dppe [1,2-bis(diphenylphosphino)ethane] and PCy_3 decreased the yield of the cycloadduct (entries 12-13), while trifurylphosphine (PFu_3) (entry 14) was ineffective. Vigorous reaction took place when tributylphosphine (PBu_3) was used as the catalyst, but only a mixture of products was obtained (entry 15). Thus PPh_3 was the best catalyst for the [3+2] cycloaddition reaction. Use of 1.0 equiv of **8a** lowered the yield (entry 10); an excess of **8a** did not improve the yield. Increasing the catalyst loading to 50 mol% slightly diminished the yield of desired product (entry 11). Thus conditions under entry 9 gave the best results.

Scheme 16



8a 3a 63 (major) 63' (minor)

Table 7. Survey of reaction conditions for the PPh_3 catalyzed [3+2] cycloaddition leading to functionalized cyclopentenes[a]

Entry	Catalyst	Solvent	Yield (%)[b] **63** + **63'**
1	PPh_3	Toluene	76
2	PPh_3	CH_3CN	48
3	PPh_3	DMF	54
4	PPh_3	THF	74
5	PPh_3	PEG-400	33
6	PPh_3	$(EtO)_2CO$	72
7	PPh_3	DCM	35
8	PPh_3	EtOH	57
9	**PPh_3**	**1,4-Dioxane**	**80**
10	PPh_3	1,4-Dioxane	76[d]
11	PPh_3	1,4-Dioxane	77[e]
12	dppe	1,4-Dioxane	56
13	PCy_3	1,4-Dioxane	45
14	PFu_3	1,4-Dioxane	N.R.[f]
15	PBu_3	1,4-Dioxane	Complex

[a]Reaction conditions: Enynal **3a** (1.0 mmol), allenoate **8a** (1.2 mmol), catalyst (10 mol%), solvent (5 mL), rt for 12 h unless otherwise noted. [b]Isolated yields (includes pure major isomer + the remaining mixture containing both the isomers obtained during isolation).

[c]Starting material enynal remained. [d]One equiv of allene was used. [e]50 mol% of PPh_3 was used. [f]Reaction was carried out at 70 ^oC for 2 days.

After establishing the optimized reaction conditions, we turned our attention to the substrate scope and limitations of triphenylphosphine catalyzed [3+2] cycloaddition between allenoates and 2-(1-alkynyl)-2-alken-1-als (Scheme 17). Both electron–donating and electron-withdrawing groups on ring R^2 gave the desired [3+2] cycloadducts (Table 8, entries 2-10) in good yields, but electron releasing groups enhanced the yield. Similarly, both electron-donating and electron-withdrawing groups on ring R^1 also worked well, but the electron withdrawing $–NO_2$ group marginally reduced the yield (entries 11-14). The yields were good even for $R^2 = Me_3Si$ (entry 15). Allenoates with R^3 = Me or Bn also afforded good yields (entries 16-17). The reaction was completed within 12 h. The major isomers **63-79** were isolated in pure form as viscous liquids in all the cases. All these compounds are rather unstable at room temperature (25 ^oC) for >1 day and hence had to be preserved at low temperatures. In these products, a singlet at δ ~9.9 in the ^1H NMR spectra shows the presence of aldehydic proton. Signals at δ ~198 and ~163 in the ^{13}C NMR spectra show both aldehydic and ester functionalities; two signals at δ ~90 and ~85 suggest the presence of an internal alkyne. Among the minor isomers, we have isolated **63'**, **67'** and **76'** in pure form. The structure of the minor isomer **63'** was confirmed by single crystal X-ray structural analysis (Figure 8).

Scheme 17

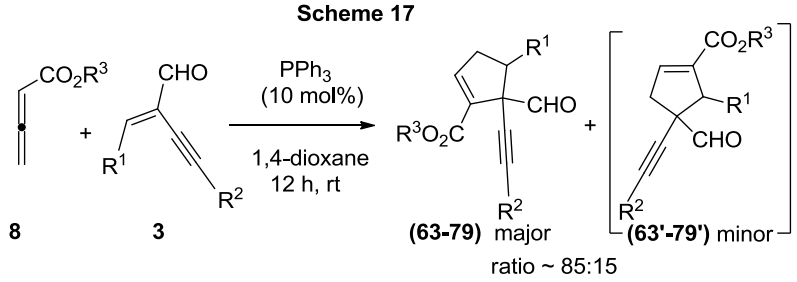
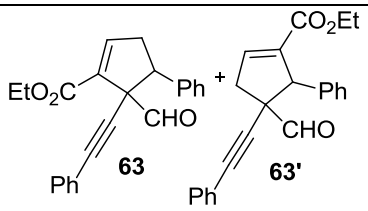
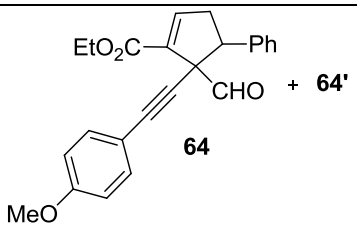
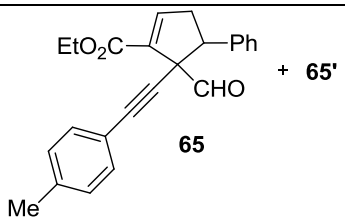
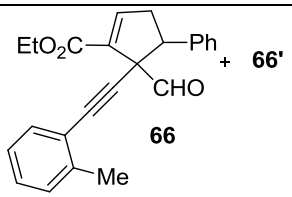
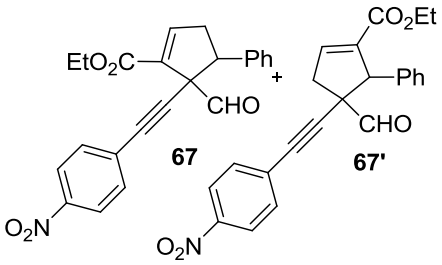
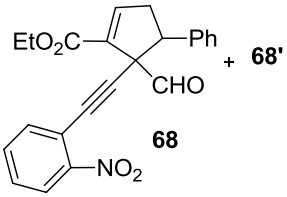
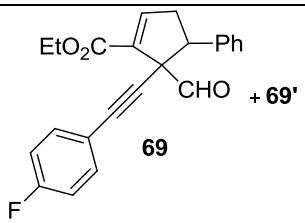
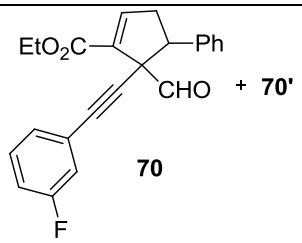
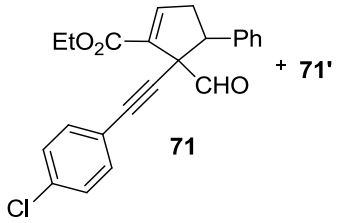
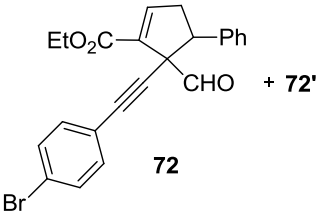
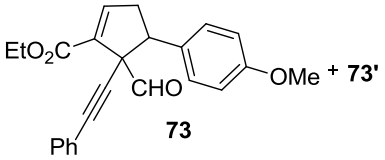
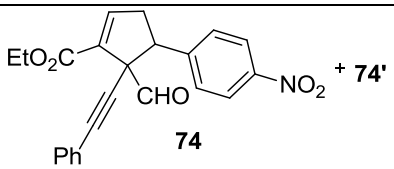
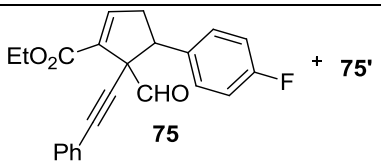
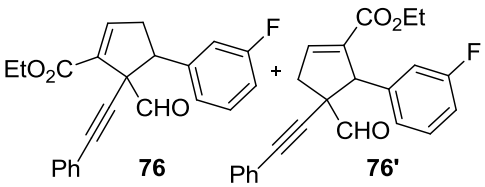
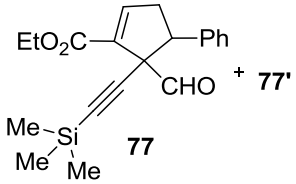
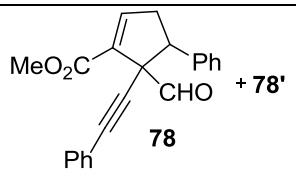
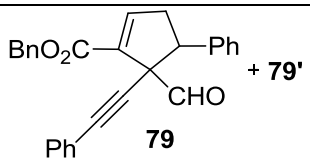


Table 8 Substrate scope for the phosphine catalyzed [3+2] cycloaddition of allenoates **8a-c** with enynals **3a-o**[a]

Entry	Allenoate	Enynal	Functionalized cyclopentene derivatives	Combined yield (%)[b] (**major** +

				minor)
1	**8a**	**3a**		80 (5:1.0)
2	**8a**	**3b**		88 (5:0.8)
3	**8a**	**3c**		74 (5:1.0)
4	**8a**	**3d**		83 (5:0.9)
5	**8a**	**3e**		68 (5:1.5)
6	**8a**	**3f**		62 (5:1.5)
7	**8a**	**3g**		64 (5:1.0)

8	**8a**	**3h**		72 (5:0.9)
9	**8a**	**3i**		65 (5:0.8)
10	**8a**	**3j**		55 (5:0.9)
11	**8a**	**3k**		80 (5:0.9)
12	**8a**	**3l**		58 (5:2.0)
13	**8a**	**3m**		77 (5:1.3)
14	**8a**	**3n**		75 (5:0.9)
15	**8a**	**3o**		77 (5:0.9)

16	**8b**	**3a**		74 (5:0.9)
17	**8c**	**3a**		77 (5:1.0)

[a]Conditions: Enynal **3** (1.0 mmol), allenoate **8** (1.2 mmol), PPh_3 (0.1 mmol), 1,4-dioxane (5 mL), rt for 12 h. [b]Isolated yields and isomeric ratio showed in parentheses (based on ^1H NMR of crude reaction mixture).

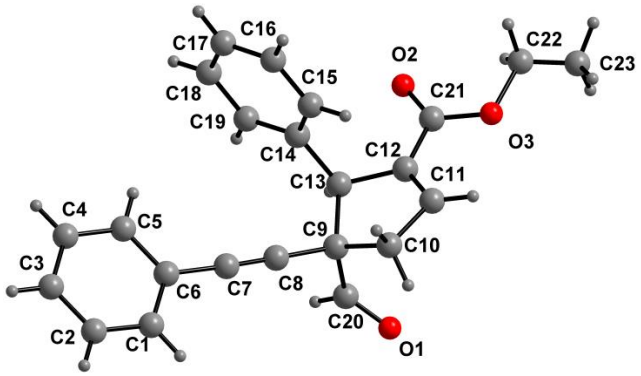


Figure 8. Molecular structure of compound **63'.** Selected bond lengths [Å] with esds in parentheses: C(9)-C(10) 1.525(3), C(10)-C(11) 1.493(3), C(11)-C(12) 1.309(4), C(12)-C(13) 1.493(3), C(9)-C(13) 1.566(3).

2.8 Gold catalyzed ring transformation and 1,2-alkyl migration of cyclopentenes 63-79

Compounds of type **63-79** have a reactive –*CHO* and an alkyne group juxtaposed on the same carbon and are consequently interesting substrates in gold catalysis. The alkynophilic character of gold(I),[1d, 2b, 2d-e, 7a, 8b-e, 71] therefore, is what we wanted to exploit in this section. Thus we used the 1,2-alkyl migration strategy[54-60, 72] on compounds **63-79** for the construction of substituted benzofurans under gold-catalysis.

2.8.1 Synthesis of highly substituted benzofurans from cyclopentenes

To start with, the reaction of functionalized cyclopentene **63** with 5 mol% each of gold(I) carbene complex (IPrAuCl) and AgOTf at rt for 3 days in 1,4-dioxane afforded substituted benzofuran **81** in 50% yield (Table 9, entry 1). In the absence of AgOTf, this transformation was forbidden (entry 2). Use of Ph_3PAuCl/AgOTf catalytic system at rt

for 2 days resulted in 65% yield (entry 3). Fortunately, increasing the temperature to 100 ^{o}C and reaction time to 24 h increased the yield to 76% (entry 5). Among the tested solvents, 1,4-dioxane showed better results (entries 5-9). Although AgOTf itself is active, only 58% yield was obtained in this case (entry 10). Gold catalysts like AuCl and $NaAuCl_4.2H_2O$ gave very poor yields. Furthermore, increase the catalytic loading did not benefit this transformation. Thus the optimal reaction conditions for this transformation are: Ph_3PAuCl/AgOTf (5 mol%), 1,4-dioxane (2 mL) as a solvent at 100 ^{o}C for 24 h.

Scheme 18

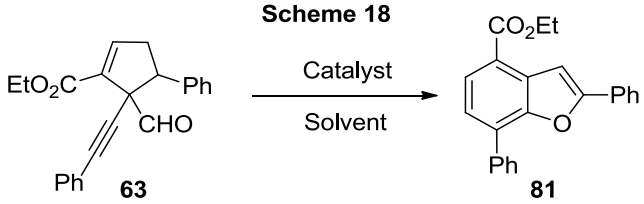


Table 9. Details on screening of solvents and catalysts for the synthesis of benzofurans **81-97**[a]

Entry	Catalyst	Solvent	Time	T[^{o}C]	Yield (%)[b]
1	IPrAuCl/AgOTf	1,4-Dioxane	3 days	rt	50
2	IPrAuCl	1,4-Dioxane	3 days	rt	N.R.
3	Ph_3PAuCl/AgOTf	1,4-Dioxane	2 days	rt	65
4	$Ph_3PAuCl/AgSbF_6$	1,4-Dioxane	2 days	rt	61
5	**Ph_3PAuCl/AgOTf**	**1,4-Dioxane**	**24 h**	**100 ^{o}C**	**76**
6	Ph_3PAuCl/AgOTf	DCE	24 h	80 ^{o}C	67
7	Ph_3PAuCl/AgOTf	CH_3CN	24 h	100 ^{o}C	44
8	Ph_3PAuCl/AgOTf	MeOH	2 days	80 ^{o}C	25
9	Ph_3PAuCl/AgOTf	DMF	2 days	100 ^{o}C	24
10	AgOTf	1,4-Dioxane	24 h	100 ^{o}C	58
11	AuCl/AgOTf	1,4-Dioxane	2 days	100 ^{o}C	20
12	$NaAuCl_4.2H_2O$/AgOTf	1,4-Dioxane	2 days	100 ^{o}C	28

[a]Conditions: One of functionalized cyclopentenes **63-79** (0.3 mmol), [Au]-catalyst (5 mol%), [Ag]-catalyst (5 mol%), and 1,4-dioxane (2 mL) were used. [b]Isolated yields.

Having the optimal reaction conditions in our hands, we explored the substrate scope of the reaction by using various [3+2] cycloadducts **63-79**. The results are summarized in Scheme 19 and Table 10. The yields were in general, good to excellent (Table 10). A point worth-noting here is that the substrate **77** undergoes elimination of trimethylsilyl group resulting in **95** in excellent yield (entry 15). As can be seen readily, cyclo-isomerized compounds (benzofurans) **81-97** have two hydrogen atoms less than that in their precursors, suggesting dehydrogenation. To our knowledge such a dehydrogenation leading to aromatization has not been reported thus far in related systems. The absence of carbonyl and alkyne groups in ^{13}C NMR spectrum of **81** suggested the involvement of these two groups in the cyclization process. For the sake of foolproof evidence, the structures of **81** and **86** were confirmed by X-ray crystallographic analysis (Figure 9). These structures also confirmed the identity of the precursors **63-79**.

Scheme 19

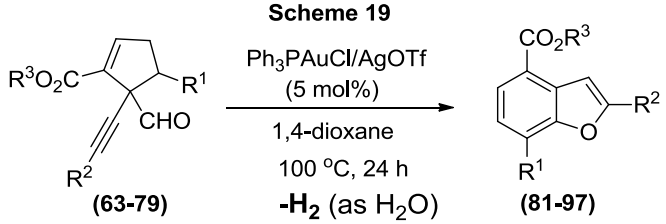
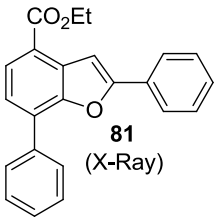
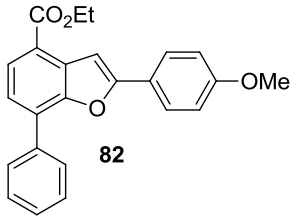
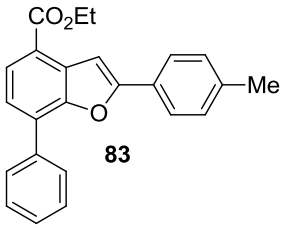
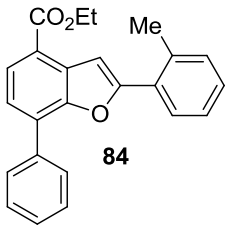
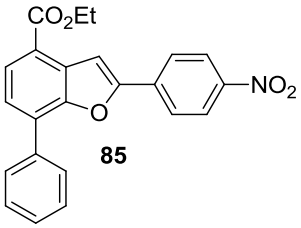
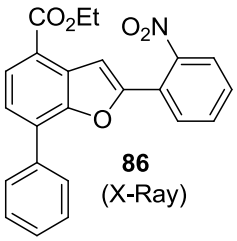
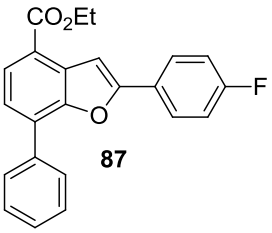
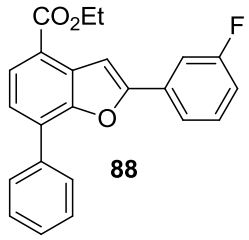
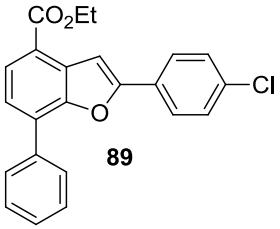
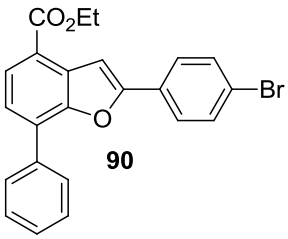
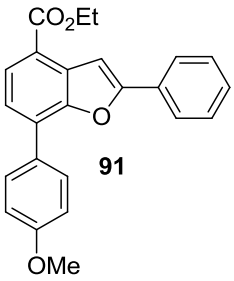
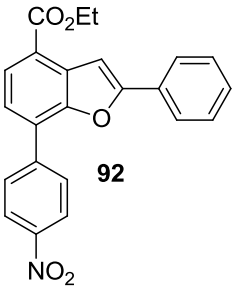
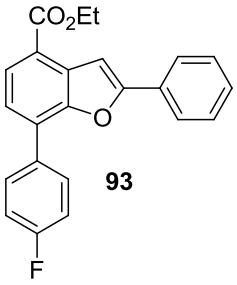
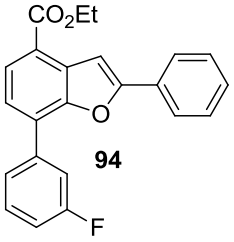
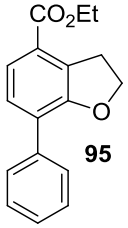
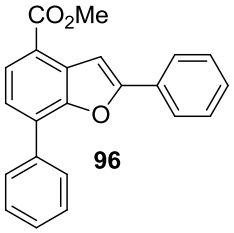
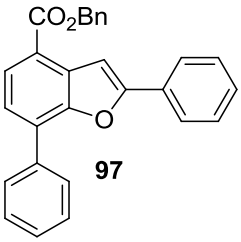


Table 10. Gold catalyzed synthesis of substituted benzofurans **81-97** from highly functionalized [3+2] cyclopentenes **63-79**[a]

Entry	Cyclopentenes	Trisubstituted benzofurans	yield (%)[b]
1	**63**	 **81** (X-Ray)	76

2	**64**	 **82**	80
3	**65**	 **83**	81
4	**66**	 **84**	77
5	**67**	 **85**	74
6	**68**	 **86** (X-Ray)	72
7	**69**	 **87**	81

8	**70**	 **88**	84
9	**71**	 **89**	86
10	**72**	 **90**	74
11	**73**	 **91**	78
12	**74**	 **92**	68

13	**75**	 **93**	84
14	**76**	 **94**	85
15	**77**	 **95**	89
16	**78**	 **96**	83
17	**79**	 **97**	80

[a]Conditions: Cyclopentenes **63-79** (0.3 mmol), [Au]-catalyst (5 mol%), [Ag]-catalyst (5 mol%), and 1,4-dioxane (2 mL) were used. [b]Isolated yields.

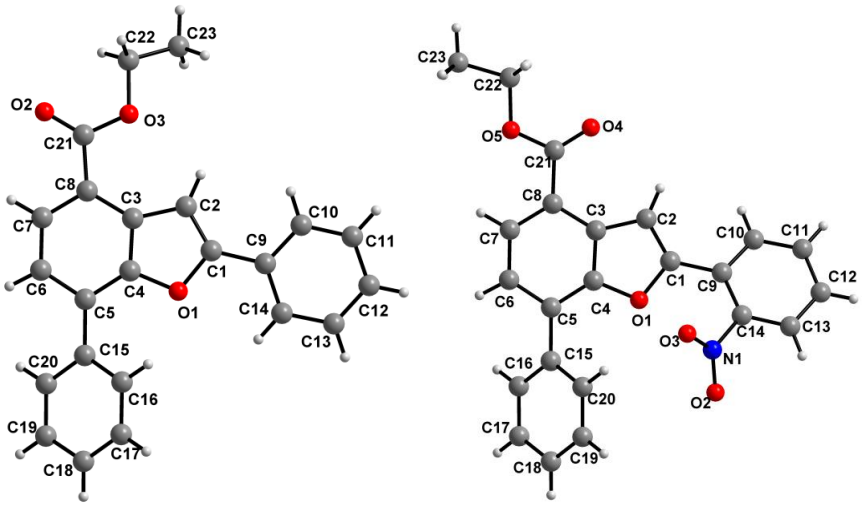
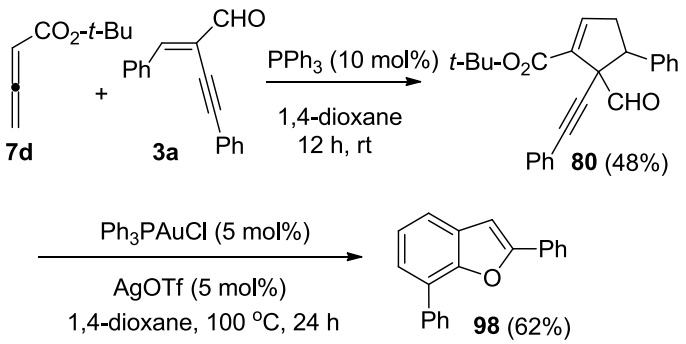


Figure 9. Molecular structures of compounds **81** (left) and **86** (right) Selected bond lengths [Å] with esd's in parentheses: Compound **81** C(4)-O(1) 1.376(2), O(1)-C(1) 1. 383(2), C(1)-C(2) 1.342(3), C(2)-C(3) 1.436(3), C(3)-C(4) 1.393(3), C(4)-C(5) 1.393(3), C(5)-C(6) 1.399(3), C(6)-C(7) 1.388(3), C(7)-C(8) 1.378(3), C(8)-C(3) 1.404(3). (b). Compound **86**: C(4)-O(1) 1.3718(18), O(1)-C(1) 1.3777(18), C(1)-C(2) 1.346(2), C(2)-C(3) 1.433(2), C(3)-C(4) 1.3940(19), C(4)-C(5) 1.392(2), C(5)-C(6) 1.395(2), C(6)-C(7) 1.389(2), C(7)-C(8) 1.388(2), C(8)-C(3) 1.408(2).

In the above reactions, if the allenoate $H_2C=C=CH(COO\text{-}t\text{-}Bu)$ (**8d**) is used, the final product **98** after gold catalysis is the one in which decarboxylation also has taken place (Scheme 20). This feature may perhaps be used in cases when one does not require the carboxylate group in the aromatic ring.

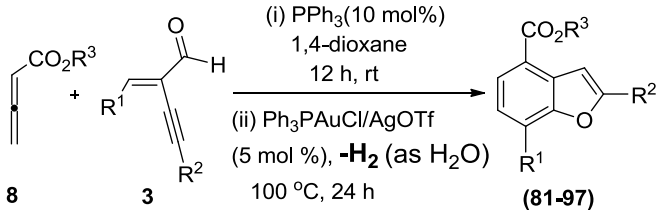
Scheme 20



2.8.2 One pot synthesis of benzofurans from allenoates and enynals - Combined phosphine and gold catalysis

Synthetically, it is best if we can devise a one pot strategy since this would alleviate the problem of isolating intermediates. The yields therefore, will at least be marginally higher. Indeed in the above synthesis, we could accomplish this and the results are shown in Scheme 21. The overall yield of the substituted benzofurans **81-97** was 5-6% higher than that from the two step method involving isolation of intermediate cyclopentenes of type **63-79**.

Scheme 21



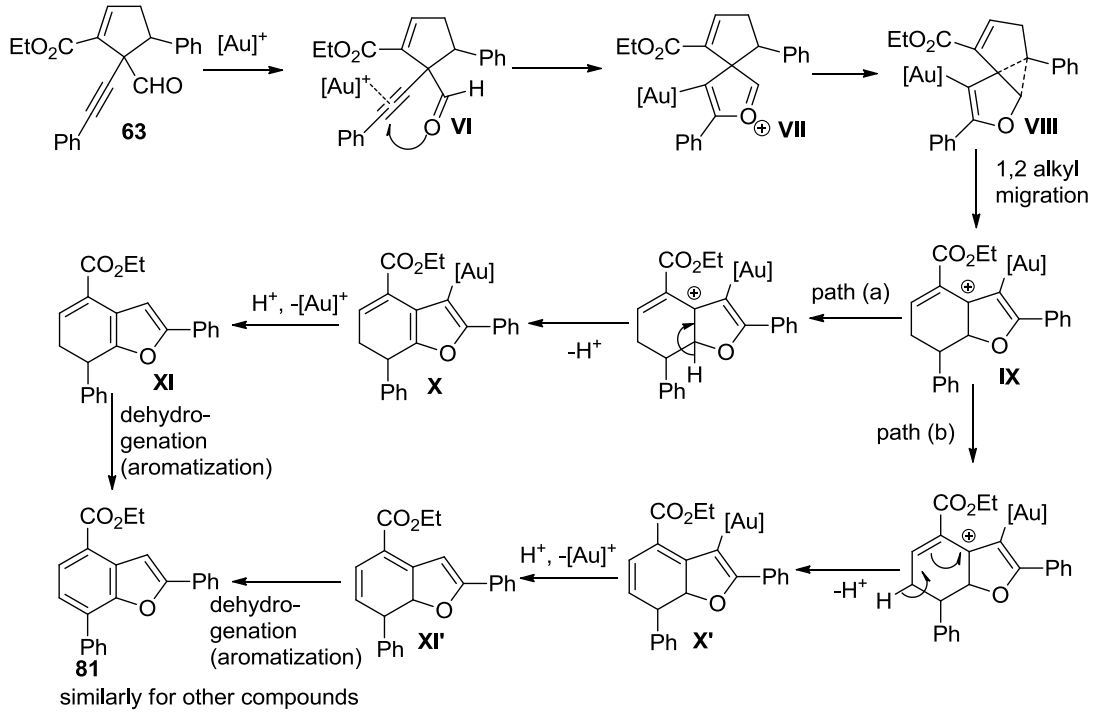
8 **3** **(81-97)**

81, 65% (X-ray)	**86**, 58% (X-ray)	**91**, 70%	**96**, 70%
82, 74%	**87**, 67%	**92**, 50%	**97**, 73%
83, 68%	**88**, 62%	**93**, 71%	
84, 66%	**89**, 65%	**94**, 72%	
85, 64%	**90**, 52%	**95**, 74%	

2.8.3 Plausible pathway for the gold catalyzed cycloisomerization/ alkyl migration/ dehydrogenation of cyclopentenes 63-80

Initially, gold activates the alkyne end of **63** and generates **VI**. Subsequent intramolecular attack of carbonyl oxygen leads to spiro-bicyclic intermediate **VII**.[56a, 57] 1,2-Alkyl migration in **VII** results in allylic cationic vinyl gold intermediate **IX**. Intermediate **X/X'** is formed by deprotonation of **IX** (pathway a or b). Proto-deauration of **X/X'** followed by aromatization results in the functionalized benzofuran **81**. Removal of two hydrogen atoms (aromatization) may have taken place by elimination of water. At least in our case, it appears that pathway a is favored because the product mixture (starting from **63**) immediately after column chromatography exhibits the presence of compound **81** and another species with a CH_2 group [^1H and ^{13}C (DEPT) NMR] consistent with the presence of **XI** (Figures 10-12). Over a period of ca 24 h, this intermediate disappeared and only the product **81** was observed (Scheme 22).

Scheme 22



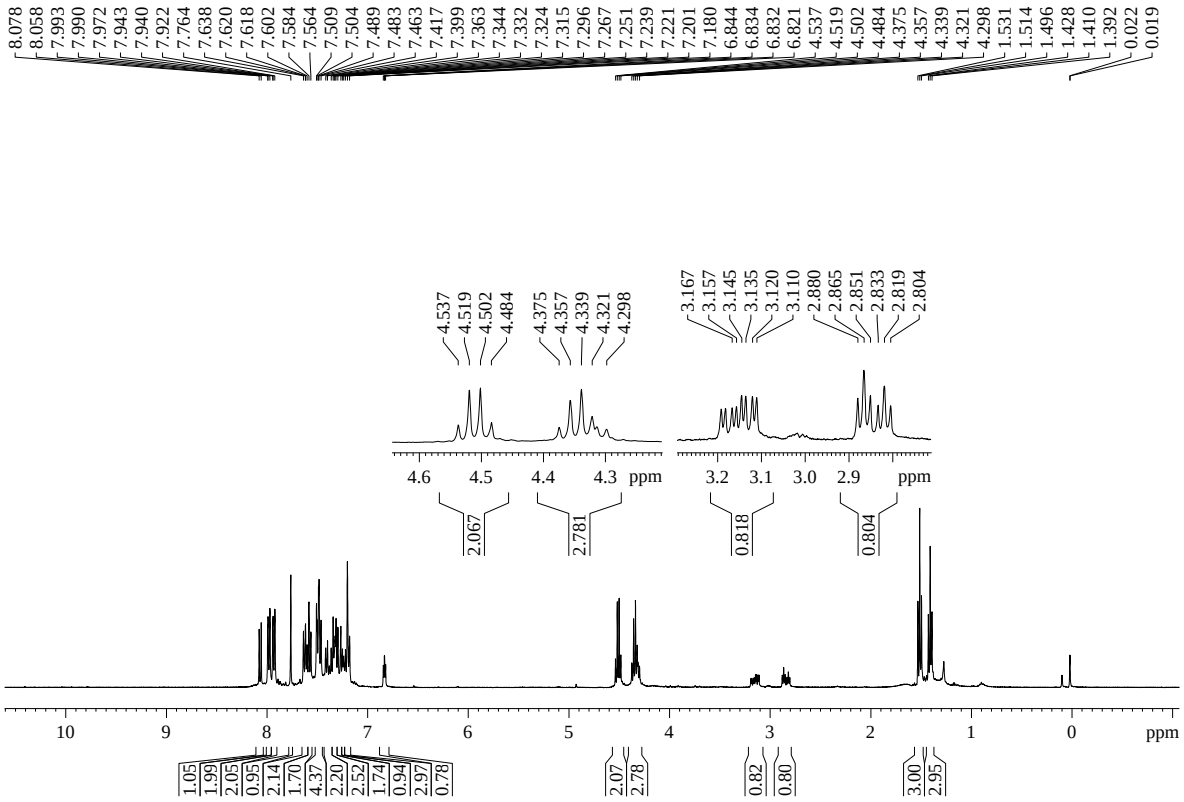


Figure 10. ^{1}H NMR spectrum of intermediate **XI+81**

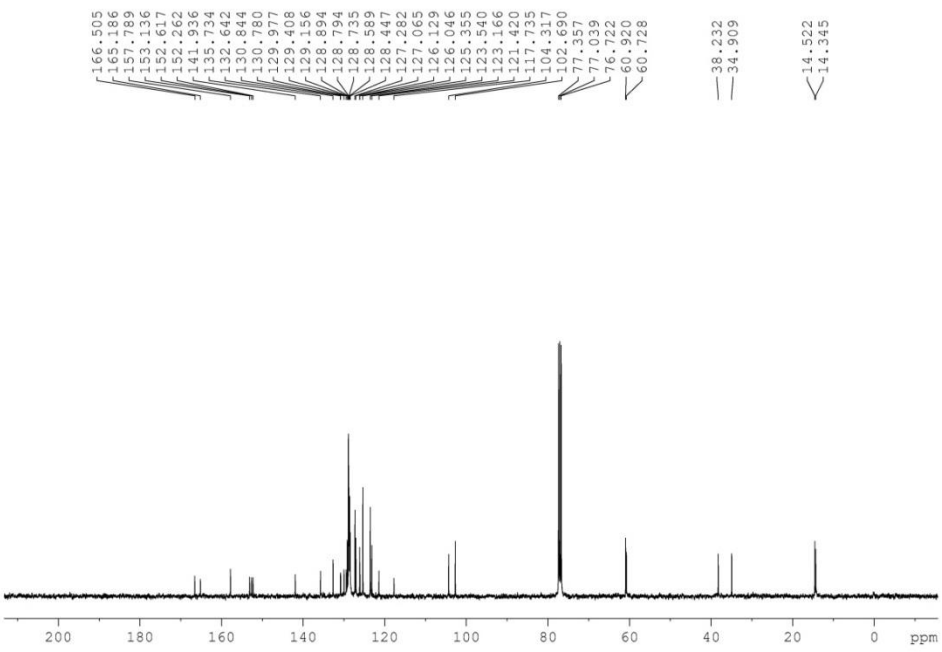


Figure 11. ^{13}C NMR spectrum of intermediate **XI+81**

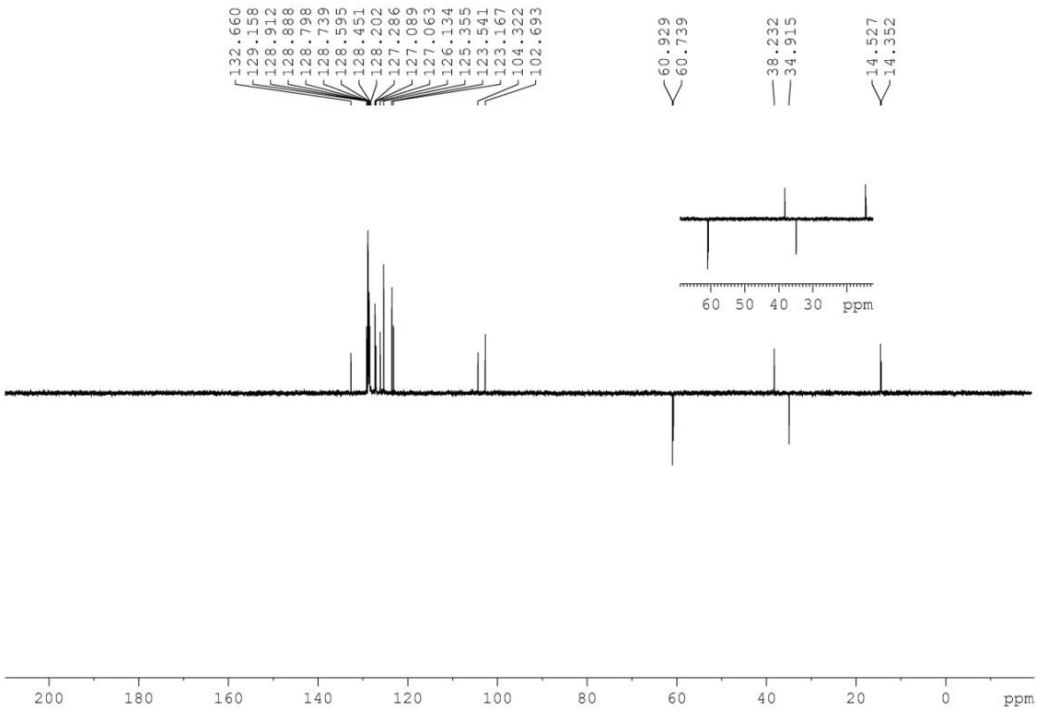
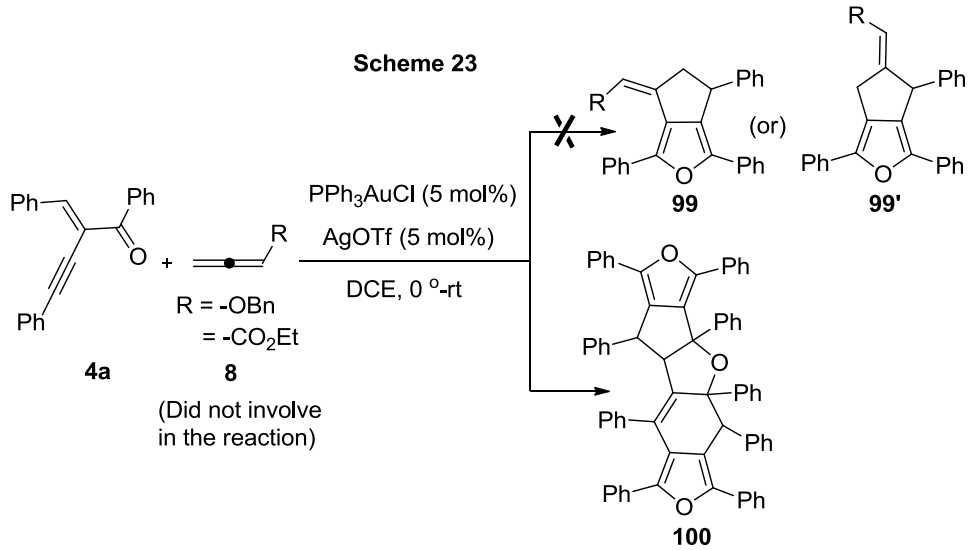


Figure 12. DEPT spectrum of intermediate **XI+81**

2.9 Reactivity of enynone 4a with allenoate 8 in the presence of gold catalyst

We attempted the reaction between enynone **4a** and allene **8** in the presence of PPh_3AuCl (5 mol%) and AgOTf (5 mol%) in DCE solvent (Scheme 23). After stirring the reaction mixture at rt for 15 mints, TLC showed the complete consumption of starting material but with a number of products. Interestingly, however, we isolated a terrace amount of the product **100** by column chromatography and fortunately, we obtained a couple of crystals. Though the quality of the data was poor, we could decipher the structure which is shown in Figure 13. It is essentially a trimer of **4a**, but with three furan rings, of which one is saturated.

Scheme 23



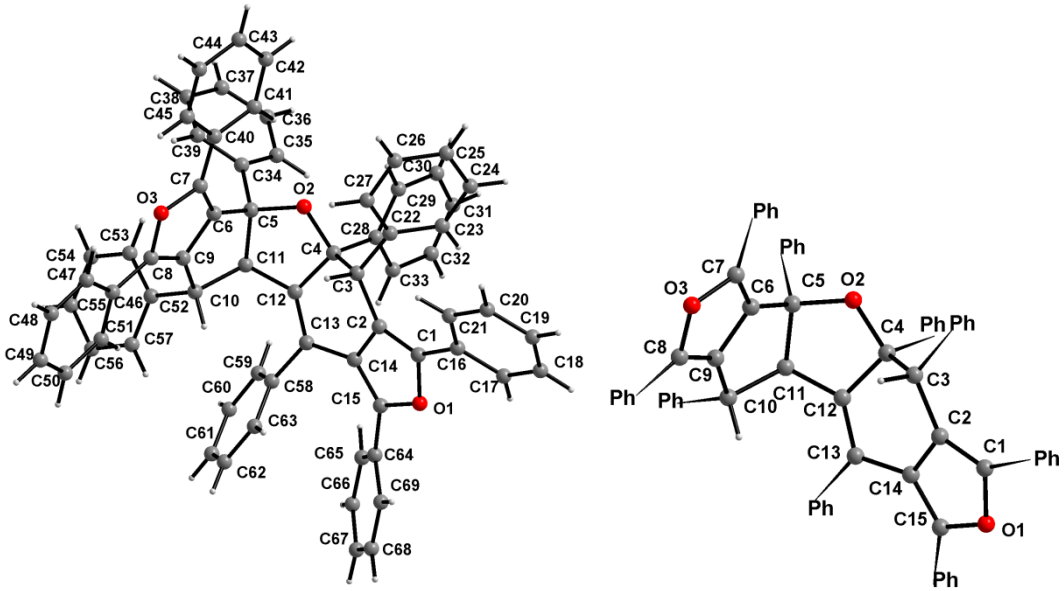
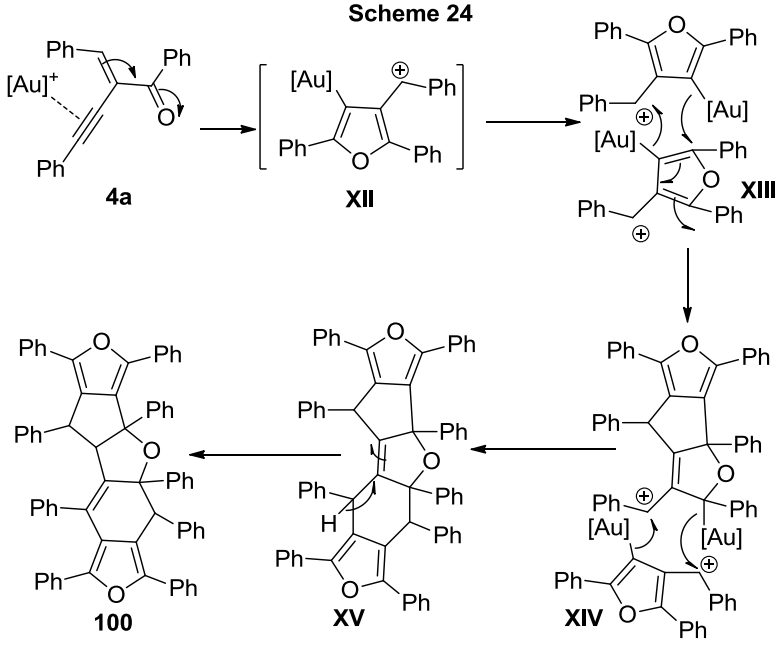


Figure 13. Molecular structure of compound **100.** Solvent molecule is omitted for clarity. Selected bond lengths [Å] with esds in parentheses: C(1)-C(2) 1.361(7), C(2)-C(3)

1.516(7), C(3)-C(4) 1.569(7), C(4)-O(2) 1.443(6), O(2)-C(5) 1.451(6), C(5)-C(6) 1.502(7), C(6)-C(7) 1.362(7), C(7)-O(3) 1.381(6), O(3)-C(8) 1.385(6), C(8)-C(9) 1.362(7), C(9)-C(10) 1.503(7), C(10)-C(11) 1.582(7), C(11)-C(12) 1.490(7), C(12)-C(13) 1.347(7), C(13)-C(14) 1.473(7), C(14)-C(15) 1.362(7), C(15)-O(1) 1.376(6).

It appears that initially alkyne moiety of enynone is activated by the gold catalyst which is followed by the nucleophilic attack of carbonyl oxygen leading to furanyl gold carbocation **XII**. [12a, 13a, 16, 68] In this tandem process, three molecules of **XII** together undergo ring forming/isomerization providing the trimer **100** *via* intermediates (**XIII-XV**). This reaction although interesting, still needs elaboration and product yield maximization.

Scheme 24



SUMMARY – PART A

1. A new gold catalyzed regioselective [3+3] cycloaddition reaction of enynones with benzyl azides that affords fused heterobicyclic furo[3,4-d][1,2,3]triazines has been developed. This methodology is further elaborated to enynals also for providing [3+3] cycloadducts. Interestingly though, enynones with an alkyl group attached to carbonyl tend to undergo [3+2] cycloaddition by using the -*ene* part only. We have also demonstrated the ring cleavage reaction of furo[3,4-d][1,2,3]triazines with CAN resulting in highly substituted 1,2,3-triazines in excellent yields. Both furo[3,4-d][1,2,3]triazines and the derived 1,2,3-triazines show good fluorescence activity.

2. We have developed DABCO catalyzed regioselective synthesis of functionalized dihydropyrans by the [2+4] cycloaddition of allenoates with enynals or enynones.

3. In contrast to DABCO catalyzed reaction of allenoates and enynals, triphenylphosphine catalyzed reaction of the same substrates takes place *via* [3+2] cycloaddition to afford highly functionalized cyclopentenes.

4. The cyclopentenes synthesized as above are utilized in [Au]/[Ag] catalyzed cycloisomerization/1,2-alkyl migration/dehydrogenation (aromatization) resulting in trisubstituted benzofurans. Synthesis of these trisubstituted benzofurans is accomplished by a direct ***one pot*** route from the allenoate and enynal. Interestingly, the intermediate cyclopentene obtained from the allenoate $H_2C{=}C{=}CH(COO\text{-}t\text{-}Bu)$ undergoes facile decarboxylation under the [Au]/[Ag] catalysis to lead to a carboxylate-free benzofuran.

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.[73] All operations, unless otherwise specified, were carried out under dry nitrogen atmosphere using standard vacuum line techniques.[74] Room temperature (rt) refers to ca 25 ^{o}C in this thesis.

Thin layer chromatographies (TLC) were done on aluminum plates coated with silica gel containing F254 indicator and the spots were visualized by UV light.

Column chromatography was performed on silicagel 100-200 mesh, using ethyl acetate and hexane mixture as eluent.

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: ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded using 5 mm tubes on a Bruker 400 MHz and 500 NMR spectrometer [field strengths: 400,100 and 376 MHz (for 400 MHz NMR spectrometer) and 500, 125, and 470 MHz (for 500 MHz NMR spectrometer) respectively] in $CDCl_3$ solution (unless specified otherwise) with shifts referenced to $SiMe_4$ (^{1}H, ^{13}C: $\delta = 0$) or $CFCl_3$ (^{19}F: $\delta = 0$). All *J* values are in Hz.

LC-MS and HRMS: LC-MS equipment were 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.

Absorbance and Fluorescence Spectroscopy: UV−visible absorption spectra and fluorescence spectra (THF solution) were recorded on a Fluorolog spectrofluorometer.

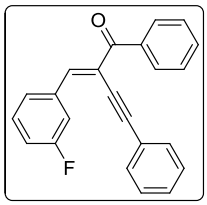
HPLC: HPLC analysis was performed using Daicel Chiralpak AD-H.

The starting materials, *trans*-cinnamaldehyde and *trans*-4-nitro-cinnamaldehyde are commercially available. *Trans*-cinnamaldehyde was used after distillation. 4-Methoxy, 4-fluoro, and 3-fluoro substituted cinnamaldehydes were prepared by utilizing the literature reports.[75] 2-Iodo-cinnamaldehydes **1a-e** and 2-iodo-cyclohexenone **2** were synthesized by following the reported methods.[61] Enynals **3a-o** and enynones **4a-n**, **5**, and **6** were prepared by using standard literature reports.[62] Azides **7a-k** were synthesized following known procedures. [63] Allenes **8a-d** were prepared by using established protocol.[64]

3.1 Synthesis of enynone precursors 4a-n, 5, and 6

The enynone substrates were synthesized from Grignard reaction of corresponding enynal with aryl/alkyl bromide, followed by the oxidation with MnO_2.[62c] Out of these, compounds **4c** and **4d** are new.

Compound 4c



Yield: 1.00 g (84%, yellow solid).

Mp: 60-62 ^{o}C.

IR (KBr): 3053, 2192, 1660, 1589, 1496, 1441, 1277, 1222, 1145, 986, 904, 778, 756, 718 cm^{-1}.

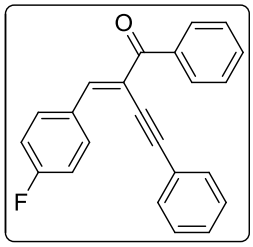
^{1}H NMR: δ 8.12-8.09 (m, 1H), 8.05 (d, *J* = 7.6 Hz, 2H), 7.52 (d, *J* = 7.6 Hz, 1H), 7.65-7.61 (m, 2H), 7.53 (t, *J* = 7.6 Hz, 2H), 7.48-7.41 (m, 3H), 7.38-7.35 (m, 3H), 7.19-7.15 (m, 1H).

^{13}C NMR: δ 193.0, 162.7 (*J* = 244.4 Hz), 143.1 (*J* = 2.8 Hz), 137.0, 136.9, 136.8, 132.8, 131.4, 130.1, 130.0, 129.8, 129.1, 128.5, 128.2, 126.7 (*J* = 2.7 Hz), 122.3 (*J* = 42.2 Hz), 117.4 (*J* = 21.5 Hz), 116.1 (*J* = 22.7 Hz), 102.0, 86.8.

LC-MS: *m/z* 327 $[M+1]^{+}$.

Anal. Calcd. for $C_{23}H_{15}FO$: C, 84.64; H, 4.63; Found: C, 84.52; H, 4.68.

Compound 4d



Yield: 0.87 g (88%, yellow solid).

Mp: 62-64 ^{o}C.

IR (KBr): 3052, 2186, 1666, 1605, 1573, 1512, 1452, 1310, 1233, 1156, 959, 751, 690 cm^{-1}.

^{1}H NMR: δ 8.17 (dd, *J* = 8.8 Hz, 5.6 Hz, 2H), 8.04 (d, *J* = 7.2 Hz, 2H), 7.64-7.60 (m, 2H), 7.52 (t, *J* = 7.6 Hz, 2H), 7.44-7.37 (m, 5H), 7.18 (t, *J* = 8.8 Hz, 2H).

^{13}C NMR: δ.193.2, 163.8 (*J* = 251.4 Hz), 143.7, 137.1, 132.6, 132.5, 132.4, 131.4, 131.2 (*J* = 3.3 Hz), 129.7, 129.0, 128.5, 128.1, 122.7, 120.5, 115.8 (*J* = 21.4 Hz), 101.0, 87.0.

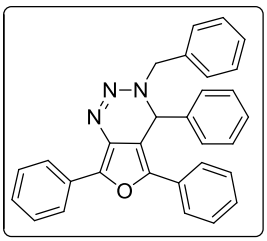
LC-MS: *m/z* 327 $[M+1]^{+}$.

Anal. Calcd. for $C_{23}H_{15}FO$: C, 84.64; H, 4.63; Found: C, 84.75; H, 4.58.

3.2 Representative procedure for the gold-catalyzed [3+3] cycloaddition of enynones 4a-m with azides 7a-k: Synthesis of furan fused 1,2,3-triazines 9-32

To an oven dried 5 mL RBF, LAu(CH_3CN)SbF_6 (L = [(2-biphenyl)di-*tert*-butylphosphine]) (0.015 mmol) and benzyl azide **7a** (0.36 mmol) in DCE (1 mL) were added, the mixture was kept at 0 ^{o}C and the contents stirred for 5 min. (*E*)-2-Benzylidene-1,4-diphenylbut-3-yn-1-one (**4a**, 0.30 mmol) in DCE was added dropwise to the above mixture. After completion of the reaction, as monitored by TLC, the solvent was evaporated under vacuum. The residue was then purified by silica gel column chromatography by using hexane:EtOAc (49:1) as the eluent to afford 3-benzyl-4,5,7-triphenyl-3,4-dihydrofuro[3,4-d][1,2,3]triazine **9**. Compounds **10-32** were prepared following the same procedure and by using the same molar quantities.

Compound 9



Yield: 0.111 g (84%, yellow solid).

Mp: 160-162 °C.

IR (KBr): 3052, 3030, 2926, 2855, 1600, 1485, 1419, 1364, 1249, 1156, 1074, 942, 910, 762, 696 cm^{-1}.

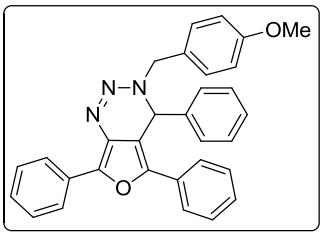
^1H NMR: δ 8.37 (d, *J* = 7.6 Hz, 2H), 7.52 (t, *J* = 7.6 Hz, 2H), 7.45-7.25 (m, 15H), 7.20 (t, *J* = 7.2 Hz, 1H), 5.58 (s, 1H), 5.25 (d, *J* = 15.2 Hz, 1H), 4.39 (d, *J* = 15.2 Hz, 1H).

^{13}C NMR: δ 145.1, 144.5, 139.9, 135.9, 129.7_0, 129.6_6, 129.0_2, 128.9_7, 128.8, 128.7, 128.5, 128.3_4, 128.2_8, 128.2_5, 128.1, 127.7, 125.6, 125.0, 107.0, 56.9, 55.9.

HRMS (ESI): Calcd. for $C_{30}H_{24}N_3O$ $[M^+ + H]$: *m/z* 442.1919. Found: 442.1918.

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

Compound 10



Yield: 0.110 g (78%, yellow solid).

Mp: 154-156 °C.

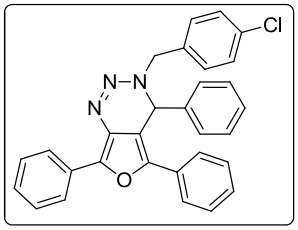
IR (KBr): 3063, 3024, 2827, 1610, 1512, 1484, 1435, 1243, 1166, 1123, 1079, 1029, 947, 766 cm^{-1}.

^1H NMR: δ 8.37 (d, *J* = 8.0 Hz, 2H), 7.51 (t, *J* = 7.6 Hz, 2H), 7.43-7.25 (m, 12H), 7.22-7.18 (m, 1H), 6.96 (d, *J* = 8.0 Hz, 2H), 5.56 (s, 1H), 5.19 (d, *J* = 14.8 Hz, 1H), 4.32 (d, *J* = 14.8 Hz, 1H), 3.85 (s, 3H).

^{13}C NMR: δ 159.5, 144.9, 144.3, 139.9, 129.7, 129.0, 128.7, 128.5, 128.4, 128.2, 127.7, 127.6, 125.6, 125.1, 125.0, 114.4, 107.0, 56.4, 55.6, 55.3.

HRMS (ESI): Calcd. for $C_{31}H_{26}N_3O_2$ [M^++H]: *m/z* 472.2025. Found: 472.2025.

Compound 11



Yield: 0.106 g (74%, yellow solid).

Mp: 120-122 °C.

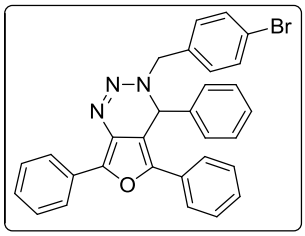
IR (KBr): 3063, 3025, 1589, 1496, 1458, 1436, 1260, 1129, 1074, 1008, 942, 762 cm^{-1}.

^{1}H NMR: δ 8.37-8.35 (m, 2H), 7.51 (t, *J* = 7.6 Hz, 2H), 7.40-7.26 (m, 14H), 7.23-7.19 (m, 1H), 5.52 (s, 1H), 5.17 (d, *J* = 15.2 Hz, 1H), 4.37 (d, *J* = 15.2 Hz, 1H).

^{13}C NMR: δ 145.3, 144.5, 139.6, 134.4, 133.9, 129.6$_3$, 129.5$_9$, 129.5$_6$, 129.2, 129.1, 128.9, 128.8, 128.5, 128.4, 128.3, 127.8, 125.6, 125.0, 124.9, 106.8, 56.2, 56.1.

HRMS (ESI): Calcd. for $C_{30}H_{23}ClN_3O$ [M^++H]: *m/z* 476.1529. Found: 476.1529.

Compound 12



Yield: 0.086 g (55%, yellow solid).

Mp: 160-162 °C.

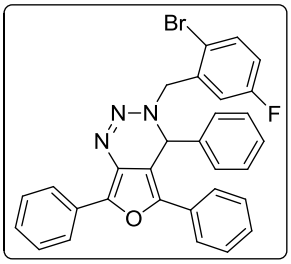
IR (KBr): 3063, 3025, 2921, 1671, 1600, 1485, 1447, 1403, 1266, 1123, 1068, 1008, 948, 767, 685 cm^{-1}.

^{1}H NMR: δ 8.37-8.34 (m, 2H), 7.55-7.49 (m, 4H), 7.40-7.32 (m, 6H), 7.30-7.25 (m, 6H), 7.21 (t, *J* = 7.2 Hz, 1H), 5.52 (s, 1H), 5.14 (d, *J* = 15.2 Hz, 1H), 4.35 (d, *J* = 15.2 Hz, 1H).

^{13}C NMR: δ 145.4, 144.6, 139.7, 135.0, 132.1, 129.9, 129.6, 129.1, 128.8, 128.7, 128.5, 128.3, 128.2, 127.8, 125.6, 125.1, 124.9, 122.0, 106.8, 56.3, 56.1.

HRMS (ESI): Calcd. for $C_{30}H_{23}BrN_3O$ [M^++H] and [M^++H+2]: *m/z* 520.1024, 522.1024. Found: 520.1029, 522.1017.

Compound 13



Yield: 0.106 g (65%, yellow solid).

Mp: 162-164 °C.

IR (KBr): 3058, 2921, 1660, 1585, 1490, 1463, 1441, 1266, 1129, 1074, 1030, 942, 773, 690 cm^{-1}.

^{1}H NMR: δ 8.37 (d, *J* = 8.0 Hz, 2H), 7.58-7.50 (m, 3H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.41-7.30 (m, 8H), 7.26-7.22 (m, 1H), 7.18-7.15 (m, 1H), 6.96-6.91 (m, 1H), 5.66 (s, 1H), 4.99 (d, *J* = 16.0 Hz, 1H), 4.74 (d, *J* = 16.0 Hz, 1H).

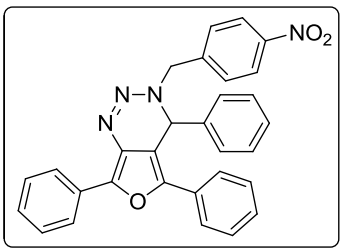
^{13}C NMR: δ 162.3 (d, *J* = 246.4 Hz), 145.7, 144.5, 139.7, 138.1 (d, *J* = 6.9 Hz), 134.3 (d, *J* = 7.8 Hz), 129.6 (d, *J* = 2.6 Hz), 129.2, 129.0, 128.8, 128.7, 128.6, 128.2, 127.9, 125.8, 125.0, 124.9, 117.6, 117.0, 116.8, 116.6, 107.0, 57.6, 56.6.

^{19}F NMR δ -113.48.

LC/MS *m/z* 538 $[M]^+$ and 540 $[M+2]^+$.

Anal. Calcd. for $C_{30}H_{21}BrFN_3O$: C, 66.92; H, 3.93; N, 7.80; Found: C, 66.85; H, 3.87; N, 7.91.

Compound 14



Yield: 0.077 g (53%, yellow solid).

Mp: 138-140 °C.

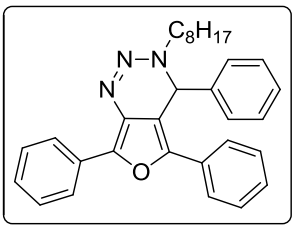
IR (KBr): 3068, 2915, 1660, 1595, 1490, 1452, 1397, 1266, 1068, 1008, 942, 926 cm^{-1}.

^1H NMR: δ 8.36 (d, *J* = 8.4 Hz, 2H), 7.55-7.50 (m, 4H), 7.40-7.32 (m, 6H), 7.30-7.25 (m, 6H), 7.21 (t, *J* = 7.2 Hz, 1H), 5.52 (s, 1H), 5.14 (d, *J* = 15.2 Hz, 1H), 4.35 (d, *J* = 15.2 Hz, 1H).

^{13}C NMR: δ 145.4, 144.6, 139.7, 135.0, 132.1, 129.9, 129.6$_0$, 129.5$_9$, 129.0, 128.8, 128.7, 128.5, 128.3, 128.2, 127.8, 125.6, 125.1, 124.9, 122.0, 106.8, 56.3, 56.2.

HRMS (ESI): Calcd. for $C_{30}H_{23}N_4O_3$ $[M^+ + H]$: *m/z* 487.1770. Found: 487.1775.

Compound 15



Yield: 0.120 g (86%, yellow solid).

Mp: 92-94 °C.

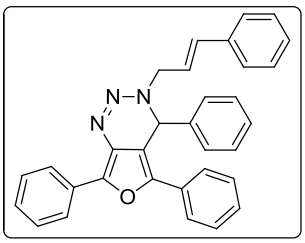
IR (KBr): 3063, 2921, 2855, 1595, 1485, 1447, 1403, 1310, 1145, 1068, 1019, 948, 756, 690 cm^{-1}.

^1H NMR: δ 8.35 (d, *J* = 8.0 Hz, 2H), 7.51-7.48 (m, 4H), 7.38-7.27 (m, 8H), 7.25-7.23 (m, 1H), 5.74 (s, 1H), 3.77-3.70 (m, 1H), 3.46-3.39 (m, 1H), 1.83-1.67 (m, 2H), 1.33-1.28 (m, 10H), 0.89 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR: δ 144.7, 144.1, 140.5, 129.9, 129.8, 129.0, 128.7, 128.6$_3$, 128.5$_9$, 128.1, 128.0, 127.7, 125.5, 125.2, 125.0, 107.5, 57.4, 53.5, 31.8, 29.3, 29.2, 27.8, 26.7, 22.7, 14.1.

HRMS (ESI): Calcd. for $C_{31}H_{34}N_3O$ $[M^+ + H]$: *m/z* 464.2702. Found: 464.2706.

Compound 16



Yield: 0.101 g (72%, yellow solid).

Mp: 156-158 °C.

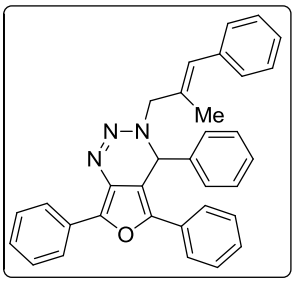
IR (KBr): 3058, 3030, 2909, 1605, 1496, 1447, 1260, 1123, 1074, 948, 767, 690 cm^{-1}.

^1H NMR: δ 8.36 (d, *J* = 8.2 Hz, 2H), 7.51 (t, *J* = 8.0 Hz, 2H), 7.45 (t, *J* = 7.6 Hz, 4H), 7.39-7.31 (m, 11H), 7.22 (t, *J* = 7.2 Hz, 1H), 6.65 (d, *J* = 16.0 Hz, 1H), 6.32-6.25 (m, 1H), 5.81 (s, 1H), 4.76-4.71 (m, 1H), 4.14-4.08 (m, 1H).

^{13}C NMR: δ 145.1, 144.4, 140.0, 136.3, 134.4, 129.7, 129.1, 128.7_3, 128.6_9, 128.6, 128.3, 128.1, 127.8, 126.6, 125.6, 125.1, 124.0, 107.2, 56.4, 55.7.

HRMS (ESI): Calcd. for $C_{32}H_{26}N_3O$ $[M^+ + H]$: *m/z* 468.2076. Found: 468.2073.

Compound 17



Yield: 0.103 g (70%, yellow solid).

Mp: 88-90 °C.

IR (KBr): 3058, 3031, 2921, 1606, 1496, 1425, 1326, 1260, 1129, 1085, 1008, 943, 773, 696 cm^{-1}.

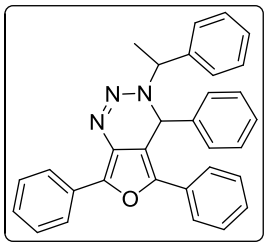
^1H NMR: δ 8.39-8.37 (m, 2H), 7.54-7.47 (m, 4H), 7.41-7.37 (m, 9H), 7.35-7.30 (m, 4H), 7.26-7.22 (m, 1H), 6.54 (s, 1H), 5.75 (s, 1H), 4.68 (d, *J* = 14.8 Hz, 1H), 4.05 (d, *J* = 14.8 Hz, 1H), 1.98 (s, 3H).

^{13}C NMR: δ 145.1, 144.5, 140.2, 137.1, 132.9, 129.8, 129.7, 129.1, 128.8, 128.7, 128.5, 128.3$_9$, 128.3$_7$, 128.3, 127.9, 127.0, 125.6, 125.1$_3$, 125.0$_8$, 107.2, 62.1, 55.9, 15.9.

LC/MS *m/z* 482 $[M+1]^+$.

Anal. Calcd. for $C_{33}H_{27}N_3O$: C, 82.30; H, 5.65; N, 8.73; Found: C, 82.21; H, 5.63; N, 8.82.

Compound 18



Yield: 0.104 g (76%, yellow solid).

Mp: 180-182 °C.

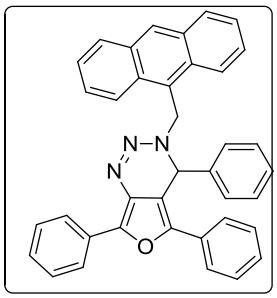
IR (KBr): 3056, 3025, 2926, 1605, 1490, 1458, 1430, 1271, 1205, 1140, 1079, 1025, 937, 767, 685 cm^{-1}.

^{1}H NMR: δ 8.38 (d, *J* = 8.0 Hz, 2H), 7.51 (t, *J* = 7.6 Hz, 2H), 7.44-7.43 (m, 4H), 7.39-7.32 (m, 9H), 7.23-7.24 (m, 2H), 7.19 (t, *J* = 7.6 Hz, 1H), 5.57 (s, 1H), 4.64 (qrt, *J* = 6.8 Hz, 1H), 1.73 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR: δ 144.6, 144.5, 142.1, 140.7, 129.8, 129.7, 129.0$_4$, 128.9$_5$, 128.7, 128.4, 128.3, 128.1, 127.9, 127.6, 126.9, 125.5, 125.2, 125.1, 107.1, 61.7, 57.3, 22.6.

HRMS (ESI): Calcd. for $C_{31}H_{26}N_3O$ $[M^+$+H]: *m/z* 456.2076. Found: 456.2076.

Compound 19



Yield: 0.132 g (80%, yellow solid).

Mp: 220-222 °C.

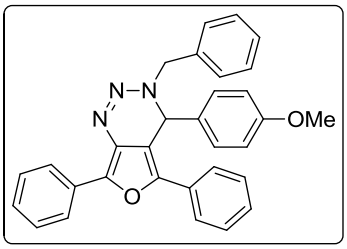
IR (KBr): 3068, 3035, 2938, 1605, 1592, 1486, 1448, 1427, 1272, 1150, 1075, 1017, 942, 766, 688 cm^{-1}.

^1H NMR: δ 8.52 (s, 1H), 8.31-8.29 (m, 2H), 8.22-8.20 (m, 2H), 8.07-8.04 (m, 2H), 7.51-7.44 (m, 6H), 7.35-7.30 (m, 6H), 7.25-7.20 (m, 4H), 7.18-7.14 (m, 1H), 6.03 (d, *J* = 14.8 Hz, 1H), 5.64 (d, *J* = 14.8 Hz, 1H), 5.50 (s, 1H).

^{13}C NMR: δ 145.2, 143.9, 140.8, 131.5, 131.4, 129.7, 129.6, 129.2, 129.0, 128.9, 128.7, 128.4, 128.2, 127.8, 127.7, 126.4, 125.8, 125.6, 125.1, 124.7, 124.4, 107.8, 56.6, 50.5.

HRMS (ESI): Calcd. for $C_{38}H_{28}N_3O$ $[M^+ + H]$: *m/z* 542.2232. Found: 542.2225.

Compound 20



Yield: 0.099 g (70%, yellow solid).

Mp: 110-112 °C.

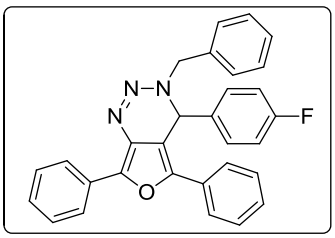
IR (KBr): 3047, 3019, 2953, 2921, 2833, 1611, 1512, 1496, 1447, 1425, 1255, 1173, 1101, 1068, 948, 822, 762, 685 cm^{-1}.

^1H NMR: δ 8.38-8.36 (m, 2H), 7.51 (t, *J* = 8.0 Hz, 2H), 7.43-7.37 (m, 8H), 7.30-7.18 (m, 5H), 6.88 (d, *J* = 8.0 Hz, 2H), 5.52 (s, 1H), 5.23 (d, *J* = 15.2 Hz, 1H), 4.41 (d, *J* = 15.2 Hz, 1H), 3.81 (s, 3H).

^{13}C NMR: δ 159.8, 144.9, 144.3, 135.9, 132.1, 129.8, 129.7, 129.6, 129.0, 128.7, 128.5, 128.3, 128.2, 128.1, 127.6, 125.6, 125.2, 125.0, 114.3, 107.3, 56.8, 55.3.

HRMS (ESI): Calcd. for $C_{31}H_{26}N_3O_2$ $[M^+ + H]$: *m/z* 472.2025. Found: 472.2024.

Compound 21



Yield: 0.108 g (78%, yellow solid).

Mp: 152-154 °C.

IR (KBr): 3047, 3030, 2926, 2866, 1605, 1490, 1447, 1227, 1156, 1085, 1079, 937, 833, 762, 690 cm^{-1}.

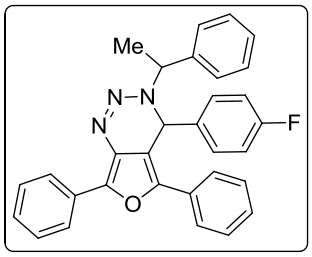
^{1}H NMR: δ 8.36 (d, *J* = 7.6 Hz, 2H), 7.52 (t, *J* = 7.6 Hz, 2H), 7.46-7.35 (m, 8H), 7.30-7.25 (m, 4H), 7.23-7.19 (m, 1H), 7.05 (t, *J* = 8.4 Hz, 2H), 5.58 (s, 1H), 5.25 (d, *J* = 15.2 Hz, 1H), 4.38 (d, *J* = 15.2 Hz, 1H).

^{13}C NMR: δ 162.7 (*J* = 246.7 Hz), 145.3, 144.5, 135.7_3 (*J* = 3.1 Hz), 135.6_5, 130.1 (*J* = 8.4 Hz), 129.6 (*J* = 5.9 Hz), 129.0, 128.8, 128.5, 128.4, 128.2_1, 128.1_8, 127.9, 125.6, 125.0, 124.8, 116.0 (*J* = 21.7 Hz), 106.8, 56.9, 55.1.

^{19}F NMR : δ -112.35.

HRMS (ESI): Calcd. for $C_{30}H_{23}FN_3O$ $[M^+ + H]$: *m/z* 460.1825. Found: 460.1828.

Compound 22



Yield: 0.111 g (78%, yellow solid).

Mp: 174-176 °C.

IR (KBr): 3058, 3026, 1606, 1507, 1430, 1233, 1151, 1074, 948, 816, 762, 690 cm^{-1}.

^{1}H NMR: δ 8.38-8.35 (m, 2H), 7.50 (t, *J* = 8.0 Hz, 2H), 7.45-7.24 (m, 12H), 7.21-7.17 (m, 1H), 7.04 (t, *J* = 8.4 Hz, 2H), 5.56 (s, 1H), 4.60 (qrt, *J* = 6.8 Hz, 1H), 1.73 (d, *J* = 6.8 Hz, 3H).

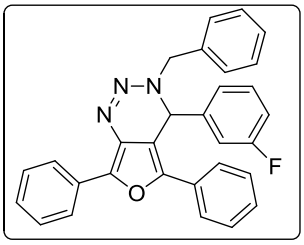
^{13}C NMR: δ 162.6 (*J* = 246.9 Hz), 144.6 (*J* = 26.9 Hz), 141.9, 136.5 (*J* = 3.4 Hz), 130.1, 130.0, 129.7, 129.5, 129.1, 128.7, 128.4, 128.2, 128.0, 127.8, 126.8, 125.5, 125.2, 124.9, 116.0 (*J* = 21.8 Hz), 106.9, 61.6, 56.4, 22.6.

^{19}F NMR : δ -112.44.

LC/MS *m/z* 475 $[M+1]^+$.

Anal. Calcd. for $C_{31}H_{24}FN_3O$: C, 78.63; H, 5.11; N, 8.87; Found: C, 78.53; H, 5.06; N, 8.95.

Compound 23



Yield: 0.103 g (75%, yellow solid).

Mp: 170-172 °C.

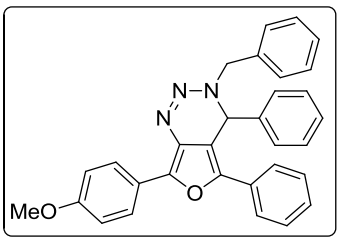
IR (KBr): 3063, 2921, 1595, 1490, 1425, 1364, 1255, 1096, 1074, 942, 910, 762, 696 cm^{-1}.

^1H NMR: δ 8.40-8.38 (m, 2H), 7.53 (t, *J* = 7.6 Hz, 2H), 7.47-7.28 (m, 11H), 7.25-7.21 (m, 1H), 7.11 (d, *J* = 8.0 Hz, 1H), 7.06-7.01 (m, 2H), 5.60 (s, 1H), 5.29 (d, *J* = 15.0 Hz, 1H), 4.41 (d, *J* = 15.0 Hz, 1H).

^{13}C NMR: δ 163.1 (*J* = 247.0 Hz), 145.5, 144.6, 142.2, 142.1, 135.6, 130.6 (*J* = 8.1 Hz), 129.5 (*J* = 5.6 Hz), 129.1, 128.8, 128.6, 128.4, 128.2, 127.9, 125.7, 125.0, 124.7, 124.0 (*J* = 2.7 Hz), 115.9 (*J* = 21.1 Hz), 115.3 (*J* = 21.7 Hz), 106.3, 57.0, 55.3.

HRMS (ESI): Calcd. for $C_{30}H_{23}FN_3O$ $[M^+ + H]$: *m/z* 460.1825. Found: 460.1829.

Compound 24



Yield: 0.091 g (64%, yellow solid).

Mp: 150-152 °C.

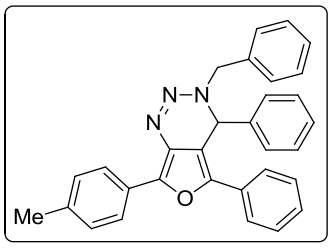
IR (KBr): 3063, 3030, 2932, 2849, 1600, 1490, 1436, 1222, 1074, 942, 827, 762, 690 cm^{-1}.

^1H NMR: δ 8.32-8.30 (m, 2H), 7.45-7.24 (m, 14H), 7.19-7.15 (m, 1H), 7.06-7.04 (m, 2H), 5.55 (s, 1H), 5.23 (d, *J* = 14.8 Hz, 1H), 4.37 (d, *J* = 14.8 Hz, 1H), 3.92 (s, 3H).

^{13}C NMR: δ 159.8, 145.5, 143.7, 139.9, 136.0, 129.8, 129.0, 128.9, 128.7, 128.5, 128.3_2, 128.2_7, 128.0, 127.5, 127.2, 124.8, 123.9, 122.7, 114.3, 107.0, 56.8, 55.9, 55.4.

HRMS (ESI): Calcd. for $C_{31}H_{26}N_3O_2$ [M^++H]: *m/z* 472.2025. Found: 472.2026.

Compound 25



Yield: 0.090 g (66%, yellow solid).

Mp: 198-200 °C.

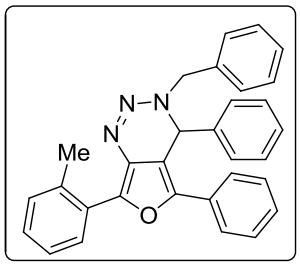
IR (KBr): 3063, 3030, 2915, 2860, 1595, 1512, 1447, 1403, 1255, 1068, 959, 811, 696 cm^{-1}.

^{1}H NMR: δ 8.28 (d, *J* = 8.0 Hz, 2H), 7.46-7.31 (m, 14H), 7.27 (t, *J* = 7.2 Hz, 2H), 7.19 (t, *J* = 7.2 Hz, 1H), 5.58 (s, 1H), 5.25 (d, *J* = 14.8 Hz, 1H), 4.40 (d, *J* = 14.8 Hz, 1H), 2.46 (s, 3H).

^{13}C NMR: δ 145.5, 144.1, 139.9, 138.4, 136.0, 129.8, 129.5, 129.0_1, 128.9_7, 128.7, 128.5, 128.4, 128.3, 128.1, 127.6, 127.0, 125.6, 125.0, 124.6, 107.0, 56.9, 55.9, 21.6.

HRMS (ESI): Calcd. for $C_{31}H_{26}N_3O$ [M^++H]: *m/z* 456.2076,. Found: 456.2075.

Compound 26



Yield: 0.102 g (75%, yellow solid).

Mp: 96-98 °C.

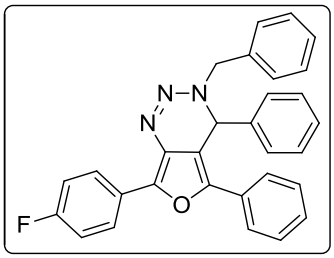
IR (KBr): 3063, 3025, 2920, 1600, 1496, 1425, 1348, 1310, 1266, 1101, 1058, 931, 762, 707 cm^{-1}.

^{1}H NMR: δ 8.39 (d, *J* = 7.6 Hz, 1H), 7.47-7.33 (m, 15H), 7.28 (t, *J* = 7.6 Hz, 2H), 7.22-7.18 (m, 1H), 5.62 (s, 1H), 5.27 (d, *J* = 15.2 Hz, 1H), 4.40 (d, *J* = 15.2 Hz, 1H), 2.76 (s, 3H).

^{13}C NMR: δ 147.1, 144.7, 140.0, 136.2, 135.9, 131.5, 130.1, 129.8, 129.1, 129.0, 128.8, 128.7, 128.6, 128.4, 128.3, 128.1, 127.6, 126.1, 125.3, 124.8, 106.5, 56.9, 55.9, 22.1.

HRMS (ESI): Calcd. for $C_{31}H_{26}N_3O$ [M^++H]: *m/z* 456.2076. Found: 456.2077.

Compound 27



Yield: 0.110 g (80%, yellow solid).

Mp: 170-172 °C.

IR (KBr): 3068, 3030, 1600, 1501, 1452, 1348, 1227, 1151, 1090, 1068, 948, 833, 696 cm^{-1}.

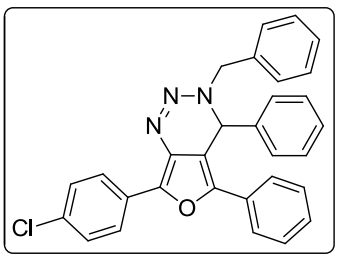
^{1}H NMR: δ 8.37-8.33 (m, 2H), 7.45-7.29 (m, 13H), 7.25-7.19 (m, 4H), 5.56 (s, 1H), 5.24 (d, *J* = 15.2 Hz, 1H), 4.39 (d, *J* = 15.2 Hz, 1H).

^{13}C NMR: δ 162.7 (*J* = 247.6 Hz), 144.5, 144.3, 139.8, 135.8, 131.5, 129.6, 129.1, 129.0, 128.9, 128.8, 128.5, 128.4, 128.3 (*J* = 3.1 Hz), 128.1, 127.8, 127.5, 127.4, 126.1 (*J* = 3.0 Hz), 125.0, 124.6, 115.9 (*J* = 21.8 Hz), 106.9, 56.9, 55.9.

^{19}F NMR δ -112.21.

HRMS (ESI): Calcd. for $C_{30}H_{23}FN_3O$ [M^++H]: *m/z* 460.1825. Found: 460.1827.

Compound 28



Yield: 0.110 g (80%, yellow solid).

Mp: 170-172 °C.

IR (KBr): 3068, 3030, 1600, 1501, 1452, 1348, 1227, 1151, 1090, 1068, 948, 833, 696 cm^{-1}.

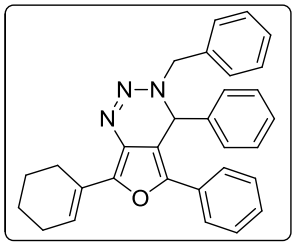
^1H NMR: δ 8.31 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.46-7.25 (m, 14H), 7.21 (t, *J* = 7.2 Hz, 1H), 5.25 (s, 1H), 5.24 (d, *J* = 15.2 Hz, 1H), 4.40 (d, *J* = 15.2 Hz, 1H).

^{13}C NMR: δ 144.9, 143.9, 139.8, 135.7, 133.9, 129.5, 129.0_5, 128.9_8, 128.9_7, 128.8, 128.5, 128.3_0, 128.2_8, 128.2, 128.1, 127.9, 126.7, 125.2, 125.1, 107.0, 57.0, 56.0.

LC/MS *m/z* 476 $[M+1]^+$.

Anal. Calcd. for $C_{30}H_{22}ClN_3O$: C, 75.70; H, 4.66; N, 8.83; Found: C, 75.58; H, 4.71; N,8.76.

Compound 29



Yield: 0.075 g (56%, yellow solid).

Mp: 178-180 °C.

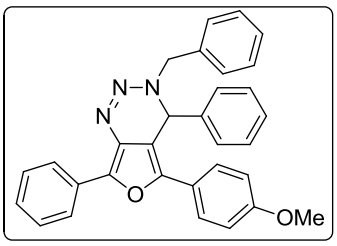
IR (KBr): 3057, 3024, 2920, 2854, 1649, 1599, 1495, 1446, 1177, 1068, 734, 690 cm^{-1}.

^1H NMR: δ 7.43-7.29 (m, 11H), 7.25-7.20 (m, 3H), 7.14 (t, *J* = 7.0 Hz, 1H), 6.97 (br, 1H), 5.49 (s, 1H), 5.19 (d, *J* = 15.2 Hz, 1H), 4.33 (d, *J* = 15.2 Hz, 1H), 2.80 (br, 2H), 2.38 (br, 2H), 1.87-1.85 (m, 2H), 1.77-1.75 (m, 2H).

^{13}C NMR: δ 147.4, 143.0, 140.0, 136.1, 129.9, 129.0_1, 128.9, 128.8, 128.6, 128.4, 128.3, 128.2, 128.0, 127.9, 127.3, 124.8, 124.1, 106.7, 56.7, 55.8, 25.9, 25.1, 22.4, 22.1.

HRMS (ESI): Calcd. for $C_{30}H_{28}N_3O$ $[M^+ + H]$: *m/z* 446.2232. Found: 446.2236.

Compound 30



Yield: 0.113 g (80%, yellow solid).

Mp: 80-82 °C.

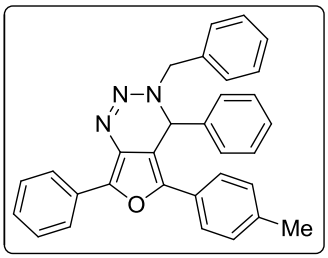
IR (KBr): 3052, 3030, 2921, 2833, 1600, 1584, 1485, 1458, 1430, 1315, 1249, 1107, 1019, 948, 756, 690 cm^{-1}.

^1H NMR: δ 8.32-8.30 (m, 2H), 7.50-7.40 (m, 8H), 7.36-7.34 (m, 1H), 7.26-7.18 (m, 4H), 7.04-7.01 (m, 2H), 6.93 (t, *J* = 7.6 Hz, 1H), 6.82 (d, *J* = 8.4 Hz, 1H), 5.70 (s, 1H), 5.35 (d, *J* = 14.8 Hz, 1H), 4.37 (d, *J* = 14.8 Hz, 1H), 3.49 (s, 3H).

^{13}C NMR: δ 155.3, 145.2, 142.3, 140.9, 136.2, 130.0, 129.7, 129.1, 128.8, 128.7, 128.6, 128.0, 127.9, 127.0, 125.4, 124.9, 120.8, 119.3, 110.8, 109.4, 57.4, 55.4, 54.7.

HRMS (ESI): Calcd. for $C_{31}H_{26}N_3O_2$ $[M^+ + H]$: *m/z* 472.2025. Found: 472.2024.

Compound 31



Yield: 0.093 g (68%, yellow solid).

Mp: 182-184 °C.

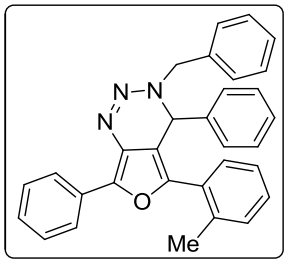
IR (KBr): 3068, 3030, 2910, 1605, 1512, 1485, 1452, 1430, 1266, 1112, 1068, 948, 816, 696 cm^{-1}.

^1H NMR: δ 8.38 (d, *J* = 8.0 Hz, 2H), 7.52 (t, *J* = 7.2 Hz, 2H), 7.44-7.27 (m, 13H), 7.08 (d, *J* = 8.0 Hz, 2H), 5.57 (s, 1H), 5.25 (d, *J* = 14.8 Hz, 1H), 4.40 (d, *J* = 14.8 Hz, 1H), 2.31 (s, 3H).

^{13}C NMR: δ 144.8, 140.0, 137.8, 135.9, 129.8, 129.2, 129.0$_1$, 128.9$_7$, 128.7, 128.4, 128.3, 128.1$_2$, 128.0$_9$, 126.9, 125.5, 125.1, 125.0, 106.3, 56.9, 55.9, 21.3.

HRMS (ESI): Calcd. for $C_{31}H_{26}N_3O$ [M^++H]: *m/z* 456.2076. Found: 456.2075.

Compound 32



Yield: 0.103 g (76%, yellow solid).

Mp: 62-64 °C.

IR (KBr): 3057, 3030, 2926, 1605, 1513, 1490, 1436, 1353, 1260, 1156, 1118, 1063, 948, 827, 625 cm^{-1}.

^{1}H NMR: δ 8.30-8.28 (m, 2H), 7.48 (t, *J* = 7.6 Hz, 2H), 7.42-7.34 (m, 6H), 7.29-7.26 (m, 3H), 7.19 (t, *J* = 7.6 Hz, 1H), 7.14 (d, *J* = 7.2 Hz, 1H), 7.09-7.06 (m, 2H), 7.00 (t, *J* = 7.2 Hz, 1H), 6.75 (d, *J* = 7.6 Hz, 1H), 5.38 (s, 1H), 5.26 (d, *J* = 15.2 Hz, 1H), 4.32 (d, *J* = 15.2 Hz, 1H), 2.19 (s, 3H).

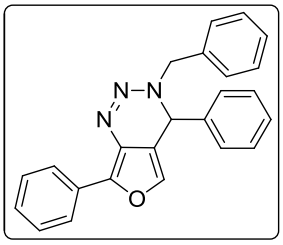
^{13}C NMR: δ 146.2, 145.3, 140.6, 137.7, 135.9, 130.5, 129.9, 129.5, 129.0, 128.9, 128.8, 128.7, 128.5, 128.4, 128.0$_7$, 128.0$_5$, 127.6, 125.3$_4$, 125.2$_5$, 123.8, 108.3, 57.1, 55.6, 20.4.

HRMS (ESI): Calcd. for $C_{31}H_{26}N_3O$ [M^++H]: *m/z* 456.2076. Found: 456.2074.

3.3 Representative procedure for the synthesis of furo[3,4-d][1,2,3]triazine derivatives 33-38 from enynals (3a-b, 3d, and 3h-i) and azides 7a-b

Compounds **33-38** were prepared following the same procedure and the same molar quantities as described for compounds **9-32**. But after the addition of all components, the reaction was continued at 70 ^{o}C for 10 h.

Compound 33



Yield: 0.080 g (73%, yellow solid).

Mp: 130-132 °C.

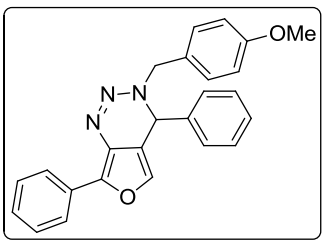
IR (KBr): 3053, 3030, 1540, 1485, 1479, 1458, 1392, 1353, 1315, 1255, 1101, 1063, 899, 762 cm^{-1}.

^1H NMR: δ 7.66-7.64 (m, 2H), 7.46-7.26 (m, 13H), 6.21 (s, 1H), 5.76 (s, 1H), 5.20 (d, *J* = 14.8 Hz, 1H), 4.25 (d, *J* = 14.8 Hz, 1H).

^{13}C NMR: δ 152.3, 149.2, 140.9, 134.8, 129.7, 129.1, 129.0, 128.9, 128.8, 128.6, 128.3, 128.2, 127.6, 124.0, 104.4, 103.3, 60.5, 57.2.

HRMS (ESI): Calcd. for $C_{24}H_{20}N_3O$ $[M^+ + H]$: *m/z* 366.1606. Found: 366.1605.

Compound 34



Yield: 0.089 g (75%, gummy liquid).

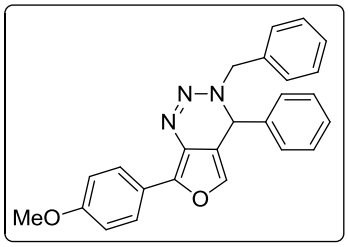
IR (Neat): 2920, 2860, 1610, 1517, 1484, 1451, 1397, 1309, 1254, 1183, 1095, 1024, 766. cm^{-1}.

^1H NMR: δ 7.65-7.63 (m, 2H), 7.45-7.34 (m, 6H), 7.30-7.29 (m, 1H), 7.28-7.27 (m, 1H), 7.23 (d, *J* = 9.0 Hz, 2H), 6.93 (d, *J* = 9.0 Hz, 2H), 6.20 (s, 1H), 5.74 (s, 1H), 5.13 (d, *J* = 14.5 Hz, 1H), 4.18 (d, *J* = 14.5 Hz, 1H), 3.85 (s, 3H).

^{13}C NMR: δ 159.6, 152.2, 149.2, 141.0, 130.0, 129.7, 129.1, 128.9, 128.7, 128.2, 127.6, 126.5, 124.0, 114.3, 104.3, 103.3, 60.3, 56.7, 55.3.

HRMS (ESI): Calcd. for $C_{25}H_{22}N_3O_2$ $[M^+ + H]$: *m/z* 396.1712. Found: 396.1710.

Compound 35



Yield: 0.081 g (68%, yellow solid).

Mp: 148-150 °C.

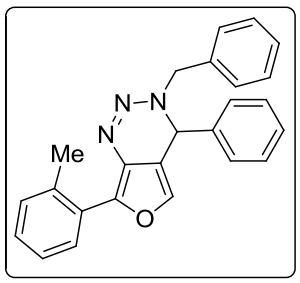
IR (KBr): 2964, 2932, 2838, 1611, 1496, 1458, 1397, 1255, 1173, 1101, 1068, 937, 701 cm^{-1}.

^1H NMR: δ 7.58 (d, *J* = 8.8 Hz, 2H), 7.45-7.37 (m, 5H), 7.33-7.28 (m, 5H), 6.90 (d, *J* = 8.8 Hz, 2H), 6.08 (s, 1H), 5.74 (s, 1H), 5.18 (d, *J* = 14.8 Hz, 1H), 4.23 (d, *J* = 14.8 Hz, 1H), 3.84 (s, 3H).

^{13}C NMR: δ 159.7, 152.5, 148.8, 141.0, 134.9, 129.1, 128.9_3, 128.8_7, 128.6, 128.2, 127.6, 125.6, 122.7, 114.2, 104.5, 101.7, 60.5, 57.1, 55.3.

HRMS (ESI): Calcd. for $C_{25}H_{22}N_3O_2$ $[M^+ + H]$: *m/z* 396.1712. Found: 396.1720.

Compound 36



Yield: 0.082 g (70%, gummy liquid).

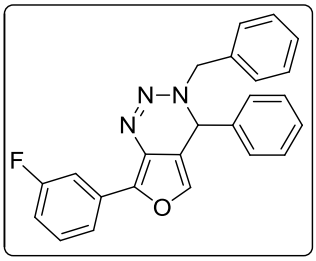
IR (Neat): 3068, 3025, 2926, 2099, 1688, 1600, 1490, 1457, 1392, 1310, 1101, 1074, 1025, 937, 762, 701 cm^{-1}.

^1H NMR: δ 7.75-7.73 (m, 1H), 7.45-7.40 (m, 6H), 7.35-7.29 (m, 5H), 7.23-7.21 (m, 2H), 6.11 (s, 1H), 5.79 (s, 1H), 5.20 (d, *J* = 15.2 Hz, 1H), 4.26 (d, *J* = 15.2 Hz, 1H), 2.45 (s, 3H).

^{13}C NMR: δ 152.0, 148.8, 140.9, 134.9, 134.8, 131.3, 129.1, 129.0, 128.9, 128.7, 128.3, 128.2, 127.7, 127.1, 126.1, 106.8, 104.0, 60.5, 57.2, 22.1.

HRMS (ESI): Calcd. for $C_{25}H_{22}N_3O$ $[M^+ + H]$: *m/z* 380.1763. Found: 380.1767.

Compound 37



Yield: 0.085 g (72%, gummy liquid).

IR (Neat): 3068, 3030, 2920, 1625, 1605, 1589, 1485, 1457, 1397, 1342, 1266, 1194, 1096, 1025, 948, 778, 696 cm^{-1}.

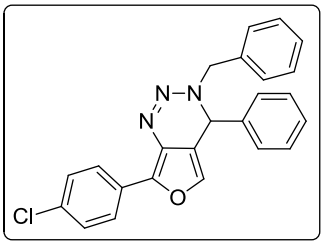
^1H NMR: δ 7.44-7.38 (m, 8H), 7.35-7.31 (m, 4H), 7.29-7.27 (m, 1H), 7.00-6.95 (m, 1H), 6.23 (s, 1H), 5.75 (s, 1H), 5.20 (d, *J* = 15.2 Hz, 1H), 4.25 (d, *J* = 15.2 Hz, 1H).

^{13}C NMR: δ 163.1 (d, *J* = 244.4 Hz), 150.9 (d, *J* = 3.4 Hz), 149.4, 140.8, 134.7, 131.7 (d, *J* = 8.4 Hz), 130.8, 130.4 (d, *J* = 8.8 Hz), 129.2, 129.1, 128.9, 128.6, 128.3, 127.6, 119.6 (d, *J* = 2.9 Hz), 115.0 (d, *J* = 21.0 Hz), 110.9 (d, *J* = 23.6 Hz), 104.3, 60.5, 57.3.

^{19}F NMR: δ -112.48.

HRMS (ESI): Calcd. for $C_{24}H_{19}FN_3O$ $[M^+ + H]$: *m/z* 384.1512. Found: 384.1510.

Compound 38



Yield: 0.079 g (66%, yellow solid).

Mp: 140-142 °C.

IR (KBr): 3063, 3030, 2932, 1622, 1540, 1490, 1468, 1452, 1386, 1315, 1238, 1101, 1068, 1008, 932, 893, 701 cm^{-1}.

^1H NMR: δ 7.56 (d, *J* = 8.4 Hz, 2H), 7.46-7.27 (m, 12H), 6.20 (s, 1H), 5.75 (s, 1H), 5.20 (d, *J* = 14.8 Hz, 1H), 4.25 (d, *J* = 14.8 Hz, 1H).

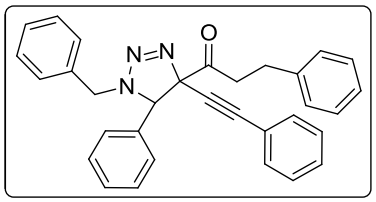
^{13}C NMR: δ 151.1, 149.3, 140.8, 134.7, 133.9, 129.1_4, 129.0_6, 129.0, 128.9, 128.6, 128.3, 128.2, 127.6, 125.2, 104.4, 103.7, 60.5, 57.3.

HRMS (ESI): Calcd. for $C_{24}H_{19}ClN_3O$ [M^++H]: *m/z* 400.1216. Found: 400.1217.

3.4 Synthesis of highly functionalized triazole derivatives 39-41

Compounds **39-41** were prepared following the same procedure and the same molar quantities as described for compounds **9-32**.

Compound 39



Yield: 0.077 g (65%, gummy liquid).

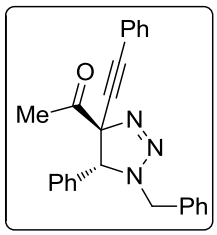
IR (Neat): 3030, 2920, 2214, 1730, 1605, 1506, 1462, 1364, 1271, 1150, 1073, 1024, 761, 706.cm^{-1}.

^{1}H NMR: δ 7.40-7.38 (m, 3H), 7.35-7.33 (m, 3H), 7.30-7.26 (m, 6H), 7.23-7.19 (m, 4H), 7.14-7.11 (m, 2H), 7.00-6.98 (m, 2H), 5.27 (d, *J* = 15.2 Hz, 1H), 5.04 (s, 1H), 4.28 (d, *J* = 15.2 Hz, 1H), 3.58-3.40 (m, 2H), 3.00 (t, *J* = 7.6 Hz, 2H).

^{13}C NMR: δ 199.3, 140.6, 134.6, 134.1, 131.5, 128.8, 128.7, 128.5_3, 128.4_6, 128.4_3, 128.3_5, 128.1, 121.6, 93.2, 91.8, 81.9, 63.7, 52.1, 40.8, 29.8.

HRMS (ESI): Calcd. for $C_{32}H_{28}N_3O$ [M^++H]: *m/z* 470.2232. Found: 470.2229.

Compound 40



Yield: 0.068 g (60%, gummy liquid).

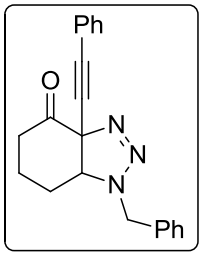
IR (Neat): 3058, 2926, 2849, 1715, 1666, 1627, 1556, 1501, 1458, 1397, 1266, 1167, 1068, 756, 701 cm^{-1}.

^{1}H NMR: δ 7.41-7.39 (m, 3H), 7.35-7.27 (m, 6H), 7.24-7.20 (m, 2H), 7.15-7.13 (m, 2H), 7.05-7.03 (m, 2H), 5.28 (d, *J* = 14.8 Hz, 1H), 5.06 (s, 1H), 4.29 (d, *J* = 14.8 Hz, 1H), 2.69 (s, 3H).

^{13}C NMR: δ 197.7, 134.6, 134.2, 131.5, 128.8$_0$, 128.7$_7$, 128.7, 128.5, 128.4, 128.1, 121.7, 93.2, 92.1, 81.9, 63.4, 52.1, 26.8.

HRMS (ESI): Calcd. for $C_{25}H_{22}N_3O$ [M^++H]: *m/z* 380.1763. Found: 380.1763.

Compound 41



Yield: 0.074 g (75%, gummy liquid).

IR (Neat): 3063, 2937, 2855, 1704, 1644, 1485, 1452, 1359, 1216, 1096, 1030, 756, 690 cm^{-1}.

^{1}H NMR: δ 7.53-7.51 (m, 2H), 7.44-7.31 (m, 8H), 4.17 (d, *J* = 14.0 Hz, 1H), 3.81 (d, *J* = 14.0 Hz, 1H), 2.69-2.63 (m, 2H), 2.20-2.01 (m, 3H), 1.98-1.93 (m, 1H), 1.72-1.66 (m, 1H).

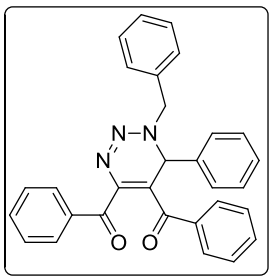
^{13}C NMR: δ 202.8, 138.7, 132.1, 128.6, 128.5, 128.3, 127.9, 127.2, 122.4, 86.9, 82.7, 58.6, 52.8, 44.2, 36.8, 23.4, 19.2.

HRMS (ESI): Calcd. for $C_{21}H_{20}N_3O$ [M^++H]: *m/z* 330.1606. Found: 330.1607.

3.5 General procedure for the synthesis of tetrasubstituted 1,2,3-triazine derivatives 42-45

A solution of cerium(IV) ammonium nitrate (CAN)[76] (124.5 mg, 0.22 mmol) in water (2 mL) was added dropwise to a stirring solution of the **9** (50.0 mg 0.11 mmol) in acetonitrile (3 mL). The mixture was stirred at rt for 15 min and then extracted with chloroform (3×20 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 silica gel column chromatography using ethyl acetate-hexane (1:4) as the eluent to afford (1-benzyl-6-phenyl-1,6-dihydro-1,2,3-triazine-4,5-diyl)bis(phenylmethanone) **42**. Compounds **43-45** were prepared following the same procedure and by using the same molar quantities.

Compound 42



Yield: 0.05 g (96%, gummy liquid).

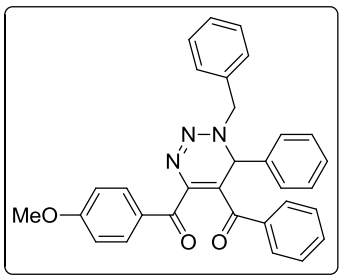
IR (Neat): 3063, 3024, 2926, 2849, 1671, 1599, 1490, 1451, 1402, 1325, 1265, 1210, 1172, 1134, 1024, 920, 695 cm^{-1}.

^1H NMR: δ 7.78 (d, *J* = 7.6 Hz, 2H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.47-7.44 (m, 3H), 7.40-7.36 (m, 7H), 7.34-7.27 (m, 5H), 7.08 (t, *J* = 7.6 Hz, 2H), 5.62 (s, 1H), 5.34 (d, *J* = 14.4 Hz, 1H), 4.67 (d, *J* = 14.4 Hz, 1H).

^{13}C NMR: δ 195.2, 191.3, 140.5, 139.0, 136.7, 135.8, 133.6, 133.0, 129.7, 129.5, 129.2, 128.9, 128.7, 128.4, 128.3_0, 128.2_6, 127.1, 119.7, 58.7, 55.1.

HRMS (ESI): Calcd. for $C_{30}H_{23}N_3O_2Na$ [M^++Na]: *m/z* 480.1688. Found: 480.1684.

Compound 43



Yield: 0.042 g (80%, gummy liquid).

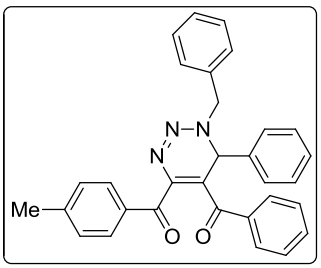
IR (Neat): 3058, 2937, 2844, 1660, 1595, 1507, 1452, 1326, 1255, 1167, 1118, 1068, 1030, 926, 696 cm^{-1}.

^1H NMR: δ 7.77 (d, *J* = 8.8 Hz, 2H), 7.46-7.43 (m, 3H), 7.40-7.37 (m, 5H), 7.35-7.28 (m, 5H), 7.09 (t, *J* = 7.6 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 5.61 (s, 1H), 5.33 (d, *J* = 14.4 Hz, 1H), 4.66 (d, *J* = 14.4 Hz, 1H), 3.87 (s, 3H).

^{13}C NMR: δ 195.4, 189.7, 164.0, 140.8, 139.1, 136.8, 133.6, 132.9, 132.2, 129.4_4, 129.3_9, 129.2, 129.1, 128.8, 128.6, 128.2_4, 128.1_9, 127.1, 119.1, 113.7, 58.7, 55.5, 55.0.

HRMS (ESI): Calcd. for $C_{31}H_{25}N_3O_3Na$ [M^++Na]: *m/z* 510.1794. Found: 510.1791.

Compound 44



Yield: 0.043 g (83%, yellow solid).

IR (KBr): 3063, 3025, 2926, 1666, 1605, 1496, 1452, 1408, 1321, 1266, 1173, 1112, 926, 690 cm^{-1}.

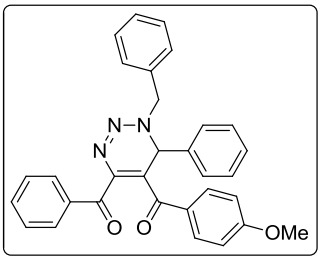
^1H NMR: δ 7.69 (d, *J* = 8.0 Hz, 2H), 7.47-7.44 (m, 3H), 7.40-7.35 (m, 5H), 7.34-7.28 (m, 5H), 7.18 (d, *J* = 8.0 Hz, 2H), 7.08 (t, *J* = 8.0 Hz, 2H), 5.61 (s, 1H), 5.34 (d, *J* = 14.4 Hz, 1H), 4.67 (d, *J* = 14.4 Hz, 1H), 2.40 (s, 3H).

^{13}C NMR: δ 195.3, 190.9, 144.6, 140.7, 139.1, 136.7, 133.6, 133.4, 132.9, 129.9, 129.5, 129.4, 129.2, 129.1, 128.8, 128.6, 128.3, 128.2, 127.1, 119.3, 58.7, 55.1, 21.8.

HRMS (ESI): Calcd. for $C_{31}H_{25}N_3O_2Na$ [M^++Na]: *m/z* 494.1845. Found: 494.1843.

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

Compound 45



Yield: 0.050 g (96%, yellow solid).

IR (KBr): 3056, 2936, 1638, 1496, 1452, 1397, 1321, 1282, 1244, 1101, 1014, 926, 696 cm^{-1}.

^1H NMR: δ 7.69-7.67 (m, 2H), 7.52-7.49 (m, 1H), 7.48-7.42 (m, 3H), 7.41-7.32 (m, 7H), 7.29-7.27 (m, 2H), 7.19-7.16 (m, 1H), 6.83 (dd, *J* = 7.5 Hz, 1.5 Hz, 1H), 6.66-6.63 (m, 1H), 6.42 (d, *J* = 7.5 Hz, 1H), 5.69 (s, 1H), 5.29 (d, *J* = 14.5 Hz, 1H), 4.66 (d, *J* = 14.5 Hz, 1H), 3.29 (s, 3H).

^{13}C NMR: δ 194.3, 191.8, 157.1, 142.2, 139.7, 135.6, 133.8, 133.4, 132.9, 130.2, 129.2, 129.1$_3$, 129.0$_6$, 129.0, 128.8, 128.7, 128.2, 127.6, 120.3, 117.5, 110.5, 58.8, 54.9, 54.1.

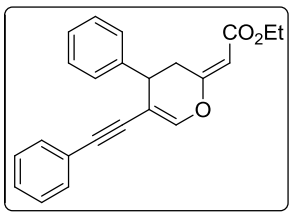
LC/MS *m/z* 489 $[M+1]^+$.

Anal. Calcd. for $C_{31}H_{25}N_3O_3$: C, 76.37; H, 5.17; N, 8.62; Found: C, 76.24; H, 5.21; N, 8.53.

3.6 Representative procedure for the DABCO catalyzed [2+4] cycloaddition reaction of enynals 3a-o/enynones 4a, and 4e-4f with allenoates 8a-d: Synthesis of highly functionalized dihydropyran derivatives 46-62

To a solution of 2-(1-alkynyl)-2-alken-1-al **3a** or 2-(1-alkynyl)-2-alken-1-one **4a** (0.4 mmol) in dry 1,4-dioxane (2 mL), DABCO (0.04 mmol) followed by alkyl 2,3-butadienoate **8a** (0.48 mmol) were added. The vessel was stoppered under nitrogen atmosphere and contents were stirred for 3 h (for compounds **46-59**) or 1 h (for compounds **60-62**) at rt. The completion of the reaction was monitored by TLC. Later, the solvent was removed under vacuum and the crude product was purified by column chromatography by using silica gel with ethyl acetate:hexane (1:99) mixture as the eluent to afford the corresponding dihydropyrans **46-62**.

Compound 46



Yield: 0.112 g (82%, white solid).

Mp: 64-66 ^{o}C.

IR (KBr): 3085, 2976, 2909, 2202, 1698, 1649, 1490, 1380, 1353, 1266, 1161, 1123, 843, 755, 690 cm^{-1}.

^{1}H NMR: δ 7.38-7.32 (m, 4H), 7.31-7.27 (m, 6H), 7.07 (s, 1H), 5.64 (s, 1H), 4.19-4.06 (m, 2H), 3.83-3.77 (m, 2H), 3.35-3.28 (m, 1H), 1.25 (t, *J* = 7.2 Hz, 3H).

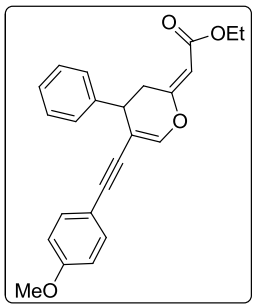
^{13}C NMR: δ 166.7, 164.2, 145.7, 140.8, 131.2, 128.5, 128.2, 128.0, 127.6, 127.1, 123.2, 104.4, 100.8, 91.5, 85.5, 59.8, 38.8, 29.9, 14.2.

LC-MS: *m/z* 345 $[M+1]^+$.

Anal. Calcd. for $C_{23}H_{20}O_3$: C, 80.21; H, 5.85. Found: C, 80.36; H, 5.79.

The enantiomeric excess was determined by HPLC with a Daicel Chiralpak AD-H column at 254 nm (hexane:2-propanol = 90:10), 0.5 mL/min; t_R= 11.2 min (major), 10.2 min (minor). $[\alpha]_D^{25}$ -89.0 (c = 0.09, $CHCl_3$), 93% ee.

Compound 47



Yield: 0.105 g (70%, white solid).

Mp: 86-88 °C.

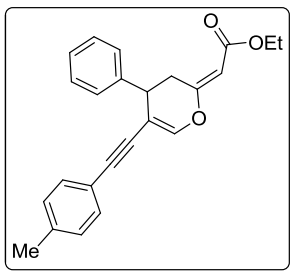
IR (KBr): 3090, 2970, 2838, 1710, 1655, 1512, 1441, 1381, 1238, 1151, 1123, 1030, 833 cm^{-1}.

^1H NMR: δ 7.35-7.29 (m, 4H), 7.25-7.23 (m, 1H), 7.19 (d, *J* = 8.8 Hz, 2H), 7.01 (s, 1H), 6.78 (d, *J* = 8.8 Hz, 2H), 5.58 (s, 1H), 4.15-4.03 (m, 2H), 3.78 (s, 3H), 3.75-3.72 (m, 2H), 3.29-3.24 (m, 1H), 1.22 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR: δ 166.7, 164.4, 159.4, 145.1, 140.8, 132.7, 128.5, 127.6, 127.0, 115.3, 113.9, 104.6, 100.7, 91.4, 84.1, 59.8, 55.3, 38.9, 29.9, 14.2.

HRMS (ESI): Calcd. for $C_{24}H_{23}O_4$ $[M^+H]$: *m/z* 375.1596. Found: 375.1591.

Compound 48



Yield: 0.103 g (72%, white solid).

Mp: 98-100 °C.

IR (KBr): 3019, 2986, 1710, 1660, 1512, 1370, 1353, 1173, 1151, 1123, 866, 811, 696 cm^{-1}.

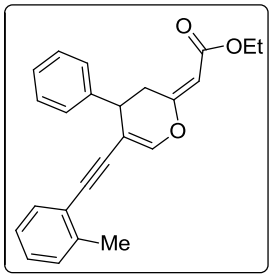
^{1}H NMR: δ 7.35-7.27 (m, 4H), 7.25-7.23 (m, 1H), 7.15 (d, *J* = 8.0 Hz, 2H), 7.05 (d, *J* = 8.0 Hz, 2H), 7.02 (s, 1H), 5.59 (s, 1H), 4.16-4.03 (m, 2H), 3.81-3.73 (m, 2H), 3.29-3.24 (m, 1H), 2.31 (s, 3H), 1.23 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR: δ 166.7, 164.3, 145.4, 140.8, 138.1, 131.1, 129.0, 128.5, 127.6, 127.0, 120.1, 104.5, 100.7, 91.7, 84.8, 59.8, 38.9, 29.9, 21.4, 14.2.

LC-MS: *m/z* 359 $[M+1]^{+}$.

Anal.Calcd. for $C_{24}H_{22}O_3$: C, 80.42; H, 6.19. Found: C, 80.31; H, 6.12.

Compound 49



Yield: 0.100 g (71%, white solid).

Mp: 68-70 °C.

IR (KBr): 3080, 3025, 2975, 2203, 1710, 1655, 1616, 1485, 1452, 1375, 1348, 1173, 1030, 860, 756, 696 cm^{-1}.

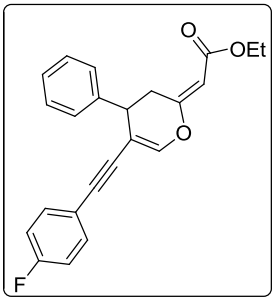
^{1}H NMR: δ 7.36-7.31 (m, 4H), 7.28-7.23 (m, 2H), 7.19-7.14 (m, 2H), 7.13-7.08 (m, 1H),7.05 (s, 1H), 5.63 (s, 1H), 4.16-4.07 (m, 2H), 3.77-3.74 (m, 1H), 3.68-3.63 (m, 1H), 3.45-3.40 (m, 1H), 2.14 (s, 3H), 1.25 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR: δ 166.7, 164.4, 145.4, 141.0, 139.9, 131.4, 129.3, 128.6, 128.0, 127.7, 127.1, 125.4, 123.0, 104.7, 100.7, 90.6, 89.4, 59.9, 39.1, 30.1, 20.4, 14.3.

LC/-MS: *m/z* 359 $[M+1]^{+}$.

Anal.Calcd. for $C_{24}H_{22}O_3$: C, 80.42; H, 6.19. Found: C, 80.34; H, 6.25.

Compound 50



Yield: 0.116 g (80%, white solid).

Mp: 88-90 °C.

IR (KBr): 3085, 2970, 2208, 1704, 1649, 1501, 1381, 1359, 1222, 1178, 1156, 1123, 866, 833, 751 cm^{-1}.

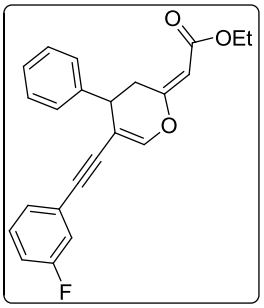
^1H NMR: δ 7.36-7.32 (m, 2H), 7.30-7.26 (m, 3H), 7.23-7.19 (m, 2H), 7.03 (s, 1H), 6.94 (d, *J* = 8.6 Hz, 2H), 5.60 (s, 1H), 4.16-4.03 (m, 2H), 3.77-3.72 (m, 2H), 3.32-3.26 (m, 1H), 1.22 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR: δ 166.7, 164.1, 162.3 (*J* = 247.5 Hz), 145.7, 140.7, 133.1 (*J* = 8.3 Hz), 128.5, 127.6, 127.1, 119.3, 115.5 (*J* = 21.9 Hz), 104.2, 100.9, 90.4, 85.2, 59.9, 38.8, 29.9,14.2.

LC-MS: *m/z* 363 $[M+1]^+$.

Anal. Calcd. for $C_{23}H_{19}FO_3$: C, 76.23; H, 5.28. Found: C, 76.12; H, 5.23.

Compound 51



Yield: 0.106 g (73%, gummy liquid).

IR (neat): 3074, 2981, 2197, 1704, 1649, 1605, 1578, 1490, 1381, 1266, 1156, 1123, 866, 789 cm^{-1}.

^1H NMR: δ 7.37-7.33 (m, 2H), 7.30-7.25 (m, 3H), 7.23-7.17 (m, 1H), 7.05 (s, 1H), 7.03-7.00 (m, 1H), 6.98-6.91 (m, 2H), 5.62 (s, 1H), 4.15-4.06 (m, 2H), 3.78-3.72 (m, 2H), 3.35-3.29 (m, 1H), 1.23 (t, *J* = 7.2 Hz, 3H).

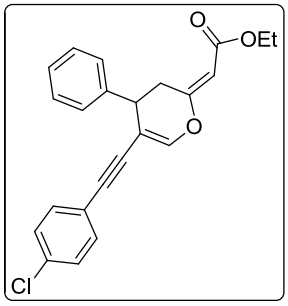
^{13}C NMR: δ 166.6, 164.0, 162.3 (*J* = 244.8 Hz), 146.2, 140.6, 129.8 (*J* = 8.3 Hz),

128.6, 127.6, 127.2, 127.1, 125.0 (J = 9.6 Hz), 117.9 (J = 22.5 Hz), 115.3 (J = 20.9 Hz), 104.1, 101.1, 90.4, 86.6, 59.9, 38.8, 29.9,14.2.

LC-MS: *m/z* 361 $[M-1]^+$.

Anal.Calcd. for $C_{23}H_{19}FO_3$: C, 76.23; H, 5.28. Found: C, 76.03; H, 5.19.

Compound 52



Yield: 0.151 g (78%, white solid).

Mp: 118-120 °C.

IR (KBr): 3085, 2970, 2893, 2208, 1715, 1638, 1484, 1375, 1353, 1260, 1145, 1117, 854, 821, 706 cm^{-1}.

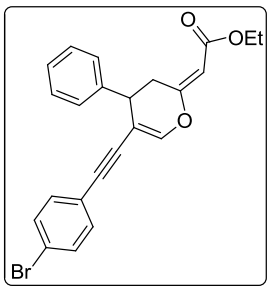
^1H NMR: δ 7.35-7.32 (m, 2H), 7.29-7.26 (m, 3H), 7.22 (d, J = 8.8 Hz, 2H), 7.15 (d, J = 8.4 Hz, 2H), 7.04 (s, 1H), 5.60 (s, 1H), 4.16-4.03 (m, 2H), 3.77-3.71 (m, 2H), 3.33-3.26 (m, 1H), 1.22 (t, J = 7.2 Hz, 3H).

^{13}C NMR: δ 166.6, 164.0, 146.0, 140.7, 133.9, 132.4, 128.6, 127.6, 127.1, 121.7, 104.2, 101.0, 90.4, 86.6, 59.9, 38.8, 29.9, 14.2.

HRMS (ESI): Calcd. for $C_{23}H_{20}ClO_3$ $[M^+ + H]$: *m/z* 379.1101. Found: 379.1101.

This compound was crystallized from acetonitrile/hexane (2:1) mixture at room temperature. X-ray structure was determined for this compound.

Compound 53



Yield: 0.108 g (64%, white solid).

Mp: 118-120 °C.

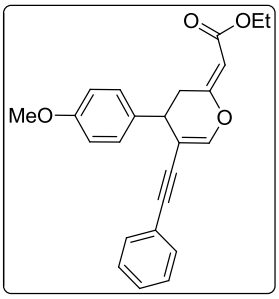
IR (KBr): 2986, 2202, 1704, 1632, 1479, 1375, 1254, 860, 810, 706, 651 cm^{-1}.

^1H NMR: δ 7.37 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 7.6 Hz, 2H), 7.29-7.24 (m, 3H), 7.08 (d, *J* = 8.4 Hz, 2H), 7.04 (s, 1H), 5.61 (s, 1H), 4.16-4.05 (m, 2H), 3.77-3.72 (m, 2H), 3.33-3.27 (m, 1H), 1.22 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR: δ 166.6, 164.0, 146.0, 140.7, 132.6, 131.5, 128.6, 127.6, 127.2, 122.1, 104.2, 101.0, 90.5, 86.8, 59.9, 38.8, 29.9,14.2.

HRMS (ESI): Calcd. for $C_{23}H_{20}BrO_3$ $[M^+ + H]$, $[M^+ + 2 + H]$: *m/z* 423.0596, 425.0596. Found: 423.0597, 425.0585.

Compound 54



Yield: 0.090 g (60%, gummy liquid).

IR (neat): 2986, 2937, 2899, 2833, 2208, 1704, 1649, 1512, 1447, 1375, 1260, 1151, 1123, 1036, 838, 756 cm^{-1}.

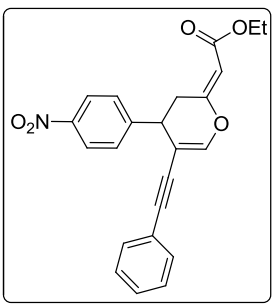
^1H NMR: δ 7.28-7.25 (m, 5H), 7.22 (d, *J* = 8.8 Hz, 2H), 7.03 (s, 1H), 6.87 (d, *J* = 8.8 Hz, 2H), 5.60 (s, 1H), 4.15-4.05 (m, 2H), 3.83-3.72 (m, 1H), 3.79 (s, 3H), 3.71 (t, *J* = 5.4 Hz, 1H), 3.23-3.17 (m, 1H), 1.23 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR: δ 166.8, 164.4, 158.6, 145.5, 132.9, 131.3, 128.6, 128.2, 128.0, 123.2, 104.7, 100.8, 91.4, 85.7, 59.9, 55.3, 38.0, 30.1, 14.3.

LC-MS: *m/z* 375 $[M+1]^+$.

Anal. Calcd. for $C_{24}H_{22}O_4$: C, 76.99; H, 5.92. Found: C, 76.91; H, 5.85.

Compound 55



Yield: 0.097 g (62%, gummy liquid).

IR (neat): 3080, 2981, 2208, 1704, 1655, 1600, 1523, 1485, 1353, 1156, 1118, 1041, 860, 751, 696 cm^{-1}.

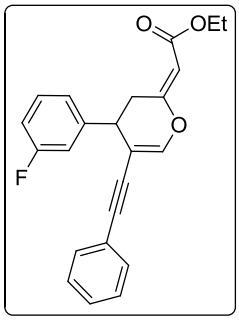
^1H NMR: δ 8.20 (d, *J* = 8.8 Hz, 2H), 7.48 (d, *J* = 8.8 Hz, 2H), 7.24 (br s, 5H), 7.08 (s, 1H), 5.64 (s, 1H), 4.14-4.05 (m, 2H), 3.90-3.85 (m, 2H), 3.28-3.21 (m, 1H), 1.22 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR: δ 166.5, 162.8, 148.3, 147.2, 146.4, 131.2, 128.6, 128.3, 123.9, 122.7, 102.9, 101.7, 92.0, 84.7, 60.1, 38.9, 29.3, 14.2.

LC-MS: *m/z* 390 $[M+1]^+$.

Anal.Calcd. for $C_{23}H_{19}NO_5$: C, 70.94; H, 4.92; N, 3.60. Found: C, 70.82; H, 4.87; N, 3.68.

Compound 56



Yield: 0.125 g (86%, white solid).

Mp: 58-60 °C.

IR (KBr): 2980, 2203, 1704, 1644, 1616, 1589, 1485, 1447, 1375, 1353, 1255, 1167, 1129, 855, 751 cm^{-1}.

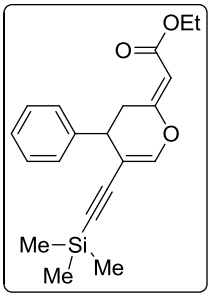
^1H NMR: δ 7.30-7.27 (m, 6H), 7.09 (d, *J* = 7.6 Hz, 1H), 7.04 (s, 1H), 7.03-6.94 (m, 2H), 5.62 (s, 1H), 4.17-4.04 (m, 2H), 3.83-3.78 (m, 1H), 3.75 (t, *J* = 5.4 Hz, 1H), 3.26-3.21 (m, 1H), 1.23 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR: δ 166.6, 163.6, 162.9 (*J* = 244.6 Hz), 145.9, 143.3, 131.2, 130.0 (*J* = 8.0 Hz), 128.3, 128.1, 123.3, 123.0, 114.6 (*J* = 21.8 Hz), 114.1 (*J* = 20.9 Hz), 103.7, 101.2, 91.6, 85.2, 59.9, 38.6, 29.6, 14.2.

LC-MS: *m/z* 363 $[M+1]^+$.

Anal. Calcd. for $C_{23}H_{19}FO_3$: C, 76.23; H, 5.28. Found: C, 76.15; H, 5.32.

Compound 57



Yield: 0.136 g (62%, white solid).

Mp: 66-68 °C.

IR (KBr): 3030, 2959, 2899, 2142, 1709, 1644, 1623, 1452, 1375, 1249, 1145, 1041, 844, 756, 690 cm^{-1}.

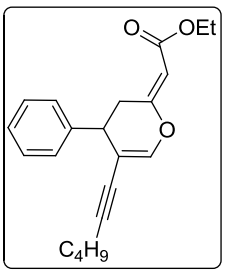
^{1}H NMR: δ 7.35-7.31 (m, 2H), 7.29-7.24 (m, 3H), 6.98 (s, 1H), 5.58 (s, 1H), 4.15-4.03 (m, 2H), 3.78-3.73 (m, 1H), 3.66 (t, *J* = 5.6 Hz, 1H), 3.24-3.19 (m, 1H), 1.23 (t, *J* = 7.2 Hz, 3H), 0.09 (s, 9H).

^{13}C NMR: δ 166.8, 164.2, 146.5, 140.6, 128.4, 128.0, 127.5, 127.0, 104.4, 101.2, 100.8, 96.7, 59.8, 38.5, 29.6, 14.2, -0.17.

LC-MS: *m/z* 341 $[M+1]^{+}$.

Anal. Calcd. for $C_{20}H_{24}O_3Si$: C, 70.55; H, 7.10. Found: C, 70.36; H, 7.21.

Compound 58



Yield: 0.074 g (57%, gummy liquid).

IR (neat): 3030, 2959, 2926, 2866, 1742, 1704, 1644, 1496, 1452, 1370, 1260, 1123, 866, 701 cm^{-1}.

^{1}H NMR: δ 7.32-7.29 (m, 2H), 7.25-7.22 (m, 3H), 6.86 (s, 1H), 5.54 (s, 1H), 4.12-4.02 (m, 2H), 3.77-3.72 (m, 1H), 3.60 (t, *J* = 5.6 Hz, 1H), 3.19-3.14 (m, 1H), 2.19 (t, *J* = 7.2 Hz, 2H), 1.40-1.35 (m, 2H), 1.29-1.24 (m, 2H), 1.21 (t, *J* = 7.2 Hz, 3H), 0.84 (t, *J* = 7.2 Hz, 3H).

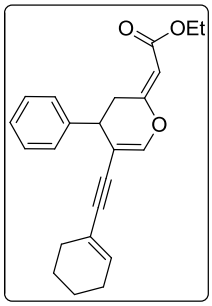
^{13}C NMR: δ 166.8, 164.5, 144.6, 141.0, 128.4, 127.5, 126.9, 104.7, 100.3, 92.3, 76.3,

59.7, 39.0, 30.7, 30.0, 21.8, 19.1, 14.2, 13.6.

LC-MS: *m/z* 325 $[M+1]^+$.

Anal. Calcd. for $C_{21}H_{24}O_3$: C, 77.75; H, 7.46. Found: C, 77.83; H, 7.41.

Compound 59



Yield: 0.093 g (67%, gummy liquid).

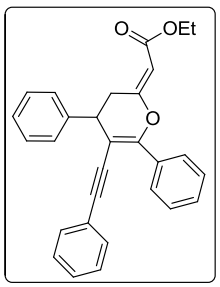
IR (neat): 3063, 3025, 2975, 2932, 2855, 1704, 1649, 1490, 1452, 1375, 1255, 1129, 1036, 734, 696 cm^{-1}.

^1H NMR: δ 7.35-7.31 (m, 2H), 7.27-7.23 (m, 3H), 6.93 (s, 1H), 5.95 (br s, 1H), 5.57 (s, 1H), 4.14-4.05 (m, 2H), 3.81-3.76 (m, 1H), 3.67 (t, *J* = 5.6 Hz, 1H), 3.24-3.19 (m, 1H), 2.07-2.01 (m, 4H), 1.61-1.54 (m, 4H), 1.23 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR: δ 166.8, 164.4, 144.9, 140.8, 134.5, 128.4, 127.5, 126.9, 120.6, 104.7, 100.5, 93.4, 82.8, 59.8, 38.9, 29.9, 29.0, 25.6, 22.2, 21.4, 14.2.

HRMS (ESI) Calcd. for $C_{23}H_{25}O_3$ $[M^+ + H]$: m/z 349.1803. Found: 349.1803.

Compound 60



Yield: 0.141 g (84%, white solid).

Mp: 90-92 °C.

IR (KBr): 2932, 1704, 1638, 1485, 1381, 1271, 1151, 1129, 838, 751, 685 cm^{-1}.

^1H NMR: δ 8.08 (d, *J* = 8.0 Hz, 2H), 7.50-7.44 (m, 3H), 7.37-7.36 (m, 4H), 7.29-7.25 (m, 4H), 7.21-7.19 (m, 2H), 5.72 (s, 1H), 4.20-4.06 (m, 2H), 3.98-

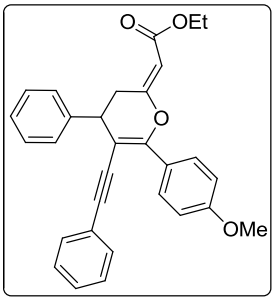
3.92 (m, 2H), 3.36-3.29 (m, 1H), 1.26 (t, J = 7.2 Hz, 3H).

^{13}C NMR: δ 167.0, 165.2, 153.5, 141.2, 133.3, 131.0, 129.5, 128.6, 128.3, 127.9, 127.7, 127.1, 123.5, 100.4, 100.2, 94.8, 88.0, 59.8, 40.8, 30.0, 14.3.

LC-MS: *m/z* 421 $[M+1]^+$.

Anal. Calcd. for $C_{29}H_{24}O_3$: C, 82.83; H, 5.75. Found: C, 82.73; H, 5.71.

Compound 61



Yield: 0.157 g (87%, white solid).

Mp: 78-80 °C.

IR (KBr): 2975, 2904, 2833, 1704, 1644, 1595, 1507, 1381, 1249, 1123, 1019, 827, 740, 685 cm^{-1}.

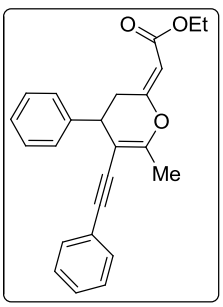
^{1}H NMR: δ 8.08 (d, J = 8.0 Hz, 2H), 7.48-7.41 (m, 3H), 7.36-7.30 (m, 4H), 7.28-7.25 (m, 1H), 7.14 (d, J = 8.4 Hz, 2H), 6.78 (d, J = 8.4 Hz, 2H), 5.71 (s, 1H), 4.18-4.07 (m, 2H), 3.97-3.94 (m, 2H), 3.78 (s, 3H), 3.33-3.27 (m, 1H), 1.24 (t, J = 7.2 Hz, 3H).

^{13}C NMR: δ 167.1, 165.4, 159.4, 152.7, 141.2, 133.4, 132.5, 129.4, 128.5, 127.9, 127.8,127.7, 127.0, 115.7, 113.9, 100.7, 100.0, 94.9, 86.6, 59.8, 55.3, 40.9, 30.1, 14.3.

LC-MS: *m/z* 451 $[M+1]^+$.

Anal. Calcd. for $C_{30}H_{26}O_4$: C, 79.98; H, 5.82. Found: C, 79.85; H, 5.76.

Compound 62



Yield: 0.124 g (85%, white solid).

Mp: 60-62 °C.

IR (KBr): 3030, 2970, 2203, 1699, 1655, 1490, 1436, 1381, 1277, 1233, 1162, 1129, 1047, 838, 751, 696 cm^{-1}.

^1H NMR: δ 7.34-7.27 (m, 5H), 7.25 (br s, 5H), 5.57 (s, 1H), 4.16-4.03 (m, 2H), 3.81-3.76 (m, 1H), 3.73 (t, *J* = 5.6 Hz, 1H), 3.23-3.17 (m, 1H), 2.27 (s, 3H), 1.23 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR: δ 167.0, 165.1, 154.7, 141.5, 131.4, 131.0, 130.8, 128.6, 128.5, 128.2, 127.8, 127.6, 126.9, 123.6, 100.0, 99.3, 93.8, 86.9, 59.8, 39.2, 30.0, 18.4, 14.3.

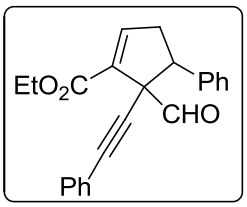
HRMS (ESI) Calcd. for $C_{24}H_{23}O_3$ [M^++H]: *m/z* 359.1647. Found: 359.1647.

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

3.7 Representative procedure for the PPh_3 catalyzed [2+4] cycloaddition reaction of enynals 3a-o with allenoates 8a-d: Synthesis of highly functionalized cyclopentene derivatives 63-80

To a solution of 2-(1-alkynyl)-2-alken-1-als **3a-o** (1.0 mmol) in dry 1,4-dioxane (5 mL) was added PPh_3 (0.1 mmol) followed by alkyl 2,3-butadienoate **8a-d** (1.2 mmol). The vessel was stoppered under nitrogen atmosphere and the contents were stirred for 12 h at rt. The progress of the reaction was monitored by TLC. Later, the solvent was removed under vacuum and crude product was purified by column chromatography by using silica gel with ethyl acetate/ hexane (1:49) mixture as the eluent to afford the corresponding cyclopentenes **63-80**. The minor isomer had a slightly lower R_f value and hence eluted after the major isomer. All the major isomers were obtained in a pure state; the minor isomer was isolated in a pure state in three cases.

Compound 63



Yield: 0.231 g (67%, gummy liquid).

IR (neat): 3057, 3025, 2981, 2197, 1710, 1627, 1490, 1375, 1326, 1255, 1129, 1101, 1030, 767, 690 cm^{-1}.

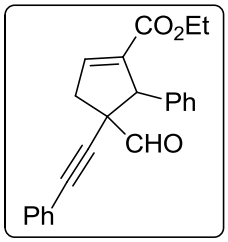
^1H NMR: δ 9.94 (s, 1H), 7.34-7.30 (m, 5H), 7.27-7.21 (m, 3H), 7.18-7.14 (m, 3H), 4.32-4.19 (m, 3H), 3.10-2.93 (m, 2H), 1.33 (t, J = 7.2 Hz, 3H).

^{13}C NMR: δ 198.2, 162.9, 146.5, 138.5, 137.3, 131.6, 129.0, 128.3, 128.1, 127.5, 122.6, 89.9, 85.1, 63.8, 61.1, 51.8, 37.5, 14.2.

LC-MS: *m/z* 345 $[M+1]^+$.

Anal. Calcd. for $C_{23}H_{20}O_3$: C, 80.21; H, 5.85. Found: C, 80.12; H, 5.91.

Compound 63'



Yield: 0.045 g (13%, white solid).

Mp: 92-94 °C.

IR (KBr): 3063, 3030, 2981, 2203, 1715, 1496, 1447, 1375, 1255, 1200, 1096, 762, 701 cm^{-1}.

^1H NMR: δ 9.62 (s, 1H), 7.38-7.30 (m, 3H), 7.28-7.22 (m, 3H), 7.20-7.16 (m, 2H), 6.97-6.95 (m, 3H), 4.50 (s, 1H), 4.13-4.02 (m, 2H), 3.34-3.29 (m, 1H), 2.95-2.91 (m, 1H), 1.15 (t, J = 7.2 Hz, 3H).

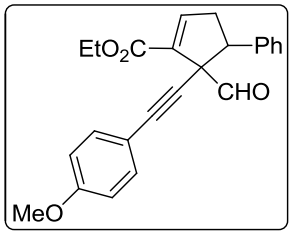
^{13}C NMR: δ 193.3, 163.5, 141.5, 138.3, 137.1, 131.6, 128.6, 128.4, 128.3, 128.1, 127.4, 122.2, 89.5, 85.0, 60.6, 58.5, 54.9, 39.2, 14.0.

LC-MS: *m/z* 345 $[M+1]^+$.

Anal. Calcd. for $C_{23}H_{20}O_3$: C, 80.21; H, 5.85. Found: C, 80.15; H, 5.76.

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

Compound 64



Yield: 0.284 g (76%, gummy liquid).

IR (neat): 2981, 2932, 2838, 2203,1704, 1595, 1512, 1458, 1381, 1260, 1173, 1036, 838, 707 cm^{-1}.

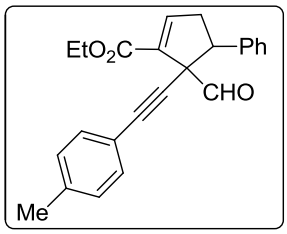
^1H NMR: δ 9.93 (s, 1H), 7.33-7.27 (m, 5H), 7.11 (d, *J* = 8.8 Hz, 3H), 6.76 (d, *J* = 8.6 Hz, 2H), 4.31-4.17 (m, 3H), 3.77 (s, 3H, -OC*H*$_3$), 3.08-2.91 (m, 2H), 1.33 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR: δ 198.5, 162.9, 159.6, 146.3, 138.7, 137.4, 133.1, 129.0, 128.6, 128.1, 127.4, 114.7, 114.1, 113.7, 89.8, 83.6, 63.8, 61.0, 55.2, 51.8, 37.5, 14.2.

LC-MS: *m/z* 375 $[M+1]^+$.

Anal. Calcd. for $C_{24}H_{22}O_4$: C, 76.99; H, 5.92. Found: C, 76.85; H, 5.98.

Compound 65



Yield: 0.205 g (61%, gummy liquid).

IR (neat): 3061, 3030, 2975, 2197, 1704, 1633, 1507, 1463, 1375, 1332, 1260, 1134, 1025, 822, 701 cm^{-1}.

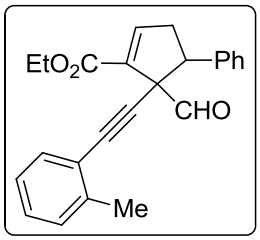
^1H NMR: δ 9.94 (s, 1H), 7.34-7.29 (m, 5H), 7.13-7.12 (m, 1H), 7.08-7.03 (m, 4H), 4.29-4.18 (m, 3H), 3.05-2.96 (m, 2H), 2.31 (s, 3H), 1.33 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR: δ 198.4, 162.9, 146.4, 138.6, 138.4, 137.4, 131.6, 129.0, 128.9, 128.1, 127.5, 119.6, 90.1, 84.4, 63.8, 61.1, 51.8, 37.5, 21.5, 14.3.

LC-MS: *m/z* 359 $[M+1]^+$.

Anal. Calcd. for $C_{24}H_{22}O_3$: C, 80.42; H, 6.19. Found: C, 80.36; H, 6.09.

Compound 66



Yield: 0.250 g (70%, gummy liquid).

IR (neat): 3063, 3030, 2981, 2191, 1709, 1616, 1490, 1457, 1369, 1254, 1030, 761, 695 cm^{-1}.

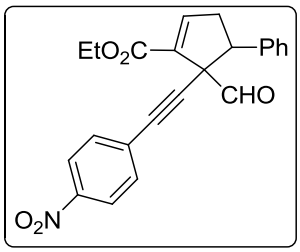
^1H NMR: δ 9.98 (s, 1H), 7.34-7.28 (m, 5H), 7.19-7.10 (m, 4H), 7.06 (t, *J* = 7.6 Hz, 1H), 4.30-4.21 (m, 3H), 3.11-2.94 (m, 2H), 2.16 (s, 3H), 1.33 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR: δ 198.3, 162.9, 146.3, 140.3, 138.6, 137.6, 131.9, 129.3, 128.9, 128.3, 128.2, 127.4, 125.3, 122.4, 88.8, 64.0, 61.1, 51.5, 37.4, 20.4, 14.2.

LC-MS: *m/z* 359 $[M+1]^+$.

Anal. Calcd. for $C_{24}H_{22}O_3$: C, 80.42; H, 6.19. Found: C, 80.31; H, 6.25.

Compound 67



Yield: 0.221 g (57%, gummy liquid).

IR (neat): 3063, 2975, 2931, 2844, 2235, 1731, 1709, 1632, 1594, 1512, 1342, 1265, 1106, 860, 755, 701 cm^{-1}.

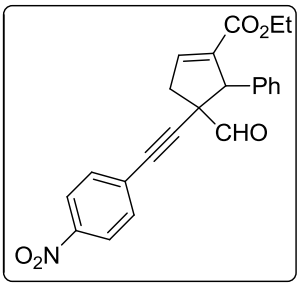
^1H NMR: δ 9.89 (s, 1H), 8.09 (d, *J* = 9.2 Hz, 2H), 7.37-7.24 (m, 7H), 7.19-7.17 (m, 1H), 4.32-4.21 (m, 3H), 3.13-2.98 (m, 2H), 1.33 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR: δ 196.7, 162.7, 147.2, 147.1, 138.3, 136.3, 132.4, 129.4, 128.8, 128.3, 127.7, 123.4, 90.7, 88.1, 64.2, 61.2, 51.4, 37.6, 14.2.

LC-MS: *m/z* 389 $[M]^+$.

Anal. Calcd. for $C_{23}H_{19}NO_5$: C, 70.94; H, 4.92; N, 3.60. Found: C, 70.85; H, 4.87; N, 3.68.

Compound 67'



Yield: 0.043 g (11%, gummy liquid).

IR (neat): 3112, 2975, 2910, 2838, 2230, 1732, 1710, 1638, 1595, 1518, 1353, 1249, 1096, 855, 756, 707 cm^{-1}.

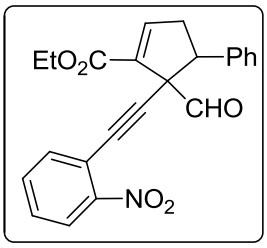
^1H NMR: δ 9.62 (s, 1H), 8.05 (d, *J* = 8.8 Hz, 2H), 7.38-7.30 (m, 3H), 7.24 (d, *J* = 7.2 Hz, 2H), 7.05 (d, *J* = 8.4 Hz, 2H), 6.98 (s, 1H), 4.54 (s, 1H), 4.15-4.02 (m, 2H), 3.37-3.31 (m, 1H), 2.99-2.94 (m, 1H), 1.16 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR: δ 192.6, 163.2, 147.1, 141.1, 138.1, 137.1, 132.3, 129.0, 128.5, 128.4, 127.6, 123.4, 90.6, 87.6, 60.7, 58.5, 55.2, 39.2, 14.0.

LC-MS: *m/z* 389 $[M]^+$.

Anal. Calcd. for $C_{23}H_{19}NO_5$: C, 70.94; H, 4.92; N, 3.60. Found: C, 71.12; H, 4.96; N, 3.71.

Compound 68



Yield: 0.185 g (48%, gummy liquid).

IR (neat): 3058, 3030, 2981, 2236, 1732, 1710, 1627, 1611, 1529, 1348, 1266, 1129, 1107, 1025, 745, 707 cm^{-1}.

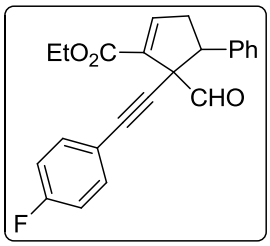
^1H NMR: δ 9.94 (s, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 7.47-7.44 (m, 1H), 7.41-7.37 (m, 1H), 7.32-7.23 (m, 5H), 7.22 (d, *J* = 7.6 Hz, 1H), 7.17 (s, 1H), 4.29-4.19 (m, 3H), 3.16-3.09 (m, 1H), 3.02-2.94 (m, 1H), 1.31 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR: δ 197.3, 162.7, 149.6, 146.9, 138.1, 136.9, 135.0, 132.7, 128.9, 128.8, 128.2, 127.6, 124.5, 117.9, 93.3, 85.2, 64.3, 61.3, 51.7, 37.5, 14.2.

LC-MS: *m/z* 390 $[M+1]^+$.

Anal. Calcd. for $C_{23}H_{19}NO_5$: C, 70.94; H, 4.92; N, 3.60. Found: C, 70.85; H, 4.86; N, 3.72.

Compound 69



Yield: 0.192 g (53%, gummy liquid).

IR (neat): 3063, 3030, 2975, 2849, 2197, 1704, 1633, 1606, 1507, 1381, 1332, 1238, 1129, 1025, 838, 701 cm^{-1}.

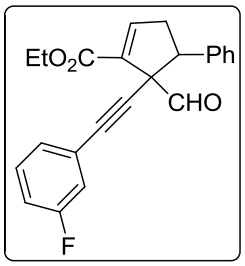
^1H NMR: δ 9.92 (s, 1H), 7.32-7.27 (m, 5H), 7.14-7.11 (m, 3H), 6.92 (t, *J* = 8.4 Hz, 2H), 4.33-4.18 (m, 3H), 3.09-2.93 (m, 2H), 1.32 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR: δ 197.9, 162.9, 162.5 (*J* = 247.9 Hz), 146.5, 138.6, 137.1, 133.5 (*J* = 8.3 Hz), 128.9, 128.1, 127.5, 118.7, 115.4 (*J* = 21.9 Hz), 88.9, 84.8, 63.9, 61.1, 51.6, 37.5, 14.2.

LC-MS: *m/z* 363 $[M+1]^+$.

Anal. Calcd. for $C_{23}H_{19}FO_3$: C, 76.23; H, 5.28. Found: C, 76.32; H, 5.21.

Compound 70



Yield: 0.233 g (61%, gummy liquid).

IR (neat): 3063, 3036, 2981, 2197, 1704, 1606, 1578, 1490, 1370, 1271, 1036, 789, 701, 685 cm^{-1}.

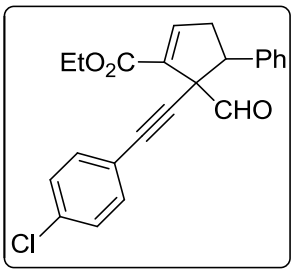
^1H NMR: δ 9.92 (s, 1H), 7.37-7.29 (m, 5H), 7.21-7.14 (m, 2H), 6.99-6.93 (m, 2H), 6.85-6.82 (m, 1H), 4.33-4.19 (m, 3H), 3.10-2.94 (m, 2H), 1.33 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR: δ 197.6, 162.8, 162.2 (*J* = 244.8 Hz), 146.7, 138.5, 137.0, 129.7 (*J* = 8.5 Hz), 128.9, 128.2, 127.6 (*J* = 5.6 Hz), 124.4 (*J* = 9.4 Hz), 118.5 (*J* = 22.7 Hz), 115.7 (*J* = 21.1 Hz), 88.7, 86.2, 63.9, 61.1, 51.6, 37.5, 14.2.

LC-MS: *m/z* 363 $[M+1]^+$.

Anal. Calcd. for $C_{23}H_{19}FO_3$: C, 76.23; H, 5.28. Found: C, 76.31; H, 5.24.

Compound 71



Yield: 0.214 g (57%, gummy liquid).

IR (neat): 3030, 2986, 2931, 2899, 2844, 1720, 1627, 1490, 1375, 1331, 1266, 1123, 1085, 1025, 838, 756, 707 cm^{-1}.

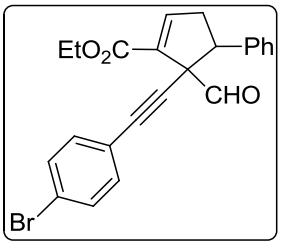
^{1}H NMR: δ 9.91 (s, 1H), 7.36-7.27 (m, 5H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.14-7.13 (m, 1H), 7.07 (d, *J* = 8.4 Hz, 2H), 4.31-4.18 (m, 3H), 3.10-2.94 (m, 2H), 1.32 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR: δ 197.7, 162.8, 146.6, 138.5, 137.0, 134.3, 132.9, 128.9, 128.5, 128.1, 127.5, 121.1, 88.8, 86.1, 63.9, 61.1, 51.6, 37.5, 14.2.

LC-MS: *m/z* 379 $[M+1]^+$.

Anal. Calcd. for $C_{23}H_{19}ClO_3$: C, 72.92; H, 5.06. Found: C, 72.85; H, 5.13.

Compound 72



Yield: 0.197 g (47%, gummy liquid).

IR (neat): 3061, 3030, 2980, 2933, 2200, 1713, 1628, 1581, 1486, 1455, 1394, 1372, 1327, 1257, 1105, 1069, 1031, 825, 700 cm^{-1}.

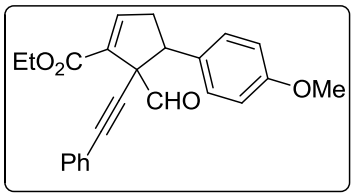
^{1}H NMR: δ 9.90 (s, 1H), 7.37-7.27 (m, 7H), 7.14 (s, 1H), 7.00 (d, *J* = 8.0 Hz, 2H), 4.28-4.18 (m, 3H), 3.09-2.95 (m, 2H), 1.32 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR: δ 197.6, 162.8, 146.7, 138.5, 136.9, 133.1, 131.4, 128.9, 128.2, 127.5, 122.6, 121.6, 88.9, 86.4, 64.0, 61.1, 51.6, 37.5, 14.3.

LC-MS: *m/z* 421 $[M-2]^+$ and 423 $[M]^+$.

Anal. Calcd. for $C_{23}H_{19}BrO_3$: C, 65.26; H, 4.52. Found: C, 65.36; H, 4.48.

Compound 73



Yield: 0.239 (68%, gummy liquid).

IR (neat): 3063, 2981, 2932, 2904, 2833, 2060, 1715, 1611, 1512, 1496, 1441, 1370, 1321, 1244, 1178, 1129, 1036, 827, 756 cm^{-1}.

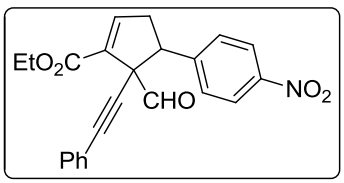
^{1}H NMR: δ 9.91 (s, 1H), 7.27-7.23 (m, 7H), 7.12 (s, 1H), 6.87 (d, *J* = 8.4 Hz, 2H), 4.33-4.12 (m, 2H), 4.13 (t, *J* = 8.8 Hz, 1H), 3.80 (s, 3H), 3.04-2.89 (m, 2H), 1.32 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR: δ 198.3, 162.9, 159.0, 146.5, 137.4, 131.7, 130.4, 130.0, 128.3, 128.1, 122.7, 113.5, 89.8, 85.2, 63.8, 61.0, 55.3, 51.3, 37.8, 14.2.

LC-MS: *m/z* 375 $[M+1]^+$.

Anal. Calcd. for $C_{24}H_{22}O_4$: C, 76.99; H, 5.92. Found: C, 76.85; H, 5.98.

Compound 74



Yield: 0.166 g (40%, gummy liquid).

IR (neat): 3080, 2986, 2849, 2208, 1715, 1600, 1529, 1359, 1260, 1112, 849, 762, 690 cm^{-1}.

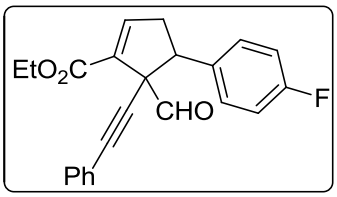
^{1}H NMR: δ 9.96 (s, 1H), 8.18 (d, *J* = 8.8 Hz, 2H), 7.50 (d, *J* = 8.8 Hz, 2H), 7.30-7.21 (m, 3H), 7.15-7.11 (m, 3H), 4.38-4.21 (m, 3H), 3.05-3.02 (m, 2H), 1.33 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR: δ 197.0, 162.6, 147.3, 146.4, 145.6, 137.3, 131.5, 130.0, 128.8, 128.3, 123.2, 122.0, 90.8, 84.1, 63.7, 61.3, 50.2, 37.4, 14.2.

LC-MS: *m/z* 390 $[M+1]^+$.

Anal. Calcd. for $C_{23}H_{19}NO_5$: C, 70.94; H, 4.92; N, 3.60. Found: C, 71.06; H, 4.87; N, 3.68.

Compound 75



Yield: 0.223 g (62%, gummy liquid).

IR (neat): 3063, 2981, 2197, 1715, 1600, 1512, 1222, 1162, 1036, 833, 690 cm^{-1}.

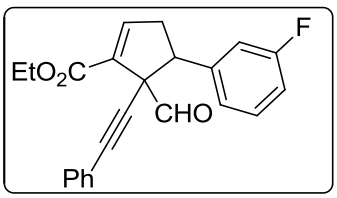
^{1}H NMR: δ 9.92 (s, 1H), 7.32-7.23 (m, 5H), 7.20-7.18 (m, 2H), 7.12-7.11 (m, 1H), 7.02 (t, *J* = 8.4 Hz, 2H), 4.33-4.17 (m, 3H), 2.97 (d, *J* = 8.4 Hz, 2H), 1.32 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR: δ 198.0, 162.8, 162.2 (*J* = 244.3 Hz), 146.2, 137.3, 134.3, 131.6, 130.5 (*J* = 7.9 Hz), 128.5, 128.2, 122.4, 115.4 (*J* = 21.1 Hz), 90.2, 84.8, 63.8, 61.1, 50.7, 37.7, 14.2.

LC-MS: *m/z* 363 $[M+1]^+$.

Anal. Calcd. for $C_{23}H_{19}FO_3$: C, 76.23; H, 5.28. Found: C, 76.15; H, 5.32.

Compound 76



Yield: 0.251g (63%, gummy liquid).

IR (neat): 3068, 2975, 2198, 1704, 1611, 1584, 1485, 1370, 1326, 1244, 1123, 1019, 789, 751 cm^{-1}.

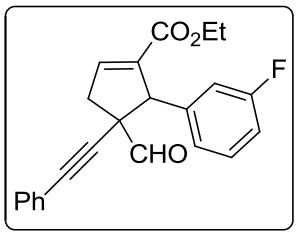
^{1}H NMR: δ 9.94 (s, 1H), 7.31-7.23 (m, 4H), 7.22-7.19 (m, 2H), 7.11-7.08 (m, 3H), 7.02-6.97 (m, 1H), 4.32-4.20 (m, 3H), 3.00-2.97 (m, 2H), 1.33 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR: δ 197.7, 162.7 (J = 243.9 Hz), 146.0, 141.2, 137.3, 131.6, 129.6, 129.5, 128.5, 128.2, 124.8, 122.4, 115.9 (J = 21.5 Hz), 114.4 (J = 20.9 Hz), 90.3, 84.6, 63.7, 61.1, 50.9, 37.4, 14.2.

LC-MS: m/z 363 $[M+1]^+$.

Anal. Calcd. for $C_{23}H_{19}FO_3$: C, 76.23; H, 5.28. Found: C, 76.31; H, 5.23.

Compound 76'



Yield: 0.048 g (12%, white solid).

Mp: 100-102 °C.

IR (neat): 3058, 2981, 2937, 1704, 1627, 1611, 1595, 1490, 1447, 1370, 1337, 1244, 1118, 1101, 1063, 844, 751 cm^{-1}.

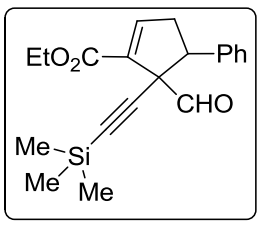
^{1}H NMR: δ 9.60 (s, 1H), 7.35-7.30 (m, 1H), 7.27-7.18 (m, 3H), 7.05-6.94 (m, 6H), 4.52 (s, 1H), 4.15-4.05 (m, 2H), 3.34-3.28 (m, 1H), 2.96-2.91 (m, 1H), 1.17 (t, J = 7.2 Hz, 3H).

^{13}C NMR: δ 192.8, 163.2, 162.9 (J = 243.9 Hz), 141.7, 141.1, 136.9, 131.5, 129.7, 129.6, 128.5, 128.2, 124.4, 122.0, 115.4 (J = 21.6 Hz), 114.3 (J = 20.9 Hz), 89.9, 84.5, 60.7, 58.3, 54.4, 39.4, 14.0.

LC-MS: m/z 363 $[M+1]^+$.

Anal. Calcd. for $C_{23}H_{19}FO_3$: C, 76.23; H, 5.28. Found: C, 76.45; H, 5.13.

Compound 77



Yield: 0.222 g (65%, gummy liquid).

IR (neat): 3036, 2959, 2899, 2844, 2164, 1721, 1627, 1496, 1381, 1321, 1249, 1112, 1036, 849, 756, 707 cm^{-1}.

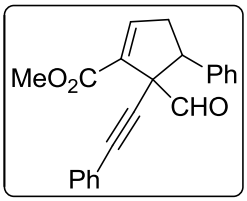
^{1}H NMR: δ 9.83 (s, 1H), 7.29-7.26 (m, 5H), 7.08 (s, 1H), 4.31-4.18 (m, 2H), 4.11 (t, *J* = 8.4 Hz, 1H), 3.02-2.86 (m, 2H), 1.30 (t, *J* = 7.2 Hz, 3H), 0.01 (s, 9H).

^{13}C NMR: δ 198.5, 162.8, 146.4, 138.4, 137.3, 129.0, 127.9, 127.3, 100.9, 95.0, 64.0, 61.0, 51.8, 37.4, 14.2, -0.31.

LC-MS: *m/z* 341 $[M+1]^{+}$.

Anal. Calcd. for $C_{20}H_{24}O_3Si$: C, 70.55; H, 7.10. Found: C, 70.45; H, 7.18.

Compound 78



Yield: 0.202 g (62%, gummy liquid).

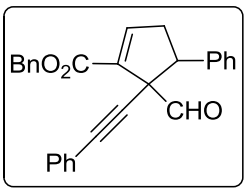
IR (neat): 3058, 3036, 2948, 2849, 2197, 1721, 1622, 1485, 1441, 1332, 1260, 1129, 1025, 756, 701 cm^{-1}.

^{1}H NMR: δ 9.94 (s, 1H), 7.37-7.29 (m, 5H), 7.27-7.22 (m, 3H), 7.18 (d, *J* = 7.6 Hz, 2H), 7.14 (s, 1H), 4.21 (t, *J* = 8.4 Hz, 1H), 3.81 (s, 3H), 3.11-2.94 (m, 2H).

^{13}C NMR: δ 198.2, 163.3, 146.8, 138.4, 137.0, 131.7, 129.0, 128.4, 128.1, 127.5, 122.6, 89.9, 84.9, 63.8, 52.1, 51.8, 37.5.

HRMS (ESI) Calcd. for $C_{22}H_{19}O_3$ $[M^{+}+H]$: *m/z* 331.1334. Found: 331.1331.

Compound 79



Yield: 0.274 g (64%, gummy liquid).

IR (neat): 3063, 3030, 2943, 2203, 1715, 1622, 1600, 1490, 1463, 1332, 1255, 1151, 756, 701 cm^{-1}.

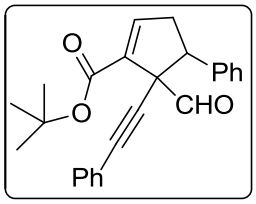
^{1}H NMR: δ 9.95 (s, 1H), 7.43-7.31 (m, 10H), 7.30-7.20 (m, 4H), 7.14-7.12 (m, 2H), 5.35-5.19 (m, 2H), 4.23 (t, *J* = 8.4 Hz, 1H), 3.11-3.04 (m, 2H).

^{13}C NMR: δ 198.1, 162.7, 147.3, 138.5, 136.8, 135.7, 131.7, 129.0, 128.6, 128.4, 128.3, 128.2, 128.1, 127.5, 122.6, 90.1, 85.0, 66.8, 63.9, 51.8, 37.6.

LC-MS: *m/z* 407 $[M+1]^+$.

Anal. Calcd. for $C_{28}H_{22}O_3$: C, 82.74; H, 5.46. Found: C, 82.58; H, 5.41.

Compound 80



Yield: 0.175 g (48%, gummy liquid).

IR (neat): 3062, 3031, 2978, 2932, 2201, 1710, 1634, 1600, 1491, 1455, 1392, 1368, 1273, 1254, 1167, 1030, 847, 757, 692 cm^{-1}.

^1H NMR: δ 8.99 (s, 1H), 7.48-7.47 (m, 2H), 7.35-7.23 (m, 6H), 7.14 (d, *J* = 7.2 Hz, 2H), 6.96 (s, 1H), 4.75 (s, 1H), 3.59-3.54 (m, 1H), 2.82-2.77 (m, 1H), 1.27 (s, 9H).

^{13}C NMR: δ 194.2, 163.0, 141.2, 137.8, 136.7, 131.8, 128.9, 128.6, 128.4, 128.2, 127.8, 122.4, 88.8, 86.6, 80.8, 61.9, 56.2, 38.8, 27.8.

LC-MS: *m/z* 373 $[M+1]^+$.

Anal. Calcd. for $C_{25}H_{24}O_3$: C, 80.62; H, 6.49. Found: C, 80.48; H, 6.41.

3.8. General procedure for the synthesis of benzofurans 81-98 from cyclopentenes 63-80

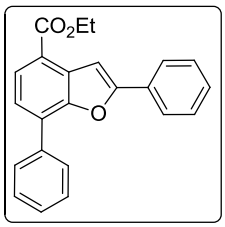
To a dry Schlenk tube, Ph_3PAuCl (5 mol%), AgOTf (5 mol%) and dry 1,4-dioxane solvent (1 mL) were added. The contents were stirred at room temperature for 0.5 h in dark. Later, cyclopentenes **63-80** (0.3 mmol) in 1,4-dioxane (1 mL) was added to the above mixture and the contents stirred at 100 ^oC for 24h. After completion of the reaction, as monitored by TLC, the solvent was evaporated under vacuum. Benzofurans **81-98** were isolated by column chromatography by using EtOAc:hexane mixture (1:99) as the eluent.

3.8.1 General procedure for the one-pot synthesis of benzofurans 81-98 from allenoates 8a-d and enynals 3a-o

To a solution of 2-(1-alkynyl)-2-alken-1-als **3a-o** (0.5 mmol) in dry 1,4-dioxane (3 mL) was added PPh_3 (0.05 mmol) followed by alkyl 2,3-butadienoate **8a-d** (0.6 mmol).

The vessel was stoppered under nitrogen atmosphere and the contents were stirred for 12 h at rt. The progress of the reaction was monitored by TLC. Later, the solvent was removed under vacuum (to remove excess of allenoate). In the meantime, to a dry Schlenk tube, Ph_3PAuCl (5 mol%), AgOTf (5 mol%) and dry 1,4-dioxane (1 mL) were added. The contents were stirred at room temperature for 0.5 h in dark. To this catalytic system was added the above mixture in dioxane (1 mL) and the contents stirred at 100 ^oC for 24h. After completion of the reaction, as monitored by TLC, the solvent was evaporated under vacuum. Benzofuran **81-98** was isolated by column chromatography by using EtOAc:hexane mixture (1:99) as the eluent.

Compound 81



Yield: 0.078 g (76%, white solid).

Mp: 84-86 ^oC.

IR (KBr): 2980, 1726, 1447, 1375, 1282, 1222, 1140, 1030, 811, 756, 685 cm^{-1}.

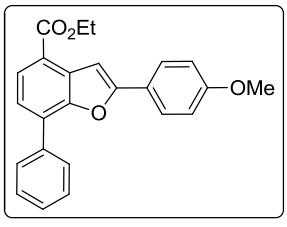
^1H NMR: δ 8.06 (d, *J* = 8.0 Hz, 1H), 7.98 (d, *J* = 7.2 Hz, 2H), 7.93 (d, *J* = 7.2 Hz, 2H), 7.76.(s, 1H), 7.58 (t, *J* = 7.6 Hz, 2H), 7.51-7.46 (m, 4H), 7.40 (t, *J* = 7.2 Hz, 1H), 4.53-4.48 (m, 2H), 1.50 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR: δ 166.5, 157.8, 152.3, 135.7, 130.8, 130.0, 129.4, 129.2, 128.9, 128.8, 128.5, 126.1, 125.4, 123.2, 121.4, 102.7, 60.9, 14.6.

HRMS (ESI): Calcd. for $C_{22}H_{19}O_3$ $[M^+ + H]$: *m/z* 331.1334. Found: 331.1331.

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

Compound 82



Yield: 0.089 g (80%, white solid).

Mp: 68-70 °C.

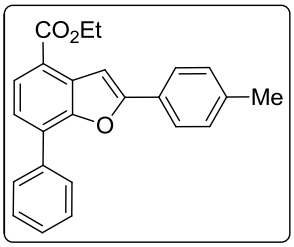
IR (KBr): 2964, 2926, 2833, 1704, 1606, 1501, 1381, 1266, 1178, 1041, 816, 762 cm^{-1}.

^1H NMR: δ 8.04 (d, *J* = 8.4 Hz, 1H), 7.97 (d, *J* = 7.2 Hz, 2H), 7.86 (d, *J* = 8.8 Hz, 2H), 7.61.(s, 1H), 7.57 (t, *J* = 7.6 Hz, 2H), 7.49-7.45 (m, 2H), 7.00 (d, *J* = 8.8 Hz, 2H), 4.52-4.47 (m, 2H), 3.88 (s, 3H), 1.50 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR: δ 166.6, 160.4, 158.0, 152.1, 139.3, 135.8, 131.2, 129.1, 128.9, 128.8, 128.4, 126.9, 126.0, 122.8, 122.7, 121.0, 114.4, 101.1, 60.9, 55.4, 14.5.

HRMS (ESI): Calcd. for $C_{24}H_{21}O_4$ $[M^+ + H]$: *m/z* 373.1440. Found: 373.1441.

Compound 83



Yield: 0.081 g (76%, white solid).

Mp: 70-72 °C.

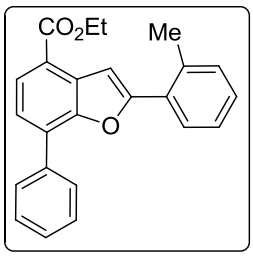
IR (KBr): 2921, 1726, 1441, 1386, 1266, 1145, 1041, 806, 756, 690 cm^{-1}.

^1H NMR: δ 8.05 (d, *J* = 8.0 Hz, 1H), 7.99-7.97 (m, 2H), 7.82 (d, *J* = 8.0 Hz, 2H), 7.70.(s, 1H), 7.60-7.56 (m, 2H), 7.50-7.46 (m, 2H), 7.29-7.27 (m, 2H), 4.53-4.48 (m, 2H), 2.42 (s, 3H), 1.51 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR: δ 166.6, 158.1, 152.1, 139.3, 135.8, 130.9, 129.6, 129.3, 128.9, 128.8, 128.4, 127.2, 126.0, 125.3, 122.9, 121.2, 101.9, 60.9, 21.5, 14.5.

HRMS (ESI): Calcd. for $C_{24}H_{21}O_3$ $[M^+ + H]$: *m/z* 357.1490. Found: 357.1486.

Compound 84



Yield: 0.082 g (77%, white solid).

Mp: 70-72 °C.

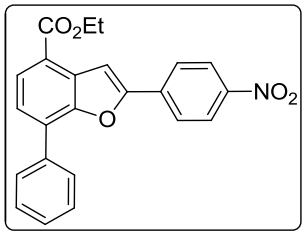
IR (KBr): 2981, 1704, 1375, 1282, 1266, 1216, 1140, 1036, 767, 701 cm^{-1}.

^1H NMR: δ 8.09 (d, *J* = 8.0 Hz, 1H), 7.96 (d, *J* = 7.2 Hz, 2H), 7.89-7.88 (m, 1H), 7.65 (s, 1H), 7.58-7.51 (m, 3H), 7.46 (t, *J* = 7.2 Hz, 1H), 7.33 (br s, 3H), 4.53-4.48 (m, 2H), 2.66 (s, 3H), 1.51 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR: δ 166.5, 157.7, 151.9, 136.2, 135.7, 131.5, 130.6, 129.9, 129.5, 129.4, 129.0, 128.9, 128.8, 128.4, 128.3, 126.2, 126.0, 123.1, 121.4, 106.3, 60.9, 22.2, 14.5.

HRMS (ESI): Calcd. for $C_{24}H_{20}O_3Na$ [M^++Na]: *m/z* 379.1310. Found: 379.1310.

Compound 85



Yield: 0.086 g (74%, yellow solid).

Mp: 142-144 °C.

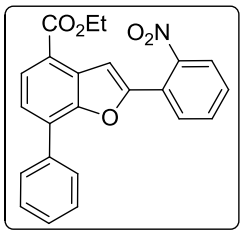
IR (KBr): 2915, 2860, 1704, 1606, 1529, 1343, 1266, 1162, 1036, 860, 816, 745, 685 cm^{-1}.

^1H NMR: δ 8.33 (d, *J* = 8.8 Hz, 2H), 8.10 (d, *J* = 8.0 Hz, 1H), 8.04 (d, *J* = 8.8 Hz, 2H), 7.97.(s, 1H), 7.95-7.93 (m, 2H), 7.62-7.56 (m, 3H), 7.51 (t, *J* = 7.4 Hz, 1H), 4.54-4.49 (m, 2H), 1.51 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR: δ 166.1, 154.9, 152.8, 147.6, 135.7, 135.3, 130.0, 129.9, 129.0, 128.8_3, 128.7_6, 126.7, 125.7, 124.6, 124.6, 124.4, 122.1, 106.3, 61.1, 14.5.

HRMS (ESI): Calcd. for $C_{23}H_{18}NO_5$ [M^++H]: *m/z* 388.1185. Found: 388.1187.

Compound 86



Yield: 0.084 g (72%, yellow solid).

Mp: 100-102 °C.

IR (KBr): 2937, 1715, 1529, 1474, 1381, 1364, 1282, 1260, 1216, 1151, 1036, 981, 838, 745 cm^{-1}.

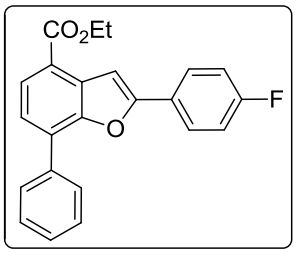
^1H NMR: δ 8.10 (d, *J* = 8.0 Hz, 1H), 7.87-7.83 (m, 4H), 7.76 (s, 1H), 7.67 (t, *J* = 7.6 Hz, 1H), 7.57-7.53 (m, 4H), 7.45 (t, *J* = 7.4 Hz, 1H), 4.52-4.47 (m, 2H), 1.50 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR: δ 166.2, 152.9, 152.7, 148.5, 135.1, 132.2, 130.3, 130.1, 129.9, 129.7, 128.8, 128.7, 126.5, 124.3, 124.1, 124.0, 122.1, 107.1, 61.1, 14.5.

HRMS (ESI): Calcd. for $C_{23}H_{17}NO_5Na$ [M^++Na] *m/z* 410.1005. Found: 410.1007.

This compound was crystallized from chloroform/hexane (2:1) mixture at room temperature. X-ray structure was determined for this sample.

Compound 87



Yield: 0.087 g (81%, white solid).

Mp: 64-66 °C.

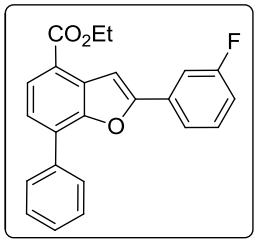
IR (KBr): 2986, 1709, 1610, 1507, 1370, 1293, 1266, 1227, 1162, 1036, 910, 816, 751 cm^{-1}.

^1H NMR: δ 8.06 (d, *J* = 8.0 Hz, 1H), 7.96-7.94 (m, 2H), 7.91-7.88 (m, 2H), 7.69 .(s, 1H), 7.58 (t, *J* = 7.4 Hz, 2H), 7.50-7.46 (m, 2H), 7.17 (d, *J* = 8.6 Hz, 2H), 4.53-4.47 (m, 2H), 1.50 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR: δ 166.4, 163.2 (*J* = 248.4 Hz), 156.9, 152.2, 135.7, 130.7, 129.4, 128.5, 127.2 (*J* = 8.2 Hz), 126.2 (*J* = 13.2 Hz), 123.2, 121.4, 116.0 (*J* = 21.9 Hz), 102.4, 60.9, 14.5.

HRMS (ESI): Calcd. for $C_{23}H_{18}FO_3$ [M^++H]: *m/z* 361.1240. Found: 361.1242.

Compound 88



Yield: 0.091 g (84%, white solid).

Mp: 106-108 °C.

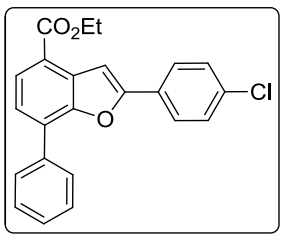
IR (KBr): 2959, 1721, 1611, 1480, 1375, 1277, 1222, 1140, 1030, 849, 762 cm^{-1}.

^1H NMR: δ 8.07 (d, *J* = 8.0 Hz, 1H), 7.95 (d, *J* = 7.2 Hz, 2H), 7.78 .(s, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.61-7.57 (m, 3H), 7.53-7.49 (m, 2H), 7.47-7.41 (m, 1H), 7.11-7.07 (m, 1H), 4.53-4.48 (m, 2H), 1.51 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR: δ 166.4, 163.1 (*J* = 244.4 Hz), 156.3, 152.3, 135.6, 132.0 (*J* = 8.2 Hz), 130.6, 130.5, 130.4, 129.6, 128.9, 128.6, 126.3, 123.7, 121.6, 121.0, 116.0 (*J* = 21.2 Hz), 112.2 (*J* = 23.4 Hz), 103.7, 61.0, 14.5.

HRMS (ESI): Calcd. for $C_{23}H_{18}FO_3$ [M^++H]: *m/z* 361.1240. Found: 361.1237.

Compound 89



Yield: 0.097 g (86%, white solid).

Mp: 116-118 °C.

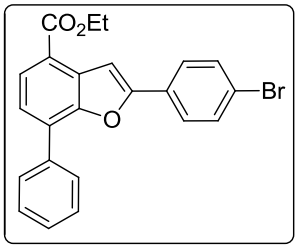
IR (KBr): 2981, 1699, 1479, 1381, 1282, 1282, 1266, 1151, 1096, 1041, 822, 756, 696 cm^{-1}.

^1H NMR: δ 8.05 (d, *J* = 8.0 Hz, 1H), 7.94 (d, *J* = 7.6 Hz, 2H), 7.82 (d, *J* = 8.4 Hz, 2H), 7.73.(s, 1H), 7.58 (t, *J* = 7.4 Hz, 2H), 7.49 (d, *J* = 7.6 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H), 4.53-4.47 (m, 2H), 1.50 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR: δ 166.4, 156.6, 152.3, 135.6, 135.0, 130.6, 129.5, 129.2, 128.9, 128.8, 128.5, 126.5, 126.2, 123.4, 121.5, 103.1, 61.0, 14.5.

HRMS (ESI): Calcd. for $C_{23}H_{18}ClO_3$ [M^++H]: *m/z* 377.0944. Found: 377.0944.

Compound 90



Yield: 0.093 g (74%, white solid).

Mp: 120-122 °C.

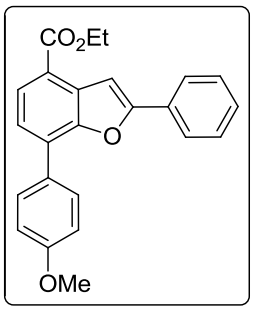
IR (KBr): 2981, 1710, 1589, 1479, 1381, 1282, 1255, 1151, 1041, 811, 756, 701 cm^{-1}.

^1H NMR: δ 8.06 (d, *J* = 8.0 Hz, 1H), 7.94 (d, *J* = 7.6 Hz, 2H), 7.76 (d, *J* = 8.8 Hz, 3H), 7.60-7.56 (m, 4H), 7.49 (t, *J* = 8.0 Hz, 2H), 4.53-4.47 (m, 2H), 1.50 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR: δ 166.4, 156.6, 152.3, 135.6, 132.1, 130.6, 129.5, 128.9, 128.8, 128.5, 126.7, 126.3, 123.5, 123.2, 121.5, 103.2, 61.0, 14.5.

HRMS (ESI): Calcd. for $C_{23}H_{18}BrO_3$ $[M^+ + H]$ and $[M^+ + H + 2]$: *m/z* 421.0438, 423.0439. Found: 421.0440, 423.0422.

Compound 91



Yield: 0.087 g (78%, white solid).

Mp: 74-76 °C.

IR (KBr): 3057, 2926, 2833, 1704, 1605, 1512, 1446, 1369, 1282, 1254, 1156, 1029, 805, 734 cm^{-1}.

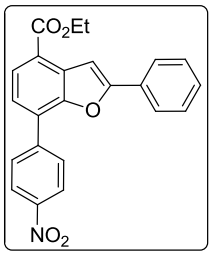
^1H NMR: δ 8.04 (d, *J* = 8.0 Hz, 1H), 7.94 (t, *J* = 7.2 Hz, 4H), 7.61.(s, 1H), 7.50-7.45 (m, 3H), 7.41-7.40 (m, 1H), 7.11 (d, *J* = 8.8 Hz, 2H), 4.52-4.47 (m, 2H), 3.92 (s, 3H), 1.50 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR: δ 166.6, 159.9, 157.7, 152.1, 130.7, 130.1, 129.7, 129.1, 128.9, 128.1, 126.2, 125.3, 122.6, 120.8, 114.3, 102.7, 60.8, 55.4, 14.5.

LC-MS: *m/z* 373 $[M+1]^+$.

Anal. Calcd. for $C_{24}H_{20}O_4$: C, 77.40; H, 5.41. Found: C, 77.26; H, 5.48.

Compound 92



Yield: 0.079 g (68%, yellow solid).

Mp: 148-150 °C.

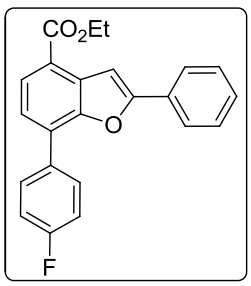
IR (KBr): 2920, 1715, 1594, 1583, 1512, 1375, 1353, 1260, 1145, 1040, 860, 816, 745 cm^{-1}.

^{1}H NMR: δ 8.44 (d, *J* = 8.4 Hz, 2H), 8.15-8.08 (m, 3H), 7.91 (d, *J* = 7.6 Hz, 2H), 7.77 (s, 1H), 7.53-7.43 (m, 4H), 4.55-4.49 (m, 2H), 1.52 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR: δ 166.1, 158.2, 152.2, 147.6, 142.2, 131.1, 129.6, 129.5, 129.0, 126.7, 126.2, 125.4, 124.0, 123.2, 123.0, 102.7, 61.2, 14.5.

HRMS (ESI): Calcd. for $C_{23}H_{18}NO_5$ $[M^+ + H]$: *m/z* 388.1185. Found: 388.1181.

Compound 93



Yield: 0.091 g (84%, White solid).

Mp: 100-102 °C.

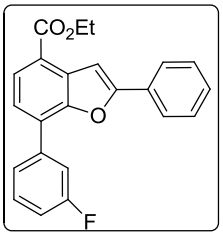
IR (KBr): 2975, 1710, 1600, 1529, 1375, 1288, 1216, 1140, 1036, 921, 816, 756, 685 cm^{-1}.

^{1}H NMR: δ 8.05 (d, *J* = 8.0 Hz, 1H), 7.97-7.90 (m, 4H), 7.75 (s, 1H), 7.50-7.39 (m, 4H), 7.29 (s, 1H), 7.25 (s, 1H), 4.53-4.48 (m, 2H), 1.51 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR: δ 166.4, 162.9 (*J* = 247.0 Hz), 157.8, 152.1, 131.7, 130.8, 130.6 (*J* = 8.0 Hz), 129.9, 129.2, 128.9, 128.3, 126.1, 125.3, 122.9, 121.5, 115.8 (*J* = 21.3 Hz), 102.7, 60.9, 14.5.

HRMS (ESI): Calcd. for $C_{23}H_{17}FO_3Na$ [M^++Na]: *m/z* 383.1060. Found: 383.1060.

Compound 94



Yield: 0.092 g (85%, white solid).

Mp: 58-60 °C.

IR (KBr): 2981, 1715, 1605, 1474, 1441, 1375, 1282, 1195, 1134, 1030, 849, 795, 690 cm^{-1}.

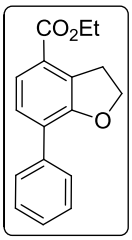
^{1}H NMR: δ 8.08 (d, *J* = 8.0 Hz, 1H), 7.94 (d, *J* = 7.6 Hz, 2H), 7.77-7.72 (m, 3H), 7.58-7.49 (m, 4H) 7.43 (t, *J* = 7.4 Hz, 1H), 7.22-7.17 (m, 1H), 4.55-4.50 (m, 2H), 1.53 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR: δ 166.3, 163.0 (*J* = 244.1 Hz), 157.9, 152.1, 137.8 (*J* = 8.1 Hz), 130.9, 130.2 (*J* = 8.2 Hz), 129.8, 129.3, 128.9, 128.0, 126.1, 125.4, 124.5 (*J* = 2.8 Hz), 123.0, 122.0, 115.8 (*J* = 22.5 Hz), 115.3 (*J* = 20.9 Hz), 102.7, 61.0, 14.5.

LC/MS: *m/z* 361 $[M+1]^+$.

Anal. Calcd. for $C_{23}H_{17}FO_3$: C, 76.65; H, 4.75. Found: C, 76.53; H, 4.71.

Compound 95



Yield: 0.072 g (89%, gummy liquid).

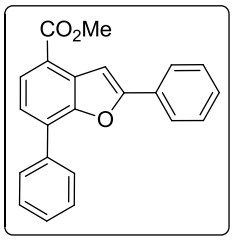
IR (Neat): 2975, 2860, 1710, 1595, 1507, 1403, 1277, 1211, 1134, 1030, 975, 756, 696 cm^{-1}.

^1H NMR: δ 7.73 (d, *J* = 8.4 Hz, 2H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.38-7.35 (m, 2H), 4.67 (t, *J* = 8.8 Hz, 2H), 4.42-4.36 (m, 2H), 3.62 (t, *J* = 8.8 Hz, 2H), 1.42 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR: δ 166.4, 157.8, 152.8, 146.6, 136.5, 130.6, 128.5, 127.9, 127.8, 127.3, 126.0, 122.3, 71.6, 60.8, 31.2, 14.4.

HRMS (ESI): Calcd. for $C_{17}H_{17}O_3$ [M^++H]: *m/z* 269.1177. Found: 269.1178.

Compound 96



Yield: 0.082 g (83%, white solid).

Mp: 118-120 °C.

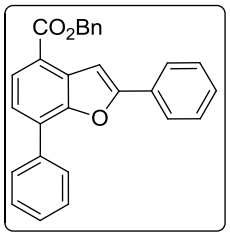
IR (KBr): 2964, 1715, 1606, 1430, 1375, 1288, 1140, 904, 816, 756, 685 cm^{-1}.

^1H NMR: δ 8.05 (d, *J* = 8.0 Hz, 1H), 7.98 (d, *J* = 7.2 Hz, 2H), 7.93 (d, *J* = 7.6 Hz, 1H), 7.74 (s, 1H), 7.58 (t, *J* = 7.6 Hz, 2H), 7.48 (t, *J* = 8.6 Hz, 4H), 7.40 (t, *J* = 7.2 Hz, 2H), 4.04 (s, 3H).

^{13}C NMR: δ 167.0, 157.9, 152.2, 135.7, 130.8, 130.0, 129.5, 129.2, 128.9, 128.8, 128.5, 126.2, 125.4, 123.2, 121.1, 102.7, 52.0.

HRMS (ESI): Calcd. for $C_{22}H_{17}O_3$ [M^++H]: *m/z* 329.1177. Found: 329.1175.

Compound 97



Yield: 0.097 g (80%, white solid).

Mp: 118-120 °C.

IR (KBr): 3052, 1699, 1578, 1447, 1381, 1260, 1156, 1041, 762, 734 cm^{-1}.

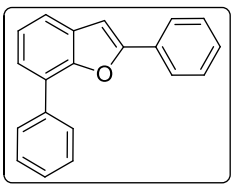
^{1}H NMR: δ 8.10 (d, *J* = 8.0 Hz, 1H), 7.97 (d, *J* = 6.8 Hz, 2H), 7.89 (d, *J* = 7.2 Hz, 2H), 7.75 (s, 1H), 7.58-7.39 (m, 12H), 5.50 (s, 2H).

^{13}C NMR: δ 166.2, 157.9, 152.3, 136.3, 135.7, 131.0, 129.9, 129.6, 129.2, 128.9_1, 128.8_7, 128.8, 128.7, 128.5, 128.3, 128.2, 126.3, 125.4, 123.2, 121.0, 102.7, 66.7.

LC/MS *m/z* 405 $[M+1]^+$.

Anal. Calcd. for $C_{28}H_{20}O_3$: C, 83.15; H, 4.98. Found: C, 83.06; H, 4.91.

Compound 98



Yield: 0.050 g (62%, gummy liquid).

IR (Neat): 3063, 3030, 2921, 2849, 1737, 1688, 1600, 1474, 1408, 1266, 1216, 1162, 904, 811 cm^{-1}.

^{1}H NMR: δ 7.97 (d, *J* = 7.2 Hz, 2H), 7.88 (d, *J* = 7.2 Hz, 2H), 7.59-7.54 (m, 3H), 7.46 (t, *J* = 7.6 Hz, 4H), 7.38-7.31 (m, 2H), 7.11 (s, 1H).

^{13}C NMR: δ 156.0, 152.0, 136.6, 130.4, 130.0, 128.8, 128.7, 128.6, 127.6, 125.3, 125.0, 123.9, 123.6, 120.1, 101.5.

LC/MS *m/z* 271 $[M+1]^+$.

Anal. Calcd. for $C_{20}H_{14}O$: C, 88.86; H, 5.22. Found: C, 88.75; H, 5.27.

HRMS (ESI): Calcd. for $C_{20}H_{15}O$ $[M^+ + H]$: *m/z* 271.1123. Found: 271.1109.

3.9 X-ray crystallography

A suitable crystal was mounted on a glass fiber (for **9**, **44**, **52**, **62**, **63'**, **81** and **86**) 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). Structures were solved and refined using standard methods.[77] 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 11-12.

Table 11. Crystal data for compounds **9**, **44**, **52**, and **62**[a]

Compound	**9**	**44**	**52**	**62**
Emp. formula	$C_{30}H_{23}N_3O$	$C_{31}H_{25}N_3O_2$	$C_{23}H_{19}ClO_3$	$C_{24}H_{22}O_3$
Formula weight	441.51	471.54	378.83	358.42
Crystal system	Monoclinic	Monoclinic	Triclinic	Monoclinic
Space group	*P*2(1)/n	*P*2(1)/n	*P*-1	*P*2(1)/n
a /Å	10.3959(14)	7.5985(7)	8.2508(4)	15.467(3)
b /Å	20.556(3)	10.1256(8)	11.0623(5)	5.7705(10)
c /Å	11.7549(16)	34.045(3)	11.3405(5)	22.341(5)
α/deg	90	90	103.306(4)	90
β/deg	109.824(2)	94.613(3)	95.478(4)	99.10(2)
γ/deg	90	90	100.900(4)	90
V /Å^3	2363.2(6)	2610.9(4)	978.61(8)	1968.9(7)
Z	4	4	2	4
D_{calc} /g cm^{-3}]	1.241	1.200	1.286	1.209
μ /mm^{-1}	0.076	0.076	1.887	0.079
F(000)	928	992	396	760
Data/ restraints/ parameters	4210/0/315	4470/0/326	3469/0/247	4472/0/246
S	0.946	1.162	1.067	1.024
R1 [I>2σ(I)]	0.0466	0.1012	0.0648	0.0701
wR2 [all data]	0.1397	0.3112	0.2040	0.1746
Max./min. residual electron dens. [eÅ^{-3}]	0.148/-0.207	0.430/-0.463	0.731/-0.460	0.159/-0.158

[a]R1 = Σ||Fo| - |Fc||/Σ|Fo| and wR2 = [Σw(Fo^2-Fc^2)^2/ΣwFo^4]$^{0.5}$

Table 12 Crystal data for compounds **63'**, **81**, and **86** [a]

Compound	**63'**	**81**	**86**
Emp. formula	$C_{23}H_{20}O_3$	$C_{23}H_{18}O_3$	$C_{23}H_{17}NO_5$
Formula weight	344.39	342.37	387.38
Crystal system	Monoclinic	Orthorhombic	Monoclinic
Space group	*P*2(1)/n	*P*ca2$_1$	*C*2/c
a /Å	11.8106(11)	12.3414(4)	15.4744(3)
b /Å	8.1876(9)	20.8549(6)	16.1876(3)
c /Å	19.816(3)	6.9482(2)	15.6267(3)
α/deg	90	90	90
β/deg	104.297(11)	90	100.3353(18)
γ/deg	90	90	90
V /Å^3	1856.9(4)	1788.32(10)	3850.85(13)
Z	4	4	8
D_{calc} /g cm^{-3}]	1.232	1.272	1.336
μ /mm^{-1}	0.081	0.669	0.784
F(000)	728	720	1616
Data/ restraints/ parameters	3263/0/240	2117/0/236	3692/0/263
S	0.963	1.075	1.146
R1 [I>2σ(I)]	0.0599	0.0411	0.0666
wR2 [all data]	0.1865	0.1049	0.1592
Max./min. residual electron dens. [eÅ^{-3}]	0.282/-0.172	0.113/-0.207	0.495/-0.693

[a] $R1 = \Sigma||Fo| - |Fc||/\Sigma|Fo|$ and $wR2 = [\Sigma w(Fo^2-Fc^2)^2/\Sigma wFo^4]^{0.5}$

References

1. (a) Bartlett, N. *Gold Bulletin* **1998**, *31*, 22. (b) Schwarz, H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4442. (c) Pyykkö, P. *Angew. Chem., Int. Ed*. **2004**, *43*, 4412. (d) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395. (e) Leyva-Pérez, A.; Corma, A. *Angew. Chem., Int. Ed*. **2012**, *51*, 614.
2. (a) Hoffmann-Röder, A.; Krause, N. *Org. Biomol. Chem.* **2005**, *3*, 387. (b) Hashmi, A. S. K.; Hutchings, G. J. *Angew. Chem., Int. Ed*. **2006**, *45*, 7896. (c) Schmidbaur, H.; Schier, A. *Organometallics* **2010**, *29*, 2. (d) Corma, A.; Leyva-Pérez, A.; Sabater, M. J. *Chem. Rev*. **2011**, *111*, 1657. (e) Bandini, M. *Chem. Soc. Rev.* **2011**, *40*, 1358. (f) Boorman, T. C.; Larrosa, I. *Chem. Soc. Rev.* **2011**, *40*, 1910. (g) Rappoport, Z.; Marek, I.; Liebman, J. F. The Chemistry of Organogold Compounds 2, John Wiley & Sons, **2015**; (h) Zheng, Z.; Wang, Z.; Wang, Y.; Zhang, L. *Chem. Soc. Rev.* DOI: 10.1039/c5cs00887e.
3. (a) Qiana, D.; Zhang, J. *Chem. Soc. Rev.* **2015**, *44*, 677. (b) Ma, J.; Zhang, L.; Zhu, S. *Curr. Org. Chem*. **2016**, *20*, 102.
4. (a) Norman, R. O. C.; Parr, W. J. E.; Thomas, C. B. *J. Chem. Soc., Perkin Trans. I* **1976**, 811. (b) Norman, R. O. C.; Parr, W. J. E.; Thomas, C. B. *J. Chem. Soc. Perkin Trans. I* **1976**, 1983.
5. Ito, Y.; Sawamura M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405.
6. (a) Teles, J. H.; Brode, S.; Chabanas, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 1415. (b) Mizushima, E.; Sato, K.; Hayashi, T.; Tanaka, M. *Angew. Chem., Int. Ed*. **2002**, *41*, 4563.
7. (a) Wang, D.; Cai, R.; Sharma, S.; Jirak, J.; Thummanapelli, S. K.; Akhmedov, N. G.; Zhang, H.; Liu, X.; Petersen, J. L.; Shi, X. *J. Am. Chem. Soc*. **2012**, *134*, 9012. (b) Jia, M.; Bandini, M. *ACS Catal*. **2015**, *5*, 1638. (c) Ranieri, B.; Escofeta, I.; Echavarren, A. M. *Org. Biomol. Chem*. **2015**, *13*, 7103. (d) Lu, Z.; Han, J.; Hammond G. B.; Xu, B. *Org. Lett*. **2015**, *17*, 4534.
8. (a) Ma, S.; Yu, S.; Gu, *Z. Angew. Chem., Int. Ed.* **2006**, *45*, 200. (b) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266. (c) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326. (d) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395. (e) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239. (f) Krause, N.; Winter, C. *Chem. Rev*. **2011**, *111*, 1994. (g) *Modern Gold Catalyzed Synthesis* (Eds.: Hashmi, A. S. K.; Toste, F. D., Wiley-VCH, Weinheim, **2012.** (h) Garayalde, D.; Nevado, C. *ACS Catal*. **2012**, *2*, 1462. (i) Gulevich, A. V.; Dudnik, A. S.; Chernyak, N.; Gevorgyan, V. *Chem. Rev*. **2013**, *113*, 3084. (j) Zhang, D.-H.; Tang, X.-Y.; Shi, M. *Acc. Chem. Res.* **2014**, *47*, 913. (k) Hashmi, A. S. K. *Chem. Rev*. **2014**, *47*, 864. (l) Takale, B. S.; Bao, M.; Yamamoto, Y. *Org. Biomol. Chem.* **2014**, *12*, 2005. (m) Zhang, Y.; Luo, T.; Yang, Z. *Nat. Prod. Rep*. **2014**, *31*, 489. (n) Obradors, C.; Echavarren, A. M. *Acc. Chem. Res.* **2014**, *47*, 902. (o) Dorel, R.; Echavarren, A. M. *Chem. Rev*. **2015**, *115*, 9028. (p) Dorel, R.; Echavarren, A. M. *J. Org. Chem.* **2015**, *80*, 7321.
9. (a) Patil, N. T.; Yamamoto, Y. *ARKIVOC* **2007**, (**v**), *6*. (b) Qian, D.; Zhang, J. *Chem. Rec.* **2014**, *14*, 280.
10. (a) Yao, T.; Zhang, X.; Larock, R. C. *J. Am. Chem. Soc*. **2004**, *126*, 11164. (b) Yao, T.; Zhang, X.; Larock, R. C. *J. Org. Chem*. **2005**, *70*, 7679.
11. Liu, X.; Pan, Z.; Shu, X.; Duan, X.; Liang, Y. *Synlett* **2006**, 1962.

12. (a) Liu, F.; Yu, Y.; Zhang, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 5505. (b) Liu, F.; Qian, D.; Li, L.; Zhao, X.; Zhang, J. *Angew. Chem., Int. Ed*. **2010**, *49*, 6669. (c) Chen, M.; Zhang, Z.-M.; Yu, Z.; Qiu, H.; Ma, B.; Wu, H.-H.; Zhang, J. *ACS Catal*. **2015**, *5*, 7488.
13. Gao, H.; Zhao, X.; Yu, Y.; Zhang, J. *Chem. –Eur. J.* **2010**, *16*, 456.
14. Gao, H.; Wu, X.; Zhang, J. *Chem. Commun*. **2010**, *46*, 8764.
15. Gao, H.; Wu, X.; Zhang. J. *Chem. –Eur. J.* **2011**, *17*, 2838.
16. He, T.; Gao, P.; Qiu, Y.-F.; Yan, X.-B.; Liu, X.-Y.; Liang, Y.-M. *RSC Adv*. **2013**, *3*, 19913.
17. Xie, X.; Du, X.; Chen, Y.; Liu, Y. *J. Org. Chem*., **2011**, *76*, 9175.
18. Zhou, G.; Zhang. J. *Chem. Commun.* **2010**, *46*, 6593.
19. Zhou, L.; Zhang, M.; Li, W.; Zhang, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 6542.
20. Wang, Y.; Zhang, P.; Qian, D.; Zhang, J. *Angew. Chem., Int. Ed.* **2015**, *54*, 14849.
21. Heffernan, S. J.; Tellam, J. P.; Queru, M. E.; Silvanus, A. C.; Benito, D.; Mahon, M. F.; Hennessy, A. J.; Andrews, B. I.; Carbery, D. R. *Adv. Synth. Catal.* **2013**, *355*, 1149.
22. Krafft, M. E.; Vidhani, D. V.; Crana, J. W.; Manoharan, M. *Chem. Commun*. **2011**, *47*, 6707.
23. Wang, T.; Zhang, J. *Dalton Trans.* **2010**, *39*, 4270.
24. Ma, J.; Jiang, H.; Zhu, S. *Org. Lett.* **2014**, *16*, 4472.
25. (a) Zimmer, R.; Reissig, H.-U. *Chem. Soc. Rev.* **2014**, *43*, 2888. (b) Lopez, F.; Mascarenas, J. *Chem. Soc. Rev.* **2014**, *43*, 2904. (c) Caneque, T.; Truscott, F. M.; Rodriguez, R.; Maestriab, G.; Malacria, M. *Chem. Soc. Rev.* **2014**, *43*, 2916. (d) Kitagaki, S.; Inagaki, F.; Mukai, C. *Chem. Soc. Rev.* **2014**, *43*, 2956. (e) Le Bras J.; Muzart, J. *Chem. Soc. Rev.* **2014**, *43*, 3003
26. (a) Bhuvan Kumar, N. N.; Nagarjuna Reddy, M.; Kumara Swamy, K. C. *J. Org. Chem*. **2009**, *74*, 5395. (b) Phani Pavan, M.; Kumara Swamy, K. C. *Synlett*. **2011**, 1288. (c) Srinivas, V.; Balaraman, E.; Sajna, K. V.; Kumara Swamy, K. C. *Eur. J. Org. Chem*. **2011**, 4222. (d) Sajna, K. V.; Kumara Swamy, K. C. *J. Org. Chem.* **2012**, *77*, 5345. (e) Rama Suresh, R.; Kumara Swamy, K. C. *J. Org. Chem.* **2012**, *77* 6959. (f) Siva Kumari, A. L.; Srinivas, V.; Kumara Swamy, K. C. *J. Chem. Sci.* **2013**, *125*, 1405. (g) Anitha, M.; Gangadhararao, G; Kumara Swamy, K. C. *Org. Biomol. Chem.* **2016**, *14*, 3591. (h) Koppanathi N.; Kumara Swamy, K. C. *Org. Biomol. Chem.* **2016**, *14*, 5079.
27. (a) Brasholz, M.; Reissig, H.-U.; Zimmer, R. *Acc. Chem. Res*. **2009**, *42*, 45. (b) Xu, D.; Drahl, M. A.; Williams, L. J. *Beilstein J. Org. Chem.* **2011,** *7*, 937. (c) Yu, S.; Ma, S. *Angew. Chem., Int. Ed*. **2012**, *51*, 3074. (d) Hoffmann-Roder, A.; Krause, N. *Angew. Chem., Int. Ed*. **2004**, *43*, 1196. (e) Rivera-Fuentes, P.; Diederich, F. *Angew. Chem., Int. Ed*. **2012**, *51*, 2818.
28. (a) Xia, Y.; Liang, Y.; Chen, Y.; Wang, M.; Jiao, L.; Huang, F.; Liu, S. *J. Am. Chem. Soc*. **2007**, *129*, 3470. (b) Liang, Y.; Liu, S.; Xia, Y.; Li, Y.; Yu, Z.-X. *Chem. –Eur. J.* **2008**, *14*, 4361. (c) Mercier, E.; Fonovic, B.; Henry, C.; Kwon, O.; Dudding, T. *Tetrahedron Lett*. **2007**, *48*, 3617. (d) Huang, G.-T.; Lankau, T.; Yu, C.-H. *Org. Biomol. Chem*. **2014**, *12*, 7297. (e) Huang, G.-T.; Lankau, T.; Yu, C.-H. *J. Org. Chem*. **2014**, *79*, 1700. (f) Wang, Z.; Xu, X.; Kwon, O. *Chem. Soc. Rev*. **2014**, *43*, 2927.
29. Li, C.; Zhang, Q.; Tong, X. *Chem. Commun.* **2010**, *46*, 7828.

30. Li, K.; Hu, J.; Liu, H.; Tong, X. *Chem. Commun*. **2012**, *48*, 2900.
31. Wang, X.; Fang, T.; Tong, X. *Angew. Chem., Int. Ed*. **2011**, *50*, 5361.
32. Chen, X.-Y.; Wen, M.-W.; Ye, S.; Wang, Z.-X. *Org. Lett*. **2011**, *13*, 1138.
33. Chen, X.-Y.; Lin, R.-C.; Ye, S. *Chem. Commun*. **2012**, *48*, 1317.
34. Zhang, X.-C.; Cao, S.-H.; Wei, Y.; Shi, M. *Org. Lett*. **2011**, *13*, 1142.
35. Wang, T.; Chen, X.-Y.; Ye, S. *Tetrahedron Lett.* **2011**, *52*, 5488.
36. Wang, Y.; Yu, Z.-H.; Zheng, H.-F.; Shi, D.-Q. *Org. Biomol. Chem*. **2012**, *10*, 7739.
37. Pei, C.-K.; Wu, L.; Lian, Z.; Shi, M. *Org. Biomol. Chem*. **2012**, *10*, 171.
38. Zhang, C.; Lu, X. *J. Org. Chem*. **1995**, *60*, 2906.
39. (a) Xu, Z.; Lu, X. *Tetrahedron Lett*. **1997**, *38*, 3461. (b) Xu, Z.; Lu, X. *J. Org. Chem.* **1998**, *63*, 5031. (c) Xu, Z.; Lu, X. *Tetrahedron Lett*. **1999**, *40*, 549.
40. Lu, Z.; Zheng, S.; Zhang, X.; Lu, X. *Org. Lett.* **2008**, *10*, 3267.
41. Na, R.; Jing, C.; Xu, Q.; Jiang, H.; Wu, X.; Shi, J.; Zhong, J.; Wang, M.; Benitez, D.; Tkatchouk, E.; Goddard. III, W. A.; Guo, H.; Kwon, O. *J. Am. Chem. Soc.* **2011**, *133*, 13337.
42. Villa, R. A.; Xu, Q.; Kwon, O. *Org. Lett*. **2012**, *14*, 4634.
43. Wang, T.; Ye, S. *Org. Biomol. Chem*. **2011**, *9*, 5260.
44. Zhang, X.-N.; Shi, M. *ACS Catal*. **2013**, *3*, 507.
45. Yang, L.-J.; Wang, S.; Nie, J.; Li, S.; Ma, J.-A. *Org. Lett*. **2013**, *15*, 5214.
46. Yang, L.-J.; Li, S.; Wang, S.; Nie, J.; Ma, J.-A. *J. Org. Chem*. **2014**, *79*, 3547.
47. Gicquel, M.; Gomez, C.; Retailleau, P.; Voituriez, A.; Marinetti, A. *Org. Lett*. **2013**, *15*, 4002.
48. Yu, H.; Zhang, L.; Yang, Z.; Li, Z.; Zhao, Y.; Xiao, Y.; Guo, H. *J. Org. Chem*. **2013**, *78*, 8427.
49. Li, E.; Huang, Y.; Liang, L.; Xie, P. *Org. Lett*. **2013**, *15*, 3138.
50. Zhao, H.; Mengab, X.; Huang, Y. *Chem. Commun.* **2013**, *49*, 10513.
51. Li, E.; Jia, P.; Liang, L.; Huang, Y. *ACS Catal*. **2014**, *4*, 600.
52. Yao, W.; Dou, X.; Lu, Y. *J. Am. Chem. Soc*. **2015**, *137*, 54.
53. Crone, B.; Kirsch, S. F. *Chem. –Eur. J.* **2008**, *14*, 3514.
54. Dudnik, A. S.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2007**, *46*, 5195.
55. Shu, X.-Z.; Liu, X.-Y.; Ji, K.-G.; Xiao, H.-Q.; Liang, Y.-M. *Chem. –Eur. J.* **2008**, *14*, 5282.
56. (a) Li, W.; Li, Y.; Zhang, J. *Chem. –Eur. J.* **2010**, *16*, 6447. (b) Li, W.; Xiao, Y.; Zhang, J. *Adv. Synth. Catal*. **2009**, *351*, 3083.
57. Li, W.; Li, Y.; Zhou, G.; Wu, X.; Zhang, J. *Chem. –Eur. J.* **2012**, *18*, 15113.
58. Hashmi, A. S. K.; Yang, W.; Rominger, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 5762.
59. Umland, K.-D.; Palisse, A.; Haug, T. T.; Kirsch, S. F. *Angew. Chem., Int. Ed*. **2011**, *50*, 9965.
60. Dudnik, A. S.; Xia, Y.; Li, Y.; Gevorgyan, V. *J. Am. Chem. Soc*. **2010**, *132*, 7645.
61. (a) Bowman, W. R.; Bridge, C. F.; Brookes, P.; Cloonan, M. O.; Leach, D. C. *J. Chem. Soc., Perkin Trans. I* **2002**, 58. (b) Shufeng, C.; Jianbo, W. *J. Org. Chem.* **2007**, *72*, 4993.
62. (a) Yao, T.; Zhang, X.; Larock, R.-C. *J. Am. Chem. Soc*. **2004**, *126*, 11164. (b) Kotikalapudi, R.; Kumara Swamy, K.-C. *Tetrahedron Lett*. **2012**, *53*,

3831. (c) He, T.; Gao, P.; Zhao, S.-C.; Shi, Y.-D.; Liu, X.-Y.; Liang, Y.-M. *Adv. Synth. Catal.* **2013**, *355*, 365.

63. (a) Chakraborty, A.; Dey, S.; Sawoo, S.; Adarsh, N. N.; Sarkar, A. *Organometallics* **2010**, *29*, 6619. (b) Khedar, P.; Pericherla, K.; Kumar, A. *Synlett* **2014**, *25*, 515.
64. Rout, L.; Harned, A.-M. *Chem. –Eur. J.* **2009**, *15*, 12926.
65. Selected recent references: (a) Migawa, M. T.; Drach, J. C.; Townsend, L. B. *J. Med. Chem.* **2005**, *48*, 3840. (b) Hunt, J. C. A.; Briggs, E.; Clarke, E. D.; Whittingham, W. G. *Bioorg. Med. Chem. Lett*. **2007**, *17*, 5222. (c) Saravanan, J.; Mohan, S.; Roy, J. J. -*Eur. J. Med. Chem*. **2010**, *45*, 4365. (d) Mueller, R.; Rachwal, S.; Varney, M. A.; Johnson, S. A.; Alisala, K.; Zhong, S.; Li, Y.–X.; Haroldsen, P.; Herbst, T.; Street, L. J. *Bioorg. Med. Chem. Lett*. **2011**, *21*, 7455. (e) Kumar, R.; Singh, A.; Singh, J.; Singh, H.; Roy, R. K.; Chaudhary, A. *Mini-Rev. Med. Chem*. **2014**, *14*, 72. (f) Lauria, A.; Alfio, A.; Bonsignore, R.; Gentile, C.; Martorana, A.; Gennaro, G.; Barone, G.; Terenzi, A.; Almerico, A. M. *Bioorg. Med. Chem. Lett*. **2014**, *24*, 3291.
66. See for example: (a) Kocienskain, P. J.; Ciabatto, D J. *J. Org. Chem*. **1973**, *38*, 3149. (b) Gompper, R.; Schoenafinger, K. *Chem. Ber*. **1979**, *112*, 1514. (c) Ohsawa, A.; Arai, H.; Ohnishi, H.; Igeta, H. *J. Chem. Soc., Chem. Commun.* **1980**, 1182. (d) Ohsawa, A, Arai, H.; Ohnishi, H.; Igeta, H. *J. Chem. Soc., Chem. Commun.* **1981**, 1174. (e) Schmidt, B. F.; Snyder, E. J.; Carroll, R. M.; Farnsworth, D. W.; Michejda, C. J.; Smith, Jr. R. H. *J. Org. Chem*. **1997**, *62*, 8660. (f) Migawa, M. T.; Townsend, L. B. *J. Org. Chem*. **2001**, *66*, 4776. (g) Butler, R. N.; Fahy, A. M.; Fox, A.; Stephens, J. C.; McArdle, P.; Cunningham, D.; Ryder, A. *J. Org. Chem.* **2006**, *71*, 5679. (h) Miura, T.; Yamauchi, M.; Kosaka, A.; Murakami, M. *Angew. Chem., Int. Ed*. **2010**, *49*, 4955. (i) Glinkerman, C. M.; Boger, D. L. *Org. Lett*. **2015**, *17*, 4002 and references cited therein.
67. (a) Tsuge, O.; Kanemasa, S.; Matsuda, K. *Chem. Lett*. **1983**, 1131. (b) Janreddy, D.; Kavala, V.; Kuo, C.–W.; Chen, W.–C.; Ramesh, C.; Kotipalli, T.; Kuo, T.–S.; Chen, M.–L.; He, C.–H.; Yao, C.–F. *Adv. Synth. Catal*. **2013**, *355*, 2918.
68. Gao, H.; Zhang, J. *Chem. –Eur. J.* **2012**, *18*, 2777.
69. For an example of Lewis acid catalyzed [3+2] cycloaddition of alkene with azide, see: Wang, Y.-C.; Xie, Y.-Y.; Qu, H.-E; Wang, H.-S.; Pan, Y.-M.; Huang, F.-P. *J. Org. Chem.* **2014**, *79*, 4463.
70. (a) Zhao, Q.-Y.; Huang, L.; Wei, Y.; Shi, M. *Adv. Synth. Catal*. **2012**, *354*, 1926. (b) Denis, J.-B.; Masson, G.; Retailleau, P.; Zhu, J. *Angew. Chem., Int. Ed*. **2011**, *50*, 5356. (c) Pei, C.-K.; Jiang, Y.; Wei, Y.; Shi, M. *Angew. Chem., Int. Ed*. **2012**, *51*, 11328. (d) Takizawa, S.; Arteaga, F.; Yoshida, Y.; Suzuki, M.; Sasai, H. *Org. Lett*. **2013**, *15*, 4142. (e) Yang, H.-B.; Zhao, Y.-Z.; Sang, R.; Wei, Y.; Shi, M. *Adv. Synth. Catal*. **2014**, *356*, 3799. (f) Wang, F.; Luo, C.; Shen, Y.-Y.; Wang, Z.-D.; Li, X.; Cheng, J.-P. *Org. Lett*. **2015**, *17*, 338.
71. Selected articles: (a) Hashmi, A. S. K. *Gold Bull.* **2003**, *36*, 3. (b) Zhang, J.; Schmalz, H.-G. *Angew. Chem., Int. Ed*. **2006**, *45*, 6704. (c) Furstner, A.; Davies, P. W. *Angew. Chem., Int. Ed*. **2007**, *46*, 3410. (d) Nevado, C. *Chimia* **2010**, *64*, 247. (d) Kotikalapudi, R.; Siva Kumari, A. L.; Kumara Swamy, K. C. *RSC Adv*. **2014**, *4*, 17717.

72. Dudnik, A. S.; Gevorgyan, V. *Angew. Chem*. **2007**, *119*, 5287; *Angew. Chem., Int. Ed*. **2007**, *46,* 5195.
73. Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*, Pergamon, Oxford, **1986**.
74. Shriver, D. F.; Dresdzon, M. A. *The Manipulation of Air Sensitive Compounds*, 2nd Ed, Wiley Interscience, New York, **1986**.
75. Thangavela, V.; Chadhab, A. *Tetrahedron* **2007**, *63*, 4126.
76. Lepage, L.; Lepage, Y. *Synthesis* **1983**, 1018.
77. (a) Sheldrick, G. M. *SADABS, Siemens Area Detector Absorption Correction*, University of Göttingen, Germany, **1996**. (b) Sheldrick, G. M. SHELX-97- *A program for crystal structure solution and refinement*, University of Göttingen, **1997**. (c) Sheldrick, G. M. *SHELXTL NT Crystal Structure Analysis Package*, Bruker AXS, Analytical X-ray System, WI, USA, **1999**, version 5.10.

PART-B

TRANSITION METAL-FREE CYCLIZATIONS OF EPOXY YNAMIDES

INTRODUCTION

Heteroatom-substituted alkynes, in particular ynamines and ynamides, are emerging as highly useful and versatile building blocks for the synthesis of numerous heterocycles.[1] The synthetic utility of ynamines is because of their predictable regioselectivity and high reactivity,[1a, 2] despite the hydrolytic sensitivity hampering the development of their chemistry. Hence ynamides were introduced as alternative precursors to ynamines. In the year 1972, Viehe and co-workers synthesized the first ynamide by the elimination of HCl from the corresponding α-chloro enamide.[3] After this report, other functionalized ynamides were explored for numerous organic transformations due to their relatively higher stability.[4] Due to the strong polarization of the triple bond by the directly attached electron donating nitrogen atom and the better coordination of the metal catalyst with the alkyne moiety, these compounds are versatile reactants (Fig. 1).

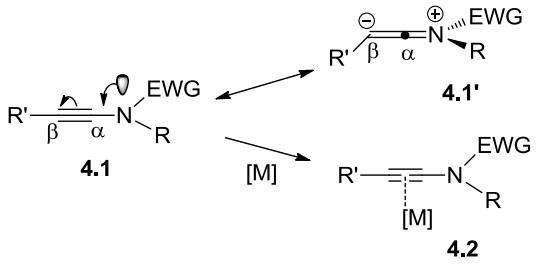
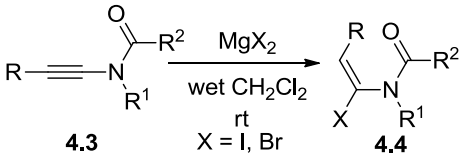


Fig. 1. A drawing showing the effect of nitrogen connected to the alkyne moiety.

In the year 2003, hydrohalogenation of ynamides was investigated by the Hsung and co-workers.[5] Thus in the presence of $MgBr_2$ or MgI_2, ynamides **4.3** were converted to *E*-α-halo-enamides **4.4** in good yields with excellent stereoselectivity (Scheme 4.1). The method involved *in situ* generated HX from the reaction of magnesium salt with wet CH_2Cl_2 and indicated that water played a crucial role during the hydrohalogenation process. We have been more interested in cyclization reactions of ynamides that lead to the products with very high regio- and stereo-selectivity.[6-7] In the following section, we shall discuss cyclizations occurring at the α-position of the ynamides.

Scheme 4.1

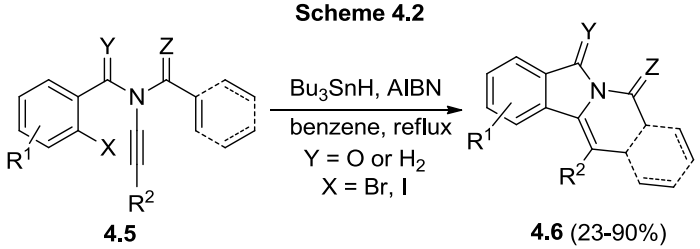


4.3 **4.4**

4.1 Cyclization involving α-position of ynamides

Max Malacria's group reported the radical-cyclization of the functionalized ynamides.[8] Thus ynamides **4.5** were transformed into polycyclic compounds **4.6** *via* two sequential cascade reactions (Scheme 4.2). Initially, ynamide is involved in a 5-*exo*-*dig* cyclization resulting in endocyclic double bond which undergoes radical cyclization *via* 6-*endo*-*trig* manner to lead to the polycyclic compounds in good yields. Intermediate steps were not elaborated in this work.

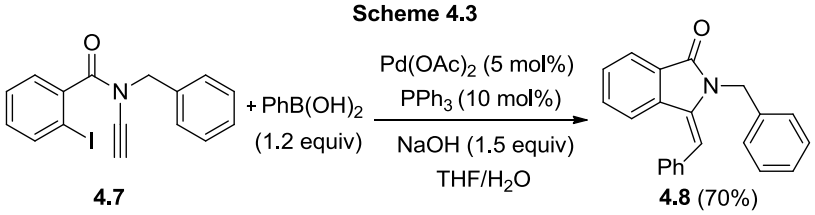
Scheme 4.2



4.5 **4.6** (23-90%)

Janine Cossy and co-workers reported the reaction of ynamides **4.7** with arylboronic acids under [Pd]-catalysis that afforded (*E*)-3-(arylmethylene) isoindolin-1-ones **4.8** stereoselectively (Scheme 4.3).[9] Under these conditions, trimethylsilylynamide is generated terminal ynamide *in situ*, which underwent Heck-Suzuki-Miyaura reaction with benzeneboronic acid providing the corresponding isoindolinone in good yields.

Scheme 4.3

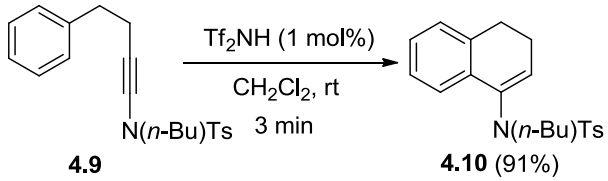


4.7 **4.8** (70%)

A Brønsted acid catalyzed cyclization of arene-ynamides **4.9** providing heterocycles **4.10** was illustrated by Hsung's group (Scheme 4.4).[10] Instead of Tf_2NH catalyst, *p*-nitrobenzenesulfonic acid (20 mol%) was used as a Brønsted acid catalyst for indole-

tethered ynamides. Stronger Brønsted acid Tf_2NH [pK_a (1,2-DCE) -11.9)] competing the protonation of the indole ring resulted in a very poor yield of the desired product. This protocol was also employed in the total synthesis of desbromoarborescidines A and C.

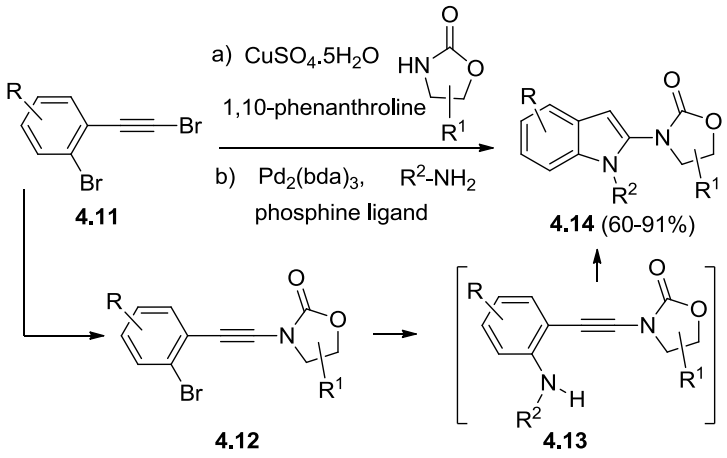
Scheme 4.4



4.9 **4.10** (91%)

Zhao's group described the synthesis of 2-amido indole derivatives **4.14** by cyclization of *ortho*-haloaryl acetylenic bromides **4.11** *via* sequential metal catalyzed C-N bond formations (Scheme 4.5).[11] Initially, o*rtho*-haloaryl substituted ynamides **4.12** are formed by amidative cross-coupling of *ortho*-haloaryl acetylenic bromides **4.11** under [Cu]-catalysis. In the next step, *N*-arylation of the *ortho*-haloaryl substituted ynamides **4.12** by using anilines, followed by 5-*endo*-*dig* cyclization in the presence of [Pd]-catalysis *via* an *in situ* produced *ortho*-aminoaryl substituted ynamides **4.13** afforded the 2-amido indoles **4.14** in good yields.

Scheme 4.5



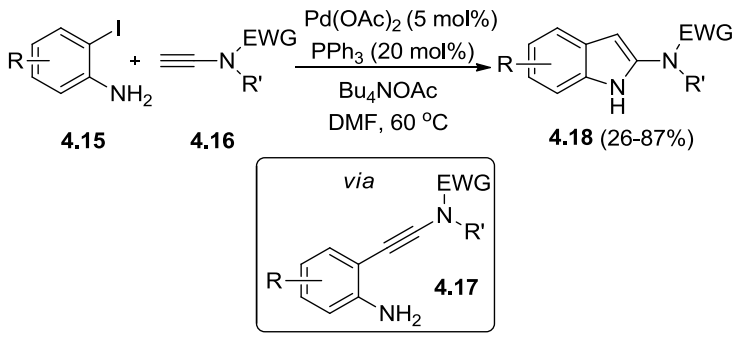
4.11 **4.14** (60-91%)

4.12 **4.13**

Synthesis of 2-amidoindoles **4.18** was achieved by Karin Dooleweerdt *et al*. from terminal ynamides **4.16** and *o*-iodoanilines **4.15** by using [Pd]-catalysis (Scheme 4.6).[12] This is a two-step sequential reaction. The reaction proceeds through Sonogashira coupling of iodoanilines and ynamides affording aryl alkynes **4.17**. In the presence of a base, alkynes **4.17** undergo hydroamination resulting in the formation of indole ring.

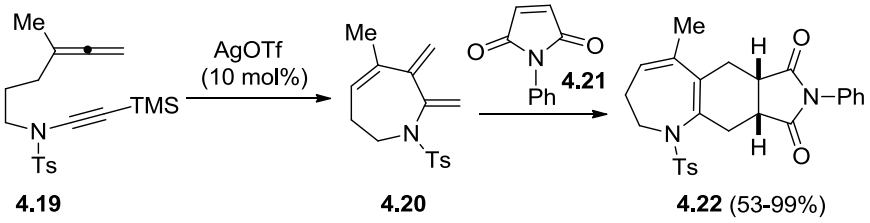
Electron withdrawing groups on the *o*-iodoanilines decrease the nucleophilicity of the -NH_2 group in the hydroamination step leading to poor yields of 2-amidoindoles. In order to overcome this problem, anilines were converted to their corresponding carbamate derivatives. This methodology was further extended for the synthesis of 2-amidobenzofurans from *o*-iodophenols and ynamides.

Scheme 4.6



Pierre Garcia *et al* have investigated the cycloisomerization of allenynamides **4.19** in the presence of silver triflate.[13] By varying the substitution on the allenic moiety and the length of the side chain, different sized nitrogen heterocycles (e.g., **4.20**) were prepared. Synthetic utility of trienes **4.20** was also demonstrated by producing polycyclic ring systems **4.22** in the presence of *N*-phenylmaleimide **4.21** *via* cycloisomerization/ Diels-Alder sequence (Scheme 4.7).

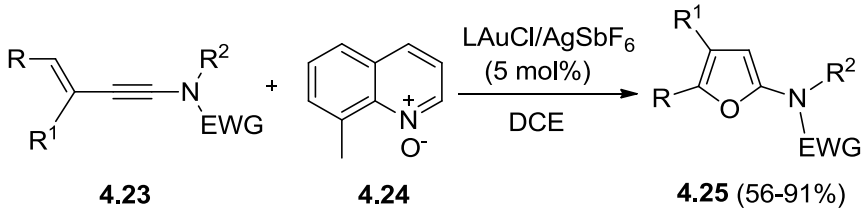
Scheme 4.7



A new gold catalyzed [4+1] cycloaddition reaction between 3-en-1-ynamides **4.23** and 8-methylquinoline oxide **4.24** affording highly substituted furans **4.25** was reported by Rai-Shung Liu and co-workers (Scheme 4.8).[14] This cycloaddition was an effective synthetic route for the heterobiaryl compounds like 2-(furanyl)-thiophene, 2-(furanyl) benzothiophene and 2-(furanyl)benzofuran. Ynamides like 4-phenyl-3-en-1-ynamide and 2-cyclohexenyl-1-ethynylamide led to dicarbonyl compound and dienylamide

respectively instead of furan derivarives. Alkyl group at the C(3)-carbon of 3-en-1-ynamides facilitates an oxa-Nazarov cyclization due to the stabilization of the gold allylic cation and providing the furan derivatives.

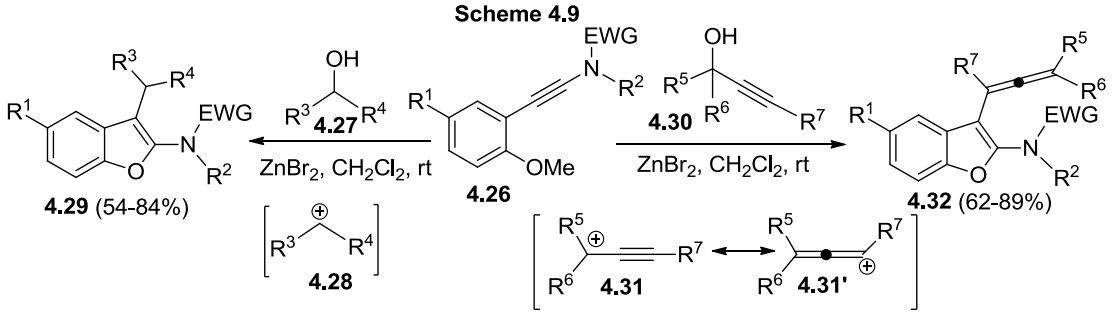
Scheme 4.8



4.23 **4.24** **4.25** (56-91%)

Jian Cao's group illustrated a facile carbocation-induced electrophilic cyclization reaction of *o*-anisole substituted ynamides **4.26** giving 3-alkyl-2-amidobenzofurans **4.29** or 3-allenyl-2-amidobenzofurans **4.32** from various substituted alcohols (Scheme 4.9).[15] But the simple phenylmethanol failed to undergo this electrophilic cyclization reaction. The mechanism involves formation of carbocation by the reaction of diarylmethanol with $ZnBr_2$ (ESI-TOF MS analysis of reaction mixture showed the existence of diphenylmethylcation). This *in situ* generated carbocation **4.28** undergoes electrophilic addition to ynamide alkyne. Subsequent cyclization *via* –OMe group affords the benzofurans which undergo demethylation by bromide ion providing the 2-amidobenzofuran **4.29**. In the case of propargyl alcohol **4.30**, allenylic carbocation **4.31'** reacts with ynamide due to the steric hindrance caused by the presence of two aryl groups leading to the formation of 3-allenyl-2-amidobenzofuran **4.32**.

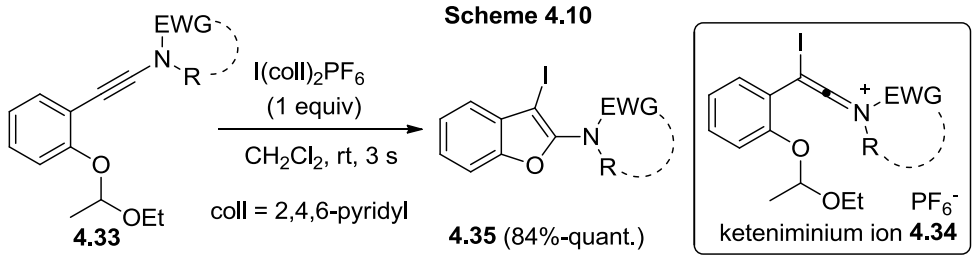
Scheme 4.9



An effective method for the construction of benzo[*b*]furans **4.35** in high yields under mild conditions by the iodocyclization of ynamides containing ethoxyethyl ether group **4.33** was described by Takashi Okitsu's group (Scheme 4.10).[16] The same group also demonstrated the utility of this methodology by synthesizing polycyclic isoquinolinones

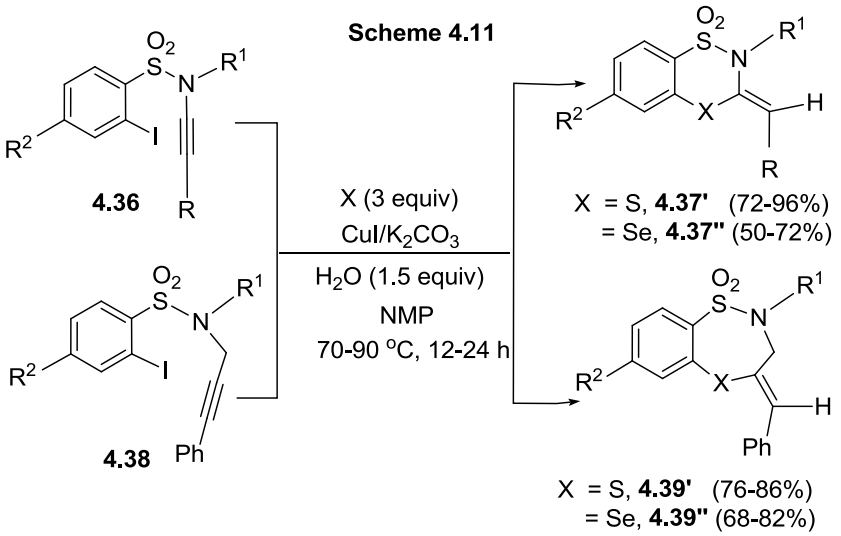
via Suzuki-Miyaura coupling/decarboxylation/lactamization. In the presence of iodinating reagent $I(coll)_2PF_6$, ynamides form keteniminium ion **4.34**. Subsequent nucleophilic attack of oxygen from the ethoxyethyl ether group on keteniminium ionic species followed by the loss of the ethoxyethyl group affords the benzo[*b*]furan **4.35**.

Scheme 4.10



A novel [Cu]-catalyzed one-pot regio- and stereo-specific synthesis of benzo[1,4,2]dithiazine 1,1-dioxides **4.37'** and benzo[1,4,2]thiaselenazine 1,1-dioxides **4.37"** by the cyclization of functionalized ynamides **4.36** with elemental sulfur/ selenium has been developed from our laboratory (Scheme 4.11).[17] This methodology was elegantly extended for the synthesis of benzodithiazepines **4.39'** and benzothiaselenazepines **4.39"**. Incorporation of ^2D at the olefinic site by using D_2O in place of water revealed the involvement of the water in the cyclization process. Selective oxidation at sulfur in benzo[1,4,2]dithiazine 1,1-dioxide by using *m*CPBA as the oxidizing agent was also described.

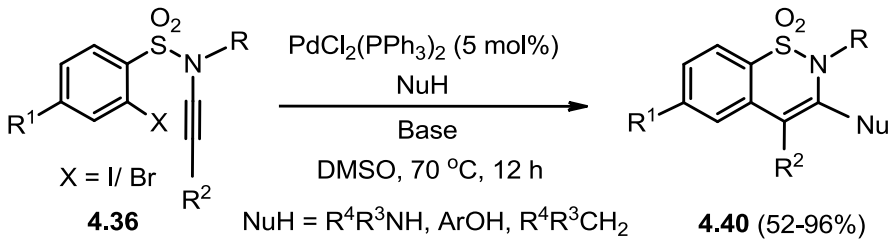
Scheme 4.11



Very recently, our group has reported an intermolecular nucleophilic attack of various nucleophiles such as sulfonamides, amines, phenols and active methylene compounds onto the functionalized ynamides **4.36** providing a wide range of hetero-substituted

benzosultams (1,2-benzothiazine 1,1-dioxides) **4.40** by using palladium catalysis (Scheme 4.12).[18] Generality of this methodology was shown by employing medicinally useful compounds like nortriptyline and eugenol as nucleophiles. Base has a significant effect in the cyclization process, depending on the nucleophile source used. DFT studies suggested that the reaction pathway involves a [Pd^{II}]-[Pd^{0}]-[Pd^{II}] cycle.

Scheme 4.12

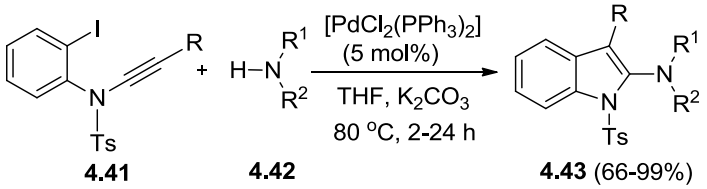


So far, we have discussed cyclization reactions of ynamides involving the α-position (to the nitrogen atom) of the alkyne. The cyclizations taking place at the β-position of ynamides are rarely explored, but examples are available and are discussed below.

4.2 Cyclization involving β-position of ynamides

Bernhard Witulski *et al*. accomplished a highly successful route for the synthesis of 2-amino indoles **4.43** from alkynyl-2-halogenanilides **4.41** and amines **4.42** by using palladium cross-coupling sequence (Scheme 4.13).[19] This methodology was elaborated to secondary amines also. Less basic amines morpholine and allylamine also worked well. Formation of σ,π-chelated palladium species played a key role and activated the triple bond by coordinating to the β-position initially. This was followed by the attack of amine to provide the indole derivatives **4.43**.

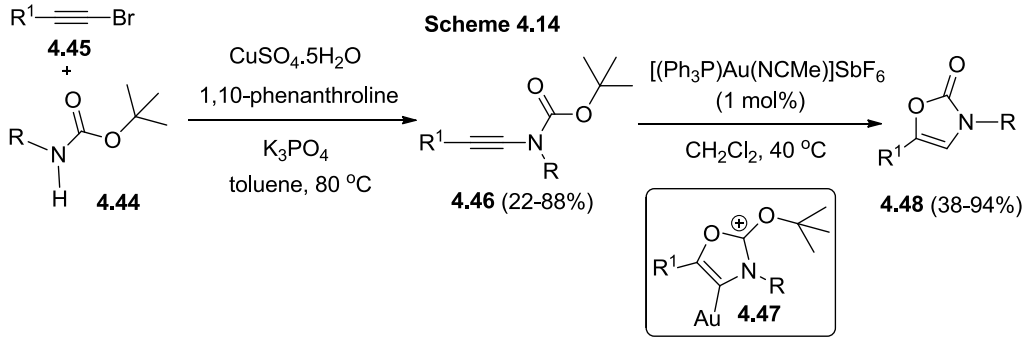
Scheme 4.13



Fabien Gagosz and coworkers established a two-step sequential route for 1,5-disubstituted oxazolones **4.48** (Scheme 4.14).[20] Thus Cu(II)-catalyzed cross-coupling reaction of bromoalkyne **4.45** with *tert*-butyloxycarbamate **4.44** resulted in *N*-alkynyl

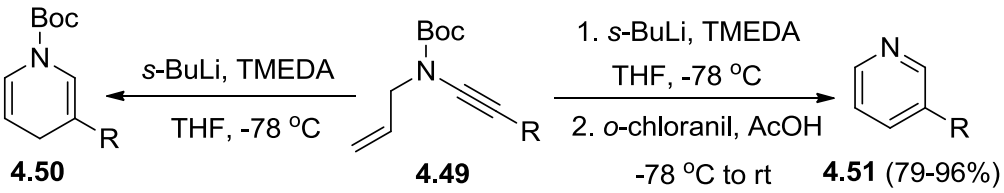
tert-butyloxycarbamates **4.46**. These ynamides **4.46** led to oxazolones **4.48** by gold(I)-catalyzed cycloisomerization in good to excellent yields. The catalyst $AgNTf_2$ (5 mol%) also furnished the desired oxazolones in decent yields. The pathway involved the activation of alkyne group of ynamides **4.46** by the gold catalyst providing stabilized cationic species **4.47**, followed by the fragmentation of C-O bond of *tert*-butyloxy group offering the neutral vinyl-gold species, which undergoes protodeauration affording oxazolones **4.48**.

Scheme 4.14



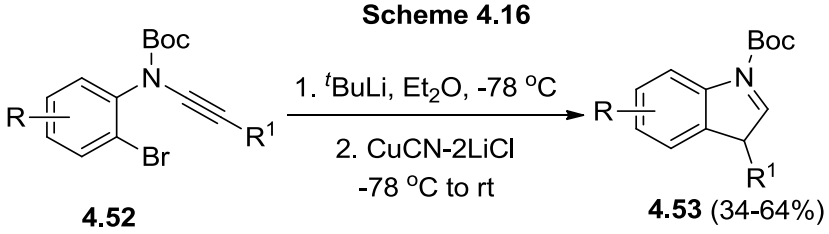
Gwilherm Evano's group explored a robust and general method for the synthesis of polysubstituted 1,4-dihydropyridines **4.50** and pyridines **4.51** from the readily available *N*-allyl-ynamides **4.49** (Scheme 4.15).[5b] This method comprises lithiation/ isomerization/ intramolecular carbolithiation sequence of ynamides **4.49**. A broad range of substituents are incorporated on the dihydropyridine ring. They also trapped the final stabilized vinyllithium intermediate by using deuterated water or methyl iodide as an electrophile. This strategy was also applied to cyclic allylamines that led to hexa- and tetra-hydroisoquinolines in moderate yields.

Scheme 4.15



A simple synthetic route for indoles was communicated by Wafa Gati *et al*. They prepared polysubstituted indoles **4.53** by intramolecular 5-*endo-dig* carbocupration of *N*-aryl-ynamides **4.52** (Scheme 4.16).[21] A variety of 3-substituted indoles were synthesized in moderate to good yields.

Scheme 4.16



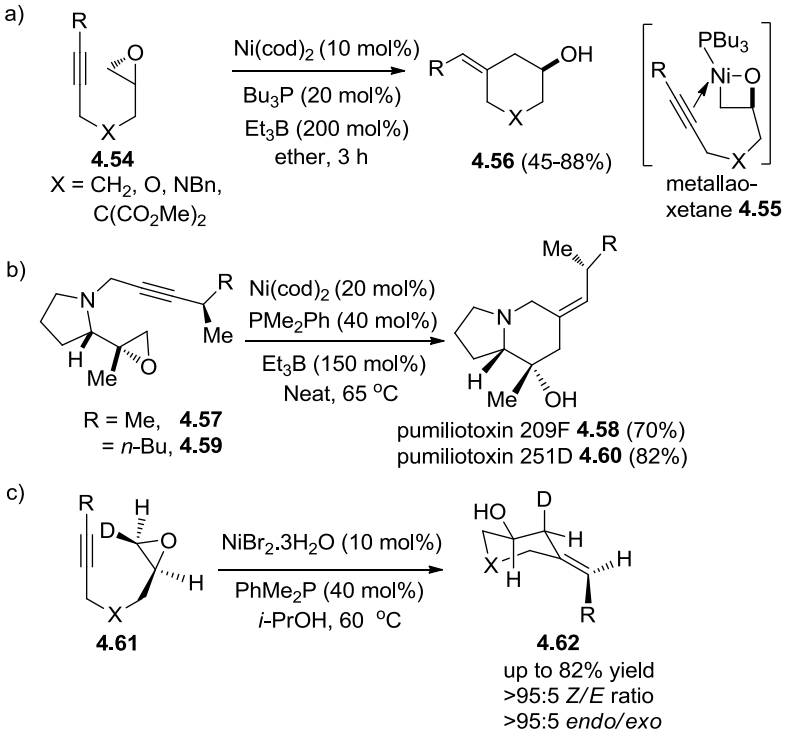
4.52 **4.53** (34-64%)

Till now, reports on the reactivity of epoxide functionalized ynamide substrates have not been reported. Hence we wanted to utilize epoxy functionalized ynamides in intramolecular or intermolecular cyclizations. Since epoxides are highly strained three membered ring compounds, that can undergo various organic transformations to furnish the *O*-containing heterocycles.[22] In particular, ring expansion reactions of epoxides are of considerable interest since multitudes of carbocycles or oxygen containing heterocycles can be generated.[23-25] Illustrative transformations of substrates containing epoxide and alkyne functionalities are discussed below.

4.3 Ring expansion reactions of epoxide and alkyne containing substrates

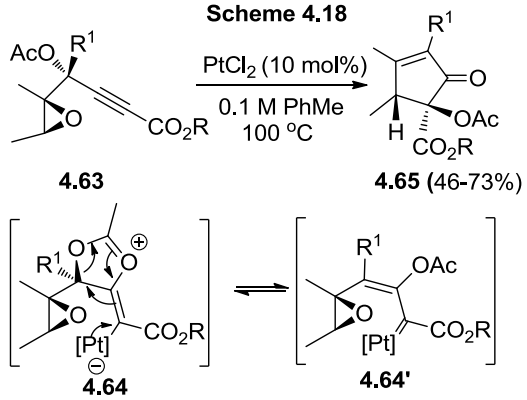
Timothy Jamison's group demonstrated a novel method for the generation of carbo/heterocycles **4.56** by the reductive coupling of epoxides **4.54** possessing alkyne functionalities by using [Ni]-salts (Scheme 4.17a).[26a] This is the first catalytic method for the reductive coupling of substrates having alkyne and epoxide. The reaction proceeds through regioselective oxidative addition of a PBu_3-Ni(0) complex onto the less hindered side of the epoxide resulting in metallaoxetane **4.55**, which then undergoes *exo-dig* cyclization with the alkyne, *β*-H elimination. Finally, reductive elimination leads to the cyclized product **4.56**. Later, the same group has utilized this strategy for the total synthesis of pumiliotoxin 209F **4.58** and 251D **4.60** with an overall yield in 25% and 17% respectively by using the substrates **4.57** and **4.59** (Scheme 4.17b).[26b] Recently, the same group showed more convenient conditions for the above reductive coupling reaction.[26c] In this protocol, they employed an air-stable and inexpensive catalytic system for the cyclization process (Scheme 4.17c).

Scheme 4.17



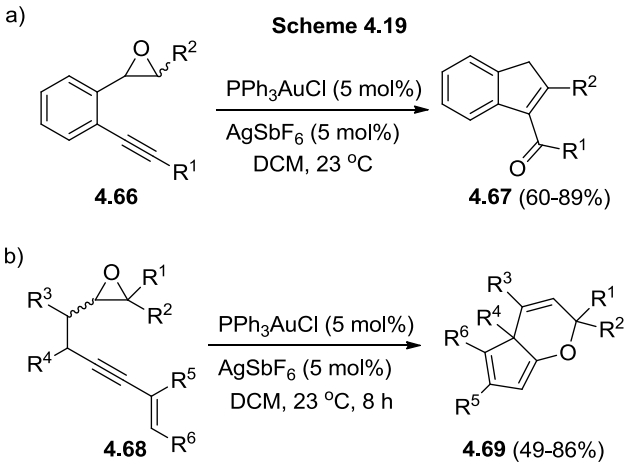
Richmond Sarpong and co-workers reported a platinum catalyzed pentannulation reaction of propargylic esters **4.63** that furnished pentannulated products **4.65** (Scheme 4.18).[27] In the presence of [Pt]-catalyst, propargylic esters **4.63** undergo 5-*exo*-*dig* cyclization to produce the zwitterion **4.64**, which is in equilibrium with the metallocarbenoid **4.64'**. Nucleophilic attack of oxygen from the epoxide and oxa-6π electrocyclization afforded the pentannulated product.

Scheme 4.18

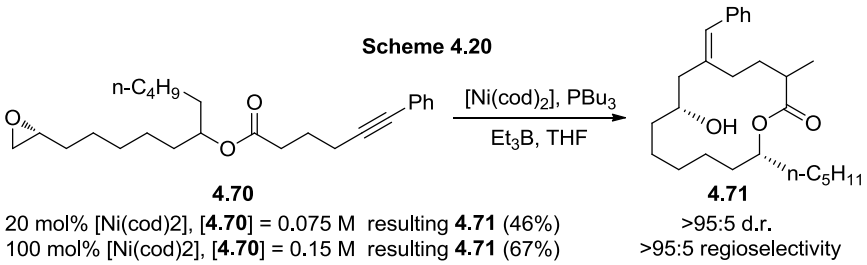


Rai-Shung Liu's group established a new strategy for the cycloisomerization of epoxy-alkynes in the presence of [Au]/[Ag] catalytic system.[28] The reaction proceeds *via*

formation of a gold carbenoid species. Cycloisomerization of aromatic alkynyl epoxides **4.66** produces carbo/heterocyclic compounds **4.67** (Scheme 4.19a). The nonaromatic epoxides **4.68** lead to polycyclic 2*H*-pyrans **4.69** *via* 6-*exo-dig* attack of the epoxide on the alkyne that generates the gold-carbenoid intermediate, which undergoes Nazarov-type cyclization in the presence of [Au]/[Ag] catalytic system (Scheme 4.19b). Formation of the gold-carbenoid intermediate was proved by trapping experiment using Ph_2SO oxidation. This cycloisomerization was successfully applied for the rapid construction of the central skeletons of natural pallidol and gibberic acid.



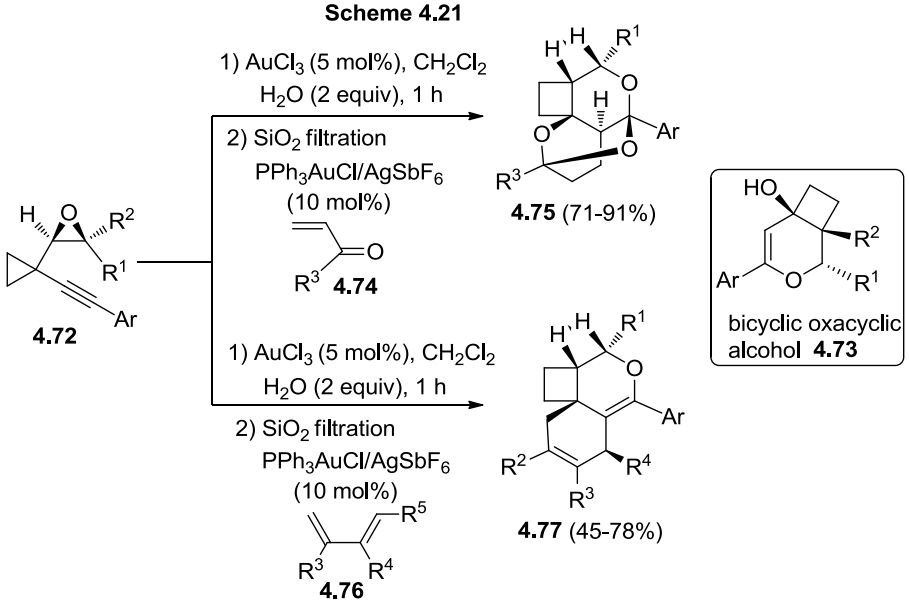
Reductive coupling of alkynyl epoxides **4.70** by using a [Ni]-catalyst resulting in the macrocycles **4.71** with high regioselectivity was described by the Timothy Jamison and co-workers (Scheme 4.20).[29] (−)-Gloeosporone was synthesized by this new approach in 10 steps with an overall yield of 6% by using 20 mol% catalyst loading, whereas 9% yield obtained was by using 100 mol% of the catalyst.



Later, the same group reported a novel method for the synthesis of oxacyclic compounds from epoxy-alkyne substrates using gold catalysis in a highly diastereoselective manner. Thus reaction of alkynyl epoxides **4.72** with enones/dienes

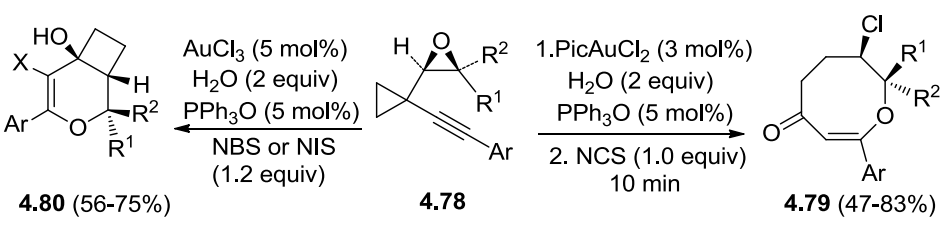
4.74/4.76 resulted in tricyclic-oxacyclic/tricyclic compounds **4.75/4.77** in excellent yields *via* two step sequential route (Scheme 4.21).[30] Initially, compound **4.72** forms bicyclic oxacyclic alcohol **4.73** in the presence of $AuCl_3$, which upon subsequent treatment with the enone/diene (2 equiv) in the presence of $PPh_3AuCl/AgSbF_6$ (10 mol%) catalytic system furnishes compound **4.75** or **4.77** as a single diastereomer with excellent sterioselectivity.

Scheme 4.21



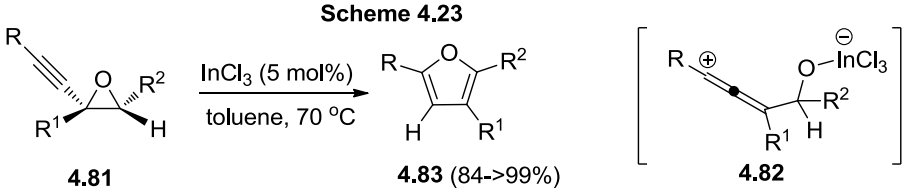
Later, the same group probed the construction of halogenated products from *cis*-1-oxiranyl-1-alkynylcyclopropanes **4.78** by using *N*-halosuccinimides and Au(III)-catalysts.[31] Two sequential ring opening reactions of **4.78** resulted in the eight-membered ether *i.e*. 3-chloro-4,5-dihydro-2*H*-oxocin-6(3*H*)-one **4.79** *via* oxacyclization/ring expansion in the presence of $AuCl_2$(Pic) and *N*-chlorosuccinimide (NCS). In contrast, the ring expansion reaction with $AuCl_3$ and NBS or NIS provided compound **4.80** (Scheme 4.22).

Scheme 4.22



Jun Yong Kang *et al*. demonstrated a useful method for the synthesis of aromatic and aliphatic 2,3,5-trisubstituted furans **4.83** from alkynyl epoxides **4.81** by using $InCl_3$ as the catalyst (Scheme 4.23).[32] These epoxy–alkynes were synthesized by the nucleophilic ring closure of propargylic alcohols which were obtained by reacting α-haloketones with lithium acetylide. The reaction proceeds through the coordination of $InCl_3$ to an epoxide generating the zwitterionic species **4.82**, followed by 1,3-hydride shift and subsequent C-O bond formation resulting in the highly substituted furans **4.83**.

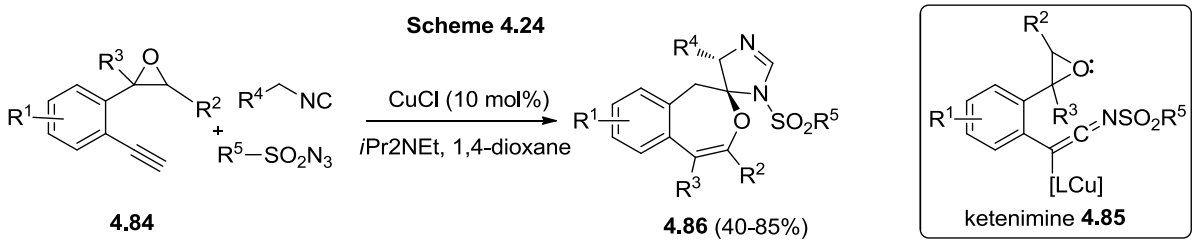
Scheme 4.23



4.81 **4.83** (84->99%) **4.82**

Jie Wu's group discovered a novel strategy for the construction of 3',5'-dihydro-1*H*-spiro[benzo[*d*]oxepine-2,4'-imidazoles] **4.86** in good yields by the reaction of 2-(2-ethynylphenyl)oxirane **4.84**, sulfonyl azide and 2-isocyanoacetate *via* ketenimine intermediate **4.85** by using a copper(I)-catalyst (Scheme 4.24).[33] Intramolecular nucleophilic attack of the epoxide on **4.85** followed by rearrangement furnished the desired product **4.86**.

Scheme 4.24



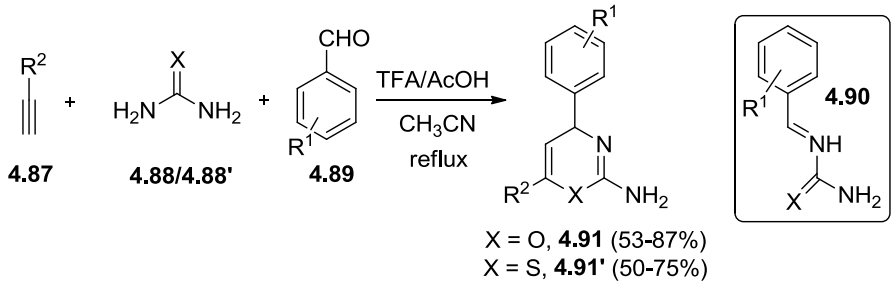
4.84 **4.86** (40-85%)

4.4 Synthesis of 1,3-oxazine and 1,4-oxazine derivatives from alkyne substrates

This section deals with synthetic routes to 1,3-/1,4-oxazines, where one of the reactants is an alkyne, that are relevant to the present study. Thus an one-pot multicomponent reaction of alkynes **4.87**, urea / thiourea **4.88/4.88'**, and aldehydes **4.89** led to 1,3-oxazine/1,3-thaiazines **4.91/4.91'** as reported by Shenlin Huang *et al*. (Scheme 4.25).[34] The reaction proceeds through condensation of aldehyde and urea or thiourea providing intermediate **4.90**. Subsequent hetero-Diels-Alder reaction of intermediate **4.90**

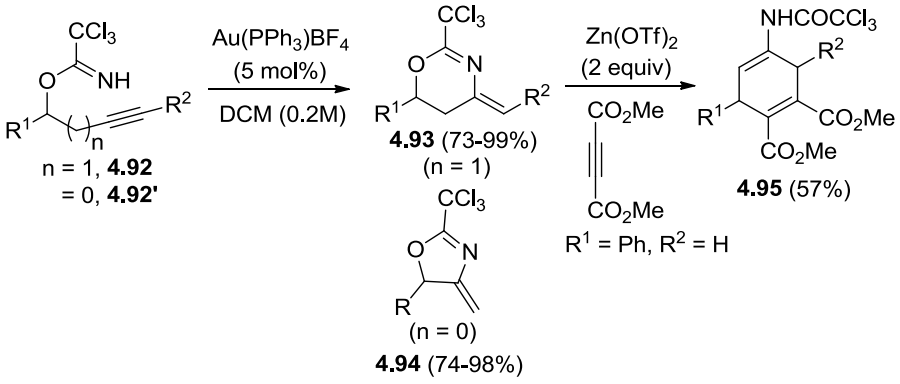
with alkyne followed by deprotonation affords 2-amino-4*H*-1,3-oxazines **4.91** or 2-amino-4*H*-1,3-thiazines **4.91'**, respectively.

Scheme 4.25



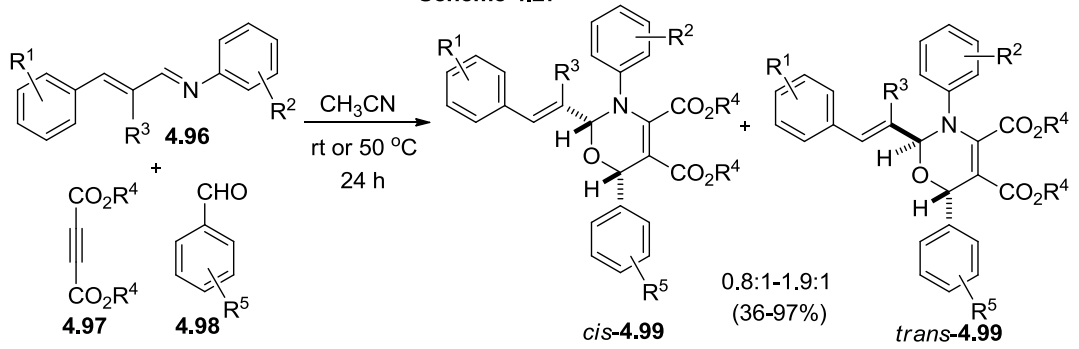
Gold catalyzed intramolecular hydroamination of trichloroacetimidates derived homopropargyl alcohols **4.92** resulting in six membered 1,3-oxazines **4.93** was reported by Seunghoon Shin's group (Scheme 4.26).[35] Propargyl alcohol derived trichloroacetimidates **4.92'** led to five membered 1,3-oxazole derivatives **4.94** by using $Au(PAr_3)SbF_6$ as the catalyst in DCE solvent. An application of thus obtained 1,3-oxazine derivatives was also reported by taking one of the 5,6 dihydro-1,3-oxazine as diene in Diels-Alder cycloaddition by using $Zn(OTf)_2$ catalyst delivering the corresponding cycloadduct **4.95**.

Scheme 4.26



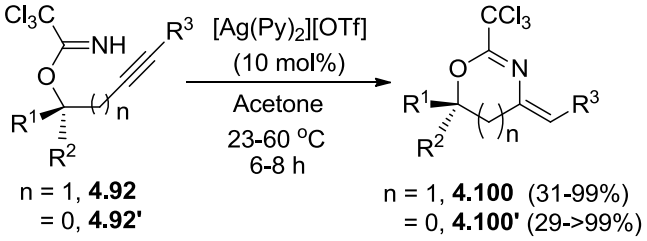
Lu's group illustrated synthesis of highly functionalized 1,3-oxazines by three component reaction of imines **4.96** with alkynes **4.97** and benzaldehydes **4.98** under mild conditions *via* 1,4-dipolar cycloaddition (Scheme 4.27).[36] Thus nucleophilic attack of imine nitrogen on the electron deficient alkynes resulted in 1,4-dipolar species, which then underwent [4+2] cycloaddition with the aldehydes leading to 1,3-oxazines.

Scheme 4.27



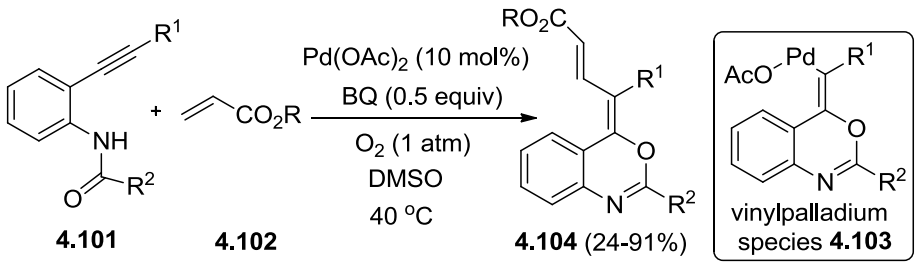
Silver complex {[Ag(py)$_2$][OTf]} catalyzed hydroamination of trichloroacetimidate derived alkynes **4.92**/**4.92'** in an intramolecular fashion resulting in 1,3-oxazines **4.100**/**4.100'** was demonstrated by Wong *et al*. (Scheme 4.28).[37] This is the first report for the hydroamination of trichloroacetimidates derived alkynes by using [Ag]-catalysis. Aryl group accommodated at R^1 position also provided the corresponding 1,3-oxazines in excellent yields. Dissociation of one of the pyridine rings from metal complex plays a key role and provides free coordination site for effective catalysis. The reaction did not progress in the presence of [(phen)Ag][OTf] due to the chelating phenanthroline ligand.

Scheme 4.28



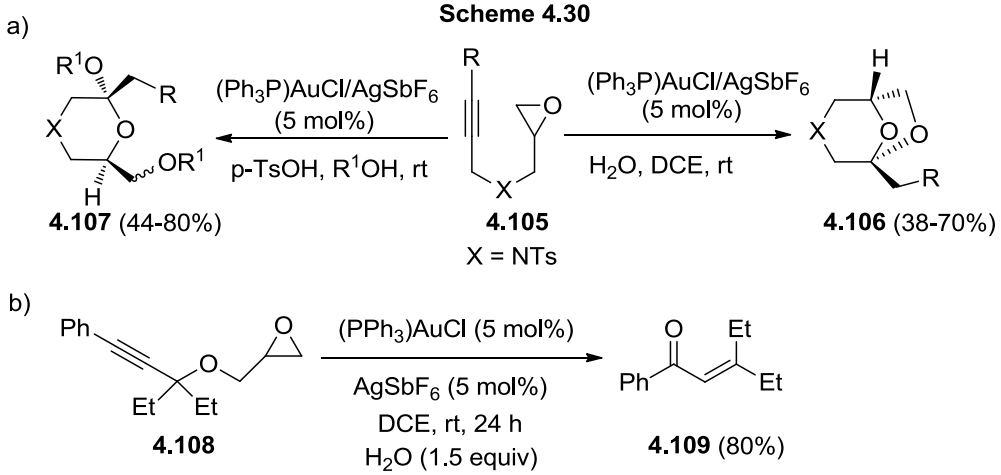
Polyene substituted 1,3-oxazines **4.104** were synthesized by Zhong-Jian Cai *et al*. from *ortho*-ethynylanilides **4.101** and alkenes **4.102** under [Pd]-catalysis *via* a 6-*exo*-*dig* cyclization and alkenylation process (Scheme 4.29).[38] The method was applicable to a wide range of substrates and gives products in moderate to excellent yields. Aliphatic substituents on the alkyne group of *ortho*-ethynylanilides gave lower yields. Initially, Pd(OAc)$_2$ activates the alkyne moiety of the *ortho*-ethynylanilides **4.101**. Subsequent nucleophilic attack of carbonyl oxygen results in vinylpalladium species **4.103**, which undergoes migratory insertion with activated alkenes followed by the reductive elimination producing the polyene-substituted benzo[d][1,3]oxazines **4.104**.

Scheme 4.29



A convenient method for the synthesis of ketals **4.106**-**4.107** *via* intermolecular addition of water or alcohols to epoxy alkynes **4.105** by using gold catalysis was illustrated by Min Shi's group (Scheme 4.30a).[39] The pathway comprises the attack of nucleophile at less hindered side of the epoxide ring followed by 6-*exo*-cycloisomerization, and subsequent addition of nucleophile to a double-bond either intra- or inter-molecularly affording the fused bicyclic ketals **4.106** and *trans*-substituted morpholines **4.107**, respectively in a highly regio- and diastereo-selective manner. Under optimized conditions, *O*-tethered alkynyl epoxide **4.108** led to α,β-unsaturated carbonyl compound **4.109** instead of the fused bicyclic ketal (Scheme 4.30b).

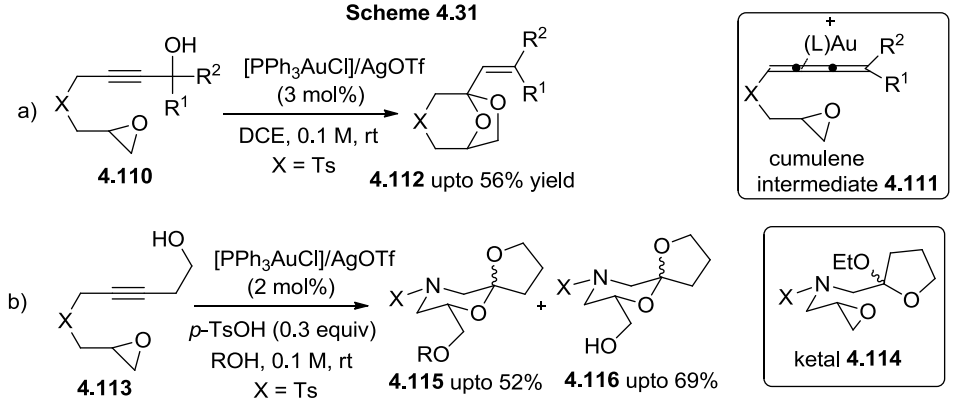
Scheme 4.30



Later, the same group studied gold catalyzed intramolecular cycloisomerization of propargylic/homopropargylic alcohols having an oxirane moiety **4.110**/**4.113** that provided the ketal/spiroketals **4.112**/**4.115**-**4.116** in moderate yields under mild conditions (Scheme 4.31a-b).[40a] In the presence of a cationic gold complex, epoxy propargylic alcohol **4.110** rearranges to cumulene intermediate **4.111**.[40b] Attack of water on this

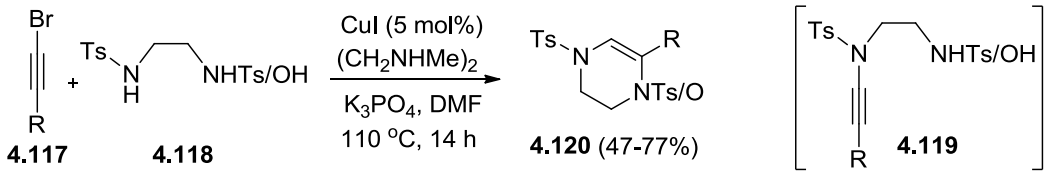
intermediate **4.111** and subsequent tautomerization of enol form results in ketone substrate. Intramolecular reaction of the ketone with epoxide in the presence of gold catalyst leads to ketals **4.112**. Homopropargylic alcohols **4.113** were transformed into ketal **4.114** upon gold catalytic activation of the alkyne, followed by the nucleophilic attack of alcohol. Subsequent ring-opening of oxirane catalyzed by a cationic gold catalyst or *p*-TsOH, followed by an intramolecular ketal-exchange led to spiroketals **4.115**-**4.116**. However, *O*-tethered epoxy propargylic alcohol failed to give the desired product under standard reaction conditions. Mechanism for the formation of spiroketals based on a series of control and ^{18}O tracer experiments was also studied.

Scheme 4.31



A convenient method for the synthesis of *N*,*N*- or *N*,*O*- heterocycles **4.120** from bromoacetylenes **4.117** and a diamine or ethanolamine **4.118** was reported by Yasuhiro Fukudome *et al*. (Scheme 4.32).[41] Initially, sulfonamide undergoes alkynylation with bromoacetylene providing the ynamide intermediate **4.119**. This is followed by hydroamination or hydroalkoxylation with the second amine or hydroxyl group to the acetylinic bond *via* a 6-*endo*-*dig* approach affording the tetrahydropyrazines or oxazines.

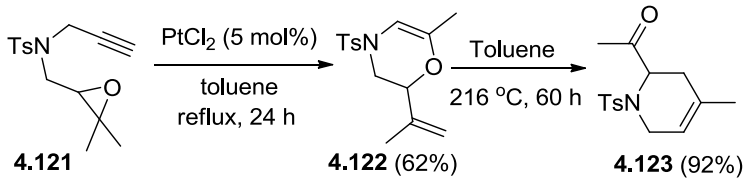
Scheme 4.32



Shiyue Fang and co-workers provided an approach for the synthesis of cyclic allyl vinyl ethers **4.122** from alkynyl epoxides **4.121** by using $PtCl_2$ as the catalyst (Scheme

4.33).[42] Hydrolysis of these allyl vinyl ethers afforded 2-hydroxymorpholine derivatives in excellent yields. However, thermal Claisen rearrangement of cyclic allyl vinyl ethers **4.122** led to piperidine derivatives **4.123**.

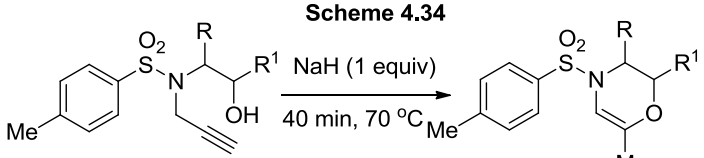
Scheme 4.33



4.121 **4.122** (62%) **4.123** (92%)

Jeh-Jeng Wang's group developed a new method for the synthesis of 1,4-oxazine **4.125** from alkynyl alcohols **4.124** (Scheme 4.34).[43] This is a base mediated, metal free atom economic approach. Grignard reaction of alkynyl aldehydes was used to prepare the corresponding diastereomeric alcohols **4.124**. In the presence of NaH, alcohols **4.124** transformed into the 1,4-oxazines **4.125** at 70 °C. The induced stereoselectivity was studied by application of Cram's rule and density functional theory calculations (DFT). The *exo-dig* attack of –OH group of alkynyl alcohols to alkyne motif led to 1,4-oxazine. This protocol was extended for the synthesis of 1,4-oxazepines.

Scheme 4.34



4.124 **4.125** (59-91%)

In the above context, it may be noted that both 1,3- and 1,4-oxazines constitute an important class of heterocycles due to their extensive range of biological activities (cf. Chart 1).[44] Thus, it would be worthwhile exercise to explore synthetic methodologies for this class of compounds.

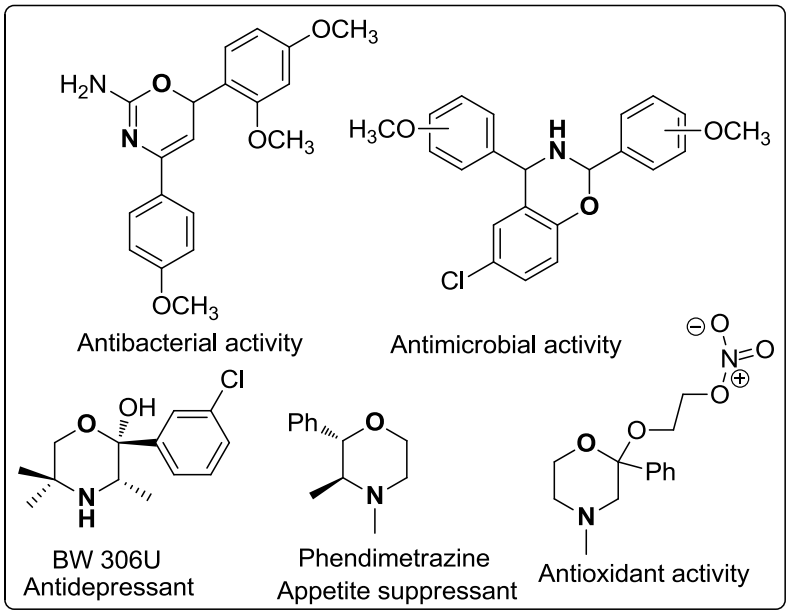


Chart 1. Biologically important oxazine derivatives

OBJECTIVES OF THE PRESENT WORK - PART B

The main aim of this part of the present work was to explore the cyclization reactions of functionalized ynamides under mild conditions given below:

(i). To synthesize diverse epoxy tethered ynamides (as substrates) and explore their reactivity under transition metal free conditions for the generation of 1,3-oxazine derivatives, and

(ii). To study the intermolecular reaction of epoxy ynamides with NaN_3 as a nucleophile in an effort to synthesize 1,4-oxazines.

RESULTS AND DISCUSSION

In this part, we discuss cyclization reactions of epoxy ynamides. Details on the precursors used in the present work are presented in sections 5.1-5.3. After this, transition metal free, base mediated intramolecular cyclization reactions of epoxy ynamides are discussed. In the last section, a highly regioselective synthesis of 1,4-oxazines by tandem-cyclization of epoxy ynamides using NaN_3 as a nucleophile is described. Characterization of the products is generally done by using mp (for solids), IR, NMR, LCMS, and HRMS/CHN with single crystal X-ray structure determination for illustrative compounds.

5.1 Synthesis of epoxy sulfonamide precursors 1a-h

The epoxy sulfonamides **1a-h**, were synthesized from a two-step protocol by following literature procedures (Scheme 1).[45] Substituted bromo alkyne precursors **2a-h** were synthesized from the corresponding alkyne substrates.[46] Phenyl propargyl bromide **3** [47] and *N*-phenyl epoxy sulfonamide **4** were prepared from reported methods (Chart 1).[48]

Scheme 1

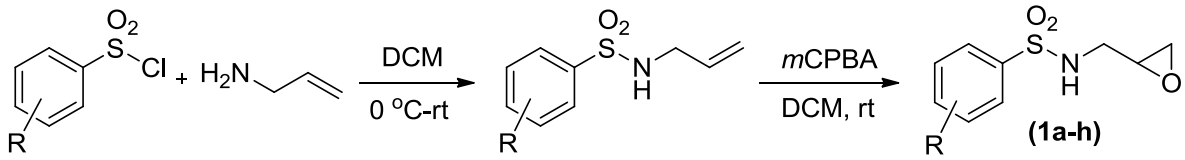
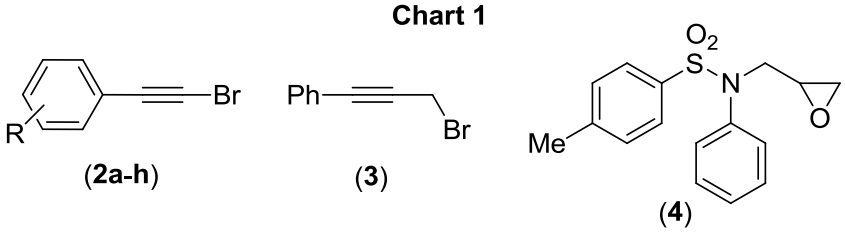


Chart 1

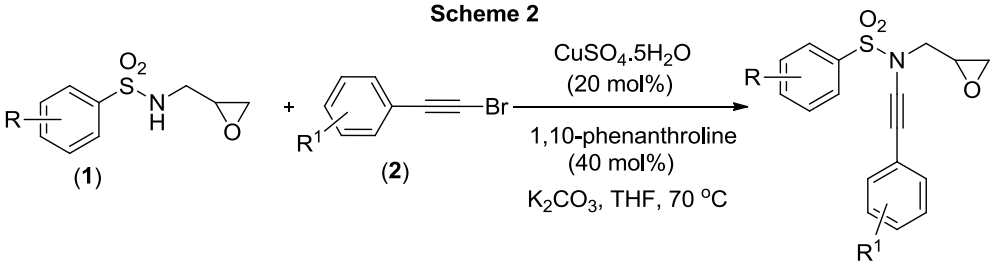


5.2 Synthesis of epoxy ynamides 5a-p

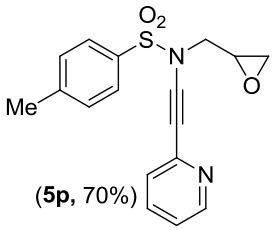
Epoxy ynamides **5a-p** are new and have been prepared by a known protocol with slight modification.[49] Thus reaction of epoxy sulfonamides with various bromo alkynes in

the presence of $CuSO_4.5H_2O$ and 1,10-phenanthroline by using K_2CO_3 base in THF provided the epoxy ynamide precursors **5a-p** in good to excellent yields (Scheme 2). For our purpose, we used THF instead of toluene as the solvent. In the latter solvent, very low yields of the desired epoxy ynamides were obtained. The identities of all these substrates **5a-p** were confirmed by IR and NMR spectra. IR spectra were particularly useful in identifying these compounds because the alkyne *C*≡*C* group displays a strong band at ~ 2200 cm^{-1}. In the ^{13}C NMR spectra, two peaks at δ ~ 80 and at δ ~ 70 due to the presence of -*C*≡*C*- group were observed.

Scheme 2



R = 4-Me,	R^1 = H	(**5a**, 85%)
R = 4-OMe,	R^1 = H	(**5b**, 88%)
R = 4-Cl,	R^1 = H	(**5c**, 82%)
R = 4-Br,	R^1 = H	(**5d**, 78%)
R = 4-*t*Bu,	R^1 = H	(**5e**, 80%)
R = 1,3,5-triisopropyl,	R^1 = H	(**5f**, 76%)
R = -H,	R^1 = H	(**5g**, 90%)
R = -(C_4H_4)-	R^1 = H	(**5h**, 77%)
R = 4-Me, R^1 = 4-OMe		(**5i**, 86%)
R = 4-Me, R^1 = 4-Me		(**5j**, 84%)
R = 4-Me, R^1 = 2-Me		(**5k**, 81%)
R = 4-Me, R^1 = 4-F		(**5l**, 77%)
R = 4-Me, R^1 = 3-F		(**5m**, 79%)
R = 4-Me, R^1 = 4-Cl		(**5n**, 75%)
R = 4-Me, R^1 = -(C_4H_4)-		(**5o**, 73%)

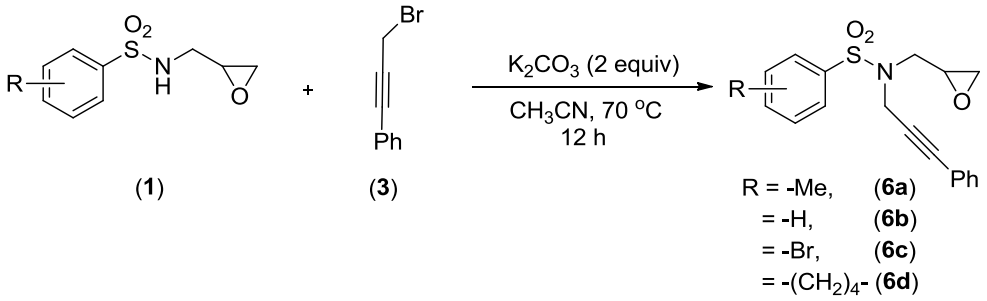


(**5p**, 70%)

5.3 Synthesis of epoxy alkynes 6a-d

Epoxy alkynes **6a-d** were prepared by following a known method from epoxy sulfonamides **1** and phenyl propargyl bromide **3** by using K_2CO_3 as a base in acetonitrile with slight modification (Scheme 3).[50]

Scheme 3



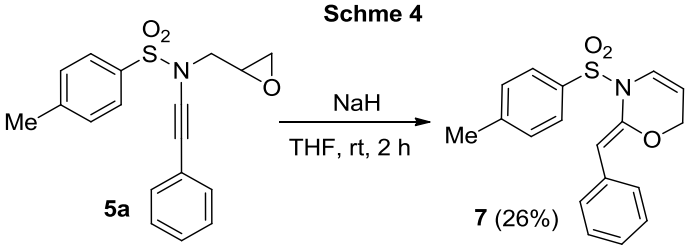
5.4 Base mediated cyclization reaction of epoxy ynamides

From the literature reports presented in Chapter 4, it is clear that ynamides are highly useful precursors for the synthesis of heterocyclic compounds by suitable organic transformations. Heterocycles possessing both nitrogen and oxygen in their core structure are present in numerous biological active compounds.[51-52] This section is devoted to a new reaction leading to 1,3-oxazines.

5.4.1 Atom economic synthesis of 1,3-oxazines 7-22 from epoxy ynamides 5a-p

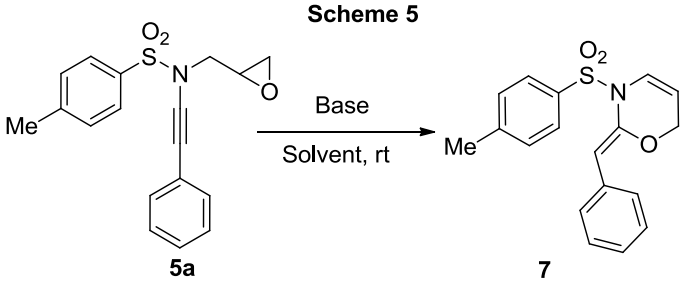
Ynamides appended with epoxide functionality are interesting substrates, since such epoxide tagged ynamide substrates **5a-p** can generate multitudes of nitrogen and oxygen containing heterocycles. Thus, in continuation of our interest in the reactivity of functionalized ynamides,[17-18, 53] herein we discuss a simple base promoted regio- and stereo-selective intramolecular 6-*exo*-*dig* cyclization of epoxy ynamides for the generation of 1,3-oxazines in an atom economic approach and in the absence of any transition metal catalyst. Thus we treated 4-methyl-*N*-(oxiran-2-ylmethyl)-*N*-(phenylethynyl) benzenesulfonamide **5a** with NaH (2 equiv) in THF for 2 h. Surprisingly, the cyclized product **7** was formed in the absence of any transition metal catalyst and was isolated in 26% yield (Scheme 4).

Schme 4



In the above reaction, the yield of product **7** did not improve by changing the solvent from THF to $(EtO)_2CO$ (Table 1, entries 2-4). Use of bases such as $NaNH_2$, NaOH and K_2CO_3 did not give the desired product (entries 5-8). To our delight, the reaction proceeded very smoothly in the presence of 2 equiv of potassium *tert*-butoxide (KO^tBu) in THF at rt (25 ^oC) affording the desired product **7** in 82% yield within 2 h with excellent regio- and stereo-selectivity (entry 9). A lower stoichiometry (one equiv) of the base, though, lowered the yield. Solvents such as 1,4-dioxane, DCM, DMF, toluene, EtOH, and Et_2O were less effective and did not enhance the yield of the product (entries 10-15). Unexpectedly, bases like NaO^tBu and LiO^tBu also did not furnish the desired product (entries 16-17). Also, DBU or TBD as the base could not effect the reaction (not shown in Table). Thus the optimal reaction conditions for this cyclization are: **5a** (1.0 equiv) in THF as the solvent and KO^tBu (2 equiv) as the base at rt for 2 h.

Scheme 5



5a **7**

Table 1: Survey of reaction conditions for the cyclization of epoxy ynamide **5a**[a]

Entry	Base	Solvent	Yield (%)[b]
1.	NaH	THF	26
2.	NaH	Toluene	N.D.
3.	NaH	DMF	traces
4.	NaH	$(EtO)_2CO$	N.D.
5.	$NaNH_2$	THF	N.D.
6.	NaOEt	THF	N.D.
7.	NaOH	THF	N.D.
8.	K_2CO_3	THF	N.D.
9.	KO^tBu	THF	82
10.	KO^tBu	1,4-Dioxane	20

11.	KO^{t}Bu	DCM	55
12.	KO^{t}Bu	DMF	traces
13.	KO^{t}Bu	Toluene	65
14.	KO^{t}Bu	EtOH	30
15.	KO^{t}Bu	Et_2O	40
16.	NaO^{t}Bu	THF	N.D.
17.	LiO^{t}Bu	THF	N.D.

[a]Reaction conditions: Epoxy ynamide **5a** (0.3 mmol), solvent (2 mL) and base (0.6 mmol) at rt (25 ^{o}C) for 2 h. [b]Isolated yield of product **7**. N.D. = Not Detected.

After establishing the optimized reaction conditions, we explored the substrate scope for this base promoted cyclization of epoxy-ynamides (Scheme 6). Both electron–donating (**7**-**8, 11**) and electron-withdrawing groups **9-10** on sulfonyl attached benzene ring gave good yields, but electron withdrawing groups (-Cl, -Br) marginally reduced the yield of the product. This methodology also tolerated the presence of a bulky group like 1,3,5-triisopropyl on sulfonyl attached phenyl group affording the desired product **12** in decent yield. Substrates having a naphthyl groups attached to -SO_2 moiety also offered the corresponding product **14** in 75% yield. The scope of this method could be extended further by changing the substituents on the alkyne attached aryl group of the epoxy ynamide. The reaction was very clean and afforded dihydro-1,3-oxazines **15-20** in 64-83% yields in a highly regioselective manner. The epoxy ynamides **5o** and **5p** possessing the naphthyl/ heterocyclic motif group attached to the alkyne also afforded the desired products **21** and **22** in 79% and 72% yield, respectively. In the IR spectra of these compounds, υ(*C*≡*C*) stretch is absent as expected. Presence of a singlet due to alkenyl =C-*H* proton at δ ~ 6.40, in ^{1}H NMR spectra and absence of peaks due to *C*≡*C* bond in the ^{13}C NMR spectra indicated the involvement of alkyne in the reaction. To further confirm the formation of cyclized product, X-ray structures were determined for compounds **7** and **21** (Figure 1). The C1-C2 distance of 1.309(4) Å in compound **7** confirmed the existence of a double bond between these two atoms. It is clear that the C4-C5 distance of 1.318(3) Å is in the double bond in range as expected. Similar parameters were observed for compound **21**.

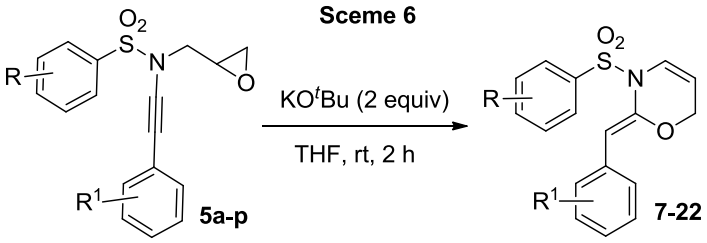
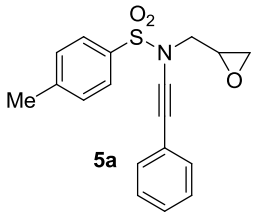
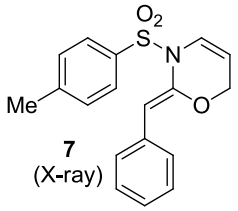
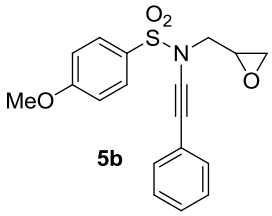
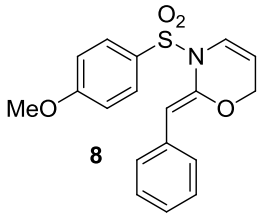
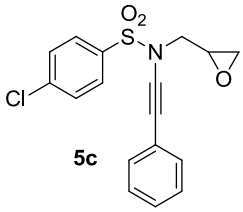
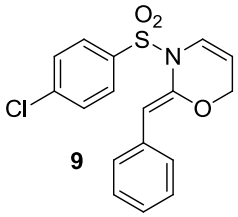
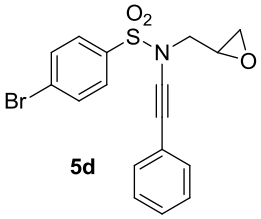
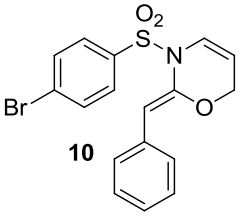
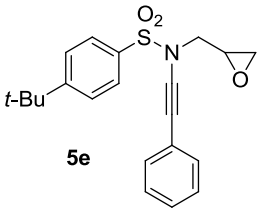
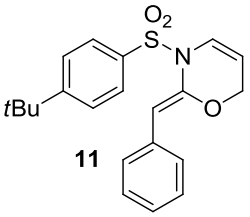
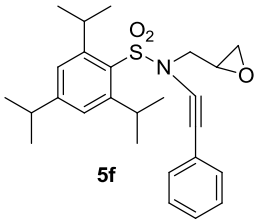
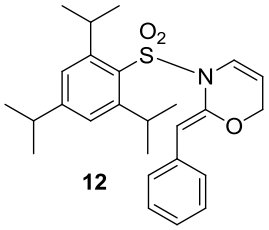
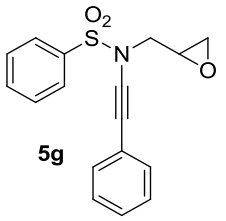
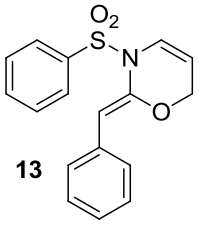
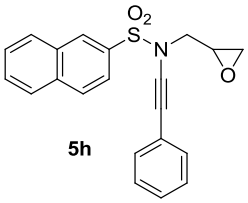
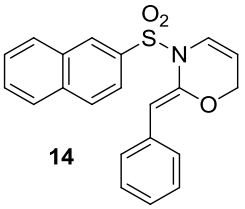
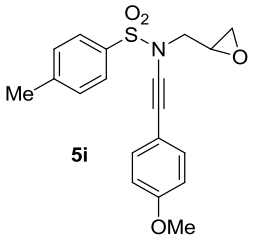
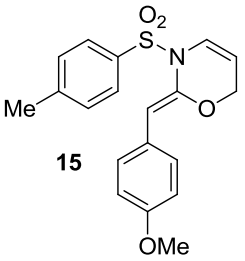
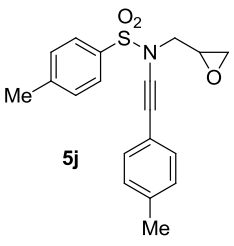
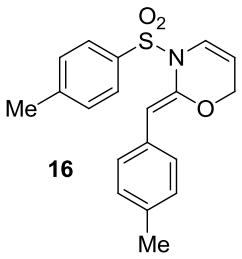
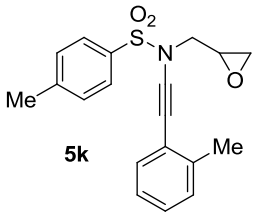
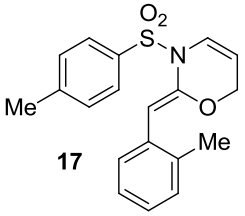
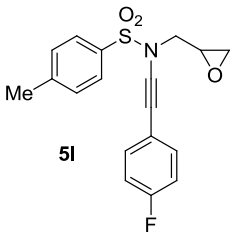
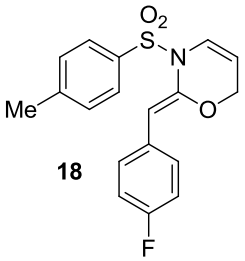
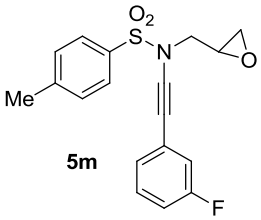
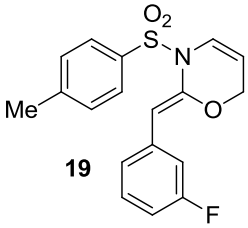
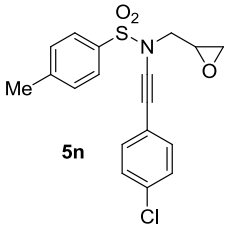
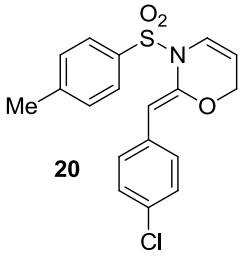
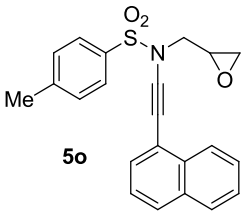
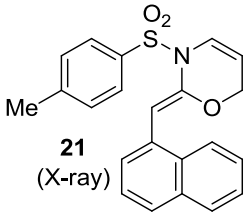
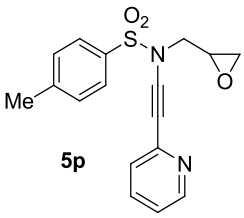
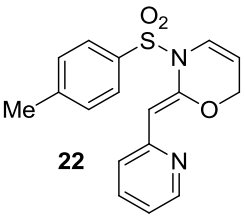


Table 2. Atom economic synthesis of 1,3-oxazines **7-22** from epoxy ynamides **5a-p** (cf. Scheme 6)[a]

Entry	Epoxy ynamides	1,3-Oxazine derivatives	Yield (%)[b]
1	 **5a**	 **7** (X-ray)	82
2	 **5b**	 **8**	79
3	 **5c**	 **9**	68
4	 **5d**	 **10**	65

5	 **5e**	 **11**	78
6	 **5f**	 **12**	66
7	 **5g**	 **13**	80
8	 **5h**	 **14**	75
9	 **5i**	 **15**	80
10	 **5j**	 **16**	71

11	 **5k**	 **17**	83
12	 **5l**	 **18**	64
13	 **5m**	 **19**	66
14	 **5n**	 **20**	74
15	 **5o**	 **21** (X-ray)	79
16	 **5p**	 **22**	72

[a]Standard conditions: Epoxy ynamide **5** (0.3 mmol) in THF (2 mL) and KO^{t}Bu (0.6 mmol) at room temperature for 1-2 h. [b]Isolated yields.

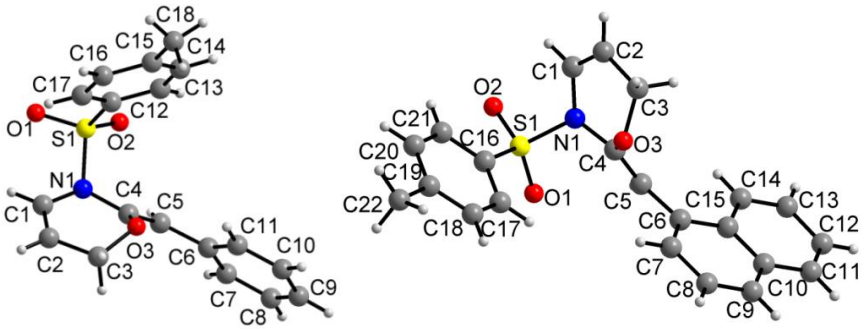
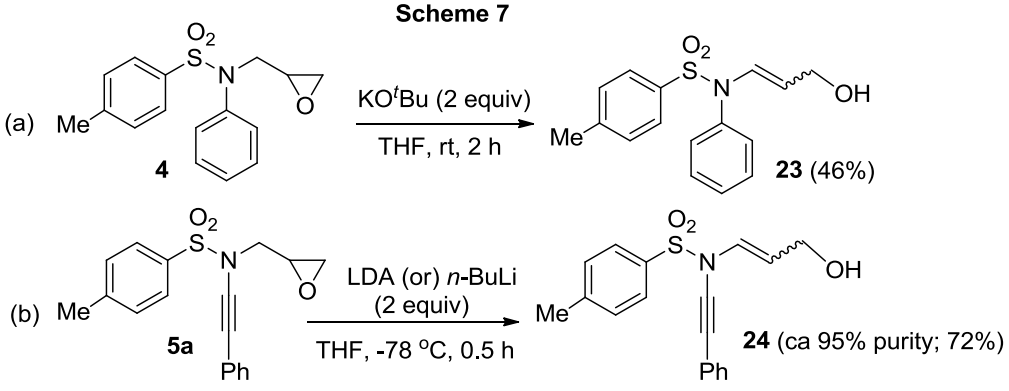


Figure 1. Molecular structure of compounds **7** (left) and **21** (right). Selected bond parameters: Compound **7** N1-C1 1.411(3), C1-C2 1.309(4), C2-C3 1.477(4), C3-O3 1.435(3), O3-C4 1.365(3), C4-N1 1.434(3), C4-C5 1.318(3) (Å). **C**ompound **21** N1-C1 1.423(2), C1-C2 1.313(3), C2-C3 1.470(3), C3-O3 1.438(2), O3-C4 1.3670(17), C4-N1 1.4304(17), C4-C5 1.321(2) (Å).

5.4.2 Control experiments

Control experiments were performed in order to know the plausible catalytic cycle. Thus the reaction of alkyne unsubstituted epoxy sulfonamide **4** with KO^{t}Bu (2 equiv) as a base in THF led to the formation of product **23** in 46% yield (Scheme 7a). This is consistent with that reported in the literature using LDA as a base.[54] The reaction of epoxy ynamide **5a** with LDA or *n*-BuLi at -78 ^{o}C for 0.5 h resulted in isomeric allyl alcohols (*E*+*Z*)-**24** (ca 95% purity; Scheme 7b); at 0 ^{o}C and above, the reaction led to a complex mixture.

Scheme 7

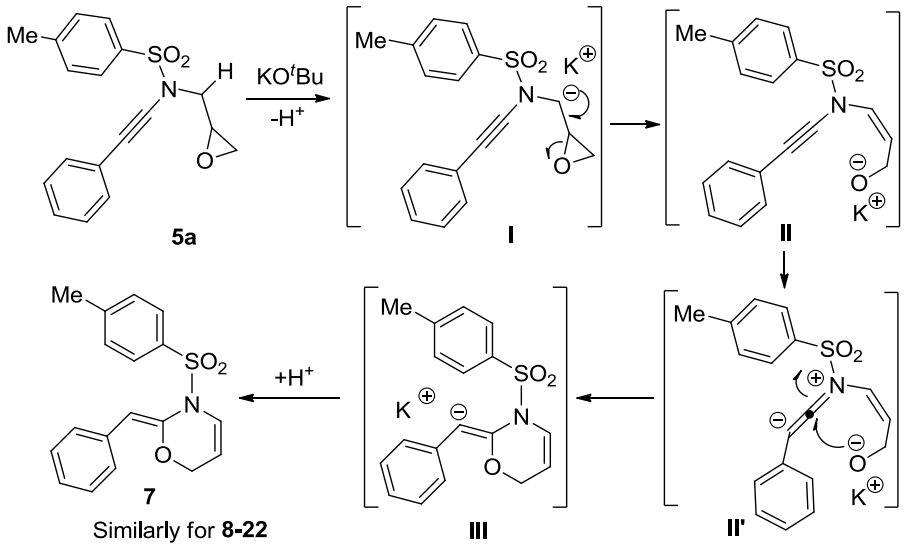


5.4.3 Possible pathway for the base mediated cyclization of epoxy ynamides

Based on the above control experiments, we propose the following pathway for the formation of compound **7** (Scheme 8). Initially, the base abstracts the proton from the

carbon atom adjacent to the nitrogen atom of epoxy ynamide **5a** resulting in carbanion **I**. This carbanion **I** undergoes rearrangement with the opening of epoxide ring affording allyl oxide ion intermediate **II**, which can take up the keteniminium structure **II'**.[1a-c] Subsequent nucleophilic attack of allyloxide ion at the α-position of keteniminium species **II'** followed by protonation provides the cyclized product **7** *via* **III**.

Scheme 8



We also attempted the reaction of epoxy ynamide **5a** with D_2O using KO^{t}Bu in THF. We did not observe the any product formation even after 6 h. Later, we checked the reaction of epoxy ynamide **5a** in THF:D_2O (3:1) mixture by taking excess of KO^{t}Bu (20 equiv). In this case, 64% deuteration took place at the alkenyl –C-*H* position. Interestingly though, we observed ~50% deuteration of one of the protons of methyl group on the tosyl moiety! This may be due to the presence of excess of base.

The attractive features of the above reaction are that the ring expansion of an epoxide to afford ***1,3-oxazines*** has been carried out in the absence of the transition metal catalyst and the reaction is ***atom economic***. In continuation to these, we discuss below an interesting reaction involving intermolecular nucleophilic attack of N_3^- on epoxy ynamides that leads to ***1,4-oxazines.***

5.5 Synthesis of 1,4-oxazines by tandem cyclization of epoxy ynamides with NaN_3

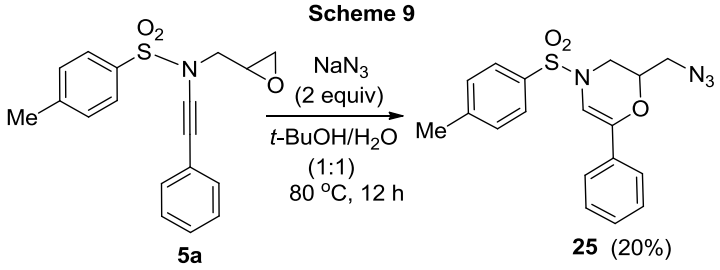
Most of the cyclization reactions of ynamides involve attack of nucleophile at the alkyne carbon α to the nitrogen atom.[7-18] As described in Chapter 4, the rather

unpredicted regio-selective cyclization (i. e. attack of nucleophile at the β-carbon) of ynamides is rarely explored.[5b, 19-21] In this context, transition metal free, regioselective synthesis of 1,4-oxazines by tandem-cyclization of epoxy ynamides in their reaction with NaN_3 is discussed below.

5.5.1 Reaction of epoxy ynamide 5a with NaN_3

In the beginning, we performed the reaction between 4-methyl-*N*-(oxiran-2-ylmethyl)-*N*-(phenylethynyl) benzene sulfonamide **5a** and NaN_3 (2 equiv) in *t*-BuOH/H_2O mixture (1:1) at 80 ^oC for 12 h. Surprisingly, the cyclized product **25** was isolated in 20% yield in the absence of any transition metal catalyst (Scheme 9).

Scheme 9



5a **25** (20%)

In the next stage, we optimized the reaction conditions to increase the yield of the cyclized product **25**. Use of *t*-BuOH alone afforded only a trace amount of the desired product (Table 3, entry 2). The cyclized product was not observed by using H_2O itself as the solvent either (entry 3). Polar protic solvents like MeOH and EtOH furnished only low yields of the cyclized product (entries 4-5). Polar aprotic solvents NMP, DMF, and DMSO also provided only traces of the cyclized compound **25** (entries 7-9). Use of solvents like CH_3CN, toluene, and 1,4-dioxane did not give any product (entries 10-12). To our delight, the reaction proceeded very smoothly in PEG-400 solvent affording the desired product **25** in 70% yield with excellent regioselectivity (entry 13). Later, we found that cyclization occurred even at room temperature (25 ^oC) and delivered the desired product **25** in 72% yield within 12 h (entry 14). Use of one equiv of NaN_3 reduced the yield of desired product (entry 15). In addition, use of gold catalyst [Johnphos[Au](CH_3CN)SbF_6] too diminished the yield of the cyclized product **25** (entry 16). For entries 4-16, it should be noted that 1 equiv of H_2O was used as a reagent. Increasing the amount of H_2O to 2 equiv decreased the yield of the product due to the formation of byproducts which were not isolated (entry 17). We checked a mixture of

solvents also. Among THF, ethanol, acetonitrile, toluene along with PEG-400, EtOH+ PEG-400 solvent system gave better yield of the product (entry 18). Under solvent free condition, there was no reaction (entry 19). Thus the optimal reaction conditions for this cyclization were: **5a** (1.0 equiv), NaN_3 (2.0 equiv), and H_2O (1 equiv) in PEG-400 solvent at rt for 12 h.

Scheme 10

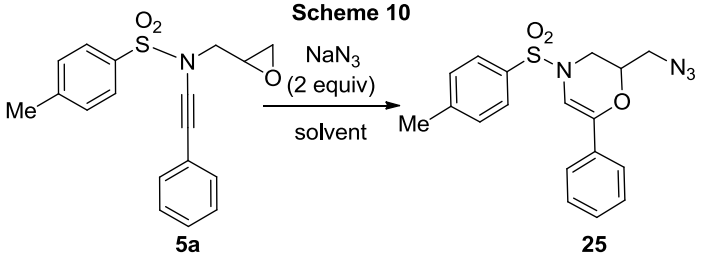


Table 3. Survey of reaction conditions for the cyclization of epoxy ynamide **5a** by using NaN_3[a]

Entry	Solvent	T (^oC)	Yield (%)[b]
1	*t*-BuOH/H_2O	80 ^oC	20
2	*t*-BuOH	80 ^oC	traces[c]
3	H_2O	80 ^oC	N.D.[c]
4	MeOH	70 ^oC	25[c]
5	EtOH	80 ^oC	36
7	NMP	80 ^oC	15
8	DMF	80 ^oC	traces
9	DMSO	80 ^oC	traces
10	CH_3CN	80 ^oC	N.D.[c]
11	Toluene	80 ^oC	N.D.[c]
12	1,4-Dioxane	80 ^oC	N.D.[c]
13	PEG-400	80 ^oC	70
14	PEG-400	rt	72
15	PEG-400	rt	58[d]
16	PEG-400	rt	46[e]

17	PEG-400	rt	52[f]
18	PEG-400+EtOH	rt	65[g]
19	-	rt	N.D.[c]

[a]Reaction conditions: Epoxy ynamide **5a** (0.15 mmol), NaN_3 (0.3 mmol), solvent (1 mL) for 12 h unless otherwise noted, Note: From entries 4-16 we used 1 equiv of H_2O as a reagent. [b]Isolated yields. [c]Unreacted starting material remained. [d]One equiv NaN_3 was used. [e]Johnphos[Au](CH_3CN)SbF_6 (5 mol%) was used. [f]Other byproducts observed when 2 equiv of H_2O was used. [g](1:1) ratio of PEG-400 + EtOH.

After having the optimized reaction conditions in hand, we explored the substrate scope for the cyclization reaction of epoxy-ynamides with sodium azide as the nucleophile (Scheme 11). Sulfonyl attached phenyl ring having both electron–releasing (**25-26**, **29**) and electron-withdrawing groups **27-28** gave good yields, but electron withdrawing groups (-Cl, -Br) marginally reduced the yield. Presence of bulky group like 1,3,5-triisopropyl on sulfonyl attached phenyl group also afforded the desired product **30** in decent yield. Substrates possessing naphthyl group attached to $-SO_2$ moiety also offered the corresponding cyclized product **32** in 64% yield. The scope of this method could be extended by changing the substituents on alkyne attached aryl group of the epoxy ynamide. The reaction was clean and afforded dihydro-1,3-oxazines **33-38** in 52-70% yields in a highly regioselective manner. A band due to N_3^- group was observed at ~ 2100 cm^{-1} in the IR spectra as expected. Also ^{13}C NMR spectra showed the absence of alkyne peaks. The structures of cyclized products **30** and **31** (Figure 2) were confirmed by single crystal X-ray diffraction. In compound **30**, The C3-C4 distance 1.327(4) Å establishes the presence of a double bond between these two atoms. Two single bonds C(5)-N(2) and O(3)-C(3) are newly formed. Similar structural features were observed in compound **31** also.

Scheme 11

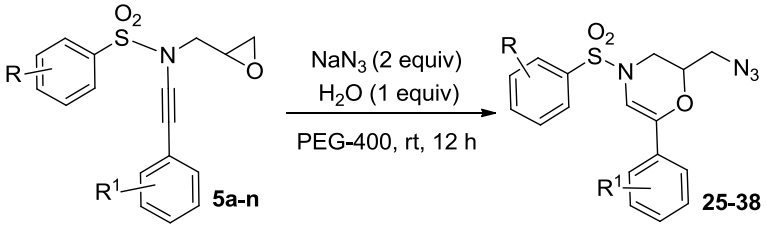
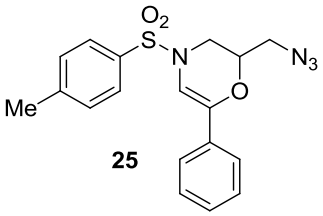
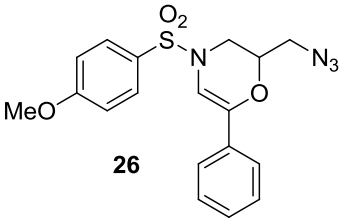
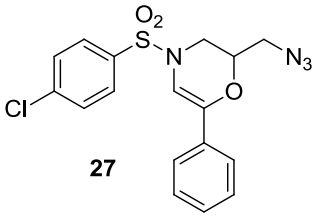
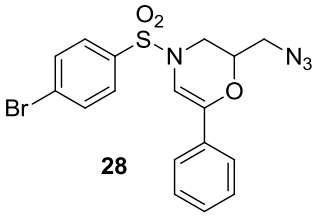
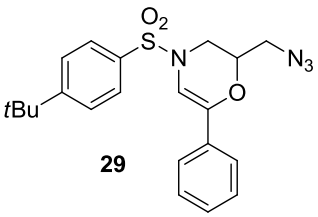
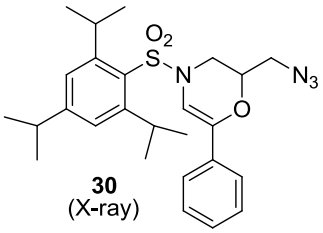
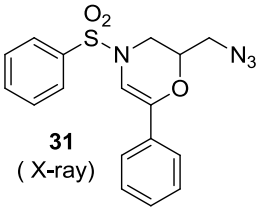
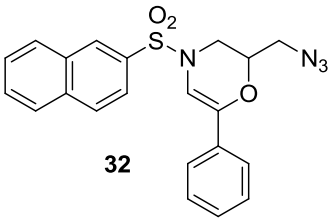
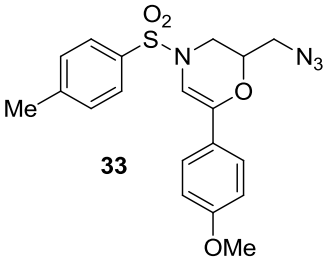
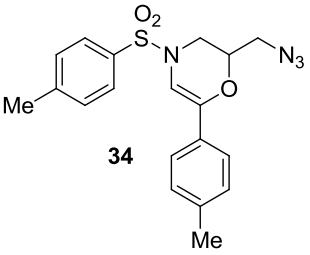
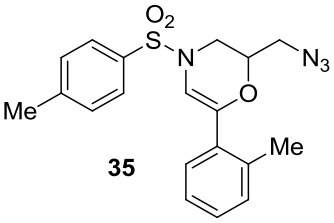
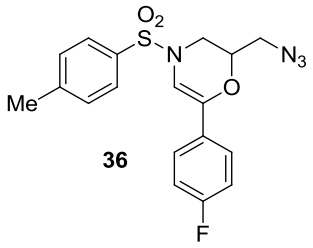
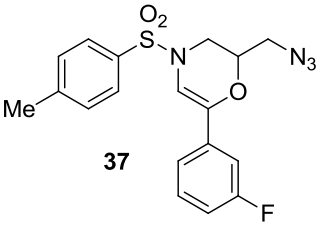
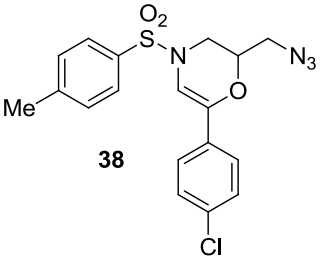


Table 4. Transition metal free synthesis of 1,4-oxazines **25-38** from epoxy ynamides **5a-n**[a]

Entry	Epoxy ynamides	1,4-Oxazine derivatives	Yield (%)[b]
1	**5a**	 **25**	72
2	**5b**	 **26**	68
3	**5c**	 **27**	56
4	**5d**	 **28**	48
5	**5e**	 **29**	65

6	**5f**	 **30** (X-ray)	70
7	**5g**	 **31** (X-ray)	66
8	**5h**	 **32**	64
9	**5i**	 **33**	66
10	**5j**	 **34**	70
11	**5k**	 **35**	56

12	**5l**	 **36**	60
13	**5m**	 **37**	55
14	**5n**	 **38**	52

[a]Reaction conditions: Epoxy ynamide **5** (0.3 mmol), NaN_3 (0.6 mmol), H_2O (0.3 mmol), PEG-400 (2 mL) at rt for 12 h unless otherwise noted. [b]Isolated yields.

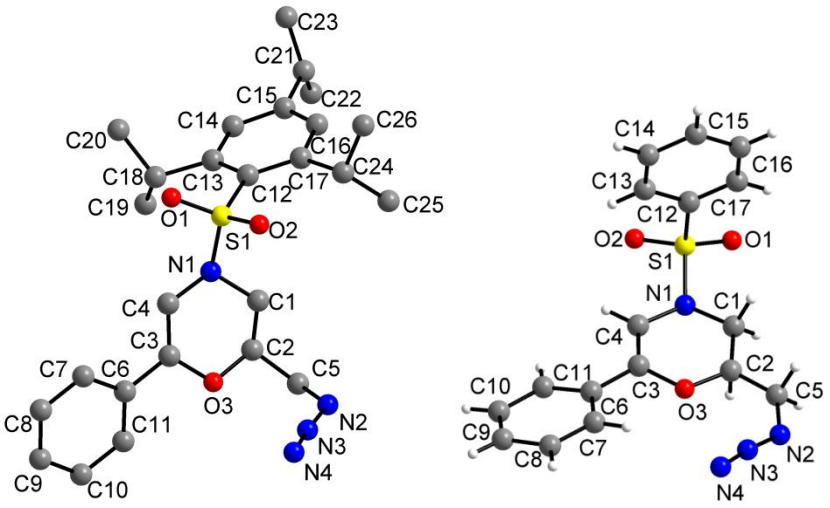


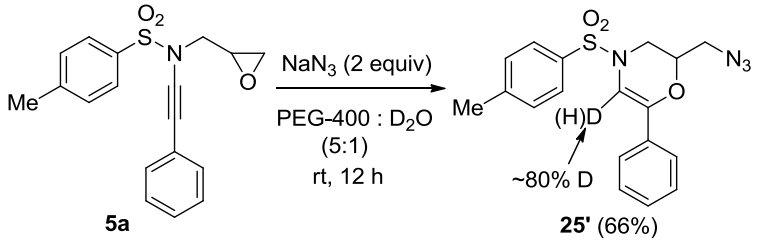
Figure 2. Molecular structures of compounds **30** (left) and **31** (right) [H-atoms are omitted for clarity]. Selected bond parameters: Compound **30** O3-C3 1.382(4), C3-C4 1.327(4), C4-N1 1.410(4), N1-C1 1.457(5), C1-C2 1.302(6), C2-C5 1.495(5), C5-N2 1.435(6), N2-N3 1.169(6), N3-N4 1.111(6), C2-O3 1.406(4) (Å). Compound **31** O3-C3

1.371(5), C3-C4 1.317(6), C4-N1 1.425(5), N1-C1 1.440(6), C1-C2 1.380(7), C2-C5 1.441(7), C5-N2 1.297(8), N2-N3 1.184(8), N3-N4 1.119(7), C2-O3 1.370(5) (Å).

5.5.2 Control experiment

To understand the plausible catalytic cycle, we have performed deuterium-labelling experiment. Thus the reaction of epoxy ynamide **5a** (1.0 equiv), NaN_3 (2.0 equiv) in PEG-400 and D_2O (5:1) mixture furnished compound **25'** (Scheme 12). Notably, ~80% deuterium incorporation was observed at the alkenyl C-*H* position of **25'**. Formation of the deuterium incorporated compound **25'** clearly suggests the key role of water as a proton source in the cyclization process.

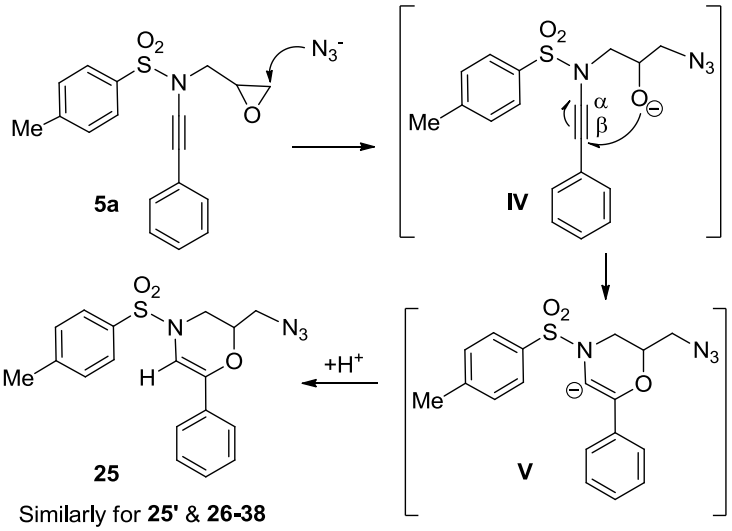
Scheme 12



5.5.3 Possible pathway for the formation of 1,4-oxazine derivative 25

On the basis of the control experiment, we propose the following pathway for the formation of compound **25** (Scheme 13). Initially, intermolecular nucleophilic attack of azide onto the less hindered side of epoxide group of epoxy ynamide leads to intermediate **IV**. Subsequent **6-*endo-dig*** attack of oxide ion at the β-position of the ynamide results in intermediate **V**. This is followed by the protonation of intermediate **V** which delivers the cyclized product **25**.

Scheme 13



5.5.4 Synthesis of 1,4-oxazines 39-42 from epoxy alkynes 6a-d

Interestingly, epoxy tethered alkyne substrates **6a-d** that contain NCH_2-C≡C moiety also underwent **6-*endo-dig*** cyclization with sodium azide affording the 1,4-oxazines **39-42** in good yields (Scheme 14). Both electron releasing and electron withdrawing groups on sulfonyl moiety worked well and gave the corresponding 1,4-oxazines **39-41** in good yields (Table 5 entries1-3). IR spectra exhibited a band at ~ 2100 cm^{-1} corresponding to azide functional group. The ^{1}H NMR spectra showed two singlets at δ ~ 6.00 (alkenyl C-*H*), δ ~ 3.30-3.40 (-CH_2 protons). The absence of alkyne peaks and the presence of a peak at δ ~ 101 due to alkenyl *C*-H carbon in ^{13}C NMR spectra supported the formation of cyclized products.

Scheme 14

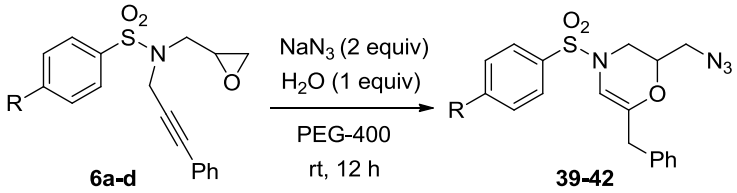
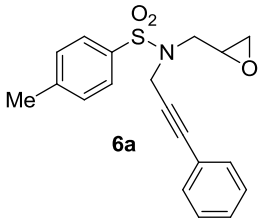
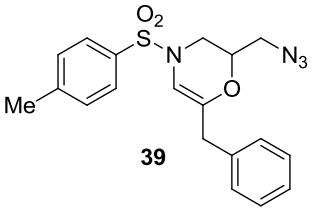
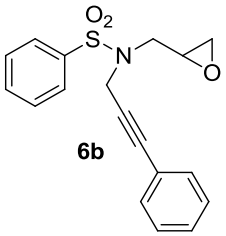
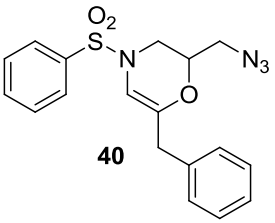
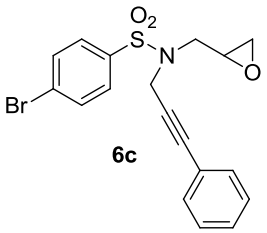
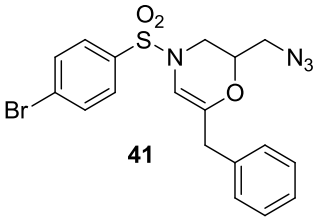
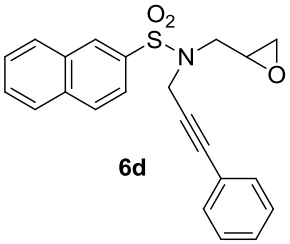
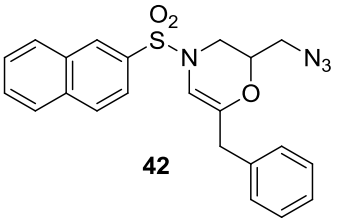


Table 5. Synthesis of 1,4-oxazines **39-42** from epoxy alkynes **6a-d**[a]

Entry	Epoxy alkynes	1,4-Oxazine derivatives	yield (%)[b]

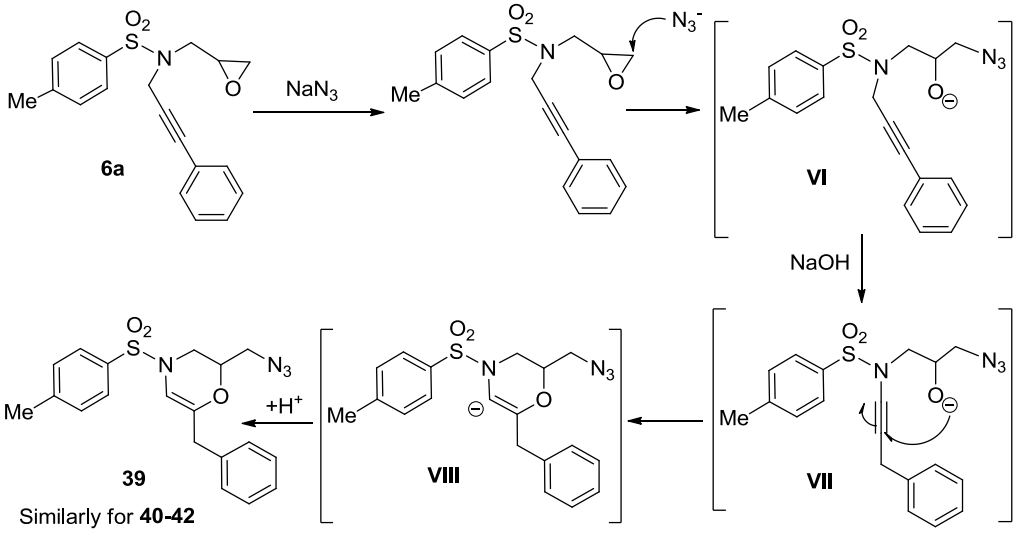
1	 **6a**	 **39**	75
2	 **6b**	 **40**	73
3	 **6c**	 **41**	66
4	 **6d**	 **42**	72

[a]Reaction conditions: Epoxy alkyne **6** (0.3 mmol), NaN_3 (0.6 mmol), H_2O (0.3 mmol), PEG-400 (2 mL) at rt for 12 h unless otherwise noted. [b]Isolated yields.

5.5.5 Possible pathway for the formation of 1,4-oxazine 39

We propose the following pathway for the formation of compound **39** (Scheme 15). Initially, intermolecular nucleophilic attack of azide onto the less hindered side of epoxide group of epoxy tethered alkynes **6a** leads to intermediate **VI**. In the presence of base, intermediate **VI** can isomerize to species **VII**.[55] Subsequent **6-*endo-dig*** attack of oxide ion at the alkyne group of **VII** results in **VIII**. Later, protonation of intermediate **VIII** delivers the cyclized product **39**.

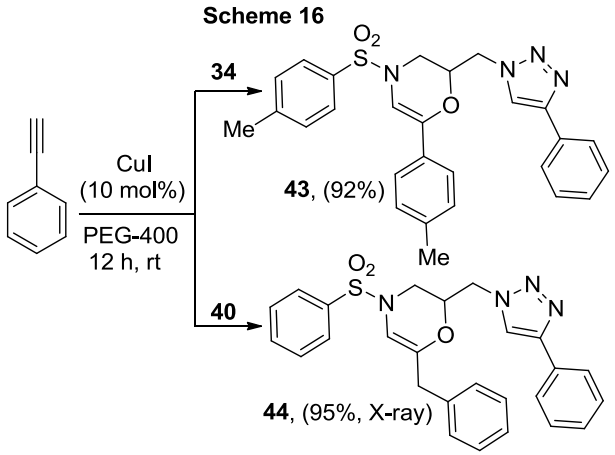
Scheme 15



5.5.6 Click reaction of compounds 34 and 40 with phenyl acetylene

We utilized the above formed 1,4-oxazines **34** and **40** possessing azide moiety in the familiar click reaction. Thus the reaction of 1,4-oxazines **34** and **40** with phenyl acetylene using CuI as a catalyst in PEG-400 at rt for 12 h afforded the corresponding triazole appended 1,4-oxazines **43**-**44** in excellent yields (Scheme 16). Formation of compounds **43**-**44** was analyzed by IR, NMR and HRMS data. The structure of compound **44** was confirmed by single crystal X-ray analysis (Figure 3). The C1-C2 distance 1.326(3) Å in compound **44** proves the existence of a double bond between these two atoms.These data indirectly prove the identity of compounds **39-42**.

Scheme 16



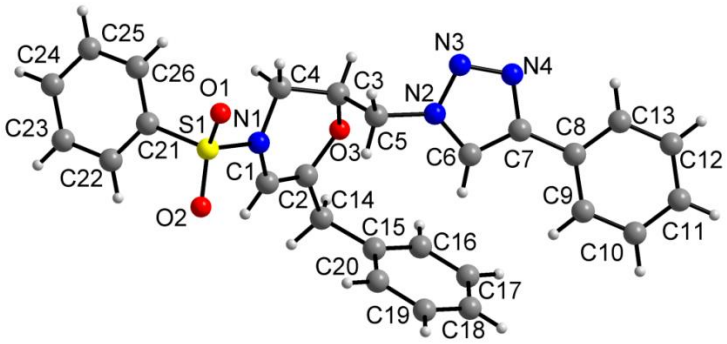
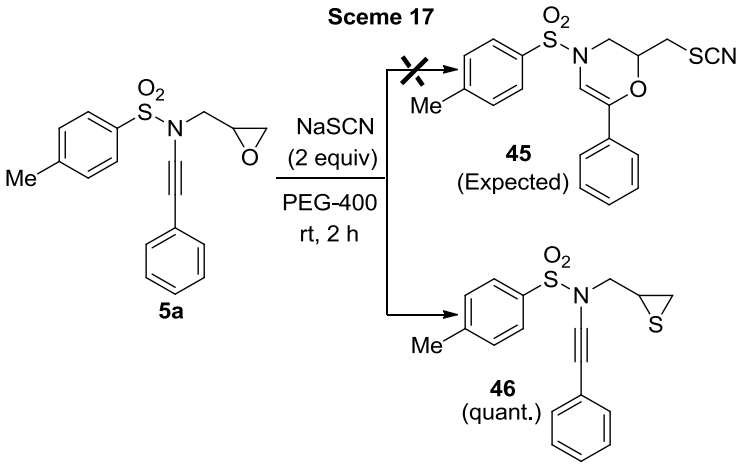


Figure 3. Molecular structure of compound **44**. Selected bond parameters: N1-C1 1.417(3), C1-C2 1.326(3), C2-O3 1.379(3), O3-C3 1.432(3), C3-C4 1.511(3), C4-N1 1.469(3), C2-C14 1.498(3), C14-C15 1.512(4), C3-C5 1.489(3), C5-N2 1.471(3), N2-N3 1.330(3), N3-N4 1.322(3), N4-C7 1.360(3), C7-C6 1.370(3), C6-N2 1.328(3) (Å).

5.6 Reaction of epoxy ynamide 5a with sodium thiocyanate

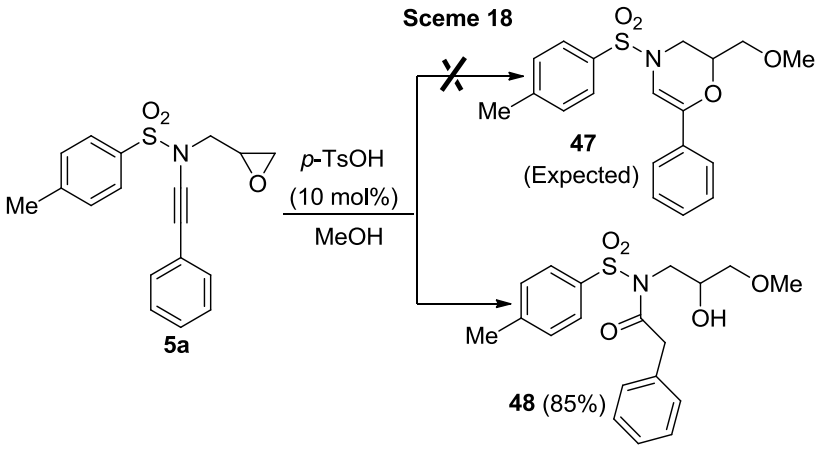
We performed the reaction of epoxy ynamide **5a** with thiocyanate (SCN^-; 2 equiv) in a manner similar to that with the azide in PEG-400 solvent. This reaction provided the thiirane ynamide **46**, instead of compound **45** that is analogous to azide products (Scheme 17). IR spectrum of compound **46** showed characteristic peak of the alkyne at 2236 cm^{-1}; this alkyne group [δ 82.2 and 71.3] was also seen clearly in the ^{13}C NMR spectrum. HRMS data showed the correct mass for compound **46**. Although synthesis of thiiranes from oxiranes is known by using NaSCN as a sulfur source,[56] the reports are rather limited in number. However, since the products of type **46** were not our synthetic targets, we did not proceed further in this direction.



5.7 Reactivity of epoxy ynamide 5a in the presence of *p*-toluene sulfonic acid (PTSA)

Treatment of epoxy ynamide **5a** with a catalytic amount of PTSA (10 mol%) in MeOH led only to the formation of MeOH/water addition product **48**. In this process, MeOH acts as a nucleophile and attacks the less hindered side of epoxide moiety. The alkyne group of **5a** is hydrolyzed due to adventitious water. Compound **48** shows characteristic peaks for -OH and -C=O groups in the IR spectrum at 3499 and 1711 cm^{-1}, respectively. ^{1}H NMR spectrum shows three singlets at δ 3.61 (2H), 3.30 (3H) and 2.44 (3H) ascribable to $–COCH_2$, OCH_3 (from MeOH), and $–CH_3$ groups. ^{13}C NMR spectrum shows a peak at δ 171.1 due to the presence of –*C*=O group. ^{13}C-DEPT NMR spectrum of compound **48** is consistent with the presence of 3 CH_2 and 2 CH_3 groups (one from tosyl and other from MeOH). HRMS data also tallies with the structure of compound **48** as shown. Since the product was not our synthetic target, we did not continue this work.

Sceme 18



SUMMARY – PART B

1. A base assisted intramolecular *6-exo-dig* closure of epoxy ynamides leading to regio- and stereo-selective synthesis of 1,3-oxazines in an atom economic approach under *transition metal free conditions* has been developed.

2. An unprecedented transition metal free regioselective cyclization of epoxy ynamides using sodium azide for the synthesis of 1,4-oxazines in a *6-endo-dig* fashion has been demonstrated. This methodology was extended to epoxy tethered alkynes. Here also, ***6****-endo-dig* mode cyclization was observed. Deuterium-labeling experiment supported the important role of water as a proton source in cyclization process. The attractive features of our methodology are the use of (a) an environmentally benign PEG-400 solvent and (b) simple sodium azide as the nucleophilic source under the transition metal free conditions.

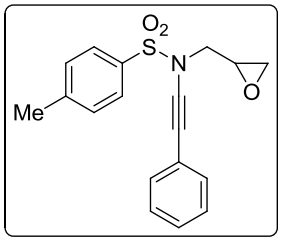
EXPERIMENTAL SECTION

Details of instruments, standards etc. are already given in Chapter 3. Epoxy sulfonamides (**1a-h**),[45] bromoalkynes (**2a-h**),[46] phenyl propargyl bromide (**3**),[47] and epoxy tethered sulfonamide (**4**)[48] were prepared by using standard literature reports. Epoxy ynamides **5a-p** were prepared following a known protocol with slight modification[49] while epoxy alkynes **6a-d** were synthesized by following a known method.[50]

6.1 Synthesis of epoxy ynamide precursors 5a-p

To a mixture of 4-methyl-*N*-(oxiran-2-ylmethyl)benzenesulfonamide **1a** (1.00 g, 4.40 mmol), $CuSO_4 \cdot 5H_2O$ (0.220 g, 0.88 mmol), 1,10-phenanthroline monohydrate (0.349 g, 1.76 mmol) and K_2CO_3 (1.520 g, 11.0 mmol) in dry THF (20 mL), (bromoethynyl)benzene **2a** (0.956 g, 5.28 mmol) was added. The vessel was stoppered under nitrogen atmosphere and heated overnight on an oil-bath maintained at 70 ^oC. The mixture was passed through celite and concentrated in vacuum. The crude product was purified by using silica gel column chromatography to obtain the pure epoxy ynamide **5a** by using hexane-ethyl acetate (8:2) as the eluent. Compounds **5b-p** were prepared following the same procedure and by using the same molar quantities.

Compound 5a



Yield: 1.224 g (85%, gummy liquid).

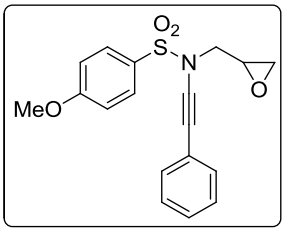
IR (Neat): 3058, 2992, 2921, 2236, 1600, 1501, 1441, 1364, 1162, 1085, 1019, 937, 751, 690 cm^{-1}.

^{1}H NMR: δ 7.89 (d, *J* = 8.0 Hz, 2H), 7.39 (d, *J* = 7.6 Hz, 4H), 7.33-7.32 (m, 3H), 3.71-3.55 (m, 2H), 3.26-3.25 (m, 1H), 2.85 (t, *J* = 4.4 Hz, 1H), 2.69-2.67 (m, 1H), 2.48 (s, 3H).

^{13}C NMR: δ 145.0, 134.3, 131.4, 129.9, 128.3, 128.0, 127.9, 122.5, 82.3, 70.7, 54.0, 49.3, 45.6, 21.7.

HRMS (ESI): Calcd. for $C_{18}H_{17}FN_3SNa$ [M^++Na]: *m/z* 350.0827. Found: 350.0829.

Compound 5b



Yield: 1.330 g (88%, gummy liquid).

IR (Neat): 3068, 3014, 2926, 2844, 2236, 1600, 1496, 1447, 1359, 1315, 1260, 1162, 1090, 1025, 942, 756, 690 cm^{-1}.

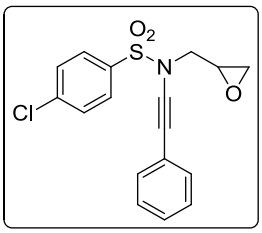
^{1}H NMR: δ 7.94 (d, *J* = 8.8 Hz, 2H), 7.40-7.38 (m, 2H), 7.32-7.30 (m, 3H), 7.05 (d, *J* = 9.2 Hz, 2H), 3.89 (s, 3H), 3.69-3.56 (m, 2H), 3.26-3.22 (m, 1H), 2.84 (t, *J* = 4.4 Hz, 1H), 2.68-2.66 (m, 1H).

^{13}C NMR: δ 163.9, 131.4, 130.1, 128.7, 128.4, 128.0, 122.6, 114.4, 82.5, 70.7, 55.8, 53.9, 49.3, 45.6.

LC-MS: *m/z* 344 $[M+1]^+$.

Anal. Calcd. for $C_{18}H_{17}NO_4S$: C, 62.96; H, 4.99; N, 4.08; Found: C, 62.86; H, 4.91; N, 4.13.

Compound 5c



Yield: 1.255 g (82%, gummy liquid).

IR (Neat): 3090, 3058, 3003, 2932, 2241, 1589, 1480, 1375, 1282, 1184, 1096, 1008, 948, 767, 696 cm^{-1}.

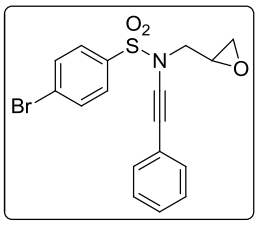
^{1}H NMR: δ 7.95 (d, *J* = 8.8 Hz, 2H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.41-7.37 (m, 2H), 7.34-7.32 (m, 3H), 3.72-3.62 (m, 2H), 3.28-3.24 (m, 1H), 2.86 (t, *J* = 4.4 Hz, 1H), 2.69-2.67 (m, 1H).

^{13}C NMR: δ 140.6, 135.7, 131.6, 129.6, 129.3, 128.4, 128.3, 122.2, 81.7, 71.0, 54.2, 49.2, 45.5.

LC-MS: *m/z* 348 $[M+1]^{+}$.

Anal. Calcd. for $C_{17}H_{14}ClNO_3S$: C, 58.70; H, 4.06; N, 4.03; Found: C, 58.85; H, 3.98; N, 4.09.

Compound 5d



Yield: 1.346 g (78%, gummy liquid).

IR (Neat): 3058, 3003, 2932, 2236, 1677, 1573, 1480, 1386, 1271, 1184, 1090, 926, 707 cm^{-1}.

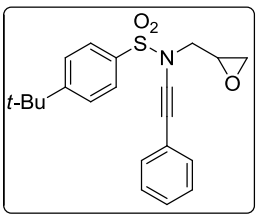
^{1}H NMR: δ 7.84 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.38-7.35 (m, 2H), 7.31-7.29 (m, 3H), 3.63 (d, *J* = 5.2 Hz, 2H), 3.24-3.20 (m, 1H), 2.82 (t, *J* = 4.4 Hz, 1H), 2.65-2.64 (m, 1H).

^{13}C NMR: δ 136.2, 132.5, 131.5, 129.3, 129.2, 128.4, 128.3, 122.1, 81.6, 71.0, 54.1, 49.1, 45.5.

LC-MS: *m/z* 392 and 394 $[M]^{+}$ and $[M+2]^{+}$.

Anal. Calcd. for $C_{17}H_{14}BrNO_3S$: C, 52.05; H, 3.60; N, 3.57; Found: C, 52.19; H, 3.68; N, 3.51.

Compound 5e



Yield: 1.301 g (80%, gummy liquid).

IR (Neat): 2964, 2866, 2230, 1600, 1447, 1364, 1266, 1178, 1107, 1014, 937, 844, 767 cm^{-1}.

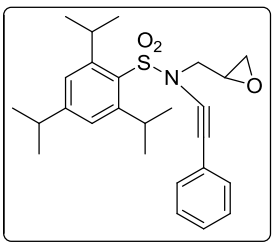
^1H NMR: δ 7.94 (d, *J* = 8.4 Hz, 2H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.41-7.39 (m, 2H), 7.32-7.30 (m, 3H), 3.69-3.58 (m, 2H), 3.28-3.24 (m, 1H), 2.84 (t, *J* = 4.4 Hz, 1H), 2.69-2.67 (m, 1H), 1.37 (s, 9H).

^{13}C NMR: δ 157.9, 134.3, 131.4, 128.4, 128.0, 127.7, 126.3, 122.6, 82.5, 70.7, 54.0, 49.4, 45.6, 35.3, 31.1.

LC-MS: *m/z* 368 $[M-1]^+$.

Anal. Calcd. for $C_{21}H_{23}NO_3S$: C, 68.27; H, 6.27; N, 3.79; Found: C, 68.36; H, 6.21; N, 3.85.

Compound 5f



Yield: 1.47 g (76%, gummy liquid).

IR (Neat): 3068, 2970, 2882, 2241, 1611, 1468, 1425, 1381, 1184, 1047, 937, 849, 756 cm^{-1}.

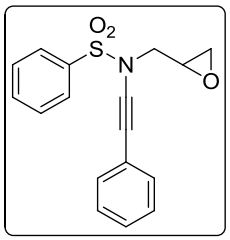
^1H NMR: δ 7.26-7.24 (m, 5H), 7.22-7.18 (m, 2H), 4.22-4.15 (m, 2H), 3.85-3.80 (m, 1H), 3.66-3.61 (m, 1H), 3.42-3.37 (m, 1H), 2.99-2.92 (m, 2H), 2.77-2.75 (m, 1H), 1.31-1.29 (m, 18H).

^{13}C NMR: δ 154.4, 152.2, 131.3, 129.8, 128.2, 127.8, 124.1, 122.7, 82.2, 72.3, 51.9, 49.4, 46.0, 34.3, 29.9, 24.9, 23.6.

LC-MS: *m/z* 440 $[M+1]^+$.

Anal. Calcd. for $C_{26}H_{33}NO_3S$: C, 71.04; H, 7.57; N, 3.19; Found: C, 71.15; H, 7.51; N, 3.26.

Compound 5g



Yield: 1.241 g (90%, gummy liquid).

IR (Neat): 3057, 2997, 2931, 2236, 1605, 1447, 1370, 1184, 1096, 1019, 937, 751 cm^{-1}.

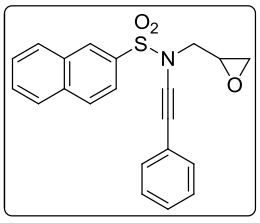
^1H NMR: δ 7.98 (d, *J* = 8.0 Hz, 2H), 7.65 (t, *J* = 7.6 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 2H), 7.37-7.35 (m, 2H), 7.28-7.27 (m, 3H), 3.61 (d, *J* = 5.2 Hz, 2H), 3.22-3.18 (m, 1H), 2.79 (t, *J* = 4.4 Hz, 1H), 2.63-2.62 (m, 1H).

^{13}C NMR: δ 137.2, 134.1, 131.5, 129.3, 128.4, 128.2, 127.8, 122.4, 82.2, 70.7, 54.1, 49.3, 45.5.

LC-MS: *m/z* 314 $[M+1]^+$.

Anal. Calcd. for $C_{17}H_{15}NO_3S$: C, 65.16; H, 4.82; N, 4.47; Found: C, 65.26; H, 4.76; N, 4.41.

Compound 5h



Yield: 1.231 g (77%, gummy liquid).

IR (Neat): 3063, 3003, 2932, 2241, 1589, 1507, 1441, 1364, 1271, 1167, 1080, 1014, 943, 866, 745 cm^{-1}.

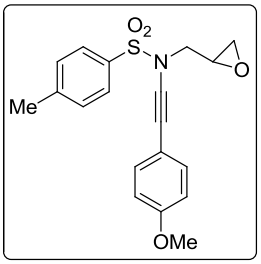
^1H NMR: δ 8.60 (s, 1H), 8.03-8.00 (m, 3H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.71-7.63 (m, 2H), 7.43-7.41 (m, 2H), 7.33-7.31 (m, 3H), 3.78-3.68 (m, 2H), 3.30-3.26 (m, 1H), 2.84 (t, *J* = 4.4 Hz, 1H), 2.70-2.69 (m, 1H).

^{13}C NMR: δ 135.4, 134.1, 132.0, 131.5, 129.6$_9$, 129.6$_5$, 129.5$_1$, 129.4$_8$, 128.4, 128.2, 128.1, 128.0, 122.6, 122.5, 82.4, 70.9, 54.2, 49.4, 45.6.

LC-MS: *m/z* 364 $[M+1]^+$.

Anal. Calcd. for $C_{21}H_{17}NO_3S$: C, 69.40; H, 4.71; N, 3.85; Found: C, 69.32; H, 4.76; N, 3.81.

Compound 5i



Yield: 1.352 g (86%, gummy liquid).

IR (Neat): 3074, 3008, 2937, 2833, 2236, 1605, 1512, 1468, 1364, 1260, 1162, 1079, 1041, 948, 838, 668 cm^{-1}.

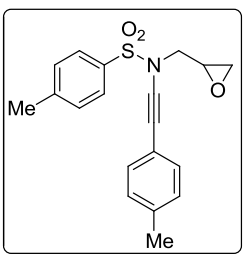
^{1}H NMR: δ 7.88 (d, *J* = 8.4 Hz, 2H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 9.2 Hz, 2H), 3.82 (s, 3H), 3.69-3.64 (m, 1H), 3.57-3.52 (m, 1H), 3.26-3.22 (m, 1H), 2.84 (t, *J* = 4.4 Hz, 1H), 2.67-2.65 (m, 1H), 2.48 (s, 3H).

^{13}C NMR: δ 159.7, 145.0, 134.3, 133.5, 129.8, 127.8, 114.4, 114.0, 80.9, 70.3, 55.3, 54.1, 49.3, 45.6, 21.7.

LC-MS: *m/z* 358 $[M+1]^+$.

Anal. Calcd. for $C_{19}H_{19}NO_4S$: C, 63.85; H, 5.36; N, 3.92; Found: C, 63.76; H, 5.41; N, 3.87.

Compound 5j



Yield: 1.262 g (84%, gummy liquid).

IR (Neat): 3003, 2915, 2236, 1595, 1512, 1364, 1173, 1079, 1019, 816, 669 cm^{-1}.

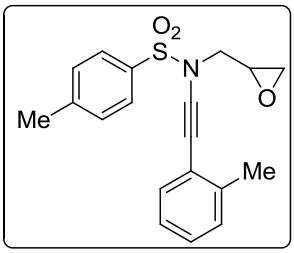
^{1}H NMR: δ 7.89 (d, *J* = 8.4 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 3.68-3.56 (m, 2H), 3.26-3.21 (m, 1H), 2.83 (t, *J* = 4.4 Hz, 1H), 2.67-2.65 (m, 1H), 2.46 (s, 3H), 2.35 (s, 3H).

^{13}C NMR: δ 145.0, 138.3, 134.3, 131.5, 129.9, 129.1, 127.8, 119.4, 81.7, 70.6, 54.1, 49.3, 45.6, 21.7, 21.5.

LC-MS: *m/z* 342 $[M+1]^{+}$.

Anal. Calcd. for $C_{19}H_{19}NO_3S$: C, 66.84; H, 5.61; N, 4.10; Found: C, 66.72; H, 5.56; N, 4.21.

Compound 5k



Yield: 1.217 g (81%, gummy liquid).

IR (Neat): 3063, 2997, 2926, 2236, 1600, 1490, 1359, 1167, 1085, 1019, 942, 806, 756 cm^{-1}.

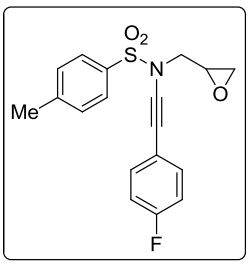
^{1}H NMR: δ 7.89 (d, *J* = 8.4 Hz, 2H), 7.40-7.34 (m, 3H), 7.22-7.20 (m, 2H), 7.17-7.12 (m, 1H), 3.73-3.59 (m, 2H), 3.28-3.24 (m, 1H), 2.85 (t, *J* = 4.4 Hz, 1H), 2.69-2.68 (m, 1H), 2.48 (s, 3H), 2.41 (s, 3H).

^{13}C NMR: δ 145.1, 139.8, 134.4, 131.5, 129.9, 129.5, 128.0, 127.8, 125.6, 122.4, 86.1, 69.7, 54.1, 49.3, 45.5, 21.7, 20.7.

LC-MS: *m/z* 340 $[M-1]^{+}$.

Anal. Calcd. for $C_{19}H_{19}NO_3S$: C, 66.84; H, 5.61; N, 4.10; Found: C, 66.72; H, 5.68; N, 4.16.

Compound 5l



Yield: 1.170 g (77%, gummy liquid).

IR (Neat): 3063, 3003, 2926, 2241, 1595, 1501, 1359, 1222, 1167, 1085, 1014, 948, 838, 663 cm^{-1}.

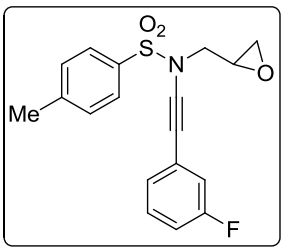
^{1}H NMR: δ 7.86 (d, *J* = 8.0 Hz, 2H), 7.38-7.34 (m, 4H), 6.99 (t, *J* = 8.8 Hz, 2H), 3.65-3.56 (m, 2H), 3.23-3.19 (m, 1H), 2.81 (t, *J* = 4.4 Hz, 1H), 2.66-2.63 (m, 1H), 2.45 (s, 3H).

^{13}C NMR: δ 162.4 (d, *J* = 247.8 Hz), 145.1, 134.3, 133.6, 133.5, 129.9, 127.8, 118.6 (d, *J* = 3.6 Hz), 115.6 (d, *J* = 22.0 Hz), 82.0, 69.6, 54.0, 49.3, 45.4, 21.7.

LC-MS: *m/z* 346 $[M+1]^{+}$.

Anal. Calcd. for $C_{18}H_{16}FNO_3S$: C, 62.59; H, 4.67; N, 4.06; Found: C, 62.45; H, 4.59; N, 4.18.

Compound 5m



Yield: 1.201 g (79%, gummy liquid).

IR (Neat): 3057, 2981, 2241, 1578, 1436, 1364, 1271, 1173, 1123, 1014, 877, 740 cm^{-1}.

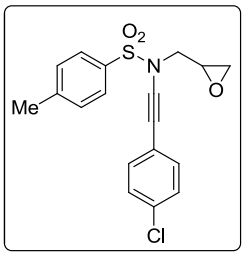
^{1}H NMR: δ 7.84 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.26-7.22 (m, 1H), 7.15-7.13 (m, 1H), 7.06-6.96 (m, 2H), 3.62-3.60 (m, 2H), 3.23-3.19 (m, 1H), 2.82 (t, *J* = 4.4 Hz, 1H), 2.65-2.63 (m, 1H), 2.45 (s, 3H).

^{13}C NMR: δ 162.3 (d, *J* = 244.9 Hz), 145.2, 134.2, 130.0, 129.9, 127.8, 127.1$_1$, 127.0$_8$, 124.4 (d, *J* = 9.5 Hz), 117.9 (d, *J* = 22.5 Hz), 115.2 (d, *J* = 21.0 Hz), 83.3, 69.8 (d, *J* = 35.0 Hz), 54.0, 49.3, 45.5, 21.7.

LC-MS: *m/z* 346 $[M+1]^+$.

Anal. Calcd. for $C_{18}H_{16}FNO_3S$: C, 62.59; H, 4.67; N, 4.06; Found: C, 62.47; H, 4.58; N, 4.12.

Compound 5n



Yield: 1.194 g (75%, gummy liquid).

IR (Neat): 3074, 2920, 2849, 2235, 1726, 1594, 1490, 1364, 1177, 1084, 936, 832, 723 cm^{-1}.

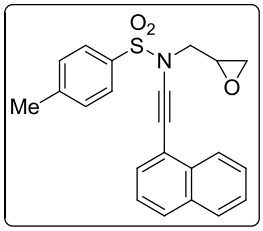
^{1}H NMR: δ 7.87 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.32-7.26 (m, 4H), 3.63-3.61 (m, 2H), 3.25-3.21 (m, 1H), 2.83 (t, *J* = 4.4 Hz, 1H), 2.66-2.64 (m, 1H), 2.47 (s, 3H).

^{13}C NMR: δ 145.2, 134.3, 133.9, 132.6, 129.9, 128.6, 127.8, 121.1, 83.2, 69.7, 54.0, 49.3, 45.5, 21.7.

LC-MS: *m/z* 362 $[M-1]^+$.

Anal. Calcd. for $C_{18}H_{16}ClNO_3S$: C, 59.75; H, 4.46; N, 3.87; Found: C, 59.67; H, 4.52; N, 3.81.

Compound 5o



Yield: 1.213 g (73%, gummy liquid).

IR (Neat): 3058, 2991, 2926, 2241, 1594, 1495, 1358, 1254, 1177, 1001, 1046, 936, 799, 696 cm^{-1}.

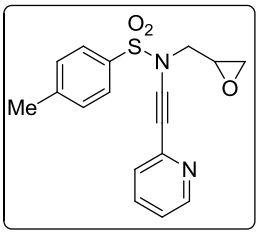
^1H NMR: δ 8.30 (d, *J* = 8.0 Hz, 1H), 7.98-7.96 (m, 2H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.82 (d, *J* = 8.4 Hz, 1H), 7.65-7.53 (m, 3H), 7.46-7.42 (m, 1H), 7.37 (d, *J* = 8.0 Hz, 2H), 3.77-3.75 (m, 2H), 3.36-3.32 (m, 1H), 2.89 (t, *J* = 4.4 Hz, 1H), 2.74-2.73 (m, 1H), 2.45 (s, 3H).

^{13}C NMR: δ 145.2, 134.4, 133.3, 133.2, 130.0, 129.9, 128.4_4, 128.3_5, 127.9, 126.9, 126.5, 126.2, 125.3, 120.3, 87.0, 69.2, 54.1, 49.5, 45.6, 21.7.

LC-MS: *m/z* 378 $[M+1]^+$.

Anal. Calcd. for $C_{22}H_{19}NO_3S$: C, 70.00; H, 5.07; N, 3.71; Found: C, 70.15; H, 5.12; N, 3.76.

Compound 5p



Yield: 1.012 g (70%, gummy liquid).

IR (Neat): 3090, 2935, 2230, 1584, 1458, 1364, 1255, 1167, 1085, 1014, 773 cm^{-1}.

^1H NMR: δ 8.54-8.53 (m, 1H), 7.90 (d, *J* = 8.4 Hz, 2H), 7.64 (t, *J* = 7.6 Hz, 1H), 7.39-7.36 (m, 3H), 7.21-7.17 (m, 1H), 3.71-3.59 (m, 2H), 3.27-3.23 (m, 1H), 2.83 (t, *J* = 4.4 Hz, 1H), 2.68-2.67 (m, 1H), 2.45 (s, 3H).

^{13}C NMR: δ 149.9, 145.3, 143.1, 136.1, 134.3, 130.0, 127.8, 126.5, 122.3, 82.6, 71.0, 53.9, 49.2, 45.7, 21.7.

LC-MS: *m/z* 329 $[M+1]^+$.

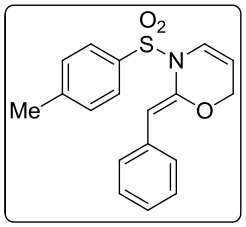
Anal. Calcd. for $C_{17}H_{16}N_2O_3S$: C, 62.18; H, 4.91; N, 8.53; Found: C, 62.07; H, 4.86; N, 8.45.

6.2 Base mediated cyclization of epoxy ynamides 5a-p: Representative procedure for the synthesis of dihydro-1,3-oxazines 7-22

To an oven dried 10 mL RBF (round bottom flask) 4-methyl-*N*-(oxiran-2-ylmethyl)-*N*-(phenylethynyl)benzenesulfonamide **5a** (0.3 mmol) in dry THF (2 mL), KO^{t}Bu (0.6

mmol) was added. The mixture was stirred under the nitrogen atmosphere for 1-2 h. After completion of the reaction as monitored by TLC, the contents were passed through a pad of celite, washed with ethyl acetate (2 x 20 mL) and concentrated *in vacuo*. The residue was then purified by using silica gel column chromatography using hexane-ethyl acetate (9:1) as the eluent to afford dihydro-1,3-oxazine **7**. Compounds **8-22** were prepared following the same procedure and by using the same molar quantities.

Compound 7



Yield: 0.082 g (82%, white solid).

Mp: 68-70 °C.

IR (KBr): 3008, 2926, 2871, 1666, 1600, 1447, 1353, 1238, 1167, 1080, 871, 674 cm^{-1}.

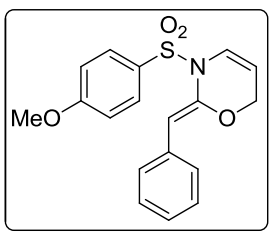
^{1}H NMR: δ 7.73 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 7.2 Hz, 2H), 7.35-7.31 (m, 4H), 7.24 (t, *J* = 7.2 Hz, 1H), 6.85 (dt, *J* ~ 8.4 and 2.0 Hz), 1H), 6.39 (s, 1H), 5.30 (dt, *J* = 8.0 and 2.8 Hz, 1H), 4.35-4.34 (br m, 2H), 2.45 (s, 3H).

^{13}C NMR: δ 144.5, 141.1, 134.6, 134.0, 129.7, 128.9, 128.4, 127.7, 127.1, 125.0, 109.4, 109.3, 66.1, 21.7.

HRMS (ESI): Calcd. for $C_{18}H_{18}NO_3S$ $[M^+ + H]$: *m/z* 328.1007. Found: 328.1007.

This compound was crystallized from ethylacetate/hexane (2:1) mixture at room temperature (25 ^{o}C). X-ray structure has been determined for this compound.

Compound 8



Yield: 0.081 g (79%, gummy liquid).

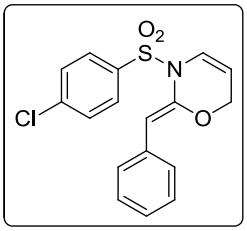
IR (Neat): 3063, 2937, 2838, 1600, 1507, 1348, 1260, 1156, 1030, 926, 844 cm^{-1}.

^{1}H NMR: δ 7.77 (d, *J* = 8.0 Hz, 2H), 7.57 (d, *J* = 7.6 Hz, 2H), 7.34 (t, *J* = 7.6 Hz, 2H), 7.25 (t, *J* = 7.6 Hz, 1H), 6.97 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.4 Hz, 1H), 6.39 (s, 1H), 5.31 (dt, *J* = 8.0 and 2.8 Hz, 1H), 4.36-4.35 (br m, 2H), 3.88 (s, 3H).

^{13}C NMR: δ 163.5, 141.1, 134.0, 129.8, 129.1, 128.9, 128.4, 127.1, 125.1, 114.2, 109.4, 109.1, 66.1, 55.6.

HRMS (ESI): Calcd. for $C_{18}H_{18}NO_4S$ [M^++H]: *m/z* 344.0956. Found: 344.0959.

Compound 9



Yield: 0.071 g (68%, white solid).

Mp: 90-92 °C.

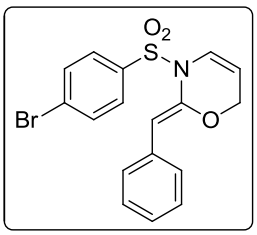
IR (KBr): 3085, 3025, 2959, 2920, 2866, 1666, 1595, 1474, 1392, 1249, 1167, 1085, 1003, 877, 822 cm^{-1}.

^{1}H NMR: δ 7.78 (d, *J* = 8.4 Hz, 2H), 7.57 (d, *J* = 7.6 Hz, 2H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.27 (t, *J* = 8.8 Hz, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 6.40 (s, 1H), 5.35 (dt, *J* = 8.0 and 2.8 Hz, 1H), 4.36-4.35 (br m, 2H).

^{13}C NMR: δ 140.6, 140.1, 135.8, 133.6, 129.4, 129.1, 129.0, 128.4, 127.4, 124.8, 110.3, 109.9, 66.2.

HRMS (ESI): Calcd. for $C_{17}H_{15}ClNO_3S$ [M^++H]: *m/z* 348.0461. Found: 348.0464.

Compound 10



Yield: 0.077 g (65%, white solid).

Mp: 78-80 °C.

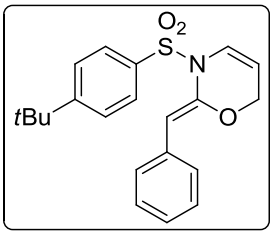
IR (KBr): 3090, 3030, 1660, 1573, 1507, 1458, 1397, 1266, 1173, 1096, 1014, 822 cm^{-1}.

^1H NMR: δ 7.71-7.64 (m, 4H), 7.58-7.56 (m, 2H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.27-7.24 (m, 1H), 6.81 (dt, *J* = 8.0 and 2.0 Hz, 1H), 6.39 (s, 1H), 5.35 (dt, *J* = 8.0 and 2.8 Hz, 1H), 4.37-4.35 (br m, 2H).

^{13}C NMR: δ 140.6, 136.4, 133.6, 132.4, 129.1, 129.0, 128.7, 128.4, 127.4, 124.8, 110.3, 109.9, 66.2.

HRMS (ESI): Calcd. for $C_{17}H_{15}BrNO_3S$ [M^++H] and [M^++H+2]: *m/z* 391.9956, 393.9956. Found: 391.9953, 393.9912.

Compound 11



Yield: 0.086 g (78%, white solid).

Mp: 120-122 °C.

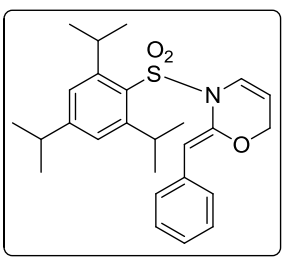
IR (KBr): 2964, 2860, 1655, 1595, 1458, 1370, 1359, 1249, 1173, 1085, 844, 762 cm^{-1}.

^1H NMR: δ 7.77 (d, *J* = 8.4 Hz, 2H), 7.58 (d, *J* = 7.6 Hz, 2H), 7.51 (d, *J* = 8.8 Hz, 2H), 7.34 (t, *J* = 7.6 Hz, 2H), 7.25 (t, *J* = 7.6 Hz, 1H), 6.87 (dt, *J* = 8.0 and 2.0 Hz, 1H), 6.39 (s, 1H), 5.31 (dt, *J* = 8.0 and *J* = 2.8 Hz, 1H), 4.36-4.35 (br m, 2H), 1.36 (s, 9H).

^{13}C NMR: δ 157.2, 141.1, 134.7, 134.0, 128.9, 128.3, 127.7, 127.5, 127.0, 126.2, 126.0, 125.0, 109.1, 109.0, 66.1, 35.2, 31.1.

HRMS (ESI): Calcd. for $C_{21}H_{24}NO_3S$ [M^++H]: *m/z* 370.1477. Found: 370.1473.

Compound 12



Yield: 0.087 g (66%, white solid).

Mp: 98-100 °C.

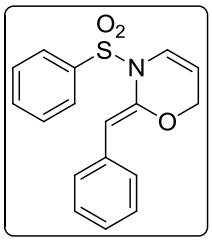
IR (KBr): 2964, 2921, 2866, 1666, 1600, 1458, 1375, 1332, 1249, 1178, 1090, 882, 701 cm^{-1}.

^1H NMR: δ 7.45 (d, *J* = 7.2 Hz, 2H), 7.28 (t, *J* = 7.2 Hz, 2H), 7.21-7.19 (m, 3H), 6.93 (dt, *J* = 8.0 and 2.0 Hz, 1H), 5.86 (s, 1H), 5.34 (dt, *J* = 8.0 and 2.8 Hz, 1H), 4.57-4.56 (br m, 2H), 4.16-4.06 (m, 2H), 2.98-2.87 (m, 1H), 1.27 (d, *J* = 6.8 Hz, 6H), 1.20 (t, *J* = 6.8 Hz, 12H).

^{13}C NMR: δ 153.7, 151.7, 141.2, 133.8, 131.6, 128.7, 128.2, 126.9, 124.3, 124.2, 108.3, 107.7, 66.6, 34.2, 30.1, 24.9, 23.5.

HRMS (ESI): Calcd. for $C_{26}H_{34}NO_3S$ $[M^+ + H]$: *m/z* 440.2259. Found: 440.2251.

Compound 13



Yield: 0.075 g (80%, gummy liquid).

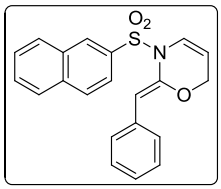
IR (Neat): 3068, 2959, 2920, 2860, 1666, 1501, 1452, 1353, 1266, 1162, 1085, 1019, 877, 789 cm^{-1}.

^1H NMR: δ 7.86 (d, *J* = 8.0 Hz, 2H), 7.66-7.62 (m, 1H), 7.58-7.56 (m, 2H), 7.52 (t, *J* = 8.0 Hz, 2H), 7.35 (t, *J* = 8.0 Hz, 2H), 7.26 (t, *J* = 7.6 Hz, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 6.41 (s, 1H), 5.32 (dt, *J* = 8.4 and 2.8 Hz, 1H), 4.34-4.33 (br m, 2H).

^{13}C NMR: δ 140.9, 137.4, 133.9, 133.5, 129.3, 129.0, 128.9, 128.4, 127.7, 127.2, 124.9, 109.7, 109.5, 66.1.

HRMS (ESI): Calcd. for $C_{17}H_{16}NO_3S$ $[M^+ + H]$: *m/z* 314.0851. Found: 314.0848.

Compound 14



Yield: 0.077 g (87%, gummy liquid).

IR (Neat): 3063, 3030, 2932, 2860, 1660, 1633, 1595, 1501, 1353, 1266, 1167, 1074, 921, 816 cm^{-1}.

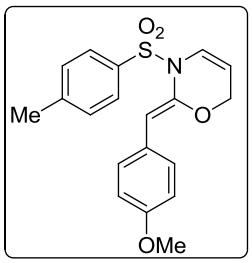
^1H NMR: δ 8.44 (s, 1H), 7.97-7.92 (m, 3H), 7.86-7.84 (m, 1H), 7.69-7.65 (m, 1H), 7.64-7.59 (m, 3H), 7.36 (t, *J* = 7.6 Hz, 2H), 7.27 (t, *J* = 7.6 Hz, 1H), 6.95 (dt, *J* = 8.4 and 2.8 Hz, 1H), 6.49 (s, 1H), 5.32 (dt, *J* = 8.0 and 2.8 Hz, 1H), 4.30-4.29 (br m, 2H).

^{13}C NMR: δ 141.0, 135.2, 134.6, 133.9, 132.1, 129.5, 129.3_2, 129.2_6, 129.1, 129.0, 128.4, 128.0, 127.6, 127.2, 125.0, 122.7, 109.8, 109.5, 66.1.

HRMS (ESI): Calcd. for $C_{21}H_{18}NO_3S$ $[M^+ + H]$: *m/z* 364.1007. Found: 364.1013.

This compound was crystallized from ethylacetate/hexane (2:1) mixture at room temperature (25 ^oC). X-ray structure has been determined for this compound.

Compound 15



Yield: 0.082 g (75%, white solid).

Mp: 68-70 °C.

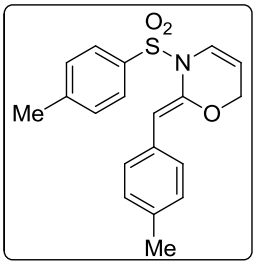
IR (KBr): 2953, 2920, 2849, 1666, 1600, 1512, 1463, 1353, 1249, 1178, 1085, 1025, 871, 806 cm^{-1}.

^1H NMR: δ 7.72 (d, *J* = 8.4 Hz, 2H), 7.52 (d, *J* = 8.8 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 6.84 (dt, *J* = 8.4 and 1.6 Hz, 1H), 6.34 (s, 1H), 5.29 (dt, *J* = 8.0 and 2.8 Hz, 1H), 4.33-4.31 (br m, 2H), 3.83 (s, 3H), 2.43 (s, 3H).

^{13}C NMR: δ 158.7, 144.3, 139.6, 134.6, 130.2, 129.7, 127.7, 126.5, 125.0, 113.8, 109.6, 109.2, 66.1, 55.3, 21.7.

HRMS (ESI): Calcd. for $C_{19}H_{20}NO_4S$ $[M^+ + H]$: *m/z* 358.1113. Found: 358.1108.

Compound 16



Yield: 0.086 g (80%, gummy liquid).

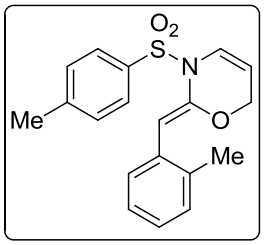
IR (Neat): 3046, 2926, 1600, 1594, 1512, 1446, 1325, 1156, 1095, 1013, 816, 673 cm^{-1}.

^1H NMR: δ 7.73 (d, *J* = 8.0 Hz, 2H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 8.8 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 6.85 (dt, *J* = 8.0 and 2.0 Hz, 1H), 6.38 (s, 1H), 5.30 (dt, *J* = 8.4 and 2.8 Hz, 1H), 4.34-4.32 (br m, 2H), 2.44 (s, 3H), 2.38 (s, 3H).

^{13}C NMR: δ 144.4, 140.5, 137.0, 134.6, 131.0, 129.7, 129.1, 128.9, 127.7, 125.0, 109.6, 109.2, 66.1, 21.7, 21.3.

HRMS (ESI): Calcd. for $C_{19}H_{20}NO_3S$ [M^++H]: *m/z* 342.1164. Found: 342.1164.

Compound 17



Yield: 0.073 g (71%, white solid).

Mp: 88-90 °C.

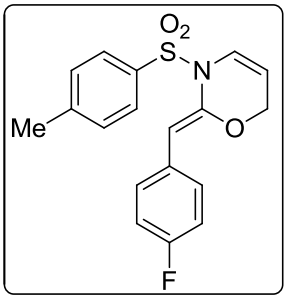
IR (KBr): 3052, 2986, 2926, 1627, 1595, 1425, 1337, 1277, 1162, 1096, 1019, 811 cm^{-1}.

^1H NMR: δ 7.76 (d, *J* = 8.4 Hz, 2H), 7.58-7.55 (m, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.22-7.15 (m, 3H), 6.88 (dt, *J* = 8.4 and 2.0 Hz, 1H), 6.52 (s, 1H), 5.31 (dt, *J* = 8.0 and 2.8 Hz, 1H), 4.31-4.30 (br m, 2H), 2.46 (s, 3H), 2.40 (s, 3H).

^{13}C NMR: δ 144.4, 140.9, 136.6, 134.7, 132.5, 130.0, 129.7, 128.8, 127.7, 127.1, 125.6, 125.1, 109.1, 107.0, 66.3, 21.7, 20.3.

HRMS (ESI): Calcd. for $C_{19}H_{20}NO_3S$ [M^++H]: *m/z* 342.1164. Found: 342.1162.

Compound 18



Yield: 0.066 g (64%, gummy liquid).

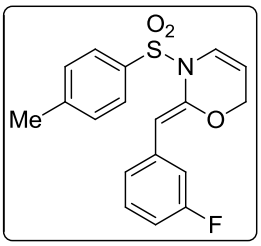
IR (Neat): 3069, 1606, 1512, 1342, 1227, 1173, 1096, 1030, 816 cm^{-1}.

^1H NMR: δ 7.71 (d, *J* = 8.0 Hz, 2H), 7.55-7.52 (m, 2H), 7.32-7.29 (m, 2H), 7.02 (t, *J* = 8.8 Hz, 2H), 6.84 (d, *J* = 8.4 Hz, 1H), 6.35 (s, 1H), 5.31 (dt, *J* = 8.0 and 2.8 Hz, 1H), 4.34-4.33 (br m, 2H), 2.45 (s, 3H).

^{13}C NMR: δ 161.7 (d, *J* = 245.6 Hz), 144.5, 140.7, 134.5, 130.5 (d, *J* = 7.7 Hz), 130.1, 129.7, 127.6, 125.0, 115.2 (d, *J* = 21.2 Hz), 109.2, 108.3, 66.1, 21.7.

HRMS (ESI): Calcd. for $C_{18}H_{17}FNO_3S$ [M^++H]: *m/z* 346.0913. Found: 346.0903.

Compound 19



Yield: 0.068 g (66%, white solid).

Mp: 86-88 °C.

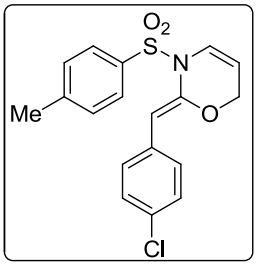
IR (KBr): 3068, 2926, 1666, 1595, 1496, 1447, 1348, 1255, 1162, 1079, 1014, 932, 827 cm^{-1}.

^1H NMR: δ 7.72 (d, *J* = 8.0 Hz, 2H), 7.39-7.36 (m, 1H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.28-7.24 (m, 2H), 6.95-6.91 (m, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 6.35 (s, 1H), 5.33 (dt, *J* = 8.0 and 2.8 Hz, 1H), 4.34-4.33 (br m, 2H), 2.44 (s, 3H).

^{13}C NMR: δ 162.8 (d, *J* = 242.2 Hz), 144.6, 141.9, 136.2 (d, *J* = 8.6 Hz), 134.5, 129.8, 129.7, 129.6, 127.6, 124.9_1, 124.8_6 (d, *J* = 2.7 Hz), 115.1 (d, *J* = 22.6 Hz), 113.8 (d, *J* = 21.5 Hz), 109.3, 107.8 (d, *J* = 2.6 Hz), 66.0, 21.7.

HRMS (ESI): Calcd. for $C_{18}H_{17}FNO_3S$ [M^++H]: *m/z* 346.0913. Found: 346.0908.

Compound 20



Yield: 0.080 g (74%, gummy liquid).

IR (Neat): 2932, 1595, 1496, 1332, 1167, 1090, 1014, 811 cm^{-1}.

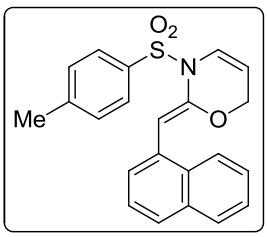
^{1}H NMR: δ 7.71 (d, *J* = 7.2 Hz, 2H), 7.49 (d, *J* = 7.6 Hz, 2H), 7.31-7.27 (m, 4H), 6.86-6.83 (m, 1H), 6.33 (s, 1H), 5.33-5.30 (m, 1H), 4.33-432 (br m, *J* = 1.6 Hz, 2H), 2.45 (s, 3H).

^{13}C NMR: δ 144.5, 141.3, 134.5, 132.5_2, 132.4_7, 130.1, 129.7, 128.5, 127.6, 125.0, 109.1, 108.0, 66.0, 21.7.

LC/MS *m/z* 475 $[M+1]^+$.

HRMS (ESI): Calcd. for $C_{18}H_{17}ClNO_3S$ $[M^+ + H]$: *m/z* 362.0617. Found: 362.0611.

Compound 21



Yield: 0.090 g (79%, white solid).

Mp: 128-130 °C.

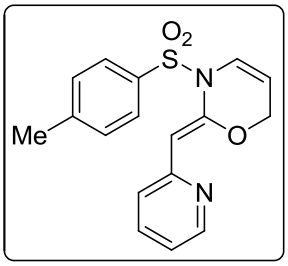
IR (KBr): 3063, 2931, 2849, 1666, 1584, 1447, 1386, 1359, 1249, 1167, 1079, 1019, 773 cm^{-1}.

^{1}H NMR: δ 8.17 (d, *J* = 8.0 Hz, 1H), 7.88 (d, *J* = 7.6 Hz, 1H), 7.81-7.77 (m, 3H), 7.65 (d, *J* = 7.2 Hz, 1H), 7.59-7.51 (m, 2H), 7.45 (t, *J* = 7.6 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.06 (s, 1H), 6.93 (dt, *J* = 8.0 and 1.6 Hz, 1H), 5.34 (dt, *J* = 8.0 and 2.8 Hz, 1H), 4.32-4.31 (br m, 2H), 2.44 (s, 3H).

^{13}C NMR: δ 144.5, 141.7, 134.6, 133.6, 131.9, 130.2, 129.8, 128.5, 127.7, 127.6, 126.7, 126.2, 125.8, 125.4, 125.1, 124.4, 109.3, 106.0, 66.4, 21.7.

HRMS (ESI): HRMS (ESI): Calcd. for $C_{22}H_{20}NO_3S$ [M^++H]: *m/z* 378.1164. Found: 378.1162.

Compound 22



Yield: 0.071 g (72%, gummy liquid).

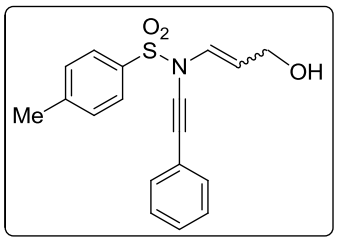
IR (Neat): 3058, 2964, 2849, 1660, 1584, 1463, 1348, 1244, 1173, 1090, 877, 811, 679 cm^{-1}.

^{1}H NMR: δ 8.59 (d, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.62-7.58 (m, 1H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.11-7.08 (m, 1H), 6.88 (d, *J* = 8.0 Hz, 1H), 6.56 (s, 1H), 5.35 (dt, *J* = 8.0 and 2.8 Hz, 1H), 4.36-4.35 (br m, 2H), 2.44 (s, 3H).

^{13}C NMR: δ 153.9, 149.4, 144.5, 143.7, 136.0, 134.7, 129.7, 127.6, 125.1, 123.6, 121.2, 108.8, 108.5, 65.9, 21.7.

HRMS (ESI): Calcd. for $C_{17}H_{17}N_2O_3S$ [M^++H]: *m/z* 329.0960. Found: 329.0962.

Compound 24



Yield: 0.072 g (72%, gummy liquid).

IR (Neat): 3357, 3050, 2931, 2869, 2244, 1665, 1588, 1485, 1381, 1185, 1082, 1010, 771, 663 cm^{-1}.

^{1}H NMR: δ 7.85-7.82 (m, ~3H), 7.43-7.33 (m, ~9H), 6.84 (d, *J* = 10.8 Hz, 1H), 5.69-5.64 (m, 1H), 4.21-4.20 (m, 2H), 2.45 (s, 3H), 1.97 (br s, 1H) (for major isomer).

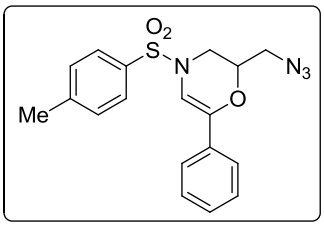
^{13}C NMR: δ 145.5, 133.6, 131.6, 130.0, 128.5, 128.4, 127.8, 126.6, 124.6, 122.0, 114.3, 77.5, 76.8, 60.8, 57.1, 21.7$_4$ (for the major isomer).

HRMS (ESI): Calcd. for $C_{18}H_{18}NO_3S$ [M^++H]: *m/z* 328.1007. Found: 328.1002.

6.3 Cyclization of epoxy ynamides 5a-n with NaN_3: Representative procedure for the synthesis of dihydro-1,4-oxazines 25-38

To a 10 mL RBF, 4-methyl-*N*-(oxiran-2-ylmethyl)-*N*-(phenylethynyl)benzenesulfonamide **5a** (0.3 mmol), NaN_3 (0.6 mmol), and H_2O (0.3 mmol) in PEG-400 solvent (2 mL) were added. The RBF was stoppered and the contents stirred at room temperature (25 ^oC) for 12 h. After completion of the reaction as monitored by TLC, the crude 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 dihydro 1,4-oxazine **25**. Compounds **25'** and **26-38** were prepared following the same procedure and by using the same molar quantities.

Compound 25



Yield: 0.090 g (82%, gummy liquid).

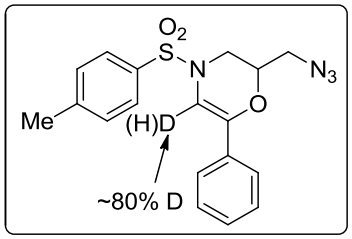
IR (Neat): 3058, 2932, 2099, 1649, 1600, 1496, 1447, 1353, 1315, 1162, 1090, 1019, 767 cm^{-1}.

^{1}H NMR: δ 7.72 (d, *J* = 8.0 Hz, 2H), 7.52 (d, *J* = 6.8 Hz, 2H), 7.39-7.35 (m, 4H), 7.33-7.29 (m, 1H), 6.78 (s, 1H), 3.88-3.85 (m, 1H), 3.67-3.62 (m, 1H), 3.51-3.46 (m, 1H), 3.39-3.35 (m, 1H), 3.18 (dd, *J* = 13.2 and 8.8 Hz, 1H), 2.45 (s, 3H).

^{13}C NMR: δ 144.5, 139.8, 133.6, 133.1, 130.1, 128.5, 128.2, 127.3, 123.7, 101.7, 71.6, 51.7, 44.9, 21.6.

HRMS (ESI): Calcd. for $C_{18}H_{18}N_4O_3S$ [M^+]: *m/z* 370.1100. Found: 370.1104.

Compound 25'



Yield: 0.085 g (66%, gummy liquid).

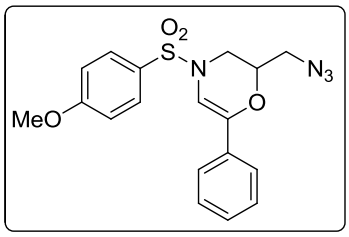
IR (Neat): 3065, 2925, 2094, 1634, 1598, 1494, 1443, 1355, 1314, 1169, 1091, 1019, 859, 771 cm^{-1}.

^{1}H NMR: δ 7.72 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 7.6 Hz, 2H), 7.39-7.29 (m, 5H), 6.78 (s, 0.2H), 3.88-3.84 (m, 1H), 3.66-3.61 (m, 1H), 3.51-3.46 (m, 1H), 3.39-3.35 (m, 1H), 3.17 (dd, *J* = 13.2 and 8.8 Hz, 1H), 2.45 (s, 3H).

^{13}C NMR: δ 144.5, 139.7, 133.6, 133.1, 130.1, 128.5, 128.2, 127.3, 123.7, 101.7, 101.4 (d, *J* = 28.0 Hz), 71.6, 51.7, 44.9, 21.6.

HRMS (ESI): Calcd. for $C_{18}H_{17}DN_4O_3SNa$ $[M^+ + Na]$: *m/z* 394.1060. Found: 394.1064.

Compound 26



Yield: 0.089 g (68%, gummy liquid).

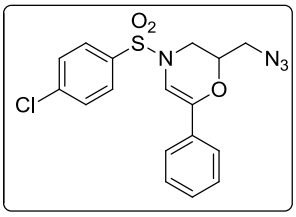
IR (Neat): 3063, 2932, 2104, 1655, 1589, 1490, 1452, 1353, 1310, 1266, 1162, 1096, 1025, 838, 668 cm^{-1}.

^{1}H NMR: δ 7.77 (d, *J* = 8.8 Hz, 2H), 7.52 (d, *J* = 6.8 Hz, 2H), 7.38-7.29 (m, 3H), 7.03-7.01 (m, 2H), 6.78 (s, 1H), 3.87 (s, 3H), 3.84_4-3.84_1 (m, 1H), 3.68-3.63 (m, 1H), 3.51-3.46 (m, 1H), 3.40-3.35 (m, 1H), 3.17 (dd, *J* = 13.2 and 8.4 Hz, 1H).

^{13}C NMR: δ 163.5, 139.8, 133.2, 129.5, 128.5, 128.2, 128.1, 123.7, 114.7, 101.8, 71.6, 55.7, 51.7, 44.9.

HRMS (ESI): Calcd. for $C_{18}H_{18}N_4O_4SNa$ $[M^+ + Na]$: *m/z* 409.0947. Found: 409.0946.

Compound 27



Yield: 0.074 g (56%, white solid).

Mp: 73-75 °C.

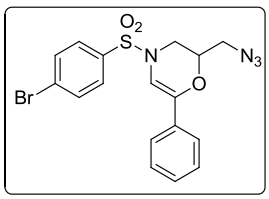
IR (KBr): 3096, 2926, 2104, 1753, 1644, 1573, 1468, 1364, 1310, 1162, 1090, 1003, 756, 685 cm^{-1}.

^{1}H NMR: δ 7.79-7.76 (m, 2H), 7.55-7.50 (m, 4H), 7.40-7.32 (m, 3H), 6.75 (s, 1H), 3.90-3.86 (m, 1H), 3.74-3.68 (m, 1H), 3.54-3.50 (m, 1H), 3.44-3.40 (m, 1H), 3.19 (dd, *J* = 13.2 and 8.8 Hz, 1H).

^{13}C NMR: δ 140.3, 140.1, 135.1, 132.9, 129.8, 128.7, 128.5, 128.4, 123.8, 101.2, 71.7, 51.6, 44.9.

HRMS (ESI): Calcd. for $C_{17}H_{15}ClN_4O_3S$ [M^+] and [M^++2]: *m/z* 390.0553 and 392.0553. Found: 390.0550 and 392.0572.

Compound 28



Yield: 0.070 g (48%, white solid).

Mp: 68-70 °C.

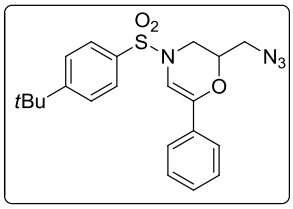
IR (KBr): 3085, 2932, 2099, 1649, 1573, 1447, 1348, 1310, 1173, 1086, 992, 899, 773 cm^{-1}.

^{1}H NMR: δ 7.70 (br, 4H), 7.53-7.50 (m, 2H), 7.39-7.31 (m, 3H), 6.74 (s, 1H), 3.90-3.86 (m, 1H), 3.74-3.69 (m, 1H), 3.54-3.50 (m, 1H), 3.44-3.40 (m, 1H), 3.19 (dd, *J* = 13.2 and 8.8 Hz, 1H).

^{13}C NMR: δ 140.3, 135.6, 132.9, 132.8, 128.7, 128.6, 128.5, 128.4, 123.8, 101.2, 71.7, 51.6, 44.9.

HRMS (ESI): Calcd. for $C_{17}H_{15}BrN_4O_4S$ [M^+] and [M^++2]: *m/z* 434.0048 and 436.0048. Found: 434.0048 and 436.0019.

Compound 29



Yield: 0.090 g (65%, gummy liquid).

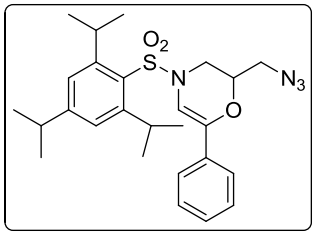
IR (Neat): 3058, 2959, 2099, 1649, 1589, 1452, 1370, 1321, 1162, 1014, 767 cm^{-1}.

^1H NMR: δ 7.79 (d, *J* = 8.4 Hz, 2H), 7.59-7.54 (m, 4H), 7.39-7.36 (m, 2H), 7.33-7.30 (m, 1H), 6.84 (s, 1H), 3.91-3.87 (m, 1H), 3.77-3.72 (m, 1H), 3.52-3.47 (m, 1H), 3.40-3.36 (m, 1H), 3.21 (dd, *J* = 12.8 and 8.4 Hz, 1H), 1.37 (s, 9H).

^{13}C NMR: δ 157.4, 139.5, 133.7, 133.2, 128.5, 128.2, 127.2, 126.5, 123.7, 101.9, 71.7, 51.7, 44.8, 35.3, 31.1.

HRMS (ESI): Calcd. for $C_{21}H_{24}N_4O_3SNa$ [M^++Na]: *m/z* 435.1467. Found: 435.1464.

Compound 30



Yield: 0.111 g (70%, White solid).

Mp: 104-106 °C.

IR (KBr): 3062, 2964, 2099, 1644, 1600, 1562, 1463, 1359, 1310, 1249, 1162, 1090, 1014, 762, 674 cm^{-1}.

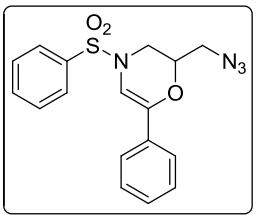
^1H NMR: δ 7.52 (d, *J* = 7.6 Hz, 2H), 7.38-7.34 (m, 2H), 7.32-7.28 (m, 1H), 7.25 (br, 2H), 6.59 (s, 1H), 4.24-4.15 (m, 3H), 3.78-3.74 (m, 1H), 3.61-3.51 (m, 2H), 3.21 (dd, *J* = 13.2 and 8.4 Hz, 1H), 2.99-2.92 (m, 1H), 1.31-1.28 (m, 18H).

^{13}C NMR: δ 154.1, 151.8, 139.6, 133.4, 129.3, 128.4, 128.0, 124.3, 123.7, 100.6, 72.3, 51.9, 43.7, 34.2, 29.8, 24.9_2, 24.9_0, 23.5.

HRMS (ESI): Calcd. for $C_{26}H_{35}N_4O_3S$ [M^++H]: *m/z* 483.2430. Found: 483.2435.

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

Compound 31



Yield: 0.082 g (66%, White solid).

Mp: 80-82 °C.

IR (KBr): 3090, 2915, 2099, 1655, 1452, 1348, 1321, 1178, 1008, 756 cm^{-1}.

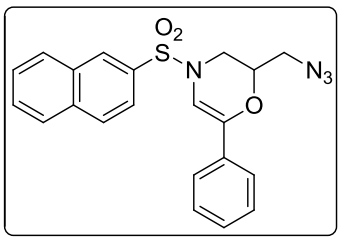
^{1}H NMR: δ 7.85 (d, *J* = 6.8 Hz, 2H), 7.66 (t, *J* = 7.2 Hz, 1H), 7.60-7.56 (m, 2H), 7.52 (d, *J* = 6.8 Hz, 2H), 7.37 (t, *J* = 7.2 Hz, 2H), 7.34-7.29 (m, 1H), 6.79 (s, 1H), 3.90-3.86 (m, 1H), 3.69-3.62 (m, 1H), 3.51-3.46 (m, 1H), 3.40-3.35 (m, 1H), 3.19 (dd, *J* = 13.2 and 8.8 Hz, 1H).

^{13}C NMR: δ 139.9, 136.6, 133.5, 133.0, 129.5, 128.5, 128.3, 127.3, 123.7, 101.6, 71.6, 51.6, 44.9.

HRMS (ESI): Calcd. for $C_{17}H_{16}N_4O_3S$ [M^+]: *m/z* 356.0943. Found: 356.0946.

X-ray structure has been determined for this compound in (2:1) DCM:hexane.

Compound 32



Yield: 0.087 g (64%, gummy liquid).

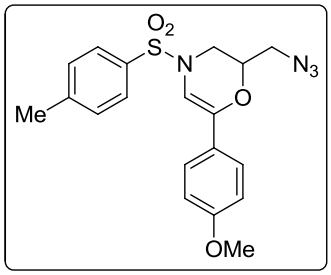
IR (Neat): 3058, 2932, 2099, 1655, 1584, 1447, 1359, 1310, 1167, 1014, 751, 663 cm^{-1}.

^{1}H NMR: δ 8.44 (s, 1H), 8.01 (d, *J* = 8.4 Hz, 2H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.82-7.80 (m, 1H), 7.72-7.64 (m, 2H), 7.52 (d, *J* = 7.2 Hz, 2H), 7.39-7.31 (m, 3H), 6.88 (s, 1H), 3.97-3.94 (m, 1H), 3.71-3.66 (m, 1H), 3.49-3.44 (m, 1H), 3.39-3.34 (m, 1H), 3.24 (dd, *J* = 13.2 and 8.8 Hz, 1H).

^{13}C NMR: δ 139.8, 135.1, 133.7, 133.1, 132.2, 129.9, 129.4, 129.3, 128.9, 128.5, 128.3, 128.1, 127.9, 123.8, 122.2, 101.7, 71.7, 51.6, 45.0.

HRMS (ESI): Calcd. for $C_{21}H_{18}N_4O_3S$ [M^+]: *m/z* 406.1100. Found: 406.1100.

Compound 33



Yield: 0.089 g (66%, gummy liquid).

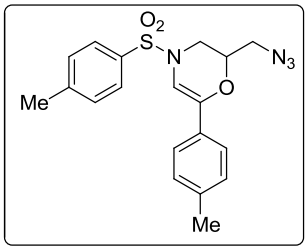
IR (Neat): 3058, 2932, 2093, 1655, 1606, 1512, 1447, 1348, 1310, 1249, 1167, 1090, 1025, 838, 663 cm^{-1}.

^{1}H NMR: δ 7.71 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 8.8 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 6.89 (d, *J* = 9.2 Hz, 2H), 6.64 (s, 1H), 3.87-3.83 (m, 1H), 3.82 (s, 3H), 3.62-3.57 (m, 1H), 3.48-3.43 (m, 1H), 3.36-3.32 (m, 1H), 3.15 (dd, *J* = 13.2 and 8.8 Hz, 1H), 2.43 (s, 3H).

^{13}C NMR: δ 159.8, 144.4, 140.1, 133.6, 130.1, 127.4, 125.3, 113.9, 100.2, 71.6, 55.4, 51.7, 44.9, 21.7.

HRMS (ESI): Calcd. for $C_{19}H_{20}N_4O_4S$ [M^+]: *m/z* 400.1205. Found: 400.1205.

Compound 34



Yield: 0.091 g (70%, Gummy liquid).

IR (Neat): 3036, 2921, 2088, 1655, 1595, 1518, 1458, 1353, 1310, 1156, 1090, 1019, 663 cm^{-1}.

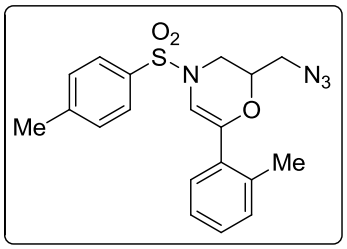
^{1}H NMR: δ 7.73 (d, *J* = 8.0 Hz, 2H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 6.76 (s, 1H), 3.89-3.86 (m, 1H), 3.65-3.60

(m, 1H), 3.49-3.44 (m, 1H), 3.38-3.34 (m, 1H), 3.18 (dd, *J* = 13.2 and 8.4 Hz, 1H), 2.45 (s, 3H), 2.38 (s, 3H).

^{13}C NMR: δ 144.4, 140.1, 138.2, 133.6, 130.4, 130.1, 129.2, 127.3, 123.7, 101.0, 71.5, 51.7, 44.9, 21.6, 21.2.

HRMS (ESI): Calcd. for $C_{19}H_{20}N_4O_3SNa$ [M^++Na]: *m/z* 407.1154. Found: 407.1154.

Compound 35



Yield: 0.073 g (56%, gummy liquid).

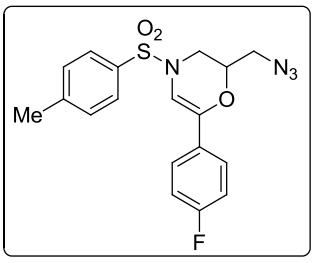
IR (Neat): 3069, 2921, 2099, 1666, 1589, 1496, 1452, 1364, 1304, 1162, 1014, 762, 668 cm^{-1}.

^{1}H NMR: δ 7.73 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.30-7.26 (m, 2H), 7.21-7.18 (m, 2H), 6.30 (s, 1H), 3.91-3.88 (m, 1H), 3.55-3.50 (m, 1H), 3.47-3.42 (m, 1H), 3.40-3.35 (m, 1H), 3.15 (dd, *J* = 13.2 and 8.8 Hz, 1H), 2.49 (s, 3H), 2.30 (s, 3H).

^{13}C NMR: δ 144.4, 141.9, 136.9, 133.5, 133.2, 130.6, 130.0, 129.1, 129.0, 127.5, 125.8, 104.3, 70.8, 51.8, 44.9, 21.7, 20.3.

HRMS (ESI): Calcd. for $C_{19}H_{20}N_4O_3S$ [M^++Na]: *m/z* 407.1154. Found: 407.1154.

Compound 36



Yield: 0.079 g (60%, gummy liquid).

IR (Neat): 3052, 2926, 2099, 1660, 1594, 1512, 1457, 1227, 1167, 1085, 838 cm^{-1}.

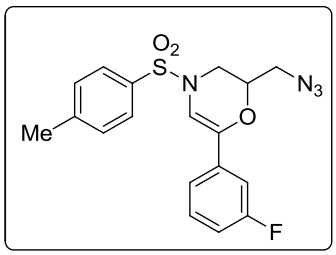
^{1}H NMR: δ 7.71 (d, *J* = 8.0 Hz, 2H), 7.49-7.46 (m, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.05 (t, *J* = 8.8 Hz, 2H), 6.70 (s, 1H), 3.88-3.84 (m, 1H), 3.65-3.62 (m,

1H), 3.50-3.45 (m, 1H), 3.39-3.35 (m, 1H), 3.16 (dd, *J* = 13.2 and 8.8 Hz, 1H), 2.45 (s, 3H).

^{13}C NMR: δ 162.6 (d, *J* = 246.4 Hz), 144.5, 139.1, 133.5, 130.2, 129.3 (d, *J* = 3.2 Hz), 127.3, 125.6 (d, *J* = 8.0 Hz), 115.4 (d, *J* = 21.7 Hz), 101.5, 71.7, 51.6, 44.8, 21.6.

HRMS (ESI): Calcd. for $C_{18}H_{17}FNO_3S$ [M^++H]: *m/z* 388.1005. Found: 388.1000.

Compound 37



Yield: 0.072 g (55%, gummy liquid).

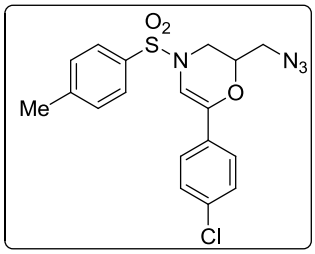
IR (Neat): 3056, 2932, 2104, 1655, 1584, 1490, 1430, 1359, 1315, 1167, 1019, 877, 663 cm^{-1}.

^{1}H NMR: δ 7.71 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.4Hz, 2H), 7.34-7.27 (m, 2H), 7.21-7.18 (m, 1H), 7.01-6.96 (m, 1H), 6.80 (s, 1H), 3.88-3.84 (m, 1H), 3.69-3.64 (m, 1H), 3.51-3.46 (m, 1H), 3.41-3.36 (m, 1H), 3.17 (dd, *J* = 13.2 and 8.8 Hz, 1H), 2.45 (s, 3H).

^{13}C NMR: δ 163.0 (d, *J* = 243.7 Hz), 144.6, 138.5 (d, *J* = 2.7 Hz), 135.4 (d, *J* = 8.1 Hz), 133.5, 130.2, 130.0 (d, *J* = 8.4 Hz), 127.3, 119.1 (d, *J* = 2.8 Hz), 114.8 (d, *J* = 21.2 Hz), 110.7 (d, *J* = 23.5 Hz), 102.7, 71.6, 51.6, 44.8, 21.6.

HRMS (ESI): Calcd. for $C_{18}H_{17}FN_4O_3S$ [M^+]: *m/z* 388.1005. Found: 388.1000.

Compound 38



Yield: 0.071 g (52%, gummy liquid).

IR (Neat): 3046, 2921, 2099, 1649, 1584, 1485, 1337, 1167, 1090, 1003, 811, 712 cm^{-1}.

^1H NMR: δ 7.71 (d, *J* = 8.0 Hz, 2H), 7.43 (d, *J* = 8.8 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.8 Hz, 2H), 6.76 (s, 1H), 3.87-3.83 (m, 1H), 3.68-3.63 (m, 1H), 3.50-3.45 (m, 1H), 3.39-3.35 (m, 1H), 3.16 (dd, *J* = 13.2 and 8.8 Hz, 1H), 2.45 (s, 3H).

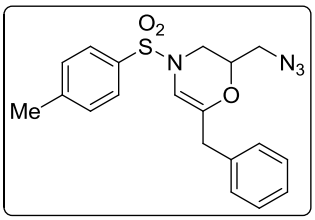
^{13}C NMR: δ 144.6, 138.8, 133.8, 133.6, 131.6, 130.2, 128.6, 127.3, 124.9, 102.1, 71.7, 51.6, 44.8, 21.6.

HRMS (ESI): Calcd. for $C_{18}H_{17}ClN_4O_3SNa$ [M^++Na] and [M^++2+Na]: *m/z* 427.0608 and 429.0608. Found: 427.0604 and 429.0572.

6.4 Synthesis of dihydro-1,4-oxazine derivatives 39-42 from epoxy tethered alkynes 6a-d

Compounds **39-42** were prepared from substrates **6a-d** by following the same procedure and the same molar quantities as illustrated for compounds **25-38**.

Compound 39



Yield: 0.087 g (75%, gummy liquid).

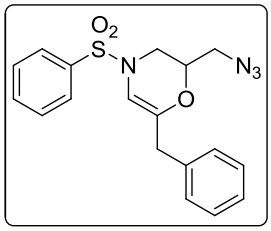
IR (Neat): 3060, 3024, 2921, 2105, 1671, 1593, 1490, 1457, 1345, 1154, 1020, 700 cm^{-1}.

^1H NMR: δ 7.68-7.65 (m, 2H), 7.36-7.30 (m, 4H), 7.27-7.24 (m, 1H), 7.20-7.18 (m, 2H), 5.98 (s, 1H), 3.73-3.70 (m, 1H), 3.44-3.39 (m, 1H), 3.36 (s, 2H), 3.30-3.20 (m, 2H), 3.04 (dd, *J* = 13.0 and 8.5 Hz, 1H), 2.46 (s, 3H).

^{13}C NMR: δ 144.3, 142.1, 137.3, 133.4, 130.0, 128.7, 128.4, 127.4, 126.7, 101.7, 71.1, 51.4, 44.6, 38.2, 21.6.

HRMS (ESI): Calcd. for $C_{19}H_{20}N_4O_3SNa$ [M^++Na]: *m/z* 407.1154. Found: 407.1159.

Compound 40



Yield: 0.081 g (73%, gummy liquid).

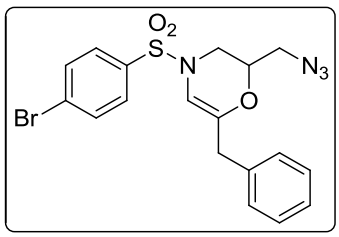
IR (Neat): 3060, 3024, 2915, 2099, 1676, 1598, 1495, 1454, 1356, 1164, 1015, 684 cm^{-1}.

^1H NMR: δ 7.79 (d, *J* = 8.0 Hz, 2H), 7.65 (t, *J* = 7.5 Hz, 1H), 7.56 (t, *J* = 7.5 Hz, 2H), 7.32 (t, *J* = 7.5 Hz, 2H), 7.27-7.24 (m, 1H), 7.19 (d, *J* = 8.0 Hz, 2H), 6.00 (s, 1H), 3.75-3.72 (m, 1H), 3.43-3.38 (m, 1H), 3.37 (s, 2H), 3.30-3.20 (m, 2H), 3.06 (dd, *J* = 13.0 and 8.0 Hz, 1H).

^{13}C NMR: δ 142.3, 137.4, 136.4, 133.5, 129.4, 128.8, 128.5, 127.4, 126.8, 101.6, 71.2, 51.3, 44.6, 38.2.

HRMS (ESI): Calcd. for $C_{18}H_{19}N_4O_3S$ $[M^+ + H]$: *m/z* 371.1178. Found: 371.1173.

Compound 41



Yield: 0.089 g (66%, gummy liquid).

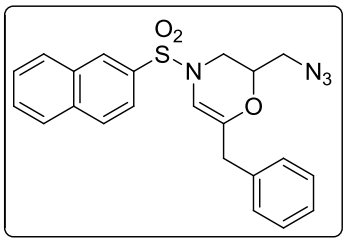
IR (Neat): 3060, 3029, 2931, 2105, 1671, 1573, 1490, 1448, 1361, 1164, 1009, 700 cm^{-1}.

^1H NMR: δ 7.70-7.68 (m, 2H), 7.64-7.62 (m, 2H), 7.32 (t, *J* = 7.5 Hz, 2H), 7.28-7.25 (m, 1H), 7.18 (d, *J* = 7.0 Hz, 2H), 5.94 (s, 1H), 3.74-3.71 (m, 1H), 3.53-3.48 (m, 1H), 3.36 (s, 2H), 3.34-3.25 (m, 2H), 3.05 (dd, *J* = 13.0 and 8.5 Hz, 1H).

^{13}C NMR: δ 142.6, 137.1, 135.5, 132.6, 128.9, 128.7, 128.5, 128.4, 126.8, 101.3, 71.2, 51.3, 44.6, 38.2.

HRMS (ESI): Calcd. for $C_{18}H_{17}BrN_4O_3SNa$ $[M^+ + Na]$ and $[M^+ + 2 + Na]$: *m/z* 471.0103 and 473.0103. Found: 471.0107 and 473.0086.

Compound 42



Yield: 0.091 g (72%, gummy liquid).

IR (Neat): 3060, 3034, 2931, 2105, 1676, 1588, 1495, 1448, 1350, 1170, 1015, 860, 746 cm^{-1}.

^{1}H NMR: δ 8.43 (s, 1H), 8.02 (d, *J* = 6.8 Hz, 2H), 7.97 (d, *J* = 6.4 Hz, 1H), 7.83-7.81 (m, 1H), 7.72-7.66 (m, 2H), 7.30-7.26 (m, 3H), 7.19-7.18 (m, 2H), 6.13 (s, 1H), 3.87-3.85 (m, 1H), 3.48-3.44 (m, 1H), 3.39 (s, 2H), 3.28-3.20 (m, 2H), 3.14 (dd, *J* = 10.4 and 6.8 Hz, 1H).

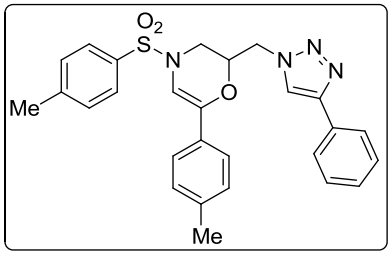
^{13}C NMR: δ 142.3, 137.3, 135.1, 133.5, 132.2, 129.7, 129.4, 129.2, 128.9, 128.7, 128.5, 128.1, 127.9, 126.8, 122.5, 101.8, 71.2, 51.3, 44.7, 38.2.

HRMS (ESI): Calcd. for $C_{22}H_{20}N_4O_3SNa$ [M^++Na]: *m/z* 443.1154. Found: 443.1155.

6.5 Click reaction of 1,4-oxazine derivatives 34 and 40

To a 10 mL RBF, 2-(azidomethyl)-6-(p-tolyl)-4-tosyl-3,4-dihydro-2H-1,4-oxazine **34** (0.3 mmol), phenylacetylene (0.3 mmol), and CuI (0.03 mmol) in PEG-400 (2 mL) were added. The RBF was stoppered and the contents stirred at rt (25 ^{o}C) for 12 h. After completion of the reaction as monitored by TLC, the crude 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 (7:3) as the eluent to afford triazolo derived 1,4-oxazine **43**. Compound **44** was prepared following the same procedure and by using the same molar quantities like compound **40**.

Compound 43



Yield: 0. 134 g (92%, White solid).

Mp: 165-167 °C.

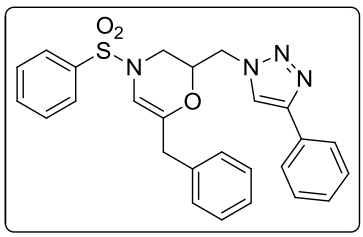
IR (KBr): 3088, 3029, 2952, 1655, 1469, 1350, 1309, 1159, 1098, 1030, 818, 766 cm^{-1}.

^{1}H NMR: δ 7.83-7.80 (m, 3H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.45 (t, *J* = 7.2 Hz, 2H), 7.39-7.30 (m, 4H), 7.15 (d, *J* = 8.4 Hz, 2H), 6.73 (s, 1H), 4.67-4.56 (m, 2H), 3.97-3.92 (m, 1H), 3.84 (dd, *J* = 13.2 and 2.0 Hz, 1H), 3.14 (dd, *J* = 13.0 and 7.6 Hz, 1H), 2.39 (s, 3H), 2.36 (s, 3H).

^{13}C NMR: δ 148.0, 144.5, 139.2, 138.4, 133.4, 130.3, 130.1, 129.2, 128.9, 128.4, 127.3, 125.8, 123.7, 121.0, 101.4, 71.0, 50.8, 44.6, 21.6, 21.2.

HRMS (ESI): Calcd. for $C_{27}H_{26}N_4O_3S$ $[M^+ + H]$: *m/z* 487.1804. Found: 487.1803.

Compound 44



Yield: 0.135 g (95%, White solid).

Mp: 164-166 °C.

IR (KBr): 3065, 3024, 2905, 1676, 1443, 1350, 1309, 1164, 1128, 1020, 948, 689 cm^{-1}.

^{1}H NMR: δ 7.77 (d, *J* = 7.5 Hz, 2H), 7.69 (d, *J* = 7.5 Hz, 2H), 7.61 (t, *J* = 7.5 Hz, 1H), 7.53 (t, *J* = 8.0 Hz, 2H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.36 (t, *J* = 7.0 Hz, 1H), 7.28-7.21 (m, 4H), 7.16 (d, *J* = 7.0 Hz, 2H), 6.10 (s, 1H), 4.47-4.36 (m, 2H), 3.80-3.76 (m, 1H), 3.68 (dd, *J* = 13.0 and 2.0 Hz, 1H), 3.36 (s, 2H), 2.97 (dd, *J* = 13.0 and 7.5 Hz, 1H).

^{13}C NMR: δ 147.9, 141.0, 137.2, 136.3, 133.5, 130.3, 129.4, 128.8, 128.6_2, 128.5_8, 128.3, 127.3, 126.9, 125.8, 120.8, 101.8, 70.8, 50.8, 44.2, 38.3.

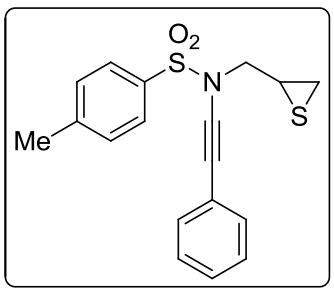
HRMS (ESI): Calcd. for $C_{26}H_{25}N_4O_3S$ [M^++H]: *m/z* 473.1647. Found: 473.1647.

X-ray structure has been determined for this compound (crystallized from acetonitrile).

6.6 Reactivity of epoxy ynamide 5a with sodium thiocyanate: Synthesis of thiirane ynamide 46

To a 10 mL RBF, 4-methyl-*N*-(oxiran-2-ylmethyl)-*N*-(phenylethynyl) benzenesulfonamide **5a** (0.3 mmol) and NaSCN (0.6 mmol) in PEG-400 (2 mL) were added. The RBF was stoppered and the contents stirred at rt (25 ^{o}C) for 2 h. After completion of the reaction as monitored by TLC, the crude 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 thiirane ynamide **46** in quantitative yield.

Compound 46



Yield: 0.103 g (quantitative, gummy liquid).

IR (KBr): 3052, 2926, 2236, 1595, 1496, 1441, 1370, 1167, 1085, 1041, 816, 751 cm^{-1}.

^{1}H NMR: δ 7.88 (d, *J* = 8.4 Hz, 2H), 7.42-7.38 (m, 4H), 7.34-7.32 (m, 3H), 3.95 (dd, *J* = 13.6 and 4.8 Hz, 1H), 3.28 (dd, *J* = 13.6 and 8.4 Hz, 1H), 3.18-3.12 (m, 1H), 2.58-2.57 (m, 1H), 2.48 (s, 3H), 2.38 (dd, *J* = 5.2 and 1.6 Hz, 1H).

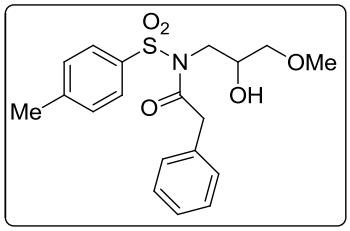
^{13}C NMR: δ 145.0, 134.5, 131.4, 129.9, 128.4, 128.0, 127.7, 122.6, 82.2, 71.3, 57.3, 30.7, 24.5, 21.7.

HRMS (ESI): Calcd. for $C_{18}H_{18}NO_2S_2$ [M^++H]: *m/z* 344.0779. Found: 344.0780.

6.7 Water and Methanol addition to epoxy ynamide 5a in the presence of *p*-toluene sulfonic acid (PTSA)

To a 10 mL RBF (round bottom flask) 4-methyl-*N*-(oxiran-2-ylmethyl)-*N*-(phenylethynyl)benzenesulfonamide **5a** (0.3 mmol) and PTSA (0.03 mmol) in MeOH solvent (2 mL) were added. The RBF was stoppered and the contents stirred at rt (25 ^{o}C) for 12 h. After completion of the reaction, as monitored by TLC, the solvent was removed under vacuum. The product *N*-(2-hydroxy-3-methoxypropyl)-2-phenyl-*N*-tosylacetamide **48** was purified by silica gel column chromatography by using hexane:EtOAc (7:3) as the eluent.

Compound 48



Yield: 0.096 g (85%, gummy liquid).

IR (KBr): 3499, 3261, 2936, 1711, 1598, 1505, 1453, 1314, 1164, 1091, 952, 812, 668 cm^{-1}.

^{1}H NMR: δ 7.71 (d, *J* = 8.4 Hz, 2H), 7.37-7.25 (m, 7H), 4.96-4.90 (m, 2H), 3.61 (s, 2H), 3.53-3.44 (m, 2H), 3.30 (s, 3H), 3.27-3.15 (m, 2H), 2.44 (s, 3H).

^{13}C NMR: δ 171.0, 143.6, 136.8, 133.7, 129.8, 129.2, 128.7, 127.3, 127.0, 71.5, 71.1, 59.3, 43.7, 41.2, 21.6.

HRMS (ESI): Calcd. for $C_{19}H_{23}NO_5SNa$ [M^{+}+Na]: *m/z* 400.1195. Found: 400.1198.

6.8 X-ray crystallography

A suitable crystal was mounted on a glass fiber (for **7**, **21**, **30**, **31**, and **44**) 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). Structures were solved and refined using standard methods.[57] 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 6-7.

Table 6. Crystal data for compounds **7**, and **21**[a]

Compound	**7**	**21**
Emp. formula	$C_{18}H_{17}NO_3S$	$C_{22}H_{19}NO_3S$
Formula weight	327.39	377.44
Crystal system	Monoclinic	Monoclinic
Space group	*P*2(1)/c	*P*2(1)/c
a /Å	13.1754(3)	19.1531(8)
b /Å	12.8893(3)	7.3529(3)
c /Å	9.6352(2)	13.8120(6)
α/deg	90	90
β/deg	97.160(2)	108.013(2)
γ/deg	90	90
V /Å^3	1623.52(7)	1849.82(13)
Z	4	4
D_{calc} /g cm^{-3}]	1.339	1.355
μ /mm^{-1}	1.893	0.198
F(000)	688	792
Data/ restraints/ parameters	3108/0/209	3662/0/246
S	1.091	1.048
R1 [I>2σ(I)]	0.0453	0.0345
wR2 [all data]	0.1408	0.0959
Max./min. residual electron dens. [eÅ^{-3}]	0.179/-0.358	0.257/-0.295

[a]R1 = Σ||Fo| - |Fc||/Σ|Fo| and wR2 = [Σw(Fo^2-Fc^2)^2/ΣwFo^4]$^{0.5}$

Table 7. Crystal data for compounds **30**, **31**, and **44**[a]

Compound	**30**	**31**	**44**
Emp. formula	$C_{26}H_{33}N_4O_3S$	$C_{17}H_{16}NO_3S$	$C_{26}H_{24}N_4O_3S$
Formula weight	481.62	356.40	472.55
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	*P*2(1)/c	*P*cab	*P*2(1)/c
a /Å	5.8986(3)	8.7500(7)	8.3734(10)
b /Å	26.6087(15)	15.7853(17)	25.188(3)
c /Å	16.7845(11)	24.961(2)	11.2668(13)
α/deg	90	90	90
β/deg	96.428(2)	90	98.394(2)
γ/deg	90	90	90
V /Å^3	2617.8(3)	3447.7(5)	2350.8(5)
Z	4	8	4
D_{calc} /g cm^{-3}]	1.222	1.373	1.335
μ /mm^{-1}	0.157	0.212	0.174
F(000)	1028.0	1488.0	992.0
Data/ restraints/ parameters	5869/0/313	3030/0/226	4149/0/307
S	1.025	1.034	1.047
R1 [I>2σ(I)]	0.0805	0.0771	0.0577
wR2 [all data]	0.2226	0.2132	0.1478
Max./min. residual electron dens. [eÅ^{-3}]	0.522/-0.568	0.391/-0.446	0.460/-0.245

[a]$R1 = \Sigma||Fo| - |Fc||/\Sigma|Fo|$ and $wR2 = [\Sigma w(Fo^2-Fc^2)^2/\Sigma wFo^4]^{0.5}$

References

1. (a) Zificsak, C. A.; Mulder, J. A.; Hsung, R. P.; Rameshkumar, C.; Wei, L. –L. *Tetrahedron* **2001**, *57*, 7575. (b) Dekorver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. *Chem. Rev*. **2010**, *110*, 5064. (c) Evano, G.; Coste, A.; Jouvin, K. *Angew. Chem., Int. Ed*. **2010**, *49*, 2840. (d) Lu, T.; Hsung, R. P. *ARKIVOC* **2014**, *i*, 127.
2. Ficini, J. *Tetrahedron* **1976**, *32*, 1449.
3. Janousek, Z.; Collard, J.; Viehe, H. G. *Angew. Chem*. **1972**, *84*, 993; *Angew. Chem., Int. Ed. Engl*. **1972**, *11*, 917.
4. (a) Saito, N.; Ichimaru, T.; Sato, Y. *Org. Lett*. **2012**, *14*, 1914. (b) Frischmuth, A.; Knochel, P. *Angew. Chem., Int. Ed*. **2013**, *52*, 10084. (c) Wang, X. –N.; Yeom, H. –S.; Fang, L. –C.; He, S.; Ma, Z. –X.; Kedrowski, B. L.; Hsung, R. P. *Acc. Chem. Res.* **2014**, *47*, 560. (d) Theunissen, C.; Métayer, B.; Henry, N.; Compain, G.; Marrot, J.; Martin–Mingot, A.; Thibaudeau, S.; Evano, G. *J. Am. Chem. Soc.* **2014**, *136*, 12528.
5. Mulder, J. A.; Kurtz, K. C. M.; Hsung, R. P.; Coverdale, H.; Frederick, M. O.; Shen, L.; Zificsak, C. A. *Org. Lett.* **2003**, *5*, 1547.
6. (a) Nissen, F.; Richard, V.; Alayrac, C.; Witulski, B. *Chem. Commun*. **2011**, *47*, 6656. (b) Gati, W.; Rammah, M. M.; Rammah, M. B.; Couty, F.; Evano, G. *J. Am. Chem. Soc.* **2012**, *134*, 9078. (c) Ghosh, N.; Nayak, S.; Sahoo, A. K. *Chem. –Eur. J.* **2013**, *19*, 9428. (d) Fujino, D.; Yorimitsu, H.; Osuka, A. *J. Am. Chem. Soc.* **2014**, *136*, 6255. (e) Karad, S. N.; Liu, R. –S. *Angew. Chem., Int. Ed*. **2014**, *53*, 9072.
7. (a) Alayrac, C.; Schollmeyer, D.; Witulski, B. *Chem. Commun*. **2009**, 1464. (b) Walker, P. R.; Campbell, C. D.; Suleman, A.; Carr, G.; Anderson, E. A. *Angew. Chem., Int. Ed*. **2013**, *52*, 9139. (c) Kiruthika, S. E.; Nandakumar, A.; Perumal, P. T. *Org. Lett*. **2014**, *16*, 4424. (d) Jadhav, A. M.; Pagar, V. V.; Huple, D. B.; Liu, R. –S. *Angew. Chem., Int. Ed*. **2015**, *54*, 3812. (e) Tokimizu, Y.; Wieteck, M.; Rudolph, M.; Oishi, S.; Fujii, N.; Hashmi, A. S. K.; Ohno, H. *Org. Lett*. **2015**, *17*, 604. (f) Lecomte, M.; Evano, G. *Angew. Chem., Int. Ed*. **2016**, *55*, 4547.
8. Marion, F.; Courillon, C.; Malacria, M. *Org. Lett*. **2003**, *5*, 5095.
9. Couty, S.; Liégault, B.; Meyer, C.; Cossy, J. *Org. Lett*. **2004**, *6*, 2511.
10. Zhang, Y.; Hsung, R. P.; Zhang, X.; Huang, J.; Slafer, B. W.; Davis, A. *Org. Lett*. **2005**, *7*, 1047.
11. Yao, P. –Y.; Zhang, Y.; Hsung, R. P.; Zhao, K. *Org. Lett*. **2008**, *10*, 4275.
12. Dooleweerdt, K.; Ruhland, T.; Skrydstrup, T. *Org. Lett*. **2009**, *11*, 221.
13. Garcia, P.; Harrak, Y.; Diab, L.; Cordier, P.; Ollivier, C.; Gandon, V.; Malacria, M.; Fensterbank, L.; Aubert, C. *Org. Lett*. **2011**, *13*, 2952.
14. Dateer, R. B.; Pati, K.; Liu, R. –S. *Chem. Commun*. **2012**, *48*, 7200.
15. Kong, Y.; Jiang, K.; Cao, J.; Fu, L.; Yu, L.; Lai, G.; Cui, Y.; Hu, Z.; Wang, G. *Org. Lett*. **2013**, *15*, 422.
16. Okitsu, T.; Nakata, K.; Nishigaki, K.; Michioka, N.; Karatani, M.; Wada, A. *J. Org. Chem.* **2014**, *79*, 5914.

17. Siva Reddy, A.; Kumara Swamy, K. C. *Org. Lett*. **2015**, *17*, 2996.
18. Siva Reddy, A.; Leela Siva Kumari, A.; Saha, S.; Kumara Swamy, K. C. *Adv. Synth. Catal.* **2016**, *358*, 1625.
19. Witulski, B.; Alayrac, C.; Tevzadze-Saeftel, L. *Angew. Chem., Int. Ed*. **2003**, *42*, 4257.
20. Istrate, F. M.; Buzas, A. K.; Jurberg, A. D.; Odabachian, Y.; Gagosz, F. *Org. Lett*. **2008**, *10*, 925.
21. Gati, W.; Couty, F.; Boubaker, T.; Rammah, M. M.; Rammah, M. B.; Evano, G. *Org. Lett.* **2013**, *15*, 3122.
22. (a) Morten, C. J.; Byers, J. A.; Van Dyke, A. R.; Vilotijevic, I.; Jamison, T. F. *Chem. Soc. Rev*. **2009**, *38*, 3175. (b) Huang, C. –Y.; Doyle, A. G. *Chem. Rev*. **2014**, *114*, 8153. (c) Rotstein, B. H.; Zaretsky, S.; Rai, V.; Yudin, A. K. *Chem. Rev*. **2014**, *114*, 8323. (d) Zhu, Y.; Wang, Q.; Cornwall, R. G.; Shi, Y. *Chem. Rev*. **2014**, *114*, 8199. (e) He, J.; Ling, J.; Chiu, P. *Chem. Rev*. **2014**, *114*, 8037. (f) Wang, C.; Luo, L.; Yamamoto, H. *Acc. Chem. Res.* **2016**, *49*, 193.
23. (a) Movassaghi, M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 2456. (b) Bartoli, G.; Bosco, M.; Carlone, A.; Locatelli, M.; Melchiorre, P.; Sambri, L. *Org. Lett*. **2005**, *7*, 1983. (c) Nishiyama, Y.; Katahira, C.; Sonoda, N. *Tetrahedron* **2006**, *62*, 5803. (d) Church, T. L.; Byrne, C. M.; Lobkovsky, E. B.; Coates, G. W. *J. Am. Chem. Soc.* **2007**, *129*, 8156. (e) Bao, W.; Liu, Y.; Lv, X.; Qian, W. *Org. Lett*. **2008**, *10*, 3899. (f) Liu, Y.; Bao, W. *Org. Biomol. Chem.* **2010**, *8*, 2700. (g) Mack, D. J.; Njardarson, J. T. *ACS Catal*. **2013**, *3*, 272. (h) Li, H.; Spannenberg, A.; Neumann, H.; Beller, M.; Wu, X. –F. *Chem*. *Commun.* **2014**, *50*, 2114.
24. (a) Taber, D. F.; He, Y.; Xu, M. *J. Am. Chem. Soc.* **2004**, *126*, 13900. (b) Lin, M. –Y.; Maddirala, S. J.; Liu, R. –S. *Org. Lett*. **2005**, *7*, 1745. (c) Yoshida, M.; Hayashi, M.; Shishido, K. *Org. Lett*. **2007**, *9*, 1643. (d) Shu, X. –Z.; Liu, X. –Y.; Xiao, H. –Q.; Ji, K. –G.; Guo, L. –N.; Qi, C. –Z.; Liang, Y. –M. *Adv. Synth. Catal.* **2007**, *349*, 2493. (e) Wen, S. –G.; Liu, W. –M.; Liang, Y. –M. *J. Org. Chem.* **2008**, *73*, 4342. (f) Blanc, A.; Tenbrink, K.; Weibel, J. –M.; Pale, P. *J. Org. Chem.* **2009**, *74*, 5342. (g) Iwata, A.; Inuki, S.; Oishi, S.; Fujii, N.; Ohno, H. *J. Org. Chem.* **2011**, *76*, 5506. (h) Gronnier, C.; Kramer, S.; Odabachian, Y.; Gagosz, F. *J. Am. Chem. Soc.* **2012**, *134*, 828. (i) Shiroodi, R. K.; Koleda, O.; Gevorgyan, V. *J. Am. Chem. Soc.* **2014**, *136*, 13146. (j) Hoffmann, M.; Weibel, J. –M.; de Frémont, P.; Pale, P.; Blanc, A. *Org. Lett*. **2014**, *16*, 908.
25. (a) Piotti, M. E.; Alper, H. *J. Org. Chem.* **1997**, *62*, 8484. (b) Hashmi, A. S. K.; Sinha, P. *Adv. Synth. Catal.* **2004**, *346*, 432. (c) Wang, L.; Maddess, M. L.; Lautens, M. *J. Org. Chem.* **2007**, *72*, 1822. (d) Cordonnier, M. –C.; Blanc, A.; Pale, P. *Org. Lett.* **2008**, *10*, 1569. (e) Blanc, A.; Tenbrink, K.; Weibel, J. –M.; Pale, P. *J. Org. Chem.* **2009**, *74*, 4360. (f) Miura, T.; Shimada, M.; de Mendoza, P.; Deutsch, C.; Krause, N.; Murakami, M. *J. Org. Chem.* **2009**, *74*, 6050. (g) Sau, M.; Rodriguez-Escrich, C.; Pericas, M. A. *Org. Lett*. **2011**, *13*, 5044.
26. (a) Molinaro, C.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 8076. (b) Woodin, K. S.; Jamison, T. F. *J. Org. Chem.* **2007**, *72*, 7451. (c) Beaver, M. G.; Jamison, T. F. *Org. Lett*. **2011**, *13*, 4140.

27. Pujanauski, B. G.; Bhanu Prasad, B. A.; Sarpong, R. *J. Am. Chem. Soc.* **2006**, *128*, 6786.
28. Lin, G. –Y.; Li, C. –W.; Hung, S. –H.; Liu, R. –S. *Org. Lett.* **2008**, *10*, 5059.
29. Trenkle, J. D.; Jamison, T. F. *Angew. Chem., Int. Ed*., **2009**, *48*, 5366.
30. Yang, C. –Y.; Lin, M. –S.; Liao, H. –H.; Liu, R. –S. *Chem. –Eur. J.* **2010**, *16*, 2696.
31. Liao, H. –H.; Liu, R. –S. *Chem. Commun*. **2011**, *47*, 1339.
32. Kang, J. Y.; Connell, B. T. *J. Org. Chem.* **2011**, *76*, 2379.
33. Li, S.; Wu, J. *Chem. Commun.* **2012**, *48*, 8973.
34. Shenlin, H.; Yuanjiang P.; Yulin, Z.; Anxin, W. *Org. Lett*. **2005**, *7*, 3797.
35. Kang, J. -E.; Kim, H. -B.; Lee, J. -W.; Shin S. *Org. Lett*. **2006**, *8*, 3537.
36. Lei, M.; Zhan, Z.; Tian, W.; Lu, P. *Tetrahedron* **2012**, *68*, 3361.
37. Wong, V. H. L.; Andy Hor, T. S.; Hii, K. K. M. *Chem. Commun.* **2013**, *49*, 9272.
38. Cai, Z. –J.; Yang, C.; Wang, S. –Y.; Ji, S. –J. *Chem. Commun*. **2015**, *51*, 14267.
39. Dai, L. –Z.; Qi, M. –J.; Shi, Y. –L.; Liu, X. –G.; Shi, M. *Org. Lett*. **2007**, *9*, 3191.
40. (a) Dai, L. –Z.; Shi, M. *Chem. –Eur. J.* **2008**, *14*, 7011. (b) Lee, S. I.; Baek, J. Y.; Sim, S. H.; Chung, Y. K. *Synthesis* **2007**, 2107.
41. Fukudome, Y.; Naito, H.; Hata, T.; Urabe, H. *J. Am. Chem. Soc.* **2008**, *130*, 1820.
42. Wang, Z.; Lin, X.; Luck, R. L.; Gibbons, G.; Fang, S. *Tetrahedron* **2009**, *65*, 2643.
43. Vandavasi, J. K.; Hu, W. –P.; Chen, H. –Y.; Senadi, G. C.; Chen, C. –Y.; Wang, J. –J. *Org. Lett*. **2012**, *14*, 3134.
44. Sladojevich, F.; Trabocchi, A.; Guarna, A. *Org. Biomol. Chem.*, **2008**, *6*, 3328.
45. Thangavela, V.; Chadhab, A. *Tetrahedron* **2007**, *63*, 4126.
46. Li, L. – S.; Wu, Y. – L. *Tetrahedron Lett*. **2002**, *43*, 2427.
47. Shufeng, C.; Jianbo, W. *J. Org. Chem.* **2007**, *72*, 4993.
48. Nie, X.; Wang, G. *J. Org. Chem*. **2006**, *71*, 4734.
49. Zhang, Y.; Hsung, R. P.; Tracey, M. R.; Kurtz, K. C. M.; Vera, E. L. *Org. Lett.* **2004**, *6*, 1151.
50. Ghosh, P.; Saha, P.; Bondalapati, S.; Indukuri, K.; Saikia, A. K. *J. Org. Chem*. **2014**, *79*, 4119.
51. (a) Joo, J. –E.; Lee, K. –Y.; Pham, V. –T.; Tian, Y. –S.; Ham, W. –H. *Org. Lett*. **2007**, *9*, 3627. (b) Thompson, A. M.; Sutherland, H. S.; Palmer, B. D.; Kmentova, I.; Blaser, A.; Franzblau, S. G.; Wan, B.; Wang, Y.; Ma, Z.; Denny, W. A. *J. Med. Chem*. **2011**, *54*, 6563. (c) Palmer, B. D.; Sutherland, H. S.; Blaser, A.; Kmentova, I.; Franzblau, S. G.; Wan, B.; Wang, Y.; Ma, Z.; Denny, W. A.; Thompson, A. M. *J. Med. Chem*. **2015**, *58*, 3036. (d) Park, S. –H.; Jin, X.; Kang, J. –C.; Jung, C.; Kim, S. –S.; Kim, S. –S.; Lee, K. –Y.; Ham, W. –H. *Org. Biomol. Chem.* **2015**, *13*, 4539. (e) Park, S. –H.; Kim, J. –Y.; Kim, J. –S.; Jung, C.; Song, D. –K.; Ham, W. H. *Tetrahedron: Asymmetry* **2015**, *26*, 657.
52. (a) Urbanski, T.; Radzikowski, Cz.; Ledochowski, Z.; Czarnocki, W. *Nature* **1956**, *178*, 1351. (b) Urbanski, T.; Gurne, D.; Slopek, S.; Mordarska, H.; Mordarski, M. *Nature* **1960**, *187*, 426. (c) Chylińska, J. B.; Urbański, T.; Mordarski, M. *J. Med. Chem*. **1963**, *6*, 484. (d) de Poel, H. V.; Guillaumet, G.; Viaud-Massuard, M. –C. *Tetrahedron Lett.* **2002**, *43*, 1205. (e) Zhang, P.; Terefenko, E. A.; Fensome, A.;

Wrobel, J.; Winneker, R.; Zhang, Z. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1313. (f) Jin, Z.; Wang, X.; Huang, H.; Liang, X.; Ye, J. *Org. Lett*. **2011**, *13*, 564.

53. Siva Reddy, A.; Nagarjuna Reddy, M.; Kumara Swamy, K. C. *RSC Adv*. **2014**, *4*, 28359.
54. Brown, J. A.; Chudasama, V.; Giles, M. E.; Gill, D. M.; Keegan, P. S.; Kerr, W. J.; Munday, R. H.; Griffin, K.; Watts, A. *Org. Biomol. Chem.* **2012**, *10*, 509.
55. (a) Galy, G. P.; Elguero, J.; Vincent, E. J.; Galy, A. M.; Barbe, J. *Synthesis* **1979**, 944. (b) Mahamoud, A.; Galy, J. P.; Vincent, E. J.; Barbe, J. *Synthesis* **1981**, 917. (c) Katritzky, A. R.; Ramer, W. H. *J. Org. Chem.* **1985**, *50*, 852. (d) Majumdar, K. C.; Ghosh, S. K. *Synth. Commun.* **1994**, *24*, 217. (e) Huang, J.; Xiong, H.; Hsung, R. P.; Rameshkumar, C.; Mulder, J. A.; Grebe, T. P. *Org. Lett.* **2002**, *4*, 2417.
56. Mirza-Aghayan, M.; Tavana, M. M.; *J. Sulfur Chem.* **2015**, *36*, 30.
57. (a) Sheldrick, G. M. SADABS, Siemens Area Detector Absorption Correction, University of Göttingen, Germany, **1996**. (b) Sheldrick, G. M. SHELX-97- A program for crystal structure solution and refinement, University of Göttingen, **1997**. (c) Sheldrick, G. M. SHELXTL NT Crystal Structure Analysis Package, Bruker AXS, Analytical X-ray System, WI, USA, **1999**, version 5.10.

A) Copies of $^{1}H/^{13}C$ NMR spectra for representative compounds

PART A: Compounds 9, 35, 40, 42, 46, 60, 63, 63', 81, 95 and 98

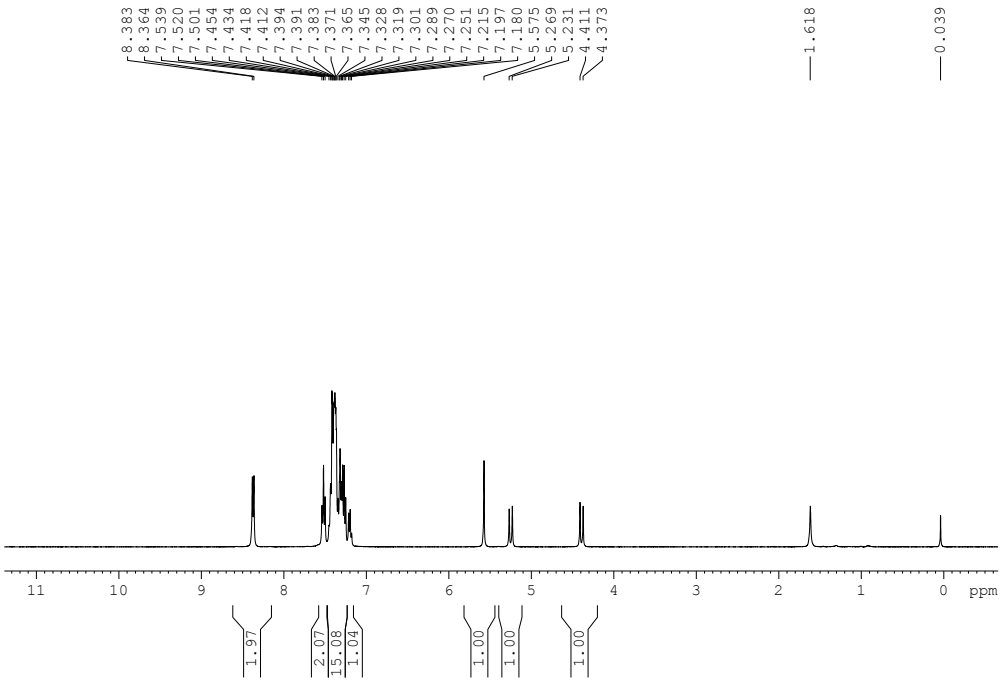


Figure A1. ^{1}H NMR spectrum of compound **9**

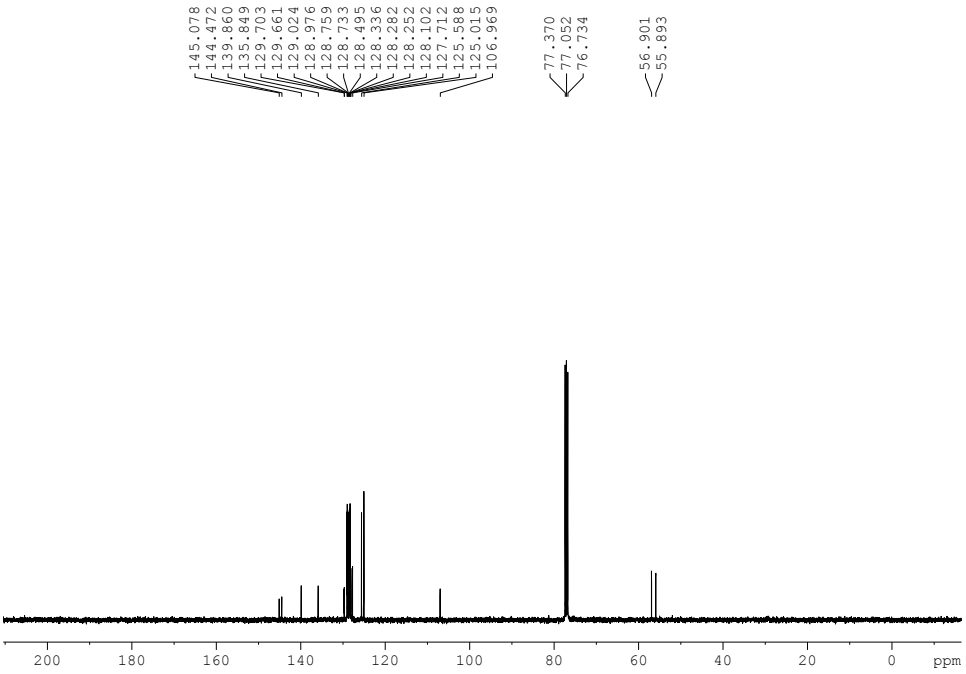


Figure A2. ^{13}C NMR spectrum of compound **9**

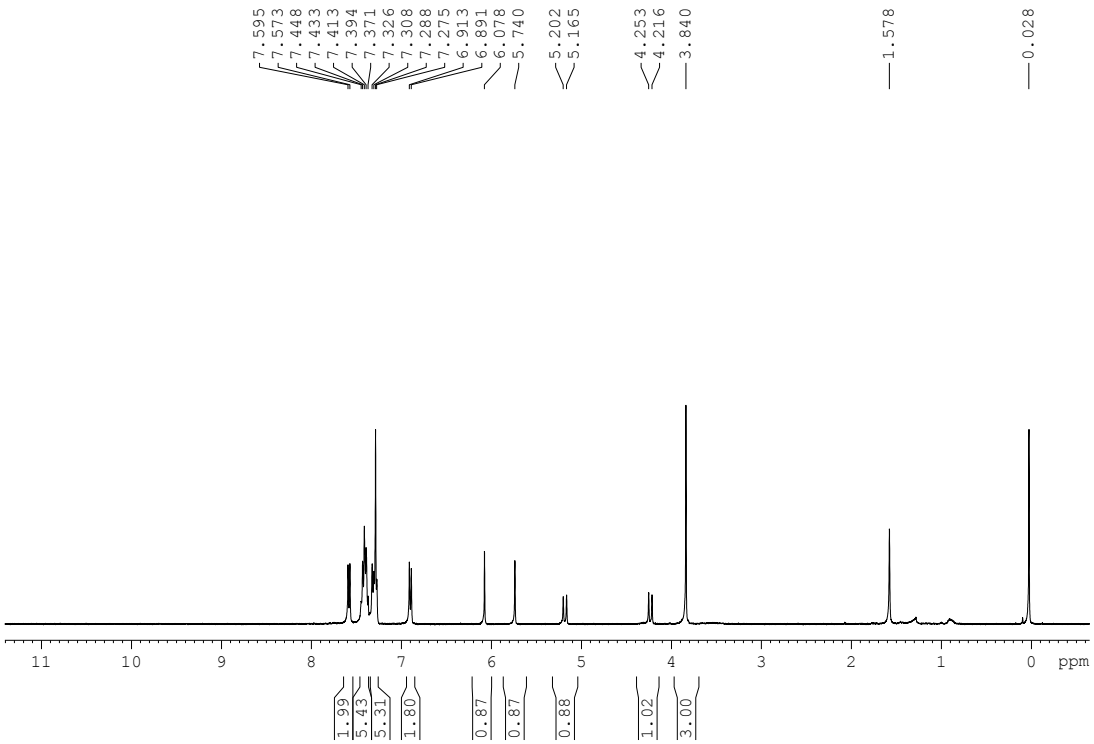


Figure A3. ^{1}H NMR spectrum of compound **35**

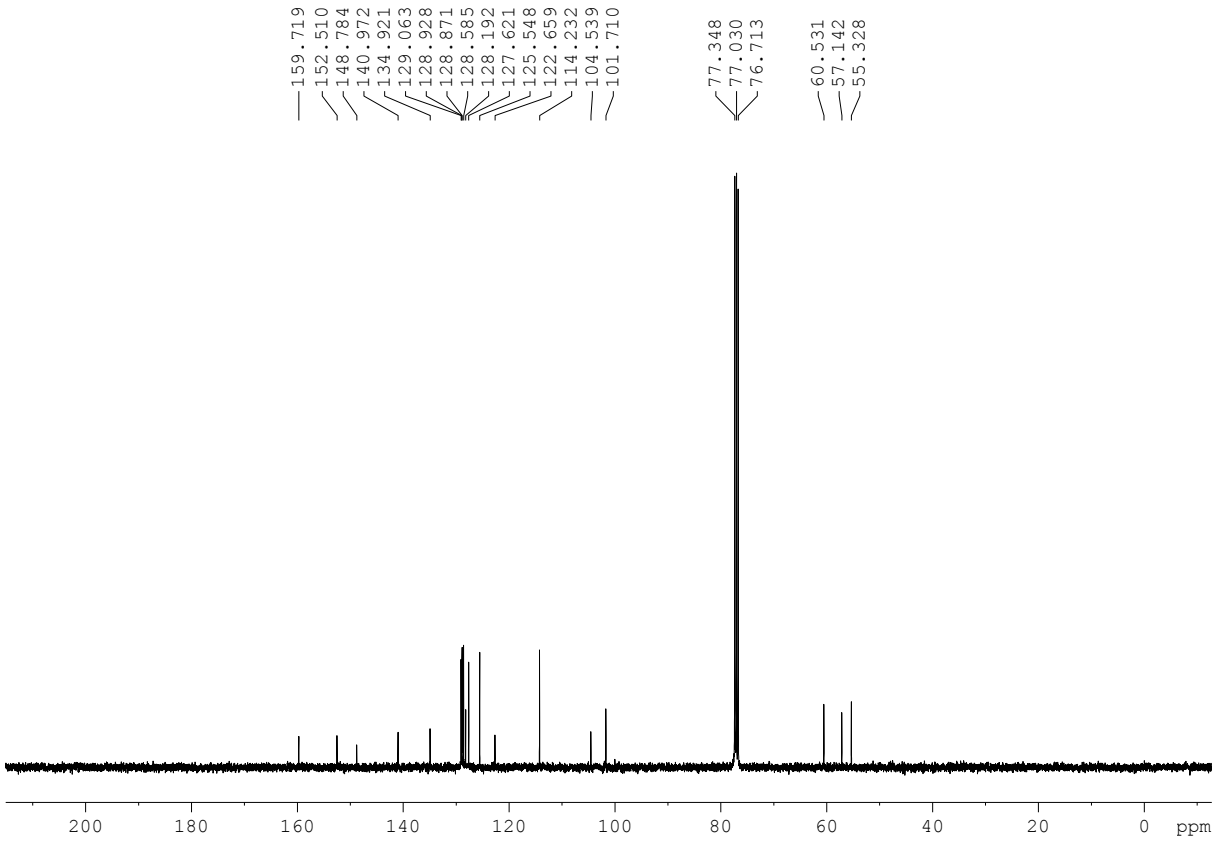


Figure A4. ^{13}C NMR spectrum of compound 3**5**

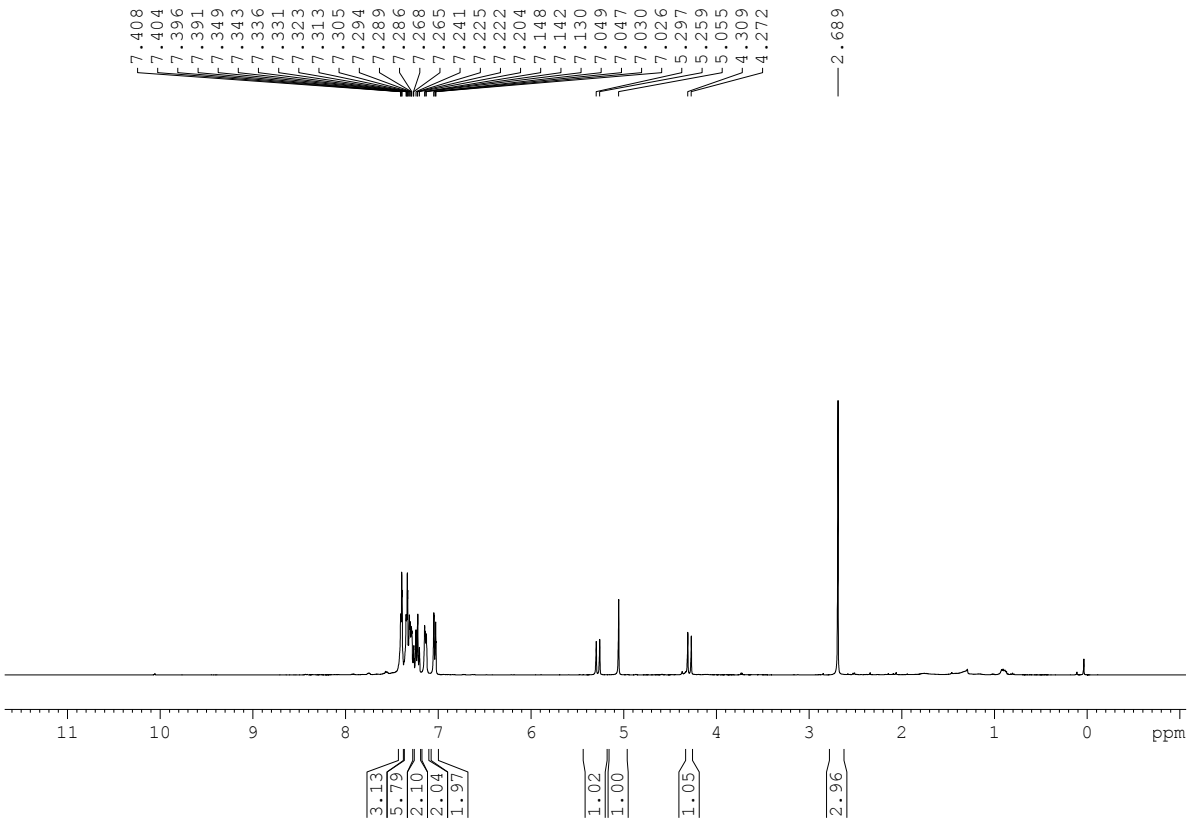


Figure A5. ^{1}H NMR spectrum of compound **40**

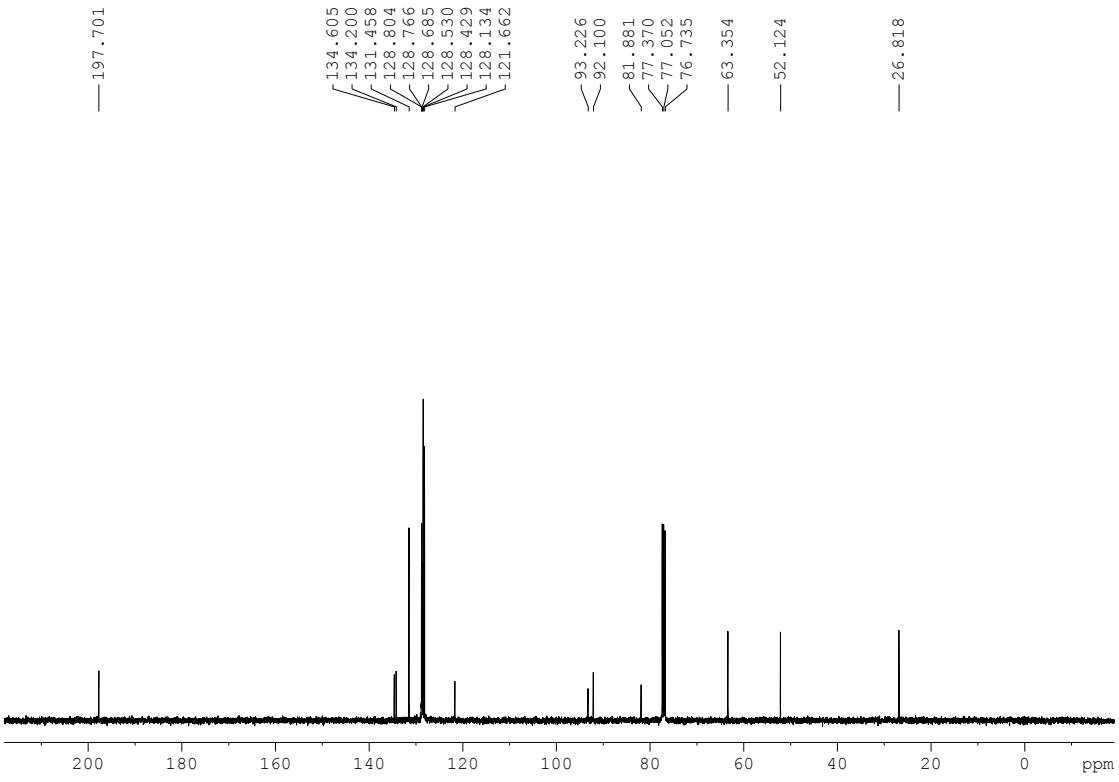


Figure A6. ^{13}C NMR spectrum of compound **40**

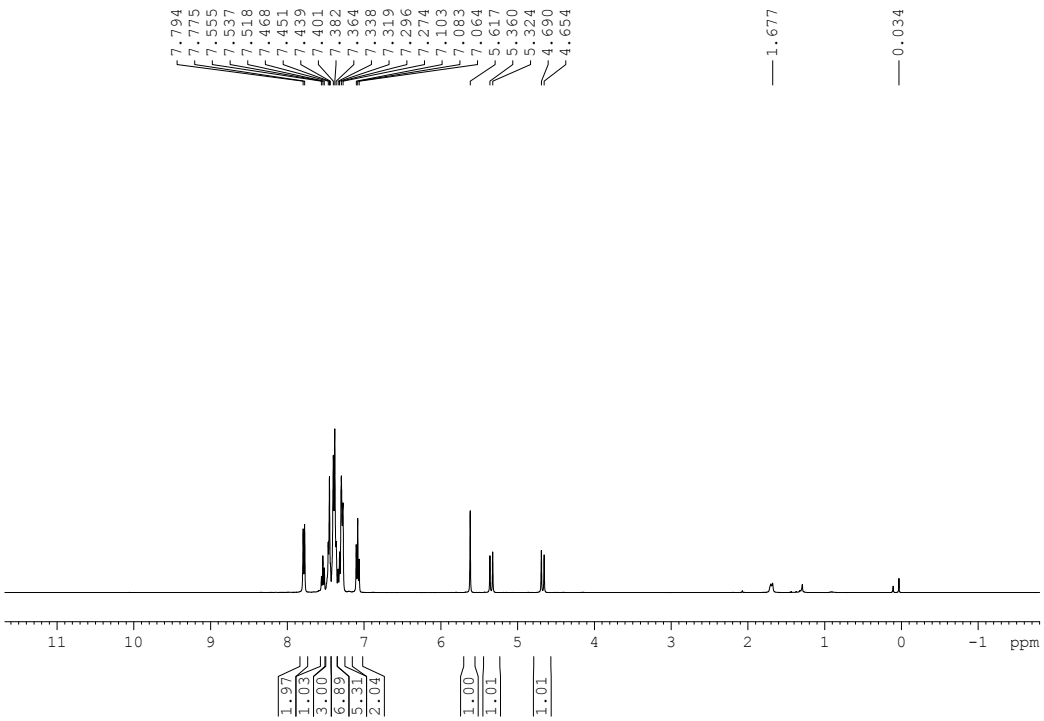


Figure A7. ^{1}H NMR spectrum of compound **42**

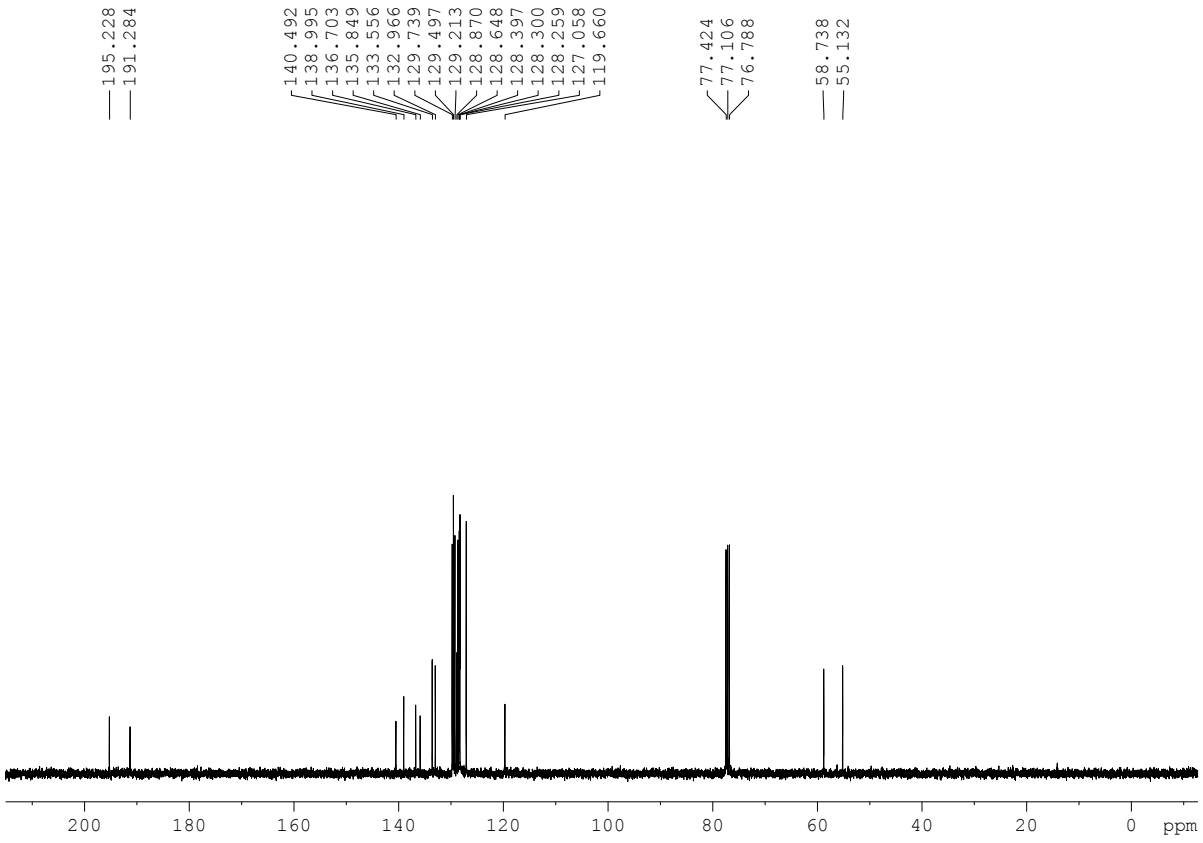


Figure A8. ^{13}C NMR spectrum of compound **42**

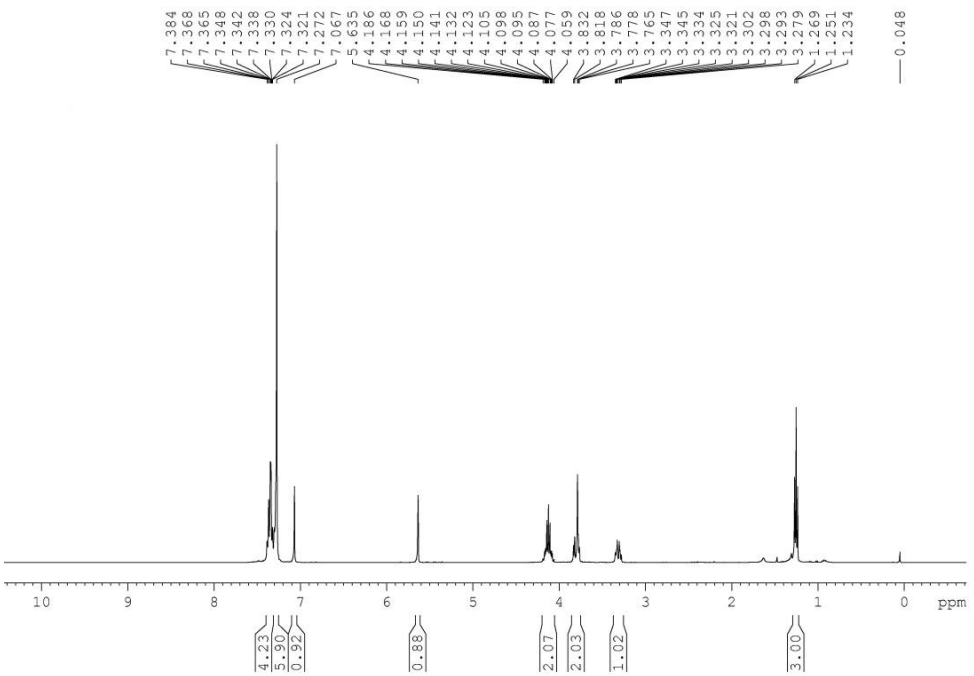


Figure A9. ^{1}H NMR spectrum of compound **46**

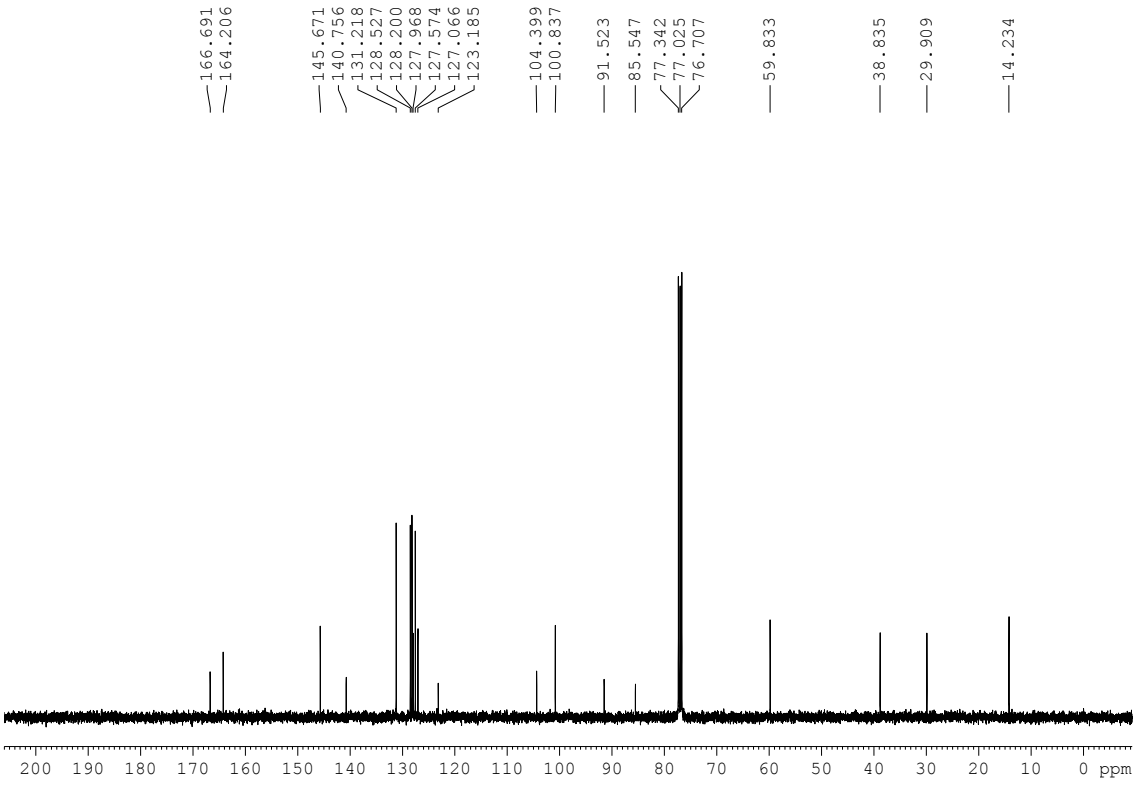


Figure A10. ^{13}C NMR spectrum of compound **46**

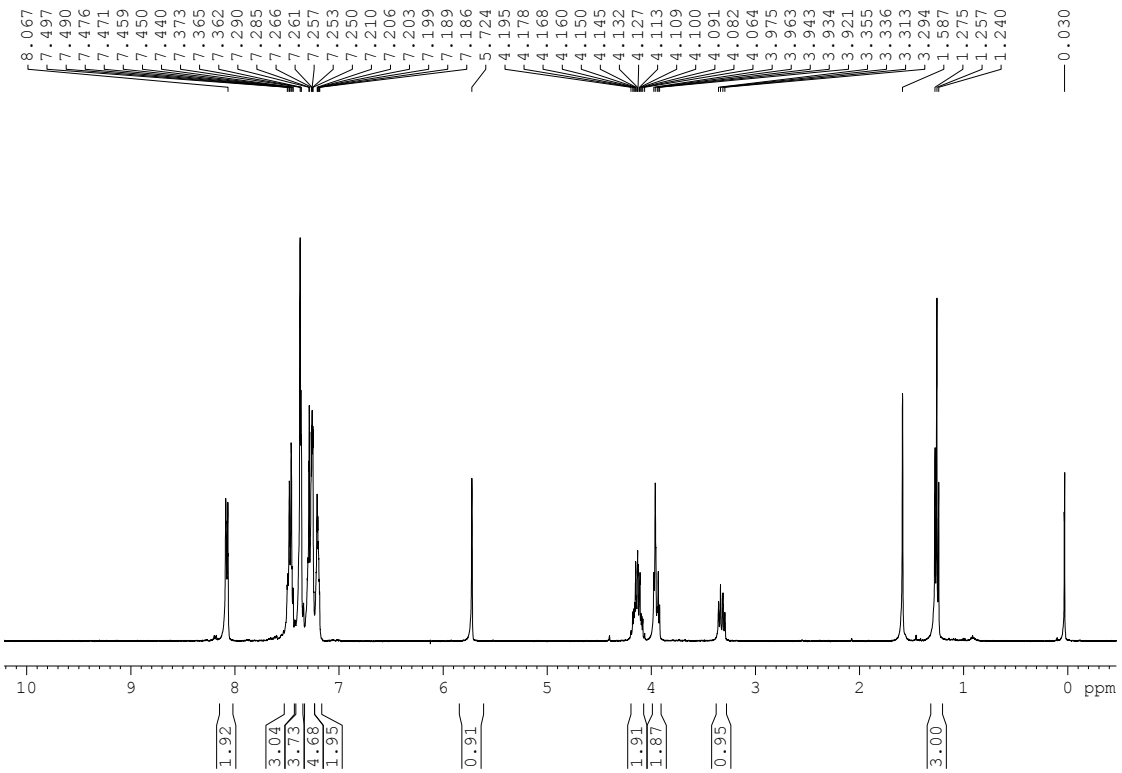


Figure A11. ^{1}H NMR spectrum of compound **60**

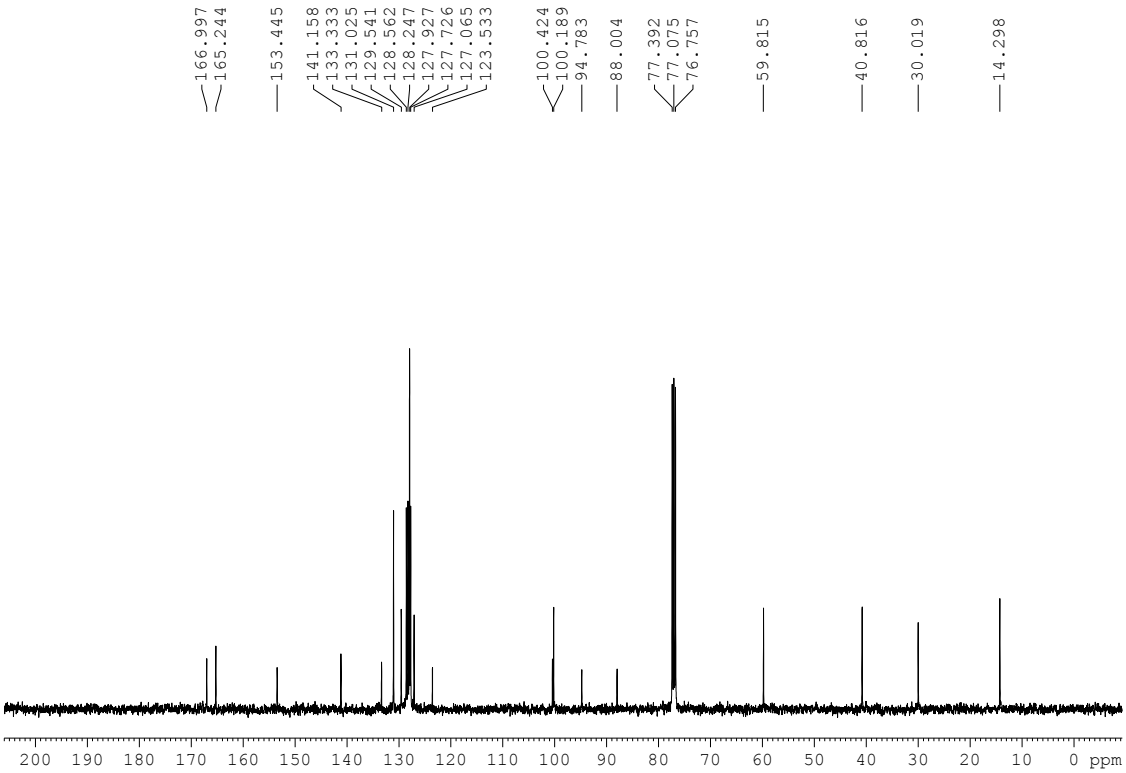


Figure A12. ^{13}C NMR spectrum of compound **60**

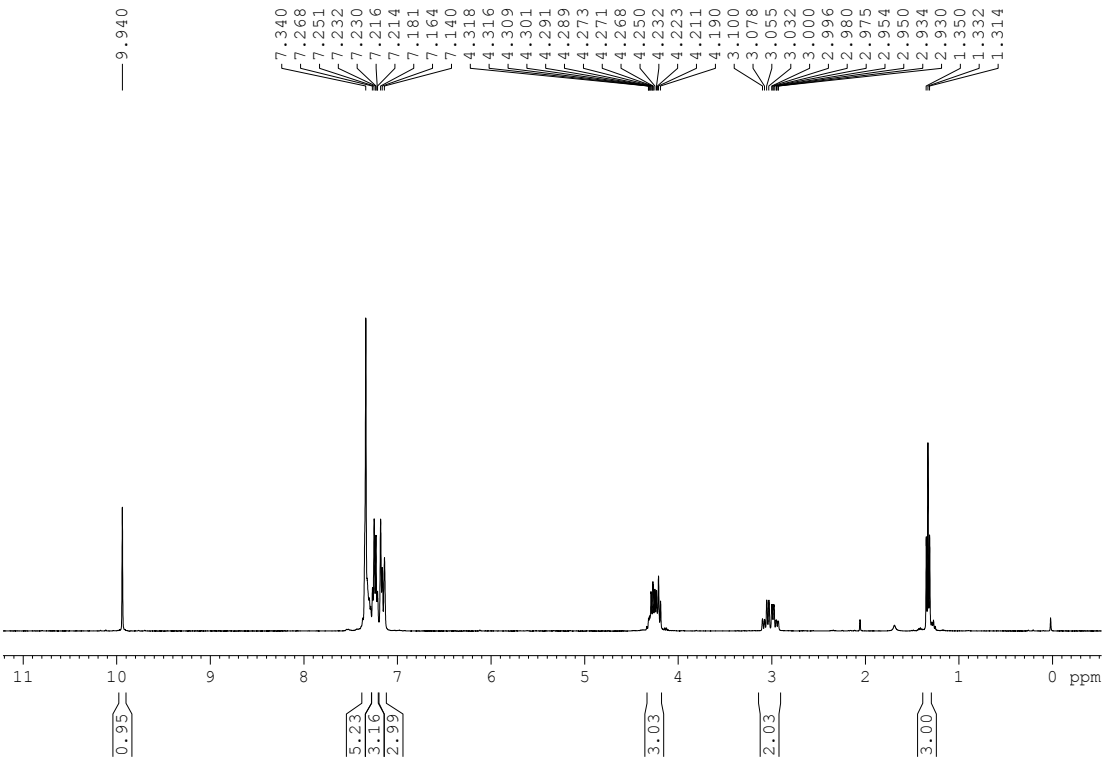


Figure A13. ^{1}H NMR spectrum of compound **63**

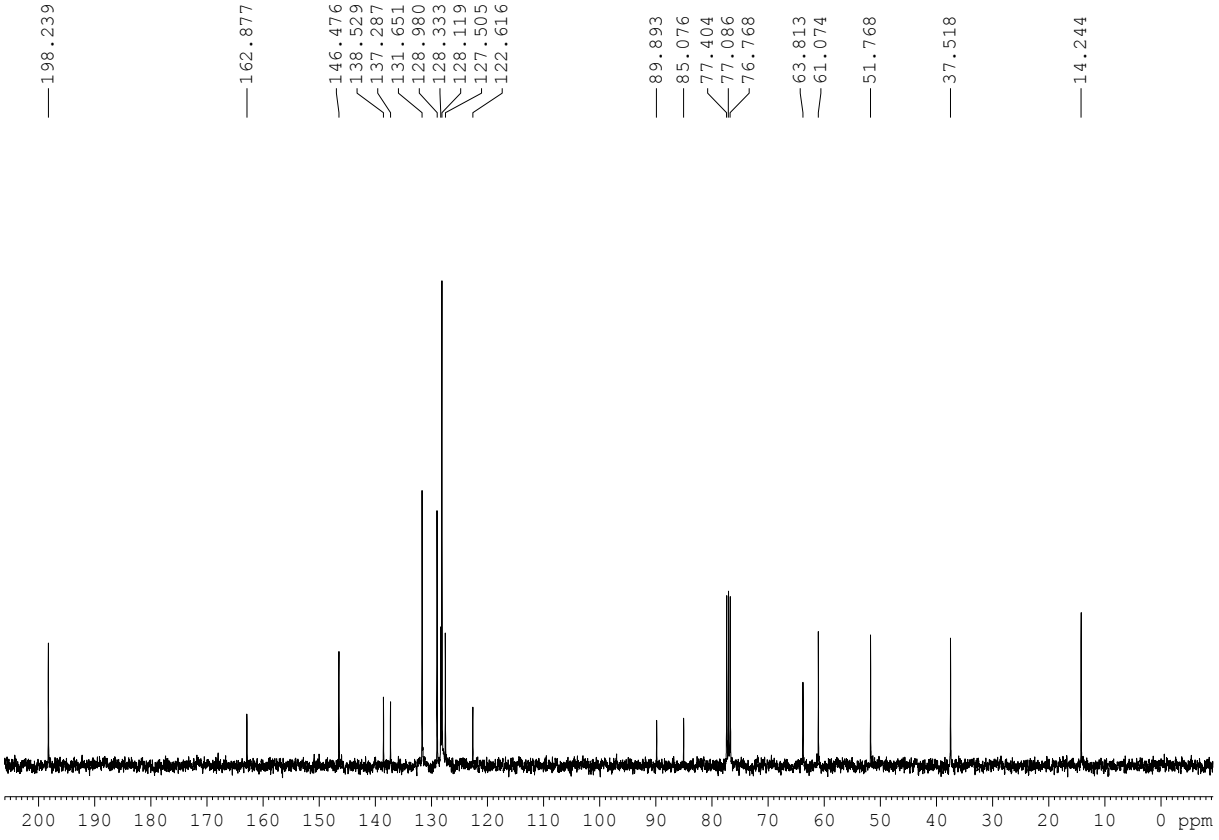


Figure A14. ^{13}C NMR spectrum of compound **63**

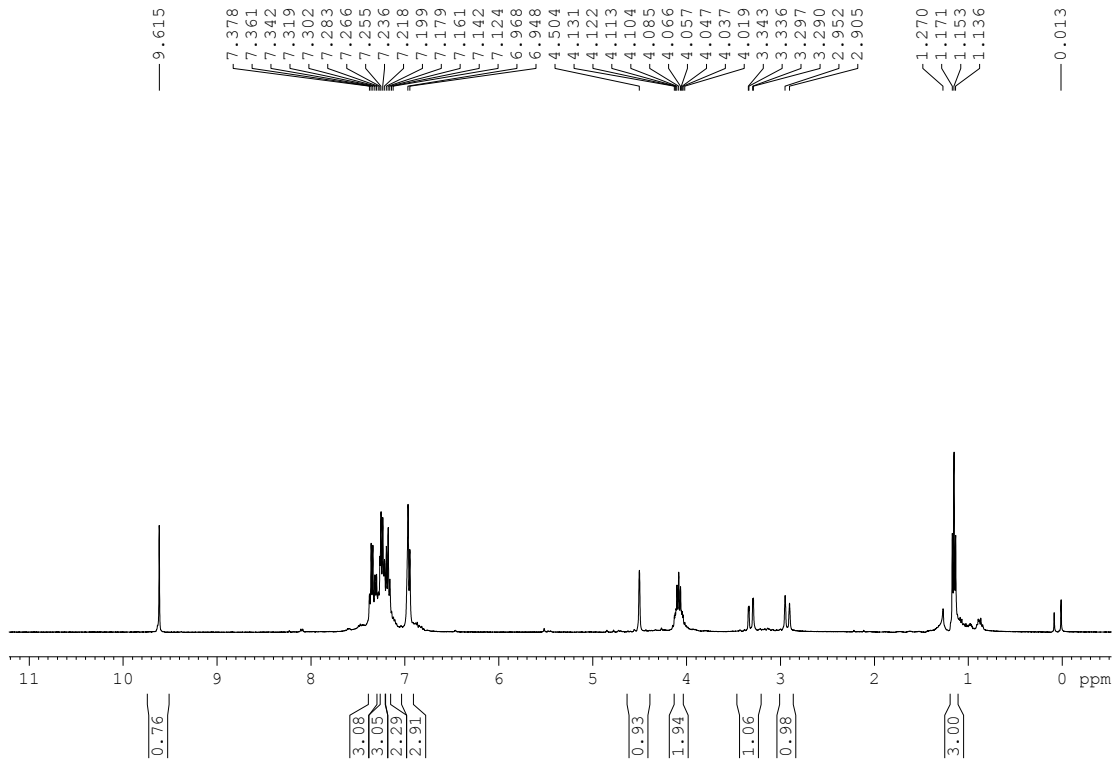


Figure A15. ^{1}H NMR spectrum of compound **63'**

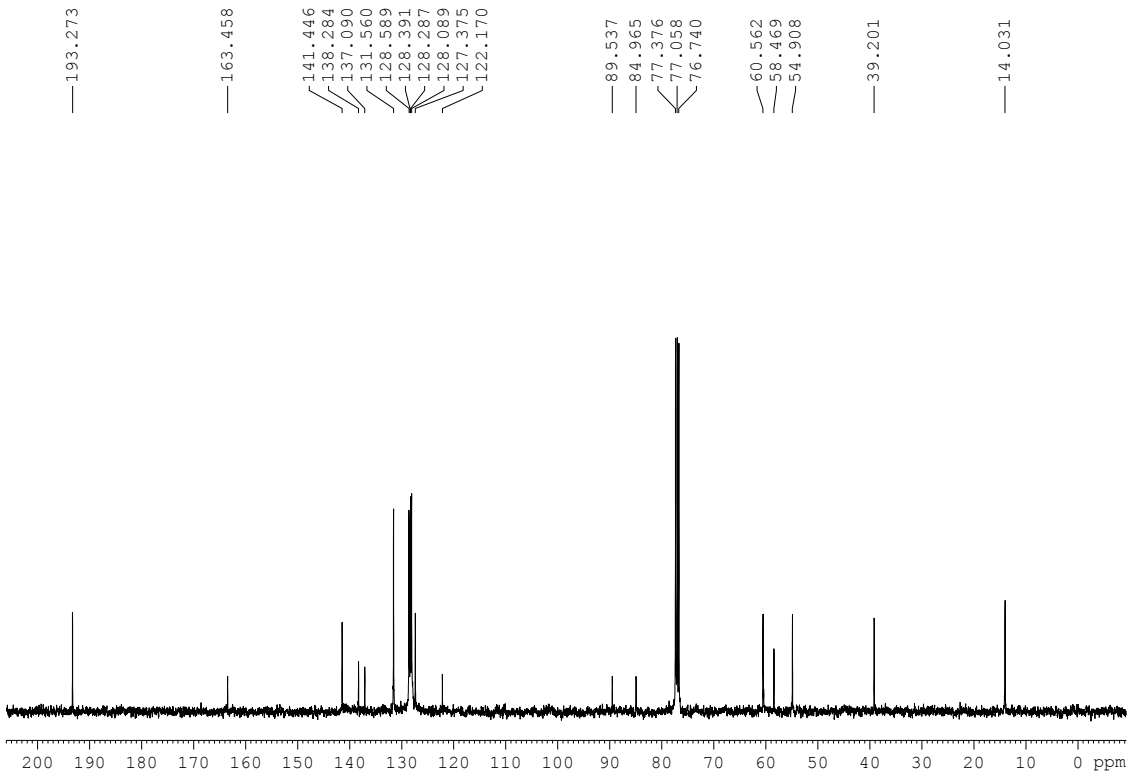


Figure A16. ^{13}C NMR spectrum of compound **63'**

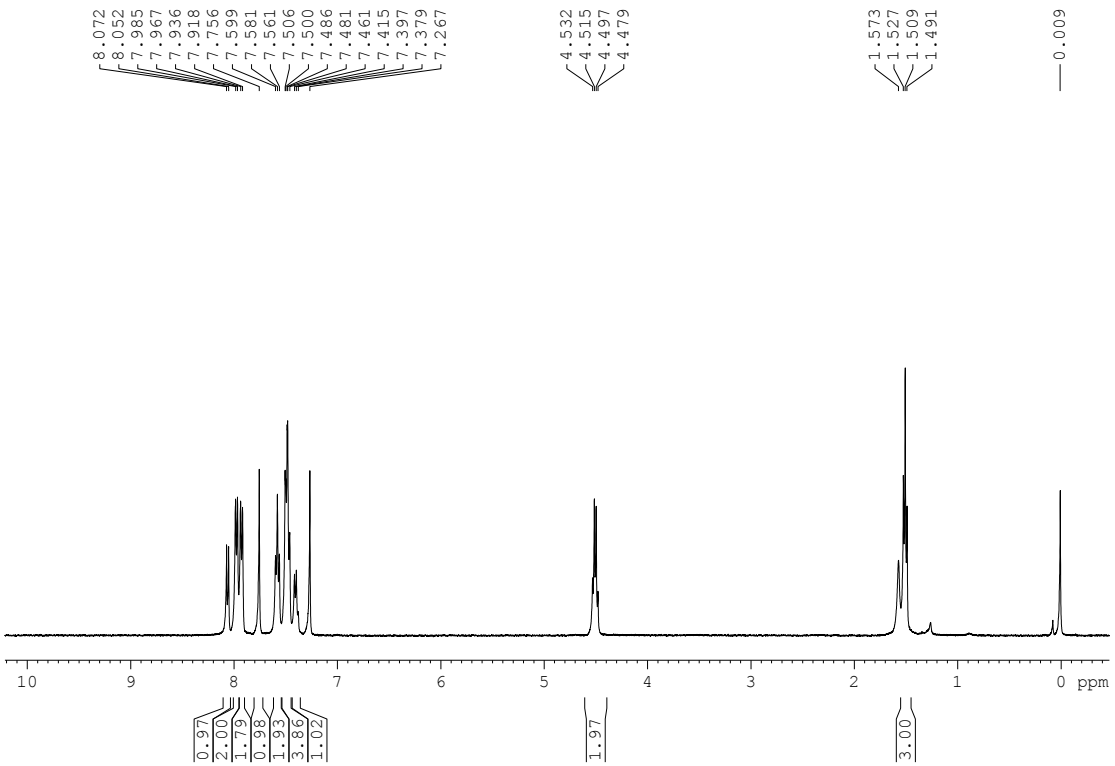


Figure A17. ^{1}H NMR spectrum of compound **81**

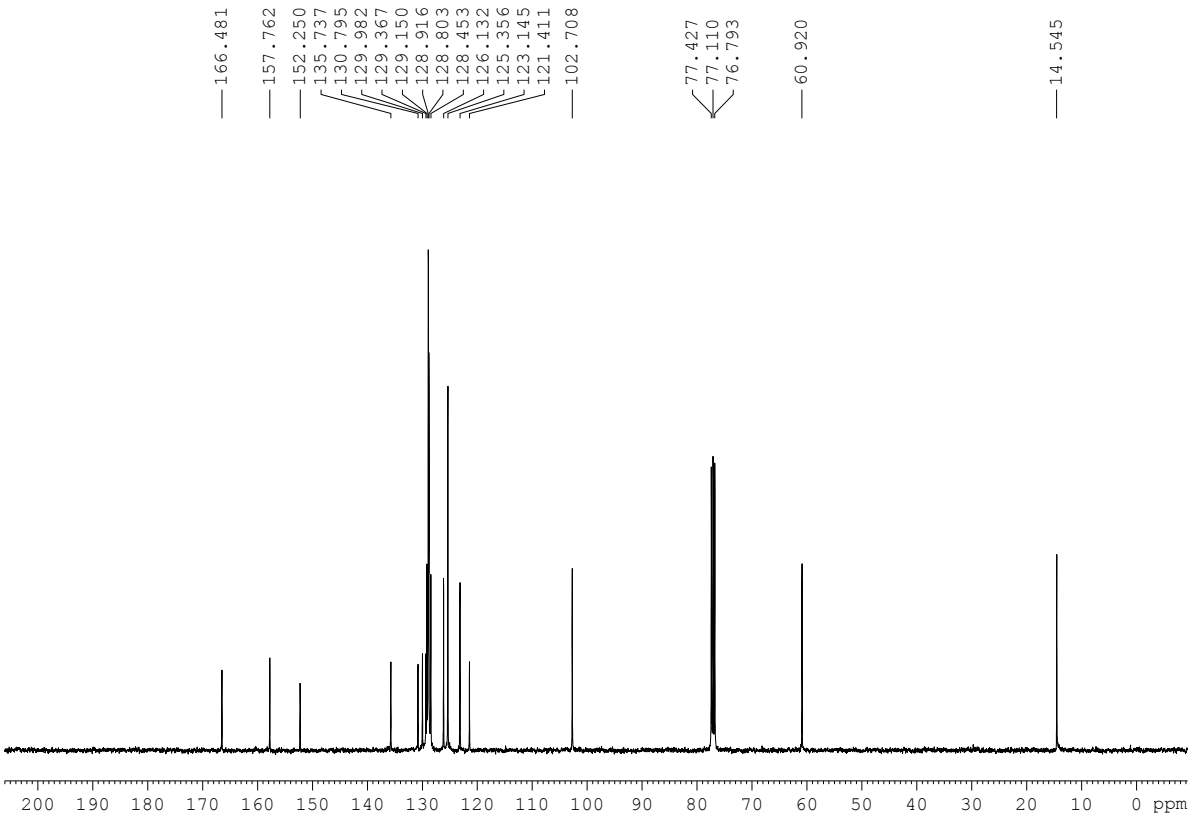


Figure A18. ^{13}C NMR spectrum of compound **81**

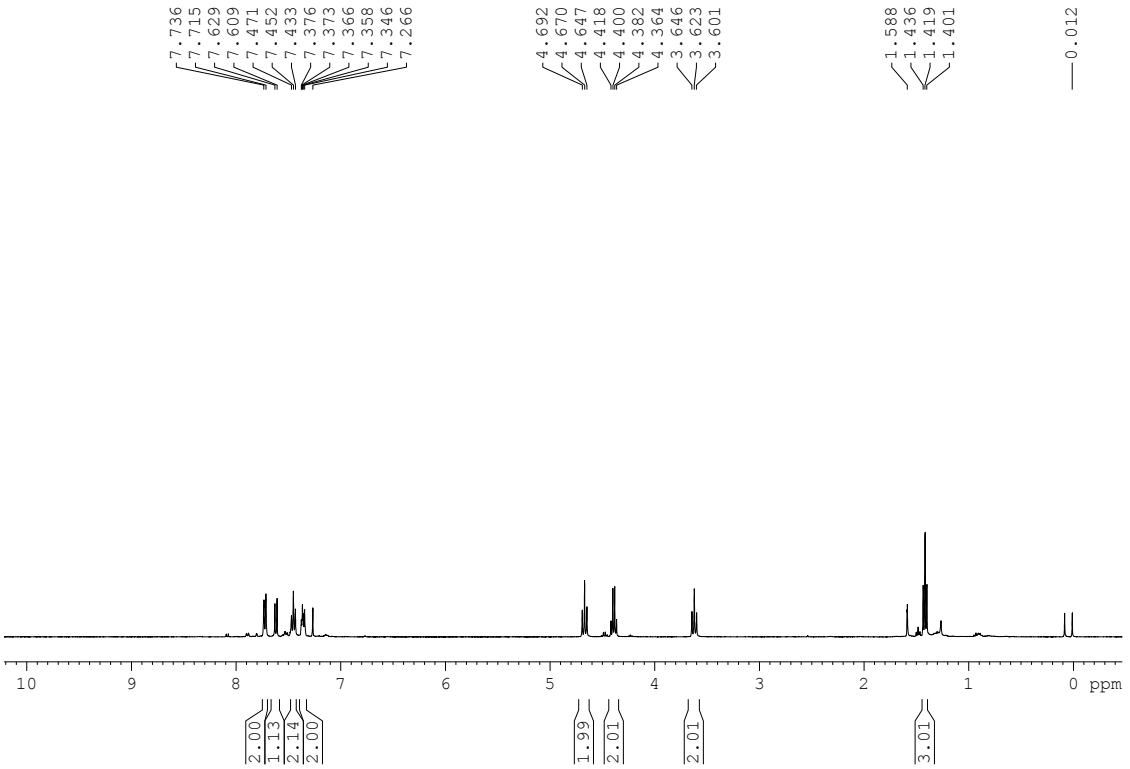


Figure A19. ^{1}H NMR spectrum of compound **95**

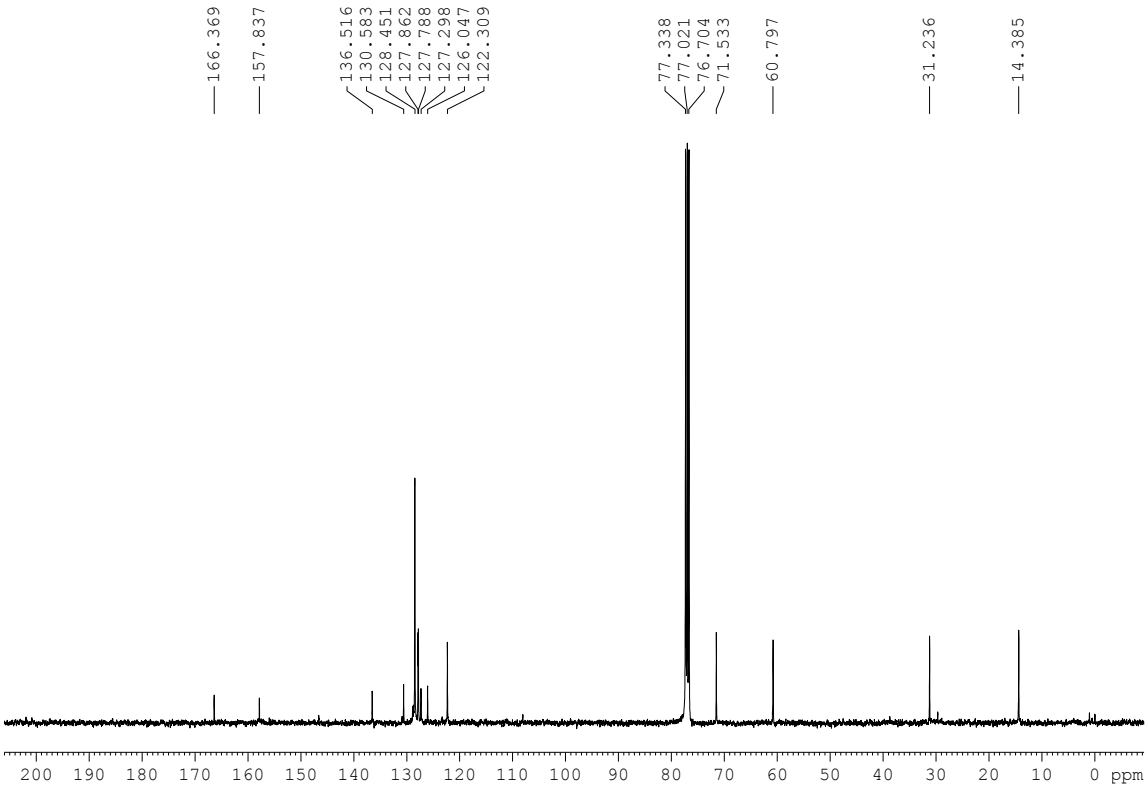


Figure A20. ^{13}C NMR spectrum of compound **95**

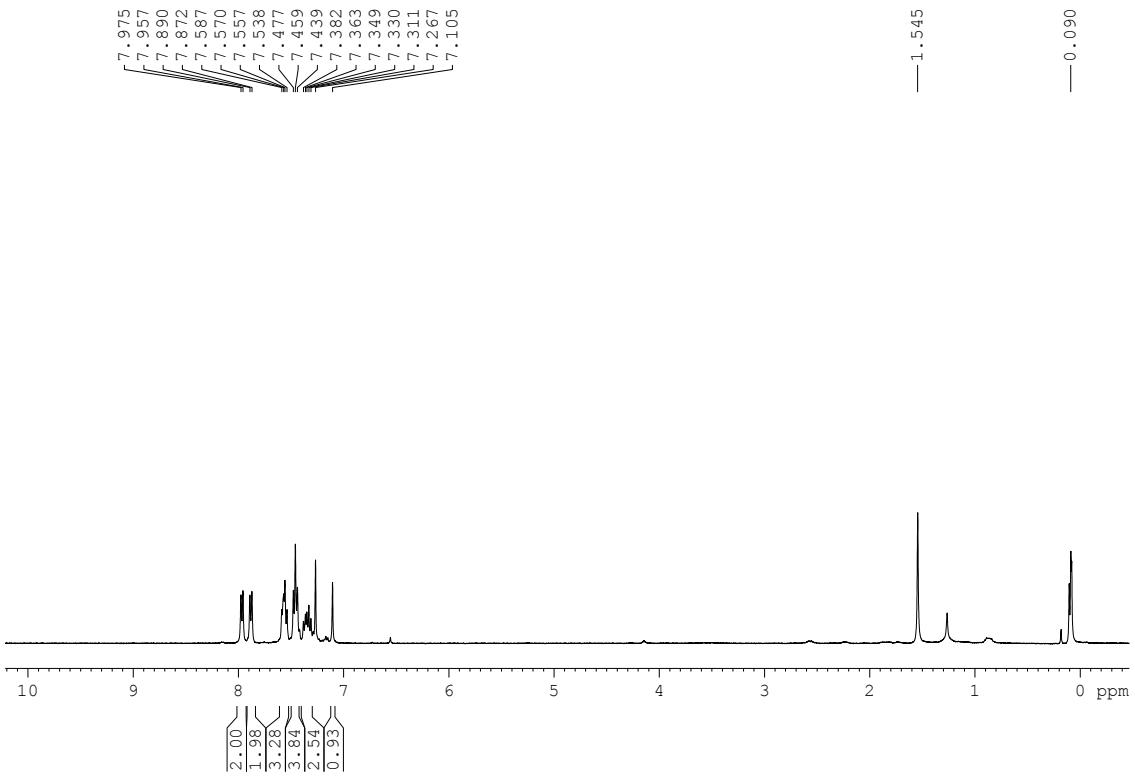


Figure A21. ^{1}H NMR spectrum of compound **98**

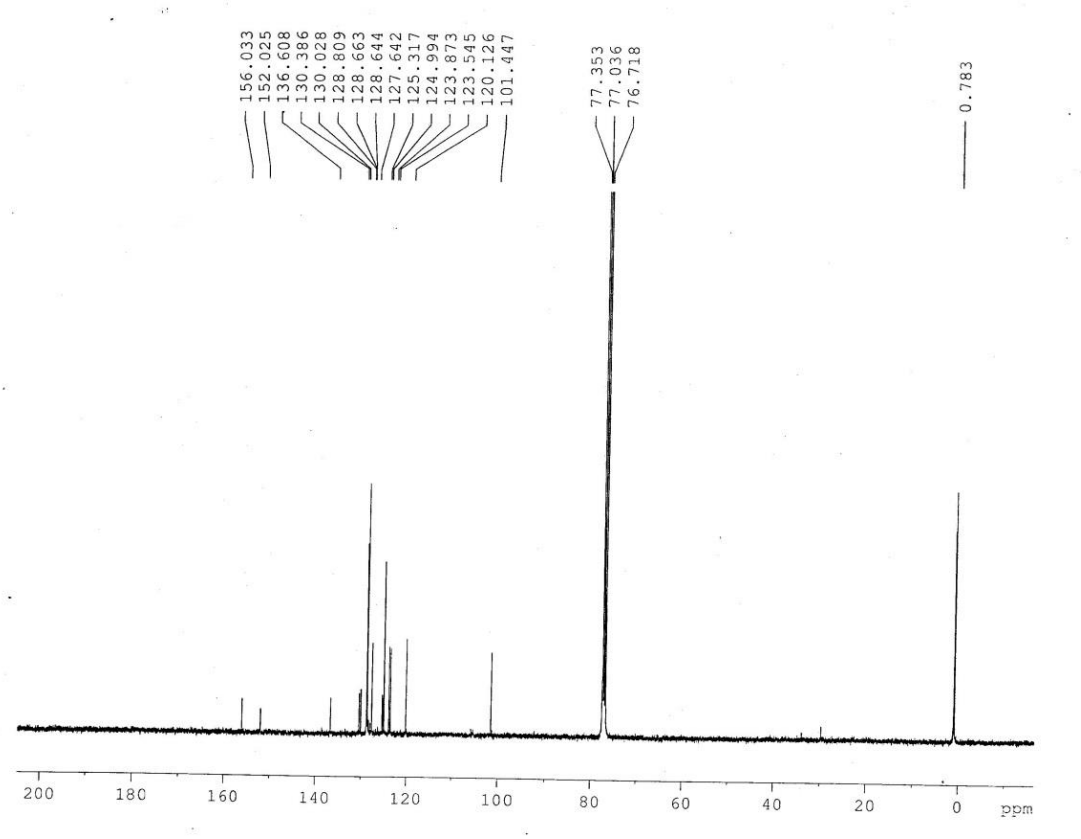


Figure A22. ^{13}C NMR spectrum of compound **98**

PART B: Compounds 5a, 7, 25, 25', 39, 44

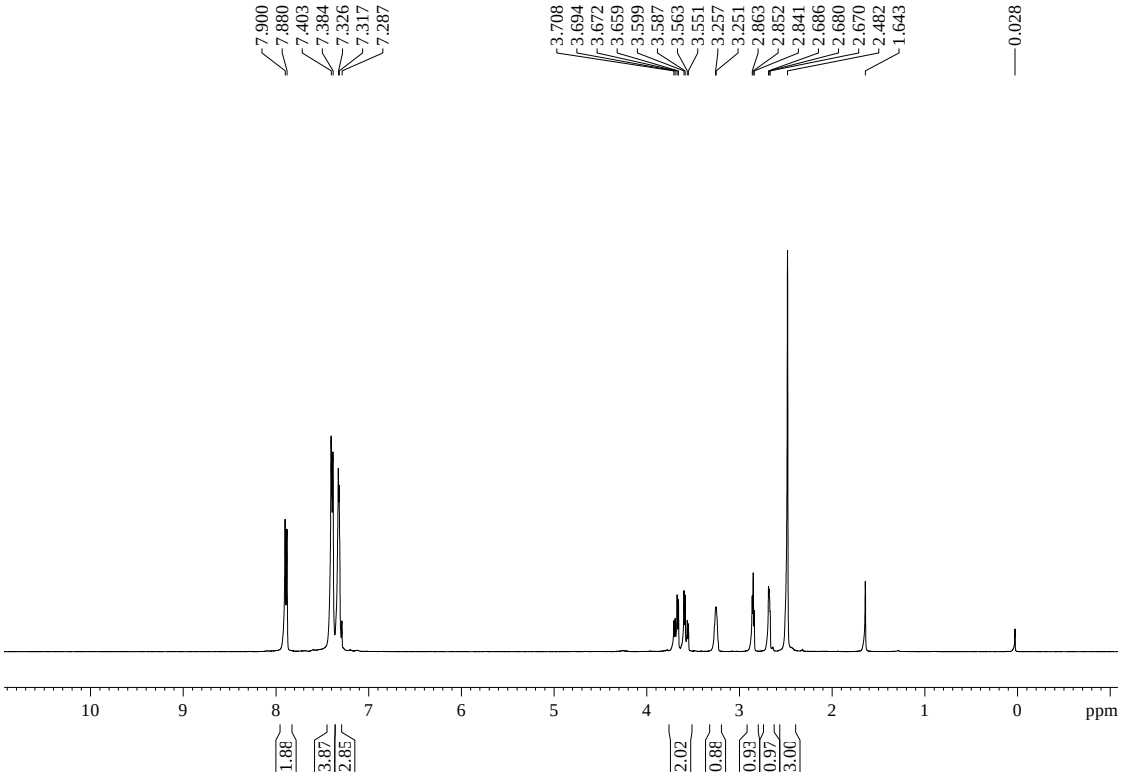


Figure A23. ^{1}H NMR spectrum of compound **5a**

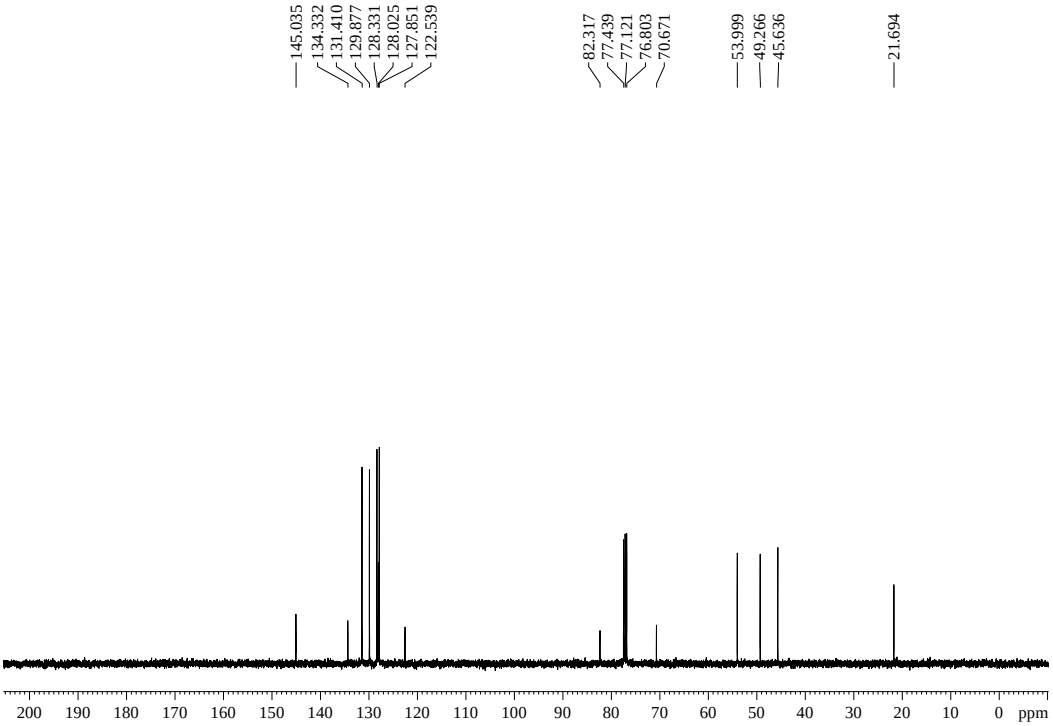


Figure A24. ^{13}C NMR spectrum of compound **5a**

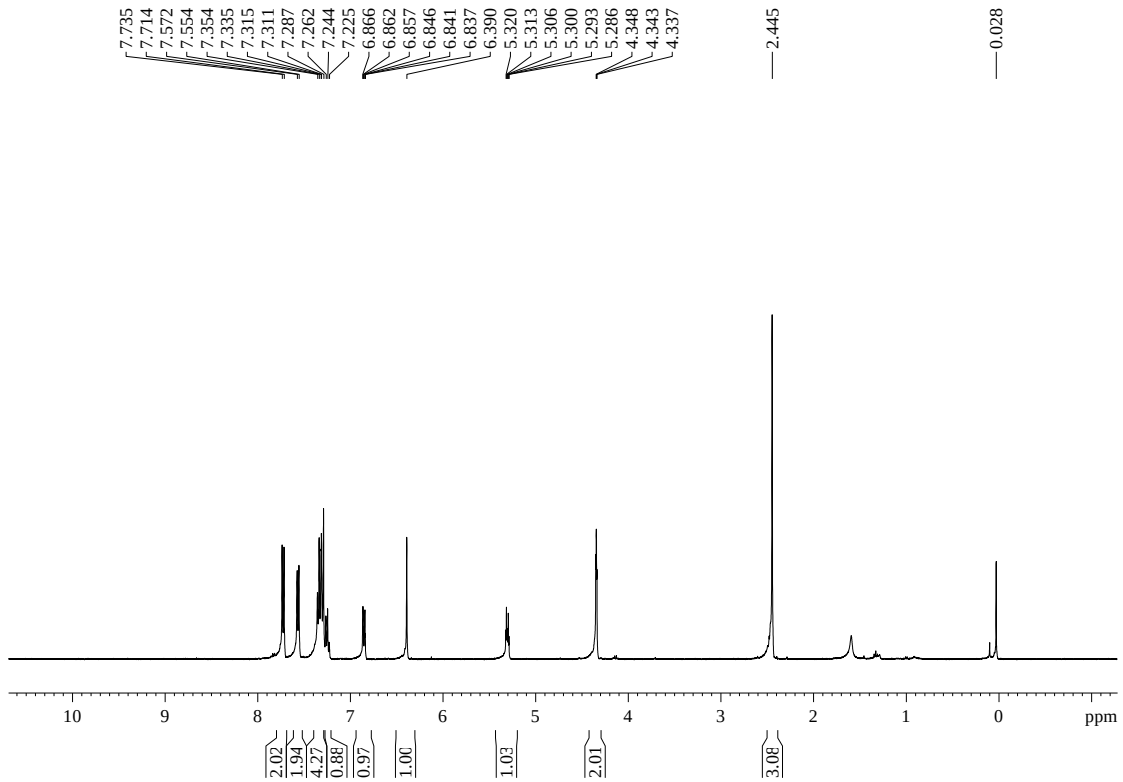


Figure A25. ^{1}H NMR spectrum of compound **7**

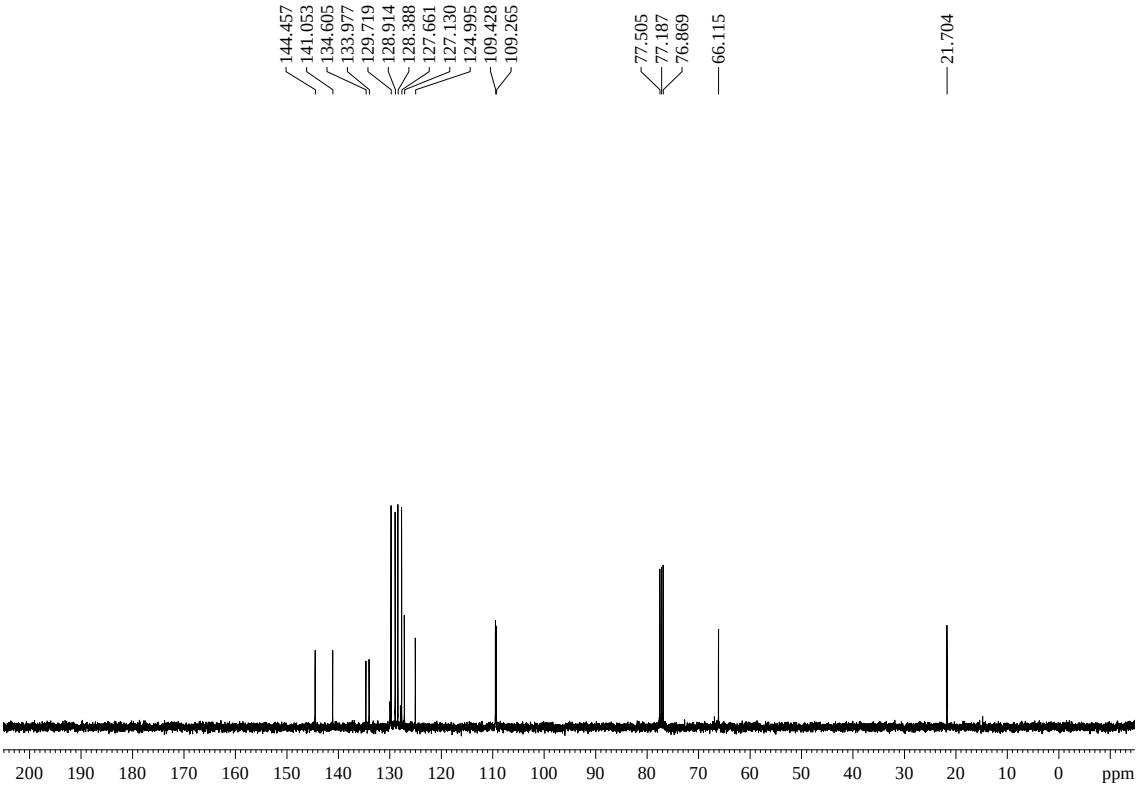


Figure A26. ^{13}C NMR spectrum of compound **7**

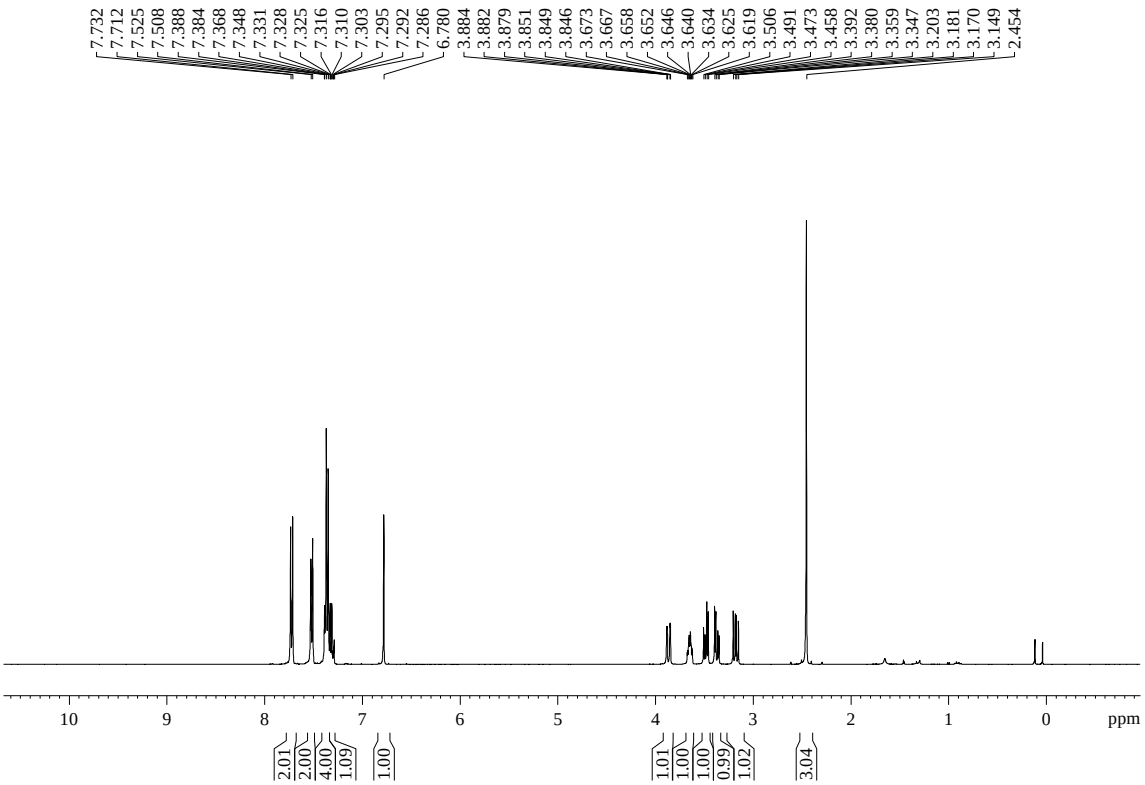


Figure A27. ^{1}H NMR spectrum of compound **25**

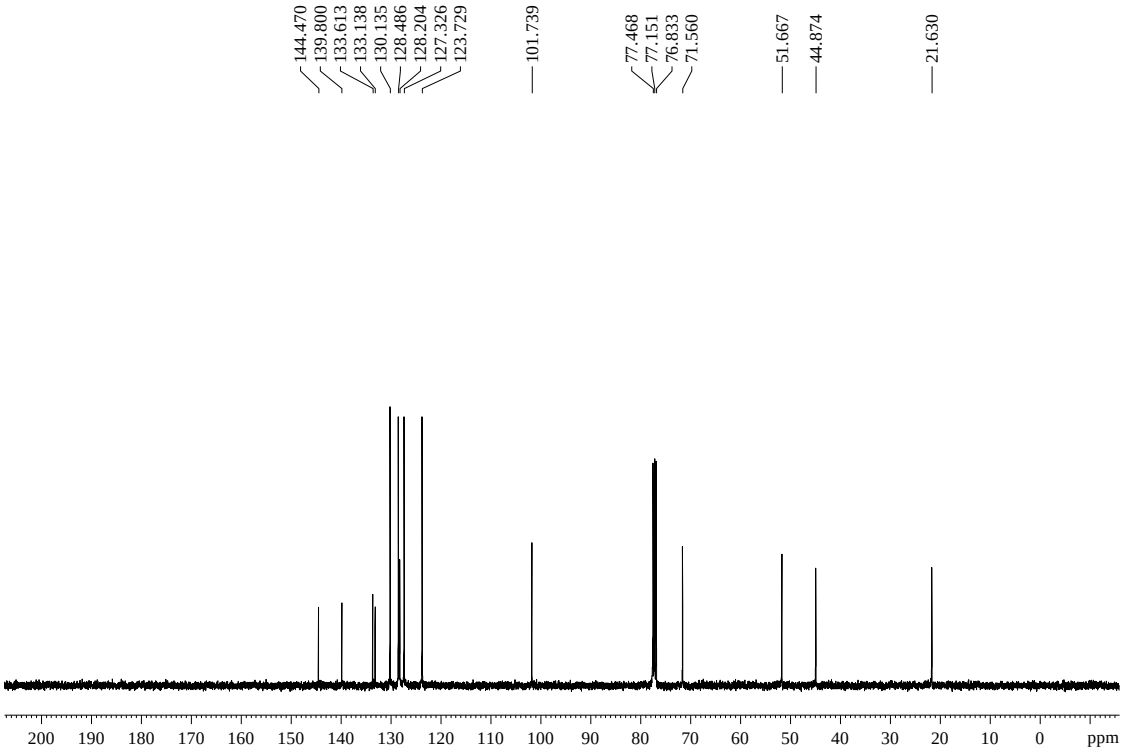


Figure A28. ^{13}C NMR spectrum of compound **25**

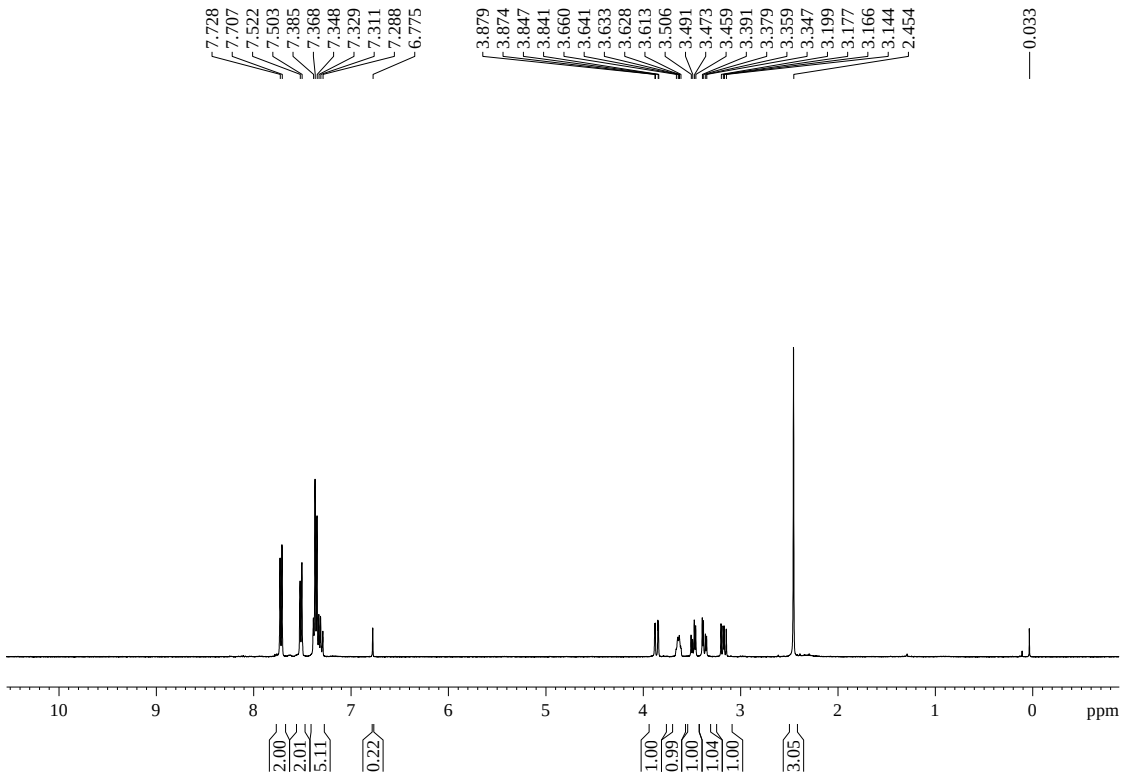


Figure A29. ^{1}H NMR spectrum of compound **25'**

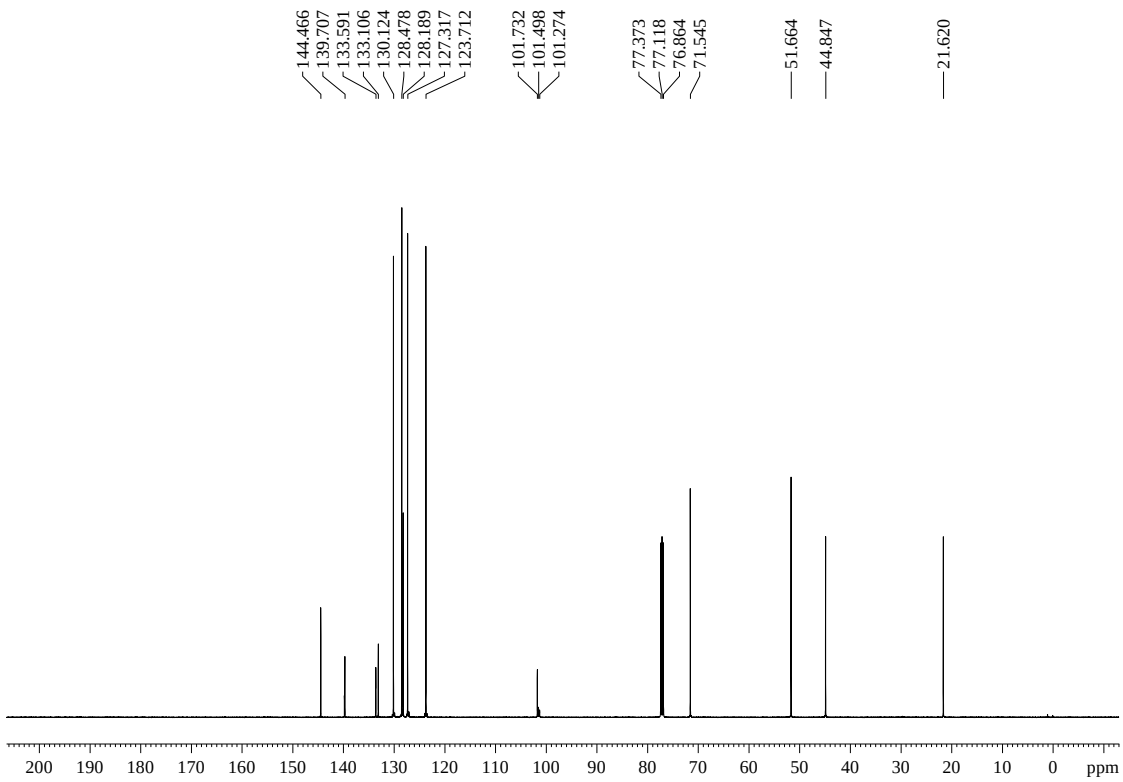


Figure A30. ^{13}C NMR spectrum of compound **25'**

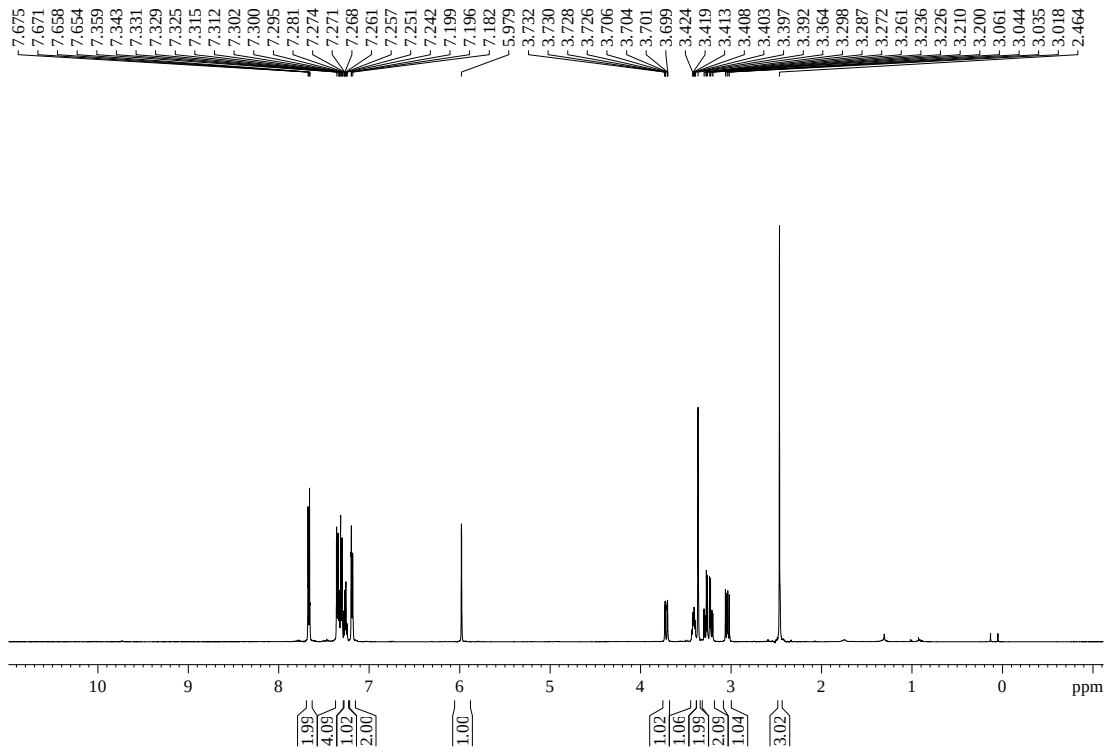


Figure A31. ^{1}H NMR spectrum of compound **39**

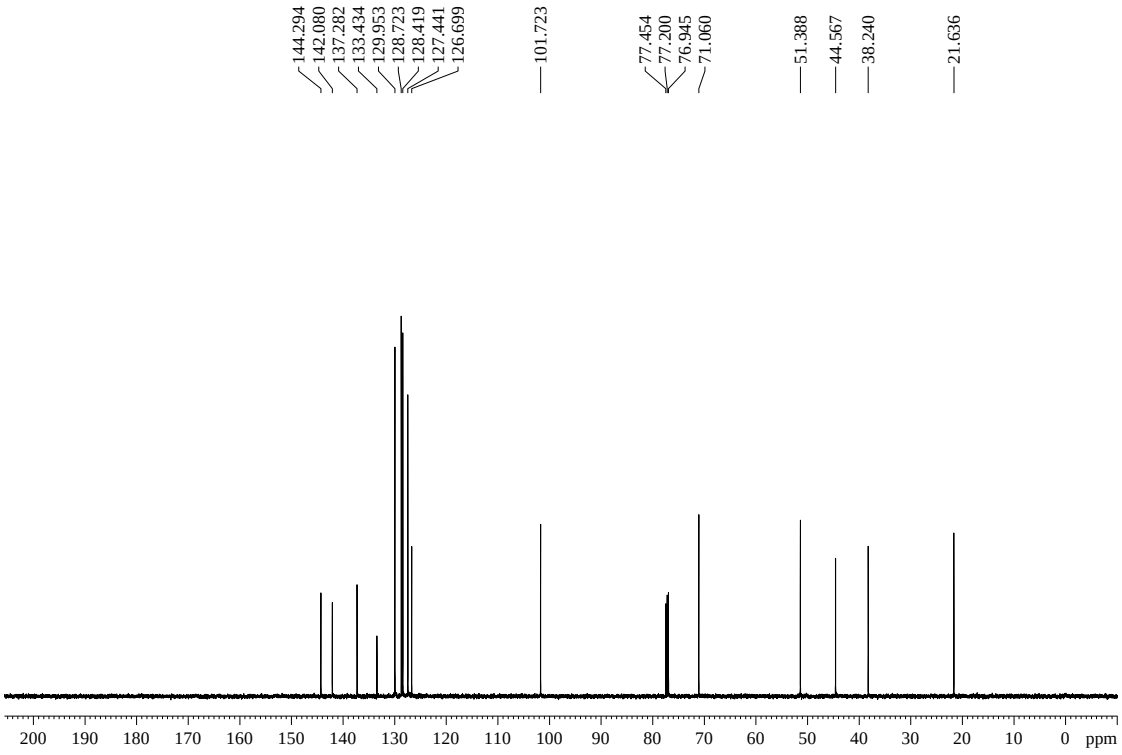


Figure A32. ^{13}C NMR spectrum of compound **39**

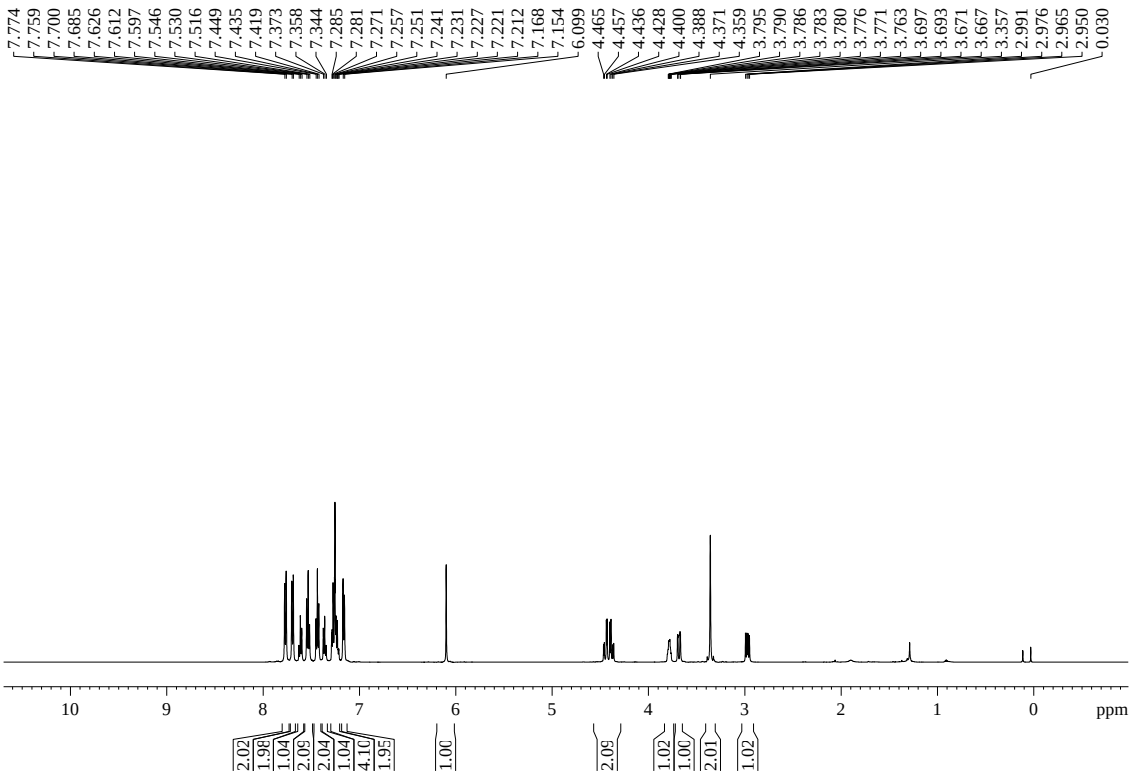


Figure A33. ^{1}H NMR spectrum of compound **44**

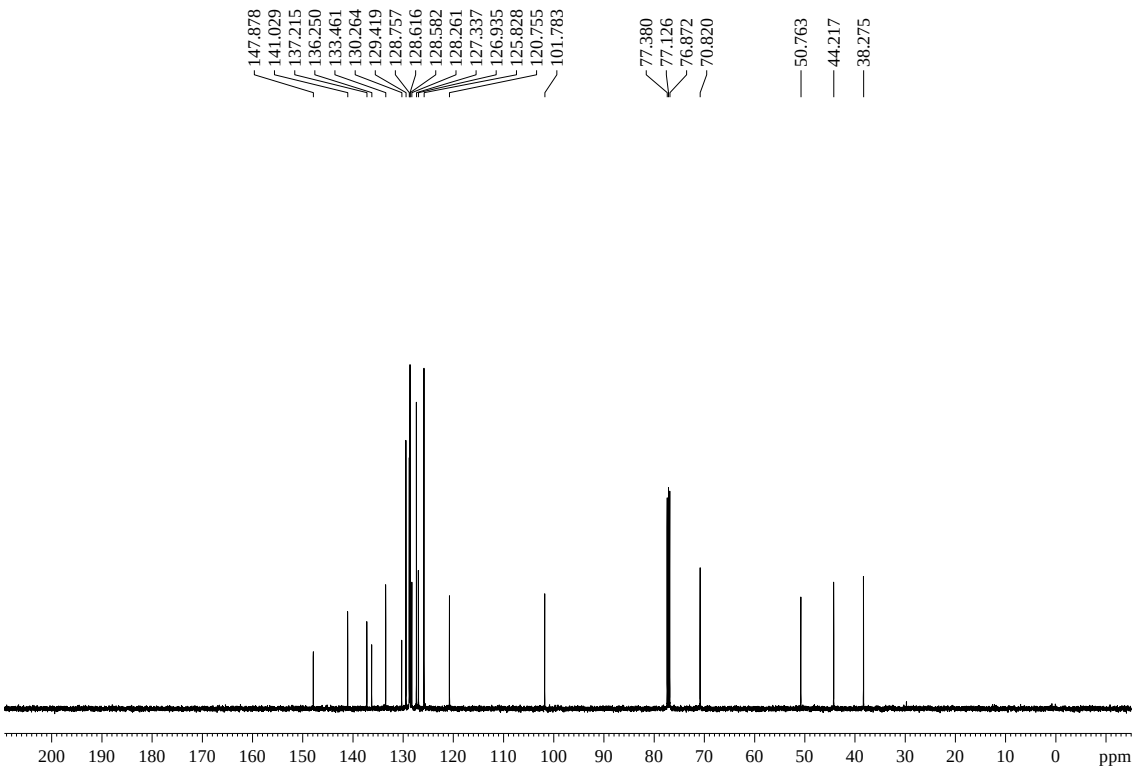


Figure A34. ^{13}C NMR spectrum of compound **44**

B) Publication numbers and atomic coordinates for X-ray structures reported in this thesis

I. Publication numbers for the published compounds

PART A: Compounds 9 and 44 Publication no. 4
Compounds 52, 62, 63', 81 and 86 Publication no. 3
(Contents, p. xiii)

II. Selected atomic coordinates for compound 100 from PART A and for compounds, 30, 31, and 44 from PART B.

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.

PART A

Compound 100

Atom	x	y	z	U(eq)
O(1)	1419(3)	3909(3)	1318(2)	19(1)
O(3)	-406(3)	9302(3)	2458(2)	22(1)
O(2)	-1300(3)	6091(3)	2829(2)	15(1)
C(11)	556(4)	7047(4)	3796(3)	12(1)
C(34)	-1316(4)	7091(4)	4122(3)	11(1)
C(9)	627(4)	8570(4)	3249(3)	11(1)
C(1)	370(5)	4040(4)	1070(3)	17(1)
C(58)	2682(4)	6456(4)	3655(3)	13(1)
C(5)	-693(4)	7054(4)	3465(3)	14(1)
C(29)	-2233(4)	4036(4)	2869(3)	16(1)
C(7)	-1153(5)	8432(4)	2586(3)	16(1)
C(2)	257(4)	4721(4)	1694(3)	11(1)
C(52)	2055(4)	8836(4)	4636(3)	15(1)
C(12)	596(4)	6126(4)	3222(3)	12(1)
C(10)	1405(4)	8135(4)	3782(3)	16(1)
C(6)	-526(4)	7975(4)	3070(3)	11(1)
C(16)	-294(5)	3438(4)	2273(4)	20(1)
C(66)	4641(5)	4640(5)	3633(4)	23(1)
C(3)	-648(4)	5213(4)	1781(3)	16(1)
C(40)	-2358(5)	8258(5)	2224(3)	21(1)
C(63)	3594(4)	6894(4)	3353(4)	17(1)
C(14)	1294(4)	5048(4)	2354(3)	14(1)
C(39)	-1534(4)	7979(4)	4433(3)	17(1)
C(35)	-1611(4)	6235(4)	4467(3)	17(1)
C(28)	-1071(4)	4456(4)	3633(3)	12(1)
C(15)	1974(4)	4530(4)	2107(3)	15(1)
C(41)	-3179(5)	7386(5)	2286(3)	21(1)
C(59)	2887(4)	6504(4)	4494(3)	15(1)
C(62)	4676(5)	7369(4)	3893(4)	21(1)
C(54)	2090(5)	9775(4)	5967(4)	22(1)
C(53)	1511(5)	9161(4)	5189(3)	16(1)
C(69)	3863(5)	4508(4)	1971(4)	23(1)
C(57)	3236(5)	9152(4)	4902(4)	19(1)
C(33)	-391(5)	3952(4)	3419(3)	19(1)
C(4)	-593(4)	5452(4)	2724(3)	13(1)
C(64)	3121(4)	4523(4)	2458(3)	14(1)
C(60)	3974(5)	6964(4)	5029(4)	20(1)
C(37)	-2305(4)	7185(5)	5428(4)	22(1)
C(30)	-2703(5)	3140(5)	3119(4)	23(1)
C(8)	693(4)	9381(4)	2867(3)	18(1)
C(46)	1584(5)	10231(4)	2755(4)	20(1)
C(13)	1502(4)	5884(4)	3089(3)	13(1)

C(38)	-2017(5)	8036(5)	5086(4)	22(1)
C(21)	-1061(4)	3778(5)	-276(3)	19(1)
C(42)	-4314(5)	7251(5)	1982(4)	27(2)
C(51)	2723(5)	10347(5)	3117(4)	27(2)
C(45)	-2715(5)	8974(5)	1833(4)	28(2)
C(22)	-1842(5)	4675(5)	1231(4)	23(2)
C(23)	-2374(5)	3592(5)	1065(4)	32(2)
C(65)	3531(5)	4557(4)	3290(4)	18(1)
C(61)	4874(4)	7405(4)	4730(4)	22(1)
C(32)	-870(5)	3053(5)	3673(4)	28(2)
C(36)	-2113(4)	6272(5)	5102(4)	20(1)
C(20)	-1686(5)	3194(5)	-1070(4)	28(2)
C(43)	-4669(5)	7957(5)	1595(4)	33(2)
C(56)	3839(5)	9789(5)	5694(4)	27(2)
C(67)	5372(5)	4666(5)	3154(4)	26(2)
C(47)	1349(5)	10935(5)	2297(4)	31(2)
C(50)	3585(6)	11145(5)	2998(4)	33(2)
C(27)	-2464(5)	5284(6)	924(4)	39(2)
C(68)	4974(5)	4587(5)	2321(4)	28(2)
C(31)	-2028(5)	2653(5)	3525(4)	26(2)
C(55)	3266(5)	10102(4)	6220(4)	27(2)
C(49)	3324(6)	11826(5)	2537(4)	35(2)
C(19)	-1524(6)	2281(6)	-1379(4)	45(2)
C(48)	2203(6)	11718(5)	2186(4)	39(2)
C(17)	-129(6)	2512(5)	-97(4)	43(2)
C(44)	-3853(5)	8827(5)	1520(4)	36(2)
C(18)	-737(7)	1952(6)	-896(5)	61(2)
C(24)	-3506(6)	3146(7)	583(4)	54(2)
C(25)	-4117(6)	3769(9)	287(5)	67(3)
C(26)	-3590(6)	4836(8)	458(5)	61(3)

PART B

Compound 30

Atom	x	y	z	U(eq)
S(1)	3555(1)	5077(0)	2561(1)	45(0)
O(1)	1704(4)	5145(1)	1955(2)	67(1)
O(3)	6801(4)	3639(1)	2249(1)	56(1)
C(12)	5425(5)	5601(1)	2615(2)	42(1)
C(3)	4901(5)	3784(1)	1744(2)	43(1)
C(4)	4102(6)	4250(1)	1739(2)	47(1)
C(17)	6279(6)	5820(1)	3356(2)	50(1)
N(1)	5160(5)	4631(1)	2231(2)	58(1)
C(13)	6013(5)	5797(1)	1877(2)	48(1)
C(6)	3988(6)	3378(1)	1203(2)	47(1)
C(15)	8224(6)	6450(1)	2637(3)	59(1)
O(2)	2975(6)	4944(1)	3332(2)	85(1)
C(16)	7653(6)	6242(1)	3332(2)	58(1)
C(7)	1794(7)	3389(1)	811(2)	59(1)
C(18)	5254(6)	5591(2)	1043(2)	63(1)
C(5)	9930(7)	3818(1)	3203(3)	71(1)
C(14)	7400(6)	6224(1)	1921(3)	62(1)
C(11)	5369(7)	2975(1)	1058(2)	65(1)
C(21)	9732(8)	6917(2)	2641(4)	91(1)
N(2)	9240(8)	3556(2)	3883(3)	101(1)
C(24)	5865(9)	5639(2)	4189(2)	79(1)
C(9)	2424(9)	2618(2)	144(3)	82(1)
C(19)	7285(8)	5460(2)	595(3)	91(1)
C(10)	4575(9)	2598(2)	533(3)	83(1)
C(20)	3653(8)	5960(2)	564(3)	94(2)
C(8)	1029(8)	3011(2)	278(2)	74(1)
C(23)	8438(8)	7369(2)	2435(4)	97(2)
C(1)	7028(9)	4458(2)	2807(4)	130(3)
C(2)	8011(10)	4036(2)	2653(4)	114(2)
C(25)	8087(14)	5495(3)	4672(3)	153(3)
C(26)	4642(14)	6021(3)	4537(4)	170(4)
N(4)	6671(14)	2917(3)	3827(3)	170(3)
C(22)	11891(9)	6840(2)	2458(6)	176(4)

Compound 31

Atom	x	y	z	U(eq)
C(12)	7737(4)	80(3)	1973(2)	53(1)
C(17)	8632(5)	-385(4)	2322(2)	65(1)
C(16)	8525(7)	-1256(4)	2326(2)	79(2)
C(15)	7541(7)	-1659(4)	1991(2)	88(2)
C(14)	6663(7)	-1204(5)	1641(2)	89(2)
C(13)	6765(5)	-337(4)	1628(2)	71(1)
C(4)	8456(5)	1402(3)	932(2)	57(1)
C(3)	9375(5)	1354(3)	515(2)	53(1)
C(2)	11531(6)	1301(5)	1076(2)	107(2)
C(1)	10637(6)	1288(5)	1531(2)	104(2)
C(5)	13158(6)	1160(5)	1088(2)	98(2)
C(6)	8878(5)	1399(3)	-49(2)	54(1)
C(7)	9803(6)	1101(3)	-454(2)	70(1)
C(8)	9330(7)	1127(4)	-980(2)	83(2)
C(9)	7949(8)	1445(4)	-1109(2)	86(2)
C(10)	7039(7)	1784(5)	-721(2)	104(2)
C(11)	7496(6)	1759(4)	-186(2)	84(2)
N(1)	9021(4)	1430(3)	1467(1)	62(1)
N(2)	14123(7)	1113(8)	695(3)	241(6)
N(3)	13869(6)	918(6)	245(3)	146(3)
N(4)	13781(8)	729(6)	-186(3)	175(4)
O(1)	8618(4)	1452(2)	2442(1)	83(1)
O(2)	6414(4)	1515(3)	1818(1)	88(1)
O(3)	10929(3)	1283(2)	570(1)	74(1)
S(1)	7875(1)	1182(1)	1961(1)	64(1)

Compound 44

Atom	x	y	z	U(eq)
S(1)	10625(1)	7169(0)	4787(1)	63(0)
O(3)	8962(2)	5801(1)	2419(2)	62(1)
O(2)	9567(2)	7601(1)	4416(2)	87(1)
N(2)	6924(3)	5275(1)	3964(2)	59(1)
C(8)	3415(3)	4495(1)	2853(2)	50(1)
C(7)	4962(3)	4743(1)	3337(2)	52(1)
N(3)	7399(3)	4789(1)	4320(2)	80(1)
C(9)	2088(3)	4801(1)	2393(2)	62(1)
N(1)	9927(2)	6664(1)	3963(2)	61(1)
N(4)	6205(3)	4459(1)	3942(2)	77(1)
C(2)	8714(3)	6322(1)	2065(2)	57(1)
C(13)	3202(3)	3950(1)	2895(2)	61(1)
C(21)	12539(3)	7322(1)	4417(2)	51(1)
C(15)	6008(3)	6240(1)	788(2)	55(1)
C(3)	9449(3)	5724(1)	3680(2)	58(1)
O(1)	10836(3)	6988(1)	5988(2)	92(1)
C(1)	9182(3)	6735(1)	2761(2)	59(1)
C(5)	8001(3)	5728(1)	4306(2)	64(1)
C(20)	5054(3)	6552(1)	1401(2)	66(1)
C(10)	622(3)	4568(1)	2004(3)	75(1)
C(22)	12694(3)	7730(1)	3643(3)	66(1)
C(16)	5279(4)	5823(1)	128(3)	72(1)
C(6)	5442(3)	5263(1)	3356(2)	58(1)
C(14)	7783(3)	6362(1)	827(2)	69(1)
C(12)	1727(4)	3722(1)	2507(3)	71(1)
C(19)	3438(4)	6456(1)	1360(3)	80(1)
C(11)	430(4)	4030(1)	2071(3)	74(1)
C(4)	10666(3)	6138(1)	4191(3)	67(1)
C(26)	13881(3)	7035(1)	4912(3)	69(1)
C(24)	15529(4)	7580(2)	3870(3)	85(1)
C(17)	3647(4)	5724(1)	88(3)	89(1)
C(23)	14196(4)	7859(1)	3379(3)	86(1)
C(18)	2720(4)	6044(2)	705(3)	86(1)
C(25)	15366(3)	7169(1)	4625(3)	80(1)