STUDIES TOWARDS UNDERSTANDING THE SCOPE OF $TiCl_4$-MEDIATED BAYLIS-HILLMAN REACTION AND SYNTHESIS OF PYRAZOLE FRAMEWORKS USING BAYLIS-HILLMAN BROMIDES

A THESIS SUBMITTED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

BY

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INDIA

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Dedication
To My Family

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 **Professor D. BASAVAIAH**.

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

MARCH, 2010 **SUPARNA ROY**

CERTIFICATE

Certified that the work embodied in this thesis entitled "**Studies towards understanding the scope of $TiCl_4$-mediated Baylis-Hillman reaction and synthesis of pyrazole frameworks using Baylis-Hillman bromides**" has been carried out by **Ms. Suparna Roy**, under my supervision and the same has not been submitted elsewhere for a degree.

Professor D. BASAVAIAH
(THESIS SUPERVISOR)

DEAN

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Suparna Roy

ABBREVIATIONS

Ac	acetyl
AcOH	acetic acid
AIBN	azobisisobutyronitrile
aq.	aqueous
Ar	aryl
BINOL	1,1′-bi-2-naphthol
Boc	*tert*-butoxycarbonyl
Bp	boiling point
t-Bu or Bu^t	*tertiar*y butyl
cat.	catalyst
Cbz	benzyloxycarbonyl
*m*CPBA	*meta*-chloroperbenzoic acid
Cy	cymene
DABCO	1,4-diazabicyclo(2.2.2)octane
DBAD	di-*tert*-butyl azodicarboxylate
DBU	1,8-diazabicyclo(5.4.0)undec-7-ene
DCE	1,2-dichloroethane
DEAD	diethyl azodicarboxylate
dec.	decompose
DEPO	diethylphosphine oxide
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminum hydride
DMAP	4-(dimethylamino)pyridine
DME	ethylene glycol dimethyl ether
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane

DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
dppp	bis(diphenylphosphanyl)propane
dr	diastereomeric ratio
de	diastereomeric excess
DYKAT	dynamic kinetic asymmetric transformation
Eq.	equation
equiv	equivalent(s)
Et	ethyl
EWG	electron withdrawing group
Hex	hexyl
HMT	hexamethylenetetramine
3-HQD	3-hydroxyquinuclidine
IBX	2-iodoxybenzoic acid
β-ICPD	*β*-isocupreidine
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
Me	methyl
Mp	melting point
MsCl	mesyl chloride
MVK	methyl vinyl ketone
NBS	*N*-bromosuccinimide
NHC	*N*-heterocyclic carbene
NMM	*N*-methylmorpholine
NMO	*N*-methylmorpholine oxide
PAP	polymer bound 4-(*N*-benzyl-*N*-methylamino)pyridine
Ph	phenyl

PMP	*para*-methoxyphenyl
i-pr/pr^{i}	isopropyl
PTA	1,3,5-triaza-7-phosphaadamantane
rt	room temperature
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBS	*tert*-butyldimethylsilyl
TEA	triethylamine
TES-Cl	chlorotriethylsilane
TFA	trifluroacetic acid
TFAA	trifluoroacetic anhydride
TfOH	trifluoromethanesulfonic acid
Tf_2O	trifluoromethanesulfonic anhydride
THF	tetrahydrofuran
TMEDA	tetramethylethylenediamine
TMG	1,1,3,3-tetramethylguanidine
TMPDA	1,1,3,3-tetramethylpropane-1,3-diamine
TMS	tetramethylsilane
TMSI	trimethylsilyl iodide
Ts	tosyl
TsOH	*para*-toluenesulfonic acid
Troc	2,2,2-trichloroethoxy carbonyl
TTMPP	tris(2,4,6-trimethoxyphenyl)phosphine
UV	ultraviolet

ABSTRACT

In recent years Baylis-Hillman reaction has attracted considerable attention of organic chemists due to its enormous synthetic utility. The Baylis-Hillman reaction is a three component atom economy carbon-carbon bond forming reaction involving the coupling of α-position of an activated alkene with an electrophile under the influence of a catalyst or catalytic system which generates interesting classes of densely functionalized molecules. Our research group has been working on different aspects of this fascinating reaction for the last several years with a view to develop Baylis-Hillman reaction as a useful synthetic tool in organic chemistry. The Baylis-Hillman adducts have been successfully used as valuable source for various organic transformations and also for one-pot multistep synthesis of various compounds of medicinal relevance.

This thesis deals with the studies towards understanding the scope of $TiCl_4$-mediated Baylis-Hillman reaction and also towards application of the Baylis-Hillman adducts for synthesis of pyrazole framework and consists of three chapters 1) Introduction 2) Objectives, Results & Discussion and 3) Experimental. The first chapter, that is, Introduction presents a brief literature survey on the recent and relevant developments in the Baylis–Hillman reaction and also on applications of the Baylis–Hillman adducts in synthetic organic chemistry.

The second chapter deals with understanding the scope of $TiCl_4$-mediated Baylis-Hillman reaction and also development of novel strategies / methodologies for synthesis of

heterocyclic and spiro compounds from the Baylis-Hillman adducts with following main objectives.

1. To study $TiCl_4$-mediated Baylis-Hillman reaction between *N*-substituted isatins and cycloalk-2-enones with an objective of developing a simple and convenient one-pot methodology for synthesizing 3-(2-hydroxyphenyl)indolin-2-ones.

2. To study $TiCl_4$-mediated Baylis-Hillman reaction between aryl 1,2-diones and cycloalk-2-enones and subsequently to transform the resulting Baylis-Hillman adducts into polycyclic fused furan ring systems.

3. To develop a novel and facile methodology for the synthesis of functionalized dihydropyrazole derivatives using the Baylis-Hillman bromides as 1,3-dipoles for cycloaddition with dialkyl azodicarboxylates, as dipolarophiles *via* [3 + 2] annulation strategy.

4. To develop a simple methodology for the synthesis of spiro-oxindole derivatives containing spiro-fused 1,2-bisalkoxycarbonyl-1*H*-pyrazole framework using the allyl bromides of Baylis-Hillman alcohols, derived from isatin derivatives and alkyl acrylates, as 1,3-dipoles for [3 + 2] annulation reaction with dialkyl azodicarboxylates, as dipolarophiles.

A simple and convenient one-pot synthesis of 3-(2-hydroxyphenyl)indolin-2-ones using Baylis-Hillman protocol

3-Aryloxindole skeleton represents an interesting class of nitrogen heterocyclic system because such kind of framework possesses various biological activities like BK channel openers and orally active growth hormone secretagogues (Figure 9). Because of these biological activities of 3-aryloxindole derivatives, development of simple and convenient methodologies for synthesis of these compounds with different substitution profiles has become an attractive and challenging area in synthetic chemistry.

We have investigated for the first time, the $TiCl_4$-mediated Baylis-Hillman reaction of *N*-substituted isatins with cycloalk-2-enones and also developed a facile one-pot synthesis of 3-(2-hydroxyphenyl)indolin-2-one derivatives (**120-130**) from *N*-substituted isatins using the Baylis-Hillman reaction as key step (Schemes 46, 47 and Table 1).

Development of a facile methodology for synthesis of polycyclic fused furans using the Baylis-Hillman adducts

Polycyclic fused furan framework is an integral part of several natural products, such as popolohuanone E, galanthamine, bisabosqual A (Figure 10) *etc* and also some of these frameworks are known to exhibit interesting biological activities such as inhibition of receptor tyrosine kinase, cytotoxicity and anti-cancer activity (Figure 10). Therefore development of facile strategies for synthesis of poly-fused furans represents an interesting endeavor in synthetic organic chemistry.

We have examined $TiCl_4$-mediated Baylis-Hillman reaction of cyclic aromatic 1,2-diones with cycloalk-2-enones (Eq. 38, Schemes 56-59 and Table 2). The resulting adducts (**144d-i**) have been successfully transformed into very important class of aromatic pentacyclic/hexacyclic fused furan ring systems (**149a-f**) (Eqs. 41, 42 and Table 3). The Baylis-Hillman adducts (**144a** and **144b**) have also been transformed into interesting spiro-fused compounds (**150a** and **150b**) (Eq. 43).

Dimethyl sulfide induced [3 + 2] annulation strategy: An efficient synthesis of functionalized dihydropyrazole derivatives using the Baylis-Hillman bromides *via* [3+2] cycloaddition reaction

Pyrazole framework belongs to an important class of heterocyclic compounds possessing different pharmacological activities such as antiviral, anticancer, anti-inflammatory/antimicrobial, COX-2 inhibitor and anti-bacterial/fungal activities (Figure 11). Pyrazole derivatives were also evaluated for cholesterol-lowering activity (Figure 11). The remarkable pharmacological and medicinal importance of pyrazole derivatives has created a need for the development of simple and efficient methodologies for synthesis of these compounds with different substitution profiles.

We have successfully used the allyl bromides, derived from Baylis-Hillman alcohols (obtained from alkyl acrylates and aldehydes), as practical source for 1,3 dipoles, to provide an interesting class of 1,2-bis(alkoxycarbonyl)-4-alkoxycarbonyl-3-aryl-2,3-dihydro-1*H*-pyrazoles (**165a-r**) *via* [3 + 2] annulation reaction with dialkyl

azodicarboxylates as dipolarophiles, in an operationally simple one-pot procedure (Eqs. 52, 53 and Table 4).

A novel synthesis of spiro-oxindole derivatives containing spiro-fused 1,2-bisalkoxy-1*H*-pyrazole framework using isatin-derived Baylis-Hillman bromides through [3+2] annulation strategy

Spiro-oxindole moiety is present in a number of naturally occurring compounds such as tasmanine, aristoteline, javaniside, spirotryprostatins A & B, horsfiline, coerulescine, welwitindolinone A isonitrile and brevianamide A (Figure 12) *etc*. Therefore development of simple and expedient synthesis of such compounds containing spiro-oxindole framework is an interesting area in organic chemistry.

We have successfully employed allyl bromides, derived from the Baylis-Hillman adducts of isatin derivatives, as useful source for 1,3 dipoles, to provide an interesting class of dihydropyrazolo spiro-oxindole derivatives, (1-alkylindolin-2-one/indolin-2-one)-3-spiro-3′-[4′-alkoxycarbonyl-1′,2′-bis(alkoxycarbonyl)-2′,3′-dihydro-1′*H*-pyrazole] (**189a-j)** *via* [3 + 2] annulation reaction with dialkyl azodicarboxylates as dipolarophiles, in a facile one-pot methodology (Eqs. 59, 60 and Table 5).

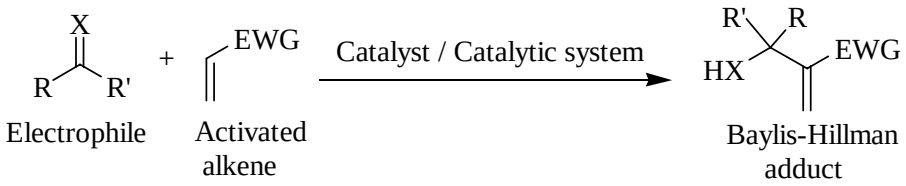
The third chapter provides detailed experimental procedures, physical constants like boiling points, melting points, IR, ^{1}H & ^{13}C NMR, mass (LC-MS) spectral data and elemental analyses.

CONTENTS

INTRODUCTION

Construction of carbon-carbon bonds is one of the most fundamental reactions in organic chemistry.[1,2] Several carbon-carbon bond forming reactions have been developed and their applications have been well documented in the literature during the last several decades.[1-10] Grignard reaction,[3] Diels-Alder reaction,[4,5] Wittig reaction,[6] aldol reaction,[7,8] Heck reaction,[9] Friedel-Crafts reaction[10] *etc*. are some such important reactions which are highly popular and well-known carbon-carbon bond forming reactions.

The Baylis-Hillman reaction[11-18] is yet another important carbon-carbon bond forming reaction which has become highly popular and powerful synthetic tool in recent years. This is an essentially three component reaction involving the coupling of α-position of activated alkene with an electrophile in the presence of a catalyst or catalytic system, providing an interesting class of highly synthetically useful multifunctional molecule in one-pot atom economical process (Eq. 1).[13-18] The Baylis-Hillman reaction is originated from a German patent[11] filed in the year 1972 by A. B. Baylis & M. E. D. Hillman (and another US patent[12] is filed in the year 1973 by M. E. D. Hillman & A. B. Baylis).



Electrophile Activated alkene Baylis-Hillman adduct

Eq. 1

R = alkyl, aryl, hetero-aryl, *etc.*
R' = H, COOR, alkyl, *etc.*
X = O, *N*-Ts, *N*-CO_2R, *N*-$PO(R)_2$, *etc.*

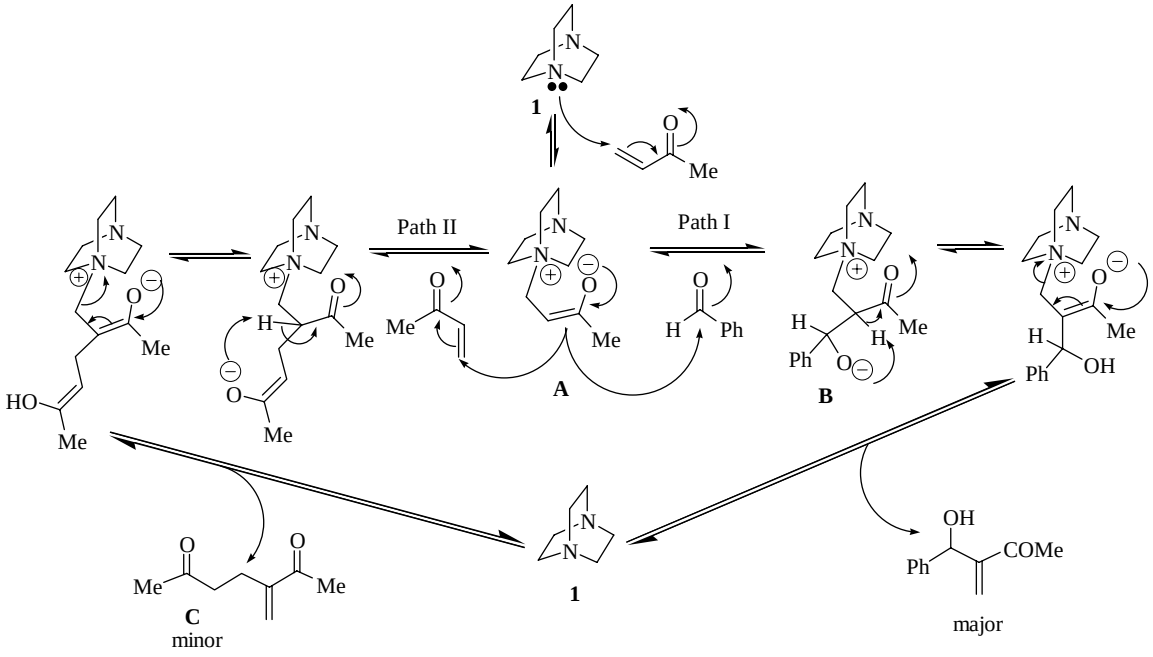
EWG= COOR, COR, CHO, CN, $PO(OEt)_2$, SO_2Ph, SO_3Ph, SOPh, *etc.*

Catalyst / Catalytic system = *tert*-amines, phosphines, Lewis acids, *etc.*

MECHANISM OF THE BAYLIS-HILLMAN REACTION

Understanding the mechanism[19-26] of the Baylis-Hillman reaction is believed to be one of the most challenging endeavors in mechanistic organic chemistry. Although there is no clear-cut evidence so far, the most widely accepted mechanism has been presented in Scheme 1 by taking the reaction between benzaldehyde (as an electrophile) and methyl vinyl ketone (as an activated olefin) in presence of DABCO (**1**) (as a catalyst), as a model case. This reaction is believed to proceed through a Michael initiated addition-elimination sequence. The first step is the Michael type nucleophilic addition of the tertiary amine to the activated alkene (methyl vinyl ketone) to produce a zwitterionic enolate **A**, which then reacts with aldehyde (benzaldehyde) in aldol fashion to generate zwitterion **B**. Subsequent proton migration followed by the release of catalyst leads to the formation of desired highly functionalized molecules (usually known as Baylis-Hillman adducts, Scheme 1, Path I). In the case of highly reactive activated alkenes (such as alkyl vinyl ketones), Michael type dimers (**C**) are formed as side products because activated alkenes themselves act as electrophiles (Scheme 1; Path II).

Scheme 1



THREE ESSENTIAL COMPONENTS—DEVELOPMENTS

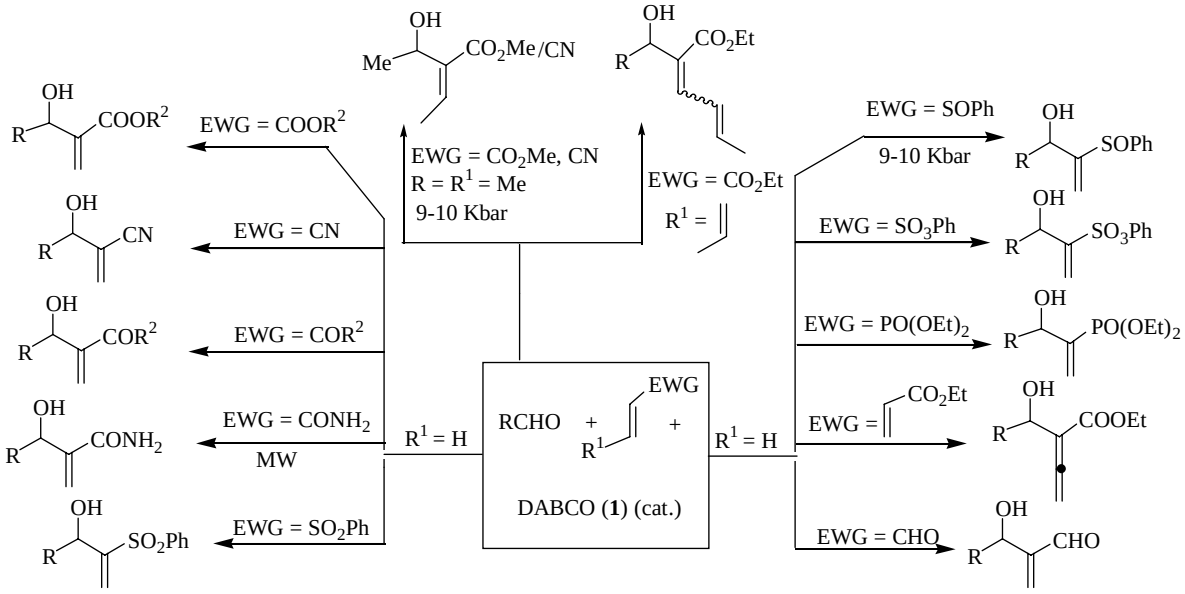
During last two decades the Baylis–Hillman reaction has witnessed tremendous growth in terms of all the three essential components, *i.e.* activated alkenes (*acyclic / cyclic*), electrophiles (*carbon / non-carbon*), and catalyst (or catalytic system) / reagents (*tert-amine / non-amine*) as evidenced by publication of six major reviews,[13-18] several mini reviews[27-33] and a large number of research papers. Applications of the Baylis-Hillman adducts in various synthetic transformation methodologies have also been well-studied.[13-18] Since there is vast literature available on different aspects of this reaction, it will not be possible to present all the developments in this section. However, some of the recent,

relevant and important developments on various aspects of this reaction are presented in this section.

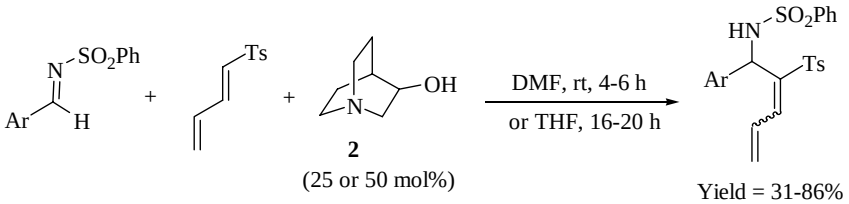
ACTIVATED ALKENES (ACYCLIC)

Variety of acyclic activated alkenes,[16] such as, alkyl/aryl acrylates,[34-37] alkyl vinyl ketones,[38-40] acrylonitrile,[39,41] acrylamides,[42] allenic esters,[43] ethyl sorbate,[44] vinyl sulphones,[45] vinyl sulphonates,[46] vinyl phosphonates[47] and acrolien[48-50] have been successfully employed in the Baylis-Hillman coupling with a number of electrophiles to provide the desired densely functionalized molecules (Scheme 2). However the β-substituted activated olefins, such as, crotononitrile[51,52] & methyl crotonate[51] and less reactive alkenes like phenyl vinyl sulfoxide[53] need high pressure to participate in Baylis-Hillman reaction (Scheme 2).

Scheme 2



Back and coworkers[54,55] reported an interesting Baylis-Hillman reaction between dienyl sulfones and aldimine derivatives in the presence of 3-hydroxyquinuclidine (3-HQD, **2**) to provide the corresponding *β*-vinyl-Baylis-Hillman adducts as a mixture of *E/Z* isomers. Representative examples are shown in Eq. 2.[54]



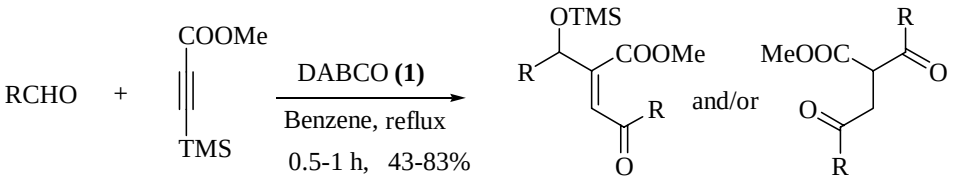
Eq. 2

Ar = C_6H_5, *p*-ClC_6H_4, *o*-ClC_6H_4, *m*-ClC_6H_4, *p*-$(CH_3O)C_6H_4$, *p*-$NO_2C_6H_4$, *p*-CNC_6H_4, *p*-$CO_2MeC_6H_4$, *α*-naphthyl

Yield = 31-86%

E/Z = 50-75/25-50

Nemoto and coworkers[56] have disclosed a new reaction of propiolate with aldehydes mediated by DABCO leading to the formation of novel *β*-functionalized Baylis-Hillman adducts involving simultaneous formation of two C-C bonds. Representative examples are presented in Eq. 3.



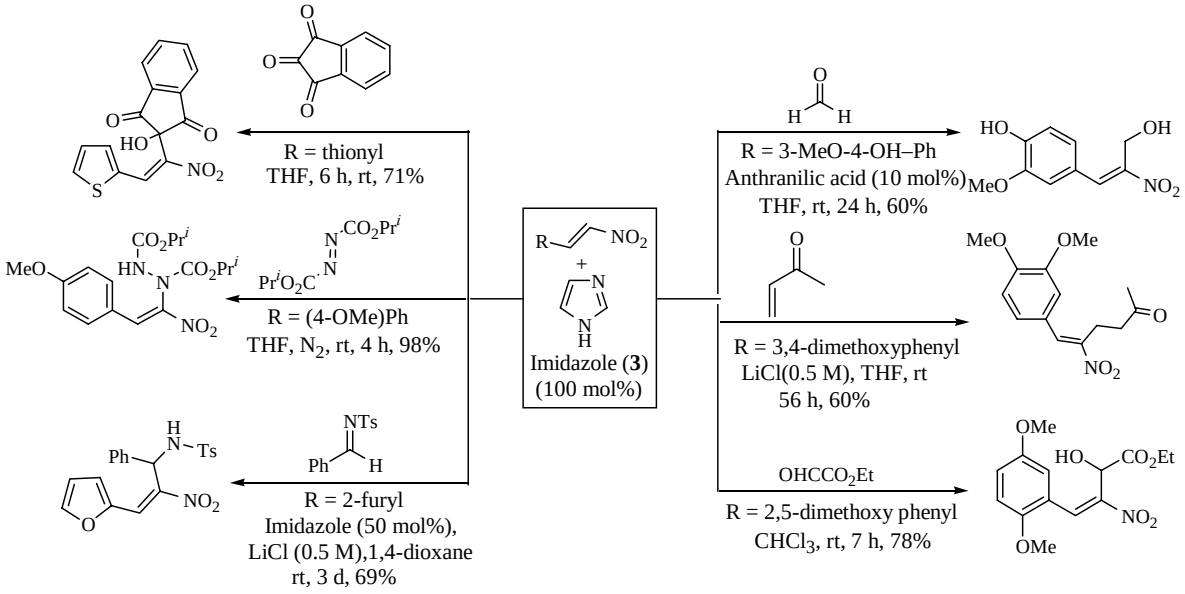
Eq. 3

R = C_6H_5, 2-MeC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4, 2-$MeOC_6H_4$, 3-$MeOC_6H_4$, 4-$MeOC_6H_4$, 4-ClC_6H_4,1-naphthyl, 2-naphthyl, 2-Br-4,5-$(MeO)_2$-C_6H_2

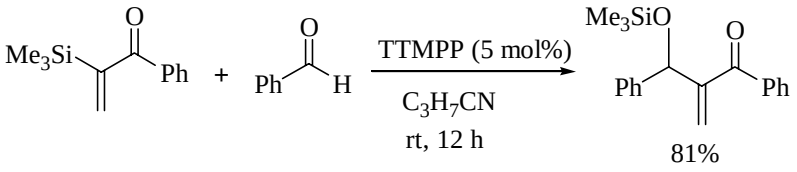
Ratio : 37-100 / 0-63

Namboothiri and coworkers[57-61] have, for the first time, demonstrated applications of conjugated nitroalkenes as activated alkenes in the Baylis-Hillman coupling with various electrophiles such as formaldehyde (formalin),[57] activated alkenes,[58] glyoxylates,[59] ninhydrin,[59] diisopropyl azodicarboxylate,[60] and *N*-tosylimines,[61] in the presence of imidazole (**3**) at room temperature. Representative examples are presented in Scheme 3.

Scheme 3



Very recently, Gevorgyan and Trofimov[62] have reported an interesting reaction between α-silylvinylaryl ketones with aryl aldehydes to produce silylated Baylis-Hillman adducts *via* a 1,3-Brook rearrangement/elimination cascade. One such example is given in Eq. 4.



Eq. 4

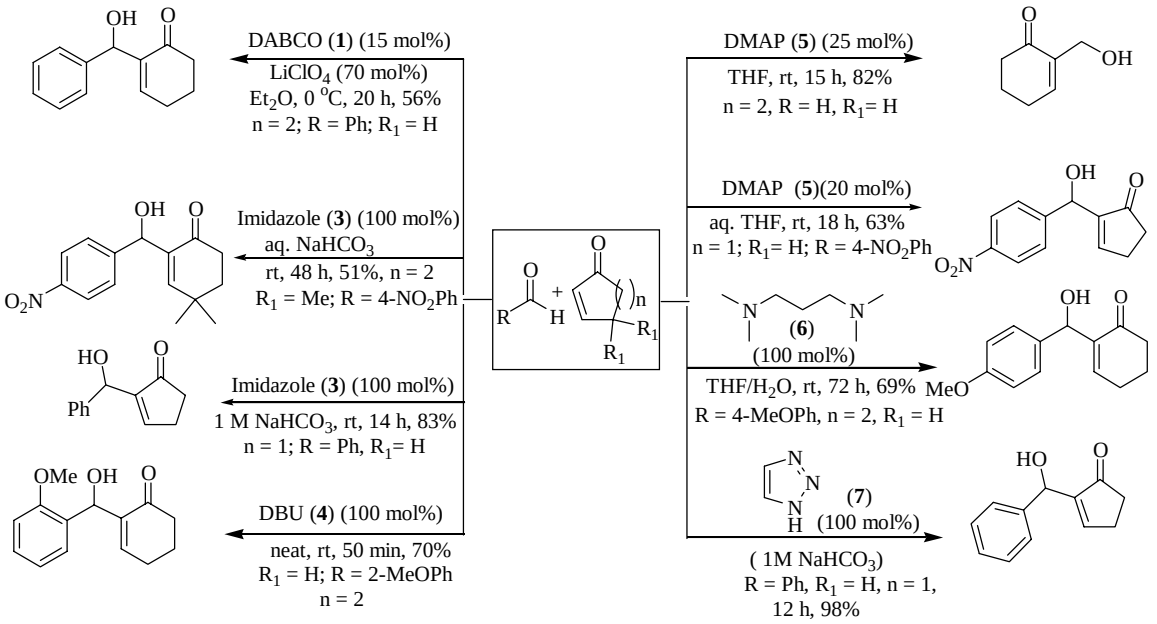
TTMPP = Tris(2,4,6-trimethoxyphenyl)phosphine

ACTIVATED ALKENES (CYCLIC)

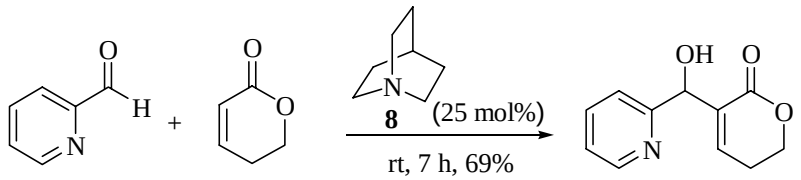
Cyclopent-2-enone, cyclohex-2-enone and their derivatives are the most commonly used cyclic enones for the Baylis-Hillman coupling with various electrophiles in the presence of various *tert*-amine catalysts, such as, DABCO (**1**),[50] imidazole (**3**)/$NaHCO_3$(1 M),[63] DBU (**4**),[64] DMAP (**5**),[65,66] TMPDA (**6**)[67] and 1,2,3-triazole (**7**)/$NaHCO_3$(1 M)[68] to provide

corresponding multifunctional molecules. Representative examples are shown in Scheme 4.

Scheme 4

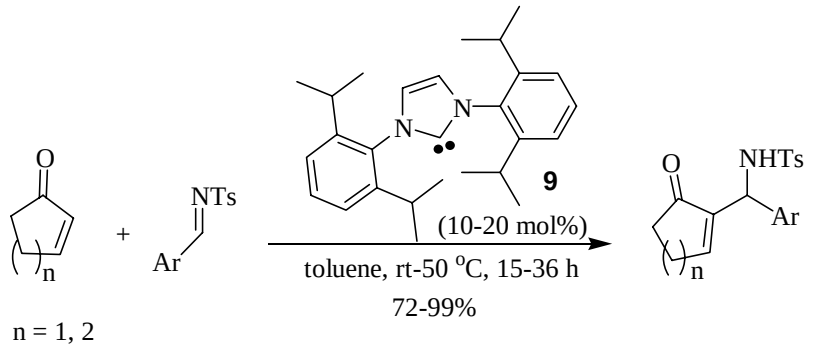


Aggarwal and coworkers,[69] have used 5,6-dihydro-2*H*-pyran-2-one as a cyclic activated alkene for coupling with aldehydes in the presence of quinuclidine (**8**). One example is presented in Eq. 5.



Eq. 5

Ye and coworkers,[70] for the first time, reported *N*-heterocyclic carbene (NHC, **9**) catalyzed Baylis-Hillman reaction of cyclic enones with a variety of *N*-tosylarylimines. Representative examples are presented in Eq. 6.

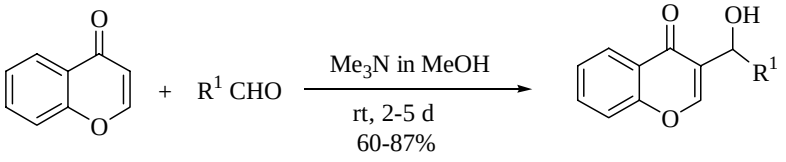


Eq. 6

n = 1, 2

Ar = C_6H_5, 4-MeC_6H_4, 4-$OMeC_6H_4$, 4-ClC_6H_4, 4-FC_6H_4, 4-$NO_2C_6H_4$, 3-$OMeC_6H_4$, 3-ClC_6H_4, 2-$OMeC_6H_4$, 2-Furyl

Recently, our research group[71] has systematically used 1-benzopyran-4(4*H*)-one, as activated alkene for coupling with various aromatic aldehydes in the presence of methanolic trimethylamine. Representative examples are presented in Eq. 7.



Eq. 7

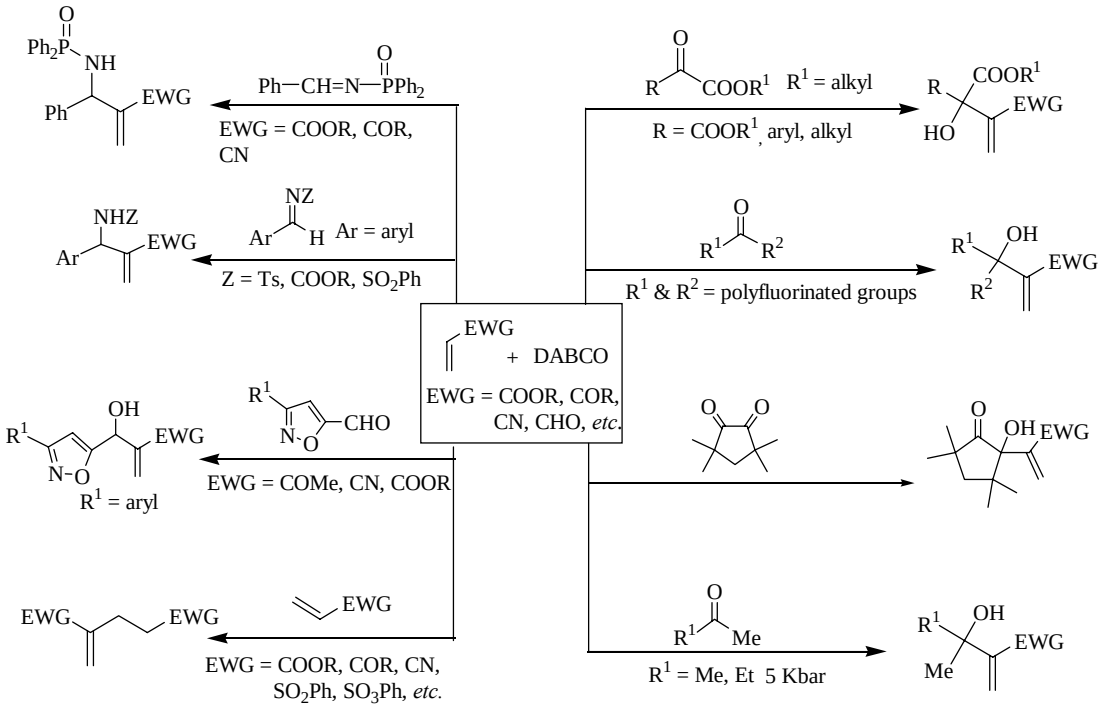
R^1 = Pyrid-2-yl, Pyrid-3-yl, Pyrid-4-yl, Fur-2-yl, Thiophen-2-yl, 2-(NO_2)Ph, 4-(NO_2)Ph

ELECTROPHILES

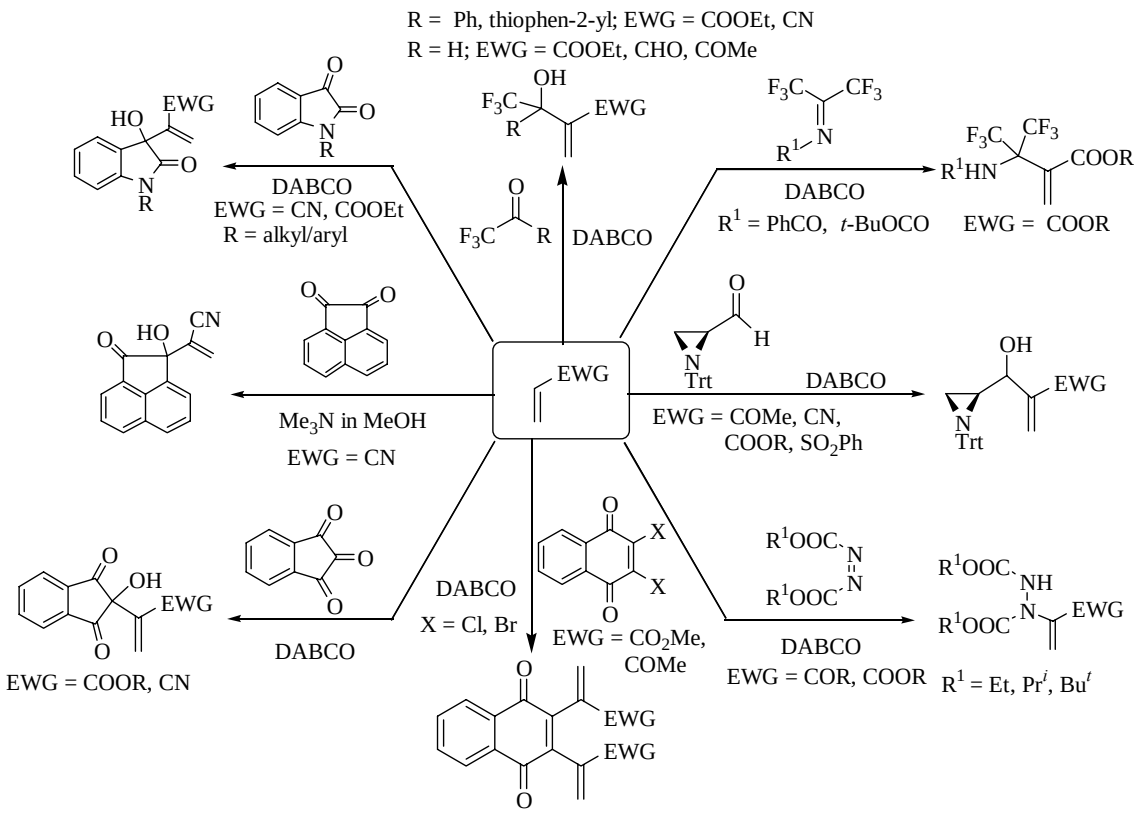
Aldehydes[16] (aliphatic, aromatic, and hetero-aromatic) are the most frequently and commonly used electrophiles in the Baylis-Hillman coupling with activated alkenes to produce densely functionalized adducts. In addition, there are several other electrophiles such as α-keto esters,[72-74] fluoro ketones,[75] aldimine derivatives,[76-79] activated alkenes,[80-83] non-enolizable 1,2-diketones,[49] *N*-arylidenediphenylphosphinamide[84] and isoxazole-5-

carboxaldehydes[85] have also been successfully employed for coupling with different activated alkenes in this reaction (Scheme 5). Comparatively less reactive simple ketones (acetone & 2-butanone)[48] do not react with activated alkenes at normal conditions. However these were brought into scope of the reaction at high pressure conditions for coupling with activated alkenes (Scheme 5). Recently, fluoro imines,[86] fluorinated aldehydes & ketones,[87,88] acenaphthenequinone,[89] azodicarboxylates,[90] 2,3-dihalo-1,4-naphthoquinone,[91] isatin derivatives,[92,93] ninhydrin[93] and *N*-trityl-aziridine-2-(*S*)-carboxaldehyde[94] have been successfully used as electrophiles in the Baylis-Hillman reaction to produce an interesting class of multifunctional molecules (Scheme 6).

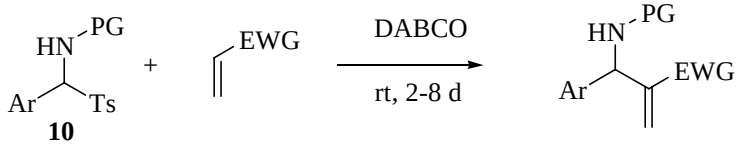
Scheme 5



Scheme 6



Gajda and Gajda[95] have demonstrated the application of *N*-Boc and *N*-Cbz protected α-amidoalkyl-*p*-tolylsulfones (**10**) as convenient electrophiles for the Baylis-Hillman reaction with activated alkenes in the presence of DABCO. Representative examples are presented in Eq. 8.

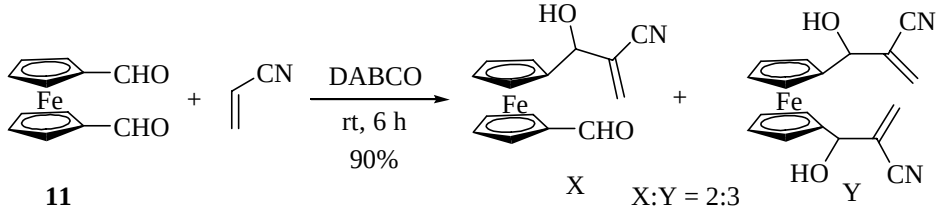


Eq. 8

10

Ar = Ph, 4-$OMeC_6H_4$, 4-BrC_6H_4, 2-$OMeC_6H_4$, 2-ClC_6H_4, 2-furyl, 3-py, 1-naphthyl
EWG = CO_2Me, CO_2Et, CN; PG = Boc, Cbz

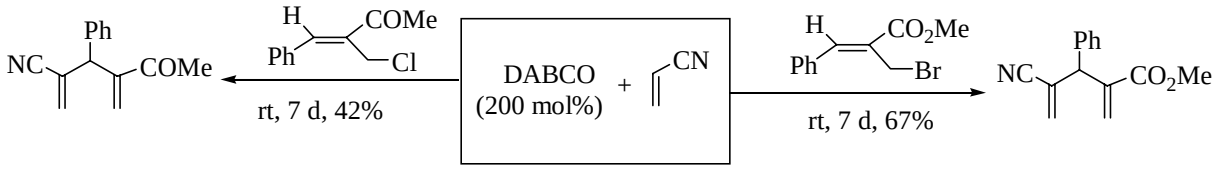
Shanmugam and coworkers[96] have successfully employed 1,1-ferrocenedialdehyde (**11**) for Baylis-Hillman coupling with acrylonitrile in the presence of DABCO to provide the corresponding mono- and bis- adducts. One such example is presented in Eq. 9.



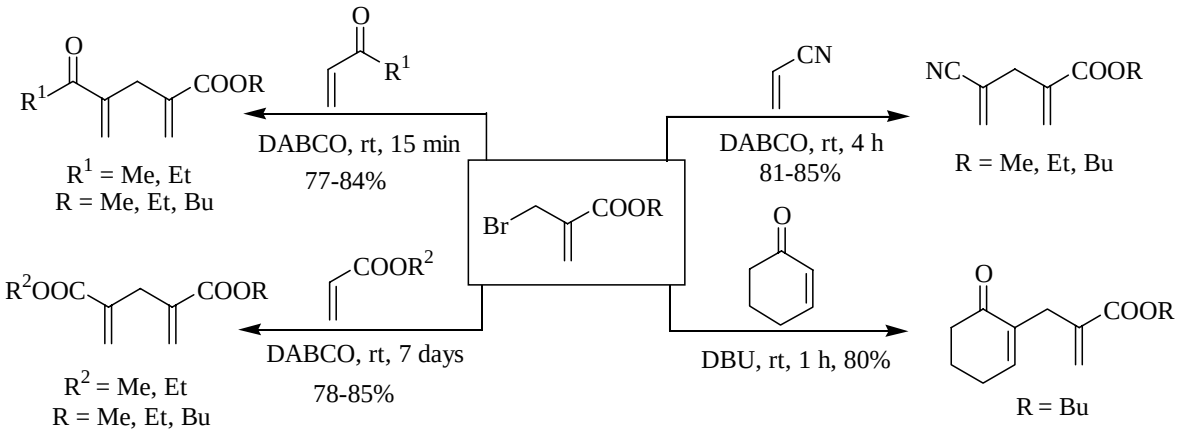
11 X X:Y = 2:3 Y **Eq. 9**

Our research group[97,98] employed, for the first time, allyl halides derived from the Baylis-Hillman adducts, as electrophiles for coupling with various activated alkenes. Thus, the reaction of allyl bromides / allyl chlorides, derived from the corresponding Baylis-Hillman adducts (obtained, from the activated alkenes, methyl acrylate and methyl vinyl ketone) with acrylonitrile in the presence of DABCO provided 3-substituted functionalized 1,4-pentadienes (Scheme 7).[97] Later, our research group has extended the same strategy to allyl bromides, derived from alkyl 3-hydroxy-2-methylenepropanoates (the corresponding Baylis-Hillman alcohols), for coupling with various activated olefins thus developing a simple methodology for one-pot synthesis of 2,4-functionalized 1,4-pentadienes (Scheme 8).[98]

Scheme 7



Scheme 8



CATALYSTS/CATALYTIC SYSTEMS

Although tertiary amines are the most widely used catalysts for the Baylis-Hillman reaction, several non-amine compounds/systems have also been used to promote this fascinating reaction. This section briefly presents applications of tertiary amine and non-amine catalysts for performing the Baylis-Hillman reaction.

TERTIARY AMINE CATALYSTS

DABCO (**1**),[69,99] is the most successful catalyst among the pool of tertiary amine based catalysts. However several other amines such as 3-hydroxyquinuclidine (**2**),[69,99] imidazole (**3**),[63,100,101] DBU (**4**),[64] DMAP (**5**),[65,66] TMPDA (**6**),[67] quinuclidine (**8**),[69] 3-acetoxyquinuclidine (**12**),[69,99] methanolic-Me_3N,[71,89,102] indolizine (**13**),[11] 3-chloroquinuclidine (**14**),[69] 3-quinuclidinone (**15**),[69] HMT (**16**),[103,104] NMM (**17**),[104] TMG (**18**),[105] TMEDA (**19**),[106] Et_3N[48] and aqueous-Me_3N[107] (Figure 1) have been successfully employed in various and specific Baylis-Hillman reactions. Recently, a variety of polymer supported DMAP derivatives, such as, PAP [polymer-bound 4-(*N*-benzyl-*N*-

methylamino)pyridine (**20**)],[108] DMAP-MSN [mesoporous silica nanosphere (**21**)],[109] and dendritic DMAP {*N*,*N*-di[3',4',5'-tri(*n*-dec-1-yloxy)benzyl]-4-aminopyridine (**22**)}[110] (Figure 1) have also been successfully employed as catalysts for the Baylis-Hillman reaction of various activated alkenes with electrophiles.

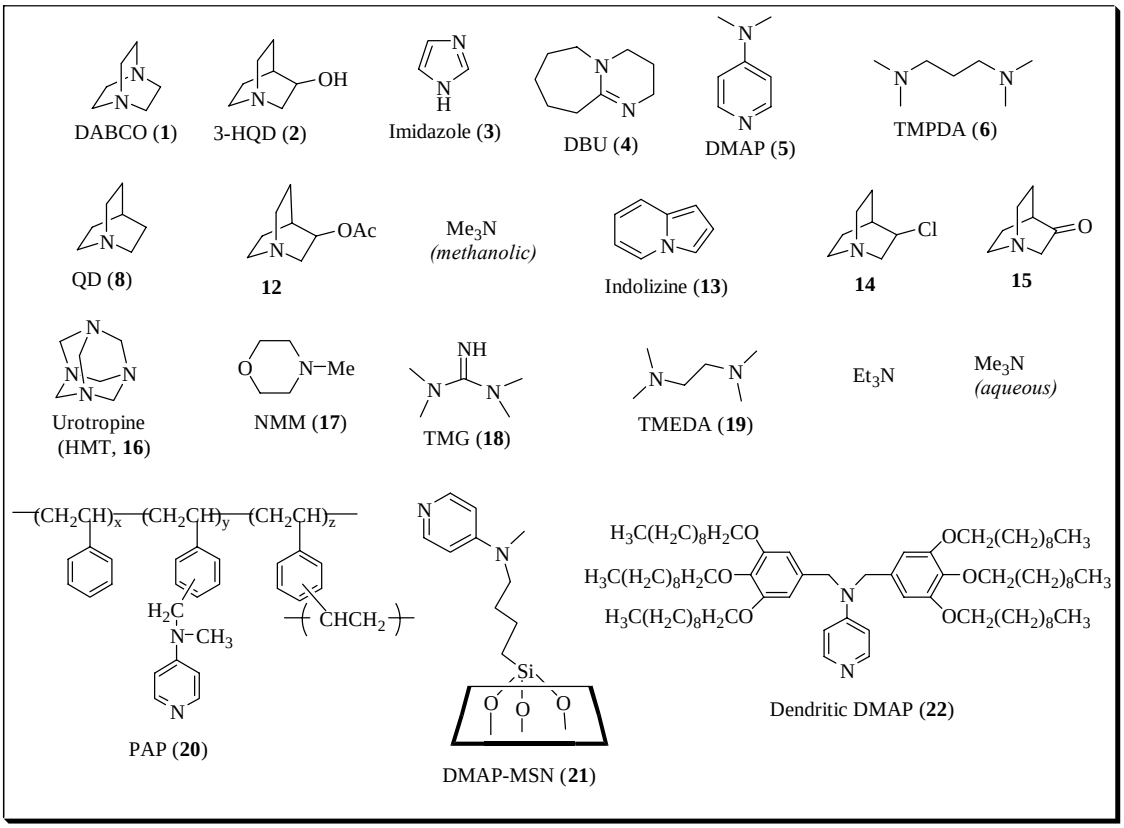
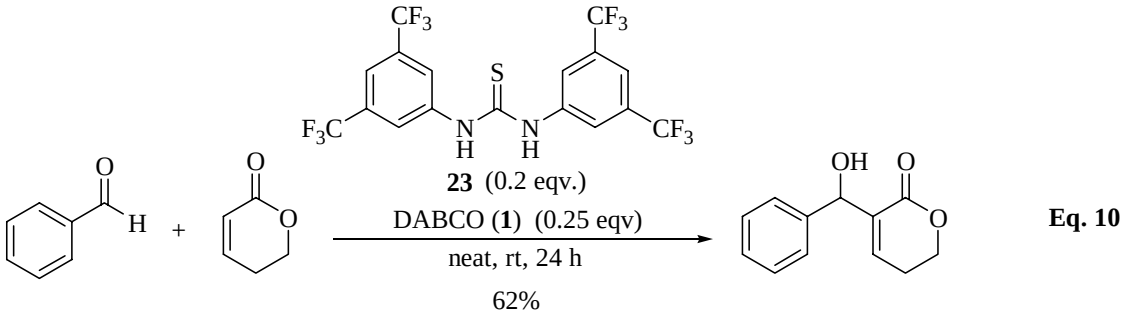


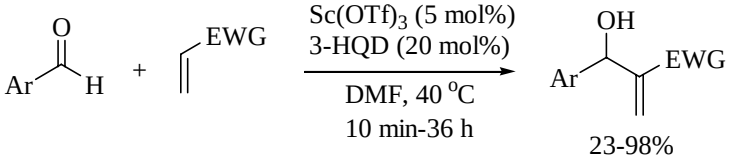
Figure 1

Nagasawa and coworkers[111] have employed a combination of thiourea (**23**) and Lewis base (DABCO/DMAP) as a new catalytic system to perform Baylis-Hillman reaction of aldehydes (alkyl/aryl) with cyclic enones. One representative example is presented in Eq. 10.



Eq. 10

Very recently, Shang and coworkers[112] have reported a combination of $Sc(OTf)_3$ and 3-HQD (**2**) as an efficient catalytic system for the Baylis-Hillman reaction of various aromatic aldehydes with alkyl acrylates and acrylonitrile. Representative examples are presented in Eq. 11.

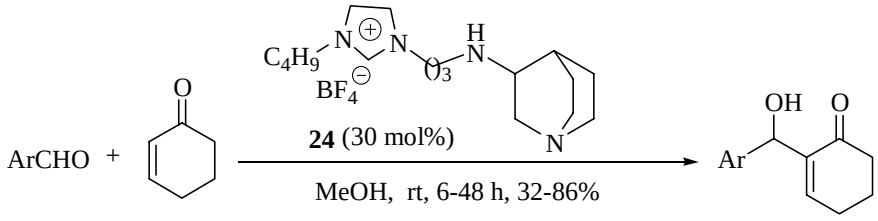


Eq. 11

EWG = COOMe, COOEt, CN

Ar = Ph, 4-OMePh, 4-ClPh, 4-NO_2Ph, 2-furyl, 2,4-Cl_2Ph.

Cheng and coworkers[113] have successfully used ionic liquids as catalysts in the Baylis-Hillman reaction. They have employed quinuclidine containing ionic liquid component (**24**) as a catalyst for a facile coupling of aromatic aldehydes with various activated alkenes (acyclic and cyclic enones) (Eq. 12).



Eq. 12

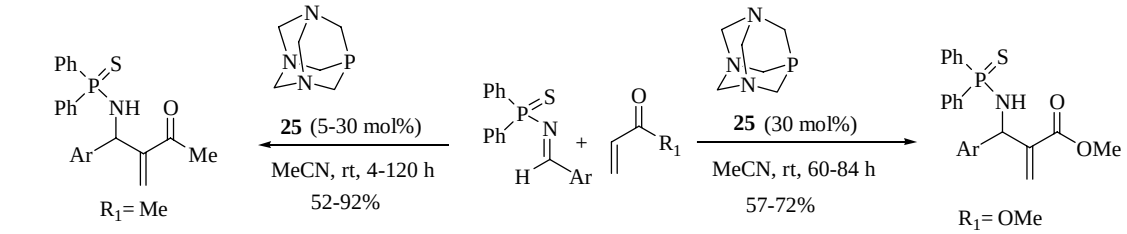
Ar = C_6H_5, 4-ClC_6H_4, 4-MeC_6H_4, 4-$NO_2C_6H_4$, 3,4-methylenedioxyphenyl

NON-AMINE CATALYSTS (CATALYTIC SYSTEMS) / REAGENTS MEDIATED BAYLIS-HILLMAN REACTIONS

Various non-amine catalysts / catalytic systems, such as, trialkyl/triaryl phosphines,[114-117] and metal complexes like $RhH(PPh_3)_4$,[118,119] $RuH_2(PPh_3)_4$,[119,120] have also been successfully employed to promote the Baylis-Hillman reaction. Several Lewis acid based catalysts such as $TiCl_4$,[121,122] R_2S-$TiCl_4$,[16,123-126] $TiCl_4$-R_3N[127], $TiCl_4$-R_4NX (X = halide),[16,128,129] R_2X-BF_3 (X = O, S),[130-132] and Et_2AlI[133,134] have been found to promote Baylis-Hillman (type) coupling reactions.

Zhou and coworkers[135] have described an interesting 1,3,5-triaza-7-phosphaadamantane (**25**, PTA) catalyzed Baylis-Hillman coupling of *N*-thiophosphoryl imines with MVK and methyl acrylate to provide the corresponding Baylis-Hillman adducts. Representative examples are presented in Scheme. 9.

Scheme 9

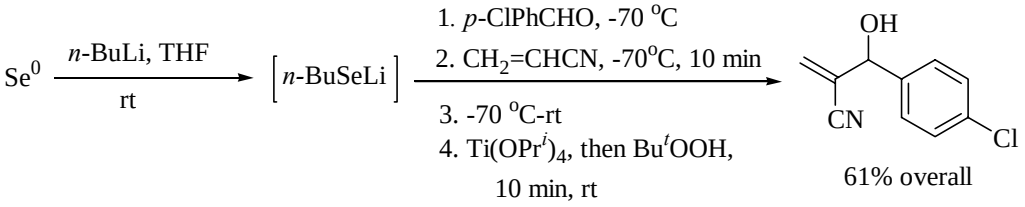


Ar = Ph, 4-MeC_6H_4,2-$MeOC_6H_4$, 2-ClC_6H_4,4-BrC_6H_4, 3-FC_6H_4, 4-$NO_2C_6H_4$, PhCH=CH

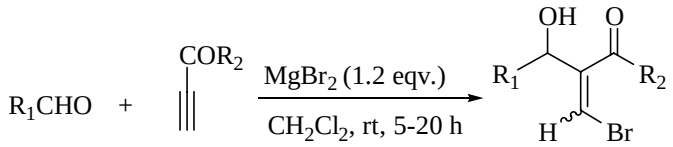
Ar = Ph, 2-ClC_6H_4, 3-FC_6H_4, 3-$F_3CC_6H_4$, 4-BrC_6H_4

Recently, Comasseto and coworkers[136] have developed a simple and efficient one-pot access to Baylis-Hillman adducts following the reaction sequence as shown in Scheme 10.

Scheme 10



Wei and coworkers[137] have successfully employed $MgBr_2$ as a promoter for Baylis-Hillman reaction between 3-butyn-2-ones (as nucleophile) and aldehydes (aryl/alkyl). Representative examples are presented in Eq. 13.

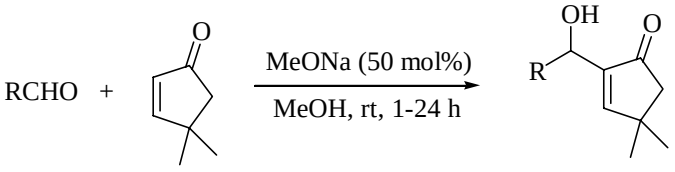


Eq. 13

R_1 = Ph, 4-MePh, 4-ClPh, 4-FPh, 4-BrPh, 4-OMePh, $CH_3CH{=}CH$, $CH_3(CH_2)_3$, Et

R_2 = Me, Pr^i, Ph

Cheng and coworkers[138] for first time, have reported an interesting methoxide anion catalyzed Baylis-Hillman reaction of enones with various aldehydes. Representative examples are presented in Eq. 14.



Eq. 14

R = Ph, 4-MePh, 2-ClPh, 4-OMePh, 4-NO_2Ph, Bu^i

ASYMMETRIC BAYLIS-HILLMAN REACTION

Asymmetric version of the Baylis-Hillman reaction can be achieved by selecting suitable chiral sources in any one of the (or two or three) essential components *i.e.,* activated alkene, electrophile and catalyst. It is also possible to perform asymmetric Baylis-Hillman reaction using appropriate chiral additives in the reaction media. Already efforts have been made in this direction and some relevant and recent developments have been described in this section.

CHIRAL ACTIVATED ALKENES:

Numerous chiral activated alkenes such as chiral acrylates (**26**-**36**)[13-18,139-146] and chiral acrylamides (**37**[147,148] & **38**[149]) (Figure 2) derived from various chiral auxiliaries were successfully employed for stereoselective Baylis-Hillman reaction with various electrophiles to provide the resulting adducts in low to high diastereoselectivities.

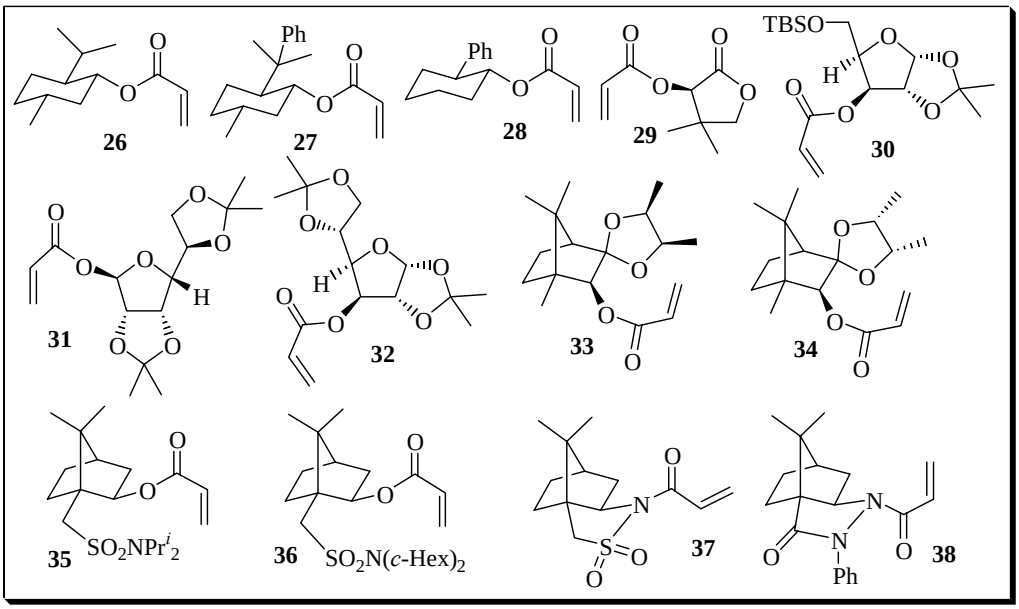
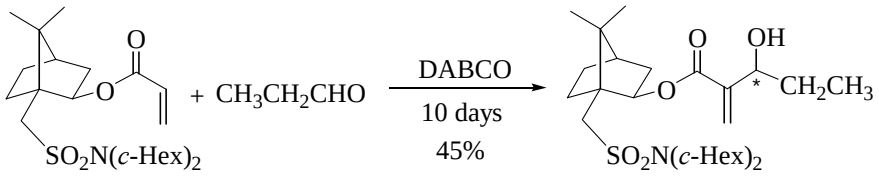


Figure 2

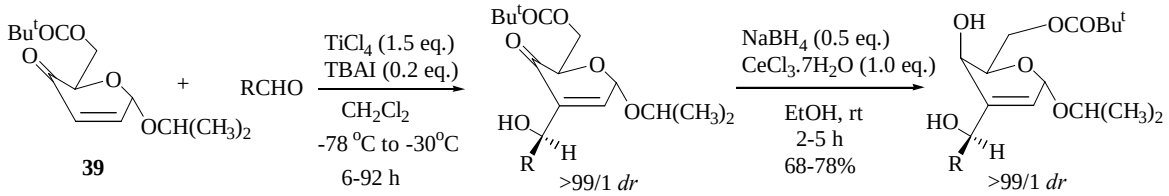
Our research group[139] has employed chiral acrylate **36** as activated alkene for diastereoselective Baylis-Hillaman reaction with different aldehydes to provide the resulting adducts in low to moderate selectivity. One example is presented in Eq. 15.



36 70% *de* **Eq. 15**

Shaw and coworkers[150] have reported an interesting Baylis-Hillman reaction of aromatic aldehydes with C-6 acyl protected enuloside (**39**) in the presence of $TiCl_4$/TBAI to provide the corresponding adducts in high diastereoselectivities. Some of these adducts were reduced with $NaBH_4/CeCl_3.7H_2O$ to give the corresponding alcohols in high diastereoselectivities. Representative examples are presented in Scheme 11.

Scheme 11



39

R = C_6H_5, 4-(F_3C)C_6H_4, 4-FC_6H_4, 2-(NO_2)C_6H_4, 3-(NO_2)C_6H_4, 4-(NO_2)C_6H_4, *n*-Pr, n-C_9H_{19}

R = 2-(NO_2)C_6H_4, 4-(NO_2)C_6H_4, *n*-C_9H_{19}

CHIRAL ELECTROPHILES

Efforts have been made towards the asymmetric Baylis-Hillman reaction using chiral electrophiles such as (*S*)-*O*-(methoxymethyl)lactaldehyde (**40**),[151] (*S*)-3-benzyloxybutyraldehyde (**41**),[152] α-dialkylamino and, α-(*N*-acylamino)aldehydes (**42**),[153,154] isopropylidene (*R*)-glyceraldehyde (**43**),[141] 1-alkenyl- or alkynyl 4-oxoazetidine-2-carbaldehydes (**44**),[155] 3-oxo-2-azetidinones (**45**),[156] (*R*)-myrtenal (**46**),[141] 2(*S*)-*N*-(4-nitrobenzoyl)pyrrolidine-2-carboxaldehyde (**47**),[154] chiral *o*-substituted benzaldehyde tricarbonyl-chromium complex (**48**)[157,158] and sugar derived aldehydes (**49-51**),[159,160] *etc.* (Figure 3), for coupling with various activated alkenes to afford the resulting adducts in low to high diastereoselectivities**.**

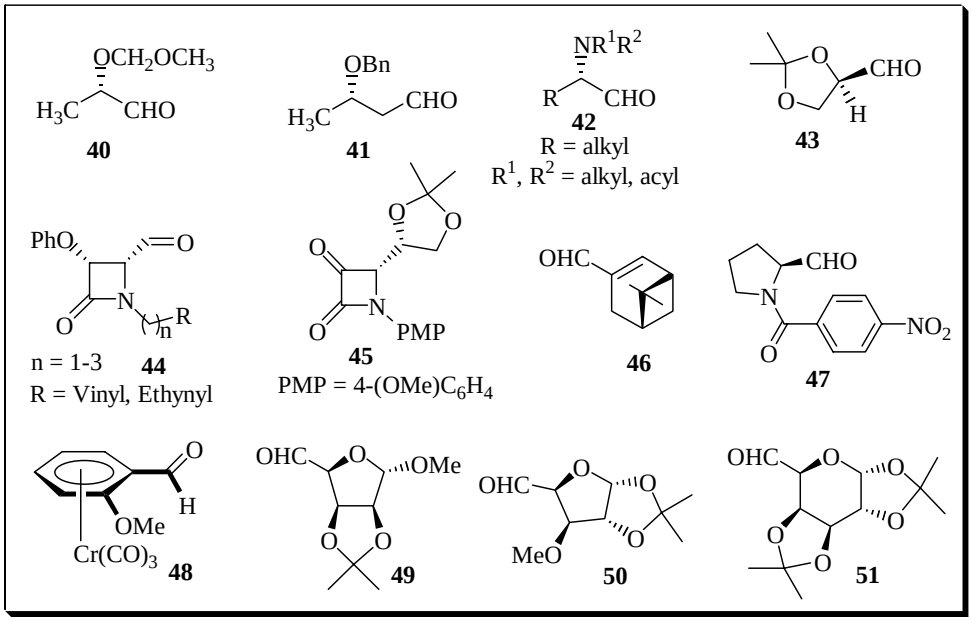
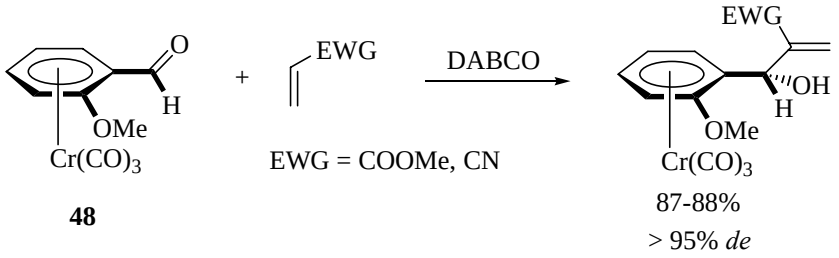


Figure 3

Kundig and coworkers[157] used chiral ortho substituted benzaldehyde tricarbonylchromium complexes (**48**) as electrophiles in the Baylis-Hillman reaction with various activated

olefins in presence of DABCO as a catalyst to afford the desired Baylis-Hillman adducts in >95% *de*. Representative examples are presented in Eq. 16.



48

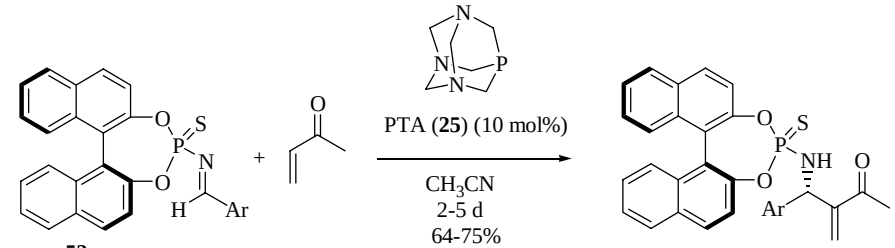
EWG = COOMe, CN

87-88%

> 95% *de*

Eq. 16

Very recently, Zhou and coworkers have used chiral *N*-thiophosphoryl imines (**52**) as chiral electrophiles for the Baylis-Hillman reaction with MVK under the catalytic influence of PTA (**25**) to obtain the corresponding adducts in fair to excellent diastereoselectivities. Representative examples are presented in Eq. 17.[161]



52

42->99% *de*

Ar = C_6H_5, 4-MeC_6H_4, 4-$(MeO)C_6H_4$, 4-$(F_3C)C_6H_4$, 2-ClC_6H_4, 4-BrC_6H_4

Eq. 17

CHIRAL CATALYSTS

Significant developments have been made in the designing of new chiral catalysts[13-18] for achieving asymmetric version of Baylis-Hillman reaction. Thus, chiral DABCO (**53**),[162,163] (*S*)- enantiopure pyrrolizidine (**54**),[164] chiral bicyclic azetidine (**55**),[165] quinidine derivatives (**56-60**),[166-170] and proline derivatives (**61**,**62**),[171-173] have been utilized as chiral catalysts in this reaction to provide the resulting adducts in moderate to good

enantioselectivities (Figure 4). Variety of bifunctional catalysts, derived from BINOL (**63-69a-d**, **70**),[174-183] have been successfully employed in the Baylis-Hillman reaction to accomplish high enantioselectivities (Figure 5).

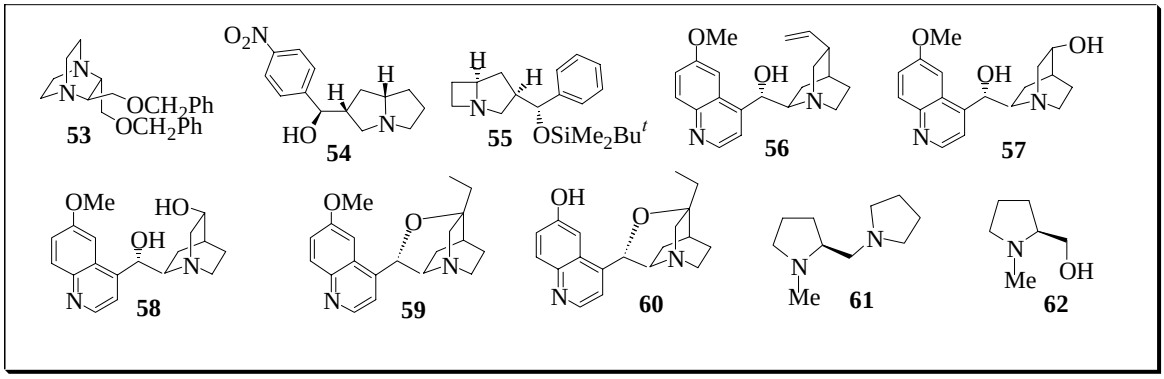


Figure 4

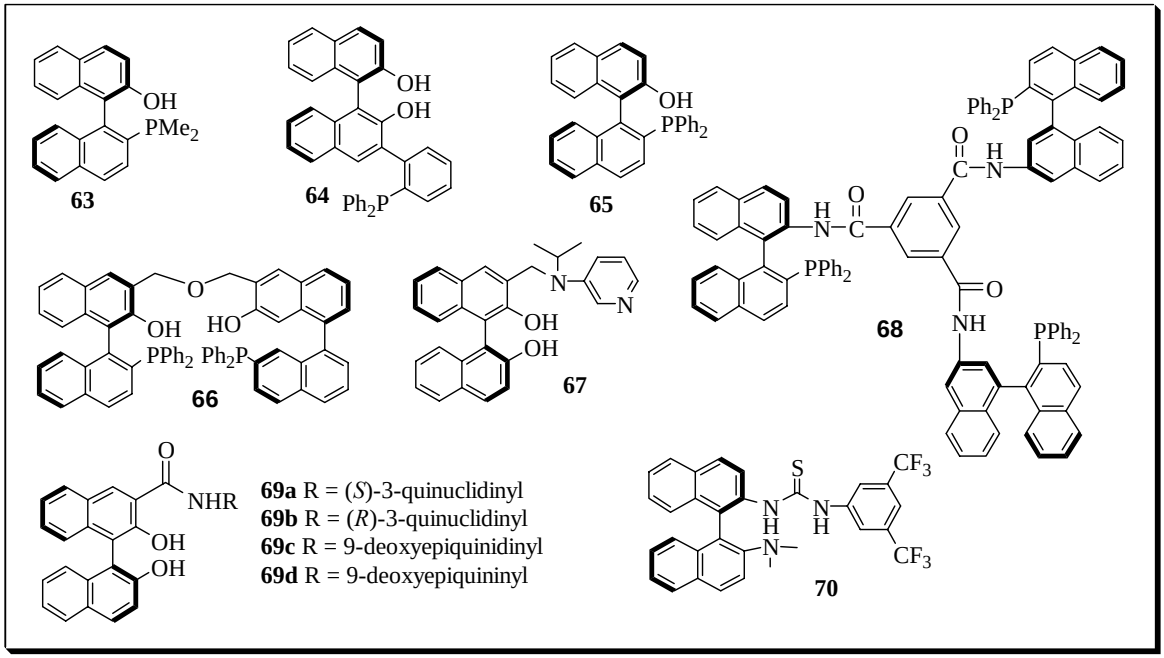
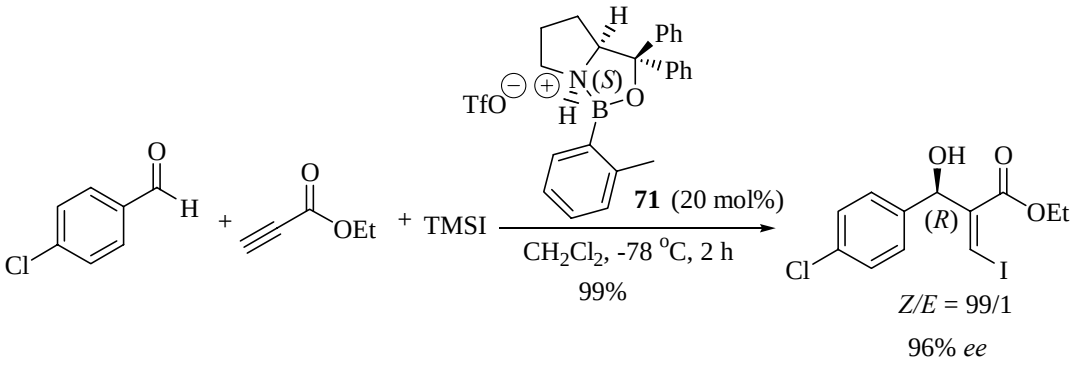


Figure 5

Recently, Ryu and coworkers[184] have employed oxazaborolidinium salt (**71**) as powerful catalyst for three-component coupling reaction among aldehydes, ethyl propiolate and

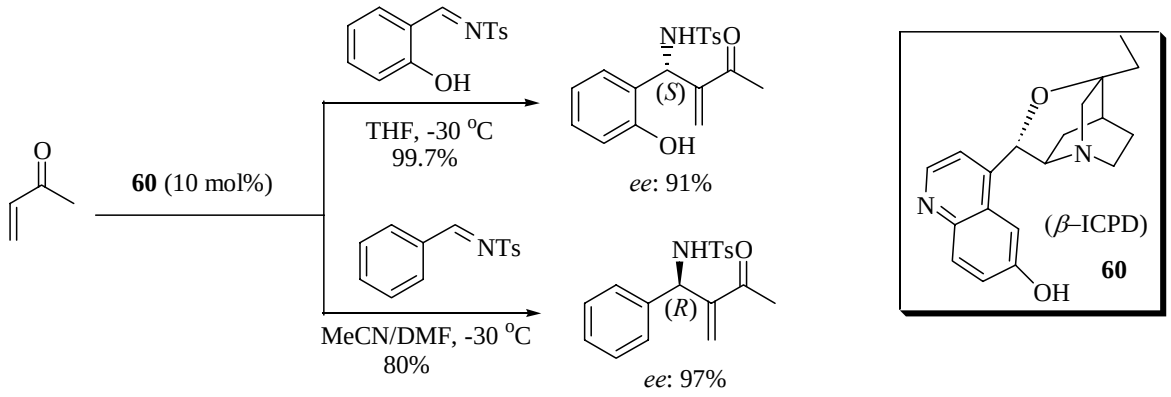
TMSI to provide chiral β-iodo Baylis-Hillman adducts in high enatiomeric purities. One example is presented in Eq. 18.



Eq. 18

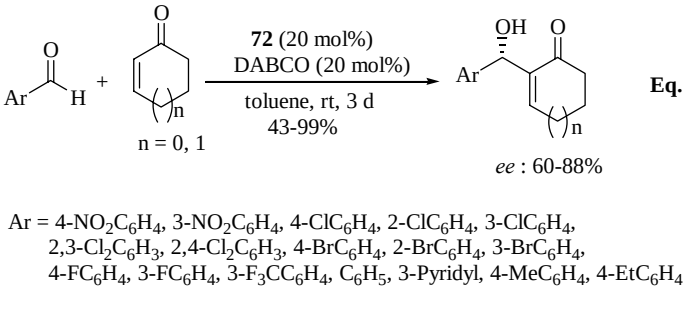
Shi and coworkers[185] have reported an effective β-isocupreidine (β-ICPD, **60**) (Lewis base) catalyzed asymmetric Baylis-Hillman reaction of aryl *N*-tosyl imines with α, β-unsaturated ketones under mild conditions to provide the corresponding adducts in high enantiomeric purities. They have observed reversal of stereoselectivity when an *ortho*-hydroxy group is introduced in aryl *N*-tosyl imines. Representative examples are presented in Scheme 12.

Scheme 12



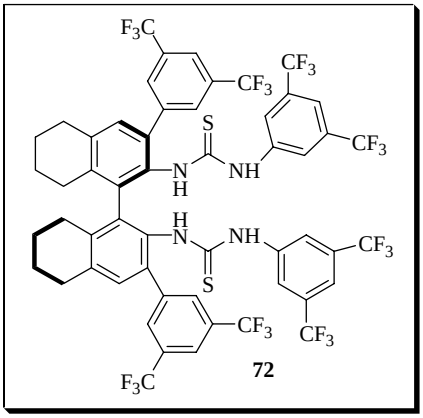
Subsequently Shi and coworkers[186] have reported asymmetric Baylis-Hillman reaction of aryl aldehydes with cyclic enones under the catalytic influence of chiral bis(thio)urea (**72**)

and DABCO which gave the corresponding adducts in moderate to good enantiomeric purities. Representative examples are presented in Eq. 19.



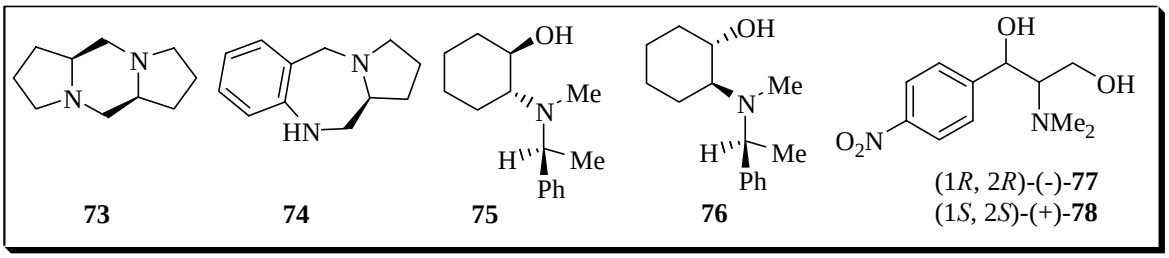
Eq. 19

Ar = 4-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 4-ClC_6H_4, 2-ClC_6H_4, 3-ClC_6H_4, 2,3-$Cl_2C_6H_3$, 2,4-$Cl_2C_6H_3$, 4-BrC_6H_4, 2-BrC_6H_4, 3-BrC_6H_4, 4-FC_6H_4, 3-FC_6H_4, 3-$F_3CC_6H_4$, C_6H_5, 3-Pyridyl, 4-MeC_6H_4, 4-EtC_6H_4



72

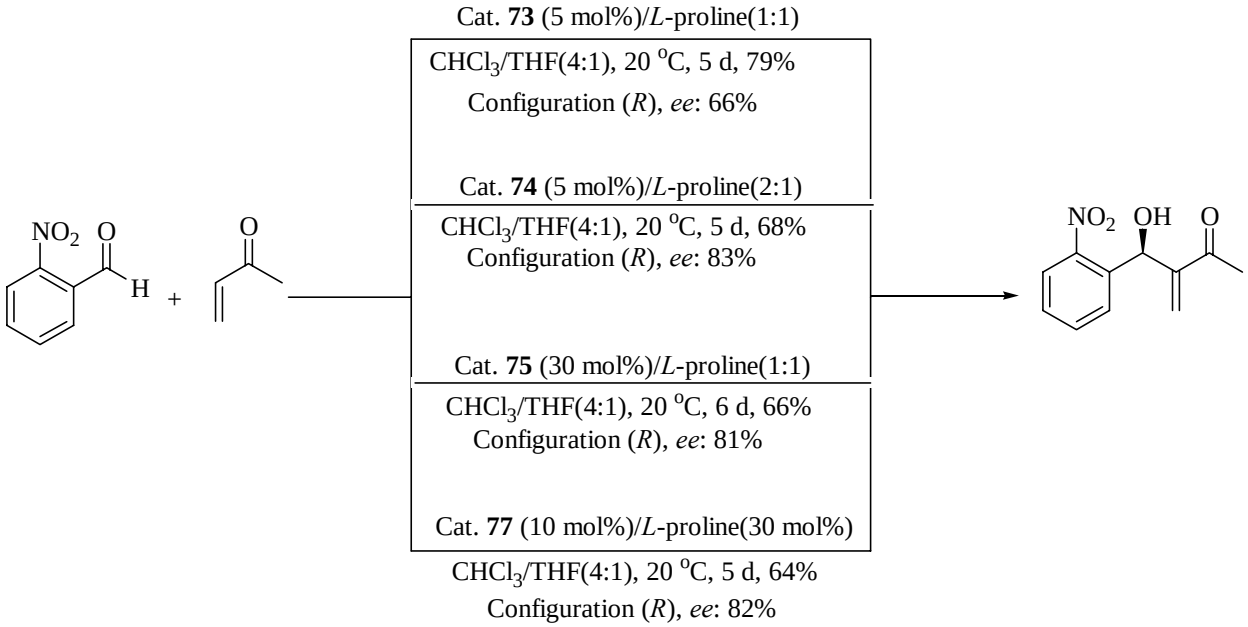
Application of chiral amines (**73-78**, Figure 6) in combination with *L*-proline as efficient co-catalysts for asymmetric Baylis-Hillman reaction between aromatic aldehydes and MVK to produce the corresponding adducts in good enantioselectivities was reported by He and coworkers.[187] Representative examples are shown in Scheme 13.



73 **74** **75** **76** (1*R*, 2*R*)-(-)-**77** (1*S*, 2*S*)-(+)-**78**

Figure 6

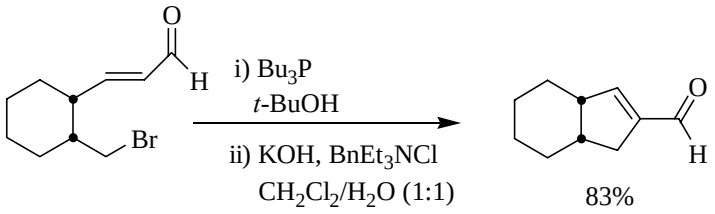
Scheme 13



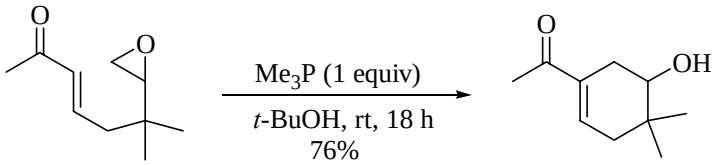
INTRAMOLECULAR BAYLIS-HILLMAN REACTION

Intramolecular version of the Baylis-Hillman reaction is yet another interesting and challenging aspect in Baylis-Hillman chemistry. Literature survey reveals that in recent years chemists have turned their attention in this direction and made considerable progress.[188-196] Some of the recent and interesting developments are presented in this section.

Kraft and coworkers[188,189] have reported phosphine induced a facile intramolecular Baylis-Hillman reactions of enone halide and enone-epoxide systems to provide interesting carbocyclic frameworks. Representative examples are presented in Eq. 20 and 21.



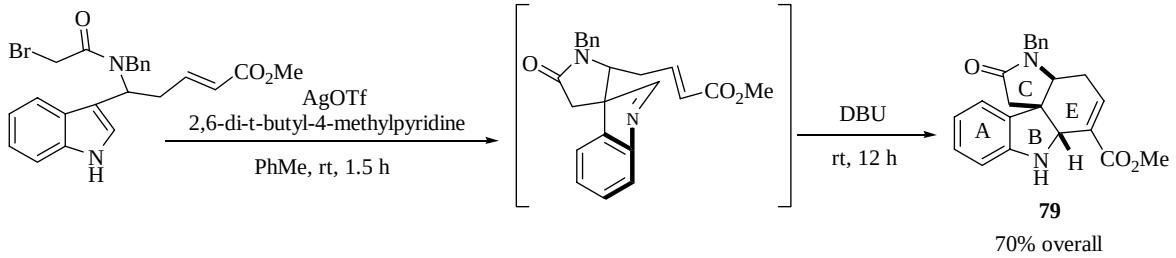
Eq. 20



Eq. 21

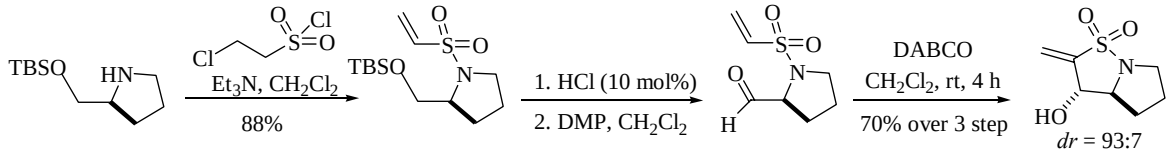
Recently, Andrade and Sirasani[197] have developed a convenient methodology by a novel sequential one-pot alkylation and intramolecular Baylis-Hillman reaction for synthesis of ABCE tetracyclic framework (**79**) of *Strychnos* alkaloids (Scheme 14)

Scheme 14

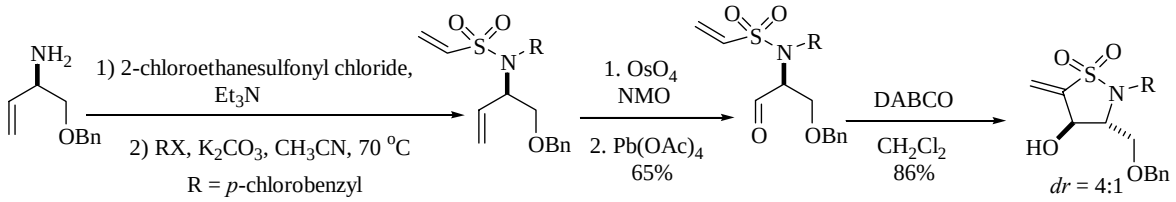


Hanson and coworkers[198,199] have utilized intramolecular Baylis-Hillman reaction as the key step to generate sultams *via* a strategy involving functional group pairing between vinyl sulfonamide and suitably protected amino alcohol/aldehyde following the reaction sequences shown in Schemes 15 and 16.

Scheme 15

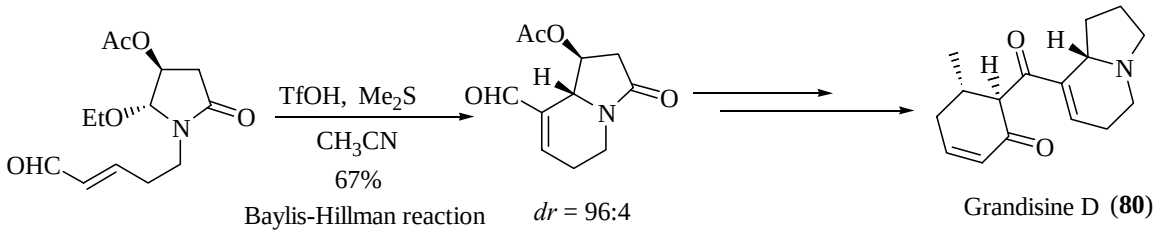


Scheme 16



Total synthesis of grandisine D (**80**) was reported by Tamura and coworkers[200] using Bronsted acid mediated intramolecular Baylis-Hillman reaction as the key step (Scheme 17).

Scheme 17



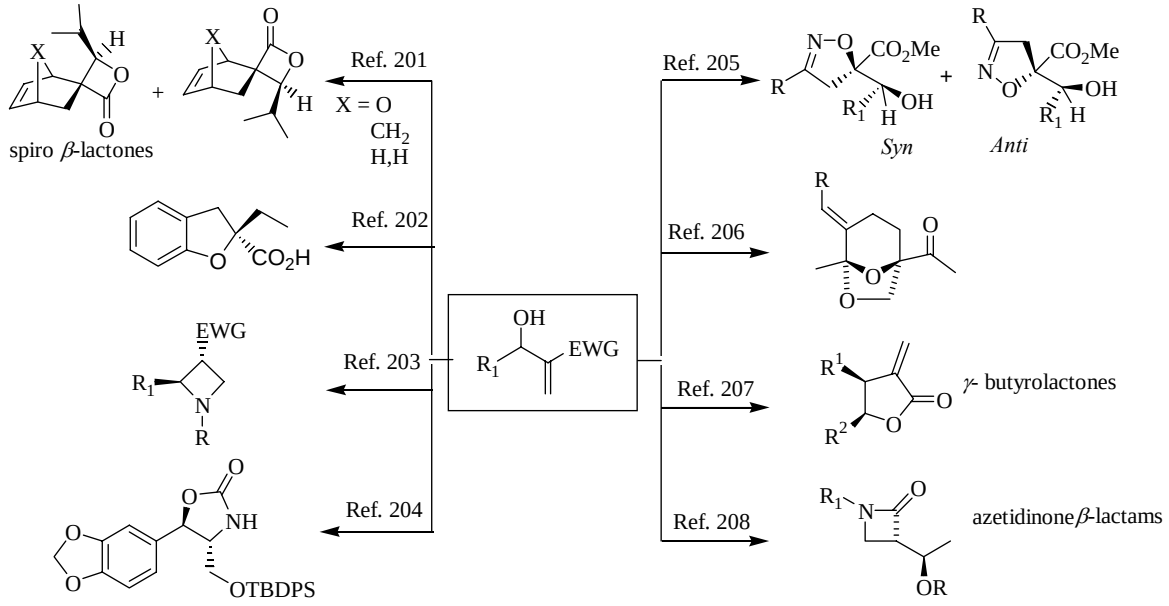
APPLICATIONS OF THE BAYLIS–HILLMAN ADDUCTS

The Baylis-Hillman adducts contain three functional groups in close proximity and thus offer opportunities to the organic chemists to develop various organic transformation methodologies *via* suitable tuning of these groups. These adducts have successfully been subjected to various organic reactions such as Friedel-Crafts reaction, Diels-Alder reaction, Heck reaction, Claisen & Arbuzov rearrangements, isomerization, hydrogenation, and photochemical reactions, ring closing metathesis, *etc*[13-18] to produce a variety of organic

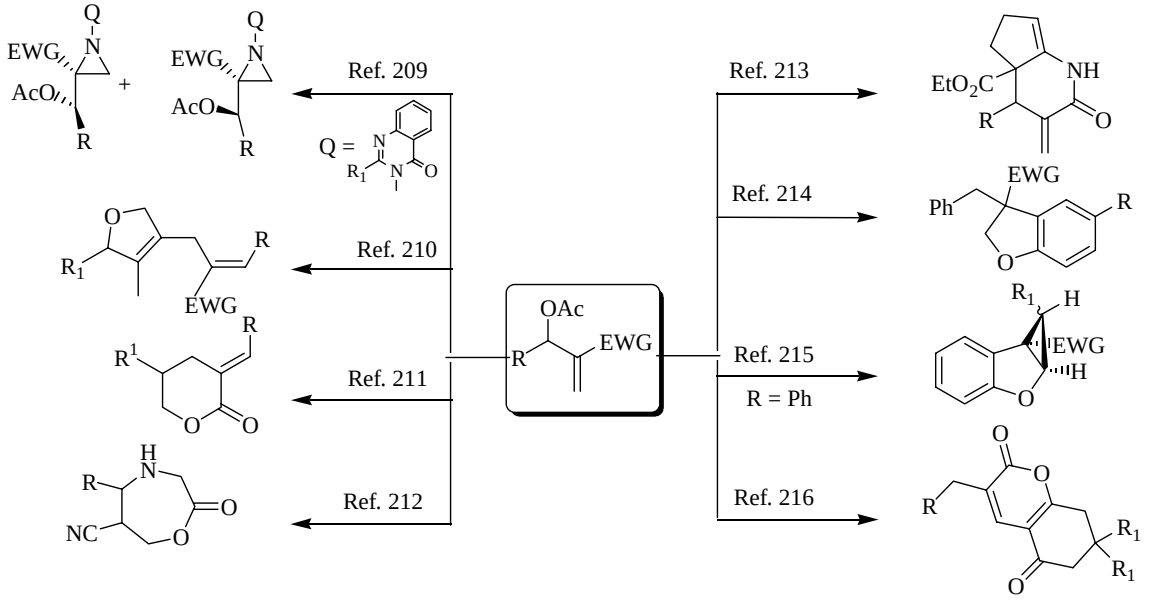
compounds of medicinal relevance. The Baylis-Hillman adducts have also been employed as valuable synthons in the synthesis of several important natural products, biologically active molecules and hetero / carbocycles.[13-18] Some of the interesting, important and recent developments in the applications of these adducts are presented in this section.

Literature survey reveals that Baylis-Hillman alcohols, acetates and bromides have already been successfully utilized for synthesis of various heterocyclic and carbocyclic frameworks. Schematic presentations of some important applications are shown below (Scheme18-20).

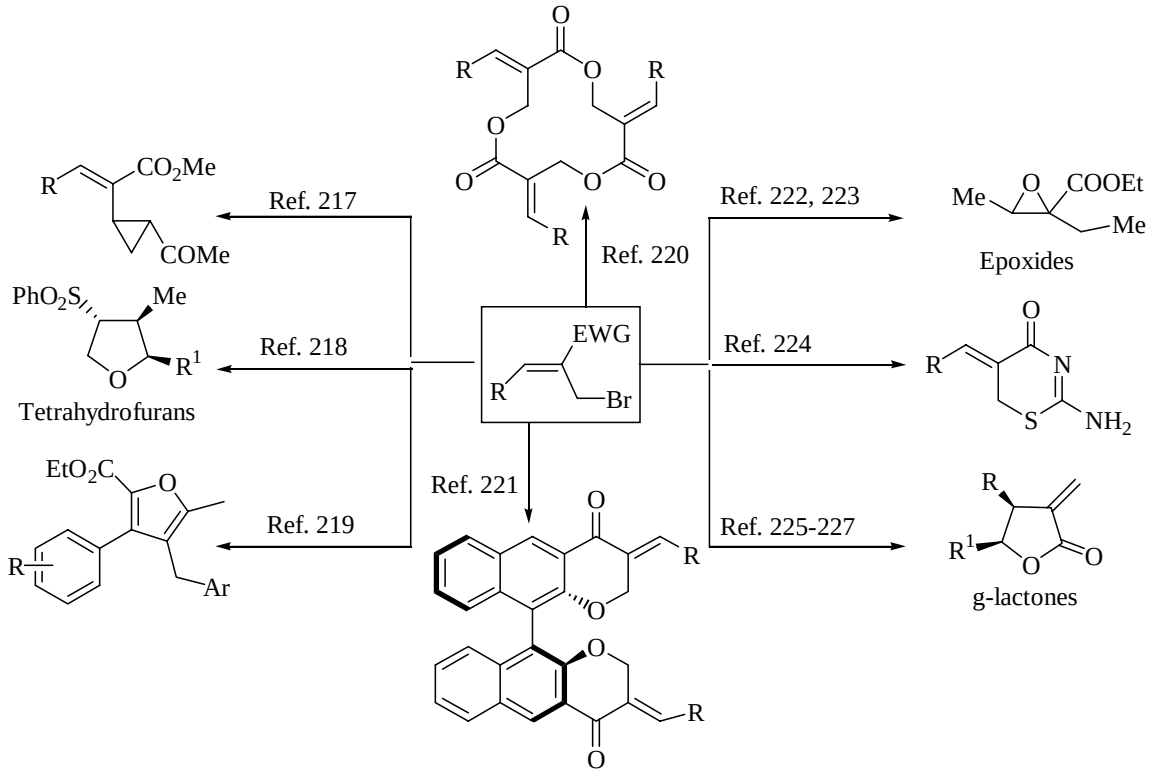
Scheme 18



Scheme 19



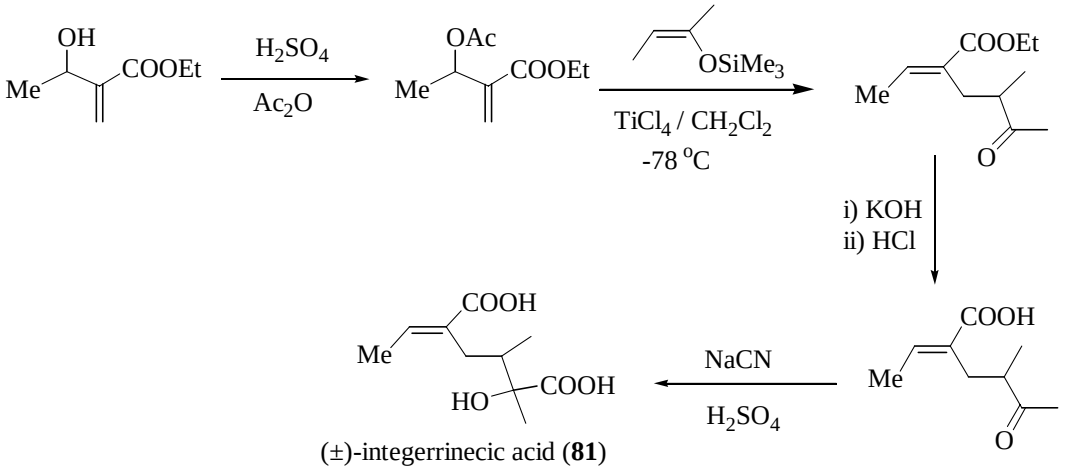
Scheme 20



SYNTHESIS OF NATURAL PRODUCTS AND BIOLOGICALLY ACTIVE COMPOUNDS FROM THE BAYLIS-HILLMAN ADDUCTS

Drewes and coworkers,[34] for the first time, used Baylis-Hillman adduct, ethyl 3-hydroxy-2-methylenebutanoate as the key starting material for synthesis of (±) integerrinecic acid (**81**) an interesting natural product following the reaction sequence as presented in Scheme 21.

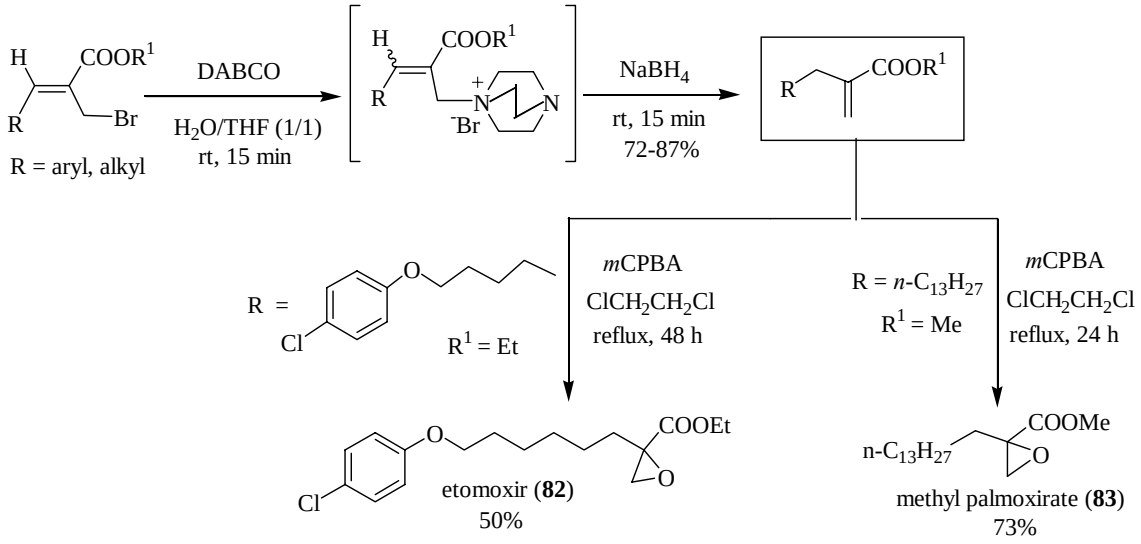
Scheme 21



(±)-integerrinecic acid (**81**)

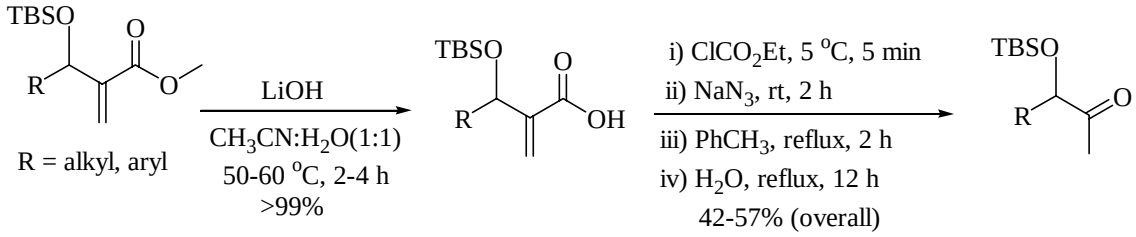
Our research group[228,229] has developed a simple and convenient methodology for the synthesis of 2-methylenealkanoates *via* the treatment of the allyl bromide (derived from Baylis-Hillman alcohol *i.e.,* 3-hydroxy-2-methylenalkanoates) with $NaBH_4$ in the presence of DABCO in aqueous media (Scheme 22). This methodology was successfully applied for the synthesis of two hypoglycemic agents, etomoxir (**82**) and methyl palmoxirate (**83**) (Scheme 22).

Scheme 22

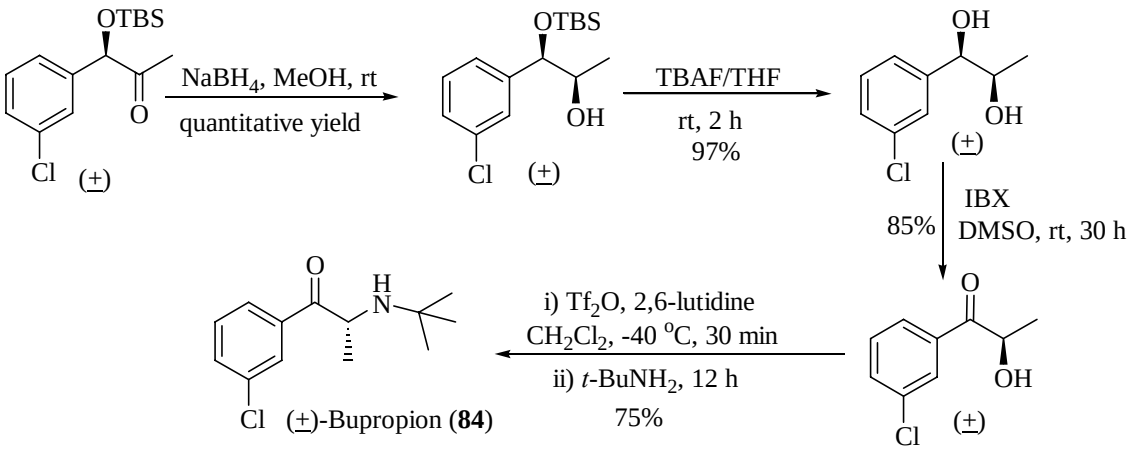


Coelho and coworkers[230] have reported an interesting methodology for synthesis of acyloins (Scheme 23) from the Baylis-Hillman adducts. This methodology has been successfully applied to the total synthesis of (±)-bupropion (**84**), (a potent inhibitor of dopamine reuptake with subtle noradrenergic reuptake and an atypical antidepressant) following the reaction sequence as shown in Scheme 24.

Scheme 23

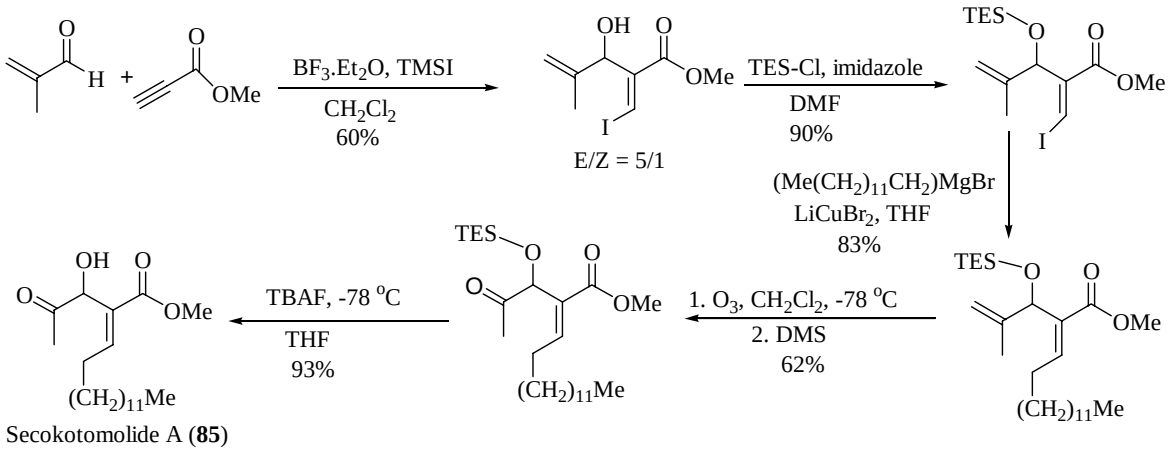


Scheme 24



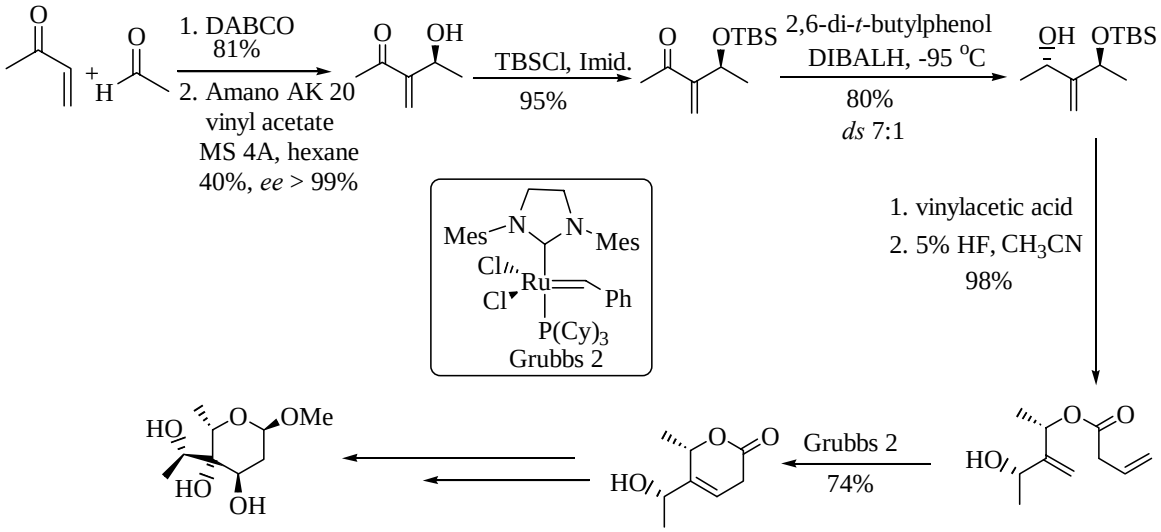
Ryu and coworkers[231] have developed a facile stereoselective methodology for obtaining *β*-iodo Baylis-Hillman esters *via* the treatment of alkylnyl ester with aldehyde in the presence of BF_3-Et_2O and TMSI. This methodology has been successfully utilized for a short synthesis of secokotomolide A (**85**) which was found to induce significant cell death in the human HeLa cell line by apoptotic-related DNA damage (Scheme 25).

Scheme 25



Koert and coworkers[232] have reported a stereoselective synthesis of methyl 7-dihydro-trioxacarcinoside B (**86**) using the Baylis-Hillman adduct derived from acetaldehyde and MVK as the starting materials. This strategy involves kinetic resolution of Baylis-Hillman adduct and ring-closing metathesis as main steps (Scheme 26).

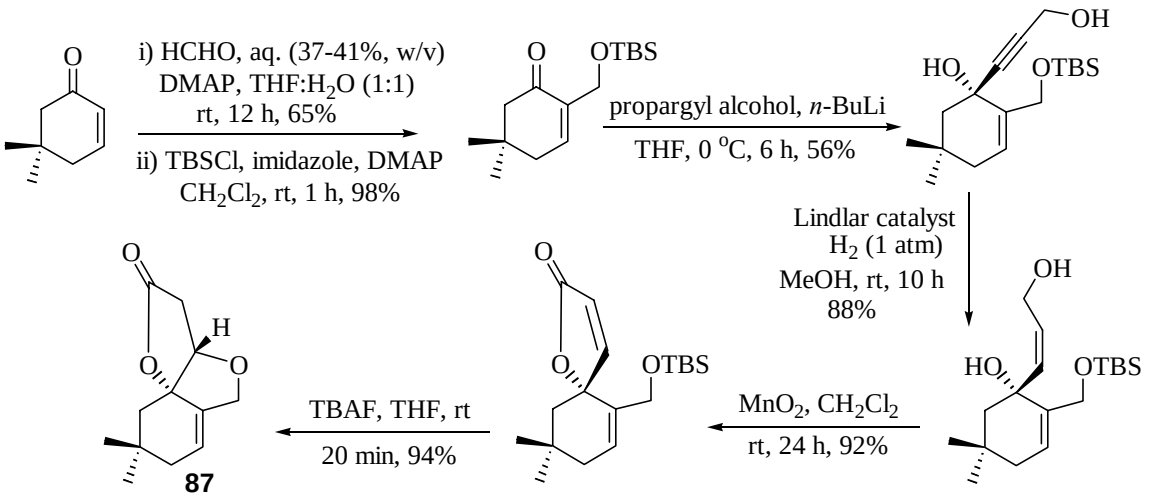
Scheme 26



Methyl 7-dihydro-trioxacarcinoside B(**86**)

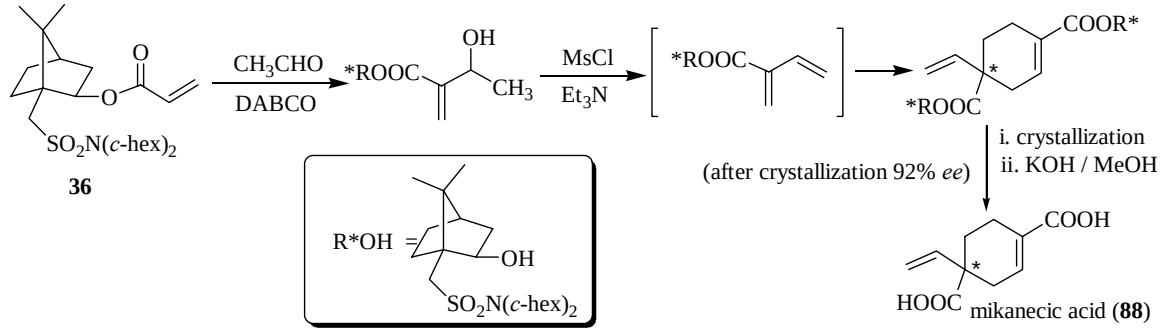
Mehta and Bhat[233] have described a concise and general approach to the tricyclic furo-furan-based core structure (**87**) present in the bioactive natural products neovibsanins A and B, from readily available Baylis-Hillman adducts following the reaction sequence as shown in Scheme 27.

Scheme 27



Our research group[234] has developed a simple enantioselective synthesis of mikanecic acid (**88**), a terpene dicarboxylic acid having a quarternary vinyl chiral centre starting from the Baylis-Hillman adduct derived *via* the reaction of chiral acrylate (**36**) and acetaldehyde, following the reaction sequence as described in Scheme 28.

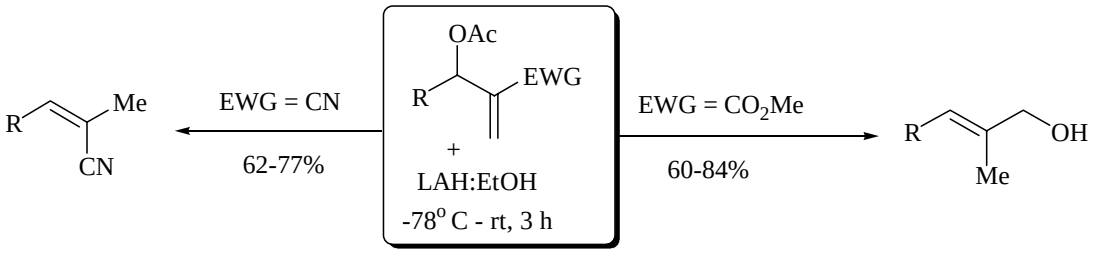
Scheme 28



Our research group[235] has reported a simple stereoselective synthesis of (2*E*)-2-methylalk-2-en-1-ols and (2*Z*)-2-methylalk-2-enenitriles *via* the treatment of acetates of the Baylis-

Hillman adducts (obtained respectively from methyl acrylate and acrylonitrile) with LAH:EtOH (Scheme 29). This methodology has also been successfully used for the synthesis of (*E*)-nuciferol (**89**), a biologically active terpene and **90**, a precursor for (*Z*)-nuciferol (Figure 7).

Scheme 29



R = C_4H_9, C_5H_{11}, C_6H_{13}, C_6H_5, 4-MeC_6H_4, 3-(4-MeC_6H_4)Bu, 4-ClC_6H_4

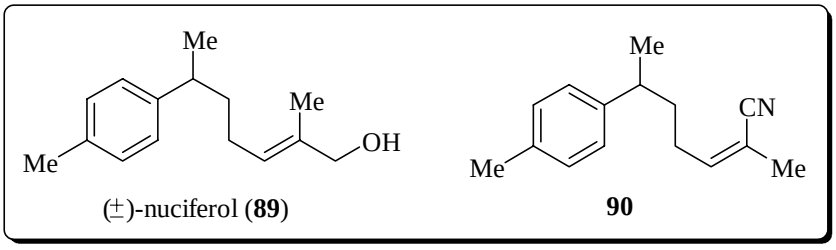
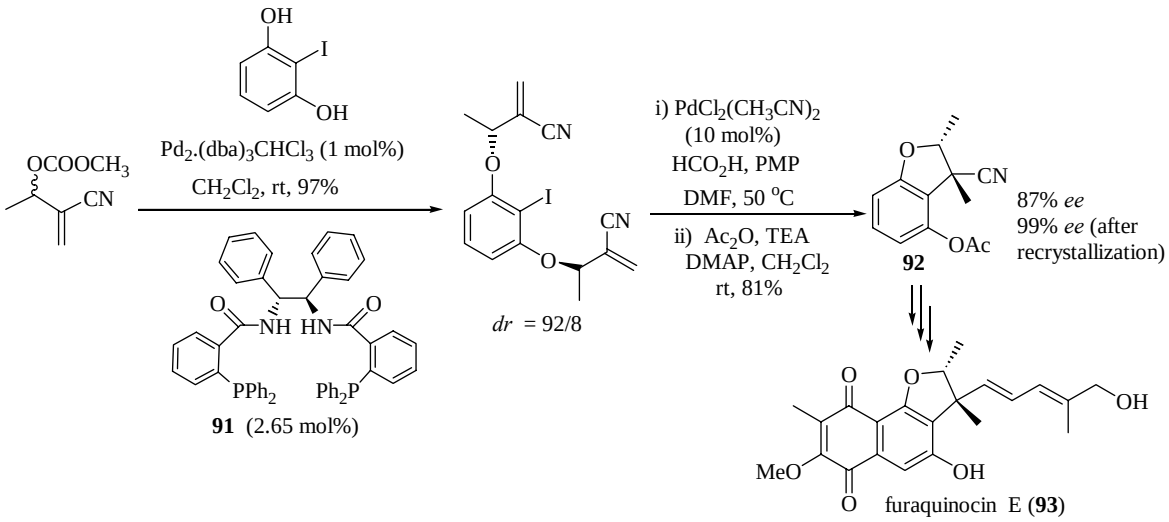


Figure 7

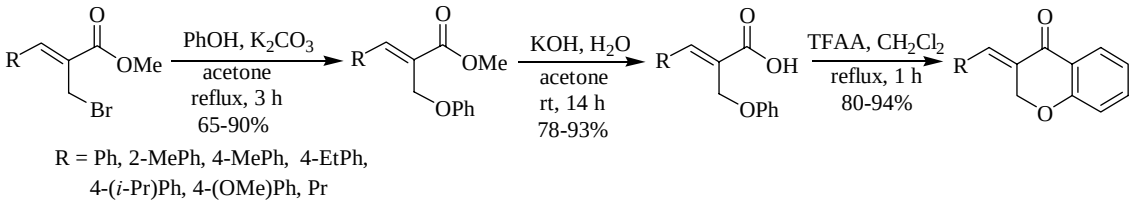
Trost and coworkers[236] have reported elegant deracemization methodology for Baylis-Hillman adducts involving the principle of DYKAT using the chiral ligand **91** in the presence of $(dba)_3Pd_2.CHCl_3$. Subsequently, this methodology has been extended to the synthesis of enantiomerically pure benzo-fused furan derivative **92** which was further transformed into furaquinocin E (**93**) following the reactions as described in Scheme 30.

Scheme 30



Our research group[237] has developed a convenient synthesis of 3-arylidene(alkylidene)-chroman-4-ones, from the Baylis-Hillman bromides, following the reaction sequence as shown in Scheme 31 and has subsequently employed this methodology for the synthesis of bonducellin methyl ether (**94**), an important natural product and 3-(4-methoxybenzylidene)-6-methoxychroman-4-one, an antifungal agent (**95**) (Figure 8).

Scheme 31



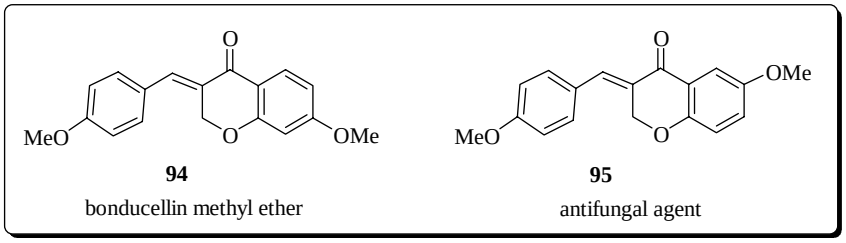
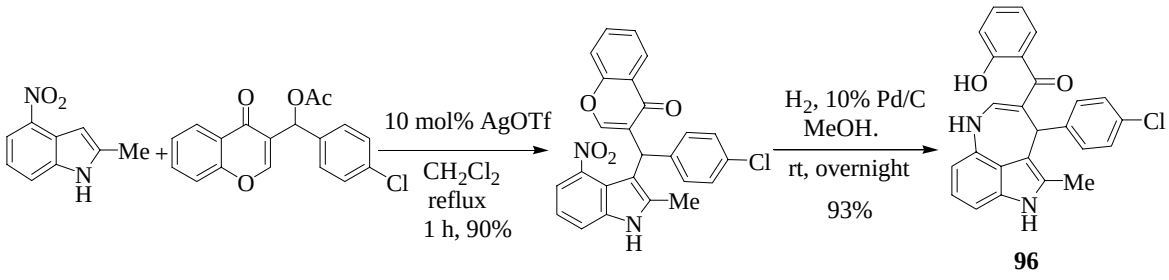


Figure 8

SYNTHESIS OF CARBOCYCLIC AND HETEROCYCLIC COMPOUNDS FROM THE BAYLIS-HILLMAN ADDUCTS

Chen and coworkers[238] have developed a mild and efficient methodology for the synthesis of tricyclic frameworks containing azepene (**96**) moiety *via* the reaction of Baylis-Hillman acetates (obtained by the reaction of chromanone derivatives with aldehydes) with indoles followed by reductive cyclization (and cleavage of C-O bond). One representative example is presented in the Scheme 32.

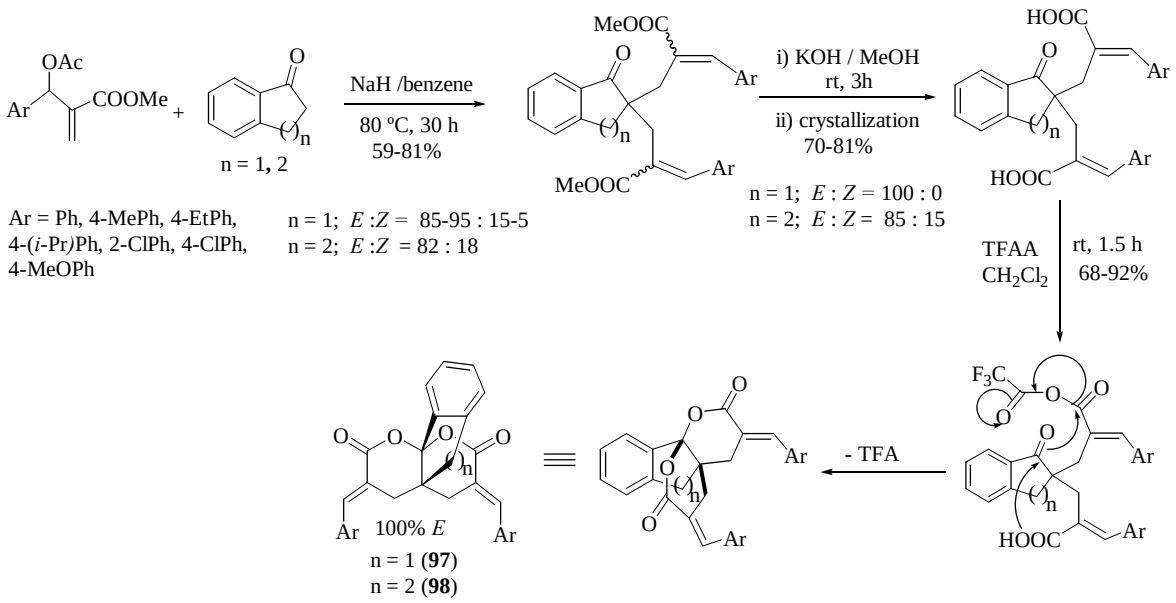
Scheme 32



A simple and convenient three-step synthesis of functionalized [4.4.3] and [4.4.4]propellano-bislactones (**97** & **98**) *via* the reaction of Baylis-Hillman acetates with

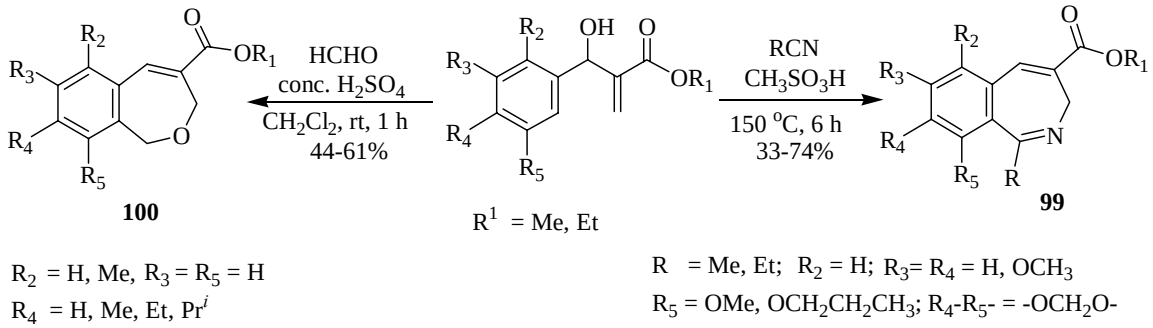
indanone and tetralone respectively following the reaction sequence as shown in Scheme 33 was developed by our research group.[239]

Scheme 33



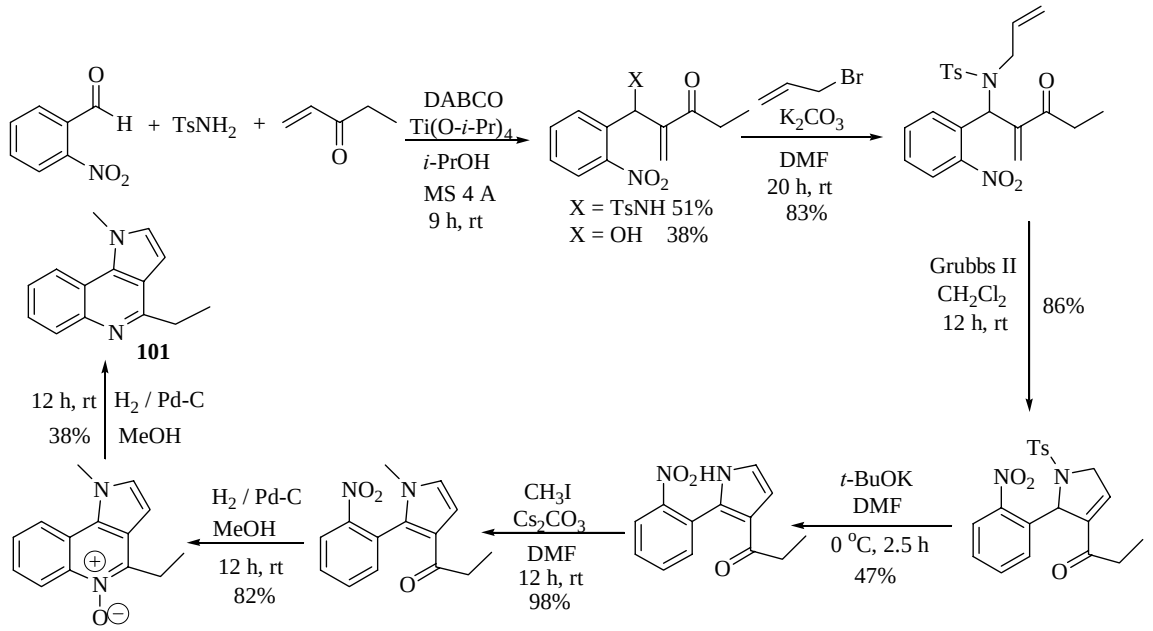
Recently, our group has elegantly transformed the Baylis-Hillman alcohols into 2-benzazepines (**99**) *via* the tandem construction of C-N and C-C bonds involving simultaneous Ritter and Houben-Hoesch reactions as presented in Scheme 34.[240] Subsequently, our research group has also reported a novel one-pot synthesis of 2-benzoxepines (**100**) *via* the reaction of the Baylis-Hillman alcohols with formaldehyde in the presence of H_2SO_4 involving tandem construction of C-O and C-C bonds as shown in the Scheme 34.[241]

Scheme 34



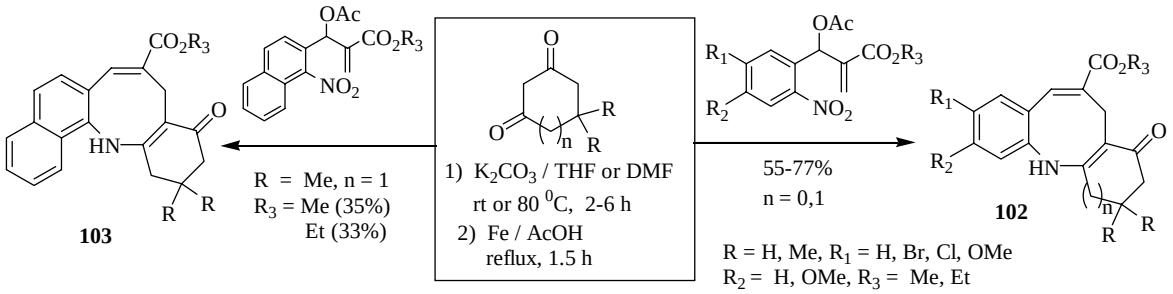
Lamaty and coworkers[242] have developed an efficient synthesis of fused pyrrolo pyridines (**101**) through a sequential Baylis-Hillman reaction, ring closing metathesis and aromatization following the reaction sequence as shown in Scheme 35.

Scheme 35



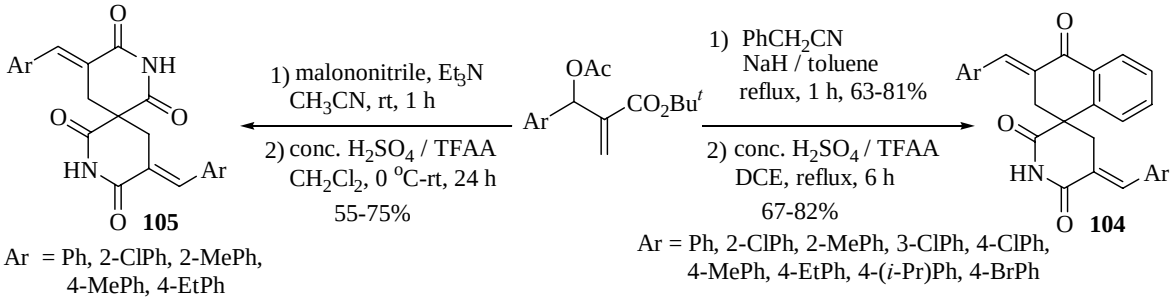
A simple, convenient, and one-pot synthesis of functionalized tri / tetracyclic frameworks (**102** & **103**) containing an important azocine moiety, from the Baylis-Hillman acetates following the reaction sequence presented in Scheme 36 was developed by our research group.[243]

Scheme 36

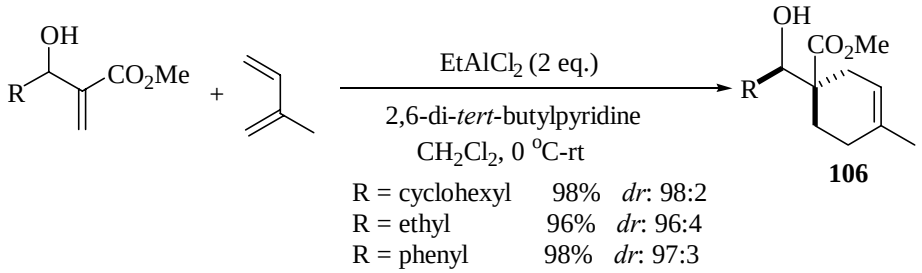


Recently, an interesting synthesis of (*E*)-arylidene-tetralone-spiro-glutarimides (**104**) from the Baylis-Hillman acetates has been reported by our research group *via* biscyclization strategy involving facile C-C and C-N bond formation methodology. Subsequently, the same strategy has been successfully employed to provide di(*E*)-arylidene-spiro-bisglutarimides (**105**) from the Baylis-Hillman acetates (Scheme 37).[244]

Scheme 37



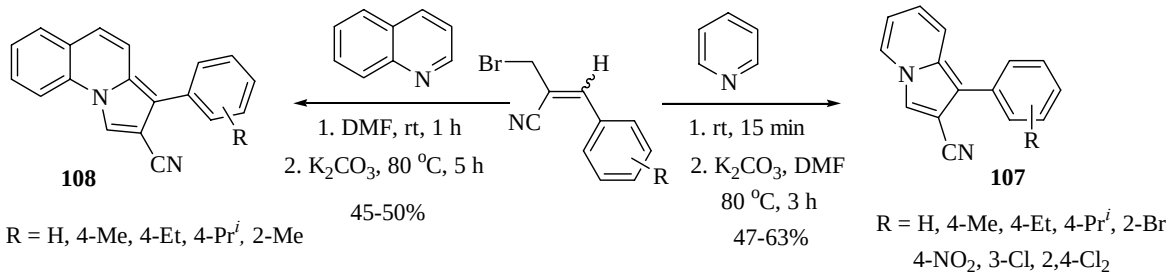
Aggarwal and coworkers[245] have meticulously used the Baylis-Hillman alcohols as excellent dienophiles in Diels-Alder reaction with dienes to provide the corresponding adducts (**106**) with complete diastereocontrol. Representative examples are presented in Eq. 22.



Eq. 22

Recently, our research group[246] has developed a convenient, facile and one-pot procedure for the synthesis of indolizine (**107**) and benzofused indolizine (**108**) from the Baylis-Hillman bromides involving 1,5-cyclization strategy (Scheme 38).

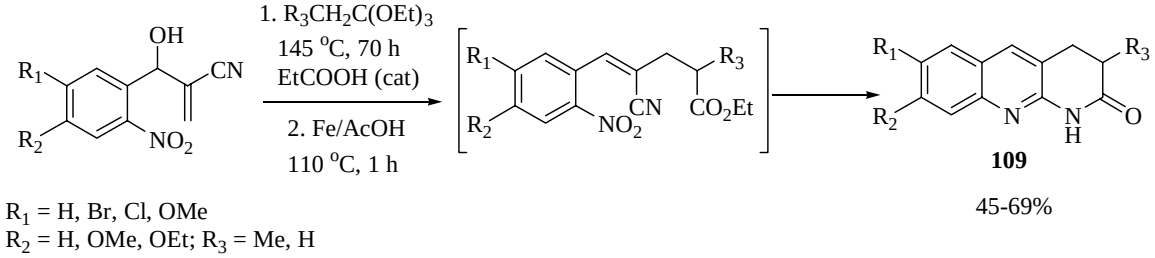
Scheme 38



Very recently, our research group[247] has developed a simple, facile and one-pot procedure for the synthesis of tri and tetracyclic heterocyclic systems containing [1,8]naphthyridin-2-

one framework (**109** & **110**) from the Baylis–Hillman alcohols. Representative examples are presented in Scheme 39 and Eq. 23.

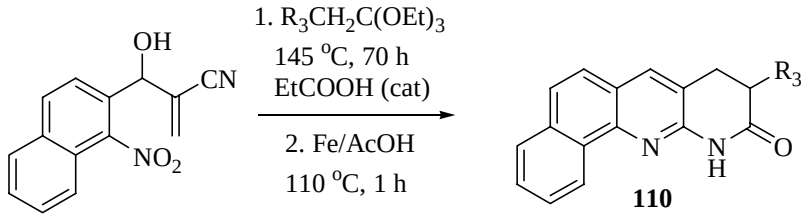
Scheme 39



109

45-69%

R_1 = H, Br, Cl, OMe
R_2 = H, OMe, OEt; R_3 = Me, H



110

R_3 = Me (59%)
H (51%)

Eq. 23

OBJECTIVES, RESULTS AND DISCUSSION

The previous chapter clearly demonstrates that the Baylis-Hillman reaction is a novel atom economical C-C bond forming reaction providing highly functionalized molecules which are of interest due to their remarkable and wide range of applicability in synthesis of various natural products and biologically active compounds. Our research group has been actively working on various aspects of this reaction since past two decades and continues to work with an objective of developing this reaction as a powerful synthetic tool in organic chemistry. This thesis deals with the studies towards understanding the scope of $TiCl_4$-mediated Baylis-Hillman reaction and also towards application of the Baylis-Hillman adducts for synthesis of pyrazole frameworks and has following objectives.

OBJECTIVES

1. To study $TiCl_4$-mediated Baylis-Hillman reaction between *N*-substituted isatins and cycloalk-2-enones with an objective of developing a simple and convenient one-pot methodology for synthesis of 3-(2-hydroxyphenyl)indolin-2-ones.
2. To study $TiCl_4$-mediated Baylis-Hillman reaction between aryl 1,2-diones and cycloalk-2-enones and subsequently to transform the resulting Baylis-Hillman adducts into polycyclic fused furan ring systems.
3. To develop a novel and facile methodology for the synthesis of functionalized dihydropyrazole derivatives using the Baylis-Hillman bromides as 1,3-dipoles for

cycloaddition with dialkyl azodicarboxylates, as dipolarophiles *via* [3 + 2] annulation strategy.

4. To develop a simple methodology for the synthesis of spiro-oxindole derivatives containing spiro-fused 1,2-bisalkoxycarbonyl-1*H*-pyrazole framework using the allyl bromides of Baylis-Hillman alcohols, derived from isatin derivatives and alkyl acrylates, as 1,3-dipoles for [3 + 2] annulation reaction with dialkyl azodicarboxylates, as dipolarophiles.

RESULTS AND DISCUSSION

A simple and convenient one-pot synthesis of 3-(2-hydroxyphenyl) indolin-2-ones using Baylis-Hillman protocol

3-Aryloxindole framework is an important structural skeleton present in various biologically active compounds (Figure 9). For example, compound **111** (SM-130686) was found to be ghrelin (ligand for growth hormone) secretagogue receptor (GHS-R),[248,249] while compounds **112** (BMS-204352) and **113** are known to be maxi-K channel openers with neuroprotective properties.[250,251]

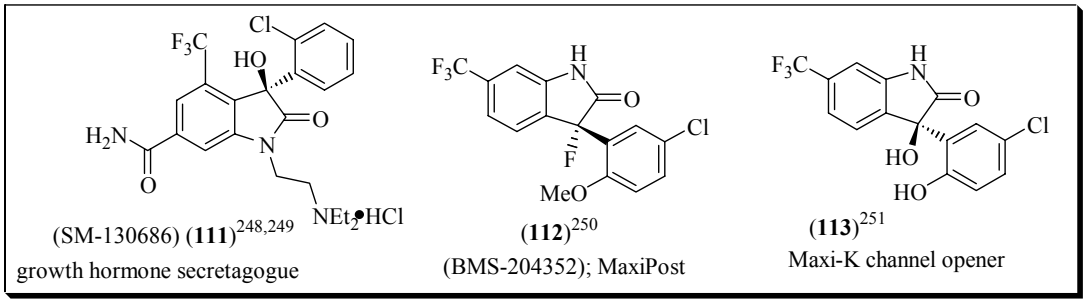
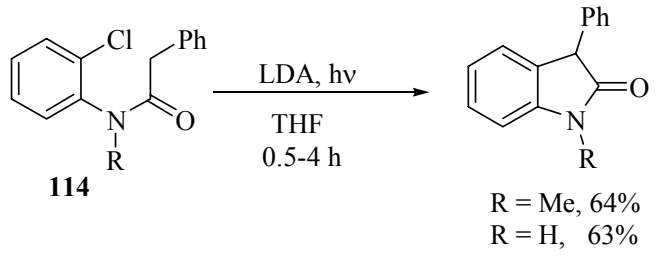


Figure 9

Because of these biological properties of 3-arylindolin-2-one derivatives, development of simple and convenient methodologies for synthesis of this framework with different substitution profiles has been and continues to be a challenging endeavor in organic and medicinal chemistry. Several synthetic strategies have been reported for synthesis of indolin-2-one derivatives in the literature. Some recent and important methods for the construction of indolin-2-ones are presented in this section.

Wolfe and coworkers[252] have reported an interesting synthesis of 3-phenylindolin-2-ones from *N*-acyl-*N*-alkyl-*o*-chloroanilines (**114**) *via* the treatment with LDA in THF followed by irradiation with near-UV light. Representative examples are presented in Eq. 24.



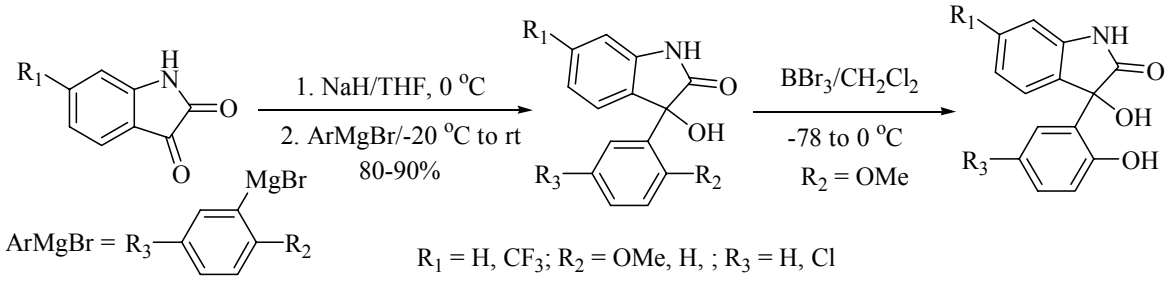
114

R = Me, 64%
R = H, 63%

Eq. 24

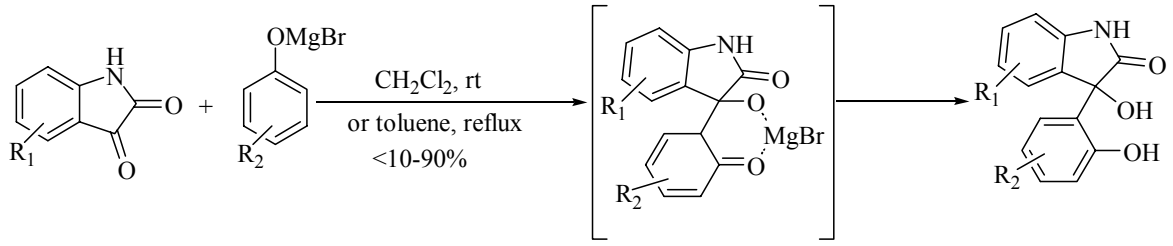
Hewawasam and coworkers[253] have reported a two step synthesis of 3-(2-hydroxyaryl)indolin-2-ones *via* the addition of an aryl Grignard reagent to sodium salt of isatin derivatives (followed by treatment with BBr_3) following the reaction sequence as shown in Scheme 40.

Scheme 40



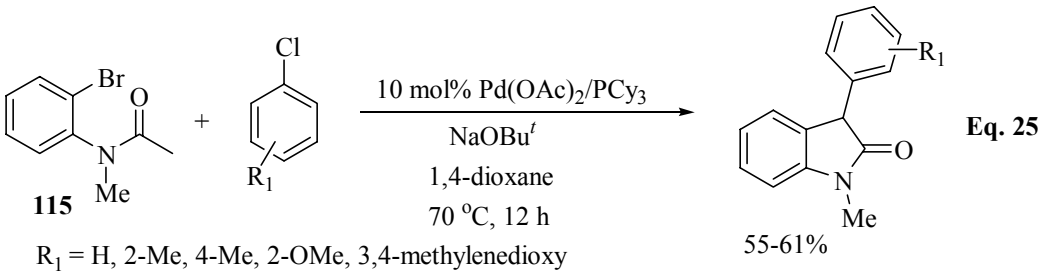
Subsequently, a simple and efficient one-step procedure for obtaining regiospecifically functionalized 3-(2-hydroxyaryl)indolin-2-ones from isatins and magnesium phenolates was also developed by the same research group (Scheme 41).[254]

Scheme 41



R_1 = H, 6-CF_3, 5-OMe, 5-NO_2, 6-I, 5-I, 4-I, 6,7-benzo;
R_2 = H, 4-OMe, 4-Me, 4-Ph, 4-Cl, 3-Cl, 3,5-Cl_2, 4-Cl, 2-F,
4-CF_3, 4-piperazine, 4-I, 3-OMe, 3-NH_2, 2-Cl, naphth-2-yl

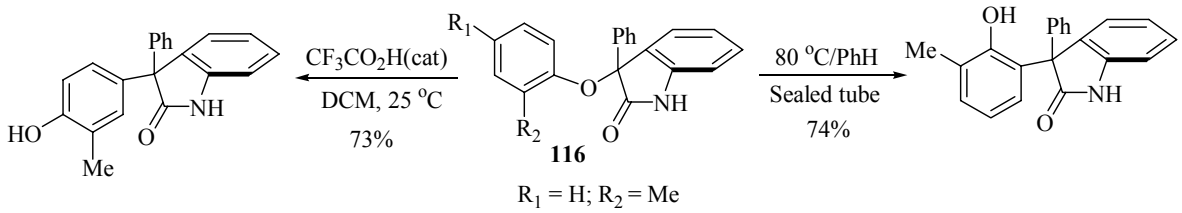
Hartwig and coworkers[255] have described a facile synthesis of 3-arylindolin-2-ones *via* tandem intra- and intermolecular arylation reactions of amide (**115**) under the catalytic influence of palladium acetate. Representative examples are presented in Eq. 25.



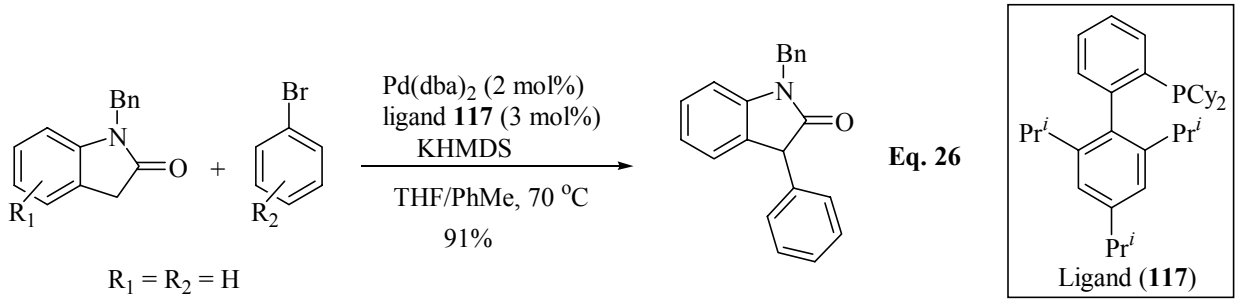
Eq. 25

Magnus and coworkers[256] have reported facile synthesis of 3-(2-hydroxyaryl)indolin-2-ones *via* a mild thermal and acid-catalyzed unusual rearrangement of *O*-aryl ethers (**116**). One example is presented in Scheme 42.

Scheme 42



Willis and Durbin[257] have described a simple synthesis of 3-arylindolin-2-ones *via* C-3 arylation of indolin-2-ones under the influence of palladium catalyst and bulky electron-rich phosphine ligand (**117**). One example is presented in Eq. 26.

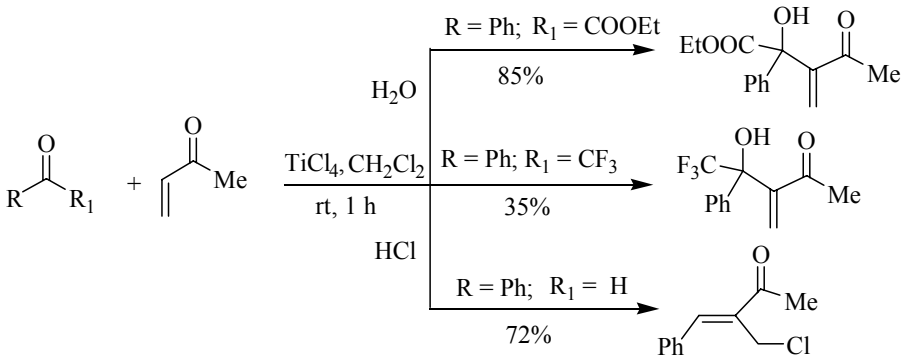


Eq. 26

Present study:

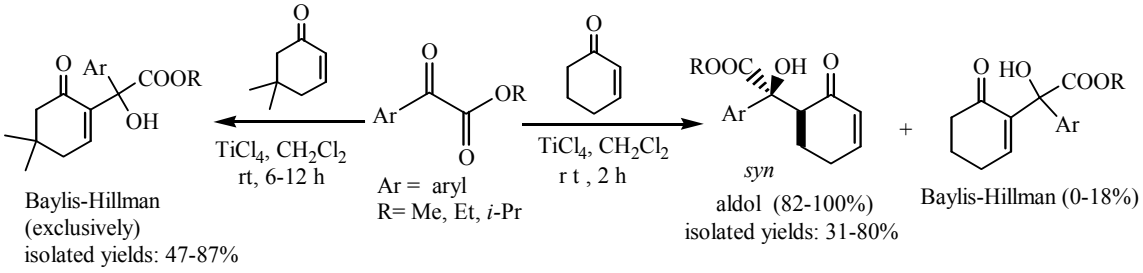
Sometime ago our research group[122] has developed titanium tetrachloride mediated Baylis-Hillman reaction of alkyl vinyl ketones with various electrophiles such as aromatic aldehydes, α-keto esters & fluoro ketones (Scheme 43).

Scheme 43

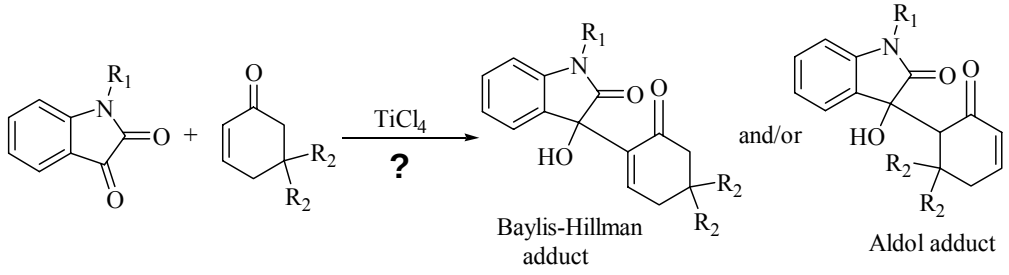


Subsequently, our research group[258] has also demonstrated the role of steric factors in directing the $TiCl_4$-mediated reaction of α-keto esters with cyclohex-2-enone derivatives. Thus cyclohex-2-enone provided the corresponding aldol adducts with high *syn*-diastereoselectivities as major product (along with the Baylis-Hillman adducts as the minor products) whereas the similar reaction of α-keto esters with 5,5-dimethylcyclohex-2-enone furnished the corresponding Baylis-Hillman adducts exclusively (Scheme 44).

Scheme 44

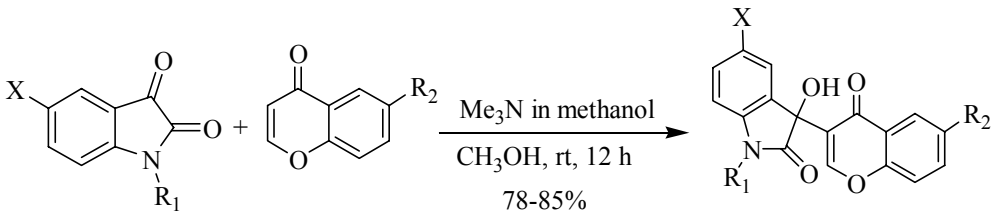


Since *N*-substituted isatin derivatives (cyclic α-keto amides) resemble the α-keto esters it occurred to us that it will be interesting to study the role of steric factors in directing the $TiCl_4$-mediated reaction of isatin derivatives with cyclohex-2-enone derivatives (in Baylis-Hillman fashion and/or in aldol fashion) (Eq. 27).



Eq. 27

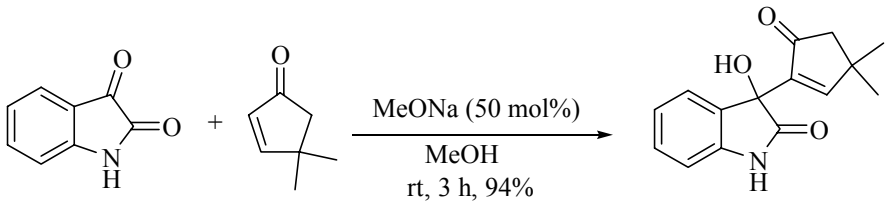
Literature survey reveals that the $TiCl_4$-mediated Baylis-Hillman reaction between isatin derivatives and cycloalk-2-enones is not yet explored. Our research group, for the first time, used 1-benzopyran-4(4*H*)-one derivatives as activated alkenes in the Baylis-Hillman reaction with isatin derivatives under the influence of methanolic trimethylamine to provide the corresponding Baylis-Hillman adducts in good yields (Eq. 28).[71]



$R_1 = CH_3, CH_2Ph, H$
$R_2 = H, CH_3$
$X = H, NO_2$

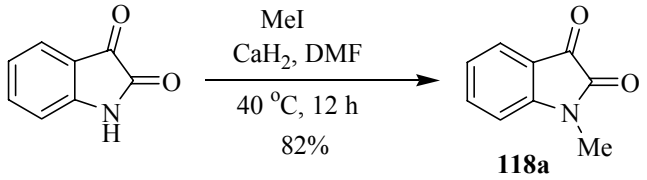
Eq. 28

Cheng and coworkers[138] have reported sodium methoxide catalyzed Baylis-Hillman reaction between isatin and substituted cyclopent-2-enone to afford the resulting adduct in excellent yield (Eq. 29).



Eq. 29

With a view to understand the scope of $TiCl_4$-mediated Baylis-Hillman reaction we have first selected 1-methylisatin (**118a**) and cyclohex-2-enone as reaction partners. The required 1-methylisatin (**118a**) was obtained *via* the reaction between isatin and methyl iodide in the presence of CaH_2 in DMF following the literature procedure (Eq. 30).[259]

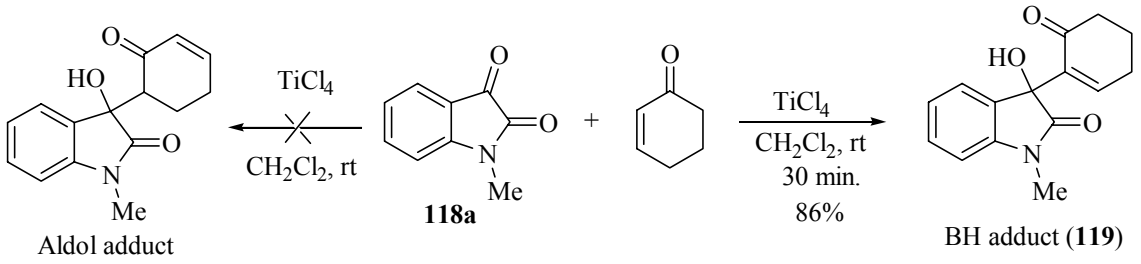


118a

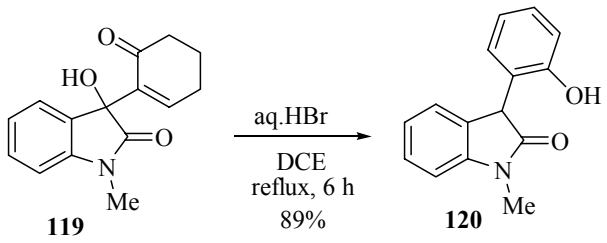
Eq. 30

We have then examined the reaction between 1-methylisatin (**118a**) and cyclohex-2-enone under the influence of $TiCl_4$ and we were pleased to notice the formation of only Baylis-Hillman adduct and complete absence of any aldol product (scheme 45). Thus the best result in this reaction was obtained when 1-methylisatin (**118a**, 1 mmol) was treated with cyclohex-2-enone (1 mmol) in the presence of $TiCl_4$ (1 mmol) at room temperature (25-28 ^oC) for 30 minutes to provide the corresponding Baylis-Hillman (B-H) alcohol, 3-hydroxy-3-(cyclohex-2-enon-2-yl)-1-methylindolin-2-one (**119**) in 86% isolated yield (scheme 45) after usual work-up followed by column chromatography (silica gel, 60% ethyl acetate in hexanes). The structure of this Baylis-Hillman alcohol **119** is in agreement with IR, ^1H NMR (Spectrum 1), ^{13}C NMR (Spectrum 2), mass spectral data and elemental analysis.

Scheme 45



Since the product is allylic alcohol which has the potential to undergo dehydration under acidic conditions leading to aromatization, it occurred to us that the longer reaction time might provide the expected phenolic derivative. Accordingly we continued the reaction for 4 h at room temperature. But we did not obtain the expected 3-(2-hydroxyphenyl)-1-methylindolin-2-one (**120**). During our efforts in achieving aromatization we noticed that the treatment of **119** with aq. HBr, in dichloroethane (DCE) at reflux temperature for 6 h, provided the required aromatized compound **120** in 89% isolated yield (Eq. 31). The structure of this product (**120**) is in agreement with IR, ^{1}H NMR (Spectrum 3), ^{13}C NMR (Spectrum 4), mass spectral data and elemental analysis.

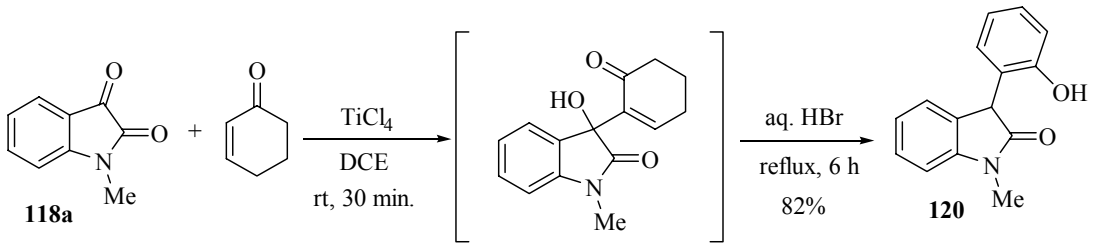


Eq. 31

Encouraged by this excellent result, we felt that if these two steps can be performed in one-pot without isolating the B-H alcohol this strategy would lead to a very simple and practical procedure for conversion of isatin derivatives into 3-(2-hydroxyphenyl)indolin-2-one derivatives *via* the Baylis-Hillman protocol. In these efforts the best result was

obtained when 1-methylisatin (**118a**, 1 mmol) was treated with cyclohex-2-enone (1 mmol) in the presence of $TiCl_4$ (1 mmol) in dichloroethane at room temperature (25-28 ^oC) for 30 min followed by the treatment of the resulting reaction mixture with aq. HBr (5 mmol) at reflux temperature for 6 h, thus providing the desired 3-(2-hydroxyphenyl)-1-methylindolin-2-one (**120**) in 82% isolated yield (Scheme 46) after usual work-up followed by column chromatography (silica gel, 30% ethyl acetate in hexanes). Spectral data (IR, ^1H NMR, ^{13}C NMR, LCMS), elemental analysis are in complete agreement with the product **120** obtained *via* the two step procedure.

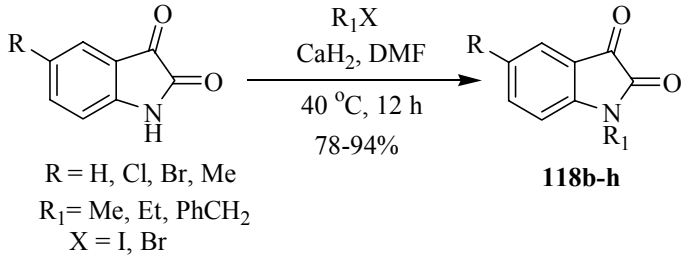
Scheme 46



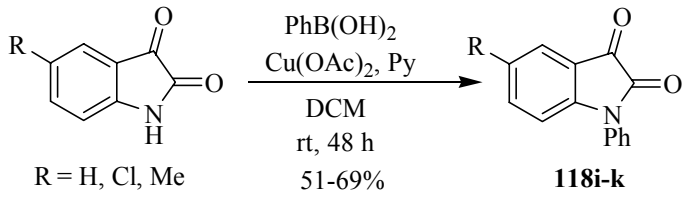
We were indeed pleased by this encouraging result as this provides a simple methodology for a facile conversion of the isatin derivative into the corresponding 3-(2-hydroxyphenyl)indolin-2-one derivative.

To understand the generality of this methodology we have employed various *N*-substituted isatins (**118b-k**) for the reaction with cyclohex-2-enone. The *N*-substituted isatin derivatives (**118b-h**) were prepared *via* the reaction of commercially available isatins with the corresponding alkyl halides in the presence of CaH_2 in DMF (Eq. 32).[259] *N*-Phenyl isatin derivatives (**118i-k**) were prepared *via* the treatment of isatin derivatives with phenyl

boronic acid under the influence of cupric acetate and pyridine, according to the known procedure (Eq. 33).[260]



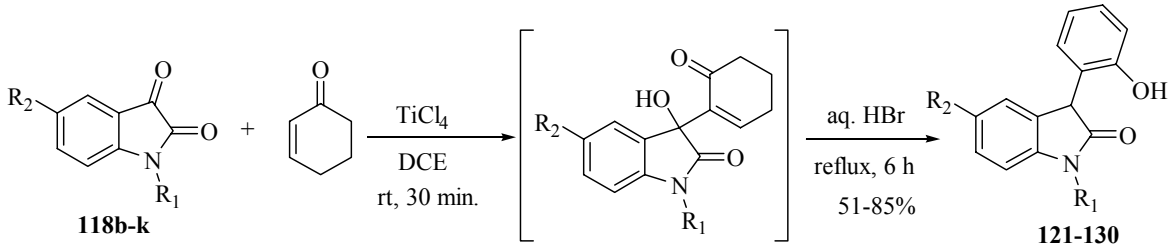
Eq. 32



Eq. 33

We have subjected these isatin derivatives (**118b-k**) for the Baylis-Hillman coupling with cyclohex-2-enone in the presence of $TiCl_4$ in dichloroethane at room temperature followed by treatment of the *in situ* generated Baylis-Hillman alcohols with aq. HBr (48%) at reflux temperature to obtain 3-(2-hydroxyphenyl)indolin-2-one derivatives (**121-130**) in 51-85% isolated yields (Scheme 47, Table 1). The structures of 3-(2-hydroxyphenyl)indolin-2-one derivatives (**121-130**) are in full agreement with IR, ^{1}H NMR (Spectra 5 & 7 for compounds **126** & **130** respectively), ^{13}C NMR (Spectra 6 & 8 for compounds **126** & **130** respectively), mass spectral data and elemental analyses. Structures of **121**, **124** and **126** were further established by single crystal X-ray data analysis (Figure X1-X3, Table I-III).

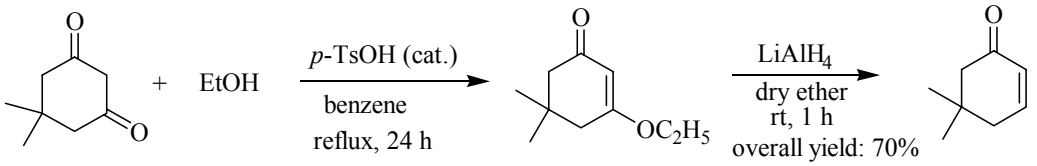
Scheme 47



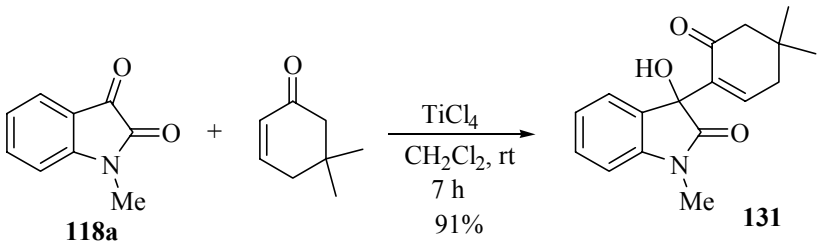
R_1 = Me, Et, $PhCH_2$, Ph
R_2 = H, Cl, Br, Me

We have also directed our studies towards the Baylis-Hillman reaction of 1-methylisatin (**118a**) and 5,5-dimethylcyclohex-2-enone in the presence of $TiCl_4$. 5,5-Dimethylcyclohex-2-enone was prepared according to the known procedure from 5,5-dimethyl-1,3-cyclohexanedione (Scheme 48).[261]

Scheme 48

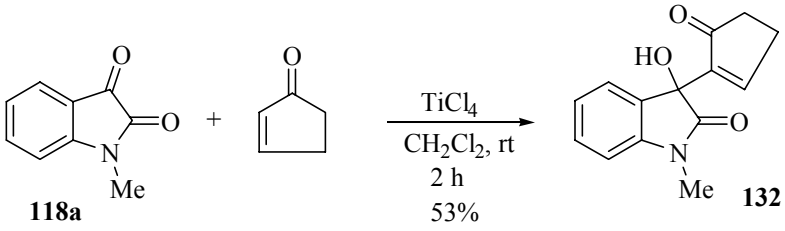


We have subjected 5,5-dimethylcyclohex-2-enone (1 mmol) to the reaction with 1-methylisatin (**118a**, 1 mmol) in the presence of $TiCl_4$ (1 mmol) in dichloromethane at room temperature for 7 h. The resulting Baylis-Hillman adduct 3-hydroxy-3-(5,5-dimethylcyclohex-2-enon-2-yl)-1-methylindolin-2-one (**131**) was obtained in 91% isolated yield (Eq. 34). The structure of this Baylis-Hillman adduct **131** is in agreement with IR, ^{1}H NMR, ^{13}C NMR, mass spectral data and elemental analysis.



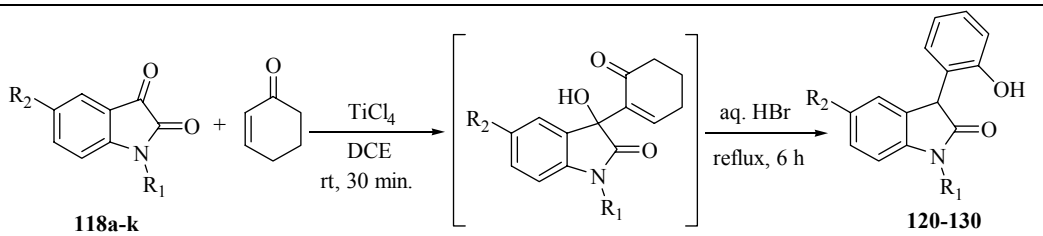
Eq. 34

Similar reaction of cyclopent-2-enone (1 mmol) with 1-methylisatin (**118a**, 1 mmol) in the presence of $TiCl_4$ (1 mmol) in dichloromethane at room temperature for 2 h furnished the corresponding Baylis-Hillman adduct, 3-hydroxy-3-(cyclopent-2-enon-2-yl)-1-methyl-indolin-2-one (**132**), in 53% isolated yield (Eq. 35). The structure of Baylis-Hillman adduct **132** is in agreement with IR, ^{1}H NMR, ^{13}C NMR, mass spectral data and elemental analysis.



Eq. 35

Table 1: Synthesis of 3-(2-hydroxyphenyl)indolin-2-ones (**120-130**)[a]



118a-k **120-130**

Entry	R_1	R_2	isatin	product[b]	mp (^oC)	yield (%)[c]
1	Me	H	**118a**	**120**	150-152	82
2	Me	Cl	**118b**	**121**[d]	186-188	76
3	Et	H	**118c**	**122**	126-128	83
4	Et	Cl	**118d**	**123**	187-189	59
5	CH_2Ph	H	**118e**	**124**[d]	147-148	65
6	CH_2Ph	Cl	**118f**	**125**	158-161	77
7	CH_2Ph	Br	**118g**	**126**[d]	179-180	63
8	CH_2Ph	Me	**118h**	**127**	101-103	85
9	Ph	H	**118i**	**128**	125-127	55
10	Ph	Cl	**118j**	**129**	128-130	51
11	Ph	Me	**118k**	**130**	174-175	54

a) All the reactions were carried out on 1 mmol scale of isatins (**118a-k**) with cyclohex-2-enone in presence of $TiCl_4$ (1 mmol) at room temperature (25-28 ^oC) followed by the treatment with aq. HBr (5 mmol) in dichloroethane at reflux temperature.

b) All the compounds were isolated as solids and fully characterized.

c) Isolated yields based on the isatins (**118a-k**).

d) Structures of the compounds **121**, **124** and **126** were further confirmed by single crystal X-ray data analysis.

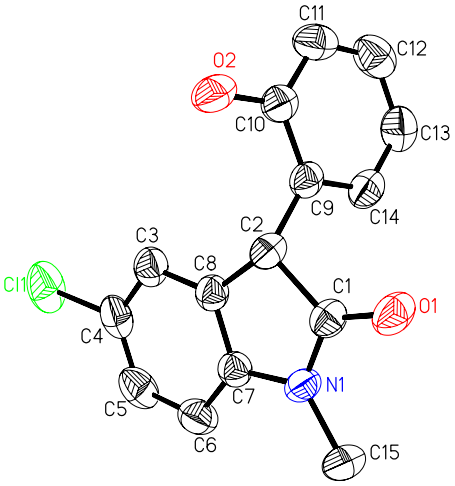


Figure X1

ORTEP diagram of the compound **121**
(Hydrogen atoms were omitted for clarity)

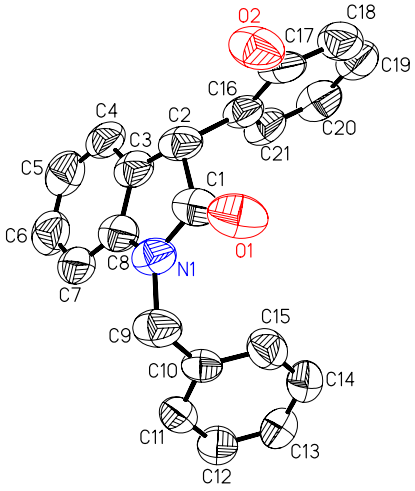


Figure X2

ORTEP diagram of the compound **124**
(Hydrogen atoms were omitted for clarity)

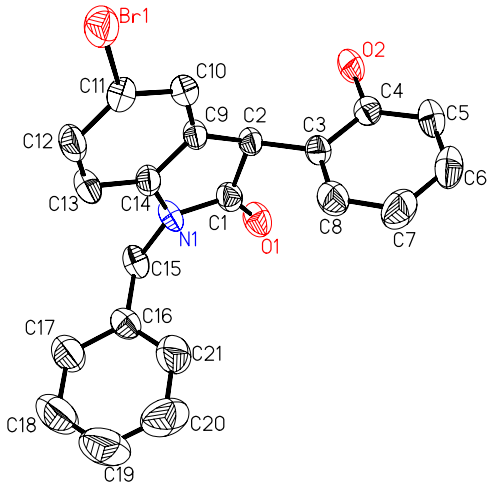


Figure X3

ORTEP diagram of the compound **126**
(Hydrogen atoms were omitted for clarity)

We have thus demonstrated for the first time, the $TiCl_4$-mediated Baylis-Hillman reaction of *N*-substituted isatins with cycloalk-2-enones and also developed a facile one-pot methodology for transformation of *N*-substituted isatins into 3-(2-hydroxyphenyl)indolin-2-one derivatives *via* the Baylis-Hillman protocol.

Table I. Crystal data and structure refinement for **121.**

Empirical formula	$C_{15}H_{12}ClNO_2$
Formula weight	273.71
Temperature	298 K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 10.132(3) Å; α = 101.957(5) deg.
	b = 10.298(3) Å; β = 95.847(5) deg.
	c = 14.543(4) Å; γ = 114.244(5) deg.
Volume	1323.5 (7) $Å^3$
Z, Calculated density	4, 1.374 Mg/m^3
Absorption coefficient	0.285 mm^{-1}
F(000)	568
Crystal size	0.30 x 0.20 x 0.12 mm
Theta range for data collection	1.46 to 25.00 deg.
Limiting indices	$-12\leq h\leq 12$, $-12\leq k\leq 12$, $-17\leq l\leq 17$
Reflections collected / unique	12842 / 4639 [R(int) = 0.0310]
Completeness to theta = 25.00	99.7%
Absorption correction	Multi-scan method (SADABS)
Max. and min. transmission	0.9666 and 0.9194
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4639 / 0 / 353
Goodness-of-fit on F^2	1.035
Final R indices [I>2sigma(I)]	R1 = 0.0436, wR2 = 0.1002
R indices (all data)	R1 = 0.0633, wR2 = 0.1117
Largest diff. peak and hole	0.202 and -0.217 e. $Å^{-3}$

Table II. Crystal data and structure refinement for **124.**

Empirical formula	$C_{21}H_{17}NO_2$
Formula weight	315.36
Temperature	298 K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 11.102(8) Å; α = 89.327(13) deg.
	b = 12.101(8) Å; β = 78.942(13) deg.
	c = 12.537(9) Å; γ = 84.167(13) deg.
Volume	1644.5(19) $Å^3$
Z, Calculated density	4, 1.261 Mg/m^3
Absorption coefficient	0.081 mm^{-1}
F(000)	664
Crystal size	0.22 x 0.13 x 0.09 mm
Theta range for data collection	1.66 to 25.17 deg.
Limiting indices	$-13\leq h\leq 13$, $-14\leq k\leq 14$, $-14\leq l\leq 14$
Reflections collected / unique	15056 / 5809 [R(int) = 0.0834]
Completeness to theta = 25.17	98.6 %
Absorption correction	Multi-scan method (SADABS)
Max. and min. transmission	0.9927 and 0.9824
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5809 / 0 / 441
Goodness-of-fit on F^2	0.942
Final R indices [I>2sigma(I)]	R1 = 0.0664, wR2 = 0.1339
R indices (all data)	R1 = 0.1835, wR2 = 0.1807
Largest diff. peak and hole	0.183 and -0.219 e. $Å^{-3}$

Table III. Crystal data and structure refinement for **126.**

Empirical formula	$C_{21}H_{16}BrNO_2$
Formula weight	394.26
Temperature	298 K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 8.024(3) Å; α = 101.870(7) deg.
	b = 10.882(4) Å; β = 105.925(7) deg.
	c = 11.554(4) Å; γ = 102.388(7) deg.
Volume	909.2(6) $Å^3$
Z, Calculated density	2, 1.438 Mg/m^3
Absorption coefficient	2.270 mm^{-1}
F(000)	400
Crystal size	0.40 x 0.15 x 0.05 mm
Theta range for data collection	1.91 to 24.99 deg.
Limiting indices	$-9\leq h\leq 9$, $-12\leq k\leq 12$, $-13\leq l\leq 13$
Reflections collected / unique	8713 / 3191 [R(int) = 0.0432]
Completeness to theta = 24.99	99.5 %
Absorption correction	Multi-scan method (SADABS)
Max. and min. transmission	0.8949 and 0.4637
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3191 / 0 / 230
Goodness-of-fit on F^2	1.240
Final R indices [I>2sigma(I)]	R1 = 0.0658, wR2 = 0.1348
R indices (all data)	R1 = 0.0792, wR2 = 0.1404
Largest diff. peak and hole	0.569 and -0.333 e. $Å^{-3}$

Development of a facile methodology for synthesis of polycyclic fused furans using the Baylis-Hillman adducts

Polycyclic fused furan framework is a vital part of several biologically active compounds (**133-135**)[262-264] and natural products,[265-268] such as Popolohuanone E (**136**),[265] Galanthamine (**137**),[266] Bisabosqual A (**138**)[267] (Figure 10) *etc*. Natural product **139**[268] was isolated from the mangrove plant *aegiceras corniculatum* (Figure 10). The biological importance of polyfused furans demands the development of efficient methodologies for obtaining such derivatives. Some recent relevance literature efforts are presented in this section.

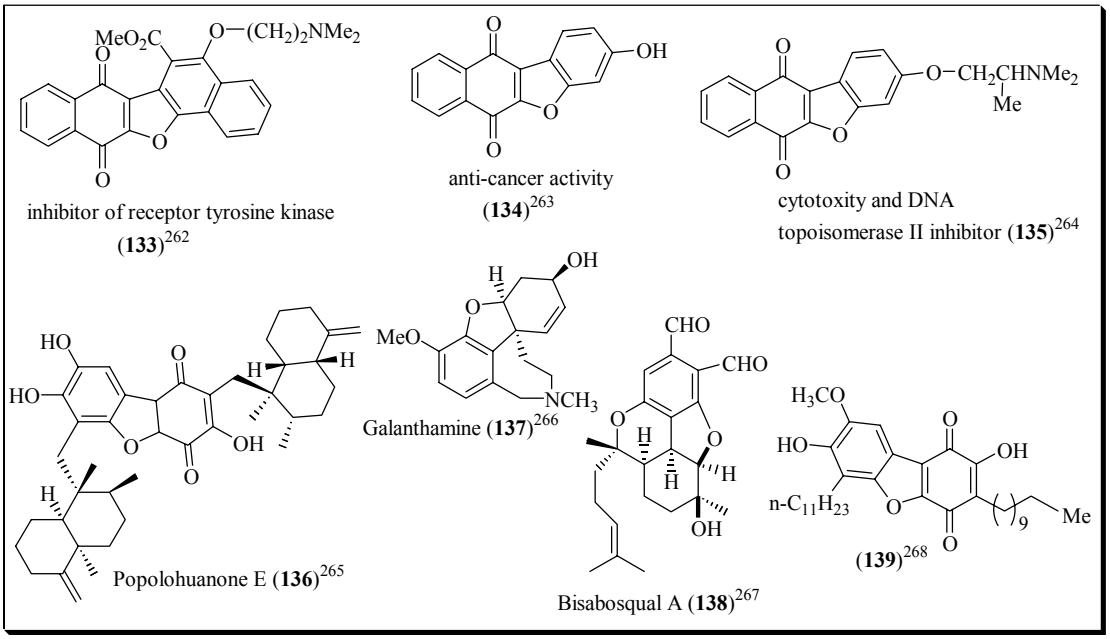
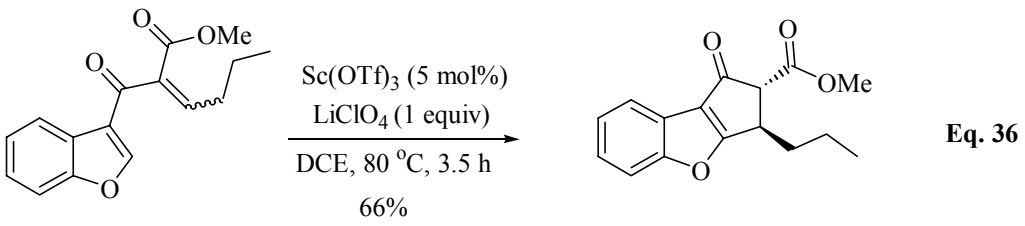


Figure 10

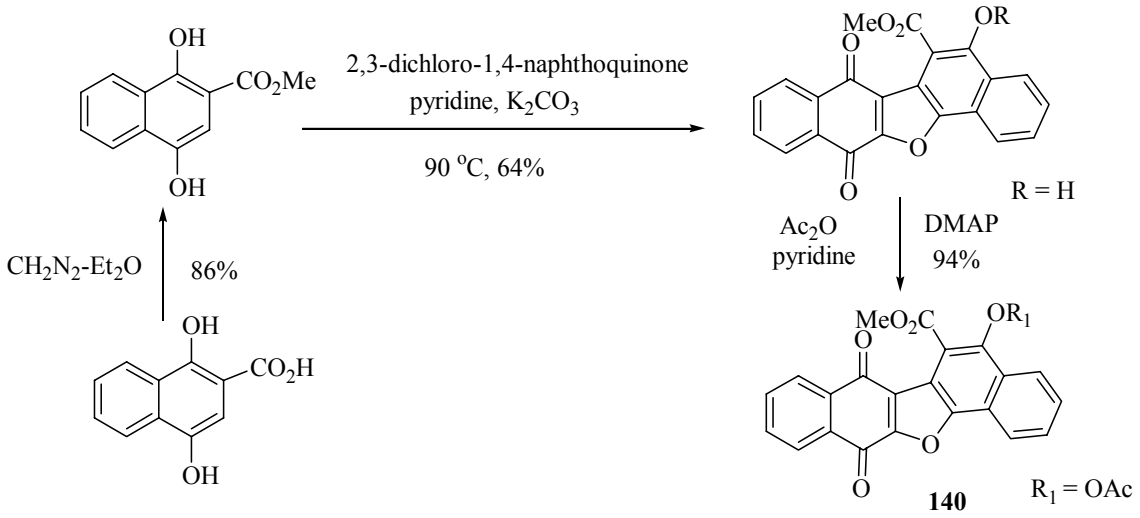
Frontier and coworkers[269] have developed a $Sc(OTf)_3$-catalyzed methodology for synthesizing fused furan ring system following the reaction as shown in Eq. 36.



Eq. 36

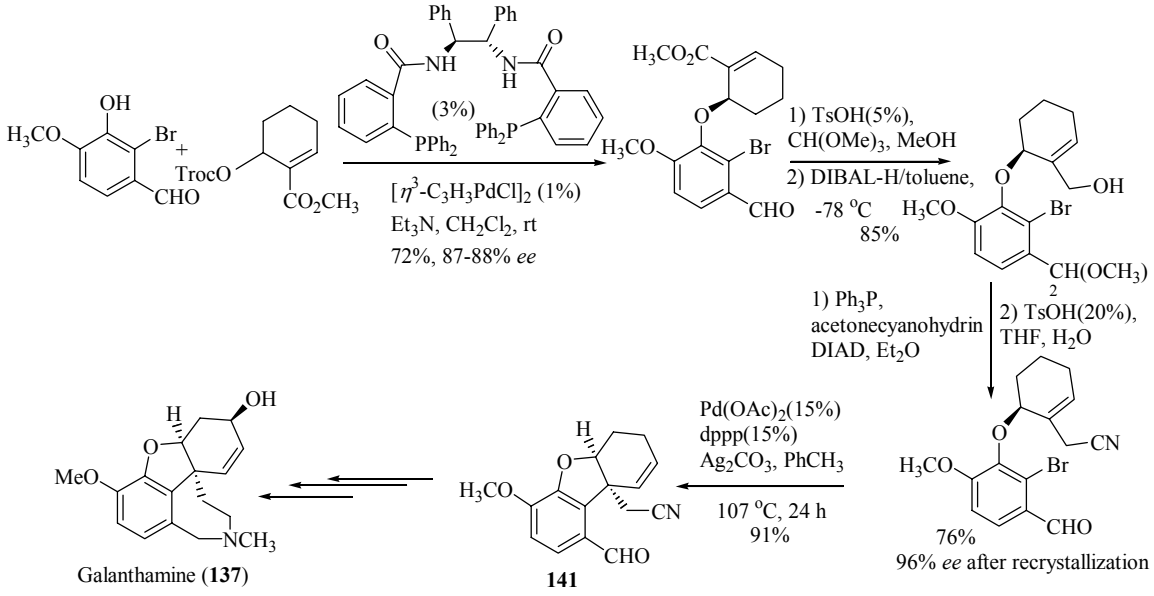
Cho and coworkers[262] have synthesized a series of dinaphtho[1,2-*b*;2',3'-*d*]furan-7,12-diones (**140**) following the reaction strategy as shown in Scheme 49 and these compounds were evaluated for their inhibitory activities against receptor tyrosine kinases.

Scheme 49



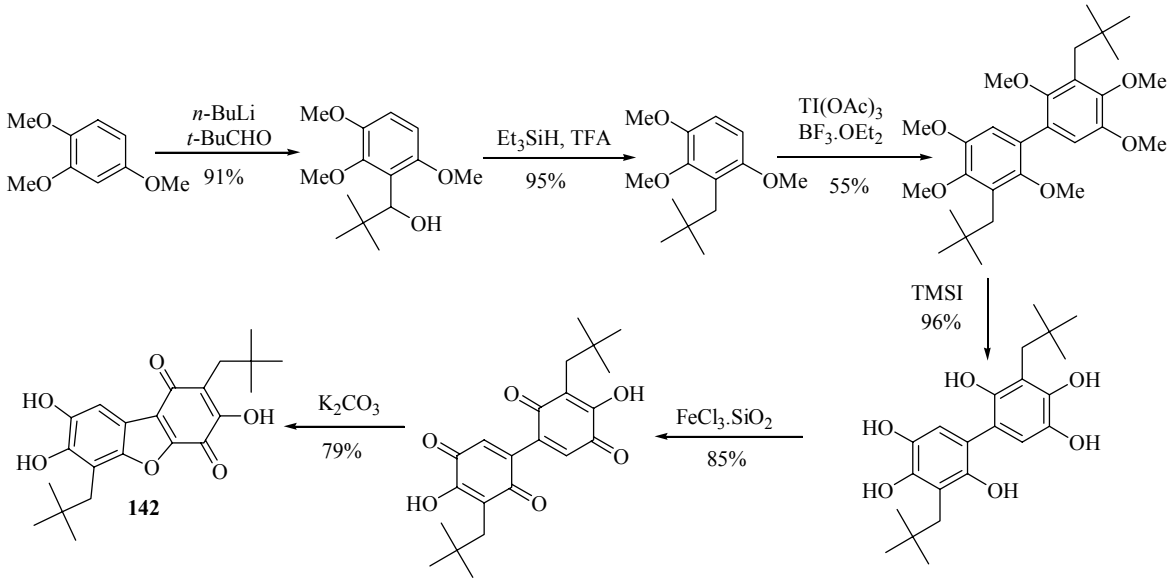
Trost and Tang[266] have developed an interesting method for synthesis of galanthamine (**137**), the parent member of the galanthamine-type *Amaryllidaceae* alkaloids using polycyclic fused furan as key intermediate (**141**) following the reaction sequence as shown in Scheme 50.

Scheme 50



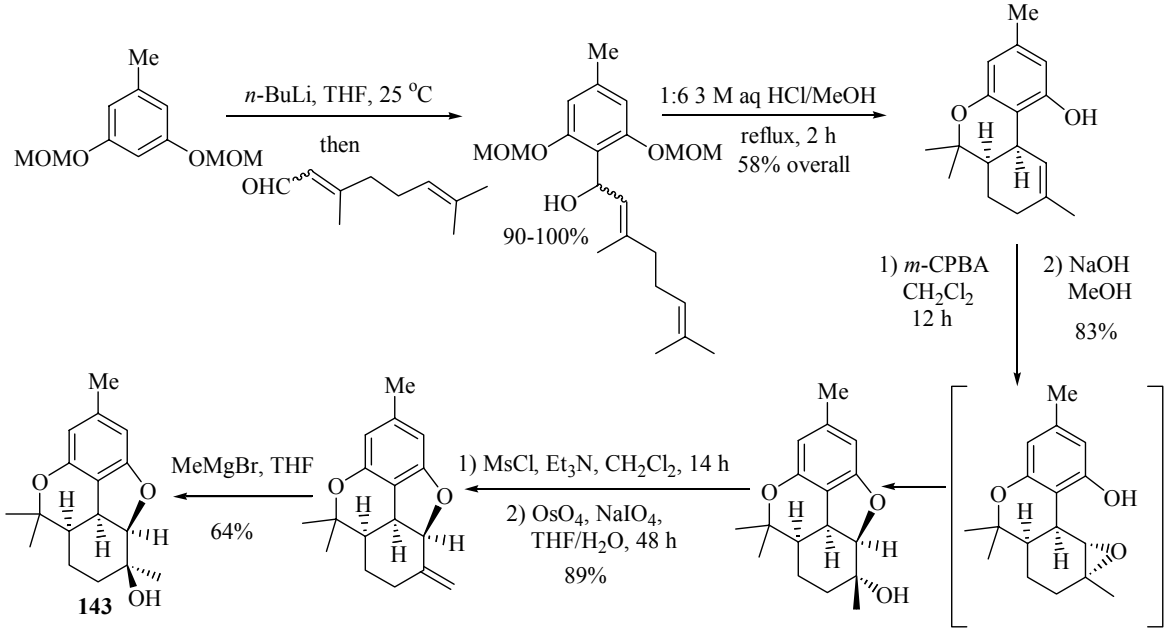
Anderson and coworkers[265] have reported a concise biomimetic synthetic route for obtaining a tricyclic dibenzofuran-1,4-dione (**142**) aromatic core of popolohuanone E (**136**) according to Scheme 51.

Scheme 51



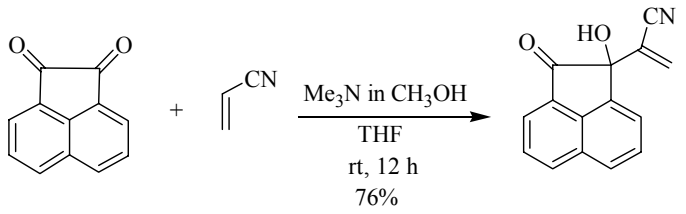
Snider and coworkers[267] have reported a short and efficient route to the tetracyclic fused furan core (**143**) of the bisabosquals following the reaction sequence as described in Scheme 52.

Scheme 52



In the preceding section we have presented our studies on $TiCl_4$-mediated Baylis-Hillman reaction between isatin derivatives and cycloalk-2-enones as reaction partners leading to one-pot synthesis of 3-(2-hydroxyphenyl)indolin-2-one derivatives.

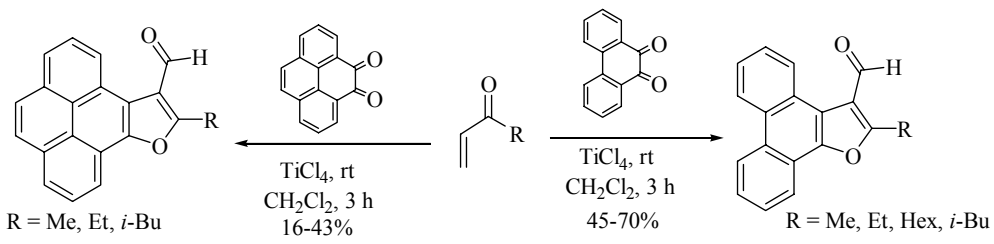
Our research group[89] has reported 1,2-acenaphthenequinone as the Baylis-Hillman electrophile for the reaction with acrylonitrile under the influence of methanolic trimethyl amine in THF to obtain the corresponding adduct in good yield (Eq. 37).



Eq. 37

Our research group also reported $TiCl_4$-mediated reaction of alkyl vinyl ketones with aryl 1,2-diones [(9,10)-phenanthrenedione and pyrene-(4,5)-dione]. In these cases usual Baylis-Hillman adducts were not isolated, instead an interesting class of furan carboxaldehydes were obtained in a straight forward manner (Scheme 53). [270]*

Scheme 53



Literature survey reveals that $TiCl_4$-mediated Baylis-Hillman reaction between aryl 1,2-diones and cycloalk-2-enones was not systematically explored. We have therefore directed our studies towards understanding $TiCl_4$-mediated Baylis-Hillman reaction between aryl 1,2-diones with cyclohex-2-enone derivatives. We have first performed the reaction between 1,2-acenaphthenequinone (1 mmol) and cyclohex-2-enone (1 mmol) in the

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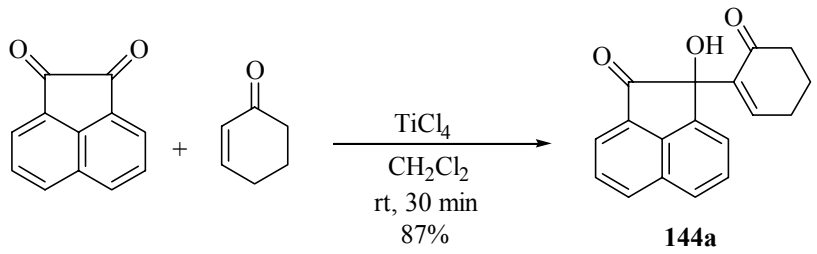
*The $TiCl_4$-mediated Baylis-Hillman reaction between aromatic 1,2-diones [(9,10)- phenanthrenedione and pyrene-(4,5)-dione] and alkyl vinyl ketones at room temperature (35-37 ^oC) (room temperature in summer in Hyderabad) provided fused furan derivatives.[270] During the present study, we noticed that the $TiCl_4$-mediated Baylis-Hillman reaction of [9,10]-phenanthrenedione with MVK at 25-28 ^oC (room temperature in winter in Hyderabad) for 3 h provided the fused furan derivative (40%) along with the corresponding B-H alcohol (30%). At 35 ^oC we obtained the fused furan derivative in 68% isolated yield.

presence of $TiCl_4$ (1 mmol) in dichloromethane at room temperature (25-28 ^oC) for 30 min. The resulting Baylis-Hillman adduct 2-hydroxy-2-(cyclohex-2-enon-2-yl)-2*H*-acenaphthylen-1-one (**144a**) was obtained in 87% isolated yield (Eq. 38) after usual work-up followed by column chromatography (silica gel, 60% ethyl acetate in hexanes). The structure of this Baylis-Hillman alcohol (**144a**) is in agreement with IR, ^1H NMR (Spectrum 9), ^{13}C NMR (Spectrum 10), mass spectral data and elemental analysis.

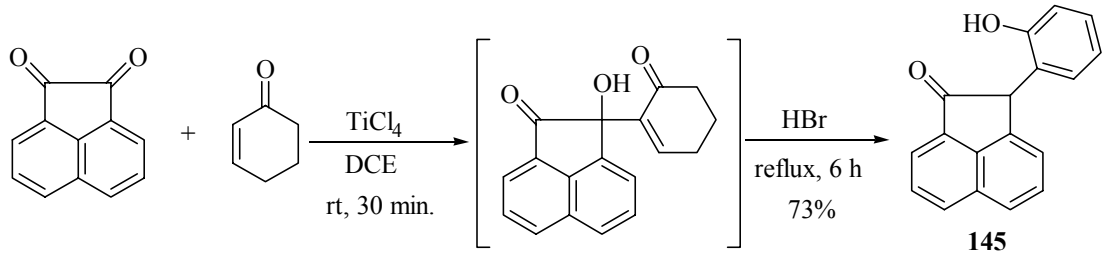


144a

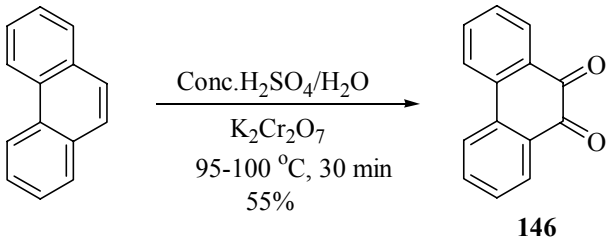
Eq. 38

With a view to obtain the phenolic derivative (aromatized compound), in one-pot, we have carried out reaction between 1,2-acenaphthenequinone (1 mmol), and cyclohex-2-enone (1 mmol) in the presence of $TiCl_4$ (1 mmol) in dichloroethane at room temperature for 30 min. Subsequent treatment of the *in situ* generated B-H alcohol with aq. HBr (5 mmol) at reflux temperature for 6 h as in the case of *N*-substituted isatins (in previous section) provided the expected phenolic compound *i.e.* 2-(2-hydroxyphenyl)-2*H*-acenaphthylen-1-one (**145**) in 73% isolated yield (Scheme 54). The structure of this compound (**145**) is in agreement with IR, ^1H NMR (Spectrum 11), ^{13}C NMR (Spectrum 12), mass spectral data and elemental analysis. Structure of compound **145** was further confirmed using single crystal X-ray data analysis (Figure X4, Table IV).

Scheme 54

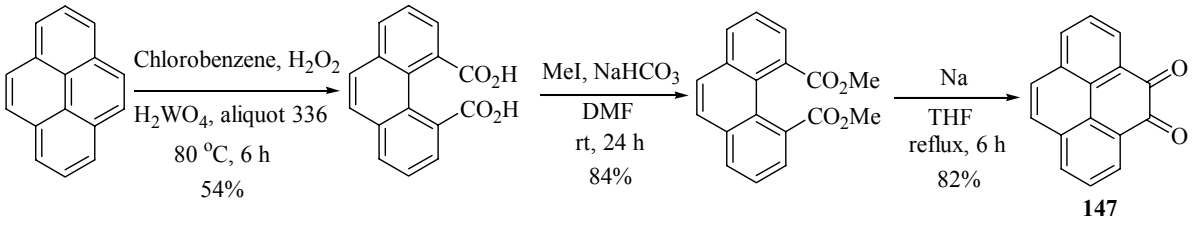


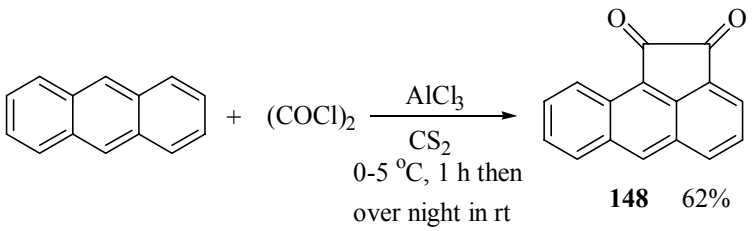
To understand the generality of this strategy we have selected three aromatic 1,2-diones, [9,10]-phenanthrenedione (**146**), pyrene-[4,5]-dione (**147**), and 1,2-aceanthrenequinone (**148**) as electrophiles for coupling with cyclohex-2-enone in the presence of $TiCl_4$ followed by treatment of the *in situ* generated B-H alcohols with aq. HBr. The required aryl 1,2-diones **146-148** were prepared following the known procedure[271-273] as presented in Eq. 39, Scheme 55 and Eq. 40 respectively. Unfortunately these electrophiles, **146-148**, did not provide the expected phenolic derivatives as these reactions were not clean. At this stage, we felt that step-wise strategy might provide the expected products.



Eq. 39[271]

Scheme 55[272]

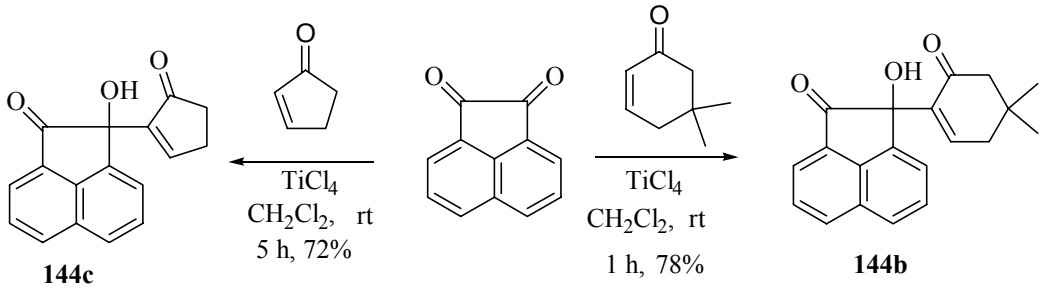




Eq. 40[273]

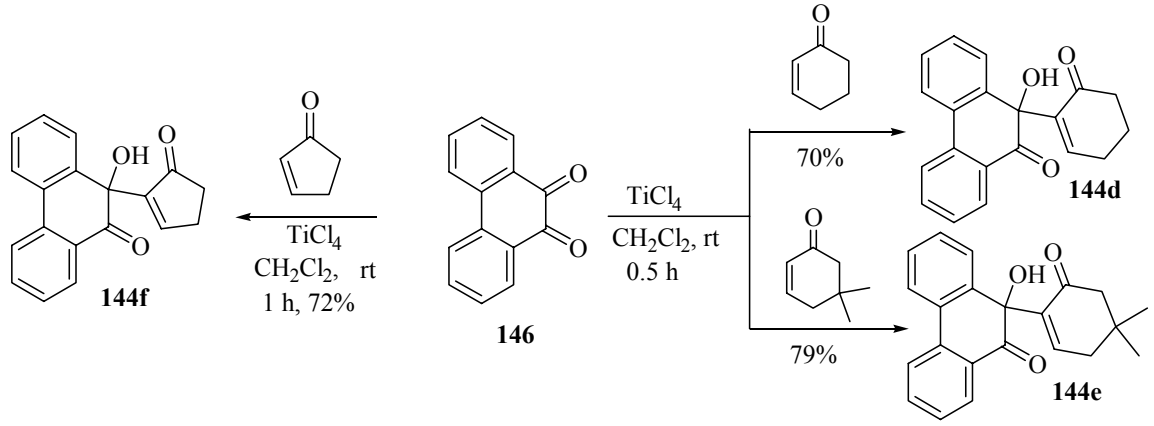
Then we have first directed our studies to understand the Baylis-Hillman reaction between cycloalk-2-enones with electrophiles, 1,2-acenaphthenequinone, [9,10]-phenanthrenedione (**146**), pyrene-[4,5]-dione (**147**), and 1,2-aceanthrenequinone (**148**) under the influence of $TiCl_4$. The corresponding Baylis-Hillman alcohols **144b-l** were obtained in 53-90% isolated yields (Schemes 56-59, Table 2). The structures of these Baylis-Hillman products (**144b-l**) are in agreement with IR, ^{1}H NMR, ^{13}C NMR, mass spectral data and elemental analyses. Our attempts to convert alcohols **144d**, **144g** and **144j** into the corresponding aromatized compounds by treatment with aq. HBr were not successful.

Scheme 56

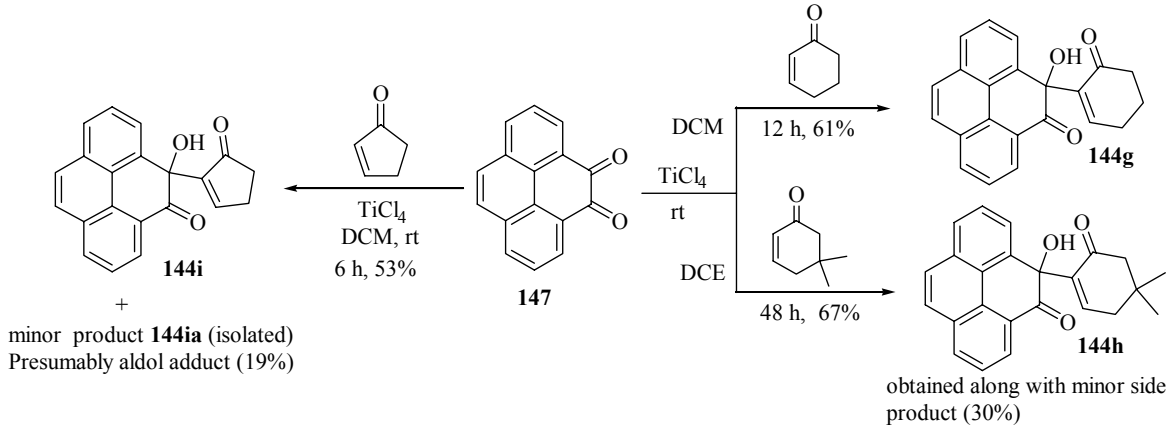


144c **144b**

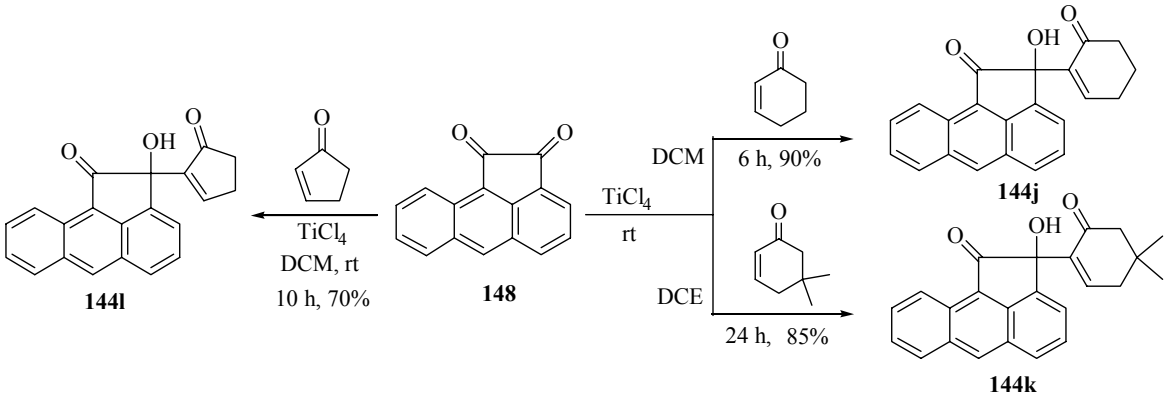
Scheme 57



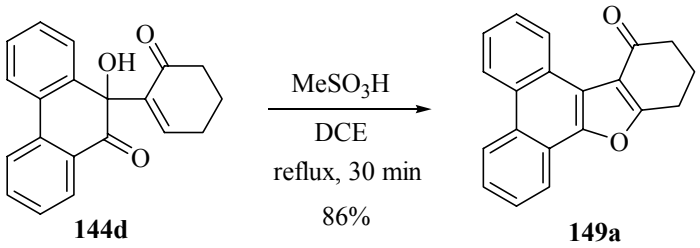
Scheme 58



Scheme 59



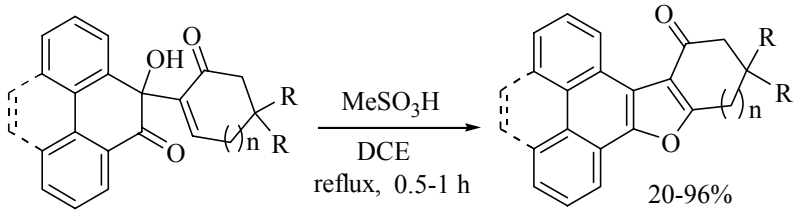
During these studies we found that the treatment of the allylic alcohol **144d** with methanesulfonic acid led to the formation of fused furan derivative (**149a**) instead of the phenolic derivative. Thus the treatment of the alcohol (**144d**, 1 mmol) with methanesulfonic acid (1 mmol) in dichloroethane at reflux temperature for 30 min provided the furan derivative, 2-oxapentacyclo[15.4.0.0.^{3,16}0.^{4,9}0.^{10,15}]henicosan-1(17),3(16),4(9),5,7,10(15),11,13-octaen-18-one (**149a**) in 86% isolated yield (Eq. 41). The structure of this compound (**149a**) is in agreement with IR, ^{1}H NMR (Spectrum 13), ^{13}C NMR (Spectrum 14), mass spectral data and elemental analysis. Structure of compound **149a** was further confirmed using single crystal X-ray data analysis (Figure X5, Table V).



144d **149a** **Eq. 41**

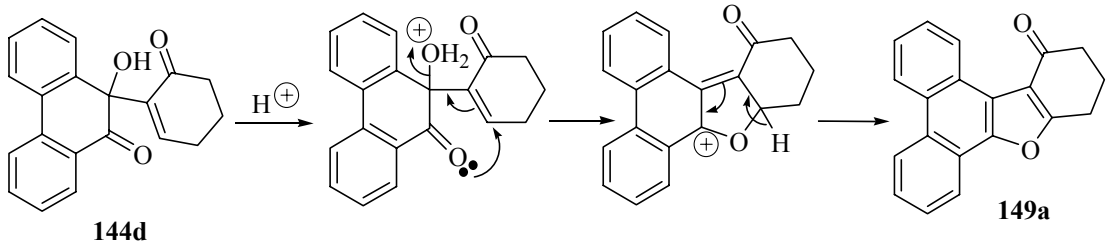
In order to understand the generality of this methodology we have transformed the Baylis-Hillman alcohols **144e-i** into the fused furan derivatives **149b-f** in 20-96% isolated yields *via* the treatment with methanesulfonic acid (Eq. 42, Table 3). The structures of these furan derivatives (**149b-f**) are in agreement with IR, ^{1}H NMR (Spectrum 15 for compound **149e**), ^{13}C NMR (Spectrum 16 for compound **149e**), mass spectral data and elemental analyses. Structure of compound **149c** was further confirmed using single crystal X-ray

data analysis (Figure X6, Table VI). A plausible mechanism for the transformation of the B-H alcohol into fused furan framework is given in Scheme 60.



144e-i R = H, Me; n = 0, 1 **149b-f** **Eq.42**

Scheme 60



144d **149a**

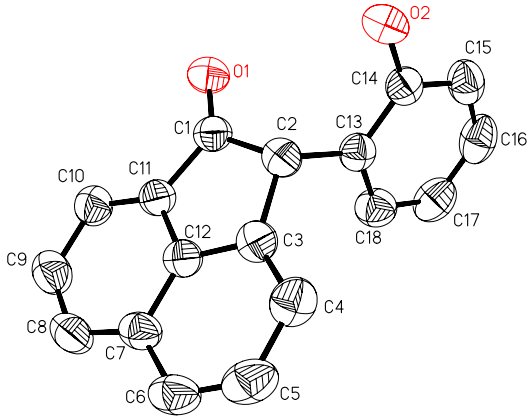
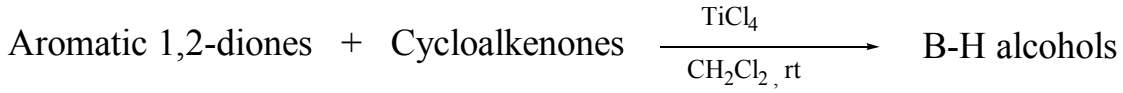
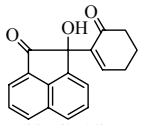
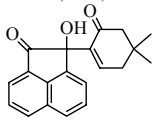
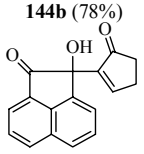
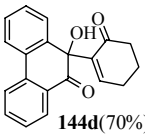
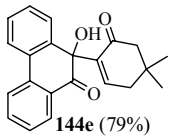
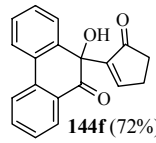
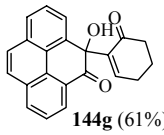
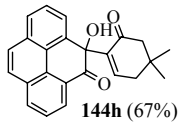
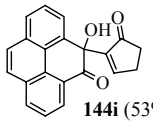
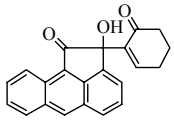
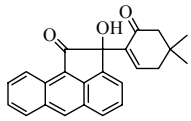
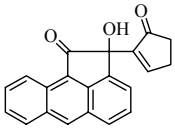


Figure X4

ORTEP diagram of the compound **145**
(Hydrogen atoms were omitted for clarity)

Table 2: Synthesis of Baylis-Hillman alcohols (**144a-l**)[a]



Entry	dione	Cycloalk-2-enone	t (h)	product[b] yield (%)[c]
1	acenaphthene-quinone	cyclohex-2-enone	0.5	 **144a** (87%)
2	acenaphthene-quinone	5,5-dimethyl cyclohex-2-enone	1	 **144b** (78%)
3	acenaphthene-quinone	cyclopent-2-enone	5	 **144c**(72%)
4	**146**	cyclohex-2-enone	0.5	 **144d**(70%)
5	**146**	5,5-dimethyl cyclohex-2-enone	0.5	 **144e** (79%)
6	**146**	cyclopent-2-enone	1	 **144f** (72%)
7	**147**	cyclohex-2-enone	12	 **144g** (61%)
8[d]	**147**	5,5-dimethyl cyclohex-2-enone	48	 **144h** (67%)
9[e]	**147**	cyclopent-2-enone	6	 **144i** (53%)
10	**148**	cyclohex-2-enone	6	 **144j** (90%)
11	**148**	5,5-dimethyl cyclohex-2-enone	24	 **144k** (85%)
12	**148**	cyclopent-2-enone	10	 **144l** (70%)

a) All the reactions were carried out on 1 mmol scale of aromatic 1,2-diones (acenaphthenequinone, **146-148**) with cycloalk-2-enones [(1 mmol) and for cyclopent-2-enone 1.5 mmol] in the presence of $TiCl_4$ (1 mmol) at room temperature (25-28 ^oC) in dichloromethane (for **144h** and **144k** DCE was used).

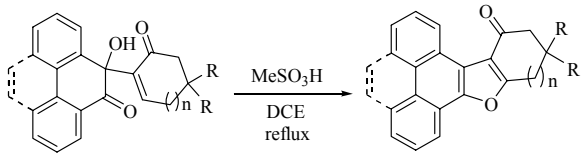
b) All compounds were isolated as solids and fully characterized.

c) Isolated yields based on the aromatic 1,2-diones (acenaphthenequinone, **146-148**).

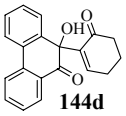
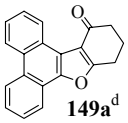
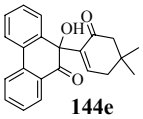
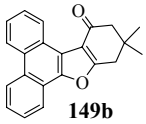
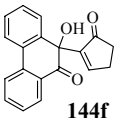
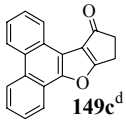
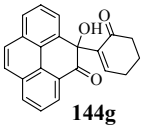
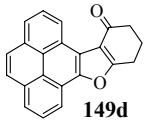
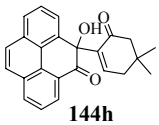
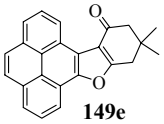
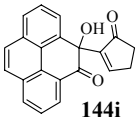
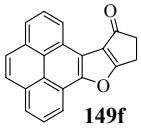
d) Compound **144h** was isolated along with side product 30% (as shown by ^1H NMR)

e) Minor side product (presumably aldol product, **144ia**) was also isolated in 19% yield along with compound **144i**.

Table 3: Synthesis of furan derivatives (**149a-f**)[a]



144d-i **149a-f**

Entry	B H alcohol	product[b]	t (min)	mp (°C)	yield (%)[c]
1	 **144d**	 **149a**[d]	30	160-162	86
2	 **144e**	 **149b**	30	178-180	89
3	 **144f**	 **149c**[d]	30	209-211	96
4	 **144g**	 **149d**	30	181-183	50
5[e]	 **144h**	 **149e**	60	216-218	43[f]
6	 **144i**	 **149f**	60	185-186	20

a) All the reactions were carried out on 1 mmol scale of Baylis-Hillman alcohols (**144d-i**) in the presence of methanesulfonic acid (1 mmol) in dichloroethane at reflux temperature.

b) All the compounds were isolated as solids and fully characterized.

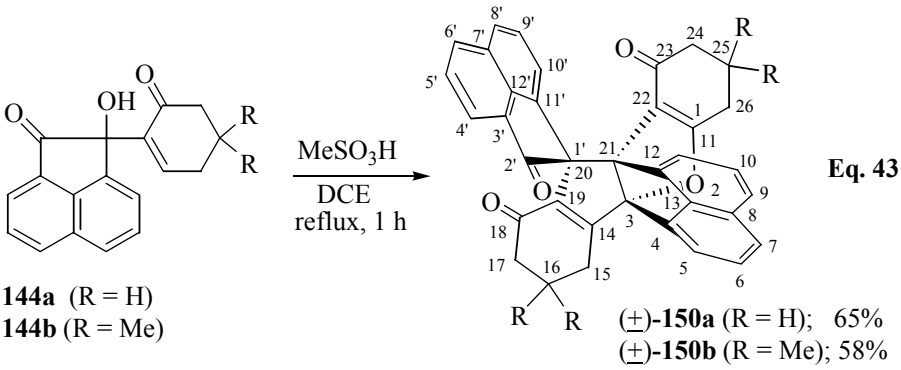
c) Isolated yields based on the Baylis-Hillman alcohols (**144d-i**).

d) Structures of compounds **149a** and **149c** were further confirmed by single crystal X-ray data analysis.

e) Baylis-Hillman adduct **144h** was used as such along with the minor side product as substrate for treatment with methanesulfonic acid.

f) Yield was calculated based on the amount of Baylis-Hillman alcohol present in the mixture.

However, similar treatment of the Baylis-Hillman alcohol, 2-hydroxy-2-(cyclohex-2-enon-2-yl)-2*H*-acenaphthylen-1-one (**144a**) with methanesulfonic acid did not provide the expected furan derivative. Instead, interesting spiro-fused compound [3*R*,20(1′)*R*,21*S* / 3*S*,20(1′)*S*,21*R*]-{2-oxaheptacyclo[20.4.0.0.^{3,21}0.^{4,13}0.^{8,13}0.^{12,13}0.^{14,19}]hexacosane-1(22),4,6,8(13),9,11,14(19)-heptaen-18,23-dione}-20-spiro-1′-acenaphthylen-2′-one (**150a**) was obtained in 65% isolated yield (Eq. 43) [when 3 equiv methanesulfonic acid was used at reflux temperature in DCE for 1 h]. Also the B-H alcohol, 2-hydroxy-2-(5,5-dimethyl-cyclohex-2-enon-2-yl)-2*H*-acenaphthylen-1-one (**144b**) gave fused furan framework **150b** under similar conditions (Eq. 43).



144a (R = H)
144b (R = Me)

(±)-**150a** (R = H); 65%
(±)-**150b** (R = Me); 58%

Eq. 43

The structures of the fused furan derivatives (**150a,b**) are in agreement with IR, ^{1}H NMR (Spectra 17 & 19 for compounds **150a** & **150b** respectively), ^{13}C NMR (Spectra 18 & 20 for compounds **150a** & **150b** respectively), mass spectral data and elemental analyses. Structure of the compound **150a** and its *cis-cis-cis* stereochemistry[#] [3*R*,20(1′)*R*,21*S*/ 3*S*,20(1′)*S*,21*R*] were determined by the single crystal X-ray data analysis (Figure X7,

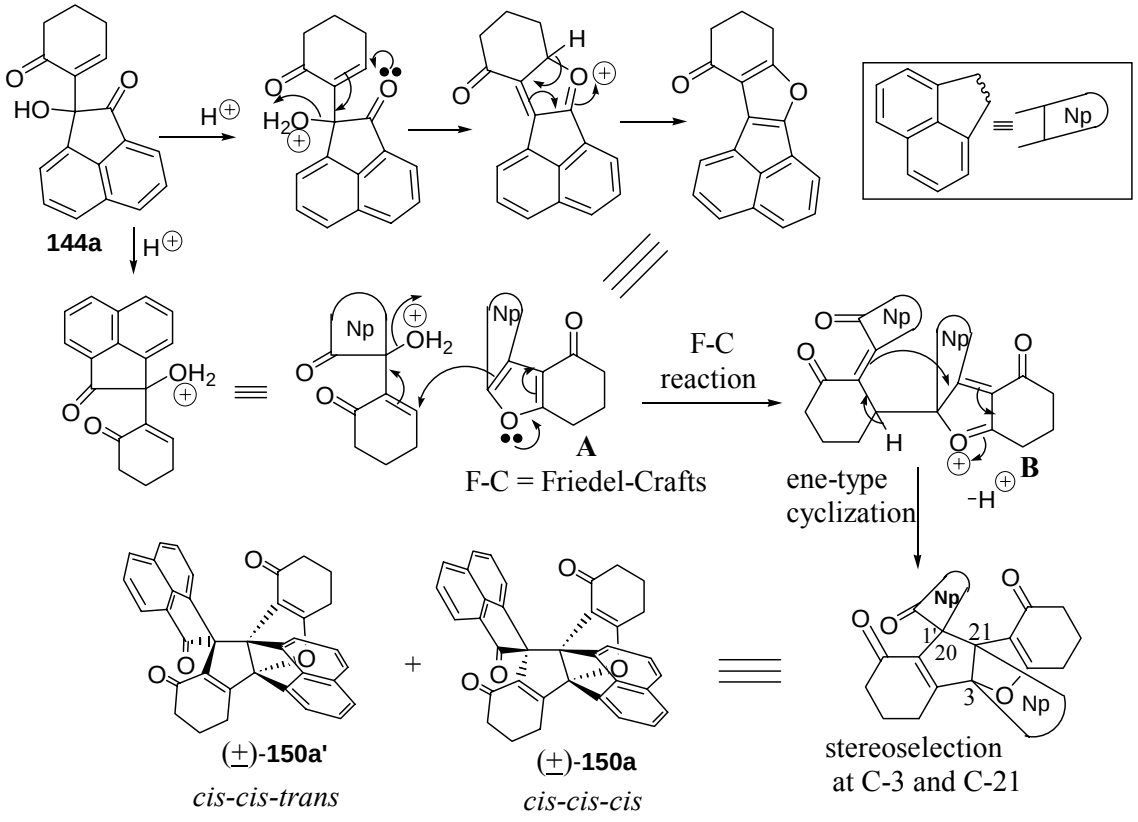
[#] *Cis-cis-cis*-stereochemistry is assigned to the compound **150a** as it contains C-C bonds (C3-C4, C12-C21, C1′-C2′), connecting acenaphthene rings, on the same side

Table VII). Structure of the compound **150b** and its stereochemistry [3*R*,20(1′)*R*,21*S*/ 3*S*,20(1′)*S*,21*R*] were assigned in analogy with that of compound **150a**. ^{13}C NMR spectrum of **150a** (Spectrum 18) shows 36 carbon signals for 36 carbons present, but the presence of more intense carbon signal at δ 127.13 questions the purity of this compound as this intense signal might correspond to two carbons. This problem becomes clearer from the ^{13}C NMR spectrum of the compound **150b** (Spectrum 20) in which 41 carbon signals appeared for 40 carbons, thus indicating the presence of one extra carbon at similar chemical shift value as in the case of compound **150a**. From this data, we presume that the extra carbon signal might be attributed to the presence of a diastereoisomer in almost equal ratio which might have different stereochemistry at one of the three chiral centers present in the molecule. The fact that the single crystal shows only one diastereomer indicates that one particular diastereoisomer might have crystallized as a single crystal while the actual compound might be a mixture of two diastereoisomers (**150a** and **150a′**, Scheme 61) of equal concentration having opposite stereochemistry at only one chiral center. From the ^{13}C NMR spectral analysis, it might be possible to attribute that except one carbon, all the other carbons in **150a** and **150a′** (Scheme 61) have the identical chemical shifts. Similar assumption can be made in the case of **150b** and its diasteroisomer.

A plausible mechanism is presented in Scheme 61. The furan intermediate **A** might react with B-H alcohol (Friedel-Crafts reaction) giving rise to the key intermediate (oxonium ion) **B**, which might then undergo ene-type cyclization in a stereoselective manner at C-3 and C-21 with *cis* orientation because of the presence of acenaphthene rings. However, the

reaction might not control stereochemistry at spiro carbon (C-1′/20) leading to the formation of two products, one with *cis-cis-cis* (**150a**) and the other with *cis-cis-trans* stereochemistry (**150a′**).

Scheme 61.



We have demonstrated, for the first time, $TiCl_4$-mediated Baylis-Hillman reaction of cyclic aromatic 1,2-diones with cycloalk-2-enones and the corresponding adducts have been successfully transformed into very important class of polycyclic fused furan ring systems.

Table IV. Crystal data and structure refinement for **145.**

Empirical formula	$C_{18}H_{12}O_2$
Formula weight	260.28
Temperature	298 K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 7.9386(16) Å; α = 68.928(3) deg.
	b = 8.9357(18) Å; β = 79.267(3) deg.
	c = 10.627(2) Å; γ = 65.496(3) deg.
Volume	639.5(2) $Å^3$
Z, Calculated density	2, 1.352 Mg/m^3
Absorption coefficient	0.087 mm^{-1}
F(000)	272
Crystal size	0.50 x 0.28 x 0.26 mm
Theta range for data collection	2.06 to 25.00 deg.
Limiting indices	$-9\leq h\leq 9$, $-10\leq k\leq 10$, $-12\leq l\leq 12$
Reflections collected / unique	6193 / 2254 [R(int) = 0.0168]
Completeness to theta = 25.00	99.8%
Absorption correction	Empirical
Max. and min. transmission	0.9776 and 0.9576
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2254 / 0 / 186
Goodness-of-fit on F^2	1.101
Final R indices [I>2sigma(I)]	R1 = 0.0405, wR2 = 0.1051
R indices (all data)	R1 = 0.0425, wR2 = 0.1069
Extinction coefficient	0.061(6)
Largest diff. peak and hole	0.157 and -0.152 e. $Å^{-3}$

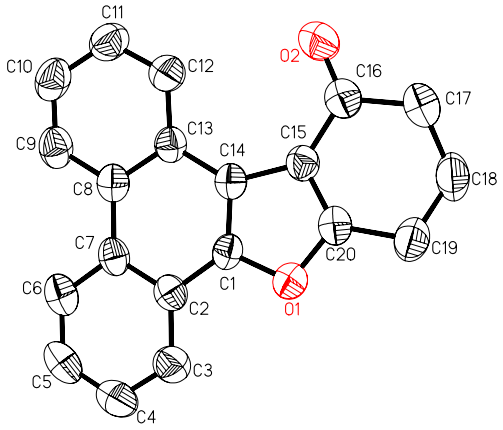


Figure X5

ORTEP diagram of the compound **149a**
(Hydrogen atoms were omitted for clarity)

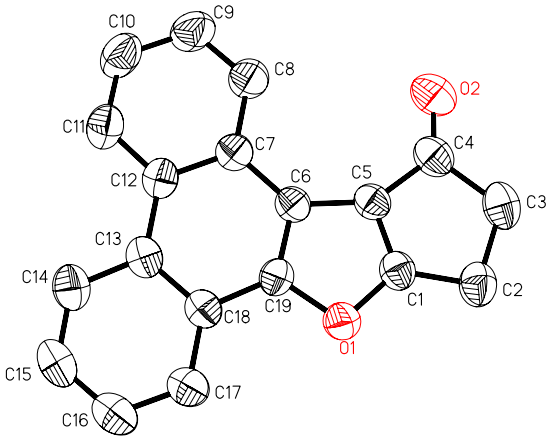


Figure X6

ORTEP diagram of the compound **149c**
(Hydrogen atoms were omitted for clarity)

Table V. Crystal data and structure refinement for **149a.**

Empirical formula	$C_{20}H_{14}O_2$
Formula weight	286.31
Temperature	298 K
Wavelength	0.71073 Å
Crystal system / Space group	Monoclinic/ P2(1)
Unit cell dimensions	a = 7.5443(7) Å; α = 90 deg.
	b = 18.8155(17) Å; β = 106.017(2) deg.
	c = 10.1375(9) Å; γ = 90 deg.
Volume	1383.2(2) $Å^3$
Z, Calculated density	4, 1.375 Mg/m^3
Absorption coefficient	0.088 mm^{-1}
F(000)	600
Crystal size	0.28 x 0.25 x 0.18 mm
Theta range for data collection	2.09 to 26.29 deg.
Limiting indices	$-9\leq h\leq 9$, $-23\leq k\leq 23$, $-12\leq l\leq 12$
Reflections collected / unique	14544 / 5517 [R(int) = 0.0386]
Completeness to theta = 26.29	98.8%
Absorption correction	Multi-scan method (SADABS)
Max. and min. transmission	0.9844 and 0.9758
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5517 / 1 / 397
Goodness-of-fit on F^2	0.911
Final R indices [I>2sigma(I)]	R1 = 0.0418, wR2 = 0.0780
R indices (all data)	R1 = 0.0620, wR2 = 0.0838
Absolute structure parameter	0.6(9)
Largest diff. peak and hole	0.178 and -0.176 e. $Å^{-3}$

Table VI. Crystal data and structure refinement for **149c.**

Empirical formula	$C_{19}H_{12}O_2$
Formula weight	272.29
Temperature	298 K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	C2/c
Unit cell dimensions	a = 24.610(2) Å; α = 90 deg.
	b = 5.4124(4) Å; β = 95.0210(10) deg.
	c = 19.5981(16) Å; γ = 90 deg.
Volume	2600.4(4) $Å^3$
Z, Calculated density	8, 1.391 Mg/m^3
Absorption coefficient	0.090 mm^{-1}
F(000)	1136
Crystal size	0.25 x 0.18 x 0.15 mm
Theta range for data collection	1.66 to 24.99 deg.
Limiting indices	$-28\leq h\leq 28$, $-6\leq k\leq 6$, $-23\leq l\leq 23$
Reflections collected / unique	11818 / 2297 [R(int) = 0.0458]
Completeness to theta = 24.99	100.0 %
Absorption correction	Multi-scan method (SADABS)
Max. and min. transmission	0.9867 and 0.9780
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2297 / 0 / 190
Goodness-of-fit on F^2	0.947
Final R indices [I>2sigma(I)]	R1 = 0.0434, wR2 = 0.0853
R indices (all data)	R1 = 0.0753, wR2 = 0.0945
Largest diff. peak and hole	0.142 and -0.123 e. $Å^{-3}$

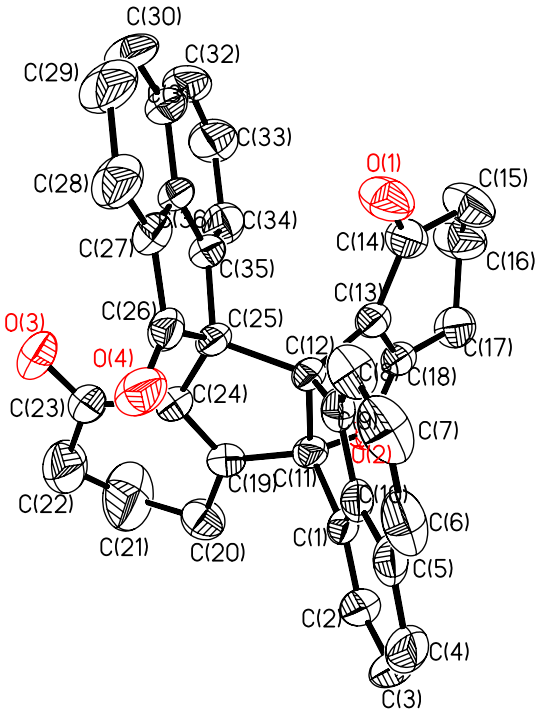


Figure X7

ORTEP diagram of the compound **150a**
(*Hydrogen atoms and one disordered dichloromethane molecule were omitted for clarity*)

Table VII. Crystal data and structure refinement for **150a.**

Empirical formula	$C_{37}H_{26}Cl_2O_4$
Formula weight	605.48
Temperature	298 K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)/n
Unit cell dimensions	a = 11.0046(13) Å; α = 90 deg.
	b = 24.044(3) Å; β = 97.252(2) deg.
	c = 11.4448(13) Å; γ = 90 deg.
Volume	3004.0(6) $Å^3$
Z, Calculated density	4, 1.339 Mg/m^3
Absorption coefficient	0.257 mm^{-1}
F(000)	1256
Crystal size	0.41 x 0.35 x 0.25 mm
Theta range for data collection	1.69 to 25.00 deg.
Limiting indices	$-13\leq h\leq 13$, $-28\leq k\leq 28$, $-13\leq l\leq 13$
Reflections collected / unique	28292 / 5243 [R(int) = 0.0623]
Completeness to theta = 25.00	98.9%
Absorption correction	Multi-scan method (SADABS)
Max. and min. transmission	0.9386 and 0.9021
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5243 / 1 / 398
Goodness-of-fit on F^2	1.031
Final R indices [I>2sigma(I)]	R1 = 0.0911, wR2 = 0.2340
R indices (all data)	R1 = 0.1239, wR2 = 0.2574
Largest diff. peak and hole	0.617 and -0.505 e. $Å^{-3}$

Dimethyl sulfide induced [3 + 2] annulation strategy: An efficient synthesis of functionalized dihydropyrazole derivatives using the Baylis-Hillman bromides

Pyrazole framework belongs to an important class of heterocyclic compounds possessing different pharmacological activities such as antiviral (**151**), anticancer (**152**), anti-inflammatory/antimicrobial (**153**), COX-2 inhibitor (**154**) and anti-bacterial/fungal (**155**) activities.[274-278] Pyrazole derivatives were also evaluated for cholesterol-lowering activity (**156**)[279] (Figure 11). Because of these remarkable pharmacological and medicinal activities of pyrazole derivatives, development of simple and efficient methodologies for synthesis of these compounds with different substitution profiles has been and continues to be a challenging and attractive endeavor in organic and medicinal chemistry.

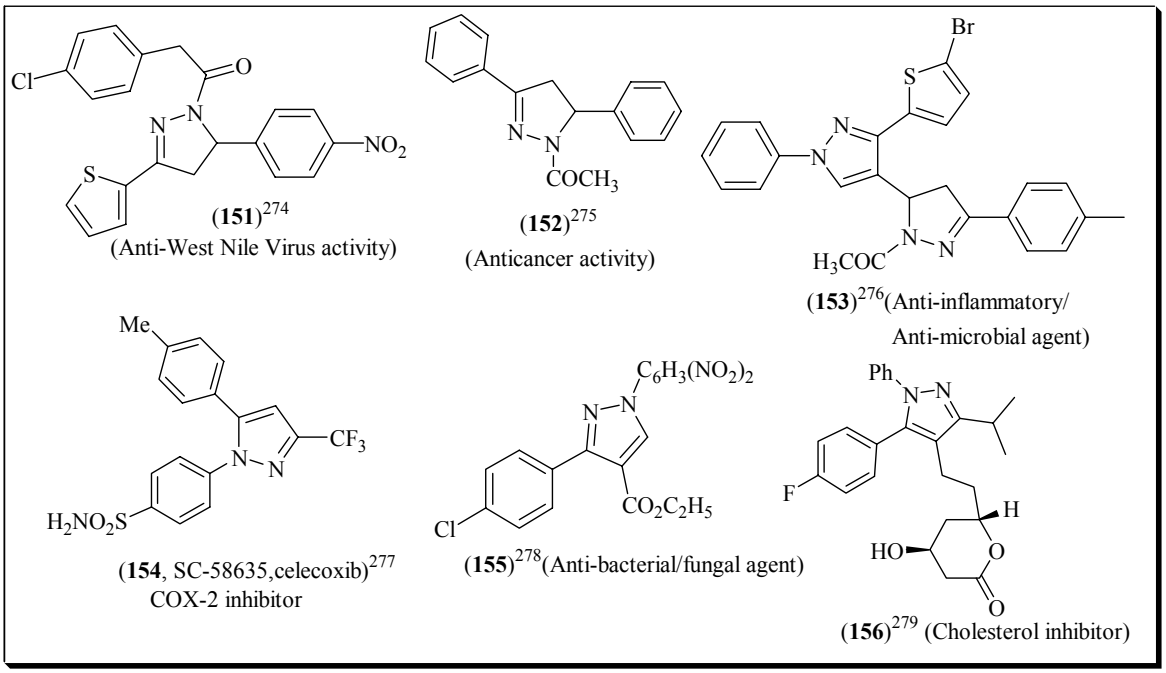
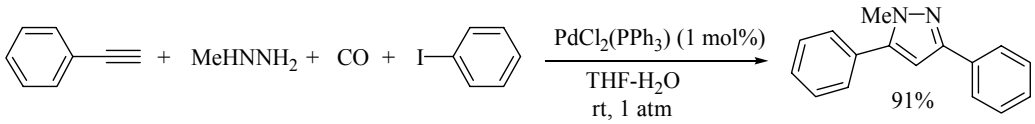


Figure 11

The frequently used methodologies for the synthesis of functionalized pyrazole derivatives involve reaction between hydrazines and alkyne derivatives or 1,3-dipolar cycloaddition reaction.

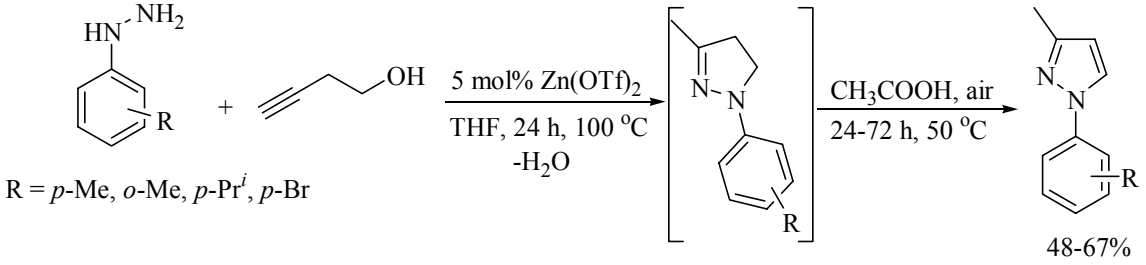
Mori and coworkers[280] have developed four component coupling of terminal alkynes, hydrazines, carbon monoxide and aryl iodides to furnish the pyrazole derivatives in the presence of a palladium catalyst. One example is shown in Eq. 44.



Eq. 44

Beller and coworkers[281] have reported a novel regioselective synthesis of aryl-substituted pyrazole derivatives *via* the reaction between substituted phenylhydrazines and 3-butynol in the presence of a catalytic amount of zinc triflate. Representative examples are shown in Scheme 62.

Scheme 62

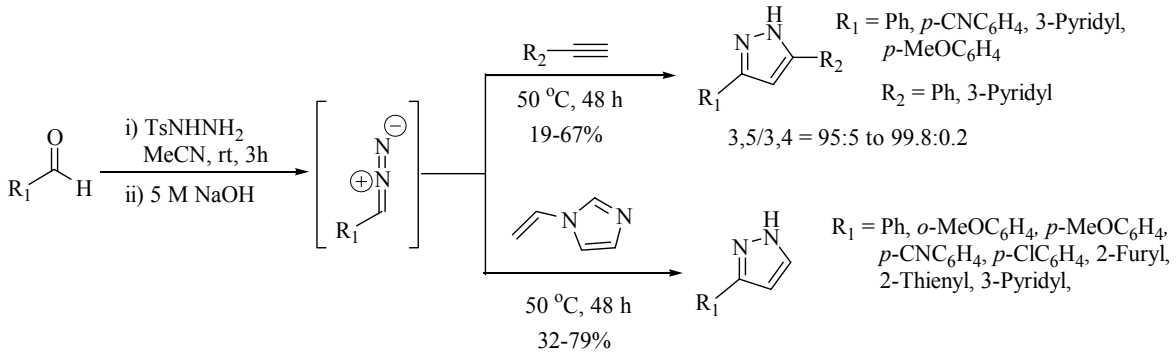


R = *p*-Me, *o*-Me, *p*-Pr^{i}, *p*-Br

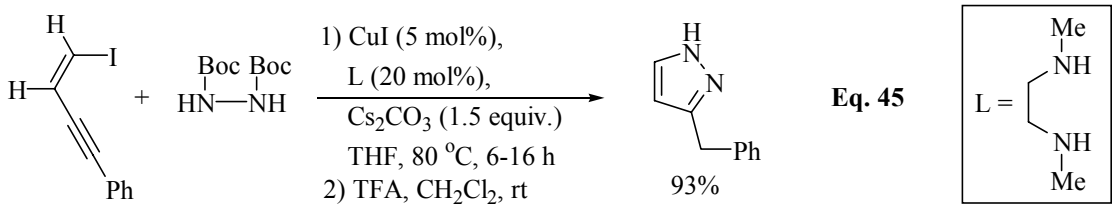
Aggarwal and coworkers[282] have developed a simple one-pot procedure for synthesis of 1*H*-pyrazoles *via* the 1,3-dipolar cycloaddition reaction of diazo compounds generated *in*

situ from aldehydes with alkyne derivatives. Similar reaction with *N*-vinylimidazole provided exclusively 3-substituted pyrazole derivatives (Scheme 63).

Scheme 63



Buchwald and coworkers[283] have reported a general, highly flexible and Cu-catalyzed domino C-N coupling/hydroamidation reaction of iodoenynes with hydrazine derivative to provide pyrazole derivatives. One example is shown in Eq. 45.



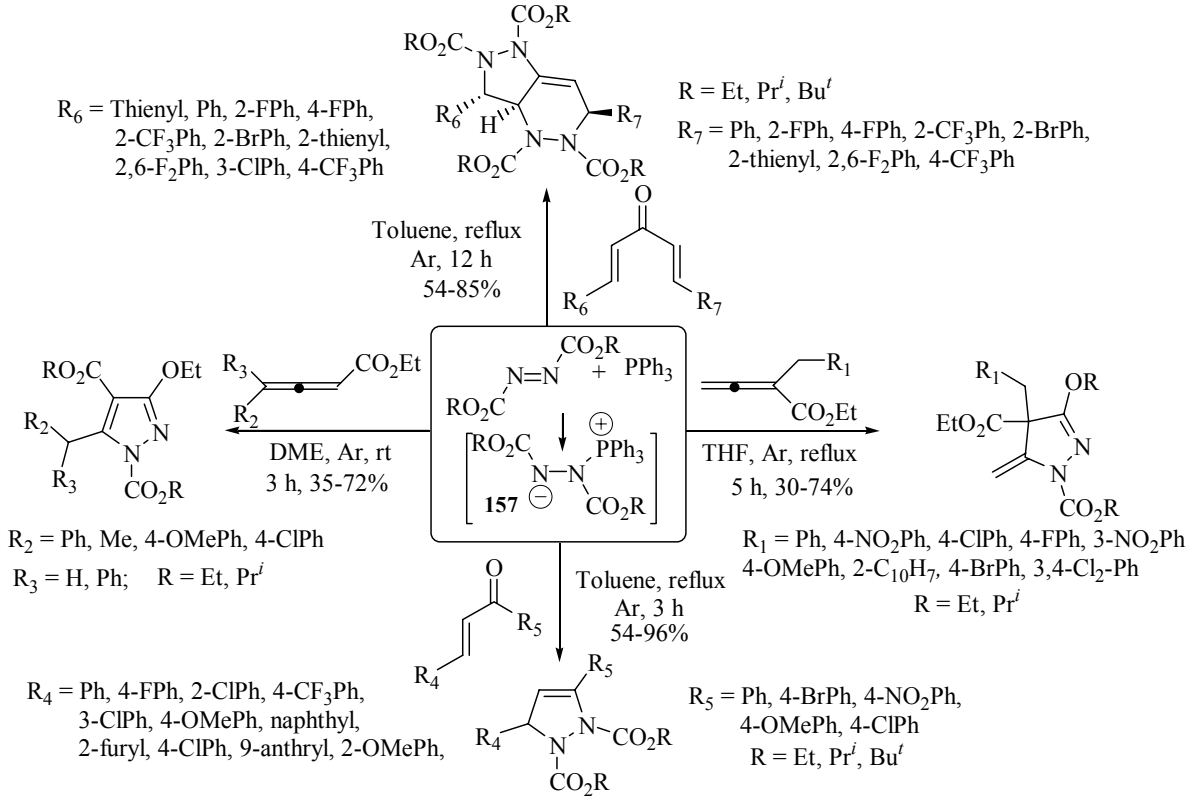
Eq. 45

Recently, the efficient use of "Huisgen Zwitterions" (**157**) for the synthesis of pyrazoles has been demonstrated in the literature. Some of the recent and important methods for the synthesis of pyrazoles are presented in this section.

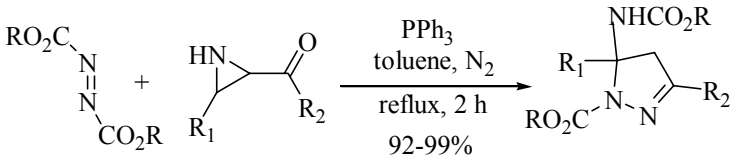
Nair and coworkers have described a facile reaction of the "Huisgen Zwitterions" (**157**) derived from triphenylphosphine and dialkyl azodicarboxylates with allenic esters to afford highly functionalized pyrazole derivatives.[284] Subsequently, they have used the "Huisgen

Zwitterions" for the reaction with chalcones and dienones to provide different pyrazole and pyrazolopyridazine derivatives.[285] Representative examples are shown in Scheme 64.

Scheme 64



Wang and coworkers[286] have described a facile access to pyrazole derivatives *via* domino reaction of the "Huisgen Zwitterions" with aziridines. Representative examples are shown in Eq. 46.



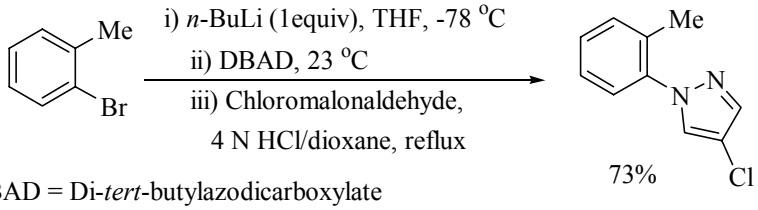
Eq. 46

R = Et, Pr^i, Bu^t

R_1 = C_6H_5, 3,4-$Me_2C_6H_3$, 4-ClC_6H_4, 4-$NO_2C_6H_4$, 2-naphthyl, 2-furyl, 3,4-$(OCH_2O)C_6H_3$

R_2 = C_6H_5, 4-$MeOC_6H_4$, 2-ClC_6H_4, 3-$NO_2C_6H_4$

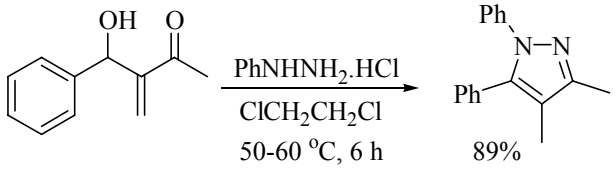
Very recently, Gerstenberger and coworkers[287] have developed a simple one-pot methodology for the synthesis of diversely functionalized pyrazole derivatives from aryl nucleophiles, di-*tert*-butylazodicarboxylate (DBAD) and 1,3-dicarbonyl or equivalent compounds according to Eq. 47 (One example is presented).



Eq. 47

DBAD = Di-*tert*-butylazodicarboxylate

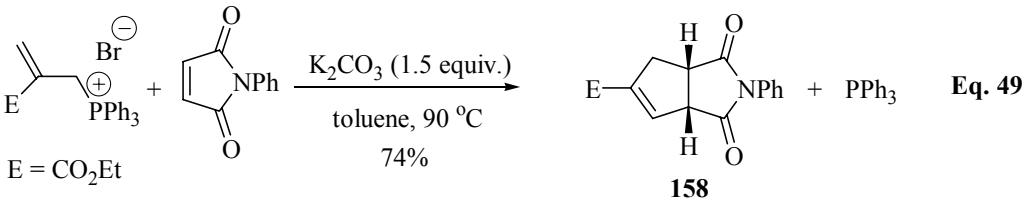
The Baylis-Hillman adducts have also been transformed into pyrazole derivatives by Kim and coworkers[288] *via* the reaction with hydrazine hydrochlorides. One example is shown in Eq. 48.



Eq. 48

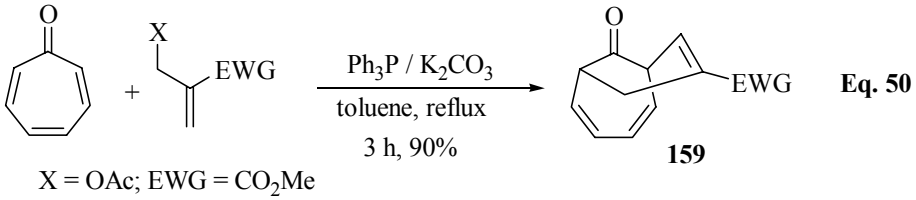
However, literature survey reveals that the application of Baylis-Hillman adducts (acetates / bromides) as 1,3-dipoles for participating in various annulation reaction has not been

systematically studied. In the year 2003, Lu and coworkers[289] for the first time, elegantly demonstrated phosphane-catalyzed [3 + 2] cycloaddition reaction between Baylis-Hillman adducts and electron deficient alkenes to provide interesting cyclopentene derivatives (**158**). One example is shown in Eq. 49.



Eq. 49

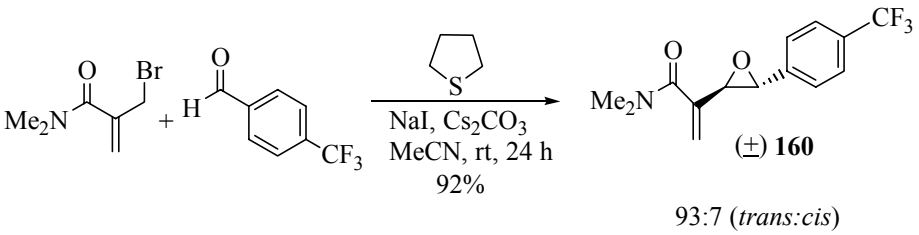
The same research group, subsequently, reported a simple and convenient methodology for synthesis of bridged nine-membered carbocycles (**159**) in excellent yields *via* the phosphine-catalyzed reaction of Baylis-Hillman acetate (bromide / chloride / *tert*-butyl carbonate) with tropone involving [3 + 6] annulation strategy (One example is shown in Eq. 50).[290]



Eq. 50

Recently, Sulfur ylides derived from Baylis-Hillman bromides were successfully used for epoxidation (**160**),[291] aziridination (**161**)[292] and cyclopropanation (**162**)[217] by various research groups (Eq. 51 and Schemes 65 & 66).

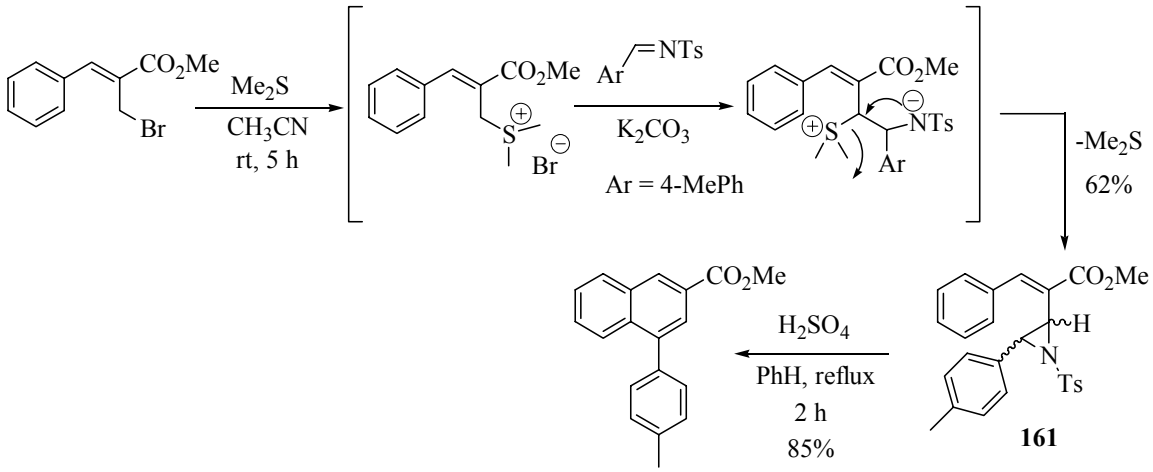
Epoxidation by Metzner and coworkers[291]



Eq. 51

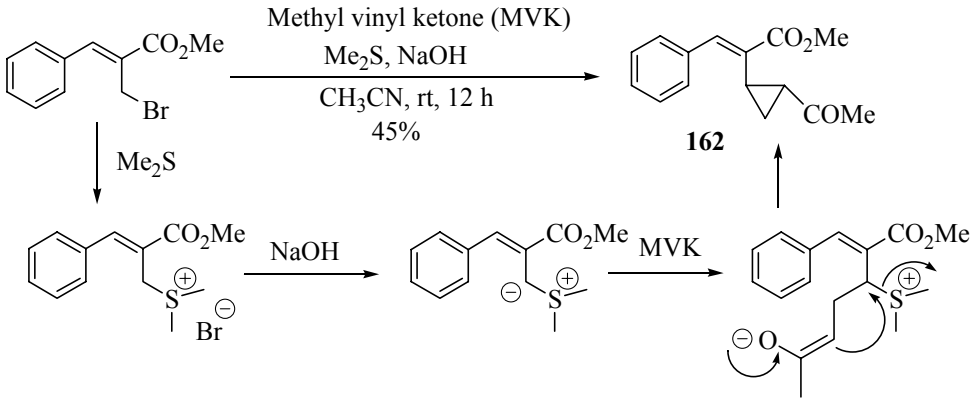
Aziridination by Kim and coworkers[292]

Scheme 65



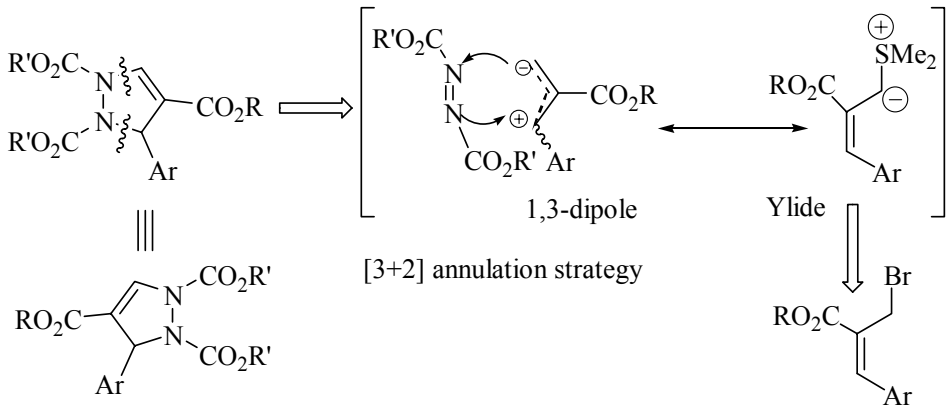
Cyclopropanation by Kim and coworkers[217]

Scheme 66



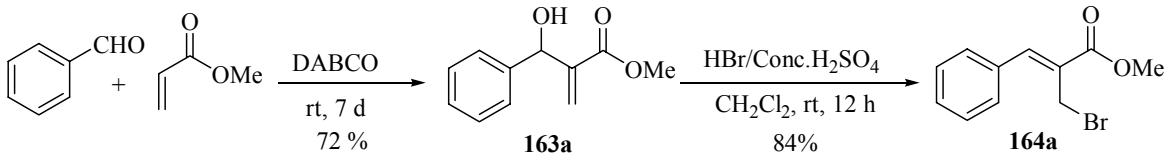
Fascinated by these reports and also in continuation of our interest in synthesis of heterocyclic compounds we felt that sulfur ylides, derived from the Baylis-Hillman bromides (BH-bromides), might in principle serve as a source of 1,3-dipoles in the presence of suitable dipolarophiles. Accordingly, we have directed our efforts to develop a simple methodology for synthesizing pyrazole derivatives following the retrosynthetic strategy (Scheme 67) assuming that dialkyl azodicarboxylates would be the appropriate dipolarophiles for [3 + 2] annulation strategy with Baylis-Hillman bromides as 1,3-dipoles.

Scheme 67

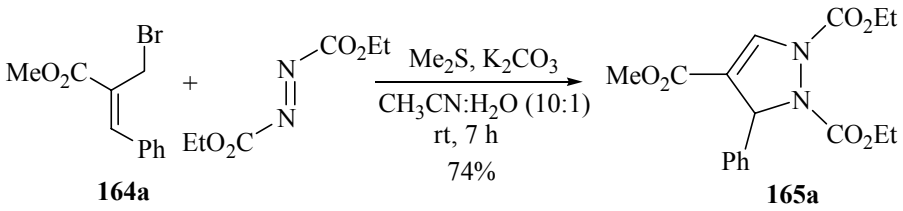


We have first selected methyl (2*Z*)-2-bromomethyl-3-phenylprop-2-enaoate (**164a**) as a source of 1,3-dipole for addition onto diethyl azodicarboxylate (DEAD) as dipolarophile. The required methyl (2*Z*)-2-bromomethyl-3-phenylprop-2-enaoate (**164a**) was prepared *via* the treatment of methyl 3-hydroxy-2-methylene-3-phenylpropanoate (**163a**) with aq. HBr (48%) in the presence of conc. H_2SO_4. Methyl 3-hydroxy-2-methylene-3-phenylpropanoate (**163a**) was in turn prepared *via* the Baylis-Hillman coupling between benzaldehyde and methyl acrylate under the catalytic influence of DABCO (Scheme 68).

Scheme 68



We have then performed the reaction between methyl (2*Z*)-2-bromomethyl-3-phenylprop-2-enoate (**164a**) and diethyl azodicarboxylate (DEAD) in presence of dimethyl sulfide. The best result in this study was obtained when we have treated Baylis-Hillman bromide **164a** (1 mmol) with diethyl azodicarboxylate (1 mmol) in the presence of Me_2S (1.2 mmol) and K_2CO_3 (1 mmol) in acetonitrile : water (1 mL : 0.1 mL) solvent system at room temperature for 7 hours to provide the expected dihydropyrazole derivative, 1,2-bis(ethoxycarbonyl)-4-methoxycarbonyl-3-phenyl-2,3-dihydro-1*H*-pyrazole (**165a)** in 74% isolated yield (Eq. 52) after usual work-up followed by column chromatography (silica gel, 20% ethyl acetate in hexanes). The structure of this dihydropyrazole derivative (**165a**) is in agreement with IR, ^{1}H NMR (Spectrum 21), ^{13}C NMR (Spectrum 22), mass spectral data and elemental analysis.

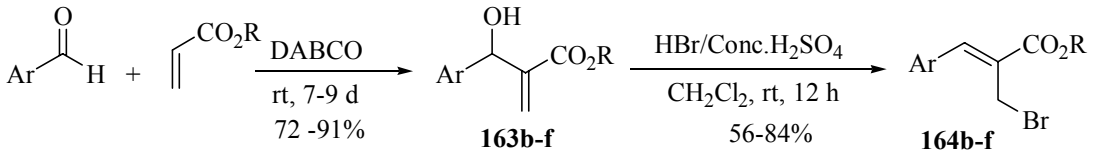


Eq. 52

With suitable condition in our hands, we have planned to understand the generality of the reaction. For this purpose, we have prepared representative Baylis-Hillman alcohols (**163b-f**) *via* the coupling of various aromatic aldehydes with alkyl acrylates in the

presence of DABCO (catalyst) and transformed them into corresponding bromides (**164b-f**) by the treatment of aq. HBr (48%) in the presence of conc. H_2SO_4 in CH_2Cl_2 (Scheme 69).

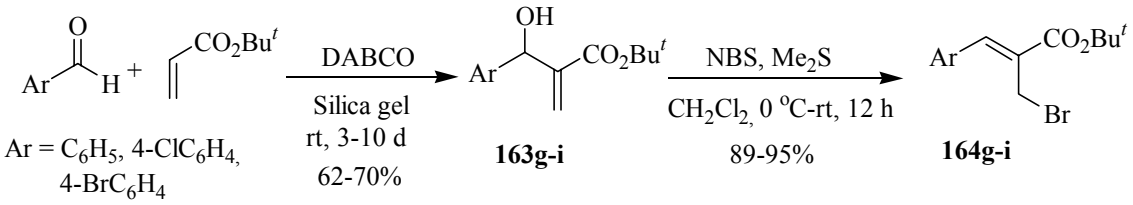
Scheme 69



Ar = Ph, 4-MePh, 4-BrPh, 3-ClPh
R = Me, *n*-Bu, Et,

We have also prepared Baylis-Hillman alcohols (**163g-i**) *via* the reaction of different aromatic aldehydes with *tert*-butyl acrylates in the presence of DABCO and silica gel. These alcohols (**163g-i**) were subsequently transformed into the corresponding bromide derivatives (**164g-i**) *via* the reaction with NBS in presence of dimethyl sulfide in CH_2Cl_2 (Scheme 70).

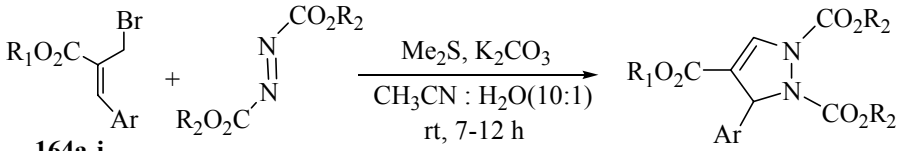
Scheme 70



Ar = C_6H_5, 4-ClC_6H_4, 4-BrC_6H_4

Then we have successfully employed Baylis-Hillman bromides (**164a-i**) as source of 1,3-dipoles for [3 + 2] cycloaddition onto diethyl and diisopropyl azodicarboxylates, as dipolarophiles, under the influence of dimethyl sulfide and potassium carbonate to provide the desired functionalized dihydropyrazole derivatives (**165b-r**) in 64-79% isolated yields

(Eq. 53, Table 4). All the dihydropyrazole derivatives were fully characterized using IR, ^{1}H NMR (Spectra 23, 25 & 27 for compounds **165g**, **165o** & **165q** respectively), ^{13}C NMR (Spectra 24, 26 & 28 for compounds **165g**, **165o** & **165q** respectively), mass spectral data and elemental analyses.



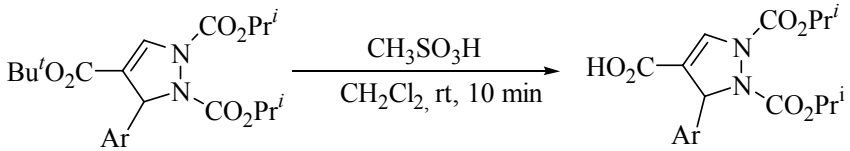
164a-i **165b-r** **Eq. 53**

Ar = C_6H_5, 4-MeC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4

R_1 = Me, Et, Bu, Bu^t; R_2 = Et, Pr^i

64-79%

With a view to confirm further the structures of dihydropyrazole derivatives (**165a-r**) we have transformed three representative pyrazole derivatives **165p-r** (containing *tert*-butyl ester group) to the corresponding acids (**166a-c**) *via* the treatment with CH_3SO_3H as white solids (Eq. 54). The structures of these dihydropyrazole acid derivatives (**166a-c**) are in full agreement with IR, ^{1}H NMR (Spectra 29 & 31 for compounds **166a** & **166b** respectively), ^{13}C NMR (Spectra 30 & 32 for compounds **166a** & **166b** respectively), mass spectral data and elemental analyses. We obtained single crystals for these acids. The X-ray data analysis of these single crystals of acids (**166a-c**) clearly confirmed the structures (Figures X8-X10, Tables VIII-X).

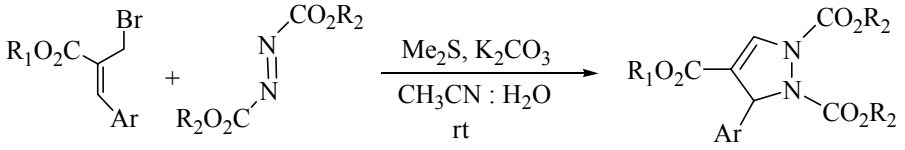


Ar = C_6H_5 (**165p**)
Ar = 4-ClC_6H_4 (**165q**)
Ar = 4-BrC_6H_4 (**165r**)

Eq. 54

Ar = C_6H_5 (**166a**, yield = 60%)
Ar = 4-ClC_6H_4 (**166b**, yield = 64%)
Ar = 4-BrC_6H_4 (**166c**, yield = 51%)

Table 4: Synthesis of dihydropyrazole derivatives (**165a-r**)[a]



164a-i **165a-r**

Entry	Ar	R_1	Bromides	R_2	t (h)	Product[b]	Yield(%)[c]
1	C_6H_5	Me	**164a**	Et	7	**165a**	74
2	C_6H_5	Et	**164b**	Et	8	**165b**	69
3	4-MeC_6H_4	Me	**164c**	Et	8	**165c**	74
4	4-BrC_6H_4	Me	**164d**	Et	10	**165d**	75
5	4-BrC_6H_4	Bu	**164e**	Et	12	**165e**	66
6	3-ClC_6H_4	Me	**164f**	Et	7	**165f**	69
7	C_6H_5	Bu^t	**164g**	Et	9	**165g**	68
8	4-ClC_6H_4	Bu^t	**164h**	Et	9	**165h**	67
9	4-BrC_6H_4	Bu^t	**164i**	Et	9	**165i**	64
10	C_6H_5	Me	**164a**	Pr^i	8	**165j**	75
11	C_6H_5	Et	**164b**	Pr^i	8	**165k**	67
12	4-MeC_6H_4	Me	**164c**	Pr^i	10	**165l**	79
13	4-BrC_6H_4	Me	**164d**	Pr^i	9	**165m**	75
14	4-BrC_6H_4	Bu	**164e**	Pr^i	12	**165n**	71
15	3-ClC_6H_4	Me	**164f**	Pr^i	7	**165o**	70
16	C_6H_5	Bu^t	**164g**	Pr^i	9	**165p**	69
17	4-ClC_6H_4	Bu^t	**164h**	Pr^i	9	**165q**[d]	67
18	4-BrC_6H_4	Bu^t	**164i**	Pr^i	9	**165r**	74

a) All the reactions were carried out in 1 mmol scale of BH bromides (**164a-i**) with 1 mmol dialkyl azodicarboxylates in presence of Me_2S (1.2 mmol) and K_2CO_3 (1 mmol) in CH_3CN (1 mL) : H_2O (0.1 mL) at room temperature.

b) All the compounds were isolated as colorless viscous liquids and fully characterized.

c) Isolated yields based on the Baylis-Hillman bromides (**164a-i**).

d) On keeping for long time this compound became solid (m.p. 110 ^oC).

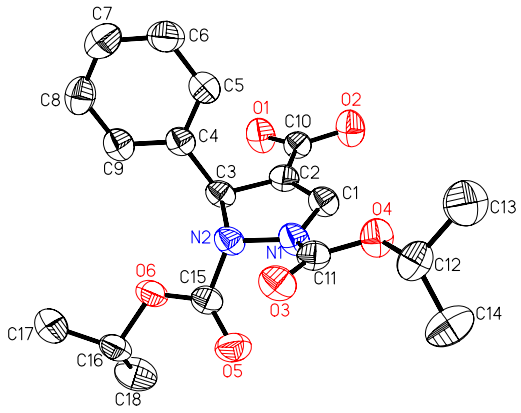


Figure X8

ORTEP diagram of the compound **166a**
(*Hydrogen atoms were omitted for clarity*)

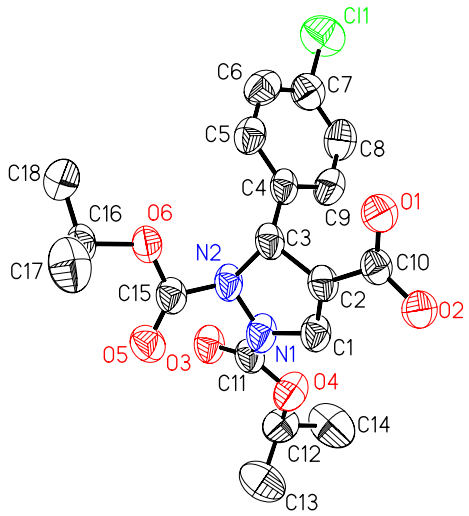


Figure X9

ORTEP diagram of the compound **166b**
(*Hydrogen atoms were omitted for clarity*)

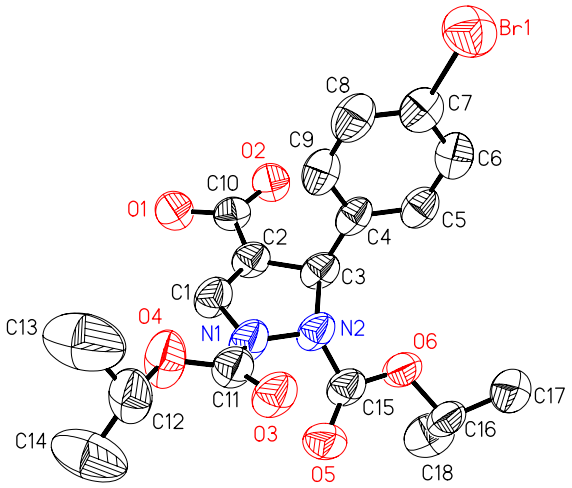
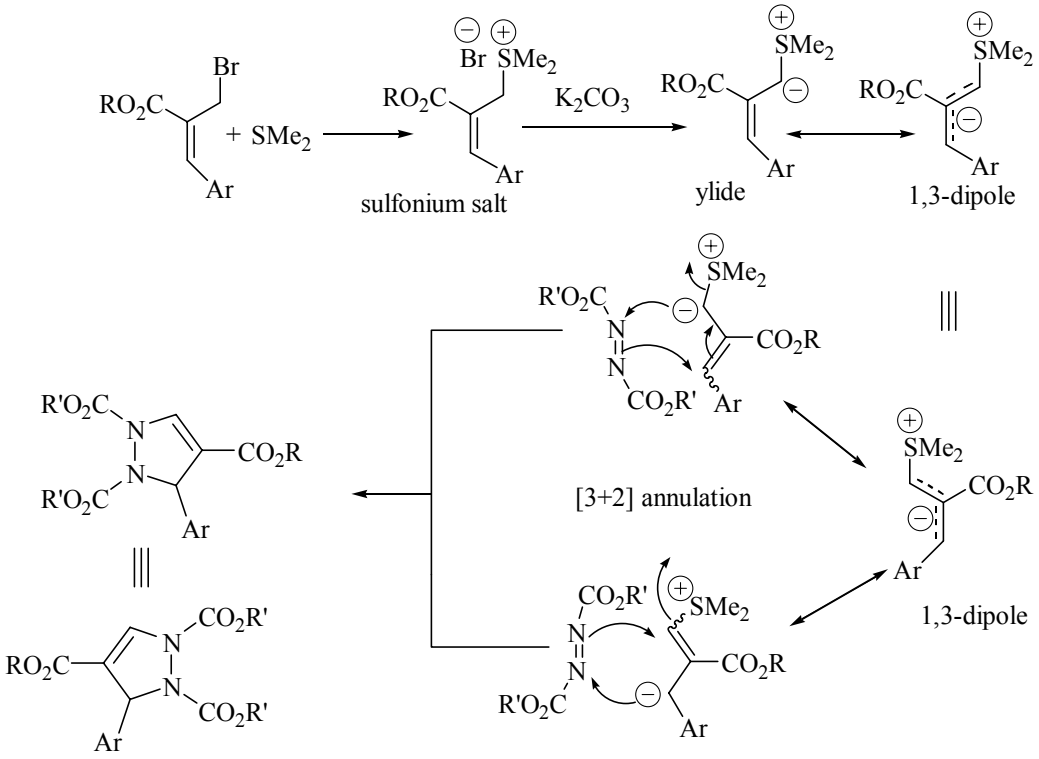


Figure X10

ORTEP diagram of the compound **166c**
(*Hydrogen atoms were omitted for clarity*)

A plausible mechanism for this interesting [3 + 2] annulation strategy is provided in Scheme 71. The reaction is believed to proceed first through the formation of sulfonium salt, *via* the reaction of Baylis-Hillman bromide with dimethyl sulfide. This sulfonium salt would, then in the presence of a base (K_2CO_3), become a ylide and serves as a 1,3-dipole, (or an equivalent) for reaction with dialkyl azodicarboxylate as dipolarophile in [3 + 2] annulation strategy, to provide the desired functionalized dihydropyrazole derivative.

Scheme 71



Thus we have successfully used the Baylis-Hillman bromides as practical source for 1,3-dipoles, to afford an interesting class of pyrazole derivatives, possessing different substitution profiles, *via* [3 + 2] annulation reaction with dialkyl azodicarboxylates as dipolarophiles, in an operationally simple one-pot procedure.

Table VIII. Crystal data and structure refinement for **166a.**

Empirical formula	$C_{18}H_{22}N_2O_6$
Formula weight	362.38
Temperature	298 K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 9.045(3) Å; α = 103.908(4) deg.
	b = 9.530(3) Å; β = 93.891(4) deg.
	c = 12.203(3) Å; γ = 114.008(4) deg.
Volume	916.3(4) $Å^3$
Z, Calculated density	2, 1.313 Mg/m^3
Absorption coefficient	0.099 mm^{-1}
F(000)	384
Crystal size	0.47 x 0.46 x 0.30 mm
Theta range for data collection	1.75 to 26.04 deg.
Limiting indices	$-11\leq h\leq 11$, $-11\leq k\leq 11$, $-14\leq l\leq 14$
Reflections collected / unique	9003 / 3538 [R(int) = 0.0440]
Completeness to theta = 26.04	97.5 %
Max. and min. transmission	0.9708 and 0.9548
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3538 / 0 / 240
Goodness-of-fit on F^2	1.052
Final R indices [I>2sigma(I)]	R1 = 0.0432, wR2 = 0.1115
R indices (all data)	R1 = 0.0512, wR2 = 0.1173
Largest diff. peak and hole	0.204 and -0.278 e. $Å^{-3}$

Table IX. Crystal data and structure refinement for **166b.**

Empirical formula	$C_{18}H_{21}ClN_2O_6$
Formula weight	396.82
Temperature	298 K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 9.6563(12) Å; α = 104.422(2) deg.
	b = 9.7707(12) Å; β = 91.659(2) deg.
	c = 12.1973(15) Å; γ = 115.368(2) deg.
Volume	994.9(2) $Å^3$
Z, Calculated density	2, 1.325 Mg/m^3
Absorption coefficient	0.228 mm^{-1}
F(000)	416
Crystal size	0.46 x 0.25 x 0.20 mm
Theta range for data collection	1.74 to 25.00 deg.
Limiting indices	$-11\leq h\leq 11$, $-11\leq k\leq 11$, $-14\leq l\leq 14$
Reflections collected / unique	9609 / 3512 [R(int) = 0.0192]
Completeness to theta = 25.00	99.8 %
Max. and min. transmission	0.9559 and 0.9025
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3512 / 0 / 249
Goodness-of-fit on F^2	1.037
Final R indices [I>2sigma(I)]	R1 = 0.0436, wR2 = 0.1149
R indices (all data)	R1 = 0.0548, wR2 = 0.1232
Largest diff. peak and hole	0.200 and -0.228 e. $Å^{-3}$

Table X. Crystal data and structure refinement for **166c.**

Empirical formula	$C_{18}H_{21}BrN_2O_6$
Formula weight	441.28
Temperature	298 K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 9.9179(8) Å; α = 104.4070(10) deg.
	b = 9.9305(8) Å; β = 91.4570(10) deg.
	c = 12.1617(10) Å; γ = 116.6200(10) deg.
Volume	1024.11(14) $Å^3$
Z, Calculated density	2, 1.431 Mg/m^3
Absorption coefficient	2.042 mm^{-1}
F(000)	452
Crystal size	0.25 x 0.22 x 0.15 mm
Theta range for data collection	1.75 to 25.80 deg.
Limiting indices	$-12\leq h\leq 12$, $-12\leq k\leq 12$, $-14\leq l\leq 14$
Reflections collected / unique	10443 / 3900 [R(int) = 0.0254]
Completeness to theta = 25.80	99.2 %
Max. and min. transmission	0.7493 and 0.6293
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3900 / 0 / 252
Goodness-of-fit on F^2	1.020
Final R indices [I>2sigma(I)]	R1 = 0.0406, wR2 = 0.0971
R indices (all data)	R1 = 0.0747, wR2 = 0.1110
Largest diff. peak and hole	0.356 and -0.329 e. $Å^{-3}$

A novel synthesis of spiro-oxindole derivatives containing spiro-fused 1,2-bisalkoxy-1*H*-pyrazole framework using isatin-derived Baylis-Hillman bromides through [3 + 2] annulation strategy

Spiro-oxindole moiety is present in a number of naturally occurring compounds such as tasmanine (**167**),[293] aristoteline (**168**),[293] javaniside (**169**),[294] spirotryprostatins A & B (**170** & **171**),[295] horsfiline (**172**),[296,297] coerulescine (**173**),[297] welwitindolinone A isonitrile (**174**),[298,299] and brevianamide A (**175**)[300] (Figure 12) *etc*.

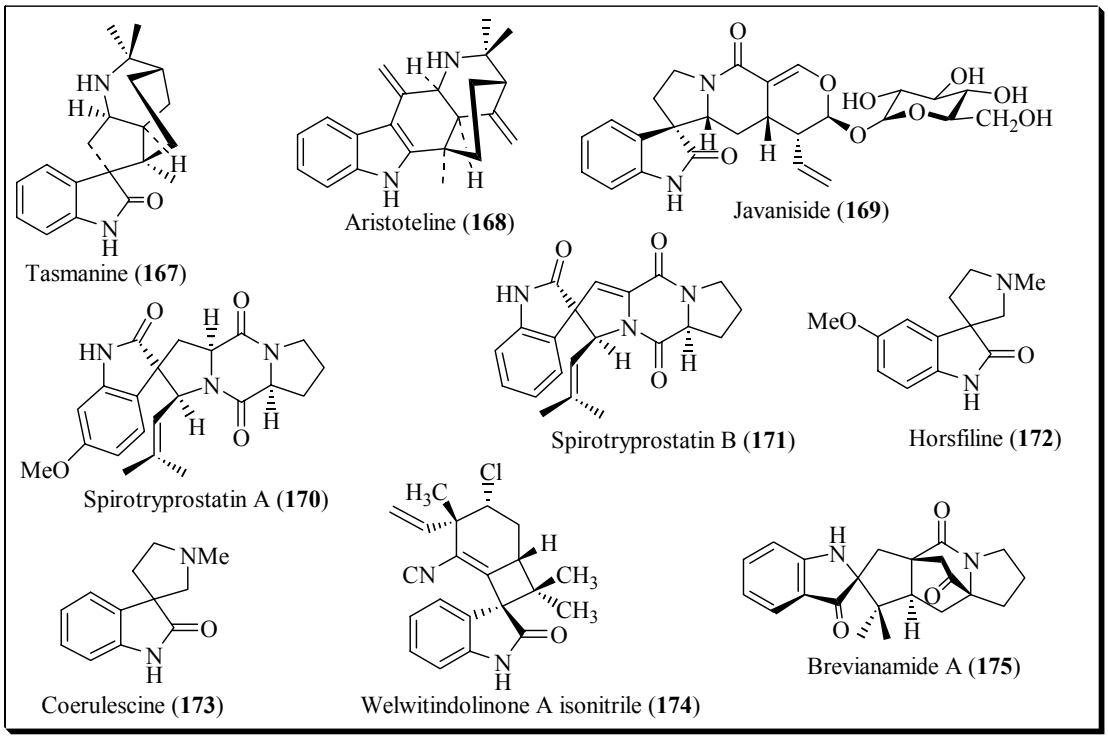
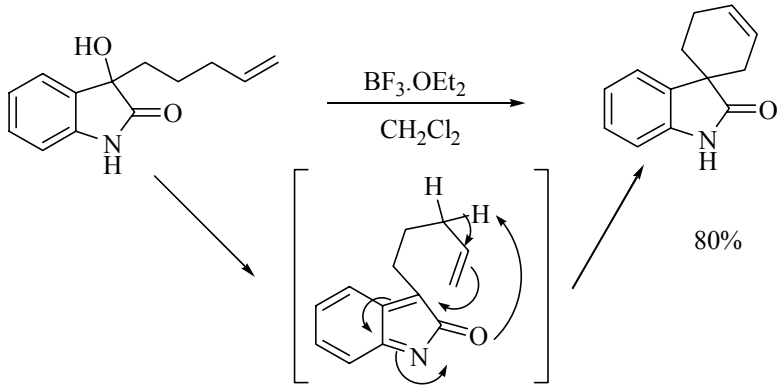


Figure 12

Therefore development of simple methodology for expedient synthesis of such compounds has become an interesting area in organic synthesis. Some of the recent literature methods for the synthesis of spiro-oxindole derivatives are presented in this section.

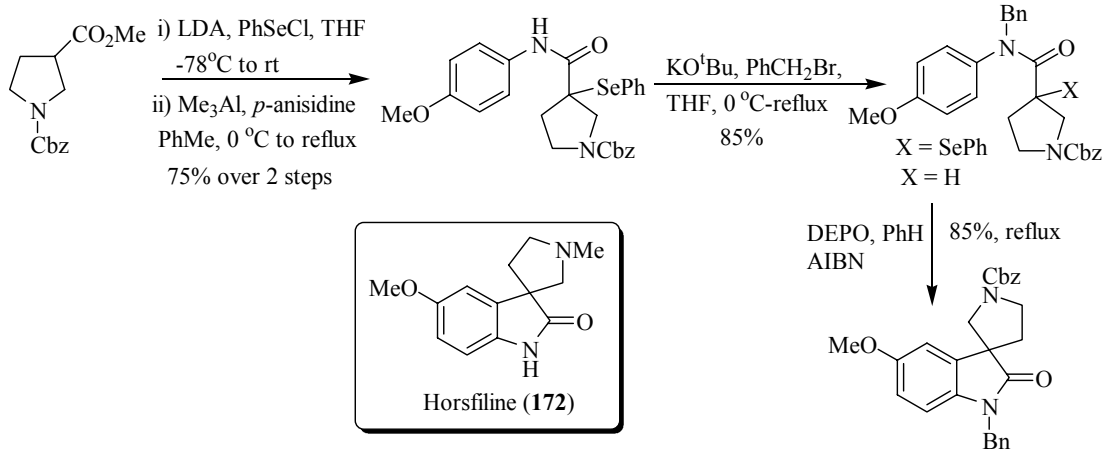
Padwa and coworkers[301] have developed BF_3-OEt_2 catalyzed cyclization of 3-hydroxy-(3-pent-4-enyl)-1,3-dihydroindole-2-one to obtain spiro-oxindoles in a simple one-pot procedure (Scheme 72).

Scheme 72

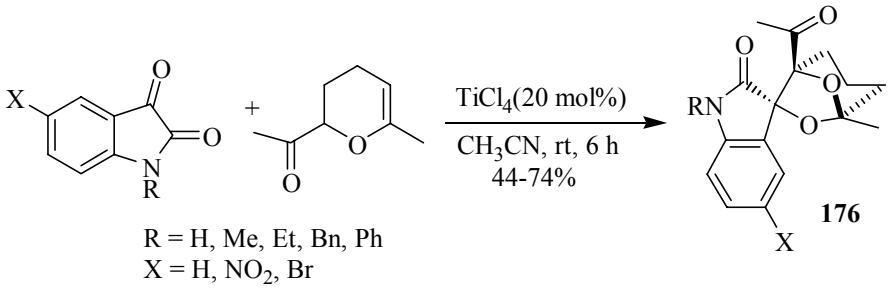


Murphy and coworkers[302] have reported a concise route to the spiro-oxindole derivative, a precursor of horsfiline (**172**) using diethylphosphine oxide (DEPO) as the key reagent following the synthetic sequence shown in Scheme 73.

Scheme 73



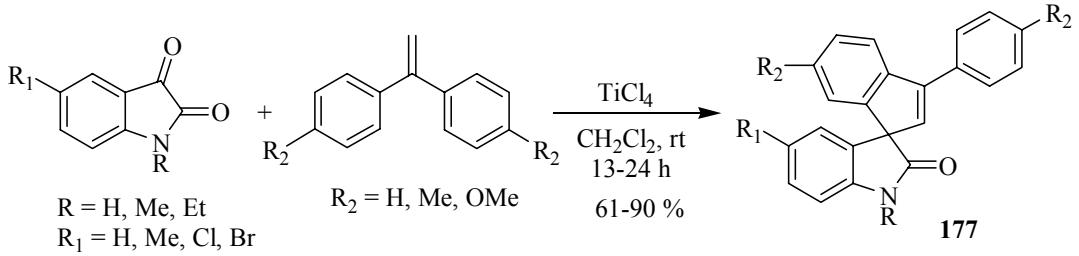
Our research group[303] has reported $TiCl_4$-catalyzed coupling of 2-acetyl-6-methyl-2,3-dihydro-4*H*-pyran with isatin derivatives for stereoselective synthesis of spiro-oxindoles (**176**) containing both the oxindole and 6,8-dioxabicyclo(3.2.1)octane moieties *via* a simple, convenient and one-pot atom economical methodology (Eq. 55).



R = H, Me, Et, Bn, Ph
X = H, NO_2, Br

Eq. 55

Recently, our research group[304] has developed a simple and one-pot $TiCl_4$-mediated strategy for synthesis of 1*H*-indene-spiro-oxindoles (**177**) involving tandem Prins and Friedel-Crafts (PFC) reactions, using diarylethylenes and isatin derivatives as reaction partners (Eq. 56).



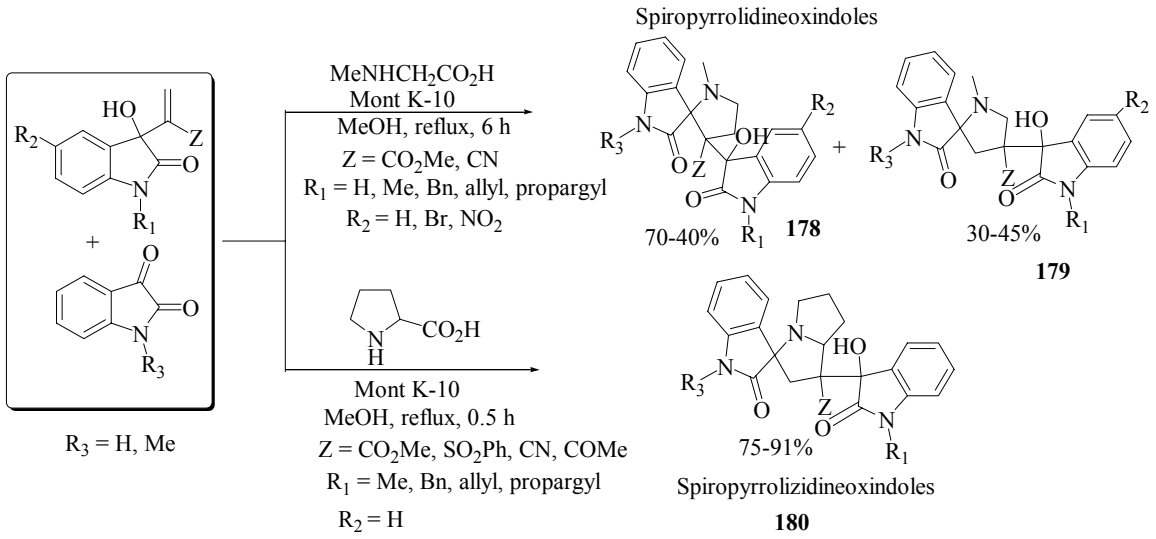
R = H, Me, Et
R_1 = H, Me, Cl, Br

R_2 = H, Me, OMe

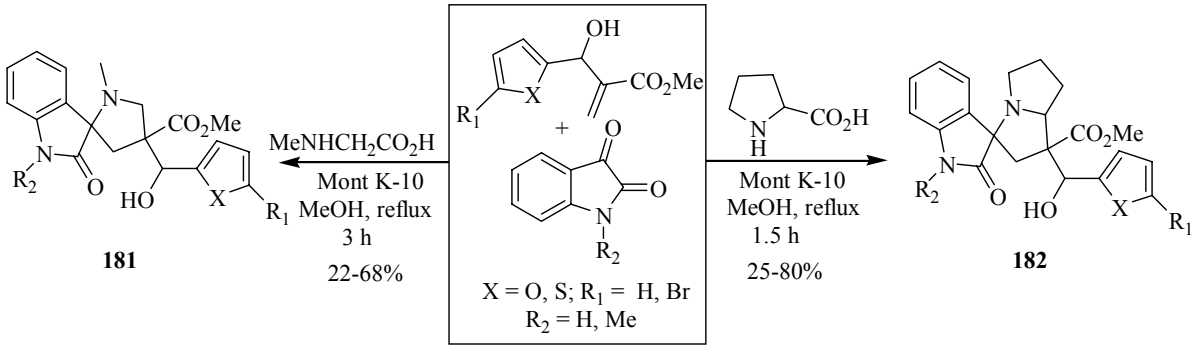
Eq. 56

Shanmugam and coworkers[305] have reported an interesting methodology for the synthesis of functionalized 3-spiropyrrolidine oxindoles (**178**, **179** & **181**) and 3-spiropyrrolizidine oxindoles (**180**, **182**) from the Baylis-Hillman adducts derived from isatin and heterocyclic aldehydes following the reaction sequence as described in Schemes 74 and 75.

Scheme 74

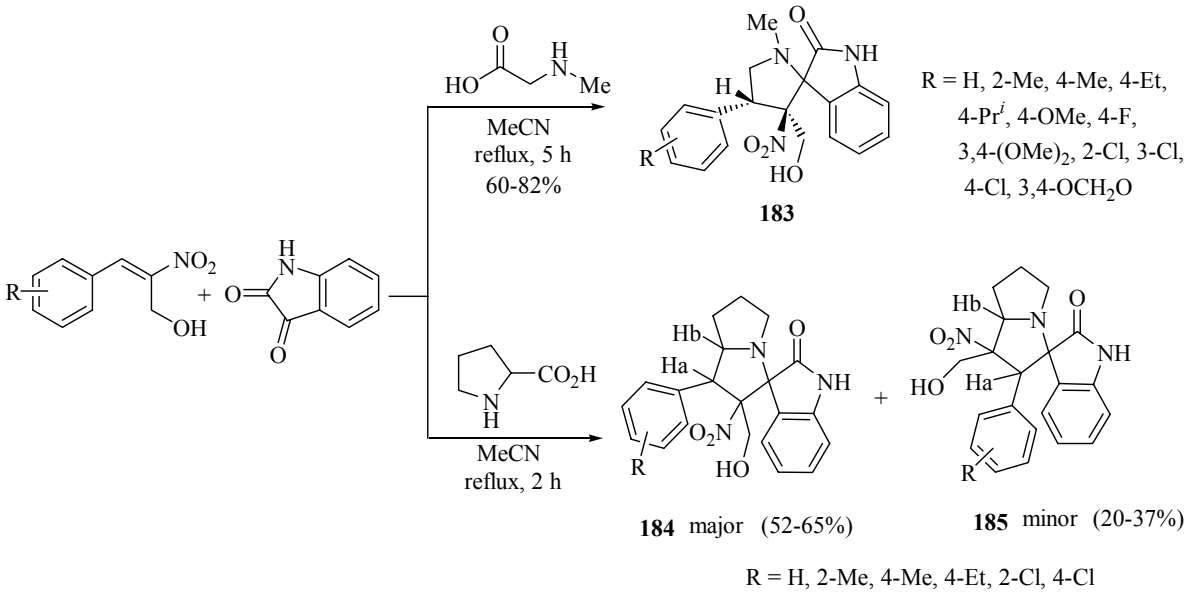


Scheme 75

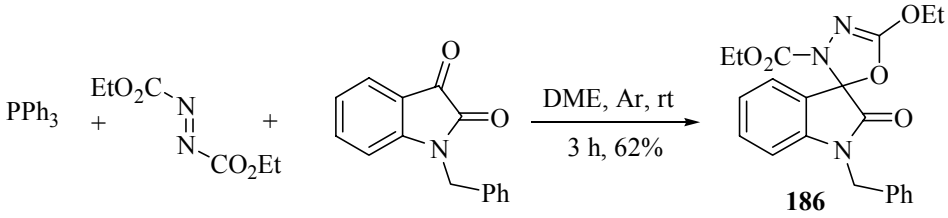


Very recently, Bakthadoss and coworkers[306] have reported novel stereoselective synthesis of functionalized pyrrolidine fused spiro-oxindoles (**183**) and pyrrolizidine fused spiro-oxindoles (**184**, **185**) using the Baylis-Hillman adducts derived from nitroolefins *via* intermolecular [3 + 2] cycloaddition reaction following the reaction sequence as described in Scheme 76.

Scheme 76



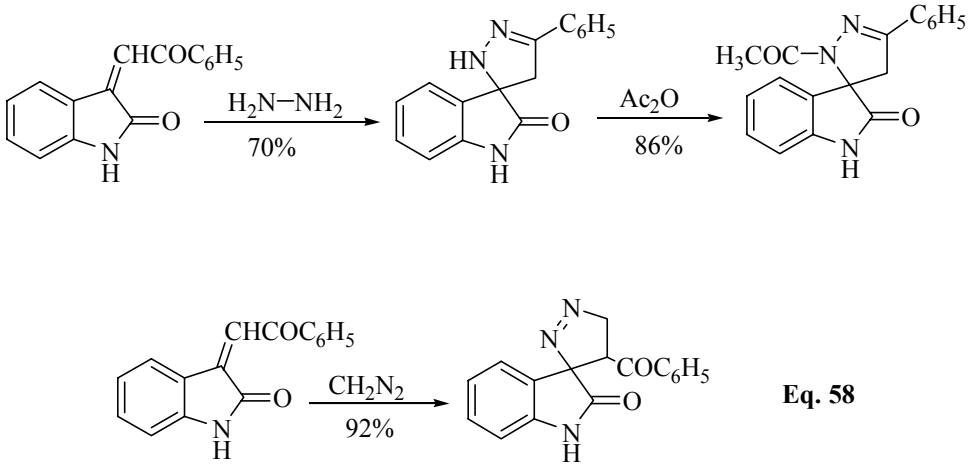
Nair and coworkers[307] have uncovered a novel synthesis of spirooxadiazoline (**186**) by treating *N*-substituted isatins with diazoesters in the presence of triphenylphosphine according to Eq. 57 (one example is presented).



Eq. 57

An interesting synthesis of pyrazoline fused spiro-oxindoles was reported by Otomasu and coworkers[308] *via* the reaction of 2-oxo-3-indolylidene compounds with hydrazine hydrate or with diazometahne (Scheme 77 and Eq. 58).

Scheme 77

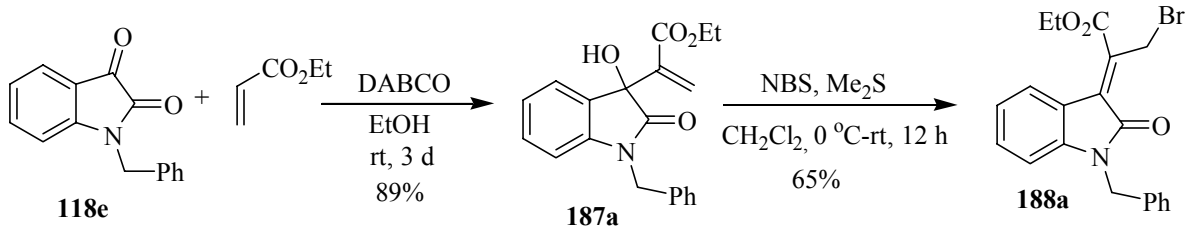


Eq. 58

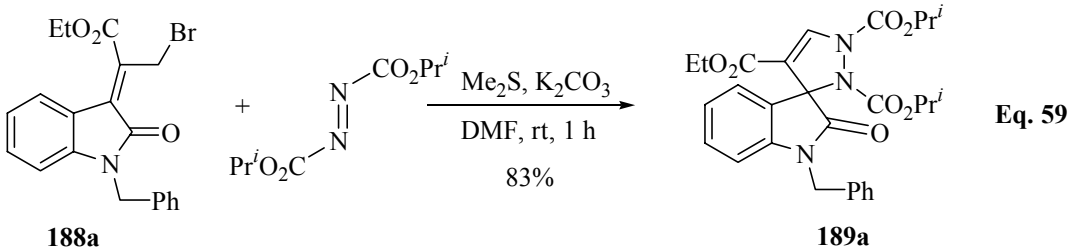
In the previous section we have already presented our work on the synthesis of pyrazole framework *via* [3 + 2] annulation strategy using Baylis-Hillman bromides as 1,3-dipoles. We have planned to extend this strategy for synthesis of spiro-oxindole derivatives containing spiro-fused 1*H*-pyrazole derivatives using the bromides of Baylis-Hillman alcohols derived from isatin derivatives and alkyl acrylates, as 1,3-dipoles for cycloaddition reaction with dialkyl azodicarboxylates as dipolarophiles.

We have then first selected the Baylis-Hillman bromide, (*Z*)-3-(1-ethoxycarbonyl-2-bromo)ethylidene-1-benzylindolin-2-one (**188a**) and diisopropyl azodicarboxylate as the reaction partners. The required Baylis-Hillman adduct was synthesized from the Baylis-Hillman alcohol, ethyl 2-(1-benzyl-3-hydroxyindolin-2-on-3-yl)-2-methylenethanoate (**187a**) by treatment of NBS in presence of dimethyl sulphide in dichloromethane. The alcohol (**187a**) was in turned prepared *via* the Baylis-Hillman coupling of *N*-benzylisatin (**118e**) and ethyl acrylate under the catalytic influence of DABCO (Scheme 78).[92]

Scheme 78



We have performed reaction between Baylis-Hillman bromide (*Z*)-3-(1-ethoxycarbonyl-2-bromo)ethylidene-1-benzylindolin-2-one (**188a**) (1 mmol) with diisopropyl azodicarboxylate (1 mmol) in the presence of Me_2S (1.2 mmol) and K_2CO_3 (1 mmol) in DMF (1 mL) at room temperature for 1 h to provide the expected dihydropyrazole fused spiro-oxindole derivative, (1-benzylindolin-2-on)-3-spiro-3′-[4′-ethoxycarbonyl-1′,2′-bis(isopropoxycarbonyl)-2′,3′-dihydro-1′*H*-pyrazole] (**189a)** in 83% isolated yield (Eq. 59) after usual work-up followed by column chromatography (silica gel, 25% ethyl acetate in hexanes). The structure of this dihydropyrazole fused spiro-oxindole derivative (**189a**) is in agreement with IR, ^{1}H NMR (Spectrum 33), ^{13}C NMR (Spectrum 34), mass spectral data and elemental analysis.

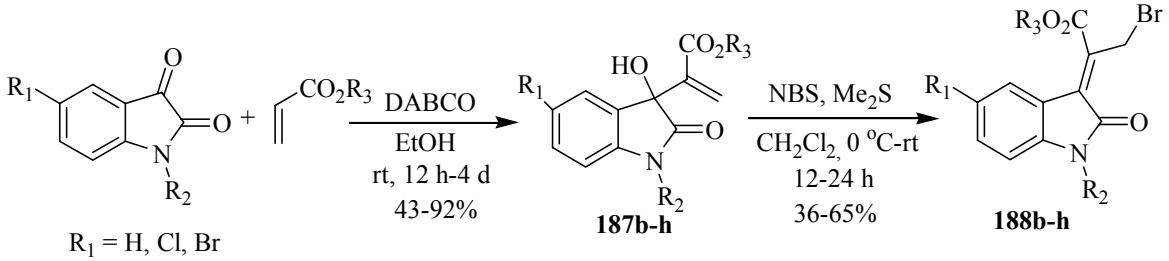


Eq. 59

To understand the generality of the reaction we have prepared representative Baylis-Hillman alcohols (**187b-h**) *via* the coupling of various isatin derivatives with alkyl acrylates in the presence of DABCO and transformed them into corresponding bromides

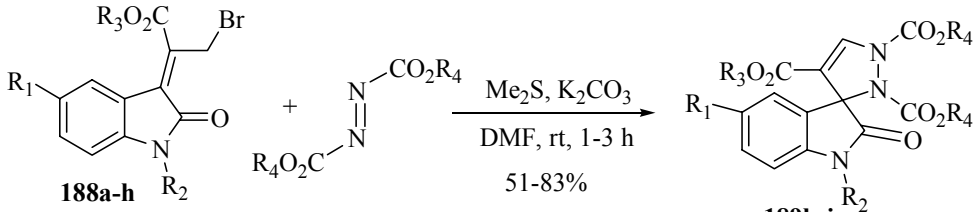
(**188b-h**) by the treatment of NBS in the presence of dimethyl sulfide in CH_2Cl_2 (Scheme 79).

Scheme 79



R_1 = H, Cl, Br
R_2 = CH_2Ph, Me, H
R_3 = Et, Me

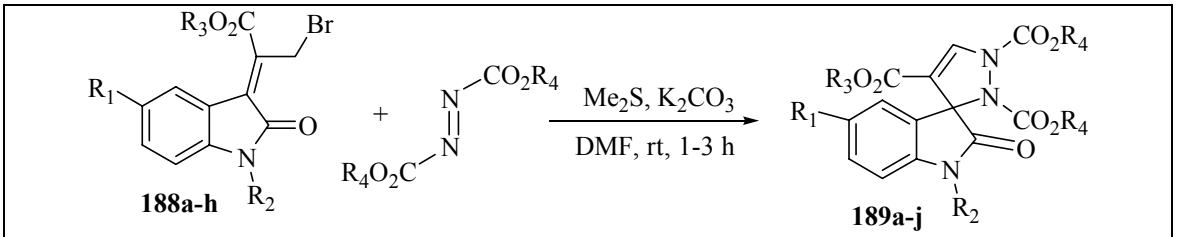
We have then successfully employed these Baylis-Hillman bromides (**188a-h**) as source of 1,3-dipoles for [3 + 2] cycloaddition onto diethyl and diisopropyl azodicarboxylates, as dipolarophiles, under the influence of dimethyl sulfide and potassium carbonate to provide the desired functionalized dihydropyrazolo spiro-oxindole derivatives (**189b-j**) in 51-83% isolated yields (Eq. 60, Table 5). All the dihydropyrazolo spiro-oxindole derivatives (**189b-j**) were fully characterized using IR, ^{1}H NMR (Spectra 35, 37 & 39 for compounds **189e**, **189g** & **189h** respectively), ^{13}C NMR (Spectra 36, 38 & 40 for compounds **189e**, **189g** & **189h** respectively), mass spectral data and elemental analyses. Compound **189c** and **189f** were further confirmed using single crystal X-ray data analysis (Figures X11 & X12, Tables XI & XII).



Eq. 60

R_1 = H, Cl, Br
R_2 = H, Me, CH_2Ph
R_3 = Me, Et
R_4 = Et, Pr^i

Table 5: Synthesis of dihydropyrazolo spiro-oxindole derivatives (**189a-j**)[a]



Entry	R_1	R_2	R_3	R_4	bromide	t (h)	product[b]	mp (^oC)	Yield(%)[c]
1	H	CH_2Ph	Et	Pr^i	**188a**	1	**189a**	72-74	83
2	Cl	CH_2Ph	Et	Pr^i	**188b**	1	**189b**	82-84	76
3	H	CH_2Ph	Et	Et	**188a**	1	**189c**[d]	151-152	61
4	H	CH_2Ph	Me	Pr^i	**188c**	1	**189d**	156-158	70
5	H	Me	Et	Pr^i	**188d**	2	**189e**	151-153	53
6	Cl	Me	Et	Pr^i	**188e**	3	**189f**[d]	162-164	55
7	H	H	Et	Pr^i	**188f**	1	**189g**	98-100	53
8	Cl	H	Et	Pr^i	**188g**	1	**189h**	161-162	51
9	Br	H	Et	Pr^i	**188h**	1	**189i**	170-171	59
10	Br	H	Et	Et	**188h**	1	**189j**	118-120	51

a) All the reactions were carried out in 1 mmol scale of BH bromides (**188a-h**) with 1 mmol dialkyl azodicarboxylates in presence of Me_2S (1.2 mmol) and K_2CO_3 (1 mmol) in DMF at room temperature.

b) All the compounds were isolated as solids and fully characterized.

c) Isolated yields based on the BH bromides (**188a-h**).

d) Structures of these compounds were further confirmed by single crystal X-ray data analysis.

Interesting observations in NMR spectra:

We have interesting observations in ^1H and ^{13}C NMR spectra of these spiro compounds (**189a-j**). In ^1H NMR spectra the protons of ester groups attached to nitrogen and benzylic

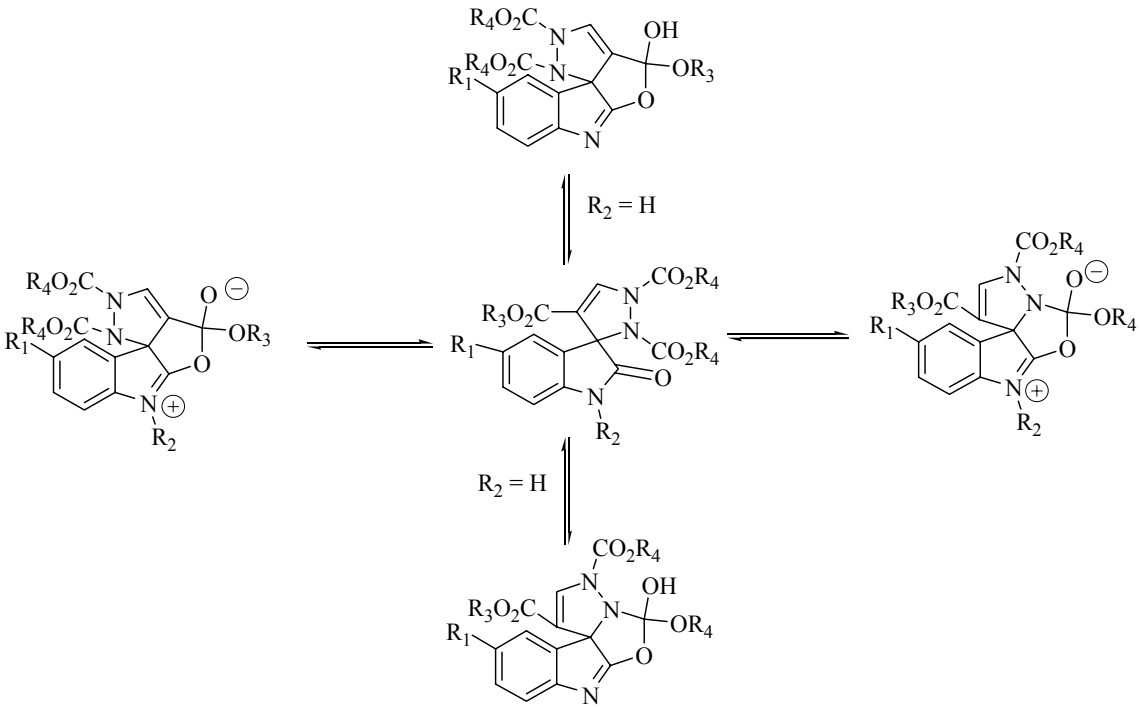
protons at 1-position appeared as broad signals. Similarly, a number of carbons signals appeared as broad or low intensity peaks. The details are given below (Table 6).

Table 6

Compounds	Low intensity / broad peaks (^{13}C signals)
189a	δ 71.42, 73.94, 113.31, 143.19, 151.31,153.28.
189b	δ 71.78, 73.74, 112.76, 129.38, 151.49, 153.22.
189c	δ 113.29, 151.77.
189d	δ 71.46, 73.86, 112.62, 143.09, 150.96,153.19.
189e	δ 71.22, 73.83, 112.97, 127.82, 151.27, 153.04.
189f	δ 71.66, 73.68, 109.05, 112.29, 129.45, 151.16, 153.29.
189g	δ 112.77, 128.31, 151.20, 153.33, 174.75.
189h	δ 112.24, 129.77, 151.09, 153.08, 174.45.
189i	δ 112.94, 130.33, 150.92, 153.22, 174.05.
189j	δ 14.18, 63.58, 112.13, 129.85, 151.36, 153.66, 174.12.

Although there is no evidence, we feel that it is reasonable to attribute the broadening of signals due to the existence of two (dynamic) structures which are probably in equilibrium in solution. Tentative dynamic structures are given in Scheme 80.

Scheme 80



In the case of indoline derivatives without any substitution at N-1 (**189g-j**) ester carbonyl peaks (C=O) appeared as broad signals with less intensity which to some extent might support the structural equilibrium as shown in Scheme 80.

To understand the exact reason for broadening of peaks in NMR spectra and the possible dynamic structures further studies are required which are underway in our laboratory.

Thus, we have successfully employed isatin-derived Baylis-Hillman bromides as useful source for 1,3 dipoles, to provide an interesting class of densely functionalized dihydropyrazolo spiro-oxindole derivatives, *via* [3 + 2] annulation reaction with dialkyl azodicarboxylates as dipolarophiles, in a facile one-pot procedure.

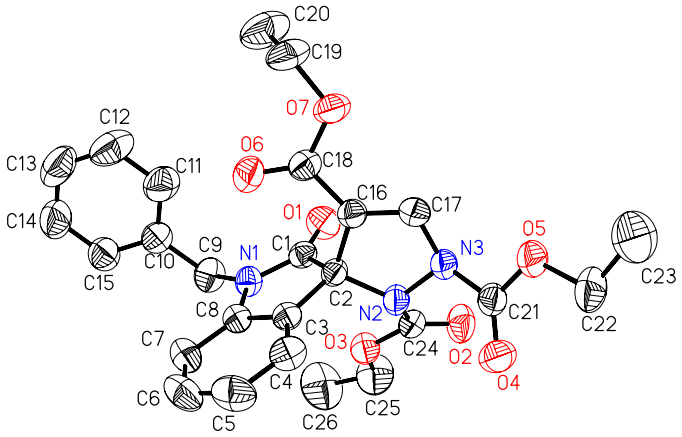


Figure X11

ORTEP diagram of the compound **189c**
(Hydrogen atoms were omitted for clarity)

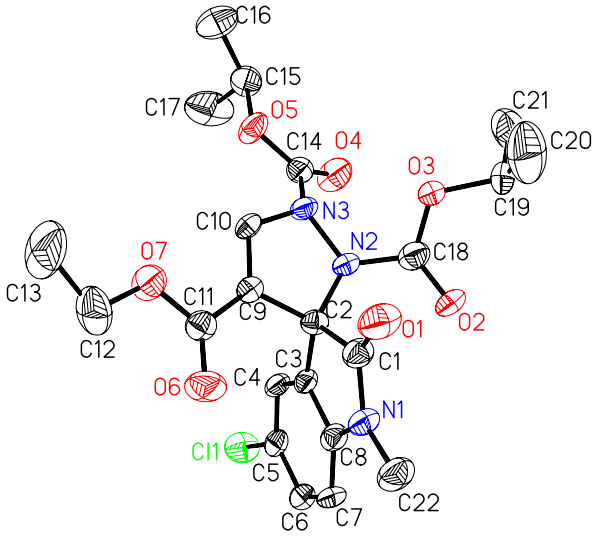


Figure X12

ORTEP diagram of the compound **189f**
(Hydrogen atoms were omitted for clarity)

Table XI. Crystal data and structure refinement for **189c.**

Empirical formula	$C_{26}H_{27}N_3O_7$
Formula weight	493.51
Temperature	298 K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)/n
Unit cell dimensions	a = 11.2923(12) Å; α = 90 deg.
	b = 15.9650(16) Å; β = 101.516(2) deg.
	c = 14.3728(15) Å; γ = 90 deg.
Volume	2539.0(5) $Å^3$
Z, Calculated density	4, 1.291 Mg/m^3
Absorption coefficient	0.095 mm^{-1}
F(000)	1040
Crystal size	0.18 x 0.16 x 0.16 mm
Theta range for data collection	1.93 to 25.00 deg.
Limiting indices	$-13\leq h\leq 13$, $-18\leq k\leq 18$, $-17\leq l\leq 17$
Reflections collected / unique	24115 / 4474 [R(int) = 0.0431]
Completeness to theta = 25.00	100.0 %
Absorption correction	Multi-scan method (SADABS)
Max. and min. transmission	0.9850 and 0.9831
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4474 / 0 / 328
Goodness-of-fit on F^2	1.086
Final R indices [I>2sigma(I)]	R1 = 0.0558, wR2 = 0.1253
R indices (all data)	R1 = 0.0718, wR2 = 0.1335
Largest diff. peak and hole	0.193 and -0.172 e. $Å^{-3}$

Table XII. Crystal data and structure refinement for **189f.**

Empirical formula	$C_{22}H_{26}ClN_3O_7$
Formula weight	479.91
Temperature	298 K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)/c
Unit cell dimensions	a = 11.106(5) Å; α = 90 deg.
	b = 9.933(4) Å; β = 100.043(8) deg.
	c = 21.999(9) Å; γ = 90 deg.
Volume	2389.7(17) $Å^3$
Z, Calculated density	4, 1.334 Mg/m^3
Absorption coefficient	0.206 mm^{-1}
F(000)	1008
Crystal size	0.40 x 0.24 x 0.12 mm
Theta range for data collection	1.86 to 25.00 deg.
Limiting indices	$-13\leq h\leq 13$, $-11\leq k\leq 11$, $-26\leq l\leq 26$
Reflections collected / unique	22215 / 4199 [R(int) = 0.0358]
Completeness to theta = 25.00	100.0 %
Absorption correction	Multi-scan method (SADABS)
Max. and min. transmission	0.9756 and 0.9220
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4199 / 0 / 304
Goodness-of-fit on F^2	1.075
Final R indices [I>2sigma(I)]	R1 = 0.0503, wR2 = 0.1160
R indices (all data)	R1 = 0.0627, wR2 = 0.1228
Largest diff. peak and hole	0.267 and -0.152 e. $Å^{-3}$

CONCLUSIONS

We have achieved considerable success in our objectives on understanding the $TiCl_4$-mediated Baylis-Hillman reaction and also on application of the Baylis-Hillman adducts stated in the beginning of this section.

We have examined for the first time, the $TiCl_4$-mediated Baylis-Hillman reaction of *N*-substituted isatin (**118a**) with cyclohex-2-enone to obtain the corresponding Baylis-Hillman adduct (**119**) and also developed a facile one-pot methodology for synthesis of 3-(2-hydroxyphenyl)indolin-2-one derivatives (**120-130**) from *N*-substituted isatins (**118a-k**) and cyclohex-2-enones *via* the $TiCl_4$-induced Baylis-Hillman reaction followed by successive dehydration and aromatization under the influence of aq. HBr.

We have also investigated $TiCl_4$-mediated Baylis-Hillman reaction of cyclic aromatic 1,2-diones with cycloalk-2-enones to obtain the corresponding adducts (**144a-l**). The resulting Baylis-Hillman adducts **144d-i** have been successfully transformed into pentacyclic and hexacyclic fused furan ring systems (**149a-f**) *via* the treatment of methanesulfonic acid. Spiro-fused heptacyclic furan ring systems (**150a,b**) were obtained from the Baylis-Hillman adducts **144a,b** under the influence of methanesulfonic acid.

We have successfully used the Baylis-Hillman bromides *i.e* alkyl (2*Z*)-2(bromomethyl)-3-arylprop-2-enoates (**164a-i**) as useful source for 1,3 dipoles, to provide an interesting class of pyrazole derivatives [3-aryl-1,2-bisalkoxycarbonyl-4-alkoxycarbonyl-2,3-dihydro-1*H*-

pyrazole (**165a-r**)], possessing different substitution profiles, *via* [3 + 2] annulation reaction with dialkyl azodicarboxylates as dipolarophiles, in an operationally simple one-pot procedure.

Allyl bromides (**188a-h**) obtained from the Baylis-Hillman alcohols, derived from isatin derivatives and alkyl acrylates, have been successfully used for a facile [3 + 2] annulation reaction with dialkyl azodicarboxylates to provide an interesting class of dihydropyrazolo spiro-oxindole derivatives (**189a-j**).

EXPERIMENTAL

Melting Points: All melting points were recorded on a Superfit (India) capillary melting point apparatus and are uncorrected.

Boiling Points: Boiling points refer to the temperature measured using short path distillation units and are uncorrected.

Infrared Spectra: Infrared spectra were recorded on a JASCO FT / IR-5300 spectrophotometer. All the spectra were calibrated against polystyrene absorption at 1601 cm^{-1}. Solid samples were recorded as KBr wafers and liquid samples as thin film between NaCl plates or solution spectra in CH_2Cl_2.

Nuclear Magnetic Resonance Spectra: Proton magnetic resonance spectra and carbon-13 magnetic resonance spectra were recorded on a BRUKER-AC-200 and BRUKER-AVANCE-400 spectrometers. ^1H NMR (400 MHz) spectra for all the samples were measured in chloroform-*d*, unless otherwise mentioned (δ = 2.50 ppm for ^1H NMR in the case of DMSO-d_6), with TMS (δ = 0 ppm) as an internal standard. ^{13}C NMR (50 MHz / 100 MHz) spectra for all the samples were measured in chloroform-*d*, unless otherwise mentioned (in the case of DMSO-d_6, δ = 39.70 ppm its middle peak of the septet), with its middle peak of the triplet (δ = 77.10 ppm) as an internal standard. Spectral assignments are as follows: (1) chemical shifts on the δ scale, (2) standard abbreviation for multiplicity,

that is, s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet, dd = doublet of doublet, td = triplet of doublet, dt = doublet of triplet, br = broad, bs = broad singlet, dABq = doublet of AB quartet, tABq = triplet of AB quartet. (3) number of hydrogens integrated for the signal, (4) coupling constant *J* in Hertz.

Mass Spectral Analysis: Shimadzu LCMS 2010A mass spectrometer.

Elemental Analysis: Elemental analyses were performed on a Thermo Finnigan Flash EA 1112-CHN analyzer.

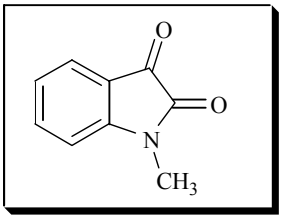
X-ray Crystallography: The X-ray diffraction measurements were carried out at 293 K on a Bruker SMART APEX CCD area detector system equipped with a graphite monochromator and a Mo-K_α fine-focus sealed tube (λ = 0.71073 Å) operated at 1500 W power (50 kV, 30 mA). The detector was placed at a distance of 4.995 cm from the crystal. The frames were integrated with the Bruker SAINT Software package using a narrow-frame algorithm. Data were corrected for absorption effects using the multi-scan technique (SADABS). The structure was solved and refined using the Bruker SHELXTL (Version 6.1) Software package.

General: All the solvents were dried and distilled using suitable drying agents before use. Moisture sensitive reactions were carried out using standard syringe-septum techniques under nitrogen atmosphere. All reactions were monitored using Thin Layer Chromatography (TLC).

1-Methylisatin (118a):

This compound was prepared following the known procedure.[259]

A suspension of isatin (30 mmol, 4.413 g) and powdered CaH_2 (60 mmol, 2.525 g) in DMF (40 mL) was heated at 40 ^oC with stirring for 20 minutes. Iodomethane (150 mmol, 21.291 g) was added to the reaction mixture and stirring continued for 12 h at the same temperature. The reaction mixture was cooled to room temperature and poured into ice-cold water and extracted with ethyl acetate (4 x 25 mL). Combined organic layer was dried over anhydrous Na_2SO_4. Solvent was evaporated and the residue, thus obtained, was purified by column chromatography (silica gel, 30% ethyl acetate in hexanes) to provide the desired compound (**118a**) as brick red solid in 82% (3.960 g) isolated yield.



Mp: 130-132 ^oC (lit.[259] 133-134 ^oC)

IR (KBr): ν 1747, 1728, 1606 cm^{-1}

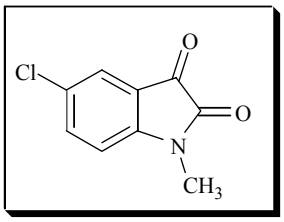
^1H NMR (400 MHz): δ 3.25 (s, 3H), 6.89 (d, 1H, J = 8.4 Hz), 7.08-7.18 (m, 1H), 7.53-7.67 (m, 2H).

^{13}C NMR (100 MHz): δ 26.17, 109.99, 117.33, 123.79, 125.12, 138.47, 151.40, 158.18, 183.34.

5-Chloro-1-methylisatin (118b):

This compound was obtained *via* the reaction between 5-chloroisatin and methyl iodide in

the presence of CaH_2, following the similar procedure as described for the compound **118a**, as red solid.



Reaction time: 12 h

Yield: 79%

Mp: 172-174 ^{o}C (lit.[309] 171-173 ^{o}C)

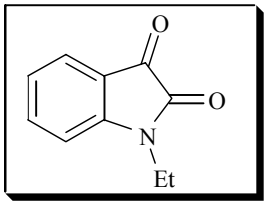
IR (KBr): ν 1745, 1732, 1608 cm^{-1}

^{1}H NMR (400 MHz): δ 3.26 (s, 3H), 6.87 (d, 1H, *J* = 8.0 Hz), 7.54-7.61 (m, 2H).

^{13}C NMR (100 MHz): δ 26.43, 111.26, 118.32, 125.29, 129.75, 137.80, 149.77, 157.74, 182.37.

1-Ethylisatin (118c):

This compound was obtained *via* the reaction between isatin and bromoethane in the presence of CaH_2 in DMF, following the similar procedure as described for the compound **118a**, as red solid.



Reaction time: 12 h

Yield: 80%

Mp: 87-89 ^{o}C (lit.[310] 86-87 ^{o}C)

IR (KBr): ν 1739, 1732, 1610 cm^{-1}

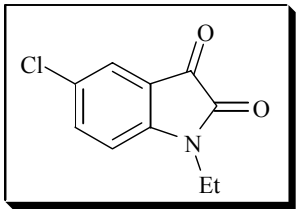
^{1}H NMR (400 MHz): δ 1.32 (t, 3H, *J* = 7.2 Hz), 3.79 (q, 2H, *J* = 7.2 Hz), 6.91 (d,

1H, *J* = 8.0 Hz), 7.08-7.17 (m, 1H), 7.55-7.67 (m, 2H).

^{13}C NMR (100 MHz): δ 12.54, 34.98, 110.08, 117.64, 123.66, 125.48, 138.39, 150.70, 157.90, 183.73.

5-Chloro-1-ethylisatin (118d):

This compound was obtained as brick red solid *via* the reaction of 5-chloroisatin and bromoethane in the presence of CaH_2 in DMF, following the similar procedure as described for the compound **118a**.



Reaction time: 12 h

Yield: 78%

Mp: 132-134 ^{o}C

IR (KBr): ν 1736, 1734, 1608 cm^{-1}

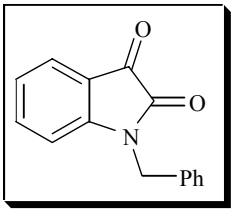
^{1}H NMR (400 MHz): δ 1.31 (t, 3H, *J* = 7.2 Hz), 3.79 (q, 2H, *J* = 7.2 Hz), 6.87 (d, 1H, *J* = 9.2 Hz), 7.52-7.60 (m, 2H).

^{13}C NMR (100 MHz): δ 12.45, 35.16, 111.38, 118.46, 125.36, 129.44, 137.72, 148.96, 157.34, 182.70.

1-Benzylisatin (118e):

Treatment of isatin with benzyl bromide in the presence of CaH_2 in DMF afforded the title

compound as brick-red solid, following similar procedure as described for compound **118a**.



Reaction time: 12 h

Yield: 81%

Mp: 128-130 ^{o}C (lit.[259]133-134 ^{o}C)

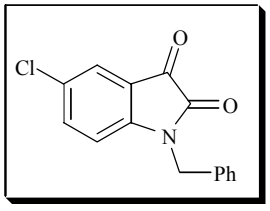
IR (KBr): ν 1741, 1732, 1612 cm^{-1}

^{1}H NMR (400 MHz): δ 4.92 (s, 2H), 6.78 (d, 1H, *J* = 8.0 Hz), 7.03-7.13 (m, 1H), 7.27-7.40 (m, 5H), 7.43-7.53 (m, 1H), 7.60 (d, 1H, *J* = 7.2 Hz).

^{13}C NMR (100 MHz): δ 44.10, 111.06, 117.75, 123.91, 125.44, 127.48, 128.21, 129.10, 134.58, 138.36, 150.79, 158.33, 183.28.

1-Benzyl-5-chloroisatin (118f):

This compound was obtained *via* the treatment of 5-chloroisatin with benzyl bromide in the presence of CaH_2 in DMF, following similar procedure as described for compound **118a**, as brick-red solid.



Reaction time: 12 h

Yield: 88%

Mp: 139-141 ^{o}C

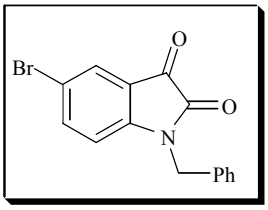
IR (KBr): ν 1755, 1730, 1602 cm^{-1}

^{1}H NMR (400 MHz): δ 4.92 (s, 2H), 6.73 (d, 1H, *J* = 8.4 Hz), 7.27-7.40 (m, 5H), 7.43 (dd, 1H, *J* = 8.4 Hz and 2.0 Hz), 7.55 (d, 1H, *J* = 2.0 Hz).

^{13}C NMR (100 MHz): δ 44.22, 112.37, 118.55, 125.30, 127.44, 128.38, 129.19, 129.77, 134.11, 137.70, 149.00, 157.76, 182.28.

1-Benzyl-5-bromoisatin (118g):

This compound was prepared *via* the reaction between 5-bromoisatin and benzyl bromide in the presence of CaH_2 in DMF, following similar procedure as described for compound **118a**, as brick-red solid.



Reaction time: 12 h

Yield: 85%

Mp: 149-152 ^{o}C

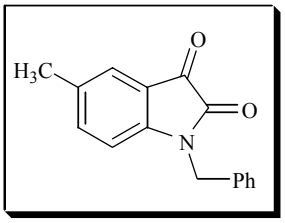
IR (KBr): ν 1732, 1726, 1602 cm^{-1}

^{1}H NMR (400 MHz): δ 4.92 (s, 2H), 6.67 (d, 1H, *J* = 8.4 Hz), 7.27-7.40 (m, 5H), 7.58 (dd, 1H, *J* = 8.4 Hz and 2.0 Hz), 7.70 (d, 1H, *J* = 2.0 Hz).

^{13}C NMR (100 MHz): δ 44.26, 112.78, 116.84, 118.94, 127.46, 128.23, 128.43, 129.23, 134.10, 140.56, 149.47, 157.60, 182.13.

1-Benzyl-5-methylisatin (118h):

Treatment of 5-methylisatin with benzyl bromide in the presence of CaH_2 in DMF afforded the title compound as brick-red solid, following similar procedure as described for compound **118a**.



Reaction time: 12 h

Yield: 94%

Mp: 143-145 ^{o}C

IR (KBr): ν 1728, 1618 cm^{-1}

^{1}H NMR (400 MHz): δ 2.29 (s, 3H), 4.90 (s, 2H), 6.66 (dd, 1H, *J* = 8.0 Hz and 2.0 Hz), 7.22-7.39 (m, 6H), 7.40 (s, 1H).

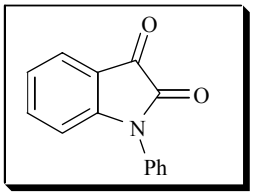
^{13}C NMR (100 MHz): δ 20.69, 44.08, 110.89, 117.77, 125.76, 127.47, 128.15, 129.06, 133.76, 134.72, 138.77, 148.61, 158.45, 183.56.

1-Phenylisatin (118i):

This compound was prepared following the reported procedure.[260]

A suspension of isatin (5 mmol, 0.735 g), phenylboronic acid (10 mmol, 1.22 g), cupric acetate (5 mmol, 0.905 g) and pyridine (10 mmol, 0.79 g) in CH_2Cl_2 (30 mL) was stirred at room temperature for 48 h. Saturated aqueous NH_4Cl solution (10 mL) was added to the reaction mixture and stirred for 10 minutes. Organic layer was separated and aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). Combined organic layer was dried over anhydrous Na_2SO_4. Solvent was evaporated and the crude product, thus obtained, was purified by

column chromatography (silica gel, 20% ethyl acetate in hexanes) to afford the desired compound (**118i**) as red solid in 69% (0.769 g) isolated yield.



Mp: 136-138 ^{o}C (lit.[311] 137-139 ^{o}C)

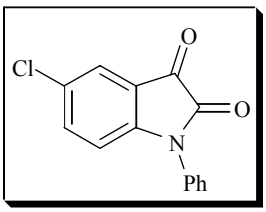
IR (KBr): ν 1743, 1608 cm^{-1}

^{1}H NMR (400 MHz): δ 6.89 (d, 1H, *J* = 8.0 Hz), 7.13-7.21 (m, 1H), 7.38-7.49 (m, 3H), 7.50-7.60 (m, 3H), 7.60-7.71 (m, 1H).

^{13}C NMR (100 MHz): δ 111.30, 117.44, 124.31, 125.54, 125.97, 128.80, 129.94, 132.86, 138.39, 151.62, 157.30, 182.88.

5-Chloro-1-phenylisatin (118j):

This compound was obtained *via* the treatment of 5-chloroisatin with phenylboronic acid under the influence of cupric acetate and pyridine, following similar procedure as described for compound **118i**, as dark-red solid.



Reaction time: 48 h

Yield: 60%

Mp: 179-180 ^{o}C

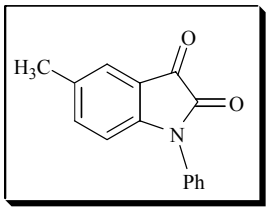
IR (KBr): ν 1732, 1602 cm^{-1}

^{1}H NMR (400 MHz): δ 6.86 (d, 1H, *J* = 8.8 Hz), 7.37-7.52 (m, 4H), 7.53-7.61 (m, 2H), 7.64 (d, 1H, *J* = 2.0 Hz).

^{13}C NMR (100 MHz): δ 112.67, 118.34, 125.39, 125.94, 129.12, 130.10, 130.13, 132.60, 137.77, 149.98, 156.77, 181.98.

5-Methyl-1-phenylisatin (118k):

Treatment of 5-methylisatin with phenylboronic acid under the influence of cupric acetate and pyridine afforded the title compound, following similar procedure as described for compound **118i**, as dark-red solid.



Reaction time: 48 h

Yield: 51%

Mp: 178-180 ^{o}C

IR (KBr): ν 1743, 1722, 1618 cm^{-1}

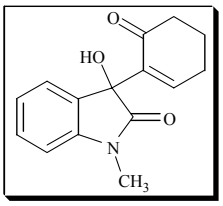
^{1}H NMR (400 MHz): δ 2.35 (s, 3H), 6.80 (d, 1H, *J* = 8.0 Hz), 7.32-7.60 (m, 7H).

^{13}C NMR (100 MHz): δ 20.72, 111.18, 117.59, 125.88, 125.90, 128.69, 129.94, 133.15, 134.25, 138.82, 149.58, 157.49, 183.19.

3-Hydroxy-3-(cyclohex-2-enon-2-yl)-1-methylindolin-2-one (119):

To a stirred solution of 1-methylisatin (**118a**) (1 mmol, 0.161 g) and cyclohex-2-enone (1 mmol, 0.096 g, 0.096 mL) in CH_2Cl_2 (1 mL) $TiCl_4$ (1 mmol, 0.5 mL of 2 M solution in CH_2Cl_2) was added at 0 ^{o}C. The reaction mixture was stirred for 30 minutes at room temperature (25-28 ^{o}C). Water (2 mL) was then added to the reaction mixture and

extracted with CH_2Cl_2 (3 x 5 mL). Combined organic layer was dried over anhydrous Na_2SO_4. Solvent was evaporated and the residue, thus obtained, was subjected to column chromatography (silica gel, 60% ethyl acetate in hexanes) to afford the desired product (**119**) as yellow solid in 86% (0.220 g) isolated yield.



Mp: 159-161 ^oC

IR (KBr): ν 3375, 1703, 1672, 1612 cm^{-1}

^1H NMR (400 MHz): δ 1.85-2.06 (m, 2H), 2.27-2.43 (m, 2H), 2.44-2.52 (m, 2H), 3.22 (s, 3H), 4.08 (bs, 1H), 6.83 (d, 1H, *J* = 7.6 Hz), 6.96-7.04 (m, 1H), 7.13 (d, 1H, *J* = 7.2 Hz), 7.27-7.34 (m, 1H), 7.36-7.43 (m, 1H).

^{13}C NMR (100 MHz): δ 22.39, 25.83, 26.41, 38.37, 76.00, 108.58, 122.81, 123.58, 129.92, 130.09, 138.30, 144.37, 147.74, 176.63, 198.29.

LCMS (*m/z*): 258 $(M+H)^+$

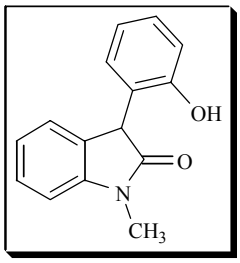
Analysis calc'd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44;

Found: C, 70.15; H, 5.82; N, 5.55.

3-(2-Hydroxyphenyl)-1-methyindolin-2-one (120):

To a stirred solution of 3-hydroxy-3-(cyclohex-2-enon-2-yl)-1-methylindolin-2-one (**119**) (1 mmol, 0.257 g) in dichloroethane (1 mL) HBr (48%, 5 mmol, 0.405 g, 0.271 mL) was added at room temperature (25-28 ^oC) and the reaction mixture was heated under reflux for

6 h. The reaction mixture was allowed to cool to room temperature and diluted with water (5 mL). Organic layer was separated and aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). Combined organic layer was dried over anhydrous Na_2SO_4. Solvent was evaporated and the crude product, thus obtained, was purified through column chromatography (silica gel, 30% ethyl acetate in hexanes) to afford the desired product (**120**) as yellow solid in 89% (0.212 g) isolated yield.



Mp: 150-152 ^{o}C

IR (KBr): ν 3180, 1680 cm^{-1}

^{1}H NMR (400 MHz): δ 3.24 (s, 3H), 5.11 (s, 1H), 6.77-6.86 (m, 1H), 6.89 (d, 1H, *J* = 7.2 Hz), 6.96 (d, 1H, *J* = 8.0 Hz), 7.05 (d, 1H, *J* = 8.0 Hz), 7.15-7.24 (m, 2H), 7.34 (d, 1H, *J* = 7.2 Hz), 7.38-7.47 (m, 1H), 9.20 (s, 1H).

^{13}C NMR (100 MHz): δ 26.62, 47.92, 109.08, 118.96, 120.75, 123.23, 123.29, 126.13, 126.32, 127.32, 128.74, 129.27, 144.56, 156.20, 178.58.

LCMS (*m/z*): 240 $(M+H)^{+}$

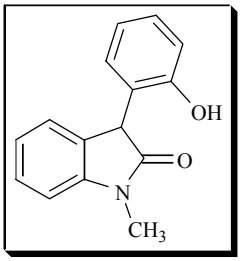
Analysis calc'd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85;

Found: C, 75.46; H, 5.50; N, 5.91.

One-pot synthesis of 3-(2-hydroxyphenyl)-1-methylindolin-2-one (120):

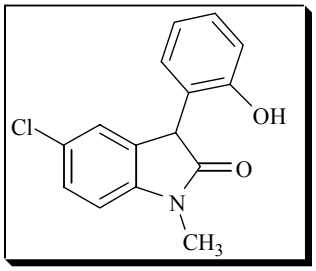
To a stirred solution of 1-methylisatin **(118a)** (1 mmol, 0.161 g) and cyclohex-2-enone (1 mmol, 0.096 g, 0.096 mL) in dichloroethane (2 mL) $TiCl_4$ (1 mmol, 0.5 mL of 2 M solution in CH_2Cl_2) was added at 0 ^oC. The reaction mixture was stirred for 30 minutes at room temperature (25-28 ^oC). HBr (48%, 5 mmol, 0.405 g, 0.271 mL) was added to the reaction mixture and heated under reflux for 6 h. The reaction mixture was allowed to cool to room temperature and diluted with water (5 mL). Organic layer was separated and aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). Combined organic layer was dried over anhydrous Na_2SO_4. Solvent was evaporated and the crude product, thus obtained, was purified through column chromatography (silica gel, 30% ethyl acetate in hexanes) to afford the desired product (**120**) as yellow solid in 82% (0.195 g) isolated yield.

Spectral data (IR, ^1H NMR, ^{13}C NMR and LCMS) and melting point are in complete agreement with that of **120** prepared in two step procedure.



5-Chloro-3-(2-hydroxyphenyl)-1-methylindolin-2-one (121):

This compound was obtained as light yellow solid *via* the Baylis-Hillman reaction of 5-chloro-1-methylisatin (**118b**) with cyclohex-2-enone in the presence of $TiCl_4$ at room temperature, followed by dehydration and aromatization using aqueous HBr (48%) at reflux temperature, following the similar procedure as described for compound **120**.



Reaction time: (0.5 + 6) h

Yield: 76%

Mp: 186-188 ^{o}C

IR (KBr): ν 3163, 1680 cm^{-1}

^{1}H NMR (400 MHz): δ 3.24 (s, 3H), 5.07 (s, 1H), 6.80-6.93 (m, 3H), 6.95 (d, 1H, *J* = 8.0 Hz), 7.12-7.22 (m, 1H), 7.28 (s, 1H), 7.36 (dd, 1H, *J* = 8.4 Hz and 1.6 Hz), 8.67 (s, 1H).

^{13}C NMR (100 MHz): δ 26.77, 47.92, 109.84, 118.73, 120.94, 122.68, 126.26, 127.51, 128.52, 128.66, 128.75, 129.50, 143.09, 155.78, 178.03.

LCMS (*m/z*): 274 $(M+H)^{+}$, 276 $(M+2+H)^{+}$

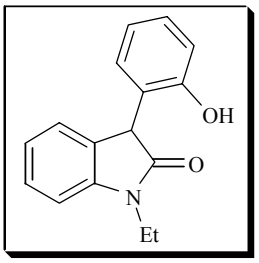
Analysis calc'd for $C_{15}H_{12}ClNO_2$: C, 65.82; H, 4.42; N, 5.12;

Found: C, 65.68; H, 4.45; N, 5.16.

1-Ethyl-3-(2-hydroxyphenyl)indolin-2-one (122):

This compound was obtained *via* the $TiCl_4$-mediated Baylis-Hillman reaction of 1-ethylisatin (**118c**) with cyclohex-2-enone at room temperature, followed by dehydration and aromatization under the influence of aqueous HBr (48%) at reflux temperature, following the similar procedure as described for compound **120**, as light yellow solid.

Reaction time: (0.5 + 6) h



Yield: 83%

Mp: 126-128 ^{o}C

IR (KBr): ν 3271, 1682 cm^{-1}

^{1}H NMR (400 MHz): δ 1.28 (t, 3H, *J* = 7.2 Hz), 3.78 (q, 2H, *J* = 7.2 Hz), 5.09 (s, 1H), 6.78-6.86 (m, 1H), 6.90 (d, 1H, *J* = 7.2 Hz), 6.98 (d, 1H, *J* = 8.0 Hz), 7.01-7.08 (m, 1H),* 7.13-7.23 (m, 2H), 7.31-7.44 (m, 2H), 9.20 (bs, 1H). (*unresolved dd)

^{13}C NMR (100 MHz): δ 12.64, 35.26, 48.01, 109.22, 118.98, 120.74, 123.08, 123.31, 126.35, 126.56, 127.32, 128.68, 129.25, 143.67, 156.26, 178.24.

LCMS (*m/z*): 254 $(M+H)^{+}$

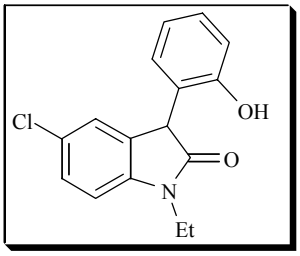
Analysis calc'd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53;

Found: C, 75.92; H, 6.12; N, 5.50.

5-Chloro-1-ethyl-3-(2-hydroxyphenyl)indolin-2-one (123):

Treatment of 5-chloro-1-ethylisatin (**118d**) with cyclohex-2-enone in the presence of $TiCl_4$ at room temperature, followed by dehydration and aromatization under the influence of aqueous HBr (48%) at reflux temperature afforded the title compound as light yellow solid, following the similar procedure as described for compound **120**.

Reaction time: (0.5 + 6) h



Yield: 59%

Mp: 187-189 ^{o}C

IR (KBr): ν 3232, 1674 cm^{-1}

^{1}H NMR (400 MHz): δ 1.27 (t, 3H, *J* = 7.6 Hz), 3.71-3.84 (m, 2H), 5.05 (s, 1H), 6.78-6.91 (m, 3H), 6.95 (d, 1H, *J* = 8.0 Hz), 7.11-7.19 (m, 1H), 7.28 (s, 1H), 7.34 (dd, 1H, *J* = 8.4 Hz and 1.6 Hz), 8.68 (s, 1H).

^{13}C NMR (100 MHz): δ 12.54, 35.40, 47.98, 109.92, 118.64, 120.89, 122.76, 126.41, 127.54, 128.53, 128.57, 128.91, 129.46, 142.17, 155.82, 177.70.

LCMS (*m/z*): 288 $(M+H)^{+}$, 290 $(M+2+H)^{+}$

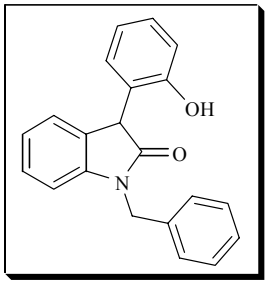
Analysis calc'd for $C_{16}H_{14}ClNO_2$: C, 66.79; H, 4.90; N, 4.87;

Found: C, 66.65; H, 4.88; N, 4.77.

1-Benzyl-3-(2-hydroxyphenyl)indolin-2-one (124):

This compound was prepared from 1-benzylisatin (**118e**) *via* the reaction with cyclohex-2-enone in the presence of $TiCl_4$ at room temperature, followed by dehydration and aromatization under the influence of aqueous HBr (48%) at reflux temperature, following the similar procedure as described for compound **120**, as light yellow solid.

Reaction time: (0.5 + 6) h



Yield: 65%

Mp: 147-148 ^{o}C

IR (KBr): ν 3279, 1682 cm^{-1}

^{1}H NMR (400 MHz): δ 4.90 & 4.95 (ABq, 2H, *J* = 15.6 Hz), 5.18 (s, 1H), 6.78-6.87 (m, 2H), 6.91 (d, 1H, *J* = 7.2 Hz), 7.01 (d, 1H, *J* = 8.0 Hz), 7.08-7.21 (m, 2H), 7.22-7.34 (m, 7H), 8.96 (bs, 1H).

^{13}C NMR (100 MHz): δ 44.20, 47.93, 110.03, 118.82, 120.84, 123.27, 123.35, 126.08, 126.63, 127.35, 127.55, 127.88, 128.59, 128.93, 129.31, 135.24, 143.70, 156.10, 178.70.

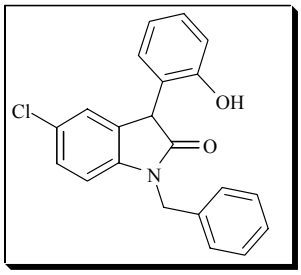
LCMS (*m/z*): 316 $(M+H)^{+}$

Analysis calc'd for $C_{21}H_{17}NO_2$: C, 79.98; H, 5.43; N, 4.44;

Found: C, 79.85; H, 5.47; N, 4.40.

1-Benzyl-5-chloro-3-(2-hydroxyphenyl)indolin-2-one (125):

This compound was obtained as light yellow solid *via* the reaction between 5-chloro-1-benzylisatin (**118f**) and cyclohex-2-enone in the presence of $TiCl_4$ at room temperature, followed by dehydration and aromatization using aqueous HBr (48%) at reflux temperature, following the similar procedure as described for compound **120**.



Reaction time: (0.5 + 6) h

Yield: 77%

Mp: 158-161 ^{o}C

IR (KBr): ν 3190, 1693 cm^{-1}

^{1}H NMR (400 MHz): δ 4.89 & 4.95 (ABq, 2H, *J* = 15.6 Hz), 5.14 (s, 1H), 6.72 (d, 1H, *J* = 8.0 Hz), 6.81-6.98 (m, 3H), 7.12-7.37 (m, 8H), 8.46 (s, 1H).

^{13}C NMR (100 MHz): δ 44.30, 47.94, 110.81, 118.45, 120.98, 122.73, 126.13, 127.30, 127.85, 128.02, 128.49, 128.75, 128.92, 129.01, 129.54, 134.89, 142.12, 155.62, 178.11.

LCMS (*m/z*): 350 $(M+H)^{+}$, 352 $(M+2+H)^{+}$

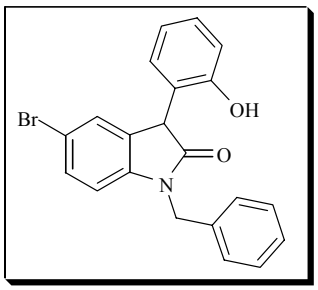
Analysis calc'd for $C_{21}H_{16}ClNO_2$: C, 72.10; H, 4.61; N, 4.00;

Found: C, 72.18; H, 4.55; N, 4.12.

1-Benzyl-5-bromo-3-(2-hydroxyphenyl)indolin-2-one (126):

This compound was obtained *via* the $TiCl_4$-mediated Baylis-Hillman reaction of 1-benzyl-5-bromoisatin (**118g**) with cyclohex-2-enone at room temperature, followed by dehydration and aromatization under the influence of aqueous HBr (48%) at reflux temperature, following the similar procedure as described for compound **120**, as light yellow solid.

Reaction time: (0.5 + 6) h



Yield: 63%

Mp: 179-180 ^{o}C

IR (KBr): ν 3188, 1687 cm^{-1}

^{1}H NMR (400 MHz): δ 4.89 & 4.95 (ABq, 2H, *J* = 16.0 Hz), 5.15 (s, 1H), 6.68 (d, 1H, *J* = 8.4 Hz), 6.81-6.89 (m, 1H), 6.91 (d, 1H, *J* = 6.4 Hz), 6.96 (d, 1H, *J* = 8.0 Hz), 7.12-7.21 (m, 1H), 7.22-7.43 (m, 7H), 8.41 (s, 1H).

^{13}C NMR (100 MHz): δ 44.28, 47.90, 111.28, 116.04, 118.44, 121.02, 122.75, 127.30, 127.89, 128.02, 128.85, 129.01, 129.31, 129.54, 131.39, 134.88, 142.64, 155.59, 177.95.

LCMS (*m/z*): 394 $(M+H)^{+}$, 396 $(M+2+H)^{+}$

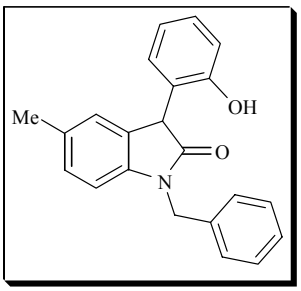
Analysis calc'd for $C_{21}H_{16}BrNO_2$: C, 63.97; H, 4.09; N, 3.55;

Found: C, 63.85; H, 4.13; N, 3.62.

1-Benzyl-3-(2-hydroxyphenyl)-5-methylindolin-2-one (127):

Treatment of 1-benzyl-5-methylisatin (**118h**) with cyclohex-2-enone in the presence of $TiCl_4$ at room temperature, followed by dehydration and aromatization under the influence of aqueous HBr (48%) at reflux temperature afforded the title compound as orange solid, following the similar procedure as described for compound **120**.

Reaction time: (0.5 + 6) h



Yield: 85%

Mp: 101-103 ^{o}C

IR (KBr): ν 3273, 1682 cm^{-1}

^{1}H NMR (400 MHz): δ 2.34 (s, 3H), 4.88 & 4.92 (ABq, 2H, *J* = 16.0 Hz)$^{\#}$, 5.16 (s, 1H), 6.72 (d, 1H, *J* = 8.0 Hz), 6.79-6.88 (m, 1H), 6.93 (d, 1H, *J* = 7.2 Hz), 7.00-7.10 (m, 2H), 7.11-7.38 (m, 7H), 9.00 (br, 1H).

$^{\#}$ long peaks of both the parts of ABq merged and appeared as a single peak at δ 4.90.

^{13}C NMR (100 MHz): δ 21.23, 44.20, 48.00, 109.81, 118.92, 120.82, 123.48, 126.47, 126.90, 127.32, 127.50, 127.85, 128.91, 129.28, 132.97, 135.30, 141.30, 156.17, 178.64.

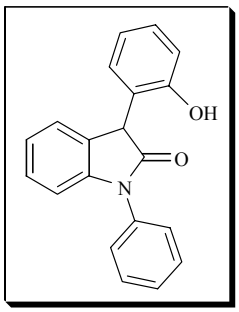
LCMS (*m/z*): 330 $(M+H)^{+}$

Analysis calc'd for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81; N, 4.25;

Found: C, 80.35; H, 5.76; N, 4.36.

3-(2-Hydroxyphenyl)-1-phenylindolin-2-one (128):

This compound was prepared from 1-phenylisatin (**118i**) and cyclohex-2-enone *via* the Baylis-Hillman reaction in the presence of $TiCl_4$ at room temperature, followed by dehydration and aromatization under the influence of aqueous HBr (48%) at reflux temperature, following the similar procedure as described for compound **120**, as light yellow solid.



Reaction time: (0.5 + 6) h

Yield: 55%

Mp: 125-127 ^{o}C

IR (KBr): ν 3304, 1693 cm^{-1}

^{1}H NMR (400 MHz): δ 5.27 (s, 1H), 6.83-6.95 (m, 2H), 6.99-7.09 (m, 2H), 7.17-7.27 (m, 2H), 7.28-7.35 (m, 1H), 7.36-7.47 (m, 4H), 7.49-7.58 (m, 2H), 8.78 (br, 1H).

^{13}C NMR (100 MHz): δ 48.28, 110.38, 119.11, 120.98, 123.41, 123.69, 126.19, 126.38, 126.50, 126.63, 127.65, 128.67, 129.45, 129.82, 133.86, 144.76, 156.11, 178.10.

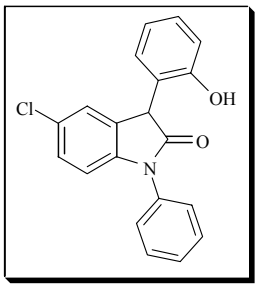
LCMS (*m/z*): 302 $(M+H)^{+}$

Analysis calc'd for $C_{20}H_{15}NO_2$: C, 79.72; H, 5.02; N, 4.65;

Found: C, 79.56; H, 5.08; N, 4.61.

5-Chloro-3-(2-hydroxyphenyl)-1-phenylindolin-2-one (129):

This compound was obtained as light yellow solid *via* the Baylis-Hillman coupling of 5-chloro-1-phenylisatin (**118j**) with cyclohex-2-enone in the presence of $TiCl_4$ at room temperature, followed by dehydration and aromatization using aqueous HBr (48%) at reflux temperature, following the similar procedure as described for compound **120**.



Reaction time: (0.5 + 6) h

Yield: 51%

Mp: 128-130 ^{o}C

IR (KBr): ν 3339, 1701 cm^{-1}

^{1}H NMR (400 MHz): δ 5.19 (s, 1H), 6.80 (d, 1H, *J* = 8.4 Hz), 6.84-6.95 (m, 2H), 7.00 (d, 1H, *J* = 7.2 Hz), 7.12-7.20 (m, 1H), 7.22-7.27 (m, 1H), 7.28 (s, 1H), 7.34-7.47 (m, 3H), 7.48-7.58 (m, 2H), 8.18 (s, 1H).

^{13}C NMR (100 MHz): δ 48.24, 111.02, 118.38, 120.98, 122.82, 126.17, 126.55, 128.15, 128.46, 128.77, 128.84, 129.00, 129.58, 129.90, 133.78, 143.14, 155.50, 177.45.

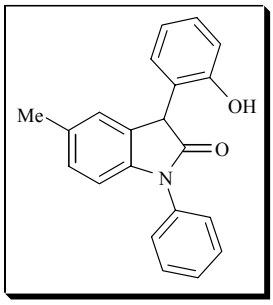
LCMS (*m/z*): 336 $(M+H)^{+}$, 338 $(M+2+H)^{+}$

Analysis calc'd for $C_{20}H_{14}ClNO_2$: C, 71.54; H, 4.20; N, 4.17;

Found: C, 71.65; H, 4.25; N, 4.07.

3-(2-Hydroxyphenyl)-5-methyl-1-phenylindolin-2-one (130):

Treatment of 5-methyl-1-phenylisatin (**118k**) with cyclohex-2-enone in the presence of $TiCl_4$ at room temperature, followed by dehydration and aromatization under the influence of aqueous HBr (48%) at reflux temperature provided the title compound as light yellow solid, following the similar procedure as described for compound **120**.



Reaction time: (0.5 + 6) h

Yield: 54%

Mp: 174-175 ^{o}C

IR (KBr): ν 3300, 1695 cm^{-1}

^{1}H NMR (400 MHz): δ 2.36 (s, 3H), 5.22 (s, 1H), 6.78 (d, 1H, *J* = 8.0 Hz), 6.81-6.90 (m, 1H), 6.96 (d, 1H, *J* = 7.6 Hz), 7.01 (d, 1H, *J* = 7.6 Hz), 7.08 (d, 1H, *J* = 8.0 Hz), 7.11-7.25 (m, 2H), 7.34-7.44 (m, 3H), 7.45-7.57 (m, 2H), 8.78 (s, 1H).

^{13}C NMR (100 MHz): δ 21.20, 48.22, 109.98, 118.69, 120.74, 123.51, 126.50, 126.64, 126.85, 127.82, 128.43, 128.83, 129.28, 129.71, 133.34, 134.10, 142.26, 156.01, 178.05.

LCMS (*m/z*): 316 $(M+H)^{+}$

Analysis calc'd for $C_{21}H_{17}NO_2$: C, 79.98; H, 5.43; N, 4.44;

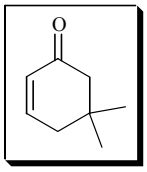
Found: C, 79.85; H, 5.36; N, 4.53.

5,5-Dimethylcyclohex-2-enone:

This compound was prepared following the known procedure.[261]

A stirred solution of 5,5-dimethyl-1,3-cyclohexanedione (150 mmol, 21 g) and *p*-toluenesulfonic acid (0.6 g) in absolute ethanol (20 mL) and benzene (170 mL) was heated under reflux for 24 h with continuous removal of water. The reaction mixture was

fractionally distilled to collect enol ether as colorless liquid. The collected enol ether was diluted with ether and lithium aluminum hydride (40 mmol, 1.52 g) was added portion wise at room temperature over a period 1 h at room temperature. The reaction mixture was poured into water and diluted with aqueous H_2SO_4 carefully. Organic layer was separated and aqueous layer was extracted with ether (3 x 25 mL). Combined organic layer was dried over anhydrous Na_2SO_4. Solvent was evaporated and the residue, thus obtained, was distilled under reduced pressure to afford the desired compound as colorless liquid in 70% (13 g) isolated yield.



Bp: 67-69 ^{o}C/10 mm (lit.[261] 74-75 ^{o}C/11 mm)

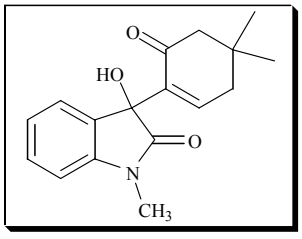
IR (Neat): ν 1678 cm^{-1}

^{1}H NMR (400 MHz): δ 1.05 (s, 6H), 2.20-2.27 (m, 2H), 2.28 (s, 2H), 6.03 (td, 1H, *J* = 10.4 Hz & 2.0 Hz), 6.86 (td, 1H, *J* = 10.4 Hz & 4.0 Hz).

^{13}C NMR (100 MHz): δ 28.27, 33.82, 39.83, 51.72, 128.89, 148.42, 199.90.

3-Hydroxy-3-(5,5-dimethylcyclohex-2-enon-2-yl)-1-methylindolin-2-one (131):

This compound was obtained *via* the $TiCl_4$-mediated Baylis-Hillman reaction between 1-methylisatin (**118a**) and 5,5-dimethylcyclohex-2-enone, following the similar procedure as described for the compound **119**, as white solid.



Reaction time: 7 h

Yield: 91%

Mp: 144-146 ^{o}C

IR (KBr): ν 3342, 1701, 1670, 1630, 1610 cm^{-1}

^{1}H NMR (400 MHz): δ 0.98 (s, 3H), 1.02 (s, 3H), 2.17 & 2.24 (ABq, 2H, *J* = 16.0 Hz), 2.36 (d, 2H, *J* = 4.0 Hz), 3.22 (s, 3H), 4.02 (s, 1H), 6.84 (d, 1H, *J* = 7.6 Hz), 6.95-7.03 (m, 1H), 7.12 (d, 1H, *J* = 6.8 Hz), 7.24-7.34 (m, 2H).

^{13}C NMR (100 MHz): δ 26.41, 27.90, 28.36, 34.03, 39.87, 51.92, 75.92, 108.64, 122.84, 123.46, 129.94, 130.06, 137.41, 144.42, 145.41, 176.57, 198.35.

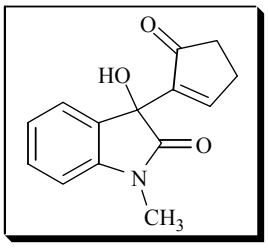
LCMS (*m/z*): 286 $(M+H)^{+}$

Analysis calc'd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91;

Found: C, 71.35; H, 6.78; N, 4.98.

3-Hydroxy-3-(cyclopent-2-enon-2-yl)-1-methylindolin-2-one (132):

This compound was obtained as gray solid *via* the reaction of 1-methylisatin (**118a**) with cyclopent-2-enone under the influence of $TiCl_4$, following the similar procedure as described for the compound **119**.



Reaction time: 2 h

Yield: 53%

Mp: 136-138 ^{o}C

IR (KBr): ν 3350, 1697, 1687, 1610 cm^{-1}

^{1}H NMR (400 MHz): δ 2.42-2.49 (m, 2H), 2.59-2.67 (m, 2H), 3.22 (s, 3H), 4.57 (br, 1H), 6.86 (d, 1H, *J* = 7.6 Hz), 7.02-7.12 (m, 1H), 7.30-7.38 (m, 2H), 7.52 (t, 1H, *J* = 2.8 Hz).

^{13}C NMR (100 MHz): δ 26.47, 26.75, 35.36, 75.20, 108.71, 123.31, 124.54, 129.04, 130.32, 143.87, 144.11, 160.42, 175.42, 208.19.

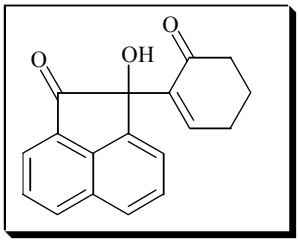
LCMS (*m/z*): 244 $(M+H)^{+}$

Analysis calc'd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76;

Found: C, 69.21; H, 5.33; N, 5.72.

2-Hydroxy-2-(cyclohex-2-enon-2-yl)-*2H*-acenaphthylen-1-one (144a):

To a stirred solution of 1,2-acenaphthenequinone (1 mmol, 0.182 g) and cyclohex-2-enone (1 mmol, 0.096 g, 0.096 mL) in CH_2Cl_2 (1 mL) $TiCl_4$ (1 mmol, 0.5 mL of 2 M solution in CH_2Cl_2) was added at 0 ^{o}C. The reaction mixture was stirred for 30 minutes at room temperature (25-28 ^{o}C). Water (2 mL) was then added to the reaction mixture and extracted with CH_2Cl_2 (3 x 5 mL). Combined organic layer was dried over anhydrous Na_2SO_4. Solvent was evaporated and the residue, thus obtained, was subjected to column chromatography (silica gel, 60% ethyl acetate in hexanes) to afford the desired product (**144a**) as yellow solid in 87% (0.242 g) isolated yield.



Mp: 177-178 ^{o}C

IR (KBr): ν 3427, 1712, 1666, 1604 cm^{-1}

^{1}H NMR (400 MHz): δ 1.87-2.05 (m, 2H), 2.23-2.39 (m, 2H), 2.40-2.50 (m, 2H), 3.92 (bs, 1H), 7.36 (t, 1H, *J* = 4.4 Hz), 7.42 (d, 1H, *J* = 6.8 Hz), 7.56-7.62 (m, 1H), 7.70-7.78 (m, 1H), 7.86 (d,1H, *J* = 8.0 Hz), 7.99 (d, 1H, *J* = 6.8 Hz), 8.09 (d, 1H, *J* = 8.0 Hz).

^{13}C NMR (100 MHz): δ 22.39, 25.87, 38.21, 79.88, 120.30, 122.30, 125.76, 128.40, 128.47, 130.81, 131.45, 131.72, 139.39, 139.75, 141.58, 147.99, 198.65, 202.61.

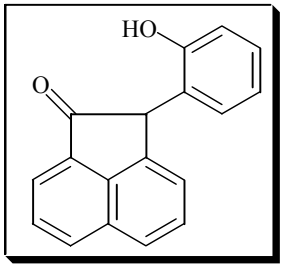
LCMS (*m/z*): 279 $(M+H)^{+}$

Analysis calc'd for $C_{18}H_{14}O_3$: C, 77.68; H, 5.07;

Found: C, 77.56; H, 5.12.

2-(2-Hydroxyphenyl)-*2H*-acenaphthylen-1-one (145):

This compound was obtained as white solid *via* the Baylis-Hillman reaction of 1,2-acenaphthenequinone with cyclohex-2-enone in the presence of $TiCl_4$ at room temperature, followed by aromatization using aqueous HBr (48%) at reflux temperature, following the similar procedure as described for compound **120**.



Reaction time: (0.5 + 6) h

Yield: 73%

Mp: 194-196 ^{o}C

IR (KBr): ν 3287, 1695 cm^{-1}

^{1}H NMR (400 MHz): δ 5.43 (s, 1H), 6.76-6.85 (m, 1H), 6.89 (d, 1H, *J* = 7.6 Hz), 7.08 (d, 1H, *J* = 7.6 Hz), 7.15-7.23 (m, 1H), 7.55 (d, 1H, *J* = 6.8 Hz), 7.66-7.85 (m, 2H), 7.93 (d, 1H, *J* = 8.4 Hz), 7.98-8.04 (m, 2H), 8.19 (d, 1H, *J* = 8.0 Hz).

^{13}C NMR (100 MHz): δ 53.98, 118.79, 121.08, 122.98, 123.03, 124.80, 124.84, 127.99, 128.54, 128.79, 129.09, 131.09, 132.14, 132.72, 136.46, 143.12, 155.59, 206.67.

LCMS (*m/z*): 261 $(M+H)^{+}$

Analysis calc'd for $C_{18}H_{12}O_2$: C, 83.06; H, 4.65;

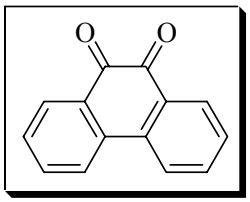
Found: C, 82.90; H, 4.71.

[9,10]-Phenanthrenedione (146):

This compound was prepared following the known procedure.[271]

To a mixture of phenanthrene (22 mmol, 4 g) and H_2SO_4 (40 mL) in water (80 mL) at 90-95 ^{o}C was added potassium dichromate (24 g) portion wise to maintain temperature at 110-115 ^{o}C. After the addition was complete heating was continued for further 30 minutes. The reaction mixture was poured into ice-cold water. The precipitate obtained was separated

and crystallized from glacial acetic acid to provide pure [9,10]-phenanthrenedione (**146**) in 55% (2.516 g) yield.



Mp: 207-208 ^{o}C (lit.[271] 206 ^{o}C)

IR (KBr): ν 1672 cm^{-1}

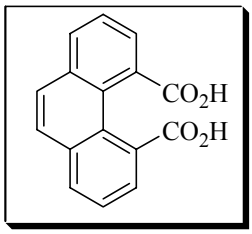
^{1}H NMR (400 MHz): δ 7.40-7.51 (m, 2H), 7.64-7.75 (m, 2H), 7.98 (d, 2H, *J* = 8.0 Hz), 8.15 (dd, 2H, *J* = 8.0 Hz and 1.2 Hz).

^{13}C NMR (100 MHz): δ 124.03, 129.63, 130.53, 131.07, 135.89, 136.08, 180.35.

Pyrene-4,5-dione (147):

This compound was prepared following the known procedure.[272]

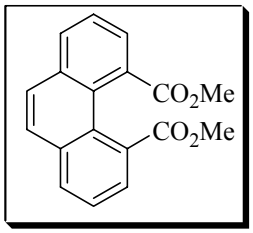
i) 4,5-Phenanthrenedicarboxylic acid: To the stirred suspension of pyrene (25 mmol, 5.05 g), H_2WO_4 (1.25 mmol, 0.31 g) and aliquot 336 (1 mmol, 0.40 mL) in chlorobenzene (15 mL) was added H_2O_2 (30%, 25 mL) at an appropriate rate to maintain gentle reflux. The reaction mixture was heated at 80 ^{o}C for 6 h and then cooled to 0 ^{o}C and filtered to remove solid particles. The filtrate was dissolved in 1.25 M NaOH (180 mL) and decolorized with activated charcoal and neutralized with glacial acetic acid to afford a brown precipitate, which was used as such for the next step.



Yield: 54% (3.59 g)

Mp: 249-251 ^{o}C [lit.[272] 248-250 ^{o}C]

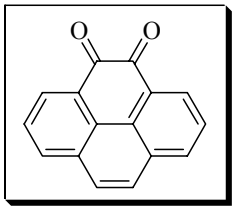
ii) Dimethyl 4,5-phenanthrenedicarboxylate: To a stirred slurry of 4,5-phenanthrenedicarboxylic acid (15.5 mmol, 3.59 g) and $NaHCO_3$ (88 mmol, 7.4 g) in DMF (100 mL) was added a solution of iodomethane (220 mmol, 13.7 mL) in DMF (50 mL) at room temperature. The reaction mixture was stirred for 24 h at the same temperature then diluted with ethyl acetate (250 mL), washed with water and dried over anhydrous Na_2SO_4. Solvent was evaporated and the residue, thus obtained, was purified by column chromatography (silica gel, 25% ethyl acetate in hexanes) to provide the title compound as yellow solid in 84% (3.82 g) isolated yield.



Mp: 158-160 ^{o}C [lit.[272] 159-161 ^{o}C]

iii) Pyrene-4,5-dione (147): To a refluxing mixture of sodium (40 mmol, 0.92 g) in THF (30 mL) was added dimethyl 4,5-phenanthrenedicarboxylate (10 mmol, 2.94 g) in THF. The reaction mixture was heated under reflux for 3 h and additional sodium (30 mmol, 0.69 g) was added during the period of 3 h. The dark red solution was cooled to room temperature. After removal of residual sodium the reaction mixture was poured into ethyl acetate (200 mL) containing water (100 mL) and the resulting emulsion was left to stand overnight. Organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 100 mL). The combined organic layer was dried over anhydrous Na_2SO_4.

Solvent was evaporated and the residue, thus obtained, was purified by column chromatography (silica gel, 30% ethyl acetate in hexanes) to provide the pure product (**147**) as brown solid in 82% (1.90 g) isolated yield.



Mp: >285 ^{o}C (lit.[272] 302-304 ^{o}C)

IR (KBr): ν 1668 cm^{-1}

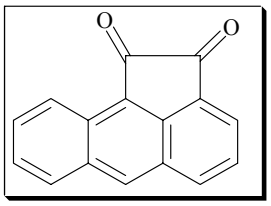
^{1}H NMR (400 MHz): δ 7.61-7.71 (m, 2H), 7.74 (s, 2H), 8.05 (d, 2H, *J* = 8.0 Hz), 8.37 (d, 2H, *J* = 7.2 Hz).

^{13}C NMR (100 MHz): δ 127.28, 127.99, 128.31, 130.05, 130.11, 132.00, 135.72, 180.32.

1,2-Aceanthrenequinone (148):

This compound was prepared following the known procedure.[273]

To a stirred mixture of anthracene (14 mmol, 2.5 g) and aluminum chloride (26 mmol, 3.5 g) in carbon disulfide (40 mL), oxalyl chloride (60 mmol, 5 mL) was added at 0-5 ^{o}C. The reaction mixture was stirred at 0 ^{o}C for 1 h and overnight at room temperature. The black tarry product was poured into ice-cold water. The resulting mixture was subjected to distillation to removed carbon disulfide and then cooled. The orange solid thus obtained, was washed with saturated aqueuos solution of Na_2CO_3 and with water and dried. The crude product was purified by column chromatography (silica gel, 30% ethyl acetate in hexanes) to furnish the desired product (**148**) as brown solid in 62% (2.00 g) isolated yield.



Mp: 270-272 °C (lit.[273] 270-273 °C)

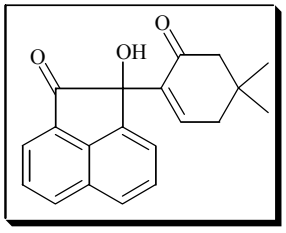
IR (KBr): ν 1734, 1703 cm^{-1}

^{1}H NMR (400 MHz): (30%DMSO-d_6 in $CDCl_3$) δ 7.67-7.76 (m, 1H), 7.77-7.89 (m, 2H), 8.03 (d, 1H, *J* = 6.8 Hz), 8.26 (d, 1H, *J* = 8.4 Hz), 8.41 (d, 1H, *J* = 8.4 Hz), 8.98 (s, 1H), 9.02 (d, 1H, *J* = 8.8 Hz).

^{13}C NMR (100 MHz): (DMSO-d_6) δ 122.25, 123.83, 124.40, 127.37, 128.17, 128.48, 128.81, 129.06, 130.87, 131.39, 133.13, 133.26, 134.92, 146.47, 188.38, 189.25.

2-Hydroxy-2-(5,5-dimethylcyclohex-2-enon-2-yl)-*2H*-acenaphthylen-1-one (144b):

This compound was obtained as gray solid *via* the Baylis-Hillman reaction between 1,2-acenaphthenequinone and 5,5-dimethylcyclohex-2-enone under the influence of $TiCl_4$, following the similar procedure as described for the compound **144a**.



Reaction time: 1 h

Yield: 78%

Mp: 176-177 °C

IR (KBr): ν 3325, 1709, 1666, 1602 cm^{-1}

^{1}H NMR (400 MHz): δ 0.98 (s, 3H), 1.02 (s, 3H), 2.16 and 2.21 (ABq, 2H, *J* = 16.0 Hz), 2.35 (d, 2H, *J* = 4.4 Hz), 3.84 (s, 1H), 7.19-7.31

(m, 1H), 7.42 (d, 1H, J = 6.8 Hz), 7.53-7.65 (m, 1H), 7.70-7.78 (m, 1H), 7.86 (d, 1H, J = 8.4 Hz), 7.99 (d, 1H, J = 7.2 Hz), 8.09 (d, 1H, J = 8.0 Hz).

^{13}C NMR (100 MHz): δ 28.12, 28.18, 34.05, 39.96, 51.81, 79.83, 120.20, 122.34, 125.81, 128.42, 128.50, 130.89, 131.48, 131.77, 138.52, 139.75, 141.67, 145.65, 198.78, 202.59.

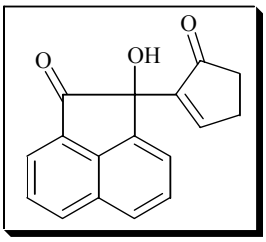
LCMS (*m/z*): 305 $(M-H)^+$

Analysis calc'd for $C_{20}H_{18}O_3$: C, 78.41; H, 5.92;

Found: C, 78.49; H, 5.84.

2-Hydroxy-2-(cyclopent-2-enon-2-yl)-*2H*-acenaphthylen-1-one (144c):

This compound was obtained as gray solid *via* the Baylis-Hillman reaction of 1,2-acenaphthenequinone with cyclopent-2-enone under the influence of $TiCl_4$, following the similar procedure as described for the compound **144a**.



Reaction time: 5 h

Yield: 72%

Mp: 152-154 ^{o}C

IR (KBr): ν 3427, 1728, 1674, 1610 cm^{-1}

^{1}H NMR (400 MHz): δ 2.40-2.52 (m, 2H), 2.53-2.66 (m, 2H), 4.95 (bs, 1H), 7.30 -7.41 (m, 1H),* 7.57-7.70 (m, 2H), 7.71-7.80 (m, 1H), 7.91

(d, 1H, J = 8.0 Hz), 7.99 (d, 1H, J = 7.2 Hz), 8.13 (d, 1H, J = 8.4 Hz). (*unresolved triplet)

^{13}C NMR (100 MHz): δ 26.84, 35.29, 79.19, 121.24, 122.74, 125.93, 128.59, 128.88, 130.64, 130.79, 132.05, 138.80, 141.74, 144.53, 160.54, 201.95, 208.95.

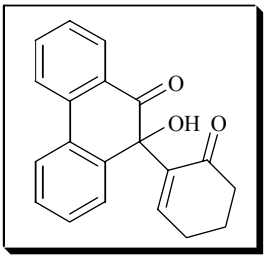
LCMS (*m/z*): 265 $(M+H)^+$

Analysis calc'd for $C_{17}H_{12}O_3$: C, 77.26; H, 4.58;

Found: C, 77.09; H, 4.63.

10-Hydroxy-10-(cyclohex-2-enon-2-yl)-10*H*-phenanthren-9-one (144d):

This compound was obtained as yellow solid *via* the the Baylis-Hillman coupling of [9,10]-phenanthrenedione (**146**) with cyclohex-2-enone in the presence of $TiCl_4$ at room temperature, following the similar procedure as described for compound **144a**.



Reaction time: 0.5 h

Yield: 70%

Mp: 110-112 ^{o}C

IR (KBr): ν 3431, 1703, 1668, 1601 cm^{-1}

^{1}H NMR (400 MHz): δ 1.70-1.99 (m, 2H), 2.15-2.44 (m, 4H), 4.77 (s, 1H), 6.78 (t, 1H, J = 4.0 Hz)), 7.33-7.48 (m, 3H), 7.57-7.70 (m, 2H), 7.82-7.95 (m, 3H).

^{13}C NMR (100 MHz): δ 22.21, 26.09, 38.74, 78.54, 122.86, 123.87, 127.71, 127.89, 128.53, 128.90, 129.19, 129.39, 130.85, 134.27, 136.76, 137.73, 140.88, 148.78, 198.56, 200.08.

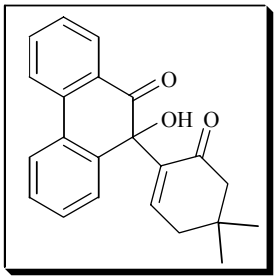
LCMS (*m/z*): 303 $(M-H)^+$

Analysis calc'd for $C_{20}H_{16}O_3$: C, 78.93; H, 5.30;

Found: C, 78.81; H, 5.36.

10-Hydroxy-10-(5,5-dimethylcyclohex-2-enon-2-yl)-10*H*-phenanthren-9-one (144e):

This compound was prepared *via* $TiCl_4$-mediated Baylis-Hillman reaction between [9,10]-phenanthrenedione (**146**) and 5,5-dimethylcyclohex-2-enone as yellowish solid, following the similar procedure as described for compound **144a**.



Reaction time: 0.5 h

Yield: 79%

Mp: 76-78 ^oC

IR (KBr): ν 3429, 1705, 1668, 1599 cm^{-1}

^{1}H NMR (400 MHz): δ 0.69 (s, 3H), 0.96 (s, 3H), 2.01-2.28 (m, 4H), 4.71 (s, 1H), 6.61 (t, 1H, *J* = 4.8 Hz), 7.32-7.48 (m, 3H), 7.57-7.70 (m, 2H), 7.81-7.90 (m, 3H).

^{13}C NMR (100 MHz): δ 26.98, 28.59, 33.87, 40.03, 52.24, 78.56, 122.86, 123.96, 127.50, 127.67, 128.50, 128.89, 129.15, 129.60, 130.95,

134.17, 136.73, 137.58, 140.00, 146.78, 198.64, 200.35.

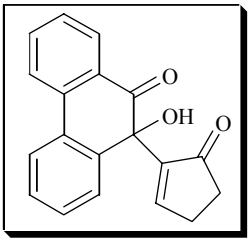
LCMS (*m/z*): 331 $(M-H)^+$

Analysis calc'd for $C_{22}H_{20}O_3$: C, 79.50; H, 6.06;

Found: C, 79.39; H, 6.12.

10-Hydroxy-10-(cyclopent-2-enon-2-yl)-10*H*-phenanthren-9-one (144f):

Baylis-Hillman coupling of [9,10]-phenanthrenedione (**146**) with cyclopent-2-enone (1.5 equiv) in the presence of $TiCl_4$ afforded the title compound as gray solid, following the similar procedure as described for compound **144a**.



Reaction time: 1 h

Yield: 72%

Mp: 108-110 ^oC

IR (KBr): ν 3466, 1699, 1682, 1599 cm^{-1}

^1H NMR (400 MHz): δ 2.22-2.47 (m, 4H), 5.40 (s, 1H), 6.97 (s, 1H),* 7.33-7.50 (m, 3H), 7.60-7.70 (m, 1H), 7.72-7.80 (m, 1H), 7.82-7.96 (m, 3H). [* Unresolved triplet]

^{13}C NMR (100 MHz): δ 26.15, 35.55, 77.76, 123.00, 123.97, 127.30, 128.07, 128.30, 128.65, 128.95, 129.59, 129.97, 134.91, 137.21, 137.83, 145.30, 162.17, 198.99, 207.16.

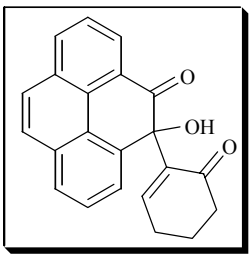
LCMS (*m/z*): 289 $(M-H)^+$

Analysis calc'd for $C_{19}H_{14}O_3$: C, 78.61; H, 4.86;

Found: C, 78.79; H, 4.91.

5-Hydroxy-5-(cyclohex-2-enon-2-yl)-5*H*-pyren-4-one (144g):

Treatment of pyrene-4,5-dione (**147**) with cyclohex-2-enone in the presence of $TiCl_4$ at room temperature afforded the title compound as light yellow solid, following the similar procedure as described for compound **144a**.



Reaction time: 12 h

Yield: 61%

Mp: 191-192 ^oC

IR (KBr): ν 3391, 1668, 1662, 1620 cm^{-1}

^1H NMR (400 MHz): δ 1.81-2.05 (m, 2H), 2.18-2.52 (m, 4H), 4.02 (s, 1H), 7.18 (t, 1H, *J* = 4.0 Hz), 7.60-7.68 (m, 1H), 7.69-7.77 (m, 2H), 7.78-7.84 (m, 2H), 7.86 (d, 1H, *J* = 7.6 Hz), 8.13 (d, 1H, *J* = 8.0 Hz), 8.36 (dd, 1H, *J* = 7.6 Hz and 0.8 Hz).

^{13}C NMR (100 MHz): δ 22.30, 25.87, 38.47, 76.92, 124.71, 126.36, 126.46, 126.74, 127. 03, 127.50, 127.59, 127.73, 128.16, 129.40, 131.22, 131.73, 133.97, 137.79, 142.65, 146.91, 198.35, 198.42.

LCMS (*m/z*): 327 $(M-H)^+$

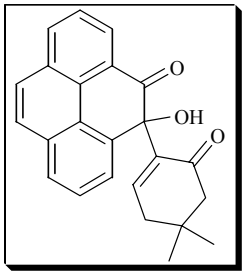
Analysis calc'd for $C_{22}H_{16}O_3$: C, 80.47; H, 4.91;

Found: C, 80.35; H, 4.84.

5-Hydroxy-5-(5,5-dimethylcyclohex-2-enon-2-yl)-5*H*-pyren-4-one (144h):

This compound was obtained as yellow solid *via* the reaction between pyrene-4,5-dione (**147**) and 5,5-dimethylcyclohex-2-enone in the presence of $TiCl_4$, following the similar procedure as described for the compound **144a**.

This B-H adduct was obtained as a major product along with a minor side product in 70:30 ratio (on the basis of NMR studies) in 67% isolated (mixture) yield.



Reaction time: 48 h

Yield: 67%

Mp: 172-174 ^{o}C

IR (KBr): ν 3429, 1693, 1658, 1620 cm^{-1}

^{1}H NMR (400 MHz): δ 0.90 (s, 3H), 1.02 (s, 3H), 2.10 and 2.17 (ABq, 2H, *J* = 16.0 Hz), 2.28 and 2.36 (dABq, 2H, *J* = 4.0 Hz and 18.8 Hz), 3.96 (s, 1H), 7.08 (t, 1H, *J* = 4.0 Hz), 7.59-7.96 (m, 6H)*, 8.13 (d, 1H, *J* = 8.0 Hz), 8.36 (d, 1H, *J* = 8.0 Hz).

In addition to the above peaks (due to the Baylis-Hillman adduct) peaks at δ 1.15 (s), 1.24 (s), 2.53 and 2.58 (ABq, *J* = 16.0 Hz), 3.65 (s), 7.15 (s), 8.19 (d, *J* = 8.0 Hz), 8.41 (d, *J* = 8.0 Hz) appeared and these are attributed to the side product.

* This multiplet also contains peaks relating to the side product.

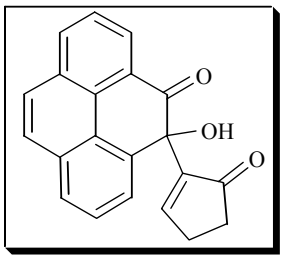
^{13}C NMR (100 MHz): δ 25.43, 26.05, 28.08, 34.07, 39.87, 45.99, 51.91, 51.93, 75.31, 76.67, 77.31, 124.23, 124.68, 126.30, 126.45, 126.72, 126.77, 126.92, 127.00, 127.13, 127.18, 127.49, 127.53, 127.56, 127.69, 128.17, 128.97, 129.30, 129.38, 131.21, 131.40, 131.77, 132.13, 133.97, 134.69, 134.92, 135.98, 137.71, 141.72, 144.67, 154.99, 196.60, 197.12, 198.27, 198.43, 202.99 (mixture of two compounds).

Reaction between pyrene-4,5-dione (147) and cyclopent-2-enone:

Reaction of pyrene-4,5-dione (**147**) and cyclopent-2-enone in the presence of $TiCl_4$ provided the mixture of **144i** and **144ia**, following the similar procedure, as described for compound **144a**.

Column chromatography of this mixture (**144i/144ia**) provided 5-hydroxy-5-(cyclopent-2-enon-2-yl)-5*H*-pyren-4-one **(144i)** in 53% yield (more polar) and also provided a minor product which is tentatively assigned as the aldol addition product [5-hydroxy-5-(cyclopent-2-enon-5-yl)-5*H*-pyren-4-one (**144ia**)] in 19% yield (mixture of *syn*/*anti* isomer).

5-Hydroxy-5-(cyclopent-2-enon-2-yl)-5*H*-pyren-4-one (144i):



Reaction time: 6 h

Yield: 53%

Mp: 77-79 ^{o}C

IR (KBr): ν 3458, 1693, 1680, 1620 cm^{-1}

^{1}H NMR (400 MHz): δ 2.19-2.45 (m, 4H), 5.64 (s, 1H), 6.64-6.72 (m, 1H), 7.63-7.73 (m, 2H), 7.74-7.84 (m, 2H), 7.87 (d, 1H, *J* = 8.0 Hz), 7.94 (d, 1H, *J* = 7.6 Hz), 8.10 (d, 1H, *J* = 8.0 Hz), 8.24 (d, 1H, *J* = 7.2 Hz).

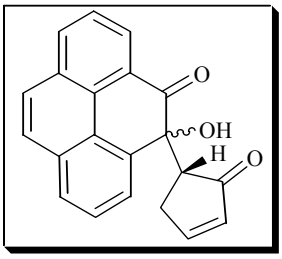
^{13}C NMR (100 MHz): δ 26.13, 35.54, 78.60, 124.13, 125.81, 126.35, 127.01, 127.05, 127.15,127.58, 127.97, 128.17, 129.54, 131.00, 131.59, 134.22, 137.89, 145.53, 161.63, 198.36, 207.34.

LCMS (*m/z*): 313 $(M-H)^{+}$

Analysis calc'd for $C_{21}H_{14}O_3$: C, 80.24; H, 4.49;

Found: C, 80.45; H, 4.43.

5-Hydroxy-5-(cyclopent-2-enon-5-yl)-5*H*-pyren-4-one (144ia):



Reaction time: 6 h

Yield: 19%

Mp: 160-162 ^{o}C

IR (KBr): ν 3472, 1693 cm^{-1}

^{1}H NMR (400 MHz): δ 2.09-2.40 and 2.70-3.01 (2m, 3H),[#] 4.48 and 5.46 (2s, 1H), 6.02-6.09 and 6.12-6.19 (2m, 1H), 7.39-8.40 (m, 9H).[#]

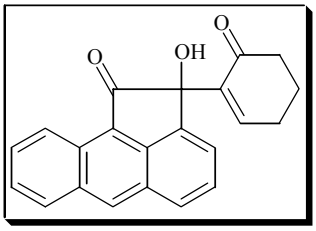
The underlined peaks with low intensity arise due to the presence of minor isomer of aldol adduct. (major:minor = 76:24).

[#] *Also contains peaks belonging to the minor product.*

^{13}C NMR (100 MHz): δ 31.33, 31.52, 53.20, 54.81, 79.80, 80.78, 123.82, 123.94, 124.15, 126.04, 126.18, 126.45, 126.60, 126.73, 127.05, 127.22, 127.40, 127.48, 127.53, 127.83, 127.94, 128.14, 129.06, 129.34, 129.77, 130.11, 130.75, 131.19, 131.83, 132.05, 133.42, 134.13, 134.64, 135.75, 137.76, 139.80, 162.92, 164.54, 200.14, 203.22, 206.70, 207.98 (mixture of diastereomers).

2-Hydroxy-2-(cyclohex-2-enon-2-yl)-2*H*-aceanthrylen-1-one (144j):

This compound was prepared as yellow solid *via* the Baylis-Hillman reaction between 1,2-aceanthrenequinone (**148**) and cyclohex-2-enone in the presence of $TiCl_4$, following the similar procedure as described for compound **144a**.



Reaction time: 6 h

Yield: 90%

Mp: 204-206 ^{o}C

IR (KBr): ν 3404, 1703, 1670, 1649 cm^{-1}

^{1}H NMR (400 MHz): δ 1.89-2.07 (m, 2H), 2.27-2.52 (m, 4H), 4.27 (s, 1H), 7.34

(t, 1H, J = 4.0 Hz), 7.42 (d, 1H, J = 6.8 Hz), 7.49-7.65 (m, 2H), 7.66-7.78 (m, 1H), 7.93 (d, 1H, J = 8.8 Hz), 8.12 (d, 1H, J = 8.4 Hz), 8.65 (s, 1H), 9.10 (d, 1H, J = 8.4 Hz).

^{13}C NMR (100 MHz): δ 22.44, 25.97, 38.47, 80.29, 119.96, 124.65, 124.79, 125.90, 126.53, 127.66, 128.47, 128.74, 129.15, 129.38, 132.64, 133.72, 139.06, 140.18, 143.60, 148.16, 199.13, 202.76.

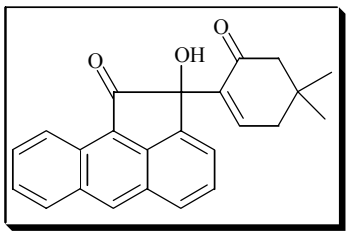
LCMS (*m/z*): 327 $(M-H)^+$

Analysis calc'd for $C_{22}H_{16}O_3$: C, 80.47; H, 4.91;

Found: C, 80.59; H, 4.99.

2-Hydroxy-2-(5,5-dimethylcyclohex-2-enon-2-yl)-2*H*-aceanthrylen-1-one (144k):

This compound was obtained as yellow solid *via* $TiCl_4$-mediated Baylis-Hillman reaction between 1,2-aceanthrenequinone (**148**) and 5,5-dimethylcyclohex-2-enone, following the similar procedure as described for compound **144a**.



Reaction time: 24 h

Yield: 85%

Mp: 176-178 ^{o}C

IR (KBr): ν 3404, 1707, 1668, 1620 cm^{-1}

^{1}H NMR (400 MHz): δ 1.00 (s, 3H), 1.03 (s, 3H), 2.20 and 2.25 (ABq, 2H, J = 16.4 Hz), 2.35 (d, 2H, J = 4.4 Hz), 4.13 (s, 1H), 7.22 (t, 1H,

J = 4.4 Hz), 7.43 (d, 1H, *J* = 6.4 Hz), 7.52-7.67 (m, 2H), 7.69-7.80 (m, 1H), 7.95 (d, 1H, *J* = 8.8 Hz), 8.14 (d, 1H, *J* = 8.4 Hz), 8.67 (s, 1H), 9.12 (d, 1H, *J* = 8.8 Hz).

^{13}C NMR (100 MHz): δ 28.13, 28.19, 34.04, 39.99, 52.01, 80.14, 119.77, 124.70, 124.82, 125.90, 126.51, 127.64, 128.50, 128.72, 129.10, 129.36, 132.59, 133.69, 138.18, 140.19, 143.63, 145.78, 199.12, 202.69.

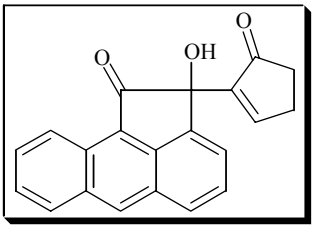
LCMS (*m/z*): 355 $(M-H)^+$

Analysis calc'd for $C_{24}H_{20}O_3$: C, 80.88; H, 5.66;

Found: C, 80.71; H, 5.72.

2-Hydroxy-2-(cyclopent-2-enon-2-yl)-2*H*-aceanthrylen-1-one (144l):

Treatment of 1,2-aceanthrenequinone (**148**) with cyclopent-2-enone (1.5 equiv) in the presence of $TiCl_4$ *via* the Baylis-Hillman coupling reaction at room temperature afforded the title compound as dark solid, following the similar procedure as described for compound **144a**.



Reaction time: 10 h

Yield: 70%

Mp: 216-217 ^oC

IR (KBr): ν 3501, 1693, 1620 cm^{-1}

^{1}H NMR (400 MHz): δ 2.46-2.54 (m, 2H), 2.56-2.64 (m, 2H), 5.01 (bs, 1H), 7.35 (t, 1H, *J* = 4.0 Hz), 7.56-7.69 (m, 3H), 7.71-7.81 (m, 1H), 7.99 (dd, 1H, *J* = 1.6 Hz and 7.2 Hz), 8.15 (d, 1H, *J* = 8.4 Hz), 8.71 (s, 1H), 9.10 (d, 1H, *J* = 8.8 Hz).

^{13}C NMR (100 MHz): δ 26.80, 35.40, 79.34, 120.87, 123.69, 124.79, 126.07, 126.76, 127.94, 128.40, 128.81, 129.46, 129.51, 133.26, 133.75, 139.18, 143.89, 144.44, 160.42, 201.85, 209.25.

LCMS (*m/z*): 315 $(M+H)^{+}$

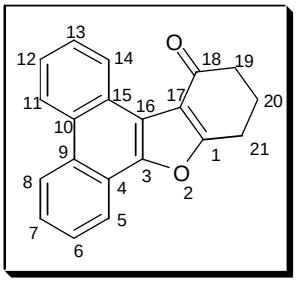
Analysis calc'd for $C_{21}H_{14}O_3$: C, 80.24; H, 4.49;

Found: C, 80.44; H, 4.53.

2-Oxapentacyclo[15.4.0.0.^{3,16}0.^{4,9}0.^{10,15}]henicosan-1(17),3(16),4(9),5,7,10(15),11,13-octaen-18-one (149a):

To a stirred solution of 10-hydroxy-10-(cyclohex-2-enon-2-yl)-10*H*-phenanthrene-9-one (**144d**, 1 mmol, 0.304 g) in dichloroethane (2 mL) methanesulfonic acid (1 mmol, 0.096 g, 0.064 mL) was added at room temperature (25-28 ^{o}C) and the reaction mixture was heated under reflux for 30 minutes. The reaction mixture was allowed to cool to room temperature and diluted with water (3 mL) and extracted with CH_2Cl_2 (3 x 5 mL). Combined organic layer was dried over anhydrous Na_2SO_4. Solvent was evaporated and the residue, thus obtained, was subjected to column chromatography (silica gel, 5% ethyl acetate in

hexanes) to provide the desired product (**149a**) as yellow solid in 86% (0.247 g) isolated yield.



Mp: 160-162 ^{o}C

IR (KBr): ν 1666, 1618 cm^{-1}

^{1}H NMR (400 MHz): δ 2.18-2.34 (m, 2H), 2.66 (t, 2H, *J* = 6.0 Hz), 3.04 (t, 2H, *J* = 6.0 Hz), 7.53-7.64 (m, 3H), 7.65-7.73 (m, 1H), 8.09-8.20 (m, 1H), 8.52-8.68 (m, 2H), 9.62 (d, 1H, *J* = 8.0 Hz).

^{13}C NMR (100 MHz): δ 22.19, 24.36, 39.18, 117.37, 119.50, 120.41, 121.34, 122.85, 123.24, 125.80, 126.37, 126.90, 127.14, 127.36, 128.47, 128.77, 129.54, 148.75, 169.53, 194.28.

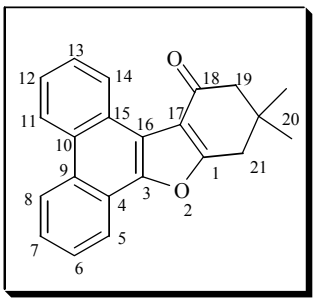
LCMS (*m/z*): 287 $(M+H)^{+}$

Analysis calc'd for $C_{20}H_{14}O_2$: C, 83.90; H, 4.93;

Found: C, 83.73; H, 4.88.

20,20-Dimethyl-2-oxapentacyclo[15.4.0.0.^{3,16}0.^{4,9}0.^{10,15}]henicosan-1(17),3(16),4(9),5,7, 10(15),11,13-octaen-18-one (149b):

Treatment of 10-hydroxy-10-(5,5-dimethylcyclohex-2-enon-2-yl)-10*H*-phenanthren-9-one (**144e**) with methanesulfonic acid provided the title compound as white solid, following the similar procedure as described for compound **149a**.



Reaction time: 0.5 h

Yield: 89%

Mp: 178-180 ^{o}C

IR (KBr): ν 1666, 1610 cm^{-1}

^{1}H NMR (400 MHz): δ 1.22 (s, 6H), 2.57 (s, 2H), 2.97 (s, 2H), 7.58-7.67 (m, 3H), 7.68-7.76 (m, 1H), 8.20-8.28 (m, 1H), 8.63-8.73 (m, 2H), 9.65 (dd, 1H, *J* = 0.8 Hz and 8.0 Hz).

^{13}C NMR (100 MHz): δ 28.47, 34.65, 38.12, 53.36, 117.36, 118.36, 120.44, 121.43, 122.90, 123.29, 125.87, 126.37, 126.95, 127.21, 127.41, 128.50, 128.79, 129.48, 149.14, 168.66, 193.70.

LCMS (*m/z*): 315 $(M+H)^{+}$

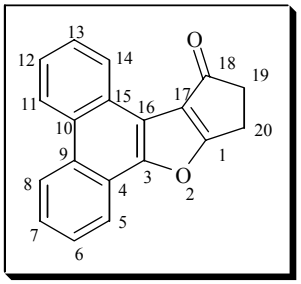
Analysis calc'd for $C_{22}H_{18}O_2$: C, 84.05; H, 5.77;

Found: C, 84.12; H, 5.71.

2-Oxapentacyclo[15.3.0.0.^{3,16}0.^{4,9}0.^{10,15}]cosan-1(17),3(16),4(9),5,7,10(15),11,13-octaen-18-one (149c):

This compound was prepared as brown solid *via* the treatment of 10-hydroxy-10-cyclopent-2-enon-2-yl)-10*H*-phenanthren-9-one (**144f**) with methanesulfonic acid, following the similar procedure as described for compound **149a**.

Reaction time: 0.5 h



Yield: 96%

Mp: 209-211 ^{o}C

IR (KBr): ν 1699, 1618 cm^{-1}

^{1}H NMR (400 MHz): δ 3.00-3.12 (m, 4H), 7.52-7.72 (m, 4H), 8.02-8.11 (m, 1H), 8.49-8.60 (m, 2H), 8.63 (d, 1H, *J* = 7.6 Hz).

^{13}C NMR (100 MHz): δ 22.82, 41.62, 116.19, 120.38, 121.89, 122.87, 123.40, 126.19, 126.31, 126.46, 126.78, 127.05, 127.47, 127.98, 128.14, 129.52, 154.96, 184.27, 194.69.

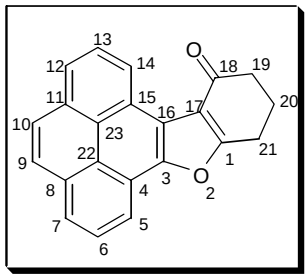
LCMS (*m/z*): 273 $(M+H)^{+}$

Analysis calc'd for $C_{19}H_{12}O_2$: C, 83.81; H, 4.44;

Found: C, 83.75; H, 4.48.

2-Oxahexacyclo[15.4.0.0.^{3,16}1.^{4,8}2.$^{4(8),11}$2.$^{4(8),15}$]tricosane-1(17),3(16),4(22),5,7,9,11,13, 15(23)-nonaen-18-one (149d):

This compound was prepared as yellow solid *via* the treatment of 5-hydroxy-5-(cyclohex-2-enon-2-yl)-5*H*-pyren-4-one (**144g**) with methanesulfonic acid, following the similar procedure as described for compound **149a**.



Reaction time: 0.5 h

Yield: 50%

Mp: 181-183 ^{o}C

IR (KBr): ν 1662, 1618 cm^{-1}

^1H NMR (400 MHz): δ 2.26-2.42 (m, 2H), 2.73 (t, 2H, *J* = 6.0 Hz), 3.11 (t, 2H, *J* = 6.0 Hz), 7.89-8.20 (m, 6H), 8.31(d, 1H, *J* = 7.6 Hz), 9.85 (d, 1H, *J* = 8.0 Hz).

^{13}C NMR (100 MHz): δ 22.32, 24.45, 39.21, 116.93, 118.08, 119.88, 120.66, 123.06, 123.63, 124.81, 125.26, 125.86, 126.32, 126.39, 126.47, 126.69, 128.46, 131.38, 131.63, 149.38, 169.70, 194.38.

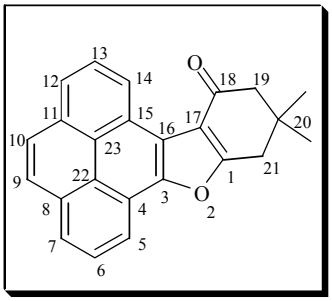
LCMS (*m/z*): 311 $(M+H)^+$

Analysis calc'd for $C_{22}H_{14}O_2$: C, 85.14; H, 4.55;

Found: C, 85.25; H, 4.49.

20,20-Dimethyl-2-oxahexacyclo[15.4.0.0.^{3,16}1.^{4,8}2.$^{4(8),11}$2.$^{4(8),15}$]tricosane-1(17),3(16), 4(22),5,7,9,11,13,15(23)-nonaen-18-one (149e):

Treatment of 5-hydroxy-5-(5,5-dimethylcyclohex-2-enon-2-yl)-5*H*-pyren-4-one (**144h**) with methanesulfonic acid provided the title compound, following the similar procedure as described for compound **149a**, as white solid.



Reaction time: 1 h

Yield: 43%

Mp: 216-218 ^oC

IR (KBr): ν 1664, 1610 cm^{-1}

^{1}H NMR (400 MHz): δ 1.25 (s, 6H), 2.61 (s, 2H), 3.02 (s, 2H), 7.96-8.22 (m, 6H), 8.44 (d, 1H, *J* = 7.6 Hz), 9.89 (d, 1H, *J* = 8.0 Hz).

^{13}C NMR (100 MHz): δ 28.61, 34.87, 38.34, 53.49, 117.03, 118.16, 118.84, 120.88, 123.16, 123.69, 124.90, 125.36, 126.00, 126.44, 126.51, 126.81, 128.54, 131.48, 131.76, 149.87, 168.94, 193.92.

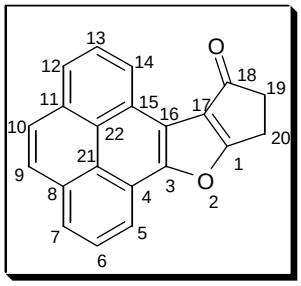
LCMS (*m/z*): 339 $(M+H)^+$

Analysis calc'd for $C_{24}H_{18}O_2$: C, 85.18; H, 5.36;

Found: C, 85.00; H, 5.41.

2-Oxahexacyclo[15.3.0.0.^{3,16}1.^{4,8}2.$^{4(8),11}$2.$^{4(8),15}$]docosane-1(17),3(16),4(21),5,7,9,11,13, 15(22)-nonaen-18-one (149f):

This compound was prepared *via* the treatment of 5-hydroxy-5-(cyclopent-2-enon-2-yl)-5*H*-pyren-4-one (**144i**) with methanesulfonic acid, following the similar procedure as described for compound **149a**, as yellowish solid.



Reaction time: 1 h

Yield: 20%

Mp: 185-186 ^oC

IR (KBr): ν 1693, 1600 cm^{-1}

^{1}H NMR (400 MHz): δ 3.05-3.17 (m, 4H), 7.88-8.06 (m, 4H), 8.07-8.17 (m, 2H),

8.24 (d, 1H, *J* = 7.6 Hz), 8.84 (d, 1H, *J* = 7.6 Hz).

^{13}C NMR (100 MHz): δ 22.94, 41.68, 116.67, 117.14, 121.07, 122.48, 123.59, 125.08, 125.19, 125.21, 125.68, 126.02, 126.62, 127.15, 128.11, 131.34, 131.66, 155.54, 184.40, 194.82.

LCMS (*m/z*): 297 $(M+H)^+$

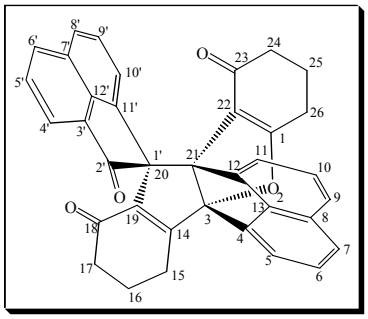
Analysis calc'd for $C_{21}H_{12}O_2$: C, 85.12; H, 4.08;

Found: C, 85.02; H, 4.15.

[3*R*,20(1′)*R*,21*S*/3*S*,20(1′)*S*,21*R*]-{2-oxaheptacyclo[20.4.0.0.^{3,21}0.^{4,13}0.^{8,13}0.^{12,13}0.^{14,19}] hexacosane-1(22),4,6,8(13),9,11,14(19)-heptaen-18,23-dione}-20-spiro-1′-acenaphthylen-2′-one (150a) (Racemic compound)**:**

To a stirred solution of 2-hydroxy-2-(cyclohex-2-enon-2-yl)-*2H*-acenaphthylen-1-one (**144a**) (1 mmol, 0.278 g) in dichloroethane (2 mL) methanesulfonic acid (3 mmol, 0.288 g, 0.194 mL) was added at room temperature (25-28 ^{o}C) and the reaction mixture was heated under reflux for 1 h. The reaction mixture was allowed to cool to room temperature and diluted with water (3 mL) and extracted with CH_2Cl_2 (3 x 5 mL). Combined organic layer was dried over anhydrous Na_2SO_4. Solvent was evaporated and the residue, thus obtained, was subjected to column chromatography (silica gel, 45% ethyl acetate in hexanes) to provide the desired product (**150a**) as white solid in 65% (0.169 g) isolated yield.

Mp: 280 ^{o}C (dec.)



IR (KBr): ν 1726, 1684, 1653, 1614 cm^{-1}

^1H NMR (400 MHz): δ 1.72-2.03 (m, 4H), 2.10-2.45 (m, 5H), 2.52-2.66 (m, 1H), 2.91-3.20 (m, 2H), 7.05 (d, 1H, *J* = 6.8 Hz), 7.25 (d, 1H, *J* = 6.8 Hz), 7.35-7.43 (m, 1H), 7.44-7.52 (m, 1H), 7.56-7.63 (m, 1H), 7.66 (d, 1H, *J* = 8.4 Hz), 7.70 (d, 1H, *J* = 7.2 Hz), 7.73-7.79 (m, 1H), 7.81-7.88 (m, 2H), 7.92 (d, 1H, *J* = 6.8 Hz), 8.11 (d, 1H, *J* = 8.4 Hz).

^{13}C NMR (100 MHz): δ 21.27, 22.83, 22.92, 24.59, 36.39, 37.88, 69.93, 74.67, 77.30, 113.48, 116.74, 120.18, 120.58, 121.96, 123.83, 123.85, 124.97, 127.13, 127.55, 128.29, 128.82, 130.53, 131.54, 131.85, 133.48, 137.28, 137.85, 140.93, 141.62, 142.25, 142.82, 158.96, 174.74, 192.67, 195.74, 202.02.

LCMS (*m/z*): 519 $(M-H)^+$

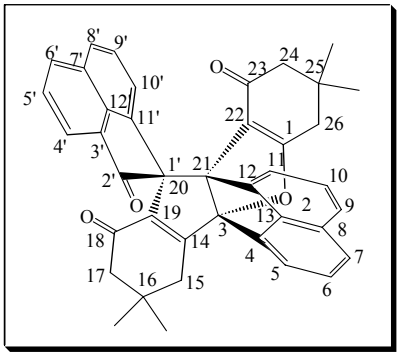
Analysis calc'd for $C_{36}H_{24}O_4$: C, 83.06; H, 4.65;

Found: C, 83.13; H, 4.62.

[3*R*,20(1′)*R*,21*S*/3*S*,20(1′)*S*,21*R*]-{16,16,25,25-Tetramethyl-2-oxaheptacyclo[20.4.0.0.^{3,21}0.^{4,13}0.^{8,13}0.^{12,13}0.^{14,19}]hexacosane-1(22),4,6,8(13),9,11,14(19)-heptaen-18,23-dione}-20-spiro-1′-acenaphthylen-2′-one (150b) (Racemic compound)**:**

This compound was obtained as yellow solid *via* the treatment of 2-hydroxy-2-(5,5-

dimethylcyclohex-2-enon-2-yl)-2*H*-acenaphthylen-1-one (**144b**) with methanesulfonic acid, following the similar procedure as described for compound **150a**.



Reaction time: 1 h

Yield: 58%

Mp: 196-198 ^{o}C

IR (KBr): ν 1724, 1682, 1664, 1616 cm^{-1}

^{1}H NMR (400 MHz): δ 0.68 (s, 3H), 1.10 (s, 3H), 1.12 (s, 3H), 1.21 (s, 3H), 1.66 and 1.85 (ABq, 2H, *J* = 16.0 Hz), 2.10-2.28 (m, 3H)*, 2.47 (d, 1H, *J* = 17.6 Hz)*, 2.92 and 2.97 (ABq, 2H, *J* = 18.0 Hz), 7.03 (d, 1H, *J* = 6.8 Hz), 7.19 (d, 1H, *J* = 7.2 Hz), 7.33-7.40 (m, 1H), 7.42-7.51 (m, 1H), 7.53-7.67 (m, 2H), 7.68-7.79 (m, 2H), 7.80-7.92 (m, 3H), 8.11 (d, 1H, *J* = 8.0 Hz).

*The doublet at δ 2.47 is part of ABq whose other two peaks are merged with the multiplet at δ 2.10-2.28

^{13}C NMR (100 MHz): δ 27.55, 28.11, 29.39, 29.76, 33.49, 35.01, 36.94, 38.32, 50.99, 51.78, 69.71, 75.00, 77.30, 113.55, 115.42, 120.04, 120.51, 121.91, 123.42, 123.88, 124.96, 127.11, 127.38, 127.51, 128.25, 128.83, 130.64, 131.53, 131.89, 133.52, 137.18, 138.04, 139.81, 141.47, 142.45, 142.83, 157.04,

173.89, 192.17, 195.65, 201.80.

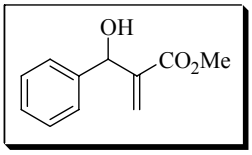
LCMS (*m/z*): 577 $(M+H)^+$

Analysis calc'd for $C_{40}H_{32}O_4$: C, 83.31; H, 5.59;

Found: C, 83.41; H, 5.51.

Methyl 3-hydroxy-2-methylene-3-phenylpropanoate (163a):

A mixture of benzaldehyde (50 mmol, 5.306 g), methyl acrylate (75 mmol, 6.456 g) and DABCO (15 mol%, 0.841 g) was kept at room temperature for 7 days. The reaction mixture was diluted with ether (50 mL) and washed with 2 N HCl (20 mL), water (20 mL) and aqueous $NaHCO_3$ solution (20 mL) successively. The organic layer was dried over anhydrous Na_2SO_4 and evaporated. The residue, thus obtained, was purified by column chromatography (silica gel, 10% ethyl acetate in hexanes) to provide the desired product (**163a**) in 72% (6.90 g) isolated yield as a colorless liquid.



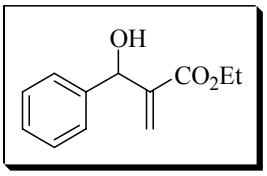
IR (Neat): ν 3477, 1714, 1631 cm^{-1}

^1H NMR (400 MHz): δ 3.01 (d, 1H, J = 4.5 Hz), 3.72 (s, 3H), 5.56 (s, 1H), 5.83 (s, 1H), 6.33 (s, 1H), 7.22-7.43 (m, 5H).

^{13}C NMR (50 MHz): δ 51.89, 73.02, 125.92, 126.63, 127.79, 128.40, 141.35, 142.08, 166.75

Ethyl 3-hydroxy-2-methylene-3-phenylpropanoate (163b):

This compound was obtained as colorless liquid *via* the Baylis-Hillman reaction between benzaldehyde and ethyl acrylate in the presence of DABCO as a catalyst, following the similar procedure as described for the compound **163a**.



Reaction time: 8 days

Yield: 81%

IR (Neat): ν 3441, 1712, 1630 cm^{-1}

^{1}H NMR (400 MHz): δ 1.23 (t, 3H, *J* = 7.2 Hz), 3.07 (d, 1H, *J* = 5.6 Hz), 4.17 (q, 2H, *J* = 7.2 Hz), 5.55 (d, 1H, *J* = 5.6 Hz), 5.81 (s, 1H), 6.33 (s, 1H), 7.23-7.44 (m, 5H).

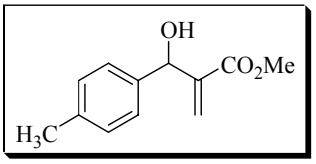
^{13}C NMR (50 MHz): δ 13.91, 60.77, 72.90, 125.44, 126.63, 127.62, 128.25, 141.45, 142.35, 166.22.

Methyl 3-hydroxy-2-methylene-3-(4-methylphenyl)propanoate(163c):

Baylis-Hillman reaction of 4-methylbenzaldehyde with methyl acrylate under the catalytic influence of DABCO provided the title compound following the similar procedure as described for the compound **163a**, as a colorless viscous liquid

Reaction time: 7 days

Yield: 82%



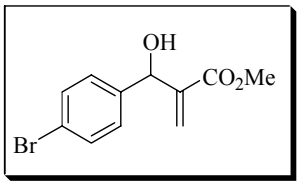
IR (Neat): ν 3447, 1716, 1630 cm^{-1}

^1H NMR (400 MHz): δ 2.33 (s, 3H), 2.92 (d, 1H, *J* = 5.6 Hz), 3.71 (s, 3H), 5.53 (d, 1H, *J* = 5.6 Hz), 5.84 (s, 1H), 6.32 (s, 1H), 7.14 (d, 2H, *J* = 8.0 Hz), 7.25 (d, 2H, *J* = 8.0 Hz).

^{13}C NMR (50 MHz): δ 21.16, 51.92, 73.12, 125.83, 126.58, 129.18, 137.57, 138.44, 142.20, 166.82.

Methyl 3-(4-bromophenyl)-3-hydroxy-2-methylenepropanoate (163d):

This compound was prepared as a white solid *via* the DABCO catalyzed Baylis-Hillman reaction between 4-bromobenzaldehyde and methyl acrylate following the similar procedure as described for the compound **163a**.



Reaction time: 8 days

Yield: 80%

Mp: 58-60 °C

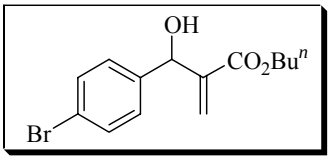
IR (KBr): ν 3341, 1720, 1635 cm^{-1}

^1H NMR (400 MHz): δ 3.05 (d, 1H, *J* = 5.8 Hz), 3.73 (s, 3H), 5.51 (d, 1H, *J* = 5.7 Hz), 5.82 (s, 1H), 6.34 (s, 1H), 7.25 (d, 2H, *J* = 8.4 Hz), 7.47 (d, 2H, *J* = 8.4 Hz).

^{13}C NMR (50 MHz): δ 52.04, 72.66, 121.78, 126.31, 128.37, 131.55, 140.43, 141.69, 166.63.

Butyl 3-(4-bromophenyl)-3-hydroxy-2-methylenepropanoate (163e):

This compound was obtained as colorless liquid *via* the reaction between 4-bromobenzaldehyde and *n*-butyl acrylate in the presence of DABCO (Cat) following the similar procedure as described for compound **163a**.



Reaction time: 7 days

Yield: 91%

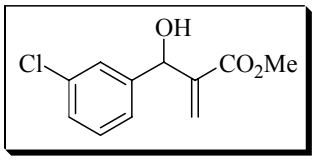
IR (Neat): ν 3466, 1714, 1631 cm^{-1}

^1H NMR (400 MHz): δ 0.90 (t, 3H, *J* = 7.2 Hz), 1.24-1.39 (m, 2H), 1.53-1.66 (m, 2H), 3.10 (d, 1H, *J* = 6.0 Hz), 4.12 (t, 2H, *J* = 6.8 Hz), 5.50 (d, 1H, *J* = 6.0 Hz), 5.80 (s, 1H), 6.33 (s, 1H), 7.25 (d, 2H, *J* = 8.4 Hz), 7.47 (d, 2H, *J* = 8.4 Hz).

^{13}C NMR (50 MHz): δ 13.66, 19.12, 30.52, 64.94, 72.68, 121.70, 126.00, 128.40, 131.48, 140.55, 141.93, 166.24.

Methyl 3-(3-chlorophenyl)-3-hydroxy-2-methylenepropanoate (163f):

This compound was prepared *via* the treatment of 3-chlorobenzaldehyde with methyl acrylate in the presence of DABCO as a catalyst, as a colorless liquid, following the similar procedure as described for compound **163a**.



Reaction time: 9 days

Yield: 79%

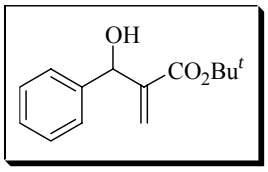
IR (Neat): ν 3458, 1712, 1631 cm^{-1}

^{1}H NMR (400 MHz): δ 3.20 (br, 1H), 3.73 (s, 3H), 5.52 (s, 1H), 5.84 (s, 1H), 6.36 (s, 1H), 7.26 (bs, 3H), 7.37 (s, 1H).

^{13}C NMR (50 MHz): δ 52.06, 72.56, 124.81, 126.58, 126.75, 127.94, 129.68, 134.32, 141.45, 143.46, 166.56.

tert-Butyl 3-hydroxy-2-methylene-3-phenylpropanoate (163g):

To a solution of benzaldehyde (20 mmol, 2.12 g) and DABCO (3 mmol, 0.336 g) in *tert*-butyl acrylate (30 mmol, 3.845 g) was added silica gel (230-400 mesh, 4 g) and mixed thoroughly. The resulting solid reaction mixture was left at room temperature for 3 days. Ethyl acetate was added to the reaction mixture and stirred for 15 min and filtered. The residue was washed with ethyl acetate (3 x 20 mL). The filtrate and washings were combined. Solvent was evaporated and the crude, thus obtained, was purified using column chromatography (silica gel, 5% ethyl acetate in hexanes) to obtain the desired product (**163g**) as colorless liquid in 70% (3.276 g) isolated yield.



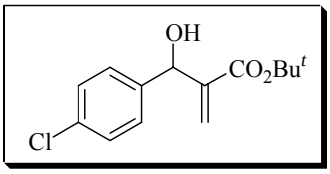
IR (Neat): ν 3447, 1712, 1631 cm^{-1}

^{1}H NMR (400 MHz): δ 1.39 (s, 9H), 3.10 (d, 1H, J = 6.0 Hz), 5.50 (d, 1H, J = 6.0 Hz), 5.70-5.74 (m, 1H), 6.23-6.27 (m, 1H), 7.24-7.40(m,5H).

^{13}C NMR (50 MHz): δ 28.03, 73.67, 81.77, 125.47, 126.59, 127.74, 128.42, 141.65, 143.43, 165.76.

***tert*-Butyl 3-(4-chlorophenyl)-3-hydroxy-2-methylenepropanoate (163h):**

This compound was obtained as a colorless liquid *via* the reaction between 4-chlorobenzaldehyde and *t*-butyl acrylate under the catalytic influence of DABCO following the similar procedure as described for compound **163g**.



Reaction time: 10 days

Yield: 63%

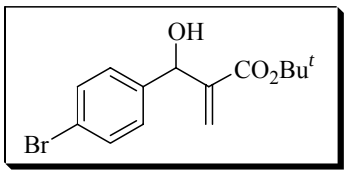
IR (Neat): ν 3327, 1714, 1639 cm^{-1}

^1H NMR (400 MHz): δ 1.41 (s, 9H), 3.16 (d, 1H, *J* = 6.0 Hz), 5.45 (d, 1H, *J* = 6.0 Hz), 5.69 (s, 1H), 6.24 (s, 1H), 7.31 (s, 4H).

^{13}C NMR (50 MHz): δ 28.00, 72.90, 81.90, 125.46, 128.01, 128.50, 133.44, 140.29, 143.20, 165.56.

***tert*-Butyl 3-(4-bromophenyl)-3-hydroxy-2-methylenepropanoate (163i):**

This compound was prepared as white solid *via* the DABCO catalyzed Baylis-Hillman coupling between 4-bromobenzaldehyde and *t*-butyl acrylate, following the similar procedure as described for the compound **163g**.



Reaction time: 10 days

Yield: 62%

Mp: 62-64 ^oC (lit.[312] 61-63 ^oC)

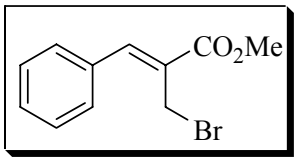
IR (KBr): ν 3323, 1716, 1639 cm^{-1}

^{1}H NMR (400 MHz): δ 1.41 (s, 9H), 3.16 (d, 1H, *J* = 6.0 Hz), 5.45 (d, 1H, *J* = 6.0 Hz), 5.69 (s, 1H), 6.24 (s, 1H), 7.25 (d, 2H, *J* = 8.0 Hz), 7.47 (d, 2H, *J* = 8.0 Hz).

^{13}C NMR (100 MHz): δ 28.01, 72.96, 81.93, 121.57, 125.59, 128.34, 131.45, 140.78, 143.06, 165.54.

Methyl (2*Z*)-2-bromomethyl-3-phenylprop-2-enoate (164a):

To a stirred solution of methyl 3-hydroxy-2-methylene-3-phenylpropanoate (**163a**) (20 mmol, 3.84 g) in CH_2Cl_2 (50 mL) was added HBr (48%, 40 mmol, 3.23 g) followed by dropwise addition of conc. H_2SO_4 (20 mmol, 1.961 g) at 0 ^oC. The reaction mixture was stirred at room temperature for 12 h. Reaction mixture was poured into ice-cold water (20 mL). Organic layer was separated and the aqueous layer was extracted with ether (3 x 10 mL). Combined organic layer was dried over anhydrous Na_2SO_4 and evaporated. The crude, thus obtained, was subjected to column chromatography (silica gel, 5% ethyl acetate in hexanes) to afford the pure product (**164a**) as colorless liquid in 84% (4.284 g) isolated yield.



IR (Neat): ν 1716, 1626 cm^{-1}

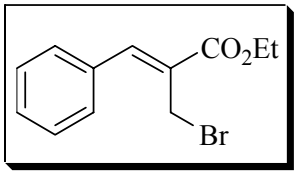
^{1}H NMR (400 MHz): δ 3.88 (s, 3H), 4.40 (s, 2H), 7.36-7.52 (m, 3H), 7.57 (d, 2H, *J* = 7.2 Hz), 7.83 (s, 1H).

^{13}C NMR (50 MHz): δ 26.69, 52.38, 128.69, 128.84, 129.56, 134.20, 142.88,

166.53.

Ethyl (2*Z*)-2-bromomethyl-3-phenylprop-2-enoate (164b):

Treatment of ethyl 3-hydroxy-2-methylene-3-phenylpropanoate (**163b**) with HBr (48%) in the presence of H_2SO_4 following the similar procedure as described for the compound **164a**, provided the title compound as colorless liquid.



Reaction time: 12 h

Yield: 72%

IR (Neat): ν 1714, 1626 cm^{-1}

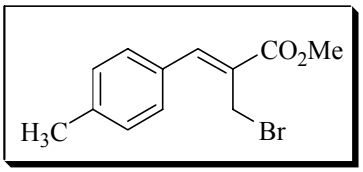
^{1}H NMR (400 MHz): δ <u>1.16</u> & 1.38 (2t, 3H, *J* = 7.2 Hz), <u>4.20</u> & 4.34 (2q, 2H, *J* = 7.2 Hz), 4.40 (s, 2H), 7.35-7.52 (m, 3H), 7.57 (d, 2H, *J*= 7.2 Hz), <u>7.02</u> & 7.82 (2s, 1H).

^{13}C NMR (50 MHz): δ 14.32, 26.88, <u>33.20</u>, 61.50, 128.93, 129.66, 134.41, 138.61, 142.69, 166.19.

The underlined chemical shift values are attributed to the corresponding minor (E)-isomer (5-7%).

Methyl 2(*Z*)-2-bromomethyl-3-(4-methylphenyl)prop-2-enoate (164c):

This compound was prepared *via* the treatment of methyl 3-hydroxy-2-methylene-3-(4-methylphenyl)propanoate (**163c**) with aqueous HBr (48%) in the presence of H_2SO_4 following the similar procedure as described for the compound **164a**, as colorless liquid.



Reaction time: 12 h

Yield: 83%

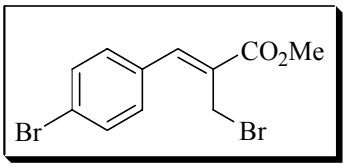
IR (Neat): ν 1712, 1626 cm^{-1}

^1H NMR (400 MHz): δ 2.39 (s, 3H), 3.87 (s, 3H), 4.41 (s, 2H), 7.27 (d, 2H, *J* = 8.0 Hz), 7.48 (d, 2H, *J* = 8.0 Hz), 7.80 (s, 1H).

^{13}C NMR (50 MHz): δ 21.40, 27.00, 52.33, 127.77, 129.64, 129.83, 131.43, 140.07, 143.07, 166.73.

Methyl 2(*Z*)-2-bromomethyl-3-(4-bromophenyl)prop-2-enoate (164d):

This compound was obtained as white solid *via* the treatment of methyl 3-(4-bromo-phenyl)-3-hydroxy-2-methylenepropanoate (**163d**) with HBr (48%) in the presence of H_2SO_4 following the similar procedure as described for the compound **164a**.



Reaction time: 12 h

Yield: 77%

Mp: 52-54 ^oC

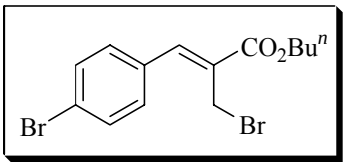
IR (KBr): ν 1711, 1614 cm^{-1}

^1H NMR (400 MHz): δ 3.88 (s, 3H), 4.34 (s, 2H), 7.44 (d, 2H, *J* = 8.4 Hz), 7.59 (d, 2H, *J* = 8.4 Hz), 7.74 (s, 1H).

^{13}C NMR (50 MHz): δ 26.20, 52.52, 124.11, 129.39, 131.09, 132.16, 133.10, 141.47, 166.29.

Butyl 2(*Z*)-2-bromomethyl-3-(4-bromophenyl)prop-2-enoate (164e):

Treatment of butyl 3-(4-bromophenyl)-3-hydroxy-2-methylenepropanoate (**163e**) with aqueous HBr (48%) in the presence of H_2SO_4 afforded the title compound following the similar procedure as described for the compound **164a**, as white solid.



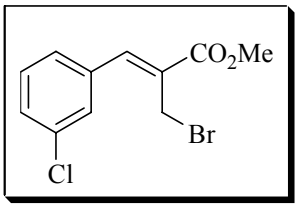
Reaction time:	5 days
Yield:	57%
Mp:	40-42 ^{o}C
IR (KBr):	ν 1709, 1618 cm^{-1}
^{1}H NMR (400 MHz):	δ <u>0.87</u> & 0.97 (2t, 3H, *J* = 7.2 Hz), <u>1.17-1.28</u> & 1.41-1.54 (2m, 2H), 1.67-1.79 (m, 2H), <u>4.14</u> & 4.28 (2t, 2H, *J* = 6.8 Hz), 4.34 (s, 2H), 7.44 (d, 2H, *J* = 8.4 Hz), 7.59 (d, 2H, *J* = 8.4 Hz), <u>6.95</u> & 7.72 (2s, 1H).
^{13}C NMR (50 MHz):	δ 13.76, <u>19.10</u>, 19.27, 26.28, <u>30.38</u>, 30.74, <u>33.63</u>, <u>65.23</u>, 65.48, 124.03, 129.81, <u>130.36</u>, 131.12, <u>131.38</u>, 132.18, 133.25, <u>137.52</u>, 141.23, 165.92.

The underlined chemical shift values are attributed to the corresponding minor (E)-isomer (5-7%).

Methyl 2(*Z*)-2-bromomethyl-3-(3-chlorophenyl)prop-2-enoate (164f):

This compound was obtained as white solid *via* the treatment of methyl 3-(3-chlorophenyl)

-3-hydroxy-2-methylenepropanoate (**163f**) with HBr (48%) in the presence of H_2SO_4, following the similar procedure as described for the compound **164a**.

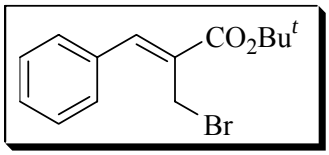


Reaction time:	12 h
Yield:	56%
Mp:	68-70 ^oC
IR (KBr):	ν 1712, 1624 cm^{-1}
^1H NMR (400 MHz):	δ 3.82 (s, 3H), 4.27 (s, 2H), 7.26-7.43 (m, 3H), 7.46 (s, 1H), 7.67 (s, 1H).
^{13}C NMR (50 MHz):	δ 25.99, 52.62, 127.45, 129.44, 129.59, 130.19, 134.92, 135.99, 141.16, 166.24.

***tert*-Butyl (2*Z*)-2-bromomethyl-3-phenylprop-2-enoate (164g):**

To a stirred suspension of NBS (20 mmol, 3.559 g) in CH_2Cl_2 (20 mL) dimethyl sulfide (40 mmol, 2.485 g) was added dropwise at 0 ^oC under N_2 atmosphere. The resulting yellow suspension was stirred for 1 h at the same temperature. Then a solution of *tert*-butyl 3-hydroxy-2-methylene-3-phenylpropanoate (**163g**) (10 mmol, 2.34 g) in CH_2Cl_2 (10 mL) was added and stirring continued for 6 h at room temperature. The yellow suspension was turned into reddish clear solution. The reaction mixture was treated with aqueous $NaHCO_3$ solution (10 mL). Organic layer was separated and the aqueous layer was extracted with ether (2 x 10 mL). Combined organic layer was dried over anhydrous Na_2SO_4. Solvent was

evaporated and the crude, thus obtained, was subjected to column chromatography (silica gel, 5% ethyl acetate in hexanes) to afford the desired product (**164g**) as colorless liquid in 95% (2.831 g) isolated yield.



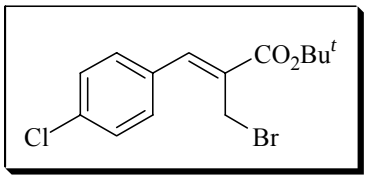
IR (Neat): ν 1712, 1628 cm^{-1}

^{1}H NMR (400 MHz): δ 1.57 (s, 9H), 4.35 (s, 2H), 7.34-7.48 (m, 3H), 7.54 (d, 2H, *J* = 7.2 Hz), 7.73 (s, 1H).

^{13}C NMR (100 MHz): δ 27.15, 28.12, 81.66, 128.83, 129.30, 129.47, 130.49, 134.62, 141.78, 165.20.

***tert*-Butyl 2(*Z*)-2-bromomethyl-3-(4-chlorophenyl)prop-2-enoate (164h):**

This compound was prepared by the treatment of *tert*-butyl 3-(4-chlorophenyl)-3-hydroxy-2-methylenepropanoate (**163h**) with NBS in the presence of dimethyl sulfide, following the similar procedure as described for the compound **164g**, as white solid.



Reaction time: 6 h

Yield: 89%

Mp: 46-48 ^{o}C

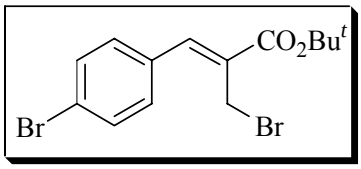
IR (KBr): ν 1707, 1622 cm^{-1}

^{1}H NMR (400 MHz): δ 1.57 (s, 9H), 4.30 (s, 2H), 7.42 (d, 2H, *J* = 8.4 Hz), 7.48 (d, 2H, *J* = 8.4 Hz), 7.66 (s, 1H).

^{13}C NMR (100 MHz): δ 26.70, 28.11, 81.90, 129.15, 130.80, 131.04, 133.03, 135.41, 140.36, 164.94.

tert-Butyl 2(*Z*)-2-bromomethyl-3-(4-bromophenyl)prop-2-enoate (164i):

Treatment of *tert*-butyl 3-(4-bromophenyl)-3-hydroxy-2-methylenepropanoate (**163i**) with NBS in the presence of dimethyl sulfide afforded the title compound as white solid, following the similar procedure as described for the compound **164g**.



Reaction time: 6 h

Yield: 94%

Mp: 70-72 °C

IR (KBr): ν 1711, 1628 cm^{-1}

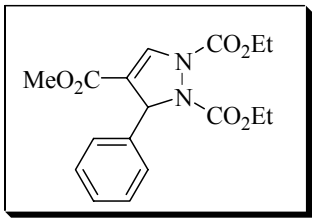
^{1}H NMR (400 MHz): δ 1.57 (s, 9H), 4.29 (s, 2H), 7.41 (d, 2H, *J* = 8.4 Hz), 7.58 (d, 2H, *J* = 8.4 Hz), 7.63 (s, 1H).

^{13}C NMR (100 MHz): δ 26.68, 28.14, 81.96, 123.77, 131.00, 131.18, 132.14, 133.51, 140.42, 164.96.

1,2-Bis(ethoxycarbonyl)-4-methoxycarbonyl-3-phenyl-2,3-dihydro-1*H*-pyrazole (165a):

To a stirred solution of methyl 2(*Z*)2-bromomethyl-3-phenylprop-2-enoate (**164a,** 1 mmol, 0.256 g) and dimethyl sulfide (1.2 mmol, 0.074 g, 0.088 mL) in CH_3CN (1 mL) and H_2O (0.1 mL) solvent system K_2CO_3 (1 mmol, 0.138 g) and diethyl azodicarboxylate (1mmol,

0.174 g) were added successively at room temperature. After stirring at room temperature for 7 h (reaction monitored by TLC), solvent was removed under reduced pressure. Water (5 mL) was added to the residue and extracted with ether (3 × 5 mL). Combined organic layer was dried over anhydrous Na_2SO_4 and solvent was evaporated. The crude product, thus obtained, was subjected to column chromatography (silica gel, 20% ethyl acetate in hexanes) to afford **165a** as a colorless viscous liquid in 74% (0.258 g) isolated yield.



IR (Neat): ν 1766, 1714, 1626 cm^{-1}

^1H NMR (400 MHz): δ 1.29-1.37 (m, 6H), 3.68 (s, 3H), 4.20-4.37 (m, 4H), 6.03 (s, 1H), 7.27-7.39 (m, 5H), 7.70 (s, 1H).

^{13}C NMR (100 MHz): δ 14.27, 51.61, 63.35, 63.62, 67.29, 114.49, 126.54, 128.25, 128.62, 135.93, 138.66, 151.46, 157.10, 162.89.

LCMS (*m/z*): 349 $(M+H)^+$

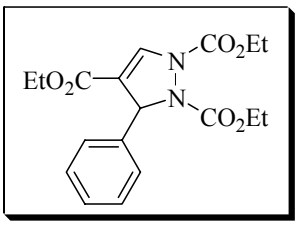
Analysis calc'd for $C_{17}H_{20}N_2O_6$: C, 58.61; H, 5.79; N, 8.04;

Found: C, 58.54; H, 5.84; N, 8.01.

1,2,4-Tris(ethoxycarbonyl)-3-phenyl-2,3-dihydro-1*H*-pyrazole (165b):

This compound was obtained as colorless viscous liquid *via* the reaction of ethyl (2*Z*)-2-bromomethyl-3-phenylprop-2-enoate (**164b**) with diethyl azodicarboxylate in the presence

of dimethyl sulfide and K_2CO_3, following the similar procedure as described for compound **165a**.



Reaction time: 8 h

Yield: 69%

IR (Neat): ν 1772, 1730, 1631 cm^{-1}

^1H NMR (400 MHz): δ 1.21 (t, 3H, *J* = 7.2 Hz), 1.31 (t, 3H, *J* = 7.2 Hz), 1.33 (t, 3H, *J* = 7.2 Hz), 4.06-4.40 (m, 6H), 6.02 (s, 1H), 7.27-7.40 (m, 5H), 7.69 (s, 1H).

^{13}C NMR (100 MHz): δ 14.12, 14.34, 60.63, 63.39, 63.65, 67.42, 115.02, 126.63, 128.25, 128.63, 135.76, 138.83, 151.60, 157.20, 162.54.

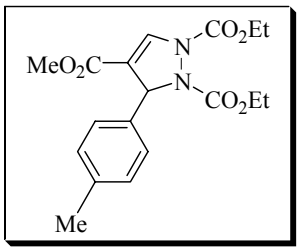
LCMS (*m/z*): 361 $(M-H)^+$

Analysis calc'd for $C_{18}H_{22}N_2O_6$: C, 59.66; H, 6.12; N, 7.73;

Found: C, 59.58; H, 6.16; N, 7.69.

1,2-Bis(ethoxycarbonyl)-4-methoxycarbonyl-3-(4-methylphenyl)-2,3-dihydro-1*H*-pyrazole (165c):

Treatment of methyl 2(*Z*)-2-bromomethyl-3-(4-methylphenyl)prop-2-enoate (**164c**) with diethyl azodicarboxylate in the presence of dimethyl sulfide and K_2CO_3 provided the title compound, following the similar procedure as described for compound **165a**, as colorless viscous liquid.



Reaction time: 8 h

Yield: 74%

IR (Neat): ν 1761, 1720, 1628 cm^{-1}

^1H NMR (400 MHz): δ 1.29-1.36 (m, 6H), 2.32 (s, 3H), 3.68 (s, 3H), 4.19- 4.37 (m, 4H), 5.99 (s, 1H), 7.14 (d, 2H, *J* = 8.0 Hz), 7.23 (d, 2H, *J* = 8.0 Hz) 7.69 (s, 1H).

^{13}C NMR (100 MHz): δ 14.35, 21.15, 51.66. 63.36, 63.64, 67.24, 114.67, 126.55, 129.39, 135.86, 135.93, 138.10, 151.60, 157.19, 163.03.

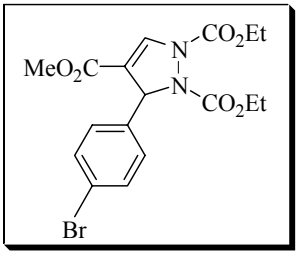
LCMS (*m/z*): 363 $(M+H)^+$

Analysis calc'd for $C_{18}H_{22}N_2O_6$: C, 59.66; H, 6.12; N, 7.73;

Found: C, 59.42; H, 6.16; N, 7.78.

3-(4-Bromophenyl)-1,2-bis(ethoxycarbonyl)-4-methoxycarbonyl-2,3-dihydro-1*H*-pyrazole (165d):

This compound was prepared as colorless viscous liquid *via* the (3 + 2) cycloaddition reaction of methyl 2(*Z*)-2-bromomethyl-3-(4-bromophenyl)prop-2-enoate (**164d**) and diethyl azodicarboxylate in the presence of dimethyl sulfide and K_2CO_3, following the similar procedure as described for compound **165a**.



Reaction time: 10 h

Yield: 75%

IR (Neat): ν 1770, 1716, 1628 cm^{-1}

^1H NMR (400 MHz): δ 1.28-1.37 (m, 6H), 3.69 (s, 3H), 4.20-4.38 (m, 4H), 5.99 (s, 1H), 7.24 (d, 2H, *J* = 8.0 Hz), 7.46 (d, 2H, *J* = 8.0 Hz), 7.69 (s, 1H).

^{13}C NMR (100 MHz): δ 14.37, 51.81, 63.60, 63.86, 66.77, 114.07, 122.43, 128.43, 131.88, 136.26, 137.84, 151.49, 157.04, 162.89.

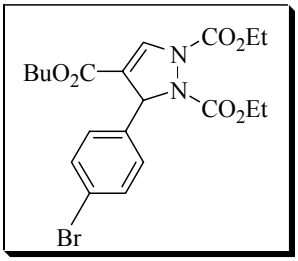
LCMS (*m/z*): 427 $(M+H)^+$, 429 $(M+2+H)^+$

Analysis calc'd for $C_{17}H_{19}BrN_2O_6$: C, 47.79; H, 4.48; N, 6.56;

Found: C, 47.96; H, 4.44; N, 6.50.

3-(4-Bromophenyl)-4-butoxycarbonyl-1,2-bis(ethoxycarbonyl)-2,3-dihydro-1*H*-pyrazole (165e):

This compound was obtained as colorless viscous liquid *via* the reaction of butyl 2(*Z*)-2-bromomethyl-3-(4-bromophenyl)prop-2-enoate (**164e**) with diethyl azodicarboxylate in the presence of dimethyl sulfide and K_2CO_3, following the similar procedure as described for compound **165a**.



Reaction time: 12 h

Yield: 66%

IR (Neat): ν 1772, 1712, 1628 cm^{-1}

^1H NMR (400 MHz): δ 0.88 (t, 3H, *J* = 7.6 Hz), 1.22-1.38 (m, 8H), 1.52-1.60 (m,

2H), 4.00-4.08 (m, 1H), 4.10-4.18 (m, 1H), 4.20-4.37 (m, 4H), 5.97 (s, 1H), 7.24 (d, 2H, J = 8.0 Hz), 7.46 (d, 2H, J = 8.0 Hz), 7.68 (s, 1H).

^{13}C NMR (100 MHz): δ 13.62, 14.35, 19.03, 30.57, 63.52, 63.80, 64.62, 66.83, 114.47, 122.36, 128.47, 131.79, 136.04, 137.93, 151.56, 157.04, 162.51.

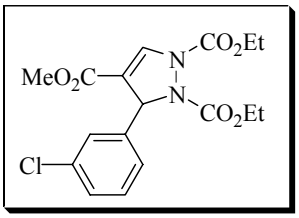
LCMS (*m/z*): 469 $(M+H)^+$, 471 $(M+2+H)^+$

Analysis calc'd for $C_{20}H_{25}BrN_2O_6$: C, 51.18; H, 5.37; N, 5.97;

Found: C, 51.11; H, 5.43; N, 6.00.

3-(3-Chlorophenyl)-1,2-bis(ethoxycarbonyl)-4-methoxycarbonyl-2,3-dihydro-1*H*-pyrazole (165f)

This compound was obtained as colorless viscous liquid *via* (3 + 2) annulation reaction of methyl 2(*Z*)-2-bromomethyl-3-(3-chlorophenyl)prop-2-enoate (**164f**) and diethyl azodicarboxylate in the presence of dimethyl sulfide and K_2CO_3, following the similar procedure as described for compound **165a**.



Reaction time: 7 h

Yield: 69%

IR (Neat): ν 1759, 1720, 1626 cm^{-1}

^{1}H NMR (400 MHz): δ 1.32 (t, 3H, J = 7.2 Hz), 1.35 (t, 3H, J = 7.2 Hz), 3.70 (s,

3H), 4.21-4.41 (m, 4H), 6.00 (s, 1H), 7.24-7.31 (bs, 3H), 7.34 (s, 1H), 7.71 (s, 1H).

^{13}C NMR (100 MHz): δ 14.32, 51.76, 63.57, 63.83, 66.70, 113.87, 124.86, 126.86, 128.48, 129.99, 134.54, 136.36, 140.70, 151.41, 156.97, 162.78.

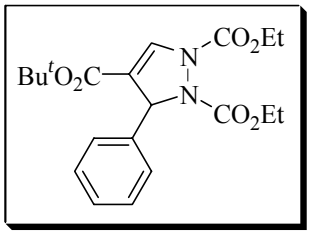
LCMS (*m/z*): 381 $(M-H)^+$, 383 $(M+2-H)^+$

Analysis calc'd for $C_{17}H_{19}ClN_2O_6$: C, 53.54; H, 5.00; N, 7.32;

Found: C, 53.37; H, 5.07; N, 7.27.

4-*tert*-Butoxycarbonyl-1,2-bis(ethoxycarbonyl)-3-phenyl-2,3-dihydro-1*H*-pyrazole (165g):

This compound was obtained *via* the (3 + 2) annulation reaction between *tert*-butyl (2*Z*)-2-bromomethyl-3-phenylprop-2-enoate (**164g**) and diethyl azodicarboxylate under the influence of dimethyl sulfide and K_2CO_3, following the similar procedure as described for compound **165a** as colorless viscous liquid.



Reaction time: 9 h

Yield: 68%

IR (Neat): ν 1757, 1711, 1628 cm^{-1}

^{1}H NMR (400 MHz): δ 1.31 (t, 3H, *J* = 7.2 Hz), 1.32 (t, 3H, *J* = 6.8 Hz), 1.37 (s, 9H), 4.19-4.36 (m, 4H), 5.95 (s, 1H), 7.27-7.36 (m, 5H), 7.61

(s, 1H).

^{13}C NMR (100 MHz): δ 14.38, 28.07, 63.33, 63.57, 67.62, 81.46, 116.72, 126.76, 128.21, 128.58, 135.33, 139.04, 151.85, 157.30, 161.88.

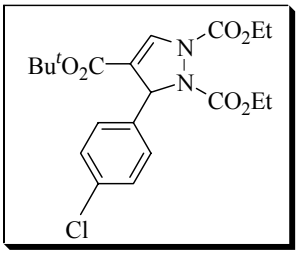
LCMS (*m/z*): 389 $(M-H)^+$

Analysis calc'd for $C_{20}H_{26}N_2O_6$: C, 61.53; H, 6.71; N, 7.18;

Found: C, 61.72; H, 6.74; N, 7.23.

4-*tert*-Butoxycarbonyl-3-(4-chlorophenyl)-1,2-bis(ethoxycarbonyl)-2,3-dihydro-1*H*-pyrazole (165h):

[3 + 2] Annulation reaction of *tert*-butyl 2(*Z*)-2-bromomethyl-3-(4-chlorophenyl)prop-2-enoate (**164h**) with diethyl azodicarboxylate under the influence of dimethyl sulfide and K_2CO_3 afforded the title compound, following the similar procedure as described for compound **165a**, as colorless viscous liquid.



Reaction time: 9 h

Yield: 67%

IR (Neat): ν 1770, 1722, 1628 cm^{-1}

^{1}H NMR (400 MHz): δ 1.29-1.36 (m, 6H), 1.39 (s, 9H), 4.20-4.36 (m, 4H), 5.93 (s, 1H), 7.26-7.34 (m, 4H), 7.60 (s, 1H).

^{13}C NMR (100 MHz): δ 14.34, 28.06, 63.43, 63.67, 66.86, 81.65, 116.18, 128.18, 128.75, 134.03, 135.50, 137.62, 151.74, 157.11, 161.71.

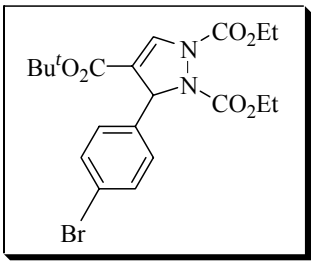
LCMS (*m/z*): 423 $(M-H)^+$, 425 $(M+2-H)^+$

Analysis calc'd for $C_{20}H_{25}ClN_2O_6$: C, 56.54; H, 5.93; N, 6.59;

Found: C, 56.77; H, 5.85; N, 6.58.

3-(4-Bromophenyl)-4-*t*-butoxycarbonyl-1,2-bis(ethoxycarbonyl)-2,3-dihydro-1*H*-pyrazole (165i):

Treatment of *tert*-butyl 2(*Z*)-2-bromomethyl-3-(4-bromophenyl)prop-2-enoate (**164i**) with diethyl azodicarboxylate in the presence of dimethyl sulfide and K_2CO_3 provided the title compound *via* (3 + 2) annulation reaction, following the similar procedure as described for compound **165a**, as colorless viscous liquid.



Reaction time: 9 h

Yield: 64%

IR (Neat): ν 1757, 1705, 1628 cm^{-1}

^1H NMR (400 MHz): δ 1.29-1.36 (m, 6H), 1.39 (s, 9H), 4.20-4.36 (m, 4H), 5.91 (s, 1H), 7.23 (d, 2H, *J* = 8.4 Hz), 7.46 (d, 2H, *J* = 8.4 Hz), 7.59 (s, 1H).

^{13}C NMR (100 MHz): δ 14.33, 28.06, 63.42, 63.66, 66.88, 81.64, 116.09, 122.20, 128.48, 131.69, 135.50, 138.11, 151.70, 157.07, 161.68.

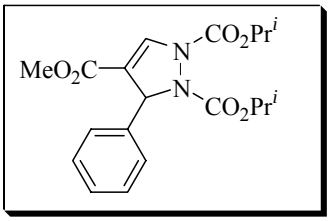
LCMS (*m/z*): 467 $(M-H)^+$, 469 $(M+2-H)^+$

Analysis calc'd for $C_{20}H_{25}BrN_2O_6$: C, 51.18; H, 5.37; N, 5.97;

Found: C, 51.37; H, 5.38; N, 6.05.

1,2-Bis(isopropoxycarbonyl)-4-methoxycarbonyl-3-phenyl-2,3-dihydro-1*H*-pyrazole (165j):

(3 + 2) Annulation reaction of methyl (2*Z*)-2-bromomethyl-3-phenylprop-2-enoate (**164a**) and diisopropyl azodicarboxylate furnished the title compound under the influence of dimethyl sulfide and K_2CO_3, following the similar procedure as described for compound **165a**, as colorless viscous liquid.



Reaction time: 8 h

Yield: 75%

IR (Neat): ν 1772, 1716, 1626 cm^{-1}

^1H NMR (400 MHz): δ 1.25-1.37 (m, 12H), 3.68 (s, 3H), 4.97-5.15 (m, 2H), 6.01 (s, 1H), 7.25-7.39 (m, 5H), 7.69 (s, 1H).

^{13}C NMR (100 MHz): δ 21.72, 21.76, 21.77, 21.83, 51.52, 67.12, 71.40, 71.78, 114.30, 126.50, 128.11, 128.53, 136.07, 138.87, 151.06, 156.69, 162.95.

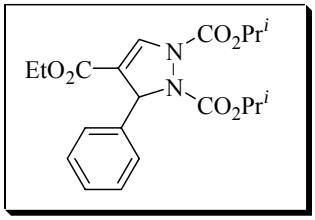
LCMS (*m/z*): 377 $(M+H)^+$

Analysis calc'd for $C_{19}H_{24}N_2O_6$: C, 60.63; H, 6.43; N, 7.44;

Found: C, 60.42; H, 6.42; N, 7.36.

4-Ethoxycarbonyl-1,2-bis(isopropoxycarbonyl)-3-phenyl-2,3-dihydro-1*H*-pyrazole (165k):

This compound was prapared as colorless viscous liquid *via* the reaction of ethyl (2*Z*)-2-bromomethyl-3-phenylprop-2-enoate (**164b**) and diisopropyl azodicarboxylate in the presence of dimethyl sulfide and K_2CO_3, following the similar procedure as described for compound **165a**.



Reaction time: 8 h

Yield: 67%

IR (Neat): ν 1759, 1712, 1626 cm^{-1}

^1H NMR (400 MHz): δ 1.20 (t, 3H, *J* = 7.2 Hz), 1.25-1.37 (m, 12H), 4.06-4.22 (m, 2H), 4.96-5.15 (m, 2H), 6.00 (s, 1H), 7.25-7.39 (m, 5H), 7.67 (s, 1H).

^{13}C NMR (100 MHz): δ 14.09, 21.79, 21.83, 21.90, 60.54, 67.25, 71.43, 71.80, 114.83, 126.59, 128.11, 128.53, 135.90, 139.03, 151.21, 156.79, 162.61.

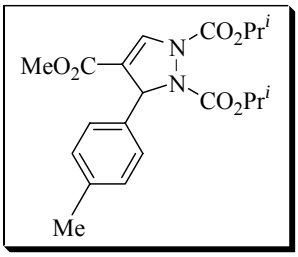
LCMS (*m/z*): 391 $(M+H)^+$

Analysis calc'd for $C_{20}H_{26}N_2O_6$: C, 61.53; H, 6.71; N, 7.18;

Found: C, 61.59; H, 6.77; N, 7.11.

1,2-Bis(isopropoxycarbonyl)-4-methoxycarbonyl-3-(4-methylphenyl)-2,3-dihydro-1*H*-pyrazole (165l):

Treatment of methyl 2(*Z*)-2-bromomethyl-3-(4-methylphenyl)prop-2-enoate (**164c**) with diisopropyl azodicarboxylate in the presence of dimethyl sulfide and K_2CO_3 provided the title compound, following the similar procedure as described for compound **165a**, as colorless viscous liquid.



Reaction time: 10 h

Yield: 79%

IR (Neat): ν 1768, 1714, 1626 cm^{-1}

^1H NMR (400 MHz): δ 1.25-1.35 (m, 12H), 2.31 (s, 3H), 3.67 (s, 3H), 4.96-5.14 (m, 2H), 5.97 (s, 1H), 7.13 (d, 2H, *J* = 8.0 Hz), 7.22 (d, 2H, *J* = 8.0 Hz), 7.68 (s, 1H).

^{13}C NMR (100 MHz): δ 21.06, 21.75, 21.80, 21.87, 51.53, 67.03, 71.34, 71.75, 114.43, 126.46, 129.25, 136.00, 136.03, 137.88, 151.14, 156.73, 163.03.

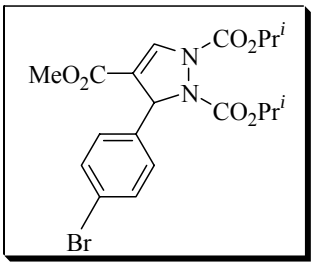
LCMS (*m/z*): 391 $(M+H)^+$

Analysis calc'd for $C_{20}H_{26}N_2O_6$: C, 61.53; H, 6.71; N, 7.18;

Found: C, 61.29; H, 6.76; N, 7.20.

3-(4-Bromophenyl)-1,2-bis(isopropoxycarbonyl)-4-methoxycarbonyl-2,3-dihydro-1*H*-pyrazole (165m):

The compound was obtained as colorless viscous liquid *via* the (3 + 2) cycloaddition reaction of methyl 2(*Z*)-2-bromomethyl-3-(4-bromophenyl)prop-2-enoate (**164d**) and diisopropyl azodicarboxylate in the presence of dimethyl sulfide and K_2CO_3, following the similar procedure as described for compound **165a**.



Reaction time: 9 h

Yield: 75%

IR (Neat): ν 1763, 1716, 1626 cm^{-1}

^{1}H NMR (400 MHz): δ 1.24-1.35 (m, 12H), 3.69 (s, 3H), 4.96-5.14 (m, 2H), 5.96 (s, 1H), 7.23 (d, 2H, *J* = 8.4 Hz), 7.45 (d, 2H, *J* = 8.4 Hz), 7.67 (s, 1H).

^{13}C NMR (100 MHz): δ 21.86, 21.91, 21.96, 51.77, 66.65, 71.75, 72.13, 113.89, 122.33, 128.42, 131.82, 136.44, 138.09, 151.12, 156.66, 163.00.

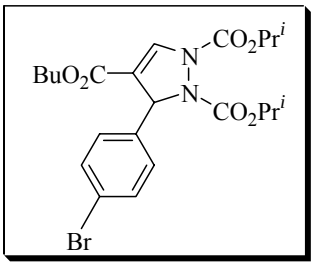
LCMS (*m/z*): 455 $(M+H)^+$, 457 $(M+2+H)^+$

Analysis calc'd for $C_{19}H_{23}BrN_2O_6$: C, 50.12; H, 5.09; N, 6.15;

Found: C, 50.20; H, 5.18; N, 6.10.

3-(4-Bromophenyl)-4-butoxycarbonyl-1,2-bis(isopropoxycarbonyl)-2,3-dihydro-1*H*-pyrazole (165n):

This compound was prepared as colorless viscous liquid *via* the reaction of butyl 2(*Z*)-2-bromomethyl-3-(4-bromophenyl)prop-2-enoate (**164e**) with diisopropyl azodicarboxylate in the presence of dimethyl sulfide and K_2CO_3, following the similar procedure as described for compound **165a**.



Reaction time: 12 h

Yield: 71%

IR (Neat): ν 1770, 1714, 1626 cm^{-1}

^{1}H NMR (400 MHz): δ 0.88 (t, 3H, *J* = 7.6 Hz), 1.22-1.37 (m, 14H), 1.51-1.59 (m, 2H), 4.00-4.08 (m, 1H), 4.10-4.18 (m, 1H), 4.96-5.14 (m, 2H), 5.95 (s, 1H), 7.23 (d, 2H, *J* = 8.4 Hz), 7.45 (d, 2H, *J* = 8.4 Hz), 7.67 (s, 1H).

^{13}C NMR (100 MHz): δ 13.64, 19.05, 21.84, 21.90, 21.94, 30.59, 64.60, 66.74, 71.68, 72.07, 114.32, 122.27, 128.48, 131.75, 136.25, 138.19, 151.24, 156.68, 162.64.

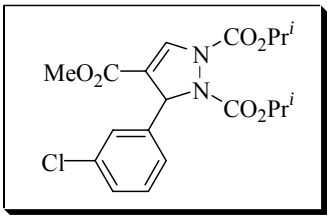
LCMS (*m/z*): 497 $(M+H)^+$, 499 $(M+2+H)^+$

Analysis calc'd for $C_{22}H_{29}BrN_2O_6$: C, 53.13; H, 5.88; N, 5.63;

Found: C, 53.19; H, 5.77; N, 5.69.

3-(3-Chlorophenyl)-1,2-bis(isopropoxycarbonyl)-4-methoxycarbonyl-2,3-dihydro-1*H*-pyrazole (165o):

This compound was obtained as colorless viscous liquid *via* (3 + 2) annulation reaction of methyl 2(*Z*)-2-bromomethyl-3-(3-chlorophenyl)prop-2-enoate (**164f**) with diisopropyl azodicarboxylate in the presence of dimethyl sulfide and K_2CO_3, following the similar procedure as described for compound **165a**.



Reaction time: 7 h

Yield: 70%

IR (Neat): ν 1772, 1736, 1624 cm^{-1}

^1H NMR (400 MHz): δ 1.28 (d, 3H, *J* = 6.0 Hz), 1.32 (d, 3H, *J* = 6.0 Hz), 1.34 (d, 6H, *J* = 6.8 Hz), 3.70 (s, 3H), 4.96-5.16 (m, 2H), 5.98 (s, 1H), 7.23-7.30 (m, 3H), 7.33 (s, 1H), 7.69 (d, 1H, *J* = 0.8 Hz).

^{13}C NMR (100 MHz): δ 21.84, 21.90, 21.94, 51.76, 66.60, 71.78, 72.16, 113.86, 124.91, 126.82, 128.41, 129.95, 134.57, 136.57, 140.97, 151.16, 156.64, 162.93.

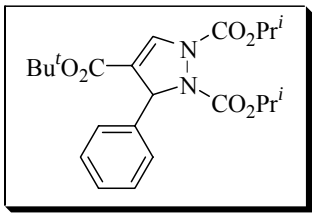
LCMS (*m/z*): 411 $(M+H)^+$, 413 $(M+2+H)^+$

Analysis calc'd for $C_{19}H_{23}ClN_2O_6$: C, 55.54; H, 5.64; N, 6.82;

Found: C, 55.50; H, 5.66; N, 6.94.

4-*tert*-Butoxycarbonyl-1,2-bis(isopropoxycarbonyl)-3-phenyl-2,3-dihydro-1*H*-pyrazole (165p):

This compound was obtained *via* the (3 + 2) annulation reaction between *tert*-butyl (2*Z*)-2-bromomethyl-3-phenylprop-2-enoate (**164g**) and diisopropyl azodicarboxylate under the influence of dimethyl sulfide and K_2CO_3, following the similar procedure as described for compound **165a**, as colorless viscous liquid.



Reaction time: 9 h

Yield: 69%

IR (Neat): ν 1757, 1716, 1626 cm^{-1}

^{1}H NMR (400 MHz): δ 1.25-1.35 (m, 12H), 1.37 (s, 9H), 4.96-5.13 (m, 2H), 5.92 (s, 1H), 7.27-7.35 (m, 5H), 7.60 (s, 1H).

^{13}C NMR (100 MHz): δ 21.86, 21.90, 21.94, 21.98, 28.08, 67.49, 71.39, 71.74, 81.38, 116.59, 126.78, 128.11, 128.51, 135.54, 139.29, 151.54, 156.93, 162.00.

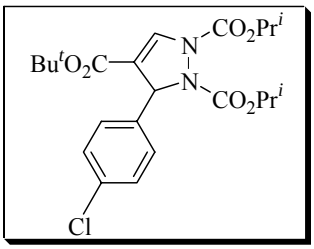
LCMS (*m/z*): 417 $(M-H)^+$

Analysis calc'd for $C_{22}H_{30}N_2O_6$: C, 63.14; H, 7.23; N, 6.69;

Found: C, 63.34; H, 7.20; N, 6.78.

4-*tert*-Butoxycarbonyl-3-(4-chlorophenyl)-1,2-bis(isopropoxycarbonyl)-2,3-dihydro-1*H*-pyrazole (165q):

Treatment of *tert*-butyl 2(*Z*)-2-bromomethyl-3-(4-chlorophenyl)prop-2-enoate (**164h**) with diisopropyl azodicarboxylate under the influence of dimethyl sulfide and K_2CO_3 afforded the title compound, following the similar procedure as described for compound **165a**, as colorless viscous liquid. (On standing for long time this compound became solid).



Reaction time: 9 h

Yield: 67%

Mp: 110 ^{o}C

IR (Neat): ν 1757, 1714, 1628 cm^{-1}

^{1}H NMR (400 MHz): δ 1.25-1.35 (m, 12H), 1.39 (s, 9H), 4.96-5.13(m, 2H), 5.90 (s, 1H), 7.25-7.33 (m, 4H), 7.58 (s, 1H).

^{13}C NMR (100 MHz): δ 21.87, 21.97, 28.14, 66.81, 71.62, 71.96, 81.65, 116.10, 128.23, 128.76, 134.00, 135.76, 137.92, 151.50, 156.81, 161.90.

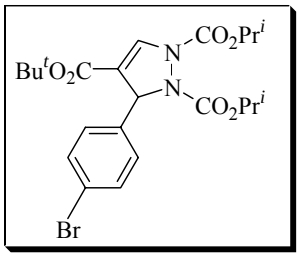
LCMS (*m/z*): 453 $(M+H)^{+}$, 455 $(M+2+H)^{+}$

Analysis calc'd for $C_{22}H_{29}ClN_2O_6$: C, 58.34; H, 6.45; N, 6.18;

Found: C, 58.17; H, 6.46; N, 6.24.

3-(4-Bromophenyl)-4-*tert*-butoxycarbonyl-1,2-bis(isopropoxycarbonyl)-2,3-dihydro-1*H*-pyrazole (165r):

Treatment of *tert*-butyl 2(*Z*)-2-bromomethyl-3-(4-bromophenyl)prop-2-enoate (**164i**) with diisopropyl azodicarboxylate in the presence of dimethyl sulfide and K_2CO_3 furnished the title compound *via* (3 + 2) annulation reaction, following the similar procedure as described for compound **165a**, as colorless viscous liquid.



Reaction time: 9 h

Yield: 74%

IR (Neat): ν 1761, 1714, 1628 cm^{-1}

^{1}H NMR (400 MHz): δ 1.25-1.35 (m, 12H), 1.39 (s, 9H), 4.96-5.14 (m, 2H), 5.89 (s, 1H), 7.21 (d, 2H, *J* = 8.4 Hz), 7.45 (d, 2H, *J* = 8.4 Hz), 7.58 (d, 1H, *J* = 0.8 Hz).

^{13}C NMR (100 MHz): δ 21.81, 21.87, 21.91, 28.08, 66.78, 71.54, 71.89, 81.57, 115.95, 122.11, 128.49, 131.64, 135.70, 138.37, 151.39, 156.71, 161.80.

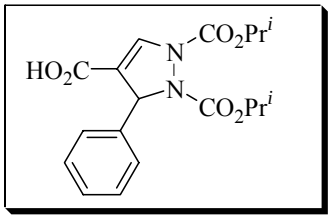
LCMS (*m/z*): 495 $(M-H)^+$, 497 $(M+2-H)^+$

Analysis calc'd for $C_{22}H_{29}BrN_2O_6$: C, 53.13; H, 5.88; N, 5.63;

Found: C, 53.40; H, 5.80; N, 5.61.

1,2-Bis(isopropoxycarbonyl)-3-phenyl-2,3-dihydro-1*H*-pyrazole-4-carboxylic acid (166a):

To the stirred solution of 4-*t*-butoxycarbonyl-1,2-bis(isopropoxycarbonyl)-3-phenyl-2,3-dihydro-1*H*-pyrazole (**165p**, 0.5 mmol, 0.209 g) in CH_2Cl_2 (1 mL) methanesulfonic acid (1.5 mmol, 0.144 g) was added at room temperature. After stirring for 10 min. the reaction mixture was diluted with water (5 mL) and organic layer was separated. Aqueous layer was extracted with CH_2Cl_2 (3×5 mL). Combined organic layer was dried over anhydrous Na_2SO_4. Solvent was evaporated and the solid, thus obtained, was subjected to column chromatography (silica gel) using 100% ethyl acetate to afford **166a** as a white solid in 60% (0.11 g) isolated yield.



Mp: 142 ^oC

IR (KBr): ν 3200-2500, 1774, 1736, 1668, 1608 cm^{-1}

^1H NMR (400 MHz): δ 1.15-1.35 (m, 12H), 4.87-5.10 (m, 2H), 5.90 (s, 1H), 7.15-7.35 (m, 5H), 7.71 (s, 1H), 10.00 (b, 1H).

^{13}C NMR (100 MHz): δ 21.87, 21.91, 21.99, 67.05, 71.78, 72.26, 113.39, 126.69, 128.37, 128.73, 138.31, 138.77, 150.81, 156.84, 167.97.

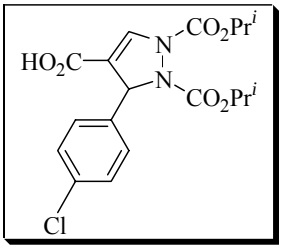
LCMS (*m/z*): 363 $(M+H)^+$

Analysis calc'd for $C_{18}H_{22}N_2O_6$: C, 59.66; H, 6.12; N, 7.73;

Found: C, 59.74; H, 6.14; N, 7.81.

3-(4-Chlorophenyl)-1,2-bis(isopropoxycarbonyl)-2,3-dihydro-1*H*-pyrazole-4-carboxylic acid (166b):

This acid was obtained as white solid by the treatment of 4-*t*-butoxycarbonyl-3-(4-chlorophenyl)-1,2-bis(isopropoxycarbonyl)-2,3-dihydro-1*H*-pyrazole (**165q**) with methanesulfonic acid, following the similar procedure as described for compound **166a**.



Reaction time: 10 min

Yield: 64%

Mp: 145 ^{o}C

IR (KBr): ν 3200-2500, 1757, 1714, 1684, 1622 cm^{-1}

^{1}H NMR (400 MHz): δ 1.25-1.39 (m, 12H), 2.60 (br, 1H), 4.96-5.15 (m, 2H), 5.96 (s, 1H), 7.28-7.34 (m, 4H), 7.77 (s, 1H).

^{13}C NMR (100 MHz): δ 21.85, 21.91, 21.93, 21.97, 66.41, 71.98, 72.47, 112.97, 128.14, 128.93, 134.28, 137.35, 138.45, 150.78, 156.69, 167.64.

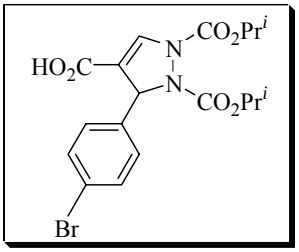
LCMS (*m/z*): 397 $(M+H)^{+}$, 399 $(M+2+H)^{+}$

Analysis calc'd for $C_{18}H_{21}ClN_2O_6$: C, 54.48; H, 5.33; N, 7.06;

Found: C, 54.61; H, 5.30; N, 7.02.

3-(4-Bromophenyl)-1,2-bis(isopropoxycarbonyl)-2,3-dihydro-1*H*-pyrazole-4-carboxylic acid (166c):

This compound was obtained *via* the treatment of 3-(4-bromophenyl)-4-*t*-butoxy carbonyl-1,2-bis(isopropoxycarbonyl)-2,3-dihydro-1*H*-pyrazole (**165r**) with methanesulfonic acid, following the similar procedure as described for compound **166a**, as white solid.



Reaction time: 10 min

Yield: 51%

Mp: 130-132 ^{o}C

IR (KBr): ν 3200-2500, 1732, 1716, 1682, 1616 cm^{-1}

^{1}H NMR (400 MHz): δ 1.26-1.38 (m, 12H), 4.92-5.15 (m, 2H), 5.94 (s, 1H), 7.22 (d, 2H, *J* = 8.4 Hz), 7.45 (d, 2H, *J* = 8.4 Hz), 7.78 (s, 1H), 9.80 (br, 1H).

^{13}C NMR (100 MHz): δ 21.85, 21.92, 21.96, 66.45, 71.98, 72.47, 112.87, 122.46, 128.46, 131.88, 137.85, 138.53, 150.74, 156.66, 167.85.

LCMS (*m/z*): 441 $(M+H)^{+}$, 443 $(M+2+H)^{+}$

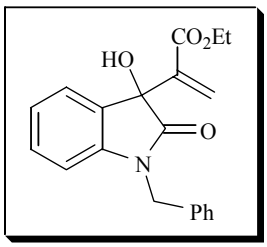
Analysis calc'd for $C_{18}H_{21}BrN_2O_6$: C, 48.99; H, 4.80; N, 6.35;

Found: C, 49.00; H, 4.85; N, 6.21.

Ethyl 2-(1-benzyl-3-hydroxyindolin-2-on-3-yl)-2-methylenethanoate (187a):

This compound was prepared following the reported procedure.[92]

A solution of 1-benzylisatin (**118e**) (10 mmol, 2.37 g), ethyl acrylate (20 mmol, 2 g) and DABCO (1.5 mmol, 0.168 g) in ethanol (50 mL) was stirred at room temperature for 3 days. On completion of reaction ethanol was removed, the residue was dissolved in EtOAc (100 mL) and washed with 2 N HCl (20 mL) followed by water (20 mL). Organic layer was dried over anhydrous Na_2SO_4. Solvent was evaporated and the crude product was subjected to column chromatography (silica gel, 25% ethyl acetate in hexanes) to provide the desired compound (**187a**) as white solid in 89% (2.99 g) isolated yield.



Mp: 138-140 ^{o}C

IR (KBr): ν 3341, 1699, 1693, 1614 cm^{-1}

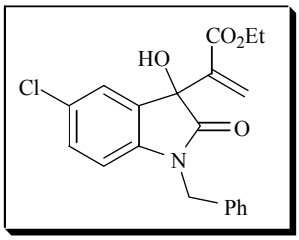
^{1}H NMR (400 MHz): δ 1.08 (t, 3H, *J* = 6.8 Hz), 3.88-4.02 (m, 1H), 4.03-4.24 (m, 2H), 4.89 and 4.94 (ABq, 2H, *J* = 16.0 Hz), 6.43 (s, 1H), 6.58 (s, 1H), 6.70 (d, 1H, *J* = 7.6 Hz), 6.95-7.04 (m, 1H), 7.12-7.50 (m, 7H).

^{13}C NMR (100 MHz): δ 13.89, 44.14, 61.05, 76.33, 109.71, 123.06, 123.90, 127.44, 127.67, 127.90, 128.81, 129.66, 130.08, 135.56, 139.32, 143.72, 164.69, 176.56.

Ethyl 2-(1-benzyl-5-chloro-3-hydroxyindolin-2-on-3-yl)-2-methylenethanoate (187b):

This compound was prepared *via* the Baylis-Hillman reaction of 1-benzyl-5-chloroisatin (**118f**) and ethyl acrylate in the presence of DABCO, following the similar procedure as

described for compound **187a**, as white solid.



Reaction time: 4 days

Yield: 85%

Mp: 132-134 ^{o}C

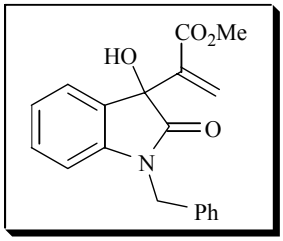
IR (KBr): ν 3354, 1712, 1697, 1614 cm^{-1}

^{1}H NMR (400 MHz): δ 1.14 (t, 3H, *J* = 7.2 Hz), 3.96-4.20 (m, 3H), 4.88 and 4.93 (ABq, 2H, *J* = 16.0 Hz), 6.45 (s, 1H), 6.58-6.68 (m, 2H), 7.12-7.20 (m, 2H), 7.22-7.40 (m, 5H).

^{13}C NMR (100 MHz): δ 13.96, 44.28, 61.27, 76.20, 110.79, 124.52, 127.37, 127.86, 128.32, 128.47, 128.92, 129.96, 131.28, 135.08, 138.92, 142.27, 164.49, 176.27.

Methyl 2-(1-benzyl-3-hydroxyindolin-2-on-3-yl)-2-methylenethanoate (187c):

The Baylis-Hillman reaction of 1-benzylisatin (**118e**) and methyl acrylate under the catalytic influence of DABCO provided the title compound, following the similar procedure as described for compound **187a**, as white solid.



Reaction time: 5 days

Yield: 60%

Mp: 191-192 ^{o}C (lit.[93] 193-194 ^{o}C)

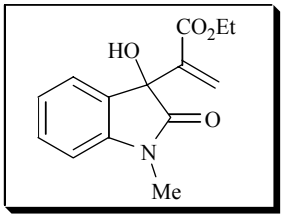
IR (KBr): ν 3342, 1711, 1697, 1614 cm^{-1}

^1H NMR (400 MHz): δ 3.56 (s, 3H), 4.18 (s, 1H), 4.87 and 4.97 (ABq, 2H, *J* = 15.6 Hz), 6.47 (s, 1H), 6.58 (s, 1H), 6.70 (d, 1H, *J* = 7.6 Hz), 6.94-7. 02 (m, 1H), 7.12-7.36 (m, 5H), 7.39 (d, 2H, *J* = 7.2 Hz).

^{13}C NMR (100 MHz): δ 44.16, 52.06, 76.27, 109.78, 123.06, 123.86, 127.45, 127.65, 128.16, 128.80, 129.52, 130.12, 135.55, 139.07, 143.68, 165.09, 176.61.

Ethyl 2-(3-hydroxy-1-methylindolin-2-on-3-yl)-2-methylenethanoate (187d):

This compound was prepared *via* the Baylis-Hillman coupling of 1-methylisatin (**118a**) with ethyl acrylate under the catalytic influence of DABCO, following the similar procedure as described for compound **187a**, as white solid.



Reaction time: 7 days

Yield: 92%

Mp: 133-135 °C (lit.[92] 142-143 °C)

IR (KBr): ν 3327, 1726, 1703, 1616 cm^{-1}

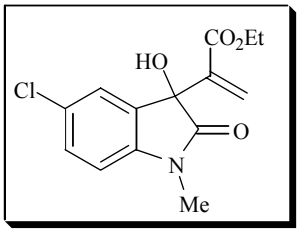
^1H NMR (400 MHz): δ 1.10 (t, 3H, *J* = 7.2 Hz), 3.22 (s, 3H), 3.93-4.10 (m, 2H), 4.25 (bs, 1H), 6.43 (s, 1H), 6.57 (s, 1H), 6.84 (d, 1H, *J* = 7.6 Hz), 6.97-7.07 (m, 1H), 7.16 (d, 1H, *J* = 7.6 Hz), 7.28-7.37

(m, 1H).

^{13}C NMR (100 MHz): δ 13.85, 26.41, 60.95, 76.19, 108.56, 123.00, 123.81, 127.82, 129.60, 130.14, 139.36, 144.49, 164.60, 176.44.

Ethyl 2-(5-chloro-3-hydroxy-1-methylindolin-2-on-3-yl)-2-methylenethanoate (187e):

Treatment of 5-chloro-1-methylisatin (**118b**) with ethyl acrylate in the presence of catalytic amount of DABCO afforded the title compound, following the similar procedure as described for compound **187a**, as white solid.



Reaction time: 4 days

Yield: 76%

Mp: 144-146 ^{o}C

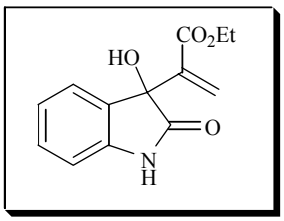
IR (KBr): ν 3312, 1718, 1697, 1614 cm^{-1}

^{1}H NMR (400 MHz): δ 1.16 (t, 3H, *J* = 7.2 Hz), 3.22 (s, 3H), 3.97 (s, 1H), 3.99-4.14 (m, 2H), 6.43 (s, 1H), 6.60 (s, 1H), 6.78 (d, 1H, *J* = 8.4 Hz), 7.15 (d, 1H, *J* = 2.0 Hz), 7.30 (dd, 1H, *J* = 2.0 Hz and 8.4 Hz).

^{13}C NMR (100 MHz): δ 13.94, 26.61, 61.23, 76.10, 109.62, 124.52, 128.25, 128.39, 130.07, 131.11, 138.96, 143.12, 164.45, 176.07.

Ethyl 2-(3-hydroxyindolin-2-on-3-yl)-2-methylenethanoate (187f):

This compound was prepared *via* the Baylis-Hillman reaction of isatin and ethyl acrylate in the presence of DABCO, following the similar procedure as described for compound **187a**, as yellow solid.



Reaction time: 2 days

Yield: 43%

Mp: 142-144 ^{o}C

IR (KBr): ν 3315, 1714, 1704, 1618 cm^{-1}

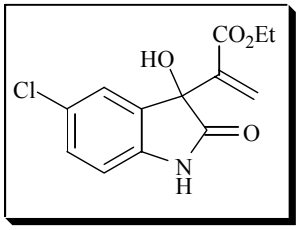
^{1}H NMR (400 MHz) (DMSO-d_6): δ 0.99 (t, 3H, *J* = 6.8 Hz), 3.80-3.99 (m, 2H), 6.39 (d, 1H, *J* = 2.0 Hz), 6.44 (d, 1H, *J* = 2.0 Hz), 6.48 (s, 1H), 6.80 (d, 1H, *J* = 8.0 Hz), 6.84-6.92 (m, 1H), 6.95 (d, 1H, *J* = 7.2 Hz), 7.16-7.24 (m, 1H), 10.30 (s, 1H).

^{13}C NMR (100 MHz) (DMSO-d_6): δ 13.52, 60.25, 75.30, 109.52, 121.28, 123.25, 126.89, 129.29, 131.77, 140.14, 143.22, 164.10, 177.03.

Ethyl 2-(5-chloro-3-hydroxyindolin-2-on-3-yl)-2-methylenethanoate (187g):

The Baylis-Hillman reaction of 5-chloroisatin and ethyl acrylate under the catalytic influence of DABCO provided the title compound, following the similar procedure as described for compound **187a**, as white solid.

Reaction time: 12 h



Yield: 53%

Mp: 200-201 ^{o}C

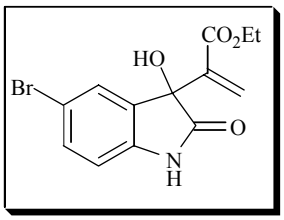
IR (KBr): ν 3371, 1722, 1705, 1616 cm^{-1}

^{1}H NMR (400 MHz) (DMSO-d_6): δ 1.03 (t, 3H, *J* = 7.2 Hz), 3.86-4.05 (m, 2H), 6.42 (s, 1H), 6.49 (s, 1H), 6.70 (s, 1H), 6.83 (d, 1H, *J* = 8.0 Hz), 6.97 (s, 1H), 7.26 (d, 1H, *J* = 8.4 Hz), 10.49 (s, 1H).

^{13}C NMR (100 MHz) (DMSO-d_6): δ 13.57, 60.48, 75.25, 111.07, 123.35, 125.21, 127.74, 129.13, 133.85, 139.36, 142.14, 163.99, 176.71.

Ethyl 2-(5-bromo-3-hydroxyindolin-2-on-3-yl)-2-methylenethanoate (187h):

Treatment of 5-bromoisatin with ethyl acrylate in the presence of catalytic amount of DABCO afforded the title compound, following the similar procedure as described for compound **187a**, as yellow solid.



Reaction time: 2 days

Yield: 52%

Mp: 186-188 ^{o}C

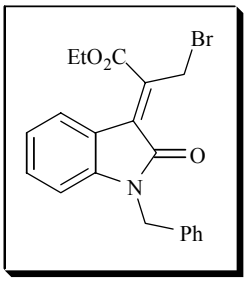
IR (KBr): ν 3377, 1724, 1705, 1616 cm^{-1}

^{1}H NMR (400 MHz) (DMSO-d_6): δ 1.04 (t, 3H, *J* = 7.2 Hz), 3.85-4.03 (m, 2H), 6.42 (s, 1H), 6.49 (s, 1H), 6.70 (s, 1H), 6.79 (d, 1H, *J* = 8.0 Hz), 7.09 (d, 1H, *J* = 1.2 Hz), 7.39 (dd, 1H, *J* = 8.0 Hz), 10.49 (s, 1H).

^{13}C NMR (100 MHz) (DMSO-d_6): δ 13.55, 60.46, 75.18, 111.61, 112.79, 126.01, 127.72, 131.96, 134.21, 139.34, 142.53, 163.96, 176.54.

(*Z*)-3-(1-Ethoxycarbonyl-2-bromo)ethylidene-1-benzylindolin-2-one (188a):

To a stirred suspension of NBS (20 mmol, 3.559 g) in CH_2Cl_2 (50 mL) dimethyl sulfide (40 mmol, 2.485 g) was added dropwise at 0 ^oC under N_2 atmosphere. The resulting yellow suspension was stirred for 1 h at the same temperature. Then ethyl 2-(1-benzyl-3-hydroxyindolin-2-on-3-yl)-2-methylenethanoate (**187a**) (10 mmol, 3.37 g) was added portion wise and stirring continued for 12 h at room temperature. The yellow suspension was turned into reddish clear solution. The reaction mixture was treated with aqueous $NaHCO_3$ solution (10 mL). Organic layer was separated and the aqueous layer was extracted with dichloromethane (2 x 10 mL). Combined organic layer was dried over anhydrous Na_2SO_4. Solvent was evaporated and the crude, thus obtained, was subjected to column chromatography (silica gel, 10% ethyl acetate in hexanes) to afford the desired product (**188a**) as orange solid in 65% (2.60 g) isolated yield.



Reaction time: 12 h

Yield: 65%

Mp: 138-140 ^oC

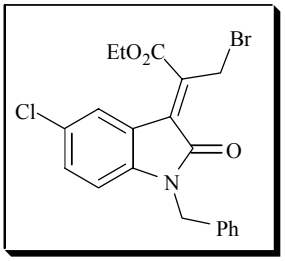
IR (KBr): ν 1724, 1697, 1606 cm^{-1}

^{1}H NMR (400 MHz): δ 1.42 (t, 3H, *J* = 6.8 Hz), 4.48 (q, 2H, *J* = 6.8 Hz), 4.92 (s,

2H), 5.27 (s, 2H), 6.68 (d, 1H, *J* = 7.6 Hz), 6.91-7.00 (m, 1H), 7.16-7.36 (m, 6H), 7.50 (d, 1H, *J* = 7.6 Hz).

^{13}C NMR (100 MHz): δ 14.17, 25.64, 43.63, 62.39, 109.34, 119.89, 122.54, 124.59, 127.32, 127.54, 127.80, 128.89, 131.49, 135.45, 137.65, 143.17, 166.54, 167.04.

(*Z*)-3-(1-Ethoxycarbonyl-2-bromo)ethylidene-1-benzyl-5-chloroindolin-2-one (188b): Treatment of ethyl 2-(1-benzyl-5-chloro-3-hydroxyindolin-2-on-3-yl)-2-methylenethano-ate (**187b**) with NBS in the presence of dimethyl sulfide afforded the title compound as red solid, following the similar procedure as described for the compound **188a**.



Reaction time: 12 h

Yield: 62%

Mp: 128-130 ^{o}C

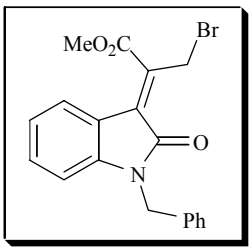
IR (KBr): ν 1711, 1628, 1602 cm^{-1}

^{1}H NMR (400 MHz): δ 1.45 (t, 3H, *J* = 7.2 Hz), 4.50 (q, 2H, *J* = 7.2 Hz), 4.91 (s, 2H), 5.26 (s, 2H), 6.60 (d, 1H, *J* = 8.4 Hz), 7.17 (dd, 1H, *J* = 8.4 Hz), 7.22-7.37 (m, 5H), 7.50 (d, 1H, *J* = 2.0 Hz).

^{13}C NMR (100 MHz): δ 14.11, 25.30, 43.75, 62.67, 110.24, 121.20, 125.05, 126.75, 127.28, 127.99, 128.99, 131.12, 135.01, 139.23, 141.57, 166.09, 166.66.

(*Z*)-3-(1-Methoxycarbonyl-2-bromo)ethylidene-1-benzylindolin-2-one (188c):

This compound was prepared *via* the treatment of methyl 2-(1-benzyl-3-hydroxyindolin-2-on-3-yl)-2-methylenethanoate (**187c**) with NBS in the presence of dimethyl sulfide following the similar procedure as described for the compound **188a**, as red solid.



Reaction time: 12 h

Yield: 60%

Mp: 119-120 ^{o}C

IR (KBr): ν 1734, 1699, 1606 cm^{-1}

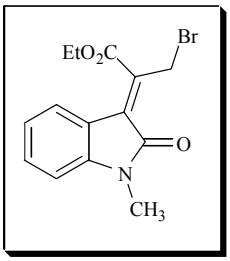
^{1}H NMR (400 MHz): δ 4.00 (s, 3H), 4.92 (s, 2H), 5.26 (s, 2H), 6.68 (d, 1H, *J* = 8.0 Hz), 6.92-7.01 (m, 1H), 7.16-7.37 (m, 6H), 7.45 (d, 1H, *J* = 7.6 Hz).

^{13}C NMR (100 MHz): δ 25.58, 43.64, 53.01, 109.39, 119.81, 122.62, 124.53, 127.31, 127.83, 127.91, 128.91, 131.61, 135.41, 137.21, 143.22, 166.97, 167.05.

(*Z*)-3-(1-Ethoxycarbonyl-2-bromo)ethylidene-1-methylindolin-2-one (188d):

This compound was obtained as red solid *via* the treatment of ethyl 2-(3-hydroxy-1-methylindolin-2-on-3-yl)-2-methylenethanoate (**187d**) with NBS in the presence of dimethyl sulfide, following the similar procedure as described for the compound **188a**.

Reaction time: 24 h



Yield: 64%

Mp: 123-125 ^{o}C

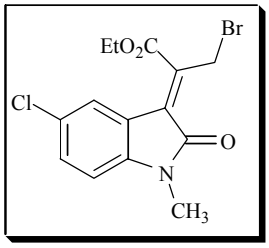
IR (KBr): ν 1718, 1701, 1606 cm^{-1}

^{1}H NMR (400 MHz): δ 1.42 (t, 3H, *J* = 7.2 Hz), 3.22 (s, 3H), 4.47 (q, 2H, *J* = 7.2 Hz), 5.23 (s, 2H), 6.78 (d, 1H, *J* = 7.6 Hz), 6.95-7.05 (m, 1H), 7.30-7.38 (m, 1H), 7.49 (d, 1H, *J* = 8.0 Hz).

^{13}C NMR (100 MHz): δ 14.14, 25.60, 26.04, 62.33, 108.35, 119.79, 122.48, 124.60, 127.82, 131.57, 137.26, 144.00, 166.54, 166.96.

(*Z*)-3-(1-Ethoxycarbonyl-2-bromo)ethylidene-5-chloro-1-methylindolin-2-one (188e):

This compound was prepared *via* the treatment of ethyl 2-(5-chloro-3-hydroxy-1-methylindolin-2-on-3-yl)-2-methylenethanoate (**187e**) with NBS in the presence of dimethyl sulfide, following the similar procedure as described for the compound **188a**, as red solid.



Reaction time: 12 h

Yield: 61%

Mp: 130-132 ^{o}C

IR (KBr): ν 1705, 1602 cm^{-1}

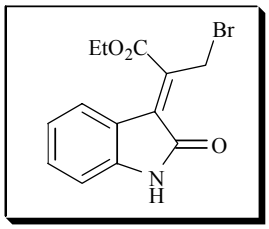
^{1}H NMR (400 MHz): δ 1.44 (t, 3H, *J* = 7.2 Hz), 3.21 (s, 3H), 4.49 (q, 2H, *J* = 7.2 Hz), 5.22 (s, 2H), 6.71 (d, 1H, *J* = 8.4 Hz), 7.29 (dd, 1H, *J* =

2.0 Hz and 8.4 Hz), 7.51 (d, 1H, *J* = 2.0 Hz).

^{13}C NMR (100 MHz): δ 14.09, 25.26, 26.18, 62.61, 109.19, 121.03, 125.09, 127.03, 127.89, 131.18, 138.80, 142.42, 166.06, 166.55.

(*Z*)-3-(1-Ethoxycarbonyl-2-bromo)ethylidenindolin-2-one (188f):

The compound was obtained *via* the treatment of ethyl 2-(3-hydroxyindolin-2-on-3-yl)-2-methylenethanoate (**187f**) with NBS in the presence of dimethyl sulfide, following the similar procedure as described for the compound **188a**, as red solid.



Reaction time: 12 h

Yield: 56%

Mp: 132-133 ^{o}C

IR (KBr): ν 3192, 1726, 1699, 1612 cm^{-1}

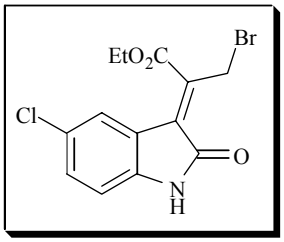
^{1}H NMR (400 MHz): δ 1.43 (t, 3H, *J* = 7.2 Hz), 4.48 (q, 2H, *J* = 7.2 Hz), 5.21 (s, 2H), 6.87 (d, 1H, *J* = 7.6 Hz), 6.93-7.02 (m, 1H), 7.22-7.32 (m, 1H), 7.48 (d, 1H, *J* = 7.6 Hz), 8.94 (bs, 1H).

^{13}C NMR (100 MHz): δ 14.15, 25.48, 62.42, 110.40, 120.44, 122.53, 124.89, 128.16, 131.68, 137.71, 141.40, 166.49, 169.21.

(*Z*)-3-(1-Ethoxycarbonyl-2-bromo)ethylidene-5-chloroindolin-2-one (188g):

The Baylis-Hillman adduct, ethyl 2-(5-chloro-3-hydroxyindolin-2-on-3-yl)-2-methylenethanoate (**187g**) on treatment with NBS in the presence of dimethyl sulfide

provided the title compound as red solid, following the similar procedure as described for compound **188a**.



Reaction time: 24 h

Yield: 45%

Mp: 169-170 ^{o}C

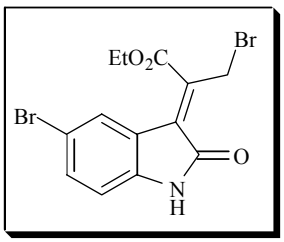
IR (KBr): ν 3196, 1728, 1701, 1610 cm^{-1}

^{1}H NMR (400 MHz): δ 1.45 (t, 3H, *J* = 7.2 Hz), 4.51 (q, 2H, *J* = 7.2 Hz), 5.19 (s, 2H), 6.80 (d, 1H, *J* = 8.0 Hz), 7.25 (s, 1H), 7.51 (s, 1H), 8.46 (bs, 1H).

^{13}C NMR (100 MHz) (DMSO-d_6): δ 13.79, 25.87, 62.33, 111.76, 121.02, 124.13, 125.57, 127.64, 131.53, 137.75, 141.55, 165.53, 167.47.

(*Z*)-3-(1-Ethoxycarbonyl-2-bromo)ethylidene-5-bromoindolin-2-one (188h):

Treatment of ethyl 2-(5-bromo-3-hydroxyindolin-2-on-3-yl)-2-methylenethanoate (**187h**) with NBS in the presence of dimethyl sulfide afforded the title compound as red solid, following the similar procedure as described for the compound **188a**.



Reaction time: 12 h

Yield: 36%

Mp: 174-175 ^{o}C

IR (KBr): ν 3192, 1728, 1701, 1608 cm^{-1}

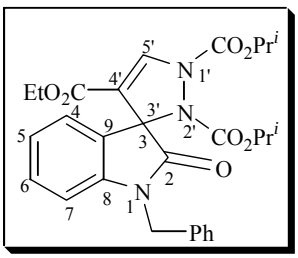
^1H NMR (400 MHz): δ 1.46 (t, 3H, *J* = 6.8 Hz), 4.44-4.57 (m, 2H), 5.18 (s, 2H), 6.74 (d, 1H, *J* = 8.0 Hz), 7.40 (dd, 1H, *J* = 1.2 Hz and 8.0 Hz), 7.65 (d, 1H, *J* = 1.6 Hz), 8.21 (bs, 1H).*

* ^1H NMR shows some impurities (isomer) 5-10%.

^{13}C NMR (100 MHz) (DMSO-d_6): δ 14.27, 26.33, 62.78, 112.70, 113.63, 121.96, 127.31, 127.94, 134.77, 138.17, 142.36, 166.02, 167.79.

(1-Benzylindolin-2-one)-3-spiro-3′-[4′-ethoxycarbonyl-1′,2′-bis(isopropoxycarbonyl)-2′,3′-dihydro-1′*H*-pyrazole] (189a):

To a stirred solution of (*Z*)-3-(1-ethoxycarbonyl-2-bromo)ethylidene-1-benzylindolin-2-one (**188a,** 1 mmol, 0.400 g) and dimethyl sulfide (1.2 mmol, 0.074 g, 0.088 mL) in DMF (1 mL), K_2CO_3 (1 mmol, 0.138 g) and diisopropyl azodicarboxylate (1 mmol, 0.202 g) were added successively at room temperature. After stirring at room temperature for 1 h (reaction monitored by TLC), the reaction mixture was diluted with water (2 mL) and extracted with dichloromethane (3×5 mL). Combined organic layer was dried over anhydrous Na_2SO_4 and solvent was evaporated. The crude product, thus obtained was subjected to column chromatography (silica gel, 25% ethyl acetate in hexanes) to afford **189a** as white solid in 83% (0.432 g) isolated yield.



Mp: 72-74 °C

IR (KBr): ν 1757, 1733, 1722, 1705, 1620 cm^{-1}

^{1}H NMR (400 MHz): δ 0.60-1.43 (m, 15H)*, 3.80-3.94 (m, 1H), 3.99-4.12 (m, 1H), 4.70-5.23 (m, 4H), 6.66 (d, 1H, *J* = 6.4 Hz), 6.95-7.03 (m, 1H), 7.12-7.39 (m, 5H), 7.47 (d, 2H, *J* = 7.6 Hz), 7.82 (s, 1H).

* This contains a triplet at δ 0.96 (*J* = 7.2 Hz), a broad peak at δ 1.15 and multiplet at δ 1.34-1.43.

^{13}C NMR (100 MHz): δ 13.91, 21.73, 21.91, 44.82, 60.65, 71.42,# 72.70, 73.94,# 109.32, 113.31,* 123.10, 123.88, 127.67, 128.73, 130.16, 135.56, 139.16, 143.19,# 151.31,* 153.28,# 161.04, 172.69.

: Low intensity peak; * : Broad low intensity peak

LCMS (*m/z*): 522 $(M-H)^+$, 523 $(M+2-H)^+$

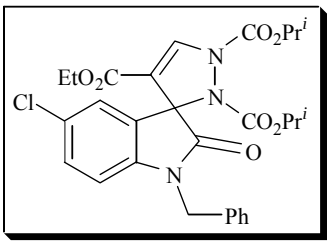
Analysis calc'd for $C_{28}H_{31}N_3O_7$: C, 64.48; H, 5.99; N, 8.06;

Found: C, 64.55; H, 5.92; N, 8.11.

(1-Benzyl-5-chloroindolin-2-one)-3-spiro-3′-[4′-ethoxycarbonyl-1′,2′-bis(isopropoxy carbonyl)-2′,3′-dihydro-1′*H*-pyrazole] (189b):

This compound was obtained as brown solid *via* (3 + 2) annulation reaction of (*Z*)-3-(1-ethoxycarbonyl-2-bromo)ethylidene-1-benzyl-5-chloroindolin-2-one (**188b**) with

diisopropyl azodicarboxylate in the presence of dimethyl sulfide and K_2CO_3, following the similar procedure as described for compound **189a**.



Reaction time: 1 h

Yield: 76%

Mp: 82-84 ^{o}C

IR (KBr): ν 1770, 1743, 1720, 1630 cm^{-1}

^{1}H NMR (400 MHz): δ 0.70-1.50 (m, 15H)*, 3.87-4.01 (m, 1H), 4.02-4.19 (m, 1H), 4.80-5.23 (m, 4H), 6.57 (bs, 1H), 7.12-7.21 (m, 2H), 7.22-7.41 (m, 3H), 7.45 (d, 2H, *J* = 7.2 Hz), 7.80 (s, 1H).

* This contains a triplet at δ 1.03 (*J* = 7.2 Hz), a broad peak at δ 1.19 and multiplet at δ 1.38-1.50.

^{13}C NMR (100 MHz): δ 13.98, 21.72, 21.89, 44.93, 60.85, 71.78,# 72.92, 73.74,# 110.39, 112.76,* 124.54, 127.56, 127.77, 128.47, 128.82, 129.38,# 130.08, 135.04, 139.36, 141.67, 151.49,* 153.22,* 160.90, 172.39.

: Low intensity peak; * : Broad low intensity peak

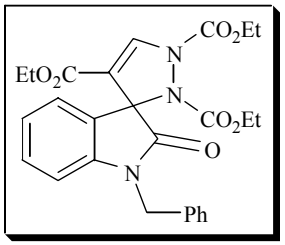
LCMS (*m/z*): 556 $(M+H)^{+}$, 558 $(M+2+H)^{+}$

Analysis calc'd for $C_{28}H_{30}ClN_3O_7$: C, 60.48; H, 5.44; N, 7.56;

Found: C, 60.35; H, 5.48; N, 7.61.

(1-Benzylindolin-2-one)-3-spiro-3′-[1′,2′,4′-tris(ethoxycarbonyl)-2′,3′-dihydro-1′*H*-pyrazole] (189c):

[3 + 2] Annulation reaction of (*Z*)-3-(1-ethoxycarbonyl-2-bromo)ethylidene-1-benzyl-indolin-2-one (**188a**) with diethyl azodicarboxylate under the influence of dimethyl sulfide and K_2CO_3 afforded the title compound, following the similar procedure as described for compound **189a**, as white solid.



Reaction time: 1 h

Yield: 61%

Mp: 151-152 ^{o}C

IR (KBr): ν 1766, 1743, 1714, 1628 cm^{-1}

^{1}H NMR (400 MHz): δ 0.70-1.51 (m, 9H),* 3.82-3.97 (m, 2H), 4.00-4.20 (m, 2H), 4.28-4.47 (m, 2H), 4.96 (s, 2H), 6.69 (bs, 1H), 6.97-7.08 (m, 1H), 7.12-7.40 (m, 5H), 7.46 (d, 2H, *J* = 7.2 Hz), 7.84 (s, 1H).

* This contains a broad peak at δ 0.88 and two triplets at δ 0.99 (*J* = 7.6 Hz) and δ 1.37 (*J* = 7.2 Hz).

^{13}C NMR (100 MHz): δ 13.89, 14.35, 44.70, 60.71, 63.13, 64.24, 74.00, 109.39, 113.29,* 123.16, 123.85, 127.54, 128.70, 130.26, 135.47, 138.87, 143.05, 151.77,* 153.72, 160.92, 172.52.

* : Broad low intensity peak

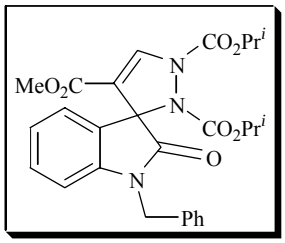
LCMS (*m/z*): 494 $(M+H)^+$

Analysis calc'd for $C_{26}H_{27}N_3O_7$: C, 63.28; H, 5.51; N, 8.51;

Found: C, 63.19; H, 5.56; N, 8.65.

(1-Benzylindolin-2-one)-3-spiro-3′-[1′,2′-bis(isopropoxycarbonyl)-4′-methoxycarbonyl-2′,3′-dihydro-1′*H*-pyrazole] (189d):

Treatment of (*Z*)-3-(1-methoxycarbonyl-2-bromo)ethylidene-1-benzylindolin-2-one (**188c**) with diisopropyl azodicarboxylate in the presence of dimethyl sulfide and K_2CO_3 provided the title compound *via* (3 + 2) annulation reaction, following the similar procedure as described for compound **189a**, as white solid.



Reaction time: 1 h

Yield: 70%

Mp: 156-158 °C

IR (KBr): ν 1770, 1736, 1716, 1630 cm^{-1}

^1H NMR (400 MHz): δ 0.60-1.48 (m, 12H),* 3.49 (s, 3H), 4.61-5.29 (m, 4H), 6.68 (d, 1H, *J* = 6.4 Hz), 6.95-7.06 (m, 1H), 7.10-7.40 (m, 5H), 7.48 (d, 2H, *J* = 7.2 Hz), 7.82 (s, 1H).

* This contains two broad peaks at δ 0.69 and δ 1.16 followed by multiplet at δ 1.31-1.48.

^{13}C NMR (100 MHz): δ 21.74, 21.90, 44.80, 51.74, 71.46,# 72.75, 73.86,# 109.41,

112.62,* 123.15, 123.91, 127.64, 128.75, 130.26, 135.53, 139.31, 143.09,# 150.96,* 153.19,# 161.48, 172.65.

: Low intensity peak; * : Broad low intensity peak

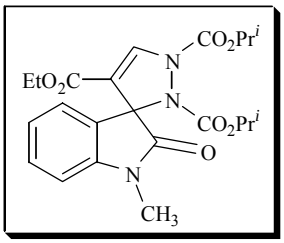
LCMS (*m/z*): 508 $(M+H)^+$

Analysis calc'd for $C_{27}H_{29}N_3O_7$: C, 63.89; H, 5.76; N, 8.28;

Found: C, 63.80; H, 5.81; N, 8.35.

(1-Methylindolin-2-one)-3-spiro-3′-[4′-ethoxycarbonyl-1′,2′-bis(isopropoxycarbonyl) -2′,3′-dihydro-1′*H*-pyrazole] (189e):

This compound was obtained as white solid *via* the (3 + 2) cycloaddition reaction of (*Z*)-3-(1-ethoxycarbonyl-2-bromo)ethylidene-1-methylindolin-2-one (**188d**) and diisopropyl azodicarboxylate in the presence of dimethyl sulfide and K_2CO_3, following the similar procedure as described for compound **189a**.



Reaction time: 2 h

Yield: 53%

Mp: 151-153 ^oC

IR (KBr): ν 1770, 1736, 1716, 1630 cm^{-1}

^1H NMR (400 MHz): δ 0.75-1.50 (m, 15H),* 3.25 (s, 3H), 3.89-4.06 (m, 2H), 4.82 (bs, 1H), 5.05-5.20 (m, 1H), 6.82 (d, 1H, *J* = 7.6 Hz), 6.99-7.09 (m, 1H), 7.16 (d, 1H, *J* = 7.2 Hz), 7.28-7.40 (m, 1H),

7.78 (s, 1H).

* This contains a triplet at δ 1.04 (J = 7.2 Hz), a broad peak at δ 1.13 and multiplet at δ 1.30-1.50.

^{13}C NMR (100 MHz): δ 13.87, 21.57, 21.83, 26.65, 60.60, 71.22,# 72.63, 73.83,# 107.98, 112.97,* 123.05, 123.92, 127.82,# 130.28, 138.89, 143.73, 151.27,* 153.04,# 161.00, 172.44.

: Low intensity peak; * : Broad low intensity peak

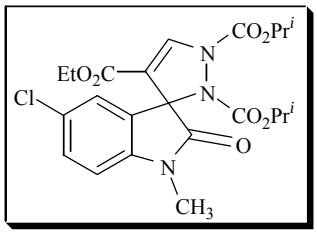
LCMS (*m/z*): 446 $(M+H)^+$

Analysis calc'd for $C_{22}H_{27}N_3O_7$: C, 59.32; H, 6.11; N, 9.43;

Found: C, 59.41; H, 6.15; N, 9.39.

(5-Chloro-1-methylindolin-2-one)-3-spiro-3′-[4′-ethoxycarbonyl-1′,2′-bis(isopropoxy carbonyl)-2′,3′-dihydro-1′*H*-pyrazole] (189f):

[3 + 2] Annulation reaction of (*Z*)-3-(1-ethoxycarbonyl-2-bromo)ethylidene-5-chloro-1-methylindolin-2-one (**188e**) with diisopropyl azodicarboxylate provided the title compound under the influence of dimethyl sulfide and K_2CO_3 in CH_3CN:H_2O (10:1), following the similar procedure as described for compound **189a**, as gray solid.



Reaction time: 3 h

Yield: 55%

Mp: 162-164 ^oC

IR (KBr): ν 1751, 1743, 1716, 1622 cm^{-1}

^1H NMR (400 MHz): δ 0.81-1.46 (m, 15H),* 3.25 (s, 3H), 4.00 (q, 2H, *J* = 7.2 Hz), 4.86 (bs, 1H), 5.06-5.21 (m, 1H), 6.77 (d, 1H, *J* = 8.0 Hz), 7.15 (s, 1H), 7.31 (d, 1H, *J* = 8.0 Hz), 7.78 (s, 1H).

***** This contains a broad peak at δ 0.97, a triplet at δ 1.09 (*J* = 7.2 Hz), a broad peak at δ 1.15 and multiplet at δ 1.33-1.46.

^{13}C NMR (100 MHz): δ 13.99, 21.63, 21.90, 26.85, 60.85, 71.66,* 72.93, 73.68,# 109.05,# 112.29,* 124.69, 128.43, 129.45,* 130.26, 139.17, 142.36, 151.16,* 153.29,* 160.94, 172.21.

: Low intensity peak; * : Broad low intensity peak

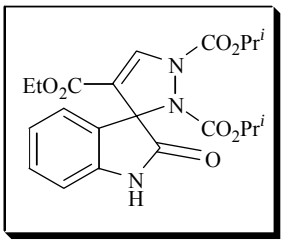
LCMS (*m/z*): 480 $(M+H)^+$, 482 $(M+2+H)^+$

Analysis calc'd for $C_{22}H_{26}ClN_3O_7$: C, 55.06; H, 5.46; N, 8.76;

Found: C, 55.12; H, 5.39; N, 8.87.

(Indolin-2-one)-3-spiro-3′-[4′-ethoxycarbonyl-1′,2′-bis(isopropoxycarbonyl)-2′,3′-dihydro-1′*H*-pyrazole] (189g):

This compound was obtained as reddish brown solid *via* the reaction of (*Z*)-3-(1-ethoxycarbonyl-2-bromo)ethylidenindolin-2-one (**188f**) and diisopropyl azodicarboxylate in the presence of dimethyl sulfide and K_2CO_3, following the similar procedure as described for compound **189a**.



Reaction time: 1 h

Yield: 53%

Mp: 98-100 ^{o}C

IR (KBr): ν 3337, 1770, 1749, 1726, 1622 cm^{-1}

^{1}H NMR (400 MHz): δ 0.80-1.50 (m, 15H),* 3.89-4.20 (m, 2H), 4.84 (bs, 1H), 5.02-5.20 (m, 1H), 6.85 (d, 1H, *J* = 7.6 Hz), 6.97-7.08 (m, 1H), 7.15 (d, 1H, *J* = 7.2 Hz), 7.24 (d, 1H, *J* = 7.6 Hz), 7.81 (s, 1H), 8.72 (bs, 1H).

* This contains a broad peak at δ 0.87, a triplet at δ 1.07 (*J* = 6.8 Hz), a broad peak at δ 1.19 and multiplet at δ 1.30-1.50.

^{13}C NMR (100 MHz): δ 13.84, 21.48, 21.91, 60.85, 71.81, 72.78, 74.35, 110.16, 112.77*, 123.09, 124.35, 128.31,* 130.33, 139.04, 141.07, 151.20,* 153.33,* 161.15, 174.75.*

* : Broad low intensity peak

LCMS (*m/z*): 430 $(M-H)^{+}$

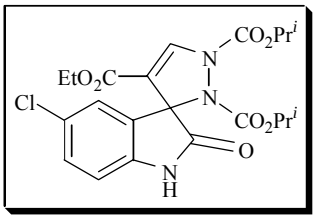
Analysis calc'd for $C_{21}H_{25}N_3O_7$: C, 58.46; H, 5.84; N, 9.74;

Found: C, 58.55; H, 5.80; N, 9.82.

(5-Chloroindolin-2-one)-3-spiro-3′-[4′-ethoxycarbonyl-1′,2′-bis(isopropoxycarbonyl) -2′,3′-dihydro-1′*H*-pyrazole] (189h):

Treatment of (*Z*)-3-(1-ethoxycarbonyl-2-bromo)ethylidene-5-chloroindolin-2-one (**188g**)

with diisopropyl azodicarboxylate in the presence of dimethyl sulfide and K_2CO_3 provided the title compound *via* (3 + 2) annulation reaction, following the similar procedure as described for compound **189a**, as white solid.



Reaction time: 1 h

Yield: 51%

Mp: 161-162 ^{o}C

IR (KBr): ν 3223, 1768, 1736, 1709, 1626 cm^{-1}

^{1}H NMR (400 MHz): δ 0.80-1.50 (m, 15H),* 3.92-4.15 (m, 2H), 4.88 (bs, 1H), 5.06-5.20 (m, 1H), 6.76 (d, 1H, *J* = 7.2 Hz), 7.12 (s, 1H), 7.21 (d, 1H, *J* = 7.2 Hz), 7.78 (s, 1H), 8.57 and 8.80 (2br, 1H).

* This contains a triplet at δ 1.11 (*J* = 6.8 Hz) and a broad peak at δ 1.19 merged together and multiplet at δ 1.30-1.50.

^{13}C NMR (100 MHz): δ 13.86, 21.44, 21.86, 21.87, 61.02, 72.13, 73.01, 74.24, 111.32, 112.24,* 124.85, 128.27, 129.77,* 130.31, 139.25, 139,73, 151.09,* 153.08,* 161.02, 174.45.*

* : Broad low intensity peak

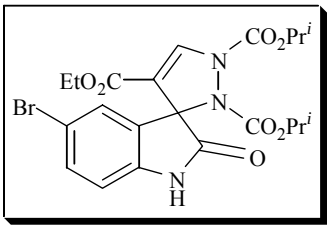
LCMS (*m/z*): 464 $(M-H)^{+}$, 466 $(M+2-H)^{+}$

Analysis calc'd for $C_{21}H_{24}ClN_3O_7$: C, 54.14; H, 5.19; N, 9.02;

Found: C, 54.25; H, 5.15; N, 9.08.

(5-Bromoindolin-2-one)-3-spiro-3′-[4′-ethoxycarbonyl-1′,2′-bis(isopropoxycarbonyl) -2′,3′-dihydro-1′*H*-pyrazole] (189i):

Treatment of (*Z*)-3-(1-ethoxycarbonyl-2-bromo)ethylidene-5-bromoindolin-2-one (**188h**) with diisopropyl azodicarboxylate under the influence of dimethyl sulfide and K_2CO_3 afforded the title compound, following the similar procedure as described for compound **189a**, as brown solid.



Reaction time: 1 h

Yield: 59%

Mp: 170-171 ^{o}C

IR (KBr): ν 3227, 1768, 1743, 1734, 1709, 1624 cm^{-1}

^{1}H NMR (400 MHz): δ 0.90-1.50 (m, 15H),* 3.95-4.15 (m, 2H), 4.90 (bs, 1H), 5.05-5.21 (m, 1H), 6.73 (d, 1H, *J* = 8.0 Hz), 7.26 (s, 1H), 7.38 (d, 1H, *J* = 8.0 Hz), 7.78 (s, 1H), 8.20 (br, 1H).

* This contains a triplet at δ 1.12 (*J* = 6.8 Hz), a broad peak at δ 1.20 and multiplet at δ 1.31-1.50.

^{13}C NMR (100 MHz): δ 13.89, 21.45, 21.90, 61.05, 72.17, 73.02, 74.15, 111.78, 112.94,* 115.50, 127.63, 130.33,* 133.21, 139.27, 140.18, 150.92,* 153.22,* 161.03, 174.05.*

* : Broad low intensity peak

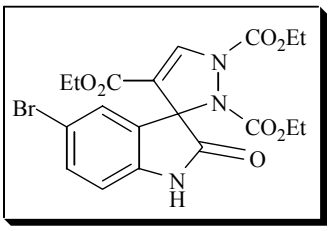
LCMS (*m/z*): 508 $(M-H)^+$, 510 $(M+2-H)^+$

Analysis calc'd for $C_{21}H_{24}BrN_3O_7$: C, 49.42; H, 4.74; N, 8.23;

Found: C, 49.51; H, 4.70; N, 8.28.

(5-Bromoindolin-2-one)-3-spiro-3′-[1′,2′,4′-tris(ethoxycarbonyl)-2′,3′-dihydro-1′*H*-pyrazole] (189j):

This compound was obtained as reddish brown solid *via* the (3 + 2) annulation reaction of (*Z*)-3-(1-ethoxycarbonyl-2-bromo)ethylidene-5-bromoindolin-2-one (**188h**) with diethyl azodicarboxylate in the presence of dimethyl sulfide and K_2CO_3, following the similar procedure as described for compound **189a**.



Reaction time: 1 h

Yield: 51%

Mp: 118-120 ^{o}C

IR (KBr): ν 3306, 1753, 1714, 1620 cm^{-1}

^{1}H NMR (400 MHz): δ 1.00-1.47 (m, 9H)*, 3.95-4.29 (m, 4H), 4.30-4.49 (m, 2H), 6.74 (d, 1H, *J* = 8.4 Hz), 7.27 (s, 1H), 7.38 (d, 1H, *J* = 8.0 Hz), 7.82 (s, 1H), 8.58 (bs, 1H).

* This contains a triplet at δ 1.13 (*J* = 7.2 Hz), a broad peak at δ 1.27 and a triplet at δ 1.39 (*J* = 7.2 Hz).

^{13}C NMR (100 MHz): δ 13.89, 14.18,* 14.37, 61.13, 63.58,* 64.53, 74.26, 111.89, 112.13,* 115.61, 127.63, 129.85,* 133.32, 139.06, 140.10,

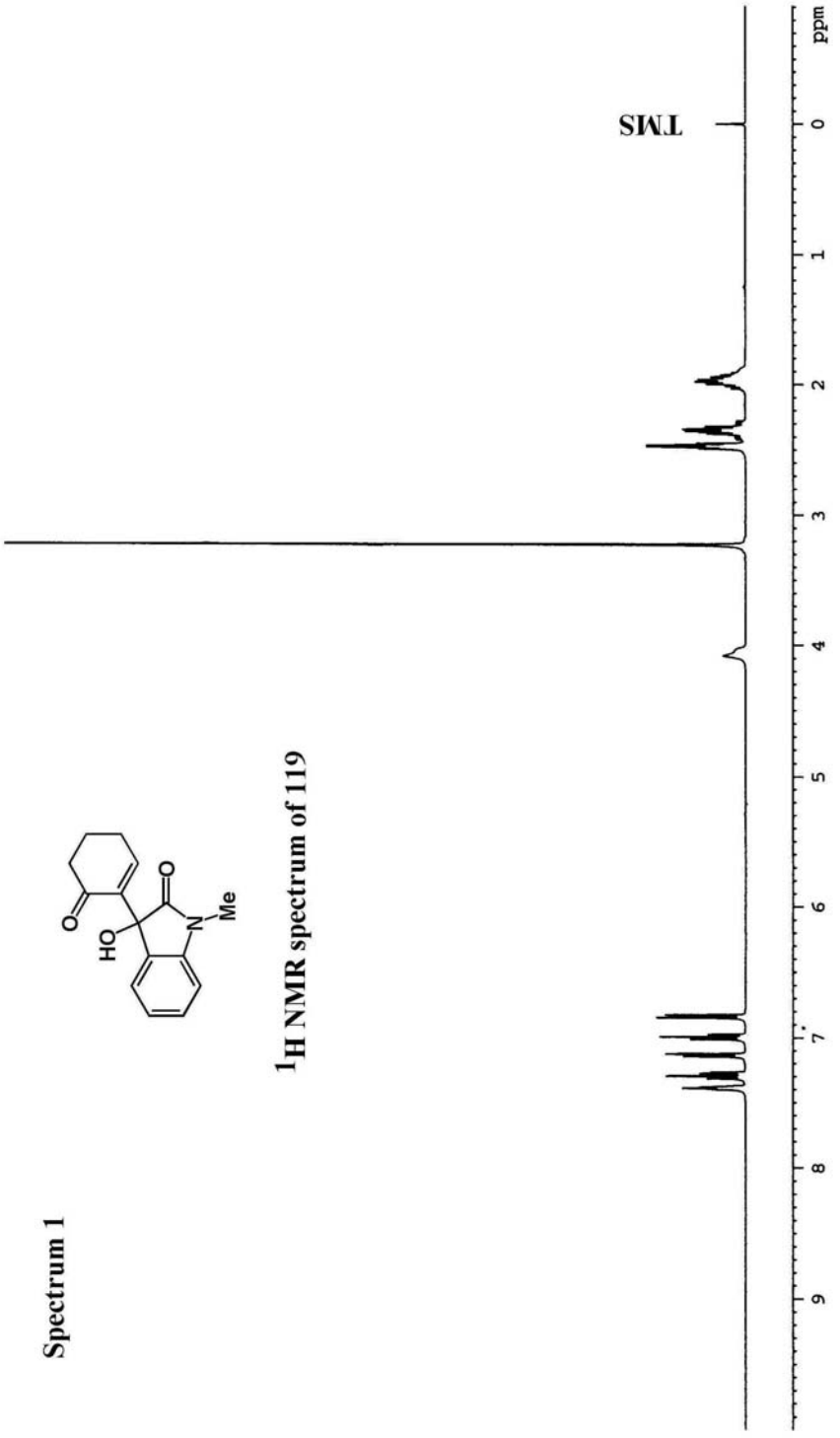
151.36,* 153.66,* 160.95, 174.12.*

* : Broad low intensity peak

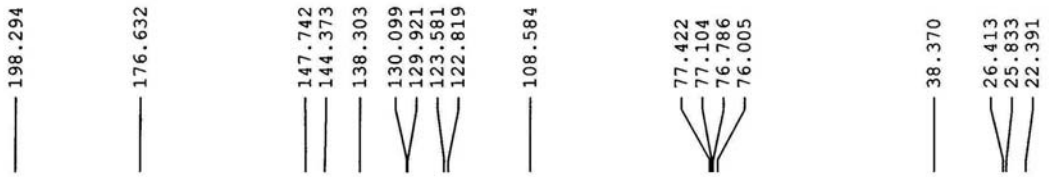
LCMS (*m/z*): 480 $(M-H)^+$, 482 $(M+2-H)^+$

Analysis calc'd for $C_{19}H_{20}BrN_3O_7$: C, 47.32; H, 4.18; N, 8.71;

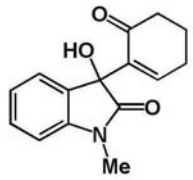
Found: C, 47.25; H, 4.22; N, 8.76.



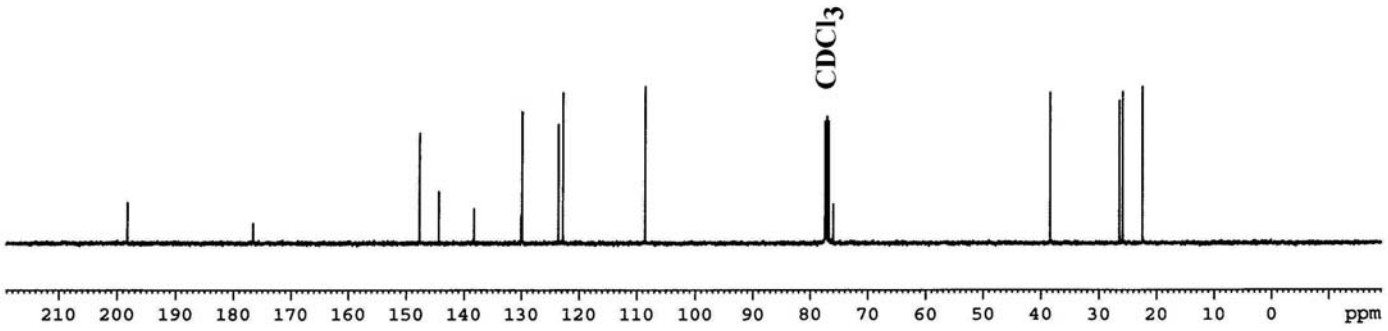
^{1}H NMR spectrum of 119



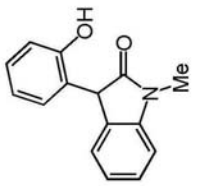
Spectrum 2



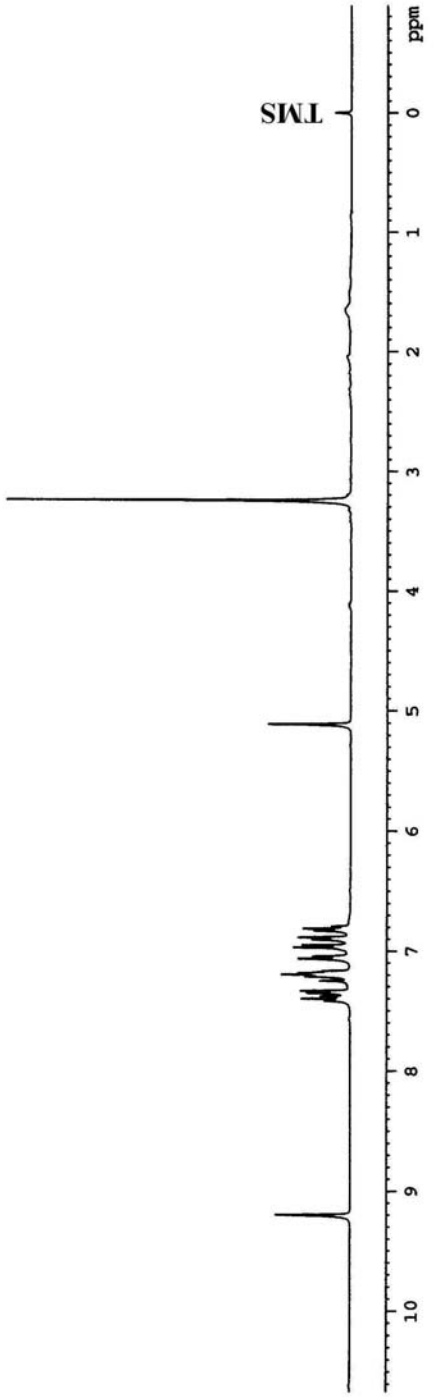
^{13}C NMR spectrum of 119

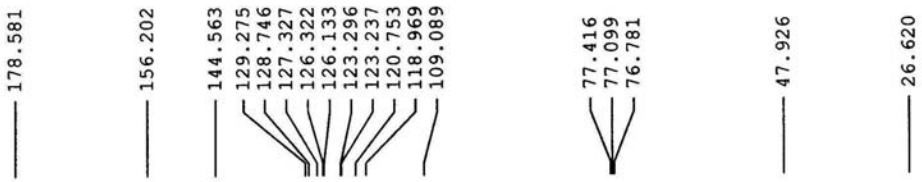


Spectrum 3

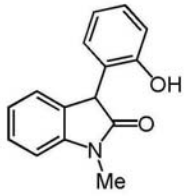


^{1}H NMR spectrum of 120

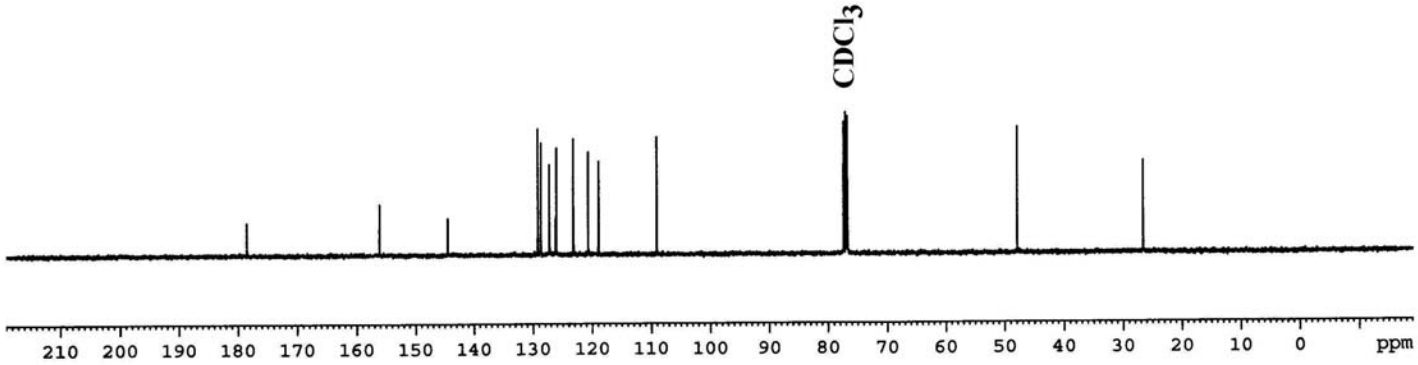




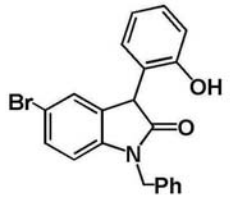
Spectrum 4



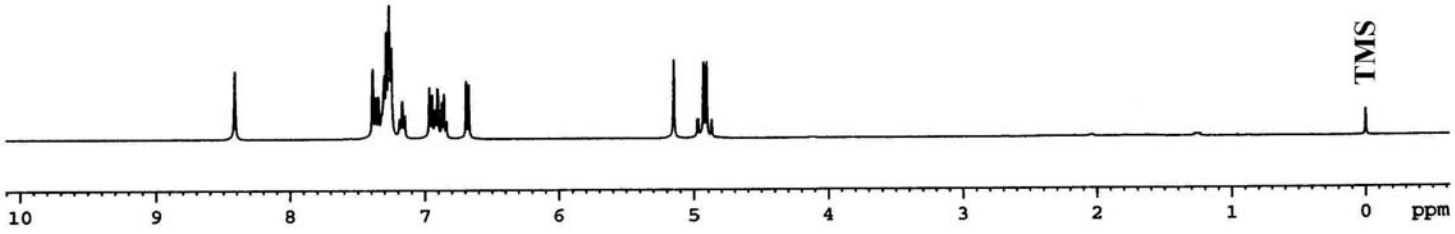
^{13}C NMR spectrum of 120

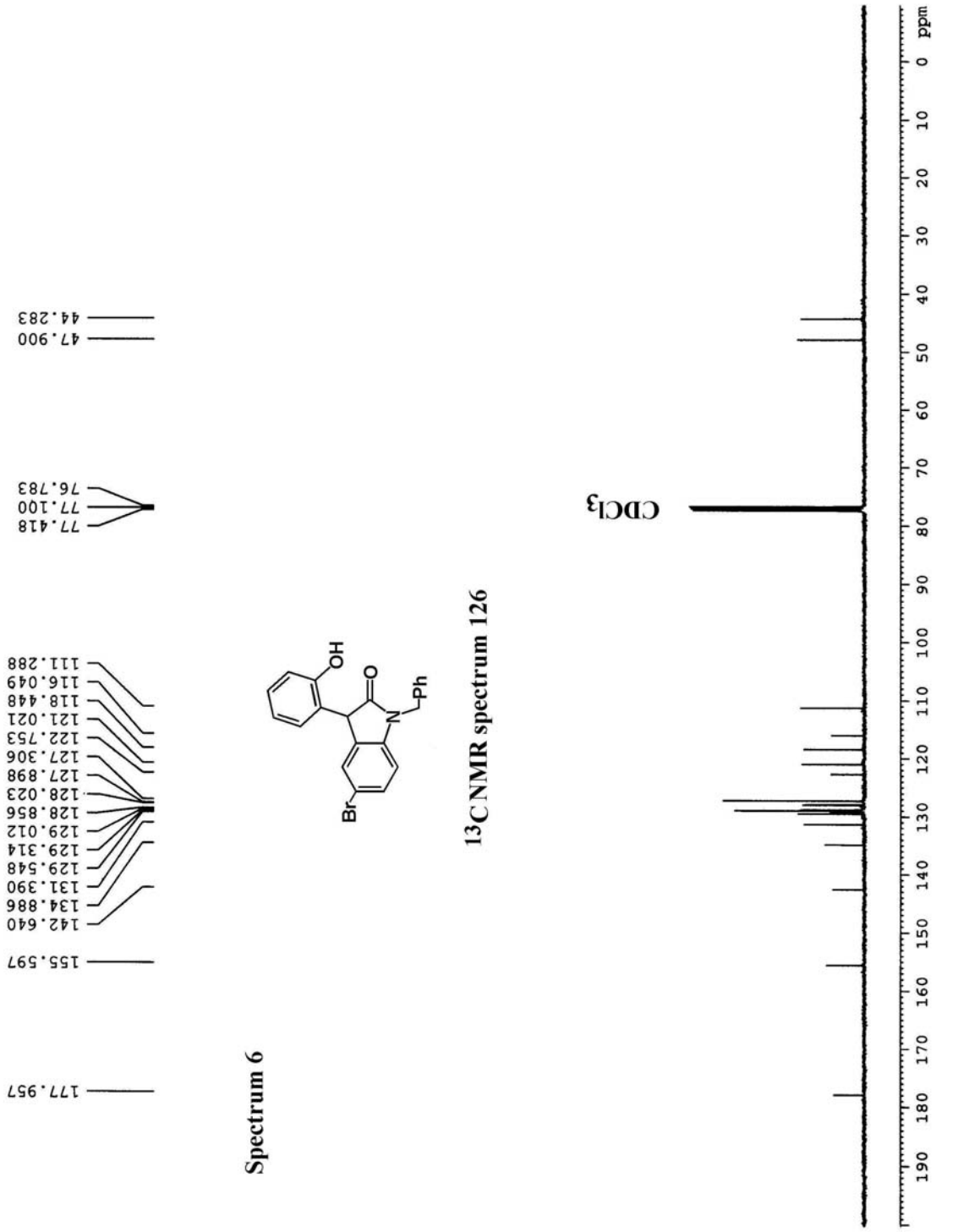


Spectrum 5



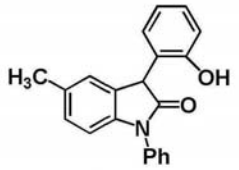
^{1}H NMR spectrum of 126



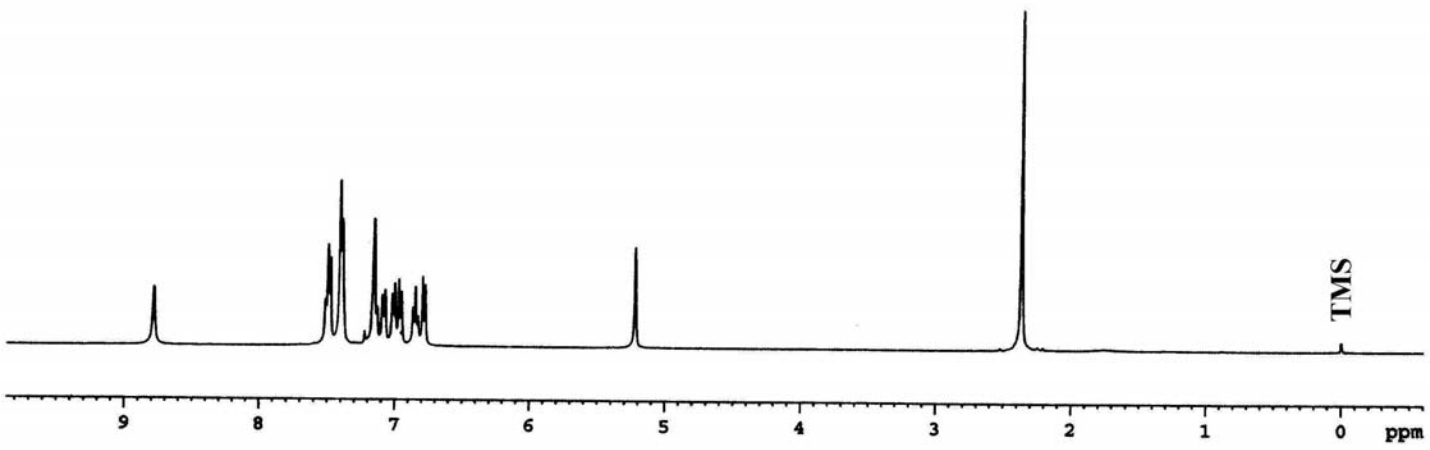


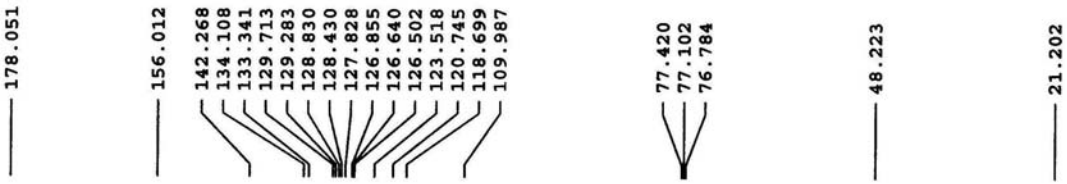
^{13}C NMR spectrum 126

Spectrum 7

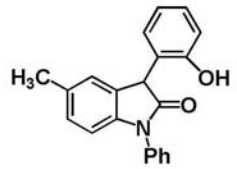


^{1}H NMR spectrum of 130

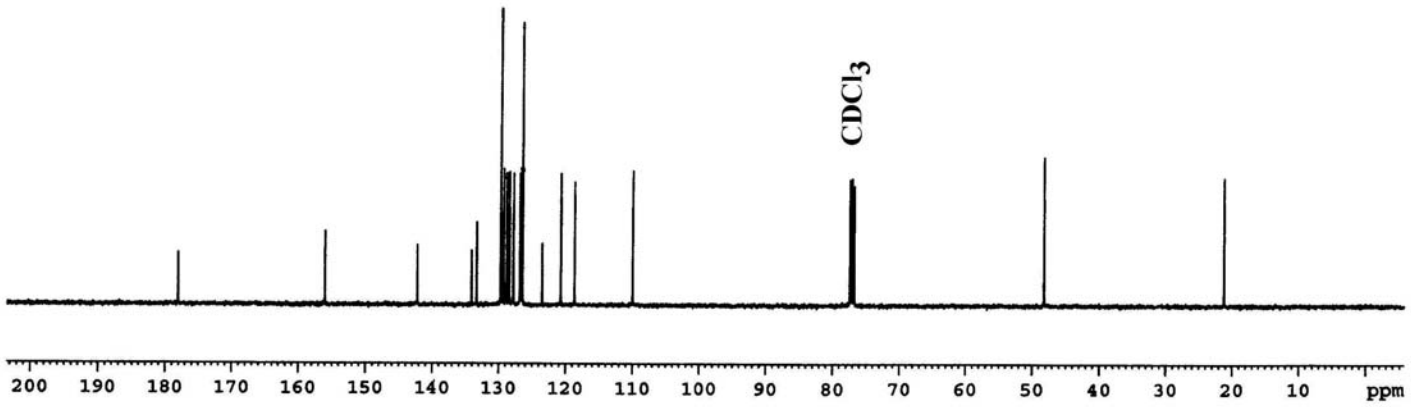




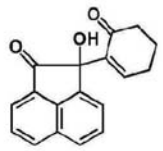
Spectrum 8



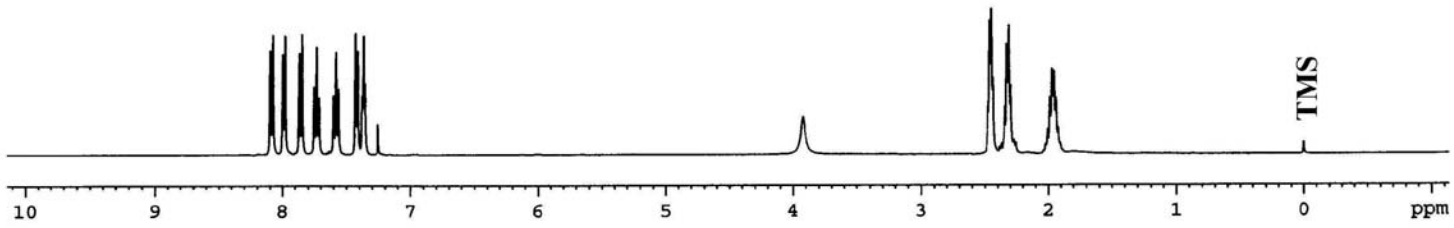
^{13}C NMR spectrum of 130

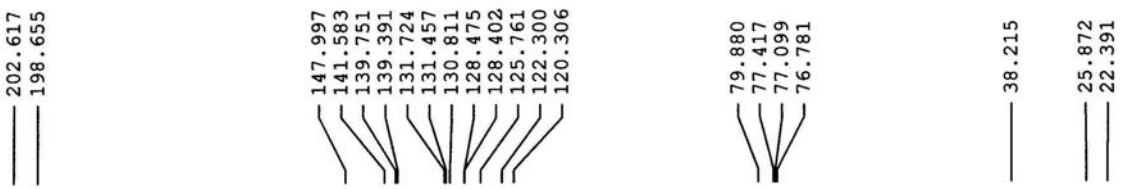


Spectrum 9

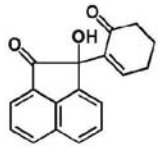


^{1}H NMR spectrum of 144a

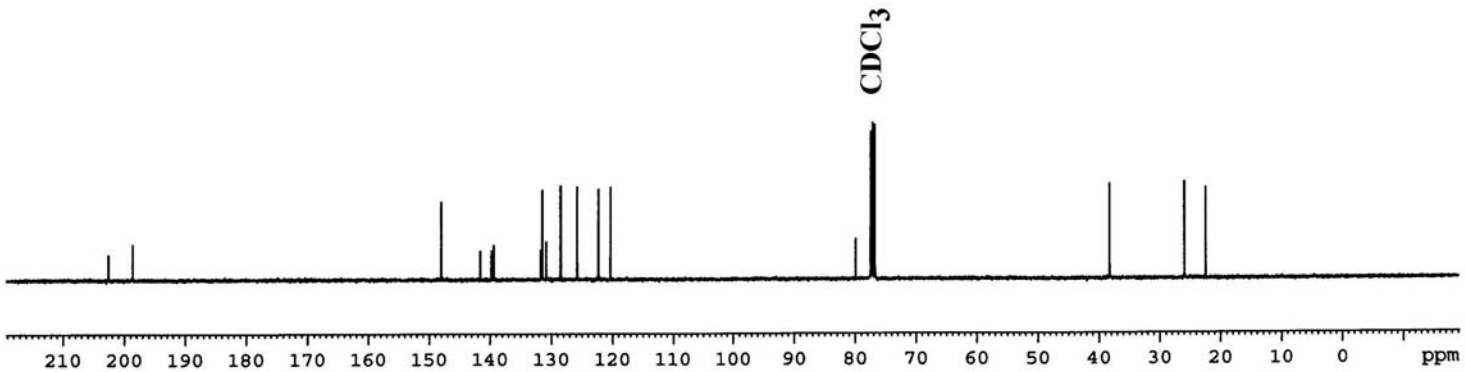




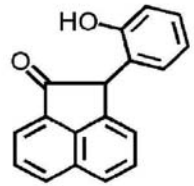
Spectrum 10



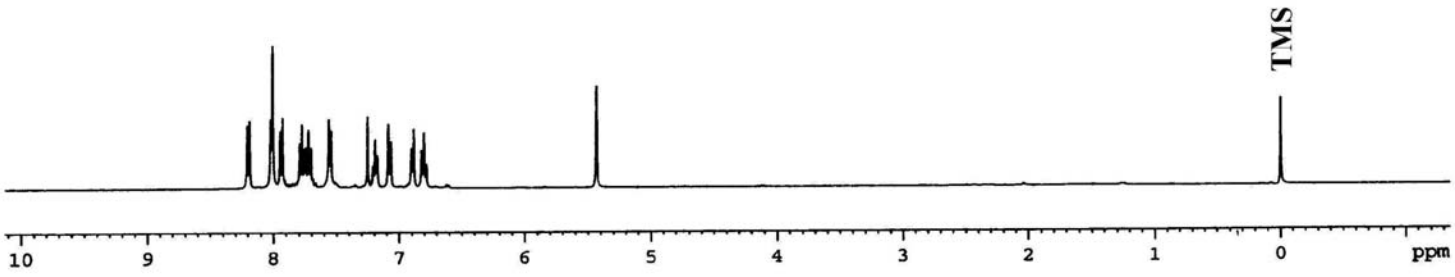
^{13}C NMR spectrum of 144a

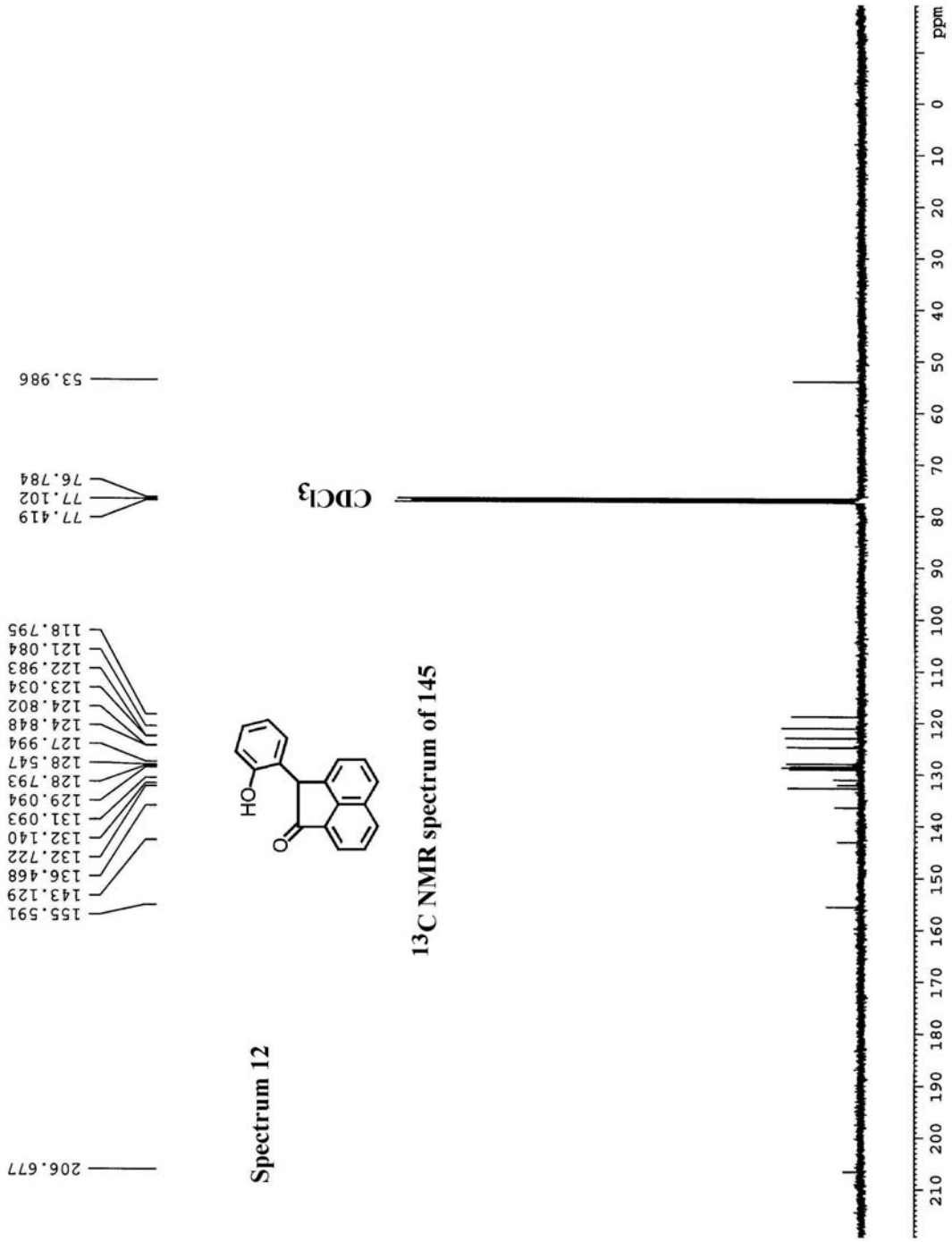


Spectrum 11

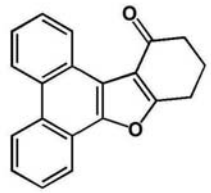


^{1}H NMR spectrum of 145

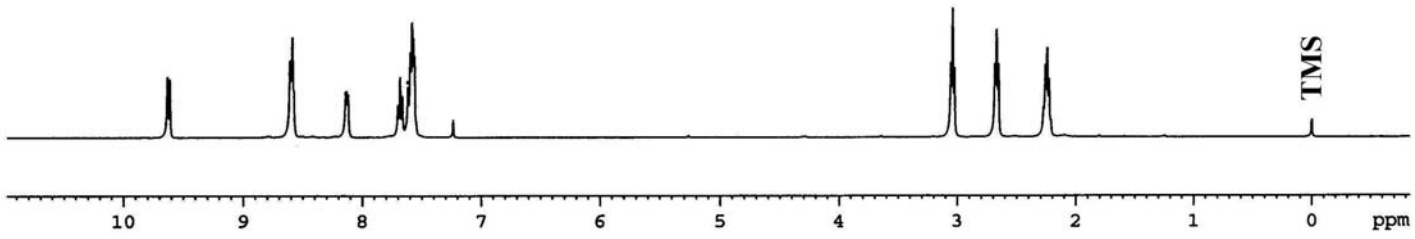


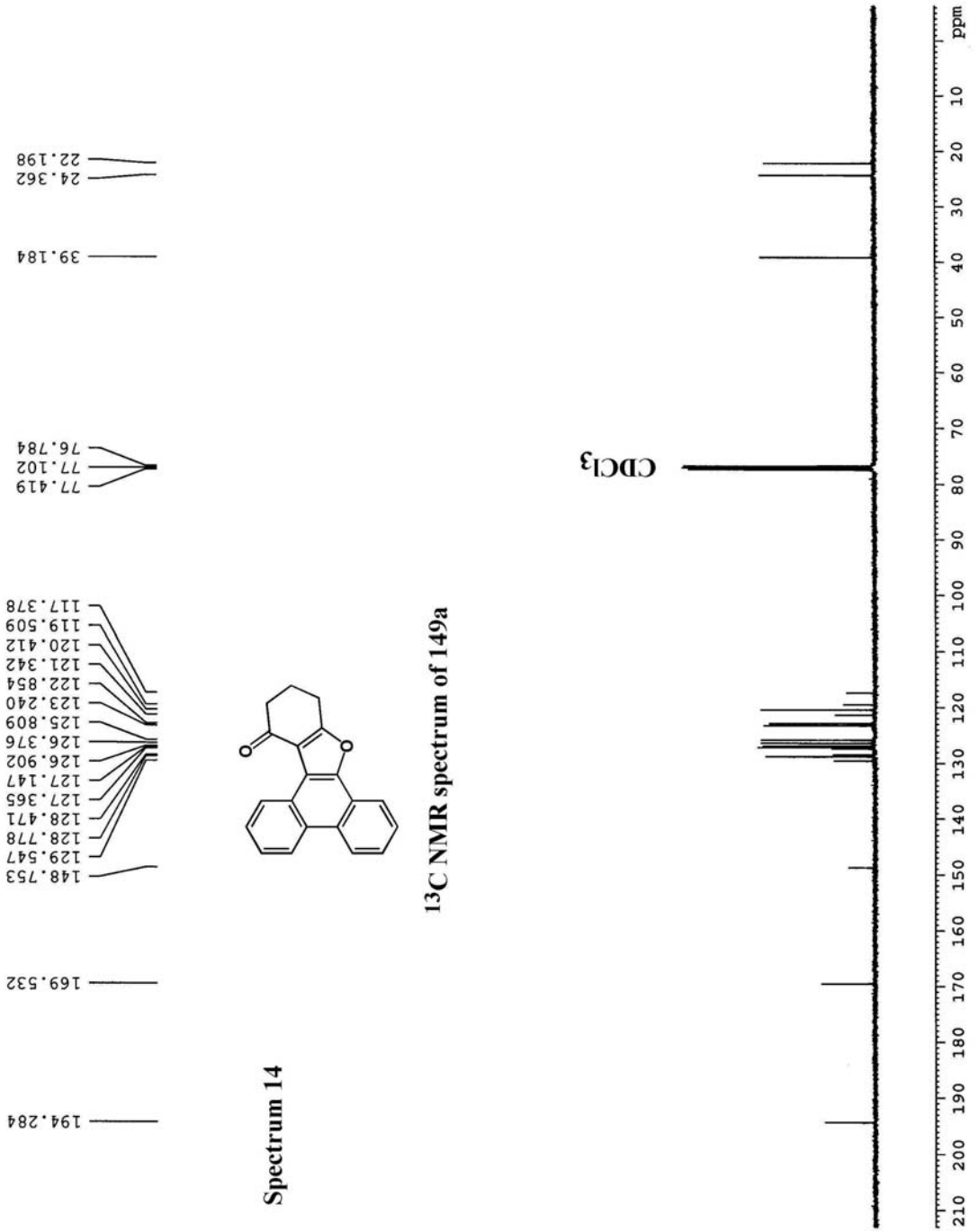

Spectrum 12
^{13}C NMR spectrum of 145
CDCl3
HO
O
206.677
155.591
143.129
136.468
132.722
132.140
131.093
129.094
128.793
128.547
127.994
124.848
124.802
123.034
122.983
121.084
118.795
77.419
77.102
76.784
53.986
ppm

Spectrum 13



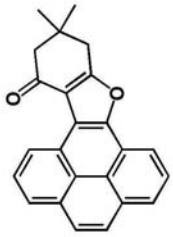
^{1}H NMR spectrum of 149a





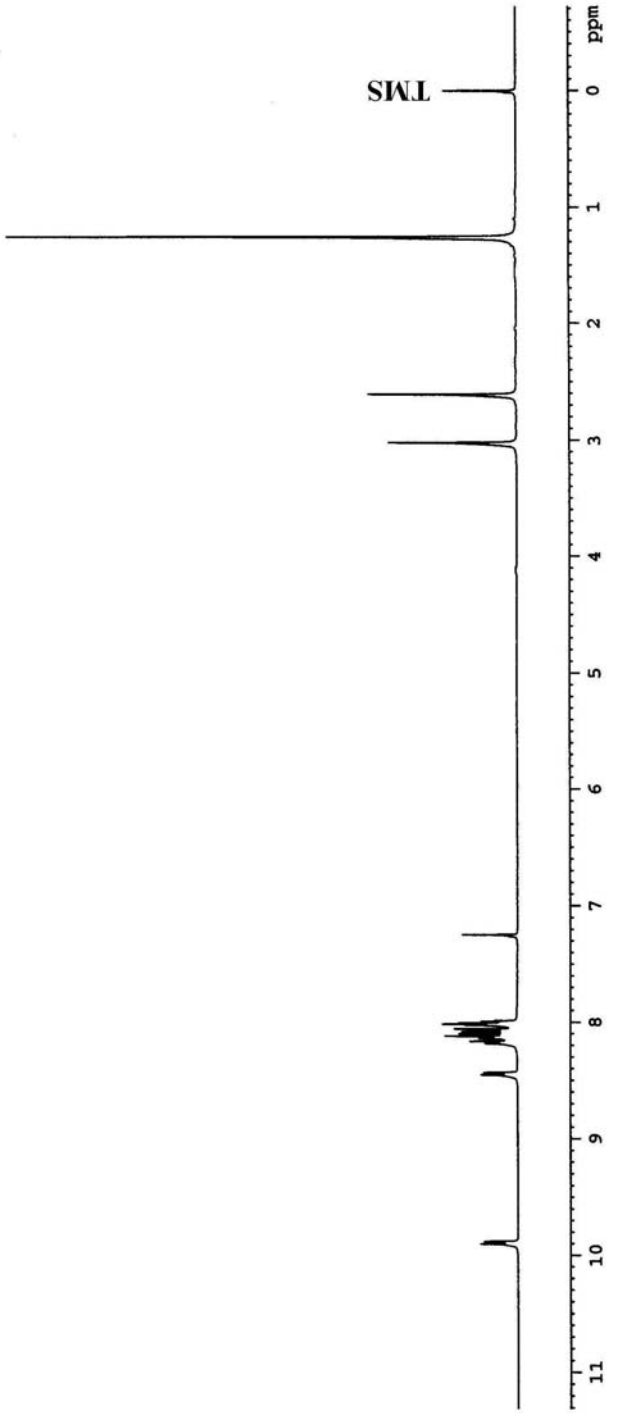
Spectrum 14

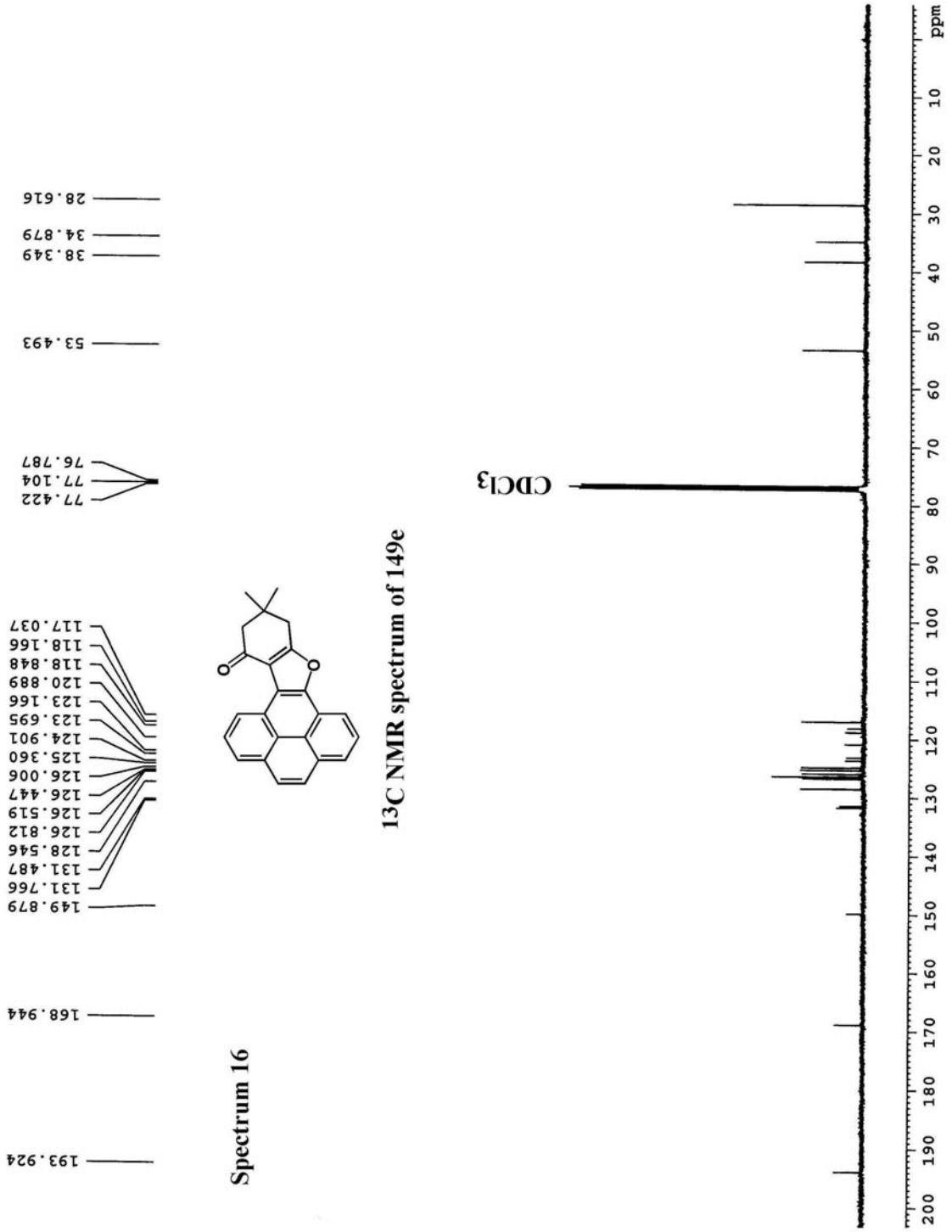
^{13}C NMR spectrum of 149a



Spectrum 15

^{1}H NMR spectrum of 149e

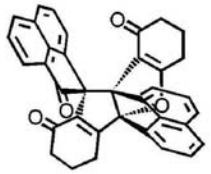




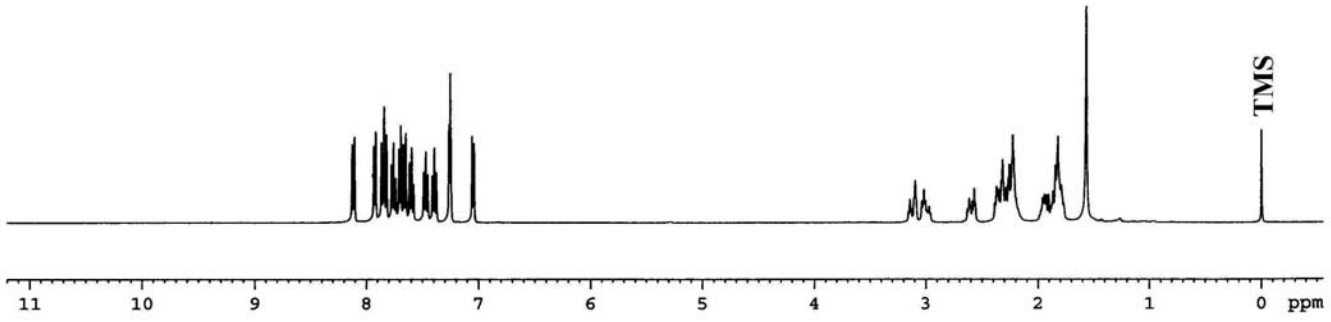
Spectrum 16

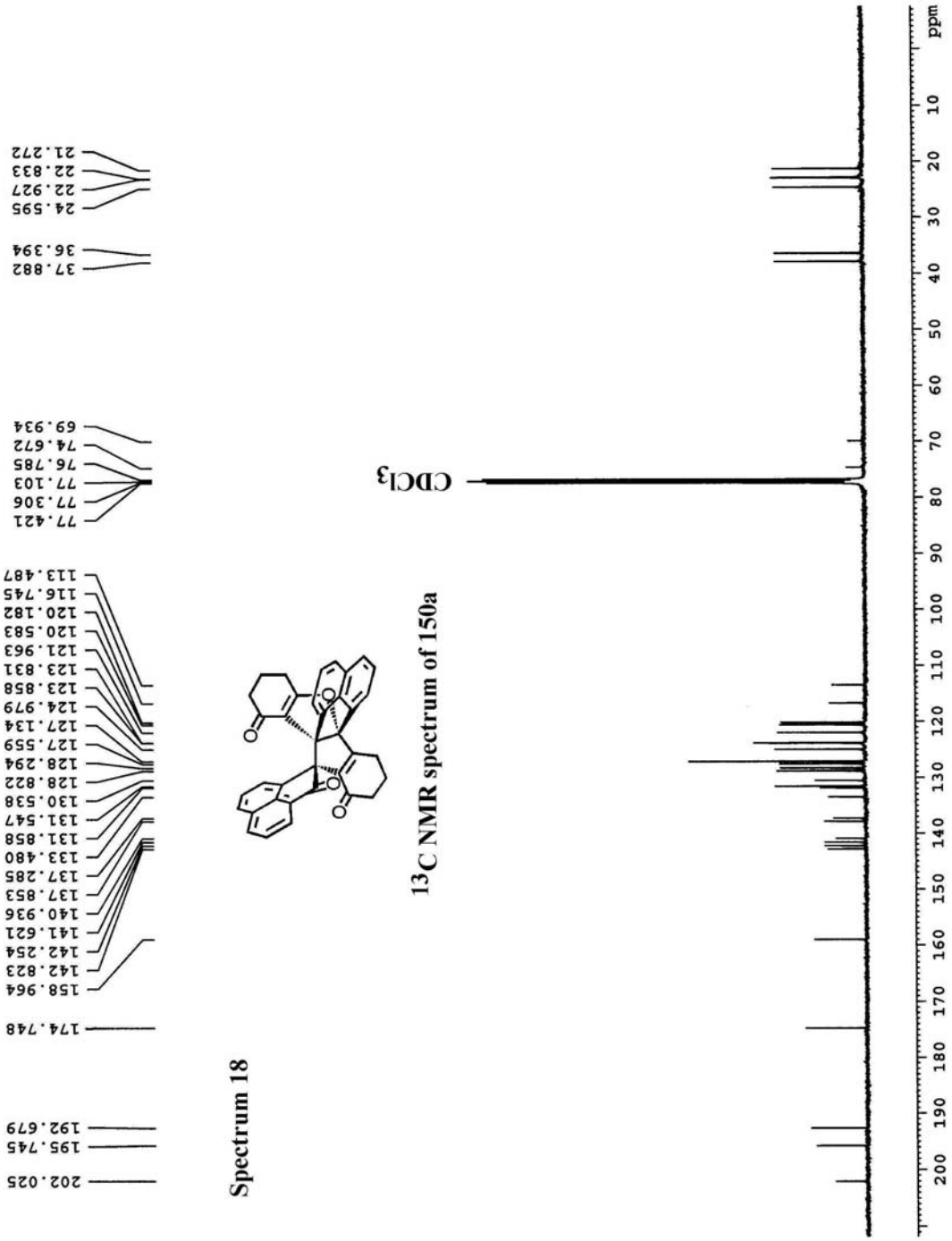
^{13}C NMR spectrum of 149e

Spectrum 17

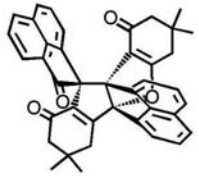


^{1}H NMR spectrum of 150a

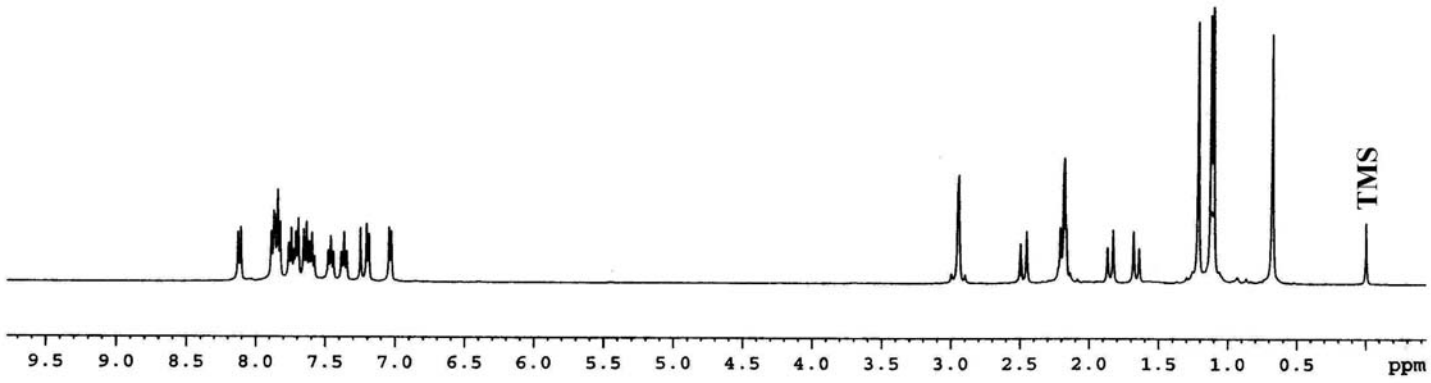


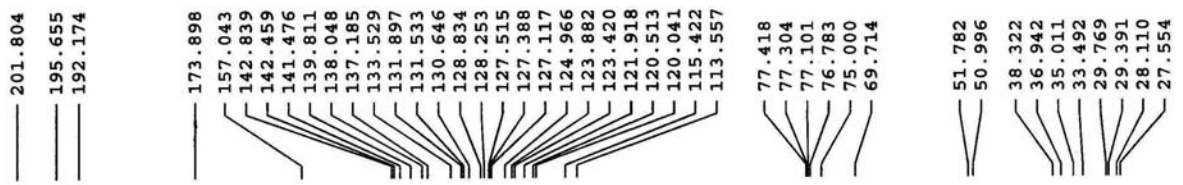

Spectrum 18
^{13}C NMR spectrum of 150a
CDCl3
ppm

Spectrum 19

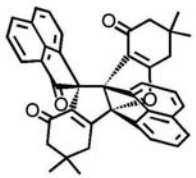


^{1}H NMR spectrum of 150b

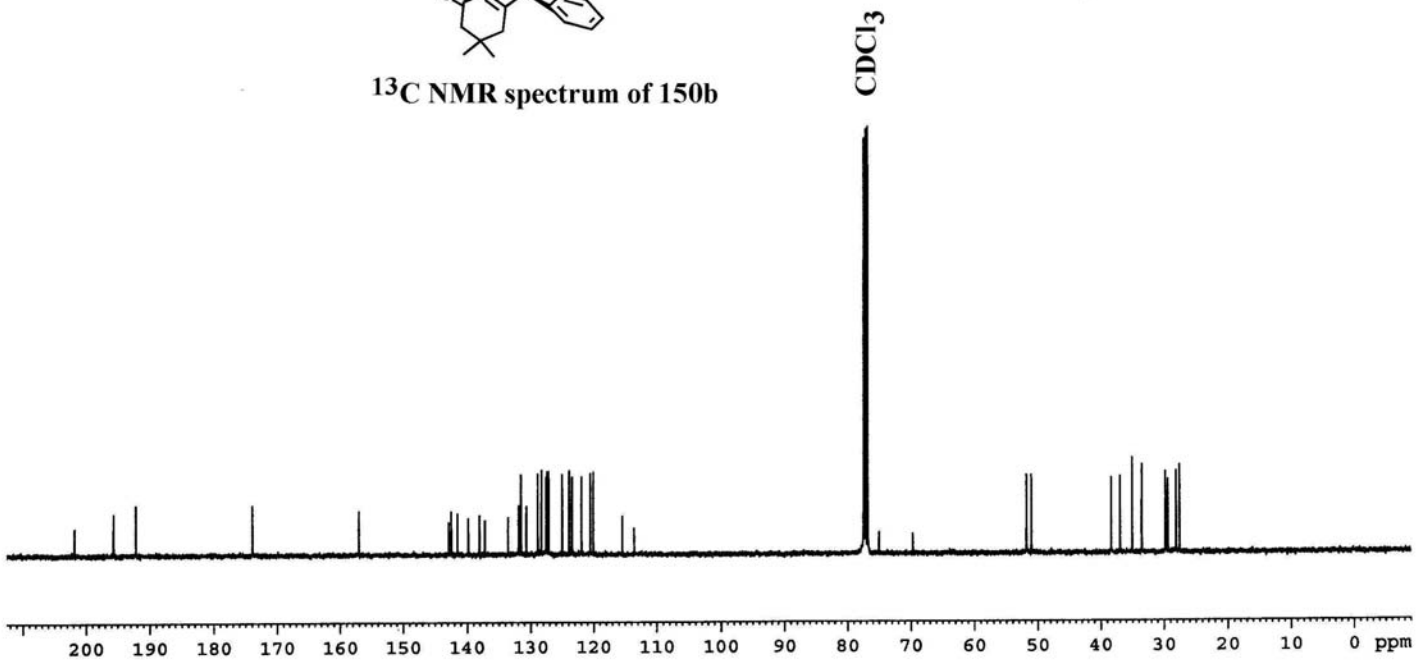




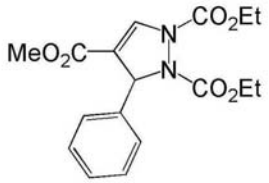
Spectrum 20



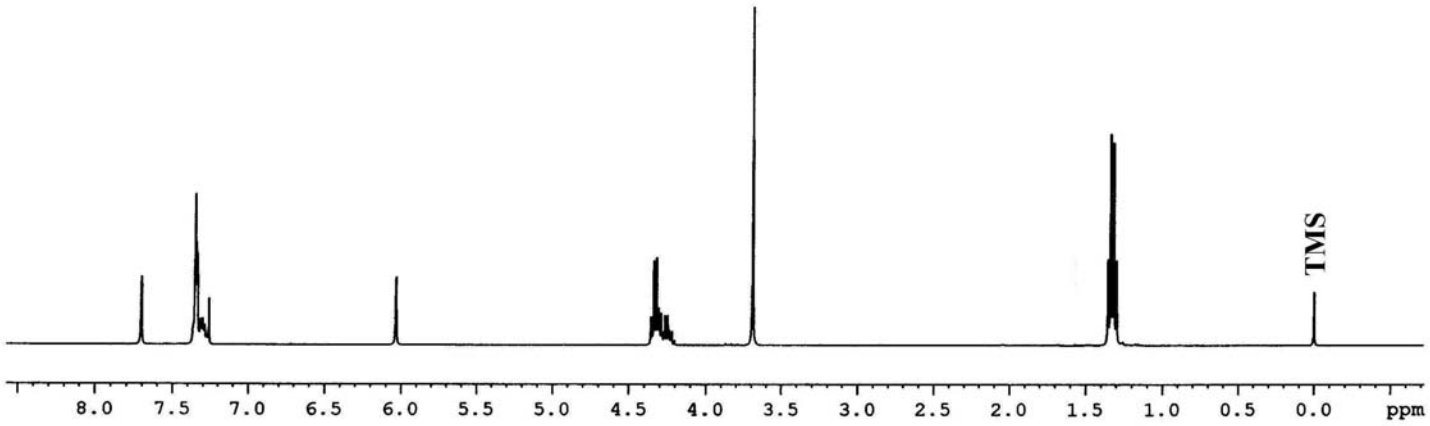
^{13}C NMR spectrum of 150b

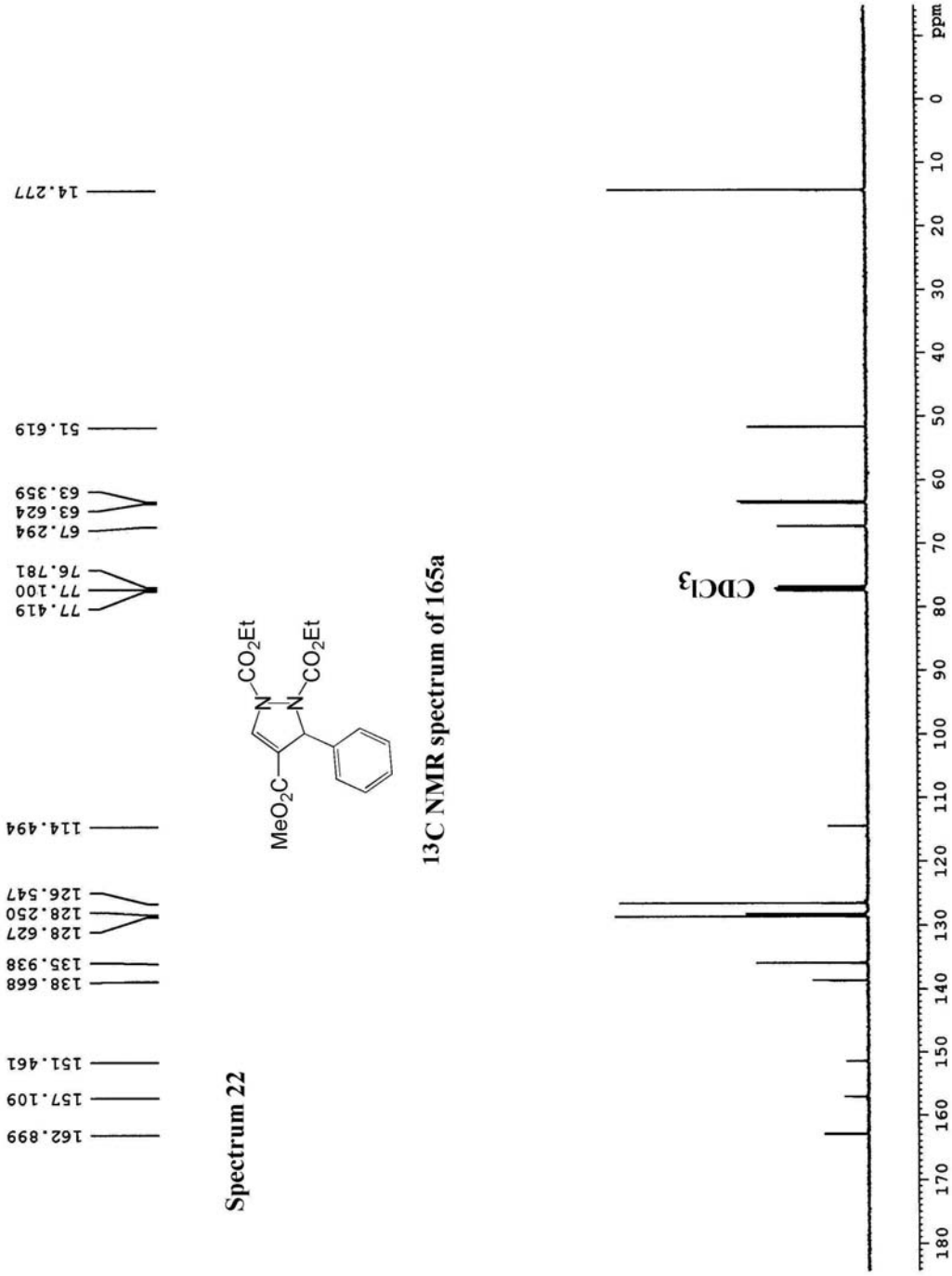


Spectrum 21



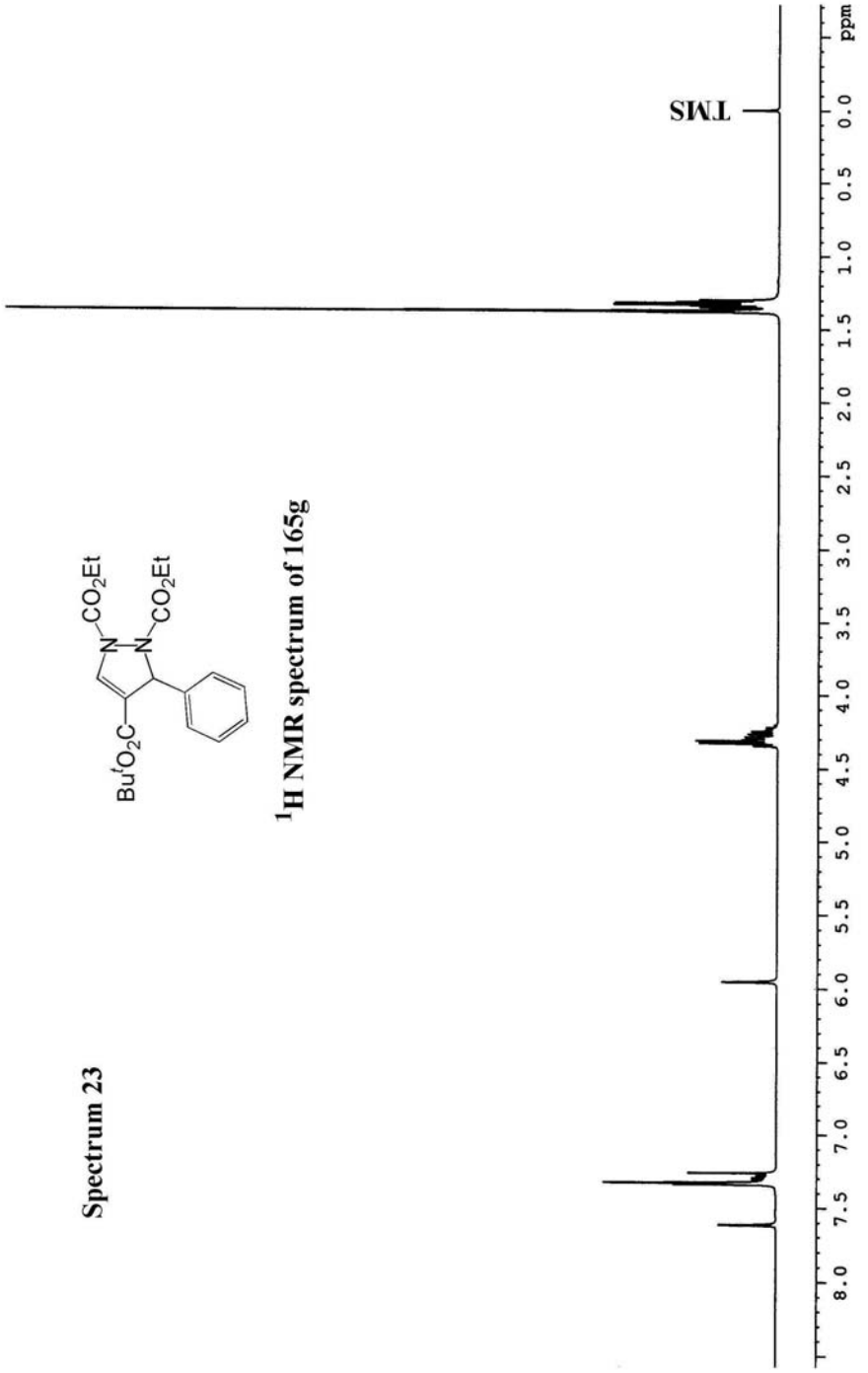
^{1}H NMR spectrum of 165a

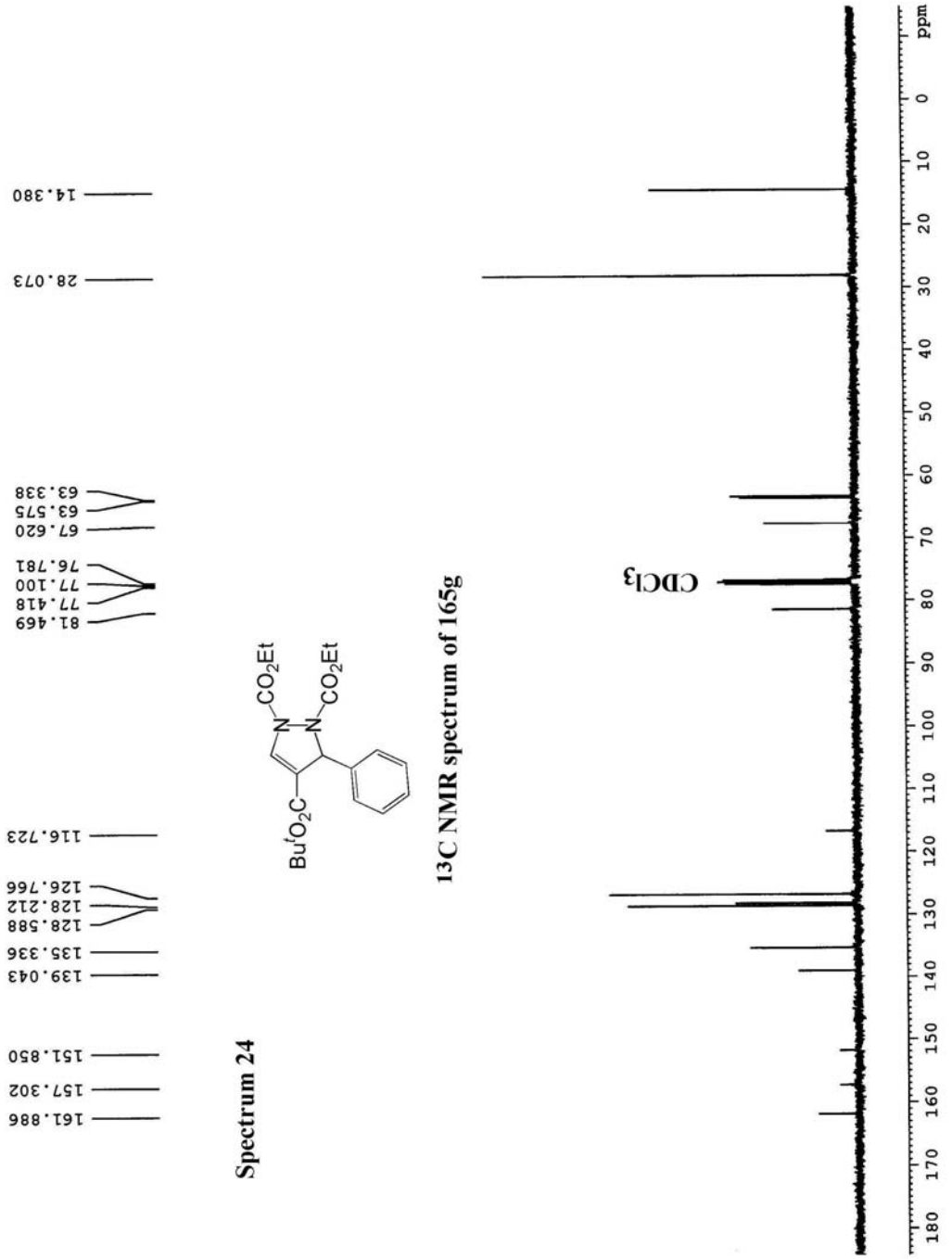




Spectrum 22

^{13}C NMR spectrum of 165a

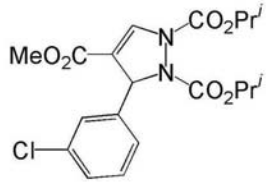

Spectrum 23
^{1}H NMR spectrum of 165g
CO_2Et
CO_2Et
Bu^tO_2C
TMS
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm



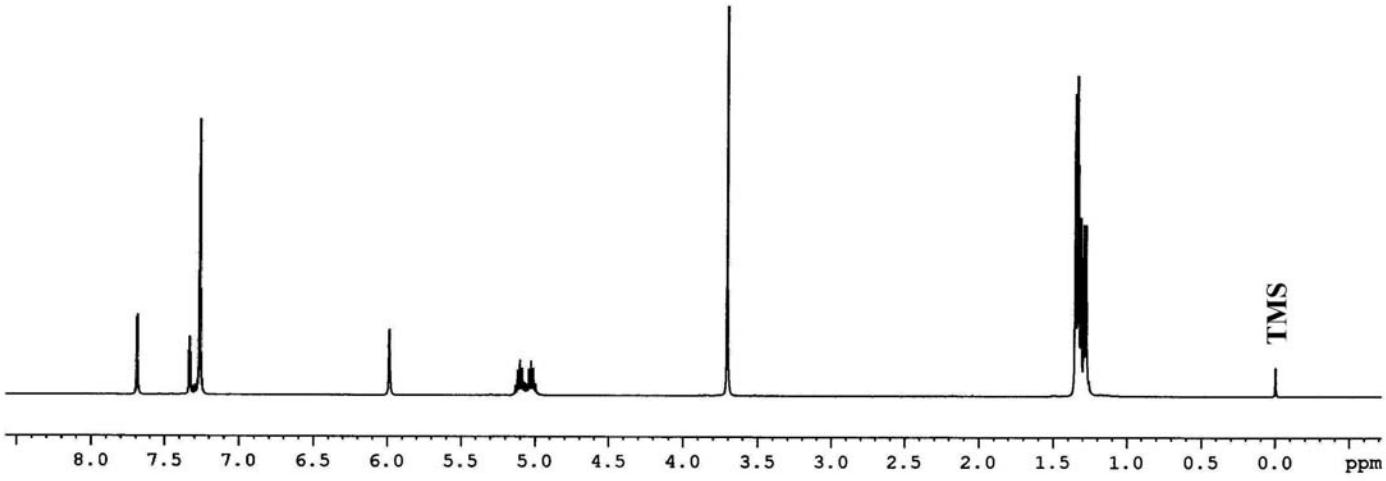
Spectrum 24

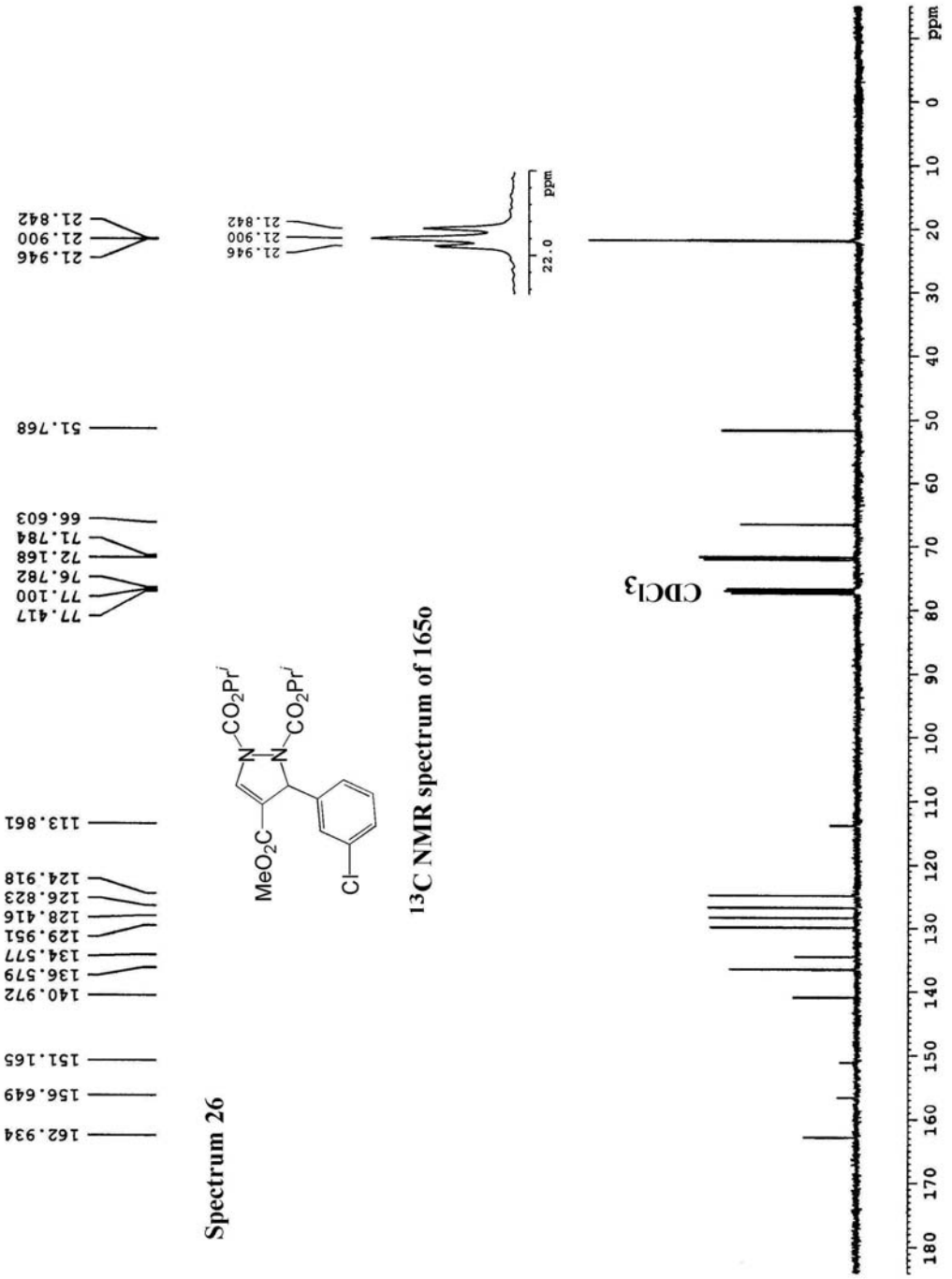
13C NMR spectrum of 165g

Spectrum 25

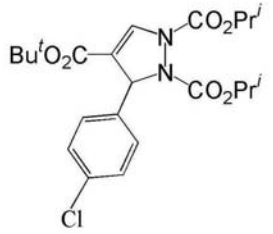


^{1}H NMR spectrum of 165o

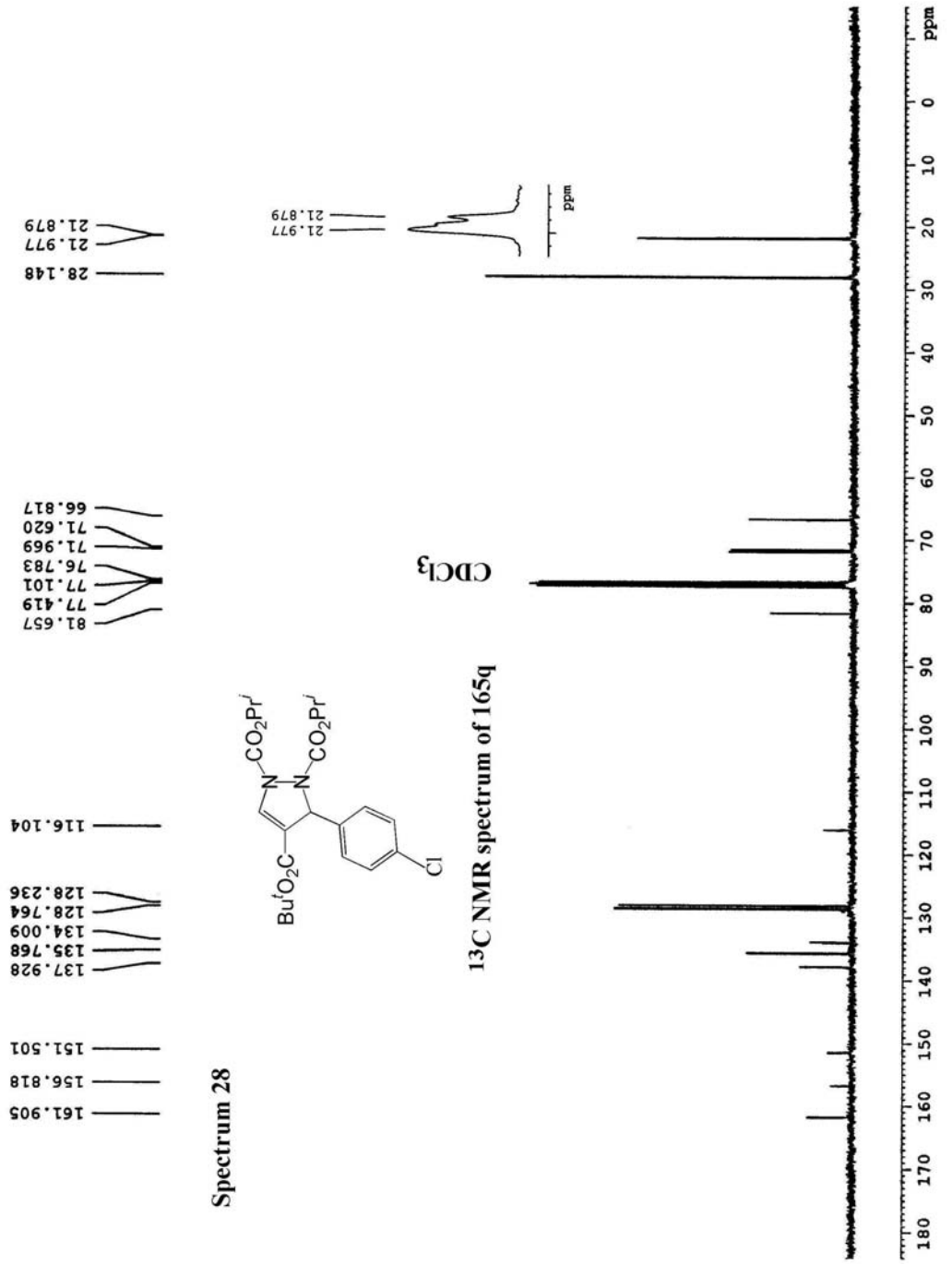



Spectrum 26
^{13}C NMR spectrum of 165o
CDCl3
CO2Pr^i
CO2Pr^i
MeO2C
Cl
ppm

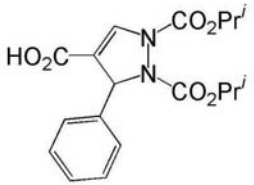
Spectrum 27



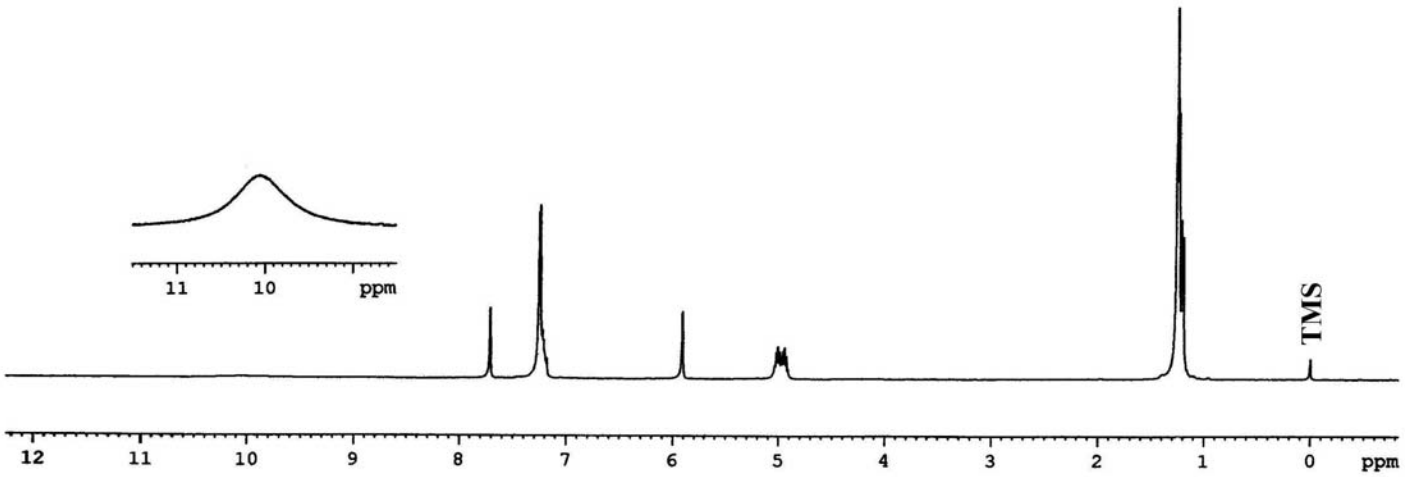
^{1}H NMR spectrum of 165q

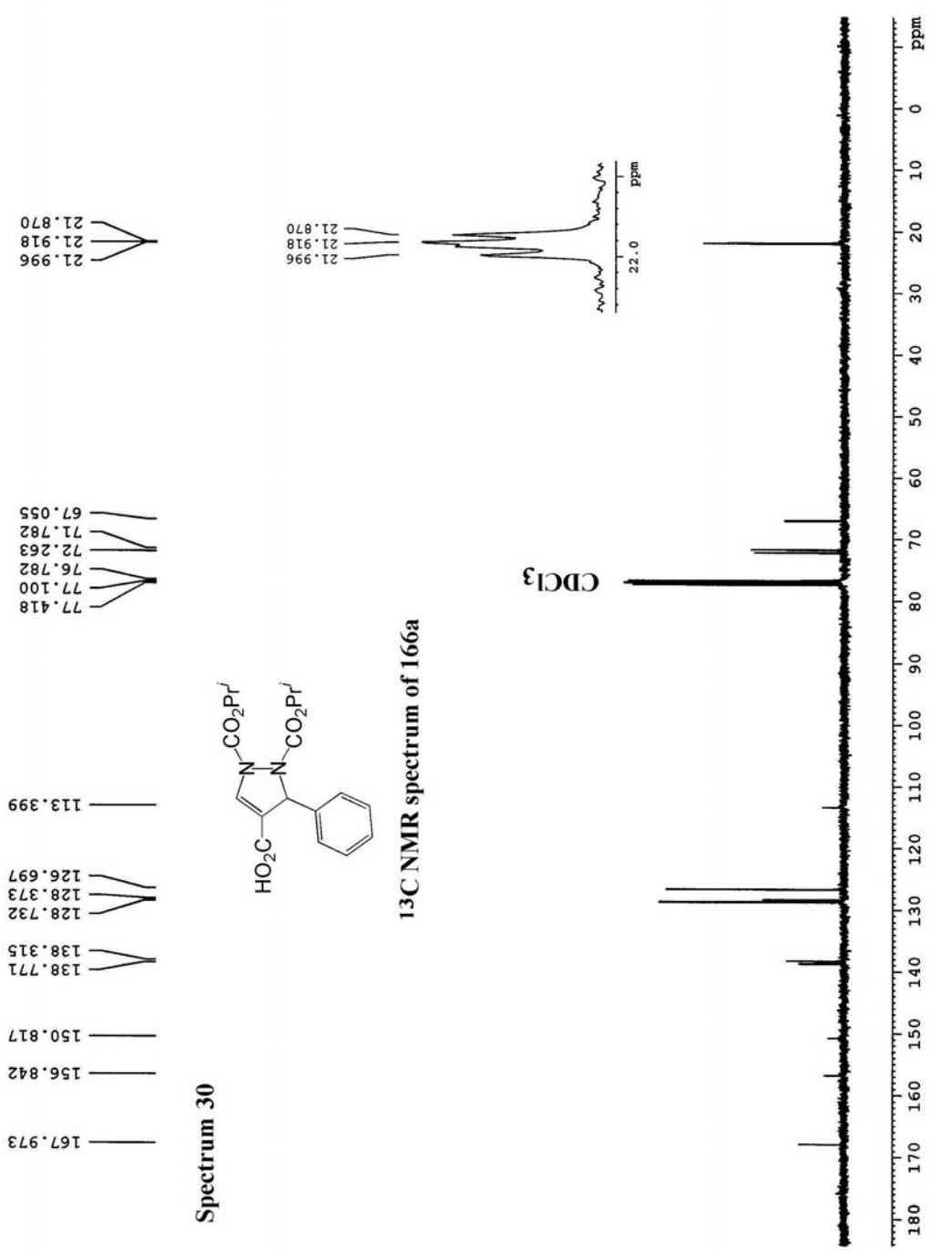

Spectrum 28
161.905
156.818
151.501
137.928
135.768
134.009
128.764
128.236
116.104
81.657
77.419
77.101
76.783
71.969
71.620
66.817
28.148
21.977
21.879
^{13}C NMR spectrum of 165q
$CDCl_3$
21.977
21.879
ppm
ppm

Spectrum 29

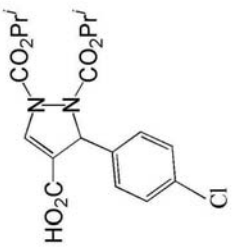


^{1}H NMR spectrum of 166a

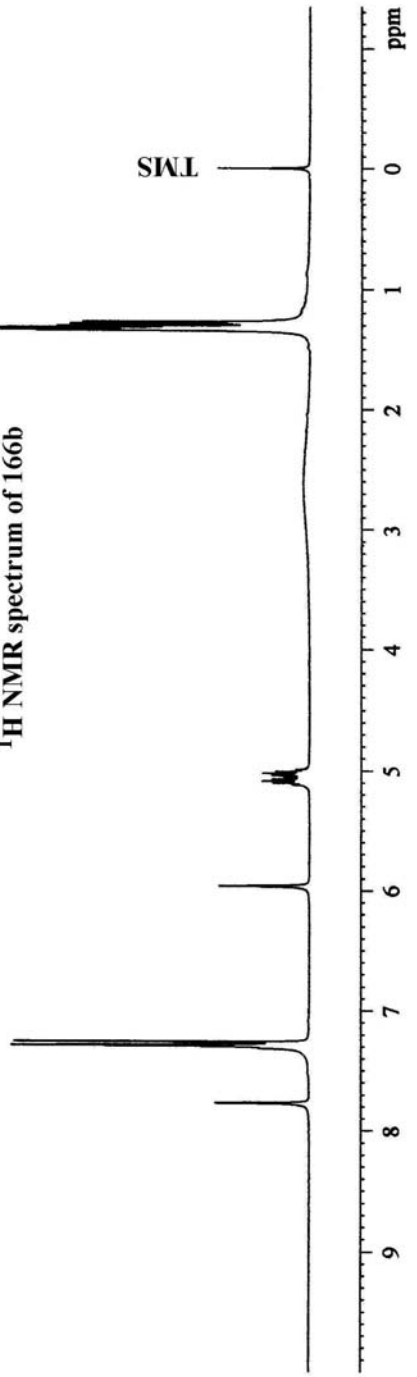


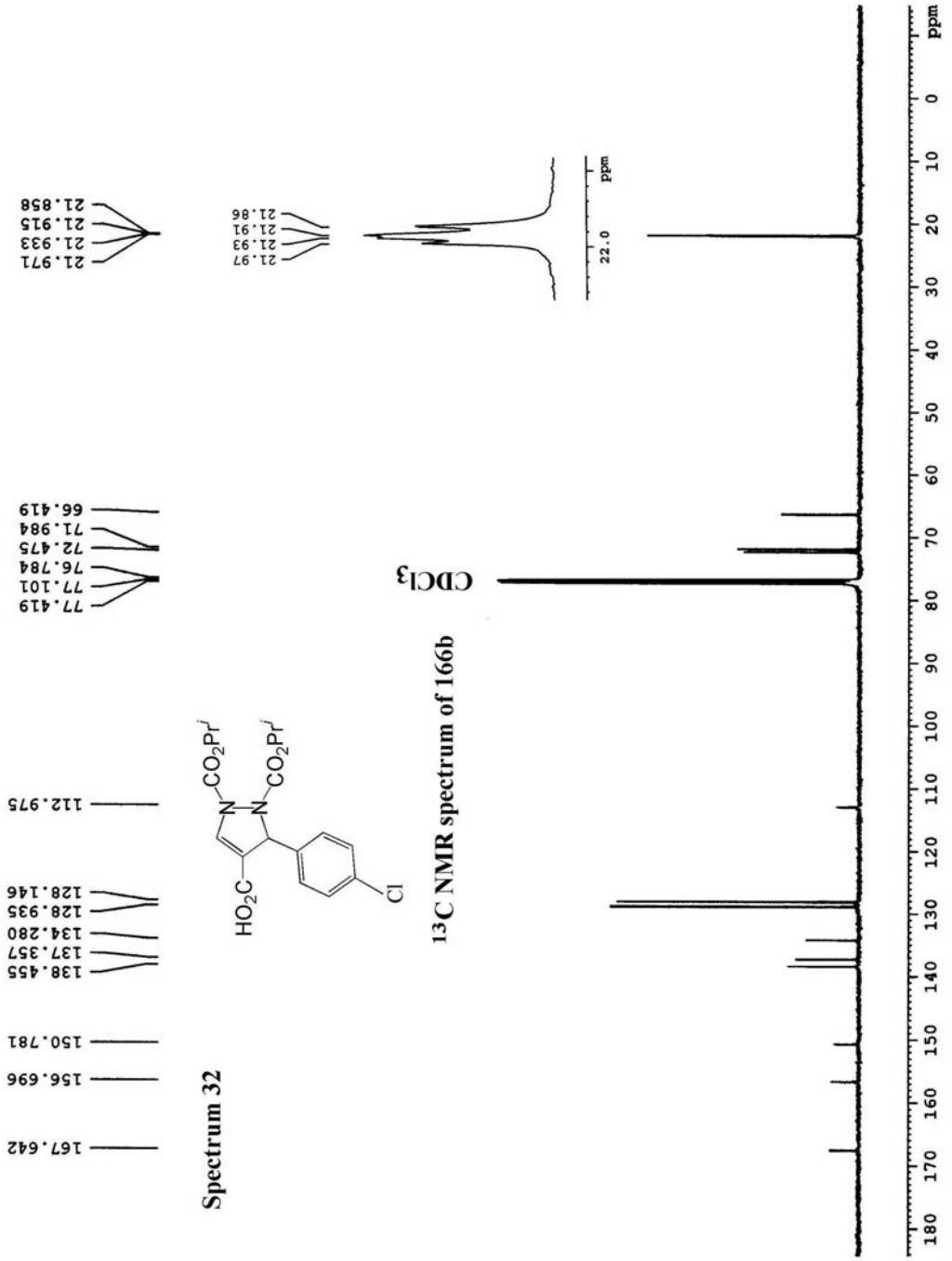

Spectrum 30
13C NMR spectrum of 166a
CDCl3
CO2Pri
CO2Pri
HO2C
N
N
167.973
156.842
150.817
138.771
138.315
128.732
128.373
126.697
113.399
77.418
77.100
76.782
72.263
71.782
67.055
21.996
21.918
21.870
22.0
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180

Spectrum 31

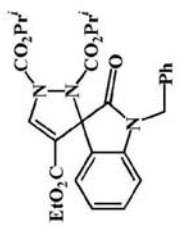


^{1}H NMR spectrum of 166b

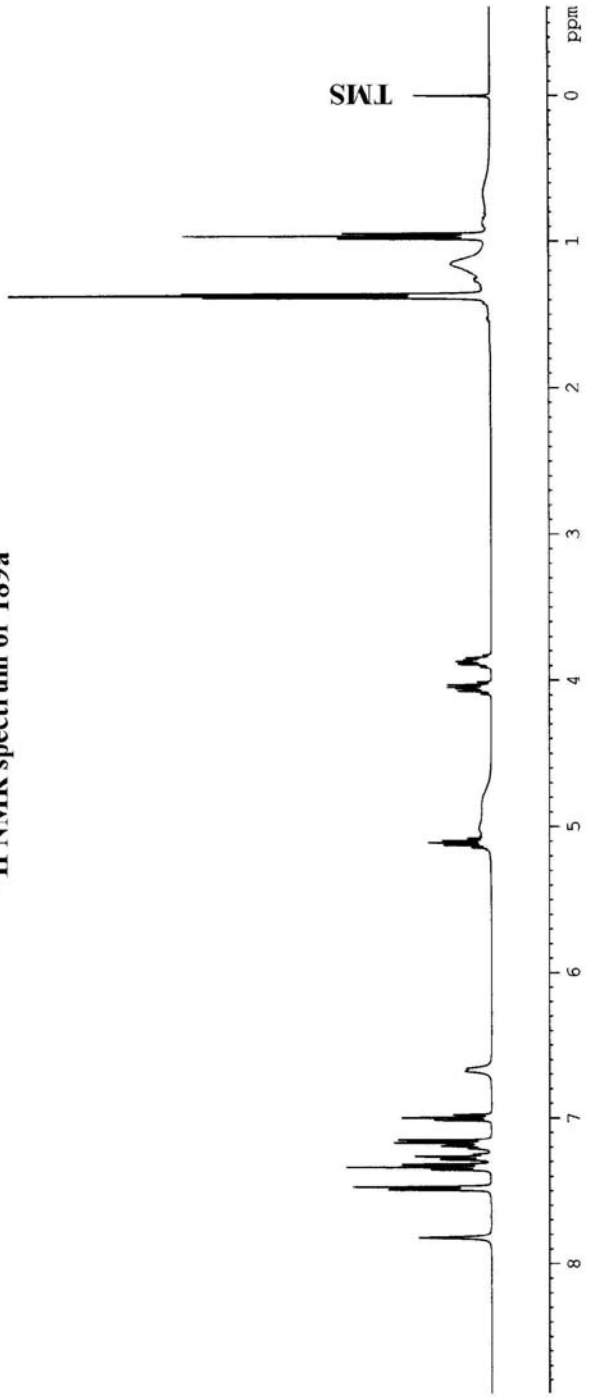


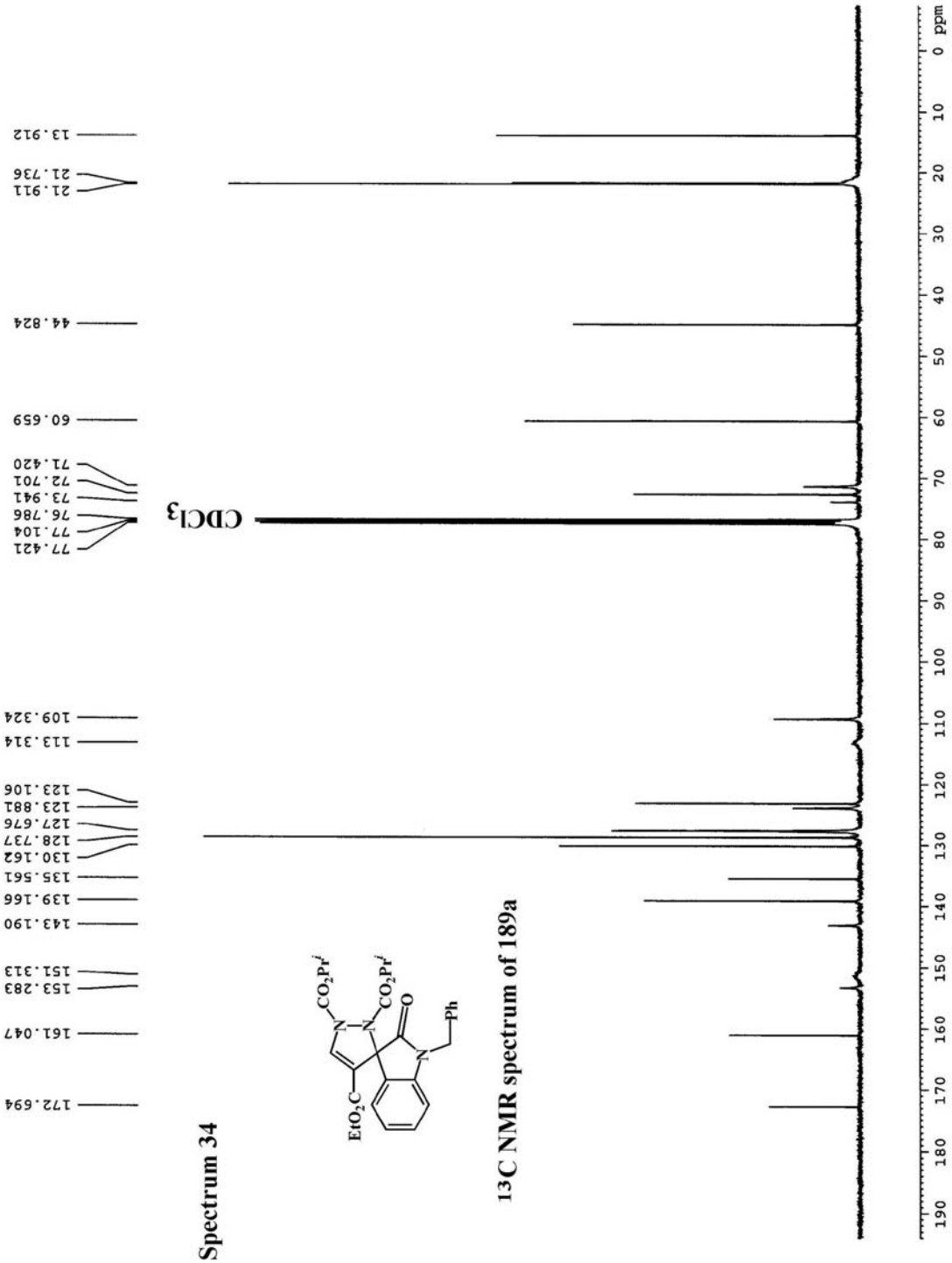

Spectrum 32
167.642
156.696
150.781
138.455
137.357
134.280
128.935
128.146
112.975
77.419
77.101
76.784
72.475
71.984
66.419
21.971
21.933
21.915
21.858
21.97
21.93
21.91
21.86
22.0
ppm
CDCl3
13C NMR spectrum of 166b
CO2Pri
CO2Pri
HO2C
Cl
ppm

Spectrum 33

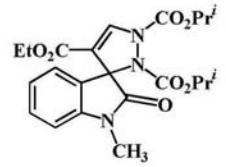


^{1}H NMR spectrum of 189a

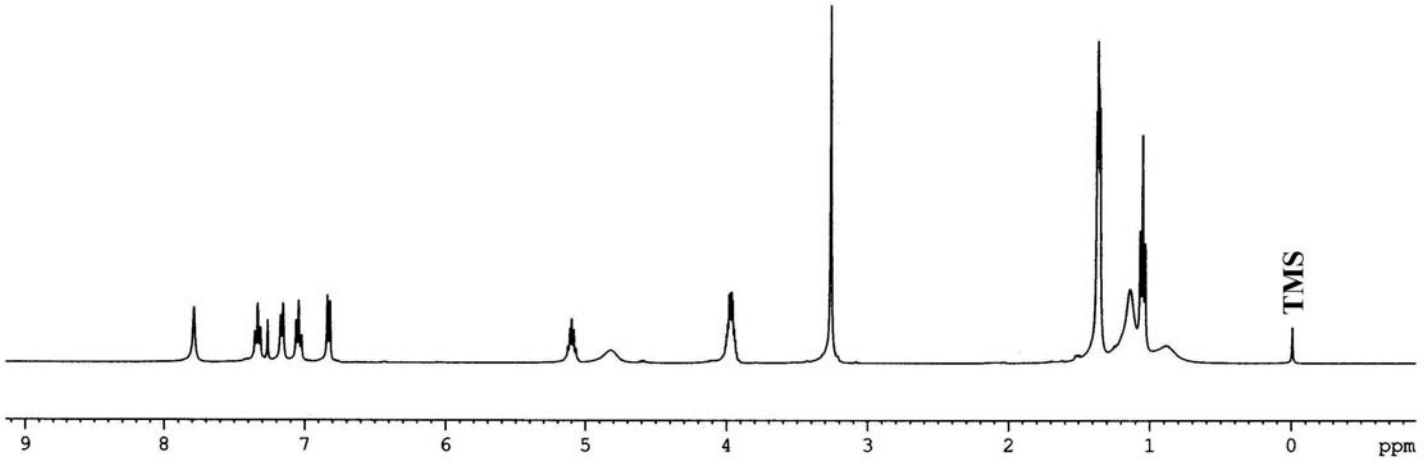


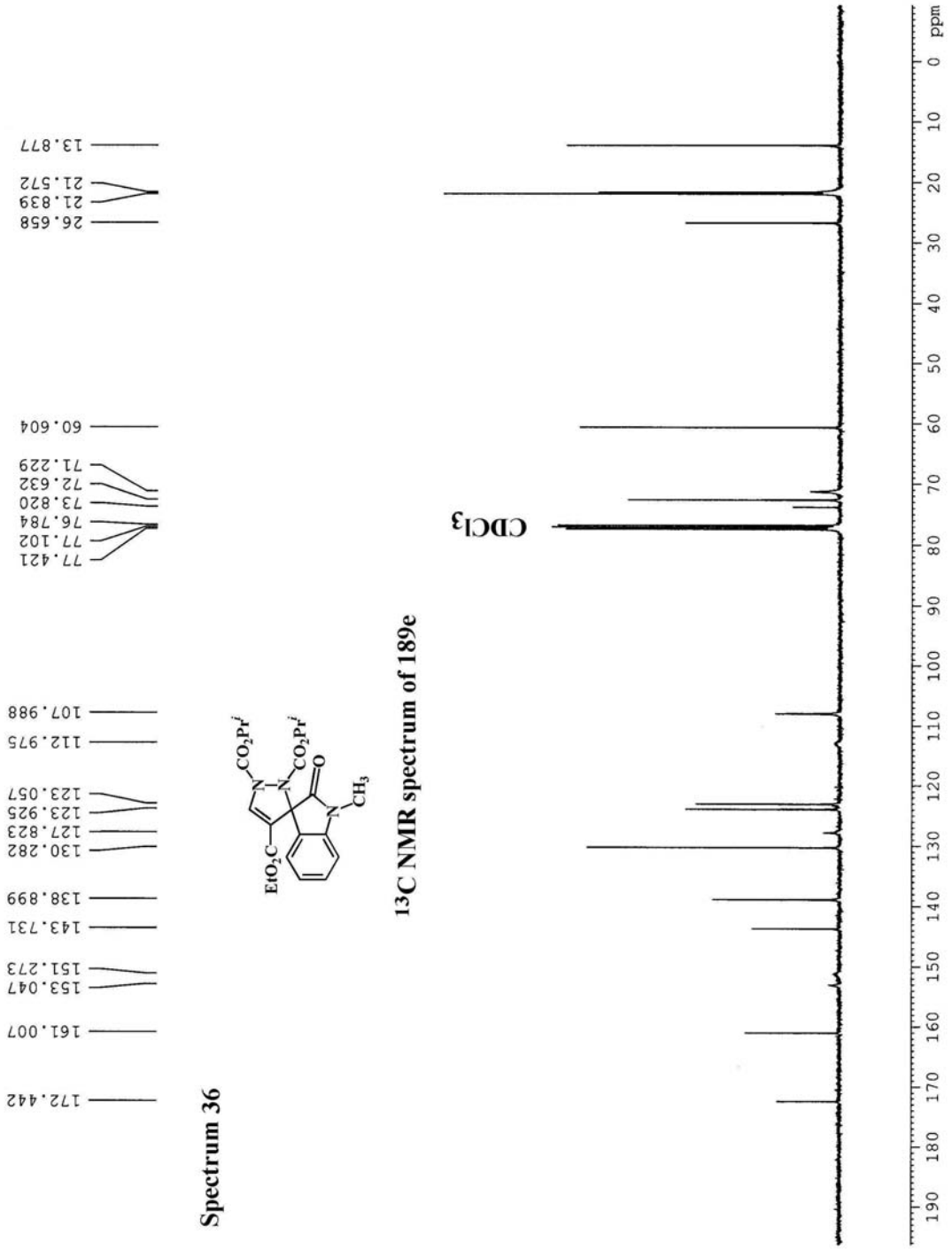

Spectrum 34
13C NMR spectrum of 189a
CDCl3
CO2Pri
CO2Pri
O
Ph
EtO2C
172.694
161.047
153.283
151.313
143.190
139.166
135.561
130.162
128.737
127.676
123.881
123.106
113.314
109.324
77.421
77.104
76.786
73.941
72.701
71.420
60.659
44.824
21.911
21.736
13.912
0 ppm

Spectrum 35

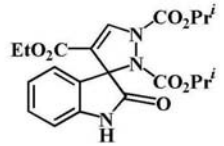


^{1}H NMR spectrum of 189e

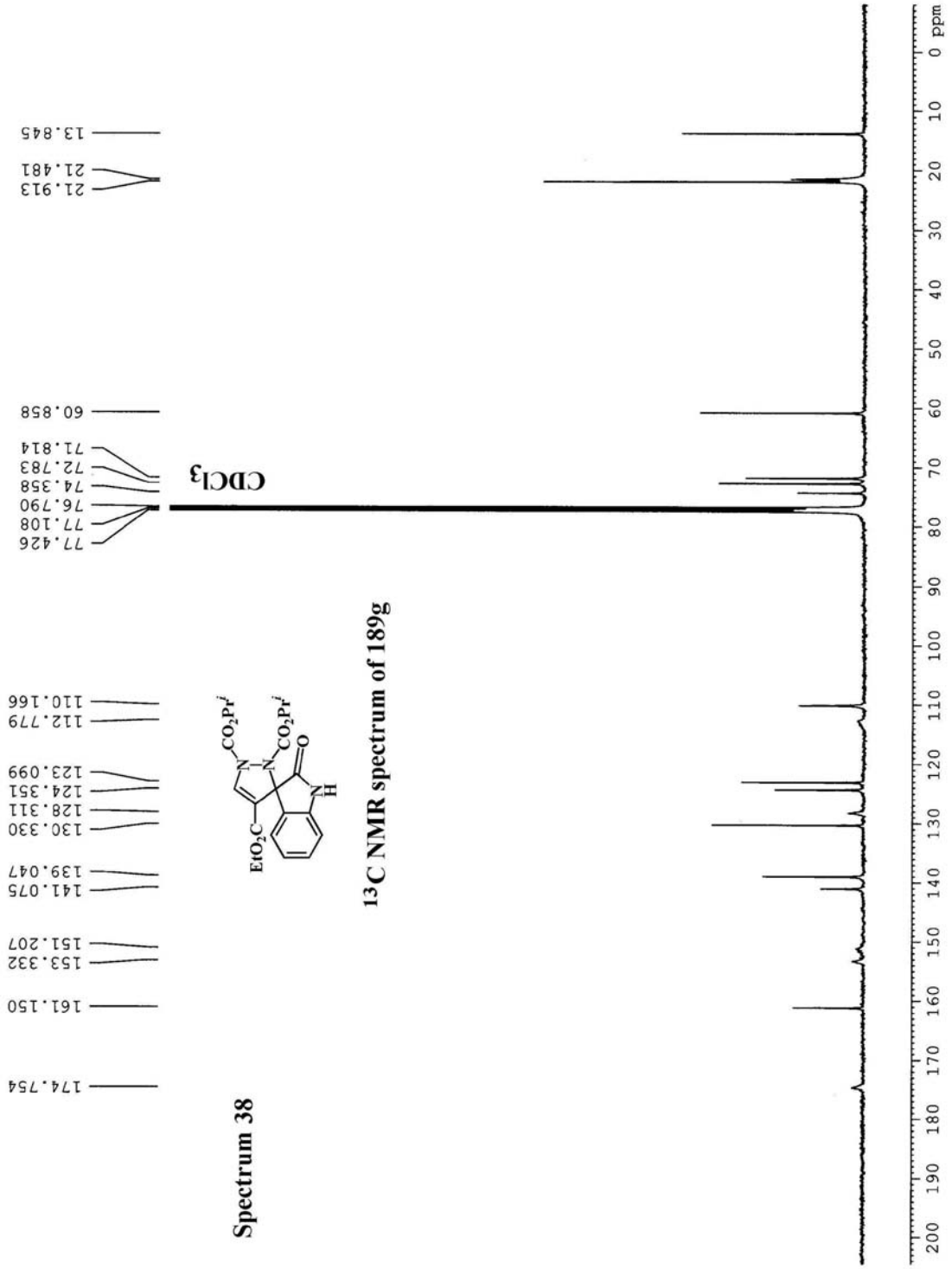


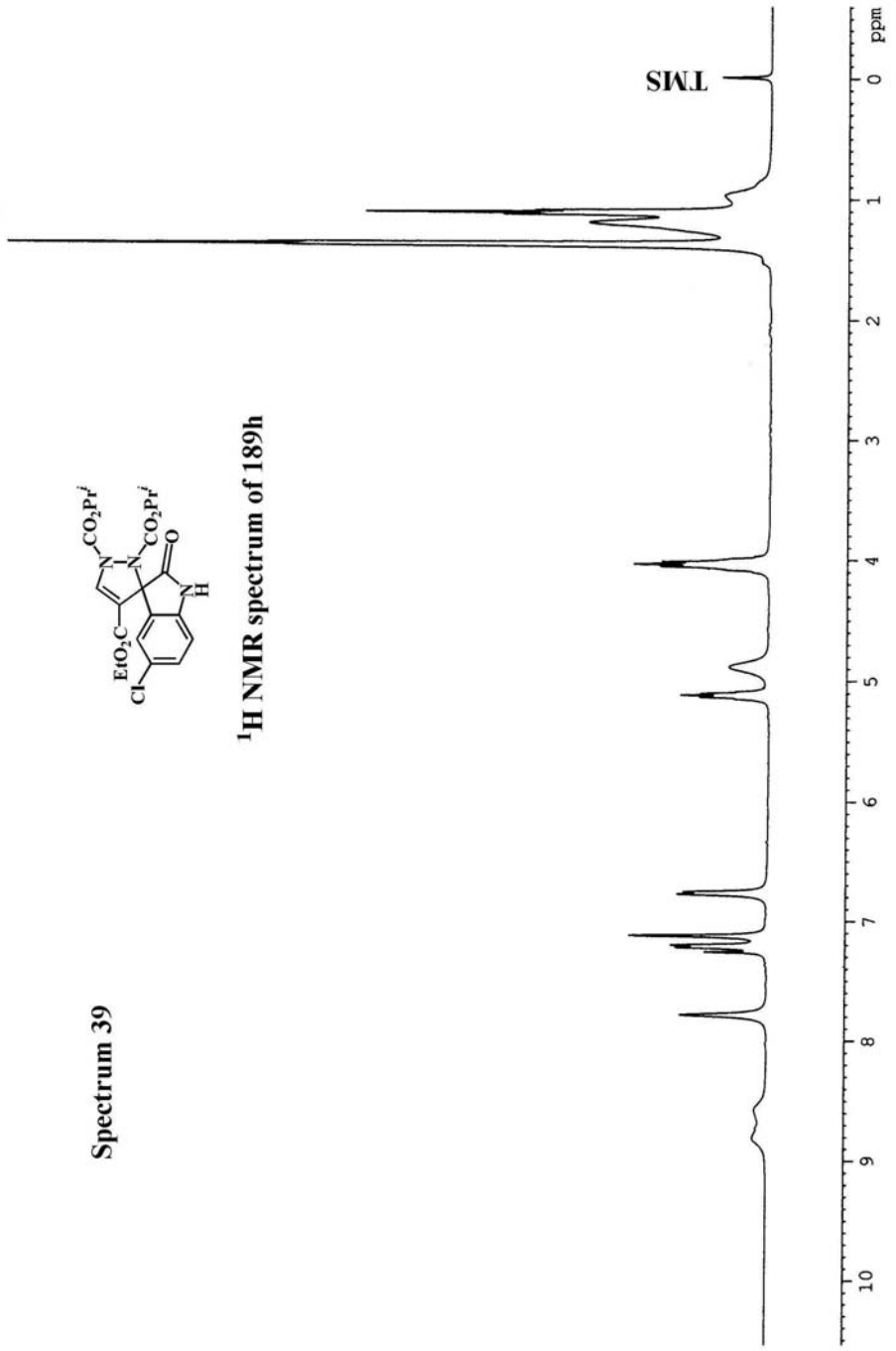

Spectrum 36
13C NMR spectrum of 189e
CDCl3
CO2Pri
CO2Pri
O
CH3
EtO2C
172.442
161.007
153.047
151.273
143.731
138.899
130.282
127.823
123.925
123.057
112.975
107.988
77.421
77.102
76.784
73.820
72.632
71.229
60.604
26.658
21.839
21.572
13.877
ppm

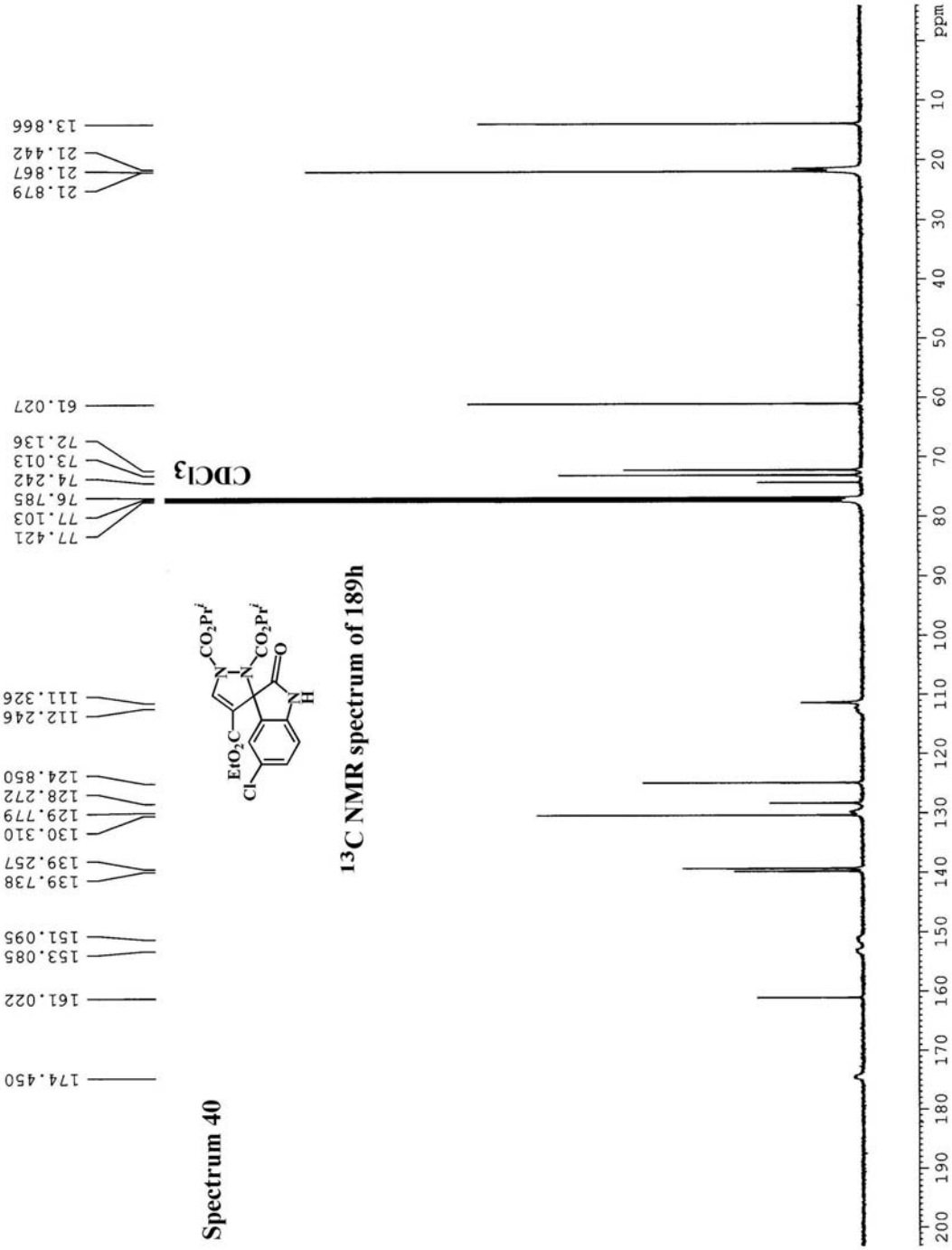
Spectrum 37



^{1}H NMR spectrum of 189g


Spectrum 38
13C NMR spectrum of 189g
CDCl3
CO2Pri
CO2Pri
EtO2C
O
N
H
13.845
21.481
21.913
60.858
71.814
72.783
74.358
76.790
77.108
77.426
110.166
112.779
123.099
124.351
128.311
130.330
139.047
141.075
151.207
153.332
161.150
174.754
ppm


Spectrum 39
^{1}H NMR spectrum of 189h
TMS
ppm
0
1
2
3
4
5
6
7
8
9
10



^{13}C NMR spectrum of 189h

APPENDIX

(X-RAY CRYSTALLOGRAPHIC DATA)

Table I. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for compound **121**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
C(1)	6606(2)	5174(2)	3151(2)	40(1)
C(2)	6086(2)	3986(2)	3684(2)	39(1)
C(3)	6533(2)	1611(2)	3365(2)	46(1)
C(4)	7176(2)	869(2)	2804(2)	51(1)
C(5)	7906(3)	1410(3)	2122(2)	56(1)
C(6)	8035(2)	2740(3)	1975(2)	51(1)
C(7)	7407(2)	3480(2)	2533(2)	39(1)
C(8)	6656(2)	2929(2)	3219(2)	38(1)
C(9)	4440(2)	3314(2)	3640(2)	38(1)
C(10)	3885(2)	2938(2)	4432(2)	41(1)
C(11)	2378(3)	2348(3)	4393(2)	54(1)
C(12)	1421(3)	2129(3)	3576(2)	61(1)
C(13)	1947(3)	2471(3)	2778(2)	57(1)
C(14)	3448(3)	3061(2)	2817(2)	48(1)
C(15)	8083(3)	5744(3)	1905(2)	52(1)
C(16)	3924(2)	7486(2)	986(2)	40(1)
C(17)	3537(2)	6303(2)	1530(2)	39(1)
C(18)	2242(3)	6299(2)	3008(2)	47(1)
C(19)	1700(3)	7096(3)	3617(2)	52(1)
C(20)	1820(3)	8451(3)	3550(2)	56(1)
C(21)	2458(3)	9048(2)	2846(2)	50(1)
C(22)	2959(2)	8238(2)	2225(2)	40(1)
C(23)	2873(2)	6883(2)	2304(1)	39(1)
C(24)	2566(2)	4759(2)	880(1)	36(1)
C(25)	3177(2)	3819(2)	529(1)	37(1)
C(26)	2277(3)	2415(2)	-81(2)	48(1)
C(27)	778(3)	1958(3)	-353(2)	55(1)
C(28)	169(3)	2881(3)	-16(2)	55(1)
C(29)	1056(2)	4263(2)	594(2)	45(1)
C(30)	3811(3)	9873(2)	1105(2)	50(1)

Cl(1)	7056(1)	-797(1)	2979(1)	75(1)
Cl(2)	811(1)	6343(1)	4477(1)	76(1)
N(1)	7380(2)	4832(2)	2518(1)	39(1)
N(2)	3595(2)	8573(2)	1432(1)	40(1)
O(1)	6376(2)	6279(2)	3263(1)	52(1)
O(2)	4879(2)	3160(2)	5217(1)	54(1)
O(3)	4434(2)	7496(2)	255(1)	55(1)
O(4)	4651(2)	4307(2)	827(1)	48(1)

Table II. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for compound **124**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
C(1)	10384(4)	7945(4)	1572(5)	68(1)
C(2)	10042(4)	8843(3)	2473(4)	65(1)
C(3)	10121(4)	8187(4)	3475(4)	67(1)
C(4)	9903(4)	8504(4)	4569(5)	78(1)
C(5)	10126(4)	7709(6)	5339(5)	89(2)
C(6)	10549(4)	6634(5)	5046(5)	88(2)
C(7)	10748(4)	6299(4)	3976(5)	74(1)
C(8)	10543(4)	7091(4)	3196(5)	68(1)
C(9)	10978(4)	5901(3)	1495(4)	75(1)
C(10)	9864(4)	5259(3)	1611(3)	58(1)
C(11)	9842(4)	4225(4)	2068(4)	73(1)
C(12)	8821(5)	3638(4)	2147(4)	80(1)
C(13)	7813(4)	4104(4)	1771(4)	73(1)
C(14)	7807(4)	5132(4)	1324(4)	77(1)
C(15)	8828(5)	5706(4)	1249(4)	76(1)
C(16)	8835(4)	9528(3)	2412(4)	62(1)
C(17)	8819(4)	10395(4)	1669(4)	70(1)
C(18)	7733(5)	10991(4)	1559(4)	79(1)
C(19)	6637(5)	10731(4)	2187(5)	84(2)
C(20)	6631(5)	9887(5)	2939(4)	84(2)
C(21)	7732(4)	9283(4)	3029(4)	72(1)
C(22)	4053(4)	6454(4)	2215(3)	55(1)
C(23)	3943(3)	7384(3)	1387(3)	52(1)

C(24)	3521(3)	8391(3)	2114(4)	53(1)
C(25)	3245(4)	9496(4)	1851(4)	68(1)
C(26)	2968(4)	10265(4)	2715(5)	75(1)
C(27)	2949(4)	9944(4)	3769(4)	72(1)
C(28)	3211(3)	8840(4)	4029(4)	62(1)
C(29)	3497(3)	8087(3)	3174(4)	52(1)
C(30)	3876(3)	6310(3)	4229(3)	57(1)
C(31)	4984(4)	6502(3)	4693(3)	50(1)
C(32)	6134(4)	6283(4)	4092(4)	78(1)
C(33)	7150(5)	6427(5)	4523(6)	101(2)
C(34)	7013(6)	6785(5)	5586(7)	107(2)
C(35)	5867(6)	7010(4)	6184(5)	100(2)
C(36)	4859(4)	6864(4)	5736(4)	75(1)
C(37)	5168(3)	7441(3)	621(3)	48(1)
C(38)	6013(4)	8127(3)	850(4)	64(1)
C(39)	7140(4)	8170(4)	192(4)	74(1)
C(40)	7440(4)	7508(4)	-724(4)	69(1)
C(41)	6627(4)	6816(3)	-976(3)	63(1)
C(42)	5484(4)	6795(3)	-306(3)	52(1)
N(1)	10699(3)	6967(3)	2073(3)	67(1)
N(2)	3809(3)	6929(3)	3230(3)	53(1)
O(1)	10402(3)	8027(3)	607(3)	92(1)
O(2)	9938(3)	10639(3)	1100(3)	91(1)
O(3)	4332(3)	5459(2)	2056(2)	75(1)
O(4)	4630(3)	6131(3)	-520(3)	71(1)

Table III. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for compound **126**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
C(1)	2064(7)	3112(5)	6442(4)	39(1)
C(2)	-7(6)	2690(4)	5970(4)	36(1)
C(3)	-808(6)	3710(4)	6542(4)	36(1)
C(4)	-1750(6)	4353(4)	5788(5)	35(1)
C(5)	-2466(7)	5284(5)	6307(5)	48(1)
C(6)	-2219(8)	5608(5)	7563(6)	57(2)

C(7)	-1299(9)	4971(6)	8322(6)	64(2)
C(8)	-619(8)	4022(5)	7792(5)	53(1)
C(9)	-468(6)	1389(4)	6243(4)	37(1)
C(10)	-2090(7)	541(5)	6074(4)	40(1)
C(11)	-2090(7)	-614(5)	6410(5)	43(1)
C(12)	-515(7)	-916(5)	6893(5)	48(1)
C(13)	1134(7)	-53(5)	7067(5)	47(1)
C(14)	1133(7)	1095(5)	6735(4)	37(1)
C(15)	4495(7)	2124(5)	7266(5)	45(1)
C(16)	5256(7)	2261(5)	8649(5)	44(1)
C(17)	6369(10)	1523(7)	9053(6)	79(2)
C(18)	7156(12)	1676(9)	10307(7)	108(3)
C(19)	6827(11)	2556(9)	11178(7)	95(2)
C(20)	5748(10)	3310(8)	10804(7)	86(2)
C(21)	4961(9)	3149(6)	9524(6)	70(2)
N(1)	2629(5)	2124(4)	6844(4)	40(1)
O(1)	3080(5)	4136(3)	6468(3)	51(1)
O(2)	-1985(5)	3991(4)	4545(4)	48(1)
Br(1)	-4351(1)	-1791(1)	6195(1)	56(1)

Table IV. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for compound **145**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
C(1)	925(2)	3435(2)	2976(1)	44(1)
C(2)	1601(2)	2083(2)	2215(1)	45(1)
C(3)	2291(2)	3015(2)	858(1)	46(1)
C(4)	3032(2)	2570(2)	-278(2)	58(1)
C(5)	3518(2)	3790(3)	-1413(2)	65(1)
C(6)	3264(2)	5395(2)	-1414(2)	60(1)
C(7)	2501(2)	5902(2)	-249(1)	49(1)
C(8)	2132(2)	7490(2)	-54(2)	60(1)
C(9)	1409(2)	7771(2)	1155(2)	61(1)
C(10)	969(2)	6521(2)	2247(2)	54(1)
C(11)	1277(2)	4980(2)	2077(1)	44(1)
C(12)	2043(2)	4667(2)	856(1)	43(1)

C(13)	3005(2)	396(2)	3026(1)	43(1)
C(14)	2448(2)	-938(2)	3858(1)	44(1)
C(15)	3725(2)	-2445(2)	4660(2)	57(1)
C(16)	5523(2)	-2615(2)	4651(2)	64(1)
C(17)	6093(2)	-1304(2)	3839(2)	63(1)
C(18)	4835(2)	187(2)	3034(2)	54(1)
O(1)	238(2)	3237(1)	4116(1)	57(1)
O(2)	640(1)	-705(1)	3835(1)	54(1)

Table V. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for compound **149a**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
C(1)	5992(3)	5671(1)	8586(2)	43(1)
C(2)	4869(3)	6099(1)	7524(2)	46(1)
C(3)	4509(3)	6816(1)	7698(2)	58(1)
C(4)	3388(3)	7190(1)	6641(3)	65(1)
C(5)	2606(3)	6853(1)	5406(3)	67(1)
C(6)	2951(3)	6156(1)	5217(2)	59(1)
C(7)	4119(3)	5751(1)	6266(2)	47(1)
C(8)	4577(3)	5008(1)	6092(2)	48(1)
C(9)	4004(3)	4669(1)	4807(2)	60(1)
C(10)	4474(3)	3986(1)	4608(2)	66(1)
C(11)	5500(3)	3597(1)	5719(2)	65(1)
C(12)	6075(3)	3899(1)	6985(2)	57(1)
C(13)	5668(3)	4608(1)	7206(2)	45(1)
C(14)	6347(3)	4966(1)	8506(2)	43(1)
C(15)	7477(3)	4771(1)	9884(2)	46(1)
C(16)	8318(3)	4125(1)	10535(2)	60(1)
C(17)	9448(4)	4203(1)	12016(2)	75(1)
C(18)	8838(4)	4787(1)	12808(2)	74(1)
C(19)	8724(3)	5498(1)	12077(2)	61(1)
C(20)	7691(3)	5384(1)	10623(2)	50(1)
C(21)	460(3)	5212(1)	7543(2)	48(1)
C(22)	-285(3)	5895(1)	7163(2)	49(1)
C(23)	-1498(3)	6047(1)	5862(2)	57(1)

C(24)	-2167(3)	6720(2)	5573(3)	67(1)
C(25)	-1674(3)	7246(2)	6561(3)	71(1)
C(26)	-508(3)	7106(1)	7835(3)	62(1)
C(27)	239(3)	6422(1)	8182(2)	50(1)
C(28)	1512(3)	6251(1)	9515(2)	50(1)
C(29)	2164(3)	6778(1)	10510(2)	63(1)
C(30)	3376(3)	6635(1)	11743(2)	67(1)
C(31)	4001(3)	5948(2)	12062(2)	64(1)
C(32)	3403(3)	5411(1)	11123(2)	57(1)
C(33)	2155(3)	5551(1)	9836(2)	46(1)
C(34)	1566(3)	5012(1)	8799(2)	47(1)
C(35)	1871(3)	4250(1)	8669(2)	52(1)
C(36)	2812(3)	3695(1)	9605(3)	68(1)
C(37)	2804(4)	2972(1)	8957(3)	94(1)
C(38)	1271(5)	2819(2)	7720(3)	112(1)
C(39)	830(4)	3385(1)	6653(3)	71(1)
C(40)	974(3)	4079(1)	7365(2)	54(1)
O(1)	95(2)	4649(1)	6640(1)	55(1)
O(2)	3552(3)	3777(1)	10819(2)	98(1)
O(3)	6828(2)	5943(1)	9871(1)	52(1)
O(4)	8239(3)	3553(1)	9959(2)	89(1)

Table VI. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for compound **149c**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
C(1)	540(1)	-889(3)	6785(1)	46(1)
C(2)	163(1)	-2893(3)	6552(1)	58(1)
C(3)	268(1)	-2970(4)	5788(1)	64(1)
C(4)	688(1)	-977(4)	5662(1)	55(1)
C(5)	838(1)	158(3)	6325(1)	45(1)
C(6)	1162(1)	2044(3)	6687(1)	42(1)
C(7)	1553(1)	3832(3)	6505(1)	44(1)
C(8)	1733(1)	3905(4)	5848(1)	58(1)
C(9)	2103(1)	5651(4)	5685(1)	70(1)
C(10)	2302(1)	7354(4)	6173(1)	69(1)

C(11)	2130(1)	7305(3)	6816(1)	58(1)
C(12)	1753(1)	5556(3)	7011(1)	45(1)
C(13)	1568(1)	5454(3)	7699(1)	45(1)
C(14)	1733(1)	7187(3)	8214(1)	56(1)
C(15)	1555(1)	7049(4)	8854(1)	61(1)
C(16)	1214(1)	5150(4)	9024(1)	60(1)
C(17)	1040(1)	3424(3)	8545(1)	53(1)
C(18)	1205(1)	3574(3)	7881(1)	44(1)
C(19)	1020(1)	1961(3)	7342(1)	43(1)
O(1)	631(1)	122(2)	7422(1)	50(1)
O(2)	838(1)	-469(3)	5104(1)	80(1)

Table VII. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for compound **150a**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
C(1)	4551(3)	1043(1)	-703(3)	39(1)
C(2)	4596(4)	707(2)	-1660(4)	55(1)
C(3)	5556(5)	309(2)	-1614(5)	69(1)
C(4)	6403(5)	253(2)	-668(6)	68(2)
C(5)	6399(4)	595(2)	331(4)	56(1)
C(6)	7224(4)	597(2)	1380(5)	68(1)
C(7)	7089(4)	963(2)	2240(5)	69(1)
C(8)	6139(4)	1362(2)	2171(4)	54(1)
C(9)	5302(3)	1370(2)	1191(3)	38(1)
C(10)	5441(3)	989(1)	279(3)	40(1)
C(11)	3677(3)	1497(1)	-442(3)	35(1)
C(12)	4190(3)	1733(1)	802(3)	33(1)
C(13)	4504(3)	2318(1)	475(3)	37(1)
C(14)	5101(4)	2749(2)	1227(4)	46(1)
C(15)	5299(5)	3292(2)	608(4)	63(1)
C(16)	4444(5)	3397(2)	-489(4)	68(1)
C(17)	4319(4)	2921(2)	-1338(4)	50(1)
C(18)	4188(3)	2399(1)	-684(3)	37(1)
C(19)	2402(3)	1318(1)	-354(3)	37(1)
C(20)	1540(4)	1089(2)	-1350(4)	52(1)

C(21)	267(5)	1100(4)	-1058(6)	112(2)
C(22)	68(5)	957(3)	106(5)	87(2)
C(23)	932(4)	1211(2)	1075(4)	56(1)
C(24)	2110(3)	1397(2)	738(3)	40(1)
C(25)	3081(3)	1682(1)	1574(3)	36(1)
C(26)	3438(3)	1353(2)	2737(3)	42(1)
C(27)	3441(4)	1746(2)	3724(3)	46(1)
C(28)	3779(4)	1696(2)	4914(4)	65(1)
C(29)	3585(5)	2161(3)	5622(4)	83(2)
C(30)	3081(5)	2637(3)	5186(4)	75(2)
C(31)	2726(4)	2706(2)	3963(4)	58(1)
C(32)	2146(4)	3165(2)	3355(5)	66(1)
C(33)	1836(4)	3146(2)	2173(5)	64(1)
C(34)	2076(4)	2679(2)	1488(4)	51(1)
C(35)	2652(3)	2239(2)	2030(3)	40(1)
C(36)	2949(3)	2244(2)	3265(3)	42(1)
C(37)	7828(19)	-124(6)	5482(13)	440(20)
Cl(2)	8067(6)	-250(2)	4331(4)	282(3)
Cl(1A)	7190(30)	450(6)	5640(30)	720(30)
Cl(1B)	8550(20)	319(7)	6361(11)	436(18)
O(1)	5447(3)	2679(1)	2267(3)	63(1)
O(2)	3691(2)	1955(1)	-1289(2)	42(1)
O(3)	708(3)	1246(2)	2089(3)	84(1)
O(4)	3618(3)	858(1)	2782(3)	65(1)

Table VIII. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for compound **166a**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
C(1)	3431(2)	10171(2)	3265(1)	42(1)
C(2)	3020(2)	9231(2)	2183(1)	39(1)
C(3)	1564(2)	7657(2)	2055(1)	38(1)
C(4)	-4(2)	7385(2)	1319(1)	39(1)
C(5)	-287(2)	8652(2)	1166(1)	52(1)
C(6)	-1704(2)	8373(2)	459(2)	61(1)
C(7)	-2844(2)	6831(2)	-96(1)	61(1)

C(8)	-2589(2)	5560(2)	62(1)	57(1)
C(9)	-1177(2)	5836(2)	766(1)	48(1)
C(10)	3841(2)	9590(2)	1232(1)	40(1)
C(11)	2037(2)	10030(2)	4953(1)	40(1)
C(12)	2863(2)	12474(2)	6439(1)	49(1)
C(13)	3033(3)	14074(2)	6355(2)	74(1)
C(14)	4178(3)	12573(3)	7296(2)	77(1)
C(15)	1567(2)	6600(2)	3740(1)	42(1)
C(16)	433(2)	3734(2)	3309(1)	48(1)
C(17)	-1120(3)	2452(2)	2534(2)	80(1)
C(18)	1889(3)	3381(3)	3191(2)	73(1)
N(1)	2480(2)	9370(1)	3953(1)	45(1)
N(2)	1424(1)	7766(1)	3286(1)	41(1)
O(1)	3500(1)	8531(1)	319(1)	55(1)
O(2)	4925(1)	11070(1)	1420(1)	57(1)
O(3)	991(1)	9239(1)	5388(1)	49(1)
O(4)	2974(1)	11602(1)	5305(1)	50(1)
O(5)	2284(1)	6858(1)	4681(1)	55(1)
O(6)	688(1)	5178(1)	2966(1)	52(1)

Table IX. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for compound **166b**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
C(1)	6421(2)	-71(2)	6688(2)	61(1)
C(2)	6810(2)	838(2)	7761(2)	55(1)
C(3)	8276(2)	2340(2)	7883(1)	54(1)
C(4)	9694(2)	2489(2)	8560(2)	53(1)
C(5)	10876(2)	3963(2)	9124(2)	62(1)
C(6)	12180(3)	4131(3)	9753(2)	71(1)
C(7)	12296(2)	2797(3)	9809(2)	68(1)
C(8)	11157(3)	1324(3)	9251(2)	74(1)
C(9)	9855(3)	1172(2)	8631(2)	66(1)
C(10)	6018(2)	496(2)	8730(2)	54(1)
C(11)	7877(2)	-16(2)	5028(2)	59(1)
C(12)	7042(3)	-2450(3)	3552(2)	72(1)

C(13)	5794(4)	-2623(4)	2717(2)	106(1)
C(14)	6912(5)	-3973(4)	3672(3)	117(1)
C(15)	8399(2)	3411(2)	6209(2)	58(1)
C(16)	9583(3)	6238(2)	6655(2)	65(1)
C(17)	8273(4)	6655(4)	6833(2)	101(1)
C(18)	11085(3)	7443(3)	7377(2)	102(1)
Cl(1)	13926(1)	2969(1)	10595(1)	102(1)
N(1)	7394(2)	677(2)	5989(1)	67(1)
N(2)	8436(2)	2238(2)	6653(1)	60(1)
O(1)	6570(2)	1423(2)	9703(1)	68(1)
O(2)	4745(2)	-808(2)	8489(1)	71(1)
O(3)	8948(2)	714(2)	4613(1)	68(1)
O(4)	6927(2)	-1555(2)	4676(1)	78(1)
O(5)	7778(2)	3181(2)	5275(1)	71(1)
O(6)	9250(2)	4798(2)	6980(1)	70(1)

Table X. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for compound **166c**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
C(1)	1342(4)	-15(4)	1674(3)	70(1)
C(2)	1755(3)	880(3)	2751(2)	60(1)
C(3)	3230(3)	2359(3)	2879(2)	60(1)
C(4)	4599(3)	2466(3)	3528(2)	56(1)
C(5)	5806(4)	3911(4)	4101(3)	66(1)
C(6)	7071(4)	4033(4)	4703(3)	74(1)
C(7)	7136(4)	2687(4)	4721(3)	72(1)
C(8)	5968(4)	1235(4)	4141(3)	82(1)
C(9)	4710(4)	1145(4)	3555(3)	74(1)
C(10)	985(3)	521(4)	3727(3)	57(1)
C(11)	2788(4)	18(4)	21(2)	71(1)
C(12)	1962(4)	-2413(4)	-1446(3)	87(1)
C(13)	1971(8)	-3805(7)	-1266(4)	163(2)
C(14)	675(7)	-2771(7)	-2283(4)	145(2)
C(15)	3390(4)	3448(4)	1208(3)	65(1)
C(16)	4658(4)	6267(4)	1676(3)	71(1)

C(17)	6161(5)	7426(5)	2387(3)	107(1)
C(18)	3425(5)	6724(5)	1873(4)	107(1)
N(1)	2303(3)	721(3)	972(2)	76(1)
N(2)	3369(3)	2265(3)	1641(2)	66(1)
O(1)	-281(3)	-769(3)	3492(2)	74(1)
O(2)	1555(2)	1448(3)	4707(2)	69(1)
O(3)	3875(3)	733(2)	-371(2)	77(1)
O(4)	1812(3)	-1501(3)	-340(2)	100(1)
O(5)	2797(3)	3232(3)	267(2)	79(1)
O(6)	4248(3)	4817(2)	1989(2)	76(1)
Br(1)	8852(1)	2797(1)	5531(1)	105(1)

Table XI. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for compound **189c**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
C(1)	5034(2)	8924(1)	2108(1)	39(1)
C(2)	5355(2)	9541(1)	2958(1)	37(1)
C(3)	6471(2)	9144(1)	3539(1)	37(1)
C(4)	7211(2)	9402(1)	4359(2)	51(1)
C(5)	8191(2)	8908(2)	4747(2)	65(1)
C(6)	8412(2)	8179(2)	4312(2)	67(1)
C(7)	7681(2)	7912(2)	3474(2)	54(1)
C(8)	6710(2)	8409(1)	3104(1)	39(1)
C(9)	5833(2)	7577(1)	1622(2)	54(1)
C(10)	5415(2)	6770(1)	1994(2)	50(1)
C(11)	4412(3)	6755(2)	2403(2)	72(1)
C(12)	4021(3)	6009(2)	2724(2)	86(1)
C(13)	4612(3)	5277(2)	2616(2)	86(1)
C(14)	5599(3)	5287(2)	2201(2)	83(1)
C(15)	6002(2)	6031(2)	1900(2)	63(1)
C(16)	4278(2)	9651(1)	3426(1)	41(1)
C(17)	3969(2)	10451(1)	3425(2)	47(1)
C(18)	3695(2)	8940(1)	3786(2)	45(1)
C(19)	1949(2)	8475(2)	4314(2)	66(1)
C(20)	1343(3)	7936(2)	3530(2)	94(1)

C(21)	5187(2)	11712(1)	3406(2)	47(1)
C(22)	4729(3)	12904(2)	4220(2)	70(1)
C(23)	3736(4)	13256(2)	4573(3)	134(2)
C(24)	5780(2)	10625(1)	1786(2)	43(1)
C(25)	6853(3)	10167(2)	638(2)	79(1)
C(26)	7361(3)	9393(2)	352(2)	104(1)
N(1)	5842(2)	8284(1)	2264(1)	41(1)
N(2)	5526(2)	10416(1)	2661(1)	44(1)
N(3)	4699(2)	10956(1)	2992(1)	46(1)
O(1)	4187(1)	8997(1)	1451(1)	58(1)
O(2)	5470(2)	11264(1)	1375(1)	64(1)
O(3)	6469(1)	10032(1)	1526(1)	50(1)
O(4)	6178(2)	11954(1)	3382(1)	62(1)
O(5)	4355(1)	12100(1)	3768(1)	60(1)
O(6)	4131(2)	8254(1)	3887(1)	70(1)
O(7)	2615(1)	9141(1)	3970(1)	58(1)

Table XII. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for compound **189f**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
C(1)	8773(2)	2161(2)	9060(1)	46(1)
C(2)	7510(2)	2880(2)	9023(1)	38(1)
C(3)	7699(2)	3689(2)	9613(1)	37(1)
C(4)	6947(2)	4570(2)	9841(1)	40(1)
C(5)	7366(2)	5153(2)	10411(1)	42(1)
C(6)	8512(2)	4875(2)	10741(1)	48(1)
C(7)	9277(2)	3985(2)	10511(1)	47(1)
C(8)	8860(2)	3394(2)	9944(1)	40(1)
C(9)	10641(2)	1873(3)	9850(1)	59(1)
C(10)	6506(2)	1824(2)	8950(1)	37(1)
C(11)	5710(2)	2050(2)	8438(1)	37(1)
C(12)	6537(2)	658(2)	9359(1)	45(1)
C(13)	5600(3)	-1443(3)	9497(1)	70(1)
C(14)	4648(3)	-2301(3)	9152(2)	108(1)
C(15)	5149(2)	4078(2)	7823(1)	44(1)

C(16)	3126(2)	4156(3)	7240(1)	55(1)
C(17)	2394(3)	4868(4)	7641(2)	91(1)
C(18)	2430(3)	3121(3)	6820(1)	81(1)
C(19)	8032(2)	4105(2)	8126(1)	48(1)
C(20)	8483(2)	4671(3)	7137(1)	64(1)
C(21)	8966(3)	3508(4)	6840(2)	112(1)
C(22)	7764(3)	5639(4)	6689(1)	86(1)
Cl(1)	6420(1)	6270(1)	10723(1)	59(1)
N(1)	9463(2)	2489(2)	9616(1)	45(1)
N(2)	7133(2)	3677(2)	8449(1)	41(1)
N(3)	6017(2)	3151(2)	8115(1)	39(1)
O(1)	9044(2)	1397(2)	8681(1)	65(1)
O(2)	7305(2)	469(2)	9808(1)	67(1)
O(3)	5619(2)	-187(2)	9161(1)	57(1)
O(4)	5357(2)	5241(2)	7755(1)	63(1)
O(5)	4125(1)	3414(2)	7625(1)	52(1)
O(6)	7638(1)	4144(2)	7524(1)	61(1)
O(7)	9020(2)	4436(2)	8397(1)	66(1)

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LIST OF PUBLICATIONS

1. Dimethyl Sulfide Induced [3+2] Annulation Strategy: An Efficient Synthesis of Functionalized Dihydropyrazole Derivatives Using the Baylis-Hillman Bromides
   Deevi Basavaiah and **Suparna Roy** *Org. Lett*. **2008**, *10*, 1819-1822.

2. Towards chiral diamines as chiral catalytic precursors for borane-mediated enantioselective reduction of prochiral ketones
   Deevi Basavaiah, Utpal Das and **Suparna Roy** *J. Chem. Sci.* **2009**, *121*, 1003-1010.

3. Towards understanding the scope of Baylis-Hillman Reaction: Synthesis of 3-(2-hydroxyphenyl)indolin-2-ones and polycyclic fused furans
   Deevi Basavaiah, **Suparna Roy** and Utpal Das (*under revision*).