SYNTHESIS OF NOVEL 3-SPIRO HETEROCYCLIC OXINDOLES AND SILICACHLORIDE MEDIATED SYNTHETIC TRANSFORMATIONS OF MORITA-BAYLIS-HILLMAN ADDUCTS

THESIS SUBMITTED TO
THE UNIVERSITY OF KERALA
IN FULFILMENT OF THE REQUIREMENTS
FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY
IN CHEMISTRY
UNDER THE FACULTY OF SCIENCE

BY
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UNDER THE SUPERVISION OF
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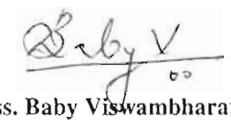
KERALA, INDIA

FERBRUARY 2009

Dedicated to my beloved mother

DECLARATION

I hereby declare that the matter embodied in the thesis entitled **"SYNTHESIS OF NOVEL 3-SPIRO HETEROCYCLIC OXINDOLES AND SILICACHLORIDE MEDIATED SYNTHETIC TRANSFORMATIONS OF MORITA-BAYLIS-HILLMAN ADDUCTS"** is the result of the investigations carried out by me at the Chemical Sciences and Technology Division of National Institute for Interdisciplinary Science and Technology (CSIR), Trivandrum, under the supervision of **Dr. P. Shanmugam** and the same has not been submitted elsewhere for any other degree.



Miss. Baby Viswambharan

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This is to certify that the work embodied in the thesis entitled "**SYNTHESIS OF NOVEL 3-SPIRO HETEROCYCLIC OXINDOLES AND SILICACHLORIDE MEDIATED SYNTHETIC TRANSFORMATIONS OF MORITA-BAYLIS-HILLMAN ADDUCTS**" has been carried out by **Miss. Baby Viswambharan** under my supervision at the Chemical Science and Technology Division of National Institute for Interdisciplinary Science and Technology (CSIR), Trivandrum and the same has not been submitted elsewhere for any other degree.

P. Shanmugam

P. SHANMUGAM
(Thesis Supervisor)

Trivandrum
February, 2009

ACKNOWLEDGEMENTS

It is with great respect and immense pleasure that I put on record my deep sense of gratitude to my research supervisor **Dr. P. Shanmugam** *for suggesting me interesting research topics and for his care, motivation and constructive criticism throughout my doctoral studies.*

I am grateful to Prof. T. K. Chandrasekhar, Dr. B. C. Pai, former and present Directors, NIIST, for providing all the laboratory facilities to carry out this work.

My sincere thanks are also due to

- ✓ *Dr. G. Vijay Nair for his inspiration and support.*
- ✓ *Dr. Mangalam S. Nair, Dr. A. Jayalekshmy, Dr. R. Luxmi Varma and Dr. K.V. Radhakrishnan, Scientists, Organic Chemistry Section for their support.*
- ✓ *Ms. M. V. Sarhithra, Mr. V. Vaithiyanathan and Mr. K. Selvakumar for the excellent companionship and support throughout these studies.*
- ✓ *Mrs. S. Viji for HRMS, Mrs. Saumini Mathew, Mr. Thirumalai Kumaran and Mr. R. Adarsh for recording NMR spectra, Mr. D. Deepak Vishnu for IR spectra.*
- ✓ *Dr. S. Anas, Dr.V.S. Sajisha, Mr. L. Praveen, Ms. P. S. Hema, Mrs. D. B. Ambily Raj, Mrs. D. B. Mansheeja, Dr. B. Remadevi for their valuable support during my doctoral study.*
- ✓ *Dr. S. P. Rajasingh, Dr. Beena James, Dr. A.T. Biju, Dr. N. Abhilash, Dr. V. Sreekumar, Dr. N. Vidya, Dr. K. Syam Krishnan, Ms. Shelly Clair George, Ms. T. Sreeja, Dr. E. R. Anabha, Mr. Jabi John, Ms. V. B. Ganga, Mr. P. B. Beneesh, Mr. Jinesh M. Kuthanapillil, Mr. Rony Rajan Paul, Mr. C.R. Sinu, Ms. Nayana Joseph, Ms. Rani Rajan, Mr. K. V. Jobi, Mr. Vimal Varghese and Ms. Joshni John for their camaraderie and support.*
- ✓ *Dr.S. Savithri and Dr. Sivakumar for their care and help.*
- ✓ *All the present and former members of the Organic Chemistry Section and my friends at NIIST.*
- ✓ *All faculty members of the Department of Chemistry, SSV College, Valayanchirangara, MA College, Kothamangalam and St. Joseph's College, Moolamattam for their constant support and inspiration.*
- ✓ *CSIR, New Delhi for financial assistance.*

I thank my father and brother for their love and care throughout my life. Finally, I bow my head in front of The God, Almighty for giving me the strength to overcome all difficulties in fulfilling my ambitions.

Baby Viswambharan

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CHAPTER 5

ABBREVIATIONS

AcOH	:	acetic acid	FC	:	Friedel-Craft
Ar	:	argon	HOMO	:	Highest occupied molecular orbital
AIBN	:	azo bis isobutyro nitrile	HRMS	:	high resolution mass spectra
AMY	:	azomethine ylide	Hz	:	Hertz
BINOL	:	1,1'-bi-2-naphthol	IR	:	infra red
CAN	:	cericammonium nitrate	J	:	coupling constant
CNDO	:	complete neglect of differentialoverlap	LUMO	:	lowest unoccupied molecular orbital
			m	:	multiplet
CSA	:	camphor sulphonic acid	MBH	:	Morita-Baylis-Hillman
d	:	doublet	Me	:	methyl
dd	:	doublet of doublet	mg	:	milligram
DABCO	:	1,4-diazabicyclo[2.2.2]-octane	mL	:	milliliter
DBU	:	1,8-dizabicyclo[5.4.0]undac-7-ane	MS	:	molecular sieves
			MVK	:	methyl vinyl ketone
DEPT		distortionless Enhancement by Polarization Transfer	MWNT	:	multi walled nanotubes
			NMR	:	nuclear magnetic resonance
DMAD	:	dimethyl acetelenedicarboxylate	*p*	:	para
DMAP	:	dimethylamino pyridine	Ph	:	phenyl
DMDO	:	dimethyl dioxirane	PEG	:	poly ethelene glycole
DMSO	:	dimethyl sulphoxide	PPTS	:	pyridinium *p*-toluene sulphonate
DMF	:	dimethyl formamide	PTSA		*para*-toluene sulphonic acid
EDG	:	electron donating group	ppm	:	parts per million
EI	:	electron impact	^{i}Pr	:	isopropyl
Et	:	ethyl	q	:	quartet
FAB	:	fast atom bombardment	RT	:	room temperature

RCM	:	ring closing metathesis	TBDMS	:	tertiarybutyldimethylsilyl
s	:	singlet	THF	:	tetrahydrofuran
SWNT	:	single walled nanotubes	TLC	:	thin layer chromatography
t	:	triplet	TMS	:	tetramethylsilyl
TMSOTf	:	trimethylsilyltriflate	TFA	:	trifluoroacrtic acid
TMSI	:	trimethylsilyliodide	*Tert*	:	tertiary
TMM	:	trimethylene methane	UV	:	ultra violet
THP	:	tetrahydropyranyl			

CHAPTER 1

A Brief Account of the Morita-Baylis-Hillman Reaction and An Overview of Azomethine Ylide Cycloaddition

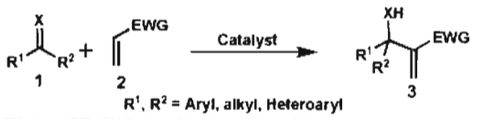
1.1 Introduction

Continuing development in synthetic organic chemistry relies on discovering new, high yielding and selective reactions. The Morita-Baylis-Hillman (MBH) reaction[1] has seen tremendous development in this point of view and as the MBH adducts and their derivatives have recently gained considerable attention of synthetic organic chemists. Exploration of novel synthetic applications of MBH adducts have became a major area of current research. The central theme of the present study is the synthetic application of MBH adducts of isatin towards the synthesis of novel 3-spiro heterocyclic oxindoles using azomethine ylide 1,3-dipolar cycloaddition chemistry. In order to put things in perspective, a brief introduction on Morita-Baylis-Hillman reaction and its importance in organic synthesis and an overview on azomethine ylide cycloadditions are given in the following sections.

1.2 The Morita-Baylis-Hillman reaction

Ever since the discovery of the reaction of an α-position of an activated alkene **2** and an electrophile **1** catalyzed by trialkylphosphine or a tertiary amine, usually diazobicyclo[2.2.2]-octane (DABCO), by A. B. Baylis and M. E. D Hillman in 1972, organic practitioners are looking at the various synthetic aspects of the reaction (Scheme 1.1).[2-5] Imines can also participate in the reaction if they are properly activated.[6] Named after that, the (MBH) reaction has become a powerful tool for the atom-economical construction of C-C bond formation, giving α-methelene-β-hydroxyl carbonyl or α-methelene-β-amino carbonyl derivatives, which comprises a contiguous assembly of three different functional groups. These adducts play an important role in bringing latitude to

organic synthesis and in the construction of complex molecular architectures as potential synthons.[7]



Scheme 1.1

1.3 Mechanism of MBH reaction

According to Hill and Isaacs, mechanism of amine catalyzed MBH reaction, methyl acrylate (as an activated olefin) and benzaldehyde (as an electrophile) reacts to form MBH adduct under catalytic influence of DABCO as a model case, is believed to proceed through the Michael initiated addition–elimination sequence (Figure 1.1; Path I).[8] The I[st] step in this catalytic cycle involves the Michael-type nucleophilic addition of the tertiary amine to the activated alkene (methyl acrylate) to produce a zwitterionic enolate **A**, which makes a nucleophilic attack on to the aldehyde in an Aldol fashion to generate zwitterion **B**, subsequent proton migration and release of the catalyst provides the adduct. McQuade *et al.* have proposed a new mechanism involving a hemiacetal intermediate, (Figure 1.1; path II), based on the reaction rate in aprotic solvent where they determined the rate is second order in aldehyde and first order in DABCO.[9]

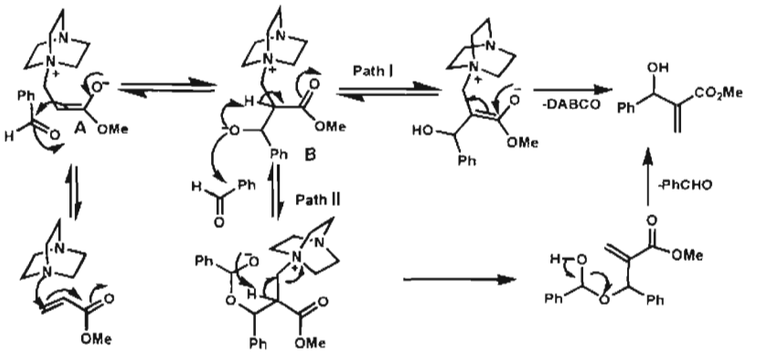


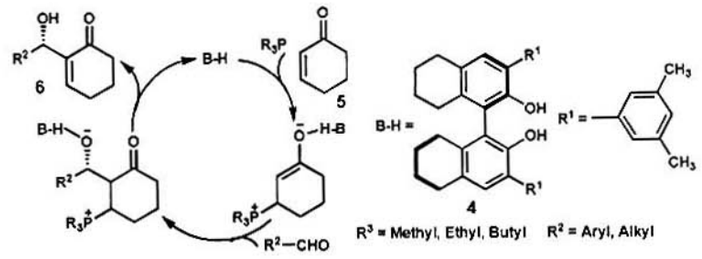
Figure 1.1

1.4 Catalysts for MBH reaction

In recent years it has been established that small organic molecules which does not contain a metal atom can catalyze chemical reaction with high selectivity and are known as organocatalysts.[10] Being a prototypical nucleophile induced transformation; the MBH/aza-MBH reactions are indeed ideal candidates for the development of organocatalysts. Any hetero atom or the possibility of hydrogen bonding that can stabilize the intermediate will increase the rate of the reaction. The following subsections outline the various catalysts used in MBH reaction.

1.4.1 Phosphine mediated MBH reaction

In 1968, Morita[11] *et al.* described a tricyclohexylphosphine catalyzed reaction, named as "Carbinol Addition". However, the yield (20%) and the rate of the reaction (several days) were extremely poor. Later several reports came with a series of phosphine catalysts, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl,[12] Bu_3P in presence of Lewis acid additives (activate the carbonyl group) such as racemic 1,1'-bi-2-naphthol (BINOL),[13] trialkylphosphonium salt,[14a] Et_3Al,[14b] *etc.*, essentially some of them were asymmetric version of the MBH reaction.



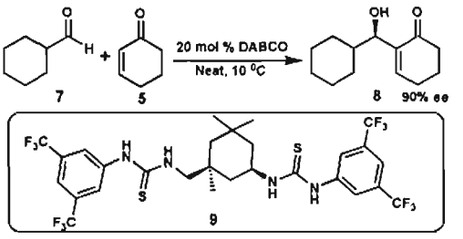
Scheme 1.2

Schaus and McDoudal[15] introduced a chiral Brønsted acid catalyst derived from BINOL **4**, which in combination with PEt_3, led to enantiomeric excess up to 96% and good to moderate yields for a variety of aldehydes in the reaction with 2-cyclohexen-1-one **5**. During their investigation, two structural features of the catalyst were found to be important for achieving high

enantioselectivity viz. (i) saturation of the (R)-BINOL derivative and (ii) substitution at the 3,3-positions as in scheme 1.2.

1.4.2 Amine as a catalyst

In 1972, Anthony Baylis and Melville Hillman from Celanese Corporation were granted a German patent for performing the reaction of benzaldehyde and an activated alkene using a tertiary amine catalyst instead of phosphine catalyst.[1] A verity of tertiary amines like DABCO, DBU, quinuclidine, 3-hydroxy quinuclidine, indolizine, imidazole, *etc*, have been reported to catalyze the MBH reaction with a high degree of conversion and with higher rate.[16] They also reported that DABCO as the most successful catalyst. The first application of (thio) urea catalysts for the MBH reaction was reported by Connon and Maher The asymmetric version[17] was disclosed by Wang *et al.* with a chiral bifunctional catalyst carrying a Brønsted basic tertiary amine and a quasi-Lewis acidic thiourea group attached to a chiral scaffold.[18] Berkessel *et al.* reported an improved bis(thio)urea catalysts **9** derived from isophoronediamine [3-(aminomethyl)-3,5,5-trimethylcyclohexylamine, IPDA] for the asymmetric MBH reaction of aldehyde **7** with activated alkene **5** in the presence of DABCO (Scheme1.3) .[19]

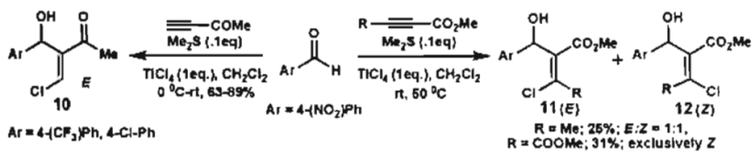


Scheme 1.3

1.4.3 Chalcogenide mediated MBH reaction

After the first report from Kataoka *et al.*, [20a,b] different chalcogenides are known to catalyze the MBH reaction in combination with a verity of Lewis acids such as $BF_3.OEt_3$, $SnCl_4$, $AlCl_3$, $EtAlCl_2$, Et_2AlCl, HfCl, $TiCl_4$, *etc* and it has been found $TiCl_4$ offers a better result. The chalcogeno-MBH reaction has some merits, [21a, b] namely, it will complete within hours and can be applicable

to thioesters[21c] and ketoesters[21d] for which the MBH reaction give unsatisfactory results. Even activated alkynes react with aldehydes in presence of $TiCl_4$ and dimethyl suphide provides β-halo-α-(hydroxyalkyl) acrylate **10**.[22] The β-halo MBH adducts **11** and **12** can be formed even from β-substiuted alkynes (Scheme 1.4).



Scheme 1.4

A plausible mechanism of chalcogenide mediated MBH reaction have been proposed by Kataoka in which dual activation to the activated alkene is provided by chalcogenides (**13 - 16**), acting as a nucleophile and $TiCl_4$ acting as a Lewis acid (Figure 1.2).

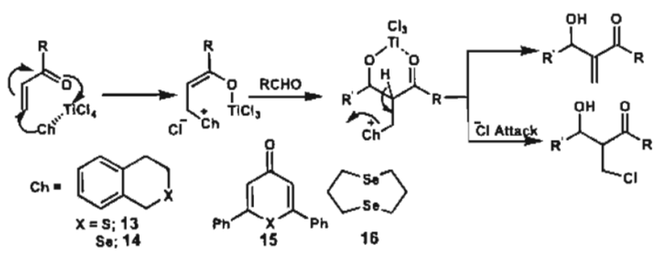
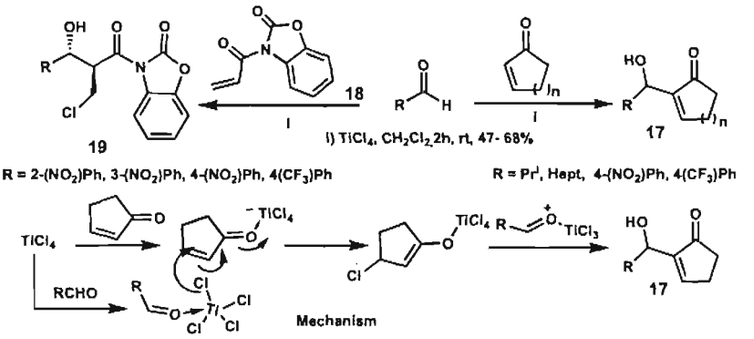


Figure 1.2

1.4.4 $TiCl_4$ mediated MBH reaction

It is worth mentioning here that the pioneering work of Taniguchi *et al.* who examined the reaction between $\alpha\beta$-acetylenic ketones and aldehydes in the presence of various combination of reagents such as $TiCl_4$/TMSI, TMSOTf/TMSI, $TiCl_4$/Bu_4NI, *etc.*[23] Later Li *et al.* reported a $TiCl_4$ mediated reaction of cycloalkenones and aldehydes (without the use of a base) to provide the desired adduct **17**. However, $\alpha\beta$-unsaturated *N*-acyl benzoxazoline **18** reacted with a propensity to form β-halogenated aldol product **19** as a major one. They have proposed a plausible mechanism of the reaction in which $TiCl_4$

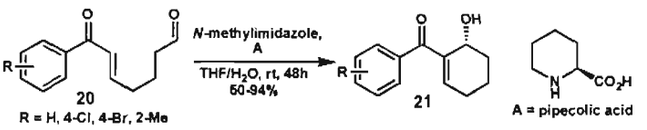
performed as the dual activation reagent for both the components (Scheme 1.5).[24]



Scheme 1.5

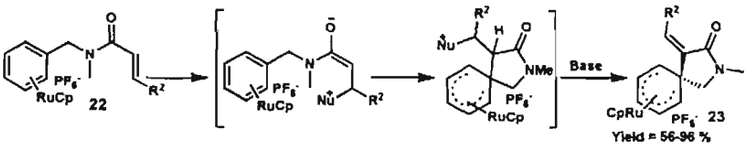
1.5 Intramolecular MBH reaction

Intramolecular MBH reaction offers the best route for the creation of cyclic compounds as first reported by Murphy and co-workers in 1997.[25] Recently, Miller and co-workers used a co-catalyst system involving *N*-methylimidazole and pipecolinic acid **A** for intramolecular MBH reaction of 7-oxo-7-arylhept-5-enal **20** for the synthesis of cycloalkene derivative **21** with a high level of enantioselectivity (Scheme 1.6).[26] However, proline gave low enantioselectivity.



Scheme 1.6

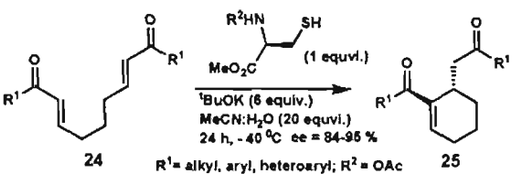
More recently, organometallic variation of MBH cyclization has been reported by Pigge and co-workers. *N*-benzyl acryl amide-ruthenium complex **22** was transformed in to the spirocyclic derivative **23** in the presence of Bu_3P and NaH. The ruthenium-arene complex served as an electrophile (Scheme 1.7).[27]



Scheme 1.7

1.6 The Rauhut-Currier reaction

A phosphine catalyzed dimerisation of activated alkene has been patented by Rauhut and Currier in 1963.[28] Recently, an intramolecular enantioselective version of the reaction catalyzed by protected cysteine has been reported by Miller and Aroyen (Scheme 1.8). In the thiolate mediated isomerisation of **24** to **25**, water as an additive plays a significant role in enantiomeric excess.[29]



Scheme 1.8

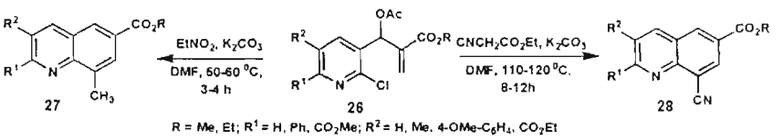
1.7 Developments in reactions of Morita-Baylis-Hillman adducts:- Application towards heterocycle synthesis.

As mentined earliar, the presence of diverse functional groups in the MBH adducts plays an important role in bringing latitude to organic synthesis for the construction of complex molecular assemblies. Since these functional groups are in close proximity, they should, in principle, be useful for stereoselective transformations through appropriate tuning either individually or two at a time or collectively. The MBH adduct and its derivatives such as allylic acetates and allylic halides undergo a variety of reactions and could efficiently be exploited for the generation of cyclic scaffolds. Several efforts have already been meticulously and articulately made in these directions, leading to the development of simple methodologies with high degree of stereoselectivities. In fact, some of these strategies were successfully employed in the synthesis of various biologically active molecules and natural products.

Particularly, during the last five years, applications of MBH adducts have been extensively investigated and number of organic synthetic transformation methodologies were developed. The following sections describe some of the synthetic applications of various MBH adducts in organic synthesis.

1.7.1 Aromatic substitution reaction: Synthesis of quinolines

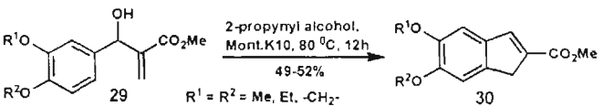
Suitably substituted MBH adducts can undergo intramolecular aromatic electrophilic substitution reaction and to give heterocyclic ring systems such as quinolines,[30a, b] naphthalenes,[30c-e] coumarins,[30f] indoles,[30g] *etc*. Recently, Rao *et al.* reported that the acetyl derivatives of MBH adduct **26** derived from 2-chloronicotinaldehyde undergo a S_N2' reaction with nitroethane or ethyl cyanoacetate and an intramolecular aromatic substitution and elimination (S_N-Ar elimination) led to the formation quinolenes **27** and **28** which exhibited substantial antibacterial and antifungal activities. The reaction is shown in scheme 1.9.[31]



Scheme 1.9

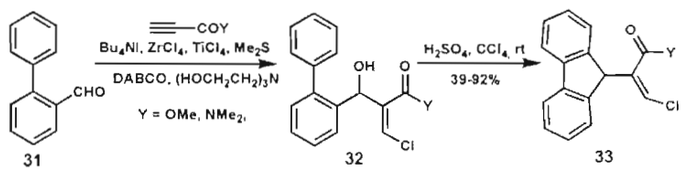
1.7.2 Friedel-Craft reaction

After the stereoselective synthesis of trisubstituted alkenes[32a] and thereby benzazepines and benzoxepines[32b,c] by Basavaiah *et al.*, exploiting Friedel-Crafts reaction on MBH adducts, several groups have been working on this reaction. Recently, our group has reported an efficient and eco-friendly protocol for the synthesis of indene derivative **29** from MBH adduct **30** via Montmorillonite K-10 mediated intramolecular Friedel-Crafts (FC) reaction (Scheme 1.10).[33]



Scheme 1.10

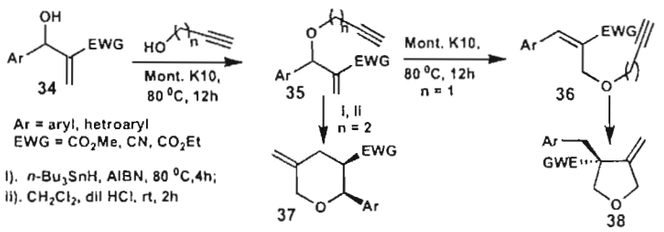
More recently, Lee *et al.* demonstrated the synthesis of 2-(9-flurenyl) acrylic acid derivatives **33** *via* an intermolecular FC reaction of MBH adduct of 2-biphenyl carbaldehyde **31** with activated alkyne (Scheme 1.11).[34]



Scheme 1.11

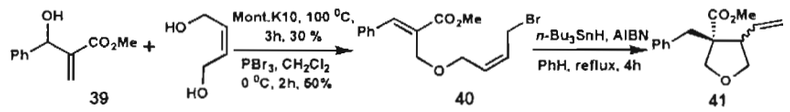
1.7.3 Radical cyclization

Radical cyclization reactions have been extensively applied to the MBH chemistry for the construction of oxygen containing heterocyclic compounds. Synthesis of highly substituted dihydrofurans, pyrans and oxepenes from alkenyl propargyl ethers of MBH adducts using radical cyclization protocol have been first reported by our group. Accordingly, mont-K10 catalyzed isomerisation of MBH adducts with propargyl alcohol yielded two regioisomers **35** and **36** which underwent radical cyclization with *n*-Bu_3SnH/AIBN to form the vinylstannanes which upon protio-destannylation reaction with 1N HCl afforded the oxacycles **37** and **38** in good yield (Scheme 1.12).[35]



Scheme 1.12

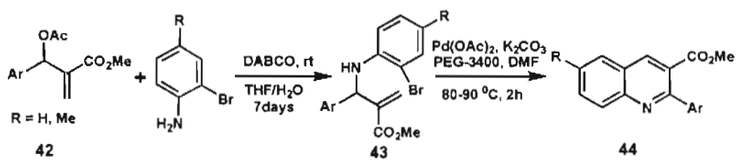
Followed by these results, Kim and co-workers used radical cyclization protocol for the synthesis of oxa- and aza-heterocycles.[36] Recently, the authors have achieved the synthesis of 3,4-trisubstituted-2,5-dihydro furan **41** *via* the isomerisation of the MBH adduct **39** with *cis*-but-2-ene-1,4-diol followed by bromination and radical cyclization, in good yields (Scheme 1.13).[37]



Scheme 1.13

1.7.4 Heck Coupling

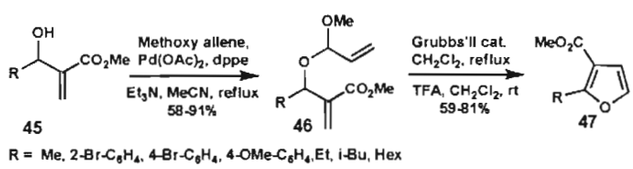
Several reports are known for the construction of bi- and tricyclic systems from appropriately functionalized MBH adducts **45** using the Heck coupling.[38] Very recently, Kim and co-workers have demonstrated the synthesis of 2-arylquinoline **44** via a Pd-mediated sequential Heck coupling and a concomitant aerobic oxidation from the *N*-bromoaryl substituted MBH adduct **43** (Scheme 1.14).[39]



Scheme 1.14

1.7.5 Metathesis

Ring closing metathesis (RCM) using Grubbs catalysts offers a best route for the synthesis of ring compounds and was first introduced in MBH chemistry by Paquette and Mendez-Andino for the synthesis of α-methelene-γ-lactones fused to medium and large rings.[40a] For the synthesis of 2,3-disubstituted furan **47**, Donohoe *et al.* transformed the MBH adduct to a mixed acetate **46** which on RCM followed by aromatization yielded **47** (Scheme 1.15).[40b]

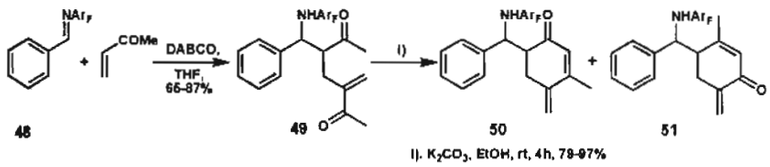


R = Me, 2-Br-C_6H_4, 4-Br-C_6H_4, 4-OMe-C_6H_4,Et, i-Bu, Hex

Scheme 1.15

1.7.6 Aldol reaction

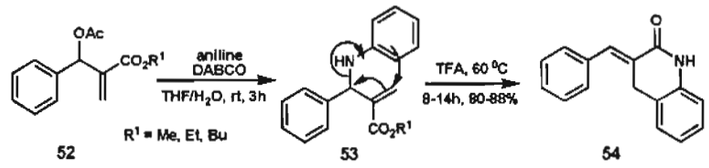
Reactions, either S_N2 or S_N2', of MBH acetate with activated methelene compound afforded synthons which have been successfully employed for the Aldol reaction to afford cyclic compounds.[41] Zhu *et al.* reported a double aza MBH reaction between per and poly fluorophenyl aromatic aldemines **48** with methyl vinyl ketone (MVK) and the adduct **49** thus obtained underwent Aldol reaction to yield fluorine containing alkelidene-2-cyclohexen-1-ones **50** and **51** as a mixture of regioisomers as outlined in scheme 1.16.[42]



Scheme 1.16

1.7.7 Claisen rearrangement

Claisen rearrangement in MBH chemistry was demonstrated by Basavaiah and co-workers and the method offers a way to fused benzocarbocycles.[43] Later, Batra and co-workers developed a strategy for the synthesis of 3-aryledene-2-quinolones **54**, a starting material for an anti tubercular compound R207910. S_N2 reaction of MBH acetate **52** with aniline resulted *N,N*-diaryl allylaniline **53** which on TFA catalyzed [3,3]-Claisen rearrangement afforded **54** (Scheme 1.17).[44]

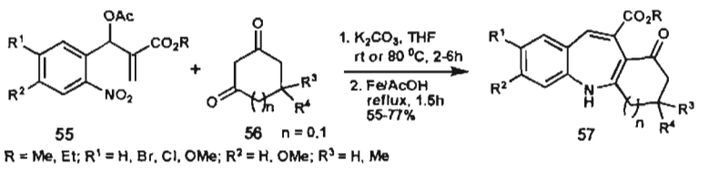


Scheme 1.17

1.7.8 Reductive cyclization

Reductive cyclization strategies have found broad application in the formation of polycyclic compounds in MBH chemistry. Reduction of a nitro group either in the aromatic chain or in the side chain of MBH adducts to amino group and its condensation with a carbonyl group furnished fused

heterocyclic ring.[45] Very recently, Basavaiah *et al.* have demonstrated a one pot synthesis of azocine moiety **57** from the reaction of acetate protected MBH adduct **55** carrying a nitro group at the second position with 1,3-cycloalkane diones **56** and followed by reductive cyclization using Fe/AcOH (Scheme 1.18).[46]



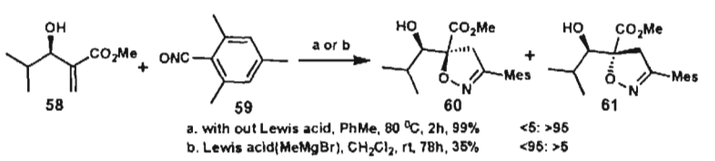
Scheme 1.18

1.7.9 Cycloaddition reactions

The activated double bond of MBH adduct can act as a dipolarophile for cycloaddition reaction. This includes the (1) 1,3-dipolar cycloadditions[47], (2) Diels-Alder reaction and (3) (n+n) annulation reaction.

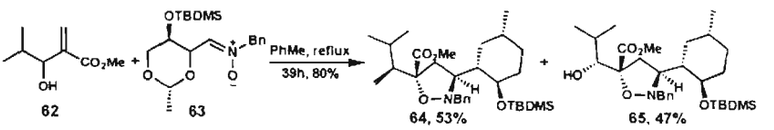
1.7.9.1 1,3-Dipolar cycloaddition reaction

1,3-Dipolar reaction of mesitonitrile oxide with MBH adduct was first demonstrated by Fisera and co-workers. In his report, mesitonitrile **59** was added to the double bond of MBH adduct **58** to form the isoxazolidine **60** and **61**, diasterioselectively. On the addition of a Lewis acid (Grignard Reagent), the diastereoselectivity was found to be reversed (Scheme 1.19).[48]



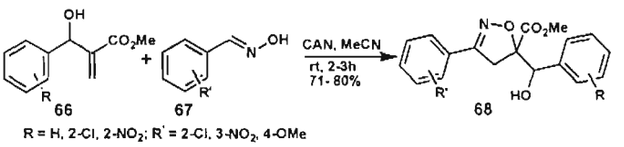
Scheme 1.19

Later, the same authors have reported the 1,3-dipolar cycloadditions of chiral nitrone **63** to MBH adduct **62** (*β*-hydroxy-*α*-methylene esters) which proceeded to afford corresponding diastereomeric 3,5,5-trisubstituted isoxazolidines **64** and **65** with complete regioselectivity in good yields (Scheme 1.20).[49a] The rate of the reaction was found to increase under microwave irradiation condition.[49b]



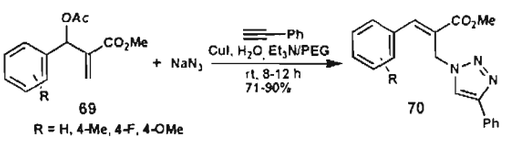
Scheme 1.20

CAN mediated cycloaddition of aldoxime with MBH adduct have been reported by Das *et al.* They synthesised isoxazoline **68** in high yields (Scheme 1.21).[50]



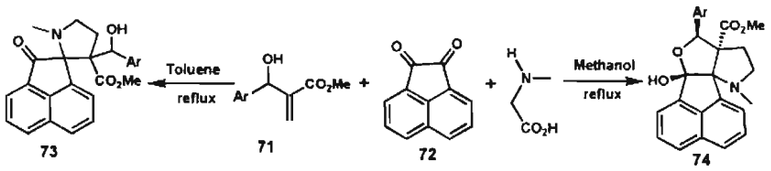
Scheme 1.21

Sreedhar and co-workers have reported a Cu(I)-catalyzed one-pot regioselective synthesis of 1,4-disubstituted 1,2,3-triazole **70** in high yield.[51a] The method involved a nucleophilic displacement of the acetyl group in the MBH acetate **69** with sodium azide followed by 1,3-dipolar cycloaddition of terminal alkyne in poly ethylene glycol PEG (Scheme 1.22). Simultaneously, Chandrasekhar *et al.* demonstrated the synthesis of similar triazoles by using Cu(0) and $CuSO_4$ as a reagent in ethanol.[51b]



Scheme 1.22

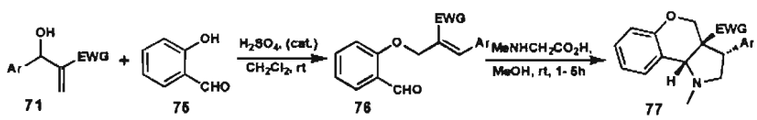
Raghunathan *et al.* have reported the synthesis of novel spiro heterocycle **73** *via* a 1,3-dipolar cycloaddition reaction of nonstabilized azomethine ylide (generated *insitu* by the decarboxylative condensation of di-ketone **71** with sarcosine) and the MBH adduct **71** in refluxing toluene.[52a] In methanol, an unusual nucleophilic attack of the hydroxyl group to the ketone occurred and resulted the tricyclic product **74**. Later, the authors have improved the yields of the product by carrying out the reaction in a microwave irradiation condition (Scheme 1.23).[52b]



73 71 72 74

Scheme 1.23

The synthesis of a series of tricyclic chromone[4,3,b]pyridine **77** through an intramolecular azomethine ylide cycloaddition reaction of **76** was accomplished by Raghunathan *et al.* Improved yields of the same products were obtained when the reaction was carried out under ultrasonication (Scheme 1.24).[53]

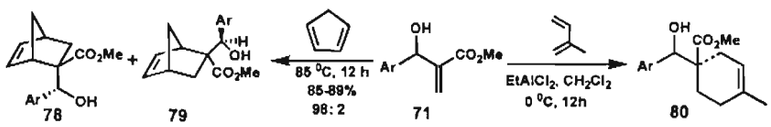


71 75 76 77

Scheme 1.24

1.7.9.2 Diels-Alder reaction

In 2005, Aggarwal *et al.* have reported the first Diels-Alder reaction on MBH adduct **71** with dienes and observed that under thermal condition *exo* isomer is favoured over *endo* isomer. However, the presence of Lewis acid had no effect on the ratio of *exo* **78** to *endo* **79.**[54] When ethyl aluminium chloride was used as Lewis acid, they observed high diastereoselectivity in the cycloaddition of isoprene and adduct **71**(Scheme 1.25).



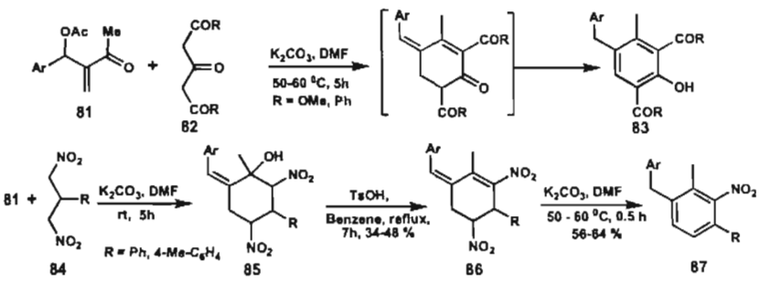
78 79 71 80

Scheme 1.25

1.7.9.3 (*n+n*) Annulatoin

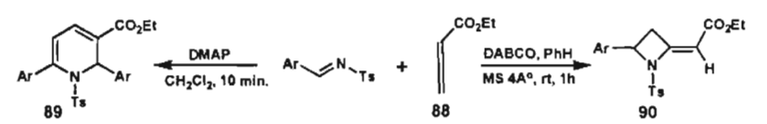
Kim and co-workers achieved the synthesis of poly substituted phenols **83** from MBH acetate **81**, 1,3-dielectrophilic unit, *via* a (3+3) annulation of 1,3- acetone dicarboxylate **82** in DMF.[55a] They have recently reported the

synthesis of poly substituted nitrobenzene adopting the same strategy, in which 1,3-dinitroalkene served as the 1,3-dinuclear component (Scheme 1.26).[55b]



Scheme 1.26

Shi *et al.* reported an abnormal MBH reaction between *N*-tosylimine and allenes such as ethyl-2,3-butadienoate **88**, catalyzed by DMAP and obtained dihydropyridine **89** *via* a [4+2] cycloaddition pathway. They observed the formation of an azetidine **90** derivative when DABCO was used as base (Scheme 1.27).[56]



Ar = Ph, 4-F-C_6H_4, 4-Me-C_6H_4, 4-Cl-C_6H_4, 4-F-C_6H_4, 4-Br-C_6H_4, 3-F-C_6H_4

Scheme 1.27

1.8 Azomethine ylides: Survey of literature

Cycloaddition reactions constitute a greener area in synthetic organic chemistry. Among which 1,3- dipolar cycloaddition reactions have figured prominently in both synthetic and mechanistic organic chemistry point of view for the regio and stereocontrolled synthesis of five membered heterocyclic ring systems. [57] After the first report in 1976, 1,3-dipolar cycloaddition using azomethine ylide, impressive developments have been appeared in this area with the establishment of various useful methods for the generation of azomethine ylide. This method is applied for the construction of pyrrolidine and pyrrole ring containing natural products and is expanding rapidly.[58]

1.8.1 Structure of AMY

Azomethine ylides (AMY) are 1,3-dipoles of allyl anion type with a C-N-C backbone having four delocalized electrons in three parallel π atomic orbitals, perpendicular to the plane of the dipole[59] and providing a bent type Zwitter ionic structure. Four resonance structures can be shown for AMY's as shown in Figure 1.3. In the most common representation, octet structure, the central nitrogen atom is positive and the negative charge is distributed over carbon. The extent of negative charge on each carbon is determined by the nature of substituent on this carbon.[60]

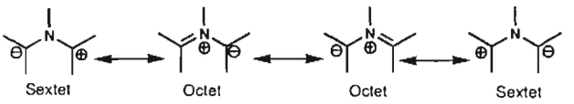


Figure 1.3

1,3-dipolar cycloaddition of AMY with a π system involves a 6 π electrons [$_{\pi}4_{s}+_{\pi}2_{s}$] and takes place by a thermally allowed suprafacial process according to Woodward-Hoffmann rule.[61] Although in general the cycloaddition reactions are thought to be concerted, both the carbon-carbon bonds are formed at the same time, the involvement of a singlet diradical of a Zwitter ionic species cannot be ruled out.[62] But the stereospecificity of AMY cycloaddition, the relative stereochemistry of the substituent on the alkene dipolarophile is retained, favours the concerted nature of the reaciton.[63]

CNDO/2π (Complete Neglect of Differential Overlap) calculations of energies of the various orbitals involved have revealed that non-stabilized AMYs are all electron rich species, characterized by highest occupied molecular orbitals (HOMOs) and lowest unoccupied molecular orbitals (LUMOs), and preferentially reacting with electron deficient alkenes[64] due to large HOMO-LUMO energy gap. But according to Sustman, AMY cycloaddition reactions are classified as type I in which the dominant interaction is between the $HOMO_{dipole}$ with $LUMO_{dipolarophlic}$ (HOMO controlled) as shown in figure 1.4. An electron withdrawing group at the alkene and an electron donating group at dipole increases the reaction rate.[65]

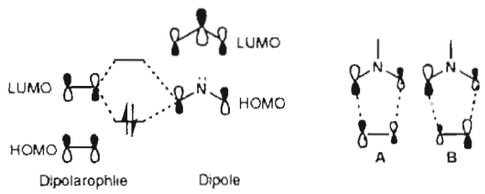


Figure 1.4

The regioselectivity in the cycloaddition of AMY can be predicted on the basis of unequal magnitude of terminal co-efficient of the HOMO and the LUMO of the dipole and the direction in which the maximal frontier molecular orbital (FMO) overlaping is allowed between the orbitals of closest energy.[66] But the energy difference between the transition states A and B are usually small, the rate of formation of both the regio isomers are possible. Steric and conformational effect also play an important role in detecting the regio isomers, and is clearly beneficial in terms of enhancing the selectivity process.

The stereochemical aspects of AMY dipolar cycloaddition, four chiral centers are generated and a high degree of stereoselectivity is typically obtained. The chiral centers at the carbon atom 2 and 5 of the newly formed five membered ring are derived from the AMY. Out of the four possible geometries of azomethine ylide, W, U and two S-shaped ylides, W and U lead to 2,5-cis-substituted pyrrolidine and two S form lead to 2,5-trans-disubstituted product (Figure 1.5). Mixtures of stereoisomers can also result from isomerisation of the ylide.

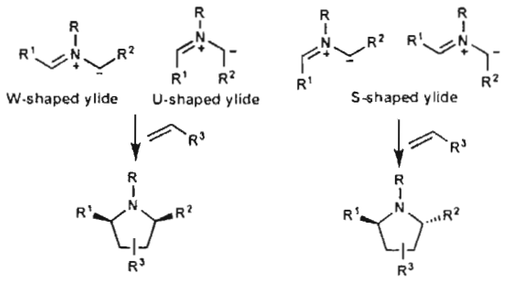


Figure 1.5

The 3,4-chiral centers of the newly formed pyrrolidine ring derived from the alkene geometry. *Cis*- and *trans*- alkene leads to *cis*- and *trans*-disubstituted pyrrolidine rings, respectively. Furthermore, the cycloaddition reactions are normally stereoselective where the substituents on the dipolarophile can adopt generally an *endo* orientation analogous to isoelectronic Diels-Alder reaction.[67]

1.8.2 Classification of AMY based on electronic structure

AMYs are classified as (a) non-stabilized (b) stabilized non-metalated and (c) stabilized metalated depending on their electronic structures. AMY with an α- electron withdrawing substituent, an ester functionality, are stabilized. Further, the ylide is stabilized additionally by chelation of the central nitrogen and the carbonyl group with a metal center (Figure 1.6).

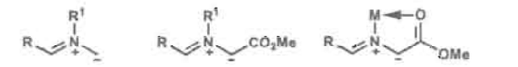


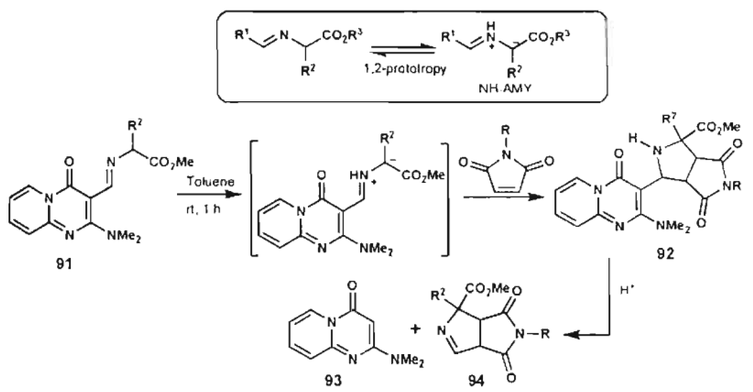
Figure 1.6

1.8.3 Classification based on generation of AMY and reactivity

For the generation of required azomethine ylide, five different methods are known and are explained in the following sections.

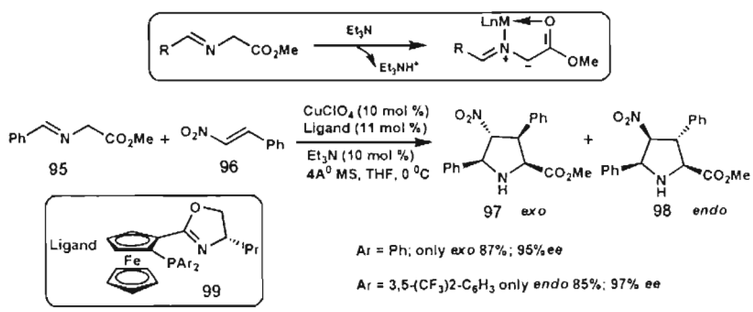
1.8.3.1 From imines

N-unsubstituted azomethine ylides are accessible by thermal or uncatalyzed isomerisation of imines and was first reported by Grigg and Kemp in 1977.[68] Recently, Noguchi and co-workers used an aldemine **91**, derived from 2-(*N*,*N*-dimethylamino)pyrido[1,2-a]pyrimidine-4(4H)-one-3-aldehyde and (DL)-phenyl glycene methyl ester for AMY generation and cycloaddition with *N*-benzyl succinimide. The cycloadduct **92** on acid catalyzed fragmentation yielded the bycyclic product **94** which is a C-unsubstituted nitrile ylide addition product (Scheme 1.28).[69]



Scheme 1.28

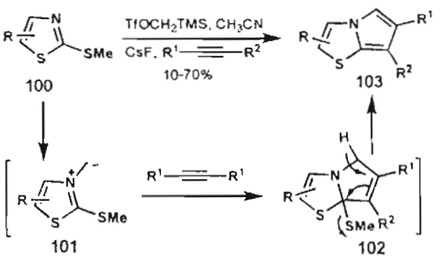
An alternative to thermal activation of imines, bearing an electron withdrawing group at α to nitrogen, for the formation of the required AMY is the addition of metal salts such as lithium bromide or sliver acetate, and a base such as trimethyl amine in polar aprotic solvents.[70] Several stereoselective versions for the use of AMY, in the presence of chiral ligands were also reported. In 2006, Hou *et al.* reported a highly enantio- and diasterioselective synthesis of pyrrolidine **97** and **98** catalyzed by Cu^{I}- *P,N*-ferrocene system **99** for the cycloaddition of nitroalkene **96** to a benzyl imino eater **95** derived from glycene (Scheme 1.29).[71]



Scheme 1.29

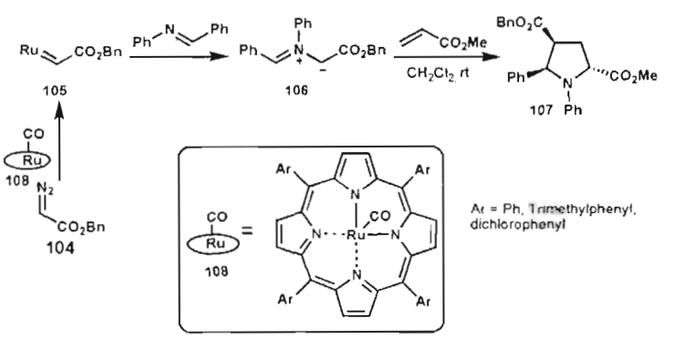
Alkylation of nitrogen atom of relatively stable imines, aromatic or formamidines, provide a method to prepare an iminium ion and subsequent deprotonation or a desilylation to azomethine ylides.[72] Thiazolium azomethine

ylide **101**, generated by the deprotonation of the quaternary methyl salt of 1,3-thiazole **100**, equipped with a thiomethane group, participate in an efficient [3+2] cycloaddition reaction with acetylene derivatives to yield the adduct **102** which on elimination of the methanethiol as leaving group yielded the pyrrole[2,1-b]thiazole **103** in excellent yield. A pitfall of this reaction is the elimination leading to aromatization which excludes the separate oxidation step (Scheme 1.30).[72c]



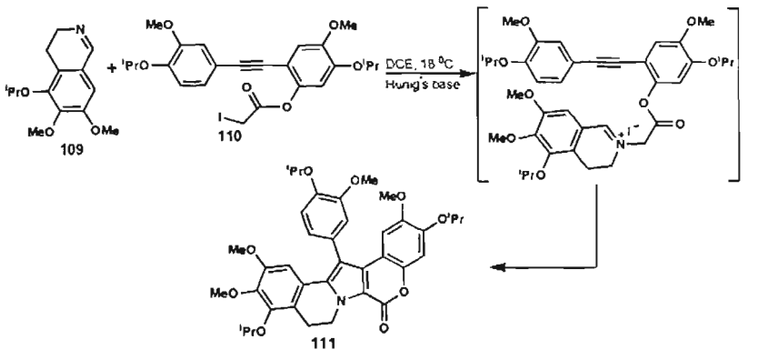
Scheme 1.30

An alternative approach to the formation of azomethine ylides from imines involves the addition of carbene. Chi-Ming and co-workers reported a ruthenium-porphyrin complex **108** catalyzed tandem azomethine ylide **106** formation from *N*-phenyl benzylamine and diazoester **104** and the inter molecular cycloaddition reaction with acrylate to form functionalized pyrrolidine **107** in excellent yield (Scheme 1.31).[73]



Scheme 1.31

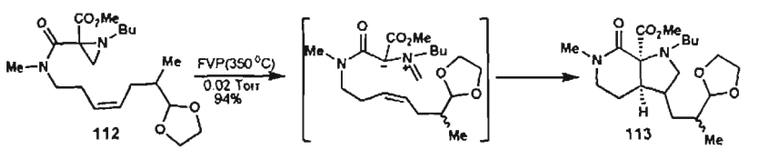
AMY derived from *N*-substituted pyridinium ion can be used to synthesis complex heterocyclic molecules. For the total synthesis of Lamellarin K **111**, a marine natural product, Banwell and co-workers used isoquinoline based AMY cycloaddition for the construction of the central pyrrole moiety (Scheme 1.32).[74]



Scheme 1.32

1.8.3.2 From aziridines

Electrocyclic ring opening of aziridines through the breakage of C-C bond offers a method for the generation of AMY at high temperature as observed by Heine and Huisgen in 1960s and will add to alkenes and alkynes.[75] Heathcock and co-workers used the aziridine **112**, incorporating an alkene as the internal dipolarophile, for AMY cycloaddition as a means of constructing the core **113** of Sarain natural product as depicted in scheme 1.33.[76]

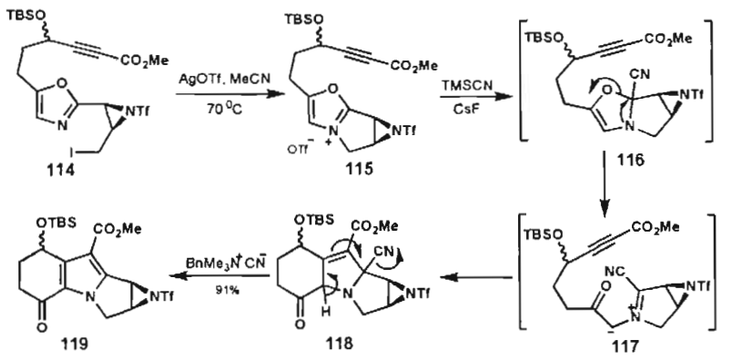


Scheme 1.33

1.8.3.3 From heterocycle

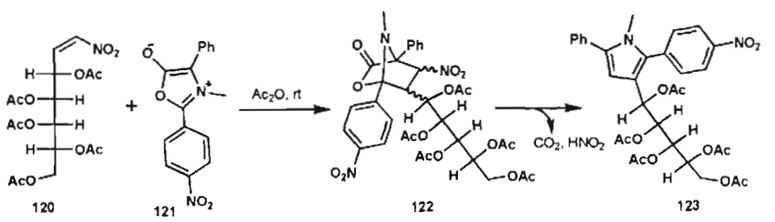
Pyrolysis of acyl aziridine has led to the concept aziridine/ylide/4-oxazoline tuatomeric equilibrium and the rearrangement of 4-oxazoline, accomplished by a nucleophilic addition to oxazole, became an alternative

precursor to AMY generation. In an enantiocontrolled route to the synthesis of aziridinomintosene, Vedejs and co-workers used a silver triflate- promoted internal alkylation of the 4-oxazole **114** with the iodide subunit, gave the 4-oxazolium salt **115**, which then underwent ylide generation/ cycloaddition/HCN loss in the presence of benzyl trimethyl ammonium cyanide to give the pyrrole **119** in 91% yield (Scheme 1.34).[77]



Scheme 1.34

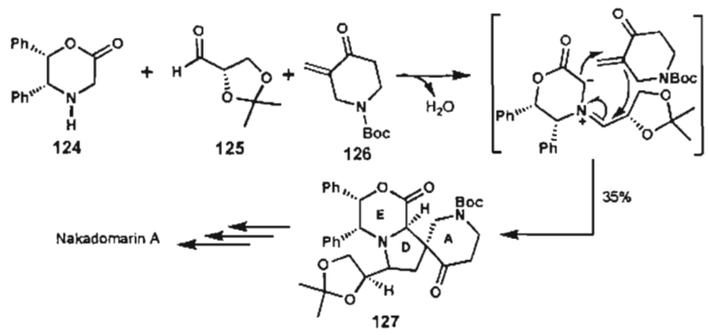
Munchnone **121** or meso-ionic Δ^2-oxazolium-5-oxide is known to behave like cyclic AMY and can undergo 1,3 dipolar cycloaddition with alkenes and alkynes to form pyrroles and pyrrolines, respectively with the elimination of a carbon dioxide molecule. The dipolar cycloaddition reaction of 3-methyl-2-(4-nitrophenyl)-4-phenyl-1,3-oxazolium-5-olate **121** and chiral nitroalkene **120** derived from D-*galacto*- and D-*manno*-hept-1-enitols were found to proceed in a regiospecific manner to afford acyclic pyrrole *C*-nucleosides **123** in a satisfactory yield (Scheme 1.35).[78]



Scheme 1.35

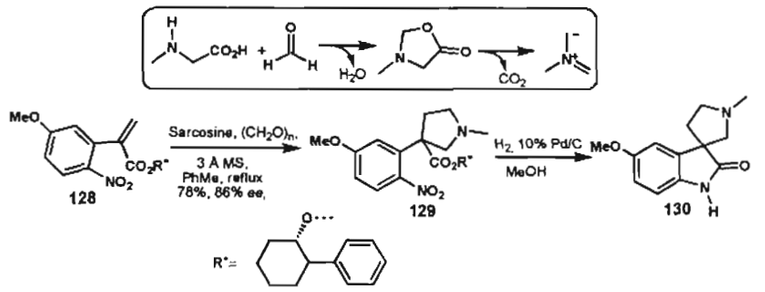
1.8.3.4 From aldehyde

The simplest approach to generate an azomethine ylide is the reaction of a secondary amine with electron withdrawing substituent at α-position such as carboxylic ester group, with an aldehyde as reported by Confalone and co-workers.[79] A number of aldehydes react with secondary amine and undergo easy deprotonation in a non-polar solvent. For the asymmetric synthesis of the ADE fragment **127**, especially the AD-spirocyclic system of Nakadomarin A, a naturally occurring alkaloid from *Amphimedon* sponge, Williams and co-workers used an asymmetric azomethine ylide derived form diphenyl morpholinone **124** as described in scheme 1.36.[80] The AMY generated is stabilized as it contains an electron withdrawing group that can be stabilized *via* charge delocalization.



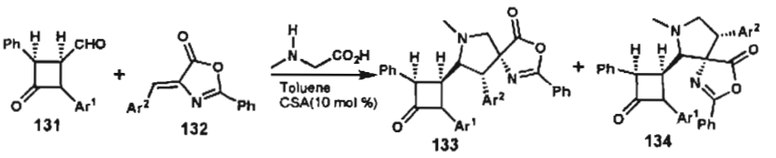
Scheme 1.36

Thermal decarboxilative route, as reported by Tsuge *et al.*[81], is a well known and widely used method for the generation of unstabilized AMY from an aldehyde and an α-amino acid and its cycloaddition with an alkene or alkyne offers a good method for the generation of pyrrolidine ring. This has been well investigated by Grigg and co-workers using a variety of aldehydes and amino acids in toluene or in DMF.[82] [3+2]-cycloaddition of AMY, derived form sarcosine and paraformaldehyde, to nitroaryl substituted chiral acrylate **128** forms the key intermediate for the total synthesis of (-)-Horsfiline. [83] Resultant pyrrolidine **129** on reductive cyclization yielded **130** (Scheme 1.37).



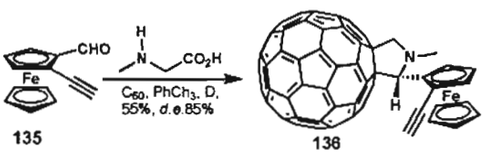
Scheme 1.37

In 2005, Raghunathan *et al.* used an AMY, derived from β-lactam substituted aldehyde **131** and sarcosine, for the cycloaddition to (Z)-2-phenyl-4-arylidine-5-(4H)-oxazoline **132** to yield two regioisomeric spiro cycloadducts **133** and **134** catalyzed by camphor sulphonic acid (CSA) (Scheme 1.38).[84]



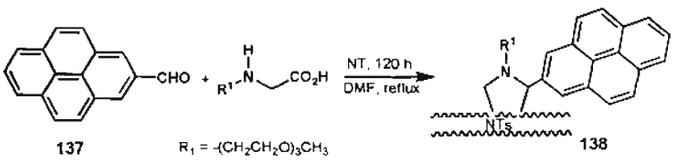
Scheme 1.38

Asymmetric synthesis of chiral ferrocenyl fulleropyrrolidine **136** has been achieved from azomethine ylide tethered to ferrocene, and its cycloaddition to fullerene as reported by Raint *et. al* and the methodology has been applied to the preparation of a C_2-symmetric enantiopure fullerene dimer (Scheme 1.39).[85]



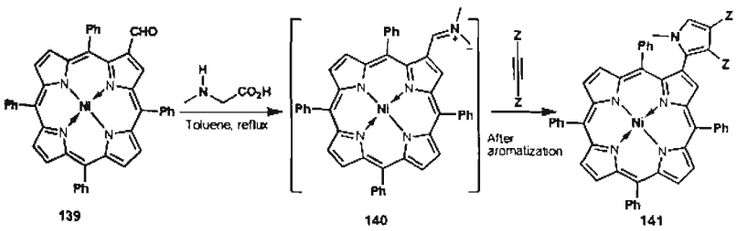
Scheme1.39

AMY generated from pyrene aldehyde **137** and modified glycene underwent cycloaddition with both single walled (SWNT) and multi walled nanotubes (MWNT) in refluxing DMF for 120 hours which has led to high level of solubility and aggregation to both SWNT and MWNT (Scheme 1.40).[86]



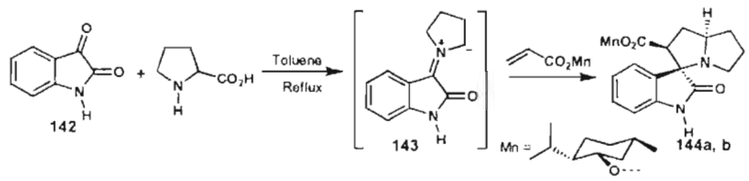
Scheme 1.40

Reed and co-workers reported the *in situ* generation of AMY **140** from the reaction (*β*-formyl-meso-tetraphenylporpyrinato)-nickel (II) **139** with *N*-methyl glycene and its cycloaddition to fullerene.[87a] Later, Cavaleiro *et al.* synthesized *β*-substituted meso-tetrahydroporphyrin using the ylide **140** with various dipolarophile. When dimethylacetelene dicarboxylate (DMAD) was used as dipolarophile, the cycloadduct thus formed was aromatized to pyrrole **141** (Scheme 1.41).[87b]



Scheme 1.41

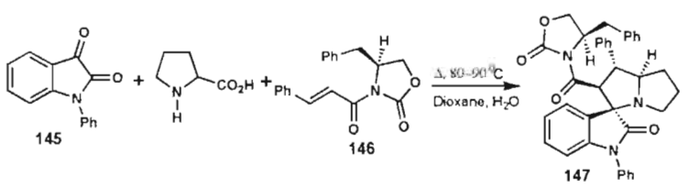
Isatin (1H-indole-2,3-dione) **142** when reacted with amino acid such as pipecolic acid, proline, sarcosine, *etc.*, furnished cyclic azomethine ylide **143**, which reacts with a verity of dipolarophile yielded spiropyrrolidine oxindole derivatives.[88] Asymmetric version of the reaction has been reported by appending a chiral tether to the ester moiety of the acrylate. Isatin, proline and (1R, 2S, 5R) menthylacrylate reacted stereo- and regioselectively in boiling acetonitrile to give a 9:1 mixture diastereomers **144a** and **144b** in 85% in combined yield. The structure of the major isomer (2R, 3S, 5R) was confirmed by single crystal X ray analysis (Scheme 1.42).[89]



Scheme 1.42

According to Pardasani *et al.*, geometry optimization studies have shown that AMY possesess a planar structure and instead of envelop structure and proline ring is planar and lies in the same plane of the oxindole moiety. During cycloaddition, due to the inward movement of the proline and thus the steric hindrance with the isatin ring, the possibility of front side attack is ruled out. Both the HOMO and LUMO of the dipole show uneven distribution of electron density along with the C-N-C dipole. In the HOMO case, the orbital co-efficient is larger at C_1 than C_2. The dipolarophile favours the endo approach.[90]

Synthesis of enantiomerically pure spirooxindole **147** was achieved by Ganguly *et al.* by the reaction of isatin **145**, proline and a chiral cinnamamide derivative **146** on heating at 80 - 90 ^{0}C in dioxane - water solvent system (Scheme 1.43).[91]



Scheme 1.43

1.9 Present Work

Literature presented above shows the novel and potential synthetic applications of Morita-Baylis-Hillman adducts due to the presence of diverse functional groups in it. Strucutrally, the MBH adduct is a homoallylic alcohol and can undergo a variety of reactions. The 1,3-dipolar [3+2]-cycloaddition reactions of MBH adducts with AMY are less explored in the literature. The focal theme of the thesis is the novel synthetic transformations of MBH adducts

of isatin with AMY's. Isatin is a pharmacologically important molecule and can form MBH adduct as it possess an electrophilic carbonyl group. Isatin readily undergoes MBH adducts formation with a verity of electrophiles. However, the chemistry and synthetic use of isatin derived MBH adducts have not been well explored till 2005. We have initiated the search of synthetic use of isatin derived MBH adducts and the results are presented as part of this research work.

Accordingly, the first phase of the thesis deals with the synthesis of novel spiro heterocyclic oxindole from MBH adducts of isatin. Sepecifically, the synthesis of novel spiropyrrolidine and spiropyrrolizidine bis- and mono-oxindoles were achieved from MBH adducts of isatin and heteroaldehydes with azomethine ylide (AMY) 1,3- dipolar cycloaddition reaction is discussed in the Chapter 2. As an extension of the cycloaddition study, the synthesis of dispiropyrrolidine and dispiropyrrolizidine oxindoles from isomerised MBH adducts by the azomethine ylide [3+2]-cycloaddition forms the subject matter of the Chapter 3. Bromo isomerised MBH adducts have been successfully used as nucleophilic partner for indium mediated carbonyl addition for the synthesis of 3-spirolactone oxindolole has been described in the Chapter 4.

The second phase of the thesis involves a study on silicachloride catalyzed functionalization of simple MBH adducts for the synthesis of trisubstituted alkenes appended with allyl chlorides, aryls and ethers. The details are presented in Chapter 5.

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CHAPTER 2

Synthesis of 3-Spiropyrrolizidine and 3-Spiropyrrolidine Oxindoles from MBH Adducts of Isatin and Heteroaldehydes *via* Azomethine ylide [3+2]-Cycloaddition

2.1 Introduction

Polycyclic nitrogen-containing heterocycles are found as basic skeleton of numerous alkaloid natural products and physiologically active compounds.[1] Spiro heterocyclic compounds are quite interesting among them as they possess unique spiro fusion between rings and often the spiro centers are responsible for the biological activity. Based on the structural motifs derived from tryptamine, the spirooxindole alkaloids belong to a family of natural products and that were first isolated from plants of the *Apocyanacae* and *Rubiaceae* families (Figure 2.1).

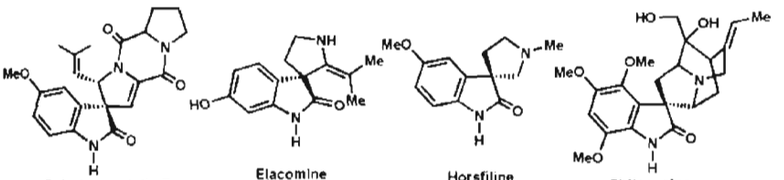


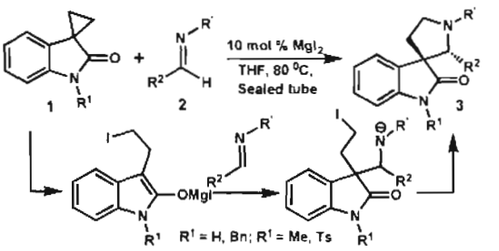
Figure 2.1: *Natural products with spirooxindole core structure*

Oxindoles derivatised at C3 as spirocarbo- and heterocyclics, spirolactones and spirocyclic ethers are elegant targets in organic synthesis due to their significant biological activities.[2] Construction of these molecular architectures became important as it forms the structural motifs of many of the naturally occurring molecules and served as potential synthetic intermediates for the total synthesis of alkaloids, drug intermediates *etc.*[3] Hence, it is important to update the literature on various methods of synthesis and applications of spirooxindole derivatives. The following section describes the literature-known methods for the construction of spirooxindoles.

2.1.1 Recent reports towards the synthesis of spirooxindoles

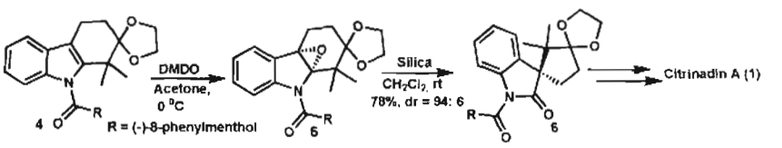
A number of synthetic methods have been developed in pursuit of the spirooxindole structure including intermolecular alkylations,[4] palladium-catalyzed reactions,[5] cycloadditions[6] and sigmatropic rearrangements.[7]

A magnesium iodide catalyzed ring expansion of spirocyclopropane oxindole **1** with imine **2** was reported by Carreira and co-workers to access the pyrrolidinyl spirooxindole structure **3** in which the dual role of MgI_2 as Lewis acid activation as well as a nucleophilic counter ion to promote ring expansion, has also been proposed.[8a] Later, the same authors have applied this strategy for the synthesis of natural products such as Horsfiline[8b], Strychnofoline[8c,d] and Spirotryprostatin B (Scheme 2.1).[8c]



Scheme 2.1: *Synthesis of* **3** *via* MgI_2 *catalyzed ring expansion reaction*

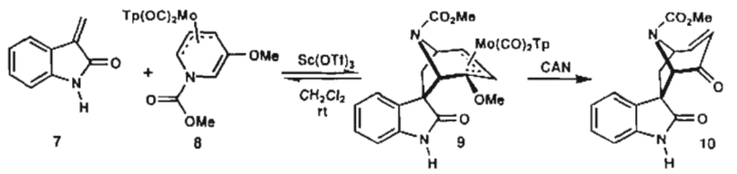
Recently, Martin *et al.* have shown an oxidative rearrangement of 2,3-disubstituted indole **4**, with a chiral 8-phenylmenthol, to afford the spiro-oxindole ring system **6** of Citrinadin A, a natural product isolated from *Pencillium citrinum*, with an excellent control over absolute stereochemistry at the spiro center as shown in scheme 2.2.[9] Dimethyl dioxirane (DMDO) oxidises **4** to its epoxide **5** which on silica catalyzed rearrangement afforded **6**.



Scheme 2.2: *Silica catalyzed rearrangement of epoxide* **5**

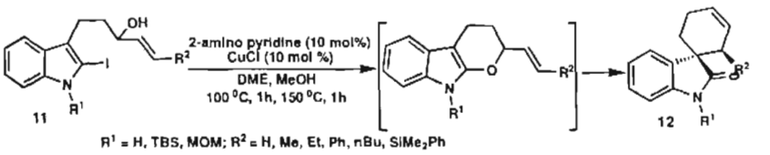
An enantio controlled synthesis of spirooxindole has been achieved by a [5+2] cycloaddition between 3-methelene-2-oxindole **7** and the pyridyl ring of

the pyridinyl-π-complex **8** to afford a spirooxindole complex **9** and then it was converted to the spiropyridine oxindole **10** by Liebeskind and Malinakova. The cycloaddition was found to be reversible using $EtAlCl_2$ (Scheme 2.3).[10]



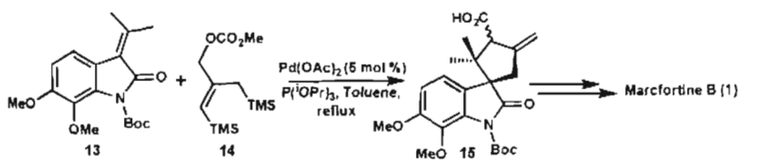
Scheme 2.3: *Synthesis of spirooxindole* **10** *via [5+2]-cycloaddition*

Kobayashi *et al.* adopted a copper chloride catalyzed Ullmann coupling followed by Claisen rearrangement of 2-haloindole **11**, tethered with a suitably spaced allyl alcohol at the 3 position, for the synthesis of 3-spiro-2-oxindoles **12**. The configuration of the product indicate that the Claisen rearrangement proceeds through a boat like transition state (Scheme 2.4). However, *cis* allyl alcohol did not give any product.[11]



Scheme 2.4: *Intramolecular Ullmann coupling and Claisen rearrangement*

Trost and Chan first demostrated the Pd catalyzed trimethylenemethane **14** (TMM) for [3+2]-cycloaddition reaction in 1979.[12a] For the total synthesis of Marcfortine B (1), an alkaloid isolated from various *Penicillium* species, Trost *et al.* used this TMM cycloaddition to indolidene **13** for the construction of the spirooxindole core **15** as explained in scheme 2.5.[12b]



Scheme 2.5: *TMM cycloaddition with indolidene*

All these synthetic advances have been fueled by the continued isolation of biologically active spirooxindole containing natural products. The common

structural feature of these molecules is the oxindole unit which can be derived from isatin **16** - a naturally occurring molecule (Figure 2.2). Isatin and its derivatives have been serving as potential synthons for alkaloids, drug intermediates and clinical pharmaceuticals.[13] Hence, the following section outlines a brief account on the synthesis and application of isatin in organic synthesis.

2.1.2 Isatin

Isatin **16** (1H-indole-2,3-dione, Figure 2.2), a naturally occurring compound[14a] was first obtained by Erdman and Laurent in 1841 as a product from the oxidation of indigo by nitric and chromic acids.[14b] The synthetic versatility of isatin has led to the extensive use of this compound in organic synthesis owing to the biological properties of its derivatives.

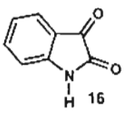
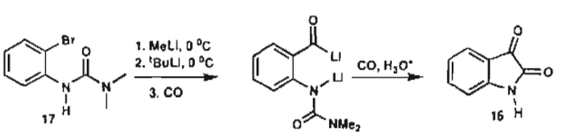


Figure 2.2: *Isatin*

2.1.3 Synthesis of Isatin

Several reports are known for the synthesis of isatin **16** in its substituted and unsubstituted form.[15] The most recent one involves a metal-halogen exchange method in which the synthesis of isatin was achieved by lithiation of *ortho*-bromophenylurea **17**, carbonylation and subsequent intramolecular cyclization to give **16** in 79% yield (Scheme 2.6).[15c]



Scheme 2.6: *Synthesis of isatin*

2.1.4 Reactivity of isatin toward heterocycles synthesis

Many synthetic methodologies have been described for the conversion of isatins to other heterocyclic systems. The reactivity patterns of the isatins have been studied extensively by several groups and are summarized as follows.

a) Reduction of the heterocyclic ring, leading to indoles and their derivatives.

b) Oxidation of the heterocyclic ring: Conversion of isatin to isatoic anhydride and its subsequent conversion to other heterocyclic systems.

c) Nucleophilic addition at position C-3, which may be further manipulated by a cyclization process, with or without N1-C2 bond cleavage or by a *spiro*-annulation at position C-3.

d) Nucleophilic substitution at position C-2, leading to the opening of the heterocyclic ring. This process may be followed by an intramolecular or by an intermolecular *exo-trig* cyclization.

A pictorial representation of the synthetic transformations of isatins to other carbo- and heterocyclic compounds is outlined in figure 2.3.[14]

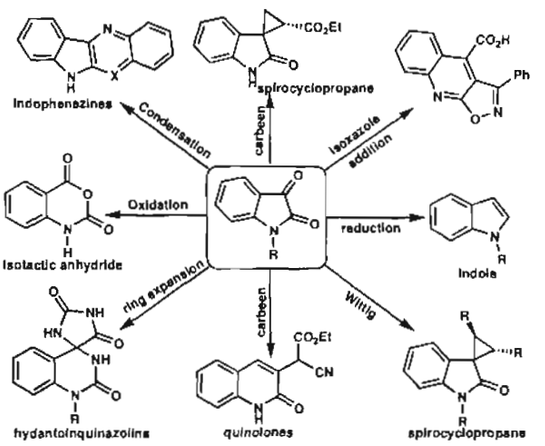
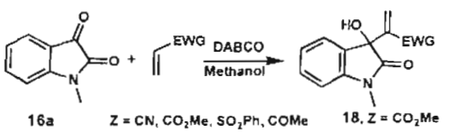


Figure 2.3: *Isatin: synthetic application towards heterocycles*

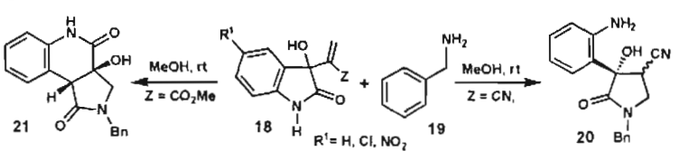
2.1.5 Synthesis of MBH adduct from isatin

It is generally accepted that ketones form MBH adducts under relatively extreme conditions, with a few exceptions. Simon J. Garden and Janet M. S. Skaklep first reported that isatin derivatives readily react with acrylic acid derivatives in ethanol and or ethanol/THF mixtures in the presence of a catalytic quantity of DABCO to give the MBH adduct **18** in excellent yields (Scheme 2.7).[16]



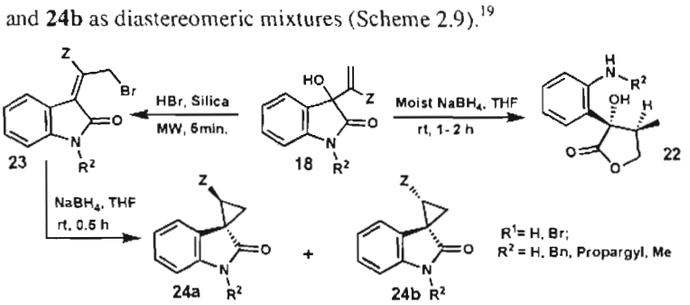
Scheme 2.7: *Synthesis of Morita-Baylis-Hillman adducts of Isatin*

Recently, Kim and co-workers reported the synthesis of 3-aryl-3-hydroxypyrrolidine-2-one **20** from MBH adducts of isatin **18** and acrylonitrile *via* a sequential Michael addition, condensation and ring opening pathway. Interestingly, when adducts derived from methylacrylate was used, a tricyclic product **21** was formed *via* recondensation and the formation of a new amide linkage (Scheme 2.8).[17]



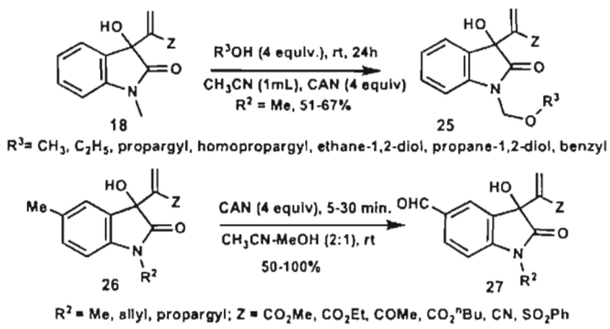
Scheme 2.8: *Synthesis of 3-aryl lactam*

Stereoselective synthesis of γ-butyro lactone **22** has been demonstrated by our group from MBH adduct of isatin **18** with sodiumborohydride *via* reductive cyclization protocol in moist THF (Scheme 2.9).[18] Interestingly, reductive cyclization of the bromo isomerised MBH adduct **23** with sodiumborohydride, on the other hand, yielded spiro-3-cyclopropane oxindoles **24a** and **24b** as diastereomeric mixtures (Scheme 2.9).[19]



Scheme 2.9: *Reductive cleavage to 3-aryl lactone and reductive cyclization to spirocyclopropane oxindole*

Cerium Ammonium Nitrate (CAN) is a well known *as a* single electron oxidiser. Recent investigations in our laboratory have uncovered the reactivity pattern of the isatin derived MBH adduct with CAN. When *N*-methyl isatin adduct **18** was treated with CAN and alcohol in acetonitrile, the *N*-methyl group underwent oxidation to ether **25** of the respective alcohol and the results were found applicable only with MBH adducts and not with simple *N*-methyl isatin, *N*-methyl spiro cyclopropane oxindoles, *N*-methyl isatin oximes, *etc.* Similar studies using the 5-methyl isatin adduct **26** resulted in 5-formyl substituted MBH adduct **27** which can further undergo a second Baylis-Hillman adduct formation at the formyl group (Scheme 2.10).[20]



Scheme 2.10: *CAN mediated oxidation of MBH adducts of isatin to ether and aldehyde derivatives*

2.2 Present Work

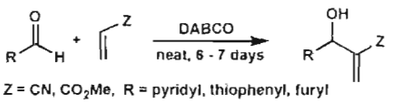
Morita-Baylis-Hillman adducts derived from isatin are highly functionalized, as it possess an oxindole moiety at the first position of the allylic alcohol and less attention has been devoted to the synthetic transformations of these adducts. Particularly, the double bond of the MBH adduct is highly activated due to disubstitution (the oxindole group and the electron withdrawing substitutent), can act as a dipolarophile for [3+2]-cycloaddition reaction with azomethine ylides (AMY) which eventually lead to the formation of pyrrolidine ring with an oxindole substitution. The detailed study on the 1,3-dipolar cycloaddition reaction of cyclic and acyclic azomethine ylides derived from decarboxylative condensation of isatin and

sarcosine (acyclic amino acid) or proline (cyclic amino acid), with double bond of MBH adducts derived from isatin, furfural and thiophene aldehyde is the subject matter of this chapter.

2.3 Results and Discussion

2.3.1 Preparation of MBH adducts

All the isatin derived MBH adducts for the present study were prepared from the corresponding isatin derivatives and activated alkenes following the literature procedures.[16] The heteroaryl MBH adducts were obtained by the DABCO catalyzed reaction of the respective hetero aldehydes with activated alkenes under neat condition (Scheme 2.11).



Scheme 2.11: *Preparation of MBH adduct*

The Morita-Baylis-Hillman adducts synthesised from isatin, pyridine, furan and thiophene aldehydes with various activated alkenes for the present study as depicted in figure 2.4.

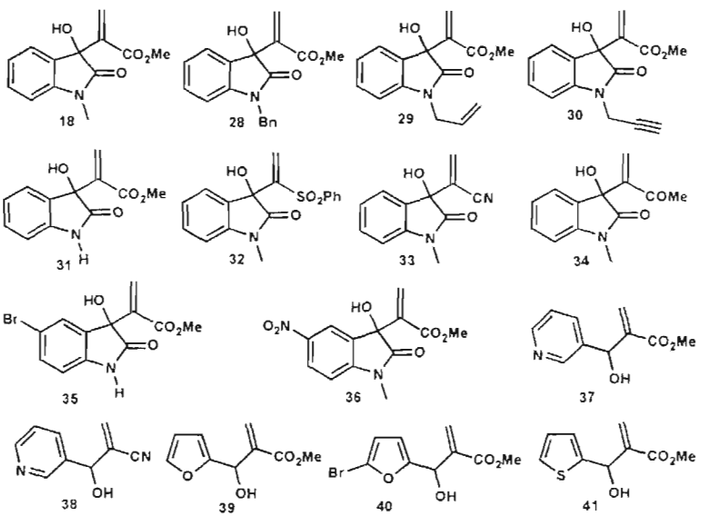
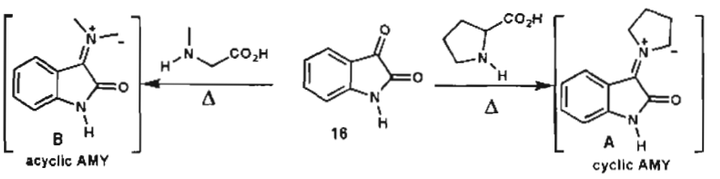


Figure 2.4: *MBH adducts of 1-substituted isatin and heteroaldehydes*

2.3.2 Generation of azomethine ylides (AMY)

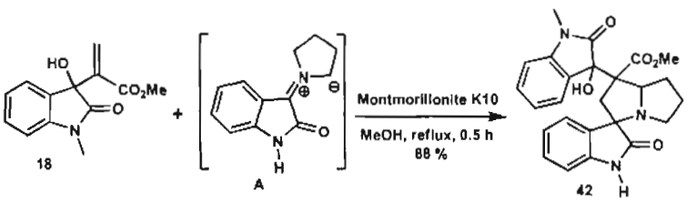
The AMYs used in the 1,3-dipolar cycloaddition reaction have generated *in situ* following Tsuge route[21] that is the thermal decarboxylative method. As per the procedure reported in the literature, the cyclic ylide **A** and the acyclic ylide **B** were generated form isatin **16** and proline (cyclic amino acid) and sarcosine (*N*-methyl glycine), respectively by refluxing in methanol with eco-friendly montmorillonite K10 clay catalyst (Scheme 2.12).



Scheme 2.12: *Generation of cyclic and acyclic AMYs*

2.3.3 Reaction of MBH adducts of isatin with cyclic AMY "A"

Preliminary studies were initiated by the reaction of MBH adduct of *N*-methylisatin **18** and *in situ* generated cyclic azomethine ylide **A** in methanol was refluxed for 0.5 hour with montmorillonite K10 clay catalyst. The reaction afforded spiropyrrolizidine oxindole derivative **42** in 88% yields after purification by column chromatography (Scheme 2.13). The cyclic AMY was generated *in situ* from isatin and proline by a thermal decarboxylative method.



Scheme 2.13: *Synthesis of spiro-pyrrolidine bis-oxindole*

The structure of the product **42** was confirmed by detailed spectroscopic analysis (IR, ^{1}H NMR, ^{13}C NMR and HRMS). Thus, FTIR of compound **42** showed the presence of ester and amide carbonyl groups due to absorptions at 1731 and 1720 cm^{-1} respectively and the hydroxyl group showed absorption at 3287 cm^{-1}. In the ^{1}H NMR spectrum (Figure 2.5), the six pyrrolizidine ring

protons were appeared as multiplets and doublets of doublets in the region of δ 1.34-2.86. A singlet at δ 3.20 with integration of three protons indicates the presence of methyl group attached to nitrogen. Two mutually coupled geminal protons of the pyrrolizidine ring were apparent as doublets, with a coupling constant J = 14.1Hz centered at δ 3.26 and 3.51, respectively. The methoxy protons were amenable at δ 3.46. The methine proton of the pyrrolizidine ring appeared as a doublet of doublet with coupling constants J = 6.3Hz, J = 8.4Hz centered at δ 4.90. In addition, the spectrum showed a broad singlet at δ 5.65 and a singlet at δ 8.37 and was discernible for the protons on hydroxyl and the amide group and these protons were found exchangeable with D_2O. All the aromatic protons were appeared as doublets and singlets in the region of δ 6.67-7.50.

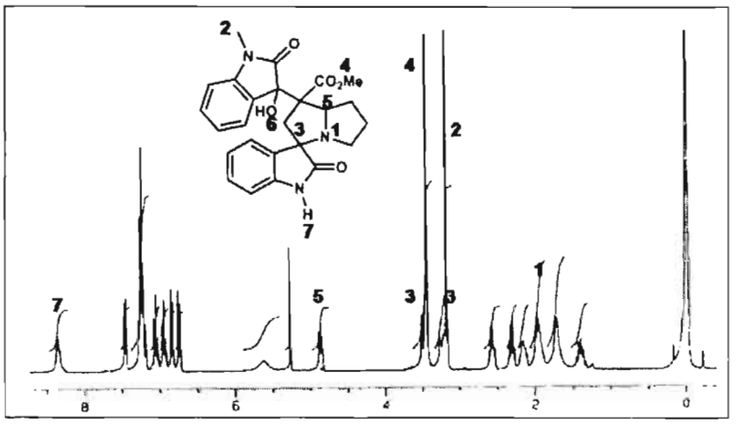


Figure 2.5: *^1H NMR spectrum of compound* **42**

Analysis of the ^{13}C NMR spectrum of **42** showed signals at δ 26.6 and δ 52.0 due to the methyl carbon attached to nitrogen of the oxindole moiety and the methoxy carbon of the ester group, respectively (Figure 2.6). The three quaternary carbons, attached to hydroxyl group, spiro carbon and the carbon attached to the ester group were visible at δ 75.6, 65.6 and 60.5 respectively and were confirmed by the DEPT-135 spectrum (Figure 2.7). The methylene carbons of the pyrrolizidine ring were observed at δ 26.6, 42.4, 43.0 and 60.3.

All the aromatic carbons were resonated between the range δ 107.9-144.2. The three carbonyl carbons *viz. a viz.* the ester and the two amide carbonyl of the oxindole moiety resonated at δ 182.2, 176.8 and 172.4 respectively. The structure was finally confirmed by the FAB mass spectral value as it showed the molecular ion peak at *m/z* = 448.65 (M+1).

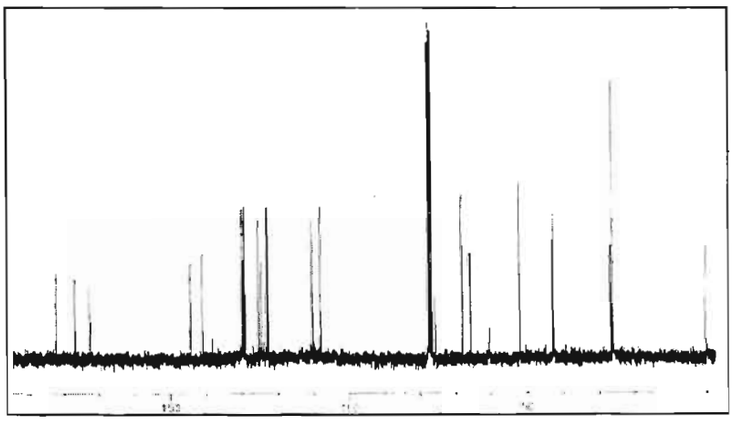


Figure 2.6: *^{13}C NMR spectrum of compound* **42**

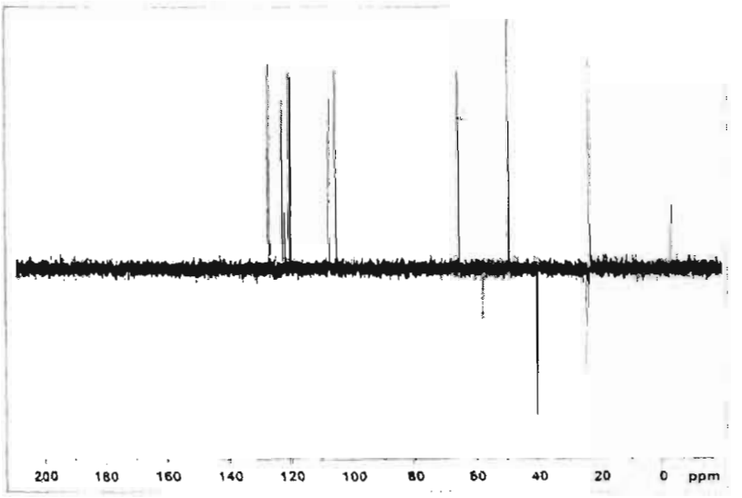


Figure 2.7: *DEPT-135 spectrum of compound* **42**

2.3.4. Optimization study: Effect of solvent and catalyst load

In order to check the effect of solvent and catalyst requirement, reactions in 1,4-dioxane, toluene and methanol as solvents and with and without montmorillonite K10 clay catalyst were tested. The MBH adduct **18** was used for the model study. After several test reactions, a combination of methanol as a solvent and 100% w/w and montmorillonite K10 clay catalyst gave better yields and found as optimum condition. Freshly activated clay at a temperature of 110 ^{0}C gave better yield than preactivated clay. Reaction in 1,4-dioxane provided same yield as that of methanol but longer reaction time was required. In toluene, poor yield of the product (~20%) was observed even with longer reaction time. At higher temperature, greater than 100 ^{0}C, adduct decomposed to the corresponding isatin especially when toluene was used as a solvent. The results are summarized in table 2.1.

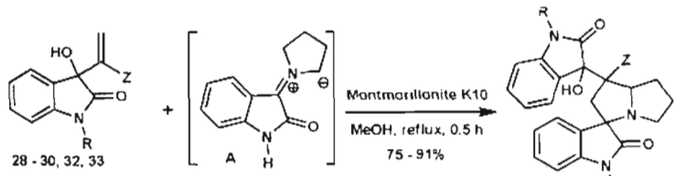
Table 2.1: Reaction of 18 with A; Effect of Solvent and Catalyst

Entry	Solvent[a]	Mont.K10(wt %)	Time	Yield (%)
1	1,4-Dioxane	-	1	80
2	1,4-Dioxane	100	1	85
3	Methanol	-	0.5	85
4	Methanol	100	0.5	88
5	Toluene	-	12	15
6	Toluene	100	12	20

a: Temperature 68 ^{0}C

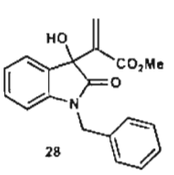
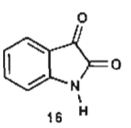
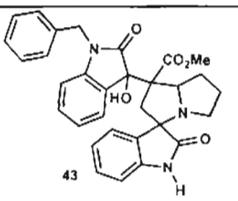
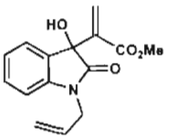
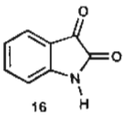
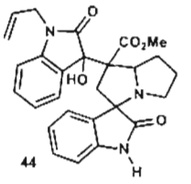
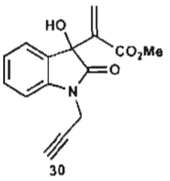
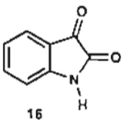
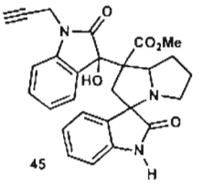
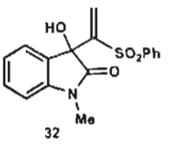
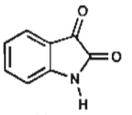
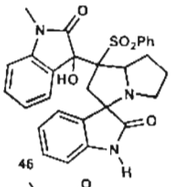
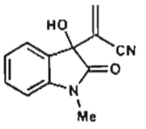
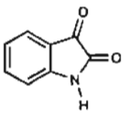
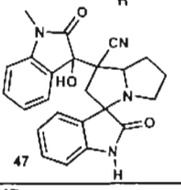
2.3.5 Generality of cycloaddition of cyclic AMY with MBH adducts

In order to exemplify the reaction with various MBH adducts, adducts **28-30, 32-33** were subjected to 1,3-dipolar cycloaddition with cyclic AMY(**A**) (Scheme 2.14) under optimized condition. All reactants underwent the [3+2] cycloaddition reaction smoothly and provided the corresponding highly functionalized spiropyrrolizidine bisoxindole derivatives **43 - 47** in good yields and the results are shown in table 2.2.



Scheme 2.14: *Synthesis of spiropyrrolizidine bis-oxindoles*

Table 2.2: Genarality of the cyclic AMY cycloaddition with various MBH adducts

entry	substrate	isatin	product	yield (%)
1	 28	 16	 43	85
2	 29	 16	 44	90
3	 30	 16	 45	89
4	 32	 16	 46	75
5	 33	 16a	 47	91[a]

a: Mixture of inseparable sterioisomers determined by ^{1}H NMR;

It should be noted that the 1,3-dipolar cycloaddition reaction repoted herein are tolarable with functional groups such as allyl, benzyl and propargyl substitutions in MBH adducts. The structure of *N*-propargyl spirooxindole derivative **45** was established by detailed spectral analysis. Thus, the proton NMR spectrum of compound **45** showed two separate multiplets in the chemical shift range δ 1.35-2.61 which were amenable to the pyrrolizidine ring protons and was merged with terminal alkyne proton. The isolated pyrrolidine ring protons were coupled mutually with a coupling constant J = 15Hz and appeared as two doublets. One of the protons has merged with the ester methoxy proton and appeared at δ 3.42 and the other was centered at δ 3.55. The two methelene protons of the *N*-propargyl group were observed as two doublets, with a coupling constant of J = 17.7Hz, and are centered at δ 4.15 and δ 4.79. A multiplet centered at δ 4.90 was indicative of the methine proton attached to the nitrogen of the pyrrolizidine ring. All the aromatic protons were resonated as multiplets in the chemical shift range δ 6.8-7.4. The hydroxyl proton was visible at δ 5.84 as a broad singlet and a singlet at δ 9.27 was amenable to amide proton (Figure 2.8).

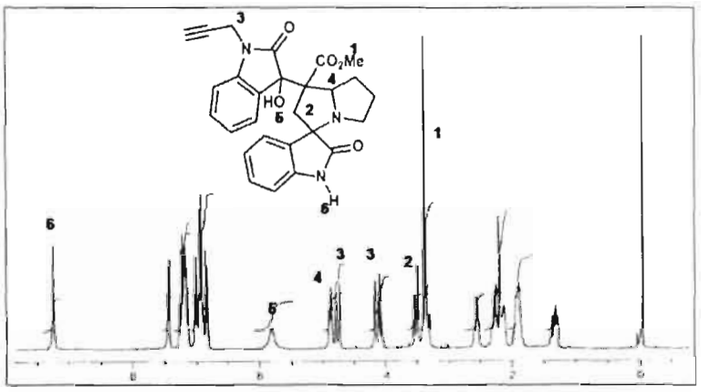


Figure 2.8: *^{1}H NMR of compound* **45**

The ^{13}C NMR spectrum of compound **45** showed a signal at δ 52.2 and was assigned to the methoxy carbon of the ester group. The carbon attached to the carbomethoxy group was seen at δ 60.2. The alkyne carbons resonated at δ

72.1 and δ 75.1. The spiro carbon was amenable to a signal at δ 68.1. The carbon attached with the hydroxyl group resonated at δ 76.5. The carbonyl carbons were visible in the downfield region and were discernible at δ 172.2, 175.6 and 182.4 (Figure 2.9). Final proof of the assigned structure was obtained from the FAB mass spectrum as it showed a molecular ion peak at *m/z* = 472.00 (M+1). The detailed spectral data of all the compounds are listed in experimental section given at the end of the chapter.

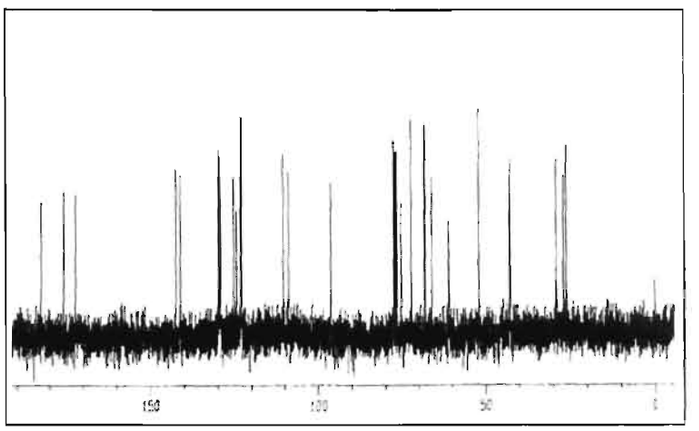
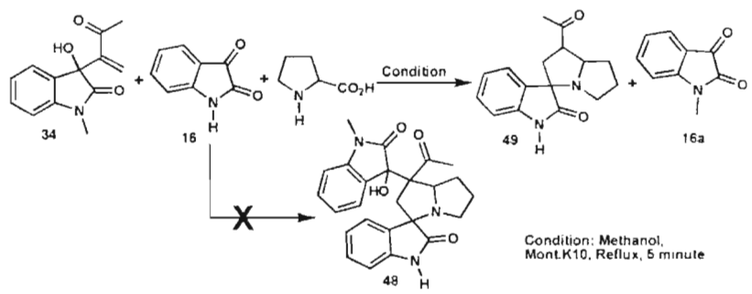


Figure 2.9: *^{13}C NMR of compound* **45**

2.3.6 Formation of spiropyrrolizidine mono-oxindole 49

When the adduct **34** derived from *N*-methylisatin and MVK was subjected to 1,3-dipolar cycloaddition with cyclic AMY under optimized condition, TLC showed that the reaction completed in 5 minutes and after column chromatography, isolated a crystalline solid in 60% yield together with *N*-methyl isatin **16a**. It was surprising that, from the proton NMR and the mass spectral data, the compound was identified as spiropyrrolizidine mono-oxindole **49** and not the expected spiropyrrolizidine bis-oxindole **48** (Scheme 2.15).



Scheme 2.15: *Formation of spiropyrrolizidine mono-oxindole*

The structure of the compound **49** was arrived based on spectroscopic studies. Thus, in the ^{1}H NMR spectrum of **49**, all the methelene protons were appeared as multiplets in the region of δ 1.63-3.12. Of which, the methyl protons of the acyl moiety were resonated at δ 2.24 as a singlet and the methine proton of the carbon attached to the acyl moiety was visible as a multiplet centered at δ 2.28. The methine proton attached to the pyrrolizidine ring was apparent as a multiplet centered at δ 4.15. All the four aromatic protons appeared as multiplets in the chemical shift range δ 6.96-7.29 and the proton of the amide nitrogen can readily be distinguishable at δ 9.30 as a singlet (Figure 2.10). Final proof of the structure was obtained on the basis of FAB mass spectrum as it showed a (M+1) peak at *m/z* = 271.41 (Figure 2.11).

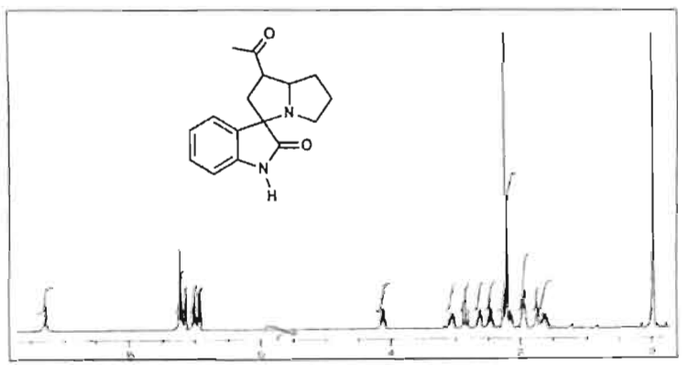


Figure 2.10: *^{1}H NMR of compound* **49**

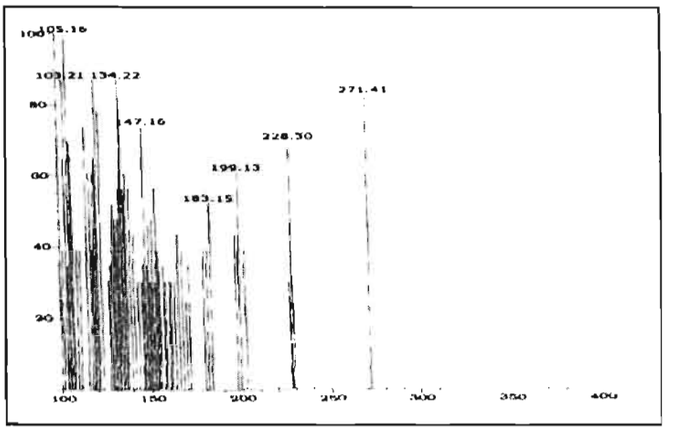
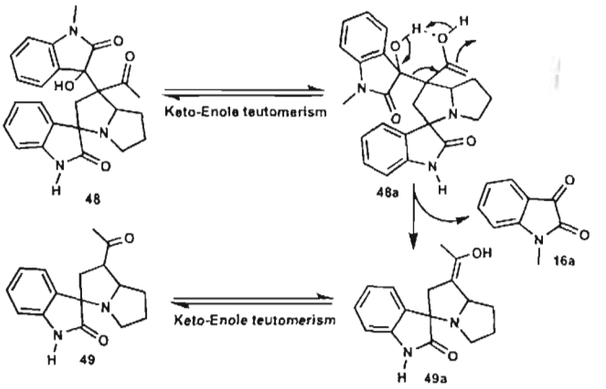


Figure 2.11: *FAB mass spectrum of compound* **49**

2.3.7 Formation of spiropyrrolizidine mono-oxindole 49: Mechanistic rationalization

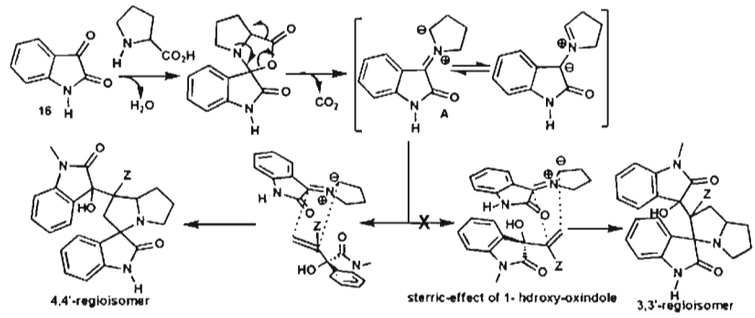
Formation spiropyrrolidine mono-oxindole **49** can be explained by a rearrangement followed by elimination through enol **48a**. Slightly acidic clay can enhance the enolization of the acyl group of the pyrrolizidine ring **48** and the enol is stabilized by the hydrogen bond with the hydroxyl group at the oxindole moiety. This is followed by an elimination of the parent isatin from which the MBH is formed gave **49** and steps involved is schematically represented in scheme 2.16.



Scheme 2.16: *Mechanism of the formation* **49** from **48**

2.3.8 Formation of spiropyrrolizidine bisoxindole: Mechanistic Postulate

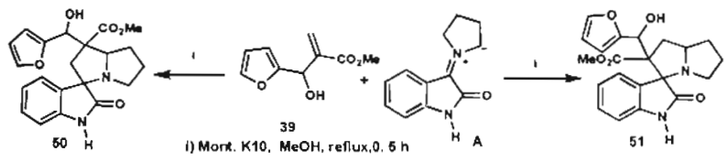
In an initial event, the reaction between isatin and proline forms the cyclic ylide **A**, *via* Tsuge route. Subsequent cycloaddition of unstabilized cyclic azomethine ylide **A** to the double bond of the MBH adducts of isatin affords the spiropyrrolizidine bis-oxindole. Rather than the secondary orbital interaction leading to the 3,3'-disubstituted pyrrolizidine, there exist two sterric factors which lead to the formation of the 4,4'-disubstituted pyrrolizidine. First factor is the sterric hindrance between the isatin ring and the proline ring of the azomethine ylide. Second factor is the hindrance offered by the 3-hydroxy oxindole which lie in a plane perpendicular to the plane of the double bond of the activated alkene (Scheme 2.17).



Scheme 2.17: *Mechanism for the formation of the 4,4-disubstituted spiropyrrolizidine bisoxindole*

2.3.9 AMY cycloaddition with MBH adducts of heteroaldehydes

Having excellent preliminary results, we then turned our attention to examine the reaction of MBH adducts derived from hetero aromatic aldehydes and cyclic azomethine ylide **A**. The MBH adduct **39** derived from furfural and methyl acrylate was treated with isatin, proline and Mont. K10 in refluxing methanol for 1.5 hours. It was interesting to note that instead of the formation of the expected 4,4'-disubstituted spiropyrrolizidine oxindole **50,** other regio isomer 3,3'-disubstituted spiropyrrolizidine oxindole **51** was obtained in 80% yield after column chromatography and spectroscopic analysis (Scheme 2.18).



Scheme 2.18: *Synthesis of 3,3'-disubstituted spiropyrrolizidine oxindole*

The overturn in regioselectivity and the structure of **51** was established by spectroscopic analysis. In the proton NMR spectrum of **51,** all the pyrrolizidine ring protons were appeared as well-separated multiplets in the region of δ 1.44-2.77. The other possible regio isomer **50** was ruled out because the pyrrolizidine methelene proton did not appear as two mutually coupled doublets as observed in the case of the reaction of **A** with isatin derived adducts as discussed earlier in this chapter. In addition, the methoxy protons of the ester group were visible at δ 3.70 and the proton of the hydroxyl group was seen at δ 1.89 as a broad singlet. A signal at δ 8.80 was amenable to the hydrogen of the amide linkage (Figure 2.12). The ^{13}C NMR spectrum showed a signal at δ 73.2 due to the presence of spiro carbon. The ester and the amide carbonyls were visible at δ 170.5 and 180.3 (Figure 2.13). All other carbon signals were consistent with the assigned structure. Final proof on the structure was arrived from its FAB mass spectrum as it showed molecular ion peak at *m/z* = 383.40 (M+1).

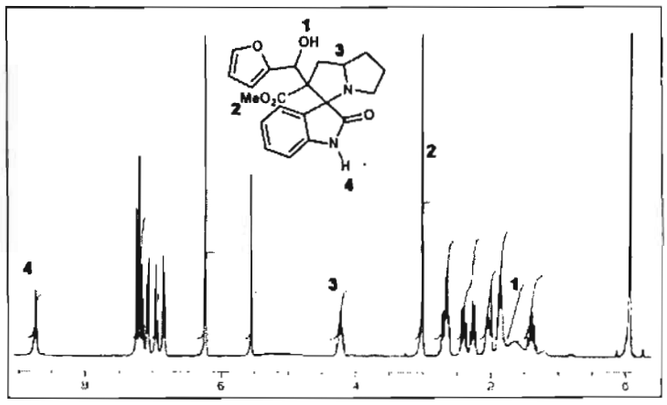


Figure 2.12: *^1H NMR spectrum of* **51**

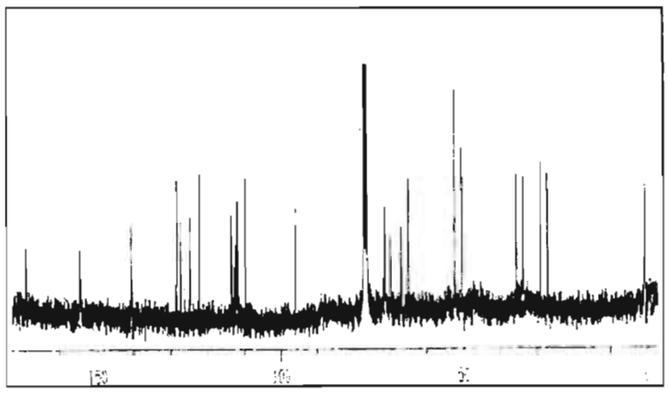
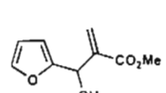
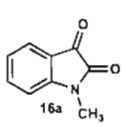
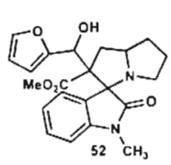
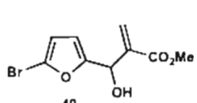
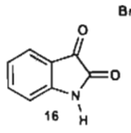
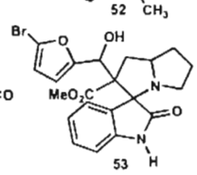
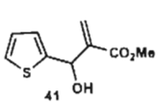
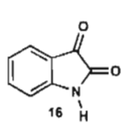
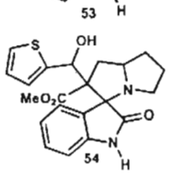


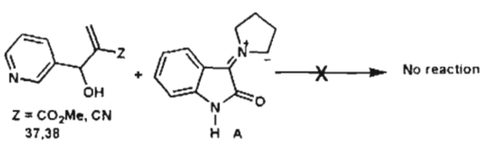
Figure 2.13: *^{13}C NMR spectrum of* **51**

Interesting results obtained from furfural derived adduct with cyclic ylide **A** prompted us to extend the cycloaddition studies to MBH adducts of other heteroaldehydes (**39-41**) with cyclic ylides generated from isatin **16** and *N*-methylisatin **16a**. These reactions under optimised reaction conditions furnished novel oxindole derivatives **52–54** with a 3'-heterocyclic (furan/thiophene) substituents in moderate to good yields as summarized in table 2.3.

Table 2.3: Genarality of the reaction with various heteroarylderived adducts

Entry	Substrate	Isatin	Product	Yield (%)
1	 39	 16a	 52	35
2	 40	 16	 53	60
3	 41	 16	 54	25

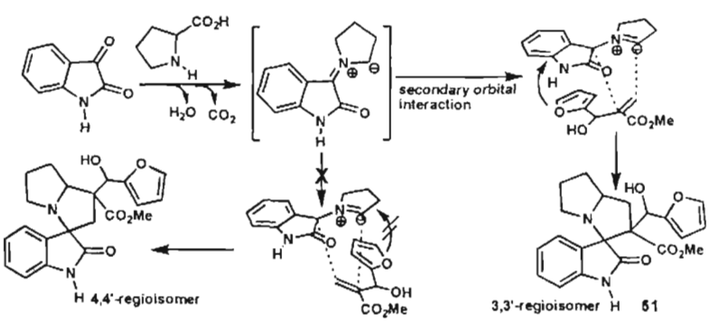
It is noteworthy that the pyridine derived MBH adducts **37** and **38** did not undergo cycloaddition with AMY even after several trails with variables such as solvent, temperature and reaction time (Scheme 2.19).



Scheme 2.19: *Attempted AMY cycloaddition of pyridine derived MBH adducts*

2.3.10 Formation of regioisomer 51: Mechanistic Postulate.

The dipole **A** was cyclo-added to the double bond of the MBH adduct **39** in a regioselective manner to afford the spiropyrrolidine oxindole **51**. In the case of isatin derived adduct, the sterric effect offered by the 3-hydroxy indole moiety directs the transition state in such a way to get the 4,4'-disubstituted-pyrrolidizine but in the case of heteroaryl derived MBH adducts, the extent sterric effect is less as the heterocyclic ring is in the same plane as that of the double bond. Thus, the observed 3,3'-regioisomer is formed exclusively (Scheme 2.20).

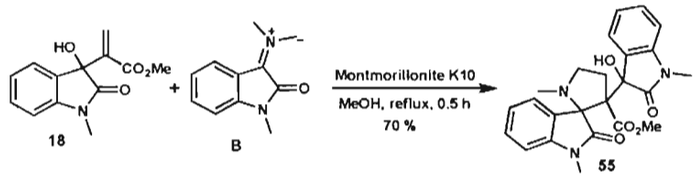


Scheme 2.20: *Mechanism of formation* **51**

2.3.11 Reaction of MBH adducts of isatin with acyclic AMY "B"

Subsequent to the preliminary study, we directed the study to [3+2]-cycloaddition reaction of MBH adducts with acyclic azomethine ylide **B** derived from sarcosine and isatin under optimized reaction conditions. Thus, the MBH adduct **18** derived from *N*-methylisatin was subjected to 1,3-dipolar cycloaddition reaction with acyclic AMY **B** (generated *in situ* from isatin and

sarcosine) under optimized condition afforded spiro cycloadduct **55** in 75% yield after purification (Scheme 2.21).



Scheme 2.21: *Synthesis of spiropyrrolidine bisoxindole*

The structure of **55** was determined on the basis of detailed spectroscopic analysis. Presence of ester and the amide carbonyl functional groups were confirmed by an IR absorption at 1723 cm^{-1} and at 1712 cm^{-1}, respectively and the absorption at 3272 cm^{-1} corresponds to the hydroxyl group. In the proton NMR spectrum, a broad singlet at δ 1.75 was indicative of the hydroxyl proton and the signal was found exchangeable with D_2O. Four singlets at δ 1.87, 2.98, 3.00 and 3.36 were assigned to protons at pyrrolidine nitrogen, the two amide nitrogen and the methoxy protons of the ester moiety, respectively. A multiplet centered at δ 3.20 was amenable to the mutually coupled four pyrrolidine ring protons. The aromatic protons were visible at the down field region of the spectrum in the chemical shift range δ 6.60-7.30 as shown in figure 2.14. The FAB mass analysis showed a molecular peak *m/z* = 435.97 which were exactly matching with the calculated value.

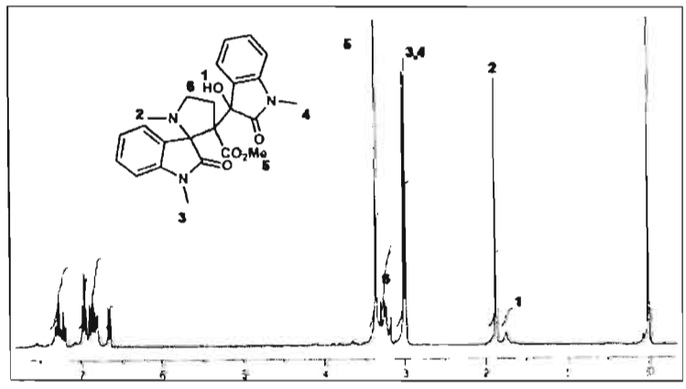


Figure 2.14: *^{1}H NMR spectrum of* **55**

In the carbon-13 NMR of **55**, the presence of the spiro carbon was confirmed from a peak observed at δ 67.1. All the sp^2 hybridized carbons were resonated in the region δ 107.5-144.2. Two methyl carbons of the amide linkage were seen at δ 28.5. Two peaks at δ 51.3 and 51.4 were discernable to the ester methyl carbon and the methelene carbon attached to the nitrogen. The amide and the ester carbonyls were confirmed with its resonance signals at δ 171.1, 175.9 and 178.1, respectively (Figure 2.15). All other carbons were identified as consistent to the assigned structure.

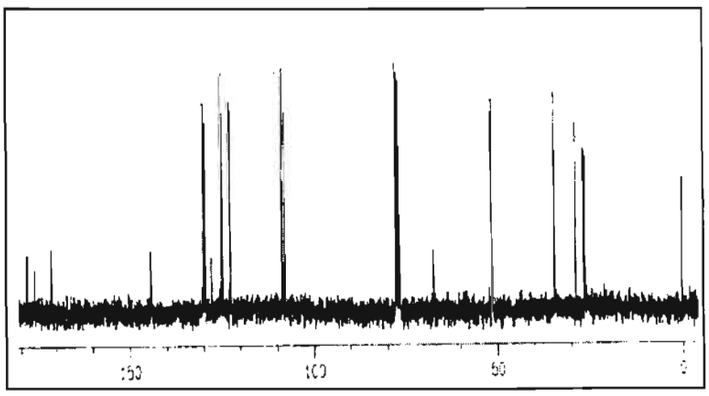
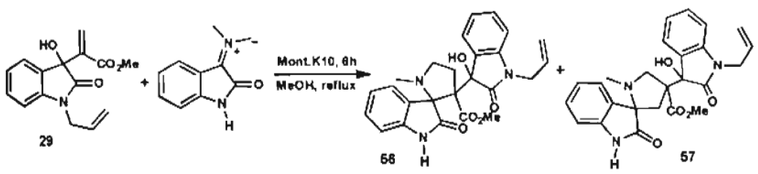


Figure 2.15: *^{13}C NMR spectrum of* **55**

It was interesting to note that when the MBH adduct **29** derived from *N*-allyl isatin was refluxed in methanol with acyclic azomethine ylide **B** in presence of Mont. K10 as catalyst for 6 hours, two regioisomers **56** and **57** were obtained 45% and 30% in yields, respectively (Scheme 2.22).



Scheme 2.22: *Formation of two regioisomers*

The structures of both the regioisomers **56** and **57** were confirmed by spectral studies. Both regioisomers **56** and **57** had a FAB mass of *m/z* = 448.31 (M+1) and were further characterized from their proton NMR spectrum as they

showed different coupling pattern of the pyrrolidine ring methelene protons as shown in figures 2.16 and 2.17. In the proton NMR spectrum of the 3,3'-disubstituted isomer **56**, a broad singlet at δ 1.71 was amenable to the hydroxyl group. The methyl protons of the amide nitrogen and the ester carbonyl were visible as singlets at δ 2.04 and 3.06, respectively. The four pyrrolidine methelene protons in the compound **56** was resonated as multiplets centered at δ 3.26. Two doublet of doublets centered at δ 4.10 (J = 6Hz and J = 18Hz) and 4.20 (J = 6Hz and J = 15Hz) was indicative of the allyl methelene protons at the amide nitrogen. A doublet centered at δ 5.12 with a coupling constant J = 10.2Hz and another doublet with a coupling constant J = 15.9Hz was agreeable to protons *cis* and *trans* to the methine proton. The methine proton resonated as a multiplet centered at δ 5.65 and the proton of the amide nitrogen appeared as a singlet at δ 8.55 (Figure 2. 16).

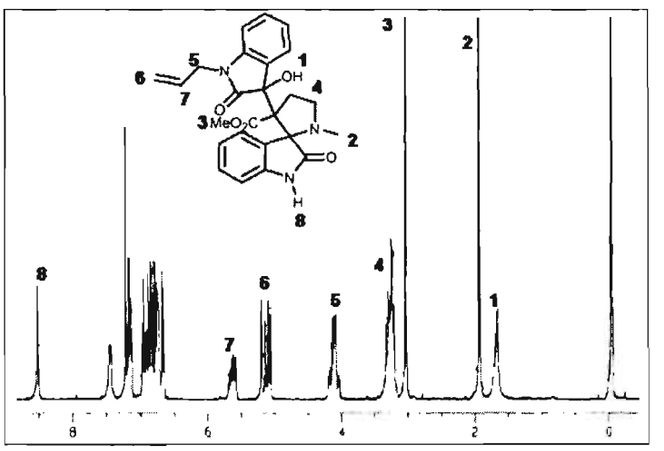


Figure 2.16: *^{1}H NMR spectrum of* **56**

Similarly, in the proton NMR spectrum of the compound **57**, all the pyrrolidine ring protons were appeared as well separated doublets. Two methelene protons attached to the spiro carbon resonated as two doublets centered at δ 3.07 and 3.29 with a coupling constant J = 15 Hz, while the methelene protons attached to the pyrrolidine nitrogen appeared as mutually

coupled doublets centered at δ 3.58 and merged with multiplet at 4.37 with a coupling constant J=12 Hz. One of these protons was found merged with the methelene protons attached to the amide nitrogen as shown in the figure 2.17.

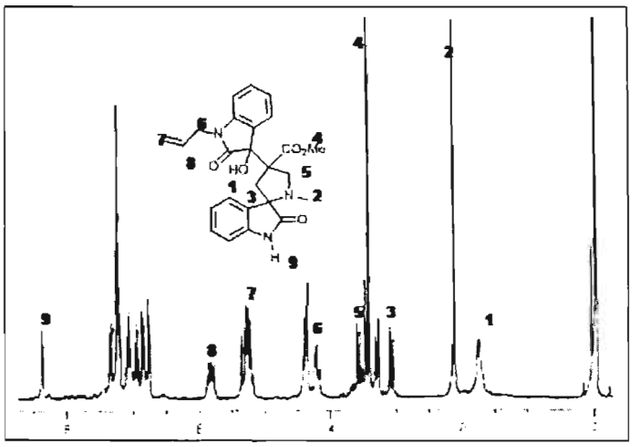
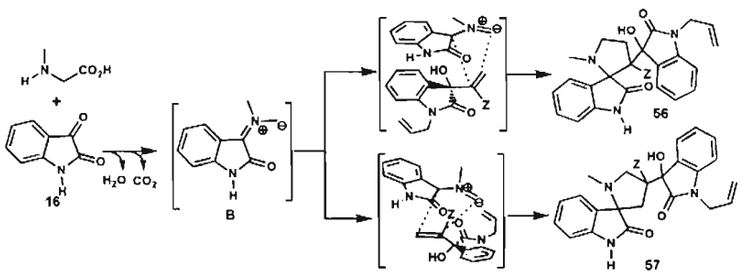


Figure 2.17: *^{1}H NMR spectrum of* **57**

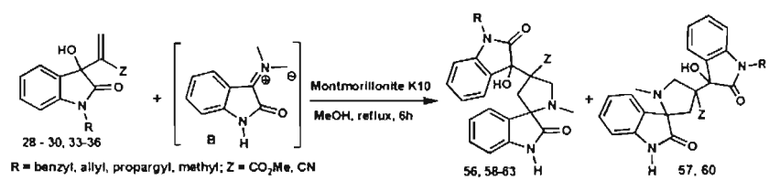
2.3.12 Formation of regioisomers 56 and 57: Mechanistic Outlook

The acyclic azomethine ylide **B** generated *in situ* by the decarboxylative condensation of isatin **16** and *N*-methyl glycene can undergo cycloaddition with MBH adduct **29**, regioselectively. The sterric effect during the formation of the pyrrolidine ring to the aryl ring of the oxindole moiety is nearly equal. Hence, during the cycloaddition, no sterric effect of the pyrrolidine ring will be there competing to the secondary interaction of the aryl ring of 1-hydroxy indole. However, in the case of *N*-allyl substituted oxindole MBH adduct another competing interaction of the double bond of the allyl group to the oxindole of the AMY exists. Thus, two possible orientation will be possible which results in the formation of two regioisomers **56** and **57** as explained in scheme 2.23.



Scheme 2.23: *Mechanism of formation of regioisomers*

To show the reaction is general in nature, a number of MBH adducts of isatin **23-30, 33-36** were reacted with AMY **B** under optimized condition. All the reactions underwent smoothly and provided mixture of regioisomers in excellent combined yield (Scheme 2.24; Table 2.4).



Scheme 2.24: *Generality of the reaction*

Table 2.4: Generality of the reaction with various MBH adducts with acyclic AMY "B"

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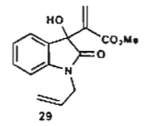
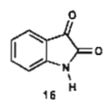
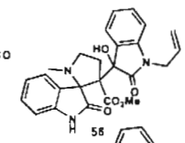
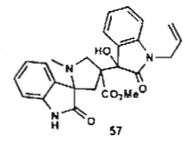
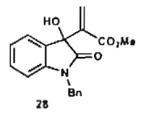
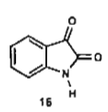
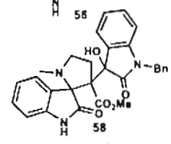
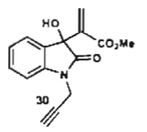
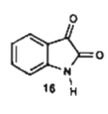
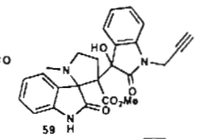
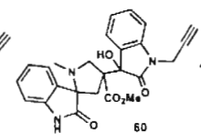
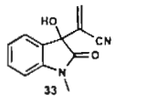
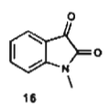
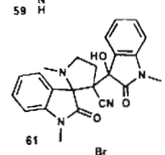
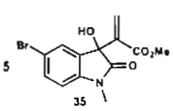
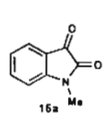
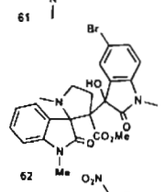
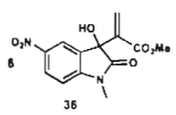
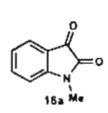
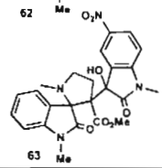
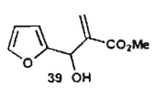
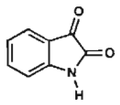
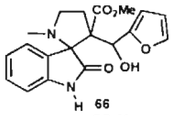
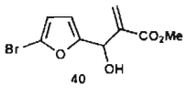
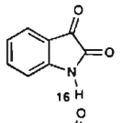
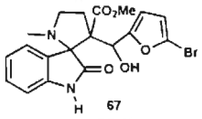
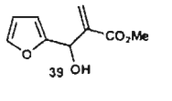
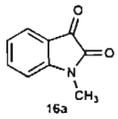
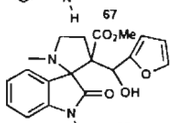
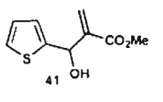
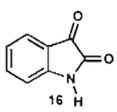
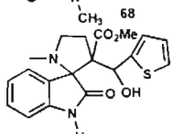
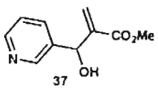
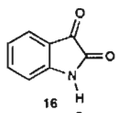
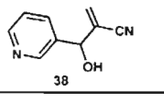
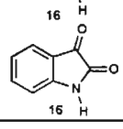
1	 29	 16	 56	 57	40	35
2	 28	 16	 58	-	70	-
3	 30	 16	 59	 60	40	36
4	 33	 16	 61	-	65	-
5	 35	 16a	 62	-	70	-
6	 36	 16a	 63	-	60	-

2.3.13 Cycloaddition reaction of MBH adducts of heteroaldehydes with acyclic AMY

The MBH adduct derived from heteroaldehyde underwent 1,3-dipolar cycloaddition reaction with acyclic AMY "**B**" providing the products similar to that of with cyclic AMY "**A**". However, the reactions were found low yielding as adducts found decomposing at the reaction temperature. To our dismay, pyridine derived adduct was intact for the cycloaddition reaction. The results are shown in table 2.5.

Table 2.5: Generality of AMY cycloaddition of heteroaryl derived MBH adducts

Entry	Substrate	Isatin	Product	Yield %
1	 39	 16	 66	68
2	 40	 16	 67	50
3	 39	 16a	 68	30
4	 41	 16	 69	22
5	 37	 16	-	-
6	 38	 16	-	-

2.4 Conclusion

1. We have developed an efficient synthetic route for the construction of functionalized spiropyrrolizidine and pyrrolidine oxindoles with oxindole and heteroaryl substituents starting from MBH adducts of isatin and heteroaldehydes *via* [3+2]-cycloaddition reaction with cyclic and acyclic azomethine ylides **A** and **B**.
2. The cyclic and acyclic ylides were generated *in situ* by Tsuge route *via* condensation followed by thermal decarboxylation.
3. The MBH adduct with substituents varied from 1-hydroxy-*N*-alkylindoles, 1-hydroxyl-1-hetero aryl-methyl, ester, cyano, and phenyl-sulphones were used for cycloaddition study.
4. All the products were characterized by spectroscopic methods

5. Formation of regioisomers was explained based on detailed mechanistic rationalization based on sterric and secondary orbital interactions during the cycloaddition.
6. Pyridine derived MBH adducts were intact during [3+2] cycloaddition reaction with AMYs.
7. The synthesized compounds were amenable to further synthetic transformation towards the total synthesis of many complex alkaloid natural products.

2.5 Experimental

General Considerations

All the reactions were carried out in oven-dried glassware. Progress of reactions was monitored by Thin Layer Chromatography (on glass plate coated with silica gel containing calcium sulfate as the binder; visualization was effected by exposure to UV light and iodine). Purification of crude compounds was done by column chromatography using silica gel (100-200 mesh) using hexane-ethylacetate mixture as eluent. NMR spectra were recorded at 300.1 MHz (^{1}H) and 75.3 MHz (^{13}C), respectively on a Brucker Avance DPX-300 spectrometer. Chemical shifts are reported in δ (ppm) relative to TMS (^{1}H) or $CDCl_3$ (^{13}C) as internal standards. FTIR spectra were recorded on Bomem MB series FT-IR spectrometer; absorbences are reported in cm^{-1}. FAB mass /HRMS were measured at the JMS 600 JEOL Mass Spectrometer. Yields refer to quantities obtained after chromatography.

General procedure for the preparation of MBH adducts of isatin

To a stirred solution of isatin (1 equiv.) and methyl acrylate (1.5 equiv.) in THF/methanol/ethanol (5 mL) was added DABCO (0.5 equiv.). The mixture was stirred at room temperature for 2-3 days. After completion, (monitored by TLC) the reaction mixture was diluted and washed with HCl (0.25 M, 50 mL), extract with ethyl acetate (3 X 20 mL), dried over Na_2SO_4 and then evaporated the solvent under reduced pressure. Purification of the crude mixture through

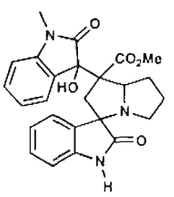
column chromatography (hexane/ethyl acetate mixture as eluent) afforded the MBH adducts in 70-95 % yields.

General experimental procedure for 1,3-dipolar cycloaddition

A mixture of MBH adduct (0.404 mmol), L-(-) proline (0.485 mmol), isatin (0.404mmol) and montmorillonite K-10 Clay (100% w/w) in methanol (1 mL) was refluxed. After the reaction (TLC), the crude mixture was filtered through a pad of celite and then purified by silica gel column chromatography (hexane/ethyl acetate mixture as eluent) to afford products in very good yields.

Synthesis of spiropyrrolizidine bisoxindole 42 from MBH adduct 18

Following the general cycloaddition procedure, a mixture of methyl 2-(3-hydroxy-1-methyl-2-oxoindolin-3-yl)-acrylate **18** (100 mg, 0.404 mmol), L-(-) proline (55 mg, 0.485 mmol), isatin (59 mg, 0.404 mmol) and montmorillonite K-10 Clay (100 mg, 100% w/w) in methanol (1 mL) was refluxed for 30 minutes to afford **42** in 88% yield (159.08 mg, eluent: 35% ethyl acetate:hexane).



42

IR (neat) ν_{max}: 753, 1091, 1347, 1470, 1614, 1720, 1731, 2950, 3287 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.34-1.47 (m, 1H), 1.97-2.07 (m, 2H), 2.13-2.43 (m, 1H), 2.29-2.37 (dd, 1H, *J* = 8.2 Hz, *J* = 15 Hz), 2.56-2.86 (dd, 1H, *J* = 8.1Hz, *J* = 13.1 Hz), 3.20 (s, 3H), 3.21-3.29 (d, 1H, *J* = 14.1 Hz), 3.46 (s, 3H), 3.49-3.54 (d, 1H, *J* = 14.1 Hz), 4.87-4.92 (dd, 1H, *J* = 6.3 Hz, *J* = 8.4 Hz), 5.65 (s, 1H), 6.67-6.78 (d, 1H, *J* = 9 Hz), 6.85-6.88 (d, 1H, *J* = 9Hz), 6.95-7.00 (t, 1H, *J* = 9 Hz), 7.05-7.01 (t, 1H, *J* = 6Hz), 7.21-7.30 (m, 3H), 7.47-7.50 (d, 1H, *J* = 9 Hz), 8.37 (s, 1H).

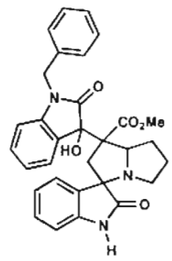
^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 26.6, 26.7, 42.4, 43.0, 52.0, 60.3, 65.6, 68.1, 75.6, 107.9, 110.2, 122.6,

123.1, 123.8, 124.4, 125.3, 128.9, 129.2, 129.61, 129.9, 140.9, 144.2, 172.4, 176.8, 182.2.

LRMS (FAB) for $C_{25}H_{25}N_3O_5$, Calcd (M^+): 447.48; Found m/z: 448.65 (M+1).

Synthesis of spiropyrrolizidine bisoxindole 43 from MBH adduct 28

Following the general procedure, a mixture of methyl 2-(1-benzyl-3-hydroxy -2-oxoindolin-3-yl)-acrylate **28** (100 mg, 0.309 mmol), L-(-) proline(42 mg, 0.371 mmol), isatin (45 mg, 0.309 mmol) and montmorillonite K-10 Clay (100 mg, 100% w/w) in methanol (1 mL) was refluxed for 30 minutes to afford **43** in 85% yield (137.58 mg, eluent: 30% ethyl acetate:hexane).



43

IR (neat) ν_{max}: 754, 1034, 1113, 1465, 1610, 1732, 2919, 3351 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.33-1.46 (m, 1H), 1.93-2.00 (m, 2H), 2.15-2.21 (m, 1H), 2.30-2.38 (dd, 1H, *J* = 8.1 Hz, *J* = 14.4 Hz), 2.63-2.71 (m, 1H), 3.11 (s, 3H), 3.36-3.41 (d, 1H, *J* = 15 Hz), 3.54-3.59 (d, 1H, *J* = 15 Hz), 4.76-4.81 (d, 1H, *J* = 15 Hz), 4.93-5.03 (m, 2H), 6.30 (s, 1H), 6.73-6.76 (d, 1H, *J* = 9 Hz), 6.87-6.91 (m, 2H), 7.01-7.06 (t, 1H, *J* = 6 Hz), 7.14-7.36 (m, 6H), 7.43-7.45 (m, 3H), 10.04 (s, 1H).

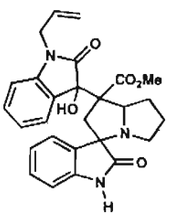
^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 25.4, 26.4, 42.1, 42.5, 43.3, 51.2, 60.7, 65.5, 67.5, 72.0, 74.5, 76.5, 108.2, 109.8, 111.1, 122.0, 122.0, 123.6, 124.6, 127.2, 127.5, 128.2, 128.6, 129.0, 129.2, 135.7, 141.4, 142.9, 172.0, 176.5, 181.5.

LRMS (FAB) for $C_{31}H_{29}N_3O_5$, Calcd (M^+): 523.21; Found m/z: 524.83 (M+1).

Synthesis of spiropyrrolizidine bisoxindole 44 from MBH adduct 29

Following the general procedure, methyl 2-(1-allyl-3-hydroxy-2-oxoindolin-3-yl)-acrylate **29** (100 mg, 0.365 mmol), L-(-) proline (50 mg,

0.439 mmol), isatin (53.7 mg, 0.365 mmol) and montmorillonite K-10 Clay (100 mg, 100% w/w) in methanol (1 mL) was refluxed for 30 minutes to afford **44** in 90% yield (155.6 mg, eluent: 35% ethyl acetate:hexane).



44

IR (neat) ν_{max}: 753, 1222, 1359, 1459, 1469, 1614, 1723, 2951, 3272 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.35-1.47 (m, 1H), 1.94-1.99 (m, 2H), 2.07-2.19 (m,1H), 2.19-2.36 (dd, 1H, *J* = 15 Hz, *J* = 8.1 Hz), 2.56-2.63 (dd, 1H, *J* = 8.1 Hz, *J* = 13.2 Hz), 3.27-3.31 (d, 1H, *J* = 14.1 Hz), 3.46 (s, 3H), 3.50-3.55 (d, 1H, *J* = 4.1 Hz), 4.19-4.26 (dd, 1H, *J* = 7 Hz, *J* = 15.9 Hz), 4.37-4.44 (dd, 1H, *J* = 5.1 Hz, *J* = 15.9 Hz), 4.89-4.89 (dd, 1H, *J* = 6Hz, *J* = 8.4 Hz), 5.20-5.23 (dd, 1H, *J* = 0.9Hz, *J* = 10.3 Hz), 5.32-5.38 (dd, 1H, *J* = 0.9 Hz, *J* = 17.1Hz), 5.69 (bs, 1H), 5.80-5.93 (m, 1H), 6.77-6.79 (d, 1H, *J* = 7.8 Hz), 6.86-6.89 (d, 1H, *J* = 7.5 Hz), 6.93-6.98 (t, 1H, *J* = 7.5 Hz), 7.04-7.09 (t, 1H, *J* = 6.9 Hz), 7.23-7.27 (m, 3H), 7.47-7.5 (d, 1H, *J* = 7.2 Hz), 8.81 (s, 1H).

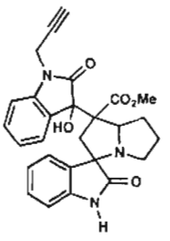
^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 26.0, 26.6, 42.4(2C), 43.0, 51.9, 56.0, 65.7, 68.1, 75.4, 76.5, 108.7, 110.1, 118.0, 122.5, 123.0, 124.4, 125.3, 129.1, 129.5, 129.7, 131.5, 140.8, 143.5, 176.4, 178.4, 182.0.

LRMS (FAB) for $C_{27}H_{27}N_3O_5$, Calcd (M^+): 473.19; Found m/z: 474.69 (M+1).

Synthesis of spiropyrrolizidine bisoxindole 45 from MBH adduct 30

Following the general procedure, a mixture of methyl 2-(3-hydroxy-2-oxo-1-(prop-2-ynyl)indolin-3-yl)acrylate **30** (100 mg, 0.404 mmol), L-(-) proline (55 mg, 0.485 mmol), isatin (59 mg, 0.404 mmol) and montmorillonite K-10 Clay (100 mg, 100% w/w) in methanol (1 mL) was refluxed for 30

minutes to afford **45** in 89% yield (169.3 mg, eluent: 35% ethyl acetate:hexane).



45

IR (neat) ν_{max}: 753, 1223, 1355, 1470, 1488, 1614, 1731, 1730, 2124, 2924, 3287, 3288 cm^{-1}.

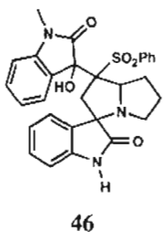
^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.35-1.42 (m, 1H), 1.92-1.96 (m, 2H), 2.14-2.33 (m, 3H), 2.59-2.63 (m, 1H), 3.42 (s, 4H), 3.53-3.58 (d, 1H, *J* = 15 Hz), 4.12-4.21 (d, 1H, *J* = 17.7 Hz), 4.76-4.83 (d, 1H, *J* = 17.7 Hz), 4.88-4.93 (m, 1H), 5.84 (bs, 1H), 6.80-7.20 (m, 4H), 7.21-7.27 (m, 3H), 7.45-7.48 (d, 1H, *J* = 7.2Hz), 9.27 (s, 1H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 26.9, 29.1, 42.6, 42.8, 52.2, 60.2, 68.1, 72.1, 75.1, 76.5, 96.1, 108.8, 110.4, 112.8, 123.1, 124.3, 125.2, 129.1, 129.2, 129.3, 129.4, 129.7, 141.0, 142.3, 172.1, 175.6, 182.4.

LRMS (FAB) for $C_{27}H_{25}N_3O_5$, Calcd (M^+): 471.10; Found m/z: 472.00 (M+1).

Synthesis of spiropyrrolizidine bisoxindole 46 from MBH adduct 32

Following the general procedure, of methyl 3-hydroxy-1-methyl-3-(1-(phenylsulfonyl)vinyl)indolin-2-one **32** (100 mg, 0.404 mmol), L-(-) proline (55 mg, 0.485 mmol), isatin (59 mg, 0.404 mmol) and montmorillonite K-10 Clay (100 mg, 100% w/w) in methanol (1 mL) was refluxed for 30 minutes to afford **46** in 75% yield (160.3 mg, eluent: 40% ethyl acetate:hexane).



46

IR (neat) ν_{max}: 751, 1094, 1139, 1304, 1470, 1613, 1727, 2925, 3274 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.42 (m, 1H), 2.08-2.13 (m, 2H), 2.15-2.18 (m, 1H), 2.31-2.33 (m, 1H), 2.72-2.79 (m, 2H), 3.25 (s, 3H), 3.48-3.64 (two d, 2H, *J* = 15 Hz,), 5.23 (bs, 1H), 6.33-6.35 (m, 1H), 6.51 (m, 1H), 6.77-6.79 (d, 1H, *J* = 6 Hz), 6.91-6.93 (d, 1H,

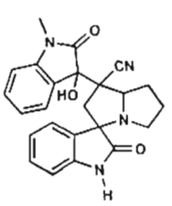
J = 6 Hz), 7.09-7.35 (m, 8H), 7.65-7.68 (d, 1H, J = 3 Hz), 8.40 (s, 1H)

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 21.0, 25.7, 26.3, 26.6, 42.1, 43.8, 65.3, 69.8, 78.2, 108.4, 110.4, 122.5, 123.7, 125.1, 125.5, 127.6, 128.3, 129.2, 129.3, 129.6, 130.3, 132.2, 140.6, 144.8, 171.1, 175.4.

LRMS (FAB) for $C_{29}H_{27}N_3O_5S$, Calcd (M^+): 529.61; Found m/z: 530.55 (M+1).

Synthesis of spiropyrrolizidine bisoxindole 47 from MBH adduct 33

Following the general procedure, a mixture of methyl 2-(3-hydroxy-1-methyl-2-oxoindolin-3-yl)acrylonitrile **33** (100 mg, 0.466 mmol), L-(-) proline (64.4 mg, 0.559 mmol), isatin (68 mg, 0.466 mmol) and montmorillonite K-10 Clay (100 mg, 100% w/w) in methanol (1 mL) was refluxed for 30 minutes to afford **47** in 91% yield (175 mg, eluent: 60% ethyl acetate:hexane).



47

IR (neat) ν_{max}: 760, 822, 1026, 1471, 1614, 1648, 1722, 2125, 2251, 2679, 3260, 3430 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 0.83-0.88 (m, 1H), 1.25-1.29 (m, 1H), 1.72-1.77 (m, 3H), 1.90-1.96 (m, 3H), 2.11-2.13 (m, 1H), 2.15-2.17 (m,1H), 2.42-2.47 (m, 1H), 2.54-2.61(m, 1H), 2.66-2.71 (2.81-2.91), 3.23 (s, 3H), 3.25 (s, 3H), 3.62-3.67 (d, 1H, J = 15Hz), 3.76-3.81 (d, 1H, J = 15Hz), 4.36-4.40 (m, 1H), 4.50 (bs, 1 H), 4.71-4.75 (m, 1H), 5.73 (bs, 1H), 6.85-6.91 (m, 4H), 7.05-7.14 (m, 4H), 7.26-7.29 (m, 2H), 7.36-7.39 (m, 2H), 7.41-7.52 (m, 4H), 7.85 (bs, 1H), 8.09 (bs, 1H).

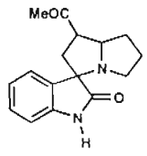
^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 15.8, 22.1, 22.5, 26.3, 26.8, 26.9, 28.4, 29.5, 43.8, 44.1, 45.0, 45.8, 51.0, 53.0, 53.1, 66.1, 66.9, 67.0, 75.3, 75.4,

108.2, 108.4, 110.4, 122.2, 122.6, 122.7, 124.8, 125.0, 125.5, 126.1, 127.2, 128.5, 129.0, 129.2, 130.3, 141.6, 143.3, 143.8, 174.9, 175.1, 180.3, 180.4.

LRMS (FAB) for $C_{24}H_{22}N_4O_3$, Calcd (M^+): 414.17; Found m/z: 415.58 (M+1).

Synthesis of spiropyrrolizidine monooxindole 49 from MBH adduct 34

Following the general procedure, a mixture of methyl 3-hydroxy-1-methyl-3-(3-oxobut-1-en-2-yl)indolin-2-one **34** (100 mg, 0.432 mmol), L-(-) proline (59 mg, 0.518 mmol), isatin (59 mg, 0.432 mmol) and montmorillonite K-10 Clay (100 mg, 100% w/w) in methanol (1 mL) was refluxed for 5 minutes to afford **49** in 60% yield (167.64 mg, eluent: 30% ethyl acetate:hexane).



49

IR (neat) ν_{max}: 1720, 1745, 3297 cm^{-1}.

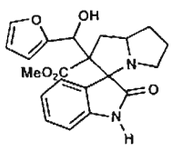
^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.63-1.70 (m, 1H), 1.95-1.99 (m, 2H), 2.28 (m, 5H), 2.49-2.52 (m, 1H), 2.65-2.68 (m, 1H), 2.83-2.91 (m, 1H), 3.05-3.20 (m, 1H), 4.14-4.16 (m, 1H), 6.96-7.07 (m, 2H), 7.18-7.29 (m, 2H), 9.31 (s, 1H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 28.8, 32.4, 42.9, 47.5, 57.5, 67.5, 68.5, 71.7, 108.5, 110.9, 121.4, 124.7, 128.9, 140.8, 181.7, 207.1

LRMS (FAB) for $C_{16}H_{18}N_2O_5$, Calcd (M^+): 270.32; Found m/z : 271.41 (M+1).

Synthesis of spiropyrrolizidine monooxindole 51 from MBH adduct 39

Following the general procedure, a mixture of methyl-2-((furan-2-yl)(hydroxy)methyl)acrylate **39** (100 mg, 0.548 mmol), L-(-) proline (75 mg, 0.658 mmol), isatin (80.6 mg, 0.548 mmol) and montmorillonite K-10 Clay (100 mg, 100% w/w) in methanol (1 mL) was refluxed for 1.5 hours to afford **51** in 80% yield (167.64 mg, eluent: 25% ethyl acetate:hexane).



51

IR (neat) ν_{max}: 1715, 1745, 3297 cm^{-1}.

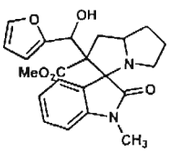
^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.44-1.48 (m, 1H), 1.89 (bs, 1H), 1.91-1.94 (m, 2H), 2.04-2.09 (m, 1H), 2.30-2.33 (m, 1H), 2.44-2.49 (m, 1H), 2.67-2.77 (m, 2H), 3.70 (s, 3H), 4.26-4.28 (m, 1H), 5.60 (s, 1H), 6.28 (s, 2H), 6.89-7.30 (m, 5H), 8.80 (s, 1H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 29.2, 30.2, 33.9, 34.2, 50.6, 52.5, 65.3, 67.2, 73.2, 108.6, 110.4, 110.8, 123.5, 127.3, 128.4, 130.5, 140.7, 143.3, 152.8, 170.5, 180.3.

LRMS (FAB) for $C_{21}H_{22}N_2O_5$, Calcd (M^+): 382.41; Found m/z: 383.40 (M+1).

Synthesis of spiropyrrolizidine monooxindole 52 from MBH adduct 39

Following the general procedure, a mixture of methyl 2-((furan-2-yl)(hydroxy)methyl)acrylate **39** (100 mg, 0.548 mmol), L-(-) proline (75 mg, 0.658 mmol), isatin (88 mg, 0.548 mmol) and montmorillonite K-10 Clay (100 mg, 100% w/w) in methanol (1 mL) was refluxed for 1.5 hours to afford **52** in 35% yield (75.9 mg, eluent: 25% ethyl acetate:hexane).



52

IR (neat) ν_{max}: 1712, 1745, 3435 cm^{-1}.

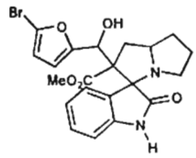
^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.42-1.47 (m, 1H), 1.87-1.94 (m, 2H), 2.07-2.09 (m, 1H), 2.21-2.24 (m, 1H), 2.41-2.46 (m, 1H), 2.61-2.75 (m, 2H), 3.01 (s, 3H), 3.30 (s, 3H), 4.21-4.31 (m, 1H), 5.26 (bs, 1H), 5.52 (s, 1H), 6.26-6.27 (m, 1H), 6.83-7.31 (m, 5H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 26.7, 26.9, 29.2, 33.7, 34.1, 47.0, 51.4, 66.1, 71.2, 71.9, 107.8, 108.1, 109.9, 122.4, 125.8, 127.1, 129.4, 142.0, 143.8, 153.0, 171.2, 178.4.

LRMS (FAB) for $C_{22}H_{24}N_2O_5$, Calcd (M^+): 396.44; Found m/z: 397.22 (M+1).

Synthesis of spiropyrrolizidine monooxindole 53 from MBH adduct 40

Following the general procedure, a mixture of methyl 2-((5-bromofuran-2-yl)(hydroxy)methyl)acrylate **40** (100 mg, 0.383 mmol), L-(-) proline (52.9 mg, 0.459 mmol), isatin (56.3 mg, 0.383 mmol) and montmorillonite K-10 Clay (100 mg, 100% w/w) in methanol (1 mL) was refluxed for 1.5 hours to afford **53** in 60% yield (105.8 mg, eluent: 30% ethyl acetate:hexane).



53

IR (neat) ν_{max}: 690, 794, 1038, 1470, 1714, 1744, 3292 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.42-1.45 (m, 1H), 1.91-1.96 (m, 2H), 2.02-2.04 (m, 1H), 2.30-2.33 (m, 1H), 2.46-2.49 (m, 1H), 2.59-2.70 (m, 2H), 3.12 (s, 3H), 4.18-4.28 (m, 1H), 5.55 (s, 1H), 6.19-6.20 (d, 1H, *J* = 3 Hz), 6.30-6.31(d, 1H, *J* = 3 Hz) 6.90-7.26 (m, 5H), 9.31 (s, 1H).

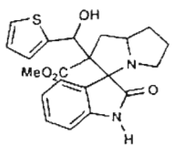
^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 29.2, 33.9, 36.0, 50.7, 52.6, 54.5, 65.3, 67.2, 72.3, 96.1, 109.3, 110.9, 111.9, 121.0, 123.6, 127.2, 130.6, 140.9, 154.8, 170.3, 180.3.

LRMS (FAB) for $C_{21}H_{21}BrN_2O_5$, Calcd (M^+): 461.31; Found m/z: 461.46 (M^+).

Synthesis of spiropyrrolizidine monooxindole 54 from MBH adduct 41

Following the general procedure, a mixture of methyl methyl 2-(hydroxy(thiophen-2-yl)methyl)acrylate **41** (100 mg, 0.504 mmol), L-(-) proline (69 mg, 0.605 mmol), isatin (74 mg, 0.504 mmol) and montmorillonite K-10 Clay (100 mg, 100% w/w) in methanol (1 mL) was refluxed for 1.5 hours to afford **54** in 25% yield (50.24 mg, eluent: 30% ethyl acetate:hexane).

IR (neat) ν_{max}: 694, 749, 1015, 1039, 1248, 1470, 1613, 1711, 1786, 2917, 2950, 3098, 3197, 3434 cm^{-1}.



54

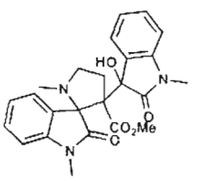
^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.59-1.61 (m, 1H), 1.91-1.93 (m, 2H), 2.03-2.09 (m, 2H), 2.26-2.43 (m, 2H), 2.68-2.73 (m, 2H), 3.08 (s, 3H), 4.29 (m, 1H), 5.84 (s, 1H), 6.74-7.26 (m, 7H), 7.97 (s, 1H).

^{13}C NMR($CDCl_3$/TMS, 75.3 MHz): δ 29.2, 29.6, 33.5, 34.0, 61.3, 66.1, 71.2, 73.5, 107.9, 111.3, 124.3, 124.6, 125.9, 126.3, 129.5, 142.8, 143.8, 153.1, 171.3, 178.3.

LRMS (FAB) for $C_{21}H_{22}N_2O_4S$, Calcd (M^+): 398.48; Found m/z: 399.60 (M+1).

Synthesis of spiropyrrolizidine monooxindole 55 from MBH adduct 18

Following the general procedure, a mixture of methyl 2-(3-hydroxy-1-methyl-2-oxoindolin-3-yl)-acrylate **18** (100 mg, 0.404 mmol), sarcosine (43 mg, 0.375 mmol), isatin (59 mg, 0.404 mmol) and montmorillonite K-10 Clay (100mg, 100% w/w) in methanol (1 mL) was refluxed for 6 hours to afford **55** in 70% yield (123.29 mg, eluent: 35% ethyl acetate:hexane).



55

IR (neat) ν_{max}: 753, 1091, 1347, 1470, 1614, 1712, 1723, 2950, 3272 cm^{-1}.

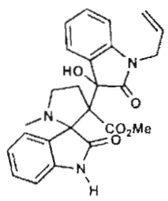
^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.75 (bs,1H), 1.87 (s, 3H), 2.98 (s, 3H), 3.00 (s, 3H), 3.17-3.22 (m, 3H), 3.36 (s, 4H), 6.64-6.66 (d, 1H, J = 6 Hz), 6.80-6.86 (m, 3H), 6.93-6.98 (m, 2H), 7.20-7.30 (m, 2H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 25.9, 26.4, 28.5 (2C), 34.2 (2C), 51.3, 51.4, 67.1, 107.5, 108.3 (2C), 122.3, 122.5, 124.6, 127.6 (2C), 129.2, 129.7, 143.9, 144.2, 171.1, 175.9, 178.1.

LRMS (FAB) for $C_{24}H_{25}N_3O_5$, Calcd (M^+): 435.47; Found m/z: 435.97 (M^+).

Synthesis of spiropyrrolidine bisoxindole 56 and 57 from MBH adduct 29

Following the general procedure, a mixture of methyl 2-(1-allyl-3-hydroxy-2-oxoindolin-3-yl)acrylate **29** (100 mg, 0.365 mmol), sarcosine (39 mg, 0.439 mmol), isatin (53 mg, 0.365 mmol) and montmorillonite K-10 Clay (100mg, 100% w/w) in methanol (1 mL) was refluxed for 6 hour to afford **56** and **57** in 40% (65.30 mg, 35% ethyl acetate:hexane) and 35% yieldsrespectively (57.14 mg, eluent: 35% ethyl acetate:hexane).



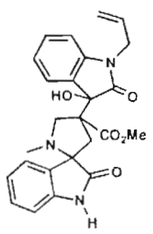
56

IR (neat) ν_{max}: 751, 1102, 1366, 1467, 1612, 1676, 1712, 2923, 3269 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.71 (bs, 1H), 2.04 (s, 3H), 3.06 (s, 3H), 3.24-3.32 (m, 4H), 4.05-4.13 (dd, 1H, *J* = 6 Hz, *J* = 18 Hz), 4.15-4.22 (dd, 1H, *J* = 6 Hz, *J* = 15 Hz), 5.10-5.13 (d, 1H, *J* = 10.2 Hz), 5.17-5.23 (d, 1H, *J* = 15.9 Hz), 5.60-5.73 (m, 1H) 6.69-6.72 (d, 1H, *J* = 9 Hz), 6.78-7.01(m, 5H), 7.17-7.21 (m, 1H), 7.47 (s, 1H), 8.55 (s, 1H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 28.4, 34.3 (2C), 42.3, 51.0 (2C), 51.5, 66.9, 108.6, 110.2, 118.0, 122.1, 122.7 (2C), 125.0, 128.0, 129.2, 129.6, 129.9, 131.1, 141.5, 143.0, 171.1, 172.1, 179.8.

LRMS (FAB) for $C_{25}H_{25}N_3O_5$, Calcd (M^+): 447.48; Found m/z: 448.31(M+1).



57

IR (neat) ν_{max}: 751, 1102, 1366, 1467, 1612, 1676, 1712, 2923, 3269 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.74 (bs, 1H), 2.02 (s, 3H), 3.05-3.10 (d, 1H, *J* = 15 Hz), 3.27-3.31(d, 1H, *J* = 14.7 Hz) 3.4 (s, 3H), 3.56-3.60 (d, 1H, *J* = 12 Hz), 4.17-4.24 (dd, 1H, *J* = 6Hz, *J* = 15 Hz), 4.35-4.42 (m, 2H), 5.19-5.36 (m, 2H), 5.79-5.88 (m, 1H), 6.75-6.78 (d, 1H, *J* = 9 Hz), 6.81-684 (d, 1H, *J* = 9 Hz), 6.92-6.97 (t, 1H, *J* = 9 Hz), 7.04-709

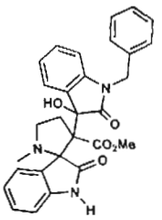
(t, 1H, J = 9 Hz), 7.20-7.25 (m, 3H), 7.33-7.36 (d, 1H, J = 9 Hz), 8.3 (s, 1H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 28.1, 34.0, 35.4, 38.1, 51.9, 53.8, 59.6, 75.4, 108.1, 109.1, 111.2, 113.0, 118.6, 121.9, 124.3, 126.2 (2C), 129.9, 130.5, 131.3, 141.1, 143.2, 173.4, 176.0, 181.8.

LRMS (FAB) for $C_{25}H_{25}N_3O_5$, Calcd (M^+): 447.48; Found m/z: 448.42(M+1).

Synthesis of spiropyrrolidine bisoxindole 58 from MBH adduct 28

Following the general procedure, a mixture of methyl methyl 2-(1-benzyl-3-hydroxy-2-oxoindolin-3-yl)acrylate **28** (100 mg, 0.309 mmol), sarcosine (33 mg, 0.371 mmol), isatin (45 mg, 0.309 mmol) and montmorillonite K-10 Clay (100mg, 100% w/w) in methanol (1 mL) was refluxed for 6 hours to afford **58** in 65% yield (99.9 mg, eluent: 35% ethyl acetate:hexane).



58

IR (neat) ν_{max}: 754, 1034, 1113, 1465, 1610, 1732, 2919, 3351 cm^{-1}.

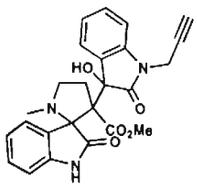
^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 2.04 (s, 3H), 2.55 (s, 3H), 3.19-3.34 (m, 4H), 4.44-4.49 (d, 1H, J = 15 Hz), 4.82-4.89 (d, 1H, J = 15 Hz), 6.45 (s, 1H), 6.68-6.75 (m, 2H), 6.92-7.00 (m, 3H), 7.09-7.26 (m, 6H), 7.31-7.85 (m, 2H), 8.02 (s, 1H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 23.2, 37.6, 48.0, 49.5, 52.5, 60.8, 76.3, 84.9, 121.4 (2C), 124.2, 125.4, 126.2, 127.0 (2C), 127.5 (2C), 128.4, 128.9 (2C), 129.5 (2C), 131.4, 139.7, 141.7, 152.7, 166.3, 170.2, 177.5

LRMS (FAB) for $C_{29}H_{27}N_3O_5$, Calcd (M^+): 497.54; Found m/z: 497.60 (M^+).

Synthesis of spiropyrrolidine bisoxindoles 59 and 60 from MBH adduct 30

Following the general procedure, a mixture of methyl 2-(3-hydroxy-2-oxo-1-(prop-2-ynyl)indolin-3-yl)acrylate **30** (100 mg, 0.368 mmol), sarcosine (39 mg, 0.441 mmol), isatin (54 mg, 0.368 mmol) and montmorillonite K-10 Clay (100 mg, 100% w/w) in methanol (1 mL) was refluxed for 6 hours to afford **59** in 40% (65.5 mg) and **60** in 36% yield (58.9 mg, eluent: 35% and 40% ethyl acetate:hexane).



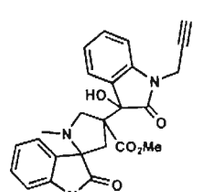
59

IR (neat) ν_{max}: 753, 1223, 1355, 1470, 1488, 1614, 1731, 1730, 2126, 2924, 3288 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.71 (bs, 1H), 1.96 (s, 3H), 2.12-2.13 (t, 1H, *J* = 2.1 Hz), 3.07 (s, 3H), 3.24-3.35 (m, 4H), 4.08-4.14 (dd, 1H, *J* = 3 Hz, *J* = 18 Hz), 4.50-4.56 (dd, 1H, *J* = 3 Hz, *J* = 18 Hz), 6.82-6.96 (m, 4H), 7.03-7.05 (m, 1H), 7.18-7.48 (m, 3H), 8.43 (s, 1H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 19.1, 28.4, 28.7, 34.3, 51.2, 52.3, 67.3, 72.2, 96.8, 108.9, 113.1, 122.3, 123.1, 124.5, 128.1, 129.2, 129.7, 131.1, 134.6, 141.2, 142.3, 171.0, 175.3, 179.9.

LRMS (FAB) for $C_{25}H_{23}N_3O_5$, Calcd (M^+): 445.16; Found m/z: 446.05(M+1).



60

IR (neat) ν_{max}: 753, 1223, 1355, 1470, 1488, 1614, 1731, 1730, 2124, 2924, 3287 cm^{-1}.

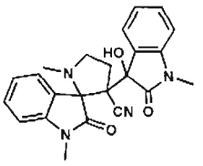
^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 2.14 (s, 3 H), 2.25-2.27 (t, 1H, *J* = 3 Hz), 3.12-3.17 (d, 1H, *J* = 14.1 Hz), 3.34-3.38 (d, 1H, *J* = 13.8 Hz), 3.45 (s, 3H), 3.57-3.61 (d, 1H, *J* = 12 Hz), 4.17-4.24 (dd, 1H, *J* = 3 Hz, *J* = 18 Hz), 4.38-4.42 (d, 1H, *J* = 12 Hz), 4.76-4.82 (dd, 1H, *J* = 3 Hz, *J* = 18 Hz), 5.42 (brs, 1H), 6.87-6.89 (d, 1H, *J* = 6 Hz), 6.99-7.00 (m, 2H), 7.10-7.12 (m, 2H), 7.23-7.40 (m, 3H), 8.45 (s, 1H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 29.2, 34.5, 52.9, 57.8, 59.4, 70.6, 72.3, 75.1, 76.7, 109.1, 109.8, 123.1, 123.6, 124.8, 125.2, 127.8, 129.3, 129.7, 130.1, 140.7, 141.9, 172.9, 175.8, 181.3.

LRMS (FAB) for $C_{25}H_{23}N_3O_5$, Calcd (M^+): 445.16; Found m/z: 446.05(M+1).

Synthesis of spiropyrrolidine bisoxindole 61 from MBH adduct 33

Following the general procedure, a mixture of 2-(3-hydroxy-1-methyl-2-oxoindolin-3-yl)acrylonitrile (100 mg, 0.466 mmol), sarcosine (34 mg, 0.389 mmol), isatin (68 mg, 0.466 mmol) and montmorillonite K-10 Clay (100 mg, 100% w/w) in methanol (1 mL) was refluxed for 6 hours to afford **61** in 65% yield (121.87 mg, eluent: 50% ethyl acetate:hexane).



61

IR (neat) ν_{max}: 751, 1095, 1347, 1372, 1470, 1613, 1725, 2124, 2250, 2851, 2932, 3062, 3368 cm^{-1}.

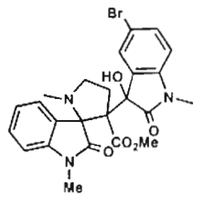
^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.78 (bs, 1H), 1.88 (s, 3H), 2.68-2.72 (m, 1H), 2.92 (s, 3H), 3.05(s, 3H), 3.20-3.28 (m, 1H), 3.41-3.44 (m, 1H), 3.89-3.98 (m, 1H), 6.32-6.34 (d, 1H, J = 6 Hz), 6.54-6.66 (m, 2H), 7.01-7.44 (d, 4H, J = 6 Hz), 7.72-7.74 (d, 1H, J = 6 Hz).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 27.7 , 31.1, 36.1, 39.4, 46.1, 51.5, 82.6, 90.2, 116.7, 118.1, 120.2, 121.2, 122.2, 124.1, 124.2, 126.1, 131.4, 143.1, 143.8, 152.1, 170.1, 173.6.

LRMS (FAB) for $C_{23}H_{22}N_4O_3$, Calcd (M^+): 402.16; Found m/z: 402.36(M^+).

Synthesis of spiropyrrolidine bisoxindole 62 from MBH adduct 35

Following the general procedure, a mixture of methyl 2-(5-bromo-3-hydroxy-2-oxoindolin-3-yl) acrylate **35** (100 mg, 0.320 mmol), sarcosine (34 mg, 0.384 mmol), isatin (47 mg, 0.320 mmol) and montmorillonite K-10 Clay (100 mg, 100% w/w) in methanol (1 mL) was refluxed for 6 hour to afford **62** in 70% yield (112.06 mg, eluent: 40% ethyl acetate:hexane).



62

IR (neat) ν_{max}: 539, 756, 1237, 1445, 1471, 1613, 1681, 1732, 2924, 3282, cm^{-1}.

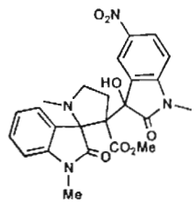
^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.80 (bs, 1H), 1.87 (s, 3H), 3.11 (s, 3H), 3.14-3.24 (m, 2H), 3.29 (s, 6H), 6.50-6.52 (d, 5H, *J* = 6 Hz), 6.84-6.87 (m, 3H), 6.96-6.98 (m, 1H), 7.01-7.35 (m, 3H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): 25.5, 33.2, 35.2, 49.4, 52.9, 66.7, 76.5, 107.4, 109.9, 112.0, 115.0, 121.6, 123.7, 127.2, 130.5, 131.4, 133.6, 140.1, 144.1, 170.9, 177.6, 178.1.

LRMS (FAB) for $C_{23}H_{22}BrN_3O_5$, Calcd (M^+): 500.34; Found m/z: 500.28(M^+).

Synthesis of spiropyrrolidine bisoxindole 65 from MBH adduct 36

Following the general procedure, a mixture of methyl 2-(3-hydroxy-5-nitro-2-oxoindolin-3-yl)acrylate **36** (100 mg, 0.359 mmol), sarcosine (38 mg, 0.413 mmol), N-methylisatin (57 mg, 0.359 mmol) and montmorillonite K-10 Clay (100 mg, 100% w/w) in methanol (1 mL) was refluxed for 6 hours to afford **65** in 60% yield (99.6 mg, eluent: 40% ethyl acetate:hexane).



65

IR (neat) ν_{max}: 1337, 1469, 1519, 1616, 1738, 2920, 3328 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 2.10 (s, 3H), 3.09-3.14 (d, 1H, *J* = 15 Hz), 3.14 (s, 3H), 3.30-3.35 (d, 1H, *J* = 15 Hz), 3.38-3.48 (d, 1H, *J* = 12 Hz), 3.40 (s, 3H), 3.54-3.58 (d, 1H, *J* = 12 Hz), 5.90 (brs, 1H), 6.85-6.91 (t, 2H, *J* = 9 Hz), 7.09-7.14 (t, 1H, *J* = 6 Hz), 7.26-7.30 (m, 1H), 7.30-7.34 (d, 1H, *J* = 9 Hz), 8.12 (s, 1H), 8.26-8.29 (m, 2H).

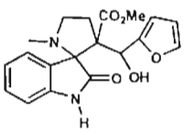
^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 21.0, 26.5, 34.4, 37.8, 53.0, 57.8, 59.3, 70.7, 74.9, 107.6, 110.16, 120.5, 123.7, 125.0, 127.3, 129.2, 129.3, 129.6, 140.7,

143.2, 149.6, 172.8, 176.9, 181.6.

LRMS (FAB) for $C_{23}H_{22}N_4O_7$, Calcd (M^+): 466.44; Found m/z: 467.39(M+1).

Synthesis of spiropyrrolidine monooxindole 66 from MBH adduct 39

Following the general procedure, a mixture of methyl 2-((furan-2-yl)(hydroxy)methyl)acrylate **39** (100 mg, 0.548 mmol), sarcosine (58 mg, 0.658 mmol), isatin (80 mg, 0.548 mmol) and montmorillonite K-10 Clay (100 mg, 100% w/w) in methanol (1 mL) was refluxed for 3 hours to afford **66** in 68% yield (126.9mg, eluent: 35% ethyl acetate:hexane).



66

IR (neat) ν_{max}: 1715, 1729, 3340 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 2.04 (s, 3H), 2.81-2.85 (m, 2H), 2.98-3.00 (m, 1H), 3.11 (s, 3H), 3.39-3.48 (m, 1H), 5.31(bs, 1H), 5.72 (s, 1H), 6.28-6.3 (m, 2H), 6.92-7.28 (m, 5H), 9.05 (s, 1H).

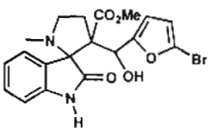
^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 25.1, 29.6, 50.5, 54.5, 65.6, 69.0, 70.5, 108.8, 109.4, 111.2, 123.5, 125.5, 126.9, 127.0, 128.4, 140.7, 153.0, 170.4, 177.1

LRMS (FAB) for $C_{19}H_{20}N_2O_5$, Calcd (M^+): 356.37; Found m/z: 357.23 (M+1).

Synthesis of spiropyrrolidine monooxindole 67 from MBH adduct 40

Following the general procedure, a mixture of methyl methyl 2-((5-bromofuran-2-yl)(hydroxy)methyl)acrylate **40** (100 mg, 0.383 mmol), sarcosine (40 mg, 0.459 mmol), isatin (56 mg, 0.383 mmol) and montmorillonite K-10 Clay (100 mg, 100% w/w) in methanol (1 mL) was refluxed for 6 hours to afford **67** in 50% yield (180mg, eluent: 30% ethyl acetate:hexane).

IR (neat) ν_{max}: 669, 1715, 1749, 3257cm^{-1}.



67

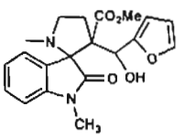
^{1}H NMR($CDCl_3$/TMS, 300.1 MHz): δ 2.05 (s, 3H), 2.72-2.83 (m, 2H), 2.95-3.02 (m, 1H), 3.17 (s, 3H), 3.40-3.46 (m, 1H), 5.33 (bs, 1H), 5.52 (s, 1H), 6.23-6.24(d, 1H, *J* = 3 Hz), 6.36-6.37 (d, 1H, *J* = 3 Hz), 6.95-7.27 (s, 4H), 9.24 (s, 1H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 29.2, 29.9, 50.7, 54.5, 65.3, 67.2, 72.3, 96.1, 109.3, 110.9, 111.9, 121.0, 123.6, 127.2, 130.6, 140.9, 154.8, 170.3, 180.3.

LRMS (FAB) for $C_{19}H_{19}BrN_2O_5$, Calcd (M^+): 434.05; Found m/z: 434.00 (M^+).

Synthesis of spiropyrrolidine monooxindole 68 from MBH adduct 39

Following the general procedure, a mixture of methyl methyl 2-((furan-2-yl)(hydroxy)methyl)acrylate **39** (100 mg, (100 mg, 0.383 mmol), sarcosine (40 mg, 0.459 mmol), *N*-methylisatin (56 mg, 0.383 mmol) and montmorillonite K-10 Clay (100 mg, 100% w/w) in methanol (1 mL) was refluxed for 6 hours to afford **68** in 30% yield (42.5mg, eluent: 30% ethyl acetate:hexane).



68

IR (neat) ν_{max}: 1715, 1744, 3418 cm^{-1}.

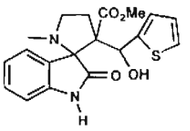
^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.96 (s, 3H), 2.77-2.84 (m, 2H), 2.97-2.99 (m, 1H), 3.06 (s, 3H), 3.32 (s, 3H) , 3.41-3.45 (m, 1H), 5.26 (brs, 1H), 5.64 (s, 1H), 6.26-6.31 (m, 2H), 6.87-7.61 (m, 5H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 25.1, 26.1, 26.5, 35.3, 51.5, 52.4, 65.6, 69.8, 108.0, 109.9, 122.4, 123.7, 125.6, 129.4, 138.3, 141.9, 143.4, 153.2, 170.0, 174.0.

LRMS (FAB) for $C_{20}H_{22}N_2O_5$, Calcd (M^+): 370.40; Found m/z: 371.17(M+1).

Synthesis of spiropyrrolidine monooxindole 69 from MBH adduct 41

Following the general procedure, a mixture of methyl methyl 2-(hydroxy(thiophen-2-yl)methyl)acrylate **41** (100 mg, 0.504 mmol), sarcosine (53.8 mg, 0.604 mmol), isatin (74 mg, 0.504 mmol) and montmorillonite K-10 Clay (100 mg, 100% w/w) in methanol (1 mL) was refluxed for 1.5 hours to afford **69** in 25 % yield (46.9mg, eluent: 30% ethyl acetate:hexane).



69

IR (neat) ν_{max}: 1717, 1742, 3434 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 2.05 (s, 3H), 2.74-2.82 (m, 2H), 2.99-3.03 (m, 1H), 3.10 (s, 3H), 3.40-3.58 (m, 1H), 5.31(bs, 1H), 5.97 (s, 1H), 6.79-7.26 (m, 7H), 8.64 (s, 1H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 24.6, 35.3, 51.4, 52.3, 67.2, 71.5, 110.0, 122.4, 124.4, 124.6, 125.3, 126.0, 126.1, 129.4, 140.3, 143.0, 170.3, 176.6.

LRMS (FAB) for $C_{19}H_{20}N_2O_4S$, Calcd (M^+): 372.44; Found m/z: 373.00 (M+1).

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CHAPTER 3

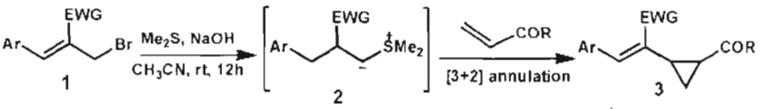
Synthesis of 3, 3'-Dispiropyrrolidine - and 3, 3'-Dispiropyrrolizidine bisoxindoles from Isomerised MBH Adducts of Isatin *via* [3+2]-cycloaddition

3.1 Introduction

Recent years have witnessed an explosive growth in the applications of Morita-Baylis-Hillman adducts and its derivatives in synthetic organic chemistry. The consecutive array of three functional groups in MBH adducts can be tuned, either all at a time or individually, for synthetic transformations and offers a route for the construction of complex molecular frameworks.[1] The MBH adducts could be readily transformed into allyl acetates and allyl bromides *via* acetylation and bromination and the reaction is tantamount to the Michael addition. The MBH adducts and their derivatives undergo a variety of reactions, leading to products, which could efficiently be exploited for the generation of carbo- and heterocyclic scaffolds. As the focal theme of this chapter is the studies on [3+2]-cycloaddition of azomethine ylide with isomerised MBH adducts of isatin (allyl bromides and allyl ethers derivatives), a brief discussion on the reactions exhibited by isomerised MBH adducts is warranted. Hence, the following section outlines a brief account on the recent literature-known for the synthetic transformations of isomerised allyl derivatives of MBH adducts.

3.2 Synthetic use of allyl bromide and allyl ether derivatives of MBH adducts

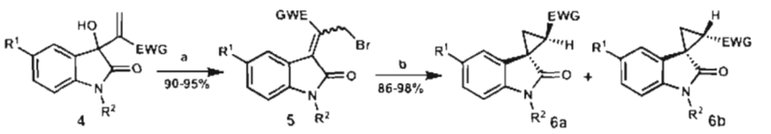
In 2006, Kim *et al.* reported the formation of vinyl cyclopropane **3** from isomerised bromo derivative of MBH adduct **1** on treatment with methyl vinyl ketone (MVK), dimethyl sulphide and a base. In the proposed mechanism, the sulfonium ion formed from **1** and the Me_2S was converted to the ylide **2** which then added to the double bond of MVK afforded **3** (Scheme 3.1).[2]



Ar = C_6H_5, 4-Me-C_6H_4, 4-Cl-C_6H_4; EWG = CN, Ester; R = Me, Et, ^{i}Pr

Scheme 3.1: *Vinyl cyclopropanation via sulphur ylide*

Recently, our group has demonstrated the synthesis of 3-spirocyclopropane-2-indolones from bromo isomerised MBH adducts of isatin **4**. A tandem hydride addition followed by elimination of the bromide ion resulted in the formation of diastereomeric and separable mixture of spirocyclopropane-2-indolones **6a** and **6b** in excellent combined yield (Scheme 3.2). Interestingly, both the *Z*- and *E*- bromo isomers upon individual reductive cyclization reactions afforded the same mixture of diastereomeric 3-spirocyclopropane-indolones.[5]

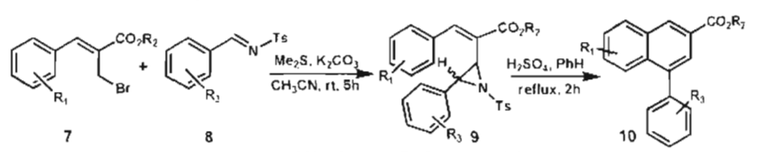


R^1 = H, Br; R^2 = Me, Bn, Propargyl; EWG = CN, CO_2Et

a = aq.HBr, Silica, MW, 3 Min.; b = $NaBH_4$, THF, rt, 0.5h

Scheme 3.2: *Synthesis of 3-spirocyclopropane via reductive cyclization*

Kim *et al.* reported a regioselective synthesis of 1-aryl naphthalene derivative **10** *via* an intramolecular Friedel-Crafts type ring opening reaction of *N*-tosylaziridine **9**, which in turn, were obtained by the reaction of the appropriate *N*-tosylimine **8** with cinnamyl bromide **7** which was obtained from MBH adduct, in the presence of Me_2S and K_2CO_3 (Scheme 3.3).[1]

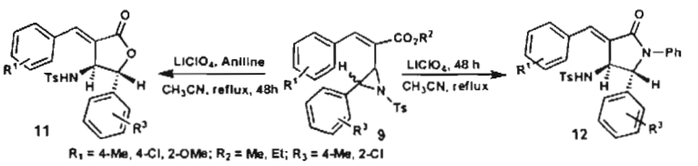


R_1 = 4-Me, 4-Cl, 2-OMe; R_2 = Me, Et; R_3 = 4-Me, 2-Cl

Scheme 3.3: *Synthesis of naphthalene derivative via aziridine*

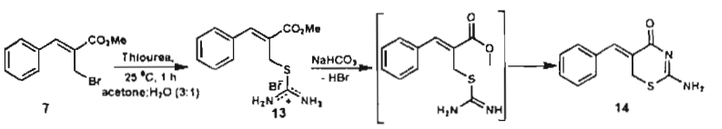
Later, the same group has reported the synthesis of 3-arylidenelactam **12** and 3-arylidenelactone **11** from *N*-tosyl aziridine **9**. When **9** was refluxed in acetonitrile with lithium perchlorate and aniline for 24 hours, 3-arylidenelactam

12 was the sole product and in the absence of external nucleophile, 3-arylidene lactone **11** was the sole product. In the proposed mechanism, a regioselective ring opening of the **9** form a more stable benzylic cation which undergo nucleophilic attack and followed by lactonization sequence afforded the observed products (Scheme 3.4).[5]



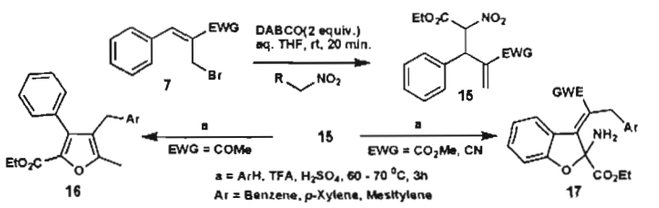
Scheme 3.4: *Synthesis of lactams and lactones via aziridine MBH derivatives*

Recently, Sa and co-workers have demonstrated the formation 1,3-thiazin-4-one **14** from bromo isomerised MBH adduct **7** by a reaction with thiourea in presence of a base. The authors have proved the intermediate of the reaction is isothiouronium bromide salt **13** by conducting the reaction in the absence of base and isolated the intermediate (Scheme 3.5).[6]



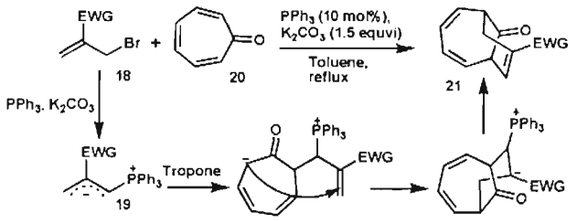
Scheme 3.5: *Synthesis of 1,3-thiazin-4-one*

Regioselective introduction of various nucleophiles at the benzylic position of the MBH adducts have been achieved from its allyl bromide by the treatment with nucleophile and DABCO in THF.[7] This methodology was used extensively by Kim *et al.* for the synthesis of MBH derivative **15** and thereby 2-amino-2,3-dihydrobenzofuran derivative **17** and fully substituted furan **16** (Scheme 3.6).[8]



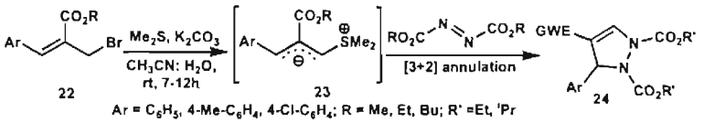
Scheme 3.6: *Functionalization at the benzylic position of MBH adduct*

MBH derived allyl bromides have been used as a dipole equivalent for the [3+6] annulation reaction with tropone as reported by Lu *et al.* The allyl bromide **18** forms the phosponium salt with triphenyl phosphine which on deprotonation with a base generates the ylide **19**. The ylide **19** then on annulation with tropone **20** yield the product **21** (Scheme 3.7).[9]



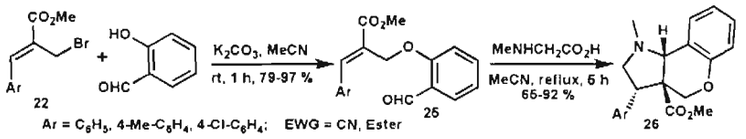
Scheme 3.7: *MBH allyl bromide as a component in phosphorus ylide reaction*

Basavaiah *et al.* reported the synthesis of functionalized dihydropyrazole **24** from bromo isomerised MBH adducts using the sulphur ylide chemistry. Sulfonium salt obtained from the cinnamyl bromide **22** and dimethyl sulphide forms the ylide **23** in the presence of potassium carbonate. The ylide **23** then serves as a 1,3-dipole equivalent for the annulation reaction with dialkylazo dicarboxylate (Scheme 3.8).[10]



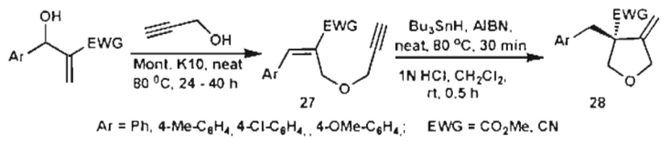
Scheme 3.8: *Synthesis of dihydropyrazole from allylbromide via sulphur ylide*

Bakthadoss *et al.* utilized the allyl bromide **22** obtained from MBH adduct for the highly regio and stereoselective synthesis of tricyclic chromeno-[4,3,b]-pyrrolidine **26** frameworks *via* a substitution reaction with salicylaldehyde followed by intramolecular AMY cycloaddition with the double bond (Scheme 3.9).[11]



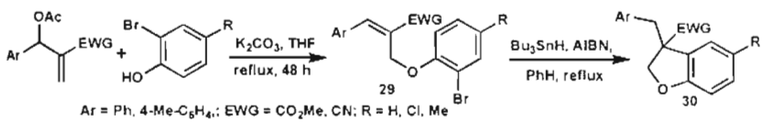
Scheme 3.9: *Synthesis of chromeno-[4,3,b]-pyrrolidine using AMY*

Allyl ethers generated from MBH adducts were extensively used for the construction of oxygen containing heterocycles. Some of the reactions include radical cyclization, Friedel-Crafts reaction, *etc.* Our group has reported the synthesis of highly substituted tetrahydrofuran ring systems using radical cyclization protocol. Radical cyclization of alkenyl propargyl ether **27** with freshly distilled *n*-Bu_3SnH in the presence of catalytic AIBN yielded the vinyl stannane through *5-exo-trig* cyclization. The vinylstannane on protio destannylation with 1N HCl afforded the exo-methelene-tetrahydrofuran **28** (Scheme 3.10).[12] The same methodology has been extended for the synthesis of tetrahydropyrans and oxetanes from alkenyl homopropargyl ether derivatives.



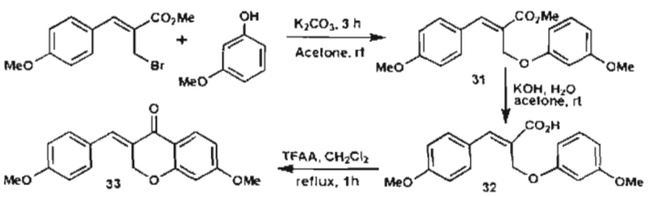
Scheme 3.10: *Synthesis tetrahydrofuran via radical cyclization*

Followed by this report, Kim *et al.* pursued the strategy for the synthesis of 3,3-disubstituted-2,3-dihydrobenzofuran **30** from alkenyl bromophenolic ether **29** *via* a *5-exo-trig* cyclisation under the influence of *n*-Bu_3SnH/AIBN in benzene at reflux condition (Scheme 3.11).[13] The allyl phenolic ethers were synthesised from the acetates of MBH adducts and phenol derivative *via* a base mediated S_N2 type reaction.



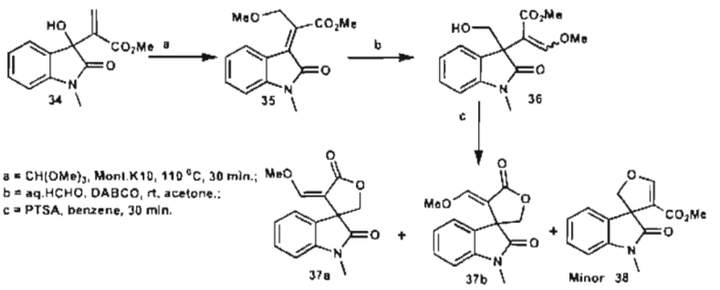
Scheme 3.11: *Benzofuran synthesis*

MBH adducts can easily be converted to the corresponding phenolic ethers. Basavaiah *et al.* developed a short and convenient method for the synthesis of a natural product bonducellin methyl ether, 3-arylidene (alkylidene)-chroman-4-one **33**, from the allyl phenyl ether **31**. The method follows intramolecular Friedel-Crafts reaction (Scheme 3.12).[14]



Scheme 3.12: *Synthesis of bonducellin methyl ether*

A concise stereoselective synthesis of 3-spiro-α-methylene-γ-butyrolactone oxindoles from MBH adducts of isatin has been achieved from our group. The MBH adduct **34** underwent isomerisation with trimethyl orthoformate in the presence of Mont. K10 clay catalyst yielded the allyl methyl ether **35** which on base catalyzed second MBH reaction with formaldehyde yielded adduct **36**. An acid catalyzed lactonization **36** resulted in the formation of *E*- and *Z* isomers of 3-spiro-α-methylene-γ-butyrolactone oxindoles **37a** and **37b** along with a minor amount of spiro furan derivative **38** (Scheme 3.13).[15]



Scheme 3.13: *Synthesis of spirolactone oxindole from isomerised MBH adduct*

3.3 Present Work

As discussed above, the MBH derived allyl bromides and allyl ethers display a wide range of reactivity towards the synthesis of many carbo and heterocyclic ring systems. Further, isatin derived adducts readily undergo isomerisation into allyl bromides and allyl ethers. Presence of an oxindole moiety at the γ position enlarges its synthetic utility for the construction of nitrogen containing polycycles with complex molecular core structures. Although simple MBH derived allyl derivatives were well explored for various

synthetic transformations, isatin derived MBH allyl derivatives attained less attention towards synthesis of novel spiro heterocycles. As discussed in the first chapter, cycloaddition reactions of azomethine ylide play significant role in the construction of pyrrolidine and pyrrolizidine ring systems. With the objective of expanding the scope of these allyl halides and allyl ethers derived from Morita-Baylis-Hillman adduct of isatin in synthetic organic chemistry, we wish to extend the 1,3- dipolar cycloaddition strategy of azomethine ylide towards the synthesis of dispiropyrrolidine and dispiropyrrolizidine oxindoles. The details are subject matter of this chapter and discussed as follows.

3.4 Results and Discussion

3.4.1 Reterosynthetic analysis

The retrosynthetic analysis of the present synthetic plan is outlined in figure 3.1. Accordingly, synthesis of the dispiropyrrolidine bisoxindoles and dispiropyrrolizidine bisoxindoles can be achieved by a [3+2]-cycloaddition reaction of azomethine ylides (acyclic **A** and cyclic **B**) with bromo or methoxy isomerised MBH adduct of isatin. The MBH adducts of isatin and cyclic and acyclic AMY can be prepared from a common precursor isatin.

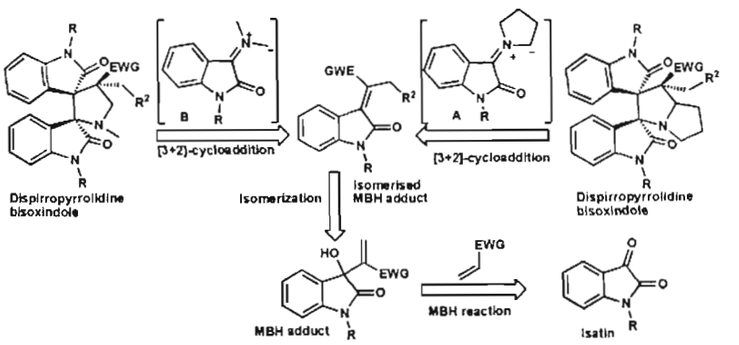
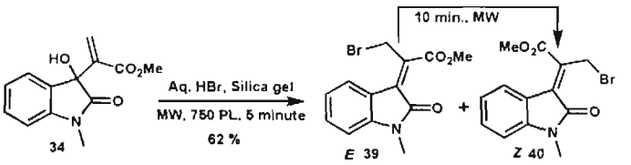


Figure 3.1: *Reterosynthetic analysis for the synthesis of dispiropyrrolidine bisoxindole*

3.4.2 Preparation of bromo isomerised MBH adducts of isatin

According to the retrosynthetic analysis, the starting precursor bromo isomerised MBH adducts **39** and **40** was prepared from the MBH adduct **34** of *N*-methylisatin by treatment with aqueous HBr in the presence of silica gel

(100-200 mesh) and under solvent free microwave irradiation condition. The *E*-isomer **39** was converted to the Z-isomer **40** by increasing microwave irradiation time (*ca.* 10 min) (Scheme 3.14).



Scheme 3.14: *Isomerisation of MBH adducts of isatin with aq. HBr*

The geometries of isomers **39** and **40** were established based on ^{1}H NMR chemical shift analysis. Thus, the methylene protons of E-isomer **39** were observed at δ 5.23 while for the Z-isomer **40** at δ 4.49 as shown in figures 3.2 and 3.3. The major Z-isomer **40** was purified and used for the cycloaddition study with AMY. All the isatin derived MBH adducts were prepared from the corresponding isatins and activated alkene following the procedures described in section 2.4.1.[16]

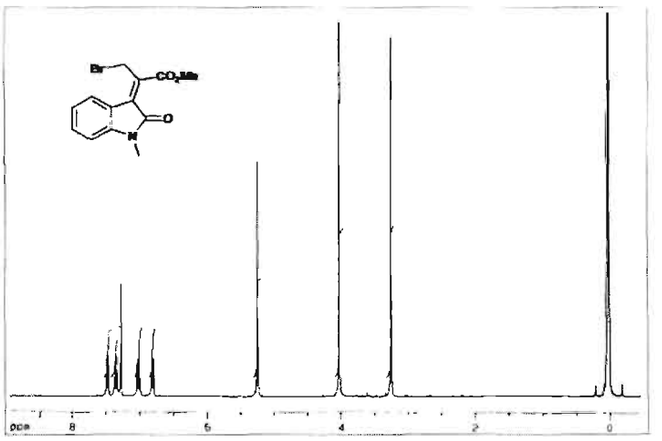


Figure 3.2: *Proton NMR spectrum of* **39**

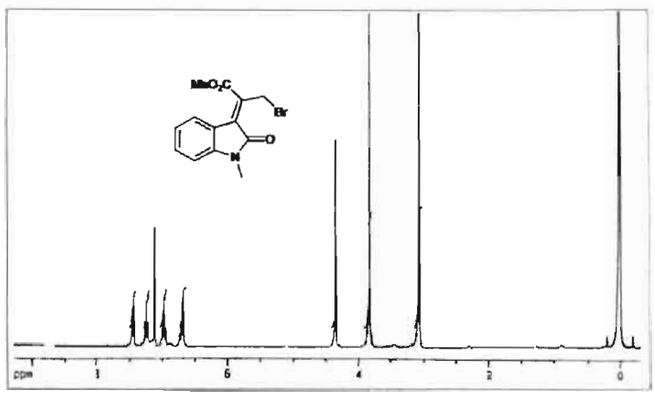
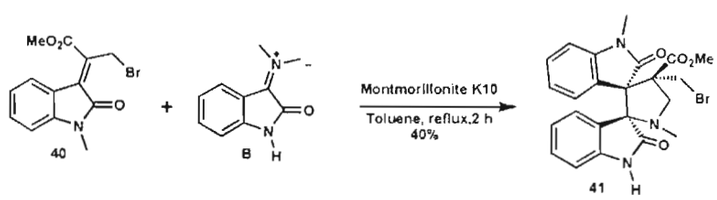


Figure 3.3: *Proton NMR spectrum of* **40**

3.4.3 1,3- Dipolar cycloaddition reaction of bromoisomerised MBH adduct 40 with acyclic AMY

In a pilot experiment, the Z-isomer **40** was treated with acyclic azomethine ylide (generated *in situ* from sarcosine and isatin) in refluxing toluene in presence of montmorillonite K10 clay as the catalyst. The reaction afforded highly substituted 3,3`-dispiropyrrolidine bisoxindole **41** in 40% yield as shown in scheme 3.15.



Scheme 3.15: *Model study for dispiropyrrolidine bisoxindole*

Inroder to improve the yield of the reaction, optimization of the reaction was carried out in different solvents (methanol, toluene, acetonitrile and dioxane) and with and without montmorillonite K10 clay catalyst. A remarkable increase in the yield (75%) of **41** was observed with methanol as the solvent and freshly activated 100% w/w of montmorillonite K10 clay as a catalyst under reflux for 2 h. The reactions in acetonitrile and dioxane provided the expected compound **41** in moderate yields. The results of the optimization study is presented in table 3.1

Table 3.1: Solvent and Catalyst screening

entry	solvent (a)	mont.K10 (wt%)	time (h)	yield (%)
1	1,4-Dioxane (100 ^{0}C)	100	12	85
2	Methanol (68 ^{0}C)	-	4	60
3	Methanol (68 ^{0}C)	100	2	75
4	Toluene (100 ^{0}C)	100	4	40
5	Acetonitrile (65 ^{0}C)	100	12	20

a: Temperature

The structure of compound **41** was confirmed by the spectroscopic studies. The presence of two amide carbonyl groups was confirmed from the merged absorptions in the FTIR spectrum at 1731 cm^{-1} and the ester group at 1735 cm^{-1}. The proton NMR spectrum of **41** showed two singlets at δ 2.20 and 2.97 which were indicative of the methyl groups attached to the nitrogen of the pyrrolidine ring and at the amide of the oxindole moiety. The ester methoxy protons were amenable to a singlet at δ 3.60. The two doublets centred at δ 3.54 and δ 3.72 with coupling constants J = 9.0Hz indicating the presence of two pyrrolidine ring protons. Two mutually coupled protons at the carbon attached to bromine were visible as two doublets centred at δ 4.44 and δ 4.88 with a coupling constant J = 9.0Hz. A singlet at δ 7.64 was due to the free hydrogen attached to the nitrogen of the oxindole moiety. The aromatic protons of the oxindole moiety appeared as well separated multiplets in the chemical shift range δ 6.53-7.47. A singlet at δ 7.64 was due to the proton attached to nitrogen (Figure 3.4). In the ^{13}C NMR spectrum of compound **41**, a peak at δ 51.9 was indicative of the methoxy carbon. The two spiro carbons were resonated at δ 59.5 and δ79.3. Two carbonyl carbons of the oxindole ring were observed at δ 175.2 and 177.3. The ester carbonyl was visible at δ 180.1 (Figure 3.5). Two peaks in the mass spectrum of the compound **41** at m/z = 484.29 (M^+) and m/z = 486.21(M+2) confirms the presence of bromine atom in the molecule and thereby assigned final structure as **41**.

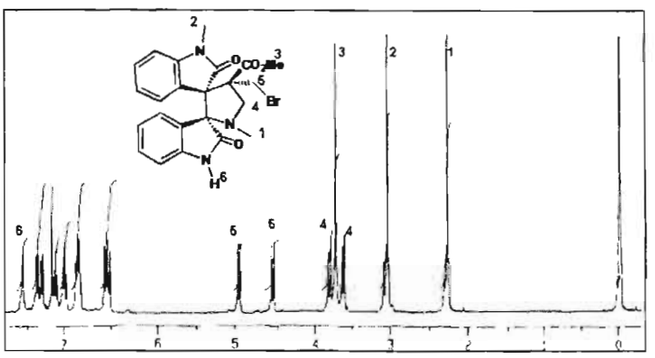


Figure 3.4: *Proton NMR spectrum of* **41**

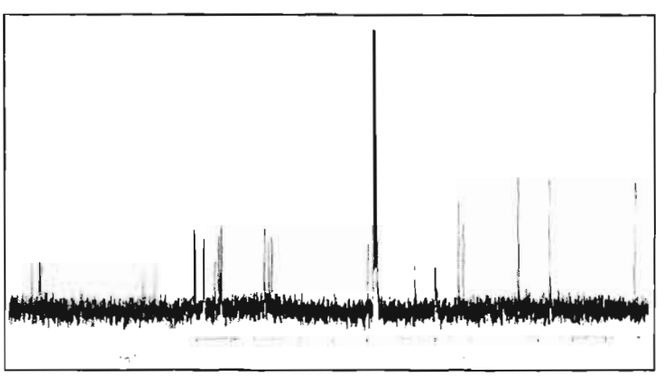
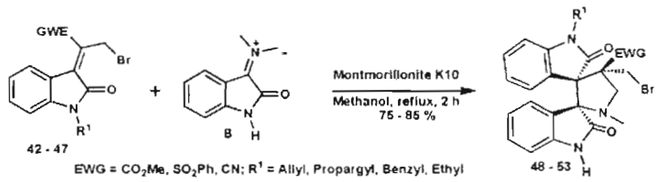


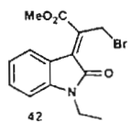
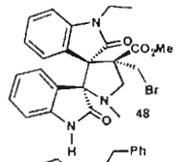
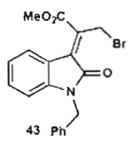
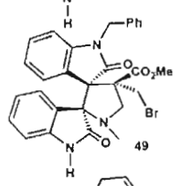
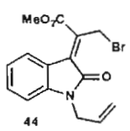
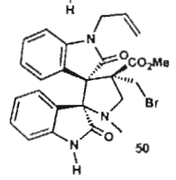
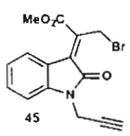
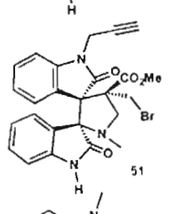
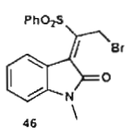
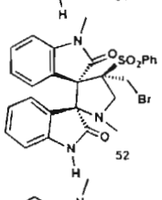
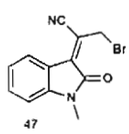
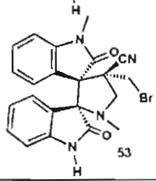
Figure 3.5: *^{13}C NMR spectrum of* **41**

To show the general nature of the reaction, a number of bromo isomerised MBH adducts of isatin **42 - 47** bearing different substituents (ester, sulfone, nitrile and substituents on the isatin nitrogen (methyl, benzyl, propargyl and allyl) were reacted with acyclic azomethine ylide **B** (generated from isatin and sarcosine) under optimized conditions (Scheme 3.16). The cycloaddition reaction afforded highly functionalized dispiropyrrolidine bisoxindoles **48 - 53** in excellent yields (75-85%). All the new compounds were thoroughly characterized by the spectroscopic methods (IR, ^{1}H, ^{13}C NMR and FAB-mass spectra). The results are summarized in Table 3.2.



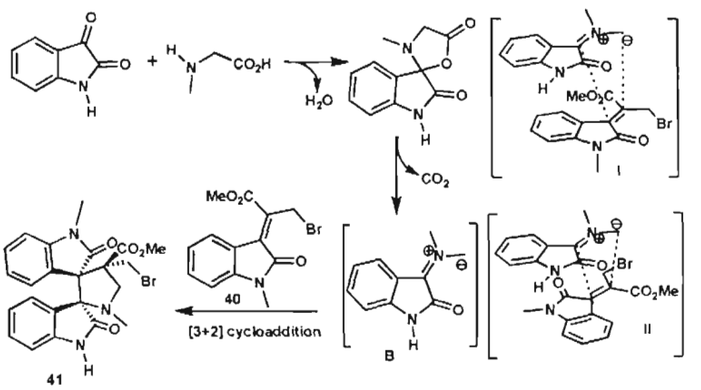
Scheme 3.16: *General nature of the cycloaddition reaction*

Table 3.2: Generality of the reaction of various bromoisomerised MBH adducts with AMY

entry	substrate	product	yield (%)
1	 42	 48	75
2	 43 Ph	 49	85
3	 44	 50	82
4	 45	 51	80
5	 46	 52	75
6	 47	 53	78

3.4.4 Formation of dispiropyrrolidine bisoxindole: Mechanistic Postulate

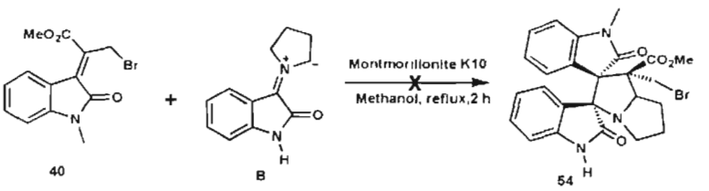
Isatin and sarcosine undergo condensation and decarboxylation *via* Tsuge route to form the acyclic azomethine ylide **B**.[17] Subsequent addition of this unstabilized azomethine ylide **B** to the double bond of the isomerised MBH adduct to form the dispiropyrrolidine bisoxindoles (Scheme 3.17).



Scheme 3.17: *Mechanistic Postulate*

The geometry of alkene fixes two stereogenic centres of the newly formed pyrrolidine ring, as the cycloaddition of azomethine ylide is highly concerted and stereospecific. *Endo/Exo* selectivity of the products was arrived based on literature analogy.[18] Secondary orbital interactions between the two oxindole moieties, favours the transition state **I** than **II** thereby leading to the formation of the product (Scheme 3.17).

To our dismay the [3+2] cycloaddition reaction of cyclic azomethine ylide **A** (generated from proline and isatin) with isomerised MBH adduct **40** failed to provide the expected dispiropyrrolidine bisoxindole **54** under optimized condition. This may probably due to the steric effect of the bulky bromine atom at the allylic position which hinders the approach of the cyclic dipole A (Scheme 3.18).

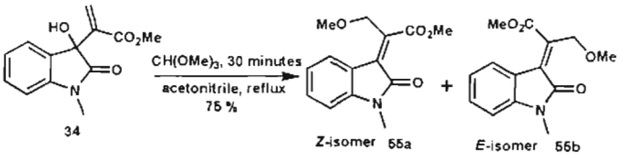


Scheme 3.18: *Model study for dispiropyrrolizidine bisoxindole*

As a logical extension of the cycloaddition reaction of the bromo isomerised MBH adducts with AMY, we explored the [3+2]-cycloaddition reactivity pattern to a number of methoxy isomerised MBH adducts (**55-58**) derived from isatin with cyclic **A** and acyclic azomethine ylides **B**. To achieve this feat, we first synthesized the methoxy isomerised MBH adducts of isatin as described below.

3.4.5 Preparation of methoxyisomerised MBH adduct of isatin

The methoxyisomerised MBH adduct **55** was prepared by refluxing the MBH adduct **34** in acetonitrile with excess of trimethyl orthoformate catalyzed by freshly activated Mont. K10 clay for half an hour. The reaction furnished Z-isomer **55a** and *E*-isomer **55b** in 75% and 3% yields respectively as shown in scheme 3.19.[15] The major Z-isomer was used for subsequent cycloaddition reaction.



Scheme 3.19: *Synthesis of allyl methyl ethers*

The formation of **55a** was arrived from the proton NMR spectrum as appearance of singlet peak at δ 4.99 indicates the presence of methylene protons of the ether linkage as shown in figure 3.6. Detailed spectral data of compound **55a** is provided in the experimental part.

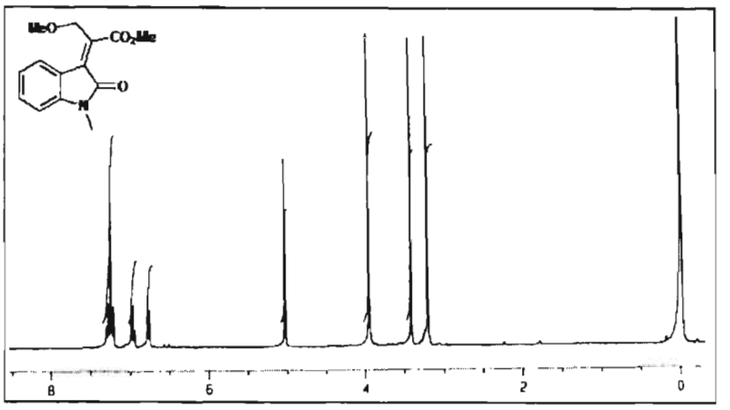
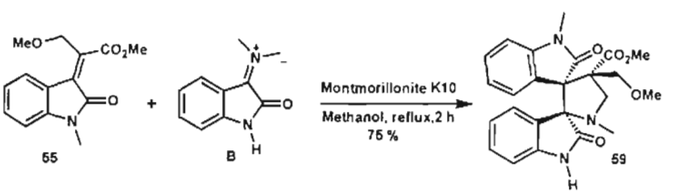


Figure 3.6: *Proton NMR spectrum of* **55**

3.4.6 [3+2]-Cycloaddition reaction of methoxyisomerised MBH adduct 55 with acyclic AMY

The methoxyisomerised MBH adduct **55** of *N*-methyl isatin was subjected to cycloaddition reaction with acyclic azomethine ylide **B** (derived from sarcosine and isatin) in refluxing methanol using Mont. K10 clay as a catalyst for 2 hours. The reaction afforded the methoxymethyl substituted dispiropyrrolidine bisoxindole **59** as sole product in 75% yield after column purification (Scheme 3.20).



Scheme 3.20: *Reaction of dipole B with* **55**

The structure of compound **59** was confirmed using spectroscopic analysis. In the IR spectrum, compound **59** showed carbonyl absorptions at 1731 cm^{-1} and 1730 cm^{-1}. In the proton NMR, four singlets with chemical shift δ 2.22, 2.96, 3.29 and 3.38 were amenable to the methyl protons attached to pyrrolidine ring, amide nitrogen, methoxy of ether and the ester methyl groups, respectively. A pair of doublets, with a coupling constant J = 9 Hz visible at

chemical shift centred at δ 3.49 and 4.32, were due to the methylene protons of the pyrrolidine nitrogen and another pair of doublets with a coupling constant *J* = 9 Hz centred at δ 3.55 and 4.63 were discernible to the methylene protons attached to the ether linkage. All the aromatic protons were seen in the downfield region ranges from δ 6.48 to 7.50. The proton attached to the amide nitrogen appeared at δ 8.11 as a singlet (Figure 3.7).

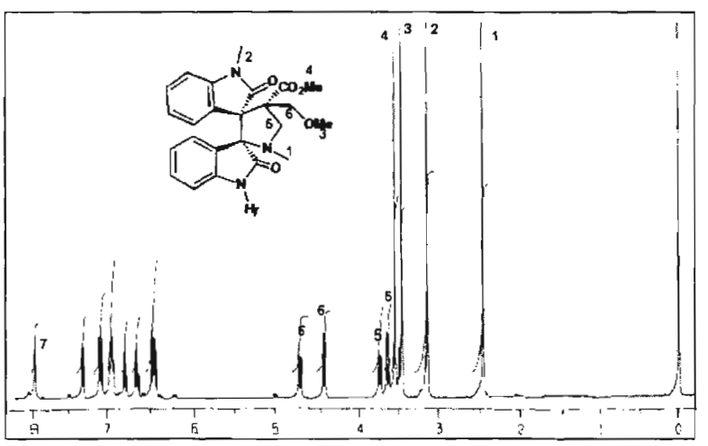


Figure 3.7: *Proton NMR spectrum of* **59**

In the ^{13}C NMR spectrum of **59**, the two spiro carbons were resonated at δ 63.5 and 78.5. The methoxy carbons of the ester and the ether were appeared at δ 58.0 and 59.1. Peaks at δ 171.5, 172.6 and 177.1 were indicative of the amide and the ester carbonyls (Figure 3.8). The structure was finally confirmed by mass spectral analysis value as it showed a molecular ion peak at m/z = 435.35 (M^+).

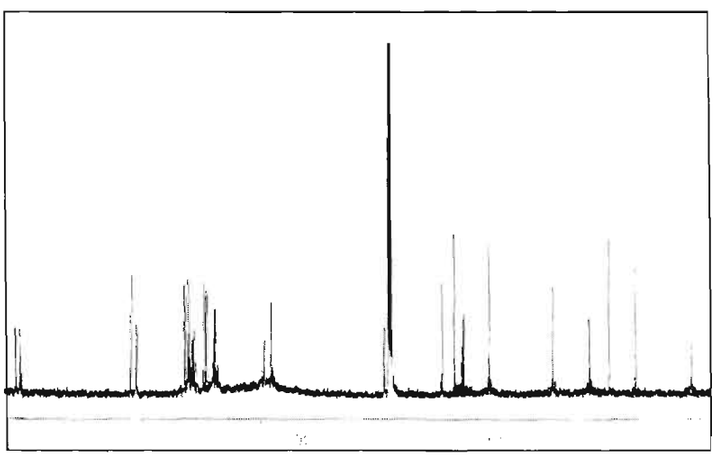
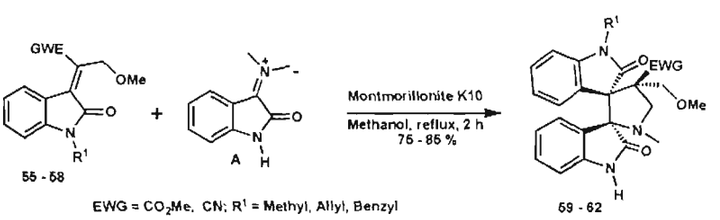


Figure 3.8: *Carbon-13 NMR spectrum of* **59**

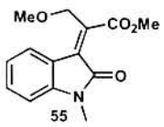
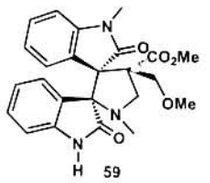
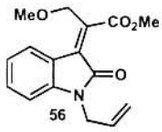
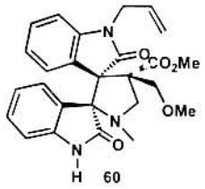
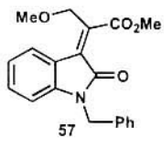
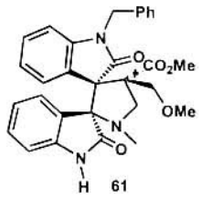
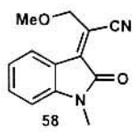
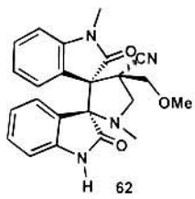
The general nature of the cycloaddition reaction was tested using methoxy isomerised MBH adducts **55-58** with various substituents at amide nitrogen and at the activated alkenes as shown in scheme 3.21. The methoxy isomerised adducts were prepared according to the procedure described in section 2.5.3. All the substrates underwent the 1,3-dipolar cycloaddition reaction smoothly under optimized condition to afford the corresponding dispiropyrrolidine oxindoles **59** - **62** in excellent yield.



Scheme 3.21: *Generalization of the [3+2]-cycloaddition reaction*

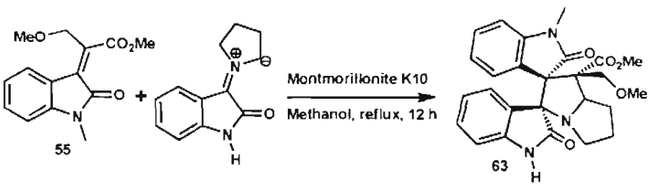
All the new compounds were thoroughly characterized by spectroscopic methods (IR, ^{1}H, ^{13}C NMR and FAB-mass spectra). The results are presented in table 3.3. Complete spectral characterizations of all new compounds are given in the experimental section.

Table 3.3: Genarality of the AMY cycloaddition with methoxy isomerised MBH adducts

entry	substrate	product	yield (%)
1	 55	 59	75
2	 56	 60	85
3	 57	 61	80
4	 58	 62	82

Reaction condition: 1equvi. isatin, 1.2 equvi. sarcosine, 100% Mont. K10, Methanol, reflux.

Further extension of this method for the synthesis of dispiropyrrolizidine bisoxindoles using cyclic AMY **A** was successful although the reaction was low yielding. The reaction of **55** with AMY **A** (generated from isatin and proline) in refluxing methanol and Mont. K-10 as the catalyst yielded compound **63** only in 45% yield (Scheme 3.22).



Scheme 3.22: *Cycloaddition of* **55** *with cyclic AMY* **A**

The structure of **63** has been confirmed from the spectroscopic analysis. Thus, the IR spectrum showed an absorbance at 3443 cm^{-1} confirming the N-H stretching vibration. The amide and the ester functionalities were confirmed by the absorption at 1714 cm^{-1} and 1723 cm^{-1}.

The proton NMR of compound **63** showed five different multiplets for the pyrrolizidine ring methylene protons in the range δ 2.04-2.78. The amide methyl and the ester methyl protons were discernable to a singlet at δ 2.97 and the ether methyl proton at δ 3.32. The methylene protons of the ether linkage was appeared as two mutually coupled doublets centred at δ 3.92 and δ 5.24 with a coupling constant J = 9.3 Hz. A multiplet at δ 4.94 was indicative of the methine proton of the pyrrolizidine ring. All the aromatic protons were observed in the downfield range δ 6.43-7.75. The amide proton was visible at δ 7.63 (Figure 3.9).

In the ^{13}C NMR spectrum, all the aliphatic carbons were observed in the up field region from δ 22.6 - 71.8. The two spiro carbons were observed at δ 69.5 and δ 78.6. Two peaks at δ 171.3 and 172.4 were indicative of the amide carbonyl carbons. The ester carbonyl carbon was resonated at δ 178.8(Figure 3.10).

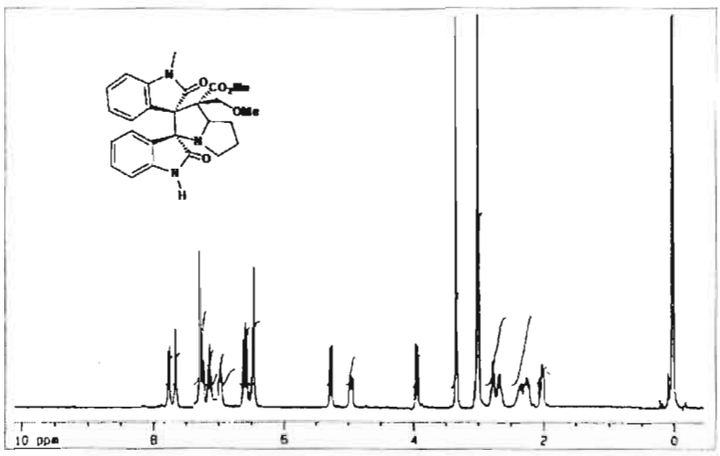


Figure 3.9: *Proton NMR spectrum of* **63**

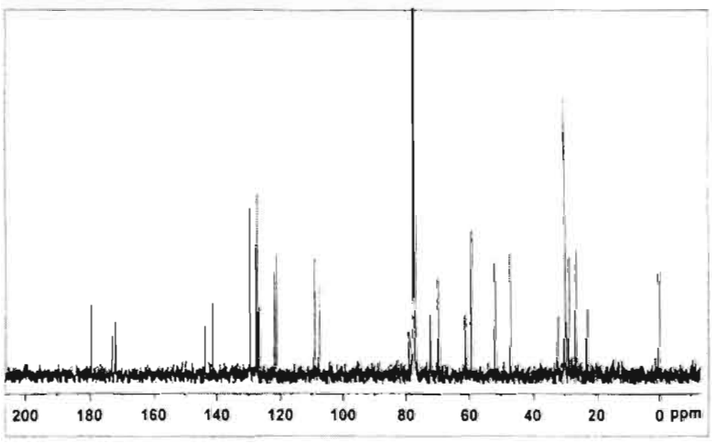


Figure 3.10: *13-Carbon NMR spectrum of* **63**

Finally the structure was confirmed by a molecular ion peak at *m/z* = 462.43 in mass spectral analysis.

3.5 Conclusions

From the above study, the major conclusions arrived are summarized as follows.

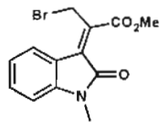
1. A novel synthesis of dispiropyrrolidine bisoxindoles using cycloaddition of cyclic and acyclic azomethine ylide strategy has been achieved.
2. The starting material isatin substituted allyl bromides and allyl ethers can readily be accessed from corresponding MBH adducts of isatin by isomerization reaction.
3. Regarding cycloaddition reaction, acyclic azomethine ylide were found to be highly reactive towards isomerised MBH adduct whereas cyclic ylides were found unreactive towards allyl derivatives due to the steric nature of bulky bromine atom.
4. A plausible mechanism of the reaction is established.
5. All the new compounds were thoroughly characterized by spectroscopic methods.

3.6 Experimental

General experimental procedure for the preparation of bromo isomerised MBH adducts of isatin:

A mixture of MBH derived from isatin (100 mg, 0.382 mmol) was added to 4 equiv. of 46% HBr and silica gel (0.2 g) and made as slurry. The slurry was subjected to microwave irradiation (750 W, 5 seconds pulse) over a period of 3 min. It was further irradiated (10 minutes) to get a single isomer as a sole product. The hot crude mixture was cooled to room temperature and then extracted with CH_2Cl_2 and the organic phase was washed with water. The organic layer was separated and dried (Na_2SO_4) and concentrated *in vacuo*. The crude mixture was purified by silica gel column chromatography using a gradient elution with hexane and hexane and EtOAc as eluent to afford pure isomerised bromo derivatives **39** and **40** in 95% combined yield.

Spectral data for compound 39



39

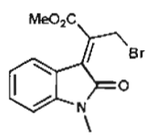
IR (Neat) ν_{max}: 543, 751, 1157, 1202, 1284, 1470, 1605, 1700, 1725, 2851, 3071 cm^{-1}.

^{1}H NMR($CDCl_3$/TMS, 300.1 MHz): δ 3.25 (s, 3H), 4.00 (s, 3H), 5.23 (s, 2H), 6.78-6.80 (d, 1H, *J* = 8 Hz), 6.98-7.01 (d, 1H, *J* = 8 Hz), 7.32-7.35 (d, 1H, *J* = 8 Hz), 7.46-7.47 (d, 1H, *J* = 8 Hz).

^{13}C NMR($CDCl_3$/TMS, 75.3 MHz): δ 25.4, 27.0, 52.9, 108.3, 122.8, 124.5, 128.8, 131.3, 136.4, 144.4, 166.8, 167.1.

LRMS (FAB) for $C_{13}H_{12}BrNO_2$, Calcd *m/z*: 310.14(M^+); Found *m/z*: 310.25 (M^+) and 312.24 (M+2).

Spectral data for compound 40



40

IR (Neat) ν_{max}: 543, 751, 1097, 1157, 1203, 1284, 1470, 1605, 1700, 1725, 2851, 3071 cm^{-1}.

^{1}H NMR($CDCl_3$/TMS, 300.1 MHz): δ 3.20 (s, 3H), 3.96 (s, 3H), 4.49 (s, 2H), 6.83-6.84 (d, 1H, *J* = 8 Hz), 7.10-7.13 (d, 1H, *J* = 8 Hz), 7.32-7.35 (d, 1H, *J* = 8 Hz), 7.37-7.39 (d, 1H, *J* = 8 Hz).

^{13}C NMR($CDCl_3$/TMS, 75.3 MHz): δ 25.4, 26.0, 52.9, 108.3, 122.5, 124.5, 128.1, 131.6, 136.8, 144.0, 166.8, 167.2.

LRMS (FAB) for $C_{13}H_{12}BrNO_2$, Calcd (M^+) *m/z*: 310.14; Found *m/z*: 310.22 (M^+) and 312.22 (M+2).

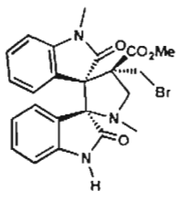
General experimental procedure for the cycloaddition of isomerised MBH adducts with cyclic and acyclic azomethine ylides

A mixture of isomerised MBH adduct of isatin (100 mg, 0.404 mmol), L-(-) proline or sarcosine (1.2 equiv.), isatin (1.2 equiv.) and montmorillonite K-10 clay (100% w/w) in methanol (1 mL) was refluxed for 2-12 hours. After

completion of the reaction (TLC), the crude mixture was filtered through a pad of celite and then purified by silica gel column chromatography to afford pure products (45-85%).

Synthesis of 41 from 40 and AMY "A" *via* [3+2]-cycloaddition

A mixture of (Z)-methyl 3-bromo-2-(1-methyl-2-oxoindolin-3-ylidene) propanoate **40** (100 mg, 0.322 mmol), sarcosine (34 mg, 0.386 mmol), isatin (56.9 mg, 0.386 mmol) and montmorillonite K-10 clay (100% w/w) in methanol (1 mL) was refluxed for 2 hours to afford **41** in 75% yield (116 mg, eluent: 35% EtOAc:Hexane).



41

IR (neat) ν_{max}: 1225, 1355, 1470, 1480, 1614, 1731, 1735, 2124, 2928, 3210 cm^{-1}.

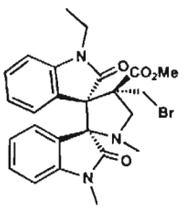
^{1}H NMR($CDCl_3$/TMS, 300.1 MHz): δ 2.2 (s, 3H), 2.97 (s, 3H), 3.54 (d, 1H, *J* = 9Hz), 3.60 (s, 3H), 3.73 (d, 1H, *J* = 9Hz), 4.45 (d, 1H, *J* = 9Hz), 4.89 (d, 1H, *J* = 9Hz), 6.53- 6.60 (m, 2H), 6.92- 6.95 (m, 2H), 7.10-7.12 (m, 1H), 7.22- 7.38 (m, 1H), 7.38-7.47 (m, 2H), 7.64 (s, 1H)

^{13}C NMR($CDCl_3$/TMS, 75.3 MHz): δ 26.7, 35.3, 51.9, 53.7, 59.5, 65.6, 79.3, 107.8, 108.3, 110.2, 122.4, 122.8, 124.1, 126.6, 128.5, 131.2, 133.3, 141.4, 144.8, 175.2, 177.3, 180.1

LRMS (FAB) for $C_{23}H_{22}BrN_3O_4$, Calcd (M^+) *m/z*: 484.34; Found m/z: 484.29 (M^+) and 486.21 (M+2).

Synthesis of 48 from 42 and AMY "A" *via* [3+2]-cycloaddition

A mixture of (Z)-methyl 3-bromo-2-(1-ethyl-2-oxoindolin-3-ylidene) propanoate **42** (100 mg, 0.308 mmol), sarcosine (32.9 mg, 0.37 mmol), isatin (59.6 mg, 0.370 mmol) and montmorillonite K-10 clay (100% w/w) in methanol (1 mL) was refluxed for 2 hours to afford **48** in 75% yield (118 mg, eluent: 35% EtOAc:Hexane).



48

IR (neat) ν_{max}: 756, 1170.2, 1355, 1373, 1468, 1473, 1489, 1610, 1705, 1755, 3054 cm^{-1}.

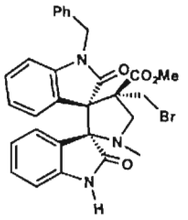
^{1}H NMR($CDCl_3$/TMS, 300.1 MHz): δ 0.98-1.029 (t, 3H), 2.20 (s, 3H), 2.94 (s, 3H), 3.47-3.54 (m, 3H), 3.63 (s, 3H), 3.77-3.81 (d, 1H, *J* = 10 Hz,), 4,47- 4.50 (d, 1H, *J* = 10 Hz), 4.90-4.93 (d, 1H, *J* = 8.7 Hz,), 6.46-6.49 (d, 1H, *J* = 6Hz,), 6.56- 6.59 (d, 1H, *J* = 9 Hz,), 6.90-6.95 (m, 2H), 7.15-7.19 (m, 2H), 7.31-7.33 (d, 1H, *J* = 6 Hz), 7.49-7.51 (d, 1H, *J* = 3Hz)

^{13}C NMR($CDCl_3$/TMS, 75.3 MHz): δ 13.8, 25.4, 34.6, 35.6, 39.8, 52.8, 59.4, 59.8, 60.6, 65.3, 79.1, 107.9, 108.5, 111.1, 121.7, 130.1, 130.4, 144.0, 144.3, 174.7, 175.6, 176.9.

LRMS (FAB) for $C_{25}H_{26}BrN_3O_4$, Calcd (M^+): 512.39; Found m/z: 512.10 (M^+) and 512.06 (M+2).

Synthesis of 49 from 43 and AMY "A" *via* [3+2]-cycloaddition

A mixture of (Z)-methyl 2-(1-benzyl-2-oxoindolin-3-ylidene)-3-bromopropanoate **43** (100 mg, 0.289 mmol), sarcosine (27 mg, 0.310 mmol), isatin (38 mg, 0.289 mmol) and montmorillonite K-10 clay (100% w/w) in methanol (1 mL) was refluxed for 2 hours to afford **49** in 85% yield (136 mg, eluent: 35% EtOAc:Hexane).



49

IR (neat) ν_{max}: 1170, 1358, 1370, 1470, 1470, 1490, 1615, 1705, 1750, 3056, 3258 cm^{-1}.

^{1}H NMR($CDCl_3$/TMS, 300.1 MHz): δ 2.27 (s, 3H), 3.23 (s, 3H), 3.54 - 3.57 (d, 1H, *J* = 9.9Hz), 3.88 - 3.91 (d, 1H, *J* = 9.6Hz), 4.38 - 4.43 (d, 1H, *J* = 15 Hz), 4.68 - 4.80 (m, 2H), 4.95 - 5.00 (d, 1H, *J* = 15 Hz), 6.36 - 6.39 (d, 1H, *J* = 9Hz), 6.62 - 6.64 (m, 3H), 6.67 - 6.77 (m, 1H), 6.95 - 6.98 (m, 2H), 7.11-7.20 (m, 4H), 7.35-7.37 (d, 1H, *J* = 9Hz), 7.55-7.57 (d, 1H, *J* = 6 Hz),

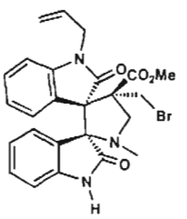
7.60 (s, 1H).

^{13}C NMR($CDCl_3$/TMS, 75.3 MHz): δ 18.5, 34.2, 42.4, 52.5, 55.8, 58.4, 66.1, 77.4, 109.1, 109.3, 122.2, 122.5, 124.6, 125.7, 126.5, 127.6, 128.9, 129.4, 129.8, 138.2, 141.9, 143.6, 171.8, 172.9, 175.8.

LRMS (FAB) for $C_{29}H_{26}BrN_3O_4$, Calcd (M^+): 560.43; Found m/z: 560.22 (M^+) and 562.22 (M+2).

Synthesis of 50 from 44 and AMY "A" *via* [3+2]-cycloaddition

A mixture of (*Z*)-methyl 2-(1-allyl-2-oxoindolin-3-ylidene)-3-bromopropanoate **44** (100 mg, 0.297 mmol), sarcosine (31 mg, 0.356 mmol), isatin (43 mg, 0.297 mmol) and montmorillonite K-10 clay (100% w/w) in methanol (1 mL) was refluxed for 2 hours to afford **50** in 82% yield (124 mg, eluent: 35% EtOAc:Hexane).



50

IR (neat) ν_{max}: 755, 1477, 1485, 1615, 1730, 1733, 2928, 3265 cm^{-1}.

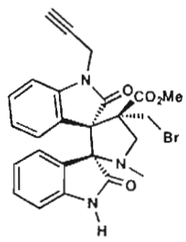
^{1}H NMR($CDCl_3$/TMS, 300.1 MHz): δ 2.21 (s, 3H), 3.54 - 3.56 (d, 1H, *J* = 8.9 Hz), 3.63 (s, 3H), 3.72 - 3.75 (d, 1H, *J* = 10.2 Hz), 4.11 - 4.14 (m, 2H), 4.44 - 4.48 (d, 1H, *J* = 10.2 Hz), 4.83 - 4.88 (dd, 2H, *J* = 13.2 Hz, *J* = 3.6Hz), 5.02 - 5.06 (d, 1H, *J* = 10.2Hz), 5.48 - 5.55 (m, 1H), 6.52 - 6.54 (d, 1H, *J* = 7.8Hz), 6.57 - 6.60 (d, 1H, *J* = 9Hz), 6.69- 6.88 (m, 2H), 7.10 - 7.21 (m, 2H), 7.38 (s, 1H), 7.40-7.47 (m, 2H).

^{13}C NMR($CDCl_3$/TMS, 125.77 MHz): δ 31.1, 35.1, 42.2, 49.0, 52.7, 59.5, 79.5, 109.3, 117.6, 122.9, 127.4, 127.5, 129.3, 129.8, 130.8, 141.1, 143.1, 149.4, 172.1, 173.5, 176.5.

LRMS (FAB) for $C_{25}H_{24}BrN_3O_4$, Calcd (M^+): 510.37; Found m/z: 510.21 (M^+) and 511.12 (M+2).

Synthesis of 51 from 45 and AMY "A" *via* [3+2]-cycloaddition

A mixture of (*Z*)-methyl 3-bromo-2-(1-methyl-2-oxoindolin-3-ylidene) propanoate **45** (100 mg, 0.322 mmol), sarcosine (34 mg, 0.386 mmol), isatin (56.9 mg, 0.386 mmol) and montmorillonite K-10 clay (100% w/w) in methanol (1 mL) was refluxed for 2 hours to afford **51** in 80% yield (131 mg, 35% EtOAc:Hexane).



51

IR (neat) ν_{max}: 750, 1470, 1488, 1614, 1731, 1730, 2924, 3287 cm^{-1}.

^{1}H NMR($CDCl_3$/TMS, 300.1 MHz): δ 1.25- 1.28 (m, 1H), 2.18 (s, 3H), 3.52 (d, 1H, *J* = 8.5Hz), 3.60 (s, 3H), 3.74 (d, 1H, *J* = 9.8Hz), 4.39 (d, 2H, *J* = 9.8Hz), 4.97 (d, 1H, *J* = 8.6Hz), 6.51- 6.53 (m, 2H), 6.80-6.86 (m, 2H), 7.02 - 7.06 (m, 2H), 7.25 (t, 1H, *J* = 6Hz), 7.43 (d, 1H, *J* = 6Hz), 7.47 (d, 1H, *J* = 6Hz), 9.67 (s, 1H).

^{13}C NMR($CDCl_3$/TMS, 75.3 MHz): δ 36.2, 48.7, 57.1, 59.4, 61.2, 63.3, 64.4, 78.5, 79.5, 79.9, 108.2, 109.2, 116.1, 120.7, 125.3, 128.1, 128.5, 131.7, 140.2, 141.9, 142.4, 172.5, 172.7, 178.

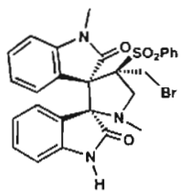
LRMS (FAB) for $C_{25}H_{22}BrN_3O_4$, Calcd (M^+): 508.36; Found m/z: 508.69 (M^+) and M+2 = 510.71.

Synthesis of 52 from 46 and AMY "A" *via* [3+2]-cycloaddition

A mixture of (*E*)-3-(2-bromo-1-(phenylsulfonyl)ethylidene)-1-methylindolin-2-one **46** (100 mg, 0.254 mmol), sarcosine (27 mg, 0.305 mmol), isatin (37 mg, 0.254 mmol) and montmorillonite K-10 clay (100% w/w) in methanol (1 mL) was refluxed for 2 hours to afford **52** in 75% yield (105 mg, eluent: 35% EtOAc:Hexane).

IR (neat) ν_{max}: 750, 1135, 1310, 1470, 1488, 1614, 1730, 1731, 2924, 3287 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 2.23 (s, 3H), 3.00 (s, 3H), 3.90-3.94 (d, 1H, *J* = 11.1 Hz), 4.02-4.06



52

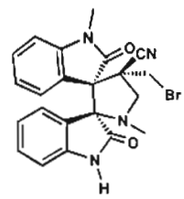
(d, 1H, J = 10.8Hz), 4.79- 4.83 (d, 1H, J = 11.1Hz), 4.99-5.03 (d, 1H, J = 11.1Hz), 6.49- 6.89 (t, 1H, J = 7.8 Hz), 6.89 -6.99 (m, 7H), 7.07- 7.12 (m, 2H), 7.17 – 7.22 (t, 1H, J = 6 Hz), 7.41- 7.43 (d, 1H, J = 6 Hz), 7.47 (s, 1H), 7.89-7.91 (d, 1H, J = 6 Hz).

^{13}C NMR($CDCl_3$/TMS, 75.3 MHz): δ 23.7, 30.8, 37.5, 42.4, 53.1, 66.7, 78.7, 120.7, 121.4, 123.5, 124.2, 126.2, 128.4, 128.8, 129.8, 129.9, 132.2, 135.3, 139.7, 141.4, 152.7, 172.0, 178.6.

LRMS (FAB) for $C_{27}H_{24}BrN_3O_4S$, Calcd (M^+): 556.46; Found m/z: 556.38 (M^+) and 558.39 (M+2).

Synthesis of 53 from 47 and AMY "A" *via* [3+2]-cycloaddition

A mixture of (*Z*)-3-bromo-2-(1-methyl-2-oxoindolin-3-ylidene)propanenitrile (100 mg, 0.360 mmol), sarcosine (38 mg, 0.433 mmol), isatin (53 mg, 0.360 mmol) and montmorillonite K-10 clay (100% w/w) in methanol (1 mL) was refluxed for 2 hours to afford **53** in 78% yield (126 mg, eluent: 35% EtOAc:Hexane).



53

IR (neat) ν_{max}: 755, 1478, 1480, 1624, 1730, 1731, 2125, 2251, 2922, 3280 cm^{-1}.

^{1}H NMR($CDCl_3$/TMS, 300.1 MHz): δ 2.51 (s, 3H), 2.99 (s, 3H), 3.57 - 3.60 (d, 1H, J = 10.2Hz), 3.78- 3.82 (d, 1H, J = 10.2), 4.31- 4.32 (d, 1H, J = 4.1Hz), 4.34-4.35 (d, 1H, J = 10.2Hz), 6.49 - 6.51 (d, 2H, J = 7.8Hz), 6.87 - 6.96 (m, 2H), 7.03-7.09 (t, 1H, J = 7.5Hz), 7.14-7.16 (d, 1H, J = 6Hz), 7.68 - 7.30 (d, 1H, J = 7.5Hz), 7.50 (s, 1H), 7.82-7.84 (d, 1H, 7.8 Hz).

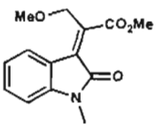
^{13}C NMR($CDCl_3$/DMSO/TMS, 125.7 MHz): δ 25.4, 34.1, 35.9, 47.8, 60.4, 61.6, 78.0, 107.3, 109., 119.9, 121.2, 121.3, 121.3, 121.4, 121.8, 121.9, 125.1, 126.3, 128.9, 129.5, 142.4, 143.0, 171.4, 175.2.

LRMS (FAB) for $C_{22}H_{19}BrN_4O_2$, Calcd (M^+): 451.31; Found m/z: 451.28 (M^+) and 453.39 (M+2).

General experimental procedure for the preparation of methoxy isomerised MBH adducts of isatin

A mixture of MBH adducts (100 mg, 0.404 mmol), excess of trimethyl orthoformate (3mL) and montmorillonite K-10 Clay (50% w/w) without any solvent was heated at 110 °C for 30 minutes. After the reaction (TLC), the crude mixture was purified by a silica gel column chromatography to afford Z - isomerised product **55** in good yield.

Spectral data for compound 55a



55a

IR (neat) ν_{max}: 1083, 1260, 1378, 1462, 1620, 1712, 2916, 2957cm^{-1}.

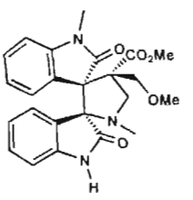
^{1}**H NMR**($CDCl_3$/TMS, 300.1 MHz): δ 3.15 (s, 3H), 3.36 (s, 3H), 3.39 (s, 3H), 4.99 (s, 2H), 6.72 - 6.74 (d, 1H, *J* = 8Hz), 6.91 - 6.94 (t, 1H, *J* = 8Hz), 7.17 - 7.19 (d, 1H, *J* = 8Hz), 7.22 - 7.25 (t, 1H, *J* = 8Hz).

^{13}**C NMR**($CDCl_3$/TMS, 75.3 MHz): δ 25.9, 52.61, 59.1, 68.1, 108.2, 119.6, 122.4, 122.6, 124.9, 130.4, 141.6, 143.6, 167.0, 167.5.

LRMS (FAB) for $C_{14}H_{15}NO_4$, Calcd (M^+): 261.27; Found m/z: 262.38 (M+2).

Synthesis of 59 from 55 and AMY "A" *via* [3+2]-cycloaddition

A mixture of (Z)-methyl 3-bromo-2-(1-methyl-2-oxoindolin-3-ylidene) propanoate **55** (100 mg, 0.382 mmol), sarcosine (40.9 mg, 0.459 mmol), isatin (56.9 mg, 0.382 mmol) and montmorillonite K-10 clay (100% w/w) in methanol (1 mL) was refluxed for 2 hours to afford **59** in 75% yield (124 mg, eluent: 30% EtOAc:Hexane).



59

IR (neat) ν_{max}: 753, 1083, 1223, 1355, 1470, 1488, 1614, 1730, 1731, 2924, 3287 cm^{-1}.

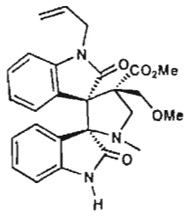
^{1}H NMR($CDCl_3$/TMS, 300.1 MHz): δ 2.22 (s, 3H), 2.96 (s, 3H), 3.29 (s, 3H), 3.38 (s, 3H), 3.49 (d, 1H, *J* = 9Hz), 3.59 (d, 1H, *J* = 9Hz), 4.33 (d, 1H, *J* = 9Hz), 4.65 (d, 1H, *J* = 9Hz), 6.48 - 6.59 (m, 2H), 6.78 - 6.79 (m, 1H), 6.93-6.94 (m, 1H), 7.09 - 7.13 (m, 2H), 7.23 - 7.28 (m, 1H), 7.49 (d, 1H, *J* = 9Hz), 8.11 (s, 1H).

^{13}C NMR($CDCl_3$/TMS, 75.3 MHz): δ 25.8, 34.6, 51.9, 58.0, 59.1, 60.3, 63.5, 78.5, 107.0, 107.5, 109.2, 121.5, 121.8, 124.1, 124.8, 127.2, 128.1, 129.6, 130.5, 141.8, 143.3, 171.5, 172.6, 177.1.

LRMS (FAB) for $C_{24}H_{25}N_3O_5$ Calcd (M^+): 435.47; Found m/z: 435.35 (M^+).

Synthesis of 56 from 60 and AMY "A" *via* [3+2]-cycloaddition

A mixture of (*Z*)-methyl 2-(1-allyl-2-oxoindolin-3-ylidene)-3-methoxypropanoate **56** (100 mg, 0.348 mmol), sarcosine (37.2 mg, 0.417 mmol), isatin (51 mg, 0.348 mmol) and montmorillonite K-10 clay (100% w/w) in methanol (1 mL) was refluxed for 2 hours to afford **60** in 85% yield (136 mg, eluent: 30% EtOAc:Hexane).



60

IR (neat) ν_{max}: 753, 1083, 1222, 1359, 1459, 1469, 1614, 1723, 2951, 3272 cm^{-1}.

^{1}H NMR($CDCl_3$/TMS, 300.1 MHz): δ 2.24 (s, 3H), 3.33 (s, 6H), 3.45 - 3.48 (d, 1H, *J* = 9Hz), 3.92 - 3.94 (m, 1H), 4.12 (d, 1H, *J* = 9Hz), 4.28 (d, 1H, *J* = 9Hz), 4.64 - 4.67 (m, 2H), 4.91 - 4.95 (m, 1H), 5.35 - 5.42 (m, 1H), 6.51 (d, 1H, *J* = 6Hz), 6.59 (d, 1H, *J* = 6Hz), 6.78 (t, 1H, *J* = 6Hz), 6.92 (t, 1H, *J* = 6Hz), 7.05-7.13 (m, 2H), 7.22(d, 1H, *J* = 6Hz), 7.29 (d, 1H, *J* = 6Hz), 7.50 (d, 1H, *J* = 6Hz), 8.01 (s, 1H).

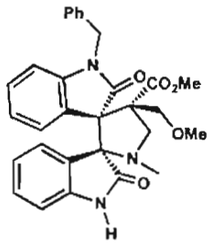
^{13}C NMR($CDCl_3$/TMS, 75.3 MHz): δ 35.2, 47.7, 51.4,

58.1, 58.4, 59.2, 60.3, 63.4, 76.5, 78.4, 108.1, 109.2, 116.8, 121.6, 122.1, 124.3, 125.1, 127. 2, 128.5, 129.4, 130.7, 141.9, 142.4, 171.5, 172.2, 177.3.

LRMS (FAB) for $C_{26}H_{27}N_3O_5$, Calcd (M^+): 461.51; Found m/z: 461.89 (M^+).

Synthesis of 57 from 61 and AMY "A" *via* [3+2]-cycloaddition

A mixture of (Z)-methyl 2-(1-benzyl-2-oxoindolin-3-ylidene)-3-methoxypropanoate **57** (100 mg, 0.296 mmol), sarcosine (31 mg, 0.356 mmol), isatin (43 mg, 0.296 mmol) and montmorillonite K-10 clay (100% w/w) in methanol (1 mL) was refluxed for 2 hours to afford **61** in 80% yield (121 mg, eluent: 35% EtOAc:Hexane).



61

IR (neat) ν_{max}: 750, 1082, 1359, 1450, 1463, 1612, 1720, 2950, 3275 cm^{-1}.

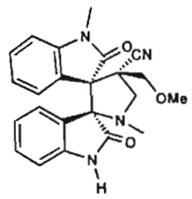
^{1}H NMR($CDCl_3$/TMS, 300.1 MHz): δ 2.27 (s, 3H), 3.27 (s, 3H), 3.36 (s, 3H), 3.47-3.50 (d, 1H, *J* = 9.6Hz), 3.67-3.70 (d, 1H, *J* = 7.2Hz), 4.37-4.40 (d, 1H, *J* = 8.4 Hz), 4.44-4.49 (d, 1H, *J* = 15.9 Hz), 4.64-4.67 (d, 1H, *J* = 9.6Hz), 4.95 - 5.00 (d, 1H, *J* = 15.6 Hz), 6.34 - 6.37 (d, 1H, *J* = 7.5 Hz), 6.58 - 6.61 (d, 1H, *J*= 9Hz), 6.66-6.68 (d, 2H, *J* = 6 Hz), 6.67-6.82 (t, 1H, *J* = 9Hz), 6.90 - 6.99 (m, 2H), 7.08 - 7.19 (m, 4H), 7.33 - 7.36 (d, 1H, *J* = 9Hz), 7.44 (s, 1H), 7.55 - 7.57 (d, 1H, *J* = 6Hz).

^{13}C NMR($CDCl_3$/TMS, 75.3 MHz): δ 15.5, 35.2, 43.4, 51.5, 57.9, 59.13, 59.3, 63.6, 78.4, 108.5, 109.2, 121.8, 122.5, 125.6, 126.75, 127.5, 128.6, 128.7, 129.0, 129.6, 135.2, 141.9, 142.6, 172.8, 173.9, 176.8.

LRMS (FAB) for $C_{30}H_{29}N_3O_5$, Calcd (M^+): 511.56; Found m/z: 512.51 (M+1).

Synthesis of 58 from 62 and AMY "A" *via* [3+2]-cycloaddition

A mixture of (*E*)-3-methoxy-2-(1-methyl-2-oxoindolin-3-ylidene) propanenitrile **58** (100 mg, 0.322 mmol), sarcosine (34 mg, 0.386 mmol), isatin (56.9 mg, 0.386 mmol) and montmorillonite K-10 clay (100% w/w) in methanol (1 mL) was refluxed for 2 hours to afford **62** in 82% yield (160 mg, eluent: 35% EtOAc:Hexane).



62

IR (neat) ν_{max}: 752, 1085, 1471, 1481, 1624, 1730, 1731, 2125, 2251, 2922, 3280 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 2.20 (s, 3H), 3.14 (s, 3H), 3.15 (s, 3H), 3.43-3.46 (d, 1H, *J* = 9.1 Hz), 3.78-3.81 (d, 1H, *J* = 8.7 Hz), 4.16-4.22 (m, 2H), 6.52-6.54 (d, 1H, *J* = 6 Hz) 6.61-6.64(d, 1H, *J* = 9 Hz), 6.68-6.94 (m, 2H), 7.07-7.14 (m, 2H), 7.35-7.38 (d, 1H, *J* = 9Hz), 7.80-7.83 (d, 1H, *J* = 9 Hz), 8.74 (s, 1H).

^{13}C NMR($CDCl_3$/TMS, 75.3 MHz): δ 25.8, 35.0, 47.4, 58.7, 60.1, 60.8, 75.5, 78.3, 107.4, 110.5, 121.8, 122.7, 126.5, 127.1, 129.4, 129.9, 130.2, 141.1, 142.1, 143.6, 172.7, 176.9.

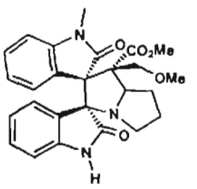
LRMS (FAB) for $C_{23}H_{22}N_4O_3$, Calcd (M^+): 402.16; Found m/z: 402.44 (M^+).

Synthesis of 55 from 63 and AMY "A" *via* [3+2]-cycloaddition

A mixture of (Z)-methyl 3-methoxy-2-(1-methyl-2-oxoindolin-3-ylidene) propanoate **55** (100 mg, 0.382 mmol), L-proline (52 mg, 0.459 mmol), isatin (56.3 mg, 0.382 mmol) and montmorillonite K-10 clay (100% w/w) in methanol (1 mL) was refluxed for 2 hours to afford **63** in 45% yield (79 mg, eluent: 35% EtOAc:Hexane).

IR (neat) ν_{max}: 750, 1082, 1359, 1450, 1463, 1612, 1713, 1723, 2950, 3443 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 2.04-2.09 (m, 2H), 2.19-2.34 (m, 2H), 2.64-2.78 (m, 2H), 2.97(s, 6H), 3.32 (s, 3H), 3.91-3.94 (d, 1H, *J* = 9.3Hz), 4.91-



63

4.96 (m, 1H), 5.23-5.26 (d, 1H, J = 9.3Hz), 6.43-6.50 (m, 2H), 6.54-6.60 (m, 2H), 6.92-6.95 (m, 1H), 7.04 - 7.11 (m, 1H), 7.25-7.28 (m, 1H), 7.63 (s, 1H), 7.73-7.75 (d, 1H, J = 7.4Hz)

^{13}C NMR ($CDCl_3$/TMS, 125.7 MHz): δ 22.6, 28.3, 29.6, 31.9, 46.7, 51.5, 58.8, 60.8, 69.5, 71.8, 78.6,107.2, 108.8, 120.9, 121.7, 126.2, 126.9, 128.8, 140.8, 143.1, 171.3, 172.4, 178.8.

LRMS (FAB) for $C_{26}H_{27}N_3O_5$, Calcd (M$^+$): 461.50; Found m/z: 462.43 (M+1).

3.7 References

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CHAPTER 4

Synthesis of 3-spirolactone oxindoles from bromo isomerised MBH adducts of isatin using Indium chemistry

4.1 Introduction

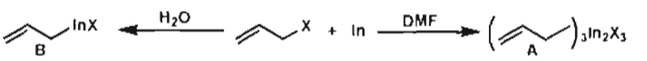
Morita-Baylis-Hillman (MBH) adducts and their derivatives such as halides, acetates, ethers *etc*. play an important role as synthons for a wide spectrum of natural products. Among various derivatives of MBH adduct, allyl bromides owe prime importance as these have well been used especially in phosphorous and sulphur ylide chemistry as a component for the generation of dipoles for the construction of cyclic scaffolds. Some of the prominent discoveries in this area have been discussed in the previous chapters. The subject matter of this chapter is the introduction of MBH derived oxindole substituted allyl bromides to indium chemistry for the allylation of formaldehyde for the synthesis homoallylic alcohols and thereby synthesis of 3-spirolactone oxindoles. Hence, it is worth to scan the recent literature for general synthetic use of indium metal.

4.2 Allylation reactions using Indium (0)

Metal mediated reactions are well known in the myriad of C-C bond forming reactions since the successful introduction of magnesium metal in the Grignard reaction. During the last few decades, indium,[1] one of the latest entries to the metal mediated reaction, has received widespread interest to synthetic organic practitioners due to its water tolerant nature, low basicity, low heterophilicity and mild reaction conditions.[2] It is also less affected by air or oxygen at ambient temperature. As the first ionisation potential of indium is comparable with alkali metals, it is an ideal candidate for single electron transfer.

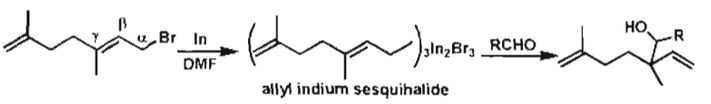
Allyl indium reagents generated *in situ* are attractive candidates as nucleophilic partners in Barbier-type allylation to amines[3a] and aldehydes,[3b,c] hydrazones,[3d] to produce homoallylic alcohols or amines due to their functional group tolerance and low toxicity. It has played a significant role in many other reactions[4] such as elimination, coupling, reduction *etc*.

The reaction of metallic indium with allyl halides in highly polar solvents such as DMF or THF at room temperature afforded the corresponding indium sesquihalide $R_3In_2X_3$ **A**.[5] But the reactions of allyl indium reagent in aqueous media proceeded through a transient allyl indium species **B** (Scheme 4.1).[6]



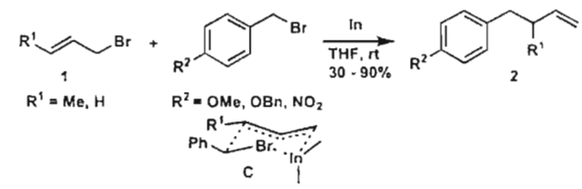
Scheme 4.1: *Reactive species in indium mediated allylation reactions*

The addition of indium reagent to the carbonyl compound is highly regioselective that the addition takes place only through the γ-carbon of the allyl halide (Scheme 4.2).[7]



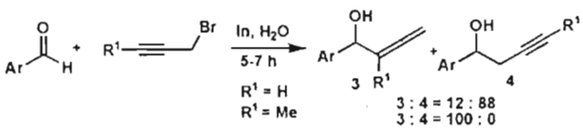
Scheme 4.2: *Regioselectivity of indium mediated allylation*

Although indium has been extensively used in carbonyl allylation, it is also a potential reagent in other domains like coupling reactions. Recently, Ranu *et al.* have described the regioselective cross-coupling of γ-substituted allyl bromide **1** with activated benzyl bromide using indium as catalyst for the synthesis of terminal alkene **2** as described in scheme 4.3. In the proposed mechanism, allylation was preceded through a cyclic transition state **C**. Benzyl bromides with electron donating substituents gave better yields than with electron withdrawing substituents.[8]



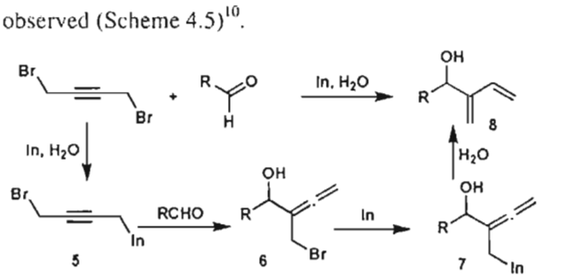
Scheme 4.3: *Indium catalyzed coupling reaction*

Other than allyl halides, propargyl halides were also used in indium chemistry. Indium mediated coupling of unsubstituted propargyl bromide with aldehyde afforded homopropargyl alcohol **4**, however γ-substituted propargyl bromide gave allenic alcohol **3** (Scheme 4.4).[9]



Scheme 4.4: *Indium mediated propargylation reaction*

Indium mediated coupling of 1,4-dibromobutyne with carbonyl compounds in aqueous medium yielded 1,3-butadien-2-yl methanol **8**. The reaction was likely to precede *via* an organoindium intermediate[6] **5** which reacted with carbonyl compound to give the allenyl bromide **6**. This again reacts with indium to give a second intermediate **7** which on quenching with water yields the desired 1,3-butadien-2-yl methanol **8**. Due to the steric demand, reaction of the second intermediate with another molecule of aldehyde was not observed (Scheme 4.5)[10].

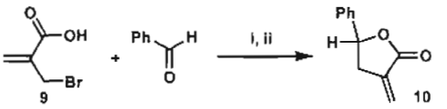


Scheme 4.5: *Synthesis of butadiene derivative*

4.2.1 Branched allyl bromides in indium chemistry

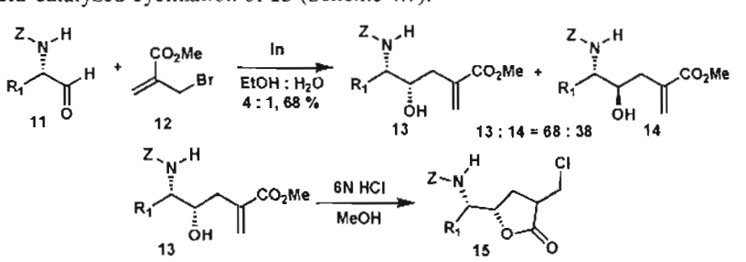
β-Branched allylic bromides were successfully used in the indium chemistry for the allylation reaction. Substituent at the β-position of the resulting homoallylic alcohol offers a route to the synthesis of cyclic frame works.

A one pot synthesis of α-methylene-γ-lactone **10** was achieved by the group of Yus *et al.* from the reaction of 2-(bromomethyl)acrylic acid **9** and carbonyl compounds in presence of indium powder followed by hydrolysis with aqueous hydrochloric acid (Scheme 4.6).[11]



Scheme 4.6: *Allylation with bromo methyl acrylic acid and lactonization*

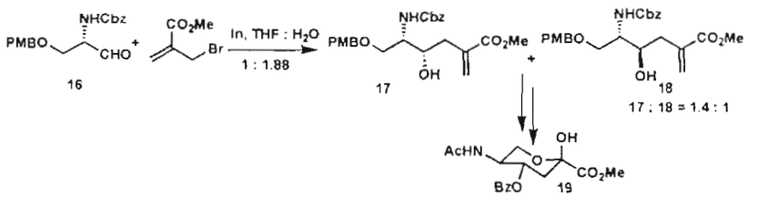
Podlech and co-workers have shown that α-amino aldehyde **11** can be cleanly transformed into δ-amino alkyl substituted γ-hydroxy-α-methylenecarboxylic esters **13** and **14** with high yields without racemisation by an indium-mediated Barbier reaction of **12**. The preference for the *syn*-configured product **13** was explained by a chelate model (Zimmerman-Traxler like transition state).[12] α-Methylene lactone **15** was effectively accessible by acid-catalyzed cyclization of **13** (Scheme 4.7).[13]



Scheme 4.7: *Synthesis of δ-amino-γ-hydroxy-α-methylenecarboxylic esters*

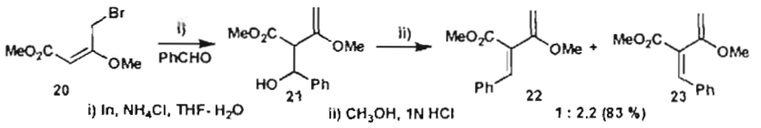
Followed by these results, Halcomp and co-workers have used an indium mediated allylation of a protected serine derived aldehyde **16** for the synthesis of a six-carbon truncated sialic acid **19** analogue. The allylation

reaction resulted in *syn* **17** and *anti* **18** diastereomers in the ratio of 1.4: 1 when the reaction was carried out in THF: H_2O mixture (1:1) as described in scheme 4.8.[14]



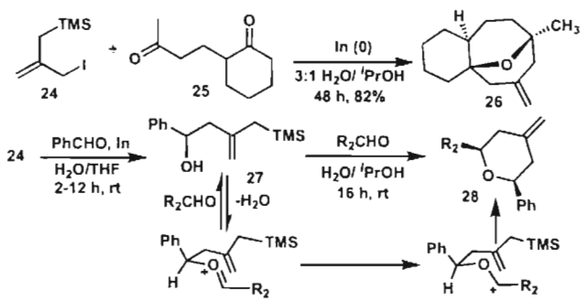
Scheme 4.8: *Synthesis of sialic acid derivative via indium mediated allylation*

Paquette and co-workers reported the formation of a Knoevenagel type adducts **22** and **23** from hydrolysis of a β-hydroxy ester **21** which was obtained from the addition of methyl (*E*)-4-bromo-3-methoxy crotonate **20** to aldehydes in the presence of indium metal and water as shown in scheme 4.9.[15]



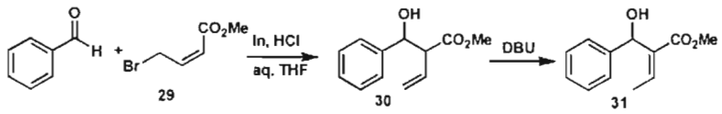
Scheme 4.9: *Knoevenagel type adduct formation using indium metal*

Minehan *et al.* reported that the reaction of 3-iodo-2-[(trimethylsilyl) methyl]-propene **24** and indium in isopropanol-water mixture with 1,5-dicarbonyl compound **25** yielded eight membered oxa-bridged carbocycles **26**.[16a] Later, they have extended the methodology for the synthesis of *cis*-2,6-disubstituted tetrahydropyran **28**. In the presence of indium metal, compound **24** reacts sequentially with aldehydes to provide terahydropyran **28** through an allylation followed by a Prins cyclization reaction (Scheme 4.10).[16b]



Scheme 4.10: *Synthesis of oxa-bridged carbocycles and tetrahydropyrans*

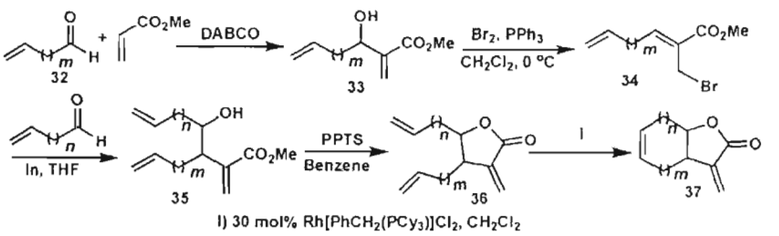
Lee and co-workers developed a new method for the synthesis of *E*-β-methyl MBH adduct **31** with high selectivity using an indium mediated allylation reaction of **29** with benzaldehyde followed by a base mediated isomerization. The initial allylation reaction of aromatic aldehydes was largely accelerated by hydrochloric acid (Scheme 4.11).[17]



Scheme 4.11: *Synthesis of (E)-β-methyl MBH adduct*

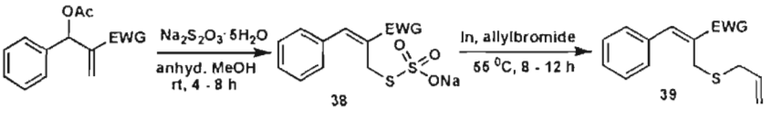
4.2.2 Morita-Baylis-Hillman adduct in indium chemistry

In 1999, Paquette and co-workers reported a general procedure for the synthesis of larger ring fused α-methylene-γ-lactone **37** from bromoisomerized MBH adducts of ω-unsaturated aldehyde **34**.[18] Indium mediated allylation of bromoisomerized MBH adducts with ω-unsaturated aldehyde **32** or other aldehydes, followed by lactonization with pyridinium *p*-toluenesulphate (PPTS) afforded the lactone **36** which on ring closing metathesis yielded the fused lactone **37** as explained in scheme 4.12.



Scheme 4.12: *Synthesis of fused ring lactones*

Very recently Zang *et al.* have reported a stereoselective synthesis of diallyl sulfide **39** *via* an indium promoted one-pot reaction of sodium thiosulphate, allyl bromide with acetates of Morita-Baylis-Hillman adduct. The *in situ* formed sodium salt of Z-allyl thiosulphate **38** from MBH acetate in methanol underwent indium mediated allylation to form unsymmetrical diallyl sulphide **39** (Scheme 4.13).[19]



Scheme 4.13: *Addition to sulphur atom*

4.3 Scope of the Present Study

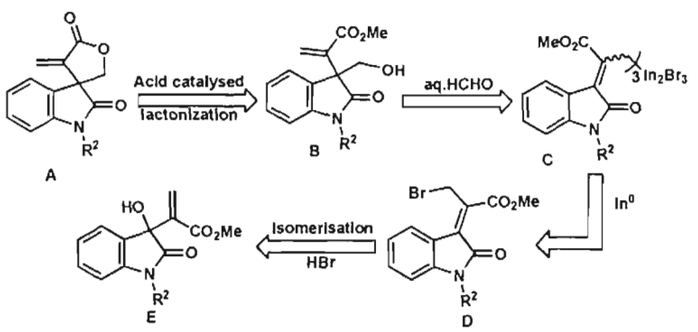
Literature survey revealed that indium mediated allylation reactions are important due to its reactions with regioselectivity and chemoselectivity. In the introduction part of chapter three, it has been shown that the application of isomerised derivatives of MBH adducts in synthetic organic chemistry. Among the various derivatives of MBH adducts, allyl bromides pave much attention as they can play a valuable role in the ylide chemistry especially the sulphur and the phosphorous ylides. However, only scant attention has been given to the indium mediated allylation reactions of allyl bromides derived from MBH adducts. From the literature survey, we speculated that the allyl bromides derived from MBH adducts of isatin have not been exploited for the construction of complex molecular frame works. Presence of an oxindole moiety at the 3rd position of the allyl bromide, make them an ideal candidate for carbonyl allylation using the indium chemistry. It is noted that the indium

mediated oxindolidino allyl bromide has been used for the allylation of aldehyde for the first time to prepare highly functionalised 2-oxindolidino homoallylic alcohols. The homoallylic alcohols thus obtained was subjected to lactonization to afford functionalized 3-spirolactoneoxindoles. The details of this study are the subject matter of this chapter.

4.4 Results and Discussion

4.4.1 Retrosynthetic analysis

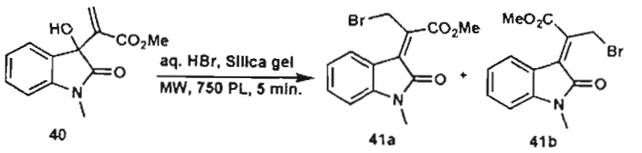
The synthesis of 3-spirolactone-2-oxindole **A** can be achieved from the homoallylic alcohol **B** by an acid catalyzed lactonization. Homoallylic alcohol **B** can be accessed from the isomerised bromo derivative **D** of MBH adduct **E** of isatin using indium mediated allylation with formaldehyde. The retrosynthetic analysis is outlined in scheme 4.14.



Scheme 4.14: *Retrosynthetic analysis*

4.4.2 Preparation of bromoisomerised MBH adduct

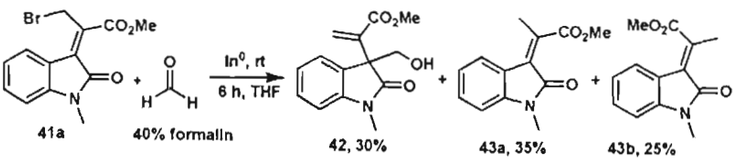
The bromoisomerised MBH adducts **41a** (*E*-isomer) and **41b** (*Z*-isomer) were prepared from the MBH adduct of *N*-methylisatin **40** by the procedure described in chapter three experimental part (Scheme 4.15). All the isatin derived MBH adducts were prepared from corresponding isatins and activated alkenes following the procedures given in section 3.6.[20]



Scheme 4.15: *Preparation of allyl bromides from isatin*

4.4.3 Indium mediated homoallylation of (*E*)-methyl 3-bromo-2-(1-methyl-2-oxoindolin-3-ylidene) propanoate

Preliminary study has been initiated by exposing a mixture of isatin derived *E*-allyl bromide **41a** and 40% formaldehyde in water with indium metal in DMF. The mixture was stirred at room temperature for 3 hours. The reaction afforded the homoallylic alcohol **42** in 30% yield, α-reduced alkenes **43a** in 35% yield and **43b** in 25% (*Z* and *E*) yield after quenching with saturated ammonium chloride (Scheme 4.16).



Scheme 4.16: *Indium mediated allylation of 41a*

The structure of compound **42** was arrived from spectroscopic analysis (IR, ^{1}H NMR, and HRMS). Thus, the IR spectrum of **42** showed a broad absorbance at 3412 cm^{-1} and was indicative of the presence of hydroxyl group. The ester and the amide carbonyls were shown absorbencies at 1739 cm^{-1} and 1715 cm^{-1}. In the proton NMR spectrum, compound **42** showed a broad singlet at δ 1.70 and were indicative of the hydroxyl proton which was exchangeable with D_2O. Two methyl groups at the amide nitrogen and the ester group were discernable at δ 3.30 and 3.50, respectively. The homoallylic methylene protons were confirmed from a pair of mutually coupled doublets at δ 3.79 and δ 4.15 with a coupling constant J = 11.4Hz. Two singlets at δ 6.26 and δ 6.64 were indicative of the geminal protons of the alkene. The aromatic protons were appeared in the down field range δ 6.88-7.30 (Figure 4.1). The FAB mass

spectrum showed a molecular ion peak at *m/z* = 262.38 (Figure 4.2) and hence confirmed the structure of the product.

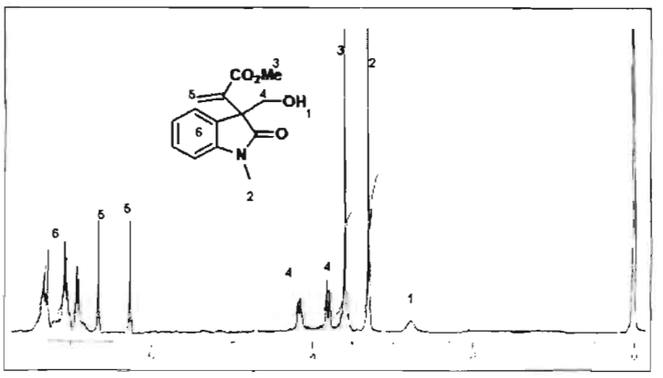


Figure 4.1: *^{1}H NMR spectrum of* **42**

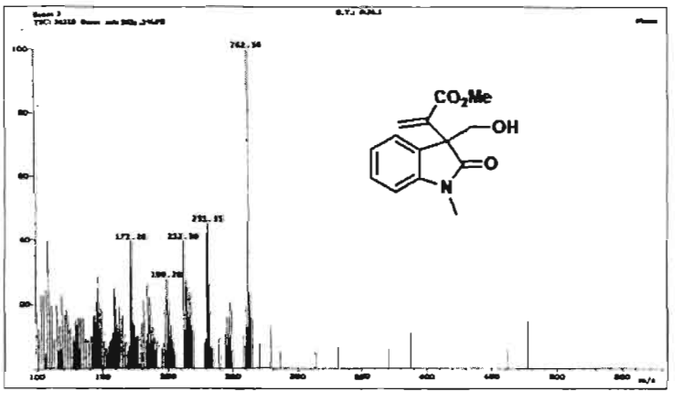


Figure 4.2: *FAB mass spectrum of* **42**

Similarly, the structure of α-reduced products were established based on the NMR and the mass spectral analysis. In the proton NMR spectrum of the *Z*-isomer **43a**, the methyl group attached to the alkene was observed at δ 2.65 and the amide methyl and ester methyl protons were resonated at δ 3.23 and 3.96, respectively. The aromatic protons were observed at the down field range from δ 6.79 - 7.31 (Figure 4.3). The analysed structure was further confirmed by the mass spectral analysis as it showed a molecular ion peak at *m/z* = 232.38.

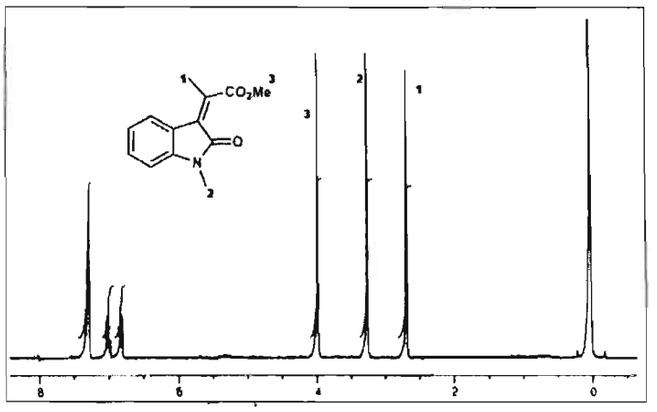


Figure 4.3: *^{1}H NMR spectrum of compound* **43a**

Similarly, in the proton NMR spectrum of *E*-isomer **43b,** the methyl group attached to the double bond was observed at δ 2.44. Two singlets at δ 3.23 and δ 3.96 were discernable to the methyl groups of the ester group and the amide nitrogen of the oxindole moiety, respectively. The down field signals in the chemical shift range from δ 6.81-7.54 were discernable to the aromatic protons of the oxindole moiety (Figure 4.4).

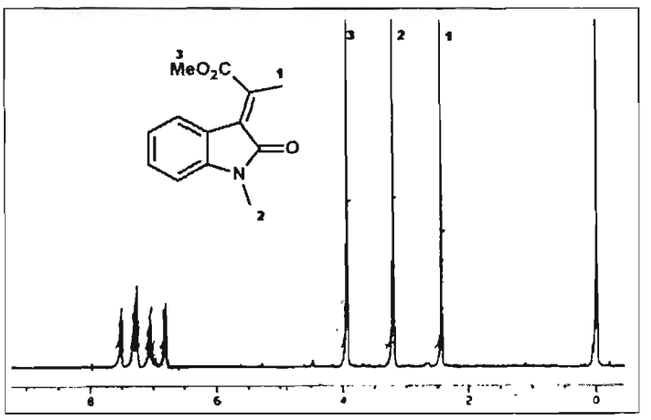


Figure 4.4: *^{1}H NMR spectrum of* **43b**

Further, the ^{13}C NMR spectrum of **43b** showed three methyl carbons at δ 17.9, 25.8 and 52.7 which were characteristic of the methyl groups attached

to the alkene, nitrogen and ester, respectively. The ester carbonyl carbon was observed at δ 165.7 and the amide carbonyl carbon of the oxindole moiety appeared at δ 170.6 (Figure 4.5).

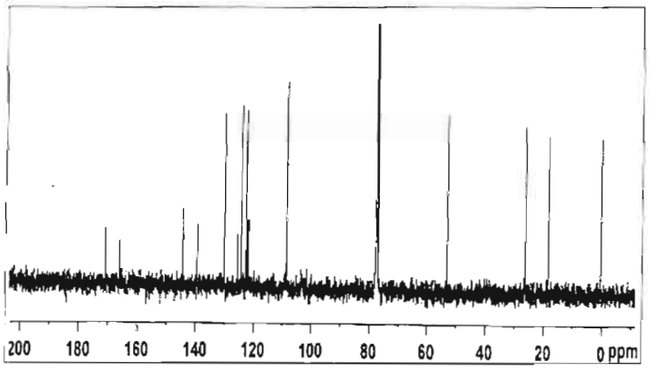


Figure 4.5: *^{13}C NMR spectrum of* **43b**

The assigned structure was further confirmed by the mass spectral analysis, as it showed a molecular ion peak at m/z = 2 32.35.

4.4.4 Optimization of allylation reaction

To improve the yield of the homoallylic alcohol **42** and thereby to minimize the yield of the α-reduced alkenes **43a** and **43b**, we have carried out an optimization study with various solvents. Among the various solvents tested, DMF was found to be the solvent of choice as no α-reduced products were observed. Acetonitrile gave comparable yields of **42** but the α-reduced products were also formed and also took long reaction time for the completion of the reaction. The results are shown in table 4.1.

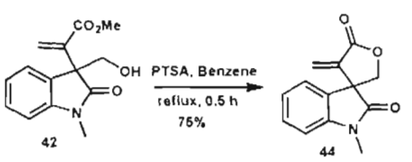
Table 4.1: Optimization of allylation reaction in various solvents

Entry	Solvent	Yield %	
		Homoallylic alcohol	α-reduced alkene
1	THF	30	60
2	DMF	78	-
3	Acetonitrile	70	20

40 % formaline was used as electrophile in all the cases

4.4.5 Lactonization of homoallylic alcohol 42

The homoallylic alcohol was subjected to lactonization to get the spiro oxindole. Thus, the homoallylic alcohol **42** in benzene with a catalytic amount of p-toluenesulphonic acid was refluxed for half an hour to yield the α-methylene-γ-lactone spirooxindole **44** in 75% yield (Scheme 4.17).



Scheme 4.17: *Lactonization of homoallylic alcohol*

The structure of **44** was confirmed from the detailed spectroscopic studies. Thus, the IR spectrum of **44** showed the key lactone carbonyl absorption at 1766 cm^{-1}. The amide carbonyl absorption was seen at 1715 cm^{-1}. In the NMR spectrum of the compound, the methyl group at the amide resonated at δ 3.26 as a singlet. The methelene protons of the lactone ring appeared as two mutually coupled doublets with a coupling constant J = 9.30Hz at chemical shift δ 4.43 and δ 4.69. Two exocyclic methylene protons were observed as two uncoupled singlets at δ 5.35 and δ 6.31. The aromatic protons were resonated in the down field range δ 6.37-7.40 (Figure 4.6). In the ^{13}C NMR spectrum of **44**, the methyl carbon of the amide nitrogen appeared at δ 27.1 and the spiro carbon was observed at δ 54.5. The methelene carbon of the lactone ring appeared at δ 73.0. The lactone and the amide carbonyls were observed at δ 168.4 and δ 175.5, respectively. The spectrum is reproduced in figure 4.7. The low resolution mass spectrum of the compound showed a (M+1) peak at m/z = 230.30 which further supports the analyzed structure.

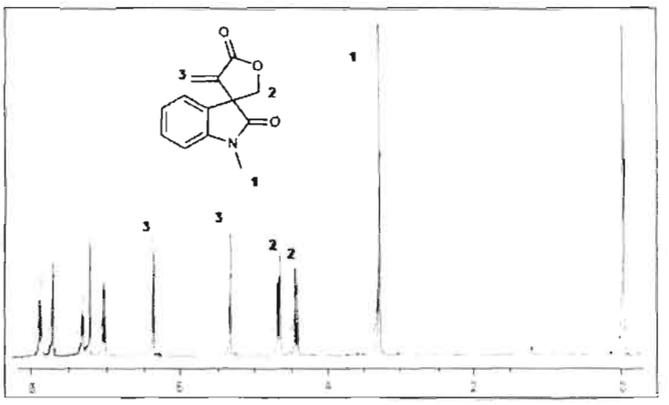


Figure 4.6: *^{1}H NMR spectrum of* **44**

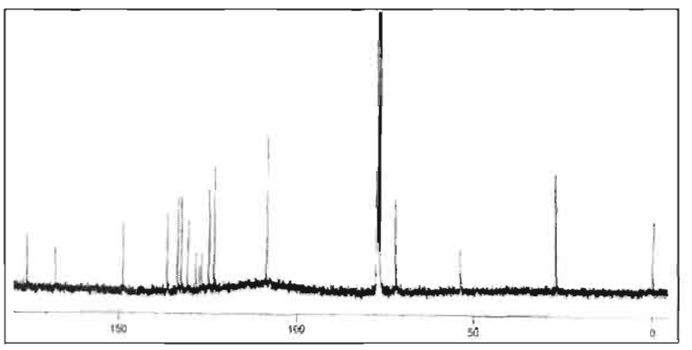
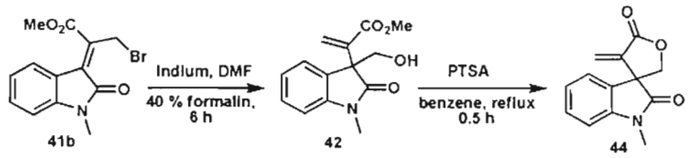


Figure 4.7: *^{13}C NMR spectrum of* **44**

4.4.6 Indium mediated allylation and lactonization of (*Z*)-methyl 3-bromo-2-(1-methyl-2-oxoindolin-3-ylidene) propanoate

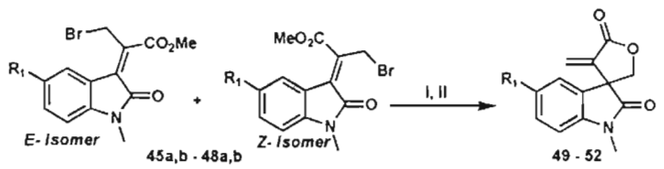
Interestingly, when Z-isomer **41b** was used as the allyl bromide counterpart for the indium mediated allylation reaction with formaldehyde and subsequent lactonization using PTSA in refluxing benzene, **44** was obtained as the sole product as confirmed by the NMR spectrum (Scheme 4.18).



Scheme 4.18: *Allylation and lactonization using Z-isomer* **42**

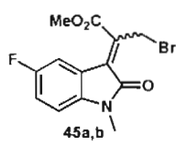
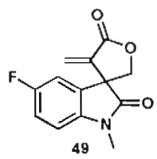
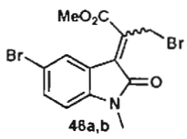
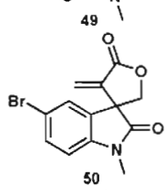
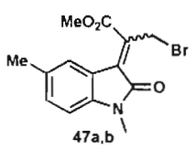
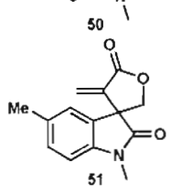
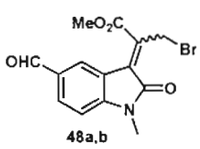
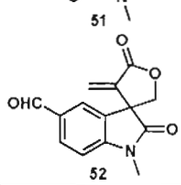
It should be noted that both *E*- and *Z*- allyl derivatives of MBH adducts afforded same spirolactone under optimized condition. Hence, for the rest of the allylation/lactonization study, we chose a mixture of the *E*- and *Z*-isomerised allyl bromides for the synthesis of homoallylic alcohols and the spirolactone. The homoallylic alcohol **42** was used for lactonization without separation of *E* and *Z* isomers (Scheme 4.19).

The reaction was found to be general with various 5-aryl substituted allyl bromides, 5-fluoro, bromo, methyl and aldehyde, derived from MBH adducts of isatin. The results are summarized in table 4.2. All the new compounds were characterized by detailed spectroscopic analysis and are given in the experimental part.



Scheme 4.19: *Allylation and lactonization bromoisomerised MBH adducts*

Table 4.2: Synthesis of 5-aryl substituted-α-methylene-γ-butyrolactone spirooxindoles

entry	substrate	product	yield (%)
1	 45a,b	 49	75
2	 46a,b	 50	80
3	 47a,b	 51	85
4	 48a,b	 52	69

4.5 Mechanism of the synthesis of spirolactone oxindole

The mechanism proposed for the synthesis of homoallylic alcohol involves the formation of a transient allylindium species **A** from *E*- and *Z*-allyl bromides and indium metal in DMF: water solvent system. This allyl indium species then reacts with the electrophilic aldehyde through a cyclic transition state **B**.[6] In the transition state **B**, there exist an additional interaction between the carbonyl of the ester group and the indium metal thereby creating a tri co-ordinate indium (Figure 4.8). From the transition state, it can be seen that the addition is taking place through a hindered tertiary carbanionic center (the oxindole bearing carbon atom). Homoallylic alcohol is formed after acidification. It is likely that the allylindium reagent is not geometrically stable[21] as the reactions of both *Z*- and *E*-allyl bromide afforded the same product. In the second step, the homoallylic alcohol thus formed undergoes

lactonization when exposed to an acid leading to the formation of the spirolactone.

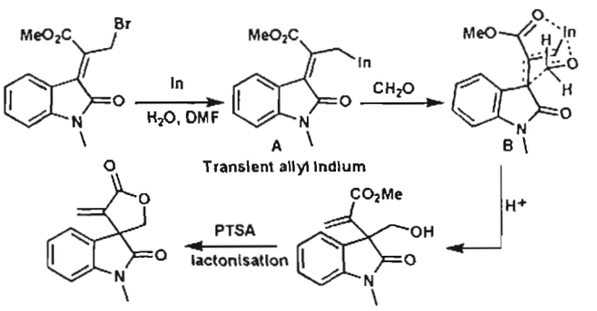
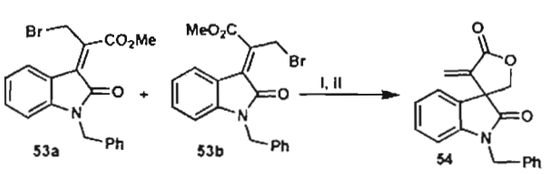


Figure 4.8: *Mechanism of the reaction*

When the mixtures of *N*-benzyl substituted allyl bromides **53a** and **53b** were treated with indium metal and aqueous formaldehyde in DMF for 6 hours, the reaction yielded after acidification the corresponding homoallylic alcohol which on subsequent lactonization using catalytic amount of PTSA in refluxing benzene yielded the *N*-benzyl substituted lactone **54** in 75% yield (Scheme 4.20).



Condition: i) In (1.2 equvl.), 40 % formalin (2.2 equvl.), DMF (1 mL), 6 h
ii) PTSA (0.2 equvl.), benzene (1 mL), 0.5 h

Scheme 4.20: *Allylation and lactonization of* **53a/53b**

In the IR spectrum of **54**, an absorbance observed at 1779 cm^{-1} confirms the presence of lactone carbonyl carbon. The amide carbonyl was shown absorbance at 1715 cm^{-1}. In the proton NMR spectrum of **54**, two mutually coupled multiplets with a coupling constant J = 9Hz centred at δ 4.47 and δ 4.76 indicate the presence of the two methylene protons of the lactone moiety. Another pair of doublet centred at δ 4.82 and δ 5.05 with a coupling constant J = 15Hz was discernable to the benzylic methylene protons at cyclic amide nitrogen. The exocyclic methelene protons appeared as two well separated

singlets at δ 5.36 and δ 6.40. All the aromatic protons were observed in the down field with chemical shift ranging from δ 6.85-7.38 (Figure 4.9).

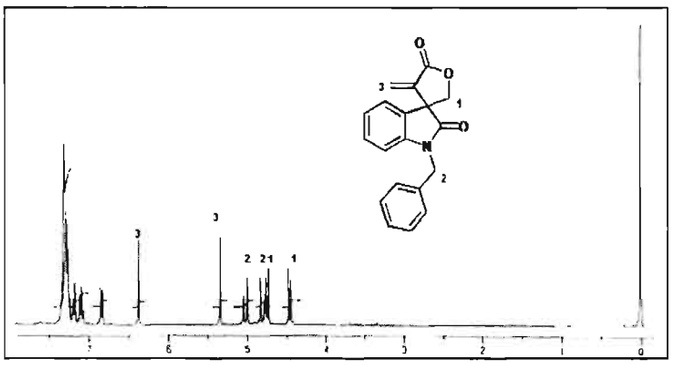


Figure 4.9: *^{1}H NMR spectrum of* **54**

In the ^{13}C NMR spectrum of **54**, the methylene carbon of the benzylic group resonated at δ 44.0. The spiro carbon was observed at δ 60.3. The methylene carbon of the lactone showed a signal at δ 76.5. All the sp^2 carbons were resonated in the range 107.6-140.8. The ester and the amide carbonyls were discernable to two signals at δ 168.2 and δ 175.5 respectively (Figure 4.10).

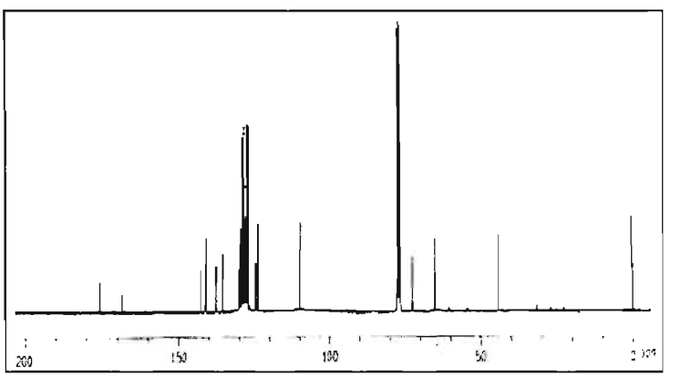
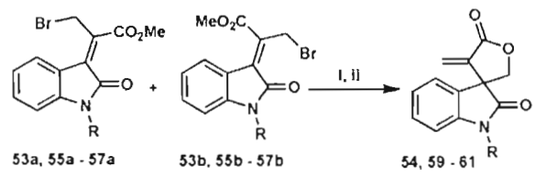


Figure 4.10: *^{13}C NMR spectrum of* **54**

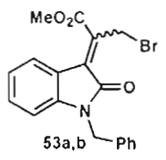
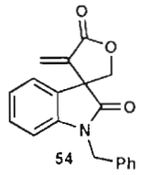
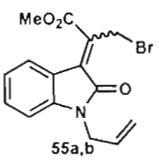
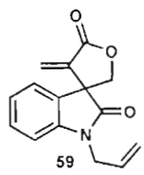
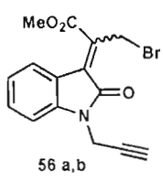
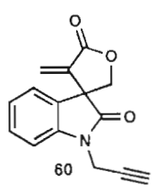
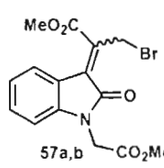
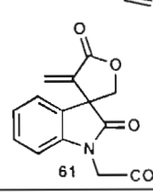
Further, the structure was confirmed by low resolution mass spectrum as it showed a molecular ion peak at *m/z* = 306.56.

The reaction was found to be general with various allyl bromides having different substituents **53a,b, 55a,b-57a,b** (Table 4.3, entries 1-4) at the oxindole nitrogen. In all the cases, the spirolactone oxindoles **54, 59-61** were obtained in excellent yields. All new compounds were characterized by usual spectroscopic analysis.



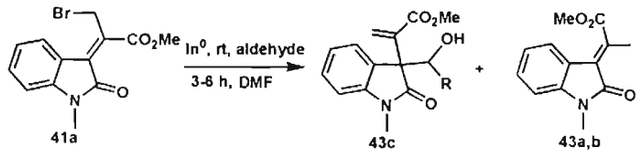
Scheme 4.21: *Allylation and lactonization using N-substituted allyl bromide*

Table 4.3: Synthesis of *N*-substituted α-methylene-γ-lactone-spirooxindoles

entry	substrate	product	yield (%)
1			75
2			80
3			65
4			75

4.6 Attempted allylation reaction with various aldehydes

To broaden the scope of the reaction, various aldehydes were tested for the synthesis of substituted homoallylic alcohol and were displayed in table 4.4.



Scheme 4.22: Attempted allylation with aldehydes

Table 4.4: Attempted allyltion with various aldehydes

entry	aldehyde	yield %	
		43c	43a/b
1	Paraformaldehyde	30	-
2	40% formaldehyde	78	-
3	Acetaldehyde	-	80
4	Benzaldehyde	-	75
5	Crotonaldehyde	-	78

Condition: In(1.2 equiv.), DMF, rt, 6 h

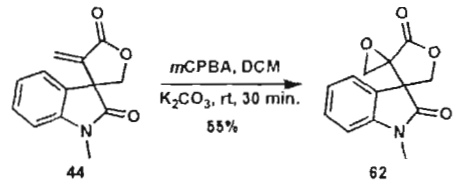
Out of several aldehydes tested, only 40% formaldehyde gave the desired product in good yield. Paraformaldehyde gave only 30% of the homoallyl alcohol. To our dismay other aldehydes such as acetaldehyde, benzaldehyde and crotonaldehyde did not give the homoallylic alcohol; instead reduced alkene was the sole product. The failure of the reaction is apparently due to the low nucleophilic tertiary carbanionic center and the hindrance of the oxindole moiety prevents the approach of substituted aldehyde.

4.7 Synthetic transformations of the Lactone

The potential functional groups present in the products obtained above prompted us to explore further synthetic applications. To demonstrate a few, we prepared dispiro lactone *via* epoxidation and a second MBH adduct from the spirolactone oxindoles. These are discussed in the following sections.

4.7.1 Synthesis of dispiro lactone epoxide

The lactone **44** was treated with m-chloroperbenzoic acid (mCPBA) and potassium carbonate in dichloromethane at room temperature yielded the spiro-epoxide **62** in 55% yield (Scheme 4.23).



Scheme 4.23: *Synthesis of dispiro lactone epoxide*

Structure of **62** has been confirmed by the spectral analysis. In the proton NMR spectrum of the compound, a singlet at δ 3.20 indicates the presence of the amide methyl group. Two well separated doublets centered at δ 3.39 and δ 3.83 with a coupling constant J = 12Hz were discernable to the methylene protons of the epoxide ring. The methylene protons of the lactone ring was observed as two mutually coupled doublets centered at δ 4.26 and δ 4.80 with a coupling constant J = 9Hz (Figure 4.11). LRMS spectrum showed a peak at m/z = 246.38 this further supports the structure of the compound.

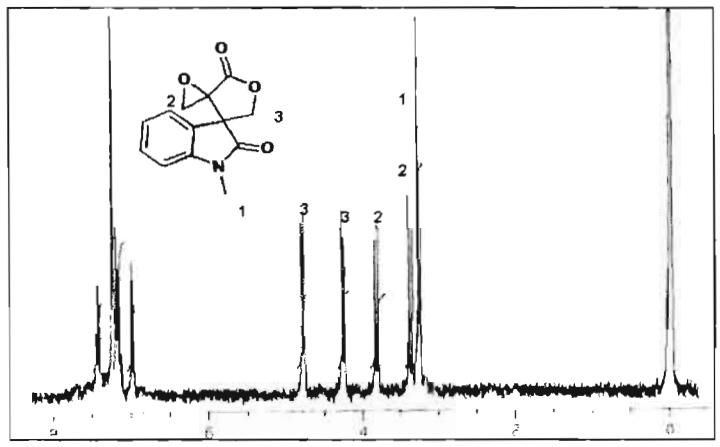
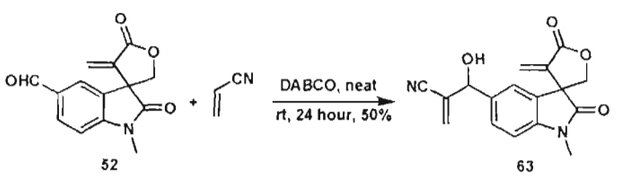


Figure 4.11: *^{1}H NMR spectrum of* **62**

4.7.2 Synthesis of a Second Morita-Baylis-Hillman adduct from spirolactone 52

Interestingly, the spirolactone **52** having an aldehyde substituent at the aromatic ring successfully underwent the MBH reaction with acrylonitrile/DABCO to highly functionalized spirolactone oxindole derivative **63** (Scheme 4.24).



Scheme 4.24: *Second MBH adduct formation*

In the proton NMR spectrum of the **63**, a broad signal at δ 1.98 was indicative of the OH group. The amide methyl protons were resonated at δ 3.32 as a singlet and the methylene protons of the lactone ring were observed as two mutually coupled doublets at δ 4.47 and δ 4.70 with a coupling constant of J = 9 Hz. The methine proton attached to the hydroxyl group appeared as a singlet at δ 5.36. Protons at the exocyclic methelene group at the lactone ring were observed at δ 5.58 and δ 5.63. The protons of the methelene group attached to the nitrile were resonated at δ 5.59 and at δ 6.41. Three aromatic protons were resonated in the low field region. In the LRMS spectrum a peak at m/z = 311.30 corresponds to the (M+1) peak of assigned structure (Figure 4.12).

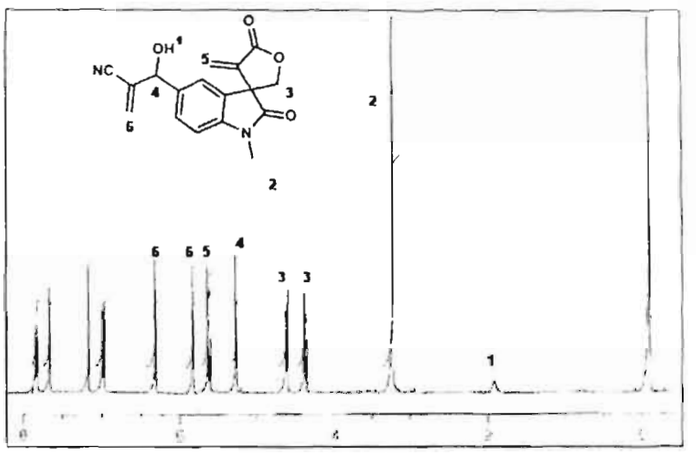


Figure 4.12: *^{1}H NMR spectrum of* **63**

4.8 Conclusions

1. We have synthesized highly functionalized α-methylene-γ-butyrolactone-3-spirooxindoles using an organoindium reagent generated *in situ* from the bromoisomerised MBH adducts of isatins and indium with formaldehyde.
2. A plausible reaction mechanism has been proposed.
3. However, indium catalyzed allylation reactions with other aldehydes such as benzaldehyde, crotonaldehyde and acetaldehyde were failed to give the desired homoallylic alcohol.
4. Synthetic utilities of spirolactones have been demonstrated with two lactones by preparing a dispiro lactone epoxide and a second Morita-Baylis-Hillman adduct

4.9 Experimental

General experimental considerations and procedure for the preparation of bromoisomerised MBH adducts of isatin has been discussed in section 3.6 under experimental section.

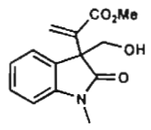
General procedure for the homoallylation and lactonization

A mixture of bromoisomerised MBH adduct (100 mg), 40% aqueous formaldehyde (2.2 equiv.) and indium powder (1.6 equiv.) in DMF (1 mL) was stirred at room temperature for 6 hours. After completion (TLC), the reaction was quenched with saturated ammonium chloride and stirred further for half an hour. The resulting homoallylic alcohol was extracted with ethyl acetate, dried and concentrated. The crude homoallylic alcohol in benzene (1 mL) was subjected to lactonization with PTSA (0.2 equiv.) under reflux for 30 min. After the completion of the reaction (TLC), PTSA was removed by washing with water. The organic layer was washed with brine, evaporated *in vacuo* and purified by silica gel column chromatography to afford the products (65-85%).

Synthesis of methyl 2-(3-(hydroxymethyl)-1-methyl-2-oxoindolin-3-yl) acrylate 42

Following the general procedure, a mixture of *E*- and *Z*-methyl-3-bromo-2-(1-methyl-2-oxoindolin-3-ylidene) propanoate **41a,b** (100 mg, 0.323 mmol), 40% aqueous formaldehyde (2.2 equiv., 0.02mL, 0.709 mmol) and indium powder (1.6 equiv., 59 mg, 0.515 mmol) in THF (1 mL) was stirred at room temperature for 5 hours. The reaction was quenched with saturated ammonium chloride and stirred further for half an hour. The resulting mixture was extracted with ethyl acetate and purified to afford the homoallylic alcohol **42** (30%, 25.5 mg), *Z*-alkene **43a** (20%, 14.9 mg) and *E*-alkene **43b** (25%, 18.6 mg).

methyl-2-(3-(hydroxymethyl)-1-methyl-2-oxoindolin-3-yl)acrylate 42



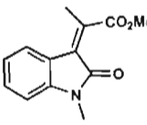
IR (neat) ν_{max}: 1115, 1613, 1739, 2920, 3412 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.70 (bs, 1H), 3.30 (s, 3H), 3.50 (s, 3H), 3.78-3.81 (d, 1H, *J* = 11.4Hz) 4.13-4.17 (d, 1H, *J* = 11.4Hz), 6.26 (s, 1H), 6.64 (s, 1H),

42 6.88-6.91 (m, 1H), 7.00-7.05 (m, 2H), 7.20-7.30 (m, 1H).

LRMS (FAB) for $C_{14}H_{15}NO_4$, Calcd (M^+): 261.27; Found m/z: 262.38 (M+1).

(*Z*)-methyl-2-(1-methyl-2-oxoindolin-3-ylidene)propanoate 43a



43a

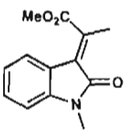
IR (neat) ν_{max}: 1613, 1715, 3004 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 2.65 (s, 3H), 3.2 (s, 3H), 3.9 (s, 3H), 6.79-6.81 (d, 1H, *J* = 7.8Hz), 6.95-7.00 (d, 1H, *J* = 7.8Hz), 7.26-7.31 (d, 2H, *J* = 7.8Hz).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 10.2, 30.5, 52.3, 121.5, 122.7, 124.3, 126.6, 128.2, 134.6, 139.2, 141.4, 167.2, 168.7.

LRMS (FAB) for $C_{13}H_{13}NO_3$, Calcd (M^+): 231.24; Found m/z: 232.38 (M+1).

(*E*)-methyl-2-(1-methyl-2-oxoindolin-3-ylidene) propanoate 43b



43b

IR (neat) ν_{max}: 1613, 1715, 2995 cm^{-1}.

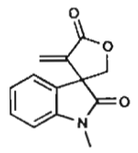
^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 2.44 (s, 3H), 3.23 (s, 3H), 3.96 (s, 3H), 6.81-6.84 (d, 1H, *J* = 7.8Hz), 7.03-7.08 (d, 1H, *J* = 7.8Hz), 7.29-7.34 (d, 1H, *J* = 7.8Hz), 7.51-7.54 (d, 1H, *J* = 7.8Hz).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 17.9, 25.8, 52.7, 108.2, 121.5, 122.2, 124.0, 125.3, 129.8, 131.00, 139.1, 144.1, 165.7, 170.6.

LRMS (FAB) for $C_{13}H_{13}NO_3$, Calcd (M^+): 231.24; Found m/z: 232.35 (M+1).

Synthesis of spirolactone oxindole 44

Following the general procedure, the homoallylic alcohol **42** in benzene (1 mL) was subjected to lactonization with PTSA (0.2 equiv.) under reflux for 30 min. After completion of the reaction (TLC), PTSA was removed by washing with water and purified to afford **44** (17.4 mg, 78%, eluent: 25% ethyl acetate:hexane).



44

IR (neat) ν_{max}: 1115, 1613, 1715, 1766, 2920 cm^{-1}.

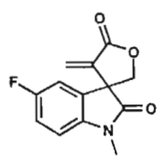
^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 3.26 (s, 3H), 4.41-4.44 (d, 1H, *J* = 9.3Hz), 4.68-4.71 (d, 1H, *J* = 9.3Hz), 5.35 (s, 1H), 6.31 (s, 1H), 6.91-6.94 (d, 1H, *J* = 6Hz), 7.11-7.21 (m, 2H), 7.36-7.40 (d, 1H, *J* = 6Hz).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 27.1, 54.5, 73.0, 108.2, 109.2, 109.5, 122.5, 123.2, 130.3, 137.5, 143.8 168.47, 175.5.

LRMS (FAB) for $C_{13}H_{11}NO_3$, Calcd (M^+): 229.23; Found m/z: 230.30 (M+1).

Spirolactone oxindole 49

Following the literature procedure, a mixture of *E*- and *Z*-methyl-3-bromo-2-(5-fluoro-1-methyl-2-oxoindolin-3-ylidene)propanoate **45a,b** (100 mg, 0.304), 40% aqueous formaldehyde (20 mg/0.018 mL, 0.666 mmol) and indium powder (56 mg, 0.487 mmol) in DMF (1 mL) was stirred at room temperature for 5 hours. The reaction was quenched with saturated ammonium chloride and stirred further for half an hour. The resulting homoallylic alcohol was extracted with ethyl acetate, concentrated and subjected to lactonization with PTSA (0.2 equiv.) in refluxing benzene (1 mL) for 30 min. to afford **49** (56 mg, 75%, eluent: 25% ethyl acetate:hexane).



49

IR (neat) ν_{max}: 1115, 1613, 1715, 1772, 2920 cm^{-1}.

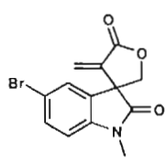
^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 3.20 (s, 3H) 4.40-4.43 (d, 1H, *J* = 9Hz), 4.68-4.71 (d, 1H, *J* = 9Hz) 5.38 (s, 1H), 6.39 (s, 1H), 6.84-6.89 (m, 2H), 7.36-7.37 (m, 1H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 26.9, 54.5, 72.2, 109.4, 111.3, 111.6, 115.9, 116.2, 124.8, 136.8, 139.5, 167.8, 174.9.

LRMS (FAB) for $C_{13}H_{10}NFO_3$, Calcd (M^+): 247.22; Found m/z: 248.64 (M+1).

Spirolactone oxindole 50

Following the literature procedure, a mixture of *E*- and *Z*-methyl-3-bromo-2-(5-bromo-1-methyl-2-oxoindolin-3-ylidene)propanoate **46a,b** (100 mg, 0.257 mmol), 40% aqueous formaldehyde (17 mg/0.18 mL, 0.576 mmol) and indium powder (47 mg, 0.411 mmol) in DMF (1 mL) was stirred at room temperature for 5 hours. The reaction was quenched with saturated ammonium chloride and stirred further for half an hour. The resulting homoallylic alcohol was extracted with ethyl acetate, concentrated and subjected to lactonization with PTSA (0.2 equiv.) in refluxing benzene (1 mL) for 30 min to afford **50** (63.3 mg, 80%, eluent: 25% ethyl acetate:hexane).



50

IR (neat) ν_{max}: 1114, 1346, 1490, 1715, 1770, 2851, 2918, 3054 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 3.24 (s, 3H); 4.39-4.42 (d, 1H, *J* = 9Hz), 4.66-4.69 (d, 1H, *J* = 9Hz), 5.38 (s, 1H), 6.39 (s, 1H), 6.80-6.82 (d, 1H, *J* = 6Hz), 7.31 (s, 1H), 7.50-7.52 (d, 1H, *J* = 6Hz).

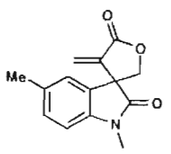
^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 26.8, 54.2, 72.2, 110.2, 116.2, 124.9, 126.5, 131.9, 132.5, 136.7, 142.6, 167.7, 174.6.

LRMS (FAB) for $C_{13}H_{10}BrNO_4$, Calcd (M^+): 308.13; Found m/z: 308.12, 310.50 (M+1).

Spirolactone oxindole 51

Following the literature procedure, a mixture of *E*- and *Z*-methyl-3-bromo-2-(1,5-dimethyl-2-oxoindolin-3-ylidene)propanoate **47a,b** (100 mg, 0.308 mmol), 40% aqueous formaldehyde (20 mg/0.018 mL, 0.678 mmol) and indium powder (56 mg, 0.493 mmol) in DMF (1 mL) was stirred at room temperature for 5 hours. The reaction was quenched with saturated ammonium chloride and stirred further for half an hour. The resulting homoallylic alcohol was extracted with ethyl acetate, concentrated and subjected to lactonization

with PTSA (0.2 equiv.) in refluxing benzene (1 mL) for 30 min to afford **51** (63.6 mg, 85%, eluent: 20% ethyl acetate:hexane).



51

IR (neat) ν_{max}: 1112, 1617, 1714, 1770 2921 cm^{-1}.

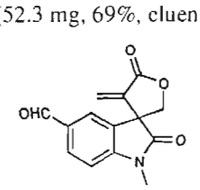
^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 2.34 (s, 3H), 3.20 (s, 3H); 4.40-4.70 (d, 1H, *J* = 9Hz), 4.67-4.70 (d, 1H, *J* = 9Hz), 5.36 (s, 1H), 6.36 (s, 1H), 6.80-6.82 (d, 1H, *J* = 6Hz), 7.01 (s, 1H), 7.16-7.18 (d, 1H, *J* = 6Hz).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 20.9, 26.7, 54.3, 72.6, 109.1, 123.7, 124.4, 129.8, 130.6, 133.5, 137.4, 141.0, 168.3, 175.2.

LRMS (FAB) for $C_{14}H_{13}NO_3$, Calcd (M^+): 243.25; Found m/z: 244.39 (M+1).

Spirolactone oxindole 52

Following the literature procedure, a mixture of *E*- and *Z*-methyl-3-bromo-2-(5-formyl-1-methyl-2-oxoindolin-3-ylidene) propanoate **48a,b** (100 mg, 0.295 mL), 40% aqueous formaldehyde (19 mg/0.018 mL, 0.650 mmol) and indium powder (54 mg, 0.473 mmol) in DMF (1 mL) was stirred at room temperature for 6 hours. The reaction was quenched with saturated ammonium chloride and stirred further for half an hour. The resulting homoallylic alcohol was extracted with ethyl acetate, concentrated and subjected to lactonization with PTSA (0.2 equiv.) in refluxing benzene (1 mL) for 30 min to afford **52** (52.3 mg, 69%, eluent: 25% ethyl acetate:hexane).



52

IR(neat) ν_{max}: 1347, 1610, 1688, 1731, 1770, 2925 cm^{-1}.

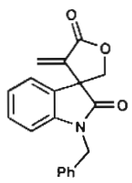
^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 3.32 (s, 3H); 4.45-4.48 (d, 1H, *J* = 9Hz), 4.69-4.72 (d, 1H, *J* = 9Hz), 5.36 (s, 1H), 6.41 (s, 1H), 7.07-7.09 (d, 1H, *J* = 6Hz), 7.75 (s, 1H), 7.92-7.94 (d, 1H, *J* = 6Hz), 9.91 (s, 1H).

^{13}C NMR($CDCl_3$/TMS, 75.3 MHz): δ 27.1, 53.9, 72.1, 105.4, 123.6, 125.0, 130.9, 132.7, 133.7, 136.6, 148.9, 175.4, 190.1, 197.6.

LRMS (FAB) for $C_{14}H_{11}NO_4$, Calcd (M^+): 257.24; Found m/z: 258.6 (M+1).

Spirolactone oxindole 54

Following the literature procedure, a mixture of *E*- and *Z*-methyl-2-(1-benzyl-2-oxoindolin-3-ylidene)-3-bromopropanoate **53 a,b** (100 mg, 0.258 mmol), 40% aqueous formaldehyde (17 mg/0.015 mL, 0.567 mmol) and indium powder (47 mg, 0.414 mmol) in DMF (1 mL) was stirred at room temperature for 6 hours. The reaction was quenched with saturated ammonium chloride and stirred further for half an hour. The resulting homoallylic alcohol was extracted with ethyl acetate, concentrated and subjected to lactonization with PTSA (0.2 equiv.) in refluxing benzene (1 mL) for 30 min. to afford **54** (59 mg, 75, eluent: 25% ethyl acetate:hexane).



54

IR (neat)ν_{max}: 1115, 1613, 1715, 1770, 2920, 3031 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 4.46-4.49 (d, 1H, *J* = 9Hz), 4.75-4.78 (d, 1H, *J* = 9Hz), 4.80-4.85 (d, 1H, *J* = 15Hz), 5.02-5.07 (d, 1H, *J* = 15Hz), 5.36 (s, 1H), 6.40 (s, 1H), 6.85-6.87 (d, 1H, *J* =6Hz), 7.28-7.32(m, 2H), 7.33-7.38 (m, 6H).

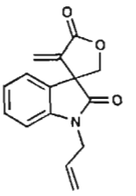
^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 44.0, 60.3, 76.5, 107.6, 123.2, 123.7, 124.4, 126.0, 126.4, 126.8, 127.2, 127.4, 127.9, 128.4, 137.4, 140.8, 142.6, 168.2, 175.5.

LRMS (FAB) for $C_{19}H_{15}NO_3$, Calcd (M^+): 305.10; Found m/z: 306.56 (M+1).

Spirolactone oxindole 59

Following the literature procedure, a mixture of *E*- and *Z*-methyl-2-(1-allyl-2-oxoindolin-3-ylidene)-3-bromopropanoate **55a,b** (100 mg, 0.297 mmol), 40% aqueous formaldehyde (19 mg/0.018 mL, 0.654 mmol) and indium powder (54 mg, 0.475 mmol) in DMF (1 mL) was stirred at room temperature for 6 hours. The reaction was quenched with saturated ammonium chloride and stirred further for half an hour. The resulting homoallylic alcohol was extracted with ethyl acetate, concentrated and subjected to lactonization

with PTSA (0.2 equiv.) in refluxing benzene (1 mL) for 30 min. to afford **59** (60.6 mg, 80%, eluent: 25% ethyl acetate:hexane).



59

IR (neat) ν_{max}: 1026, 1359, 1467, 1612, 1715, 1770, 2850, 2918, 3054 cm^{-1}.

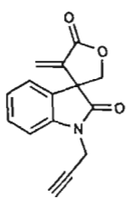
^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 4.20-4.41 (m, 2H), 4.43-4.46 (d, 1H, *J* = 9Hz), 4.70-4.73 (d, 1H, *J* = 9Hz), 5.22-5.29 (m, 2H), 5.35 (s, 1H), 5.79-5.91 (m, 1H) 6.37 (s, 1H), 6.90-6.93 (d, 1H, *J* = 6Hz), 7.10-7.14 (m, 1H), 7.19-7.21 (m, 1H), 7.29-7.37 (m, 1H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 42.0, 54.3, 72.5, 109.7, 118.1, 123.3, 123.7, 124.4, 129.5, 130.1, 130.7, 137.5, 142.8, 168.1, 175.0.

LRMS (FAB) for $C_{15}H_{13}NO_3$, Calcd (M^+): 255.28; Found m/z: 256.47 (M+1).

Spirolactone oxindole 60

Following the literature procedure, a mixture of *E*- and *Z*-methyl-3-bromo-2-(2-oxo-1-(prop-2-ynyl)indolin-3-ylidene)propanoate **56 a,b** (100 mg, 0.299 mmol), 40% aqueous formaldehyde (19 mg/0.018 mL, 0.658 mmol) and indium powder (55 mg, 0,478 mmol) in DMF (1 mL) was stirred at room temperature for 6 hours. The reaction was quenched with saturated ammonium chloride and stirred further for half an hour. The resulting homoallylic alcohol was extracted with ethyl acetate, concentrated and subjected to lactonization with PTSA (0.2 equiv.) in refluxing benzene (1 mL) for 30 min. to afford **60** (56 mg, 74%, eluent: 2% ethyl acetate:hexane).



60

IR (neat) ν_{max}: 1115, 1613, 1715, 1771, 2920, cm^{-1}.

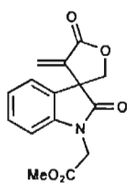
^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 2.28-2.30 (t, 1H, *J* = 2.4Hz), 4.40-4.44 (d, 1H, *J* = 9Hz), 4.52-4.53 (d, 1H, *J* = 2.4Hz), 4.54-4.55 (d, 1H, *J* = 2.4Hz), 4.70- 4.73 (d, 1H, *J* = 9Hz), 5.37 (s, 1H), 6.30 (s, 1H), 7.13-7.23 (m, 3H), 7.38-7.43 (m, 1H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 29.8, 54.4, 72.4, 72.8, 76.5, 103.6, 123.3, 123.4, 124.4, 129.6, 130.1, 137.6, 141.8, 167.8, 174.5.

LRMS (FAB) for $C_{15}H_{11}NO_3$ Calcd (M^+): 253.25; Found m/z: 254.47 (M+1).

Spirolactone oxindole 61

A mixture of isomerized MBH adduct **57a,b** (100 mg), 40% aqueous formaldehyde (1.2 equiv.) and indium powder (1.6 equiv.) in DMF (1 mL) was stirred at room temperature for 6 hours. The reaction was quenched with saturated ammonium chloride and stirred further for half an hour. The resulting homoallylic alcohol was extracted with ethyl acetate, concentrated and subjected to lactonization with PTSA (0.2 equiv.) in refluxing benzene (1 mL) for 30 min. to afford **61** (55%, eluent: 20% ethyl acetate:hexane).



61

IR (neat) ν_{max}: 1113, 1615, 1715,1775, 2920, cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 3.97 (s, 3H), 4.32 (s, 2H), 4.57-4.61 (d, 1H, *J* = 9Hz), 4.83-4.86 (d, 1H, *J* = 9Hz), 5.51 (s, 1H), 6.11 (s, 1H), 7.13 (m, 1H), 7.17 (m, 2H), 7.19 (m, 1H).

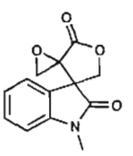
^{13}C NMR($CDCl_3$/TMS, 75.3 MHz): δ 47.6, 49.3, 51.6, 76.8, 122.1, 124.4, 124.9, 127.8, 127.9, 142.6, 144.9, 169.6, 170.0, 171.2.

LRMS (FAB) for $C_{15}H_{13}NO_5$ Calcd (M^+): 287.26; Found m/z: 288.31 (M+1).

Synthesis of Dispiro lactone epoxide 62 from spirolactone 44

A solution of **44** (50 mg, 0.218 mmol) in dichloromethane (1 mL) was cooled to 0 ^{0}C in an ice bath. K_2CO_3 (45 mg, 0.327 mmol) was added and followed by mCPBA (45 mg, 0.261 mmol). Allow the reaction mixture to attain room temperature. After stirring the reaction mixture in room temperature for half an hour, $Na_2S_2O_3$ (35 mg, 0.218 mmol) was added and stirred for half an hour. After completing the reaction, diluted with dichloromethane, washed with water (2 X 10 ml water). The organic layer was

dried over Na_2SO_4, concentrated *in vacuo* and purified through silica gel column chromatography to get **62** (30 mg, 55%, eluent: 30% ethyl acetate:hexane).



62

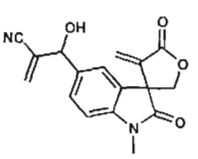
IR (neat) ν_{max}: 1613, 1715, 1750, 3004 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 3.20 (s, 3H), 3.37-3.41 (d, 1H, *J* = 12Hz), 3.81-3.85 (d, 1H, *J* = 12Hz), 4.25-4.28 (d, 1H, *J* = 9Hz), 4.78-4.82 (d, 1H, *J* = 9Hz), 6.99-7.02 (d, 1H, *J* = 9Hz), 7.14-7.26 (m, 2H), 7.42-7.47 (t, 1H, *J* = 9 Hz)

LRMS (FAB) for $C_{13}H_{11}NO_4$, Calcd (M^+): 245.24; Found m/z: 246.38 (M+1).

Transformation of 52 to second MBH adduct 63

A mixture of **52** (50 mg, 0.199 mmol), acrylonitryle (20 mg, 0.398 mmol) and DABCO (cat.) was allowed to stir for 24 hours. Purification of the crude reaction mixture through silica column chromatography yielded the adduct **63** in 50% (30 mg) yield.



63

IR (neat) ν_{max}: 1613, 1715, 1750, 3004, 3282 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.98 (s, 1H), 3.32 (s, 3H), 4.45-4.48 (d, 1H, *J* = 9Hz), 4.69-4.72 (d, 1H, *J* = 9Hz), 5.36 (s, 1H), 5.58 (s, 2H), 5.63 (s, 1H), 6.41 (s, 1H), 7.06-7.09 (d, 1H, *J* = 6Hz), 7.75 (s, 1H), 7.91-7.96 (d, 1H, *J* = 6Hz)

LRMS (FAB) for $C_{17}H_{14}N_2O_4$, Calcd (M^+): 310.30; Found m/z: 311.41 (M+1).

4.10 References

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CHAPTER 5

Silicachloride Mediated Synthetic Transformation of Morita-Baylis-Hillman Adducts

5.1 Introduction

With a strong urge to develop new methods for carbon-carbon and carbon-heteroatom bond forming reactions starting from Morita-Baylis-Hillman (MBH) adducts, organic chemists are looking for a new type of operationally simple and efficient catalytic system. Currently there is general interest in heterogeneous catalytic systems because of its importance in chemical industry and in development of new technologies.[1] Stereoselective construction of (*E*)-trisubstituted alkenes appended with functional groups are one of the difficult tasks in organic synthesis and only a few methods are known.[2] The MBH adducts can act as a synthons for highly functionalized *E*-trisubstituted alkenes. The isomerization of acetates of the MBH adducts, for the formation of *E/Z* alkenes, catalyzed by trimethylsilyl trifluoromethanesulfonate,[2c] trifluoroacetic acid,[3] benzyl trimethylammonium fluoride[4] and Montmorillonite K10 clay-microwave[5] are known in the literature. The isomerization of non-activated MBH adducts to allyl bromides using bromodimethyl sulfonium bromide,[6] and isomerization-arylation using metal catalysts with aryl boronic acid[7] have also been reported. In quest of novel and an alternative catalystic systems for the isomerization of MBH adducts into trisubstitued olefins, we were interested to make use of the literature known, stable and efficient hetreogeneous catalyst "Silicachloride". In this chapter, a detailed discussion on the investigation of isomerization and functionalisation of MBH adducts using silicachloride, a heterogeneous catalyst, has been described. Since the catalyst used herein is silicachloride, a brief introduction on its prepartion and uses in synthetic trasformations as catalyst is discussed as follows.

5.2 A literature review on silicachloride

Silicachloride (SiO_2-Cl) is an extensively used heterogeneous solid catalyst for a number of chemical transformations and are affected by the reagents immobilized on the porous solid support of the modified silica.[8]

5.2.1 Synthesis of silicachloride

Silicachloride can be prepared from cheap starting materials such as silica gel and thionyl chloride with high yields (Scheme 5.1). During the reaction, some of the silanol groups on the surface have been replaced by chlorine atoms.

$$SiO_2 \quad + \quad SOCl_2 \xrightarrow{\text{Reflux, 48 h}} SiO_2\text{-}Cl$$

Scheme 5.1: *Synthesis of silicachloride*

Since, the Si-Cl bond on the surface is weak and labile any nucleophile can attack on this centre. This solid polymeric compound is a mild oxophilic reagent and its handling is much easier than thionyl chloride which has disadvantages like toxicity and corrosive vapours. The catalyst is a white greyish fine powder and the surface structure can be pictorially represented as shown in figure 5.1.

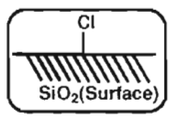


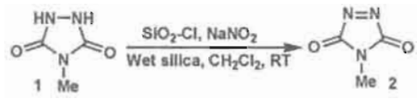
Figure 5.1: *Structure of silicachloride*

As it is a heterogeneous catalyst, it can easily be removed by filtration from the reaction mixture. The advantages of silica-modified silicachloride in organic synthesis are that the catalyst is stable, efficient, operationally simple, and convenient in handling, inexpensive, solid, heterogeneous and acidic in nature.[9]

5.2.2 Application of silicachloride in organic synthesis

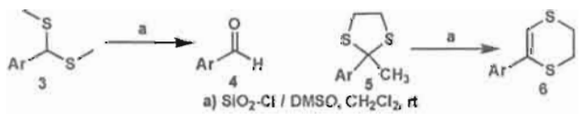
Silicachloride catalyst is known to mediate a variety of organic reactions and some of them are listed here. These transformations have advantages such as enhanced reaction rates, higher yields and greater selectivity.

Urazole **1** was converted to corresponding triazolinedione **2** in excellent yield with a combination of silicachloride, wet silica and sodium nitrite in dichloromethane at room temperature and was reported by Zolfingol and co-workers and the reaction is shown in scheme 5.2. Bisurazols also underwent similar trasformations smoothly.[10a] Later, for the same synthetic transformation, the authors have used oxone instead of sodium nitrite.[10b]

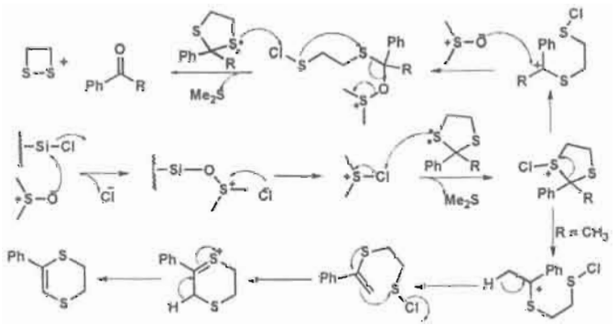


Scheme 5.2: *Oxidation of urazoles to triazolinedione*

Firrouzabadhi *et al.* used efficiently a combination of silicachloride/ DMSO as a heterogeneous catalytic system for deprotection of thioacetal **3** to an aldehyde **4** in dry DCM at room temperature. Thioketal, without enolizable hydrogen adjacent to a sulfur atom, was easily converted to the corresponding ketone and thioketal **5** with enolizable methyl or methylene groups underwent ring expansion reaction to afford 1, 4-dithiepin and 1, 4-dithiin **6** in good yield (Scheme 5.3a). In these reactions, SiO_2-Cl acted as an oxophilic and also an activating reagent for DMSO to generate dimethylsulfonium chloride and also act as oxygen source for the reactions (Scheme 5.3b).[11]

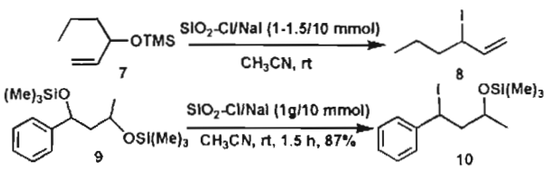


Scheme 5.3a: *Deprotection of thioacetal and rearrangement of thioketal*



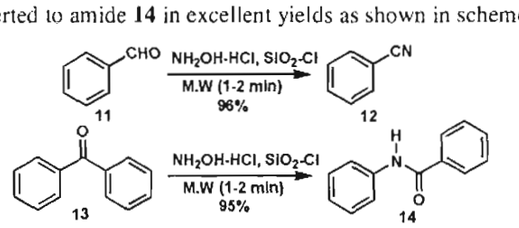
Scheme 5.3b: *Mechanism of deprotection and thioketal formation*

Iranpoor and coworkers reported a direct and highly selective conversion of benzylic, allylic, propargylic TMS, TBDMS and THP ethers into their corresponding iodides with SiO_2-Cl/NaI reagent system in CH_3CN at room temperature. It is also found that aliphatic silyl and tetrahydropyranyl ethers remained almost intact under similar reaction conditions (Scheme 5.4).[12]



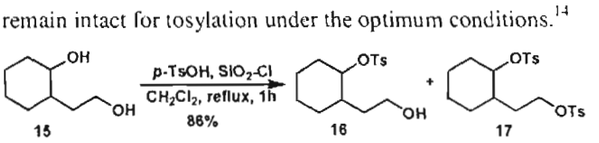
Scheme 5.4: *Conversion of allylic, benzylic, propargylic silyl ethers to iodides*

Under solvent free conditions, aldehyde **11** was efficiently and rapidly converted into the corresponding nitrile **12** by treatment with $NH_2OH{\cdot}HCl$ under microwave irradiation using SiO_2-Cl as a catalyst as reported by Das *et al.* The reaction between **11** and $NH_2OH{\cdot}HCl$ produce aldoxime which then underwent dehydration to afford the nitrile **12**. Under similar conditions, ketone **13** was converted to amide **14** in excellent yields as shown in scheme 5.5.[13]



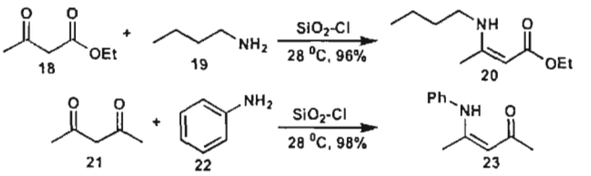
Scheme 5.5: *Conversion of aldehydes to nitrile and ketones to amide*

Das *et al.* reported the selective tosylation of secondary alcohols over primary alcohols using silicachloride with *p*-toluene sulphonic acid (PTSA) in dichloromethane under reflux condition (Scheme 5.6). Phenols and tertiary alcohols remain intact for tosylation under the optimum conditions.[14]



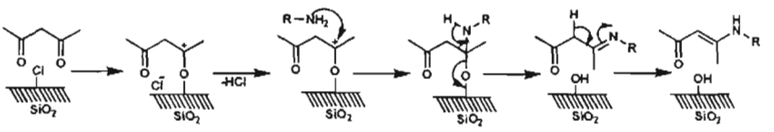
Scheme 5.6: *Selective protection of secondary alcohols*

For the regio- and chemoselective eneamination of β-dicarbonyl compounds, Gholap and co-workers used SiO_2-Cl as a catalyst under solvent free conditions. They achieved the formation of β-amino-α,β-unsaturated ester **20** from **18** and **19**. Amines like ammonium acetate, primary and secondary amines at room temperature reacted smoothly (Scheme 5.7a).[15]



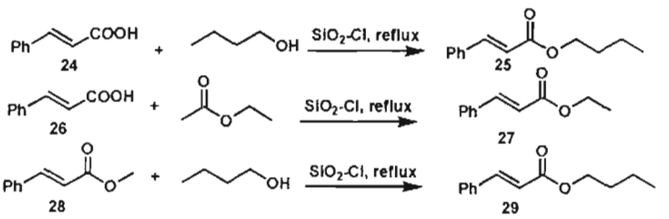
Scheme 5.7a: *Synthesis of β-amino-α,β-unsaturated esters and ketones*

The Si-Cl bond in SiO_2-Cl is labile and it can give rise a Lewis acid centre on silica. The chloride ion can easily displaced by the oxygen atom of the 1,3-dicarbonyl compounds thereby creating a cationic centre at the ketone. A nucleophilic attack of the amine at this centre leads to the formation of imine followed by tautomerism lead to the formation of the products (Scheme 5.7b).



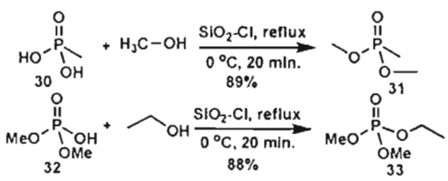
Scheme 5.7b: *Mechanism of β-amino-α,β-unsaturated ester formation*

Das and co-workers used silicachloride as a multipurpose catalyst for the esterification of carboxylic acid, acidolysis of ethyl acetate and also the alcoholysis of ethyl acetate as explained in scheme 5.8.[16a] Kaushik *et al.* extended this methodology for the esterification of *N*-protected aminoacids.[16b]



Scheme 5.8: *SiO_2-Cl catalyst for esterification, acidolysis and alcoholysis*

Recently, Kaushik and co-workers used SiO_2-Cl as an effective heterogeneous catalyst for rapid esterification of alkyl/aryl phosphonic/phosphoric acids to their corresponding alkyl/aryl phosphonates/phosphates at room temparature. When the methyl phosphonic acid was treated with silicachloride in dry methanol at 0 ^{0}C yielded the methyl ester in 89% yield (Scheme 5.9). It is likely that silicachloride acts as acid, which protonates the phosphoric or phosphonic acid followed by attack of an alkoxide ion on the phosphorous atom results in esterification of the corresponding acids.[17]



Scheme 5.9: *Esterification of phosphonic and phosphoric acid*

5.3 Present Work

From the literature described above it is understandable that, recently, heterogeneous catalysts like silicachloride have proven to be useful catalyst for various organic transformations. These transformations are effected by the reagents immobilized on the porous solid supports of the modified silica and have advantages such as enhanced reaction rate, higher yields, greater selectivity and ease of manipulation over the conventional solution phase reactions. To the best of our knowledge, the usage of silicachloride for the synthetic transformations of MBH adduct is unexplored to date. Thus, the present objective is a detailed study on the synthesis of functionalized trisubstituted olefins appended with chlorine, aryl, and ether functional groups catalyzed by silicachloride, a heterogeneous catalyst, from various MBH adducts.

5.4 Results and Discussions

5.4.1 Preparation of silicachloride

Silicachloride was prepared from freshly activated silica (60-120 mesh) by refluxing with thionyl chloride for 48 hours. The resulted white greyish powder was used for the isomerization study.

The Morita-Baylis-Hillman adducts for the isomerization study was prepared according to the literature procedure and are listed in figure 5.2.

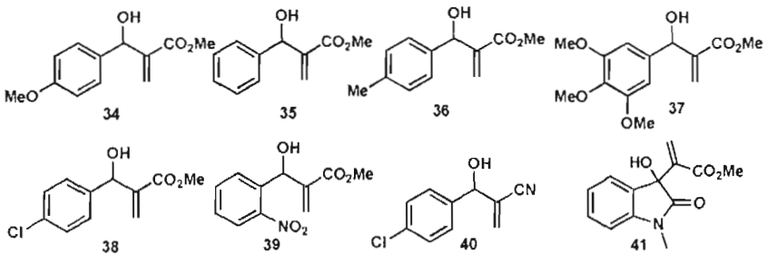
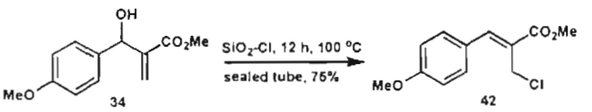


Figure 5.2: *MBH adducts used for the isomerization study*

5.4.2 SiO_2-Cl mediated synthesis of allyl chlorides from MBH adducts

In an initial experiment, the MBH adduct derived from *p*-methoxy benzaldehyde **34** was heated with SiO_2-Cl for 12 hour in a sealed tube condition. The reaction yielded only the *Z*- isomer **42** of the corresponding allyl chloride in 75% isolated yield as colourless oil (Scheme 5.10). The sturcture of compound **42** was established by spectral means.

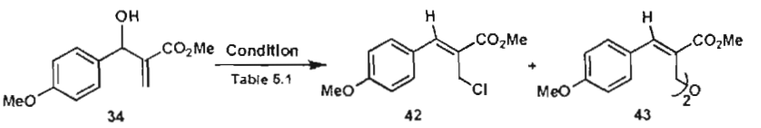


Scheme 5.10: *Isomerization-chlorination of MBH adduct*

5.4.3 Optimization of reaction condition

In order to get a maximum yield of **42**, we have carried out an optimization study as follows. When the adduct **34** was heated with silicachloride at 140 ^{0}C for 12 h without any solvent, isomerized-chlorinated

product **42** was obtained in 20% yield and the dimerized product **43** in 30% yield. An attempt of the reaction of the adduct **34** in dichloromethane was stirred with freshly prepared SiO_2-Cl at room temperature for 12 h and the reaction furnished unchanged starting material. Repetition of the reaction in refluxing CH_2Cl_2 for 12 h provided starting material quantitatively. The reaction mixture without any solvent was heated at 140 ^{0}C to afford **43** in 30% yields. However, the reaction mixture without any solvent on irradiation in a microwave oven (750 Power Level) for 5 min. afforded compounds **42** and **43** in 30% and 50% yields, respectively. To improve the yield of isomerized-chlorinated product **42**, an optimized condition was found to be heating the mixture of MBH adduct and SiO_2-Cl in a sealed tube at 100 ^{0}C for 12 h and the reaction afforded compound **42** in 75% yield (Scheme 5.11). The results are shown in the table 5.1.



34 42 43

Scheme 5.11: *Optimization study*

Table 5.1: Optimization of reaction condition

Entry	Condition	Isomerized product Chlorinated (A)	Yields (%) Dimer (B)
1	SiO_2-Cl, 140 °C rt, 12 h	20	30
2	SiO_2-Cl, CH_2Cl_2 rt, 12 h	-	-
3	SiO_2-Cl, CH_2Cl_2, 12 h, reflux	-	-
4	SiO_2-Cl, 5min, mw 750 PL	30	50
5	SiO_2-Cl, neat, 100 °C, sealed tube, 12 h	75[a]	-

a: isolated yield

5.4.4 Catalyst loading

The reactivity of the SiO_2-Cl in this reaction was also tested by the variation in loading weight percentage of the catalyst and the reaction time. We

have used 100% w/w of the catalyst and varying the catalyst by percentage loading and irradiation time did not alter the yields.

The structure of **42** was established on the basis of spectroscopic analysis. Thus, the IR spectrum of **42** showed a sharp absorption at 1712 cm^{-1} indicating the presence of ester carbonyl group. In the proton NMR spectrum of the compound, the methoxy protons of the aromatic ring and the ester group resonated as a singlet at δ 3.87 and the allyl methylene protons were appeared at δ 4.52 as a singlet. The aromatic protons were appeared as two mutually coupled doublets with a coupling constant J = 8.70 Hz and centered at δ 6.97 and δ 7.56. A singlet at δ 7.83 was indicative of the alkene proton (Figure 5.3). In the ^{13}C spectrum of the compound, the methoxy carbon at the ester and at the aromatic ring appeared at δ 52.3 and δ 55.3, respectively. The ester carbonyl carbon was visible at δ 160.9 (Figure 5.4). The structure was finally confirmed from high resolution mass spectral analysis as it showed a molecular ion peak at m/z =240.0564.

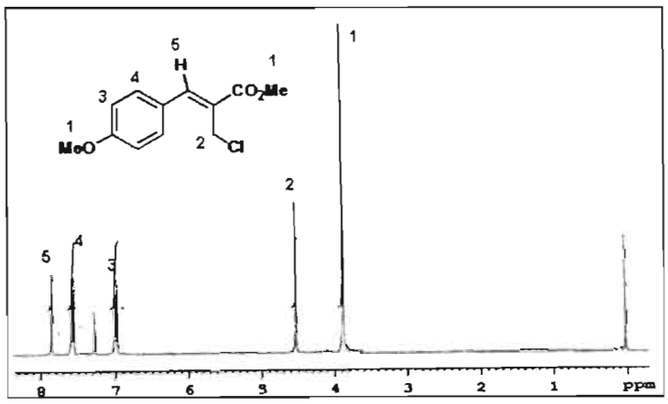


Figure 5.3: *^1H NMR spectrum of* **42**

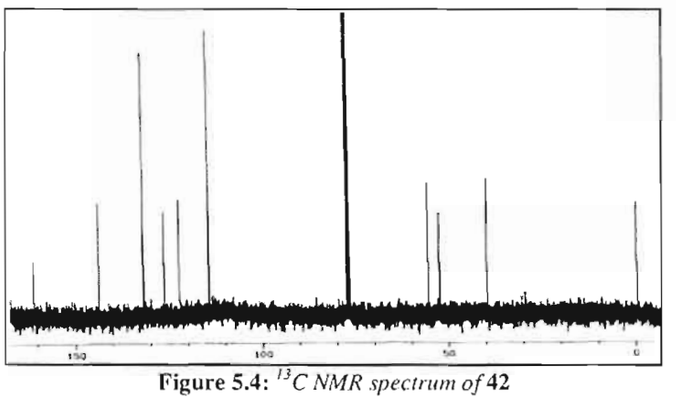
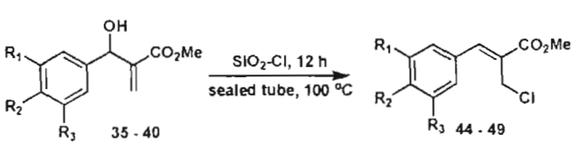


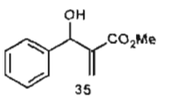
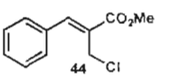
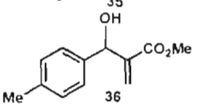
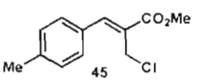
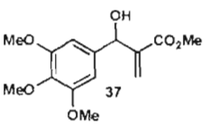
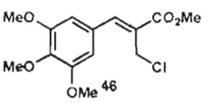
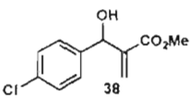
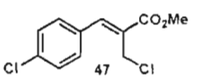
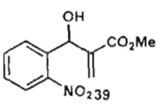
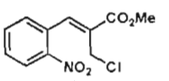
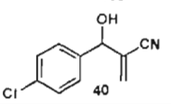
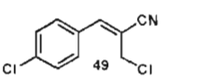
Figure 5.4: *^{13}C NMR spectrum of* **42**

As the preliminary experiment showed promising result on the isomerization-chlorination reaction, we were prompted to examine the reaction with other simple MBH adducts (Scheme 5.12). Thus, the adduct **35** under optimized conditions afforded the isomerized-chlorinated derivative **44** in 58% yield (Table 5.2, entry 1). Similarly, the other MBH adducts underwent the isomerization-chlorination reaction smoothly under optimized conditions to produce good yields of the desired products (Table 5.2, entries 2-6). In all the cases, only the Z-isomer of the allyl chloride was isolated. All the compounds were purified by column chromatography and characterized by spectroscopic methods. The results obtained are tabulated in table 5.2.



Scheme 5.12: *Generalization of the isomerization chlorination reaction*

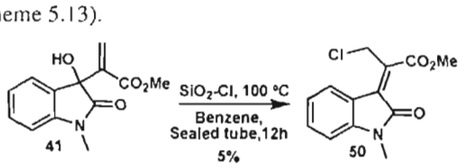
Table 5.2: Isomerization-chlorination of MBH adducts with silicachloride

entry	substrate	chlorinated product (A)	yield (%)
1	 35	 44	58
2	 36	 45	78
3	 37	 46	42[a]
4	 38	 47	39
5	 39	 48	-
6	 40	 49	50

a: reaction time 2 h

It should be noted that adduct bearing an electron withdrawing group at the aryl ring afforded neither desired allylchlorides nor the dimerized compounds (Table 5.2, entry 5). However, adduct bearing halogen substitutions on the aryl ring and a nitrile group at the activated alkene, afforded only moderate yields of allyl chlorides (Table 5.2, entry 6).

Reactivity and suitability of various MBH adducts for the reaction was tested using adduct **41** derived from isatin and furnished only 5% of chlorinated compound **50** (Scheme 5.13).



Scheme 5.13: *Isomerization of MBH adducts of isatin*

Adducts **51-53** derived from hetero aromatic aldehydes *viz. a viz.* thiophene, furan and pyridine yielded neither chlorinated nor dimerised compound (Figure 5.5). The adducts were found to undergo decomposition on the catalyst surface.

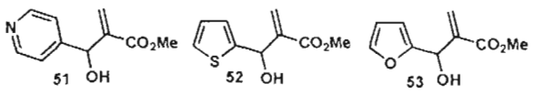
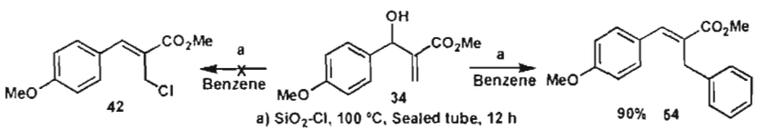


Figure 5.5: *Hetero aryl derived MBH adducts found to undergo decomposition*

5.4.5 SiO_2-Cl mediated isomerization-arylation of MBH adducts

The successful isomerization-chlorination reaction of MBH adducts with silicachloride prompted us to further explore the reaction in the presence of simple aromatic hydrocarbons in order to trap the reactive intermediate with aromatic hydrocarbons (Scheme 5.14). As expected, the Friedel-Crafts type reaction was observed for the adduct **34** with two equivalents of benzene in the presence of SiO_2-Cl. The reaction occurred smoothly and afforded highly functionalized arylated trisubstituted alkenes **54** in excellent yields.



Scheme 5.14: *Friedel-Crafts type arylation of MBH adducts*

It was observed that only the *E*-isomer **54** was formed as evidenced by ^{1}H NMR spectroscopic analysis. Thus, the compound **54** showed a singlet at δ 3.71, integrating six protons, and was discernable to the ester methoxy protons. The benzylic methylene protons appeared at δ 3.95 as a singlet. The aromatic protons were appeared as a multiplet in the down field region from δ 7.19 to 7.34. The alkene proton was resonated at δ 7.93 as a singlet as shown in figure 5.6. The carbon-13 NMR spectrum of the **54** showed signals at δ 33.4, 51.5 and 55.3 that correspond to the benzylic and the ester methyl groups, respectively. All the sp^2 hybridized carbons were appeared in the range δ 109.5 to 139.3. The ester carbonyl carbon appeared at δ 168.6 (Figure 5.7). The structure was

further confirmed by the HR-mass spectral analysis as it showed a molecular ion peak at *m/z*= 282.368.

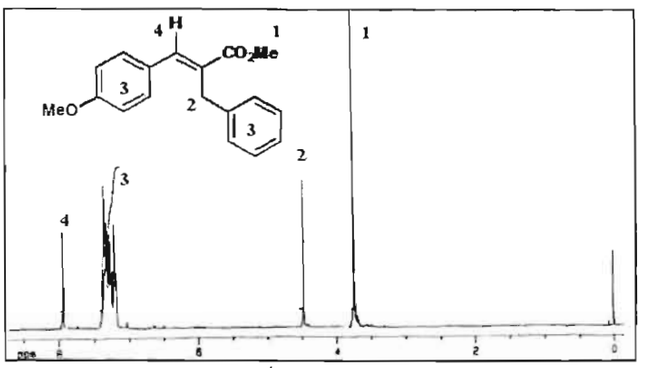


Figure 5.6: *^{1}H NMR spectrum of* **54**

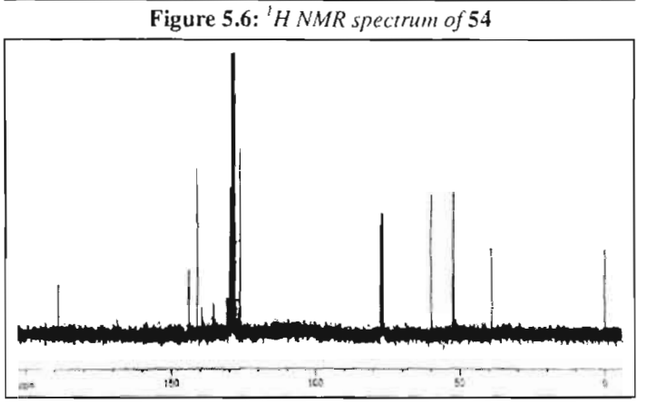
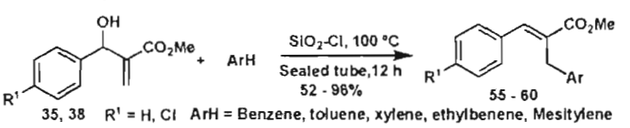


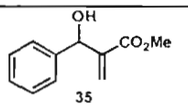
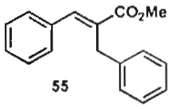
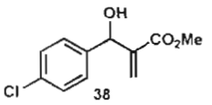
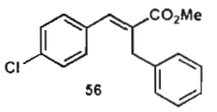
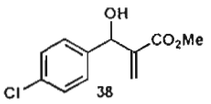
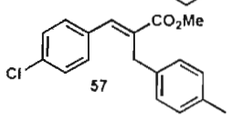
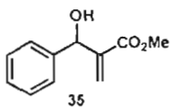
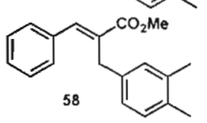
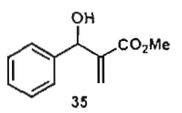
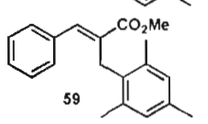
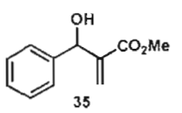
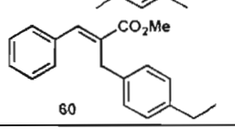
Figure 5.7: *^{13}C NMR spectrum of* **54**

To show the general nature of the reaction, experiments with other aromatic hydrocarbons such as toluene, *o*-xylene, mesitylene, and ethyl benzene were tested and afforded the corresponding isomerised-arylated compounds in excellent yields (Table 5.3, entries 3-6). All the compounds were characterized by spectroscopic analysis such as IR, NMR and HRMS.



Scheme 5.15: *Friedel-Crafts type arylation of MBH adduct*

Table 5.3: Isomerization–arylation of MBH adducts

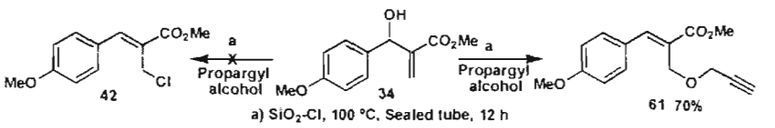
entry	substrate	arene	product (A)	yields (%)
1	 35	Benzene	 55	95
2	 38	Benzene	 56	96
3	 38	Toluene	 57	95
4	 35	Xylene	 58	90[a]
5	 35	Mesitylene	 59	52
6	 35	Ethylbenzene	 60	70

a: mixture of ortho and para-isomers were obtained

GCMS analysis of the compound **57** (Table 5.3, entry 3) showed two peaks having the same mass at different retention time and we found these are *o*- and *p*-isomers in the ratio of 3:7 and are inseparable by column chromatography. Experiments with higher aromatic compounds naphthalene and indole did not yield any characteristic products.

5.4.6 SiO_2-Cl mediated synthesis of allyl ethers from MBH adducts

The successful isomerization of MBH adducts with SiO_2-Cl and SiO_2-Cl/aromatic compounds prompted us to further explore the reaction in the presence of saturated and unsaturated alcohols so as to functionalize adducts as ethers. When the adduct **34** derived from methoxy benzaldehyde was heated with propargyl alcohol in presence of 100 w/w % silicachloride for 12 hour afforded only the *E*- isomer **61** in 70% yield (Scheme 5.16).



Scheme 5.16: *Synthesis of allyl ether*

The structure of **61** was confirmed by usual spectroscopic analysis. In the IR spectrum, the terminal alkyne C-H stretching absorption was observed at 3289 cm^{-1} and the absorption corresponding to the carbon-carbon triple bond was observed at 2113 cm^{-1}. Absorption at 1714 cm^{-1} corresponds to the ester carbonyl group. In the ^1H NMR spectrum, the terminal alkyne proton appeared as a triplet centred at δ 2.49 with a coupling constant J = 3Hz. A singlet at δ 3.82 was discernable to the methoxy protons attached to the aryl ring and the ester group. The doublet with a chemical shift centred at δ 4.29 (J = 3Hz) was indicative of the methylene proton attached to the triple bond. The methylene group attached to the alkene was observed as a singlet at δ 4.43 and the aromatic protons were observed in the downfield range δ 7.55-7.57 as well separated doublets. The alkene proton appeared at δ 7.90 (Figure 5.8) which indicates the *E*-geometry of the alkene.

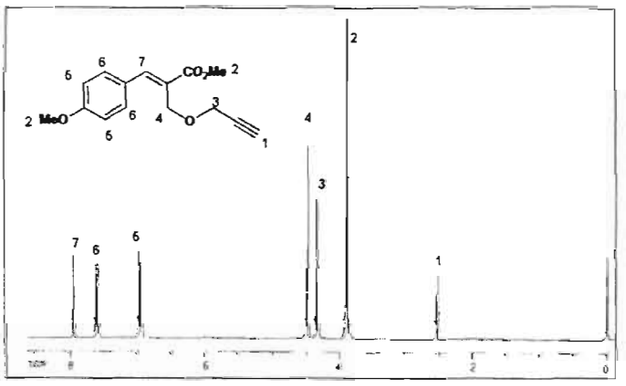


Figure 5.8: *^1H NMR spectrum of* **61**

The ^{13}C NMR spectrum of **61** showed four discrete signals at δ 52.0, 53.6, 55.2 and 57.8 that were corresponding to carbons of the ether linkage. The sp hybridized carbons were observed at δ 64.3 and δ 74.6. The sp^2 hybridized carbons were resonated in the range from δ 79.6 to 160.8. The ester

carbonyl was observed at δ 168.1 (Figure 5.9). Finally, the structure was confirmed from the high resolution mass spectral analysis as it showed a molecular ion peak at *m/z*=260.1072.

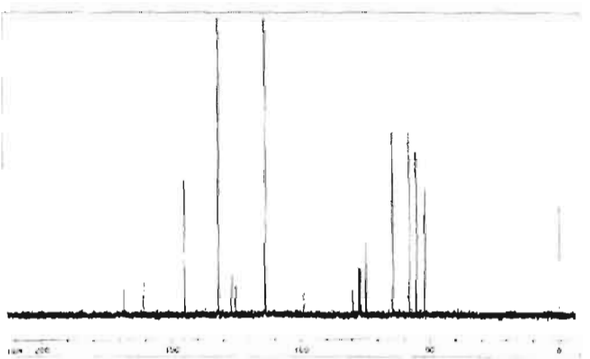
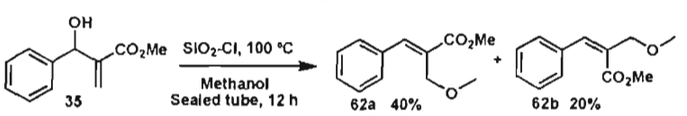


Figure 5.9: *^{13}C NMR spectrum of* **61**

However, when adduct **35** derived from benzaldehyde was treated with methanol under optimized condition, the reaction yielded both the *E*- **62a** (40%) and Z- **62b** (20%) isomer after purification as shown in scheme 5.17.



Scheme 5.17: *Formation of E- and Z-isomeric ethers*

Structure of **62a** and **62b** were confirmed by the NMR analysis. The major isomer **62b** showed two singlets for the ether methyl and ester methyl protons at δ 3.44 and 3.84, respectively. The CH_2 protons were appeared at δ 4.2 as a singlet. A multiplet in the range δ 7.37-7.53 was indicative of the aromatic protons. A singlet at δ 7.94 was discernable to the olefin proton (Figure 5.10).

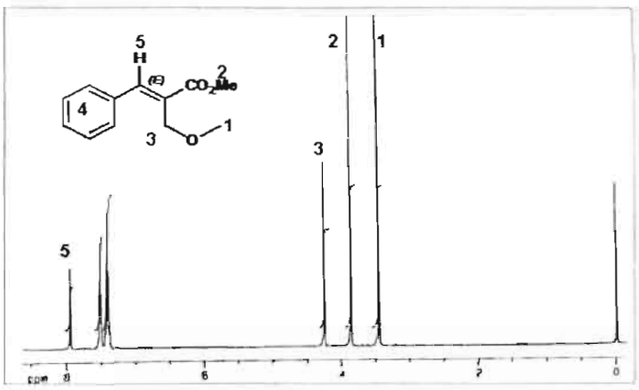


Figure 5.10: *^{1}H NMR spectrum of* **62b**

In the carbon-13 NMR spectrum, the methoxy carbon of the ester group appeared at δ 52.1. The CH_2 and the CH_3 protons of the ether moicty appeared at δ 66.4 and at δ 58.2. The sp^2 hybridized carbons were appeared in the range from δ 128.4-144.7. Ester carbonyl was observed at δ 168.0 (Figure 5.11). The structure was confirmed by the HRMS analysis as it showed a molecular ion peak at *m/z* =206.0942.

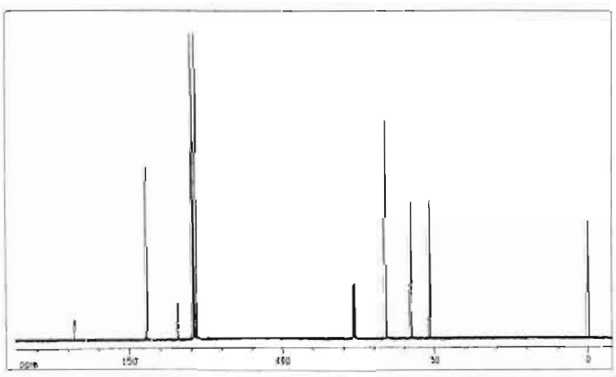


Figure 5.11: *^{13}C NMR spectrum of* **62b**

Similarly, the minor *Z*-isomer **62b** showed two singlets at δ 3.41 and δ 3.68 and was indicative of the two methyl proton at the ester and the ether moiety in the proton NMR spectrum. The methylene protons were discernable as a singlet at δ 4.25. The olefin proton appeared as a singlet at δ 6.90 and the aromatic protons were observed in the range δ 7.28-7.35 (Figure 5.12). In the

^{13}C NMR spectrum of the compound, the methyl carbons were resonated at δ 51.8 and δ 58.2, respectively. The signal at δ 74.2 corresponds to the CH_2 carbon. The sp^2 hybridized carbons were resonated in the chemical shift range from δ 124.8 to 135.8. The ester carbonyl was visible at δ 168.6 as shown in figure 5.13. A molecular ion peak in the HRMS spectrum at *m/z*=206.0943 confirms the final structure of the compound.

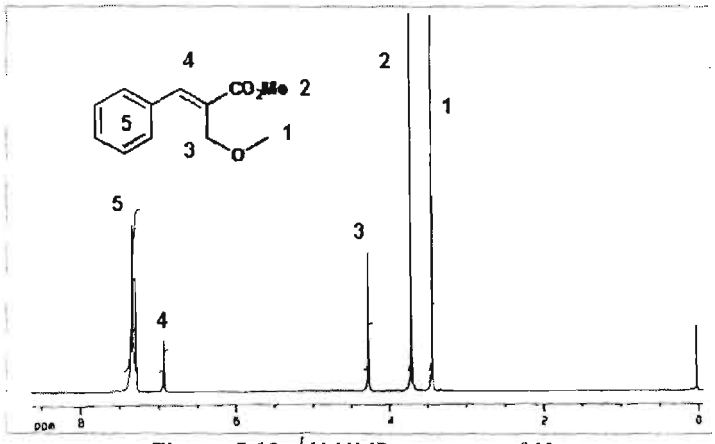


Figure 5.12: *^1H NMR spectrum of* **62a**

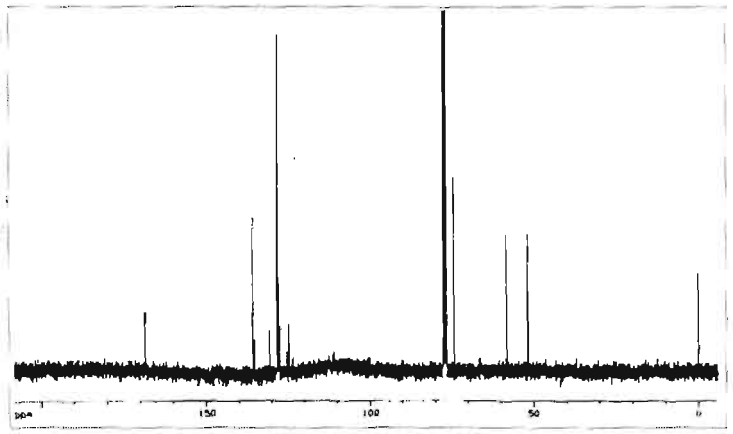
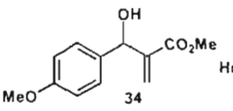
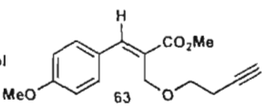
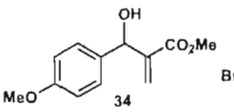
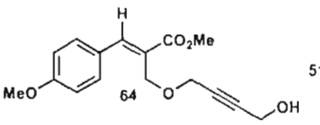
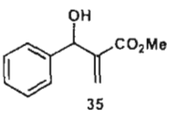
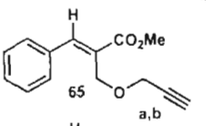
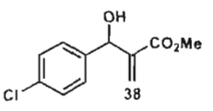
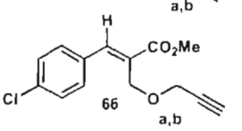
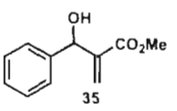
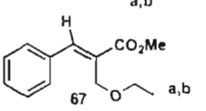
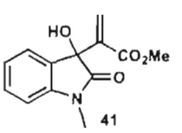
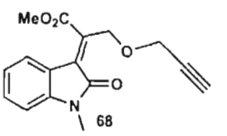
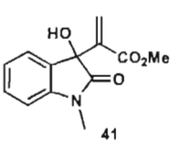
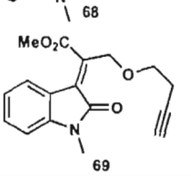


Figure 5.13: *^{13}C NMR spectrum of* **62a**

The adduct **34** when treated with homopropargyl alcohol and but-2-yne-1,4-diol yielded the corresponding ethers **63** and **64** under optimized condition. But the adduct **34**, when treated with benzyl alcohol, the reaction neither

yielded the dimer nor the ether. In all the cases, only *E*- isomers were obtained as sole product (Table 5.4, entries 1 and 2).

Table 5.4: Isomerization–etherification of Morita-Baylis–Hillman adducts

entry	substrate	alcohols	product (A)	yields (%)
1	 34	Homopropargyl alcohol	 63	80
2	 34	But-2-yne-1,2-diol	 64	51
3	 35	Propargyl alcohol	 65 a,b	64
4	 38	Propargyl alcohol	 66 a,b	85
5	 35	Ethanol	 67 a,b	65[b]
6	 41	Propargyl alcohol	 68	15
7	 41	Homopropargyl alcohol	 69	5

b: E and Z isomer

Analogous reactivity pattern was observed for adduct derived from benzaldehyde **35** and 4-chlorobenzaldehyde **38** when reacted with propargyl alcohol and ethanol. It was found that from the reaction mixture, *E*- isomer was formed as a major constituent. Isatin derived adduct **41**, when treated with propargyl alcohol under optimized reaction condition yielded the propargyl

ether **68** in 15% yields. All the compounds were characterized by the spectroscopic analysis (Table 5.4).

5.4.7 Mechanistic Considerations

A plausible mechanism for the reaction of isomerization-chlorination, arylation and etherification is postulated and shown in figure 5.14. The Si-Cl bond is weak and can give rise to Lewis acid-centred intermediates. The chloride ion in SiO_2-Cl could be displaced by the hydroxyl group of the MBH adduct to form tight ion pairs that upon nucleophilic attack with chloride or aryl or alkoxy nucleophiles in an S_N' fashion to form isomerized derivatives.

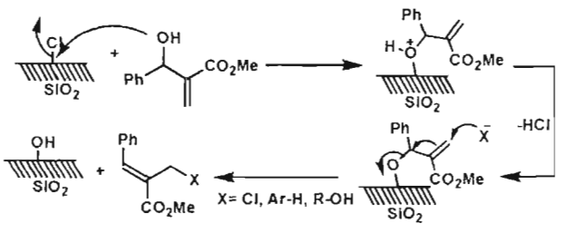
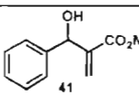
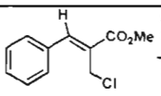
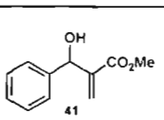
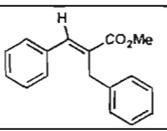
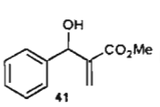
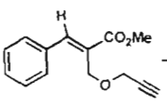


Figure 5.14: *Mechanisum of the isomerization*

5.4.8 Reactivity and efficiency of SiO_2-Cl Vs Thionyl chloride

The efficiency and necessity of SiO_2-Cl was compared with thionyl chloride for isomerization-chlorination, arylation, and etherification reactions. The reaction was compared and demonstrated with MBH adduct **11** as substrate.

Table 5. 5: Comparison of Silicachloride with Thionylchloride

entry	type of reaction	substrate	product (A)	condition	yields (%)
1	Isomerization-chlorination			$SOCl_2$, Neat Sealed Tube	77
2				SiO_2-Cl, Neat Sealed Tube	73
3	Isomerization-arylation			$SOCl_2$, Neat Benzene, Sealed Tube	0
4				SiO_2-Cl, Neat Benzene, Sealed Tube	90
5	Isomerization-etherification			$SOCl_2$, Neat Propargyl alcohol Sealed Tube	10
6				SiO_2-Cl, Neat Propargyl alcohol Sealed Tube	75

As shown in table 5.5, in the case of the isomerization-chlorination reaction, there was no difference in the yield of product formation (Table 5.5, entry 1 and 2). However, in the cases of arylation and etherification reactions, it was found that the SiO_2-Cl catalyst is essential as the yields are significantly higher with SiO_2-Cl than thionyl chloride (Table 5.5, entries 3 and 4). Further, unlike thionyl chloride, which is difficult to handle, the advantages of the SiO_2-Cl catalyst are that it is stable, efficient and easy to handle.

5.5 Conclusions

1. SiO_2-Cl has been used as a multipurpose catalyst for the one-pot isomerization-chlorination, arylation and ether formation of activated and non-activated MBH adducts under neat condition.
2. It should be noted that the arylation reaction afforded excellent yields of the products.
3. A mechanism of the reaction is discussed.
4. The advantages of SiO_2-Cl in organic synthesis are that the catalyst is stable, efficient, operationally simple and convenient in handling, inexpensive, solid, heterogeneous and acidic in nature.
5. From the comparative study with thionyl chloride, it was obvious that for isomerization-chlorination, both the catalysts are found good. However, for arylation and ether formation reactions, SiO_2-Cl catalyst was found good.

5.6 Experimental

Preparation of SiO_2-Cl Catalyst

Silica gel (10 g) was oven-dried (120 ^{0}C under vacuum) in a round-bottomed flask (250 mL) which was equipped with a condenser and a drying tube, and thionyl chloride (40 mL) was added. The mixture was refluxed for 40 h. The unreacted thionyl chloride was distilled off under vacuum. The resulting white greyish powder was flame-dried and stored in a tightly capped bottle. This SiO_2-Cl catalyst can be used for a month without losing its activity.

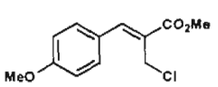
General Experimental procedure for silicachloride mediated isomerization of Morita-Baylis-Hillman adducts:

A mixture of MBH adduct (1 mmol), freshly prepared silicachloride (100% w/w) and alcohol/benzene (as reagent, 2 equiv.) were heated in an oven-dried sealed tube at 100 ^{0}C for 12 h. The crude mixture was diluted with CH_2Cl_2 and filtered through a pad of Celite and dried over anhydrous Na_2SO_4, concentrated under vacuum and was purified by silica gel (100-200 mesh) column chromatography, with gradient mixture of hexane/ethyl acetate as eluent to afford the products.

Isomerization–chlorination of MBH adducts

(Z)-methyl 2-(chloromethyl)-3-(4-methoxyphenyl)acrylate 42

Following the general procedure, a mixture of methyl 2-(hydroxy(4-methoxyphenyl)methyl)acrylate **34** (100 mg, 0.449 mmol), and freshly prepared silicachloride (100% w/w) were taken in an oven-dried sealed tube and heated at 100 ^{0}C for 12 h afforded **42** as a colourless oil (75%, 81 mg, eluent: 2% ethyl acetate:hexane).



42

IR (neat) ν_{max}: 837, 1026, 1259, 1604, 1712 cm^{-1}.

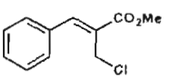
^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 3.87 (s, 6H), 4.52 (s, 2H), 6.97 (d, 2H, *J* = 8.7Hz), 7.56 (d, 2H, *J* = 8.7Hz), 7.83 (s, 1H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 39.5, 52.3, 55.3, 113.5, 114.3 (2C), 125.8, 126.6, 131.8 (2C), 143.7, 160.9

HRMS (EI) for $C_{12}H_{13}ClO_3$; Calcd (M^+): 240.0553; Found m/z: 240.0564 (M^+).

(Z)-methyl 2-(chloromethyl)-3-phenylacrylate 44

Following the general procedure, a mixture of methyl 2-(hydroxy(phenyl)methyl)acrylate **35** (100 mg, 0.520 mmol) and freshly prepared silicachloride (100% w/w) were taken in an oven-dried sealed tube and heated at 100 ^{0}C for 12 h and afforded **44** as a colourless oil (58%, 63.5 mg, eluent: 2% ethyl acetate:hexane).



44

IR (neat) ν_{max}: 761, 1626, 1714 cm^{-1}.

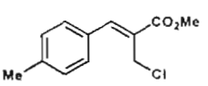
^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 3.85 (s, 3H), 4.24 (s, 2H), 7.38-7.53 (m, 5H), 7.93 (s, 1H).

^{13}C NMR($CDCl_3$/TMS, 75.3 MHz): δ 52.2, 58.3, 114.4, 128.5 (2C), 128.6, 129.8 (2C), 134.7, 144.7, 168.1.

HRMS (EI) for $C_{11}H_{11}ClO_2$; Calcd (M^+): 210.0448; Found m/z: 210.0454 (M^+).

(Z)-methyl 2-(chloromethyl)-3-p-tolylacrylate 45

Following the general procedure, a mixture of methyl 2-(hydroxy(p-tolyl)methyl)acrylate **36** (100mg, 0.484 mmol) and freshly prepared silicachloride (100% w/w) were taken in an oven-dried sealed tube and heated at 100 ^{0}C for 12 h afforded **45** as a colourless oil (78%, 84 mg, eluent : 2% ethyl acetate:hexane).



45

IR (neat) ν_{max}: 812, 1629, 1714 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 2.40 (s, 3H), 3.87 (s, 3H), 4.49 (s, 2H), 7.26 (d, 2H, J = 8.1 Hz), 7.46 (d, 2H, J = 8.1 Hz), 7.85 (s, 1H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 21.4, 39.1, 52.3, 123.0, 126.0, 127.7, 129.7 (2C), 141.2, 143.9 (2C), 166.0

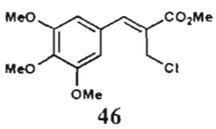
HRMS (EI) for $C_{12}H_{13}ClO_2$; Calcd (M^+): 224.0604 Found m/z: 224.0615 (M^+).

(Z)-methyl 2-(chloromethyl)-3-(3,4,5-trimethoxyphenyl)acrylate 46

Following the general procedure, a mixture of methyl 2-(hydroxy(3,4,5-trimethoxyphenyl)methyl)acrylate **37** (100 mg, 0.354 mmol) and freshly prepared silicachloride (100% w/w) were taken in an oven-dried sealed tube and heated at 100 ^{0}C for 2 h afforded **46** as a colourless oil (42%, 44.7 mg, eluent: 2% ethyl acetate:hexane).

IR (neat) ν_{max}: 779, 1042, 1259, 1622, 1714 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 3.88 (s, 3H), 3.90 (s, 9H), 4.52 (s, 2H), 6.86 (s, 2H), 7.83 (s, 1H).



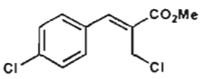
46

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 39.6, 52.4, 56.1 (2C), 60.8, 106.9, 127.4, 129.4 (2C), 141.0, 144.1, 153.3 (2C), 166.6.

HRMS (EI) for $C_{14}H_{17}ClO_5$; Calcd (M^+): 300.0765; Found m/z: 300.0775 (M^+).

(Z)-methyl 2-(chloromethyl)-3-(4-chlorophenyl)acrylate 47

Following the general procedure, a mixture of methyl 2-((4-chlorophenyl)(hydroxy)methyl)acrylate **38** (100 mg, 0.441 mmol) and freshly prepared silicachloride (100% w/w) were taken in an oven-dried sealed tube and heated at 100 ^{0}C for 12 h afforded **47** as a colourless oil (39%, 42 mg, eluent : 2% ethyl acetate:hexane).



47

IR (neat) ν_{max}: 836, 1632, 1716 cm^{-1}.

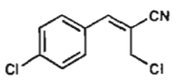
^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 3.88 (s, 3H), 4.43 (s, 2H), 7.42 (d, 2H, J = 8.4 Hz), 7.49 (d, 2H, J = 8.4 Hz), 7.81 (s, 1H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 38.5, 52.7, 123.5, 129.4 (2C), 131.1 (2C), 141.3, 142.5, 146.5, 166.6.

HRMS (EI) for $C_{11}H_{10}Cl_2O_2$; Calcd (M^+): 244.0058; Found m/z: 244.0072 (M^+).

(Z)-2-(chloromethyl)-3-(4-chlorophenyl)acrylonitryle 49

Following the general procedure, a mixture of 2-((4-chlorophenyl)(hydroxy)methyl)acrylonitrile **40** (100 mg, 0.516 mmol) and freshly prepared silicachloride (100% w/w) were taken in an oven-dried sealed tube and heated at 100 ^{0}C for 12 h afforded **49** as a colourless oil (50%, 54 mg, eluent : 2% ethyl acetate:hexane).



49

IR (neat) ν_{max}: 823, 1618, 2219 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 4.31 (s, 2H), 7.18 (s, 1H), 7.43 (d, 2H, J = 8.7Hz), 7.73 (d, 2H, J

= 8.7Hz).

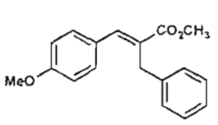
^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 45.6, 108.1, 117.8, 129.3 (2C), 130.4 (2C), 137.4, 145.1, 146.5.

HRMS (EI) for $C_{10}H_7Cl_2N$; Calcd (M^+): 212.0753, Found m/z: 212.0968 (M^+).

Isomerization-arylation of MBH adducts

(E)-methyl -2-benzyl-3-(4-methoxyphenyl)acrylate 54

Following the general procedure, a mixture of methyl 2-(hydroxy(4-methoxyphenyl)methyl)acrylate **34** (100 mg, 0.449 mmol), benzene (70 mg, 0.898 mmol) and freshly prepared silicachloride (100% w/w) were taken in an oven-dried sealed tube and heated at 100 ^{0}C for 12 h afforded **54** as a colourless oil (90%, 114 mg, eluent : 2% ethyl acetate:hexane).



54

IR (neat) ν_{max}: 1498, 1590, 1639, 1715, 3063 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 3.71 (s, 6H), 3.95 (s, 2H), 7.19-7.34 (m, 9H), 7.93 (s, 1H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 33.4, 51.5, 55.3, 109.5, 126.8, 128.5, 128.5, 128.7, 128.8, 128.9, 129.1, 129.5, 129.6, 130.7, 139.3, 168.6.

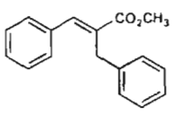
HRMS (EI) for $C_{18}H_{18}O_3$; Calcd (M^+): 282.3337, Found m/z: 282.368 (M^+).

(E)-methyl -2-benzyl-3-phenylacrylate 55

Following the general procedure, a mixture of methyl 2-(hydroxy(4-methoxyphenyl)methyl)acrylate **35** (100 mg, 0.520 mmol), benzene (81 mg, 1.04 mmol) and freshly prepared silicachloride (100% w/w) were taken in an oven-dried sealed tube and heated at 100 ^{0}C for 12 h afforded **55** as a colourless oil (95%, 124 mg, eluent : 2% ethyl acetate:hexane).

IR (neat) ν_{max}: 1493, 1592, 1633, 1714, 3060 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ .3.72 (s, 3H), 3.93 (s, 2H), 7.18-7.35 (m, 10H), 7.94 (s, 1H).



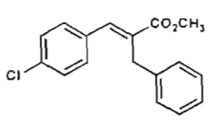
55

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 32.1, 51.3, 107.5, 121.8, 127.5, 127.6, 128.7, 128.8, 128.9, 129.3, 129.7, 129.7, 131.7, 138.3, 168.9.

HRMS (EI) for $C_{17}H_{16}O_2$; Calcd (M^+): 252.1168, Found m/z: 252.1158 (M^+).

(E)-methyl-2-benzyl-3-(4-chlorophenyl)acrylate 56

Following the general procedure, a mixture of methyl 2-(hydroxy(4-methoxyphenyl)methyl)acrylate **38** (100 mg, 0.442 mmol), benzene (68.9 mg, 0.884 mmol) and freshly prepared silicachloride (100% w/w) were taken in an oven-dried sealed tube and heated at 100 ^{0}C for 12 h afforded **56** a as colourless oil. (96%, 121.5 mg, eluent : 2% ethyl acetate:hexane).



56

IR (neat) ν_{max}: 1493, 1592, 1633, 1714, 3060 cm^{-1}.

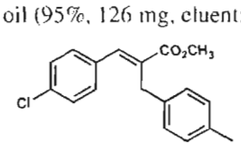
^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 3.73 (s, 3H), 3.97 (s, 2H), 7.15-7.83 (m, 9H), 7.86 (s, 1H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 33.0, 52.1, 128.5, 128.6, 128.7 (2C), 128.9 (2C), 129.1, 129.4 (2C), 130.4 (2C), 130.8, 133.6, 139.5, 168.3.

HRMS (EI) for $C_{17}H_{15}ClO_2$; Calcd (M^+): 286.0761, Found m/z: 286.0755 (M^+).

(E)-methyl -2-(4-methylbenzyl)-3-(4-methoxyphenyl)acrylate 57

Following the general procedure, a mixture of methyl 2-(hydroxy(4-methoxyphenyl)methyl)acrylate **38** (100 mg, 0.442 mmol), toluene (81.4 mg, 0.893 mmol) and freshly prepared silicachloride (100% w/w) were taken in an oven-dried sealed tube and heated at 100 ^{0}C for 12 h afforded **57** as a colourless oil (95%, 126 mg, eluent: 2% ethyl acetate:hexane).



57

IR (neat) ν_{max}: 1493, 1592, 1633, 1714, 3060 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 2.20 (s, 3H), 2.22 (s, 3H), 3.64 (s, 3H), 3.65 (s, 3H), 3.78 (s, 2H), 3.79 (s, 2H), 6.8-7.3 (m, 18H), 7.75 (s, 1H), 7.82 (s,

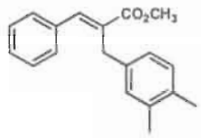
1H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 19.2, 20.8, 30.8, 32.5, 38.6, 51.5, 126.1, 126.6, 128.6, 130.4 (3C), 133.4 (3C), 139.3, 139.8, 168.2.

HRMS (EI) for $C_{18}H_{17}ClO_2$; Calcd (M^+) 300.0917, Found m/z: 300.0915 (M^+).

(E)-methyl 2-(3,4-dimethylbenzyl)-3-phenylacrylate 58

Following the general procedure, a mixture of methyl 2-(hydroxy(4-methoxyphenyl)methyl)acrylate **35** (100 mg, 0.520 mmol), xylene (110.4 mg, 1.04 mmol) and freshly prepared silicachloride (100% w/w) were taken in an oven-dried sealed tube and heated at 100 ^{0}C for 12 h afforded **58** as a colourless oil (90%, 131 mg, eluent: 2% ethyl acetate:hexane).



58

IR (neat) ν_{max}: 1493, 1592, 1633, 1714, 3060 cm^{-1}.

^{1}H NMR($CDCl_3$/TMS, 300.1 MHz): δ 2.26 (s, 6H), 3.65 (s, 3H), 3.92 (s, 2H), 6.80-7.30 (m, 8H), 7.82 (s, 1H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 19.2, 19.5, 20.87, 30.8, 32.5, 38.6, 51.5, 126.1, 126.6, 128.6, 130.4 (3C), 133.4 (3C), 139.3, 139.8, 168.6.

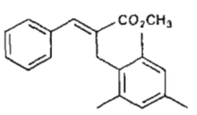
HRMS (EI) for $C_{19}H_{20}O_2$; Calcd (M^+):280.1463., Found m/z: 280.1455 (M^+).

(E)-methyl 2-(2,4,6-trimethylbenzyl)-3-phenylacrylate 59

Following the general procedure, a mixture of methyl 2-(hydroxy(4-methoxyphenyl)methyl)acrylate **35** (100 mg, 0.520 mmol), mesitylene (124.9 mg, 1.04 mmol) and freshly prepared silicachloride (100% w/w) were taken in an oven-dried sealed tube and heated at 100 ^{0}C for 12 h afforded **59** as a colourless oil (52%, 79.54 mg, eluent: 2% ethyl acetate:hexane).

IR (neat) ν_{max}: 1493, 1592, 1633, 1714, 3060 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 2.20 (s, 9H), 3.62 (s, 3H), 3.92 (s, 2H), 6.81-7.32 (m, 7H), 7.62 (s,



59

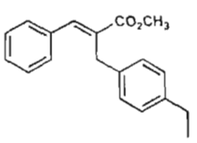
1H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 19.2, 19.5, 20.1, 20.8, 30.8, 32.5, 38.6, 51.5, 126.1, 126.6, 128.6, 130.4 (3C), 133.4 (3C), 139.3, 139.8, 168.4.

HRMS (EI) for $C_{20}H_{22}O_2$; Calcd (M^+):294.1625, Found m/z: 294.1620 (M^+).

(E)-methyl 2-(4-ethylbenzyl)-3-phenylacrylate 60

Following the general procedure, a mixture of methyl 2-(hydroxy(4-methoxyphenyl)methyl)acrylate **35** (100mg, 0.520 mmol), ethylbenzene (110.4 mg, 1.04 mmol) and freshly prepared silicachloride (100% w/w) were taken in an oven-dried sealed tube and heated at 100 ^{0}C for 12 h afforded **60** as a colourless oil (70%,102 mg, eluent: 2% ethyl acetate:hexane).



60

IR (neat) ν_{max}: 1493, 1592, 1630, 1711, 3062 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.31 (t, 3H, J = 2.1Hz), 2.26 (q, 2H, J = 2.1Hz), 3.65 (s, 3H), 3.92 (s, 2H), 6.8-7.3 (m, 9H), 7.92 (s, 1H)

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 19.2, 19.5, 20.8, 30.8, 32.5, 38.6, 51.5, 126.1, 126.6, 128.6, 130.4 (3C), 133.4 (3C), 139.3, 139.8, 168.6.

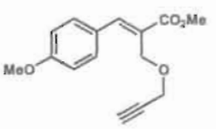
HRMS (EI) for $C_{19}H_{20}O_2$; Calcd (M^+):280.1463, Found m/z: 280.1456 (M^+).

Isomerization–etherification of MBH adducts

(*E*)-methyl3-(4-methoxyphenyl)-2-((prop-2-ynyloxy)methyl)acrylate 61

Following the general procedure, a mixture of methyl 2-(hydroxy(4-methoxyphenyl)methyl)acrylate **34** (100 mg, 0.449 mmol), freshly prepared silicachloride (100% w/w) and propargyl alcohol (50 mg, 0.898 mmol) were taken in an oven-dried sealed tube and heated at 100 ^{0}C for 12 h afforded **60** as a colourless oil (70%, 89.2 mg, eluent: 2% ethyl acetate:hexane).

IR (neat) ν_{max}: 1178, 1605,1714, 2113, 3289 cm^{-1}.



61

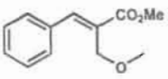
^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 2.49-2.50 (t, 1H, *J* = 3Hz,), 3.82 (s, 3H), 3.83 (s, 3H), 4.28-4.29 (d, 2H, *J* = 3Hz), 4.43 (s, 2H), 6.91-6.94 (d, 2H, *J* = 8.7Hz), 7.55-7.57 (d, 2H, *J* = 8.7Hz), 7.90 (s, 1H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 52.0, 53.6, 55.2, 57.8, 64.3, 74.6, 79.6, 98.8, 113.9, 125.4, 127.0, 132.0, 145.1, 160.1, 168.1.

HRMS (EI) for $C_{15}H_{16}O_4$; Calcd (M^+): 260.1049; Found m/z: 260.1072 (M^+).

(*E*)-methyl 2-(methoxymethyl)-3-phenylacrylate 62a

Following the general procedure, a mixture of methyl 2-(hydroxy(phenyl)methyl)acrylate **35** (100 mg, 0.520 mmol), freshly prepared SiO_2-Cl (100% w/w) and methanol (33.3 mg, 1.04 mmol) were taken in a sealed tube and heated at 100 ^{0}C for 12 h afforded **62a** (42 mg, 40%) and **62b** (20%, 21.4 mg, eluent: 5% ethyl acetate:hexane) as a colourless oil.



62a

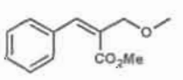
IR (neat) ν_{max}: 1237, 1633, 1715, 3412 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ (s, 3H), 3.68 (s, 3H), 4.25 (s, 2H), 6.90 (s, 1H), 7.28-7.35 (m, 5H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 51.8, 58.2, 74.2, 124.8, 127.7, 128.4, 130.7, 135.2, 135.8, 168.6.

HRMS (EI) for $C_{12}H_{14}O_3$; Calcd (M^+): 206.0943; Found m/z: 206.0943 (M^+).

(*Z*)-methyl 2-(methoxymethyl)-3-phenylacrylate 62b



62b

IR (neat) ν_{max}: 1237, 1633, 1715 cm^{-1}.

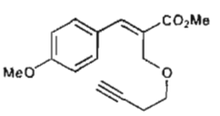
^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz):δ 3.44 (s, 3H), 3.84 (s, 3H), 4.24 (s, 2H), 7.37-7.53 (m, 5H), 7.94 (s, 1H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 52.1, 58.2, 66.4, 128.4, 128.6, 129.3, 129.7, 134.6, 144.7, 168.0.

HRMS (EI) for $C_{12}H_{14}O_3$; Calcd (M^+): 206.0943; Found m/z: 206.0942 (M^+).

(*E*)-methyl2-((but-3-ynyloxy)methyl)-3-(4-methoxyphenyl)acrylate 63

Following the general procedure, a mixture of methyl 2-(hydroxy(4-methoxyphenyl)methyl)acrylate **34** (100 mg, 0.449 mmol), freshly prepared silicachloride (100% w/w) and homopropargyl alcohol (62.9 mg, 0.898 mmol) were taken in an oven-dried sealed tube and heated at 100 ^{0}C for 12 h afforded **63** as a colourless oil (80%, 98.4 mg, eluent: 5% ethyl acetate:hexane).



63

IR (neat) ν_{max}: 1121, 1605, 1715, 2119, 3295 cm^{-1}.

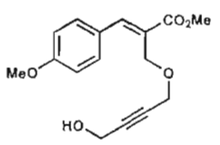
^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 2.01 - 2.03 (t, 1H, *J* = 2.7Hz), 2.51-2.57 (dt, 2H, *J* = 2.7Hz, *J* = 6.9 Hz), 3.70-3.72 (t, 2H, *J* = 6.6 Hz,), 3.82 (s, 3H), 3.83 (s, 3H), 4.36 (s, 2H), 6.90-6.95 (m, 2H), 7.55-7.59 (m, 2H), 7.90 (s, 1H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 19.7, 51.9, 55.2, 64.9, 68.4, 69.1, 81.4, 113.9, 125.7, 127.1, 131.9, 144.9, 160.7, 168.2.

HRMS (EI) for $C_{16}H_{18}O_4$; Calcd (M$^+$): 274.1205; Found m/z: 274.1210 (M$^+$).

(*E*)-methyl2-((4-hydroxybut-2-ynyloxy)methyl)-3-(4-methoxyphenyl) acrylate 64

Following the general procedure, a mixture of methyl 2-(hydroxy(4-methoxyphenyl)methyl)acrylate **34** (100 mg, 0.449 mmol), freshly prepared silicachloride (100% w/w) and propane-1,4-diol (77.29 mg, 0.898 mmol) were taken in an oven-dried sealed tube and heated at 100 ^{0}C for 12 h afforded **64** as a colourless oil (80%, 93.4 mg, eluent: 5% ethyl acetate:hexane).



64

IR (neat) ν_{max}: 1119, 1436, 1632, 1745, 2319, 3445 cm^{-1}.

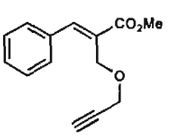
^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 2.20 (bs, 1H), 3.76 (s, 3H), 4.23 (s, 4H), 4.32 (s, 2H), 7.30-7.48 (m, 5H), 7.86 (s, 1H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 50.8, 52.21, 58.1, 63.9, 81.3, 85.0, 129.9, 134.3, 136.7, 145.1, 168.0.

HRMS (EI) for $C_{15}H_{16}O_4$; Calcd (M^+): 260.1049; Found m/z: 260.1035 (M^+).

(*E*)-methyl 3-phenyl-2-((prop-2-ynyloxy)methyl)acrylate 65a

Following the general procedure, a mixture of methyl 2-(hydroxy(phenyl)methyl)acrylate (100 mg, 0.520 mmol), freshly prepared silicachloride (100% w/w) and propargyl alcohol (78.4 mg, 1.04 mmol) were taken in an oven-dried sealed tube and heated at 100 ^{0}C for 12 h afforded *E*-(60 %, 71.7 mg, eluent: 2% ethyl acetate:hexane) **65a** and *Z*-isomer (4%, 5 mg, eluent: 5% ethyl acetate:hexane) **65b** as a colourless oil.



65a

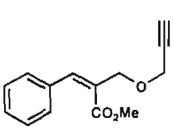
IR (neat) ν_{max}: 1076, 1633, 1714, 2116, 3291 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 2.47-2.48 (t, 1H, *J* = 2.1Hz), 3.83 (s, 3H), 4.27-4.28 (d, 2H, *J* = 2.1 Hz,), 4.41 (s, 2H), 7.30-7.40 (m, 3H), 7.54-7.58 (m, 2H), 7.94 (s, 1H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 52.1, 57.9, 64.1, 74.6, 79.5, 127.9, 128.4, 129.3, 129.9, 134.4, 145.1, 167.8.

HRMS (EI) for $C_{14}H_{14}O_3$; Calcd (M^+): 230.0943; Found m/z: 230.0929 (M^+).

(*Z*)-methyl 3-phenyl-2-((prop-2-ynyloxy)methyl)acrylate 65b



65b

IR (neat) ν_{max}: 1076, 1633, 1714, 2116, 3291 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 2.51-2.53 (t, 1H, *J* = 2.4Hz,), 3.83 (s, 3H), 4.40 (s, 2H), 4.83-4.84 (d, 2H, *J* = 2.4Hz), 7.30-7.40 (m, 3H), 7.54-7.58 (m, 2H), 7.99 (s, 1H).

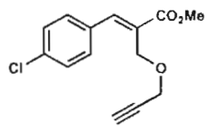
^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 52.5, 58.0, 64.0, 74.9, 79.5, 127.3, 128.5, 129.7, 130.0, 134.2,

146.0, 166.5.

HRMS (EI) for $C_{14}H_{14}O_3$; Calcd (M^+): 230.0943; Found m/z: 230.0935 (M^+).

(*E*)-methyl3-(4-chlorophenyl)-2-((prop-2-ynyloxy)methyl)acrylate 66a

Following the general procedure, a mixture of methyl 2-((4-chlorophenyl)(hydroxy)methyl)acrylate **38** (100 mg, 0.441 mmol), freshly prepared silicachloride (100% w/w) and propargyl alcohol (49.4 mg, 0.882 mmol) were taken in an oven-dried sealed tube and heated at 100 ^{0}C for 12 h afforded *E*- (80 %, 93 mg, eluent: 2% ethyl acetate:hexane) and **66a** and *Z*-isomer (5 %, 6 mg, 5% ethyl acetate:hexane) **66b** as colourless oil.



66a

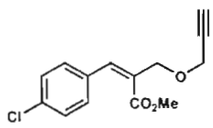
IR (neat) ν_{max}:1633, 1714, 2116, 2951, 3297, cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 2.50-2.51 (t, 1H, *J* = 2.1Hz), 3.84 (s, 3H), 4.27-4.28 (d, 2H, *J* = 2.1Hz), 4.37 (s, 2H), 7.35-7.39 (m, 2H), 7.51-7.87 (m, 2H), 7.87 (s, 1H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 52.5, 58.0, 63.8, 74.8, 79.4, 128.3, 128.6, 131.2, 132.7, 135.5, 143.7, 167.5.

HRMS (EI) for $C_{14}H_{13}ClO_3$; Calcd (M^+): 264.0553; Found m/z: 264.0534 (M^+).

(Z)-methyl 2-(chloromethyl)-3-(4-methoxyphenyl)acrylate 66b



66b

IR (neat) ν_{max}: 1633, 1714, 2116, 2951, 3297 cm^{-1}.

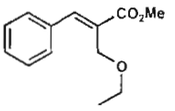
^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 2.52-2.54 (t, 1H, *J* = 2.4Hz), 3.83 (s, 3H), 4.39 (s, 2H), 4.84-4.85 (d, 2H, *J* = 2.4Hz), 7.35-7.39 (m, 2H), 7.51-7.87 (m, 2H), 7.92 (s, 1H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 52.5, 58.0, 63.8, 74.9, 79.3, 128.74, 129.7, 131.3, 132.5, 135.8, 144.6, 166.2.

HRMS (EI) for $C_{14}H_{13}ClO_3$; Calcd (M^+): 264.0553; Found m/z: 264.0530 (M^+).

(E)-methyl-2-(ethoxymethyl)-3-phenylacrylate 67a

Following the general procedure, a mixture of methyl-2-(hydroxy(phenyl)methyl)acrylate **34** (100 mg, 0.520 mmol), freshly prepared silicachloride (100% w/w) and ethyl alcohol (47.9 mg, 1.04 mmol) were taken in an oven-dried sealed tube and heated at 100 ^{0}C for 12 h afforded *E*- (40%, 45.8 mg, eluent: 2% ethyl acetate:hexane) **67a** and *Z*- isomer (15 %, 17.1 mg, eluent: 5% ethyl acetate:hexane) **67b** as colourless oil.



67a

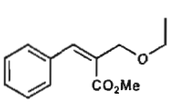
IR (neat) ν_{max}: 1237, 1633, 1715 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.11 (d, 3H, *J* = 2.1Hz) 3.43 (q, 2H, *J* = 2.1Hz), 3.85 (s, 3H), 4.23 (s, 2H), 7.35-7.50 (m, 5H), 7.92 (s, 1H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 15.1, 58.2, 62.1, 67.4, 128.1, 128.4, 129.5, 129.6, 134.1, 145.7, 168.2.

HRMS (EI) for $C_{13}H_{16}O_3$; Calcd (M^+): 220.2643; Found m/z: 220.2635 (M^+).

(*Z*)-methyl-2-(ethoxymethyl)-3-phenylacrylate 67b



67b

IR (neat) ν_{max}: 1237, 1633, 1715 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.11 (d, 3H, *J* = 2.7Hz), 3.41(t, 2H, *J* = 2.7Hz), 3.67 (s, 3H), 4.23 (s, 2H), 6.92 (s, 1H), 7.27-7.34 (m, 5H).

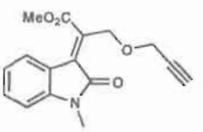
^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 15.2, 52.8, 67.2, 74.2, 127.5, 127.6, 128.4, 131.7, 133.2, 135.8, 168.0.

HRMS (EI) for $C_{13}H_{16}O_3$; Calcd (M^+): 220.2643; Found m/z: 220.0564 (M^+).

(E)-methyl-2-(1-methyl-2-oxoindolin-3-ylidene)-3-(prop-2-ynyloxy)propanoate 68

Following the general procedure, a mixture of methyl 2-(3-hydroxy-1-methyl-2-oxoindolin-3-yl)acrylate **41** (100 mg, 0.404 mmol), freshly prepared SiO_2-Cl (100% w/w) and propargyl alcohol (45.2 mg, 0.808 mmol) were taken

in an oven-dried sealed tube and heated at 100 ^{0}C for 12 h afforded **68** as a colourless oil (15%, 17 mg, eluent: 10% ethyl acetate:hexane).



68

IR (neat) ν_{max}: 1614, 1710, 1714, 2100, 3298 cm^{-1}.

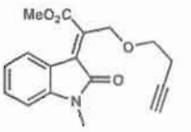
^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 2.46-2.49 (t, 1H, *J* = 2.34 Hz), 3.22 (s, 3H), 3.97 (s, 3H), 4.24-4.29 (d, 2H, *J* = 2.34 Hz), 5.22 (s, 2H), 6.79-6.81 (d, 1H, *J* = 7.84 Hz), 6.97-7.03 (t, 1H, *J* = 7.69 Hz), 7.28-7.34 (m, 2H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 30.5, 52.3, 60.3, 63.1, 76.4, 78.4, 121.5, 122.7, 124.3, 126.6, 128.2, 139.4, 140.3, 144.6, 169.8, 172.4

HRMS (EI) for $C_{16}H_{15}NO_4$; Calcd (M^+): 285.2946; Found m/z: 285.1290 (M^+).

(*E*)-methyl-3-(but-3-ynyloxy)-2-(1-methyl-2-oxoindolin-3-ylidene)propanoate 69

Following the general procedure, a mixture of methyl 2-(3-hydroxy-1-methyl-2-oxoindolin-3-yl)acrylate **41** (100 mg, 0.404 mmol), freshly prepared SiO_2-Cl (100% w/w) and homopropargyl alcohol (56.6 mg, 0.808 mmol) were taken in a sealed tube and heated at 100 ^{0}C for 12 h afforded **69** as a colourless oil (5%, 60.46mg, eluent: 2% ethyl acetate:hexane).



69

IR (neat) ν_{max}: 1076, 1633, 1720, 2116, 3291 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS, 300.1 MHz): δ 1.97(s, 1H), 2.45-2.49 (m, 2H), 3.22 (s, 3H), 3.39-3.65 (m, 2H), 3.97 (s, 3H), 5.17 (s, 2H), 6.79-6.81 (d, 1H, *J* = 7.5 Hz,), 6.97-7.02 (t, 1H, *J* = 7.5Hz), 7.28-7.34 (m,2H).

^{13}C NMR ($CDCl_3$/TMS, 75.3 MHz): δ 30.5, 32.2, 52.5, 63.4, 68.6, 69.7, 86.7, 121.5, 122.7, 122.3, 126.6, 137.6, 140.8, 144.6, 172.4, 175.8.

HRMS (EI) for $C_{17}H_{17}NO_4$; Calcd (M^+): 299.3212; Found m/z: 299.3217 (M^+).

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SUMMARY

The thesis entitled "**SYNTHESIS OF NOVEL 3-SPIRO HETEROCYCLIC OXINDOLES AND SILICACHLORIDE MEDIATED SYNTHETIC TRANSFORMATIONS OF MORITA-BAYLIS-HILLMAN ADDUCTS**" embodies the results of detailed investigations carried out on exploration of novel synthetic transformation of Morita-Baylis-Hillman (MBH) adducts for

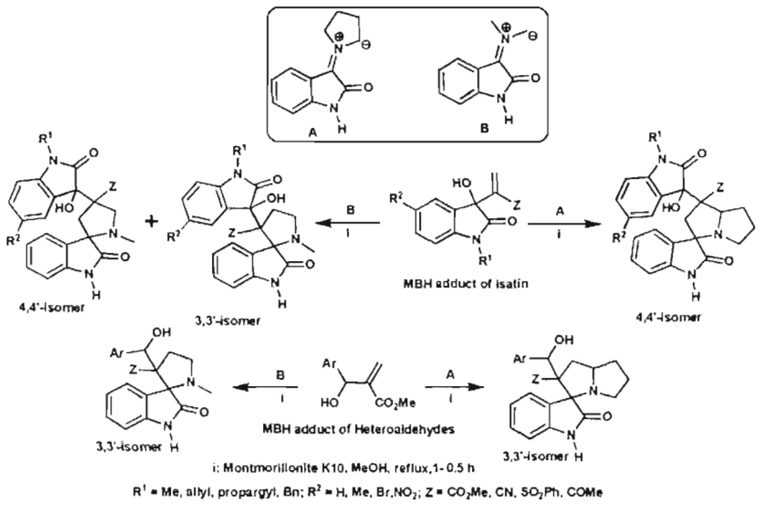
1. The construction of spiro heterocyclic oxindoles using 1,3-dipolar cycloaddition of azomethine ylides and
2. Synthesis of functionalized allyl derivatives using silicachloride as a catalyst.

At the outset a brief account of the Morita-Baylis-Hillman reaction, its importance in organic synthesis and an overview on azomethine ylides are described in Chapter 1. For convenience, synthetic applications of MBH adducts are categorized in reaction type and azomethine ylide (AMY) cycloaddition are categorized according to the mode of generation of AMY and suitable examples were given from the literature.

The first phase of the thesis is dealing with the synthesis of novel spiro heterocyclic oxindole using azomethine ylide (AMY) cycloaddition and indium mediated allylation reaction from isatin derived isomerised MBH adducts. Isatin, a pharmacologically important molecule, can form MBH adduct as it possess an electrophilic carbonyl group. The chemistry of isatin derived MBH adduct is less explored.

Chapter 2 describes the synthesis of novel 3-spiropyrrolizidine and 3-spiropyrrolidine oxindoles from MBH adducts of isatin and heteroaldehydes *via* 1,3- dipolar cycloaddition of azomethine ylides. Azomethine ylides were generated *in situ* from isatin and proline/sarcosine *via* Tsuge route (the thermal decarboxylative condensation). Cyclic azomethine ylide **A** was added to the activated double bond of isatin derived MBH adduct regioselectively to afford

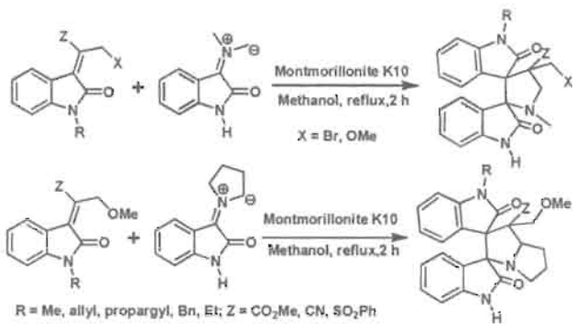
4,4'-disubstituted spiropyrrolizidine bisoxindole in excellent yield. On the other hand, the heteroaryl derived MBH adducts gave 3,3'-disubstituted spiropyrrolizidine oxindoles on [3+2]-cycloaddition with cyclic AMY "**A**". The regioselectivity may be due to the sterric hindrance between the oxindole moieties. However, the mode of addition of acyclic ylide **B** with isatin and heteroaryl derived MBH adducts showed different regioselectivity since 3,3'-disubstituted spiropyrrolizidine oxindoles were formed exclusively. In the case of *N*-allyl and *N*-propargyl isatin derived MBH adduct both the regioisomers were formed (Scheme 1).



Scheme 1

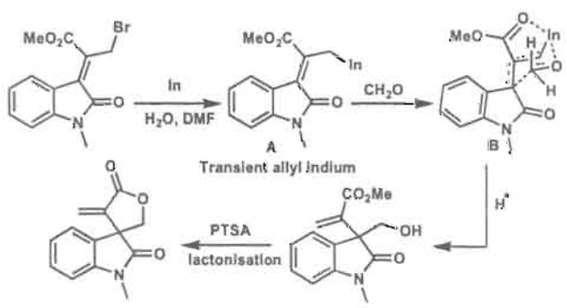
In Chapter 3, synthesis of 3, 3'-dispiropyrrolidine - and 3, 3'-dispiropyrrolizidine bisoxindoles from bromo and methoxy isomerised MBH adducts of isatin *via* [3+2]- AMY cycloaddition is described. Both methoxy and bromo isomerised MBH adducts reacted smoothly with acyclic AMY **B** and yielded highly substituted dispiropyrrolidine bisoxindoles. Methoxy isomerised MBH adduct showed less reactivity towards the cycloaddition with cyclic azomethine ylide **A** and yielded dispiropyrrolizidine oxindole in

moderate yields whereas the bromo isomerised MBH adduct underwent decomposition at the reaction condition (Scheme 2).



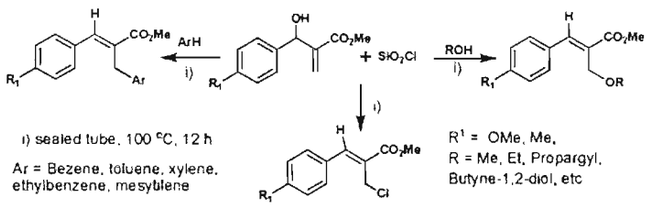
Scheme 2

The third chapter describes the successful synthesis of 3-spirolactone oxindole from MBH adduct derived allylbromide. As the bromo isomerised MBH adduct is an allyl bromide with an oxindole substitution at the γ-position, it could be good nucleophilic partner for the carbonyl allylation using indium metal. In the presence of indium metal allylbromide reacts with formaldehyde to afford the homoallylic alcohol with an oxindole substitution at the 2[nd] position and after lactonization with PTSA yielded spirolactone in very good yield (Scheme 3). Other aldehydes failed to give the desired product and may be due to the bulky tertiary carbanionic center.



Scheme 3

The last and fifth chapter of the thesis involves the isomerisation functionalisation of MBH adduct with silicachloride. Silicachloride (SiO_2Cl) is an extensively used heterogeneous solid catalyst for number chemical transformations. An efficient synthesis of allylchlorides was achieved from MBH adducts of simple aldehydes by the treatment with silicachloride (Scheme 4). On the other hand, allyl aryls and allyl ethers were obtained from MBH adduct by the treatment with silicachloride/arene and silicachloride/ alcohol respectively. The efficiency of silicachloride catalyst was compared with thionyl chloride and found silicachloride gave best results.



Scheme 4

List of Publications

1. Shanmugam, P.; Vaithiyanathan, V.; **Viswambharan, B.** Synthesis of functionalized 3-spirocyclopropane-2-indolones from isomerised Baylis-Hillman adducts of isatin *Tetrahedron*, **2006**, *62*, 4342-4347.
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